APPLICATION OF ORGANOCATALYSIS TO THE SYNTHESIS OF PHARMACEUTICALLY RELEVANT SCAFFOLDS: CHIRAL AZIRIDINES AND β-FLUOROAMINES; TOTAL SYNTHESIS OF STEMAPHYLLINE; AND DISCOVERY OF SELECTIVE PAR4 ANTAGONISTS.

By

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To the love of my life, Rachael;

and my family:

Cathy, Bill, Randy

Tracie, Travis, Travis, Cameron, and Evan

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LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
5-HT1D	5-hydroxytryptamine (serotonin) receptor subtype 1D
Å	Angstrom(s)
AA	arachidonic acid
Ac	acetyl
acac	acetylacetone
AChE	acetylcholinesterase
ADP	adenosine diphosphate
α	specific rotation
AP	activating peptide
aq	aqueous
Ar	aryl
ATP	adenosine triphosphate
BACE	beta-secretase
biphephos	6,6′-[(3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)*bis*(oxy)] *bis*(dibenzo[d,f][1,3,2]dioxaphosphepin)
BMS	Bristol-Myers-Squib
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
br	broad
BSA	bovine serum albumin

Bu	butyl
Bz	benzoyl
c	concentration (in g/100mL)
calc	calculated
cat	catalyst
Cbz	carboxybenzyl
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
CNS	central nervous system
conc	concentration
conv	conversion
CRC	concentration-response curve
CSA	camphorsulfonic acid
CVX	convulxin
Cy_3P	tricyclohexylphosphine
CYP450	cytochrome P450
CyPr	cyclopropyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamido)sulfur trifluoride

DBA	*tris*(dibenzylideneacetone)dipalladium(0)
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddt	doublet of doublet of triplets
DEA	diethanolamine
DEAD	diethylazodicarboxylate
DEB	diepoxybutane
DET	diethyl tartrate
DFI	2,2-difluoro-1,3-dimethyl imidazolidine
DIAD	diisopropylazodicarboxylate
DIBAL	diisobutylaluminum hydride
diox	dioxane
DIPEA	*N*,*N*-diisopropylethylamine
dm	doublet of multiplets
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethyl sulfide

DMSO	dimethyl sulfoxide
DPM	diphenylmethyl
DPPA	diphenylphosphoryl azide
DPPF	1,1'-*bis*(diphenylphosphino)ferrocene
dq	doublet of quartets
dr	diasteromeric ratio
dt	doublet of triplets
dtd	doublet of triplet of doublets
ED50	effective dose for 50% of test subjects
ee	enantiomeric excess
ELSD	evaporative light scattering detector
eq	equivalent(s)
ES	electrospray
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethyl amine
Et_3SiH	triethylsilane
EtCN	propionitrile
EtOAc	ethyl acetate
EtOH	ethanol
FDA	Food and Drug Administration

g	gram(s)
G_i	inhibitory G protein subunit
GP	glycoprotein
GPCR	G-protein coupled receptor
G_q	stimulatory G protein subunit
Grubbs II	Grubbs second generation catalyst
GSK	Glaxo-Smith-Kline
h	hour(s)
H_2O	water
HATU	O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
hERG	human ether a-go-go-related gene
Hex	hexanes
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
IC50	half maximal inhibitory concentration
Im	imidazole
IPA	isopropyl alcohol

i-Pr	isopropyl
J	coupling constant (in Hz)
kcal	kilocalorie(s)
kg	kilogram(s)
KHMDS	potassium *bis*(trimethylsilyl)amide
LAB	lithium amidotrihydroborate
LAH	lithium aluminum hydride
LC50	lethal concentration for 50% of test subjects
LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LHMDS	lithium *bis*(trimethylsilyl)amide
M	molar (moles per liter)
m	multiplet
mCPBA	*meta*-chloroperoxybenzoic acid
MCTS	metal-chelate transition state
Me	methyl
Me_3P	trimethylphosphine
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MHz	megahertz

MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MNBA	2-methyl-6-nitrobenzoic acid
mol	mole(s)
MOM	methoxymethyl
MPM	4-methyoxybenzyl
Ms	mesyl
MS	molecular sieves
Ms_2O	mesyl anhydride
$NaBH(OAc)_3$	sodium triacetoxyborohydride
NaHMDS	sodium *bis*(trimethylsilyl)amide
napt	naphthyl
nBuLi	n-butyllithium
NCS	*N*-chlorosuccinimide
ND	not determined
NFSI	*N*-fluorobenzenesulfonimide
nM	nanomolar
NMCTS	nonmetal-chelate transition state
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide

NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
^{o}C	degrees Celsius
oct	octet
p	para
p	pentet
PAR	protease activated receptor
pd	pentet of doublets
Pd/C	palladium on carbon
Ph	phenyl
Ph_3P	triphenylphosphine
PhMe	toluene
Phth	phthalimide
PI3-kinase	phosphatidylinositide 3-kinase
Pip	piperidine
Piv	pivaloyl
pKa	acid dissociation constant
PKC	protein kinase C
PLA2	phospholipase A2
PLC	phospholipase C
PLD	phospholipase D

pM	picomolar
PMB	phenylmagnesium bromide
ppm	parts per million
PS	polymer-supported
psi	pounds (of pressure) per square inch
q	quartet
qt	quartet of triplets
R	any organic substituent
RCM	ring-closing metathesis
Rf	retention factor
$Rh(acac)(CO)_2$	(acetylacetonato)dicarbonylrhodium(I)
rt	room temperature
rxn	reaction
s	singlet
sat	saturated
SCH	Schering-Plough
sec	second(s)
SEM	standard error of the mean
sept	septet
sext	sextet
SFC	supercritical fluid chromatograph

t	tert
t	triplet
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetra-n-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyl dimethylsilyl
t-Bu	*tert*-butyl
td	triplet of doublets
temp	temperature
Tf	triflyl
Tf_2O	triflyl anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
TOF	time of flight
Tol	toluene
TPAP	tetrapropylammonium perruthenate
tR	retention time
TRA	thrombin receptor antagonist

Trp	tryptophan
Ts	tosyl
Ts_2O	tosyl anhydride
TXA2	thromboxane A2
UV	ultraviolet
VU	Vanderbilt University
δ	chemical shifts (in ppm)
Δ	heat
μg	microgram(s)
μM	micromolar
μm	micrometer(s)
μW	microwave heating

CHAPTER 1

APPLICATION OF ORGANOCATALYSIS TO THE SYNTHESIS OF PHARMACEUTICALLY RELEVANT SCAFFOLDS: CHIRAL AZIRIDINES AND β-FLUOROAMINES

1. 1. General Access to Chiral *N*-Alkyl Terminal Aziridines via Organocatalysis

1.1.1 Importance of Aziridines

Aziridines are an important class of three-membered heterocycles containing one nitrogen atom with a rapidly expanding scope of applications in organic synthesis.[1] Aziridines are useful reactive substrates in synthetic chemistry, as they can undergo a variety of transformations involving ring opening. This reactivity is attributed primarily to the Baeyer strain energy of approximately 27 kcal/mol for the 3-membered ring.[2] Release of this strain energy through nucleophilic ring opening allows for regio- and stereoselective installation of a wide range of functionalities in a 1,2 relationship to the nitrogen.[3] In addition to being useful synthetic intermediates, aziridines can also be found in various biologically active natural products. As powerful akylating agents, aziridines have an inherent *in vivo* potency, often based on toxicity rather than specific activity.[4] Aziridine-containing natural products, such as the mitomycins and azinomycins, have shown potent antitumor activity. Structure-activity relationships have shown that the aziridine ring is essential for the anti-tumor activity (Figure 1.1.1.1).[5]

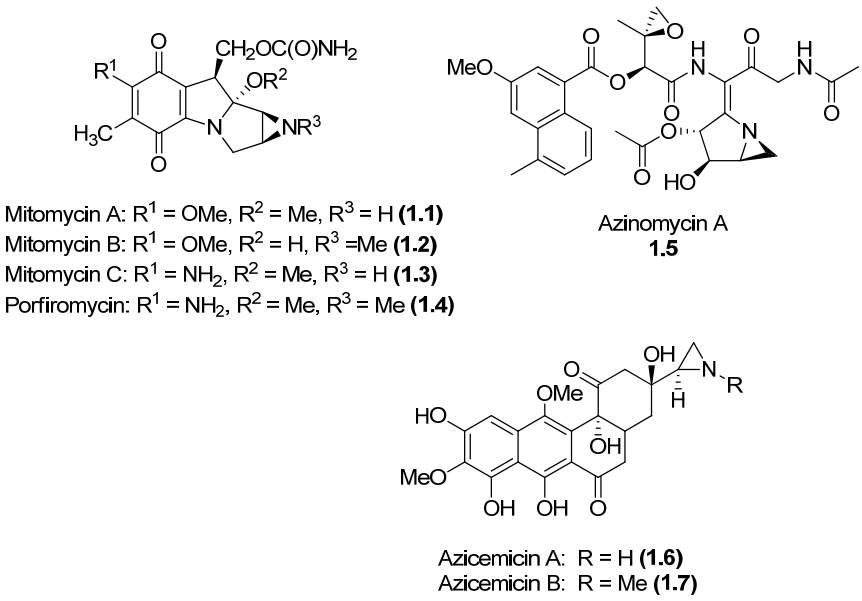


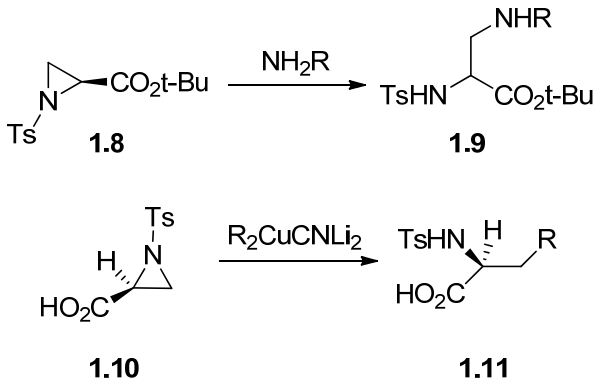
Figure 1.1.1.1 Aziridine-containing, biologically active natural products.

Aziridines can be grouped into two main classes, the activated and non-activated aziridines. Activated aziridines have *N*-electron-withdrawing groups (typically a tosyl group), while non-activated aziridines are typically *N*-alkyl or *N*-aryl substituted. The presence of the *N*-electron-withdrawing group in activated aziridines causes the ring to be susceptible to opening via nucleophilic attack. Unactivated aziridines, on the other hand, require activation by quaternization, protonation, or Lewis-acid activation in order to achieve ring opening.[6]

1.1.2 Reactivity of Aziridines

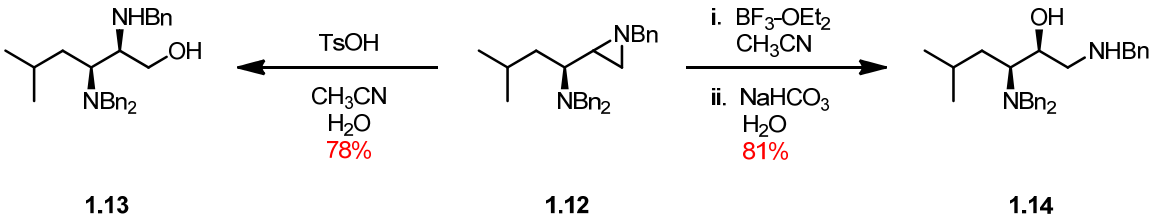
Similar to their cousin epoxides, aziridines undergo nucleophilic ring opening as their most widely-used transformation.[4] There are numerous examples in the literature using carbon-based as well as heteroatom-based nucleophiles to open these highly strained ring systems. For instance, primary amines attack aziridine-2-*t*-butyl carboxylate

at the least-hindered β-carbon to give diamino-propionic acid derivatives, which can be useful in the synthesis of cyclosporine analogs.[7] Aziridine-2-carboxylate can be ring opened with higher-order cuprates via attack at the least hindered carbon to give protected amino acid derivatives (Scheme 1.1.2.1).[8]



Scheme 1.1.2.1 Ring opening of activated aziridines by amine and carbon nucleophiles.

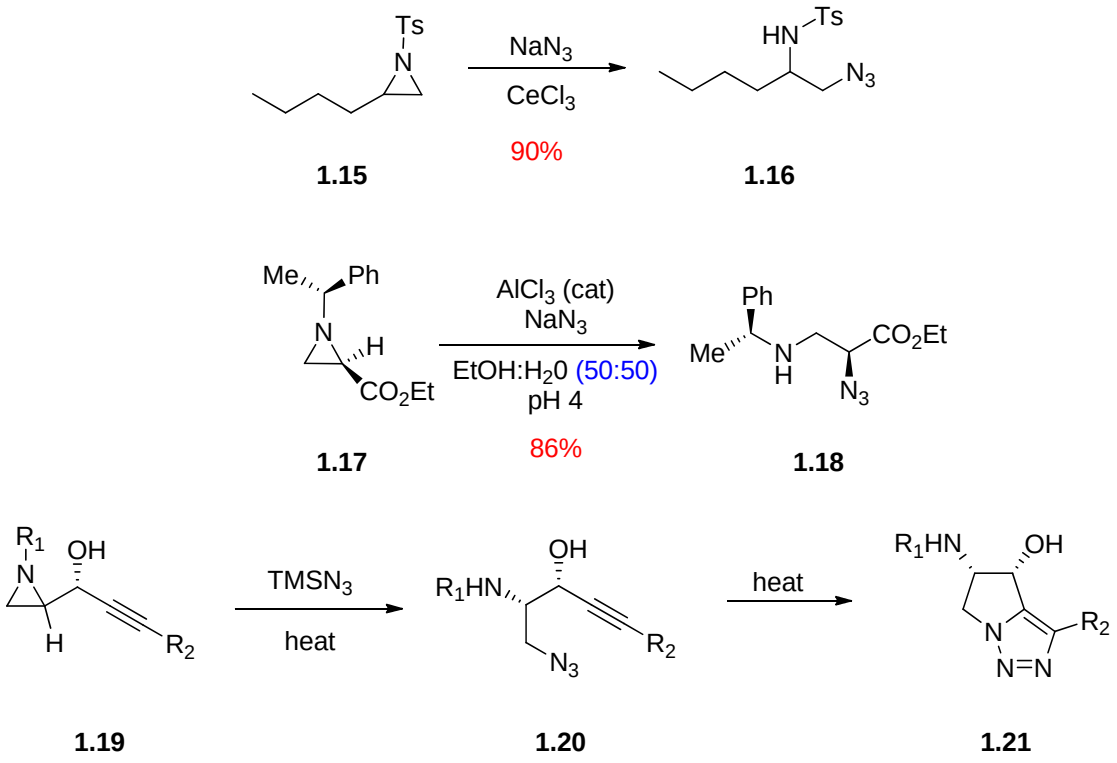
In the case of amino aziridines, the regioselectivity of the nucleophilic attack can be controlled simply by changing the reaction conditions. Using a protic acid such as *p*-toluenesulfonic acid leads to attack of water at the least hindered C-3 position. Using an aprotic Lewis acid, such as boron trifluoride etherate, leads to anchimeric assistance from the neighboring amino substituent leading to activation and attack at C-2 (Scheme 1.1.2.2).[9]



1.13 **1.12** **1.14**

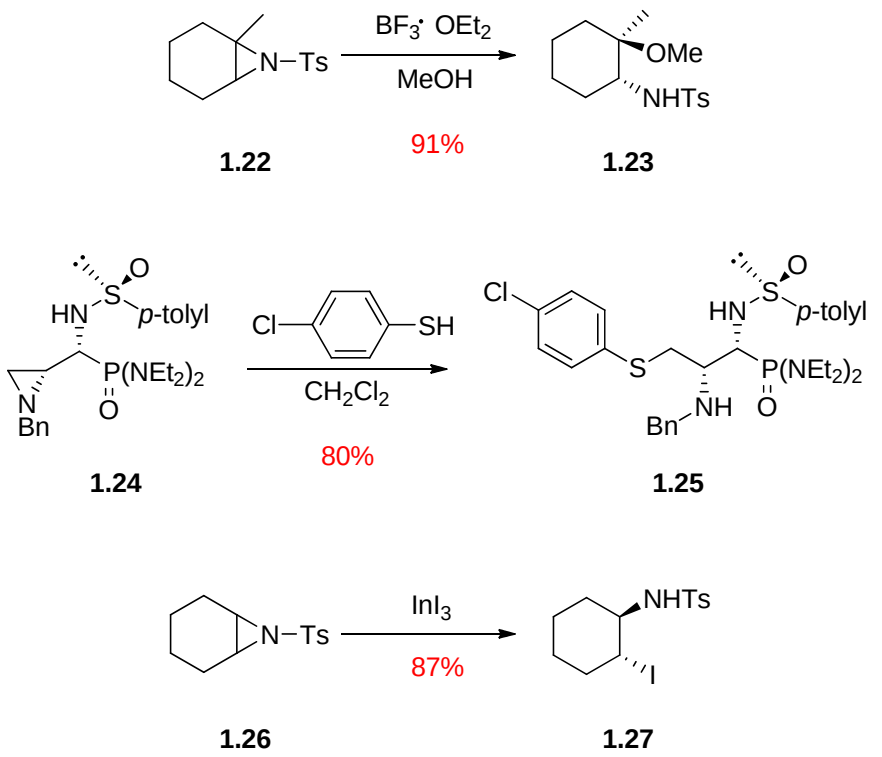
Scheme 1.1.2.2 Aziridine reactivity controlled by reaction conditions.

The azide anion is often used as a nitrogen-nucleophile in aziridine ring opening to obtain 1,2-diamines following a reduction of the azido group. For example, tosyl aziridines are readily transformed to azido amines upon treatment with NaN_3 and $CeCl_3$.[10] Unactivated aziridines can also undergo similar azide opening in the presence of Lewis acids, such as $AlCl_3$.[11] Treatment of aziridinyl-propargylic alcohols with trimethylsilyl azide ($TMSN_3$) affords amino alcohols, which upon further heating can undergo an intramolecular 1,3-cycloaddition between the azide and the alkyne (click chemistry) to form the corresponding bicyclic triazoles. (Scheme 1.1.2.3).[12]



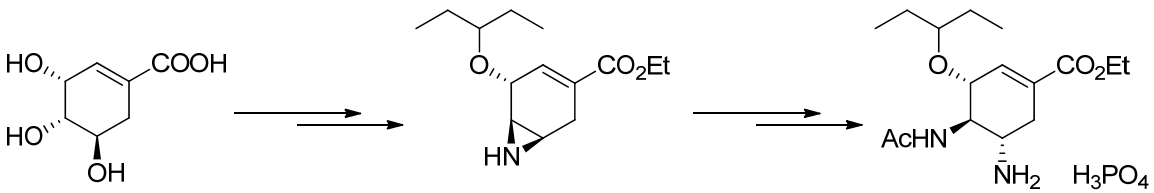
Scheme 1.1.2.3 Ring-opening reaction by azide anion.

Ring-opening reactions can also be accomplished by attack of oxygen-, sulfur-, and halogen-based nucleophiles, as shown below in Scheme 1.1.2.4. Facile ring cleavage of the asymmetrical bicyclic aziridine 1.22 with methanol in the presence of boron trifluoride etherate gives the product of attack at the more-substituted aziridine carbon.[13] Sulfur-based nucleophiles are equally suitable partners for ring-opening reactions, as shown by the reaction of *p*-chlorothiophenol with the functionalized sulfinylaziridine 1.24 to give the corresponding sulfide in 80% yield.[14] Indium trihalides are competent reagents in promoting the halide-mediated opening of aziridines, as demonstrated by the conversion of *N*-tosyl aziridine 1.26 to the iodo-amine derivative 1.27.[15]



Scheme 1.1.2.4 Ring-opening reaction by heteroatom nucleophiles.

Ring opening of aziridines and aziridinium ions has played an important role in the synthesis of pharmaceutical intermediates as well as in the total synthesis of natural products. The current commercial production method of oseltamivir (Tamiflu), developed by Gilead Sciences and later modified by Hoffmann-La Roche, makes use of an aziridine ring opening by sodium azide in the presence of H_2SO_4 (Scheme 1.1.2.5). [16]



1.28 **1.29** **1.30**

Scheme 1.1.2.5 Commercial synthesis of Tamiflu.

There have since been many improvements in the synthesis of oseltamivir including the Trost synthesis, which is the shortest synthesis to date (10 steps). All of the improved routes make use of an aziridine ring opening as one of the key steps Figure 1.1.2.1.[17-20]

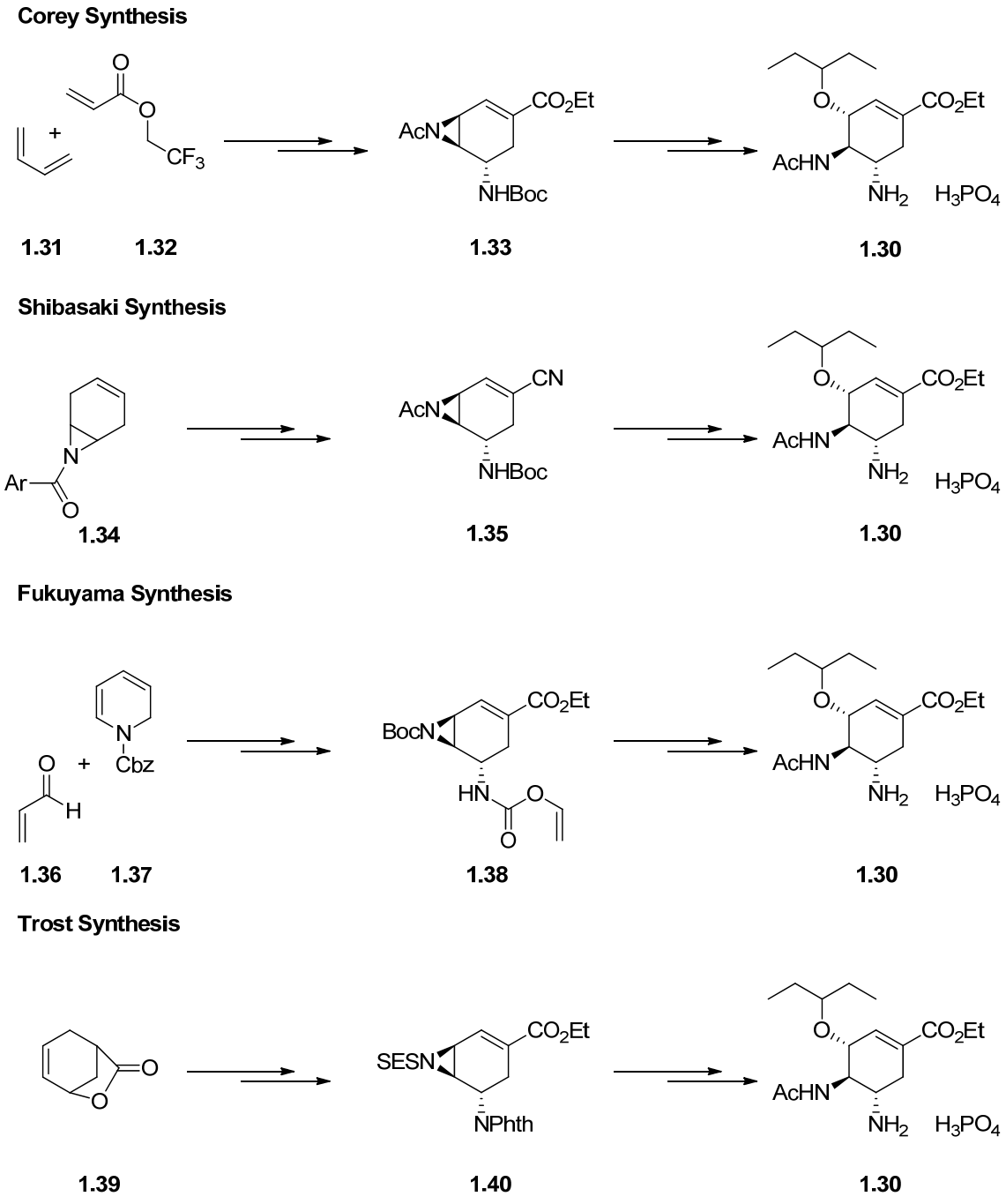
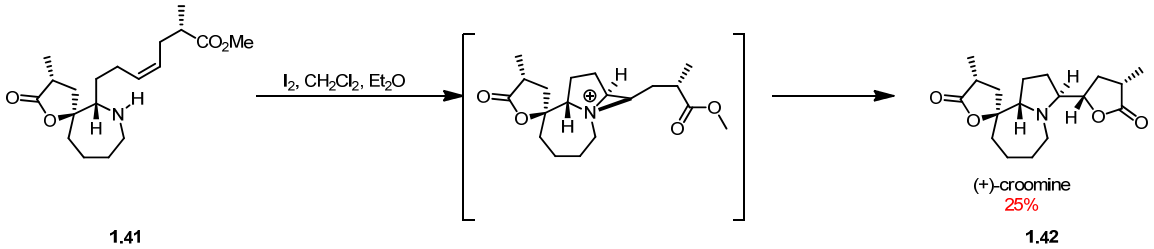


Figure 1.1.2.1 Improved syntheses of oseltamivir via aziridine ring opening.

Williams *et. al*. made use of an aziridinium ion in the total synthesis of the *Stemona* alkaloid (+)-croomine. Treatment of secondary amine 1.41 with iodide allowed

for initial formation of the iodoamination intermediate, followed by nucleophilic anchimeric assistance by the vicinal tertiary amine to provide the intermediate aziridinium salt. Capture of the salt by the proximate ester resulted in net retention of stereochemistry and afforded direct conversion to (+)-croomine (Scheme 1.1.2.6).[21]

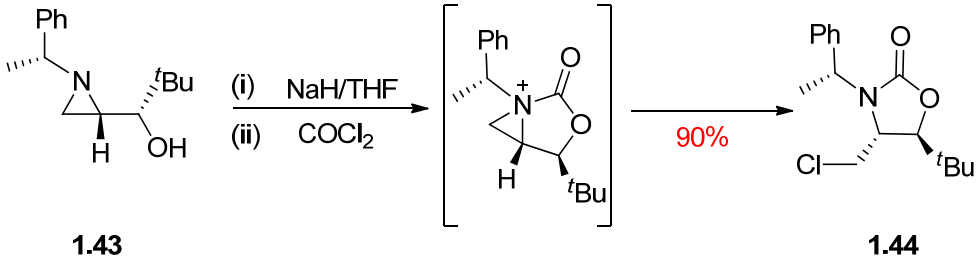


1.41 1.42

Scheme 1.1.2.6 Aziridinium ion in the total synthesis of (+)-croomine.

1.1.3 Rearrangement Chemistry of Aziridines

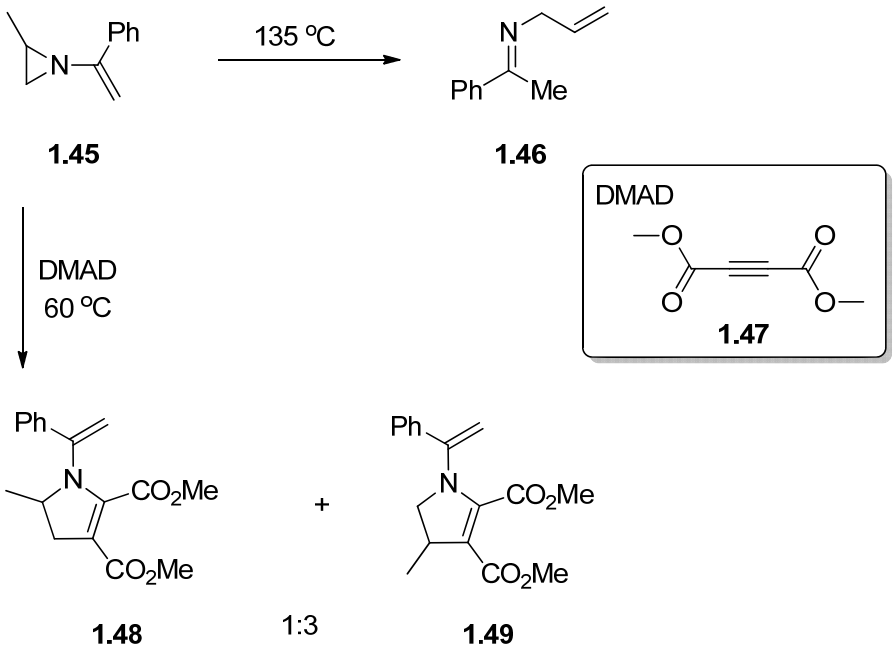
In addition to ring-opening chemistry, aziridines can also undergo a variety of rearrangements both thermally and non-thermally. Ha and co-workers disclosed the synthesis of a substituted oxazolidinone from an aziridine (Scheme 1.1.3.1). This ring expansion involves nucleophilic attack of the nitrogen center leading to formation of a short-lived bicyclic intermediate, which undergoes ring-opening via nucleophilic attack by chloride to give the oxazolidinone with retention of stereochemistry.[22]



1.43 **1.44**

Scheme 1.1.3.1 Nonthermal rearrangement of aziridines.

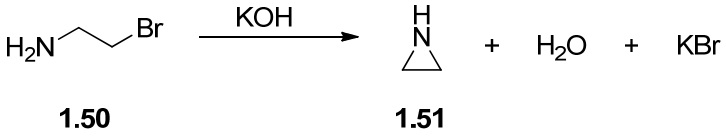
Heating an *N*-alkenyl aziridine to 135 °C affords the imine as a result of a thermal 1,5 hydrogen shift. When heating the same aziridine in the presence of dimethyl acetylenedicarboxylate (DMAD), a formal [3+2] cycloaddition occurs, giving a mixture of two regioisomers depending on which carbon center of the aziridine participates in the cyclization (Scheme 1.1.3.2).[23] Other known rearrangements of aziridines include [3+3] annulation reactions, ring expansion (with heterocumulenes, isocyanates, nitriles and carbonylative ring expansion) and radical reactions.[3]



Scheme 1.1.3.2 Thermal rearrangement of aziridines.

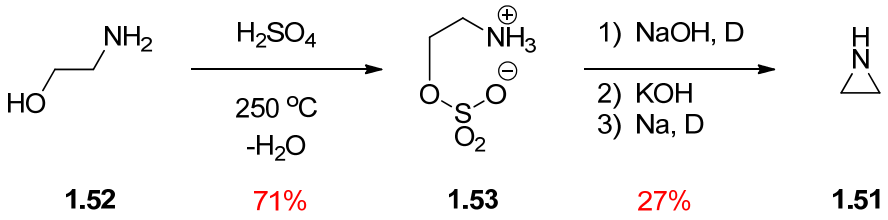
1.1.4 Synthesis of Aziridines

In 1888, the first synthesis of aziridines was reported by Gabriel. His synthesis of the parent aziridine was accomplished via nucleophilic ring closure of *vic*-haloamines (Scheme 1.1.4.1).[24]



Scheme 1.1.4.1 Gabriel synthesis of aziridines.

A similar approach was later developed by Wenker in 1935.[25] His approach involved treatment of *vic*-aminoalcohols with sulfuric acid at high temperatures to form the sulfonate salt followed by treatment with base to obtain the aziridine (Scheme 1.1.4.2).



Scheme 1.1.4.2 Wenker synthesis of aziridines.

Since the classic work of Gabriel and Wenker, the synthetic scope of aziridines has broadened tremendously and more mild conditions for aziridine formation have been developed. Using modern methods, aziridines can be made from addition to olefins (nitrene transfer to alkenes and addition/elimination sequences), addition to imines (carbene methodology, aza-Darzens approaches, and ylide-mediated strategies), and intramolecular nucleophilic substitution (Figure 1.1.4.1).[4]

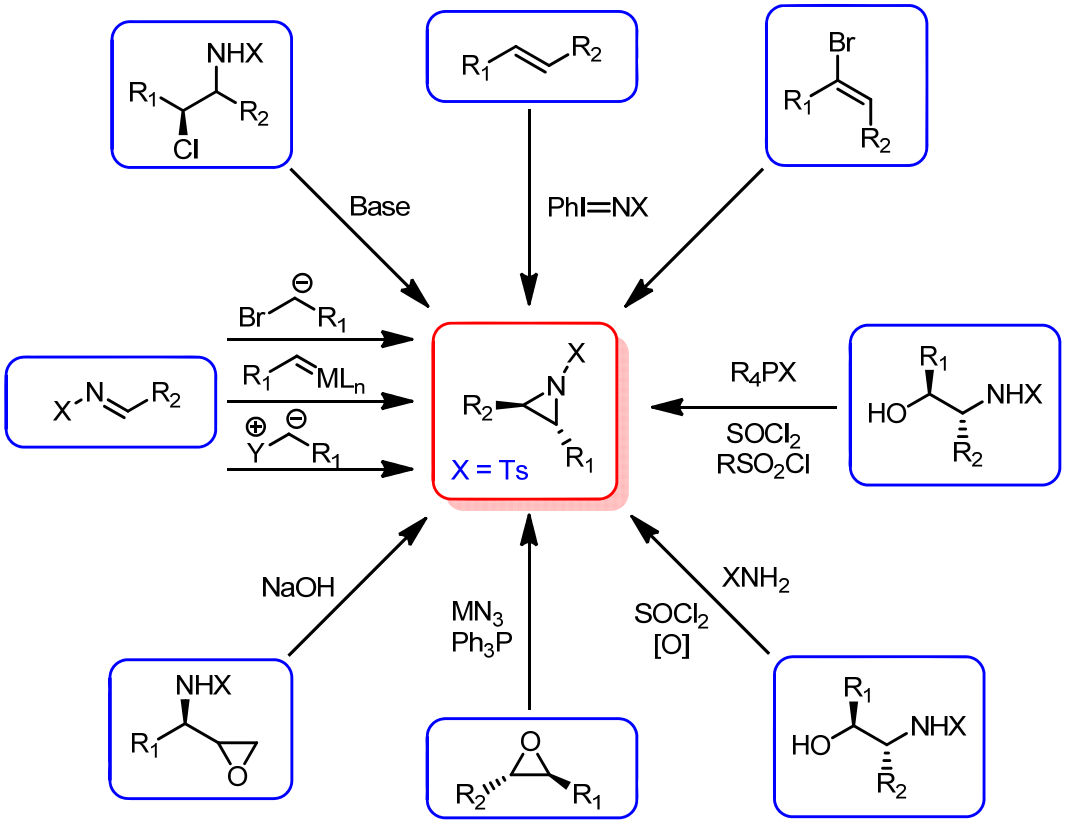
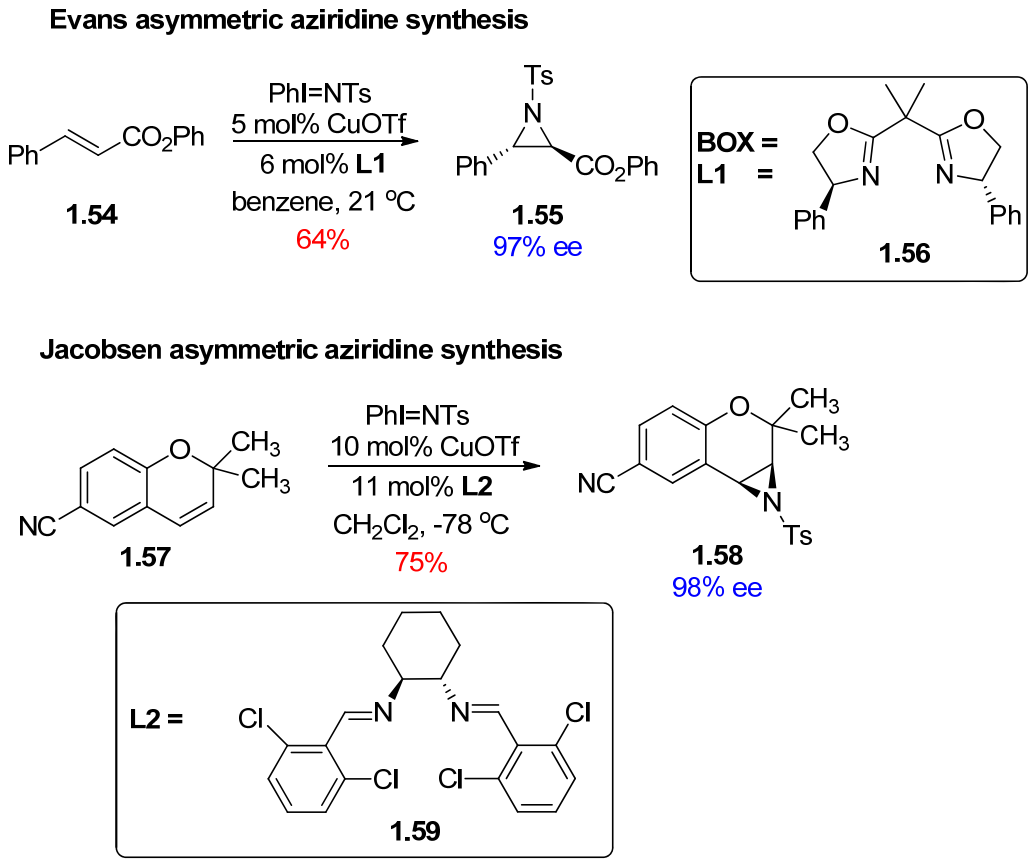


Figure 1.1.4.1 Synthetic approaches toward aziridines.

1.1.5 Aziridine Formation via Nitrene Addition to Alkenes

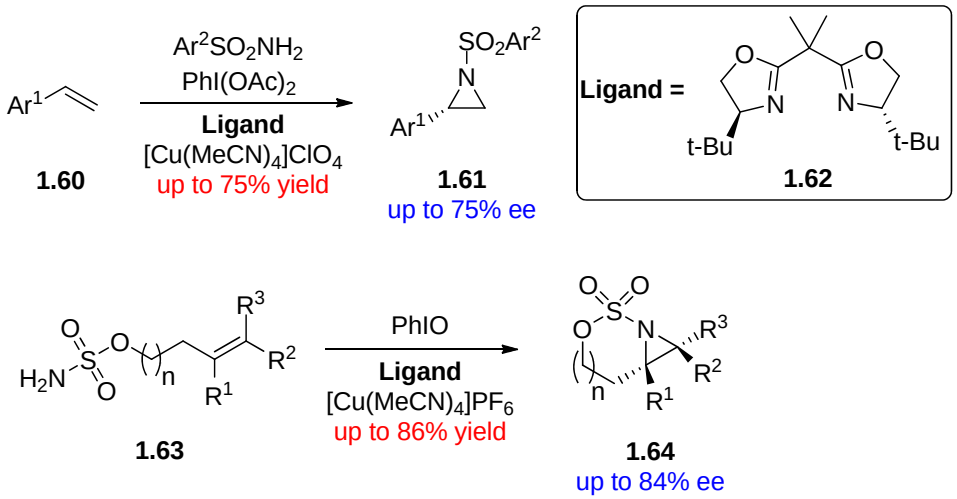
Nitrene addition to olefins is one of the most common approaches to the formation of aziridines but requires a reagent to facilitate the nitrene transfer. Several metal-based reagents (copper, manganese, rhodium) have been developed to generate the nitrene source which, in the presence of chiral ligands, provides a route for catalytic asymmetric aziridination. In 1993, Evans[26] and Jacobsen[27] were the first to report catalytic asymmetric synthesis of aziridines utilizing copper-(I)-complexes generated from chiral bisoxazoline (BOX) or diimine ligands (Scheme 1.1.5.1).



Scheme 1.1.5.1 Asymmetric aziridination via copper-catalyzed nitrene.

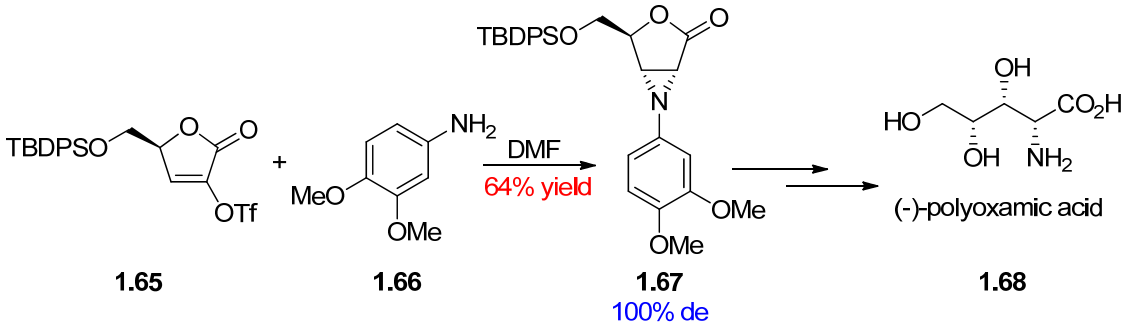
Che and co-workers reported the asymmetric synthesis of an aziridine via a copper-bisoxazoline complex and nitrene precursor generated from a hypervalent iodine reagent and sulfonamides.[28] Dauban and co-workers later reported an intramolecular copper-catalyzed aziridination using the same chiral bisoxazoline ligand. The sulfamates were subjected to iodosylbenzene and $[Cu(MeCN)_4]PF_6$ to give the corresponding aziridines in good yields and enantioselectivities (Scheme 1.1.5.2).[29]

Intramolecular aziridination of sulfamates



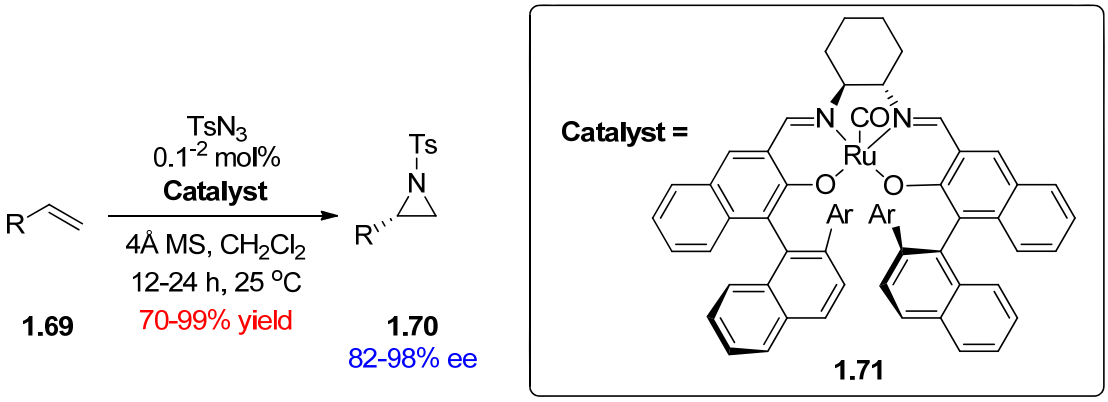
Scheme 1.1.5.2 Aziridination of alkenes mediated by bisoxazoline ligand.

Another aziridination method utilizing the approach of addition to olefins is aziridination through an addition–elimination sequence. Dodd and co-workers utilized a Michael-type addition-elimination sequence in the total synthesis of the non-natural enantiomer of polyoxamic acid (Scheme 1.1.5.3).[30]



Scheme 1.1.5.3 Synthesis of (-)-polyoxamic acid via addition-elimination sequence.

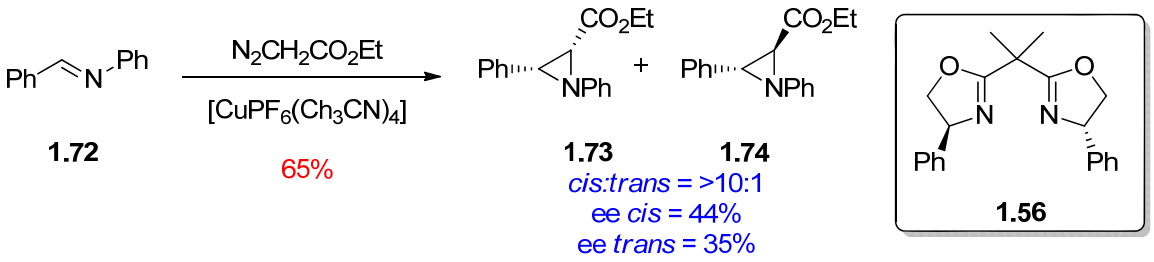
Decomposition of organic azides can also be used as a method in the aziridination of olefins. Using a ruthenium salen complex, Katsuki and coworkers reported an improvement in the scope of olefins that can be used to form aziridines. The nitrene addition occurred in moderate to excellent yield with enantiomeric excess (ee) up to 98% (Scheme 1.1.5.4).[31]



Scheme 1.1.5.4 Aziridination via organyl azides using ruthenium salen complex.

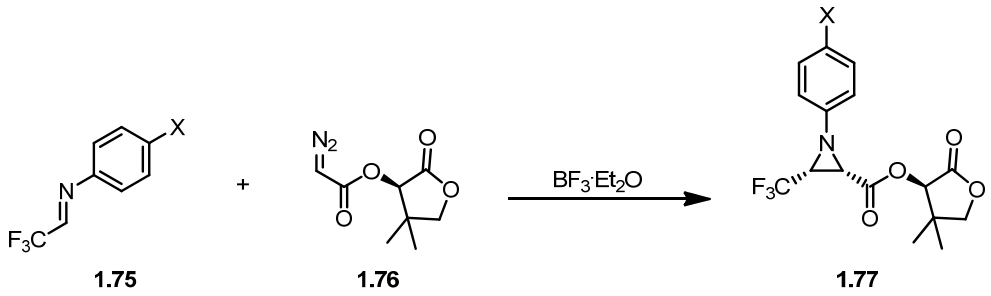
1.1.6 Aziridines via Addition to Imines

Aziridine formation from imines can be subdivided into three major areas: carbene methodology, α-haloenolates (aza-Darzens), and ylide chemistry. The addition of carbenes, generated from diazo compounds, to imines is well known and is an attractive route to aziridines due to generally good yields and high stereoselectivities. The Jacobsen group has been active in the area of asymmetric aziridine synthesis using carbenoid transfer to imines employing copper salts and the BOX ligands. This reaction proceeds through the addition of a metallocarbene derived from ethyl diazoacetate and copper(I)hexafluorophosphate adding to *N*-arylaldimines (Scheme 1.1.6.1).[32]



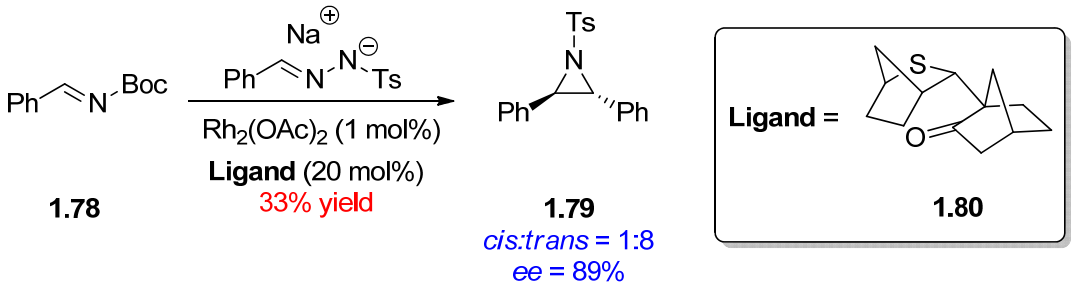
Scheme 1.1.6.1 Aziridine synthesis via carbenoid transfer to imines.

Akiyama and co-workers have developed a route towards chiral CF_3-substituted aziridines utilizing Lewis acid mediated aziridination of aldimines with chiral diazoacetates (Scheme 1.1.6.2).[33]



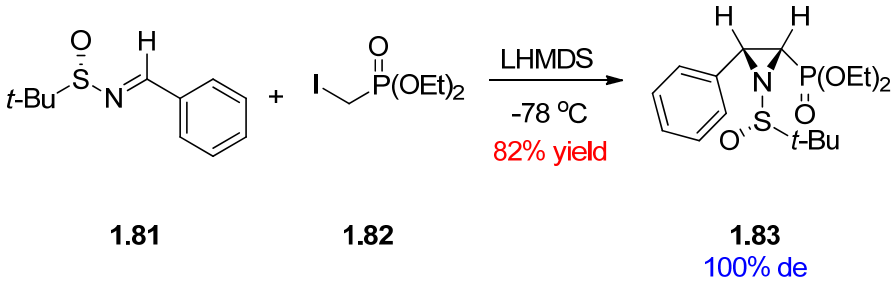
Scheme 1.1.6.2 Aziridination of aldimines with chiral diazoacetates.

A strategy which is analogous to the carbene methods is the reaction of sulfur and iodine ylides with imines to generate the desired aziridines. These ylides react with imines to give β-sulfonium or β-iodonium amide anions, which undergo nucleophilic ring closure to give aziridines. Aggarwal and co-workers have been active in this area, utilizing chiral sulfides to access *trans*-disubstituted aziridines (Scheme 1.1.6.3).[34]



Scheme 1.1.6.3 Chiral aziridines from sulfur ylides.

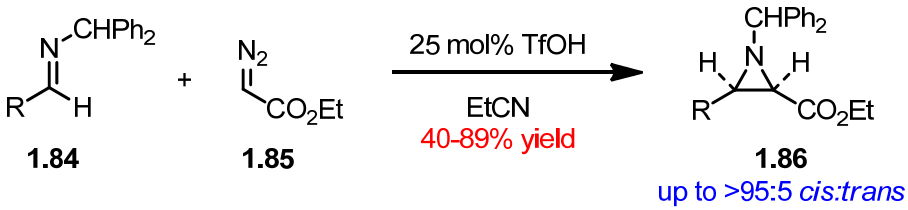
The aza-Darzens is a common, efficient approach in the synthesis of aziridines. This approach is similar to the Darzens synthesis of epoxides but uses imines rather than aldehydes or ketones. An enolate is often generated using a lithium base, with the reaction proceeding through a Zimmerman-Traxler transition state. Davis and co-workers reported the asymmetric synthesis of *cis*-*N*-sulfinylaziridine-2-phosphonate as a single diastereomer in good yield. The asymmetric aza-Darzens reaction involves the addition of an iodophosphonate anion to a chiral sulfinimine (Scheme 1.1.6.4).[35]



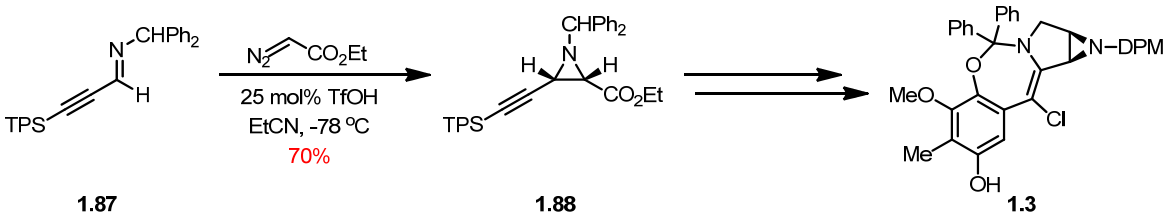
Scheme 1.1.6.4 Aza-Darzens reaction of a chiral imine.

In 2003, Johnston and co-workers reported a Brønsted acid-catalyzed direct aza-Darzens synthesis of *N*-alkyl-*cis*-aziridines.[36] This method facilitates construction of more Lewis basic and functionally diverse *N*-alkyl aziridines under mild conditions, with

no by-products forming as a result of acid-promoted aziridine ring-opening (Scheme 1.1.6.5). This method has also been applied in the stereoselective synthesis of polycyclic aziridines en route towards the total synthesis of mitomycin C (Scheme 1.1.6.6).[37]



Scheme 1.1.6.5 Brønsted-acid-catalyzed aza-Darzens synthesis of aziridines.

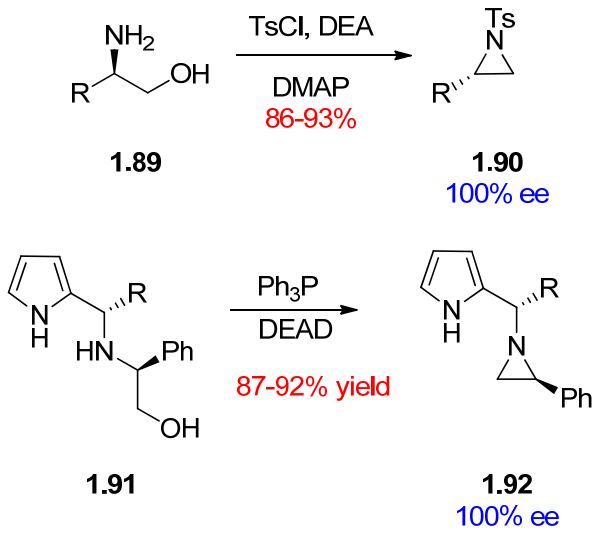


Scheme 1.1.6.6 Brønsted-acid-catalyzed aza-Darzens towards synthesis of mitomycin C.

1.1.7 Aziridination via Intramolecular Substitution

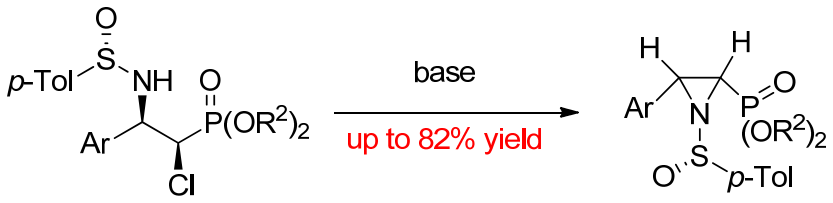
Since the first example reported by Gabriel in 1888, the nucleophilic ring closure of an amine with a vicinal leaving group has been one of the most utilized routes to aziridines. Intramolecular displacement can be achieved using 1,2-amino alcohols, 1,2-azido alcohols, 1,2-amino halides, 1,2-amino sulfides, 1,2-amino selenides, or epoxides.[1] However, in order to use this route to obtain enantiopure azirdines, non-racemic starting materials are required.

In recent years, there have been several reports describing the synthesis of simple chiral aziridines starting from 1,2-amino alcohols. For example, Badia and co-workers reported a simple procedure for the preparation of chiral *N*-tosyl-2-alkyl aziridines in a single step involving a sequential one-pot *N*-tosylation and *O*-tosylation followed by an intramolecular substitution to afford chiral aziridines.[38] Similarly, the synthesis of enantiopure pyrrole-aziridines was reported by Savoia and co-workers. The treatment of enantiopure β-hydroxyamines derived from (*S*)-phenylglycinol bearing a pyrrole moiety with triphenylphosphine and diethylazodicarboxylate (DEAD) proceeds through an intramolecular Mitsonobu reaction, leading to enantiopure pyrrole-aziridines in excellent yields (Scheme 1.1.7.1).[39]



Scheme 1.1.7.1 Synthesis of aziridines from 1,2-amino alcohols.

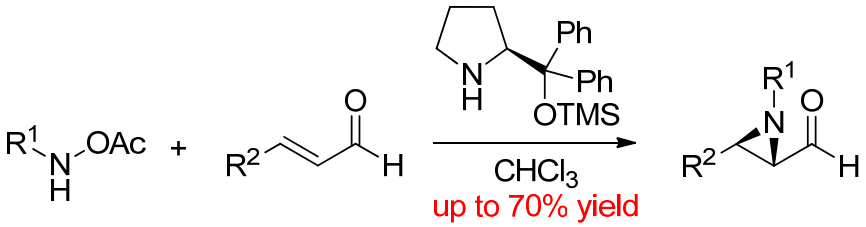
Davis and co-workers have reported the synthesis of *N*-sulfinylaziridine-2-phosphonates, in high yields and enantioselectivities, via a base induced cyclization of β-amino-α-chlorophosphonates (Scheme 1.1.7.2).[40]



1.93 **1.94**
100% ee

Scheme 1.1.7.2 Synthesis of *N*-sulfinylaziridine-2-phosphonates.

In 2007, Cordova and co-workers reported an organocatalytic aziridination of α,β-unsaturated aldehydes with acylated hydroxycarbamates. Utilizing a chiral silyl-protected pyrrolidine alcohol, 2-formylaziridines were achieved in moderate yields with moderate to high diastereoselectivities and enantioselectivities (Scheme 1.1.7.3).[41]

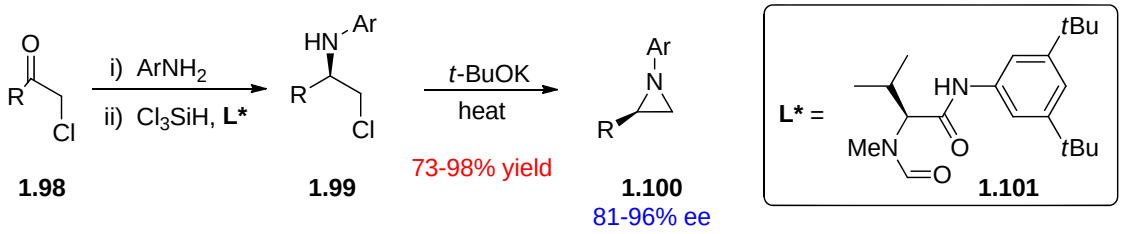


1.95 **1.96** **1.97**
up to 82% dr
up to 99% ee

Scheme 1.1.7.3 Organocatalytic aziridination of α,β-unsaturated aldehydes.

Many of the classical methods for aziridine synthesis incorporate a *p*-toluenesulfonyl moiety or some other electron withdrawing group as the *N*-substituent. Despite the usefulness and prevalence of aziridines, synthetic routes to the non-activated

class are limited in terms of generality and diversity of the *N*-substituent. The synthesis of enantiopure, unactivated, terminal aziridines with diversity at the *N*-substituent is extremely rare.[1] One recent example was reported by Kocovsky and co-workers for the synthesis of terminal diarylaziridines by organocatalytic enantioselective reductive amination of α-chloroketones followed by base-induced intramolecular cyclization of the corresponding α-chloroamines (Scheme 1.1.7.4).[20] However, this method lacks generality and substrate scope as only *N*-arylaziridines can be formed.



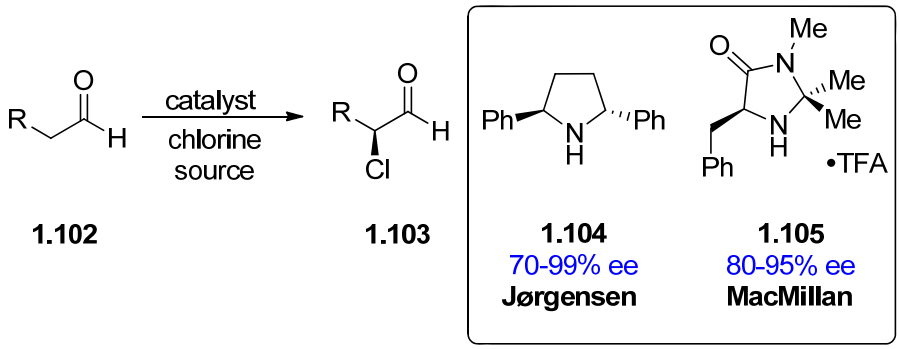
1.98 **1.99** **1.100** 81-96% ee **1.101**

Scheme 1.1.7.4 Synthesis of 1,2-diaryl aziridines.

Since there are few synthetic methods in the literature for the preparation of enantiopure *N*-alkylziridines, and due to their utility as synthetic intermediates,[43] we set out to develop a methodology that would allow for the rapid enantioselective synthesis of *N*-alkyl terminal aziridines.

1.1.8 General Access to *N*-Alkyl Terminal Aziridines

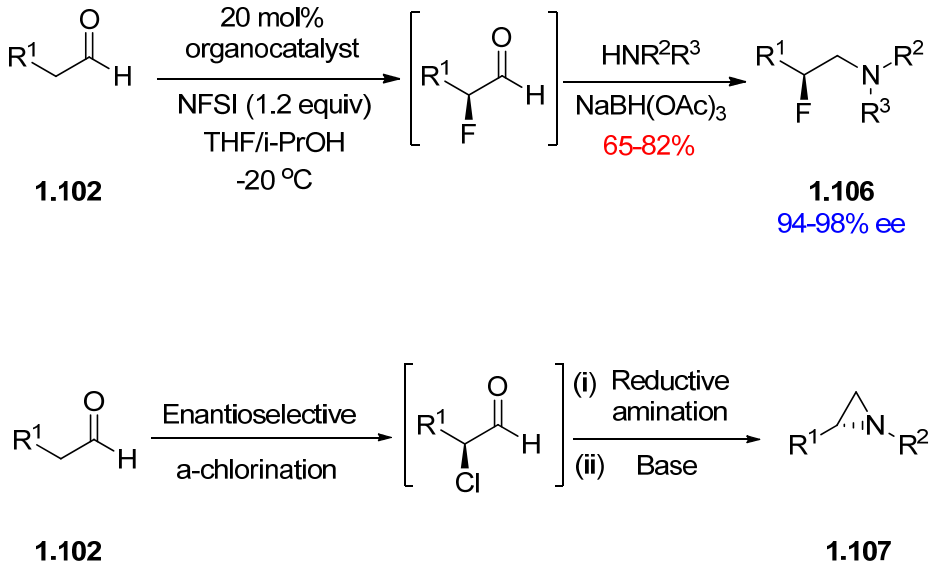
Previously, Jørgensen[44] and MacMillan[45] reported the use of various pyrrolidine-based catalysts for the direct α-chlorination of aldehydes with excellent asymmetric induction (Scheme 1.1.8.1).



1.102 **1.103** **1.104** 70-99% ee **Jørgensen** **1.105** 80-95% ee **MacMillan**

Scheme 1.1.8.1 Organocatalytic enantioselective α-chlorination of aldehydes.

Based on this work and previous work in our lab towards the asymmetric synthesis of enantiopure β-fluoroamines by way of selective fluorination using a proline-based catalyst followed by reductive amination,[46] we reasoned that an analogous α-chlorination/reductive amination sequence to give enantioenriched β-chloroamines would represent an attractive approach to chiral *N*-alkyl aziridines (Scheme 1.1.8.2).

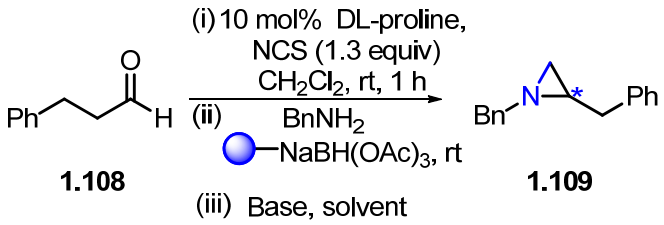


Scheme 1.1.8.2 Organocatalytic approach to chiral β-fluoroamines and envisioned route to chiral *N*-alkyl terminal aziridines.

For a one-pot protocol involving a reductive amination step, we could not use the MacMillan α-chlorination chemistry, as that route employs a chloroquinone as the chlorinating agent and acetone as the solvent. The Jørgensen route was an attractive starting point, as *N*-chlorosuccinimide (NCS) is the chlorinating agent and the optimized solvent is 1,2-dichloroethane (DCE). We first set out to determine if this proposal would allow access to a broad range of racemic *N*-alkyl terminal aziridines. DL-proline-catalyzed chlorination of aldehydes with NCS, followed by reductive amination with primary amines and subsequent base-induced neighboring group displacement with KOH in THF/H_2O at 65 °C proved to be the ideal conditions to provide racemic aziridines in up to 70% yield for the three step, one-pot protocol (average of 90% per step). Importantly, KOH was the only base screened that provided 100% conversion to the aziridine. A screen of other organic (ie. Et_3N, pyridine, DBU, KO*t*-Bu) and inorganic

(ie.,NaH, K2CO3) bases provided less than 50% conversion to the desired aziridine, and in many cases resulted in elimination of the chloride (Table 1.1.8.1).

Table 1.1.8.1 Screening of bases for aziridine ring closure.

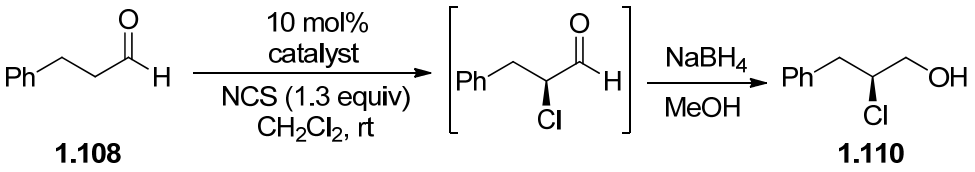


entry	Base	Solvent	time	temp (°C)	conv (%)
1	Et_3N	CH_2Cl_2	2 days	25	<30
2	Pyridine	CH_2Cl_2	2 days	25	<30
3	DBU	CH_2Cl_2	24 h	25	>40
4	NaH	THF	16 h	25	mixture
5	*t*-BuOK	THF	16 h	25	>60
6	K_2CO_3	THF/DMF/Acetone	24 h	85	<50
7	KOH	THF:H_2O (1:1)	24 h	65	100
8	Et_3N	CH_2Cl_2	24 h	45	<60
9	Pyridine	CH_2Cl_2	24 h	45	<50
10	DBU	CH_2Cl_2	24 h	45	<60

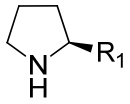
Our efforts then focused on developing an enantioselective one-pot protocol. To ensure we had optimal conditions for the enantioselective chlorination of aldehydes, we elected to survey a set of organocatalysts employing NCS as the chlorinating agent (Table 1.1.8.2). This study demonstrated that the Jørgensen catalyst (diphenylpyrrolidine) was optimal (>97% conversion and 95% ee). In order to determine the degree of enantioselectivity by chiral HPLC, the aldehydes were reduced to the corresponding β-chloroalcohols. Organocatalysts 1.120, 1.121, 1.22, and 1.123 had never before been employed for this transformation and provided moderate

enantioselectivities and comparable conversions (>95%), but lower enantioselectivity (56-90% ee).

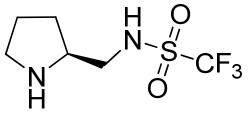
Table 1.1.8.2 Screening of organocatalysts for α-chlorination.



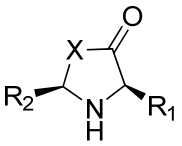
1.108 **1.110**



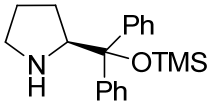
1.111: R_1 = CH_2-pyrrolidine = ND
1.112: R_1 = $CONH_2$ = 77% ee
1.113: R_1 = COOH = 16% ee
1.114: R_1 = CH_2OH = 53% ee
1.115: R_1 = CONH-Naphthyl = ND



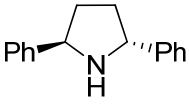
1.123
90% ee



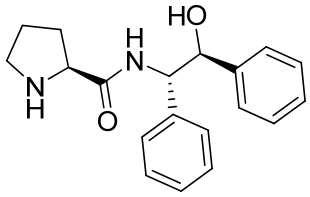
1.105: R_1 = Bn, R_2 =$(CH_3)_2$, X = NCH_3 = 18% ee
1.116: R_1 = H, R_2 = *t*-butyl, X = NCH_3 = <10% ee
1.117: R_1 = Bn, R_2 = *t*-butyl, X = NCH_3 = ND
1.118: R_1 = Bn, R_2 = 2-methylfuran, X = NCH_3 = ND
1.119: R_1 = H, R_2 = *t*-butyl, X = CH_2 = ND



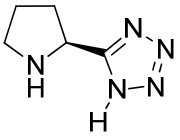
1.120
82% ee



1.104
95% ee



1.121
56% ee



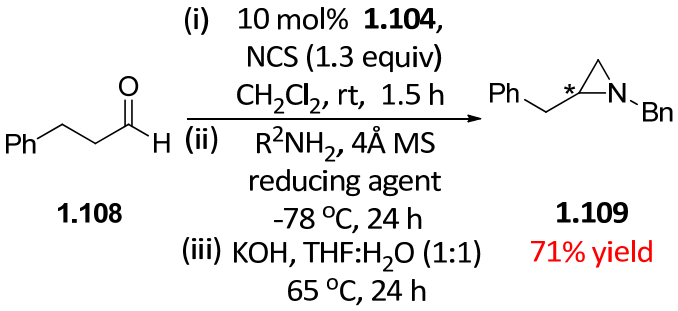
1.122
75% ee

As summarized in Table 1.1.8.2, Jorgensen's diphenylpyrrolidine organocatalyst and the tetrazole catalyst gave excellent conversion. Surprisingly, only 5 mol% of the tetrazole catalyst was needed to provide the desired β-chloroalcohol in excellent yield and moderate enantioselectivity. It should be mentioned that multiple solvents were also

screened, but only dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) gave acceptable yields.

With optimal chlorination conditions in hand, we attempted the three-step, one-pot protocol to deliver the aziridine enantioselectively. Utilizing the protocol shown in Table 1.1.8.1, but replacing DL-proline with the 2,5-diphenylpyrrolidine catalyst, we were disappointed to find that this approach afforded the aziridine in comparable yield, but in less than 40% ee. We investigated the most probable source of epimerization in the sequence: the room-temperature reductive amination step. Molecular sieves proved essential, and we found a direct correlation between enantioselectivity and temperature. As shown in Table 1.1.8.3, reducing the temperature for the reductive amination step to -78 °C resulted in the enantioselective synthesis of the aziridine in 71% yield for the three steps (~90% per step) and 94% ee.

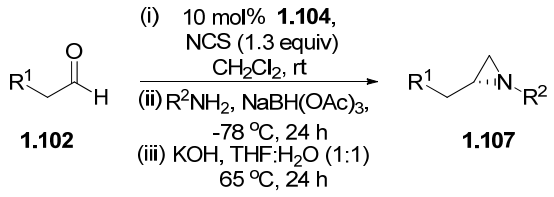
Table 1.1.8.3 Optimization of reductive amination step.

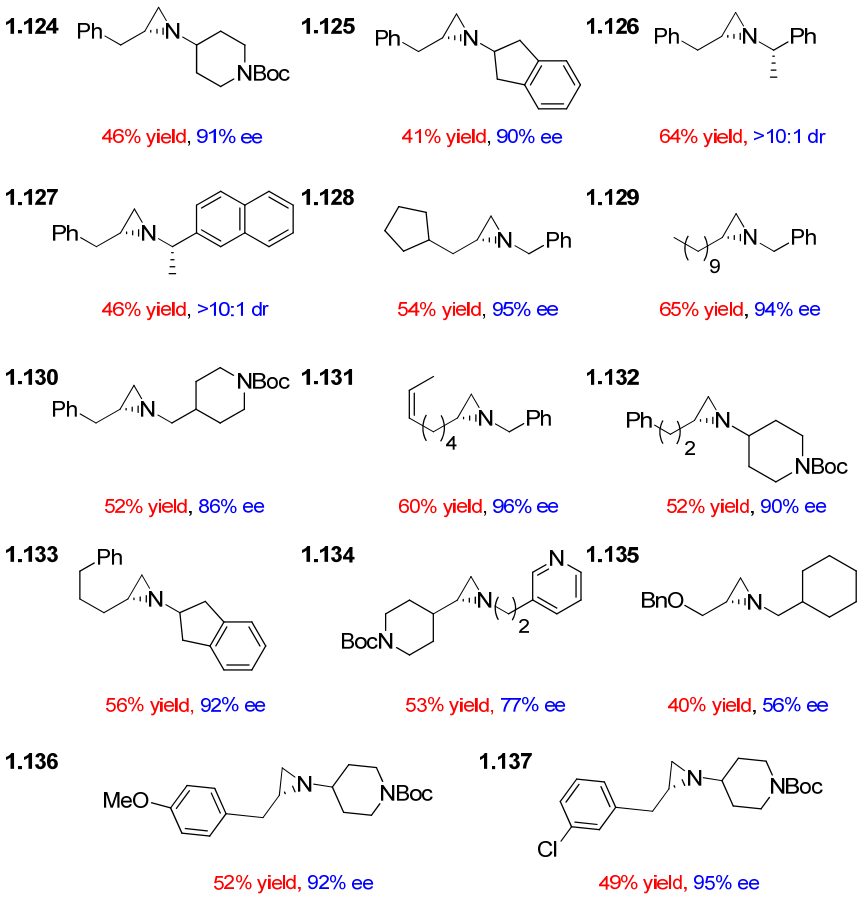


entry	Reducing agent	temp (°C)	ee (%)
1[c]	PS-NaBH(OAc)$_3$	25	45
2	NaBH(OAc)$_3$	25	68
3	NaBH(OAc)$_3$	-10	70
4	NaBH(OAc)$_3$	-20	85
5	NaBH(OAc)$_3$	-30	85
6	PS-NaBH(OAc)$_3$	-78	60
7	NaBH(OAc)$_3$	-78	94

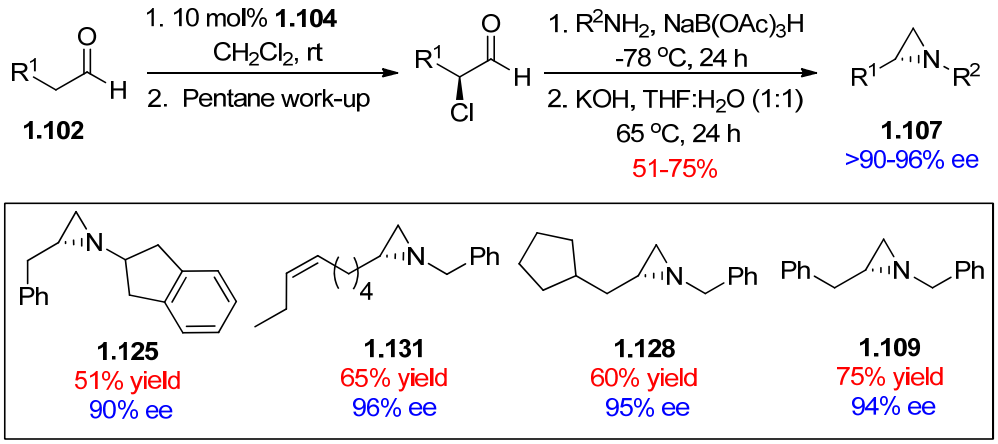
In order to determine the scope of this methodology, we prepared several *N*-alkyl terminal aziridines from different readily available aldehydes and primary amines. As shown in Table 1.1.8.4, the reaction is very general and provides chiral aziridines in overall yields of 40-65% (74-87% per step) and, in most cases, >90% ee for the three-step, one-pot protocol.

Table 1.1.8.4 Scope of one-pot aziridine formation.





Finally, modest improvements in yield and comparable enantioselectivty were observed if a workup was performed after the chlorination step. The addition of pentane to the crude reaction mixture precipitated both the succinimide and organocatalyst. Removal of the pentane, resupsension in CH_2Cl_2, and proceeding with the reductive amination and base-induced cyclization steps provided *N*-alkyl terminal aziridines in 51-75% yield and >90% ee for the two-pot protocol (Scheme 1.1.8.3).



Scheme 1.1.8.3 Two-pot procedure to chiral aziridines.

In summary, we have developed a three-step, one-pot protocol for the general enantioselective synthesis of terminal N-alkyl aziridines via organocatalysis.[47] Previous approaches to these useful moieties required long multi-step syntheses, had a lack of generality and substrate scope, and required starting materials that were not readily available. This study has led to the development of a powerful extension of the organocatalyzed enantioselective synthesis of α-chloroaldehydes for the general enantioselective synthesis of *N*-alkyl terminal aziridines in very high yields and ee. This

new methodology provides access to aziridines utilizing aldehydes and primary amines, thousands of which are commercially available.

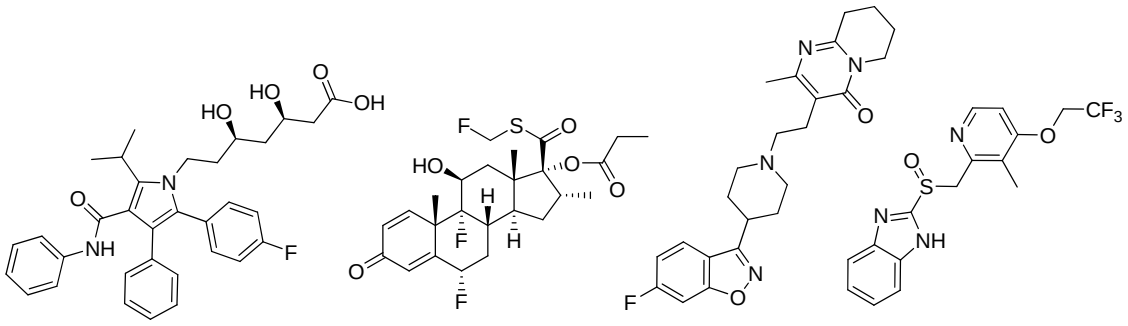
1.2: Highly Diastereoselective and General Synthesis of Primary β-Fluoroamines

1.2.1 Fluorine in Pharmaceuticals

Increasingly in recent years, researchers have utilized the unique and desirable characteristics of the fluorine atom in the creation of new drugs that have impacted the quality of life for many individuals. No other substituent has single-handedly captured the imagination of medicinal chemists to the extent that fluorine has. With its small atomic radius and ability to be both electron-withdrawing and lipophilic while maintaining the ability to accept hydrogen bonds and block metabolic liabilities, fluorine has become an essential tool in the medicinal chemist's arsenal.[48-50]

Until 1957, no fluorine-containing drug had been developed. This relatively recent trend of fluorinating compounds began its expansion in the 1970's. It is now estimated that as many as 30-40% of agrochemicals and 20% of pharmaceuticals on the market contain fluorine, including 9 of the 31 newly-licensed drugs in 2002 and half of the top 10 drugs sold in 2005. It is estimated that roughly 25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom.[48-50] Shown in Figure 1.2.1.1 are a few examples of fluorinated drugs on the market, including the current top-selling drug, Pfizer's cholesterol lowering medicine atorvastatin (*Lipitor*);[51] the inhaled corticosteroid fluticasone (*Advair*, *Flonase*, GSK); the atypical antipsychotic risperidone

(*Risperdal*, Janssen-Cilag); and the proton-pump inhibitor lansoprazole (*Prevacid*, Novartis).



1.138
Atorvastatin
(Cholesterol lowering)

1.139
Fluticasone
(Corticosteroid)

1.140
Risperidone
(Antipsychotic)

1.141
Lansoprazole
(PPI)

Figure 1.2.1.1 Examples of pharmaceuticals containing fluorine.

1.2.2 Effects of the Fluorine Substituent

The reasoning behind a fluorine substitution in a molecule is based on the unique characteristics of the fluorine atom, especially its small size and high electronegativity. The small size of the fluorine atom is a distinctive characteristic; with a van der Waals radius similar to that of hydrogen and oxygen (Table 1.2.2.1), a fluorine atom is a reasonable substitution for a hydrogen atom or hydroxyl group in a bioactive compound with respect to steric requirements at receptor binding sites.[50]

Fluorine is also the most electronegative element on the periodic table. As a consequence of this electronegativity, fluorine makes a very strong bond with carbon (Table 1.2.1), and it is often introduced into a target compound in order to improve the metabolic stability by blocking sites that are prone to metabolism such as oxidation by cytochrome P450s (CYP450s). As a result of these unique electronic properties, fluorine may modulate the physicochemical properties of a molecule such as acidity and basicity,

lipophilicity, hydrogen bonding ability, and even the overall conformation of the molecule.[48,52]

Table 1.2.2.1 Physiochemical properties of the carbon-fluorine bond.

Element	Electronegativity	Bond Length (CH2X, Å)	Van der Waals radius (Å)	Bond energy (kcal/mol)
H	2.1	1.09	1.20	99
F	4.0	1.34	1.35	116
C	2.6	1.54	1.70	84
O	3.5	1.43	1.40	85
Cl	3.0	1.77	1.80	81
Br	2.8	1.94	1.85	68
I	2.5	2.14	1.98	57

1.2.3 Metabolic Stability of Fluorinated Compounds

In order for an orally administered drug to be effective, it must be able to withstand the physiological pH in the stomach long enough to enter the blood stream and be transported in sufficient quantity to the site of action. It must then perform its desired task efficiently and be metabolized at an appropriate rate into non-toxic materials. Metabolic stability is one of the most crucial factors in determining the bioavailability of a drug molecule. Low metabolic stability due to CYP450-mediated oxidation processes is a common problem in drug discovery. The incorporation of fluorine has been widely used to alter the pharmacokinetic properties of compounds and block metabolically labile sites. Metabolism can be affected by addition of fluorine either directly at or adjacent to the metabolic site. In the lead optimization studies of the cholesterol inhibitor ezetimibe

(Schering-Plough), the first generation of the drug produced a complex metabolic mixture in the bile of rats, which proved to be more potent than the drug itself. The primary metabolism pathways were found to be dealkylation of the *N*-1 and C-4 methoxyphenyl groups, *para* hydroxylation of the C-3 side chain phenyl group, and benzylic oxidation. The benzylic (*S*)-hydroxy group and C-4 hydroxy groups proved to be beneficial and led to an increase in potency. The non-productive metabolism was blocked by incorporation of fluorine at the remaining metabolically labile sites. The result was a second-generation drug which was found to be 400 times more potent and required lower, less frequent dosing due to the improved metabolic stability *in vivo* (Figure 1.2.3.1).[53]

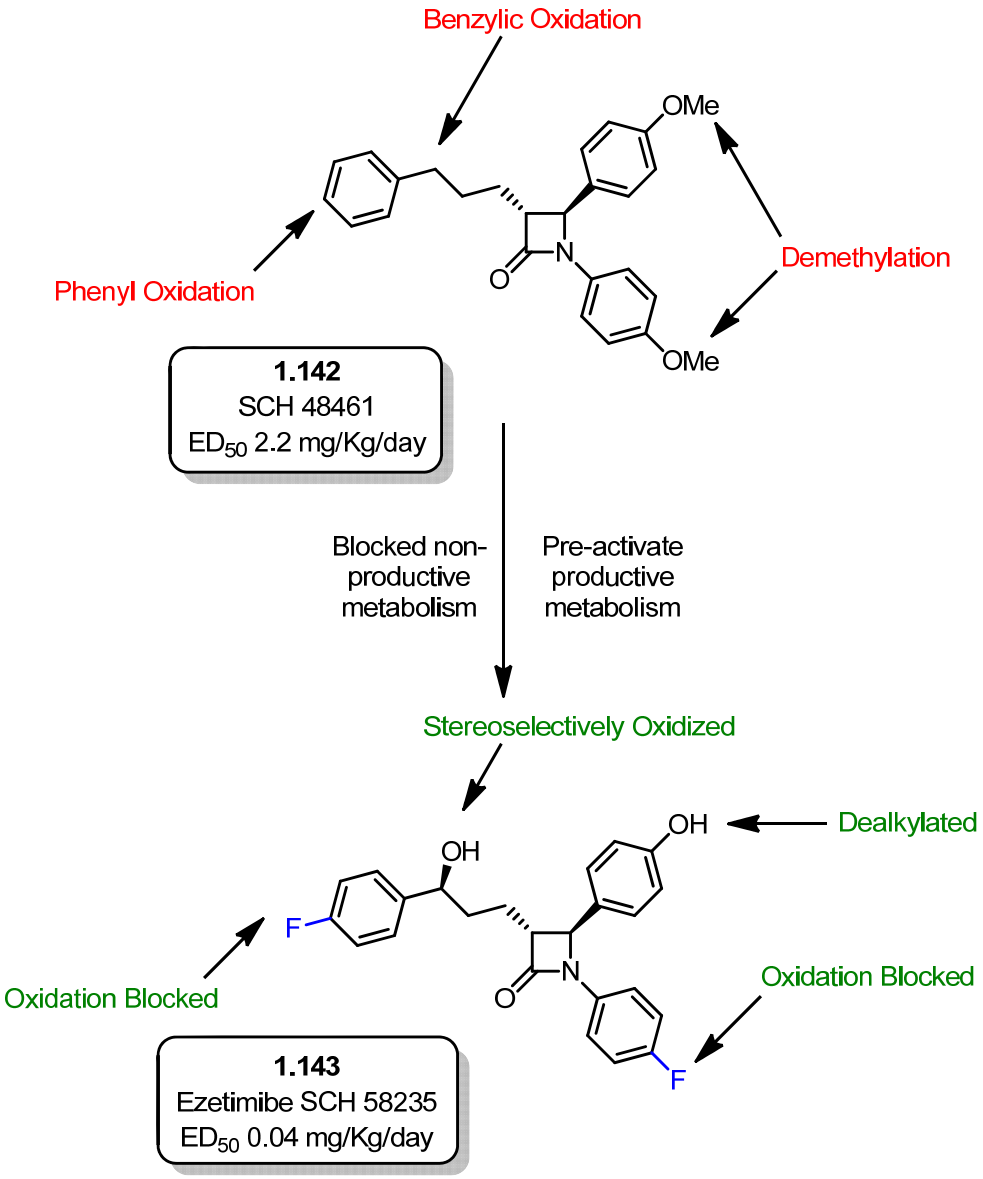


Figure 1.2.3.1 Effect of fluorine on drug metabolism.

1.2.4 Acidity and Basicity Effects from Fluorine

As an incredibly electronegative substituent, fluorine has strong effects on the acidity (and basicity) of neighboring functional groups.[48-50] For instance, the inductive effects of a single β-fluorine atom are pronounced, lowering the pKa of a linear aliphatic amine (non-fluorinated pKa ~10.7) to pKa ~9.0. These effects are additive, with a β,β-

difluoro substitution lowering the pKa to ~7.3 and a β-CF_3 moiety lowering the pKa to ~5.7 (Figure 1.2.4.1).[48-50] These changes can also have important consequences pharmacokinetic properties of a drug; quite often, a change in the pKa has a strong effect on the distribution and absorption of a drug in the body.

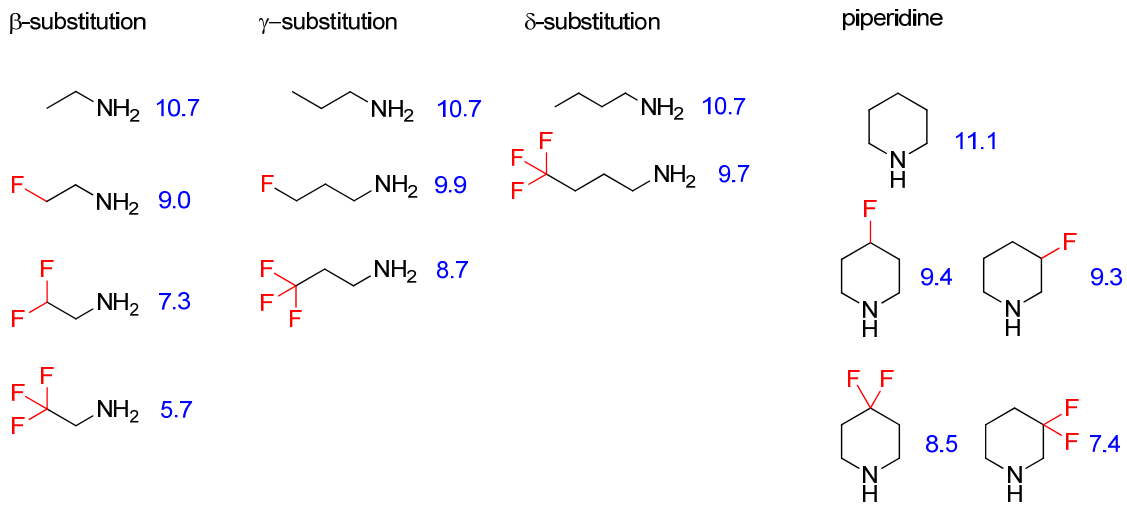


Figure 1.2.4.1 The effect of fluorine substitution on p*K*a.

For example, incorporation of fluorine into a series of 3-piperdinylindole compounds synthesized for migraine treatment (5-HT_{1D} antagonists) led to significantly improved pharmacokinetic profiles of the compounds by lowering the pKa of the piperidine nitrogen (Figure 1.2.4.2).[54]

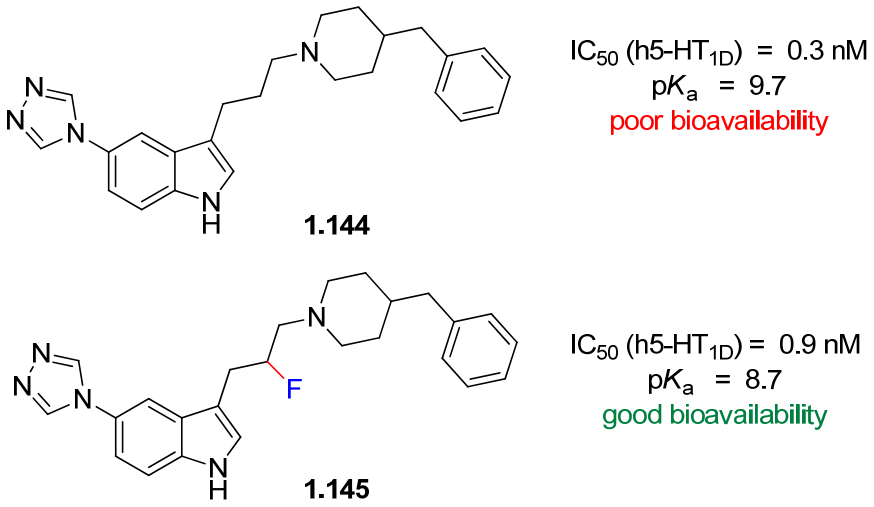
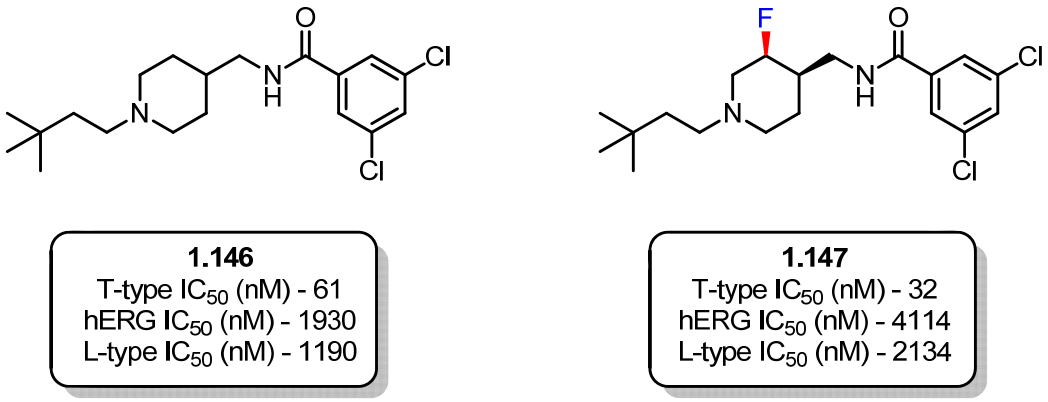


Figure 1.2.4.2 Effects of pKa values on the bioavailability and receptor binding.

1.2.5 Mitigation of Off-Target Effects

In addition to improving the pharmacokinetic profiles of compounds, the incorporation of fluorine into a drug can also diminish off-target activity. The human ether a-go-go–related gene (hERG) codes for a protein that contributes to the electrical activity of the heart and helps to coordinate the heart's beating. Activity at the hERG ion channel is a major cause of toxicity in many drug molecules. Several drug candidates have failed in clinical trials due to activity at the hERG ion channel. It is estimated that about 25-40% of all lead compounds will show some hERG activity. Drug activity at hERG results in prolonged electrocardiographic QT intervals, which can give rise to long QT syndrome. These episodes may lead to palpitations, fainting, and sudden death due to ventricular fibrillation.[55] Due to toxicity from drug-hERG interactions, the Food and Drug Administration (FDA) and the European Medicines Agency now require a thorough screening of new drugs to check for any hERG activity.[56]

Evidence has linked T-type Ca^{2+} channels to several CNS disorders, including epilepsy. Piperidine 1.146 was identified as a potent T-type calcium channel inhibitor with good selectivity against hERG and L-type channels. By reducing the basicity of the piperidine nitrogen through the addition of an electron-withdrawing β-fluorine at the 3-position of the piperidine ring, a threefold reduction in hERG activity was observed in addition to a twofold increase in potency (Figure 1.2.5.1).[57]



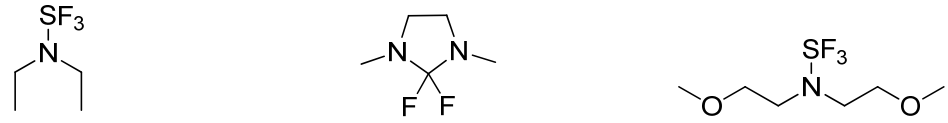
1.146
T-type IC_{50} (nM) - 61
hERG IC_{50} (nM) - 1930
L-type IC_{50} (nM) - 1190

1.147
T-type IC_{50} (nM) - 32
hERG IC_{50} (nM) - 4114
L-type IC_{50} (nM) - 2134

Figure 1.2.5.1 Modulation of hERG activity following fluorine substitution.

1.2.6 Sources of Fluorine

Organofluorine compounds are generally formed using prepared or commercially available nucleophilic, electrophilic, and radical fluorine reagents. Some common examples of nucleophilic fluorine reagents include DAST, DFI, and Deoxofluor (Figure 1.2.6.1).



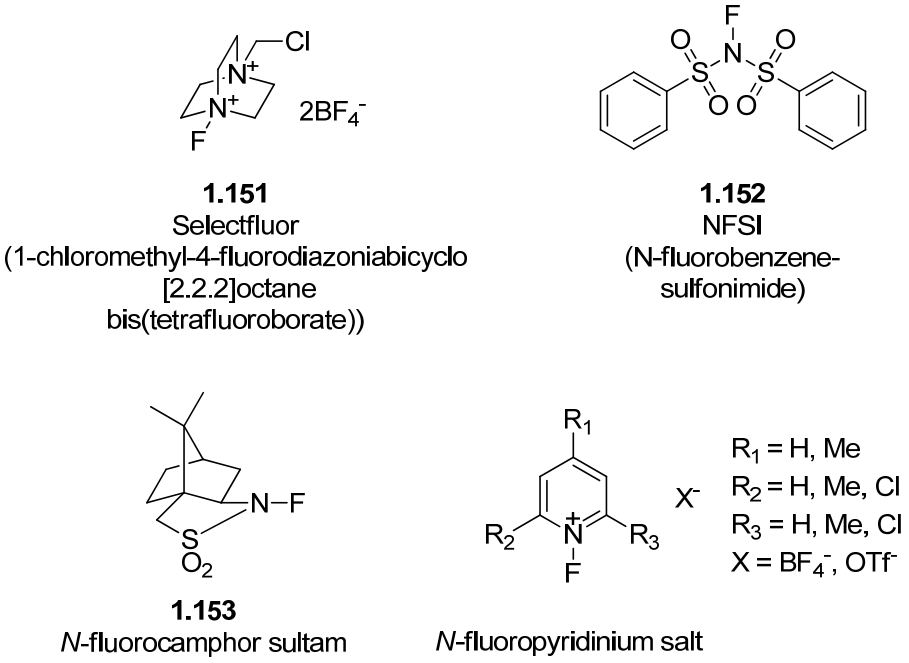
1.148
DAST
((diethylamido)sulfur trifluoride)

1.149
DFI
(2,2-difluoro-1,3-dimethyl imidazolidine)

1.150
Deoxofluor
(bis(2-methoxyethyl) aminosulfur trifluoride

Figure 1.2.6.1 Common nucleophilic fluorine reagents.

Common examples of electrophilic fluorine reagents include Selectfluor, NFSI, *N*-fluorocamphor sultam, and *N*-fluoropyridinium salt (Figure 1.2.6.2). Many methods for the synthesis of enantioenriched organofluoro compounds have been reported. Enantioselective fluorination is usually accomplished through substrate-controlled, reagent-controlled, or asymmetric catalytic conditions.



1.151
Selectfluor
(1-chloromethyl-4-fluorodiazoniabicyclo [2.2.2]octane bis(tetrafluoroborate))

1.152
NFSI
(N-fluorobenzene-sulfonimide)

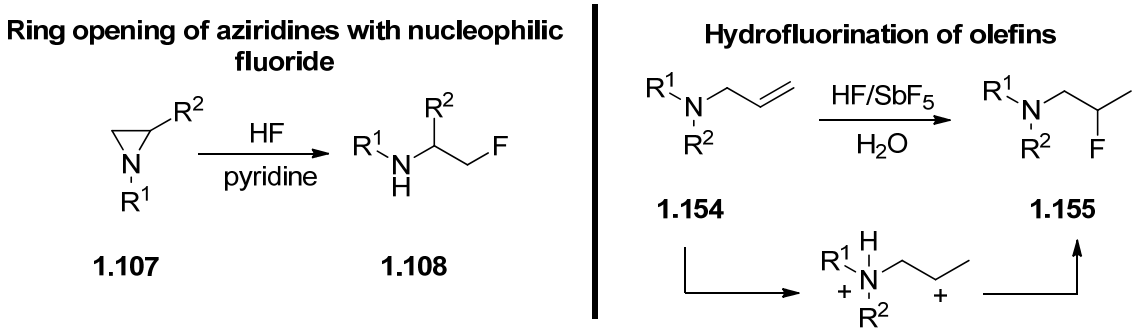
1.153
N-fluorocamphor sultam

N-fluoropyridinium salt

Figure 1.2.6.2 Common electrophilic sources of fluorine.

1.2.7 Current Methods Towards β-Fluoroamines

Despite the importance of the β-fluoroamine moiety, there are few synthetic methods in the literature for its preparation.[48-50,58] Two common methods, the ring opening of aziridines with nucleophilic fluoride sources[59] and the hydrofluorination of olefins,[60] deliver β-fluoroamines but lack generality, require starting materials that are not readily available, and/or do not provide access to enantiopure β-fluoroamines (Scheme 1.2.7.1).



Scheme 1.2.7.1 Common approaches to β-fluoroamines.

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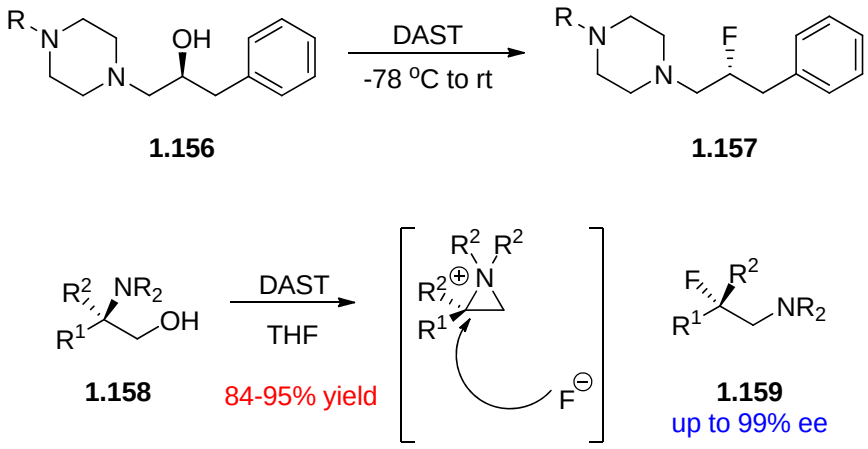
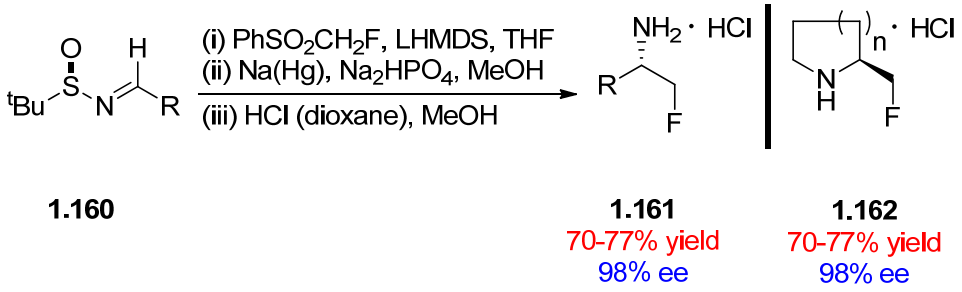
The route most utilized involves the treatment of ketones or secondary alcohols with DAST to provide β,β-difluoroamines and β-fluoroamines (with inversion of stereochemistry), respectively.[48-50,58-62] However, this method requires preparation of enantiopure secondary alcohols and can suffer from the formation of rearranged and dehydrated products, which in many cases greatly diminishes yields of the desired β-fluoroamines.[24]

Cossy and co-workers utilized DAST to achieve an enantiospecific and regioselective rearrangement of *N*,*N*-dialkyl-β-amino alcohols to give optically active β-fluoroamines (Scheme 1.2.7.2).[63]



Scheme 1.2.7.2 Synthesis of β-fluoroamines using DAST.

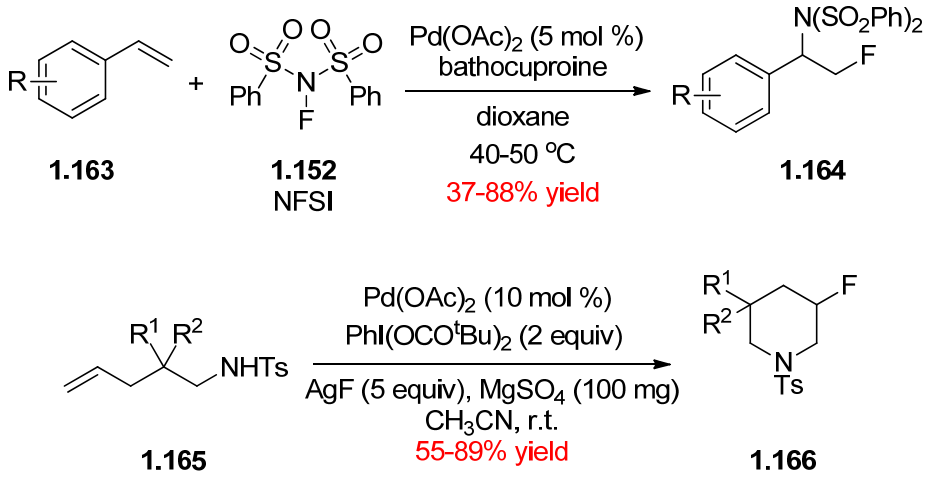
Hu and co-workers reported a highly stereoselective, nucleophilic monofluoromethylation of chiral imines with fluoromethyl phenyl sulfone to afford α-monofluoromethylamines and α-monofluoromethylated cyclic amines (Scheme 1.2.7.3).[64]



1.160 **1.161** 70-77% yield 98% ee **1.162** 70-77% yield 98% ee

Scheme 1.2.7.3 Stereoselective nucleophilic monofluoromethylation of chiral imines.

In 2009, Liu and co-workers developed a novel palladium-catalyzed intermolecular and intramolecular oxidative aminofluorination of unactivated alkenes to yield acyclic and cyclic β-fluoroamines (Scheme 1.2.7.4).[65]



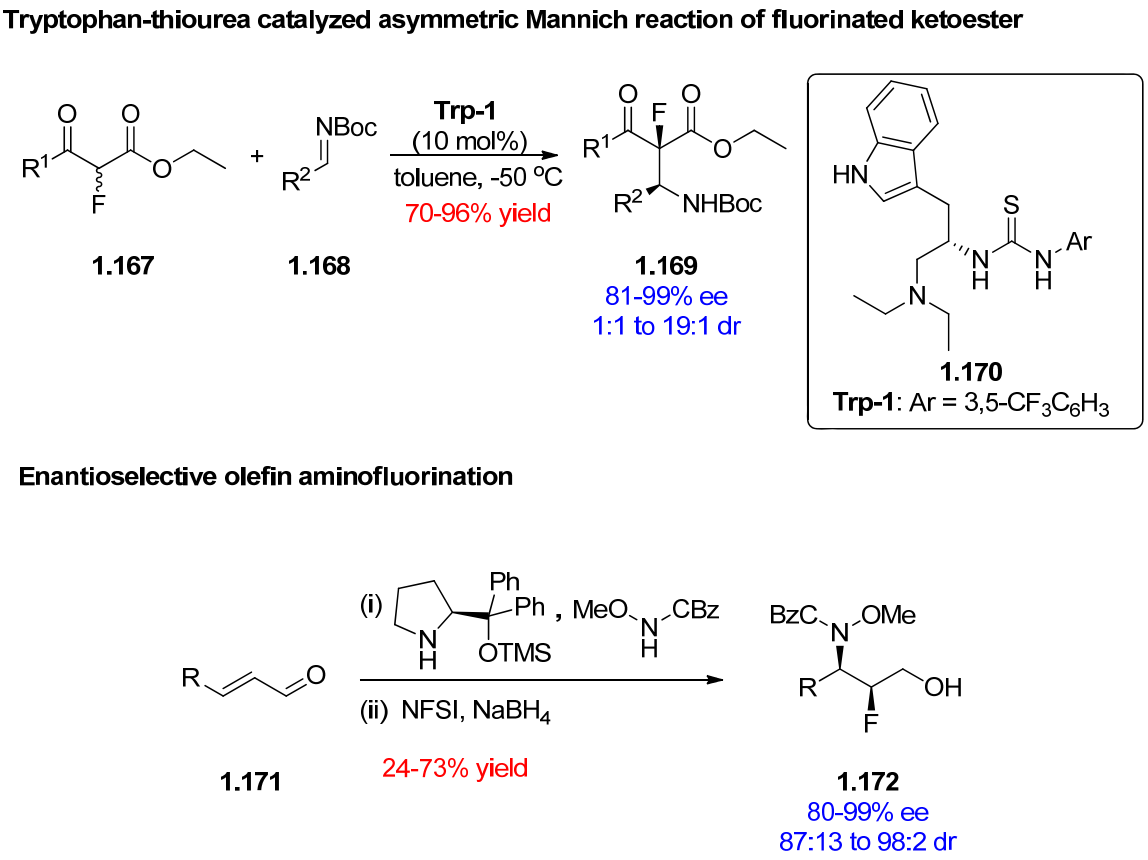
1.163 **1.152** NFSI **1.164**

1.165 **1.166**

Scheme 1.2.7.4 Palladium-catalyzed oxidative aminofluorination.

Lu and co-workers developed a novel tryptophan-based bifunctional thiourea catalyst that was effective in promoting the asymmetric Mannich reaction of an α-fluoro-β-ketoester with *N*-Boc imines to afford α-fluoro-β-amino acids in good to excellent yields, diastereoselectivity, and enantioselectivity (Scheme 1.2.7.5).[66] Brenner-Moyer

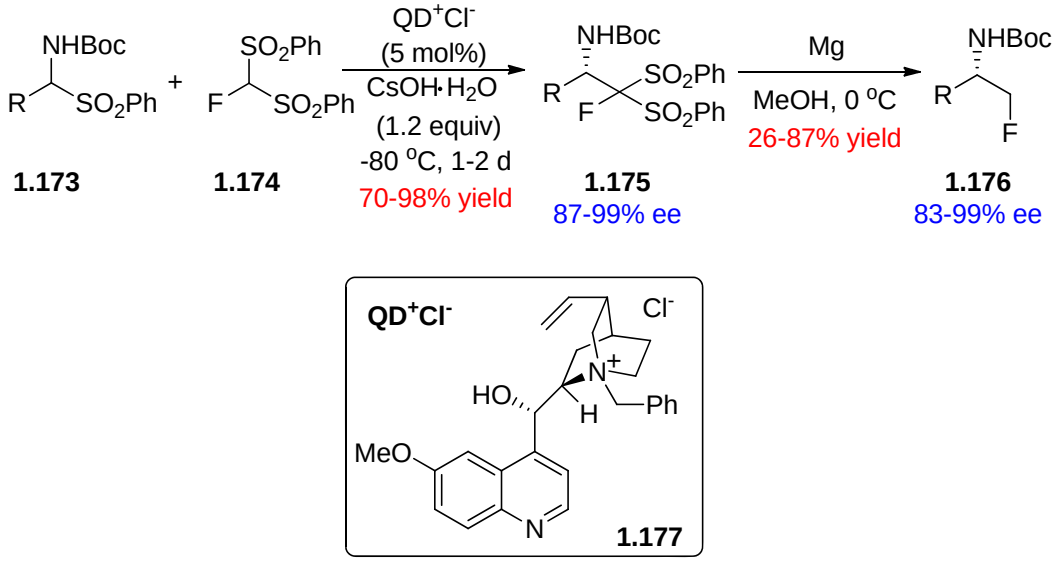
and co-workers reported an organocatalytic asymmetric olefin aminofluorination reaction. Enantiopure α-fluoro-β-amino alcohols were generated from achiral α,β-unsaturated aldehydes in low to moderate yields and excellent enantioselectivity (Scheme 1.2.7.5).[67]



Scheme 1.2.7.5 Organocatalyzed synthesis of enantiopure β-fluoroamines.

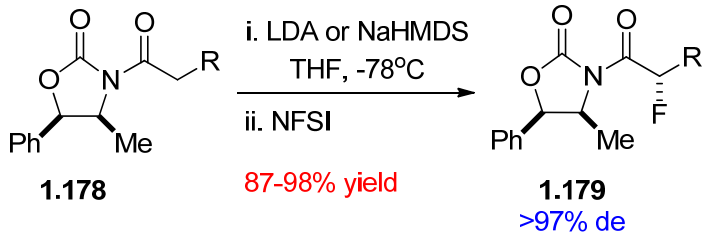
The first organocatalytic enantioselective fluorobisphenylsulfonylmethylation was developed by Toru and co-workers. Imines from α-amino sulfones, generated *in situ*, underwent a Mannich-type reaction with 1-fluorobis(phenylsulfonyl)methane to give α-fluorobisphenylsulfonyl amines in excellent yield and enantioselectivity. Further

reductive desulfonylation under Mg/MeOH conditions gave monofluoromethylated amines in high yields with retained enantiopurity (Scheme 1.2.7.6).[68]



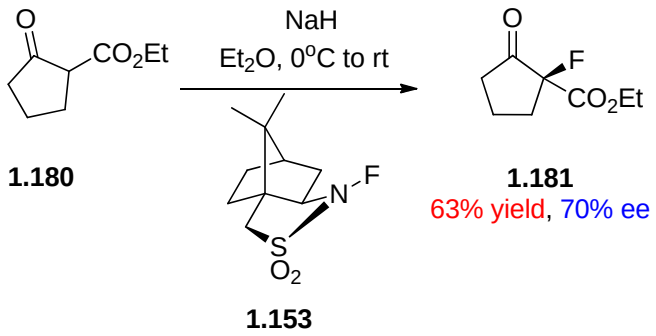
Scheme 1.2.7.6 Cinchona alkaloid-catalyzed enantioselective monofluoromethylation.

Early methods for the preparation of enantiopure organofluorine compounds relied on substrate-controlled fluorinations. This approach was commonly accomplished through enolate trapping of chiral auxiliaries, such as Evan's oxazolidinones, with an electrophilic fluorinating reagent to afford chiral α-fluorocarbonyl compounds (Scheme 1.2.7.7).[69] Enantioselective fluorinations can also be under reagent control, which utilizes stoichiometric amounts of electrophilic fluorinating reagents. Chiral *N*-fluorinating reagents such as *N*-fluorosultams, *N*-fluorosulfonamides, and *N*-fluoroammonium salts of cinchona alkaloids have been used for the enantioselective fluorination of various enolizable substrates.[70]



Scheme 1.2.7.7 Substrate-controlled enantioselective fluorination.

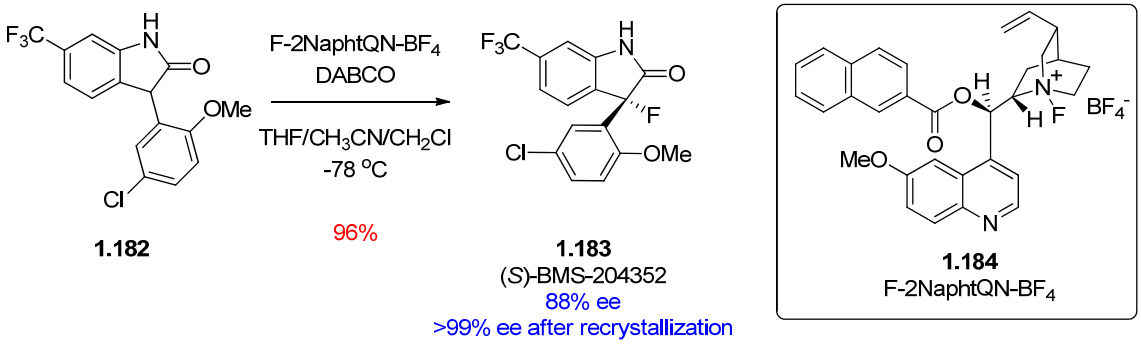
In 1988, Differding and Lang developed *N*-fluorocamphorsultams as the first enantioselective fluorinating reagents. Subjecting various achiral metal enolates generated from ketoesters led to fluorinated ketoesters in low to moderate enantioselectivities (Scheme 1.2.7.8); these results demonstrated the possibility of reagent-controlled asymmetric fluorination using a chiral electrophilic fluorine atom.[71]



Scheme 1.2.7.8 Enantioselective fluorination using *N*-fluorocamphorsultams.

One of the most remarkable demonstrations of the effectiveness of $[N\text{-}F]^+$ reagents was reported by Cahard and co-workers. A new N-fluoroammonium salt F-2NaphtQN-BF4 was developed and applied to the enantioselective synthesis of BMS-204352 (MaxiPost), a potent agonist of maxi-K channels, which is being evaluated in a

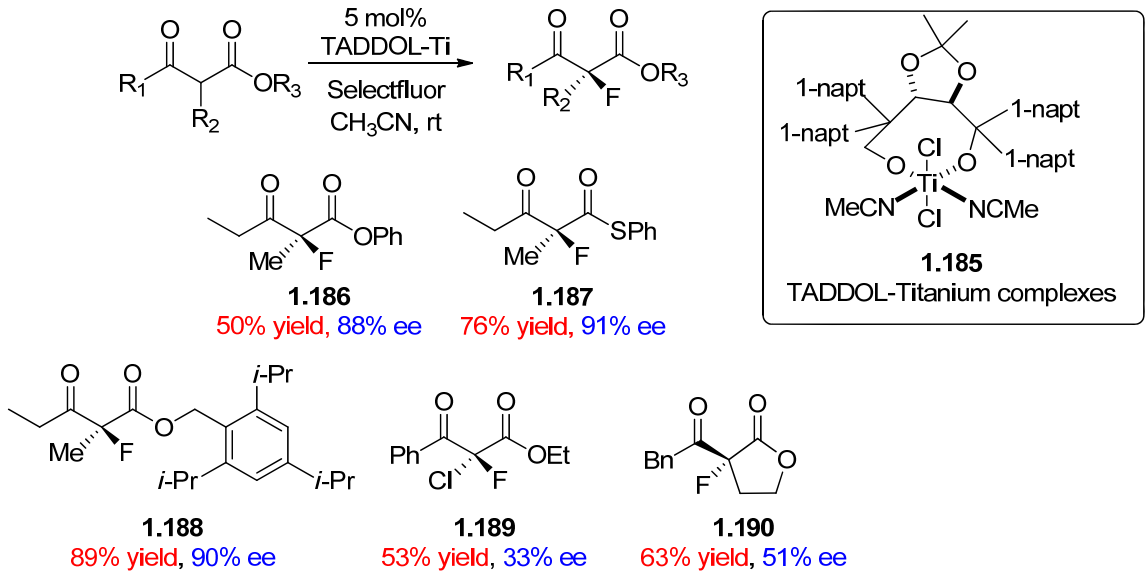
phase III clinical trial for treatment of acute ischemic stroke. Cahard and co-workers reacted an oxindole with the N-fluoroammonium salt F-2NaphtQN-BF_4 in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to yield the fluorinated product (*S*)-BMS-204352 in excellent yield and high enantioselectivity (Scheme 1.2.7.9).[72]



Scheme 1.2.7.9 Enantioselective synthesis of BMS-204352.

1.2.8 Catalytic Enantioselective Fluorination

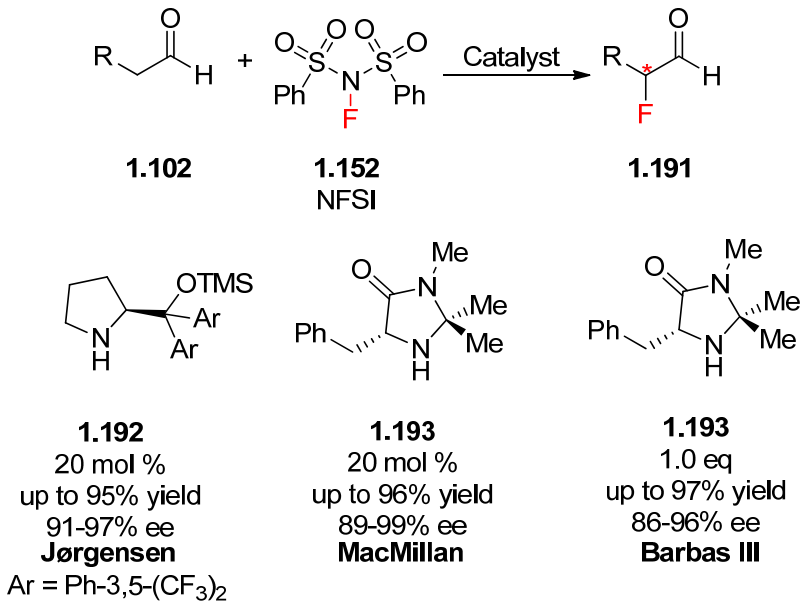
In 2000, Togni and co-workers reported the first catalytic enantioselective fluorination reaction. β-ketoesters were subjected to catalytic transition-metal complex $TiCl_2$(*R*,*R*)-TADDOL, which acted as a Lewis acid to activate the β-keto group in the presence of Selectfluor to give α-fluoro-β-ketoesters in good yields and moderate enantioselectivity (Scheme 1.2.8.1).[73]



Scheme 1.2.8.1 TADDOL-titanium catalyzed asymmetric fluorination.

1.2.9 Enantioselective α-Fluorination of Aldehydes

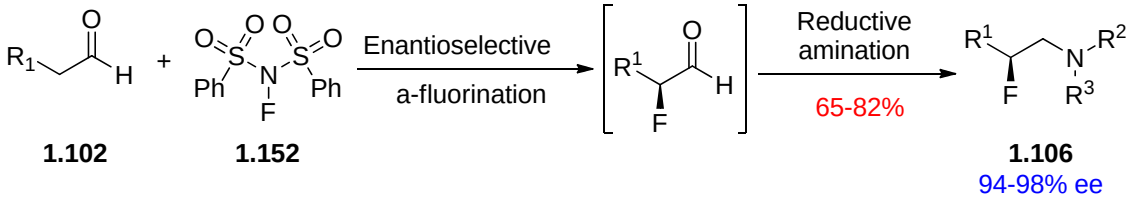
Recently, Jørgensen,[74] Barbas,[75] and MacMillan[76] concurrently reported their findings on the use of various pyrrolidines and imidazolines as catalysts for the direct α-fluorination of aldehydes with excellent asymmetric induction. Their approaches to direct enantioselective α-fluorination of aldehydes used NFSI as the electrophilic source of fluorine (Scheme 1.2.9.1). We envisioned applying this methodology towards the preparation of chiral β-fluoroamines.



Scheme 1.2.9.1 Organocatalytic enantioselective α-fluorination of aldehydes.

1.2.10 Studies Towards Organocatalyzed Synthesis of β-Fluoroamines

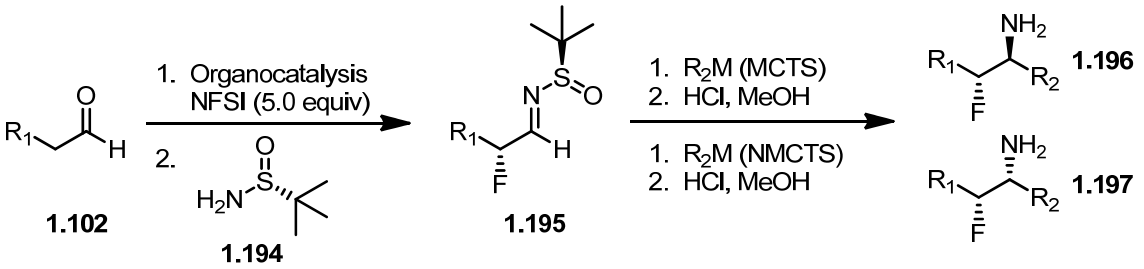
` Recently, our lab reported a one-pot protocol to provide pharmaceutically relevant chiral β-fluoroamines via organocatalysis (Scheme 1.2.10.1).[46]



Scheme 1.2.10.1 Previous work towards chiral β-fluoroamines.

One limitation of this methodology was the inability to generate primary amines with a fluorine at the β-position. We envisioned a route to access these primary β-fluoroamines using the same organocatalytic enantioselective α-fluorination of aldehydes[76] followed by condensation with a chiral sulfinamide[77-81] to afford α-fluoro-*N*-

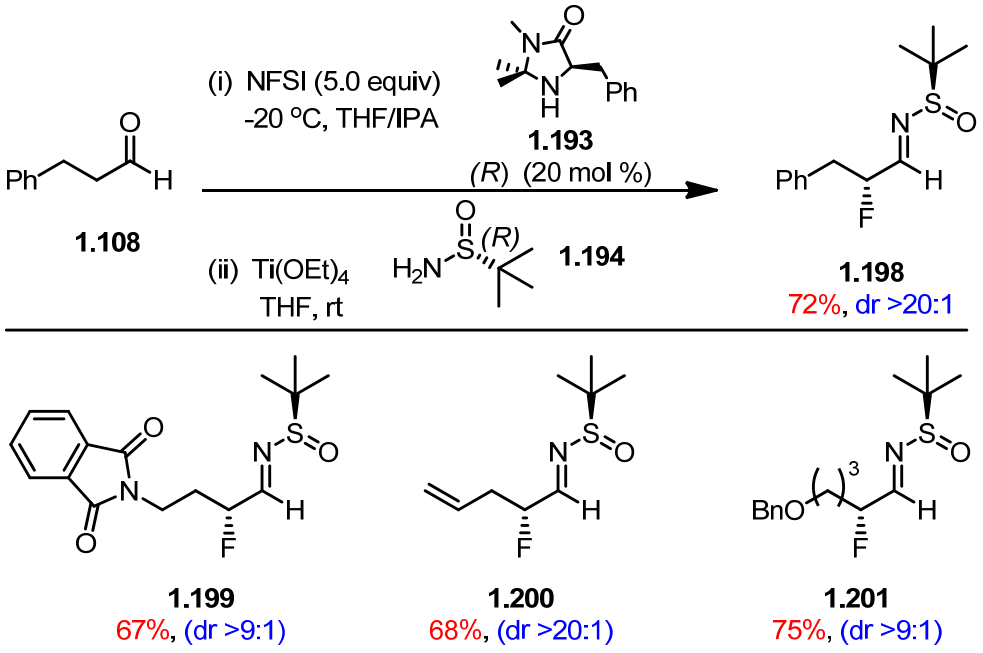
sulfinyl imines. Organometalllic additions[82-86] into the imine with subsequent deprotection of the amine would afford the chiral, primary β-fluoroamine. This methodology would allow for complete control of the two contiguous stereogenic centers, based on the chirality of the organocatalyst and sulfimine employed and on the transiton state (metal-chelate versus nonmetal-chelate transition states, MCTS and NMCTS, respectively) that the organometallic species adopts (Scheme 1.2.10.2).



Scheme 1.2.10.2 Envisioned route towards primary β-fluoroamines.

One major issue to be addressed during enantioselective fluorination of aldehydes is the need to avoid racemization of the enantioenriched fluorinated compound. Due to the instability of the fluoroaldehydes, these products were originally isolated more often as the corresponding α-fluoroalcohols after reduction with hydride sources. Key to the success of our approach was the ability to trap the incipient chiral fluoroaldehyde with the Ellman *tert*-butanesulfonamide to form the corresponding (*R)*-fluoro-N-sulfinylaldimine in high diastereomeric ratio (dr). A number of conditions were surveyed (time, desiccant, equivalents of NFSI) for the conversion of hydrocinnamaldehyde to the β-fluoro-N-sulfinylaldimine. Ultimately, we found that 5.0 equiv of NFSI, 20 mol% (5*R*)-(+)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid 1.193, $Ti(OEt)_4$ as

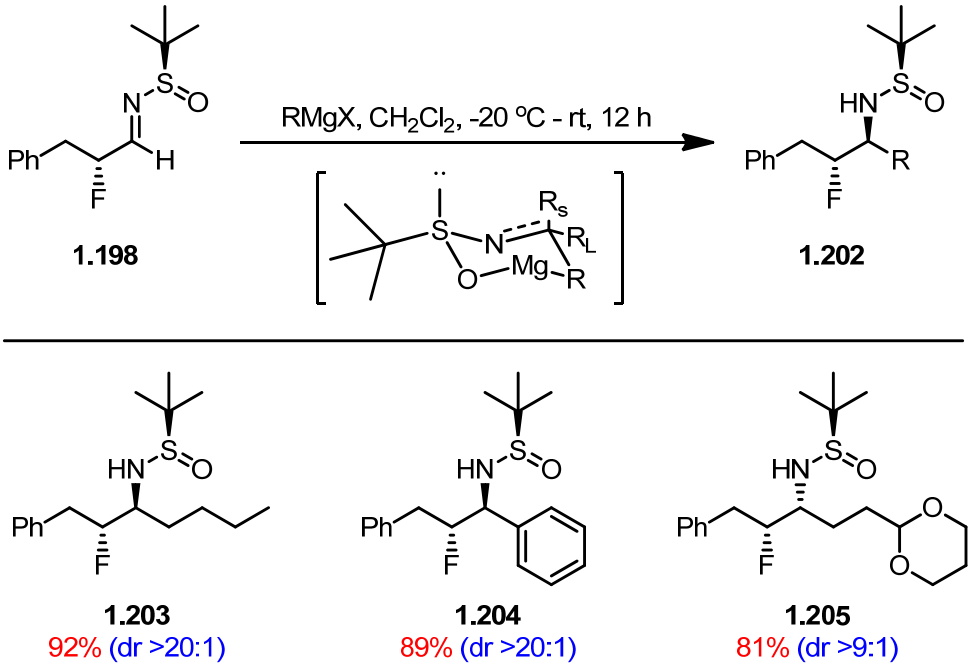
desiccant with (*R*)-tert-butanesulfinamide, and a 5 h reaction time were optimal to deliver the desired products in >20:1 dr (as judged by ^{19}F NMR). With these conditions, a variety of diverse aldehydes could be converted into their corresponding β-fluoro-N-sulfinylaldimines in good isolated yield (67-75%) for the two steps and with up to >20:1 dr (Scheme 1.2.10.3). Here, substrates with handles for further elaboration were tolerated, such as the phthalimide congener, a progenitor for basic amine analogues, the olefin for subsequent manipulations, and a benzyl protected alcohol congener.



Scheme 1.2.10.3 Preparation of α-fluoro-*N*-sulfinyl aldimines.

With (*R*)-fluoro-*N*-sulfinylaldimines in hand, we examined the addition of a number of organometallic nucleophiles to add unprecedented diversity to the primary β-fluoroamine scaffold and access derivatives which were previously unavailable. We first explored Grignard reagents (Scheme 1.2.10.4) and found that a wide range of diverse R

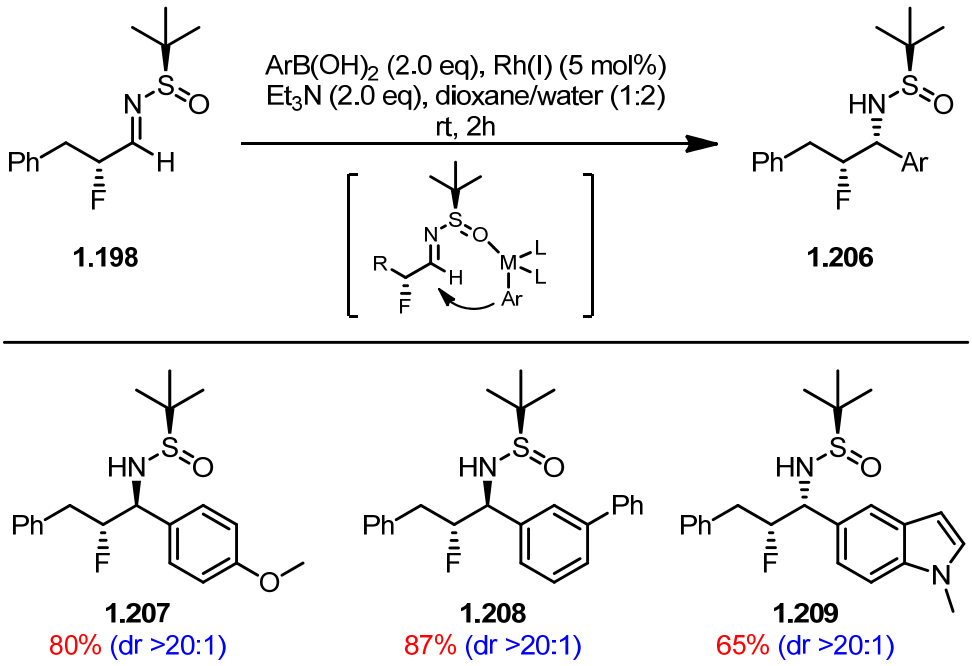
groups were tolerated, affording the sulfinamide-protected primary β-fluoroamines in good isolated yields (72-92%) and >20:1 dr (as determined by ^{19}F NMR).[45] The *anti*-diastereomer of the β-fluoroamine formed predominantly, as expected, due to the known metal-chelated transition state (see inset under arrow) for 1.203 and 1.204. The *syn*-diastereomer was formed in the case of 1.205, as a result of additional coordination to the acetal oxygen, in accordance with the work of Ellman.[82,83]



Scheme 1.2.10.4 Scope of Grignard addition.

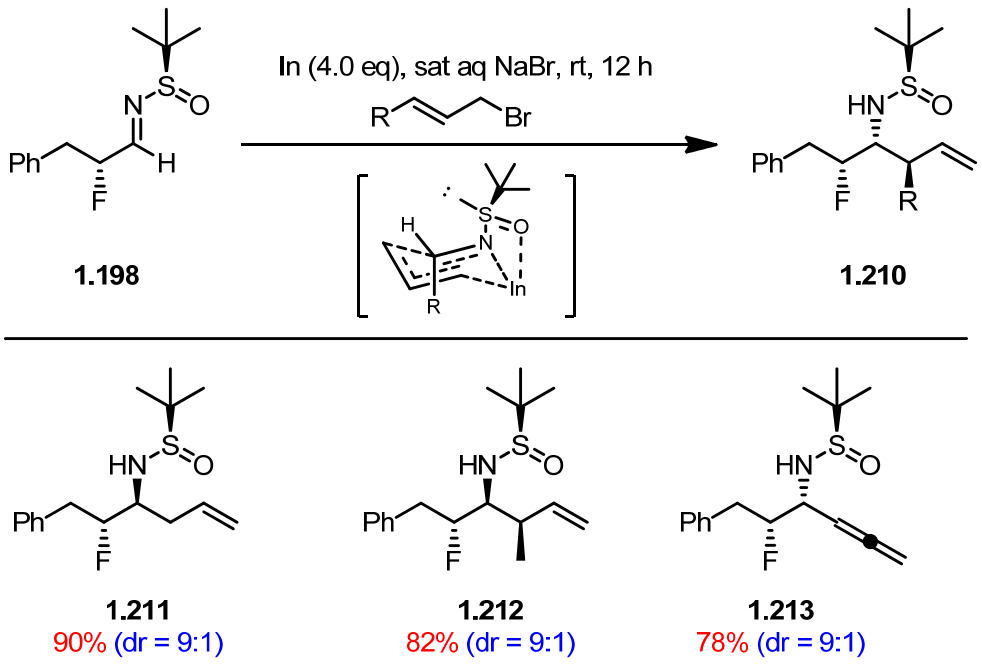
Due to the extensive diversity and availability of functionalized boronic acids, we next explored boronic acid additions. Under Batey's mild Rh(I) catalysis protocol,[84] a diverse group of aryl boronic acids (electron-rich, biaryl, and heterocyclic congeners) smoothly afforded the target adducts in 65-91% yield and all in >20:1 dr (Scheme 1.2.10.5). In this instance, the *syn*-diastereomers of the β-fluoroamines are formed based

on the known addition of the aryl rhodium species through a nonmetal-chelated transition state.[84]



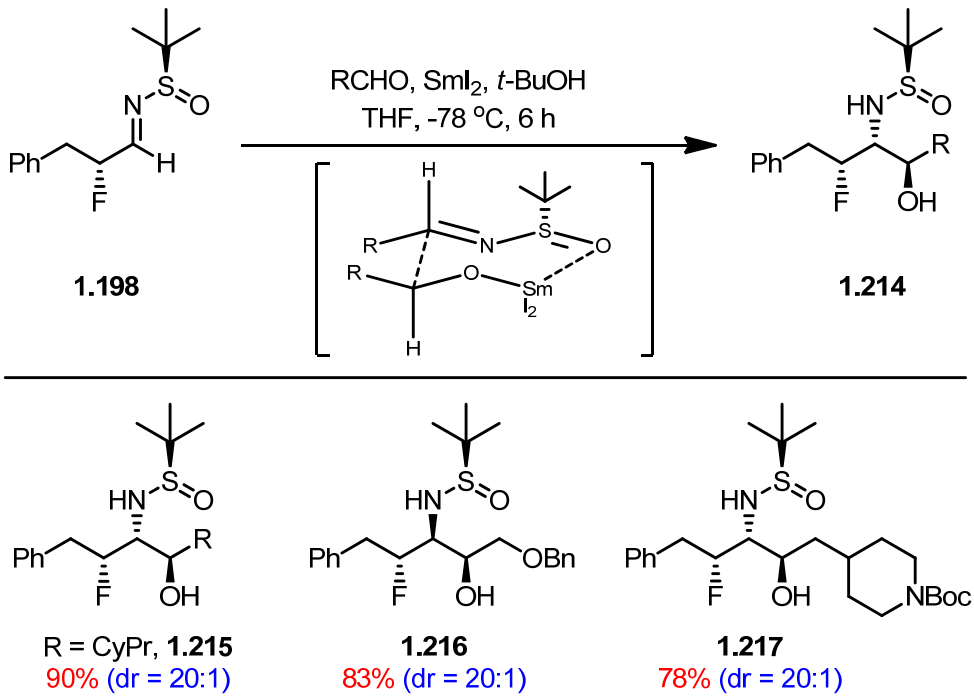
Scheme 1.2.10.5 Scope of boronic acid addition.

Lin and co-workers previously demonstrated that indium-mediated allylations (In(0), allyl bromide in aqueous NaBr) of (*R*)-*N*-tert-butanesulfinylimines provide the (*S*)-adducts as confirmed by single X-ray crystallography.[85] To further add structural diversity to the primary β-fluoroamine scaffolds accessible through our approach, we employed Lin's protocol with our β-fluoro-N-sulfinylaldimine (Scheme 1.2.10.6). As expected, anti-diastereomers of the sulfinamide-protected β-fluoroamine products were produced in good yields (66-90%) and up to 9:1 dr. Here, we could install additional stereogenic centers and allene moieties.



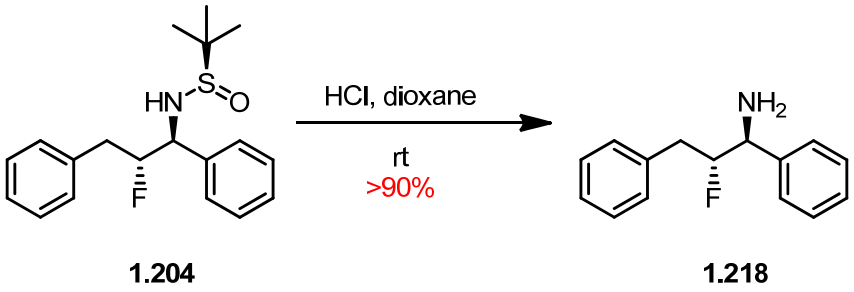
Scheme 1.2.10.6 Scope of In-mediated allylation.

We also hoped to expand this protocol to include β-amino alcohols. Following the work of Xu and Lin,[86] the SmI_2-induced reductive aldehyde cross-coupling with our β-fluoro-*N*-sulfinylaldimine (Scheme 1.2.10.7) produced the target sulfinamide-protected primary β-fluoro-β'-amino alcohols in excellent yields (80-87%) and with high dr (>20:1).



Scheme 1.2.10.7 Scope of SmI_2-induced reductive aldehyde coupling.

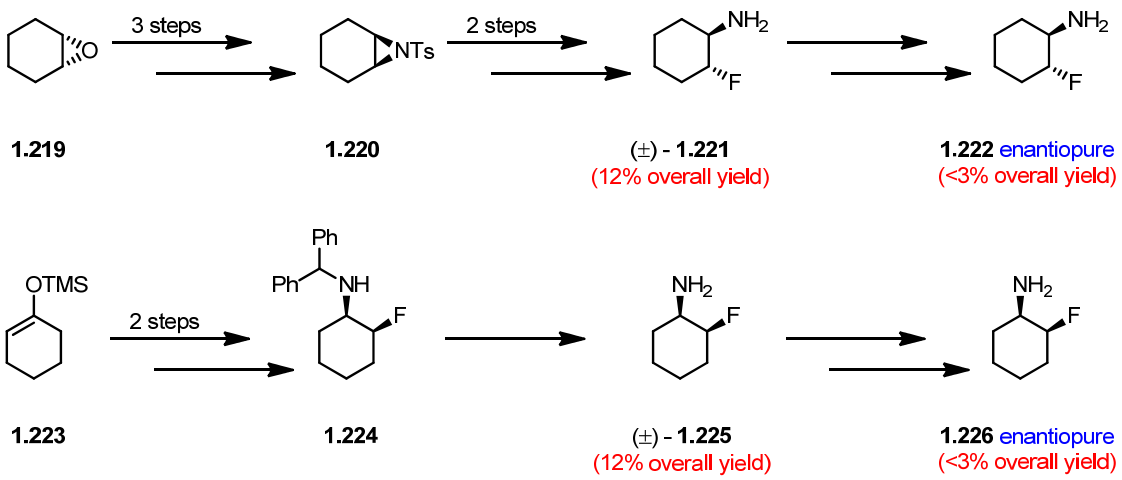
An attractive feature of the Ellman sulfonamide-protected primary amines is the generality and ease of deprotection.[77-86] Treatment of a representative example with HCl in dioxane at room temperature smoothly affords the desired primary β-fluoroamine congener in greater than 90% yield and without any loss of stereochemical integrity (Scheme 1.2.10.8). In our drug discovery efforts, we have deprotected numerous congeners of and have never encountered problems with stereochemical integrity or clean deprotections.



1.204 **1.218**

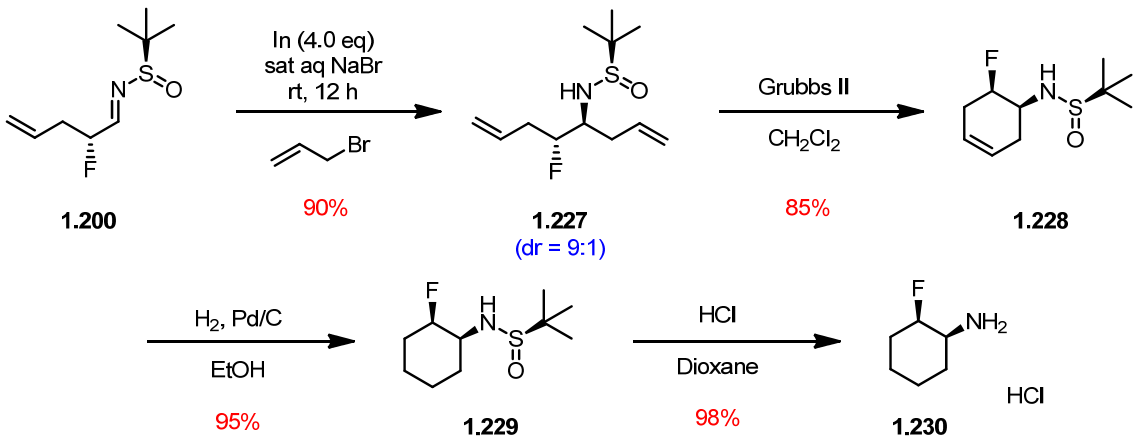
Scheme 1.2.10.8 Deprotection to afford 1° β-fluoroamines.

Finally, we wanted to apply this methodology to cyclic primary β-fluoroamines, as this pharmacophore has proven to be an important component of therapeutic agents, such as BACE inhibitors.[87,88] Classically, cyclic, racemic *trans*-primary β-fluoroamines have been prepared by the ring opening of aziridines with nucleophilic fluoride, followed by deprotection.[59,87,88] Cyclic, racemic *cis*-primary β-fluoroamines can be prepared by fluorination of a silyl enol ether, followed by reductive amination and deprotection (Figure 1.2.10.9).[87,88] Overall, yields are modest to low (average 12% overall) for the production of racemic, cyclic primary β-fluoroamines via these routes, which all contain multiple steps. In order to access enantiopure derivatives, chiral chromatography is performed on either the free amine or, more likely, a protected form that introduces a chromophore, followed by deprotection. Ultimately, pure enantiomers of *trans*- and *cis*- are arrived at in typically less than 3% overall yield.



Scheme 1.2.10.9 Standard route to *trans*- and *cis*- cyclic primary β-fluoroamines.

In contrast, our methodology can provide rapid, high-yielding access to either *cis*- or *trans*-cyclic primary β-fluoroamines with high enantioselectivity based on the chirality of the organocatalyst and the sulfinylamine employed. For example, an indium-mediated allylation with allyl bromide gives 1.227 in 90% yield and 9:1 dr (if allyl Grignard employed, the yield is comparable, but with improved dr of >20:1) (Scheme 1.2.10.10). Ring-closing metathesis with Grubbs II affords cyclohexene 1.228 in 85% yield. Hydrogenation and standard acid-mediated deprotection provide the chiral cyclic primary β-fluoroamine in 70% overall yield for the four-step sequence, a notable improvement over the classical route. The relative stereochemistry was confirmed by correlation with previously reported ^{19}F NMR shifts for *cis*- and *trans*-cyclic β-fluoroamines (-197 and-180 ppm respectively), wherein 1.230 displayed a singlet at -198 ppm.[89]



Scheme 1.2.10.10 Access to chiral, cyclic 1° β-fluoroamines.

In summary, we have developed a highly diastereoselective and general synthesis of primary β-fluoroamines using a combination of organocatalysis and Ellman *N*-sulfinylaldimine technology to enable the preparation of all possible stereoisomers in high isolated yields.[90] Importantly, this methodology provides access to primary β-fluoramine chemotypes that are generally not accessible, or difficult to prepare, through classic routes, as well as providing a significant improvement in the synthesis of cyclic primary β-fluoroamines.

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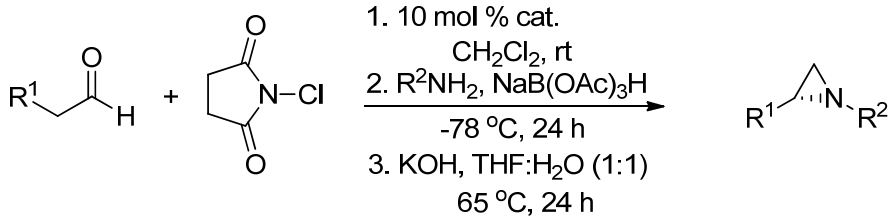
Experimental for *N*-Alkyl Terminal Aziridines

General Experimental

All reagents were purchased from Sigma-Aldrich Corp., TCI America, and Rieke Metals, Inc. and were used without purification. All polymer-supported reagents were purchased from Biotage, Inc. Analytical thin-layer chromatography (TLC) was performed on 250 μm silica gel plates from Sorbent Technologies. Visualization was accomplished via UV light and/or the use of ninhydrin and potassium permanganate solutions followed by application of heat. Chromatography was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies or Silica RediSep Rf flash columns on a CombiFlash Rf automated flash chromatography system. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 (400 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.16 ($CDCl_3$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling constant (*J*, in Hz), integration. Low resolution mass spectra (LCMS) were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra (HRMS) were recorded on a Waters Qtof-API-US Plus Acquity system with ES as the ion source. Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 1200 analytical LCMS with UV detection at 214 nm and 254 nm along with ELSD detection. Chiral separations were performed on an Agilient 1200 series HPLC and a Thar Investigator II supercritical fluid chromatograph (SFC) utilizing Chiralcel® OD, OD-Cl, OJ, and Chiralpak® IA columns. Optical rotations were acquired on a Jasco P-2000

polarimeter at 23 °C and 589nm. The specific rotations were calculated according to the equation $[\alpha]_D^{23} = \frac{100\alpha}{l\ x\ c}$ where *l* is the path length in decimeters and *c* is the concentration in g/100mL.

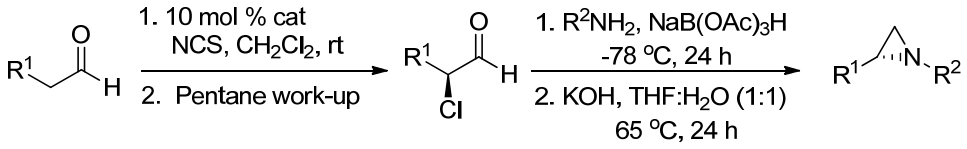
One-Pot Procedure for Chiral Aziridine Synthesis



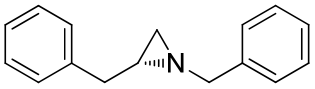
To a solution of aldehyde (1.0 eq) and catalyst (2*R*,5*R*)-2,5-diphenylpyrrolidine (0.1 eq) in CH_2Cl_2 was added *N*-chlorosuccinimide (1.3 eq) at -78 °C. The reaction mixture warmed to rt and continued stirring over a period of 1.5-2.0 h after which ground molecular sieves were added. The reaction mixture was cooled to -78 °C and a solution of amine (1.0 eq) in 2 mL of CH_2Cl_2 at -78 °C was added. This solution stirred at -78 °C for an additional 1.5-2.0 h followed by addition of sodium triacetoxyborohydride (1.2 eq) and stirring overnight at -78 °C. The reaction mixture was filtered through a pad of Celite eluting with CH_2Cl_2 and concentrated *in vacuo,* resulting in a crude oil which was then dissolved in 1:1 THF/H_2O along with KOH (6.5 eq) and stirred overnight at 65 °C. The reaction mixture was extracted with EtOAc (5x), dried over $MgSO_4$, and concentrated under vacuum to give the crude product. Purification by flash column chromatography afforded the title compounds. The enantiomeric excess was determined either by chiral HPLC or SFC analysis. The

diastereomeric ratio was determined by NMR experiments using chiral solvating agents.

Two-Pot Procedure for Chiral Aziridine Synthesis

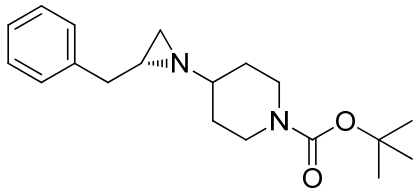


To a solution of aldehyde (1.0 eq) and catalyst (2*R*,5*R*)-2,5-diphenylpyrrolidine (0.1 eq) in CH_2Cl_2 was added *N*-chlorosuccinimide (1.3 eq) at -78 ^oC. This mixture was allowed to stir and warm to room temperature over a period of 1.5-2.0 h. The reaction was quenched by addition of excess pentane followed by filtration and concentration of the filtrate *in vacuo*. The crude product was redissolved in CH_2Cl_2 and ground molecular sieves were added. The reaction mixture was then cooled to -78 ^oC and a solution of amine (1.0 eq) in 2 mL of CH_2Cl_2 at -78 ^oC was added. This solution stirred at -78 ^oC for an additional 1.5-2.0 h followed by addition of sodium triacetoxyborohydride (1.2 eq) with stirring overnight at -78 ^oC. The reaction mixture was filtered through a pad of Celite eluting with CH_2Cl_2 and concentrated *in vacuo,* resulting in a crude oil which was then dissolved in 1:1 THF/H_2O along with KOH (6.5 eq) and stirred overnight at 65 ^oC. The reaction mixture was extracted with EtOAc (5x), dried over $MgSO_4$, and concentrated under vacuum to give the crude product. Purification by flash column chromatography afforded the title compounds. The enantiomeric excess was determined either by chiral HPLC or SFC analysis.



(*R*)-1,2-dibenzylaziridine (1.109)

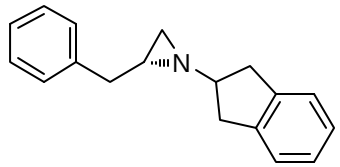
The product was prepared according to the two-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear, yellow oil (167.5 mg, 75%), which was determined to have an ee of 94% by chiral HPLC analysis (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 7.8 min, t_R (minor) = 6.8 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.29-7.25 (m, 3H); 7.24-7.18 (m, 4H); 7.18-7.13 (m, 3H); 3.40 (d, J = 1.65 Hz, 2H); 2.81 (dd, J_1 = 5.88 Hz, J_2 = 14.64 Hz, 1H); 2.60 (dd, J_1 = 5.84 Hz, J_2 = 14.64 Hz, 1H); 1.76-1.68 (m, 2H); 1.43 (d, J = 6.10 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.75, 139.35, 128.81, 128.47, 128.22, 127.11, 126.30, 64.90, 40.82, 39.48, 33.95. HRMS (TOF, ES+) $C_{16}H_{17}N$ $[M+H]^+$ calc. mass 224.1439, found 224.1432. Specific rotation $[\alpha]_D^{23}$ = +32.96° (c = 4.733, $CHCl_3$).



(*R*)-tert-butyl 4-(2-benzylaziridin-1-yl) piperidine-1-carboxylate (1.124)

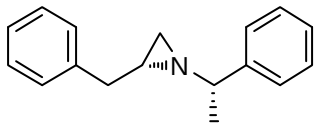
The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane with 1% Et_3N) to afford the product as a clear yellow oil (145.6 mg, 46%), which was determined to have an ee of 91% by chiral HPLC analysis (Chiralpak® IA, Isocratic 60:40 pH 9, 20mM $NH_4HCO_{3(aq)}$ /acetonitrile, t_R

(major) = 27.3 min, t_R (minor) = 30.4 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.31 (m, 2H); 7.24 (m, 3H); 3.92 (br d, *J* = 31.2 Hz, 2H); 2.84-2.56 (m, 4H); 1.72 (m, 2H); 1.59 (m, 1H); 1.45 (m, 1H); 1.45 (s, 9H); 1.35 (d, *J* = 6.4 Hz, 2H); 1.24 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.98, 139.93, 128.92, 128.50, 126.40, 79.49, 66.75, 40.35, 39.86, 32.67, 31.89, 31.44, 28.56. HRMS (TOF, ES+) $C_{19}H_{29}N_2O_2$ $[M+H]^+$ calc. mass 317.2229, found 317.2233. Specific rotation $[\alpha]_D^{23}$ = +21.82° (c = 5.133, $CHCl_3$).



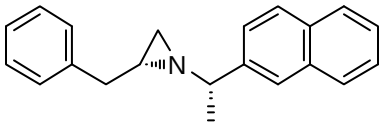
(*R*)-2-benzyl-1-(2,3-dihydro-1H-inden-2-yl) aziridine (1.125)

The product was prepared according to the two-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a dark brown oil (127.1 mg, 51%), which had an ee of 90% by chiral HPLC analysis (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 7.8 min, t_R (minor) = 6.2 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.31-7.25 (m, 2H); 7.24-7.13 (m, 4H); 7.12-7.04 (m, 3H); 3.02-2.90 (m, 2H); 2.80 (dd, J_1 = 6.70 Hz, J_2 = 15.93 Hz, 1H); 2.68 (dd, J_1 = 5.51 Hz, J_2 = 14.14 Hz, 1H); 2.63-2.54 (m, 2H); 2.24 (p, *J* = 5.51 Hz, 1H); 1.70 (d, *J* = 3.27, 1H); 1.66-1.59 (m, 1H); 1.39 (d, *J* = 6.31 Hz, 1H)**.** ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 141.98, 141.66, 140.05, 128.94, 128.45, 126.39, 126.33, 124.89, 124.64, 70.92, 40.86, 39.67, 39.60, 39.35, 33.51. HRMS (TOF, ES+) $C_{17}H_{19}N$ $[M+H]^+$ calc. mass 250.1596, found 250.1596. Specific rotation $[\alpha]_D^{23}$ = +32.96° (c = 4.733, $CHCl_3$). Specific rotation $[\alpha]_D^{23}$ = +7.19° (c = 4.867, $CHCl_3$).



(*R*)-2-benzyl-1-((*S*)-1-phenylethyl) aziridine (1.126)

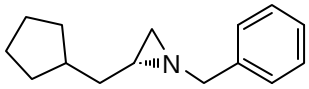
The product was prepared according to the one-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (151.9 mg, 64%), which was determined to have a dr of >10:1 by NMR with the chiral solvating agent (*R*)(-)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle alcohol). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.33-7.24 (m, 8H); 7.21-7.15 (m, 2H); 2.78 (dd, J_1 = 6.51 Hz, J_2 = 14.15 Hz, 1H); 2.67 (dd, J_1 = 6.06 Hz, J_2 = 14.14 Hz, 1H); 2.34 (q, J = 6.59 Hz, 1H); 1.66 (dq, J_1 = 3.51 Hz, J_2 = 6.34 Hz, 1H); 1.57 (d, J = 3.51 Hz, 1H); 1.28 (d, J = 6.35 Hz, 1H); 1.21 (d, J = 6.63 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 144.73, 139.98, 129.01, 128.44, 128.38, 127.02, 126.93, 126.34, 69.98, 41.80, 39.89, 33.60, 23.39. HRMS (TOF, ES+) $C_{17}H_{19}N$ $[M+H]^+$ calc. mass 238.1596, found 238.1596. Specific rotation $[\alpha]_D^{23}$ = -32.67° (c = 8.600, $CHCl_3$).



(*R*)-2-benzyl-1-((*S*)-1-(naphthalen-2-yl)ethyl) aziridine (1.127)

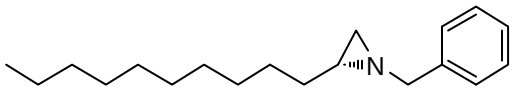
The product was prepared according to the one-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear orange oil (163.8 mg, 57%), which was determined to have a dr of >10:1 by NMR with the chiral solvating agent (*R)*(-)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle alcohol). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.76-7.70 (m, 4H); 7.45-7.41 (m, 1H); 7.36 (m, 2H); 7.26 (d, J = 4.32

Hz, 3H); 7.20-7.13 (m, 2H); 2.79 (dd, J_1 = 6.50 Hz, J_2 = 14.15 Hz, 1H); 2.67 (dd, J_1 = 6.09 Hz, J_2 = 14.15, 1H); 2.47 (q, J = 6.59 Hz, 1H); 1.69 (dq, J_1 = 3.58 Hz, J_2 = 6.31 Hz, 1H); 1.58 (d, J = 3.58 Hz, 1H); 1.29 (d, J = 6.31 Hz, 1H); 1.25 (d, J = 6.59 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 142.27, 140.01, 133.54, 132.85, 129.05, 128.50, 128.06, 127.97, 127.75, 126.40, 126.03, 125.60, 125.51, 125.28, 70.21, 42.00, 39.94, 33.73, 23.47. HRMS (TOF, ES+) $C_{21}H_{21}N$ $[M+H]^+$ calc. mass 288.1752, found 288.1746. Specific rotation $[\alpha]_D^{23}$ = -23.72° (c = 4.933, $CHCl_3$).



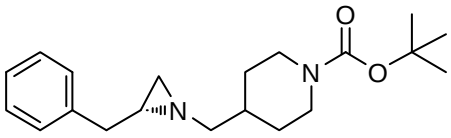
(*R*)-1-benzyl-2-(cyclopentylmethyl) aziridine (1.128)

The product was prepared according to the two-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (116.3 mg, 54%), which was determined to have an ee of 95% by chiral HPLC analysis (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 5.2 min, t_R (minor) = 4.6 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.37-7.29 (m, 4H); 7.28-7.22 (m, 1H); 3.47 (d, J = 13.20 Hz, 1H); 3.36 (d, J = 13.20 Hz, 1H); 1.85-1.75 (m, 1H); 1.75-1.62 (m, 2H); 1.60 (d, J = 3.15 Hz, 1H); 1.59-1.52 (m, 2H); 1.51-1.40 (m, 4H); 1.39 (d, J = 6.00 Hz, 1H); 1.33 (q, J = 7.90 Hz, 1H); 1.15-1.00 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.64, 128.43, 128.36, 127.10, 65.18, 39.42, 39.28, 38.87, 34.43, 32.85, 32.53, 25.24, 25.12. HRMS (TOF, ES+) $C_{15}H_{22}N$ $[M+H]^+$ calc. mass 216.1752, found 216.1752. Specific rotation $[\alpha]_D^{23}$ = +6.29° (c = 7.000, $CHCl_3$).



(*R*)-1-benzyl-2-decylaziridine (1.129)

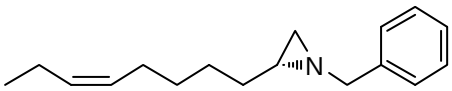
The product was prepared according to the one-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (177.7 mg, 65%), which was determined to have an ee of 94% by chiral HPLC analysis (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 4.5 min, t_R (minor) = 4.1 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.37-7.29 (m, 4H); 7.28-7.22 (m, 1H); 3.50 (d, *J* = 13.25 Hz, 1H); 3.32 (d, *J* = 13.25 Hz, 1H); 1.61 (d, *J* = 3.23 Hz, 1H); 1.49-1.16 (m, 20H); 0.88 (t, *J* = 6.67 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.64, 128.43, 128.32, 127.09, 65.20, 39.98, 34.24, 33.19, 32.07, 29.76, 29.73, 29.53, 29.49, 27.60, 22.84, 14.27. HRMS (TOF, ES+) $C_{19}H_{31}N$ $[M+H]^+$ calc. mass 274.2535, found 274.2527. Specific rotation $[\alpha]_D^{23}$ = +7.42° (c = 6.467, $CHCl_3$).



(*R*)-*tert*-butyl 4-((2-benzylaziridin-1-yl)methyl) piperidine-1-carboxylate (1.130)

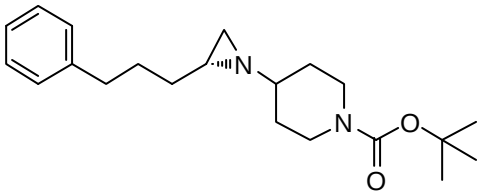
The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane with 1% Et_3N) to afford the product as a clear yellow oil (177.7 mg, 65%), which was determined to have an ee of 86% by SFC analysis (Chiralcel® OJ, 5% IPA/CO_2, t_R (major) = 3.2 min, t_R (minor) = 3.7 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.34-7.17 (m, 5H); 4.15-3.95 (br, 2H); 2.73 (dd, J_1 = 5.60 Hz, J_2 = 14.25 Hz, 1H); 2.64 (dd, J_1 = 7.00 Hz, J_2 = 14.25 Hz, 1H); 2.60-2.46 (m, 2H);

2.28 (dd, J_1 = 7.81 Hz, J_2 = 11.76 Hz, 1H); 1.91 (dd, J_1 = 5.70 Hz, J_2 = 11.76 Hz, 1H); 1.76 (d, J = 12.82 Hz, 1H); 1.71 (d, J = 3.34, 1H); 1.57-1.48 (m, 3H); 1.46 (s, 9H); 1.30 (d, J = 6.25, 1H); 1.06 (pd, J_1 = 4.15 Hz, J_2 = 12.27 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.96, 139.92, 128.86, 128.49, 126.38, 79.29, 67.36, 40.97, 39.64, 37.23, 34.32, 30.67, 30.54, 28.58. HRMS (TOF, ES+) $C_{20}H_{30}N_2O_2$ $[M+H]^+$ calc. mass 331.2386, found 331.2387. Specific rotation $[\alpha]_D^{23}$ = +32.15° (c = 0.933, $CHCl_3$).



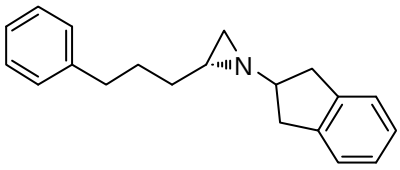
(*R*,*Z*)-1-benzyl-2-(oct-5-en-1-yl) aziridine (1.131)

The compound was prepared according to the two-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (146.0 mg, 60%), which was determined to have an ee of 96% by chiral HPLC analysis using the (2*R*,5*R*)-2,5-diphenylpyrrolidine catalyst (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 5.2 min, t_R (minor) = 4.7 min). When the compound was prepared using the (2*S*,5*S*)-2,5-diphenylpyrrolidine catalyst, the product had an ee of 94% (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 4.7 min, t_R (minor) = 5.3 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.37-7.29 (m, 4H); 7.28-7.23 (m, 1H); 5.39-5.23 (m, 2H); 3.49 (d, J = 13.25, 1H); 3.32 (d, J = 13.25, 1H); 2.06-1.93 (m, 4H); 1.61 (d, J = 3.06 Hz, 1H); 1.49-1.24 (m, 8H); 0.94 (t, J = 7.54 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.61, 131.79, 129.23, 128.44, 128.31, 127.10, 65.19, 39.88, 34.26, 33.09, 29.62, 27.22, 27.18, 20.64, 14.53. HRMS (TOF, ES+) $C_{17}H_{25}N$ $[M+H]^+$ calc. mass 244.2065, found 244.2055. Specific rotation $[\alpha]_D^{23}$ = -18.19° (c = 7.200, $CHCl_3$).



