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IRVINE

A Unified Synthetic Approach Toward the Kalihinanes

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Mary Elisabeth Daub

Dissertation Committee:
Professor Christopher D. Vanderwal, Chair
Professor Larry E. Overman
Professor Scott D. Rychnovsky

2016

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DEDICATION

To my mom for her endless love and support.
To my dad for our shared passion for organic synthesis.

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LIST OF ABBREVIATIONS

Å	Ångstrom
λ	wavelength
μ	micro
ν	frequency
$[\alpha]_D$	specific rotation at wavelength of sodium D line
°C	degrees Celsius
Ac	acetyl
ap	apparent
Bn	benzyl
bp	boiling point
br	broad
<i>n</i> Bu	<i>n</i> -butyl
<i>t</i> Bu	<i>tert</i> -butyl
<i>ca.</i>	about (Latin <i>circa</i>)
calcd	calculated
cat.	catalytic
CI	chemical ionization
cm^{-1}	wavenumber(s)
COSY	correlation spectroscopy
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMM	dimethoxymethane
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EC ₅₀	half maximal effective concentration
EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
EI	electron impact
equiv	equivalent
ee	enantiomeric excess
<i>e.g.</i>	for example (Latin <i>exempli gratia</i>)
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HPLC	high-performance liquid chromatography

HRMS	high-resolution mass spectrometry
Hz	Hertz
ICT	isocyanoterpene
IDCP	iodonium di- <i>sym</i> -collidine perchlorate
<i>i.e.</i>	that is (Latin id est)
IMDA	intramolecular Diels–Alder
IPA	isopropanol, 2-propanol
<i>i</i> Pr	isopropyl
IC ₅₀	half maximal inhibitory concentration
IR	infrared
<i>J</i>	coupling constant
K	Kelvin (absolute temperature)
kcal	kilocalorie
L	liter
LDA	lithium diisopropylamide
lit.	literature value
LLS	longest linear sequence
m	multiplet; milli
M	molar; molecular ion
<i>m/z</i>	mass to charge ratio
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MVK	methyl vinyl ketone
n	nano
n.d.	not determined; non detected
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Ph	phenyl
PhMe	toluene
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
py	pyridine
q	quartet
rt	room temperature
s	singlet
SAR	structure–activity relationships
SI	selectivity index
t	triplet
TBAB	tetrabutylammonium bromide

TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TCA	trichloroacetoxy
TCAA	trichloroacetic anhydride
TES	triethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
Teoc	2-trimethylsilylethyl carbamate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetoxy
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -teramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
TOF	time-of-flight
Ts	<i>p</i> -toluenesulfonyl (tosyl)

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CURRICULUM VITAE

Mary Elisabeth Daub

1102 Natural Sciences 2
University of California, Irvine
Irvine, CA 92697-2025
E-mail: mdaub@uci.edu

EDUCATION

Ph.D., Organic Chemistry, University of California, Irvine, CA, 2016

- Advisor: Professor Chris Vanderwal
- Thesis: A Unified Synthetic Approach Toward the Kalihinanes

B. A., Chemistry (*cum laude*), Williams College, Massachusetts, 2011

- Advisor: Professor Thomas E. Smith
- Thesis: Toward the Asymmetric Total Synthesis of Jerangolid D
- Graduated with highest honors in chemistry

RESEARCH EXPERIENCE

Graduate Research Assistant

University of California, Irvine, CA

Sept. 2011 – June 2016

- Worked on developing a unified synthesis of the kalihinanes, a family of isonitrile-containing marine diterpenoids known for their antimalarial activity
- Explored the regioselective functionalization of donor-acceptor dienes for the synthesis of substituted pyridines

Undergraduate Researcher

Williams College, Williamstown, Massachusetts

June 2010 – June 2011

- Advisor: Professor Thomas E. Smith
- Worked toward the asymmetric total synthesis of jerangolid D and achieved a formal synthesis of ambruticin

Summer Undergraduate Researcher

Williams College, Williamstown, Massachusetts

June 2009 – Aug. 2009

- Advisor: Professor Thomas E. Smith
- Worked toward a stereochemistry versatile synthesis of the C1 – C12 fragment of tedanolide C

Summer Undergraduate Researcher

Harvey Mudd College, Claremont, California

June 2008 – Aug. 2008

- Advisor: Professor Kerry K. Karukstis
- Developed the phase diagram of n-heptyl- β -thioglucoside in various solvent systems using polarized light and fluorescence microscopy and fluorescence spectroscopy

PUBLICATIONS

- **Daub, M. E.**; Prudhomme, J.; Le Roch, K.; Vanderwal, C. D. Synthesis and Potent Antimalarial Activity of Kalihinol B. *J. Am. Chem. Soc.* **2015**, *137*, 4912–4915.
- Smith, T. E.; Fink, S. J.; Levine, Z. G.; McClelland, K. A.; Zachheim, A. A.; **Daub, M. E.** Stereochemistry Versatile Synthesis of the C1–C12 Fragment of Tedanolide C. *Org. Lett.* **2012**, *14*, 1452–1455.

PRESENTATIONS

- 64th Gordon Research Conference: Natural Products, Andover, NH July 2015
Daub, M. E., Prudhomme, J., Le Roch, K., Vanderwal, C. D. “A Unified Synthetic Approach Toward the Kalihinanes”
- UCI Graduate Student and Post-Doctoral Colloquium, Irvine, CA June 2014
Daub, M. E., Vanderwal, C. D. “A Unified Synthetic Approach Toward the Kalihinanes”

AWARDS AND HONORS

Regents’ Dissertation Fellowship Award (UCI)	2016
Allergan Graduate Fellowship Recipient	2014
NSF Graduate Research Fellowship Program Honorable Mention Recipient	2013
American Institute of Chemists Award, Williams College	2011
ACS Summer Undergraduate Research Fellowship (SURF)	2010

TEACHING EXPERIENCE

Teaching Instructor

University of California, Irvine August 2015 – Sept. 2015
Co-Instructor for Introductory Organic Chemistry

Graduate Student Mentor

University of California, Irvine March 2015 – June 2016
Mentored an undergraduate researcher working toward the synthesis of pustulosaisonitrile

Teaching Assistant

University of California, Irvine Sept. 2011 – March 2016
Organic Synthesis Discussion Leader (Graduate Level)

- Winter 2016

Organic Chemistry Lab Instructor (Undergraduate Level)

- Fall 2011, Winter 2012, Spring 2012, Spring 2014, Summer 2014

Organic Chemistry Discussion Leader (Undergraduate Level)

- Winter 2013, Fall 2013, Fall 2015

General Chemistry Discussion Leader (Undergraduate Level)

- Summer 2013

Teaching Assistant

Williams College

Organic Chemistry Lab Assistant

- Fall 2009 and Spring 2010

Sept. 2009 – June 2010

Chemistry Tutor

Williams College

Chemistry Peer Tutor

- General Chemistry – Fall 2008
- Introductory Level Organic Chemistry – Spring 2009
- Intermediate Level Organic Chemistry – Fall 2009
- Physical Chemistry – Spring 2010

Sept. 2008 – June 2010

AFFILIATIONS

American Chemical Society

2011 – Present

Associate Membership in Sigma Xi

2011 – Present

Iota Sigma Pi – Honor Society for Women in Chemistry

2012 – Present

Calcium Chapter

Chapter President, 2015–2016

Chapter Vice President, 2014–2015

Chapter Secretary, 2013–2014

Chapter Activity Coordinator, 2012–2013

ABSTRACT OF THE DISSERTATION

A Unified Synthetic Approach Toward the Kalihinanes

By

Mary Elisabeth Daub

Doctor of Philosophy in Chemistry

University of California, Irvine, 2016

Professor Christopher D. Vanderwal, Chair

This dissertation describes our efforts toward developing a unified synthesis of the kalininane family of antimalarial marine isocyanoterpenes. Chapter 1 focuses on the isolation, structure determination, subclass specification, biological activity, and proposed biogenesis of the kalihinanes. Additionally, methods for the synthesis of isonitriles and previous syntheses of kalihinanes and related isocyanoterpenes are described.

Chapter 2 describes our divergent synthetic plan, featuring an oxa-Michael/Robinson annulation sequence and a Piers-type annulation for the rapid synthesis of the decalin framework of the kalihinanes. This strategy was validated with a formal synthesis of 10-isocyano-4-cadinene, and was subsequently applied toward the synthesis of kalihinanes bearing a pendant tetrahydropyran (kalihinol A) or tetrahydrofuran (kalihinol B). While the synthesis of the tetrahydropyran-containing kalihinanes has yet to be accomplished, our efforts toward tetrahydrofuran-containing kalihinanes culminated in the first synthesis of kalihinol B. An unexpected hydride shift has thwarted efforts to extend the synthesis to other tetrahydrofuran-containing kalihinanes.

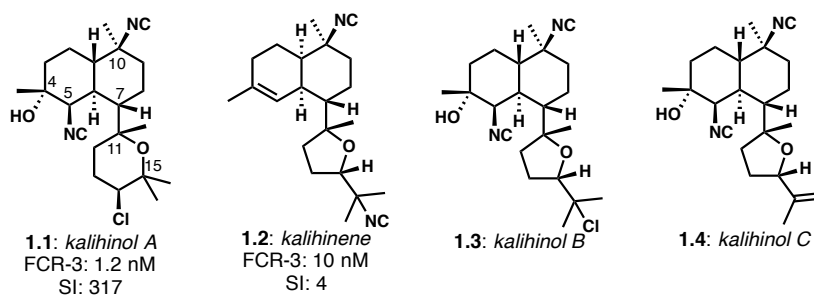
Chapter 3 focuses on the application of our strategy to the synthesis of unnatural kalihinane analogues. Several analogues have been prepared and subjected to an antiplasmodial assay. All of the synthetic isocyanoterpenes exhibited antiplasmodial activity against drug-sensitive and drug-resistant strains of *Plasmodium falciparum* ($IC_{50} < 1.2 \mu M$). Furthermore, kalihinane-based small-molecule probes have been prepared, and will be used for protein profiling in *P. falciparum*.

CHAPTER 1: INTRODUCTION TO THE KALIHINANES

1.1 Introduction

The kalihinanes are marine diterpenoids isolated primarily from sponges of the *Acanthella* genus, and are part of a larger family of antimalarial isocyanoterpenes (ICTs).¹⁻⁶ This structurally diverse family is characterized by a *cis*- or *trans*-decalin core bearing a pendant tetrahydropyran (THP) or tetrahydrofuran (THF) and a variable set of isonitrile, isocyanate, isothiocyanate, formamido, hydroxyl, and chloride substituents (Figure 1.1). Of the more than 50 kalihinanes reported to date, the antimalarial activities of only five members have been reported, exhibiting low nanomolar activity against *Plasmodium falciparum*, the malaria-causing parasite, with good to excellent selectivity.⁷ With the emergence of drug-resistant *P. falciparum* strains, research into any compounds with reported antimalarial activity and selectivity would be valuable.^{8,9} The following chapter focuses on the isolation and biological activity of the kalihinanes, the proposed biosynthesis, general methods for the synthesis of isonitriles, and previous syntheses of kalihinanes and structurally related ICTs.

Figure 1.1. Select members of the kalihinane family. (FCR-3 is a drug-resistant strain of *P. falciparum*; SI = selectivity index).



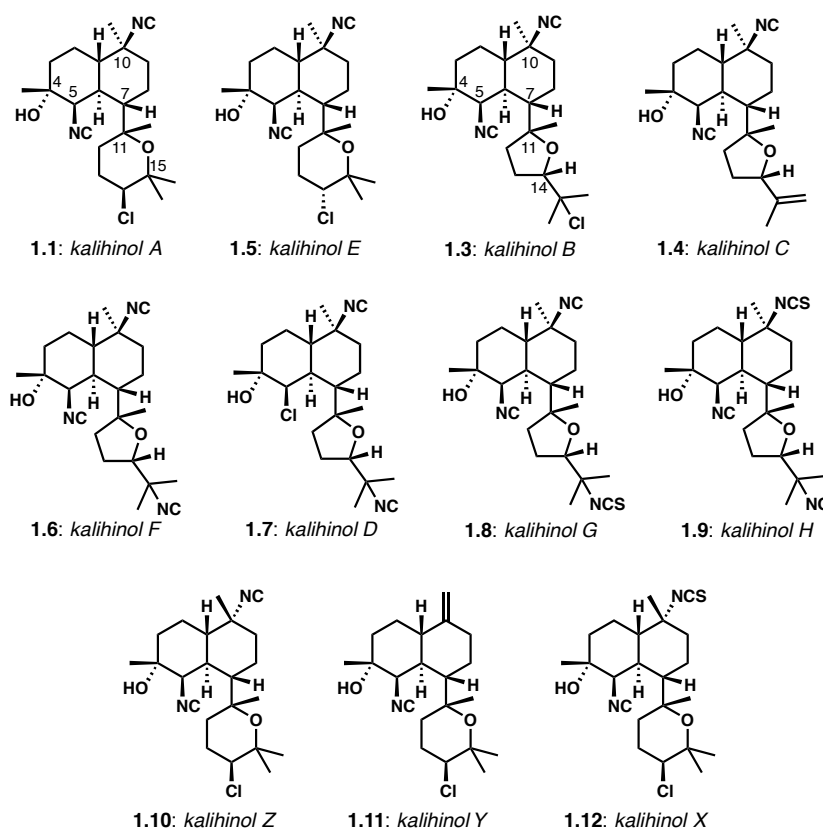
1.2 Isolation and Structure Determination

1.2.1 Initial Isolation by Scheuer and Co-Workers

In 1984, Scheuer and co-workers reported the isolation and characterization of kalihinol A (**1.1**) from a marine sponge of the genus *Acanthella*.¹⁰ The sponge was collected off the coast

of Guam, and extraction and chromatographic purification of the freeze-dried sample (30 g) afforded 11.5 mg of kalihinol A (**1.1**), along with 28.1 mg of a fraction that required subsequent purification. Both components exhibited in vitro activity against *Candida albicans*. After obtaining the spectral data, Scheuer and co-workers confirmed the structure and relative configuration of kalihinol A (**1.1**) using X-ray crystallography. Kalihinol A features a highly functionalized *trans*-decalin core with a pendant chloride-containing THP, an equatorial isonitrile at C10, and an axial isonitrile at C5 *anti* to an axial tertiary alcohol at C4. Following the initial report, Scheuer and co-workers reported the structures of kalihinol B (**1.3**), kalihinol C (**1.4**), kalihinol E (**1.5**), and kalihinol F (**1.6**), which were isolated from the other bioactive fraction.¹¹ While the structures of kalihinol E (**1.5**) and kalihinol F (**1.6**) were elucidated using X-ray crystallography, the structures of kalihinol B (**1.3**) and kalihinol C (**1.4**) were determined by comparison of their spectral properties to the other natural products. Kalihinol E (**1.5**) is the C14 epimer of kalihinol A (**1.1**), and while Scheuer and co-workers initially reversed the stereochemistry of the C14 chloride for kalihinols A and E, this was corrected in a subsequent report.¹² Kalihinol B (**1.3**), kalihinol C (**1.4**), and kalihinol F (**1.6**) share the same *trans*-decalin framework and substitution as kalihinol A (**1.1**), but rather than a pendant THP, they bear differentially substituted pendant THFs. In 1987, Scheuer and co-workers reported the structures of six additional kalihinanes: kalihinol D (**1.7**), kalihinol G (**1.8**), kalihinol H (**1.9**), kalihinol Z (**1.10**), kalihinol Y (**1.11**), and kalihinol X (**1.12**).¹² These kalihinanes retain the *trans*-decalin core with pendant THF or THP and a variable set of isonitrile, isothiocyanate, chloride, and hydroxyl substitution (Figure 1.2).

Figure 1.2. Kalihinanes reported by Scheuer and co-workers.^{10–12}

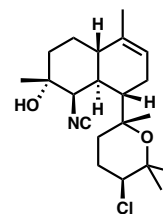
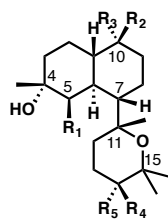


1.2.2 Subsequent Isolation Reports and Subclasses of Kalihinanes

In the three decades following the initial reports by Scheuer and co-workers, work by numerous research groups has led to the isolation of over 50 kalihinanes from *Acanthella cavernosa*, *Acanthella klethra*, and *Phakellia pulcherrima*.^{7,13–27} The kalihinanes can be divided into three general subclasses based on the substitution pattern of the decalin core.

The first subclass encompasses kalihinanes that contain the same substitution pattern of the decalin core as kalihinol A (**1.1**). These kalihinanes are characterized by a *trans*-decalin core containing an isonitrile, isothiocyanate, or formamide at C10, an axial isonitrile, isothiocyanate, or chloride at C5 *anti* to an axial tertiary alcohol at C4, and a pendant THP or THF at C7. The subclass can be further divided into two groups: (1) kalihinanes bearing a pendant THP (Table 1.1) and (2) kalihinanes bearing a pendant THF (Table 1.2).

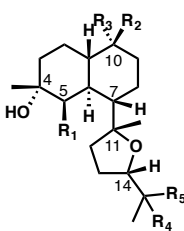
Table 1.1. Kalihinanes bearing a pendant THP.



1.26: Δ^9 -kalihinol Y
Reference 7, 22

	R₁	R₂	R₃	R₄	R₅	Reference
1.1: kalihinol A	NC	NC	CH ₃	Cl	H	10
1.10: kalihinol Z	NC	CH ₃	NC	Cl	H	12
1.11: kalihinol Y	NC	=CH ₂		Cl	H	12
1.12: kalihinol X	NC	CH ₃	NCS	Cl	H	12
1.13: 10- <i>epi</i> -kalihinol X	NC	NCS	CH ₃	Cl	H	25
1.14: kalihinol P	NCS	NC	CH ₃	Cl	H	26
1.15: 10-formamido-kalihinol A	NC	NHCHO	CH ₃	Cl	H	20
1.16: kalihinol I	NCS	CH ₃	NCS	Cl	H	15
1.17: 10- <i>epi</i> -kalihinol I	NCS	NCS	CH ₃	Cl	H	7
1.18: kalihinol J	NHCHO	CH ₃	NCS	Cl	H	15
1.19: 10-formamido-5-isothiocyanato-kalihinol A	NCS	NHCHO	CH ₃	Cl	H	20
1.20: kalihinol S	NHCHO	NCS	CH ₃	Cl	H	26
1.21: 10-formamido-5-isocyanato-kalihinol A	NCO	NHCHO	CH ₃	Cl	H	20
1.5: kalihinol E	NC	NC	CH ₃	H	Cl	11
1.22: kalihinol O	NC	NCS	CH ₃	H	Cl	26
1.23: kalihinol Q	NCS	NC	CH ₃	H	Cl	26
1.24: 10-formamido-kalihinol E	NC	NHCHO	CH ₃	H	Cl	20
1.25: kalihinol R	NCS	NCS	CH ₃	H	Cl	26

Table 1.2. Kalihinanes bearing a pendant THF.



	R ₁	R ₂	R ₃	R ₄	R ₅	Reference
1.3: <i>kalihinol B</i>	NC	NC	CH ₃	Cl	CH ₃	11
1.4: <i>kalihinol C</i>	NC	NC	CH ₃	=CH ₂		11
1.27: <i>10-isothiocyanatokalihinol C</i>	NC	NCS	CH ₃	=CH ₂		22
1.7: <i>kalihinol D</i>	Cl	NC	CH ₃	NC	CH ₃	12
1.28: <i>kalihinol T</i>	Cl	NC	CH ₃	NCS	CH ₃	26
1.6: <i>kalihinol F</i>	NC	NC	CH ₃	NC	CH ₃	11
1.29: <i>10-formamido-kalihinol F</i>	NC	NHCHO	CH ₃	NC	CH ₃	24
1.30: <i>15-formamido-kalihinol F</i>	NC	NC	CH ₃	NHCHO	CH ₃	24
1.8: <i>kalihinol G</i>	NC	NC	CH ₃	NCS	CH ₃	12
1.31: <i>10-isothiocyanatokalihinol G</i>	NC	NCS	CH ₃	NCS	CH ₃	22
1.32: <i>5,10-bis-isothiocyanatokalihinol G</i>	NCS	NCS	CH ₃	NCS	CH ₃	7
1.9: <i>kalihinol H</i>	NC	NCS	CH ₃	NC	CH ₃	12
1.33: <i>10-epi-kalihinol H</i>	NC	CH ₃	NCS	NC	CH ₃	22
1.34: <i>kalihinol K</i>	NC	=CH ₂		NC	CH ₃	22
1.35: <i>kalihinol L</i>	NCS	=CH ₂		NC	CH ₃	22

The isokalihinanes comprise the second subclass of the kalihinanes, retaining the *trans*-decalin core, the equatorial isonitrile or isothiocyanate at C10, and the pendant THP or THF at C7. However, these compounds are regioisomers of the kalihinanes, containing an equatorial isonitrile or formamide at C4 *anti* to an equatorial secondary alcohol at C5. The isokalihinanes, like the kalihinanes, can be further separated into two categories: (1) isokalihinanes containing a pendant THP (kalihinol N (**1.36**), Figure 1.3), and (2) isokalihinanes bearing a pendant THF (Table 1.3).

Figure 1.3. Structure of kalihinol N (**1.36**), an isokalihinane bearing a pendant THP.²⁶

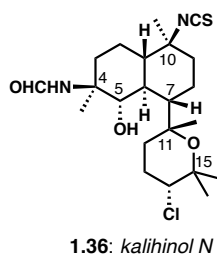
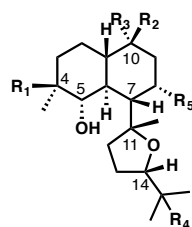


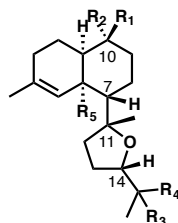
Table 1.3. Isokalihinanes bearing a pendant THF.



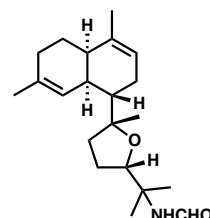
	R ₁	R ₂	R ₃	R ₄	R ₅	Reference
1.37: <i>isokalihinol B</i>	NC	NC	CH ₃	Cl	H	14
1.38: <i>isokalihinol F</i>	NC	NC	CH ₃	NC	H	13
1.39: <i>10-epi-isokalihinol F</i>	NC	CH ₃	NC	NC	H	16
1.40: <i>8-hydroxy-isokalihinol F</i>	NC	NC	CH ₃	NC	OH	23
1.41: <i>10-epi-isokalihinol H</i>	NC	CH ₃	NCS	NC	H	16
1.42: <i>kalihinol M</i>	NHCHO	NCS	CH ₃	Cl	H	26

The kalihinenes are the final subclass of the kalihinanes, whose defining structural feature is C4–C5 unsaturation. Interestingly, the kalihinenes are the only subclass containing members exhibiting a *cis*-decalin core, C6 oxidation, or a dihydropyran appendage. Like the other subclasses, the kalihinenes can also be divided into categories based on the presence of a THF appendage (Tables 1.4 and 1.5), a THP appendage (Table 1.6), or a dihydropyran appendage (Figure 1.4).

Table 1.4. Kalihinenes containing a *cis*-decalin and a pendant THF.

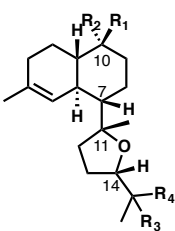


	R ₁	R ₂	R ₃	R ₄	R ₅	Reference
1.2: <i>kalihinene</i>	NC	CH ₃	NC	CH ₃	H	14
1.43: <i>10-formamido-kalihinene</i>	NHCHO	CH ₃	NC	CH ₃	H	18
1.44: <i>15-formamido-kalihinene</i>	NC	CH ₃	NHCHO	CH ₃	H	18
1.45: <i>10,15-bisformamido-kalihinene</i>	NHCHO	CH ₃	NHCHO	CH ₃	H	18
1.46: <i>6-hydroxy-kalihinene</i>	NC	CH ₃	NC	CH ₃	OH	18
1.47: <i>6-hydroxy-15-formamido-kalihinene</i>	NC	CH ₃	NHCHO	CH ₃	OH	18
1.48: <i>6-hydroxy-10-formamido-kalihinene</i>	NHCHO	CH ₃	NC	CH ₃	OH	18
1.49: <i>6-hydroxy-10-formamido-15-thiocyano-kalihinene</i>	NHCHO	CH ₃	NCS	CH ₃	OH	18



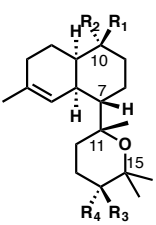
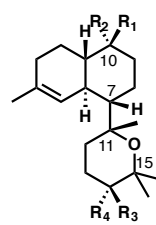
1.50: *kalihinene F*
Reference 27

Table 1.5. Kalihinenes containing a *trans*-decalin and a pendant THF.



	R ₁	R ₂	R ₃	R ₄	Reference
1.51: <i>kalihinene A</i>	CH ₃	NC	NC	CH ₃	16, 17
1.52: <i>kalihinene B</i>	NC	CH ₃	NC	CH ₃	16, 17
1.53: <i>15-isothiocyanato-1-epi-kalihinene</i>	NC	CH ₃	NCS	CH ₃	16

Table 1.6. Kalihinenes containing a *cis*- or *trans*-decalin and a pendant THP.

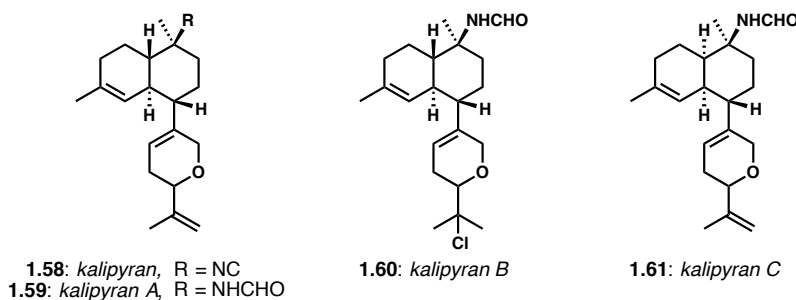



	R ₁	R ₂	R ₃	R ₄	Reference
1.54: <i>kalihinene X</i>	NHCHO	CH ₃	Cl	H	19
1.55: <i>kalihinene Z</i>	NHCHO	CH ₃	H	Cl	19

	R ₁	R ₂	R ₃	R ₄	Reference
1.56: <i>kalihinene Y</i>	NHCHO	CH ₃	Cl	H	19
1.57: <i>kalihinene E</i>	NHCHO	CH ₃	H	Cl	27

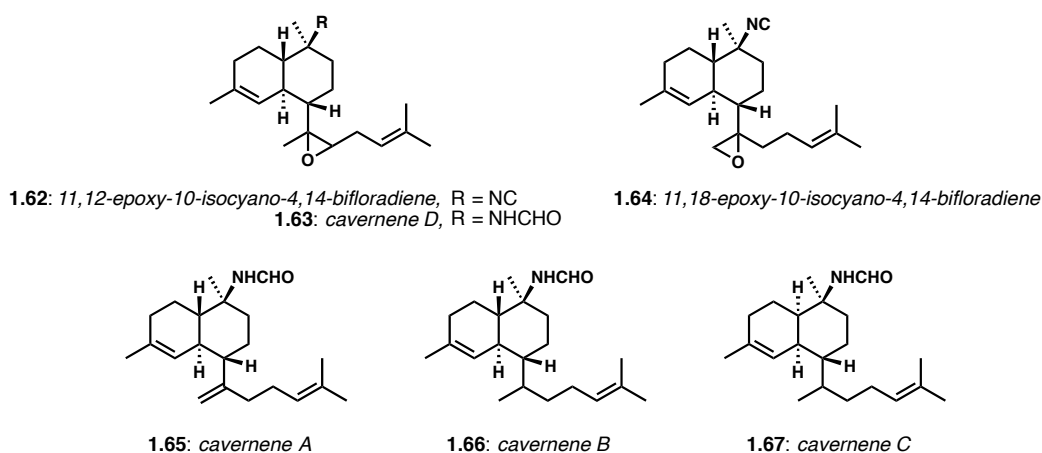
Kalihinenes bearing a dihydropyran appendage are known as the kalipyran (Figure 1.4). Faulkner and co-workers first isolated kalipyran (**1.58**) in 1994 from *Acanthella cavernosa*.¹⁶ Three additional kalipyran, kalipyran A (**1.59**), kalipyran B (**1.60**), and kalipyran C (**1.61**), containing a C10 formamide, a *trans*- or *cis*-decalin framework, and a dihydropyran appendage bearing an isopropenyl substituent or a tertiary chloride have subsequently been reported.^{21,27} The relative C14 stereochemistry of the kalipyran has yet to be determined.

Figure 1.4. The kalipyran.



The kalihinene decalin core is shared with structurally related isocyanobifloradiene epoxides **1.62** and **1.64** and the cavernenes, which lack a tricyclic framework. Garson and co-workers isolated isocyanobifloradiene epoxides **1.62** and **1.64** from *Acanthella cavernosa*.²³ These compounds have been proposed as intermediates in the biosynthesis of the kalihinanes.^{5,18} The isolation and structural determination of cavernenes A–D, related formamido-diterpenes, was recently reported.²⁷

Figure 1.5. Structurally related cavernenes and isocyanobifloradiene epoxides **1.62** and **1.64**.



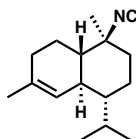
1.2.3 Absolute Configuration of the Kalihinanes

While the relative configuration of the kalihinanes was determined using X-ray crystallography, the absolute configuration was not established until 1999, when Yamada and co-workers determined the absolute configuration of kalihinol A (**1.1**) using circular dichroism spectroscopy.²⁸ The circular dichroism spectra of a derivative of kalihinol A suggested the absolute configuration of kalihinol A is 1*S*, 4*R*, 5*R*, 6*S*, 7*S*, 10*S*, 11*R*, and 14*S*, or as drawn in Figure 1.1. Yamada and co-workers confirmed the absolute stereochemistry of kalihinene X (**1.54**) when they completed its synthesis in 2001, which matched the provisional assignment established for kalihinol A.²⁹ The absolute configuration of kalihinol A was confirmed in 2011, when Miyaoka and co-workers completed the synthesis of kalihinol A (**1.1**).³⁰

1.2.4 A Structurally Related Sesquiterpene, 10-Isocyano-4-cadinene

The kalihinanes comprise only a portion of the larger family of isocyanoterpenes. In 1996, Fusetani and co-workers isolated 10-isocyano-4-cadinene (**1.68**), a sesquiterpene isocyanide, from nudibranchs of the Phyllidiidae family.³¹ Due to its structural similarities to the kalihinanes, including the *trans*-decalin core with C4–C5 unsaturation, the equatorial C10 isonitrile, and the equatorial isopropyl substituent at C7, 10-isocyano-4-cadinene (**1.68**) has often been the starting point for synthetic approaches to the kalihinanes.³² Similarly, we targeted 10-isocyano-4-cadinene (**1.68**) as we evaluated our synthetic strategy to access the *trans*-decalin framework of the kalihinanes.

Figure 1.6. Structure of 10-isocyano-4-cadinene (**1.68**), a sesquiterpene isocyanide.



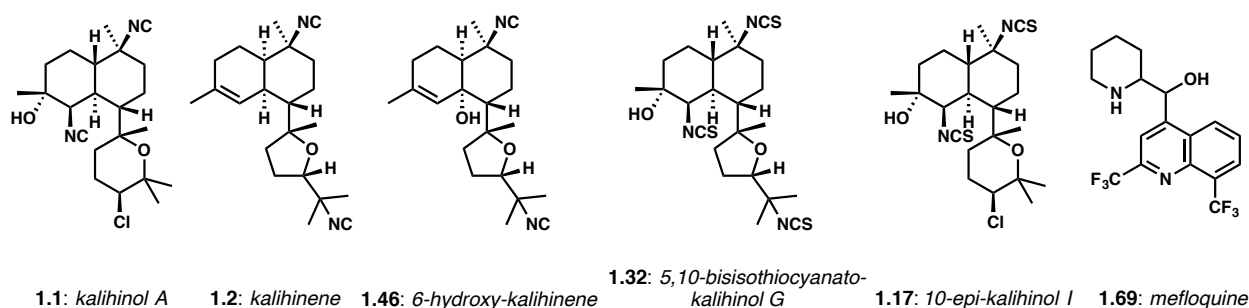
1.68: 10-isocyano-4-cadinene

1.3 Antimalarial Activity and Biological Properties of the Kalihinanes and Related ICTs

While the kalihinanes exhibit a diverse array of biological activities, including anthelmintic,^{13,15} antifouling,^{19–21,26} antimicrobial,^{10–12,24} antifungal,^{10–12,14,16} and cytotoxic^{14,25,26} activity, the kalihinanes are best known for their potent antimalarial activity.⁷ Despite the fact that the antimalarial activity of ICTs has been known since 1992, a systematic evaluation of the kalihinane family has yet to be accomplished.³³ Of the 50+ members of the kalihinane family, only five have been evaluated for antimalarial activity, likely because many were isolated before the antimalarial activity of ICTs was known. Three of those compounds tested exhibited potent antimalarial activity against *P. falciparum* with good to excellent selectivity, which is essential for antimalarial therapy (Table 1.7). The selectivity index (SI) is defined as the ratio of *P. falciparum* to FM3A cell cytotoxicity. Kalihinol A (**1.1**) was both more potent and more

selective (EC_{50} = 1.2 nM, SI = 317) than the antimalarial standard mefloquine (**1.69**) (EC_{50} = 32 nM, SI = 90). While kalihinene (**1.2**) and 6-hydroxy-kalihinene (**1.46**) also exhibited potent antimalarial activity (EC_{50} = 10 nM and 80 nM, respectively), their selectivities (SI = 4 and 15, respectively) were lower than the mefloquine standard (SI = 90). From this study, it becomes clear that the isonitrile functionality is essential for high activity (compare kalihinol A (**1.1**) and 10-epi-kalihinol I (**1.17**)).

Table 1.7. Antimalarial activities of kalihinanes that have been assayed.⁷



Compound	FCR-3 ^a EC_{50} (nM)	FM3A EC_{50} (nM)	SI ^b
1.1	1.2	380	317
1.2	10	37	4
1.46	80	1200	15
1.32	2600	700	-
1.17	>1800	-	-
1.69^c	32	2900	90

^aFCR-3 is a drug-resistant strain of *P. falciparum*.

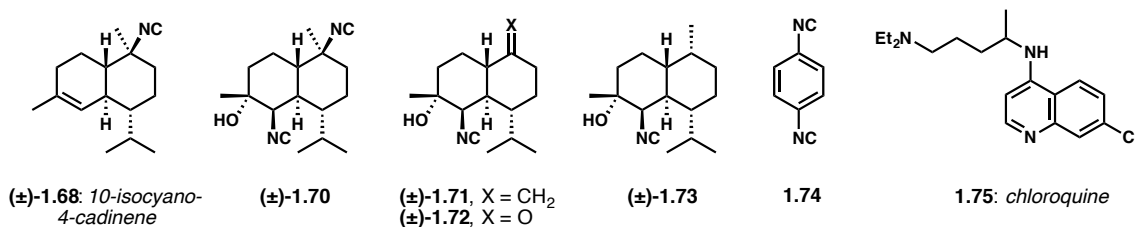
^bSelectivity index (SI) is defined as the ratio of FM3A cells cytotoxicity to FCR-3.

^cMefloquine was used as the antimalarial standard.

Since the 1998 report of the antimalarial activity of the kalihinanes, no further studies evaluating their antimalarial activity have been reported. Work by Wood and co-workers have prepared a number of simpler kalihinane analogues and determined their antiplasmodial activity, revealing limited structure-activity relationships (Table 1.8).^{34,35} Wood and co-workers evaluated nineteen kalihinane analogues in addition to six commercially-available isonitriles. They found

that all of the kalihinane analogues containing an isonitrile displayed *in vitro* antiplasmodial activity, as did one of the commercially available isonitriles (1,4-diisocyanobenzene (**1.74**)). The kalihinane analogues containing isothiocyanate, nitrile, formamide, and azide functionality in place of the isonitrile were inactive against *P. falciparum*. Of particular interest is diisocyanide **1.70**, which displays nanomolar activity against drug-resistant *P. falciparum* ($IC_{50} = 80$ nM). Diisocyanide **1.70** is structurally similar to kalihinol A (**1.1**), lacking only the pendant THP ring, suggesting that the THP is not essential for achieving high antiplasmodial activity (compare to kalihinol A (**1.1**), $EC_{50} = 1.2$ nM). However, since diisocyanide **1.70** was assayed as a racemate, the question remains whether one enantiomer is a more effective antimalarial than its antipode. These studies indicate that the presence of two isonitriles is required for potent antimalarial activity, as **1.70** is significantly more potent than compounds containing only one isonitrile (*i.e.* **1.68**, **1.71**, **1.72**, **1.73**).

Table 1.8. Kalihinane analogues displaying antiplasmodial activity.^{34,35}



Compound	HB3 ^a IC ₅₀ (μM)	Dd2 ^b IC ₅₀ (μM)	Cytotoxicity ^c
1.68	2.20	2.20	Yes
1.70	0.08	0.08	No
1.71	0.80	2.00	No
1.72	2.20	2.20	No
1.73	0.50	2.00	No
1.74	0.50	0.50	Yes
1.75^d	0.02	0.20	-

^aHB3 is a chloroquine-sensitive strain of *P. falciparum*.

^bDd2 is a chloroquine-resistant strain of *P. falciparum*.

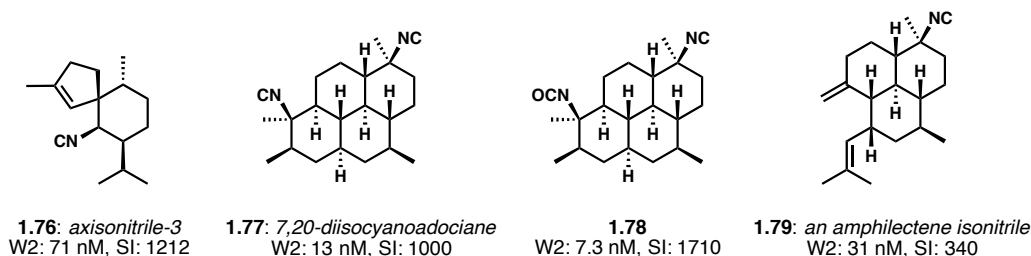
^c*In vitro* cytotoxicity was evaluated at two concentrations: 100 μM and 25 μM.

^dChloroquine (**1.75**) was used as the antimalarial standard.

Outside of the limited SAR determined by Yamada and Wood's studies on the kalihinanes and analogues, work towards elucidating the mechanism of action for the kalihinanes has been limited. In general, the malaria parasite feeds by catabolizing hemoglobin, releasing free heme. However, *P. falciparum* lacks the ability to catabolize free heme, which is toxic to the parasite. To avoid the toxic effects of free heme, *P. falciparum* sequesters the free heme that is released into hemozoin, an insoluble crystalline form of heme. While the mode of action for antimalarial drugs is not entirely understood, many clinically used antimalarial drugs are believed to disrupt hemozoin formation, allowing for the build-up of free heme, which degrades parasitic membranes, ultimately leading to parasite death.⁶ Wright and co-workers published a study suggesting the same mechanism of action for some of the isocyanoterpenoids, including those drawn in Figure 1.7.³⁶ They determined that isocyanoterpenes, including

7,20-diisocyanoadociene (**1.77**), effectively inhibit the formation of hemozoin, and also showed that they form isonitrile–heme(II) complexes. While this single-point binding of isonitriles to heme seems logical since isonitriles are known to be good ligands to metals, the question remains whether this mode of action can also be applied to the kalihinanes. Furthermore, this proposed mechanism of action for ICTs has failed to explain some general observations of SAR. For ICTs that exhibit potent antimalarial activity, isonitriles are known to be required, and in most cases, the corresponding isocyanates, formamides, and isothiocyanates are ineffective *in vitro* against *P. falciparum*. Yet, if single-point binding is the mechanism of action, then any isonitrile in theory should exhibit antimalarial activity. However, many mono-isonitriles have been shown to display modest to no *in vitro* activity against *P. falciparum*.^{35,37} Further mode of action studies for ICTs are required to understand these general observations.

Figure 1.7. Select isocyanoterpenes included in the mechanistic studies by Wright and co-workers. (W2 is a chloroquine-resistant strain of *P. falciparum*).^{33,36,38}



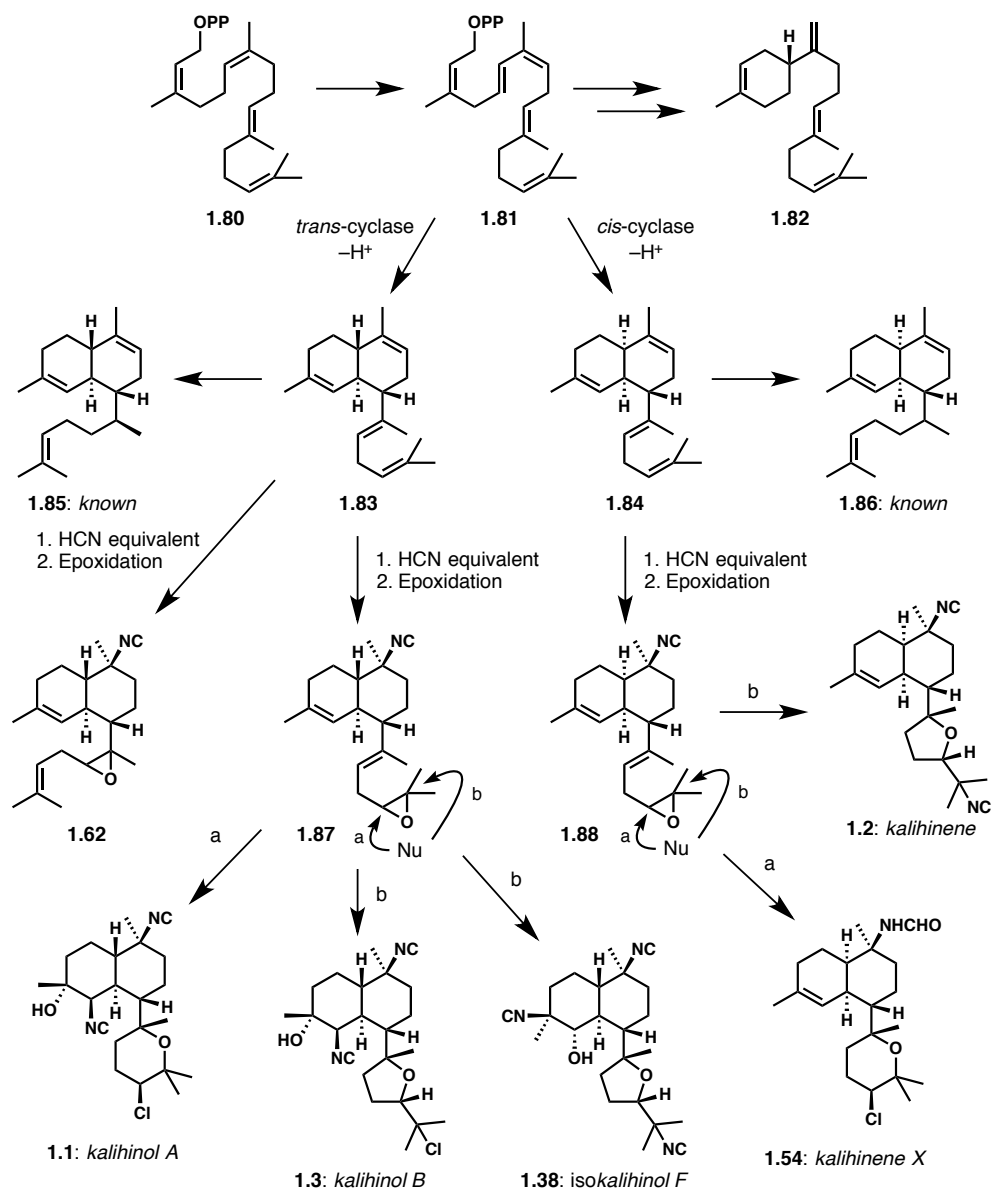
1.4 Proposed Biosynthesis of the Kalihinanes

1.4.1 Proposed Biosynthesis of the Kalihinanes and Kalipyrans

Garson and co-workers have proposed a biosynthesis of the kalihinanes, based on a modification of earlier reports by Clardy and co-workers and Chang and Scheuer (Scheme 1.1).^{5,18,39} The proposed biosynthesis begins with the enzymatic conversion of geranylgeranyl diphosphate (**1.80**) to intermediate **1.81**, which under the action of a *trans*-cyclase or a *cis*-cyclase leads to *trans*-decalin **1.83** and *cis*-decalin **1.84**, respectively. The isolation of

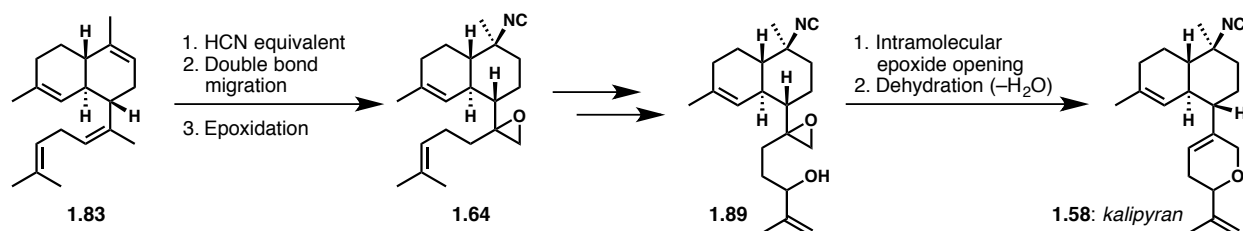
metabolites **1.85** and **1.86** supports this biosynthetic pathway. Subsequent addition of an HCN equivalent followed by enzymatic epoxidation of either the C11–C12 alkene or the C14–15 alkene affords isocyanobifloradiene epoxide **1.62** or proposed intermediates **1.87** and **1.88**. In addition to providing support for the proposed biosynthesis, the isolation of isocyanobifloradiene epoxide **1.62** proves that *Acanthella cavernosa* has the ability to epoxidize alkenes. Nucleophilic attack at C14 of the epoxide (pathway a) ultimately leads to the formation of THP kalihinols (*e.g.* **1.1**) and THP kalihinenes (*e.g.* **1.54**), while opening of the epoxide at C15 (pathway b) provides THF kalihinols (*e.g.* **1.3**), THF isokalihinols (*e.g.* **1.38**), and THF kalihinenes (*e.g.* **1.2**). Lastly, the kalihinol and isokalihinol substitution pattern at C4 and C5 results from epoxidation of the C4–C5 alkene followed by nucleophilic attack of cyanide at either C4 (isokalihinols) or C5 (kalihinols).

Scheme 1.1. Biogenesis of the kalihinanes proposed by Garson and co-workers.⁵



Isocyanobifloradiene epoxide **1.64** can be invoked as an intermediate in the proposed biosynthesis of the kalipyranes (Scheme 1.2). From *trans*-decalin **1.83**, addition of an HCN equivalent, followed by alkene migration and epoxidation leads to isocyanobifloradiene epoxide **1.64**, a metabolite isolated from *A. cavernosa*. Subsequent oxidation, intramolecular epoxide opening, and dehydration completes the proposed biosynthesis of the kalipyranes (e.g. **1.58**).

Scheme 1.2. Biogenesis of the kalipyrans proposed by Garson and co-workers.⁵



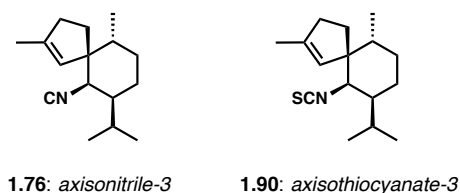
1.4.2 Biosynthetic Origins of Isonitriles and Isothiocyanates

Because isocyanoterpenes are often isolated alongside their formamide and isothiocyanatoterpene counterparts, the formamide and the isothiocyanate were initially postulated as potential biogenetic precursors to the isocyanide. However, studies have since discounted formamides as intermediates in isonitrile biosynthesis, and have further suggested that the isonitrile is the biogenetic precursor to the formamide and isothiocyanate groups found in ICTs.^{40–42} The isonitrile has been proposed to arise from the incorporation of inorganic cyanide. Isotopic labeling studies by Garson and by Karuso and Scheuer have shown that [^{14}C]-cyanide is incorporated into the isonitrile functionality of several ICTs.^{43,44} In particular, Karuso and Scheuer found that *Acanthella* sp. incorporated [^{14}C]-cyanide (1.5%) into kalihinol F (**1.6**). Upon hydrolysis of isotopically labeled kalihinol F (**1.6**), all radioactivity of the corresponding triamine was lost, indicating that the radioactivity was associated with the isocyanide carbons alone. Furthermore, Karuso and Scheuer determined that incorporation of cyanide was an enzymatic process; in the absence of sponge tissue, no incorporation of [^{14}C]-cyanide was observed.

Isonitriles and isothiocyanates have been shown to interconvert in marine sponges. Garson and co-workers have shown that [^{14}C]-cyanide is incorporated into both axisonitrile-3 (**1.76**) and axisothiocyanate-3 (**1.90**), and that [^{14}C]-thiocyanate is incorporated into

axisonitrile-3 (**1.76**) as well as axisothiocyante-3 (**1.90**) in *A. cavernosa*.⁴⁵ These results suggested that *A. cavernosa* has either the ability to interconvert the inorganic cyanide ion and the thiocyanate ion or the ability to interconvert the secondary metabolites **1.76** and **1.90**. A later study by Garson and co-workers in *Axinyssa* n.sp. suggests that both interconversions occur enzymatically.⁴⁶

Figure 1.8. Structures of axisonitrile-3 (**1.76**) and axisothiocyante-3 (**1.90**).



1.5 Methods for the Synthesis of Isonitriles

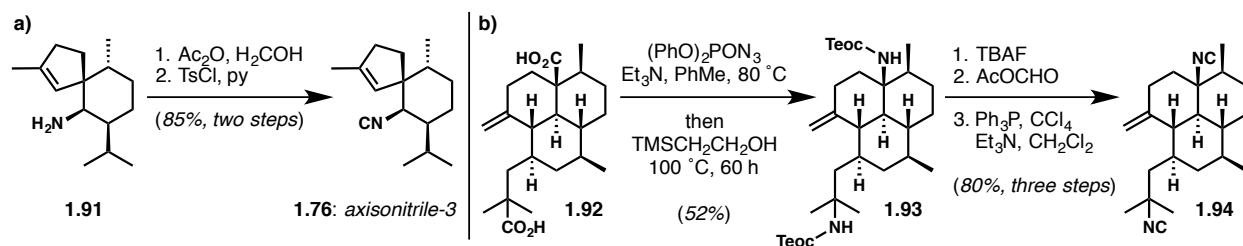
Due to the interest in ICTs from the synthetic community and the utility of isonitriles as intermediates in synthesis (*e.g.* multi-component reactions), several methods for the synthesis of isonitriles have been developed.^{6,47} In general, these methods can be separated into two categories: (1) synthesis of isonitriles by formylation and dehydration of an amine, and (2) synthesis of isonitriles by nucleophilic substitution. Unfortunately, both methods suffer from limitations, which will be described below.

1.5.1 Synthesis of Isonitriles from the Corresponding Amine

Perhaps one of the most widely used methods for the synthesis of isonitriles is formylation and dehydration of an amine. This method is versatile because any primary amine can be a precursor to an isonitrile. However, the stereoselective synthesis of secondary alkyl and tertiary alkyl amines can be challenging, limiting the utility of this method. Furthermore, the overall transformation of the amine to the isonitrile is a two-step sequence. This formylation/dehydration sequence has been widely utilized in the synthesis of ICTs. In 1978, Caine and Deutsch completed the first synthesis of an ICT, axisonitrile-3 (**1.76**), by formylation

and dehydration of amine **1.91** (Scheme 1.3a).⁴⁸ Several synthetic groups have solved the problem of stereoselective synthesis of tertiary alkyl isonitriles by taking advantage of the stereospecificity of the Curtius rearrangement.^{29,49–52} The stereochemistry of the carboxylic acid, which can often be introduced *via* stereoselective alkylation, dictates the stereochemistry of the resulting isocyanate, which is usually trapped as a carbamate or reduced directly to a formamide. In their synthesis of (±)-8.15-diisocyano-11(20)-amphilectene (**1.94**), Piers and Llinas-Brunet subjected diacid **1.92** to a Curtius rearrangement, trapping the intermediate diisocyanate as dicarbamate **1.93** (Scheme 1.3b).⁴⁹ Treatment of dicarbamate **1.93** with TBAF to unmask the primary amines followed by formylation and dehydration afforded amphilectene **1.94**. While this approach affords tertiary alkyl isonitriles stereospecifically, several steps are required to convert the carboxylic acid to the isonitrile. Additionally, late-stage homologation of a ketone into the carboxylic acid, a method often employed to install the requisite carboxylic acid for the Curtius rearrangement (see Section 1.6.2 and 1.6.4), requires a significant number of steps.

Scheme 1.3. (a) Caine and Deutsch's isonitrile installation in the synthesis of axisonitrile-3 (**1.76**).⁴⁸ (b) Piers and Llinas-Brunet's use of a Curtius rearrangement in the synthesis of **1.94**.⁴⁹



1.5.2 Synthesis of Isonitriles by Nucleophilic Substitution and other Cationic Methods

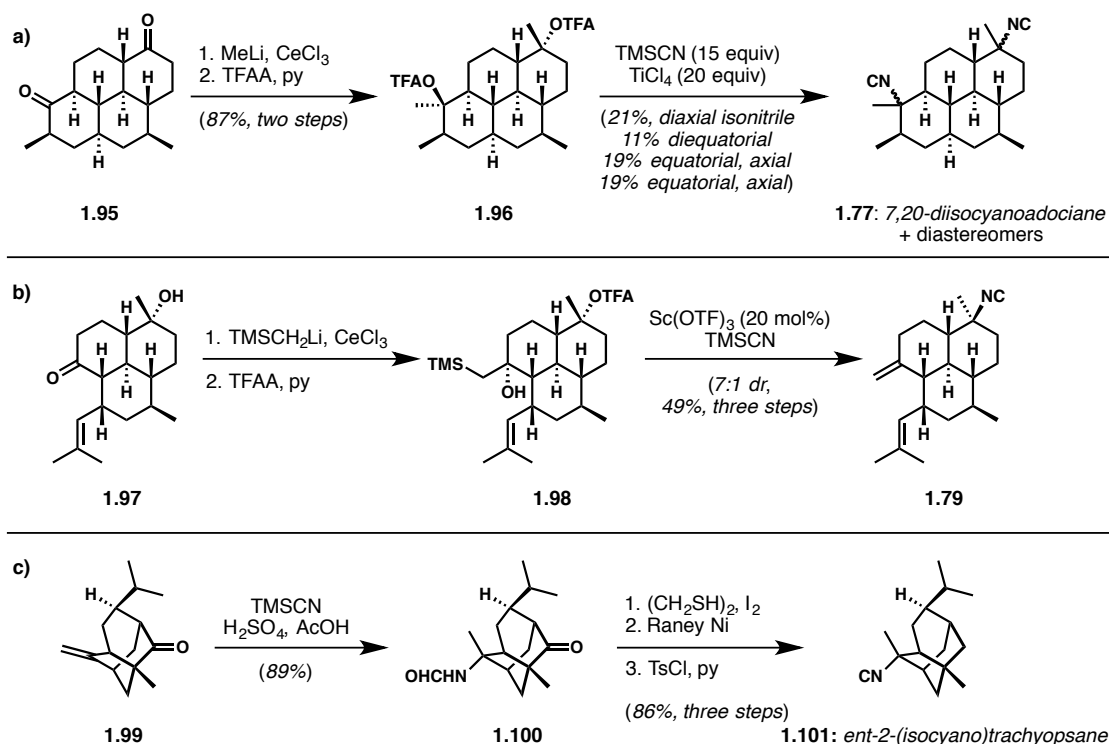
While formylation/dehydration of amines is a reliable method for the synthesis of isonitriles, a one-step, stereoselective synthesis of isonitriles from a general, easily accessible precursor is the ideal approach. While this ideal has yet to be realized, several methods for the direct installation of isonitriles *via* nucleophilic substitution have been developed. Because the

conversion of primary alcohols into isonitriles via S_N2 substitution is straightforward, the following discussion will be limited to the synthesis of secondary and tertiary alkyl isonitriles. One of the biggest challenges in the synthesis of tertiary alkyl isonitriles using cationic methods is the issue of stereocontrol. Until recently, the stereochemical outcome of S_N1 substitution reactions to install isonitriles was limited to substrate control owing to the intermediate solvent-separated carbocation.

Alcohols are attractive precursors to isonitriles, as many reliable, robust methods for their stereoselective synthesis have been developed. In their synthesis of 7,20-diisocyanoadociane (**1.77**), Corey and Magriotis found that trimethylsilyl cyanide (TMSCN) in conjunction with a Lewis acid displaces tertiary trifluoroacetates to afford tertiary alkyl isonitriles (Scheme 1.4a).⁵³ Unfortunately, this reaction suffered from poor stereoselectivity as a result of a presumed intermediate solvent-separated carbocation. Exposure of bis(trifluoroacetate) **1.96** to an excess of TMSCN (15 equiv) and titanium tetrachloride (20 equiv) afforded 7,20-diisocyanoadociane (**1.77**) along with three other diastereomers. Recently, Shenvi and co-workers have developed a general method for the invertive displacement of tertiary trifluoroacetates, which they had previously utilized in their synthesis of the amphilectene isonitrile **1.79** (Scheme 1.4b).^{54,55} They discovered that TMSCN displaces tertiary trifluoroacetates in the presence of scandium(III) triflate with high levels of stereoinversion. Shenvi and co-workers invoke an intermediate contact ion pair in the S_N1 reaction mechanism to explain the observed stereoselectivity. Exposure of trifluoroacetate **1.98** to catalytic scandium(III) triflate and TMSCN afforded amphilectene **1.79** with good diastereoselectivity. This is currently the only stereoselective method for the synthesis of tertiary alkyl isonitriles from alcohols.

Isonitriles can also be prepared from alkenes *via* a Ritter reaction followed by formamide dehydration. Srikrishna and co-workers utilized this sequence in their synthesis of *ent*-2-(isocyano)trachyopsane (**1.101**) (Scheme 1.4c).⁵⁶ Capture of a carbocation generated from alkene **1.99** with TMSCN followed by hydrolysis afforded formamide **1.100**. The ketone of **1.100** was converted into a thioketal and reduced with Raney Nickel. Subsequent dehydration of the formamide provided *ent*-2-(isocyano)trachyopsane (**1.101**). While the high diastereoselectivity of the Ritter reaction in this case was due to the tricycle[4.3.1.0^{3,8}]decane skeleton, the Ritter reaction often suffers from poor stereoselectivity.

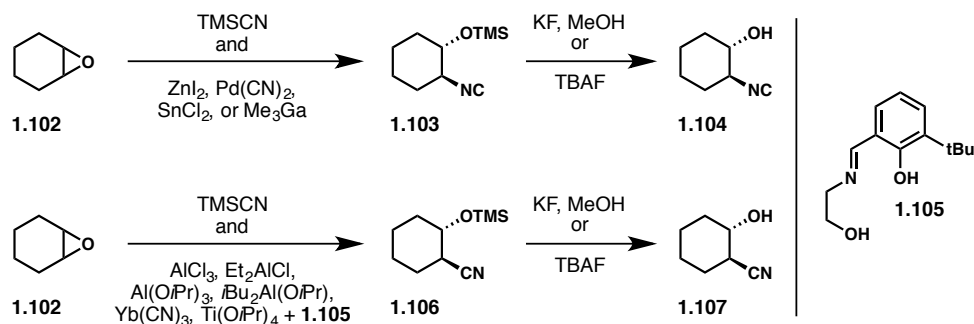
Scheme 1.4. Cationic methods for isonitrile synthesis: (a) Corey and Magriotis's synthesis of 7,20-diisocyanoadociane (**1.77**).⁵³ (b) Shenvi and co-workers' synthesis of **1.79**, an amphilectene isonitrile.⁵⁵ (c) Srikrishna and co-workers' synthesis of *ent*-2-(isocyano)trachyopsane (**1.101**).⁵⁶



The isocyanosilylation of epoxides is another tactic for the synthesis of isonitriles. This method is particularly relevant to the kalihinanes owing to the β -hydroxy-isonitrile contained in many of the natural products. Yet, it remains surprisingly absent in the synthesis of kalihinanes

and other ICTs (see Section 1.6). Because cyanide is an ambident nucleophile, reaction of cyanide nucleophiles with electrophiles can afford the nitrile or the isonitrile as the product. In general, reaction at carbon is preferred for the free cyanide ion, leading to nitriles, and only in cases where another group (*e.g.* Ag^+ or Me_3Si^+) blocks the carbon atom of the nucleophile is the isonitrile observed.^{57,58} Furthermore, reversible reactions afford the nitrile exclusively. Depending on the identity of the Lewis acid, reaction of epoxides with TMSCN can afford β -trimethylsilyloxy-nitriles or β -trimethylsilyloxy-isonitriles (Scheme 1.5). Lewis acids such as zinc iodide, palladium(II) cyanide, tin(II) chloride, and trimethylgallium produce the β -trimethylsilyloxy-isonitrile.^{59–61} Formation of a Lewis acid–TMSCN complex with these Lewis acids has not been detected and, therefore, they are believed to afford β -trimethylsilyloxy-isonitriles simply by Lewis acid activation of the epoxide and nucleophilic attack of TMSCN on nitrogen. Other Lewis acids, including aluminum chloride, diethylaluminum chloride, aluminum isopropoxide, diisobutylaluminum isopropoxide, ytterbium tricyanide, and titanium(IV) isopropoxide, yield the β -trimethylsilyloxy-nitrile.^{60,62–67} Lewis acids that generate the nitrile product have been shown to react with TMSCN to generate metal cyanide complexes. While these complexes have not been studied extensively, diethylaluminum cyanide has been reported to exist as a polymer, allowing for facile isomerization of an Al–CN complex to an Al–NC complex.⁶⁰ Isomerization to an Al–NC complex and subsequent cyanosilylation of the epoxide is a mechanism consistent with the observed β -trimethylsilyloxy-nitrile product. However, the mechanism has not been fully elucidated.

Scheme 1.5. Synthesis of a β -trimethylsilyloxy-isonitrile (**1.103**) or a β -trimethylsilyloxy-nitrile (**1.106**) from cyclohexene oxide (**1.102**).



1.6 Previous Syntheses of Kalihinanes and Related ICTs

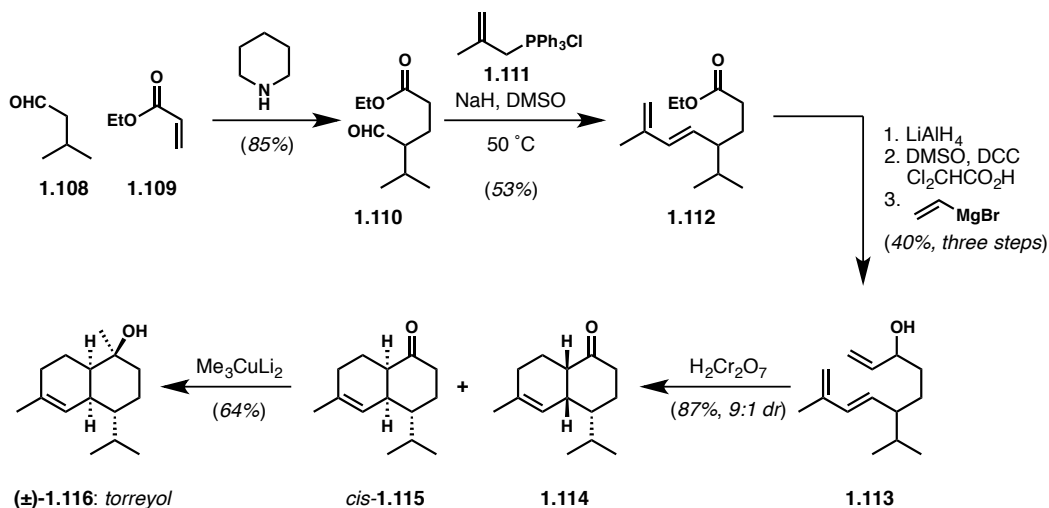
Owing to their diverse biological activity and complex structure, the kalihinanes have garnered interest from several synthetic groups, resulting in reported syntheses of five natural products. Yamada and co-workers reported the synthesis of kalihinene X (**1.54**) in 2002.²⁹ Wood and co-workers reported the synthesis of kalihinol C (**1.4**) in 2004.^{32,68} Miyaoka and co-workers reported syntheses of kalihinol A (**1.1**), kalihinol Y (**1.11**), and 10-*epi*-kalihinol I (**1.17**) in 2011 and 2012.^{30,69} Because Taber's synthesis of ($\pm$)-torreyol provided the inspiration for the synthesis of the decalin core in all reported approaches toward the kalihinanes, the synthesis of ($\pm$)-torreyol will be included in addition to a discussion of the previous syntheses of the kalihinanes below.⁷⁰ The densely functionalized decalin core in conjunction with the attached ring motif^{71,72}—the oxygen heterocycle attached to the decalin with its attendant vicinal C7/C11 stereogenic centers—are arguably the most challenging structural features of the kalihinanes. While Yamada, Wood, and Miyaoka devised strategies to solve these problems, the length and efficiency of their syntheses suffered.

1.6.1 Taber's Synthesis of ($\pm$)-Torreyol

Taber and co-workers recognized that a type 1 intramolecular Diels–Alder cycloaddition would provide the *cis*-decalin core of torreyol (**1.116**), a sesquiterpene of the cadinene family

(Scheme 1.6).⁷⁰ Enamine-mediated Michael addition of isovaleraldehyde (**1.108**) to ethyl acrylate (**1.109**) followed by Wittig olefination of the resulting keto-ester (**1.110**) afforded diene **1.112**. Conversion of ethyl ester **1.112** to an aldehyde by a reduction/oxidation sequence and subsequent addition of vinyl Grignard provided alcohol **1.113**. In their synthetic design, Taber and co-workers predicted the cycloaddition would occur *endo* via a boat transition structure to avoid nonbonding interactions incurred in the chair transition structure, leading to the *cis* ring fusion and the desired *syn* relationship between the isopropyl group and the angular hydrogens. Indeed, upon oxidation of the allylic alcohol to an enone, intramolecular Diels–Alder cycloaddition occurred spontaneously, favoring desired *cis*-decalone **1.115**. Nucleophilic methylation of decalone **1.115** completed the synthesis of (±)-torreyol (**1.116**).

Scheme 1.6. Taber's synthesis of (±)-torreyol (**1.116**).⁷⁰

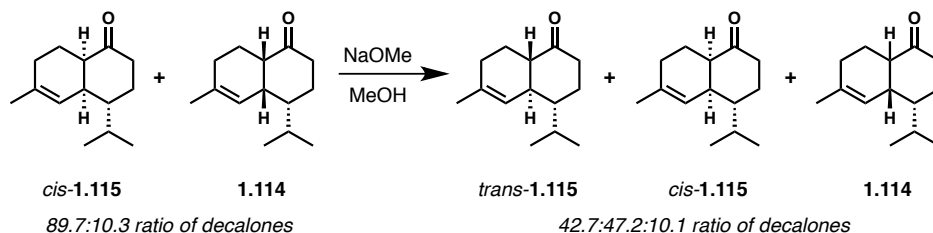


1.6.2 Matsuda's Synthesis of (+)-10-Isocyano-4-cadinene

In 2010, Matsuda and co-workers reported the first synthesis of 10-isocyano-4-cadinene (**1.68**) and determined its absolute configuration.^{73,74} While Matsuda and co-workers initially evaluated the same intramolecular Diels–Alder reaction toward the decalone core as Taber and

co-workers, they found epimerization of the mixture of **1.114** and *cis*-**1.115** to lead to an inseparable 42.7:47.2:10.1 mixture of *trans*-**1.115**, *cis*-**1.115**, and **1.114** (Scheme 1.7).

Scheme 1.7. Epimerization of decalones **1.114** and **1.115**.

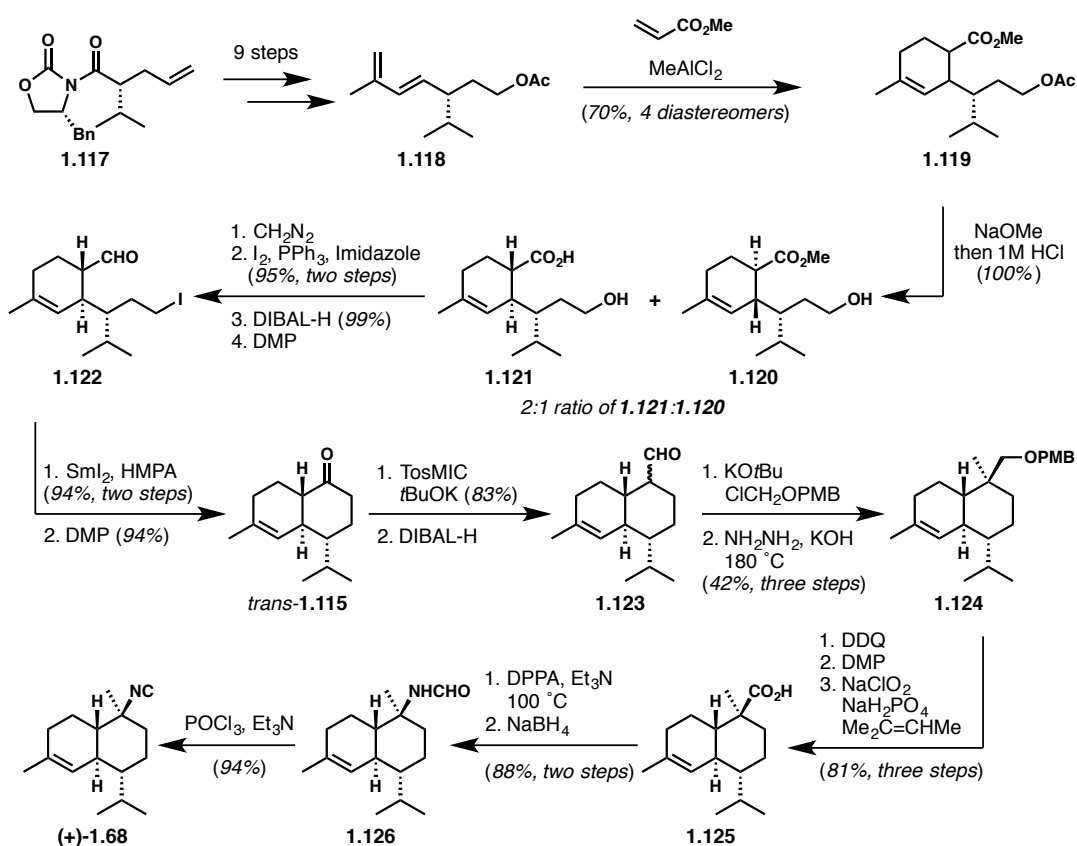


Matsuda and co-workers hoped to develop a stereoselective synthesis of *trans*-decalone **1.115** using an intermolecular Diels–Alder cycloaddition, isomerization, and a Barbier-type annulation (Scheme 1.8). They prepared diene **1.118** in nine steps from oxazolidinone **1.117**. Lewis acid-catalyzed Diels–Alder cycloaddition of diene **1.118** and methyl acrylate afforded cyclohexene **1.119** as a mixture of four diastereomers. Treatment of the mixture of diastereomers with sodium methoxide followed by selective hydrolysis yielded ester **1.120** and carboxylic acid **1.121** in a 1:2 ratio. While they examined a number of Lewis acids, ultimately methylaluminum dichloride afforded the best diastereomeric ratio (2:1 dr) of the two *trans*-cyclohexenes after the epimerization of the Diels–Alder cycloadducts.

Having established the *trans*-relationship of the substituents on cyclohexene **1.121**, a Barbier-type cyclization was employed to build the decalin core. A series of functional group interconversions (four steps) transformed carboxylic acid **1.121** into aldehyde **1.122**. A SmI₂-induced Barbier-type cyclization followed by DMP oxidation of the resulting alcohol provided *trans*-**1.115**. Homologation of ketone **1.115** to carboxylic acid **1.125** required several steps. Conversion of ketone **1.115** into aldehyde **1.123** was achieved by treatment with *p*-toluenesulfonylmethyl isocyanide (TosMIC) and subsequent reduction of the nitrile. Alkylation of aldehyde **1.123** with *p*-methoxybenzyl chloromethyl ether and Wolff–Kishner

reduction afforded decalin **1.124**. This sequence of events was required as alkylation of **1.123** yielded the equatorial alkylation product exclusively. Cleavage of the PMB ether, oxidation of the resulting alcohol with DMP, and Lindgren oxidation provided carboxylic acid **1.125**. Installation of the isonitrile was accomplished over a three-step sequence. A Curtius rearrangement of carboxylic acid **1.125** followed by reduction of the isocyanate generated formamide **1.126**. Lastly, dehydration of formamide **1.126** completed the synthesis of (+)-10-isocyano-4-cadinene (**1.68**).

Scheme 1.8. Matsuda's synthesis of (+)-10-isocyano-4-cadinene (**1.68**).⁷³



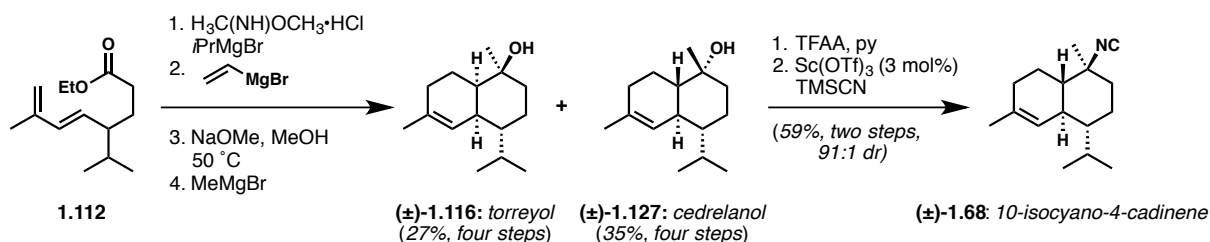
Although Matsuda and co-workers completed the first synthesis of **1.68** and the only enantioselective one to date, only 6 steps of the 29-step synthesis form carbon-carbon bonds. While the *trans* relationship of the substituents on cyclohexene **1.119** could be established exclusively by isomerization of the Diels–Alder adduct, Lewis acid-catalysis failed to control the

C6–C7 stereochemical relationship. Furthermore, after accessing decalone **1.115** in 19 steps, Matsuda and co-workers take an additional ten steps to accomplish the isonitrile installation.

1.6.3 Shenvi's Synthesis of (±)-10-Isocyano-4-cadinene from (±)-Cedrelanol

Recently, Shenvi and co-workers completed a number of syntheses of simple ICTs to demonstrate the utility of their method for the synthesis of isonitriles from alcohols (Scheme 1.4b).⁵⁴ Included in their paper was the synthesis of (±)-10-isocyano-4-cadinene (**1.68**), which employed a modified version of Taber's synthesis of torreyol (Scheme 1.9). Shenvi and co-workers employed the same general strategy, but with the addition of an epimerization step of intermediate *cis*-decalone **1.115** prior to nucleophilic methylation, ultimately providing both (±)-torreyol (**1.116**) and (±)-cedrelanol (**1.127**). Exposure of the trifluoroacetate of cedrelanol to scandium(III) triflate in TMSCN afforded (±)-10-isocyano-4-cadinene (**1.68**). Shenvi's synthesis of **1.68** (8 steps) is significantly shorter than Matsuda's synthesis (29 steps). Shenvi and co-workers' major contribution to this synthesis was the development of a method to prepare isonitriles from alcohols stereoselectively. With this method, they elaborated *trans*-decalone **1.115** to **1.68** in only three steps; Matsuda and co-workers used ten steps for this seemingly simple transformation. While the Shenvi synthesis is racemic, application of an asymmetric Michael reaction of isovaleraldehyde (**1.108**) and ethyl acrylate (**1.109**) could render the synthesis enantioselective.

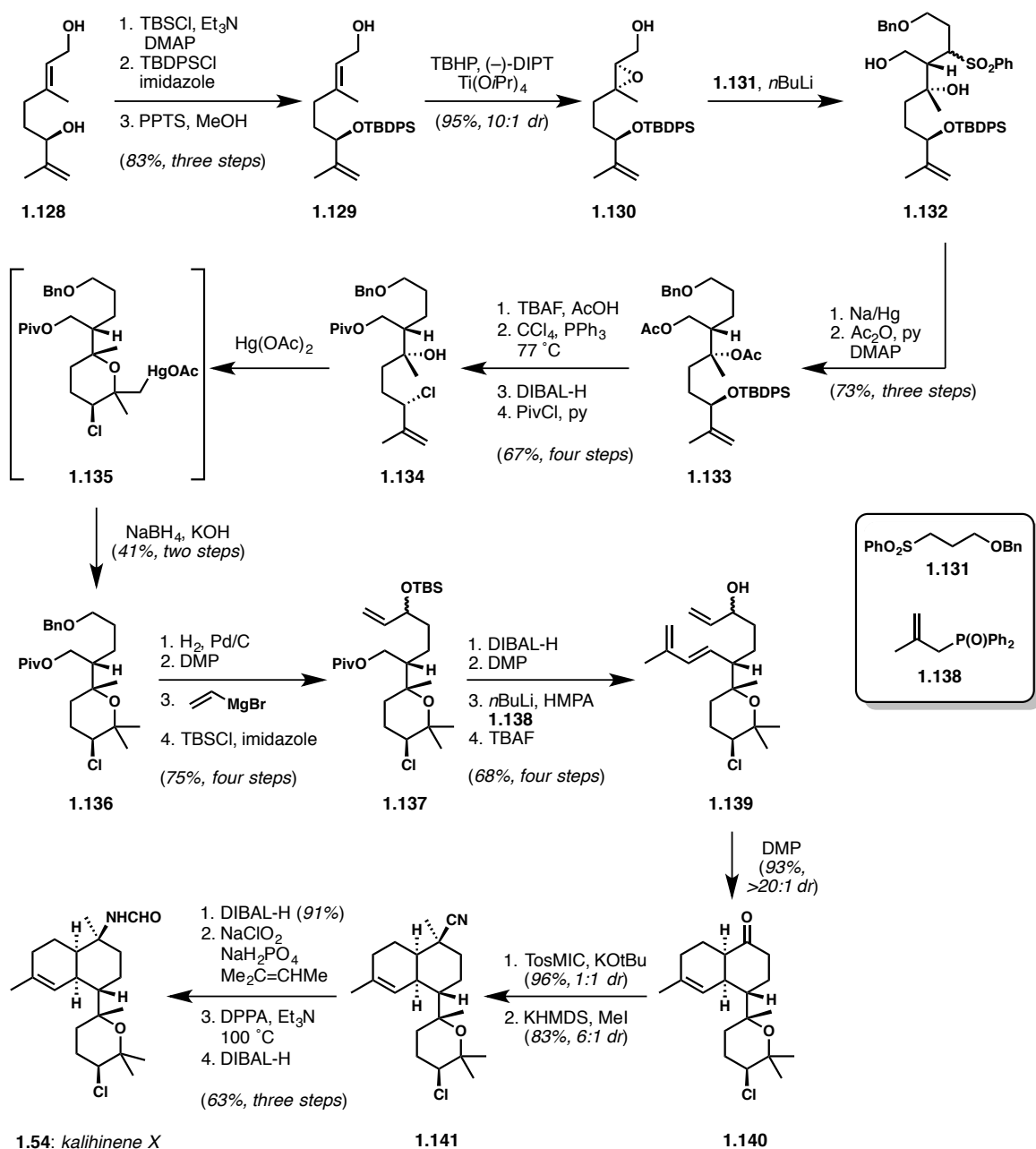
Scheme 1.9. Shenvi's synthesis of (±)-10-isocyano-4-cadinene (**1.68**).⁵⁴



1.6.4 Yamada's Synthesis of Kalihinene X

In 2002, Yamada and co-workers reported the synthesis of kalihinene X (**1.54**) (Scheme 1.10), the first synthesis of any of the kalihinanes, although Wood and co-workers had published synthetic studies toward the kalihinanes during the previous year.^{29,32} Kalihinene X (**1.54**) features a *cis*-decalin core characteristic of the kalihinenes with a C4–C5 alkene, a pendant chloride-containing THP, and a formamide at C10. Yamada approached kalihinene X in three stages: (1) THP formation after independently setting the C7, C11, and C14 stereogenic centers, (2) construction of the decalin core using an intramolecular Diels–Alder reaction, and (3) installation of the tertiary alkyl formamide. Their approach began with a three-step sequence to accomplish the mono-protection of diol **1.128**, which was derived from geranyl acetate in four steps. Sharpless asymmetric epoxidation of allylic alcohol **1.129** provided epoxide **1.130**. Nucleophilic ring opening of epoxide **1.130** with the anion of sulfone **1.131** yielded diol **1.132**, establishing the correct C7/C11 stereochemical relationship. Reductive cleavage of the sulfone and acetate protection of the alcohols provided diacetate **1.133**. Cleavage of the silyl ether and S_N2 displacement of the allylic alcohol with a chloride nucleophile set the C14 stereochemistry of the alkyl chloride. Subsequent reduction of the acetates and protection of the primary alcohol as the pivalate ester yielded alcohol **1.134**, the THP precursor. Treatment of **1.134** with mercury(II) acetate effected a 6-*exo* oxymercuration to form THP **1.136** after reduction of intermediate organomercurial **1.135**.

Scheme 1.10. Yamada's synthesis of kalihinene X (**1.54**).²⁹



Having successfully constructed the THP, Yamada and co-workers tackled the *cis*-decalin, using a strategy analogous to that employed in Taber's torreyol synthesis. Elaboration of benzyl alcohol **1.136** to TBS ether **1.137** proceeded over a four-step sequence to install the dienophile for the intramolecular Diels–Alder cycloaddition. The requisite diene was appended by cleavage of the pivalate ester of **1.137**, oxidation of the resulting alcohol to the

aldehyde, and Horner–Wadsworth–Emmons olefination with phosphonate **1.138**. Subsequent deprotection of the TBS ether provided THP **1.139**. After DMP oxidation of allylic alcohol **1.139**, the intramolecular Diels–Alder cyclization occurred spontaneously to afford *cis*-decalin **1.140** with high diastereoselectivity. Yamada and co-workers accomplished the formamide installation in an additional six steps. A Van Leusen reaction converted ketone **1.140** into a nitrile, and alkylation of the nitrile anion from predominantly the convex face provided decalin **1.141**. Nitrile reduction and Lindgren oxidation afforded a carboxylic acid, which was converted into kalihinene X (**1.54**) by a Curtius rearrangement and reduction of the resulting isocyanate.

Yamada and co-workers took advantage of the high diastereoselectivity of the intramolecular Diels–Alder cycloaddition to forge the *cis*-decalin core of the kalihinenes, but the iterative installation of the C7, C11, and C14 stereocenters and the Curtius rearrangement employed to install the formamide detracted from the efficiency of the synthesis, which was completed in 32 steps from geranyl acetate.

1.6.5 Wood's Synthesis of Kalihinol C

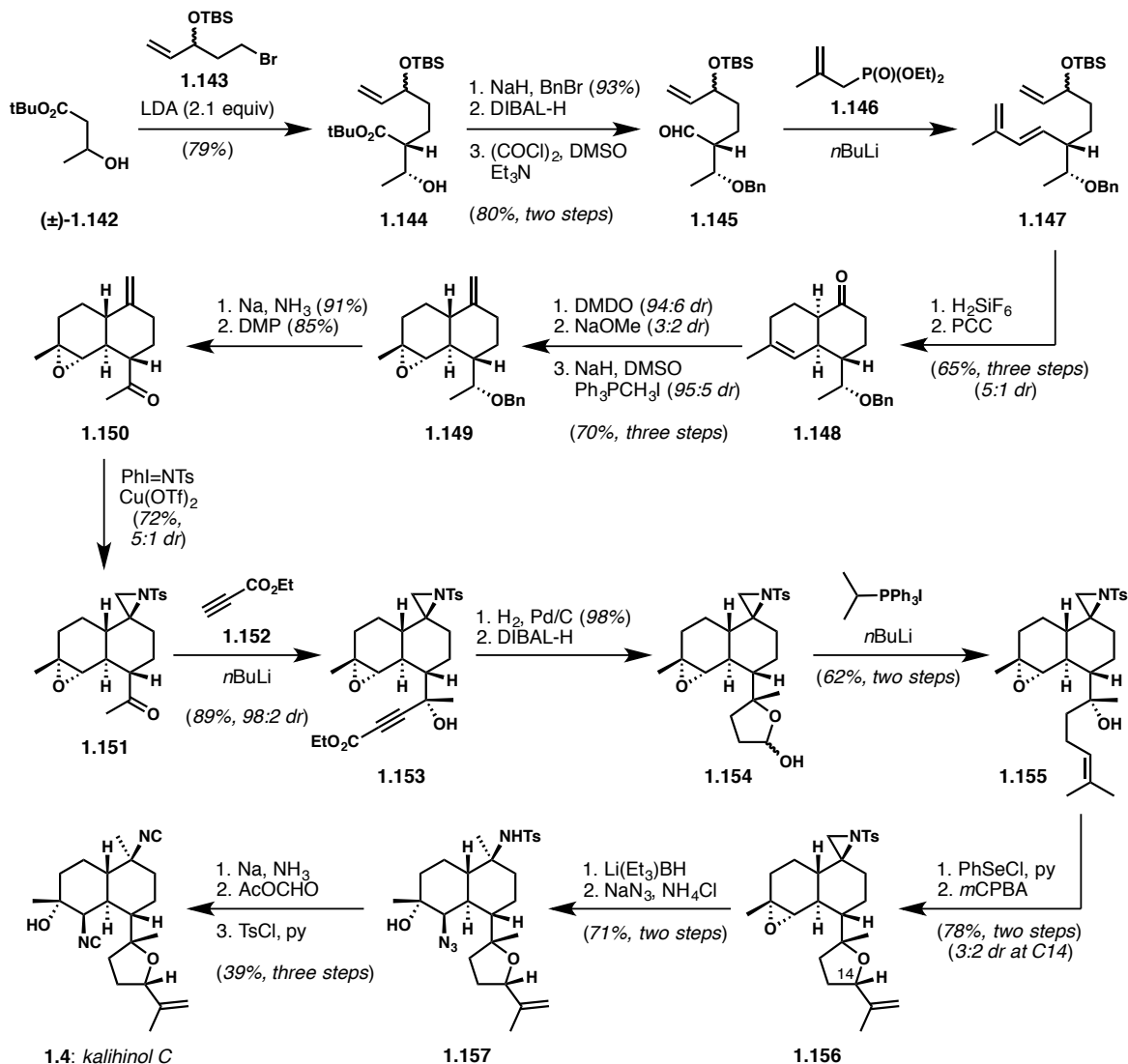
In 2004, Wood and co-workers reported the synthesis of kalihinol C (**1.4**), following up their initial studies toward the decalin framework.^{32,68} The *trans*-decalin core of kalihinol C (**1.4**) is highly functionalized, featuring a C10 isonitrile, a C4 hydroxyl *anti* to a C5 isonitrile, and a pendant isopropenyl-containing THF. Like Yamada and co-workers, Wood and co-workers employed a Diels–Alder cycloaddition to construct the decalin core, but instead appended the THF onto the completed core (Scheme 1.11). They initiated their synthesis with a Fráter–Seebach alkylation of **1.142** to afford *anti*-aldol product **1.144** with the precursor to the dienophile for the IMDA in place. Benzyl ether formation and a two-step transformation of the *t*-butyl ester to an aldehyde provided ester **1.145**. Synthesis of the diene by Horner–Wadsworth–

Emmons olefination followed by cleavage of the TBS ether and oxidation of the allylic alcohol to the enone triggered the IMDA cycloaddition, affording *cis*-decalone **1.148** as the major diastereomer (5:1 dr). Epoxidation of the alkene with DMDO and treatment with sodium methoxide provided a 3:2 mixture of *trans*- and *cis*-decalones, which converged to *trans*-decalin **1.149** after Wittig olefination. The success of this dynamic resolution of the mixture of *trans*- and *cis*-decalones relies on two factors: (1) rapid equilibration of the two decalones, and (2) a difference in reaction rate. Wittig olefination of the *trans*-decalone occurs faster than olefination of the *cis*-decalone. Because the basic reaction conditions allowed for rapid equilibration of the *trans*- and *cis*-decalones, the mixture of decalones funneled to *trans*-decalin **1.149** via the lower energy reaction pathway. Cleavage of the benzyl ether and DMP oxidation yielded ketone **1.150**.

After completing a stereoselective synthesis of the *trans*-decalin core, Wood and co-workers focused on functionalization of the core. Diastereoselective copper-catalyzed aziridination of exocyclic alkene **1.150** led to aziridine **1.151**. While Wood and co-workers initially tried to convert **1.151** into alcohol **1.155** directly with the addition of homoprenyl Grignard, they found that nucleophilic addition into sterically hindered ketone **1.151** could only be accomplished with *sp*-hybridized nucleophiles. Therefore, the synthesis of **1.155** took an additional three steps. Nucleophilic addition of the anion of ethyl propiolate (**1.152**) followed by reduction of the alkyne and lactol formation yielded **1.154**, which after Wittig olefination provided decalin **1.155**. THF closure was accomplished by selenoetherification and subsequent elimination. While the THF ring was formed exclusively, only modest levels of diastereoselectivity were observed (3:2 in favor of **1.156**). Reductive ring opening of the aziridine (**1.156**) and epoxide azidolysis provided azide **1.157**. Tosyl deprotection and azide

reduction were achieved in a single step, and formylation and dehydration of the resulting diamine afforded kalihinol C (**1.4**).

Scheme 1.11. Wood's synthesis of kalihinol C (**1.4**).⁶⁸



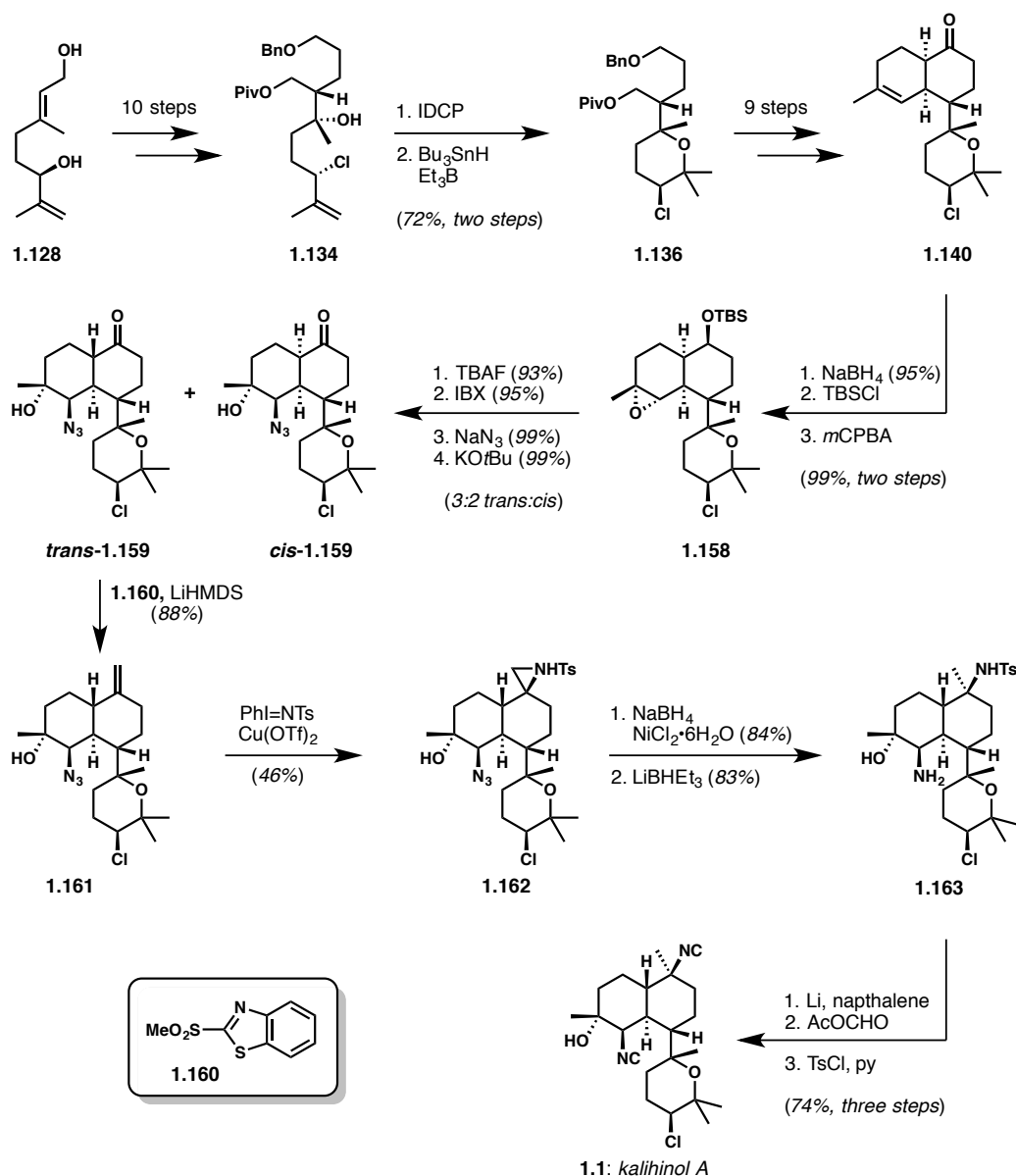
Although their synthesis of kalihinol C ultimately suffered from poor diastereoselectivity in the formation of the THF and required 26 steps to complete, Wood and co-workers discovered several solutions to synthetic problems along the way. For example, while epimerization of the epoxide derived from **1.148** afforded only modest mixtures of *trans*- and *cis*-decalones (3:2 dr), the *trans*-decalin **1.149** was isolated almost exclusively after Wittig olefination. Furthermore,

Wood and co-workers used the C7 stereocenter to control nucleophilic addition into ketone **1.151**, setting the stereochemistry at C11. Lastly, they found that aziridination of an exocyclic alkene and reductive ring opening of the aziridine lead to an equatorial amine, the precursor to the C10 equatorial isonitrile. This aziridination/reductive ring opening sequence was significantly more efficient than the other methods for the synthesis of tertiary alkyl isonitriles that were known at the time (*i.e.* Curtius rearrangement of a carboxylic acid).

1.6.6 Miyaoka's Synthesis of Kalihinol A, Kalihinol Y, and 10-Epi-kalihinol I

In 2011, Miyaoka and co-workers reported the synthesis of kalihinol A (**1.1**), the kalihinane with the most potent antimalarial activity to date, and later used synthetic intermediates to make kalihinol Y (**1.11**), and 10-epi-kalihinol I (**1.17**).^{30,69} Kalihinol A (**1.1**) has the same functionalized decalin framework as kalihinol C (**1.4**), but bears the same pendant chloro-THP as kalihinene X (**1.54**). In their synthesis of kalihinol A (**1.1**), Miyaoka and co-workers combined their previous strategy for the synthesis of the THP appendage and the decalin core with Wood's strategy for the isonitrile installations (Scheme 1.12). Miyaoka and co-workers prepared decalin **1.140** from geranyl derivative **1.128** in a sequence nearly identical to the first generation synthesis of **1.140** (Scheme 1.10), making a few improvements along the way. The only major difference in this second generation synthesis is that THP formation was accomplished *via* an intramolecular iodoetherification and reductive deiodination sequence rather than oxymercuration and reduction to afford THP **1.136**, although these two cyclization methods are conceptually identical.

Scheme 1.12. Miyaoka's synthesis of kalihinol A (**1.1**). (IDCP = iodonium di-*sym*-collidine perchlorate).³⁰

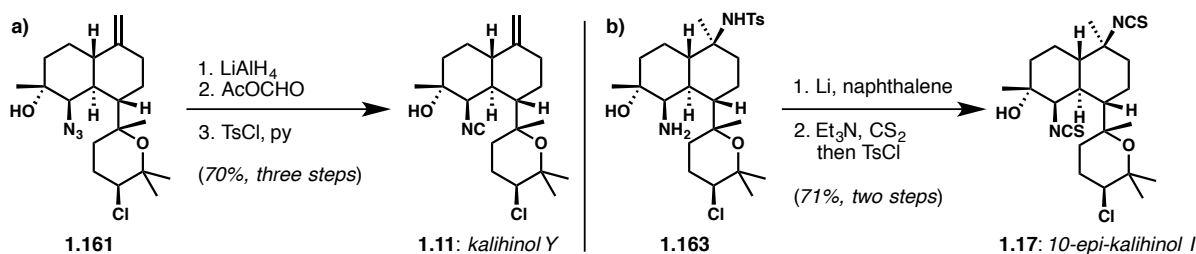


With a 21-step sequence to *cis*-decalin **1.140**, Miyaoka and co-workers turned to the Wood strategy for the installation of the isonitriles. Unfortunately, epoxidation of **1.140** suffered from poor diastereoselectivity, yielding unfavorable mixtures of β - and α -epoxides. However, after ketone reduction and TBS protection, epoxidation with *m*CPBA led to α -epoxide **1.158** as the only product. Deprotection of the TBS ether, IBX oxidation, and epoxide azidolysis provided *cis*-decalin **1.159**. Exposure of *cis*-decalin **1.159** to potassium *tert*-butoxide effected C1

epimerization, leading to a 3:2 mixture of *trans*- and *cis*-**1.159**. Julia-Kocienski olefination of *trans*-**1.159** with 2-(methylsulfonyl)benzothiazole installed the exocyclic alkene of **1.161**. Application of the same copper-catalyzed aziridination employed by Wood yielded aziridine **1.162**, which was converted to amine **1.163** by reduction of the azide and reductive ring-opening of the aziridine. Finally, tosyl deprotection, formylation of the diamine, and dehydration afforded kalihinol A (**1.1**).

Miyaoka and co-workers also prepared kalihinol Y (**1.11**) and 10-*epi*-kalihinol I (**1.17**) from intermediates in their synthesis of kalihinol A (**1.1**). Reduction of azide **1.161** to the amine and subsequent formylation and dehydration provided kalihinol Y (**1.11**) (Scheme 1.13a). Tosyl deprotection of **1.163** and conversion of the diamine to the diisothiocyanate by decomposition of the dithiocarbamic acid salt yielded 10-*epi*-kalihinol I (**1.17**) (Scheme 1.13b). While Yamada and Miyaoka's divergent synthetic strategy allowed them to elaborate one common intermediate, *cis*-decalin **1.140**, to kalihinene X (**1.54**), kalihinol A (**1.1**), kalihinol Y (**1.11**), and 10-*epi*-kalihinol I (**1.17**), they were limited to the synthesis of THP kalihinanes. Furthermore, the synthesis of *cis*-decalin **1.140** takes 25 steps from geranyl acetate, and the isonitrile installations for kalihinol A (**1.1**) require an additional 14 steps.

Scheme 1.13. Miyaoka's synthesis of (a) kalihinol Y (**1.11**) and (b) 10-*epi*-kalihinol I (**1.17**).⁶⁹



1.7 A Unified Strategy for the Synthesis of the Kalihinanes and Analogues

Although kalihinol A is the most potent of all ICTs tested to date, few kalihinanes have been studied for antimalarial properties. While Yamada, Wood, and Miyaoka completed

syntheses of several kalihinanes, the synthetic material was not subjected to the evaluation of antimalarial activity. Because of the wealth of structural diversity in the kalihinanes, an efficient synthesis providing naturally occurring kalihinanes as well as synthetic analogues would allow for an evaluation of SAR. Furthermore, a strategy amenable to the synthesis of biological probe molecules would provide insight into the mode of action of the kalihinanes against *Plasmodium* spp., which remains unclear. Therefore, we initiated a unified synthetic strategy that would ideally be applicable to many members of the kalihinane family. Our novel strategy targets the attached ring motif in a way distinct from previous approaches, allowing for the rapid construction of the decalin core. In the following chapters, our synthetic efforts toward naturally occurring kalihinanes (Chapter 2) and unnatural analogues (Chapter 3) are described. Additionally, studies on antimalarial activity and preliminary determination of SAR are included in Chapter 3.

1.8 Notes and References

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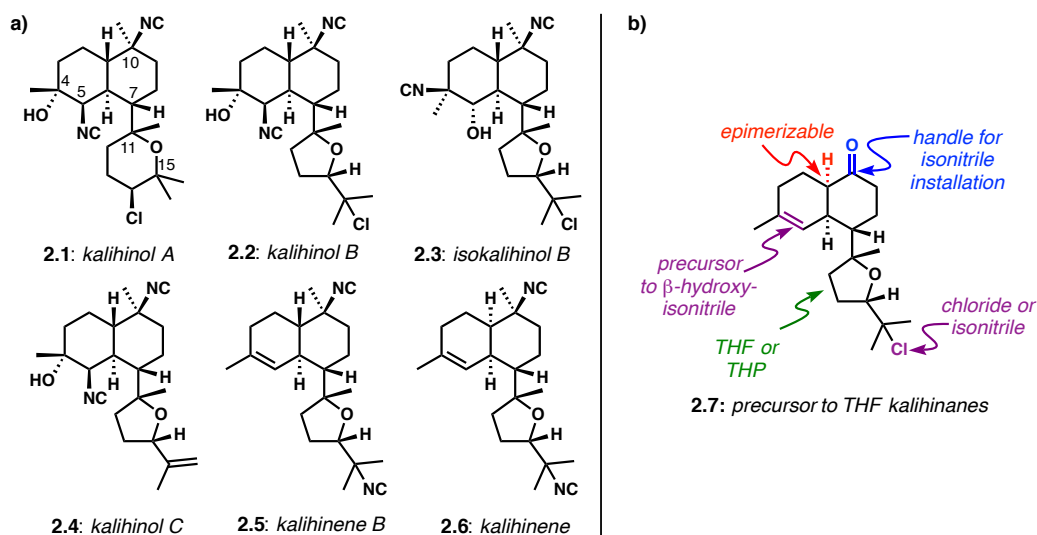
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CHAPTER 2: A UNIFIED SYNTHETIC APPROACH TOWARD THE KALIHINANES

2.1 Introduction

The structural diversity and complexity of the kalihinanes make them interesting synthetic targets; they share several structural features that might enable the design of a unified synthesis (Figure 2.1a). Virtually, all kalihinanes contain a *trans*- or a *cis*-decalin core with a C10 isonitrile, isothiocyanate, or formamide and a pendant THP or THF at C7. While the kalihinenes differ from the kalihinols and isokalihinols in their C4–C5 functionalization, we envisioned the β -hydroxy-isonitrile of the kalihinols and the isokalihinols would arise from the C4–C5 alkene in the biogenetic sense *via* epoxidation and ring opening with trimethylsilyl cyanide at C4 or C5.

Figure 2.1. (a) Select kalihinanes targeted in our unified strategy. (b) Key intermediate for our divergent synthesis.

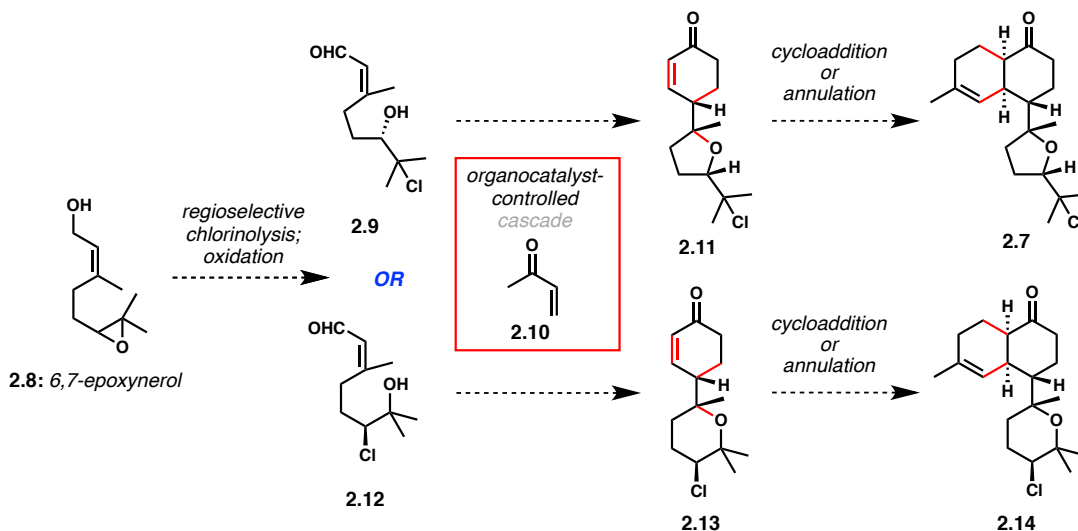


Decalone **2.7** was identified as a key intermediate in our unified approach toward the THF kalihinanes, containing three important features (Figure 2.1b): (1) the C10 ketone would serve as a functional handle for isonitrile installation, and would facilitate C1 epimerization for access to the *trans*-decalin core of the kalihinols (*e.g.* **2.1**); (2) the C4–C5 alkene, which is

retained in the kalihinenes (*e.g.* **2.5** and **2.6**), would function as the precursor to the β -hydroxy-isonitrile in the kalihinols (*e.g.* **2.1** and **2.2**) and the isokalihinols (*e.g.* **2.3**); (3) the C15 chloride would provide direct access to kalihinol B (**2.2**) and isokalihinol B (**2.3**), and would facilitate late-stage divergence to access several THF kalihinanes. For example, elimination of the C15 chloride would provide kalihinol C (**2.4**), and conversion of the C15 chloride into an isonitrile would address kalihinanes with a C15 isonitrile (*e.g.* **2.5** and **2.6**). A similar decalone bearing a pendant THP in place of the THF would serve as a key intermediate for late-stage diversification of the THP kalihinanes.

With these targets in mind, we designed a divergent, unified approach to decalones **2.7** and **2.14** to access several THF and THP kalihinanes (Scheme 2.1). Regioselective chlorinolysis of 6,7-epoxynerol (**2.8**) and subsequent oxidation would provide chlorohydrins **2.9** and **2.12**. An organocatalyst-controlled cascade featuring an oxa-Michael/Robinson annulation would afford enones **2.11** and **2.13** with the attached ring motif in place. Lastly, we envisioned utilizing a Diels–Alder cycloaddition or a Piers-type annulation to prepare decalone **2.7**, the precursor to the THF kalihinanes, and decalone **2.14**, the precursor to the THP kalihinanes.

Scheme 2.1. A unified, divergent approach to key decalone intermediates **2.7** and **2.14**.

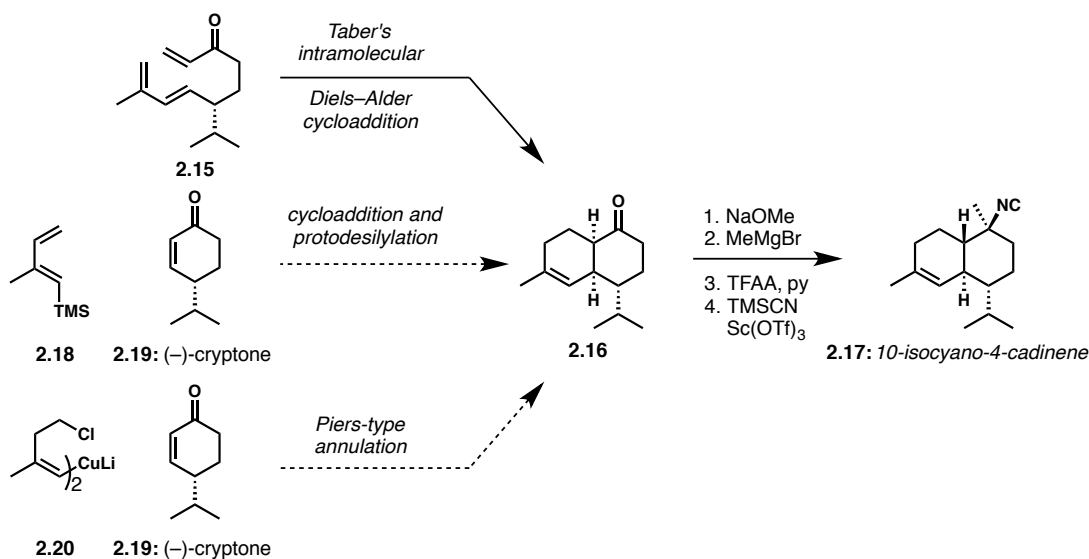


We hoped to distinguish our synthesis from previous approaches to the kalihinanes in four ways: (1) our *unified* approach would give access to THF and THP kalihinanes as well as many analogues; (2) early generation of the attached rings using an organocatalyst-controlled cascade would quickly deliver the key cyclohexenone intermediates; (3) building the ether rings *via* C11–O bond construction as opposed to the C14(15)–O bond would facilitate divergence and provide new opportunities for stereocontrol, especially for C7 and C11; (4) installation of the isonitriles in a single step would significantly reduce step count. The following chapter describes the application of our approach to the synthesis of 10-isocyano-4-cadinene (**2.17**), toward the synthesis of the THP kalihinanes, to the synthesis of kalihinol B (**2.2**), and toward the synthesis of other THF kalihinanes.