(*R*)-*tert*-butyl 4-(2-(3-phenylpropyl)aziridin-1-yl)piperidine-1-carboxylate (1.132)

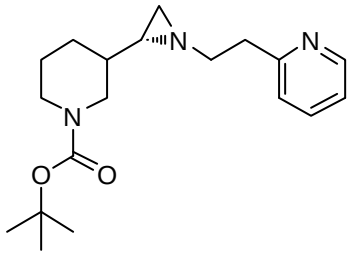
The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane with 1% Et_3N) to afford the product as a clear yellow oil (179.1 mg, 52%), which was determined to have an ee of 90% by chiral HPLC analysis (Chiralpak® IA, Isocratic 60:40 pH 9, 20mM $NH_4HCO_{3(aq)}$ /acetonitrile, t_R (major) = 68.8 min, t_R (minor) = 81.4 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.31-7.24 (m, 2H); 7.21-7.14 (m, 3H); 4.12-3.91 (br, 2H); 2.80-2.68 (m, 2H); 2.64 (t, *J* = 7.87 Hz, 2H); 1.89-1.59 (m, 5H); 1.59-1.50 (m, 3H); 1.45 (s, 9H); 1.38-1.17 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 155.03, 142.49, 128.54, 128.46, 125.88, 79.54, 66.95, 38.55, 36.01, 33.09, 32.71, 32.18, 31.61, 29.89, 28.58. HRMS (TOF, ES+) $C_{21}H_{32}N_2O_2$ $[M+H]^+$ calc. mass 345.2542, found 345.2537. Specific rotation $[\alpha]_D^{23}$ = +3.08° (c = 7.467, $CHCl_3$).



(*R*)-1-(2,3-dihydro-1H-inden-2-yl)-2-(3-phenylpropyl) aziridine (1.133)

The product was prepared according to the one-pot procedure and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a dark brown oil (155.3 mg, 56%), which was determined to have an ee of 92% by chiral HPLC analysis (Chiralcel®

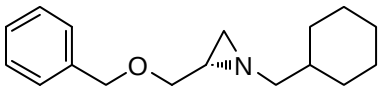
OD-Cl (Cellulose-2), 4% EtOH/hexane, t_R (major) = 6.0 min, t_R (minor) = 5.3 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.31-7.24 (m, 2H); 7.22-7.15 (m, 5H); 7.15-7.09 (m, 2H); 3.11-2.94 (m, 4H); 2.65 (t, *J* = 7.97 Hz, 2H); 2.32 (p, *J* = 6.12 Hz, 1H); 1.92-1.68 (m, 2H); 1.56 (d, *J* = 3.32 Hz, 1H); 1.54-1.40 (m, 2H); 1.39-1.28 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 142.58, 141.87, 141.84, 128.58, 128.46, 126.54, 126.50, 125.87, 124.92, 124.75, 71.21, 39.88, 39.38, 35.99, 33.44, 32.95, 29.87. HRMS (TOF, ES+) $C_{20}H_{23}N$ $[M+H]^+$ calc. mass 278.1909, found 278.1906. Specific rotation $[\alpha]_D^{23}$ = +0.42° (c = 7.067, $CHCl_3$).



tert-butyl 3-((*R*)-1-(2-(pyridin-2-yl)ethyl)aziridin-2-yl) piperidine-1-carboxylate (1.134)

The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane with 1% Et_3N followed by 1:1 MeOH/CH_2Cl_2 with 0.1% Et_3N) to afford the product as an orange oil (175.7 mg, 53%), which was determined to have an ee of 77% by chiral HPLC analysis using the (2R,5R)-2,5-diphenylpyrrolidine catalyst (Chiralcel® OD, Isocratic 5% IPA/hexane, t_R (major) = 15.1 min, t_R (minor) = 23.0 min). When the compound was prepared using the (2*S*,5*S*)-2,5-diphenylpyrrolidine catalyst, the product had an ee of 74% (Chiralcel® OD, Isocratic 2% IPA/hexane, t_R (major) = 15.7 min, t_R (minor) = 21.9 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 8.50 (d, *J* = 4.63 Hz, 1H); 7.58 (td, J_1 = 1.66 Hz, J_2 = 7.68 Hz, 1H);

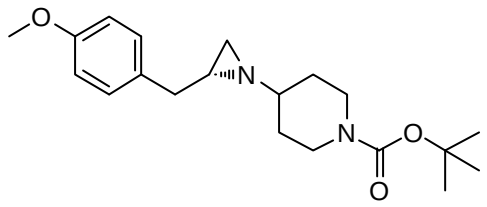
7.19 (d, *J* = 7.83 Hz, 1H); 7.10 (m, 1H); 4.23-3.96 (br, 2H); 3.10-2.94 (m, 2H); 2.82-2.72 (m, 1H); 2.71-2.55 (br, 2H); 2.53-2.43 (m, 1H); 1.81 (d, *J* = 12.69, 1H); 1.64-1.54 (m, 2H); 1.45 (s, 9H); 1.31-1.14 (m, 4H); 1.08-0.96 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 159.93, 155.01, 149.42, 136.50, 123.45, 121.42, 79.42, 61.14, 44.36, 39.72, 38.89, 32.97, 30.39, 29.46, 28.60. HRMS (TOF, ES+) $C_{19}H_{29}N_3O_2$ $[M+H]^+$ calc. mass 332.2338, found 332.2336 $[M+H\text{-}Boc]^+$ calc. mass 232.1814, found 232.1808. (*R*)-enantiomer specific rotation $[\alpha]_D^{23}$ = -9.58° (c = 5.533, $CHCl_3$). (*S*)-enantiomer specific rotation $[\alpha]_D^{23}$ = +8.24° (c = 6.800, $CHCl_3$).



(*S*)-2-((benzyloxy)methyl)-1-(cyclohexylmethyl) aziridine (1.135)

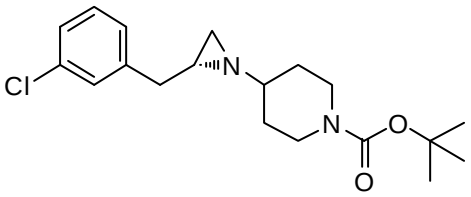
The product was prepared according to the one-pot procedure using (*S*)-5-(pyrrolidin-2-yl)-1H-tetrazole as the catalyst and purified by silica chromatography (4:1 EtOAc/hexane) to afford the product as a clear yellow oil (103.8 mg, 56%), which was determined to have an ee of 56% by SFC analysis (Chiralpak® IA, 15% IPA/CO_2, t_R (major) = 1.5 min, t_R (minor) = 1.3 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.28-7.22 (m, 4H); 7.21-7.16 (m, 1H); 4.47 (q, *J* = 11.94 Hz, 2H); 3.40 (dd, J_1 = 5.18 Hz, J_2 = 10.73 Hz, 1H); 3.34 (dd, J_1 = 6.04 Hz, J_2 = 10.36 Hz, 1H); 2.08 (dd, J_1 = 7.44 Hz, J_2 = 11.80 Hz, 1H); 1.97 (dd, J_1 = 6.16 Hz, J_2 = 11.71 Hz, 1H); 1.85-1.77 (m, 1H); 1.75-1.67 (m, 1H); 1.66-1.44 (m, 6H); 1.23-1.03 (m, 4H); 0.92-0.78 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 138.48, 128.45, 127.74, 127.65, 73.11, 72.87, 68.16, 38.85, 38.30, 32.02, 31.71, 31.68, 26.73, 26.18. HRMS (TOF, ES+) $C_{17}H_{25}NO$ $[M+H]^+$ calc.

mass 260.2014, found 260.2014. Specific rotation $[\alpha]_D^{23}$ = +32.96° (c = 4.733, $CHCl_3$). Specific rotation $[\alpha]_D^{23}$ = +8.27° (c = 6.533, $CHCl_3$).



(*R*)-tert-butyl 4-(2-(4-methoxybenzyl)aziridin-1-yl) piperidine-1-carboxylate (1.136)

The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane) to afford the product as a clear, yellow oil (180.1 mg, 52%), which was determined to have an ee of 92% by chiral HPLC analysis (Chiralpak® IA, Isocratic 60:40 pH 9, 20mM $NH_4HCO_{3(aq)}$ /acetonitrile, t_R (major) = 28.1 min, t_R (minor) = 31.8 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.17 (d, *J* = 8.48 Hz, 2H); 6.85 (d, *J* = 8.48 Hz, 2H); 4.05-3.85 (br, 2H); 3.80 (s, 3H); 2.84-2.72 (m, 1H); 2.68 (dd, J_1 = 5.15 Hz, J_2 = 14.21 Hz, 2H); 2.53 (dd, J_1 = 7.34 Hz, J_2 = 14.21 Hz, 1H); 1.77-1.69 (m, 1H); 1.67 (d, *J* = 3.36 Hz, 1H); 1.58-1.40 (m. 3H); 1.45 (s, 9H); 1.33 (d, *J* = 6.34 Hz, 2H); 1.25-1.17 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 158.25, 155.02, 132.08, 129.86, 113.90, 79.50, 66.83, 55.38, 40.58, 38.98, 32.61, 31.98, 31.48, 28.58. HRMS (TOF, ES+) $C_{20}H_{30}N_2O_3$ $[M+H]^+$ calc. mass 347.2335, found 347.2325. Specific rotation $[\alpha]_D^{23}$ = +33.20° (c = 3.133, $CHCl_3$).



(*R*)-tert-butyl 4-(2-(3-chlorobenzyl)aziridin-1-yl) piperidine-1-carboxylate (1.137)

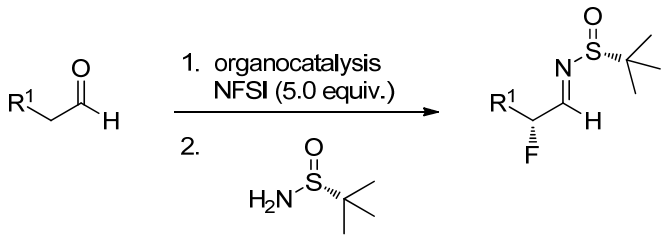
The product was prepared according to the one-pot procedure and purified by silica chromatography (1:1 EtOAc/hexane) to afford the product as a clear, orange oil (171.9 mg, 49%), which was determined to have an ee of 95% by chiral HPLC analysis (Chiralpak® IA, Isocratic 60:40 pH 9, 20mM $NH_4HCO_{3(aq)}$/acetonitrile, t_R (major) = 45.4 min, t_R (minor) = 49.4 min). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 7.28-7.18 (m, 3H); 7.15-7.11 (m, 1H); 4.04-3.79 (br, 2H); 2.87-2.66 (m, 3H); 2.55 (dd, J_1 = 7.37 Hz, J_2 = 14.08 Hz, 1H); 1.76-1.69 (m, 1H); 1.68 (d, J = 3.38 Hz, 1H); 1.62-1.52 (m, 1H); 1.52-1.38 (m, 2H); 1.45 (s, 9H); 1.36 (d, J = 6.37 Hz, 1H); 1.34-1.27 (m, 1H); 1.27-1.18 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 154.99, 141.93, 134.20, 129.75, 129.01, 127.17, 126.61, 79.51, 66.67, 39.96, 39.47, 32.65, 31.87, 31.42, 28.56. HRMS (TOF, ES+) $C_{19}H_{28}N_2O_2Cl$ $[M+H]^+$ calc. mass 351.1839, found 351.1832. Specific rotation $[\alpha]_D^{23}$ = +13.26° (c = 21.867, $CHCl_3$).

Experimental for Primary β-Fluoroamines

General Experimental

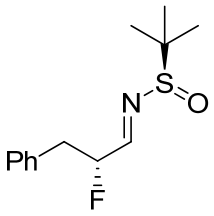
All reagents were purchased from commercial suppliers and purified as needed according to the procedures of Armarego and Chai.[1] Analytical thin-layer chromatography (TLC) was performed on 250 μm silica gel plates from Sorbent Technologies. Visualization was accomplished via UV light and/or the use of ninhydrin and potassium permanganate solutions followed by application of heat. Chromatography was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies or Silica RediSep Rf flash columns on a CombiFlash Rf automated flash chromatography system. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 (400 MHz and 100 MHz respectively). All ^{19}F NMR spectra were recorded on a Bruker DPX-300 (282 MHz). All ^{1}H and ^{13}C chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.16 ($CDCl_3$). All ^{19}F chemical shifts are reported in ppm relative to CCl_3F as an internal standard set to δ 0.00. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (*J*, in Hz), integration. Low resolution mass spectra (LCMS) were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra (HRMS) were recorded on a Waters Qtof-API-US plus Acquity system with ES as the ion source.

General Procedure for the Synthesis of β-Fluoro-*N*-Sulfinyl Aldimines



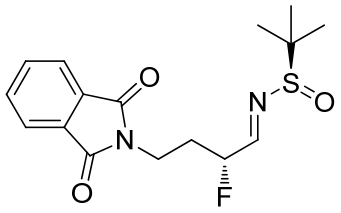
The enantioselective α-fluorination of aldehydes was accomplished using the procedure established by MacMillan and co-workers.[2] To a vial equipped with a stir bar was added (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (0.40 mmol, 0.2 eq) and *N*-fluorobenzenesulfonimide (10.0 mmol, 5.0 eq) followed by THF (9.0 mL) and *i*PrOH (1.0 mL). This solution was allowed to stir at rt until homogeneous then cooled to -20 ^{o}C. The aldehyde (2.0 mmol, 1.0 eq) was added and the reaction stirred at -20 ^{o}C for 12 h. The solution was then cooled to -78 ^{o}C, diluted with 10 mL Et_2O, and filtered through a plug of Davisil® Silica Gel, eluting with ether at -78 ^{o}C. 5.0 mL of SMe_2 was then added to the filtrate, resulting in a white precipitate. The resulting suspension was washed with sat $NaHCO_3$ (3x) and brine (1x), and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting α-fluoroaldehyde was dissolved in THF (5 mL), and $Ti(OEt)_4$ (4.0 mmol, 2.0 eq) was added followed by (*R*)-(+)-2-methyl-2-propanesulfinamide (2.0 mmol, 1.0 eq). The mixture was stirred at rt for 5 h. The reaction was then quenched by addition of an equal volume of sat $NaHCO_3$. The resulting mixture was filtered through a pad of Celite® and the filter cake rinsed with EtOAc. The filtrate was extracted with EtOAc, dried over $MgSO_4$, and concentrated. The α-fluorosulfinimines were purified by flash

column chromatography and their diastereomeric ratio determined by ^{19}F NMR experiments.



(*R*)-*N*-((*R*)-2-fluoro-3-phenylpropylidene)-2-methylpropane-2-sulfinamide (1.198)

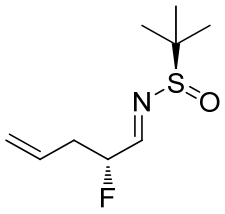
The product was prepared according to the general procedure and purified by silica chromatography (3:1 hexanes/EtOAc) to afford the product as a clear oil (72%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.17 (dd, J_1 = 3.5 Hz, J_2 = 9.4 Hz, 1H); 7.38-7.25 (m, 5H); 5.53-5.35 (dm, 1H); 3.25-3.14 (m, 2H); 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.37 (d, J = 30.1 Hz); 135.36 (d, J = 3.2 Hz); 129.71; 129.02; 127.49; 93.41 (d, J = 177.5 Hz); 57.53; 39.57 (d, J = 21.6 Hz); 22.64. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.11 (s). HRMS (TOF, ES+) $C_{13}H_{18}NOFS$ $[M+H]^+$ calc. mass 256.1171, found 256.1173.



(*R*)-*N*-((*R*)-4-(1,3-dioxoisoindolin-2-yl)-2-fluorobutylidene)-2-methylpropane-2-sulfinamide (1.199)

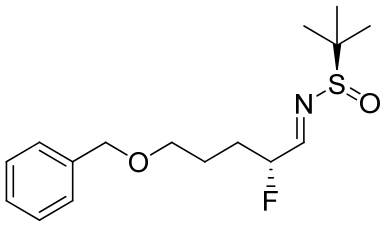
The product was prepared according to the general procedure and purified by silica chromatography (3:1 hexanes/EtOAc) to afford the product as a clear oil (67%), which

was determined to have a dr of >9:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (dd, J_1 = 3.1 Hz, J_2 = 9.8 Hz, 1H); 7.85 (m, 2H); 7.72 (m, 2H); 5.30 (dm, 1H); 3.94 (m, 2H); 2.27 (m, 2H); 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.45; 166.05 (d, J = 30.1 Hz); 134.44; 132.32; 123.71; 91.36 (d, J = 175.3 Hz); 57.71; 34.21 (d, J = 3.8 Hz); 32.03 (d, J = 20.8 Hz); 22.68. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -190.92 (s). HRMS (TOF, ES+) $C_{16}H_{19}N_2O_3FS$ $[M+H]^+$ calc. mass 339.1179, found 339.1178.



(*R*)-*N*-((*R*)-2-fluoropent-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (1.200)

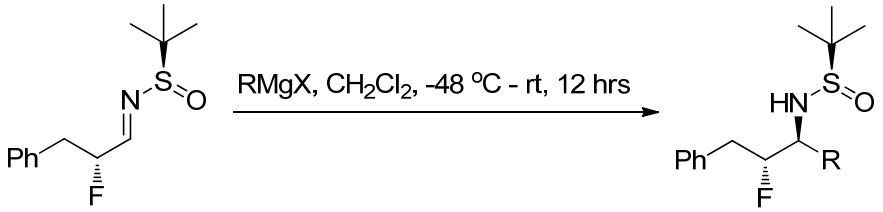
The product was prepared according to the general procedure and purified by silica chromatography (3:1 hexanes/EtOAc) to afford the product as a clear oil (68%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (dd, J_1 = 3.2 Hz, J_2 = 10.3 Hz, 1H); 5.84 (m, 1H); 5.39-4.98 (m, 3H); 2.75-2.56 (m, 2H); 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.32 (d, J = 28.5 Hz); 131.30 (d, J = 4.7 Hz); 119.86; 92.28 (d, J = 177.7 Hz); 57.64; 37.62 (d, J = 21.5 Hz); 22.76. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -189.48 (s). HRMS (TOF, ES+) $C_9H_{16}NOFS$ $[M+H]^+$ calc. mass 206.1015, found 206.1017.



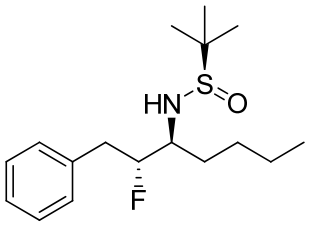
(*R*)-*N*-((*R*)-5-(benzyloxy)-2-fluoropentylidene)-2-methylpropane-2-sulfinamide (1.201)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear yellow oil (75%), which was determined to have a dr of >9:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (dd, J_1 = 3.35 Hz, J_2 = 10.33 Hz, 1H); 7.30-7.19 (m, 5H); 5.16 (dm, 1H); 4.44 (s, 2H); 3.45 (m, 2H); 2.04-1.68 (m, 4H); 1.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 199.87 (d, J = 33.9 Hz); 166.51 (d, J = 28.6 Hz); 138.37; 128.42; 127.64; 92.77 (d, J = 175.0 Hz); 72.93; 69.34; 57.26; 29.92 (d, J = 20.6 Hz); 24.78; 22.40. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -187.88 (s). HRMS (TOF, ES+) $C_{16}H_{24}NO_2FS$ $[M+H]^+$ calc. mass 314.1590, found 314.1590.

General Procedure for Grignard Addition



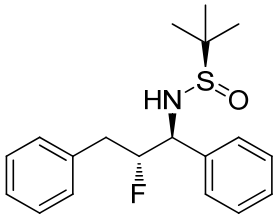
Grignard additions were done according to the general procedure by Ellman and co-workers.[3] To a solution of the *N*-*tert*-butanesulfinyl aldimine at -48 °C was added the Grignard reagent in either Et_2O or THF. The reaction stirred at -48 °C for 5 h and was then warmed to rt and stirred overnight. The reaction was quenched by the addition of sat NH_4Cl and extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash column chromatography. The diastereomeric ratio of the sulfinamide-protected primary β-fluoroamines was determined by ^{19}F NMR experiments.



(*R*)-*N*-((2*R*,3*S*)-2-fluoro-1-phenylheptan-3-yl)-2-methylpropane-2-sulfinamide (1.203)

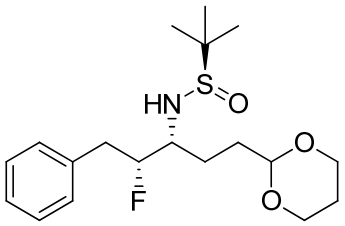
The product was prepared according to the general procedure and purified by silica chromatography (4:1–1:1 gradient EtOAc/hexane) to afford the product as a clear oil (92%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz,

$CDCl_3$) δ (ppm): 7.37-7.22 (m, 5H); 5.05 (dm, 1H); 3.57 (d, J = 9.2 Hz, 1H); 3.33 (m, 1H); 3.08 (td, J_1 = 8.6 Hz, J_2 = 14.8 Hz, 1H); 2.89 (ddd, J_1 = 4.7 Hz, J_2 = 14.5 Hz, J_3 = 31.2 Hz, 1H); 1.74-1.58 (m, 2H); 1.42-1.27 (m, 4H); 1.25 (s, 9H); 0.93 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.95 (d, J = 4.7 Hz); 129.48; 128.95; 127.09; 97.43 (d, J = 175.1 Hz); 59.86 (d, J = 20.1 Hz); 56.62; 38.13 (d, J = 21.5 Hz); 58.07 (d, J = 4.5 Hz); 28.32; 23.04; 22.68; 14.31. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.11 (s). HRMS (TOF, ES+) $C_{17}H_{28}NOFS$ $[M+H]^+$ calc. mass 314.1876, found 314.1876.



(*R*)-*N*-((1*S*,2*R*)-2-fluoro-1,3-diphenylpropyl)-2-methylpropane-2-sulfinamide (1.204)

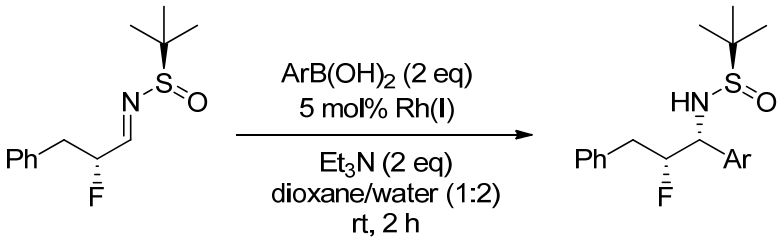
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (89%) with a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46-7.35 (m, 4H); 7.35-7.22 (m, 4H); 7.21-7.13 (d, J_1 = 7.24 Hz, 2H); 5.11 (dm, 1H); 4.51 (dm, 1H); 3.81 (d, J = 5.4 Hz, 1H); 2.87-2.69 (m, 2H); 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.56; 136.80 (d, J = 3.1 Hz); 129.30, 128.90; 128.71; 128.65; 126.94; 95.15 (d, J = 182.3 Hz); 61.72 (d, J = 19.2 Hz); 56.53; 38.30; 29.83; 22.68. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.11 (s). HRMS (TOF, ES+) $C_{19}H_{24}NOFS$ $[M+H]^+$ calc. mass 334.1641, found 334.1639.



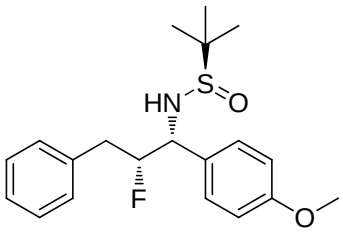
(*R*)-*N*-((2*R*,3*R*)-5-(1,3-dioxan-2-yl)-2-fluoro-1-phenylpentan-3-yl)-2-methylpropane-2-sulfinamide (1.205)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a white solid (81%) with a dr of >9:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33-7.20 (m, 5H); 5.03 (dm, *J* = 47.6 Hz, 1H); 4.54 (t, *J* = 4.3 Hz, 1H); 4.16-4.02 (m, 4H); 3.22-3.00 (m, 2H); 2.94-2.79 (m, 1H); 2.17-1.56 (m, 6H); 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 129.71; 129.32; 128.74; 126.85 (d, *J* = 8.6 Hz); 101.85 (d, *J* = 6.8 Hz); 97.23 (d, *J* = 175.9 Hz); 67.03 (d, *J* = 5.6 Hz); 59.73 (d, *J* = 7.6 Hz); 38.04 (d, *J* = 22.6 Hz); 31.54 (d, *J* = 5.70 Hz); 28.03; 25.89 (d, *J* = 3.9 Hz); 23.51; 22.88. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.11. HRMS (TOF, ES+) $C_{19}H_{30}NO_3FS$ $[M+H]^+$ calc. mass 372.2009, found 372.2006.

General Procedure for Boronic Acid Addition

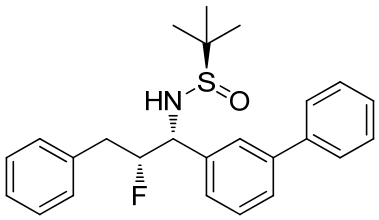


Addition of boronic acids to β-fluorosulfinimines was achieved using the methods shown by Batey and co-workers.[4] To a vial containing sulfinimine (0.25 mmol, 1.0 eq), $[Rh(COD)(MeCN)_2]BF_4$ (0.0125 mmol, 0.05 eq), and boronic acid (0.50 mmol, 2.0 eq) in dioxane (0.6 mL) was added Et_3N (0.50 mmol, 2.0 eq) and H_2O (1.2 mL). The resulting mixture was stirred at rt for 2 h. The aqueous layer was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude oil. The products were purified using flash column chromatography. The diastereomeric ratio of the sulfinamide-protected primary β-fluoroamines was determined by ^{19}F NMR experiments.



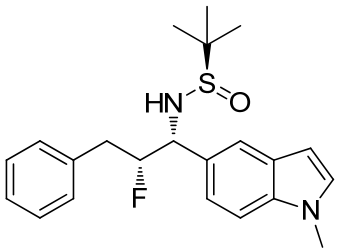
(*R*)-*N*-((1*R*,2*R*)-2-fluoro-1-(4-methoxyphenyl)-3-phenylpropyl)-2-methylpropane-2-sulfinamide (1.207)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a yellow solid (80%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.20 (m, 5H); 7.19-7.10 (m, 2H); 6.95 (d, *J* = 8.60 Hz, 2H); 5.04 (dm, 1H); 4.55-4.49 (m, 1H); 3.95 (d, *J* = 4.1 Hz, 1H); 3.86 (s, 3H); 2.85-2.69 (m, 2H); 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.64 (d, *J* = 32.2 Hz); 136.35; 129.97 (d, *J* = 22.47 Hz); 129.20 (d, *J* = 14.2 Hz); 128.51; 126.69 (d, *J* = 7.49 Hz); 114.23; 113.83; 96.45 (d, *J* = 180.6 Hz); 61.07 (d, *J* = 19.3 Hz); 58.34; 55.49 (d, *J* = 63.8 Hz); 37.60 (d, *J* = 21.0 Hz); 29.62; 22.47. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -184.63 (s). HRMS (TOF, ES+) $C_{20}H_{26}NO_2FS$ $[M+H]^+$ calc. mass 364.1747, found 364.1748.



(*R*)-*N*-((1*R*,2*R*)-1-([1,1'-biphenyl]-3-yl)-2-fluoro-3-phenylpropyl)-2-methylpropane-2-sulfinamide (1.208)

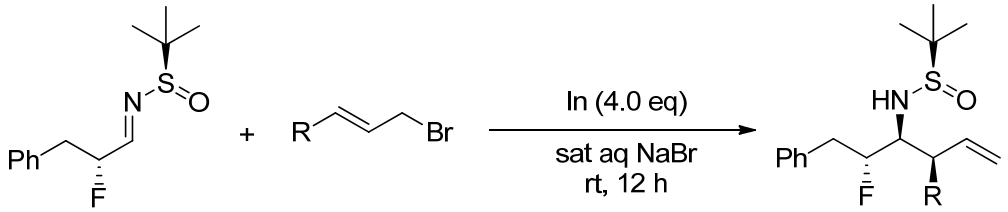
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (87%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65-7.56 (m, 4H); 7.52-7.45 (m, 3H); 7.43-7.22 (m, 5H); 7.17-7.13 (m, 2H); 4.90 (dm, 1H); 4.64 (m, 1H); 4.20 (s, 1H); 2.91 (d, J = 5.8 Hz, 1H); 2.88-2.82 (m, 1H); 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 141.99; 140.66; 137.88 (d, J = 5.80 Hz); 136.42; 129.50; 129.47; 129.01; 128.62; 127.75; 127.68; 127.65; 127.60; 127.25; 126.94; 97.12 (d, J = 180.0 Hz); 61.75 (d, J = 18.5 Hz); 55.84; 37.96 (d, J = 20.0 Hz); 22.68. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -185.00 (s). HRMS (TOF, ES+) $C_{25}H_{28}NOFS$ $[M+H]^+$ calc. mass 410.1954, found 410.1953.



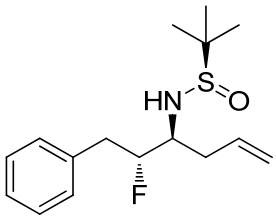
(*R*)-*N*-((1*R*,2*R*)-2-fluoro-1-(1-methyl-1H-indol-5-yl)-3-phenylpropyl)-2-methylpropane-2-sulfinamide (1.209)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a dark brown oil (65%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (s, 1H); 7.40-7.08 (m, 8H); 6.53 (d, *J* = 3.1 Hz, 1H); 4.91 (dm, *J* = 49.3 Hz, 1H); 4.68 (t, *J* = 8.7 Hz, 1H); 3.84 (s, 3H); 2.86-2.68 (m, 2H); 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.74; 129.53; 129.29; 129.15; 128.56; 128.43; 128.35; 128.26; 126.52; 121.78; 109.68; 101.19; 97.49 (d, *J* = 177.1 Hz); 61.89 (d, *J* = 18.3 Hz); 55.29; 37.73 (d, *J* = 20.3 Hz); 32.87; 22.50. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -184.26 (s). HRMS (TOF, ES+) $C_{22}H_{27}N_2OFS$ $[M+H]^+$ calc. mass 387.1906, found 387.1908.

General Procedure for In-Mediated Allylation



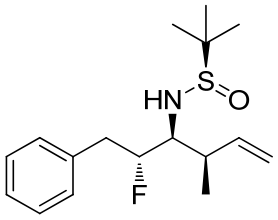
In-mediated allylation was done according to procedures published by Lin and co-workers.[5] To a vial containing sulfinimine (0.25 mmol, 1.0 eq) and indium powder (1.0 mmol, 4.0 eq) was added saturated aqueous NaBr solution (5 mL) followed by the allylic bromide (1.0 mmol, 4.0 eq). The resulting suspension stirred at rt for 12 h. The reaction was quenched by the addition of 15 mL of sat aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x), dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography to afford the allylation product. The diastereomeric ratio of the sulfinamide-protected primary β-fluoroamines was determined by ^{19}F NMR experiments.



(*R*)-*N*-((2*R*,3*S*)-2-fluoro-1-phenylhex-5-en-3-yl)-2-methylpropane-2-sulfinamide (1.211)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (90%), which

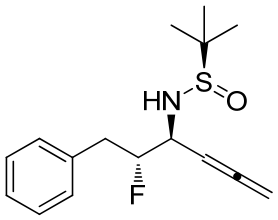
was determined to have a dr of >9:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (s, 2H); 7.31 (s, 2H); 7.27-7.21 (m, 1H); 5.79-5.67 (m, 1H); 5.11 (s, 1H); 5.07 (d, *J* = 2.96 Hz, 1H); 4.76 (dtd, J_1 = 2.60 Hz, J_2 = 6.9 Hz, J_3 = 46.5 Hz, 1H); 3.66 (d, *J* = 7.5 Hz, 1H); 3.47-3.33 (m, 1H); 3.21-3.13 (m, 1H); 3.11 (d, *J* = 6.9 Hz, 1H); 2.50-2.31 (m, 2H); 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.68; 133.97; 129.67; 128.77; 126.87; 118.54; 95.14 (d, *J* = 175.8 Hz); 57.83 (d, *J* = 19.2 Hz); 56.57; 38.21 (d, *J* = 2.5 Hz); 37.78 (d, *J* = 21.6 Hz); 22.93. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.35 (s). HRMS (TOF, ES+) $C_{16}H_{24}NOFS$ $[M+H]^+$ calc. mass 298.1641, found 298.1642.



(*R*)-N-((2*R*,3*S*,4*R*)-2-fluoro-4-methyl-1-phenylhex-5-en-3-yl)-2-methylpropane-2-sulfinamide (1.212)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (82%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.15 (m, 5H); 5.97-5.86 (m, 1H); 5.85-5.55 (m, 1H); 5.09-4.98 (m, 1H); 4.62-4.43 (dm, *J* = 47.7 Hz, 1H); 3.52-2.78 (m, 4H); 1.29 (s, 9H); 1.05 (dd, J_1 = 4.2 Hz, J_2 = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.24; 137.48; 129.42; 128.68; 126.88; 118.14; 94.96 (d, *J* = 178.7 Hz); 62.23 (d, *J* = 22.9 Hz); 60.35; 38.24 (d, *J* = 20.8 Hz); 36.62 (d, *J* = 4.4 Hz); 23.04; 16.40. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm):

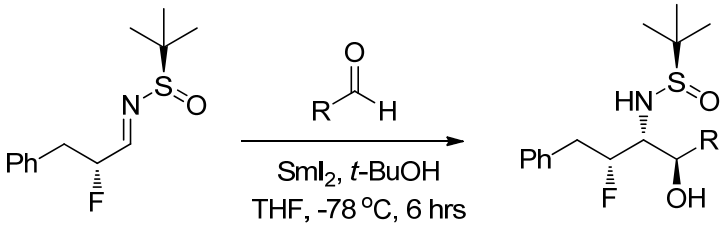
-184.09 (s). HRMS (TOF, ES+) $C_{17}H_{26}NOFS$ $[M+H]^+$ calc. mass 312.1797, found 312.1798.



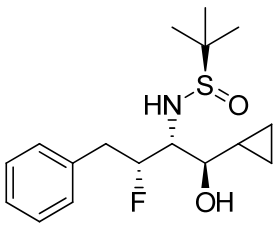
(*R*)-*N*-((2*R*,3*S*)-2-fluoro-1-phenylhexa-4,5-dien-3-yl)-2-methylpropane-2-sulfinamide (1.213)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a yellow oil (78%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38-7.18 (m, 5H); 5.48-5.31 (m, 1H); 5.05-4.97 (m, 2H); 4.82-4.63 (dm, J = 47.2 Hz, 1H); 3.86 (d, J = 9.06 Hz,1H); 3.25-3.08 (m, 1H); 3.02-2.86 (m,1H); 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 208.62; 136.62; 129.35; 128.47; 126.76; 93.15 (d, J = 179.0 Hz); 88.32 (d, J = 7.1 Hz); 72.31; 57.47; 56.29 (d, J = 25.7 Hz); 37.68 (d, J = 20.4 Hz); 22.62. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -187.09 (s). HRMS (TOF, ES+) $C_{16}H_{22}NOFS$ $[M+H]^+$ calc. mass 296.1484, found 296.1483.

General Procedure for the SmI_2-Induced Reductive Aldehyde Coupling



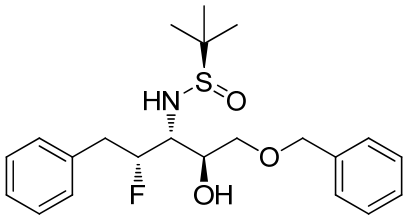
Reductive coupling of aldehydes was accomplished using the procedure established by Lu and Xin.[6] To a flame-dried flask under an argon atmosphere was added a solution of 0.1M SmI_2 in THF (1.0 mmol, 2.0 eq). The solution was cooled to -78 ^oC and a mixture of sulfinimine (0.5 mmol, 1.0 eq), *t*-butyl alcohol (1.0 mmol, 2.0 eq), and aldehyde (0.75 mmol, 1.5 eq) in 6 mL of THF was added dropwise. The reaction was stirred at -78 ^oC for 4-6 h. The reaction was quenched with the addition of 5 mL of sat aq $Na_2S_2O_3$ followed by extraction with EtOAc (3x) and purification by reverse-phase column chromatography to afford the product. The diastereomeric ratio of the sulfinamide-protected primary β-fluoroamines was determined by ^{19}F NMR experiments.



(*R*)-*N*-((1*R*,2*R*,3*R*)-1-cyclopropyl-3-fluoro-1-hydroxy-4-phenylbutan-2-yl)-2-methylpropane-2-sulfinamide (1.215)

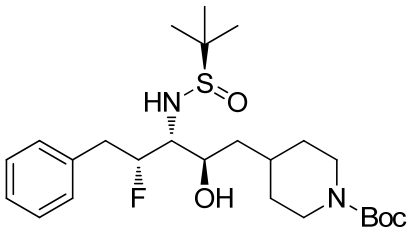
The product was prepared according to the general procedure and purified by silica

chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (87%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38-7.17 (m, 5H); 5.19 (dm, J = 46.7 Hz, 1H); 4.07 (dd, J_1 = 1.8 Hz, J_2 = 8.2 Hz, 1H); 3.44-3.02 (m, 5H); 1.32 (s, 9H); 0.62-0.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.65 (d, J = 7.32 Hz); 129.69; 128.75; 126.86; 93.22 (d, J = 175.6 Hz); 62.23 (d, J = 16.8 Hz); 56.72; 38.3; 22.99; 14.68; 3.81; 21.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -194.35 (s). HRMS (TOF, ES+) $C_{17}H_{26}NO_2FS$ $[M+H]^+$ calc. mass 328.1747, found 328.1749.



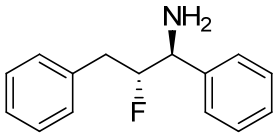
(*R*)-*N*-((2*S*,3*R*,4*R*)-1-(benzyloxy)-4-fluoro-2-hydroxy-5-phenylpentan-3-yl)-2-methylpropane-2-sulfinamide (1.216)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (83%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44-7.27 (m, 10H); 4.63 (dm, 1H); 4.55 (s, 2H); 3.97-3.93 (m, 2H); 3.54 (m, 1H); 2.97-2.60 (m, 3H); 1.55 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.58; 137.72; 129.29; 129.19; 128.47 (d, J = 3.2 Hz); 127.83; 127.75; 126.57; 93.54 (d, J = 169.7 Hz); 73.43; 71.53; 70.81; 55.90 (d, J = 21.7 Hz); 55.52; 55.33; 38.18 (d, J = 22.0 Hz); 21.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -189.07 (s). HRMS (TOF, ES+) $C_{13}H_{19}NOFS$ $[M+H]^+$ calc. mass 408.1930, found 408.1931.



tert-butyl-4-((2*R*,3*R*,4*R*)-3-((*R*)-1,1-dimethylethylsulfinamido)-4-fluoro-2-hydroxy-5-phenylpentyl)piperidine-1-carboxylate (1.217)

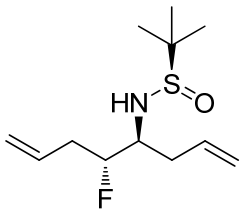
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (80%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.16 (m, 5H); 4.84 (dm, J = 47.9 Hz, 1H); 4.07 (br, 1H); 3.67 (m, 1H); 3.16-2.85 (m, 3H); 2.77-2.58 (m, 4H); 1.83-1.51 (m, 5H); 1.45 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.81; 136.63; 129.18; 128.58; 126.75; 94.14 (d, J = 173.0 Hz); 79.17; 64.23 (d, J = 22.1 Hz); 62.57; 57.43; 39.57; 38.44 (d, J = 20.1 Hz); 33.25; 32.32; 31.19; 28.39. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.40 (s). HRMS (TOF, ES+) $C_{25}H_{41}N_2O_4FS$ $[M+H]^+$ calc. mass 485.2771, found 485.2771.



(1*S*,2*R*)-2-fluoro-1,3-diphenylpropan-1-amine (1.218)

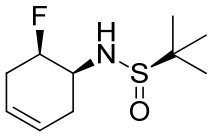
The product was prepared by treatment of (*R*)-*N*-((*1*S,2*R*)-2-fluoro-1,3-diphenylpropyl)-2-methylpropane-2-sulfinamide with excess HCl in dioxane to afford analytically pure product as a yellow solid (92%) which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42-7.11 (m, 10H); 4.91 (dm, J = 47.7

Hz, 1H); 4.14 (d, J = 15.7 Hz, 1H); 2.97-2.67 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 140.80; 137.42 (d, J = 2.2 Hz); 129.38; 128.75; 128.59; 127.92; 127.71; 126.70; 97.49 (d, J = 177.8 Hz); 58.59 (d, J = 20.9 Hz); 37.21 (d, J = 21.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -186.59 (s). HRMS (TOF, ES+) $C_{15}H_{16}NF$ $[M+H]^+$ calc. mass 230.1345, found 230.1346.



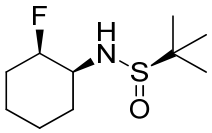
(*R*)-*N*-((4*S*,5*R*)-5-fluoroocta-1,7-dien-4-yl)-2-methylpropane-2-sulfinamide (1.227)

The product was prepared according to the general procedure and purified by silica chromatography (4:1–1:1 gradient EtOAc/hexane) to afford the product as a clear oil (90%), which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.90-5.77 (m, 2H); 5.27-5.11 (m, 4H); 4.54-4.36 (dm, 1H); 3.54-3.38 (m, 2H); 2.53-2.38 (m, 4H); 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 133.51; 133.08 (d, J = 4.6 Hz); 120.49; 118.71; 93.97 (d, J = 177.7 Hz); 57.25 (d, J = 23.2 Hz); 56.52; 36.18 (d, J = 21.5 Hz); 35.57 (d, J = 4.6 Hz); 22.95. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -189.74 (s). HRMS (TOF, ES+) $C_{12}H_{22}NOFS$ $[M+H]^+$ calc. mass 248.1484, found 248.1483.



(*R*)-*N*-((1*S*,6*R*)-6-fluorocyclohex-3-en-1-yl)-2-methylpropane-2-sulfinamide (1.228)

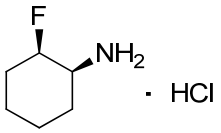
The product was prepared by treatment of (*R*)-*N*-((*4S*,*5R*)-5-fluoroocta-1,7-dien-4-yl)-2-methylpropane-2-sulfinamide with Grubbs 2nd generation catalyst to afford the cyclized product in 85% yield as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.67 (m, 1H); 5.57 (m, 1H); 4.84 (dm, 1H); 3.54 (m, 1H); 3.36 (d, *J* = 8.52 Hz, 1H); 2.61-2.25 (m, 4H); 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 124.83; 122.48; 90.37 (d, *J* = 174.13 Hz); 56.18; 54.54 (d, *J* = 19.17 Hz); 30.91 (d, *J* = 22.10 Hz); 30.41 (d, *J* = 6.03 Hz); 22.71. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -193.57 (s). HRMS (TOF, ES+) $C_{10}H_{18}NOFS$ $[M+H]^+$ calc. mass 220.1171, found 220.1171.



(*R*)-*N*-((1*S*,2*R*)-2-fluorocyclohexyl)-2-methylpropane-2-sulfinamide (1.229)

The product was prepared by treatment of (*R*)-*N*-((1*S*,6*R*)-6-fluorocyclohex-3-en-1-yl)-2-methylpropane-2-sulfinamide with 10% Pd/C in a H_2 atmosphere to afford the product as an off-white solid (95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.29 (dm, *J* = 49.2 Hz); 3.33-3.22 (m, 2H); 2.20-2.07 (m, 2H); 1.83-1.65 (m, 2H); 1.57-1.37 (m, 2H); 1.36-1.26 (m, 2H); 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 95.19 (d, *J* = 177.7 Hz); 59.45 (d, *J* = 17.0 Hz); 56.11; 32.32; 31.25 (d, *J* = 17.2 Hz); 24.33; 23.38 (d, *J* = 10.8 Hz); 22.65. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -175.84 (s) HRMS (TOF, ES+)

$C_{10}H_{20}NOFS$ $[M+H]^+$ calc. mass 222.1328, found 222.1326.



(1*S*,2*R*)-2-fluorocyclohexanamine hydrochloride (1.230)

The product was prepared by treatment of (*R*)-*N*-((1*S*,2*R*)-2-fluorocyclohexyl)-2-methylpropane-2-sulfinamide with excess HCl in dioxane to afford analytically pure product as an off-white solid (98%) which was determined to have a dr of >20:1 by ^{19}F NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.78 (br s, 1H); 3.83-3.61 (m, 1H); 3.56–3.07 (br s, 1H); 2.68-0.70 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 55.39; 30.78; 29.60; 28.71; 23.52; 22.91. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -175.98 (br s). HRMS (TOF, ES+) $C_6H_{12}NF$ $[M+H]^+$ calc. mass 118.0954, found 118.0954.

References:

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2. Beeson, T. D.; MacMillan, D. W. C.; *J. Am. Chem. Soc.*, **2005**, *127* (24), 8826-8828.
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CHAPTER 2

RAPID GENERAL ACCESS TO AZABICYCLIC RING SYSTEMS AND THE TOTAL SYNTHESIS OF STEMAPHYLLINE

2.1 Introduction

Azabicyclic ring systems are common structural subunits present in many classes of natural products and serve as important scaffolds in many biologically active compounds.[1-8] Pyrrolizidine, indolizidine, pyrrolo[1,2-α]azepine, and pyrrolo[1,2-α]azocine are examples of compounds containing an azabicyclic ring system (Figure 2.1.1). In general, synthetic approaches to azabicyclic ring systems are limited. The existing strategies for their construction rely on Staudinger-aza-Wittig,[9] 7-*exo*-tet-cyclizations,[10,11] [5+2], [4+2], and [2+2+2] cycloadditions,[12] ring-closing metathesis,[13] Mitsunobu,[14] and rearrangement chemistry[15,16]. For the larger azabicyclic ring systems, routes are rare and those reported lack stereocontrol.[8,17] Due to the importance of azabicyclic skeletons, the synthesis of these ring systems constitutes an area of current interest among synthetic chemists.

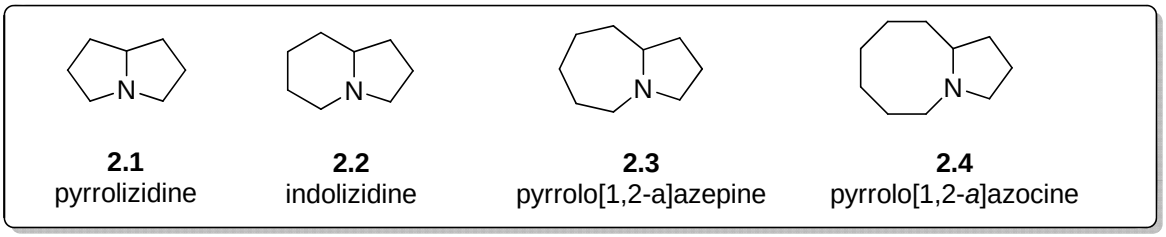


Figure 2.1.1 Azabicylic ring systems.

2.2 *Stemona* Alkaloids

Plants in the family Stemonaceae, which includes the genera *Stemona, Croomia, Stichoneuron, and Pentastemona*, are known in the Thai, Chinese, and Vietnamese vernacular as "Non Tai yak", "Bai Bu", and "Bach Bo" respectively and are often sold in local markets and herb shops for medicinal purposes.[18] There are many species within this family under multiple genera, but all are commonly referred to by the same common names, which has led to many far-reaching conclusions about their biological activity in the chemical and pharmaceutical literature. The extracts of these plants, found primarily in Asia, Malaysia, and northern Australia, have been used in traditional folk medicine in East Asia for centuries.[19] Many secondary metabolites from plants in this family possess significant biological activities and extracts from their roots have been used to treat respiratory diseases (pulmonary tuberculosis, bronchitis), parasitic infections, and as domestic insecticides.[8g]

In the period from 1975-1998, there were thirty-five known unique *Stemona* alkaloids reported in the literature.[1g] Today, the *Stemona* alkaloids represent a class of approximately 140 biogenetically intriguing and structurally unique natural products (Figure 2.2.1).[1h]

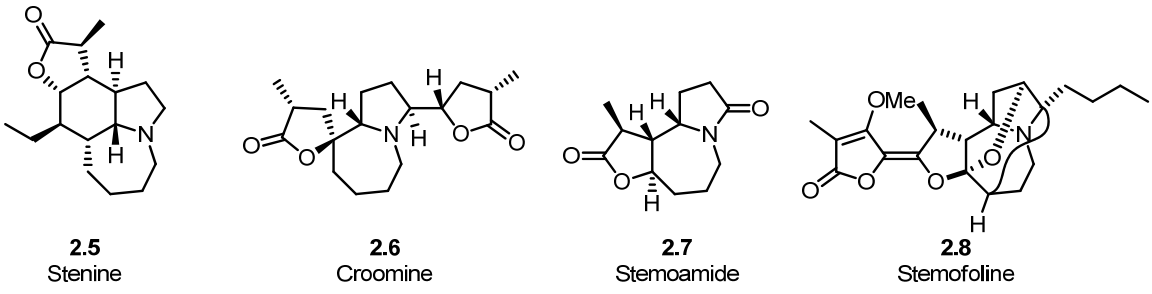


Figure 2.2.1 Selected examples of *Stemona* alkaloids.

The *Stemona* alkaloids are all polycyclic and most of them possess a central pyrrolo[1,2-*a*]azepine core while a few contain a pyrido[1,2-α]azepine core. Pilli and co-workers have classified the *Stemona* alkaloids into 8 major groups based on common structural motifs and named for the most representative member within each group. These groups, shown in figure 2.2.2, include the stenine, stemoamide, tuberostemospirone, stemonamine, stemofoline, stemocurtisine, and parvistemoline groups, as well as a miscellaneous group, which includes some *Stemona* alkaloids with a cleaved pyrrolo[1,2-*a*]azepine ring system.[1h]

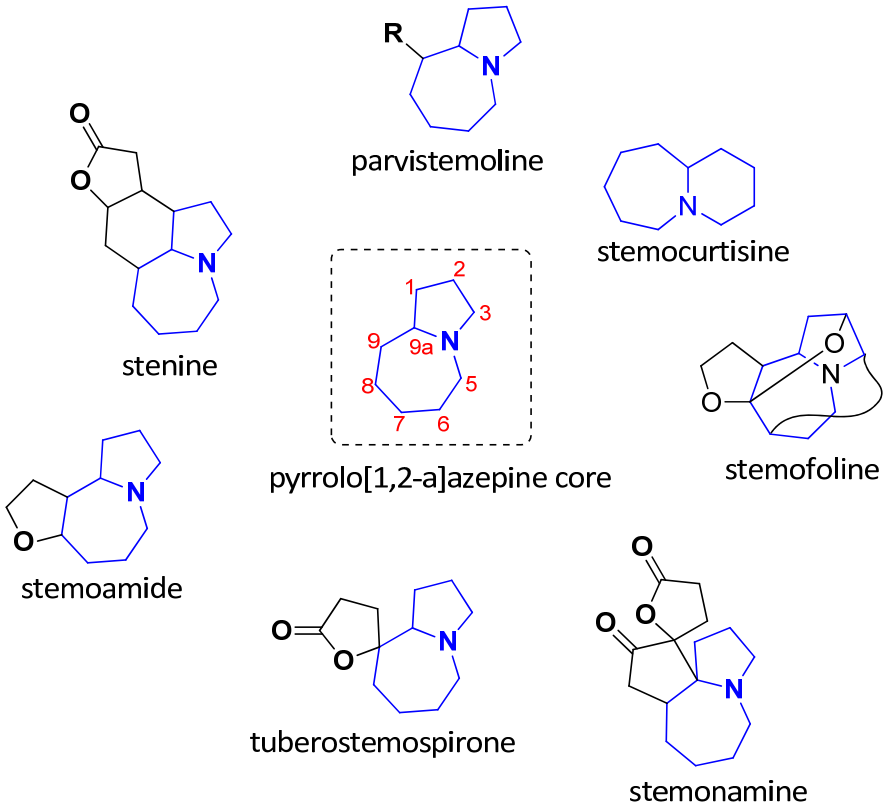


Figure 2.2.2 *Stemona* alkaloid groups and their characteristic structural features.

In 2006, Greger and co-workers proposed a different classification system for the *Stemona* alkaloids based on structural considerations and their various distributions in different species. The three skeletal types include the stichoneurine- (also known as tuberostemonine-), protostemonine-, and croomine-type alkaloids. As shown in Figure 2.2.3, the three types can be distinguished by the different carbon chains attached to C-9 of the pyrroloazepine core.[19]

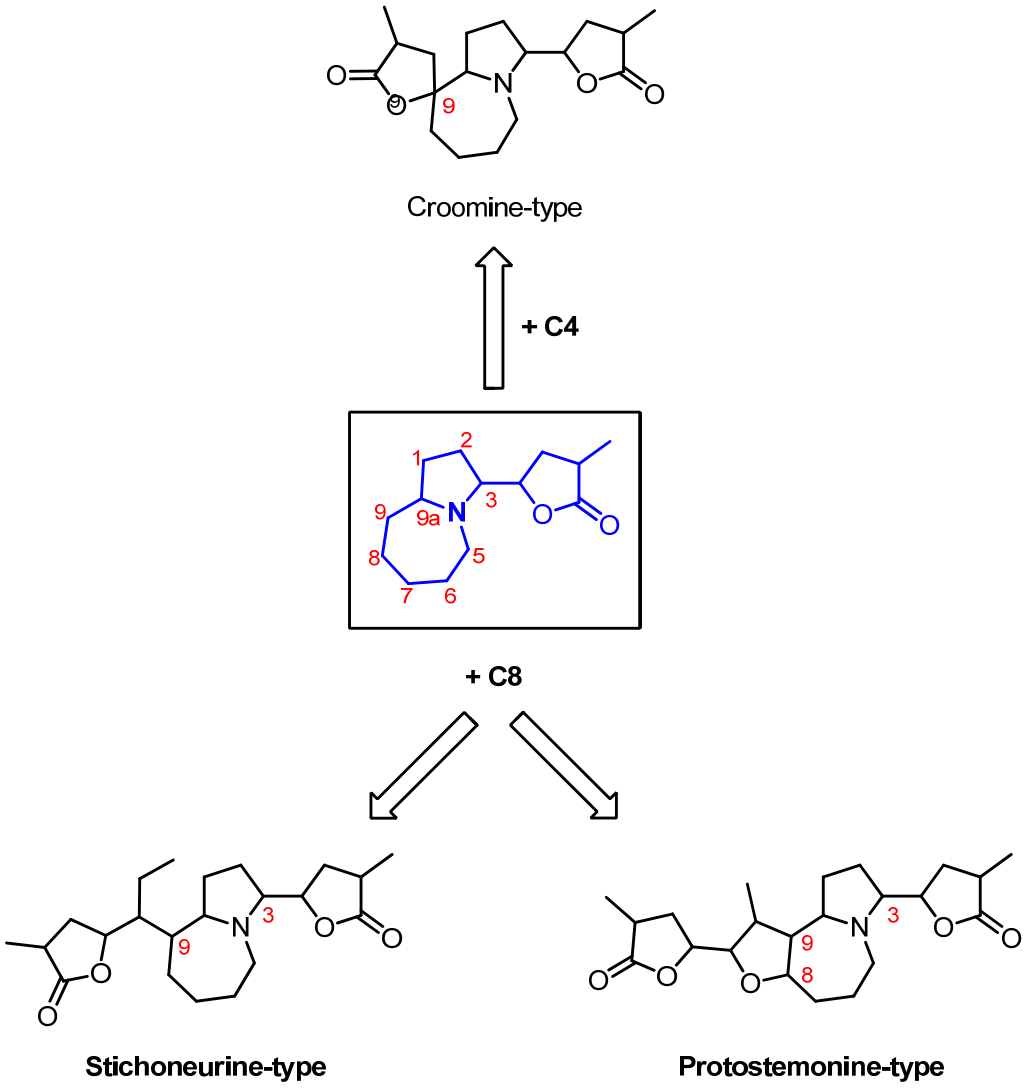


Figure 2.2.3 Greger classification of *Stemona* alkaloids.

In the stichoneurine- and protostemonine-types the C-9 chains usually contain eight carbon atoms forming a terminal lactone ring, but differ from each other in the branching pattern. In the croomine-type, the chain consists of only four carbons forming a lactone ring directly attached to C-9 in a spiro system. The first two types contain the majority of compounds. Due to their unique structural motifs, stereochemical arrangements and interesting biological activities, the synthesis of *Stemona* alkaloids has attracted considerable interest from the synthetic community.

2.3 Biosynthesis of *Stemona* Alkaloids

The biosynthetic origin of the *Stemona* alkaloids is presently not well understood. In addition to the characteristic pyrrolo[1,2-α]azepine core, *Stemona* alkaloids typically feature an eight-carbon unit attached at C-9 (as described above) and, in most cases, a further substituent at C-3. The substituent at C-9 of the azabicyclic core shows many variations which originate from cleaving and forming bonds to different types of polycyclic A/B ring systems including a series of spiro compounds, which includes the tuberostemospirone class of *Stemona* alkaloids. In 2004, Seger and co-workers proposed that the common branching at C-9 and C-3 could be of terpenoid origin, leaving C_3NC_4 as an additionally required unit to construct the pyrroloazepine system (Figure 2.3.1).[1i] The broad variability at C-9 can be explained by the typical Wagner-Meerwein-type carbon skeleton rearrangements common in terpenoid compounds.

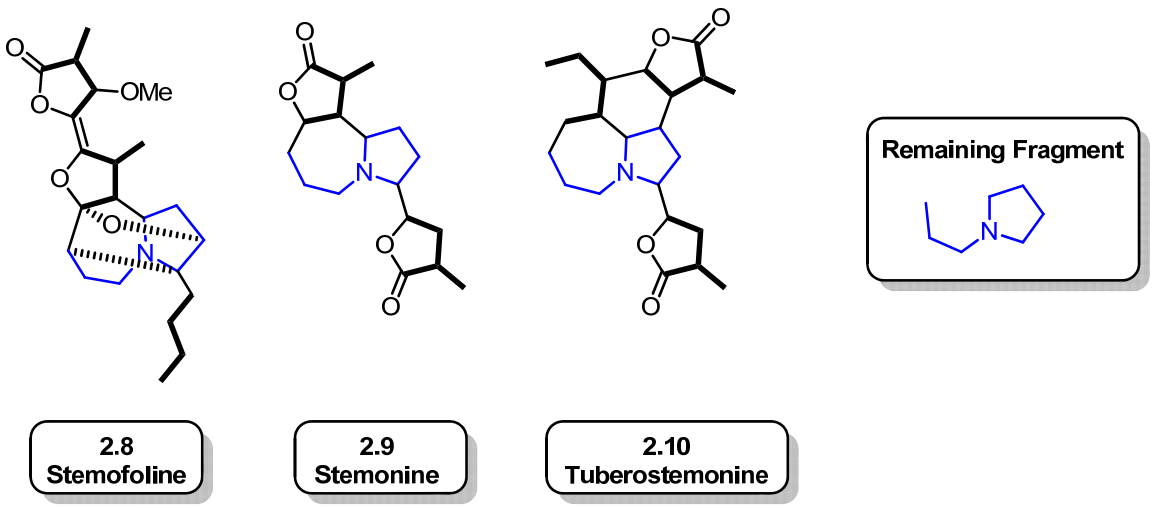


Figure 2.3.1 Terpene origin of *Stemona* alkaloid substituents.

The formation of the core could follow a pathway similar to that of the pyrrolizidine alkaloids, which utilize a homospermidine (C_4NC_4) precursor. In the biosynthesis of pyrrolizidines, the required C_4NC_4 building block originates from spermidine (C_3NC_4) and putrescine (NC_4N) via homospermidine synthase. Spermidine is biosynthesized from putrescine (which is derived from ornithine) and a C_3 unit supplied by *S*-adenosyl-L-methionine. The first step in cyclization to a pyrrolizidine system takes place through an oxidative deamination of the terminal CH_2NH_2 groups to terminal aldehydes. The resulting aldehydes cyclize to the monocyclic iminium ion, followed by formation of the hexahydropyrrolizidine-1-carbaldehyde (Figure 2.3.2).[1i]

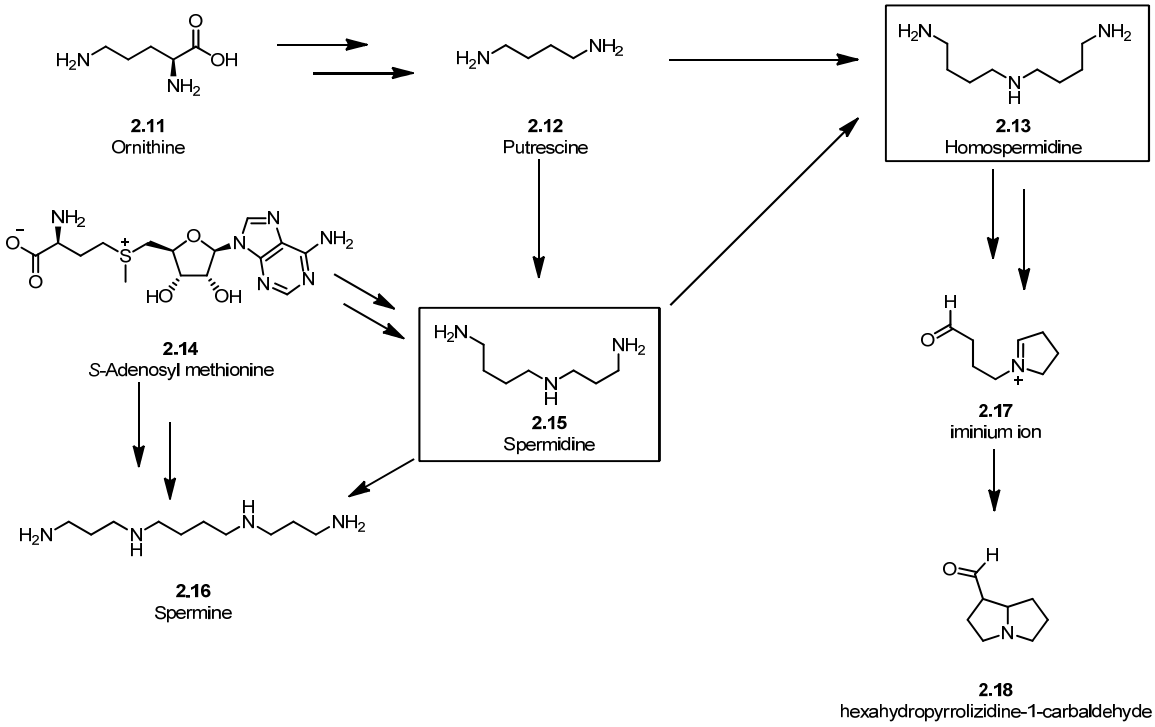


Figure 2.3.2 Biosynthetic origin of pyrrolizidine alkaloids

An analogous biosynthesis can be formulated for the pyrrolo[1,2-α]azepine system. This is shown in the proposed biosynthesis of stemofoline. The first cyclization to the iminium ion would be similar to that in the pyrrolizidine biosynthesis. The second cyclization would involve nucleophilic addition of a C_{10} geranyl unit to the iminium ion resulting in the 7,5-azabicyclic ring system. Attachment of further isoprene units followed by ring closures and oxidations results in the structure of stemofoline (Figure 2.3.3).[1i] However, there have been no adequate precursors found within the Stemonaceae family to support this proposed synthesis.[20]

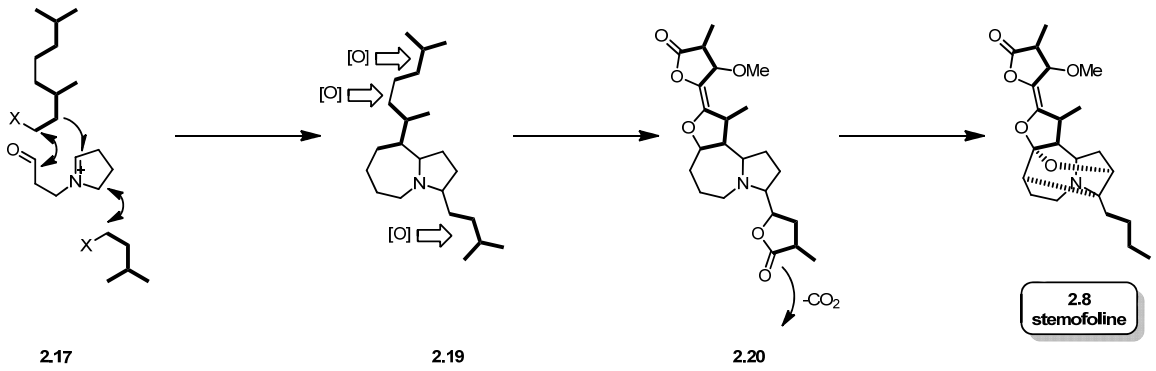


Figure 2.3.3 Proposed biosynthesis of the *Stemona* alkaloid stemofoline.

In 2009, Greger and co-workers isolated a series of alkaloids, previously found only in members of the related *Pandanus* genus, from *Stichoneuron calcicola* of the family Stemonaceae. Pandanamine was shown to be the precursor to series of pyrrolidine-type alkaloids, pandamarilactones A-D, which were also isolated from *S. calcicola*. Additionally, pandanamine can be regarded as a precursor of the *Stemona* alkaloid croomine isolated from the genus *Croomia*, which is thought to be closely related to *Stichoneuron*. Croomine-like alkaloids have been found to be widespread in different *Stemona* species. This co-occurrence of pandanamines, croomine, and stichoneurin in the family Stemonaceae represents a new argument in the biogenetic origin of *Stemona* alkaloids. It was proposed that pandanamines, which originate from leucine and glutamate, are a biosynthetic precursor to croomine and stichoneurine (Scheme 2.3.4).[1j]

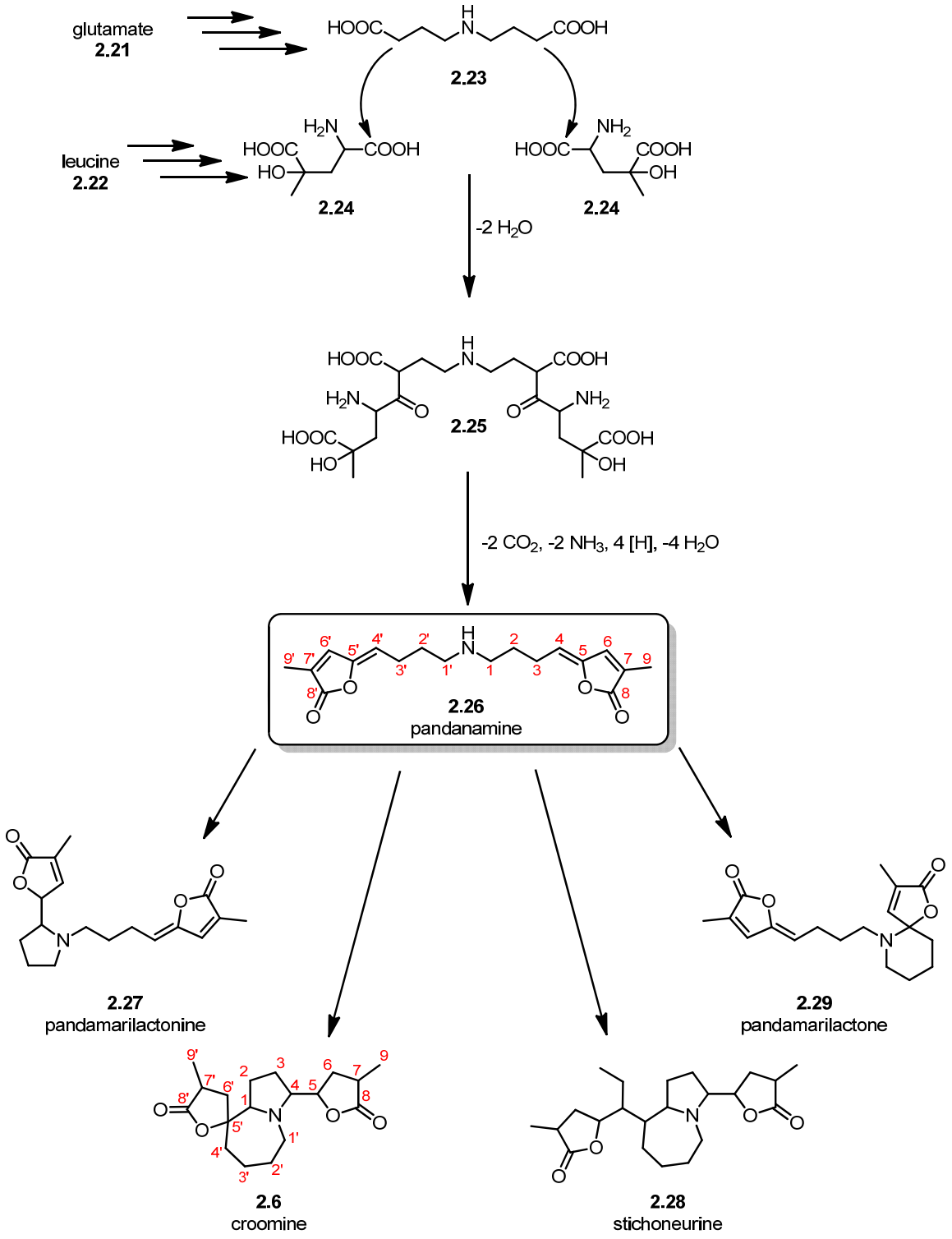
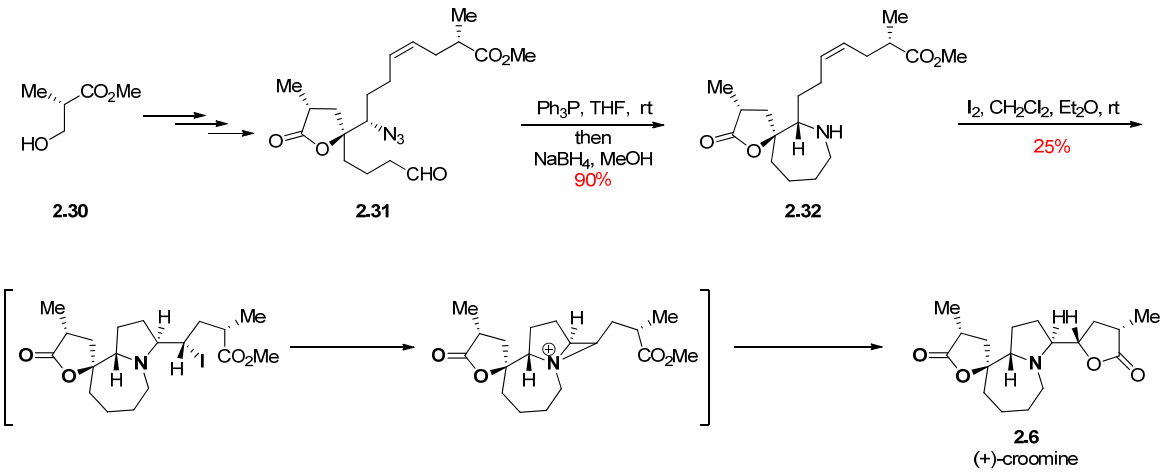


Figure 2.3.4 Possible biosynthetic origin of *Stemona* alkaloids.

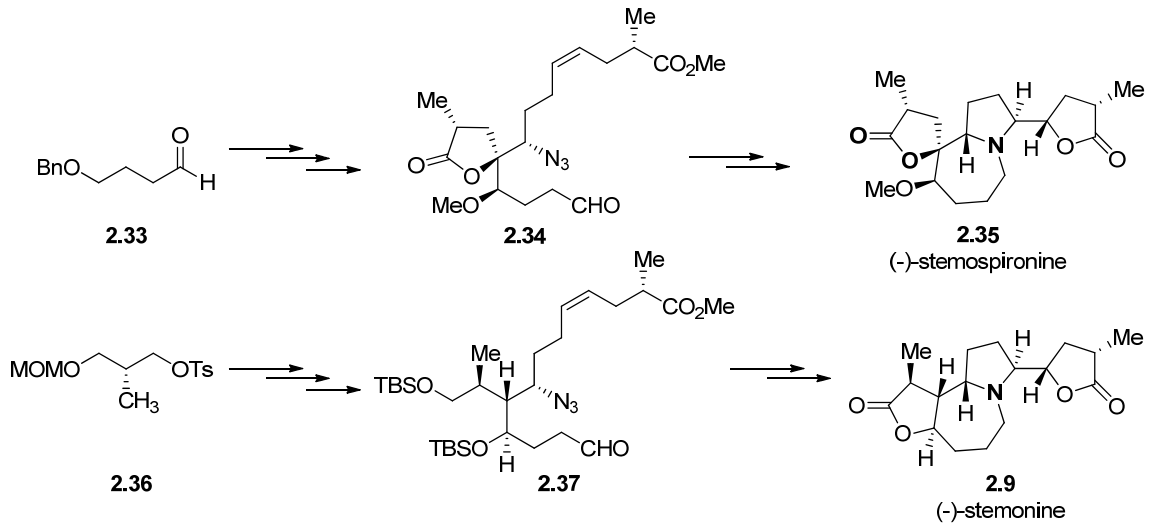
2.4 Synthetic Approaches to *Stemona* Alkaloids

In 1989 Williams and co-workers completed the first total synthesis of a *Stemona* alkaloid. In their pioneering work, the total synthesis of (+)-croomine was accomplished in a 24-step linear sequence from (2*S*)-3-(hydroxymethyl) propionate. Their strategy makes use of an azidoaldehyde in a Staudinger-aza-Wittig reaction to generate the azepine ring. The pyrrolidino-butyrolactone unit of croomine was achieved in a single step involving iodoamination, followed by nucleophilic anchimeric assistance by the vicinal tertiary amine to provide the intermediate aziridinium salt. Capture of the salt by the proximate ester resulted in net retention of stereochemistry and afforded direct conversion to (+)-croomine (Scheme 2.4.1).[9a]



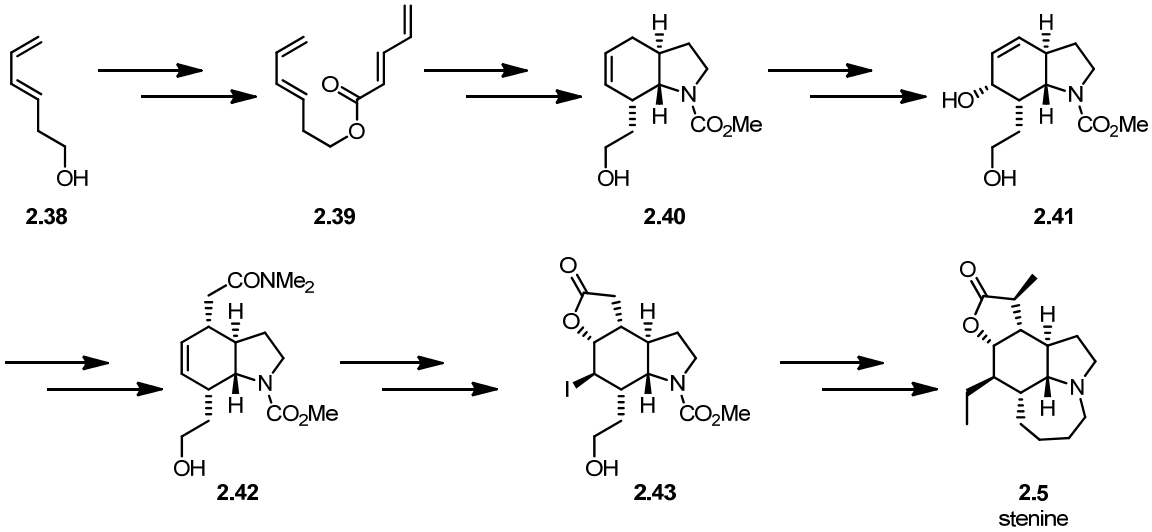
Scheme 2.4.1 Staudinger-aza-Wittig approach for the synthesis of (+)-croomine.

Similar to the approach used in the total synthesis of croomine, Williams and co-workers also accomplished the total synthesis of (-)-stemospironine and (-)-stemonine via a Staudinger-aza-Wittig reaction and iodine-induced double cyclization process (Scheme 2.4.2).[9b,c]



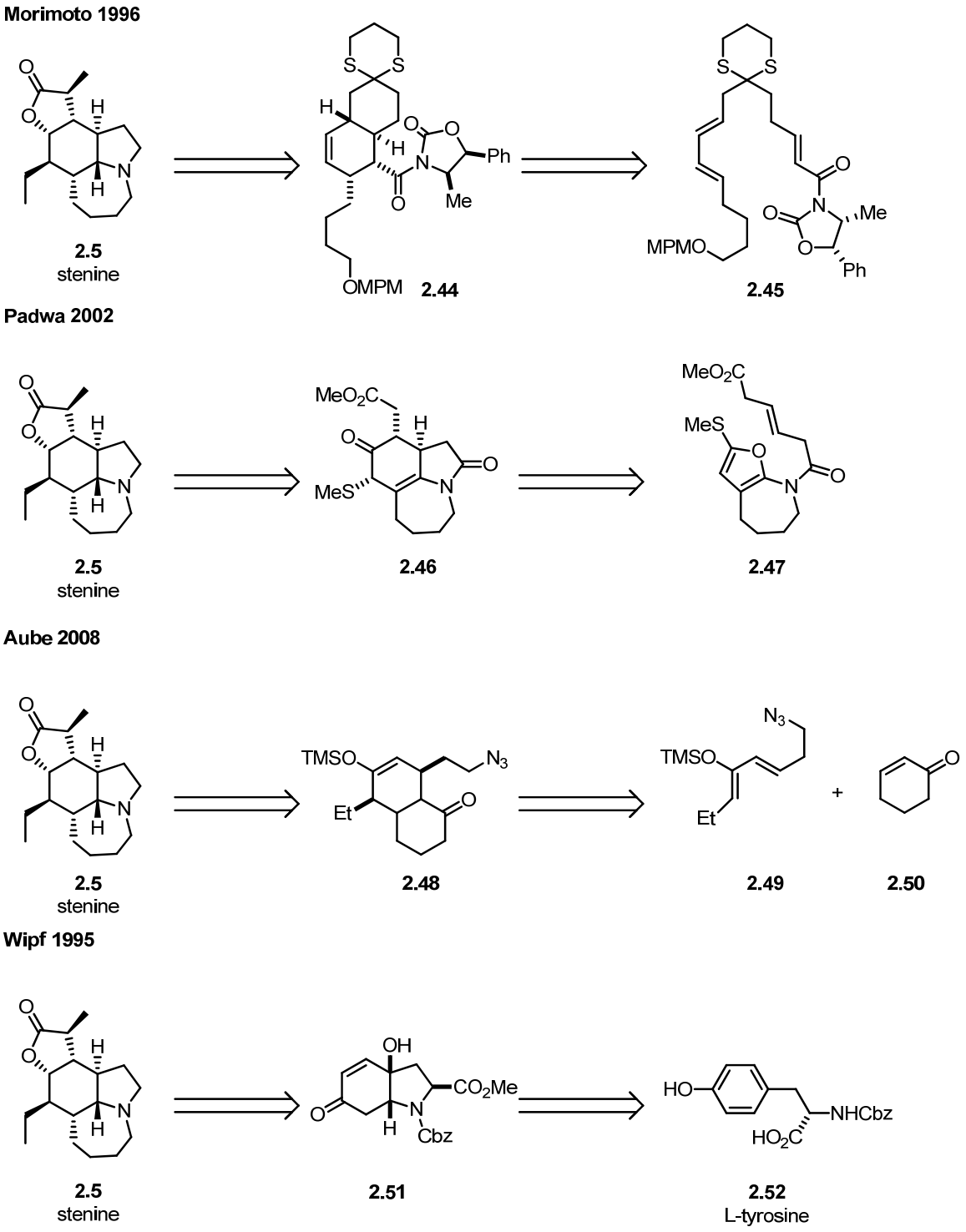
Scheme 2.4.2 Synthesis of stemospironine and stemonine.

In 1990 Hart and co-workers described a Diels-Alder approach in the first total synthesis of the *Stemona* alkaloid stenine. The key features of the synthesis include an intramolecular Diels-Alder, Curtius rearrangement, an Eschenmoser-Claisen rearrangement, and stereoselective free-radical allylation (Scheme 2.4.3).[21]



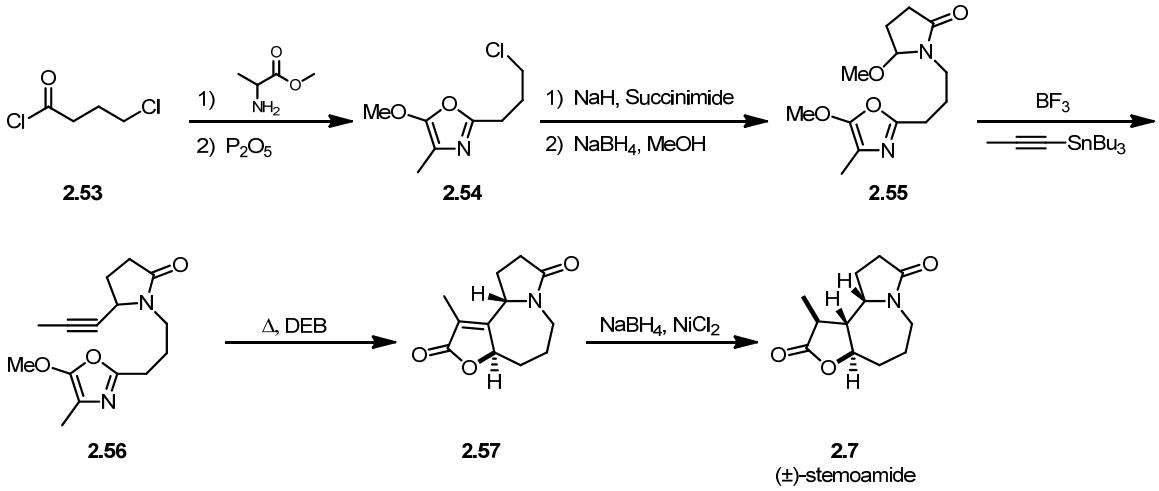
Scheme 2.4.3 Total synthesis of stenine.

Hart's synthesis of stenine set the precedent for utilizing a Diels-Alder approach to this target. Since the original synthesis, many other groups have embarked on a total synthesis of this natural product with nearly all of them making use of a Diels-Alder reaction as the key step to form the fused cyclohexane ring. Of all the completed syntheses to date, only the route used by Wipf does not employ a Diels-Alder approach. Instead his synthesis utilizes a selective reduction of a π-allyl palladium complex (Scheme 2.4.4).[22]



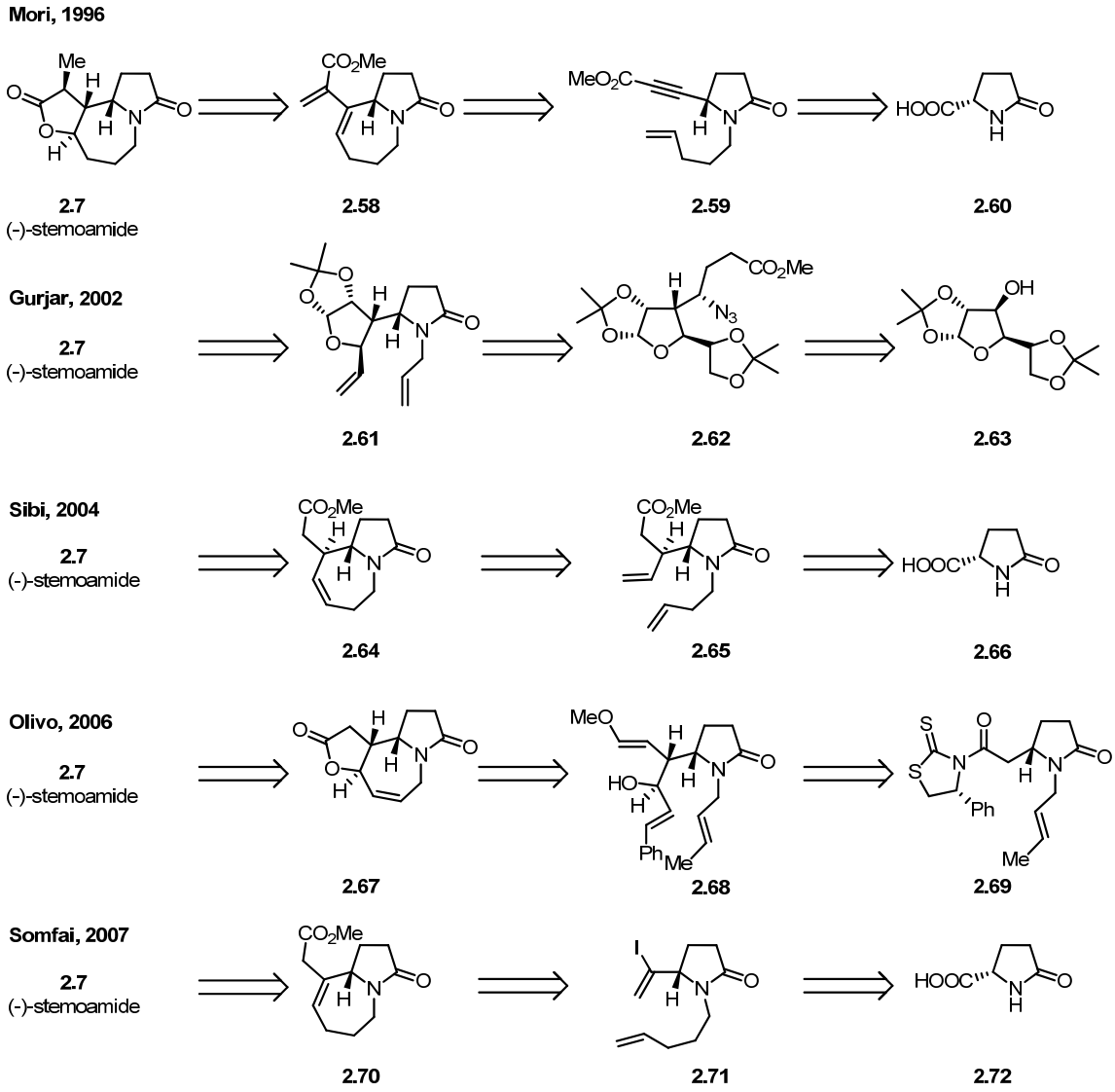
Scheme 2.4.4 Other approaches to stenine.

The Diels-Alder approach has been extended to other *Stemona* alkaloids as well. Jacobi and Lee made use of an intramolecular Diels-Alder/retro-Diels-Alder reaction in the rapid total synthesis of (±)-stemoamide, which was obtained in 7 steps and 20% overall yield (Scheme 2.4.5). The key transformation allowed for the construction of the entire tricyclic carbon skeleton in a single step.[23]



Scheme 2.4.5 Jacobi and Lee Synthesis of (±)-stemoamide.

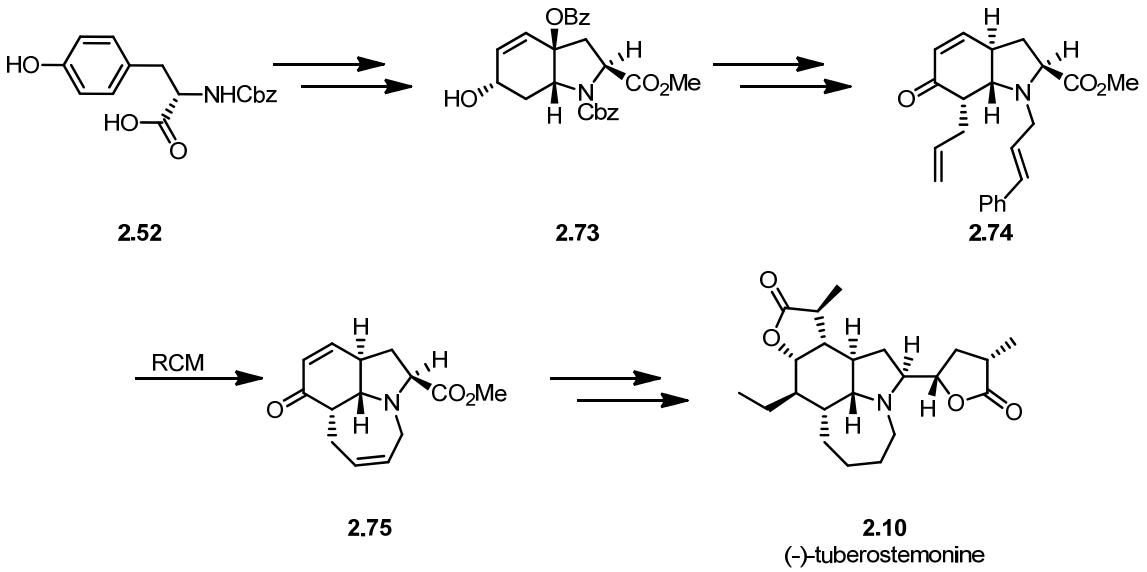
In several syntheses of the *Stemona* alkaloids, a ring-closing metathesis (RCM) is used to form the azepine ring. The pioneering work in the use of RCM was that of Mori and co-workers. The key step in their approach was an enyne intramolecular metathesis reaction. The use of RCM for the formation of the azepine ring of (-)-stemoamide has been accomplished by several groups using the RCM approach, as shown in Scheme 2.4.6.[24]



Scheme 2.4.6 Strategies toward stemoamide using an RCM approach.

In 2002, Wipf reported the total synthesis of the *Stemona* alkaloid (-)-tuberostemonine in 24 steps and 1.4% overall yield. The synthesis utilizes the same lynchpin bicyclic system used in his previous total synthesis of stenine, which is obtained in three steps from L-tyrosine. The scaffold allows for installation of nine of the ten stereogenic carbons of tuberostemonine, including the western fused lactone which is

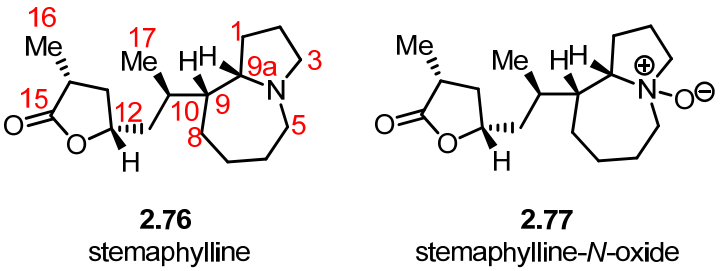
obtained by a Claisen rearrangement and halolactonization. This synthesis also features installation of the azepane ring using RCM (Scheme 2.4.7).[25]



Scheme 2.4.7 Wipf's total synthesis of (-)-tuberostemonine.

2.5 Isolation of Stemaphylline and Stemaphylline-*N*-Oxide

In 2009, stemaphylline and stemaphylline-*N*-oxide (Figure 2.5.1) were isolated from root extracts of *Stemona aphylla* plants that were collected at Mae Hong Son, Thailand, by Mungkornasawakul and co-workers.[26] The structures were elucidated by extensive NMR analysis and correlation to other previously known natural products isolated en masse.

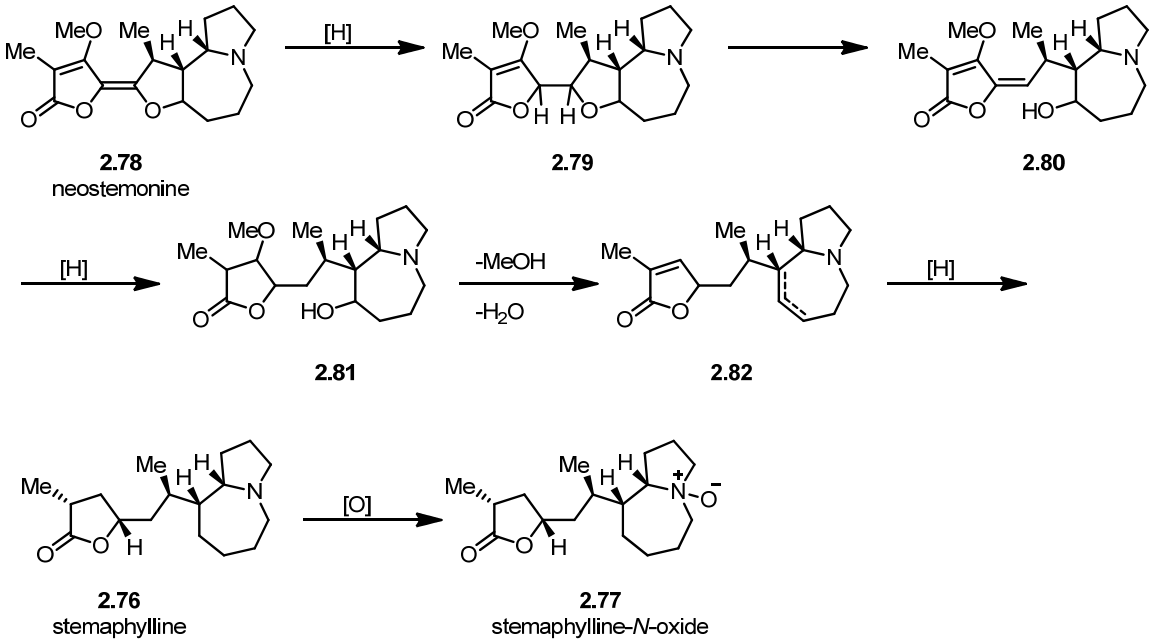


2.76
stemaphylline

2.77
stemaphylline-*N*-oxide

Figure 2.5.1 Stemaphylline and stemaphylline-*N*-oxide.

The authors suggested that stemaphylline was an extensively reduced product of neostemonine and suggested a possible mechanism for the conversion of neostemonine to stemaphylline (Scheme 2.5.1).[26]



2.78
neostemonine

2.79

2.80

2.81

2.82

2.76
stemaphylline

2.77
stemaphylline-*N*-oxide

Scheme 2.5.1 Proposed biosynthetic origin of stemaphylline.

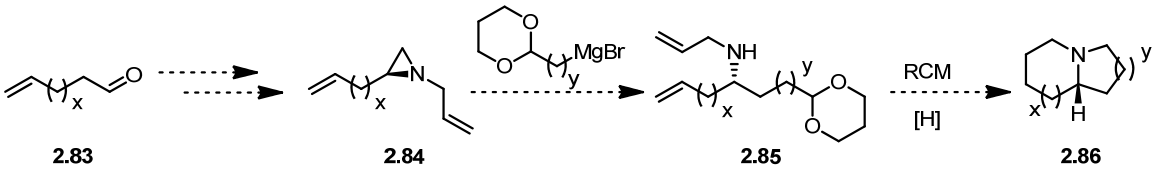
Biological assays of stemaphylline showed moderate acetylcholinesterase (AChE) inhibitory activity, moderate insecticidal activity (LC_{50} 1,824 μg/mL), and weak

antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans* (MIC 62.5-125 μg/mL).[26]

To date, there have been no reported synthetic efforts directed toward the total synthesis of stemaphylline and stemaphylline-*N*-oxide.

2.6 Previous Work Towards the Total Synthesis of Stemaphylline

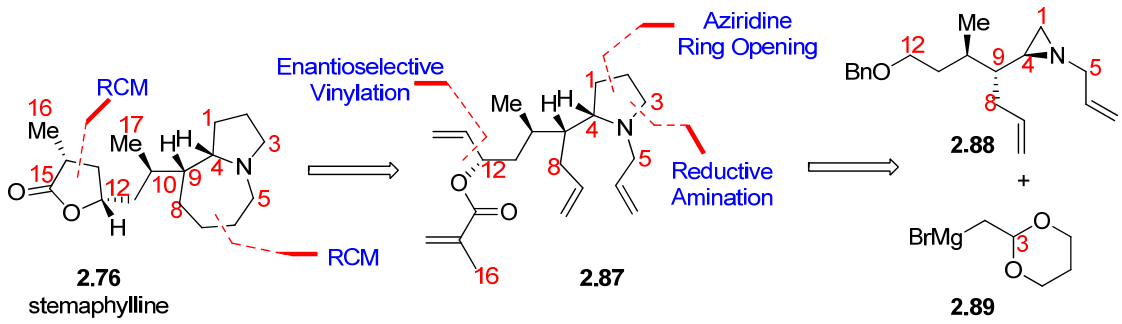
Due to the unique properties of azabicyclic-containing natural products, our lab became interested in the development of a general and asymmetric synthesis for the construction of azabicyclic ring systems and its application towards the total synthesis of stemaphylline and other biologically interesting natural products. Relying on our previously developed work on the enantioslective synthesis of *N*-alkyl aziridines,[27] we envisioned a Lewis acid mediated aziridine ring opening followed by a reductive amination/RCM sequence to access various ring sizes of the azabicylic skeleton (Scheme 2.6.1).



Scheme 2.6.1 Azabicyclic ring skeleton via *N*-alkyl aziridines.

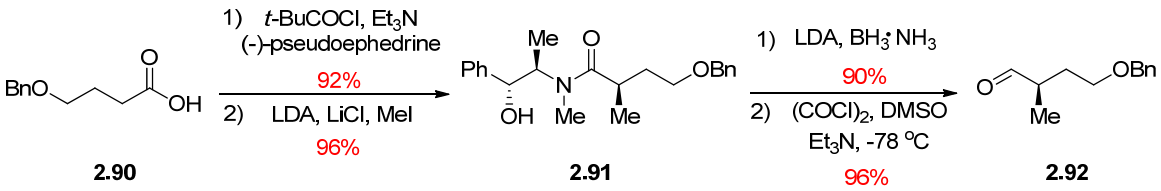
Based on the proposed approach to azabicyclic ring systems, we then developed a retrosynthesis for stemaphylline. The retrosynthetic analysis is outlined in Scheme 2.6.2. The lactone and 7-membered azepine rings could be installed via RCM. The pyrrolidine

ring would be constructed by ring opening of the aziridine and subsequent reductive amination.



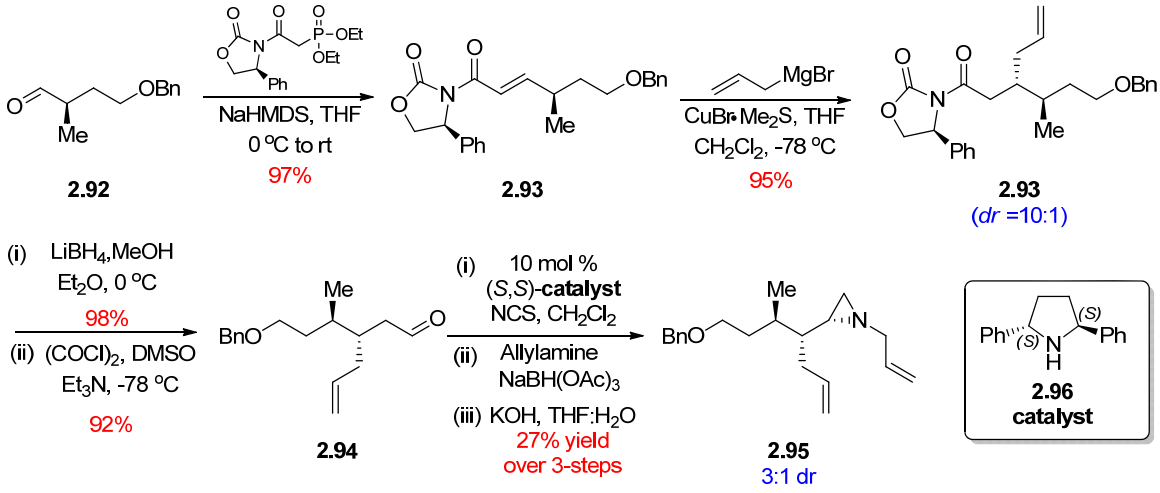
Scheme 2.6.2 Retrosynthetic analysis of stemaphylline.

Previous attempts at the synthesis of stemaphylline in our lab began with the preparation of the desired *N*-alkyl terminal aziridine (Scheme 2.6.2). Starting from 4-(benzyloxy)butanoic acid, acylation of pseudoephedrine with the mixed anhydride of the carboxylic acid derived from pivaloyl chloride followed by auxiliary-controlled asymmetric α-alkylation gave the desired alkylated product in 96% yield. A two-step protocol involving reduction with lithium amidotrihydroborate (LiH_2NBH_3, LAB) followed by Swern oxidation proceeded to give the aldehyde in 96% yield (Scheme 2.6.3).[26]



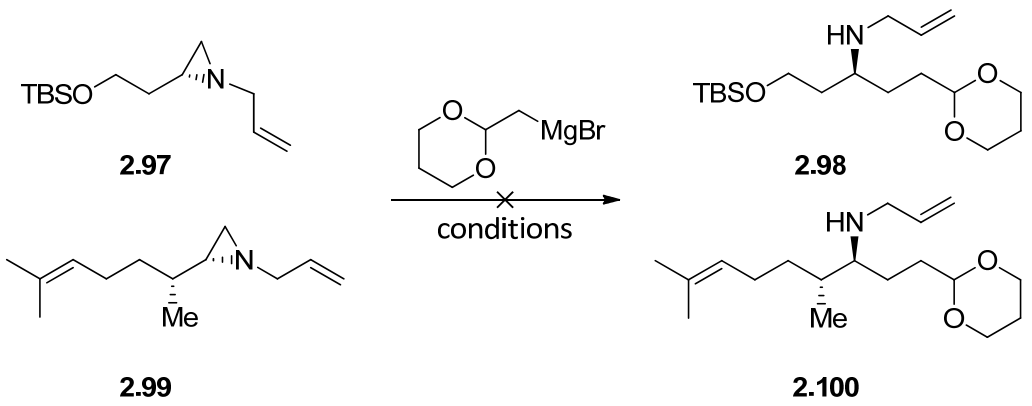
Scheme 2.6.3 Synthesis of aldehyde 2.92.

The aldehyde was subjected to a Horner-Wadsworth-Emmons reaction[28] with a chiral imide prepared from Evan's oxazolidinone (Scheme 2.6.4)[29] to give the *E*-enone in 97% yield.[30] 1,4-Conjugate addition with allyl cuprate afforded the desired addition product in 95% yield (dr=10:1).[31] Reductive cleavage of the oxazolidinone with $LiBH_4$ gave the desired primary alcohol in 98% yield, followed by a Swern oxidation of the alcohol to give the required aldehyde in 92% yield. Application of the three-step, one-pot aziridine protocol provided the 4-*epi*-aziridine in 27% yield (3:1 dr) (Scheme 2.6.4).



Scheme 2.6.4 Synthesis of 4-*epi*-aziridine 2.95.

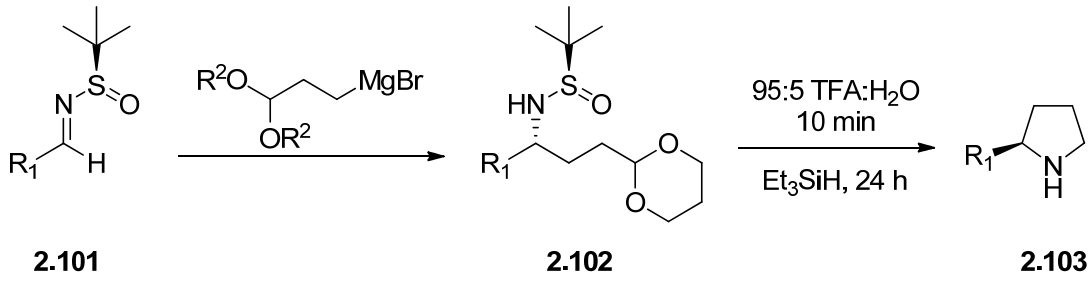
Encouraged by the progress in the synthesis of the key 4-epi-aziridine precursor, members of our lab attempted to advance model system aziridines to their corresponding azabicyclic frameworks. Regrettably, every attempt to ring-open the aziridines to the corresponding amines led to complex mixtures. Additionally, using various Lewis acid catalysts failed to give the desired product (Scheme 2.6.5). Since the aziridine route proved to be problematic, it was decided to switch to an alternate route.



Scheme 2.6.5 Failed aziridine ring opening.

2.7 Approach to Azabicyclic Ring Systems via Chiral Sulfinamides

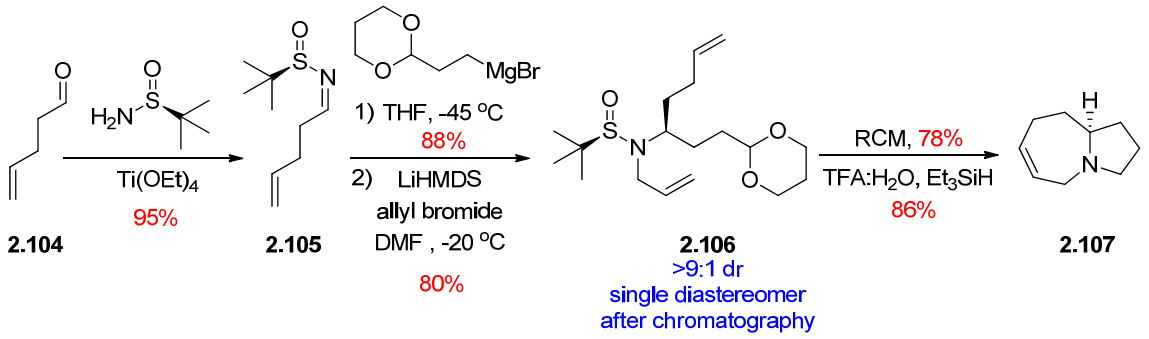
Our new route was inspired by Ellman's synthesis of chiral 2-substituted pyrrolidines (Scheme 2.7.1). In his work, it was observed that the addition of (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide proceeded with the opposite sense of induction typically observed for Grignard additions to sulfinyl aldimines.[32,33]



Scheme 2.7.1 Synthesis of chiral 2-substituted pyrrolidines.

We envisioned using a newly developed protocol involving asymmetric Grignard addition or indium-mediated allylation to the *N*-sulfinyl aldimine followed by *N*-alkylation, RCM, and finally an intramolecular reductive amination or cyclization to

afford enantiopure azabicyclic ring skeleton. Our new approach to azabicyclic rings is outlined in Scheme 2.7.2.



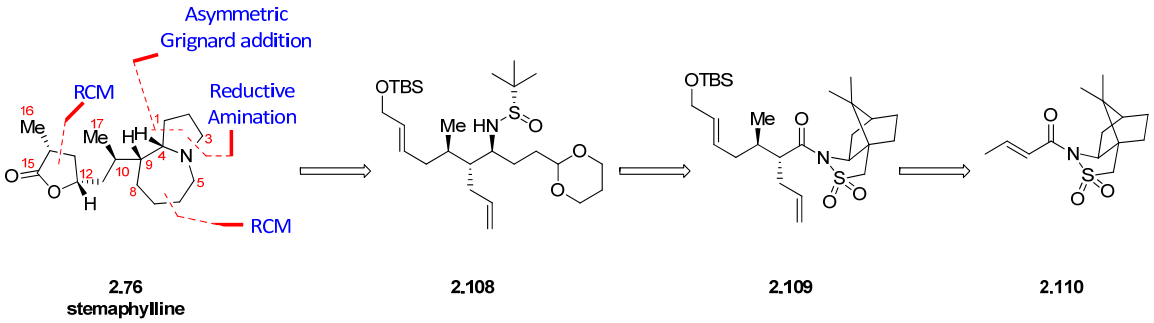
Scheme 2.7.2 Enantioenriched azabicyclic rings via chiral sulfinamides.

To test the viability of the above strategy, an azepine skeleton was prepared in excellent enantiopurity starting from 4-propenal (Scheme 2.7.2). The *N*-sulfinyl aldimines were prepared by condensation of the aldehydes in the presence of $Ti(OEt)_4$. Addition of Grignard reagent into the *N*-sulfinyl aldimine gave the desired sulfinamide in 88% yield and high diastereoselectivity (9:1 dr). The sulfinamide was isolated as a single diastereomer using silica-gel column chromatography. *N*-alkylation with allyl bromide yielded acetal 2.106 as single diastereomer. As previously noted by Ellman, the addition of the acetal Grignard reagent to the *N*-sulfinyl aldimine proceeded with the opposite sense of induction compared to that observed for other Grignard reagents. This was later confirmed through an X-ray crystal structure in the synthetic efforts towards the natural product (+)-amabiline in our lab.[34] RCM followed by acidic deprotection of the sulfinamide protecting group and acetal cleavage effected the cyclization, which upon reduction of the resulting iminium ion with triethyl silane gave the desired azepine ring in

86% yield (Scheme 2.7.2). This methodology was further developed in our lab and applied towards the general synthesis of azabicyclic ring systems and the application towards the total synthesis of several other natural products.[35,36]

2.8 Progress Towards the Total Synthesis of Stemaphylline via Chiral Sulfinamides

With the model ring systems in place, we went on to apply this new methodology to the total synthesis of stemaphylline. Outlined in Scheme 2.8.1 is our new retrosynthetic analysis of stemaphylline.

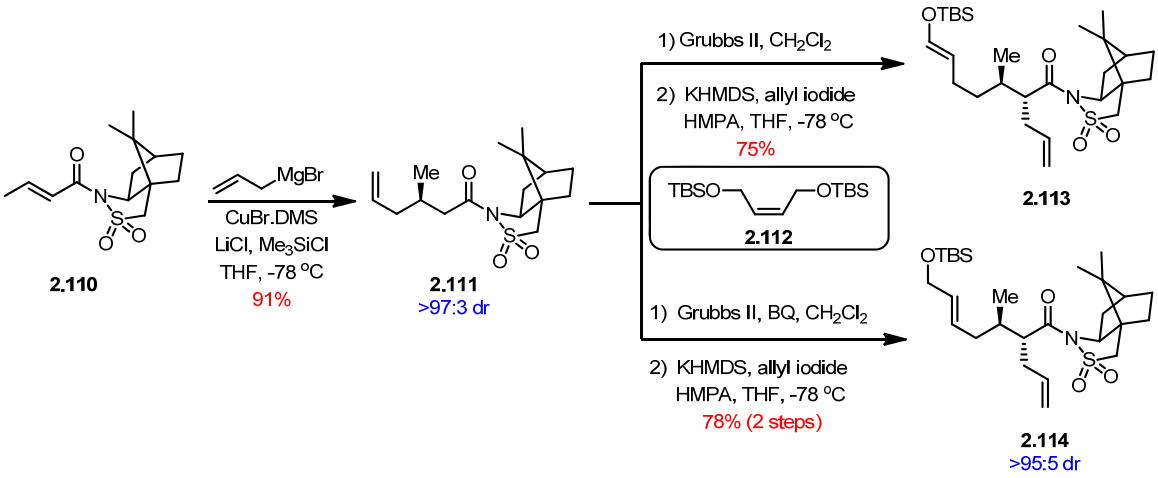


Scheme 2.8.1 Retrosynthetic analysis of stemaphylline using chiral sulfinamides.

In the new approach, the azepane ring and the western lactone could be installed through a tandem ring-closing metathesis reaction. The 5-membered ring of the azabicycle would be installed via asymmetric Grignard addition and an acid mediated global deprotection/intramolecular reductive amination protocol. The sulfinamide would be obtained from diene 2.109, while the C-10 and C-9 stereochemistry would be installed by asymmetric 1,4-conjugate addition and allylation of commercially available chiral camphor sultam (Scheme 2.8.1).

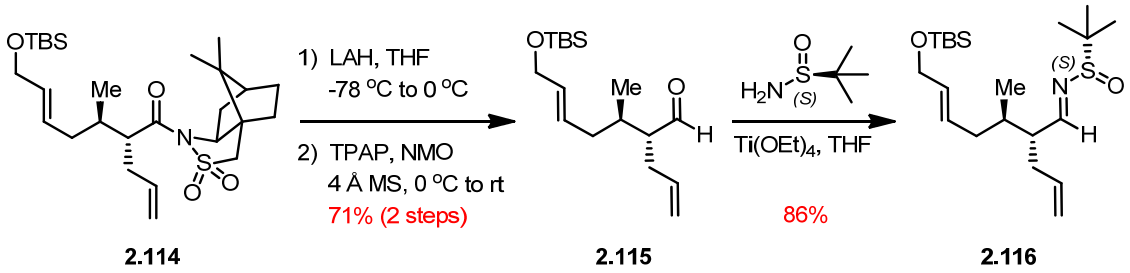
Conjugate addition of allyl cuprate into the acylated Oppolzer sultam in the presence of lithium chloride and chlorotrimethylsilane provided olefin 2.111 in 91% yield and 97:3 dr. Cross metathesis with *bis*-silyl diol 2.112 in the presence of Grubbs second generation catalyst gave exclusively the isomerized product 2.113 in 75% yield (Scheme 2.8.2).

Recently, Grubbs and co-workers reported that using 10 mol% 1,4-benzoquinone as an additive prevents olefin isomerization of a number of allylic ethers and long-chain aliphatic alkenes during olefin metathesis reactions with ruthenium catalysts.[37] Accordingly, performing the reaction in the presence of 10 mol% 1,4-benzoquinone gave the desired cross metathesis product, which was subsequently subjected to stereoselective α-allylation with potassium *bis*(trimethylsilyl)amide (KHMDS) and hexamethylphosphoramide (HMPA) to give diene 2.114 in 78% yield for 2 steps (Scheme 2.8.2).



Scheme 2.8.2 Synthesis of sultam.

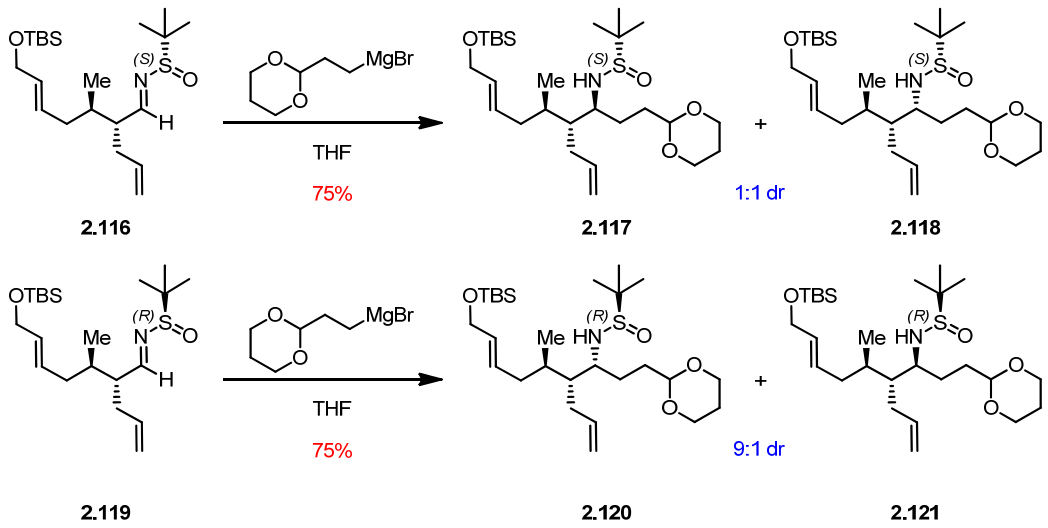
The sultam was reductively cleaved with LAH and oxidation of the resulting primary alcohol via Ley oxidation furnished the desired aldehyde in 71% over 2 steps. The *N*-sulfinyl aldimine was cleanly prepared by condensation with (*S*)-*tert*-butanesulfinamide in the presence of $Ti(OEt)_4$ in 86% yield (Scheme 2.8.3).



2.114 **2.115** **2.116**

Scheme 2.8.3 Synthesis of sulfinimine 2.116.

Addition of (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide to the chiral aldimine afforded the addition product in 75% yield but, unfortunately, in 1:1 dr. By switching to the opposite (*R*)-*tert*-butanesulfinamide, the product could be obtained in comparable yields but in 9:1 dr in favor of the undesired diastereomer (Scheme 2.8.4).

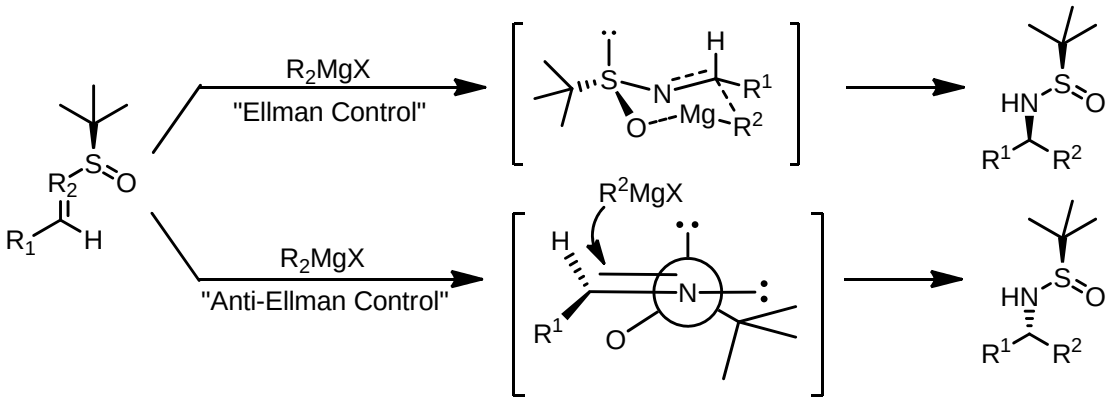


2.116 **2.117** **2.118**

2.119 **2.120** **2.121**

Scheme 2.8.4 Grignard addition to chiral aldimine.

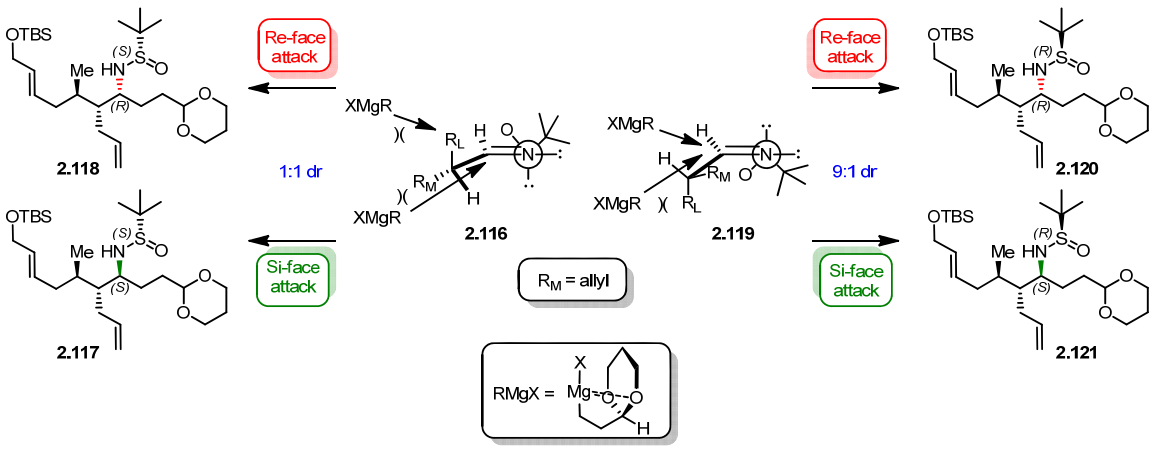
This match/mismatch reactivity can be explained through the transition state for the Grignard addition. Several early studies revealed the effects of solvent, metal, and additives on the selectivity in additions of organometallic additions to unfunctionalized *N*-*tert*-butanesulfinyl aldimines.[33,38] Based on these studies, Ellman and co-workers proposed two transition state models to explain the stereochemical outcome of these reactions (Scheme 2.8.5).



Scheme 2.8.5 Transition states for addition to aldimines.

A standard Grignard addition proceeds with "Ellman control" in a 6-membered-chelate transition state. In cases where the imine or Grignard reagent contains a heteroatom that can coordinate the magnesium, the chelate transition is disrupted and the reaction proceeds through the open transition state (Scheme 2.8.5). It is known that the (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide adds with "Anti-Ellman" control. This can be explained through an intramolecular, 5-membered chelation of the magnesium by the oxygen atoms of the acetal. This coordination disrupts the ability of the magnesium to coordinate to the sulfinamine causing the addition to proceed through the open transition state.

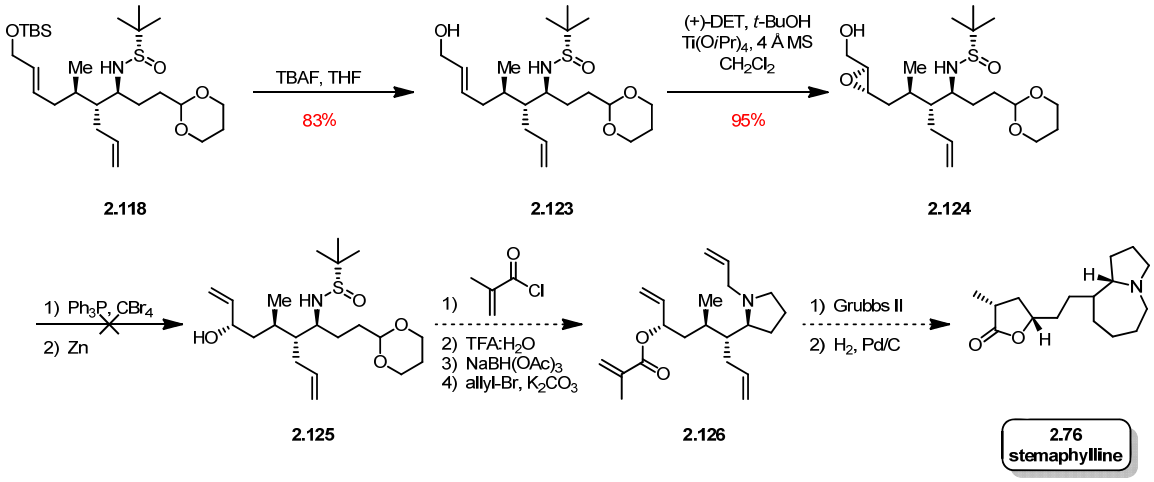
Beginning with substrate 2.116 using the (*S*)-*tert*-butanesulfinamide, and proceeding through the open transition state, attack from the re face of the imine is blocked by the *tert*-butyl group of the sulfinimine. However, attack from the si face of the imine is also hindered by the alpha-allyl group, and an attack from this face results in anti-Felkin addition product. The directing effect of the chiral *tert*-butanesulfinamide auxiliary is mismatched with the directing effects of substrate 2.116 and results in the observed poor selectivity. When (*R*)-*tert*-butanesulfinamide is used, a matched case is observed. The re face is accessible since the allyl and *tert*-butyl groups are both blocking the si face between the control of the chiral auxiliary and Felkin-Ahn control. This results in good selectivity for the undesired diastereomer (Scheme 2.8.6).



Scheme 2.8.6 Stereochemical outcome of Grignard addition to aldimine.

Despite the poor selectivity for the Grignard addition, the diastereomers were separable by column chromatography. Therefore, we elected to move forward to the epoxidation/Appel/ring-opening sequence to obtain the desired secondary allylic alcohol. Following TBAF deprotection of the allylic alcohol, the desired diastereomer of the

resulting allylic alcohol was subjected to Sharpless epoxidation conditions. The desired epoxide was cleanly formed in 95% yield. Unfortunately, attempts at the Appel reaction and subsequent elimination/ring-opening of the epoxide resulted in complex mixtures of products (Scheme 2.8.7).

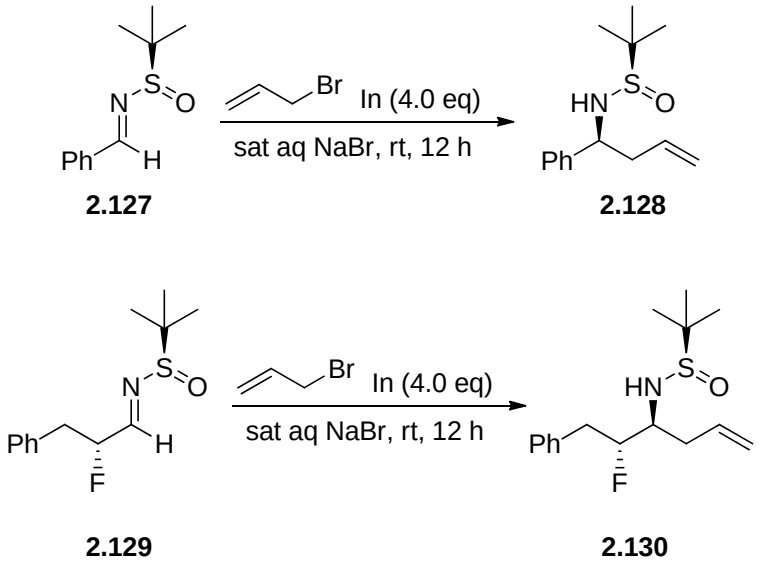


Scheme 2.8.7 Failed completion of stemaphylline via chiral sulfinamides.

With poor selectivity in the Grignard addition and no reaction in the subsequent epoxidation, we decided to explore a new route to the natural product.

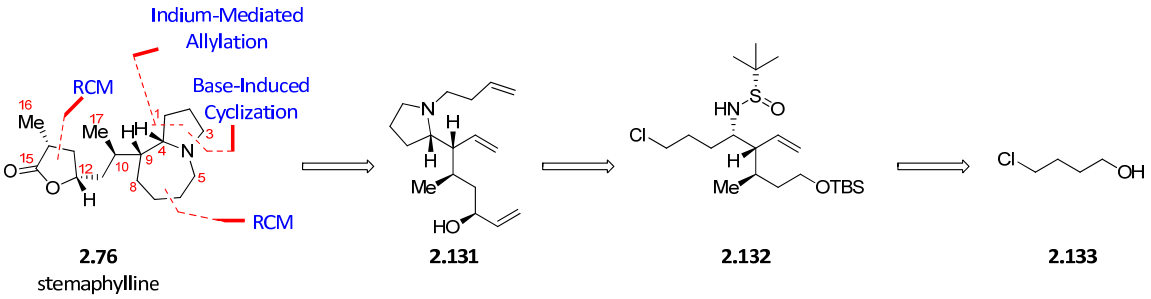
2.9 Progress Towards Stemaphylline Via Indium-Mediated Allylation

Our new route was inspired by the work of Lin and co-workers on indium-mediated allylations in aqueous sodium bromide and our previous application of this methodology in the preparation of chiral β-fluoroamines.[39,40]



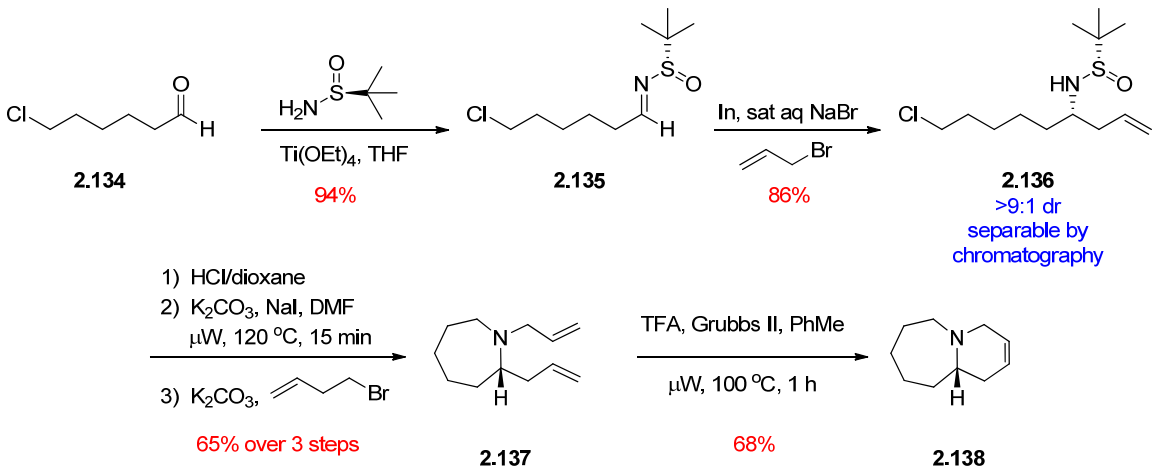
Scheme 2.9.1 Indium-mediated allylation.

Based on this work, we designed a route to stemaphylline making use of a complex allylic bromide to install the stereochemistry at C-9 and C-9a. Outlined in Scheme 2.9.2 is our new retrosynthetic analysis of stemaphylline.



Scheme 2.9.2 Retrosynthetic analysis of stemaphylline via indium-mediated allylation.

To test the viability of the above strategy, a model azabicyclic skeleton was prepared in excellent enantiopurity starting from 6-chloro-1-hexanal (Scheme 2.9.3).

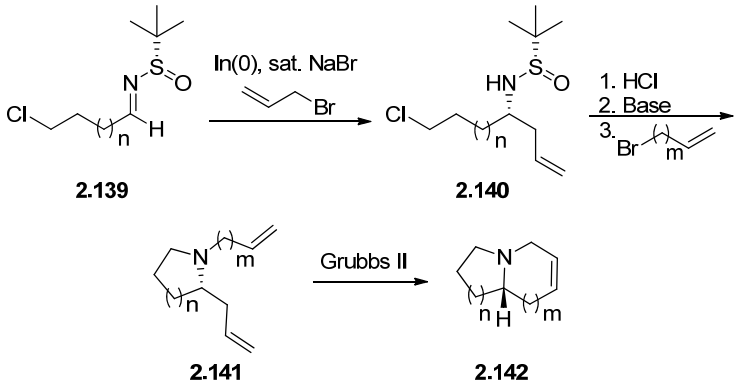


Scheme 2.9.3 Rapid, general synthesis of azabicyclic ring systems

The chloroalkyl *N*-(*tert*-butanesulfinyl)aldimine was easily prepared in 94% yield by condensing the corresponding chloroaldehyde with the Ellman (*S*)-*tert*-butanesulfinamide. A subsequent indium-mediated allylation reaction afforded the anticipated product in >9:1 diastereoselectivity and 86% yield. Acid-mediated liberation of the primary amine followed by base-induced, microwave-assisted cyclization and alkylation with allyl bromide smoothly afforded the chiral *N*-alkyl azepane in 65% yield for the three-step, one-pot reaction sequence. A survey of the literature regarding RCM methods with tertiary amines suggested that protection of the amine by *in situ* generation of ammonium salts enabled facile ring-closing.[41] Thus, treatment of diene 2.137 with trifluoroacetic acid (TFA) in toluene, followed by the addition of Grubbs II and microwave heating for 1 hour at 100 °C, provided the unsaturated pyrido[1,2-α]azepine ring system in 68% isolated yield and 35% overall yield from commercially available starting materials.

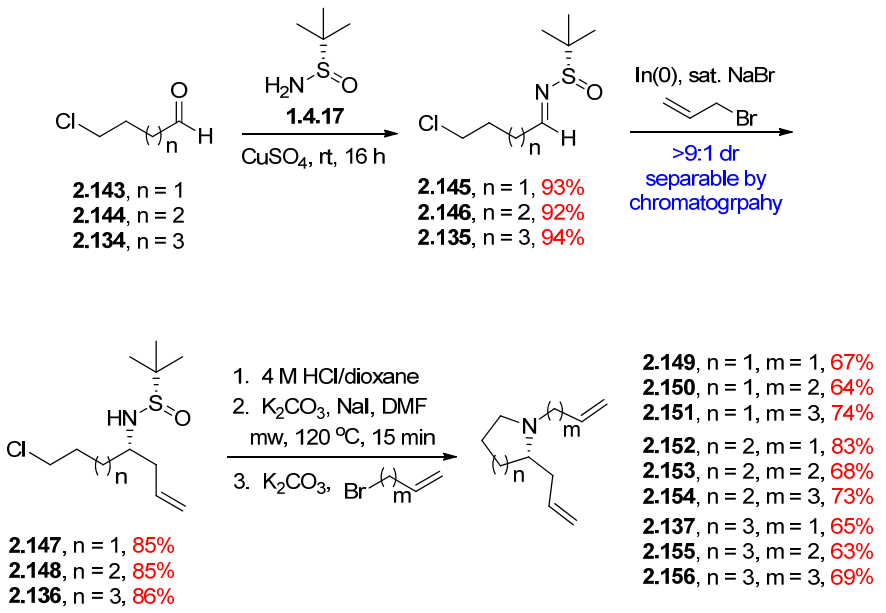
Previous efforts in our lab towards the enantioselective synthesis of azabicyclic ring systems provided a notable advance over current literature but did have some

significant drawbacks, including the need for different transformations depending on the desired ring size, inconsistencies in alkylation of the *tert*-butanesulfinyl nitrogen, and the lack of ability to access multiple rings from a single lynchpin intermediate. Encouraged by the results of our model system, we opted to develop this into a general methodology that would allow rapid access to diverse small to large azabicyclic ring systems (Scheme 2.9.4).



Scheme 2.9.4 Envisioned route to access diverse 1-azabicyclo[*m.n*.0]alkane cores.

Following the same method described above for the model system, the chloroalkyl *N*-(*tert*-butanesulfinyl)aldimines were easily prepared in 92-94% yields by condensing the corresponding chloroaldehydes with the Ellman (*S*)-*tert*-butanesulfinamide. A subsequent indium-mediated allylation reaction afforded the anticipated (*R*)-*anti*-adducts in >9:1 diastereoselectivity and 85-86% yield. Acid-mediated deprotection and base-induced, microwave-assisted cyclization and alkylation with the required allyl, butenyl and pentenyl bromides smoothly afforded the chiral *N*-alkyl ring systems in 63-83% yields for the three-step, one-pot reaction sequence (Scheme 2.9.5).



Scheme 2.9.5 Enantioselective synthesis of *N*-alkyl rings.

Yields for the RCM reaction averaged 70% for all the substrates, providing high-yielding, enantioselective access to each of the 1-azabicyclo[*m.n*.0]alkane systems. Overall yields from the commercial chloroaldehydes ranged from 29-59%. This work provides a general route to access these important azabicyclic ring systems with an embedded olefin handle for further functionalization (Figure 2.9.1).[42]

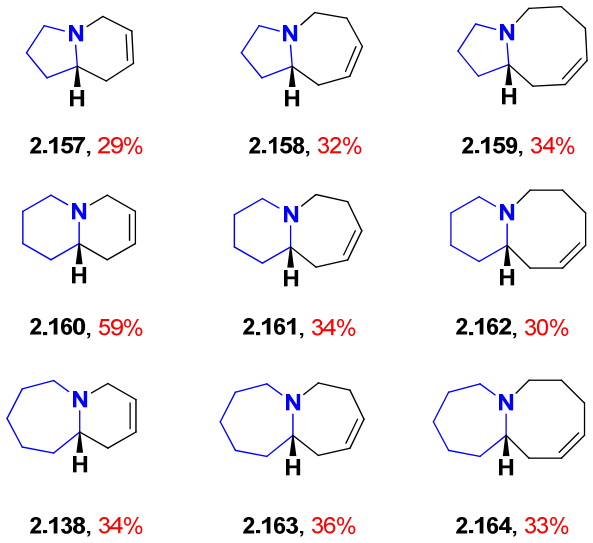
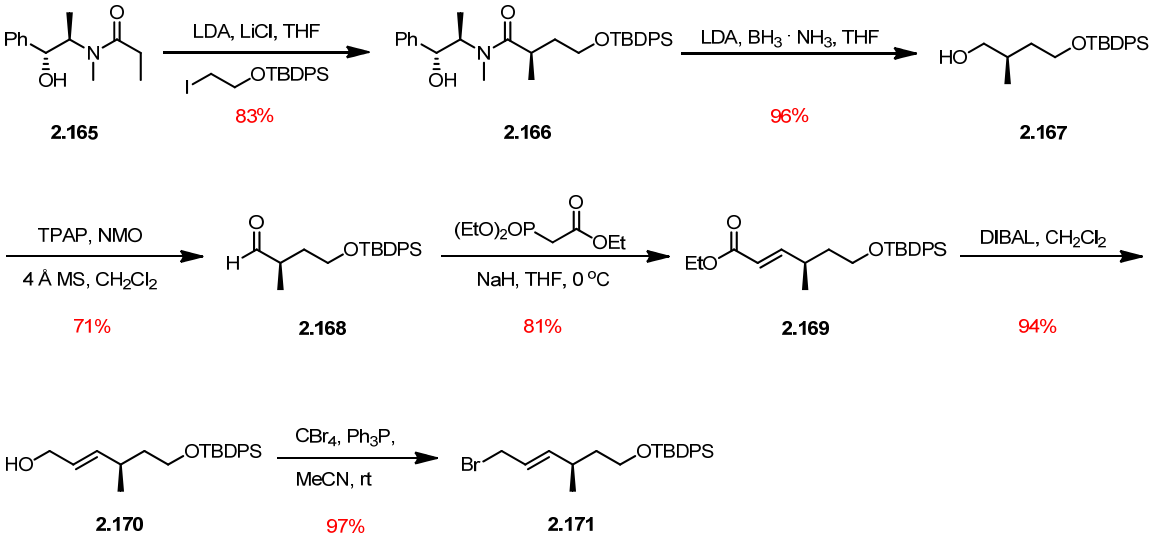


Figure 2.9.1 Mono-unsaturated 1-azabicyclo[*m.n*.0]alkane ring systems.

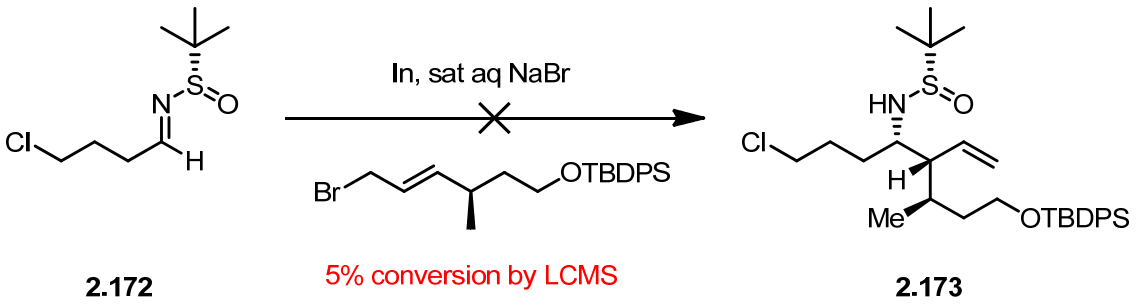
Once the conditions for the methodology were optimized, we moved on to its application in the total synthesis of stemaphylline. The required chloroalkyl *N*-(*tert*-butanesulfinyl)aldimine was easily prepared from the corresponding alcohol in 93% yield (Scheme 2.9.5). We then shifted our focus towards the synthesis of the required complex allylic bromide for the indium-mediated allylation.

The synthesis of the allylic bromide emanated from a Myers alkylation of (1*R*,2*R*)-(−)-pseudoephedrinepropionamide with TBDPS protected iodoethanol which proceeded in 83% yield. Reductive cleavage of the chiral auxiliary and subsequent Ley oxidation to the corresponding aldehyde gave the chiral, α-methyl aldehyde in 65% yield over two steps. The aldehyde was subjected to a Horner-Wadsworth-Emmons olefination with triethyl phosphonoacetate to give the α,β-unsaturated ester in 81% yield. Reduction of the ester to the allylic alcohol with diisobutylaluminum hydride (DIBAL) followed by an Appel reaction afforded the allylic bromide in 89% yield over two steps (Scheme 2.9.7).



Scheme 2.9.6 Synthesis of allylic bromide.

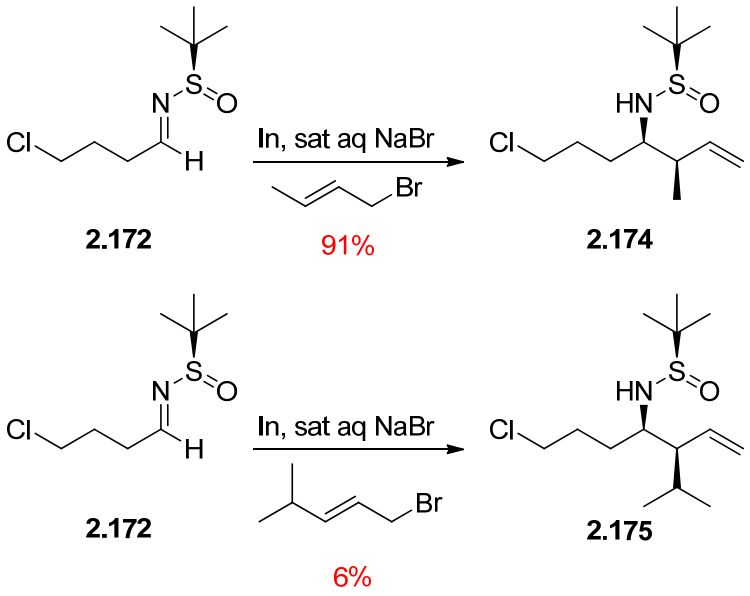
With the allylic bromide in hand we attempted the indium-mediated allylation on the chloroalkyl imine. Regrettably, the allylation resulted in only starting material after stirring for 3 days at room temperature, and only about 5% conversion to product by LCMS after heating for an additional 3 days with no isolatable product (Scheme 2.9.8).



Scheme 2.9.7 Attempted indium-mediated allylation in route to stemaphylline.

Based on these results, we decided to perform a screen of allylic bromides to test the limits of the indium-mediated allylation. Using crotyl bromide, we found that the

indium-mediated allylation smoothly provided the allylated product in 91% yield. When 1-bromo-4-methylpent-2-ene was used, the allylated product was obtained in only 6% isolated yield. This indicated that when branching is introduced into the allylic bromide at the 4-position the reactivity is greatly reduced (Scheme 2.9.9). Based on these results we chose to explore a new way to intercept the same intermediates from the indium route.

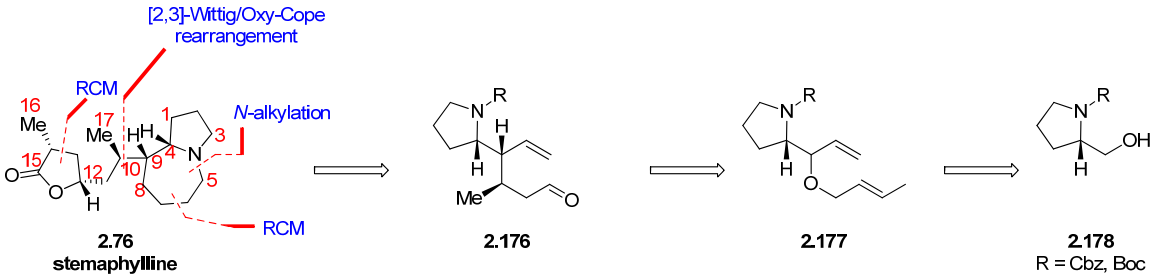


Scheme 2.9.8 Effect of olefin substitution on indium-mediated allylation.

2.10 Stemaphylline Via Tandem [2,3]-Wittig/Oxy-Cope Rearrangement

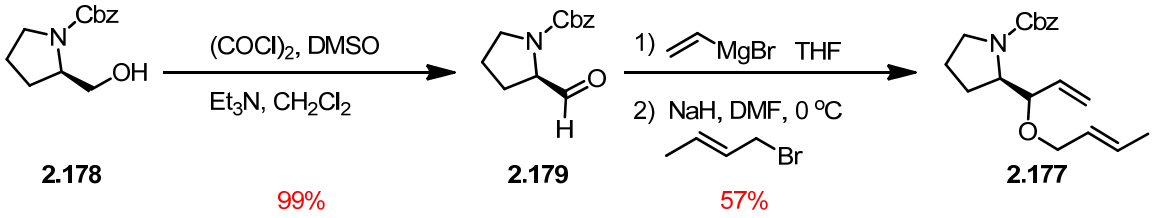
After the unsuccessful indium addition, we explored ways to access intermediate 2.132 using different chemistry, as we felt that the later steps in that route were feasible. This led us to start from the chiral pool using L-proline, eliminating the need to synthesize the pyrrolidine ring of the pyrrolo[1,2-α]azepine core and allowing us to start with the stereocenter at C-9a already set. Greeves and co-workers have shown that *bis*-allylic ethers can undergo a stereoconvergent, one-pot tandem [2,3]-Wittig/anionic oxy-

Cope rearrangement to give δ,ε-unsaturated aldehydes.[43] Based on this precedent, we designed a route to stemaphylline using this tandem rearrangement starting from L-prolinol to access the aldehyde intermediate 2.176. Outlined in Scheme 2.10.1 is our new retrosynthetic analysis of stemaphylline using this method.



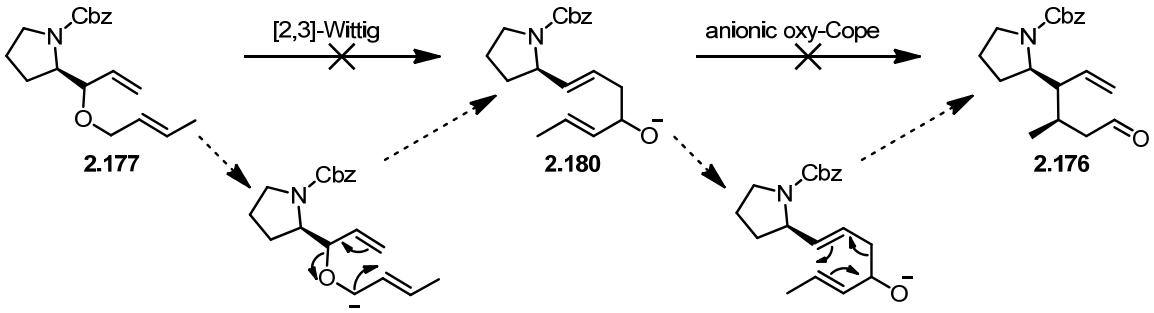
Scheme 2.10.1 Retrosynthetic analysis of stemaphylline via tandem rearrangement.

We began our synthesis from commercially available *Z*-L-prolinol. Oxidation of the alcohol to the aldehyde via Swern oxidation proceeded smoothly in 99% yield. Addition of vinyl Grignard followed by alkylation of the resulting allylic alcohol with crotyl bromide generated the requisite *bis*-allylic ether needed for the tandem rearrangement in 57% yield over two steps (Scheme 2.10.2).



Scheme 2.10.2 Synthesis of *bis*-allylic ether.

After successfully preparing the *bis*-allylic ether, we attempted the tandem rearrangement sequence. Disappointingly, after screening multiple sets of conditions (bases, solvents, temperatures, *N*-protecting groups), we were unable to achieve the rearrangement and observed only decomposition of starting material (Scheme 2.10.3).



Scheme 2.10.3 Tandem rearrangement in route to stemaphylline.

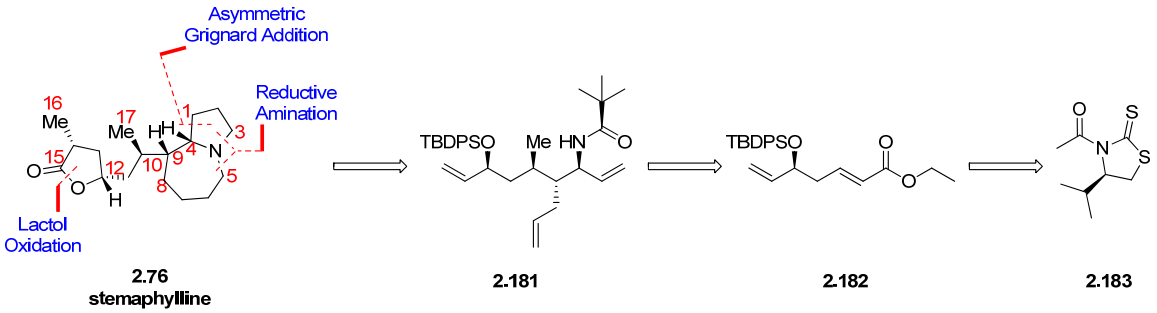
After very briefly exploring other routes, we chose to go back to our most successful route to date using chiral sulfonamides and try to solve the problems with setting the stereochemistry at the allylic alcohol and amine stereocenter.

2.11 Total Synthesis of Stemaphylline Via Chiral Sulfonamides, Revisited

In order to solve some of the problems we encountered in the previous sulfonamide route, we wanted to design a synthesis of stemaphylline in which the stereocenter at C-12 was set early in the synthesis. Due to the reversal in selectivity of the Grignard addition using (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide, we preferred to use a Grignard that would proceed through normal "Ellman" selectivity.

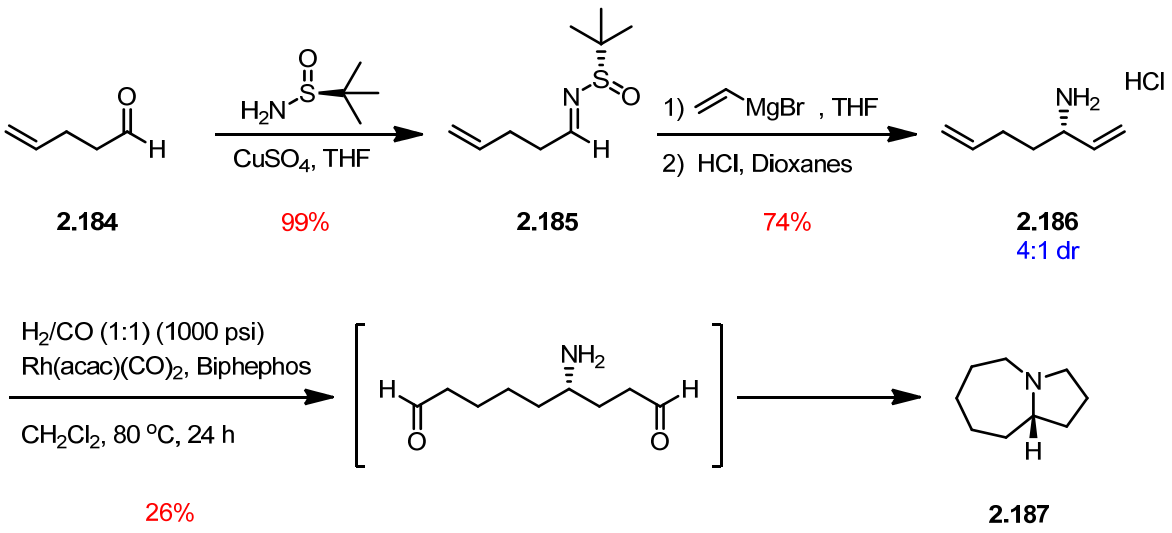
In the new approach, the azabicyclic ring system could be closed through a tandem reductive amination in conjunction with a lactol ring closure. The required *tris*-

aldehyde intermediate could be generated from a hydroformylation reaction on the corresponding triolefin.[44] The remaining C-9 and C-10 stereocenters could be set through an oxazolidinone-controlled α-alkylation and conjugate addition respectively while C-12 could be installed through a Nagao-type acetate aldol reaction (Scheme 2.11.1).[45-47]



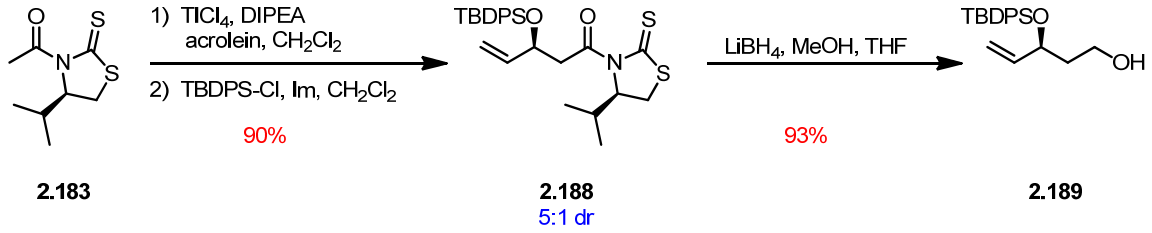
Scheme 2.11.1 Retrosynthetic analysis of stemaphylline using hydroformylation.

To test the feasibility of the hydroformylation reaction, a model system was constructed to form a simple azabicyclic ring system. Starting from 4-pentenal, condensation with (*S*)-*tert*-butanesulfinamide followed by addition of vinyl Grignard and deprotection of the amine afforded the chiral dienamine 2.186 in 73% yield and 4:1 dr. Treatment of the amine with Rh(acac)$(CO)_2$ and biphephos under 1000 psi of 1:1 H_2/CO (syngas) at 80 ^oC for 24 hours cleanly gave the saturated pyrrolo[1,2-α] azepine ring system in 26% yield for the six-step, one-pot sequence (Scheme 2.11.2). Studies towards further development of this methodology are ongoing in our lab.



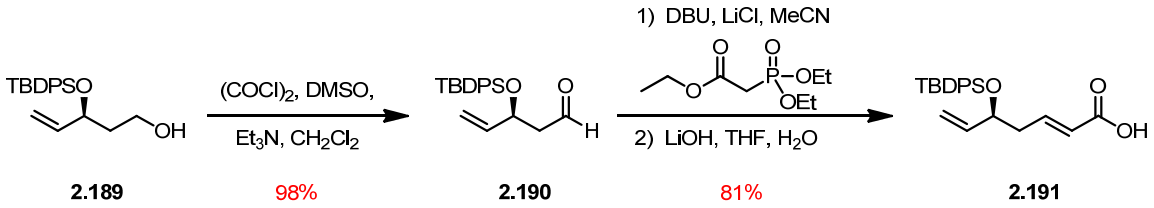
Scheme 2.11.2 Hydroaminomethylation model system.

With encouraging results in the model system, we proceeded with the application of this methodology towards the synthesis of stemaphylline. Starting from (4*R*)-3-acetyl-4-isopropyl-1,3-thiazolidine-2-thione, an acetate aldol reaction with acrolein gave the aldol product in 90% yield and 5:1 dr.[47] The desired diastereomer can be separated via silica chromatography in up to 75% yield. Protection of the secondary alcohol as the *tert*-butyldiphenylsilyl (TBDPS) ether proceeded in 95% yield. Reductive cleavage of the auxiliary with $LiBH_4$ afforded the chiral 1,3-diol 2.189 in 93% yield (Scheme 2.11.3)



Scheme 2.11.3 Synthesis of 1,3-diol 2.189.

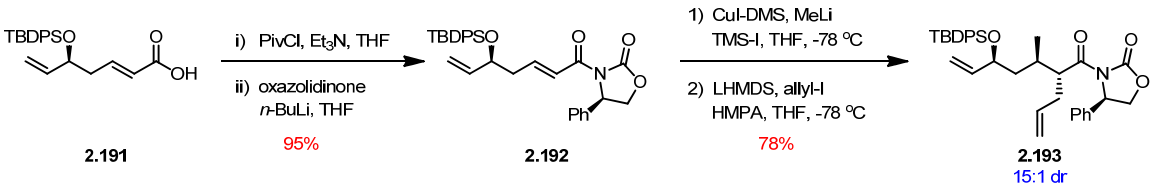
Swern oxidation of the primary alcohol 2.189 afforded the aldehyde in 98% yield, which was then subjected to mild Horner-Wadsworth-Emmons olefination conditions with triethyl phosphonoacetate and DBU to give the α,β-unsaturated ether ester in 90% yield. Hydrolysis of the ester with LiOH to carboxylic acid 2.191 proceeded in up to 90% yield (81% over 2 steps) (Scheme 2.11.4).



2.189 98% **2.190** 81% **2.191**

Scheme 2.11.4 Synthesis of α,β-unsaturated carboxylic acid 2.191.

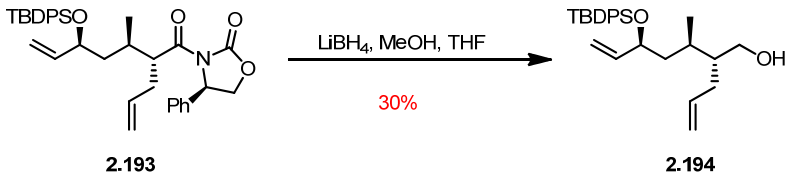
Coupling of the Evans (*R*)-4-phenyl-2-oxazolidinone auxiliary to the acid followed by conjugate addition using Li[MeCuI]/TMSI, (obtained from MeLi and CuI-0.75DMS) gave the *anti-s-cis* conformation of the methyl group in 90% yield and 17:1 dr.[46] Directed installation of the alpha allyl group by the same auxiliary proceeded in 87% yield and 15:1 dr (Scheme 2.11.5).[45]



2.191 95% **2.192** 78% **2.193** 15:1 dr

Scheme 2.11.5 Installation of C-9 and C-10 stereocenters.

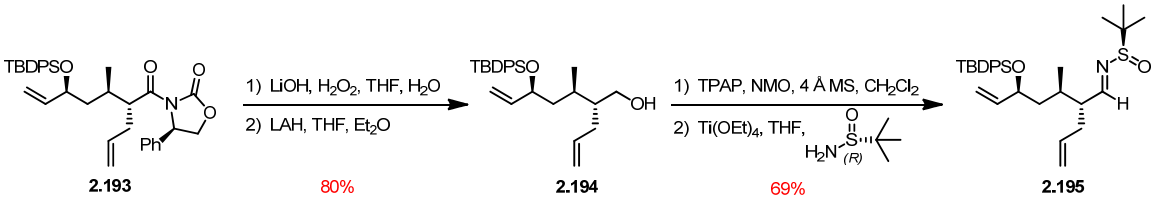
Attempts at reductive cleavage of the auxiliary using $LiBH_4$ afforded the desired alcohol in only 30% yield (Scheme 2.11.6).



2.193 2.194

Scheme 2.11.6 Cleavage of oxazolidinone auxiliary.

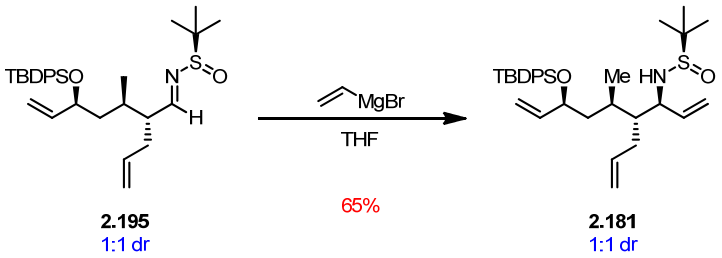
In order to more efficiently make use of our material at this stage, we opted to use a two-step removal of the oxazolidinone in an attempt to obtain the alcohol in better yields. Hydrolysis of the oxazolidinone to the carboxylic acid with LiOH and H_2O_2 followed by reduction of the acid with LAH afforded the desired alcohol in 80% yield over two steps, a drastic improvement over the single step reduction. Oxidation of the alcohol using Ley oxidation conditions provided the aldehyde in 85% yield. Condensation with (*R*)-*tert*-butanesulfinamide provided the chiral imine in 81% yield (69% over two steps) (Scheme 2.11.7).



2.193 80% 2.194 69% 2.195

Scheme 2.11.7 Synthesis of chiral imine 2.195.

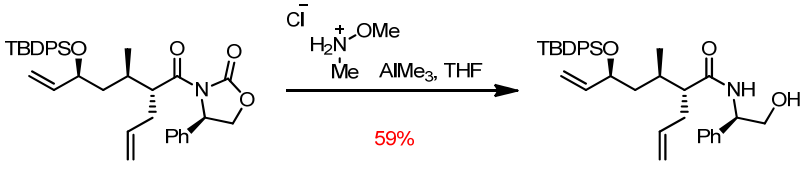
Addition of vinyl Grignard to the imine proceeded in a moderate 65% yield and 1:1 diastereoselectivity with the diastereomers separable by column chromatography (Scheme 2.11.8).



2.195 1:1 dr **2.181** 1:1 dr

Scheme 2.11.8 Grignard addition to sulfinimine.

In an attempt to improve the selectivity for the desired diastereomer, we investigated other ways to set the amine stereocenter. Attempts at preparation of the Weinreb amide directly from oxazolidinone 2.193 through a transamination reaction with $AlMe_3$ resulted in production of the 1,2-amino alcohol formed as a result of ring opening of the oxazolidinone, rather than the desired Weinreb amide (Scheme 2.11.9).



2.193 **2.196**

Scheme 2.11.9 Ring opening of oxazolidinone.

This unexpected result, however, proved to be beneficial. The amino alcohol could be crystallized from $MeCN/H_2O$ to yield X-ray suitable crystals. Crystals were

obtained as thin, colorless needles. Due to significant positional disorder in the structure, diffraction quality was poor at high angles requiring the use of a rotating-anode to obtain sufficient completeness for determination of the absolute structure. The molecule crystallized in the orthorhombic space group $P2_12_12_1$ with 2 molecules in the asymmetric unit. The absolute configuration was determined with a Flack parameter of -0.0032, with an e.s.d. of 0.0383. (Figure 2.11.1).

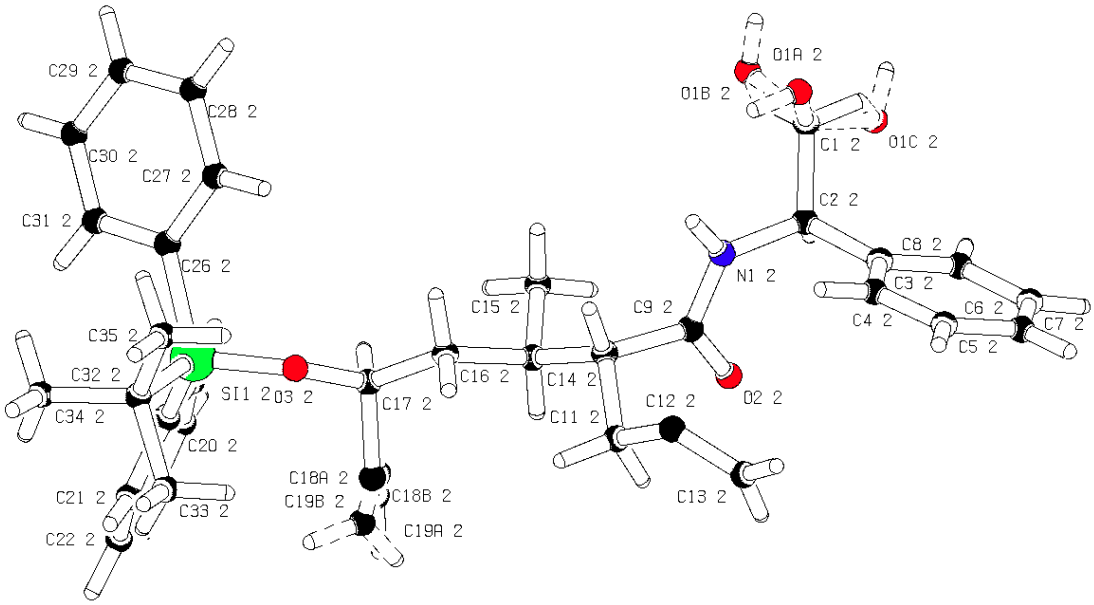
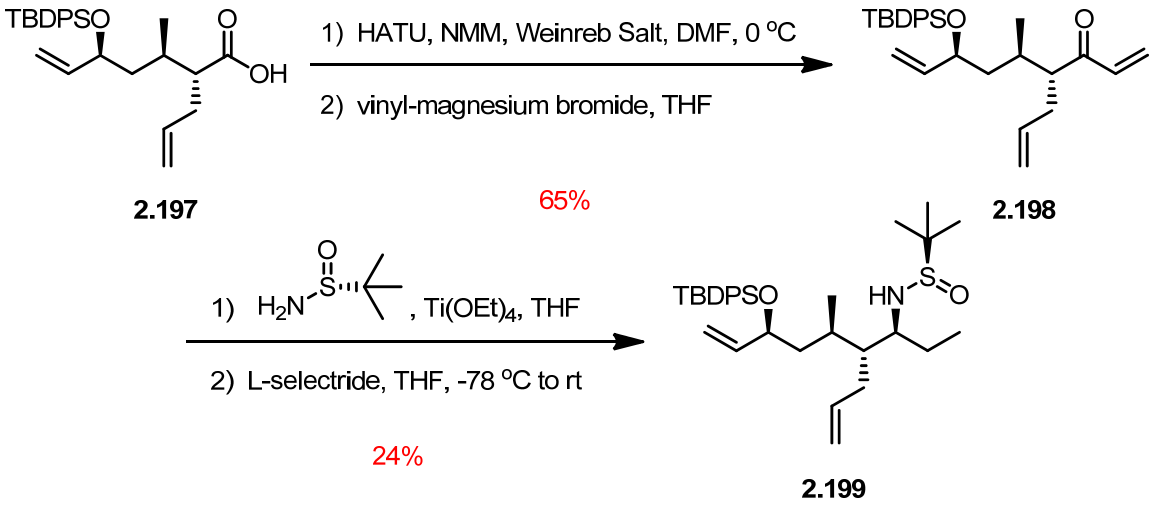


Figure 2.11.1 X-ray crystal structure of amino alcohol 2.195.

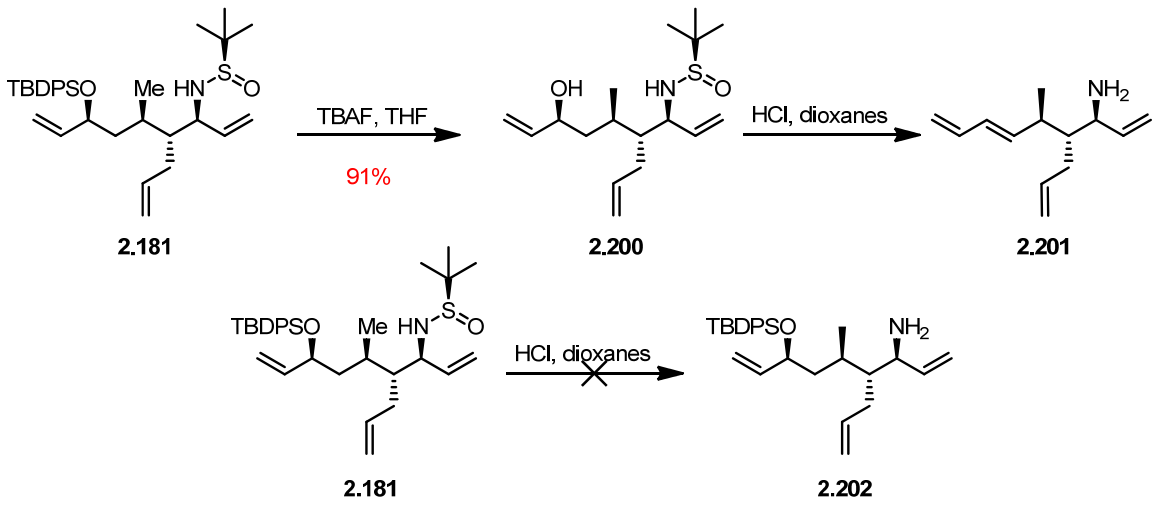
We successfully synthesized the Weinreb amide from carboxylic acid 2.197 in 85% yield. Addition of vinyl Grignard to the Weinreb amide cleanly afforded the terminal vinyl ketone 2.198 in 77% yield. Condensation with (*R*)-*tert*-butanesulfinamide yielded the chiral ketimine in poor yields, up to 24%. Attempted reduction of the

ketimine with L-selectride resulted in 1,4-reduction of the terminal olefin, followed by 1,2-reduction of the imine (Scheme 2.11.10).



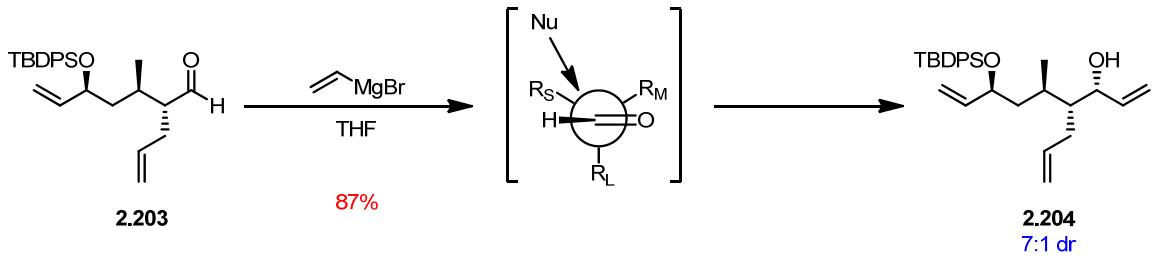
Scheme 2.11.10 Attempted selective ketimine reduction.

In order to test the key hydroformylation step, the material was carried forward with the 1:1 selectivity observed with addition of vinyl Grignard to the sulfinimine as shown in Scheme 2.11.8. Deprotection of the alcohol with TBAF cleanly afforded the allylic alcohol in 91% yield. All attempts to liberate the amine under standard acidic conditions resulted in elimination of the allylic alcohol. All efforts to deprotect the amine with the alcohol protected as the TBDPS silyl ether also resulted in complex mixtures of products with the primary product being a result of elimination (Scheme 2.11.11).



Scheme 2.11.11 Attempted global deprotection

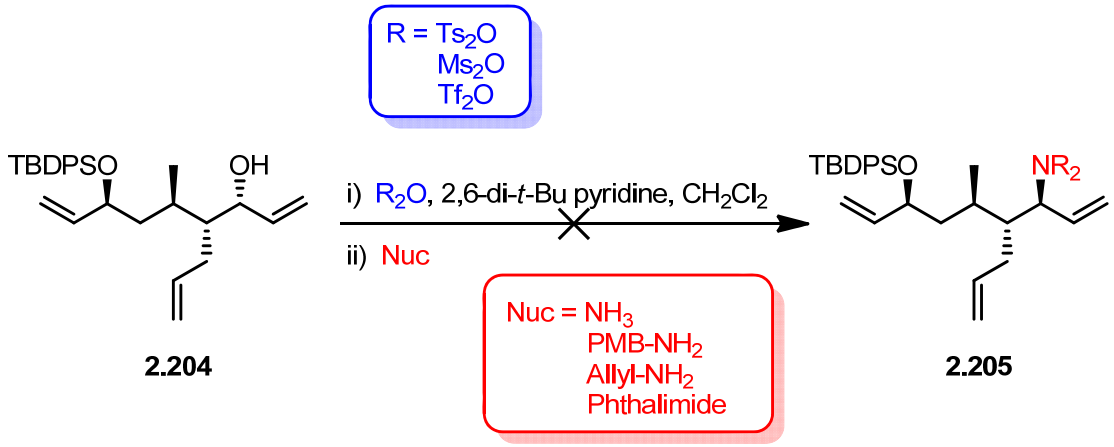
In an attempt to improve the selectivity at the amine stereocenter and eliminate the need for an acidic deprotection of the amine, vinyl Grignard was added through Felkin-Ahn control to aldehyde 2.203 to give the allylic alcohol 2.204 in 87% yield and 7:1 dr (Scheme 2.11.12).



Scheme 2.11.12 Felkin-Ahn controlled addition to aldehyde 2.203.

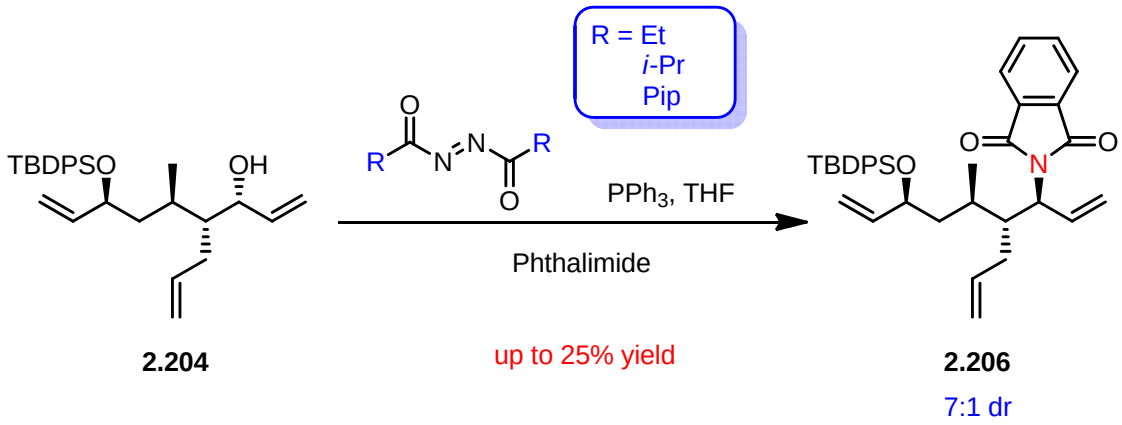
We then explored ways to convert the alcohol to a leaving group and displace it with an amine nucleophile. Unfortunately, after converting the alcohol to the tosylate,

mesylate, and triflate derivatives, only S_N2' products were recovered upon treatment with a number of amine nucleophiles (Scheme 2.11.13).



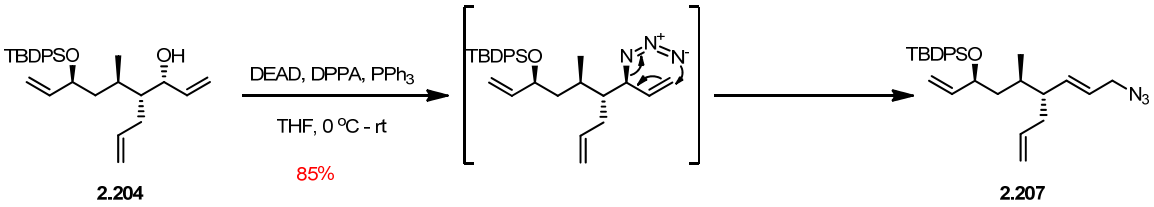
Scheme 2.11.13 Attempted S_N2 displacement of allylic alcohol 2.204.

Treatment of alcohol 2.204 under Mitsunobu conditions, using phthalimide as the nucleophilic functional group, resulted in a low yield of the desired amine product. This reaction proved to be unreliable, as product was not always obtained and yields were inconsistent and low (Scheme 2.11.14).



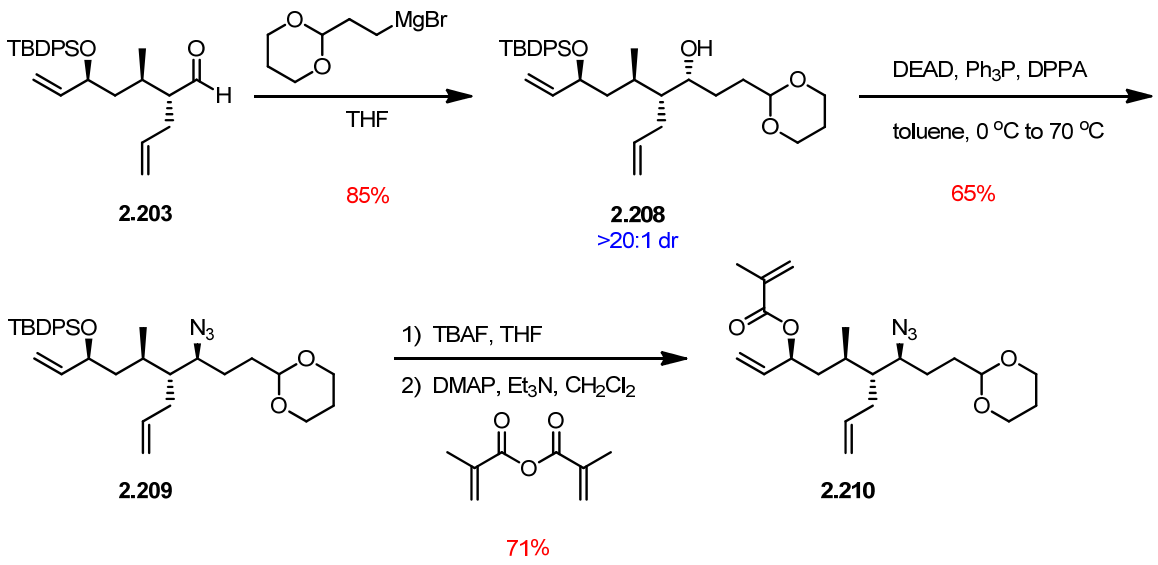
Scheme 2.11.14 Attempted amine incorporation via Mitsunobu conditions.

Treatment of alcohol 2.204 under the same Mitsunobu conditions using diphenylphosphoryl azide (DPPA) resulted in an 85% yield of a product with the correct mass by LCMS. NMR analysis revealed the presence of only 8 vinylic protons, suggesting that once the azide was incorporated, it underwent a [3,3]-sigmatropic rearrangement to give the terminal allylic azide (Scheme 2.11.15).



Scheme 2.11.15 [3,3]-sigmatropic rearrangement of allylic azide

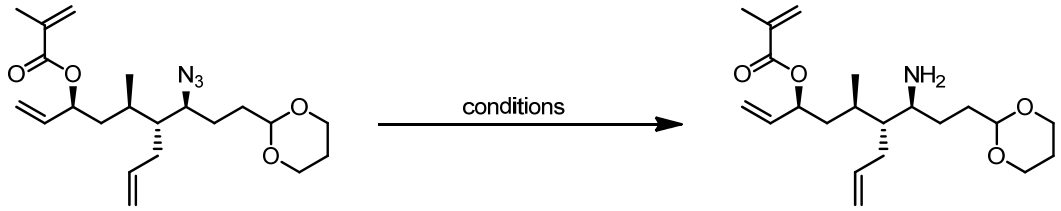
Encouraged by the selectivity in the Grignard addition to the aldehyde, we sought to eliminate the possibility of the S_N2' addition product. Therefore, we abandoned the hydroformylation approach by returning to the use of (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide as a nucleophile and subsequent acid mediated ring closure of the pyrrolidine ring. Felkin-Ahn-controlled addition to the aldehyde proceeded in 84% yield and >20:1 dr. Displacement of the alcohol under Mitsunobu conditions using diphenylphosphoryl azide (DPPA) afforded the secondary azide in only 26% yield. TBAF deprotection of the allylic alcohol followed by acylation with methacrylic anhydride gave the α,β-unsaturated ester in 71% yield over two steps (Scheme 2.11.16).



Scheme 2.11.16 Mitsunobu installation of the azide.

Initial attempts at reducing the azide through Staudinger reduction conditions resulted in only starting material. A survey of other known azide reduction conditions resulted in either recovery of starting material or complex mixtures of products.[48] A reduction of the azide using sodium-mercury amalgam in refluxing ethanol resulted in only trace amounts of the amine after heating for 24 hours (Table 2.11.1).[49]

Table 2.11.1 Survey of azide reduction conditions.



2.210 2.211

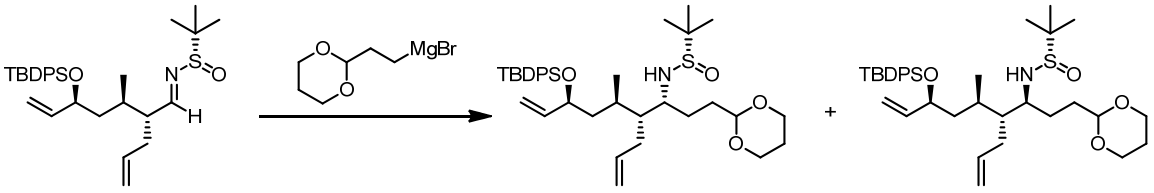
entry	Reducing Agent	Solvent	TIme	Temperature (°C)	Results
1	Ph_3P	THF/H_2O	24 h	rt	no rxn
2	$SnCl_2$	MeOH	3 h	rt	no rxn
3	$CoCl_2$, $NaBH_4$	H_2O	10 min	rt	complex mix
4	In, NH_4Cl	EtOH	3 h	70	no rxn
5	TMS-I	MeCN	10 min	0	complex mix
6	Lindlar Cat, H_2	EtOH	16 h	rt	olefin reduction
7	$InCl_3$, Et_3SiH	MeCN	1 h	0	complex mix
8	Bu_3P	Tol, Diox	6 h	85	no rxn
9	Zn, NH_4Cl	EtOH	1.5 h	85	no rxn
10	Me_3P	Diox	6 h	85	no rxn
11	Na, Hg	EtOH	24 h	70	trace amine

With poor, inconsistent yields in the azide installation and slow progress in its reduction, we opted to return to the original installation of the amine stereocenter through Grignard addition to the Ellman sulfinimine. Even with 1:1 selectivity, the ability to separate the diastereomers would afford more of the desired amine product than the multi-step azide installation/reduction sequence.

Addition of (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide proceeded in good yield (84%) and 1:1 dr. Upon further investigation, we found that Ellman and co-workers had reported some success in improving their diastereoselectivity in Grignard additions to sulfinimines by forming the Grignard reagents in Et_2O rather than THF in order to reduce the chelating ability of the solvent.[33] Unfortunately, we found that (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide does not readily form in Et_2O. Instead of using Et_2O, we sought to reduce the amount of THF in the reaction by forming the Grignard at 3.0 M

concentration, a three-fold increase from the 1.0 M concentration used previously. While the Grignard reagent will form at this high concentration, it was observed to partially precipitate out of solution. Addition of the 3.0 M Grignard to a solution of sulfinylimine in CH_2Cl_2 (0.2 M) resulted in a slight increase in diastereoselectivity (1.5:1); however, this selectivity was in favor of the undesired diastereomer. We subsequently found that the Grignard reagent could form cleanly in 2-methyltetrahydrofuran at a concentration of 3.0 M, resulting in a further increase in selectivity for the undesired diastereomer to 2.5:1. Additional dilution of the sulfinylimine in CH_2Cl_2 to 0.1 M resulted in an 86% overall yield with 4:1 selectivity in favor of the undesired diastereomer. These results suggest that non-coordinating solvents may deteriorate or reverse the selectivity of the Ellman chiral auxiliary in this case (Table 2.11.2).

Table 2.11.2 Grignard addition to sulfinimine.



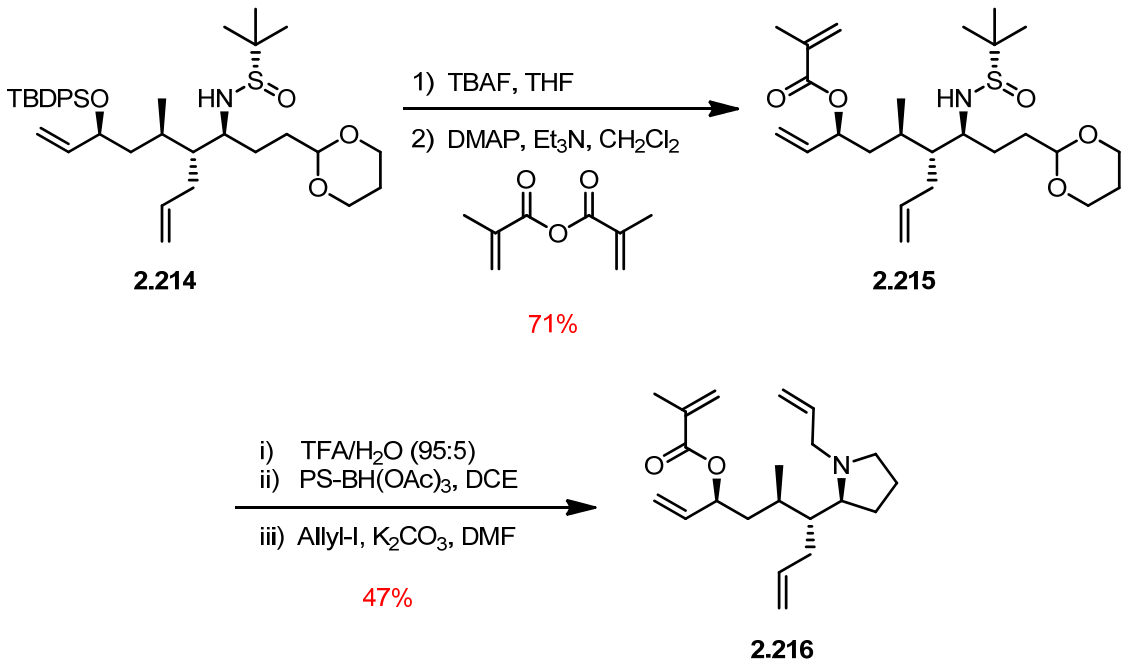
2.212 **2.213** **2.214**

Entry	Solvent	Imine Conc.	RMgX Solvent	RMgX Conc.	% Yield	dr
1	CH_2Cl_2	0.2 M	THF	1.0 M	90	1:1
2	CH_2Cl_2	0.2 M	Ether	1.0 M	no rxn	-
3	CH_2Cl_2	0.2 M	THF	3.0 M	61	1.5:1
4	CH_2Cl_2	0.2 M	2-Me THF	3.0 M	83%	2.7:1
5	CH_2Cl_2	0.1 M	2-Me THF	3.0 M	86%	4:1

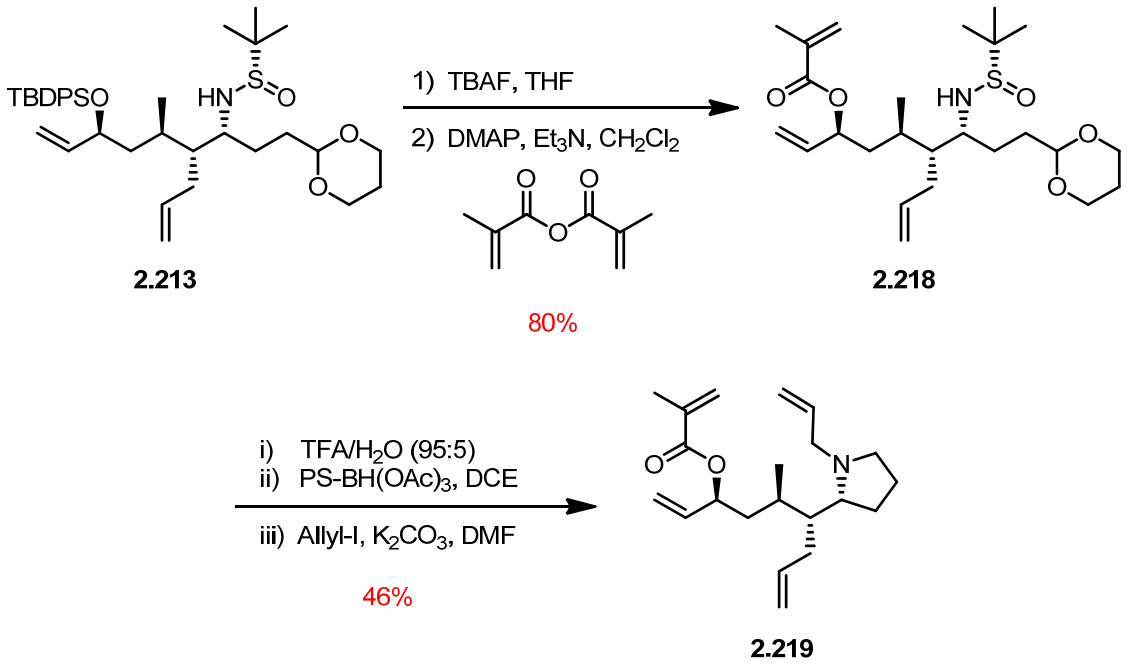
*In all cases, Grignard was added at -45 °C followed by warming to rt and stirring for 18 h.

Unable to improve the selectivity for the desired Grignard addition product, we moved forward with our effort toward the total synthesis of stemaphylline. Silyl

deprotection of the allylic alcohol with TBAF followed by acylation with methacrylic anhydride gave the α,β-unsaturated ester in 80% yield over two steps (Scheme 2.11.17). We then focused on a one-pot sequence involving global deprotection/cyclization of the amine and the acetal, reductive amination, and alkylation to give the *N*-allyl pyrrolidine ring. Treatment with 95:5 TFA/H_2O at room temperature for 5 min followed by removal of the solvent *in vacuo* gave the crude imine. Resuspension in 1,2-dichloroethane (DCE) followed by addition of polymer-supported triacetoxyborohydride (PS-$BH(OAc)_3$) and rotation for 3 hours gave the saturated pyrrolidine ring. After filtration (to remove the polymer supported reagent) and concentration, the crude pyrrolidine was resuspended in DMF, followed by addition of allyl iodide and K_2CO_3. After stirring for an additional 3 hours, the reaction was quenched and purified to give the *N*-allyl pyrrolidine in 47% yield for the 5-step, one-pot sequence (Scheme 2.11.17). The corresponding stereoisomer bearing the opposite amine stereocenter was also synthesized in an analogous fashion with similar yields (Scheme 2.11.18).



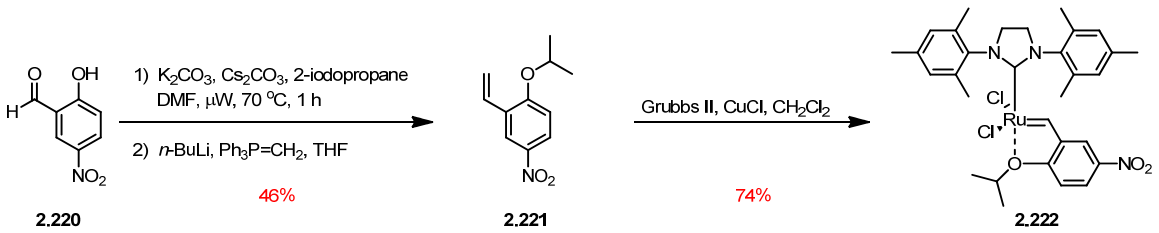
Scheme 2.11.17 Synthesis of tandem-RCM precursor.



Scheme 2.11.18 Synthesis of C-9a epimeric tandem-RCM precursor.

With the allyl-pyrrolidine in hand, we were ready to attempt the tandem ring-closing metathesis reaction to close the 7-membered ring of the azabicyclic core and the α,β-unsaturated gamma lactone. Having larger quantities of the undesired pyrrolidine from our studies on the asymmetric Grignard addition, we chose to first explore the tandem ring closing metathesis with this substrate. It is well established in the literature that compounds containing basic nitrogen atoms are problematic substrates for olefin metathesis. It is assumed that the basic nitrogen can coordinate to the metal center and interfere with catalytic activity. In our previous work on the formation of azabicyclic ring systems, we circumvented this by forming the TFA salt of our tertiary amines.[42] This allowed for the successful closure of rings of varying sizes using Grubbs second generation catalyst. Initial attempts using 1.0 eq of TFA and 10 mol% of Grubbs II at 40 ^{o}C overnight resulted in a single ring closure observable by LCMS. An additional 10 mol% was added and the reaction was heated to 80 ^{o}C, after which the major product was still from the mono-ring closure with only a hint of a *bis*-closure product visible by LCMS. Unfortunately, attempts to isolate this *bis* ring closure product by reverse-phase chromatography were unsuccessful.

Grela and co-workers reported a catalyst, related to that of Hoveyda, with improved reactivity and mild reaction conditions for challenging ring closing metathesis reactions, including a protected nitrogen-containing azepane ring and a trisubstituted α,β-unsaturated δ lactone. This catalyst was easily obtained in a three-step synthesis (Scheme 2.11.19) and was shown to operate under very mild conditions (0 ^{o}C to room temperature).[50]



Scheme 2.11.19 Synthesis of Grela catalyst.

Encouraged by these findings, we prepared this catalyst and applied it in our tandem ring closing metathesis.

We found that 15 mol% of the Grela catalyst in toluene at room temperature was optimal to obtain the single ring closure product after stirring overnight. Initial NMR studies of the single ring closure product clearly showed the presence of both vinylic protons of the methacrylate group, which indicated that the lactone ring had not closed first. As shown in Figure 2.11.2, there are two competing 7-membered rings that could form in the RCM of tetraolefin 2.219. We hoped that the more sterically accessible olefins (C-6 and C-7) would close preferentially (2.224) over the 7-membered ring between C-7 and C-13 (2.223). 2-D NMR analysis supported the assignment of ring closure between C-6 and C-7, indicated by the presence of signals between C-7 and C-5 (HMBC, TOCSY), which would not be present in azepine 2.223. We also did not observe a signal between C-7 and C-12, further supporting the presence of the pyrrolo[1,2-α]azepine ring system.

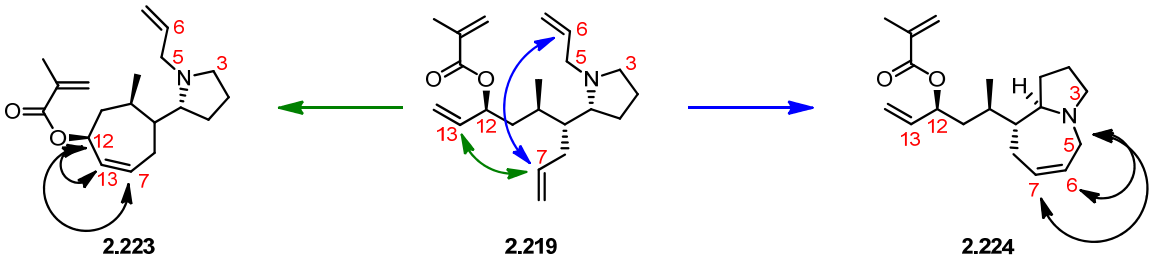


Figure 2.11.2 Possible ring closures and their key 2D-NMR correlations.

Encouraged by the results of the single ring closure, we then added an additional 25 mol% catalyst and heated the reaction to 90 ^{o}C with continued stirring for 24 hours. By this method, we were able to obtain the product of tandem ring closure (2.225) in 26% isolated yield after purification via reverse phase chromatography.

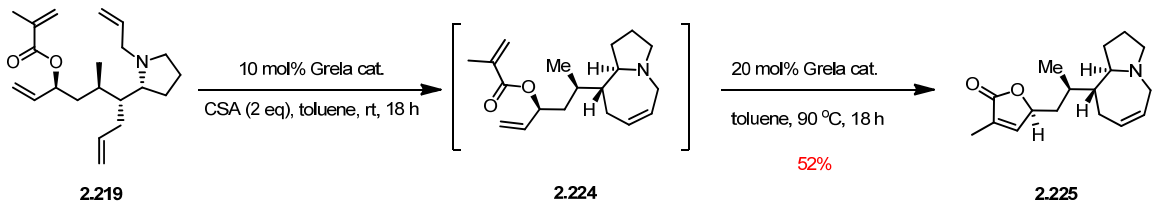
With this result, we next studied the effect of the acid on the closure of the azepine ring, examining acids with a range of pKa values (see Table 2.11.3). Without an acid additive, the reaction did not progress. CSA, possessing a pKa value in the middle of the acids surveyed, was found to provide the greatest degree of conversion as measured by LC/MS (entry 5). Doubling the amount of CSA to 2 equiv was found to greatly improve the efficiency of the reaction (entry 6), resulting in complete consumption of tetraene within 6 h and affording 65% isolated yield of pyrroloazepine 2.224.

Table 2.11.3 Acid screen for tandem ring closing reaction.

Entry	Acid (pK_a)	Equiv.	Catalyst	**2.216 : 2.224**
1	--	--	Grela (10%)	no conv.
2	TFA (-0.25)	1	Grela (10%)	1:4.5
3	PTSA (-2.8)	1	Grela (10%)	1:2.2
4	AcOH (4.76)	1	Grela (10%)	>1:20
5	CSA (1.2)	1	Grela (10%)	1:1.3
6	CSA (1.2)	2	Grela (10%)	>20:1

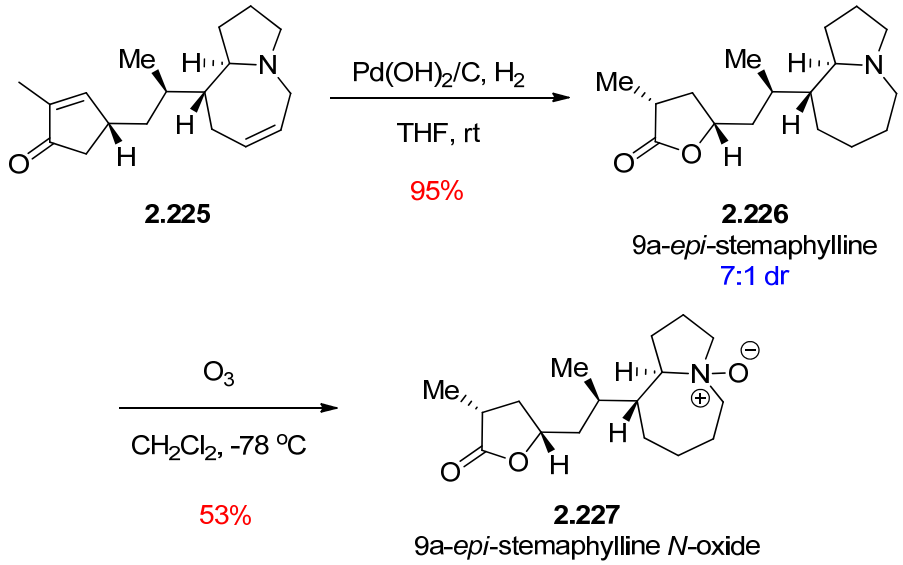
*To a solution of tetraene in toluene was added an acid. After stirring for 10 minutes a catalyst (10%) was added and stirring was continued at rt for 7 h.

With optimized conditions for closure of the azepine ring, we applied these conditions (Table 2.11.3, entry 6) to the tandem ring closure of tetraene 2.219, heating the reaction to 90 ^{o}C after complete conversion to 2.224. While conversion to *bis*-ring closure product was observed by LC/MS (~20% conversion), the use of additional catalyst (2 x 10 mol%) and extended heating was required for full conversion of 2.224 to 2.225. A small selection of metathesis catalysts were screened with these optimized conditions (Hoveyda Grubbs II, Zhan 1B, Grubbs II, Schrock catalyst). Grela catalyst and Hoveyda Grubbs II were found to be optimal and exhibited comparable activity. Thus, reaction of tetraene 2.219 in the presence of CSA (2 equiv) and Grela catalyst 2.222 (3 x 10 mol%) afforded 2.225 in 52% isolated yield (Scheme 5). Full 2-D NMR characterization of 2.225 supported our structural assignment of the tandem ring closure product.



Scheme 2.11.20 *Bis* ring-closing metathesis of epimeric tetraene.

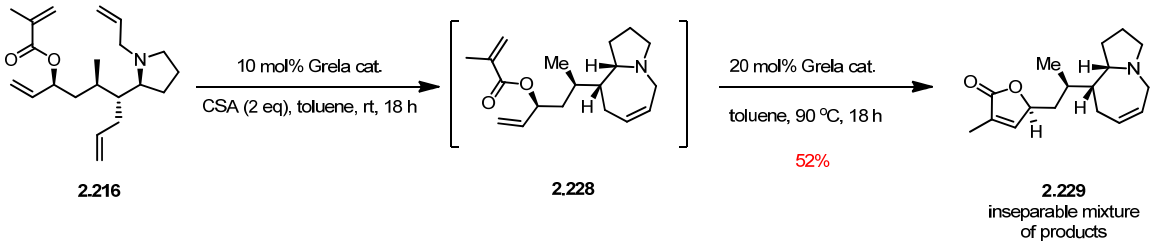
As shown in Scheme 2.11.21, intermediate 2.225 was carried forward to unnatural analog 9a-*epi*-stemaphylline 2.226 through olefin reduction employing Pearlman's catalyst,[51] which also set the final C-14 stereocenter in 95% yield and 7:1 dr. Reaction of 2.226 in the presence of O_3 led to the corresponding *N*-oxide 2.227 (53% yield).[52]



Scheme 2.11.21 Synthesis of 9a-*epi*-stemaphylline and 9a-*epi* stemaphylline *N*-oxide.

With successful conditions for the tandem ring closing metathesis reaction, we turned our attention toward the synthesis of stemaphylline, subjecting pyrollidine tetraene 2.216 to the optimized tandem ring closing metathesis reaction conditions. Suprisingly,

the ring closure proceeded more slowly than expected, and upon isolation an inseparable mixture of products was obtained. In consideration that olefin migration could be leading to epimerization, we tested the addition of 1,4-benzoquinone, reported to suppress undesirable olefin migration;[53] however, a mixture of *bis*-ring closure products was still observed, wherein the C-12 carbon of the lactone was epimerized.



Scheme 2.11.22 Attempted *bis* ring closing metathesis

To elucidate when the suspected epimerization was occuring, the reaction was stopped after closure of the azepine ring in the presence of Hoveyda Grubbs II, CSA, and 1,4-benzoquinone at room temperature. Isolation of mono-ring closure product 2.228 demonstrated that a single product was formed and that closure of the γ-lactone was the problematic step. Unfortunately, subjection of 2.228 to a variety of acid additives and RCM catalysts was ineffective in suppressing the formation of the mixture of products.

In an attempt to gain insight into the differences in reactivity between tetraene 2.216 and 2.219 and azepeines 2.224 and 2.228, the four compounds were sketched and minimized using the MMFF force field to an energy gradient of <0.01 while preserving the stereochemistry. These calculations were performed using MOE (v2012.10; Chemical Computing Group; www.chemcomp.com).

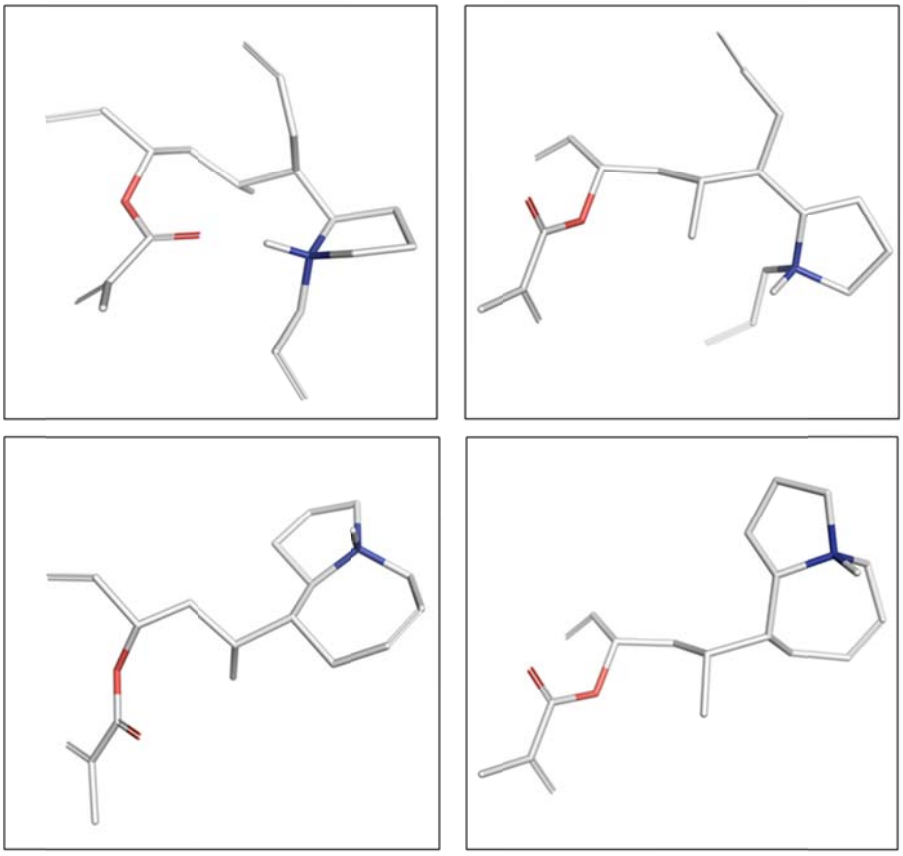
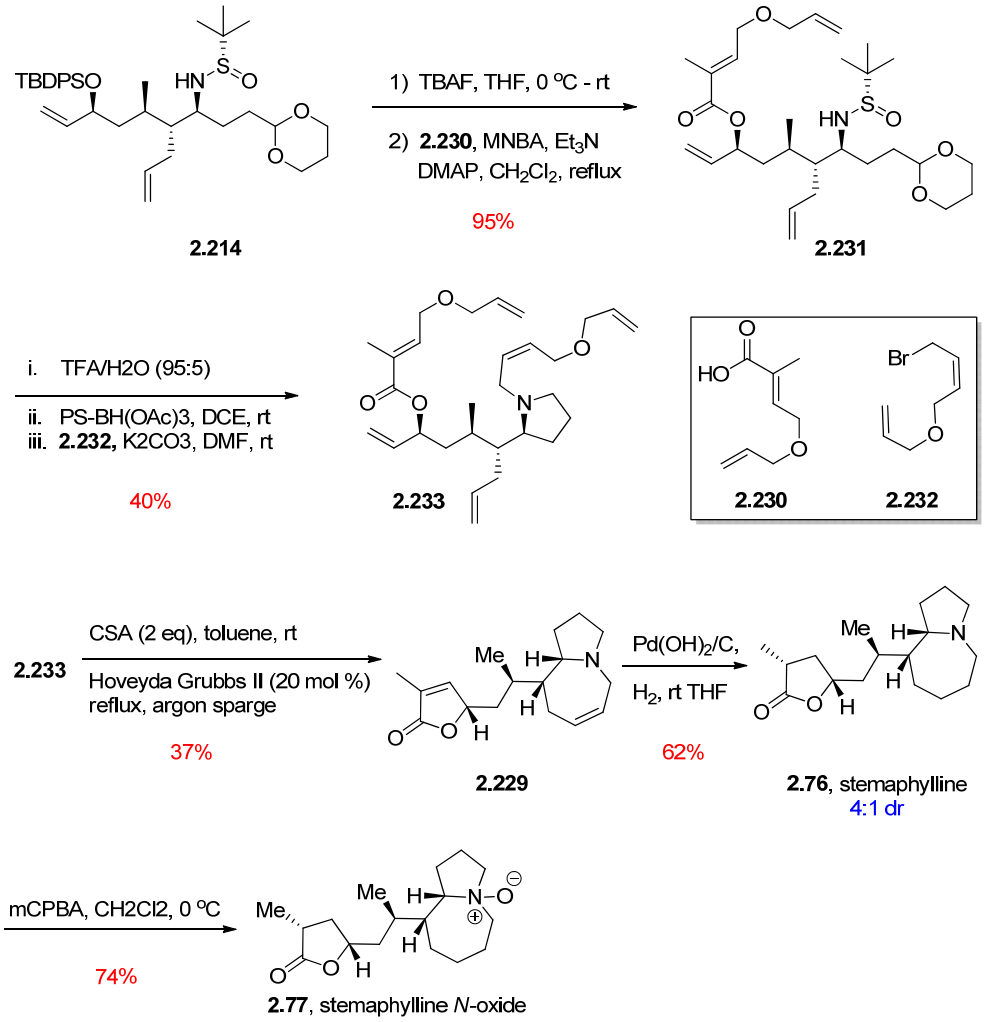


Figure 2.11.3 Energy minimized 3D structures of 2.216 (top left), 2.219 (top right), 2.224 (bottom left), and 2.228 (bottom right).

The resulting 3-dimensional structures revealed that tetraene 2.216 possesses an intramolecular hydrogen bond which could preorganize the substrate for ring closing metathesis. In contrast, tetraene 2.219 possesses a more disordered conformation with the olefins splayed apart, providing a possible rationale for the lower reactivty of tetraene 2.219 in the RCM reaction. Examination of azepines 2.224 and 2.228 revealed a striking difference in the orientation of the α,β-unsaturated ester and its proximity to the olefin RCM partner. While the two olefins in intermediate 2.224 are in close proximity, the reacting olefins in 2.228 are pointed away from one another. This disfavorable

orientation of the γ-lactone in 2.228 then allows for competing reaction pathways or epimerization of the C-12 stereocenter during the course of the reaction.

From this analysis, we began investigation of methods to expedite the closure of the γ-lactone in order to prevent the suspected epimerization. Recently, Hoye and coworkers have developed a relay ring closing metathesis (RRCM) strategy[54] to accelerate reactivity for difficult substrates and as a means to preload the ruthenium metathesis catalyst at a desired olefin to improve selectivity. Incorporating dienes 2.230[55] and 2.232[56] into intermediate 2.214, we arrived at RRCM substrate 2.233 in order to determine if directing the formation of the ruthenium alkylidene would prove beneficial. Reaction at room temperature revealed significant amounts of truncation products, presumably intermediates 2.216 and 2.228. However, vigorous reflux and argon sparge led to rapid formation of the desired ring closing metathesis product 2.229 with, excitingly, only minor epimerization (10:1). Reduction with Pearlman's catalyst[53] afforded stemaphylline in 62% yield and with 4:1 selectivity at the C-12 stereocenter. Spectral and rotation data of the synthetic material was generally in agreement with that reported for the natural product 2.76, though complicated by the by the presence of a 4:1 ratio of inseparable products.[26] Further confirmation was acheived by conversion to stemaphylline *N*-oxide 2.77. Attempts to form the *N*-oxide in the presence of O_3 was ineffective; however formation with mCPBA in CH_2Cl_2 at 0 °C afforded stemaphylline *N*-oxide 2.77 in 74% yield, isolated as a single isomer (Scheme 2.11.23).



Scheme 2.11.23 Relay RCM approach to stemaphylline and stemaphylline *N*-oxide.

The synthetic 2.77 was in complete agreement with the spectral and rotation data reported for the natural product, thus completing the first total synthesis of both 2.76 and 2.77.[26] Furthermore, the observed fragmentation pattern of the synthetic material matched that reported by Mungkornasawakul and coworkers (Figure 2.11.4). High resolution mass spectrometry (HRMS) fragmentation data of the reduced product clearly demonstrated the presence of the pyrrolo[1,2-α]azepine ring system and a fragment ion at *m/z* 180 ($[M - C_5H_7O_2]^+$), which corresponds to the loss of an α-methyl-γ-butyrolactone moiety often found in *Stemona* alkaloids.

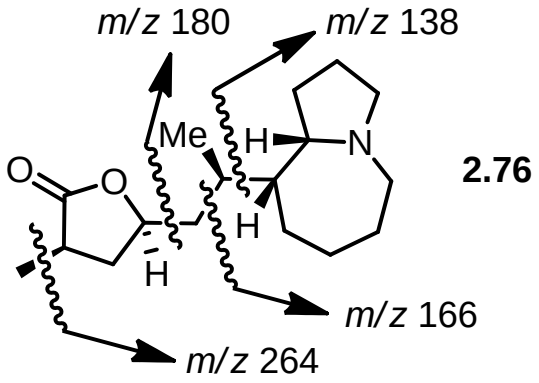


Figure 2.11.4 High resolution mass spec fragment analysis of 2.76

In conclusion, we have completed the first total synthesis of both stemaphylline 2.76 (19 steps) and stemaphylline *N*-oxide 2.77 (20 steps), via a tandem *bis*-RCM strategy, as well as unnatural 9a-*epi*-stemaphylline 2.226 and 9a-*epi*-stemaphylline *N*-oxide 2.227. The linear tetraene substrate leading to 2.226 and 2.227 was found by modelling to be pre-organized for the *bis*-tandem RCM, and smoothly afforded the desired unnatural products; however, the tetraene corresponding to natural 2.76 and 2.77 was disorganized, leading to lower reactivity and ruthenium alklyidene-mediated epimerization. Thus, adopting a relay ring closing metathesis (RRCM) strategy enabled access to 2.76 and 2.77. Biological evaluation of both natural and unnatural analogues is underway and will be reported in due course.

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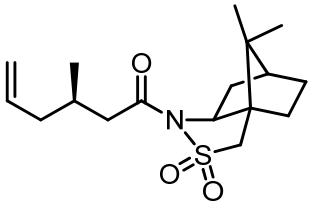
General Experimental

All reagents were purchased from commercial suppliers and purified as needed according to the procedures of Armarego and Chai1. Analytical thin-layer chromatography (TLC) was performed on 250 μm silica gel plates from Sorbent Technologies. Visualization was accomplished via UV light, and/or the use of potassium permanganate and phosphomolybdic acid solutions followed by application of heat. Chromatography was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies or Silica RediSep Rf flash columns on a CombiFlash Rf automated flash chromatography system. All 1H and 13C NMR spectra were recorded on a Bruker AV-400 (400 MHz and 100 MHz respectively). All 1H and 13C chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.16 (CDCl3) and δ 7.16 and δ 128.06 (C6D6). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration. Low resolution mass spectra (LCMS) were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra (HRMS) were recorded on a Waters Qtof-API-US plus Acquity system with ES as the ion source. Crystals for x-ray structure determination were mounted on a cryoloop and maintained at 100 K using a Bruker KryoFlex cryostat. Data were collected using a Bruker Microstar rotating-anode X-ray generator operated at 2.7 kW. Diffraction data were collected using Montel multi-layer confocal optics and a Bruker X8 kappa axis goniometer with a Bruker Proteum PT135 CCD area detector. Diffraction data scans were calculated using Cosmo software and the diffraction data integrated and scaled using Proteum2 software. Absorption correction was applied using SADABS (Sheldrick, 2006). The space group

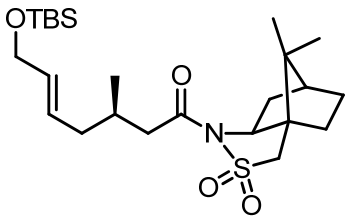
was determined using XPREP (Sheldrick, 2006). Diffraction data were phased and a molecular model was built using SIR2011 (Burla, et al., 2012). Refinement was performed using SHELXL (Sheldrick, 2006). Manual inspection of the refinement was done using COOT (Emsley & Cowtan, 2004) and PLATON (Spec, 2006).



(3*R*)-1-((6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo [c]isothiazol-1-yl)-3-methylhex-5-en-1-one (2.111)

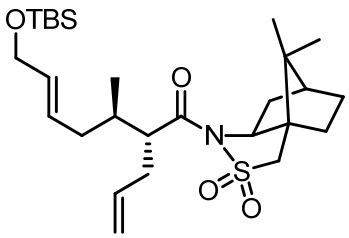
A solution of CuBr·DMS (1.46 eq) and LiCl (1.6 eq) in THF (0.5 M) at -78 ^{o}C was transferred to a solution of allylmagnesium bromide (1.2 eq) at -78 ^{o}C in THF via cannula. TMS-Cl (1.5 eq) was added followed by a solution of (*E*)-1-((6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)but-2-en-1-one in THF (0.3 M). The reaction continued stirring at -78 ^{o}C for 3 h. The reaction was quenched by the addition of 9:1 NH_4Cl/NH_4OH, partitioned between ether and water, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated *in vacuo*. Purification via flash chromatography (Hex:EtOAc 9:1) afforded the pure desired in 91% overall yield and 9:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.76 (ddt, J_1 = 23.9, J_2 = 10.6, J_3 = 7.1 Hz, 1H); 5.03 (d, J_1 = 6.2 Hz, 1H); 4.99 (s, 1H); 3.87 (t, J_1 = 6.2 Hz, 1H); 3.45 (q, J = 13.3 Hz, 2H); 2.75 (dd, J_1 = 16.0 Hz, J_2 = 6.3 Hz, 1H); 2.48 (dd, J_1 = 16.3 Hz, J_2 = 7.5 Hz, 1H); 2.22 (sext, J = 6.8 Hz, 1H); 2.12-1.97 (m, 4H); 1.96-1.83 (m, 3H); 1.45-1.30 (m, 2H); 1.15 (s, 3H); 0.98-0.94 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.60; 136.64; 116.73; 65.38; 53.20; 48.44; 47.89; 44.81; 42.24; 41.07; 38.72; 33.00; 29.84;

26.62; 20.95; 20.04; 19.68.



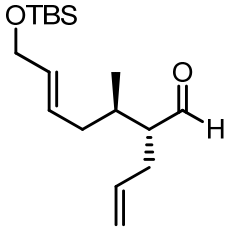
(3*R*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-1-((6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-methylhept-5-en-1-one

To a solution of (3*R*)-1-((6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-methylhex-5-en-1-one in DCM (0.25 M) was added (*Z*)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene (3.5 eq) and benzoquinone (0.1 eq). Grubbs II (0.05 eq) was added and the reaction stirred at 40 ^{o}C overnight. The reaction was cooled and concentrated under vacuum. Purification via flash chromatography (Hex:EtOAc 9:1) afforded the pure desired in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.65-5.50 (m, 2H); 4.12 (d, J = 4.5 Hz, 2H); 3.87 (t, J = 6.3 Hz, 1H); 3.45 (q, J = 13.8 Hz, 2H); 2.74 (dd, J_1 = 16.0 Hz, J_2 = 6.0 Hz, 1H); 2.48 (dd, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 1H); 2.19 (sext, J = 6.8 Hz, 1H); 2.14-2.02 (m, 3H); 2.01-1.92 (m, 1H); 1.92-1.83 (m, 3H); 1.58 (s, 1H); 1.45-1.29 (m, 2H); 1.14 (s, 3H0; 0.98-0.92 (m, 6H); 0.89 (s, 9H); 0.06 (s, 6H).



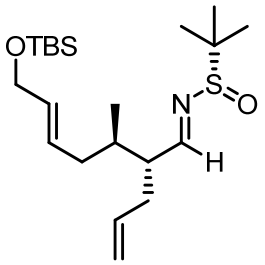
(2*R*,3*R*,*E*)-2-allyl-7-((*tert*-butyldimethylsilyl)oxy)-1-((6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-methylhept-5-en-1-one (2.114)

To a solution of (2*R*,3*R*,*E*)-2-allyl-7-((*tert*-butyldimethylsilyl)oxy)-3-methylhept-5-enal in THF (0.15 M) at -78 ^{o}C was added KHMDS (1.05 eq) dropwise. The reaction was stirred at -78 ^{o}C for 1.5 h. A solution of allyl iodide (3.0 eq) and HMPA (3.0 eq) in THF (1.5 M) was transferred to the reaction via cannula. The reaction continued stirring at -78 ^{o}C for 4 h. The reaction was quenched by the addition of brine, partitioned between Et_2O and water, extracted with Et_2O (3x), dried over Na_2SO_4, and concentrated. Purification via flash chromatography (Hex:EtOAc 9:1) afforded the pure desired in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.87-5.73 (m, 1H); 5.64-5.53 (m, 1H); 5.11-4.92 (m, 2H); 4.12 (d, J = 3.3 Hz, 1H); 3.90 (t, J = 6.4 Hz, 1H); 3.46 (q, J = 13.9 Hz, 2H); 3.05-2.96 (m, 1H); 2.53-2.44 (m, 1H); 2.43-2.33 (m, 1H); 2.04 (d, J = 6.3 Hz, 1H); 2.00-1.80 (m, 4H); 1.44-1.29 (m, 1H); 1.15 (s, 3H); 0.97-0.92 (m, 5H); 0.90 (s, 9H); 0.06 (s, 6H).



(2*R*,3*R*,*E*)-2-allyl-7-((*tert*-butyldimethylsilyl)oxy)-3-methylhept-5-enal (2.115)

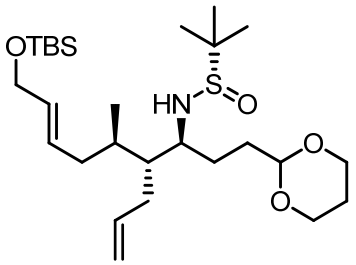
To a solution of (2*R*,3*R*,*E*)-2-allyl-7-((*tert*-butyldimethylsilyl)oxy)-1-((6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-methylhept-5-en-1-one in 4:1 Et_2O/THF (0.1 M) at 0 ^oC was added LAH (3.5 eq). The reaction was stirred at 0 ^oC for 2 h. The reaction was quenched by the addition of NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated under vacuum. The crude product was then diluted in CH_2Cl_2 (0.1 M) and 4Å MS were added (0.5g/mmol) followed by NMO (1.48 eq). After stirring at rt for 10 min, TPAP (0.1 eq) was added and the reaction continued stirring at rt for 1 h. The reaction was filtered through Celite and concentrated *in vacuo*. Purification via flash chromatography (Hex:EtOAc 9:1) afforded the pure desired aldehyde in 81% yield over 2 steps. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.69 (d, *J* = 2.6 Hz, 1H); 5.80-5.67 (m, 1H); 5.62-5.57 m, 2H); 5.11-4.99 (m, 2H); 4.13 (m, 1H); 4.13 (d, *J* = 2.7 Hz, 1H); 2.52-2.42 (m, 1H); 2.39-2.31 (m, 1H); 2.28-2.16 (m, 2H); 2.08-1.89 (m, 2H); 0.98-0.95 (m, 3H); 0.91 (s, 9H); 0.07 (s, 6H).



(*S*,*E*)-*N*-((2*R*,3*R*,*E*)-2-allyl-7-((*tert*-butyldimethylsilyl)oxy)-3-methylhept-5-en-1-ylidene)-2-methylpropane-2-sulfinamide (2.116)

To a solution of (2*R*,3*R*,*E*)-2-allyl-7-((*tert*-butyldimethylsilyl)oxy)-3-methylhept-5-enal in THF (0.2 M) was added (*S*)-(-)-2-methyl-2-propanesulfinamide (1.0 eq) followed by $Ti(OEt)_4$ (2.0 eq). After stirring at rt overnight, the reaction was quenched by the addition of $NaHCO_3$, extracted with EtOAc (5x), dried over Na_2SO_4, and concentrated

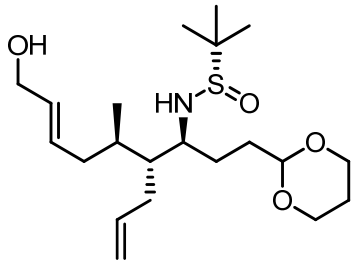
under vacuum. Purification via flash chromatography (Hex:EtOAc 9:1) afforded the pure desired aldimine in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J* = 5.9 Hz, 1H); 5.80-5.67 (m, 1H); 5.65-5.51 (m, 2H); 5.10-4.97 (m, 2H); 4.13 (d, *J* = 3.6 Hz, 1H); 2.68-2.59 (m, 1H); 2.50-2.40 (m, 1H); 2.36-2.26 (m, 1H); 2.23-2.09 (m, 1H); 2.05-1.83 (m, 2H); 1.21 (s, 9H); 0.90 (s, 9H); 0.06 (s, 6H).



(*S*)-*N*-((3*S*,4*R*,5*R*,*E*)-4-allyl-9-((*tert*-butyldimethylsilyl)oxy)-1-(1,3-dioxan-2-yl)-5-methylnon-7-en-3-yl)-2-methylpropane-2-sulfinamide (2.117)

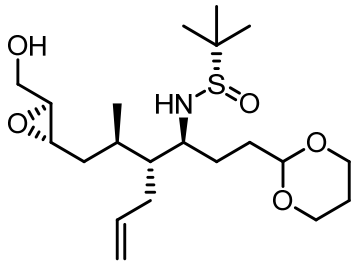
To a suspension of Mg powder (25.0 eq) in THF (1.0 M) was added an iodine crystal followed by 2-(2-bromoethyl)-1,3-dioxane (20.0 eq). The Grignard reagent was allowed to form for 1 h at rt. The Grignard was transferred via cannula to a solution of (*S*,*E*)-*N*-((2*R*,3*R*,*E*)-2-allyl-7-((*tert*-butyldimethylsilyl)oxy)-3-methylhept-5-en-1-ylidene)-2-methylpropane-2-sulfinamide in THF (0.1 M) at -48 ^{o}C. The reaction was allowed to slowly warm to rt and continued stirring overnight. The reaction was quenched by the addition of sat aq NH_4Cl followed by extraction with EtOAc (3x). After drying over Na_2SO_4 and concentrating under vacuum, the addition product was purified via flash chromatography (Hex:EtOAc 0-60%) to afford the pure product in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.02-5.82 (m, 1H); 5.64-5.49 (m, 2H); 5.09 (d, *J* = 17.2 Hz, 1H); 5.03 (d, *J* = 10.1 Hz, 1H); 4.51 (t, *J* = 5.0 Hz, 1H); 4.14-4.06 (m, 4H); 3.74 (t, *J* = 12.1 Hz, 2H); 3.59 (d, *J* = 9.5 Hz, 1H); 3.42-3.33 (m, 1H); 2.34-2.14 (m, 3H); 2.14-1.92

(m, 3H); 1.90-1.71 (m, 2H); 1.68-1.38 (m, 5H); 1.33 (d, J = 13.5 Hz, 1H); 1.19 (s, 9H); 0.90 (s, 9H); 0.06 (s, 6H).



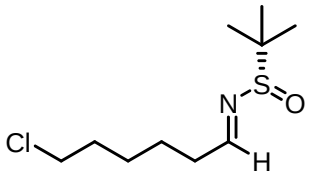
(*S*)-N-((3*S*,4*R*,5*R*,*E*)-4-allyl-1-(1,3-dioxan-2-yl)-9-hydroxy-5-methylnon-7-en-3-yl)-2-methylpropane-2-sulfinamide (2.123)

To a solution of (*S*)-*N*-((3*S*,4*R*,5*R*,*E*)-4-allyl-9-((*tert*-butyldimethylsilyl)oxy)-1-(1,3-dioxan-2-yl)-5-methylnon-7-en-3-yl)-2-methylpropane-2-sulfinamide in THF (0.1 M) at 0 ^{o}C was added TBAF (2.0 eq). The reaction was warmed to rt and continued stirring overnight. The reaction was quenched by the addition of H_2O, extracted with EtOAc, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction was purified via flash chromatography (DCM/MeOH 9:1) which afforded the product as a yellow oil in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.91-5.79 (m, 1H); 5.70-5.56 (m, 2H); 5.08 (dd, J_1 = 17.0 Hz, J_2 = 1.3 Hz, 1H); 5.02 (d, J = 10.1 Hz, 1H); 4.54 (t, J = 4.8 Hz, 1H); 4.12-4.03 (m, 4H); 3.74 (t, J = 12.1, 2H); 3.43-3.34 (m, 1H); 3.24 (d, J = 9.1 Hz, 1H); 2.30-2.12 (m, 3H); 2.05 (qt, J_1 = 12.9 Hz, J_2 = 5.0 Hz, 1H); 1.99-1.90 (m, 1H); 1.90-1.80 (m, 1H); 1.79-1.70 (m, 2H); 1.70-1.61 (m, 2H); 1.55-1.48 (m, 1H); 1.46 (t, J = 5.9 Hz, 1H); 1.32 (d, J = 13.4 Hz, 1H); 1.19 (s, 9H); 0.88 (d, J = 6.8 Hz, 3H).



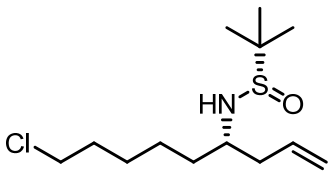
(*S*)-*N*-((3*S*,4*R*)-1-(1,3-dioxan-2-yl)-4-((*R*)-1-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)propan-2-yl)hept-6-en-3-yl)-2-methylpropane-2-sulfinamide (2.124)

To a suspension of 4Å MS in CH_2Cl_2 at -20 ^oC was added (+)-DET (1.44 eq) and Ti(O*i*Pr)$_4$ followed by stirring at -20 ^oC for 10 min. *t*-BuOOH (2.0 eq) was added and the reaction stirred for an additional 30 min. A solution of (*S*)-*N*-((3*S*,4*R*,5*R*,*E*)-4-allyl-1-(1,3-dioxan-2-yl)-9-hydroxy-5-methylnon-7-en-3-yl)-2-methylpropane-2-sulfinamide in CH_2Cl_2 (0.1 M) was added and the reaction stirred at -20 ^oC for 24 h. The reaction was quenched with 30% aq NaOH/NaCl solution, filtered through Celite, and concentrated *in vacuo*. Purification via flash chromatography (DCM/MeOH 9:1) afforded the pure desired epoxide in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.84 (ddt, J_1 = 7.0 Hz, J_2 = 10.0 Hz, J_3 = 7.3 Hz, 1H); 5.09 (d, J = 17.4 Hz, 1H); 5.03 (d, J = 10.4 Hz, 1H); 4.55 (t, J = 4.9 Hz, 1H); 4.07 (dd, J_1 = 10.9 Hz, J_2 = 4.9 Hz, 2H); 3.89 (ddd, J_1 = 12.5 Hz, J_2 = 5.4 Hz, J_3 = 2.7 Hz, 1H); 3.74 (t, J = 12.3 Hz, 2H); 3.65 (ddd, J_1 = 11.8 Hz, J_2 = 7.3 Hz, J_3 = 4.3 Hz, 1H); 3.43-3.35 (m, 1H); 3.32-3.25 (m, 1H); 2.95 (ddd, J_1 = 6.7 Hz, J_2 = 4.4 Hz, J_3 = 2.2 Hz, 1H); 2.89-2.85 (m, 1H); 2.27-2.14 (m, 2H); 2.05 (qt, J_1 = 12.6 Hz, J_2 = 5.1 Hz, 1H); 1.97-1.86 (m, 1H); 1.86-1.79 (m, 1H); 1.79-1.63 (m, 5H); 1.62-1.49 (m, 1H); 1.46-1.28 (m, 2H); 1.20 (s, 9H); 1.01 (d, J = 6.8 Hz, 3H).



(*S*,*E*)-*N*-(6-chlorohexylidene)-2-methylpropane-2-sulfinamide (2.135)

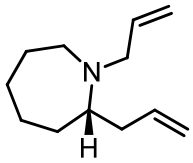
To a solution of 6-chlorohexanal (7.37 g, 54.79 mmol) in DCM (219 ml) at ambient temperature was added $CuSO_4$ (20.11 g, 126.02 mmol) and (*S*)-2-methylpropane-2-sulfinamide (7.64 g, 63.01 mmol) in a single batch. The reaction was stirred for 12 h, at which point the starting material was fully consumed by TLC analysis (4:1 Hex/EtOAc, rf = 0.35). The heterogeneous mixture was filtered through a silica pad and concentrated *in vacuo* to yield a viscous oil, which was purified by flash chromatography (4:1 Hex/EtOAc) to afford the desired product as a clear oil (12.34 g, 94%). $[\alpha]_D^{20}$ = +157.9° (*c* = 1.5, MeOH). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 8.05 (t, *J* = 4.5 Hz, 1H); 3.52 (t, *J* = 6.5 Hz, 2H); 2.53 (m, 2H); 1.79 (m, 2H); 1.66 (m, 2H); 1.51 (m, 2H); 1.18 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 169.26, 56.64, 44.82, 35.96, 32.37, 26.56, 24.78, 22.42. HRMS (TOF, ES+) $C_{10}H_{21}NOSCl$ $[M+H]^+$ calc 238.1032, found 238.1034.



(*S*)-*N*-((*S*)-9-chlorononon-1-en-4-yl)-2-methylpropane-2-sulfinamide (2.136)

NaBr (380 g) was dissolved in 841 mL of deionized H_2O. To this fully dissolved saturated NaBr solution was added aldimine 2.135 (10.00g, 42.05 mmol) and indium powder (19.31 g, 168.2 mmol). The mixture was stirred vigorously for 5 min, then allyl bromide (20.35 g, 168.2 mmol) was added in a single batch. Vigorous stirring was

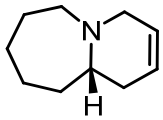
continued for 9 h, at which point the starting material was consumed by TLC analysis (1:1 Hex/EtOAc, rf = 0.34). The mixture was quenched with $NaHCO_3$ and extracted x5 with EtOAc. The organic fractions were combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield crude oil. Purification by flash chromatography (1:1 Hex/ EtOAc) afforded the desired product as a clear oil (10.10 g, 86%). $[\alpha]_D^{20}$ = +25.7° (*c* = 1.5, MeOH). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.77 (m, 1H);5.15 (m, 2H); 3.52 (t, *J* = 6.5Hz, 2H); 3.30 (sextet, *J* = 6.1 Hz, 1H); 3.21 (br d, *J* = 6.1 Hz, 1H); 2.35 (dp, J_1 = 6.5 Hz, J_2 = 10.4 Hz, 2H); 1.763 (quint., *J* = 6.5 Hz, 2H); 1.53- 1.32 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 134.23, 119.14, 55.92, 54.83, 45.08, 40.56, 34.91, 32.60, 26.88, 24.92, 22.79. HRMS (TOF, ES+) $C_{13}H_{27}NOSCl$ $[M+H]^+$ calc. 280.1502, found 280.1504.



(*S*)-1,2-diallylazepane (2.137)

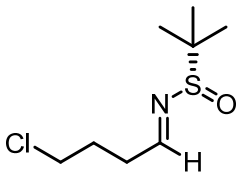
A 4N solution of HCl / dioxanes (14.92 ml) was cooled to 0°C and slowly added to a microwave vial containing sulfinamide 2.136 (2.0 g, 7.15 mmol). Solution was then brought to ambient temperature and stirred for an additional 45 min, and concentrated *in vacuo* to afford the deprotected amine as the HCl salt in quantitative yield. The amine was dissolved in DMF (35.9 mL), then K_2CO_3 (1.98 g, 14.34 mmol) and NaI (1.18 g, 7.89 mmol) were added in a single batch. The vial was sealed and submitted to microwave irradiation at 120°C for 15 min. LC/MS analysis showed full consumption of starting material to the cyclized secondary amine. Allyl bromide (0.954 g, 7.89 mmol)

was then added to the pale yellow solution at ambient temperature, and stirring was continued for 4 h. Mixture was dissolved in 5% LiCl solution and extracted with Et_2O (5 x 40 mL). Organic fractions were combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield a pale yellow crude oil. Purification by flash chromatography (1:1 Hex/EtOAc) afforded the desired product as a clear oil (0.82g, 64%). $[\alpha]_D^{20}$ = -5.0° (*c* = 0.9, MeOH). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.82 (m, 2H); 5.19-4.93 (m, 4H); 3.22 (m, 2H); 2.85 (m, 1H); 2.70 (m, 2H); 2.26 (m, 1H); 2.06 (m, 1H); 1.75 (m, 1H); 1.66-1.38 (m, 7H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 137.98, 137.51, 115.99, 115.66, 62.45, 55.71, 49.83, 39.34, 32.65, 28.88, 27.53, 25.78. HRMS (TOF, ES+) $C_{12}H_{22}N$ $[M+H]^+$ calc. 180.1752, found 180.1751.



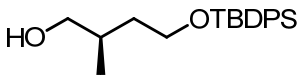
(*S*)-octahydropyrido[1,2-α]azepine unsat-7 (2.138)

To a solution of diene 2.137 (106 mg, 0.59 mmol) in toluene (11.8 mL) was added trifluoroacetic acid (71 mg, 0.62 mmol) and Grubbs II (49 mg, 0.06 mmol). Solution was submitted to microwave irradiation for 1 h at 100°C. The toluene was removed *in vacuo*, and the crude residue purified to afford the desired product as the TFA salt (94 mg, 60%). $[\alpha]_D^{20}$ = +45.2° (*c* = 1.25, MeOH). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.88 (m, 1H); 5.64 (m, 1H); 3.94 (m, 1H); 3.57 (m, 2H); 3.18-3.04 (m, 2H); 2.73 (t, 1H); 2.25 (m, 1H); 2.24-1.92 (m, 3H); 1.89-1.72 (m, 3H); 1.58 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 126.83, 120.24, 63.64, 55.70, 54.32, 31.93, 30.59, 27.21, 26.00, 21.96. HRMS (TOF, ES+) $C_{10}H_{18}N$ $[M+H]^+$ calc. 152.1439, found 152.1440.



(*S*,*E*)-*N*-(4-chlorobutylidene)-2-methylpropane-2-sulfinamide (2.145)

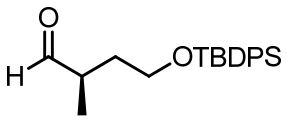
To a solution of 4-chlorobutanal in THF (0.1 M) was added (*S*)-(-)-2-methyl-2-propanesulfinamide (1.0 eq) followed by $Ti(OEt)_4$ (2.0 eq). After stirring at rt overnight, the reaction was quenched by the addition of $NaHCO_3$, extracted with EtOAc (5x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex:EtOAc 9:1) afforded the pure desired aldimine in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 (t, J = 4.0 Hz, 1H); 3.63 (td, J_1 = 6.4 Hz, J_2 = 1.9 Hz, 2H); 2.74-2.68 (m, 2H); 2.18-2.10 (m, 2H); 1.20 (s, 9H).



(*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-1-ol (2.167)

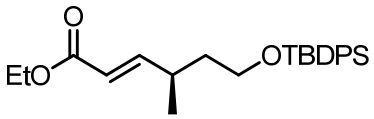
To a solution of LiCl (7.0 eq) and *i*-Pr_2NH (2.1 eq) in THF was added *n*-BuLi (2.2 eq). The reaction was stirred at -78 ^{o}C for 10 min then warmed to 0 ^{o}C and stirred for 20 min. A solution of (1*S*,2*S*)-pseudoephedrinepropionamide (1.0 eq) in THF (0.1 M) was then added to the solution of LDA at -78 ^{o}C via cannula. The reaction was stirred at -78 ^{o}C for 30 min, 0 ^{o}C for 30 min, and rt for 30 min. The reaction was then recooled to -78 ^{o}C and tert-butyl(2-iodoethoxy)diphenylsilane (2.0 eq) in THF (5.0 M) was added dropwise. The reaction stirred at -78 ^{o}C for 2 h followed by stirring at rt for 4 h. The reaction was quenched with sat aq NH_4Cl, extracted 3x with EtOAc, dried over Na_2SO_4, and

concentrated *in vacuo*. Purification via flash chromatography (Hex:EtOAc 3:2) afforded the pure product in 83% yield. To a solution of LDA (4.2 eq) in THF (0.2 M) at 0 ^{o}C was added $BH_3 \cdot NH_3$ complex. After stirring at 0 ^{o}C for 15 min and rt for 15 min, a solution of (*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylbutanamide (1.0 eq) in THF (0.2 M) was added followed by stirring at rt for 2 h. The reaction was quenched with sat aq NH_4Cl, extracted with EtOAc (4x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the pure product in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (d, J = 7.1 Hz, 4H); 7.46-7.36 (m, 6H); 3.8-3.66 (m, 2H); 3.56-3.44 (m, 2H); 2.41 (dd, J_1 = 6.6 Hz, J_2 = 5.8 Hz, 1H); 1.85 (sext, J = 6.5 Hz, 1H); 1.68-1.58 (m, 1H); 1.54-1.45 (m, 1H); 1.06 (s, 9H); 0.90 (d, J = 6.8 Hz, 3H).



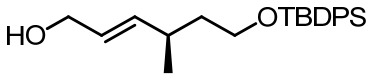
(*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutanal (2.168)

To a solution of (*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutan-1-ol (1.0 eq) in CH_2Cl_2 was added 4Å MS (0.5g/mmol) followed by NMO (1.48 eq). The reaction stirred at rt for 10 min after which TPAP (0.1 eq) was added. The reaction continued stirring at rt for 2h. The reaction was then filtered through Celite and concentrated. Purification via flash chromatography (Hex:EtOAc 9:1) afforded the pure product as a yellow oil in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.68 (d, J = 1.5 Hz, 1H); 7.67-7.63 (m, 4H); 7.46-7.35 (m, 6H); 3.77-3.65 (m, 2H); 2.58 (sext, J = 6.9 Hz, 1H); 2.06-1.96 (m, 1H); 1.67-1.57 (m, 1H); 1.08 (d, J = 7.2 Hz, 3H); 1.04 (s, 9H).



(*R*,*E*)-ethyl 6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhex-2-enoate (2.169)

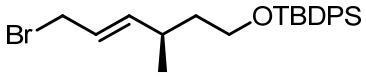
To a suspension of NaH (3.5 eq) in THF (0.75 M) at 0 ^{o}C was added triethyl phosphonoacetate (3.5 eq) followed by stirring at 0 ^{o}C for 10 min. A solution of (*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-methylbutanal in THF (0.2 M) was added via cannula and the reaction stirred at 0 ^{o}C for 1 h. The reaction was then quenched by the addition of sat aq NH_4Cl, extracted with EtOAc x3, dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex/EtOAc 9:1) afforded the pure α,β-unsaturated ester in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (d, J = 7.6 Hz, 4H); 7.45-7.35 (m, 6H); 6.86 (dd, J_1 = 15.8 Hz, J_2 = 8.0 Hz, 1H); 5.77 (d, J = 15.6 Hz, 1H); 4.18 (q, J = 7.2 Hz, 2H); 3.66 (t, J = 6.1 Hz, 2H); 2.58 (sept, J = 7.0 Hz, 1H); 1.69-1.55 (m, 2H); 1.29 (t, J = 7.1 Hz, 3H); 1.04 (s, 9H); 1.03 (d, J = 8.0 Hz, 3H).



(*R*,*E*)-6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhex-2-en-1-ol (2.170)

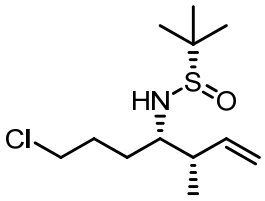
To a solution of (*R*,*E*)-ethyl 6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhex-2-enoate in CH_2Cl_2 (0.1 M) at -78 ^{o}C was added DIBAL-H (3.7 eq). The reaction stirred at -78 ^{o}C for 1 h after which the reaction was quenched with Rochelle's salt and warmed to rt. Extraction with EtOAc (3x), drying over Na_2SO_4, and concentration *in vacuo* gave the crude product. Purification via flash chromatography (Hex/EtOAc 9:1-4:1) afforded the pure allylic alcohol in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69-7.64 (m,

4H); 7.46-7.35 (m, 6H); 5.60-5.47 (m, 2H); 4.06-4.00 (m, 2H); 3.67 (t, *J* = 6.4 Hz, 2H); 2.39 (sept, *J* = 6.4 Hz, 1H); 1.64-1.49 (m, 2H); 1.06 (s, 9H); 0.98 (d, *J* = 6.8 Hz, 3H).



(*R*,*E*)-((6-bromo-3-methylhex-4-en-1-yl)oxy)(*tert*-butyl)diphenylsilane (2.171)

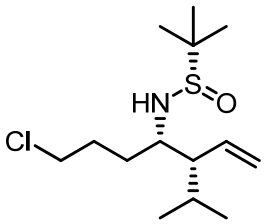
To a solution of (*R*,*E*)-6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhex-2-en-1-ol in MeCN at rt was added Ph_3P followed by CBr_4. The reaction stirred at rt for 1 h after the reaction was quenched with H_2O, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex/EtOAc 95:5) afforded the pure allylic bromide in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69-7.64 (m, 4H); 7.46-7.35 (m, 6H); 5.67-5.54 (m, 2H); 3.91-3.87 (m, 2H); 3.66 (t, *J* = 6.3 Hz, 2H); 2.42 (sept, *J* = 7.0 Hz, 1H); 1.63-1.47 (m, 2H); 1.05 (s, 9H); 0.98 (d, *J* = 6.7 Hz, 3H).



(*S*)-*N*-((3*S*,4*S*)-7-chloro-3-methylhept-1-en-4-yl)-2-methylpropane-2-sulfinamide (2.174)

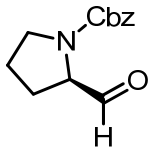
To a solution of (*S*,*E*)-*N*-(4-chlorobutylidene)-2-methylpropane-2-sulfinamide in sat aq NaBr was added indium powder (4.0 eq) followed by crotyl bromide (4.0 eq). The reaction was vigorously stirred at rt for 24 h. The reaction was quenched by the addition of sat aq $NaHCO_3$, extracted with EtOAc (5x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex/EtOAc 1:1) afforded the pure

product in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.74-5.62 (m, 1H); 5.24-5.12 (m, 2H); 3.54 (t, J = 6.2 Hz, 2H); 3.37 (d, J = 8.3 Hz, 1H); 3.20-3.10 (m, 1H); 2.74-2.61 (m, 1H); 2.00-1.88 (m, 1H); 1.81-1.67 (m, 2H); 1.43-1.31 (m, 1H); 1.21 (s, 9H); 1.06 (d, J = 6.9 Hz, 3H).



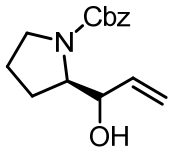
(*S*)-*N*-((3*S*,4*S*)-7-chloro-3-isopropylhept-1-en-4-yl)-2-methylpropane-2-sulfinamide (2.175)

To a solution of (*S,E*)-*N*-(4-chlorobutylidene)-2-methylpropane-2-sulfinamide in sat aq NaBr was added indium powder (4.0 eq) followed by (*E*)-1-bromo-4-methylpent-2-ene (4.0 eq). The reaction was vigorously stirred at rt for 24 h. The reaction was quenched by the addition of sat aq $NaHCO_3$, extracted with EtOAc (5x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex/EtOAc 1:1) afforded the pure product in 6% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.52 (dt, J_1 = 17.0 Hz, J_2 = 10.3 Hz, 1H); 5.29 (dd, J_1 = 10.2 Hz, J_2 = 2.4 Hz, 1H); 5.23 (dd, J_1 = 17.0 Hz, J_2 = 2.3 Hz, 1H); 3.54 (t, J = 6.7 Hz, 2H); 2.75-2.67 (m, 1H); 2.24-2.10 (m, 1H); 2.04-1.88 (m, 1H); 1.81-1.60 (m, 4H); 1.21 (s, 9H); 0.98 (d, J = 6.6 Hz, 3H); 0.87 (d, J = 6.6 Hz, 3H).



(*R*)-benzyl 2-formylpyrrolidine-1-carboxylate (2.179)

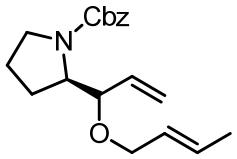
To a solution of oxalyl chloride (1.1 eq) in CH_2Cl_2 (1.0 M) at -78 ^oC was slowly added DMSO (2.2 eq). After stirring at -78 ^oC for 30 min, a solution of Z-D-prolinol in CH_2Cl_2 was added followed by stirring at -78 ^oC for an additional 1 h. Et_3N (5.0 eq) was added and the reaction was allowed to warm to rt. The reaction was quenched with NH_4Cl, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via flash chromatography (Hex:EtOAc 1:1) afforded the desired product 99% yield. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.54 (d, J = 41.9 Hz, 1H); 7.41-7.27 (m, 5H); 5.17 (d, J = 4.3 Hz, 1H); 5.13 (s, 1H); 4.25 (dt, J_1 = 39.2 Hz, J_2 = 6.3 Hz, 1H); 3.65-3.48 (m, 2H); 2.20-1.97 (m, 2H); 1.97-1.78 (m, 2H).



(*R*)-benzyl 2-((*S*)-1-hydroxyallyl)pyrrolidine-1-carboxylate

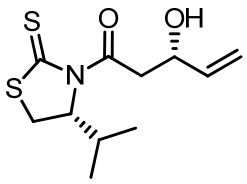
To a solution of (*R*)-benzyl 2-formylpyrrolidine-1-carboxylate in THF (0.5 M) at 0 ^oC was added vinylmagnesium bromide (1.5 eq). The reaction stirred at 0 ^oC for 1.5 h after which sat aq NH_4Cl was added to quench the reaction. Extraction with EtOAc (3x), drying over Na_2SO_4, and concentration *in vacuo* afforded the crude product. Purification via flash chromatography (Hex/EtOAc 3:1) afforded the pure allylic alcohol in 95% yield. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39-7.27 (m, 5H); 5.88-5.74 (m, 1H); 5.32

(d, *J* = 17.4 Hz, 1H); 5.22-5.10 (m, 3H); 4.71-4.60 (m, 1H); 4.32-4.06 (m, 1H); 4.06-3.85 (m, 1H); 3.65-3.51 (m, 1H); 3.44-3.25 (m, 1H); 1.96-1.68 (m, 4H).



(*R*)-benzyl 2-((*S*)-1-((*E*)-but-2-en-1-yloxy)allyl)pyrrolidine-1-carboxylate (2.177)

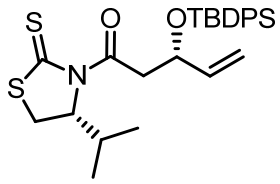
To a solution of (*R*)-benzyl 2-((*S*)-1-hydroxyallyl)pyrrolidine-1-carboxylate in THF at 0 ^{o}C was added NaH (1.5 eq). After warming to rt and stirring for 30 min, crotyl bromide (3.0 eq) was added and the reaction continued stirring overnight. The reaction was quenched by the addition of sat aq NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography afforded the pure product in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41-7.27 (m, 5H); 5.81-5.40 (m, 3H); 5.35-5.03 (m, 4H); 4.40-3.62 (m, 4H); 3.60-3.36 (m, 1H); 3.36-3.23 (m, 1H); 2.11-1.51 (m, 5H); 1.49-1.19 (m, 2H).



(*S*)-3-hydroxy-1-((*R*)-4-isopropyl-2-thioxothiazolidin-3-yl)pent-4-en-1-one

To a solution of (R)-1-(4-isopropyl-2-thioxothiazolidin-3-yl)ethanone (11.23 g, 55.21 mmol, 1.0 eq) in CH2Cl2 (0.25 M) under argon at -48 °C was added TiCl4 (10.8 mL, 98.27 mmol, 1.78 eq) dropwise followed by N,N-diisopropylethylamine (17.02 mL, 97.72 mmol, 1.77 eq) dropwise. After stirring at –48 °C for 2 h, the reaction mixture is

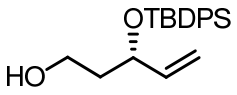
cooled to -78 °C and acrolein (3.80 mL, 55.21 mmol, 1.0 eq) is added dropwise. The reaction stirred at -78 °C for 30 min. The reaction is quenched by addition of pH 7 phosphate buffer and warmed to room temperature. The aqueous layer is extracted with CH2Cl2 and the combined organic extracts are dried over NaSO4 and concentrated in vacuo. Purification via flash chromatography (Hex:EtOAc 4:1) affords the desired product as a yellow oil in 90% overall yield and 5:1 dr. The pure desired diastereomer can be isolated in 75% yield (10.74 g). [α]20¦D = -358.3 (c = 1.02, CHCl3). 1H NMR (400 MHz, CDCl3) δ (ppm): 5.85 (ddd, J1 = 17.2 Hz, J¬2 = 10.5 Hz, J3 = 5.4 Hz, 1H); 5.24 (d, J = 17.2 Hz, 1H); 5.11-5.04 (m, 2H); 4.63-4.56 (m, 1H); 3.56-3.44 (m, 2H); 3.25 (dd, J1 = 17.5 Hz, J2 = 8.8 Hz, 1H); 3.12 (br, 1H); 2.98 (d, J = 11.6 Hz, 1H); 2.29 (oct, J = 6.7 Hz, 1H); 0.99 (d, J = 6.9 Hz, 3H); 0.91 (d, J = 6.9 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ (ppm): 202.90; 172.04; 138.90; 115.00; 71.30; 68.52; 44.94; 30.67; 30.61; 18.94; 17.66. HRMS (TOF, ES+) C11H17NO2S2 [M+Na]+ calc. mass 282.0598, found 282.0596.



(*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-((*R*)-4-isopropyl-2-thioxothiazolidin-3-yl)pent-4-en-1-one (2.188)

To a solution of (S)-3-hydroxy-1-((R)-4-isopropyl-2-thioxothiazolidin-3-yl)pent-4-en-1-one (20.1 g, 77.49 mmol, 1.0 eq) in CH_2Cl_2 (0.2 M) at 0 ºC was added imidazole (5.54 g, 81.36 mmol, 1.05 eq) followed by TBDPS-Cl (21.16 mL, 81.36 mmol, 1.05 eq). The reaction was allowed to warm to rt and continue stirring overnight. The reaction was

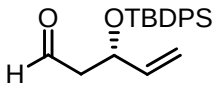
filtered through celite and concentrated under vacuum. Purification via silica chromatography (Hex:EtOAc 4:1) afforded the desired product as a yellow oil in 95% yield (36.64 g). $[\alpha]_D^{20}$ = -139.7 (c = 0.69, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70-7.65 (m, 4H); 7.45-7.33 (m, 6H); 5.90 (ddd, J_1 = 17.0 Hz, J_2 = 10.3 Hz, J_3 = 6.5 Hz, 1H); 5.03 (dt, J_1 = 17.2 Hz, J_2 = 1.4 Hz, 1H); 4.96 (dt, J_1 = 10.3 Hz, J_2 = 1.3 Hz, 1H); 4.89-4.83 (m, 1H); 4.78-4.71 (m, 1H); 3.73 (dd, J_1 = 17.0 Hz, J_2 = 6.7 Hz, 1H); 3.35 (dd, J_1 = 11.4 Hz, J_2 = 8.0 Hz, 1H), 3.27 (dd, J_1 = 17.0 Hz, J_2 = 5.8 Hz, 1H), 2.94 (dd, J_1 = 11.4 Hz, J_2 = 1.0 Hz, 1H); 2.29 (oct, J = 6.7 Hz, 1H); 1.03 (s, 9H); 1.00 (d, J = 6.7 Hz, 3H); 0.90 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 202.76; 170.94; 139.80; 136.07; 136.01; 134.14; 133.85; 129.69; 127.58; 127.54; 115.31; 71.64; 71.56; 46.27; 30.84; 30.58; 27.11; 19.44; 19.20; 17.78. HRMS (TOF, ES+) $C_{27}H_{35}NO_2S_2Si$ [M+H]+ calc. mass 498.1957, found 498.1960.



(*S*)-3-((*tert*-butyldiphenylsilyl)oxy)pent-4-en-1-ol (2.189)

To a solution of (S)-3-((tert-butyldiphenylsilyl)oxy)-1-((R)-4-isopropyl-2-thioxothiazolidin-3-yl)pent-4-en-1-one (15.45 g, 31.04 mmol, 1.0 eq) in THF (0.1 M) under argon at 0 °C is added methanol (5.0 mL, 124 mmol, 4.0 eq) followed by 2.0 M LiBH4 solution in THF (46.5 mL, 93.11 mmol, 3.0 eq) dropwise. The reaction was allowed to stir for 45 min at 0 °C. The reaction was quenched with NH4Cl solution, extracted 3x with EtOAc, dried over Na2SO4, and concentrated under vacuum. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 93% yield (9.83 g). [α]20¦D = 0.7 (c = 0.70, CHCl3). 1H NMR

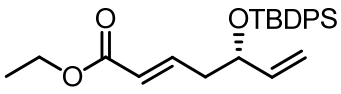
(400 MHz, CDCl3) δ (ppm): 7.75-7.66 (m, 4H); 7.48-7.34 (m, 6H); 5.86 (ddd, J1 = 16.9 Hz, J¬2 = 10.5 Hz, J3 = 6.2 Hz, 1H); 5.06 (dt, J1 = 17.2 Hz, J2 = 1.4 Hz, 1H); 5.01 (dt, J1 = 10.4 Hz, J2 = 1.3 Hz, 1H); 4.44 (m, 1H); 3.75 (m, 1H); 3.65 (m, 1H); 1.92 (br, 1H); 1.81 (m, 1H); 1.70 (m, 1H); 1.10 (s, 9H). 13C NMR (100 MHz, CDCl3) δ (ppm): 140.18; 136.12; 136.03; 133.91; 133.74; 129.94; 129.82; 127.77; 127.60; 114.99; 73.35; 59.56; 39.45; 27.16; 19.43. HRMS (TOF, ES+) C21H28O2Si [M+H]+ calc. mass 341.1937, found 341.1935.



(*S*)-3-((*tert*-butyldiphenylsilyl)oxy)pent-4-enal (2.190)

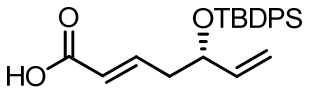
To a flame-dried flask equipped with a stir bar, under argon, was added CH2Cl2 (71 mL) followed by (COCl)2 (3.12 mL, 35.66 mmol, 1.2 eq). The reaction was cooled to -78 oC and DMSO (4.64 mL, 65.38 mmol, 2.2 eq) was added dropwise. After stirring at -78 oC for 30 min, a solution of (S)-3-((tert-butyldiphenylsilyl)oxy)pent-4-en-1-ol (10.12 g, 29.72 mmol, 1.0 eq) in CH2Cl2 (0.25 M) was added dropwise. The reaction was allowed to stir at -78 oC for 30 min after which NEt¬3 (5.0 eq) was added followed by warming to rt. The reaction was quenched with NH4Cl, extracted with CH2Cl2, dried over Na2SO4, and concentrated in vacuo. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 98% yield (9.86 g). [α]20¦D = 6.7 (c = 0.73, CHCl3). 1H NMR (400 MHz, CDCl3) δ (ppm): 9.71 (t, J = 2.6 Hz, 1H); 7.72-7.65 (m, 4H); 7.48-7.35 (m, 6H); 5.91 (ddd, J¬1 = 17.0 Hz, J2¬ = 10.4 Hz, J3 = 5.9 Hz); 5.15 (dt, J1 = 17.1 Hz, J2 = 1.3 Hz, 1H); 5.07 (dt, J1 = 10.5 Hz, J2 = 1.3 Hz, 1H); 4.67 (m, 1H); 2.53-2.48 (m, 2H); 1.09 (s, 9H). 13C NMR (100 MHz, CDCl3) δ (ppm):

201.57; 139.30; 136.00; 133.61; 133.50; 130.07; 129.90; 127.86; 127.68; 115.60; 70.36; 50.84; 27.07; 19.41. HRMS (TOF, ES+) C21H26O2Si [M+H]+ calc. mass 339.1780, found 339.1777.



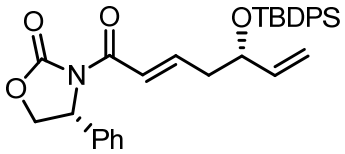
(*S*,*E*)-ethyl 5-((*tert*-butyldiphenylsilyl)oxy)hepta-2,6-dienoate

To a suspension of dried LiCl (1.40 g, 33.11 mmol, 1.2 eq) in MeCN (0.1 M) in a flame-dried flask under argon was added DBU (4.21 mL, 27.59 mmol, 1.0 eq), triethyl phosphonoacetate (6.77 mL, 33.11 mmol, 1.2 eq), and (S)-3-((tert-butyldiphenylsilyl)oxy)pent-4-enal (9.34 g, 27.59 mmol, 1.0 eq). The reaction stirred at rt for 2 h. The reaction is quenched by the addition of pH 7 buffer followed by extraction with EtOAc. The organic extracts were dried over Na2SO4 and concentrated under vacuum. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 90% yield (10.14 g). [α]20¦D = 53.9 (c = 0.87, CHCl3). 1H NMR (400 MHz, CDCl3) δ (ppm): 7.75-7.66 (m, 4H); 7.48-7.35 (m, 6H); 6.91 (dt, J1 = 7.5 Hz, J2 = 15.7 Hz, 1H); 5.84 (ddd, J1 = 16.9 Hz, J2 = 10.4 Hz, J3 = 6.2 Hz, 1H); 5.76 (d, J = 15.7 Hz, 1H); 5.14-5.02 (m, 2H); 4.32 (q, J = 5.9 Hz, 1H); 4.20 (q, J = 7.1 Hz, 2H); 2.39-2.33 (m, 2H); 1.30 (t, J = 7.1 Hz, 3H); 1.12 (s, 9H). 13C NMR (100 MHz, CDCl3) δ (ppm): 166.30; 144.66; 139.66; 136.00; 135.97; 134.01; 133.79; 129.85; 129.73; 127.69; 127.55; 123.79; 115.30; 73.57; 60.16; 40.63; 27.08; 19.40; 14.34. HRMS (TOF, ES+) C25H32O3Si [M+H]+ calc. mass 409.2199, found 409.2202.



(*S,E*)-5-((*tert*-butyldiphenylsilyl)oxy)hepta-2,6-dienoic acid (2.191)

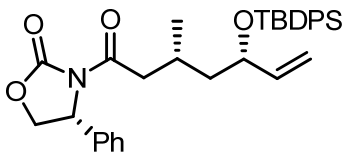
To a solution of (S,E)-ethyl 5-((tert-butyldiphenylsilyl)oxy)hepta-2,6-dienoate (9.76 g, 23.89 mmol, 1.0 eq) in 3:1 THF/H2O (0.2 M) under argon was added LiOH (5.72 g, 238.88 mmol, 10.0 eq). The resulting solution was heated to 55 oC for 18 hrs. The reaction was cooled to rt and acidified to pH 2 by slow addition of HCl. The solution was then extracted with EtOAc, dried over Na2SO4, and concentrated in vacuo. Purification via flash chromatography (Hex:EtOAc 1:1) afforded the desired product as a clear, colorless oil in 89% yield (8.09 g). [α]20¦D = 58.1 (c = 1.04, CHCl3). 1H NMR (400 MHz, CDCl3) δ (ppm): 7.74-7.63 (m, 4H); 7.49-7.34 (m, 6H); 7.00 (dt, J1 = 7.3 Hz, J2 = 15.7 Hz, 1H); 5.82 (ddd, J1 = 16.8 Hz, J2 = 10.3 Hz, J3 = 6.2 Hz, 1H); 5.74 (d, J = 15.7 Hz, 1H); 5.14-5.03 (m, 2H); 4.36-4.29 (m, 1H); 2.36 (t, J = 6.4 Hz, 2H); 1.10 (s, 9H). 13C NMR (100 MHz, CDCl3) δ (ppm): 172.00; 147.84; 139.59; 136.07; 136.03; 134.01; 133.79; 129.97; 129.81; 127.80; 127.63; 123.19; 115.51; 73.22; 40.70; 27.13; 19.44. HRMS (TOF, ES+) C23H28O3Si [M+Na]+ calc. mass 403.1705, found 403.1708.



(*R*)-3-((*S,E*)-5-((*tert*-butyldiphenylsilyl)oxy)hepta-2,6-dienoyl)-4-phenyloxazolidin-2-one (2.192)

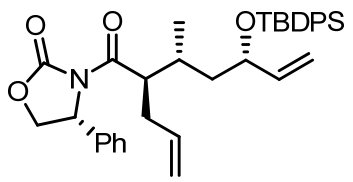
To a solution of (S,E)-5-((tert-butyldiphenylsilyl)oxy)hepta-2,6-dienoic acid (7.23 g, 19.00 mmol, 1.0 eq), in THF (0.1 M), under argon at -78 oC, was added NEt3 (3.18 mL,

22.79 mmol, 1.2 eq) followed by dropwise addition of pivaloyl chloride (2.62 mL, 21.28 mmol, 1.12 eq). The reaction was allowed to stir at -78 oC for 15 min followed by stirring at 0 oC for 15 min. In a separate flame-dried flask under argon at -78 oC was added (R)-(−)-4-Phenyl-2-oxazolidinone (3.10 g, 19.00 mmol, 1.0 eq) followed by THF (0.1 M). n-BuLi (7.98 mL, 19.90 mmol, 1.05 eq) was added dropwise followed by continued stirring at -78 oC for 30 min. The solution of mixed anhydride was cooled back down to – 78 oC and the oxazolidinone was added via cannula. After stirring at -78 oC for 20 min, the reaction warmed to rt and continued stirring for 1 h. The reaction was quenched by addition of saturated NH4Cl, extracted with EtOAc, dried over Na2SO4, and concentrated. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 95% yield (9.49 g). [α]20¦D = -8.6 (c = 0.90, CHCl3). 1H NMR (400 MHz, CDCl3) δ (ppm): 7.68-7.59 (m, 4H); 7.44-7.28 (m, 11H); 7.20 (d, J = 15.5 Hz, 1H); 7.03 (m, 1H); 5.77 (ddd, J1 = 16.90 Hz, J2 = 10.3 Hz, J3 = 6.1 Hz, 1H); 5.47 (dd, J1 = 8.6 Hz, J2 = 3.8 Hz, 1H); 5.09-4.98 (m, 2H); 4.69 (t, J = 8.7 Hz, 1H); 4.32-4.24 (m, 2H); 2.44-2.31 (m, 2H); 1.05 (s, 9H). 13C NMR (100 MHz, CDCl3) δ (ppm): 164.24; 153.75; 147.67; 139.61; 139.31; 136.04; 134.03; 133.80; 129.88; 129.74; 129.32; 128.79; 127.75; 127.59; 126.04; 122.50; 115.41; 73.25; 70.07; 57.85; 40.98; 27.13; 19.42. HRMS (TOF, ES+) C32H35NO4Si [M+Na]+ calc. mass 526.2414, found 526.2416.



(*R*)-3-((3*R*,5*S*)-5-((tert-butyldiphenylsilyl)oxy)-3-methylhept-6-enoyl)-4-phenyloxazolidin-2-one

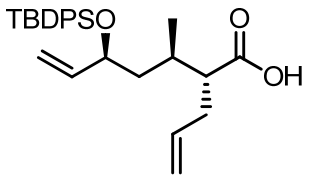
To a solution of copper iodide dimethyl sulfide complex (2.47 g, 10.40 mmol, 2.0 eq) in THF (0.23 M) under argon at -78 oC was slowly added MeLi (7.2 mL, 10.14 mmol, 1.95 eq). The reaction stirred at rt for 30 min. TMS-I (1.44 mL, 10.14 mmol, 1.95 eq) was added followed by stirring at -78 oC for an additional 5 min. A solution of (R)-3-((S,E)-5-((tert-butyldiphenylsilyl)oxy)hepta-2,6-dienoyl)-4-phenyloxazolidin-2-one (2.73 g, 5.20 mmol,1.0 eq) in THF (0.15 M) was cooled to -78 oC and transferred to the cuprate solution via cannula. After stirring at -78 oC overnight, NEt3 (7.75 mL) was added and the reaction stirred for an additional hour. The reaction was quenched by the addition of pH 10 ammonia buffer, extracted with EtOAc, dried over Na2SO4, and concentrated. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 90% yield (2.53 g) and 17:1 d.r. [α]20¦D = -20.0 (c = 0.98, CHCl3). 1H NMR (400MHz, CDCl3) d 7.67-7.63 (m, 4H), 7.41-7.29 (m, 11H), 5.73 (ddd, J = 17.1, 10.4, 7.1 Hz, 1H), 5.40 (dd, J = 8.6, 3.6 Hz, 1H), 4.94-4.87 (m, 2H), 4.65 (t, J = 8.8 Hz, 1H), 4.26 (dd, J = 8.9, 3.6 Hz, 1H), 4.13-4.08 (m, 1H), 2.82-2.67 (m, 2H), 2.01-1.92 (m, 1H), 1.52-1.46 (m, 1H), 1.41-1.35 (m, 1H), 1.04 (s, 9H), 0.63 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) □ 171.8, 153.6, 140.8, 139.1, 136.04, 135.99, 134.2, 134.1, 129.5, 129.4, 129.1, 128.6, 127.5, 127.3, 125.8, 114.6, 73.0, 69.8, 57.6, 44.6, 42.6, 27.1, 26.0, 19.7, 19.3. HRMS (TOF, ES+) C33H39NO4Si [M+Na]+ calc. mass 564.2546, found 564.2546.



(*R*)-3-((2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-enoyl)-4-phenyloxazolidin-2-one (2.193)

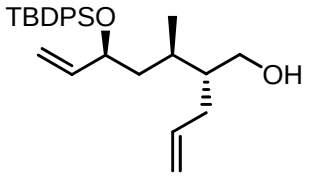
To a solution of (R)-3-((3R,5S)-5-((tert-butyldiphenylsilyl)oxy)-3-methylhept-6-enoyl)-4-phenyloxazolidin-2-one (3.1 g, 5.72 mmol, 1.0 eq) in THF (0.1 M) under argon at -78 oC under argon was added 1.0 M LiHMDS (6.3 mL, 6.29 mmol, 1.1 eq). The reaction continued stirring for 2 h at -78 oC. In a separate flask a solution of allyl iodide (1.57 mL, 17.16 mmol, 3.0 eq) and HMPA (3.0 mL, 17.16 mmol, 3.0 eq) in THF (0.5 M) was prepared and transferred to the enolate solution at -78 oC. The reaction was warmed to -45 oC and continued stirring overnight. The reaction was quenched by the addition of saturated NH4Cl, extracted with EtOAc, dried over Na2SO4, and concentrated. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 87% yield (2.89 g) and 15:1 d.r. [α]20¦D = -29.6 (c = 0.63, CHCl3). 1H NMR (400 MHz, CDCl3) δ 7.70-7.65 (m, 4H), 7.46-7.31 (m, 9 H), 7.27-25 (m, 2H), 5.75 (ddd, J = 17.2, 10.3, 7.3 Hz, 1H), 5.53-5.43 (m, 1H), 5.35 (dd, J = 8.6, 3.4 Hz, 1H), 5.00-4.92 (m, 2H), 4.77-4.72 (m, 2H), 4.55 (t, J = 8.8 Hz, 1H), 4.22 (dd, J = 8.9, 3.5 Hz, 1H), 4.15-4.10 (m, 1H), 3.82-3.77 (m, 1H), 2.29-2.21 (m, 1H), 2.13-2.09 (m, 1H), 1.72-1.66 (m, 2H), 1.33-1.27 (m, 1H), 1.08 (s, 9H), 0.66 (d, J = 6.6. Hz, 3H). 13C NMR (100 MHz, CDCl3) □ 174.5, 153.3, 140.1, 139.0, 135.8, 135.8, 134.8, 134.2, 133.9, 129.5, 129.4, 128.8, 128.4, 127.4, 127.3, 125.9, 116.7, 115.2, 73.3, 69.3, 57.7, 47.3, 40.8, 32.9, 30.9, 26.9, 19.1, 17.2. HRMS (TOF, ES+) C36H43NO4Si [M+H]+ calc. mass 582.3040,

found 582.3035.



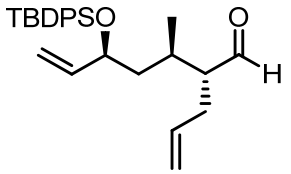
(2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-enoic acid

To a solution of (R)-3-((2R,3R,5S)-2-allyl-5-((tert-butyldiphenylsilyl)oxy)-3-methylhept-6-enoyl)-4-phenyloxazolidin-2-one (4.74 g, 8.14 mmol, 1.0 eq) in 3:1 THF/H2O (0.2 M) under argon at 0 oC was added 30% H2O2 (3.65 mL, 32.15 mmol, 3.95 eq) followed by LiOH (390 mg, 16.28 mmol, 2.02 eq). The reaction was warmed to rt and continued stirring overnight. The reaction was quenched with saturated NaHSO4 and NH4Cl, extracted with EtOAc, dried over Na2SO4, and concentrated in vacuo. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 96% yield (3.42 g). [α]20¦D = 19.8 (c = 0.75, CHCl3). 1H NMR (400MHz, CDCl3) d 7.75-7.70 (m, 4H), 7.47-7.38 (m, 6H), 5.86-5.68 (m, 2H), 5.10-4.98 (m, 4H), 4.24-4.19 (m, 1H), 2.38-2.29 (m, 2H), 2.17-2.13 (m, 1H), 1.74-1.66 (m, 2H), 1.46-1.39 (m, 1H), 1.12 (s, 9H), 0.72 (d, J = 6.7 Hz, 3H); 13C NMR (100 MHz, CDCl3) □ 180.8, 140.2, 136.0, 135.9, 135.5, 134.2, 134.0, 129.6, 129.5, 127.5, 127.4, 116.7, 115.2, 73.3, 50.4, 42.3, 33.5, 31.0, 27.0, 19.2, 16.5. HRMS (TOF, ES+) C27H36O3Si [M+H]+ calc. mass 437.2512, found 437.2514.



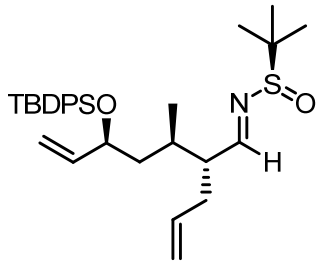
(2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-en-1-ol (2.194)

To a solution of (2R,3R,5S)-2-allyl-5-((tert-butyldiphenylsilyl)oxy)-3-methylhept-6-enoic acid (1.87 g, 4.27 mmol, 1.0 eq) in 4:1 THF/Et2O (0.1 M) under argon at 0 oC was added LiAlH4 (594 mg, 14.96 mmol, 3.5 eq). The reaction was allowed to warm to rt and continue stirring for 7 h. The reaction was cooled to 0 oC and quenched with H2O. The reaction was then warmed to rt and diluted with Et2O. Rochelle's Salt and 1.0 M NaOH were added followed by stirring for 30 min. The reaction was then filtered through Celite, extracted with EtOAc, dried over Na2SO4, and concentrated. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 84% yield (1.51 g). [α]20¦D = 35.6 (c = 0.59, CHCl3). 1H NMR (400MHz, CDCl3) d 7.70-7.65 (m, 4H), 7.45-7.34 (m, 6H), 5.83-5.69 (m, 2H), 5.04-4.95 (m, 4H), 4.16-4.11 (m, 1H), 3.47 (dd, J = 5.8, 2.1 Hz, 2H), 2.03-1.91 (m, 2H), 1.59-1.49 (m, 2H), 1.43-1.39 (m, 1H), 1.34-1.27 (m, 1H), 1.23 (bs, 1H), 1.07 (s, 9H), 0.59 (d, J = 6.9 Hz, 3H); 13C NMR (100 MHz, CDCl3) □ 140.5, 137.9, 135.95, 135.90, 134.4, 134.1, 115.8, 114.9, 73.7, 63.3, 45.7, 41.7, 33.3, 29.0, 27.0, 19.2, 16.2. HRMS (TOF, ES+) C27H38O2Si [M+H]+ calc. mass 423.2719, found 423.2723.



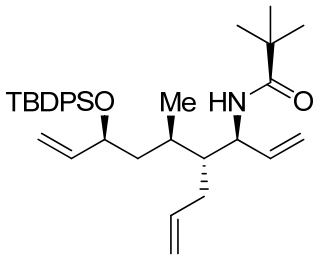
(2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-enal

To a solution of (2R,3R,5S)-2-allyl-5-((tert-butyldiphenylsilyl)oxy)-3-methylhept-6-en-1-ol (1.35 g, 3.18 mmol, 1.0 eq) in CH2Cl2 (0.1 M) under argon was added 4Å molecular sieves (0.5g/mmol) followed by NMO (551.8 mg, 4.71 mmol, 1.48 eq). The reaction was stirred at rt for 10 min after which TPAP (112 mg, 0.32 mmol, 0.1 eq) was added. The reaction continued to stir at rt for 5 h. The reaction was filtered through Celite and concentrated in vacuo. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 85% yield (1.14 g). [α]20¦D = 11.2 (c = 0.55, CHCl3). 1H NMR (400MHz, CDCl3) δ 9.52 (d, J = 2.6 Hz,1H), 7.68-7.63 (m, 4H), 7.44-7.33 (m, 6H), 5.76 (ddd, J = 17.3, 10.3, 7.0 Hz, 1H), 5.70-5.60 (m, 1H), 5.02-4.95 (m, 4H), 4.18-4.13 (m, 1H), 2.37-2.31 (m, 1H), 2.20-2.15 (m, 1H), 2.07-2.01 (m, 1H), 1.82-1.79 (m, 1H), 1.59-1.53 (m, 1H), 1.42-1.35 (m, 1H), 1.06 (s, 9H), 0.66 (d, J = 6.9 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 204.9, 140.1, 136.0, 135.9, 135.7, 134.2, 134.0, 120.7, 129.6, 127.5, 127.4, 116.7, 115.4, 73.3, 56.3, 41.9, 30.4, 29.3, 27.0, 19.2, 16.5. HRMS (TOF, ES+) C27H36O2Si [M+Na]+ calc. mass 443.2382, found 443.2383.



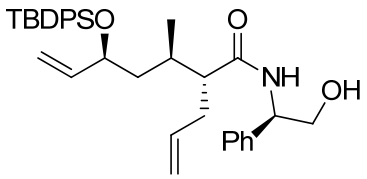
(*R,E*)-*N*-((2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-en-1-ylidene)-2-methylpropane-2-sulfinamide (2.195)

To a solution of (2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-enal (897 mg, 2.13 mmol, 1.0 eq) in THF (0.2 M) under argon was added $Ti(OEt)_4$ (1.11 mL, 5.33 mmol, 2.5 eq) followed by (S)-2-methylpropane-2-sulfinamide (284 mg, 2.34 mmol, 1.1 eq). The reaction was allowed to stir at 40 ^oC overnight. The reaction was quenched by the addition of saturated $NaHCO_3$, extracted with EtOAc, dried over sodium sulfate, and concentrated under vacuum. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 92% yield (1.03 g). $[\alpha]_D^{20}$ = -88.6 (c = 0.76, $CHCl_3$). ^1H NMR (400MHz, $CDCl_3$) δ 7.83 (d, J = 6.2 Hz, 1H); 7.70-7.62 (m, 4H); 7.45-7.32 (m, 6H); 5.75 (ddd, J_1 = 17.2 Hz, J_2 = 10.2 Hz, J_3 = 7.0 Hz, 1H); 5.64 (dddd, J_1 = 17.0 Hz, J_2 = 13.9 Hz, J_3 = 10.2 Hz, J_4 = 7.0 Hz, 1H); 5.04-4.96 (m, 2H); 4.96-4.88 (m, 2H); 4.16 (q, J = 7.2 Hz, 1H); 2.48-2.40 (m, 1H); 2.38-2.27 (m, 1H); 2.18-2.08 (m, 1H); 1.83-1.72 (m, 1H); 1.57 (ddd, J_1 = 13.2 Hz, J_2 = 8.4 Hz, J_3 = 4.8 Hz, 1H); 1.39 (ddd, J_1 = 14.1, J_2 = 9.3 Hz, J_3 = 5.3 Hz, 1H); 1.17 (s, 9H); 1.06 (s, 9H); 0.65 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.65; 140.49; 136.14; 136.07; 134.33; 134.21; 129.81; 129.66; 127.68; 127.51; 116.89; 115.25; 73.42; 56.60; 50.06; 42.68; 34.00; 31.40; 27.18; 22.65; 19.39; 16.09. HRMS (TOF, ES+) $C_{31}H_{45}NO_2SSi$ [M+Na]+ calc. mass 546.2838, found 546.2841.



_N_-((3_S_,4_R_,5_R_,7_S_)-4-allyl-7-((_tert_-butyldiphenylsilyl)oxy)-5-methylnona-1,8-dien-3-yl)pivalamide (2.181)

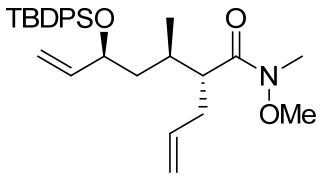
To a solution of (*S,E*)-*N*-((2*R*,3*R*,5*S*)-2-allyl-5-((tert-butyldiphenylsilyl)oxy)-3-methylhept-6-en-1-ylidene)-2-methylpropane-2-sulfinamide in CH_2Cl_2 (0.1 M) at -48 ^oC was added vinyl Grignard (1.0 M, 10.0 eq) dropwise. The reaction stirred at -48 ^oC for 7 h and was then allowed to warm to rt and continue stirring overnight. The reaction was quenched by the addition of sat aq NH_4Cl, extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography(Hex/EtOAc 1:1) afforded the pure product in 65% overall yield and 37% isolated yield of the desired diastereomer. ^1H NMR (400MHz, $CDCl_3$) δ (ppm): 7.70-7.62 (m, 4H); 7.45-7.31 (m, 6H); 5.80-5.66 (m, 2H); 5.53 (ddd, J_1 = 17.2 Hz, J_2 = 10.1 Hz, J_3 = 8.3 Hz, 1H); 5.20 (d, J = 16.0 Hz, 1H); 5.17 (d, J = 9.1 Hz, 1H); 5.06 (d, J = 18.5 Hz, 1H); 5.03 (d, J = 10.5 Hz, 1H); 4.97 (d, J = 10.6 Hz, 1H); 4.93 (d, J = 17.4 Hz, 1H); 4.05 (ddd, J_1 = 10.7 Hz, J_2 = 7.3 Hz, J_3 = 4.1 Hz, 1H); 3.83 (td, J_1 = 7.3 Hz, J_2 = 2.3 Hz, 1H); 2.10-1.92 (m, 2H); 1.66-1.57 (m, 1H); 1.57-1.48 (m, 1H); 1.41-1.33 (m, 1H); 1.28-1.18 (m, 2H); 1.16 (s, 9H); 1.06 (s, 9H); 0.59 (d, J = 7.0 Hz, 3H).



(2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-*N*-((*R*)-2-hydroxy-1-phenylethyl)-3-methylhept-6-enamide (2.196)

To a solution of Weinreb salt (301 mg, 3.09 mmol, 3.0 eq) in THF (0.5 M) under argon at 0 oC, was added AlMe3 (1.55 mL, 3.09 mmol, 3.0 eq) dropwise. The reaction stirred at 0 oC for 15 min then warmed to rt and stirred for an additional 15 min. The reaction was recooled to 0 oC and a solution of (R)-3-((2R,3R,5S)-2-allyl-5-((tert-butyldiphenylsilyl)oxy)-3-methylhept-6-enoyl)-4- phenyloxazolidin-2-one (600 mg, 1.03 mmol, 1.0 eq) in THF (0.1 M) was added. The reaction was warmed to 50 oC and stirred overnight. The product was partitioned between water and EtOAc, extracted with EtOAc (3x), dried over Na2SO4, and concentrated in vacuo. Purification via flash chromatography (Hex/EtOAc 1:1) did not afford the desired Weinreb amide, however the product of ring opening of the oxazolidinone (15) was isolated in 59% yield (338 mg). Crystals of (2R,3R,5S)-2-allyl-5-((tert-butyldiphenylsilyl)oxy)-N-((R)-2-hydroxy-1-phenylethyl)-3-methylhept-6-enamide (15) were obtained as thin, colorless needles. Due to significant positional disorder in the structure, diffraction quality was poor at high angles requiring the use of a rotating-anode to obtain sufficient completeness for determination of the absolute structure. The molecule crystallized in the orthorhombic space group P212121 with 2 molecules in the asymmetric unit. The absolute configuration was determined with a Flack parameter of -0.0032, with an e.s.d. of 0.0383. [α]20¦D = 4.3 (c = 0.43, CHCl3). 1H NMR (400MHz, CDCl3) δ (ppm): 7.72-7.62 (m, 4H); 7.44-7.27 (m, 9H); 7.25-7.19 (m, 2H); 5.94 (d, J = 6.7 Hz, 1H); 5.80 (ddd, J1 = 17.3

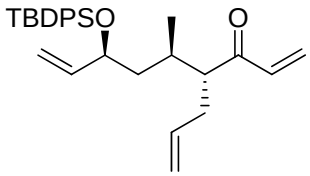
Hz, J2 = 10.4 Hz, J3 = 7.1 Hz, 1H); 5.67-5.55 (m, 1H); 5.05-4.88 (m, 5H); 4.16 (m, 1H); 3.83-3.72 (m, 2H); 2.82 (br, 1H); 2.33-2.22 (m, 1H); 2.17-2.08 (m, 1H); 1.86 (ddd, J1 = 10.6 Hz, J2 = 6.5 Hz, J3 = 4.2 Hz, 1H); 1.71-1.60 (m, 2H); 1.37 (ddd, J1 = 14.0 Hz, J2 = 10.5 Hz, J3 = 4.7 Hz, 1H); 1.08 (s, 9H); 0.70 (d, J = 6.6 Hz, 3H). 13C NMR (100 MHz, CDCl3) □ 174.70; 140.40; 139.05; 136.12; 136.08; 136.05; 134.41; 134.09; 129.79; 129.69; 128.86; 127.92; 127.67; 127.51; 126.92; 116.80; 115.44; 77.36; 73.51; 66.70; 55.97; 52.89; 42.74; 34.45; 31.69; 27.15; 19.37; 16.88.. HRMS (TOF, ES+) C35H45NO3Si [M+Na]+ calc. mass 578.3066, found 578.3065.



(2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-*N*-methoxy-N,3-dimethylhept-6-enamide

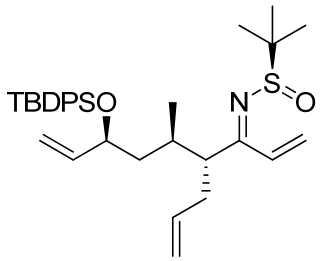
To a solution of (2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-enoic acid in DMF (0.15 M) at 0 ^{o}C was added HATU (2.0 eq) followed by Weinreb salt (2.0 eq) and *N*-methylmorpholine (NMM) (2.0 eq). The reaction was stirred at 0 ^{o}C for 18 h. The reaction as then diluted with EtOAc, quenched with NH_4Cl, extracted with EtOAc (3x), washed with 5% LiCl (1x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex/EtOAc 10-20%) afforded the pure Weinreb amide in 85% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.71-7.63 (m, 4H); 7.45-7.31 (m, 6H); 5.75 (ddd, J_1 = 17.3 Hz, J_2 = 10.3 Hz, J_3 = 7.2 Hz, 1H); 5.66 (qt, J_1 = 10.1 Hz, J_2 = 7.0 Hz, 1H); 5.06-4.89 (m, 4H); 4.18-4.08 (m, 1H); 3.56 (s, 3H); 3.11 (s, 3H); 2.69-2.56 (m, 1H); 2.36-2.25 (m, 1H); 2.17-2.07 (m, 1H); 1.75-1.56 (m, 2H); 1.32-1.22 (m,

1H); 1.06 (s, 9H); 0.60 (d, J = 6.6 Hz, 3H).



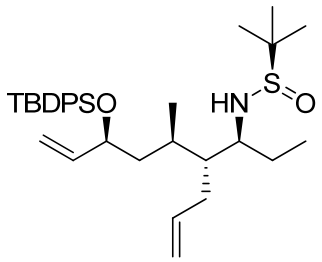
(4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnona-1,8-dien-3-one (2.198)

To a solution of (2*R*,3*R*,5*S*)-2-allyl-5-((tert-butyldiphenylsilyl)oxy)-*N*-methoxy-*N*,3-dimethylhept-6-enamide in THF (0.1 M) at 50 ^{o}C was added vinylmagnesium bromide (2.0 eq). The reaction stirred at 50 ^{o}C for 15 min and was then quenched by the addition of sat aq NH_4Cl., extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated. Purification via flash chromatography (Hex/EtOAc 9:1) afforded the pure product in 77% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.73-7.64 (m, 4H); 7.47-7.33 (m, 6H); 6.31 (dd, J_1 = 17.4 Hz, J_2 = 10.5 Hz, 1H); 6.12 (dd, J_1 = 17.4 Hz, J_2 = 1.3 Hz, 1H); 5.75 (ddd, J_1 = 17.3 Hz, J_2 = 10.4 Hz, J_3 = 7.1 Hz, 1H); 5.67 (dd, J_1 = 10.4 Hz, J_2 = 1.3 Hz, 1H); 5.62 (qt, J_1 = 13.8 Hz, J_2 = 6.9 Hz, 1H); 5.03-4.91 (m, 4H); 4.16-4.08 (m, 1H); 2.62 (ddd, J_1 = 10.0 Hz, J_2 = 5.9 Hz, J_3 = 4.2 Hz, 1H); 2.40-2.30 (m, 1H); 2.14-2.05 (m, 1H); 1.76-1.65 (m, 1H); 1.58 (ddd, J_1 = 12.9 Hz, J_2 = 9.3 Hz, J_3 = 3.3 Hz, 1H); 1.33-1.23 (m, 1H); 1.09 (s, 9H); 0.62 (d, J = 6.7 Hz, 3H).



(*R*,*E*)-*N*-((4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnona-1,8-dien-3-ylidene)-2-methylpropane-2-sulfinamide

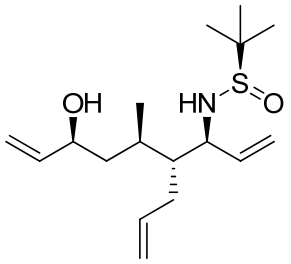
To a solution of ketone in THF (0.15 M) in a microwave vial was added (*R*)-2-methylpropane-2-sulfinamide (1.0 eq) and $Ti(OEt)_4$ (2.0 eq). The reaction was heated in the microwave at 120 ^oC for 2 h, then quenched by the addition of sat aq $NaHCO_3$, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated *in vacuo*. Purification via flash chromatography (Hex/EtOAc 4:1) afforded the pure ketamine in 24% yield. ^1H NMR (400MHz, $CDCl_3$) δ (ppm): 7.70-7.61 (m, 4H); 7.45-7.31 (m, 6H); 5.78-5.53 (m, 3H); 5.00-4.86 (m, 6H); 4.14-4.04 (m, 1H); 2.71-2.60 (m, 1H); 2.38-2.24 (m, 1H); 2.19-2.07 (m, 1H); 1.74-1.55 (m, 3H); 1.24 (s, 9H); 1.05 (s, 9H); 0.62 (d, J = 6.7 Hz, 3H).



(*R*)-*N*-((3*S*,4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide (2.199)

To a solution of (*R,E*)-*N*-((4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnona-1,8-dien-3-ylidene)-2-methylpropane-2-sulfinamide in THF (0.1 M) at -78 ^oC was added L-selectride (3.0 eq) dropwise. The reaction was allowed to warm to rt and continue stirring for 3 h. The reaction was quenched by the addition of sat aq NH_4Cl,

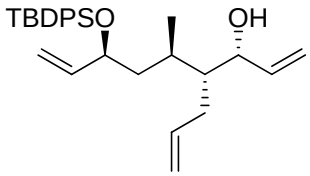
extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex/EtOAc 1:1) afforded the reduced product in 99% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.70-7.62 (m, 4H); 7.45-7.32 (m, 6H); 5.79 (ddd, J_1 = 16.9 Hz, J_2 = 11.0 Hz, J_3 = 6.9 Hz, 1H); 5.72-5.60 (m, 1H); 5.05 (s, 1H); 5.01 (d, J = 7.3 Hz, 1H); 4.98 (s, 1H); 4.94 (d, J = 4.8 Hz, 1H); 4.08 (ddd, J_1 = 10.8 Hz, J_2 = 6.9 Hz, J_3 = 4.2 Hz, 1H); 3.17-3.09 (m, 1H); 2.82 (d, J = 8.1 Hz, 1H); 2.03-1.86 (m, 2H); 1.68-1.58 (m, 2H); 1.57-1.43 (m, 4H); 1.22 (s, 9H); 1.06 (s, 9H); 0.90 (t, J = 7.2 Hz, 3H); 0.55 (d, J = 6.6 Hz, 3H).



(*R*)-*N*-((3*S*,4*R*,5*R*,7*S*)-4-allyl-7-hydroxy-5-methylnona-1,8-dien-3-yl)-2-methylpropane-2-sulfinamide (2.200)

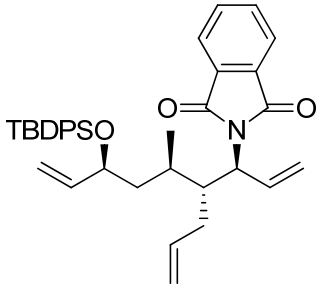
To a solution of N-((3*S*,4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnona-1,8-dien-3-yl)pivalamide in THF (0.1 M) at 0 ^{o}C was added TBAF (2.0 eq). The reaction warmed to rt and continued stirring overnight. The reaction was quenched by the addition of H_2O, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated. Purification via flash chromatography (DCM/MeOH 95:5) afforded the pure allylic alcohol in 91% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 5.89-5.72 (m, 2H); 5.65 (ddd, J_1 = 17.3 Hz, J_2 = 10.2 Hz, J_3 = 8.2 Hz, 1H); 5.28-5.18 (m, 3H); 5.16-5.05 (m, 3H); 4.13 (q, J = 6.7 Hz, 1H); 3.97-3.91 (m, 1H); 3.55 (d, J = 2.2 Hz, 1H); 2.32-2.23 (m, 1H); 2.20-2.10 (m, 1H); 1.90-1.80 (m, 1H); 1.65-1.50 (m, 3H); 1.45-1.37 (m, 1H); 1.19 (s,

9H); 1.02 (d, *J* = 6.9 Hz, 3H).



(3*R*,4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnona-1,8-dien-3-ol (2.204)

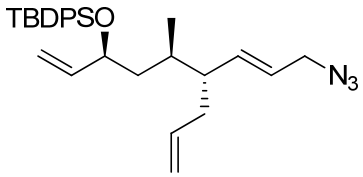
To a solution of (2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-enal in THF at -78 ^{o}C was added vinylmagnesium bromide (1.1 eq). The reaction continued stirring at -78 ^{o}C overnight. The reaction was quenched by the addition of sat aq NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated *in vacuo*. Purification via flash chromatography (Hex/EtOAc 50-100%) afforded the pure allylic alcohol in 87% yield and 7:1 dr. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.71-7.63 (m, 4H); 7.45-7.32 (m, 6H); 5.84-5.69 (m, 3H); 5.21-5.07 (m, 2H); 5.04-4.91 (m, 4H); 4.15-4.07 (m, 2H); 2.17-2.08 (m, 1H); 2.07-1.97 (m, 1H); 1.70-1.48 (m, 3H); 1.39-1.28 (m, 2H); 1.06 (s, 9H); 0.62 (d, *J* = 6.7 Hz, 3H).



2-((3*S*,4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnona-1,8-dien-3-yl)isoindoline-1,3-dione (2.206)

To a solution of (3*R*,4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnona-

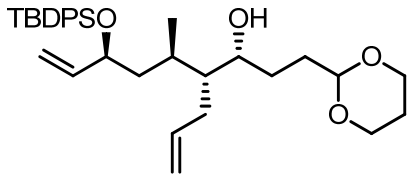
1,8-dien-3-ol in THF (0.2 M) at 0 °C was added Ph_3P (1.05 eq) and phthalimide (1.05 eq). DEAD (1.05 eq) was added dropwise and the reaction was warmed to rt and stirred overnight. The reaction was partitioned between H_2O and EtOAc, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated *in vacuo*. Purification via flash chromatography (Hex/EtOAc 10-90%) afforded the pure product in up to 26% isolated yield and 7:1 dr. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.82-7.77 (m, 2H); 7.72-7.65 (m, 2H); 7.62-7.54 (m, 4H); 7.43-7.27 (m, 6H); 6.23-6.12 (m, 1H); 5.80-5.68 (m, 1H); 5.43 (ddd, J_1 = 17.7 Hz, J_2 = 10.3 Hz, J_3 = 8.0 Hz, 1H); 5.26 (d, J = 17.1 Hz, 1H); 5.15 (d, J = 10.0 Hz, 1H); 4.97-4.90 (m, 2H); 4.60-4.47 (m, 2H); 4.28 (dd, J_1 = 10.3 Hz, J_2 = 1.4 Hz, 1H); 3.89-3.82 (m, 1H); 2.44-2.36 (m, 1H); 2.13-2.04 (m, 1H); 2.02-1.92 (m, 1H); 1.50-1.41 (m, 1H); 1.33-1.20 (m, 2H); 0.98 (s, 9H); 0.53 (d, J = 6.3 Hz, 3H).



(((3*S*,5*R*,6*R*,*E*)-6-allyl-9-azido-5-methylnona-1,7-dien-3-yl)oxy)(*tert*-butyl) diphenylsilane (2.207)

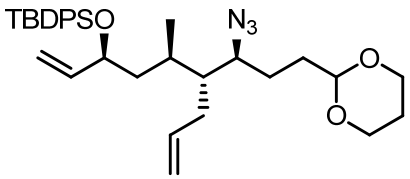
To a solution of (3*R*,4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-5-methylnona-1,8-dien-3-ol in toluene (0.1 M) at 0 °C was added Ph_3P (1.05 eq) and DPPA (1.05 eq). DEAD (1.05 eq) was added dropwise and the reaction was heated to 50 °C and stirred overnight. The reaction was partitioned between H_2O and EtOAc, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex/EtOAc 10-90%) afforded the pure terminal allylic azide in 85% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.74-7.65 (m, 4H); 7.48-7.34 (m, 6H); 5.80

(ddd, J_1 = 17.1 Hz, J_2 = 10.3 Hz, J_3 = 7.0 Hz, 1H); 5.70-5.57 (m, 1H); 5.43 (dd, J_1 = 15.3 Hz, J_2 = 8.5 Hz, 1H); 5.35-5.26 (m, 1H); 5.00-4.91 (m, 4H); 4.15 (q, J = 6.9 Hz, 1H); 3.64 (d, J = 6.4 Hz, 2H); 2.10-1.99 (m, 2H); 1.99-1.90 (m, 1H); 1.62-1.52 (m, 1H); 1.47 (ddd, J_1 = 13.3 Hz, J_2 = 8.2 Hz, J_3 = 4.8 Hz, 1H); 1.40-1.31 (m, 1H); 1.09 (s, 9H); 0.61 (d, J = 6.9 Hz, 3H).



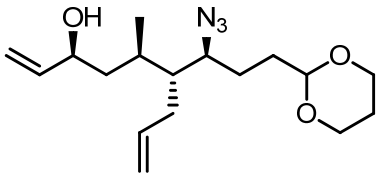
(3*R*,4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-1-(1,3-dioxan-2-yl)-5-methylnon-8-en-3-ol (2.208)

To a solution of (2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-enal in THF at -78 ^{o}C was added (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide (1.1 eq). The reaction continued stirring at -78 ^{o}C overnight. The reaction was quenched by the addition of sat aq NH_4Cl, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated *in vacuo*. Purification via flash chromatography (Hex/EtOAc 50-100%) afforded the pure alcohol in 85% yield and 7:1 dr. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.71-7.63 (m, 4H); 7.45-7.32 (m, 6H); 5.85-5.70 (m, 2H); 5.03-4.86 (m, 4H); 4.53 (t, J = 4.8 Hz, 1H); 4.16-4.06 (m, 4H); 3.75 (t, J = 11.1 Hz, 2H); 3.60-3.54 (m, 1H); 2.19-2.05 (m, 2H); 2.04-1.96 (m, 1H); 1.73-1.64 (m, 2H); 1.56-1.46 (m, 3H); 1.43-1.29 (m, 3H); 1.23-1.16 (m, 1H); 1.06 (s, 9H); 0.60 (d, J = 6.9 Hz, 3H).



(((3*S*,5*R*,6*R*)-6-((*S*)-1-azido-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl)oxy)(*tert*-butyl)diphenylsilane (2.209)

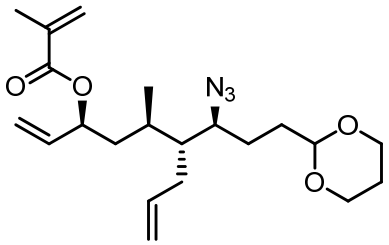
To a solution of (3*R*,4*R*,5*R*,7*S*)-4-allyl-7-((*tert*-butyldiphenylsilyl)oxy)-1-(1,3-dioxan-2-yl)-5-methylnon-8-en-3-ol in toluene (0.1 M) at 0 ^{o}C was added Ph_3P (1.05 eq) and DPPA (1.05 eq). DEAD (1.05 eq) was added dropwise and the reaction was heated to 70 ^{o}C and stirred overnight. The reaction was partitioned between H_2O and EtOAc, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated under vacuum. Purification via flash chromatography (Hex/EtOAc 10-90%) afforded the pure terminal allylic azide in 65% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.71-7.63 (m, 4H); 7.45-7.32 (m, 6H); 5.75 (ddd, J_1 = 17.2 Hz, J_2 = 10.2 Hz, J_3 = 7.3 Hz, 1H); 5.63 (qt, J_1 = 10.2 Hz, J_2 = 6.4 Hz, 1H); 5.03-4.84 (m, 4H); 4.43 (t, J = 5.3 Hz, 1H); 4.12-4.03 (m, 3H); 3.76-3.66 (m, 2H); 2.72-2.49 (m, 2H); 2.14-1.94 (m, 4H); 1.61-1.50 (m, 4H); 1.48-1.37 (m, 1H); 1.36-1.27 (m, 1H); 1.05 (s, 9H); 0.71 (d, J = 6.9 Hz, 3H).



(3*S*,5*R*,6*R*)-6-((*S*)-1-azido-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-ol

To a solution of (((3*S*,5*R*,6*R*)-6-((*S*)-1-azido-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl)oxy)(*tert*-butyl)diphenylsilane in THF (0.1 M) at 0 ^{o}C was added TBAF (2.0 eq). The reaction warmed to rt and continued stirring overnight. The reaction was

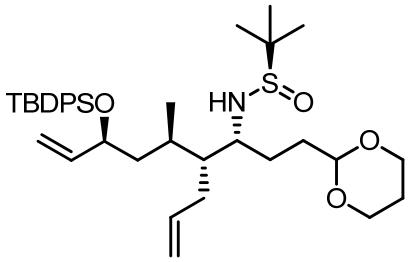
quenched by the addition of H_2O, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated. Purification via flash chromatography (DCM/MeOH 95:5) afforded the pure allylic alcohol in 93% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 5.83 (ddd, J_1 = 17.1 Hz, J_2 = 10.5 Hz, J_3 = 6.0 Hz, 1H); 5.74 (qt, J_1 = 6.4 Hz, J_2 = 12.8 Hz, 1H); 5.31-5.14 (m, 2H); 5.13-4.92 (m, 3H); 4.49 (t, J_1 = 5.4 Hz, 1H); 4.12-4.02 (m, 3H); 3.73 (td, J_1 = 12.3 Hz, J_2 = 2.4 Hz, 2H); 2.85-2.62 (m, 2H); 2.41-2.22 (m, 1H); 2.18-1.99 (m, 3H); 1.84-1.53 (m, 4H); 1.45 (ddd, J_1 = 14.3 Hz, J_2 = 8.8 Hz, J_3 = 5.5 Hz, 1H); 1.36-1.29 (m, 1H); 1.00 (d, J_1 = 6.9 Hz, 3H).



(3*S*,5*R*,6*R*)-6-((*S*)-1-azido-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl methacrylate (2.210)

To a solution of (3*S*,5*R*,6*R*)-6-((*S*)-1-azido-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-ol in CH_2Cl_2 at 0 ^{o}C was added Et_3N (3.0 eq), DMAP (1.0 eq), and methacrylic anhydride (2.2 eq). The reaction warmed to rt and continued stirring for 3.5 h. The reaction was quenched by the addition of H_2O, extracted with EtOAc (3x), dried over Na_2SO_4, and concentrated. Purification via flash chromatography (DCM/MeOH 95:5) afforded the pure compound in 76% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 6.11 (s, 1H); 5.78 (ddd, J_1 = 17.1 Hz, J_2 = 10.5 Hz, J_3 = 6.3 Hz, 1H); 5.70 (qt, J_1 = 6.6 Hz, J_2 = 9.9, 1H); 5.57-5.53 (m, 1H); 5.26-5.10 (m, 4H); 5.05-4.91 (m, 2H); 4.49 (t, J = 5.2 Hz, 1H); 4.12-4.05 (m, 2H); 3.81-3.68 (m, 2H); 2.75 (d, J = 6.6 Hz, 1H); 2.34-2.22 (m, 1H);

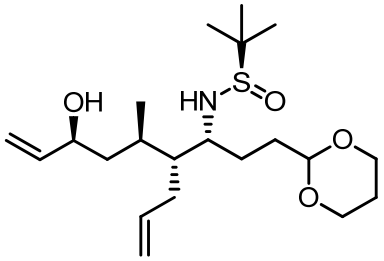
2.15-1.99 (m, 3H); 1.94 (s, 3H); 1.73-1.58 (m, 4H); 1.36-1.29 (m, 1H); 1.02 (d, J = 7.2 Hz, 3H).



(*R*)-*N*-((*3S,4R,5R,7S*)-4-allyl-7-((tert-butyldiphenylsilyl)oxy)-1-(1,3-dioxan-2-yl)-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide, (2.213)

To a solution of (*R*)-*N*-((*2R,3R,5S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-en-1-ylidene)-2-methylpropane-2-sulfinamide (723 mg, 1.38 mmol, 1.0 eq) in CH_2Cl_2 (0.1 M) under argon at -45 ^oC was added (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide (27.6 mL, 1.0 M in THF, 20.0 equiv) dropwise via cannula. The reaction was allowed to warm to room temperature and continue stirring for 24 h. The reaction was quenched with NH_4Cl, extracted with EtOAc, dried over sodium sulfate, and concentrated. Purification via flash chromatography (Hex:EtOAc 50-100%) afforded the desired product as a clear, colorless oil in 86% yield and 10:1 dr. The pure desired diastereomer can be isolated in 78% yield (689 mg). $[\alpha]_D^{20}$ = -9.7 (c = 0.38, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70-7.61 (m, 4H); 7.45-7.31 (m, 6H); 5.84-5.69 (m, 2H); 5.09-4.92 (m, 4H); 4.44 (t, J = 4.6 Hz, 1H); 4.08 (dd, J_1 = 11.0 Hz, J_2 = 5.2 Hz, 3H); 3.78-3.68 (m, 2H); 3.41 (d, J = 6.0 Hz, 1H); 3.31-3.23 (m, 1H); 2.13-1.97 (m, 2H); 1.71-1.63 (m, 1H); 1.63-1.48 (m, 5H); 1.48-1.39 (m, 2H); 1.36-1.29 (m, 1H); 1.29-1.20 (m, 2H); 1.16 (s, 9H); 1.06 (s, 9H); 0.61 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.60;

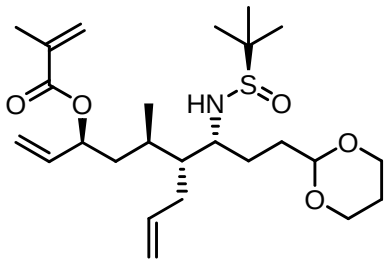
139.36; 136.11; 136.07; 134.51; 134.29; 129.75; 129.62; 127.66; 127.50; 116.37; 115.36; 102.22; 73.92; 67.00; 66.98; 57.94; 55.97; 46.91; 40.99; 31.74; 31.25; 28.80; 27.80; 27.18; 25.92; 22.98; 19.35; 18.22. HRMS (TOF, ES+) $C_{37}H_{57}NO_4SSi$ [M+H]+ calc. mass 640.3852, found 640.3856.



(*R*)-*N*-((3*R*,4*R*,5*R*,7*S*)-4-allyl-1-(1,3-dioxan-2-yl)-7-hydroxy-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide

To a solution of (*R*)-*N*-((*3S,4R,5R,7S*)-4-allyl-7-((tert-butyldiphenylsilyl)oxy)-1-(1,3-dioxan-2-yl)-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide (930 mg, 1.45 mmol, 1.0 eq) in THF (0.1 M) under argon at 0 ^{o}C was added 1.0 M TBAF (5.0 mL, 5.08 mmol, 3.5 eq). The reaction was warmed to rt and continued stirring overnight. The reaction was quenched by the addition of saturated NH_4Cl, extracted with EtOAc, dried over sodium sulfate, and concentrated *in vacuo*. Purification via flash chromatography (EtOAc 100%) afforded the desired product as a clear, colorless oil in 97% yield (565 mg). $[\alpha]_D^{20}$ = -45.8 (c = 1.01, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.89-5.76 (m, 2H); 5.23 (d, *J* = 17.2 Hz, 1H); 5.14-5.06 (m, 2H); 5.04 (d, *J* = 10.2 Hz, 1H); 4.48 (t, *J* = 3.9 Hz, 1H); 4.16 (q, *J* = 6.6 Hz, 1H); 4.07 (dd, J_1 = 11.0, J_2 = 5.0, 2H); 3.78-3.68 (m, 2H); 3.52 (d, *J* = 6.6 Hz, 1H); 3.39-3.31 (m, 1H); 2.25-2.18 (m, 2H); 2.05 (qt, J_1 = 13.1 Hz, J_2 = 5.1 Hz, 1H); 1.94 (br, 1H); 1.84-1.73 (m, 1H); 1.70-1.49 (m, 6H); 1.42 (ddd, J_1 = 14.3

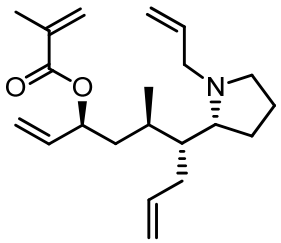
Hz, J_2 = 9.3 Hz, J_3 = 5.9 Hz, 1H); 1.36-1.29 (m, 1H); 1.18 (s, 9H); 1.02 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.13; 139.18; 116.54; 115.49; 102.16; 72.29; 67.00; 58.31; 56.10; 46.87; 40.58; 31.83; 31.74; 29.93; 28.71; 25.89; 22.99; 19.17. HRMS (TOF, ES+) $C_{21}H_{39}NO_4S$ [M+H]+ calc. mass 402.2678, found 402.2681.



(3*S*,5*R*,6*R*)-6-((*R*)-1-((*R*)-1,1-dimethylethylsulfinamido)-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl methacrylate (2.218)

To a solution of (*R*)-*N*-((3*R*,4*R*,5*R*,7*S*)-4-allyl-1-(1,3-dioxan-2-yl)-7-hydroxy-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide (490 mg, 1.22 mmol, 1.0 eq) in CH_2Cl_2 (0.1 M) under argon at 0 ^oC was added NEt_3 (0.43 mL, 3.05 mmol, 2.5 eq) and DMAP (15 mg, 0.12 mmol, 0.1 eq). Methacrylic anhydride (0.4 mL, 2.68 mmol, 2.2 eq) was added dropwise and the reaction was warmed to rt and continued stirring for 3.5 hours. The reaction was quenched by the addition of saturated NH_4Cl, extracted with EtOAc, dried over sodium sulfate, and concentrated *in vacuo*. Purification via flash chromatography (EtOAc 50-100%) afforded the desired product as a clear, colorless oil in 82% yield (467 mg). $[\alpha]_D^{20}$ = -32.8 (c = 1.05, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 6.10 (s, 1H); 5.87-5.73 (m, 2H); 5.55 (s, 1H); 5.36-5.25 (m, 2H); 5.20 (d, J = 10.5 Hz, 1H); 5.10 (dd, J_1 = 17.3 Hz, J_2 = 1.6 Hz, 1H); 5.04 (dd, J_1 = 10.2 Hz, J_2 = 1.4 Hz, 1H); 4.48 (t, J = 4.3 Hz, 1H); 4.08 (dd, J_1 = 10.7 Hz, J_2 = 5.0 Hz, 2H); 3.78-3.69 (m, 2H); 3.51

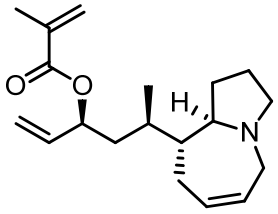
(d, J = 5.9 Hz, 1H); 3.41-3.33 (m, 1H); 2.24-2.16 (m, 2H); 2.05 (qt, J_1 = 13.2 Hz, J_2 = 5.0 Hz, 1H); 1.93 (s, 3H); 1.83-1.48 (m, 9H); 1.36-1.29 (m, 1H); 1.18 (s, 9H); 1.04 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.68; 139.07; 136.73; 136.38; 125.52; 117.76; 116.72; 102.12; 74.49; 67.02; 66.99; 57.59; 56.04; 46.44; 37.49; 31.72; 31.36; 29.74; 28.43; 25.91; 23.00; 18.45; 18.38. HRMS (TOF, ES+) $C_{37}H_{57}NO_4SSi$ [M+Na]+ calc. mass 470.2940, found 470.2943.



(3*S*,5*R*,6*R*)-6-((*R*)-1-allylpyrrolidin-2-yl)-5-methylnona-1,8-dien-3-yl methacrylate, (2.219)

To a vial containing (3*S*,5*R*,6*R*)-6-((*R*)-1-((*R*)-1,1-dimethylethylsulfinamido)-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl methacrylate (440 mg, 0.94 mmol, 1.0 eq), was added 95:5 TFA/H_2O (0.2 M). The reaction was allowed to stir at rt for 5 min, followed by dilution in 5 mL of toluene. The resulting crude imine was concentrated *in vacuo* and resuspended in 5 mL toluene and concentrated. The crude imine was then dissolved in DCE (0.1 M) followed by addition of PS-$BH(OAc)_3$ (2.0 g, 4.7 mmol, 5.0 eq). The reaction mixture was rotated at rt for 2 h. The crude pyrrolidine was then filtered through celite eluting with DCM and MeOH. The solution was concentrated and dissolved in DMF (0.2 M). K_2CO_3 (260 mg, 1.88 mmol, 2.0 eq) and allyl iodide (0.086 mL, 0.94 mmol, 1.0 eq) were added and the reaction was stirred at rt for 2 h, after which an additional 0.5 eq of allyl iodide (0.043 mL) was added. After stirring at rt for an

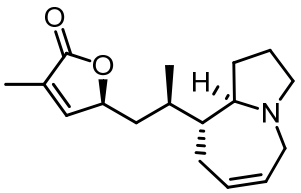
additional hour, the reaction was filtered through celite eluting with DCM and MeOH, concentrated in vacuo, and purified by reverse phase chromatography (10-90% H_2O/MeCN) to afford the pure product in 46% isolated yield (143 mg). $[\alpha]_D^{20}$ = 80.5 (c = 0.49, $CHCl_3$). ^{1}H NMR (400MHz, C_6D_6) δ 6.20 (s, 1H); 5.93-5.73 (m, 3H); 5.68-5.60 (m, 1H); 5.29 (d, J = 17.2 Hz, 1H); 5.22 (t, J = 1.6 Hz, 1H); 5.14 (dd, J_1 = 17.2 Hz, J_2 = 1.1 Hz, 1H); 5.07-4.96 (m, 4H); 3.34-3.26 (m, 1H); 3.07-2.99 (m, 1H); 2.60 (dd, J_1 = 14.0, J_2 = 7.6 Hz, 1H); 2.42-2.35 (m, 1H); 2.18-1.96 (m, 4H); 1.87 (s, 3H); 1.83 (ddd, J_1 = 12.1 Hz, J_2 = 8.8 Hz, J_3 = 3.3 Hz, 1H); 1.68-1.58 (m, 1H); 1.58-1.38 (m, 5H); 1.04 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 166.20; 139.56; 137.39; 137.30; 137.06; 124.93; 117.27; 115.92; 115.22; 74.85; 66.25; 58.43; 54.23; 45.57; 38.46; 33.84; 29.04; 27.53; 23.34; 20.06; 18.50. HRMS (TOF, ES+) $C_{21}H_{34}NO_2$ [M+H]+ calc. mass 332.2590, found 332.2589.



(3*S*,5*R*)-5-((9*R*,9a*R*)-2,3,5,8,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)hex-1-en-3-yl methacrylate, (2.224)

To a solution of (3*S*,5*R*,6*R*)-6-((*R*)-1-allylpyrrolidin-2-yl)-5-methylnona-1,8-dien-3-yl methacrylate (27 mg, 0.081 mmol, 1.0 eq) in toluene (0.005 M) under argon was added CSA (37.6 mg, 0.162 mmol, 2.0 eq) and Grela catalyst (5.5 mg, 0.0081 mmol, 0.1 eq). The reaction continued stirring for 6 h at rt before being concentrated *in vacuo*. The reaction was purified via reverse phase chromatography (MeCN/H_2O 10-90%) to afford

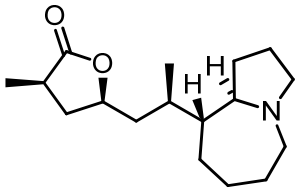
the pure product of single ring closure in 65% yield (16.0 mg). $[\alpha]_D^{20}$ = 11.9 (c = 0.26, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 6.10 (s, 1H); 5.91-5.81 (m, 1H); 5.81-5.69 (m, 2H); 5.55 (s, 1H); 5.34-5.25 (m, 2H); 5.21 (d, *J* = 10.3 Hz, 1H); 3.41 (dd, J_1 = 15.2 Hz, J_2 = 6.6 Hz, 1H); 3.09 (t, *J* = 8.2 Hz, 1H); 2.87 (d, *J* = 15.2 Hz, 1H); 2.40-2.24 (m, 4H); 2.05-1.87 (m, 2H); 1.94 (s, 3H); 1.82-1.50 (m, 5H); 1.46-1.31 (m, 2H); 1.00 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 166.70; 136.82; 136.27; 132.07; 128.84; 125.44; 118.02; 74.93; 71.23; 57.81; 54.09; 49.77; 35.71; 32.27; 31.66; 26.00; 21.54; 19.17; 18.45. HRMS (TOF, ES+) $C_{19}H_{30}NO_2$ [M+H]+ calc. mass 304.2277, found 304.2278.



(*S*)-5-((*R*)-2-((9*R*,9a*R*)-2,3,5,8,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)propyl)-3-methylfuran-2(5H)-one, (2.225)

To a solution of (3*S*,5*R*,6*R*)-6-((*R*)-1-allylpyrrolidin-2-yl)-5-methylnona-1,8-dien-3-yl methacrylate (27.5 mg, 0.083 mmol, 1.0 eq) in toluene (0.005 M) under argon was added CSA (38.5 mg, 0.166 mmol, 2.0 eq) followed by stirring for 10 min at rt. Grela catalyst (5.6 mg, 0.0083 mmol, 0.1 eq) was added and the reaction was allowed to stir at rt for 7.5 h. An additional 10 mol% catalyst (5.6 mg) was added and the reaction continued stirring for 15 h at 90 ^{o}C. An additional 10 mol% catalyst (5.6 mg) was then added and the reaction continued stirring for an additional 8 h. The reaction was then concentrated *in* vacuo and purified via reverse phase chromatography (MeCN/H_2O 10-90%) to afford the pure product of *bis*-ring closure in 52% yield (11.9 mg). $[\alpha]_D^{20}$ = 76.9 (c = 0.20,

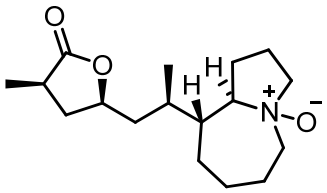
$CHCl_3$). ^1H NMR (500MHz, $CDCl_3$) δ (ppm): 7.05 (s, 1H); 5.83-5.75 (m, 1H); 5.73-5.65 (m, 1H); 4.90 (m, 1H); 3.45 (dd, J_1 = 15.5 Hz, J_2 = 6.0 Hz, 1H); 3.08 (t, J = 8.3 Hz, 1H); 2.86 (d, J = 15.5 Hz, 1H); 2.42 (dd, J_1 = 12.8 Hz, J_2 = 4.3 Hz, 1H); 2.34-2.23 (m, 2H); 2.04-1.95 (m, 1H); 1.92 (s, 3H); 1.93-1.85 (m, 1H); 1.83-1.63 (m, 4H); 1.61-1.53 (m, 1H); 1.52-1.46 (m, 1H); 1.45-1.39 (m, 1H); 1.05 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 174.23; 148.60; 130.93; 130.20; 129.14; 80.76; 70.46; 57.75; 54.79; 50.30; 35.82; 32.61; 32.49; 25.71; 21.87; 19.87; 10.85. HRMS (TOF, ES+) $C_{17}H_{26}NO_2$ [M+H]+ calc. mass 276.1964, found 276.1964.



(3*R*,5*S*)-3-methyl-5-((*R*)-2-((9*R*,9a*R*)-octahydro-1H-pyrrolo[1,2-a]azepin-9-yl)propyl)dihydrofuran-2(3H)-one (9a-*epi*-stemaphylline), (2.226)

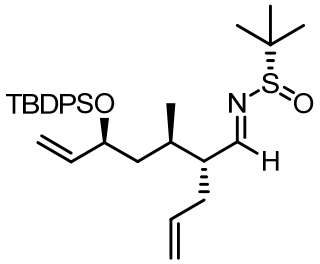
To a solution of (*S*)-5-((*R*)-2-((9*R*,9a*R*)-2,3,5,8,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)propyl)-3-methylfuran-2(5H)-one (18.1 mg, 0.066 mmol, 1.0 eq) in THF (0.025 M) at rt was added $Pd(OH)_2/C$ (4.5 mg, 0.25 eq). The reaction was then bubbled with hydrogen gas for 3 min, placed under an atmosphere of hydrogen (via balloon) and stirred at rt for 12 h. The reaction was then filtered through a pad of Celite and concentrated. Purification via reverse phase chromatography ($MeCN/H_2O$ 10-90%) afforded the pure product in 95% yield (17.5 mg). $[\alpha]_D^{20}$ = 27.7 (c = 0.68, $CHCl_3$). ^1H NMR (500MHz, $CDCl_3$) δ (ppm): 4.39-4.32 (m, 1H); 3.12-3.05 (m, 1H); 3.04-2.97 (m, 1H); 2.70-2.60 (m, 1H); 2.51 (ddd, J_1 = 12.5 Hz, J_2 = 8.4 Hz, J_3 = 5.3 Hz, 1H); 2.47-2.38

(m, 1H); 2.37-2.27 (m, 1H); 2.26-2.16 (m, 1H); 2.08-1.96 (m, 1H); 1.86-1.75 (m, 2H); 1.73-1.51 (m, 9H); 1.45-1.31 (m, 3H); 1.27 (d, J = 7.1 Hz, 3H); 1.00 (d, J = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 179.51; 78.33; 70.33; 58.53; 54.78; 51.85; 37.80; 36.86; 35.98; 32.34; 28.24; 25.28; 22.29; 19.67; 15.22. HRMS (TOF, ES+) $C_{17}H_{29}NO_2$ [M+H]+ calc. mass 280.2277, found 280.2275.



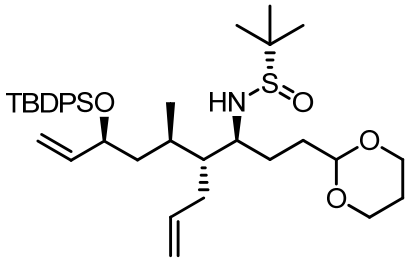
(9*R*,9a*R*)-9-((*R*)-1-((2*S*,4*R*)-4-methyl-5-oxotetrahydrofuran-2-yl)propan-2-yl)decahydropyrrolo[1,2-a]azepine 4-oxide (9a-*epi*-stemaphylline-*N*-oxide), (2.227)

To a solution of 9a-*epi*-stemaphylline (16.3 mg, 0.058 mmol, 1.0 eq) in DCM (0.005 M), was bubbled ozone for 3 min. Upon completion, the reaction was concentrated and purified via reverse phase chromatography (MeCN/H_2O 10-90%) to afford the pure *N*-oxide in 53% yield (9.1 mg). $[\alpha]_D^{20}$ = 18.1 (c = 0.33, $CHCl_3$). ^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 4.40-4.33 (m, 1H); 3.69-3.62 (m, 1H); 3.61-3.54 (m, 1H); 3.53-3.46 (m, 1H); 3.26-3.15 (m, 2H); 2.71-2.63 (m, 1H); 5.56-2.45 (m, 3H); 2.43-2.35 (m, 1H); 2.21 (ddd, J_1 = 5.4 Hz, J_2 = 11.4 Hz, J_3 = 23.4 Hz, 1H); 2.15-2.10 (m, 1H); 2.09-2.00 (m, 1H); 1.94-1.79 (m, 3H); 1.75-1.65 (m, 3H); 1.64-1.57 (m, 1H); 1.46-1.33 (m, 3H); 1.30-1.22 (m, 1H); 1.27 (d, J = 7.2 Hz, 3H); 1.05 (d, J = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 179.29; 81.12; 77.77; 72.24; 66.26; 42.96; 37.74; 36.65; 35.98; 31.92; 28.68; 25.47; 24.47; 21.73; 20.06; 19.16; 15.15. HRMS (TOF, ES+) $C_{17}H_{30}NO_3$ [M+H]+ calc. mass 296.2226, found 296.2226.



(*S*)-*N*-((*2R,3R,5S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-en-1-ylidene)-2-methylpropane-2-sulfinamide, (2.212)

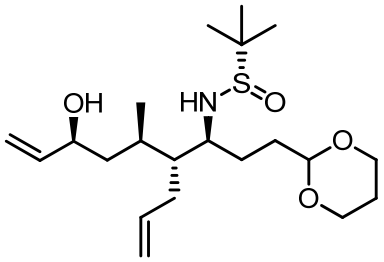
To a solution of (2*R*,3*R*,5*S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-enal (990 mg, 2.35 mmol, 1.0 eq) in THF under argon was added $Ti(OEt)_4$ (1.23 mL, 5.88 mmol, 2.5 eq) followed by (*S*)-2-methylpropane-2-sulfinamide (313 mg, 2.59 mmol, 1.1 eq). The reaction was allowed to stir at 40 ^oC overnight. The reaction was quenched by the addition of saturated $NaHCO_3$, extracted with EtOAc, dried over sodium sulfate, and concentrated under vacuum. Purification via flash chromatography (Hex:EtOAc 4:1) afforded the desired product as a clear, colorless oil in 92% yield (1.13 g). $[\alpha]_D^{20}$ = 108.8 (c = 0.76, $CHCl_3$). ^1H NMR (400MHz, $CDCl_3$) δ 7.87 (d, J = 6.0 Hz, 1H); 7.68-7.62 (m, 4H); 7.45-7.32 (m, 6H); 5.73 (ddd, J_1 = 17.4 Hz, J_2 = 10.4 Hz, J_3 = 7.3 Hz, 1H); 5.64 (dddd, J_1 = 17.0 Hz, J_2 = 13.7 Hz, J_3 = 10.2 Hz, J_4 = 6.8 Hz, 1H); 5.03-4.93 (m, 3H); 4.89 (d, J = 17.2 Hz, 1H); 4.17-4.09 (m, 1H); 2.50-2.42 (m, 1H); 2.38-2.28 (m, 1H); 2.19-2.09 (m, 1H); 1.82-1.72 (m, 1H); 1.55 (ddd, J_1 = 13.3 Hz, J_2 = 8.7 Hz, J_3 = 4.4 Hz, 1H); 1.44-1.35 (m, 1H); 1.17 (s, 9H); 1.05 (s, 9H); 0.66 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.50; 140.42; 136.13; 136.06; 134.30; 134.19; 129.81; 129.67; 127.70; 127.51; 116.82; 115.45; 73.50; 56.78; 50.24; 42.78; 33.78; 31.42; 27.17; 22.64; 19.39; 16.07. HRMS (TOF, ES+) $C_{31}H_{45}NO_2SSi$ [M+H]+ calc. mass 524.3019, found 524.3018.