2.2 Synthesis of (±)-10-Isocyano-4-cadinene

Our synthetic studies toward the kalihinanes began with the synthesis of 10-isocyano-4-cadinene (**2.17**), which serves as a good model system for the kalihinanes, containing an isopropyl group in place of the pendant THF or THP. All previous approaches to the kalihinanes employ an IMDA first utilized in Taber's synthesis of torreyol (Scheme 2.2).¹ We recognized that a cycloaddition or an annulation onto cryptone (**2.19**), which can be prepared using an asymmetric Robinson annulation, would rapidly construct the decalin framework of 10-isocyano-4-cadinene (**2.17**).² The following section details our initial evaluation of an intermolecular Diels–Alder cycloaddition toward the decalin framework and the successful completion of a formal synthesis of (±)-10-isocyano-4-cadinene (**2.17**) using a Piers-type annulation.³

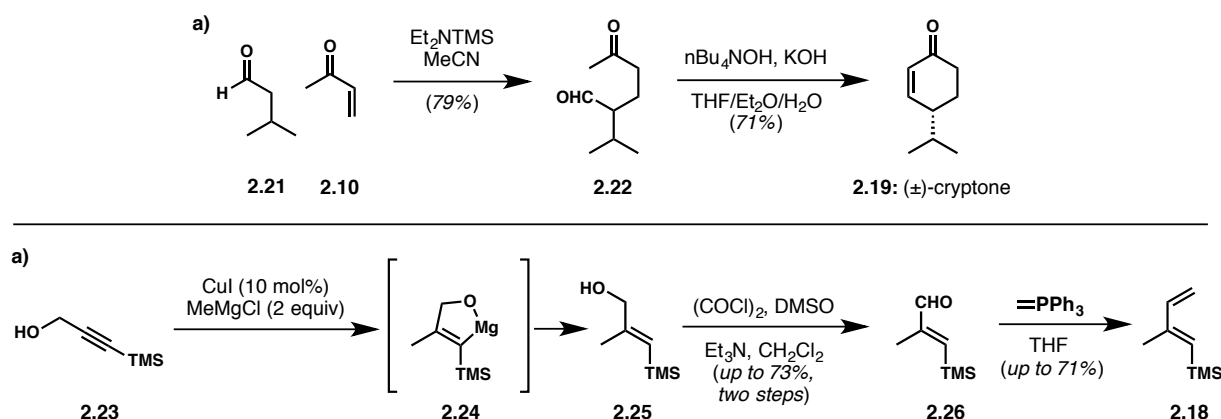
Scheme 2.2. Previous approaches to decalone **2.16** compared to our strategies.



2.2.1 An Intermolecular Diels–Alder Approach to the Decalin Core

Our strategies toward the decalin core of 10-isocyano-4-cadinene (**2.17**) began with the synthesis of cryptone (**2.19**) using a two-step Robinson annulation sequence (Scheme 2.3a).² Cryptone (**2.19**) was prepared *via* Michael addition of isovaleraldehyde (**2.18**) to methyl vinyl ketone (**2.10**) followed by an aldol condensation under phase transfer conditions. Preparation of silyl diene **2.18** proceeded over a three-step sequence (Scheme 2.3b) analogous to the known synthesis of (*E*)-1-trimethylsilyl-1,3-butadiene.⁴ Copper-catalyzed carbometalation of propargyl alcohol **2.23** afforded allylic alcohol **2.25**.⁵ Chelation of the alkoxide to vinylmagnesium species **2.24** is responsible for the high *E* selectivity of the carbometalation.⁶ Oxidation of **2.25** under Swern conditions yielded enal **2.26** in up to 73% over two steps. Wittig olefination of enal **2.26** afforded diene **2.18** in up to 71%. The variable yields of these reactions are due to the volatility of these substrates and the instability of diene **2.18** to protic conditions.

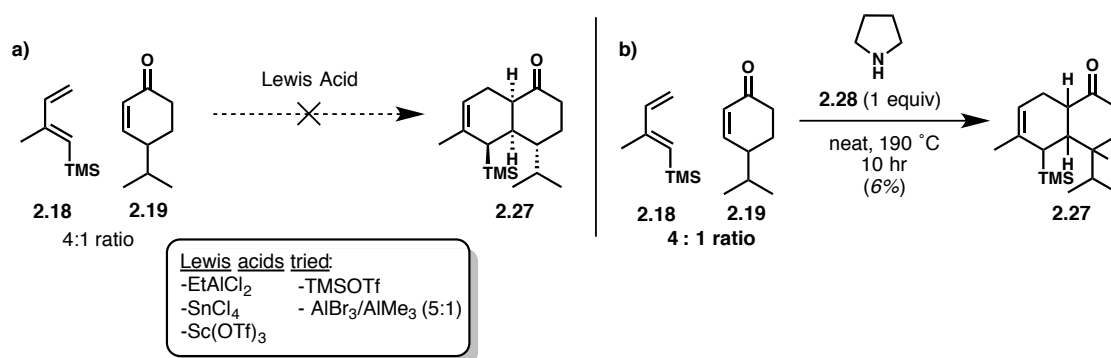
Scheme 2.3. (a) Synthesis of cryptone (**2.19**).² (b) Synthesis of silyl diene **2.18**.



With cryptone (**2.19**) and diene **2.18** in hand, various conditions were examined to effect the intermolecular Diels–Alder reaction (Scheme 2.4). Lewis acids known to promote Diels–Alder cycloadditions of enones with unactivated dienes, including EtAlCl_2 ,^{7,8} SnCl_4 ,⁹ $\text{Sc}(\text{OTf})_3$,¹⁰ and TMSOTf ,^{7,8,11} led only to decomposition of the diene and recovered enone, except for TMSOTf , which did not produce identifiable products. Additionally, a 5:1 $\text{AlBr}_3/\text{AlMe}_3$ combination,¹² which is known to catalyze sterically demanding cycloadditions, led to recovered starting material. Heating a neat 4:1 mixture of diene **2.18** and enone **2.19** to 190 °C for 36 hours did not afford cycloadduct **2.27**; however, the same conditions with the addition of one equivalent of pyrrolidine led to cycloadduct **2.27**, albeit in 6% yield.¹³ Although the stereochemistry of cycloadduct **2.27** was never determined, the *endo* product with addition of the diene to the face opposite the isopropyl group (**2.27**, Scheme 2.4a) was the predicted product.¹⁴ Furthermore, the methyl group should direct the regioselectivity of the cycloaddition. Typically, 1-substituted dienes with electron-donating groups lead to *ortho* cycloadducts. However, theoretical studies for 1-trimethylsilyl-1,3-butadiene have shown that the HOMO is only slightly polarized, and Diels–Alder cycloadditions with unsymmetrical dienophiles revealed poor regioselectivity.^{4,15} Because the trimethylsilyl group is only a poor directing group, the methyl

group on C2 of the diene should direct regioselectivity and afford desired cycloadduct **2.27**. Because this Diels–Alder reaction proved to be challenging owing to its sterically demanding nature and the poorly activated diene and dienophile, we explored a Piers-type annulation as an alternative strategy to access the decalin framework.

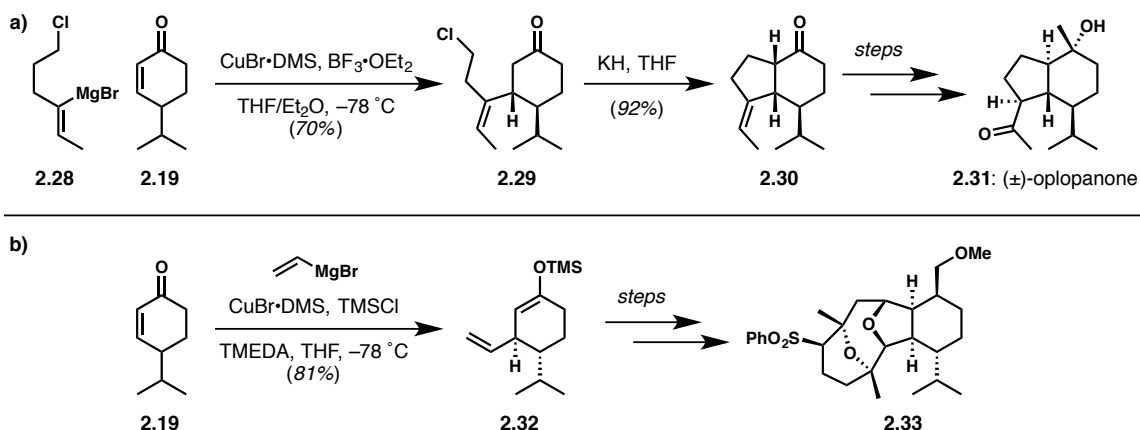
Scheme 2.4. (a) Attempted Lewis acid-catalyzed intermolecular Diels–Alder cycloaddition. (b) Intermolecular Diels–Alder cycloaddition using iminium catalysis.



2.2.2 A Piers-type Annulation to Complete the Synthesis of (±)-10-Isocyano-4-cadinene

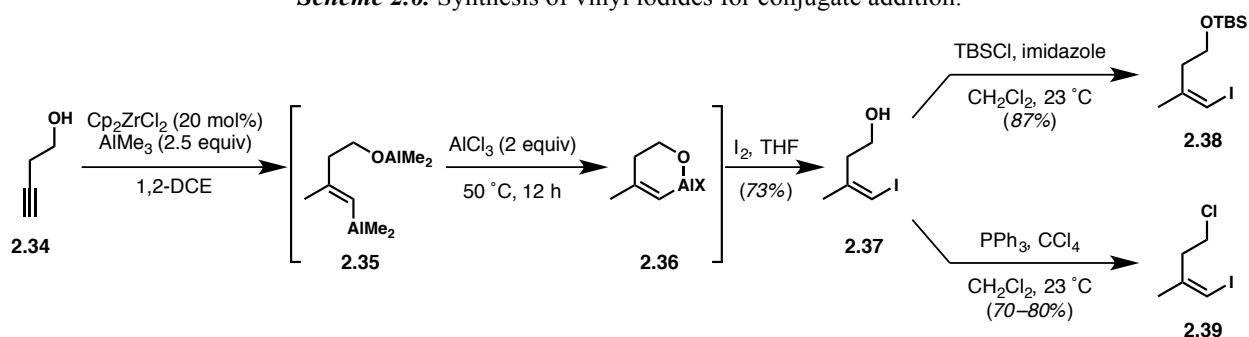
After abandoning the intermolecular Diels–Alder approach to the decalin core, we evaluated a conjugate addition/intramolecular alkylation sequence. Piers and co-workers first developed annulations of this type, which have been used extensively in natural product synthesis for ring annulation onto cyclic enones.¹⁶ Not only have several groups utilized vinyl cuprate addition to cryptone (**2.19**) in synthesis, but Piers and co-workers have also had success completing an annulation onto **2.19** in their synthesis of (±)-oplopanone (**2.31**) (Scheme 2.5).^{17–19} Several reports of successful conjugate addition to cryptone (**2.19**) utilize a cuprate derived from a Grignard reagent (*e.g.* **2.28**) and copper(II) bromide dimethylsulfide complex. The presence of the γ -isopropyl substituent results in a strong preference for *anti* addition (>20:1 dr), but requires a Lewis acid (*e.g.* BF₃•OEt₂ or TMSCl) to promote reactivity.

Scheme 2.5. Cuprate addition to cryptone (**2.19**) used in (a) Piers's synthesis of ($\pm$)-oplopanone (**2.31**) and (b) Molander's synthesis of the core of the sclerophytin diterpenes.^{17,19}



We prepared two vinyl iodides (**2.38** and **2.39**) to determine the optimal conditions for the conjugate addition with cryptone (Scheme 2.6). The desired *trans*-relationship of the methyl group and the iodide can be accessed using a zirconium-catalyzed carboalumination procedure developed by Negishi and co-workers.^{20,21} Zirconium-catalyzed carboalumination of 3-butyn-1-ol (**2.34**) initially gives the (*E*)-intermediate organoalane **2.35**. The addition of aluminum chloride promotes *E* to *Z*-isomerization (**2.35** to **2.36**), yielding the desired vinyl iodide **2.37** after treatment with iodine. Alcohol **2.37** can be easily converted into TBS ether **2.38** or chloride **2.39**.

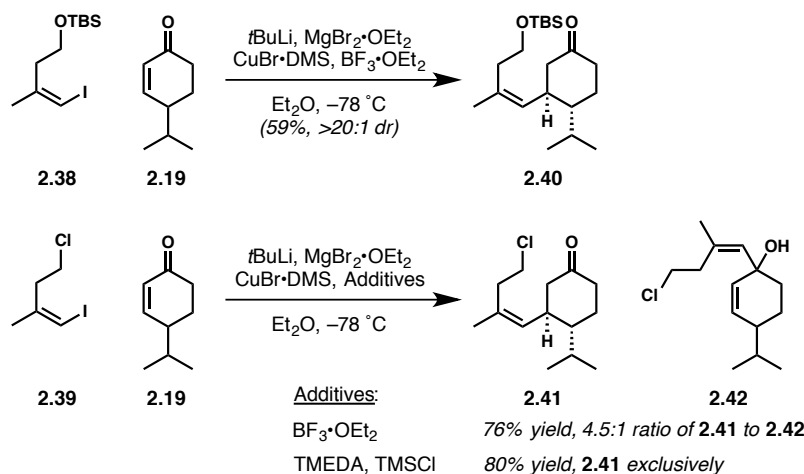
Scheme 2.6. Synthesis of vinyl iodides for conjugate addition.



We first evaluated the Piers conditions for conjugate addition to cryptone (Scheme 2.7).¹⁷ Conjugate addition of a cuprate derived from **2.38** to cryptone (**2.19**) in the presence of BF₃·OEt₂

afforded ketone **2.40** as a single diastereomer. However, application of these reaction conditions to vinyl iodide **2.39** led to a 4.5:1 ratio of 1,4- to 1,2-addition products **2.41** and **2.42** when $\text{BF}_3 \cdot \text{OEt}_2$ was used as the Lewis acid. Fortunately, we found that using TMEDA as an additive and TMSCl as the Lewis acid suppressed the competitive 1,2-addition, providing **2.41** as the sole product.¹⁹

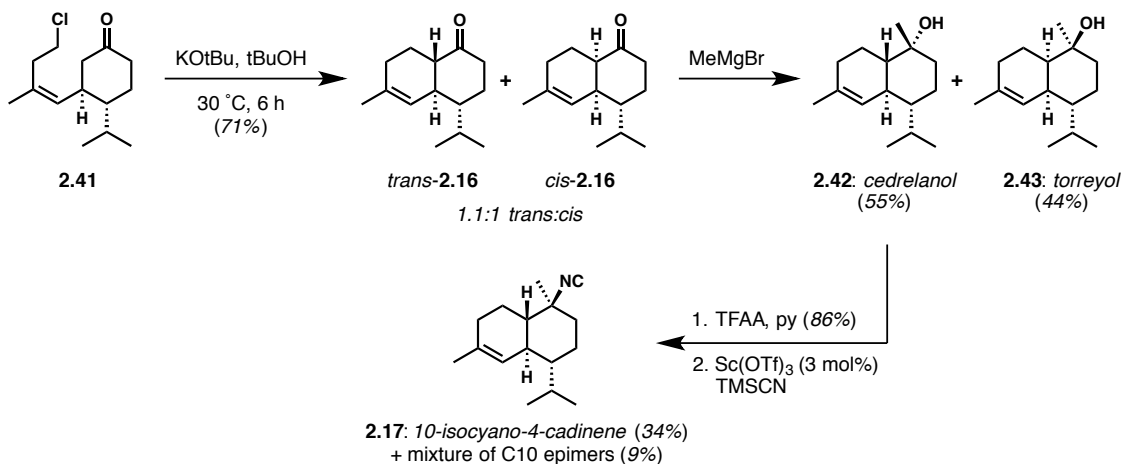
Scheme 2.7. Comparison of the conjugate addition of cuprates derived from **2.38** and **2.39**.



Intramolecular alkylation of conjugate addition product **2.41** was accomplished with potassium *tert*-butoxide, yielding decalones **2.16** as a 1.1:1 mixture of diastereomers (Scheme 2.8).²² While alkylation initially affords *cis*-decalone **2.16**, the kinetic product, excess base allows for equilibration to a thermodynamic mixture of *cis*- and *trans*-**2.16**. We also examined potassium hydride as a base for this intramolecular alkylation. However, alkylation with potassium hydride proved to be irreproducible with competitive elimination of the alkyl chloride as the major byproduct. With the synthesis of decalones **2.16**, we intercepted Shenvi's synthesis of (±)-10-isocyano-4-cadiene (**2.17**).³ Nucleophilic methylation of the mixture of decalones **2.16** afforded the sesquiterpenes cedrelanol (**2.42**) and torreyol (**2.43**). Formation of a trifluoroacetate from cedrelanol and treatment with TMSCN and scandium(III) triflate yielded (±)-10-isocyano-4-cadinene (**2.17**) in 34% along with 9% of a mixture of two diastereomers.

While this transformation was lower yielding in our hands, we were able to reproduce the stereoselective transformation reported by Shenvi and co-workers to complete the synthesis of the natural product.

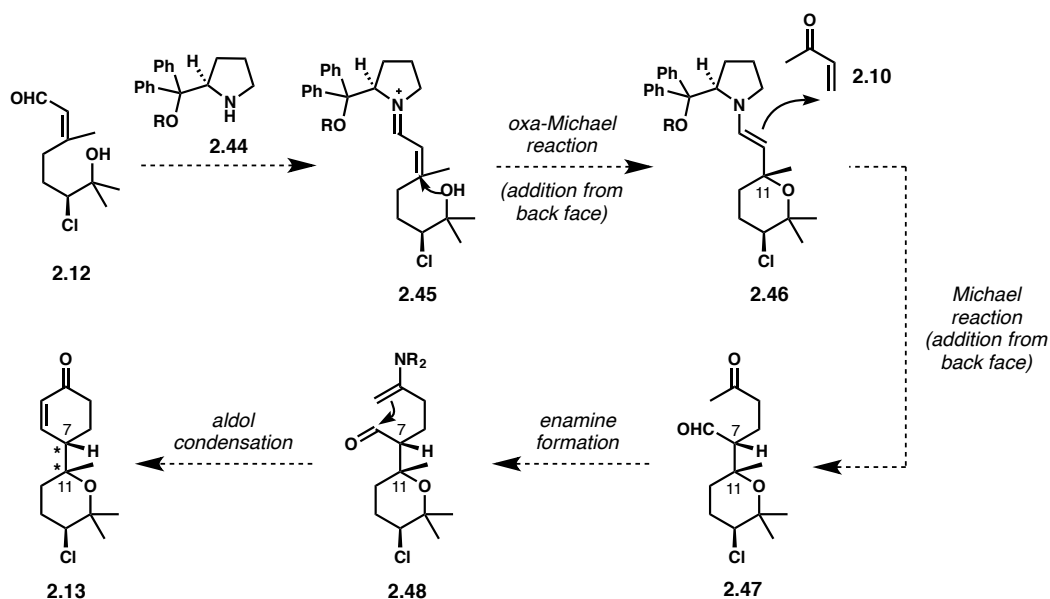
Scheme 2.8. Synthesis of (±)-10-isocyano-4-cadinene (**2.17**).



2.3 Progress Toward the Synthesis of THP Kalihinanes

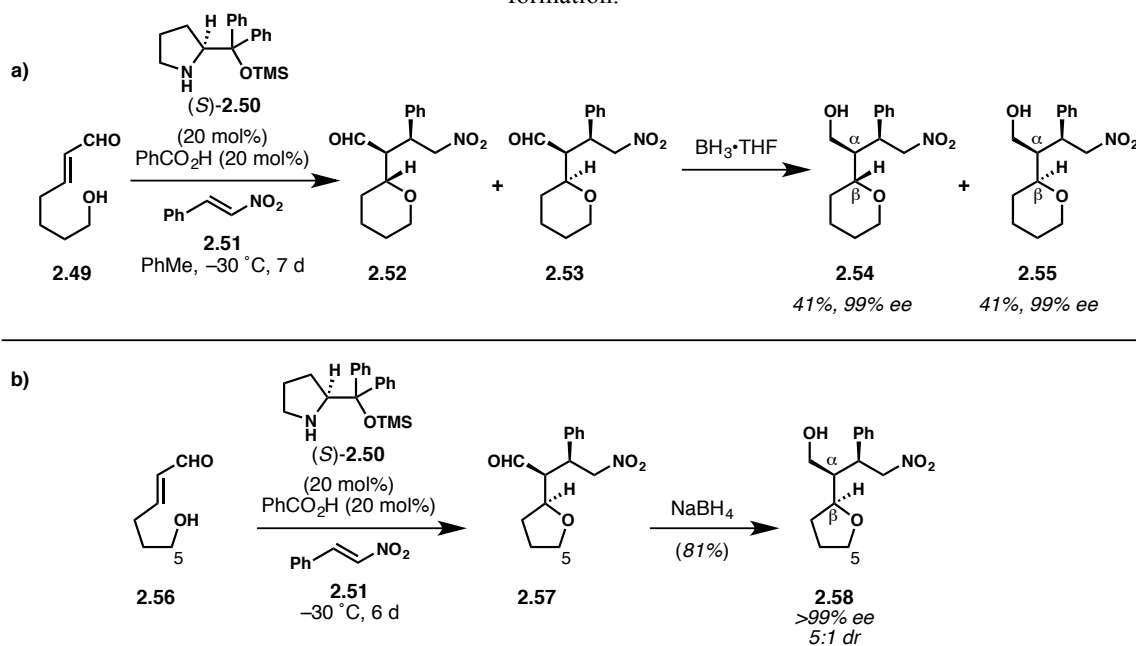
Having validated our strategy to access the decalin core of the kalihinanes using a Piers-type annulation, we evaluated the oxa-Michael/Robinson annulation sequence to prepare the cyclohexenone containing the attached ring motif characteristic of the kalihinanes (Scheme 2.9). When we designed the oxa-Michael/Robinson annulation sequence, we hoped to find an organocatalyst that would perform three functions: (1) the organocatalyst would control oxa-Michael addition of the pendant alcohol to α,β -unsaturated iminium ion **2.45**, setting the desired C11 stereocenter; (2) the organocatalyst would control Michael addition of enamine **2.46** to MVK (**2.10**), setting the C7 stereocenter; (3) the organocatalyst would effect an intramolecular aldol condensation *via* enamine intermediate **2.48** to complete the cascade, providing enone **2.13**. Not only would our proposed sequence use catalyst control to establish the C7/C11 stereochemical relationship, but it would also forge the attached ring motif early in the synthesis in a single step.

Scheme 2.9. A closer look at the proposed organocatalytic oxa-Michael/Robinson annulation cascade.



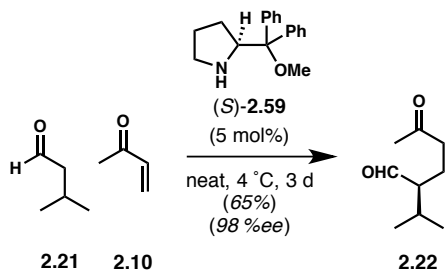
Brenner-Moyer and co-workers have examined a related oxa-Michael/intermolecular Michael cascade with β -nitrostyrene for the synthesis of THPs and THFs (Scheme 2.10).^{23,24} For unsubstituted THPs, they found that exposure of aldehyde **2.49** to diphenylprolinol silyl ether **2.50** effected an oxa-Michael/Michael cascade affording a 1:1 mixture of THPs **2.54** and **2.55** after reduction (Scheme 2.10a). For this system, the catalyst effectively controlled the α -stereocenter, but was unable to control the β -stereocenter. Unlike the THP system, treatment of enal **2.56** with diphenylprolinol silyl ether **2.50** accomplished the oxa-Michael/Michael cascade leading to **2.58** after reduction as a single diastereomer in high enantiomeric excess (Scheme 2.10b). In this case, the catalyst was able to control both the α - and β -stereocenters. Furthermore, the addition of a substituent at the 5 position of the THF had no impact on the stereochemical outcome; the catalyst continued to control both the α - and β -stereocenters. These results indicated that we might be able to find a catalyst to accomplish our proposed oxa-Michael/Robinson annulation cascade and control the C7 and C11 stereocenters.

Scheme 2.10. Related oxa-Michael/intermolecular Michael cascade for (a) THP formation and (b) THF formation.^{23,24}



Gellman and co-workers have shown that diphenylprolinol methyl ether (**2.59**) is an effective catalyst for the intermolecular Michael addition of simple aldehydes to methyl vinyl ketone (**2.10**) (Scheme 2.11).²⁵ While several classes of amines have been shown to be competent for both iminium and enamine catalysis, we first examined the diphenylprolinol catalysts because of the studies by Gellman and Brenner-Moyer.^{26,27}

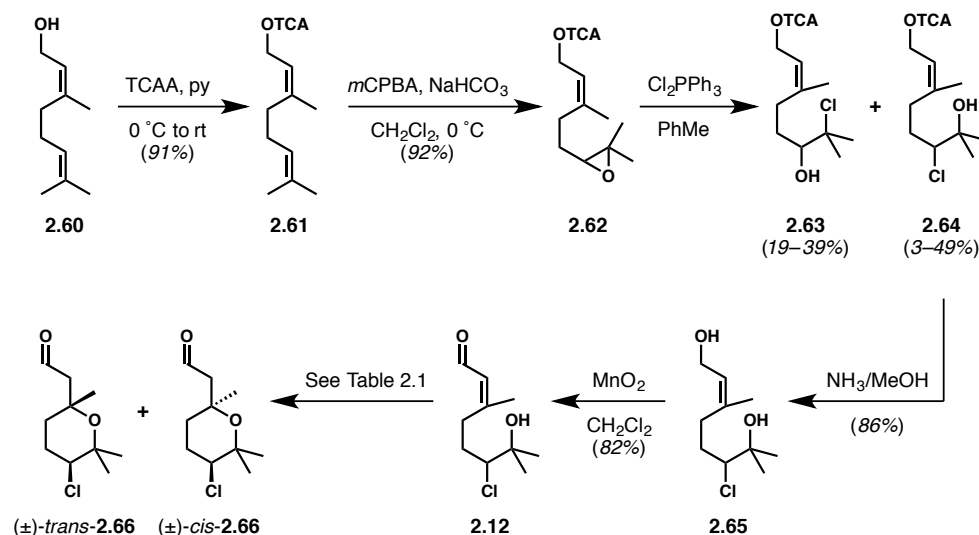
Scheme 2.11. Gellman's enantioselective organocatalytic intermolecular Michael reaction.²⁵



Studies toward THP kalihinanes initiated with the synthesis of enal **2.12**, which can be prepared from nerol in five steps *via* chlorinolysis of 6,7-epoxyneryl trichloroacetate (**2.62**) (Scheme 2.12). Epoxidation of neryl trichloroacetate (**2.61**) with *m*CPBA provided 6,7-

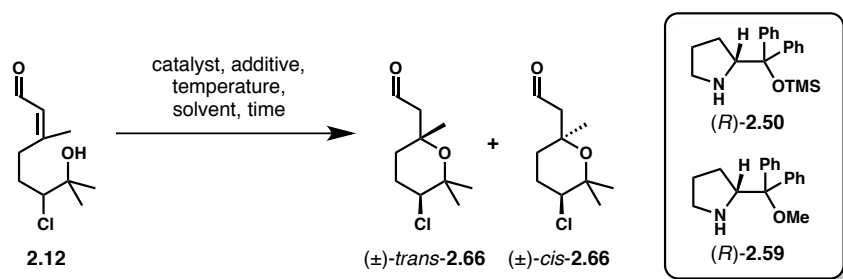
epoxyneryl trichloroacetate (**2.62**). Chlorinolysis of epoxide **2.62** with triphenylphosphine dichloride yielded a mixture of chlorohydrins **2.63** and **2.64**.²⁸ Removal of the trichloroacetate and allylic oxidation yielded enal **2.12**. This sequence required the use of the trichloroacetate protecting group instead of the more commonly used acetate owing to the sensitivity of chlorohydrin **2.64** to epoxide formation under basic conditions.

Scheme 2.12. Evaluation of the oxa-Michael reaction to make THP **2.66**.



We used enal **2.12** to determine the optimal conditions for the oxa-Michael reaction (Table 2.1). Both diphenylprolinol silyl ether **2.50** and diphenylprolinol methyl ether **2.59** are competent iminium catalysts for the oxa-Michael reaction, leading to similar conversions and diastereomeric ratios (compare entries 1 and 2). We observed similar outcomes without an additive (entry 3), with acidic additives (entries 2 and 6), and with basic additives (entry 5). Lastly, increasing the catalyst loading (compare entries 3, 8, and 9) had no impact on the reaction conversion. Because of the reversibility of the oxa-Michael reaction, we suspected that we were observing a thermodynamic distribution of products. Therefore, we subjected **2.66** (1:1.4 *trans*:*cis*) to the reaction conditions, resulting in a 3:1 mixture of **2.66** (2:1 *trans*:*cis*) and enal **2.12**, indicating that the retro-oxa Michael reaction occurred (Scheme 2.13).

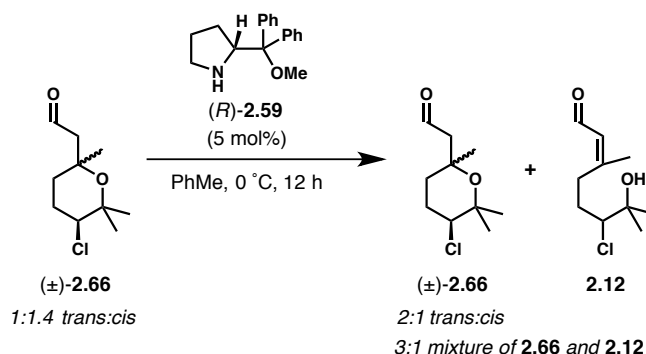
Table 2.1. Iminium-catalyzed intramolecular oxa-Michael reaction.



Entry	Catalyst (mol%)	Additive (mol%)	Temp.	Solvent	Time (h)	Conversion ^a	dr (<i>trans</i> : <i>cis</i>)
1	2.50 (20)	PhCO ₂ H (20)	0 °C	PhMe	18	62%	2:1
2	2.59 (20)	PhCO ₂ H (20)	0 °C	PhMe	18	62%	1.7:1
3	2.59 (20)	none	0 to 23 °C	PhMe	24	70%	1.7:1
4	2.59 (20)	TBAB (100)	0 to 23 °C	CH ₂ Cl ₂	48	Trace	N/A
5	2.59 (20)	LiOAc (20)	0 to 23 °C	PhMe	18	74%	1.8:1
6	2.59 (20)	CSA (20)	0 to 23 °C	PhMe	48	61%	1.5:1
7	2.59 (20)	4-NO ₂ -phenol (20)	0 to 23 °C	PhMe	6	Trace ^b	N/A
8	2.59 (30)	none	0 °C	PhMe	24	78%	1.7:1
9	2.59 (40)	none	0 °C	PhMe	24	77%	1.7:1
10	2.59 (20)	none	0 °C	PhMe ^c	24	80%	2:1
11	2.59 (20)	none	0 °C	MeOH ^c	24	45%	3.5:1

^aDetermined by integration of aldehyde peaks in the crude ¹H NMR spectrum. ^bDecomposition of starting material was observed. ^cSolvent used without drying by passage over an alumina column.

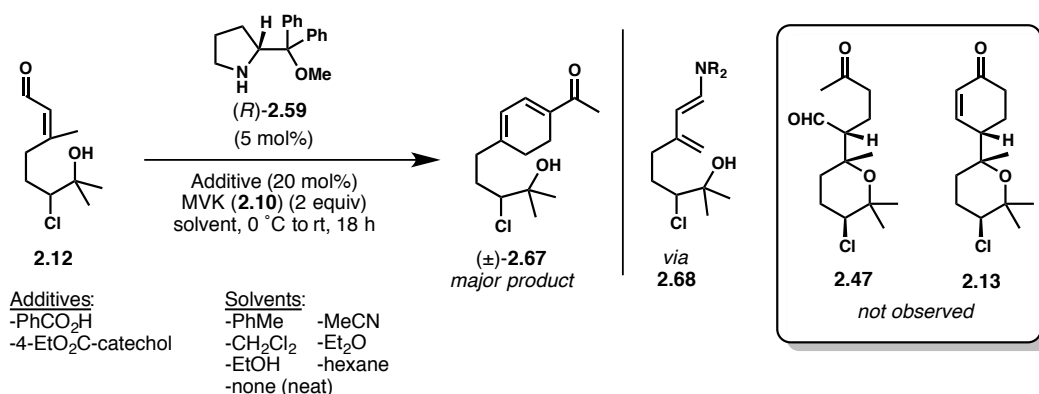
Scheme 2.13. The reversibility of the oxa-Michael reaction.



Upon exposure of enal **2.12** to prolinol catalyst **2.59** in the presence of methyl vinyl ketone (**2.10**), methyl ketone **2.67** was isolated as the major product; presumably, this product

was formed by a formal Diels–Alder cycloaddition of dienamine **2.68** and methyl vinyl ketone (Scheme 2.14).²⁹ Neither the desired intermolecular Michael adduct (**2.47**) nor the desired Robinson annulation product (**2.13**) was observed. We examined a few additives and a number of solvents, but in all cases, we observed formation of methyl ketone **2.67** as the major product of a complex mixture. We suspected that the other minor products observed were diastereomeric annulation products, a result of using racemic material. Therefore, we decided to prepare enantiopure THP **2.66** using a different method to simplify the reaction outcome. Furthermore, by starting with cyclized adduct **2.66** rather than enal **2.12**, we hoped that the intermolecular Michael reaction to afford **2.47** would outcompete the undesired annulation (**2.67**).

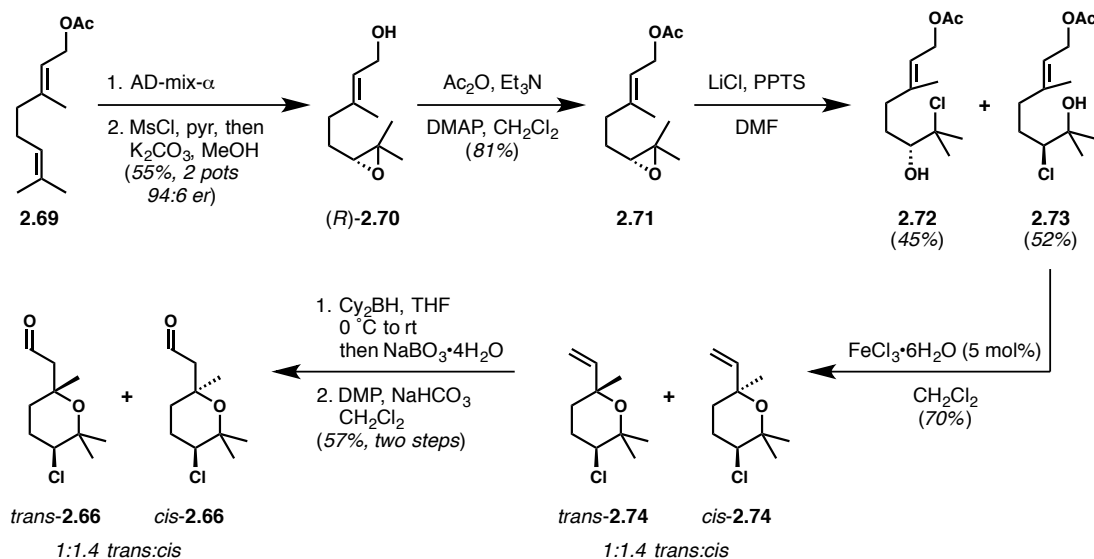
Scheme 2.14. Evaluation of the oxa-Michael/Michael cascade.



The synthesis of enantioenriched (*R*)-6,7-epoxygeraniol (**2.70**) can be accomplished in two steps using a Sharpless asymmetric dihydroxylation of geranyl acetate (**2.69**) followed by chemoselective mesylation of the secondary alcohol and epoxide formation (Scheme 2.15).³⁰ Protection of the primary alcohol as the acetate followed by epoxide chlorinolysis provided chlorohydrins **2.72** and **2.73**. We found the combination of lithium chloride and PPTS to be a reliable alternative to triphenylphosphine dichloride.^{31–33} However, we were unable to find conditions to favor the formation of **2.73** exclusively, and a 1:1.2 ratio of **2.72** to **2.73** is the best we have achieved. Iron-catalyzed cationic π -cyclization of chlorohydrin **2.73** provided a 1:1.4

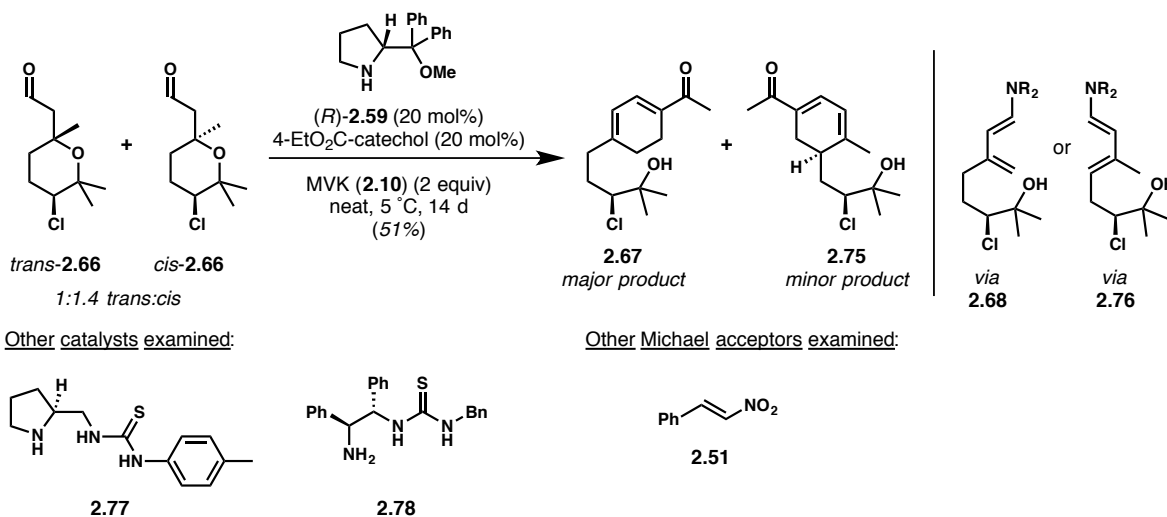
mixture of *trans*- and *cis*-THP **2.74**.³⁴ A hydroboration-oxidation/oxidation sequence afforded *trans*-aldehyde **2.66** and *cis*-aldehyde **2.66** in enantioenriched form.

Scheme 2.15. Synthesis of enantioenriched THP **2.66**.



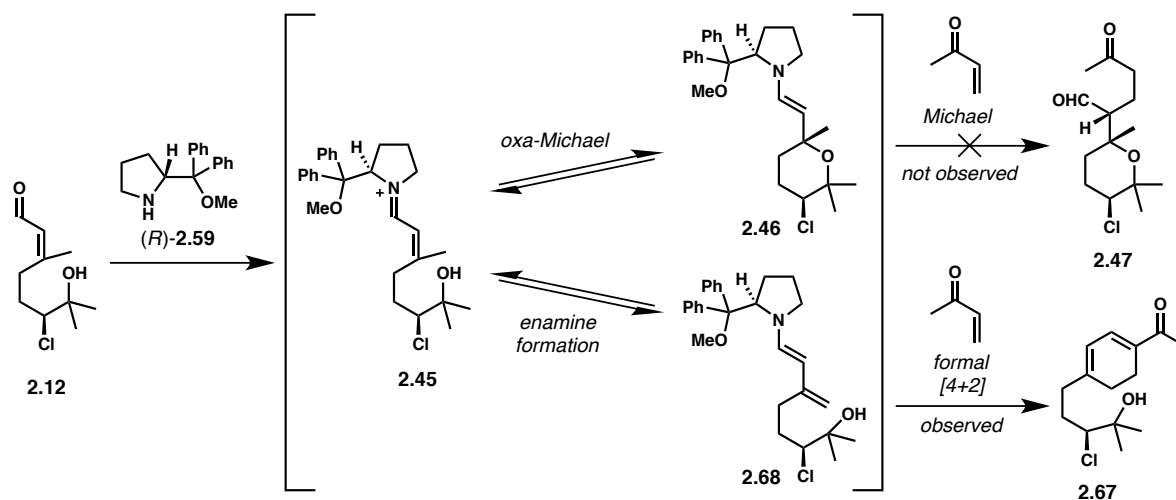
Treatment of a mixture of *trans*- and *cis*-aldehydes (**2.66**) with prolinol catalyst **2.59** and 4-EtO₂C-catechol in MVK afforded only the undesired Diels–Alder products **2.67** and **2.75**, arising from intermediate dienamines **2.68** and **2.76**, respectively (Scheme 2.16). In addition to the prolinol derived catalysts, we evaluated bifunctional thiourea catalysts **2.77** and **2.78**, which have been shown to be competent catalysts for intermolecular Michael reactions of simple aldehydes with nitroalkenes.^{35–38} Unfortunately, exposure of *trans*-**2.66** and *cis*-**2.66** to thiourea **2.77** and MVK provided methyl ketone **2.67**, along with a thermodynamic mixture of *trans*-**2.66**, *cis*-**2.66**, and retro-oxa-Michael product **2.12**. Furthermore, the use of thiourea **2.78** as the catalyst led only to recovery of starting material (**2.66**) and retro-oxa-Michael product **2.12**. Lastly, we attempted to use a more electron-deficient Michael acceptor, β -nitrostyrene (**2.51**), but again, only Diels–Alder cycloadducts resulting from reaction of dienamines **2.68** and **2.76** with β -nitrostyrene were observed.

Scheme 2.16. Attempted intermolecular Michael reaction of aldehyde **2.66**.



While we have not extensively examined all classes of organocatalysts, the thermodynamic mixture of enal **2.12** and oxa-Michael adduct **2.66** limits the success of the cascade (Scheme 2.17). We have shown that diphenylprolinol methyl ether **2.59** catalyzes the intermolecular oxa-Michael reaction of enal **2.12** via presumed intermediate α,β -unsaturated iminium ion **2.45** to provide oxa-Michael adduct **2.66** after hydrolysis of enamine **2.46**. Furthermore, oxa-Michael adduct **2.66** is thermodynamically preferred over enal **2.12**. However, the reaction of dienamine **2.68** with MVK is faster than that for enamine **2.46**, likely due to the fully substituted center at C11 of enamine **2.46**. Therefore, the starting materials funneled to the undesired annulation product (**2.67**) via the lowest energy reaction pathway. The unfavorable reaction outcome encouraged us to consider the THF ring system instead as we postulated the oxa-Michael reaction would be thermodynamically favored.

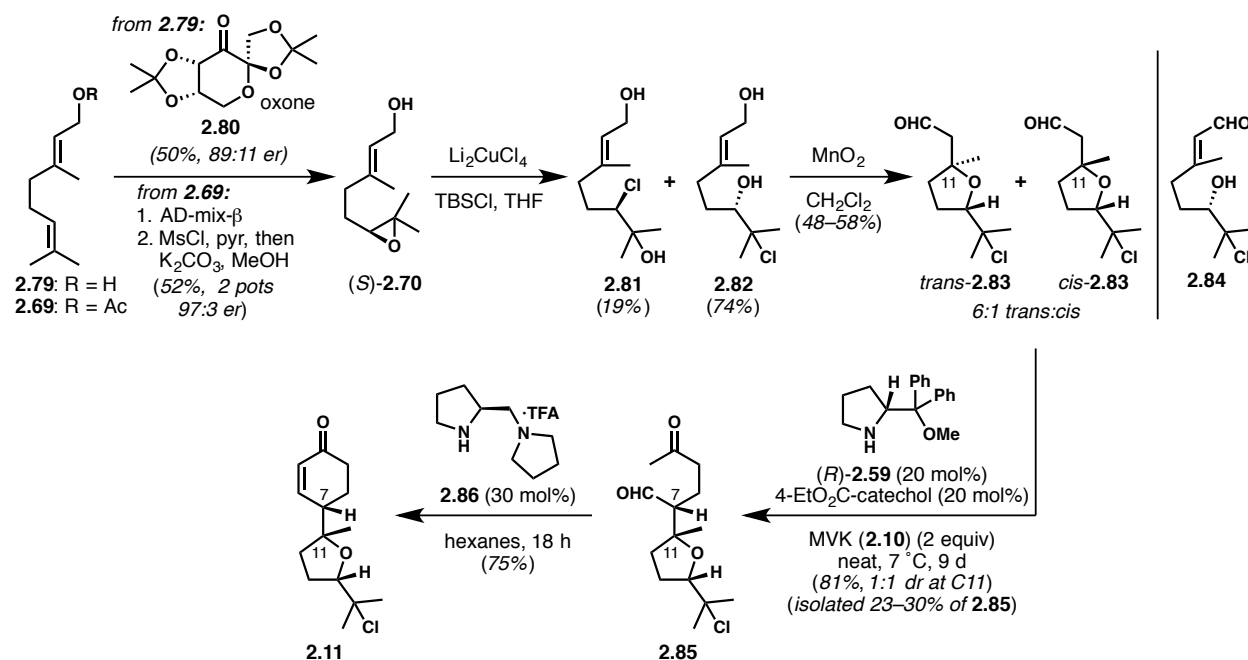
Scheme 2.17. A detailed examination of the formal Diels–Alder cycloaddition.



2.4 Synthesis of Kalihinol B

Our studies toward the kalihinanes bearing the THF appendage met with more success and have resulted in the first synthesis of kalihinol B.³⁹ Synthesis of the THF kalihinanes begins with *(S)*-6,7-epoxygeraniol (**2.70**), the enantiomer of *(R)*-**2.70** used toward the synthesis of kalihinol A (**2.1**). Shi epoxidation of geraniol (**2.79**) afforded *(S)*-6,7-epoxygeraniol (**2.70**) in one step with moderate enantioselectivity (89:11 *er*) (Scheme 2.18).⁴⁰ Alternatively, a two-pot procedure using Sharpless dihydroxylation of geranyl acetate (**2.69**) provided *(S)*-**2.70** in 97:3 *er*.³⁰ Regioselective epoxide chlorinolysis using dilithium tetrachlorocuprate in the presence of *tert*-butyldimethylchlorosilane yielded desired chlorohydrin **2.82** (74% yield) along with 16% of the regioisomer (**2.81**).⁴¹ Allylic oxidation triggered cyclization of the secondary alcohol, affording THF **2.83** with predominantly the incorrect C11 configuration. Unlike the allylic oxidation of **2.65** in our studies toward the THP kalihinanes, we never observed enal **2.84**. While the spontaneous *oxa-Michael* reaction gave THF **2.83** with the undesired C11 configuration, the reversibility of the *oxa-Michael* reaction during the subsequent intermolecular *Michael* reaction provided a pathway for correction of the C11 stereocenter.

Scheme 2.18. Evaluation of the oxa-Michael/Robinson annulation sequence toward kalihinol B (**2.2**).

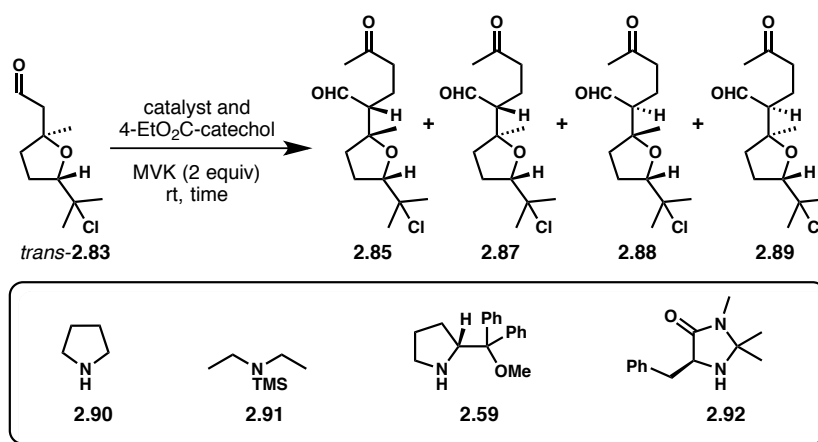


Exposure of aldehyde **2.83** to prolinol catalyst **2.59** effected the desired intermolecular Michael reaction, resulting in a 1:1 mixture of Michael adducts epimeric at C11 with 23–30% of **2.85** isolated. The catalyst effectively controlled the configuration at C7 and facilitated a partial correction of the C11 center, a result of the reversibility of the oxa-Michael reaction under the reaction conditions.^{23,24} In fact, the diastereomeric ratio of **2.83** (1.2:1 favoring the desired *cis*-isomer) rapidly reaches equilibrium under the reaction conditions. However, unlike the THP system, the equilibrium for the THF oxa-Michael reaction completely favors the cyclized products (**2.83**). As a result, the desired intermolecular Michael reaction between THF **2.83** and methyl vinyl ketone is the favored pathway rather than the formal Diels–Alder cycloaddition observed for THP kalihinanes (Scheme 2.17).

While we ultimately determined diphenylprolinol methyl ether **2.59** to be the most effective catalyst for the intermolecular Michael reaction of *trans*-**2.83** with MVK, we examined three other catalysts for this transformation (Table 2.2). When (diethylamino)trimethylsilane

(**2.91**) was used without any additives, the retro-oxa-Michael reaction was slow, leading to a higher ratio of *trans*-THFs **2.87** and **2.89** in the product distribution (entry 2).⁴² However, upon addition of ethyl 3,4-dihydroxybenzoate to the reaction mixture, equilibration of *trans*-**2.83** was observed, and (diethylamino)trimethylsilane (**2.91**) effected the intermolecular Michael reaction with low diastereoselectivity (entry 3). Diphenylprolinol methyl ether **2.59** proved to be the most effective catalyst, providing keto-aldehydes **2.85** and **2.87** in a nearly 1:1 ratio (entries 4–6). While imidazolidinone catalyst **2.92** favored formation of the desired keto-aldehyde (**2.85**) over the C11 epimer (**2.87**), the overall low conversion to product limited its synthetic utility (entries 8 and 9).⁴³ Nevertheless, this result suggests that an imidazolidinone catalyst could be found to accomplish a dynamic kinetic resolution of *cis*- and *trans*-**2.83** to provide keto-aldehyde **2.85** exclusively.

Table 2.2. Intermolecular Michael reaction of *trans*-**2.83** with methyl vinyl ketone (MVK).



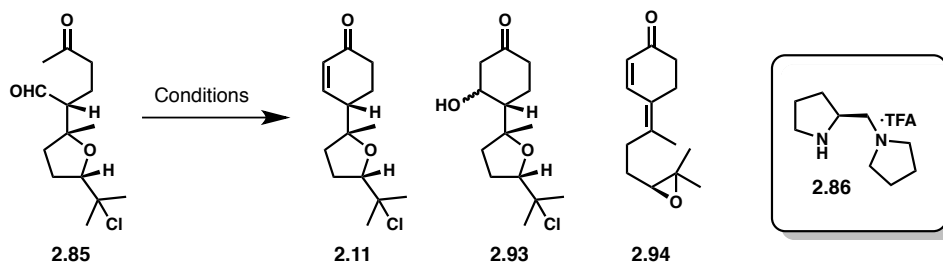
Entry ^a	Catalyst (mol%)	4-EtO ₂ C-catechol (mol%)	Time	Approx. Conversion (%) ^b	dr 2.85:2.87:2.88:2.89 ^b
1	2.90 (20)	20	2 d	0	N/A
2	2.91 (50)	0	5 d	45	1.1 : 2.8 : 1.0 : 5.3 ^c
3	2.91 (50)	20	6 d	67	1.9 : 1.0 : 1.4 : 1.4
4 ^d	2.59 (5)	20	3 d	90 ^e	6.1 : 6.0 : 1.0 : 1.4
5	2.59 (20)	20	9 d ^f	100	15.7 : 15.3 : 1.0 : 1.4
6 ^d	2.59 (20)	20	9 d ^f	100	3.5 : 3.8 : 1.0 : 1.1
7 ^g	2.59 (5)	20	3 d	61	1.2 : 1.0 : 8.8 : 10.6 ^h
8 ^g	2.92 (20)	20	3 d	13	14.3 : 3.8 : 1.0 : 2.4 ^h
9 ^g	2.92 (50)	20	3 d	23	8.1 : 2.6 : 1.0 : 1.7 ^h

^aThe enantiomeric excess of *trans*-**2.83** used in the reaction was 93% unless otherwise indicated. ^bDetermined by integration of aldehyde peaks in the crude ¹H NMR spectrum. ^cThe retro-oxa-Michael reaction was slow under the reaction conditions. ^dThe enantiomeric excess of *trans*-**2.83** was 78%. ^eThe crude reaction mixture was more complex and the isolated yields of keto-aldehydes **2.85** and **2.87** were lower than those for the reaction run at 7 °C. ^fReaction temperature: 7 °C. ^gUsed the enantiomer of *trans*-**2.83**. ^hDr of the enantiomers of **2.85:2.87:2.88:2.89**.

Prolinol catalyst **2.59** did not accomplish the desired Robinson annulation in one step; therefore, aldol condensation of **2.85** was catalyzed by diamine **2.86** to afford enone **2.11** in 75% yield (Scheme 2.18).⁴⁴ Keto-aldehyde **2.85** proved sensitive to basic conditions, and more typical aldol condensation conditions with hydroxide/alkoxide bases were less reliable (Table 2.3).² Because diamine **2.86** is known to be a poor catalyst for intermolecular Michael additions, we combined **2.83**, methyl vinyl ketone (MVK), and catalysts **2.59** and **2.86** in the hopes of completing a one-pot Robinson annulation.⁴⁵ While Michael product **2.85** slowly accumulated in

the usual 1:1 diastereomeric ratio, cyclohexenone **2.11** was not observed. Nonetheless, we were able to complete the synthesis of cyclohexenone **2.11** in only five or six steps from geraniol or geranyl acetate.

Table 2.3. Optimization of the aldol condensation of keto-aldehyde **2.85**.

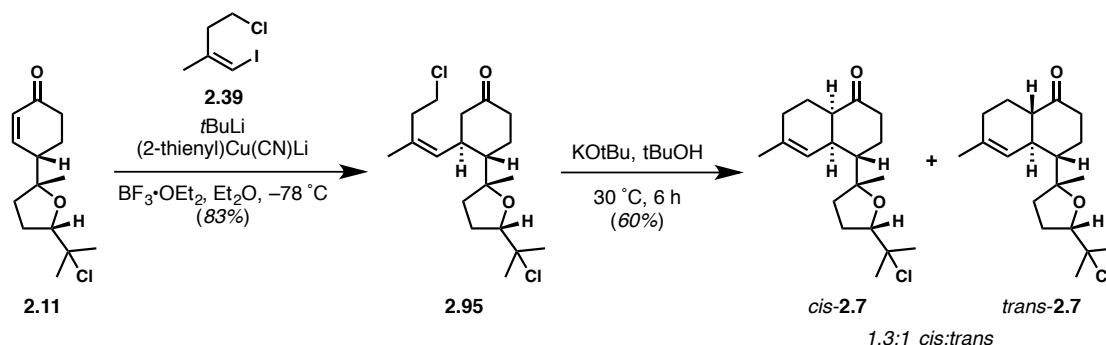


Entry	Conditions	Yield 2.11 (%)
1	<i>n</i> Bu ₄ NOH, KOH, THF/Et ₂ O/H ₂ O, 50 °C, 3 h	26 ^a
2	KOtBu, THF, 0 °C, 5 min	N/A ^b
3	LiOH•H ₂ O (1 equiv), MeOH, 0 °C, 1h; then Et ₃ N, DCM, MsCl	31
4	LiOH (1 equiv), <i>i</i> PrOH, rt, 48 h	36
5	LiOiPr (1 equiv), <i>i</i> PrOH, rt, 24 h	43 ^c
6	Catalyst 2.86 (30 mol%), hexanes, 21 h	75 ^d

^aThe major product isolated was **2.94** (40%). ^bDecomposition of **2.85**. ^cOther products isolated: **2.93** (14%) and **2.94** (8%). ^dIsolated an additional 8% of **2.11** as a mixture of diastereomers.

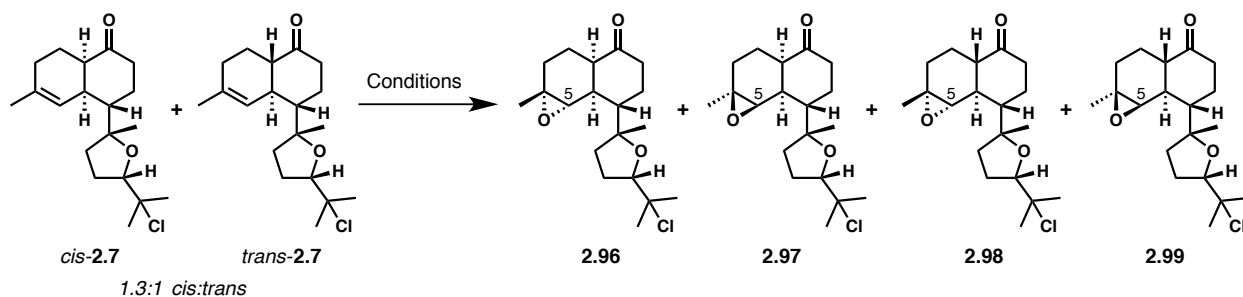
A Piers-type annulation was accomplished *via* diastereoselective conjugate addition followed by intramolecular alkylation (Scheme 2.19). The conditions for the conjugate addition of a cuprate derived from **2.39** into cryptone (Scheme 2.7) were not effective for the conversion of enone **2.11** to ketone **2.95**. Fortunately, changing the copper source to lithium 2-thienylcyanocuprate with BF₃•OEt₂ as the Lewis acid proved to be high yielding and diastereoselective, providing ketone **2.95** as a single diastereomer in 83% yield. Subsequent intramolecular alkylation using potassium *tert*-butoxide afforded **2.7** as a 1.3:1 mixture of *cis*- and *trans*-decalins that was not easily resolved. The 1.3:1 ratio of decalin isomers likely reflects the thermodynamic ratio of **2.7**. Mixtures enriched (by chromatography) in either isomer converged under similar conditions to a 1.2:1 ratio favoring the *cis*-decalin isomer.

Scheme 2.19. A Piers-type annulation to provide the decalin core of kalihinol B.



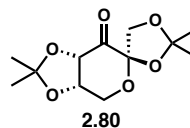
We examined a few methods for the epoxidation of the mixture of *cis*- and *trans*-**2.7** (Table 2.4). For both the *cis*- and *trans*-decalones (**2.7**), epoxidation with *m*CPBA slightly favored the undesired β -epoxides (**2.97** and **2.99**) (entries 1 and 2). Switching to DMDO reversed the diastereoselectivity for both *cis*- and *trans*-decalones (**2.7**), affording the desired α -epoxides (**2.96** and **2.98**), although the diastereoselectivity was modest (3:1 α : β for *cis*, 9:1 α : β for *trans*, entry 3). Complete diastereoselective epoxidation for both *cis*- and *trans*-**2.7** could be achieved using a Shi epoxidation (entry 4). However, Shi epoxidation of *trans*-**2.7** was slower than that for *cis*-**2.7**, and this reaction stalled at 57% conversion.

Table 2.4. Diastereoselectivity of epoxidation of the mixture of *cis*- and *trans*-decalones **2.7**.



Entry	Conditions ^a	Product Distribution ^b 2.96:2.97; 2.98:2.99
1	<i>m</i> CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 0 °C	1:1.5; 1:1.3
2	<i>m</i> CPBA, NaHCO ₃ , Et ₂ O, 0 °C	1:1.4; 1:2.3
3	Oxone, acetone, NaHCO ₃ , 0 °C	3:1; 9:1
4	Shi catalyst 2.80 , ^d oxone, K ₂ CO ₃ Bu ₄ NHSO ₄ , MeCN/DMM/H ₂ O, -10 °C	>20:1; >20:1 ^c

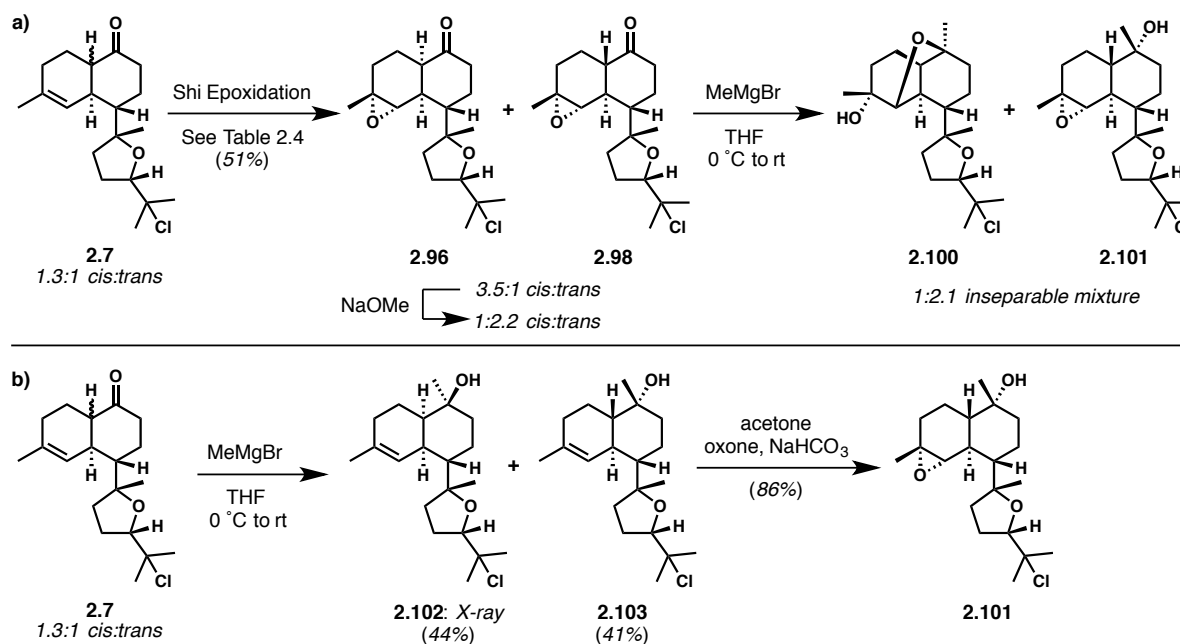
^aPerformed on a 1.3:1 mixture of *cis*- and *trans*-**2.7**. ^bDetermined by integration of the C5-H resonance in the crude ¹H NMR spectrum. ^cReaction stalled at 57% conversion. ^dShi catalyst:



After epoxidation of the C4–C5 alkene, we discovered that the decalones equilibrated to a 1:2.2 *cis:trans* mixture of **2.96** and **2.98** under basic conditions (Scheme 2.20a). Nucleophilic methylation of the 1:2.2 mixture afforded cyclized product **2.100** and *trans*-decalin **2.101**. Cyclized product **2.100** resulted from the addition of methyl Grignard reagent to the convex face of *cis*-decalone **2.96** followed by epoxide ring-opening with the resulting alkoxide. Alternatively, we explored a nucleophilic methylation/epoxidation sequence to access *trans*-decalin **2.101** (Scheme 2.20b). Stereoselective nucleophilic methylation of the isomeric mixture of **2.7** affords *cis*-decalin **2.102** and *trans*-decalin **2.103**. While *trans*-decalin **2.103** failed to crystallize, X-ray crystal structure analysis of *cis*-decalin **2.102** indicated that the stereochemistry of the attached ring motif matched that found in the natural product. Epoxidation of *trans*-decalin **2.103** using DMDO generated *in situ* yielded the desired α-epoxide (**2.101**) as a single diastereomer, whereas

a decrease in diastereoselectivity was observed for epoxidation of **2.103** with *m*CPBA (2:1 $\alpha:\beta$). The model for diastereoselectivity remains unclear; DMDO epoxidation of the C7 isopropyl analogue of **2.103** suffers from poor diastereoselectivity (1.6:1 $\alpha:\beta$, see Section 3.2), suggesting that the C7 THF appendage is responsible for the high levels of diastereoselectivity observed (>20:1 dr). Even though the ratio of *cis*- and *trans*-decalones was more favorable after epoxidation of the C4–C5 alkene, we ultimately determined the nucleophilic methylation/epoxidation sequence to be more attractive for three reasons: (1) diastereoselective epoxidation of *trans*-decalin **2.103** could be achieved without the use of chiral reagents; (2) *cis*-decalin **2.102** and *trans*-decalin **2.103** are easily separable; (3) *cis*-decalin **2.102** is potentially useful for the synthesis of the kalihinenes (**2.6**).

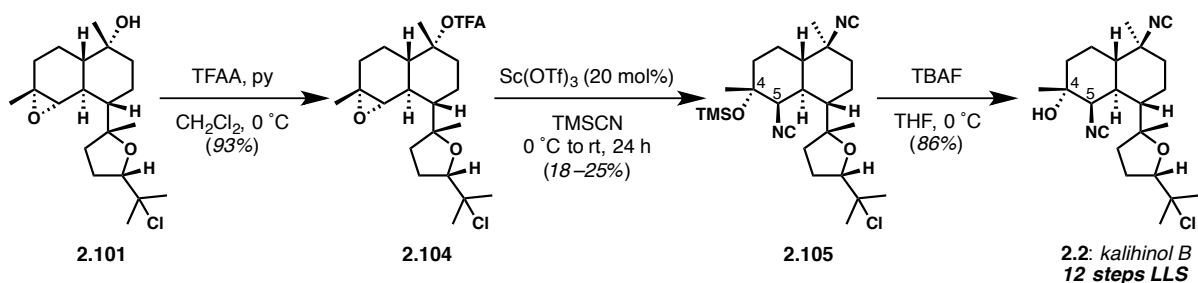
Scheme 2.20. Elaboration of *cis*- and *trans*-**2.7**: (a) an epoxidation/nucleophilic methylation sequence and (b) a nucleophilic methylation/epoxidation sequence.



At this stage, we looked to Shenvi's conditions for invertive tertiary trifluoroacetate displacement by trimethylsilyl cyanide for the installation of the isonitriles (Scheme 2.21).³ Conversion of tertiary alcohol **2.101** to trifluoroacetate **2.104** followed by exposure to

scandium(III) triflate and trimethylsilyl cyanide effected rapid isocyanosilylation of the epoxide and much slower invertive displacement of the trifluoroacetate, providing diisocyanide **2.105**. Desilylation of tertiary TMS ether **2.105** gave (+)-kalihinol B (**2.2**). The isonitrile introduction result is noteworthy for the two aspects of regiocontrol in the epoxide isocyanolysis. While the Fürst–Plattner principle predicts *trans*-diaxial nucleophilic opening of the epoxide at the least hindered C5 position, it was not clear whether the isonitrile or the nitrile would predominate (see Section 1.5.2). While the relatively low overall yield of this three-step sequence is largely due to competitive elimination of the axial tertiary trifluoroacetate, it is a marked improvement on the alternative known method for installing the requisite isonitriles (formylation and dehydration of a primary amine). Direct installation of the isonitriles is critical to achieving a concise synthesis, in which the natural product is obtained in 12 or 13 steps from geraniol or geranyl acetate. Synthetic (+)-kalihinol B (**2.2**) was subjected to the SYBR Green parasite proliferation assay to test for antiparasmodial activity against wild-type *P. falciparum* (3D7 strain) and the chloroquine-resistant parasite (Dd2 strain).⁴⁶ It exhibited potent antimalarial activity against both drug-sensitive and drug-resistant strains of *P. falciparum* (IC₅₀ = 8.4 nM for 3D7 and 4.6 nM for Dd2, see Section 3.4 for details).

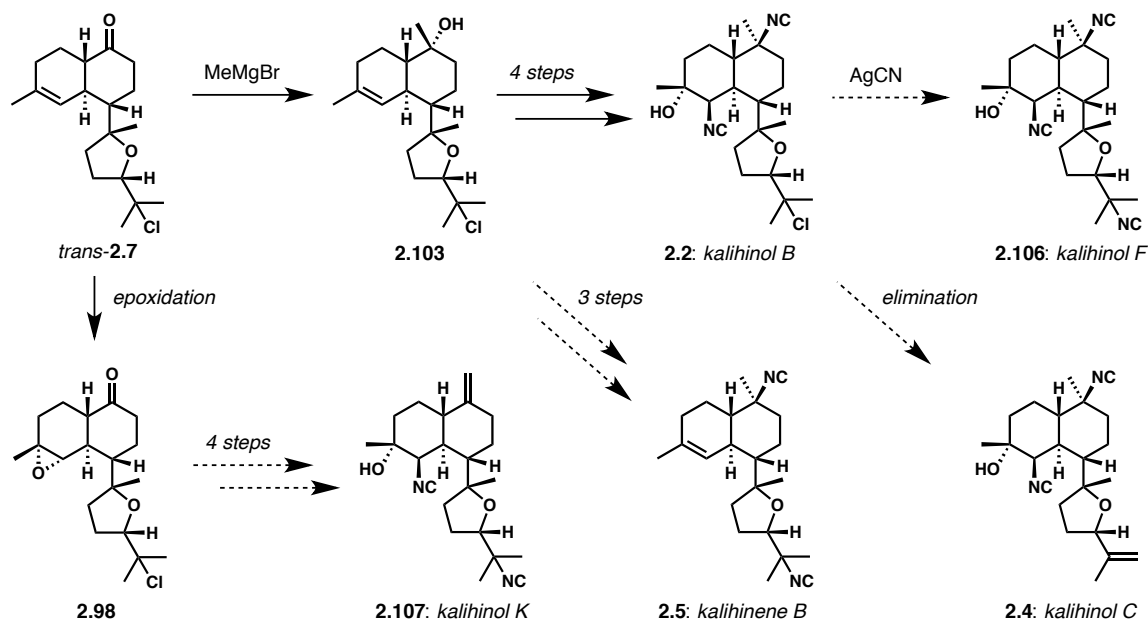
Scheme 2.21. Completion of the synthesis of kalihinol B (**2.2**).



2.5 Progress Toward the Synthesis of Other THF Kalihinanes

Having validated our approach with the synthesis of kalihinol B (**2.2**), we targeted other THF kalihinanes with intermediates in the kalihinol B synthesis (Scheme 2.22). We planned to prepare kalihinol F (**2.106**) and kalihinol C (**2.4**) from kalihinol B (**2.2**). Conversion of the tertiary chloride of kalihinol B (**2.2**) to an isonitrile would provide kalihinnol F (**2.106**); alternatively, elimination of the tertiary chloride would afford kalihinol C (**2.4**). Additionally, we proposed to elaborate **2.103** to kalihinene B (**2.5**) via a three-step isonitrile installation sequence. Lastly, we planned to access kalihinol K (**2.107**) from *trans*-**2.7** via an epoxidation, Wittig olefination, and isonitrile installation sequence.

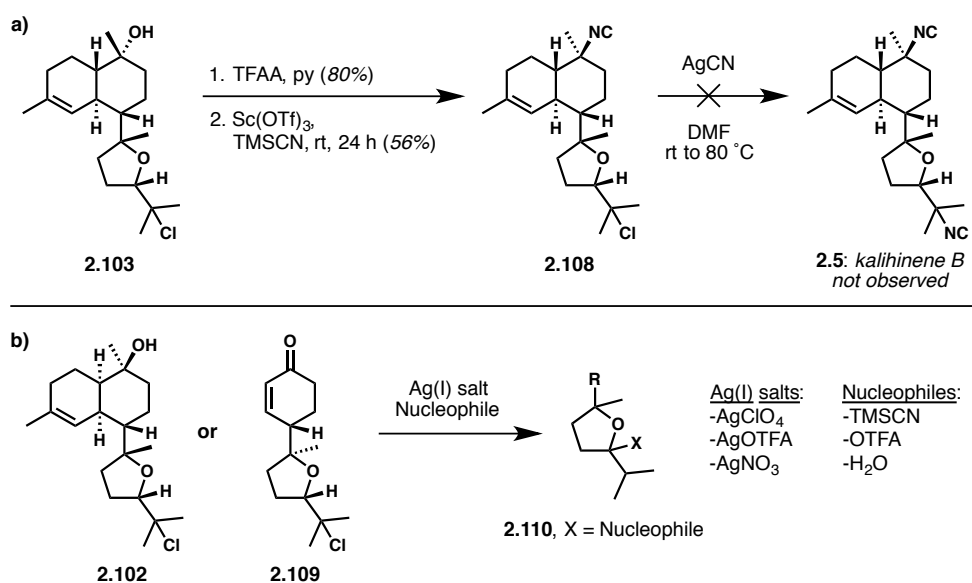
Scheme 2.22. A divergent approach toward other THF kalihinanes.



The ability to access kalihinol F (**2.106**), kalihinol K (**2.107**), and kalihinene B (**2.5**) hinged on the conversion of the tertiary chloride to the tertiary alkyl isonitrile; therefore, we targeted kalihinene B (**2.5**) to find a method to accomplish this (Scheme 2.23). Invertive displacement of the trifluoroacetate of **2.103** using scandium(III) triflate and trimethylsilyl cyanide provided isocyanide **2.108**. We found this reaction to be higher yielding for substrates

containing a C4–C5 alkene instead of the epoxide; however, the lower yield of the diisocyanide installation could simply be a reflection of a modest yield for successive isonitrile syntheses. Treatment of isocyanide **2.108** with AgCN did not accomplish the desired substitution reaction. Only starting material was observed after stirring **2.108** and AgCN in DMF at room temperature for 12 hours, and heating to 80 °C resulted in decomposition. Generally, isonitrile synthesis using AgCN is an S_N2 process, and only works well for primary alkyl halides.⁴⁷ Therefore, we turned our attention to chloride abstraction with other silver(I) salts and subsequent carbocation capture with a nucleophile.^{48–50} We employed both *cis*-decalin **2.102** and enone **2.109** as model systems to evaluate this transformation. Unfortunately, the only reactivity we observed for both **2.102** and **2.109** was chloride abstraction followed by a hydride shift to generate an oxocarbenium ion and subsequent trapping with the nucleophile to provide rearranged products (**2.110**). Because we had difficulty manipulating the tertiary chloride, we targeted diol **2.111**, which would facilitate isonitrile synthesis in a single step from the corresponding bis(trifluoroacetate) (Scheme 2.24).

Scheme 2.23. Initial approach toward the synthesis of kalihinene B (**2.5**).



2.111

1. TFAA, py
 2. Sc(OTf)₃, TMSCN

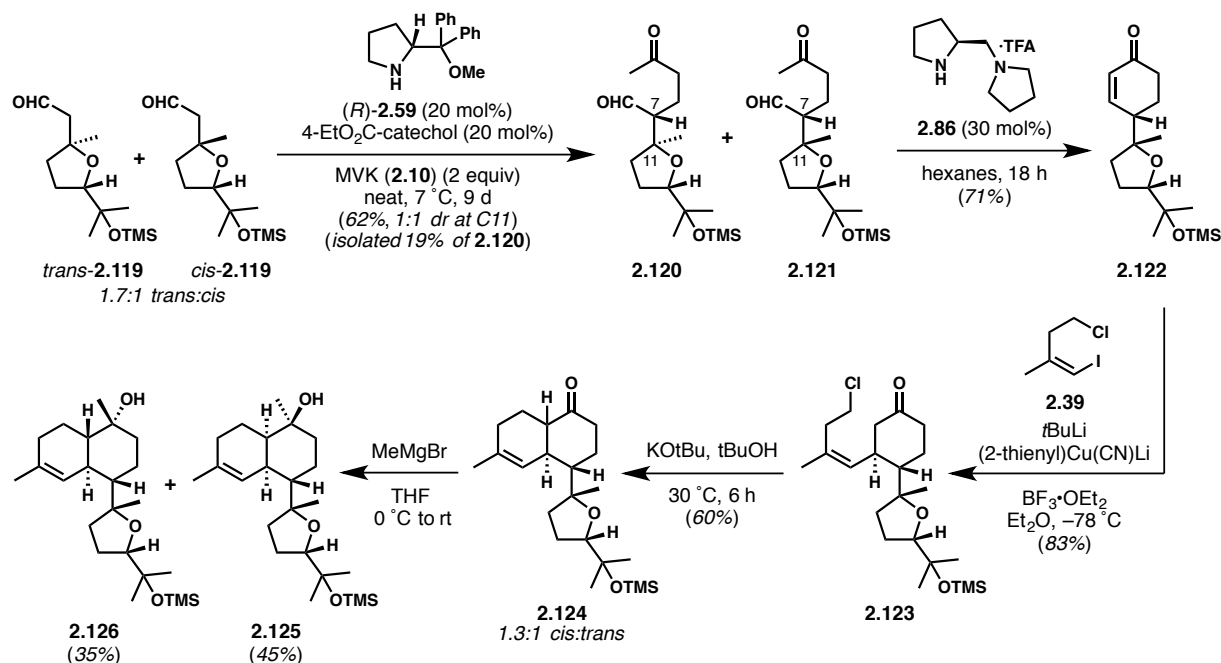
2.5: kalihinene B

Scheme 2.25. Synthesis of THFs bearing the tertiary (a) hydroxyl or (b) silyl ether.



The two-step Robinson annulation developed in the synthesis of kalihinol B (**2.2**) worked well for the synthesis of enone **2.122**. Exposure of the mixture of *trans*- and *cis*-**2.119** to the optimized intermolecular Michael conditions provided a 1:1 mixture of keto-aldehydes **2.120** and **2.121**, epimeric at C11. Aldol condensation of pure **2.121** (isolated in 19% from the mixture of **2.120** and **2.121**) using diamine catalyst **2.86** afforded enone **2.122** in 71% yield. Application of the Piers-type annulation used toward kalihinol B yielded decalone **2.124** as a 1.3:1 mixture of *cis*- and *trans*-isomers, favoring the undesired *cis*-isomer as before. Diastereoselective nucleophilic methylation of the mixture of decalones afforded *cis*-decalin **2.125** and *trans*-decalin **2.126**.

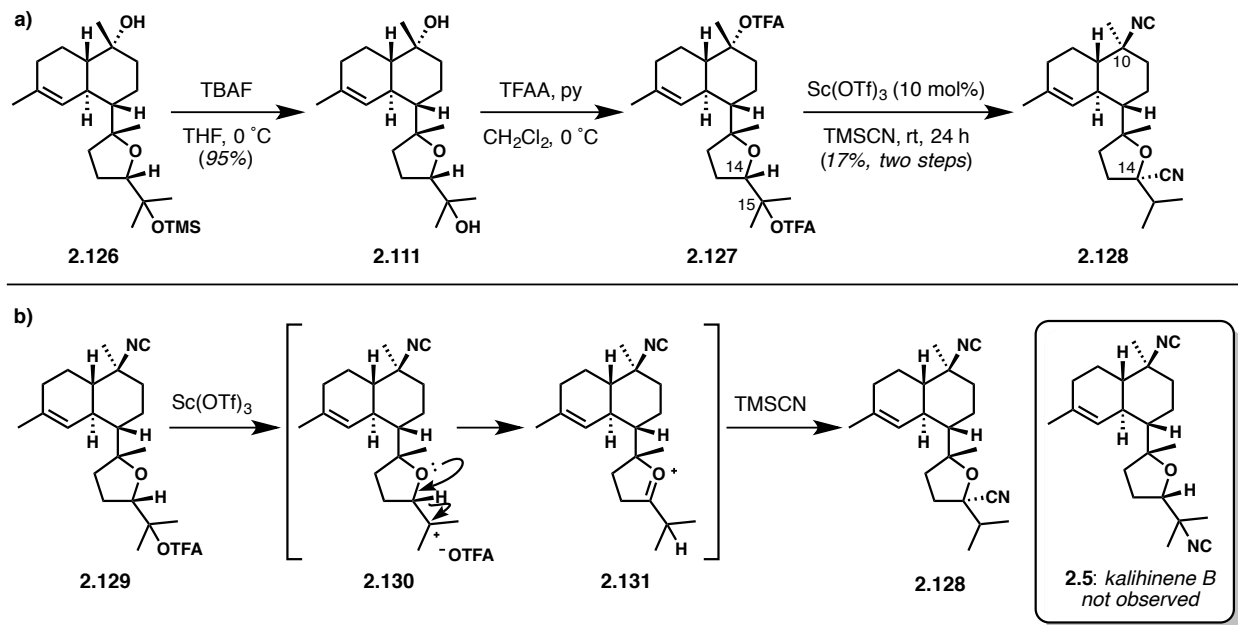
Scheme 2.26. Synthesis of the decalin core (**2.126**) using the Robinson annulation and Piers-type annulation.



With the *trans*-decalin core in hand, we evaluated conditions for the installation of the isonitriles (Scheme 2.27). Cleavage of the TMS ether using TBAF provided target diol **2.111**, which was converted into bis(trifluoroacetate) **2.127**. Treatment of **2.127** with scandium(III) triflate in TMSCN provided hydride shift product **2.128**. While the invertive displacement of the

C10 trifluoroacetate was accomplished under the reaction conditions to afford isocyanide **2.129**, subsequent ionization of the C15 trifluoroacetate triggered a C14–C15 hydride shift to form oxocarbenium ion **2.131**. Finally, capture of the oxocarbenium ion **2.131** with TMSCN gave the hydride shift product **2.128**, bearing a C14 nitrile. While we were able to isolate isocyanide **2.129** in addition to elimination products, kalihinene B (**2.5**) was not observed. Reaction of TMSCN with cyclic oxocarbenium ions is known to provide the nitrile as the product. Woerpel and co-workers have shown that cyanide addition of silyl cyanides to cyclic oxocarbenium ions proceeds via nucleophilic activation of silicon to form a pentacoordinate siliconate ion, which is responsible for cyanide transfer.⁵¹ We were unable to confirm the relative stereochemistry of the C14 nitrile, but nucleophilic addition proceeding *via* a staggered transition-state structure to the more stable conformation of the five-membered ring oxocarbenium ion would provide **2.128**.

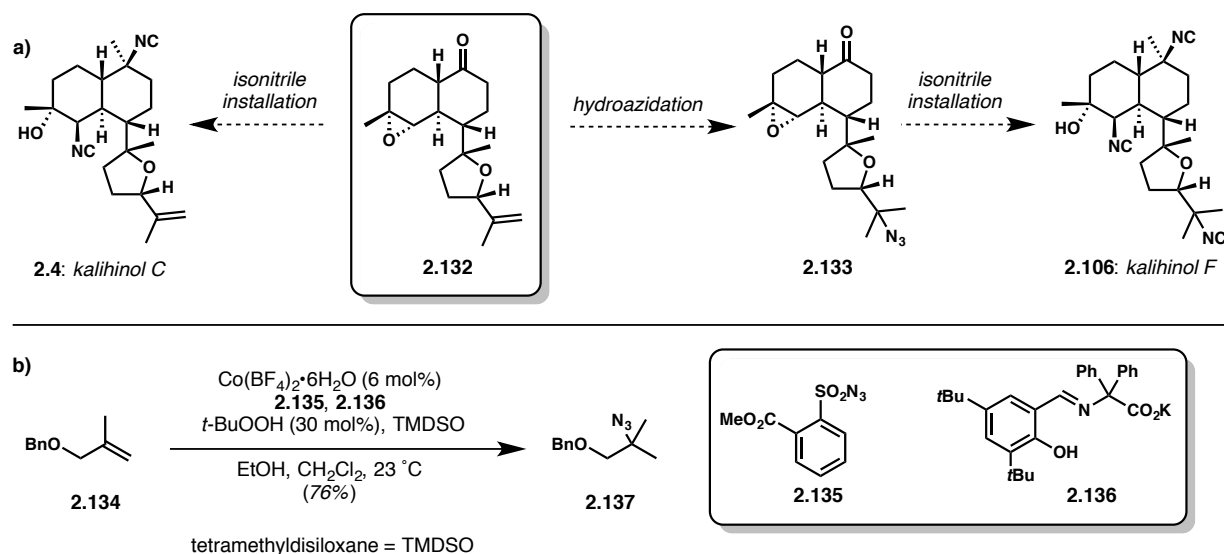
Scheme 2.27. Synthesis of kalihinene B (**2.5**) thwarted by a hydride shift.



Our results indicated that the installation of a C15 isonitrile using cationic methods would be challenging to accomplish. However, by using radical methods for isonitrile synthesis, we hoped to avoid the undesired the hydride shift. We envisioned that we would be able to

accomplish a hydroazidation of **2.132**, an intermediate toward the synthesis of kalihinol C (**2.4**) (Scheme 2.28a). By targeting the THF bearing the pendant isopropenyl substituent (**2.132**), not only would we be able to access kalihinol C after elaboration of the decalin core, but we would also be able to access kalihinanes containing a C15 isonitrile (*e.g.* kalihinol F) *via* reduction of the azide and formylation/dehydration of the resulting amine. Carreira and co-workers have shown that hydroazidation of several alkenes, including 1,1-disubstituted allylic ethers, can be accomplished using a cobalt catalyst (Scheme 2.28b).⁵²

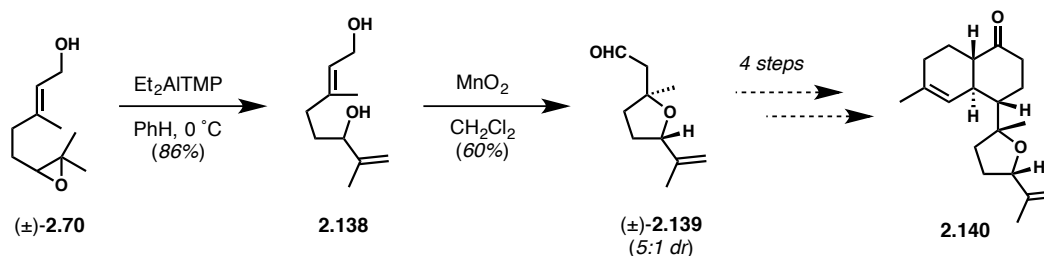
Scheme 2.28. (a) Proposed synthesis of kalihinanes containing a C15 isonitrile by hydroazidation of an intermediate in the synthesis of kalihinol C (**2.4**). (b) Carreira's method for hydroazidation of alkenes.⁵²



We have been able to access allylic alcohol **2.138** *via* regiospecific isomerization of 6,7-epoxygeraniol (**2.70**) using diethylaluminum 2,2,6,6-tetramethylpiperidine, a method developed by Yamamoto and co-workers (Scheme 2.29).^{53,54} While we were initially concerned with the selective oxidation of the primary allylic alcohol of **2.138** in the presence of a secondary allylic alcohol, the desired oxidation with MnO_2 was faster than oxidation of the secondary allylic alcohol. Furthermore, the spontaneous oxa-Michael reaction was fast enough to function as a protecting group for the secondary allylic alcohol, and we were able to prepare THF **2.139** in

good yield as a 5:1 mixture of *trans*- and *cis*-isomers. After preparing enantiopure THF **2.139**, subsection to the Robinson annulation and Piers-type annulation sequence will provide decalin **2.140**. From decalin **2.140**, we plan to prepare kalihinol C (**2.4**) and to explore the hydroazidation approach toward the THF kalihinanes containing a C15 isonitrile.

Scheme 2.29. Synthesis of THF **2.139** bearing the pendant alkene.



2.6 Conclusions

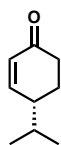
We have validated our approach toward the THF kalihinanes with the first synthesis of kalihinol B in only 12 steps from geraniol. While some transformations in our synthesis would benefit from improved selectivity, even in its current form our achievement is the most concise synthesis of any of the kalihinanes because nearly all of the steps generate key C–O, C–Cl, C–C, or C–N bonds. In principle, this design would permit access to THP-containing kalihinanes, but they remain elusive owing to an undesired, formal [4+2] cycloaddition. Furthermore, we have attempted to access other THF kalihinanes using our unified synthetic design, but an undesired hydride shift has precluded the use of cationic methods for the synthesis of the C15 isonitrile.

2.7 Experimental Procedures

General Experimental Methods. All reactions were performed under an inert atmosphere of argon using oven-dried or flame-dried glassware and Teflon® coated stir bars. Solvents were dried by passage through columns of activated alumina, and *tert*-butyl alcohol was distilled from calcium hydride prior to use. Trimethylsilyl cyanide and methyl vinyl ketone were purified by distillation prior to use. Commercial reagents were used as received unless noted otherwise, and all other reagents were prepared using known literature procedures. Lithium chloride was flame-dried under vacuum prior to use. Reactions were monitored by thin-layer chromatography (TLC) performed on 250 μm silica gel 60 plates with 254 nm fluorescent indicator from EMD Chemicals using UV light as a visualizing agent and $\text{KMnO}_4/\text{H}_2\text{SO}_4$, *p*-anisaldehyde or ceric ammonium molybdate and heat as developing agents. Flash chromatography was performed on EMD Chemicals (40-63 μm) silica gel. NMR spectra were recorded on a Bruker 500 MHz or a Bruker 600 MHz spectrometer. Chemical shifts are reported in parts per million using residual non-deuterated solvent as an internal standard (CDCl_3 : 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR). Data are reported as follows: chemical shift, multiplicity (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant(s) in Hz, integration. NMR spectra were obtained at 298 K unless otherwise noted. FT-IR spectra were recorded on a Varian 640-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter operating on the sodium D-line (589 nm) using a 50 mm path-length cell and are reported as: $[\alpha]_{\text{D}}^{\text{T}}$ (concentration in g/100 mL, solvent). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC using a Chiralpak AS-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries Ltd. with visualization at 254 nm. High resolution mass spectra (HRMS)

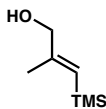
were recorded on a Waters LCT Premier spectrometer using ESI-TOF (electrospray ionization-time of flight) or CI-TOF (chemical ionization-time of flight). Melting points (mp) are uncorrected and were measured on a Mel-Temp II melting point apparatus.

Experimental Procedures and Characterization Data



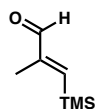
2.19: (±)-cryptone

(±)-Cryptone (2.19). The title compound was prepared according to the literature procedure using a two-step Robinson annulation sequence.² The spectral data for this compound are consistent with those reported in the literature.⁵⁵ ¹H NMR (CDCl₃, 500 MHz) δ 6.89 (dt, *J* = 10.5, 2.0 Hz, 1H), 6.00 (dd, *J* = 10.5, 2.5 Hz, 1H), 2.50 (dt, *J* = 16.5, 4.0 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.32 – 2.25 (m, 1H), 2.04 – 1.96 (m, 1H), 1.86 – 1.71 (m, 1H), 0.96 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 200.2, 154.5, 129.8, 42.6, 37.5, 31.6, 25.4, 19.8, 19.6.



2.25

(*E*)-2-methyl-3-(trimethylsilyl)prop-2-en-1-ol (2.25). The title compound was prepared according to the literature procedure.⁵ The spectral data for this compound are consistent with those reported in the literature. ¹H NMR (CDCl₃, 500 MHz) δ 5.51 (s, 1H), 4.01 (d, *J* = 6.0 Hz, 2H), 1.77 (s, 3H), 0.13 (2, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 153.3, 121.1, 69.0, 18.5, 0.11.



2.26

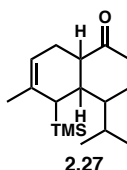
(E)-2-Methyl-3-(trimethylsilyl)prop-2-en-1-al (2.26). To a solution of oxalyl chloride (1.81 mL, 21.1 mmol) in CH_2Cl_2 (42 mL) at -78°C was added DMSO (2.99 mL, 42.1 mmol) in CH_2Cl_2 (8.4 mL) dropwise *via* addition funnel over 15 min. After gas evolution ceased (ca. 15 min), a solution of (E)-2-methyl-3-(trimethylsilyl)prop-2-en-1-ol (**2.25**) (2.76 g, 19.1 mmol) in CH_2Cl_2 (38 mL) was added dropwise *via* addition funnel over 25 min. After 45 min, triethylamine (13.3 mL, 95.7 mmol) was added dropwise *via* addition funnel over 15 min. The solution was allowed to warm to room temperature, and was stirred at room temperature for 1 h. Water was added to the reaction mixture, and the aqueous layer was extracted three times with CH_2Cl_2 . The combined organic extracts were washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2 , 5% EtOAc/Hexanes) to afford the title compound as a pale yellow liquid (0.786 g, 28%). ^1H and ^{13}C NMR spectra are in complete accordance with those previously reported.⁵⁶ ^1H NMR (CDCl_3 , 600 MHz) δ 9.41 (s, 1H), 6.70 (s, 1H), 1.89 (s, 3H), 0.23 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.1, 153.6, 152.4, 13.5, -0.73 .



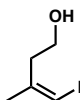
2.18

(E)-2-Methyl-1-(trimethylsilyl)buta-1,3-diene (2.18). This reaction is a modification of Jung *et al.*⁴ To a solution of methyltriphenylphosphonium bromide (3.70 g, 10.4 mmol) in THF (90 mL) at 0°C was added *n*-butyllithium (4.14 mL, 2.50 M in THF). The pale orange solution was allowed to warm to room temperature. After 1 h, **2.26** (1.05 g, 7.40 mmol) was added in THF (2

mL) *via* cannula in one portion. The solution was stirred at room temperature for 10 min. The reaction mixture was diluted with pentane and filtered through a plug of Florisil®. The reaction mixture was concentrated by distillation of the solvents through a 2" Vigreux column. The crude residue was purified by Kugelrohr distillation (150–200 mm Hg, ABT: 115 °C), yielding the title compound as a clear liquid (0.738 g, 71%). ¹H NMR (CDCl₃, 500 MHz) δ 6.39 (dd, *J* = 17.5, 10.5, 1H), 5.55 (s, 1H), 5.18 (d, *J* = 17.5, 1H), 5.03 (d, *J* = 10.5, 1H), 1.90 (s, 3H), 0.14 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 150.2, 143.5, 132.6, 113.0, 17.0, 0.10; IR (thin film) ν 3089, 2998, 2955, 2897, 1578, 1441, 1379, 1248, 854, 838 cm⁻¹; HRMS (CI) *m* / *z* calcd for C₈H₁₆SiH (M + H)⁺ 141.1100, found 141.1096.



Cycloadduct 2.27. A mixture of (±)-cryptone (**2.19**) (25 mg, 0.18 mmol), pyrrolidine (15 μL, 0.18 mmol), and (*E*)-2-methyl-1-(trimethylsilyl)buta-1,3-diene (**2.18**) (100 mg, 0.73 mmol) was heated to 190 °C in a sealed vial for 10 h. The crude reaction mixture was purified by flash column chromatography (SiO₂, 1:1:98 EtOAc/Et₃N/Hexanes) to afford the title compound as a white solid (2.9 mg, 6%). The structure has tentatively been assigned to **2.27**. ¹H NMR (CDCl₃, 500 MHz) δ 5.30 (br s, 1H), 2.5 – 2.2 (m, 6H), 2.15 – 2.08 (m, 1H), 2.00 – 1.90 (m, 2H), 1.90 – 1.82 (m, 1H), 1.73 (s, 3H), 1.65 – 1.60 (m, 2H), 0.85 (d, *J* = 7, 3H), 0.81 (d, *J* = 7, 3H), 0.13 (s, 9H).



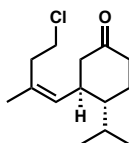
2.37

(Z)-4-Iodo-3-methyl-3-buten-1-ol (2.37). The title compound was prepared according to the literature procedure.^{20,21} The spectral data for this compound are consistent with those reported in the literature. ¹H NMR (CDCl₃, 500 MHz) δ 6.00 (d, *J* = 0.5 Hz, 1H), 3.78 (t, *J* = 6.8 Hz, 2H), 2.53 (t, *J* = 6.8 Hz, 2H), 1.94 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 144.6, 76.6, 60.5, 41.8, 24.0.



2.39

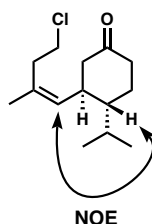
(Z)-4-Chloro-1-iodo-2-methyl-1-butene (2.39). To a solution of alcohol **2.37** (1.54 g, 7.27 mmol) in CH₂Cl₂ (73 mL) at room temperature was added triphenylphosphine (9.53 g, 36.3 mmol) in one portion, followed by CCl₄ (7.01 mL, 72.7 mmol) dropwise via syringe. The reaction mixture was allowed to stir for one hour. The solvent was concentrated *in vacuo* (150 – 200 mm Hg). The crude residue was purified using flash chromatography (SiO₂, 1% Et₂O/pentane), yielding the title compound as a pale yellow liquid (1.18 g, 70%). ¹H NMR (CDCl₃, 500 MHz) δ 6.06 (s, 1H), 3.61 (t, *J* = 7.3 Hz, 2H), 2.70 (t, *J* = 7.3 Hz, 2H), 1.95 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 143.9, 77.5, 41.6, 41.5, 23.9; IR (thin film) ν 2967, 2911, 2847, 1433, 1263, 1167 cm⁻¹; HRMS (CI) *m/z* calcd for C₅H₈ClI (M)⁺ 229.9359, found 229.9357.

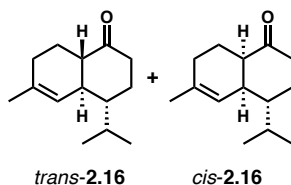


2.41

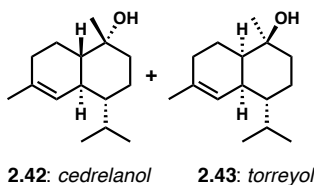
Ketone 2.41. To a solution of vinyl iodide **2.39** (0.346 g, 1.50 mmol) in Et₂O (6 mL, previously sparged with argon gas for 20 min) at –78 °C was added *tert*-butyllithium (2.1 mL, 1.45 M in

pentane, 3.01 mmol) dropwise *via* syringe. After 20 min, freshly prepared $\text{MgBr}_2 \cdot \text{OEt}_2$ (2.2 mL, ~1 M suspension in Et_2O , 2.15 mmol) was added dropwise *via* syringe. After 20 min, $\text{CuBr} \cdot \text{DMS}$ (0.155 g, 0.752 mmol) was added in one portion. TMEDA (0.11 mL, 0.752 mmol) was added dropwise *via* syringe immediately afterwards. After 30 min at -78°C , TMSCl (0.11 mL, 0.859 mmol) was added dropwise *via* syringe followed by a solution of ($\pm$)-cryptone (**2.19**) (98.9 mg, 0.716 mmol) in Et_2O (0.5 mL). The transfer was completed with an additional portion of Et_2O (0.5 mL). After allowing the reaction mixture to stir for 2 h at -78°C , the reaction was quenched with 9:1 saturated NH_4Cl solution/ NH_4OH (15 mL). After warming to room temperature, the reaction mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with 1 M HCl (15 mL), saturated NaHCO_3 solution (15 mL), and brine (15 mL). The organic phase was dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 5% EtOAc /hexanes) to afford the title compound (138.2 mg, 80%) as a white solid (mp $55\text{--}57^\circ\text{C}$). ^1H NMR (CDCl_3 , 600 MHz) δ 5.10 (d, $J = 9.6$ Hz, 1H), 3.54 (t, $J = 7.2$ Hz, 2H), 2.61 – 2.50 (m, 2H), 2.50 – 2.43 (m, 2H), 2.42 – 2.31 (m, 2H), 2.14 (ap t, $J = 13.2$ Hz, 1H), 2.02 – 1.88 (m, 2H), 1.73 (s, 3H), 1.52 – 1.40 (m, 2H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.73 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 211.4, 131.8, 131.6, 47.9, 47.1, 42.4, 41.2, 40.6, 35.2, 27.9, 24.5, 22.9, 21.9, 16.1; IR (thin film) ν 2957, 2870, 1714, 1455, 1368, 1259, 1202, 1066 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{23}\text{ClONa}$ ($\text{M} + \text{Na}$) $^+$ 265.1335, found 265.1329. ^1H -NOESY-2D (500 MHz, CDCl_3) spectra were obtained for ketone **2.41** and selected NOE interactions are shown.





***cis*- and *trans*-Decalones 2.16.** To a solution of alkyl chloride **2.41** (0.292 g, 1.20 mmol) in *tert*-butyl alcohol (6.0 mL) at 30 °C was added potassium *tert*-butoxide (1.10 mL, 1.6 M in THF, 1.81 mmol) dropwise *via* syringe. After stirring for 6 h at 30 °C, the reaction was quenched with saturated NH₄Cl solution (6 mL). The aqueous layer was extracted with pentane (3 x 15 mL), and the combined organic extracts were washed with water (3 x 10 mL) and with brine (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 5% Et₂O/pentane) to afford a 1.1:1 mixture of *trans*- and *cis*-decalones (176.4 mg, 71%) as a colorless oil, which was characterized as a mixture. The spectral data for these compounds are consistent with those reported in the literature.^{57,1} ¹H NMR (CDCl₃, 500 MHz) δ 5.55 (s, 1H), 5.32 (s, 1H), 2.52 (br s, 1H), 2.49 – 2.11 (m, 7H), 2.11 – 1.95 (m, 8H), 1.95 – 1.85 (m, 1H), 1.85 – 1.78 (m, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.62 – 1.38 (m, 6H), 1.00 (d, *J* = 5.0 Hz, 3H), 0.99 (d, *J* = 5.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 214.8, 213.1, 136.0, 135.1, 124.4, 121.6, 51.2, 46.9, 46.1, 45.2, 44.4, 41.2, 39.0, 38.4, 29.8, 28.6, 26.9, 26.5, 25.5, 24.0, 23.9, 23.8, 23.1, 22.0, 21.70, 21.65, 17.9, 15.1.

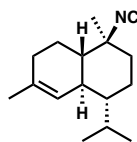


(±)-Torreyol (2.42) and (±)-cedrelanol (2.43). Methylmagnesium bromide (1.9 mL, 2.25 M in Et₂O, 4.27 mmol) was added dropwise to a solution of a mixture of *cis*- and *trans*-decalones **2.16**

(0.176 g, 0.855 mmol) in THF (8.6 mL) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature for 30 min, and the reaction was quenched with saturated aqueous NH₄Cl solution (10 mL) at 0 °C. The aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% EtOAc/hexanes), yielding (±)-cedrelanol (**2.42**) (0.106 g, 55%) as a colorless oil and (±)-torreyol (**2.43**) (0.084 g, 44%) as a white solid (mp 109–110 °C, lit.¹ mp 108.5–109 °C). The spectral data for these compounds are consistent with those reported in the literature.^{1,3,58}

(±)-Cedrelanol (**2.42**): ¹H NMR (CDCl₃, 600 MHz) δ 5.55 (br s, 1H), 2.22 – 2.15 (m, 1H), 2.04 – 1.89 (m, 4H), 1.74 (dt, *J* = 13.1, 2.9 Hz, 1H), 1.67 (s, 3H), 1.50 – 1.45 (m, 1H), 1.45 – 1.29 (m, 3H), 1.22 (s, 3H), 1.09 (t, *J* = 10.3 Hz, 1H), 1.01 (tt, *J* = 11.4, 3.2 Hz, 1H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 134.5, 122.8, 70.8, 48.1, 46.8, 40.4, 37.9, 31.0, 28.6, 26.3, 23.9, 22.7, 21.5, 19.9, 15.3.

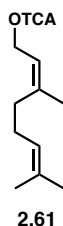
(±)-Torreyol (**2.43**): ¹H NMR (CDCl₃, 600 MHz) δ 5.52, (d, *J* = 4.3 Hz, 1 H), 2.06 – 1.92 (m, 4H), 1.92 – 1.86 (m, 1H), 1.66 (s, 3H), 1.63 – 1.47 (m, 6H), 1.35 – 1.24 (m, 2H), 1.30 (s, 3H), 1.15 – 1.05 (m, 1H) 0.89 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 134.5, 124.7, 72.7, 45.6, 44.2, 36.9, 35.4, 31.3, 28.1, 26.5, 23.8, 21.8, 21.7, 18.6, 15.4.



(±)-**2.17**: 10-isocyano-4-cadinene

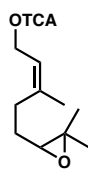
(±)-**10-Isocyano-4-cadinene (2.17)**. The title compound was prepared according to the literature procedure.³ A mixture of (±)-cedrelanol (**2.42**) (28.3 mg, 0.127 mmol) and pyridine (50 μL, 0.508 mmol) in CH₂Cl₂ (1.3 mL) at 0 °C was treated with trifluoroacetic anhydride (40 μL, 0.255

mmol). After 15 minutes, the reaction was quenched with 1 M HCl (2 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic extracts were washed with water (5 mL), washed with saturated NaHCO₃ solution (5 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. A portion of the crude trifluoroacetate (15.9 mg, 0.0499 mmol) was dissolved in TMSCN (50 µL), and a solution of scandium(III) trifluoromethanesulfonate (~0.7 mg, 0.0015 mmol) in TMSCN (50 µL) was added. After 4 h at room temperature, the reaction was quenched with TMEDA (20 µL) and the volatiles were removed under reduced pressure. The crude residue was dissolved in hexanes (5 mL), washed with saturated aqueous NaHCO₃ solution (5 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 30% CH₂Cl₂/hexanes) to afford the title compound (3.9 mg, 34%) as a thin film along with a mixture of diastereomers (1.1 mg, 9%). The spectral data for this compound are consistent with those reported in the literature.³ ¹H NMR (CDCl₃, 600 MHz) δ 5.46, (s, 1 H), 2.22 – 2.13 (m, 1H), 2.12 – 1.94 (m, 4H), 1.82 (td, *J* = 13.3, 4.0 Hz, 1H), 1.73 (t, *J* = 10.8 Hz, 1H), 1.68 (s, 3H), 1.59 (dq, *J* = 13.3, 3.3 Hz, 1H), 1.50 (t, *J* = 11.0 Hz, 1H), 1.34 (dd, *J* = 12.3, 5.8 Hz, 1H), 1.30 (s, 3H), 1.12 (qd, *J* = 13.0, 3.5 Hz, 1H), 1.06 (tt, *J* = 12.0, 3.0 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 152.1 (br t, *J* = 4.3 Hz), 135.5, 121.4, 60.9 (br t, *J* = 5.1 Hz), 48.1, 46.3, 40.7, 38.0, 30.8, 26.0, 23.9, 23.8, 21.5, 20.3, 20.1, 15.2.



Neryl Trichloroacetate (2.61). To a solution of nerol (11.4 mL, 64.8 mmol) in THF (130 mL) was added pyridine (10.5 mL, 77.8 mmol). The reaction mixture was cooled to 0 °C, and

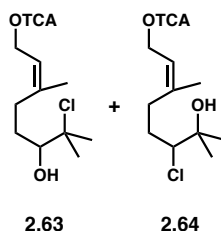
trichloroacetic anhydride (14.2 mL, 77.8 mmol) was added dropwise via syringe. After 5 min, the reaction mixture was allowed to warm to room temperature. After 30 min, the reaction mixture was diluted with hexanes (200 mL), washed with water (4 x 200 mL), saturated NaHCO₃ solution (1 x 200 mL), and brine (1 x 200 mL). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 3% EtOAc/hexanes) to afford neryl trichloroacetate (17.6 g, 91%) as a colorless oil. ¹H NMR (CDCl₃, 500 MHz) δ 5.43 (t, *J* = 7.5 Hz, 1H), 5.10 (t, *J* = 7.0 Hz, 1H), 4.83 (d, *J* = 7.5 Hz, 2H), 2.21 – 2.14 (m, 2H), 2.14 – 2.09 (m, 2H), 1.80 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 162.1, 145.8, 132.7, 123.4, 117.1, 90.2, 66.0, 32.4, 26.7, 25.8, 23.8, 17.8; IR (thin film) ν 2969, 2930, 2858, 1764, 1446, 1378, 1231, 960, 827, 682 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₂H₁₇Cl₃O₂Na (M + Na)⁺ 321.0192, found 321.0178.



2.62

6,7-Epoxyneryl trichloroacetate (2.62). To a solution of neryl trichloroacetate (17.6 g, 58.8 mmol) in CH₂Cl₂ (590 mL) was added NaHCO₃ (10.9 g, 129.5 mmol) in one portion. The reaction mixture was cooled to 0 °C, and *m*-chloroperoxybenzoic acid (14.5 g, 64.7 mmol) was added portionwise. After 2 h, the reaction was quenched with saturated Na₂S₂O₅ solution (300 mL) to destroy excess *m*-chloroperoxybenzoic acid. After stirring the reaction mixture for 30 min at room temperature, the aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic extracts were washed with water (1 x 300 mL), saturated NaHCO₃ solution (1 x 300 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 5% EtOAc/hexanes) to afford 6,7-epoxyneryl trichloroacetate

(17.0 g, 92%) as a colorless oil. ^1H NMR (CDCl_3 , 500 MHz) δ 5.48 (t, J = 7.5 Hz, 1H), 4.86 (d, J = 7.5 Hz, 2H), 2.72 (t, J = 6.3 Hz, 1H), 2.38 – 2.26 (m, 2H), 1.83 (s, 3H), 1.70 – 1.62 (m, 2H), 1.32 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 161.9, 144.9, 117.6, 90.0, 65.6, 63.6, 58.5, 29.0, 27.5, 24.9, 23.6, 18.8; IR (thin film) ν 2965, 2928, 2877, 1764, 1448, 1379, 1233, 960, 828, 682 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{Cl}_3\text{O}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 337.0141, found 337.0126.