(S)-N-((3S,4R,5R,7S)-4-allyl-7-((tert-butyldiphenylsilyl)oxy)-1-(1,3-dioxan-2-yl)-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide, (2.214)

To a solution of (*S*)-*N*-((*2R,3R,5S*)-2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylhept-6-en-1-ylidene)-2-methylpropane-2-sulfinamide (867 mg, 1.66 mmol, 1.0 eq) in CH_2Cl_2 (0.1 M) under argon at -45 ^oC was added (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide (16.5 mL, 1.0 M in THF, 10.0 equiv) dropwise. The reaction was allowed to warm to room temperature and continue stirring for 24 h. The reaction was quenched with NH_4Cl, extracted with EtOAc, dried over sodium sulfate, and concentrated. Purification via flash chromatography (Hex:EtOAc 50-100%) afforded the desired product as a clear, colorless oil in 95% yield and 1.2:1 dr. The pure desired diastereomer can be isolated in 51% yield (542 mg). $[\alpha]_D^{20}$ = 35.9 (c = 1.68, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70-7.62 (m, 4H); 7.44-7.31 (m, 6H); 5.93-5.82 (m, 1H); 5.77 (ddd, J_1 = 17.5 Hz, J_2 = 10.5 Hz, J_3 = 7.3 Hz, 1H); 5.08-4.90 (m, 4H); 4.46 (t, J = 4.6 Hz, 1H); 4.11-4.03 (m, 3H); 3.77-3.66 (m, 2H); 3.56 (d, J = 9.3 Hz, 1H); 3.27-3.19 (m, 1H); 2.13-1.97 (m, 3H); 1.81-1.62 (m, 4H); 1.54-1.42 (m, 2H); 1.40-1.28 (m, 3H); 1.27-1.20 (m, 1H); 1.17 (s, 9H); 1.05 (s, 9H); 0.57 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.59; 140.36; 136.06; 136.01; 134.38; 134.25; 129.66; 129.53; 127.59; 127.42; 115.78; 115.25; 102.33; 102.03; 73.95; 66.93; 66.89; 59.70; 56.07; 48.76; 43.11; 35.23; 32.35; 30.94; 27.10; 26.08; 25.91; 25.83;

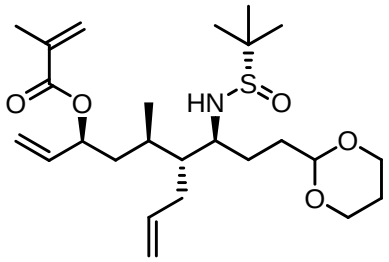
23.97; 22.89; 19.29; 17.78. HRMS (TOF, ES+) $C_{37}H_{57}NO_4SSi$ [M+Na]+ calc. mass 640.3852, found 640.3856.



(S)-N-((3S,4R,5R,7S)-4-allyl-1-(1,3-dioxan-2-yl)-7-hydroxy-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide

To a solution of (S)-N-((3S,4R,5R,7S)-4-allyl-7-((tert-butyldiphenylsilyl)oxy)-1-(1,3-dioxan-2-yl)-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide (595 mg, 0.93 mmol, 1.0 eq) in THF (0.1 M) under argon at 0 ^{o}C was added TBAF (3.25 mL, 3.25 mmol, 3.5 eq). The reaction was warmed to rt and continued stirring overnight. The reaction was quenched by the addition of saturated NH_4Cl, extracted with EtOAc, dried over sodium sulfate, and concentrated *in vacuo*. Purification via flash chromatography (EtOAc 100%) afforded the desired product as a clear, colorless oil in 97% yield (362 mg). $[\alpha]_D^{20}$ = 28.4 (c = 0.80, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.95-5.81 (m, 2H); 5.25 (d, J = 17.3 Hz, 1H); 5.15-5.07 (m, 2H); 5.04 (d, J = 10.1 Hz, 1H); 4.50 (t, J = 4.8 Hz, 1H); 4.33-4.25 (m, 1H); 4.09 (dd, J_1 = 11.0 Hz, J_2 = 5.1 Hz, 2H); 3.80-3.70 (m, 3H); 3.34 (tt, J_1 = 9.5 Hz, J_2 = 3.1 Hz, 1H); 2.31-2.13 (m, 2H); 2.13-1.99 (m, 2H); 1.97-1.88 (m, 1H); 1.82 (ddd, J_1 = 13.6 Hz, J_2 = 6.7 Hz, J_3 = 4.3 Hz, 1H); 1.78-1.67 (m, 2H); 1.66-1.50 (m, 4H); 1.49-1.37 (m, 2H); 1.36-1.30 (m, 1H); 1.20 (s, 9H); 0.97 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.24; 139.73; 116.26; 114.99; 102.19; 72.02;

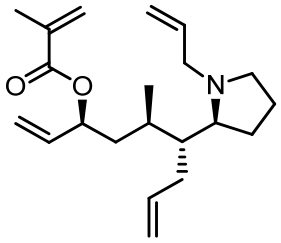
67.05; 59.21; 56.30; 48.09; 41.23; 32.48; 32.28; 30.43; 27.34; 25.93; 23.03; 19.34. HRMS (TOF, ES+) $C_{21}H_{40}NO_4S$ [M+H]+ calc. mass 402.2678, found 402.2681.



(3S,5R,6R)-6-((S)-1-((S)-1,1-dimethylethylsulfinamido)-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl methacrylate, (2.215)

To a solution of (S)-N-((3S,4R,5R,7S)-4-allyl-1-(1,3-dioxan-2-yl)-7-hydroxy-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide (563 mg, 1.4 mmol, 1.0 eq) in CH_2Cl_2 (0.1 M) under argon at 0 ^oC was added NEt_3 (0.49 mL,. 3.5 mmol, 2.5 eq) and DMAP (85.5 mg, 0.70 mmol, 0.5 eq). Methacrylic anhydride (0.46 mL, 3.08 mmol, 2.2 eq) was added dropwise and the reaction was warmed to rt and continued stirring for 3.5 hours. The reaction was quenched by the addition of saturated NH_4Cl, extracted with EtOAc, dried over sodium sulfate, and concentrated *in vacuo*. Purification via flash chromatography (EtOAc 50-100%) afforded the desired product as a clear, colorless oil in 73% yield (483 mg). $[\alpha]_D^{20}$ = 36.6 (c = 0.80, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 6.11 (s, 1H); 5.97-5.84 (m, 1H); 5.78 (ddd, J_1 = 17.4 Hz, J_2 = 10.4 Hz, J_3 = 7.0, 1H); 5.55 (t, J = 1.7 Hz, 1H); 5.35-5.25 (m, 2H); 5.20 (d, J = 10.4 Hz, 1H); 5.11 (d, J = 17.3 Hz, 1H); 5.04 (d, J = 10.0 Hz, 1H); 4.51 (t, J = 5.0 Hz, 1H); 4.09 (dd, J_1 = 10.7 Hz, J_2 = 5.0 Hz, 2H); 3.79-3.69 (m, 2H); 3.56 (d, J = 9.6 Hz, 1H); 3.35 (tt, J_1 = 9.6 Hz, J_2 = 2.7 Hz, 1H); 2.27-2.14 (m, 2H); 2.07 (qt, J_1 = 13.4 Hz, J_2 = 5.0 Hz, 1H); 2.02-1.92 (m, 1H); 1.94

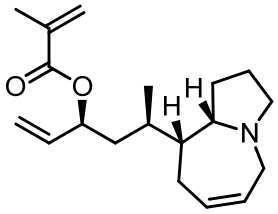
(s, 3H); 1.89-1.82 (m, 1H); 1.80-1.71 (m, 1H); 1.65-1.46 (m, 6H); 1.46-1.39 (m, 1H); 1.37-1.30 (m, 1H); 1.19 (s, 9H); 1.00 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.53; 139.74; 136.61; 136.34; 125.36; 117.58; 116.12; 101.92; 74.68; 66.89; 66.86; 59.35; 56.11; 48.69; 39.26; 32.40; 32.24; 31.55; 26.41; 25.77; 22.83; 18.32; 17.81. HRMS (TOF, ES+) $C_{25}H_{44}NO_5S$ [M+H]+ calc. mass 470.2940, found 470.2943.



(3S,5R,6R)-6-((S)-1-allylpyrrolidin-2-yl)-5-methylnona-1,8-dien-3-yl methacrylate, (2.216)

To a vial containing (3S,5R,6R)-6-((S)-1-((S)-1,1-dimethylethylsulfinamido)-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl methacrylate (287 mg, 0.61 mmol, 1.0 eq), was added 95:5 TFA/H_2O (0.2 M). The reaction was allowed to stir at rt for 5 min, followed by dilution in 5 mL of toluene. The resulting crude imine was concentrated *in vacuo* and resuspended in 5 mL toluene and concentrated. The crude imine was then dissolved in DCE (0.1 M) followed by addition of PS-$BH(OAc)_3$ (1.32 g, 3.05 mmol, 5.0 eq). The reaction mixture was rotated at rt for 2 h. The crude pyrrolidine was then filtered through celite eluting with DCM and MeOH. The solution was concentrated and dissolved in DMF (0.2 M). K_2CO_3 (253 mg, 1.83 mmol, 3.0 eq) and allyl iodide (0.056 mL, 0.61 mmol, 1.0 eq) were added and the reaction was stirred at rt for 2 h, after which an additional 0.5 eq of allyl iodide (0.028 mL) was added. After stirring at rt for an additional hour, the reaction was filtered through celite eluting with DCM and MeOH,

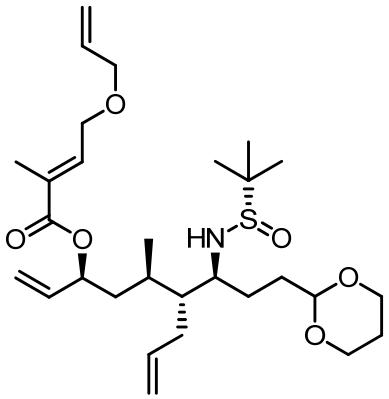
concentrated in vacuo, and purified by reverse phase chromatography (10-90% H_2O/MeCN) to afford the pure product in 47% isolated yield (97 mg). $[\alpha]_D^{20}$ = -36.2 (c = 0.48, $CHCl_3$). ^{1}H NMR (400MHz, C_6D_6) δ 6.20-6.17 (m, 1H); 5.96-5.80 (m, 2H); 5.80-5.71 (m, 1H); 5.67 (q, J = 7 Hz, 1H); 5.28 (dt, J_1 = 17.0 Hz, J_2 = 1.4 Hz, 1H); 5.23-5.15 (m, 2H); 5.08-4.96 (m, 4H); 5.07-4.96 (m, 4H); 3.52-3.44 (m, 1H); 3.06-2.99 (m, 1H); 2.65 (dd, J_1 = 13.6, J_2 = 7.7 Hz, 1H); 2.57-2.49 (m, 1H); 2.30 (td, J_1 = 8.7 Hz, J_2 = 2.6 Hz, 1H); 1.98-1.89 (m, 2H); 1.87 (s, 3H); 1.85-1.74 (m, 1H); 1.74-1.64 (m, 3H); 1.56-1.34 (m, 5H); 0.83 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 166.26; 139.79; 137.32; 137.22; 125.01; 116.93; 116.02; 115.20; 73.79; 63.41; 57.41; 53.70; 43.23; 40.25; 31.61; 30.38; 26.88; 23.95; 18.48; 16.67. HRMS (TOF, ES+) $C_{21}H_{34}NO_2$ [M+H]+ calc. mass 332.2590, found 332.2588.



(3S,5R)-5-((9R,9aS)-2,3,5,8,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)hex-1-en-3-yl methacrylate, (2.228)

To a solution of (3S,5R,6R)-6-((S)-1-allylpyrrolidin-2-yl)-5-methylnona-1,8-dien-3-yl methacrylate (10 mg, 0.03 mmol, 1.0 eq) in toluene (0.005 M) under argon was added CSA (14 mg, 0.06 mmol, 2.0 eq) and benzoquinone (0.8 mg, 0.0075 mmol, 0.25 eq). After stirring at rt for 10 min, Hoveyda Grubbs II catalyst (1.9 mg, 0.003 mmol, 10 mol%) was added and the reaction continued stirring for 15 h at rt. An additional 10 mol % catalyst (1.9 mg) was added followed by stirring at rt for an additional 8.5 h. After

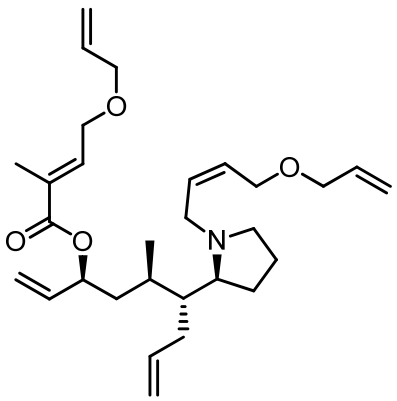
addition of 10 mol% catalyst (1.9 mg) and stirring for 15 additional h the reaction was concentrated *in vacuo*. The reaction was purified via reverse phase chromatography (MeCN/H_2O 10-90%) followed by additional purification via flash chromatography (DCM/MeOH/NH_4OH 94.9:5:0.1) to afford the product of a single ring closure in 48% yield (4.4 mg). $[\alpha]_D^{20}$ = -38.1 (c = 0.89, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 6.11 (s, 1H); 5.94-5.85 (m, 2H); 5.73-5.68 (m, 1H); 5.59-5.53 (m, 2H); 5.17 (d, J = 17.3 Hz, 1H); 5.07 (d, J = 9.8 Hz, 1H); 3.38-3.2 (m, 1H); 3.12-3.06 (m, 1H); 2.69 (dd, J_1 = 13.1 Hz, J_2 = 7.5 Hz, 1H); 2.58 (dd, J_1 = 14.0 Hz, J_2 = 8.9 Hz, 1H); 2.53-2.46 (m, 1H); 2.16-2.08 (m, 1H); 1.95 (s, 3H); 1.93-1.87 (m, 1H); 1.85 (dt, J_1 = 13.1 Hz, J_2 = 2.5 Hz, 1H); 1.79-1.71 (m, 1H); 1.70-1.58 (m, 4H); 1.55-1.47 (m, 1H); 1.42-1.34 (m, 1H); 1.01 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 166.94; 136.88; 136.59; 133.58; 131.31; 125.39; 116.51; 73.83; 65.25; 56.93; 54.21; 43.65; 41.66; 36.55; 25.51; 24.40; 22.60; 21.75; 18.49. HRMS (TOF, ES+) $C_{19}H_{30}NO_2$ [M+H]+ calc. mass 304.2277, found 304.2275.



(*E*)-(3*S*,5*R*,6*R*)-6-((*S*)-1-((*S*)-1,1-dimethylethylsulfinamido)-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl 4-(allyloxy)-2-methylbut-2-enoate, (2.231)

To a solution of triethylamine (0.347 mL, 3.43 mmol, 5.0 eq) in CH_2Cl_2 (0.1 M) under

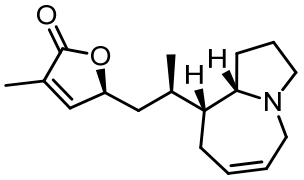
argon was added DMAP (84 mg, 0.686 mmol, 1.0 eq), 2-methyl-6-nitrobenzoic anhydride (MNBA) (590 mg, 1.715 mmol, 2.5 eq) and carboxylic acid **30** (268 mg, 1.715 mmol, 2.5 eq) at room temperature. After stirring for 10 min, (S)-N-((3S,4R,5R,7S)-4-allyl-1-(1,3-dioxan-2-yl)-7-hydroxy-5-methylnon-8-en-3-yl)-2-methylpropane-2-sulfinamide (275.6 mg, 0.686 mmol, 1.0 eq) was added. The mixture was refluxed with stirring for 3 h. The mixture was cooled down to 0 °C, and a saturated aqueous solution of NH_4Cl was added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with sat. $NaHCO_3$ and dried over MgSO4. Concentration under vacuum gave the crude product, and purification by silica gel column chromatography (1:1 Hex/EtOAc) afforded the desired product as a colorless oil in 98% yield (361 mg). $[\alpha]_D^{20}$ = 60.5 (c = 0.58, $CHCl_3$) ^{1}H NMR (400MHz, $CDCl_3$) δ 6.83 (td, J_1 = 5.9 Hz, J_2 = 1.3 Hz, 1H); 5.98-5.84 (m, 2H); 5.76 (ddd, J_1 = 17.3 Hz, J_2 = 10.4 Hz, J_3 = 7.1 Hz, 1H); 5.35-5.24 (m, 3H); 5.20 (t, J = 10.3 Hz, 2H); 5.10 (d, J = 17.3 Hz, 1H); 5.03 (d, J = 10.0 Hz, 1H); 4.51 (t, J = 4.9 Hz, 1H); 4.16 (d, J = 5.9 Hz, 2H); 4.08 (dd, J_1 = 10.9 Hz, J_2 = 4.9 Hz, 2H); 4.01 (d, J = 5.7 Hz, 2H); 3.74 (t, J = 12.3 Hz, 2H); 3.56 (d, J = 9.5 Hz, 1H); 3.34 (t, J = 10.0 Hz, 1H); 2.27-2.13 (m, 2H); 2.06 (qt, J_1 = 12.6 Hz, J_2 = 4.9 Hz, 1H); 2.00-1.92 (m, 1H); 1.83 (s, 3H); 1.80-1.70 (m, 1H); 1.68 (s, 1H); 1.63-1.38 (m, 5H); 1.33 (d, J = 13.6 Hz, 1H); 1.18 (s, 9H); 0.99 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.71; 139.90; 138.18; 136.45; 134.48; 129.61; 117.81; 117.67; 116.22; 102.06; 74.92; 71.83; 67.03; 67.00; 66.93; 59.53; 56.25; 48.83; 39.39; 32.51; 32.38; 31.71; 26.48; 25.89; 22.95; 17.91; 12.97. HRMS (TOF, ES+) $C_{29}H_{50}NO_6S$ [M+H]+ calc. mass 540.3359, found 540.3354.



(E)-(3S,5R,6R)-6-((S)-1-((Z)-4-(allyloxy)but-2-en-1-yl)pyrrolidin-2-yl)-5-methylnona-1,8-dien-3-yl 4-(allyloxy)-2-methylbut-2-enoate, (2.233)

To a vial containing (E)-(3S,5R,6R)-6-((S)-1-((S)-1,1-dimethylethylsulfinamido)-3-(1,3-dioxan-2-yl)propyl)-5-methylnona-1,8-dien-3-yl 4-(allyloxy)-2-methylbut-2-enoate (276.4 mg, 0.512 mmol, 1.0 eq), was added 95:5 TFA/H_2O (0.2 M). The reaction was allowed to stir at rt for 5 min, followed by dilution in 5 mL of toluene. The resulting crude imine was concentrated *in vacuo* and resuspended in 5 mL toluene and concentrated. The crude imine was then dissolved in DCE (0.1 M) followed by addition of PS-$BH(OAc)_3$ (1.11 g, 2.56 mmol, 5.0 eq). The reaction mixture was rotated at rt for 2 h. The crude pyrrolidine was then filtered through celite eluting with DCM and MeOH. The solution was concentrated and dissolved in DMF (0.2 M). K_2CO_3 (212 mg, 1.54 mmol, 3.0 eq) and allylic bromide **32** (118 mg, 0.61 mmol, 1.1 eq) were added and the reaction was stirred at rt for 2 h, after which, the reaction was filtered through celite eluting with DCM and MeOH, concentrated in vacuo, and purified by reverse phase chromatography (10-90% H_2O/MeCN) to afford the pure product in 40% isolated yield (97 mg). $[\alpha]_D^{20}$ = -36.2 (c = 0.48, $CHCl_3$). $[\alpha]_D^{20}$ = -42.7 (c = 1.26, $CDCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 6.83 (td, J_1 = 5.9 Hz, J_2 = 1.3 Hz, 1H); 5.96-5.88 (m, 2H); 5.76 (ddd,

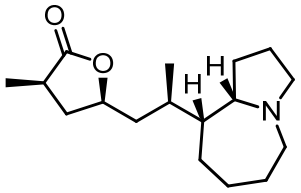
J_1 = 17.2 Hz, J_2 = 10.5 Hz, J_3 = 6.7 Hz, 1H); 5.73-5.62 (m, 3H); 5.34 (q, J = 6.9 Hz, 1H); 5.32-5.20 (m, 4H); 5.20-5.15 (m, 2H); 4.96 (d, J = 17.0 Hz, 1H); 4.91 (d, J = 10.0 Hz, 1H); 4.17 (dd, J_1 = 5.9 Hz, J_2 = 1.0 Hz, 2H); 4.12 (dd, J_1 = 12.2 Hz, J_2 = 6.0 Hz, 1H); 4.06 (dd, J_1 = 12.0 Hz, J_2 = 5.4 Hz, 1H); 4.01 (dt, J_1 = 5.7 Hz, J_2 = 1.3 Hz, 2H); 3.99-3.97 (m, 2H); 3.37 (dd, J_1 = 13.7 Hz, J_2 = 4.6 Hz, 1H); 3.07-3.00 (m, 1H); 2.79 (dd, J_1 = 13.8 Hz, J_2 = 7.2 Hz, 1H); 2.42-2.30 (m, 2H); 2.06-1.96 (m, 1H); 1.92 (dt, J_1 = 14.1 Hz, J_2 = 9.0 Hz, 1H); 1.84 (s, 3H); 1.74-1.53 (m, 9H); 0.86 (d, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.74; 139.37; 138.07; 136.69; 135.00; 134.47; 131.04; 129.59; 128.22; 117.73; 117.21; 117.17; 115.21; 74.18; 71.90; 71.31; 67.00; 66.05; 63.92; 53.71; 50.92; 43.10; 39.98; 31.19; 30.10; 26.56; 23.55; 16.47; 12.99. HRMS (TOF, ES+) $C_{29}H_{46}NO_4$ [M+H]+ calc. mass 472.3427, found 472.3429.



(S)-5-((R)-2-((9R,9aS)-2,3,5,8,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)propyl)-3-methylfuran-2(5H)-one, (2.229)

(E)-(3S,5R,6R)-6-((S)-1-((Z)-4-(allyloxy)but-2-en-1-yl)pyrrolidin-2-yl)-5-methylnona-1,8-dien-3-yl 4-(allyloxy)-2-methylbut-2-enoate (90 mg, 0.19 mmol, 1.0 eq) was placed under argon and dissolved in toluene (0.02 M). CSA (88.7 mg, 0.38 mmol, 2.0 equiv) was added and the solution was stirred for 10 min at rt. In a two neck flask equipped with a reflux condenser a solution of Hoveyda Grubbs II catalyst (23.8 mg, 0.038 mmol, 0.2 eq) was dissolved in toluene (0.007 M relative to tetraene **33**) and heated to vigorous reflux. After the solution was brought to reflux the reaction mixture was sparged with

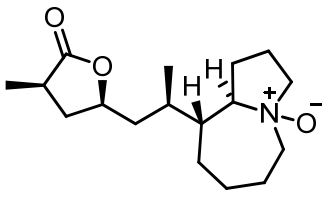
argon through the second neck of the flask. The solution of tetraene **33** and CSA in toluene was then added dropwise via syringe over ~10 min. After 20 minutes of additional heating under argon sparge the reaction mixture was concentrated *in vacuo* and purified by reverse phase chromatography (10-90% H_2O/MeCN) to afford the pure product in 37% isolated yield (19.3 mg) and with minimal epimerization (10:1). $[\alpha]_D^{20}$ = -13.0 (c = 1.26, $CHCl_3$) ^{1}H NMR (400MHz, $CDCl_3$) δ 6.14 (m, 1H); 5.72-5.67 (m, 1H); 5.49-5.44 (m, 1H); 4.47-4.42 (m, 1H); 4.47-4.42 (m, 1H); 3.20 (dd, J_1 = 16.7 Hz, J_2 = 6.2 Hz, 1H); 2.98 (d, J = 16.7 Hz, 1H); 2.81 (td, J_1 = 8.2 Hz, J_2 = 3.5 Hz, 1H); 2.54-5.48 (m, 1H); 229-2.18 (m, 2H); 1.75-1.70 (m, 1H); 1.70-1.59 (m, 6H); 1.58-1.52 (m, 1H); 1.52-1.44 (m, 2H); 1.44-1.38 (m, 1H); 1.14 (ddd, J_1 = 14.0 Hz, J_2 = 8.8 Hz, J_3 = 7.5 Hz, 1H); 0.81 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.31; 148.25; 131.15; 129.69; 128.35; 127.98; 80.16; 67.21; 54.79; 54.74; 52.43; 46.81; 39.02; 32.33; 28.10; 27.44; 23.03; 19.70; 10.64. HRMS (TOF, ES+) $C_{37}H_{57}NO_4SSi$ [M+Na]+ calc. mass 470.2940, found 470.2943.



(3*R*,5*S*)-3-methyl-5-((*R*)-2-((9*R*,9a*S*)-octahydro-1H-pyrrolo[1,2-a]azepin-9-yl)propyl)dihydrofuran-2(3H)-one (stemaphylline), (2.76)

To a solution of (S)-5-((R)-2-((9R,9aS)-2,3,5,8,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)propyl)-3-methylfuran-2(5H)-one (17.9 mg, 0.065 mmol, 1.0 eq) in THF (0.025 M) at rt was added $Pd(OH)_2$/C (5.4 mg, 0.16 eq). The reaction was then bubbled with

hydrogen gas for 3 minutes, placed under an atmosphere of hydrogen (via balloon) and stirred at rt for 12 h. An additional portion of $Pd(OH)_2$ (5.4 mg, 0.16 eq) was added and the reaction was again bubbled with hydrogen gas for 3 min, placed under an atmosphere of hydrogen (via balloon) and stirred at rt for 8 h. The reaction was then filtered through a pad of Celite and concentrated *in vacuo*. Purification via reverse phase chromatography (MeCN/H_2O 10-90%) afforded the pure product in 62% yield (11.3 mg). $[\alpha]_D^{20}$ = -36.2 (c = 0.70, $CHCl_3$). ^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 4.46-4.40 (m, 1H); 3.08-2.91 (m, 3H); 2.72-2.54 (m, 3H); 2.54-2.48 (m, 1H); 2.00-1.94 (m, 1H); 1.84-1.77 (m, 2H); 1.77-1.68 (m, 3H); 1.68-1.55 (m, 5H); 1.53-1.43 (m, 3H); 1.38-1.30 (m, 1H); 1.26 (d, *J* = 7.0 Hz, 3H); 0.98 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 179.65; 78.08; 64.87; 53.94; 52.22; 46.12; 39.59; 37.81; 35.80; 33.01; 28.15; 28.07; 27.73; 26.15; 23.73; 18.94; 14.99. HRMS (TOF, ES+) $C_{17}H_{29}NO_2$ [M+H]+ calc. mass 280.2277, found 280.2279.



(9*R*,9a*R*)-9-((*R*)-1-((2*S*,4*R*)-4-methyl-5-oxotetrahydrofuran-2-yl)propan-2-yl)decahydropyrrolo[1,2-a]azepine 4-oxide (stemaphylline-*N*-oxide), (2.77)

To a solution of stemaphylline (7.0 mg, 0.025 mmol, 1.0 eq) in CH_2Cl_2 (0.02 M) at 0 °C under argon was added mCPBA (6.8 mg, 0.028 mmol, 1.1 eq). The reaction stirred at 0 °C for 30 min, then concentrated *in vacuo*, and purified via reverse phase chromatography (MeCN/H_2O 10-90%) to afford the pure product in 74% yield (5.5 mg).

$[\alpha]_D^{20}$ = -42.3 (c = 0.22, $CHCl_3$). ^{1}H NMR (600MHz, $CDCl_3$) δ (ppm): 4.71-4.65 (m, 1H); 3.70-3.60 (m, 1H); 3.60-3.53 (m, 2H); 3.40-3.35 (m, 2H); 2.70-2.62 (m, 2H); 2.60-2.54 (m, 1H); 2.41-2.30 (m, 1H); 2.30-2.20 (m, 1H); 2.12-2.04 (m 1H); 2.00-1.88 (m, 2H); 1.87-1.80 (m, 1H); 1.80-1.71 (m, 2H); 1.70-1.64 (m, 2H); 1.62-1.50 (m, 3H); 1.44 (q, *J* = 12.2 Hz, 1H); 1.25 (d, *J* = 7.0 Hz, 3H); 0.90 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 179.94; 81.85; 76.73; 71.31; 67.48; 40.84; 38.05; 35.97; 35.42; 35.18; 25.66; 25.36; 25.32; 20.95; 19.62; 17.53; 15.21. HRMS (TOF, ES+) $C_{17}H_{30}NO_3$ [M+H]+ calc. mass 296.2226, found 296.2225.

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CHAPTER 3

DISCOVERY OF NOVEL SELECTIVE PAR4 ANTAGONISTS

3.1 Introduction to Platelet Biology

The platelet is a circulating disc-shaped cell, responsible for initiation of the hemostatic mechanisms that repair injury to the vascular endothelium. Circulating platelets do not normally encounter the connective tissue matrix that lies beneath vascular endothelial cells. Once a break within the integrity of this vascular lining occurs, platelets are exposed to, and interact with, collagen fibrils. Platelet interactions with collagen not only provide a surface for platelet adhesion, but also serve as a strong stimulus for platelet activation. This results in signaling pathways that induce platelets to change their shape, spreading along the collagen fibrils, and to secrete thromboxane A2 and ADP into the circulation. The released thromboxane A2 and ADP stimulate neighboring platelets, causing them to become activated in turn and to secrete additional thromboxane A2 and ADP. Platelet activation also causes release of α granules and dense granules, which contain numerous compounds which are involved in clotting and other functions.

Activated platelets not only secrete these substances, they also directly bind to the circulating coagulation protein fibrinogen via the abundant platelet integrin glycoprotein (GP) IIb/IIIa.[1,2] Fibrinogen can simultaneously bind two GPIIb/IIIa receptors and can therefore function as a link between two platelets. This platelet-fibrinogen-platelet connection initiates the process of platelet aggregation.[1] Since each platelet has 40,000 to

80,000 copies of GPIIb/IIIa on its surface, very large clumps (or aggregates) of platelets can assemble at the site of platelet activation.[3,4] A cross-linked fibrin clot ultimately stabilizes the growing platelet aggregate.

In addition to collagen, ADP, and thromboxane A2, other agonists can activate platelets at sites of vascular injury. Tissue factor, which is expressed on all non-vascular cells, is exposed to circulating blood upon disruption of the protective endothelial layer of the vasculature. Tissue factor can interact with factor VIIa to promote local coagulation, and ultimately the generation of thrombin, the most potent of the platelet agonists. Platelets facilitate this process by providing procoagulant phospholipids that accelerate thrombin generation. Consequently, platelet activation and fibrin deposition are intimately linked, maximizing the growth and strength of the hemostatic plug (Figure 3.1.1).

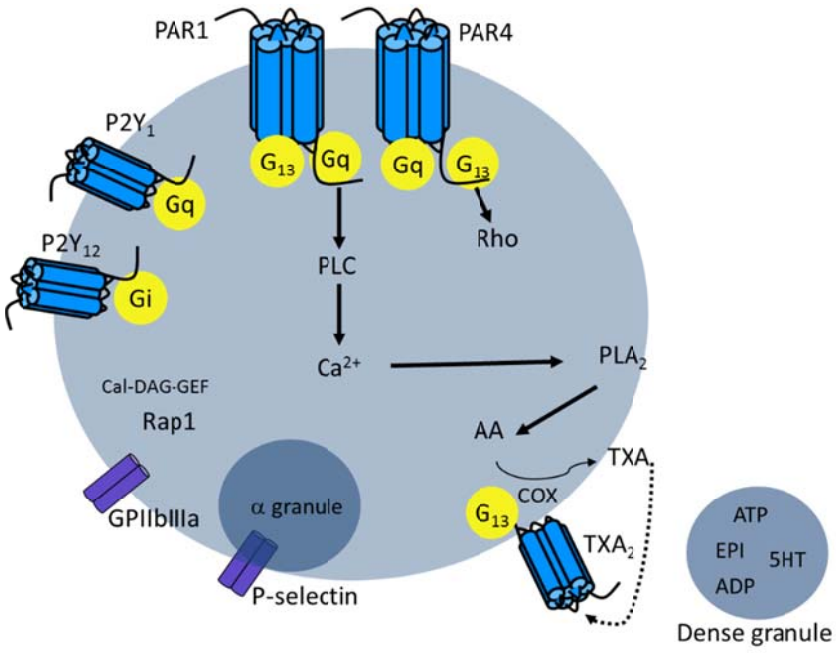


Figure 3.1.1 Biology of platelet activation.

Thrombin is an essential protein in the clotting cascade. It activates a number of coagulation factors, cleaves fibrinogen to fibrin, and regulates critical elements involved in coagulation through stimulation of a family of membrane-bound, G-protein coupled protease activated receptors (PARs) found on the surface of platelets. Thrombin is the most potent activator of platelets, and it works via PAR1 and PAR4, two subtypes of this family. Thrombin is generated at the site of injury via cleavage of prothrombin by other activated clotting factors, and it is the key activating factor of platelets, resulting in generation of a platelet plug. Thrombin is also involved in increased endothelial cell permeability and blood-brain barrier breakdown after injury.[5]

Thrombin works by cleavage of the amino terminal peptide of one arm of the extracellular portion of PAR, resulting in generation of a new "tethered ligand" which binds to the second extracellular portion of PAR and induces activation of the intracellular G-proteins, leading to the aforementioned downstream effects on platelet activity. Thrombin activates PAR1 and PAR4 in a progressive manner, with PAR1 activated at low thrombin concentrations (EC_{50} = 100 pM) and PAR4 recruited at higher thrombin concentrations (EC_{50} = 5 nM).[6] Because of PAR4's low affinity for thrombin, it is activated locally at the site of the clot as more thrombin accumulates. PAR1 is ubiquitously expressed, and PAR1 signaling is involved not only in coagulation, but also inflammation, pain, healing, and cancer metastasis,[7] while the expression of PAR4 is much more restricted, mainly to platelets and in certain brain areas and vascular beds after stress (Figue 3.1.2).[8-11]

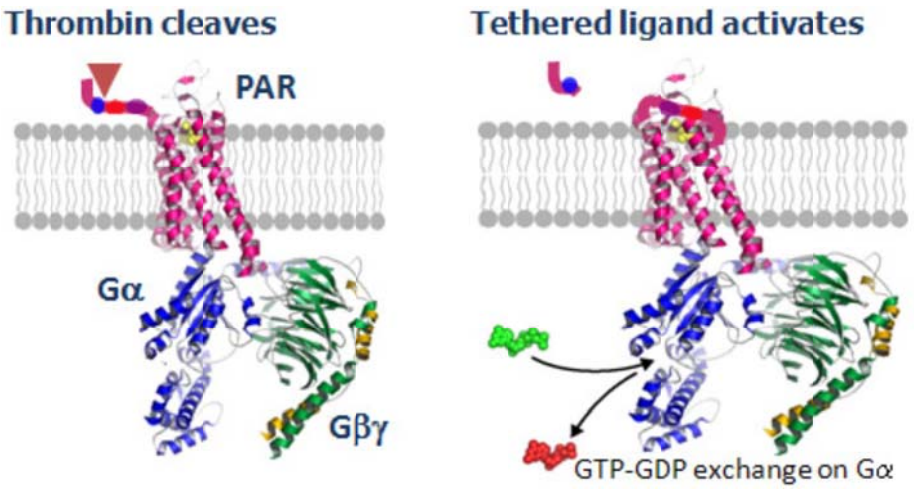


Figure 3.1.2 Activation mechanism of PARs. PARs are GPCRs whose amino terminus, exposed to the extracellular space, is a substrate for the coagulation protease thrombin. The newly exposed amino terminus serves as a "tethered ligand" to bind to the second extracellular loop of PAR, mediating receptor activation.

3.2 Preliminary Studies on PAR1 and PAR4 Activity

The binding of thrombin to PAR1 and PAR4 causes irreversible activation of the receptors, leading to platelet activation. PAR1 is the "high affinity" thrombin receptor, while PAR4 requires much higher thrombin levels for activation; such levels are probably only seen within a platelet clot. Activated platelets secrete coagulation proteases needed for generation of further thrombin at the site of the clot to activate PAR4. From preliminary data, we have determined that PAR1 activation is essential for the amplification of thrombin generation and the reaching of full endogenous thrombin potential of collagen-stimulated platelets. Because PAR1 signaling underlies multiple physiologic pathways besides only coagulation, as described above, we postulated that inhibition of PAR4 may be a more specific therapeutic target for anti-thrombosis. Most importantly, inhibition of PAR4 would not perturb signaling through the PAR1 receptor, which is essential for basic hemostasis during injury.[12]

Platelets play a critical role in thrombosis, which is necessary for normal response to injury but also a major cause of mortality and morbidity. Medical management of acute coronary syndrome and cerebrovascular injury is centered on anti-platelet therapies.[13-15] The clinical importance of platelet activation in the pathophysiology of coronary disease is reflected by the benefits of aspirin, clopidogrel, and glycoprotein (GP) IIb/IIIa inhibitors in patients with ischemic stroke.[15] The reduction in rates of MI, stroke, and sudden death with marketed oral antiplatelet drugs used singly or in combinations has been significant,[16] but the large proportion of events that are not prevented is still our leading cause of death and disability.

All of the drugs on the market that inhibit thrombosis – those that act on the clotting cascade, such as heparin, warfarin, and direct thrombin inhibitors (i.e. bivalirudin), and those that inhibit platelet activation, such as clopidogrel, GPIIb/IIIa inhibitors, and aspirin – carry risks associated with excessive bleeding and do not fully attenuate platelet activation. This can lead to delayed onset of action and long-lived effects, which is linked to adverse bleeding events. Vorapaxar, a thrombin receptor antagonist (TRA) that targets PAR1, was recently shown in Phase III clinical trials to increase clinically significant bleeding including intracranial hemorrhage.[17,18]

PARs are also widely expressed in the CNS.[8,9] PAR4-/- mice are protected from thrombosis and cerebral ischemia/reperfusion injury[19] and have prolonged tail bleeding times but no clinically apparent bleeding disorder.[20] After a stroke, PAR4 expression increases in the penumbra, the area of brain tissue surrounding the site of the stroke which is at risk for further damage.[21] These data suggest that PAR4 may be involved in

mediation of cerebrovascular injury after stroke, making it an attractive target for anti-platelet therapy as well as prevention of further morbidity after a stroke.

Platelet activation by thrombin leads to a second, much larger burst of thrombin generation through the intrinsic pathway.[22-24] Using a reconstituted thrombin generation assay with purified platelets and select coagulation factors, it has been shown that activation of PAR1 and PAR4 by their activating peptides (AP) contributes to the maintenance and amplification of thrombin generation.[25] Since PAR1 is the high-affinity thrombin receptor, it is activated earlier in the process than PAR4, the low-affinity thrombin receptor. This is illustrated dramatically in Fig. 3.2.1, which shows that antagonism of PAR1 signaling by RWJ-56110 (RWJ) dramatically inhibits thrombin generation on the platelet surface when stimulated by the collagen receptor agonist convulxin (CVX), while inhibiting PAR4 with its antagonist YD-3 much less prominently affects peak thrombin generation.

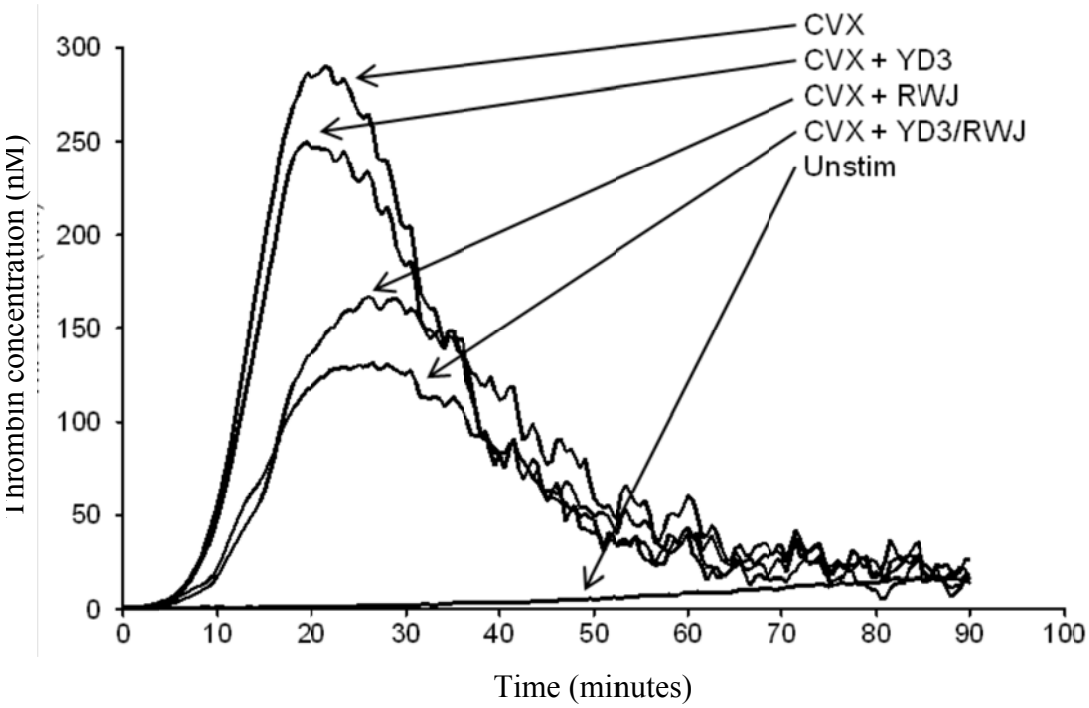


Figure 3.2.1 PAR1 antagonism inhibits collagen-stimulated, platelet-dependent thrombin generation, but PAR4 antagonism does not. Gel filtered platelets at a density of 1.5 x 10^7 cells/mL were treated with 10 μM inhibitors for 5 min prior to 5 min stimulation with 500 ng/mL convulxin (CVX). Coagulation factors II (prothrombin, 1.4 uM), X (136 nM), IXa (1 nM), and ATIII (150 ug/ml) were added in citrated solution. Thrombin generation was initiated with the fluorogenic thrombin substrate z-Gly-Gly-Arg-AMC (440 μM) and $CaCl_2$ (16.4 mM). Thrombin generation was monitored in a FlexStation II 384 at 390/460 nM. Convulxin caused peak thrombin generation of 253 ± 21.46 nM. YD-3 decreased peak thrombin generation to 246.17 ± 18.88 nM; RWJ-56110 decreased peak thrombin to 135.22 ± 25.12 nM.

These data suggest that limiting thrombin generation by antagonizing PAR1 may lead to significant unwanted bleeding risk, as platelet amplification of thrombin generation is essential for normal hemostasis. However, due to its low affinity for thrombin, PAR4 is engaged in later stages of thrombin generation. Thus, we hypothesized that PAR4 is an alternative target which could allow effective inhibition of pathologic thrombosis without disturbing critical hemostasis required for preventing clinically detrimental bleeding events.

Additionally, we have shown that PAR1 antagonism in whole blood is able to significantly prolong clotting time, which is associated with an increased bleeding phenotype, while PAR4 antagonism does not prolong clotting time in healthy individuals (Fig 3.2.2).

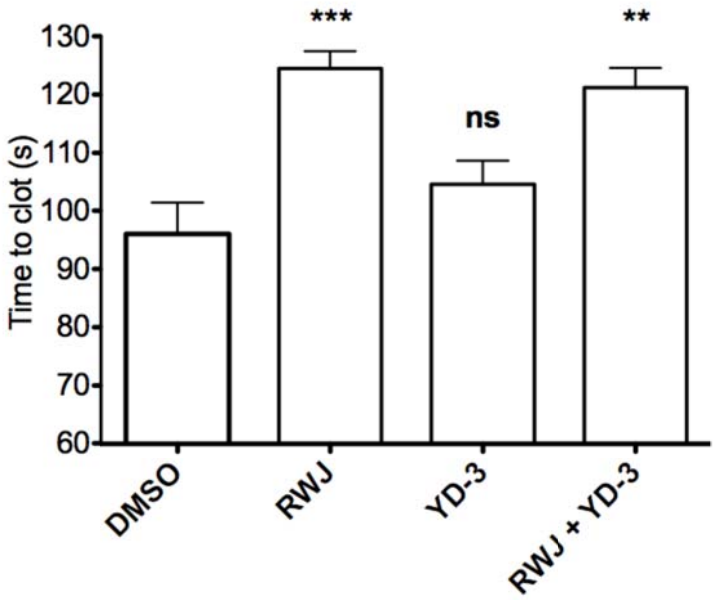


Figure 3.2.2 PAR1 antagonism, but not PAR4 antagonism prolongs, clotting time. Whole blood from healthy volunteers was treated for 10 min with either 10 μM RWJ or 10 μM YD-3 prior to initiation of clotting by the addition of 16.4 mM $CaCl_2$. Data were analyzed by Diagnostica Stago Start 4 hemostasis analyzer. RWJ prolonged the time to clot by 28.5±5.8 sec vs vehicle, whereas YD-3 failed to significantly prolong time to clot. Data is represented by mean ± SEM (n= 2 donors). **p<0.005 vs DMSO control. ***p=0.0003 vs DMSO control.

Interestingly, once PAR4 is engaged by thrombin, it is a more potent stimulator of platelets than PAR1. We have demonstrated previously that PAR1 stimulation of platelet aggregation is decreased by inhibition of several proteins, including PKC, PLD and PI3-kinase, while PAR4 mediated stimulation is not.[26,27] Furthermore, it is known that PAR1

signaling desensitizes over time, while PAR4 signaling persists.[28,29] Our data and that of others points to PAR4 as an important mediator of thrombosis.[20,30,31] Recently, it has been demonstrated that PAR4 signaling can resensitize PAR1 signaling, which will lead to amplified platelet activation in the presence of high concentrations of thrombin.[32] Our theory is that the early engagement of PAR1 by low levels of thrombin plays a critical role in initial hemostasis, but as levels of thrombin build at a site of injury (or in hypercoaguable states), PAR4 becomes engaged, resulting in strong signaling eventually leading to thrombosis. In order to test these hypotheses, we proposed to target PAR4 as a novel target for anti-platelet/anti-thrombotic therapeutics. The only published PAR4 antagonist is YD-3, and it is much too hydrophobic to be used in *in vivo* studies (Figue 3.2.3).

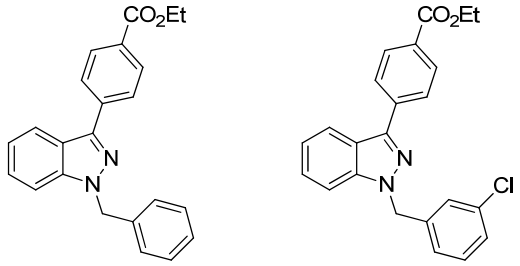


Figure 3.2.3 Known PAR4 selective antagonists.

The most difficult aspect of developing new pharmaceuticals in this field is maintaining balance between preventing pathologic thrombosis and avoiding excessive bleeding. For example, recent clinical trials showed incremental efficacy of factor Xa inhibitors in acute coronary syndrome,[33,34] though the APPRAISE-2 trial with apixaban

was terminated early due to excessive bleeding. Bleeding risk also exists for direct thrombin inhibitors currently on the market. Thrombin receptor antagonists (TRAs) have been eagerly anticipated in cardiovascular medicine; vorapaxar is a TRA in two Phase III clinical trials, TRA•CER[35] and TIMI-50. The TRA•CER trial in patients with acute coronary syndrome was discontinued early due to intracranial bleeding,[17] and the TIMI-50 secondary prevention trial in patients who had already experienced a heart attack or ischemic stroke, or had known peripheral vascular disease, was halted in patients who had previously experienced a stroke due to excessive bleeding without significant benefit.[18]

Our preliminary data provide further evidence that PAR1 is critically involved in platelet-dependent thrombin generation needed for primary hemostasis,[12] and that PAR4 is not involved in the amplification of thrombin generation (Fig. 3.2.2). The fact that PAR4 is the low-affinity thrombin receptor that is only activated once a significant amount of thrombin has been generated suggests that its inhibition will not be detrimental to primary hemostasis. However, at the start of our study, no PAR4 antagonists existed with the physiochemical properties to study the physiological effect of inhibition of PAR4 *in vivo*.

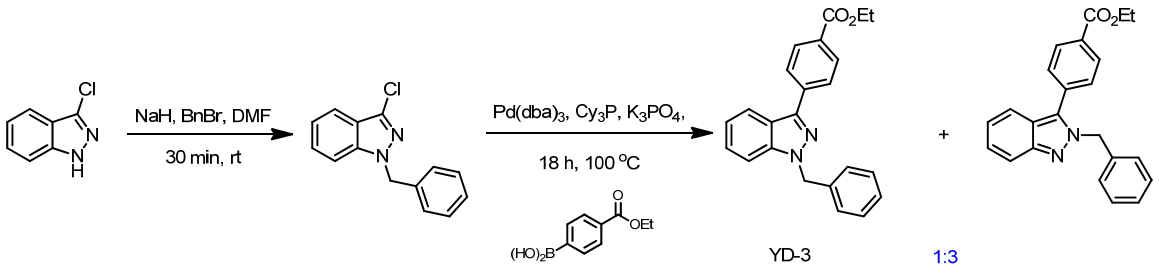
Due to the lack of tool compounds, the field's understanding of the role of PAR4 in physiological environments is limited. There are no probes available to study the role of PAR4 in thrombosis, ischemic stroke, and neurodegeneration *in vivo*. The PAR4 antagonist YD-3 was first described in 2000[36] with little further characterization or optimization (Figure 3.2.3).[37] YD-3 has poor physiochemical properties and virtually no solubility in acceptable vehicles; therefore, it is not suitable for *in vivo* studies. An

optimized, in vivo tool compound would allow us to determine basic pharmacological information about PAR4 including receptor density, mechanism of action for PAR4 antagonists and agonists, and effects on *in vivo* models of thrombosis. Such a compound would enable researchers to delineate the role of PAR4 in multiple systems and therapeutic areas.

To generate inhibitors of PAR4, we aimed to improve on YD-3, a known potent PAR4 inhibitor, by optimizing solubility, potency, and selectivity to provide a probe compound for critical physiological testing of PAR4 in thrombosis and hemostasis.

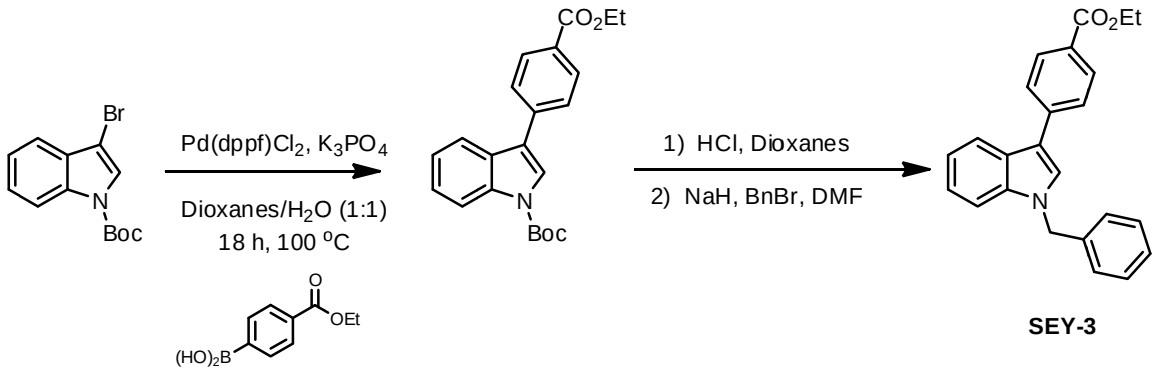
3.3 Synthetic Efforts Towards Novel PAR4-Selective Antagonists

A shortened synthetic route of YD-3 allowed our lab to independently test the potency of YD-3 mediated inhibition of PAR4 on human platelets. We were able to repeat published work confirming that YD-3 inhibits PAR4 mediated platelet aggregation.[36,37] However, this synthesis also resulted in the generation of an inactive isomer of YD-3, which comprised 75% of the final yield (Scheme 3.3.1).



Scheme 3.3.1 Shortened synthesis of YD-3.

In order to eliminate the inactive isomer and improve our yield, we used an indole scaffold to synthesize a novel compound, SEY-3. This synthetic route prevented the formation of the inactive isomer and improved overall yields (Scheme 3.3.2).



Scheme 3.3.2 Synthesis of SEY-3.

To determine if SEY-3 was active and selective, we tested its ability to inhibit agonist-induced platelet aggregation (Fig. 3.3.1).

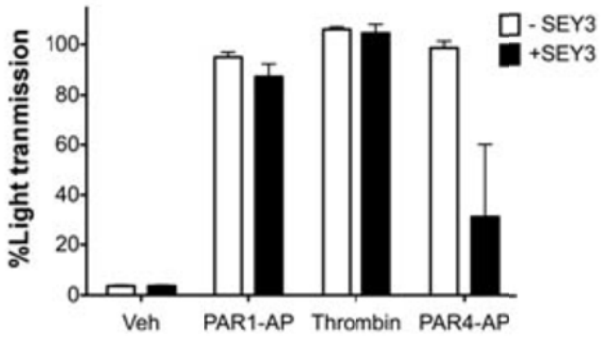


Figure 3.3.1 SEY-3 selectively inhibits PAR4 mediated platelet aggregation. Aggregometry was measured in a Chrono-Log Model 700 Aggregometer using washed human platelets at a concentration of 2.0×10^8 cells/mL resuspended in Tyrodes + 0.1% BSA. Platelets were treated for 10 minutes with 10 μM SEY-3 then stimulated with either 20 μM PAR1-AP, 2 nM Thrombin, or 200 μM PAR4-AP. Data shown is mean ± SEM (n=3 donors).

In human platelets, in addition to receptor-mediated calcium mobilization via coupling to $G\alpha_q$, PAR stimulation converts the fibrin receptor GPIIbIIIa to its high affinity fibrin binding conformation and triggers secretion of granules which express p-selectin molecules, otherwise known as CD62P. The PAC-1 antibody binds only the high affinity conformation of GPIIbIIIa and provides a way to accurately measure GPIIbIIa activation. SEY-3 retained inhibitory activity towards PAR4 mediated platelet aggregation, but not PAR1 or thrombin, suggesting that SEY-3 is selective for PAR4. Similarly, SEY-3 showed inhibitory activity selectively against PAR4 in platelet α and dense granule release by flow cytometry (Fig. 3.3.2).

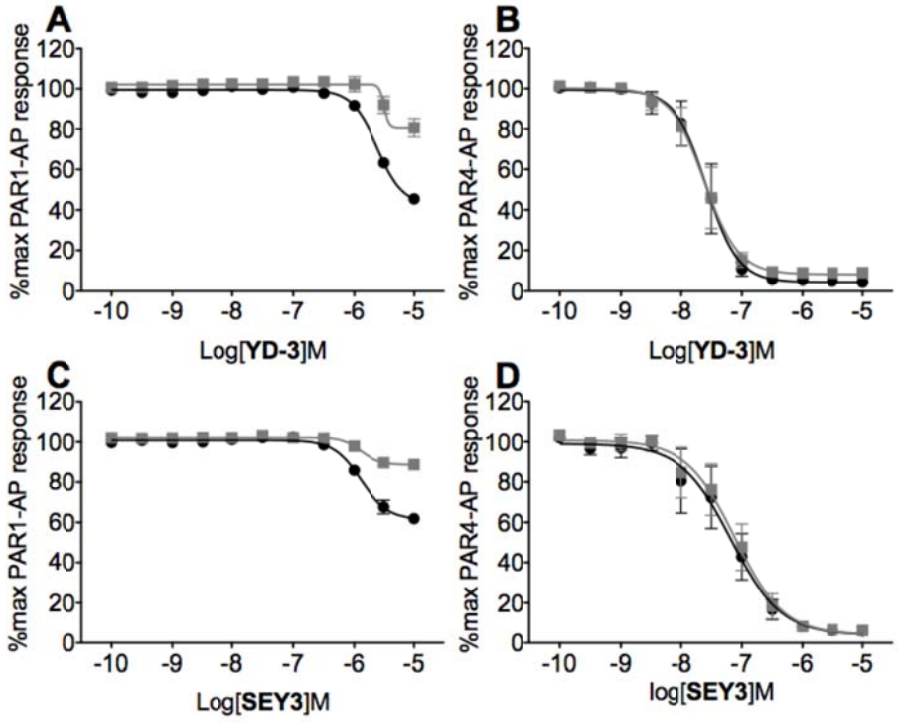


Figure 3.3.2 YD-3 and SEY-3 selectively inhibit PAR4 mediated platelet α granule release (P-selectin, gray squares) and GPIIbIIIa activation (PAC-1, black circles). Platelets were treated with indicated concentrations of antagonist followed by challenge with either 20 μM PAR1-AP (A,C) or 200 μM PAR4-AP (B,D). Flow cytometry analysis was performed. Data shown is mean±SEM (n=2 donors).

The inhibitory concentration-response curve (CRC) data suggest that SEY-3 has slightly decreased potency compared to YD-3, which is attributable to elimination of the nitrogen in the 2 position of the indazole ring. IC_{50} values for YD-3 and SEY-3 were 25 nM and 76 nM, respectively (Fig. 5B,D). Selectivity of YD-3 and SEY-3 was shown by comparing inhibition of PAR1 by both antagonists. YD-3 was approximately 100-fold selective for PAR4 verses PAR1 (IC_{50} of 2.4 μM, Fig. 3.3.2 A,B), while SEY-3 was 17-fold selective for PAR4 (PAR1 IC_{50} of 1.3 μM, Fig. 3.3.2 C,D).

The primary endogenous agonist of PAR1 and PAR4 is thrombin; therefore, we tested the ability of PAR1 and PAR4 antagonism, alone or in combination, to inhibit response from a concentration of thrombin that will typically activate both receptors. Measuring P-selectin expression, which is a marker for platelet α granule release, we found that neither antagonist alone was able to significantly inhibit thrombin-mediated platelet activation, but dual antagonism of PAR1 and PAR4 significantly reduced thrombin-mediated platelet α granule release (Fig. 3.3.3).

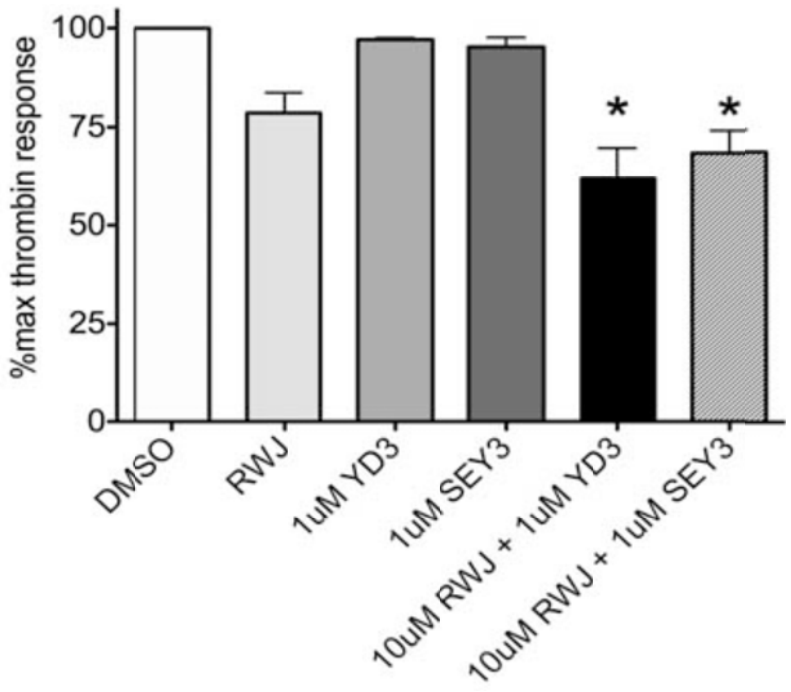


Figure 3.3.3 Dual PAR1 and PAR4 antagonism inhibits thrombin-mediated P-selectin expression. Washed human platelets were treated for 5 minutes with PAR1 antagonist RWJ56110, YD-3, SEY3 or a combination of RWJ and YD-3 or SEY3, then activated by 10 nM thrombin. Data shows mean ± SEM (n=3 donors). *$p<0.05$ versus DMSO control.

Together, these data demonstrated that we are capable of synthesizing and reproducibly testing PAR4 antagonists in human platelets *ex vivo* with several different platelet activation assays. We also demonstrated that our synthetic approach is amenable to derivatization, and the SEY-3 (indole) molecule was a viable scaffold to move forward with chemical optimization.

Using the same approach shown in scheme 3.3.2, we employed a multi-dimensional iterative parallel synthesis approach[38,39] beginning with indoles and azaindoles, which were *N*-alklyated with various commercially available benzyl and heteroarylmethyl bromides to deliver SEY-3 analogs (Figure 3.3.4).

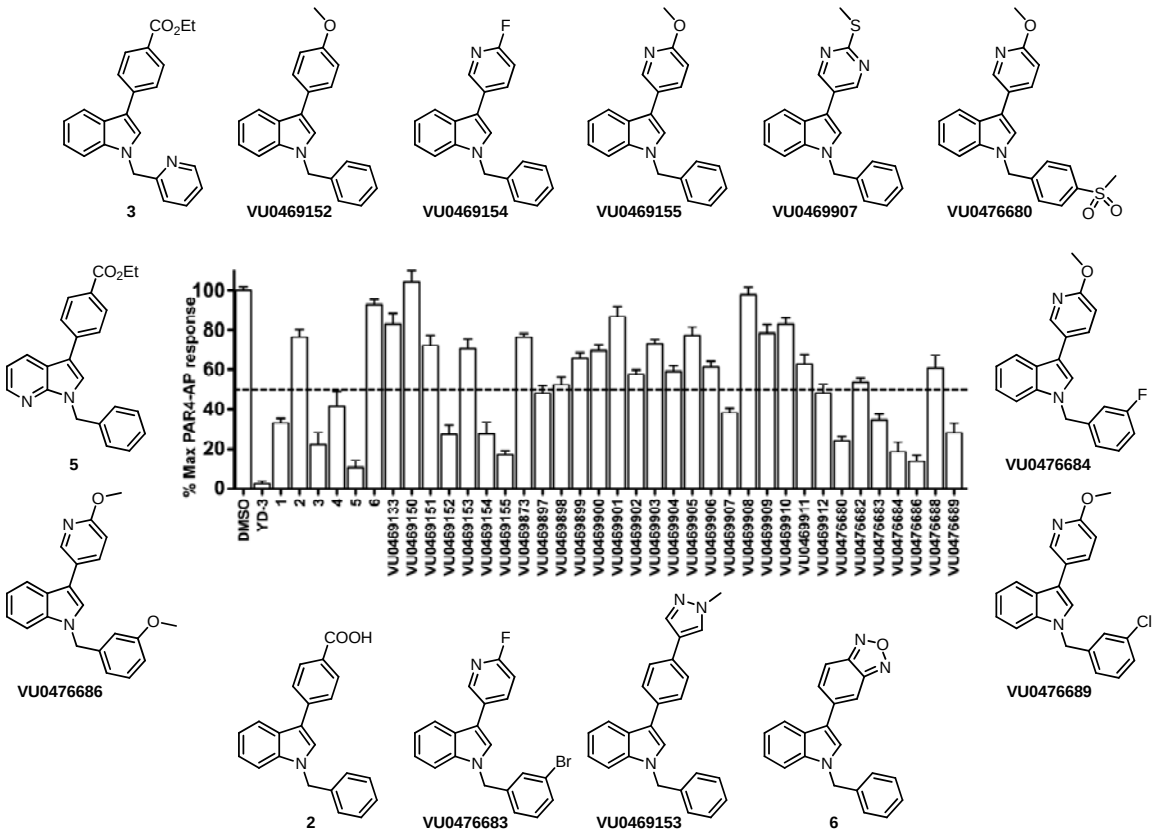


Figure 3.3.4 Selected examples from exploration of SAR around SEY-3.

Using a high-throughput calcium mobilization assay with YD-3 as a control, we determined the analogues that were effective at inhibiting the response from a submaximal concentration of PAR4 activating peptide (PAR4-AP) at 10 μM. Similar to the SAR reported previously that led to the discovery YD-3, this SAR was very shallow, with few analogues displaying activity comparable to that of YD-3. From 3 rounds of synthesis we produced 38 compounds, of which compounds SEY-3 (also known as 1), 3, 5, VU0469152, VU046154, VU0469155, VU0469907, VU0476680, VU0476683, VU0476684, VU0476686, and VU0476689 were capable of inhibiting PAR4 mediated platelet calcium mobilization to less than 50% of the maximum response, indicating that indole was a suitable replacement for the indazole core. Of note, the corresponding

carboxylic acid of the terminal ethyl ester, compound 2, was inactive, as were other ester replacements including 6 and VU0469133 (Figure 3.3.4). Of the compounds tested, only SEY-3 (1), 3, and 5 were able to fully antagonize a maximal PAR4-AP response. Other 'hits' from the screening process did not fully antagonize the PAR4 mediated GPIIbIIIa activation even at 10 μM concentration.

The addition of chlorine in the 3-position of YD-3 was previously shown to give modest improvement in the potency of YD-3 for PAR4. Because of the lack of a terminal ester, we attempted to improve upon the most potent partial antagonist – VU0469155, a 3-pyridyl-4-methoxy derivative – by adding a chlorine in the 3-position of the benzyl group, resulting in VU0476689. There was a modest improvement in the potency against PAR4, but not enough to warrant further investigation (Figure 3.3.5).

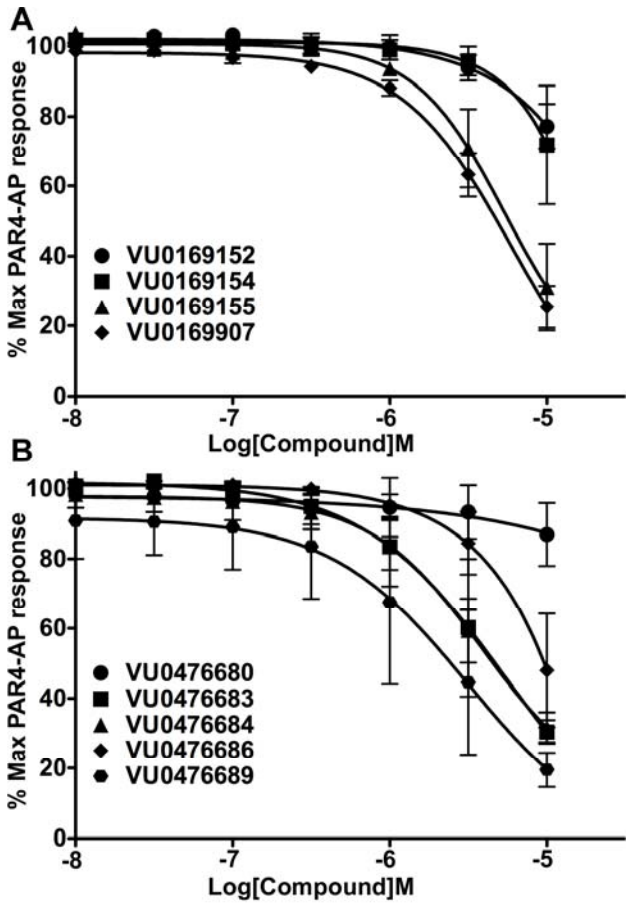


Figure 3.3.5 CRC data for VU0469155 derivatives. Platelets were treated with indicated concentrations of compound for 5 minutes prior to stimulation with 200 μM PAR4-AP. GPIIbIIIa activation was measured via flow cytometric analysis of PAC-1 binding. Data is presented as mean±SEM (n=2).

We measured potency of full antagonists against both PAR1 and PAR4 mediated GPIIbIIIa activation (via PAC-1 binding) and P-selectin expression (anti-CD62p binding) using flow cytometry. We did not observe any notable functional selectivity between the molecules' ability to inhibit GPIIbIIIa activation and P-selectin expression. SEY-3 (Figure 3.3.6 D) was less potent than YD-3 (Figure 3.3.6 B) at inhibiting PAR4 mediated responses, demonstrating IC_{50} values for PAR4 mediated GPIIbIIIa activation of 66 ± 1 nM vs 26 ± 1 nM, respectively. Both 3 and 5 were significantly less potent than either YD-3 or SEY-3, with IC_{50} for PAR4 mediated GPIIbIIIa activation of 1.0 ± 1.1 μM and

170 ± 1 nM respectively (Figure 3.3.6 F and H). However, YD-3 also inhibited PAR1-AP mediated GPIIbIIIa activation by 55% at 10 μM, a previously undocumented observation (Figure 3.3.6 A). Interestingly, SEY-3 reduced maximum PAR1-AP GPIIbIIIa response by 38% (Figure 3.3.6 C), and compounds 3 and 5 inhibited PAR1 by 31% (Figure 3.3.6 E) and 56% (Figure 3.3.6 F), respectively. Together, these data suggest that addition of nitrogen into the indole core may contribute to off-target effects against PAR1, as seen with YD-3, and that an indole can serve as a potent, highly selective PAR4 inhibitor with only modest loss of potency compared to YD-3.

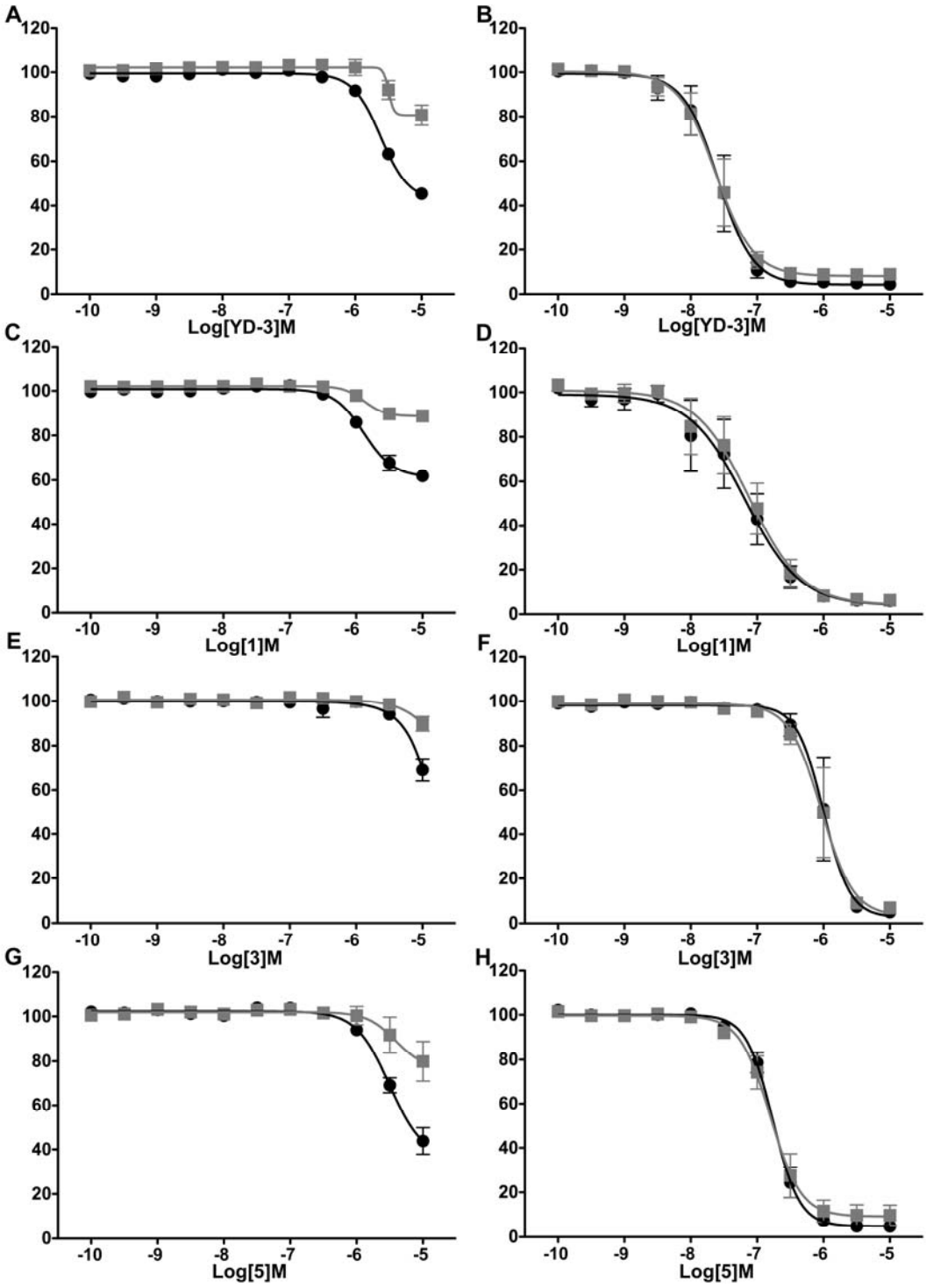


Figure 3.3.6 Selected SEY-3 analogue PAR1 and PAR4 CRC data. SEY-3 (1), 3, and 5 were compared with YD-3 potency against PAR1 and PAR4 mediated GPIIbIIIa activation and P-selectin expression. Platelets were treated with compound or DMSO control for 5 minutes prior to stimulation with 20 μM PAR1-AP (left panels) or 200 μM PAR4-AP (right panels) for 10 minutes. GPIIbIIIa activation (black circles) and P-selectin expression (gray squares) in PAR activated platelets by flow cytometry.

The PAR4 partial antagonists VU0469152, VU046154, VU0469155, VU0469907, VU0476680, VU0476683, VU0476684, VU0476686, and VU0476689 displayed a similar magnitude of inhibition against PAR1 mediated platelet activation as did YD-3, SEY-3 (1), 3, and 5 (Figure 3.3.7); however, because these compounds also did not fully antagonize PAR4 mediated platelet responses even at 10 μM, this additional loss of selectivity was felt to indicate that they were poor lead compounds.

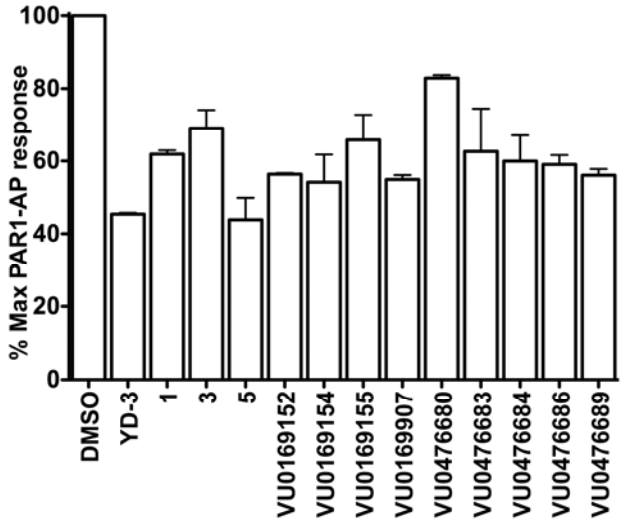


Figure 3.3.7 Compounds displayed varying degrees of off-target PAR1 inhibitory activity. Platelets were treated with 10 μM indicated antagonist for 5 minutes, followed by challenge with 20 μM PAR1-AP. Flow cytometric analysis of PAC-1 binding was used to determine GPIIbIIIa activation. Data presented as mean±SEM (n=2).

Inhibition of the PAR4-AP response does not completely describe the potency of any PAR4 antagonist. Compounds should elicit an inhibitory effect against thrombin, either alone or in combination with a PAR1 antagonist, such as RWJ-56110.[40] Against a high dose of thrombin, where both PAR1 and PAR4 are engaged,[31] PAR4 antagonists alone cannot significantly inhibit thrombin mediated GPIIbIIIa activation. We tested the ability of YD-3, SEY-3 (1), 3, and 5 to inhibit thrombin mediated GPIIbIIIa activation at

concentrations where they were selective for PAR4 (Figure 3.3.8). 10 μM RWJ-56110 alone was able to modestly inhibit thrombin mediated GPIIbIIIa activation, and when used in combination with either YD-3 or SEY-3 was able to reduce thrombin mediated signaling by 43 ± 10% and 37 ± 6%, respectively, further demonstrating that the indole scaffold provides comparable PAR4 efficacy to the parent indazole core of YD-3 (Figure 3.3.8). Neither 3 (14 ± 2% reduction) nor 5 (17 ± 2% reduction), when added in conjunction with RWJ-56110, was able to meaningfully inhibit thrombin mediated platelet GPIIbIIIa activation. These data suggest that even slight loss of antagonist potency against PAR4-AP response translates into dramatic reductions in potency against thrombin-mediated response.

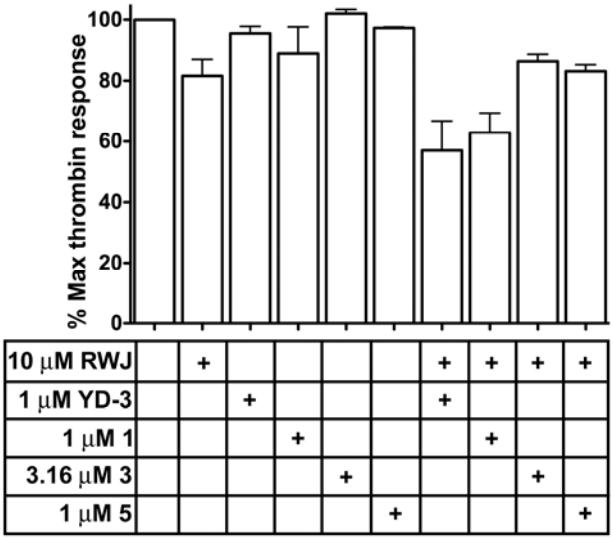


Figure 3.3.8 Dual PAR1/PAR4 inhibition significantly inhibits thrombin-mediated platelet activation. Platelets were treated with PAR1 antagonist RWJ-56110 or PAR4 full antagonist, either alone or in combination, prior to stimulation with 10 nM thrombin for 10 minutes. GPIIbIIIa activation was measured. Data reported as mean±SEM (n=3).

The activities of the full antagonists YD-3, SEY-3, 3, and 5 were assessed via a classical measurement of platelet activity, a platelet aggregation assay. Using YD-3 as a control, SEY-3 (1) and 5 were able to significantly inhibit PAR4 but not PAR1 mediated platelet aggregation in healthy subjects (Figure 3.3.9). Compound 3 also inhibited PAR4 mediated platelet aggregation versus PAR1 mediated platelet aggregation, though non-significantly (p=0.054).

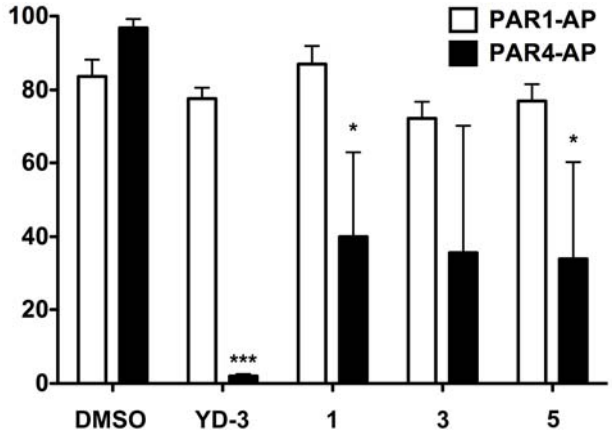


Figure 3.3.9 Full PAR4 antagonists selectively inhibit PAR4 and not PAR1 mediated platelet aggregation. Platelets were treated with YD-3, SEY-3, 3, or 5 for 10 minutes prior to stimulation with either 20 μM PAR4-AP (white bars) or 200 μM PAR4-AP (black bars). Data reported as percent light transmittance, where 100% represents fully-aggregated platelets. Unpaired two-tailed t-test vs DMSO-treated agonist control. Data displayed as mean ± SEM (n=3 or more). Means are significantly different where indicated. ***$p<0.0001$. *$p<0.05$.

To examine the putative mechanism of action of the most potent antagonists, YD-3 and SEY-3, we used PAR4-AP mediated P-selectin expression to generate twelve-point CRCs in the presence of increasing concentrations of antagonist. YD-3 was previously described as a competitive antagonist by platelet aggregation studies. We confirmed this finding by P-selectin expression. Figure 3.3.10 shows parallel rightward shifts in the

PAR4 CRC in response to increasing concentrations of compound, indicative of a competitive mechanism of action for both YD-3 (Figure 3.3.10 A) and SEY-3 (Figure 3.3.10 B).

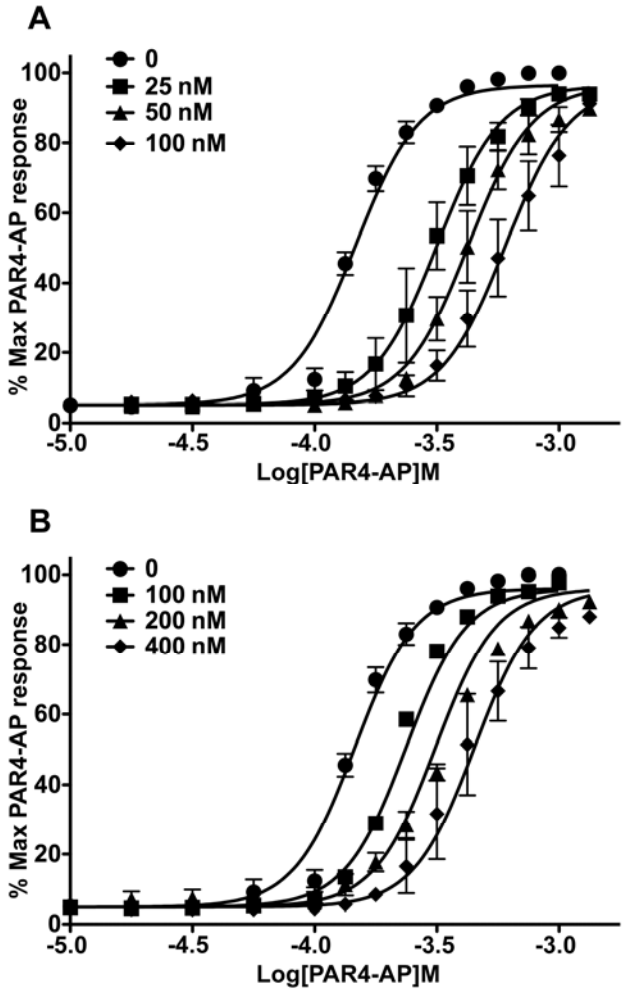


Figure 3.3.10 YD-3 and SEY-3 act as competitive antagonists against PAR4. Platelets were treated with indicated concentrations of YD-3 (A) or SEY-3 (B) for 5 minutes prior to stimulation with a full PAR4-AP. P-selectin was measured via flow cytometry. Data represented as mean±SEM (n=3).

These data indicate that indoles are a suitable scaffold for selective inhibitory activity against PAR4 mediated platelet activation and thus can serve as a novel scaffold

from which to build future anti-platelet therapeutics. Given the large number of commercially available derivatives of indoles, bromides, aryl boronic acids, and boronic esters, the synthetic routes presented are capable of rapidly generating numerous compounds. The use of a high throughput purified platelet calcium mobilization assay allows for rapid identification of molecules with inhibitory activity towards PAR4. SEY-3 retains antagonist activity against responses to both PAR4-AP and thrombin nearly equal to that of YD-3, and as such was the most potent novel compound developed during SAR exploration around YD-3. The other scaffolds 3 (2-pyridine) and 5 (azaindole) retained selectivity for PAR4 versus PAR1, but sacrificed potency against PAR4 activating peptide and, most importantly, thrombin. Both YD-3 and, to a lesser extent, SEY-3 displayed weak off-target effects against PAR1. The inability of compounds SEY-3, 3, and 5 to inhibit PAR4 mediated platelet aggregation in all volunteers may be reflective of the loss of potency of these compounds for PAR4.

Thrombin mediated GPIIbIIIa activation was not abolished even when both antagonists were added prior to stimulation. One possible explanation is that thrombin binds GPIb receptors, which may contribute to signaling.[41] Furthermore, thrombin activated PARs create tethered ligands which are essentially irreversible agonists, such that any orthosteric molecule must be either irreversible or have such high affinity that the displacement of the tethered ligand is possible. Single digit nanomolar or subnanomolar potency seems to be required for effective antagonism against thrombin mediated PAR4 signaling. Alternatively, one could envision that negative allosteric modulators may prove to be a better approach to inhibit thrombin activated PARs. Though we have identified indole as a favorable scaffold for future production of PAR4

antagonists, there is considerable room for improvement in the development of antagonists of PAR4 and, as such, efforts are underway to discover higher potency compounds.

3.4 Discovery of Novel, Selective PAR4 Antagonists

Due to the shallow SAR of SEY-3, we screened approximately 500 compounds hand-picked from the VU screening library, based on a similarity search to SEY-3, in an attempt to discover previously unexplored SAR around the indole scaffold. We identified six new scaffolds that displayed potent PAR4 inhibition (>50% at 10 μM) (Figure 3.4.1).

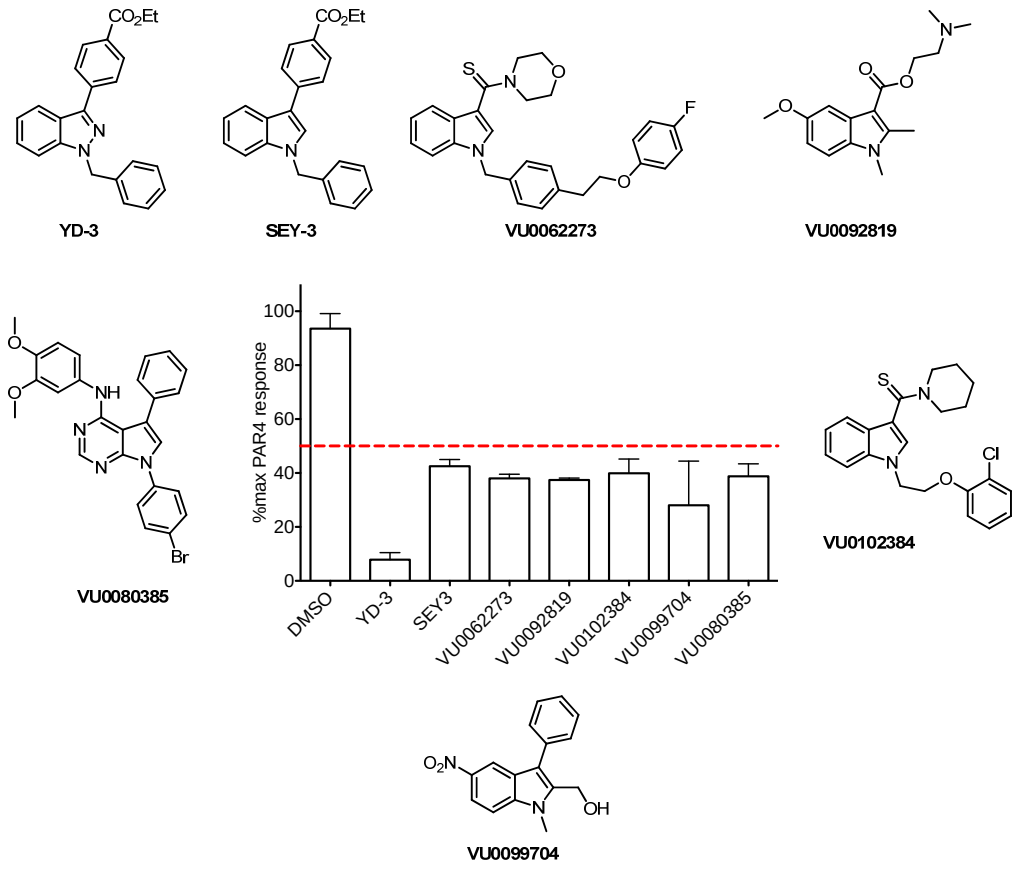
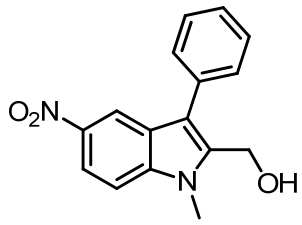
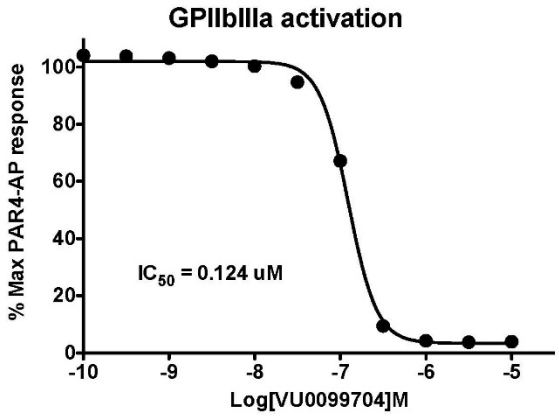


Figure 3.4.1 Novel PAR4 antagonists.

Full CRC data and selectivity studies on one of these compounds, VU0099704, revealed a selective PAR4 antagonist with an IC_{50} = 124 nM that was 81 fold selective for PAR4 over PAR1 (PAR1 IC_{50} = >10 μM) (Figure 3.4.2).



VU0099704



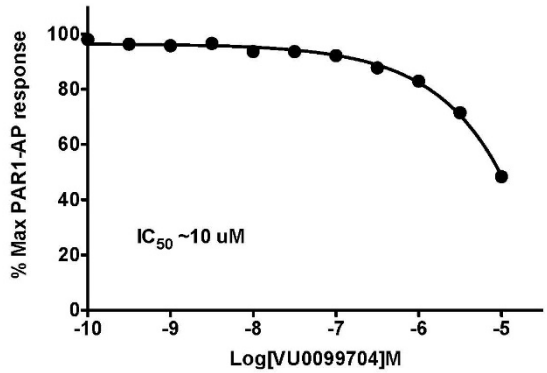


Figure 3.4.2 CRC data of VU0099704 at PAR1 and PAR4.

In summary, we have discovered a lead compound in a novel series of potent, selective PAR4 antagonists. This simple compound allows for a great deal of further derivatization which can lead to the discovery of even more potent compounds. Generation of analogues around VU0099704 is in progress in our lab.

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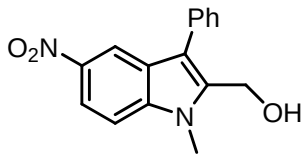
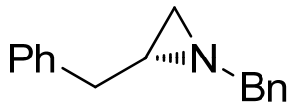
Experimental



VU0099704

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.58 (d, J = 2.1 Hz, 1H); 8.17 (dd, J_1 = 9.1 Hz, J_2 = 2.2 Hz, 1H); 7.55-7.49 (m, 2H); 7.48-7.36 (m, 4H); 4.90 (s, 2H); 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 142.11; 140.07; 137.73; 133.03; 130.00; 129.14; 127.52; 126.06; 119.46; 118.42; 117.61; 109.37; 55.08; 30.80. HRMS (TOF, ES+) $C_{16}H_{14}N_2O_3$ [M+Na]+ calc. mass 283.1083, found 283.1081.

1H



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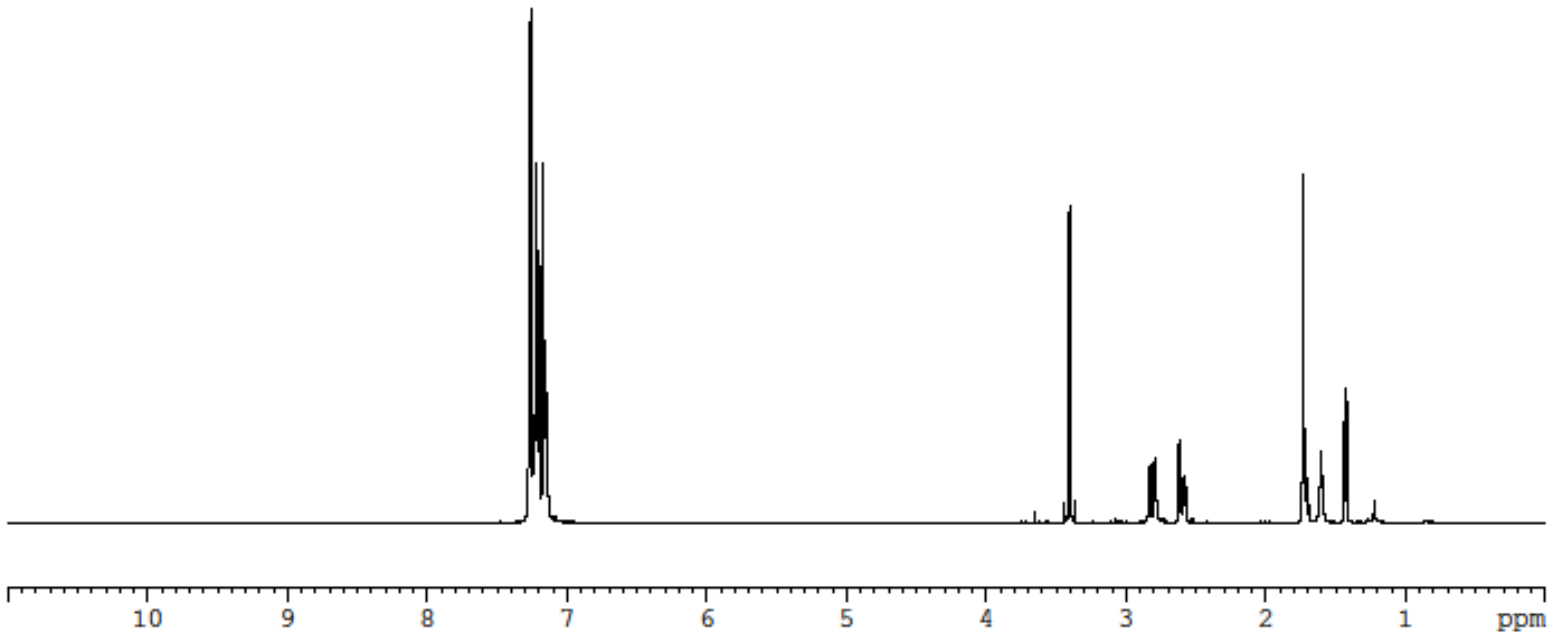

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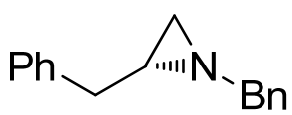

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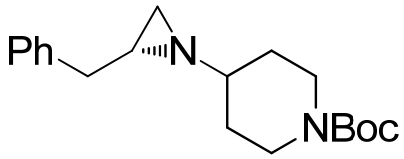

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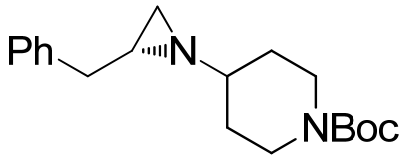

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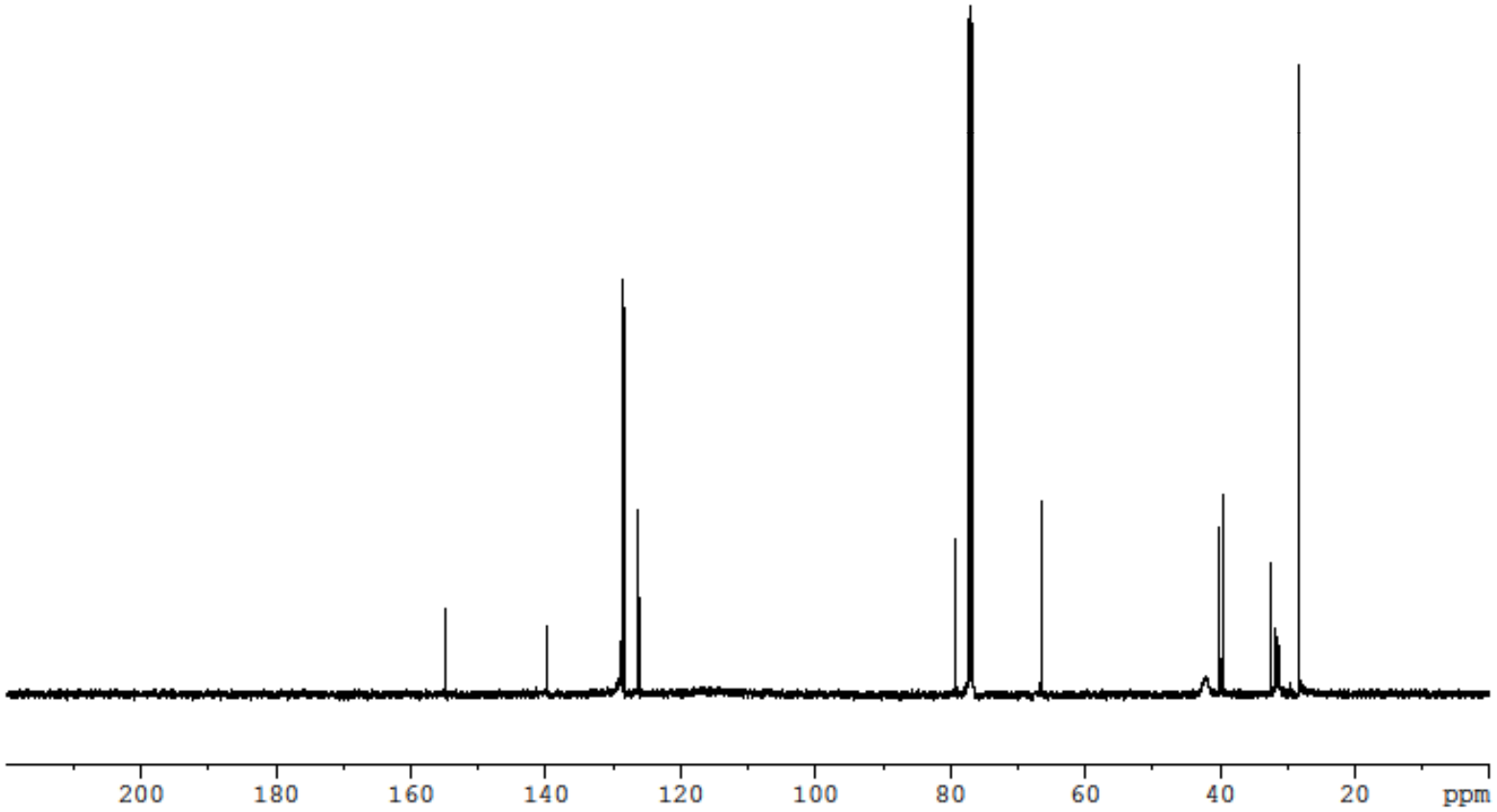

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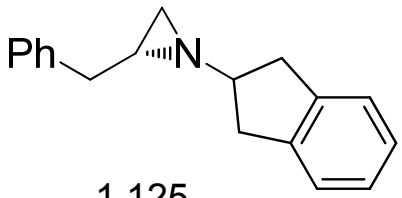

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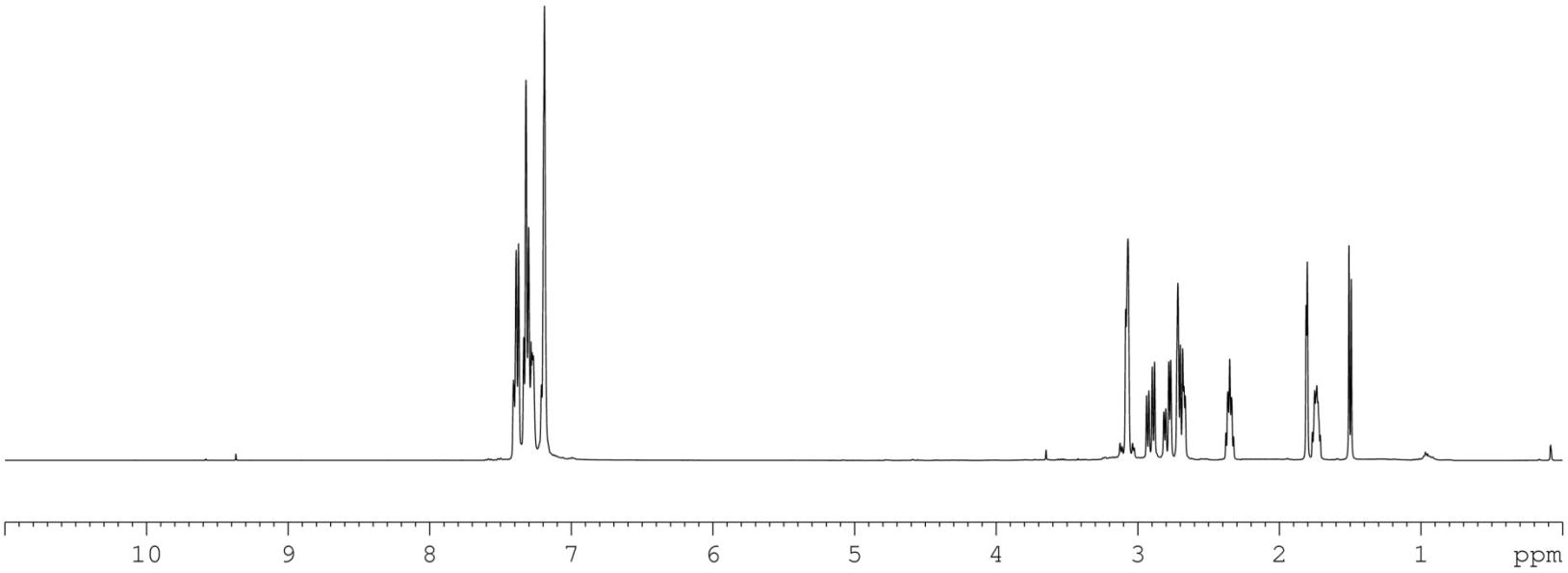

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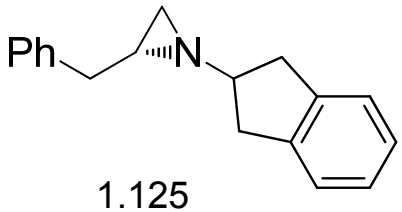

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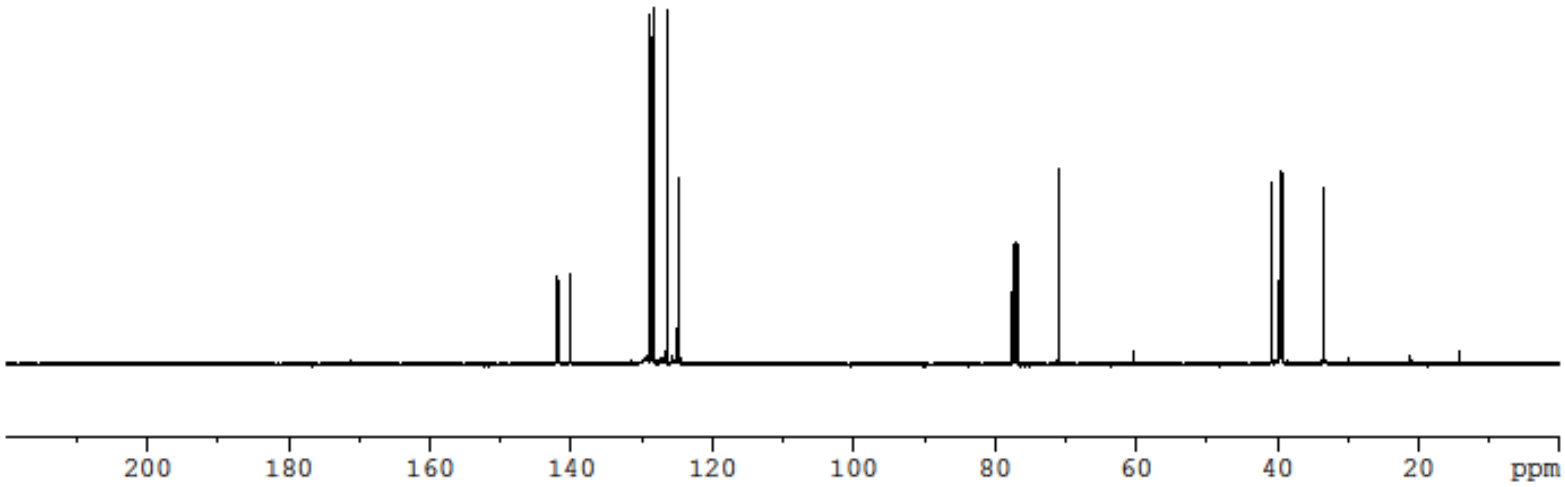

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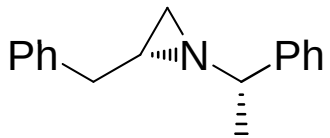

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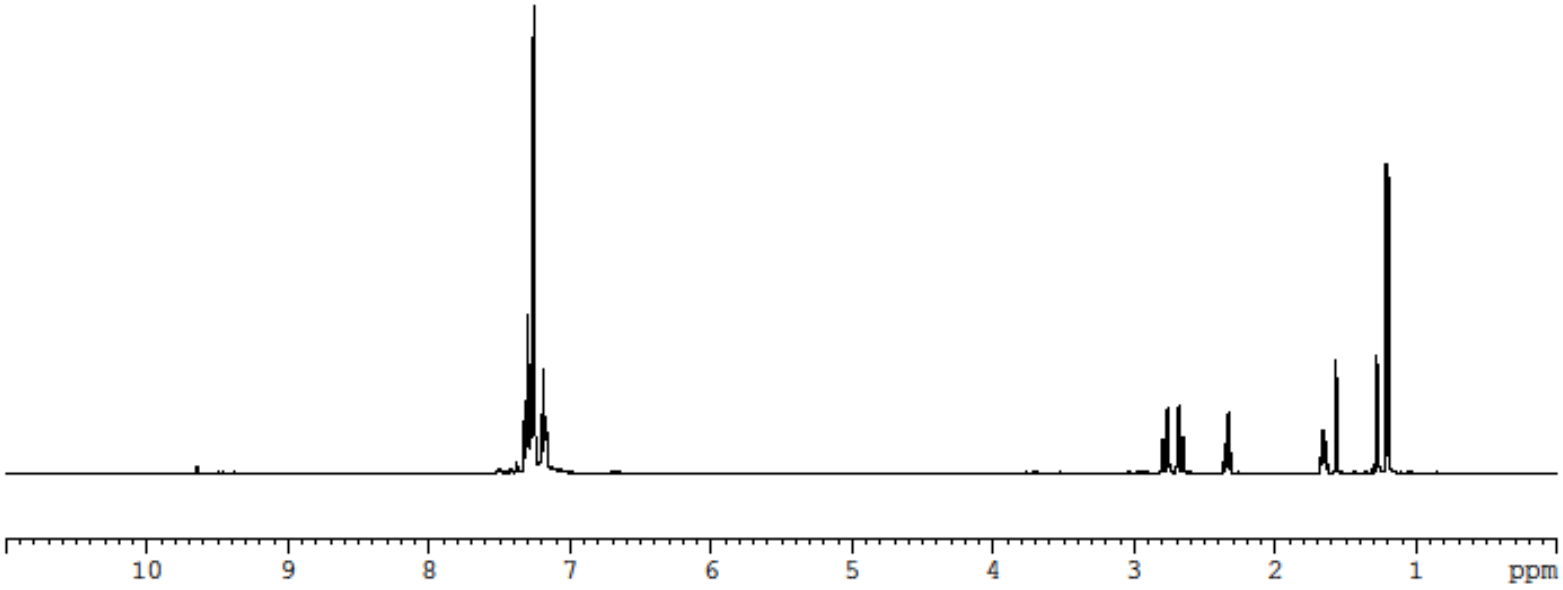

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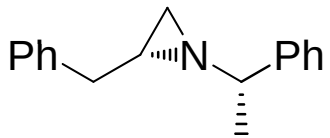

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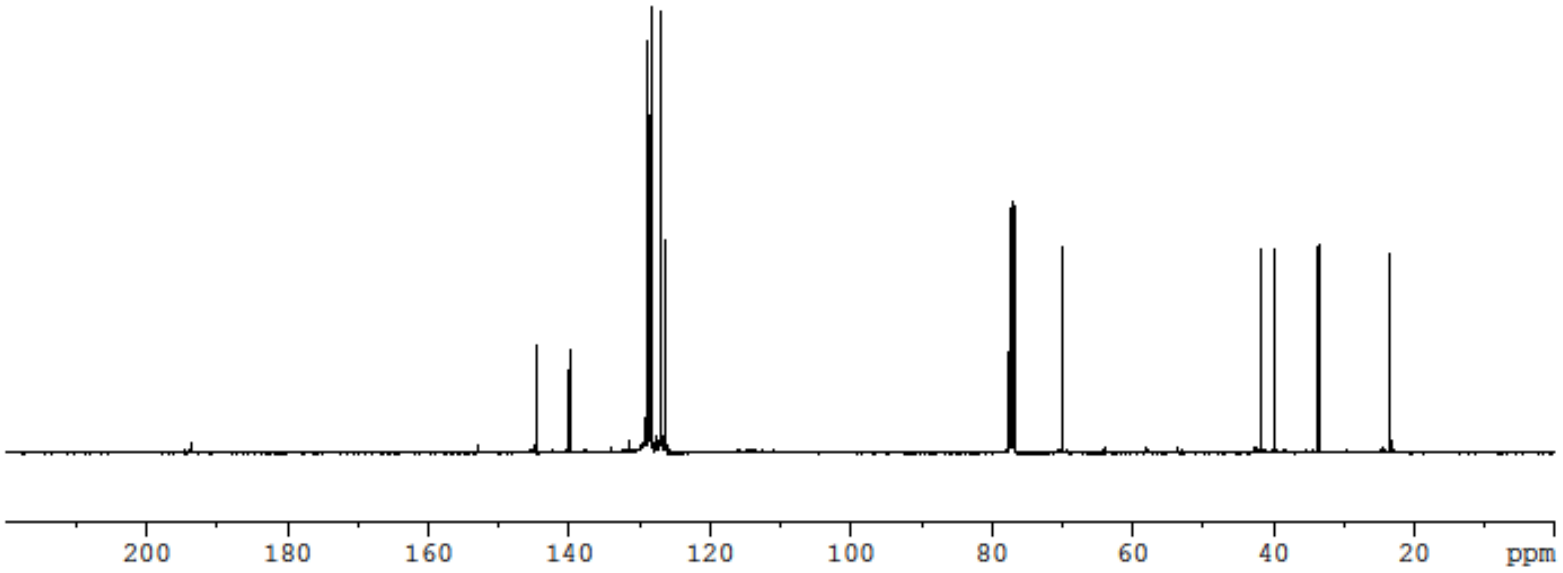

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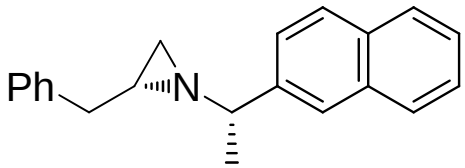

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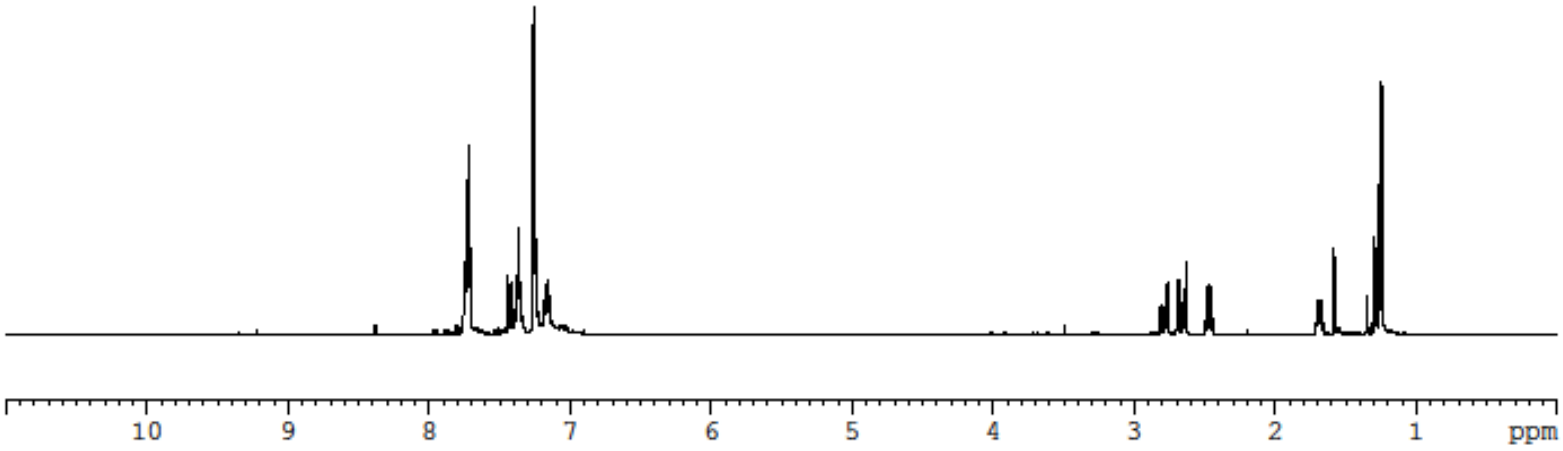

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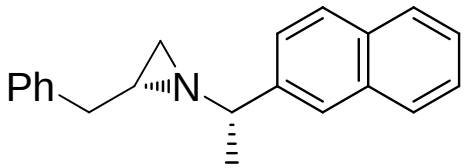

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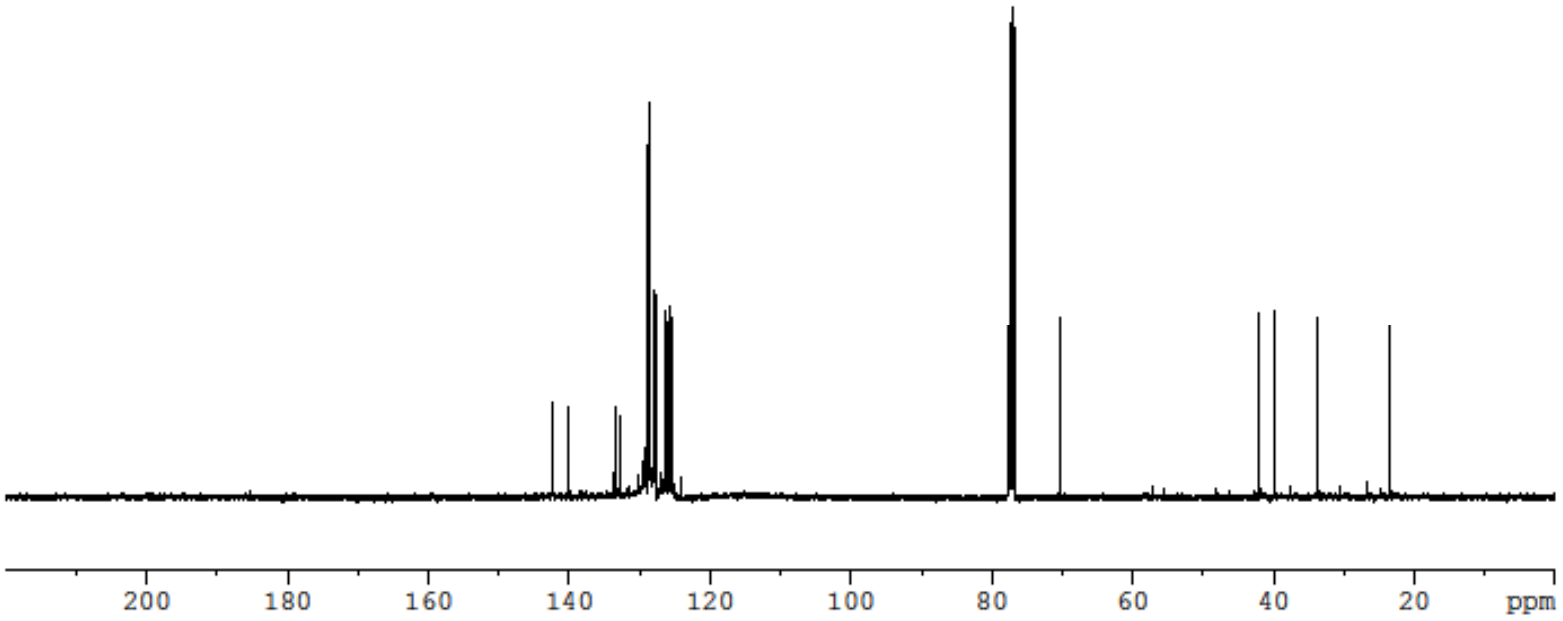

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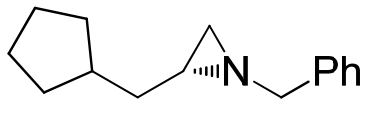

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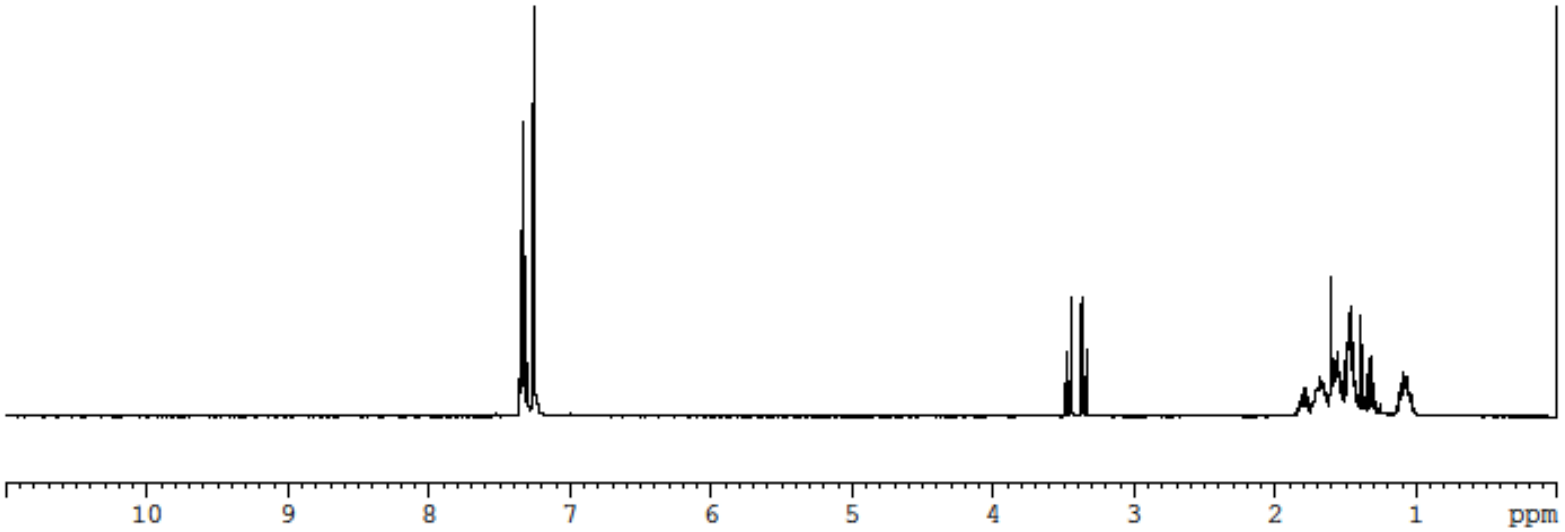

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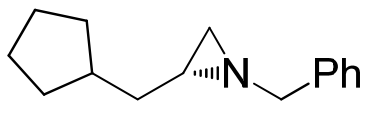

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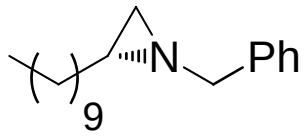

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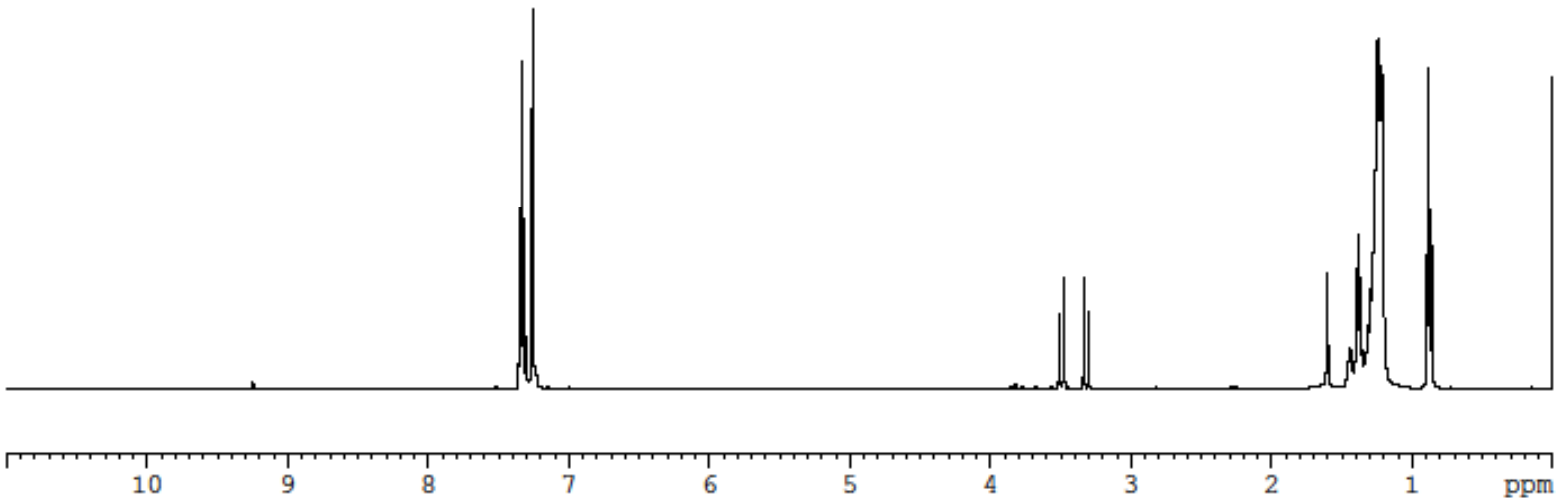

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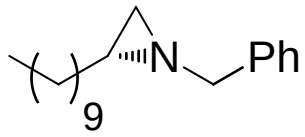

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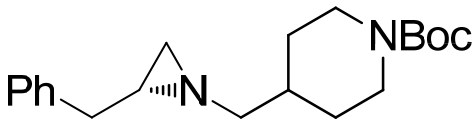

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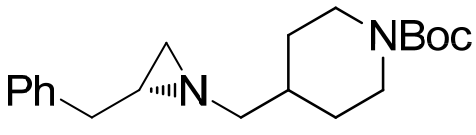

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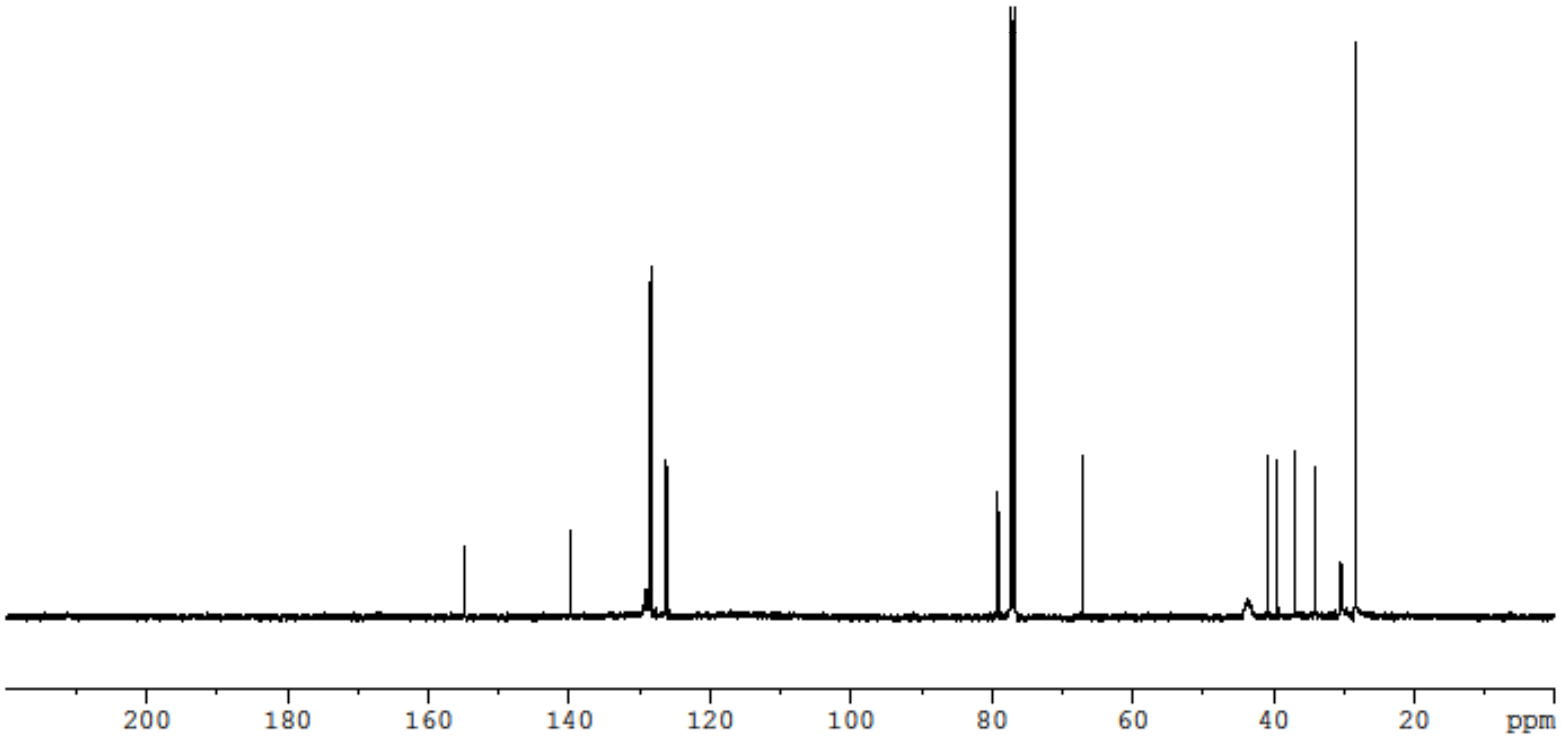

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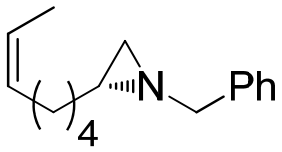

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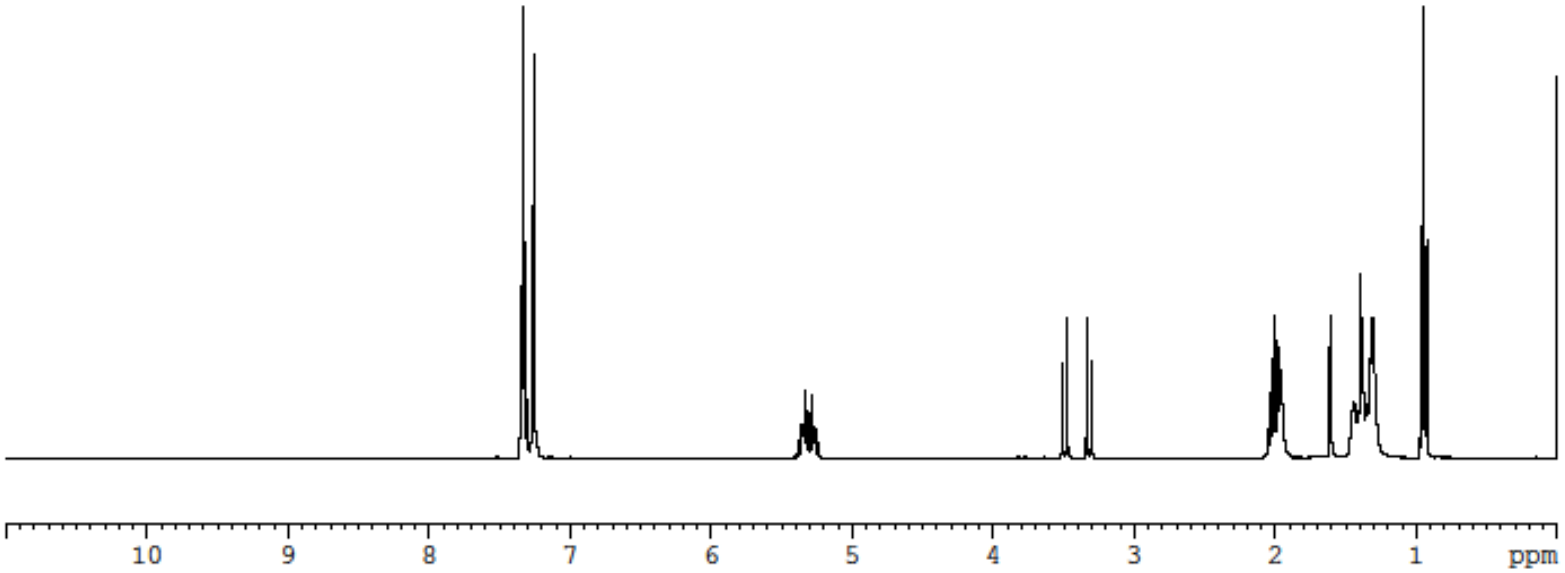

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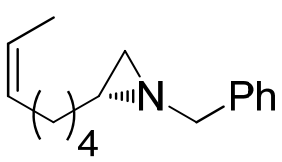

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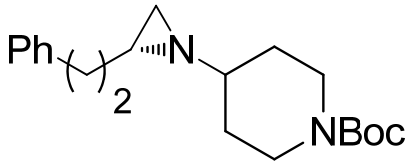

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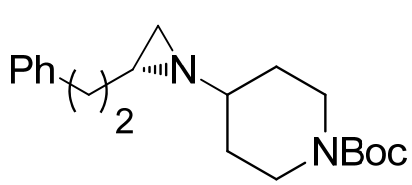

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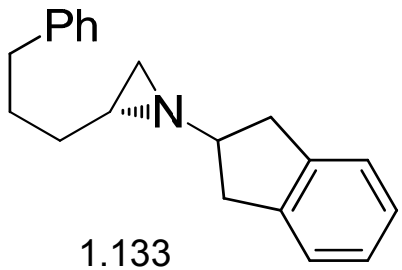

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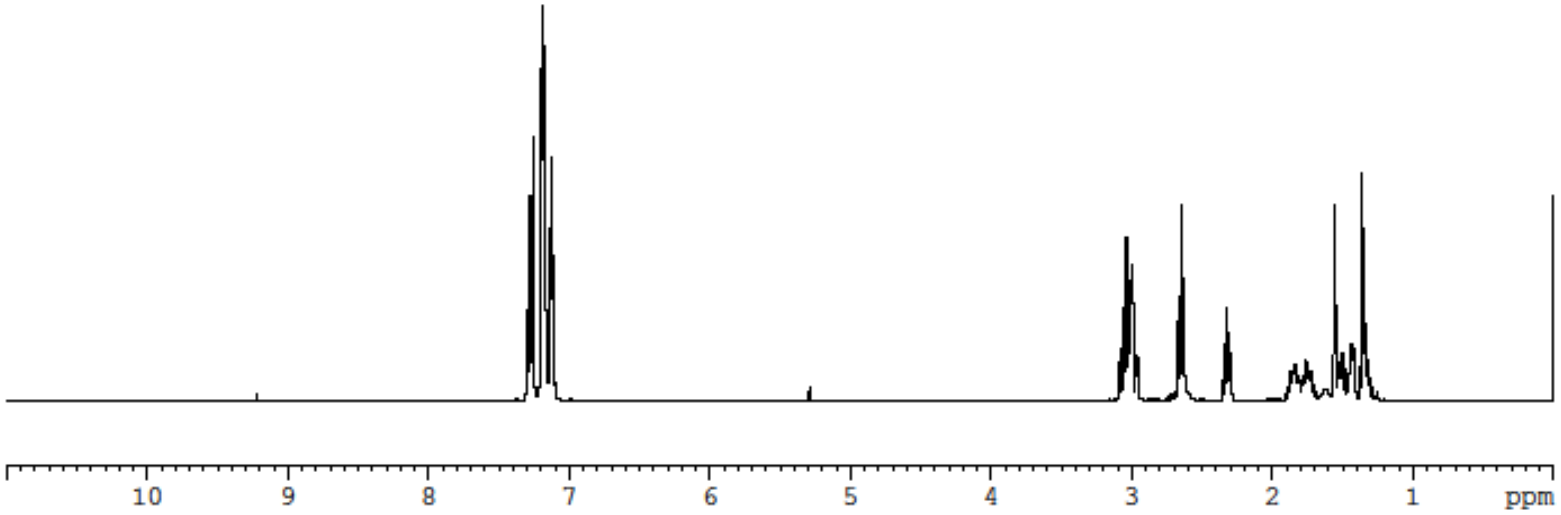

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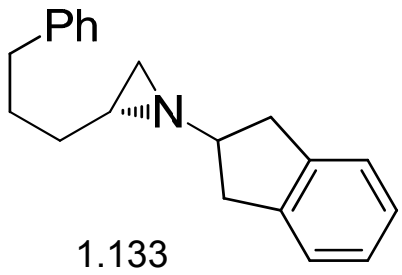

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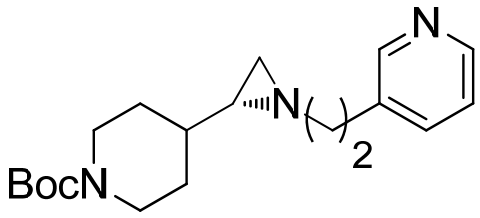

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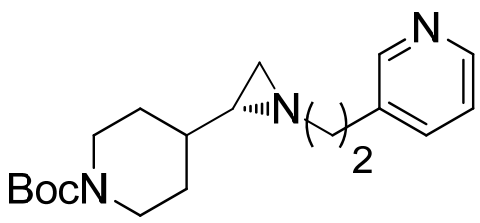

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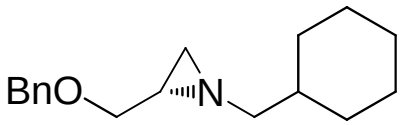

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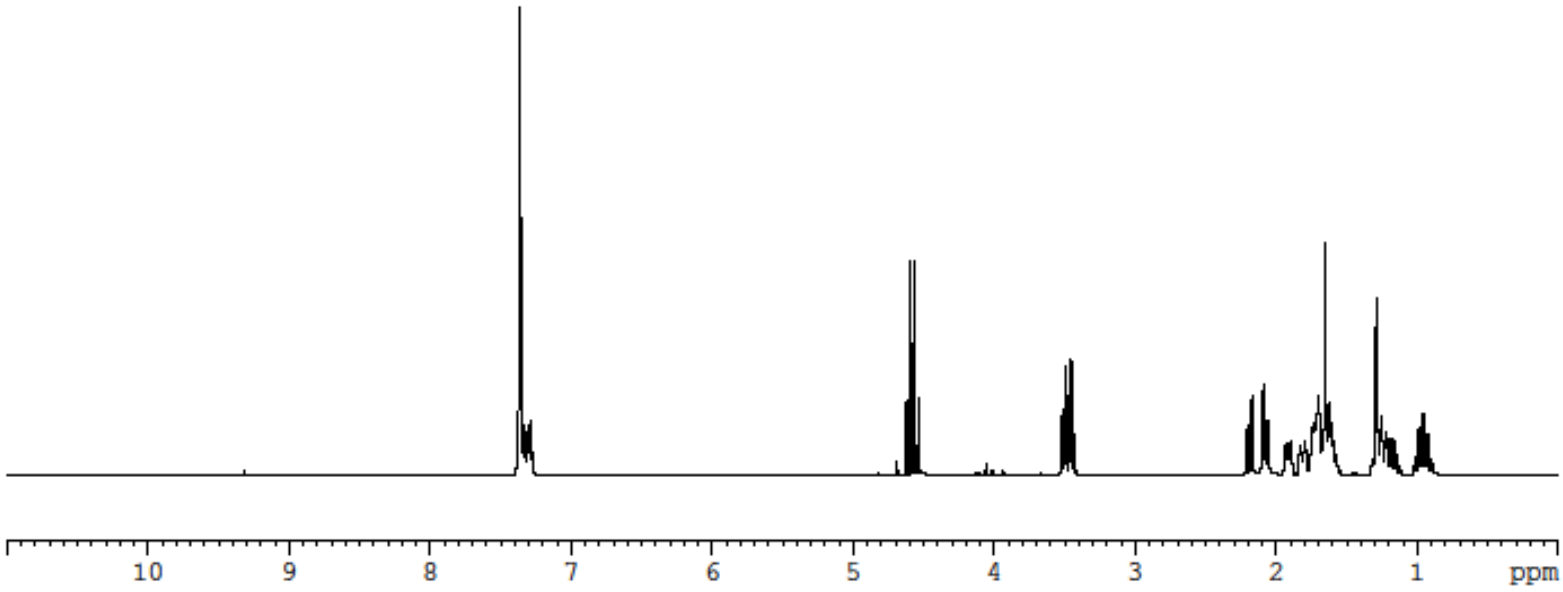

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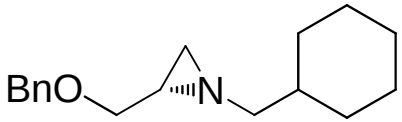

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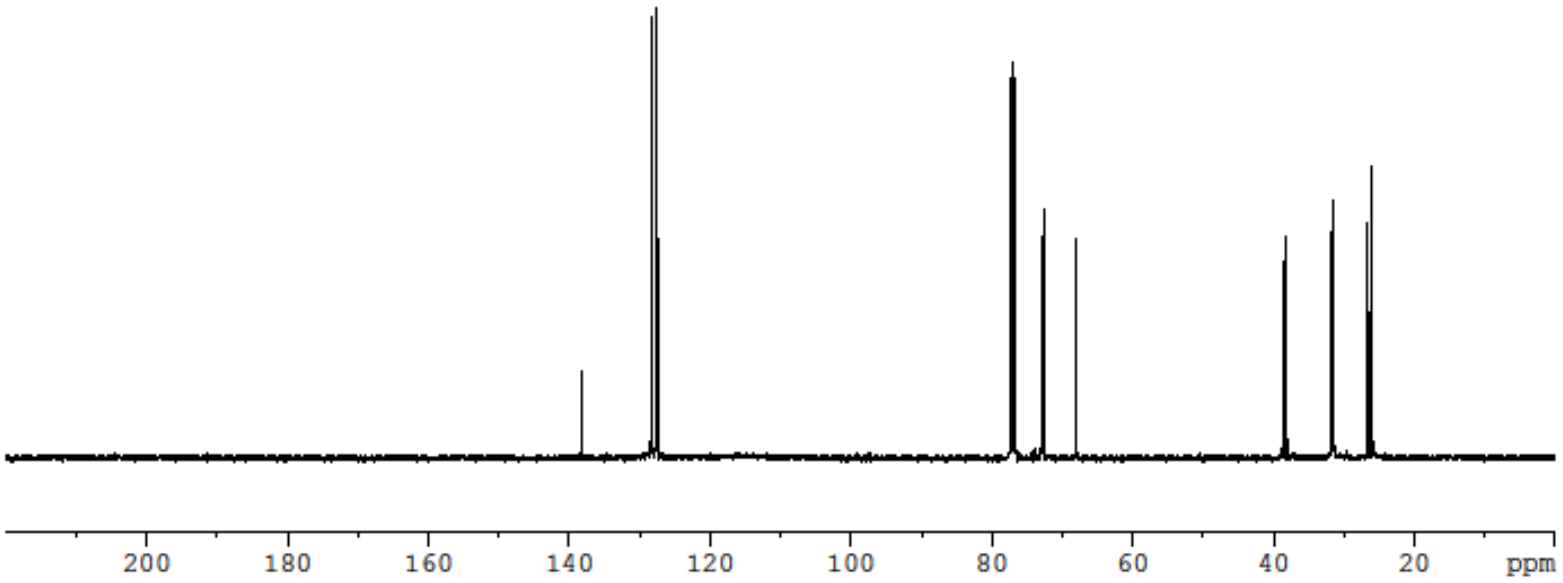

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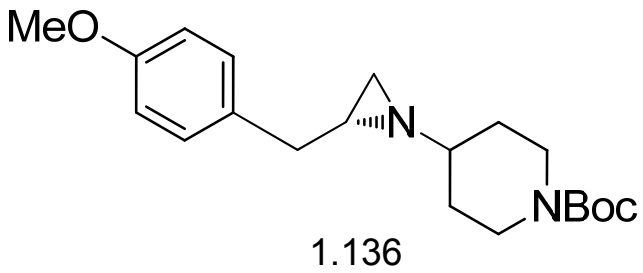

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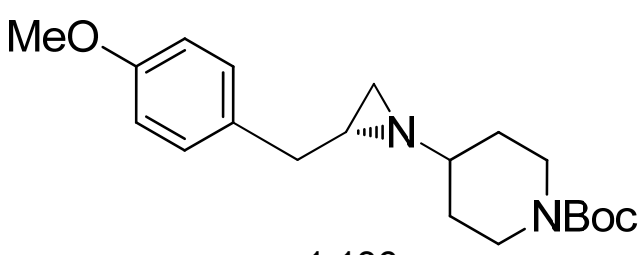

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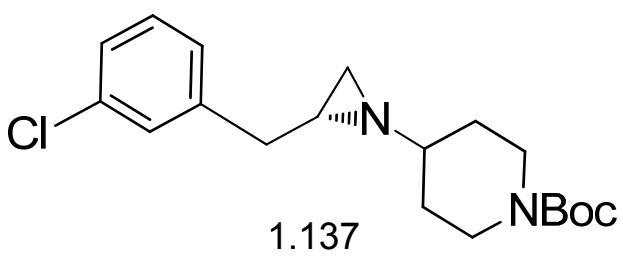

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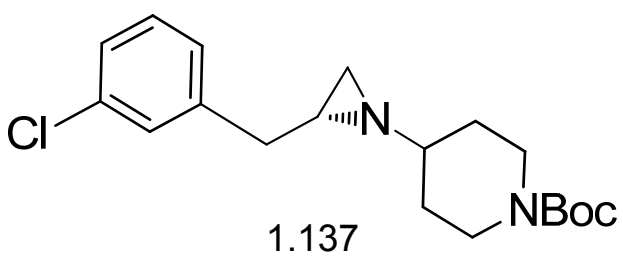


1.137

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

1.109

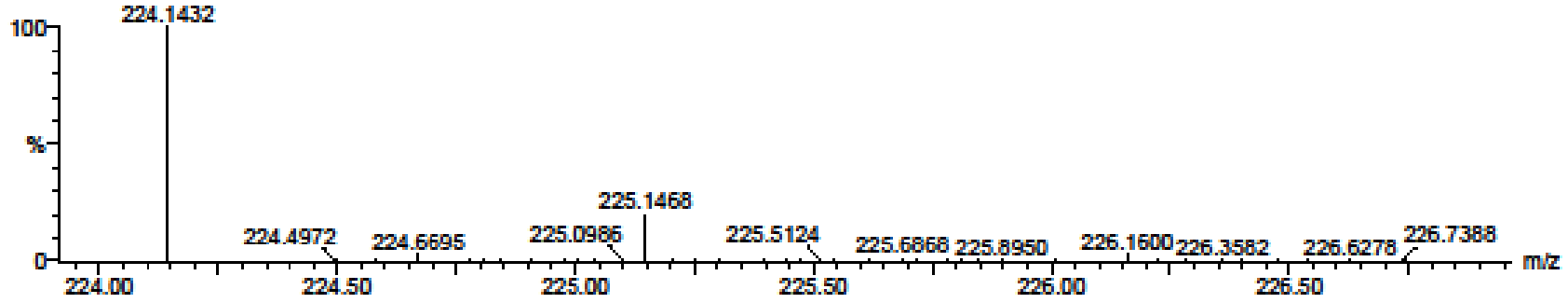
Monoisotopic Mass, Even Electron Ions
19 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200

MLS-B-Bn

S/N: UH193

18-Feb-2010
16:20:39
1: TOF MS ES+
2.05e+003

021810_mjm_058 78 (0.873) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (77:79-80:90)

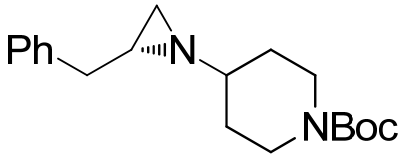


Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
224.1432	224.1439	-0.7	-3.1	8.5	0.7	C16 H18 N

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.124

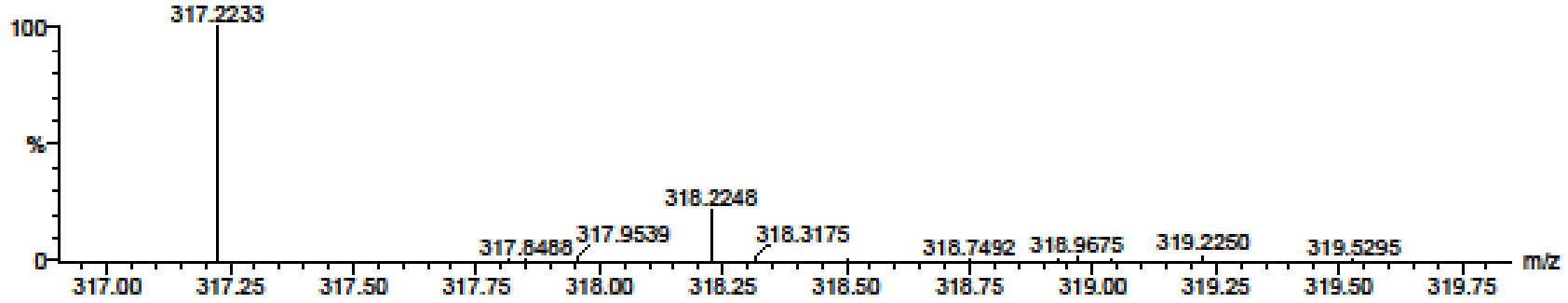
Monoisotopic Mass, Even Electron Ions
260 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200 O: 1-200

MLS-B-3

S/N: UH193

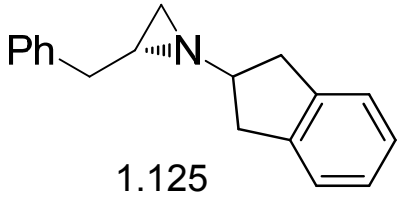
18-Feb-2010
16:00:08
1: TOF MS ES+
5.10e+002

021810_mjm_051 85 (0.950) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (83:85)



Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
317.2233	317.2229	0.4	1.3	6.5	0.1	C19 H29 N2 O2

Elemental Composition Report



1.125

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
23 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200

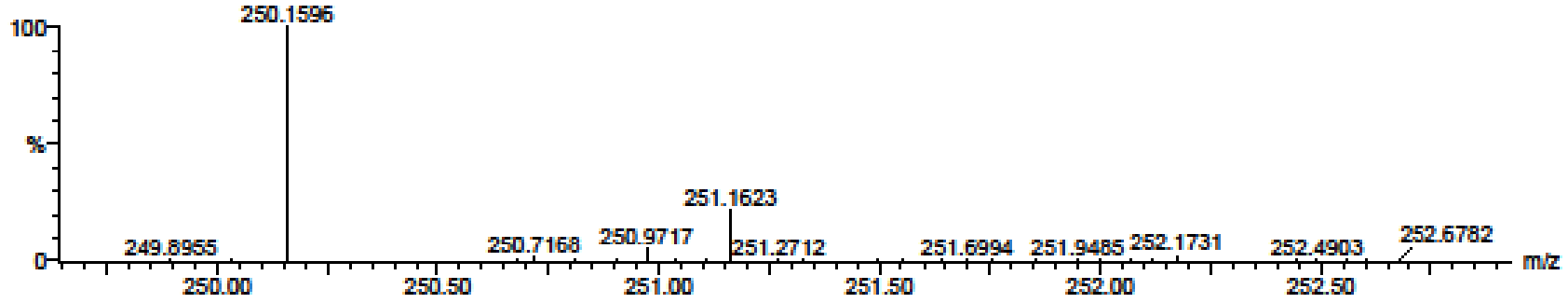
MLS-B-19

18-Feb-2010
16:11:52

S/N: UH193

021810_mjm_055 84 (0.931) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (83:85)

1: TOF MS ES+
1.46e+003

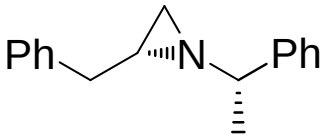


Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
250.1596	250.1596	0.0	0.0	9.5	0.3	C18 H20 N

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.126

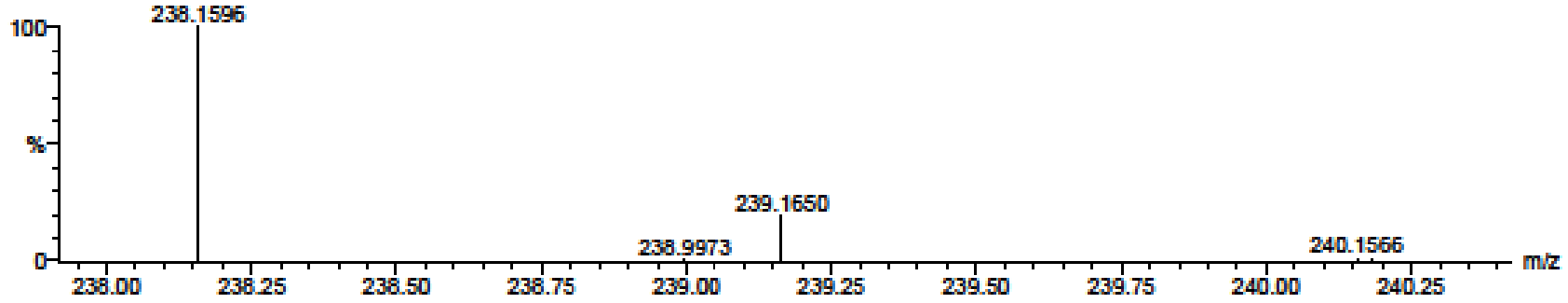
Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200

MLS-B-2

S/N: UH193

051110_mjm_003 82 (0.912) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (81:83)

12-May-2010
15:30:50
1: TOF MS ES+
8.47e+002

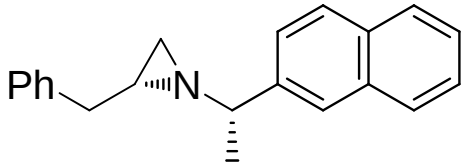


Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
238.1596	238.1596	0.0	0.0	8.5	0.0	C17 H20 N

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.127

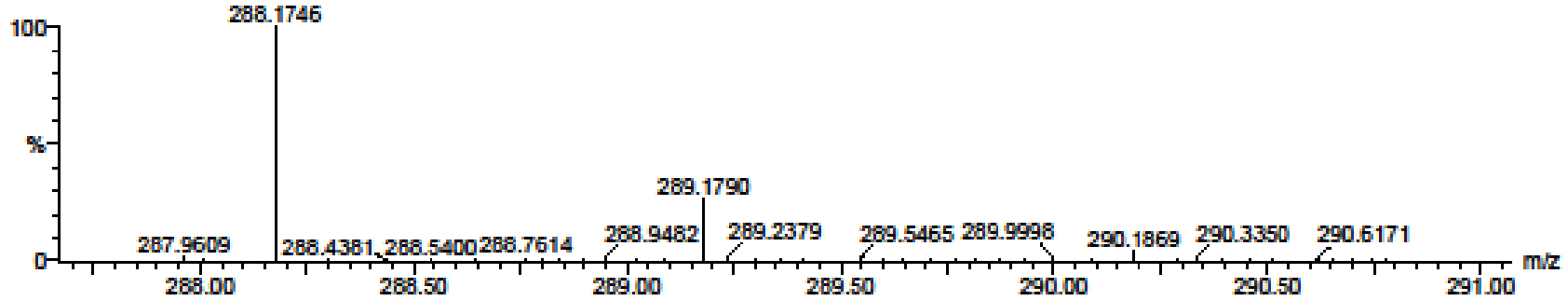
Monoisotopic Mass, Even Electron Ions
35 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200

MLS-21

S/N: UH193

032510_mjm_023 94 (1.046) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Cm (94:96)

25-Mar-2010
15:10:06
1: TOF MS ES+
1.30e+003

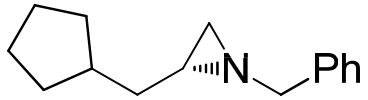


Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
288.1746	288.1752	-0.6	-2.1	11.5	1.1	C21 H22 N

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.128

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 10-500 H: 1-1000 N: 1-200

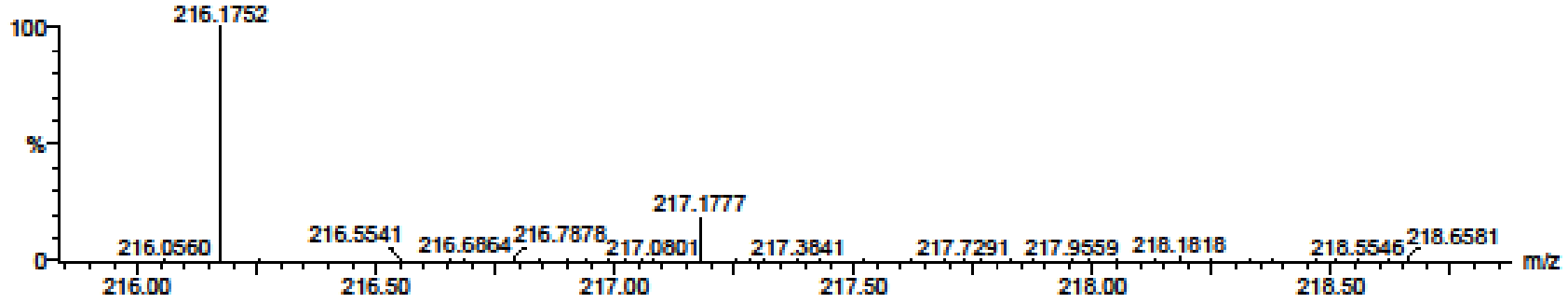
MLS-32

S/N: UH193

04-Mar-2010
15:32:57

030310_mjm_018 82 (0.911) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (81:84)

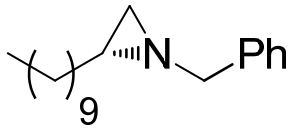
1: TOF MS ES+
2.56e+003



Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
216.1752	216.1752	0.0	0.0	5.5	0.9	C15 H22 N

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.129

Monoisotopic Mass, Even Electron Ions
31 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200

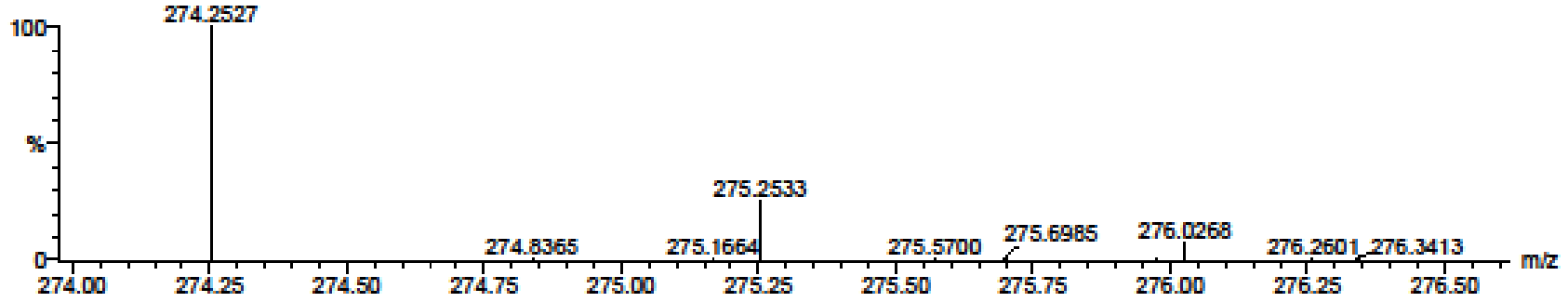
MLS-B-33

S/N: UH193

11-Mar-2010
11:11:05

031110_mjm_068 118 (1.306) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (116:118)

1: TOF MS ES+
5.25e+002

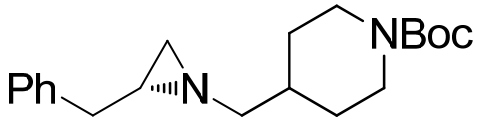


Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
274.2527	274.2535	-0.8	-2.9	4.5	0.7	C19 H32 N

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.130

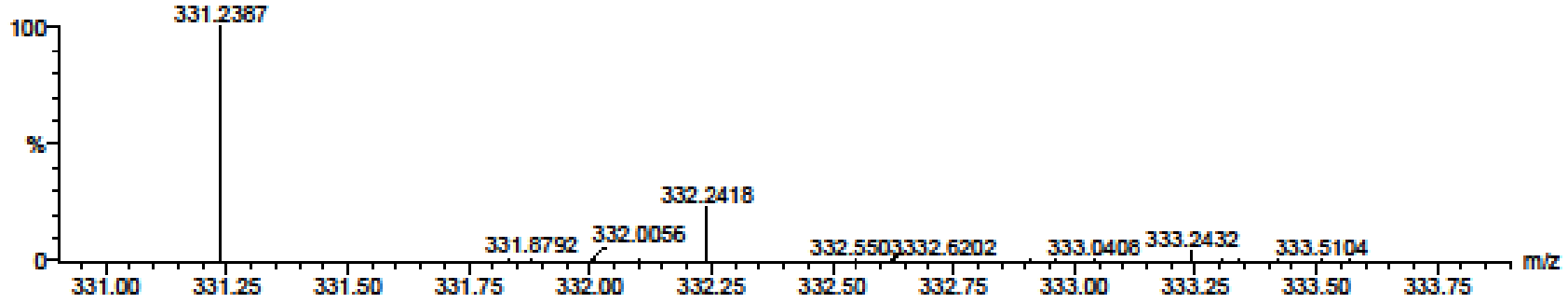
Monoisotopic Mass, Even Electron Ions
298 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200 O: 1-200

MLS-B-4

S/N: UH193

18-Feb-2010
16:06:00
1: TOF MS ES+
1.30e+003

021810_mjm_053 89 (0.988) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (87:90)

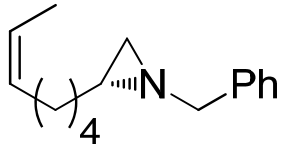


Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
331.2387	331.2386	0.1	0.3	6.5	0.3	C20 H31 N2 O2

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.131

Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200

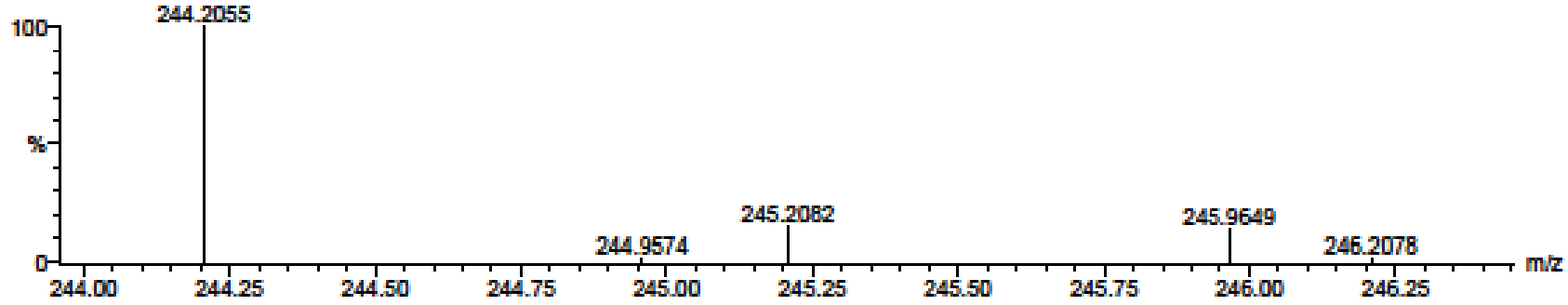
MLS-B-34

S/N: UH193

11-Mar-2010
11:14:03

031110_mjm_069 99 (1.104) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (99:101)

1: TOF MS ES+
2.82e+002

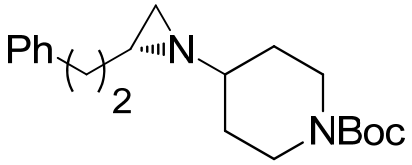


Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
244.2055	244.2065	-1.0	-4.1	5.5	1.8	C17 H26 N

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.132

Monoisotopic Mass, Even Electron Ions
339 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200 O: 1-200

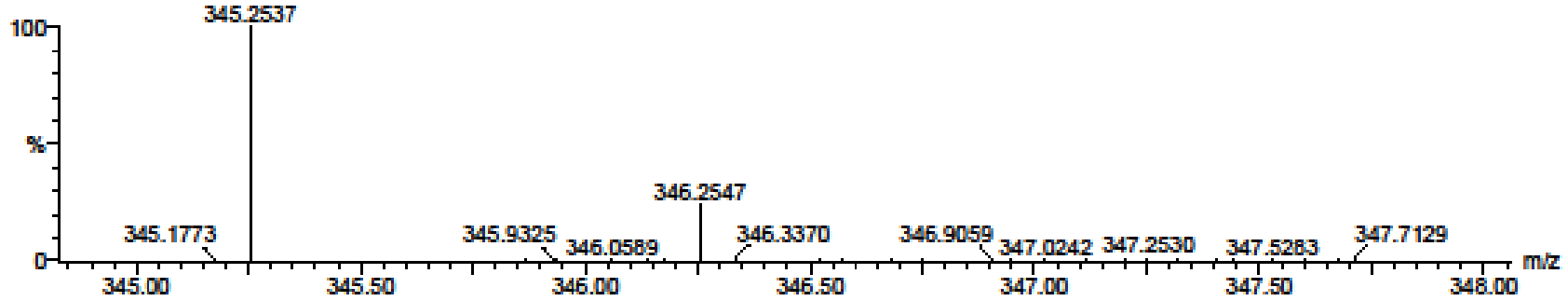
MLS-B-76

S/N: UH193

11-Mar-2010
10:15:02

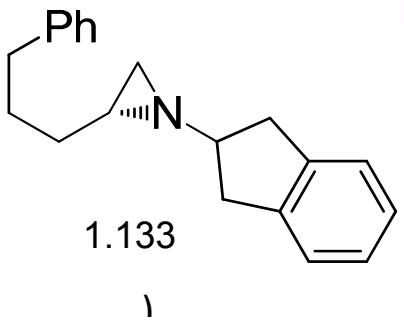
031110_mjm_049 94 (1.046) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (92:94-95:110)

1: TOF MS ES+
1.10e+003



Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
345.2537	345.2542	-0.5	-1.4	6.5	0.1	C21 H33 N2 O2

Elemental Composition Report



Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

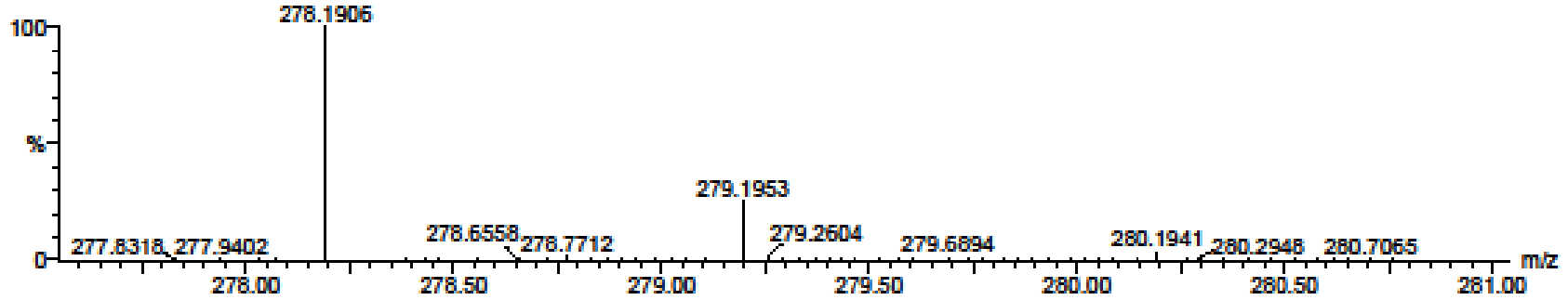
Monoisotopic Mass, Even Electron Ions
31 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200

MLS-75

S/N: UH193

032510_mjm_024 93 (1.037) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Cm (91:93)

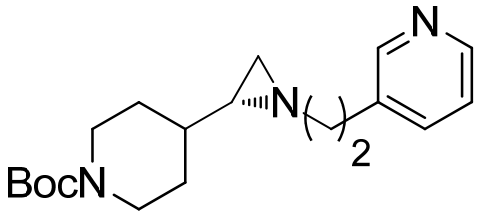
25-Mar-2010
15:13:01
1: TOF MS ES+
2.58e+003



Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
278.1906	278.1909	-0.3	-1.1	9.5	2.0	C20 H24 N

Elemental Composition Report

Multiple Mass Analysis: 2 mass(es) processed
Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.134

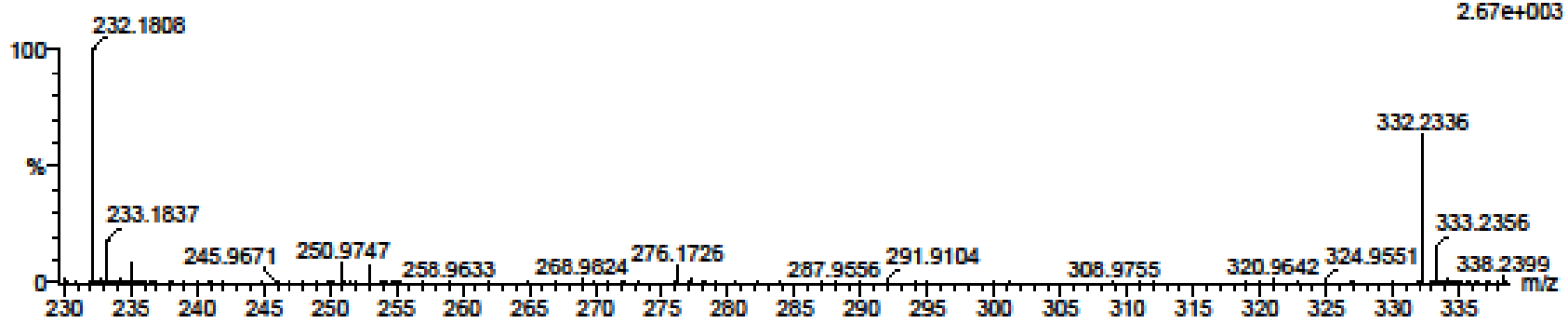
Monoisotopic Mass, Even Electron Ions
597 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 10-500 H: 1-1000 N: 1-200 O: 0-200

Boc-Pyridine

04-Mar-2010
15:18:15
1: TOF MS ES+
2.67e+003

S/N: UH193

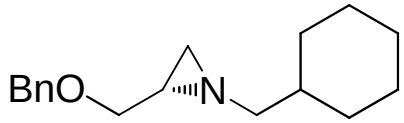
030310_mjm_013 63 (0.700) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (62:64)



Minimum:	50.00				0.0		
Maximum:	100.00		5.0	5.0	25.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
232.1808	100.00	232.1814	-0.6	-2.6	5.5	0.7	C14 H22 N3
332.2336	63.20	332.2338	-0.2	-0.6	6.5	0.0	C19 H30 N3 O2

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2



1.135

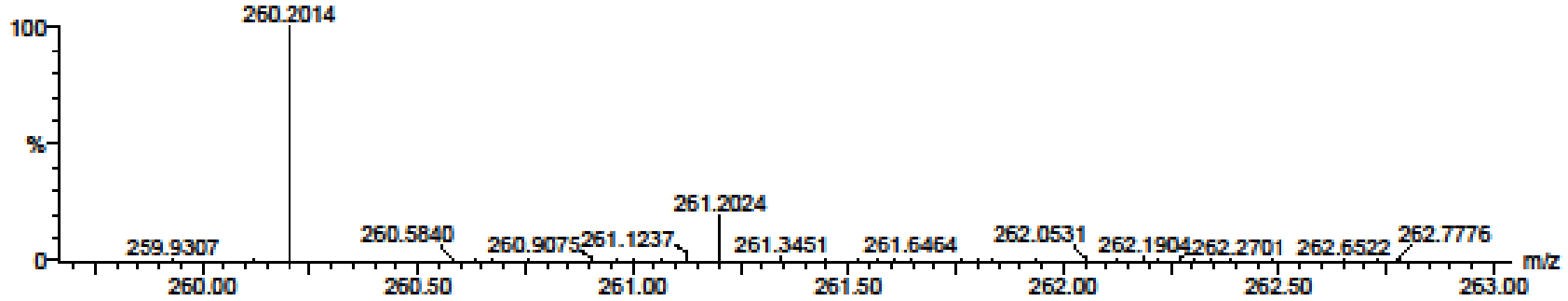
Monoisotopic Mass, Even Electron Ions
144 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200 O: 1-200

MLS-B-88

S/N: UH193

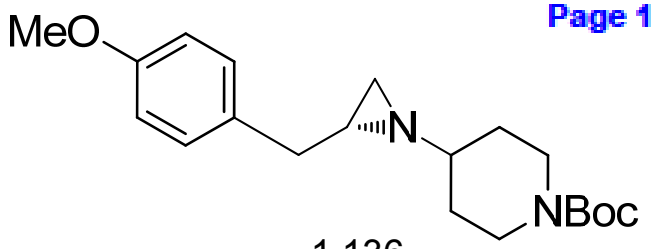
041510_mjm_025 94 (1.046) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Cm (94:97)

15-Apr-2010
14:58:52
1: TOF MS ES+
7.38e+002



Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
260.2014	260.2014	0.0	0.0	5.5	0.1	C17 H26 N O

Elemental Composition Report



1.136

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
305 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 18-500 H: 1-1000 N: 1-200 O: 1-200

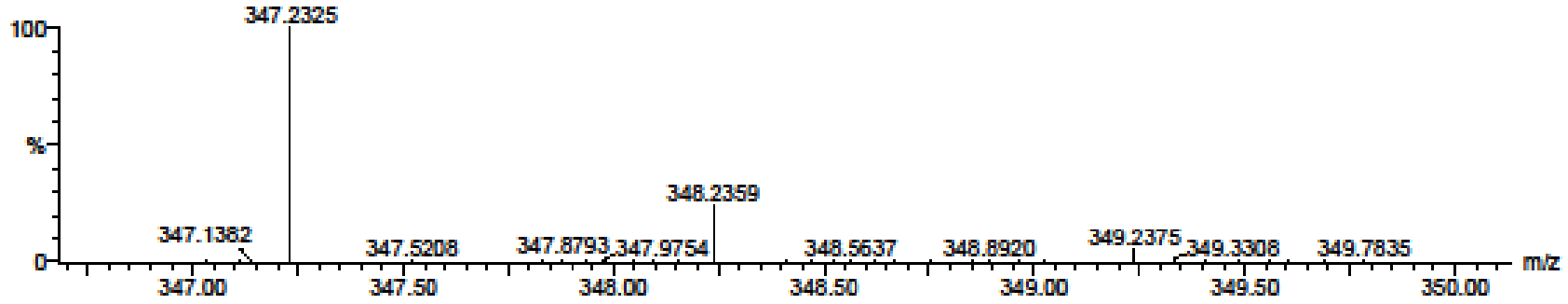
MLS-B-73

10-Mar-2010
20:01:28

S/N: UH193

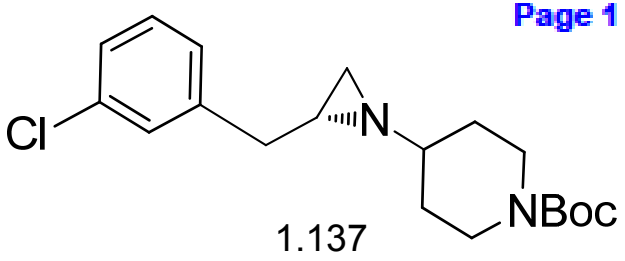
031010_MetID_028 75 (0.835) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (73:75)

1: TOF MS ES+
2.26e+003



Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
347.2325	347.2335	-1.0	-2.9	6.5	0.1	C20 H31 N2 O3

Elemental Composition Report



1.137

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = 0.0, max = 25.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
255 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-500 H: 1-1000 N: 1-200 O: 1-200 Cl: 1-1

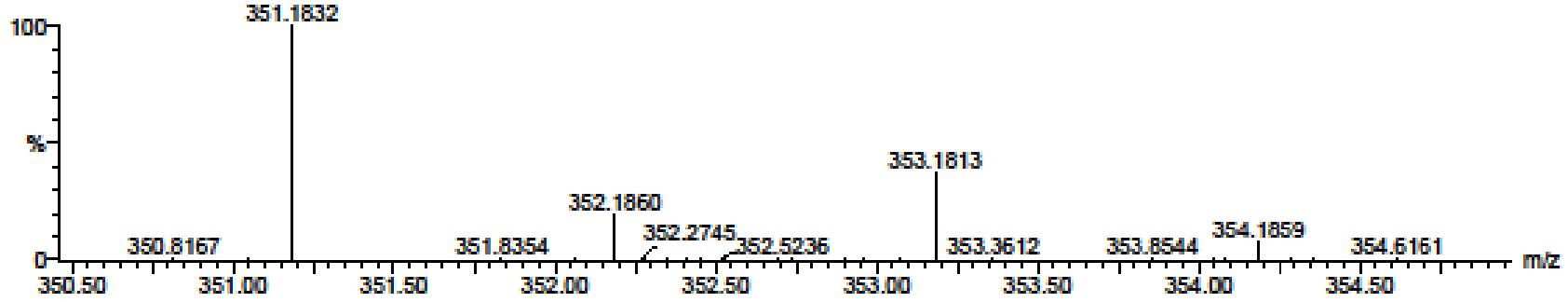
MLS-B-71

11-Mar-2010
10:04:55

S/N: UH193

031110_mjm_046 91 (1.008) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70,LS 5); Sm (SG, 2x1.00); Sb (1,40.00); Cm (90:92)

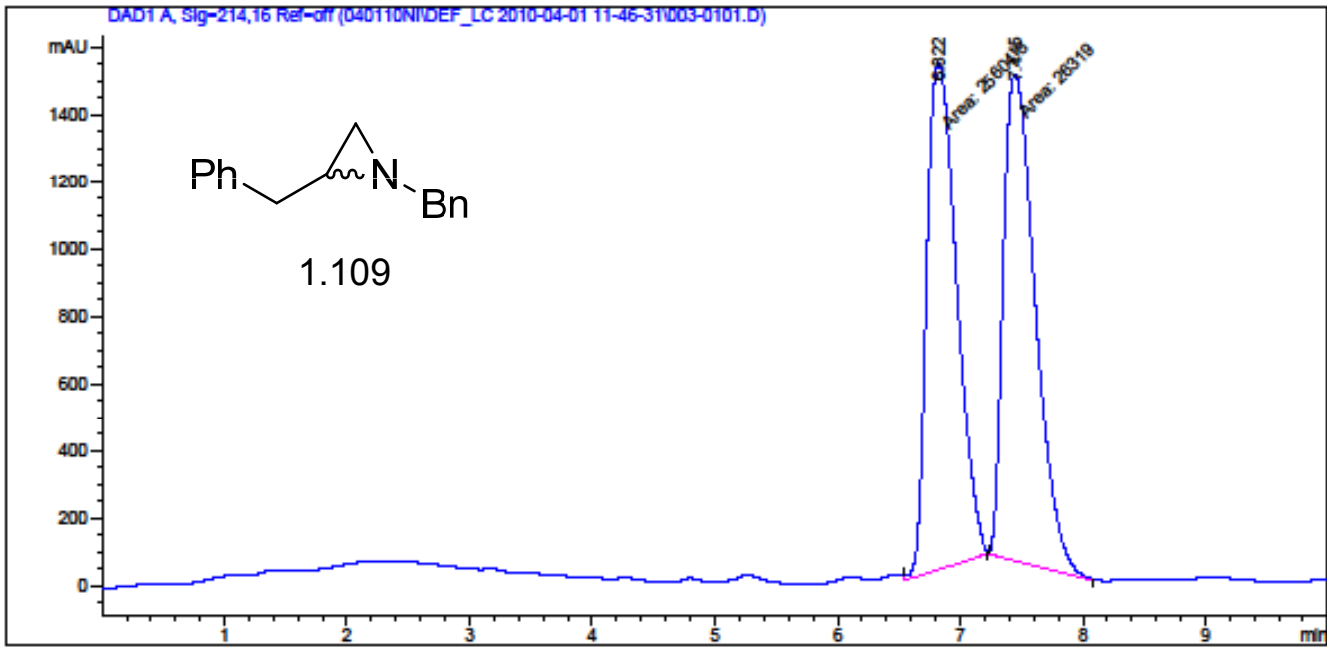
1: TOF MS ES+
1.09e+003



Minimum:				0.0		
Maximum:		5.0	5.0	25.0		
Mass	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
351.1832	351.1839	-0.7	-2.0	6.5	2.2	C19 H28 N2 O2 Cl

Data File C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-01 11-46-31\003-0101.D
Sample Name: MLS-Bn rac

```
================================================================================
                                                    Seq. Line :   1
Acq. Instrument : Instrument 1                       Location : Vial 3
Injection Date  : 4/1/2010 11:46:50 AM                    Inj :   1
                                                   Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\040110NI\DEF_LC 2010-04-01 11-46-31\OD_10MINHEX_IPA.M
Last changed    : 3/5/2010 5:13:12 PM
Analysis Method : C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-01 11-46-31\003-0101.D\DA.M (OD_
                  10MINHEX_IPA.M)
Last changed    : 3/5/2010 5:13:12 PM
Method Info     : OD 98% Hexane 2% IPA
```




```
================================================================================
                          Area Percent Report
================================================================================
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.822	MM	0.2835	2.56043e4	1505.23865	49.3118
2	7.445	MM	0.3038	2.63190e4	1444.03235	50.6882

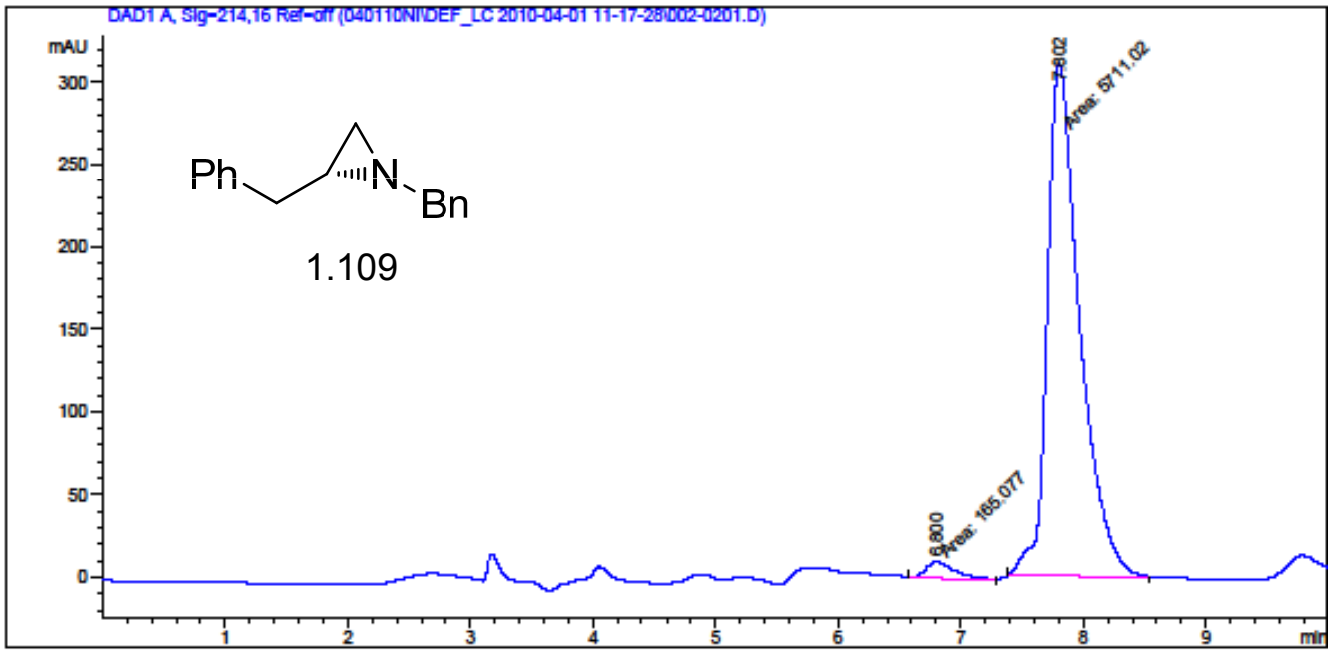
Totals : 5.19233e4 2949.27100

```
================================================================================
                          *** End of Report ***
```

Instrument 1 4/1/2010 3:21:28 PM

Data File C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-01 11-17-28\002-0201.D
Sample Name: MLS-Bn ee

```
================================================================================
                                                    Seq. Line :   2
Acq. Instrument : Instrument 1                       Location : Vial 2
Injection Date  : 4/1/2010 11:29:35 AM                    Inj :   1
                                                   Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\040110NI\DEF_LC 2010-04-01 11-17-28\OD_10MINHEX_IPA.M
Last changed    : 3/5/2010 5:13:12 PM
Analysis Method : C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-01 11-17-28\002-0201.D\DA.M (OD_
                  10MINHEX_IPA.M)
Last changed    : 3/5/2010 5:13:12 PM
Method Info     : OD 98% Hexane 2% IPA
```




```
================================================================================
                          Area Percent Report
================================================================================

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.800 MM    0.2758  165.07733    9.97511   2.8093
   2   7.802 MM    0.3060 5711.01563  311.00995  97.1907

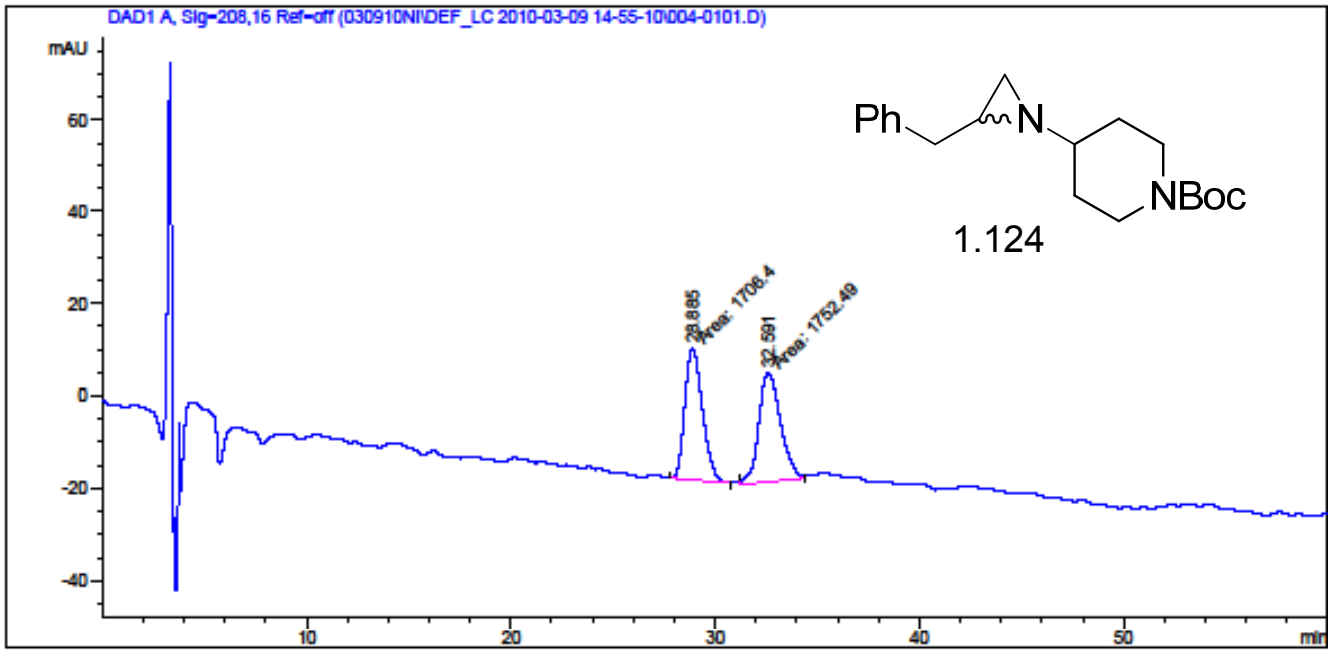
Totals :                   5876.09296  320.98506

================================================================================
                          *** End of Report ***
```

Instrument 1 4/1/2010 2:49:22 PM

Data File C:\CHEM32\1\DATA\030910NI\DEF_LC 2010-03-09 14-55-10\004-0101.D
Sample Name: 55

```
==========================================================================
                                                  Seq. Line :   1
Acq. Instrument : Instrument 1                     Location : Vial 4
Injection Date  : 3/9/2010 3:15:31 PM                   Inj :   1
                                                 Inj Volume : 20 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\030910NI\DEF_LC 2010-03-09 14-55-10\IA_AMM_ ACE.M
Last changed    : 3/9/2010 3:50:51 PM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\030910NI\DEF_LC 2010-03-09 14-55-10\004-0101.D\DA.M (IA_AMM_
                  ACE.M)
Last changed    : 2/17/2010 10:39:53 AM
Method Info     : IA 60:40 pH9 20 mM Aqueous Ammonium Bicarbonate/Acetonitrile
```




```
==========================================================================
                        Area Percent Report
==========================================================================
```

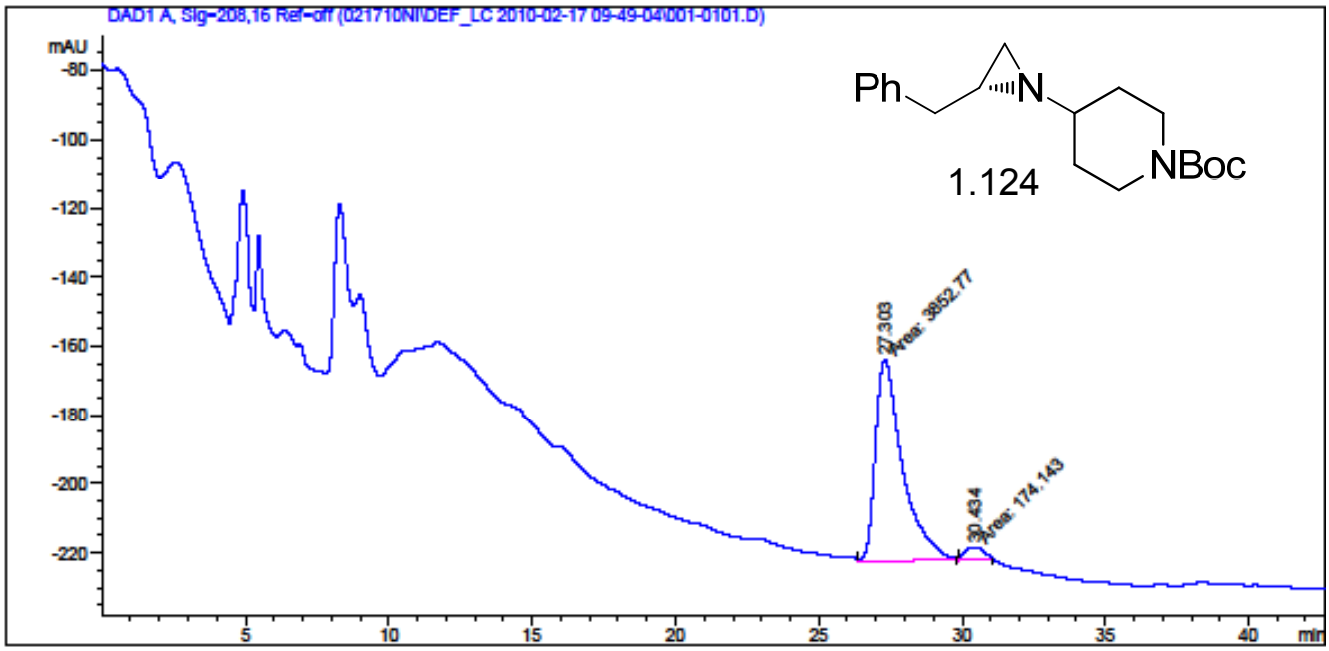
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.885	MM	1.0058	1706.39795	28.27558	49.3338
2	32.591	MM	1.2430	1752.48743	23.49722	50.6662
Totals :				3458.88538	51.77280	

```
==========================================================================
                          *** End of Report ***
```

Instrument 1 4/1/2010 3:42:12 PM

Data File C:\CHEM32\1\DATA\021710NI\DEF_LC 2010-02-17 09-49-04\001-0101.D
Sample Name: -78 2h imine

```
==========================================================================
                                                Seq. Line :   1
Acq. Instrument : Instrument 1                   Location : Vial 1
Injection Date  : 2/17/2010 9:54:22 AM                Inj :   1
                                               Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\021710NI\DEF_LC 2010-02-17 09-49-04\IA_AMM_ ACE.M
Last changed    : 2/17/2010 10:38:11 AM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\021710NI\DEF_LC 2010-02-17 09-49-04\001-0101.D\DA.M (IA_AMM_
                  ACE.M)
Last changed    : 2/17/2010 9:48:45 AM
Method Info     : IA 60:40 pH9 20 mM Aqueous Ammonium Bicarbonate/Acetonitrile
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.303 MM    1.0967 3852.77026   58.55138  95.6755
   2  30.434 MM    0.5679  174.14268    3.76536   4.3245

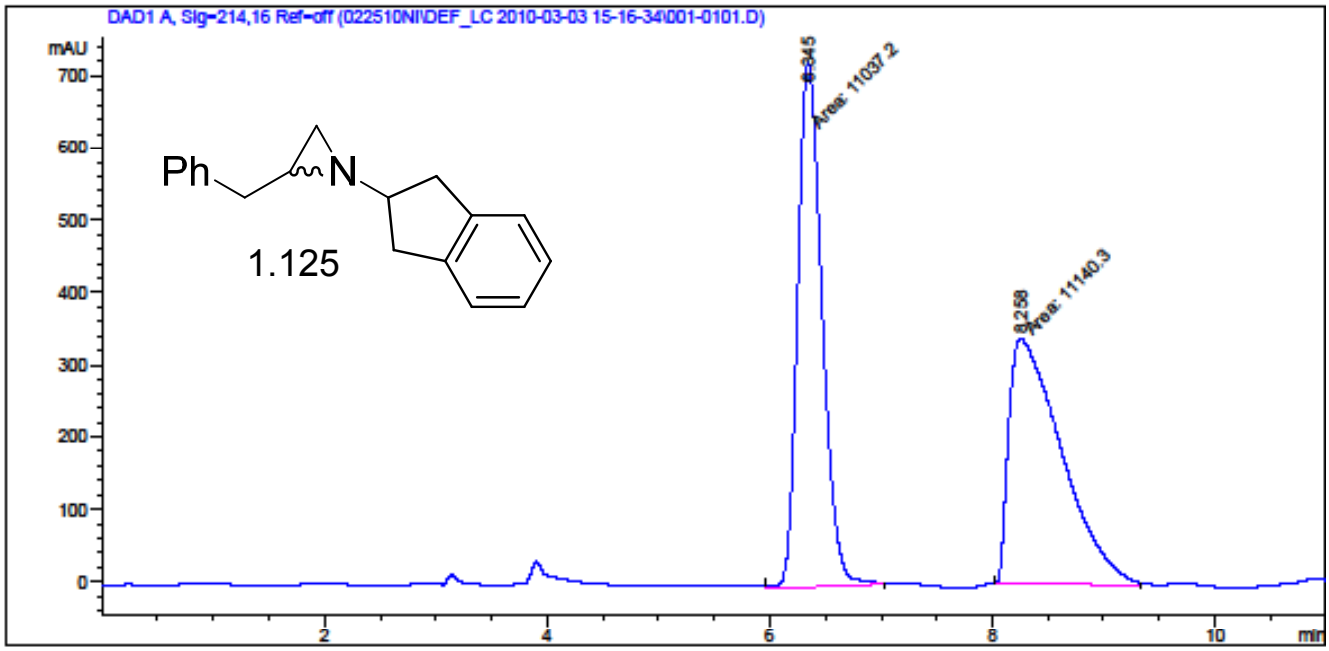
Totals :                  4026.91295   62.31675

==========================================================================
                          *** End of Report ***
```

Instrument 1 3/22/2010 1:10:38 PM

Data File C:\CHEM32\1\DATA\022510NI\DEF_LC 2010-03-03 15-16-34\001-0101.D
Sample Name: 19

```
==========================================================================
                                                    Seq. Line :   1
Acq. Instrument : Instrument 1                       Location : Vial 1
Injection Date  : 3/3/2010 3:21:55 PM                     Inj :   1
                                                   Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\022510NI\DEF_LC 2010-03-03 15-16-34\OD_HEX_IPA.M
Last changed    : 3/3/2010 3:33:08 PM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\022510NI\DEF_LC 2010-03-03 15-16-34\001-0101.D\DA.M (OD_HEX_
                  IPA.M)
Last changed    : 2/25/2010 11:30:54 AM
Method Info     : OD 98% Hexane 2% IPA
```




```
==========================================================================
                          Area Percent Report
==========================================================================
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.345	MM	0.2537	1.10372e4	724.97113	49.7674
2	8.258	MM	0.5492	1.11403e4	338.08975	50.2326

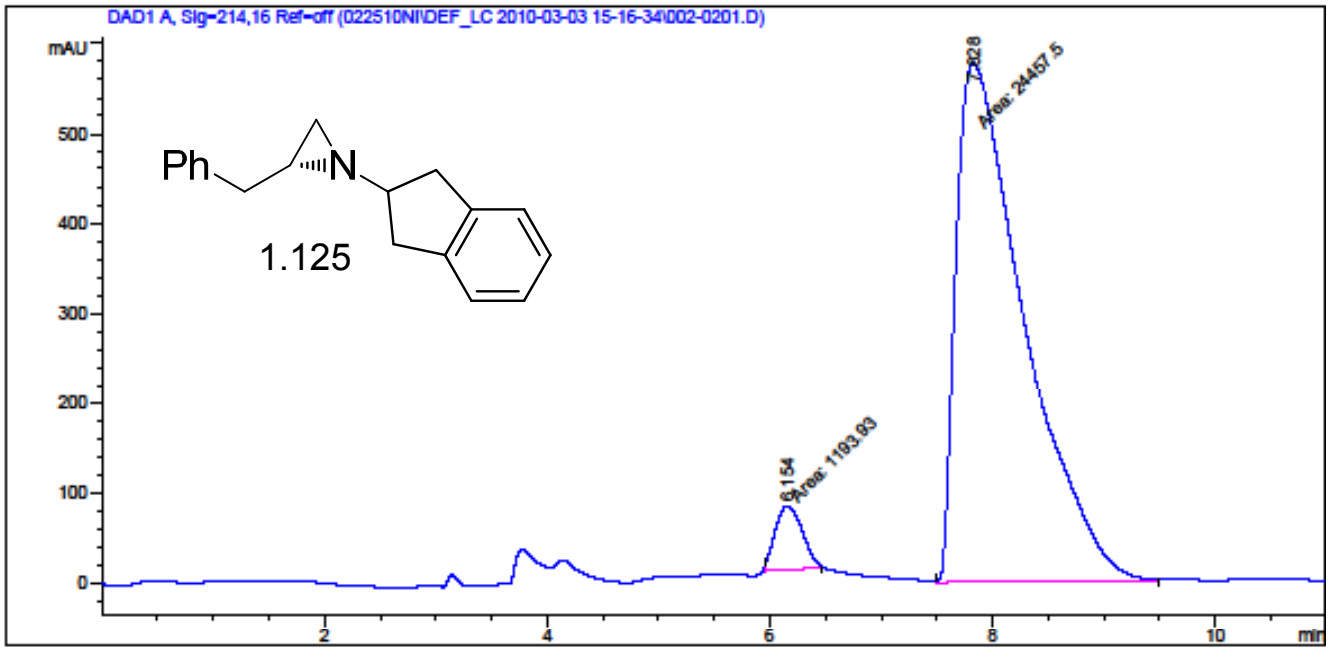
Totals : 2.21775e4 1063.06088

```
==========================================================================
                          *** End of Report ***
```

Instrument 1 3/3/2010 4:00:32 PM

Data File C:\CHEM32\1\DATA\022510NI\DEF_LC 2010-03-03 15-16-34\002-0201.D
Sample Name: 19-ee

```
==========================================================================
                                                  Seq. Line :   2
Acq. Instrument : Instrument 1                     Location : Vial 2
Injection Date  : 3/3/2010 3:34:47 PM                  Inj :   1
                                                 Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\022510NI\DEF_LC 2010-03-03 15-16-34\OD_HEX_IPA.M
Last changed    : 3/3/2010 3:34:34 PM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\022510NI\DEF_LC 2010-03-03 15-16-34\002-0201.D\DA.M (OD_HEX_
                  IPA.M)
Last changed    : 2/25/2010 11:30:54 AM
Method Info     : OD 98% Hexane 2% IPA
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.154 MM    0.2825 1193.93213   70.43901   4.6544
   2   7.828 MM    0.7074 2.44575e4   576.24487  95.3456

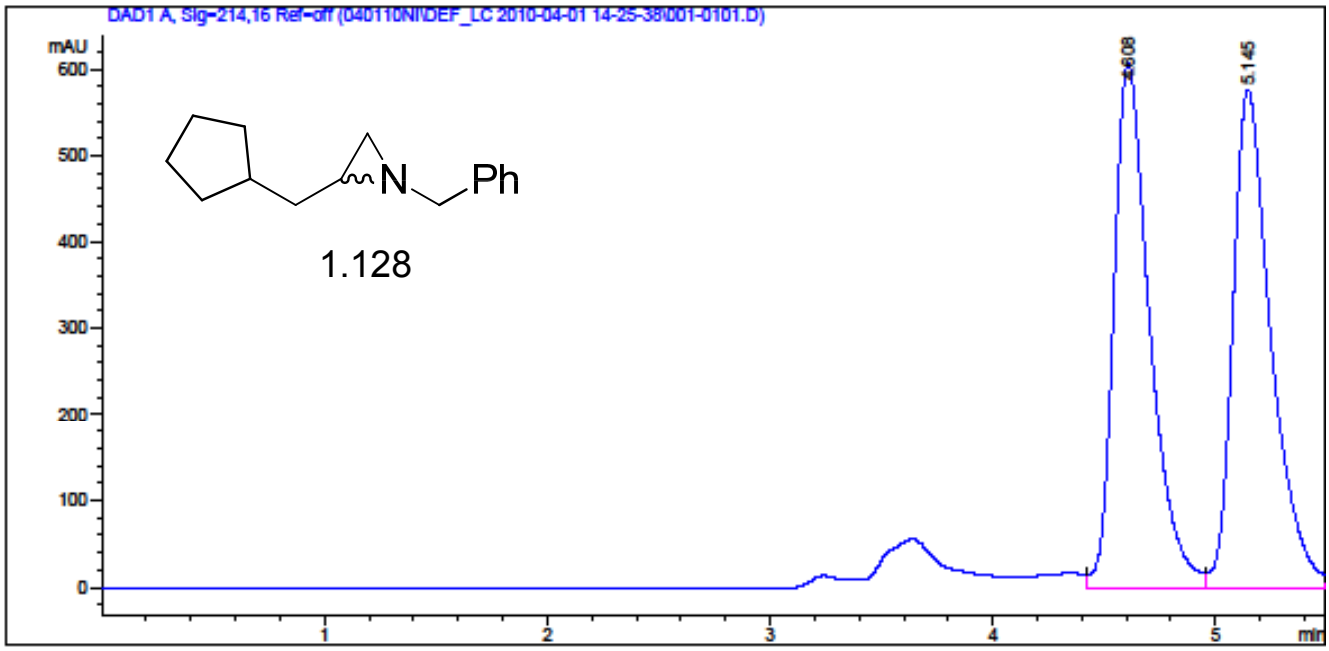
Totals :                  2.56514e4   646.68388

==========================================================================
                          *** End of Report ***
```

Instrument 1 3/3/2010 4:03:36 PM

Data File C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-01 14-25-38\001-0101.D
Sample Name: MLS-32-rac

```
==========================================================================
                                                  Seq. Line :   1
Acq. Instrument : Instrument 1                     Location : Vial 1
Injection Date  : 4/1/2010 2:25:58 PM                  Inj :   1
                                                 Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 2 µl
Acq. Method     : C:\Chem32\1\DATA\040110NI\DEF_LC 2010-04-01 14-25-38\OD_HEX_IPA.M
Last changed    : 4/1/2010 2:07:17 PM
Analysis Method : C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-01 14-25-38\001-0101.D\DA.M (OD_HEX_
                  IPA.M)
Last changed    : 4/1/2010 2:07:17 PM
Method Info     : OD 98% Hexane 2% IPA
```




```
==========================================================================
                        Area Percent Report
==========================================================================

 Peak RetTime Type  Width     Area      Height     Area
   #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
    1   4.608 VV    0.1668 6820.42090  608.41205  49.8790
    2   5.145 VBA   0.1764 6853.50146  577.57336  50.1210

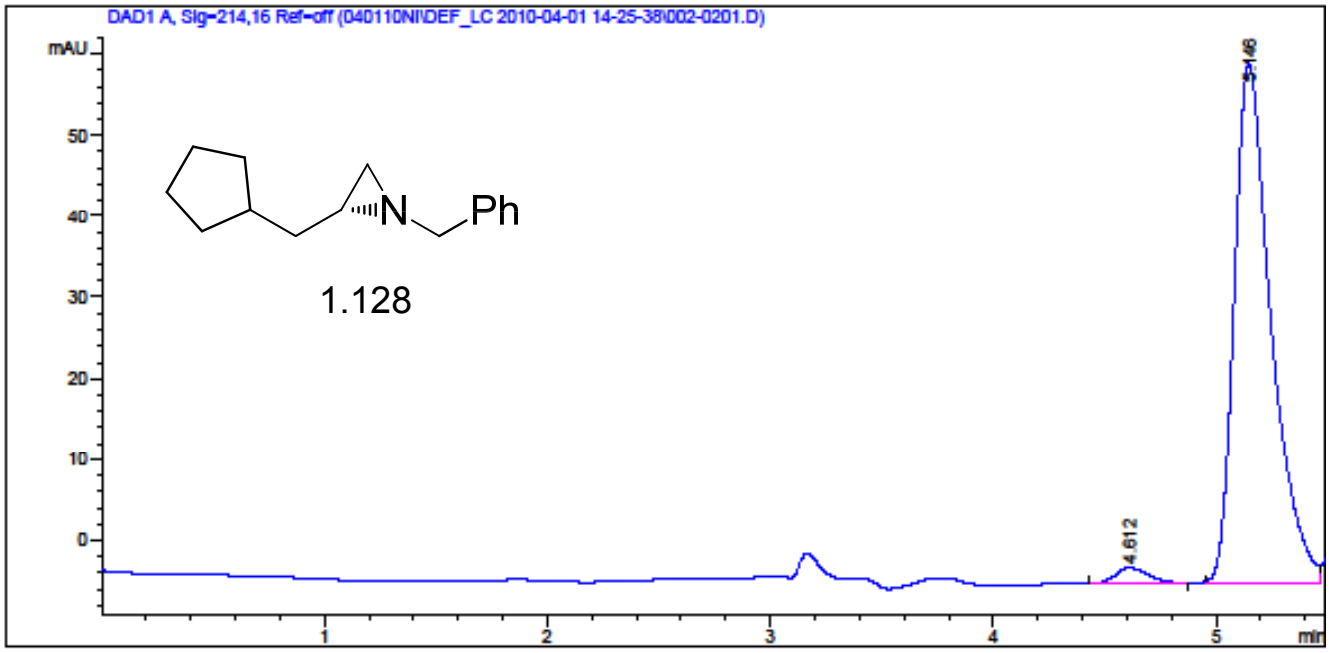
Totals :                   1.36739e4  1185.98541

==========================================================================
                          *** End of Report ***
```

Instrument 1 4/1/2010 2:45:07 PM

Data File C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-01 14-25-38\002-0201.D
Sample Name: MLS-32-ee

```
==========================================================================
                                                  Seq. Line :   2
Acq. Instrument : Instrument 1                     Location : Vial 2
Injection Date  : 4/1/2010 2:33:05 PM                  Inj :   1
                                                 Inj Volume : 5 µl
Acq. Method     : C:\Chem32\1\DATA\040110NI\DEF_LC 2010-04-01 14-25-38\OD_HEX_IPA.M
Last changed    : 4/1/2010 2:07:17 PM
Analysis Method : C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-01 14-25-38\002-0201.D\DA.M (OD_HEX_
                  IPA.M)
Last changed    : 4/1/2010 2:07:17 PM
Method Info     : OD 98% Hexane 2% IPA
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.612 BB    0.1561   18.78414    1.85609   2.5014
   2   5.146 BV    0.1693  732.14972   64.06304  97.4986

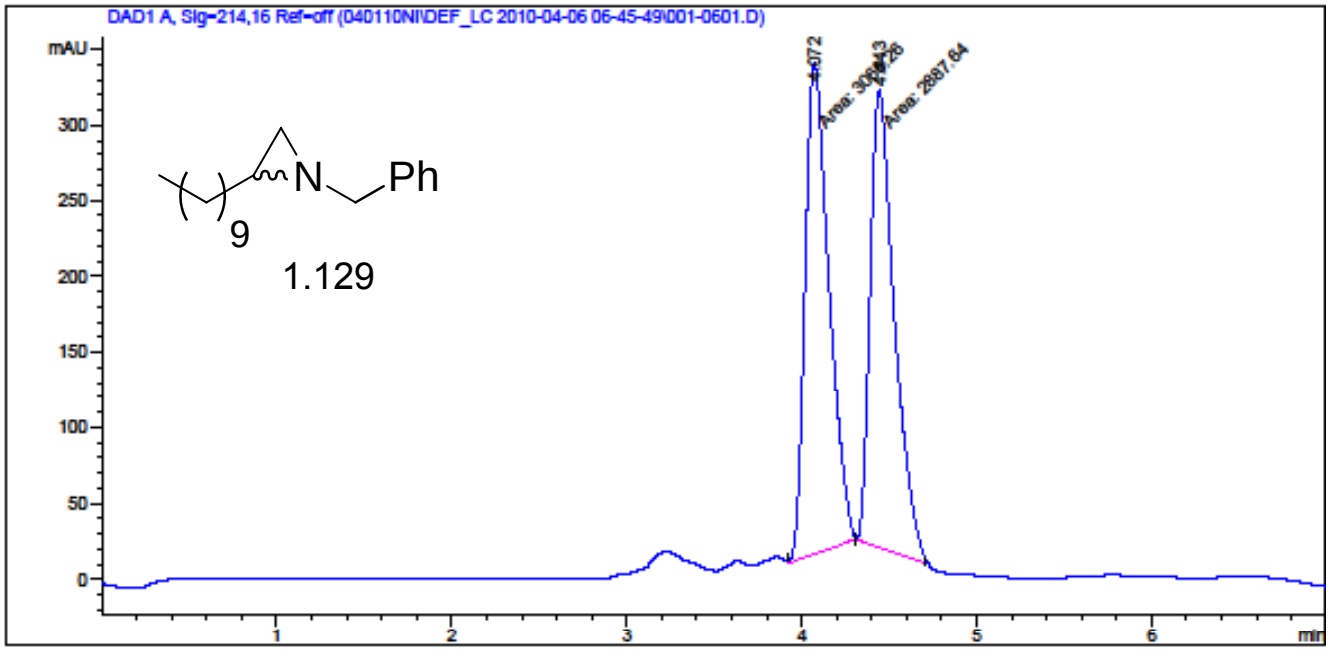
Totals :                   750.93386   65.91913


==========================================================================
                        *** End of Report ***
```

Instrument 1 4/1/2010 2:44:27 PM

Data File C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-06 06-45-49\001-0601.D
Sample Name: MLS-33-rac

```
==========================================================================
                                                  Seq. Line :   6
Acq. Instrument : Instrument 1                     Location : Vial 1
Injection Date  : 4/6/2010 9:32:14 AM                   Inj :   1
                                                 Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\040110NI\DEF_LC 2010-04-06 06-45-49\OD_HEX_IPA.M
Last changed    : 4/6/2010 9:39:53 AM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-06 06-45-49\001-0601.D\DA.M (OD_HEX_
                  IPA.M)
Last changed    : 4/2/2010 10:26:08 AM
Method Info     : OD 98% Hexane 2% IPA
```




```
==========================================================================
                        Area Percent Report
==========================================================================
```

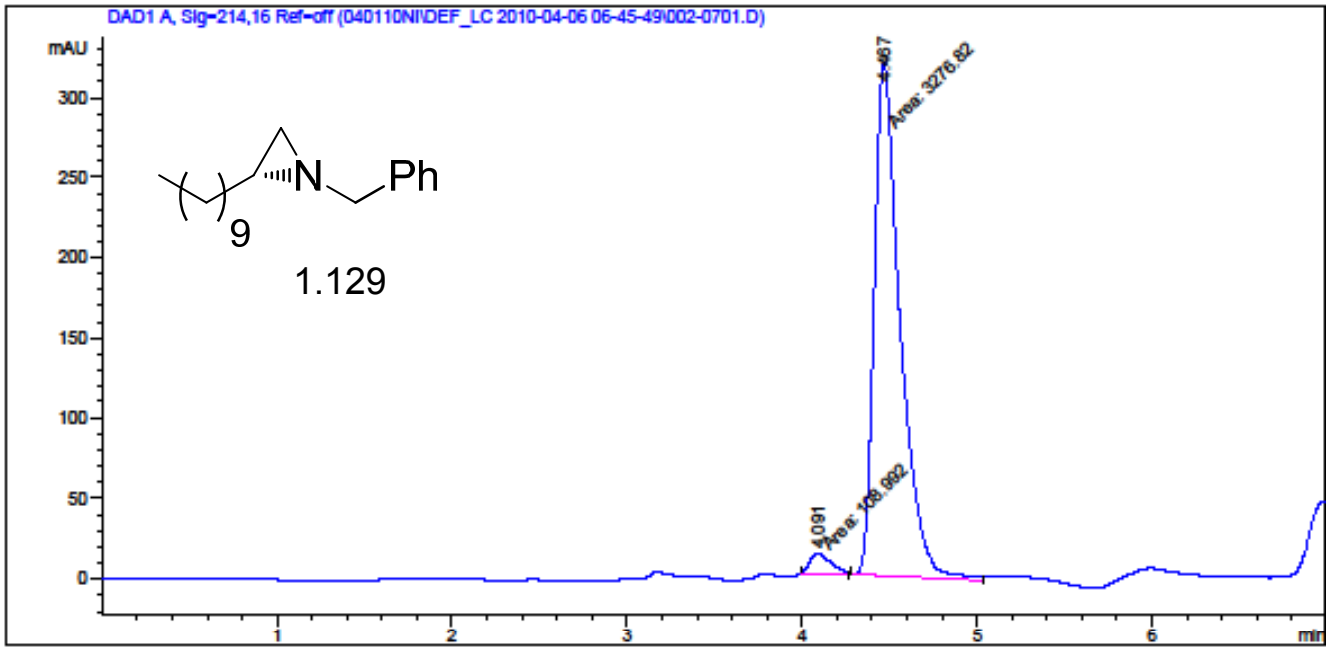
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.072	MM	0.1573	3066.26025	324.86465	51.5000
2	4.443	MM	0.1593	2887.64453	302.07690	48.5000
Totals :				5953.90479	626.94156	

```
==========================================================================
                        *** End of Report ***
```

Instrument 1 4/6/2010 9:59:48 AM

Data File C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-06 06-45-49\002-0701.D
Sample Name: MLS-33-ee

```
==========================================================================
                                                  Seq. Line :   7
Acq. Instrument : Instrument 1                     Location : Vial 2
Injection Date  : 4/6/2010 9:40:54 AM                  Inj :   1
                                                 Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\040110NI\DEF_LC 2010-04-06 06-45-49\OD_HEX_IPA.M
Last changed    : 4/6/2010 9:40:42 AM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\040110NI\DEF_LC 2010-04-06 06-45-49\002-0701.D\DA.M (OD_HEX_
                  IPA.M)
Last changed    : 4/2/2010 10:26:08 AM
Method Info     : OD 98% Hexane 2% IPA
```




```
==========================================================================
                        Area Percent Report
==========================================================================

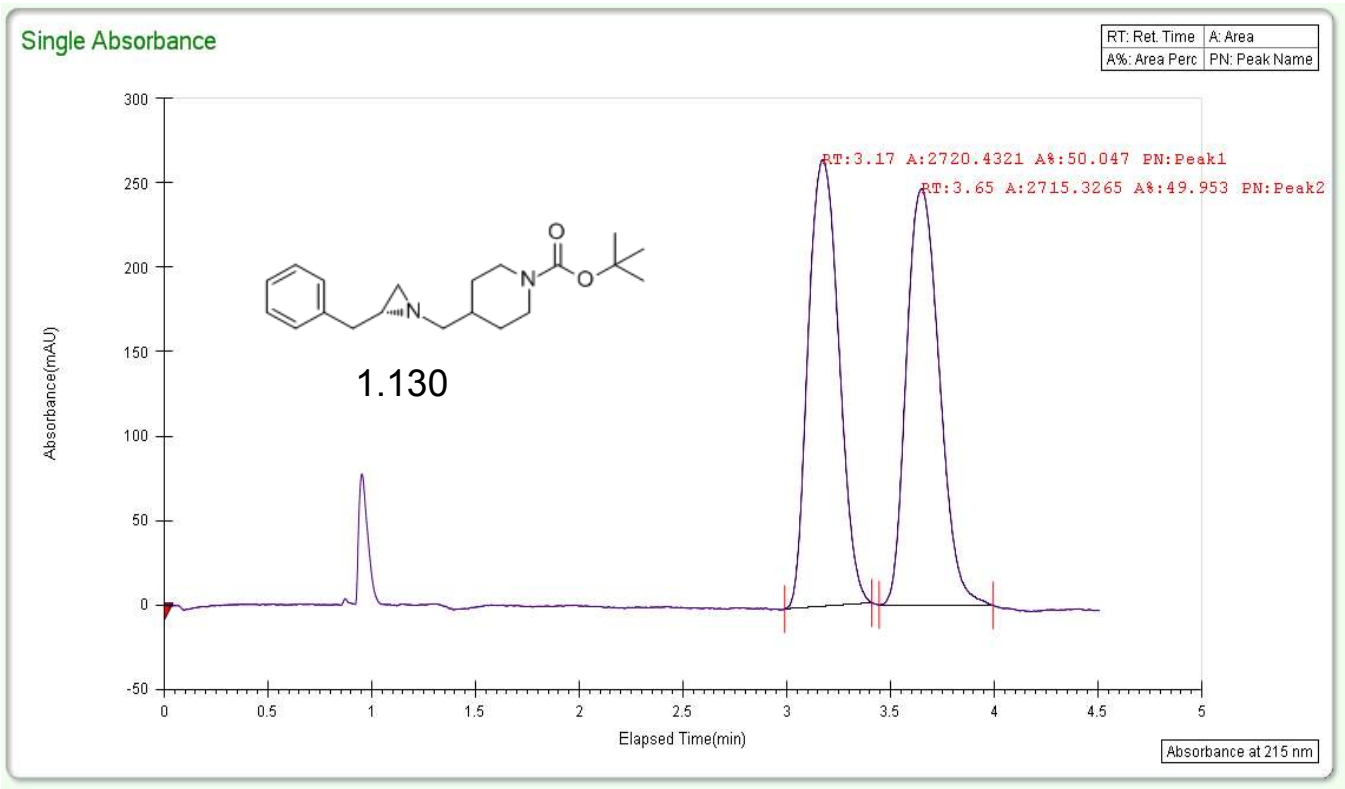
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.091 MM    0.1429  108.99228   12.71532   3.2191
   2   4.467 MM    0.1710 3276.81738  319.41690  96.7809

Totals :                   3385.80966  332.13222

==========================================================================
                        *** End of Report ***
```

Instrument 1 4/6/2010 10:01:50 AM

TharSFC



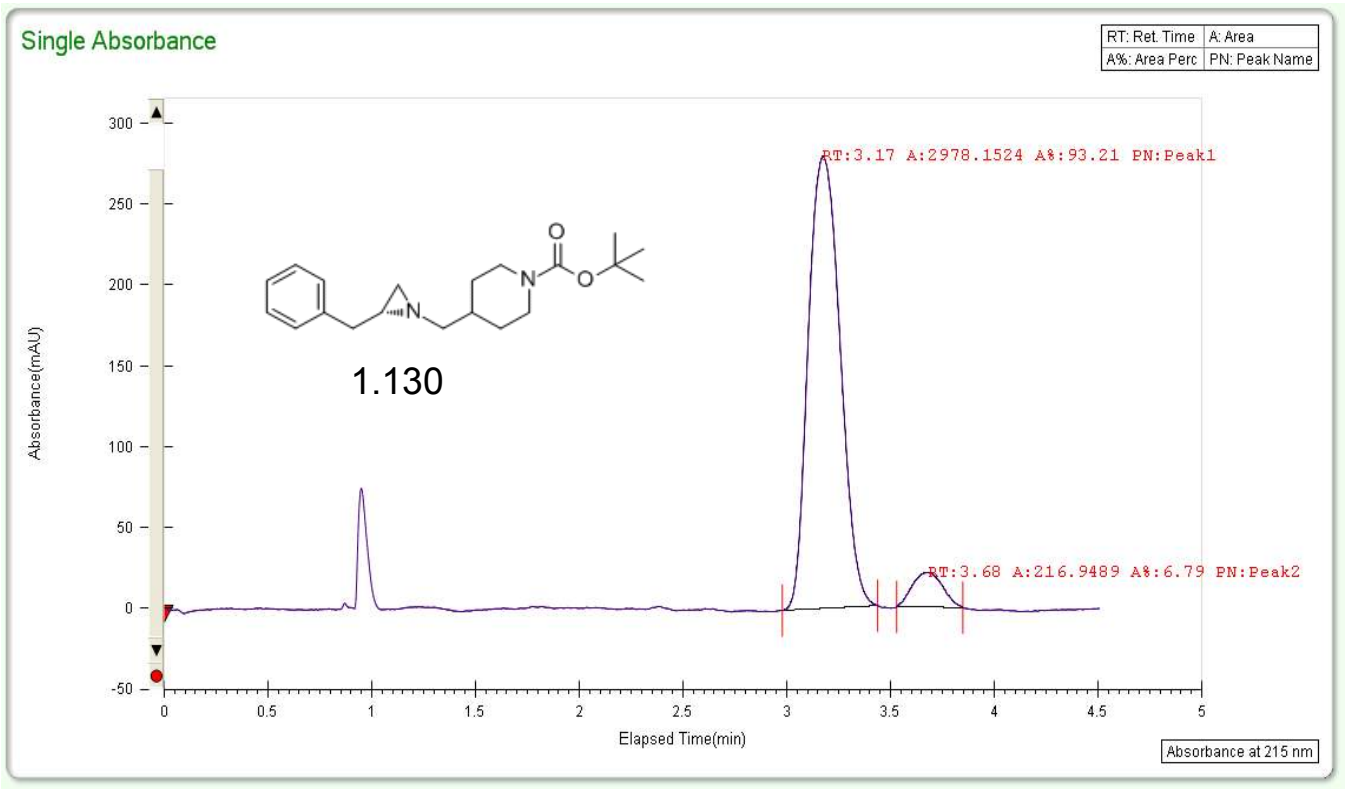
General Info		**Report Date**	4/13/2010
Log Author		**Method Name**	Chiral_screen.met
Log Date	4/13/2010 4:36:50 PM	**Notes**	
Report By	current_User		

Injection Info		**Temp**	27.6
Inj Vol	20	**Flow**	4
Solvent	IPA	**% Modifier**	5
Column	OJ	**Pressure**	100
Sample	MLS-4-rac		
Well location	P1: 1F		

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	50.047	2720.4321	3.17	264.5168	0.0032
2	49.953	2715.3265	3.65	246.8313	0.0037
Total:	100	5435.7586			

TharSFC



General Info		**Report Date**	4/13/2010
Log Author		**Method Name**	Chiral_screen.met
Log Date	4/13/2010 4:41:59 PM	**Notes**	
Report By	current_User		

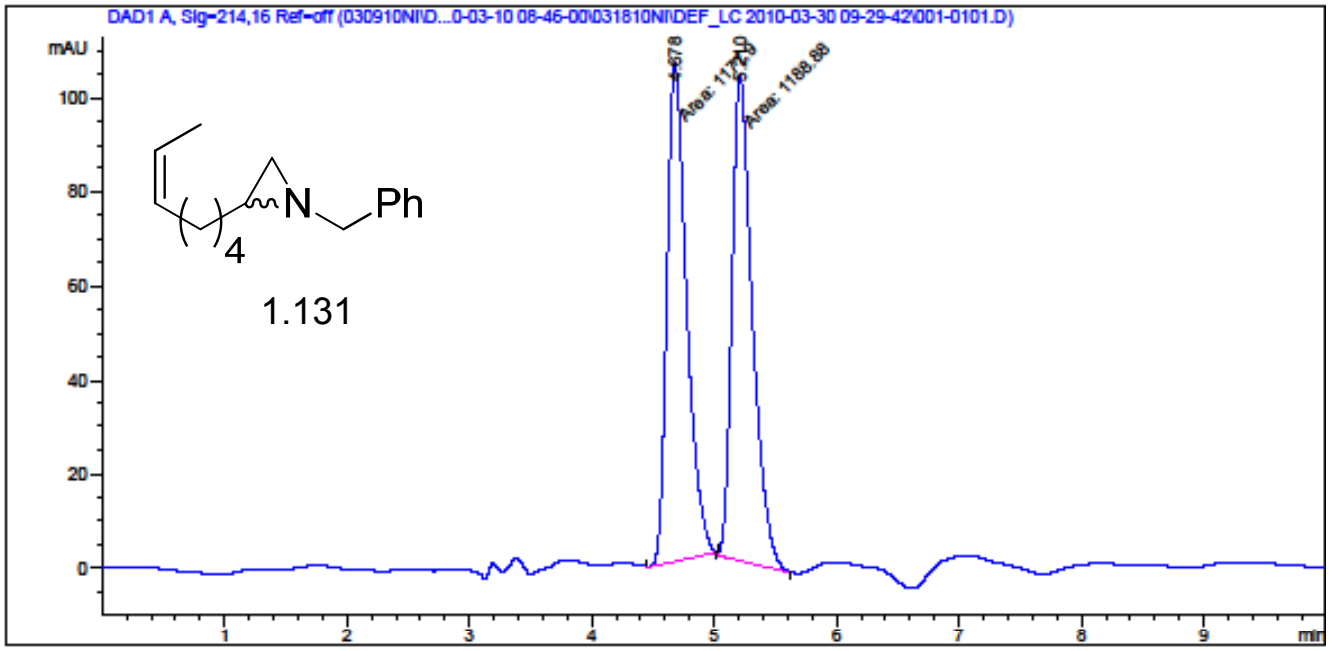
Injection Info		**Temp**	27.6
Inj Vol	20	**Flow**	4
Solvent	IPA	**% Modifier**	5
Column	OJ	**Pressure**	100
Sample	MLS-4-ee		
Well location	P1: 1E		

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	93.21	2978.1524	3.17	279.465	0.0032
2	6.79	216.9489	3.68	21.5036	0.0037
Total:	100	3195.1013			

Data File C:\CHEM32\... 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-30 09-29-42\001-0101.D
Sample Name: MLS-34

```
==========================================================================
                                                  Seq. Line :   1
Acq. Instrument : Instrument 1                     Location : Vial 1
Injection Date  : 3/30/2010 9:40:04 AM                  Inj :   1
                                                 Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 09-29-42\OD_10MINHEX_IPA.M
Last changed    : 3/5/2010 5:13:12 PM
Analysis Method : C:\CHEM32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 09-29-42\001-0101.D\DA.M (OD_10MINHEX_IPA.M)
Last changed    : 3/5/2010 5:13:12 PM
Method Info     : OD 98% Hexane 2% IPA
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.678 MM    0.1852 1177.90039  106.01453  49.7681
   2   5.210 MM    0.1918 1188.87695  103.33127  50.2319

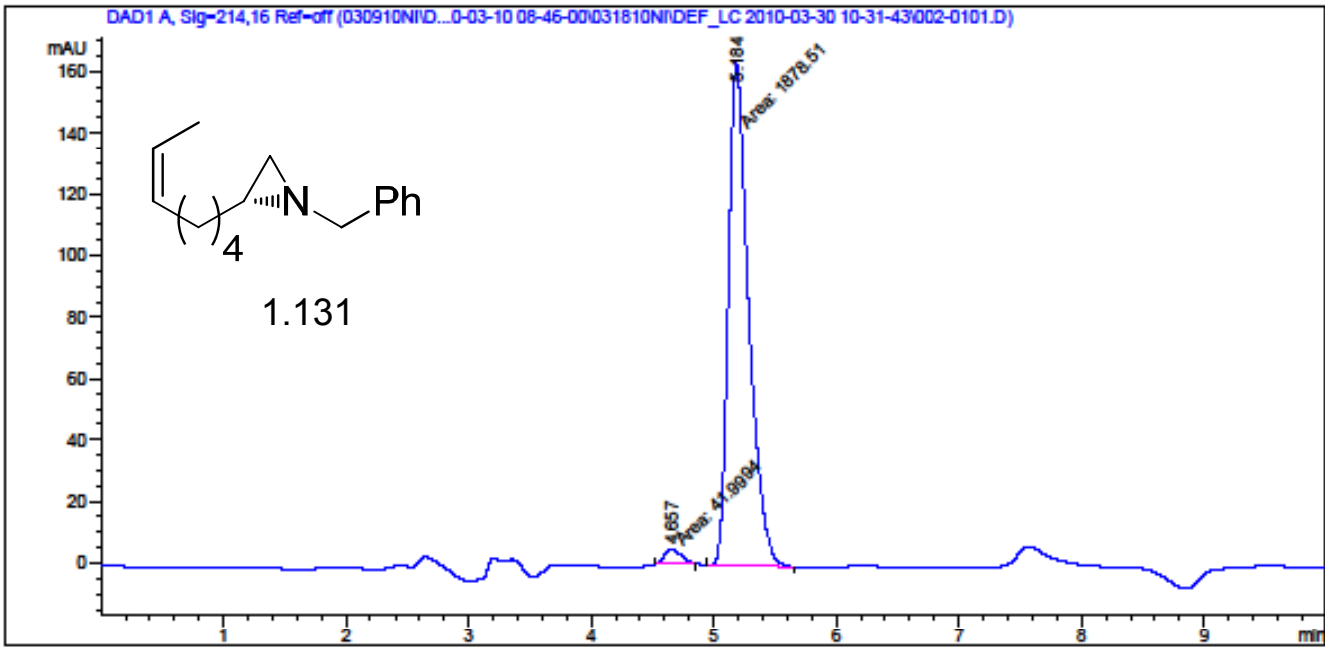
Totals :                  2366.77734  209.34579

==========================================================================
                        *** End of Report ***
```

Instrument 1 3/30/2010 3:22:16 PM

Data File C:\CHEM32\... 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-30 10-31-43\002-0101.D
Sample Name: MLS-34 ee

```
================================================================================
                                                    Seq. Line :   1
Acq. Instrument : Instrument 1                       Location : Vial 2
Injection Date  : 3/30/2010 10:32:03 AM                   Inj :   1
                                                   Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 10-31-43\OD_10MINHEX_IPA.M
Last changed    : 3/30/2010 10:31:52 AM
Analysis Method : C:\CHEM32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 10-31-43\002-0101.D\DA.M (OD_10MINHEX_IPA.M)
Last changed    : 3/5/2010 5:13:12 PM
Method Info     : OD 98% Hexane 2% IPA
```




```
================================================================================
                          Area Percent Report
================================================================================
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.657	MM	0.1608	41.99937	4.35433	2.1869
2	5.184	MM	0.1915	1878.50659	163.51439	97.8131

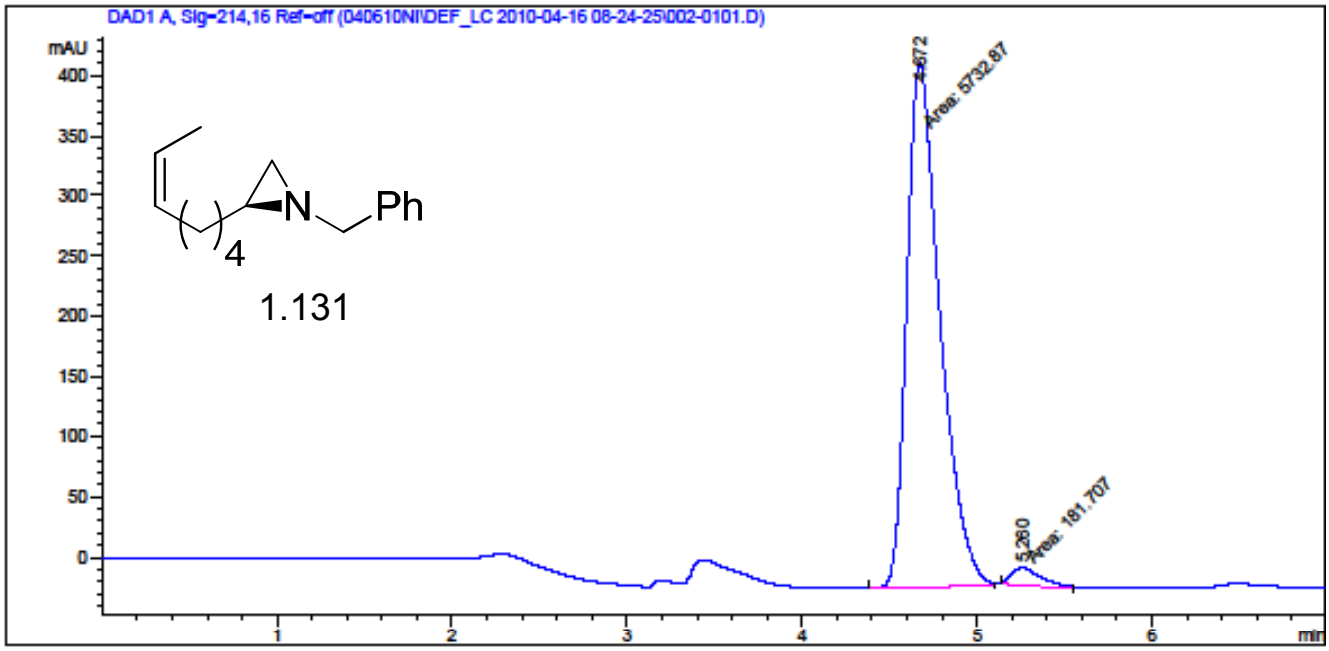
Totals : 1920.50596 167.86872

```
================================================================================
                          *** End of Report ***
```

Instrument 1 3/30/2010 3:24:33 PM

Data File C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-16 08-24-25\002-0101.D
Sample Name: 34 ee S

```
==========================================================================
                                                  Seq. Line :   1
Acq. Instrument : Instrument 1                     Location : Vial 2
Injection Date  : 4/16/2010 8:24:46 AM                Inj :   1
                                                 Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\040610NI\DEF_LC 2010-04-16 08-24-25\OD_10MINHEX_IPA.M
Last changed    : 4/16/2010 8:26:03 AM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-16 08-24-25\002-0101.D\DA.M (OD_
                  10MINHEX_IPA.M)
Last changed    : 3/5/2010 5:13:12 PM
Method Info     : OD 98% Hexane 2% IPA
```




```
==========================================================================
                        Area Percent Report
==========================================================================
```

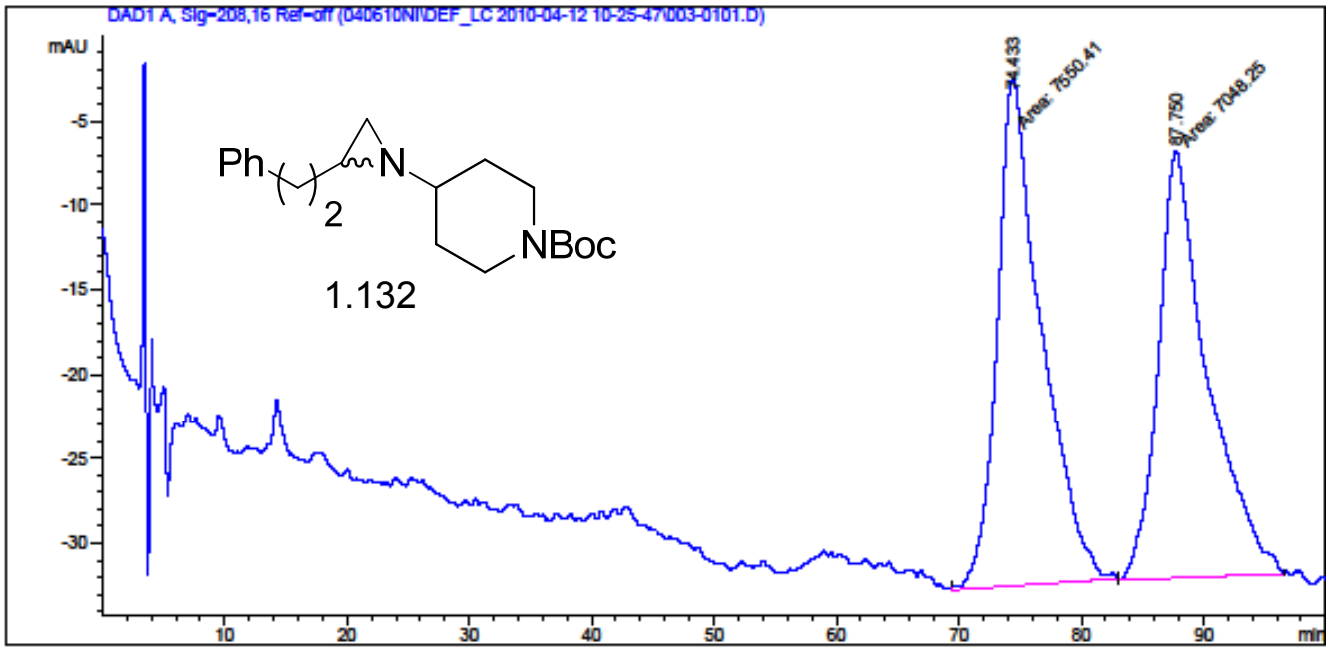
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.672	MM	0.2194	5732.87158	435.43277	96.9278
2	5.260	MM	0.2111	181.70663	14.34280	3.0722
Totals :				5914.57822	449.77557	

```
==========================================================================
                        *** End of Report ***
```

Instrument 1 4/16/2010 8:42:27 AM

Data File C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-12 10-25-47\003-0101.D
Sample Name: MLS-76-rac

```
==========================================================================
                                                Seq. Line :   1
Acq. Instrument : Instrument 1                   Location : Vial 3
Injection Date  : 4/12/2010 10:36:07 AM               Inj :   1
                                               Inj Volume : 40 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\040610NI\DEF_LC 2010-04-12 10-25-47\IA_AMM_ ACE.M
Last changed    : 4/10/2010 12:01:32 PM
Analysis Method : C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-12 10-25-47\003-0101.D\DA.M (IA_AMM_
                  ACE.M)
Last changed    : 4/10/2010 12:01:32 PM
Method Info     : IA 60:40 pH9 20 mM Aqueous Ammonium Bicarbonate/Acetonitrile
```




```
==========================================================================
                          Area Percent Report
==========================================================================
```

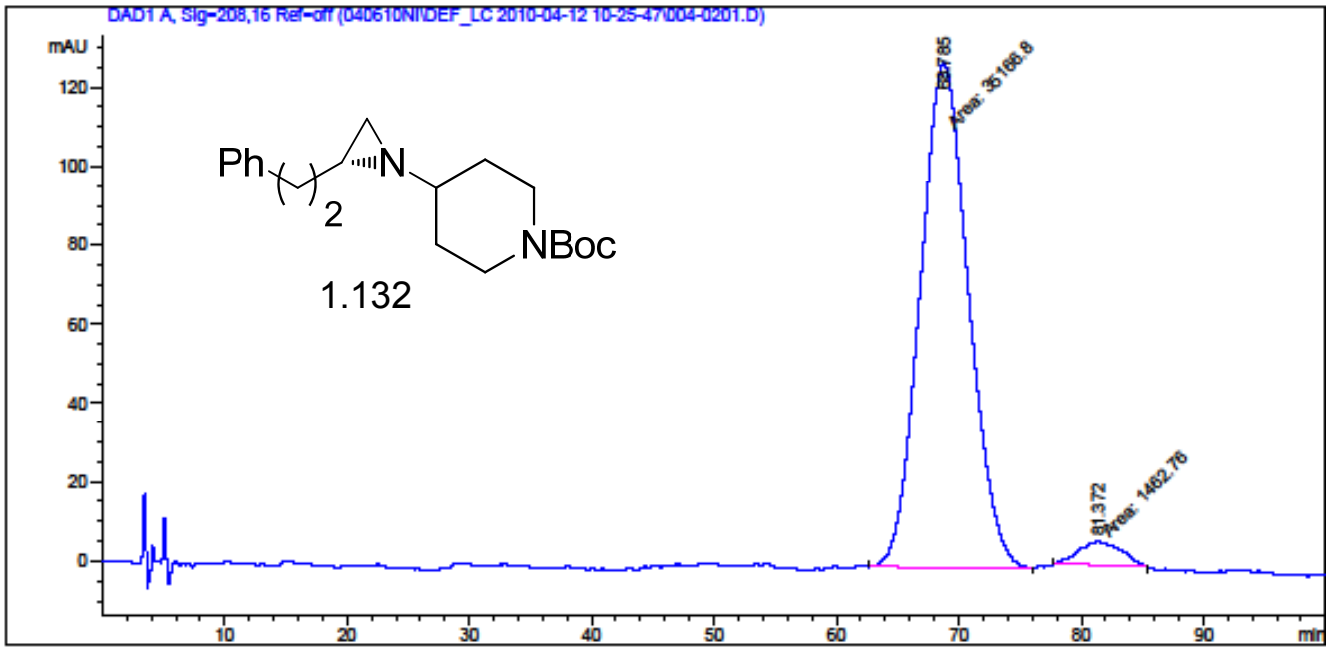
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	74.433	MM	4.1977	7550.41113	29.97870	51.7199
2	87.750	MM	4.6414	7048.24805	25.30929	48.2801
Totals :				1.45987e4	55.28799	

```
==========================================================================
                          *** End of Report ***
```

Instrument 1 4/12/2010 2:44:05 PM

Data File C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-12 10-25-47\004-0201.D
Sample Name: MLS-76-ree

```
==========================================================================
                                                Seq. Line :   2
Acq. Instrument : Instrument 1                   Location : Vial 4
Injection Date  : 4/12/2010 12:17:58 PM             Inj :   1
                                               Inj Volume : 40 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\040610NI\DEF_LC 2010-04-12 10-25-47\IA_AMM_ ACE.M
Last changed    : 4/10/2010 12:01:32 PM
Analysis Method : C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-12 10-25-47\004-0201.D\DA.M (IA_AMM_
                  ACE.M)
Last changed    : 4/10/2010 12:01:32 PM
Method Info     : IA 60:40 pH9 20 mM Aqueous Ammonium Bicarbonate/Acetonitrile
```




```
==========================================================================
                          Area Percent Report
==========================================================================
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	68.785	MM	4.5831	3.51668e4	127.88724	96.0066
2	81.372	MM	4.0738	1462.76306	5.98450	3.9934

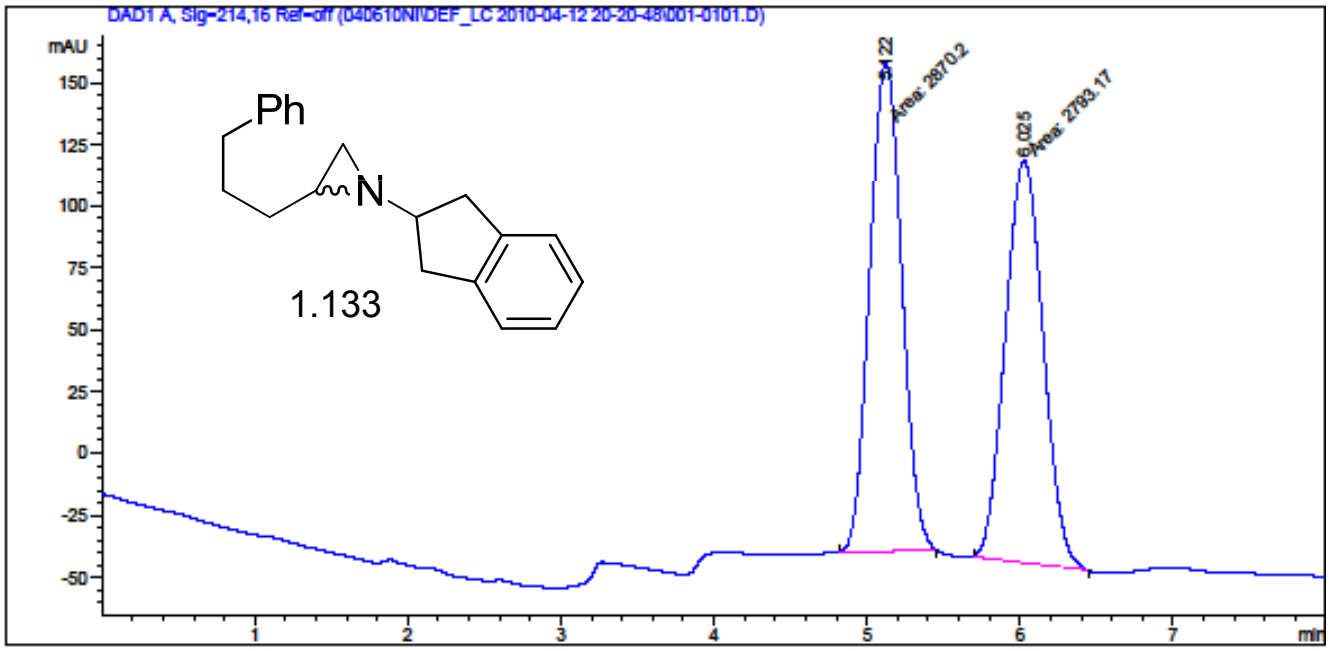
```
Totals :                  3.66296e4   133.87174

==========================================================================
                          *** End of Report ***
```

Instrument 1 4/12/2010 2:42:51 PM

Data File C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-12 20-20-48\001-0101.D
Sample Name: MLS-75-rac

```
==========================================================================
                                                  Seq. Line :   1
Acq. Instrument : Instrument 1                     Location : Vial 1
Injection Date  : 4/12/2010 8:21:10 PM                Inj :   1
                                                 Inj Volume : 5 µl
Acq. Method     : C:\Chem32\1\DATA\040610NI\DEF_LC 2010-04-12 20-20-48\OD_CL_HEX_IPA.M
Last changed    : 4/12/2010 8:28:57 PM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-12 20-20-48\001-0101.D\DA.M (OD_CL_
                  HEX_IPA.M)
Last changed    : 4/12/2010 8:20:44 PM
Method Info     : OD-Cl (Cellulose-2) 96% Hexane 4% Ethanol
```




```
==========================================================================
                        Area Percent Report
==========================================================================
```

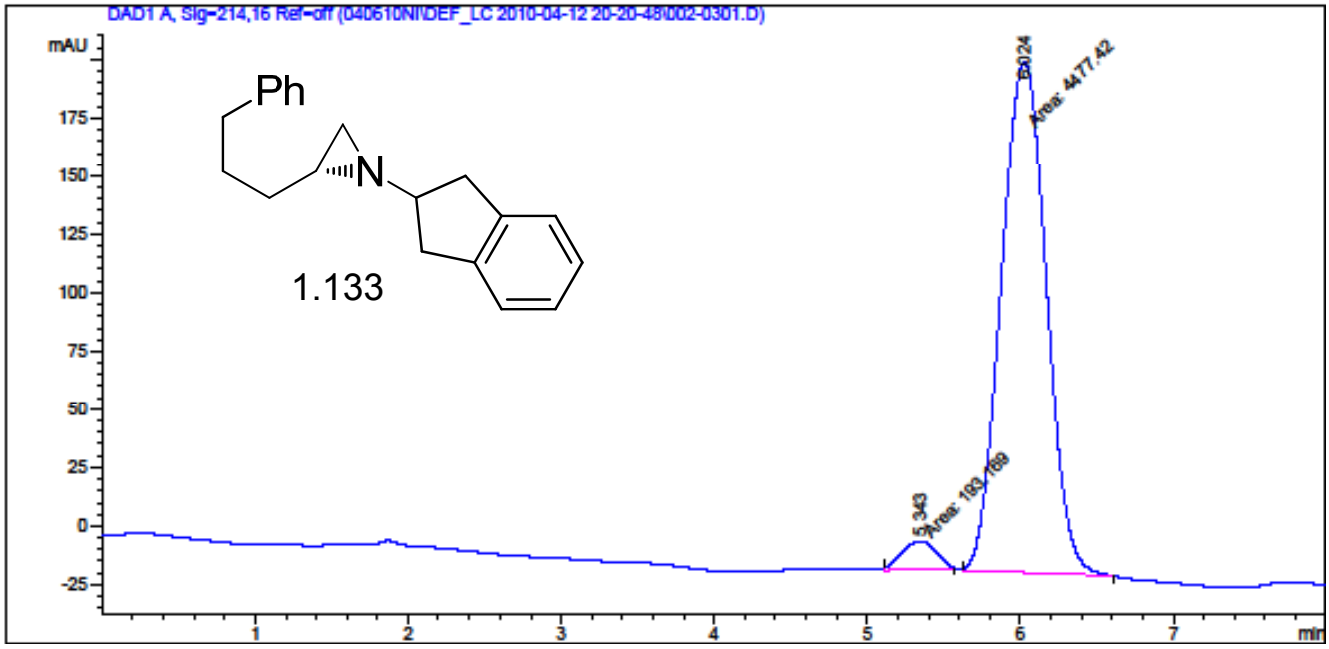
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.122	MM	0.2422	2870.20239	197.47920	50.6801
2	6.025	MM	0.2862	2793.16650	162.68050	49.3199
Totals :				5663.36890	360.15970	

```
==========================================================================
                        *** End of Report ***
```

Instrument 1 4/13/2010 6:34:20 AM

Data File C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-12 20-20-48\002-0301.D
Sample Name: MLS-75-ee

```
==========================================================================
                                                  Seq. Line :   3
Acq. Instrument : Instrument 1                     Location : Vial 2
Injection Date  : 4/12/2010 8:40:16 PM                Inj :   1
                                                  Inj Volume : 5 µl
Acq. Method     : C:\Chem32\1\DATA\040610NI\DEF_LC 2010-04-12 20-20-48\OD_CL_HEX_IPA.M
Last changed    : 4/12/2010 8:40:04 PM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-12 20-20-48\002-0301.D\DA.M (OD_CL_
                  HEX_IPA.M)
Last changed    : 4/12/2010 8:20:44 PM
Method Info     : OD-Cl (Cellulose-2) 96% Hexane 4% Ethanol
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.343 MM    0.2623  193.16943   12.27471   4.1359
   2   6.024 MM    0.3408 4477.41650  218.96121  95.8641

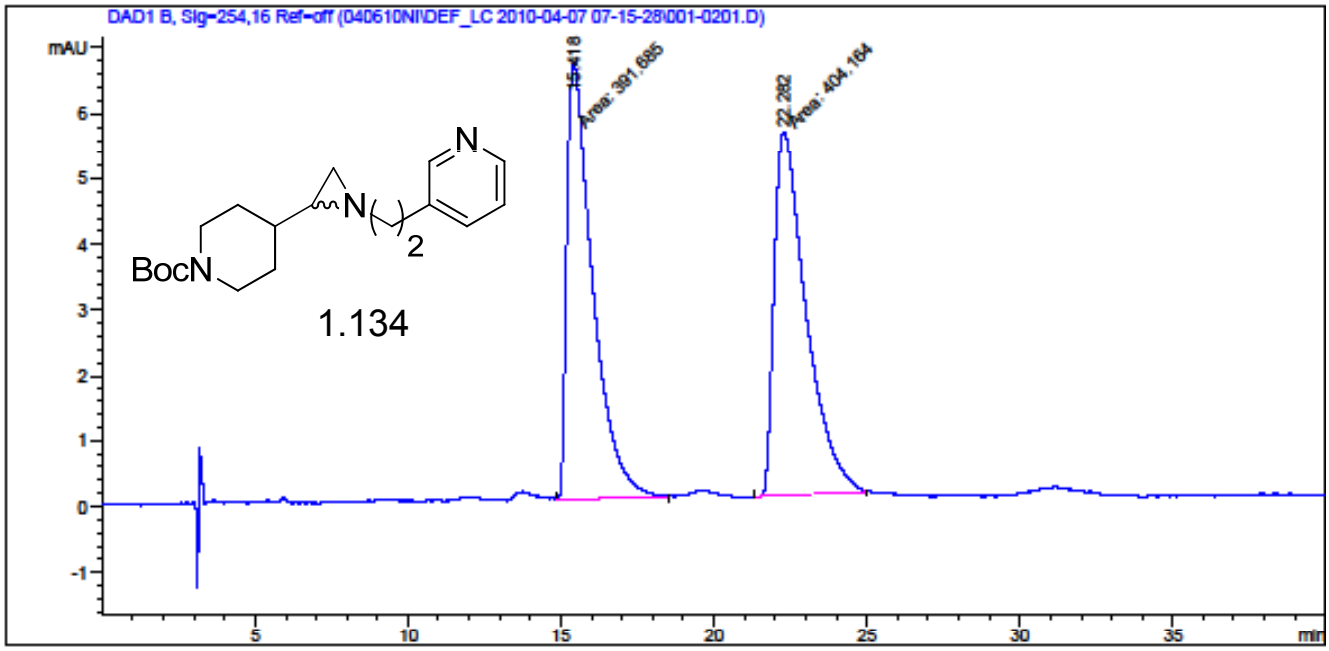
Totals :                   4670.58594  231.23592

==========================================================================
                          *** End of Report ***
```

Instrument 1 4/13/2010 6:35:38 AM

Data File C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-07 07-15-28\001-0201.D
Sample Name: Boc-py-rac

```
==========================================================================
                                                  Seq. Line :   2
Acq. Instrument : Instrument 1                     Location : Vial 1
Injection Date  : 4/7/2010 8:04:38 AM                   Inj :   1
                                                 Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\040610NI\DEF_LC 2010-04-07 07-15-28\OD_95HEX_IPA.M
Last changed    : 4/7/2010 8:43:26 AM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-07 07-15-28\001-0201.D\DA.M (OD_
                  95HEX_IPA.M)
Last changed    : 4/6/2010 6:55:22 PM
```




```
==========================================================================
                        Area Percent Report
==========================================================================
```

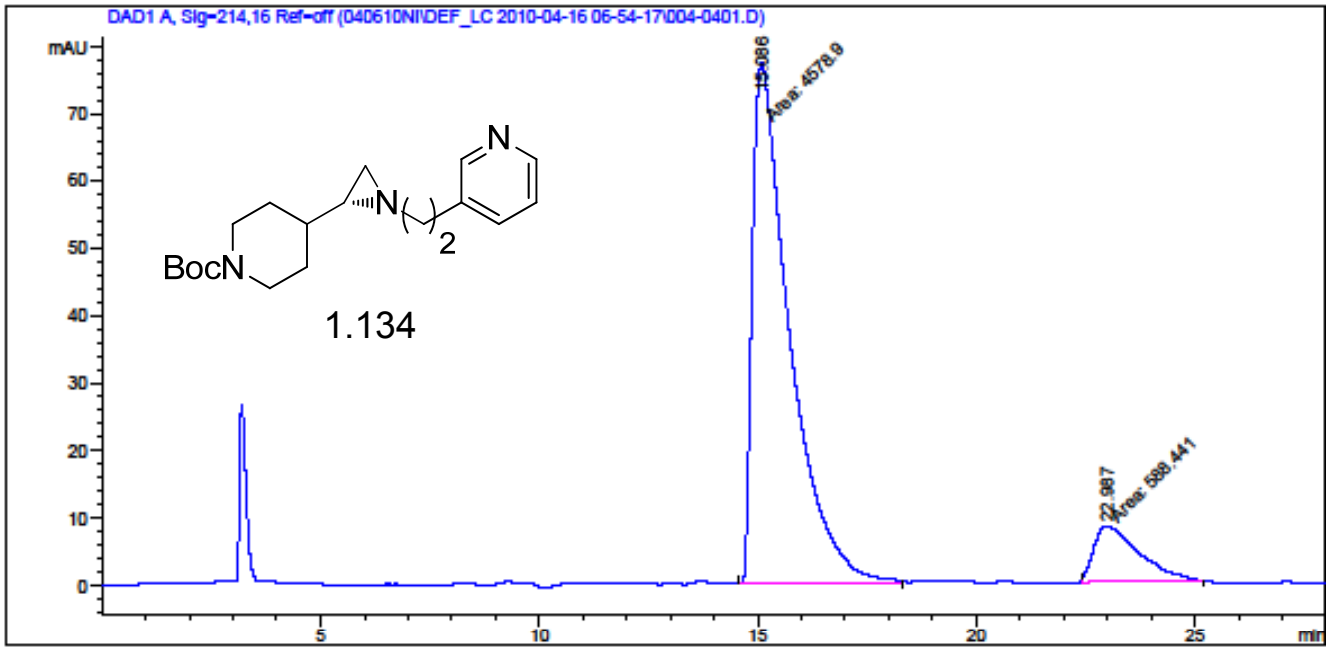
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.418	MM	0.9800	391.68451	6.66151	49.2160
2	22.282	MM	1.2128	404.16354	5.55396	50.7840
Totals :				795.84805	12.21546	

```
==========================================================================
                        *** End of Report ***
```

Instrument 1 4/7/2010 2:10:33 PM

Data File C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-16 06-54-17\004-0401.D
Sample Name: Boc-Py ee R

```
==========================================================================
                                                  Seq. Line :   4
Acq. Instrument : Instrument 1                     Location : Vial 4
Injection Date  : 4/16/2010 7:47:59 AM                Inj :   1
                                                  Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\040610NI\DEF_LC 2010-04-16 06-54-17\OD_95HEX_IPA.M
Last changed    : 4/16/2010 7:47:47 AM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-16 06-54-17\004-0401.D\DA.M (OD_
                  95HEX_IPA.M)
Last changed    : 4/14/2010 6:54:14 PM
```

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==========================================================================
                        Area Percent Report
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```

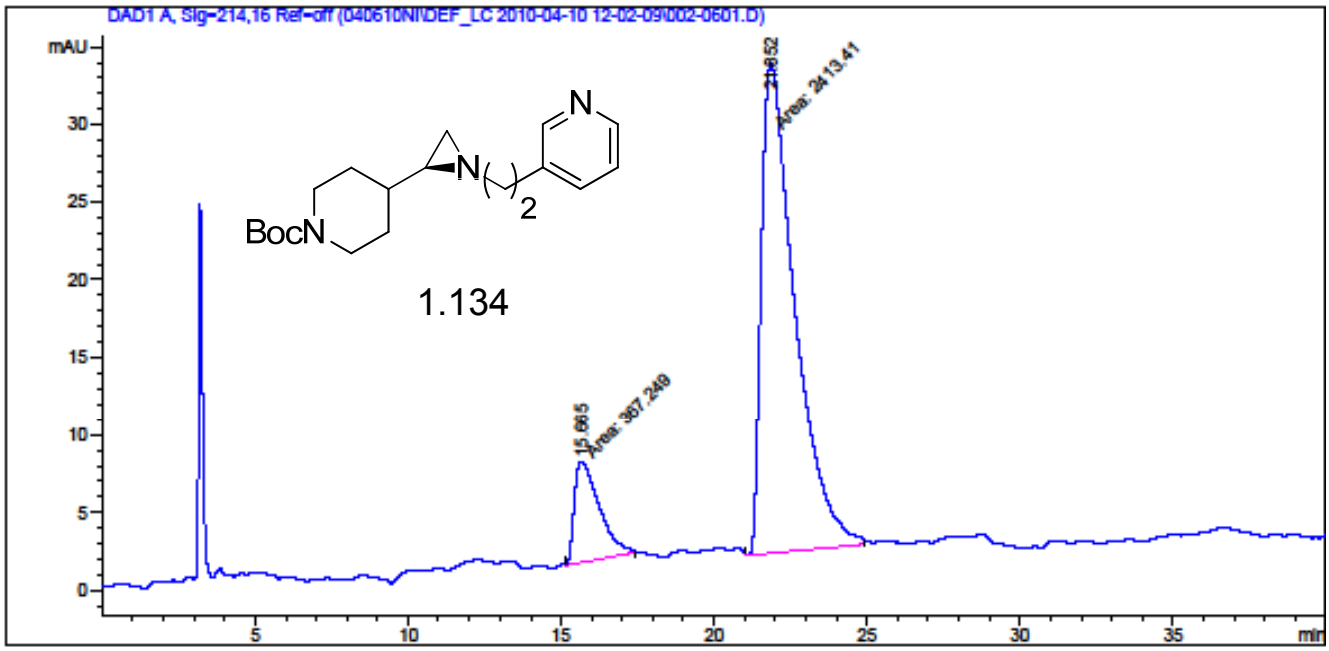
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.086	MM	0.9901	4578.90039	77.08043	88.6123
2	22.987	MM	1.1875	588.44055	8.25878	11.3877
Totals :				5167.34094	85.33921	

```
==========================================================================
                        *** End of Report ***
```

Instrument 1 4/16/2010 8:20:22 AM

Data File C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-10 12-02-09\002-0601.D
Sample Name: Boc-py-ee

```
================================================================================
                                                    Seq. Line :   6
Acq. Instrument : Instrument 1                       Location : Vial 2
Injection Date  : 4/10/2010 3:41:12 PM                    Inj :   1
                                                   Inj Volume : 5 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\040610NI\DEF_LC 2010-04-10 12-02-09\OD_95HEX_IPA.M
Last changed    : 4/10/2010 12:02:02 PM
Analysis Method : C:\CHEM32\1\DATA\040610NI\DEF_LC 2010-04-10 12-02-09\002-0601.D\DA.M (OD_
                  95HEX_IPA.M)
Last changed    : 4/10/2010 12:02:02 PM
```

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================================================================================
                          Area Percent Report
================================================================================

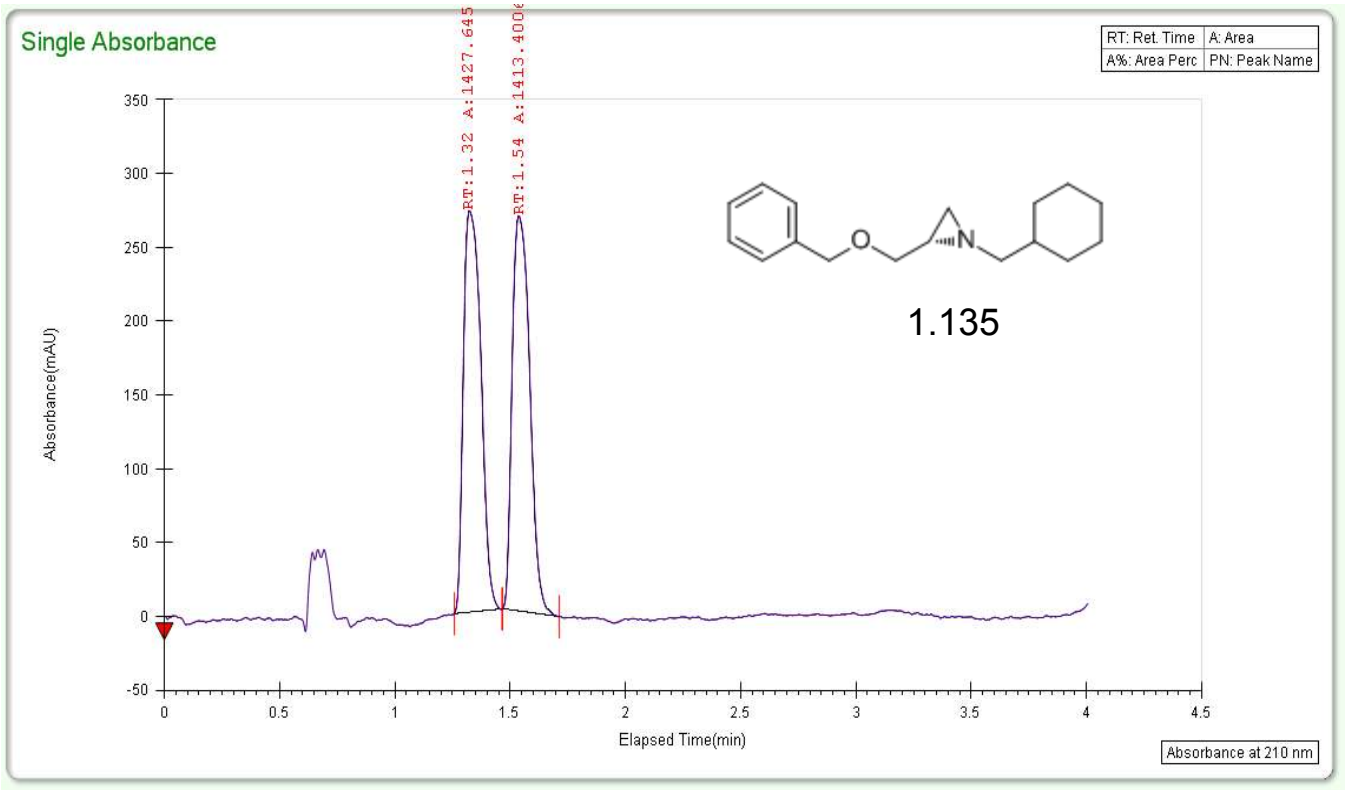
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.665 MM    0.9440  367.24945    6.48377  13.2073
   2  21.852 MM    1.2744 2413.40796   31.56180  86.7927

Totals :                  2780.65741   38.04557

================================================================================
                          *** End of Report ***
```

Instrument 1 4/16/2010 8:23:41 AM

TharSFC



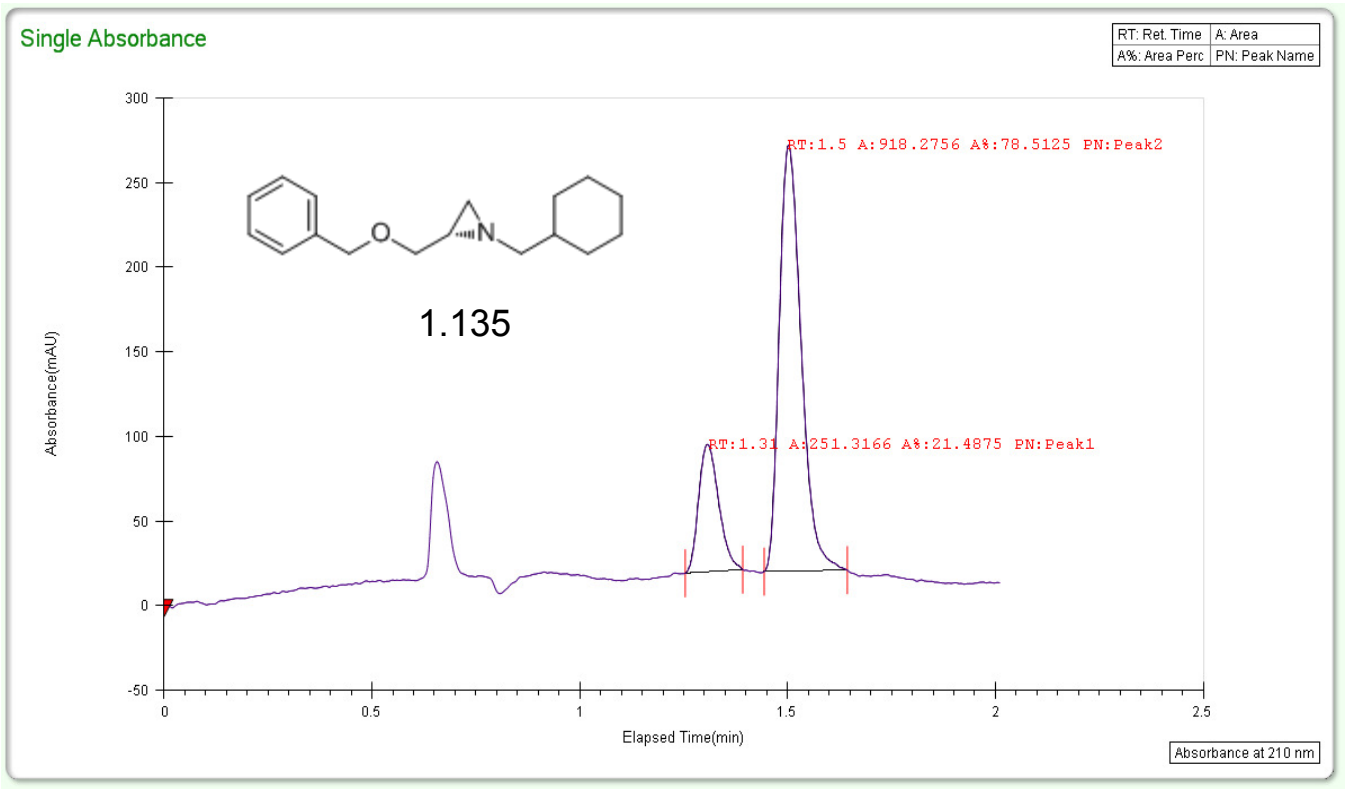
General Info		**Report Date**	4/9/2010
Log Author		**Method Name**	Chiral_screen.met
Log Date	4/9/2010 12:22:55 PM	**Notes**	
Report By	current_User		

Injection Info		**Temp**	39.7
Inj Vol	30	**Flow**	3.5
Solvent	IPA	**% Modifier**	15
Column	Column 3	**Pressure**	100
Sample	Unknown Sample		
Well location	P1: 1D		

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	50.2507	1427.645	1.32	271.9814	0.0018
2	49.7493	1413.4006	1.54	267.6807	0.0021
Total:	100	2841.0456			

TharSFC



General Info		**Report Date**	4/20/2010
Log Author		**Method Name**	Chiral_screen.met
Log Date	4/20/2010 3:00:34 PM	**Notes**	
Report By	current_User		

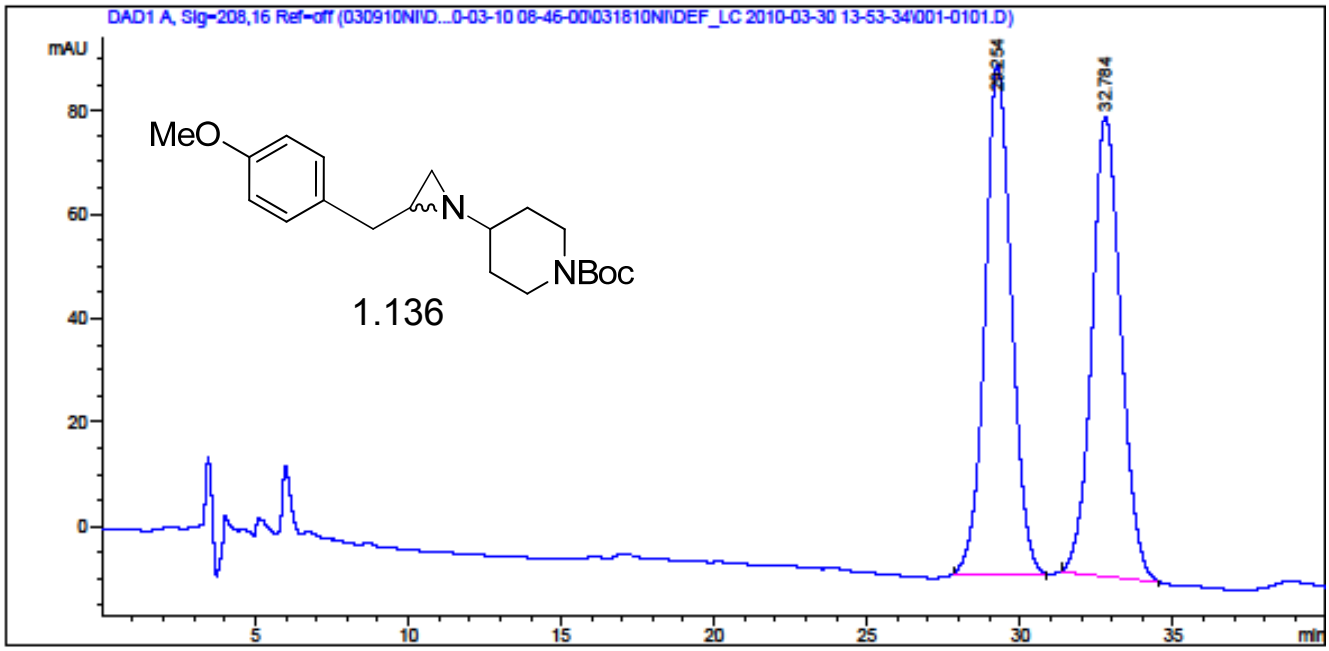
Injection Info		**Temp**	40
Inj Vol	10	**Flow**	3.5
Solvent	IPA	**% Modifier**	15
Column	IA	**Pressure**	100
Sample	Cyclo BnO ee		
Well location	P1: 1D		

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	21.4875	251.3166	1.31	75.3488	0.0015
2	78.5125	918.2756	1.5	251.7117	0.0017
Total:	100	1169.5922			

Data File C:\CHEM32\... 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-30 13-53-34\001-0101.D
Sample Name: ML873

```
==========================================================================
                                                  Seq. Line :   1
Acq. Instrument : Instrument 1                     Location : Vial 1
Injection Date  : 3/30/2010 1:54:02 PM                  Inj :   1
                                                 Inj Volume : 40 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 13-53-34\IA_AMM_ ACE.M
Last changed    : 3/30/2010 2:31:11 PM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 13-53-34\001-0101.D\DA.M (IA_AMM_ ACE.M)
Last changed    : 3/10/2010 8:45:56 AM
Method Info     : IA 60:40 pH9 20 mM Aqueous Ammonium Bicarbonate/Acetonitrile
```

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==========================================================================
                        Area Percent Report
==========================================================================
```

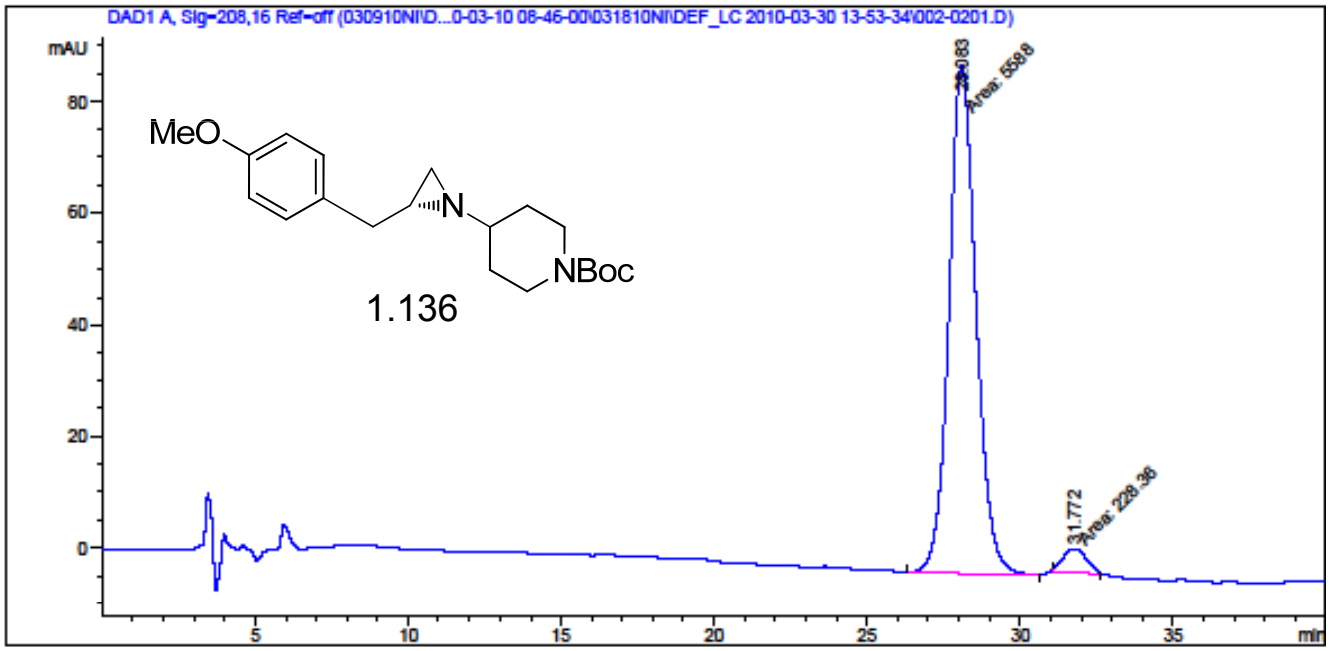
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.254	BB	0.9064	5897.01660	97.94271	50.2114
2	32.784	BB	0.9847	5847.36914	88.51182	49.7886
Totals :				1.17444e4	186.45453	

```
==========================================================================
                        *** End of Report ***
```

Instrument 1 3/30/2010 3:20:43 PM

Data File C:\CHEM32\... 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-30 13-53-34\002-0201.D
Sample Name: MLS-73 ee

```
================================================================================
                                                    Seq. Line :   2
Acq. Instrument : Instrument 1                       Location : Vial 2
Injection Date  : 3/30/2010 2:35:46 PM                    Inj :   1
                                                   Inj Volume : 40 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 13-53-34\IA_AMM_ ACE.M
Last changed    : 3/30/2010 2:35:34 PM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 13-53-34\002-0201.D\DA.M (IA_AMM_ ACE.M)
Last changed    : 3/10/2010 8:45:56 AM
Method Info     : IA 60:40 pH9 20 mM Aqueous Ammonium Bicarbonate/Acetonitrile
```




```
================================================================================
                          Area Percent Report
================================================================================
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.083	MM	1.0219	5587.99707	91.13508	96.0738
2	31.772	MM	0.8824	228.35956	4.31311	3.9262
Totals :				5816.35663	95.44819	

```
================================================================================
                          *** End of Report ***
```

Instrument 1 3/30/2010 3:19:51 PM

Data File C:\CHEM32\... 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-30 13-53-34\003-0301.D
Sample Name: MLS-71

```
==========================================================================
                                                  Seq. Line :   3
Acq. Instrument : Instrument 1                     Location : Vial 3
Injection Date  : 3/30/2010 3:17:25 PM                 Inj :   1
                                                 Inj Volume : 40 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 13-53-34\IA_AMM_ ACE.M
Last changed    : 3/30/2010 4:26:56 PM
                  (modified after loading)
Analysis Method : C:\CHEM32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  30 13-53-34\003-0301.D\DA.M (IA_AMM_ ACE.M)
Last changed    : 3/10/2010 8:45:56 AM
Method Info     : IA 60:40 pH9 20 mM Aqueous Ammonium Bicarbonate/Acetonitrile
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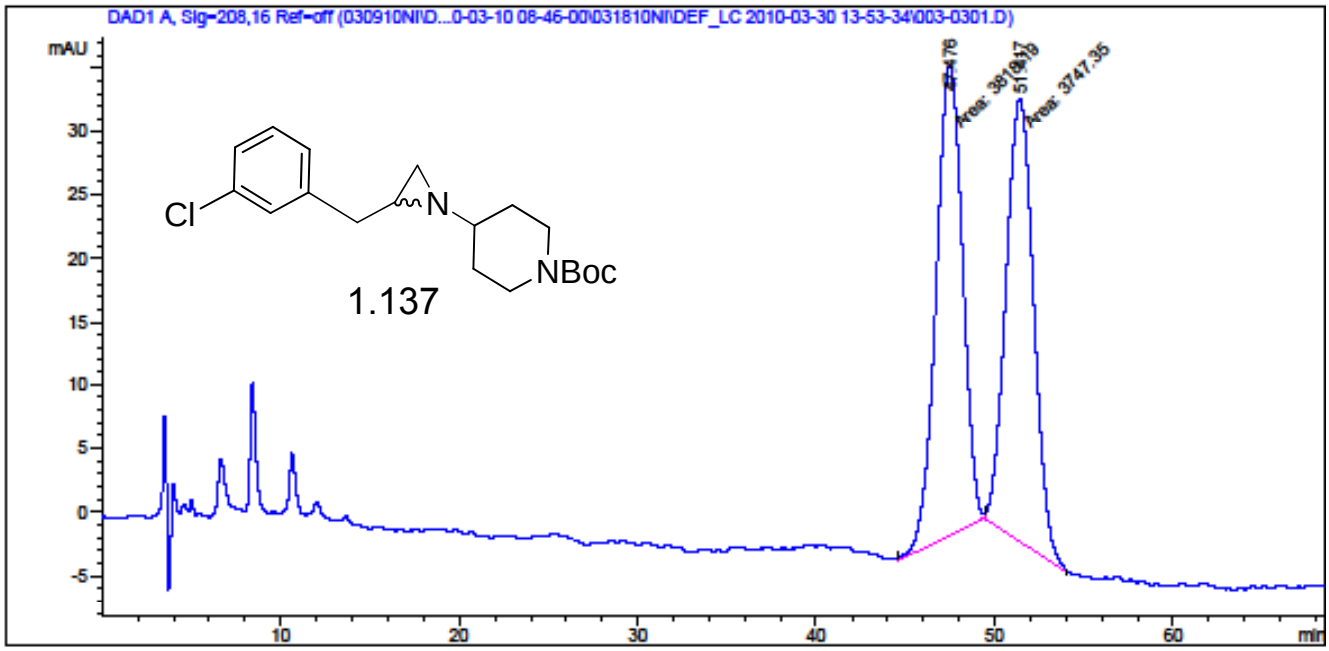


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==========================================================================
                          Area Percent Report
==========================================================================
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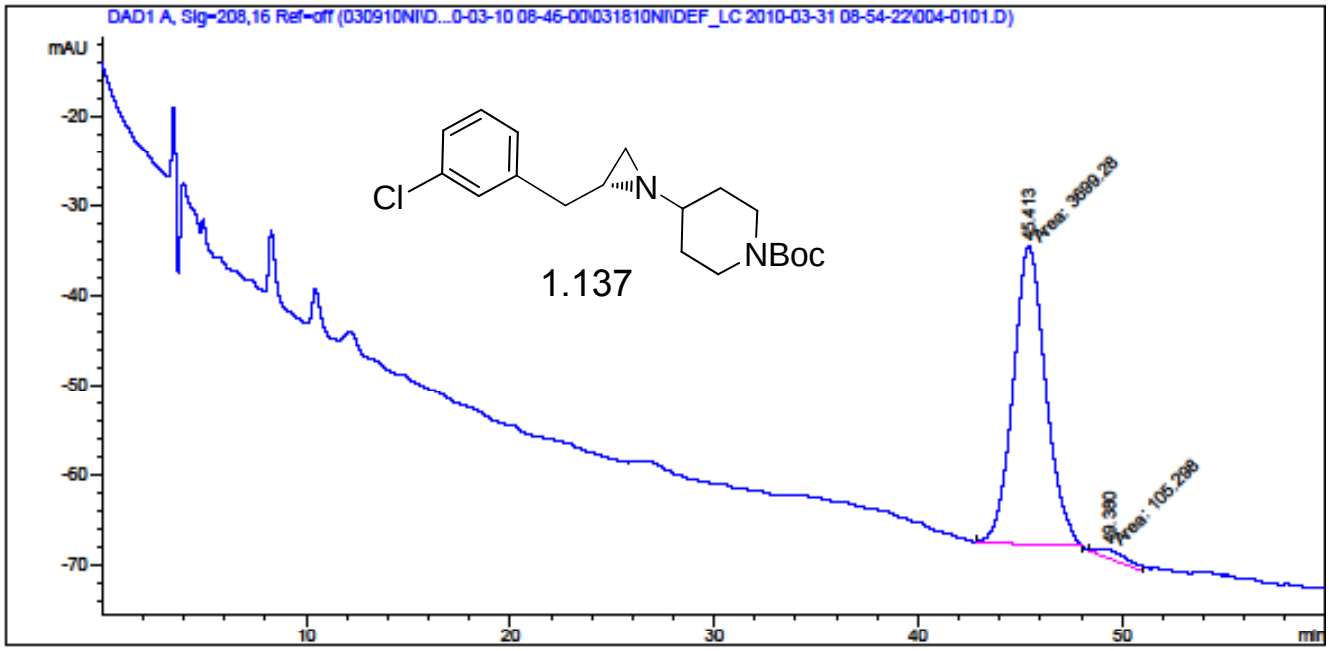
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.476	MM	1.7160	3818.18506	37.08428	50.4681
2	51.417	MM	1.7927	3747.35400	34.83973	49.5319
Totals :				7565.53906	71.92402	

```
==========================================================================
                          *** End of Report ***
```