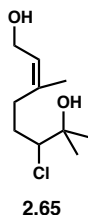


Chlorohydrins 2.63 and 2.64. To a solution of 6,7-epoxyneryl trichloroacetate (**2.62**) (1.15 g, 3.65 mmol) in toluene (37 mL) was added Cl_2PPh_3 (1.83 g, 5.48 mmol) in one portion. After 15 min, the reaction mixture was concentrated *in vacuo*, and the resulting crude residue was purified using flash chromatography (SiO_2 , 15% EtOAc/hexanes), yielding chlorohydrin **2.63** (0.517 g, 40%) as a colorless oil and chlorohydrin **2.64** (0.510 g, 40%) as a colorless oil.

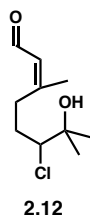
Chlorohydrin **2.63**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.49 (t, J = 7.5 Hz, 1H), 4.90 (d, J = 8.0 Hz, 2H), 3.45 (dd, J = 10.8, 1.8 Hz, 1H), 2.48 – 2.39 (m, 1H), 2.35 – 2.28 (m, 1H), 2.18 (br s, 1H), 1.81 (s, 3H), 1.78 – 1.72 (m, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 1.52 – 1.46 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.1, 145.2, 118.1, 90.1, 78.0, 75.9, 67.0, 29.4, 29.2, 28.9, 27.3, 23.5; IR (thin film) ν 3564 (br), 2975, 2936, 2875, 1763, 1447, 1381, 1233, 958 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{18}\text{Cl}_4\text{O}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 372.9908, found 372.9896.

Chlorohydrin **2.64**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.51 (t, J = 7.3 Hz, 1H), 4.89 (d, J = 7.0 Hz, 2H), 3.76 (dd, J = 11.5, 1.5 Hz, 1H), 2.46 – 2.33 (m, 2H), 2.08 (br s, 1H), 2.06 – 1.97 (m, 1H),

1.80 (s, 3H), 1.78 – 1.68 (m, 1H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.0, 144.3, 118.6, 90.1, 73.1, 72.8, 65.8, 31.2, 29.9, 26.4, 25.6, 23.5; IR (thin film) ν 3439 (br), 2975, 2937, 2875, 1763, 1445, 1379, 1231, 962 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{18}\text{Cl}_4\text{O}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 372.9908, found 372.9906.



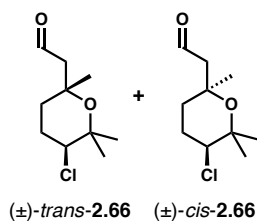
Allylic alcohol 2.65. Ammonia (1.40 mL, 2M in MeOH, 2.74 mmol) was added to a solution of chlorohydrin **2.64** (0.482 g, 1.37 mmol) in Et_2O (4.6 mL). After 1 h, water (10 mL) was added to the reaction mixture. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with 0.1 N citric acid (1 x 10 mL), saturated NaHCO_3 solution (1 x 10 mL), and brine (1 x 10 mL). The organic phase was dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 40% EtOAc /hexanes) to afford allylic alcohol **2.65** (0.244 g, 86%) as a white solid (mp 33–35 $^\circ\text{C}$). ^1H NMR (CDCl_3 , 500 MHz) δ 5.51 (t, J = 7.3 Hz, 1H), 4.17 (br s, 2H), 3.75 (dd, J = 11.5, 2 Hz, 1H), 2.40 – 2.25 (m, 2H), 1.16 (br s, 1H), 2.04 – 1.98 (m, 1H), 1.74 (s, 3H), 1.74 – 1.64 (m, 1H), 1.40 (br s, 1H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.2, 126.1, 73.3, 72.9, 59.1, 31.3, 29.5, 26.4, 25.6, 23.3; IR (thin film) ν 3352 (br), 2972, 2934, 2873, 1446, 1380, 1148, 999 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{19}\text{ClO}_2\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 229.0971, found 229.0981.



Enal 2.12. To a solution of allylic alcohol **2.65** (0.212 g, 1.03 mmol) in CH₂Cl₂ (21 mL) was added MnO₂ (2.12 g, 10 mass equivalents) in one portion. The reaction mixture was stirred for 2.5 h, filtered through a plug of SiO₂, rinsed with Et₂O (50 mL), and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO₂, 40% EtOAc/hexanes) to afford enal **2.12** (0.173 g, 82%) as a colorless oil. ¹H NMR (CDCl₃, 500 MHz) δ 9.99 (d, *J* = 7.5 Hz, 1H), 5.92 (d, *J* = 8.0 Hz, 1H), 3.75 (dd, *J* = 11.5, 2 Hz, 1H), 2.91 – 2.80 (m, 1H), 2.80 – 2.73 (m, 1H), 2.20 – 2.11 (m, 1H), 2.12 (br s, 1H), 1.98 (s, 3H), 1.88 – 1.78 (m, 1H), 1.31 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 190.8, 162.2, 129.5, 72.8, 72.4, 31.8, 30.4, 26.3, 26.0, 24.9; IR (thin film) ν 3429 (br), 2978, 2938, 2866, 2762, 1668, 1438, 1377, 1159 cm⁻¹; HRMS (ESI) *m* / *z* calcd for C₁₀H₁₇ClO₂Na (M + Na)⁺ 227.0815, found 227.0825.

General Procedure A: Intramolecular Oxa-Michael Reaction

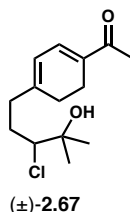
To a 1-dram vial containing the appropriate prolinol catalyst (0.2–0.4 equiv) and additive (0–1 equiv) was added enal **2.12** (1 equiv) in the specified solvent (0.4 M). The reaction mixture was stirred at the specified temperature for the specified time. The reaction mixture was diluted with EtOAc and saturated aqueous NaHCO₃ solution was added. The aqueous layer was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was analyzed using ¹H NMR spectroscopy.



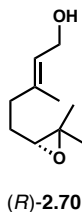
Aldehyde 2.66. The title compounds were prepared according to General Procedure A using the various conditions listed in Table 2.1. The following is a representative procedure (Entry 8, Table 2.1). Aldehyde **2.66** was prepared using enal **2.12** (13.9 mg, 0.0679 mmol), prolinol catalyst **2.59** (5.4 mg, 0.0204 mmol), and PhMe (0.17 mL). The crude material was analyzed using ^1H NMR spectroscopy. Aldehyde diastereomers *trans*-**2.66** and *cis*-**2.66** were separated for analytical purposes using flash chromatography (SiO_2 , 100% CH_2Cl_2).

trans-**2.66**: ^1H NMR (CDCl_3 , 500 MHz) δ 9.83 (t, $J = 3.0$ Hz, 1H), 3.74 (dd, $J = 11.8, 4.3$ Hz, 1H), 2.46 (dd, $J = 14.8, 2.8$ Hz, 1H), 2.36 (dd, $J = 14.8, 2.8$ Hz, 1H), 2.18 – 2.01 (m, 2H), 1.78 – 1.72 (m, 2H), 1.38 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 203.0, 76.1, 73.2, 64.5, 56.9, 36.4, 30.3, 27.0, 26.8, 23.0; IR (thin film) ν 2978, 2954, 2875, 2743, 1721, 1456, 1378, 1126, 1018, 982 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{17}\text{ClO}_2\text{NaCH}_3\text{OH}$ ($\text{M} + \text{Na} + \text{CH}_3\text{OH}$) $^+$ 259.1077, found 259.1066.

cis-**2.66**: ^1H NMR (CDCl_3 , 500 MHz) δ 9.89 (t, $J = 2.8$ Hz, 1H), 3.89 (dd, $J = 8.0, 3.5$ Hz, 1H), 2.65 (dd, $J = 15.5, 3.0$ Hz, 1H), 2.30 (dd, $J = 15.3, 2.8$ Hz, 1H), 2.25 – 2.18 (m, 1H), 2.07 – 1.98 (m, 2H), 1.60 – 1.52 (m, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 203.2, 75.3, 72.5, 64.0, 54.2, 33.2, 29.44, 29.40, 26.4, 26.2; IR (thin film) ν 2978, 2951, 2858, 2744, 1720, 1450, 1379, 1123, 1107, 1010, 987 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{17}\text{ClO}_2\text{NaCH}_3\text{OH}$ ($\text{M} + \text{Na} + \text{CH}_3\text{OH}$) $^+$ 259.1077, found 259.1067.

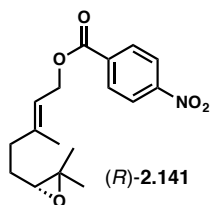


(±)-Methyl Ketone 2.67. A 2-dram vial was charged with enal **2.12** (20.3 mg, 0.0992 mmol), prolinol catalyst **2.59**⁵⁹ (5.3 mg, 0.0198 mmol), and benzoic acid (2.4 mg, 0.0198 mmol). The vial was sealed with a septum, the headspace was purged with argon, and the reaction mixture was cooled to 0 °C. Methyl vinyl ketone (50 μL, 0.595 mmol) was added *via* syringe. The solution was allowed to warm to room temperature overnight. After 12 h, the reaction mixture was concentrated *in vacuo*, and the crude residue was purified using flash chromatography (SiO₂, 20% EtOAc/hexanes) to afford methyl ketone **2.67** (17.0 mg, 67%) as the major component of a mixture of Robinson annulation products. ¹H NMR (CDCl₃, 500 MHz) δ 6.88 (d, *J* = 5.5 Hz, 1H), 5.92 (d, *J* = 5.5 Hz, 1H), 3.78 (dd, *J* = 11.3, 1.3 Hz, 1H), 2.65 – 2.40 (m, 3H), 2.35 – 2.28 (m, 1H), 2.31 (s, 3H), 2.20 – 2.10 (m, 2H), 2.10 – 2.02 (m, 1H), 1.81 – 1.71 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.4, 148.3, 135.0, 134.5, 120.0, 73.1, 72.9, 35.2, 30.7, 27.4, 26.6, 25.6, 25.1, 20.4; IR (thin film) ν 3434 (br), 3050, 2975, 2933, 2879, 1652, 1573, 1389, 1273 cm⁻¹; HRMS (ESI) *m* / *z* calcd for C₁₄H₂₁ClO₂Na (M + Na)⁺ 279.1128, found 229.1137.

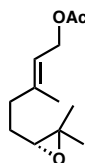


(*R,E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol (2.70). The title compound was prepared according to the literature procedure using a Sharpless dihydroxylation of geranyl

acetate.³⁰ The spectral data for this compound are consistent with those reported in the literature.³⁰ $[\alpha]_D^{23} = +10.2$ ($c = 1.0$, MeOH), lit.³⁰ $[\alpha]_D^{23} = -8.7$ ($c = 1.0$, MeOH) for the (*S*)-form; ^1H NMR (CDCl_3 , 500 MHz) δ 5.45 (t, $J = 7.0$ Hz, 1 H), 4.15 (d, $J = 6.5$ Hz, 2H), 2.71 (t, $J = 6.3$ Hz, 1H), 2.25 – 2.10 (m, 2H), 1.69 (s, 3H), 1.69 – 1.63 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.8, 124.1, 64.2, 59.4, 58.5, 36.4, 27.3, 25.0, 18.9, 16.4. The enantiomeric excess of (*R,E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol was determined as 88% after formation of the *p*-nitrobenzoyl ester.

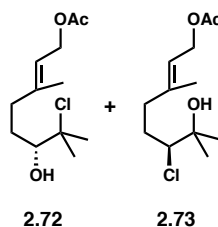


***p*-Nitrobenzoyl ester 2.141 (not shown).** A mixture of *p*-nitrobenzoic acid (4.8 mg, 0.028 mmol), dicyclohexylcarbodiimide (4.7 mg, 0.028 mmol), and DMAP (0.5 mg, 0.0020 mmol) in CH_2Cl_2 (0.28 mL) was stirred for 15 min at room temperature. 6,7-Epoxygeraniol (4.8 mg, 0.028 mmol) was added as a solution in CH_2Cl_2 (0.2 mL). The reaction was stirred for 15 h, diluted with CH_2Cl_2 , filtered through Celite, and concentrated *in vacuo*. Flash chromatography (SiO_2 , 10% EtOAc/hexanes) afforded the title compound as a clear oil (8.4 mg, 93%) in 88% ee, which was determined using chiral HPLC (Chiralpak AS-H column, 5% *i*PrOH in hexanes, flow rate of 1 mL/min). The spectral data for this compound are consistent with those reported in the literature.^{60,61} $[\alpha]_D^{23} = +4.9$ ($c = 0.46$, CHCl_3), lit.⁶¹ $[\alpha]_D^{24} = +46$ ($c = 0.4$, CHCl_3) for the (*R*)-form (91% ee); ^1H NMR (CDCl_3 , 500 MHz) δ 8.28 (d, $J = 9.0$ Hz, 2 H), 8.21 (d, $J = 9.0$ Hz, 2H), 5.52 (t, $J = 7.7$ Hz, 1H), 4.90 (d, $J = 7.5$ Hz, 2H), 2.72 (t, $J = 6.3$ Hz, 1H), 2.31 – 2.16 (m, 2H), 1.81 (s, 3H), 1.73 – 1.66 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.8, 150.6, 142.6, 136.0, 130.9, 123.7, 118.4, 64.0, 62.8, 58.5, 36.4, 27.2, 25.0, 18.9, 16.8.



2.71

(*R,E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 4-acetate (2.71). To a solution of (*R,E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol (4.74 g, 27.8 mmol) and DMAP (0.0680 g, 0.557 mmol) in CH₂Cl₂ (56 mL) was added triethylamine (5.82 mL, 41.8 mmol). The reaction mixture was cooled to 0 °C, and acetic anhydride (3.16 mL, 33.4 mmol) was added dropwise via syringe. After 30 min, the reaction mixture was allowed to warm to room temperature. Water (100 mL) and CH₂Cl₂ (40 mL) were added to the reaction mixture. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 60 mL). The combined organic extracts were washed with 1 N HCl (100 mL), saturated NaHCO₃ solution (100 mL), and brine (100 mL). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% EtOAc/hexanes) to afford the title compound (5.57 g, 81%) as a colorless oil. The spectral data for this compound are consistent with those reported in the literature.⁶² $[\alpha]_D^{21} = +2.4$ (c = 1.0, EtOH), lit.⁶³ $[\alpha]_D^{20} = +2.3$ (c = 0.96, EtOH); ¹H NMR (CDCl₃, 500 MHz) δ 5.37 (t, *J* = 7.3 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 2H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.25 – 2.10 (m, 2H), 2.04 (s, 3H), 1.72 (s, 3H), 1.69 – 1.62 (m, 2H), 1.30 (s, 3H), 1.25 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.2, 141.4, 119.0, 64.0, 61.4, 58.5, 36.3, 27.2, 25.0, 21.2, 18.9, 16.6.

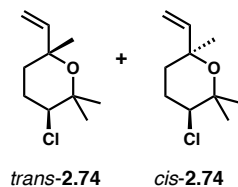


Chlorohydrins 2.72 and 2.73. To a solution of lithium chloride (11.0 g, 260 mmol) in DMF (230 mL) was added a solution of epoxide **2.71** (5.51 g, 26.0 mmol) in DMF (30 mL) via syringe. A solution of PPTS (8.48 g, 33.7 mmol) in DMF (40 mL) was added to the reaction mixture. After 1 h, water (250 mL) was added to the reaction mixture. The reaction mixture was extracted with EtOAc (3 x 200 mL), and the combined organic extracts were washed with saturated NaHCO₃ solution (300 mL) and brine (300 mL). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 15% EtOAc/hexanes) to afford chlorohydrin **2.72** (2.92 g, 45%) and chlorohydrin **2.73** (3.33 g, 52%) as colorless oils.

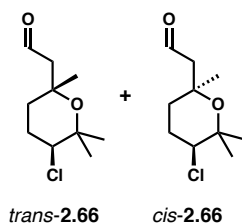
Chlorohydrin **2.72**: $[\alpha]_D^{23} = +24.0$ (c = 1.00, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 5.38 (td, *J* = 7.0, 1.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 2H), 3.47 (d, *J* = 10.0 Hz, 1H), 2.35 (ddd, *J* = 14.5, 10.0, 5.0 Hz, 1H), 2.16 – 2.09 (m, 1H), 2.05 (s, 3H), 1.78 – 1.70 (m, 1H), 1.71 (s, 3H), 1.59 (s, 3H), 1.55 (s, 3H), 1.53 – 1.48 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3, 141.8, 119.0, 78.5, 76.3, 61.4, 36.4, 29.5, 29.4, 27.2, 21.2, 16.6; IR (thin film) ν 3471 (br), 2978, 2934, 1738, 1457, 1368, 1235, 1024 cm⁻¹; HRMS (CI) *m* / *z* calcd for C₁₂H₂₁ClO₃NH₄ (M + NH₄)⁺ 266.1523, found 266.1516.

Chlorohydrin **2.73**: $[\alpha]_D^{23} = -40.2$ (c = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 5.39 (t, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 2H), 3.77 (dd, *J* = 11.5, 1.5 Hz, 1H), 2.38 (ddd, *J* = 13.8, 9.0, 4.5 Hz, 1H), 2.19 – 2.10 (m, 2H), 2.05 (s, 3H), 2.03 – 1.97 (m, 1H), 1.75 – 1.66 (m, 1H), 1.70 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3, 140.7, 119.6, 73.5, 72.9,

61.4, 37.1, 31.1, 26.5, 25.4, 21.2, 16.6; IR (thin film) ν 3459 (br), 2979, 2937, 1738, 1445, 1368, 1235, 1025, 958 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{21}\text{ClO}_3\text{Na}$ ($\text{M} + \text{Na}$)⁺ 271.1077, found 271.1066.



cis- and trans-Tetrahydropyrans 2.74. The following procedure was adapted from Guérinot *et al.*³⁴ To a solution of chlorohydrin **2.73** (1.01 g, 4.05 mmol) in CH_2Cl_2 (41 mL) was added $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.0547 g, 0.202 mmol) in one portion. After 2.5 h, the reaction mixture was purified directly using flash chromatography (SiO_2 , 100% CH_2Cl_2) to afford a 1:1.7 mixture of *cis*- and *trans*-tetrahydropyrans **2.74** (0.533 g, 70%) as a colorless oil, which was characterized as a mixture. $[\alpha]_{\text{D}}^{22} = -7.7$ ($c = 1.0$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 5.97 (dd, $J = 18.0$, 11.0 Hz, 1H), 5.91 (dd, $J = 18.0$, 11.0 Hz, 1H), 5.05 (d, $J = 18.0$ Hz, 1H), 5.00 (d, $J = 11.0$ Hz, 1H), 4.97 (d, $J = 18.0$ Hz, 1H), 4.96 (d, $J = 11.0$ Hz, 1H), 3.89 (dd, $J = 7.0$, 3.5 Hz, 1H), 3.76 (dd, $J = 12.3$, 4.3 Hz, 1H) 2.24 – 2.12 (m, 2H), 2.10 – 1.87 (m, 4H), 1.78 (ddd, $J = 14.0$, 7.3, 4.0 Hz, 1H) 1.60 (ap td, $J = 13.5$, 4 Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.9, 145.7, 111.0, 110.8, 76.6, 75.1, 74.1, 73.8, 65.2, 64.7, 34.1, 32.1, 30.2, 30.1, 29.5, 28.6, 27.9, 27.5, 26.6, 21.4; IR (thin film) ν 3083, 2978, 2952, 2877, 1451, 1382, 1367, 1146, 1066, 979, 916 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{10}\text{H}_{17}\text{ClONH}_4$ ($\text{M} + \text{NH}_4$)⁺ 206.1312, found 206.1314.

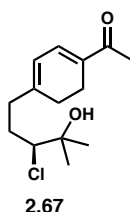


***cis*- and *trans*-Aldehydes 2.66.** A solution of $\text{BH}_3 \cdot \text{DMS}$ (0.19 mL, 2.03 mmol) in THF (3.4 mL) was cooled to 0 °C. Cyclohexene (0.41 mL, 4.05 mmol) was added dropwise *via* syringe over 2 min. After 20 min, the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was cooled to 0 °C and a 1.7:1 mixture of *cis*- and *trans*-**2.74** (0.255 g, 1.35 mmol) was added as a solution in THF (3.4 mL). The transfer was completed with additional portions of THF (2 x 0.5 mL). The reaction mixture was allowed to stir at 0 °C for one hour before allowing to warm to room temperature. After 2 h, the reaction was quenched with water (7 mL) and $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (1.04 g, 6.75 mmol) was added in one portion. The reaction mixture was allowed to stir vigorously for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 20% EtOAc /hexanes) to afford a mixture of *cis*- and *trans*-THPs contaminated with cyclohexanol. ^1H NMR and ^{13}C NMR spectra were complicated by the mixture of tetrahydropyran diastereomers and cyclohexanol contaminant. Sodium bicarbonate (0.776 g, 9.24 mmol) was added to a solution of DMP (1.57 g, 3.70 mmol) in CH_2Cl_2 (18.5 mL) in one portion. A solution of *cis*- and *trans*-THPs contaminated with cyclohexanol (0.382 g, 1.85 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 2 min. The transfer was completed with additional portions of CH_2Cl_2 (2 x 1 mL). After 30 min, the reaction was quenched with a 1:1 mixture of saturated NaHCO_3 solution and saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (20 mL), and allowed to stir until bubbling ceased (20 min). The phases were separated, and the

aqueous phase was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were washed with 1 M NaOH (30 mL) and water (30 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 100% CH₂Cl₂) to afford a 1.4:1 mixture of *cis*- and *trans*-aldehydes **2.66** (0.157 g, 57% over two steps) as a colorless oil. The diastereomers were separated for analytical purposes using flash chromatography (SiO₂, 100% CH₂Cl₂).

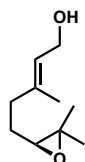
trans-**2.66**: $[\alpha]_D^{22} = -13.6$ (*c* = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 9.82 (t, *J* = 3.0 Hz, 1H), 3.74 (dd, *J* = 11.8, 4.3 Hz, 1H), 2.46 (dd, *J* = 14.8, 2.8 Hz, 1H), 2.36 (dd, *J* = 14.8, 2.8 Hz, 1H), 2.18 – 2.01 (m, 2H), 1.78 – 1.72 (m, 2H), 1.38 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 203.0, 76.1, 73.2, 64.5, 56.9, 36.4, 30.3, 27.0, 26.8, 23.0; IR (thin film) ν 2978, 2954, 2859, 2743, 1721, 1456, 1378, 1126, 1018, 982 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₀H₁₇ClO₂NaCH₃OH (M + Na + CH₃OH)⁺ 259.1077, found 259.1068.

cis-**2.66**: $[\alpha]_D^{22} = +16.3$ (*c* = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 9.89 (t, *J* = 2.8 Hz, 1H), 3.89 (dd, *J* = 8.0, 3.5 Hz, 1H), 2.65 (dd, *J* = 15.5, 3.0 Hz, 1H), 2.30 (dd, *J* = 15.3, 2.8 Hz, 1H), 2.25 – 2.18 (m, 1H), 2.07 – 1.98 (m, 2H), 1.60 – 1.52 (m, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 203.2, 75.3, 72.5, 64.0, 54.2, 33.1, 29.43, 29.40, 26.4, 26.2; IR (thin film) ν 2979, 2952, 2864, 2744, 1720, 1450, 1380, 1123, 1107, 1010, 987 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₀H₁₇ClO₂NaCH₃OH (M + Na + CH₃OH)⁺ 259.1077, found 259.1076.



Methyl Ketone 2.67. A 2-dram vial was charged with a mixture of *cis*- and *trans*-aldehydes **2.66** (0.101 g, 0.492 mmol), prolinol catalyst **2.59**⁵⁹ (0.0202 g, 0.0985 mmol), and 4-EtO₂C-catechol

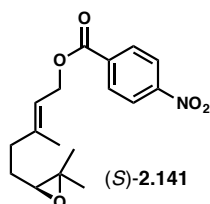
(0.0179 g, 0.0985 mmol). The vial was sealed with a septum, the headspace was purged with argon, and the reaction mixture was cooled to 0 °C. Methyl vinyl ketone (80 µL, 0.985 mmol) was added *via* syringe. The reaction mixture was allowed to stir at 0 °C until the solution became homogenous (30 min) before being placed in a 7 °C refrigerator for 9 days. The reaction mixture was purified directly using flash chromatography (SiO₂, 15:42.5:42.5 EtOAc/CH₂Cl₂/hexanes) to afford methyl ketone **2.67** (0.0650 mg, 51%) as the major component of a mixture of two Robinson annulation products. $[\alpha]_D^{23} = -13.8$ (c = 1.0, CHCl₃) ¹H NMR (CDCl₃, 500 MHz) δ 6.88 (d, *J* = 5.5 Hz, 1H), 5.92 (d, *J* = 5.5 Hz, 1H), 3.78 (dd, *J* = 11.3, 1.3 Hz, 1H), 2.65 – 2.40 (m, 3H), 2.35 – 2.28 (m, 1H), 2.31 (s, 3H), 2.20 – 2.10 (m, 2H), 2.10 – 2.02 (m, 1H), 1.81 – 1.71 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.4, 148.3, 135.0, 134.5, 119.9, 73.2, 72.9, 35.2, 30.7, 27.4, 26.6, 25.6, 25.1, 20.4; IR (thin film) ν 3433 (br), 3049, 2975, 2932, 2879, 1653, 1573, 1388, 1272 cm⁻¹; HRMS (CI) *m* / *z* calcd for C₁₄H₂₁ClO₂H (M + H)⁺ 257.1308, found 257.1305.



(S)-**2.70**

(S,E)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol (2.70). The following procedure was adopted from Wang *et al.*⁴⁰ To a mixture of geraniol (1.1 mL, 6.48 mmol) and tetrabutylammonium hydrogen sulfate (0.088 g, 0.259 mmol) in DME (65 mL) and aqueous K₂CO₃/AcOH (43 mL) (prepared by adding 0.5 mL of glacial AcOH to 100 mL of 0.1 M aqueous K₂CO₃) was added Shi catalyst **2.80**⁶⁴ (0.335 g, 1.30 mmol). The reaction mixture was cooled to 0 °C. A solution of Oxone® (1.99 g, 3.24 mmol) in aqueous Na₂(ETDA) (4 x 10⁻⁴ M) (12 mL) and a solution of K₂CO₃ (1.88 g, 13.61 mmol) in water (12 mL) were added at the same

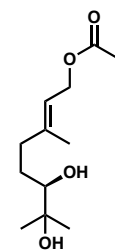
rate using a syringe pump over 1.5 h. After the addition was complete, the reaction was quenched with CH₂Cl₂ (100 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 75 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 30% EtOAc/hexanes) to afford the title compound as a colorless oil (0.555 g, 50%). The spectral data for this compound are consistent with those reported in the literature.³⁰ $[\alpha]_D^{24} = -9.6$ ($c = 1.38$, CHCl₃), lit.⁴⁰ $[\alpha]_D^{23} = +9.7$ ($c = 1.1$, CHCl₃) for the (*R*)-form (77% ee); ¹H NMR (CDCl₃, 600 MHz) δ 5.46 (t, $J = 6.3$ Hz, 1 H), 4.17 (t, $J = 6.0$ Hz, 2H), 2.71 (t, $J = 6.0$ Hz, 1H), 2.25 – 2.11 (m, 2H), 1.70 (s, 3H), 1.69 – 1.64 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 1.19 (t, $J = 5.4$ Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 138.8, 124.1, 64.2, 59.4, 58.5, 36.4, 27.3, 25.0, 18.9, 16.4. The enantiomeric excess of (*S,E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol was determined as 78% after formation of the *p*-nitrobenzoyl ester.



***p*-Nitrobenzoyl ester 2.141 (not shown).** A mixture of *p*-nitrobenzoic acid (5.1 mg, 0.031 mmol), dicyclohexylcarbodiimide (6.6 mg, 0.32 mmol), and DMAP (0.4 mg, 0.0031 mmol) in CH₂Cl₂ (0.3 mL) was stirred for 15 min at room temperature. 6,7-Epoxygeraniol (5.2 mg, 0.031 mmol), prepared *via* Shi epoxidation, was added as a solution in CH₂Cl₂ (0.2 mL). The reaction was stirred for 15 h, diluted with CH₂Cl₂, filtered through Celite, and concentrated *in vacuo*. Flash chromatography (SiO₂, 10% EtOAc/hexanes) afforded the title compound as a clear oil (9.0 mg, 93%) in 78% ee, which was determined using chiral HPLC (Chiralpak AS-H column, 5% *i*PrOH in hexanes, flow rate of 1 mL/min). The spectral data for this compound are

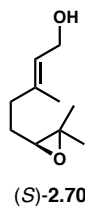
consistent with those reported in the literature.^{60,61} $[\alpha]_D^{24} = -4.0$ ($c = 0.78$, CHCl_3), lit.⁶¹ $[\alpha]_D^{24} = +46$ ($c = 0.4$, CHCl_3) for the (*R*)-form (91% ee); ^1H NMR (CDCl_3 , 600 MHz) δ 8.28 (d, $J = 9.0$ Hz, 2 H), 8.21 (d, $J = 9.0$ Hz, 2H), 5.52 (t, $J = 7.2$ Hz, 1H), 4.90 (d, $J = 7.2$ Hz, 2H), 2.72 (t, 6.3 Hz, 1H), 2.31 – 2.16 (m, 2H), 1.81 (s, 3H), 1.73 – 1.66 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.8, 150.6, 142.6, 136.0, 130.9, 123.7, 118.4, 64.0, 62.8, 58.5, 36.4, 27.2, 25.0, 18.9, 16.8.

(*R,E*)-6,7-Dihydroxy-3,7-dimethyloct-2-enyl acetate (**2.112**) and (*S,E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol (**2.70**) were prepared according to the literature procedure using a Sharpless dihydroxylation of geranyl acetate.³⁰ The spectral data for these compounds are consistent with those reported in the literature.³⁰

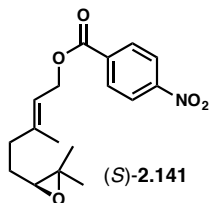


(*R*)-2.112

(*R,E*)-6,7-Dihydroxy-3,7-dimethyloct-2-enyl acetate (2.112). $[\alpha]_D^{25} = +29.0$ ($c = 1.0$, CHCl_3), lit.³⁰ $[\alpha]_D^{23} = +26.8$ ($c = 1.0$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 5.38 (t, $J = 7.0$ Hz, 1H), 4.58 (d, $J = 7.0$ Hz, 2H), 3.33 (ddd, $J = 10.5, 4.0, 1.5$ Hz, 1H), 2.37 – 2.27 (m, 2H), 2.15 – 2.06 (m, 1H), 2.04 (s, 3H), 1.71 (s, 3H), 1.64 – 1.56 (m, 1H), 1.49 – 1.39 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 142.2, 118.9, 78.2, 73.2, 61.5, 36.7, 29.6, 26.6, 23.4, 21.2, 16.6.

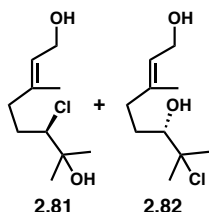


(*S,E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol (2.70). $[\alpha]_{\text{D}}^{25} = -8.2$ ($c = 1.0$, MeOH), lit.³⁰ $[\alpha]_{\text{D}}^{23} = -8.7$ ($c = 1.0$, MeOH); ^1H NMR (CDCl_3 , 500 MHz) δ 5.45 (t, $J = 7.0$ Hz, 1 H), 4.16 (d, $J = 6.0$ Hz, 2H), 2.71 (t, $J = 6.3$ Hz, 1H), 2.25 – 2.11 (m, 2H), 1.70 (s, 3H), 1.69 – 1.64 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.9, 124.1, 64.2, 59.4, 58.5, 36.4, 27.3, 25.0, 18.9, 16.4. The enantiomeric excess of (*S,E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol was determined as 93% after formation of the *p*-nitrobenzoyl ester.



***p*-Nitrobenzoyl ester 2.141 (not shown).** A mixture of *p*-nitrobenzoic acid (11.7 mg, 0.070 mmol), dicyclohexylcarbodiimide (14.5 mg, 0.070 mmol), and DMAP (0.9 mg, 0.007 mmol) in CH_2Cl_2 (0.7 mL) was stirred for 15 min at room temperature. 6,7-Epoxygeraniol (11.4 mg, 0.070 mmol), prepared *via* Sharpless asymmetric dihydroxylation, was added as a solution in CH_2Cl_2 (0.2 mL). The reaction was stirred for 15 h, diluted with CH_2Cl_2 , filtered through Celite, and concentrated *in vacuo*. Flash chromatography (SiO_2 , 10% EtOAc/hexanes) afforded the title compound as a clear oil (21.1 mg, 94%) in 93% ee, which was determined using chiral HPLC (Chiralpak AS-H column, 5% *i*PrOH in hexanes, flow rate of 1 mL/min). The spectral data for this compound are consistent with those reported in the literature.^{60,61} $[\alpha]_{\text{D}}^{25} = -3.9$ ($c = 1.48$, CHCl_3), lit.⁶¹ $[\alpha]_{\text{D}}^{24} = +46$ ($c = 0.4$, CHCl_3) for the (*R*)-form (91% ee); ^1H NMR (CDCl_3 , 500

MHz) δ 8.28 (d, J = 8.5 Hz, 2 H), 8.21 (d, J = 8.5 Hz, 2H), 5.52 (t, J = 7.0 Hz, 1H), 4.90 (d, J = 7.0 Hz, 2H), 2.72 (t, J = 6.0 Hz, 1H), 2.31 – 2.16 (m, 2H), 1.81 (s, 3H), 1.73 – 1.66 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.8, 150.6, 142.6, 136.0, 130.9, 123.7, 118.4, 64.0, 62.8, 58.5, 36.4, 27.2, 25.0, 18.9, 16.8.

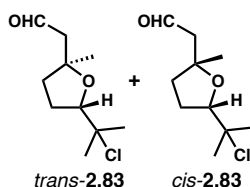


Chlorohydrins 2.81 and 2.82. To a solution of Li_2CuCl_4 (266 mL, 0.5 M in THF, 133.0 mmol) was added TBSCl (4.01 g, 26.6 mmol) in THF (10 mL). The mixture was cooled to 0 °C and the epoxide (4.53 g, 26.6 mmol) was added in THF (10 mL) dropwise via syringe. After addition of the epoxide, the reaction mixture was allowed to warm to room temperature and stirred for 30 min, after which saturated aqueous NaHCO_3 (200 mL) was added slowly. The reaction mixture was allowed to stir until bubbling ceased. The reaction mixture was diluted with water (100 mL), and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with water (300 mL), washed with brine (300 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2 , 40% EtOAc /hexanes), yielding chlorohydrin **2.82** (3.88 g, 71%) as a colorless oil and chlorohydrin **2.81** (0.897 g, 16%) as a colorless oil.

Chlorohydrin **2.81**: $[\alpha]_{\text{D}}^{25} = +43.3$ (c = 1.59, CHCl_3); ^1H NMR (CDCl_3 , 600 MHz) δ 5.48 (t, J = 6.9 Hz, 1H), 4.17 (br s, 2H), 3.80 (dd, J = 11.4, 1.2 Hz, 1H), 2.38 (ddd, J = 13.8, 8.9, 4.5 Hz, 1H), 2.18 – 2.11 (m, 1H), 2.09 (s, 1H), 2.03 – 1.96 (m, 1H), 1.76 – 1.67 (m, 1H), 1.69 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.15 (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.2, 124.7, 73.6, 72.9, 59.5, 37.2, 31.2, 26.5, 25.4, 16.4; IR (thin film) ν 3347 (br), 2977, 2932, 2879, 1669, 1443,

1381, 1157, 998 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{19}\text{ClO}_2\text{Na}$ ($\text{M} + \text{Na}$) $^{+}$ 229.0971, found 229.0966.

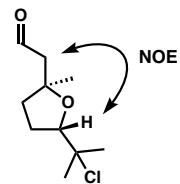
Chlorohydrin **2.82**: $[\alpha]_{\text{D}}^{25} = -24.5$ ($c = 1.00$, CHCl_3); ^1H NMR (CDCl_3 , 600 MHz) δ 5.47 (t, $J = 6.9$ Hz, 1H), 4.17 (br s, 2H), 3.49 (ddd, $J = 10.3, 5.6, 1.6$ Hz, 1H), 2.35 (ddd, $J = 14.6, 10.0, 5.0$ Hz, 1H), 2.15 – 2.10 (m, 1H), 2.09 (d, $J = 5.8$ Hz, 1H), 1.78 – 1.72 (m, 1H), 1.70 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H), 1.53 – 1.46 (m, 1H), 1.16 (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.3, 124.0, 78.5, 76.3, 59.5, 36.4, 29.6, 29.4, 27.3, 27.2, 16.4; IR (thin film) ν 3351 (br), 2976, 2931, 2874, 1670, 1456, 1385, 1117, 1081, 999 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{19}\text{ClO}_2\text{Na}$ ($\text{M} + \text{Na}$) $^{+}$ 229.0971, found 229.0974.



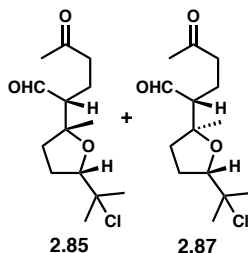
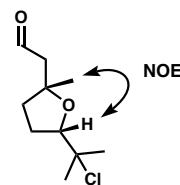
Aldehyde 2.83. To a solution of chlorohydrin **2.82** (0.301 g, 1.46 mmol) in CH_2Cl_2 (29.2 mL) was added MnO_2 (3.01 g, 10 mass equivalents). The reaction mixture was stirred for 2.5 h, filtered through a plug of SiO_2 , rinsed with Et_2O (120 mL), and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2 , 15% Et_2O /pentane) to afford a 6:1 mixture of *trans*- and *cis*-tetrahydropyrans (0.147 g, 49%) as a colorless oil. The isolated yield of the mixture of *trans*- and *cis*-tetrahydropyrans ranges from 48–58%.

trans-**2.83**: $[\alpha]_{\text{D}}^{24} = +11.6$ ($c = 1.55$, CHCl_3); ^1H NMR (CDCl_3 , 600 MHz) δ 9.82 (t, $J = 2.7$ Hz, 1H), 3.98 (t, $J = 7.2$ Hz, 1H), 2.62 (dd, $J = 15.0, 2.4$ Hz, 1H), 2.56 (dd, $J = 15.0, 3.0$ Hz, 1H), 2.08 – 1.98 (m, 2H), 1.95 – 1.83 (m, 2H), 1.55 (s, 3H), 1.53 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.3, 86.4, 82.1, 70.9, 54.1, 37.8, 29.7, 28.2, 27.8, 27.5; IR (thin film) ν 2976, 2933, 2873, 2737, 1722, 1459, 1378, 1120, 1067, 1031 cm^{-1} ; HRMS (CI) m/z calcd for

$C_{10}H_{17}ClO_2NH_4$ ($M + NH_4$)⁺ 222.1261, found 222.1254. ¹H-NOESY-2D (500 MHz, CDCl₃) spectra were obtained for *trans*-**2.83** and selected NOE interactions are shown.



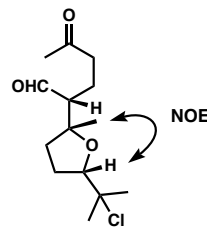
cis-**2.83**: $[\alpha]_D^{24} = -17.9$ ($c = 0.25$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 9.87 (t, $J = 2.8$ Hz, 1H), 3.98 (t, $J = 7.3$ Hz, 1H), 2.68 (dd, $J = 15.0, 2.5$ Hz, 1H), 2.56 (dd, $J = 15.0, 3.0$ Hz, 1H), 2.12 – 1.97 (m, 2H), 1.96 – 1.81 (m, 2H), 1.56 (s, 3H), 1.52 (s, 3H), 1.32 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 202.9, 85.6, 82.0, 71.4, 54.4, 37.5, 29.7, 28.8, 27.7, 26.7; IR (thin film) ν 2974, 2929, 2871, 2735, 1722, 1458, 1376, 1121, 1068, 1030 cm⁻¹; HRMS (CI) m/z calcd for $C_{10}H_{17}ClO_2NH_4$ ($M + NH_4$)⁺ 222.1261, found 222.1258. ¹H-NOESY-2D (500 MHz, CDCl₃) spectra were obtained for *cis*-**2.83** and selected NOE interactions are shown.



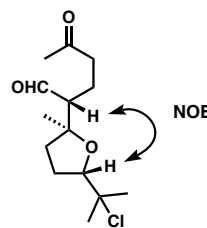
Keto-aldehydes 2.85 and 2.87. A 2-dram vial was charged with a mixture of *cis*- and *trans*-aldehydes **2.83** (0.671 g, 3.28 mmol), prolinol catalyst **2.59**⁵⁹ (0.175 g, 0.656 mmol), and 4-EtO₂C-catechol (0.120 g, 0.656 mmol). The vial was sealed with a septum, the headspace was purged with argon, and the reaction mixture was cooled to 0 °C. Methyl vinyl ketone (0.53 mL, 6.56 mmol) was added *via* syringe. The reaction mixture was allowed to stir at 0 °C until the solution became homogenous (30 min) before being placed in a 7 °C refrigerator for 9 days. The reaction mixture was purified directly using flash chromatography (SiO₂, 12.5% EtOAc/hexanes) to afford keto-aldehyde **2.85** (0.279 g, 31%) as a colorless oil and keto-aldehyde **2.87** (0.431 g,

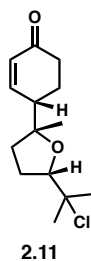
48%) containing ca. 20% other diastereomers. The isolated yield of keto-aldehyde **2.85** ranges from 23–25% when the material is derived from epoxide **2.70** that is prepared *via* Shi epoxidation (78% ee). The isolated yield of keto-aldehyde **2.85** ranges from 25–31% when the material is derived from epoxide **2.70** that is prepared *via* Sharpless asymmetric dihydroxylation (93% ee).

Keto-aldehyde **2.85**: $[\alpha]_D^{24} = -87.8$ ($c = 1.25$, CHCl_3); ^1H NMR (CDCl_3 , 600 MHz) δ 9.88 (d, $J = 1.2$ Hz, 1H), 3.98 (t, $J = 6.9$ Hz, 1H), 2.57 (ddd, $J = 18.2, 8.4, 5.4$ Hz, 1H), 2.51 (dt, $J = 11.1, 2.2$ Hz, 1H), 2.38 (dt, $J = 18.2, 7.6$ Hz, 1H), 2.12 (s, 3H), 2.10 – 2.00 (m, 3H), 1.93 – 1.85 (m, 1H), 1.82 – 1.75 (m, 1H), 1.68 – 1.60 (m, 1H), 1.57 (s, 3H), 1.52 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 208.2, 205.7, 85.7, 85.4, 71.5, 60.3, 41.7, 37.0, 30.1, 29.8, 28.8, 27.2, 23.2, 19.4; IR (thin film) ν 2975, 2933, 2870, 2732, 1717, 1455, 1369, 1165, 1119, 1091, 1072, 1030 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{23}\text{ClO}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 297.1234, found 297.1235. ^1H -NOESY-2D (500 MHz, CDCl_3) spectra were obtained for keto-aldehyde **2.85** and selected NOE interactions are shown.

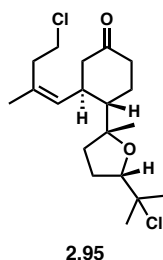


Keto-aldehyde **2.87**: $[\alpha]_D^{24} = -37.8$ ($c = 1.02$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 9.71 (d, $J = 3.0$ Hz, 1H), 3.84 (ap t, $J = 7.3$ Hz, 1H), 2.59 – 2.36 (m, 3H), 2.12 (s, 3H), 2.06 – 1.73 (m, 6H), 1.54 (s, 3H), 1.51 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 208.2, 204.6, 86.7, 84.4, 70.6, 60.3, 41.6, 35.8, 30.1, 29.7, 28.4, 27.6, 25.6, 18.9; IR (thin film) ν 2976, 2934, 2872, 2731, 1717, 1457, 1369, 1162, 1121, 1068, 1028 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{23}\text{ClO}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 297.1234, found 297.1230. ^1H -NOESY-2D (500 MHz, CDCl_3) spectra were obtained for keto-aldehyde **2.87** and selected NOE interactions are shown.



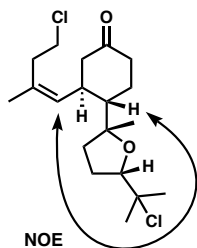


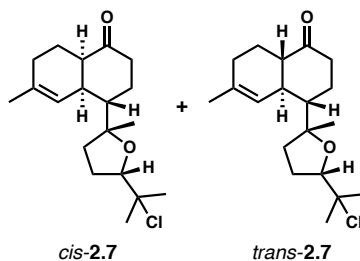
Enone 2.11. A solution of keto-aldehyde **2.85** (0.279 g, 1.02 mmol) and catalyst **2.86**⁴⁴ (0.0818 g, 0.305 mmol) in hexanes (10.2 mL, previously sparged with argon gas for 20 min) was stirred at room temperature for 21 h. The reaction mixture was concentrated *in vacuo*, and the resulting crude residue was purified using flash chromatography (SiO₂, 10 → 15% EtOAc/hexanes) to afford the title compound (0.195 g, 75%) as a colorless oil. $[\alpha]_D^{24} = -55.1$ ($c = 0.58$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.17 (d, $J = 10.5$ Hz, 1H), 6.07 (dd, $J = 10.3, 2.2$ Hz, 1H), 3.99 (t, $J = 7.0$ Hz, 1H), 2.64 (d, $J = 11.5$ Hz, 1H), 2.52 (dt, $J = 16.5, 3.5$ Hz, 1H), 2.37 (td, $J = 15.5, 5.0$ Hz, 1H), 2.12 – 1.95 (m, 3H), 1.93 – 1.86 (m, 1H), 1.80 – 1.68 (m, 2H), 1.56 (s, 3H), 1.52 (s, 3H), 1.14 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 199.9, 153.0, 130.2, 85.2, 85.0, 71.6, 46.9, 37.6, 35.7, 29.9, 28.6, 27.8, 25.5, 22.4; IR (thin film) ν 2973, 2934, 2872, 1681, 1454, 1382, 1089 cm⁻¹; HRMS (CI) m/z calcd for C₁₄H₂₁ClO₂NH₄ (M + NH₄)⁺ 274.1574, found 274.1581.



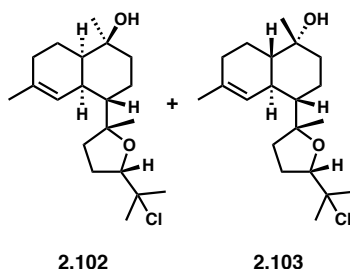
Ketone 2.95. To a solution of vinyl iodide **2.39** (0.233 g, 1.01 mmol) in Et₂O (1.7 mL, previously sparged with argon gas for 20 min) at -78 °C was added *tert*-butyllithium (1.35 mL, 1.5 M in pentane, 2.02 mmol) dropwise *via* syringe. After 20 min, lithium 2-thienylcyanocuprate solution (4.04 mL, 0.25 M in THF, 1.01 mmol) was added dropwise *via* syringe. The reaction

mixture was allowed to stir for 1 h at $-78\text{ }^{\circ}\text{C}$. A solution of enone **2.11** (0.172 g, 0.670 mmol) in Et_2O (1 mL) was added dropwise *via* syringe. The transfer was completed with an additional portion of Et_2O (0.5 mL). Immediately following this addition, $\text{BF}_3\cdot\text{OEt}_2$ (0.11 mL, 0.871 mmol) was added dropwise *via* syringe. After allowing the reaction mixture to stir for 3 h at $-78\text{ }^{\circ}\text{C}$, the reaction was quenched with 9:1 saturated NH_4Cl solution/ NH_4OH (15 mL). After warming to room temperature, the solution turned a deep blue color. The aqueous layer was extracted with Et_2O (15 mL). The combined organic extracts were washed with 9:1 saturated NH_4Cl solution/ NH_4OH (2 x 10 mL), washed with brine (10 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 10% EtOAc /hexanes) to afford the title compound (200 mg, 83%) as a white solid (mp $62\text{--}64\text{ }^{\circ}\text{C}$). $[\alpha]_{\text{D}}^{24} = -6.7$ ($c = 0.56$, CHCl_3); ^1H NMR (CDCl_3 , 600 MHz) δ 5.37 (d, $J = 9.6$ Hz, 1H), 3.91 (dd, $J = 8.4, 5.4$ Hz, 1H), 3.60 – 3.50 (m, 2H), 2.80 (qd, $J = 9.6, 4.8$ Hz, 1H), 2.57 (dt, $J = 14.7, 7.8$, 1H), 2.50 – 2.27 (m, 4H), 2.17 (dd, $J = 14.7, 10.5$ Hz, 1H), 2.09 – 1.98 (m, 2H), 1.97 – 1.89 (m, 1H), 1.84 (ddd, $J = 11.4, 8.7, 3.6$ Hz, 1H), 1.75 (quin, $J = 10.0$ Hz, 1H), 1.71 – 1.64 (m, 1H), 1.68 (s, 3H), 1.64 – 1.55 (m, 1H), 1.54 (s, 3H), 1.51 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 211.5, 133.8, 127.4, 86.3, 84.5, 72.1, 50.7, 47.6, 42.5, 40.3, 38.4, 36.8, 35.2, 30.0, 28.3, 27.3, 26.8, 23.0, 21.1; IR (thin film) ν 2968, 2932, 2873, 1716, 1456, 1375, 1076, 1028 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{19}\text{H}_{29}\text{ClO}_2$ ($\text{M} - \text{Cl}$) $^{+}$ 324.1856, found 324.1861. ^1H -NOESY-2D (500 MHz, CDCl_3) spectra were obtained for ketone **2.95** and selected NOE interactions are shown.





***cis*- and *trans*-Decalones 2.7.** To a solution of alkyl chloride **2.95** (0.205 g, 0.566 mmol) in *tert*-butyl alcohol (2.8 mL) at 30 °C was added potassium *tert*-butoxide (0.68 mL, 1 M in THF, 0.680 mmol) dropwise *via* syringe. After stirring for 8 h at 30 °C, the reaction was quenched with saturated NH₄Cl solution (15 mL). The aqueous layer was extracted with pentane (3 x 15 mL), and the combined organic extracts were washed with water (3 x 10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 5% EtOAc/hexanes) to afford a 1.3:1 mixture of *cis*- and *trans*-decalones (107.5 mg, 58%) as a colorless oil, which was characterized as a mixture. $[\alpha]_D^{24} = -74.4$ ($c = 0.64$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 6.21 (s, 1H), 5.35 (s, 1H), 4.04 (dd, $J = 9.0, 4.0$ Hz, 1H), 3.95 (dd, $J = 8.0, 6.0$ Hz, 1H), 2.81 (br s, 1H), 2.72 – 2.67 (m, 1H), 2.49 – 2.33 (m, 3 H), 2.28 – 2.14 (m, 4H), 2.13 – 1.66 (m, 20H), 1.64 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H), 1.57 – 1.38 (m, 1H), 1.20 (s, 3H), 1.09 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 215.0, 212.9, 133.6, 133.5, 127.5, 125.1, 87.1, 86.8, 84.7, 84.6, 72.1, 72.0, 51.2, 50.6, 49.7, 45.6, 44.4, 40.9, 38.6, 38.5, 36.3, 36.2, 30.1, 29.8, 29.5, 28.4, 27.6, 27.2, 27.1, 26.1, 24.0, 23.9, 23.8, 22.5, 22.2, 21.9, 18.9; IR (thin film) ν 2966, 2928, 2875, 1713, 1454, 1376, 1139, 1083, 1030 cm⁻¹; HRMS (ESI) m/z calcd for C₁₉H₂₉ClO₂Na (M + Na)⁺ 347.1754, found 347.1749.

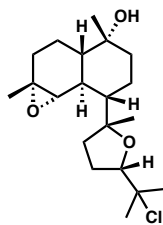


Decalins 2.102 and 2.103. Methylmagnesium bromide (0.24 mL, 2.8 M in Et₂O, 0.660 mmol) was added dropwise to a solution of a mixture of *cis*- and *trans*-decalones (42.9 mg, 0.132 mmol) in THF (1.3 mL) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature for 30 min, and the reaction was quenched with saturated aqueous NH₄Cl solution (4 mL) at 0 °C. The aqueous layer was extracted with Et₂O (3 x 4 mL). The combined organic extracts were washed with brine (6 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% EtOAc/hexanes), yielding *trans*-decalin **2.103** (18.2 mg, 40%) as a colorless oil and *cis*-decalin **2.102** (19.9 mg, 44%) as a white solid (mp 112–114 °C).

cis-Decalin **2.102**: $[\alpha]_D^{24} = +68.3$ (c = 0.75, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 5.69, (d, *J* = 4.5 Hz, 1 H), 4.00 (dd, *J* = 8.8, 4.4 Hz, 1H), 2.25 – 2.15 (m, 1H), 2.06 – 1.88 (m, 6H), 1.68 – 1.50 (m, 8H), 1.62 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H) 1.31 (s, 3 H), 1.25 – 1.13 (m, 1H), 1.12 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 130.6, 127.7, 87.0, 84.9, 72.4, 72.2, 48.9, 46.1, 37.9, 36.8, 35.3, 31.0, 30.3, 28.0, 26.9, 26.7, 26.5, 23.7, 19.8, 18.7; IR (thin film) ν 3361 (br), 2965, 2935, 2892, 2873, 1459, 1376, 1119, 1031 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₀H₃₃ClO₂Na (M + Na)⁺ 363.2067, found 363.2060. X-ray quality crystals (colorless) of *cis*-decalin **2.102** were grown by slow evaporation from pentane (see Appendix B).

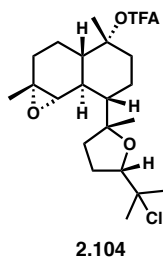
trans-Decalin **2.103**: $[\alpha]_D^{24} = -25.9$ (c = 0.56, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 6.24 (br s, 1H), 4.04 (dd, *J* = 9.0, 4.0 Hz, 1H), 2.21 – 2.15 (m, 1H), 2.05 – 1.88 (m, 6H), 1.62 (s, 3H), 1.54

(s, 3H), 1.50 (s, 3H), 1.22 (s, 3H), 1.11 (s, 3H), 1.75 – 1.08 (m, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 132.1, 126.3, 87.9, 84.6, 72.3, 70.7, 52.2, 47.6, 40.5, 38.5, 38.4, 30.8, 30.2, 28.7, 27.1, 26.0, 25.5, 23.9, 22.9, 18.7; IR (thin film) ν 3454 (br), 2965, 2933, 2871, 1458, 1376, 1120, 1081, 1032, 909 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{33}\text{ClO}_2\text{Na}$ ($\text{M} + \text{Na}$) $^{+}$ 363.2067, found 363.2058.

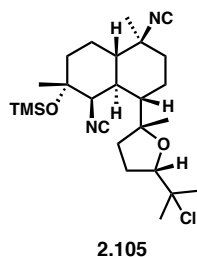


2.101

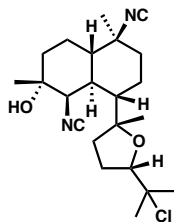
Epoxide 2.101. To a solution of decalin **2.103** (30.0 mg, 0.0880 mmol) in acetone (4.4 mL) was added saturated aqueous NaHCO_3 (2.9 mL). The resulting mixture was cooled to 0 °C and a solution of Oxone® (59.5 mg, 0.0968 mmol) in H_2O (0.60 mL) was added dropwise over 5 minutes. The reaction mixture was stirred vigorously for 30 min at 0 °C, diluted with H_2O (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were diluted with hexanes until cloudy, dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 30% EtOAc/hexanes) to afford epoxide **2.101** (26.9 mg, 86%) as a glassy oil. $[\alpha]_D^{24} = -7.0$ ($c = 0.3$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 4.11 (s, 1H), 3.98 (dd, $J = 9.0, 4.0$ Hz, 1H), 2.10 – 1.98 (m, 2H), 1.94 – 1.88 (m, 2H), 1.72 – 1.59 (m, 5H), 1.58 – 1.40 (m, 4H), 1.48 (s, 6H), 1.27 (s, 3H), 1.22 – 1.13 (m, 1H), 1.20 (s, 3H), 1.17 (s, 3 H), 1.07 (br s, 1H), 0.95 (t, $J = 11.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 87.9, 84.5, 72.2, 70.5, 61.7, 58.6, 50.8, 47.3, 40.3, 39.0, 38.3, 30.8, 29.9, 28.7, 28.0, 26.1, 26.0, 23.6, 19.4, 18.8; IR (thin film) ν 3471 (br), 2968, 2933, 2867, 1457, 1379, 1125, 1080, 1029, 912, 871 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{33}\text{ClO}_3\text{Na}$ ($\text{M} + \text{Na}$) $^{+}$ 379.2016, found 379.2009.



Trifluoroacetate 2.104. A mixture of epoxide **2.101** (26.2 mg, 0.0734 mmol) and pyridine (25 μ L, 0.294 mmol) in CH_2Cl_2 (0.73 mL) at 0 $^\circ\text{C}$ was treated with trifluoroacetic anhydride (0.1 mL, 1.44 M in CH_2Cl_2 , 0.147 mmol). After 30 minutes, the reaction was quenched with 1 M HCl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 3 mL). The combined organic extracts were washed with water (5 mL), washed with saturated NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 90% CH_2Cl_2 /hexanes) to afford the title compound (30.9 mg, 93%) as a colorless oil. $[\alpha]_D^{24} = -35.7$ ($c = 2.8$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 4.09 (s, 1H), 3.98 (dd, $J = 9.0, 4.0$ Hz, 1H), 2.73 (d, $J = 15$ Hz, 1H), 2.12 – 1.88 (m, 4H), 1.57 (s, 3H), 1.49 (s, 6H), 1.28 (s, 3H), 1.17 (s, 3H), 1.72 – 1.10 (m, 9H), 1.01 (t, $J = 11.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.2 (q, $J = 41.3$ Hz), 114.6 (q, $J = 285.4$ Hz), 88.3, 87.6, 84.6, 72.3, 61.3, 58.3, 49.7, 48.5, 38.8, 38.1, 34.7, 30.8, 29.8, 28.3, 26.0, 25.3, 23.8, 23.5, 19.4, 18.5; IR (thin film) ν 2966, 2927, 2870, 1778, 1454, 1377, 1219, 1157 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{32}\text{ClF}_3\text{O}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 475.1839, found 475.1848.



Diisocyanide 2.105. The following procedure was adopted from Pronin *et al.*³ Trifluoroacetate **2.104** (4.7 mg, 0.0085 mmol) was dissolved in a solution of scandium(III) trifluoromethanesulfonate (2.1 mg, 0.0043 mmol, briefly dried under vacuum at ~ 250-300 °C) in TMSCN (0.1 mL). After 24 h at room temperature, the reaction was quenched with TMEDA (10 µL) and the volatiles were removed under reduced pressure. The crude residue was dissolved in hexanes (4 mL), washed with saturated aqueous NaHCO₃ solution (4 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 80% CH₂Cl₂/hexanes) to afford the title compound (1.0 mg, 25%) as a thin film. $[\alpha]_D^{23} = +2.6$ (c = 0.14, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 4.34 (s, 1H), 4.08 (dd, *J* = 9.0, 4.0 Hz, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H), 1.31 (br s, 3H), 2.05 – 1.11 (m, 15H), 1.01 (s, 3H), 0.14 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 157.8 (br t), 153.3 (br t), 87.4, 84.9, 73.4, 71.3, 64.0 (br t, *J* = 5.6 Hz), 59.9 (br t, *J* = 5.6 Hz), 46.4, 42.1, 40.0, 38.6, 35.7, 32.8, 30.2, 27.5, 26.1, 25.8, 24.3, 21.7, 20.6, 17.6, 2.4; IR (thin film) ν 2953, 2933, 2131, 1457, 1384, 1252, 1188, 1038, 842 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₅H₄₁ClN₂O₂SiNa (M + Na)⁺ 487.2523, found 487.2513.



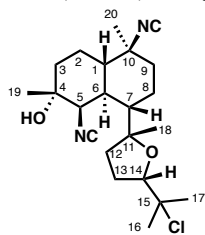
2.2: kalihinol B

Kalihinol B (2.2). To a solution of diisocyanide **2.105** (2.6 mg, 0.0056 mmol) in THF (0.1 mL) cooled to 0 °C was added TBAF (0.11 mL, 0.05 M in THF, 0.0056 mmol). After 5 minutes, the reaction was quenched with pH 7 phosphate buffer (1 mL). The aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were washed with brine (4 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 30% EtOAc/hexanes) to afford kalihinol B (1.9 mg, 86%) as a thin film. The NMR spectra (CDCl₃) for synthetic compound **2.2** match spectral data for reported natural **2.2**.^{65,66} Synthetic **2.2**: $[\alpha]_D^{24} = +7.6$ (c = 0.22, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 4.42, (br s, 1H), 4.06 (dd, *J* = 9.0, 4.0 Hz, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 1.42 (s, 3H), 1.34 (br s, 3H), 1.04 (s, 3H), 2.08 – 1.12 (m, 16H); ¹³C NMR (125 MHz, CDCl₃) δ 158.2 (br t), 153.5 (br t), 87.4, 85.0, 71.3, 70.6, 63.4 (br t, *J* = 5.6 Hz), 59.9 (br t, *J* = 5.0 Hz), 46.5, 42.3, 40.0, 38.6, 36.1, 32.7, 30.1, 28.9, 26.2, 25.8, 24.3, 21.7, 20.9, 17.9; IR (thin film) ν 3415 br (OH), 2972, 2934, 2879, 2134 (NC), 1461, 1385 (*gem*-dimethyl), 1101 (C–O–C), 1027 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₂H₃₃ClN₂O₂Na (M + Na)⁺ 415.2128, found 415.2122.

Reported natural **2.2**: $[\alpha]_D = +10$ (c = 1, CHCl₃); ¹H NMR (CDCl₃) δ 4.40, (br s, 1H), 4.03 (dd, *J* = 9, 4 Hz, 1H), 1.58 (s, 3H), 1.52 (s, 3H), 1.4 (s, 3H), 1.32 (br s, 3H), 1.02 (s, 3H), 2.10 – 0.80 (complex); ¹³C NMR (CDCl₃) δ 87.2, 84.9, 71.1, 70.4, 63.3 (br t, *J* = 5 Hz), 59.8 (br t, *J* = 5 Hz), 46.4, 42.2, 39.9, 38.4, 35.9, 32.6, 29.9, 28.7, 25.7, 25.7, 24.1, 21.6, 20.8, 17.8; IR (CHCl₃) ν

3600 (free OH), 3400 br (assoc OH), 2150 (NC), 1380 (*gem*-dimethyl), 1100 (C–O–C) cm⁻¹;
 HRMS (EI) *m/z* calcd for C₂₁H₃₀ClN₂O₂ (M – Me)⁺ 377.1996, found 377.2009.

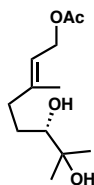
Table 2.5 Comparison of ¹³C NMR data (CDCl₃) for synthetic and natural kalihinol B (**2.2**)



2.2: *kalihinol B*
 reported structure

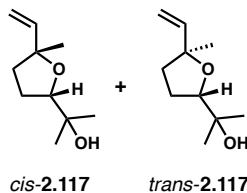
Assignment	Synthetic 2.2 (ppm)	Natural 2.2 (ppm)	Δ
1	42.3	42.2	0.1
2	21.7	21.6	0.1
3	32.7	32.6	0.1
4	70.6	70.4	0.2
5	63.4 (br t, <i>J</i> = 5.6 Hz)	63.3 (br t, <i>J</i> = 5 Hz)	0.1
6	36.1	35.9	0.2
7	46.5	46.4	0.1
8	24.3	24.1	0.2
9	40.0	39.9	0.1
10	59.9 (br t, <i>J</i> = 5.0 Hz)	59.8 (br t, <i>J</i> = 5 Hz)	0.1
11	87.4	87.2	0.2
12	38.6	38.4	0.2
13	25.8	25.7	0.1
14	85.0	84.9	0.1
15	71.3	71.1	0.2
16	30.1	29.9	0.2
17	26.2	26.1	0.1
18	17.9	17.8	0.1
19	28.9	28.7	0.2
20	20.9	20.7	0.2
Isonitrile 1	158.2 (br t)	Not Observed ^a	---
Isonitrile 2	153.5 (br t)	Not Observed ^a	---

^aIsoctyano carbon resonances were not observed due to small sample size, insufficient pulsing, and the broadness of the signals.



2.112

(*S,E*)-6,7-Dihydroxy-3,7-dimethyloct-2-enyl acetate (2.112). (*S,E*)-6,7-Dihydroxy-3,7-dimethyloct-2-enyl acetate (**2.112**) was prepared according to the literature procedure using a Sharpless dihydroxylation of geranyl acetate.³⁰ The spectral data for this compound are consistent with those reported in the literature.³⁰ $[\alpha]_D^{24} = -22.5$ ($c = 1.0$, CHCl_3), lit.³⁰ $[\alpha]_D^{23} = +26.8$ ($c = 1.0$, CHCl_3) for the (*R*)-form; ^1H NMR (CDCl_3 , 500 MHz) δ 5.39 (t, $J = 7.0$ Hz, 1H), 4.58 (d, $J = 7.5$ Hz, 2H), 3.34 (ddd, $J = 10.5, 4.5, 1.5$ Hz, 1H), 2.37 – 2.28 (m, 1H), 2.25 (d, $J = 4.5$ Hz, 1H), 2.15 – 2.06 (m, 1H), 2.05 (s, 3H), 1.98 (s, 1H), 1.72 (s, 3H), 1.64 – 1.56 (m, 1H), 1.49 – 1.39 (m, 1H), 1.21 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 142.2, 118.9, 78.2, 73.2, 61.5, 36.7, 29.6, 26.6, 23.4, 21.2, 16.6. The enantiomeric excess of **2.112** was determined as 90% by ^1H NMR analysis of its corresponding mono-(*R*)-MTPA ester. ^1H NMR (500 MHz, CDCl_3) δ 5.30 ppm (t, 1H) for the *S* enantiomer; δ 5.23 ppm (t, 1H) for the *R* enantiomer, corresponding to the methyl group on the methoxy group of the ester.

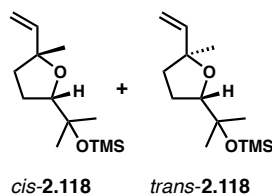


***cis*- and *trans*-Linalyl oxides (2.117).** The following procedure was adapted from Guérinot *et al.*³⁴ To a solution of diol **2.112** (4.23 g, 18.37 mmol) in CH_2Cl_2 (184 mL) was added $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1.24 g, 4.59 mmol) in one portion. After stirring at 40 °C for 5 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude residue was

purified using flash chromatography (SiO₂, 25 → 30% Et₂O/pentane) to afford a 1:1.7 mixture of *cis*- and *trans*-linalyl oxides (3.06 g, 97%) as a colorless oil. The *cis*- and *trans*-THFs were separated for analytical purposes, and the spectral data for these compounds are consistent with those reported in the literature.^{67–70}

trans-**2.117**: $[\alpha]_D^{23} = +5.7$ (c = 0.95, CHCl₃), lit.⁶⁷ $[\alpha]_D^{25} = +4.73$ (c = 2.07, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 5.88 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.19 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.00 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.79 (t, *J* = 7.3 Hz, 1H), 2.16 (s, 1H), 1.94 – 1.80 (m, 3H), 1.76 – 1.69 (m, 1H), 1.31 (s, 3H), 1.23 (s, 3H), 1.13 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 143.8, 111.5, 85.7, 83.2, 71.3, 37.6, 27.4, 27.0, 26.4, 24.3.

cis-**2.117**: $[\alpha]_D^{23} = -3.8$ (c = 0.72, CHCl₃), lit.⁶⁷ $[\alpha]_D^{25} = -2.94$ (c = 2.14, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 5.97 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.20 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.01 (dd, *J* = 10.5, 1.0 Hz, 1H), 3.86 (t, *J* = 7.3 Hz, 1H), 2.07 (s, 1H), 1.96 – 1.74 (m, 4H), 1.32 (s, 3H), 1.23 (s, 3H), 1.13 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 144.5, 111.7, 85.7, 82.9, 71.3, 38.1, 27.6, 26.6, 26.2, 24.5.

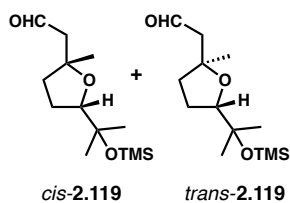


***cis*- and *trans*-Silyl ethers 2.118.** Imidazole (1.21 g, 17.8 mmol) was added in one portion to a solution of *cis*- and *trans*-linalyl oxides (**2.117**) (1.01 g, 5.92 mmol) in CH₂Cl₂ (12 mL). Chlorotrimethylsilane (1.13 mL, 8.88 mmol) was added dropwise *via* syringe. After 30 min, saturated NaHCO₃ solution (15 mL) was added to the reaction mixture. The reaction mixture was diluted with CH₂Cl₂ (10 mL) and water (10 mL). The biphasic mixture was separated, and the aqueous phase was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic phases were

washed with water (30 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 2.5% Et₂O/pentane) to afford a 1:1.7 mixture of *cis*-**2.118** and *trans*-**2.118** (1.30 g, 91%) as a colorless oil. The diastereomers were separated for analytical purposes.

trans-**2.118**: $[\alpha]_D^{23} = +7.1$ (*c* = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 5.86 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.16 (dd, *J* = 17.3, 1.8 Hz, 1H), 4.97 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.74 (t, *J* = 6.5 Hz, 1H), 1.94 – 1.75 (m, 3H), 1.71 – 1.62 (m, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 0.11 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 144.3, 111.2, 86.4, 83.4, 75.2, 37.4, 27.9, 26.7, 26.4, 25.5, 2.7; IR (thin film) ν 2972, 2873, 1465, 1365, 1249, 1171, 1044, 839 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₃H₂₆O₂SiNa (M + Na)⁺ 265.1600, found 265.1604.

cis-**2.118**: $[\alpha]_D^{23} = -0.27$ (*c* = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 5.97 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.20 (dd, *J* = 17.3, 1.8 Hz, 1H), 4.95 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.78 (t, *J* = 7.0 Hz, 1H), 1.94 – 1.86 (m, 2H), 1.85 – 1.78 (m, 1H), 1.74 – 1.65 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 0.11 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 144.8, 111.3, 86.3, 83.1, 75.2, 38.0, 27.9, 26.6, 25.73, 25.70, 2.7; IR (thin film) ν 2972, 2872, 1459, 1365, 1250, 1172, 1045, 840 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₃H₂₆O₂SiNa (M + Na)⁺ 265.1600, found 265.1597.

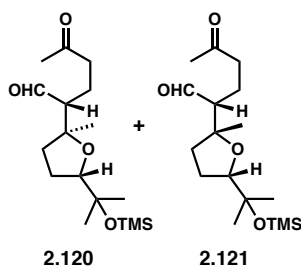


***cis*- and *trans*-Aldehydes 2.119.** A solution of BH₃•DMS (0.60 mL, 6.31 mmol) in THF (10.5 mL) was cooled to 0 °C. Cyclohexene (1.28 mL, 12.62 mmol) was added dropwise *via* syringe over 2 min. After 20 min, the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was cooled to 0 °C and a 1:1.7 mixture of *cis*- and *trans*-**2.118** (1.02 g,

4.21 mmol) was added as a solution in THF (10.5 mL). The transfer was completed with additional portions of THF (2 x 2 mL). The reaction mixture was allowed to stir at 0 °C for one hour before allowing to warm to room temperature. After 3 h, the reaction was quenched with water (30 mL) and NaBO₃•4H₂O (3.24 g, 21.04 mmol) was added in one portion. The reaction mixture was allowed to stir vigorously for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with Et₂O (3 x 60 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 20% EtOAc/hexanes) to afford a mixture of *cis*- and *trans*-THFs contaminated with cyclohexanol. ¹H NMR and ¹³C NMR spectra were complicated by the mixture of tetrahydrofuran diastereomers and cyclohexanol contaminant. Sodium bicarbonate (2.12 g, 25.18 mmol) was added to a solution of DMP (4.27 g, 10.07 mmol) in CH₂Cl₂ (40 mL) in one portion. A solution of *cis*- and *trans*-THFs contaminated with cyclohexanol (1.312 g, 5.036 mmol) in CH₂Cl₂ (5 mL) was added dropwise over 2 min. The transfer was completed with additional portions of CH₂Cl₂ (2 x 2.5 mL). After 2 h, the reaction was quenched with a 1:1 mixture of saturated NaHCO₃ solution and saturated Na₂S₂O₃ solution (50 mL), and allowed to stir until bubbling ceased (20 min). The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with 1 M NaOH (1 x 50 mL) and water (1 x 50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 8.5% Et₂O/pentane) to afford a 1:1.7 mixture of *cis*- and *trans*-aldehydes **2.119** (0.714 g, 66% over two steps) as a colorless oil. The diastereomers were separated for analytical purposes using flash chromatography (SiO₂, 100% CH₂Cl₂).

trans-**2.119**: $[\alpha]_D^{22} = +11.2$ ($c = 0.90$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 9.82 (t, $J = 3.0$ Hz, 1H), 3.73 (t, $J = 7.3$ Hz, 1H), 2.58 (dd, $J = 14.8, 2.8$ Hz, 1H), 2.52 (dd, $J = 14.5, 3.0$ Hz, 1H), 2.00 – 1.72 (m, 4H), 1.31 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 203.0, 87.0, 81.4, 74.8, 54.4, 38.0, 27.7, 27.5, 26.4, 25.9, 2.7; IR (thin film) ν 2972, 2898, 2873, 2736, 1724, 1458, 1380, 1250, 1175, 1068, 1044, 840 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{26}\text{O}_3\text{SiNa}$ ($\text{M} + \text{Na}$) $^+$ 281.1549, found 281.1554.

cis-**2.119**: $[\alpha]_D^{22} = -49.4$ ($c = 1.0$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 9.86 (dd, $J = 3.5, 2.5$ Hz, 1H), 3.77 (t, $J = 7.3$ Hz, 1H), 2.65 (dd, $J = 15.0, 2.5$ Hz, 1H), 2.46 (dd, $J = 15.0, 3.5$ Hz, 1H), 2.02 – 1.88 (m, 2H), 1.87 – 1.80 (m, 1H), 1.79 – 1.72 (m, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 203.9, 86.8, 81.4, 74.9, 54.4, 38.0, 27.3, 27.0, 26.6, 26.2, 2.6; IR (thin film) ν 2970, 2873, 2736, 1723, 1456, 1380, 1250, 1177, 1040, 840 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{26}\text{O}_3\text{SiNa}$ ($\text{M} + \text{Na}$) $^+$ 281.1549, found 281.1539.

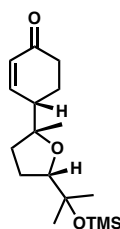


Keto-aldehydes 2.120 and 2.121. A 2-dram vial was charged with a mixture of *cis*- and *trans*-aldehydes **2.119** (0.714 g, 2.76 mmol), prolinol catalyst **2.59**⁵⁹ (0.148 g, 0.553 mmol), and 4-EtO₂C-catechol (0.101 g, 0.553 mmol). The vial was sealed with a septum, the headspace was purged with argon, and the reaction mixture was cooled to 0 °C. Methyl vinyl ketone (0.45 mL, 5.53 mmol) was added *via* syringe. The reaction mixture was allowed to stir at 0 °C until the solution became homogenous (30 min) before being placed in a 7 °C refrigerator for 9 days. The

reaction mixture was purified directly using flash chromatography (SiO₂, 12.5% EtOAc/hexanes) to afford keto-aldehyde **2.121** (0.177 g, 19%) as a colorless oil and keto-aldehyde **2.120** (0.318 g, 35%) containing ca. 25% other diastereomers.

Keto-aldehyde **2.120**: $[\alpha]_D^{22} = -48.6$ ($c = 1.0$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 9.70 (d, $J = 3.0$ Hz, 1H), 3.59 (dd, $J = 8.5, 6.5$ Hz, 1H), 2.51 (ddd, $J = 18.0, 8.5, 5.8$ Hz, 1H), 2.45 – 2.34 (m, 2H), 2.11 (s, 3H), 1.97 – 1.77 (m, 6H), 1.74 – 1.59 (m, 1H), 1.20 (s, 5H), 1.14 (s, 3H), 0.09 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 208.3, 205.1, 87.3, 83.8, 74.4, 60.6, 41.7, 35.9, 30.1, 27.5, 26.2, 26.0, 25.7, 19.0, 2.7; IR (thin film) ν 2972, 2896, 2873, 2730, 1718, 1455, 1363, 1249, 1175, 1041, 839 cm⁻¹; HRMS (CI) m/z calcd for C₁₇H₃₂O₄SiH (M + H)⁺ 329.2148, found 329.2133.

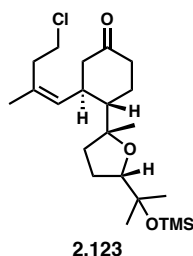
Keto-aldehyde **2.121**: $[\alpha]_D^{22} = -92.7$ ($c = 1.0$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 9.90 (br s, 1H), 3.77 (t, $J = 7.3$ Hz, 1H), 2.56 (ddd, $J = 18.0, 8.0, 5.5$ Hz, 1H), 2.50 (dt, $J = 11.0, 1.8$ Hz, 1H), 2.33 (dt, $J = 18.0, 7.5$ Hz, 1H), 2.09 (s, 3H), 2.06 – 1.77 (m, 4H), 1.70 – 1.63 (m, 1H), 1.61 – 1.52 (m, 1H), 1.23 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 0.07 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 208.3, 207.1, 87.0, 85.0, 74.9, 59.5, 41.9, 37.2, 30.1, 27.2, 26.8, 25.8, 23.4, 19.5, 2.6; IR (thin film) ν 2970, 2873, 2730, 1718, 1449, 1364, 1250, 1176, 1038, 840 cm⁻¹; HRMS (CI) m/z calcd for C₁₇H₃₂O₄SiH (M + H)⁺ 329.2148, found 329.2138.



2.122

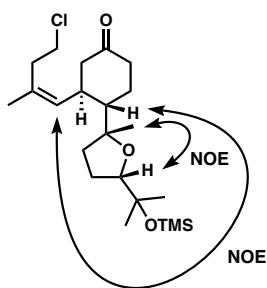
Enone 2.122. A solution of keto-aldehyde **2.121** (0.177 g, 0.539 mmol) and catalyst **2.86**⁴⁴ (43.4 mg, 0.162 mmol) in hexanes (5.4 mL, previously sparged with argon gas for 20 min) was stirred

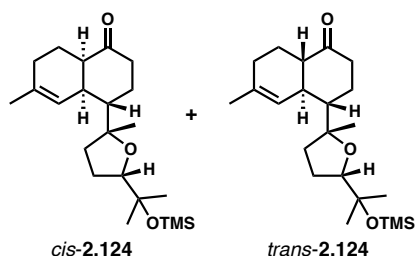
at room temperature for 21 h. The reaction mixture was concentrated *in vacuo*, and the resulting crude residue was purified using flash chromatography (SiO₂, 7.5% EtOAc/hexanes) to afford the title compound (0.119 g, 71%) as a colorless oil. $[\alpha]_D^{23} = -54.0$ ($c = 1.0$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.22 (dt, $J = 10.5, 1.5$ Hz, 1H), 6.06 (dd, $J = 10.3, 2.8$ Hz, 1H), 3.77 (t, $J = 7.0$ Hz, 1H), 2.67 – 2.60 (m, 1H), 2.50 (dt, $J = 16.3, 3.8$ Hz, 1H), 2.33 (td, $J = 15.5, 5.0$ Hz, 1H), 2.05 – 1.98 (m, 1H), 1.97 – 1.81 (m, 3H), 1.75 – 1.58 (m, 2H), 1.23 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 0.08 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 200.1, 154.2, 129.9, 86.4, 84.3, 74.9, 46.4, 37.8, 35.9, 27.3, 26.6, 26.3, 25.6, 22.7, 2.6; IR (thin film) ν 2969, 2872, 1683, 1452, 1380, 1249, 1178, 1042, 839 cm⁻¹; HRMS (ESI) m/z calcd for C₁₇H₃₀O₃SiNa (M + Na)⁺ 333.1862, found 333.1850.



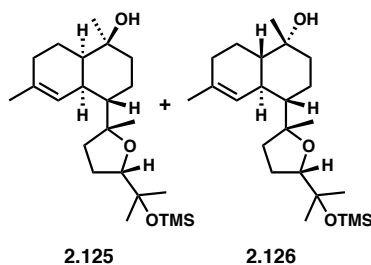
Ketone 2.123. To a solution of vinyl iodide **2.39** (0.154 g, 0.669 mmol) in Et₂O (1.1 mL, previously sparged with argon gas for 20 min) at –78 °C was added *tert*-butyllithium (0.84 mL, 1.59 M in pentane, 1.34 mmol) dropwise *via* syringe. After 20 min, lithium 2-thienylcyanocuprate solution (2.70 mL, 0.25 M in THF, 0.669 mmol) was added dropwise *via* syringe. The reaction mixture was allowed to stir for 1 h at –78 °C. A solution of enone **2.122** (0.139 g, 0.446 mmol) in Et₂O (0.5 mL) was added dropwise *via* syringe. The transfer was completed with additional portions of Et₂O (2 x 0.25 mL). Immediately following this addition, BF₃•OEt₂ (75 μ L, 0.580 mmol) was added dropwise *via* syringe. After allowing the reaction mixture to stir for 3 h at –78 °C, the reaction was quenched with 9:1 saturated NH₄Cl

solution/ NH_4OH (12 mL). After warming to room temperature, the solution turned a deep blue color. The aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with 9:1 saturated NH_4Cl solution/ NH_4OH (2 x 15 mL), washed with brine (15 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 7.5% EtOAc /hexanes) to afford the title compound (0.150 g, 81%) as a white solid (mp 56–58 °C). $[\alpha]_{\text{D}}^{23} = -4.3$ ($c = 1.0$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 5.37 (d, $J = 9.5$ Hz, 1H), 3.69 (t, $J = 6.8$ Hz, 1H), 3.61 – 3.48 (m, 2H), 2.76 (ddd, $J = 18.5, 9.8, 4.5$ Hz, 1H), 2.58 (quin, $J = 5.9$ Hz, 1H), 2.47 – 2.35 (m, 3H), 2.29 (td, $J = 15.0, 5.5$ Hz, 1H), 2.15 (dd, $J = 14.5, 10.0$ Hz, 1H), 2.11 – 2.05 (m, 1H), 1.86 (dt, $J = 9.5, 6.5$ Hz, 1H), 1.79 (ddd, $J = 11.8, 8.5, 3.8$ Hz, 1H), 1.72 – 1.62 (m, 1H), 1.68 (s, 3H), 1.62 – 1.51 (m, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 211.9, 133.9, 127.4, 85.6, 85.1, 75.3, 50.7, 47.7, 42.5, 40.4, 38.4, 36.7, 35.2, 28.1, 27.2, 25.5, 23.0, 21.8, 2.8; IR (thin film) ν 2964, 2873, 1718, 1454, 1378, 1249, 1174, 1043, 839 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{39}\text{ClO}_3\text{SiNa}$ ($\text{M} + \text{Na}$) $^+$ 437.2255, found 437.2252. ^1H -NOESY-2D (500 MHz, CDCl_3) spectra were obtained for ketone **2.123** and selected NOE interactions are shown.





***cis*- and *trans*-Decalones 2.124.** To a solution of alkyl chloride **2.123** (0.150 g, 0.362 mmol) in *tert*-butyl alcohol (1.81 mL) at 30 °C was added potassium *tert*-butoxide (0.27 mL, 1.6 M in THF, 0.434 mmol) dropwise *via* syringe. After stirring for 6 h at 30 °C, the reaction was quenched with saturated NH₄Cl solution (12 mL). The aqueous layer was extracted with pentane (4 x 10 mL), and the combined organic extracts were washed with water (3 x 10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 5% EtOAc/hexanes) to afford a 1.3:1 mixture of *cis*- and *trans*-decalones (99.7 mg, 73%) as a colorless oil, which was characterized as a mixture. $[\alpha]_D^{22} = -79.2$ ($c = 1.0$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 6.27 (s, 1H), 5.38 (s, 1H), 3.80 (t, $J = 6.3$ Hz, 1H), 3.73 (dd, $J = 7.9, 5.5$ Hz, 1H), 2.80 – 2.72 (m, 1H), 2.68 – 2.61 (m, 1H), 2.44 – 2.34 (m, 3 H), 2.26 – 2.15 (m, 4H), 2.13 – 1.38 (m, 21H), 1.64 (s, 3H), 1.58 (s, 3H), 1.20 (s, 3H), 1.18 (s, 9H), 1.17 (s, 3H), 1.07 (s, 3H), 0.11 (s, 9H), 0.10 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 215.2, 213.1, 133.1, 133.0, 127.7, 125.5, 86.4, 86.1, 85.4, 85.2, 75.6, 75.4, 51.4, 50.8, 50.0, 45.6, 44.4, 41.0, 38.8, 38.6, 36.5, 36.4, 29.9, 29.6, 28.0, 27.9, 27.2, 26.0, 25.7, 25.1, 24.8, 24.2, 23.84, 23.77, 22.7, 22.2, 22.0, 19.4, 2.77, 2.74; IR (thin film) ν 2963, 2875, 1714, 1454, 1378, 1249, 1172, 1041, 839 cm⁻¹; HRMS (ESI) m/z calcd for C₂₂H₃₈O₃SiNa (M + Na)⁺ 401.2488, found 401.2474.

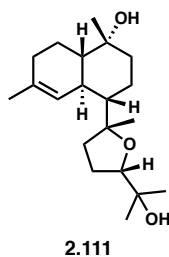


Decalins 2.125 and 2.126. Methylmagnesium bromide (0.44 mL, 3.0 M in Et₂O, 1.32 mmol) was added dropwise to a solution of a mixture of *cis*- and *trans*-decalones **2.124** (99.7 mg, 0.263 mmol) in THF (2.63 mL) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature for 30 min, and the reaction was quenched with saturated aqueous NH₄Cl solution (6 mL) at 0 °C. The aqueous layer was extracted with Et₂O (3 x 6 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% EtOAc/hexanes), yielding *trans*-decalin **2.126** (36.5 mg, 35%) as a colorless oil and *cis*-decalin **2.125** (47.1 mg, 45%) as a white solid (mp 82–84 °C).

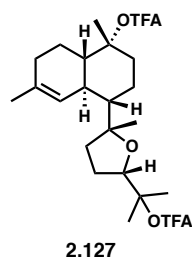
cis-Decalin **2.125**: $[\alpha]_D^{22} = +62.4$ (c = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 5.74, (d, *J* = 5.0 Hz, 1 H), 3.71 (t, *J* = 6.3 Hz, 1H), 2.24 – 2.15 (m, 1H), 2.00 – 1.80 (m, 5H), 1.66 – 1.44 (m, 9H), 1.61 (s, 3H), 1.31 (s, 3H), 1.28 – 1.10 (m, 1H), 1.13 (s, 3 H), 1.11 (s, 3H), 1.08 (s, 3H), 0.07 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 130.2, 128.1, 86.2, 85.4, 75.7, 72.5, 49.1, 46.2, 38.2, 36.9, 35.3, 31.0, 28.2, 28.0, 26.8, 25.10, 25.07, 23.6, 19.9, 18.7, 2.7; IR (thin film) ν 3370 (br), 2963, 2940, 2894, 2872, 1458, 1376, 1249, 1043, 839 cm⁻¹; HRMS (ESI) *m* / *z* calcd for C₂₃H₄₂O₃SiNa (M + Na)⁺ 417.2801, found 417.2801.

trans-Decalin **2.126**: $[\alpha]_D^{22} = -22.3$ (c = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 6.31 (s, 1H), 3.79 (dd, *J* = 7.0, 5.5 Hz, 1H), 2.17 (ap t, *J* = 10.3 Hz, 1H), 2.06 – 1.89 (m, 3H), 1.87 – 1.78 (m, 2H), 1.73 – 1.67 (m, 1H), 1.66 – 1.11 (m, 9H), 1.62 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.14

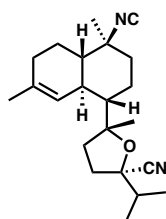
(s, 3H), 1.09 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 131.7, 126.6, 87.1, 85.1, 75.7, 70.7, 52.3, 47.8, 40.7, 38.7, 38.5, 30.9, 28.6, 28.1, 25.6, 24.8, 24.7, 23.8, 22.9, 19.1, 2.8; IR (thin film) ν 3464 (br), 2962, 2871, 1453, 1377, 1249, 1171, 1083, 1043, 839 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{42}\text{O}_3\text{SiNa}$ ($\text{M} + \text{Na}$) $^+$ 417.2801, found 417.2801.



Diol 2.111. To a solution of *trans*-decalin **2.126** (36.5 mg, 0.0925 mmol) in THF (0.93 mL) cooled to 0 °C was added TBAF (0.19 mL, 1.0 M in THF, 0.185 mmol). After 1 h, added additional TBAF (0.19 mL, 1.0 M in THF, 0.185). After 20 min, the reaction was quenched with water (5 mL). The reaction mixture was extracted with ether (4 x 5 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 15% EtOAc/hexanes) to afford diol **2.111** (28.2 mg, 95%) as a white solid (mp 98–100 °C). $[\alpha]_{\text{D}}^{23} = -21.1$ ($c = 0.77$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 6.25, (s, 1H), 3.85 (dd, $J = 7.8, 6.8$ Hz, 1H), 2.27 – 2.18 (m, 1H), 2.17 – 1.88 (m, 4H), 1.85 – 1.60 (m, 6H), 1.64 (s, 3H), 1.52 – 1.40 (m, 3H), 1.35 (ddd, $J = 24.5, 12.3, 5.8$ Hz, 1H), 1.28 – 1.12 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 132.8, 125.9, 87.1, 84.4, 71.4, 70.7, 52.3, 47.9, 40.7, 38.7, 38.5, 30.7, 28.7, 27.7, 25.8, 24.5, 24.3, 24.0, 22.8, 19.2; IR (thin film) ν 3436 (br), 2965, 2936, 2870, 1453, 1375, 1147, 1078, 892, 756 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{34}\text{O}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 345.2406, found 345.2415.



Bis(trifluoroacetate) 2.127. A mixture of diol **2.111** (10.2 mg, 0.0316 mmol) and pyridine (30 μ L, 0.371 mmol) in CH_2Cl_2 (0.32 mL) at 0 $^\circ\text{C}$ was treated with trifluoroacetic anhydride (20 μ L, 0.144 mmol). After 20 min, added additional pyridine (20 μ L, 0.247 mmol) and trifluoroacetic anhydride (20 μ L, 0.144 mmol). After 20 min, the reaction was quenched with 1 M HCl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with water (5 mL), washed with saturated NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude residue was used directly in the subsequent reaction. $[\alpha]_{\text{D}}^{23} = -30.0$ ($c = 1.0$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 6.20 (s, 1H), 4.07 (dd, $J = 9.3, 3.8$ Hz, 1H), 2.75 (dt, $J = 14.8, 3.3$ Hz, 1H), 2.33 (ap t, $J = 10.3$ Hz, 1H), 2.08 – 1.92 (m, 4H), 1.86 – 1.78 (m, 1H), 1.73 – 1.49 (m, 7H), 1.62 (s, 3H), 1.57 (s, 3H), 1.53 (s, 3H), 1.44 (td, $J = 14.3, 3.8$ Hz, 1H), 1.33 (td, $J = 12.5, 2.8$ Hz, 1H), 1.19 (t, $J = 11.8$ Hz, 1H), 1.16 – 1.06 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.3 (q, $J = 36.3$ Hz), 156.2 (q, $J = 40.8$ Hz), 132.5, 125.3, 114.6 (q, $J = 285.6$ Hz), 114.5 (q, $J = 285.3$ Hz), 89.9, 89.0, 87.6, 82.9, 51.2, 48.8, 38.2, 37.8, 34.9, 30.5, 25.1, 25.0, 23.72, 23.70, 22.6, 21.2, 21.3, 18.7; IR (thin film) ν 2962, 2931, 2877, 1779, 1456, 1375, 1220, 1156 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{32}\text{F}_6\text{O}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 537.2051, found 537.2051.



2.128

Isocyanide 2.128. The following procedure was adopted from Pronin *et al.*³ Trifluoroacetate **2.127** (10.2 mg, 0.0316 mmol) was dissolved in TMSCN (60 μ L) and cooled to 0 °C. A solution of scandium(III) trifluoromethanesulfonate (1.6 mg, 0.00316 mmol) in TMSCN (0.11 mL) was added to the reaction mixture dropwise *via* syringe. After 30 min, the reaction mixture was allowed to warm to room temperature. After 4 h, the reaction was quenched with TMEDA (20 μ L) and the volatiles were removed under reduced pressure. The crude residue was dissolved in hexanes (6 mL), washed with saturated aqueous NaHCO₃ solution (6 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 3 $\rightarrow$ 5% EtOAc/hexanes) to afford the title compound (2.0 mg, 19%) as a thin film. $[\alpha]_D^{22} = +32.1$ (c = 0.20, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 6.02 (s, 1H), 2.28 – 2.02 (m, 1H), 2.20 – 2.12 (m, 4H), 2.02 – 1.77 (m, 7H), 1.72 – 1.48 (m, 2H), 1.65 (s, 3H), 1.39 – 1.27 (m, 1H), 1.31 (br s, 3H), 1.78 – 1.00 (m, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 3H), 1.05 (d, *J* = 7.0 Hz, 3H); 4.08 (dd, *J* = 9.0, 4.0 Hz, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H), 1.31 (br s, 3H), 2.05 – 1.11 (m, 15H), 1.01 (s, 3H), 0.14 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 152.6 (br t), 133.8, 123.8, 120.8, 88.9, 85.0, 60.6 (br t, *J* = 5.1 Hz), 51.9, 47.5, 40.6, 38.9, 38.7, 37.9, 35.5, 30.4, 25.3, 24.0, 21.8, 20.3, 18.2, 17.9; IR (thin film) ν 2965, 2933, 2875, 2128, 1453, 1384, 1063 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₂H₃₂N₂ONa (M + Na)⁺ 363.2412, found 363.2417.

2.8 Notes and References

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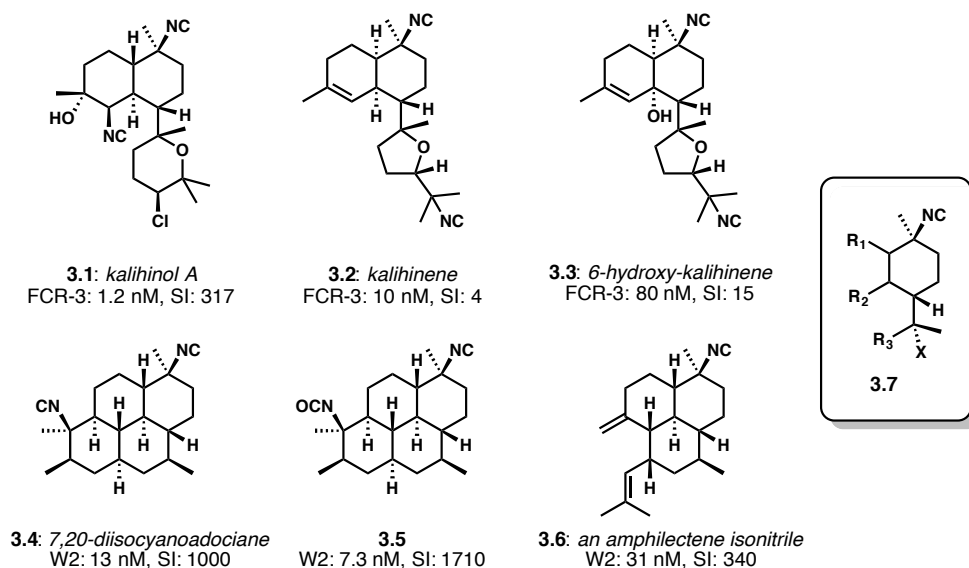
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CHAPTER 3: SYNTHESIS AND ANTIMALARIAL ACTIVITY OF KALIHINANE ANALOGUES

3.1 Introduction

Our interest in the kalihinanes stemmed from their extensive biological properties in addition to their complex structure. When we designed our synthetic approach toward the kalihinanes, we intended for the strategy to be applicable to the synthesis of analogues as well as the naturally-occurring kalihinanes. Because we were interested in evaluating the antimalarial activity of the synthetic material, determining SAR, and performing additional studies to determine the antiplasmodial mechanism of action of this class of ICTs, we initiated collaborations with two experts in the field—Professor Karine Le Roch at the University of California, Riverside and Professor Choukri Ben Mamoun at Yale University—whose laboratories have vested interests in developing new therapeutics for malaria.

Figure 3.1. The most potent antimalarial ICTs share a similar cyclohexane/tertiary isonitrile motif. (FCR-3 and W2 are drug-resistant strains of *P. falciparum*; SI = selectivity index with respect to mammalian cells).



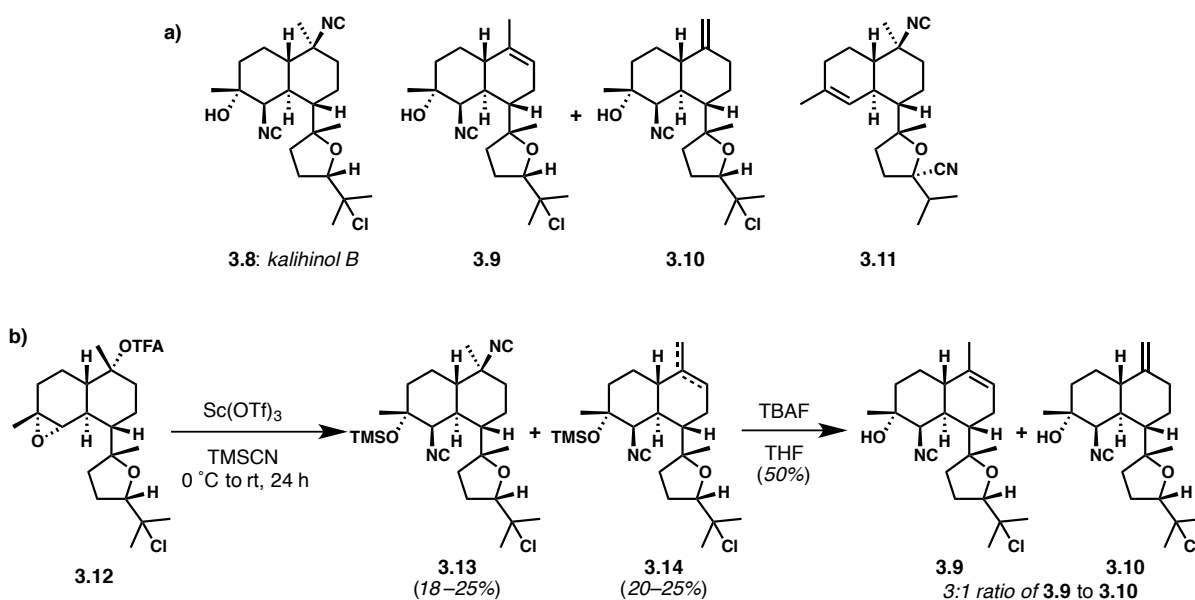
From the limited set of antimalarial activities reported to date, it is clear that potent antiplasmodial activity of the kalihinanes is correlated with the presence of two isonitriles, but

the specific location of the isonitriles is not critical (compare **3.1** and **3.2**).¹⁻³ Furthermore, we recognized that the kalihinanes share a common structural motif with other potent ICTs, namely the cyclohexane/tertiary isonitrile (**3.7**) (Figure 3.1). Our goal was to evaluate the antimalarial activity of synthetic kalihinanes and analogues to determine the general importance of this cyclohexane/tertiary isonitrile motif (**3.7**). The following chapter describes the synthesis of kalihinane analogues, the synthesis of kalihinane-based small molecule probes, and the determination of the antimalarial activity of kalihinol B and sixteen synthetic ICTs.

3.2 Synthesis of Kalihinane Analogues

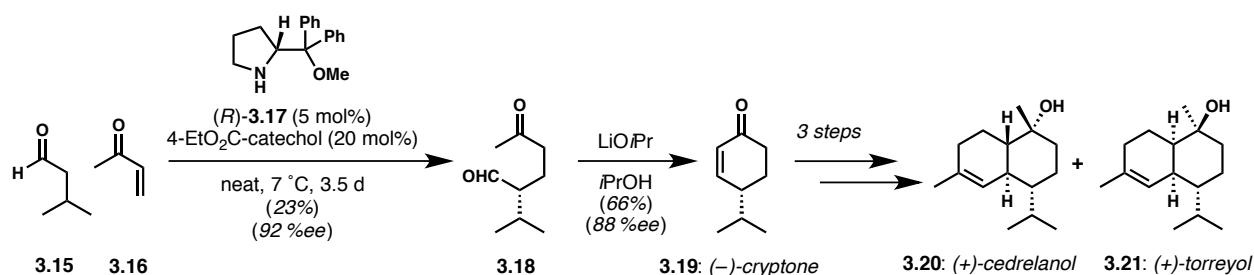
From our efforts toward the kalihinanes (see Chapter 2), we were able to access one natural product, kalihinol B (**3.8**), as well as kalihinane analogues **3.9**, **3.10**, and **3.11** (Figure 3.2a). Analogues **3.9** and **3.10** were isolated as side products in the synthesis of kalihinol B (Figure 3.2b). Isocyanosilylation of epoxide **3.12** and elimination of the tertiary trifluoroacetate rather than invertive displacement with TMSCN led to isocyanide **3.14**. Deprotection of the silyl ether provided a 3:1 mixture of alkenes **3.9** and **3.10**.

Figure 3.2. (a) Structure of kalihinol B (**3.8**) and analogues. (b) Synthesis of kalihinol B analogues **3.9** and **3.10**.



While Wood and co-workers had previously determined the antimalarial activities of several simplified kalihinane analogues as racemates (see Section 1.3), we included three of their targets in our assay to determine the antimalarial activities of the enantioenriched compounds.^{2,3} Therefore, the synthesis of the C7 isopropyl kalihinane analogues began with the preparation of (+)-cedrelanol (**3.20**) and (+)-torreyol (**3.21**) (Scheme 3.1). Enantioenriched cryptone (**3.19**) was prepared using a two-step Robinson annulation reported by Baran and co-workers.⁴ After an asymmetric enamine-catalyzed Michael addition of isovaleraldehyde (**3.15**) to methyl vinyl ketone (**3.16**), aldol condensation using lithium isopropoxide provided (–)-cryptone (**3.19**). While Baran and co-workers reported accomplishing the aldol condensation with lithium hydroxide in isopropanol, we found that the direct addition of lithium isopropoxide provided more reproducible results. Additionally, we observed a lower reaction conversion for the intermolecular Michael reaction (57% after 3.5 days) than reported in the literature.^{4,5} From **3.19**, conjugate addition, intramolecular alkylation, and nucleophilic methylation using our strategy detailed in Section 2.2.2 yielded (+)-cedrelanol (**3.20**) and (+)-torreyol (**3.21**).

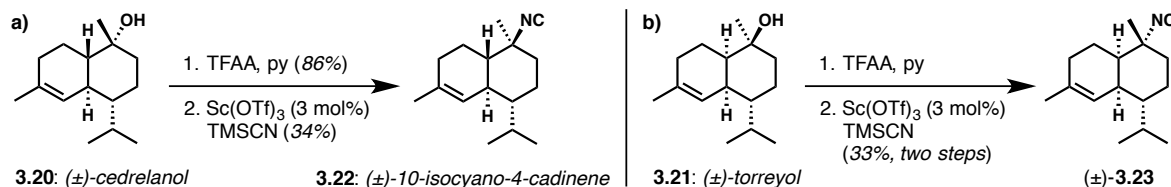
Scheme 3.1. Synthesis of (+)-cedrelanol (**3.20**) and (+)-torreyol (**3.21**).



From cedrelanol (**3.20**) and torreyol (**3.21**), we have prepared several C7 isopropyl analogues. As described in Section 2.2, we have used the protocol developed by Shenvi and co-workers for the synthesis of (±)-10-isocyano-4-cadinene (**3.22**) from cedrelanol (**3.20**) (Scheme 3.2a).⁶ Additionally, we have elaborated (±)-torreyol (**3.21**) to *cis*-decalin isocyanide

3.23 (Scheme 3.2b). Evaluation of the antimalarial activities of isocyanides **3.22** and **3.23** will enable the direct comparison of the *cis*- and *trans*-decalin core.

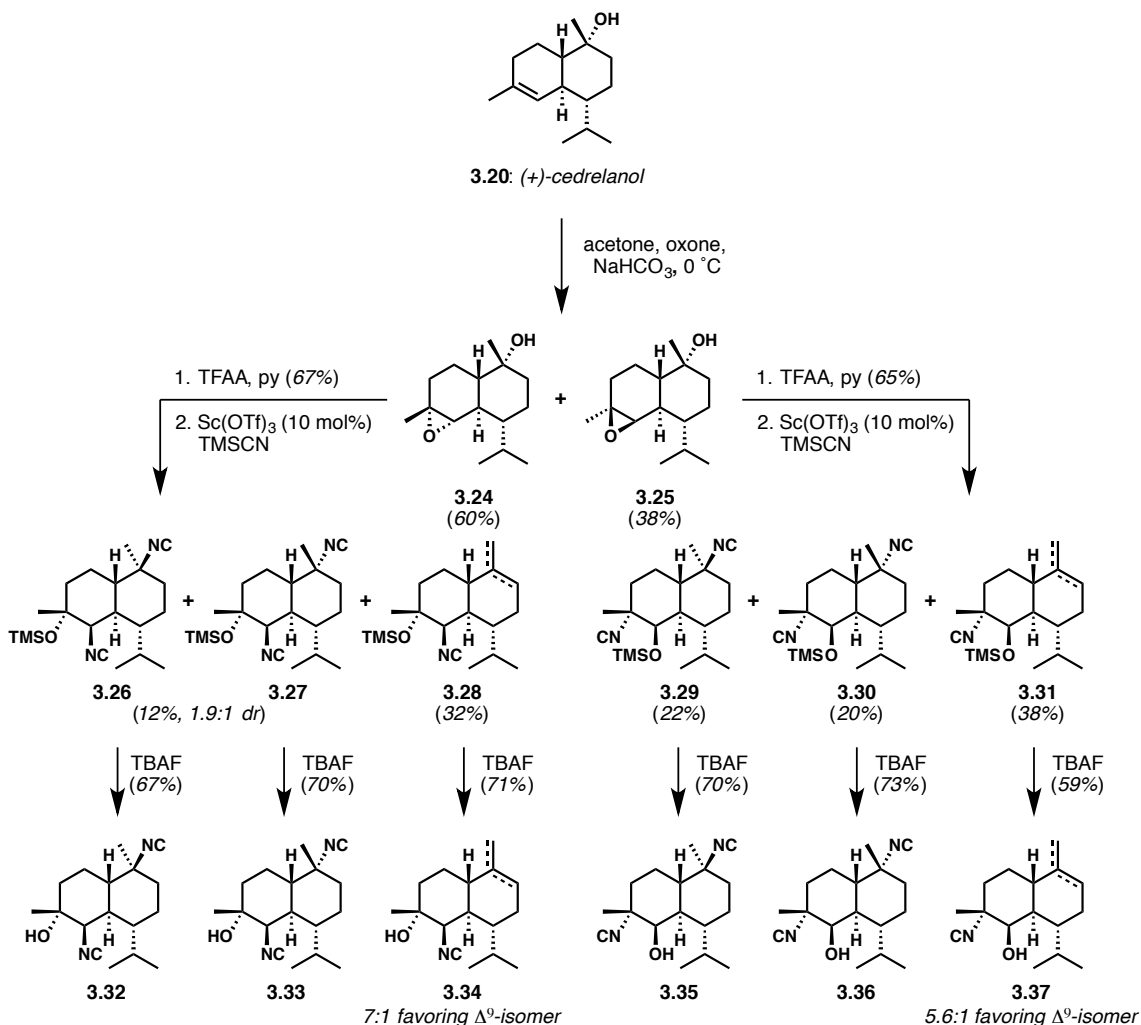
Scheme 3.2. Synthesis of (a) ($\pm$)-10-isocyano-4-cadinene (**3.22**) and (b) *cis*-decalin analogue **3.23**.



Epoxidation of (+)-cedrelanol (**3.20**) using DMDO generated *in situ* provided a 1.6:1 mixture of diastereomeric epoxides **3.24** and **3.25**, favoring the desired α -epoxide (**3.24**) (Scheme 3.3). We were surprised to observe poor selectivity as DMDO epoxidation of the *trans*-decalin bearing a C7 THF proved to be highly diastereoselective for the α -epoxide (see Section 2.4). Epoxidation of **3.20** with *m*CPBA or Davis's oxaziridine reversed the diastereoselectivity, and the β -epoxide (**3.25**) was observed as the major product. Subjection of a trifluoroacetate derived from α -epoxide **3.24** to the standard conditions for isonitrile installation provided three products. While we only observed products resulting from attack of TMSCN at C5 of the epoxide, yielding the C4/C5 diaxial product, we isolated a 1.9:1 mixture of C10 isonitrile epimers **3.26** and **3.27** in 12% yield. Unlike for the synthesis of kalihinol B (**3.8**) (Figure 3.2b), the isonitrile installation at C10 for this substrate suffered from poor diastereoselectivity. The elimination products **3.28** were isolated in 32% yield, while the remaining mass balance was attributed to unidentified decomposition pathways. Nonetheless, cleavage of the TMS ether for all three substrates provided analogue **3.32**, containing a C10 equatorial isonitrile, analogue **3.33**, containing a C10 axial isonitrile, and analogue **3.34**, lacking the C10 isonitrile. Elaboration of β -epoxide **3.25** using the Shenvi protocol was slightly more efficient. Again, we observed only products resulting from isocyanolysis of the epoxide at C4,

affording the C4/C5 diaxial product. Although the sequence gave C10 isonitrile epimers **3.29** and **3.30** in nearly a 1:1 ratio, the isolated yields were higher than those observed during the elaboration of the α -epoxide (**3.24**). In addition to the products resulting from invertive displacement at C10, we isolated elimination products **3.31** in 38% yield. Treatment of **3.29**, **3.30**, and **3.31** with TBAF gave analogues **3.35**, **3.36**, and **3.37**, respectively.

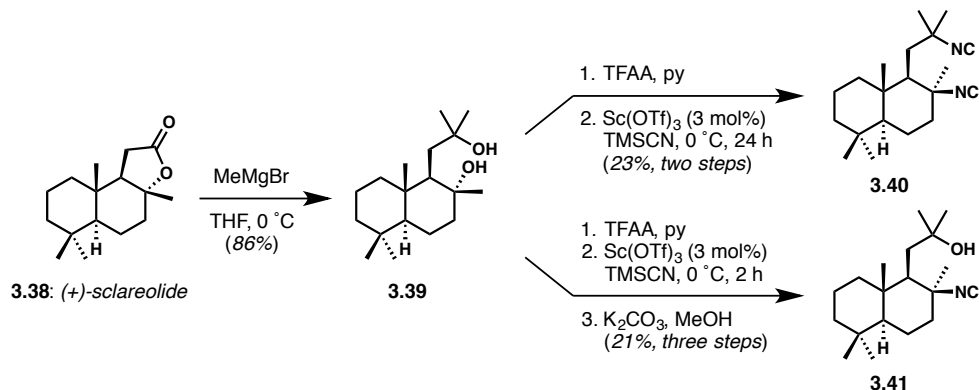
Scheme 3.3. Synthesis of C7 isopropyl analogues.



To evaluate our hypothesis on the importance of the cyclohexane/tertiary isonitrile motif (**3.7**), we prepared two unnatural terpene isonitriles (**3.40** and **3.41**) derived from (+)-sclareolide (**3.38**) (Scheme 3.4). Treatment of (+)-sclareolide (**3.38**) with methyl Grignard reagent gave diol

3.39. Using procedures adopted from Shenvi and co-workers for the synthesis of isocyanide derivatives of dihydrosclareol, we accessed diisocyanide **3.40** and isocyanide **3.41**.⁶

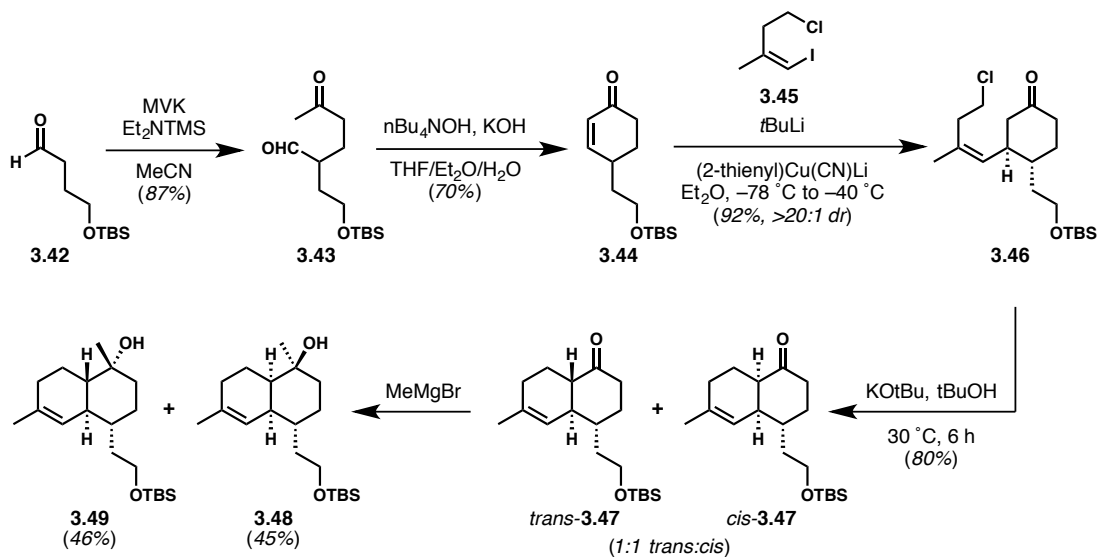
Scheme 3.4. Synthesis of isocyanides **3.40** and **3.41** from (+)-sclareolide (**3.38**).



3.3 Synthesis of Kalihinane-Based Small-Molecule Probes

In addition to determining SAR from analogue synthesis, we wanted to pursue studies to determine the mechanism of action of the kalihinanes. Therefore, we designed a kalihinane-based chemical probe to use for protein profiling in *P. falciparum* in collaboration with Professor Le Roch. We targeted *trans*-decalin **3.49** with the intention of unmasking the pendant silyl ether after isonitrile synthesis; the primary alcohol would serve as a functional handle to attach biotin or a rhodamine-based fluorophore *via* esterification (Scheme 3.5). Enone **3.44** was prepared in two steps from aldehyde **3.42** using a two-step Robinson annulation protocol, analogous to that used in the synthesis of ($\pm$)-cryptone.⁴ Diastereoselective conjugate addition into **3.44** was accomplished by treatment with a cuprate derived from vinyl iodide **3.45** at $-78\text{ }^{\circ}\text{C}$ and subsequent warming to $-40\text{ }^{\circ}\text{C}$. Addition of a Lewis acid (*e.g.* $\text{BF}_3\cdot\text{OEt}_2$ or TMSCl) lowered the diastereoselectivity of cuprate addition. Intramolecular alkylation and treatment with methyl Grignard reagent yielded *cis*-decalin **3.48** and *trans*-decalin **3.49** in a nearly 1:1 ratio.

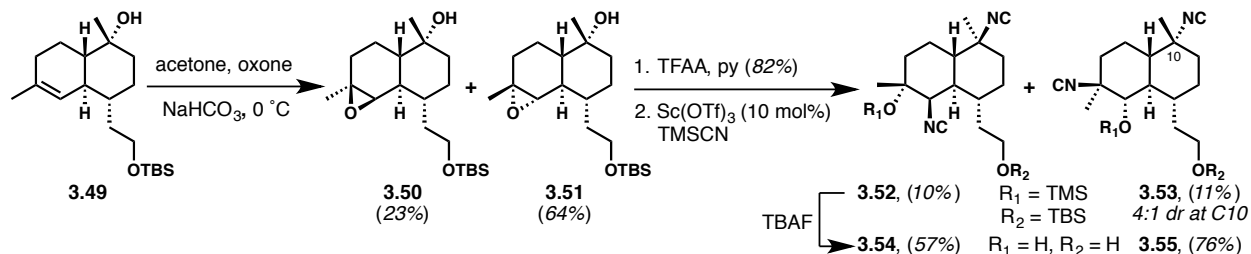
Scheme 3.5. Synthesis of the *trans*-decalin framework of the kalihinane-based chemical probe.



DMDO epoxidation of **3.49** gave a 2.8:1 mixture of epoxide diastereomers favoring desired α -epoxide **3.51** (Scheme 3.6). After trifluoroacetylation of **3.51** and exposure to scandium(III) triflate in TMSCN, we observed two diisocyanide products, **3.52** and **3.53**. In accordance with the Fürst–Plattner principle, diisocyanide **3.52** resulted from nucleophilic epoxide opening at C5 to give the C4/C5 diaxial product and invertive displacement of the C10 trifluoroacetate to afford the equatorial isonitrile. However, nucleophilic epoxide opening at C4, likely a result of chelation of the Lewis acid to the epoxide and the pendant silyl ether, afforded the C4/C5 diequatorial product **3.53**. Additionally, the C4/C5 diequatorial product (**3.53**) was isolated as a mixture of epimers at C10, of which the C10 axial isonitrile was predominant (*ca.* 4.4:1 *dr*). This result was surprising, as the C10 equatorial isonitrile, resulting from invertive displacement, is normally the major diastereomer under the reaction conditions. From our studies, we have learned that the displacement of tertiary trifluoroacetates with TMSCN is sensitive to the substitution pattern of the decalin core, and we often observe low diastereoselectivity. Diisocyanide **3.53** contains the C4/C5 substitution pattern characteristic of

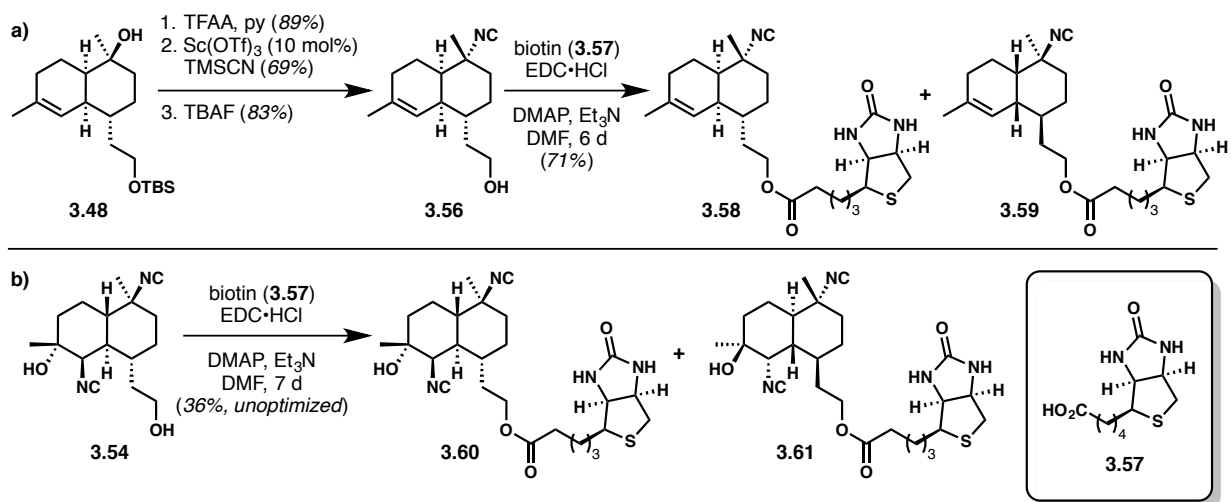
the isokalihinine decalin framework. Deprotection of the silyl ethers with TBAF provided kalihinine-based chemical probe precursor **3.54** and unnatural isokalihinine analogue **3.55**.

Scheme 3.6. Synthesis of the kalihinine-based chemical probe precursor.



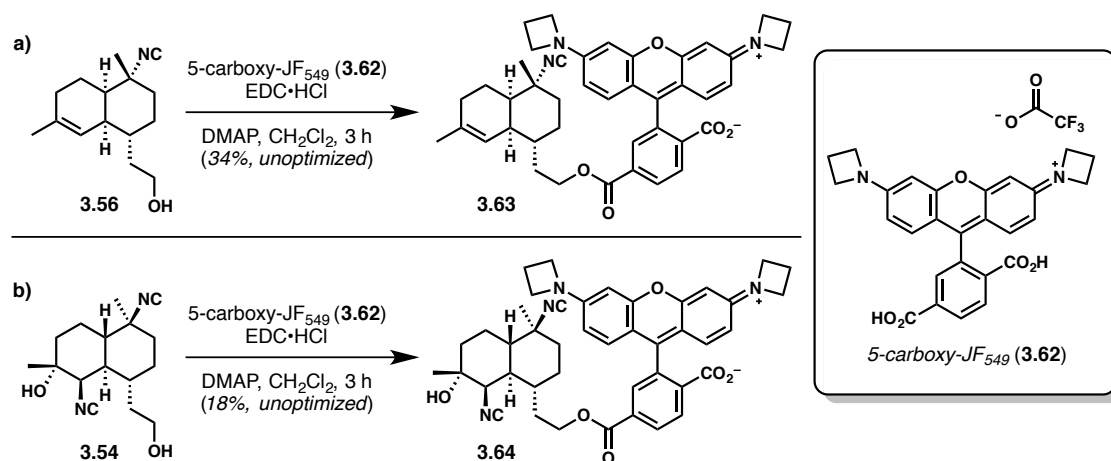
To evaluate conditions for attaching biotin (**3.57**), we prepared isocyanide **3.56** (Scheme 3.7a). Using the standard two-step sequence, the tertiary alcohol of **3.48** was converted into an isocyanide, and subsequent removal of the TBS ether gave **3.56**. We evaluated several conditions for coupling alcohol **3.56** to biotin (**3.57**). We initially examined esterification with biotin acid chloride, but we had difficulty working with the acid chloride of **3.57** owing to poor solubility. Esterification was accomplished using an EDC-coupling of **3.56** with biotin (**3.57**), providing biotinylated products **3.58** and **3.59**, a result of using racemic starting material. After determining the optimal method for biotinylation of the model system (**3.56**), we used the same conditions for esterification of diisocyanide **3.54**, affording a 1:1 mixture of biotin-conjugated probes **3.60** and **3.61** in 36% after 7 days (Scheme 3.7b).

Scheme 3.7. Biotinylation of (a) a terpene isonitrile and (b) the kalihinane-based probe.



After accomplishing the biotinylation of the molecular probe precursor, we focused on the esterification of **3.54** with a fluorescent dye to access a kalihinane-based fluorescent probe. We selected Janelia Fluor™ 549 dye owing to its superior brightness compared to tetramethylrhodamine *in vitro* and in live-cell experiments.⁷ We have successfully attached 5-carboxy-JF₅₄₉ (**3.62**) to terpene isonitrile **3.56** and to molecular probe precursor **3.54** using an EDC-coupling (Scheme 3.8). Because of a limited amount of material, we have not optimized the esterification of isocyanoterpenes **3.56** and **3.54**. Nonetheless, we have successfully prepared the kalihinane-based fluorescent probe **3.64**. In collaboration with Professor Le Roch's laboratory, we will use the biotin-conjugated probes (**3.60** and **3.61**) for pull-down assays and the fluorescent probe (**3.64**) for imaging experiments in *P. falciparum*.

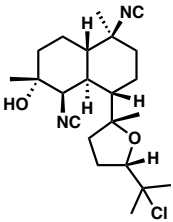
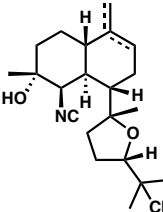
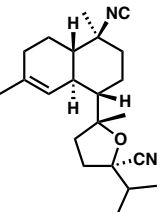
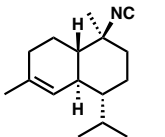
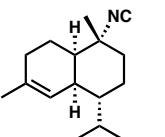
Scheme 3.8. Synthesis of (a) a terpene isonitrile fluorescent probe and (b) a kalihinane-based fluorescent probe.

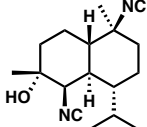
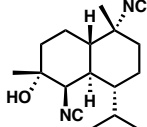
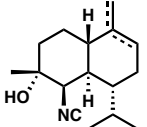
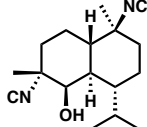
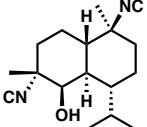


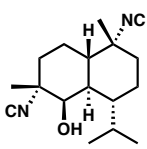
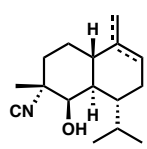
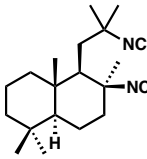
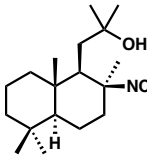
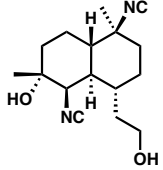
3.4 Evaluation of Antimalarial Activity

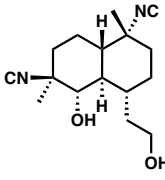
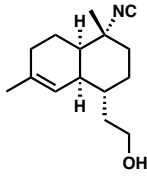
In collaboration with the Le Roch laboratory at UC Riverside, all synthetic isocyanoterpenes were subjected to the SYBR Green parasite proliferation assay to test for antiparasmodial activity against wild-type *P. falciparum* (3D7 strain) and the chloroquine-resistant parasite (Dd2 strain).⁸ The results are summarized in Table 3.1.

Table 3.1. Results of antiplasmodial assays of synthetic terpene isonitriles against *P. falciparum*.

					
	2.2: kalihinol B				
Compound	3.8	3.9+3.10 (3:1)	3.11	(±)-3.22	(±)-3.23
3D7 strain*	8.4	139	175	705	180
Dd2 strain*	4.6	144	123	247	45

					
Compound	3.32	3.33	3.34 (7:1)	3.35	(±)-3.35
3D7 strain*	12	2.9	138	15	27
Dd2 strain*	16	31	200	17	46

					
Compound	3.36	3.37 (5.6:1)	3.40	3.41	(±)-3.54
3D7 strain*	1150	312	1.9	244	302
Dd2 strain*	958	529	1.6	416	205

		
Compound	(±)-3.55	(±)-3.56
3D7 strain*	27	391
Dd2 strain*	24	516

* IC₅₀ (nM) against *P. falciparum* strains.

To our knowledge, kalihinol B (**3.8**) is the first kalihinane that has been evaluated for *in vitro* antiplasmodial activity since the 1998 report by Miyaoka and co-workers.¹ We were pleased to find that synthetic kalihinol B (**3.8**) exhibited potent antimalarial activity against both wild-type and drug-resistant strains of *P. falciparum* (IC_{50} = 8.4 nM for 3D7 and 4.6 nM for Dd2). While kalihinol B (**3.8**) was nearly as potent as its THP-counterpart, kalihinol A (**3.1**, IC_{50} = 1.2 nM for FCR-3), they have not yet been assayed against the same strains, precluding a direct comparison. Interestingly, kalihinol B (**3.8**) displayed more potent activity against the drug-resistant strain of *P. falciparum* than the drug-sensitive strain, a characteristic of several classes of ICTs.⁹

In general, all compounds we examined exhibited *in vitro* antimalarial activity (IC_{50} < 1.2 μ M). The most potent compounds (*i.e.* **3.8**, **3.32**, **3.33**, **3.35**, **3.40**, and **3.55**) contain two isonitriles, confirming the general observation that two isonitriles are required for potent activity. However, the mere presence of two isonitriles was not a general predictor of potency; diisocyanide **3.36** exhibited low *micromolar* activity, suggesting that the location of the isonitriles on the decalin core is more important than we originally thought. Comparison of kalihinane analogue **3.32** (IC_{50} = 12 nM for 3D7 and 16 nM for Dd2) and unnatural analogue **3.35** (IC_{50} = 15 nM for 3D7 and 17 nM for Dd2) indicated that a C10 equatorial isonitrile in combination with either a C5 or C4 axial isonitrile amounts to similar potency. Furthermore, we observed a two-fold increase in antimalarial activity for enantioenriched **3.35** (IC_{50} = 15 nM for 3D7 and 17 nM for Dd2) versus racemic **3.35** (IC_{50} = 27 nM for 3D7 and 46 nM for Dd2), suggesting the unnatural enantiomer displayed no *in vitro* antimalarial activity. However, the synthesis and antimalarial assay of the unnatural enantiomer should be completed for confirmation.

Surprisingly, we observed a significant decrease in potency by replacing the C7 isopropyl appendage (*i.e.* **3.32**, $IC_{50} = 12$ nM for 3D7 and 16 nM for Dd2) with a C7 hydroxyl-terminated alkyl chain (*i.e.* **3.54**, $IC_{50} = 302$ nM for 3D7 and 205 nM for Dd2). Kalihinane-based probe precursor (**3.54**) shares the same substitution pattern of the decalin core as the kalihinanes, yet exhibited antimalarial activity similar to synthetic terpenes containing only one isonitrile (compare to **3.34** and **3.37**). We suspect that the pendant alcohol may be engaging in a dipole-dipole interaction with the C5 axial isonitrile. However, because the mechanism of action for isocyanoterpenes remains largely unknown, we cannot rationalize how this might contribute to the observed reduction in potency at this time. To test our hypothesis, we plan to determine the antimalarial activity of biotin-conjugated diisocyanides **3.60** and **3.61**. We predict that esterification of the alcohol will restore the low nanomolar activity typically observed for diisocyanides with the kalihinane substitution pattern (*e.g.* **3.8** and **3.32**).

We were pleased to find that diisocyanide sclareolide derivative **3.40** exhibited potent antimalarial activity. Not only was **3.40** the most potent compound we have prepared ($IC_{50} = 1.9$ nM for 3D7 and 1.6 nM for Dd2), but it was also nearly as potent as kalihinol A (**3.1**, $IC_{50} = 1.2$ nM for FCR-3), the most potent of all ICTs tested to date. Furthermore, it was more effective against the drug-resistant strain of *P. falciparum*. Monoisocyanide sclareolide derivative **3.41** ($IC_{50} = 244$ nM for 3D7 and 416 nM for Dd2) was significantly less potent than **3.40**, indicating that while the cyclohexane/tertiary isonitrile motif may be an indicator of antimalarial activity, a second isonitrile is required to achieve greater potency. Diisocyanide sclareolide derivative **3.40** contains an axial tertiary isonitrile on the decalin framework, whereas several other isocyanoterpenes contain an equatorial tertiary isonitrile. Presently, we have not determined if

the stereochemistry of the tertiary isonitrile is important, and further studies are required to understand the general role of the cyclohexane/tertiary isonitrile motif.

The antimalarial activities of the monoisocyanide kalihinane analogues ranged from 45 to 705 nM (*i.e.* **3.9/3.10**, **3.11**, **3.22**, **3.23**, **3.34**, **3.37**, and **3.56**). These results suggest the location of the isonitrile on the decalin core is significant. While an axial isonitrile at C5 (*i.e.* **3.9/3.10** and **3.34**) displayed similar potency to an equatorial isonitrile at C10 (*i.e.* **3.11**), moving the axial isonitrile to C4 resulted in a 2.3-fold and a 2.6-fold decrease in potency for drug-sensitive and drug-resistant strains, respectively (compare **3.34** and **3.37**). Furthermore, we have determined that *cis*-decalin isocyanide **3.23** (IC₅₀ = 180 nM for 3D7 and 45 nM for Dd2) was significantly more potent than 10-isocyano-4-cadinene (**3.22**, IC₅₀ = 705 nM for 3D7 and 247 nM for Dd2) against both drug-sensitive and drug-resistant strains of *P. falciparum*. Both of these kalihinene analogues exhibited greater activity against the drug-resistant strain relative to the drug-sensitive strain. Several of the kalihinane analogues, however, were *less potent* against the chloroquine-resistant Dd2 strain (*e.g.* **3.31**, **3.32**, **3.33**, **3.34**, **3.35**, and **3.37**). While these results are consistent with the findings from the Wood group, we do not understand what factors contribute to the differences in efficacy.^{2,3}

3.5 Conclusions

Using our unified strategy, we have prepared sixteen kalihinane analogues in addition to kalihinol B (**3.8**) and determined their antimalarial activities. Furthermore, our strategy has provided access to kalihinane-based small molecule probes containing biotin and a rhodamine derivative. In collaboration with Professor Le Roch's laboratory, we will use the probes for protein profiling in *P. falciparum*. While we have made preliminary observations concerning SAR, we have not yet achieved a complete understanding of the structural elements required for

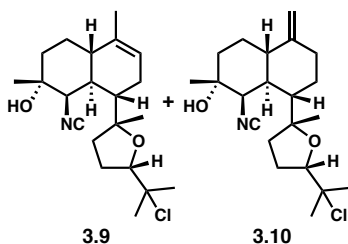
low nanomolar antiparasitic activity. To gain a full understanding of SAR among the kalihinanes, we will need to prepare several more naturally-occurring kalihinanes.

3.6 Experimental Procedures

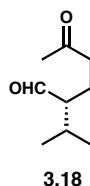
General Experimental Methods

All reactions were performed under an inert atmosphere of argon using oven-dried or flame-dried glassware and Teflon® coated stir bars. Solvents were dried by passage through columns of activated alumina, and *tert*-butyl alcohol was distilled from calcium hydride prior to use. Trimethylsilyl cyanide and methyl vinyl ketone were purified by distillation prior to use. Commercial reagents were used as received unless noted otherwise, and all other reagents were prepared using known literature procedures. Reactions were monitored by thin-layer chromatography (TLC) performed on 250 μ m silica gel 60 plates with 254 nm fluorescent indicator from EMD Chemicals using UV light as a visualizing agent and $\text{KMnO}_4/\text{H}_2\text{SO}_4$, *p*-anisaldehyde or ceric ammonium molybdate and heat as developing agents. Flash chromatography was performed on EMD Chemicals (40-63 μ m) silica gel. NMR spectra were recorded on a Bruker 500 MHz or a Bruker 600 MHz spectrometer. Chemical shifts are reported in parts per million using residual non-deuterated solvent as an internal standard (CDCl_3 : 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR). Data are reported as follows: chemical shift, multiplicity (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant(s) in Hz, integration. NMR spectra were obtained at 298 K unless otherwise noted. FT-IR spectra were recorded on a Varian 640-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter operating on the sodium D-line (589 nm) using a 50 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Analytical chiral HPLC was

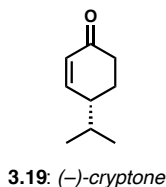
performed with an Agilent 1100 Series HPLC using a Chiralpak AS-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries Ltd. with visualization at 254 nm. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier spectrometer using ESI-TOF (electrospray ionization-time of flight) or CI-TOF (chemical ionization-time of flight). Melting points (mp) are uncorrected and were measured on a Mel-Temp II melting point apparatus.



36.9, 36.0, 34.2, 32.8, 31.2, 30.7, 30.3, 29.8, 28.79, 28.76, 28.7, 26.0, 25.9, 25.7, 25.6, 24.1, 20.9, 17.9, 17.1; IR (thin film) ν 3418 (br), 2971, 2933, 2892, 2852, 2156, 2139, 1457, 1382, 1122, 1025, 758 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{32}\text{ClNO}_2\text{Na}$ ($\text{M} + \text{Na}$)⁺ 388.2019, found 388.2006.

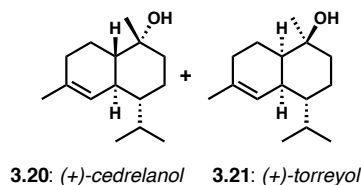


(*R*)-2-Isopropyl-5-oxohexanal (3.18). The title compound was prepared according to the literature procedure.⁴ The spectral data for this compound are consistent with those reported in the literature.^{10,11} $[\alpha]_{\text{D}}^{24} = -33.7$ ($c = 1.0$, CHCl_3), lit.¹¹ $[\alpha]_{\text{D}} = +40$ ($c = 1.72$, CDCl_3) for the (*S*)-form; ^1H NMR (500 MHz, CDCl_3) δ 9.60 (d, $J = 3.0$ Hz, 1H), 2.50 (ddd, $J = 17.5$, 8.8, 5.8 Hz, 1H), 2.36 (ddd, $J = 17.8$, 8.0, 6.8 Hz, 1H), 2.12 (s, 3H), 2.09 – 1.98 (m, 2H), 1.88 – 1.71 (m, 2H), 0.99 (d, $J = 6.5$ Hz, 3H), 0.96 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 208.2, 205.5, 57.7, 41.4, 30.2, 28.5, 20.4, 19.6, 19.5.



(-)-Cryptone (3.19). To a solution of (*R*)-2-isopropyl-5-oxohexanal (**3.18**) (0.731 mg, 4.68 mmol) in 2-propanol (15.6 mL) was added a solution of lithium isopropoxide (0.35 mL, 0.66 M in THF, 0.234 mmol). After 1 h, the reaction was quenched with saturated NH_4Cl solution (16 mL). The aqueous phase was extracted with ether (3 x 40 mL). The combined organic extracts were washed with water (2 x 20 mL), brine (1 x 20 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 10%

Et₂O/pentane) to afford (–)-cryptone (0.435 g, 66%) as a colorless oil. The spectral data for this compound are consistent with those reported in the literature.¹² $[\alpha]_D^{24} = -80.8$ ($c = 1.04$, CHCl₃), lit.¹³ $[\alpha]_D^{21} = -90$ ($c = 1.38$, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.89 (dt, $J = 10.0, 2.0$ Hz, 1H), 6.01 (dd, $J = 10.0, 2.5$ Hz, 1H), 2.51 (dt, $J = 17.0, 4.0$ Hz, 1H), 2.38 – 2.32 (m, 1H), 2.32 – 2.25 (m, 1H), 2.04 – 1.96 (m, 1H), 1.86 – 1.71 (m, 1H), 0.97 (t, $J = 7.0$ Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 200.2, 154.5, 129.8, 42.6, 37.5, 31.6, 25.4, 19.8, 19.6. The enantiomeric excess of (–)-cryptone was determined to be 88% using chiral HPLC (Chiralpak AD-H column, 2% *i*PrOH in hexanes, flow rate of 0.5 mL/min).

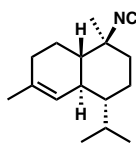


(+)-Cedrelanol (3.20) and (+)-torreyol (3.21). The title compounds were prepared from (–)-cryptone (**3.19**) according to the three-step sequence described in Section 2.7. The spectral data for these compounds are consistent with those reported in the literature.^{6,14,15}

(+)-Cedrelanol (3.20): $[\alpha]_D^{24} = +2.2$ ($c = 1.0$, CHCl₃), lit.¹⁵ $[\alpha]_D = +3.4$ ($c = 1.2$, CHCl₃); ¹H NMR (CDCl₃, 600 MHz) δ 5.55 (br s, 1H), 2.22 – 2.15 (m, 1H), 2.04 – 1.89 (m, 4H), 1.74 (dt, $J = 13.1, 2.9$ Hz, 1H), 1.67 (s, 3H), 1.50 – 1.45 (m, 1H), 1.45 – 1.29 (m, 3H), 1.22 (s, 3H), 1.09 (t, $J = 10.3$ Hz, 1H), 1.01 (tt, $J = 11.4, 3.2$ Hz, 1H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.79 (d, $J = 6.9$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 134.5, 122.8, 70.8, 48.1, 46.8, 40.4, 37.9, 31.0, 28.6, 26.3, 23.9, 22.7, 21.5, 19.9, 15.3.

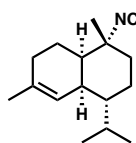
(+)-Torreyol (3.21): mp 109–110 °C, lit.¹⁴ mp 108.5–109 °C; $[\alpha]_D^{24} = +95.4$ ($c = 1.0$, CHCl₃), lit.¹⁵ $[\alpha]_D = -100.4$ ($c = 1.2$, CHCl₃) for (–)-torreyol; ¹H NMR (CDCl₃, 600 MHz) δ 5.52 (d, $J = 4.3$ Hz, 1 H), 2.06 – 1.92 (m, 4H), 1.92 – 1.86 (m, 1H), 1.66 (s, 3H), 1.63 – 1.47 (m, 6H), 1.35 –

1.24 (m, 2H), 1.30 (s, 3H), 1.15 – 1.05 (m, 1H) 0.89 (d, $J = 6.9$ Hz, 3H), 0.77 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 134.5, 124.7, 72.7, 45.6, 44.2, 36.9, 35.4, 31.3, 28.1, 26.5, 23.8, 21.8, 21.7, 18.6, 15.4.



3.22: (±)-10-isocyano-4-cadinene

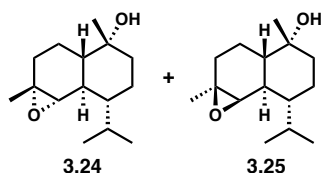
(±)-10-Isocyano-4-cadinene (3.22). The title compound was prepared according to the literature procedure.⁶ The spectral data for this compound are consistent with those reported in the literature. See Section 2.7 for details.



(±)-**3.23**

Isocyanide 3.23. The following procedure was adopted from Pronin *et al.*⁶ A mixture of (±)-torreyol (**3.21**) (30.8 mg, 0.139 mmol) and pyridine (50 μL , 0.556 mmol) in CH_2Cl_2 (1.4 mL) at 0 °C was treated with trifluoroacetic anhydride (40 μL , 0.278 mmol). After 15 minutes, the reaction was quenched with 1 M HCl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were washed with water (5 mL), washed with saturated NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude trifluoroacetate was dissolved in TMSCN (0.14 mL), and a solution of scandium(III) trifluoromethanesulfonate (3.4 mg, 0.0695 mmol) in TMSCN (0.14 mL) was added. After 3 h at room temperature, the reaction was quenched with TMEDA (20 μL) and the volatiles were removed under reduced pressure. The crude residue was dissolved in hexanes (5 mL), washed with saturated aqueous NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered, and concentrated

in vacuo. The crude residue was purified using flash chromatography (SiO₂, 30% CH₂Cl₂/hexanes) to afford the title compound (10.4 mg, 33%) as a thin film. ¹H NMR (CDCl₃, 500 MHz) δ 5.56 (d, *J* = 1.0 Hz, 1H), 2.39 – 2.32 (m, 1H), 2.07 – 1.93 (m, 3H), 1.83 (d, *J* = 13.0 Hz, 1H), 1.74 (d, *J* = 11.0 Hz, 1H), 1.65 (s, 3H), 1.61 – 1.54 (m, 1H), 1.54 – 1.37 (m, 4H), 1.42 (s, 3H), 1.31 – 1.21 (m, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 153.3 (t, *J* = 4.5 Hz), 133.6, 124.4, 62.2 (t, *J* = 4.4 Hz), 44.6, 43.6, 35.0, 33.6, 31.0, 27.9, 26.7, 23.6, 21.7, 20.0, 19.4, 15.4; IR (thin film) ν 2956, 2893, 2872, 2832, 2126, 1452, 1384, 1154, 884 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₆H₂₅NNa (M + Na)⁺ 254.1885, found 254.1880.

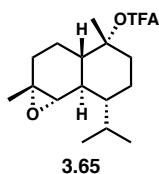
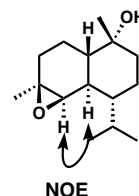


Epoxides 3.24 and 3.25. To a solution of (+)-cedrelanol (**3.20**) (0.188 g, 0.845 mmol) in acetone (42 mL) was added saturated aqueous NaHCO₃ (28 mL). The resulting mixture was cooled to 0 °C and a solution of Oxone® (0.571 g, 0.930 mmol) in H₂O (2 mL) was added dropwise over 5 minutes. The reaction mixture was stirred vigorously for 30 min at 0 °C, diluted with H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were diluted with hexanes until cloudy, dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10 → 30% EtOAc/hexanes) to afford β-epoxide **3.25** (77.1 mg, 38%) as a white solid (mp 90–93 °C) and α-epoxide **3.24** (120.4 mg, 60%) as a colorless oil.

Epoxide **3.24**: [α]_D²⁴ = +22.6 (c = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 2.94 (s, 1H), 2.32 – 2.20 (m, 1H), 2.09 (dd, *J* = 14.3, 3.8 Hz, 1H), 1.73 – 1.46 (m, 5H), 1.46 – 1.32 (m, 2H), 1.30

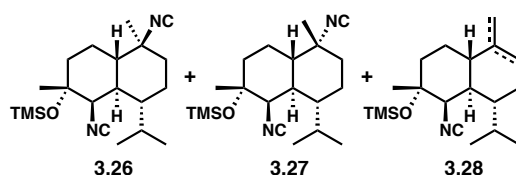
(s, 3H), 1.27 – 1.11 (m, 2H), 1.17 (s, 3H), 0.96 (d, $J = 7$ Hz, 3H), 0.88 (d, $J = 7$ Hz, 3H), 0.90 – 0.85 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 70.5, 61.5, 58.2, 47.5, 44.7, 39.9, 38.7, 30.8, 28.0, 26.4, 23.8, 21.6, 20.1, 19.7, 15.7; IR (thin film) ν 3459 (br), 2957, 2937, 2871, 2849, 1463, 1453, 1368, 1135, 1003, 876 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{26}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 261.1830, found 261.1838. ^1H -NOESY-2D (500 MHz, CDCl_3) spectra were obtained for epoxide **3.24**.

Epoxide **3.25**: $[\alpha]_{\text{D}}^{24} = +10.7$ ($c = 1.0$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 3.08 (s, 1H), 2.29 – 2.19 (m, 1H), 1.91 – 1.80 (m, 2H), 1.80 – 1.72 (m, 1H), 1.72 – 1.66 (m, 1H), 1.64 – 1.57 (m, 1H), 1.54 – 1.49 (m, 1H), 1.44 – 1.33 (m, 3H), 1.31 (s, 3H), 1.19 – 1.08 (m, 2H), 1.16 (s, 3H), 0.95 (d, $J = 6.9$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 70.9, 61.9, 58.7, 44.3, 42.4, 40.3, 38.4, 29.2, 29.1, 26.6, 25.0, 21.8, 21.4, 20.0, 15.6; IR (thin film) ν 3463 (br), 2956, 2934, 2872, 1464, 1375, 1209, 1142, 1022, 907, 845 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{26}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 261.1830, found 261.1838. ^1H -NOESY-2D (500 MHz, CDCl_3) spectra were obtained for epoxide **3.25** and selected NOE interactions are shown.



Trifluoroacetate 3.65 (not shown). A mixture of epoxide **3.24** (0.120 g, 0.505 mmol) and pyridine (0.16 mL, 2.02 mmol) in CH_2Cl_2 (5.1 mL) at 0 °C was treated with trifluoroacetic anhydride (0.14 mL, 1.01 mmol). After 30 minutes, the reaction was quenched with 1 M HCl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with water (10 mL), washed with saturated NaHCO_3 solution (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude residue was purified using flash

chromatography (SiO₂, 50% CH₂Cl₂/hexanes) to afford the title compound (0.114 g, 67%) as a colorless oil. $[\alpha]_D^{24} = -7.0$ ($c = 1.0$, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 2.91 (s, 1H), 2.75 (dt, $J = 15.0, 3.0$ Hz, 1H), 2.29 – 2.22 (m, 1H), 2.12 (dd, $J = 13.8, 4.8$ Hz, 1H), 1.76 (t, $J = 11.7$ Hz, 1H), 1.67 – 1.54 (m, 3H), 1.57 (s, 3H), 1.40 – 1.24 (m, 3H), 1.31 (s, 3H), 1.14 (qd, $J = 13.8, 3.3$ Hz, 1H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.92 (t, $J = 11.7$ Hz, 1H), 0.85 (d, $J = 6.6$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 156.2 (q, $J = 41.0$ Hz), 114.6 (q, $J = 285.4$ Hz), 88.3, 61.4, 57.9, 48.6, 43.9, 38.4, 34.3, 30.7, 26.4, 23.8, 23.7, 21.5, 19.8, 19.6, 15.2; IR (thin film) ν 2960, 2873, 1778, 1453, 1373, 1218, 1155 cm⁻¹; HRMS (ESI) m/z calcd for C₁₇H₂₅F₃O₃Na (M + Na)⁺ 357.1653, found 357.1647.



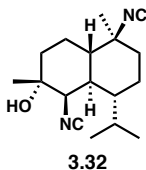
Isocyanides 3.26, 3.27, and 3.28. The following procedure was adopted from Pronin *et al.*⁶ A solution of trifluoroacetate **3.65** (62.3 mg, 0.186 mmol) in TMSCN (0.19 mL) was cooled to 0 °C. A solution of scandium(III) trifluoromethanesulfonate (9.2 mg, 0.0186 mmol) in TMSCN (0.37 mL) was added, and the reaction mixture was allowed to warm to room temperature after 1 h. After 24 h at room temperature, the reaction was quenched with TMEDA (30 µL) and the volatiles were removed under reduced pressure. The crude residue was dissolved in hexanes (10 mL), washed with saturated aqueous NaHCO₃ solution (5 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 2% EtOAc/hexanes) to afford a 6.3:1 mixture of elimination products **3.28** (18.9 mg, 32%) as a thin film and a 1.9:1 mixture of isocyanides **3.26** and **3.27** (8.0 mg, 12%) as a thin film. Isocyanides **3.26** and **3.27** were separated by column chromatography (SiO₂, 80% CH₂Cl₂/hexanes). The

6.3:1 mixture of alkene isomers (**3.28**) was characterized as a mixture; only the resonances in the ^1H and ^{13}C NMR spectra for the major Δ^9 -isomer are listed.

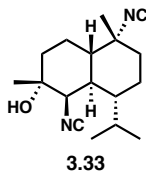
Diisocyanide **3.26**: $[\alpha]_{\text{D}}^{22} = +14.9$ ($c = 0.66$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 3.55 (s, 1H), 2.06 (dt, $J = 13.0$, 3.3 Hz, 1H), 1.94 – 1.60 (m, 8H), 1.54 – 1.40 (m, 2H), 1.45 (s, 3H), 1.30 (s, 3H), 1.11 (qd, $J = 13.3$, 3.5 Hz, 1H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.72 (d, $J = 7.0$ Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.5 (br t, $J = 4.9$ Hz), 153.1 (br t, $J = 4.4$ Hz), 73.4, 61.6 (br t, $J = 5.2$ Hz), 60.3 (br t, $J = 5.3$ Hz), 42.6, 42.1, 40.4, 35.9, 32.6, 27.5, 25.5, 21.4, 21.2, 20.6, 19.2, 14.9, 2.3; IR (thin film) ν 2956, 2874, 2131, 1456, 1384, 1252, 1184, 1038, 842 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{34}\text{N}_2\text{OSiNa}$ ($\text{M} + \text{Na}$) $^+$ 369.2338, found 369.2343.

Diisocyanide **3.27**: $[\alpha]_{\text{D}}^{24} = -7.7$ ($c = 0.34$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 3.59 (s, 1H), 2.10 – 2.01 (m, 1H), 1.97 (ap d, $J = 13.5$ Hz, 1H), 1.92 (quin of d, $J = 6.8$, 3.0 Hz, 1H), 1.75 – 1.65 (m, 5H), 1.54 – 1.34 (m, 2H), 1.44 (s, 3H), 1.41 (br s, 3H), 1.34 – 1.24 (m, 2H), 0.96 (d, $J = 6.5$ Hz, 3H), 0.79 (d, $J = 6.5$ Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.8 (br t), 155.3 (br t), 72.9, 61.6 (br t, $J = 5.3$ Hz), 61.5 (br t, $J = 4.9$ Hz), 42.3, 42.0, 39.1, 36.0, 32.3, 27.8, 27.6, 25.7, 21.3, 21.1, 19.1, 15.0, 2.4; IR (thin film) ν 2957, 2874, 2127, 1454, 1379, 1252, 1184, 1043, 869, 841 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{34}\text{N}_2\text{OSiNa}$ ($\text{M} + \text{Na}$) $^+$ 369.2338, found 369.2332.

Isocyanide **3.28**: $[\alpha]_{\text{D}}^{23} = +25.3$ ($c = 0.90$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 5.42 (s, 1H), 3.56 (s, 1H), 2.10 – 1.50 (m, 9H), 1.64 (s, 3H), 1.45 (s, 3H), 1.28 – 1.16 (m, 1H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.74 (d, $J = 6.9$ Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.3 (br t, $J = 4.8$ Hz), 135.1, 121.8, 73.7, 61.7 (br t, $J = 5.2$ Hz), 38.9, 38.4, 37.6, 34.4, 27.7, 25.6, 25.3, 23.8, 21.2, 21.0, 14.6, 2.5; IR (thin film) ν 2959, 2894, 2872, 2133, 1455, 1379, 1251, 1052, 842 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{33}\text{NOSiNa}$ ($\text{M} + \text{Na}$) $^+$ 342.2229, found 342.2215.

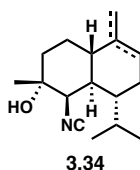


Diisocyanide 3.32. To a solution of TMS ether **3.26** (6.6 mg, 0.0190 mmol) in THF (0.2 mL) was added TBAF (40 μ L, 1.0 M in THF, 0.0381 mmol). After 1 h, the reaction was quenched with water (1 mL). The aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 20% EtOAc/hexanes) to afford diisocyanide **3.32** (3.5 mg, 67%) as a thin film. The spectral data for this compound are consistent with those reported in the literature.¹⁶ $[\alpha]_{\text{D}}^{23} = +23.3$ ($c = 0.35$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 3.63 (s, 1H), 2.07 (dt, $J = 13.0, 3.3$ Hz, 1H), 1.95 – 1.60 (m, 8H), 1.58 – 1.43 (m, 2H), 1.45 (s, 3H), 1.33 (br t, $J = 2.0$ Hz, 3H), 1.13 (qd, $J = 12.8, 3.3$ Hz, 1H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.75 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.7 (br t, $J = 4.5$ Hz), 153.1 (br t, $J = 4.6$ Hz), 70.5, 60.9 (br t, $J = 5.4$ Hz), 60.3 (br t, $J = 5.1$ Hz), 42.8, 42.4, 40.4, 36.2, 32.8, 28.9, 25.5, 21.4, 21.2, 20.9, 19.2, 15.2; IR (thin film) ν 3414 (br), 2955, 2873, 2133, 1452, 1386, 1267, 1180, 1126, 1002, 760 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{ONa}$ ($\text{M} + \text{Na}$)⁺ 297.1943, found 297.1949.



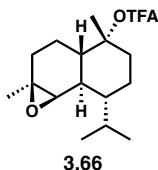
Diisocyanide 3.33. To a solution of TMS ether **3.27** (3.4 mg, 0.0098 mmol) in THF (0.2 mL) was added TBAF (20 μ L, 1.0 M in THF, 0.0196 mmol). After 1 h, the reaction was quenched with water (1 mL). The aqueous layer was extracted with ether (3 x 2 mL). The combined

organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 15% EtOAc/hexanes) to afford diisocyanide **3.33** (1.9 mg, 70%) as a thin film. $[\alpha]_{\text{D}}^{23} = -5.9$ ($c = 0.19$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 3.68 (s, 1H), 2.04 – 1.88 (m, 3H), 1.87 – 1.60 (m, 5H), 1.57 – 1.28 (m, 5H), 1.44 (s, 3H), 1.43 (br s, 3H), 0.97 (d, $J = 7.0$ Hz, 3H), 0.81 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.1 (br t, $J = 5.5$ Hz), 155.4 (br t, $J = 4.4$ Hz), 70.1, 61.3 (br t, $J = 4.4$ Hz), 60.9 (br t, $J = 5.2$ Hz), 42.5, 42.1, 39.2, 36.4, 32.4, 28.6, 27.9, 25.7, 21.4, 21.0, 19.1, 15.2; IR (thin film) ν 3428 (br), 2957, 2874, 2133, 1455, 1377, 1276, 1181, 1001, 833 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{ONa}$ ($M + \text{Na}$) $^+$ 297.1943, found 297.1934.

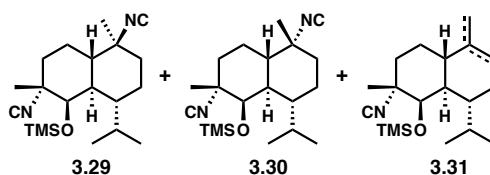


Isocyanide 3.34. To a solution of TMS ether **3.28** (9.0 mg, 0.0282 mmol) in THF (0.28 mL) was added TBAF (60 μL , 1.0 M in THF, 0.0563 mmol). After 1 h, the reaction was quenched with water (1 mL). The aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 2.5:47.5:50 EtOAc/ CH_2Cl_2 /hexanes) to afford a 7:1 mixture of isocyanides **3.34** (5.0 mg, 71%) as a thin film. The alkene isomers were characterized as a mixture; only the resonances in the ^1H and ^{13}C NMR spectra for the major Δ^9 -isomer are listed. $[\alpha]_{\text{D}}^{24} = +64.4$ ($c = 0.50$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 5.43 (s, 1H), 3.63 (s, 1H), 2.15 – 1.78 (m, 8H), 1.71 – 1.51 (m, 2H), 1.65 (s, 3H), 1.45 (s, 3H), 1.24 (qd, $J = 13.2$, 4.0 Hz, 1H), 0.95 (d, $J = 6.9$ Hz, 3H), 0.77 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.6 (br t, $J = 4.4$ Hz), 134.6, 122.0, 70.9, 60.8 (br t, $J = 5.4$ Hz), 39.2, 38.6, 37.6, 34.0, 28.5, 25.6,

25.1, 23.8, 21.2, 20.9, 14.9; IR (thin film) ν 3422 (br), 2960, 2934, 2892, 2871, 2153, 2134, 1450, 1378, 1207, 1012 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{25}\text{NONa}$ ($\text{M} + \text{Na}$)⁺ 270.1834, found 270.1833.



Trifluoroacetate 3.66 (not shown). A mixture of epoxide **3.25** (77.1 mg, 0.323 mmol) and pyridine (0.10 mL, 0.647 mmol) in CH_2Cl_2 (3.2 mL) at 0 °C was treated with trifluoroacetic anhydride (90 μL , 0.647 mmol). After 30 minutes, the reaction was quenched with 1 M HCl (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with water (10 mL), washed with saturated NaHCO_3 solution (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 40% CH_2Cl_2 /hexanes) to afford the title compound (70.1 mg, 65%) as a white solid (mp 86–88 °C). $[\alpha]_{\text{D}}^{24} = -12.5$ ($c = 1.0$, CHCl_3); ^1H NMR (CDCl_3 , 600 MHz) δ 3.11 (s, 1H), 2.75 (dt, $J = 15.0, 3.0$ Hz, 1H), 2.25 (quin of d, $J = 6.9, 3.3$ Hz, 1H), 1.92 – 1.80 (m, 3H), 1.69 – 1.64 (m, 1H), 1.61 – 1.55 (m, 1H), 1.56 (s, 3H), 1.45 (tt, $J = 11.7, 3.3$ Hz, 1H), 1.38 (td, $J = 14.4, 4.2$ Hz, 1H), 1.33 (s, 3H), 1.30 – 1.20 (m, 2H), 1.13 (qd, $J = 13.2, 3.6$ Hz, 1H), 0.95 (d, $J = 7.2$ Hz, 3H), 0.83 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.0 (q, $J = 40.8$ Hz), 114.5 (q, $J = 285.6$ Hz), 89.5, 61.5, 58.6, 43.8, 43.4, 37.9, 34.4, 28.8, 26.5, 24.9, 24.1, 21.5, 21.3, 19.6, 15.1; IR (thin film) ν 2957, 2868, 1777, 1452, 1372, 1207, 1162 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{15}\text{H}_{25}\text{O}$ ($\text{M} - \text{C}_2\text{O}_2\text{F}_3$)⁺ 221.1905, found 221.1907.

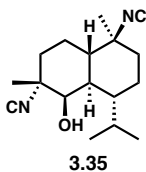


Isocyanides 3.29, 3.30, and 3.31. The following procedure was adopted from Pronin *et al.*⁶ A solution of trifluoroacetate **3.66** (18.5 mg, 0.0553 mmol) in TMSCN (50 μ L) was cooled to 0 $^{\circ}$ C. A solution of scandium(III) trifluoromethanesulfonate (2.7 mg, 0.00553 mmol) in TMSCN (0.11 mL) was added, and the reaction mixture was allowed to warm to room temperature after 1 h. After 24 h at room temperature, the reaction was quenched with TMEDA (20 μ L) and the volatiles were removed under reduced pressure. The crude residue was dissolved in hexanes (5 mL), washed with saturated aqueous NaHCO_3 solution (3 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 3% EtOAc/hexanes) to afford a 5.7:1 mixture of elimination products **3.31** (6.8 mg, 38%) as a thin film, diisocyanide **3.29** (4.3 mg, 22%) as thin film, and diisocyanide **3.30** (3.8 mg, 20%) as a thin film. The 5.7:1 mixture of alkene isomers (**3.31**) was characterized as a mixture; only the resonances in the ^1H and ^{13}C NMR spectra for the major Δ^9 -isomer are listed.

Diisocyanide **3.29**: $[\alpha]_{\text{D}}^{23} = -3.3$. ($c = 0.73$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 3.83 (s, 1H), 2.04 (dt, $J = 13.0, 3.3$ Hz, 1H), 1.95 – 1.79 (m, 3H), 1.79 – 1.64 (m, 4H), 1.63 – 1.48 (m, 2H), 1.40 (br s, 3H), 1.33 (br s, 3H), 1.30 (dt, $J = 11.5, 3.8$ Hz, 1H), 1.11 (qd, $J = 13.5, 3.3$ Hz, 1H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.81 (d, $J = 6.9$ Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.0 (br t, $J = 4.6$ Hz), 152.5 (br t, $J = 4.6$ Hz), 73.2, 61.5 (br t, $J = 5.1$ Hz), 60.5 (br t, $J = 5.1$ Hz), 41.4, 40.44, 40.37, 38.7, 31.4, 27.5, 25.7, 22.2, 21.3, 20.7, 18.9, 15.0, 1.1; IR (thin film) ν 2957, 2900, 2875, 2127, 1456, 1385, 1252, 1131, 1114, 883, 841 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{34}\text{N}_2\text{OSiNa}$ ($M + \text{Na}$)⁺ 369.2338, found 369.2338.

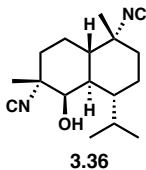
Diisocyanide **3.30**: $[\alpha]_D^{24} = -13.4$ ($c = 0.51$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 3.89 (s, 1H), 1.99 – 1.88 (m, 3H), 1.80 – 1.66 (m, 4H), 1.63 – 1.46 (m, 3H), 1.40 (br s, 6H), 1.37 – 1.20 (m, 2H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.88 (d, $J = 7.0$ Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.6 (br t, $J = 4.9$ Hz), 155.6 (br t, $J = 4.7$), 73.3, 61.2 (br t, $J = 4.6$ Hz), 60.9 (br t, $J = 5.3$ Hz), 40.9, 40.7, 39.1, 38.9, 31.3, 28.1, 27.7, 25.9, 22.1, 21.2, 18.8, 15.1, 1.1; IR (thin film) ν 2957, 2930, 2898, 2875, 2132, 1451, 1370, 1252, 1134, 1058, 840 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{34}\text{N}_2\text{OSiNa}$ ($\text{M} + \text{Na}$) $^+$ 369.2338, found 369.2331.

Isocyanide **3.31**: $[\alpha]_D^{23} = -20.5$ ($c = 1.27$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 5.40 (s, 1H), 3.89 (s, 1H), 2.17 (t, $J = 11.3$ Hz, 1H), 1.98 – 1.03 (complex, 9H), 1.64 (s, 3H), 1.40 (s, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.2 (br t, $J = 4.9$ Hz), 135.4, 121.6, 73.3, 61.7 (br t, $J = 5.1$ Hz), 41.5, 37.4, 36.1, 33.1, 27.6, 26.03, 25.99, 23.6, 21.1, 21.0, 14.7, 0.96; IR (thin film) ν 2959, 2907, 2127, 1452, 1368, 1252, 1127, 887, 841 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{33}\text{NOSiNa}$ ($\text{M} + \text{Na}$) $^+$ 342.2229, found 342.2240.

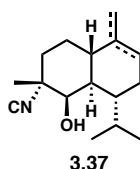


Diisocyanide 3.35. To a solution of TMS ether **3.29** (7.3 mg, 0.0211 mmol) in THF (0.21 mL) was added TBAF (40 μL , 1.0 M in THF, 0.0421 mmol). After 1 h, the reaction was quenched with water (1 mL). The aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 15% EtOAc/hexanes) to afford diisocyanide **3.35** (3.3 mg, 57%) as a thin film. $[\alpha]_D^{23} = +37.5$ ($c = 0.33$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz)

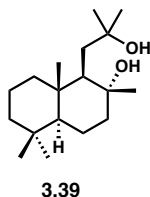
δ 3.79 (d, J = 4.7 Hz, 1H), 2.06 (dt, J = 12.8, 3.3 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.84 – 1.51 (m, 8H), 1.48 (br t, J = 1.8 Hz, 3H), 1.44 (ap tt, J = 12.0, 3.3 Hz, 1H), 1.35 (br s, 3H), 1.15 (qd, J = 13.5, 3.5 Hz, 1H), 0.94 (d, J = 6.9 Hz, 3H), 0.70 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.8 (br t), 152.7 (br t), 71.0, 61.0 (br t, J = 5.3 Hz), 60.5 (br t, J = 5.3 Hz), 41.8, 41.5, 40.6, 38.1, 31.1, 26.6, 25.8, 22.0, 21.5, 20.6, 19.4, 15.3; IR (thin film) ν 3394 (br), 2955, 2873, 2128, 1455, 1386, 1127, 1032, 759 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{ONa}$ ($\text{M} + \text{Na}$) $^{+}$ 297.1943, found 297.1954.



Diisocyanide 3.36. To a solution of TMS ether **3.30** (5.1 mg, 0.0147 mmol) in THF (0.2 mL) was added TBAF (30 μL , 1.0 M in THF, 0.0294 mmol). After 1 h, the reaction was quenched with water (1 mL). The aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 20% EtOAc/hexanes) to afford diisocyanide **3.36** (2.9 mg, 73%) as a thin film. $[\alpha]_{\text{D}}^{24} = -22.6$ (c = 0.29, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 3.86 (s, 1H), 2.01 – 1.90 (m, 3H), 1.83 – 1.60 (m, 6H), 1.59 – 1.50 (m, 1H), 1.48 (br t, J = 1.8 Hz, 3H), 1.43 – 1.33 (m, 3H), 1.41 (br t, J = 1.8 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.5 (br t), 155.8 (br t), 71.1, 61.2 (br t, J = 4.4 Hz), 60.4 (br t, J = 5.4 Hz), 41.7, 41.2, 39.3, 38.4, 31.1, 28.0, 26.8, 26.0, 21.8, 21.5, 19.3, 15.4; IR (thin film) ν 3391 (br), 2956, 2939, 2873, 2151, 2128, 1454, 1386, 1179, 1130, 1032 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{ONa}$ ($\text{M} + \text{Na}$) $^{+}$ 297.1943, found 297.1931.

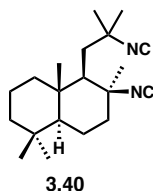


Isocyanide 3.37. To a solution of TMS ether **3.31** (12.7 mg, 0.0397 mmol) in THF (0.40 mL) was added TBAF (80 μ L, 1.0 M in THF, 0.0795 mmol). After 1 h, the reaction was quenched with water (1 mL). The aqueous layer was extracted with ether (3 x 3 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 1:49:50 EtOAc/ CH_2Cl_2 /hexanes) to afford a 5.6:1 mixture of isocyanides **3.37** (5.8 mg, 59%) as a thin film. The alkene isomers were characterized as a mixture; only the resonances in the ^1H and ^{13}C NMR spectra for the major Δ^9 -isomer are listed. $[\alpha]_{\text{D}}^{24} = -4.1$ ($c = 0.58$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 5.42 (s, 1H), 3.86 (d, $J = 4.5$ Hz, 1H), 2.11 – 1.51 (m, 10H), 1.65 (s, 3H), 1.49 (t, $J = 1.8$ Hz, 3H), 1.36 (qd, $J = 13.0, 4.0$ Hz, 1H), 0.94 (d, $J = 7.0$ Hz, 3H), 0.84 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.0 (br t, $J = 4.4$ Hz), 134.9, 122.0, 71.6, 61.1 (br t, $J = 5.2$ Hz), 41.0, 38.5, 36.5, 32.9, 26.7, 26.1, 25.7, 24.1, 21.3, 21.0, 15.3; IR (thin film) ν 3412 (br), 2957, 2932, 2870, 2151, 2128, 1451, 1387, 1367, 1038 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{25}\text{NONa}$ ($\text{M} + \text{Na}$) $^+$ 270.1834, found 270.1841.



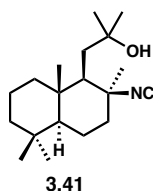
Diol 3.39. Methylmagnesium bromide (0.47 mL, 3.0 M in Et_2O , 1.40 mmol) was added dropwise to a solution of (3a*R*)-(+)-sclareolide (**3.38**) (70.0 mg, 0.280 mmol) in THF (2.8 mL) cooled to 0 $^\circ\text{C}$. The reaction mixture was allowed to warm to room temperature for 30 min, and the reaction

was quenched with saturated aqueous NH_4Cl solution (5 mL) at 0 °C. The aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 25% EtOAc /hexanes), yielding diol **3.39** (69.4 mg, 88%) as a white solid (mp 166–168 °C). $[\alpha]_D^{23} = +8.1$ ($c = 1.0$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 4.06 (s, 2H), 1.88 (dt, $J = 12.5$, 3.0 Hz, 1H), 1.74 – 1.32 (m, 7H), 1.30 – 1.07 (m, 3H), 1.27 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 0.98 – 0.82 (m, 3H), 0.87 (s, 3H), 0.78 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 73.4, 69.8, 56.3, 54.8, 44.4, 42.0, 40.1, 38.9, 38.5, 33.6, 33.3, 28.5, 25.1, 21.8, 20.4, 18.7, 15.6; IR (thin film) ν 3230 (br), 2964, 2934, 2868, 1467, 2128, 1451, 1386, 1155, 1124, 940, 756 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{34}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 305.2456, found 305.2451.



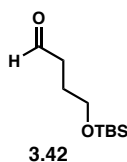
Diisocyanide 3.40. The following procedure was adopted from Pronin *et al.*⁶ A mixture of diol (**3.39**) (25.8 mg, 0.0913 mmol) and pyridine (40 μL , 0.383 mmol) in CH_2Cl_2 (0.91 mL) at 0 °C was treated with trifluoroacetic anhydride (0.1 mL, 1.92 M in CH_2Cl_2 , 0.192 mmol). After 15 minutes, the reaction was quenched with 1 M HCl (2 mL). The aqueous layer was extracted with hexanes (2 x 3 mL). The combined organic extracts were washed with water (5 mL), washed with saturated NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude trifluoroacetate was dissolved in TMSCN (0.1 mL) and cooled to 0 °C. A solution of scandium(III) trifluoromethanesulfonate (1.3 mg, 0.00274 mmol) in TMSCN (0.1 mL) was added. After 30 min, the reaction mixture was placed in a 3 °C refrigerator for 18 h. The reaction

was quenched with TMEDA (20 μ L) and the volatiles were removed under reduced pressure. The crude residue was suspended in hexanes (5 mL), washed with saturated aqueous NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 2.5% EtOAc/hexanes) to afford the title compound (6.3 mg, 23%) as a thin film. $[\alpha]_D^{24} = +17.1$ ($c = 0.60$, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 2.13 (dt, $J = 14.0, 3.0$ Hz, 1H), 1.87 – 1.31 (m, 7H), 1.53 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H), 1.29 – 1.11 (m, 3H), 1.09 – 1.75 (m, 3H), 1.04 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.0 (br t), 156.4 (br t), 61.4 (br t, $J = 4.4$ Hz), 57.4 (br t, $J = 4.8$ Hz), 55.4, 52.5, 42.0, 41.6, 40.9, 39.4, 37.9, 33.6, 33.5, 33.1, 32.6, 32.1, 21.9, 18.7, 18.1, 15.4; IR (thin film) ν 2929, 2841, 2133, 1465, 1444, 1392, 1367, 1156, 1131 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{32}\text{N}_2\text{Na}$ ($M + \text{Na}$) $^+$ 323.2463, found 323.2456.

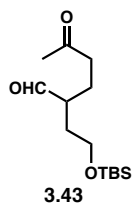


Isocyanide 3.41. The following procedure was adopted from Pronin *et al.*⁶ A mixture of diol (**3.39**) (69.4 mg, 0.246 mmol) and pyridine (80 μ L, 1.03 mmol) in CH_2Cl_2 (2.5 mL) at 0 $^\circ\text{C}$ was treated with trifluoroacetic anhydride (70 μ L, 0.516 mmol). After 15 minutes, the reaction was quenched with 1 M HCl (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with water (5 mL), washed with saturated NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude trifluoroacetate was dissolved in TMSCN (0.25 mL) and cooled to 0 $^\circ\text{C}$. A solution of scandium(III) trifluoromethanesulfonate (2.4 mg, 0.00492 mmol) in TMSCN (0.16 mL) was added. After 2 h at 0 $^\circ\text{C}$, the reaction was quenched with pyridine (50 μ L) and the volatiles were

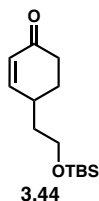
removed under reduced pressure. The crude residue was dissolved in MeOH (2 mL) and cooled to 0 °C. Potassium carbonate (68.0 mg, 0.492 mmol) was added in one portion. After 15 min, the reaction mixture was filtered and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% EtOAc/hexanes) to afford the title compound (14.8 mg, 21%) as a solid (mp 156–158 °C). $[\alpha]_D^{21} = +27.3$ (c = 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 2.10 (ap d, *J* = 14.0 Hz, 1H), 1.77 – 1.54 (m, 6H), 1.54 – 1.33 (m, 3H), 1.40 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H), 1.22 – 1.04 (m, 3H), 1.03 (s, 3H), 0.95 – 0.86 (m, 2H), 0.88 (s, 3H), 0.84 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 156.0 (br t, *J* = 4.9 Hz), 70.3, 61.7 (br t, *J* = 4.3 Hz), 55.6, 51.7, 42.3, 41.8, 40.6, 39.4, 38.9, 33.57, 33.55, 32.8, 32.3, 31.7, 21.9, 18.8, 18.2, 15.1; IR (thin film) ν 3486 (br), 2950, 2919, 2839, 2134, 1466, 1442, 1389, 1365, 1154, 1129 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₉H₃₃NONa (M + Na)⁺ 314.2460, found 314.2469.



Aldehyde 3.42. The title compound was prepared according to the literature procedure.¹⁷ The spectral data for this compound are consistent with those reported in the literature.¹⁷ ¹H NMR (500 MHz, CDCl₃) δ 9.78 (t, *J* = 1.8 Hz, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 2.49 (td, *J* = 7.0, 1.5 Hz, 2H), 1.85 (quin, *J* = 6.6 Hz, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 202.8, 62.2, 40.9, 26.0, 25.6, 18.4, –5.3.

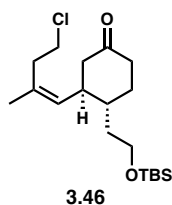


Keto-aldehyde 3.43. The following procedure was adapted from Hagiwara *et al.*¹⁰ Diethylamino(trimethyl)silane (90 μ L, 0.473 mmol) was added to a solution of aldehyde **3.42** (0.478 g, 2.36 mmol) in MeCN (7.9 mL). The reaction mixture was cooled to 0 °C and methyl vinyl ketone (0.29 mL, 3.54 mmol) was added dropwise *via* syringe. The reaction mixture was heated at reflux for 24 h, cooled to room temperature, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% EtOAc/hexanes) to afford the title compound (0.561 g, 87%) as a colorless oil. The spectral data for this compound are consistent with those reported in the literature.¹⁸ ¹H NMR (CDCl₃, 500 MHz) δ 9.57 (d, J = 2.5 Hz, 1H), 3.68 – 3.59 (m, 2H), 2.56 – 2.32 (m, 3H), 2.13 (s, 3H), 1.96 – 1.84 (m, 2H), 1.77 – 1.65 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 208.1, 204.4, 60.6, 48.7, 40.9, 32.7, 30.2, 26.0, 22.3, 18.4, –5.4.



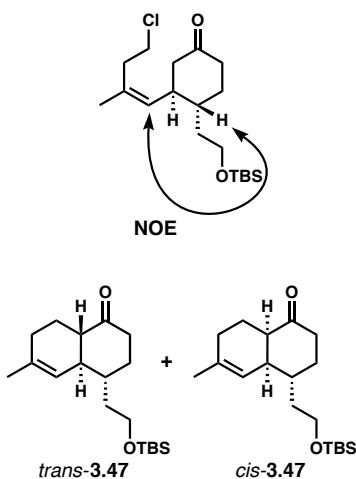
Enone 3.44. To a solution of keto-aldehyde **3.43** (2.43 g, 8.92 mmol) in Et₂O (83 mL) and THF (28 mL) was added aqueous KOH solution (89 mL, 0.3 N) and *n*Bu₄NOH (2.9 mL, 40% aq) in one portion. The reaction mixture was heated at reflux for 8 h and cooled to room temperature, at which point additional KOH (1.50 g, 26.7 mmol) was added in one portion. The reaction mixture was heated at reflux for 15 h, and cooled to room temperature. The biphasic reaction mixture was separated, and the aqueous layer was extracted with Et₂O (2 x 100 mL). The combined organic

extracts were washed with brine (100 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% EtOAc/hexanes) to afford the title compound (1.48 g, 65%) as a colorless oil. The spectral data for this compound are consistent with those reported in the literature.¹⁸ ¹H NMR (CDCl₃, 500 MHz) δ 6.90 (ddd, *J* = 10.0, 2.8, 1.3 Hz, 1H), 5.97 (ddd, *J* = 10.0, 2.5, 0.75 Hz, 1H), 3.79 – 3.67 (m, 2H), 2.68 – 2.57 (m, 1H), 2.49 (dt, *J* = 16.8, 4.8 Hz, 1H), 2.36 (ddd, *J* = 17.0, 12.3, 5.0 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.79 – 1.66 (m, 2H), 1.66 – 1.56 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 200.0, 155.4, 129.0, 60.5, 37.4, 37.0, 33.1, 28.7, 26.0, 18.4, –5.21, –5.24.



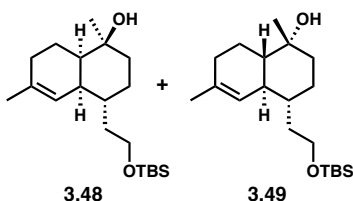
Ketone 3.46. To a solution of vinyl iodide **3.45** (0.313 g, 1.36 mmol) in Et₂O (2.3 mL, previously sparged with argon gas for 20 min) at –78 °C was added *tert*-butyllithium (1.70 mL, 1.60 M in pentane, 2.72 mmol) dropwise *via* syringe. After 20 min, lithium 2-thienylcyanocuprate solution (5.43 mL, 0.25 M in THF, 1.36 mmol) was added dropwise *via* syringe. The reaction mixture was allowed to stir for 1 h at –78 °C. A solution of enone **3.44** (0.230 g, 0.905 mmol) in Et₂O (1.0 mL) was added dropwise *via* syringe. The transfer was completed with additional portions of Et₂O (2 x 0.5 mL). After allowing the reaction mixture to warm to –40 °C and stir for 1 h, the reaction was quenched with 9:1 saturated NH₄Cl solution/NH₄OH (10 mL). After warming to room temperature, the solution turned a deep blue color. The aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic extracts were washed with 9:1 saturated NH₄Cl solution/NH₄OH (2 x 10 mL), washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified

using flash chromatography (SiO₂, 5% EtOAc/hexanes) to afford the title compound (0.298 g, 92%) as a colorless oil. ¹H NMR (CDCl₃, 500 MHz) δ 5.09 (d, *J* = 9.5 Hz, 1H), 3.71 – 3.60 (m, 2H), 3.56 – 3.48 (m, 2H), 2.55 – 2.24 (m, 6H), 2.24 – 2.10 (m, 2H), 1.88 – 1.79 (m, 1H), 1.73 (s, 3H), 1.69 – 1.59 (m, 1H), 1.39 (qd, *J* = 13.0, 4.8 Hz, 1H), 1.22 – 1.13 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 211.0, 132.0, 131.7, 61.2, 47.6, 43.4, 42.4, 41.0, 38.1, 36.3, 35.3, 31.1, 26.1, 23.0, 18.4, –5.1, –5.2; IR (thin film) ν 2954, 2930, 2897, 2857, 1717, 1255, 1096, 835, 775 cm^{–1}; HRMS (CI) *m* / *z* calcd for C₁₉H₃₅ClO₂SiNH₄ (M + NH₄)⁺ 376.2439, found 376.2437. ¹H-NOESY-2D (500 MHz, CDCl₃) spectra were obtained for ketone **3.46** and selected NOE interactions are shown.



***cis*- and *trans*-Decalones 3.47.** To a solution of alkyl chloride **3.46** (0.298 g, 0.829 mmol) in *tert*-butyl alcohol (8.3 mL) at 30 °C was added potassium *tert*-butoxide (0.62 mL, 1.6 M in THF, 0.995 mmol) dropwise *via* syringe. After stirring for 6 h at 30 °C, the reaction was quenched with saturated NH₄Cl solution (16 mL). The aqueous layer was extracted with pentane (3 x 20 mL), and the combined organic extracts were washed with water (4 x 20 mL) and brine (20 mL). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 5% EtOAc/hexanes) to afford a 1:1 mixture of *trans*-

and *cis*-decalones (176.4 mg, 71%) as a colorless oil, which was characterized as a mixture. ^1H NMR (CDCl_3 , 500 MHz) δ 5.54 (s, 1H), 5.30 (s, 1H), 3.78 – 3.62 (m, 4H), 2.51 – 2.34 (m, 4H), 2.33 – 2.25 (m, 2H), 2.22 – 1.77 (m, 14H), 1.70 – 1.29 (m, 6H), 1.67 (s, 3H), 1.63 (s, 3H), 0.897 (s, 9H), 0.895 (s, 9H), 0.059 (s, 6H), 0.058 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 214.0, 212.8, 135.7, 124.5, 122.3, 61.6, 61.1, 51.2, 47.1, 46.1, 42.2, 41.1, 38.1, 38.0, 35.9, 35.3, 34.9, 32.7, 39.8, 28.2, 28.1, 26.1, 23.81, 23.80, 23.0, 21.9, 18.4, –5.12, –5.14, –5.17. IR (thin film) ν 2953, 2928, 2857, 1713, 1472, 1254, 1100, 836, 776 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{34}\text{O}_2\text{SiNa}$ ($M + \text{Na}$) $^+$ 345.2226, found 345.2226.

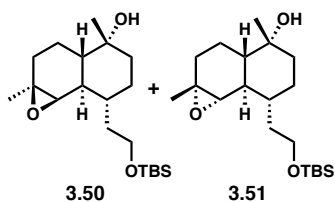


***cis*-Decalin 3.48 and *trans*-decalin 3.49.** Methylmagnesium bromide (1.54 mL, 3.0 M in Et_2O , 4.62 mmol) was added dropwise to a solution of a mixture of *cis*- and *trans*-decalones **3.47** (0.213 g, 0.923 mmol) in THF (9.2 mL) cooled to 0 $^\circ\text{C}$. The reaction mixture was allowed to warm to room temperature for 30 min, and the reaction was quenched with saturated aqueous NH_4Cl solution (12 mL) at 0 $^\circ\text{C}$. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 5 $\rightarrow$ 10% EtOAc /hexanes), yielding *trans*-decalin **3.49** (0.103 g, 46%) and *cis*-decalin **3.48** (0.101 g, 45%) as colorless oils.

***cis*-Decalin 3.48:** ^1H NMR (CDCl_3 , 500 MHz) δ 5.57 (d, $J = 4.0$ Hz, 1H), 3.71 – 3.64 (m, 1H), 3.63 – 3.56 (m, 1H), 2.03 – 1.94 (m, 2H), 1.91 – 1.81 (m, 3H), 1.72 – 1.36 (m, 6H), 1.65 (s, 3H), 1.35 – 1.22 (m, 2H), 1.30 (s, 3H), 1.10 (qd, $J = 13.0, 4.0$ Hz, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C

NMR (125 MHz, CDCl₃) δ 134.7, 124.9, 72.6, 61.7, 45.5, 40.1, 36.4, 36.2, 35.3, 31.2, 29.4, 28.0, 26.1, 23.7, 18.7, -5.08, -5.12; IR (thin film) ν 3380 (br), 2956, 2929, 2893, 2857, 1462, 1254, 1095, 835, 774 cm⁻¹; HRMS (ESI) m/z calcd for C₂₀H₃₈O₂SiNa (M + Na)⁺ 361.2539, found 361.2547.

trans-Decalin **3.49**: ¹H NMR (CDCl₃, 500 MHz) δ 5.53 (s, 1H), 3.74 – 3.67 (m, 1H), 3.67 – 3.59 (m, 1H), 2.06 – 1.86 (m, 4H), 1.85 – 1.76 (m, 1), 1.72 – 1.60 (m, 2H), 1.66 (s, 3H), 1.47 – 1.28 (m, 4H), 1.22 (s, 3H), 1.17 – 1.00 (m, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 134.3, 123.5, 70.7, 61.5, 47.8, 40.5, 40.1, 38.5, 36.1, 31.0, 28.6, 27.9, 26.1, 23.8, 22.6, 18.5, -5.07, -5.11; IR (thin film) ν 3455 (br), 2954, 2928, 2857, 1462, 1375, 1255, 1096, 835, 774 cm⁻¹; HRMS (ESI) m/z calcd for C₂₀H₃₈O₂SiNa (M + Na)⁺ 361.2539, found 361.2544.

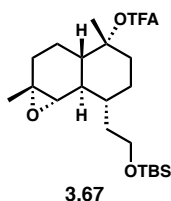


Epoxides 3.50 and 3.51. To a solution of *trans*-decalin **3.49** (0.109 g, 0.321 mmol) in acetone (16.1 mL) was added saturated aqueous NaHCO₃ (10.7 mL). The resulting mixture was cooled to 0 °C and a solution of Oxone® (0.217 g, 0.353 mmol) in H₂O (2 mL) was added dropwise over 5 minutes. The reaction mixture was stirred vigorously for 30 min at 0 °C, diluted with H₂O (20 mL) and extracted with EtOAc (4 x 20 mL). The combined organic extracts were diluted with hexanes until cloudy, dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10 → 20% EtOAc/hexanes) to afford β -epoxide **3.50** (25.7 mg, 23%) and α -epoxide **3.51** (72.4 mg, 64%) as colorless oils.

Epoxide **3.50**: ¹H NMR (CDCl₃, 500 MHz) δ 3.78 – 3.71 (m, 1H), 3.71 – 3.63 (m, 1H), 3.17 (s, 1H), 2.02 – 1.93 (m, 1H), 1.90 – 1.78 (m, 2H), 1.69 – 1.56 (m, 4H), 1.55 – 1.38 (m, 4H), 1.30 (s,

3H), 1.20 – 1.06 (m, 2H), 1.16 (s, 3H), 0.99 (s, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 70.8, 62.1, 61.3, 58.5, 41.9, 41.1, 40.1, 36.2, 35.9, 29.1, 29.0, 27.7, 26.1, 24.9, 21.7, 18.5, –5.12, –5.16; IR (thin film) ν 3480 (br), 2929, 2857, 1462, 1377, 1255, 1096, 836, 775 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{38}\text{O}_3\text{SiNa}$ ($\text{M} + \text{Na}$) $^+$ 377.2488, found 377.2488.

Epoxide **3.51**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.78 – 3.70 (m, 1H), 3.70 – 3.61 (m, 1H), 2.90 (s, 1H), 2.13 – 2.01 (m, 2H), 1.78 – 1.70 (m, 1H), 1.68 – 1.54 (m, 3H), 1.52 – 1.44 (m, 1H), 1.41 – 1.32 (m, 4H), 1.29 (s, 3H), 1.18 (s, 3H), 1.17 – 1.06 (m, 1H), 1.04 (s, 1H), 0.89 (s, 9H), 0.85 (t, J = 11.8 Hz, 1H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 70.4, 62.4, 61.1, 58.2, 47.3, 41.4, 39.7, 36.4, 36.3, 30.8, 28.6, 28.2, 26.1, 23.7, 19.6, 18.4, –5.11, –5.18; IR (thin film) ν 3481 (br), 2954, 2928, 2856, 1450, 1378, 1255, 1095, 836, 775 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{38}\text{O}_3\text{SiNa}$ ($\text{M} + \text{Na}$) $^+$ 377.2488, found 377.2483.



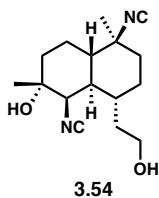
Trifluoroacetate 3.67 (not shown). A mixture of epoxide **3.51** (79.3 mg, 0.224 mmol) and pyridine (60 μL , 0.672 mmol) in CH_2Cl_2 (2.2 mL) at 0 $^\circ\text{C}$ was treated with trifluoroacetic anhydride (50 μL , 0.335 mmol). After 30 minutes, the reaction was quenched with 1 M HCl (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were washed with water (5 mL), washed with saturated NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 5% EtOAc/hexanes) to afford the title compound (82.3 mg, 82%) as a colorless oil. ^1H NMR (CDCl_3 , 500 MHz) δ 3.76 – 3.69 (m, 1H), 3.67 – 3.59 (m, 1H), 2.88 (s, 1H), 2.70 (dt, J = 14.8, 3.3 Hz, 1H), 2.15 – 2.02 (m, 2H), 1.86 – 1.79 (m, 1H), 1.68 – 1.52 (m,

3H), 1.57 (s, 3H), 1.49 – 1.21 (m, 4H), 1.30 (s, 3H), 1.05 (qd, $J = 14.0, 3.5$ Hz, 1H), 0.91 (t, $J = 11.0$ Hz, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.2 (q, $J = 41$ Hz), 114.5 (q, $J = 285.4$ Hz), 88.2, 62.0, 60.7, 58.0, 48.6, 41.2, 36.2, 35.7, 34.3, 30.8, 27.7, 26.1, 23.73, 23.65, 19.6, 18.4, $-5.17, -5.24$; IR (thin film) ν 2956, 2930, 2859, 1779, 1452, 1374, 1255, 1157, 1092, 837, 777 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{37}\text{F}_3\text{O}_4\text{SiNa}$ ($\text{M} + \text{Na}$) $^{+}$ 473.2311, found 473.2301.

Diisocyanides 3.52 and 3.53. The following procedure was adopted from Pronin *et al.*⁶ A solution of trifluoroacetate **3.67** (50.7 mg, 0.113 mmol) in TMSCN (0.11 mL) was cooled to 0 °C. A solution of scandium(III) trifluoromethanesulfonate (5.5 mg, 0.0113 mmol) in TMSCN (0.23 mL) was added, and the reaction mixture was allowed to warm to room temperature after 1 h. After 24 h at room temperature, the reaction was quenched with TMEDA (30 µL) and the volatiles were removed under reduced pressure. The crude residue was dissolved in hexanes (5 mL), washed with saturated aqueous NaHCO₃ solution (3 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 3 → 6% EtOAc/hexanes) to afford diisocyanide **3.52** (5.0 mg, 10%) as thin film and diisocyanide **3.53** (6.0 mg, 11%) as a 4:1 mixture of C10 epimers.

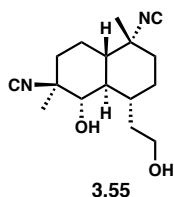
–5.19; IR (thin film) ν 2952, 2935, 2857, 2130, 1462, 1384, 1252, 1103, 1039, 840 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{25}\text{H}_{46}\text{N}_2\text{O}_2\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$) $^{+}$ 485.2996, found 485.2990.

Diisocyanide **3.53**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.71 (d, $J = 9.0$ Hz, 1H), 3.69 – 3.56 (m, 2H), 2.39 – 2.29 (m, 1H), 2.13 (dt, $J = 10.0, 3.5$ Hz, 1H), 1.98 – 1.73 (m, 4H), 1.51 – 1.06 (m, 7H), 1.41 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.28 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.1 (br t), 155.5 (br t), 81.0, 63.0 (br t, $J = 5.1$ Hz), 60.8, 60.6 (br t, $J = 4.3$ Hz), 47.8, 44.4, 38.4, 38.0, 37.9, 37.3, 28.5, 26.7, 26.1, 21.8, 20.6, 18.4, 1.5, –5.2, –5.3; IR (thin film) ν 2952, 2930, 2897, 2858, 2127, 1463, 1384, 1253, 1104, 840, 775 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{25}\text{H}_{46}\text{N}_2\text{O}_2\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$) $^{+}$ 485.2996, found 485.3009.

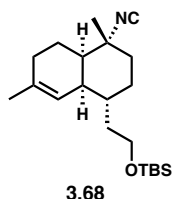


Diisocyanide 3.54. To a solution of silyl ether **3.52** (7.8 mg, 0.0169 mmol) in THF (0.2 mL) was added TBAF (90 μL , 1.0 M in THF, 0.0845 mmol). After 24 h, the reaction was quenched with saturated NaHCO_3 solution (1 mL). The reaction mixture was extracted with ether (3 $\times$ 2 mL). The combined organic extracts were washed with water (5 mL), washed with brine (5 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 2 $\rightarrow$ 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford diisocyanide **3.54** (2.7 mg, 57%) as a thin film. ^1H NMR (CDCl_3 , 500 MHz) δ 3.78 – 3.64 (s, 3H), 2.05 (dt, $J = 13.0, 3.3$ Hz, 1H), 1.96 – 1.59 (m, 9H), 1.59 – 1.31 (m, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 1.29 – 1.17 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.0 (br t), 153.2 (br t), 70.5, 61.2 (br t, $J = 5.4$ Hz), 60.21, 60.17 (br t, $J = 5.3$ Hz), 42.8, 40.2, 38.8, 34.8, 34.3, 32.7, 28.8, 26.6, 21.1, 20.8; IR (thin film) ν 3390 (br), 2937,

2871, 2134, 1451, 1384, 1122, 1036, 1003, 733 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}$ ($M + \text{Na}$)⁺ 299.1736, found 299.1733.

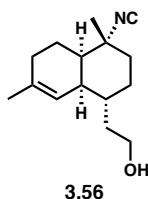


Diisocyanide 3.55. To a solution of silyl ether **3.53** (8.5 mg, 0.0184 mmol) in THF (0.2 mL) was added TBAF (0.10 mL, 1.0 M in THF, 0.0918 mmol). After 24 h, the reaction was quenched with saturated NaHCO_3 solution (1 mL). The reaction mixture was extracted with ether (3 x 2 mL). The combined organic extracts were washed with water (5 mL), washed with brine (5 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford diisocyanide **3.55** (3.9 mg, 76%) as a 4:1 mixture of C10 epimers. ^1H NMR (CDCl_3 , 500 MHz) δ 4.67 (br s, 1H), 3.90 (td, $J = 10.0$, 3.0 Hz, 1H), 3.76 (ddd, $J = 10.0$, 6.5, 4.0 Hz, 1H), 3.55 (d, $J = 10.0$ Hz, 1H), 2.56 (br s, 1H), 2.29 – 2.19 (m, 1H), 2.12 (dt, $J = 13.5$, 3.8 Hz, 1H), 2.06 – 1.17 (m, 10H), 1.42 (br s, 3H), 1.40 (br s, 3H), 1.06 (t, $J = 12.8$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.3 (br t), 153.1 (br t), 79.7, 62.8 (br t, $J = 5.6$ Hz), 60.8 (br t, $J = 4.6$ Hz), 60.1, 48.7, 42.1, 39.4, 39.1, 36.8, 36.3, 28.8, 28.2, 21.6, 19.3; IR (thin film) ν 3357 (br), 2938, 2870, 2130, 1448, 1384, 1116, 1041, 731 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}$ ($M + \text{Na}$)⁺ 299.1736, found 299.1727.



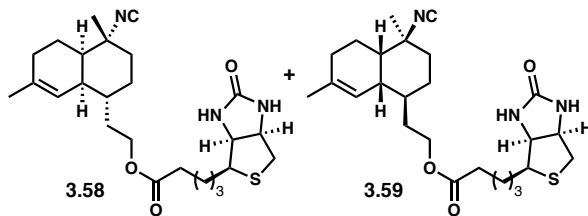
Isocyanide 3.68 (not shown). A mixture of *cis*-decalin **3.48** (0.111 g, 0.327 mmol) and pyridine (80 μL , 0.981 mmol) in CH_2Cl_2 (3.3 mL) at 0 $^\circ\text{C}$ was treated with trifluoroacetic anhydride (70

μL , 0.291 mmol). After 30 minutes, the reaction was quenched with 1 M HCl (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were washed with water (5 mL), washed with saturated NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude trifluoroacetate was dissolved in TMSCN (0.2 mL). A solution of scandium(III) trifluoromethanesulfonate (5.0 mg, 0.0101 mmol) in TMSCN (0.2 mL) was added. After 3.5 h, the reaction was quenched with TMEDA (50 μL) and the volatiles were removed under reduced pressure. The crude residue was suspended in hexanes (5 mL), washed with saturated aqueous NaHCO_3 solution (5 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO_2 , 50% CH_2Cl_2 /hexanes) to afford the title compound (48.7 mg, 69%) as a thin film. ^1H NMR (CDCl_3 , 500 MHz) δ 5.62 (d, J = 5.5 Hz, 1H), 3.73 – 3.66 (m, 1H), 3.66 – 3.57 (m, 1H), 2.22 – 2.15 (m, 1H), 2.07 – 1.79 (m, 5H), 1.72 – 1.61 (m, 2H), 1.64 (s, 3H), 1.60 – 1.28 (m, 5H), 1.42 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.5 (br t), 133.7, 124.5, 62.0 (br t, J = 4.6 Hz), 61.3, 44.5, 37.9, 36.1, 35.4, 33.4, 31.0, 27.9, 27.4, 26.1, 23.6, 19.4, 18.4, –5.07, –5.13; IR (thin film) ν 2930, 2858, 2127, 1461, 1380, 1255, 1096, 835, 775 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{37}\text{NOSiNa}$ ($M + \text{Na}$) $^+$ 370.2542, found 370.2533.

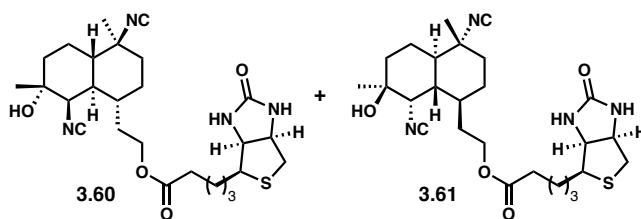


Alcohol 3.56. To a solution of silyl ether **3.68** (48.7 mg, 0.140 mmol) in THF (1.4 mL) was added TBAF (0.70 mL, 1.0 M in THF, 0.700 mmol). After 24 h, the reaction was quenched with saturated NaHCO_3 solution (2 mL). The reaction mixture was extracted with ether (3 x 3 mL). The combined organic extracts were washed with water (5 mL), washed with brine (5 mL), dried

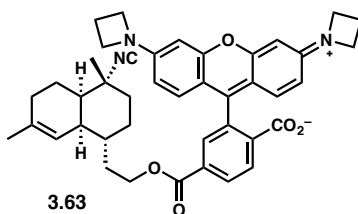
over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 1.5% MeOH/CH₂Cl₂) to afford alcohol **3.56** (27.1 mg, 83%) as a thin film. ¹H NMR (CDCl₃, 500 MHz) δ 5.62 (d, *J* = 5.5 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.70 – 3.60 (m, 1H), 2.23 – 2.13 (m, 1H), 2.09 – 1.65 (m, 7H), 1.64 (s, 3H), 1.60 – 1.28 (m, 6H), 1.42 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 153.4 (br t), 134.1, 124.1, 62.0 (br t, *J* = 4.5 Hz), 60.8, 44.5, 38.0, 36.0, 35.3, 33.2, 31.0, 27.8, 27.1, 23.6, 19.4; IR (thin film) ν 3399 (br), 2936, 2876, 2833, 2127, 1450, 1379, 1047, 855 cm⁻¹; HRMS (ESI) *m* / *z* calcd for C₁₅H₂₃NONa (M + Na)⁺ 256.1677, found 256.1677.



Isocyanides 3.58 and 3.59. A solution of biotin **3.57** (3.4 mg, 0.0141 mmol), EDC•HCl (4.9 mg, 0.0258 mmol), and DMAP (~0.5 mg, 0.004 mmol) in DMF (0.2 mL) was allowed to stir at room temperature for 1 h. Alcohol **3.56** (3.0 mg, 0.0129 mmol) and Et₃N (10 μL) were added as a solution in DMF (0.2 mL). After stirring 6 d at room temperature, saturated NH₄Cl solution (1 mL) and water (1 mL) were added. The reaction mixture was extracted with EtOAc (3 x 2 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (3 mL) and brine (3 mL). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 4% MeOH/CH₂Cl₂) to afford isocyanides **3.58** and **3.59** (4.2 mg, 71%) as a thin film. ¹H NMR and ¹³C NMR spectra were complicated by the mixture of diastereomers. IR (thin film) ν 3254 (br), 2925, 2856, 2129, 1704, 1456, 1261, 1183, 758 cm⁻¹; HRMS (ESI) *m* / *z* calcd for C₂₅H₃₇N₃O₃SNa (M + Na)⁺ 482.2453, found 482.2435.

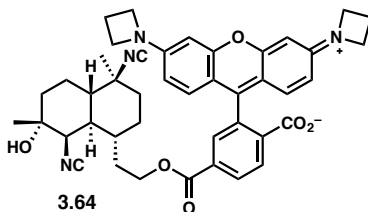


Diisocyanides 3.60 and 3.61. A solution of biotin **3.57** (2.2 mg, 0.00915 mmol), EDC•HCl (3.2 mg, 0.0166 mmol), and DMAP (~0.3 mg, 0.003 mmol) in DMF (0.2 mL) was allowed to stir at room temperature for 1 h. Diol **3.54** (2.3 mg, 0.00832 mmol) and Et₃N (10 μ L) were added as a solution in DMF (0.2 mL). After stirring 7 d at room temperature, saturated NH₄Cl solution (1 mL) and water (1 mL) were added. The reaction mixture was extracted with EtOAc (3 $\times$ 2 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (3 mL) and brine (3 mL). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 8% MeOH/CH₂Cl₂) to afford a 1:1 mixture of diisocyanides **3.60** and **3.61** (1.5 mg, 36%) as a thin film. The ¹H NMR spectrum was complicated by the mixture of diastereomers. IR (thin film) ν 3357 (br), 2928, 2867, 2134, 1698, 1461, 1266, 1176, 736 cm⁻¹; HRMS (ESI) m/z calcd for C₂₆H₃₈N₄O₄SNa (M + Na)⁺ 525.2512, found 525.2491.



Isocyanide 3.63. A solution of 5-carboxy-JF₅₄₉ (**3.62**, 2.7 mg, 0.0049 mmol), EDC•HCl (1.2 mg, 0.0065 mmol), and DMAP (~0.5 mg, 0.0043 mmol) in CH₂Cl₂ (0.1 mL) was allowed to stir at room temperature for 5 min. Alcohol **3.56** (1.0 mg, 0.0043 mmol) was added as a solution in CH₂Cl₂ (0.2 mL). After stirring 3 h at room temperature, the reaction mixture was diluted with

CH₂Cl₂ (2 mL) and saturated NaHCO₃ solution (2 mL) was added. The reaction mixture was extracted with CH₂Cl₂ (3 x 2 mL). The combined organic extracts were washed with water (2 mL). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% MeOH/CH₂Cl₂ with 0.1% v/v AcOH additive, dry load with Celite). Additional purification using flash chromatography (SiO₂, 10% MeOH (10% NH₃)/CH₂Cl₂) afforded isocyanide **3.63** (1.0 mg, 34%) as a thin, magenta film. ¹H NMR (CDCl₃, 600 MHz) δ 8.62 (s, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 2H), 6.20 (s, 2H), 6.08 (d, *J* = 8.4 Hz, 2H), 5.65 (d, *J* = 4.8 Hz, 1H), 4.51 – 4.35 (m, 2H), 3.91 (t, *J* = 7.2 Hz, 8H), 2.38 (quin, *J* = 7.2 Hz, 4H), 2.30 – 1.36 (complex), 1.68 (s, 3H), 1.45 (s, 3H); IR (thin film) ν 2925, 2856, 2128, 1763, 1720, 1611, 1596, 1380, 1298, 1217 cm⁻¹; HRMS (ESI) *m* / *z* calcd for C₄₂H₄₃N₃O₅Na (M + Na)⁺ 692.3101, found 692.3103.



Diisocyanide 3.64. A solution of 5-carboxy-JF₅₄₉ (**3.62**, 5.0 mg, 0.0088 mmol), EDC•HCl (3.1 mg, 0.0159 mmol), and DMAP (1.0 mg, 0.0080 mmol) in CH₂Cl₂ (0.1 mL) was allowed to stir at room temperature for 5 min. Alcohol **3.54** (2.2 mg, 0.0080 mmol) was added as a solution in CH₂Cl₂ (0.2 mL). After stirring 3 h at room temperature, the reaction mixture was diluted with CH₂Cl₂ (2 mL) and saturated NaHCO₃ solution (2 mL) was added. The reaction mixture was extracted with CH₂Cl₂ (3 x 2 mL). The combined organic extracts were washed with water (2 mL). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified using flash chromatography (SiO₂, 10% MeOH/CH₂Cl₂ with 0.1% v/v

AcOH additive, dry load with Celite). Additional purification using flash chromatography (SiO₂, 10% MeOH (10% NH₃)/CH₂Cl₂) afforded diisocyanide **3.64** (1.0 mg, 18%) as a thin, magenta film. ¹H NMR (CDCl₃, 500 MHz) δ 8.90 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.52 (dd, *J* = 8.8, 4.8 Hz, 2H), 6.20 (d, *J* = 2.0 Hz, 2H), 6.08 (dt, *J* = 8.6, 2.0 Hz, 2H), 4.49 – 4.39 (m, 2H), 3.92 (t, *J* = 7.3 Hz, 8H), 3.95 – 3.88 (s, 1H), 2.39 (quin, *J* = 7.2 Hz, 4H), 2.14 – 1.15 (complex), 1.52 (s, 3H), 1.36 (br s, 3H); IR (thin film) ν 2925, 2868, 2132, 1763, 1721, 1594, 1379, 1299, 1218 cm⁻¹; HRMS (ESI) *m* / *z* calcd for C₄₃H₄₄N₄O₆Cl (M + Cl)⁻ 747.2949, found 747.2957.

Procedure for the Evaluation of Antimalarial Activity of Synthetic Isocyanoterpenes

Method: Synchronized malaria parasite lines (3D7, wild type, MRA-102, and chloroquine resistant Dd2, MRA-156, MR4, ATCC[®] Manassas, VA) were cultured in the presence of a serial dilution of compound for 72 hours and proliferation evaluated with SYBR Green dye as previously described.⁸ Ninety-six well plate data was read on a Molecular Devices SpectraMAX Gemini EM fluorimeter and plotted with SigmaPlot 10 (Systat) to determine IC₅₀ values. The results are tabulated in Table 3.2. The graph used for determining the IC₅₀ of kalihinol B (**3.8**) is included as a representative of the methods employed (Figure 3.3). Jacques Prudhomme completed all antimalarial assays in the laboratory of Professor Karine Le Roch at UCR.

Acknowledgment: We thank MR4 for providing us with malaria parasites contributed by Daniel Carucci, Alister Craig, and TE Wellems.

Table 3.2. Activity of synthetic ICTs against wild-type (3D7) and chloroquine-resistant (Dd2) *P. falciparum*.

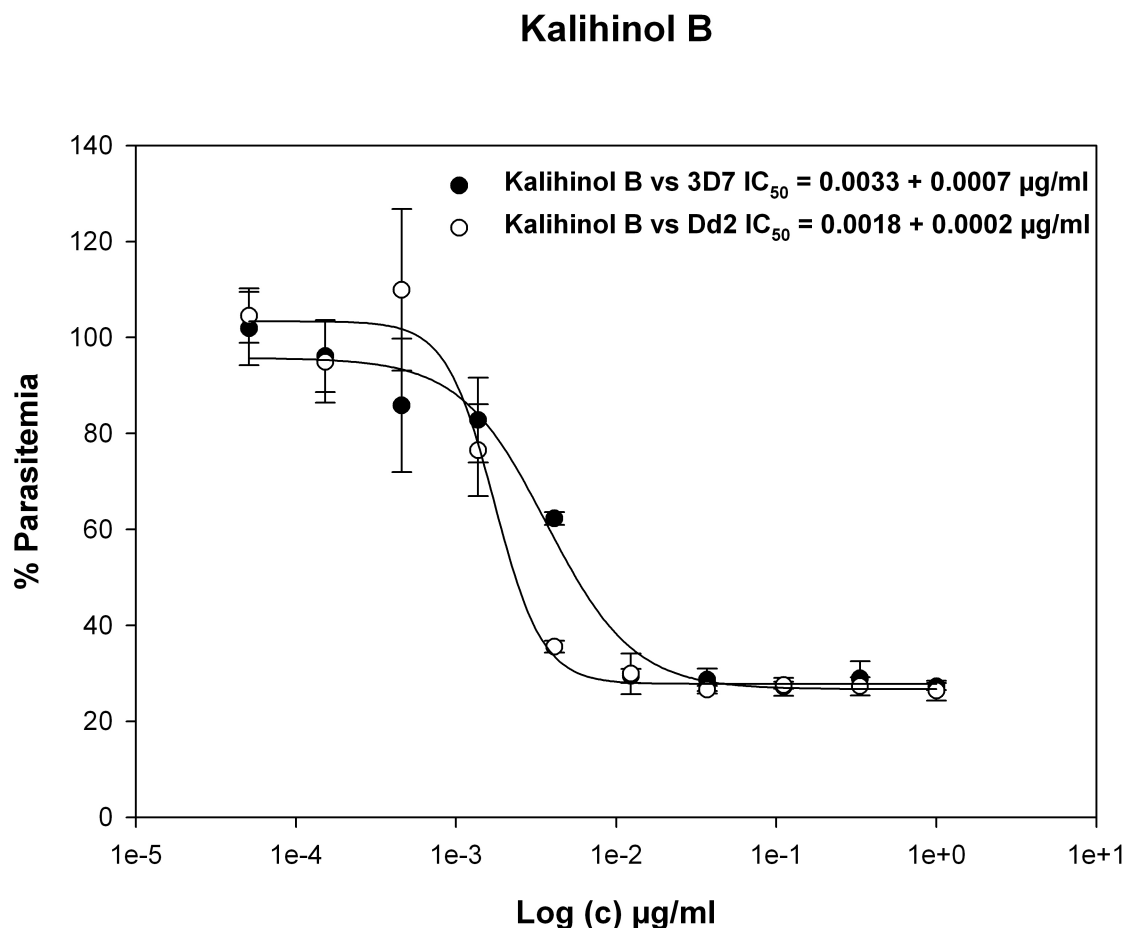
Compound	Pf strain ^a	IC50 [nM]	IC50 [μg/mL]	std error ^b	R	hillslope	Chloroquine ^c IC50 [μM]	std error
3.8	3D7	8.4	0.0033	0.0007	0.9914	1.342	0.0063	0.002
3.8	Dd2	4.6	0.0018	0.0002	0.9938	2.937	0.0399	0.0035
3.9/3.10	3D7	139	0.0508	0.0072	0.9952	2.3689	0.0052	0.0001
3.9/3.10	Dd2	144	0.0526	0.0093	0.9959	1.4242	0.0275	0.0086
3.11	3D7	175	0.0596	0.0117	0.9903	1.4691	0.0066	0.0004
3.11	Dd2	123	0.0418	0.0188	0.9808	0.6601	0.0413	0.0037
(±)-3.22	3D7	705	0.1631	0.0894	0.9899	0.5629	0.0059	0.0009
(±)-3.22	Dd2	247	0.057	0.0234	0.9961	0.5342	0.0322	0.0039
(±)-3.23^d	3D7	180	0.0417	0.0191	0.9748	0.8015	0.0091	0.0007
(±)-3.23^d	Dd2	45	0.0104	0.0073	0.9882	0.2933	0.0337	0.0031
3.32	3D7	12	0.0034	0.0006	0.9963	7.3863	0.0089	0.0018
3.32	Dd2	16	0.0043	0.0001	0.9979	4.6016	0.0497	0.0157
3.33	3D7	2.9	0.0008	0.0002	0.984	1.3984	0.0089	0.0018
3.33	Dd2	31	0.0084	0.0016	0.9917	1.5004	0.0497	0.0157
3.34	3D7	138	0.0342	0.0037	0.9935	2.6747	0.0089	0.0018
3.34	Dd2	200	0.0495	0.0089	0.9939	1.3615	0.0497	0.0157
3.35	3D7	15	0.0041	0.0006	0.9954	1.6148	0.0089	0.0018
3.35	Dd2	17	0.0047	0.0003	0.9983	3.1883	0.0497	0.0157
(±)-3.35^e	3D7	27	0.0074	0.0013	0.9927	--	0.0058	0.0005
(±)-3.35^e	Dd2	46	0.0127	0.0016	0.9918	--	0.0521	0.0274
3.36	3D7	1150	0.3155	0.0179	0.9989	2.0297	0.0089	0.0018
3.36	Dd2	958	0.2628	0.0427	0.9962	1.0929	0.0497	0.0157
3.37	3D7	312	0.0771	0.0032	0.9995	2.1804	0.0089	0.0018
3.37	Dd2	529	0.1308	0.0057	0.999	2.8612	0.0497	0.0157
3.40	3D7	1.9	0.0006	0.0002	0.9833	1.7569	0.0059	0.0009
3.40	Dd2	1.6	0.0005	0.0002	0.9903	0.7528	0.0322	0.0039
3.41	3D7	244	0.0745	0.0083	0.997	1.4462	0.0061	0.0005
3.41	Dd2	416	0.1271	0.0438	1.2621	1.2721	0.0419	0.0905
(±)-3.54^f	3D7	302	0.0836	0.018	0.9773	4.7837	0.0091	0.0007
(±)-3.54^f	Dd2	205	0.0566	0.007	0.9833	3.2312	0.0337	0.0031
(±)-3.55^g	3D7	27	0.0075	0.0009	0.9831	2.043	0.0091	0.0007
(±)-3.55^g	Dd2	24	0.0065	0.0009	0.9879	1.2806	0.0337	0.0031
(±)-3.56^g	3D7	391	0.0913	0.0458	0.9726	0.8016	0.0091	0.0007
(±)-3.56^g	Dd2	516	0.1205	0.0351	0.9795	1.4745	0.0337	0.0031

^a3D7 is a chloroquine-sensitive strain of *P. falciparum*. Dd2 is a chloroquine-resistant strain of *P. falciparum*. ^bn = 3.

^cChloroquine was used as the antimalarial standard. ^dPrecipitate at 33.3 μg/mL. ^eAverage of three separate assays.

^fPrecipitate at 11.1 μg/mL. ^gPrecipitate at 3.7 μg/mL.

Figure 3.3. IC₅₀ (μg/mL) of kalihinol B (**3.8**) against wild-type (3D7) and chloroquine-resistant (Dd2) strains of *P. falciparum*.