Instrument 1 3/31/2010 12:33:13 PM

Data File C:\CHEM32\... 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-31 08-54-22\004-0101.D
Sample Name: MLS-71 ee

```
==========================================================================
                                                Seq. Line :   1
Acq. Instrument : Instrument 1                   Location : Vial 4
Injection Date  : 3/31/2010 8:54:44 AM                Inj :   1
                                               Inj Volume : 40 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\Chem32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  31 08-54-22\IA_AMM_ ACE.M
Last changed    : 3/10/2010 8:45:56 AM
Analysis Method : C:\CHEM32\1\DATA\030910NI\DEF_LC 2010-03-10 08-46-00\031810NI\DEF_LC 2010-03-
                  31 08-54-22\004-0101.D\DA.M (IA_AMM_ ACE.M)
Last changed    : 3/10/2010 8:45:56 AM
Method Info     : IA 60:40 pH9 20 mM Aqueous Ammonium Bicarbonate/Acetonitrile
```




```
==========================================================================
                          Area Percent Report
==========================================================================
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Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.413	MM	1.8599	3699.28394	33.14989	97.2323
2	49.380	MM	1.7298	105.29849	1.01454	2.7677
Totals :				3804.58243	34.16443	

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                          *** End of Report ***
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Instrument 1 3/31/2010 12:35:59 PM

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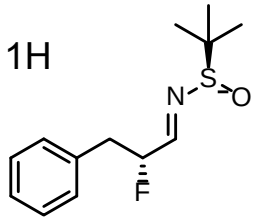

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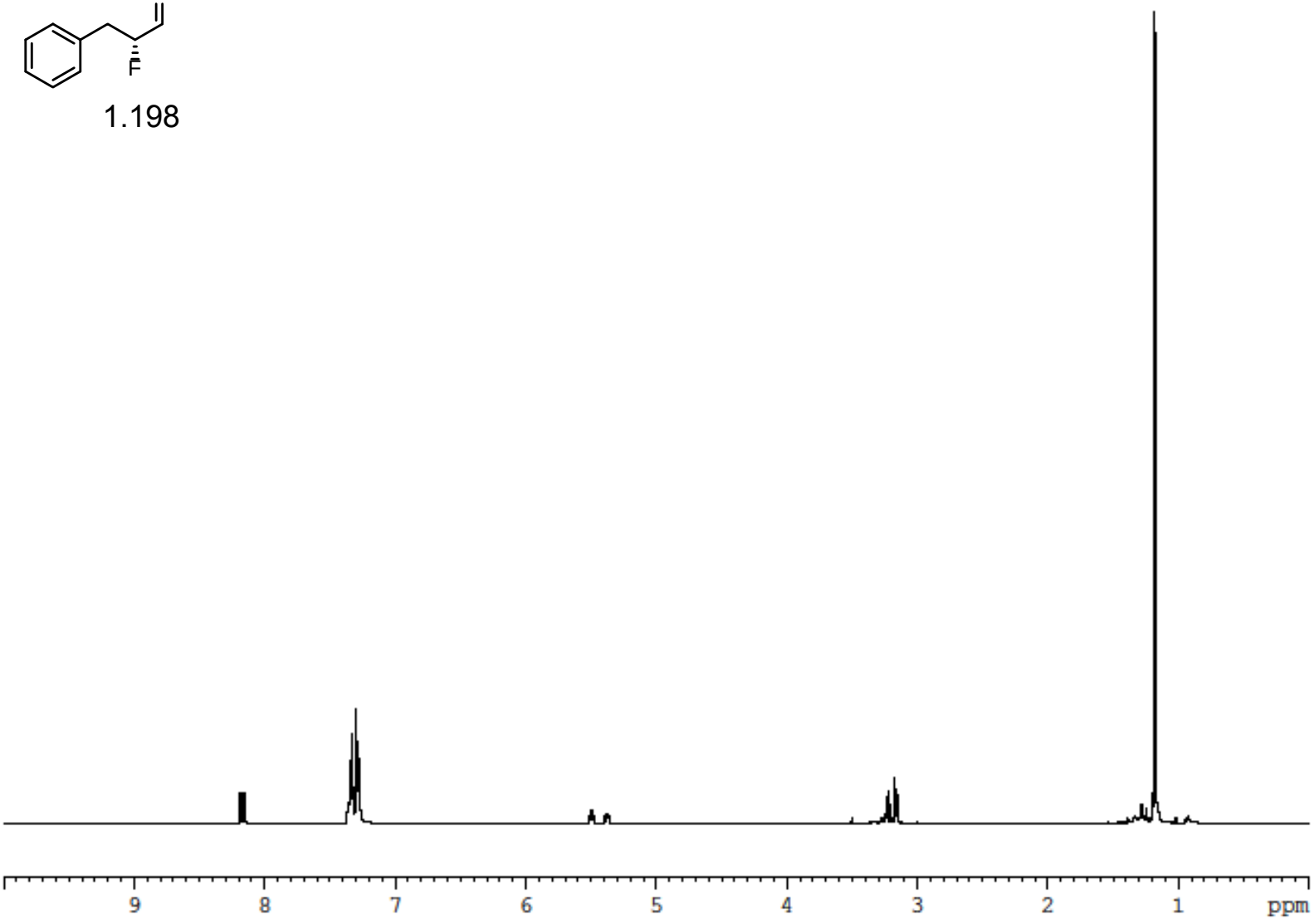

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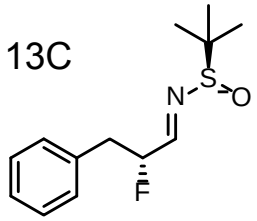

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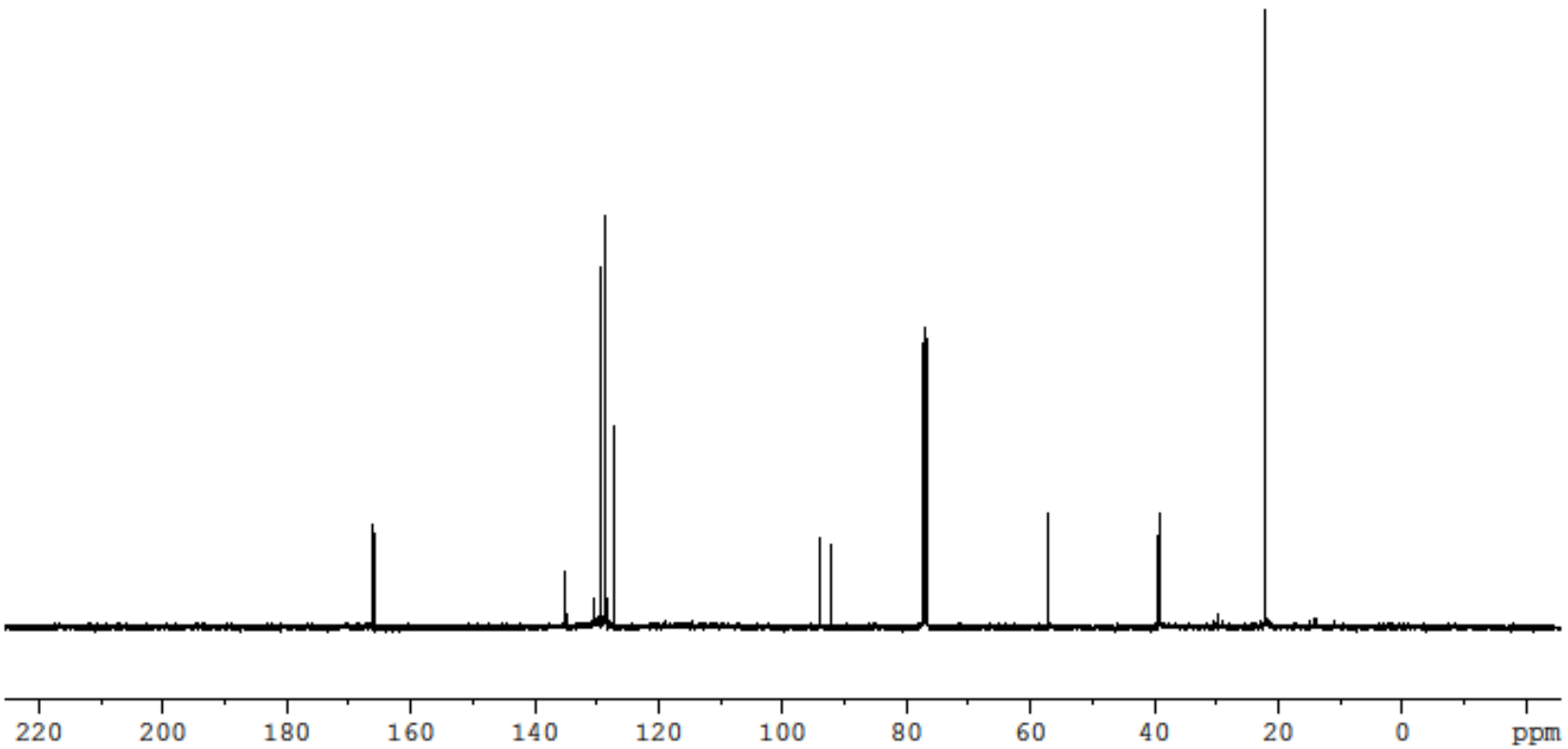

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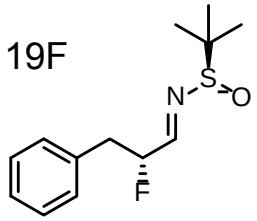

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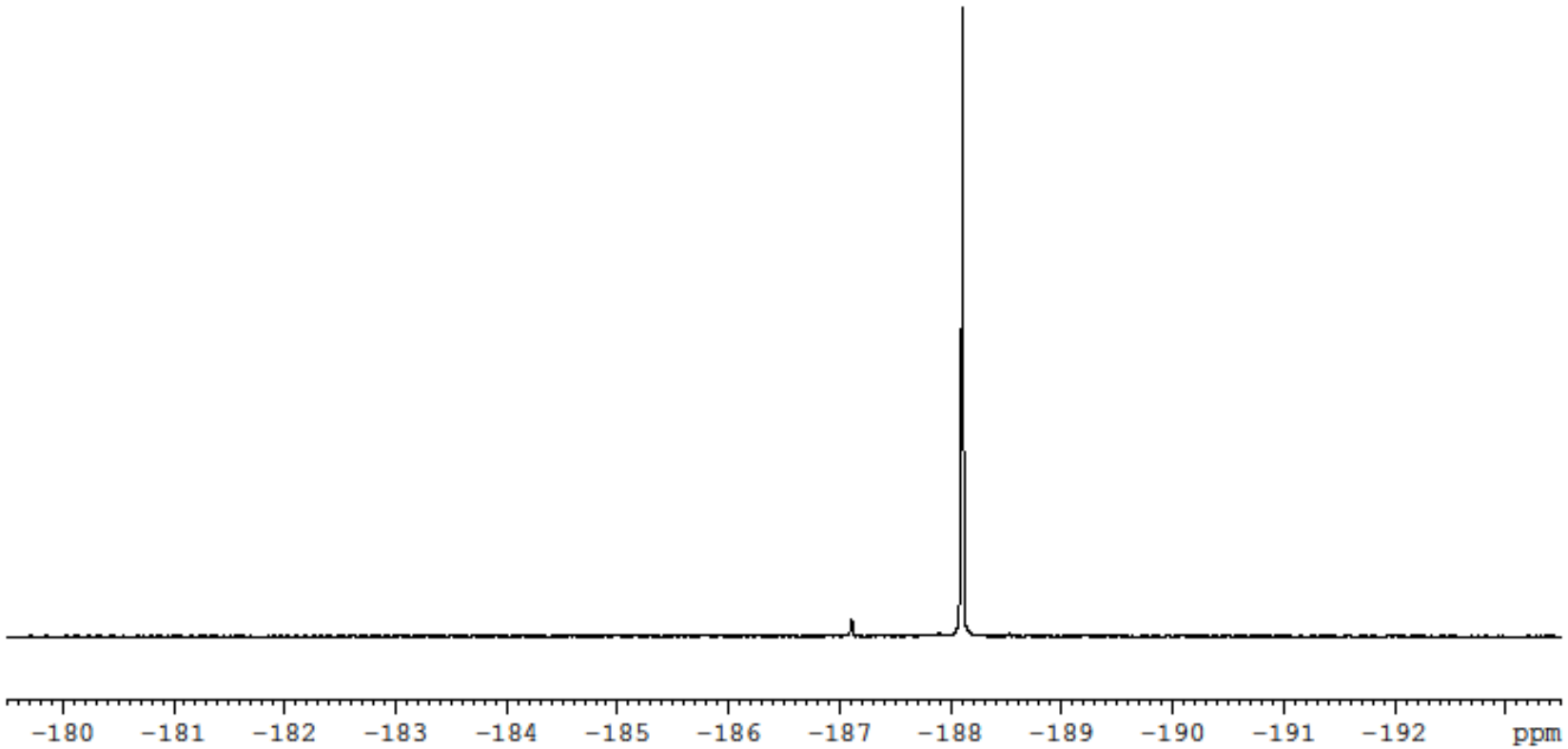

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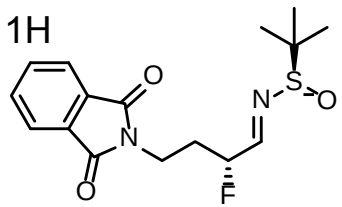

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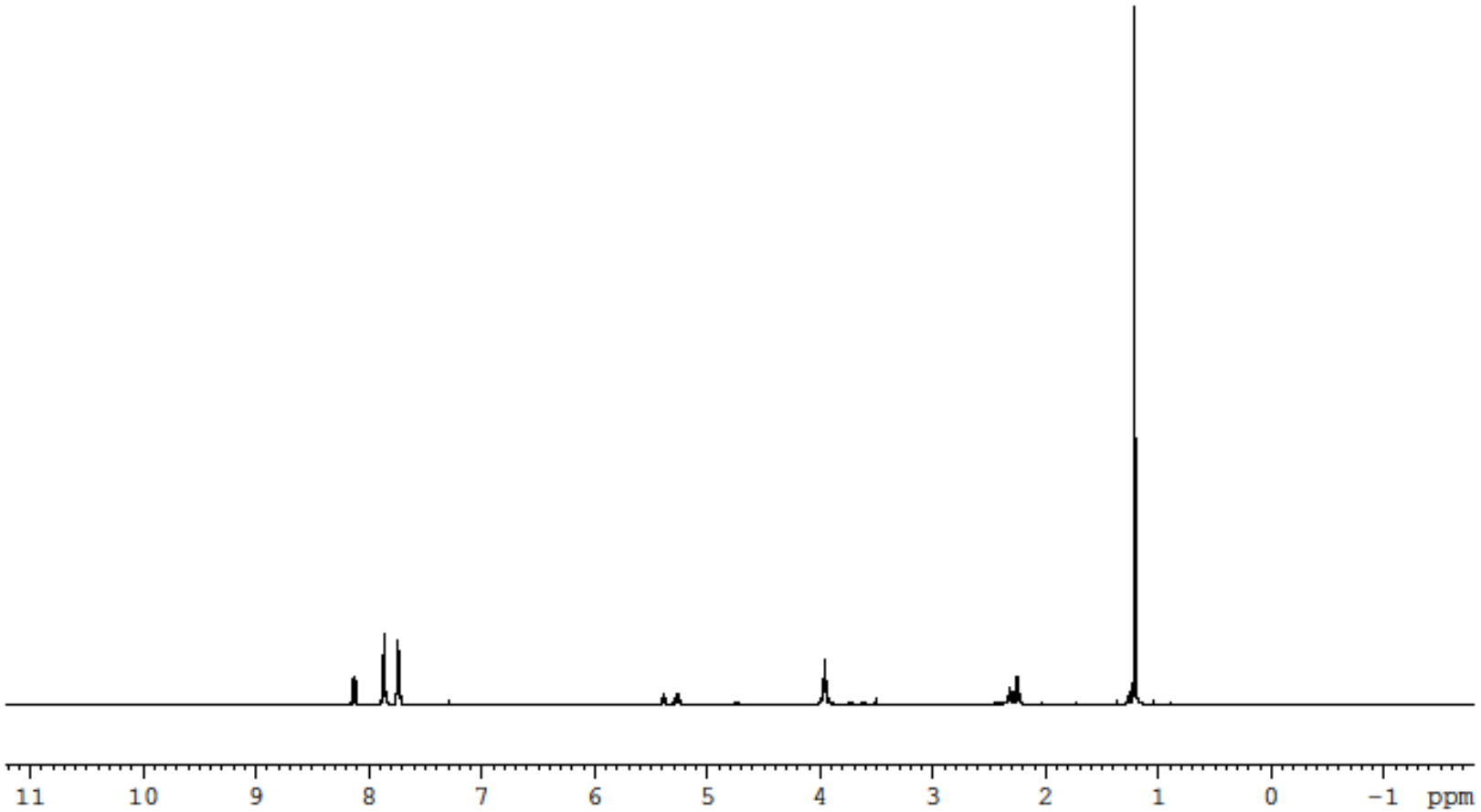

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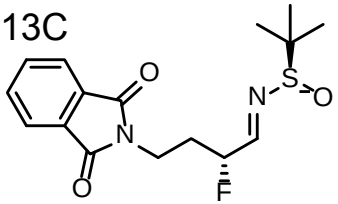

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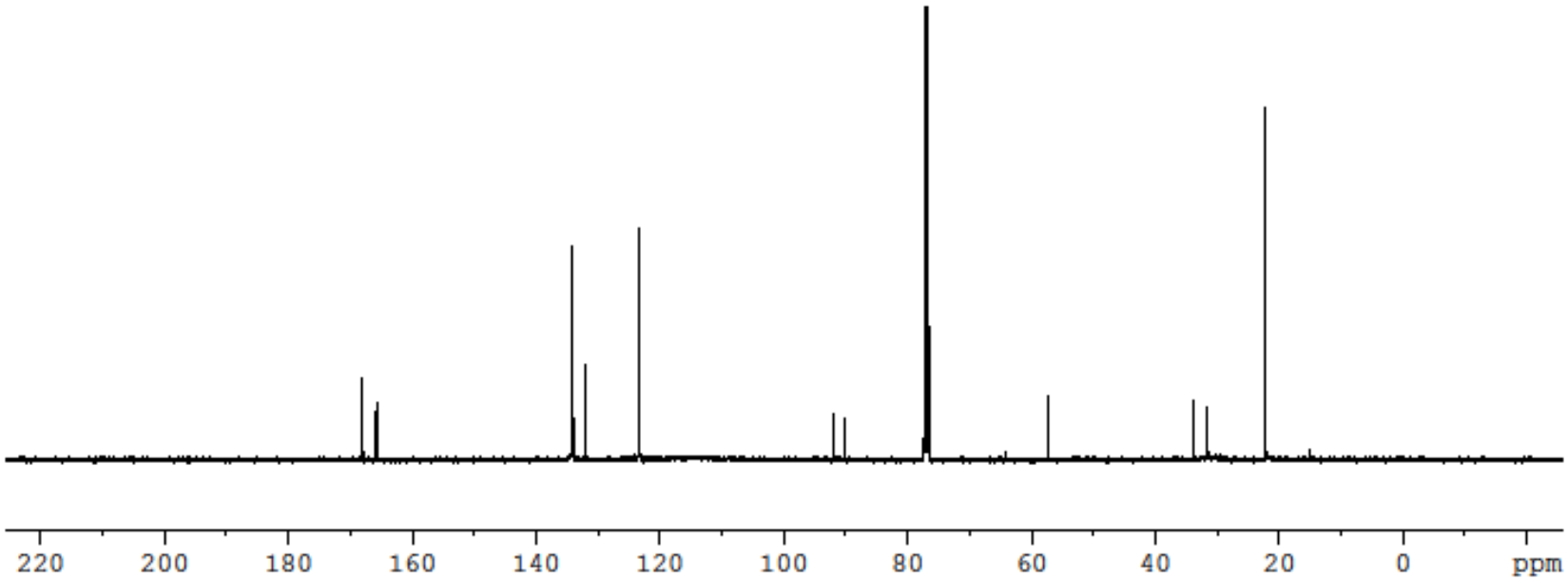

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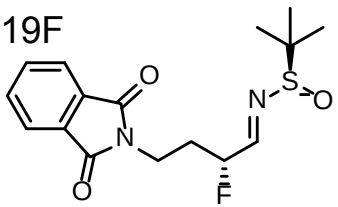

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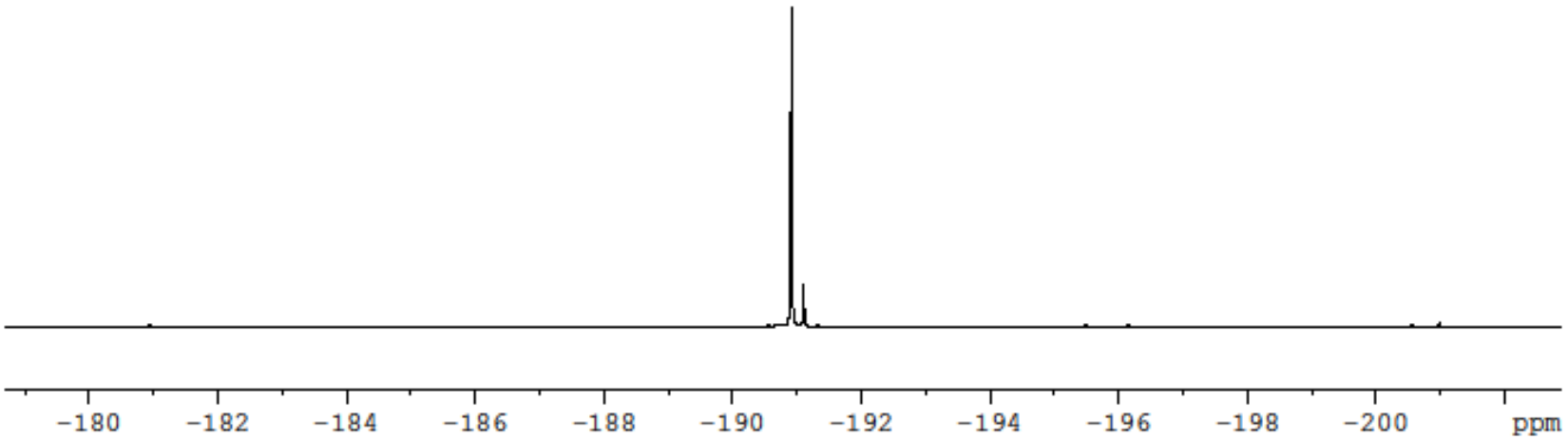

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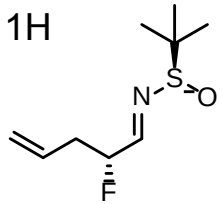

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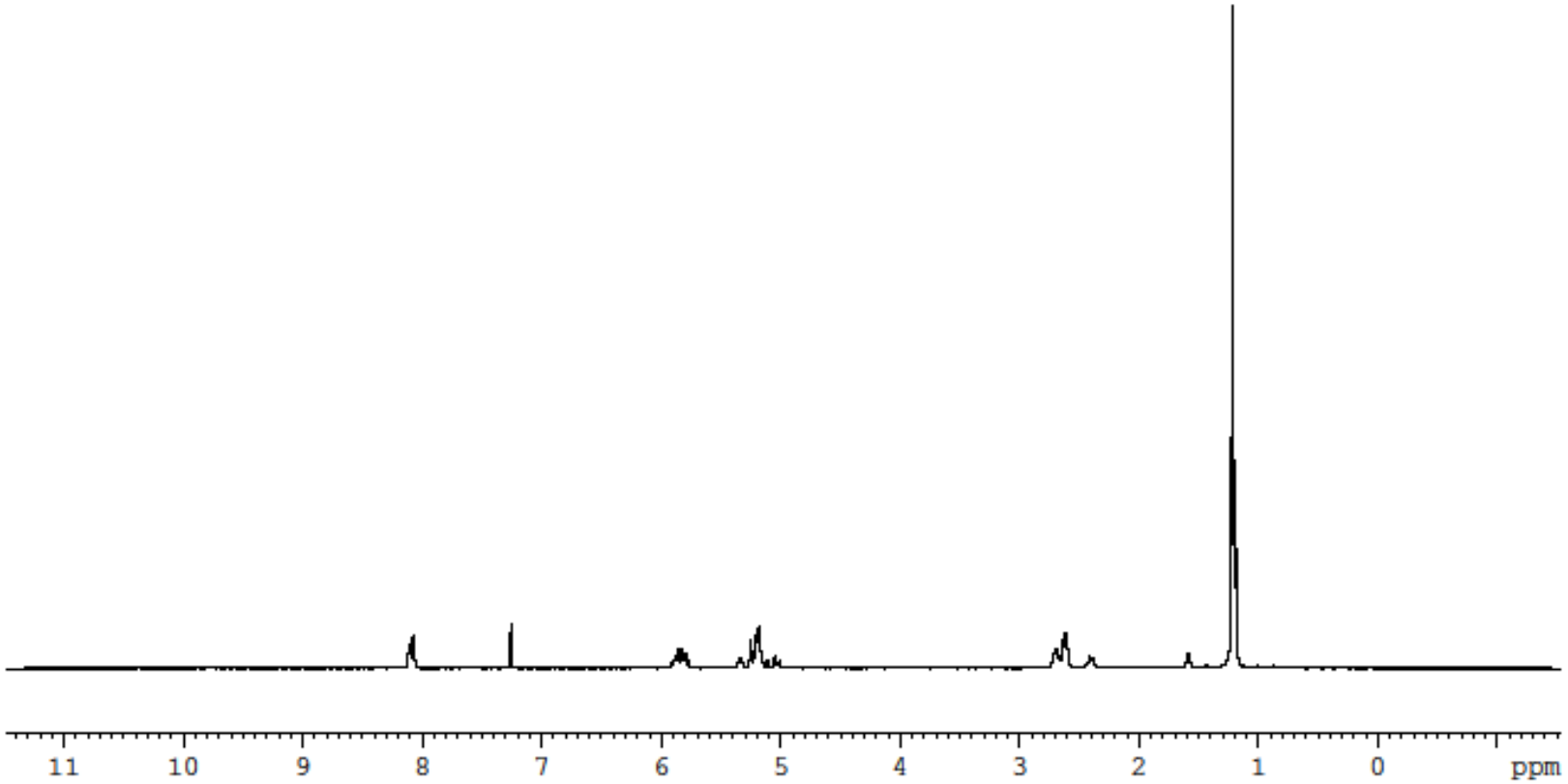

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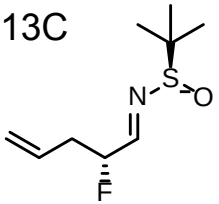

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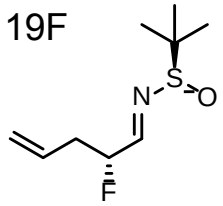

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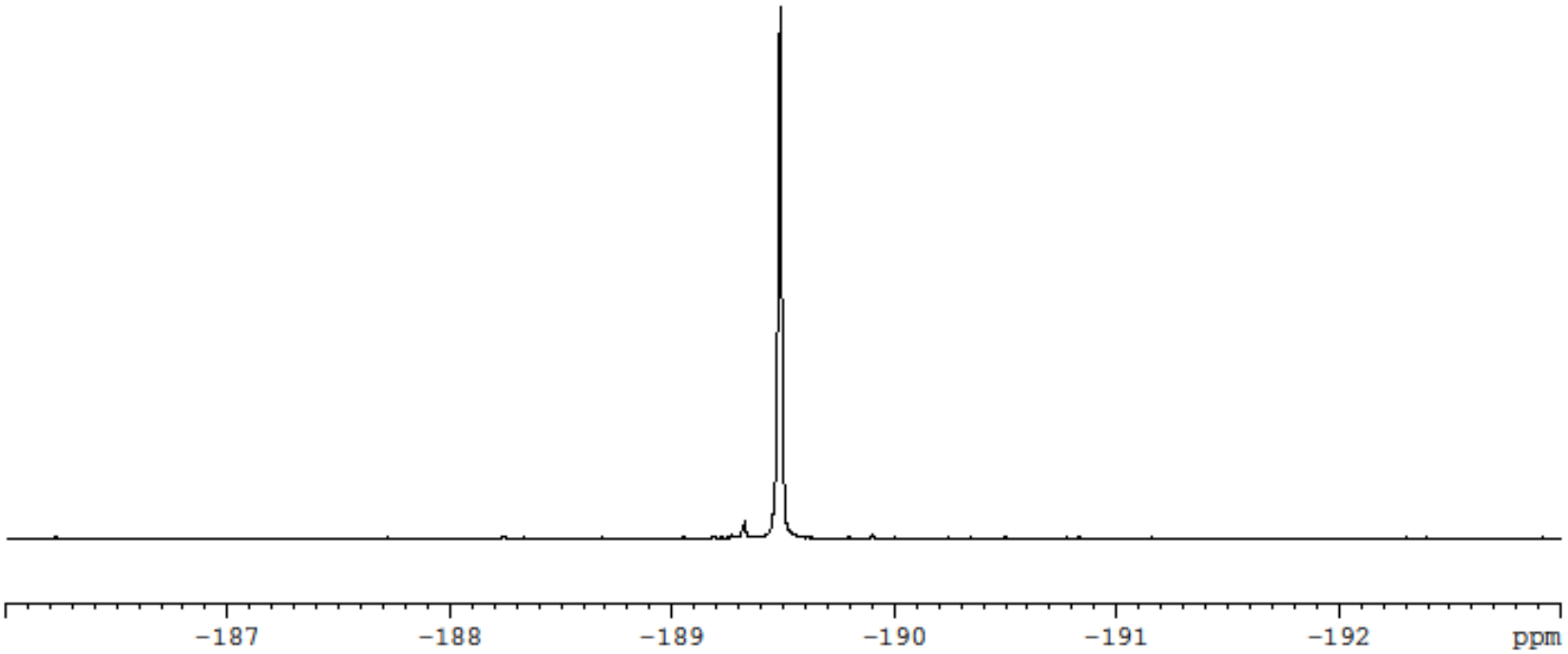

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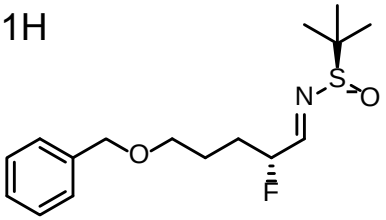

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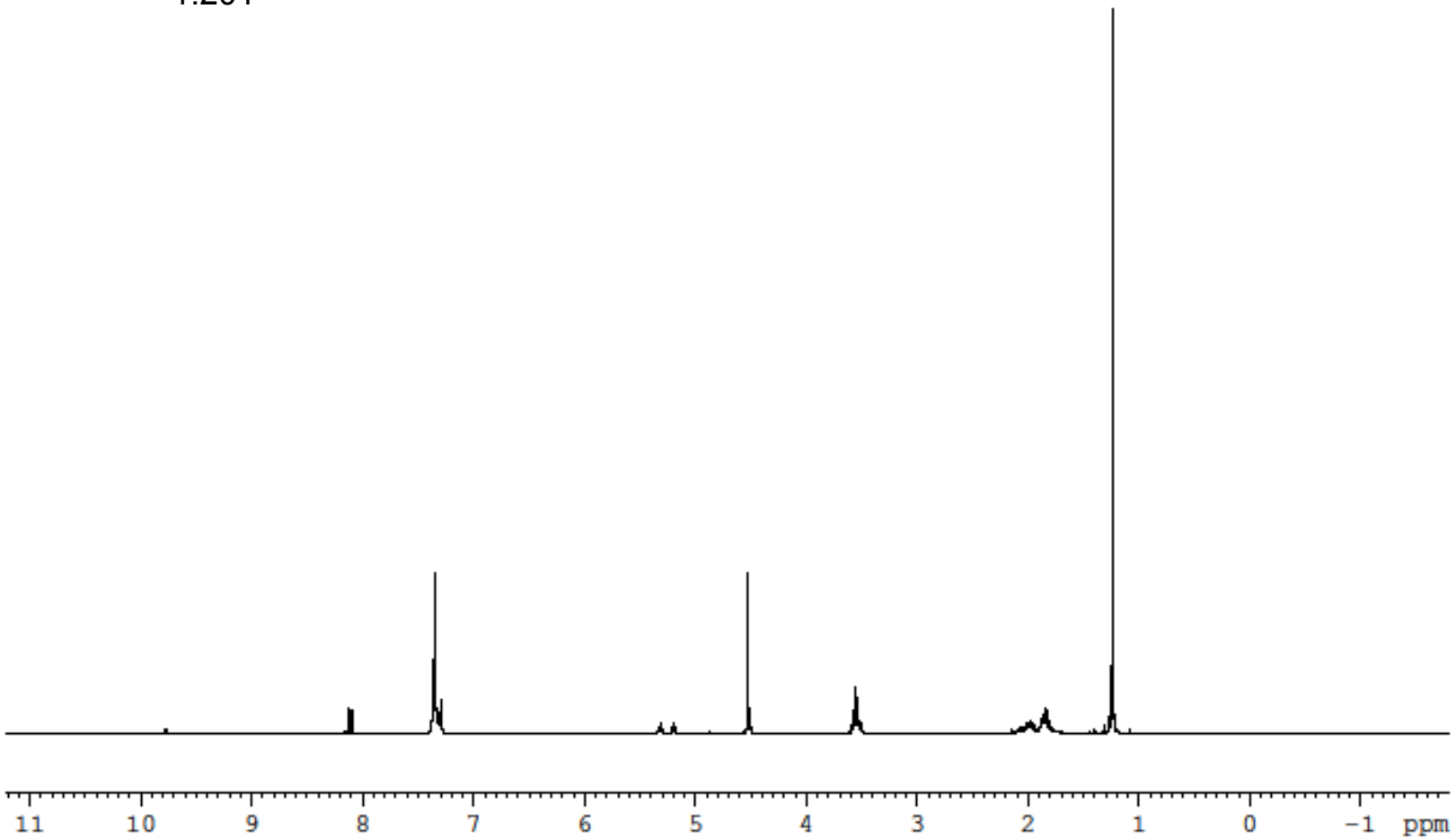

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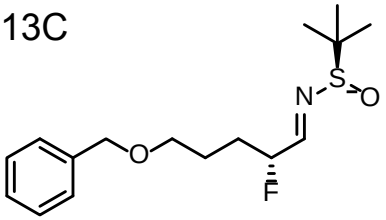

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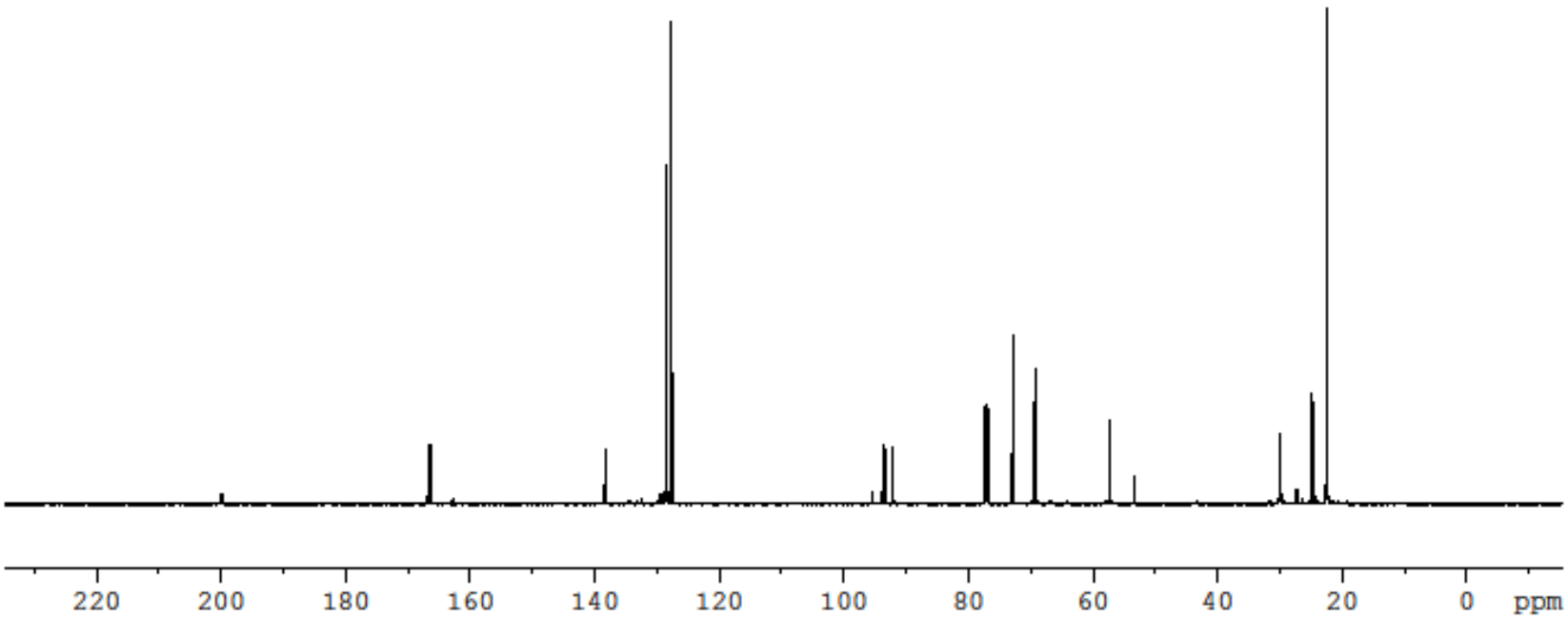

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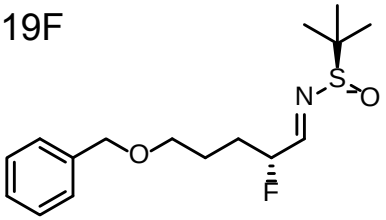

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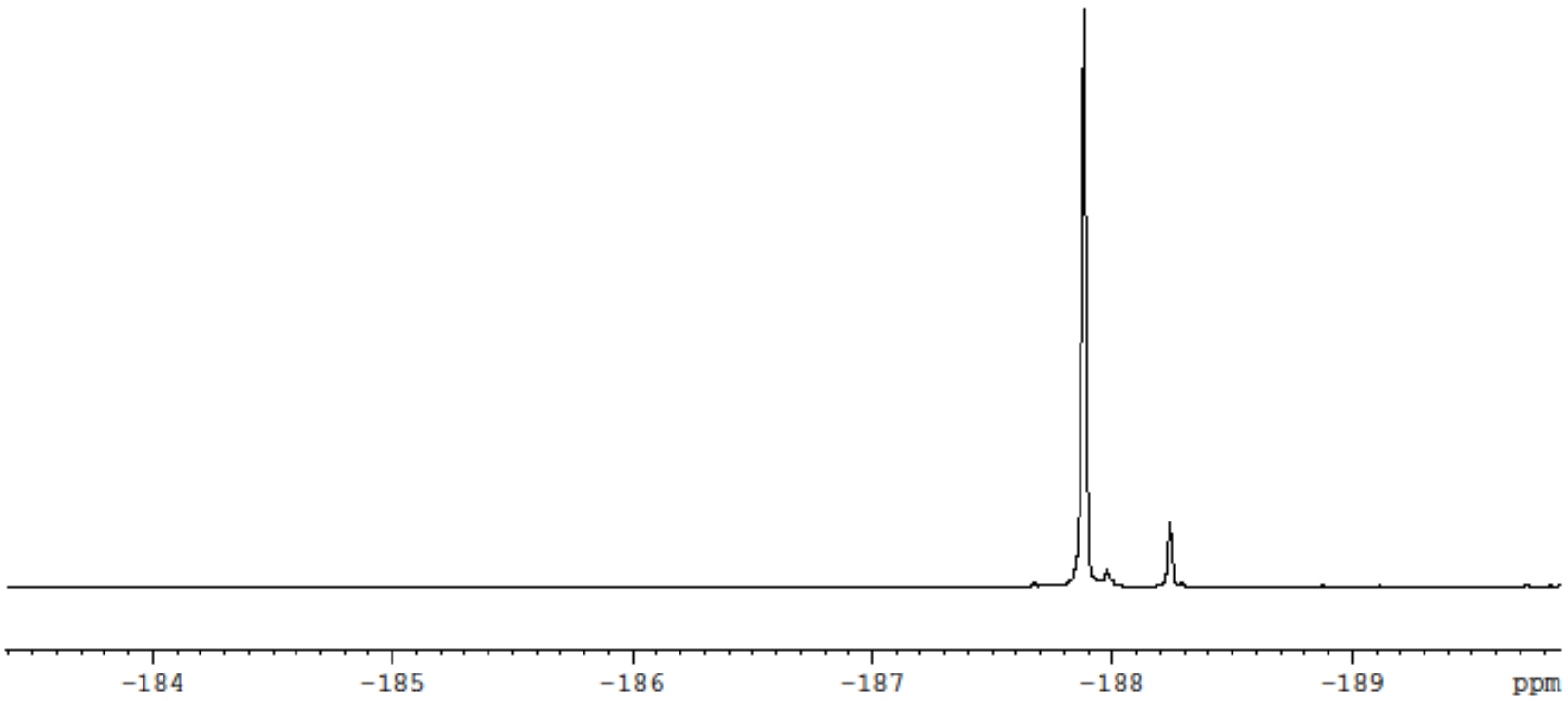

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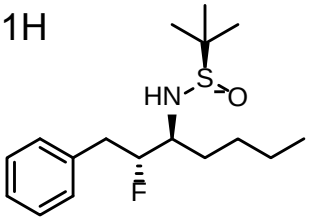

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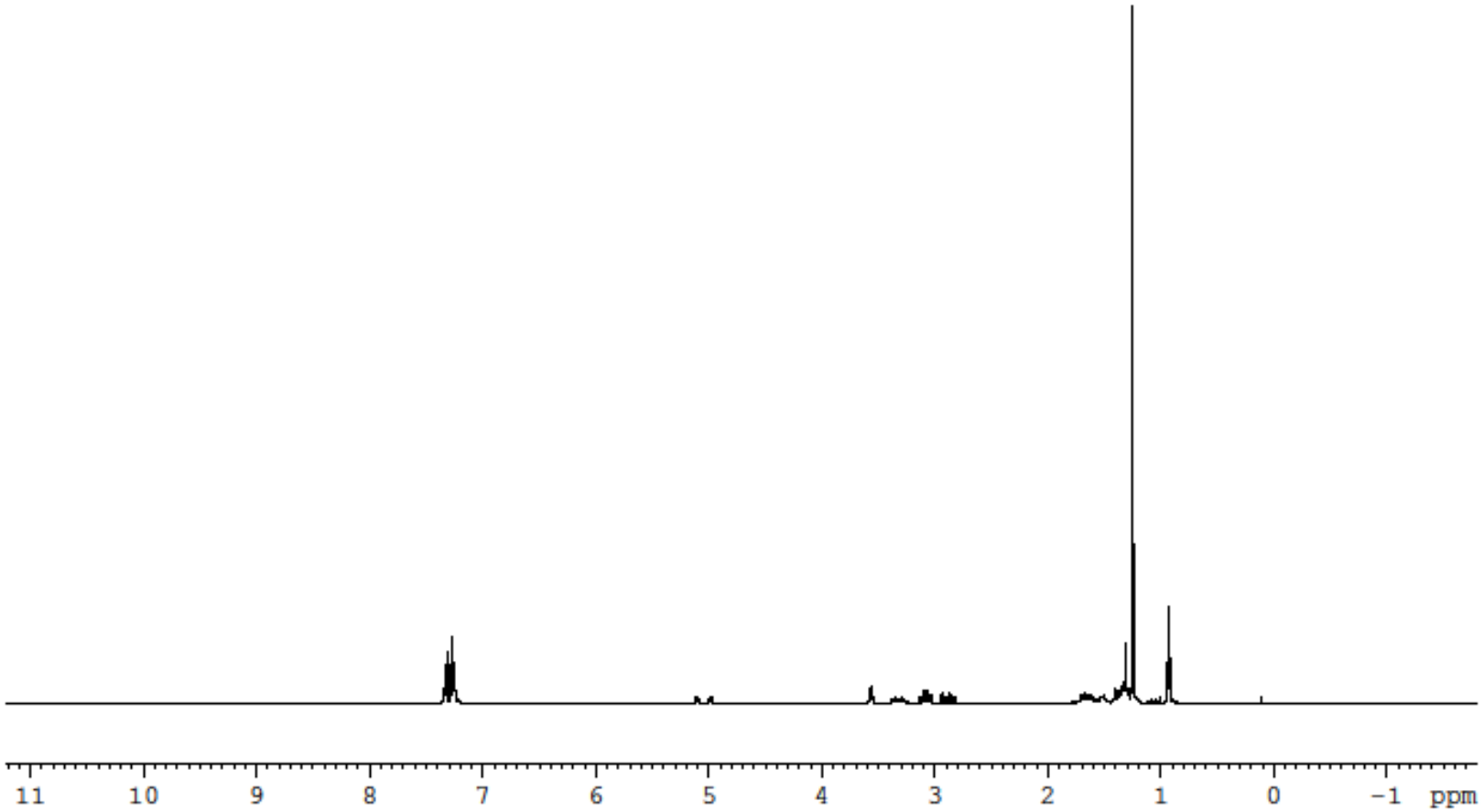

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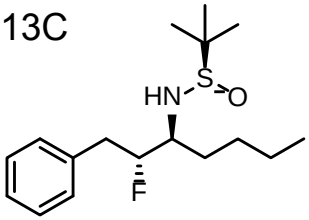

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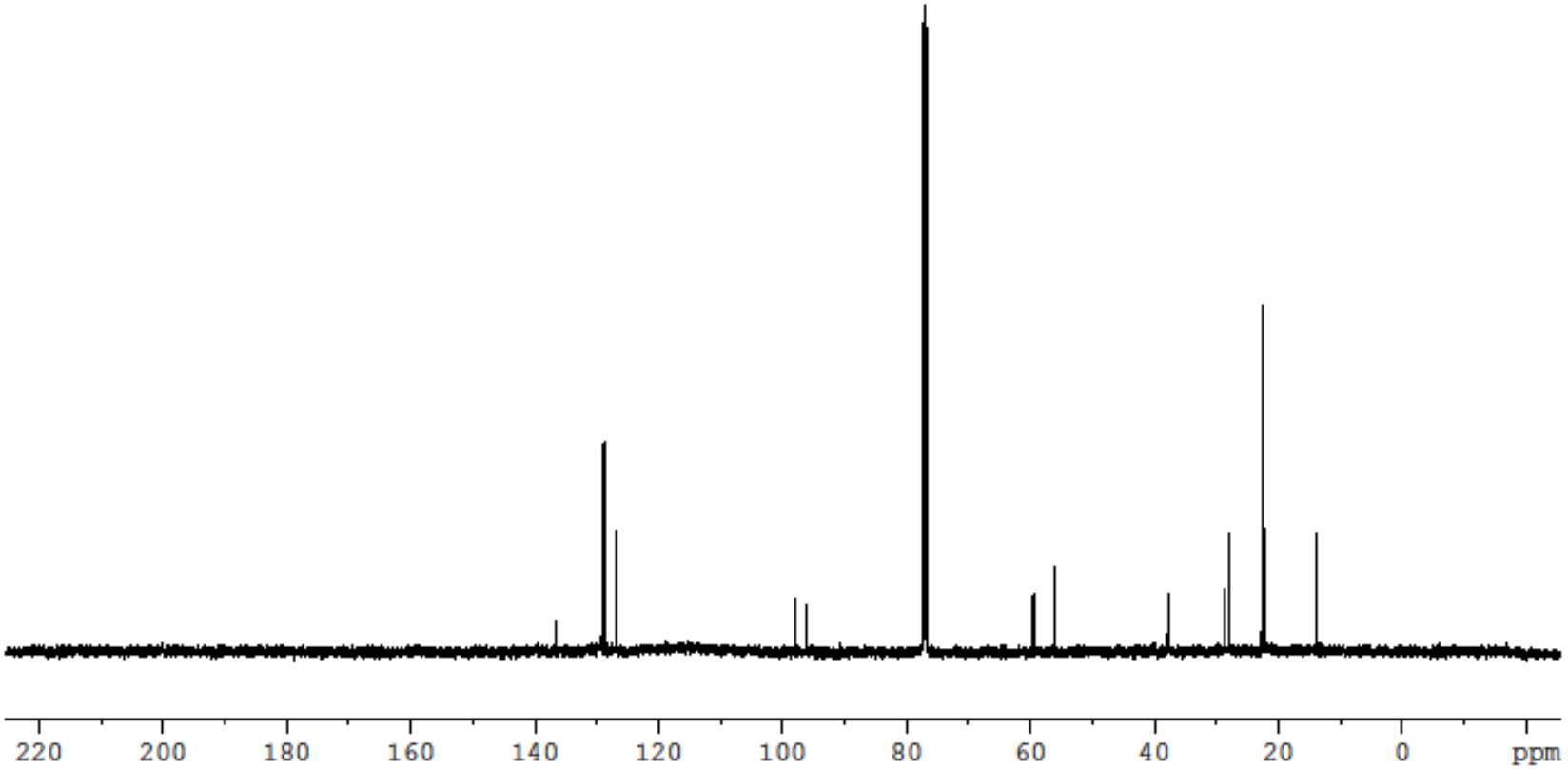

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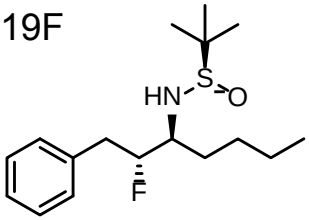

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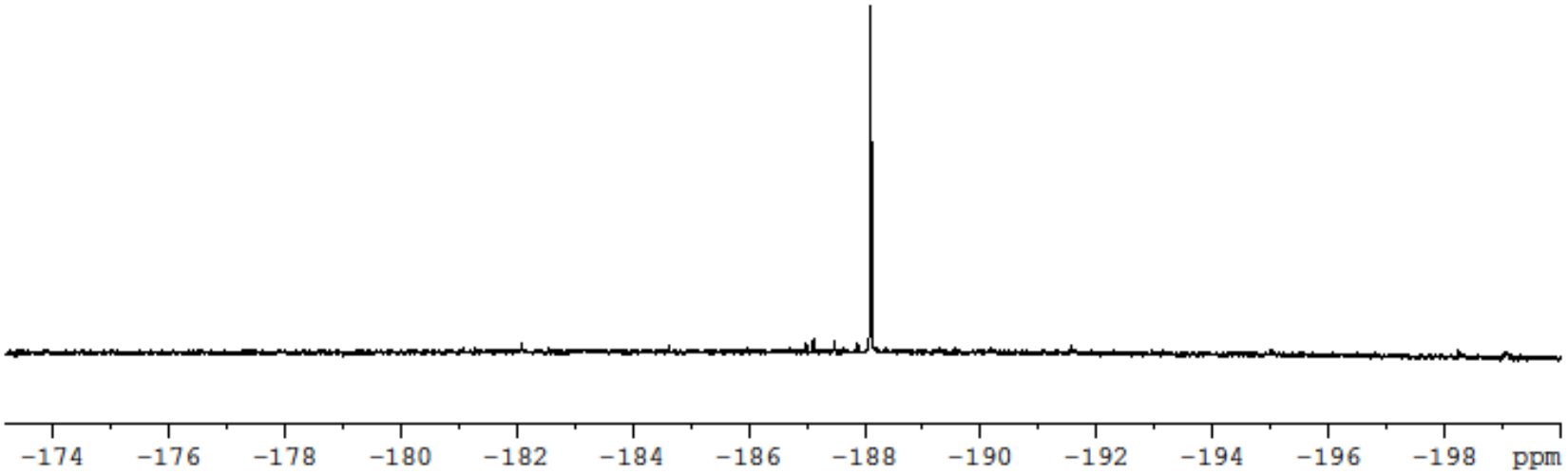

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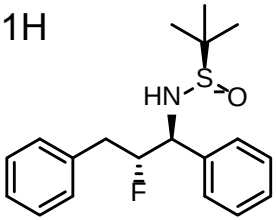

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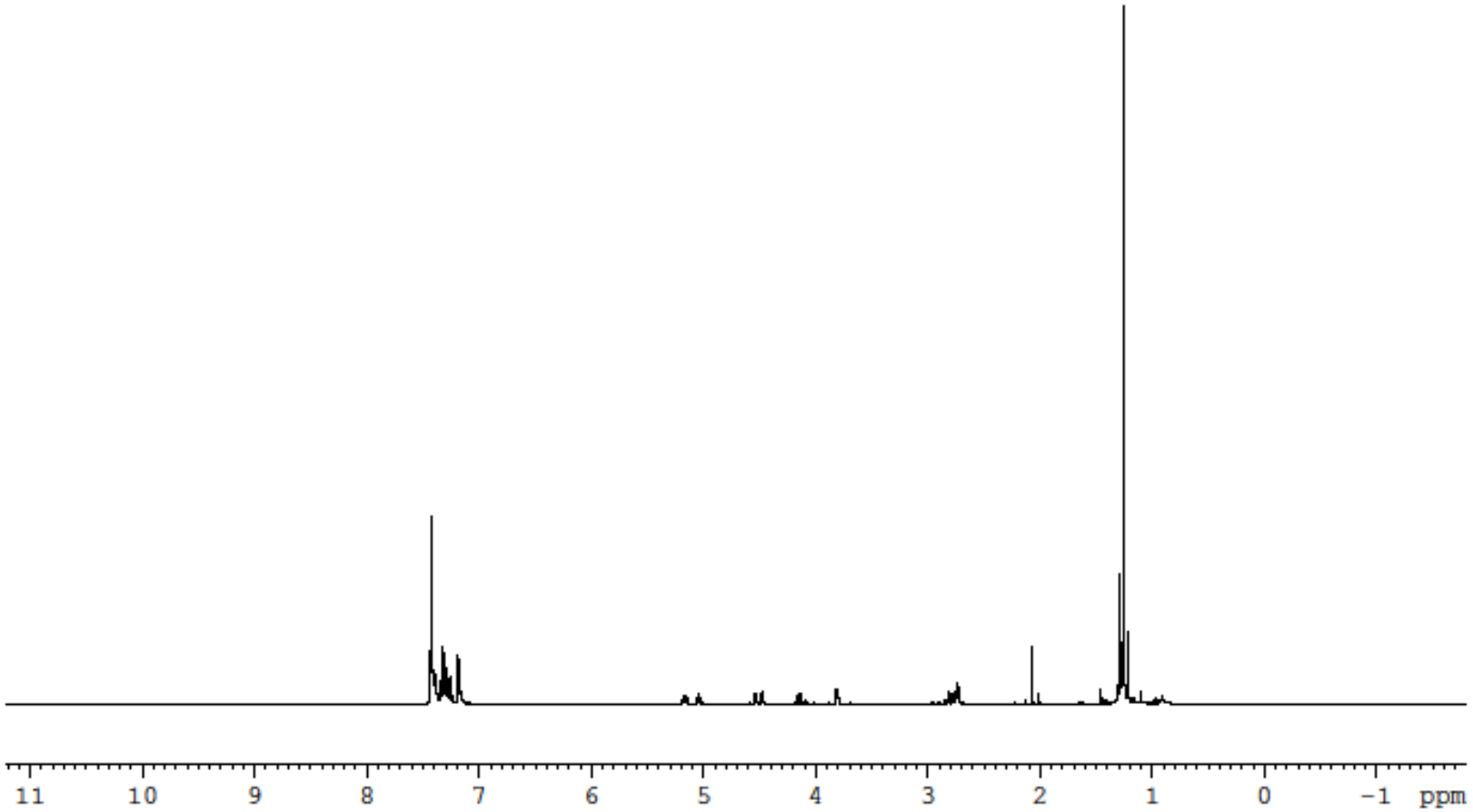

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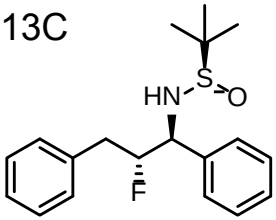

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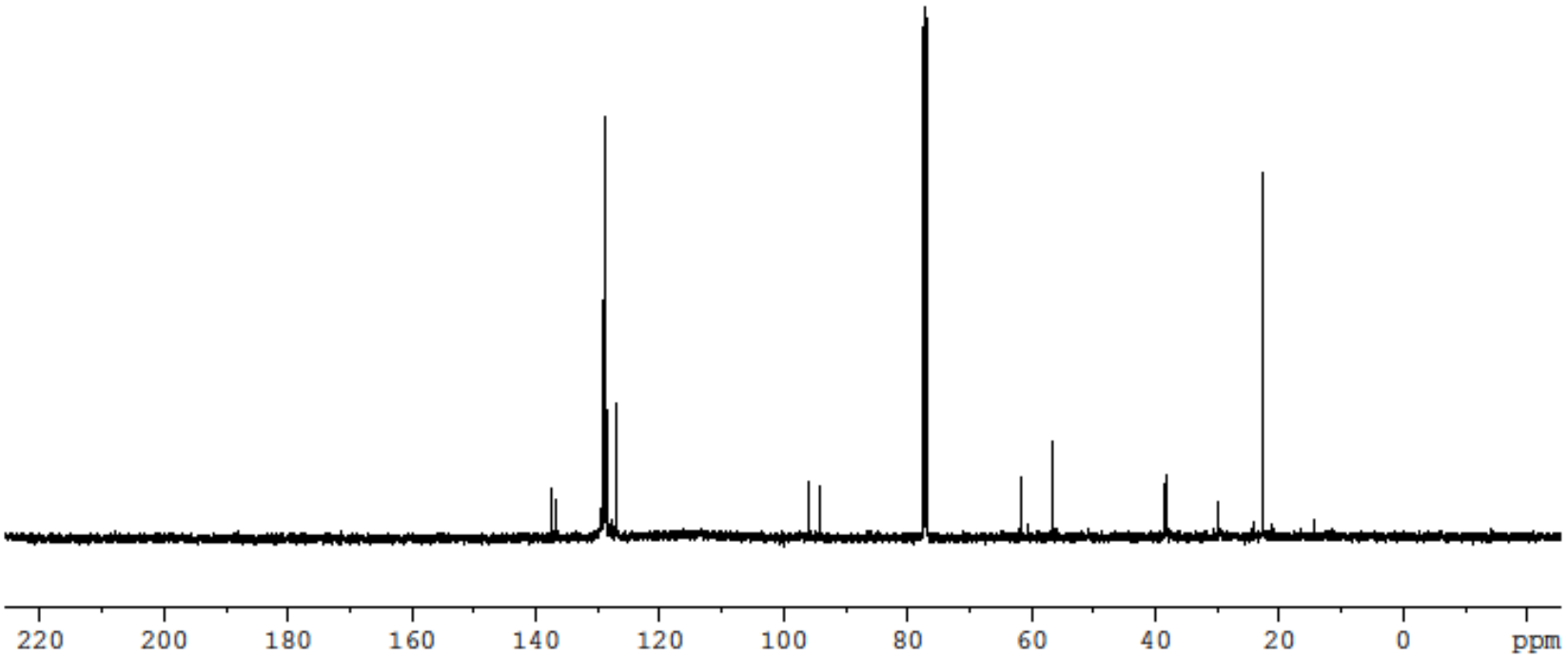

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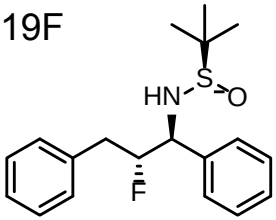

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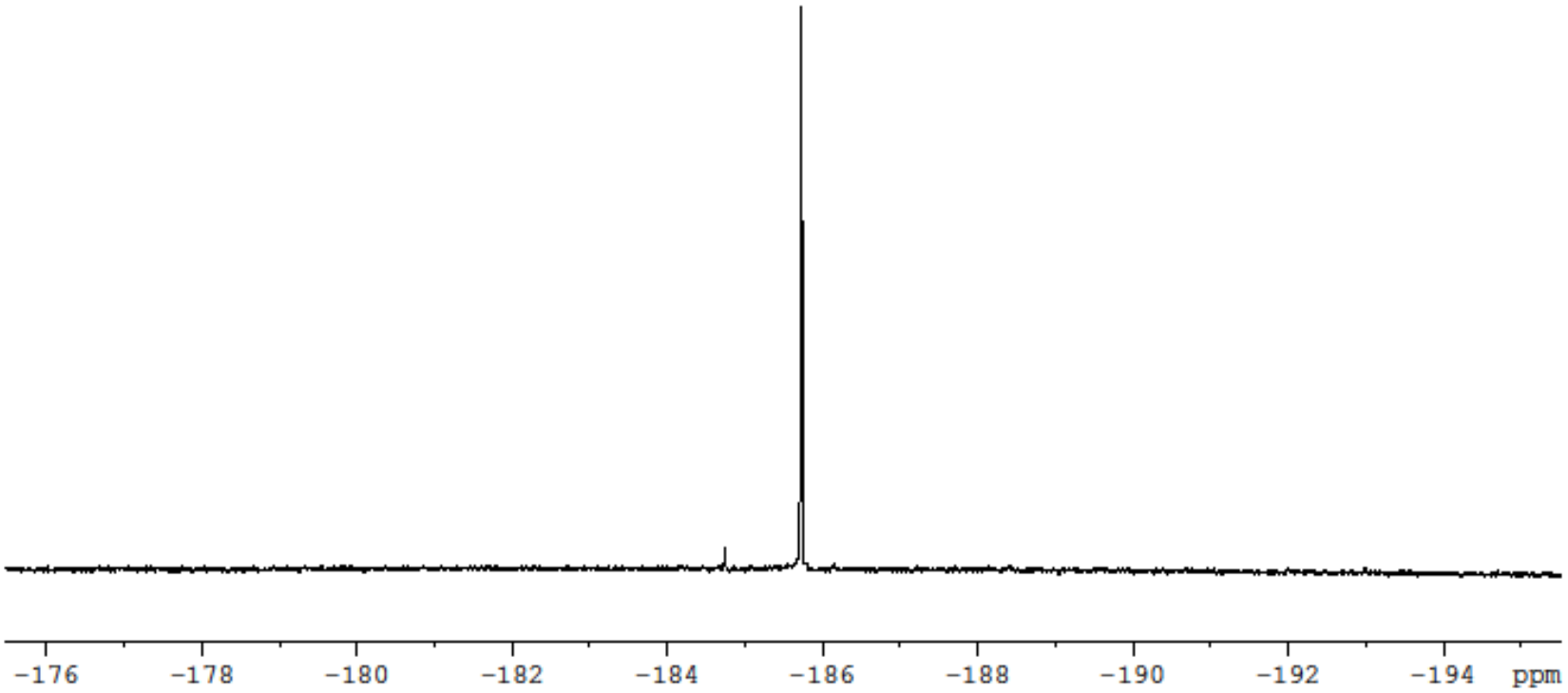

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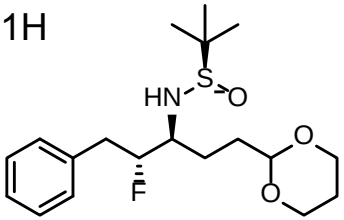

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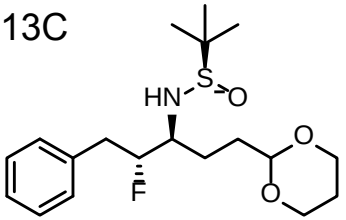

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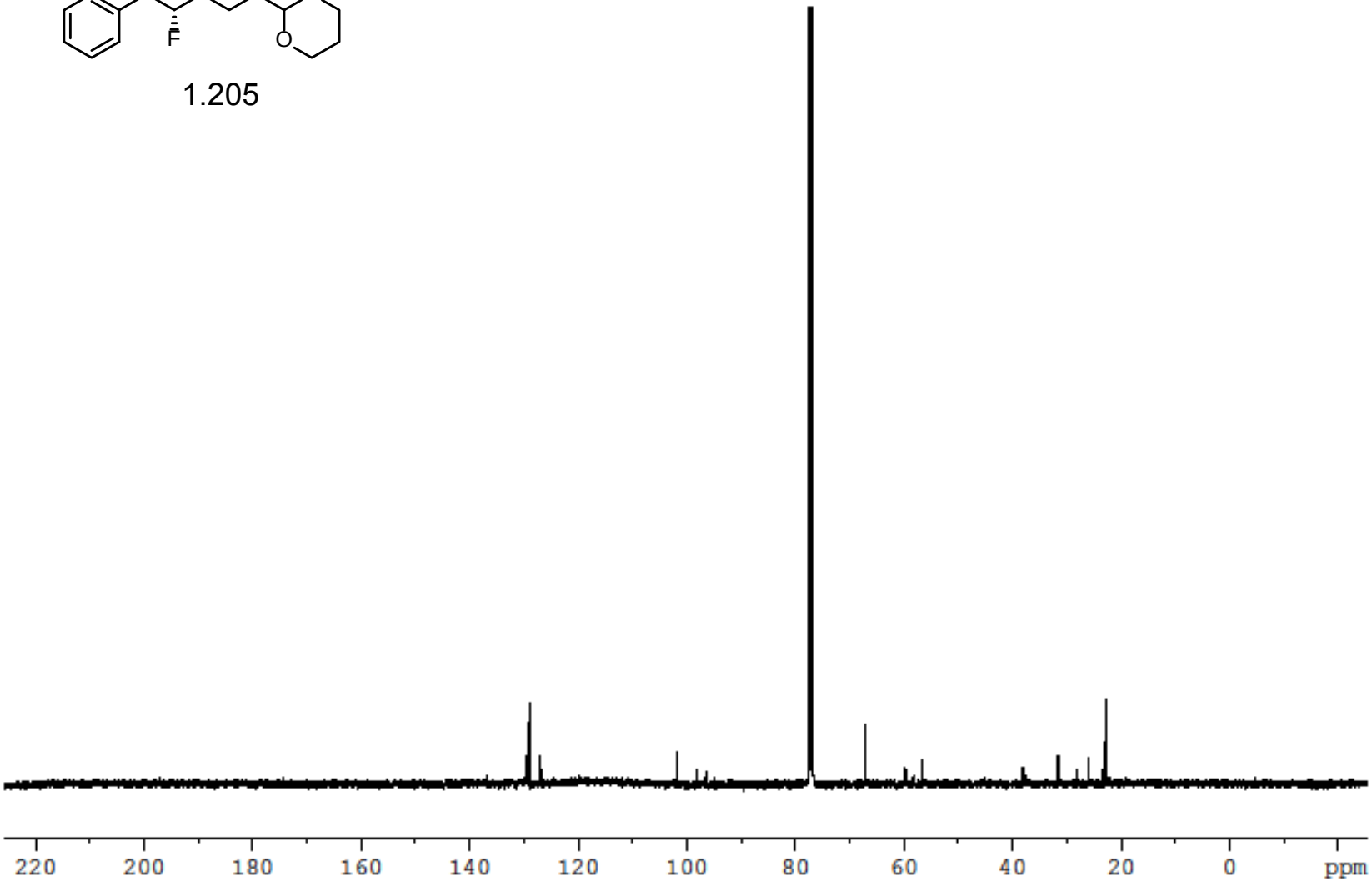

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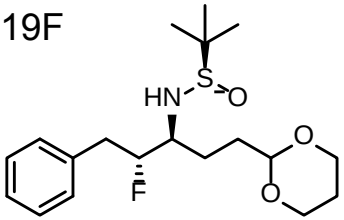

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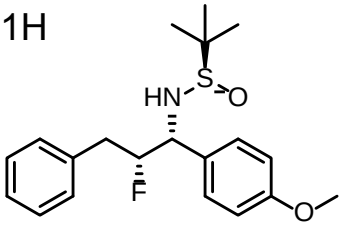

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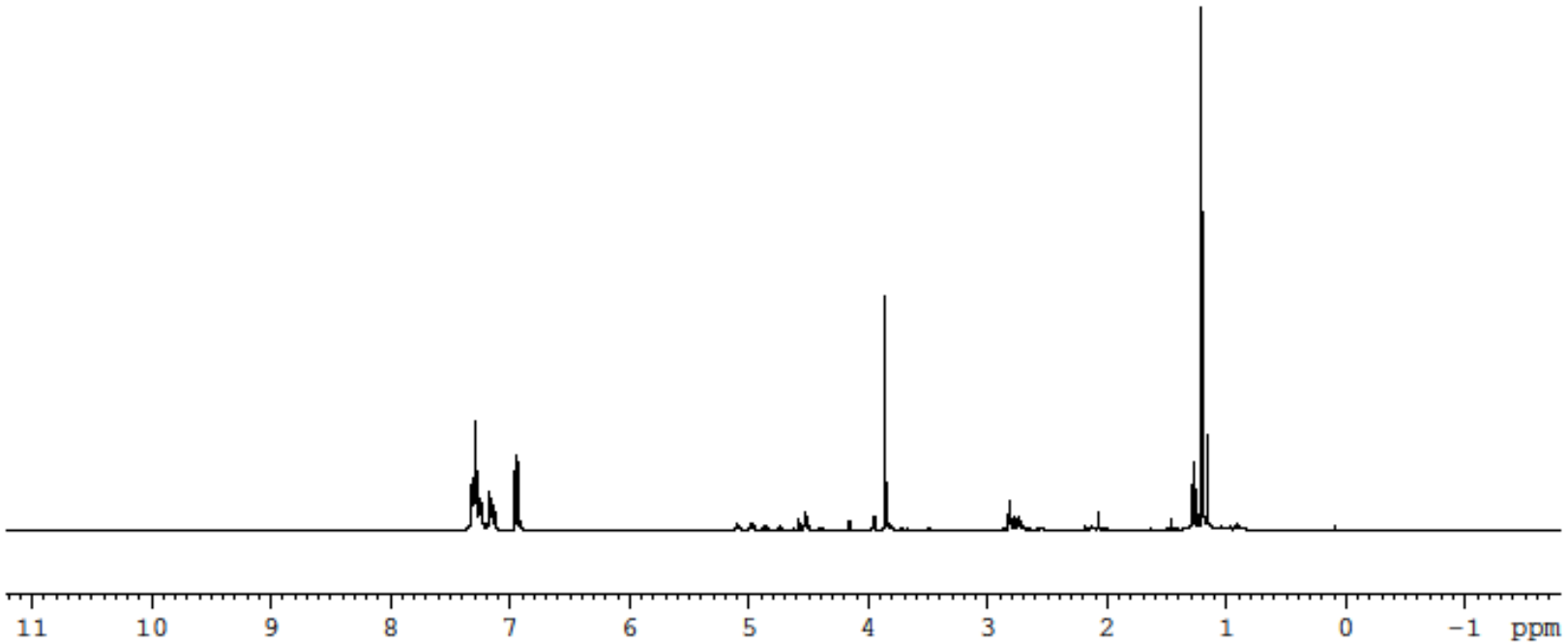

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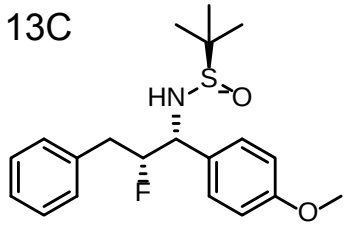

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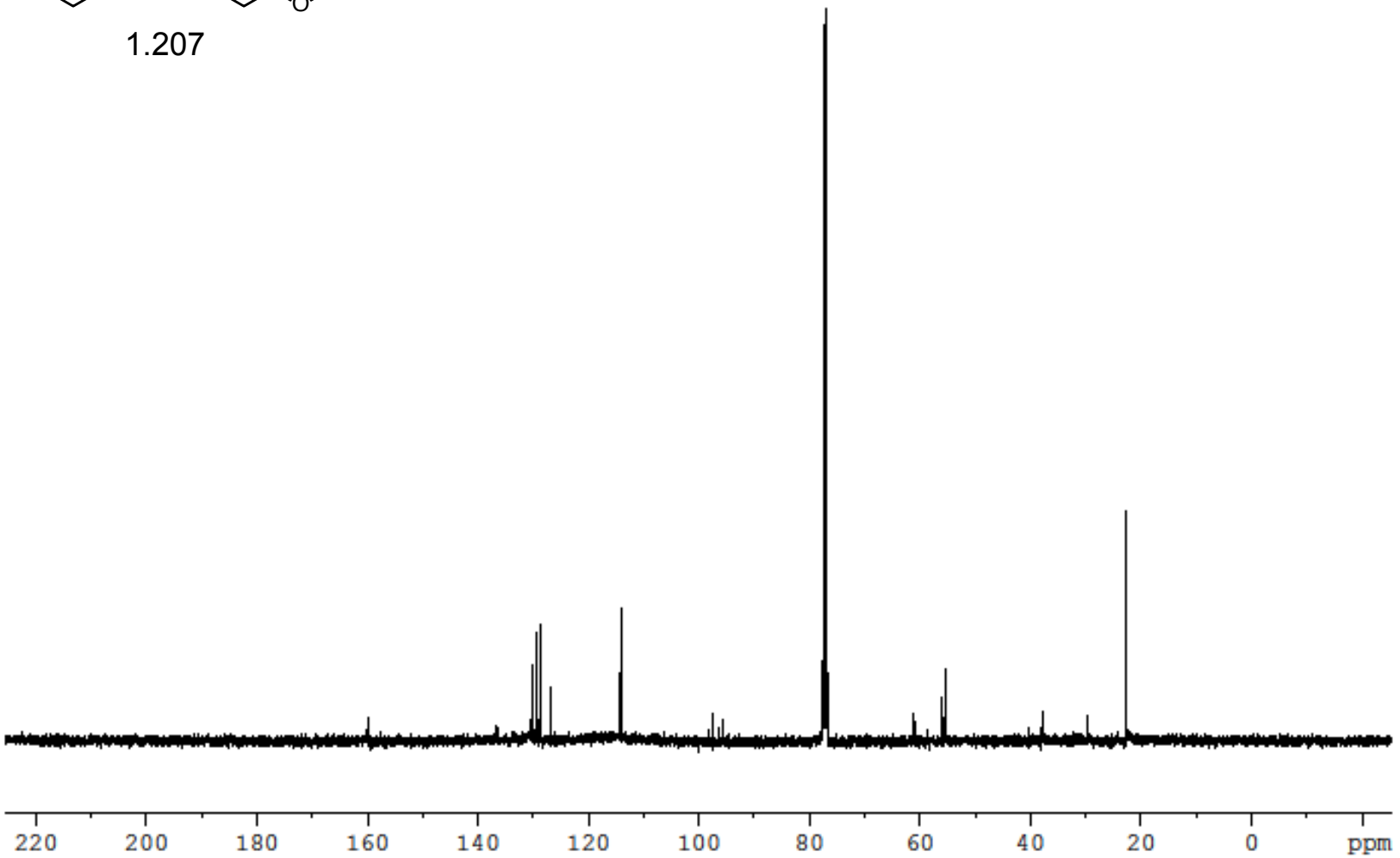

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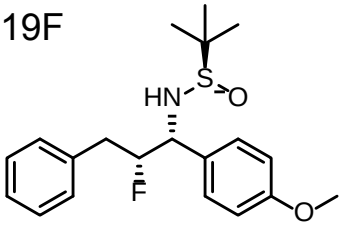

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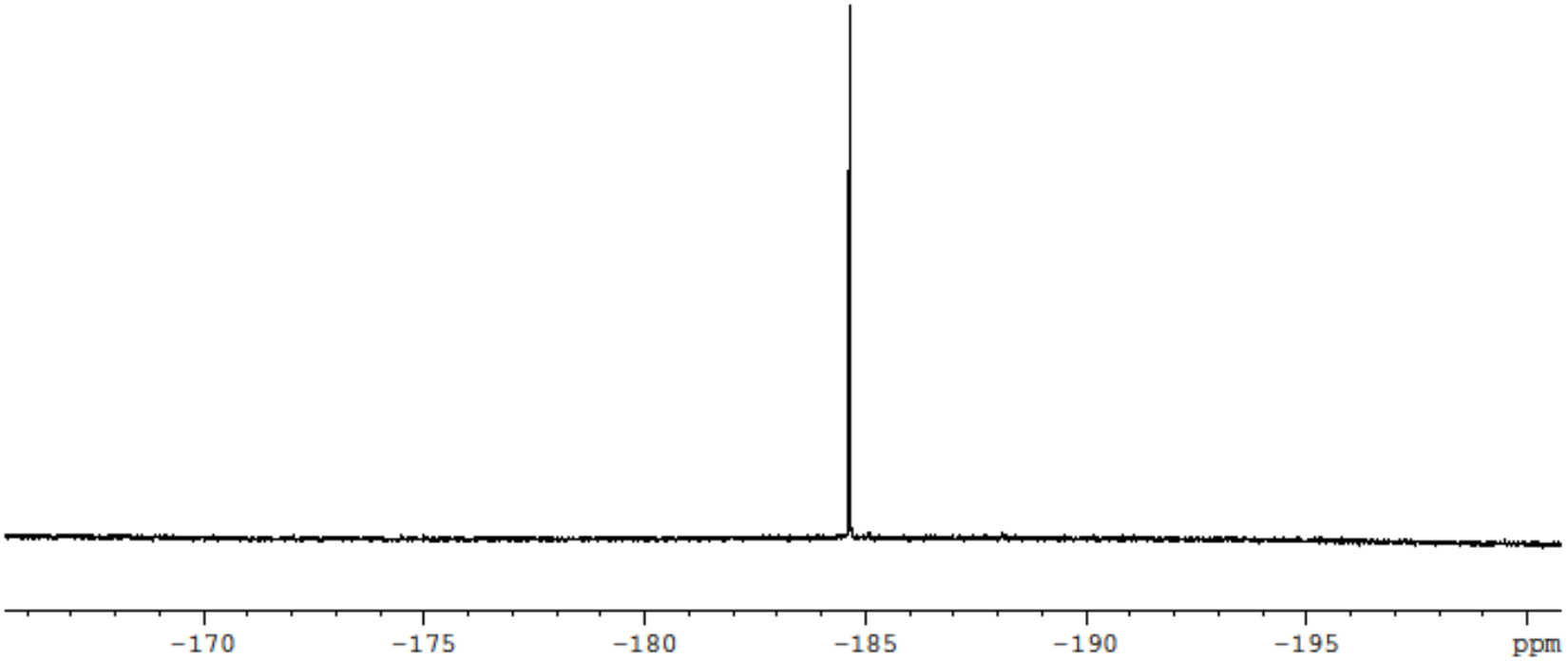

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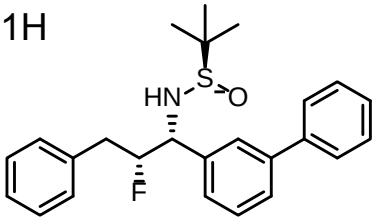

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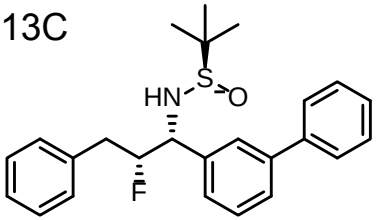

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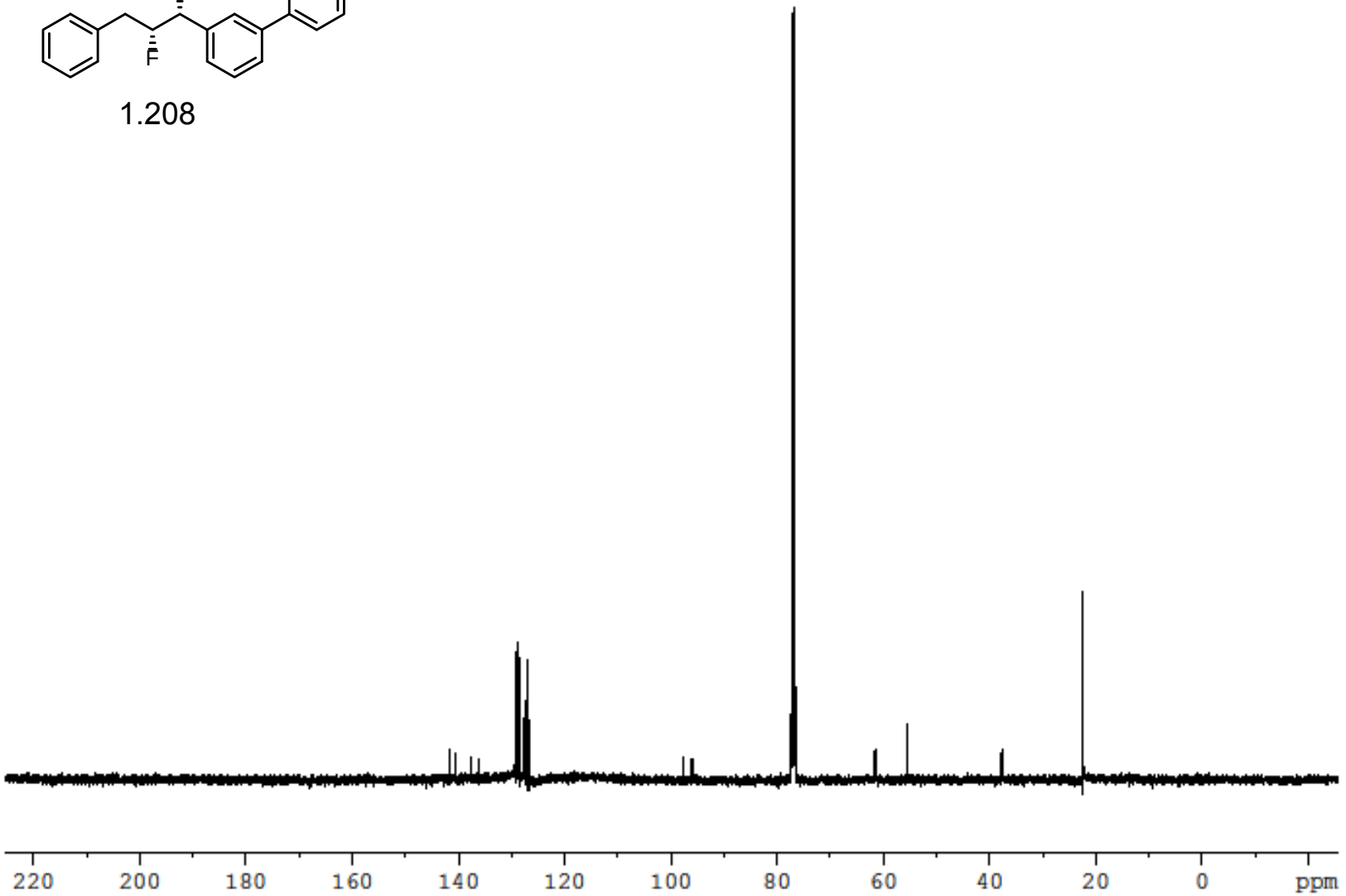

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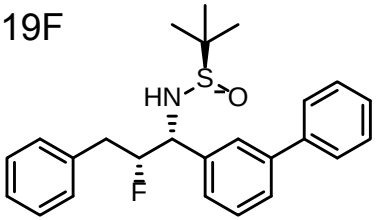
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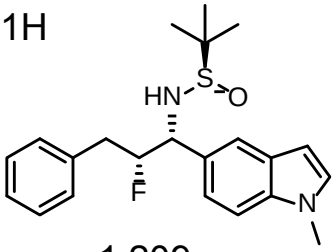

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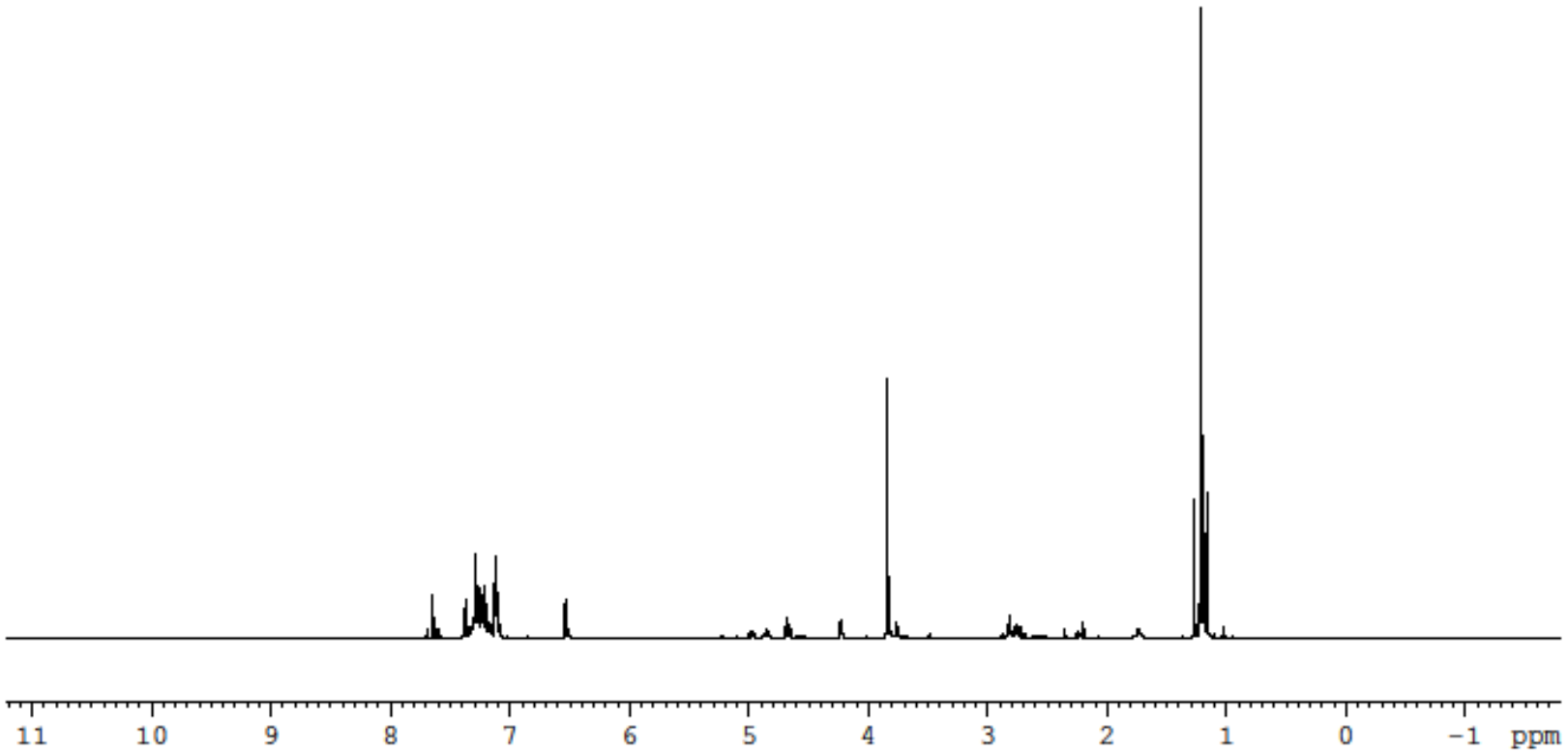

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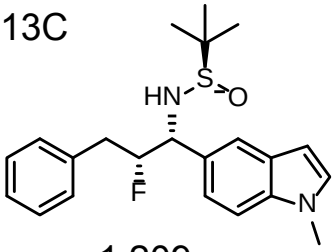

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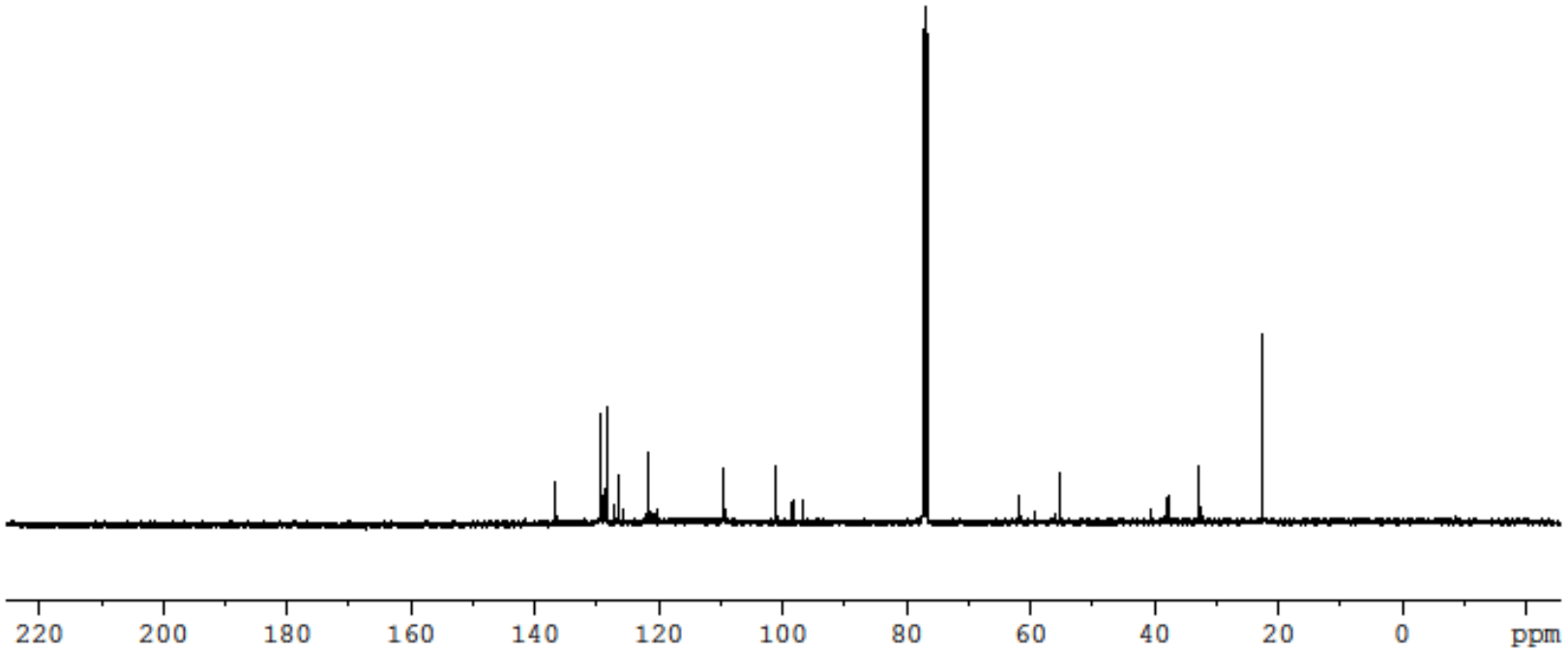

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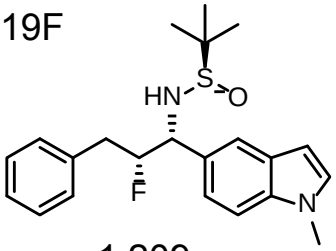

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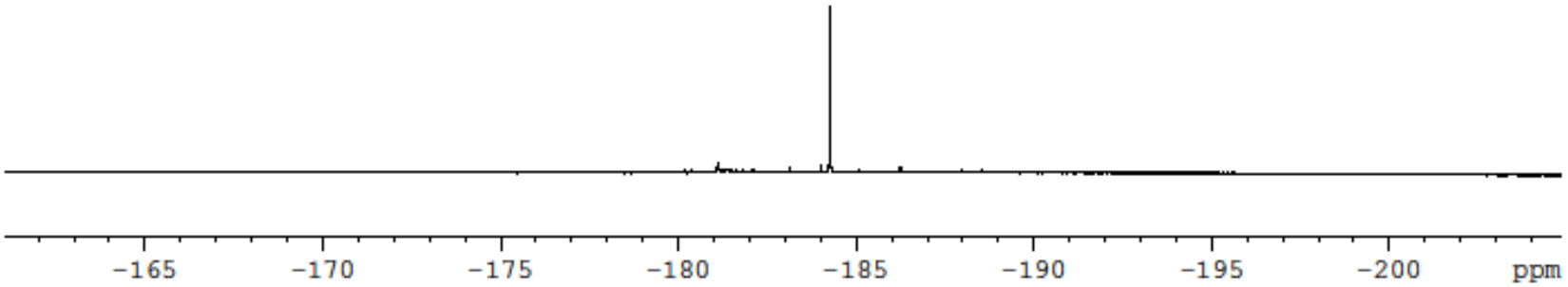

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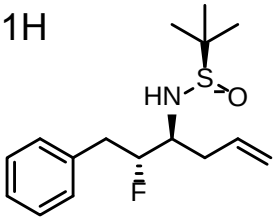

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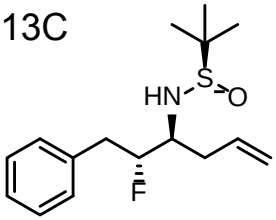

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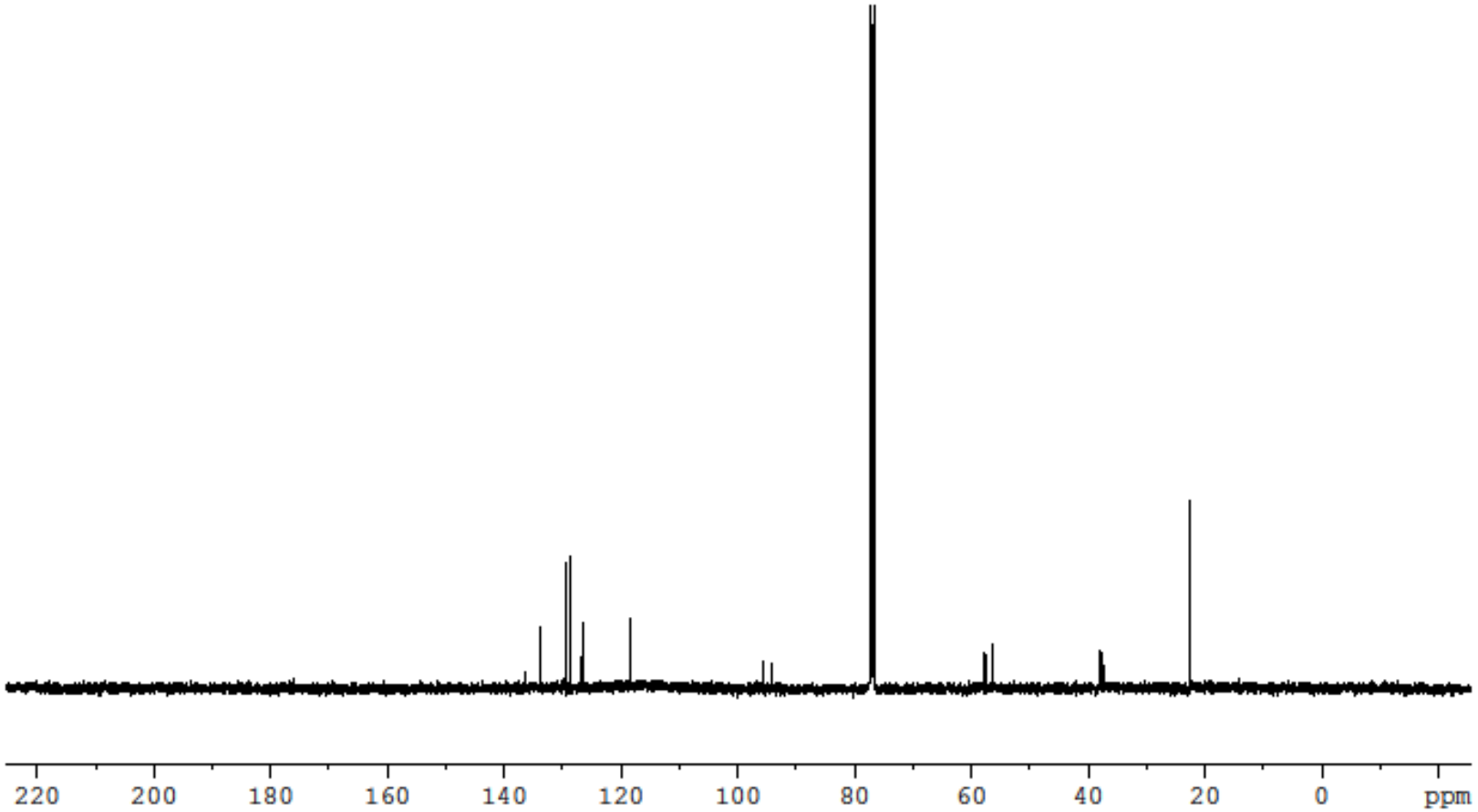

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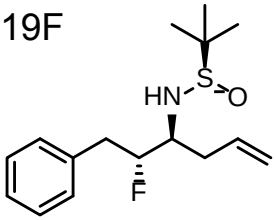

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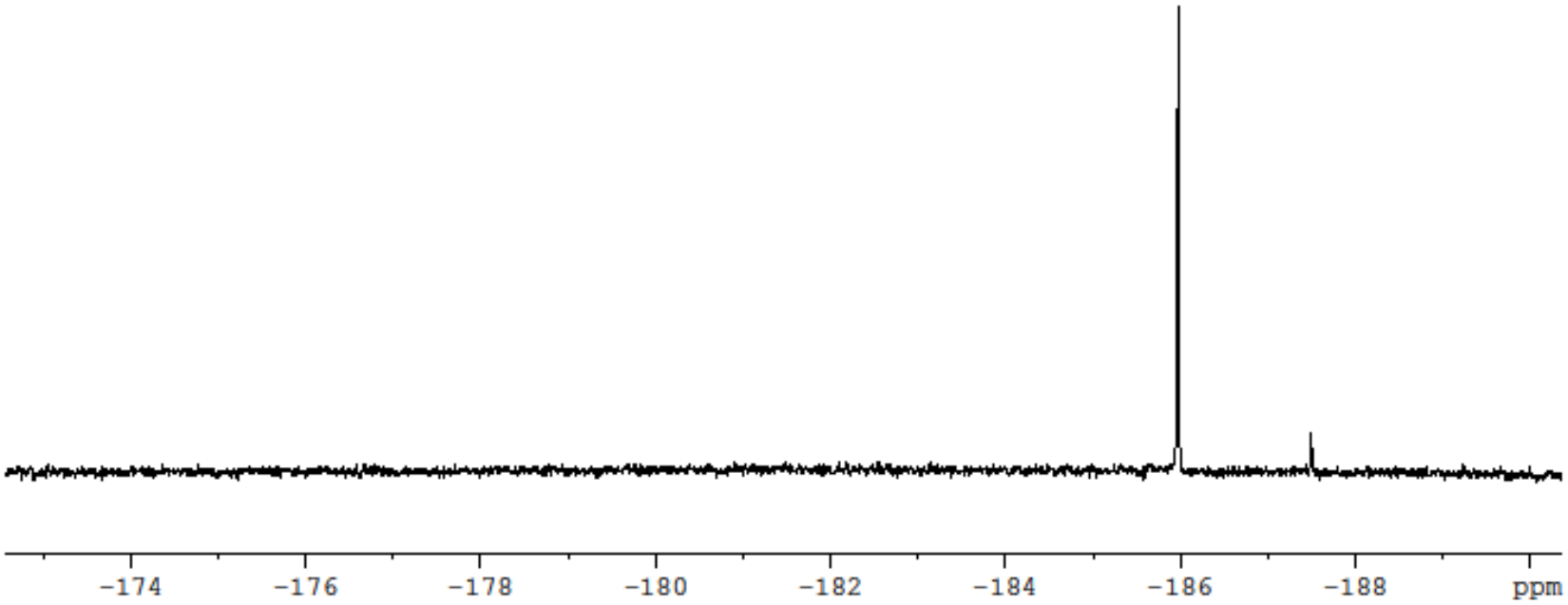

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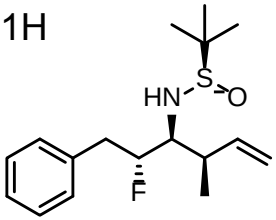

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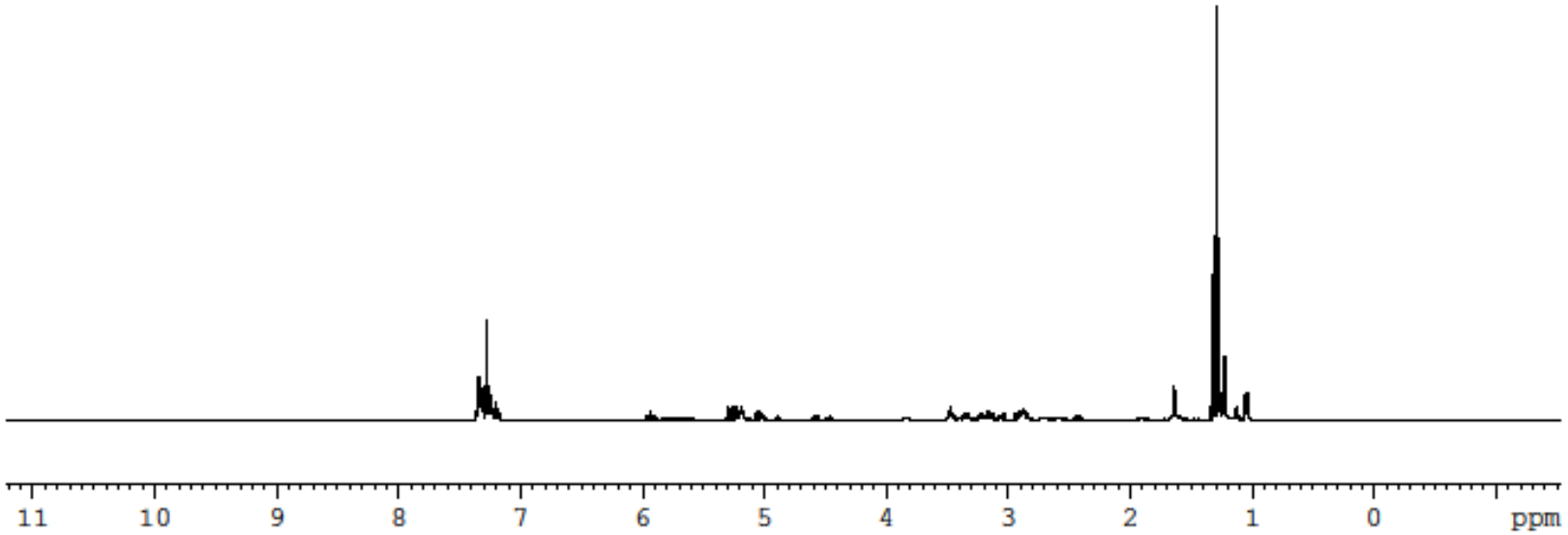

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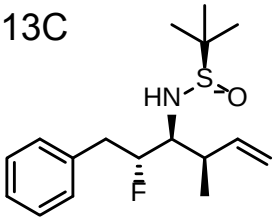

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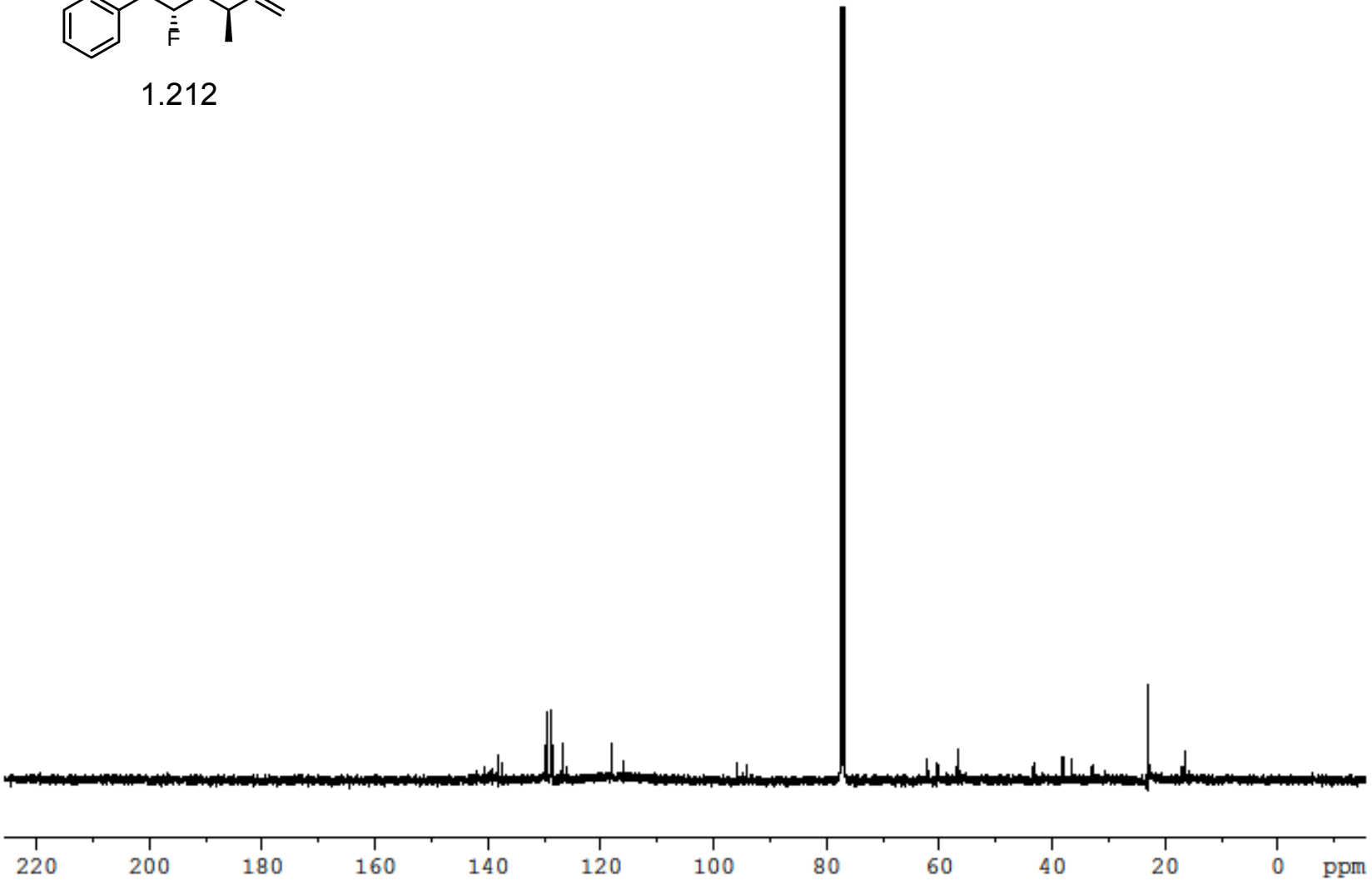

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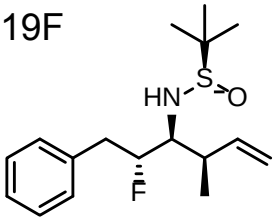

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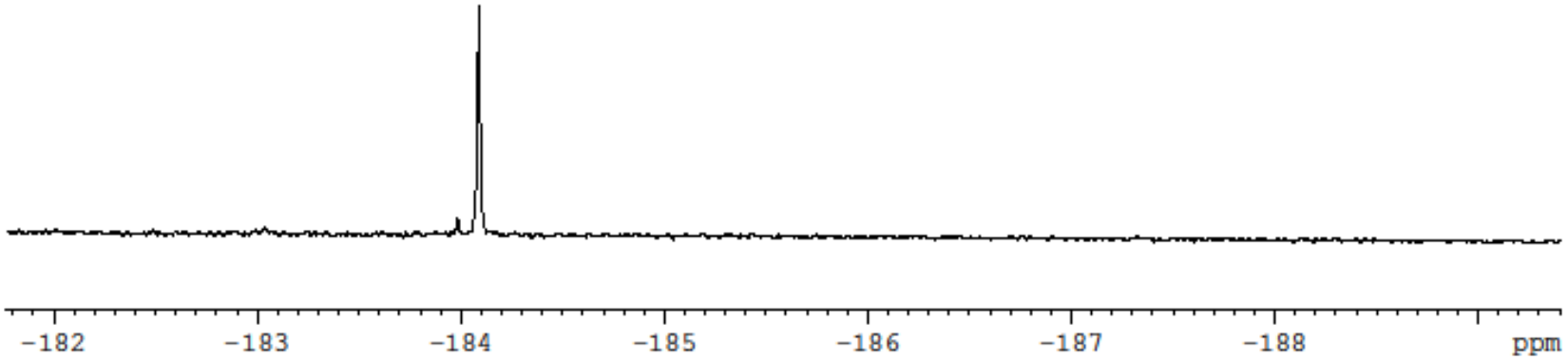

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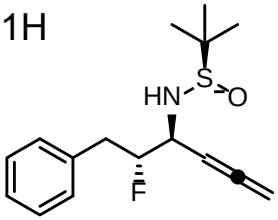

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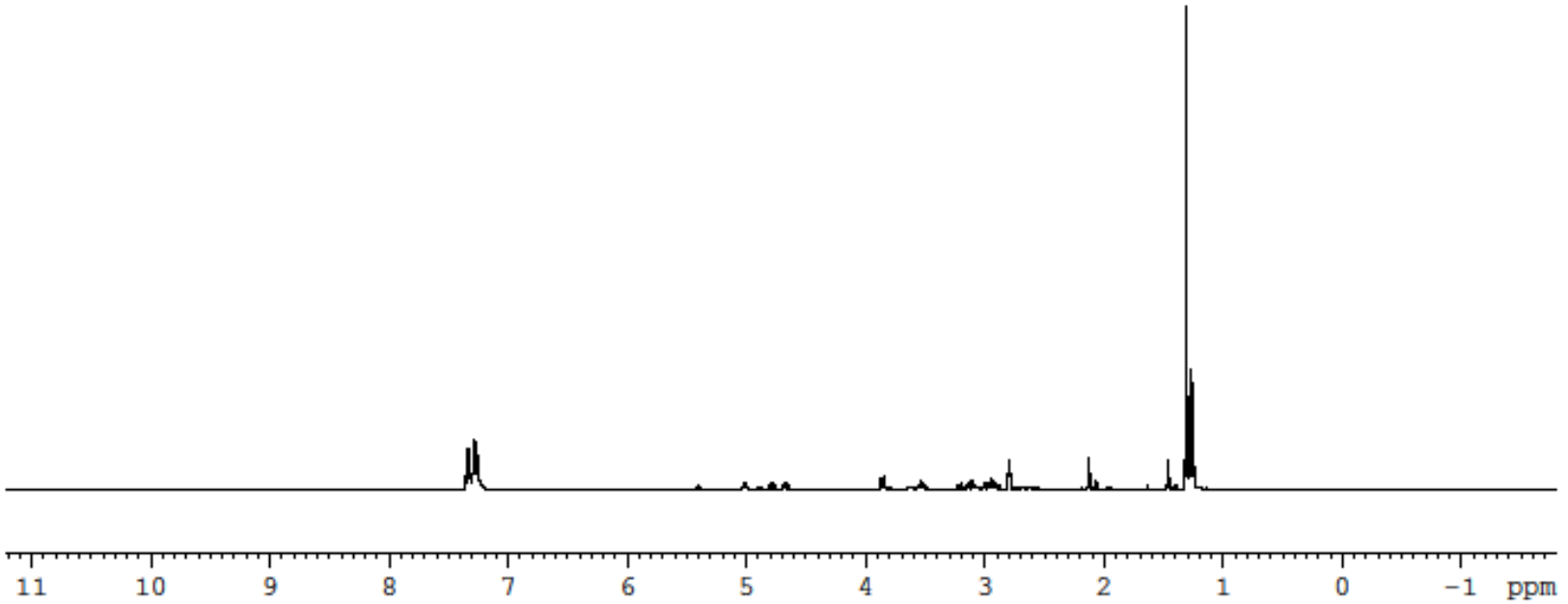

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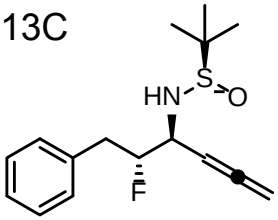

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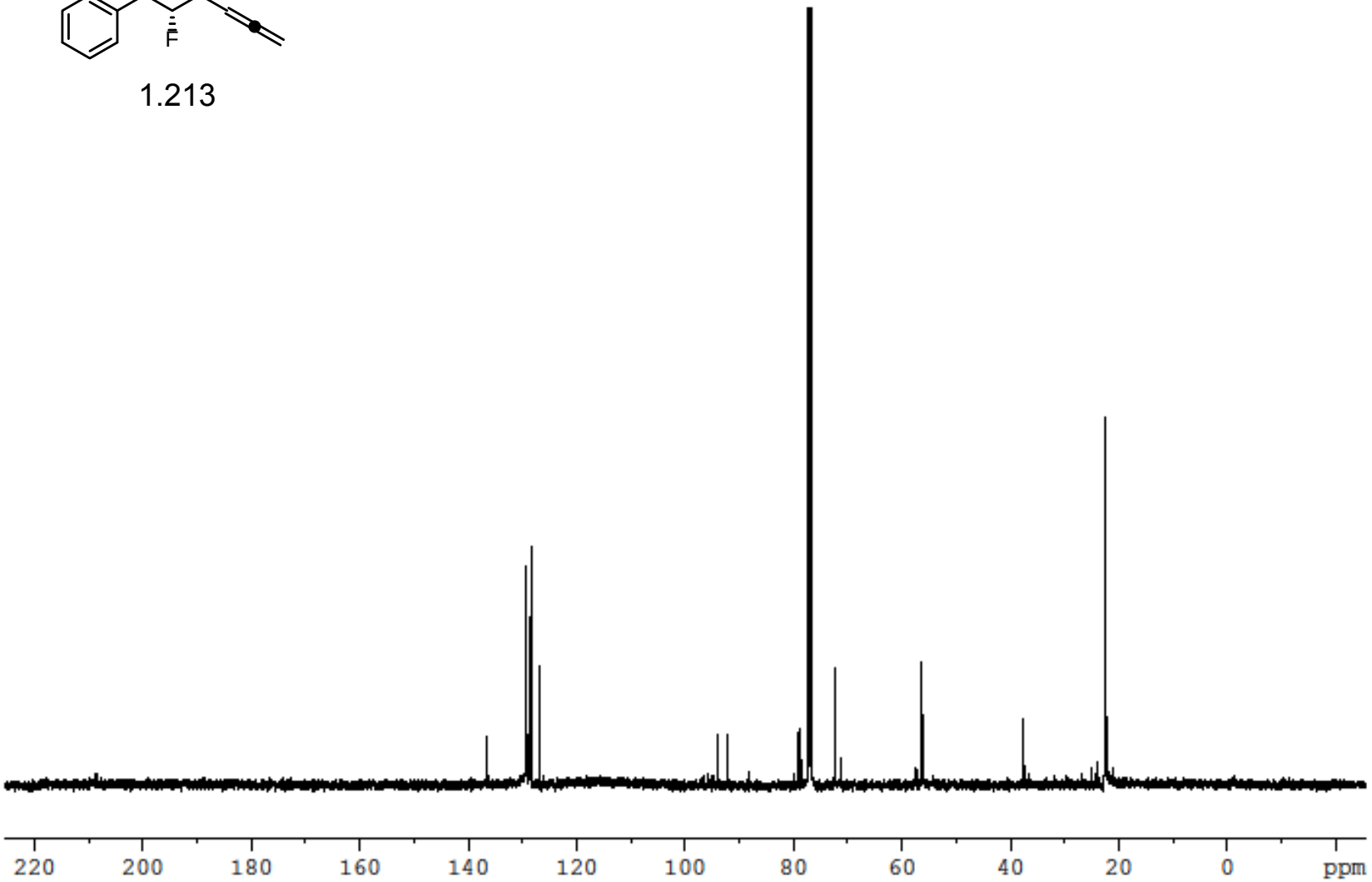

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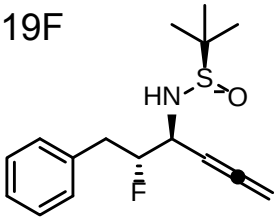

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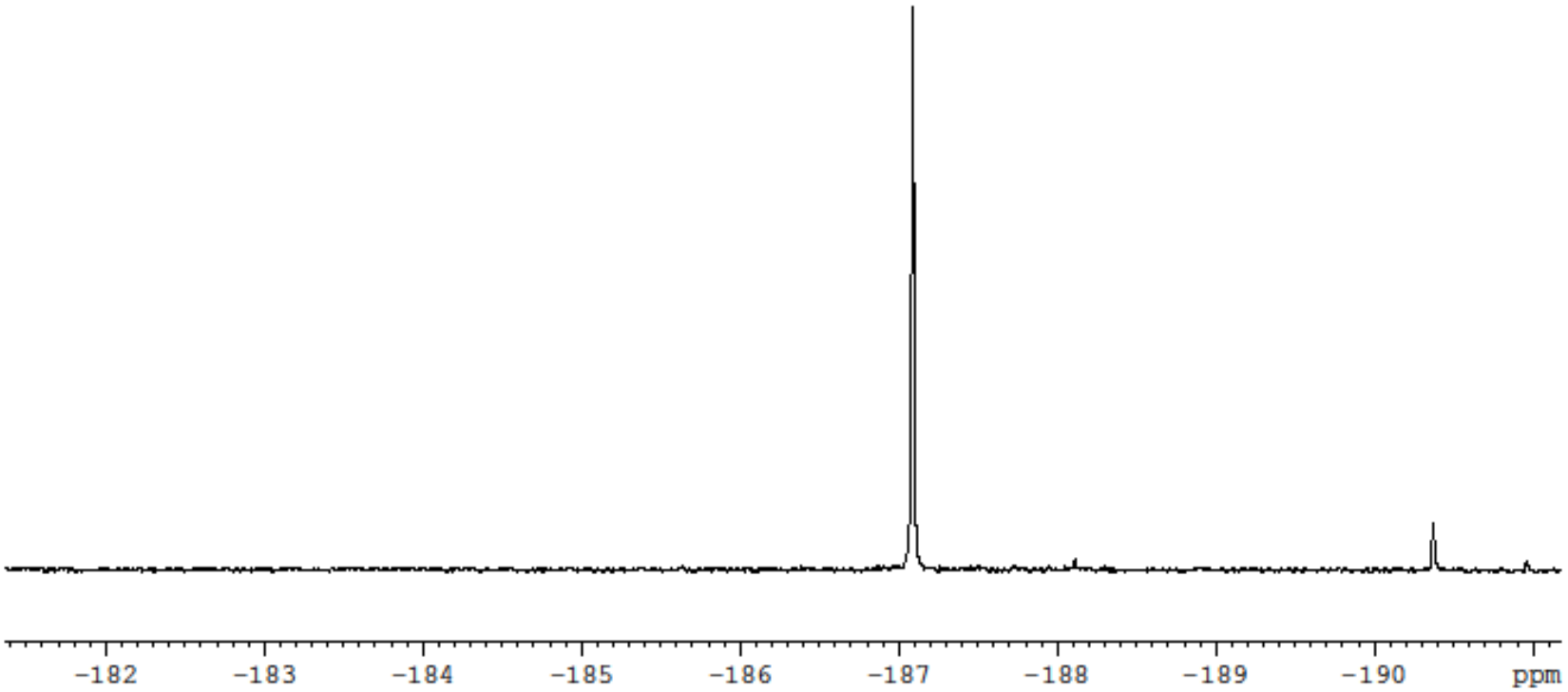

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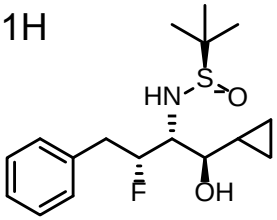

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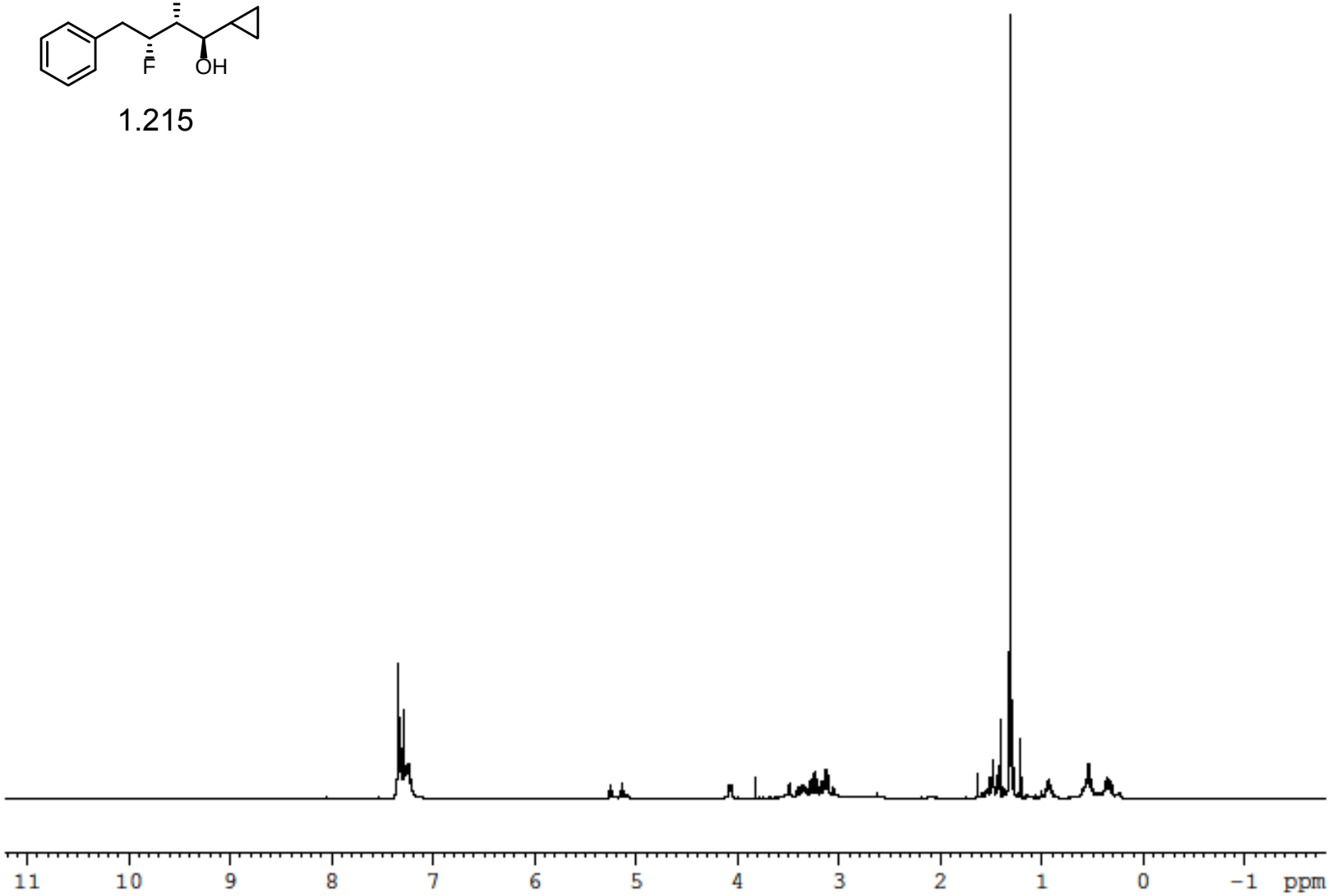

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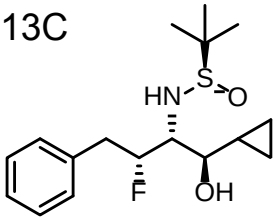

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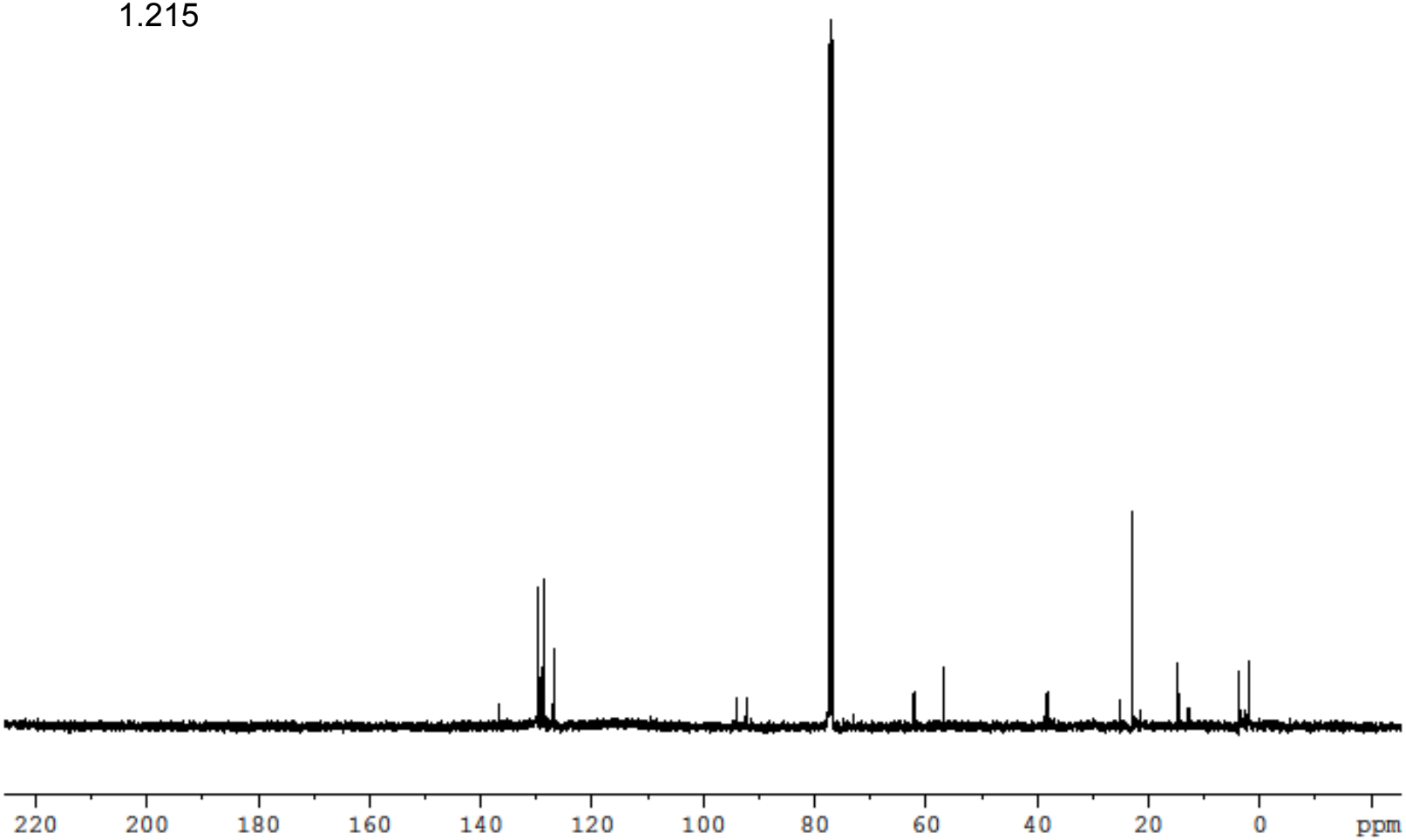

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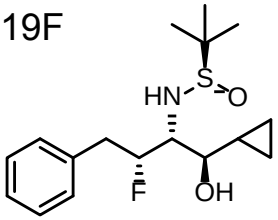

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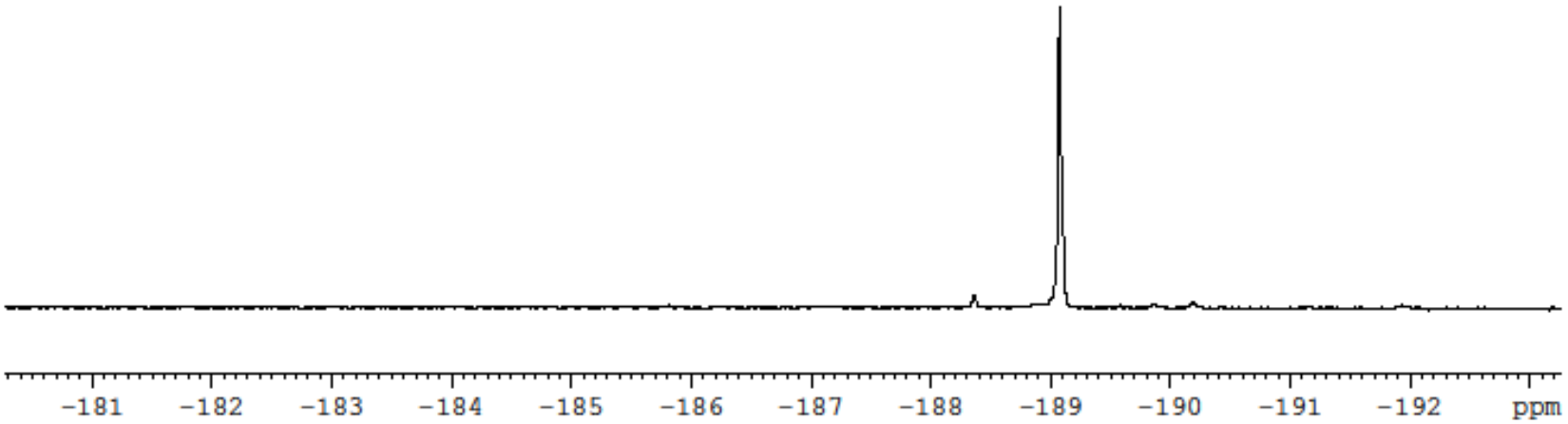

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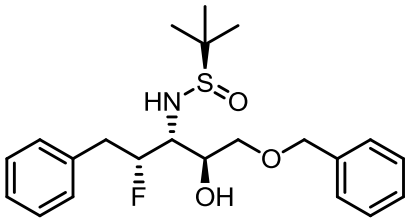

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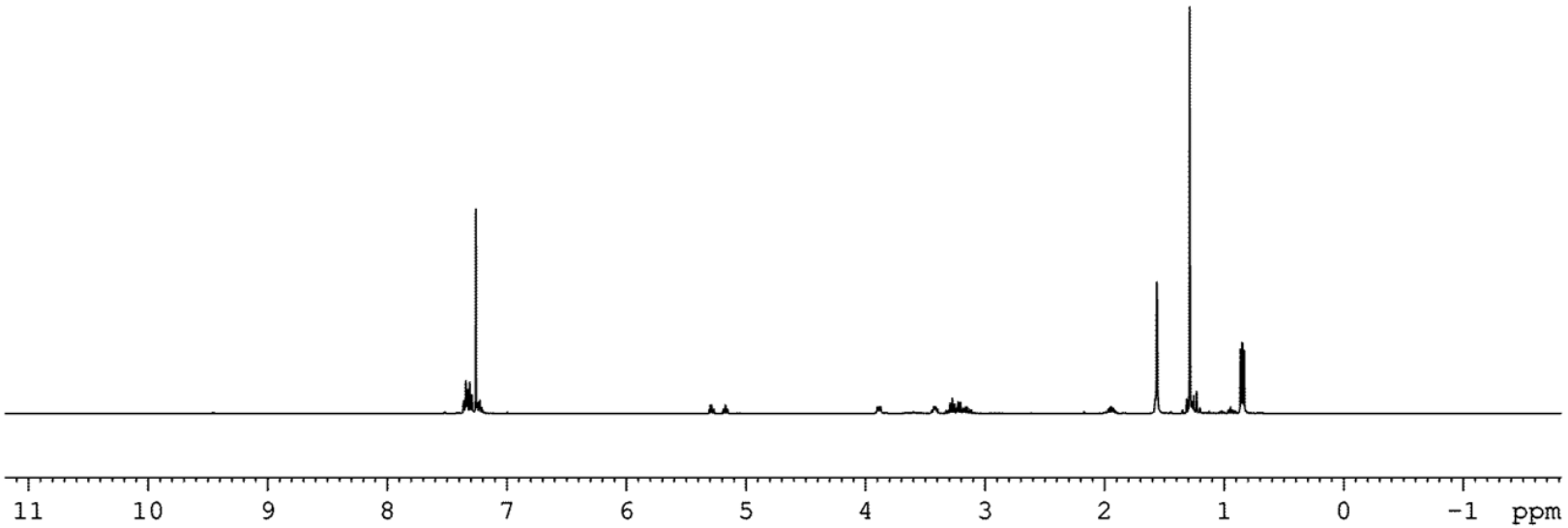

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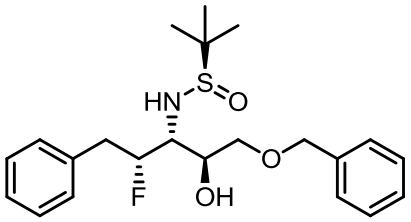

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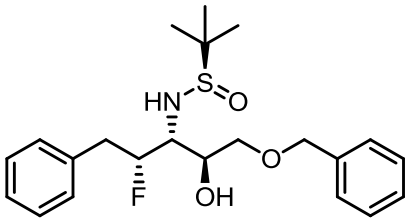

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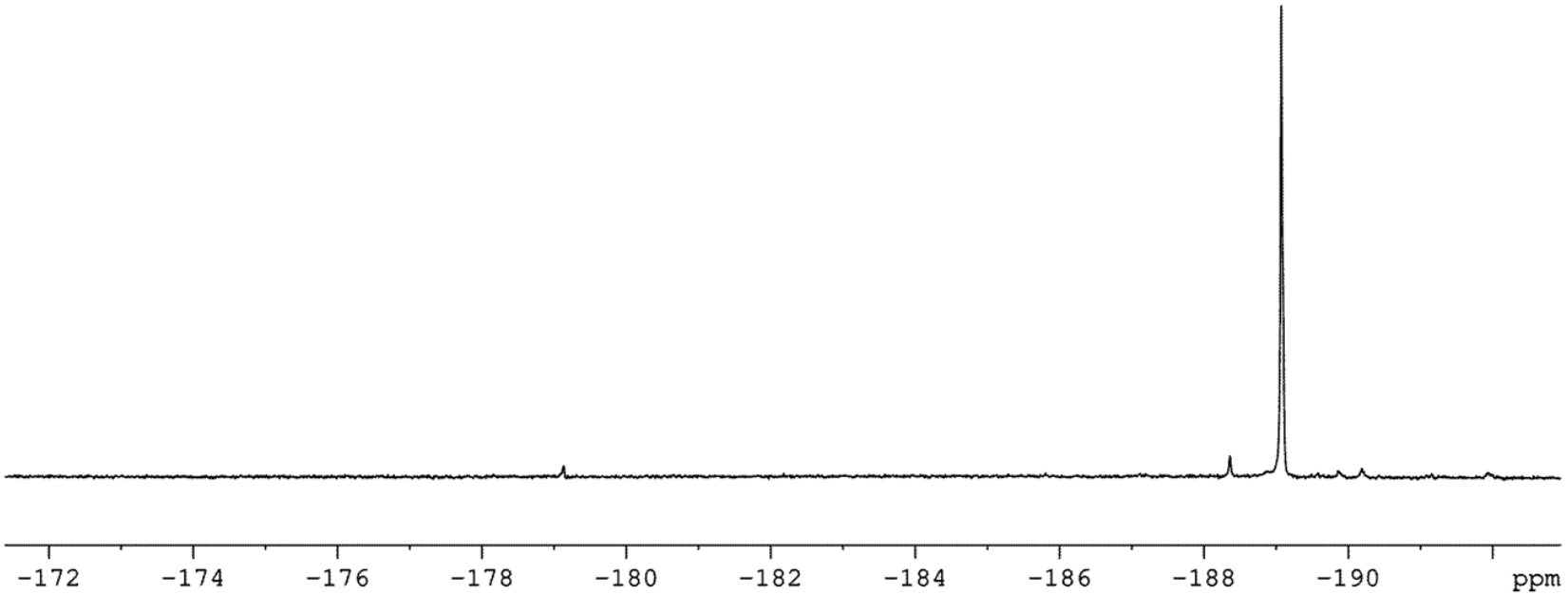