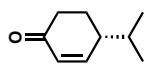


3.7 Notes and References

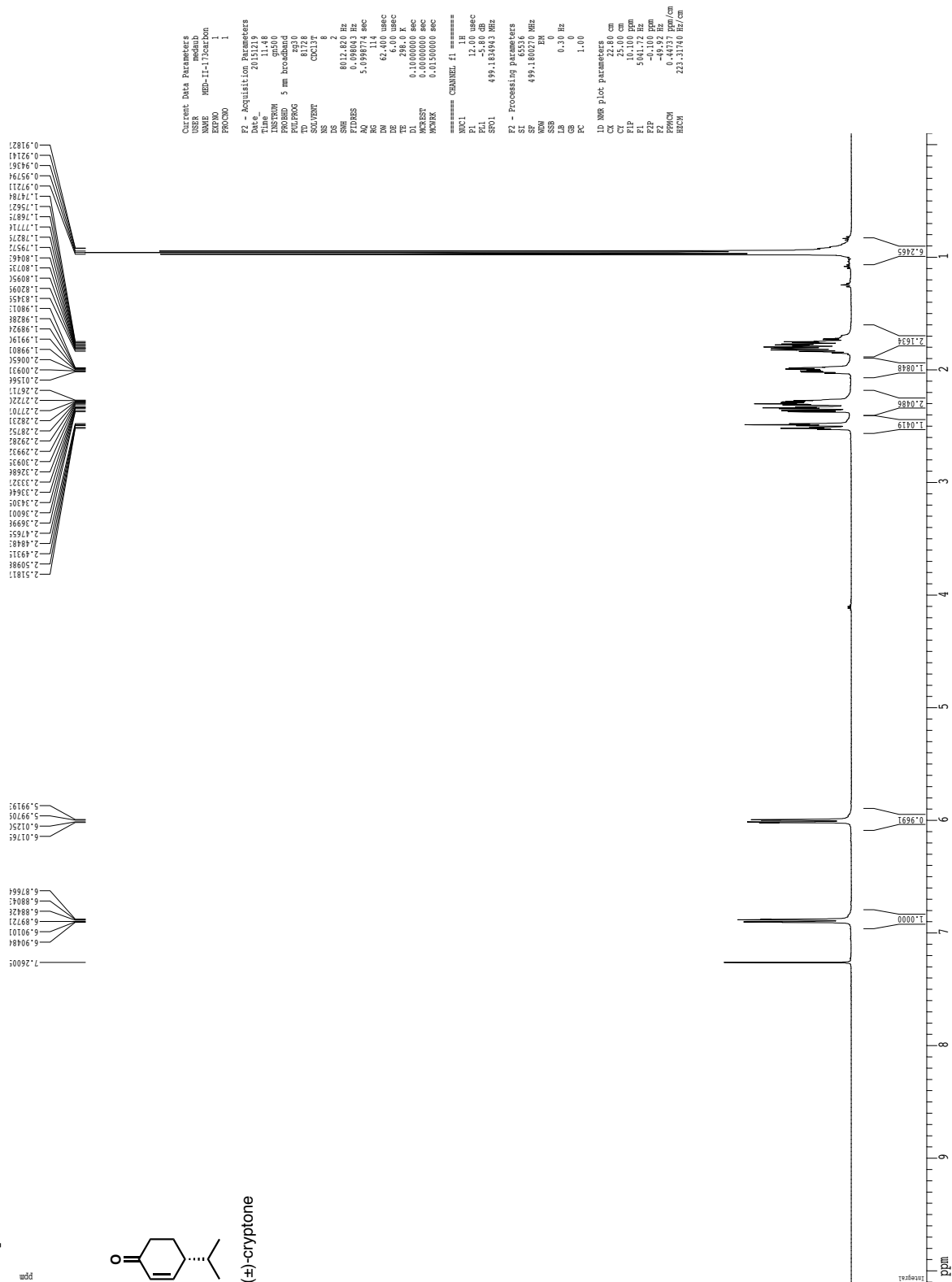
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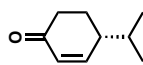
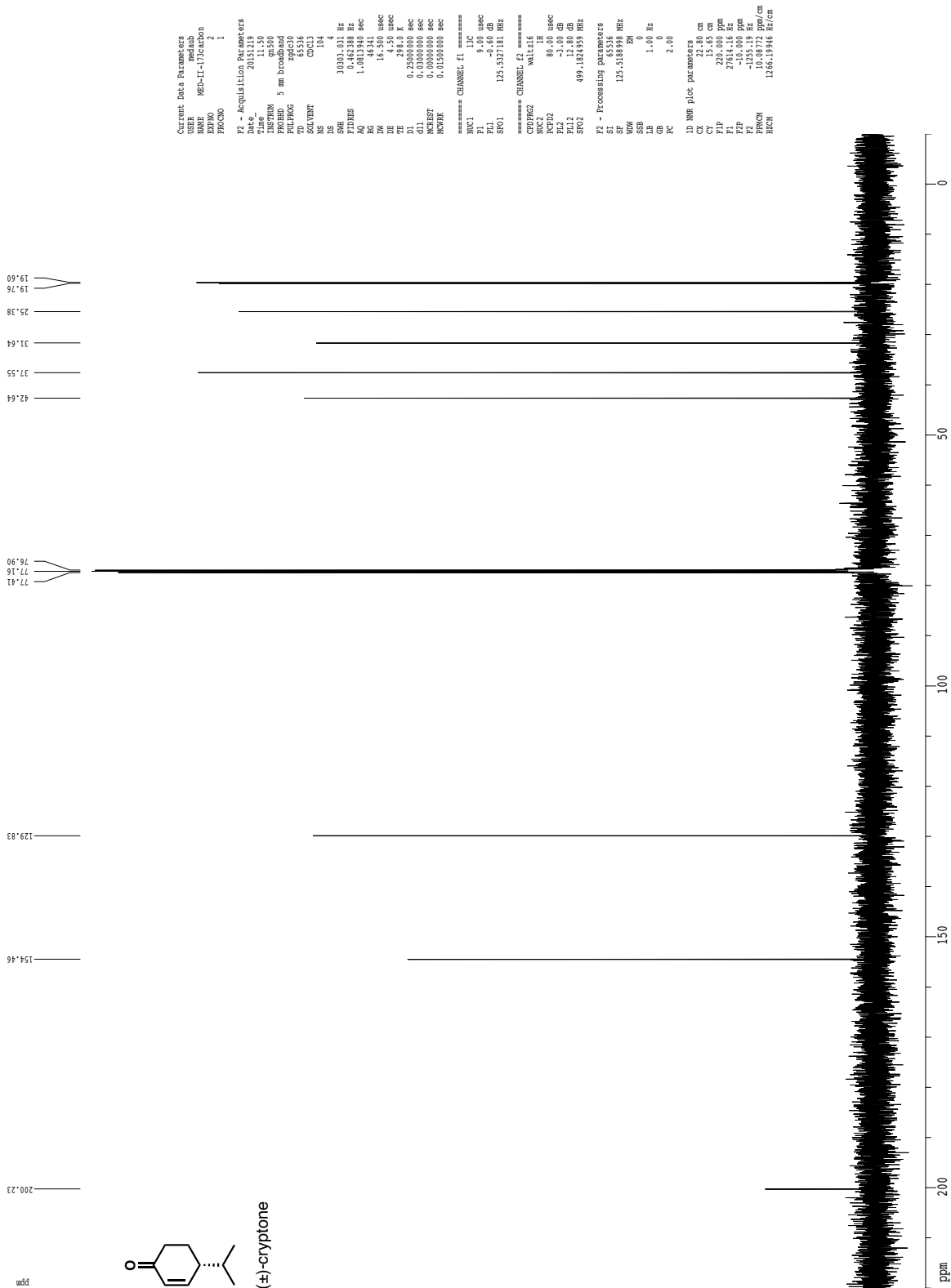
APPENDIX A: NMR and Chiral HPLC Data



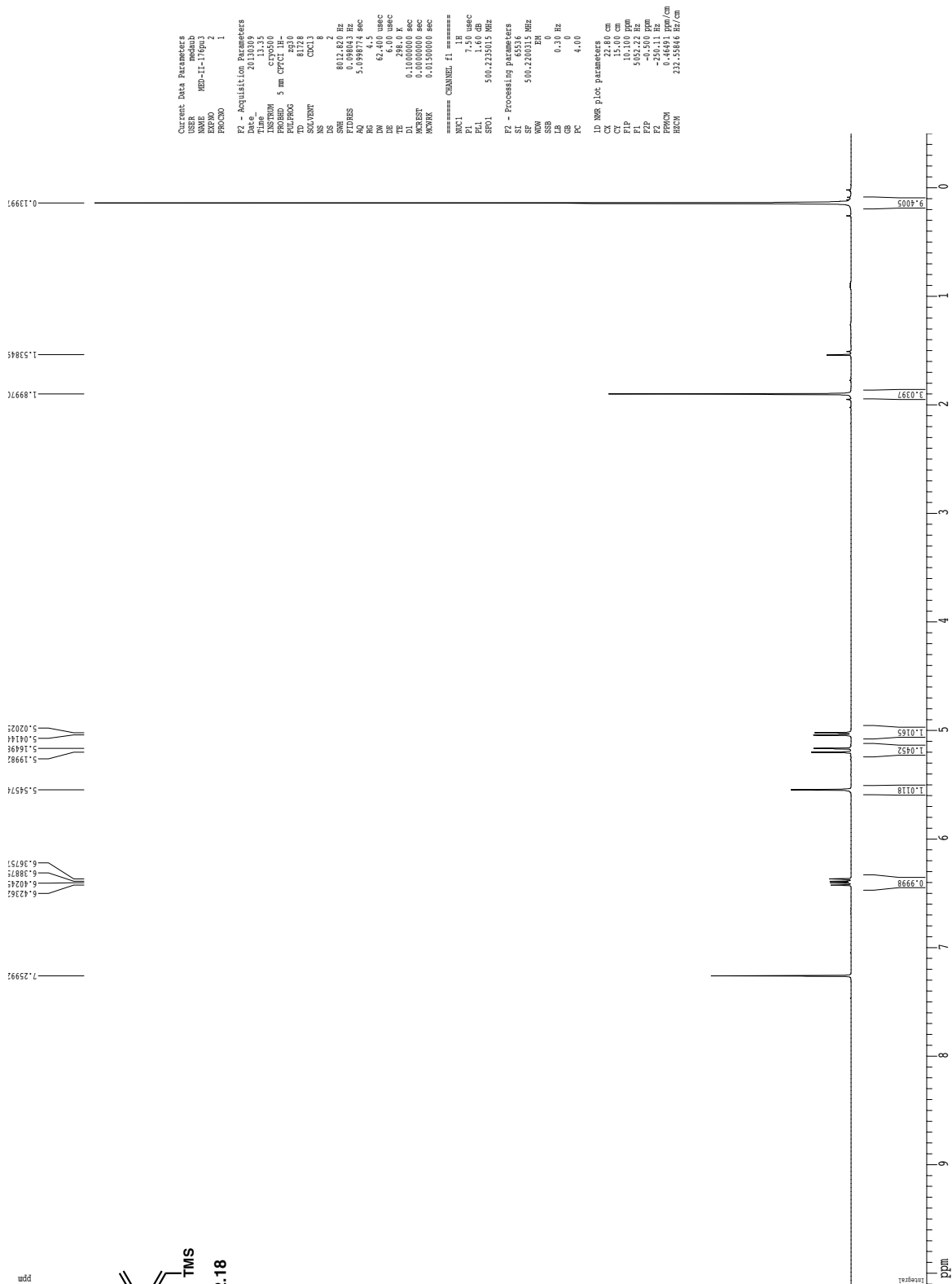
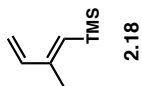
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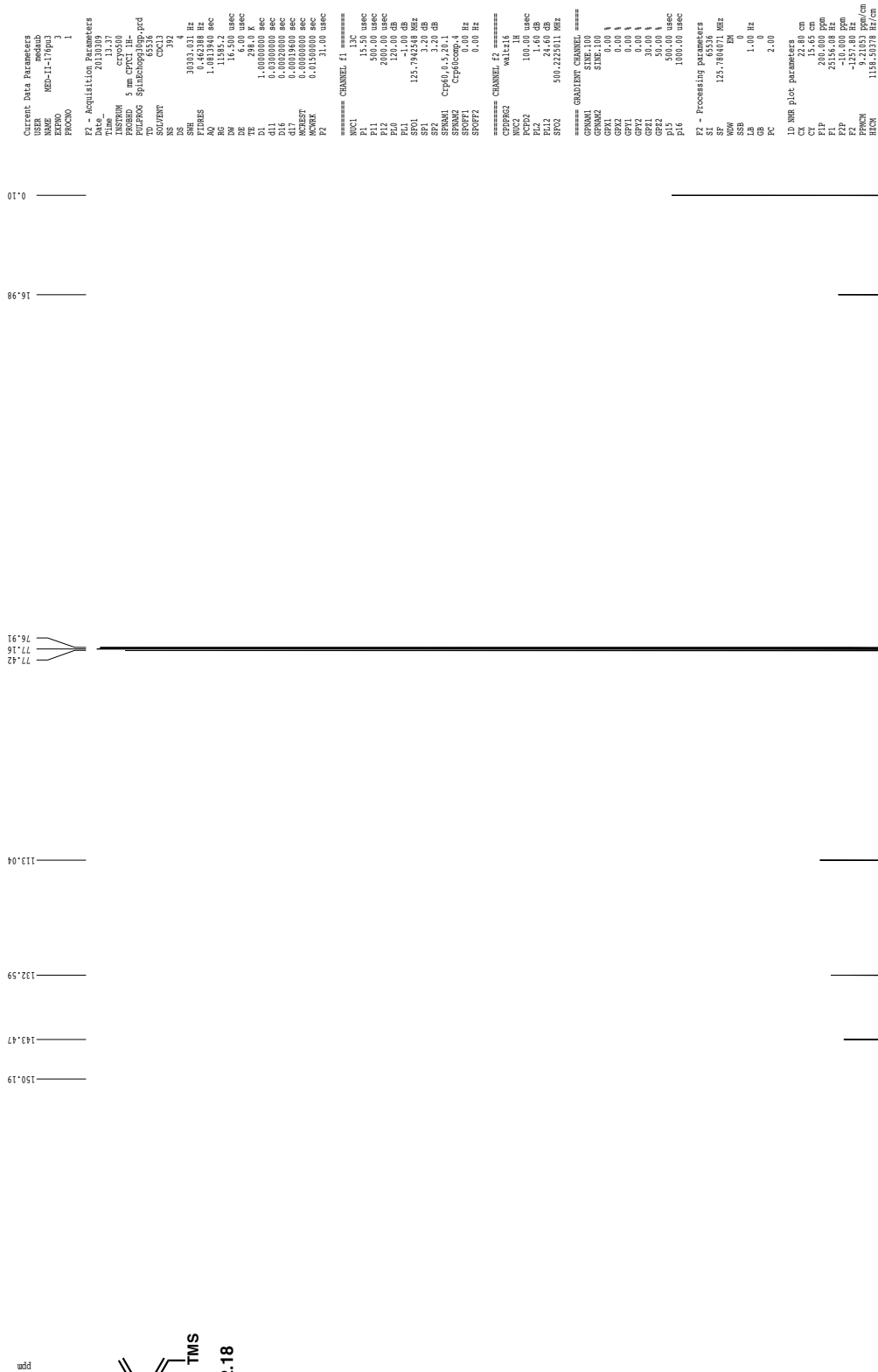
¹³C spectrum with ¹H decoupling

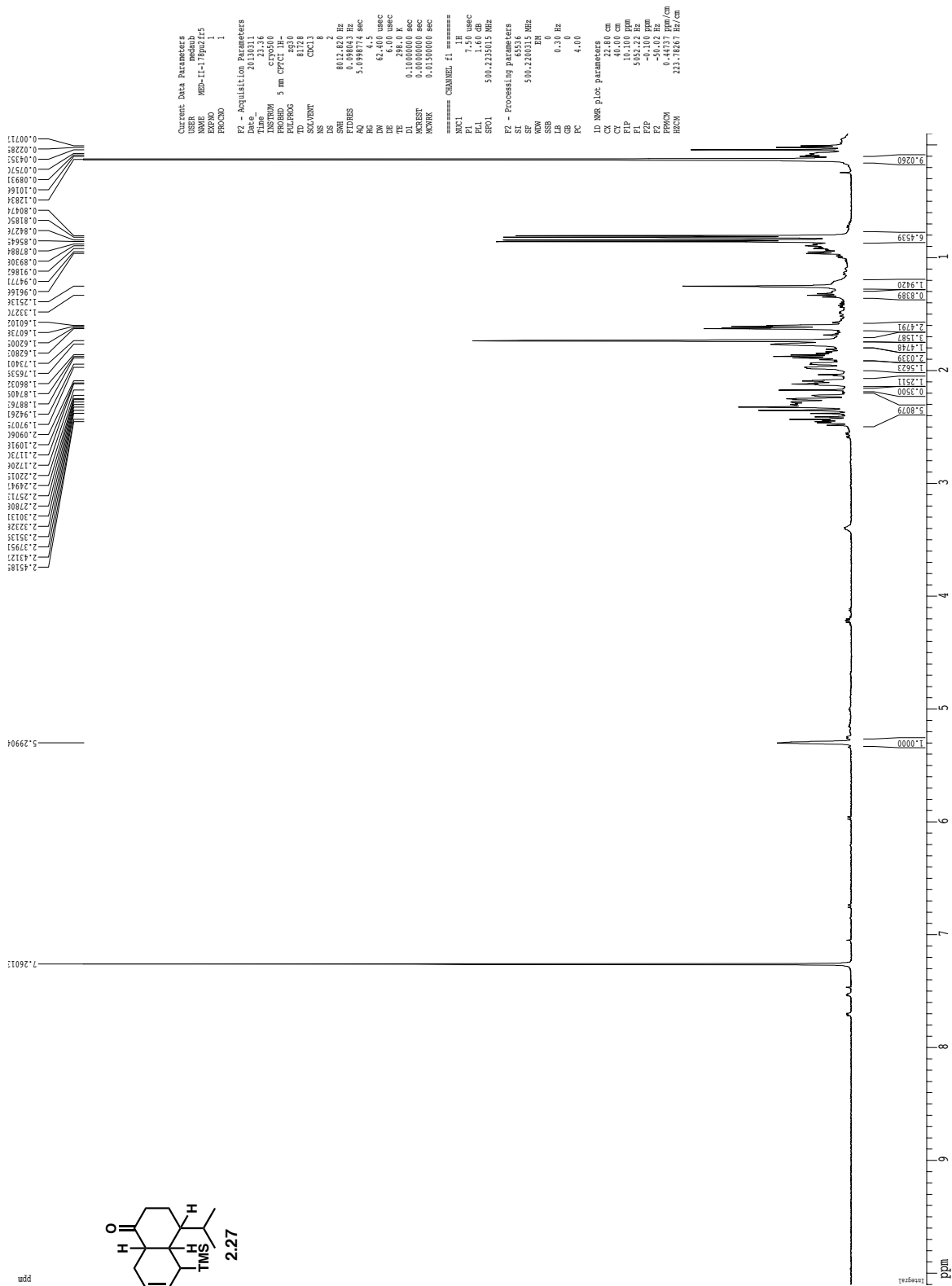
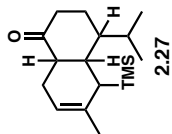


2.19: (±)-cryptone



Z-restored spin-echo ¹³C spectrum with ¹H decoupling

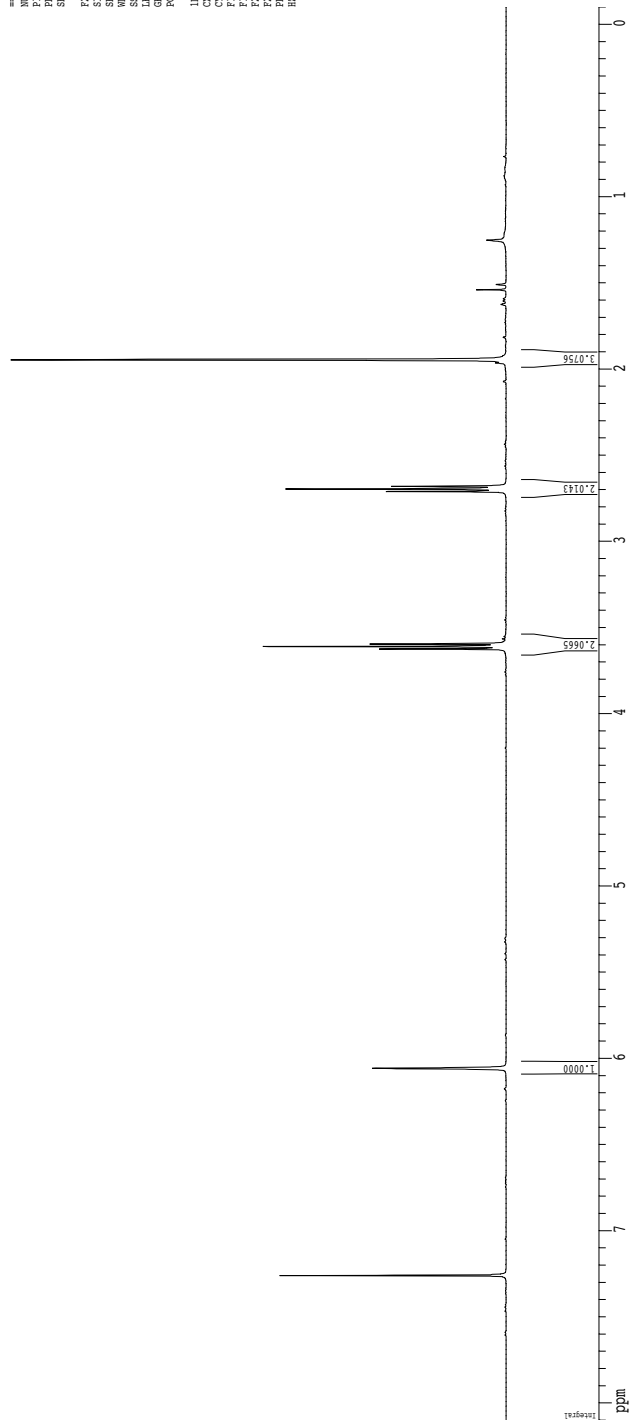
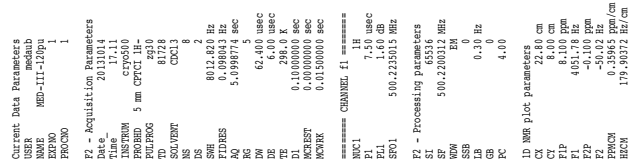
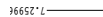
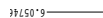
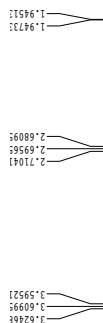




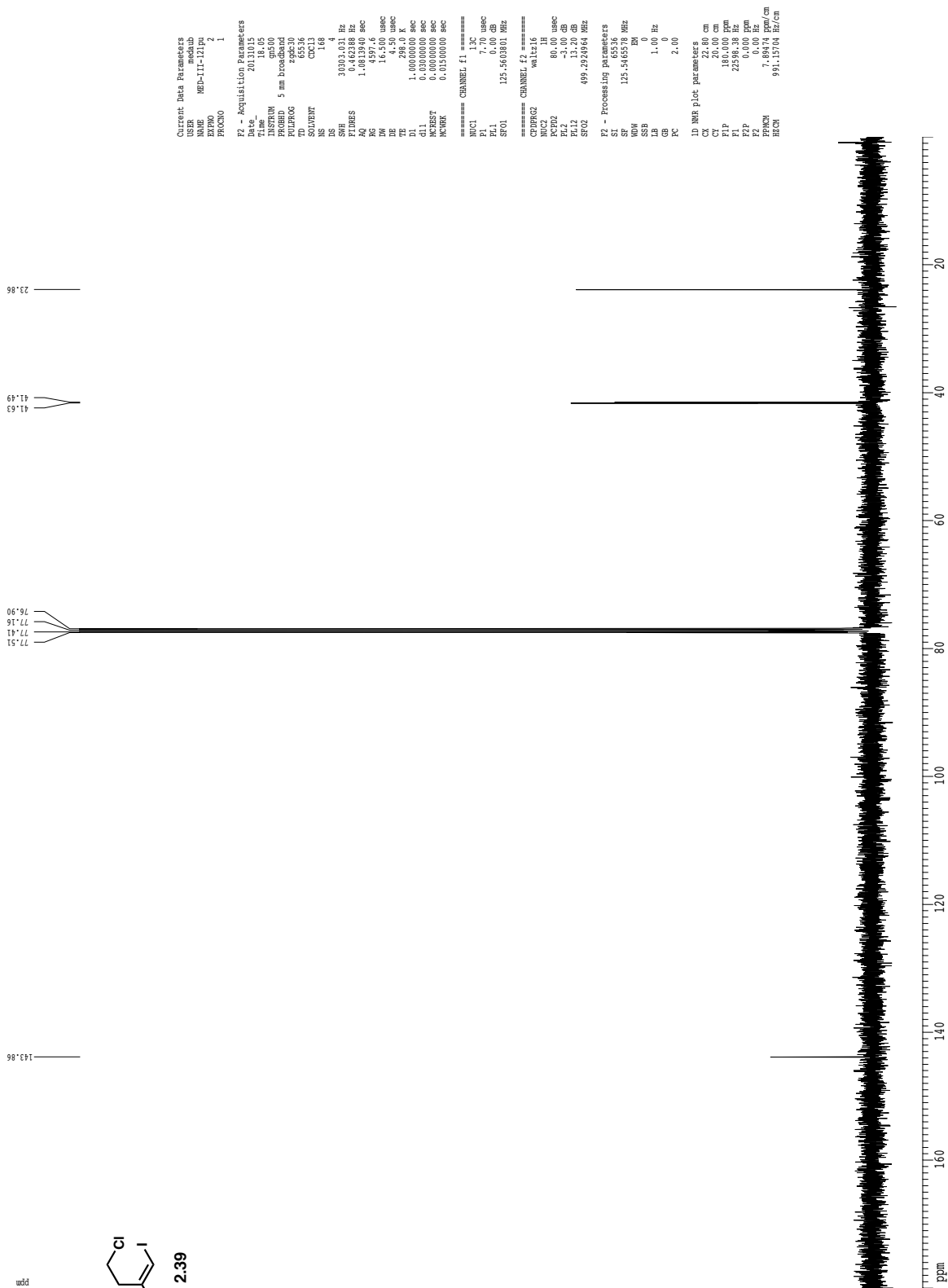
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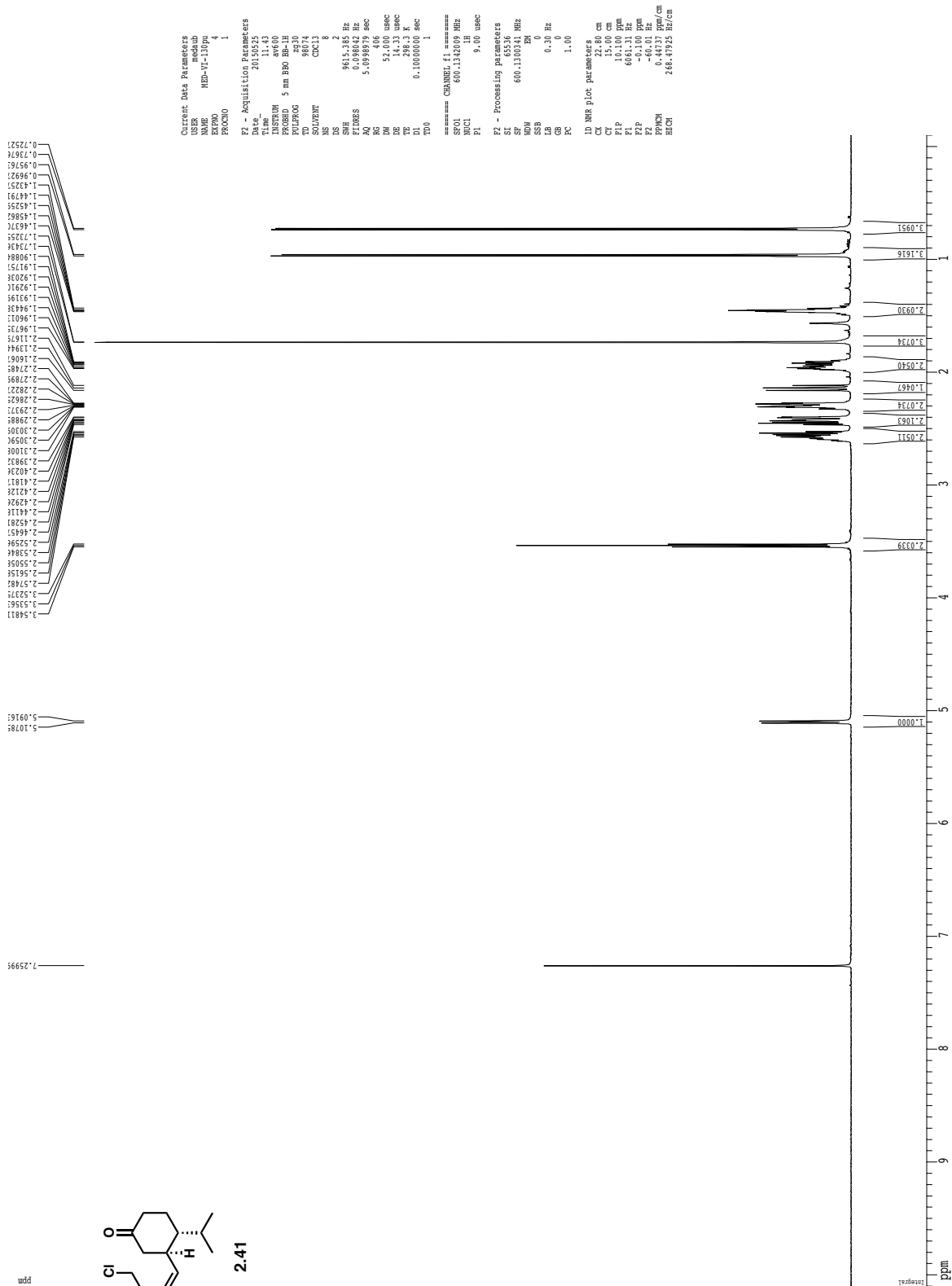
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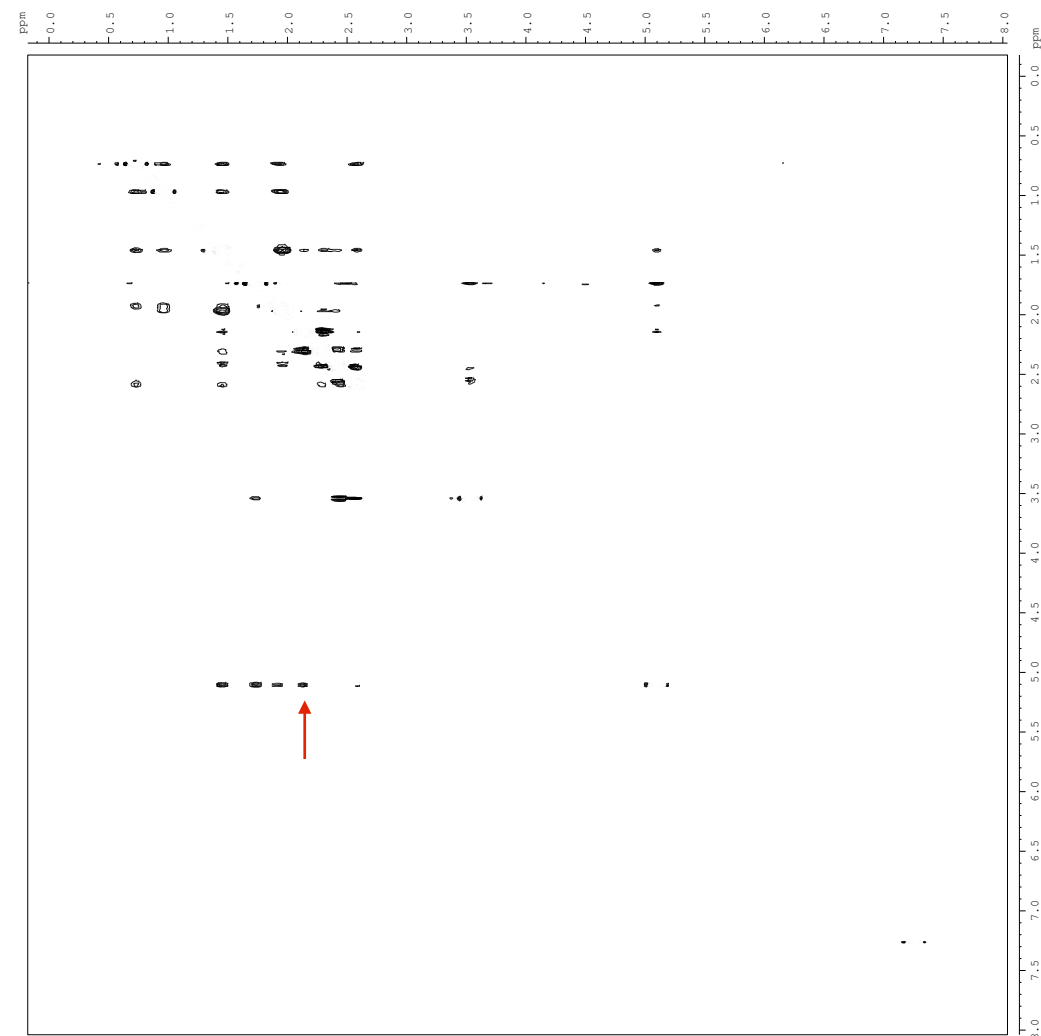


¹³C spectrum with ¹H decoupling

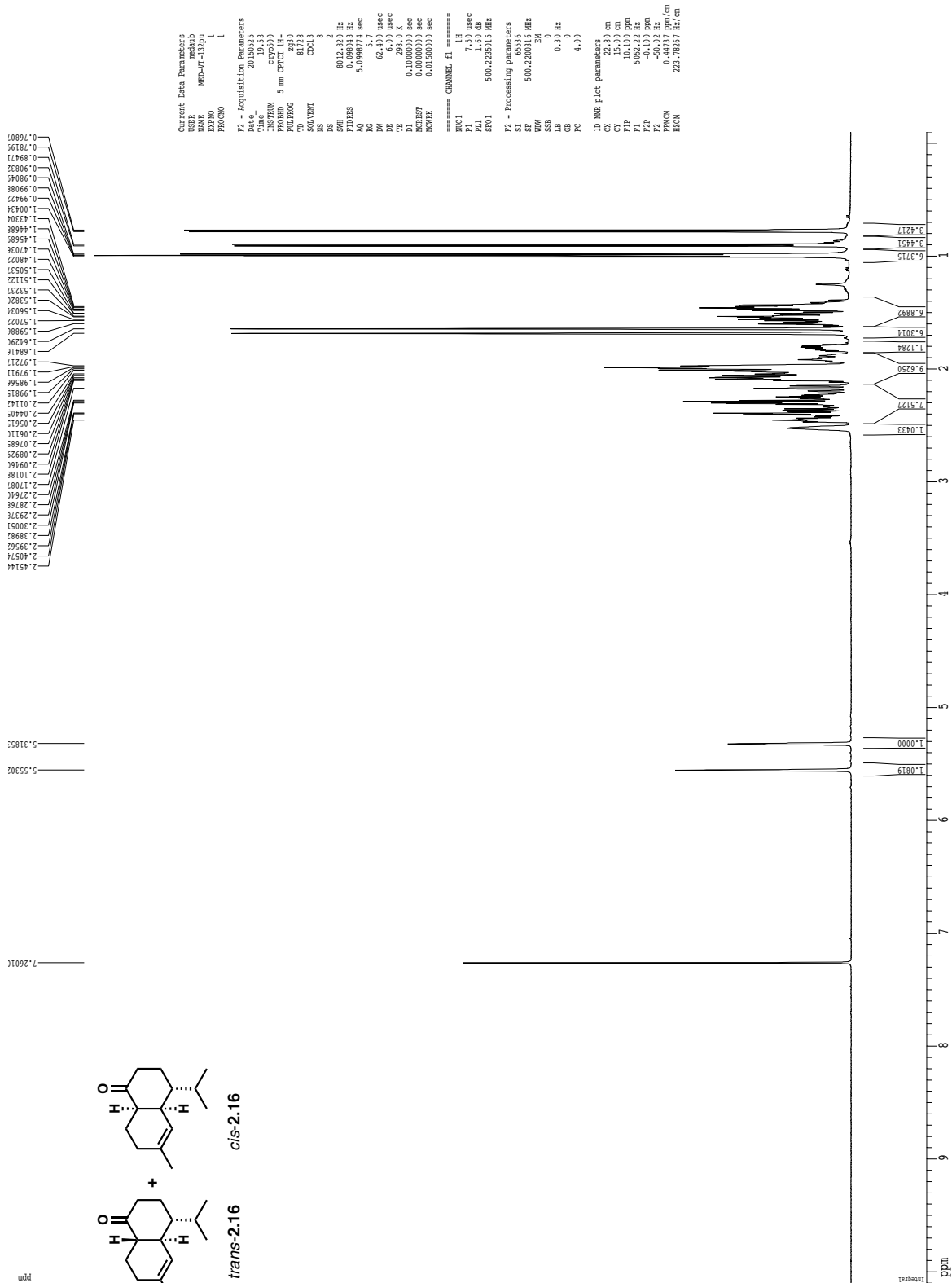
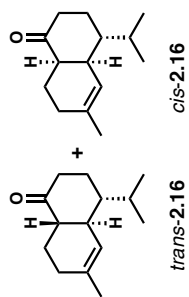


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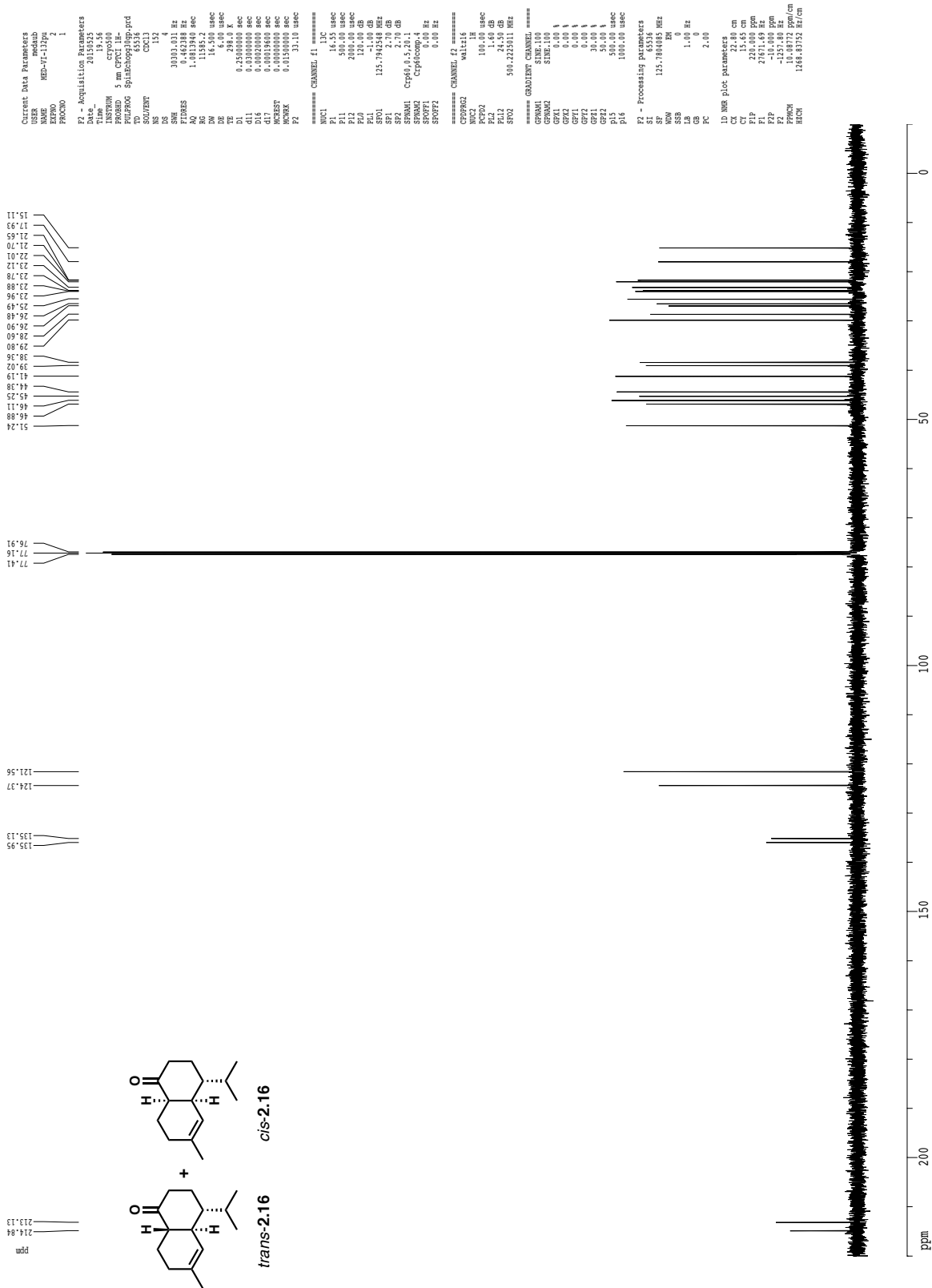




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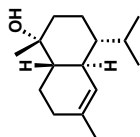


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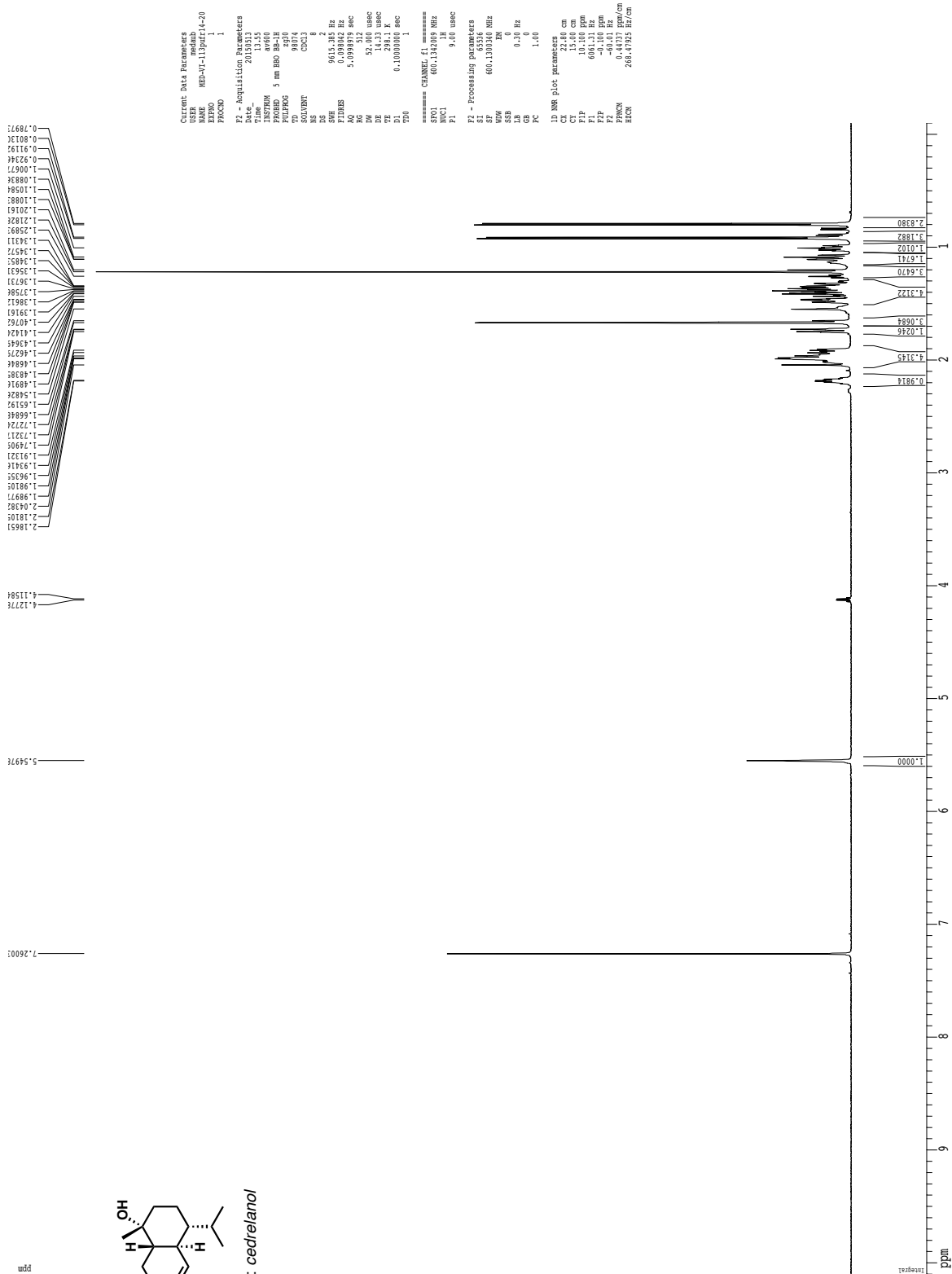


¹H spectrum

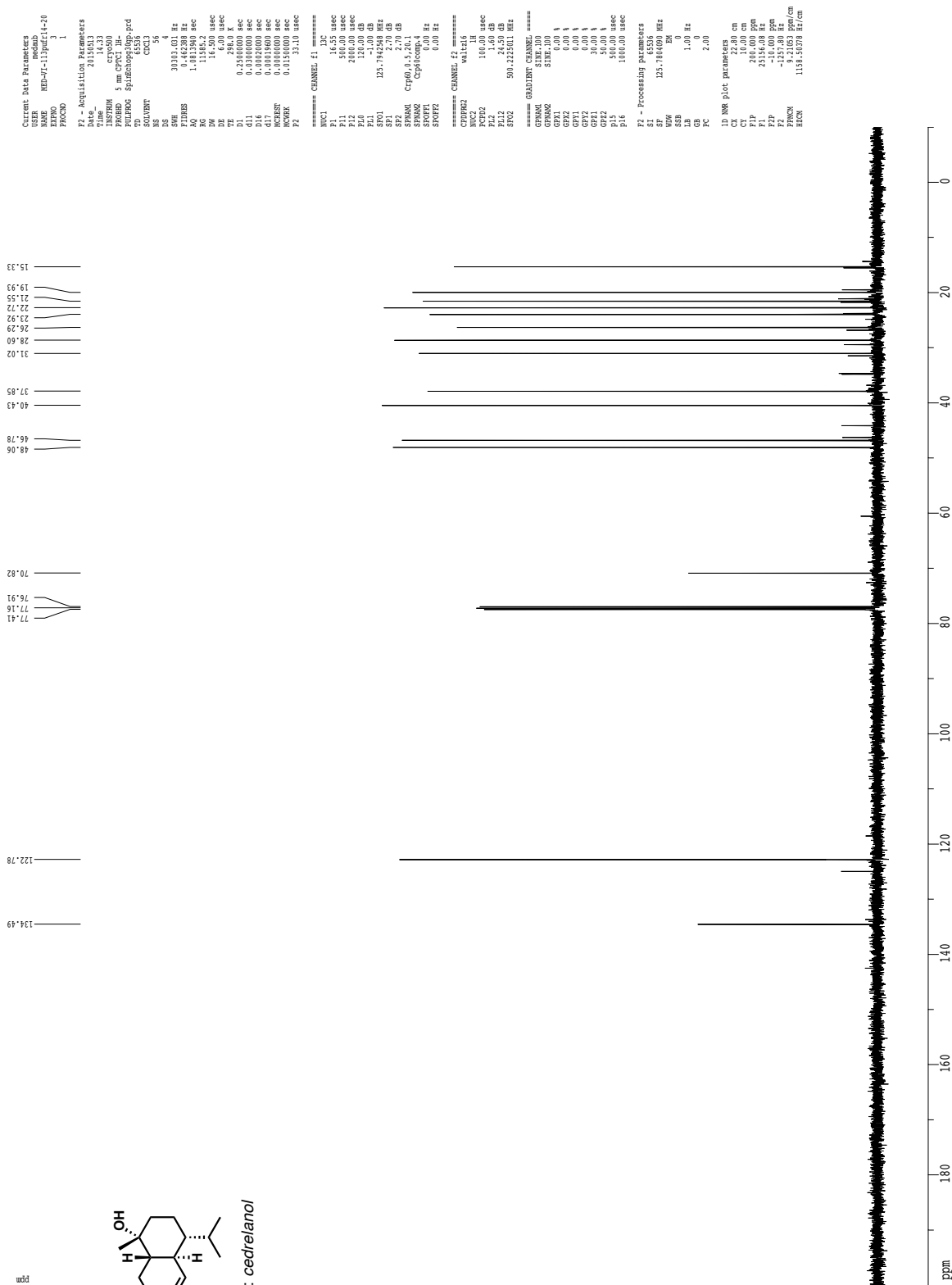
ppm



2.42: cedrelanol

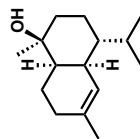


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

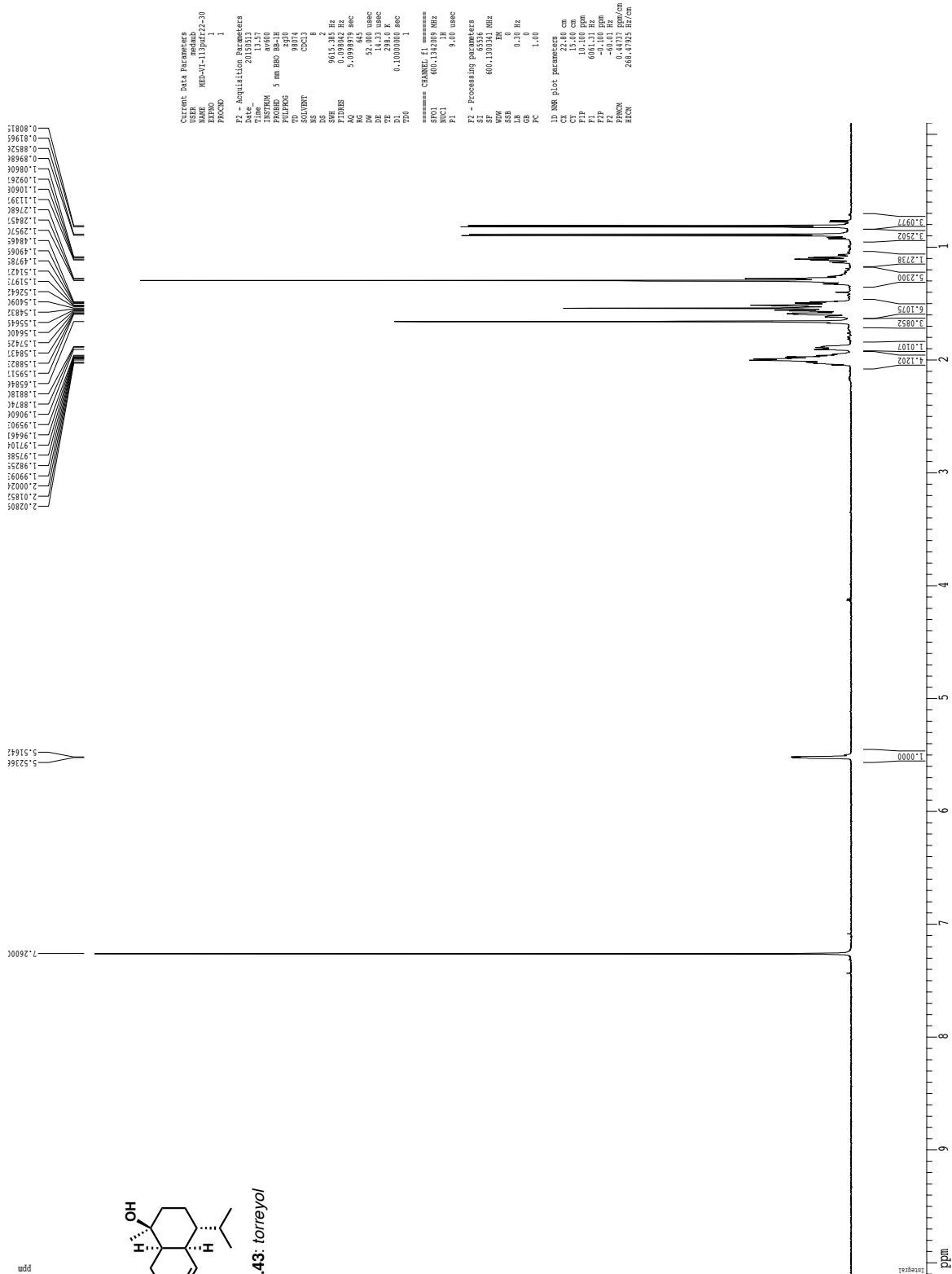


¹H spectrum

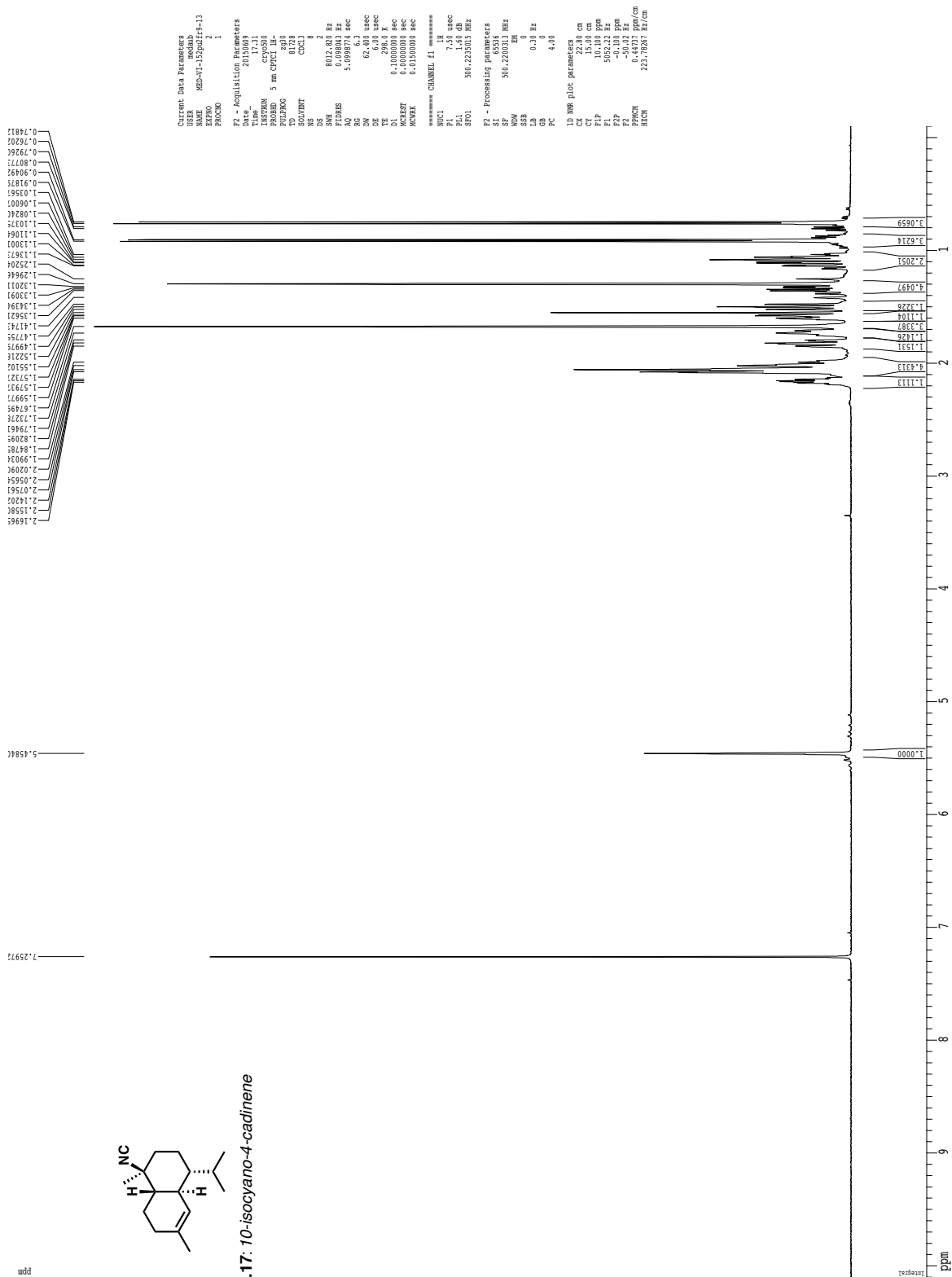
ppm

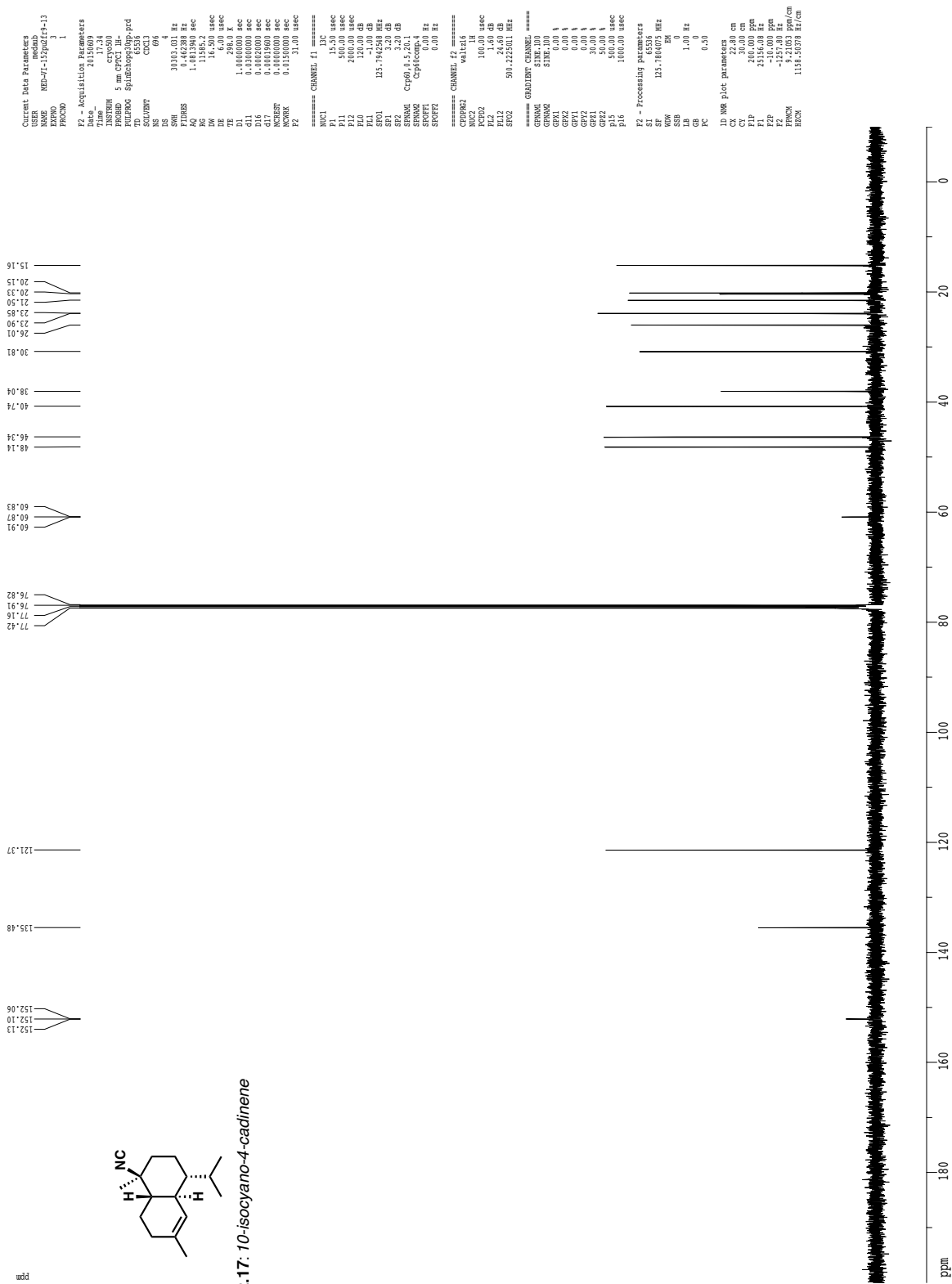


2.43 torreyol



¹H spectrum

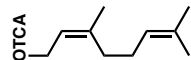




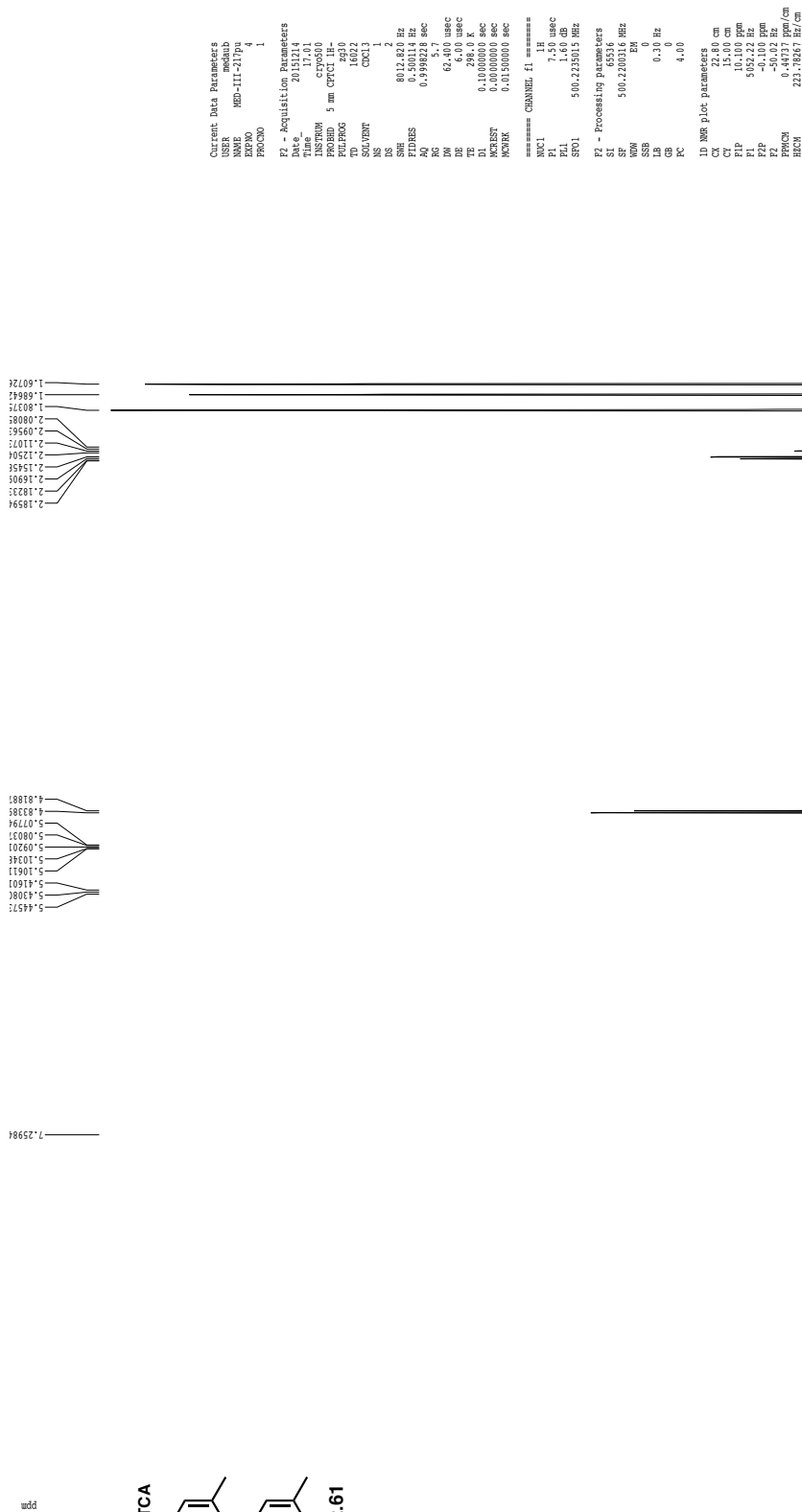
¹H spectrum

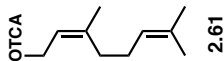
ppm

OTCA



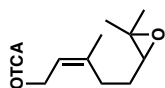
2.61





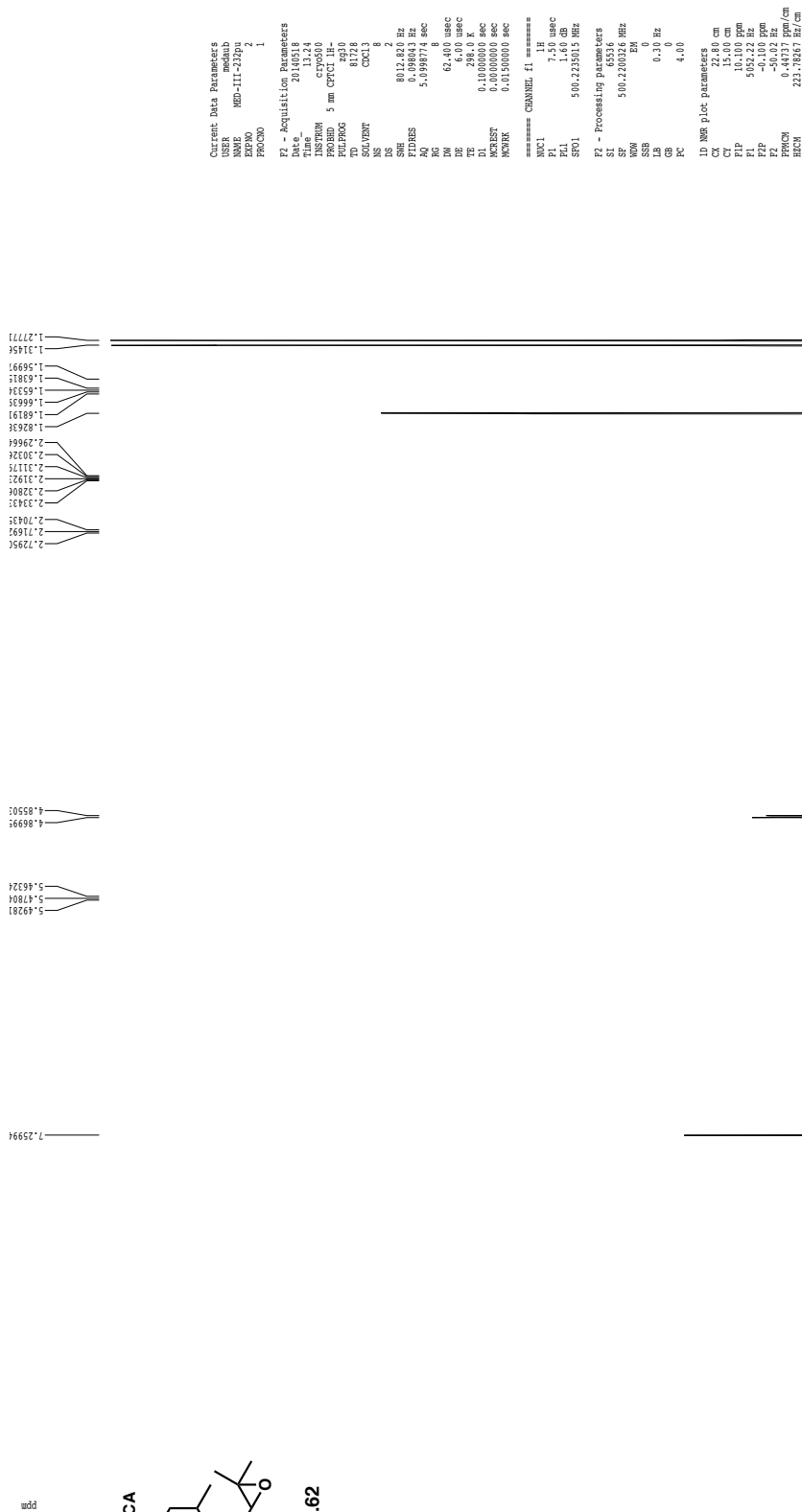
¹H spectrum

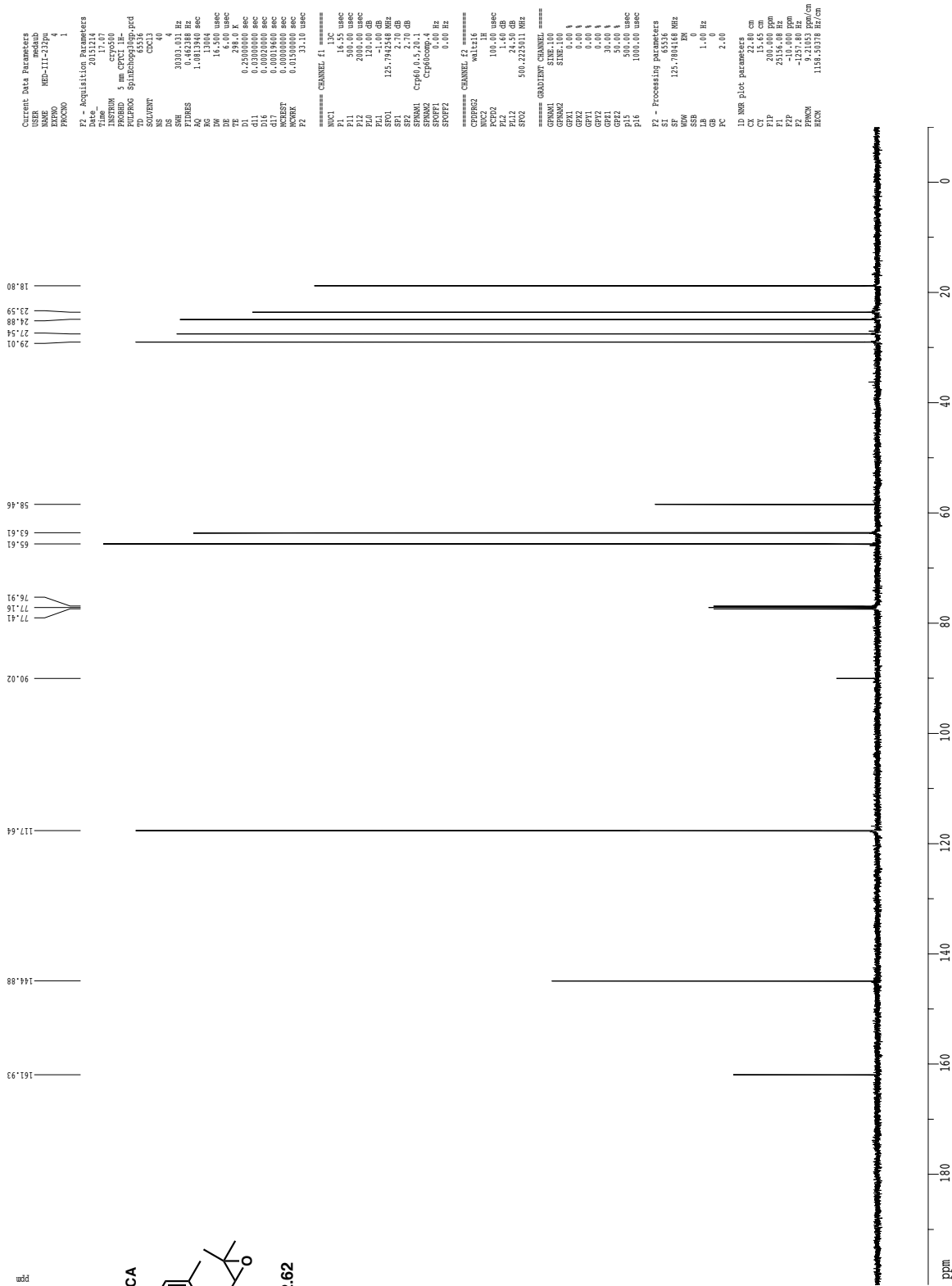
ppm



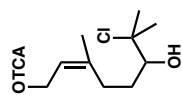
OTCA

2.62

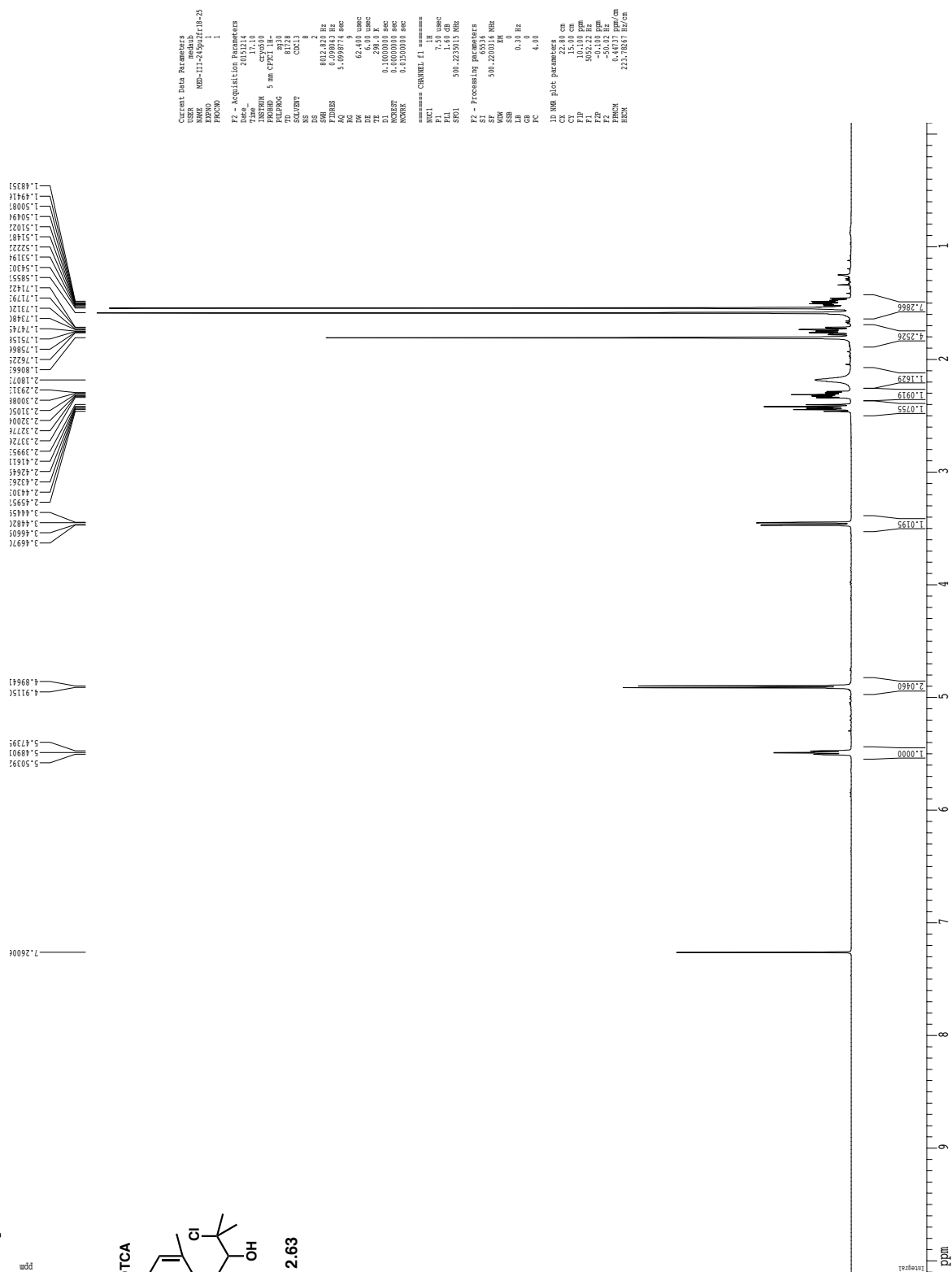


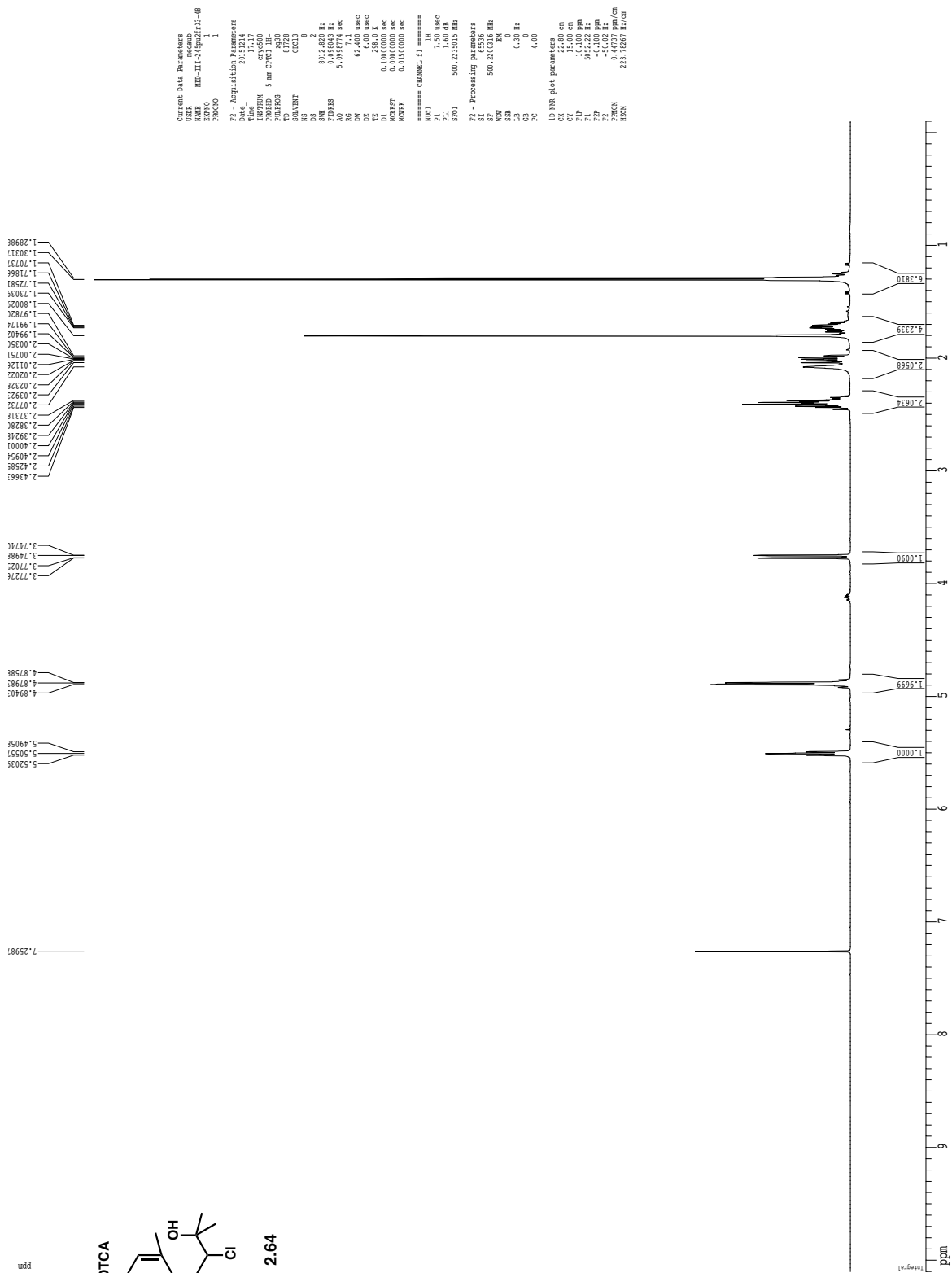


add



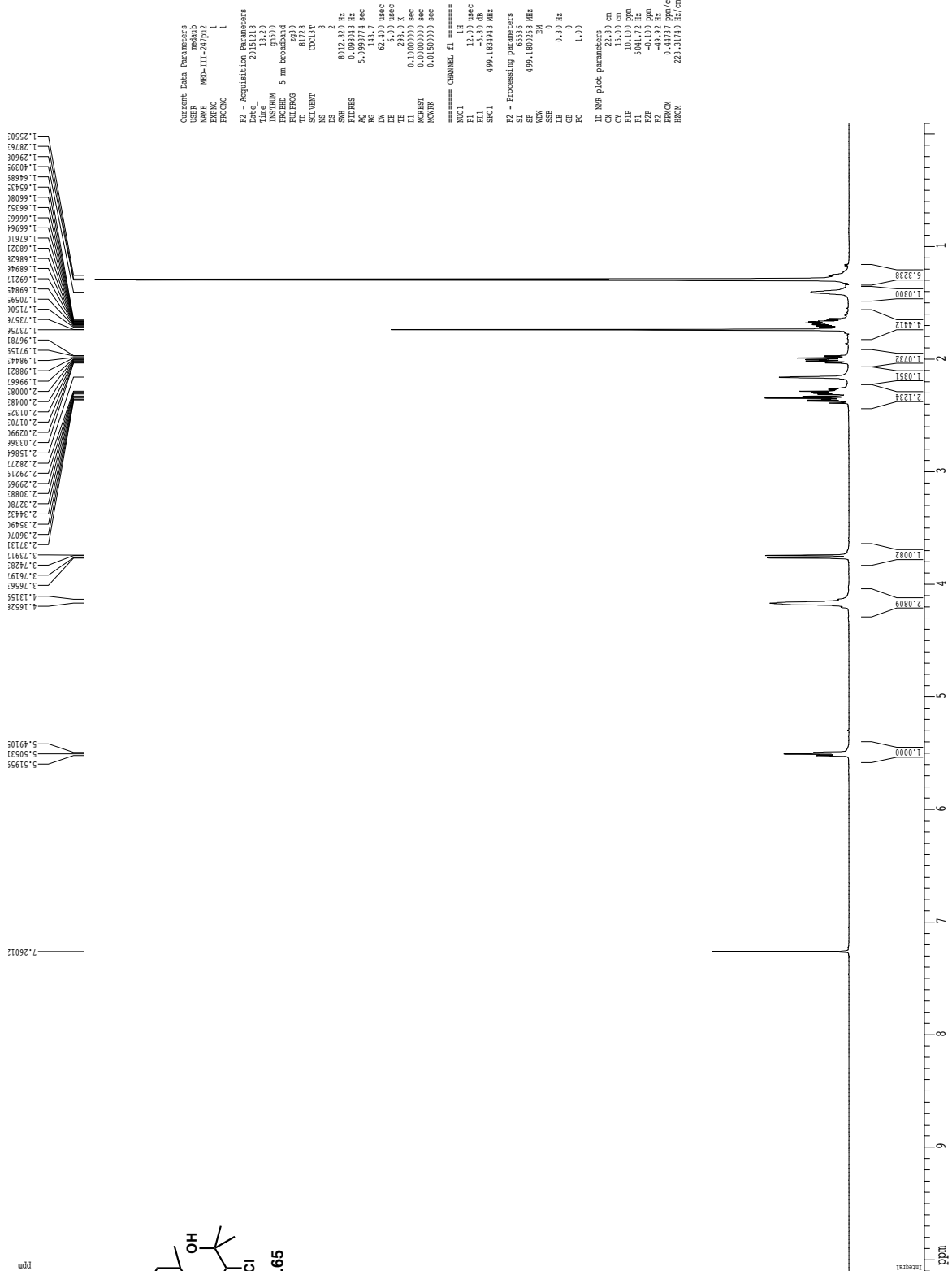
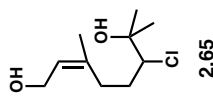
2.63



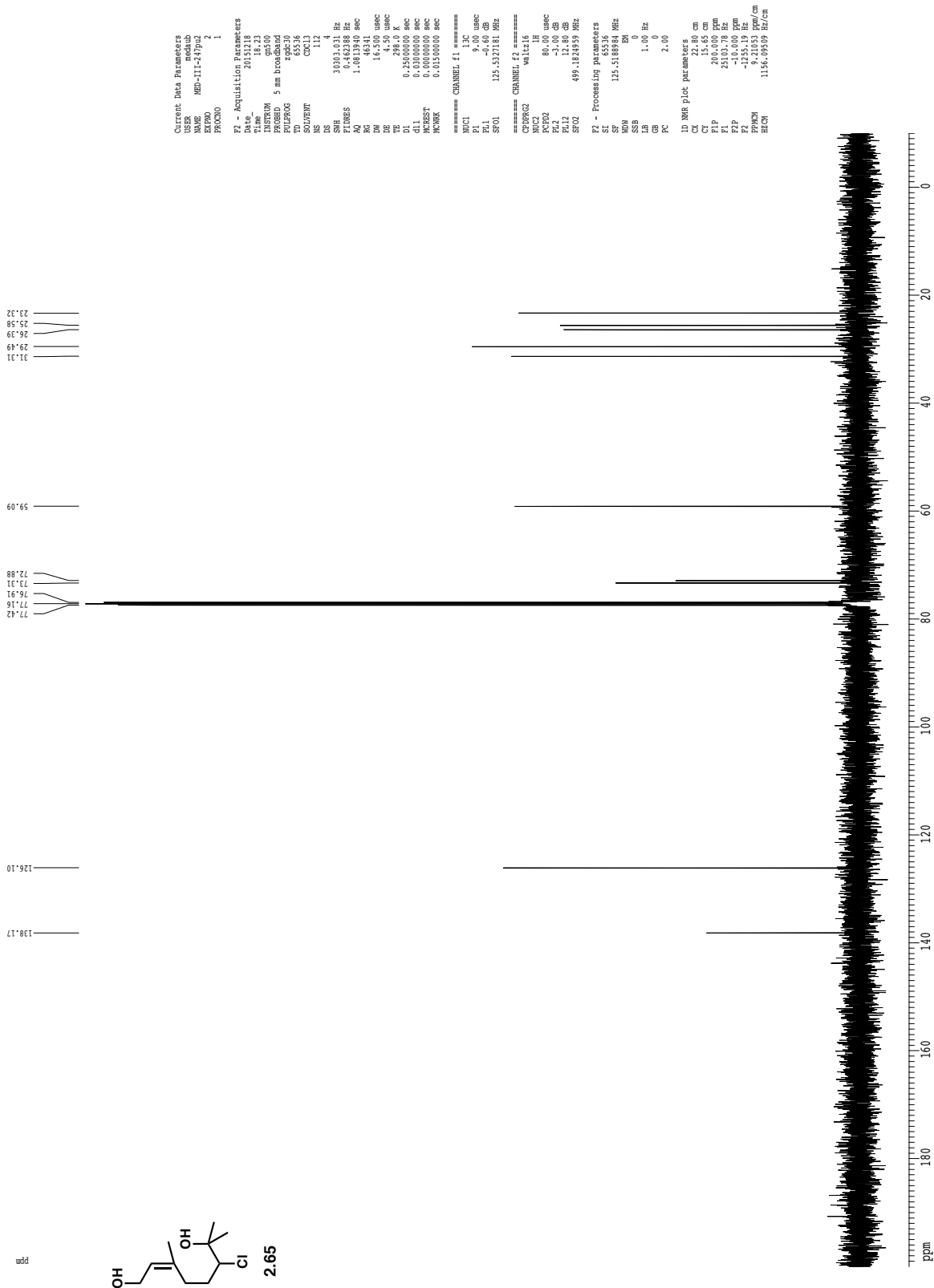


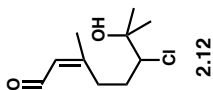
¹H spectrum

ppm



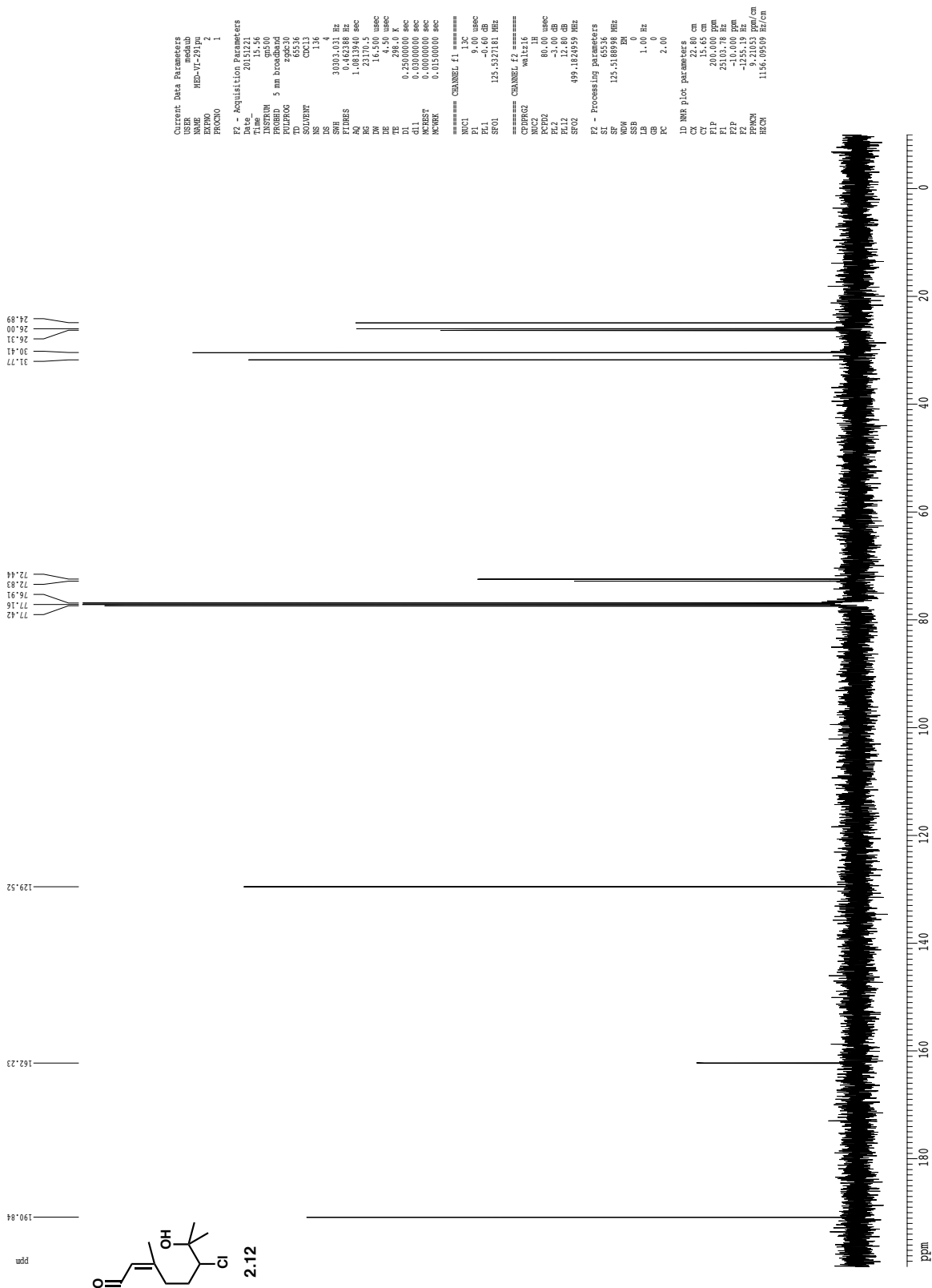
¹³C spectrum with ¹H decoupling



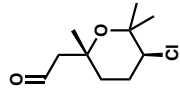
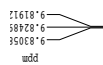


Current data Parameters		MDMS plot parameters	
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MED-VI-2919	1	MDMS-2919	1
PROCNO	1	PROCNO	1
P2 - Acquisition Parameters			
Time	2015-12-01	Time	22-04-2015
INSTRUM	g550	INSTRUM	g550
PROBHD	5 mm broadband	PROBHD	5 mm broadband
PROBPG	5 mm	PROBPG	5 mm
TO SOLVENT	CCl3F	TO SOLVENT	CCl3F
CHN1	1	CHN1	1
CHN2	2	CHN2	2
CHN3	3	CHN3	3
CHN4	4	CHN4	4
CHN5	5	CHN5	5
CHN6	6	CHN6	6
CHN7	7	CHN7	7
CHN8	8	CHN8	8
CHN9	9	CHN9	9
CHN10	10	CHN10	10
CHN11	11	CHN11	11
CHN12	12	CHN12	12
CHN13	13	CHN13	13
CHN14	14	CHN14	14
CHN15	15	CHN15	15
CHN16	16	CHN16	16
CHN17	17	CHN17	17
CHN18	18	CHN18	18
CHN19	19	CHN19	19
CHN20	20	CHN20	20
CHN21	21	CHN21	21
CHN22	22	CHN22	22
CHN23	23	CHN23	23
CHN24	24	CHN24	24
CHN25	25	CHN25	25
CHN26	26	CHN26	26
CHN27	27	CHN27	27
CHN28	28	CHN28	28
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CHN33	33	CHN33	33
CHN34	34	CHN34	34
CHN35	35	CHN35	35
CHN36	36	CHN36	36
CHN37	37	CHN37	37
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CHN40	40	CHN40	40
CHN41	41	CHN41	41
CHN42	42	CHN42	42
CHN43	43	CHN43	43
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CHN59	59	CHN59	59
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CHN61	61	CHN61	61
CHN62	62	CHN62	62
CHN63	63	CHN63	63
CHN64	64	CHN64	64
CHN65	65	CHN65	65
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CHN67	67	CHN67	67
CHN68	68	CHN68	68
CHN69	69	CHN69	69
CHN70	70	CHN70	70
CHN71	71	CHN71	71
CHN72	72	CHN72	72
CHN73	73	CHN73	73
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CHN76	76	CHN76	76
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CHN78	78	CHN78	78
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CHN80	80	CHN80	80
CHN81	81	CHN81	81
CHN82	82	CHN82	82
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CHN84	84	CHN84	84
CHN85	85	CHN85	85
CHN86	86	CHN86	86
CHN87</			

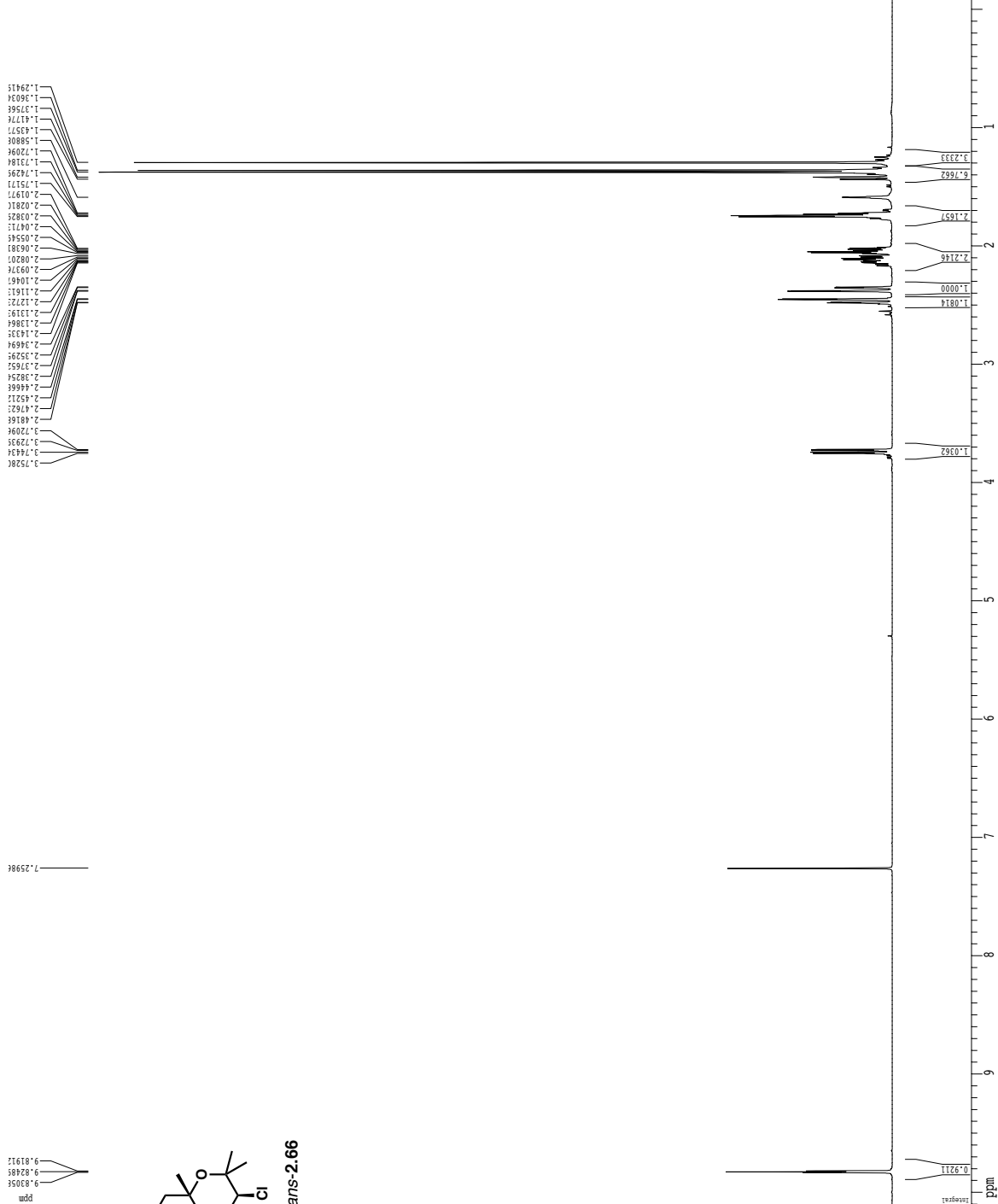
¹³C spectrum with ¹H decoupling



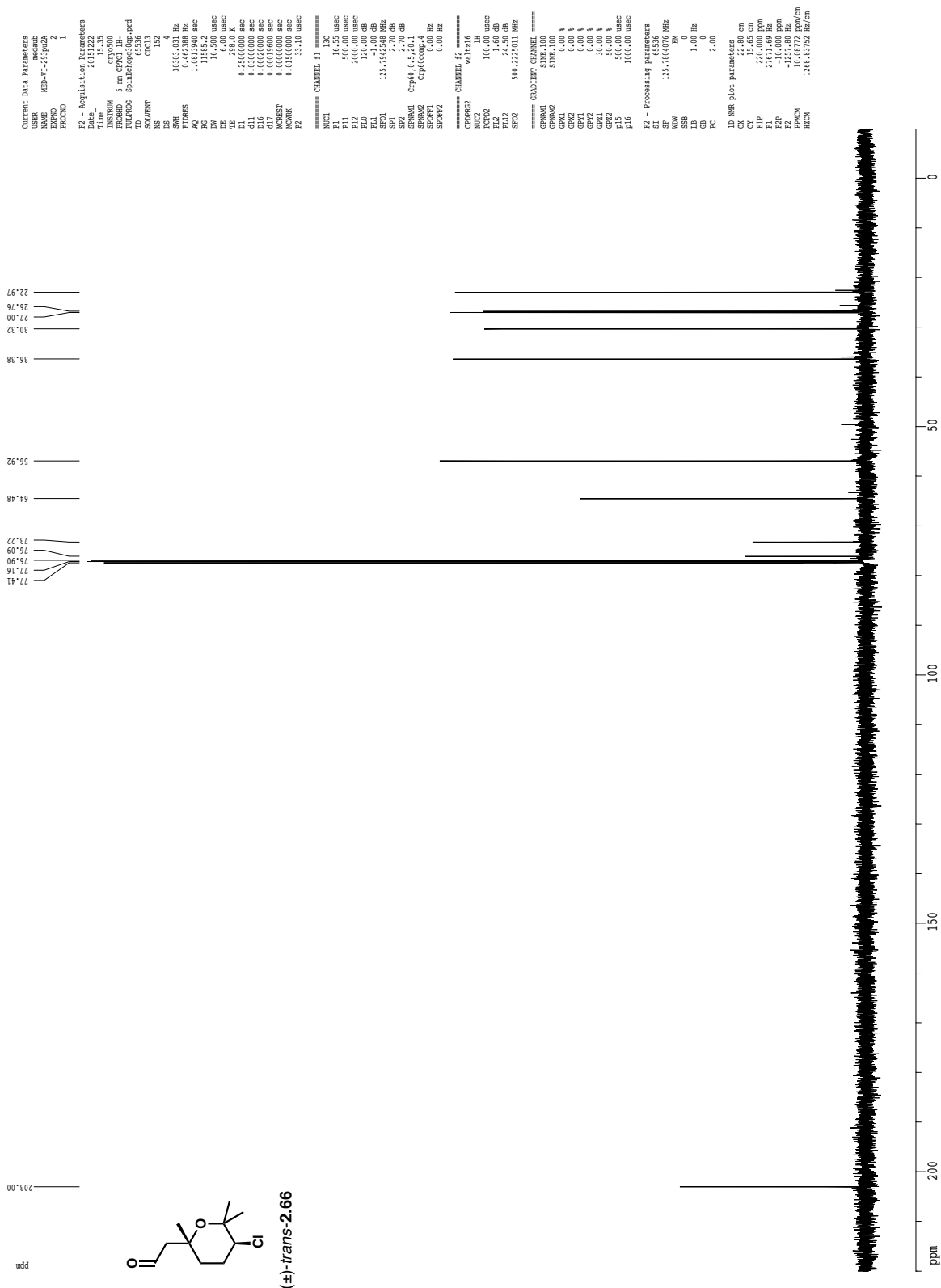
¹H spectrum



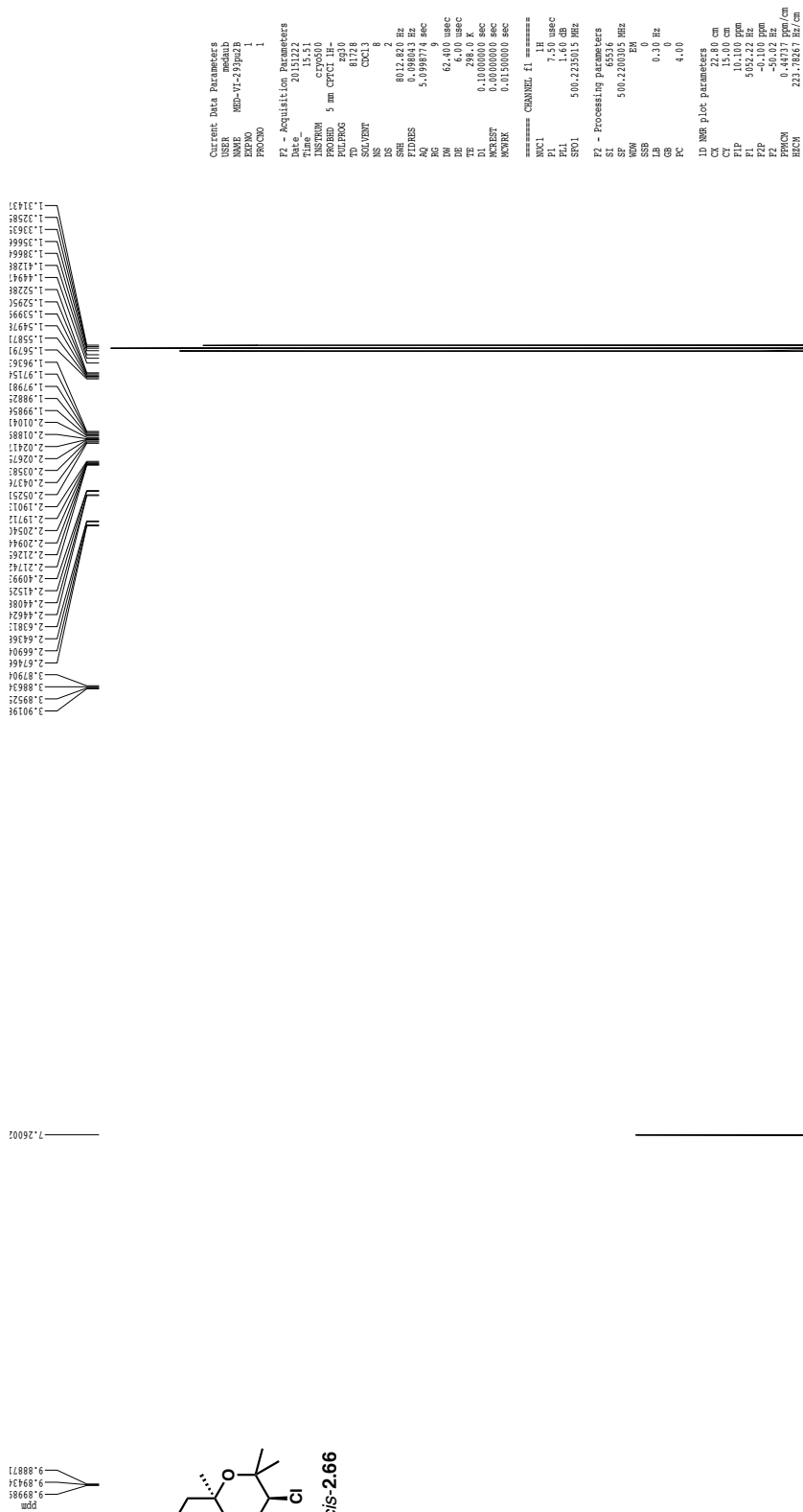
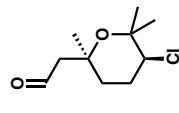
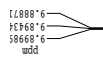
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 Time: 15:32
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 EXPNO: 1
 PROCNO: 1
 P2 - Acquisition Parameters
 Date: 20151222
 Time: 15:32
 Name: MDP-VI-213p2A
 EXPNO: 1
 PROCNO: 1
 PULPROG: zgpg30
 TD: 81728
 SOLVENT: CDCl3
 NS: 2
 DS: 2
 SWH: 8012.820 Hz
 FIDRES: 0.098943 Hz
 AQ: 5.139911 sec
 RG: 7.1
 DW: 62.400 usec
 DE: 6.00 usec
 TE: 300.2 K
 D1: 0.1000000 sec
 MACROPT: 0.0000000 sec
 MCHRG: 0.0150000 sec
 ===== CHANNEL f1 =====
 NUC1: 1H
 P1: 7.50 usec
 PL1: 0.00 dB
 SFO1: 500.235015 MHz
 P2 - Processing parameters
 SI: 32768
 SF: 500.235015 MHz
 WDW: EM
 SSB: 0
 AB: 0.10 Hz
 GB: 0
 PC: 4.00
 ID NMR Plot parameters
 SI: 32768
 SF: 500.235015 MHz
 CF: 15.00 cm
 PTP: 10.100 ppm
 FI: 592.22 Hz
 F2: -50.02 ppm
 F3: -50.02 Hz
 PRGCM: 0.44137 ppm/cm
 HCM: 223.76267 Hz/cm



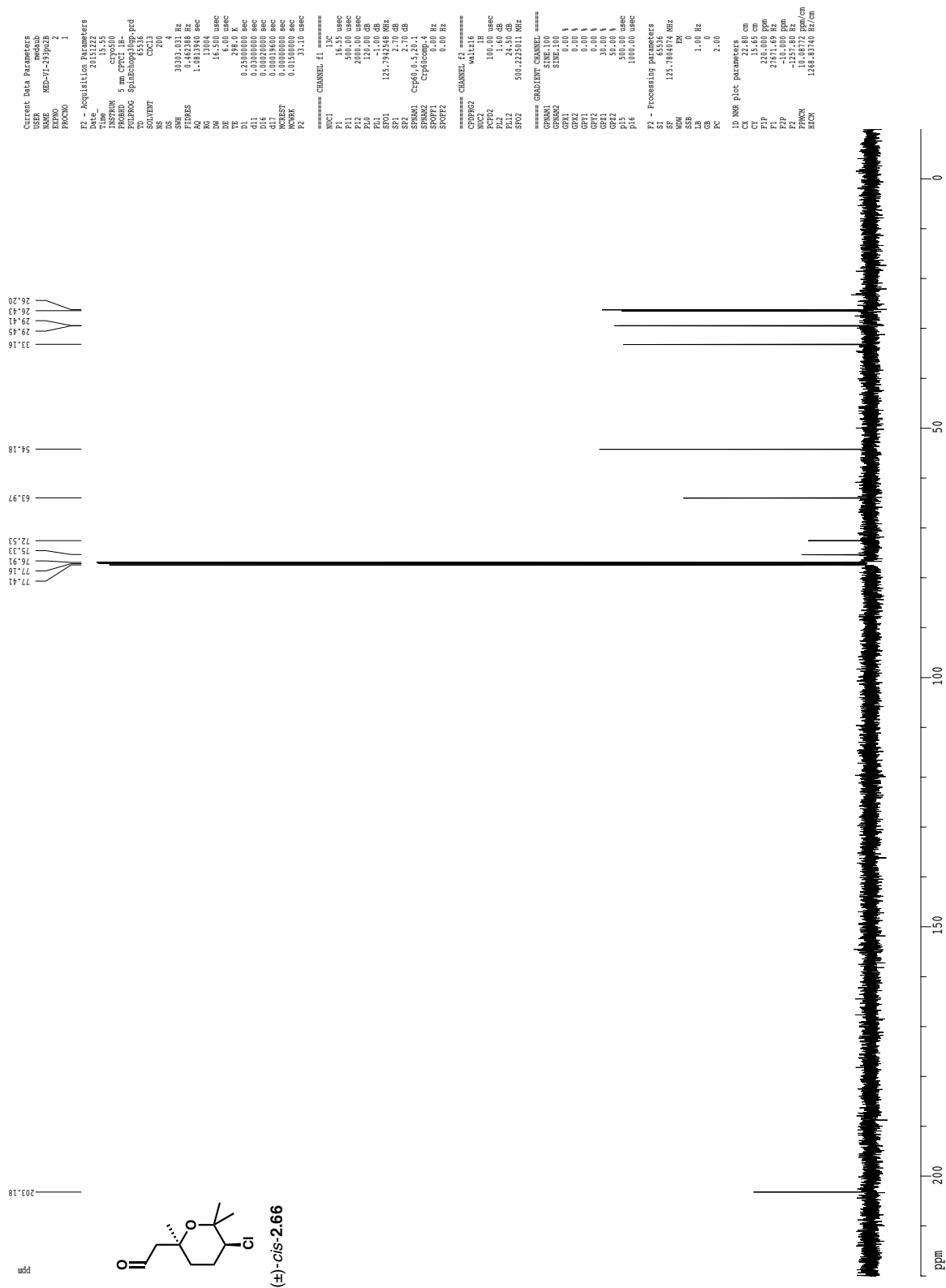
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

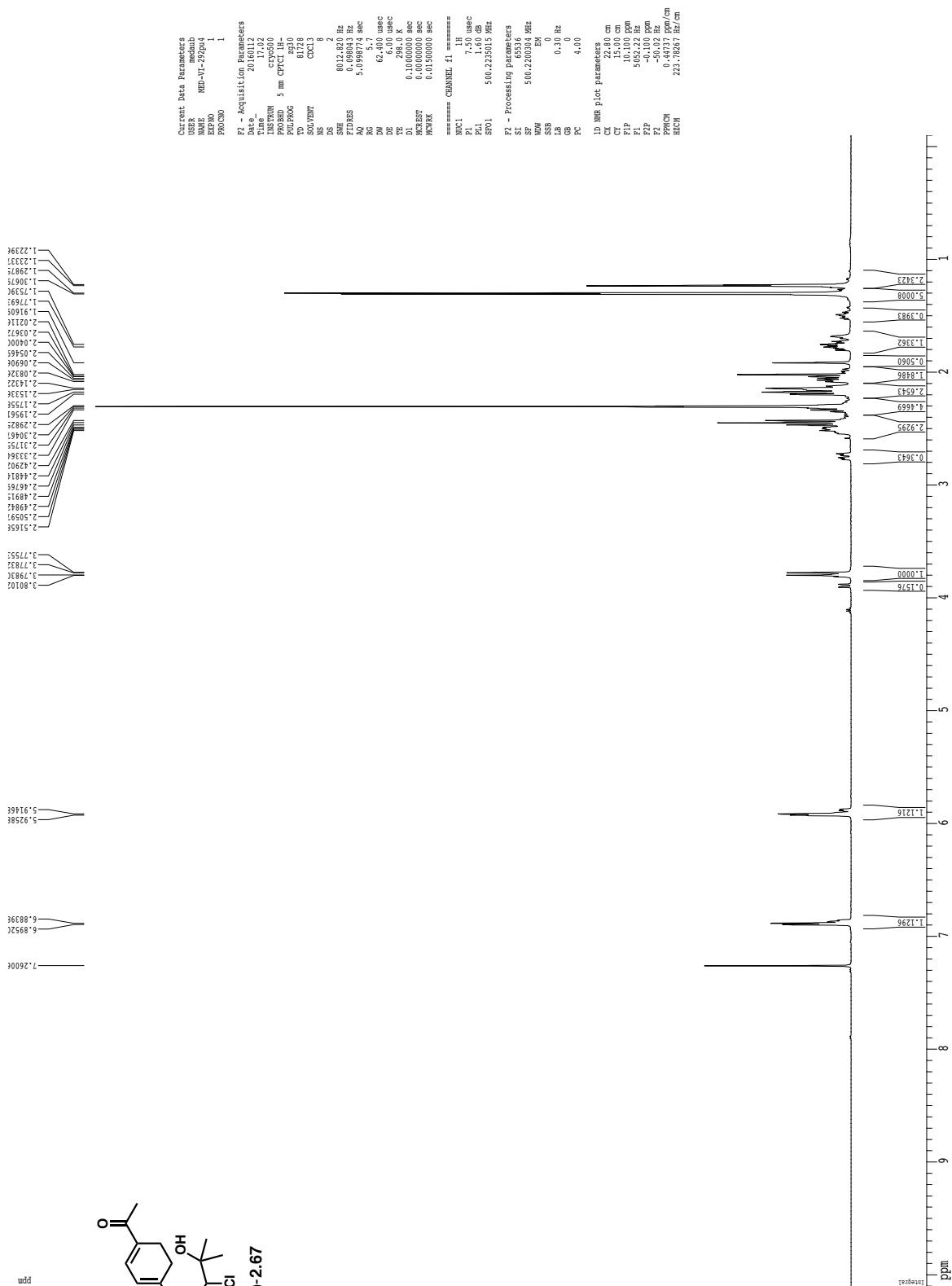
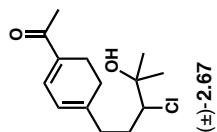


¹H spectrum

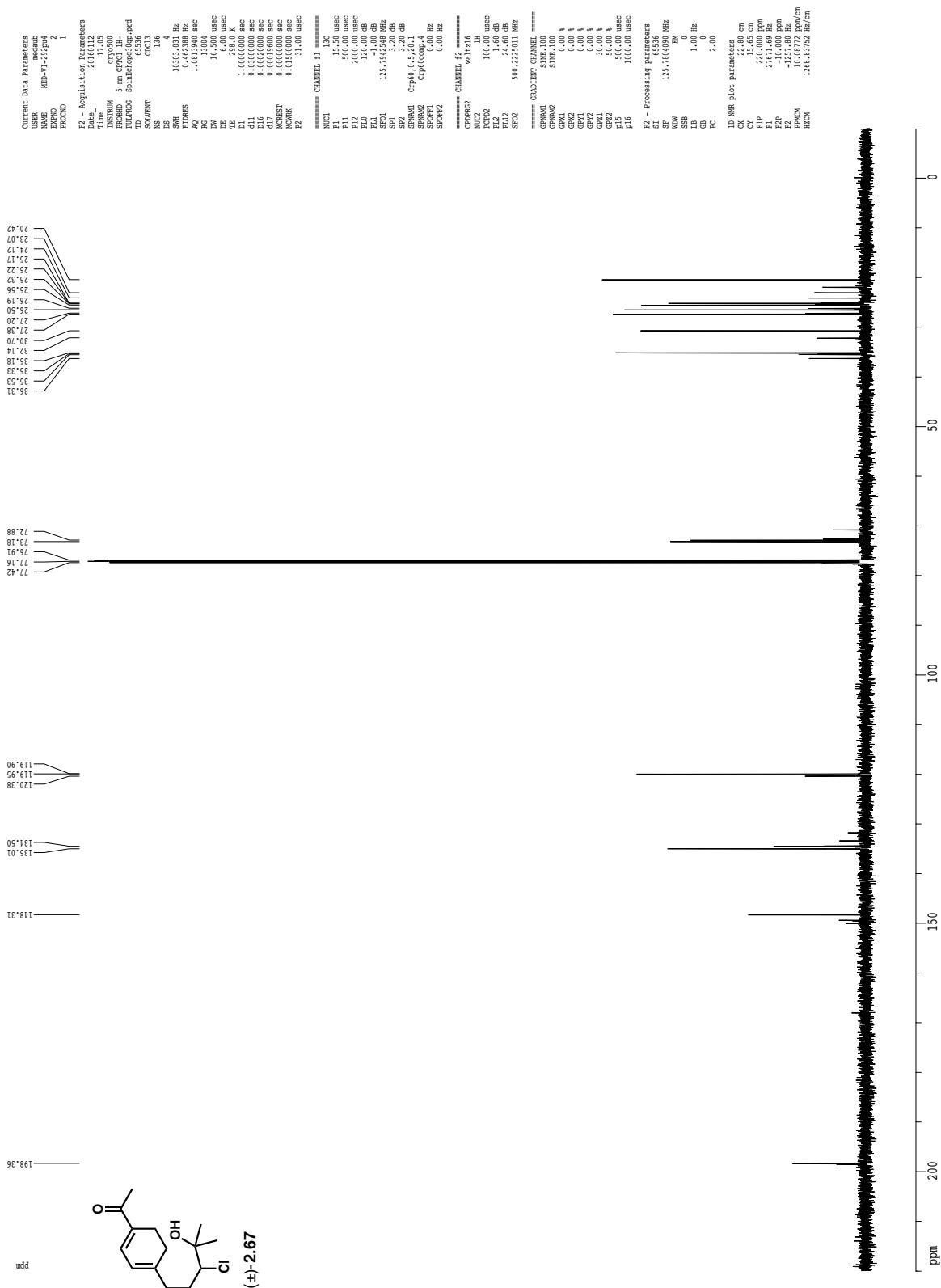


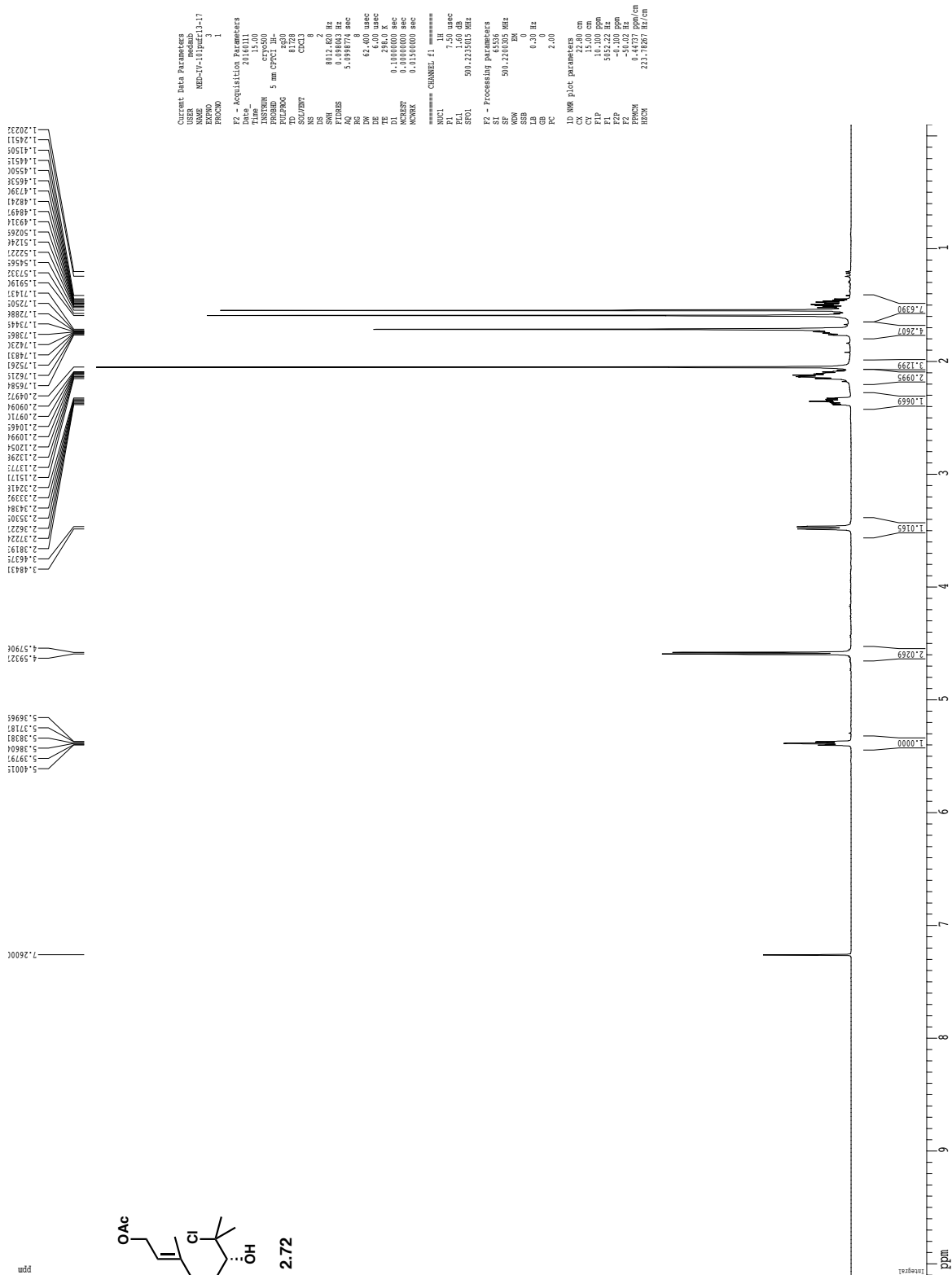
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



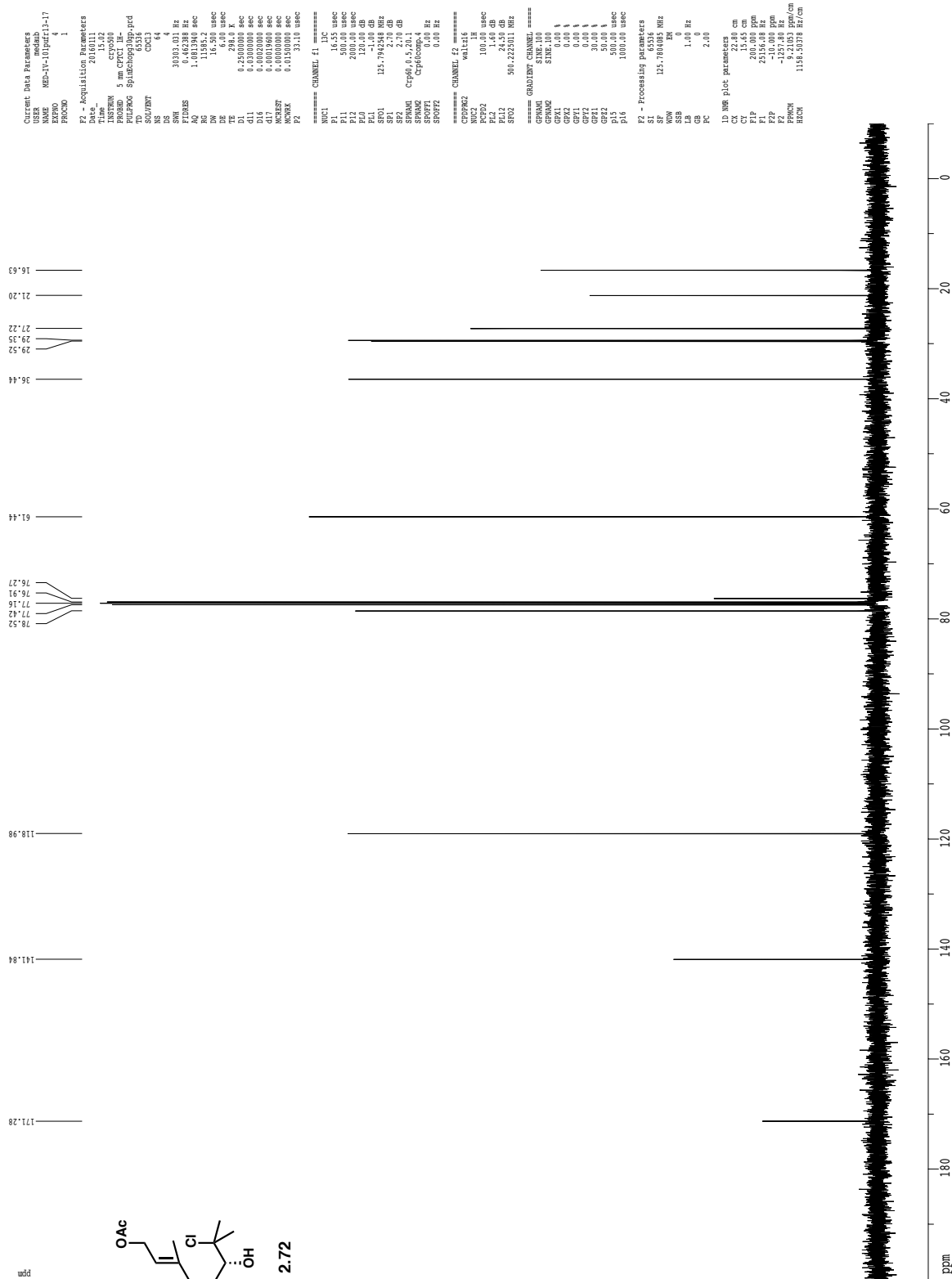


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

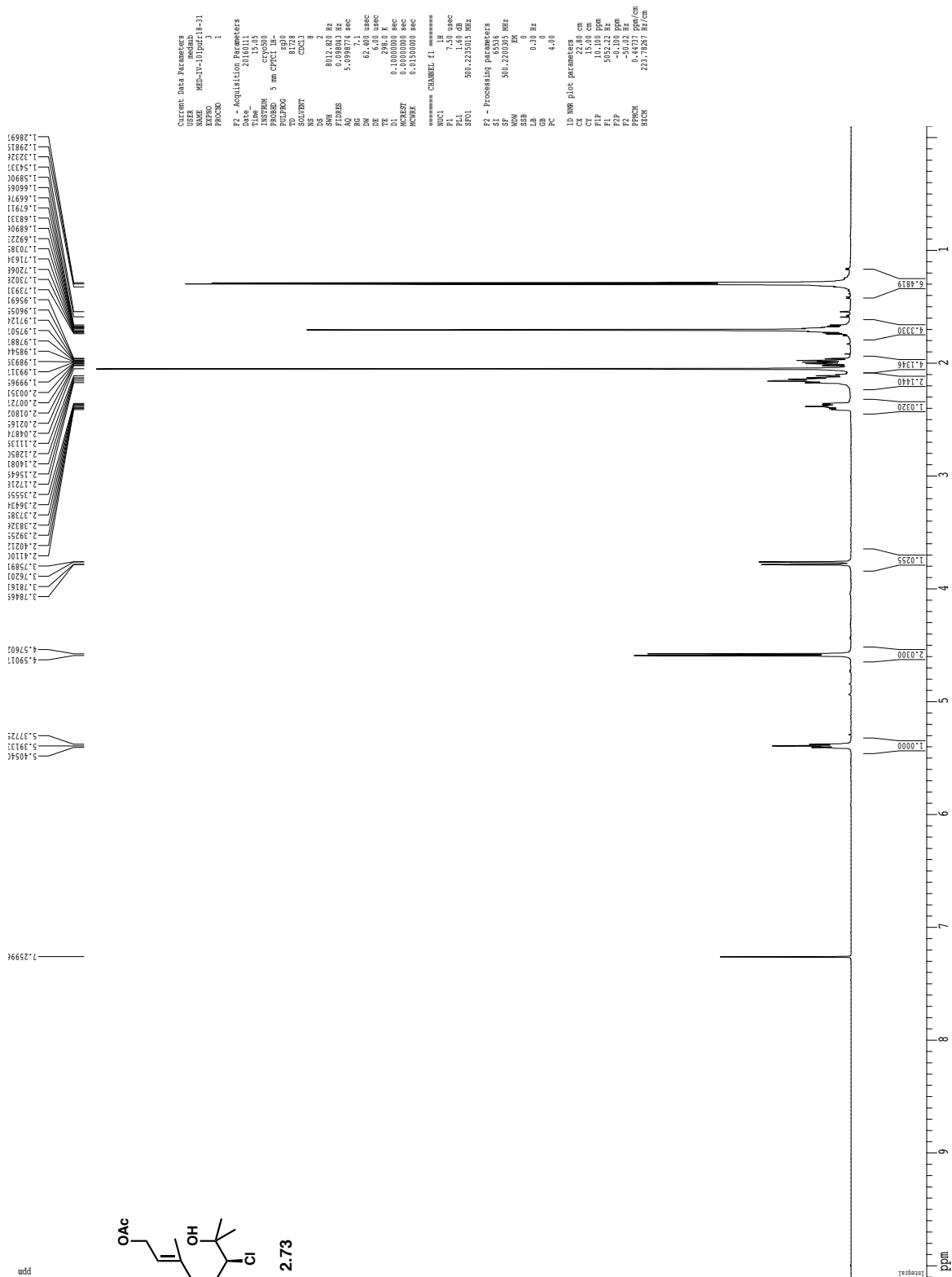


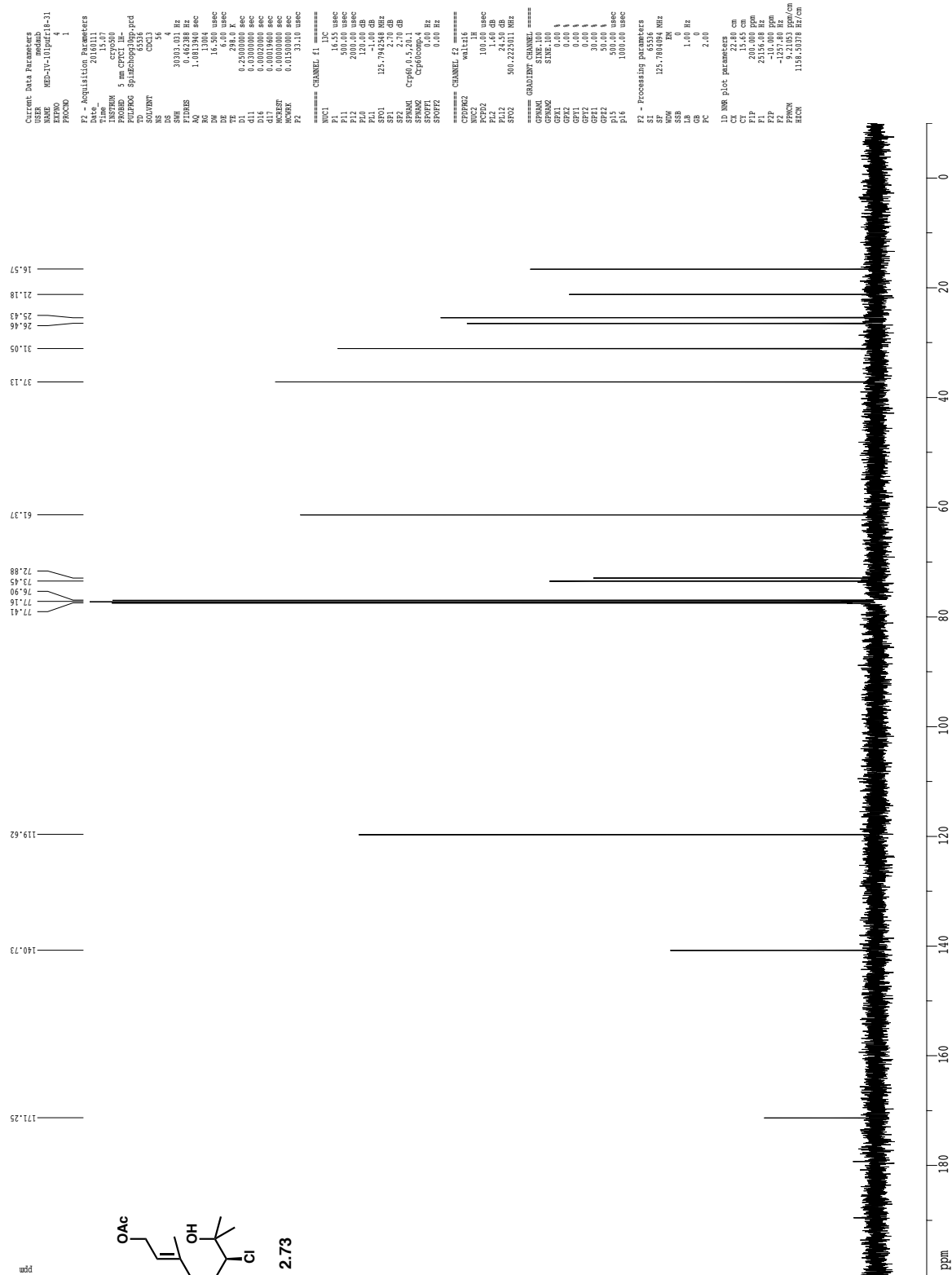


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

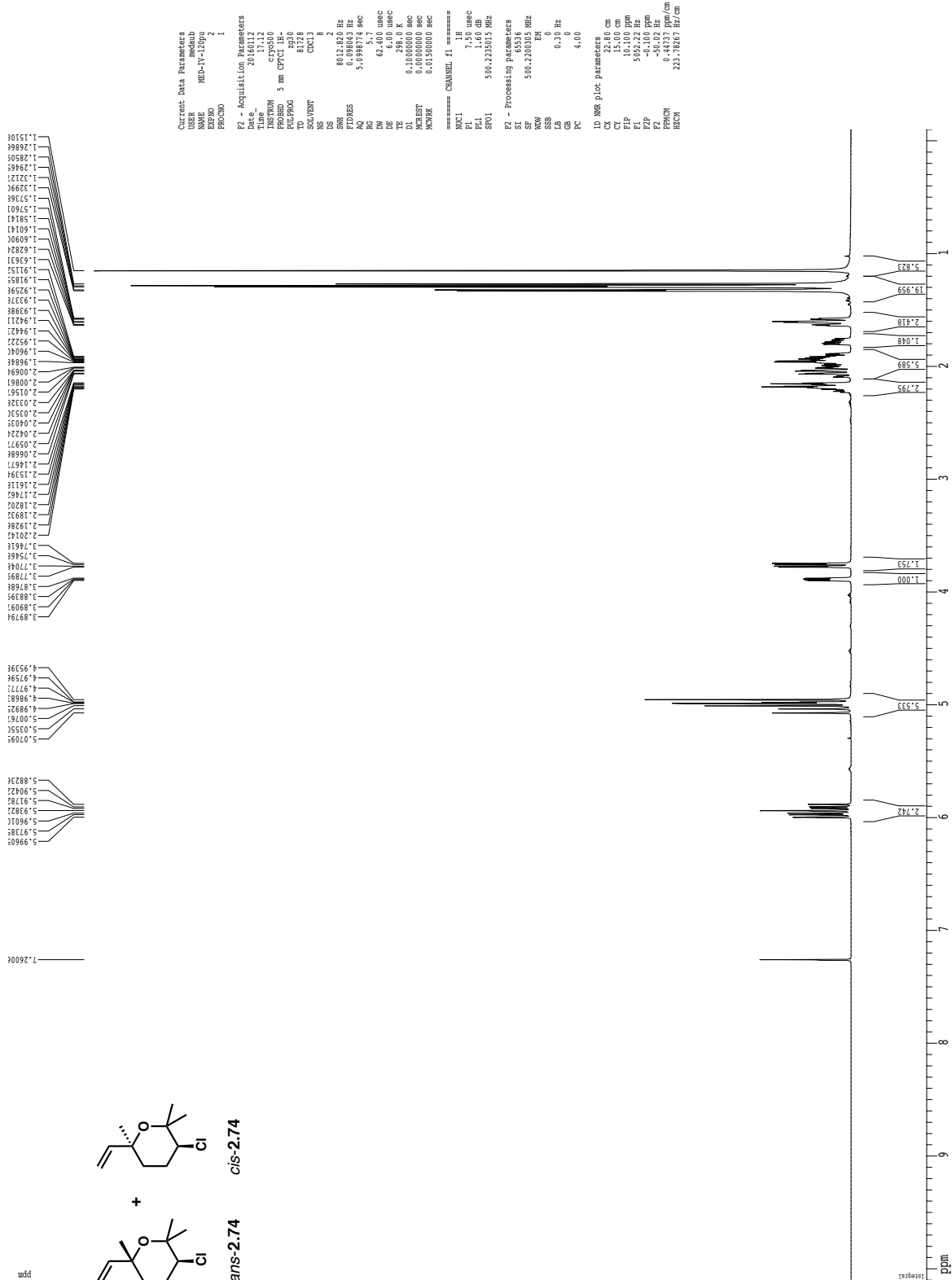


¹H spectrum

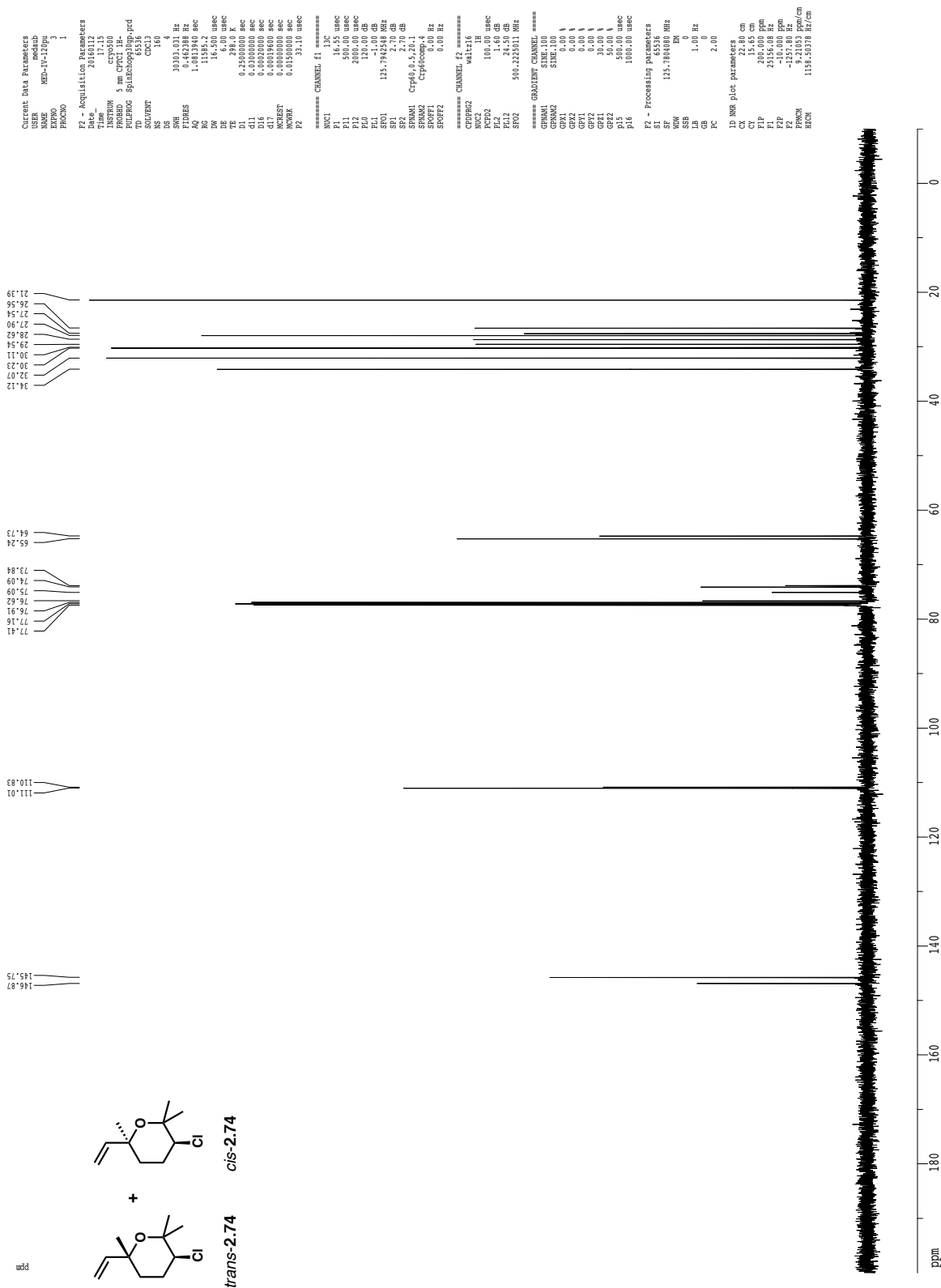


Z-restored spin-echo ^{13}C spectrum with ^1H decoupling

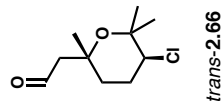
¹H spectrum



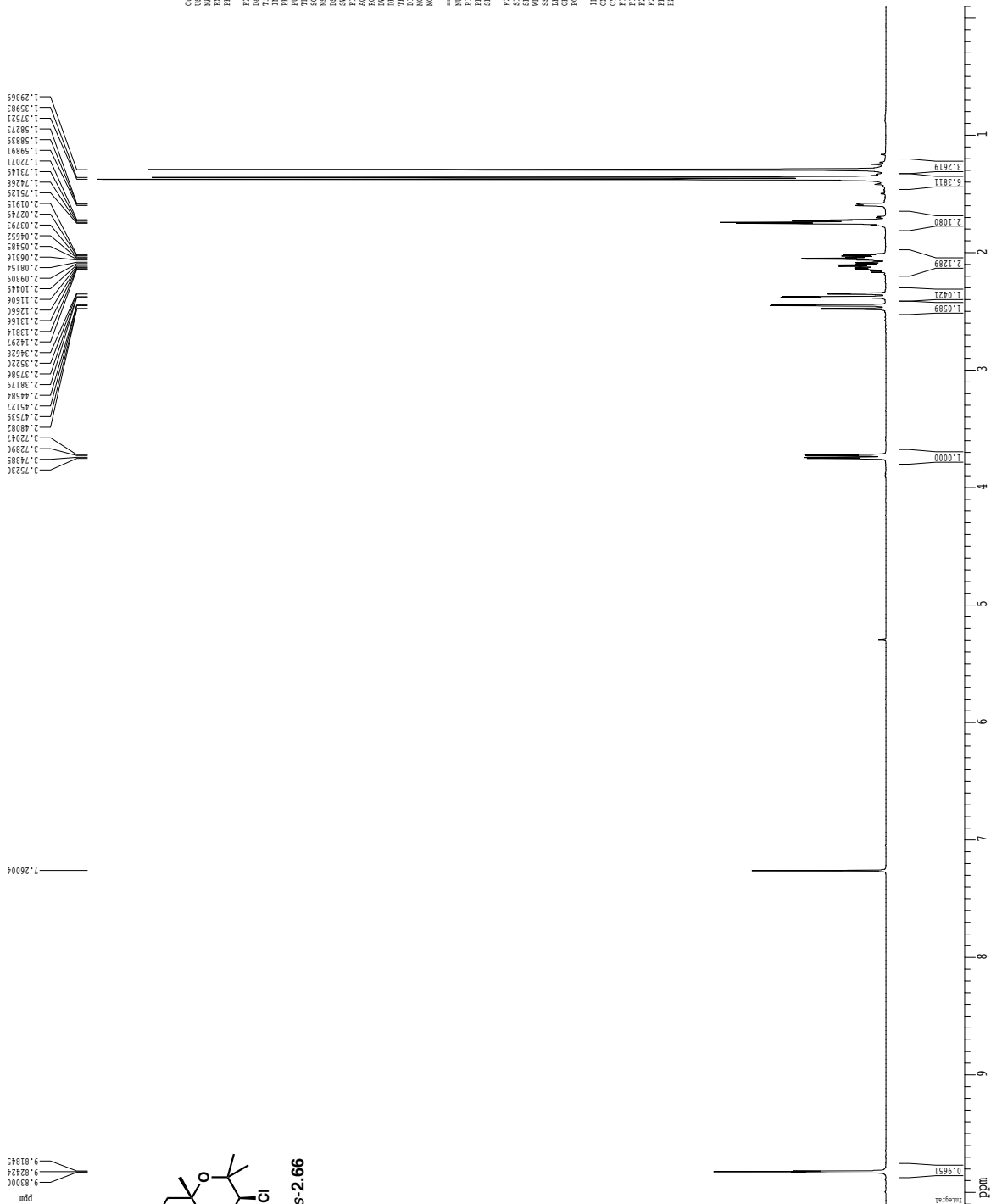
Z-restored spin-echo 13C spectrum with 1H decoupling



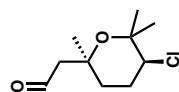
¹H spectrum



Current Data Parameters
 Name: MED-11-20ptcf11-18
 ExpNo: 1
 ProcNo: 1
 P2 - Acquisition Parameters
 Date_: 2010114
 Time: 12.05
 INSTRUM: cryo500
 PROBHD: 5 mm QNP1H
 P1: 12.00
 TO: 0.000000
 SOLVENT: CDCl₃
 NS: 2
 DS: 4
 SWE: 8012.800 Hz
 FIDRES: 0.090643 Hz
 AQ: 5.493976 sec
 RG: 6.3
 DW: 62.400 nsec
 DE: 2.400 nsec
 TE: 300.2 K
 D1: 0.10000000 sec
 d11: 0.00000000 sec
 DELTA: 0.00000000 sec
 ACQNT: 0.01300000 sec
 ===== CHANNEL f1 =====
 NUC1: 1H
 P1: 7.50 nsec
 PL1: 1.60 dB
 SFO1: 500.2235015 MHz
 P2 - Processing parameters
 SI: 65536
 SF: 500.2235015 MHz
 WDW: 500.2235015 MHz
 SSB: 0
 LB: 0.30 Hz
 GB: 0
 PC: 4.00
 D5 NMR plot parameters
 CY: 22.80 cm
 CX: 15.00 cm
 F1F: 10.100 ppm
 F2F: 50.100 ppm
 F3F: -8.100 ppm
 F2: 0.000000 Hz
 F3: 0.000000 Hz
 HZCN: 233.7827 Hz/cm

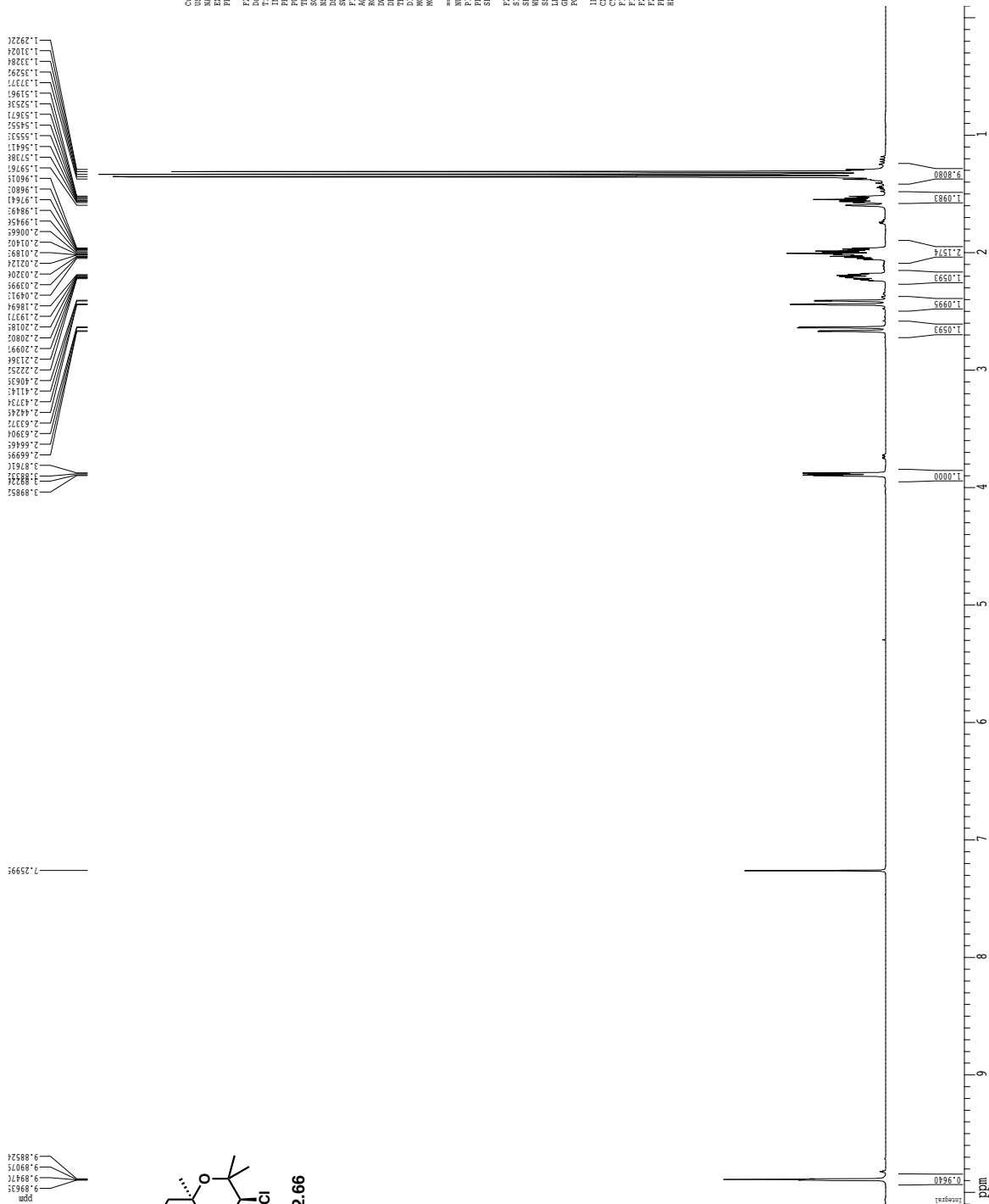


¹H spectrum

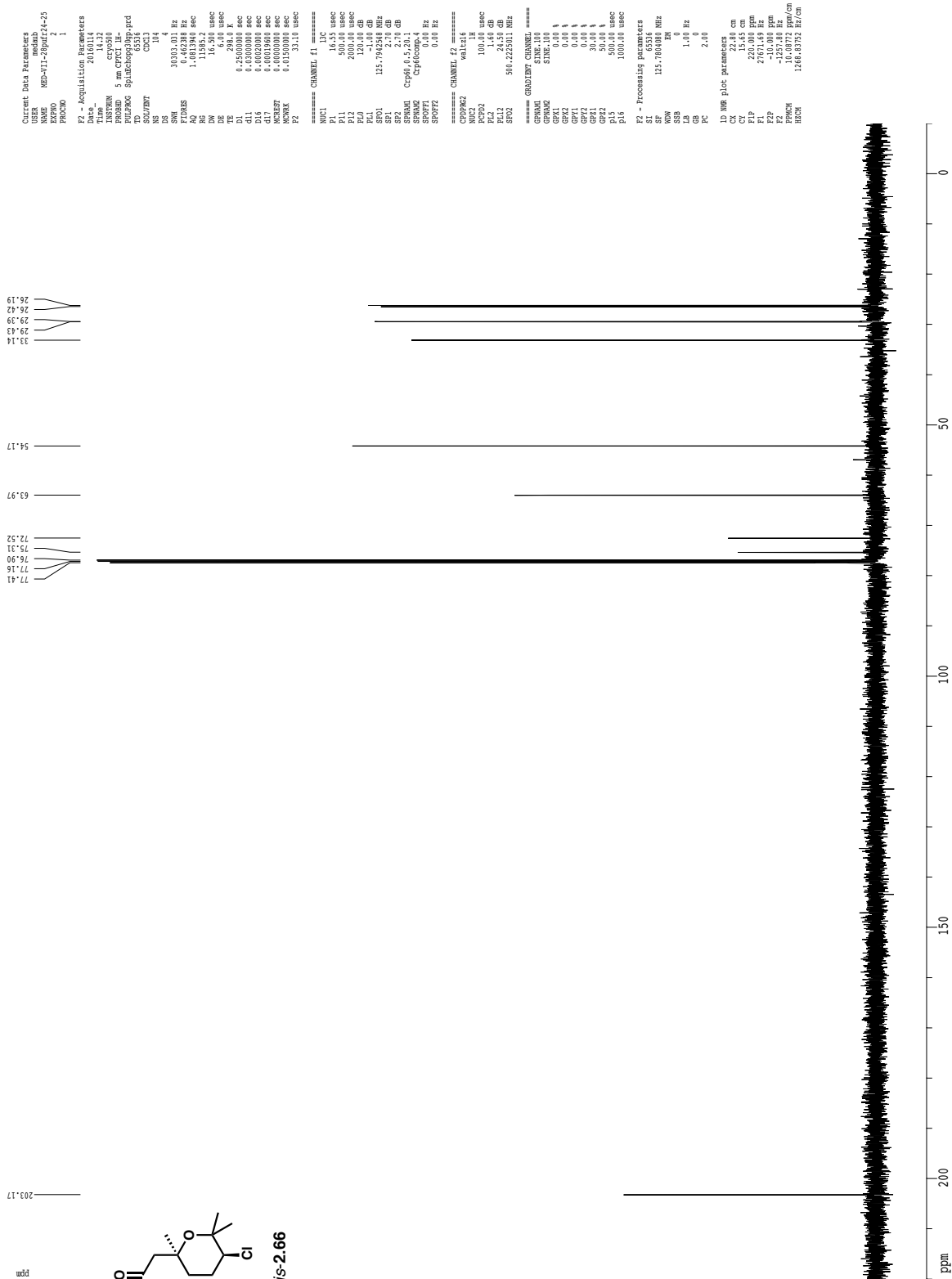


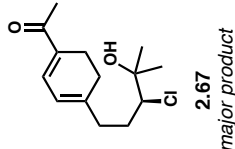
cis-2.66

Current Data Parameters
 Name MED-11-20140114-25
 EXPNO 1
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20140114
 Time 12:00:00
 INSTRUM cryo500
 PROBD 5 mm QNP1H
 P1 12.00
 TO 8178
 SOLVENT CDCl3
 NS 2
 DS 2
 SWE 8012.800 Hz
 FIDRES 0.098643 Hz
 AQ 5.493977 sec
 RG 8
 DW 62.400 usec
 DE 2.400 usec
 TE 300.2 K
 D1 0.10000000 sec
 D11 0.10000000 sec
 ACQTIME 0.00000000 sec
 ACQTIME 0.11300000 sec
 ===== CHANNEL f1 =====
 NUC1 1H
 P1 12.00 usec
 PL1 0 dB
 SFO1 500.2235015 MHz
 F2 - Processing parameters
 SI 65536
 SF 500.2235015 MHz
 WDW 0
 LB 0.30 Hz
 GB 0
 PC 4.00
 D3 NMR plot parameters
 CY 22.80 cm
 CX 15.40 cm
 FID 10.100 ppm
 F1F 500.2235015 MHz
 F2P -8.100 ppm
 F2 0.00000000 Hz
 F2P2 233.78267 Hz/cm

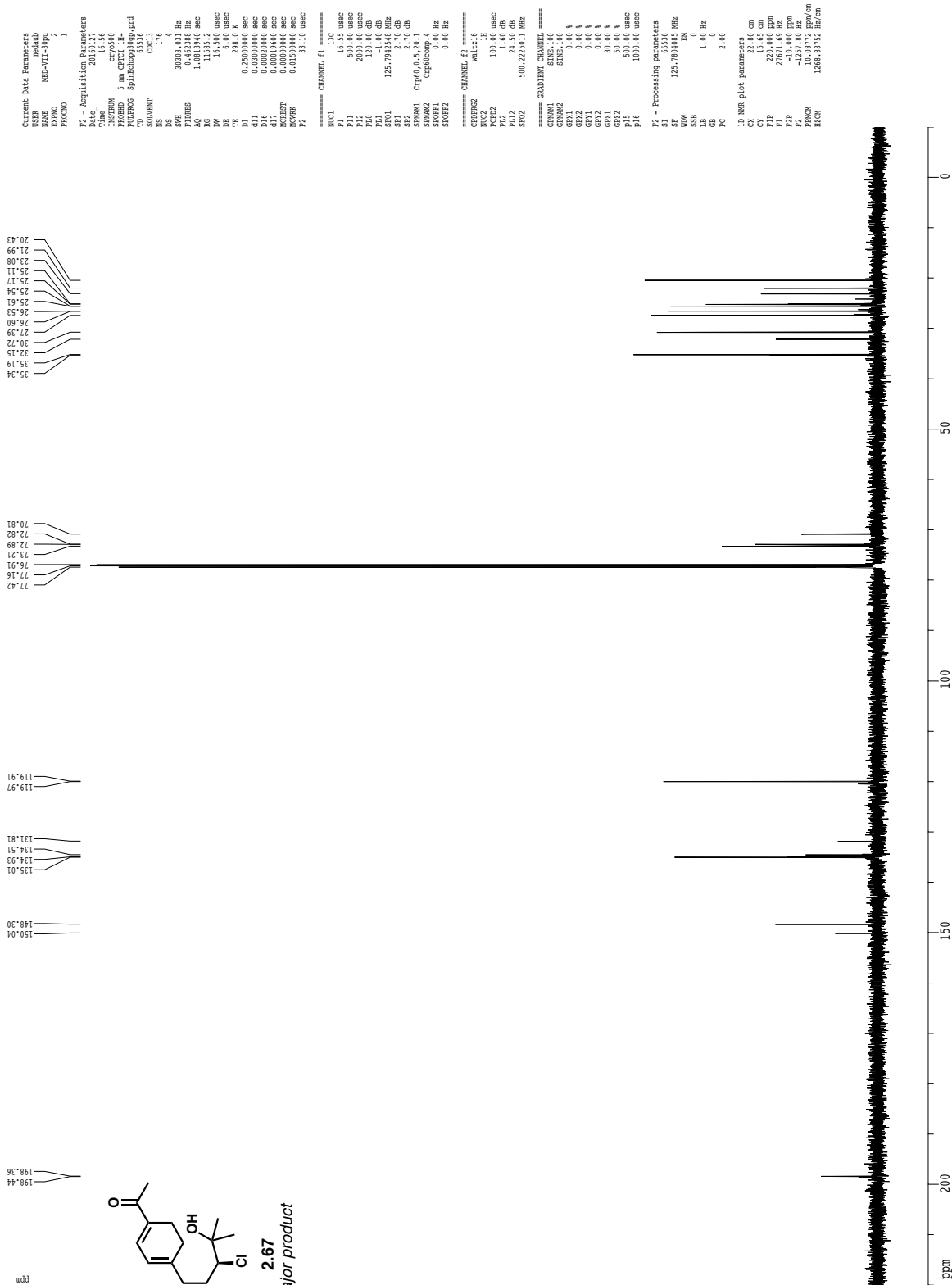


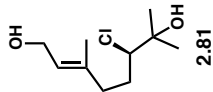
Z-restored spin-echo 13C spectrum with 1H decoupling



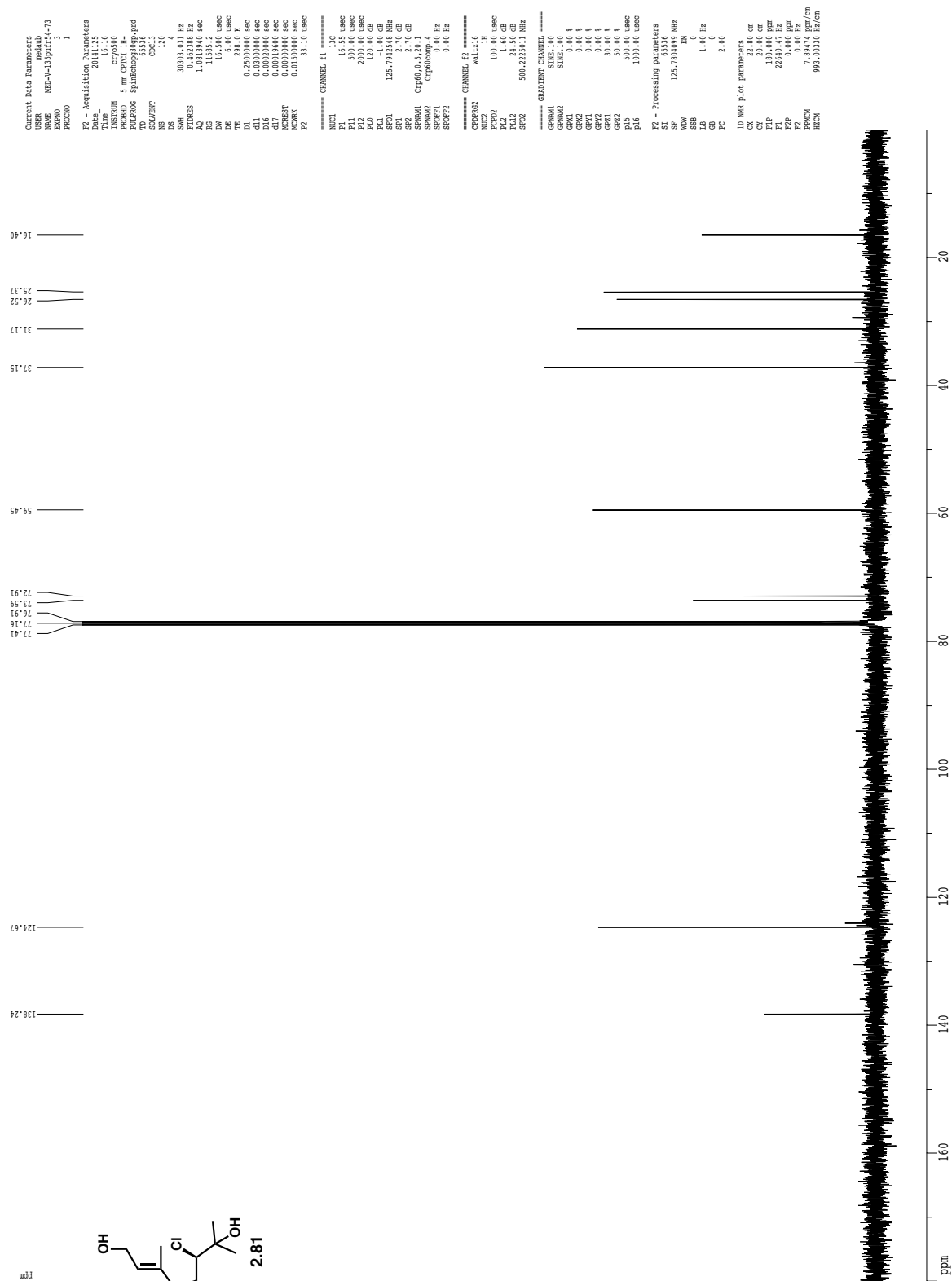


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

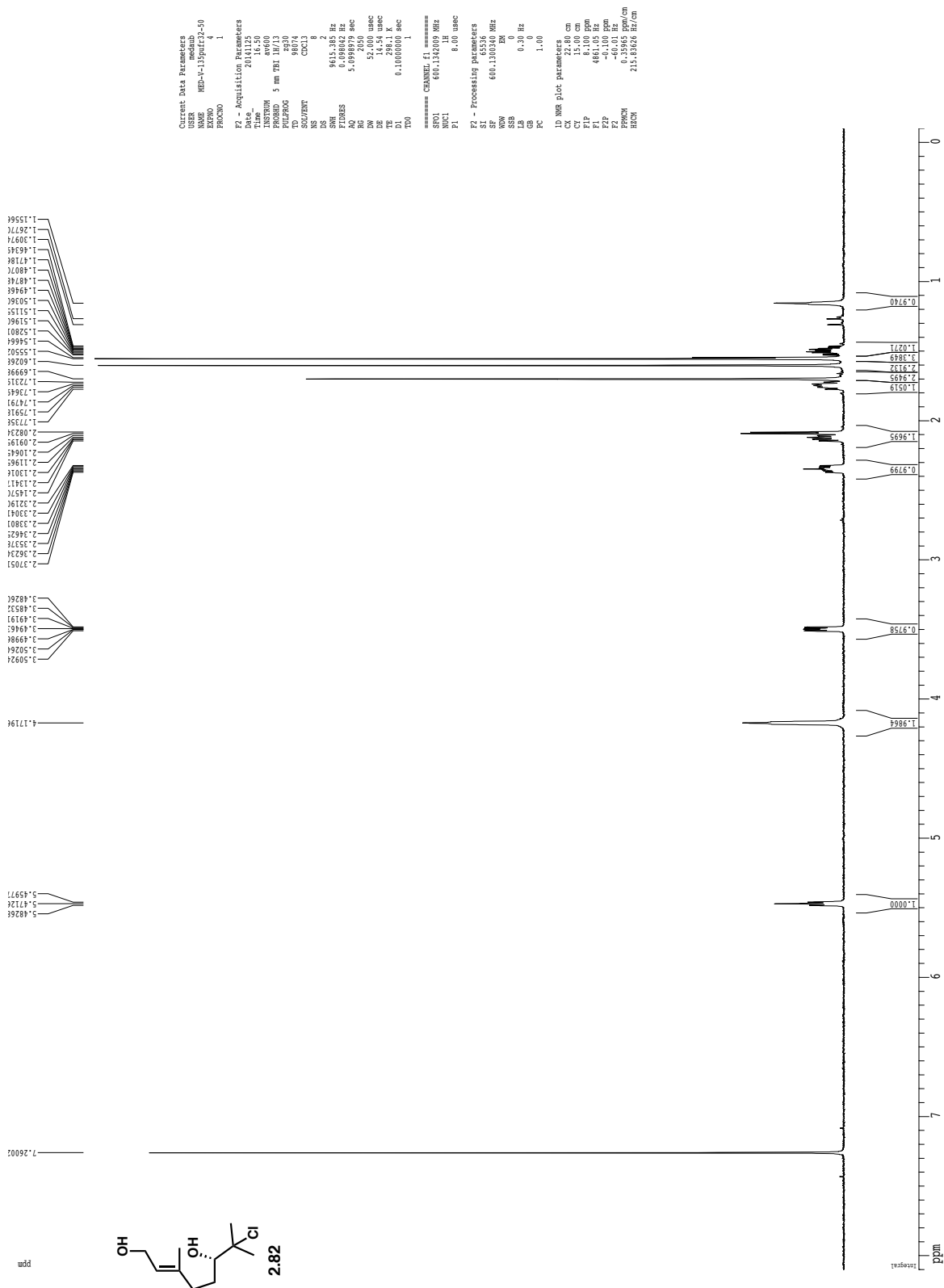




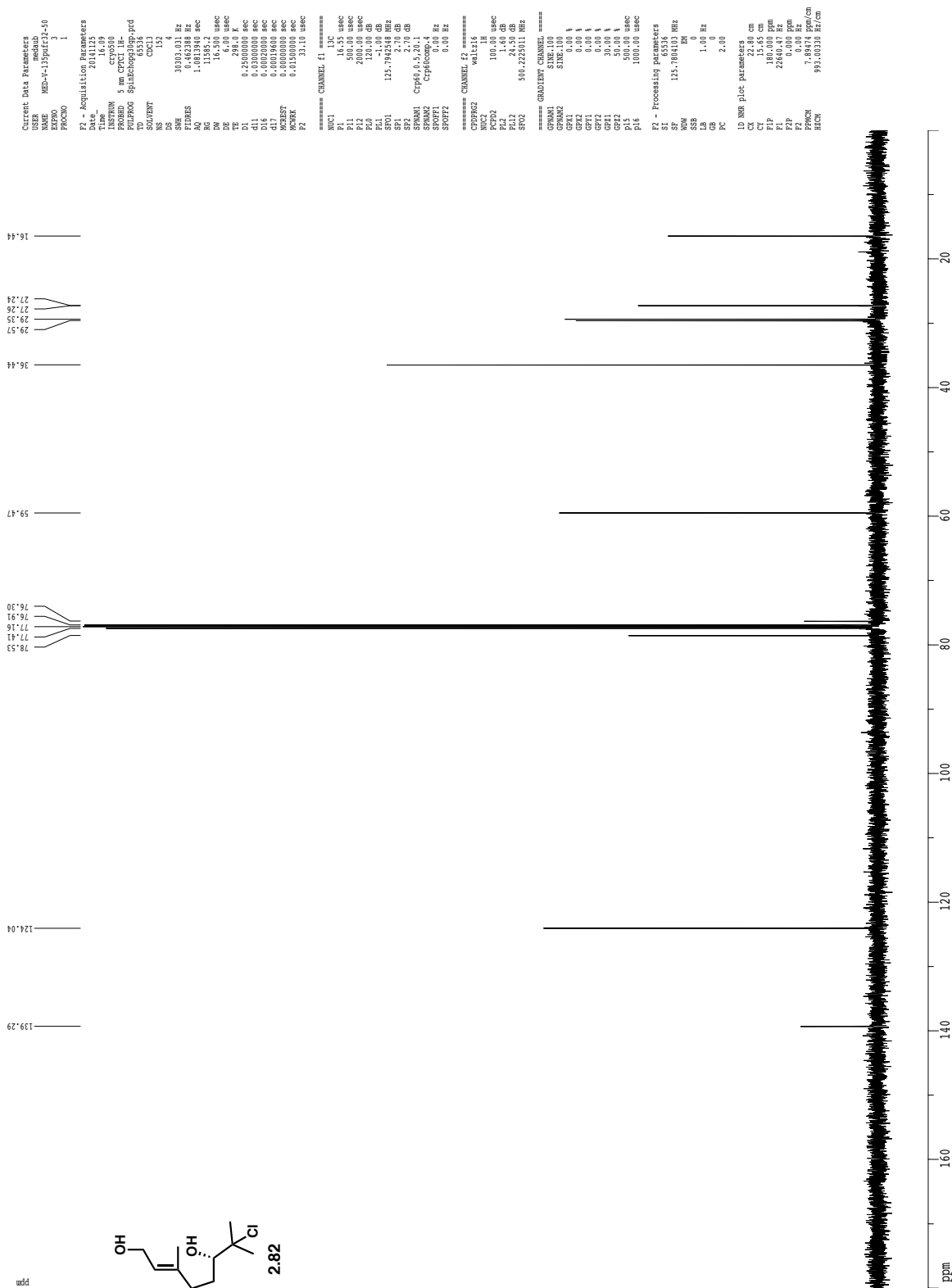
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



¹H spectrum



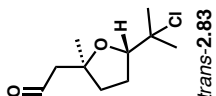
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

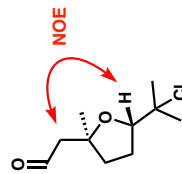


9.81544
9.82012
9.82475

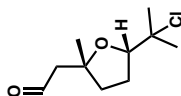
ppm



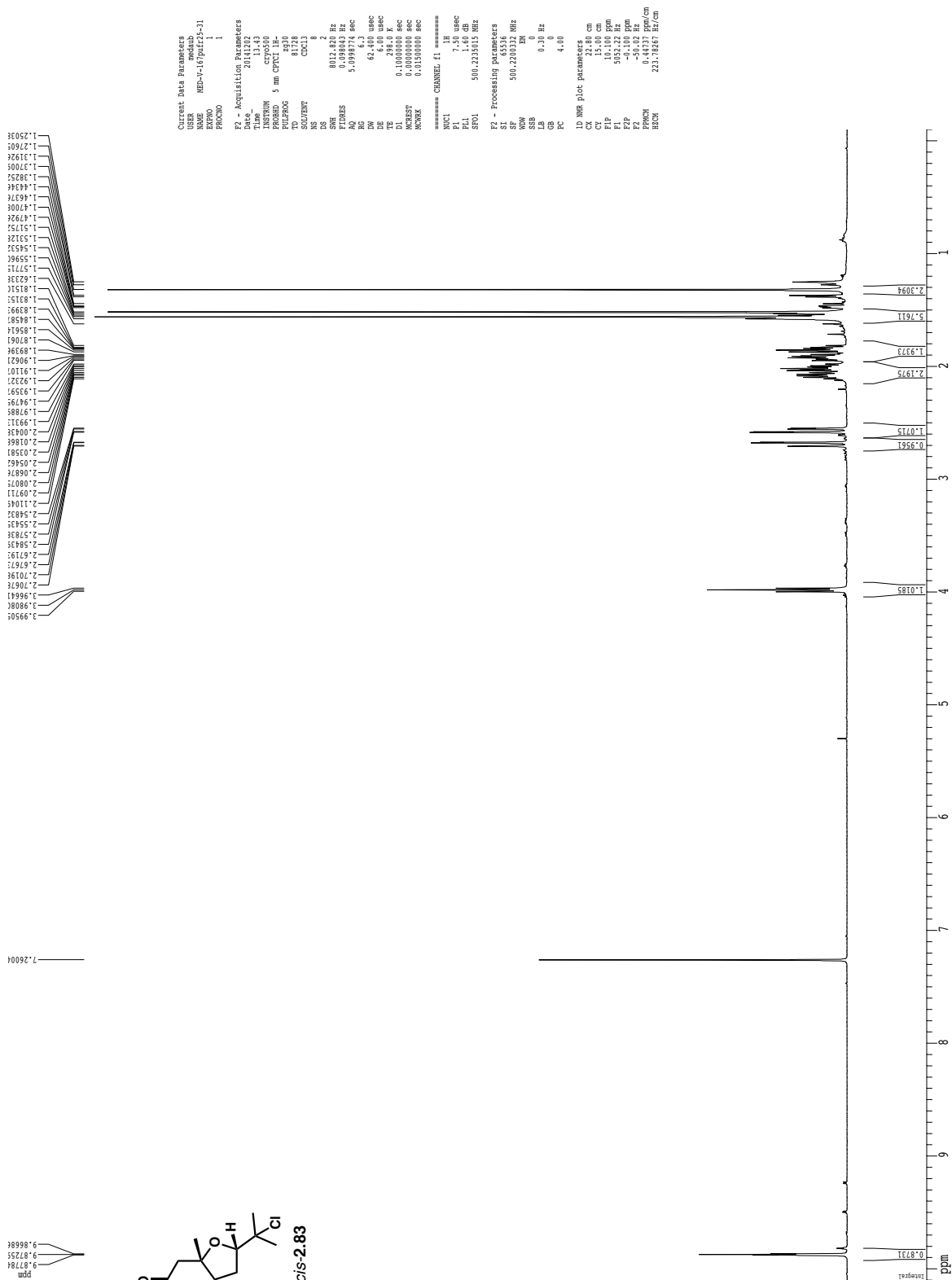
[illegible]

[illegible]

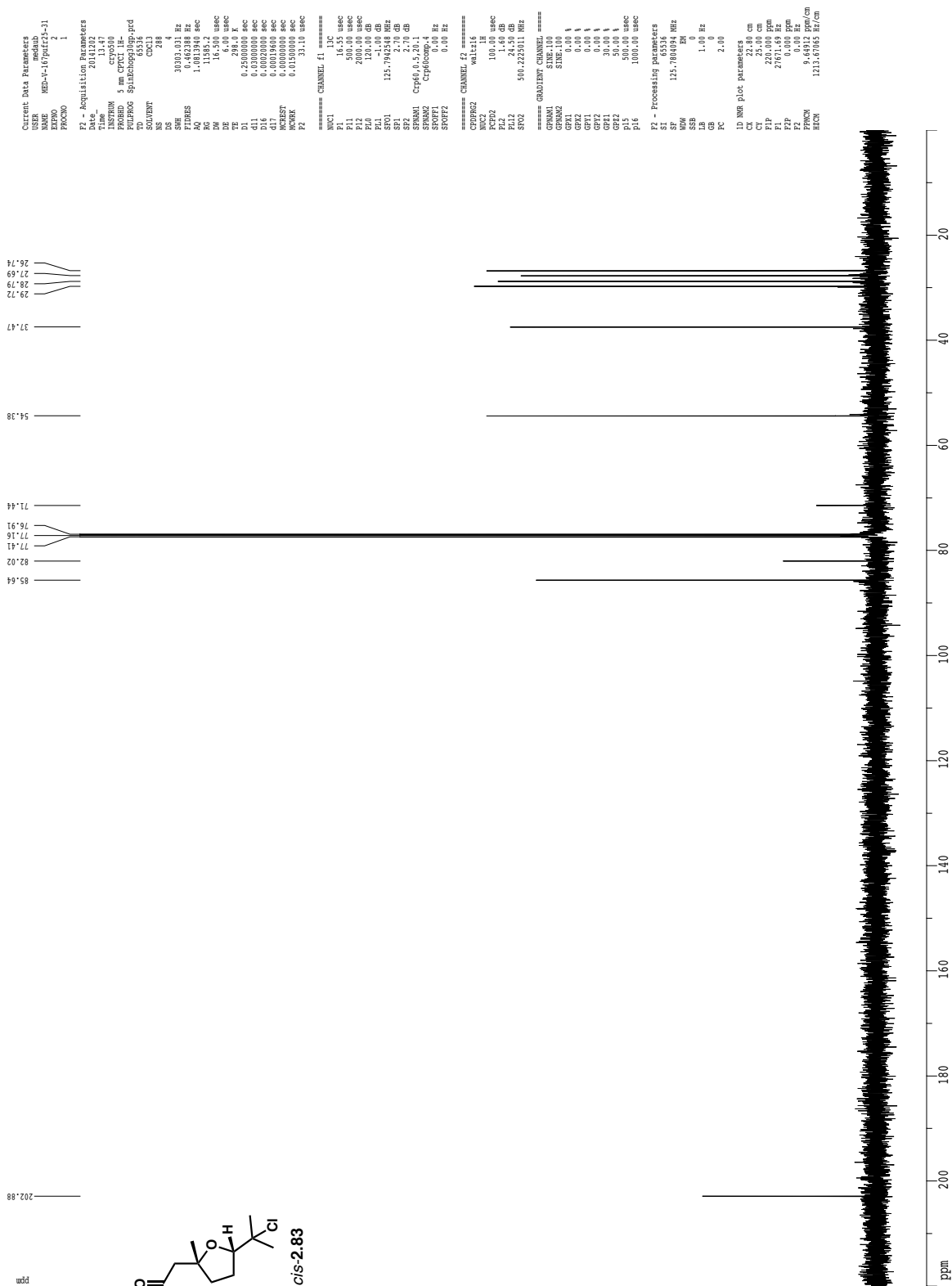
¹H spectrum

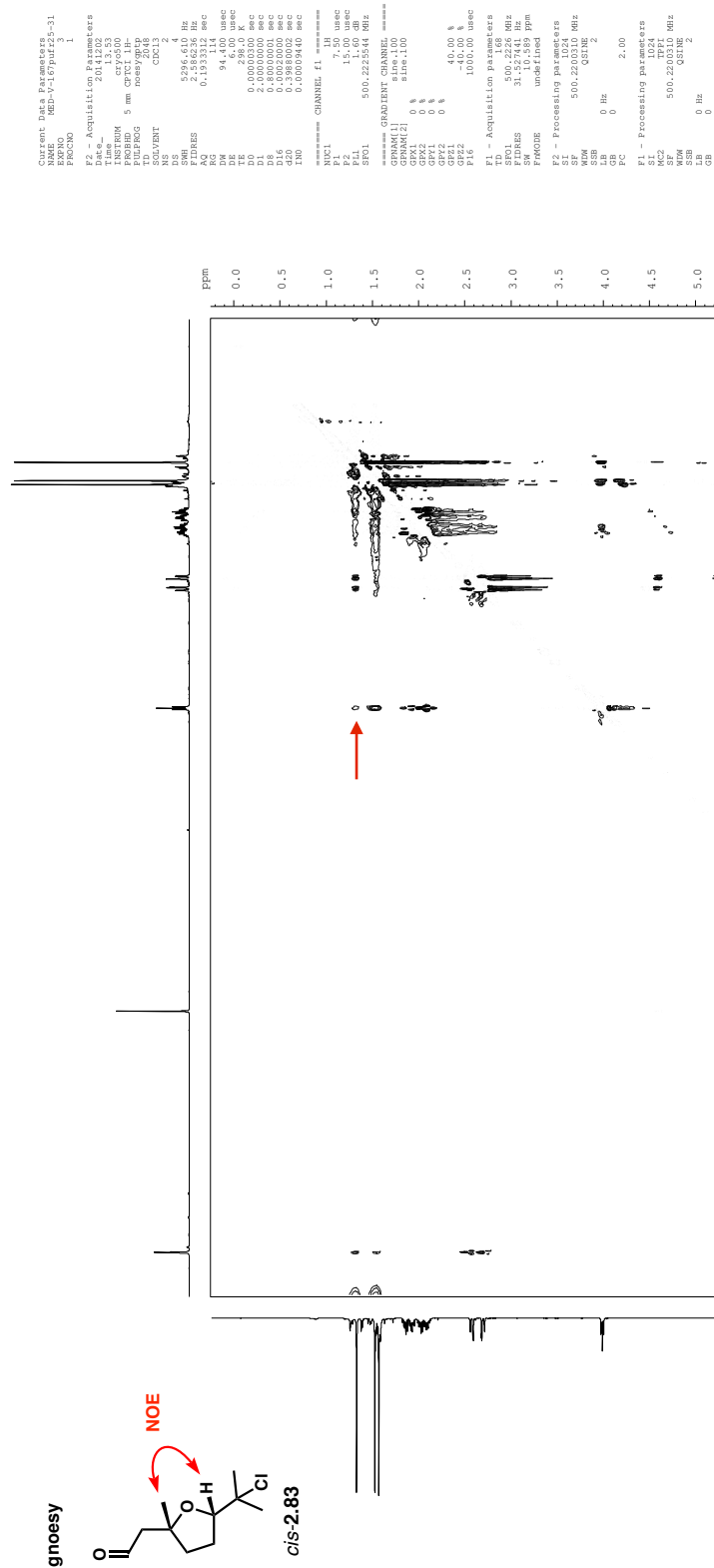


cis-2.83



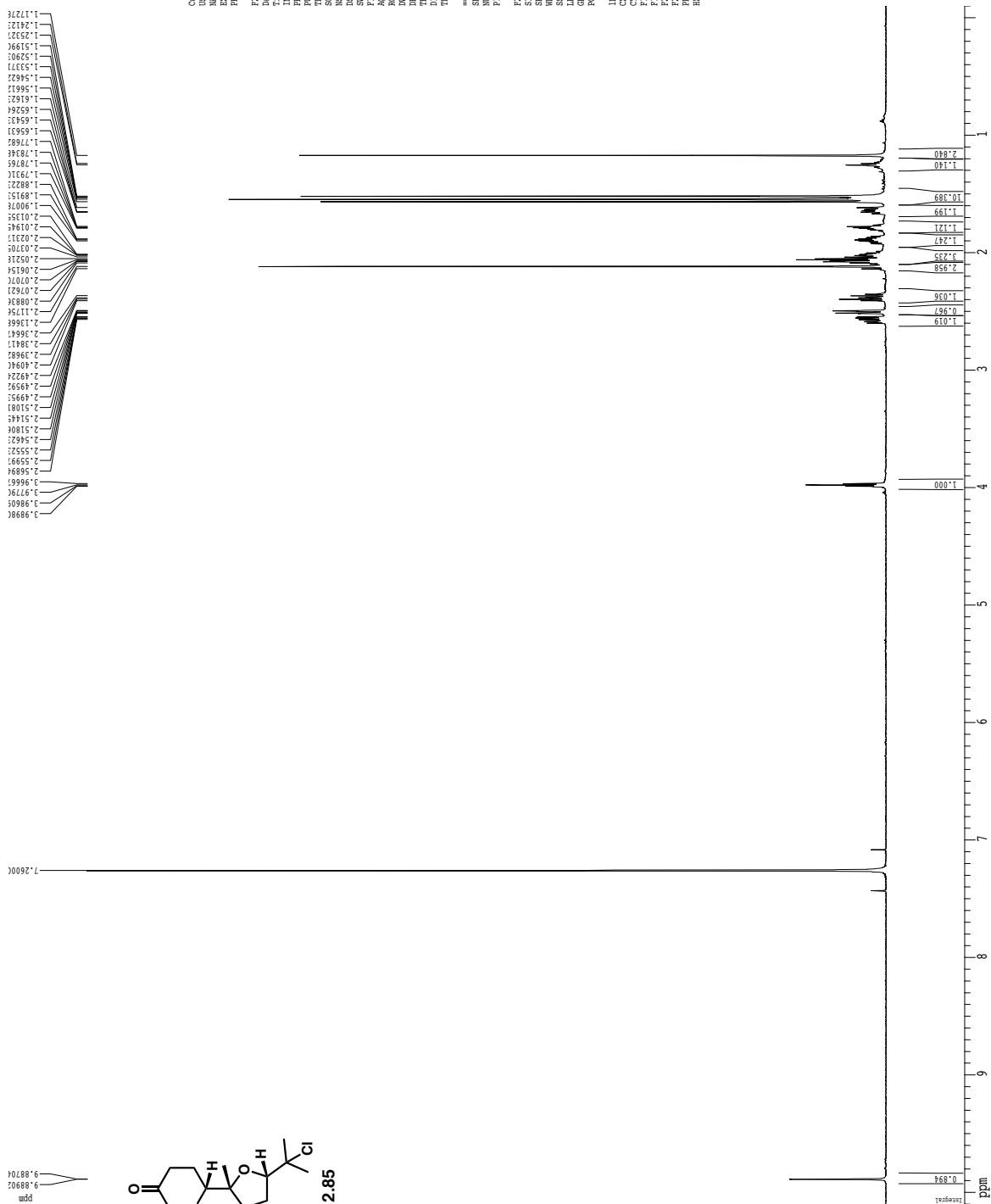
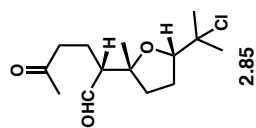
Z-restored spin-echo ¹³C spectrum with ¹H decoupling





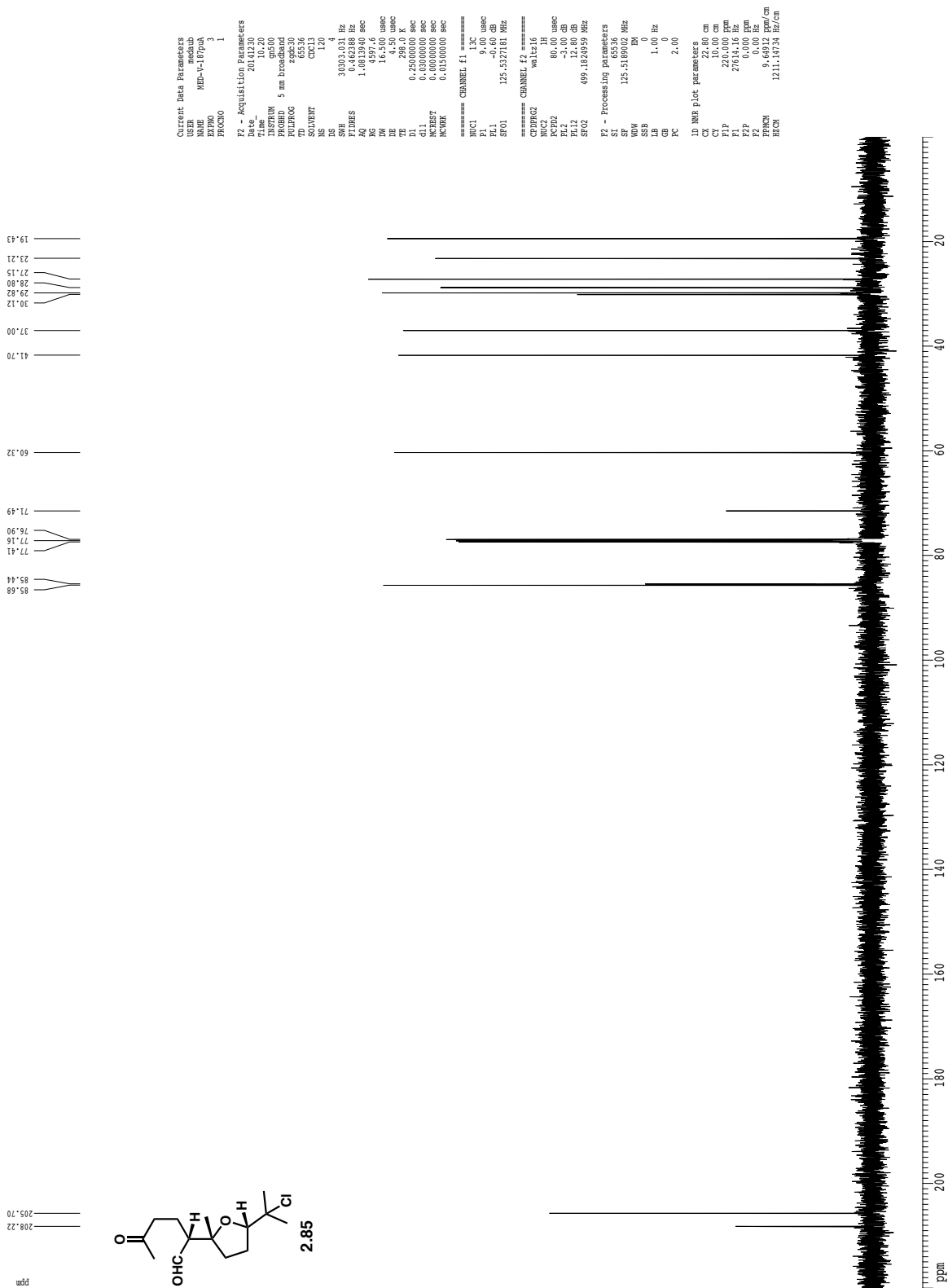
¹H spectrum

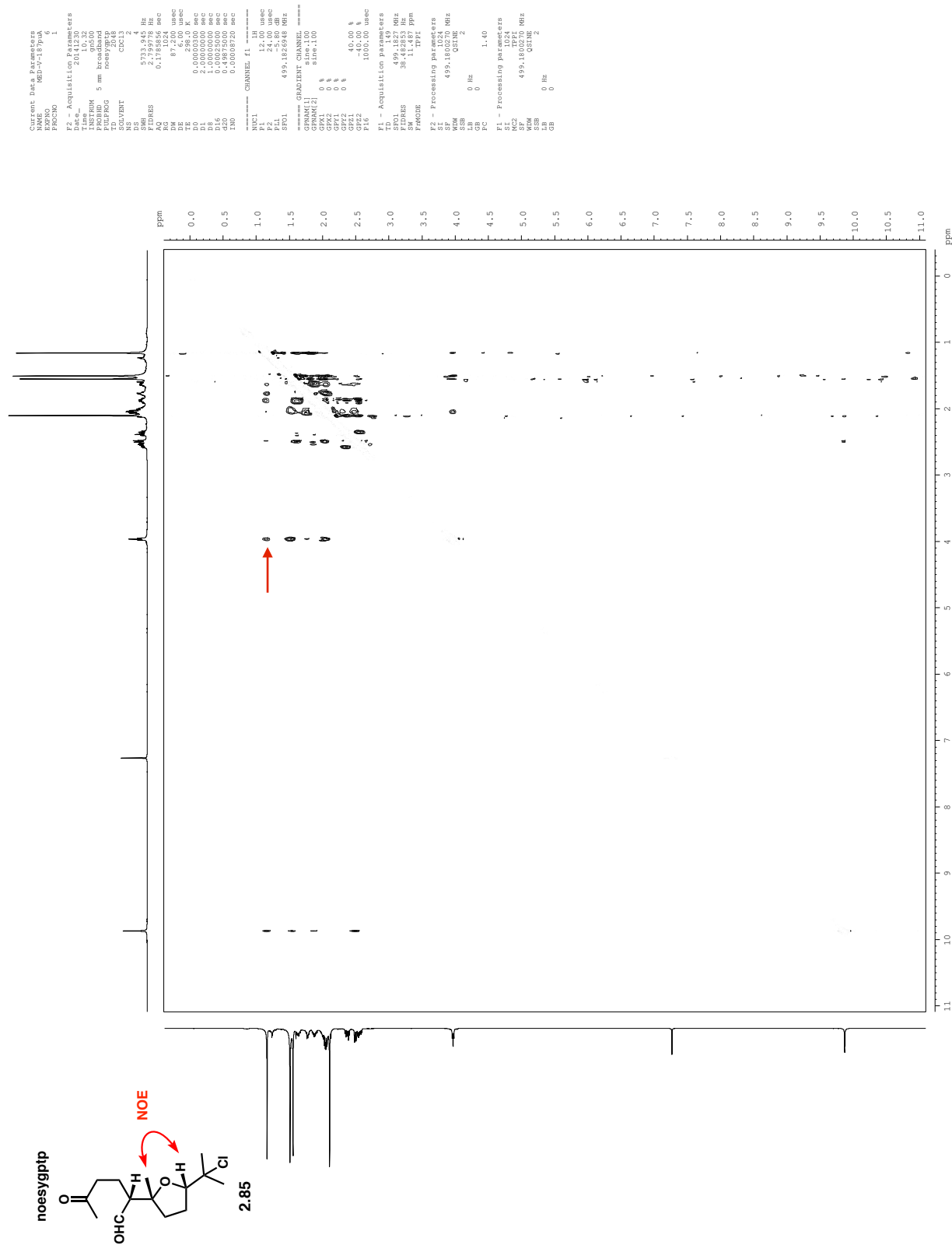
9.88704
9.88902
ppm



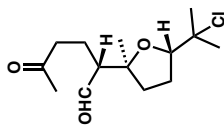
Current Data Parameters
USER modab
NAME 1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110325
Time 17:53
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zgpg30
TD 98714
SOLVENT CDCl3
NS 8
DS 2
SWH 9615.385 Hz
FIDRES 0.094042 Hz
AQ 5.0998979 sec
RG 640
RG 52.000 usec
DE 114.54 usec
TE 298.4 K
D1 0.1000000 sec
TD0 1
===== CHANNEL f1 =====
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
F2 - Processing parameters
SI 65536
SF 600.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
LD NMR p10r parameters
CX 22.80 cm
CT 5.500 cm
ETP 10.100 cm
FI 6061.31 Hz
FZP -0.100 ppm
PC 0.001 Hz
PCW 0.44131 Hz/cm
HCN 266.47925 Hz/cm

¹³C spectrum with ¹H decoupling



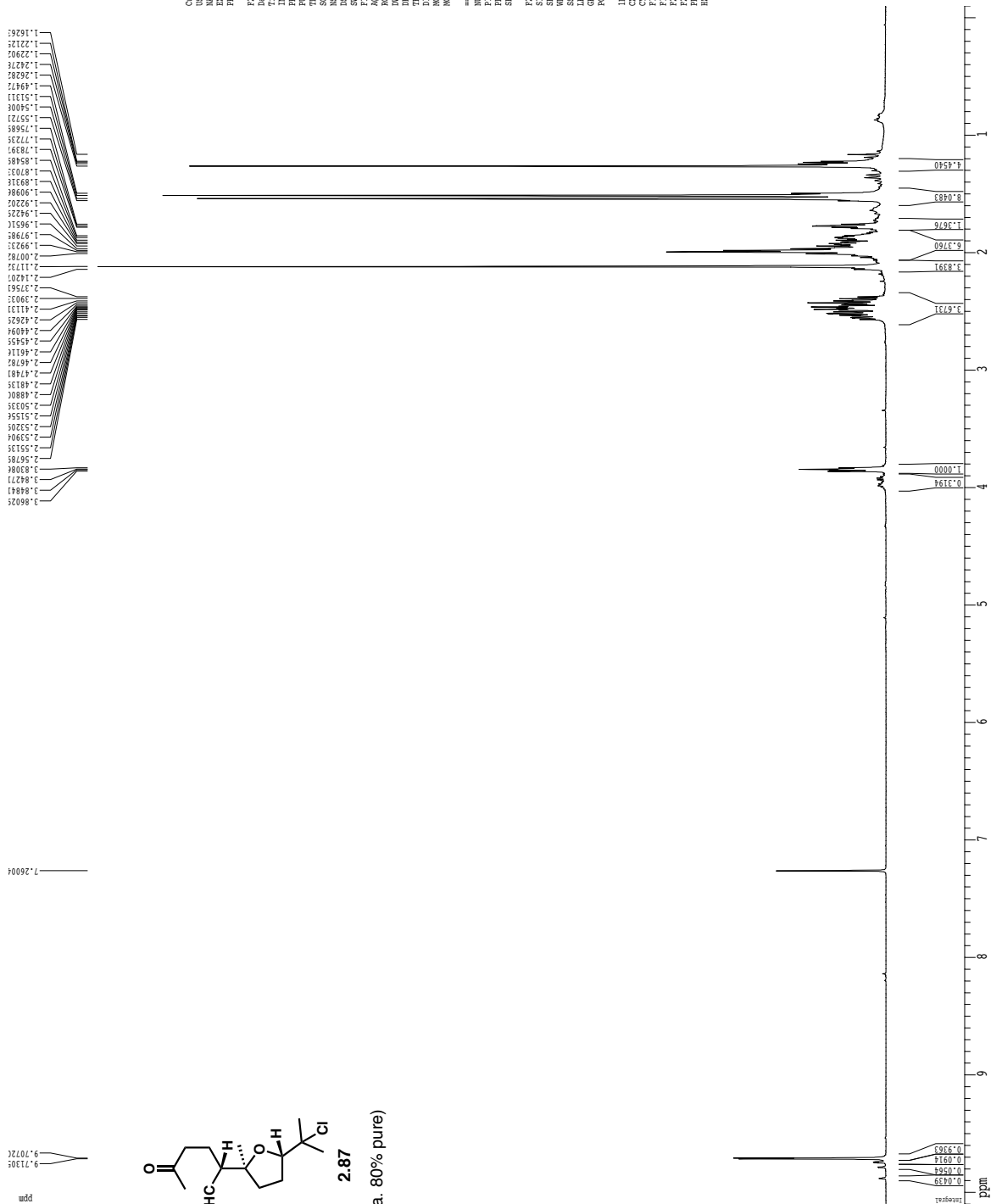


¹H spectrum

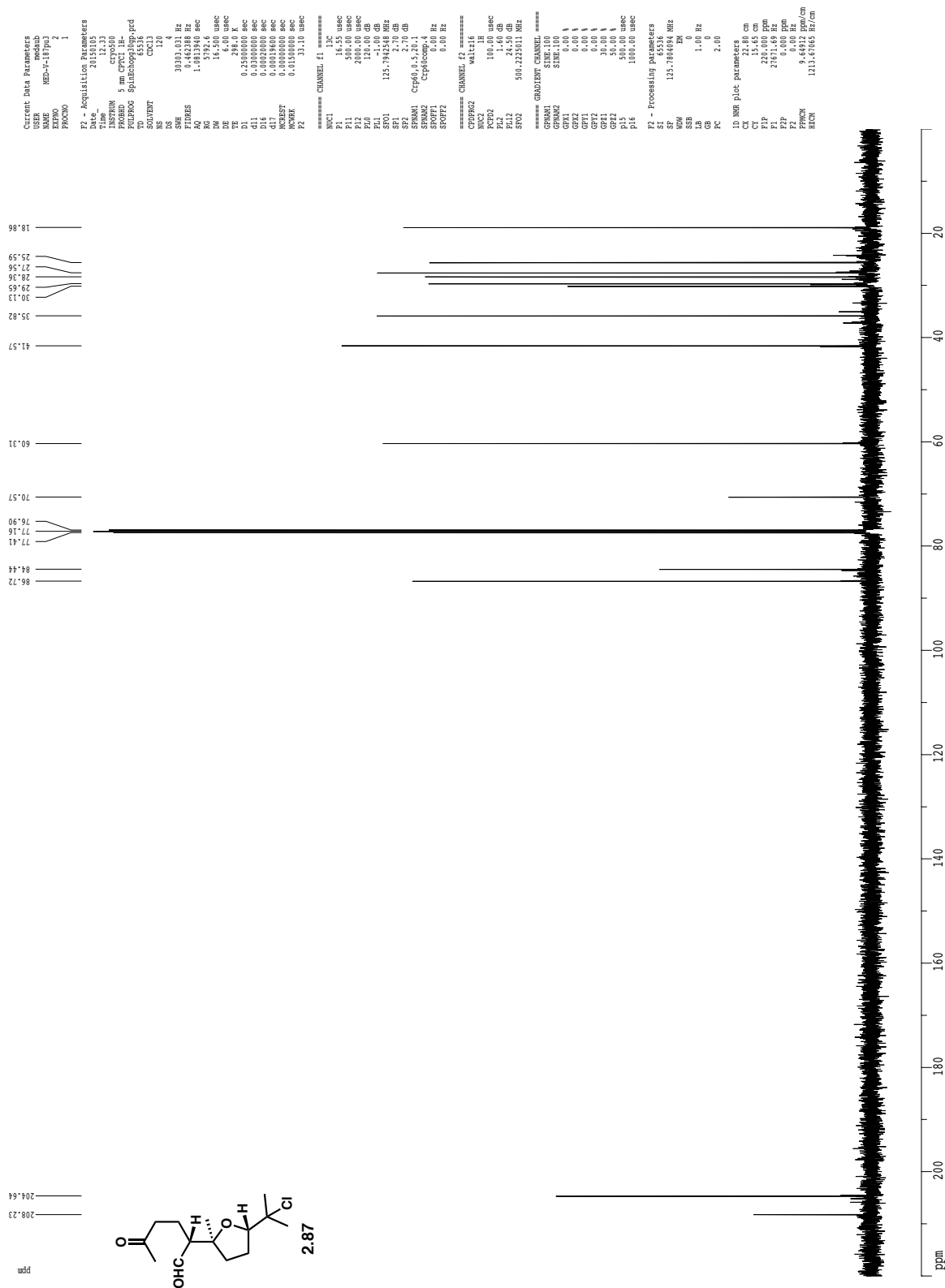


(ca. 80% pure)

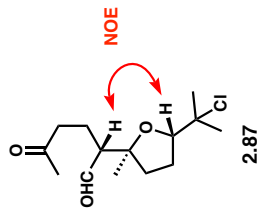
Current Data Parameters
 Date: 20150105
 Time: 12:31
 Name: 12-31
 EXPNO: 1
 PROCNO: 1
 P2 - Acquisition Parameters
 Date: 20150105
 Time: 12:31
 Name: 12-31
 EXPNO: 1
 PROCNO: 1
 PULPROG: zgpg30
 TD: 65536
 SOLVENT: CDCl3
 NS: 2
 DS: 2
 SWH: 8012.823 Hz
 FIDRES: 0.098443 Hz
 AQ: 5.1999816 sec
 RG: 31.6
 DW: 62.400 usec
 DE: 6.00 usec
 TE: 300.2 K
 D1: 0.10000000 sec
 MCREPT: 0.0000000 sec
 MCHNK: 0.0150000 sec
 ===== CHANNEL f1 =====
 NUC1: 1H
 P1: 7.50 usec
 PL1: 0.00 dB
 SFO1: 500.235015 MHz
 P2 - Processing parameters
 SI: 32768
 SF: 500.235015 MHz
 WDW: EM
 SSB: 0
 AB: 0.10 Hz
 GB: 0.00 Hz
 PC: 4.00
 ID: NMR Plot parameters
 SI: 32768
 SF: 500.235015 MHz
 CF: 15.00 cm
 PIP: 10.100 ppm
 FI: 5952.22 Hz
 F2: 2.00000000 ppm
 F2: -50.02 Hz
 PRGCM: 0.44737 ppm/cm
 HZCM: 223.76267 Hz/cm



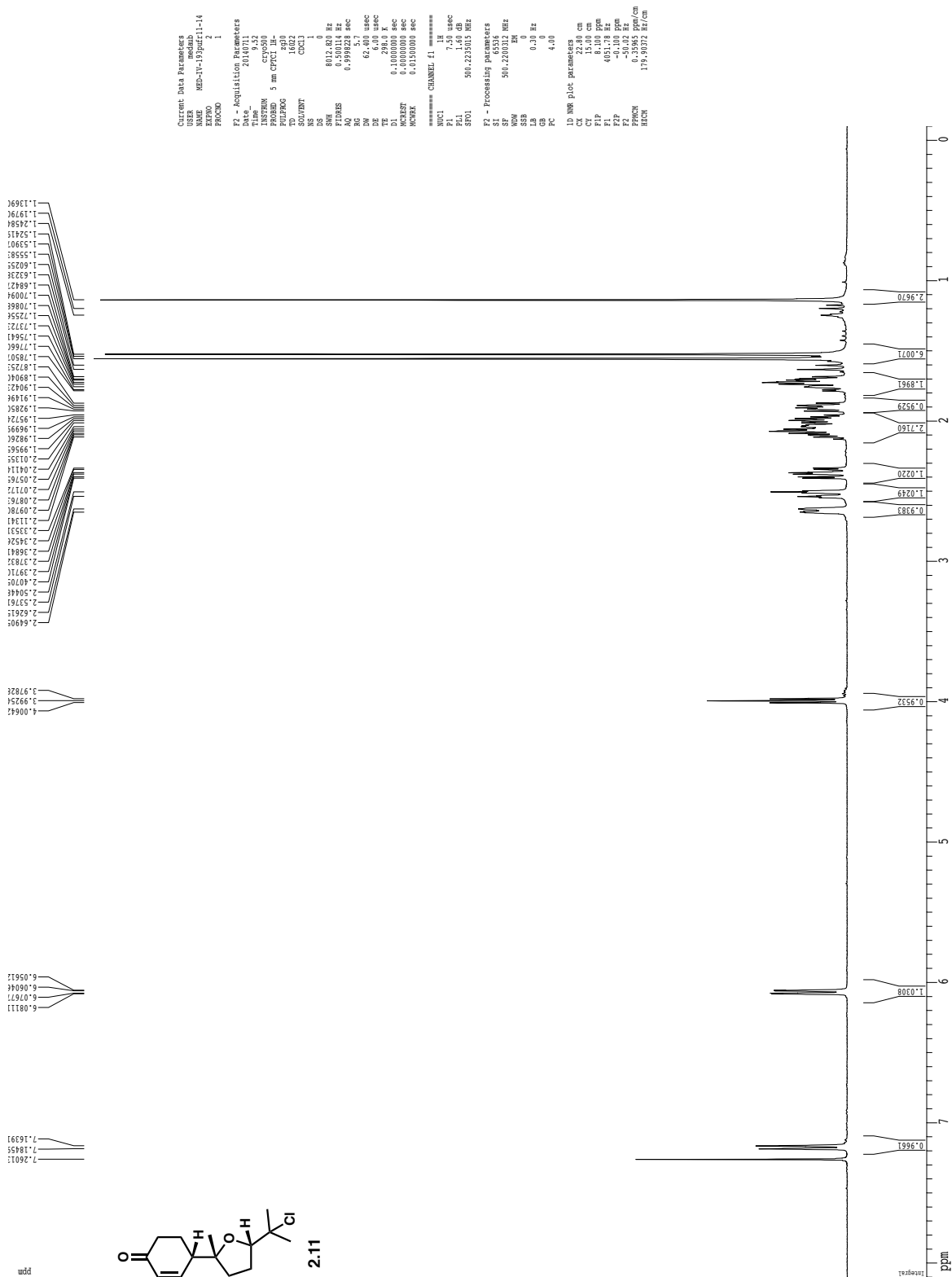
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