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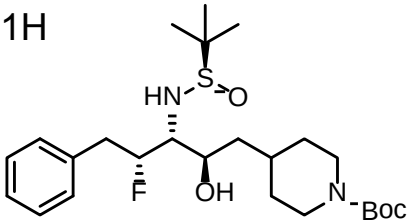

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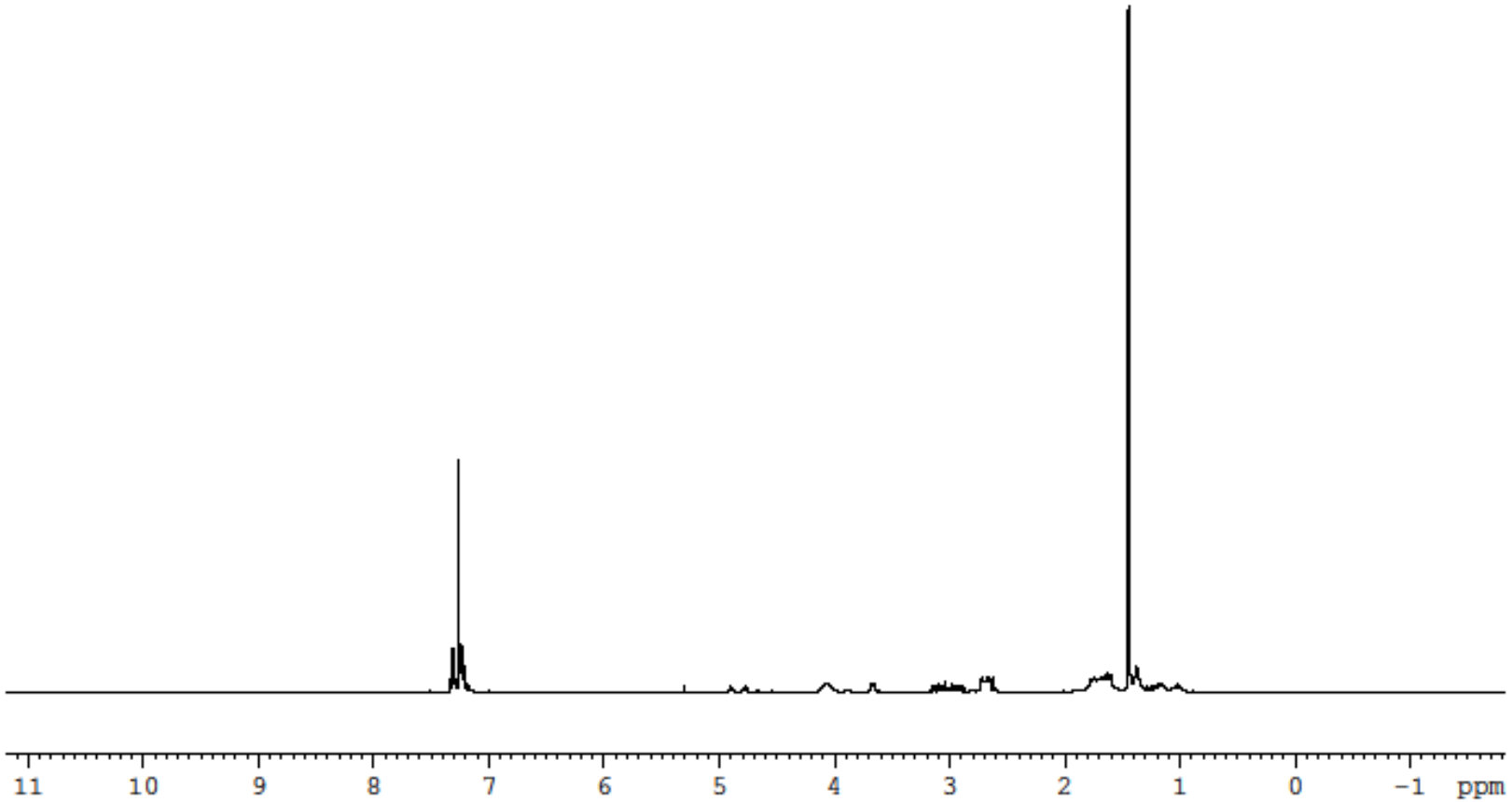

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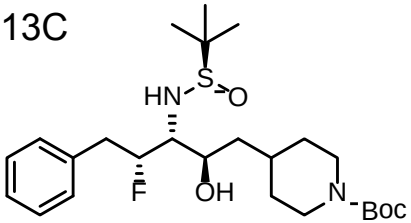

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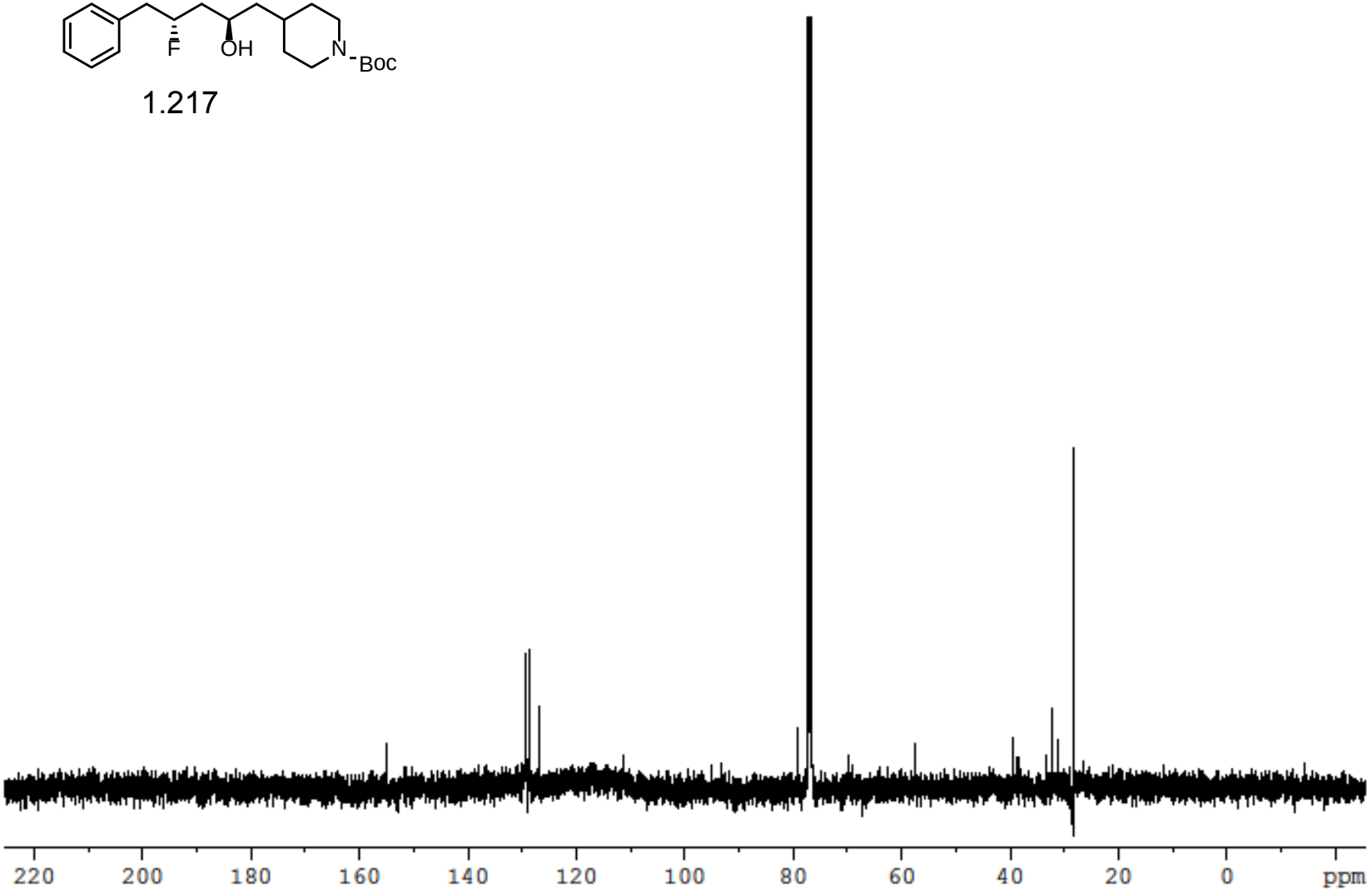

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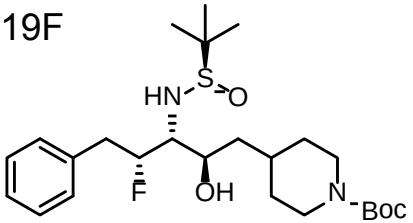

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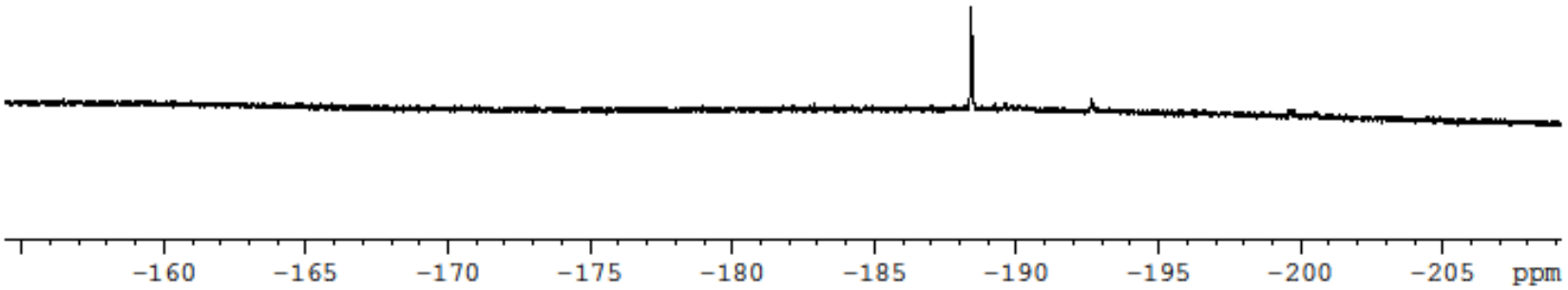

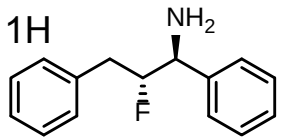

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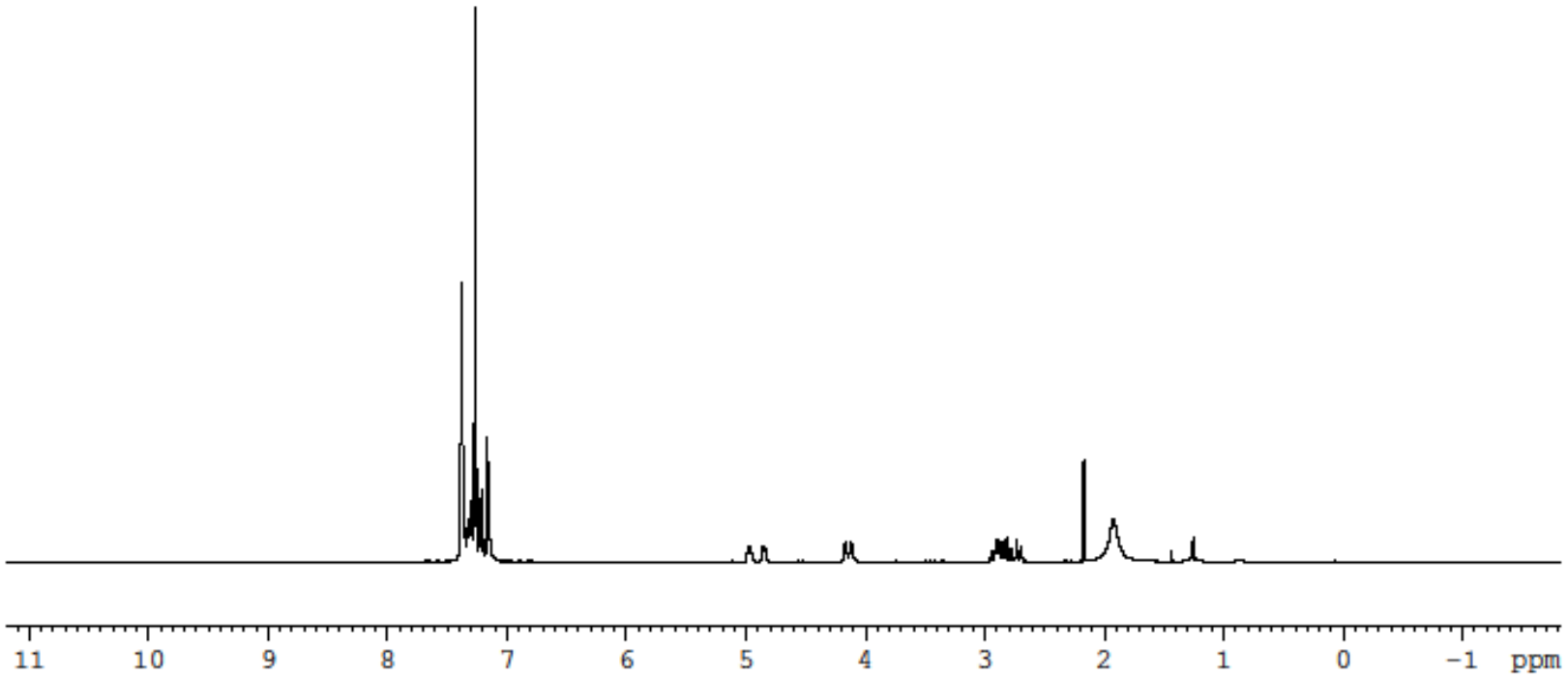

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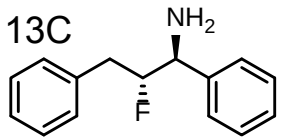

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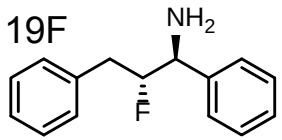

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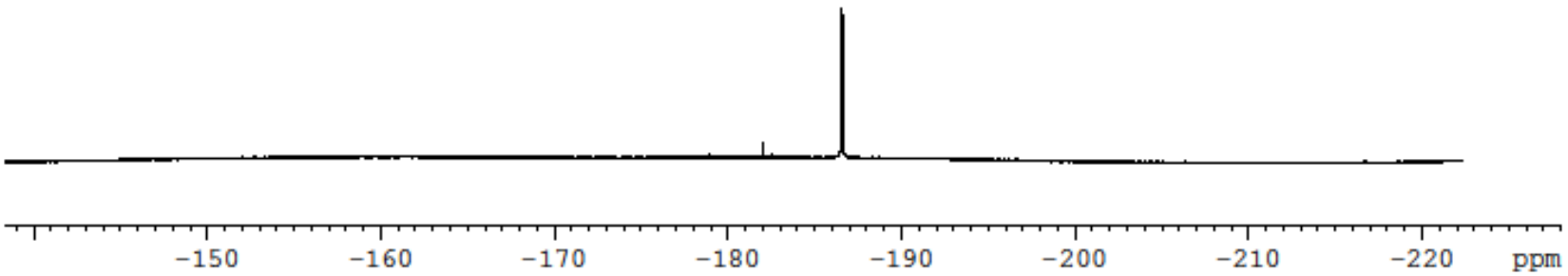

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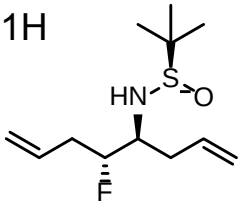

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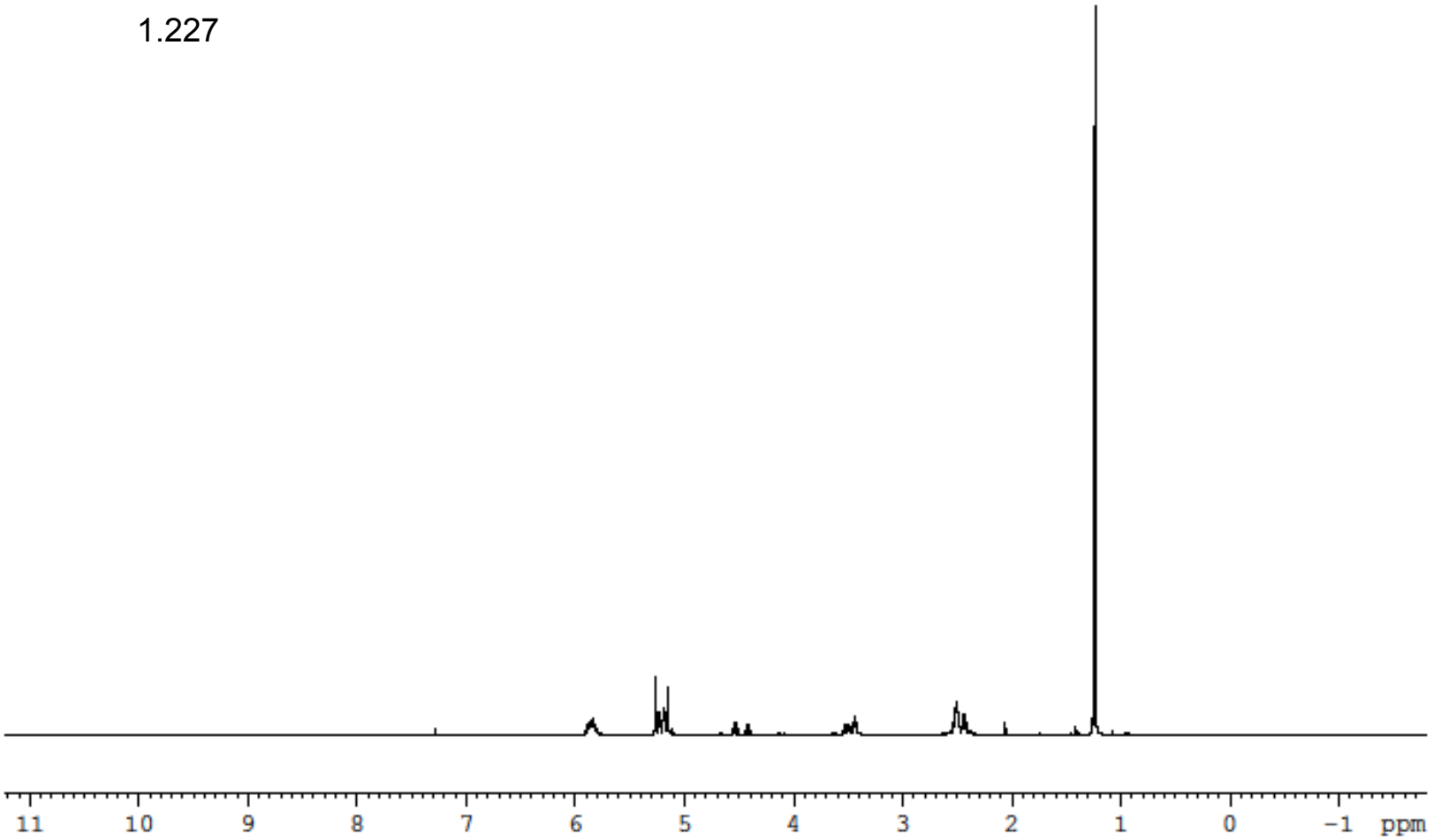

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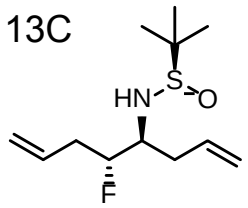

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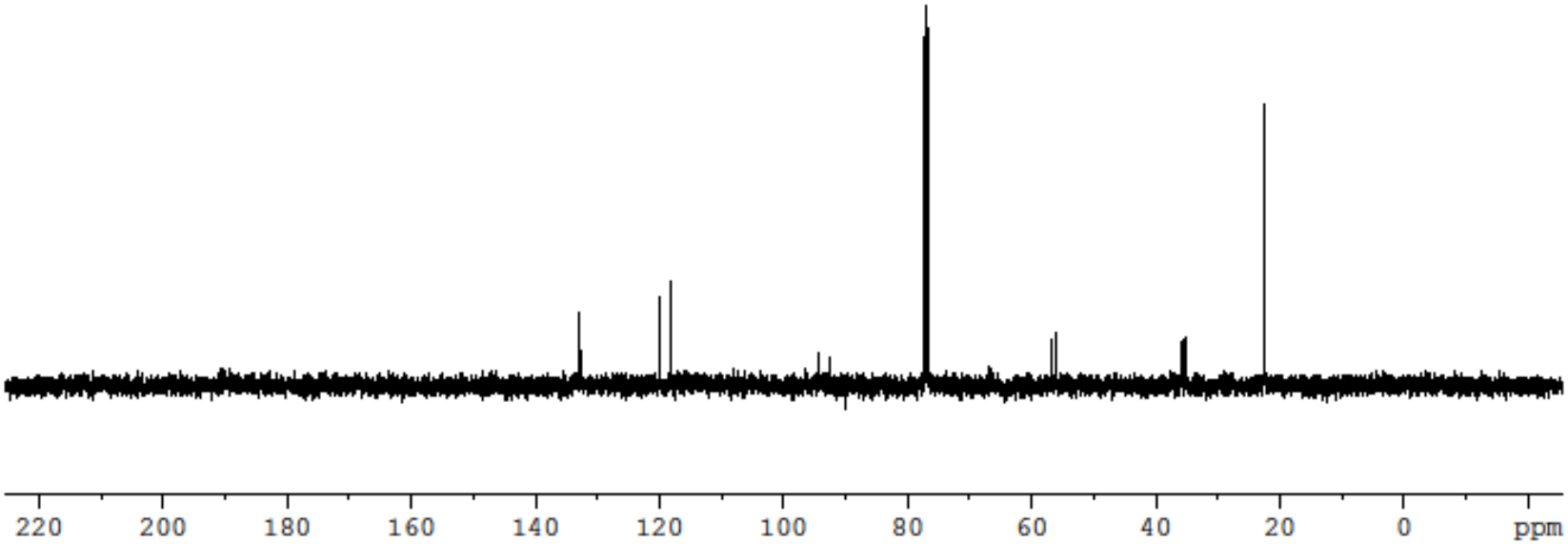

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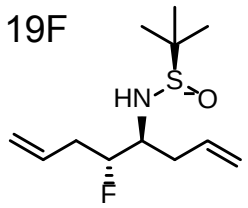

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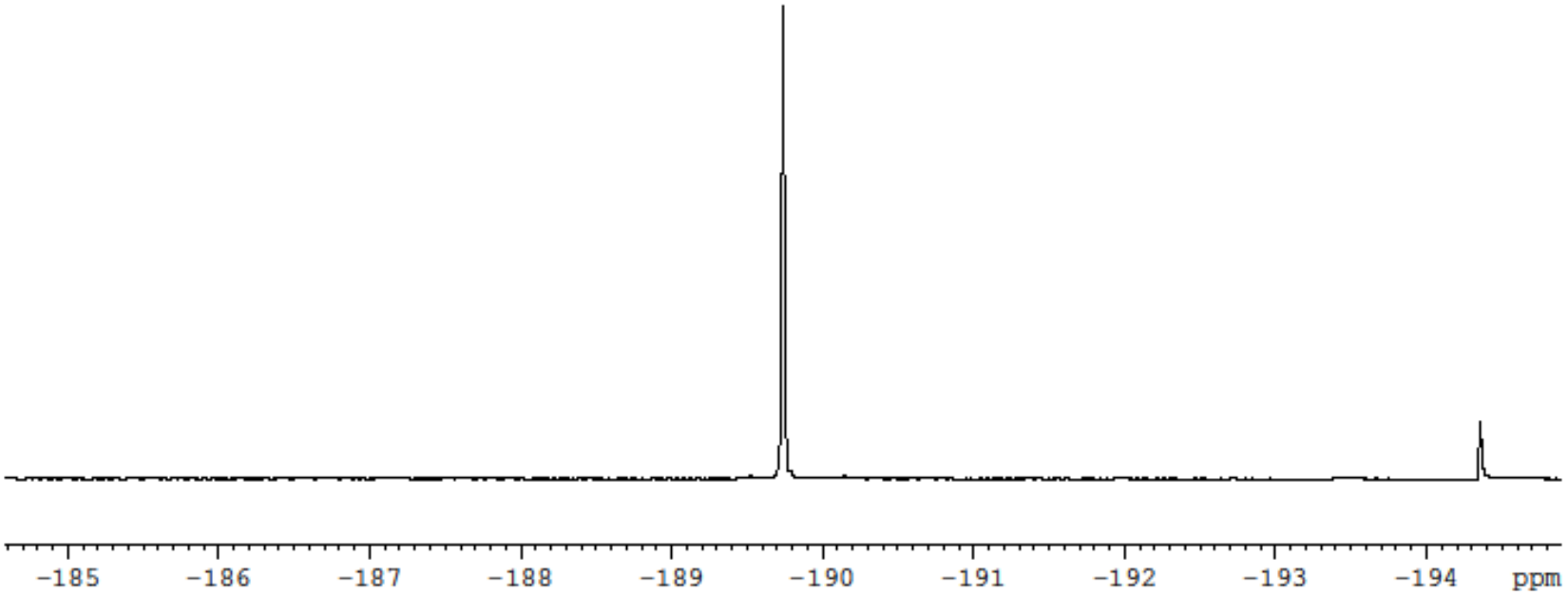

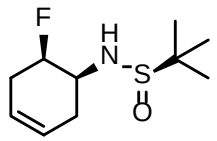

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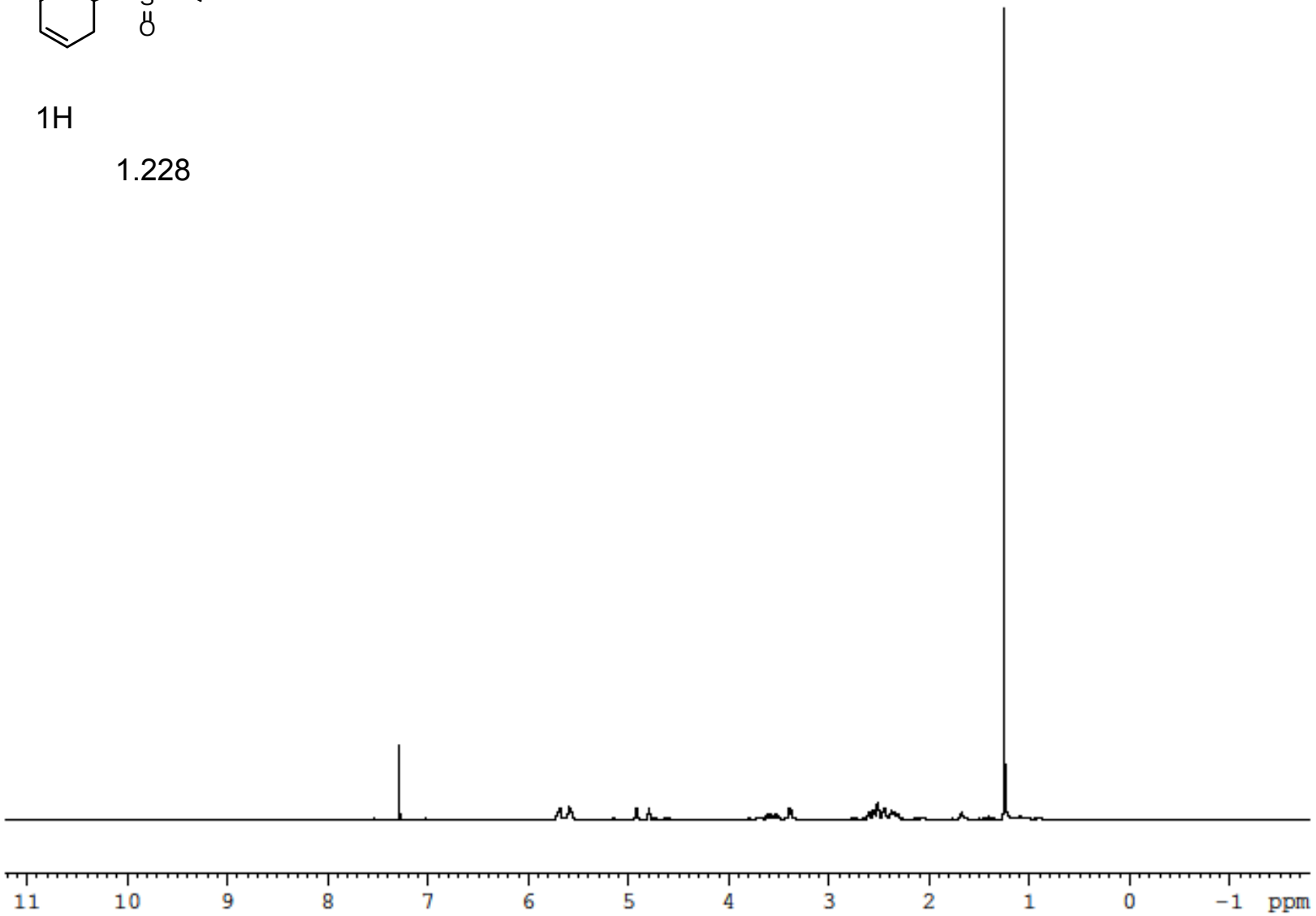

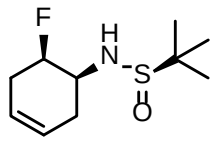

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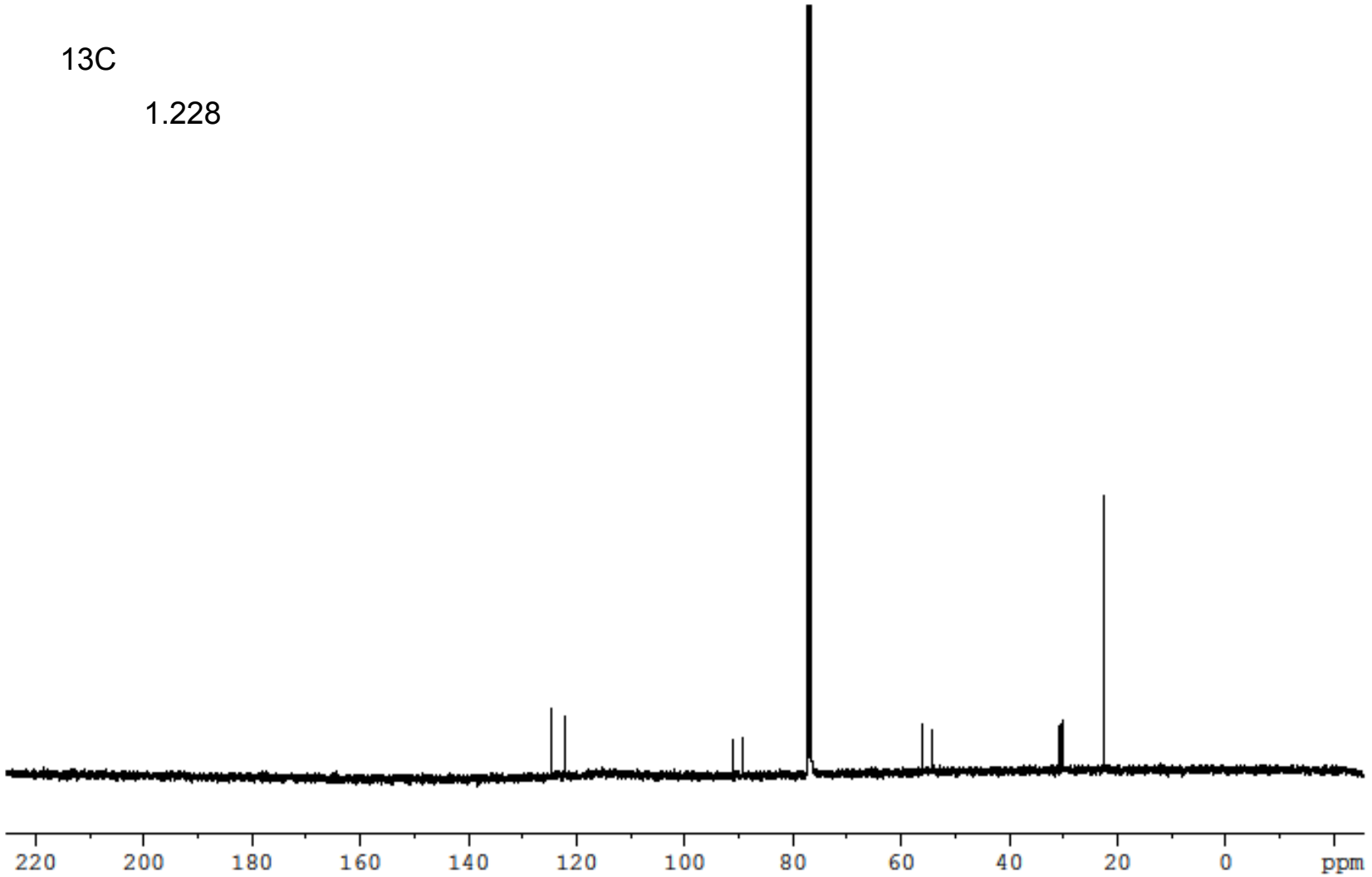

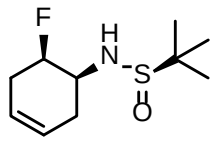

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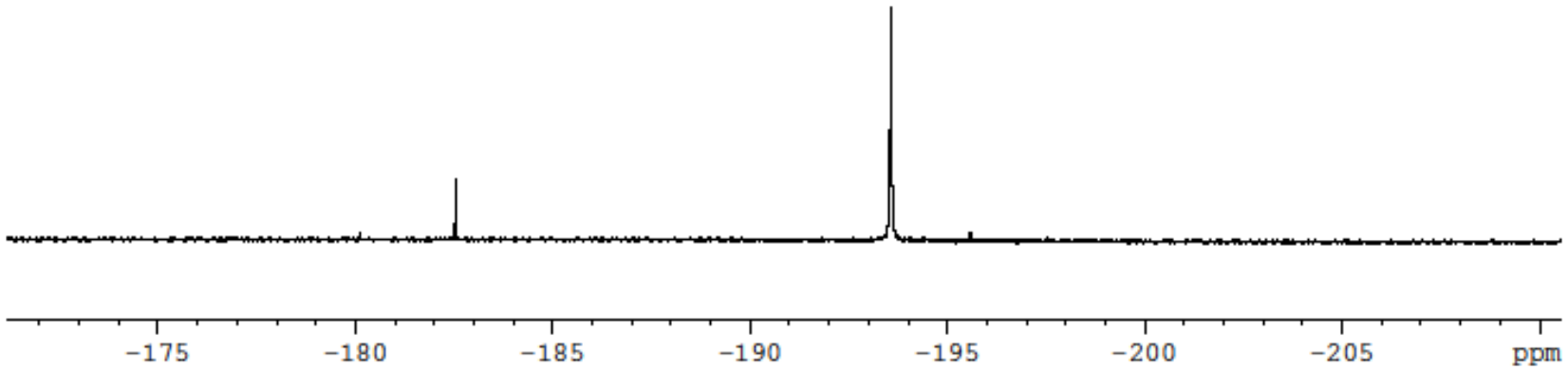

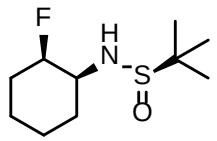

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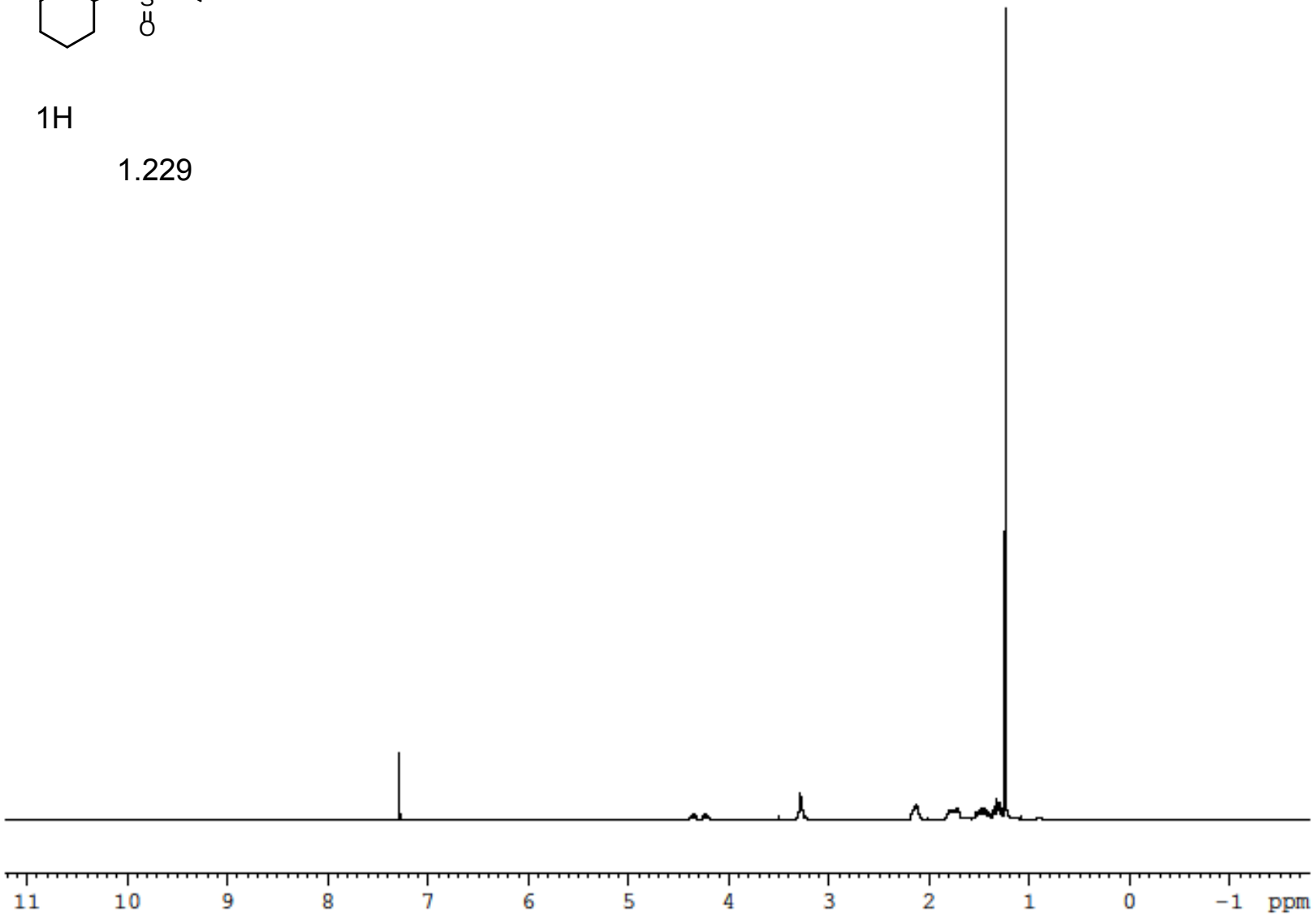

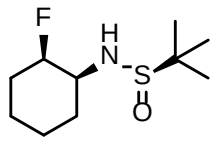

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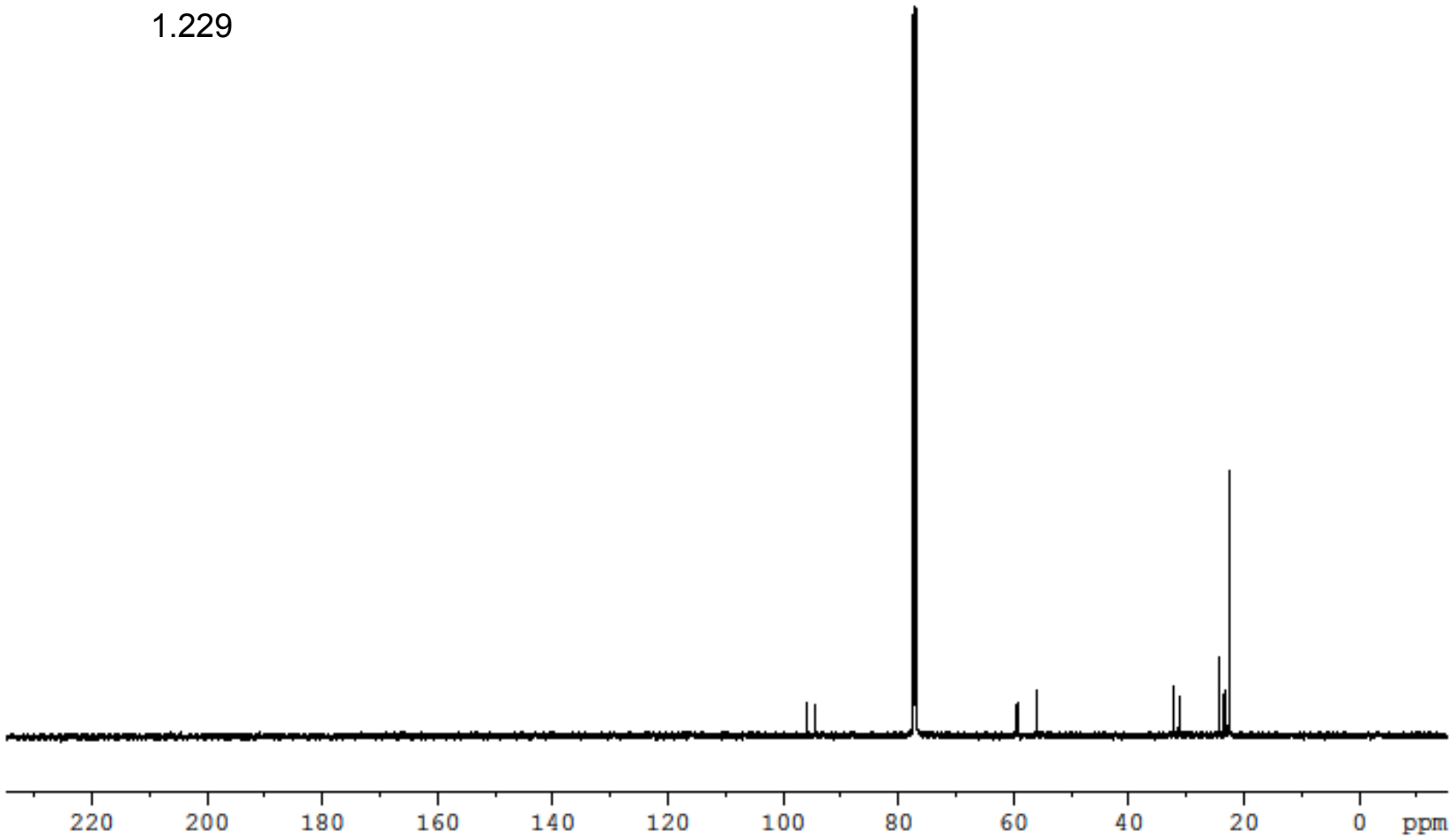

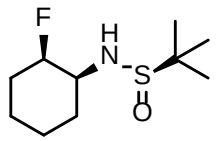

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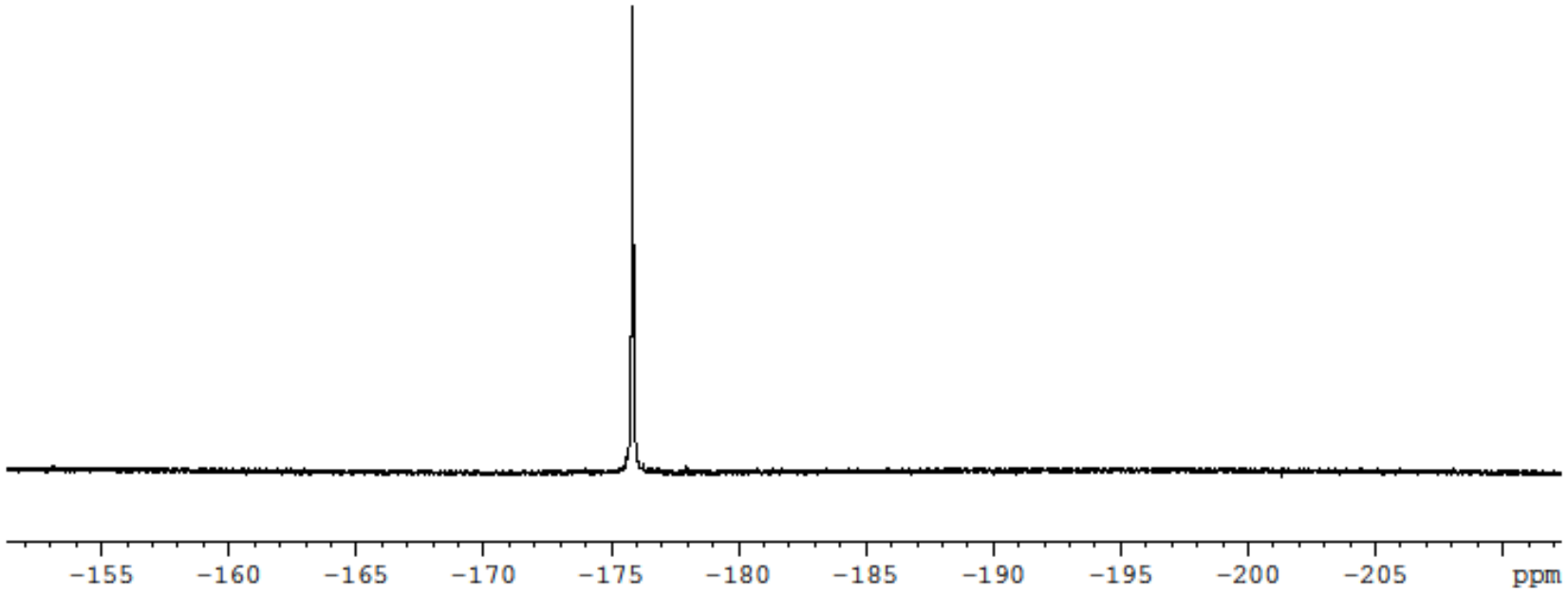

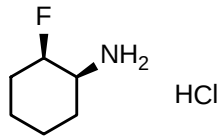

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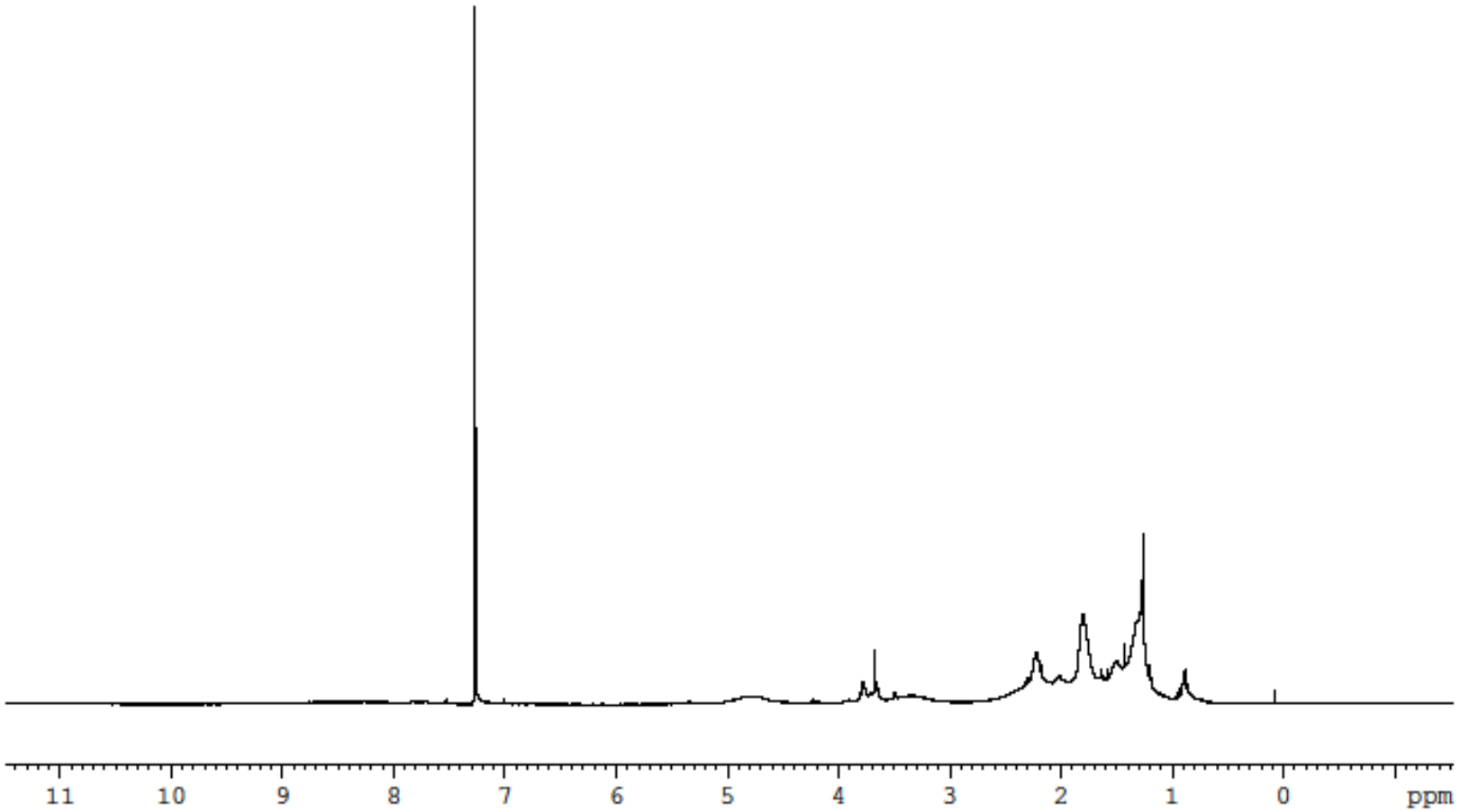

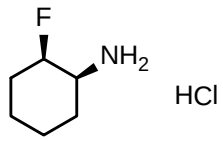

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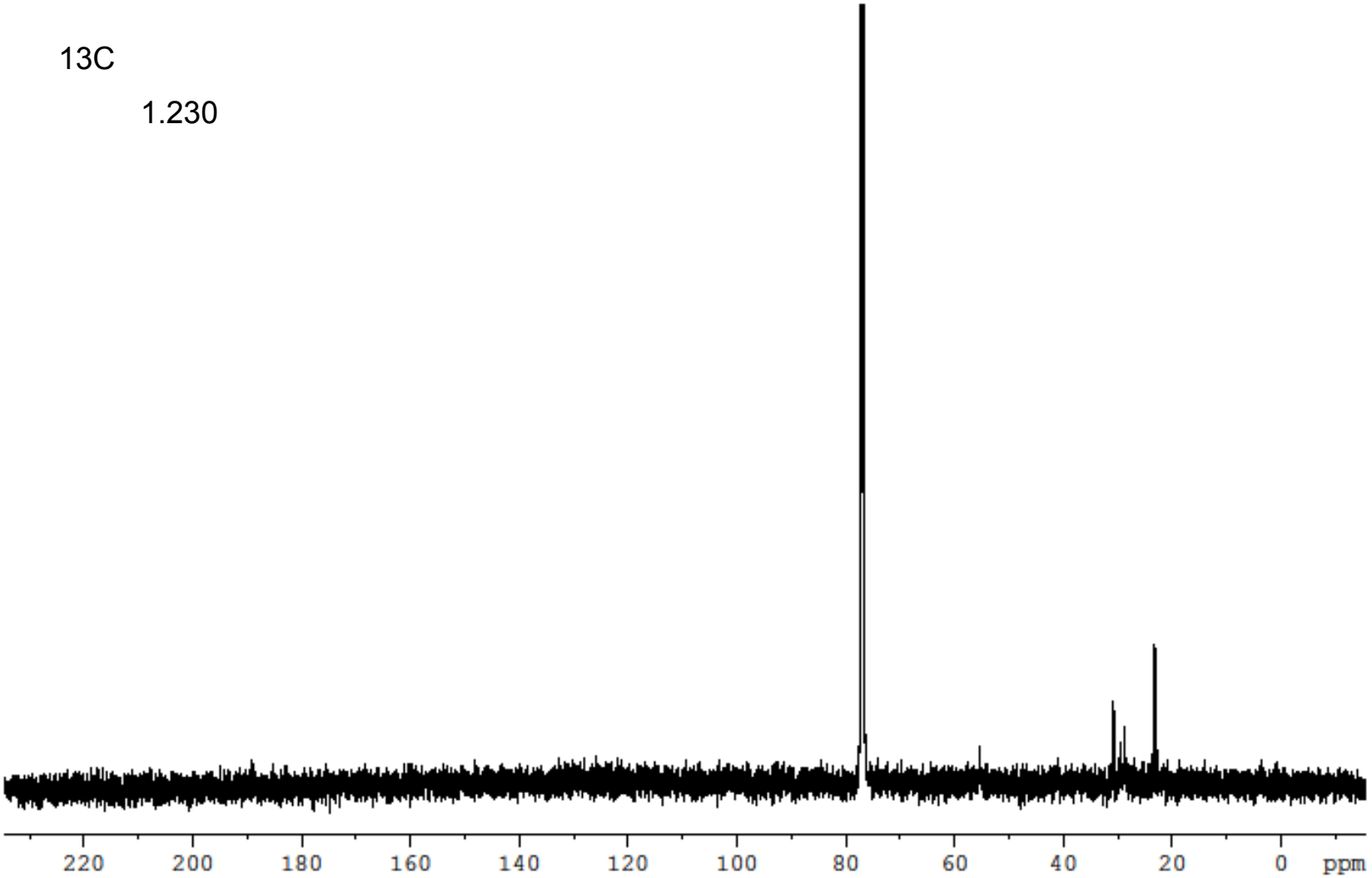

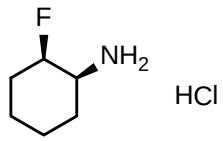

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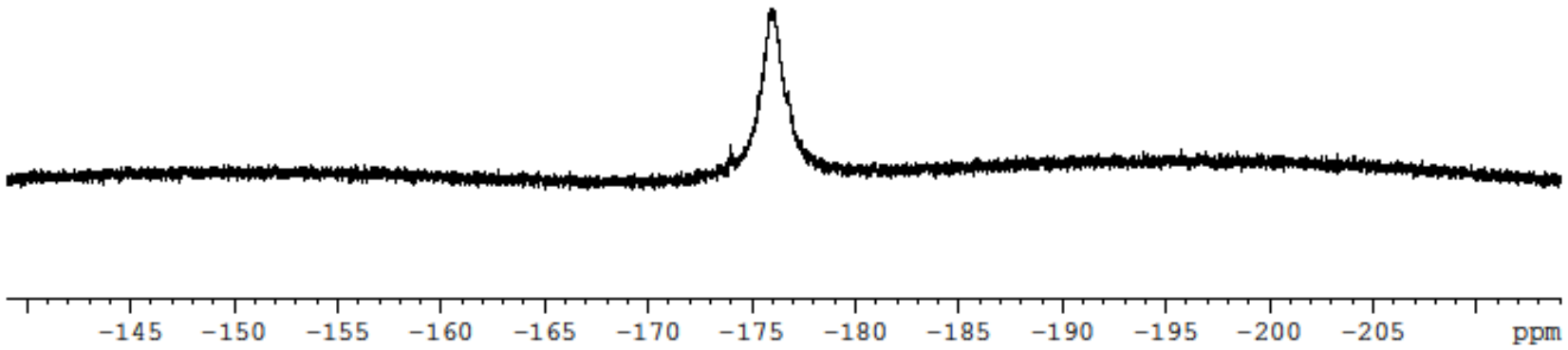

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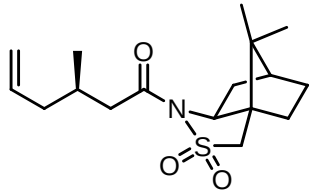

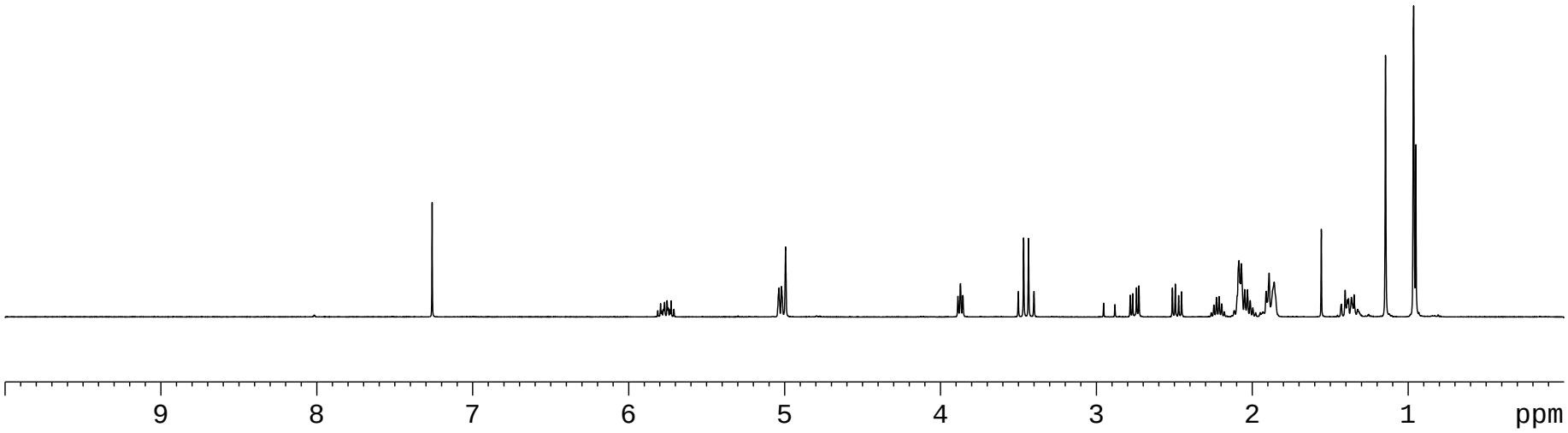

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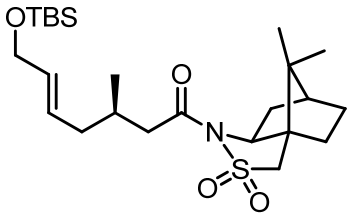

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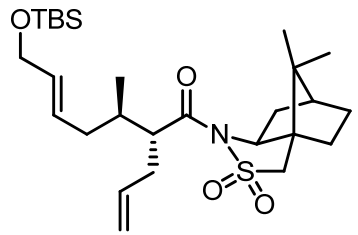

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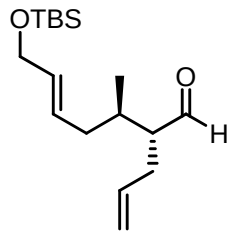

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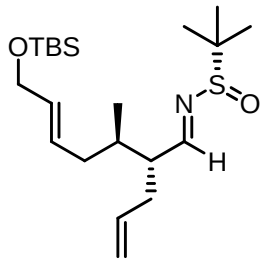

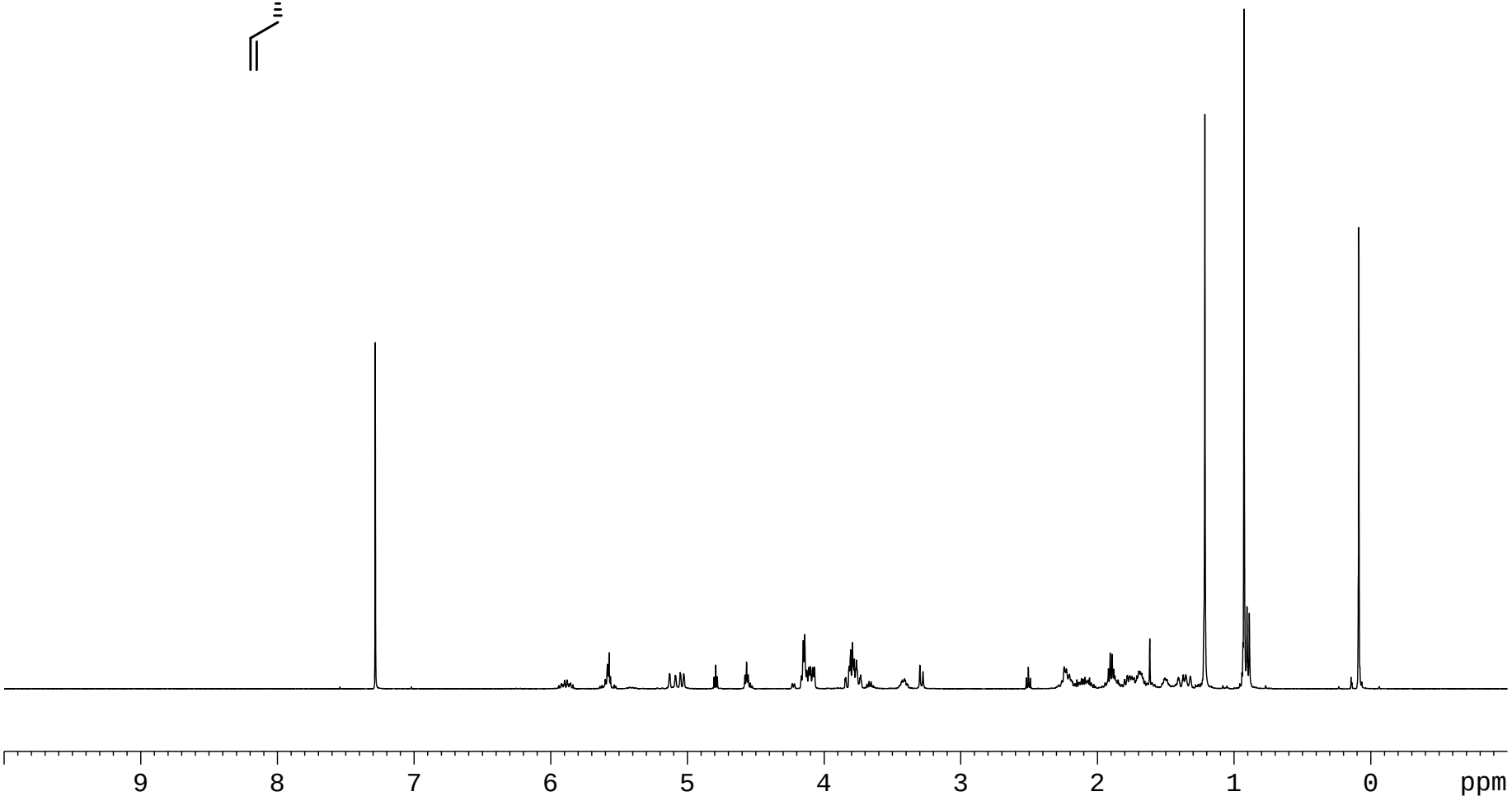

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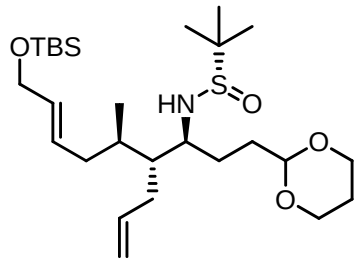

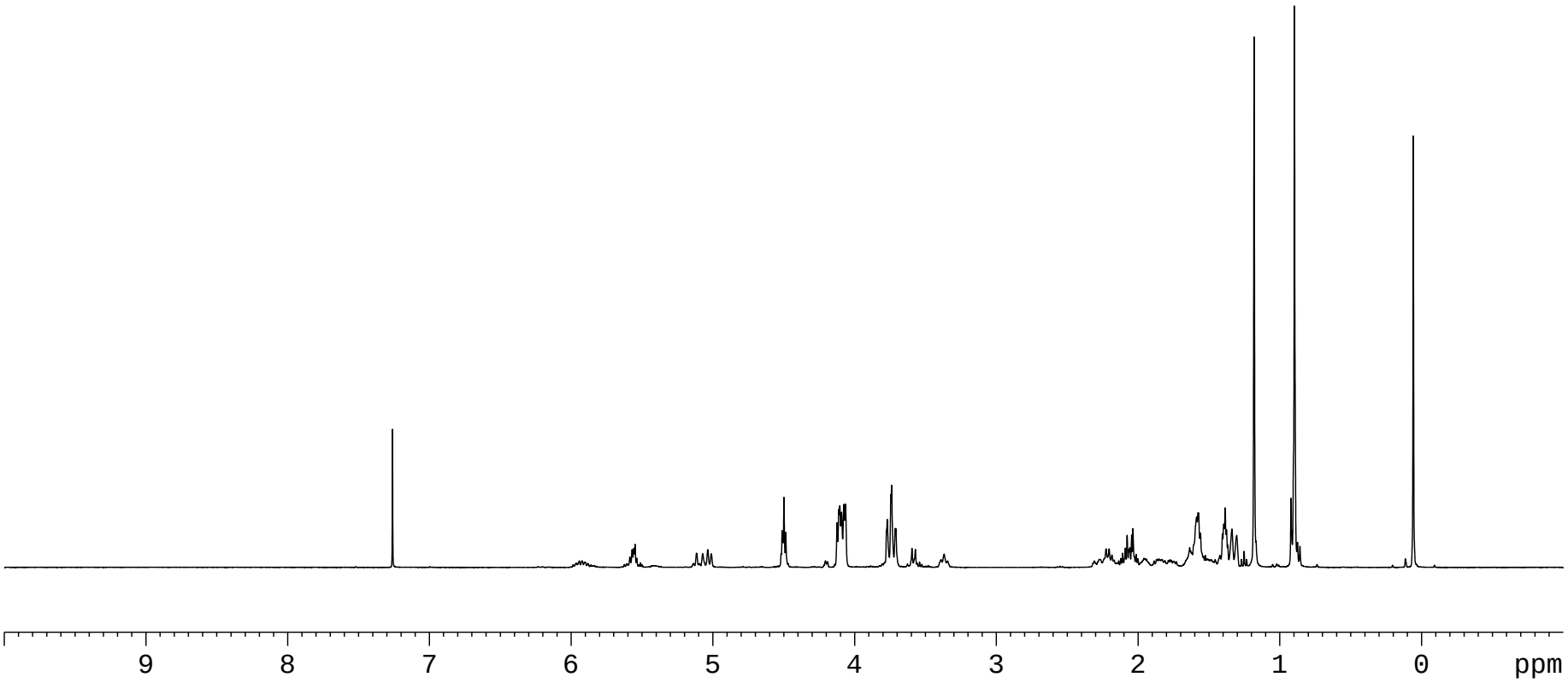

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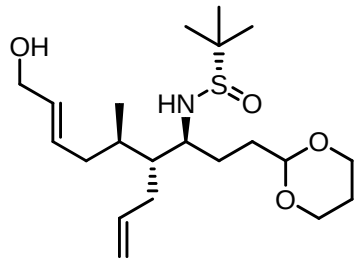

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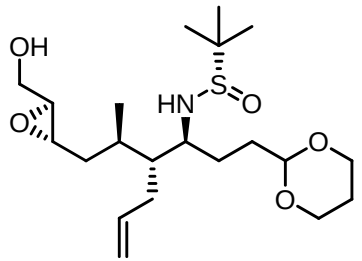

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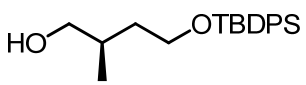

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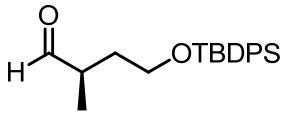

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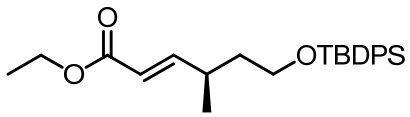

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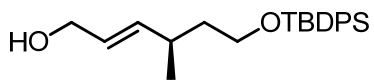

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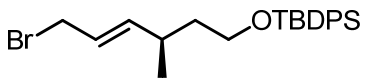

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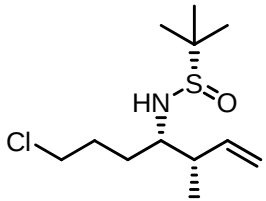

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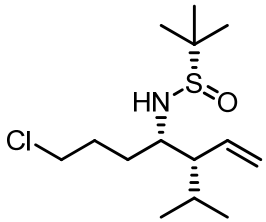

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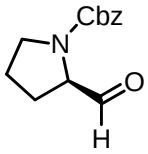

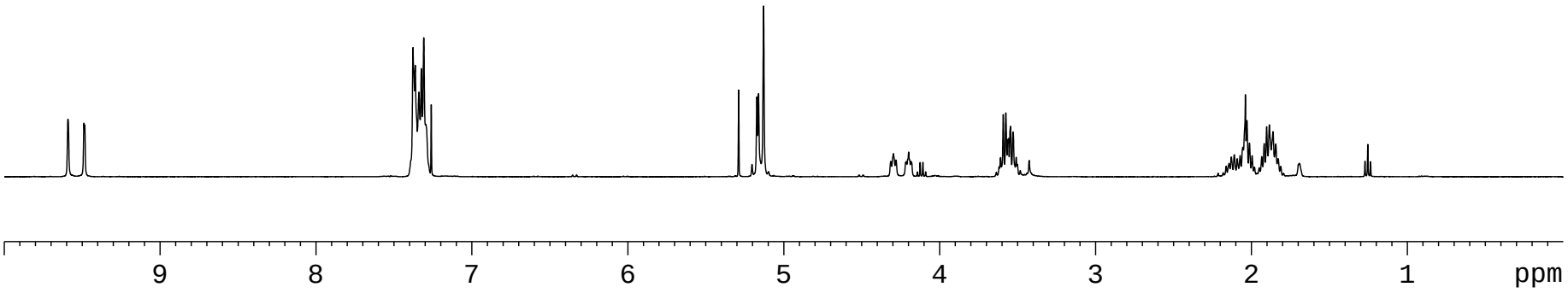

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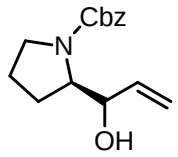

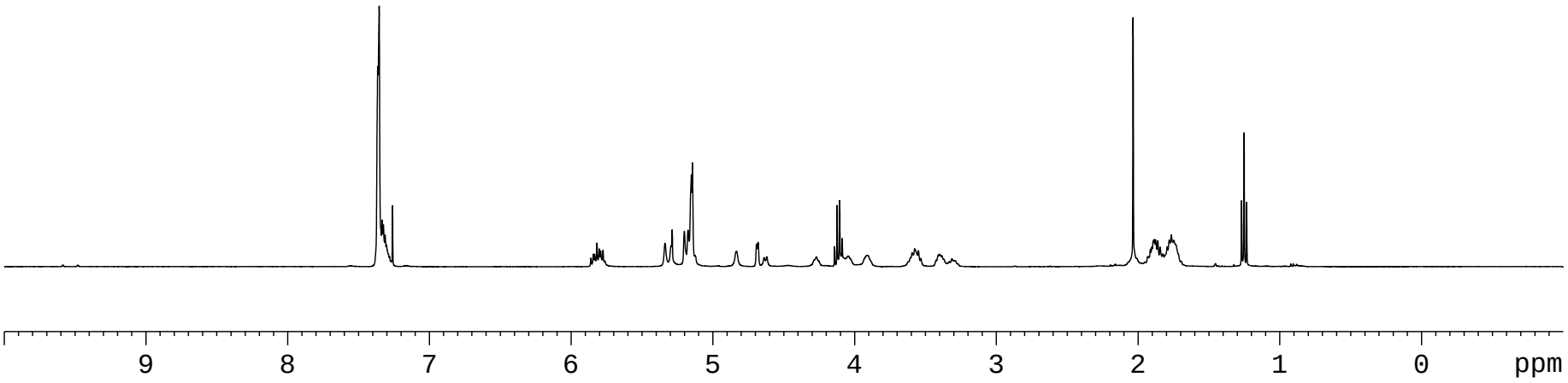

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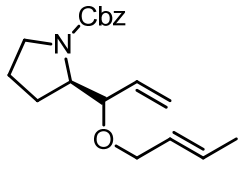

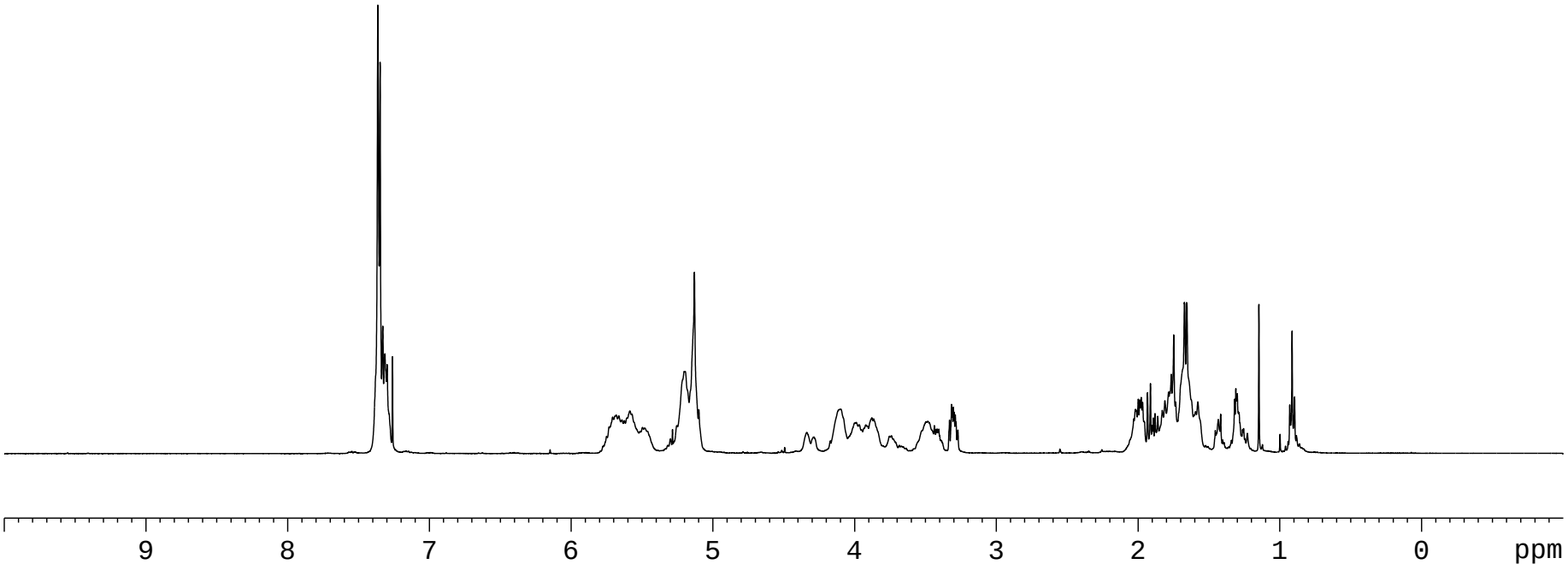

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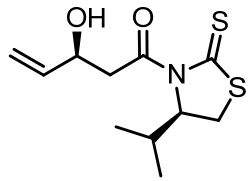

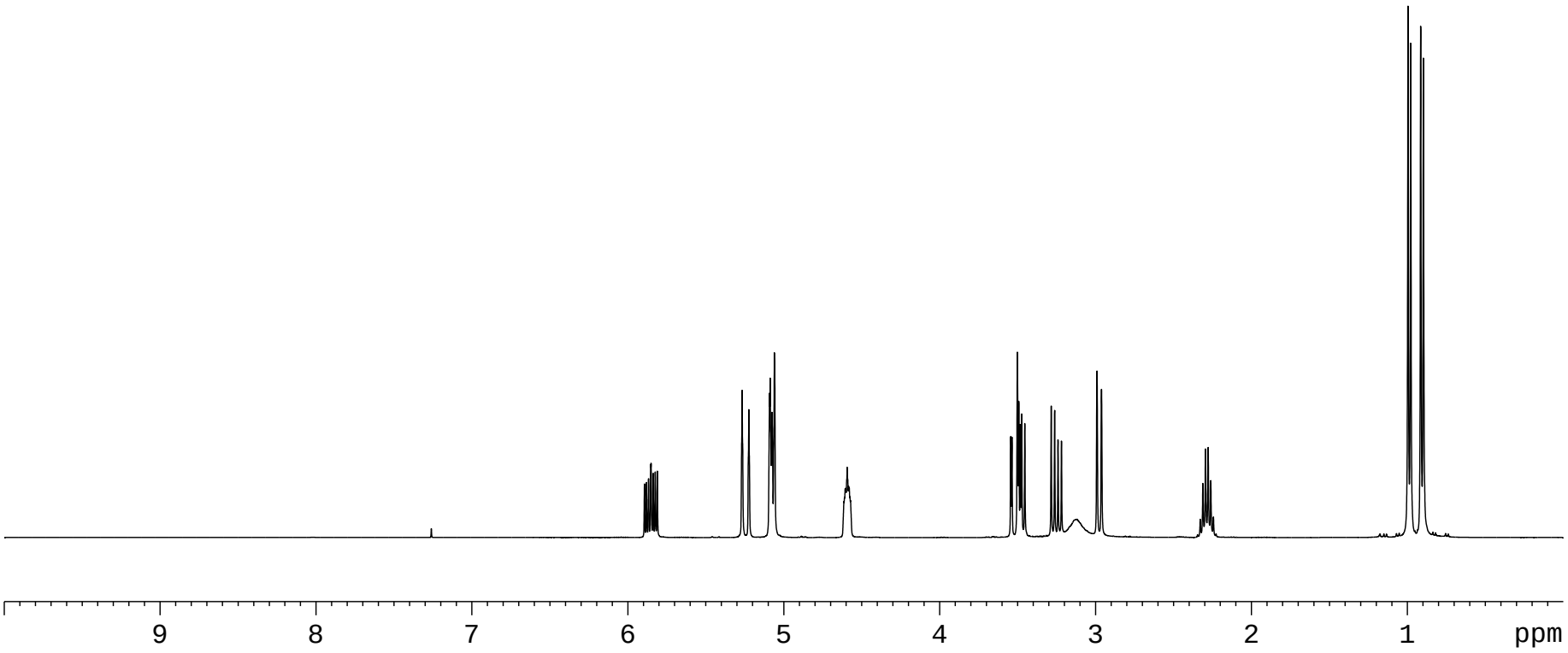

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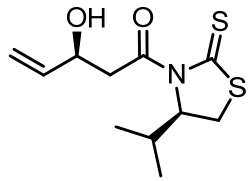

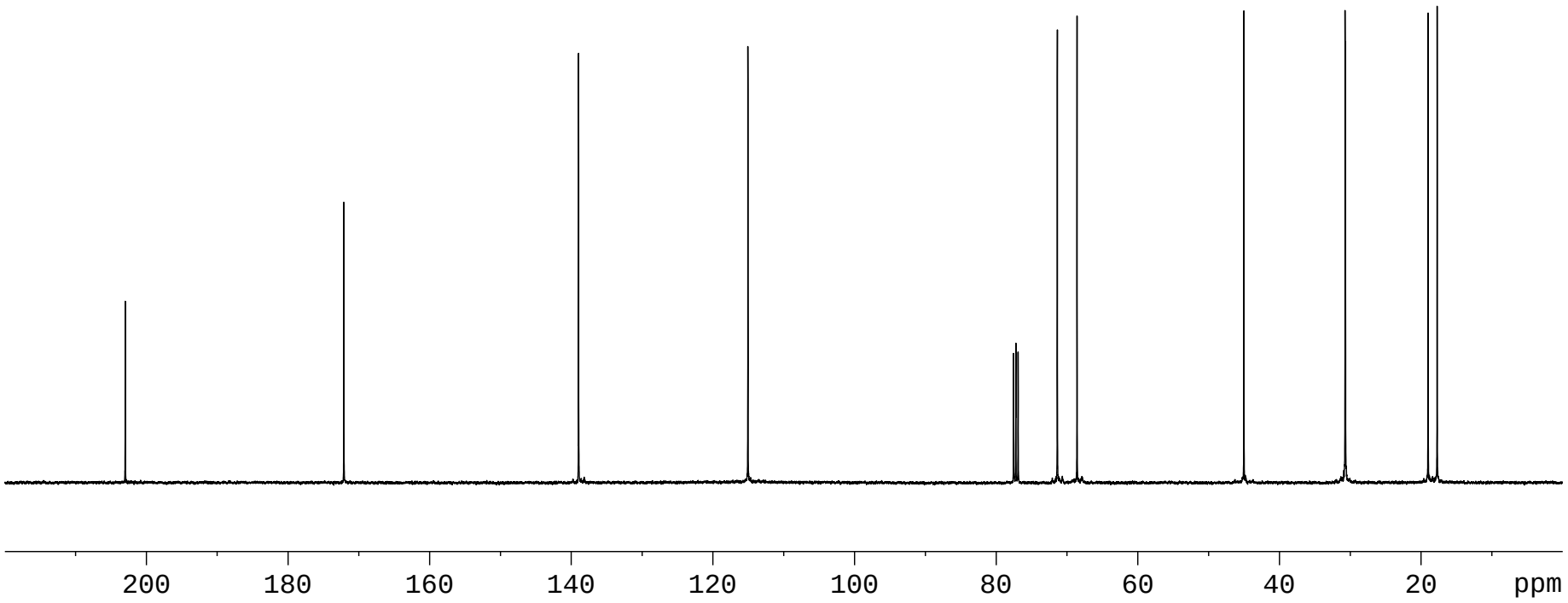

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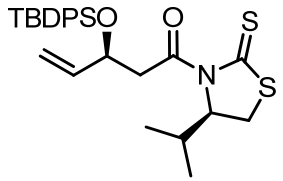

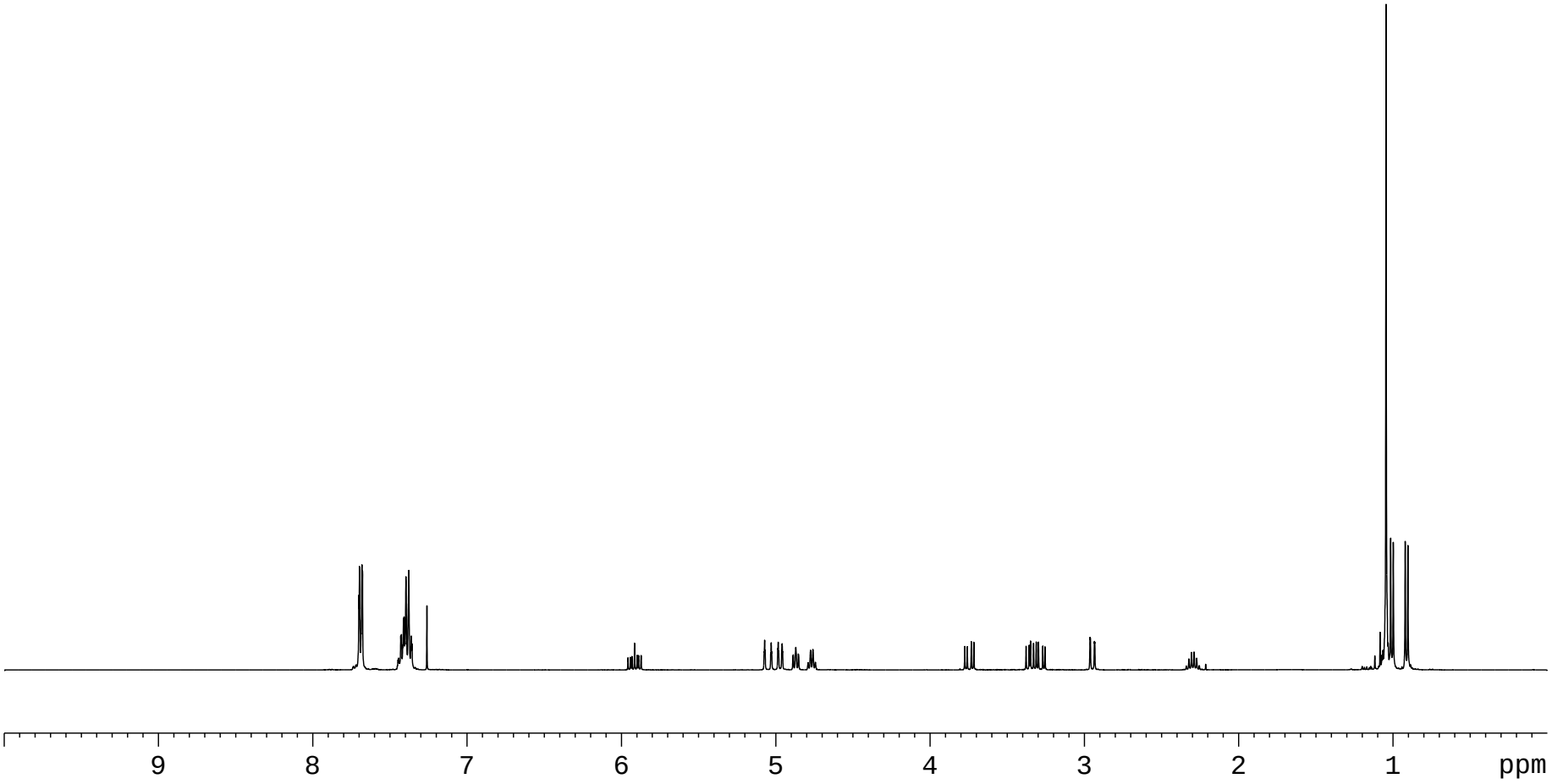

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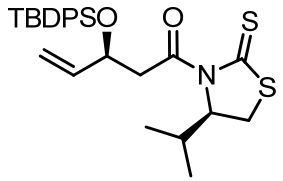

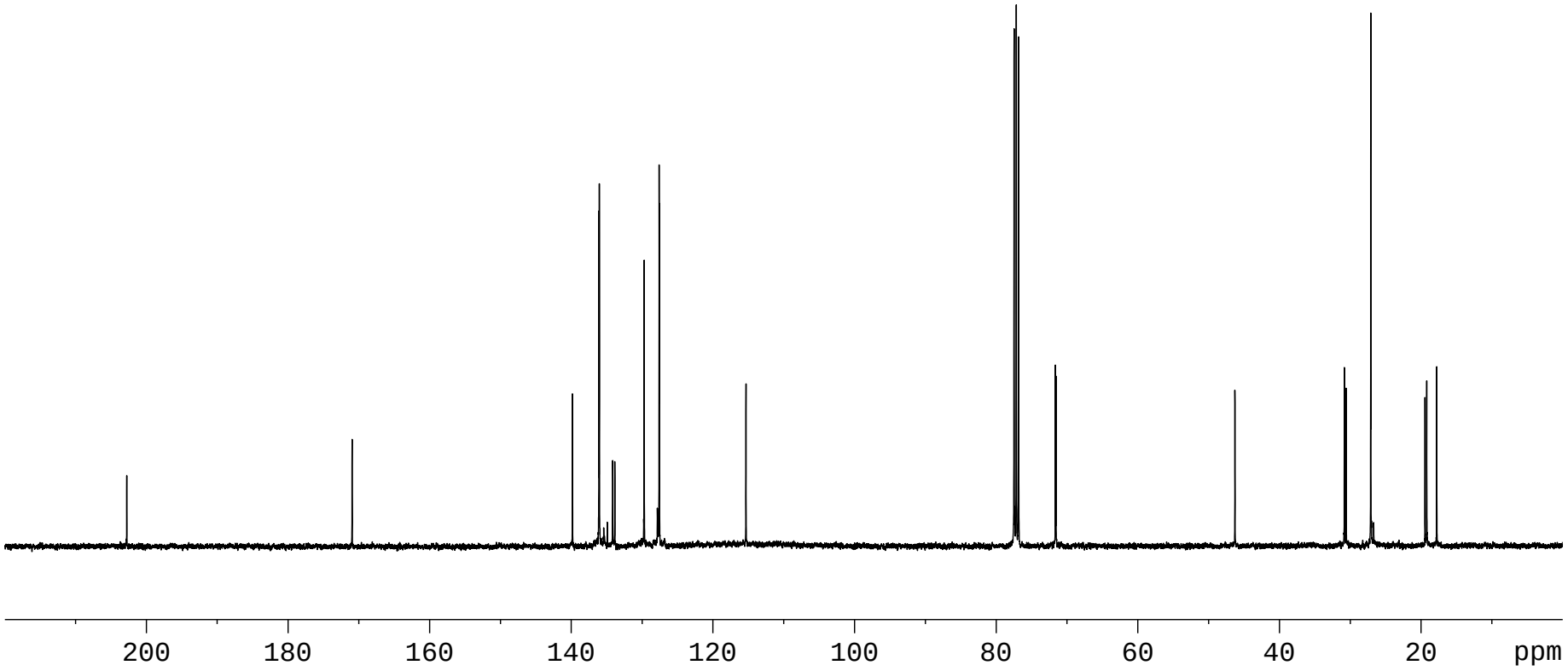

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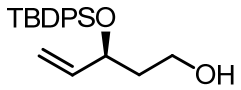

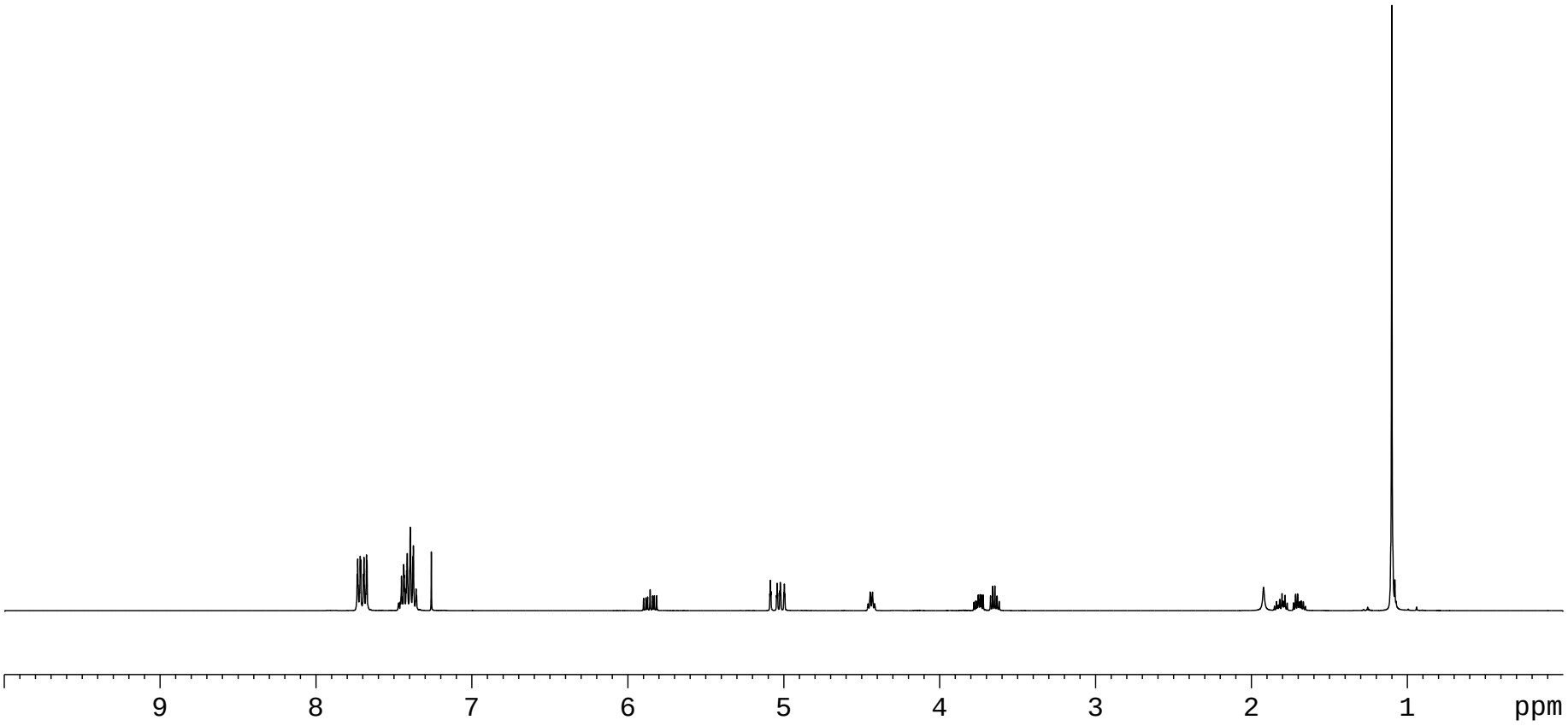

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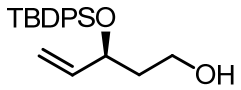

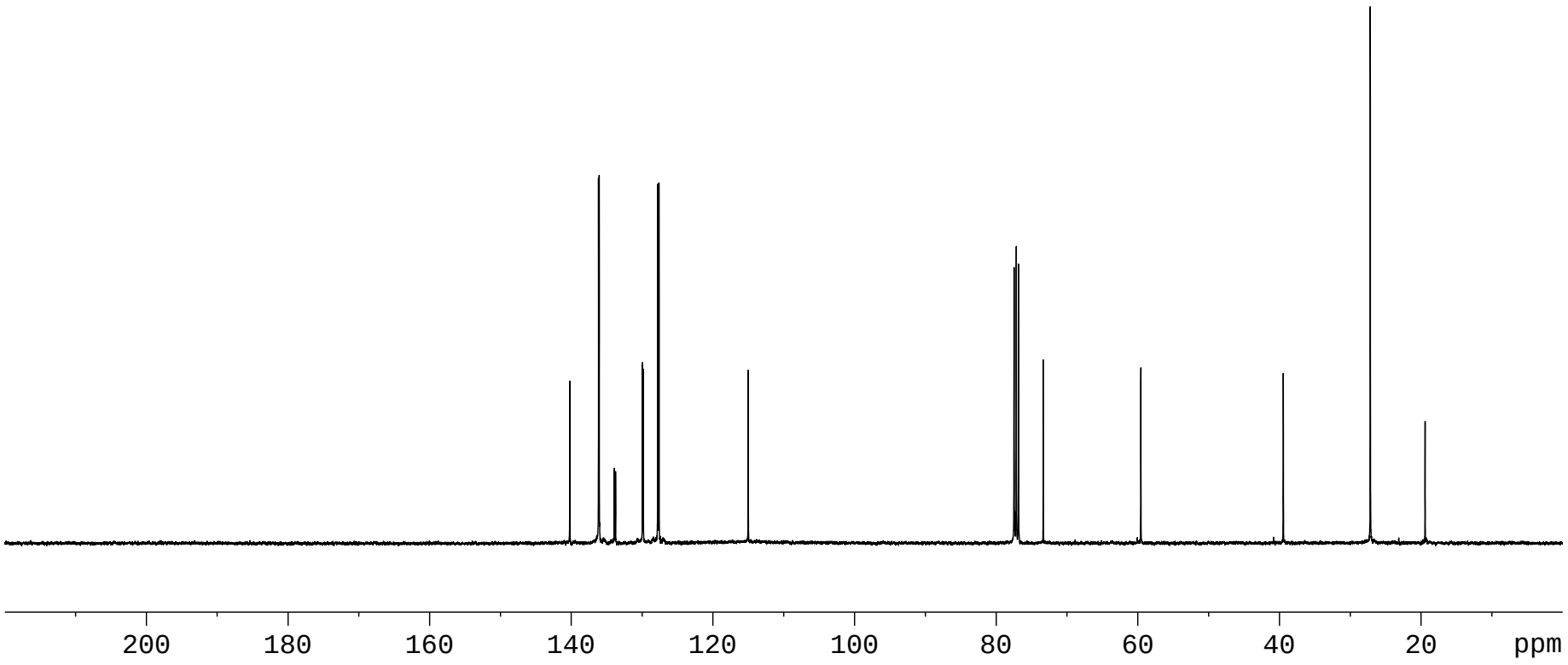

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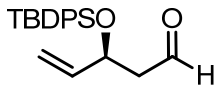

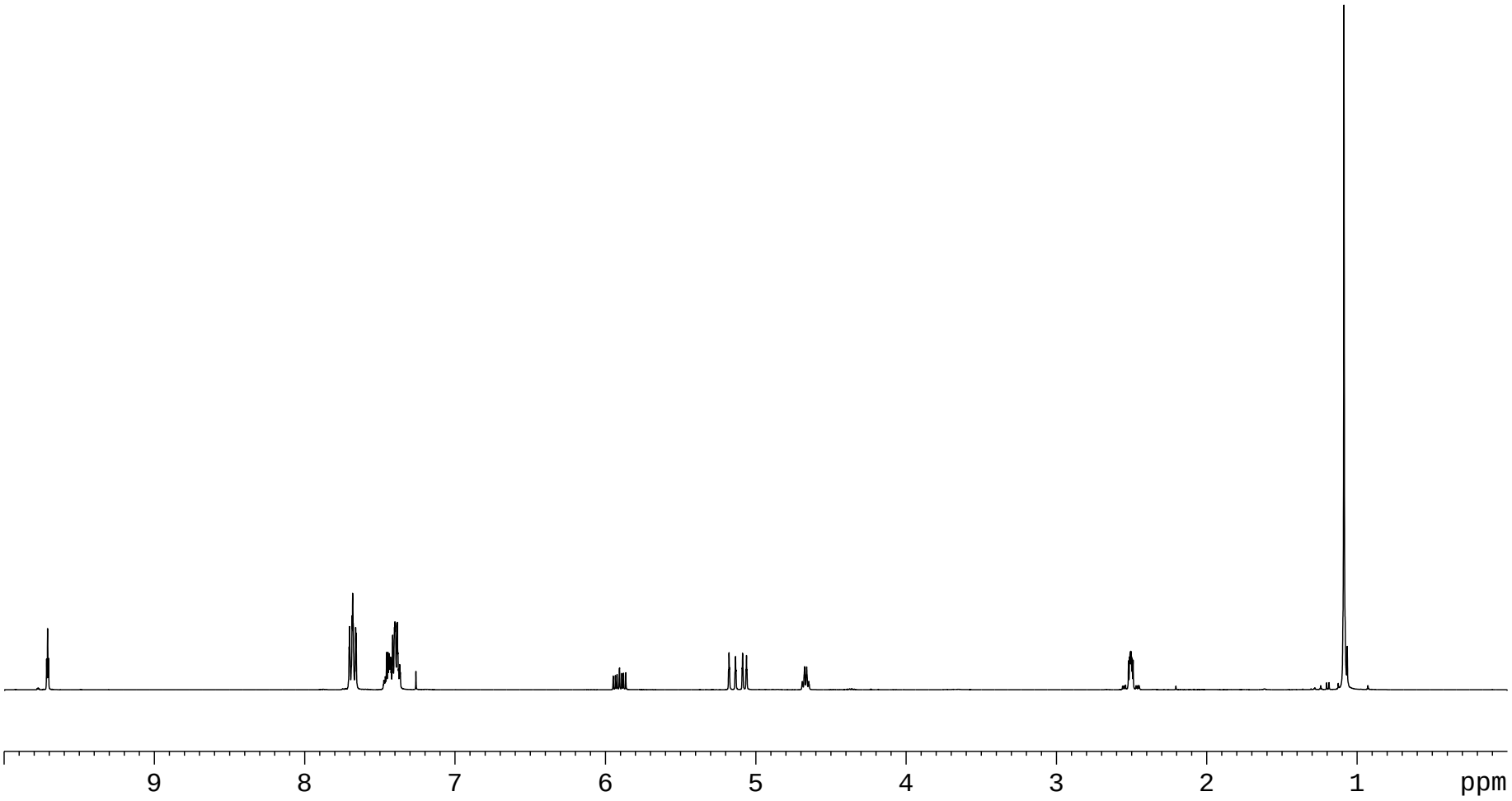

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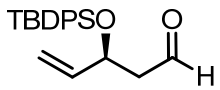

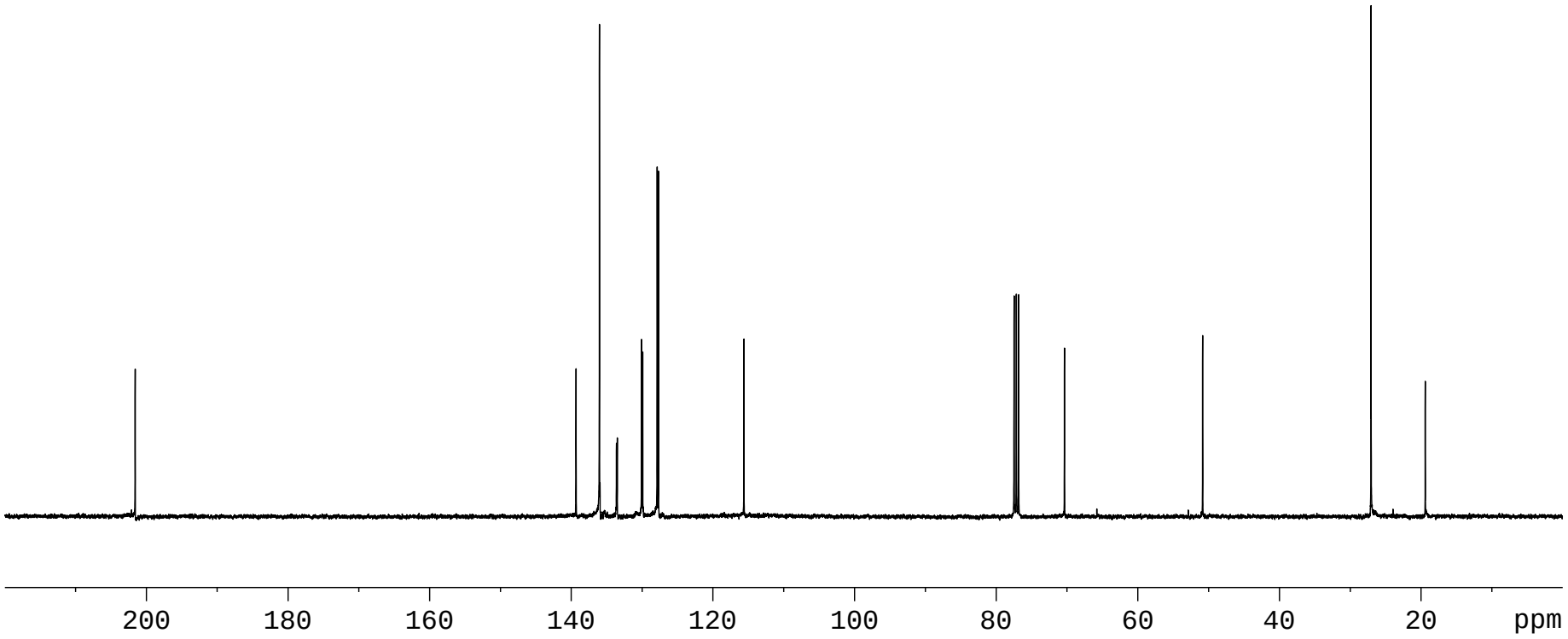

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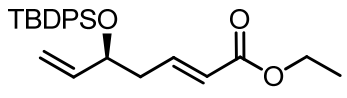

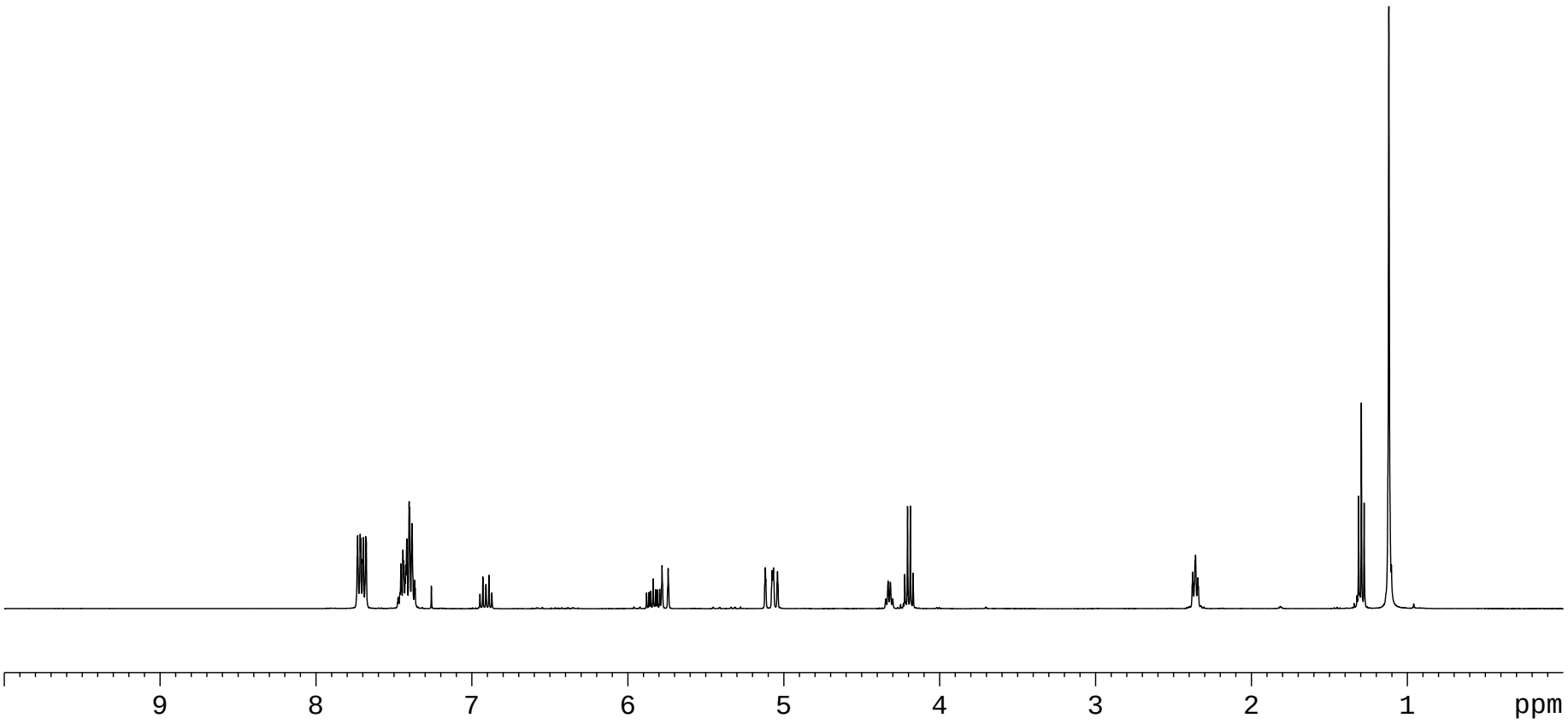

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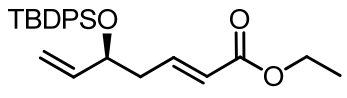

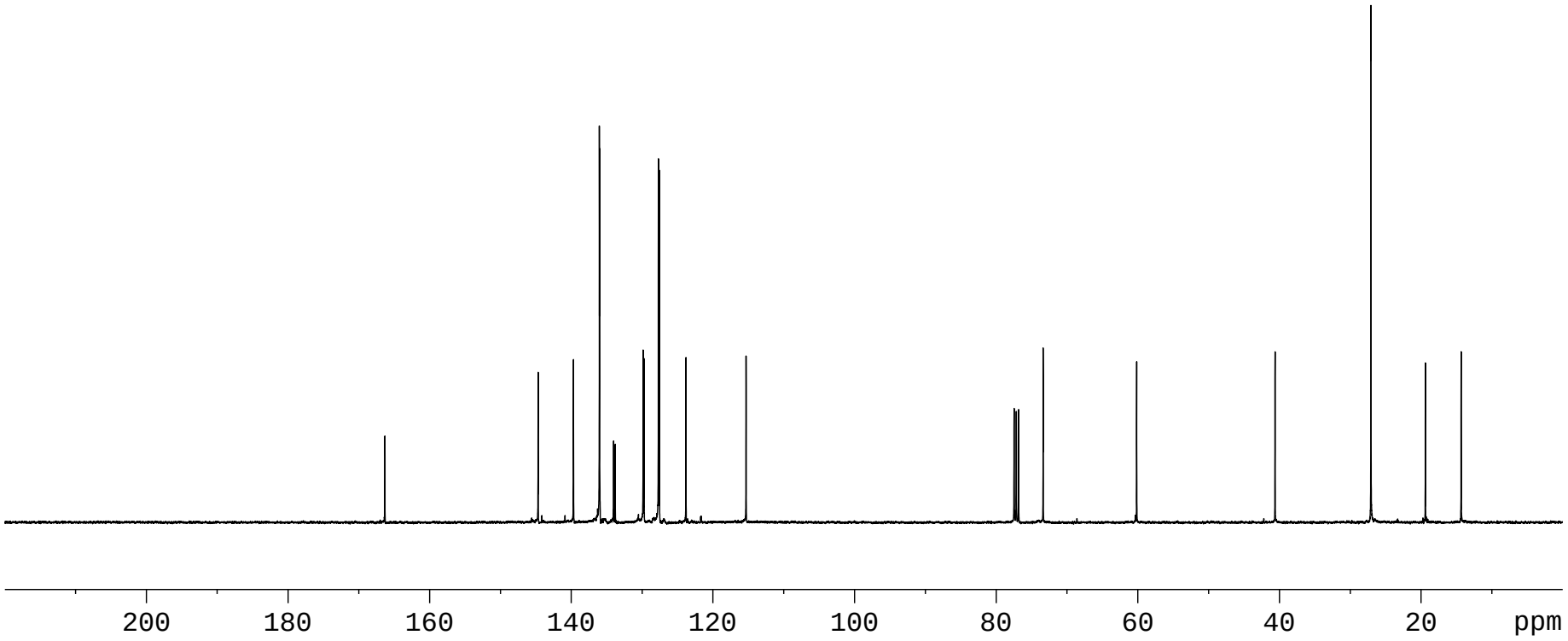

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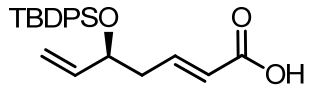

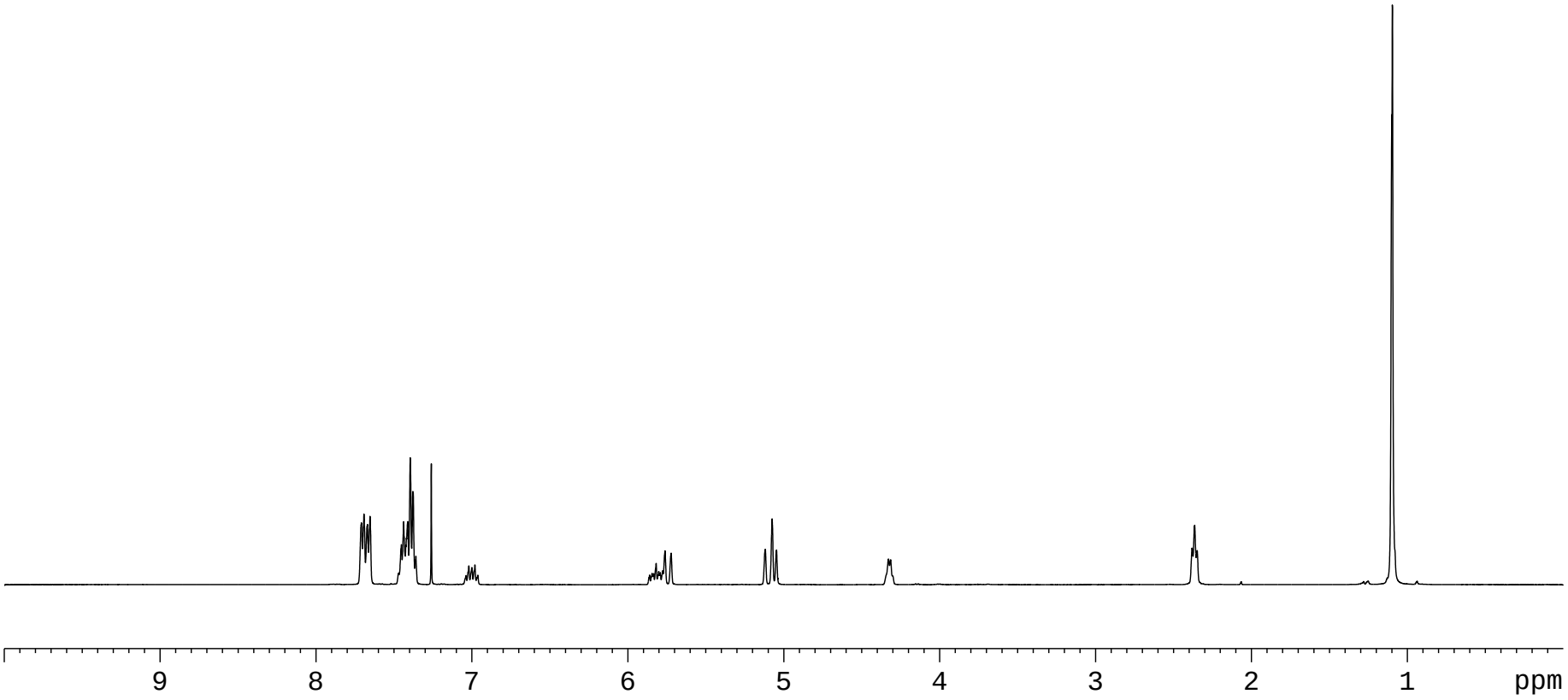

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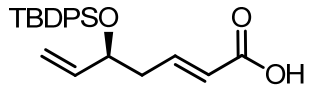

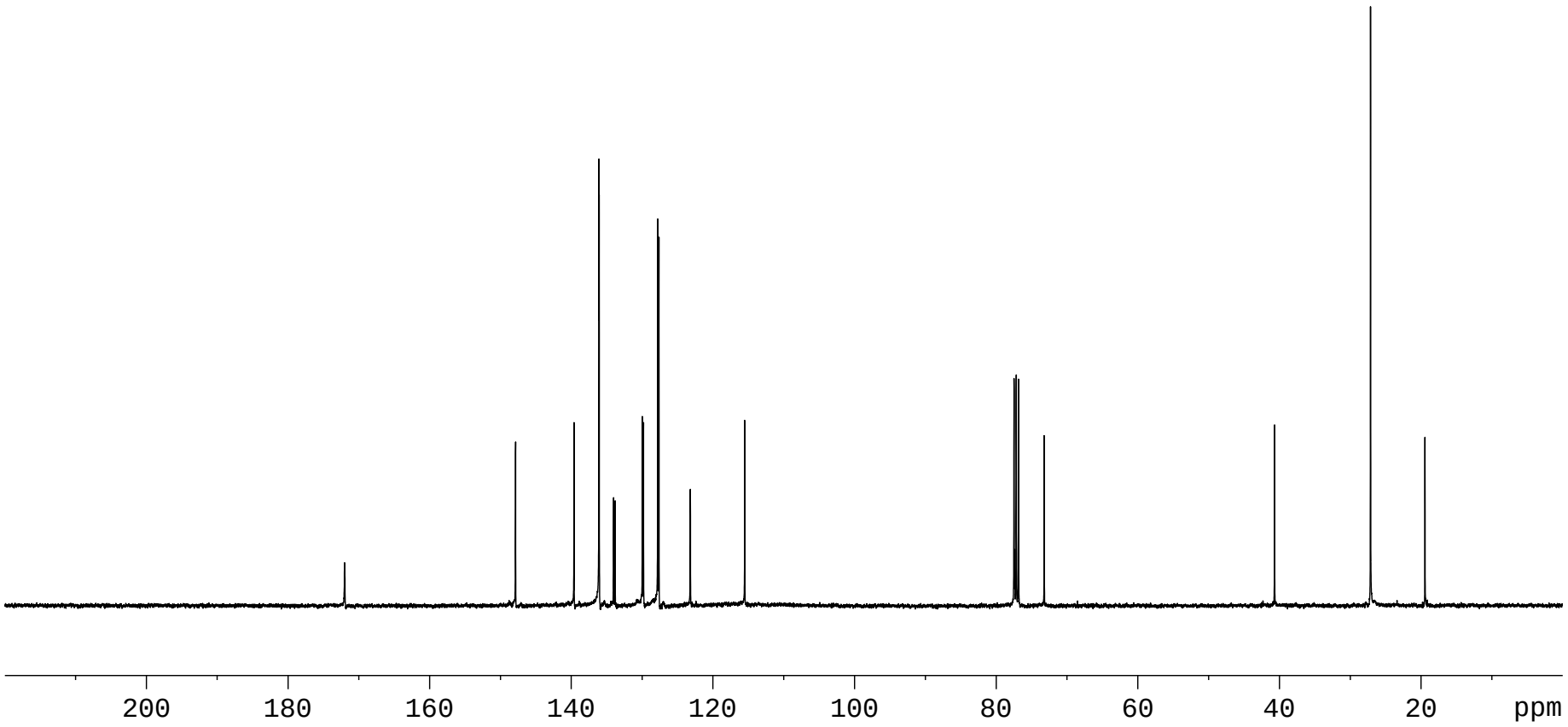

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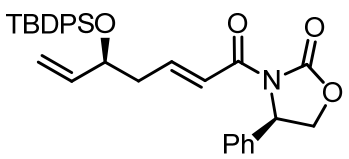

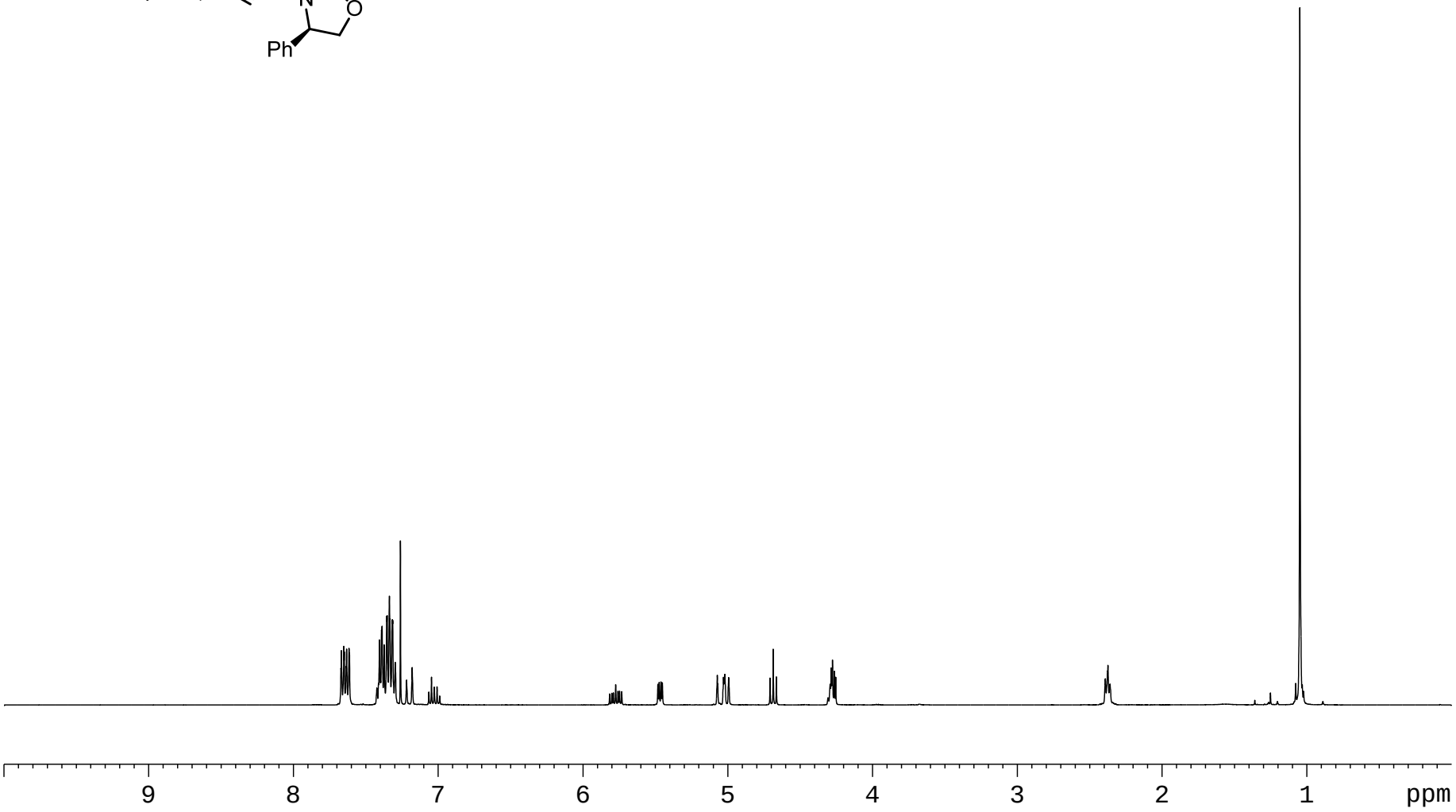

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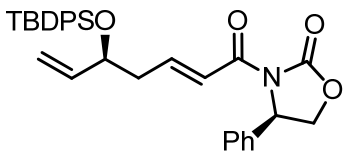

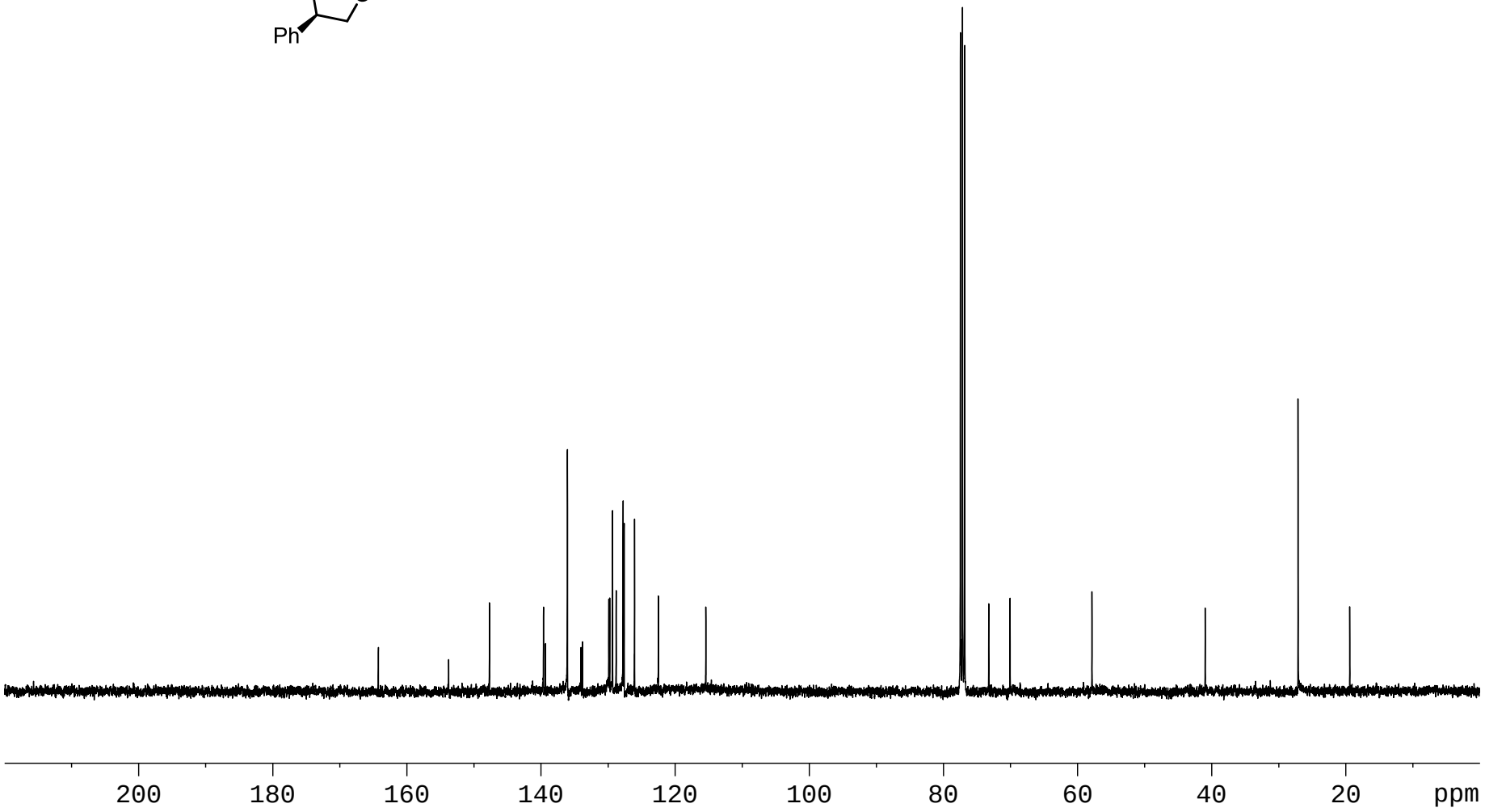

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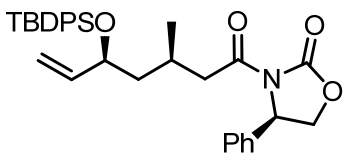

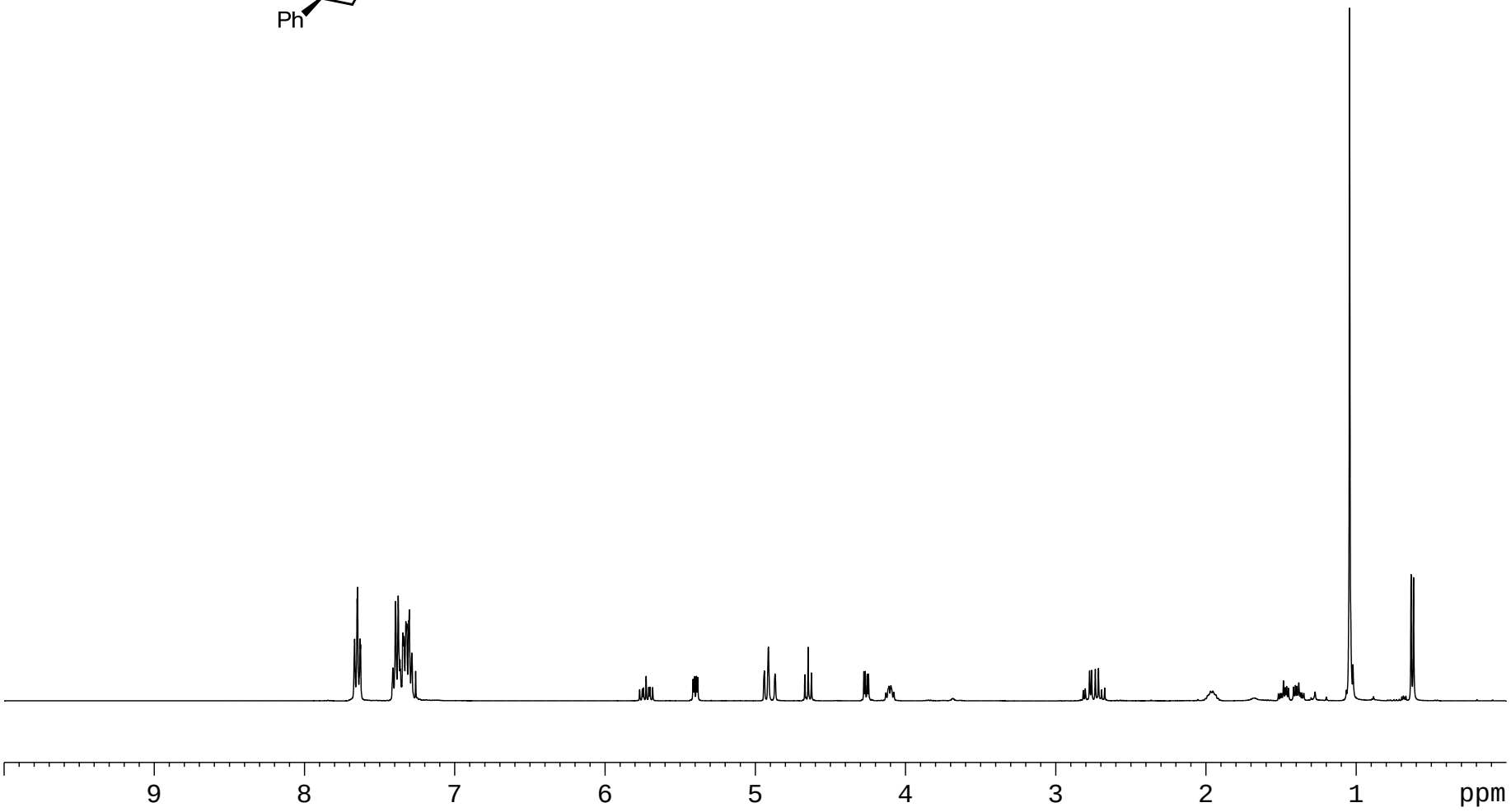

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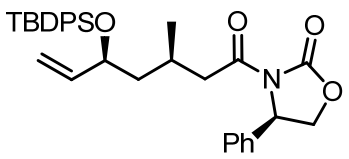

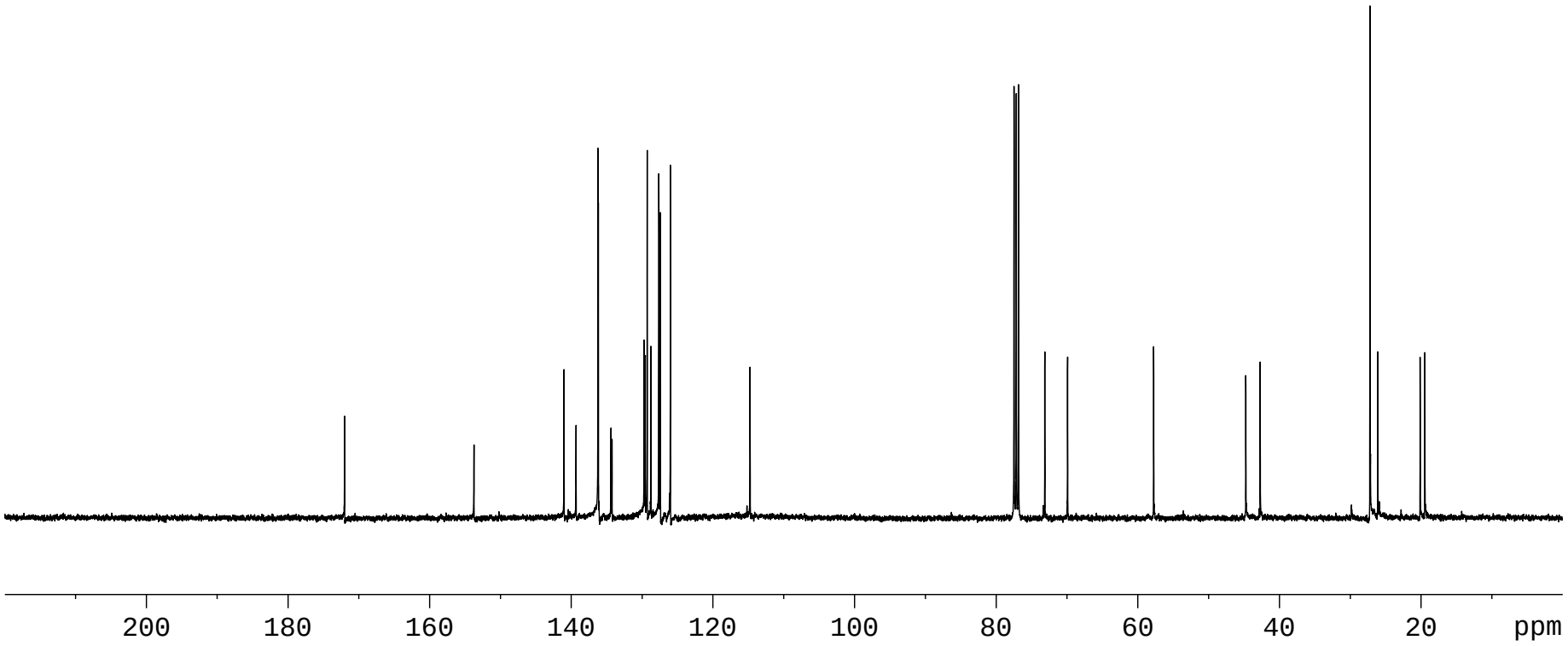

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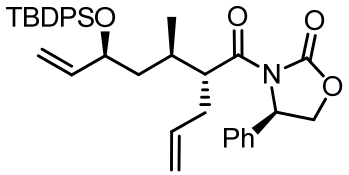

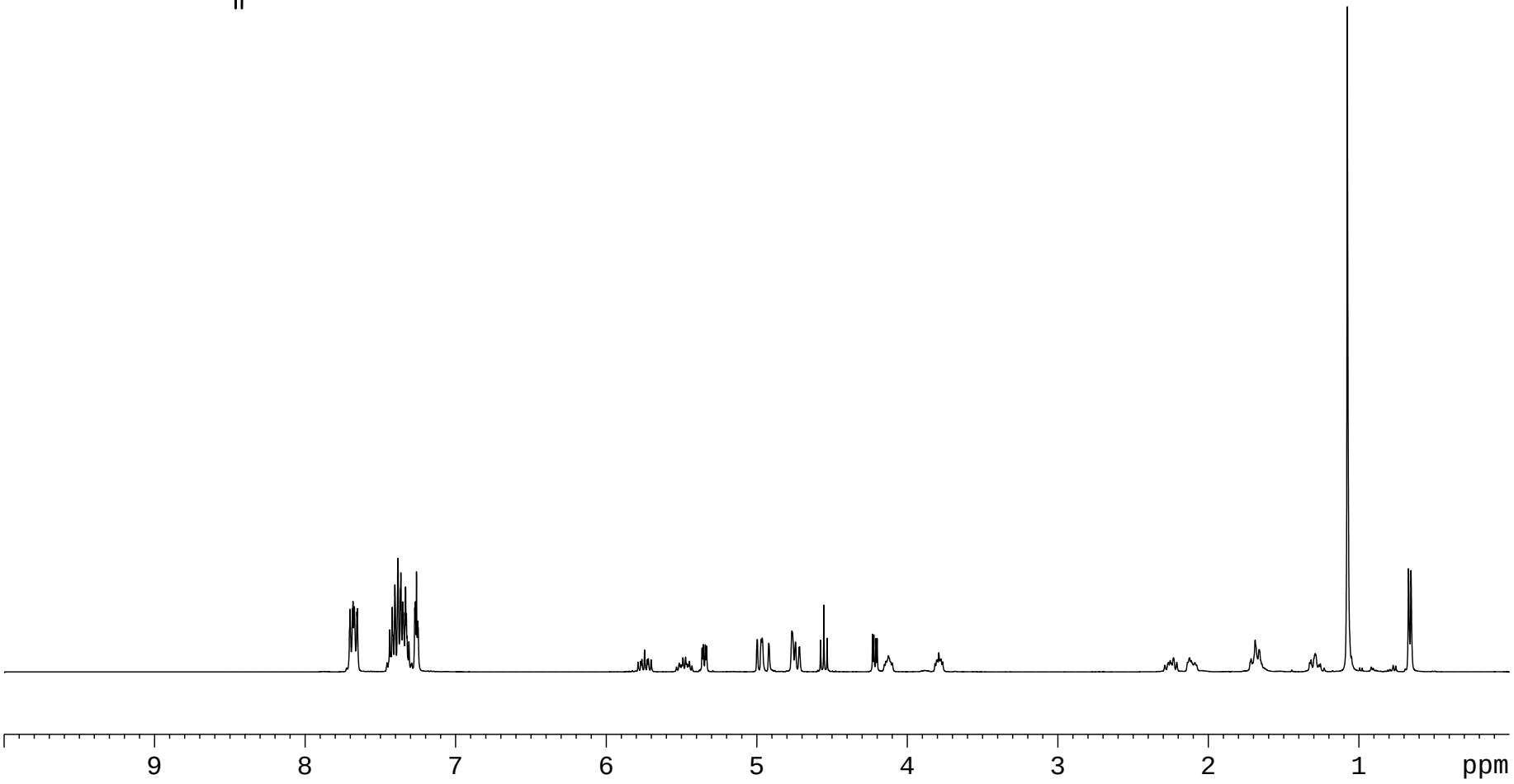

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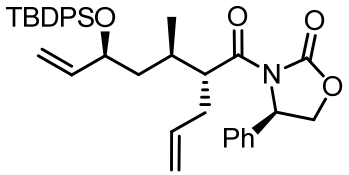

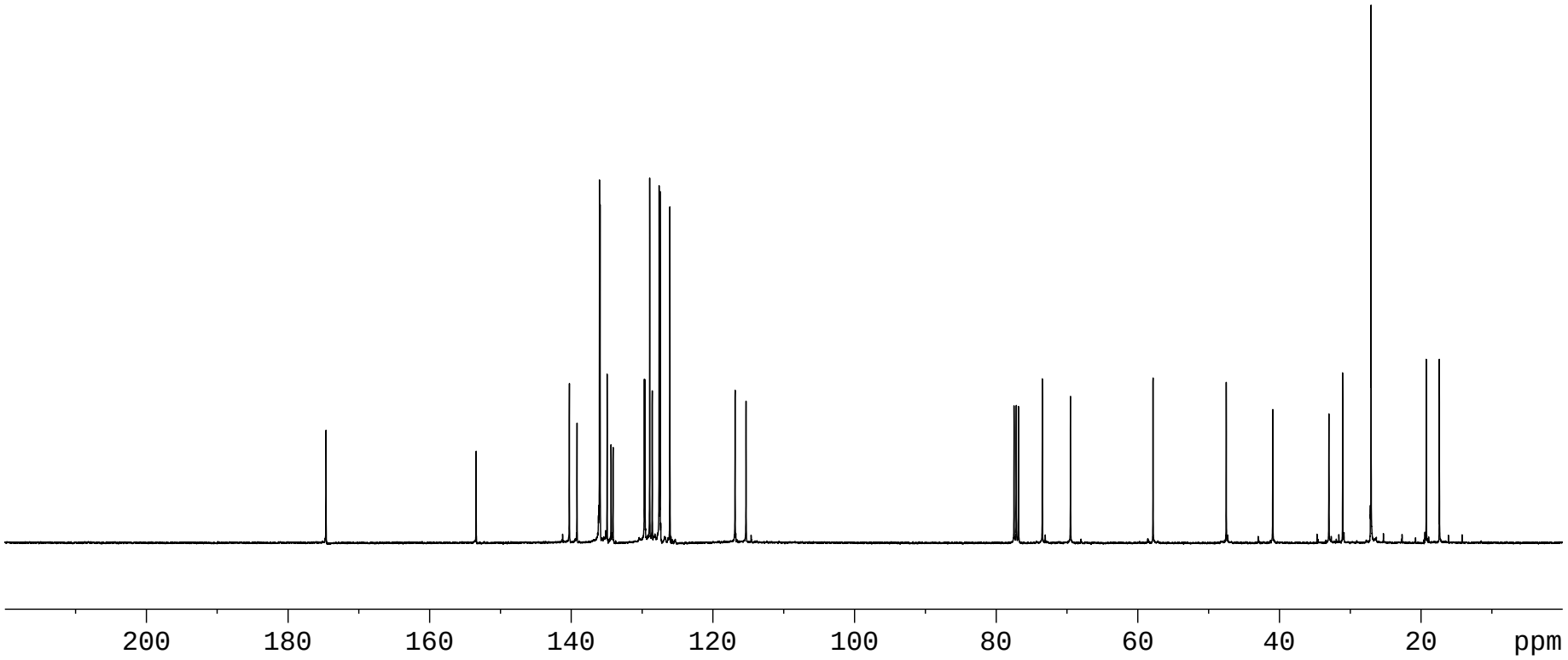

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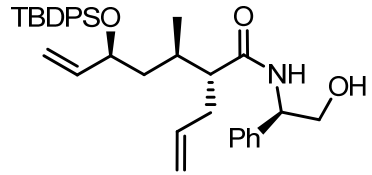

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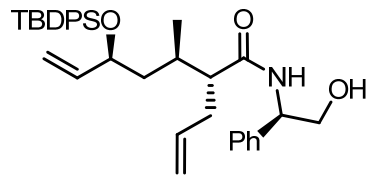

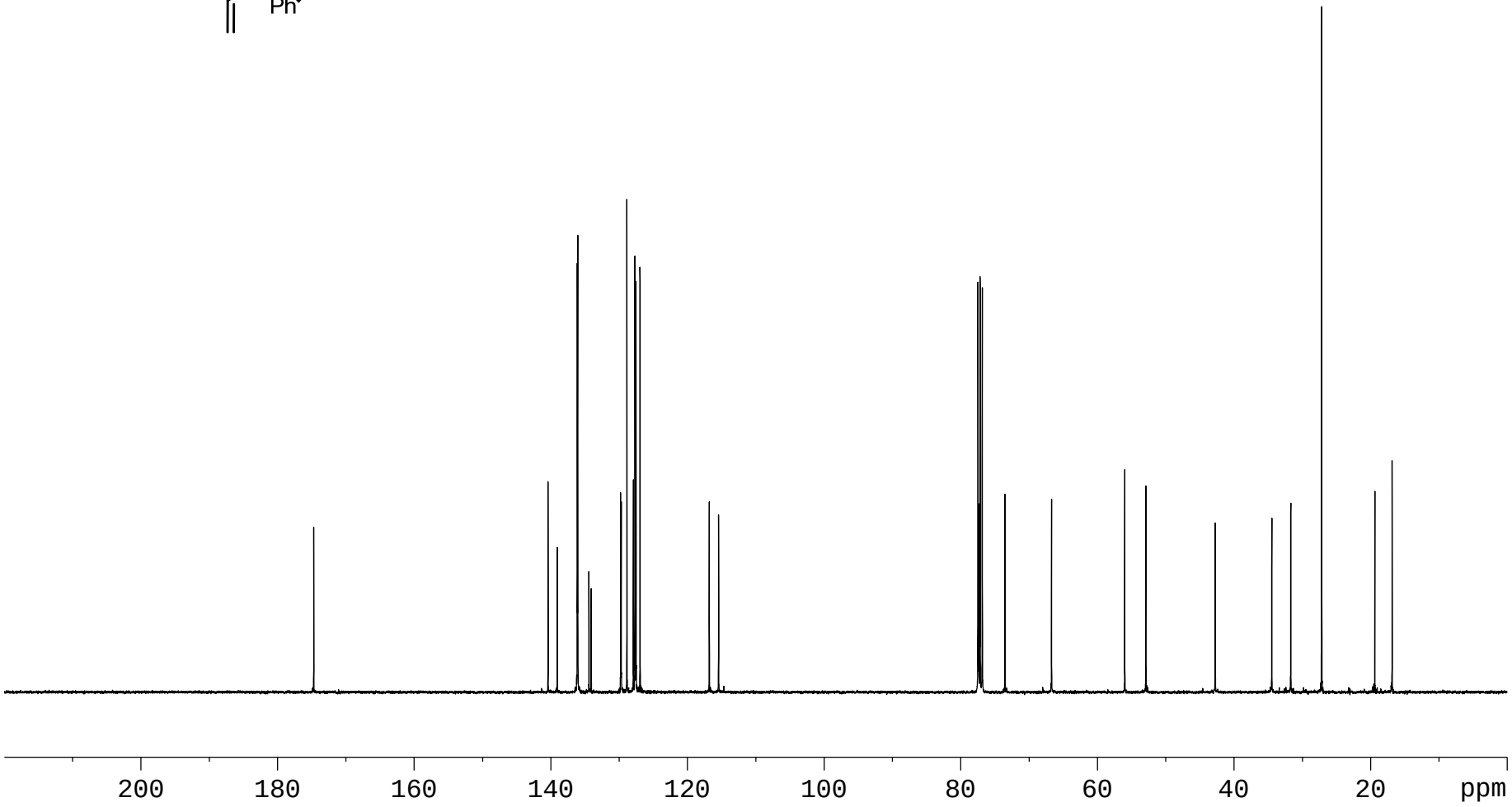

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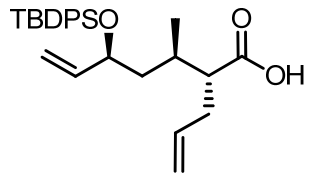

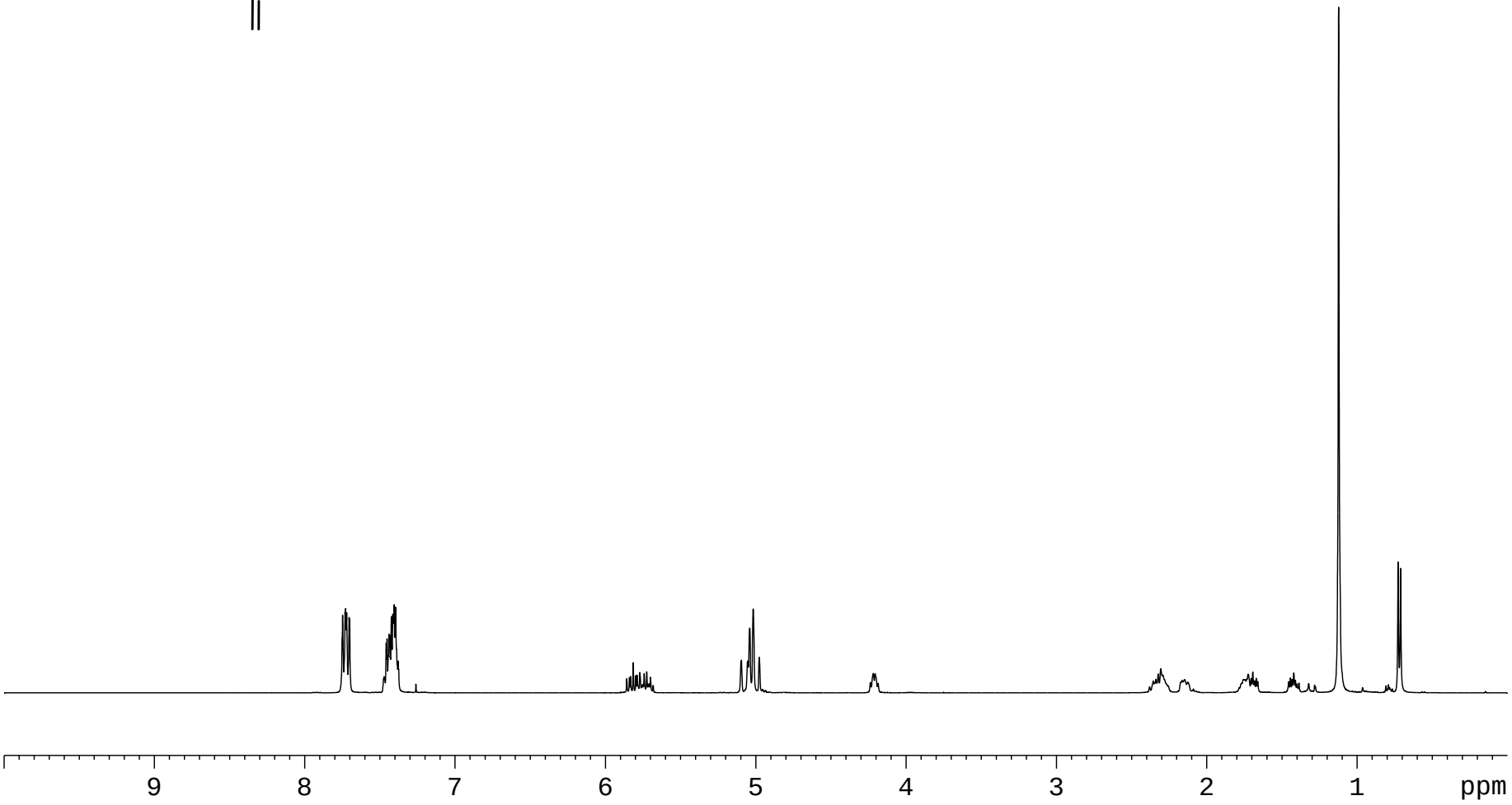

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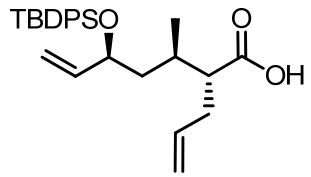

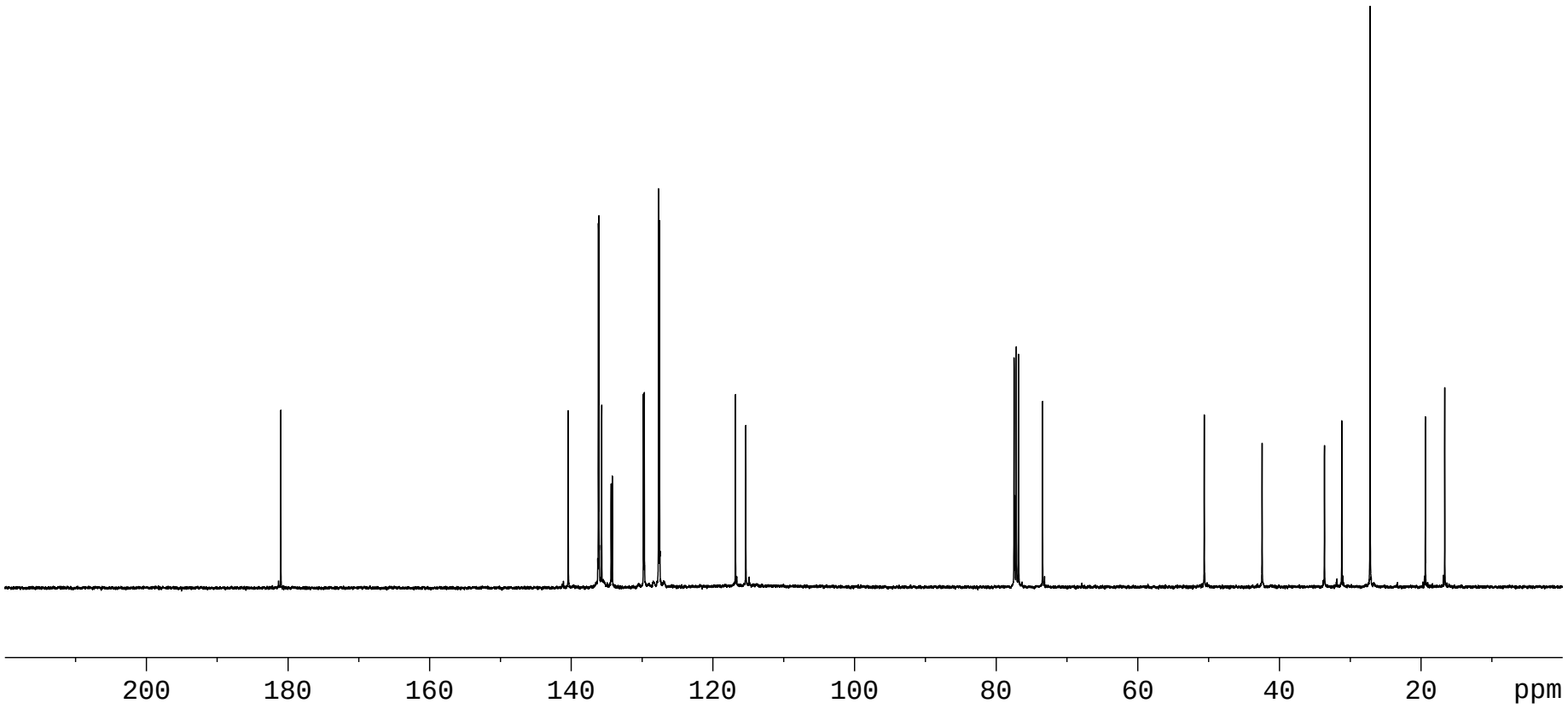

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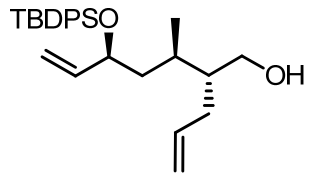

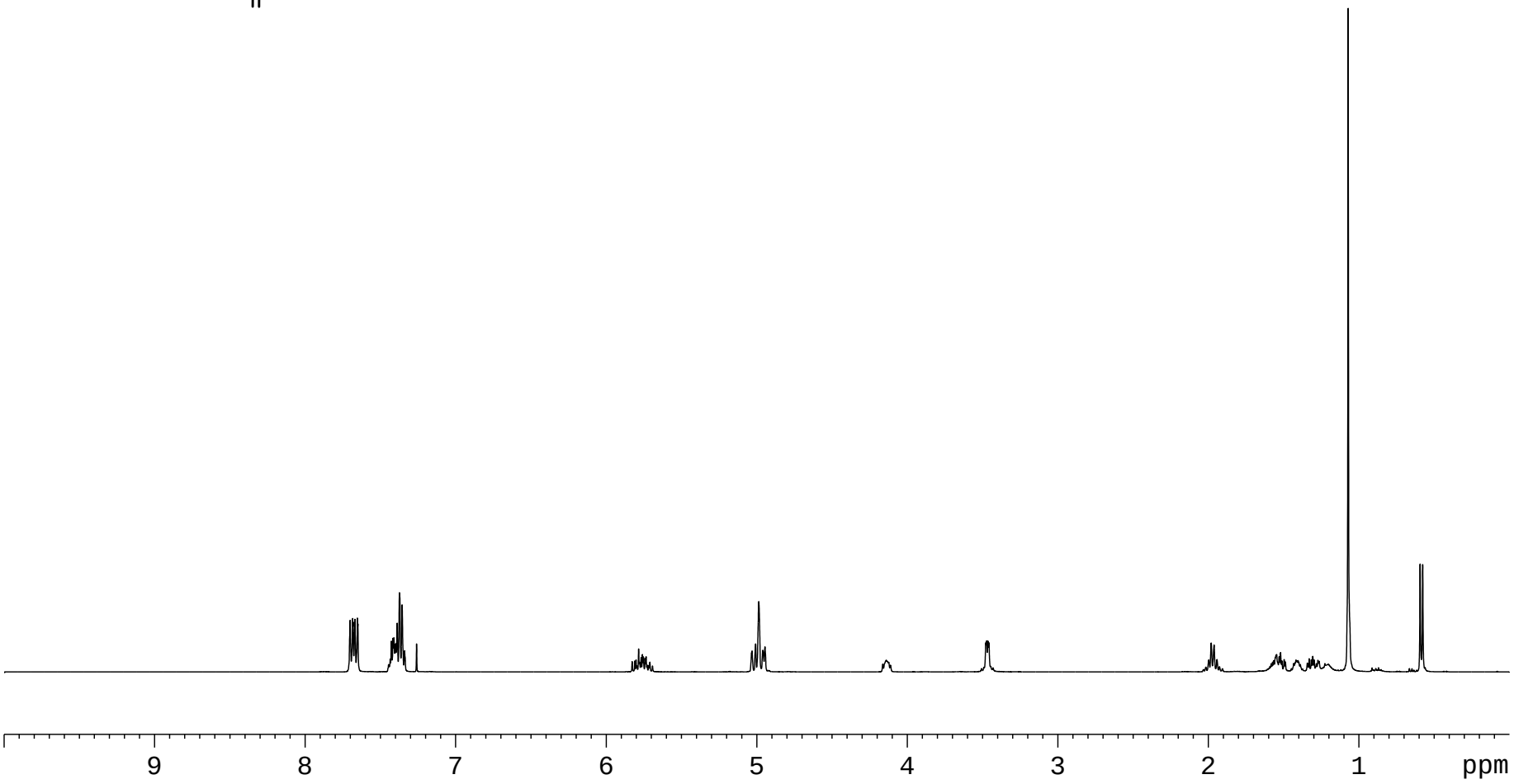

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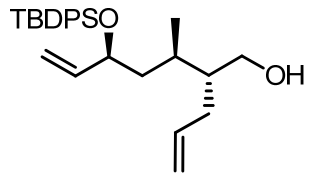
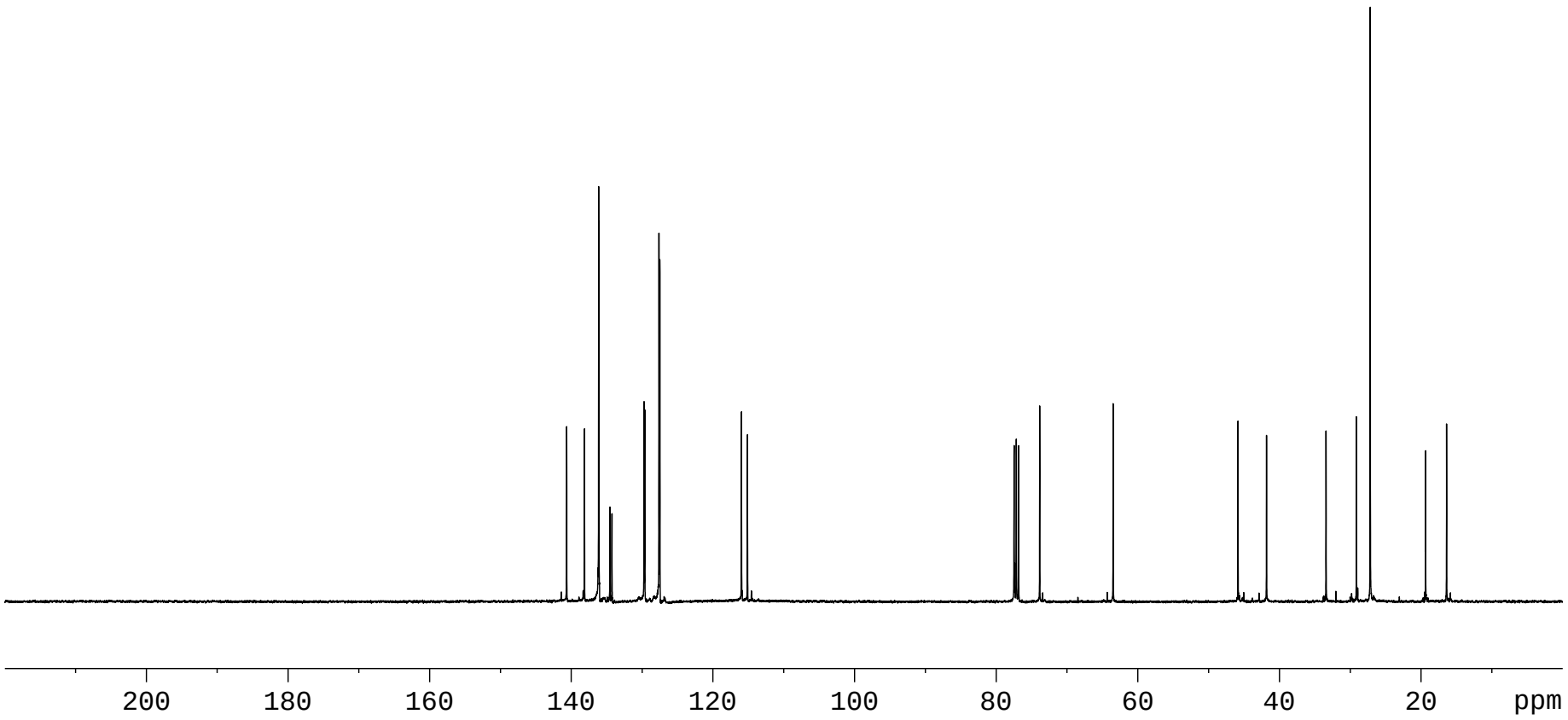
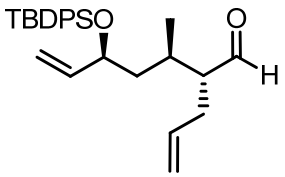
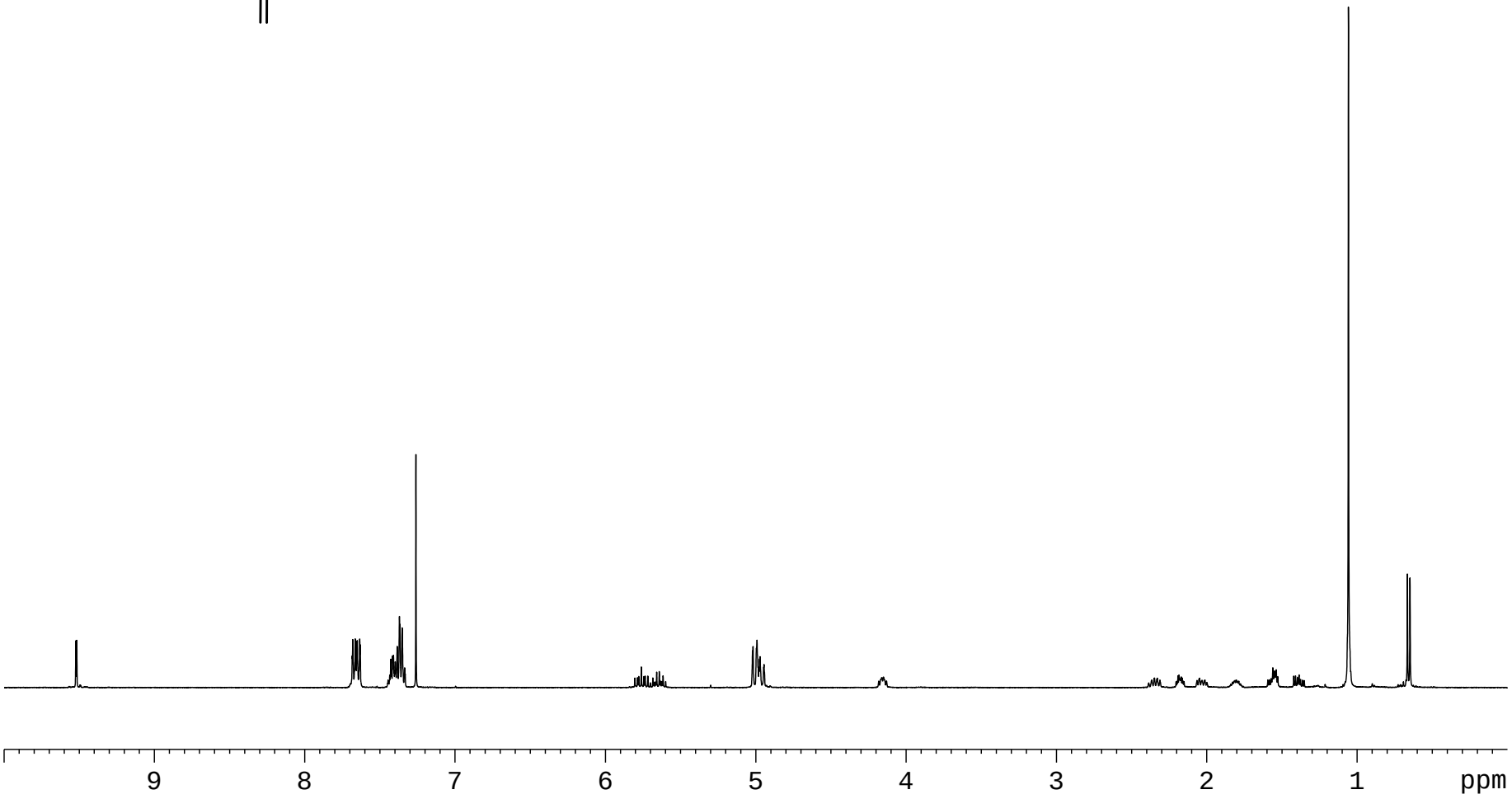


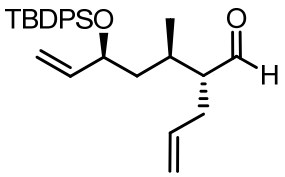


^{1}H NMR

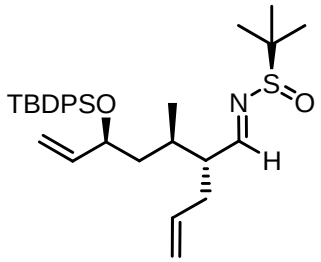




^{13}C NMR



^{1}H NMR



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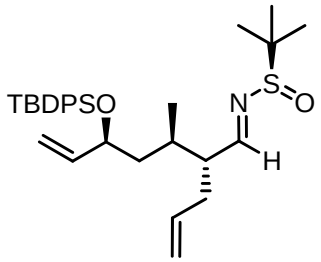

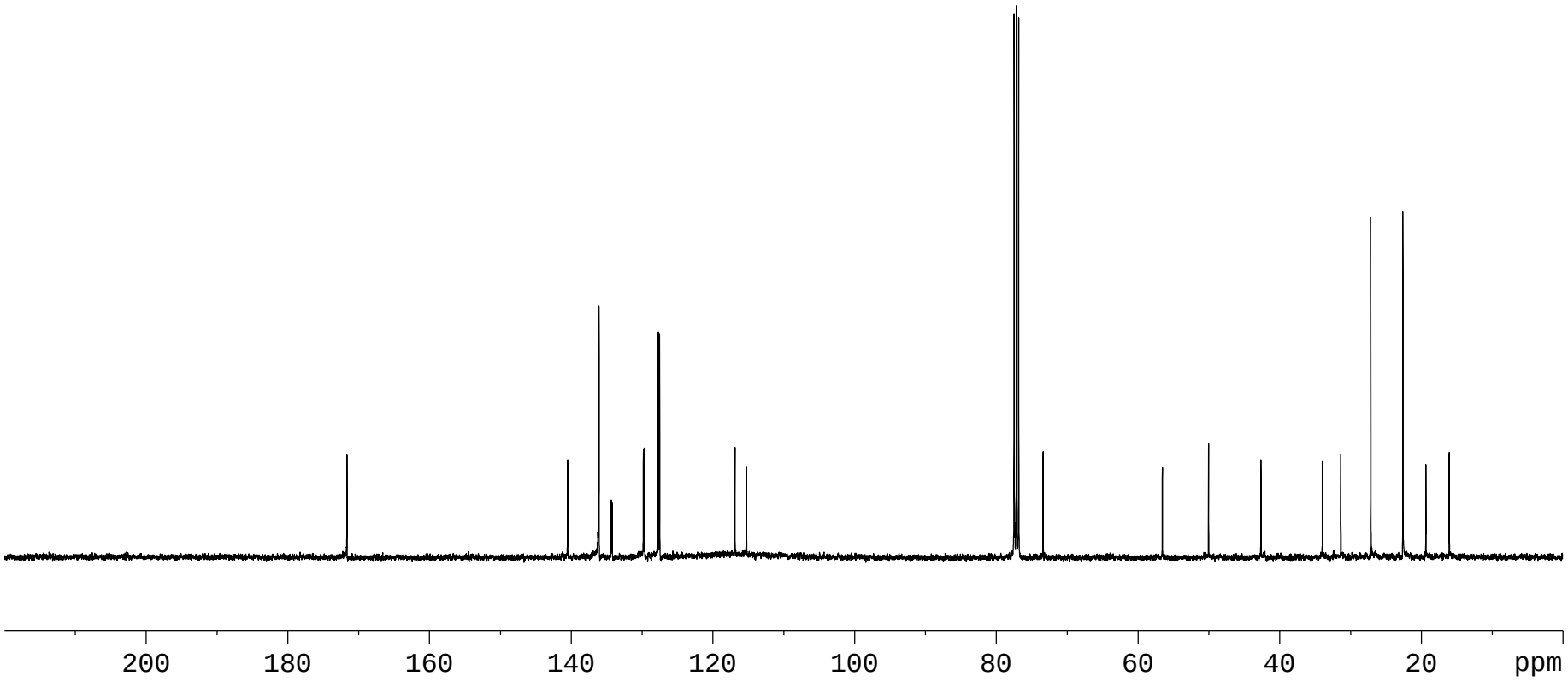

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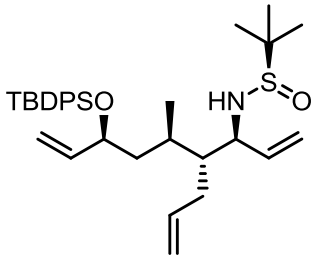

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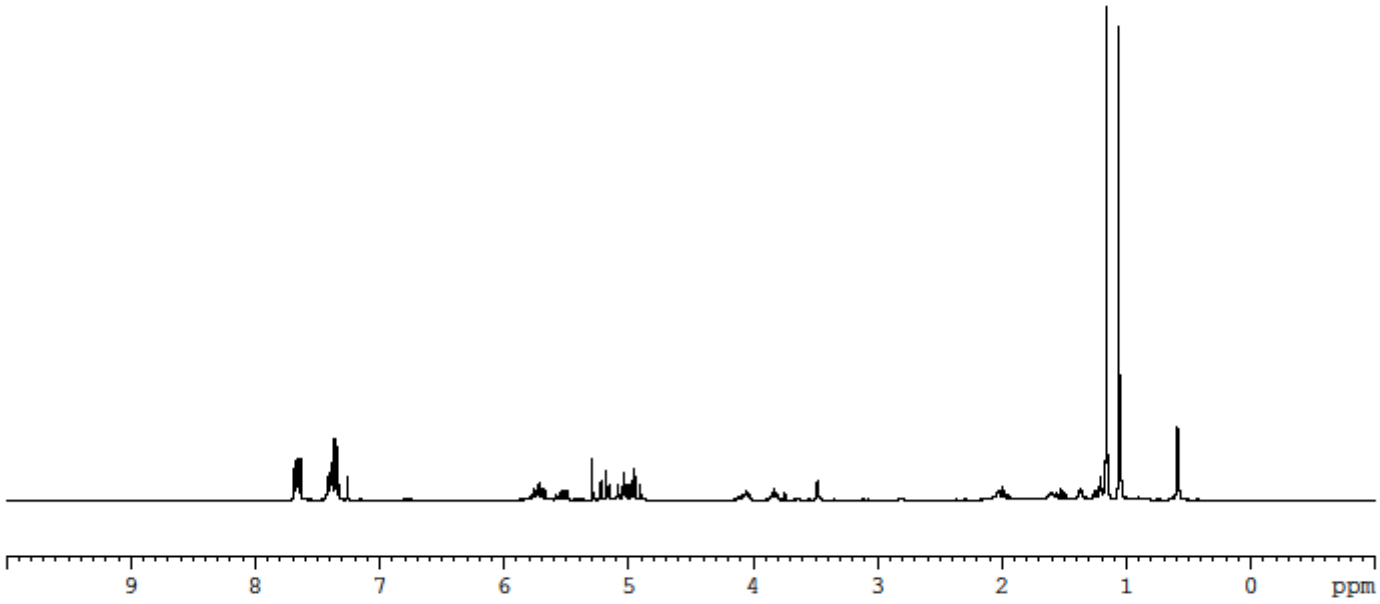

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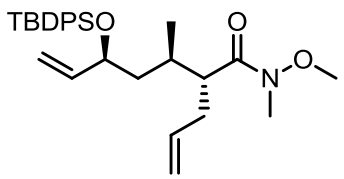

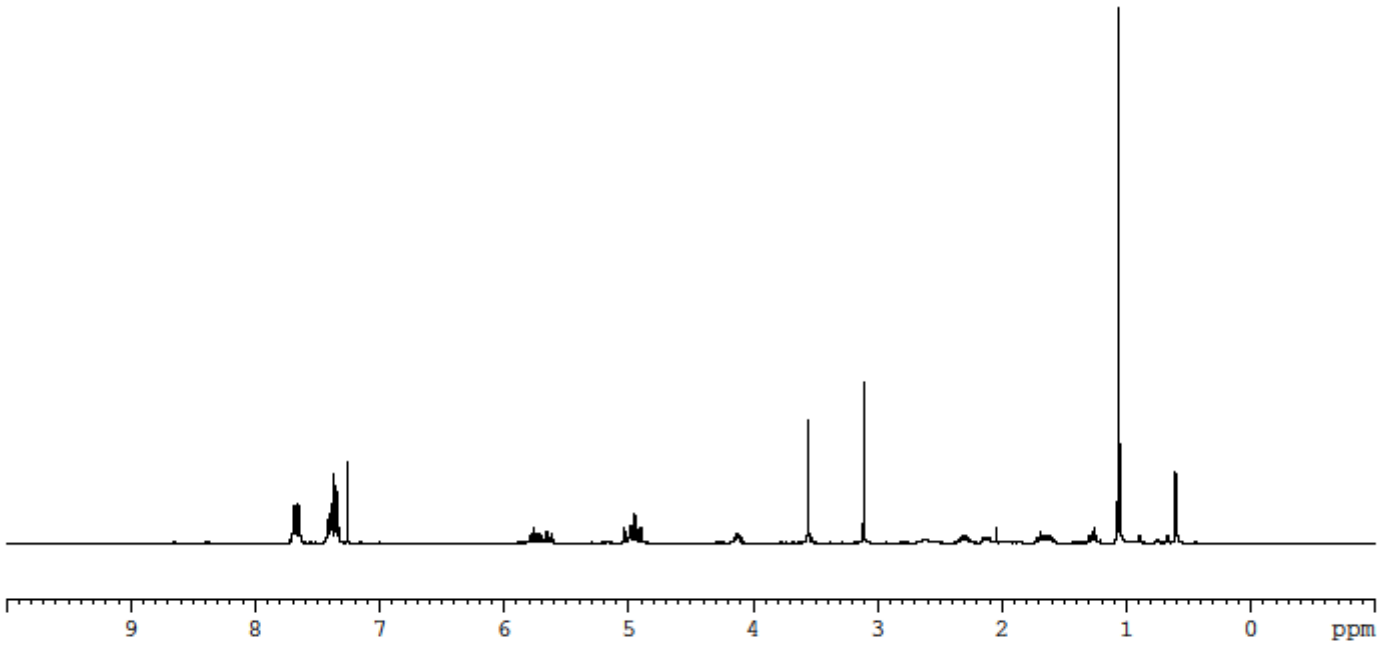

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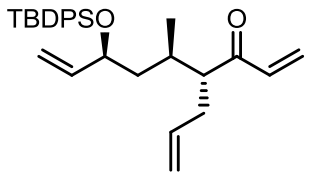

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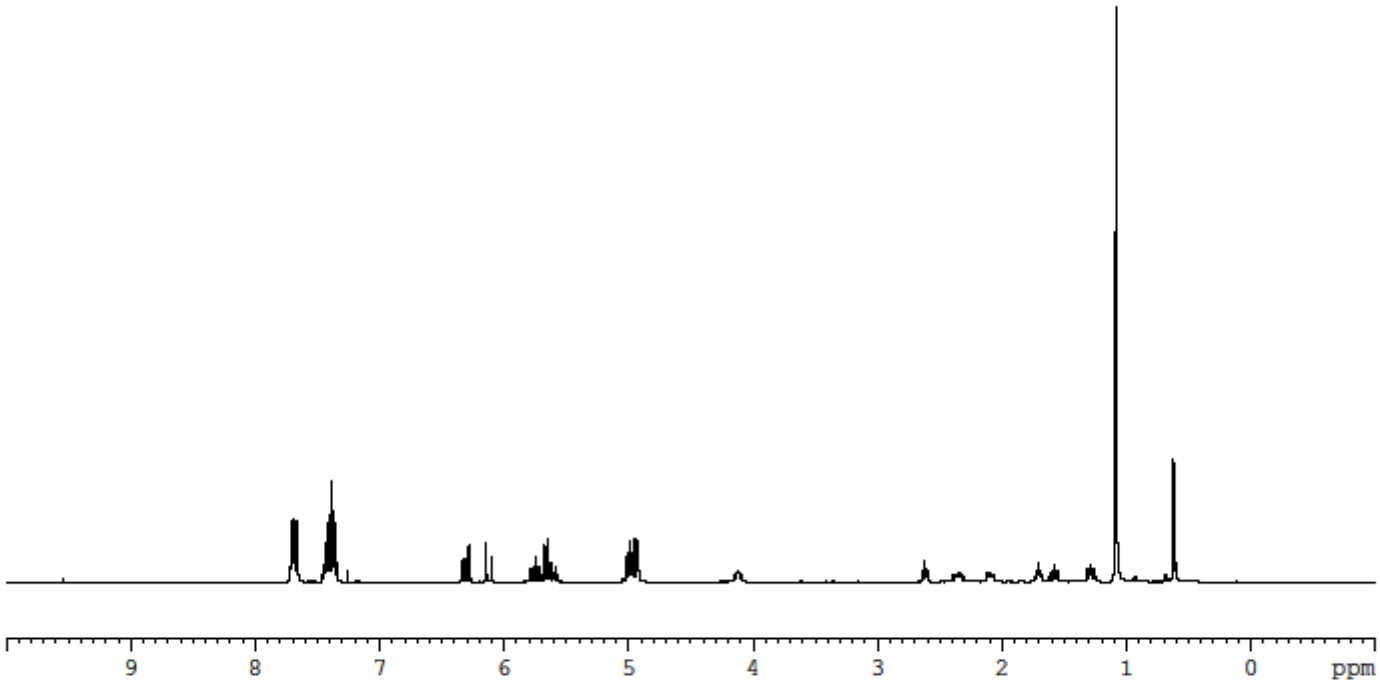

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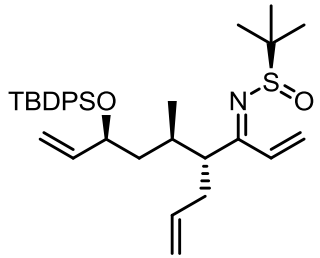

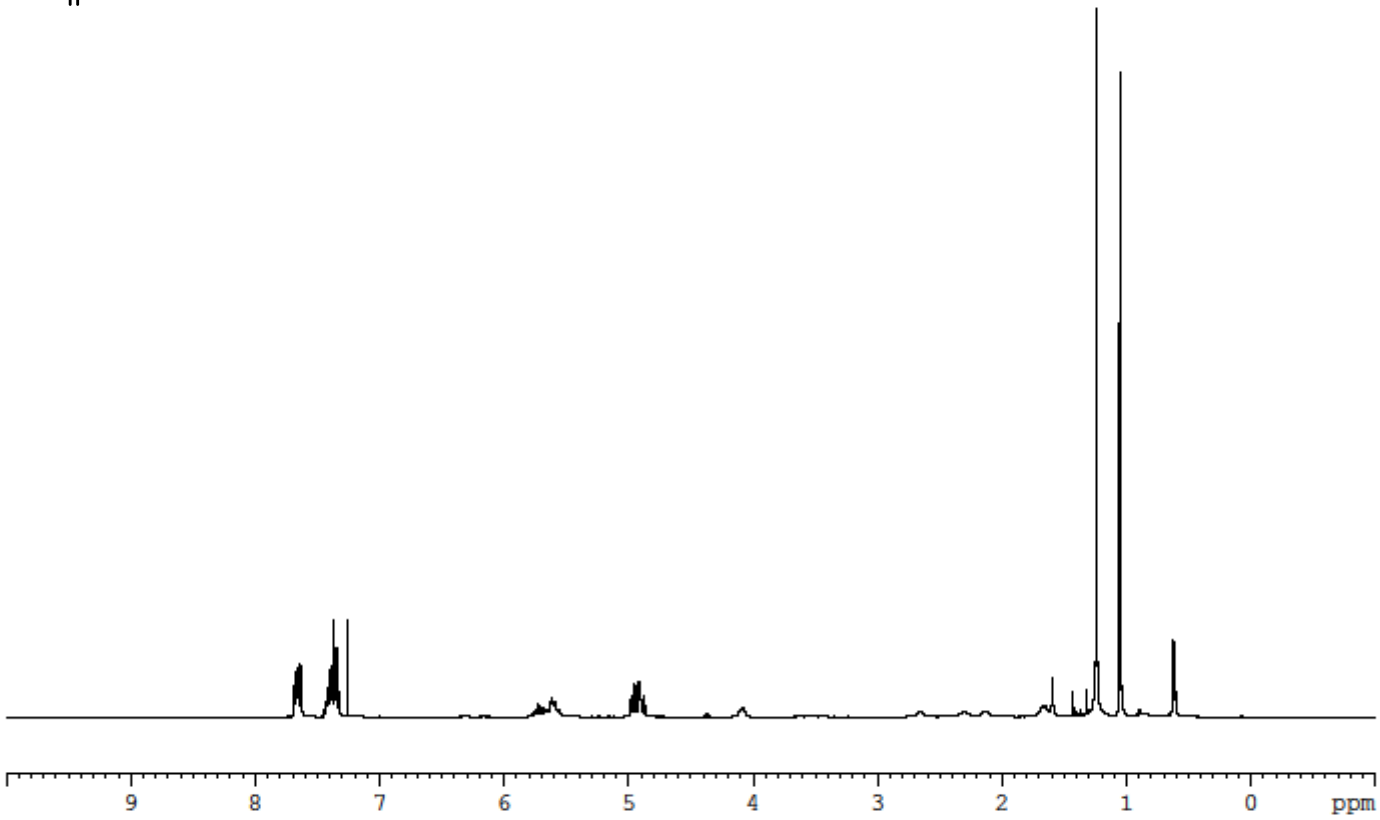

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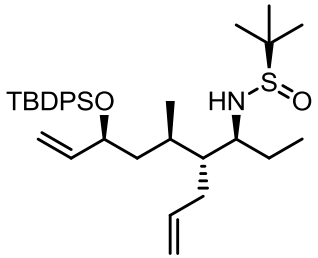

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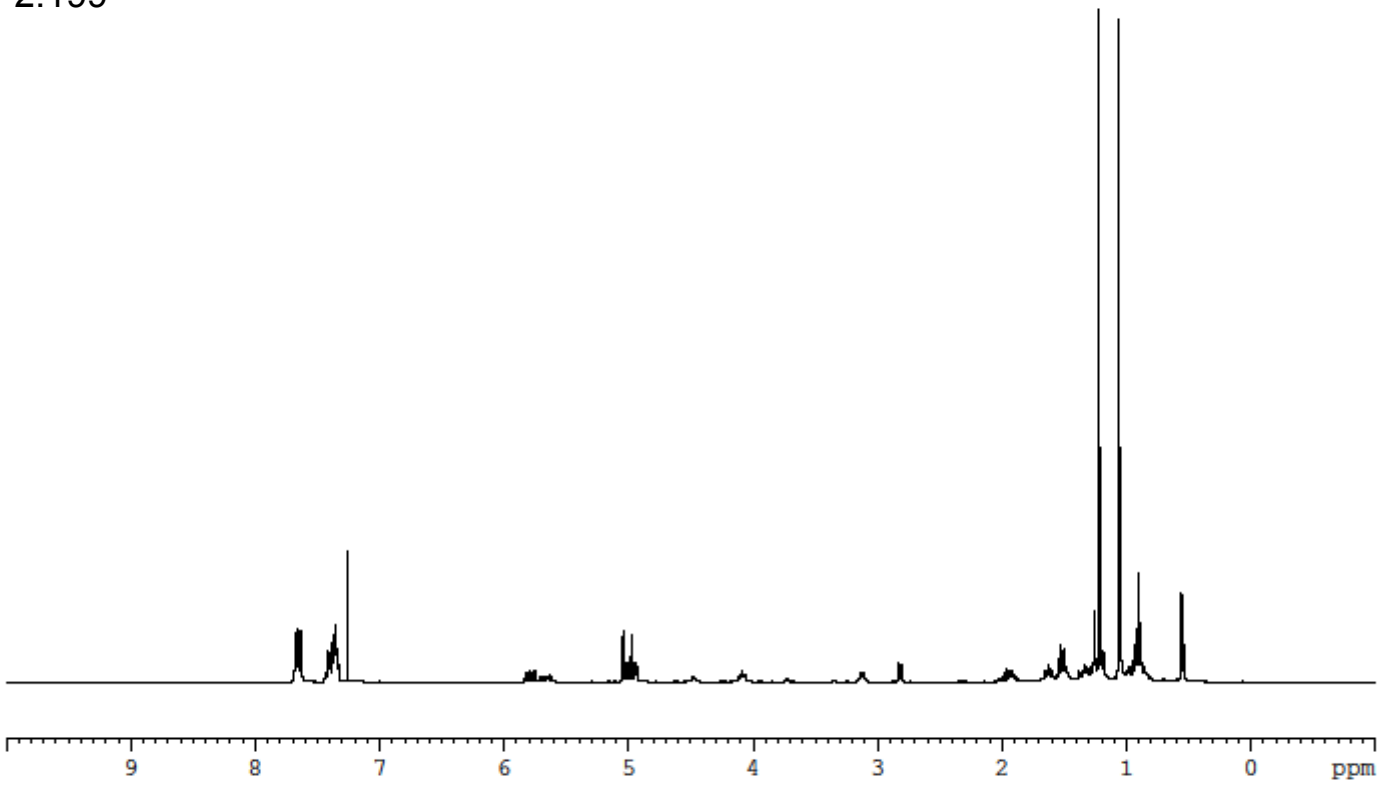

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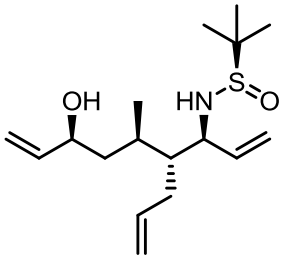

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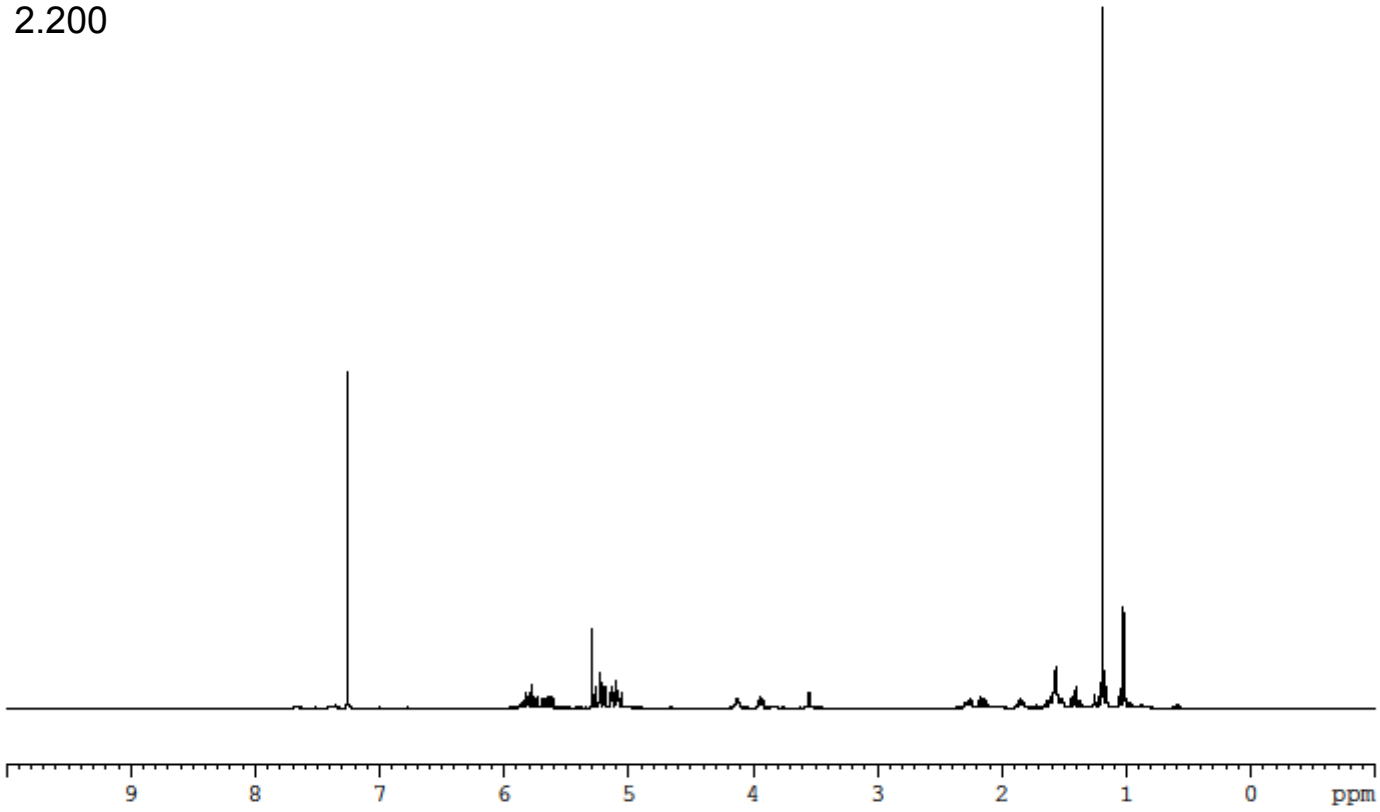

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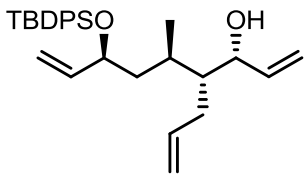