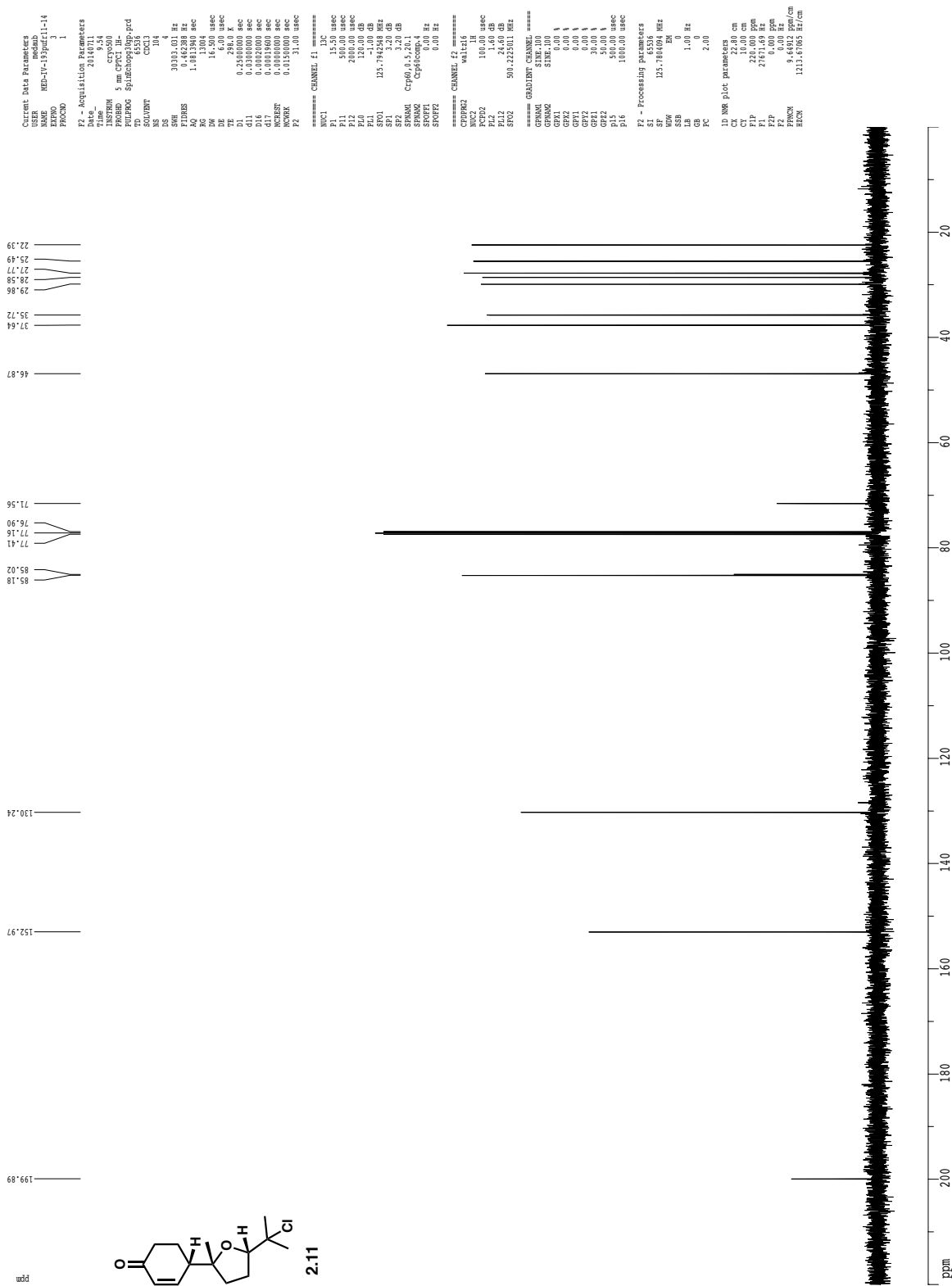


gnoesy

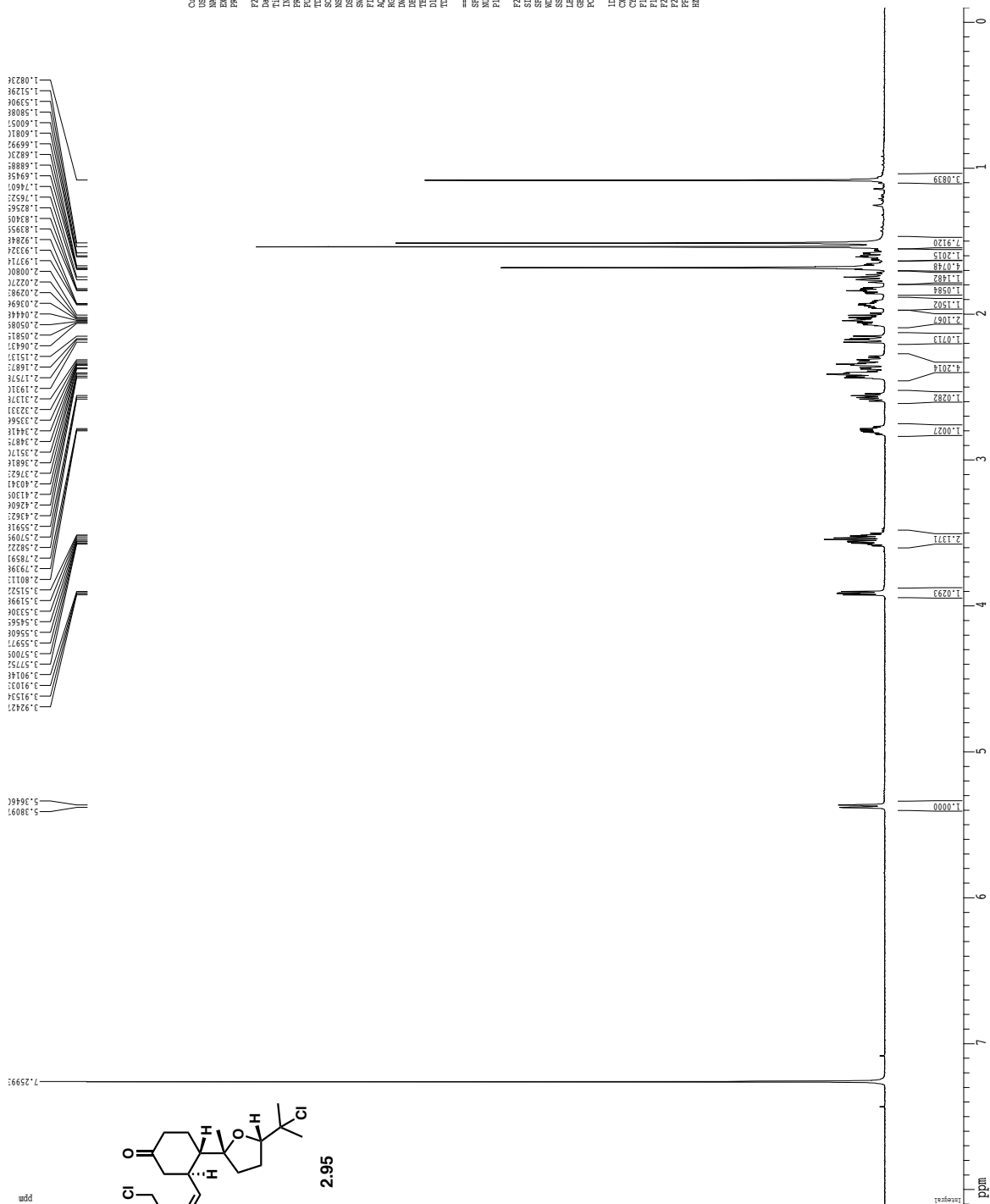


¹H spectrum

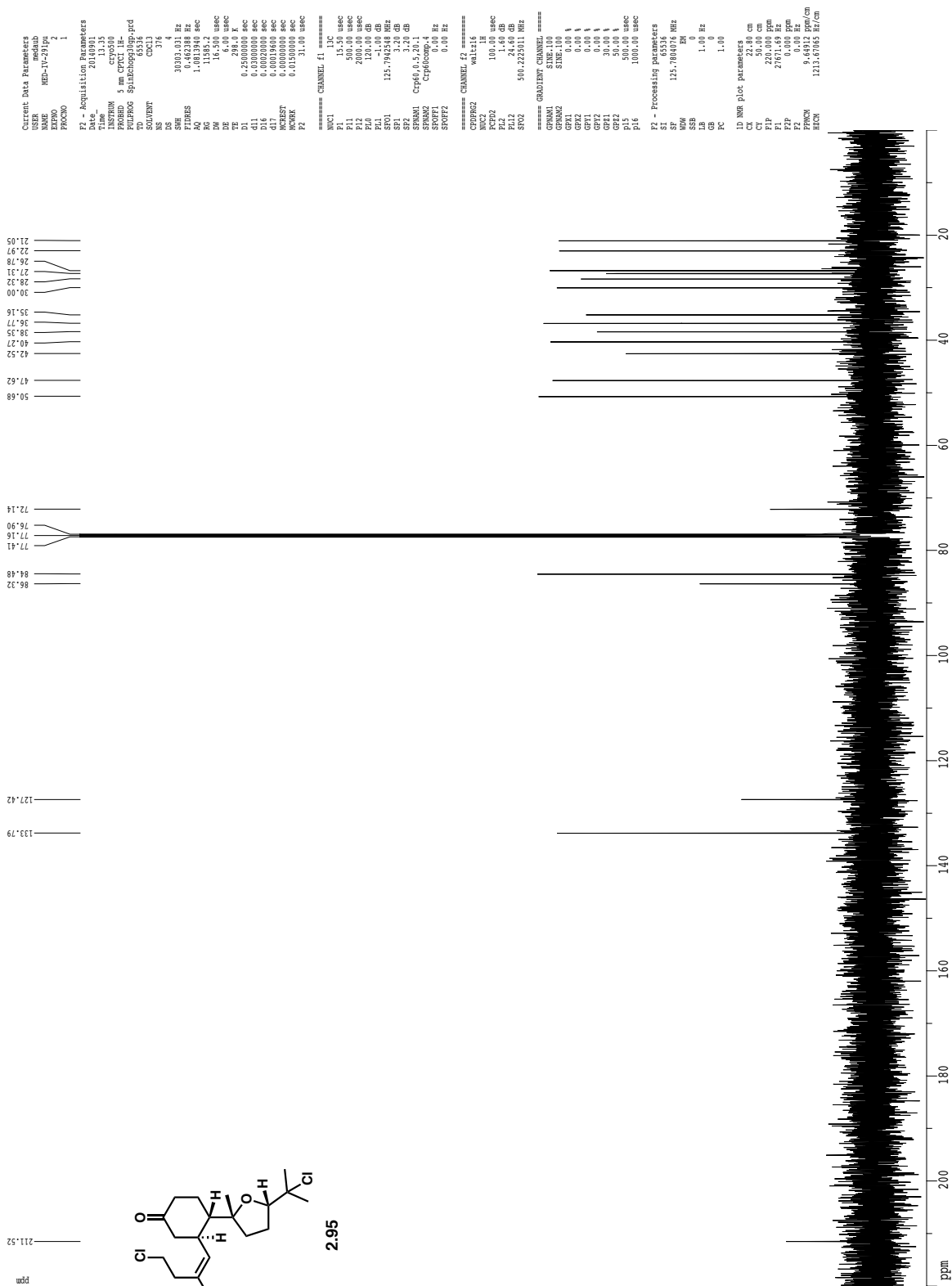


Z-restored spin-echo ^{13}C spectrum with ^1H decoupling

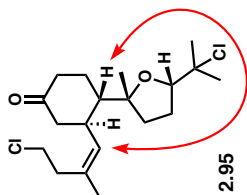
1H spectrum



Z-restored spin-echo ¹³C spectrum with ¹H decoupling



gnoesy

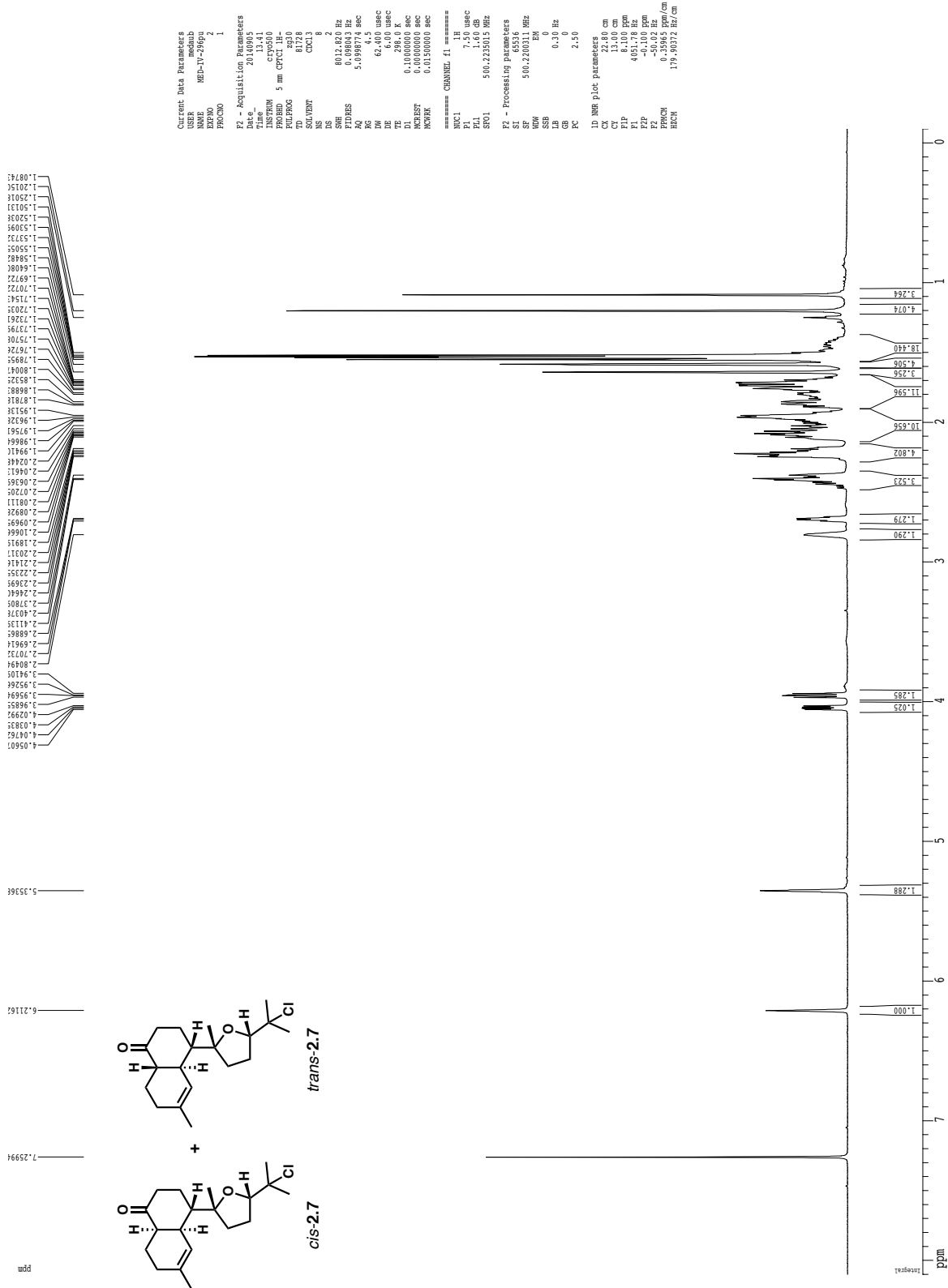


NOE

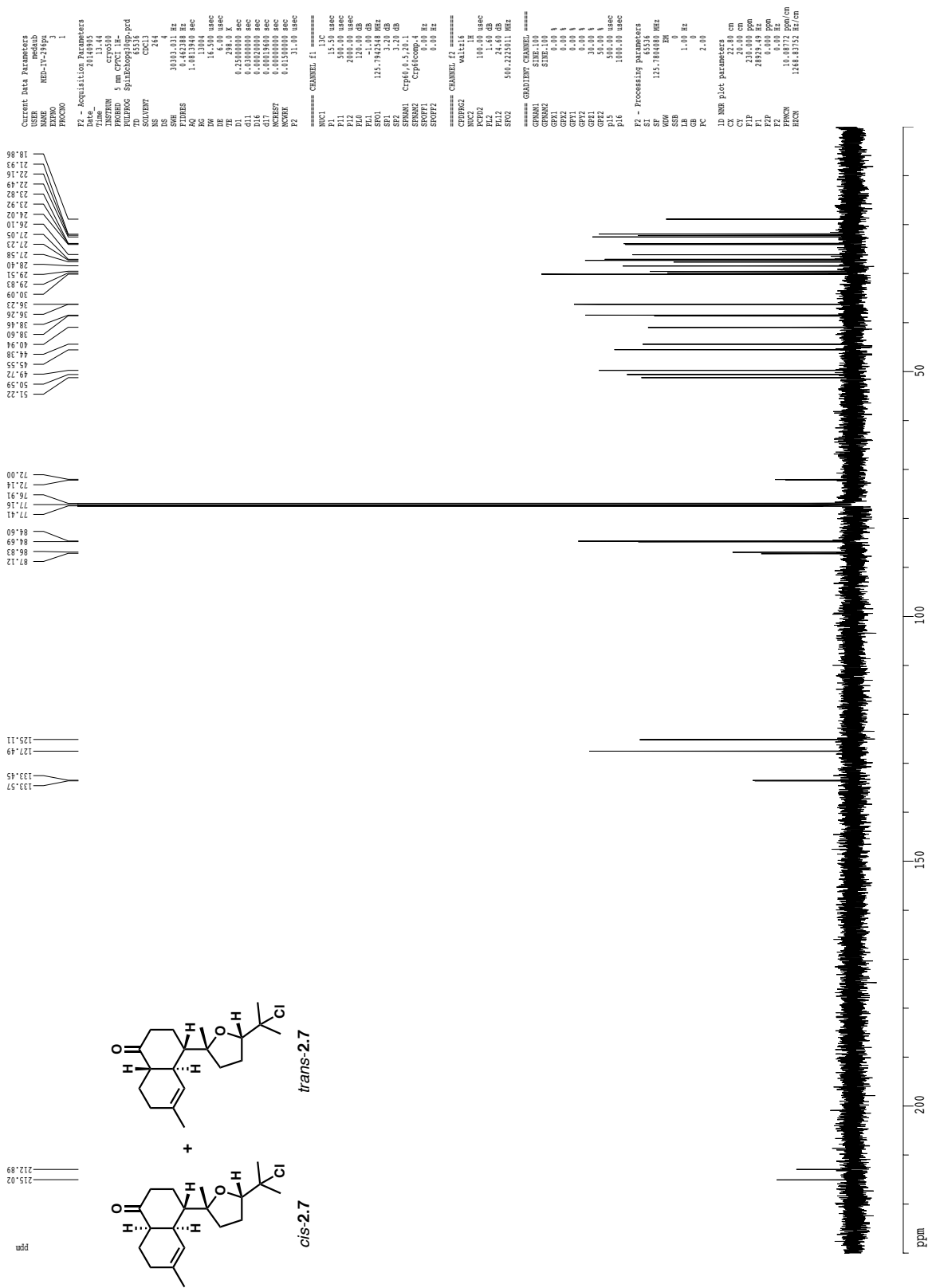
2.95



¹H spectrum

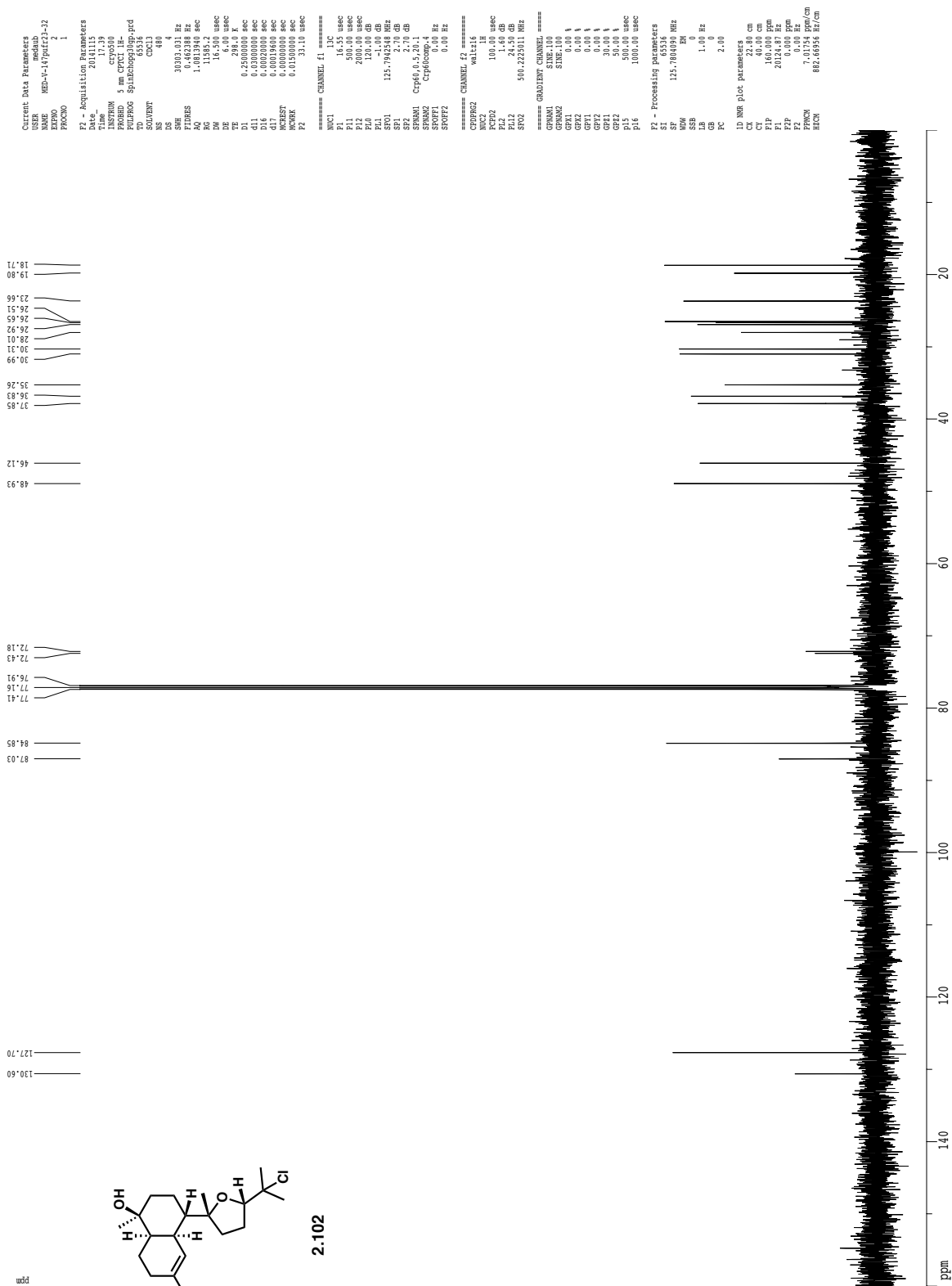


Z-restored spin-echo ¹³C spectrum with ¹H decoupling



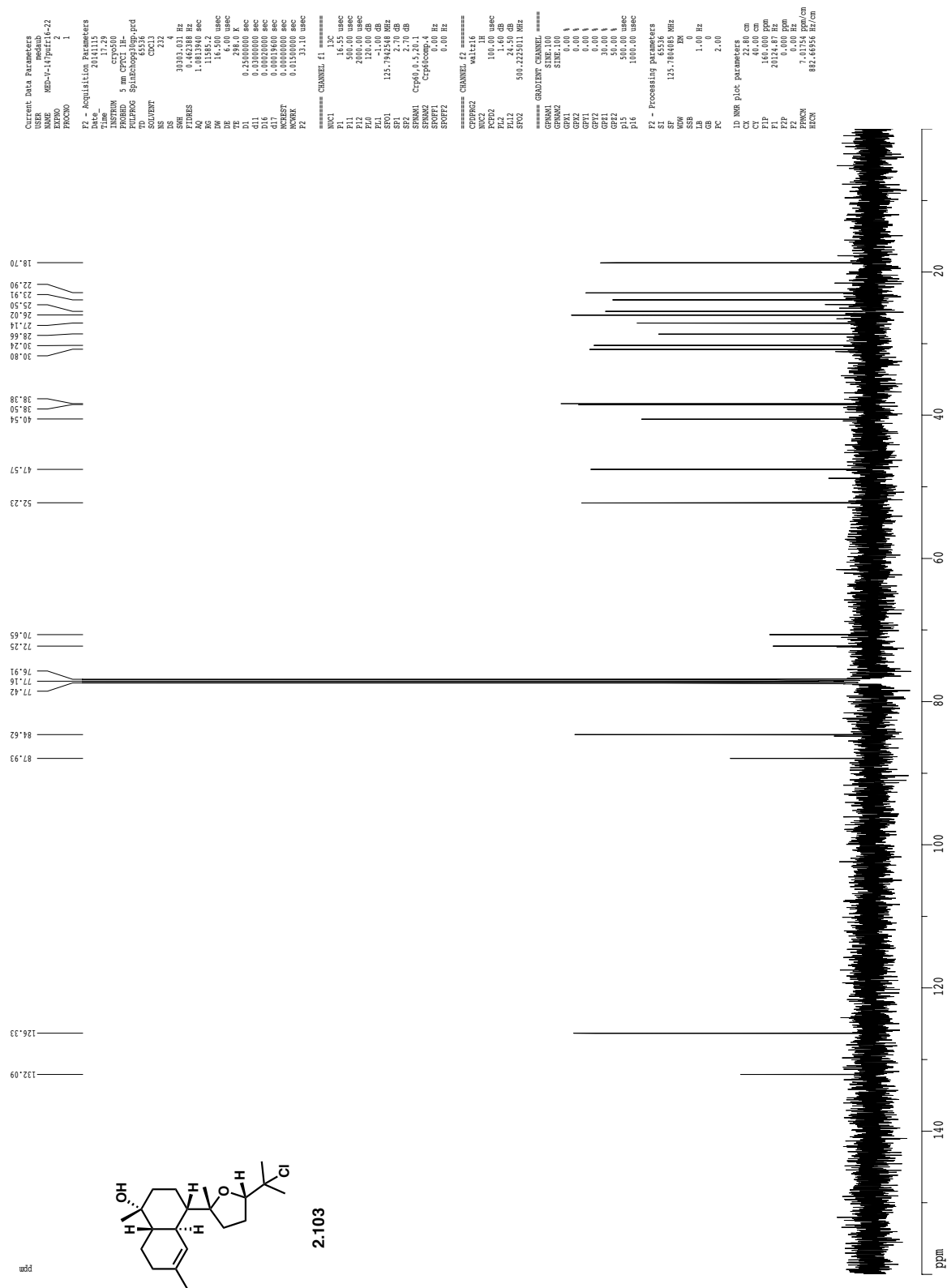


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

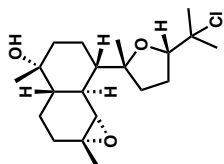




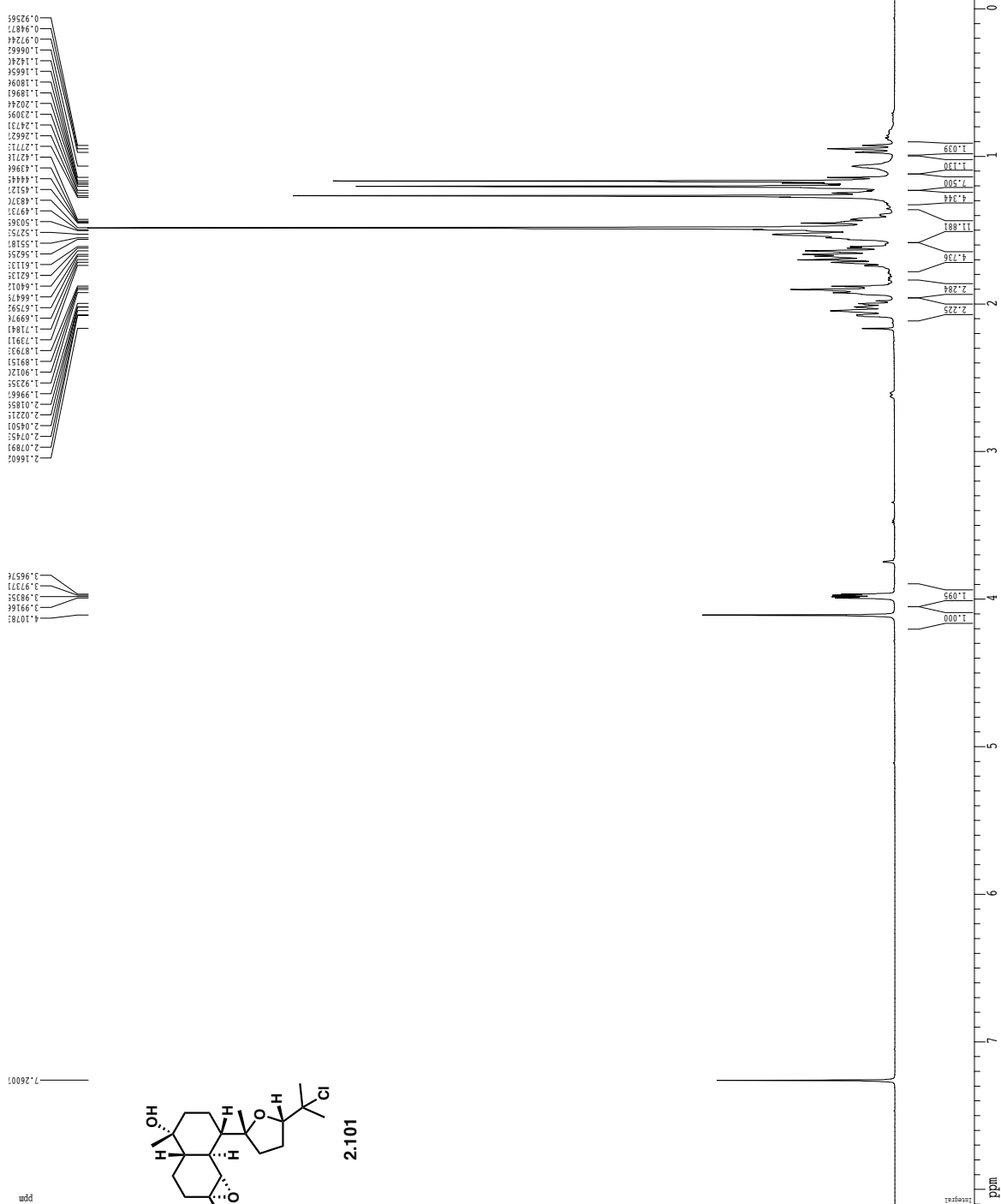
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



¹H spectrum

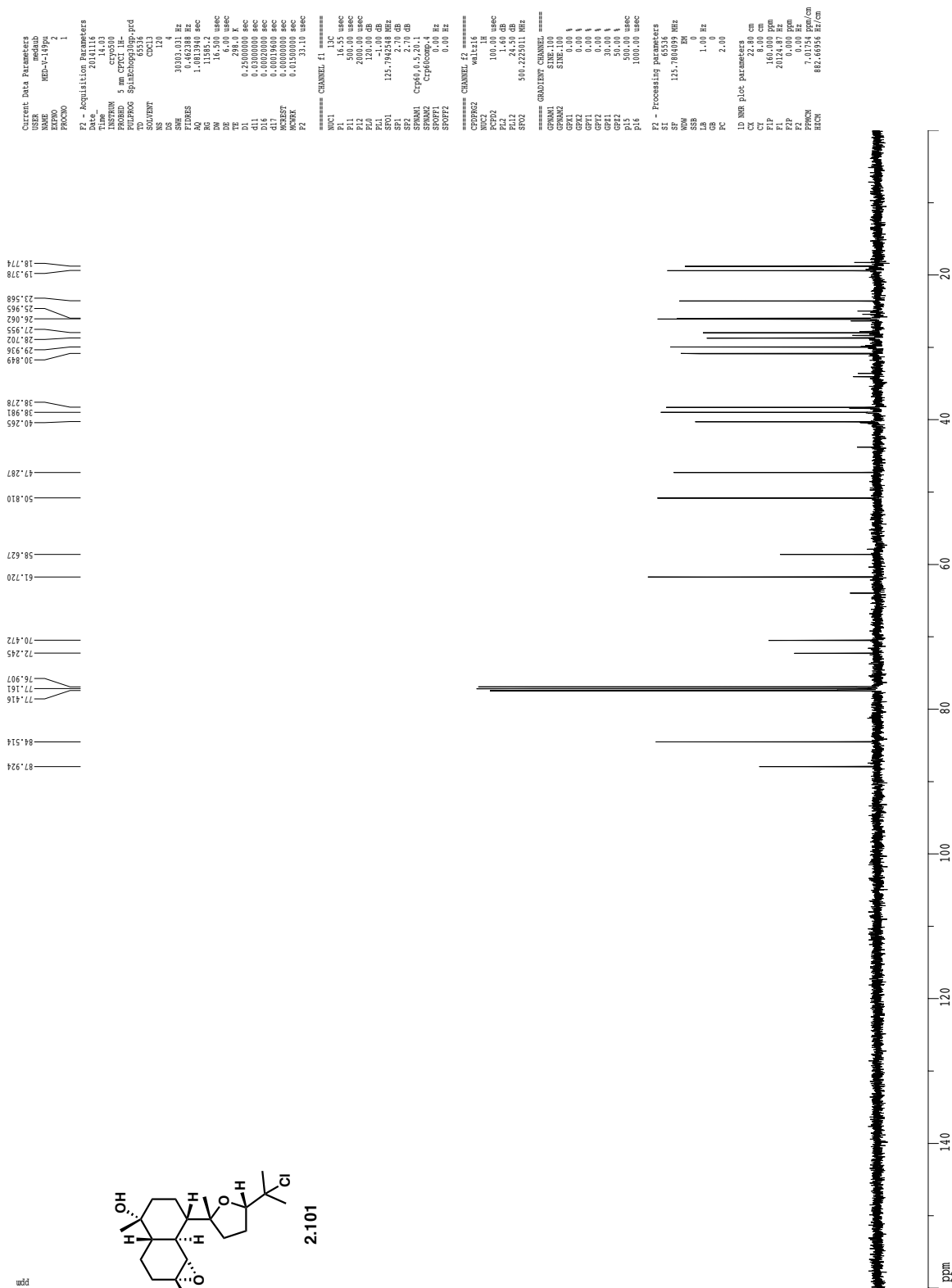


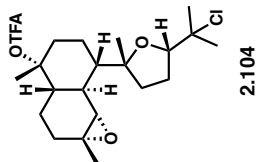
2.101



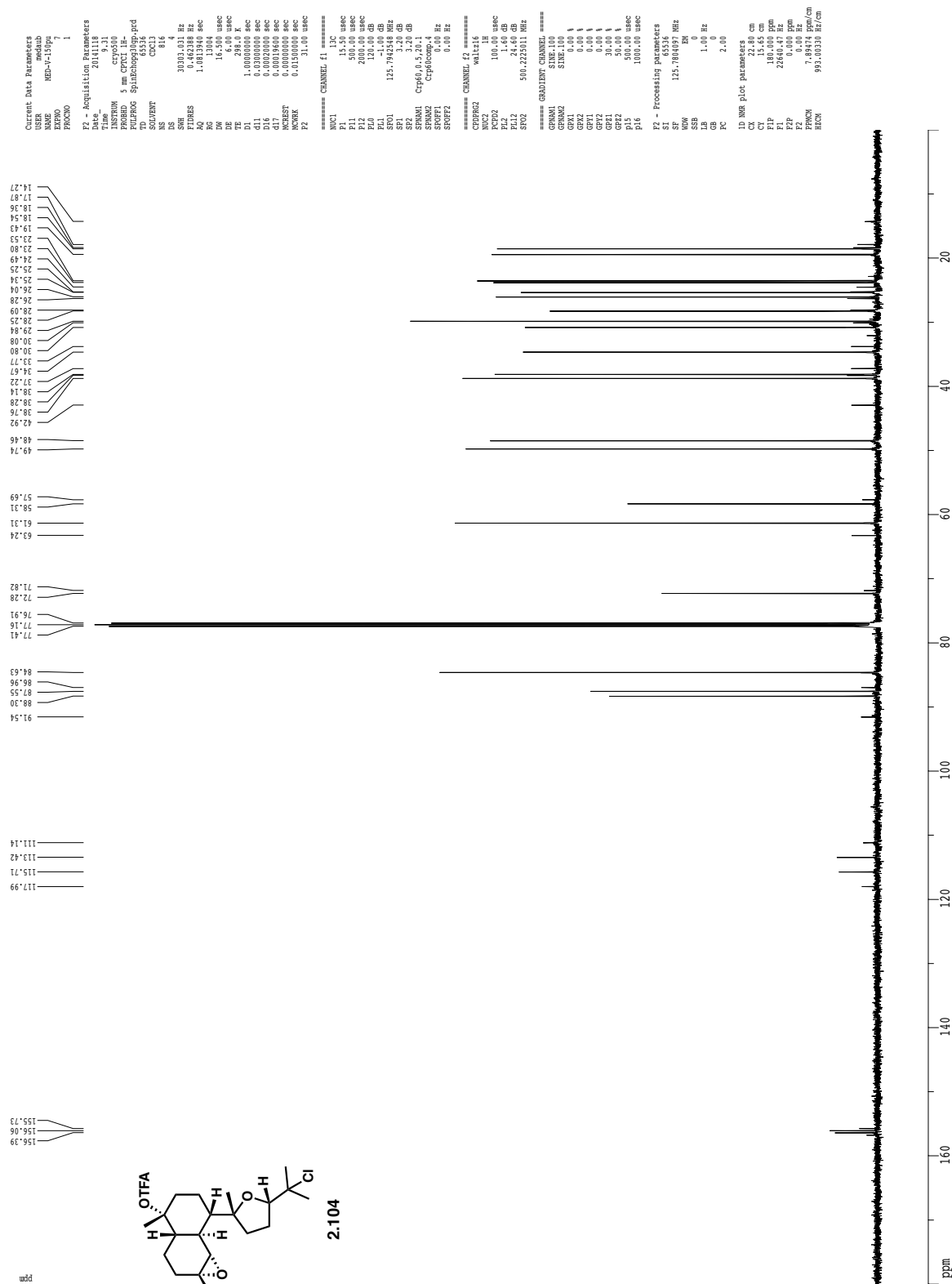
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 Date: 20141116
 Time: 14:00
 Name: MBD-J-14pp
 EXPNO: 1
 PROCNO: 1
 P2 - Acquisition Parameters
 Date: 20141116
 Time: 14:00
 Name: MBD-J-14pp
 EXPNO: 1
 PROCNO: 1
 PULPROG: zgpg30
 TD: 65536
 SOLVENT: CDCl3
 NS: 2
 DS: 2
 SWH: 8012.820 Hz
 FIDRES: 0.098943 Hz
 AQ: 5.1999645 sec
 RG: 4.5
 DW: 62.400 usec
 DE: 6.00 usec
 TE: 300.2 K
 D1: 0.10000000 sec
 MCREPT: 0.00000000 sec
 MCHNK: 0.01500000 sec
 ===== CHANNEL f1 =====
 NUC1: 1H
 P1: 7.50 usec
 PL1: 0.00 dB
 SFO1: 500.235015 MHz
 P2 - Processing parameters
 SI: 32768
 SF: 500.235015 MHz
 WDW: EM
 SSF: 0
 GB: 0.0 Hz
 CB: 5.00
 PC: 5.00
 ID NMR Plot parameters
 SI: 32768
 SF: 500.235015 MHz
 WDW: EM
 SSF: 0
 GB: 0.0 Hz
 CB: 5.00
 PC: 5.00
 FIDRES: 0.098943 Hz
 F1F2: 4051.78 Hz
 F2: 4051.78 Hz
 F2F1: -4051.78 Hz
 F2F2: -4051.78 Hz
 F2F1F2: 0.35965 ppm/cm
 F2F2F1: 179.90372 Hz/cm

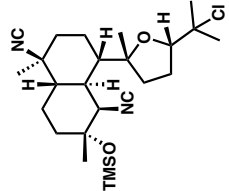
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

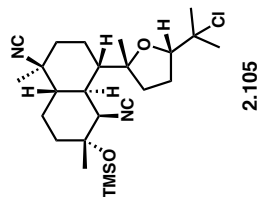




Z-restored spin-echo ¹³C spectrum with ¹H decoupling

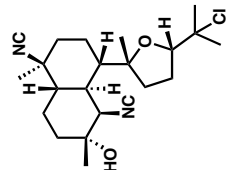




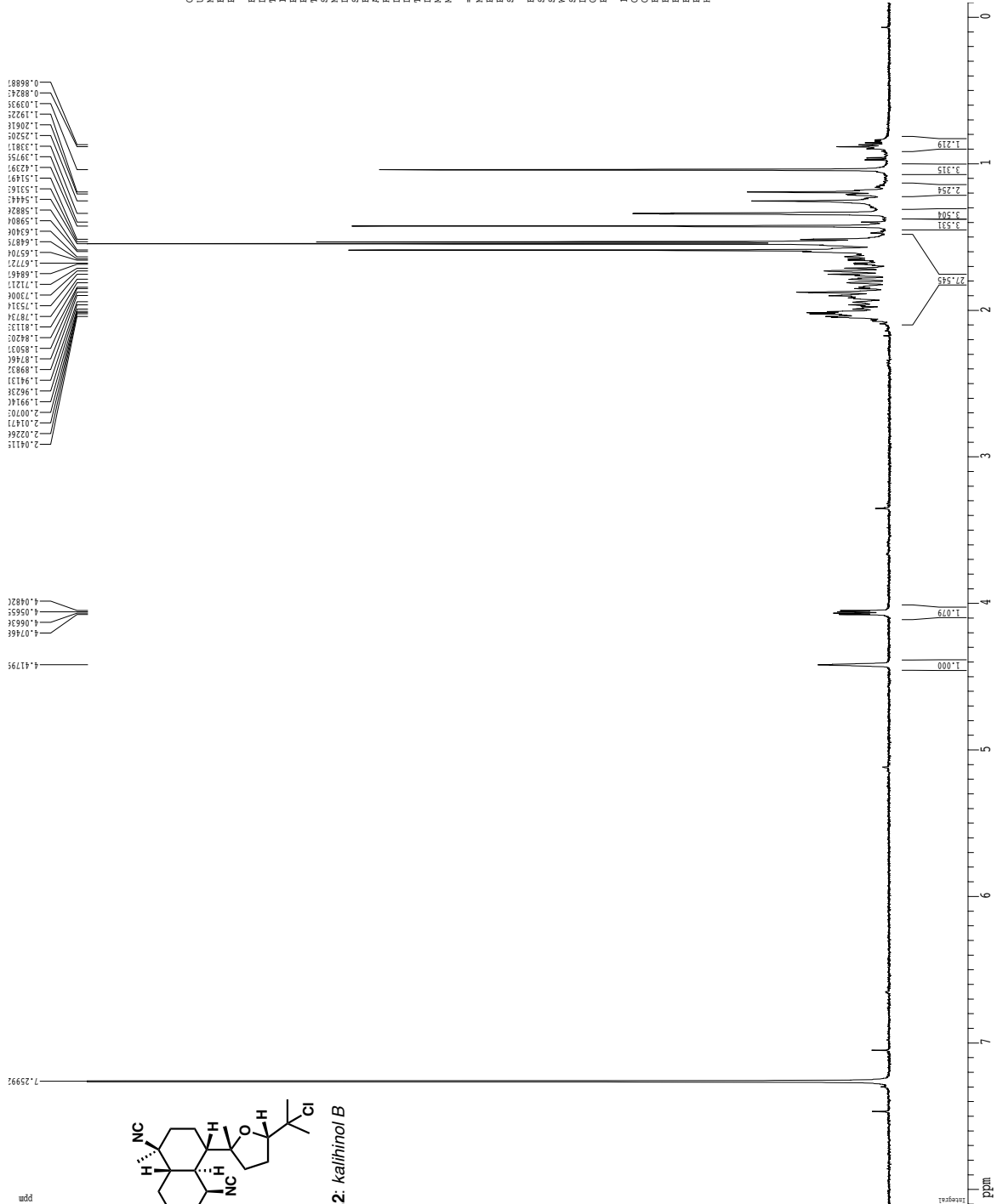


¹H spectrum

ppm

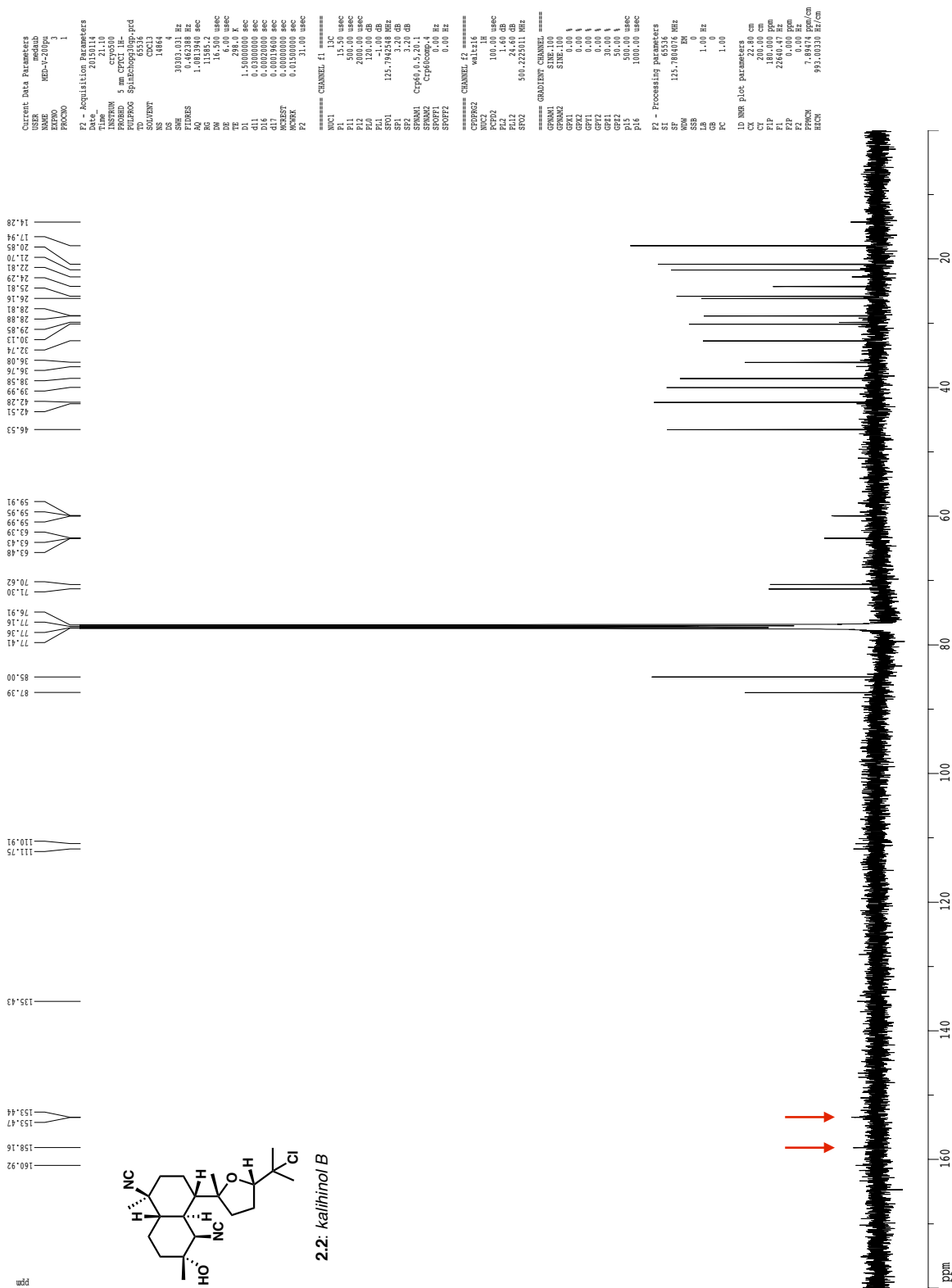


2,2:kalihinol B

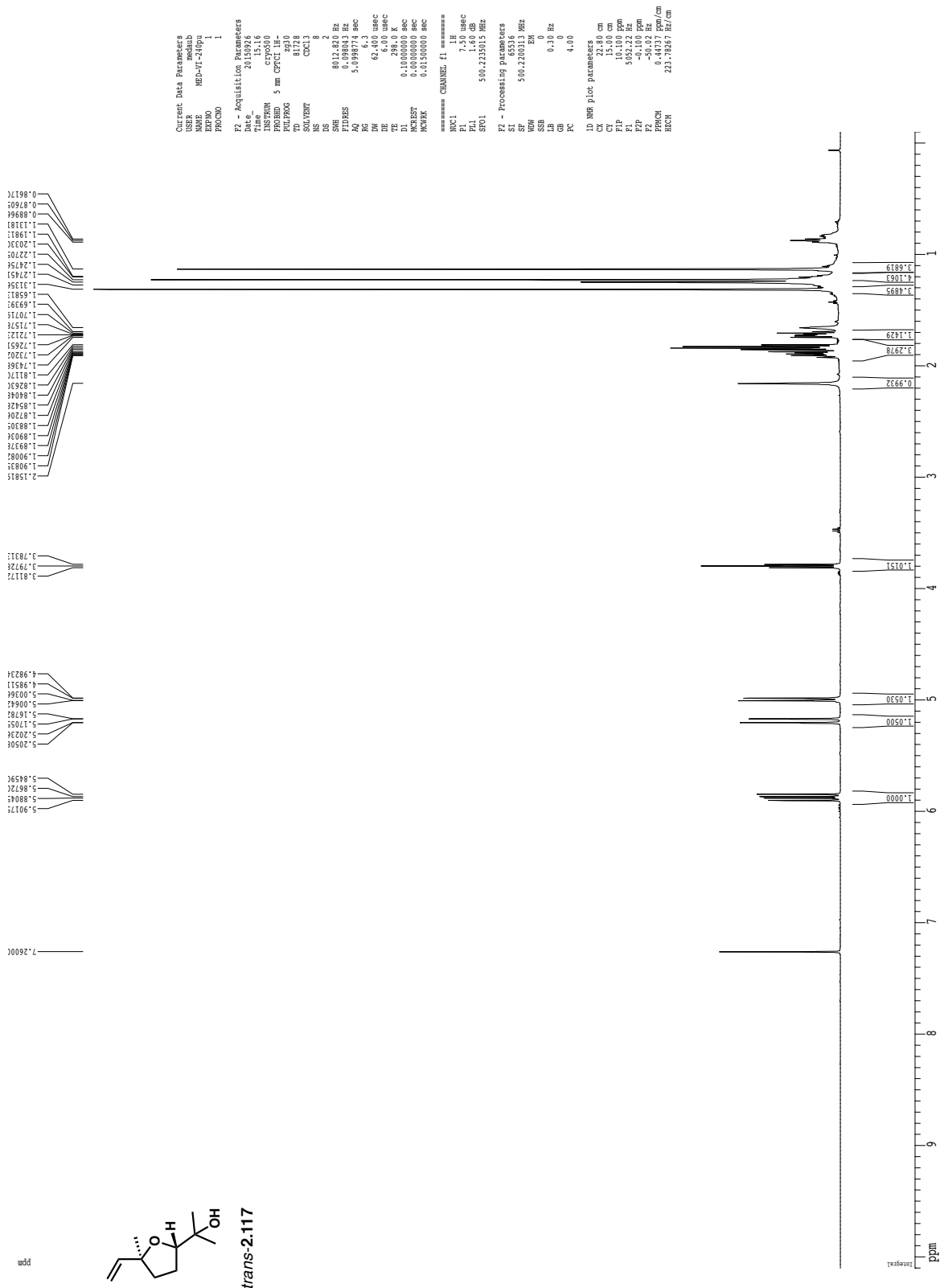


Current Data Parameters
 Name: 2,2:kalihinol B
 EXPNO: 2
 PROCNO: 1
 P2 - Acquisition Parameters
 Date_: 20150114
 Time: 21:07
 Operator: C. J. J.
 PROBHD: 5 mm CPYCI 1H
 PULPROG: zgpg30
 TD: 65536
 SOLVENT: CDCl3
 NS: 2048
 DS: 2
 SWH: 8012.823 Hz
 FIDRES: 0.098443 Hz
 AQ: 5.1399445 sec
 RG: 327.5
 DW: 62.400 usec
 DE: 6.00 usec
 TE: 300.2 K
 D1: 0.10000000 sec
 MCREPT: 0.0000000 sec
 MCNMR: 0.0150000 sec
 ===== CHANNEL f1 =====
 NUC1: 1H
 P1: 7.50 usec
 PL1: 0.00 dB
 SFO1: 500.235015 MHz
 P2 - Processing parameters
 SI: 32768
 SF: 500.235015 MHz
 WDW: EM
 SSF: 0
 GB: 0.0 Hz
 CB: 4.00
 PC: 4.00
 ID NMR Plot parameters
 SI: 32768
 SF: 500.235015 MHz
 WDW: EM
 SSF: 0
 GB: 0.0 Hz
 CB: 4.00
 PC: 4.00

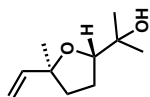
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



¹H spectrum



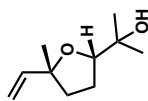
Current Data Parameters	
NAME	WATERS
EXPNO	2
PROCNO	1
F2 - Acquisition Parameters	
Date_	2015026
Time	15:59
INSTRUM	CPD100
PROBHD	5 mm CPYC1 1H
PULPROG	zgpg30
PCPDPRG2	zgpg30
SOLVENT	CDCl3
NS	104
DS	4
SWH	10303.001 Hz
FIDRES	0.462308 Hz
AQ	1.0813940 sec
RG	118.822
DW	118.822 usec
DE	6.00 usec
TE	298.0 K
D1	0.24000000 sec
d11	0.63000000 sec
D16	0.0020000 sec
d17	0.0039000 sec
DELTA	0.0039000 sec
NUC1	13C
NUC2	13C
NUC3	13C
NUC4	13C
NUC5	13C
NUC6	13C
NUC7	13C
NUC8	13C
NUC9	13C
NUC10	13C
NUC11	13C
NUC12	13C
NUC13	13C
NUC14	13C
NUC15	13C
NUC16	13C
NUC17	13C
NUC18	13C
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NUC140	13C
NUC141	13C
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NUC145	13C
NUC146	13C
NUC147	13C
NUC148	



trans-2.117

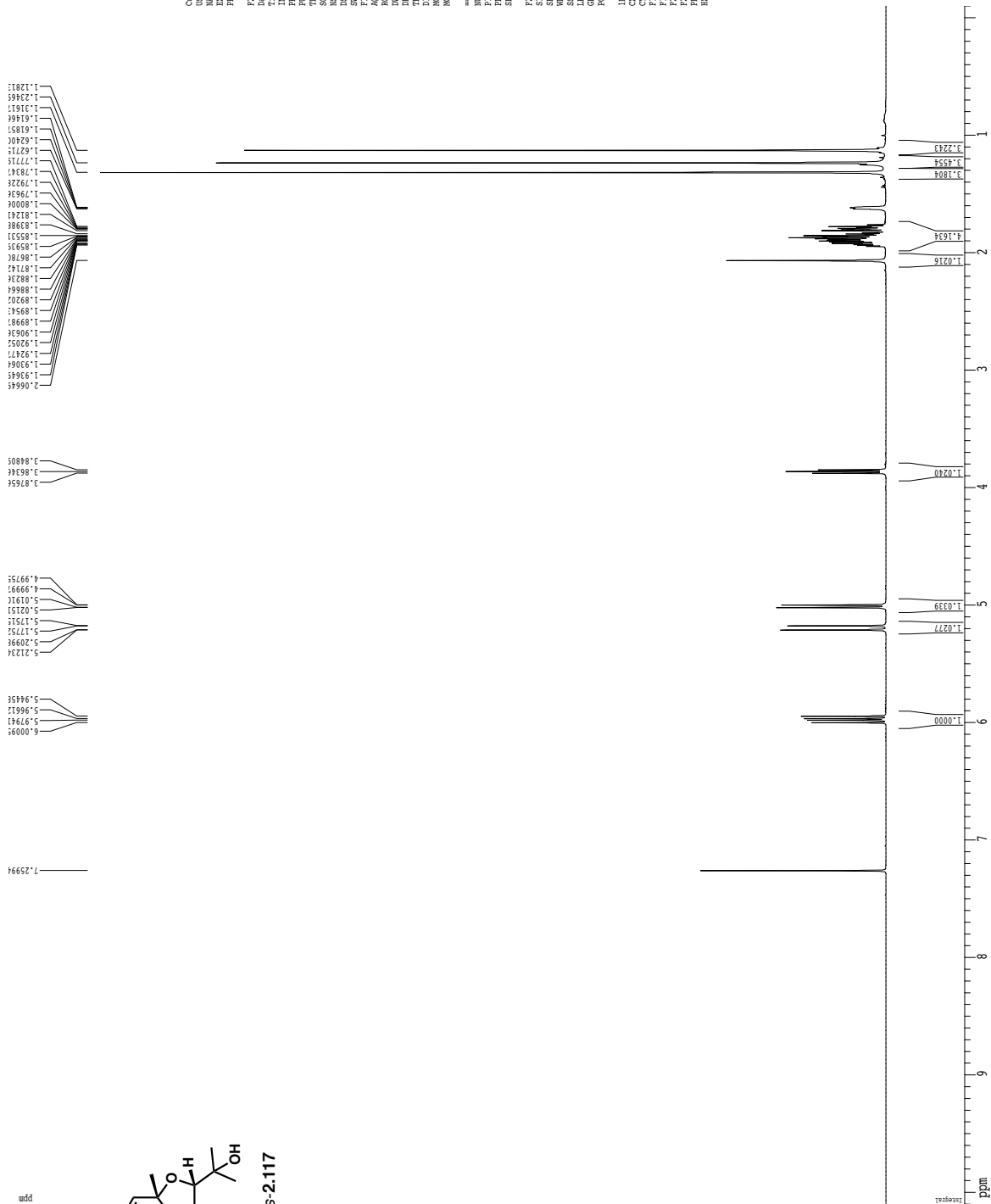
¹H spectrum

ppm

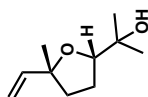
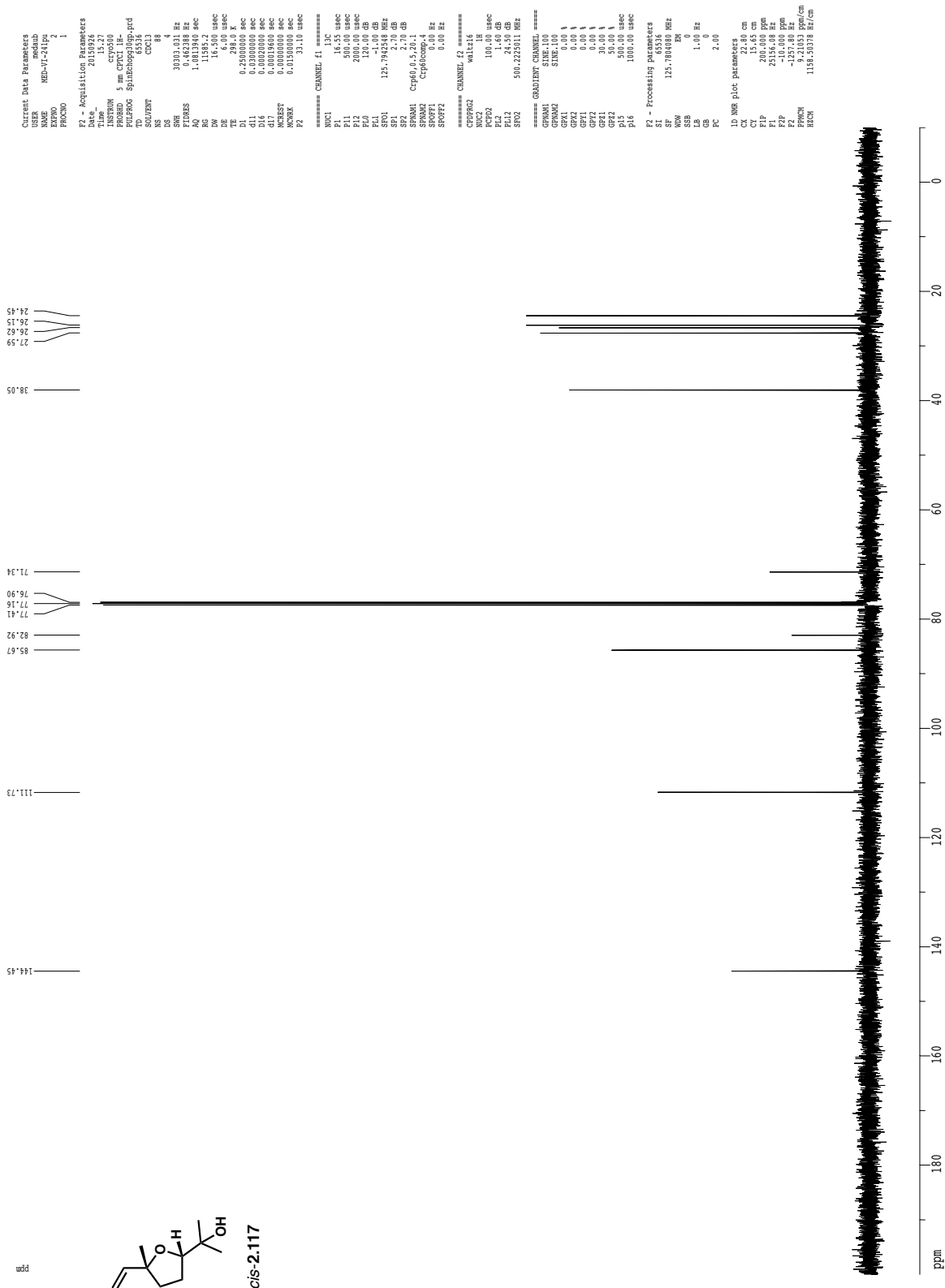


cis-2.117

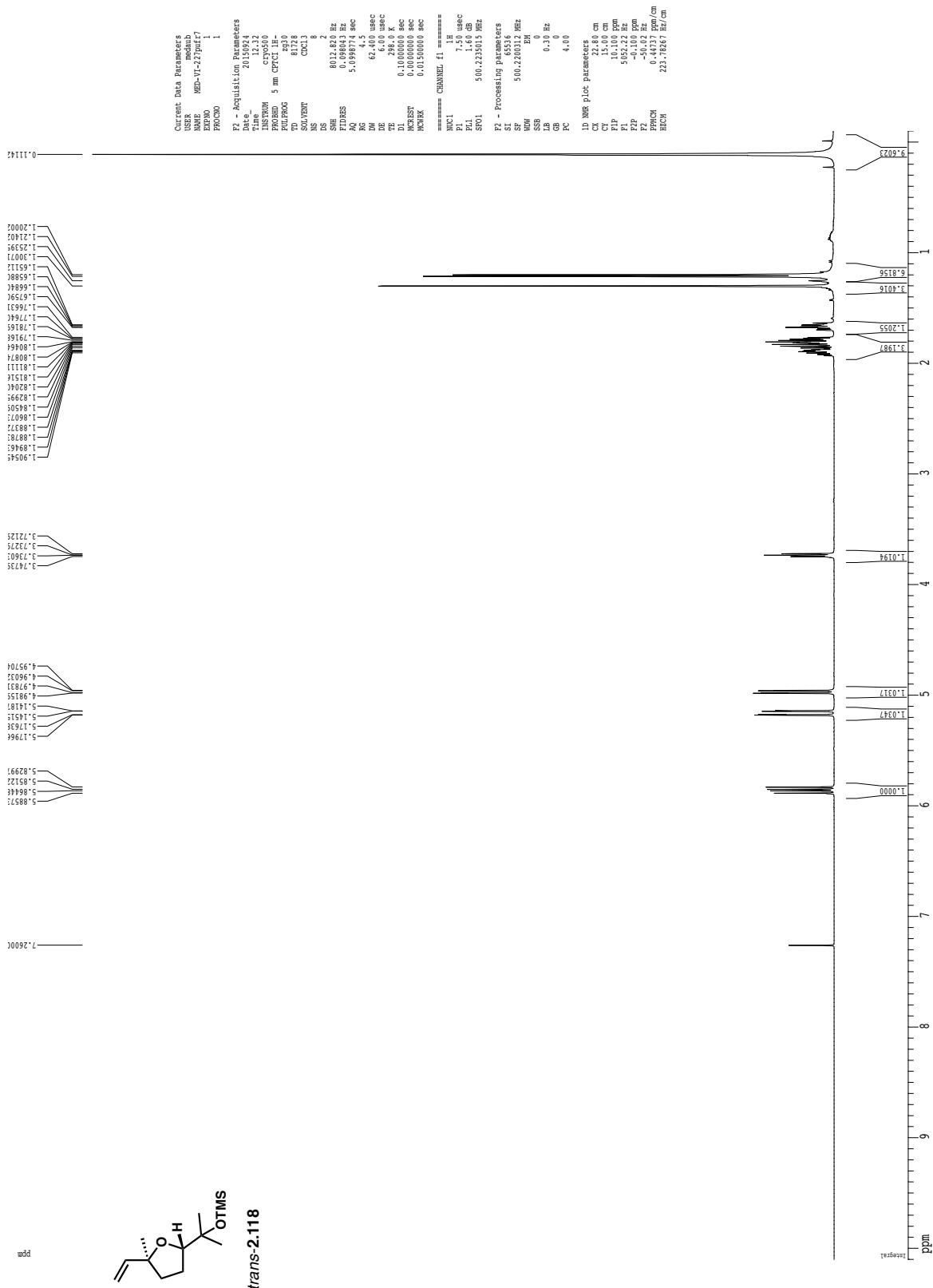
Current Data Parameters
 Date: 20150926
 Time: 15:25
 Name: *cis*-2.117
 EXPNO: 1
 PROCNO: 1
 P2 - Acquisition Parameters
 Date: 20150926
 Time: 15:25
 Name: *cis*-2.117
 EXPNO: 1
 PROCNO: 1
 PULPROG: zgpg30
 TD: 65536
 SOLVENT: CDCl₃
 NS: 2
 DS: 2
 SWH: 8012.820 Hz
 FIDRES: 0.098943 Hz
 AQ: 5.1939611 sec
 RG: 7.1
 DW: 62.400 usec
 DE: 6.00 usec
 TE: 300.2 K
 D1: 0.10000000 sec
 MCHRG: 0.0000000 sec
 MCHRG: 0.01500000 sec
 ===== CHANNEL f1 =====
 NUC1: ¹H
 P1: 7.50 usec
 PL1: 0.00 dB
 SFO1: 500.235015 MHz
 P2 - Processing parameters
 SI: 32768
 SF: 500.235015 MHz
 WDW: EM
 SSB: 0
 AB: 0.10 Hz
 GB: 0.00
 PC: 4.00
 ID: NMR Plot parameters
 SI: 32768
 SF: 500.235015 MHz
 WDW: EM
 SSB: 0
 AB: 0.10 Hz
 GB: 0.00
 PC: 4.00
 FID: 15.00 cm
 F1P: 10.100 ppm
 F2: 592.22 Hz
 F2P: 10.100 ppm
 F3: -50.02 Hz
 F3P: 0.44137 ppm/cm
 HZCM: 223.76267 Hz/cm

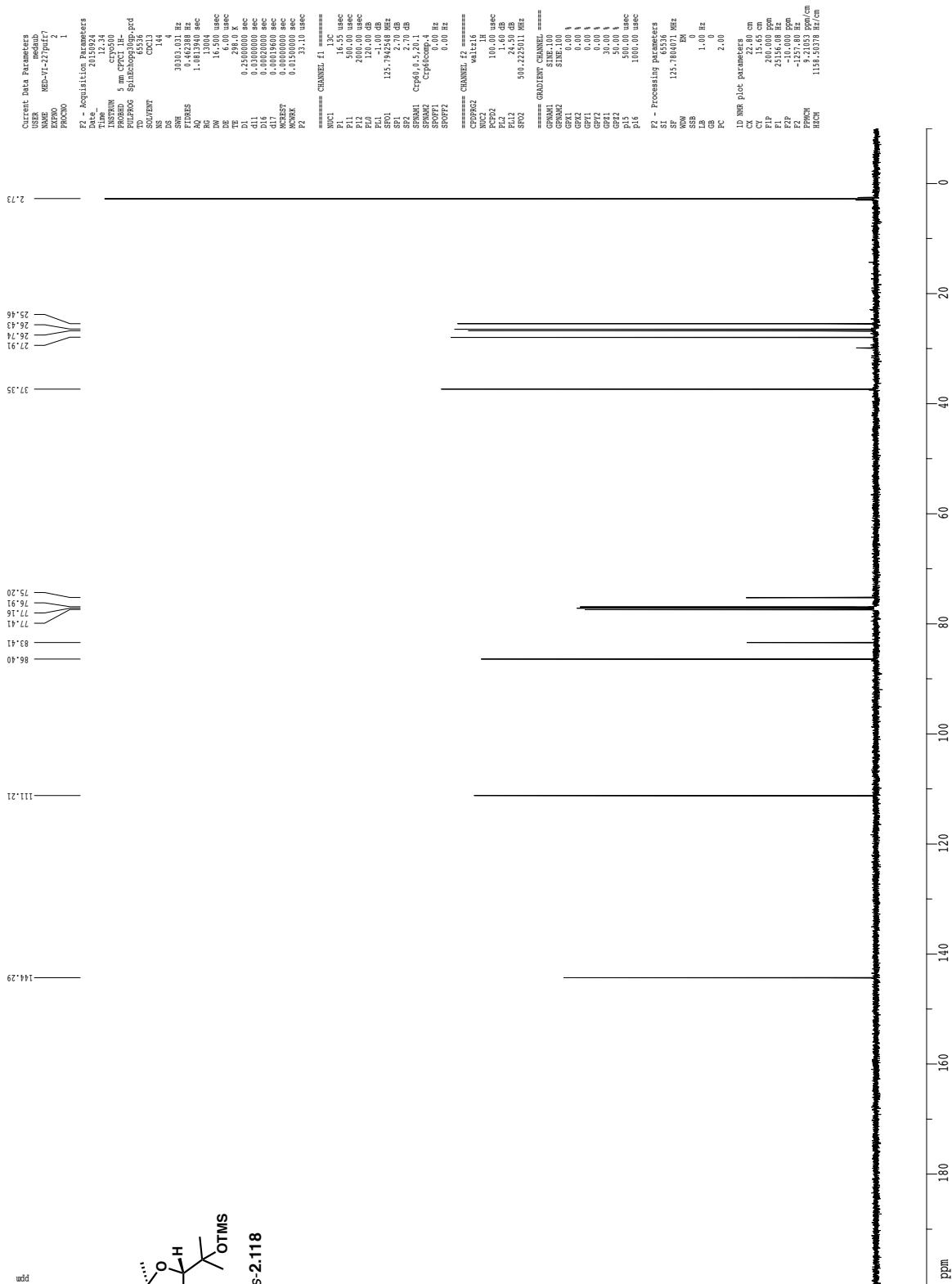
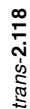


Z-restored spin-echo 13C spectrum with 1H decoupling

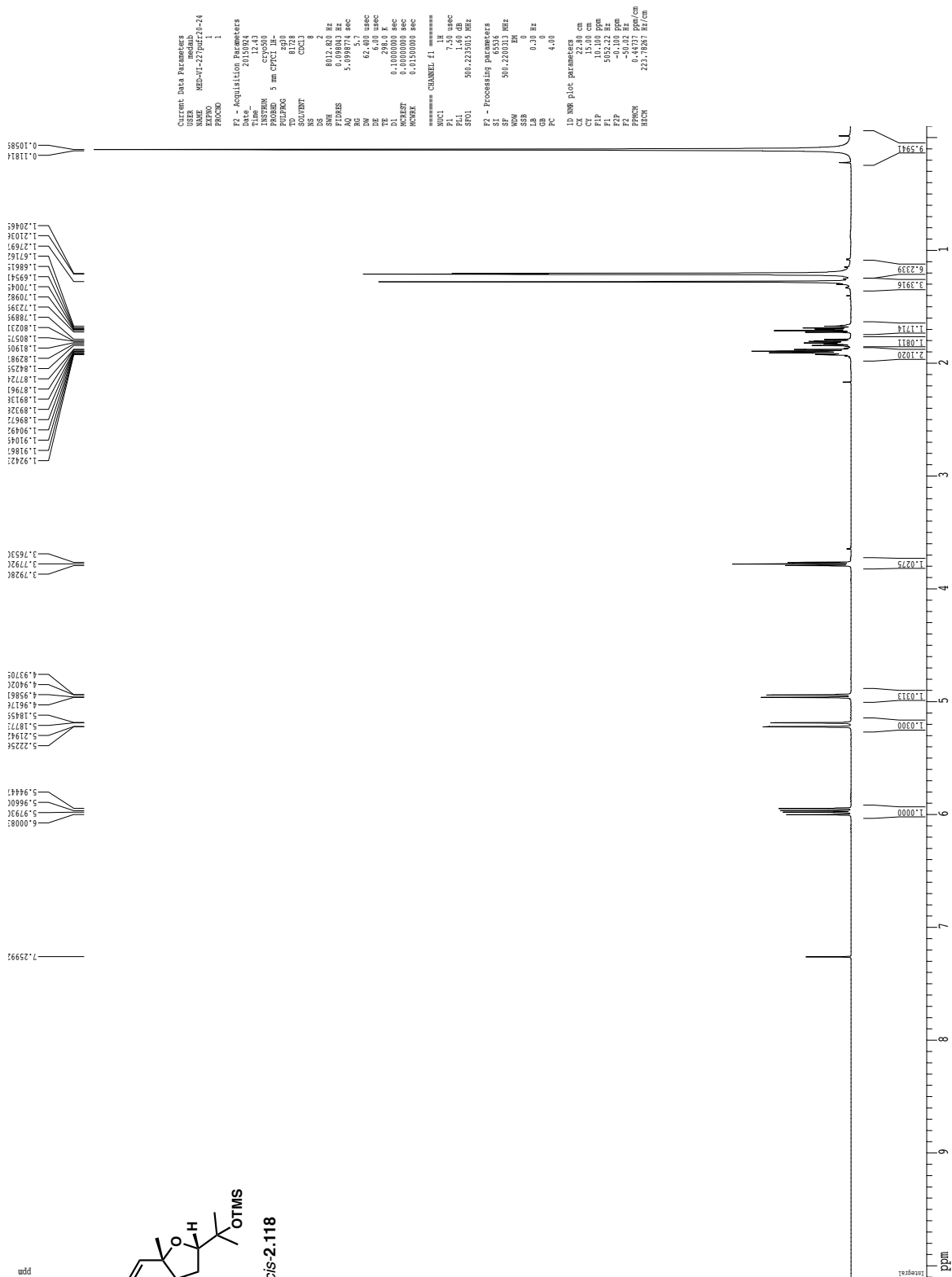


cis-2.117

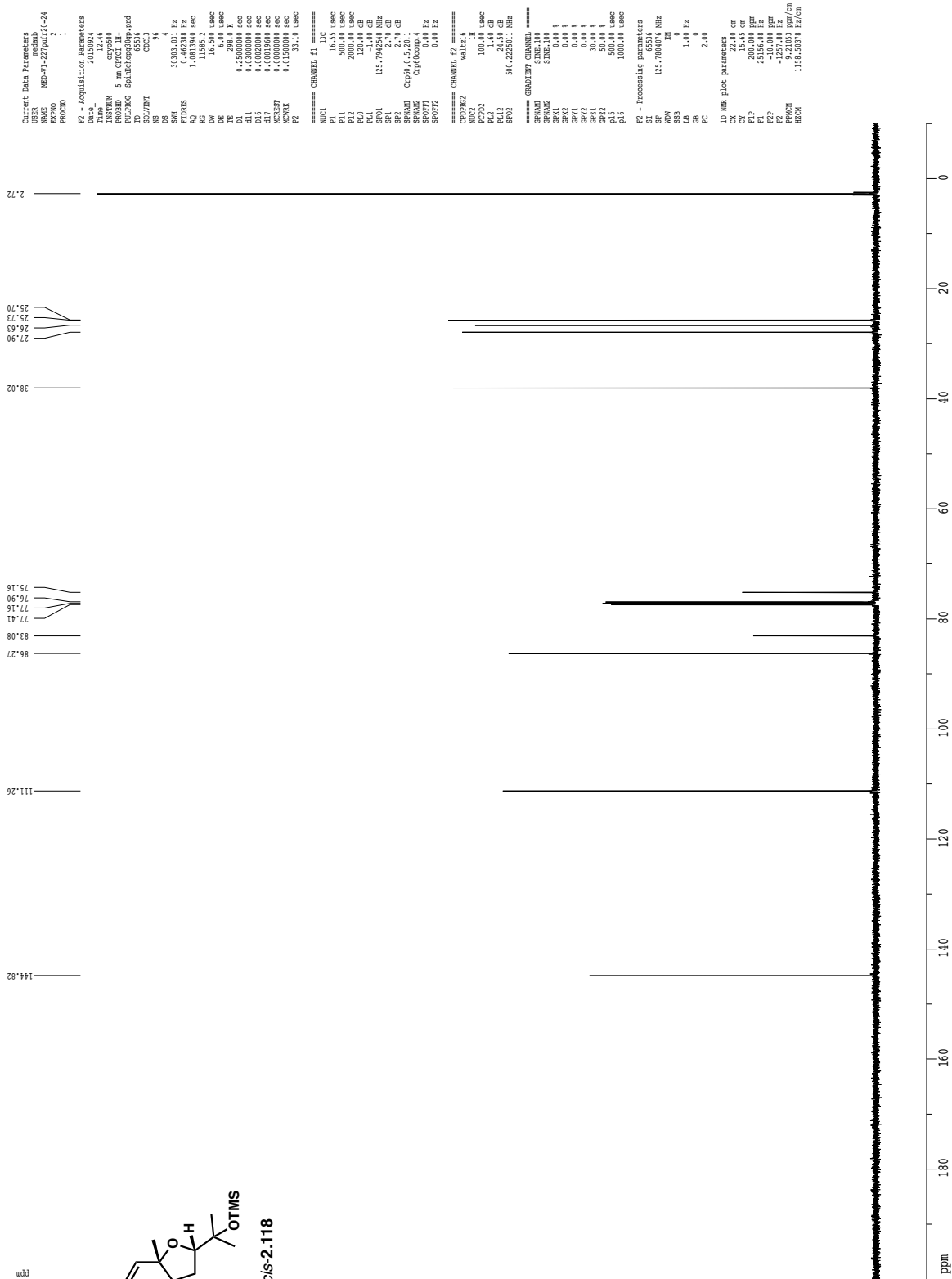




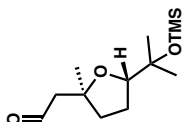
¹H spectrum



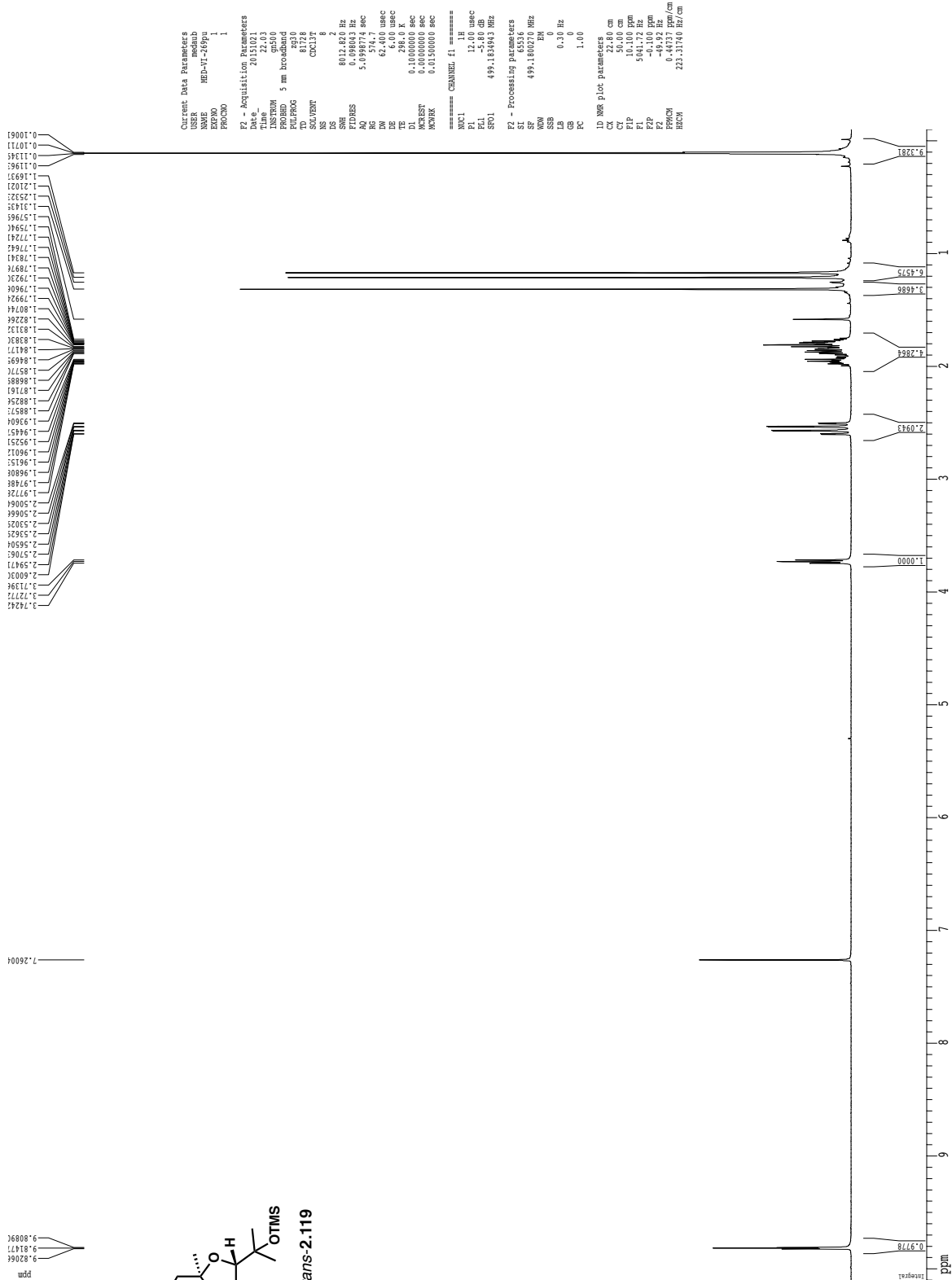
Z-restored spin-echo 13C spectrum with 1H decoupling



¹H spectrum

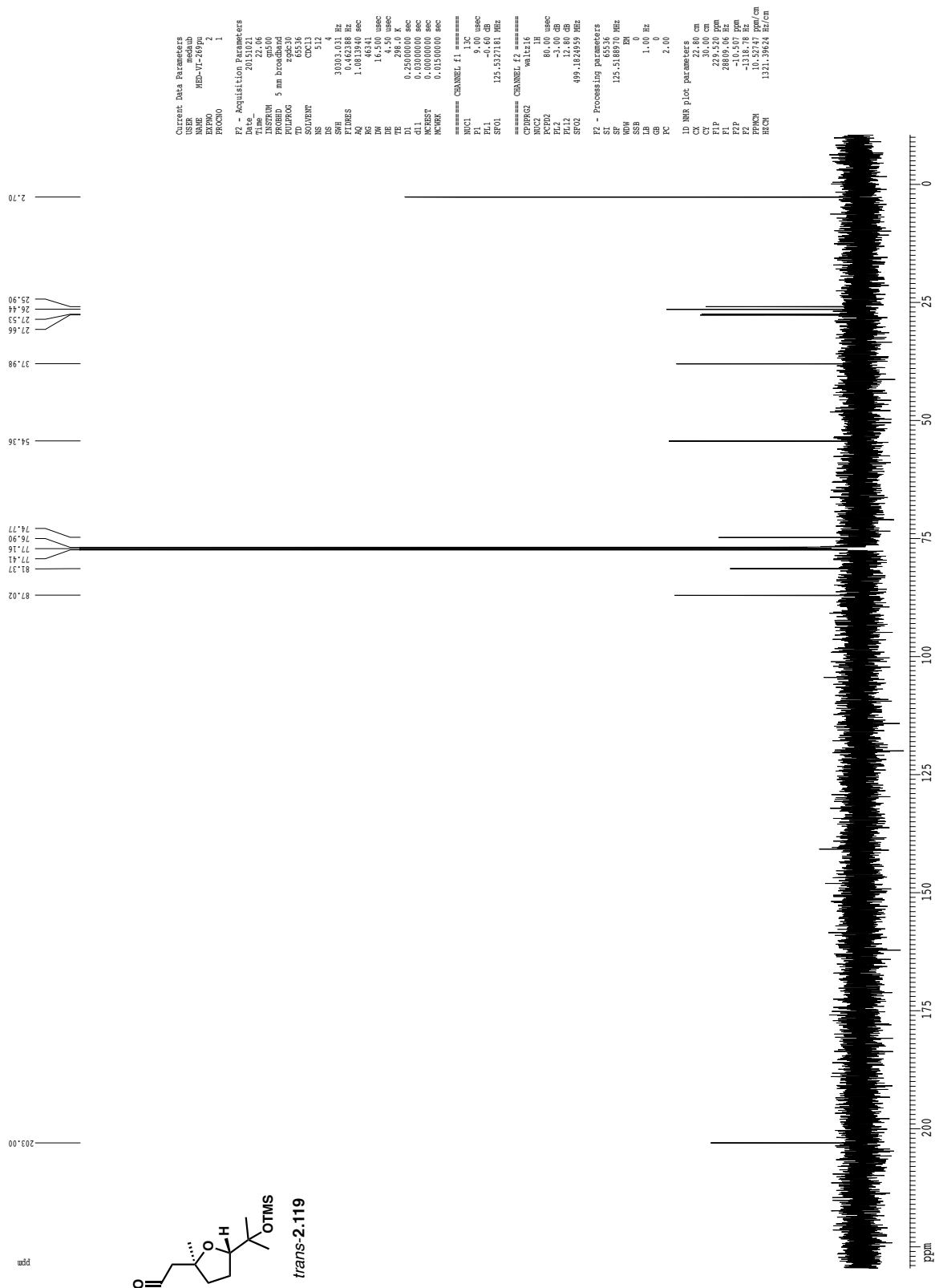


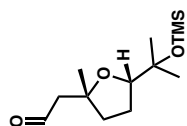
trans-2.119



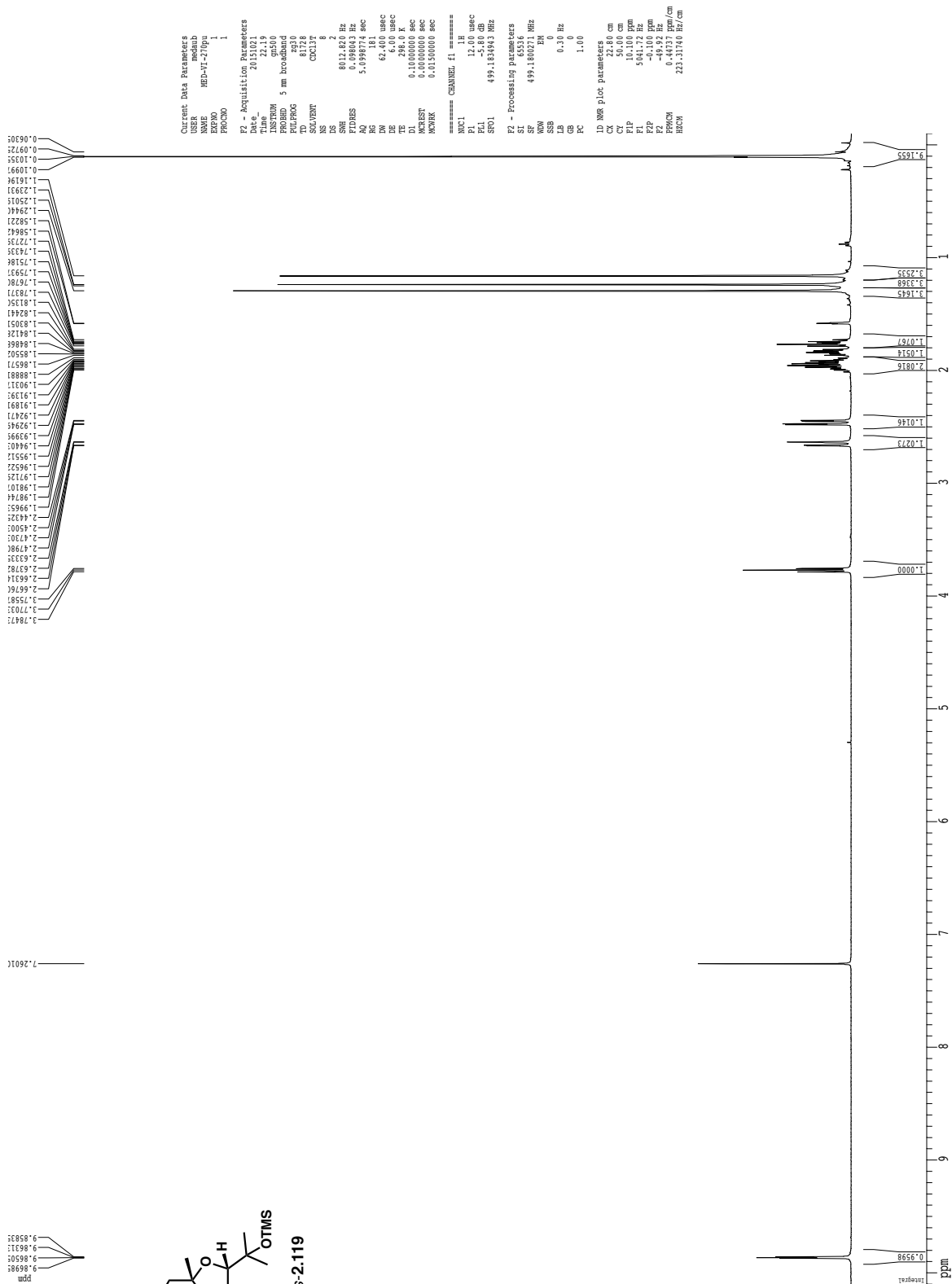
Current Data Parameters
 USER modhub
 METHOD 1D-1H
 EXPNO 1
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 2015101
 Time 22.03
 INSTRUM gms50
 PROBRG 5 mm bbo5mm30
 PULPROG zgpg30
 TO 81728
 SOLVENT CDCl3
 NS 8
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.098043 Hz
 AQ 5.0998774 sec
 RG 655.5
 DW 42.400 usec
 DE 6.00 usec
 TE 298.2 K
 T1 0.10000000 sec
 T1RHO 0.00000000 sec
 ACQTEST 0.00000000 sec
 MONPRG 0.01500000 sec
 ===== CHANNEL f1 =====
 NUC1 1H
 P1 12.00 usec
 PL1 -5.80 dB
 SFO1 499.135994 MHz
 F2 - Processing parameters
 SI 6554
 SF 499.135994 MHz
 NS 8
 DS 2
 SW 8012.820 Hz
 LB 0.30 Hz
 GB 0
 CB 0
 PC 1.00
 ID NMR plot parameters
 CX 27.80 cm
 CY 27.80 cm
 FID 10.100 ppm
 F1 5041.72 Hz
 F2 -4.100 ppm
 F3 0.000 ppm
 FWHM 0.44735 ppm/cm
 HCM 223.31740 Hz/cm

¹³C spectrum with ¹H decoupling

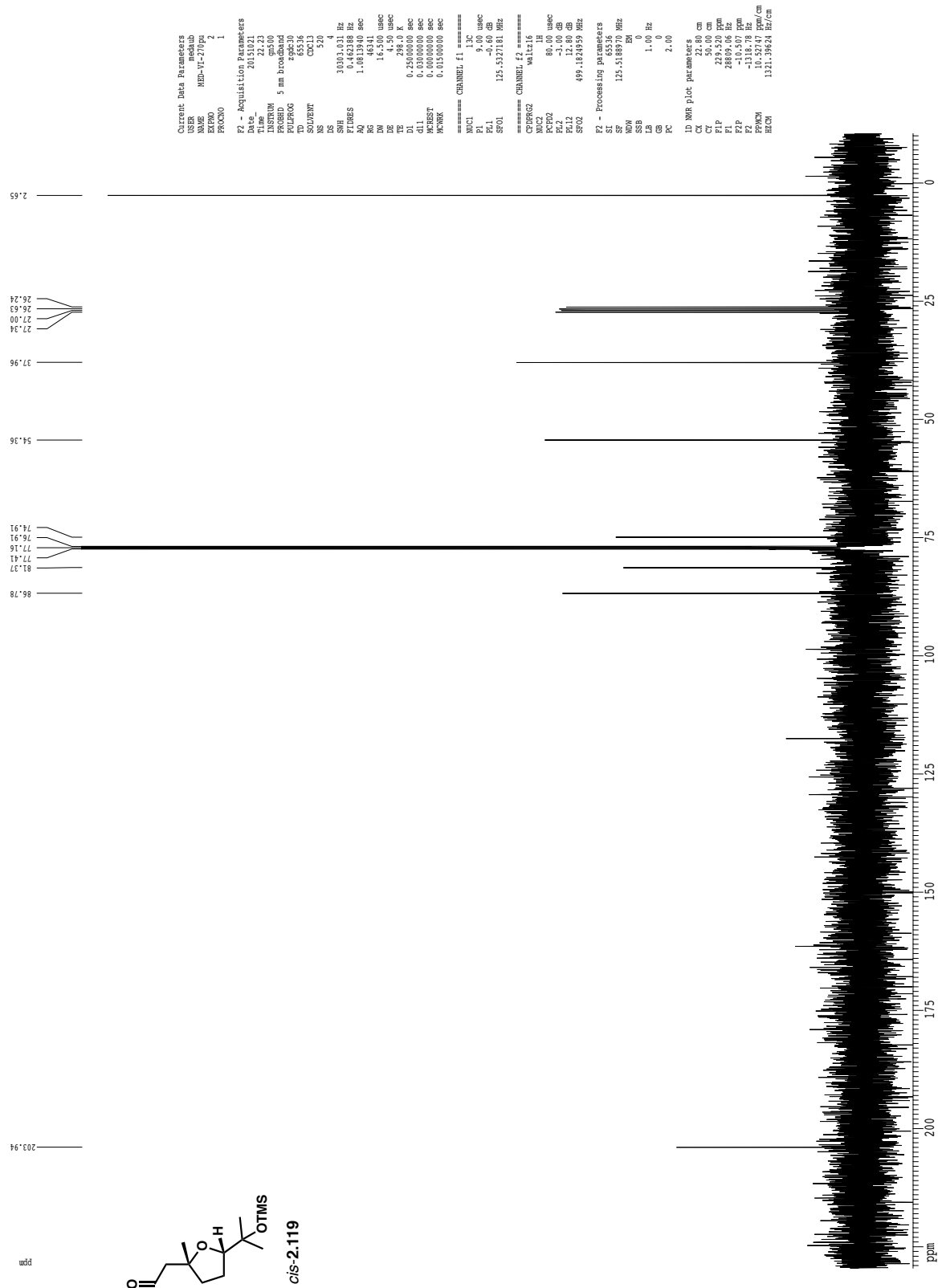


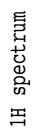


***cis*-2.119**

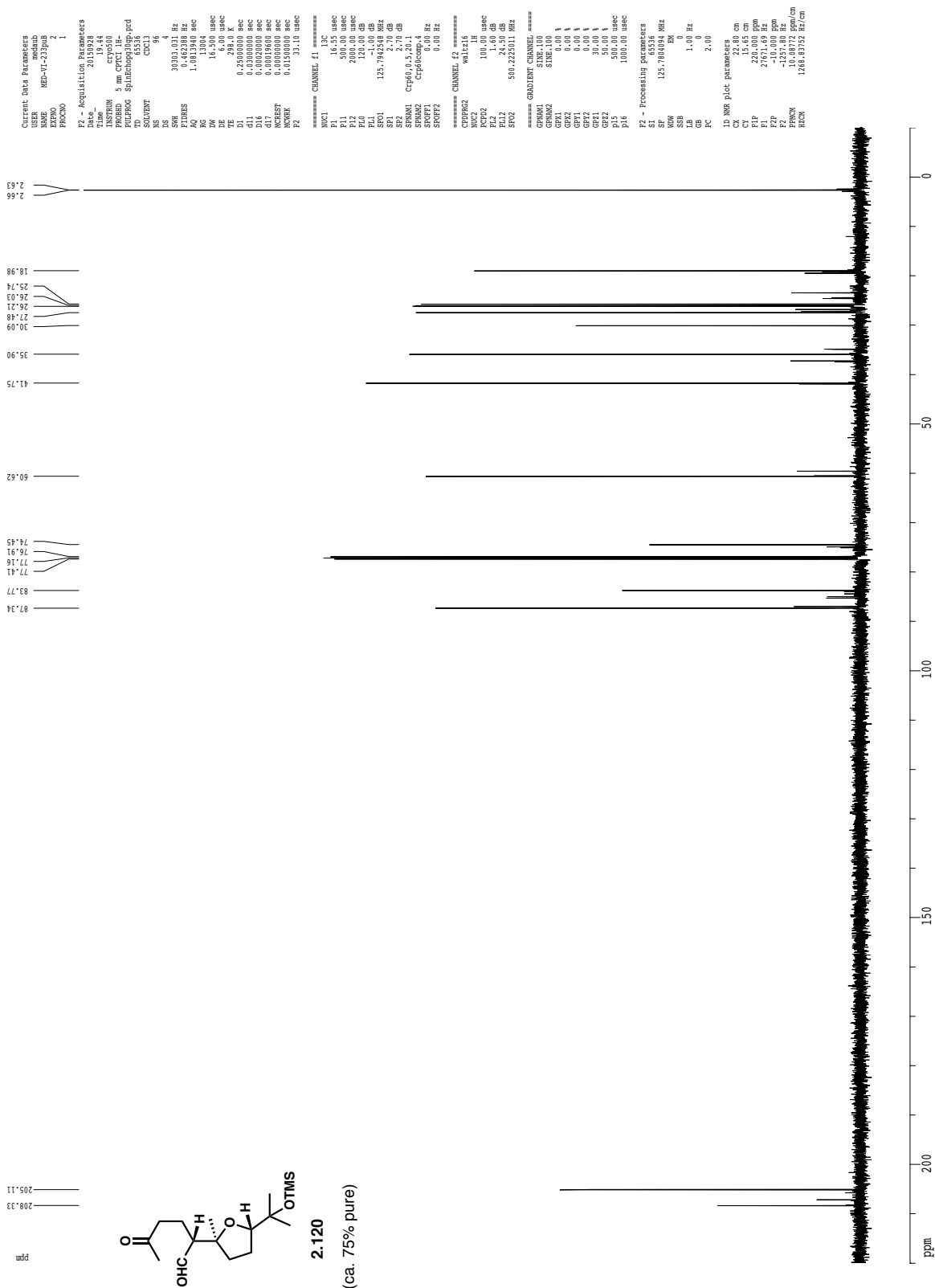


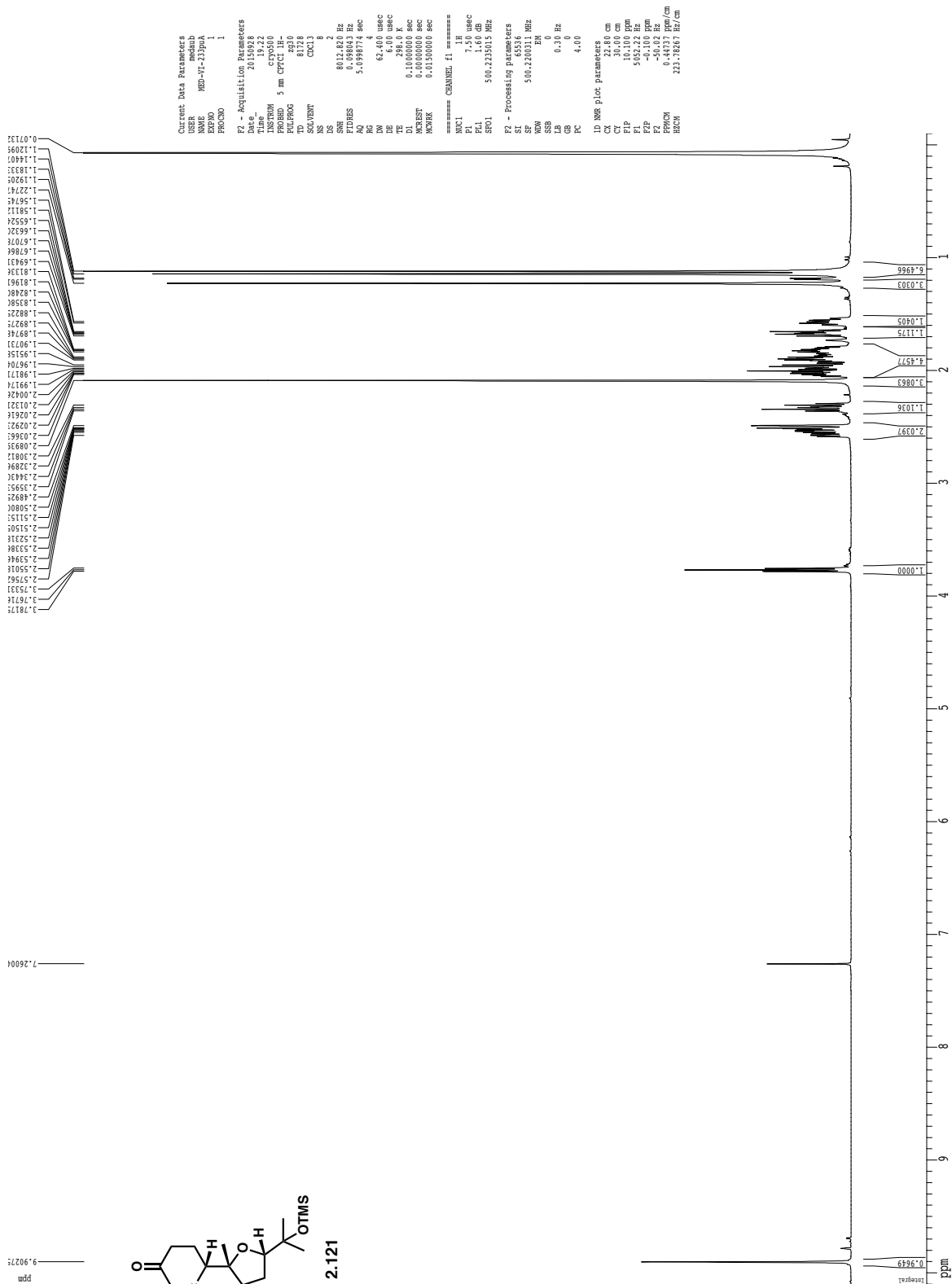
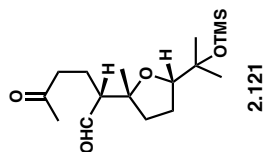
¹³C spectrum with ¹H decoupling



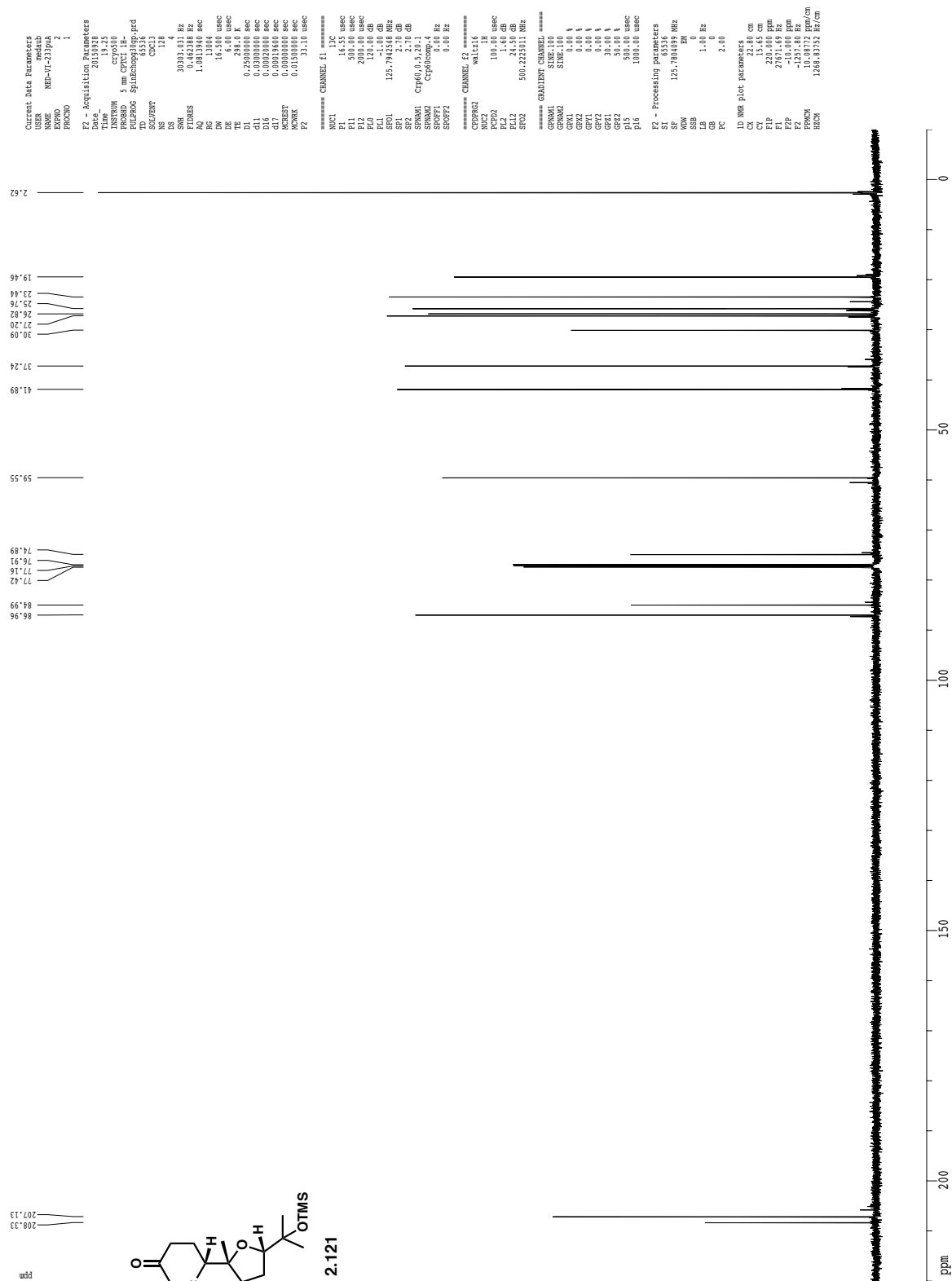


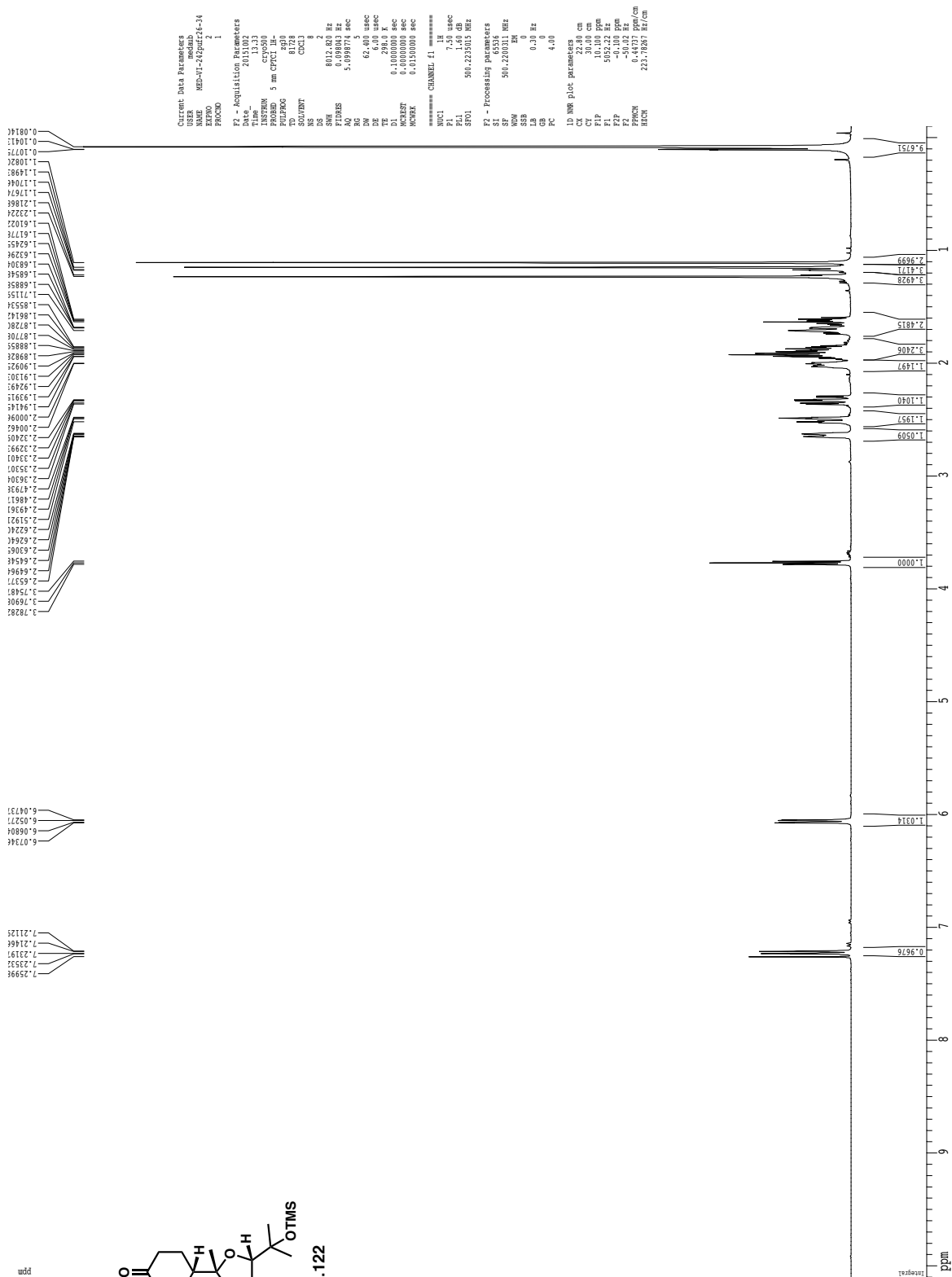
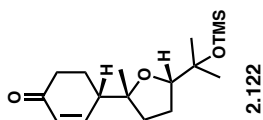
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

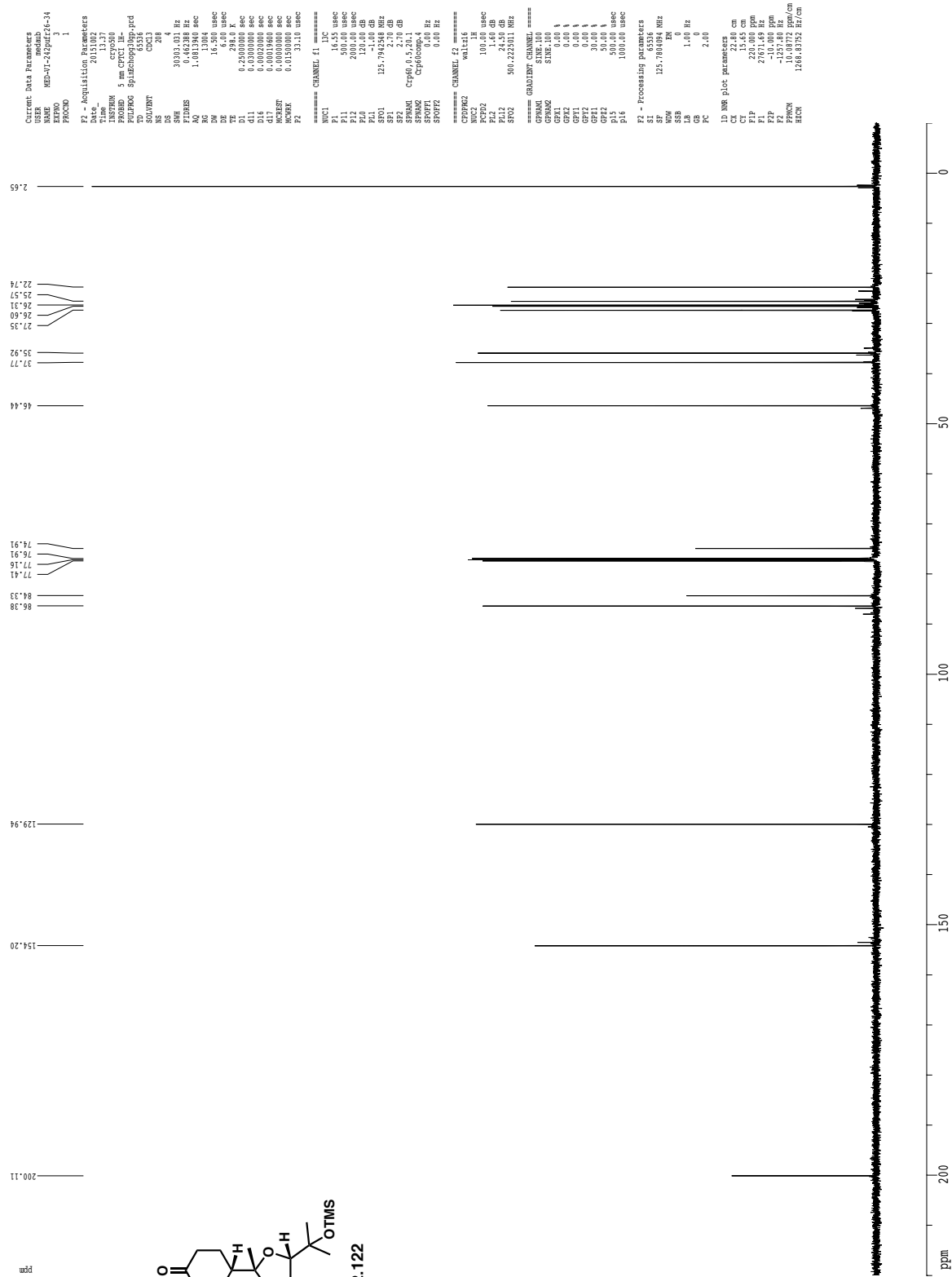
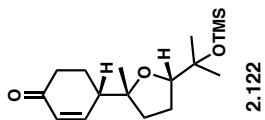


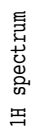


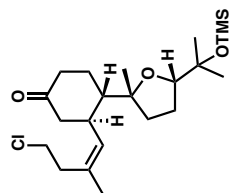
Z-restored spin-echo ^{13}C spectrum with ^1H decoupling

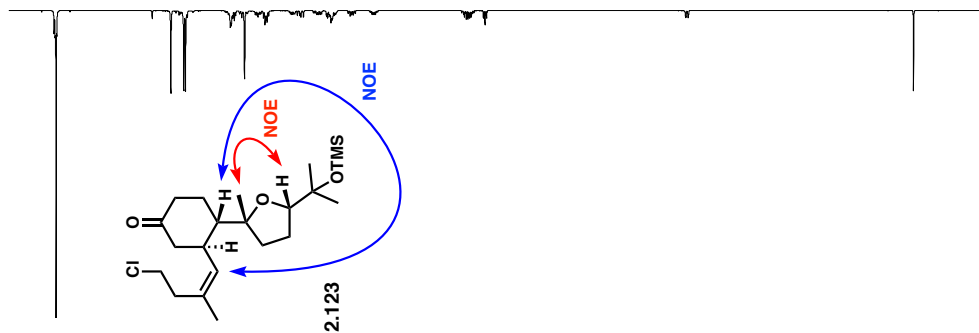
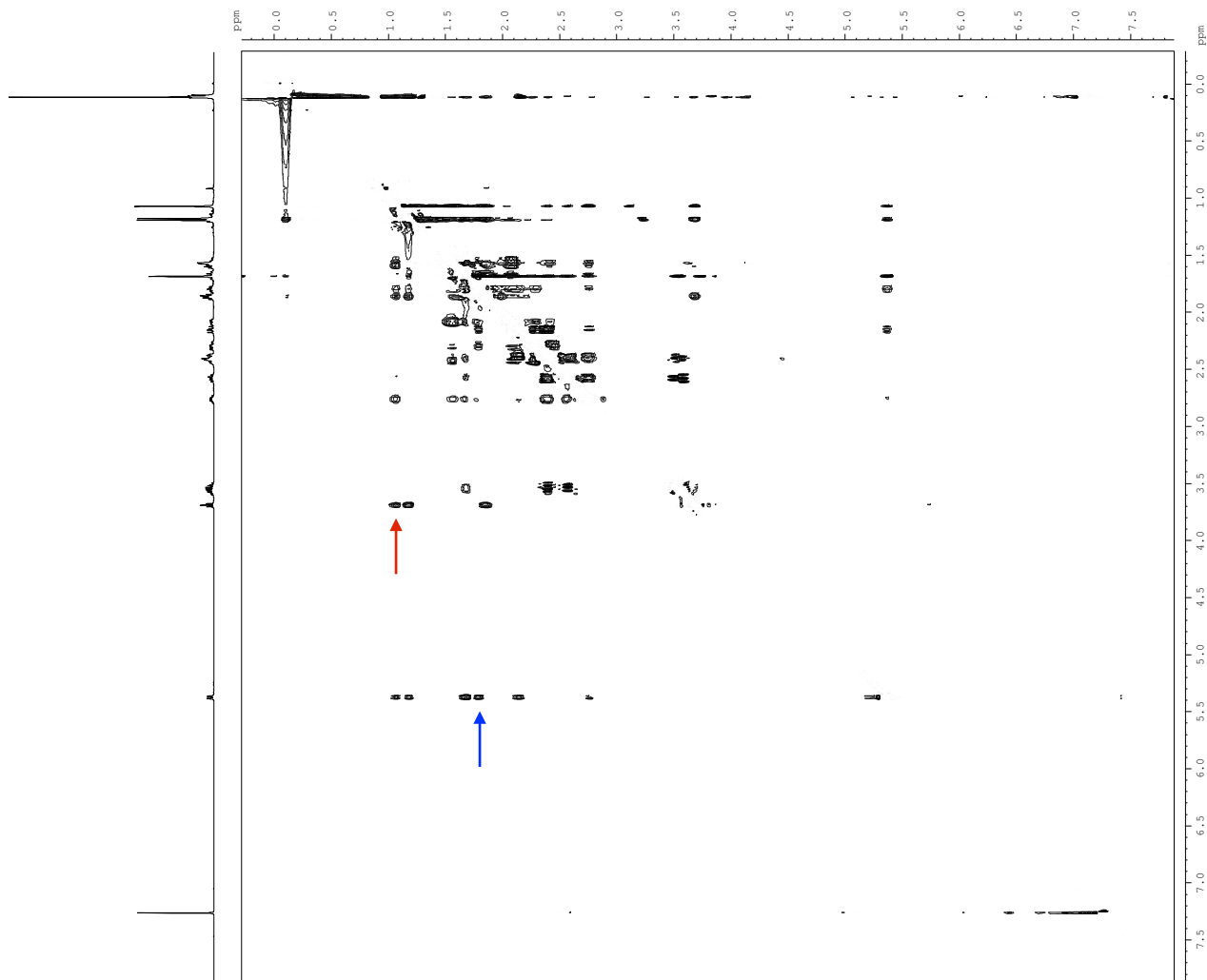




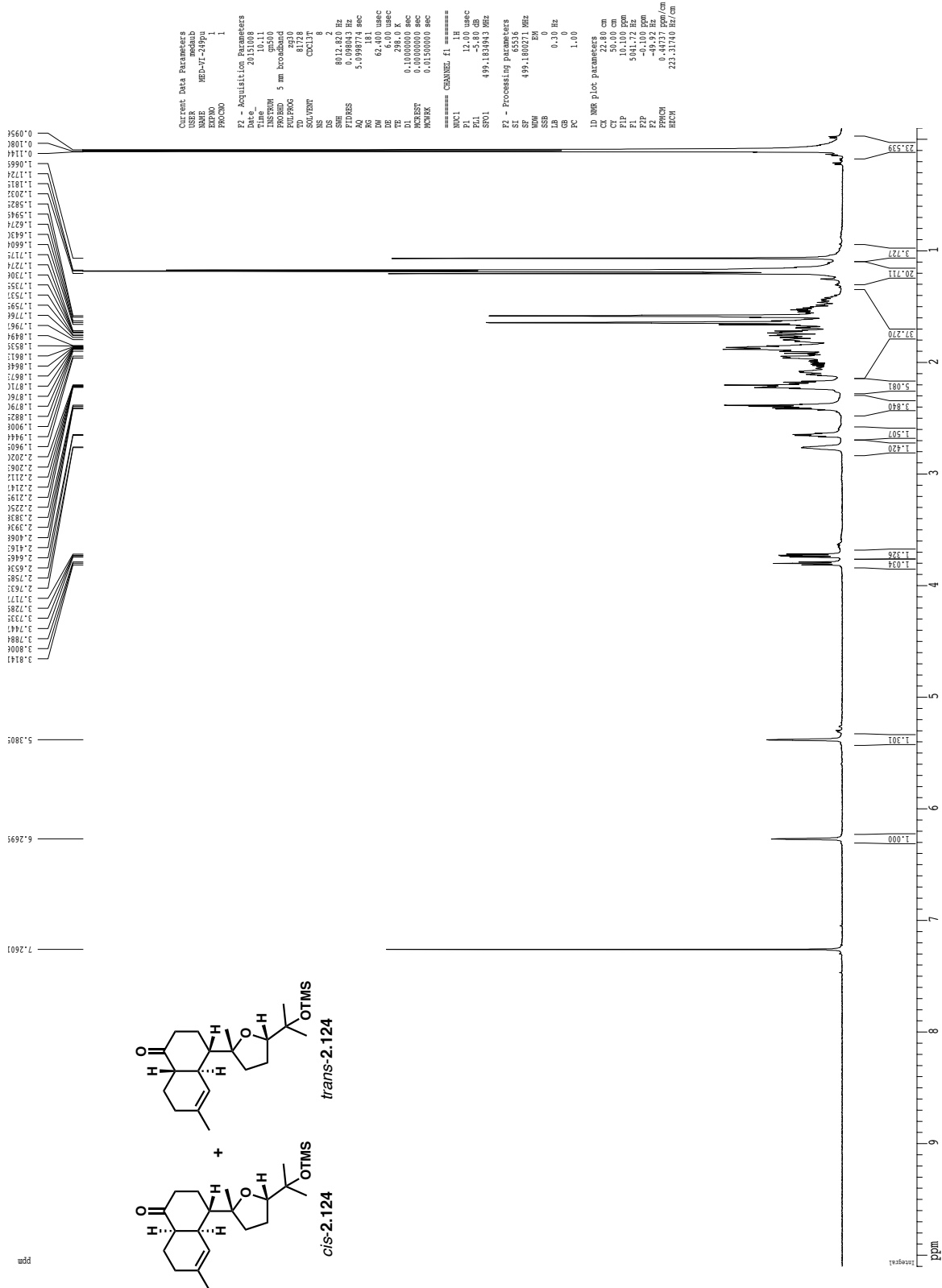




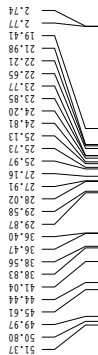
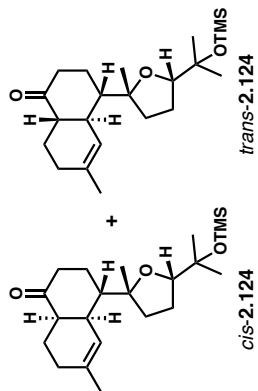