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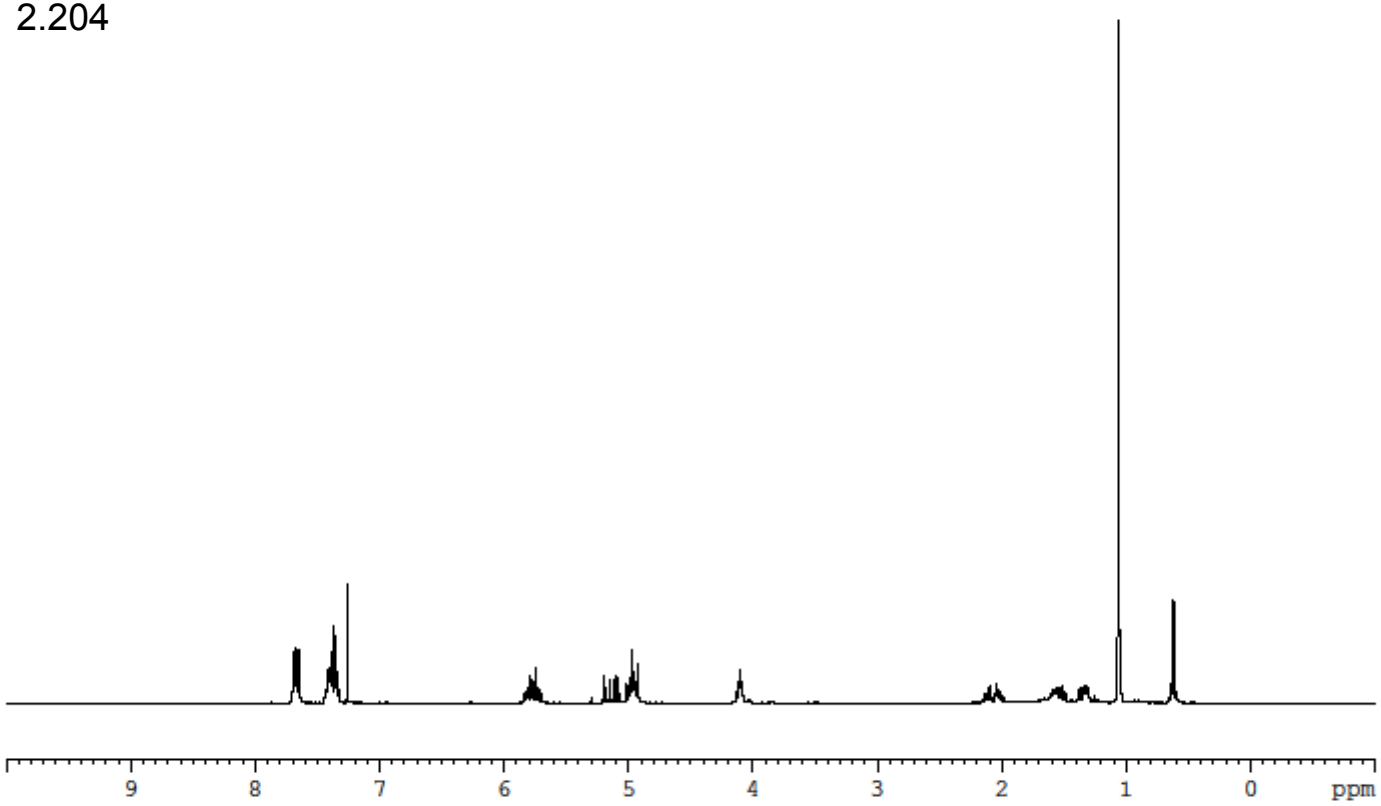

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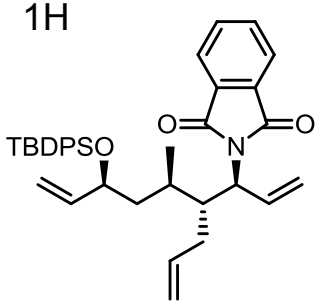

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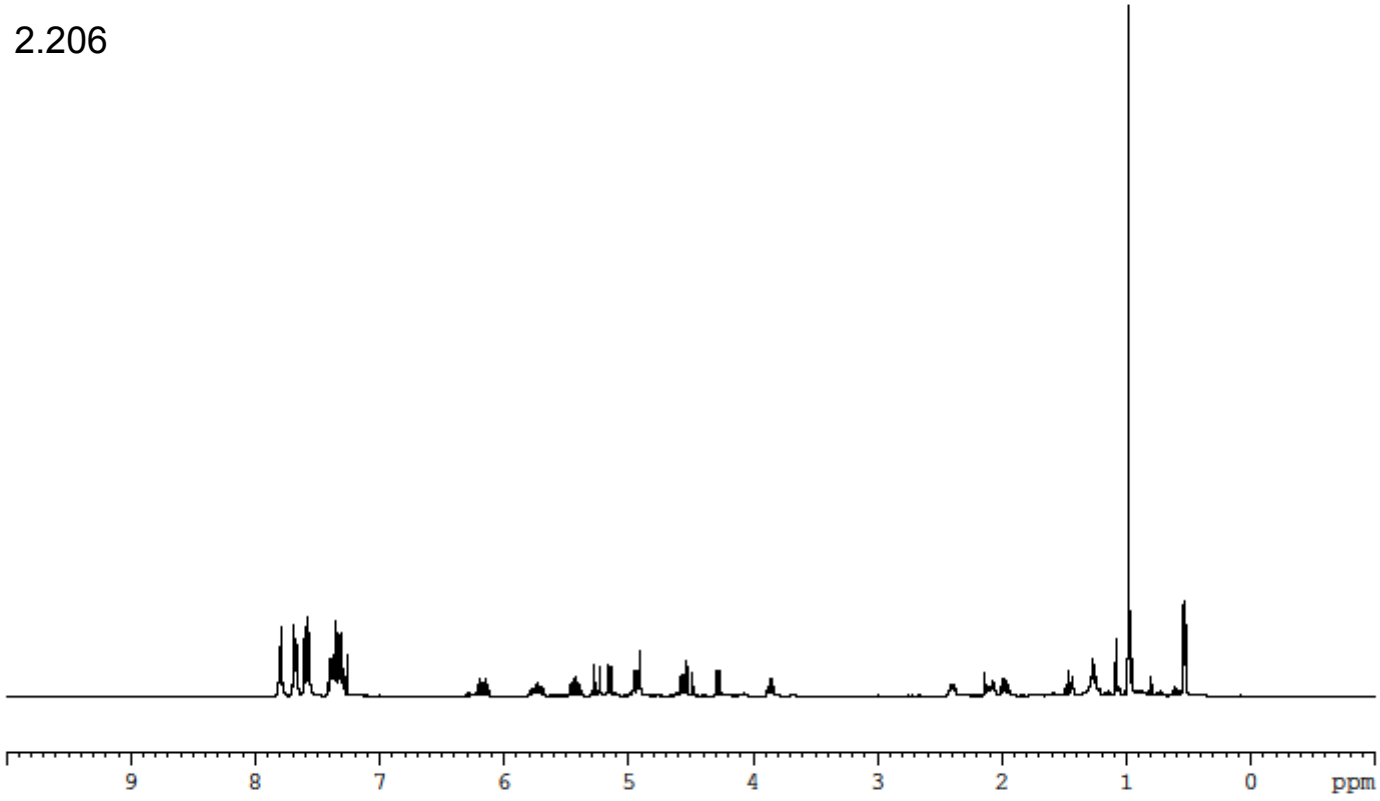

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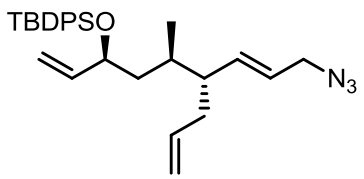

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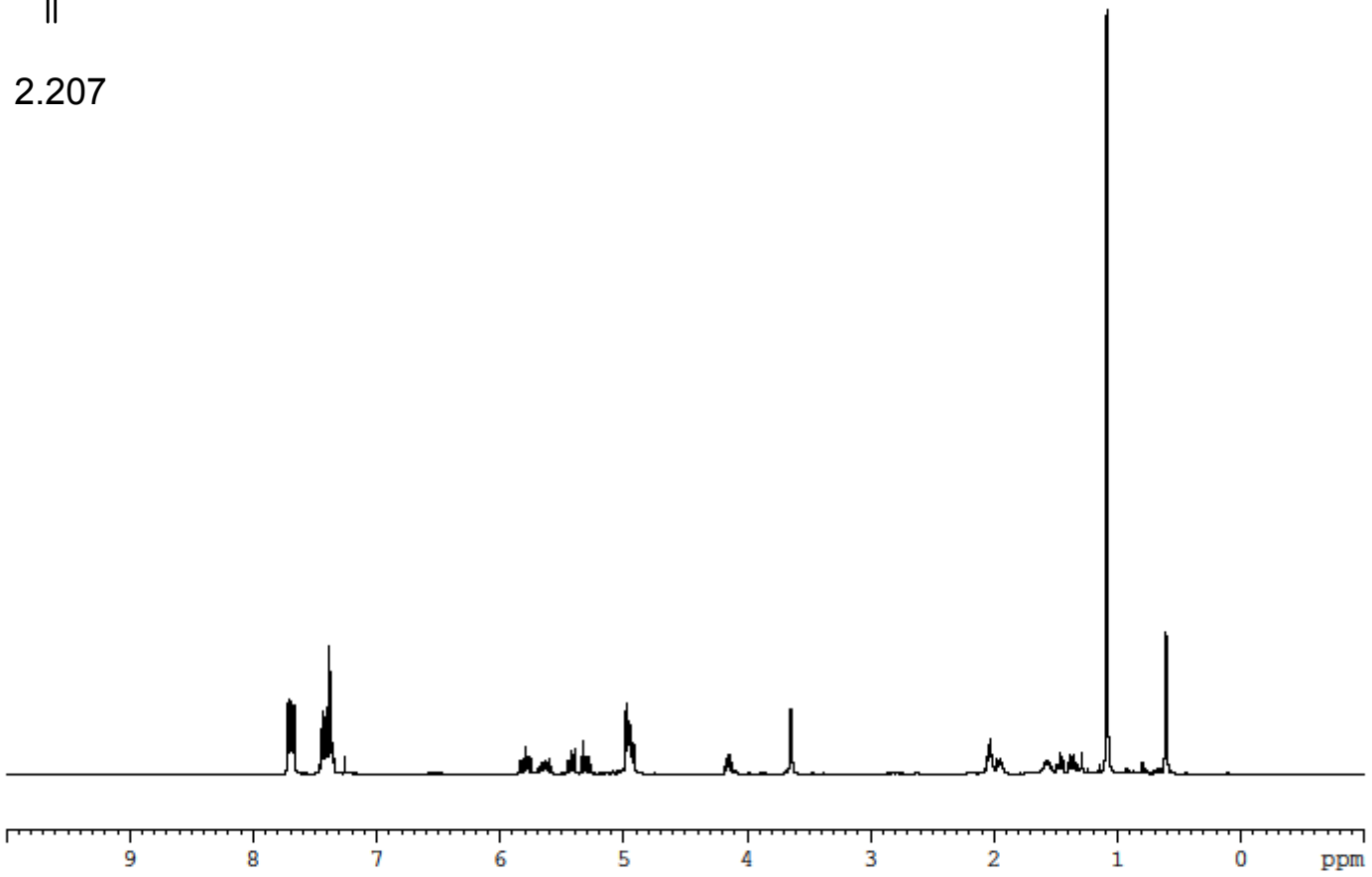

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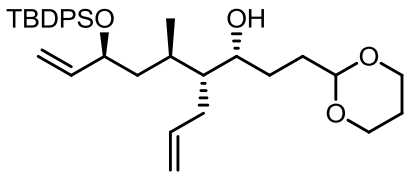

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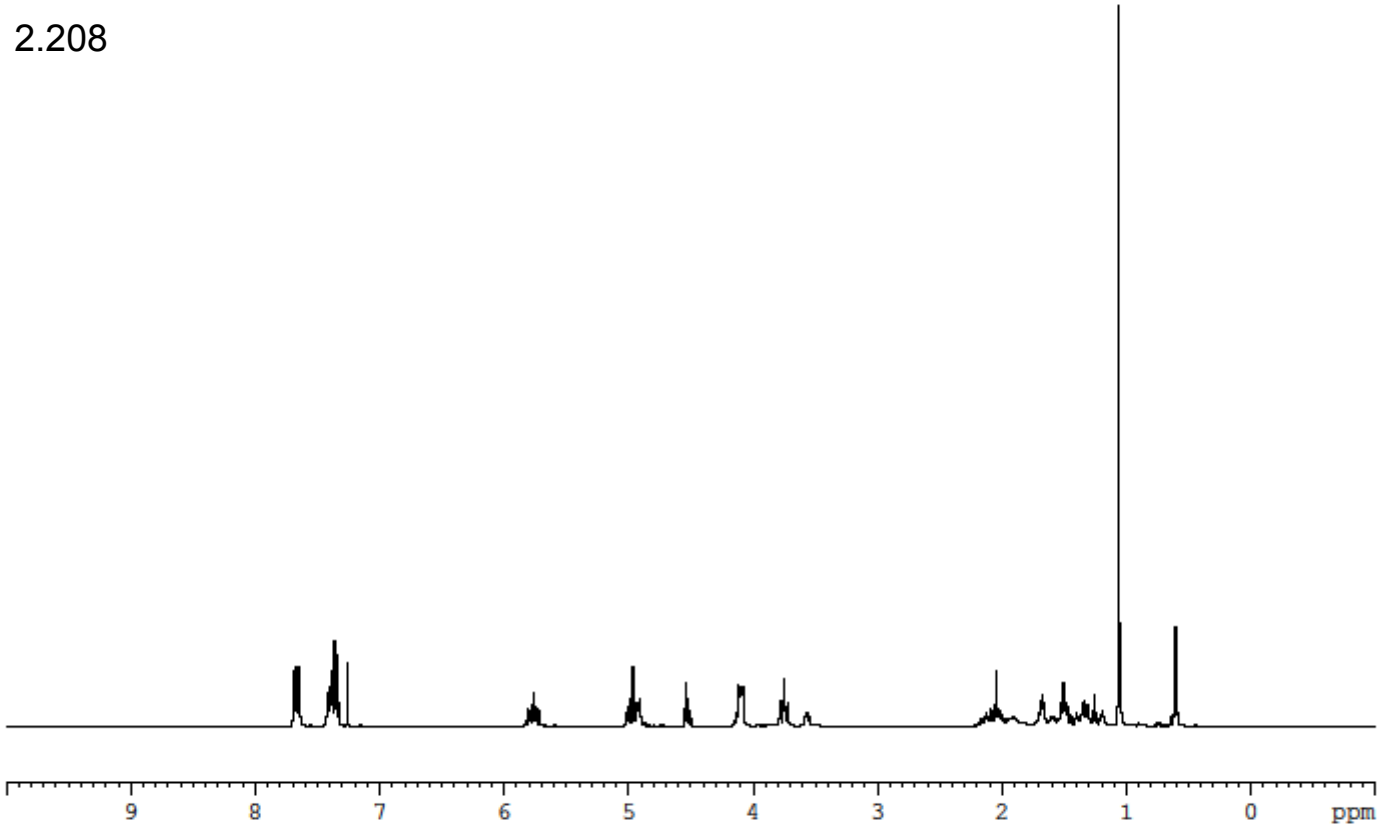

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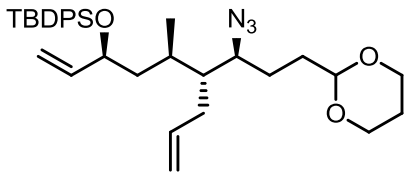

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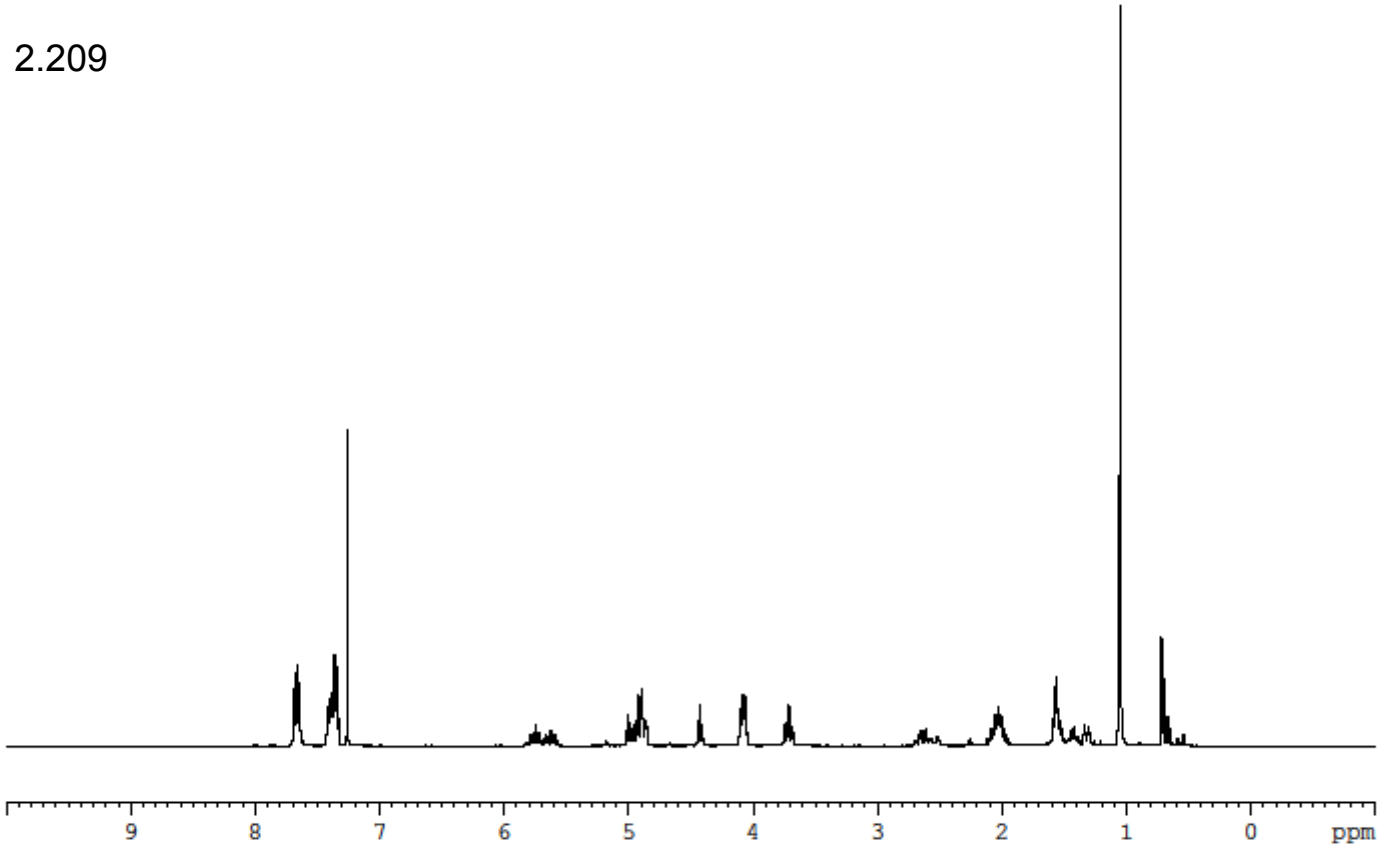

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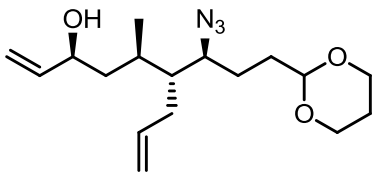

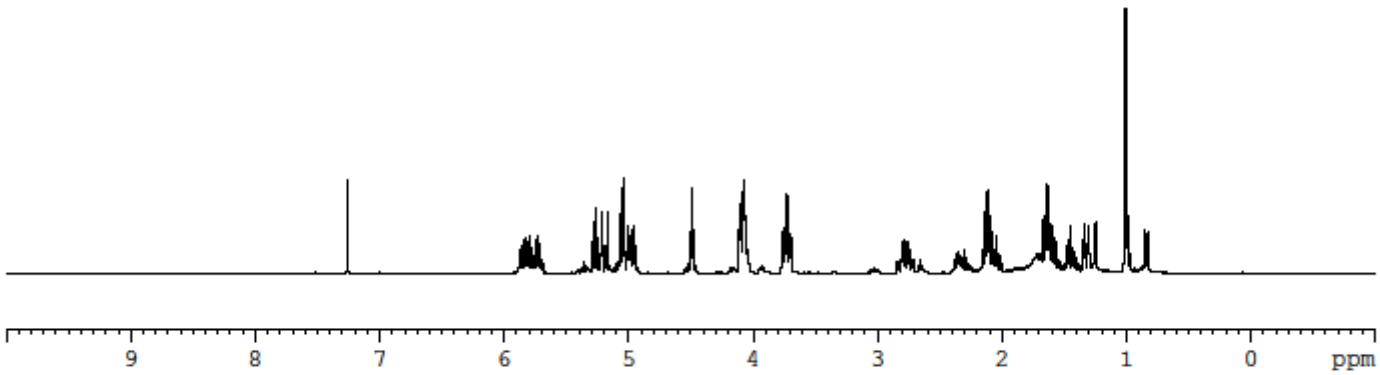

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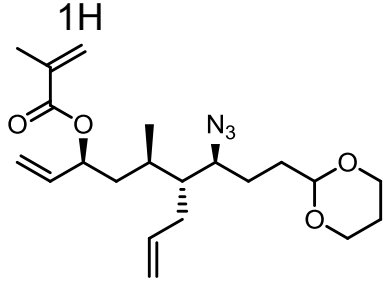

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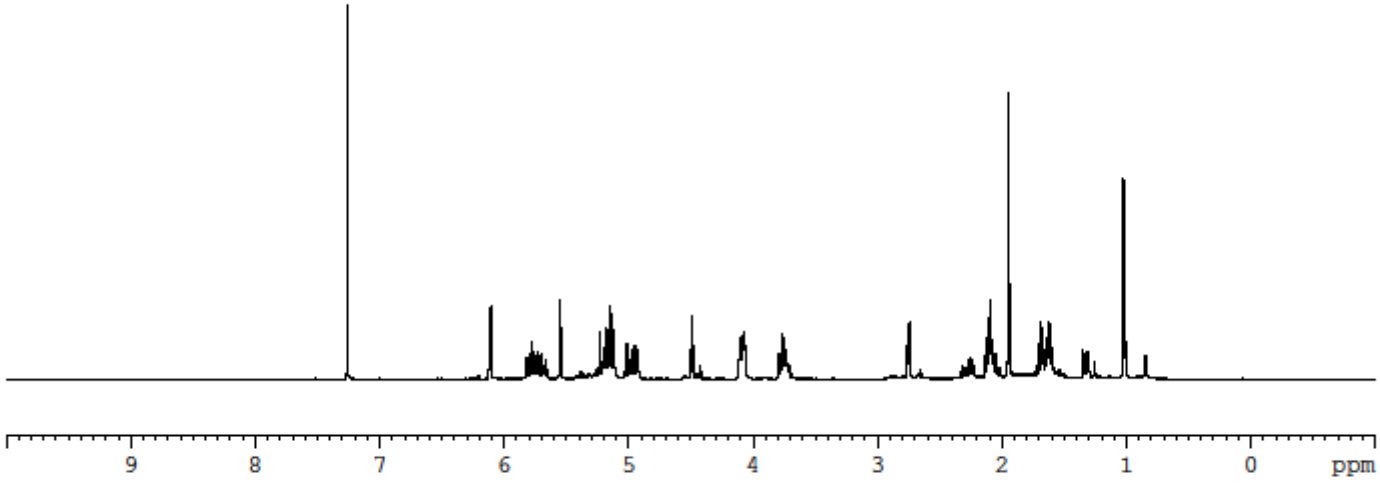

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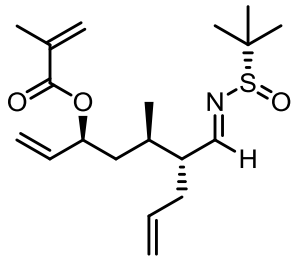

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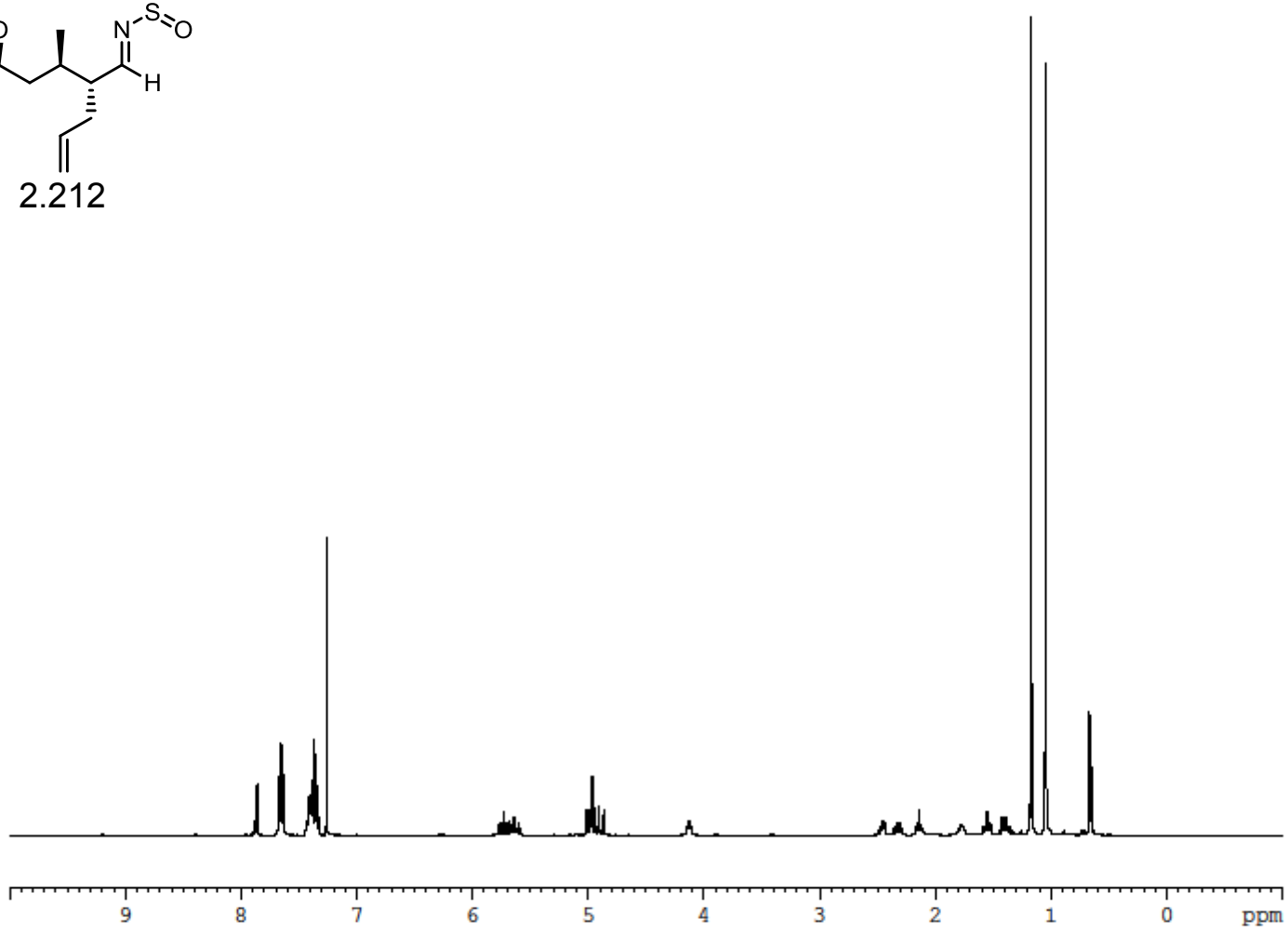
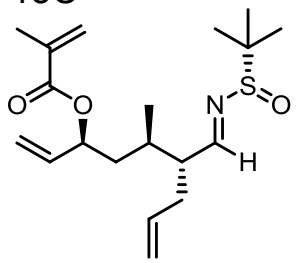
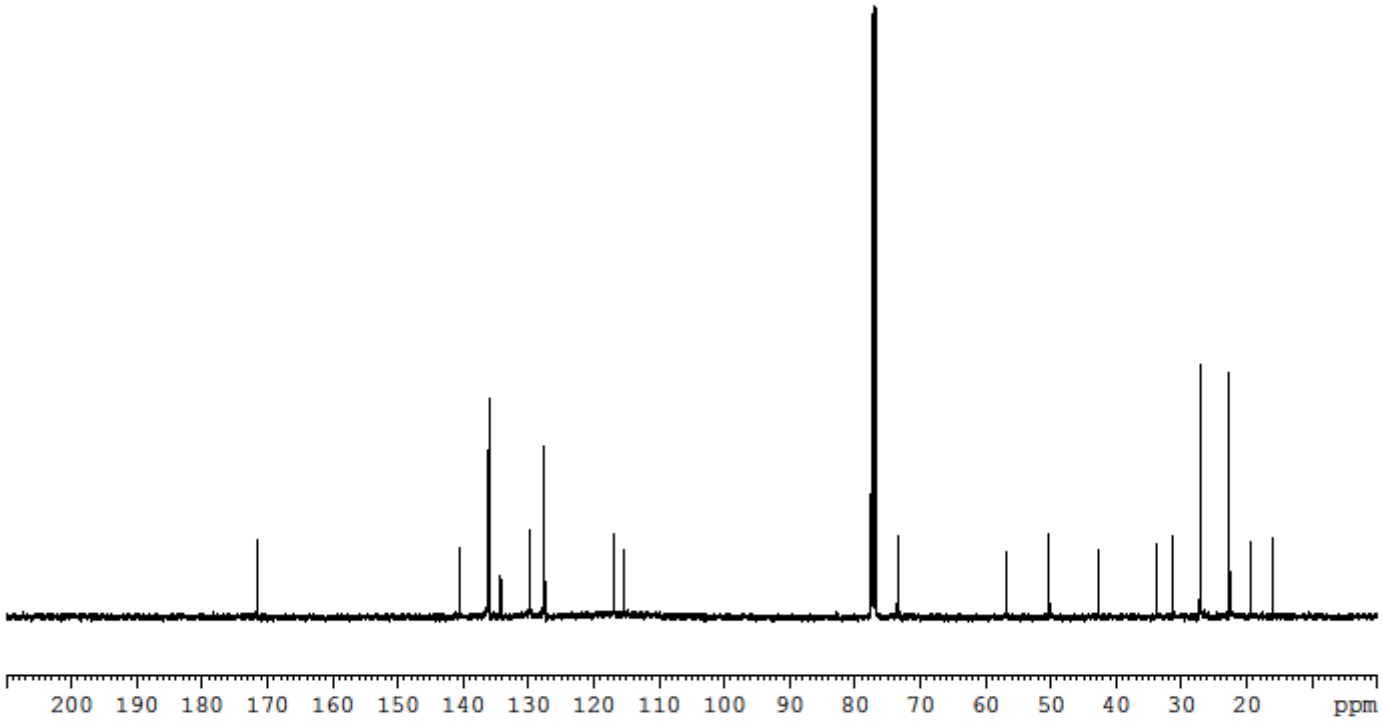


13C


O
O
N
S
O
H

2.212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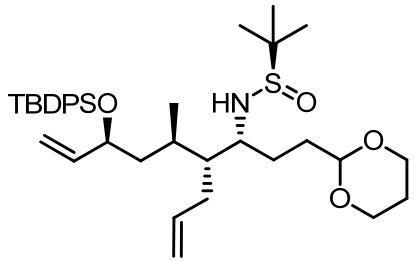
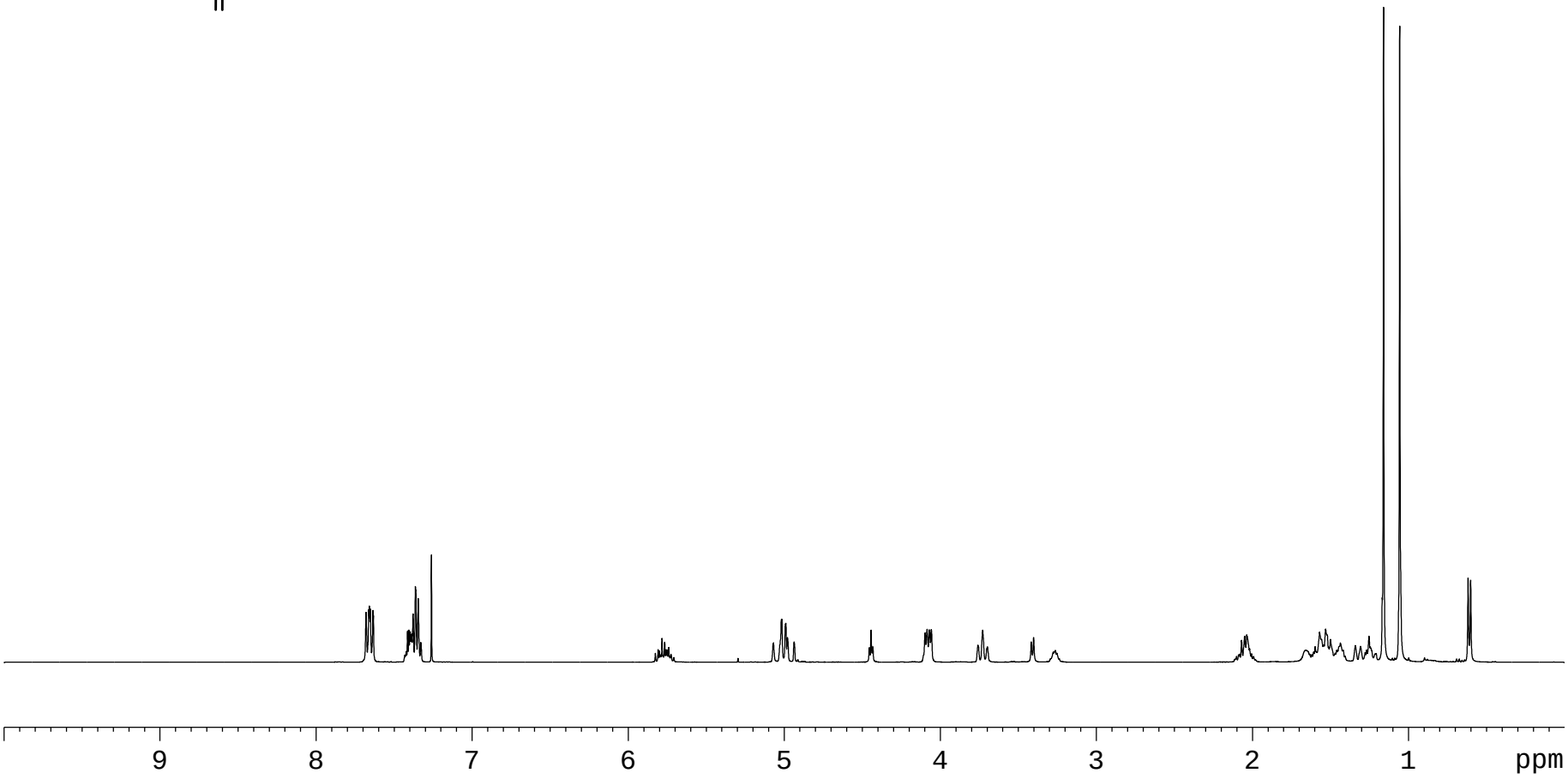
^{1}H NMR





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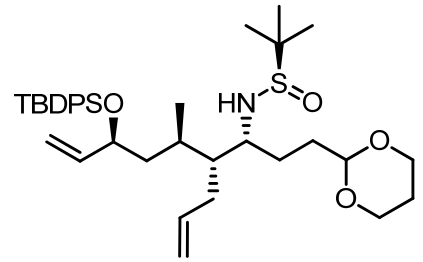
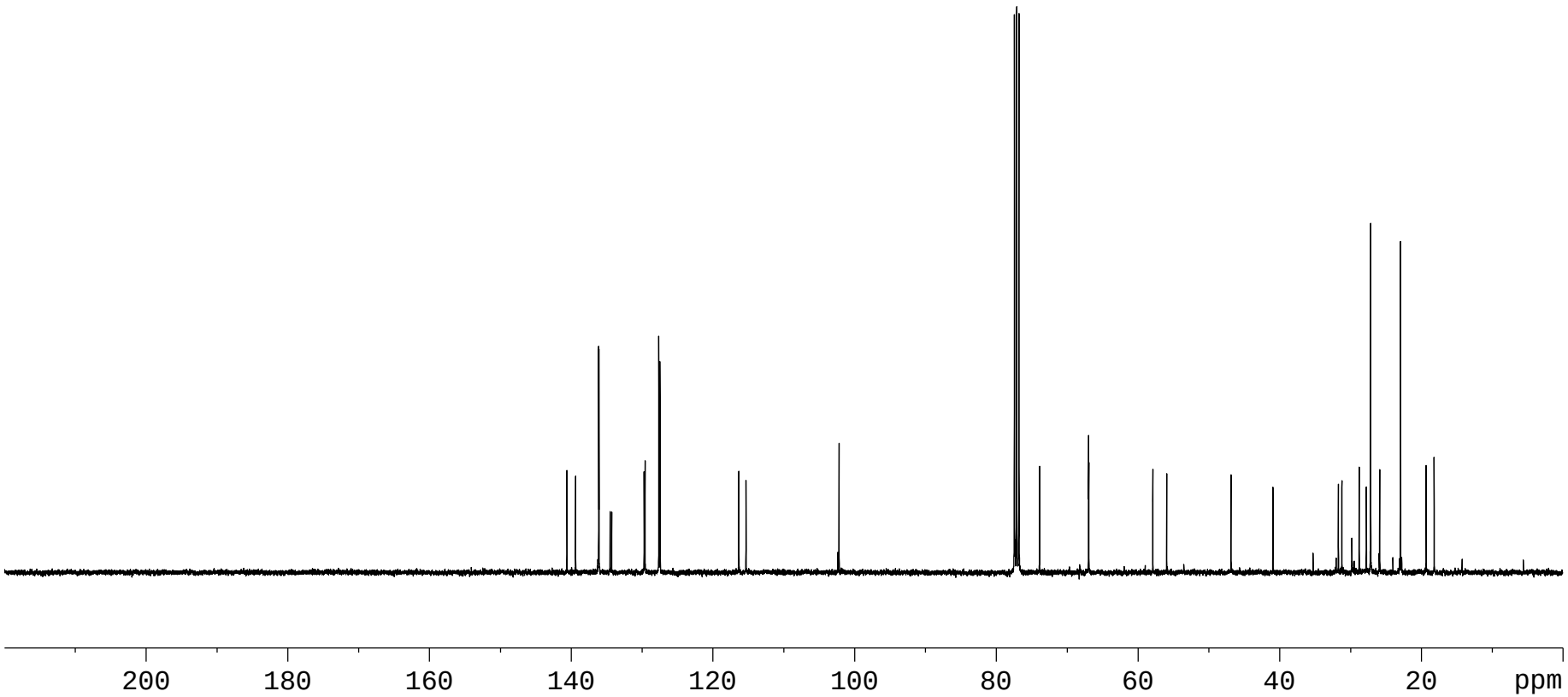
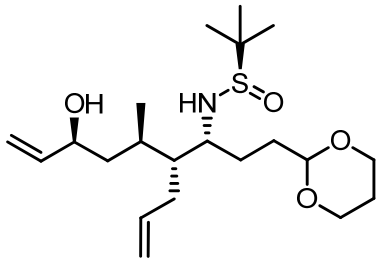
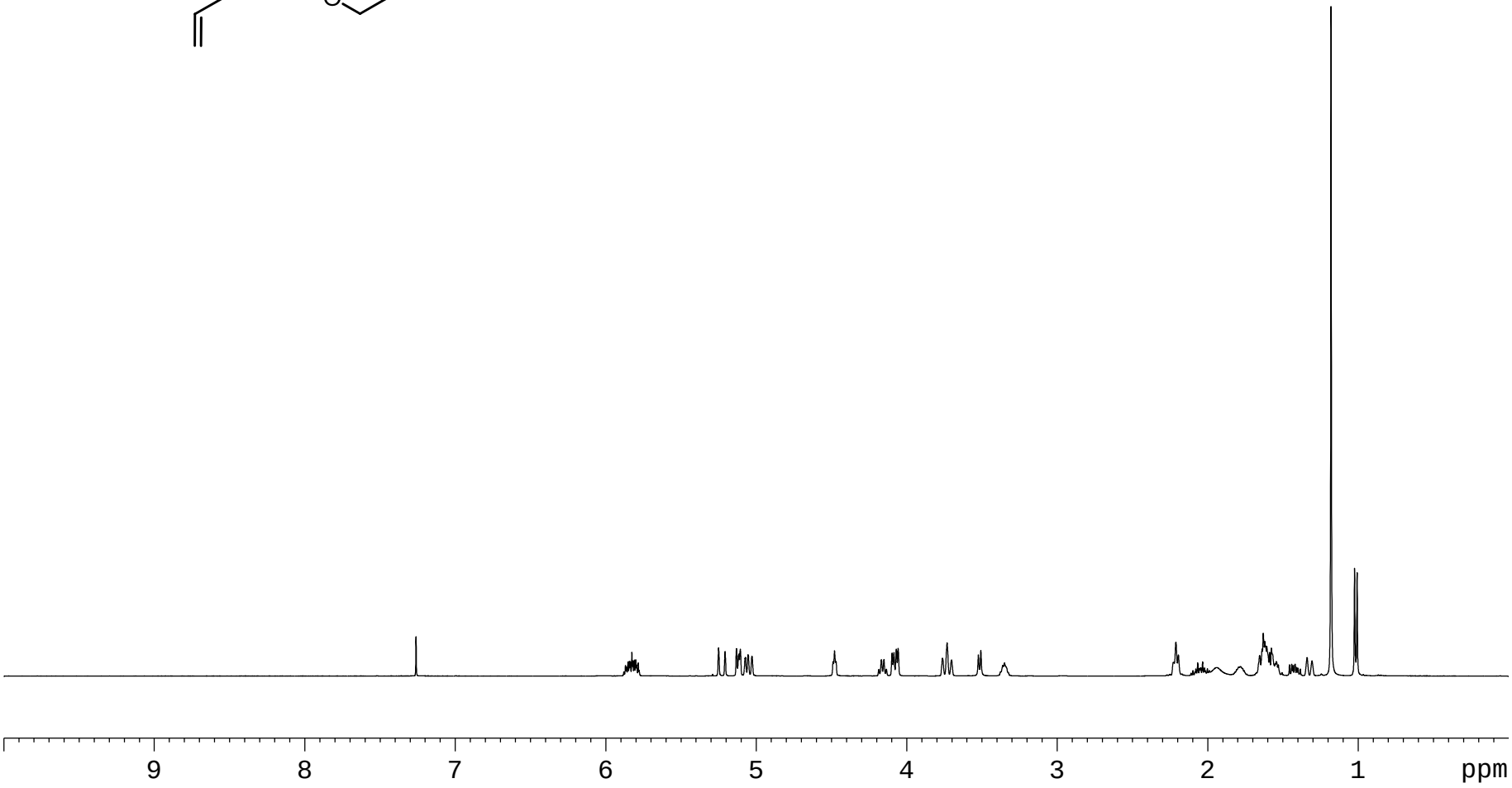


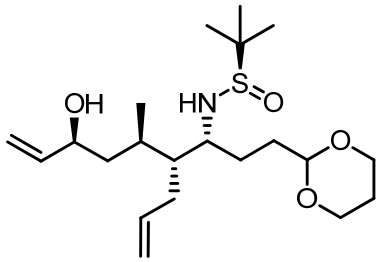


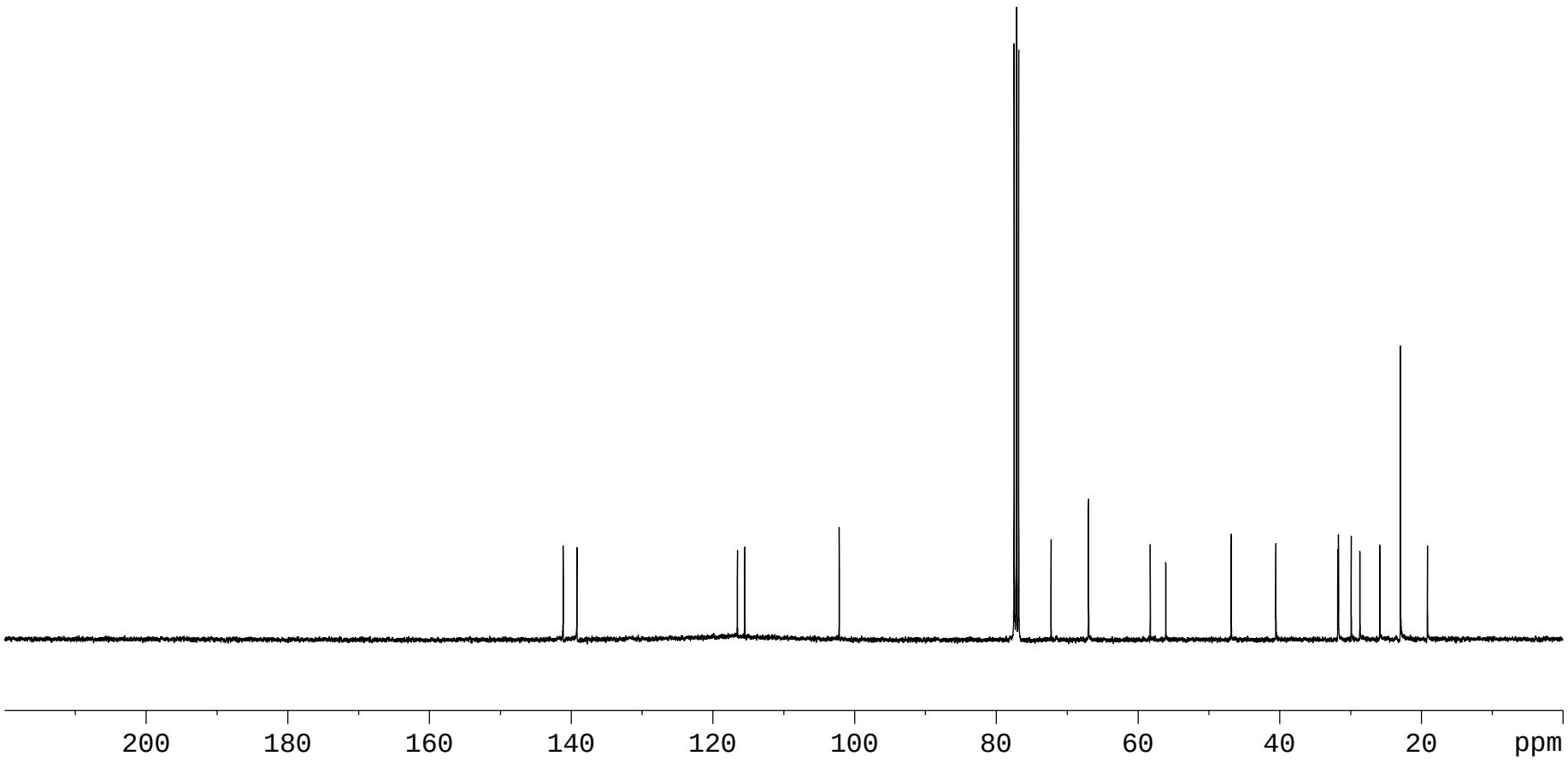
^{1}H NMR





^{13}C NMR





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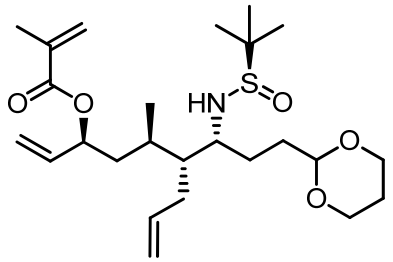

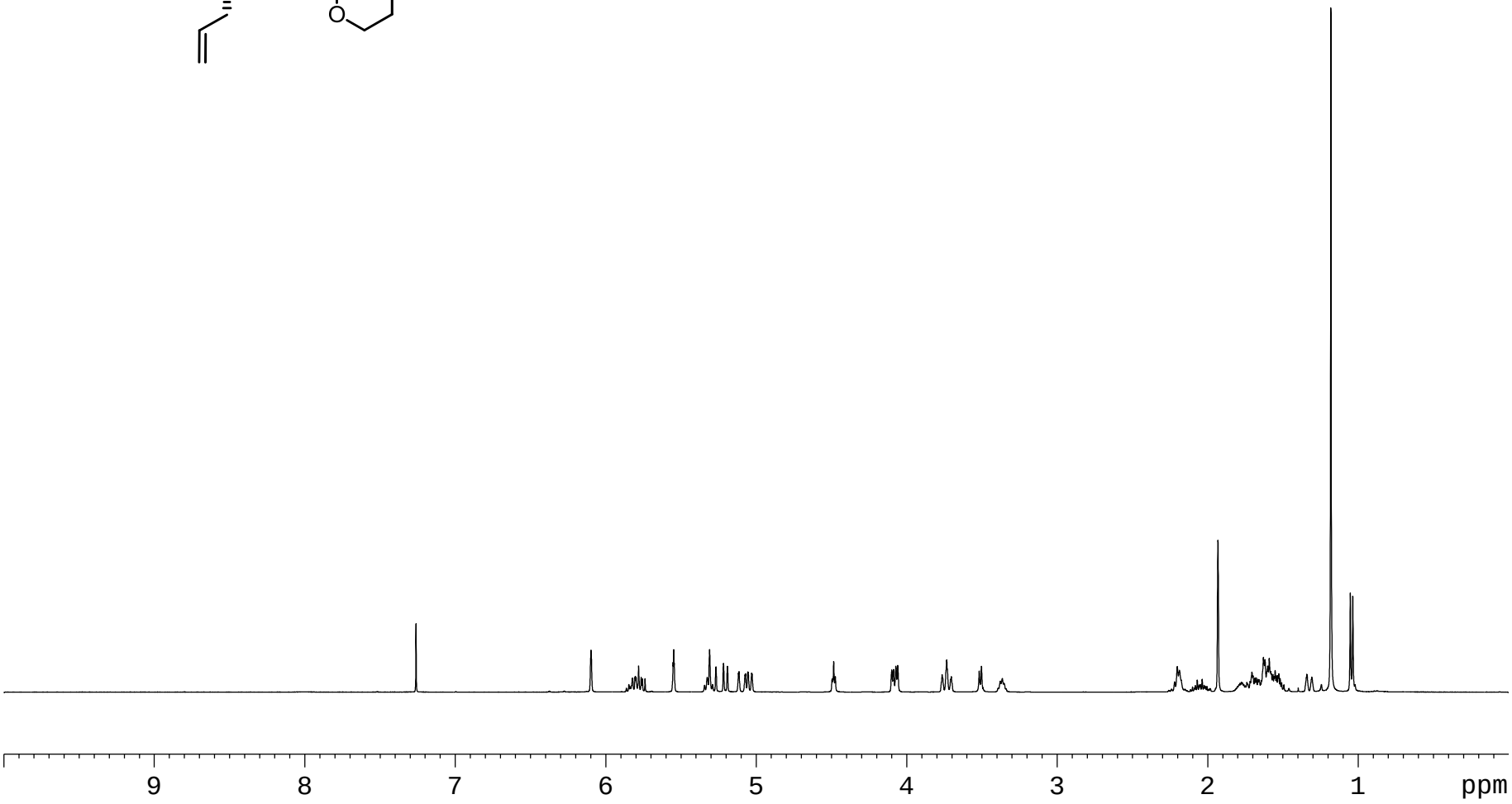

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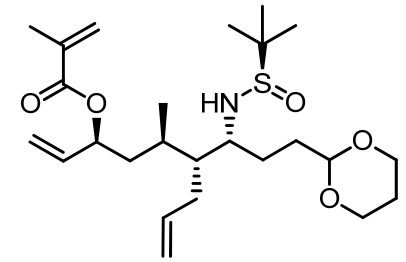

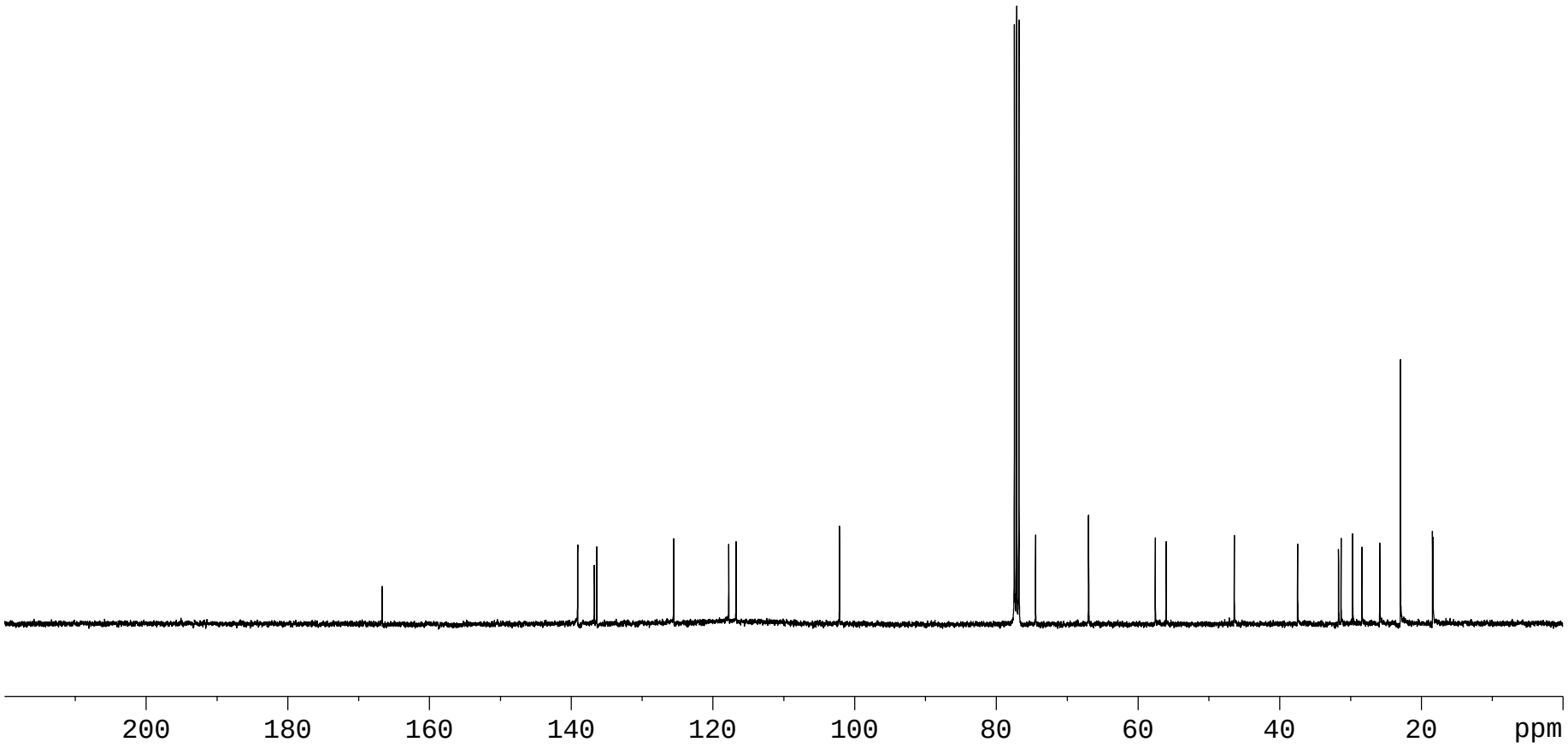

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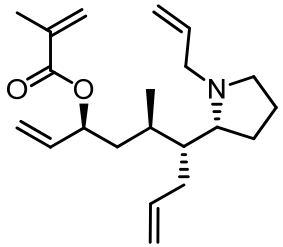
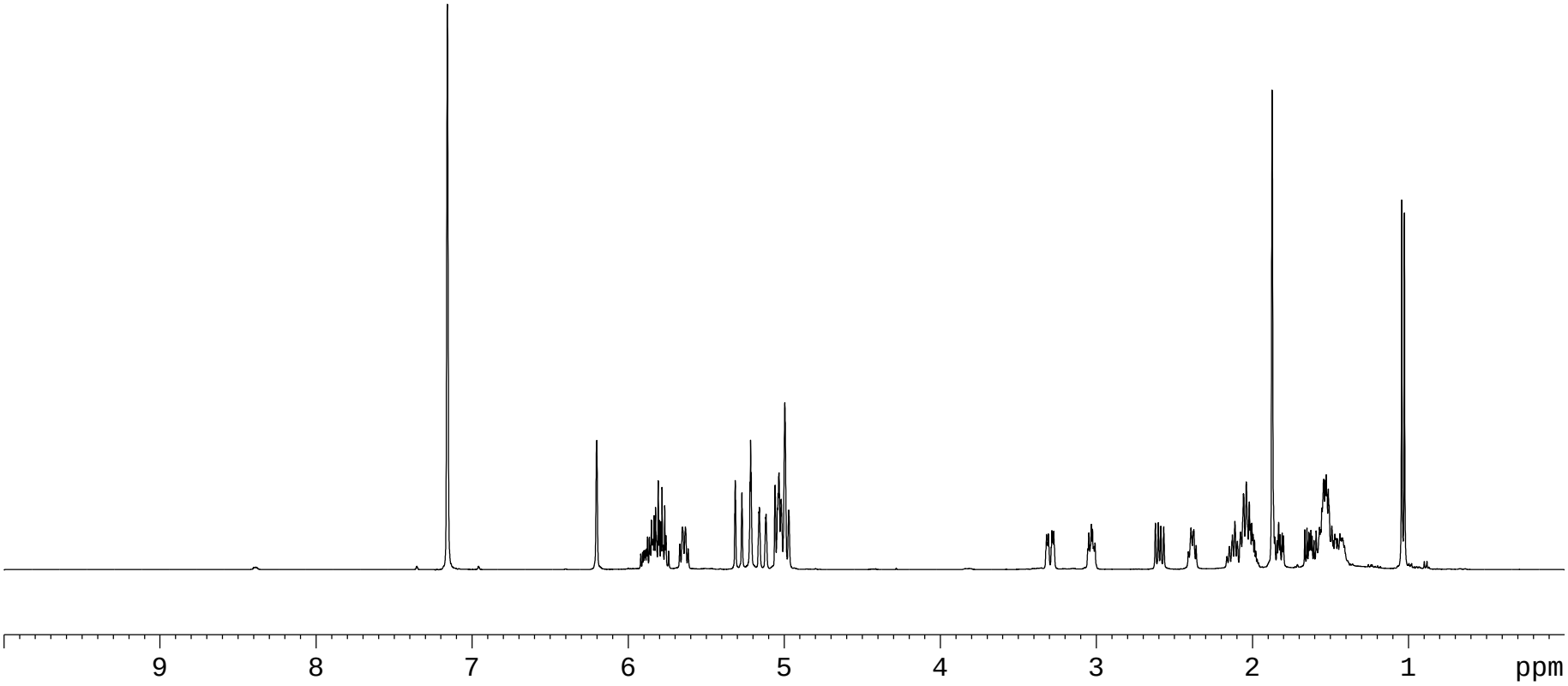
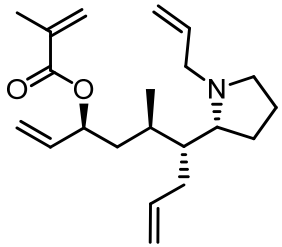




^{13}C NMR



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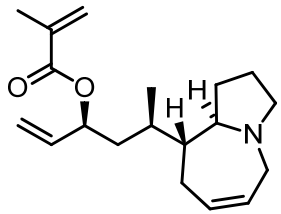

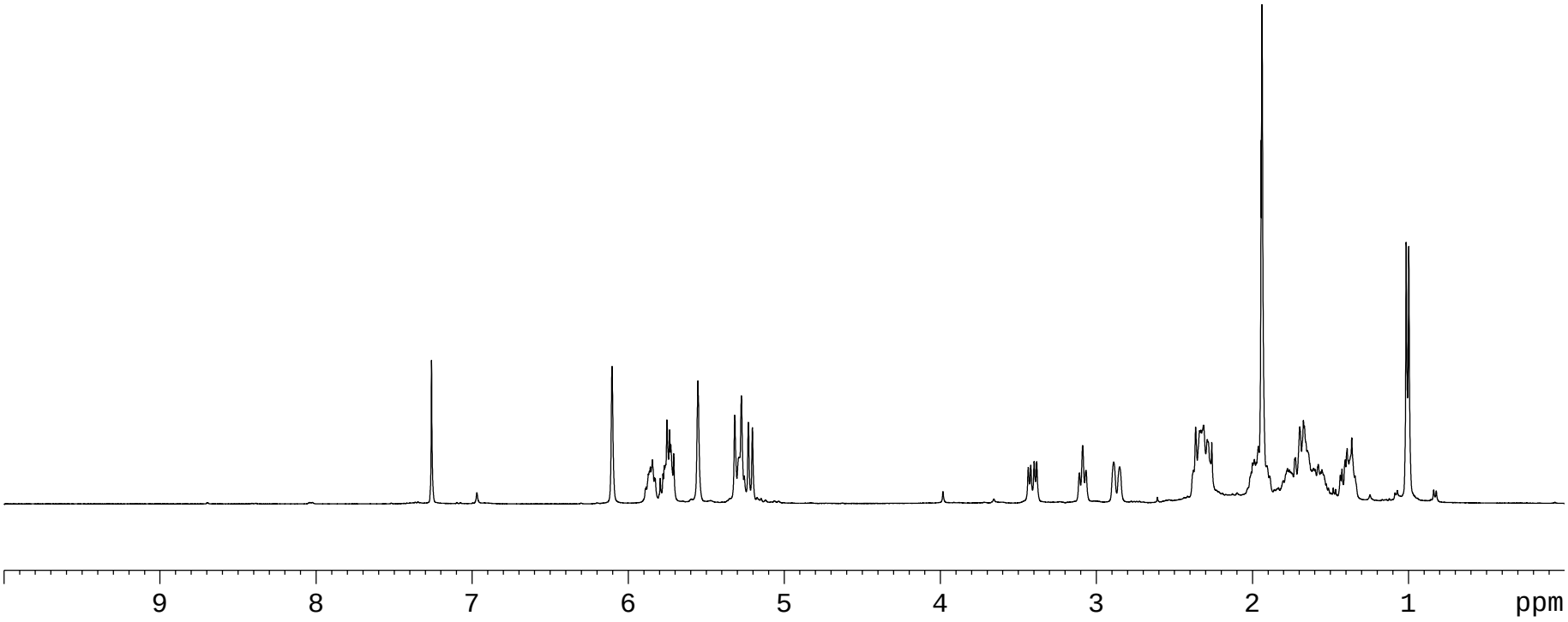

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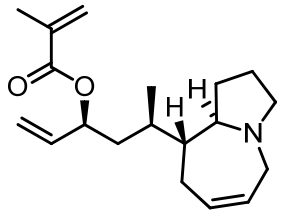
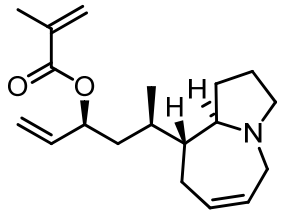


COSY NMR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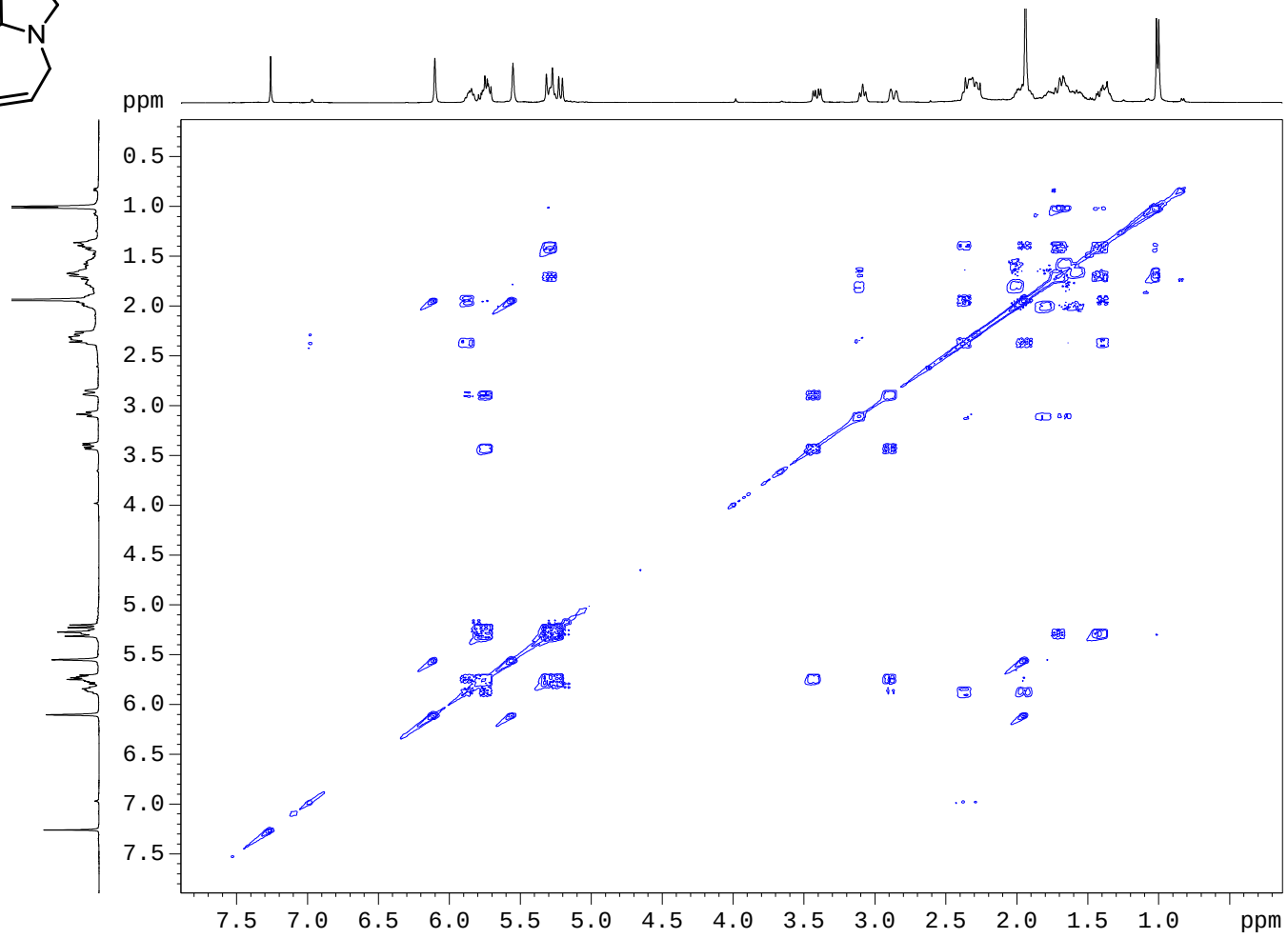
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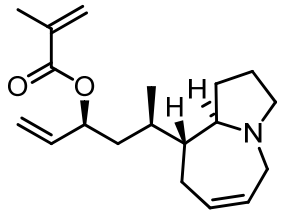
TOCSY NMR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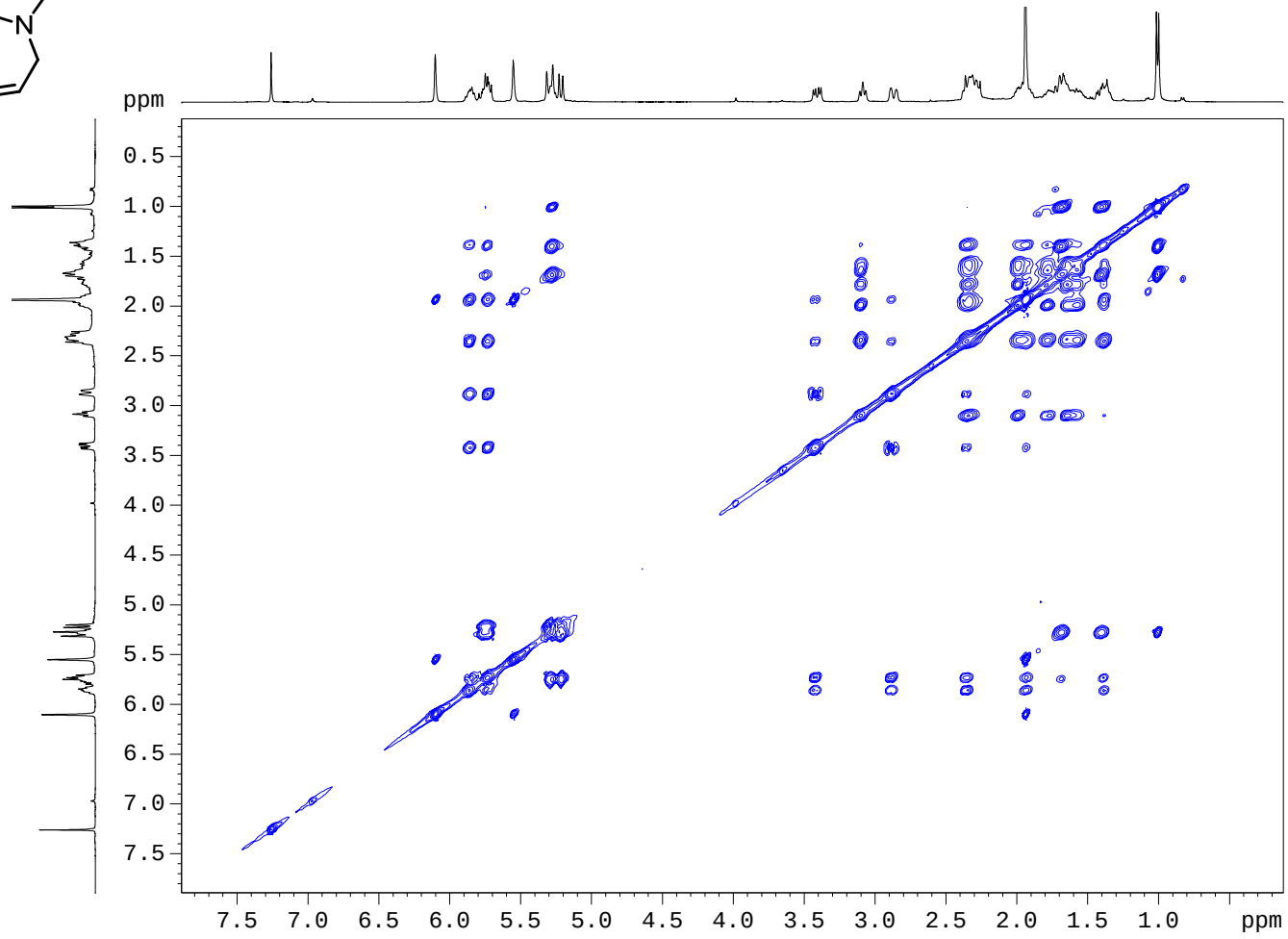
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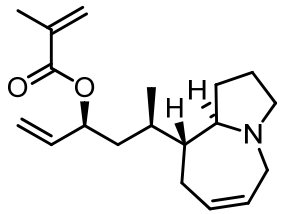
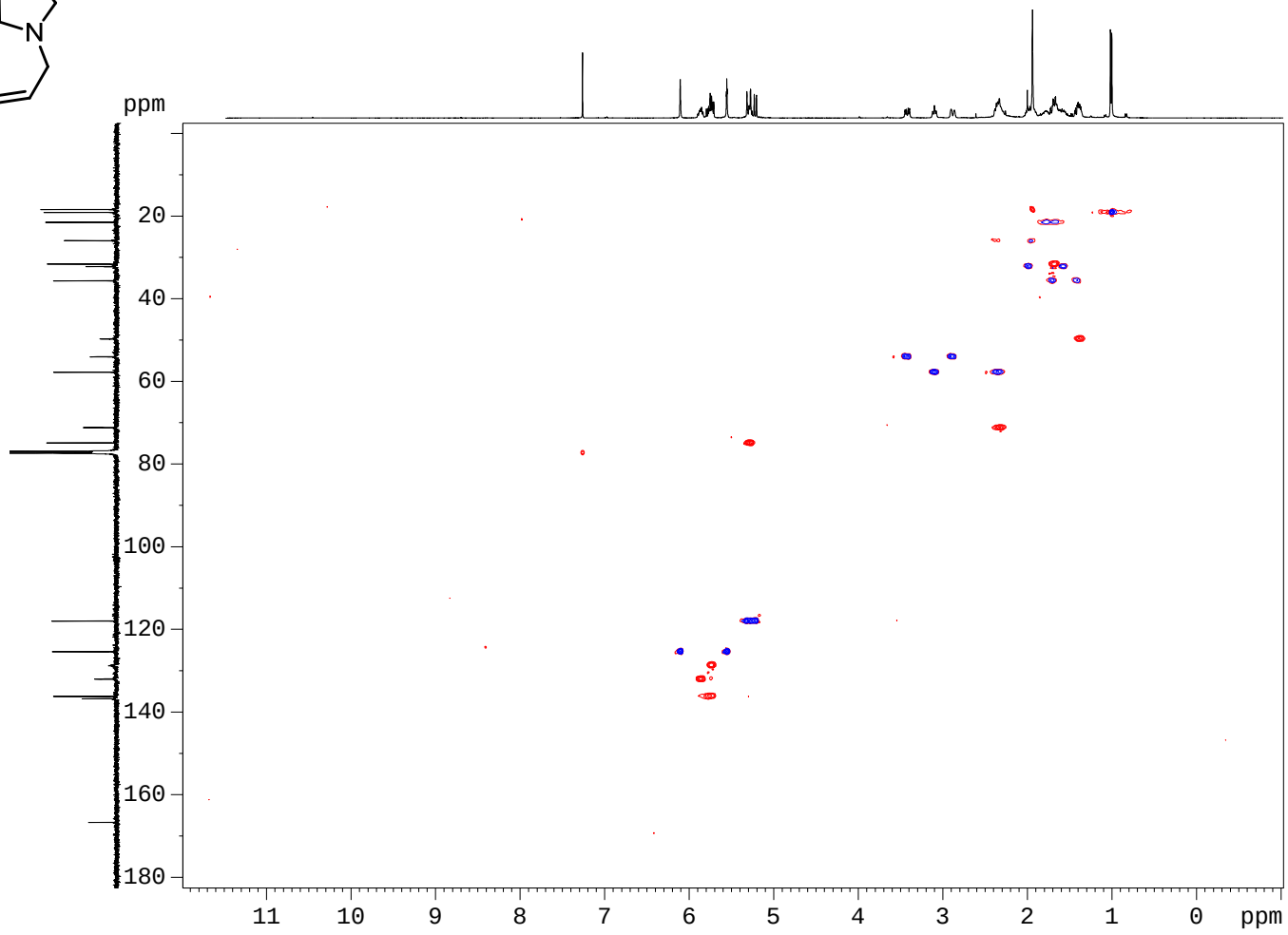
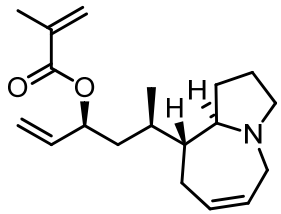
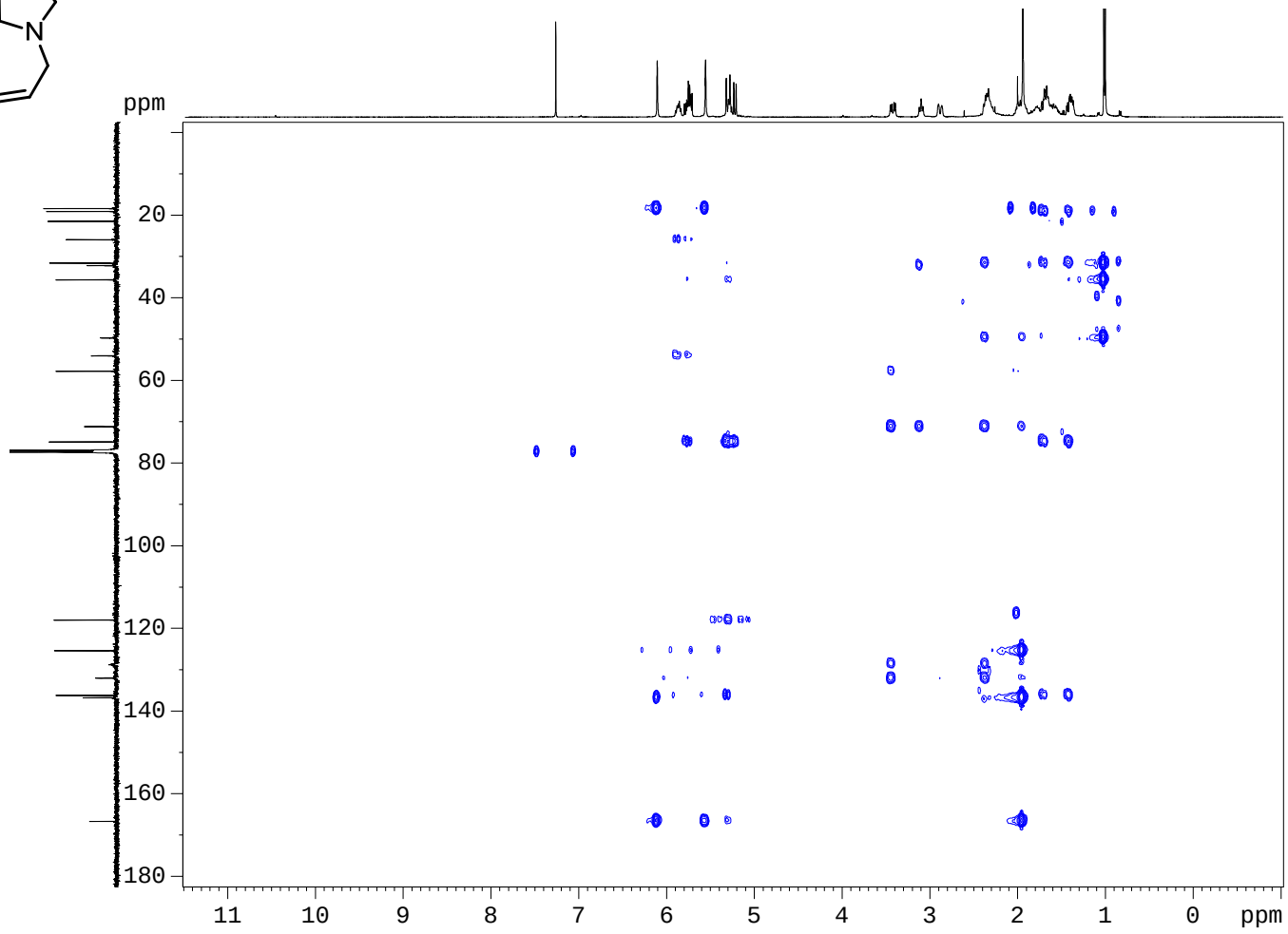
HSQC NMR



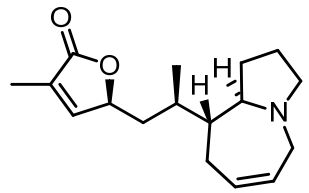


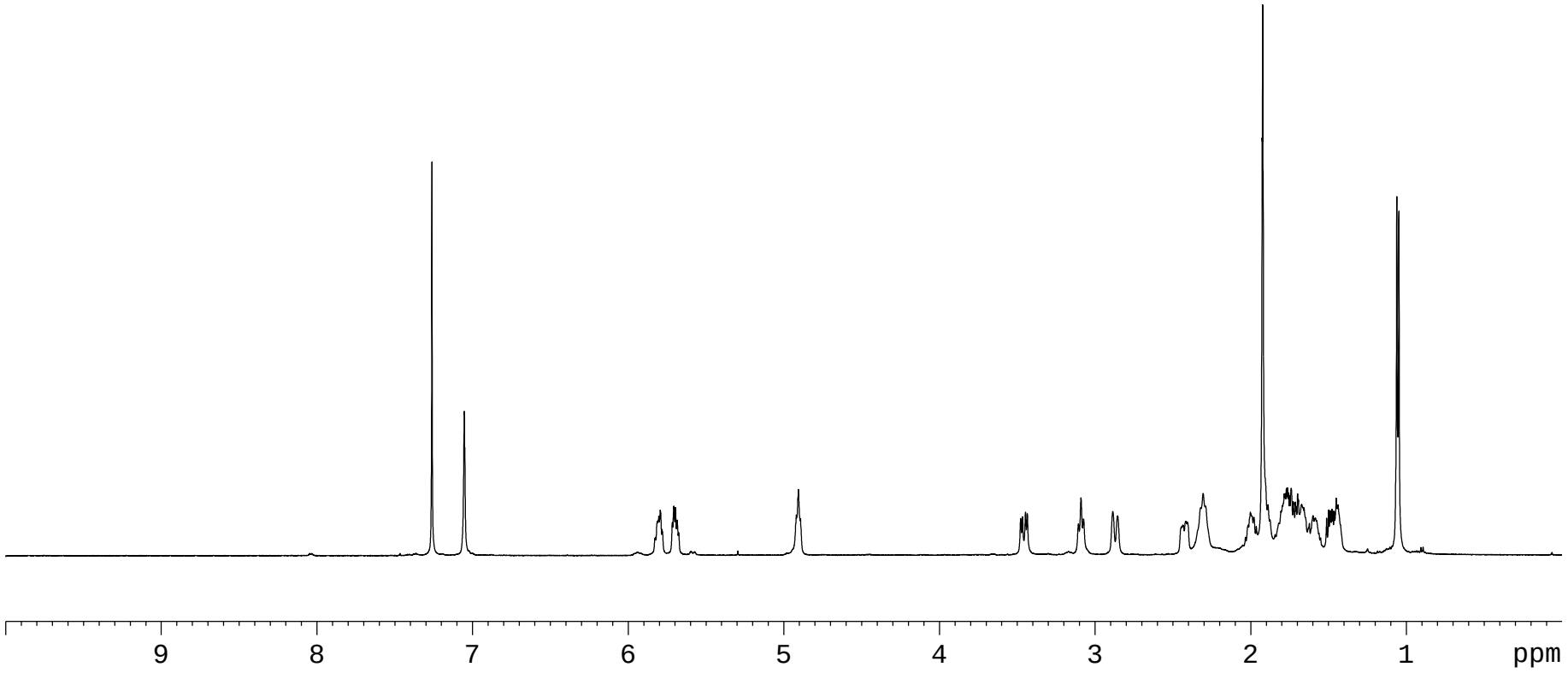
HMBC NMR



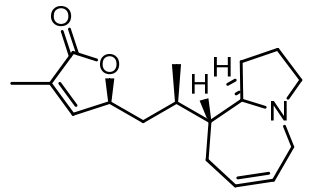


^{1}H NMR

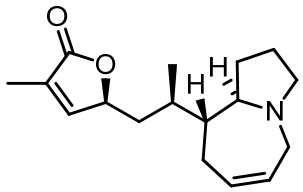




^{13}C NMR



COSY NMR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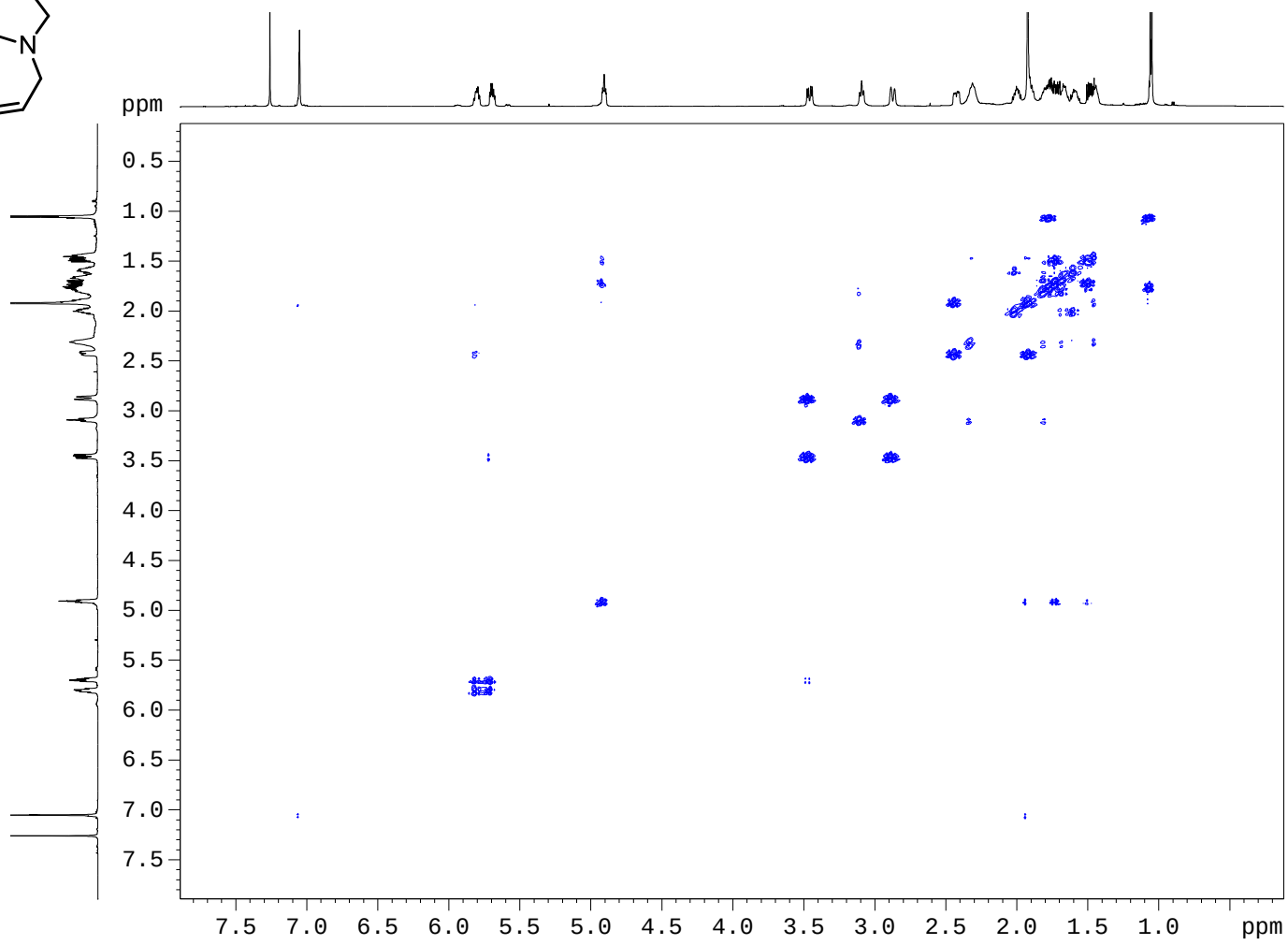
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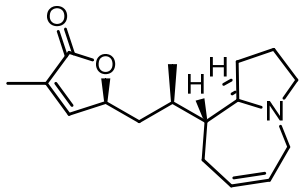
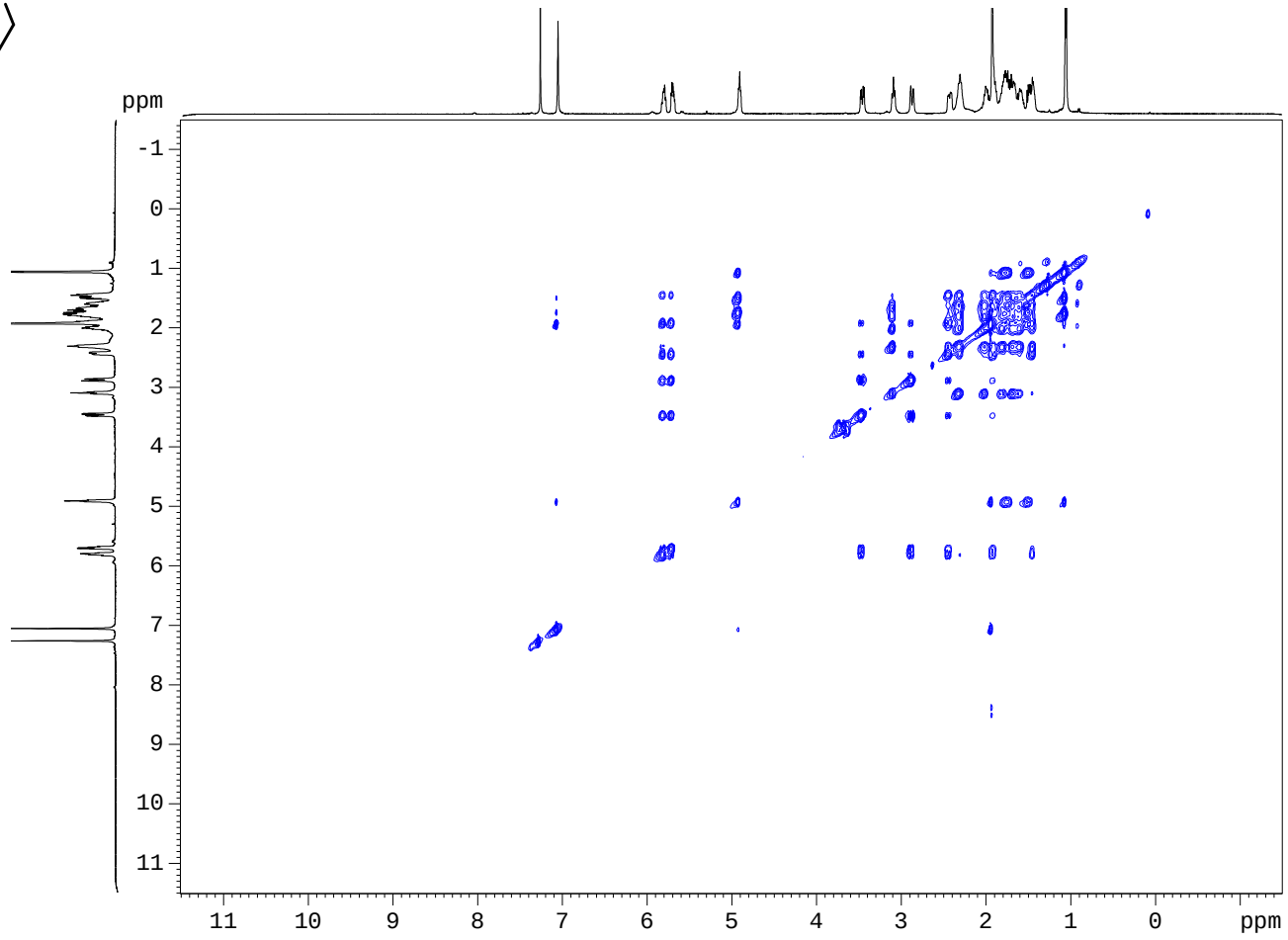
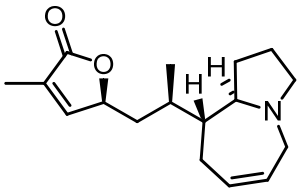
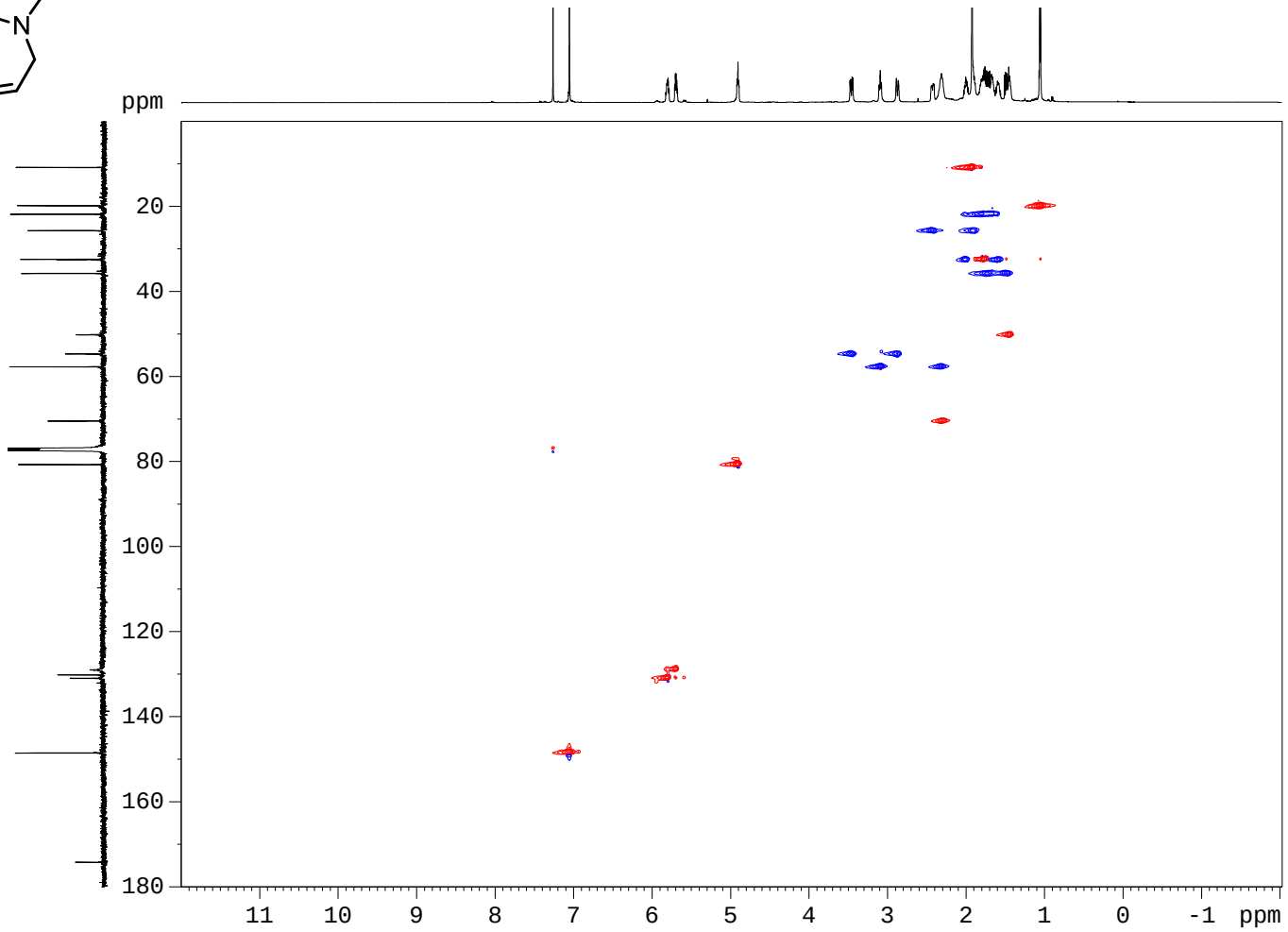
TOCSY NMR



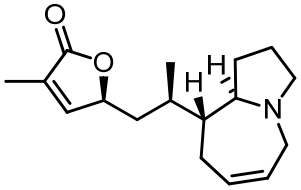


HSQC NMR





HMBC NMR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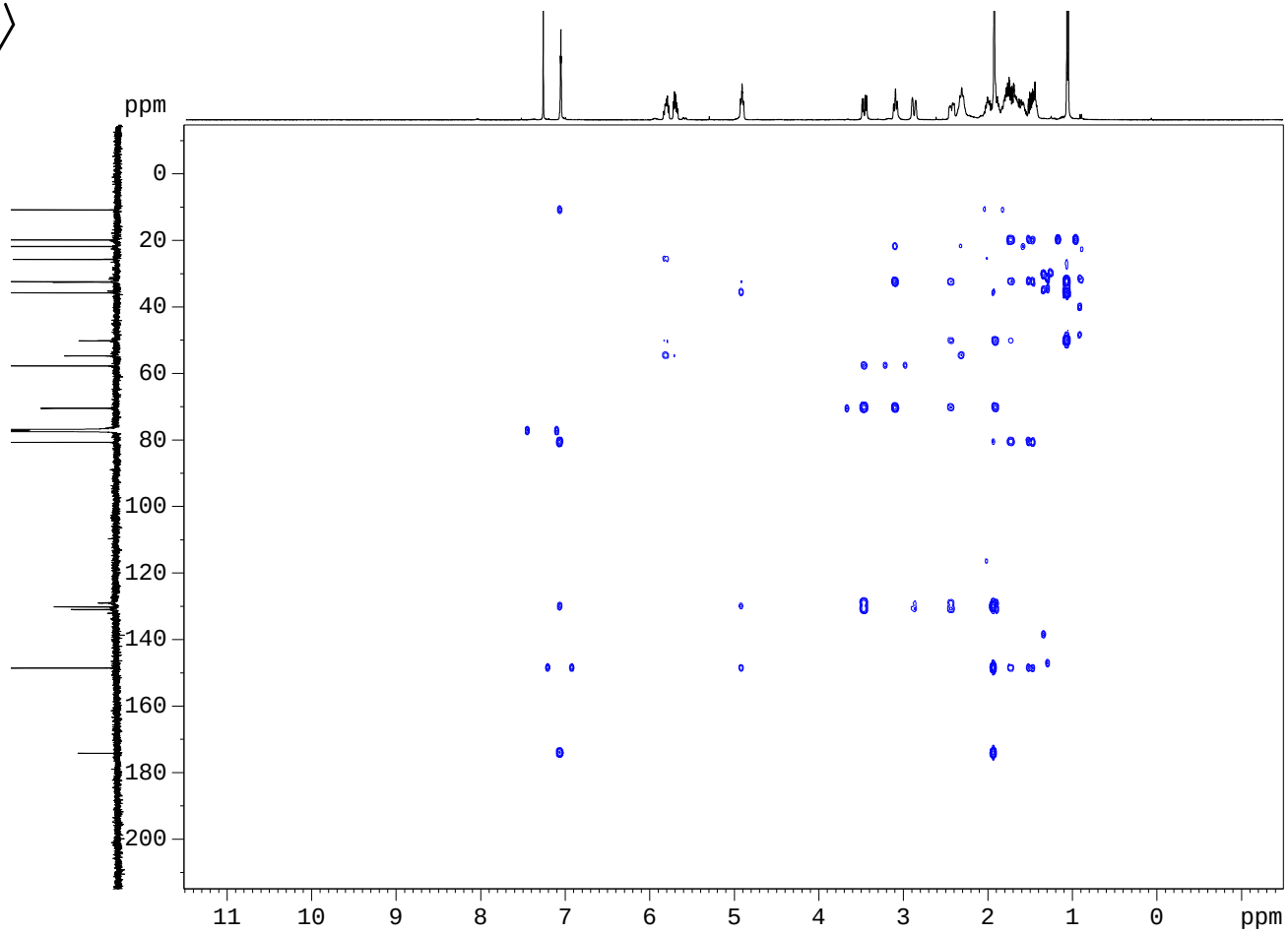
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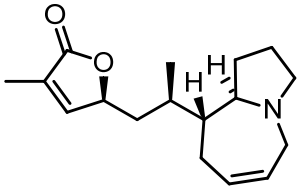
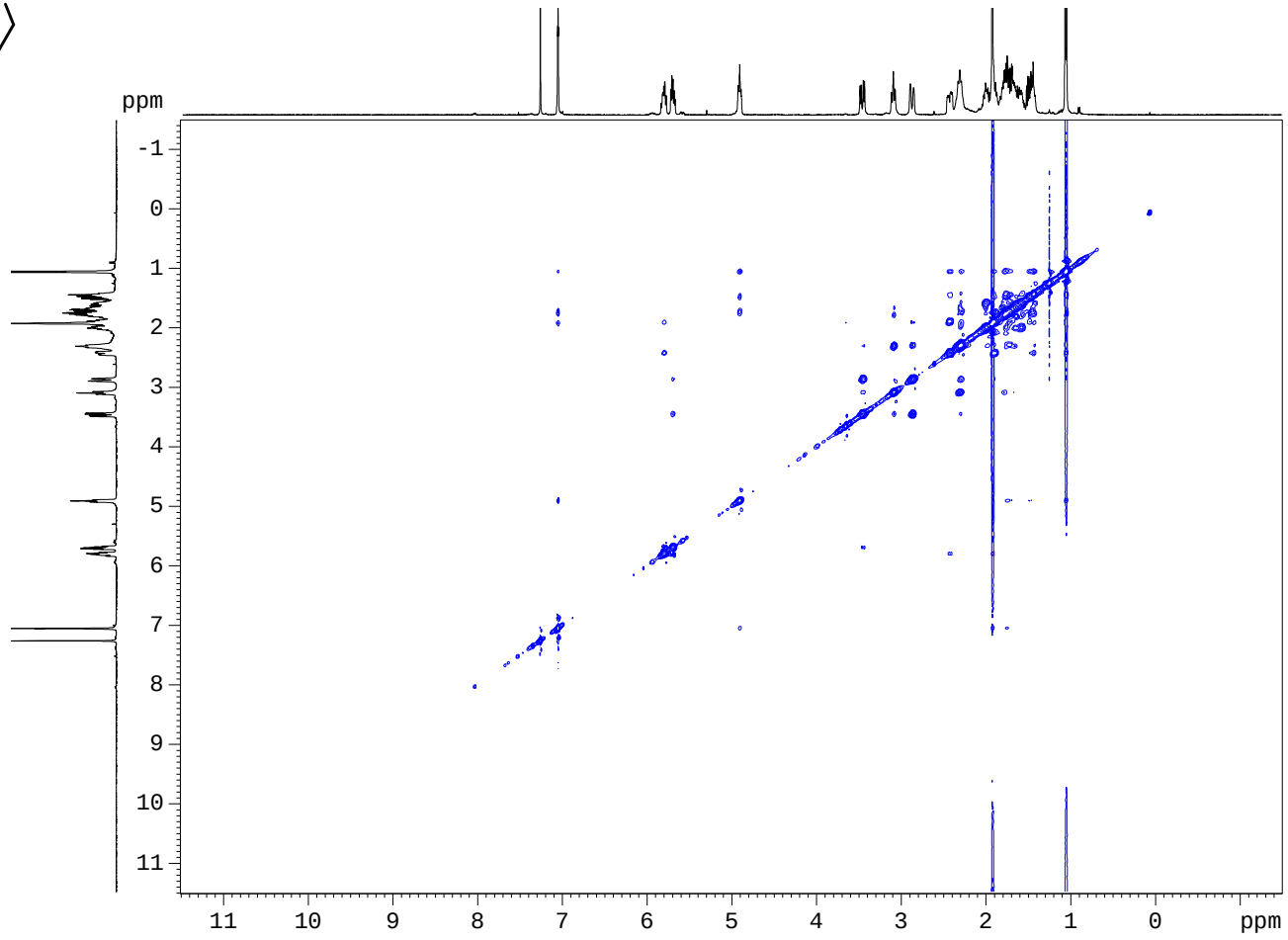
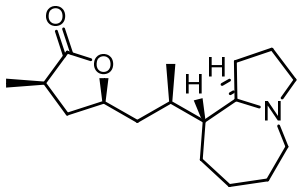
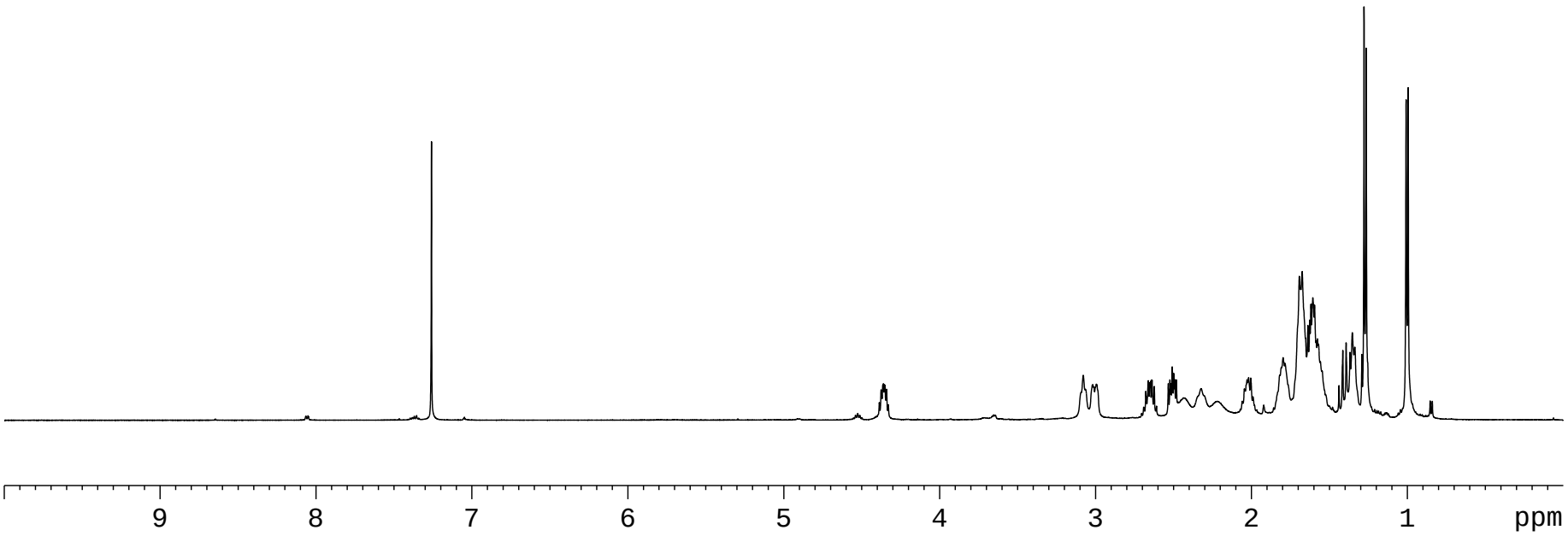
NOESY NMR



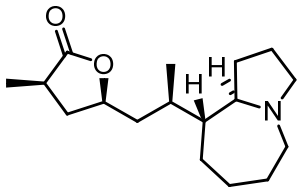


^{1}H NMR





^{13}C NMR



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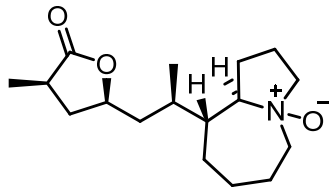

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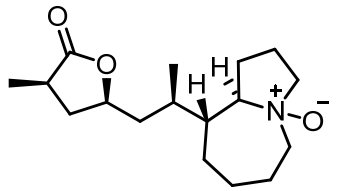
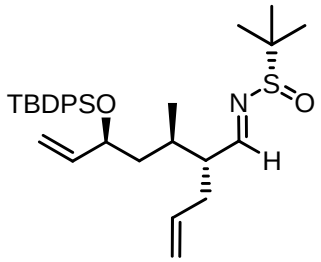
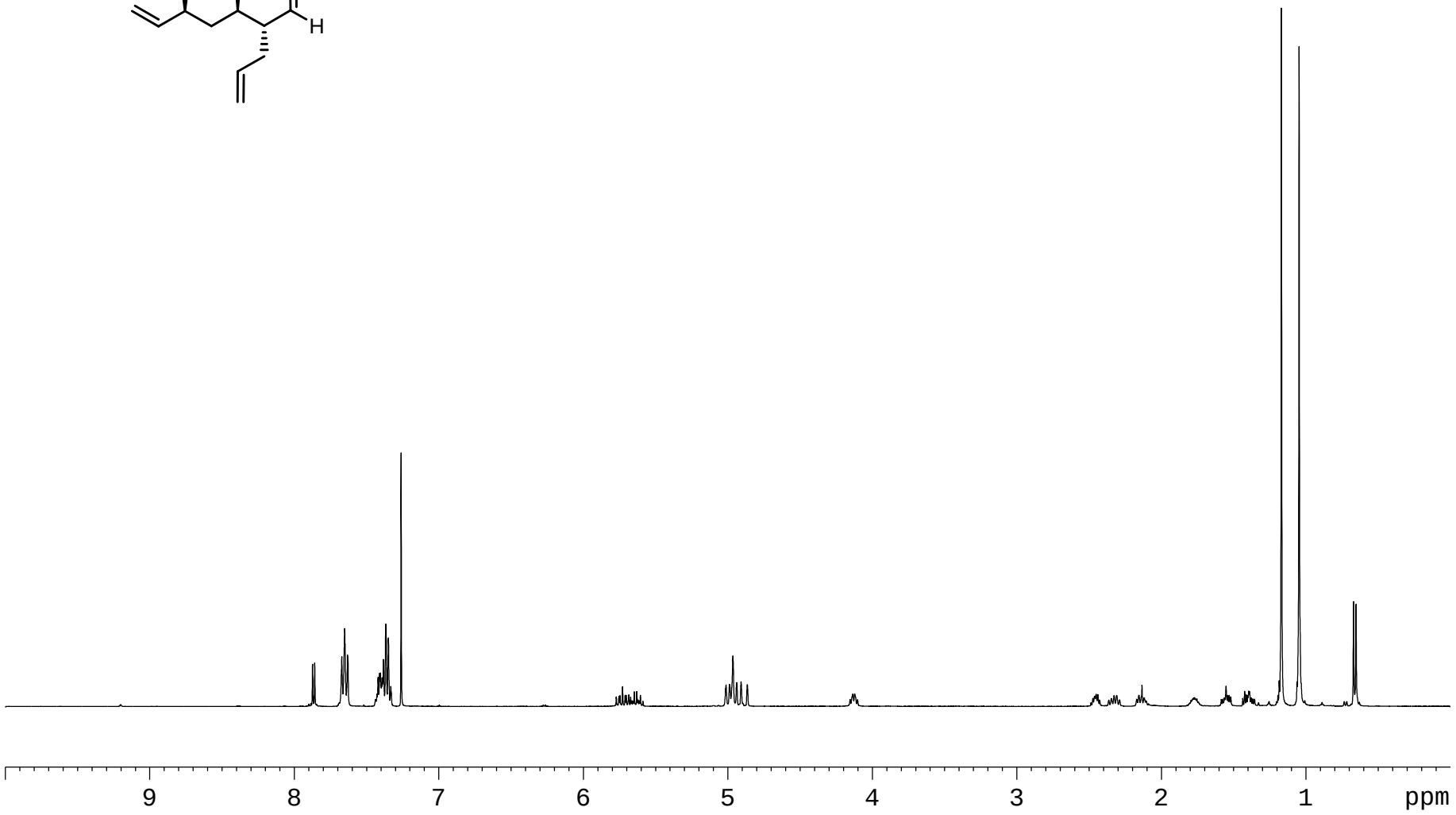


^{1}H NMR





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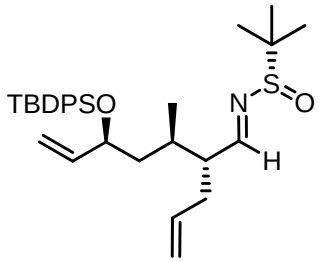

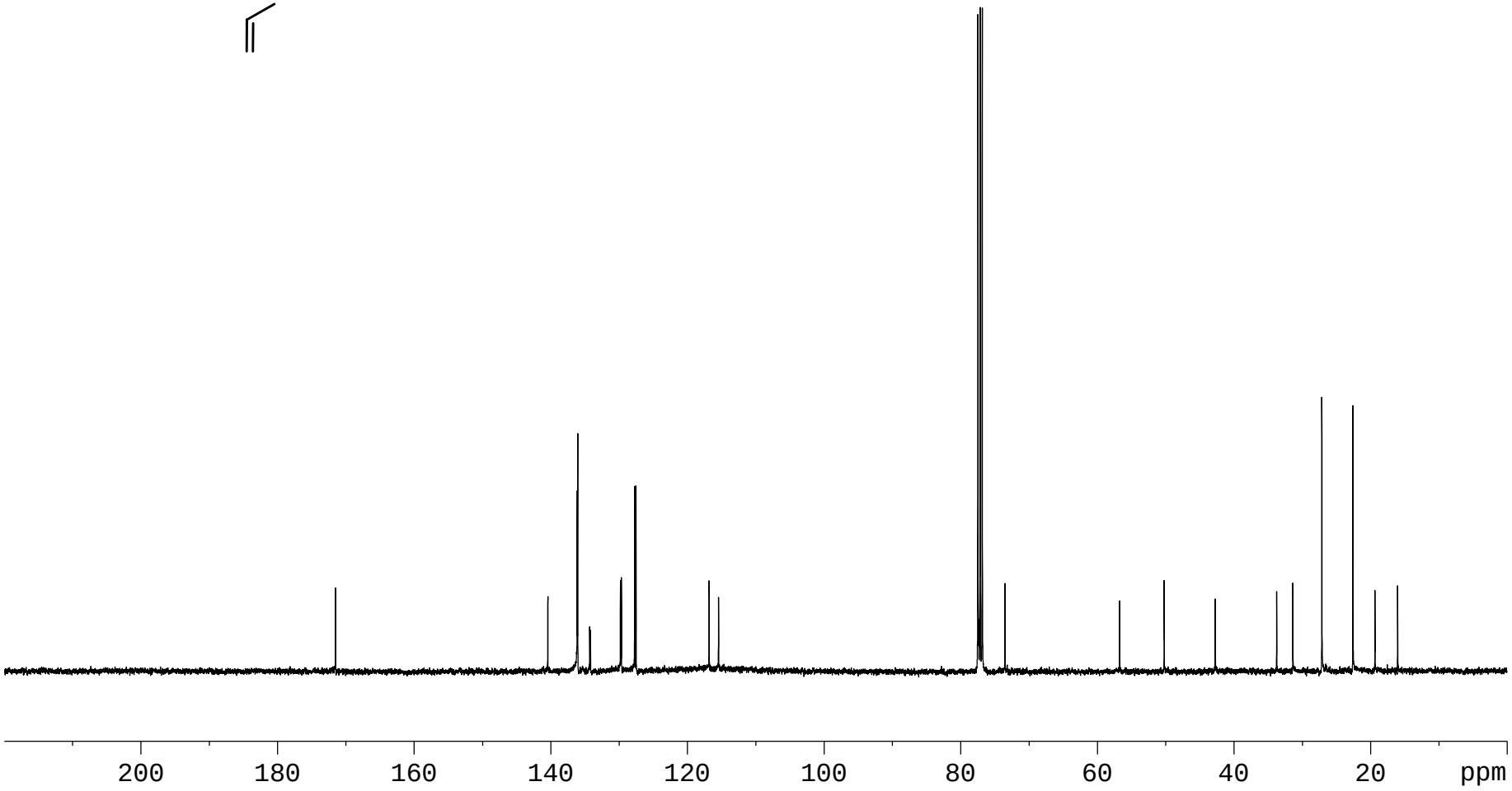

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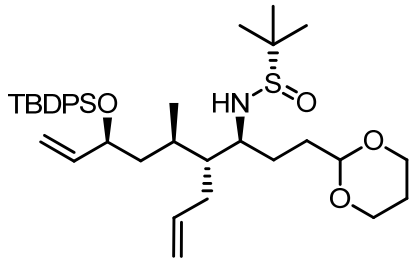

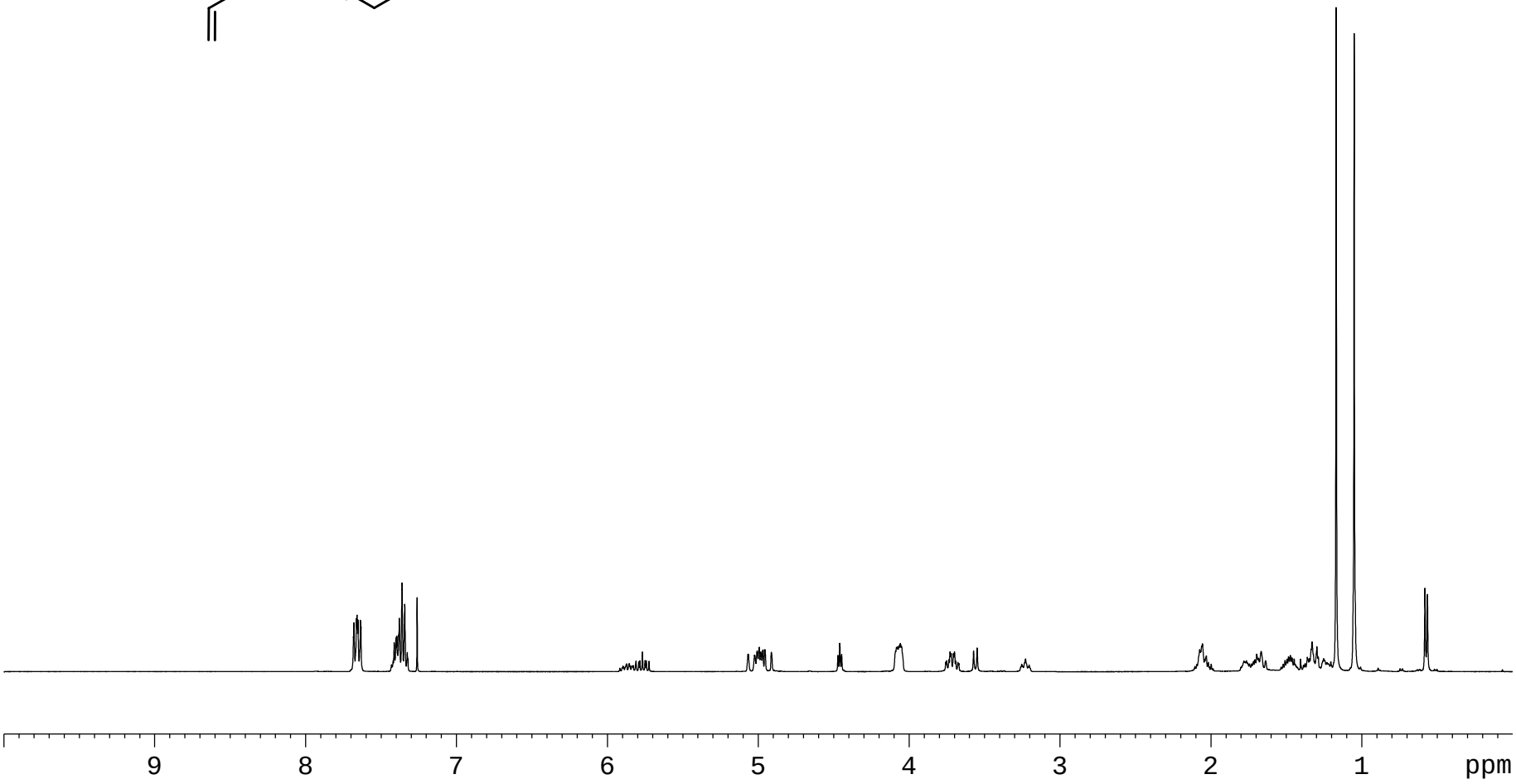

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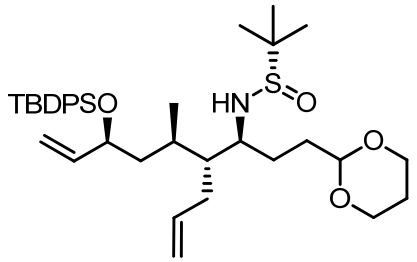
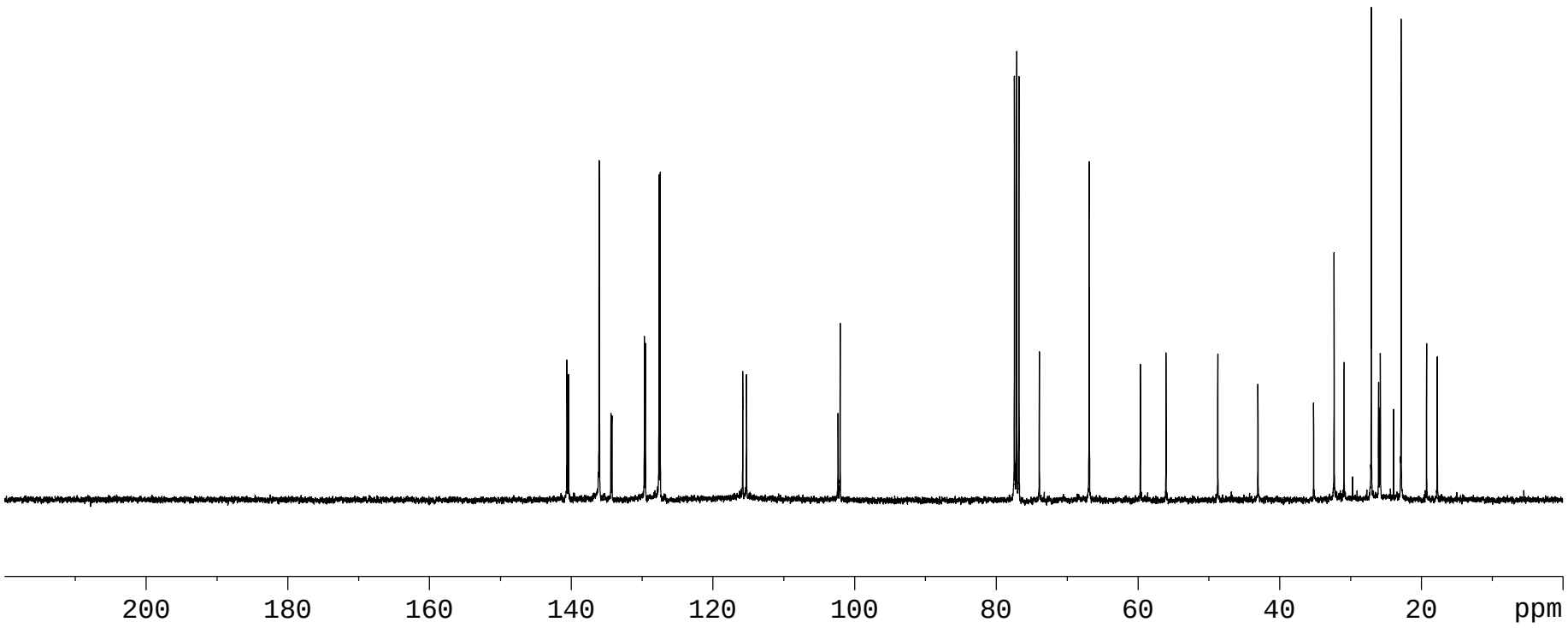
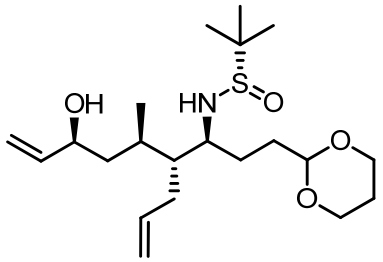
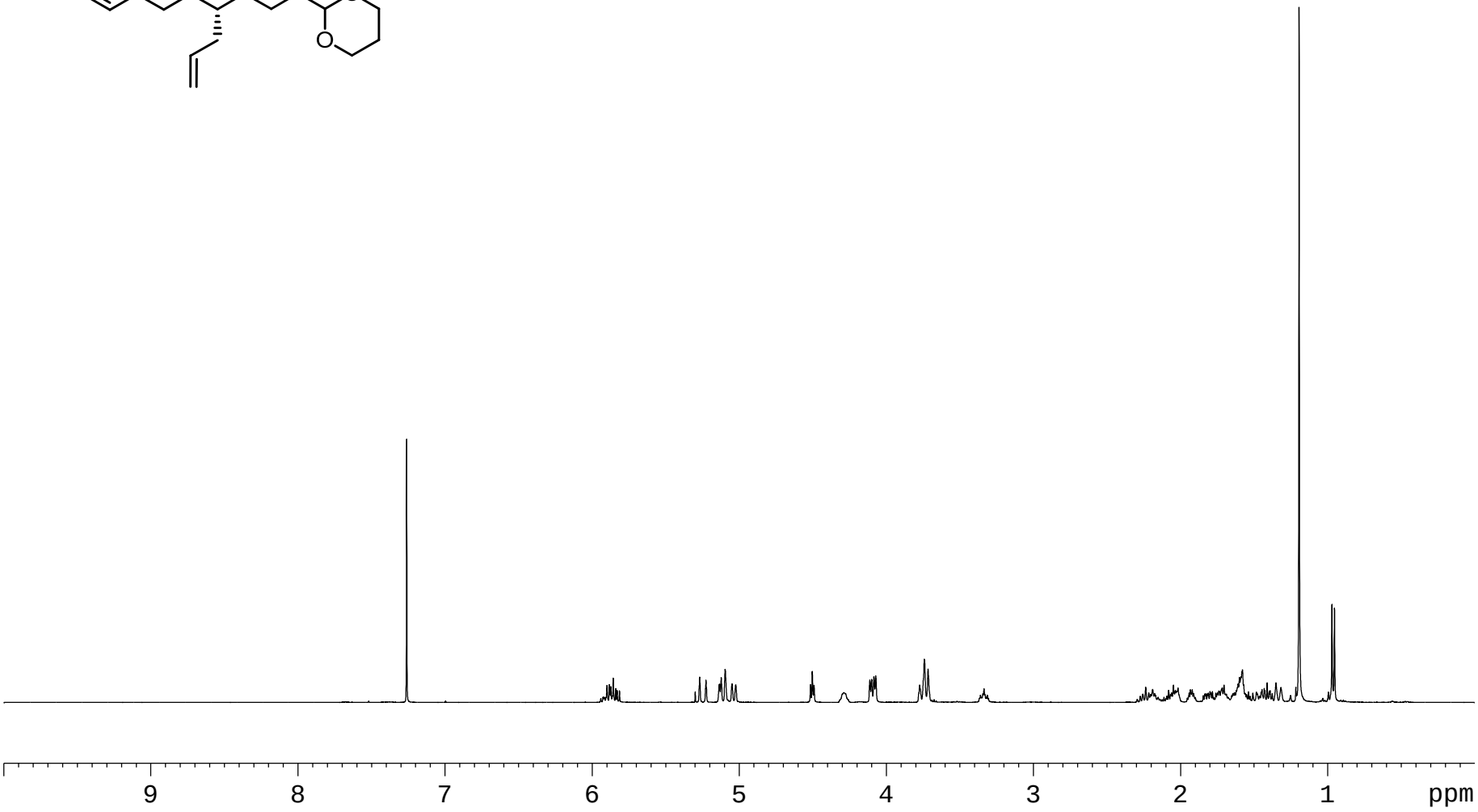




^{1}H NMR





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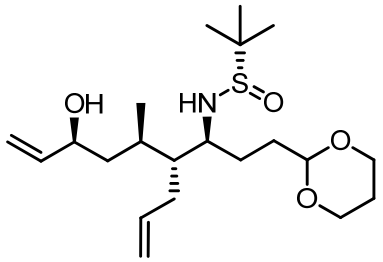

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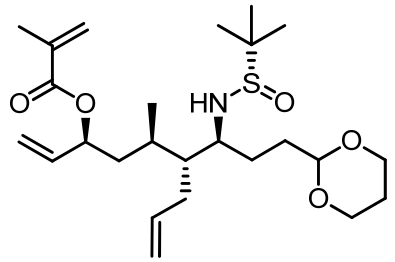

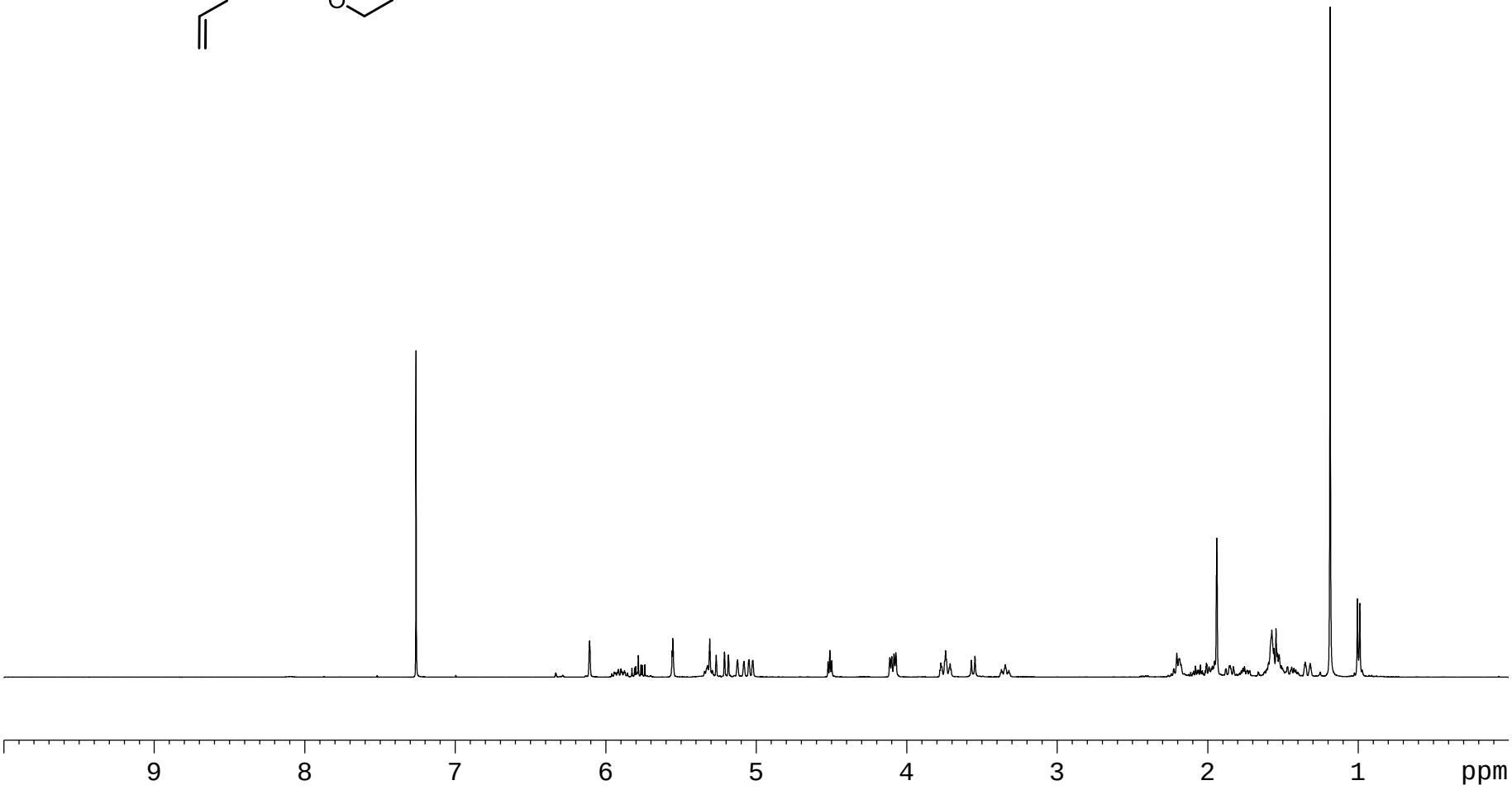

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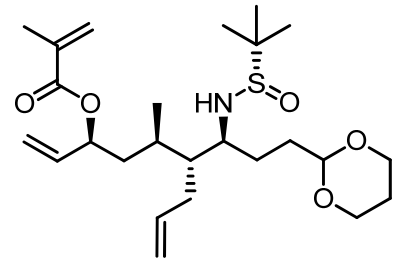

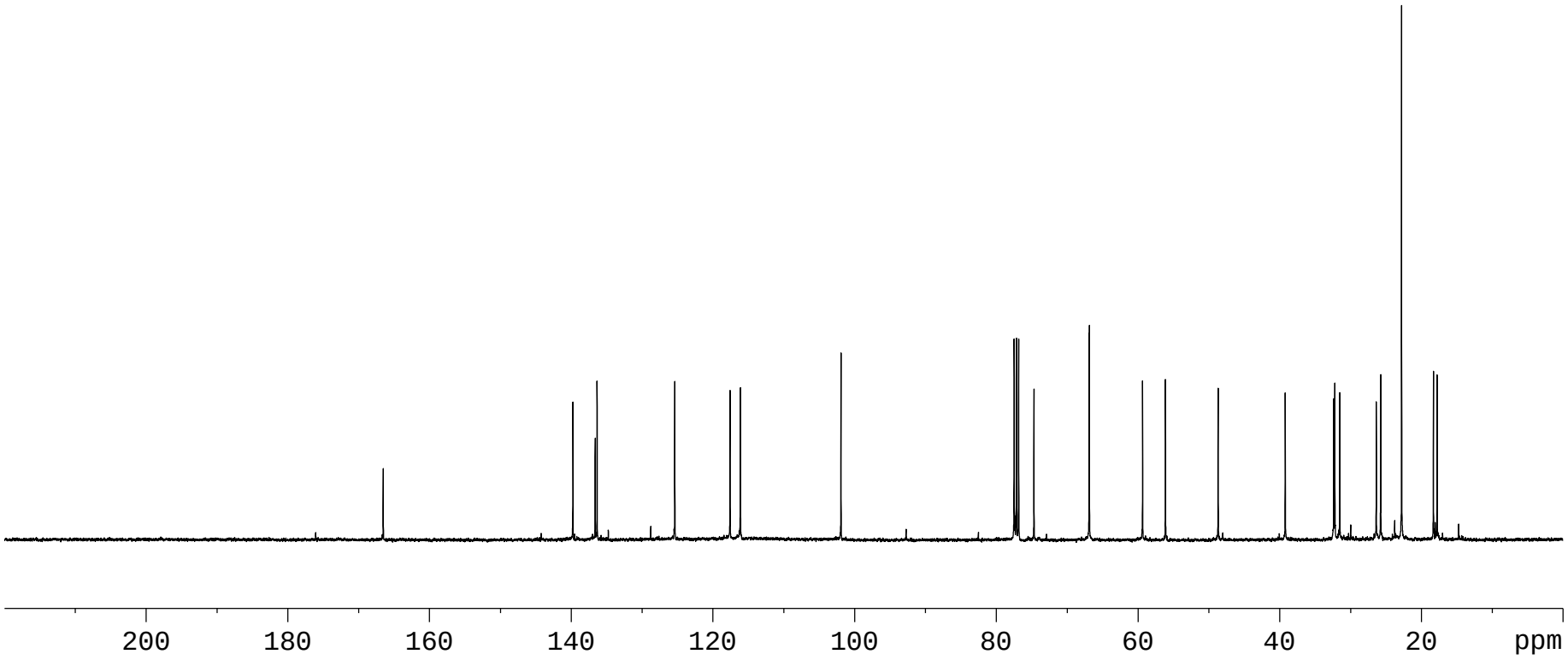

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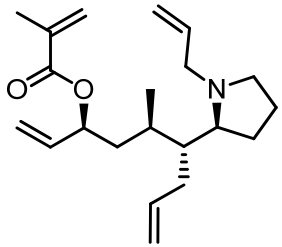

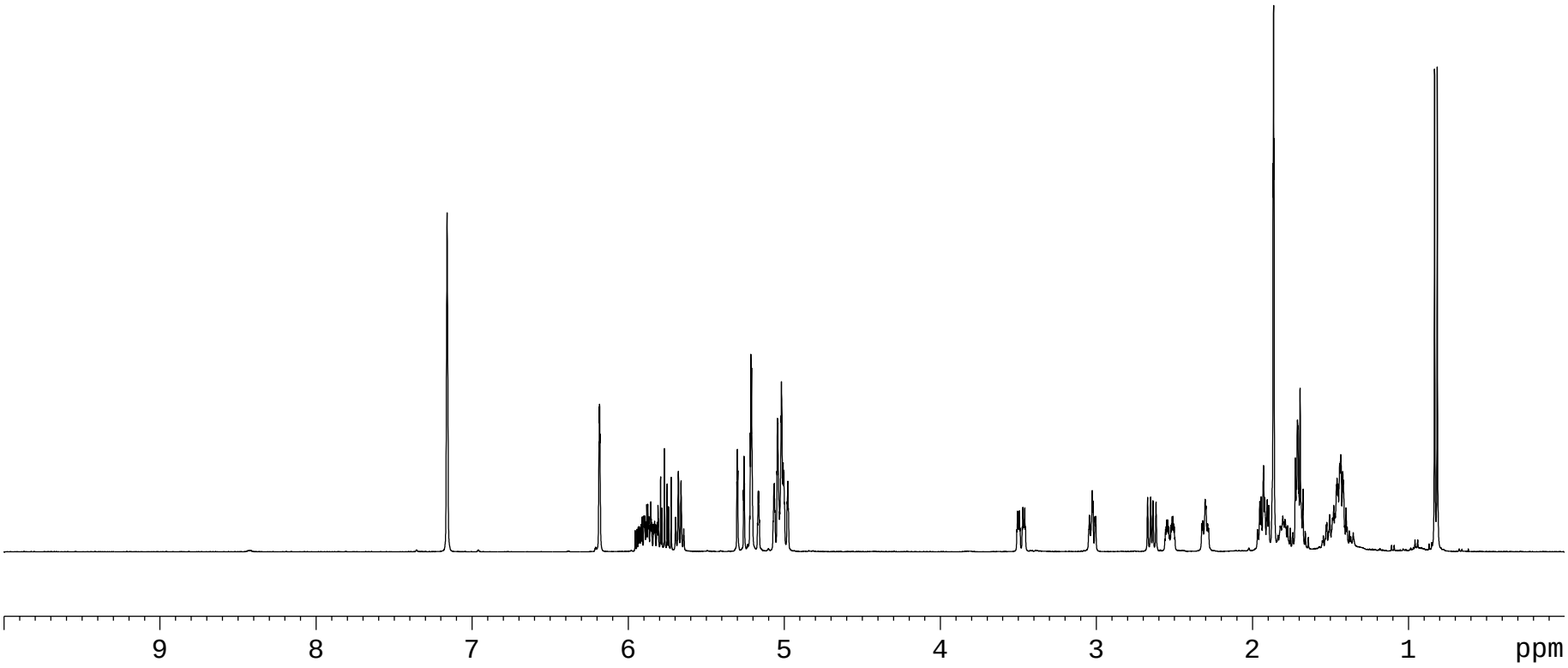

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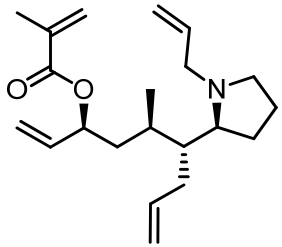

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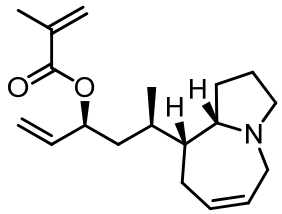

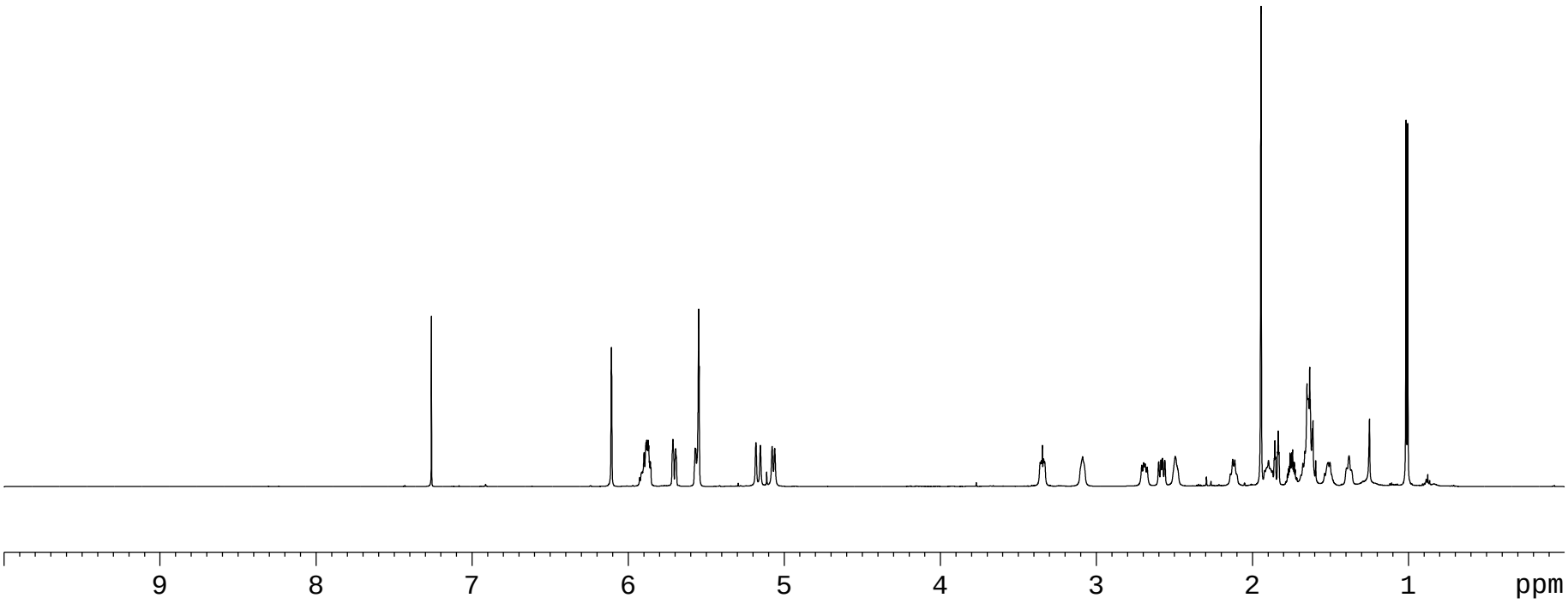

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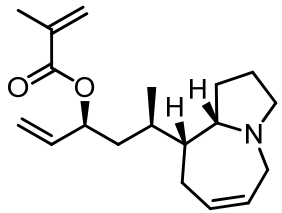

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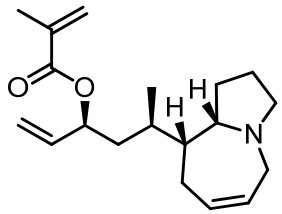

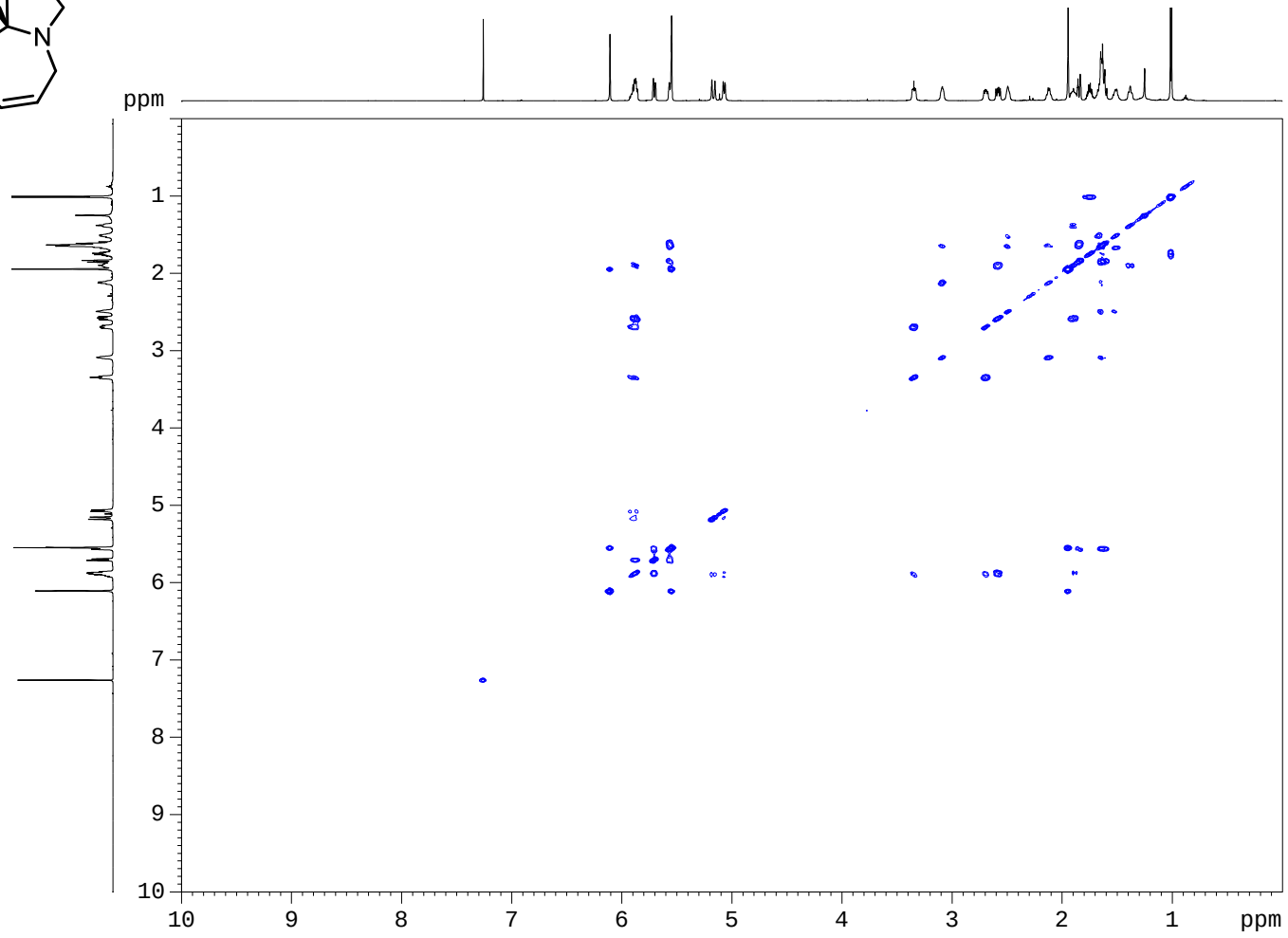

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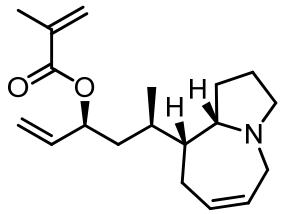

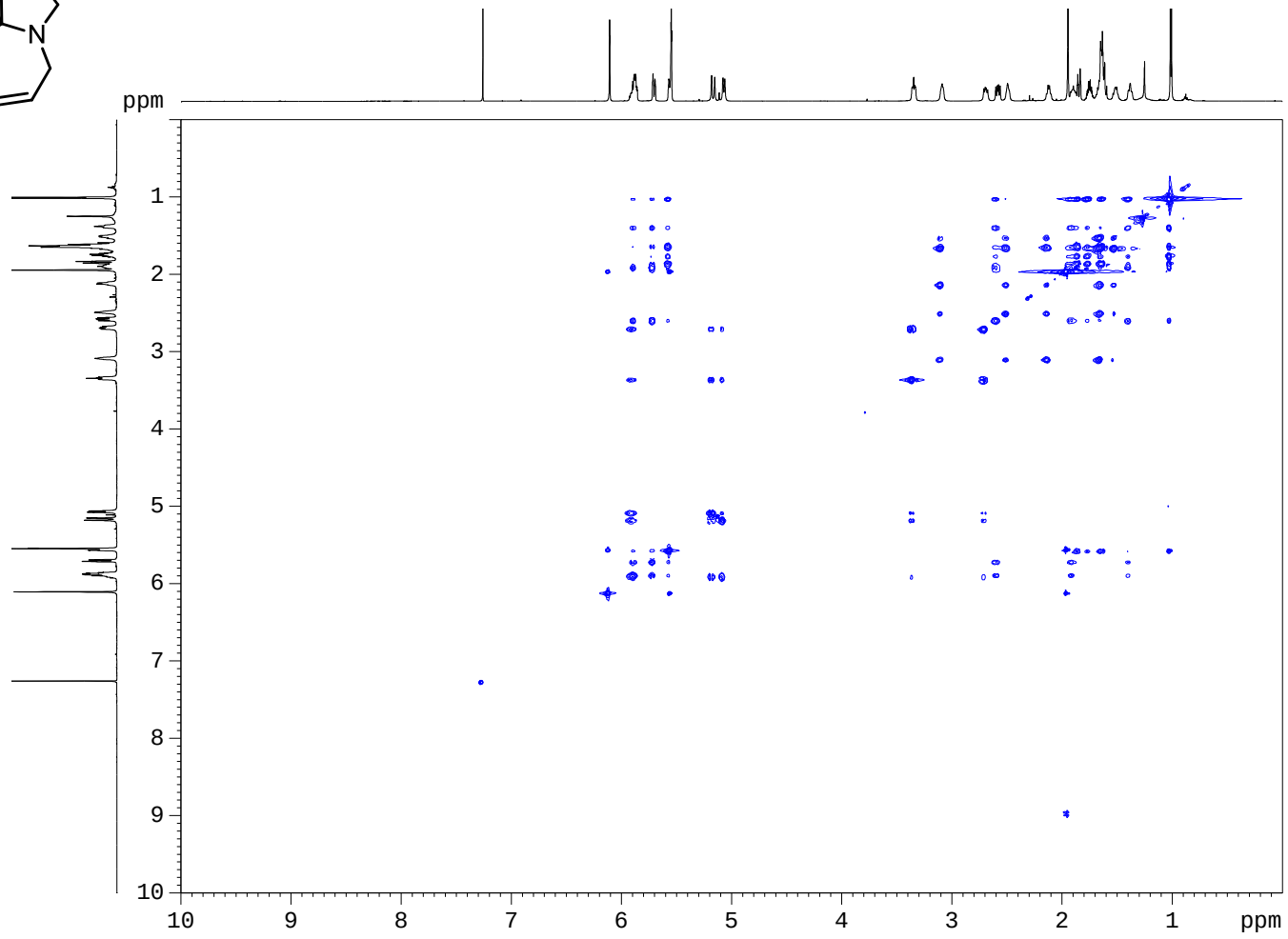

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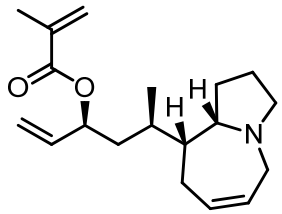
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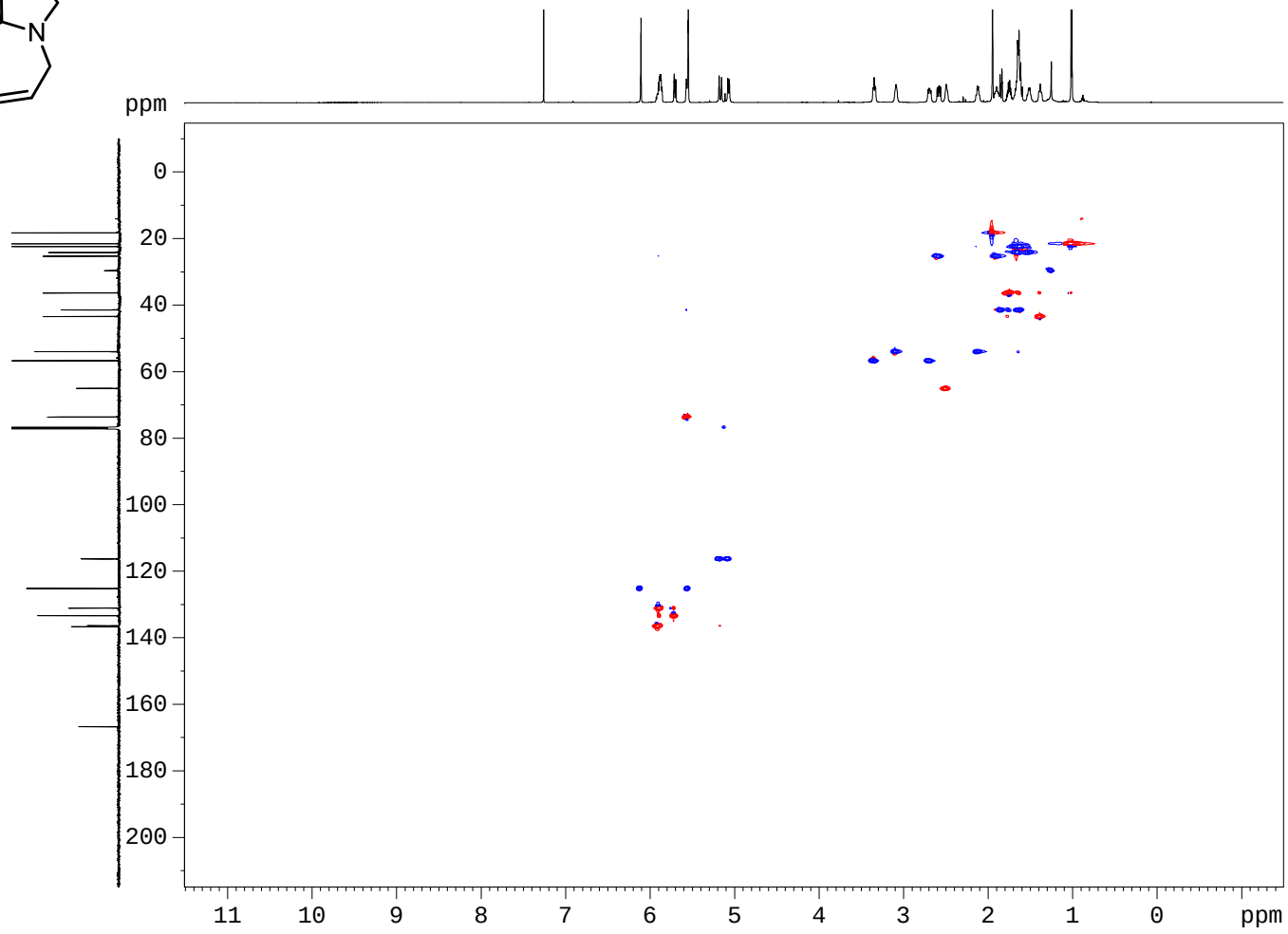
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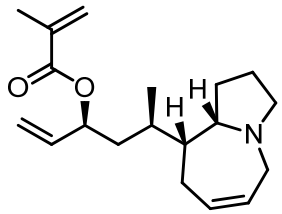
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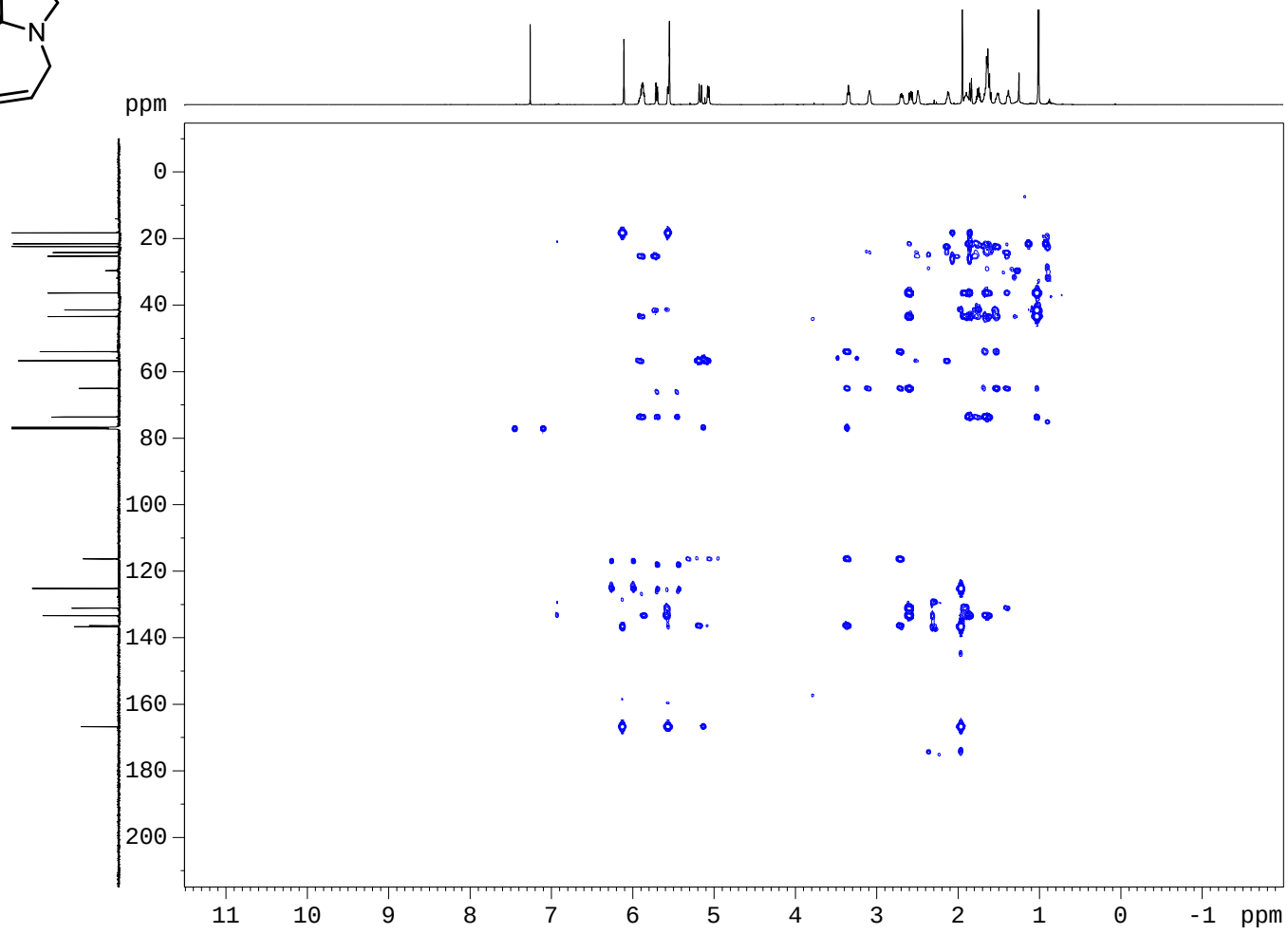
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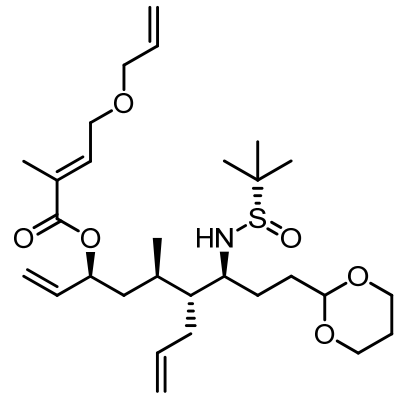

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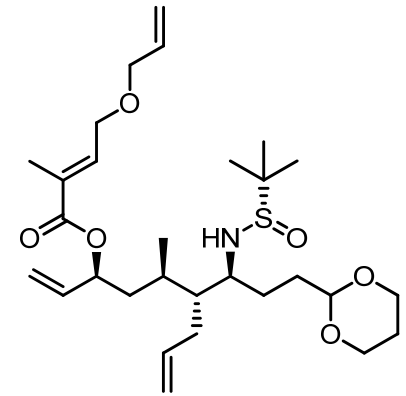

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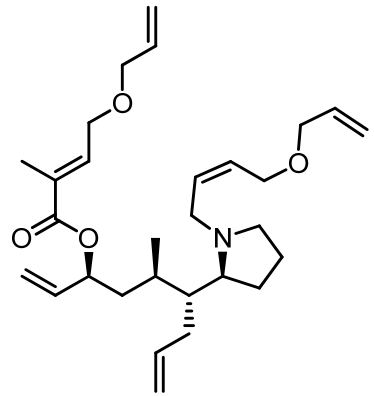

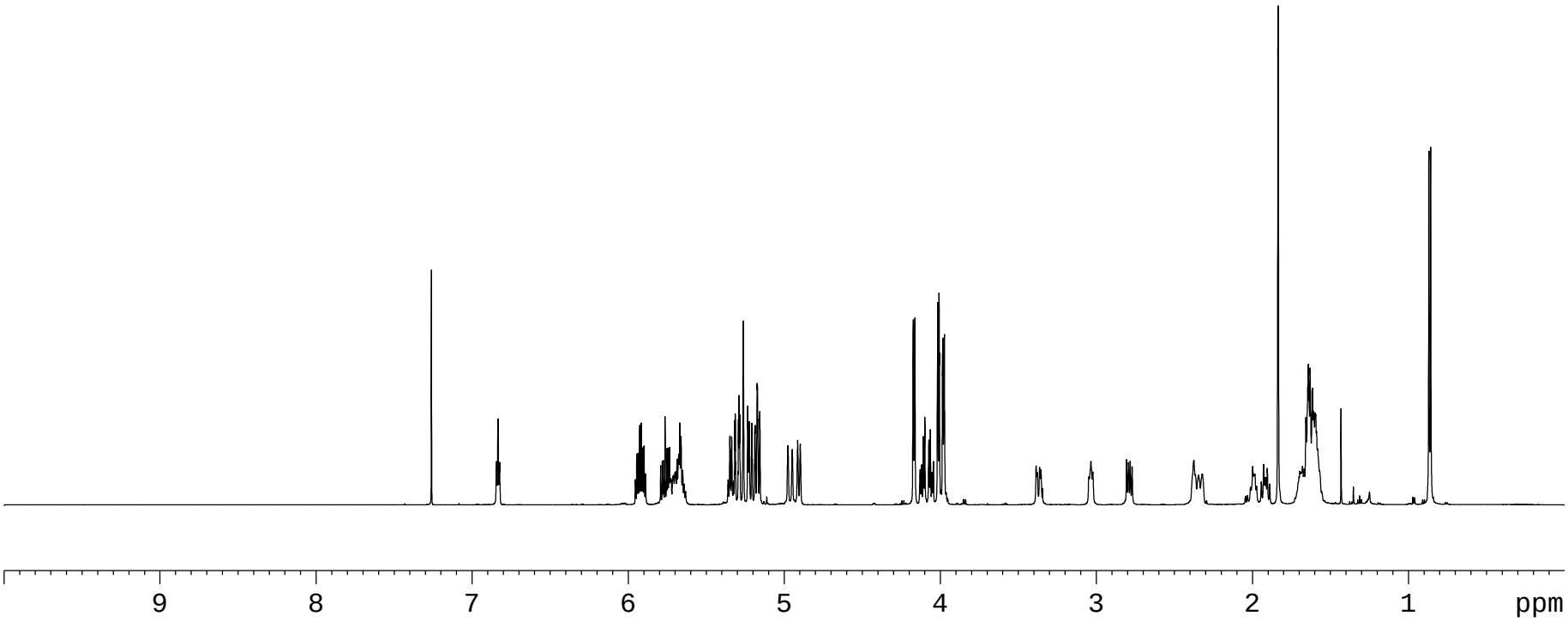

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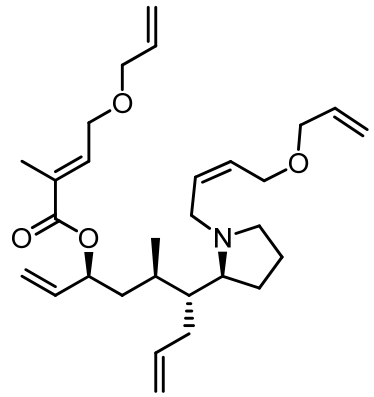

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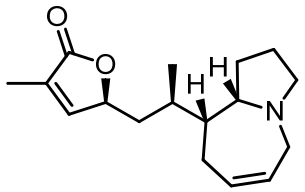

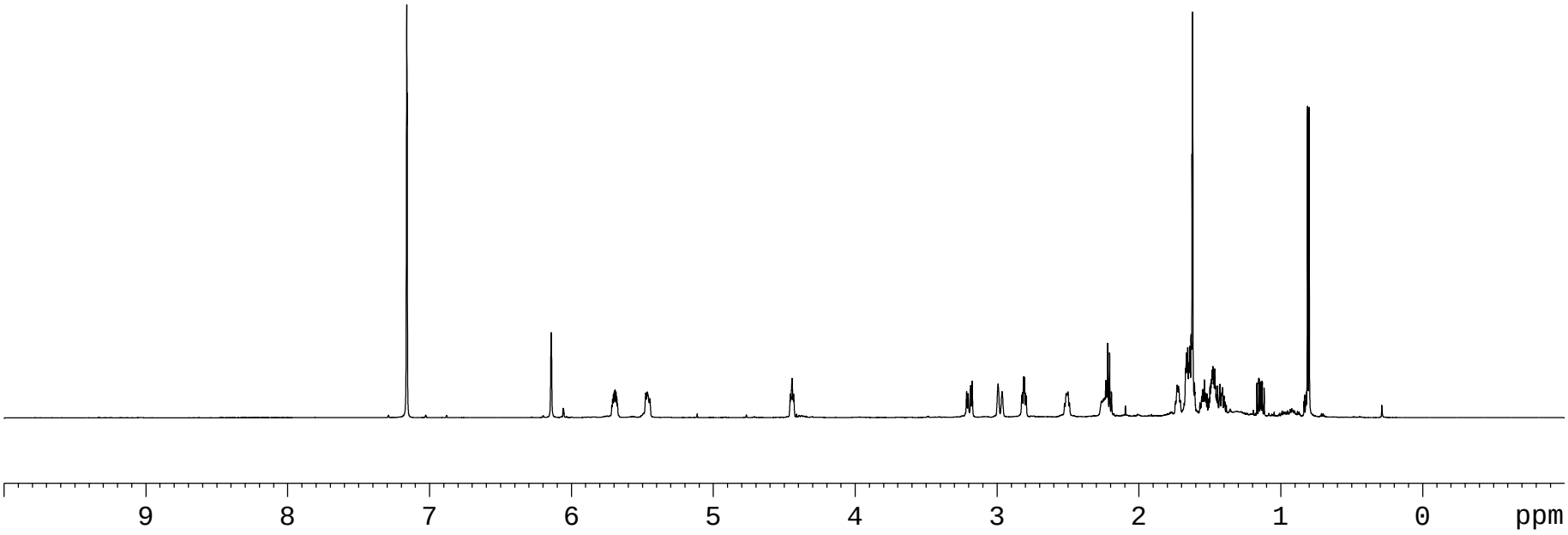

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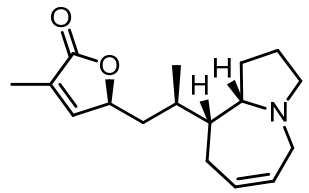

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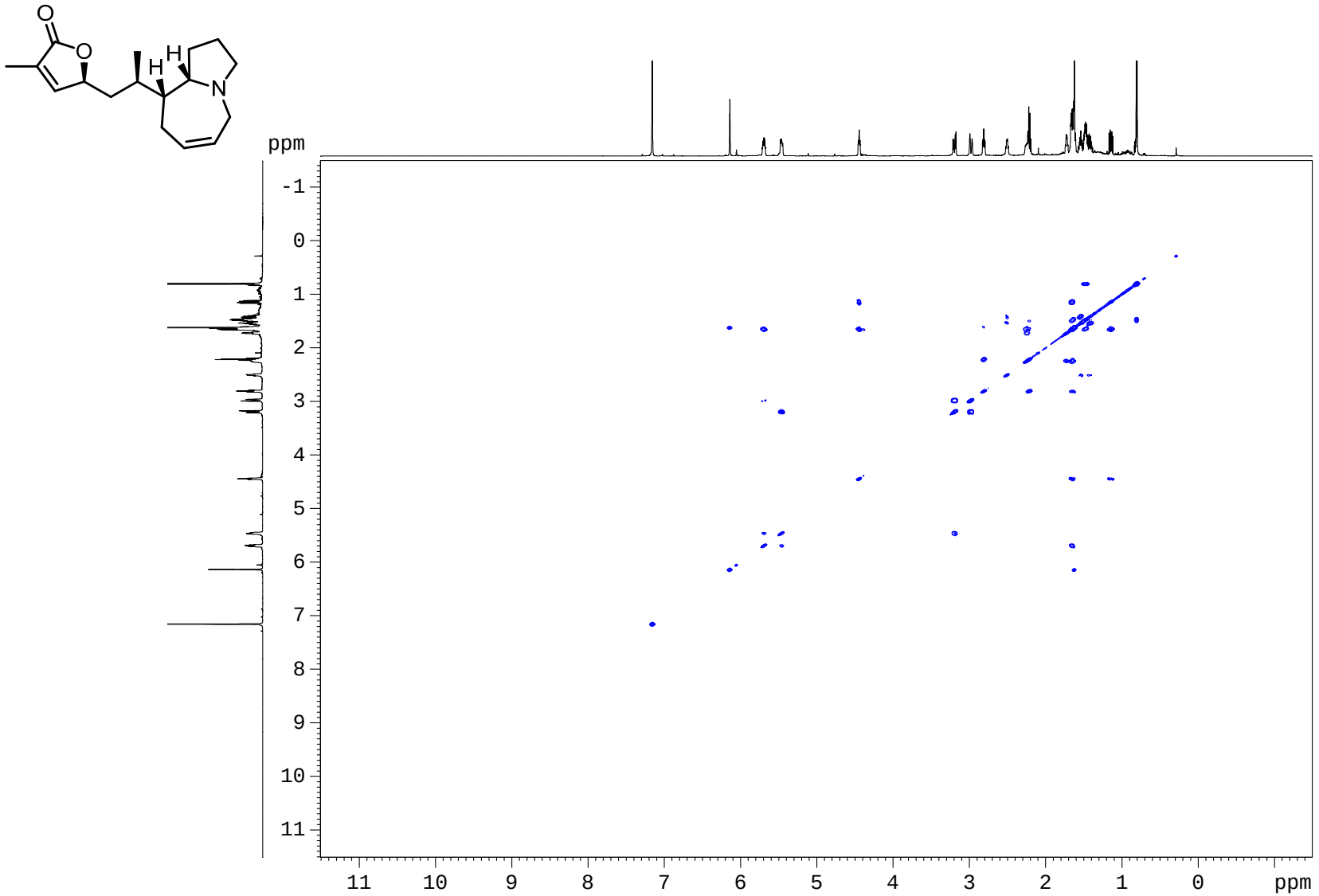

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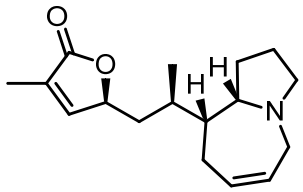

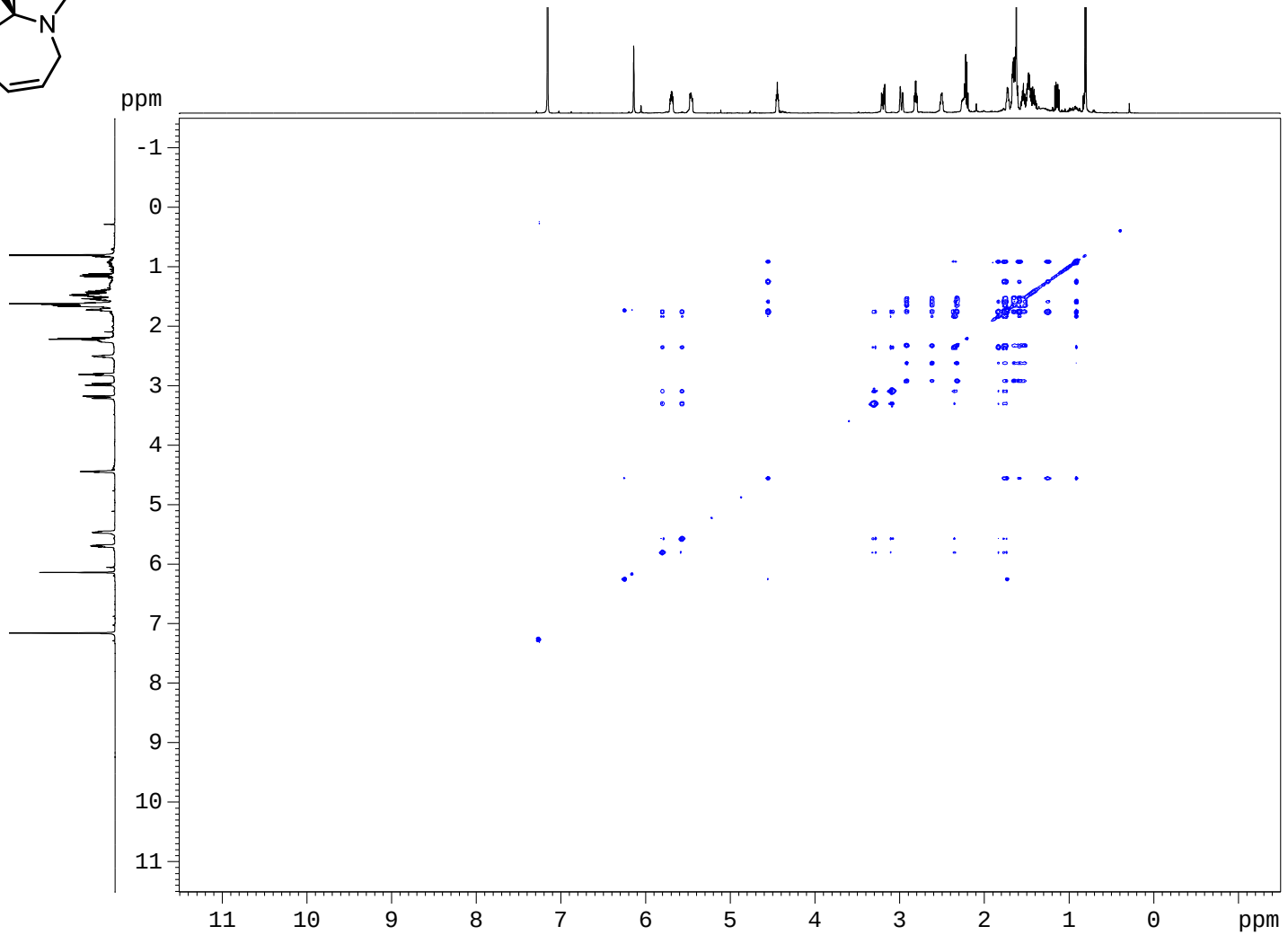

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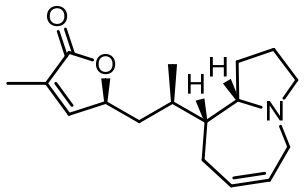
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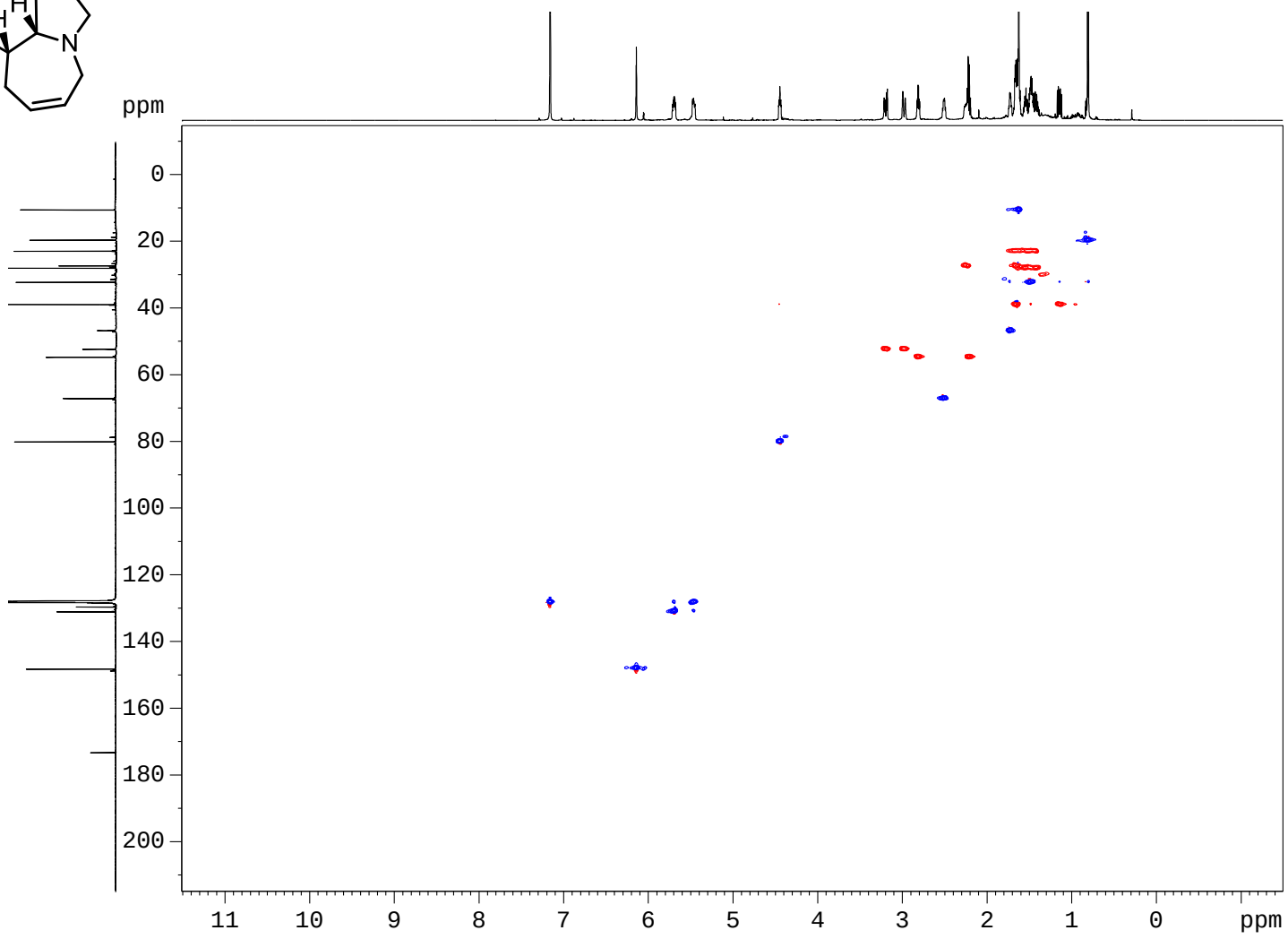
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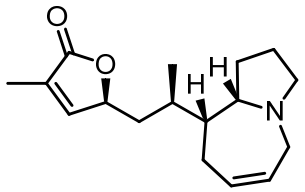
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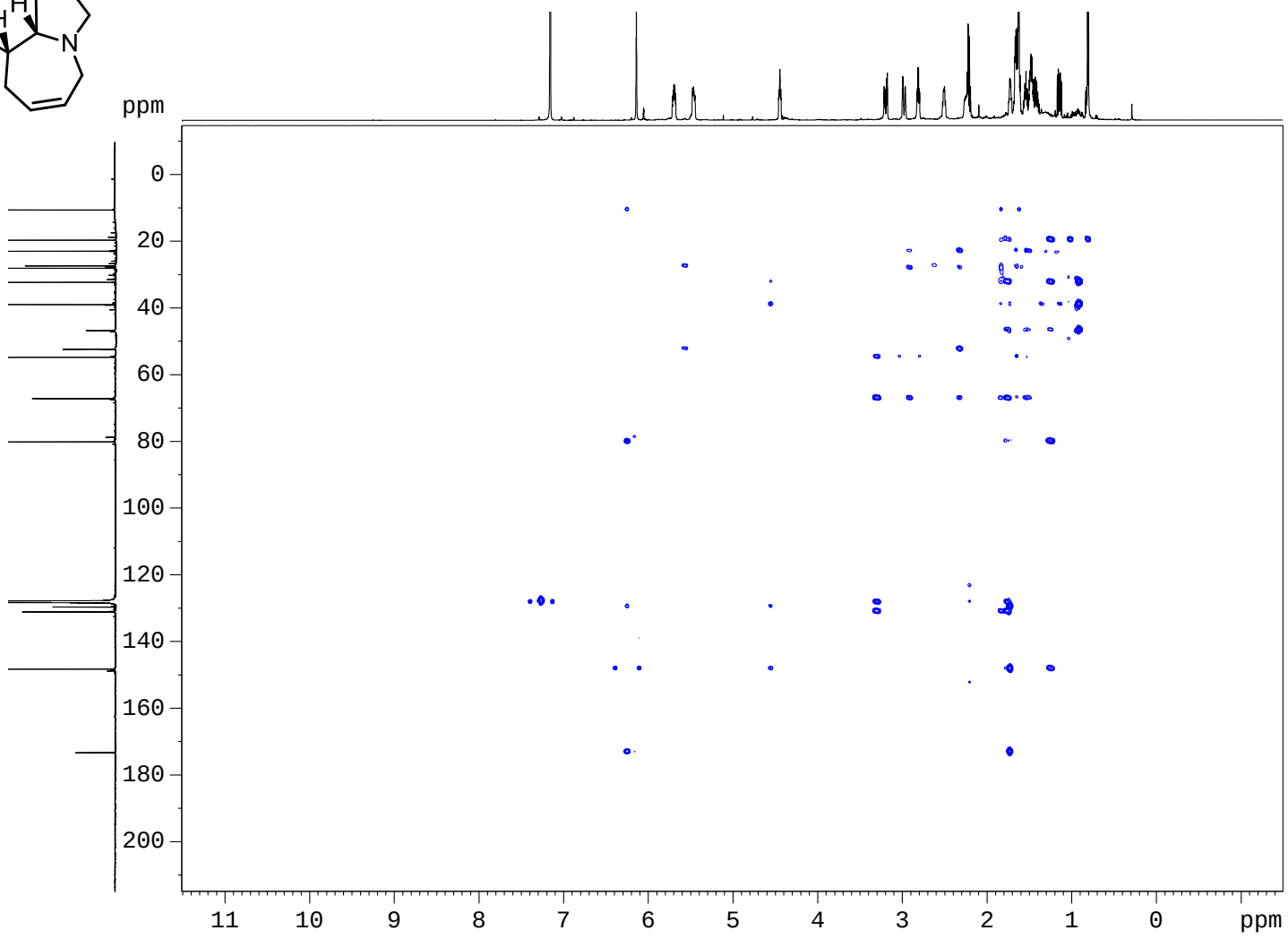
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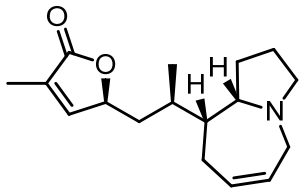
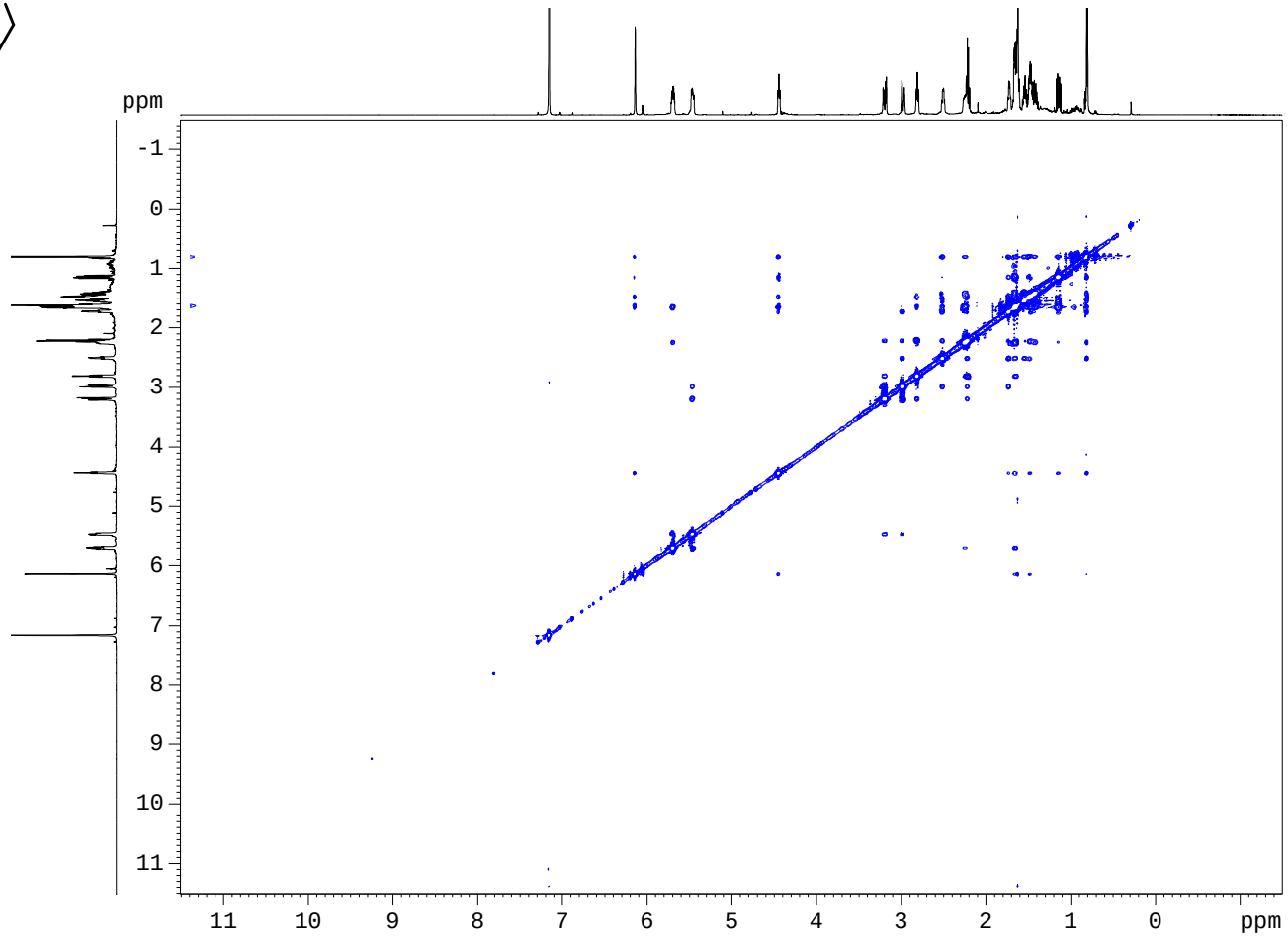
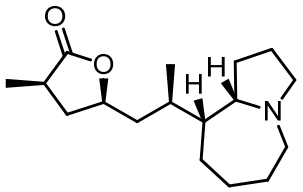
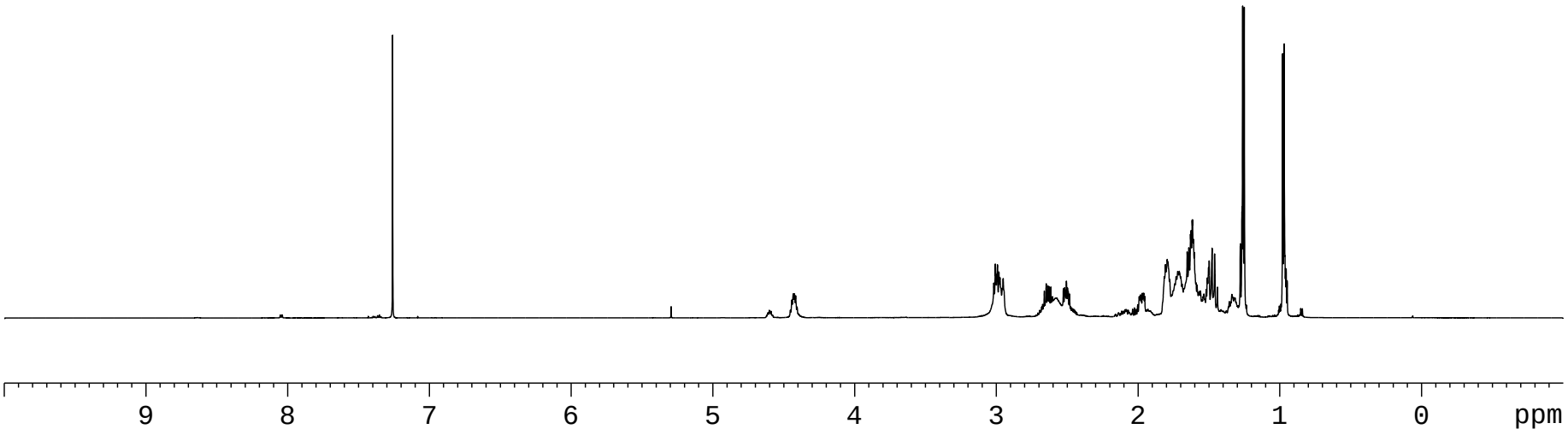




^{1}H NMR





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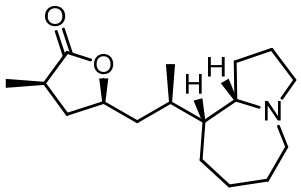

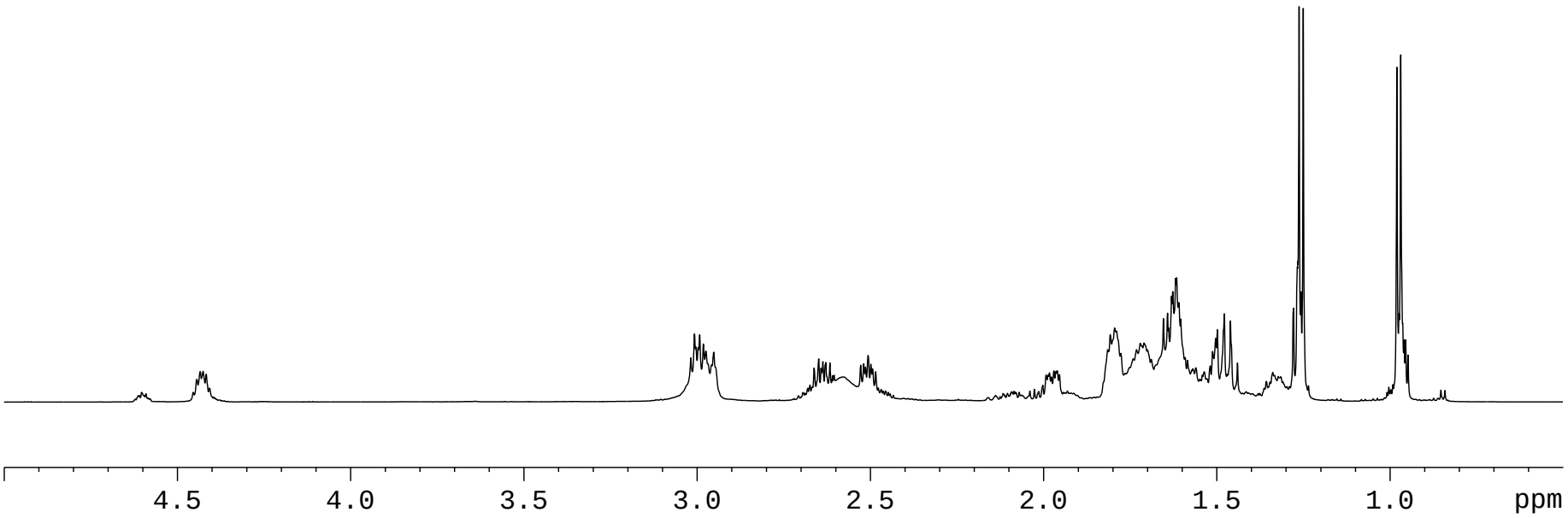

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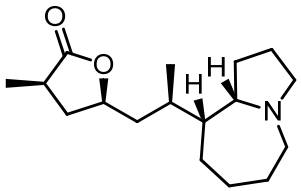

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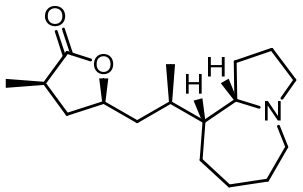

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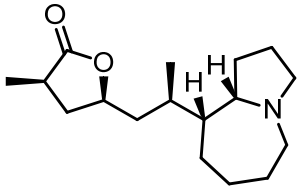

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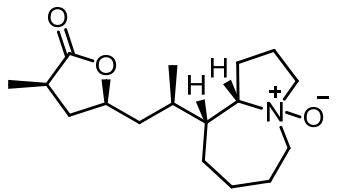

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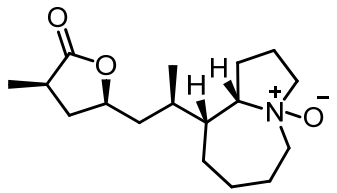

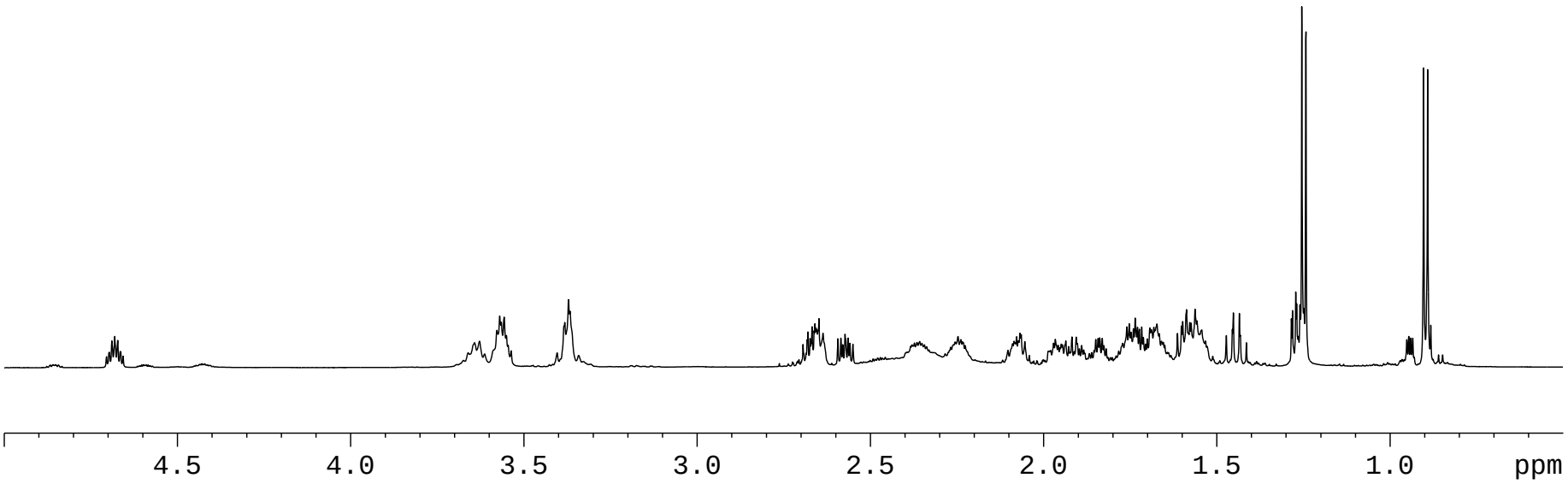

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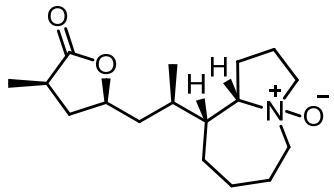

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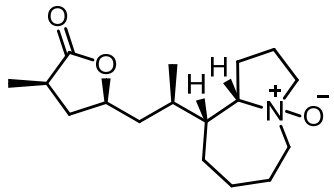

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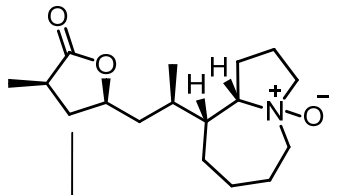
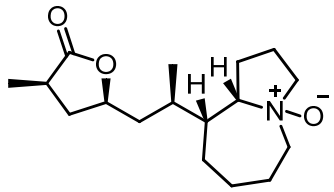
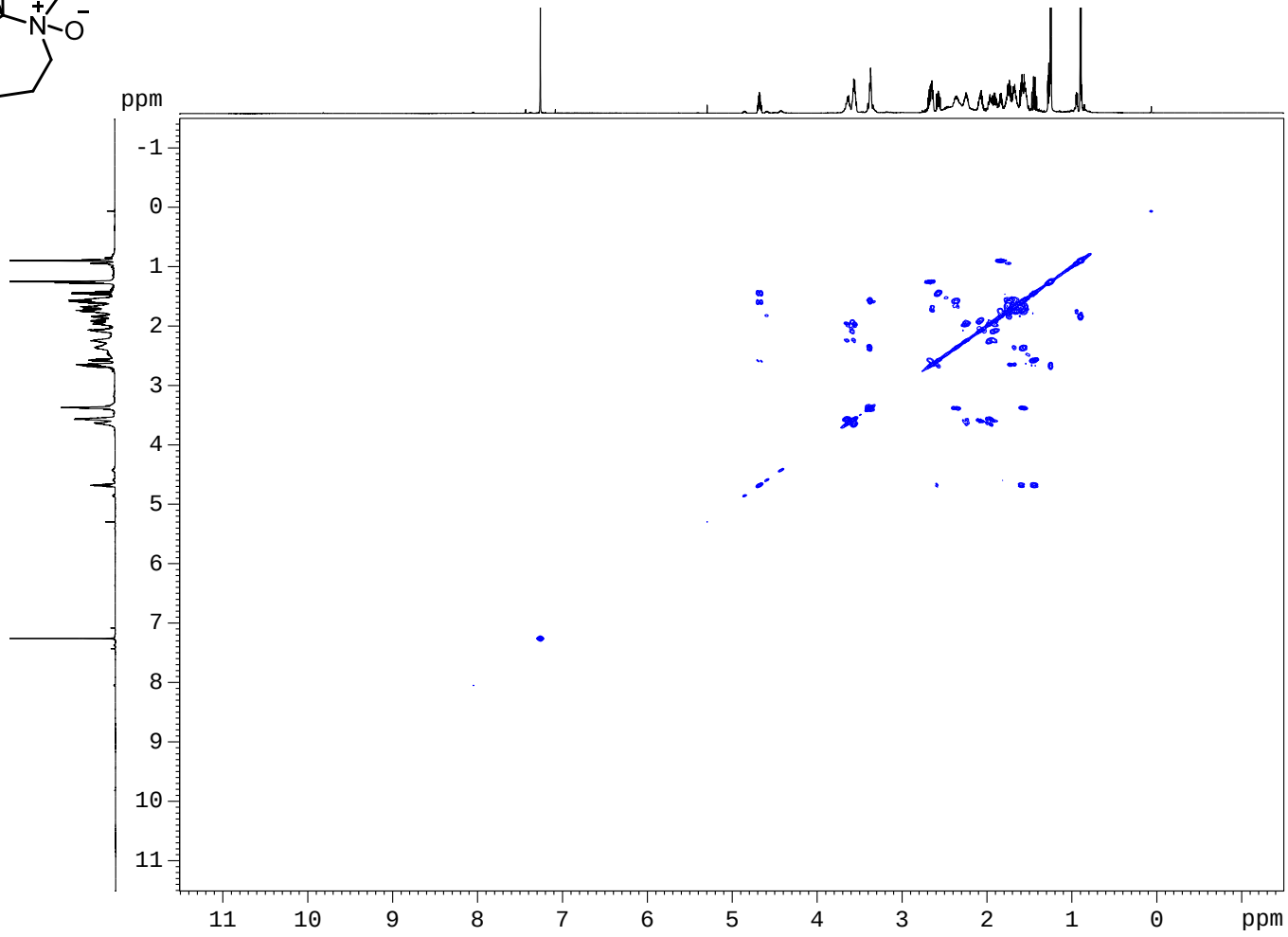


COSY NMR





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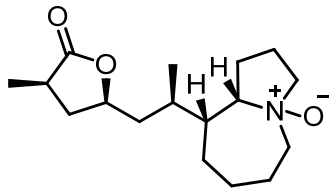
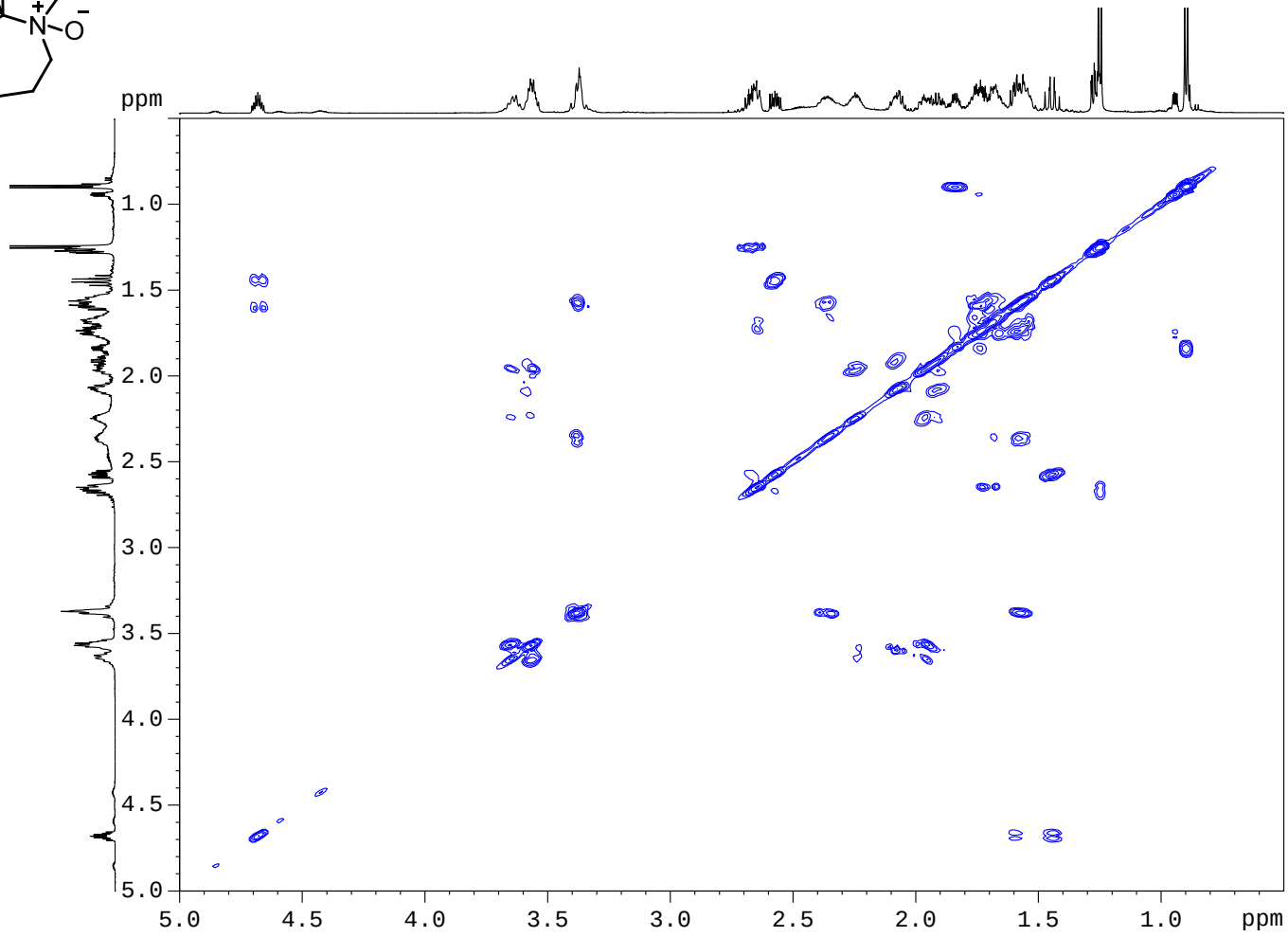
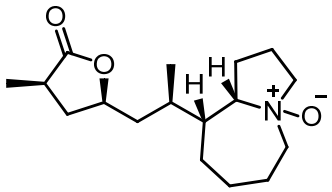




HSQC NMR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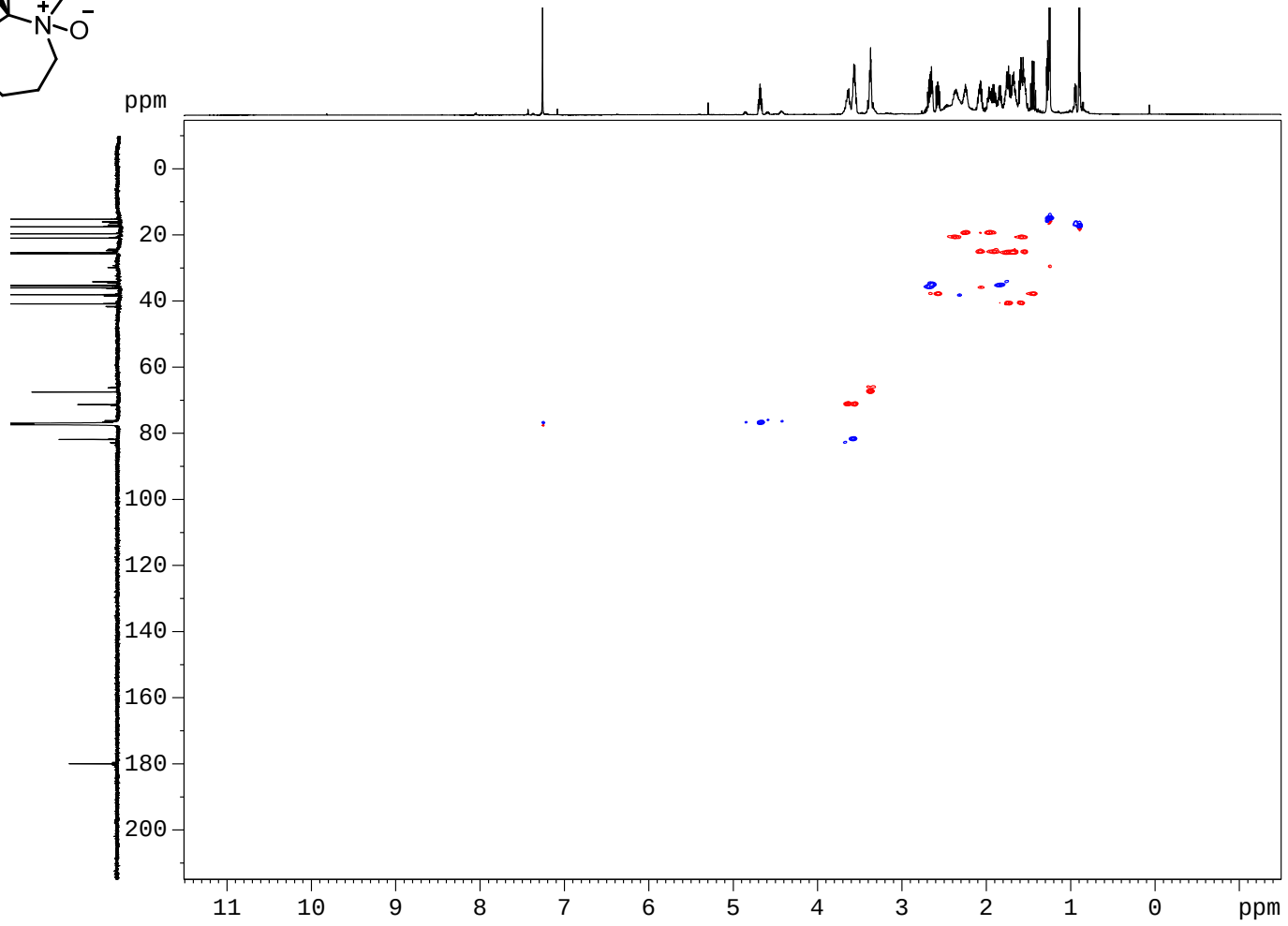
N
O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ppm

HSQC NMR