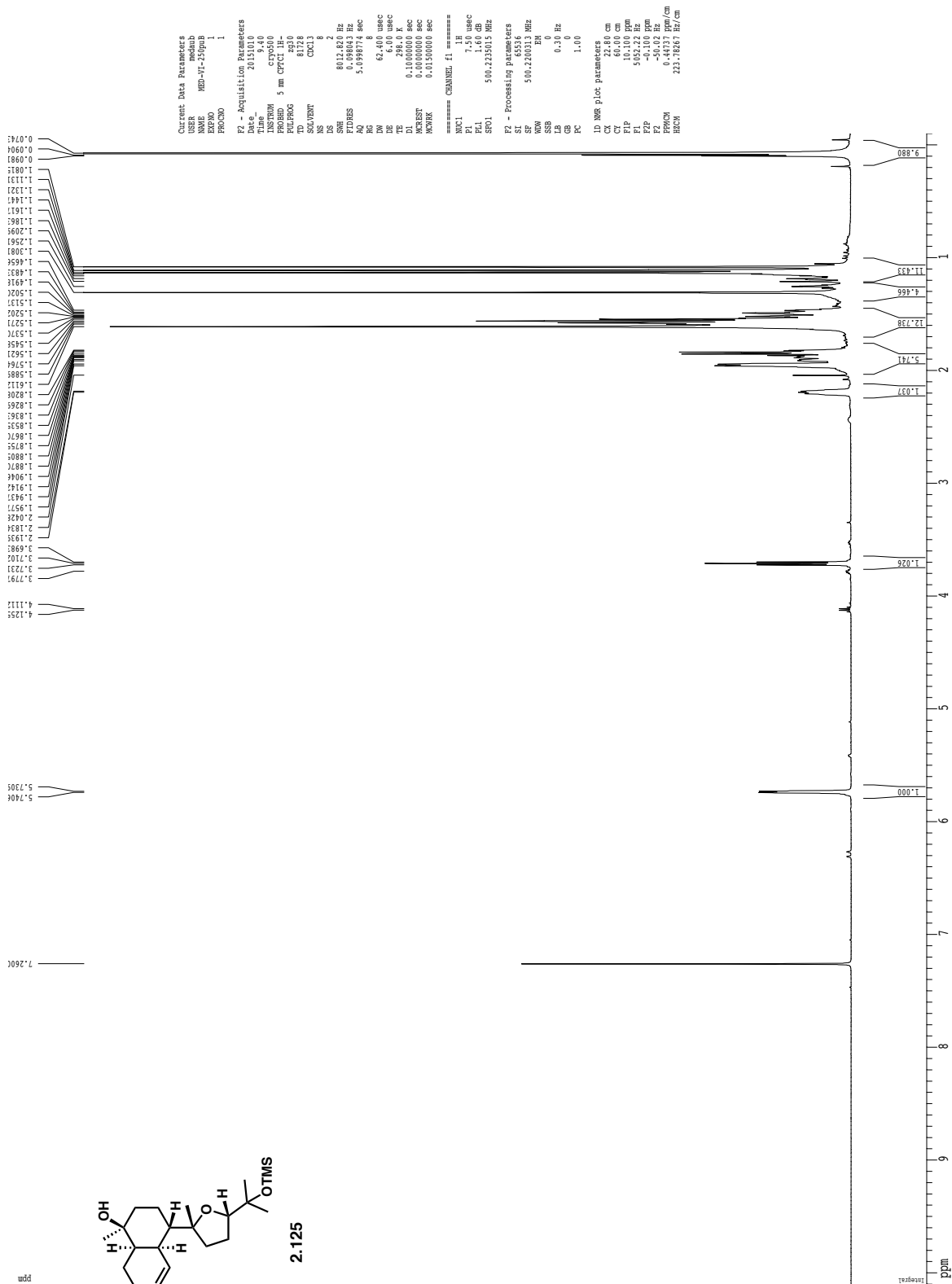
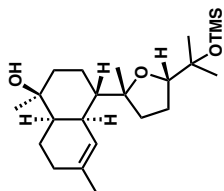
¹H spectrum



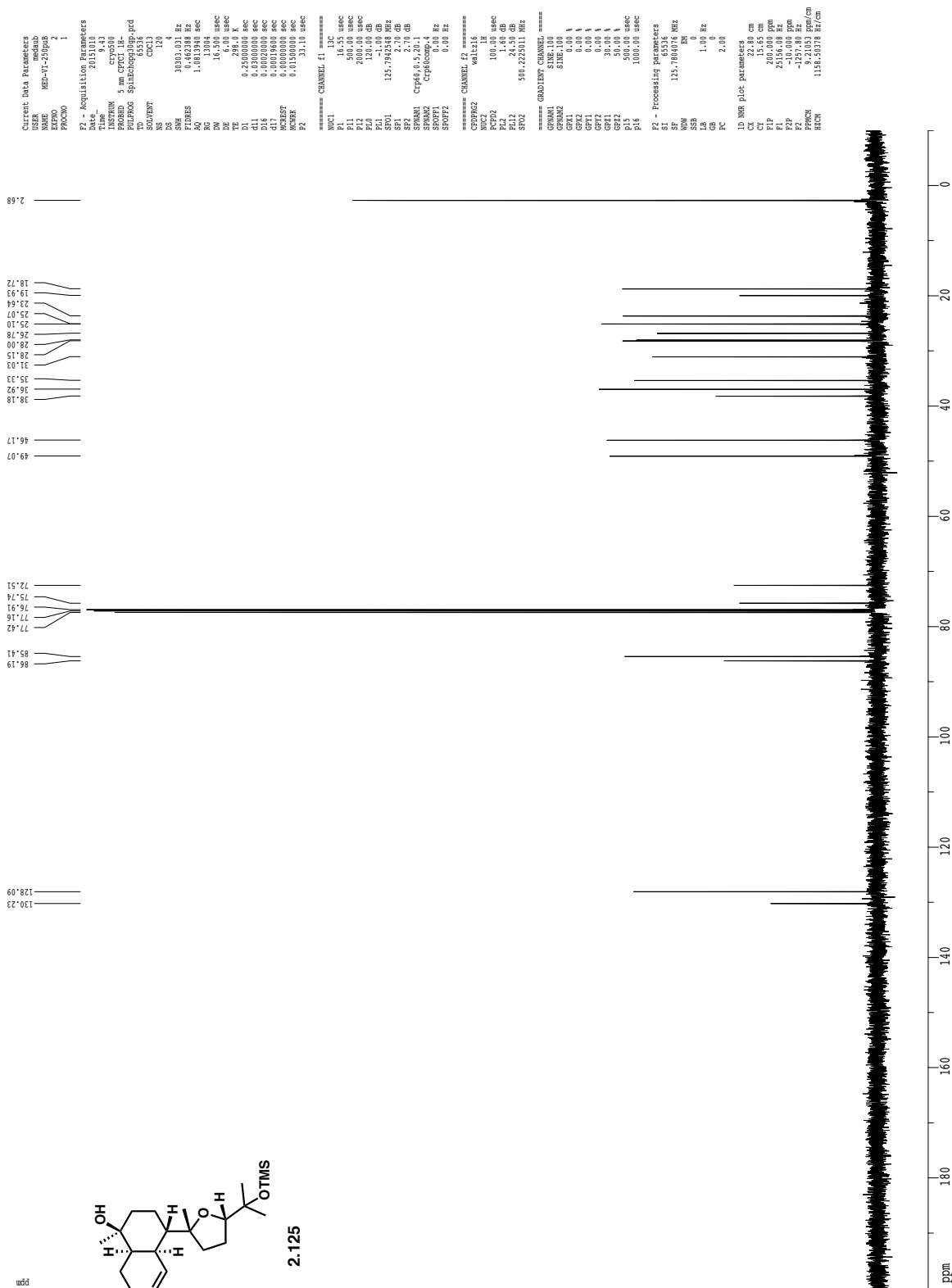
215.19
213.08
wdd



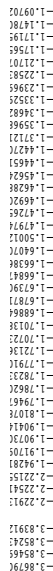
Current Data Parameters		MED-VI-24v2u		MED-VI-24v2u		MED-VI-24v2u	
USER	PARAMETER	UNIT	VALUE	UNIT	VALUE	UNIT	VALUE
EXPNO	EXPNO		1		1		1
PROCNO	PROCNO		1		1		1
F2 - Acquisition Parameters							
Date_	Date_		20151008		20151008		20151008
Time	Time		10:15		10:15		10:15
PROBHD	PROBHD		5 mm Broadband		5 mm Broadband		5 mm Broadband
PULPROG	PULPROG		zgpg30		zgpg30		zgpg30
TD	TD		65536		65536		65536
TD0	TD0		SOVHET		SOVHET		SOVHET
TD1	TD1		CO13		CO13		CO13
TD2	TD2		CO13		CO13		CO13
TD3	TD3		CO13		CO13		CO13
TD4	TD4		CO13		CO13		CO13
TD5	TD5		CO13		CO13		CO13
TD6	TD6		CO13		CO13		CO13
TD7	TD7		CO13		CO13		CO13
TD8	TD8		CO13		CO13		CO13
TD9	TD9		CO13		CO13		CO13
TD10	TD10		CO13		CO13		CO13
TD11	TD11		CO13		CO13		CO13
TD12	TD12		CO13		CO13		CO13
TD13	TD13		CO13		CO13		CO13
TD14	TD14		CO13		CO13		CO13
TD15	TD15		CO13		CO13		CO13
TD16	TD16		CO13		CO13		CO13
TD17	TD17		CO13		CO13		CO13
TD18	TD18		CO13		CO13		CO13
TD19	TD19		CO13		CO13		CO13
TD20	TD20		CO13		CO13		CO13
TD21	TD21		CO13		CO13		CO13
TD22	TD22		CO13		CO13		CO13
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TD24	TD24		CO13		CO13		CO13
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TD27	TD27		CO13		CO13		CO13
TD28	TD28		CO13		CO13		CO13
TD29	TD29		CO13		CO13		CO13
TD30	TD30		CO13		CO13		CO13
TD31	TD31		CO13		CO13		CO13
TD32	TD32		CO13		CO13		CO13
TD33	TD33		CO13		CO13		CO13
TD34	TD34		CO13		CO13		CO13
TD35	TD35		CO13		CO13		CO13
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TD37	TD37		CO13		CO13		CO13
TD38	TD38		CO13		CO13		CO13
TD39	TD39		CO13		CO13		CO13
TD40	TD40		CO13		CO13		CO13
TD41	TD41		CO13		CO13		CO13
TD42	TD42		CO13		CO13		CO13
TD43	TD43		CO13		CO13		CO13
TD44	TD44		CO13		CO13		CO13
TD45	TD45		CO13		CO13		CO13
TD46	TD46		CO13		CO13		CO13
TD47	TD47		CO13		CO13		CO13
TD48	TD48		CO13		CO13		CO13
TD49	TD49		CO13		CO13		CO13
TD50	TD50		CO13		CO13		CO13
TD51	TD51						



Z-restored spin-echo ¹³C spectrum with ¹H decoupling



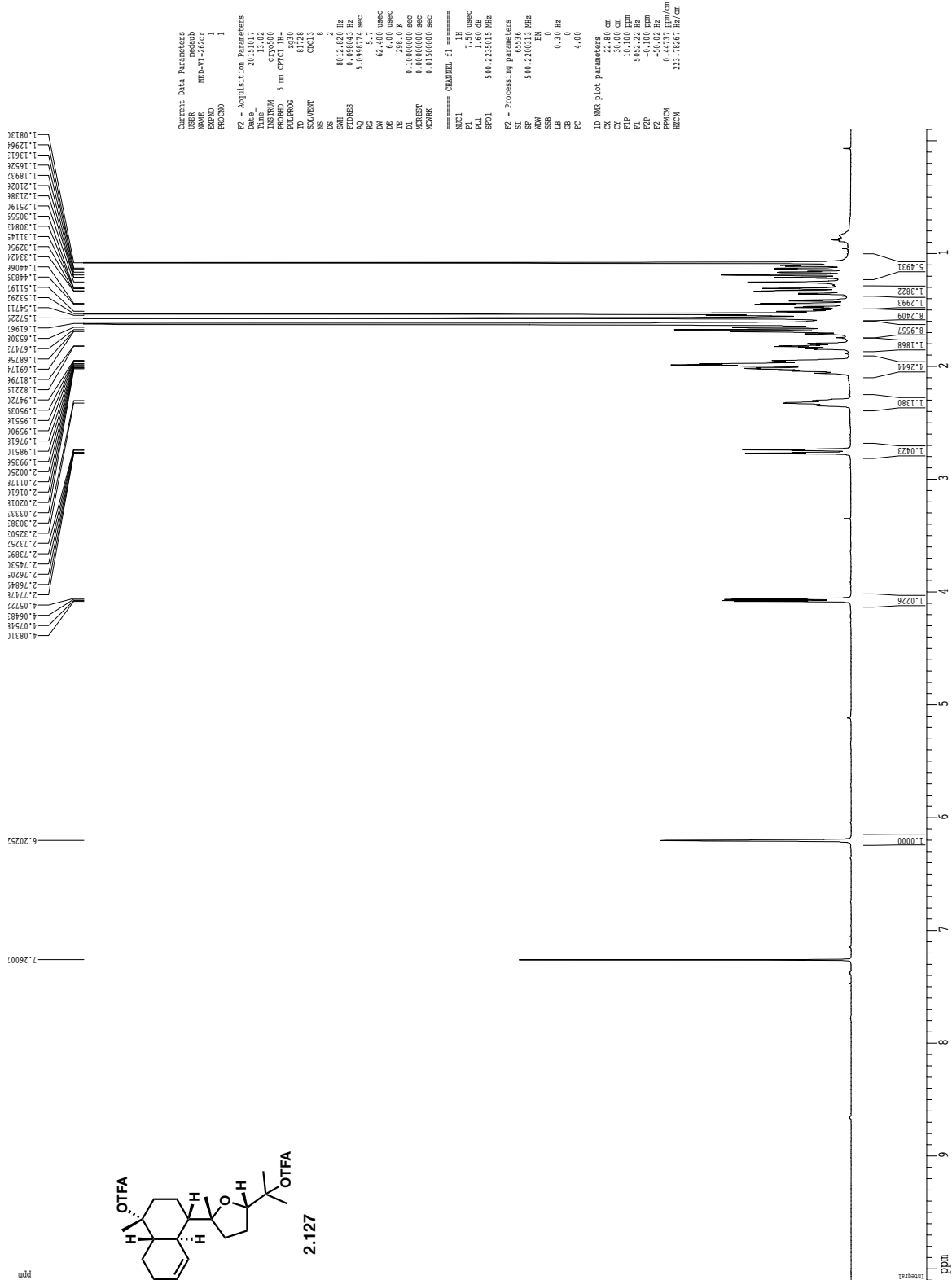
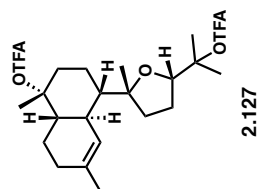




Current Data Parameters	
NAME	modlib
NAME	MPD-V252u
PROCNO	1
P2 - Acquisition Parameters	
Time	2013.27
INSTRUM	crystal
PROBHD	5 mm CPIC 1H
PULPROG	zgpg30
PRGNAME	8178
TD	65536
DO	1
DS	2
SWH	801.820 Hz
FIDRES	0.00043 Hz
AQ	5.197 sec
RG	5.7 sec
DM	62.400 sec
DE	6.00 sec
TE	300.2 K
DELTA	0.1000000 sec
DELTA2	0.0500000 sec
DELTA3	0.0300000 sec
DELTA4	0.0100000 sec
DELTA5	0.0100000 sec
DELTA6	0.0100000 sec
DELTA7	0.0100000 sec
DELTA8	0.0100000 sec
DELTA9	0.0100000 sec
DELTA10	0.0100000 sec
DELTA11	0.0100000 sec
DELTA12	0.0100000 sec
DELTA13	0.0100000 sec
DELTA14	0.0100000 sec
DELTA15	0.0100000 sec
DELTA16	0.0100000 sec
DELTA17	0.0100000 sec
DELTA18	0.0100000 sec
DELTA19	0.0100000 sec
DELTA20	0.0100000 sec
DELTA21	0.0100000 sec
DELTA22	0.0100000 sec
DELTA23	0.0100000 sec
DELTA24	0.0100000 sec
DELTA25	0.0100000 sec
DELTA26	0.0100000 sec
DELTA27	0.0100000 sec
DELTA28	0.0100000 sec
DELTA29	0.0100000 sec
DELTA30	0.0100000 sec
DELTA31	0.0100000 sec
DELTA32	0.0100000 sec
DELTA33	0.0100000 sec
DELTA34	0.0100000 sec
DELTA35	0.0100000 sec
DELTA36	0.0100000 sec
DELTA37	0.0100000 sec
DELTA38	0.0100000 sec
DELTA39	0.0100000 sec
DELTA40	0.0100000 sec
DELTA41	0.0100000 sec
DELTA42	0.0100000 sec
DELTA43	0.0100000 sec
DELTA44	0.0100000 sec
DELTA45	0.0100000 sec
DELTA46	0.0100000 sec
DELTA47	0.0100000 sec
DELTA48	0.0100000 sec
DELTA49	0.0100000 sec
DELTA50	0.0100000 sec
DELTA51	0.0100000 sec
DELTA52	0.0100000 sec
DELTA53	0.0100000 sec
DELTA54	0.0100000 sec
DELTA55	0.0100000 sec
DELTA56	0.0100000 sec
DELTA57	0.0100000 sec
DELTA58	0.0100000 sec
DELTA59	0.0100000 sec
DELTA60	0.0100000 sec
DELTA61	0.0100000 sec
DELTA62	0.0100000 sec
DELTA63	0.0100000 sec
DELTA64	0.0100000 sec
DELTA65	0.0100000 sec
DELTA66	0.0100000 sec
DELTA67	0.0100000 sec
DELTA68	0.0100000 sec
DELTA69	0.0100000 sec
DELTA70	0.0100000 sec
DELTA71	0.0100000 sec
DELTA72	0.0100000 sec
DELTA73	0.0100000 sec
DELTA74	0.0100000 sec
DELTA75	0.0100000 sec
DELTA76	0.0100000 sec
DELTA77	0.0100000 sec
DELTA78	0.0100000 sec
DELTA79	0.0100000 sec
DELTA80	0.0100000 sec
DELTA81	0.0100000 sec
DELTA82	0.0100000 sec
DELTA83	0.0100000 sec
DELTA84	0.0100000 sec
DELTA85	0.0100000 sec
DELTA86	0.0100000 sec
DELTA87	0.0100000 sec
DELTA88	0.0100000 sec
DELTA89	0.0100000 sec
DELTA90	0.0100000 sec
DELTA91	0.0100000 sec
DELTA92	0.0100000 sec
DELTA93	0.0100000 sec
DELTA94	0.0100000 sec
DELTA95	0.0100000 sec
DELTA96	0.0100000 sec
DELTA97	0.0100000 sec
DELTA98	0.0100000 sec
DELTA99	0.0100000 sec
DELTA100	0.0100000 sec
DELTA101	0.0100000 sec
DELTA102	0.0100000 sec
DELTA103	0.0100000 sec
DELTA104	0.0100000 sec
DELTA105	0.0100000 sec
DELTA106	0.0100000 sec
DELTA107	0.0100000 sec
DELTA108	0.0100000 sec

¹H spectrum

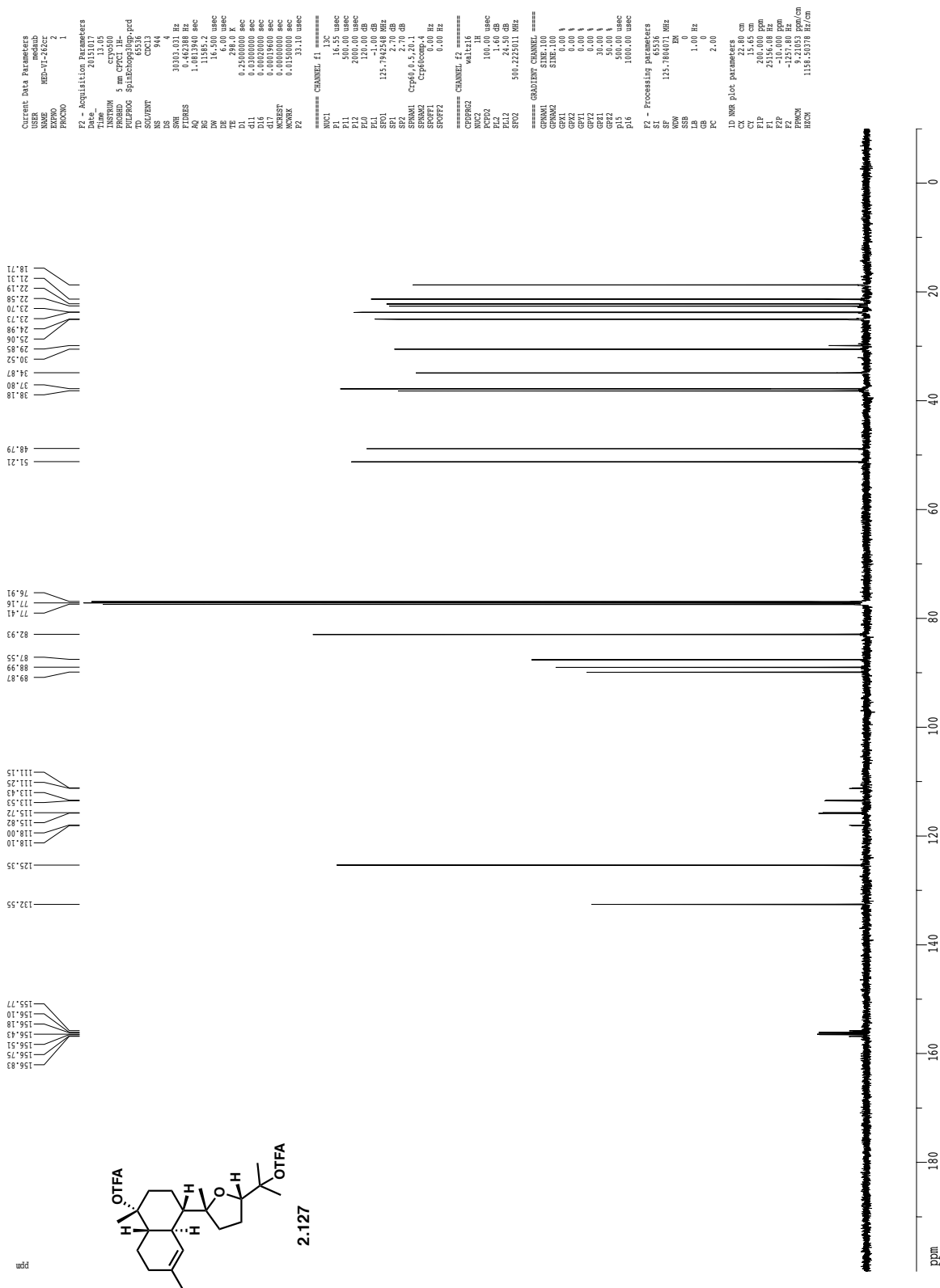
ppm

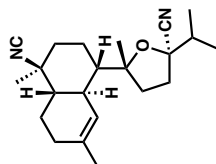


Current Data Parameters

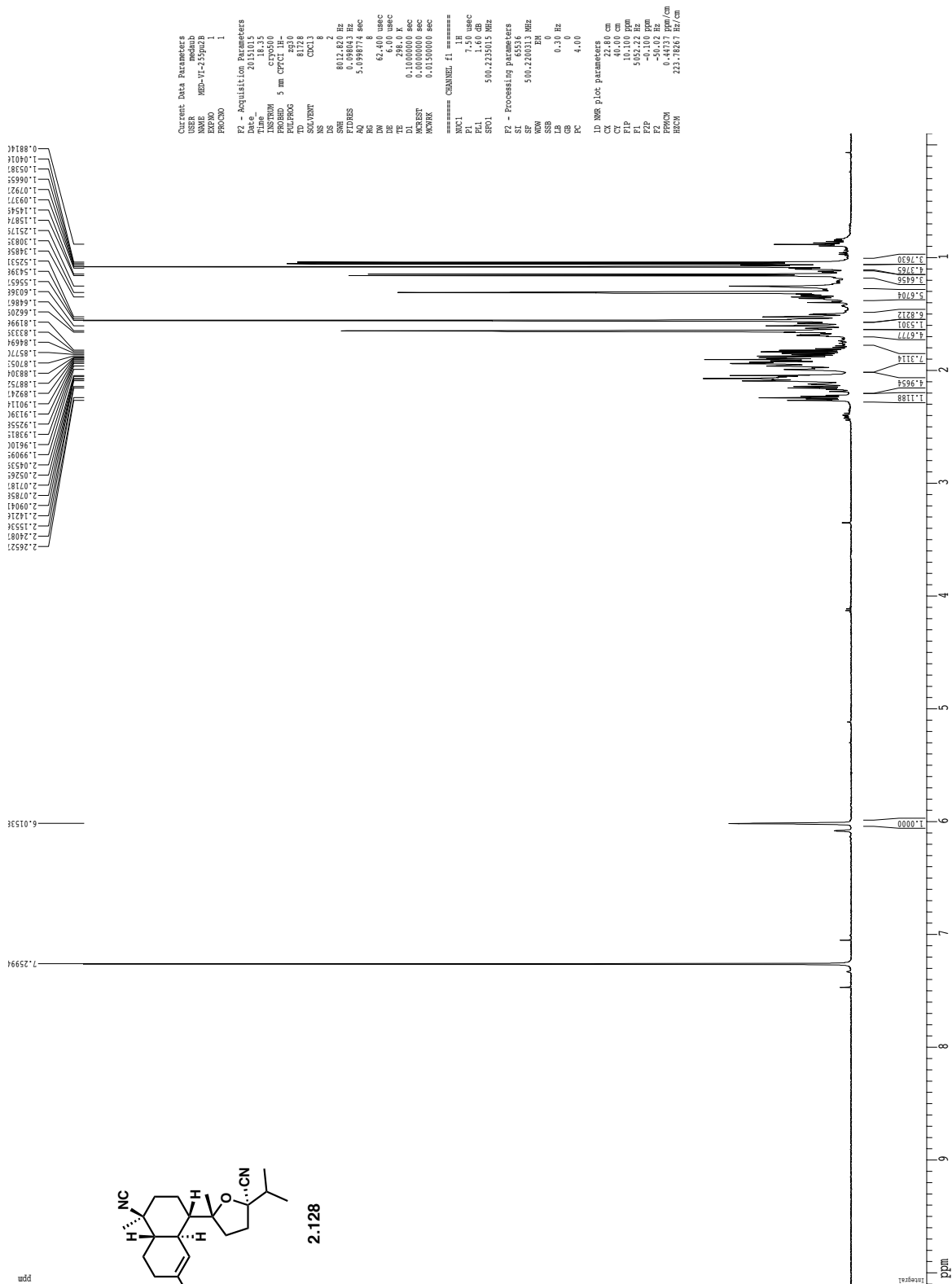
NAME	2.127
EXPNO	1
PROCNO	1
Date_	20151017
Time	13:02
PROBHD	5 mm CPYCI 1H
PULPROG	zg30
TD	81728
RG	3.00
SD	2
SNR	8012.823 Hz
NUC1	1H
NUC2	1H
FL	7.50 usec
AL	1.00 usec
STW1	500.235415 MHz
PT - Processing parameters	
SI	32768
ST	500.235415 MHz
WDW	EM
SSB	0
AB	0.10 Hz
GB	0.00
PC	4.00
ID NMR Plot parameters	
SI	32768
ST	500.235415 MHz
WDW	EM
SSB	0
AB	0.10 Hz
GB	0.00
PC	4.00
ID NMR Plot parameters	
SI	32768
ST	500.235415 MHz
WDW	EM
SSB	0
AB	0.10 Hz
GB	0.00
PC	4.00

Z-restored spin-echo ¹³C spectrum with ¹H decoupling





2.128



Current Data Parameters

NAME	MD-VI-2592a2
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20151015
Time	14:34
INSTRUM	CPDPR02
PROBHD	5 mm CPXI 1H-
PULPROG	sg1a2chopsgbgp-jrc
DELTA	0.00100000 sec
SOLVENT	CDCl3
NS	1600
DS	4
SWH	2032.074 Hz
FIDRES	0.462388 Hz
AQ	1.0013940 sec
RG	320.00
RM	15.00 usec
DE	6.00 usec
TE	298.2 K
TD	1.00000000 sec
d11	0.00000000 sec
d16	0.00200000 sec
d17	0.00019600 sec
DELTA	0.00000000 sec
WORK	0.01500000 sec
P2	31.00 usec

===== CHANNEL f1 =====

NUC1	13C
P1	15.50 usec
PL1	0.00 dB
P2	200.00 usec
PL2	200.00 dB
PL0	120.00 dB
PL11	-1.00 dB
PL12	-1.00 dB
PL13	125.794125 dB
SP1	1.25 dB
SP2	0.00 dB
SP3	0.00 dB
SP4	0.00 dB
SP5	0.00 dB
SP6	0.00 dB
SP7	0.00 dB
SP8	0.00 dB
SP9	0.00 dB
SP10	0.00 dB
SP11	0.00 dB
SP12	0.00 dB
SP13	0.00 dB
SP14	0.00 dB
SP15	0.00 dB
SP16	0.00 dB
SP17	0.00 dB
SP18	0.00 dB
SP19	0.00 dB
SP20	0.00 dB
SP21	0.00 dB
SP22	0.00 dB
SP23	0.00 dB
SP24	0.00 dB
SP25	0.00 dB
SP26	0.00 dB
SP27	0.00 dB
SP28	0.00 dB
SP29	0.00 dB
SP30	0.00 dB
SP31	0.00 dB
SP32	0.00 dB
SP33	0.00 dB
SP34	0.00 dB
SP35	0.00 dB
SP36	0.00 dB
SP37	0.00 dB
SP38	0.00 dB
SP39	0.00 dB
SP40	0.00 dB
SP41	0.00 dB
SP42	0.00 dB
SP43	0.00 dB
SP44	0.00 dB
SP45	0.00 dB
SP46	0.00 dB
SP47	0.00 dB
SP48	0.00 dB
SP49	0.00 dB
SP50	0.00 dB
SP51	0.00 dB
SP52	0.00 dB
SP53	0.00 dB
SP54	0.00 dB
SP55	0.00 dB
SP56	0.00 dB
SP57	0.00 dB
SP58	0.00 dB
SP59	0.00 dB
SP60	0.00 dB
SP61	0.00 dB
SP62	0.00 dB
SP63	0.00 dB
SP64	0.00 dB
SP65	0.00 dB
SP66	0.00 dB
SP67	0.00 dB
SP68	0.00 dB
SP69	0.00 dB
SP70	0.00 dB
SP71	0.00 dB
SP72	0.00 dB
SP73	0.00 dB
SP74	0.00 dB
SP75	0.00 dB
SP76	0.00 dB
SP77	0.00 dB
SP78	0.00 dB
SP79	0.00 dB
SP80	0.00 dB
SP81	0.00 dB
SP82	0.00 dB
SP83	0.00 dB
SP84	0.00 dB
SP85	0.00 dB
SP86	0.00 dB
SP87	0.00 dB
SP88	0.00 dB
SP89	0.00 dB
SP90	0.00 dB
SP91	0.00 dB
SP92	0.00 dB
SP93	0.00 dB
SP94	0.00 dB
SP95	0.00 dB
SP96	0.00 dB
SP97	0.00 dB
SP98	0.00 dB
SP99	0.00 dB
SP100	0.00 dB

===== CHANNEL f2 =====

CPDPRG2	waltz16
NUC2	1H
P2	100.00 usec
PL2	0.00 dB
PL12	24.60 dB
SP02	500.2225911 MHz

===== GRADIENT CHANNEL =====

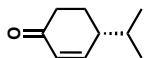
OPRM1	SINE-100
OPRM2	SINE-100
OPRM3	SINE-100
OPRM4	SINE-100



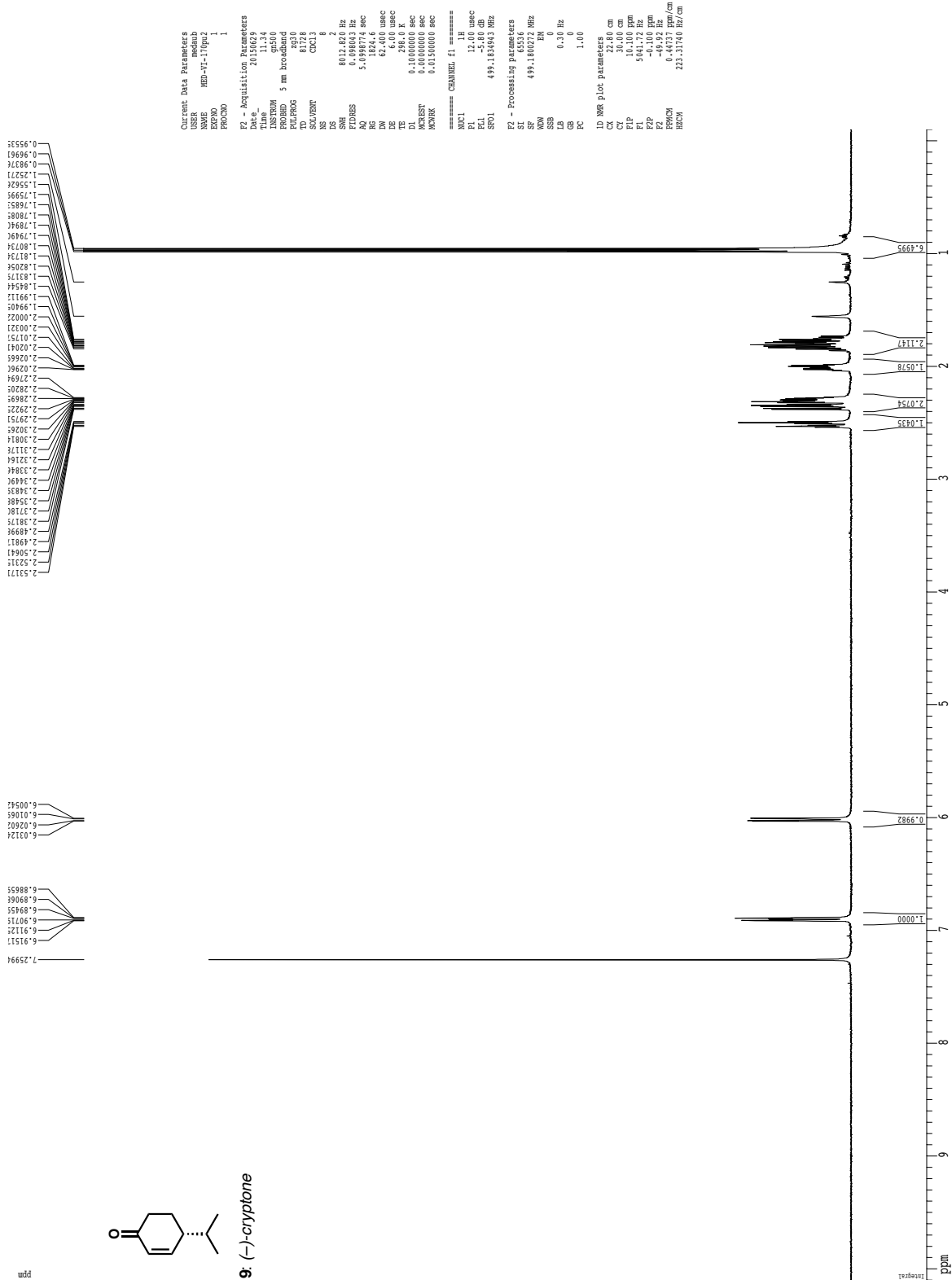
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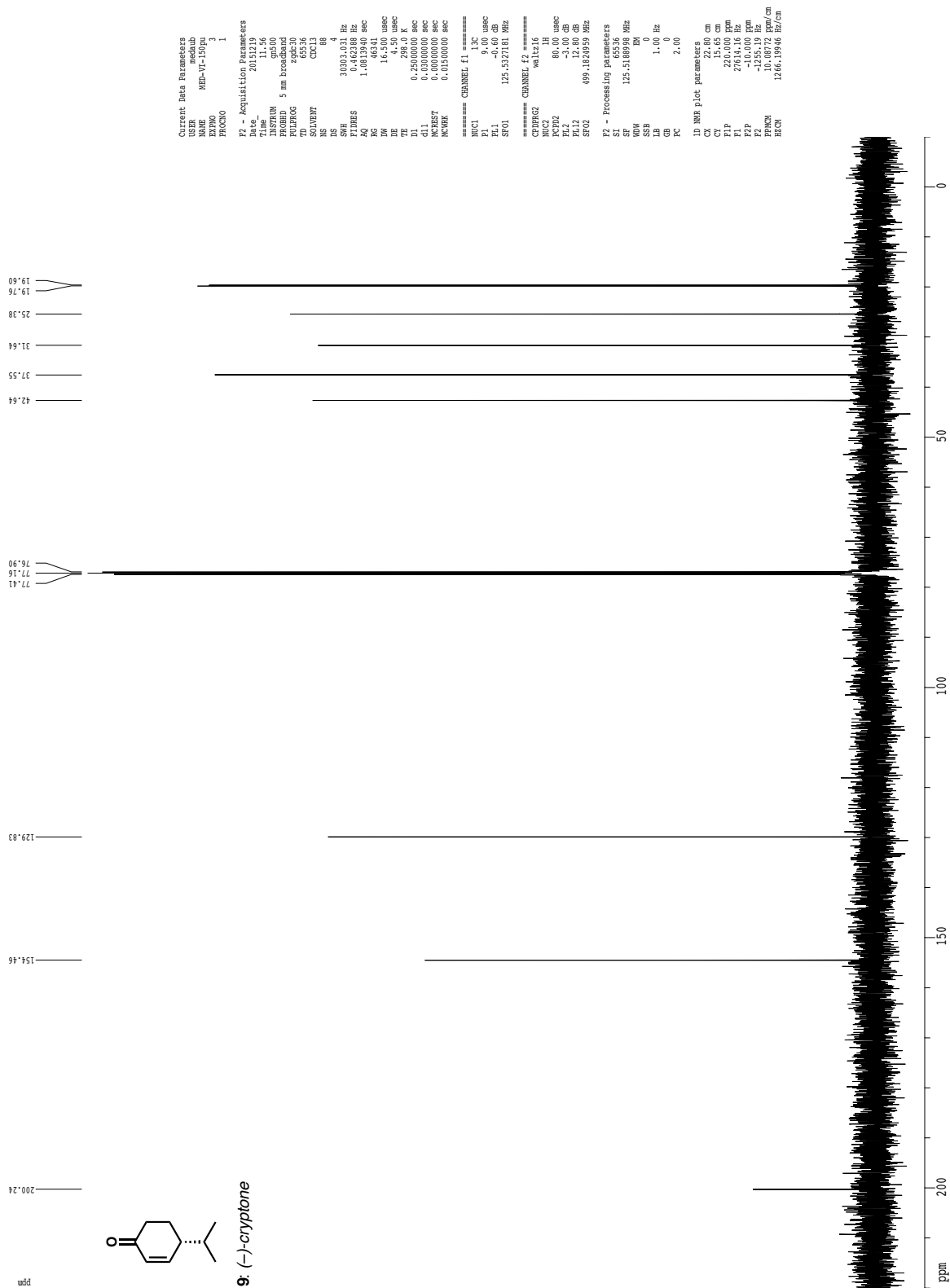




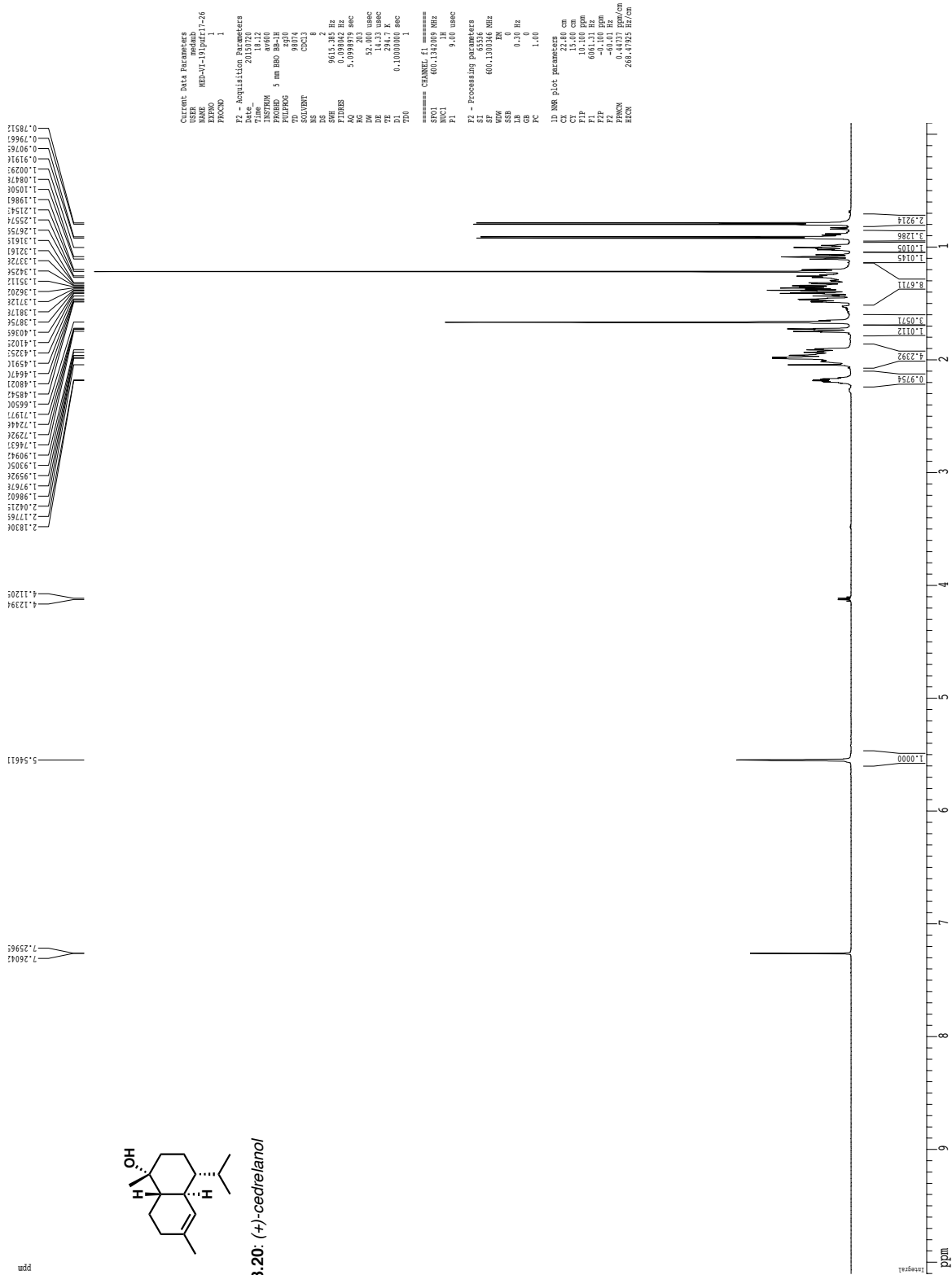
3.19: (-)-cryptone



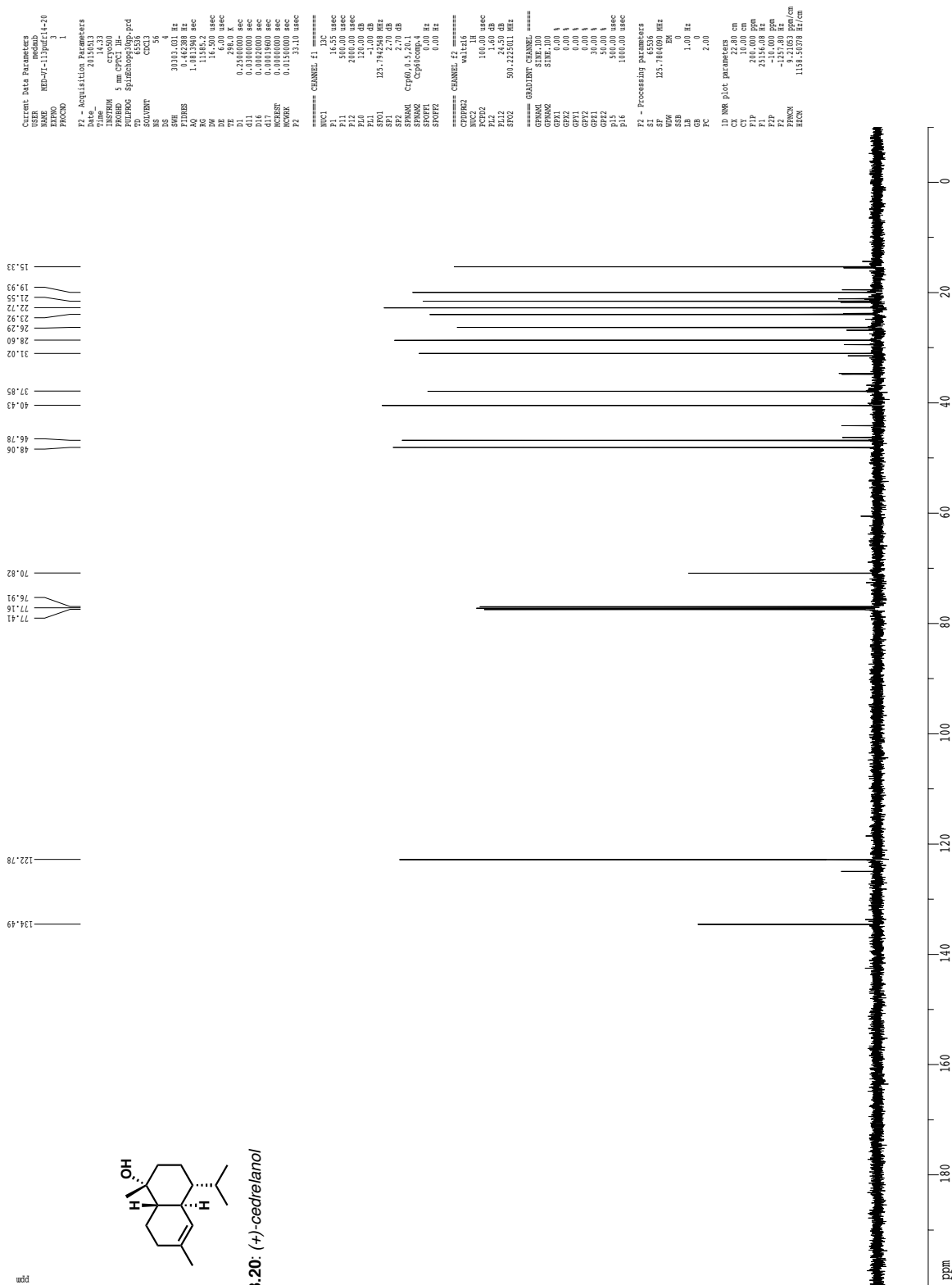
¹³C spectrum with ¹H decoupling

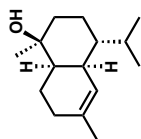


¹H spectrum

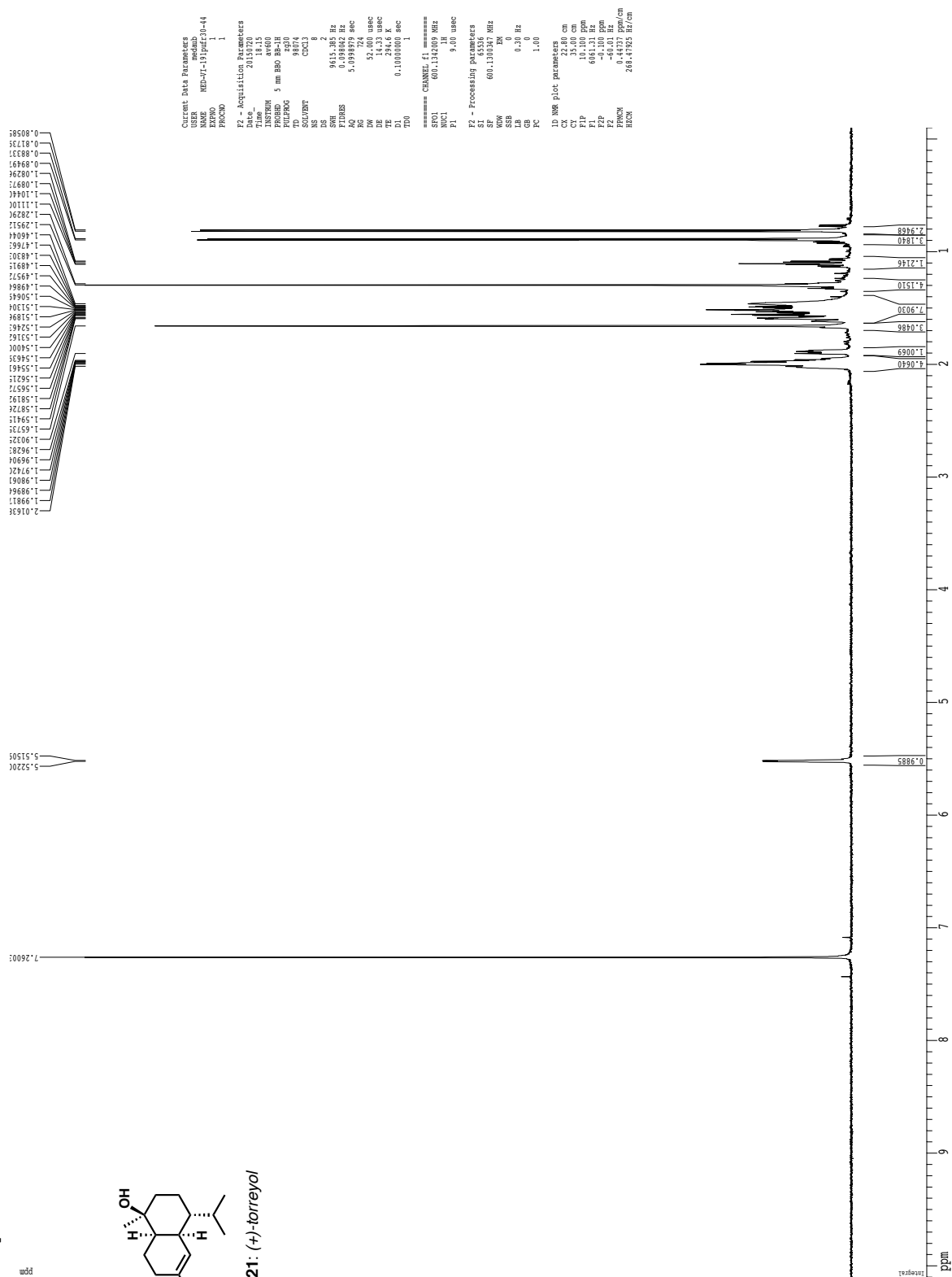


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

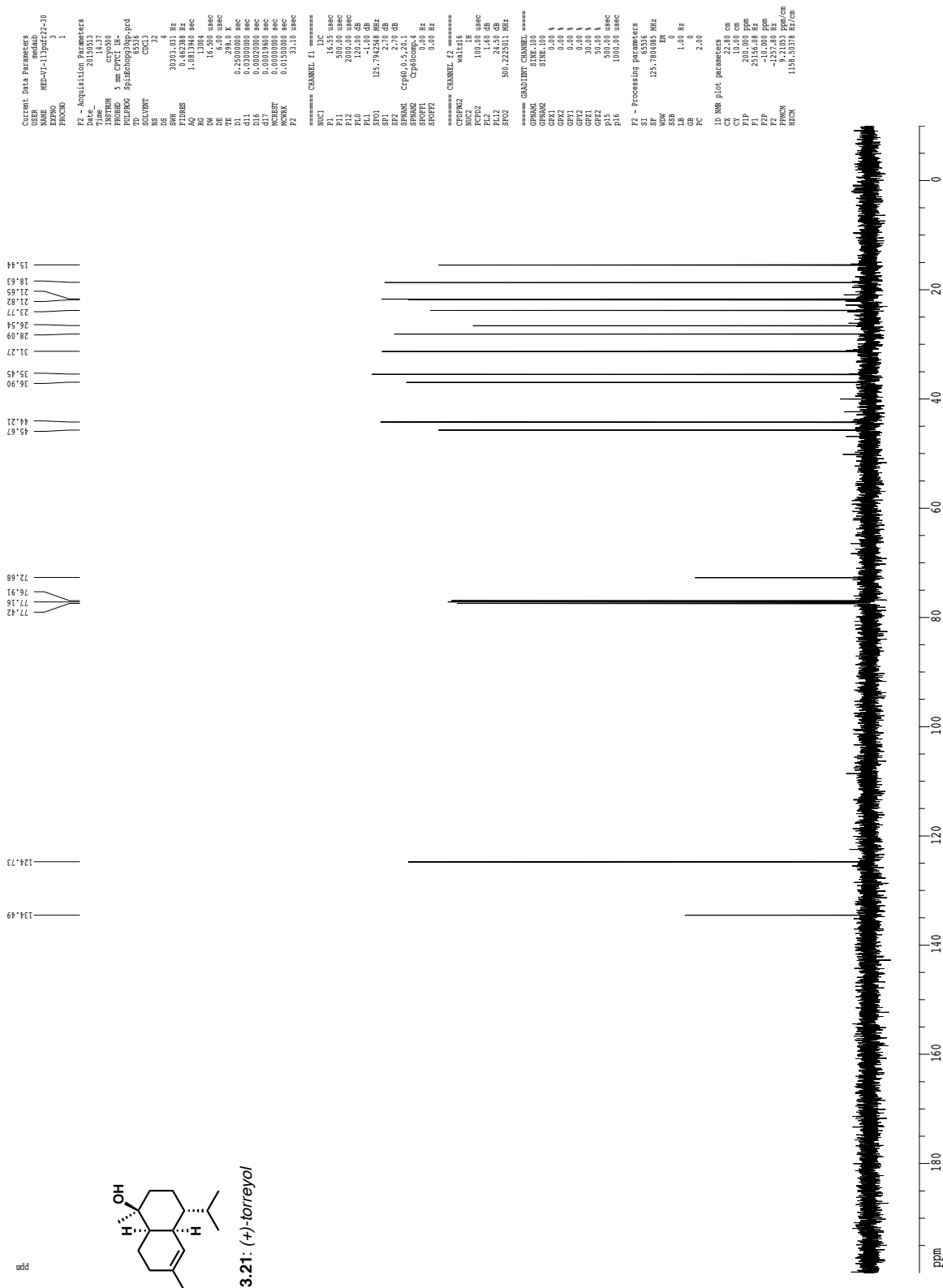




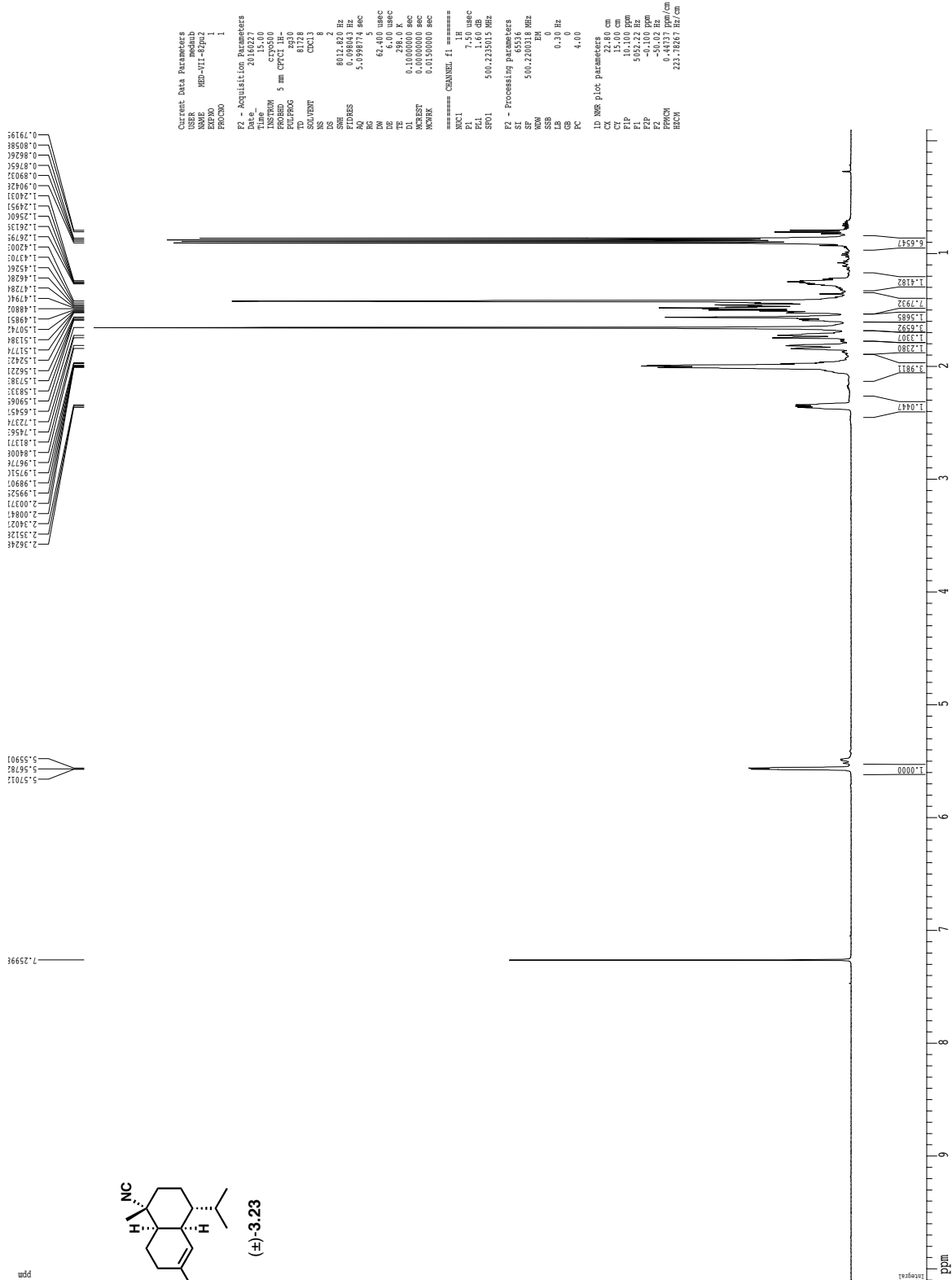
3.21: (+)-torreyol

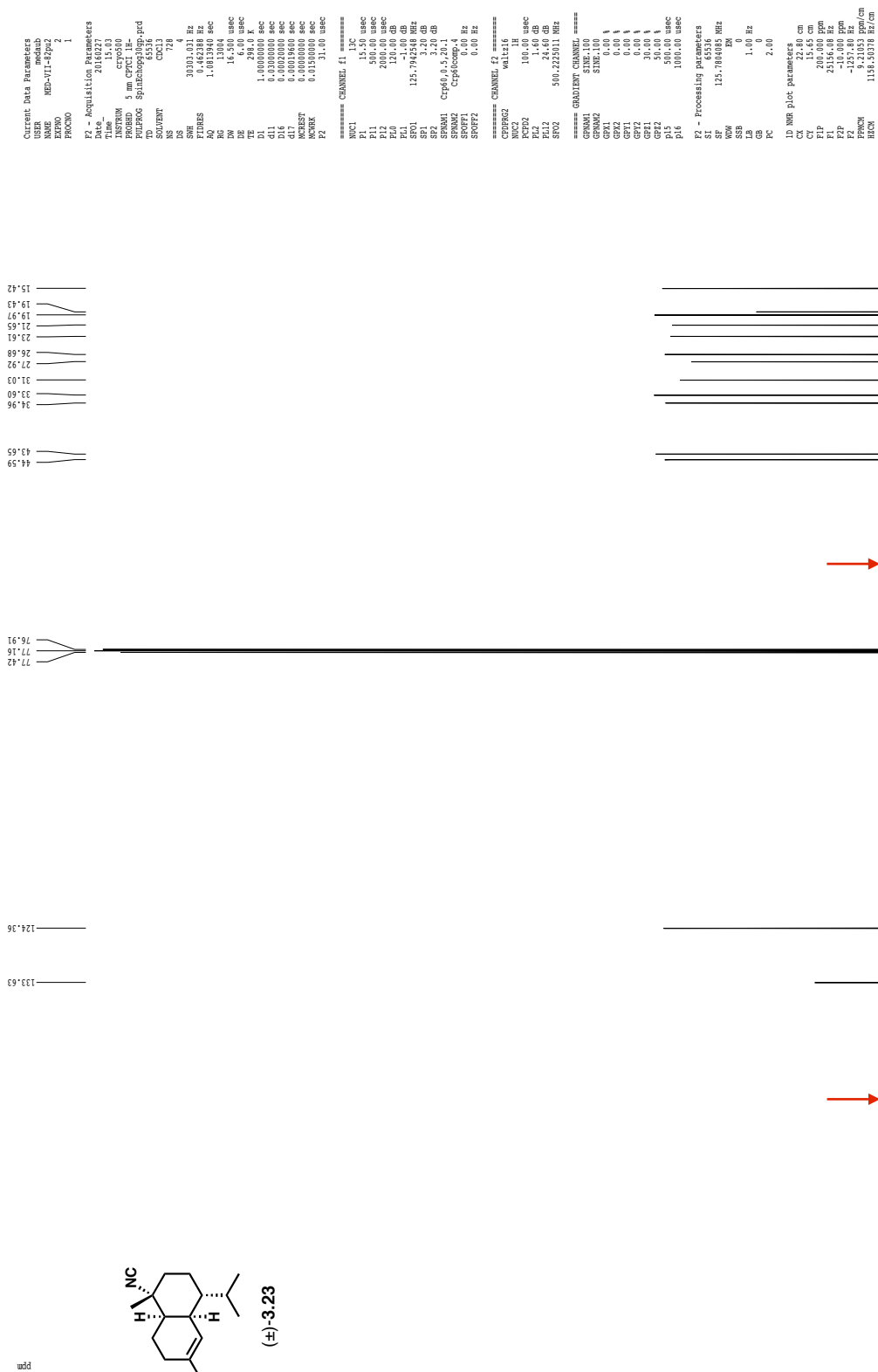


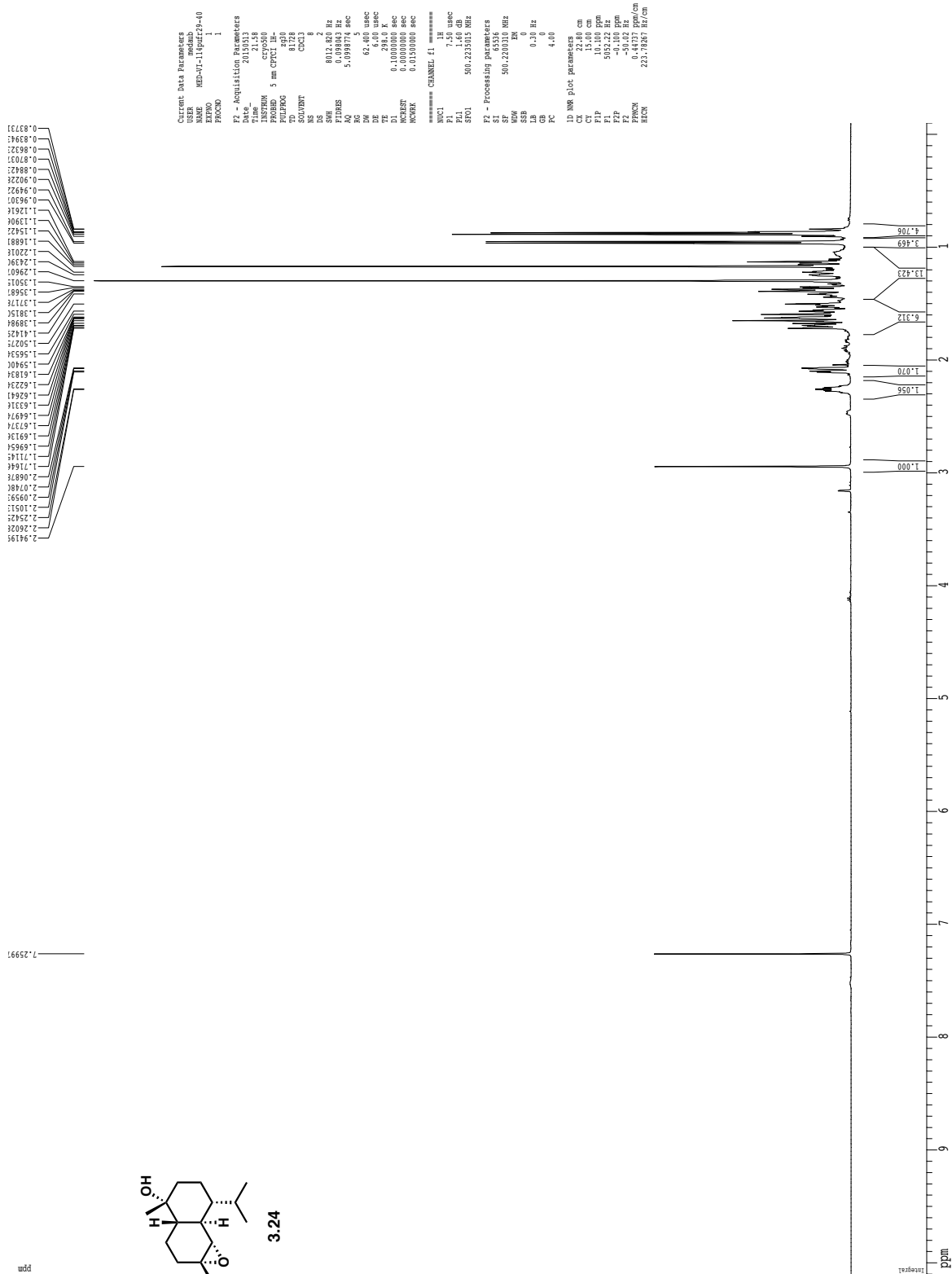
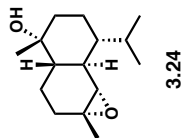
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

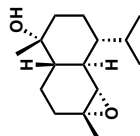


¹H spectrum

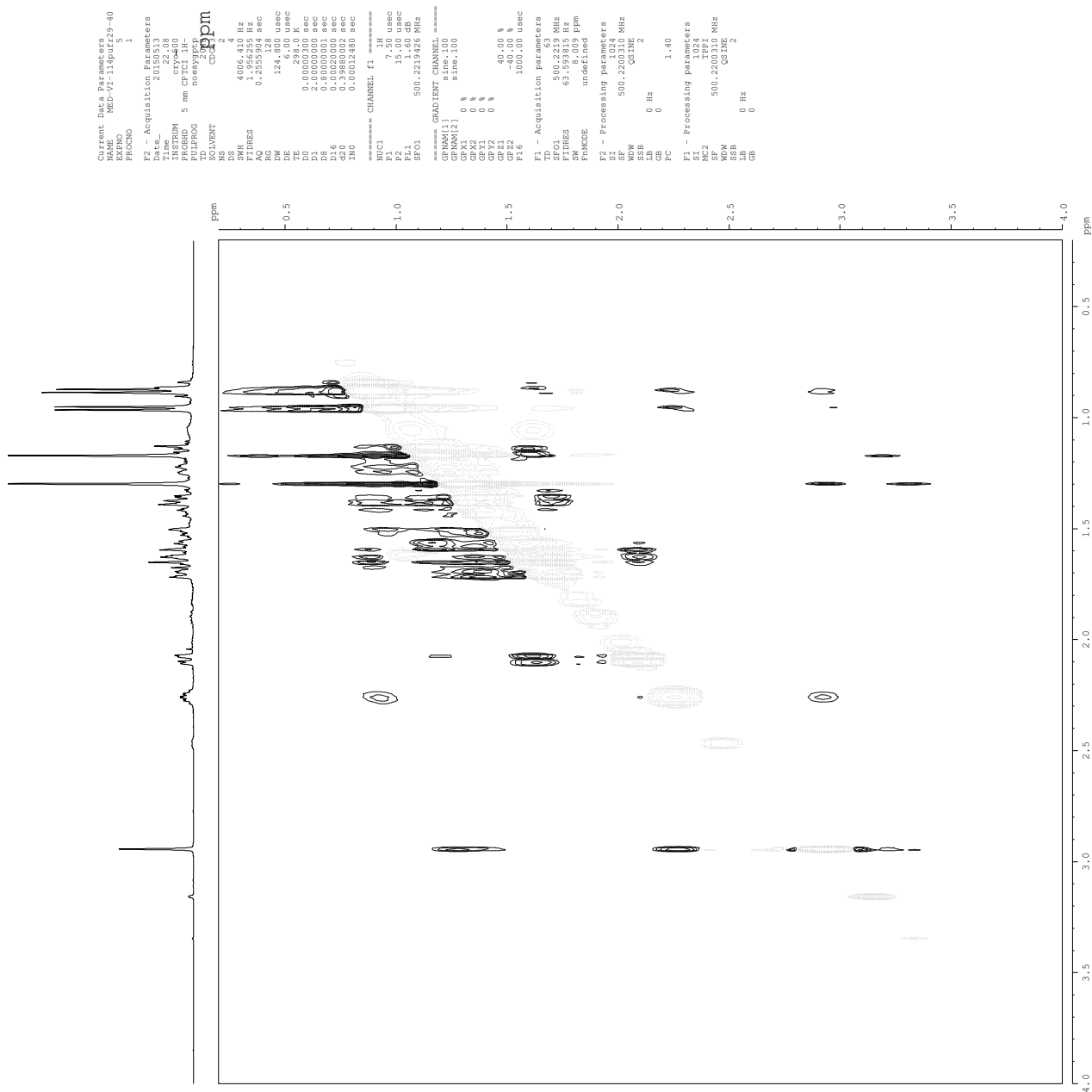






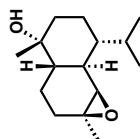


3.24

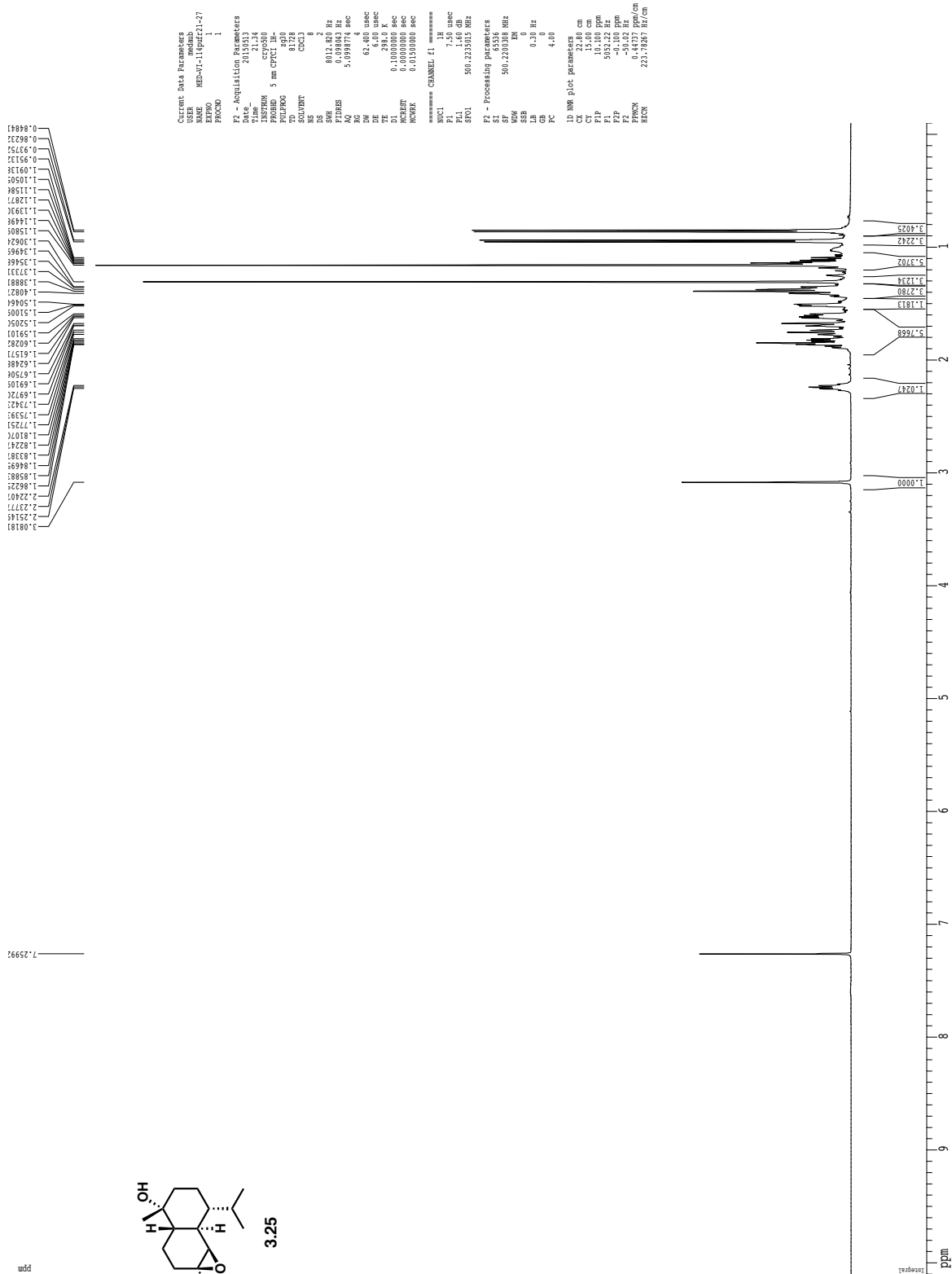
[illegible]

¹H spectrum

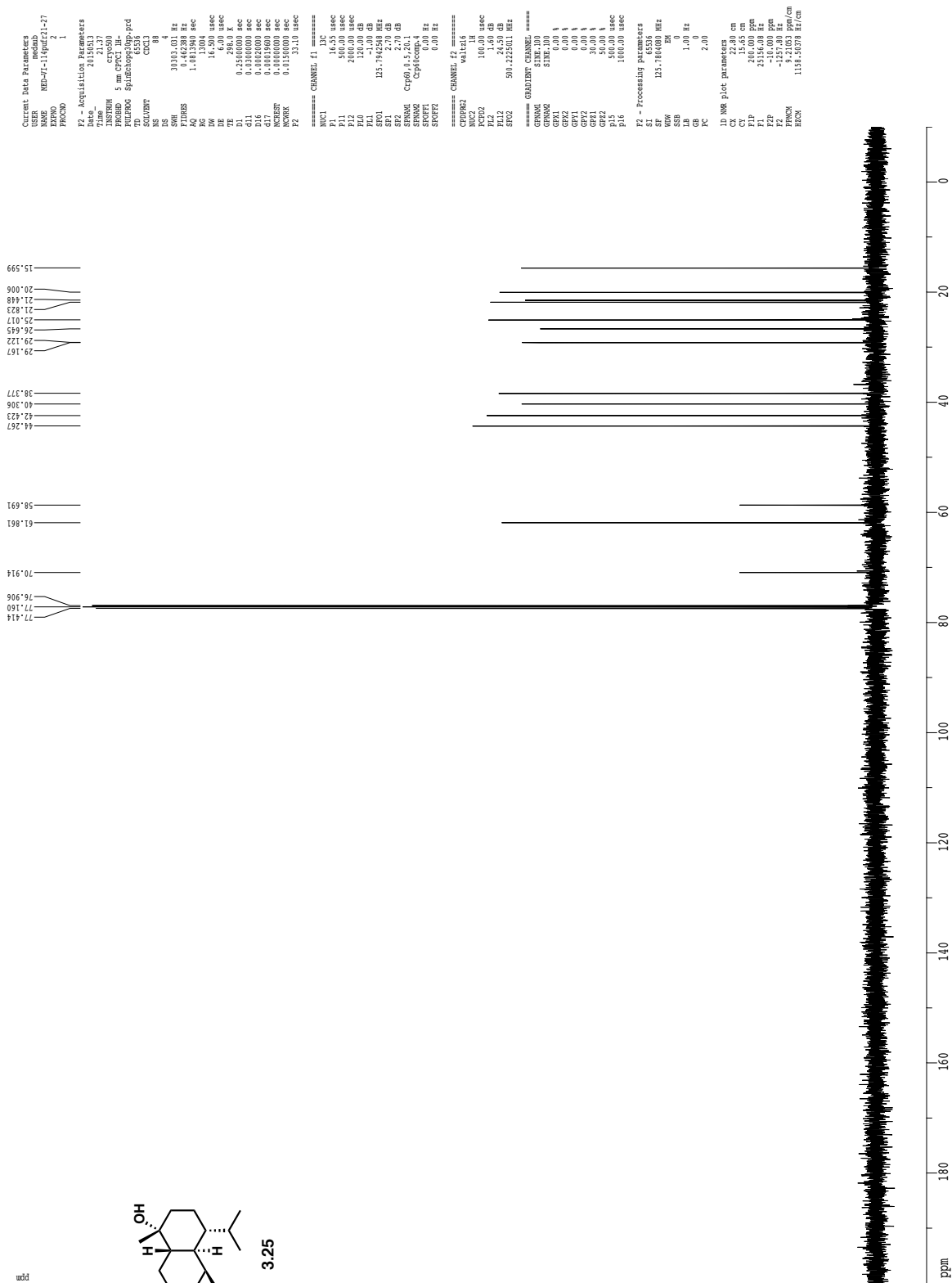
ppm

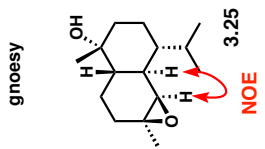


3.25

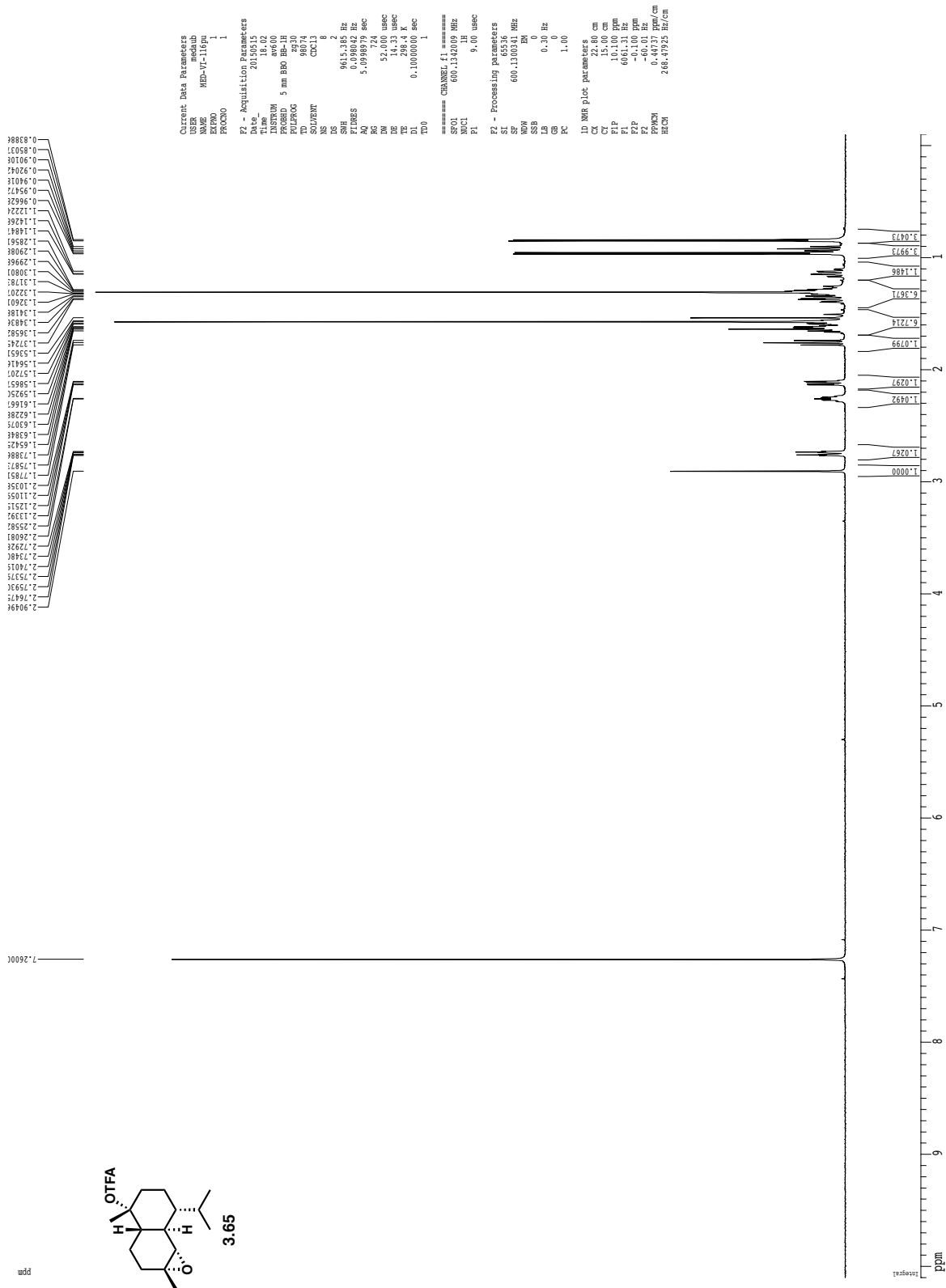


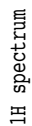
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



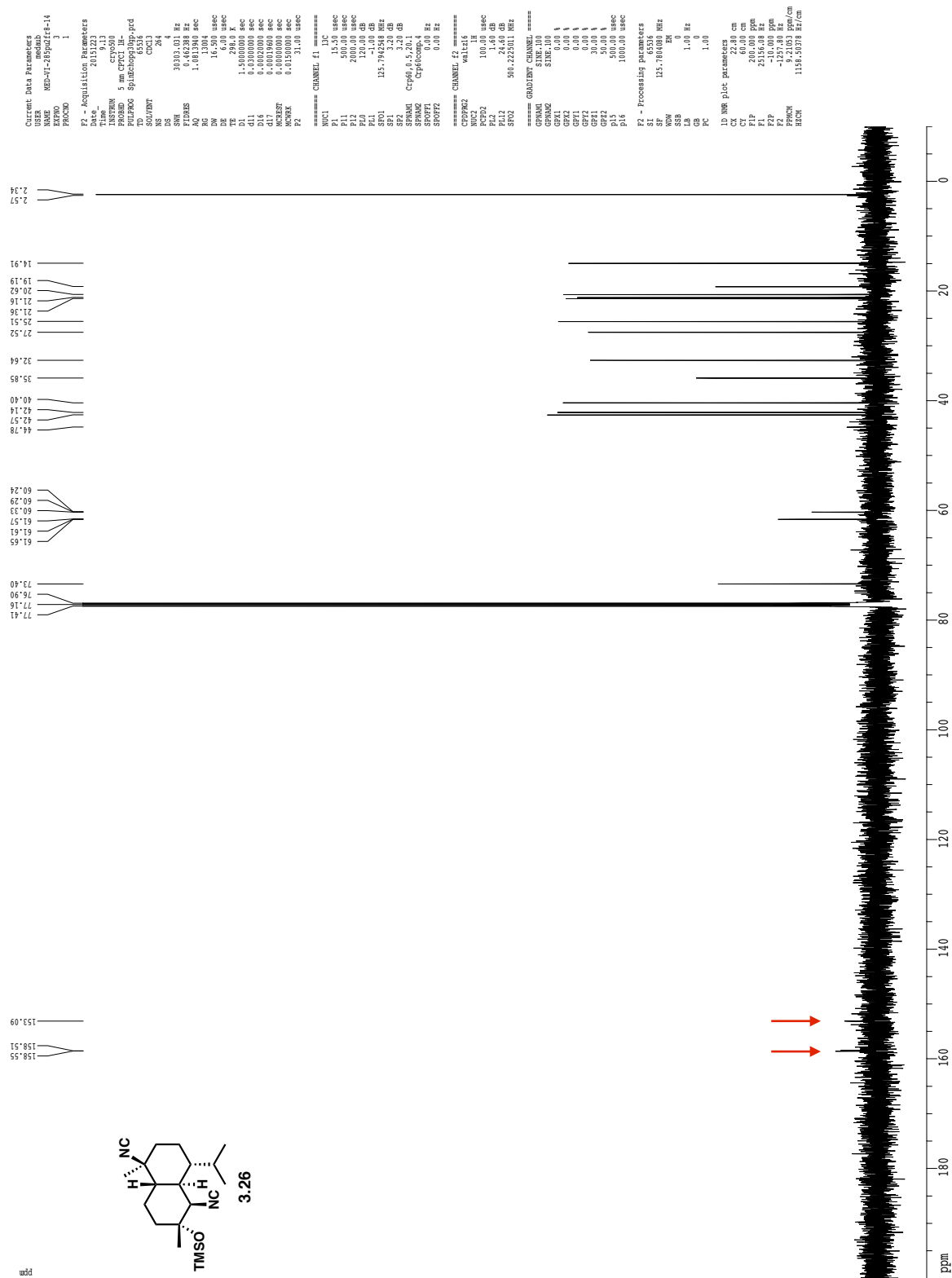


¹H spectrum

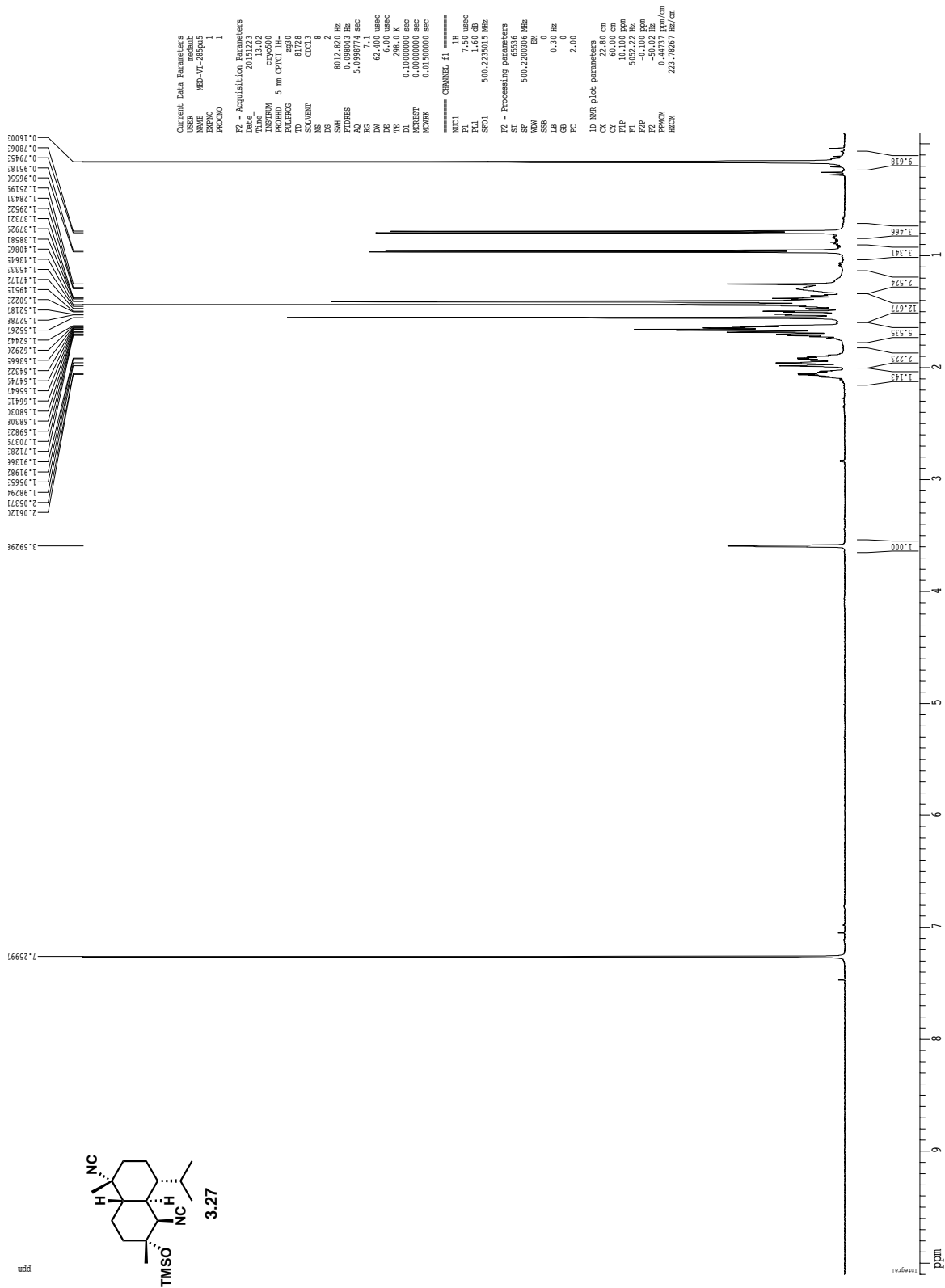




Z-restored spin-echo ¹³C spectrum with ¹H decoupling



¹H spectrum



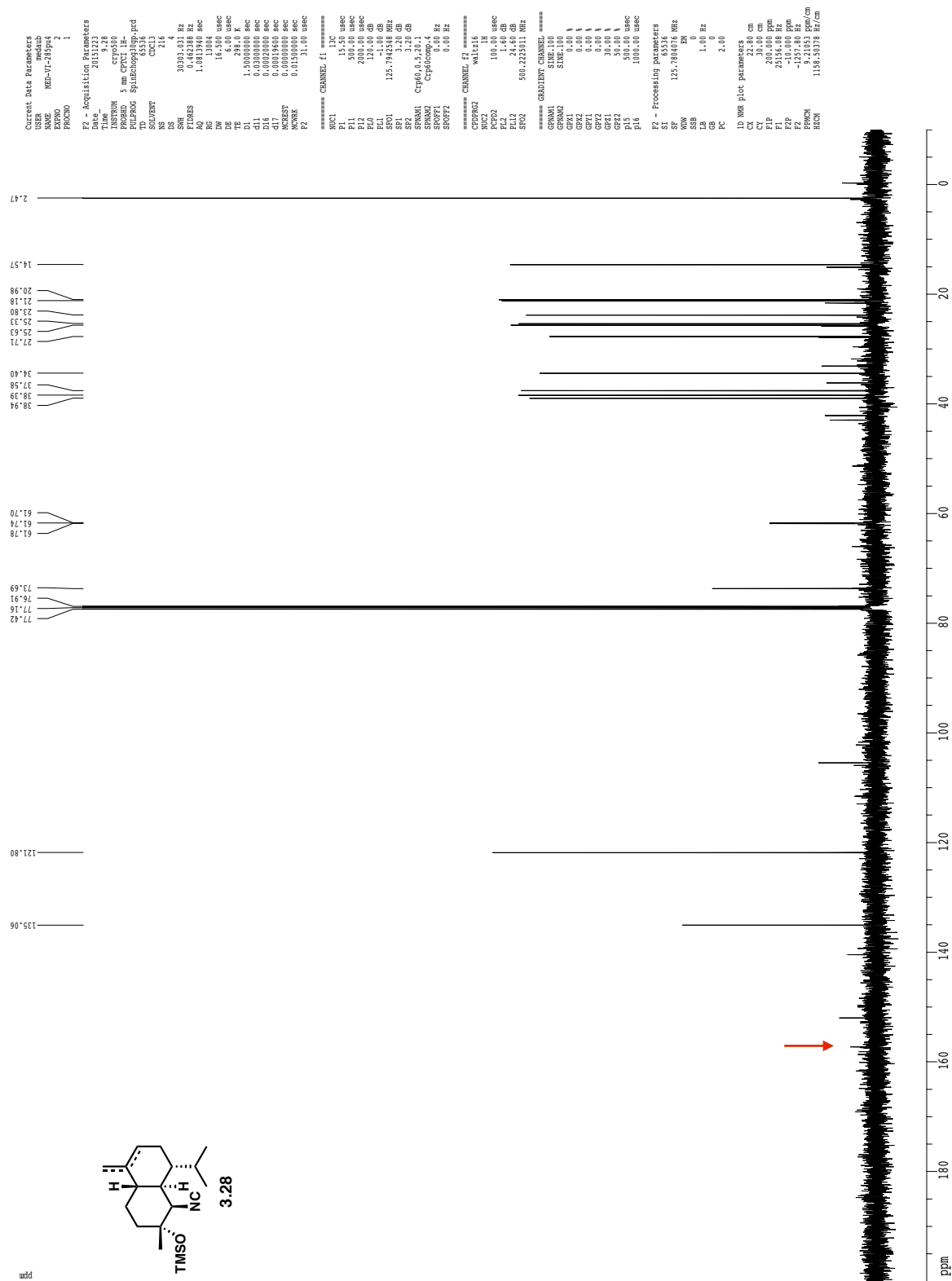
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

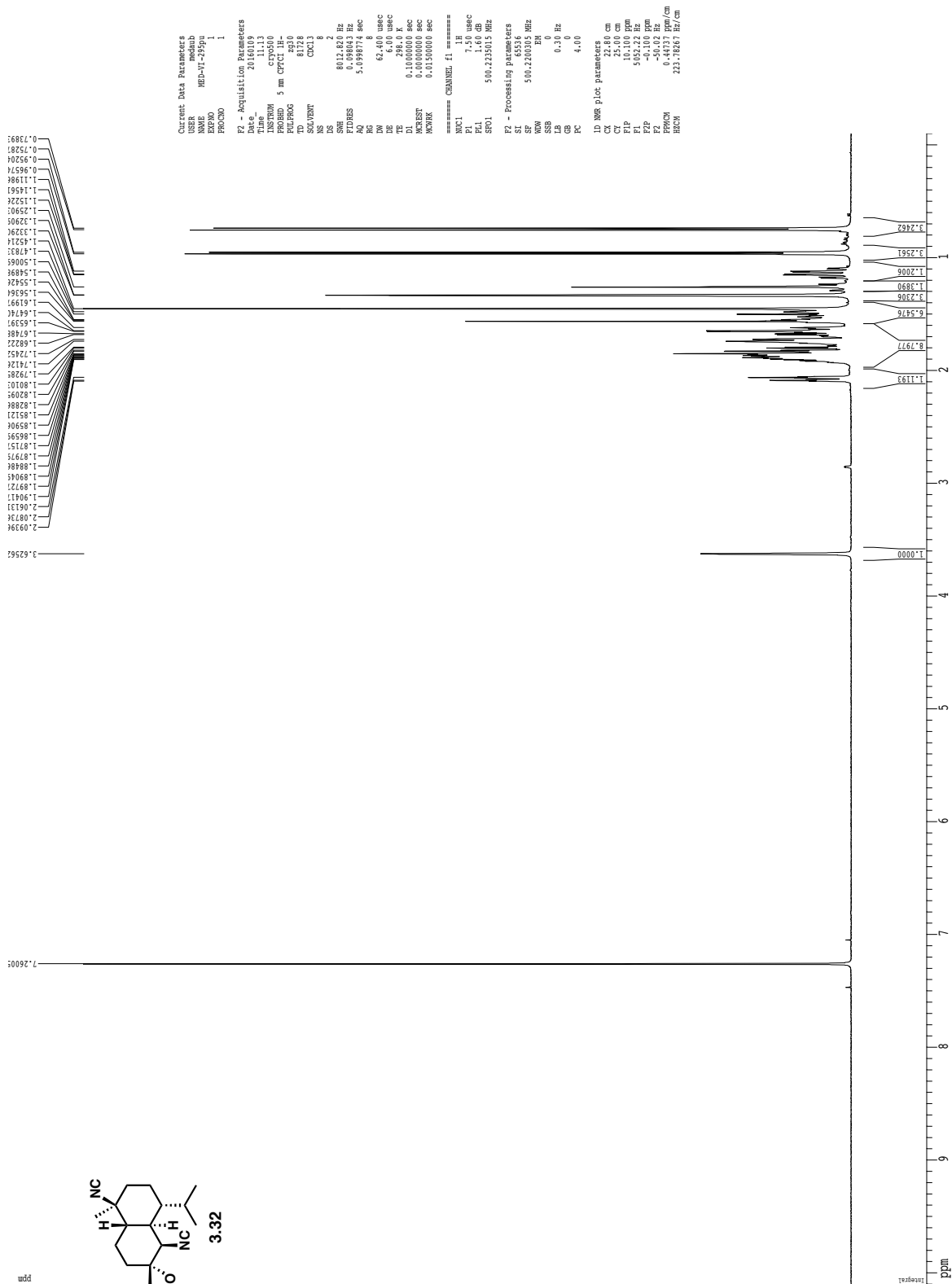
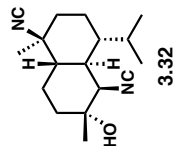


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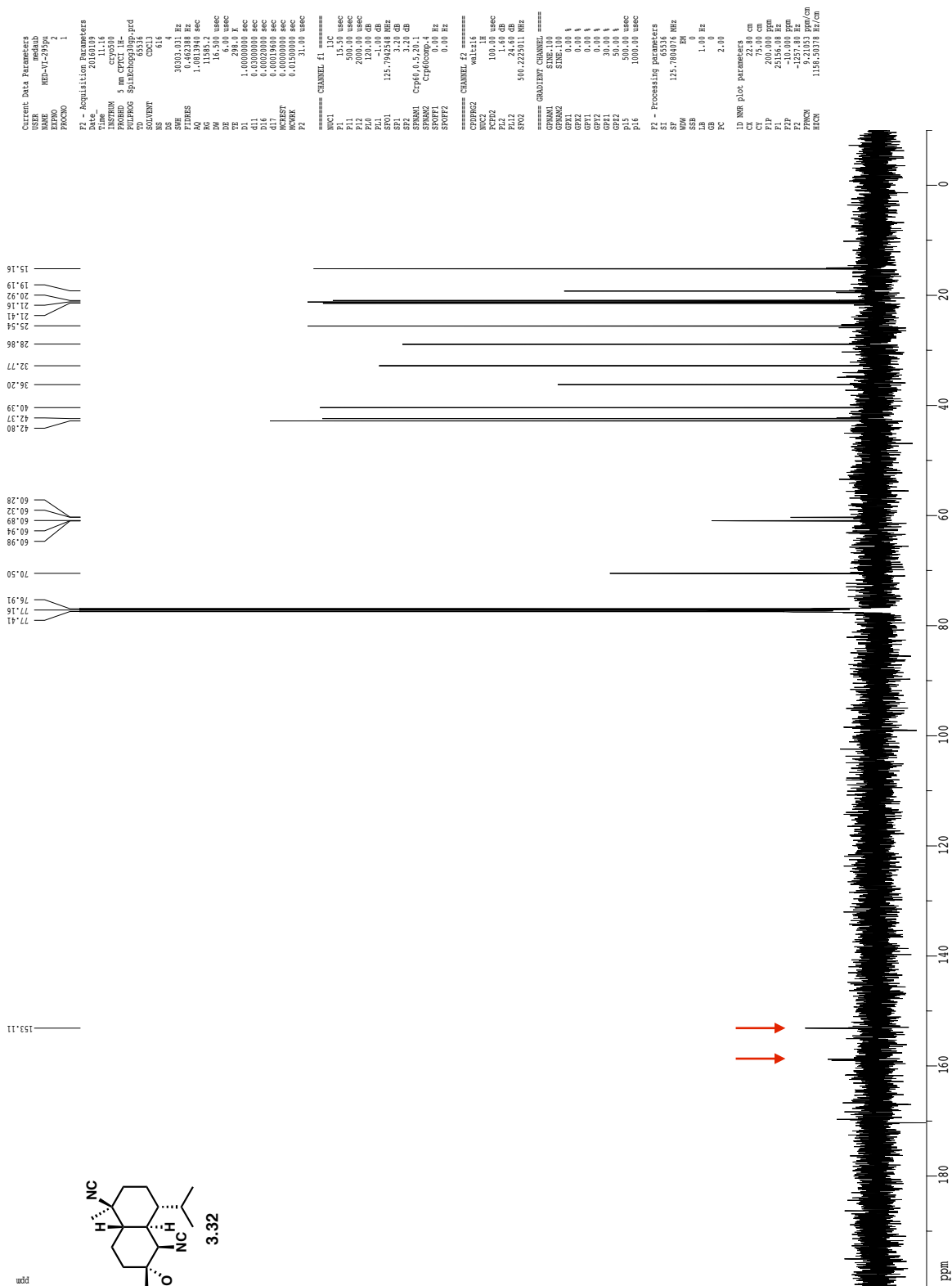


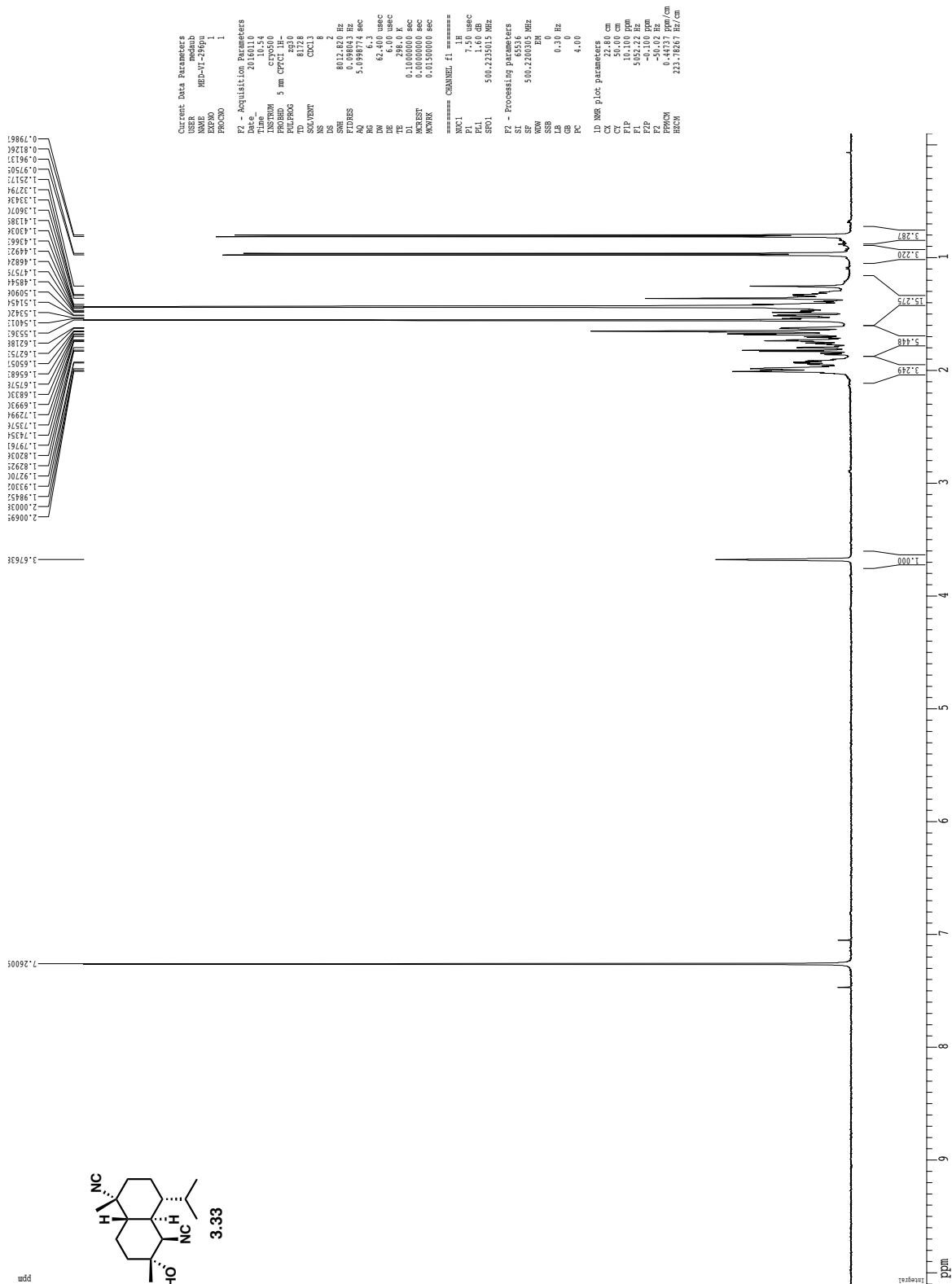
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

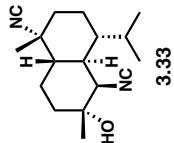
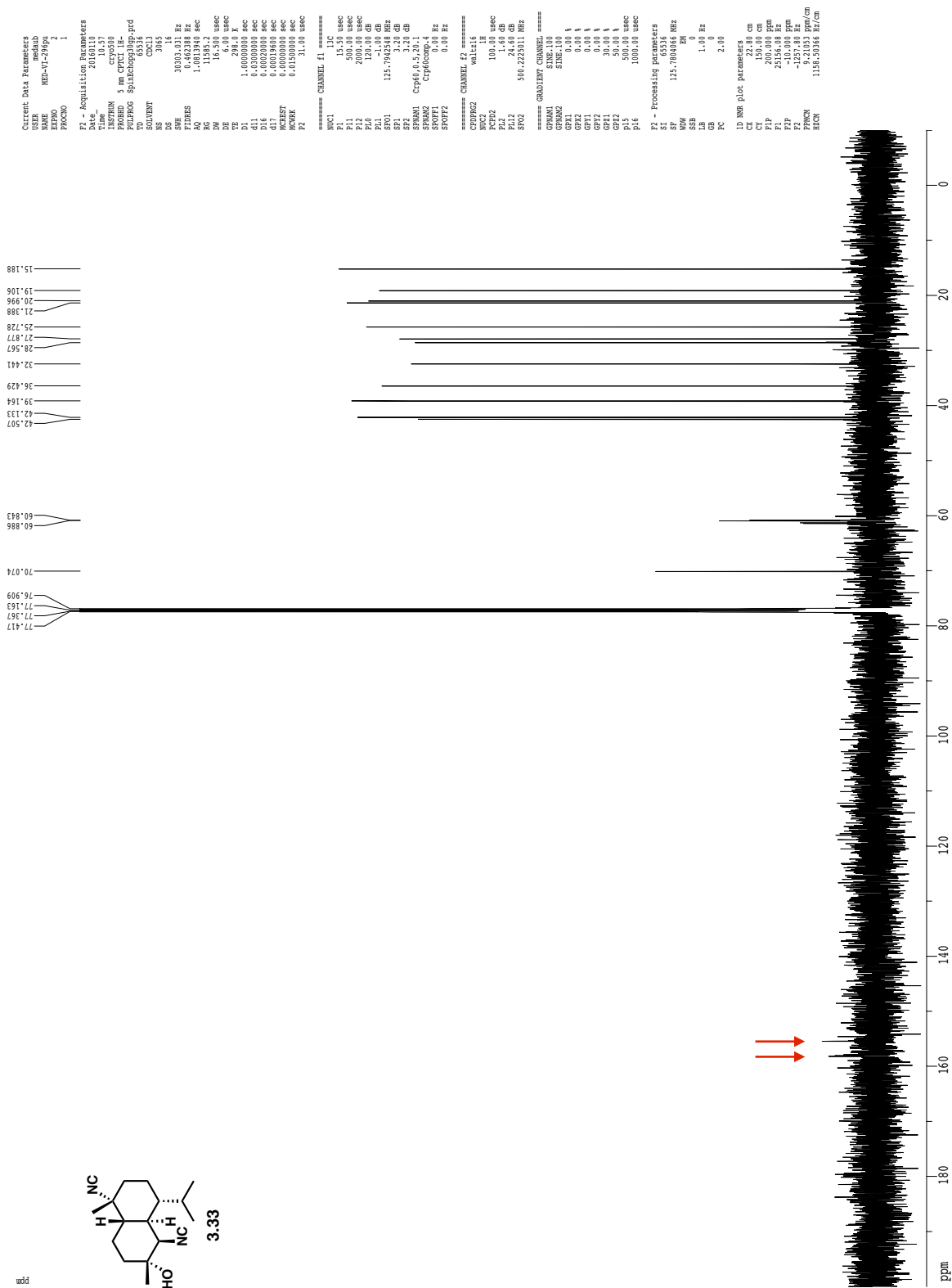


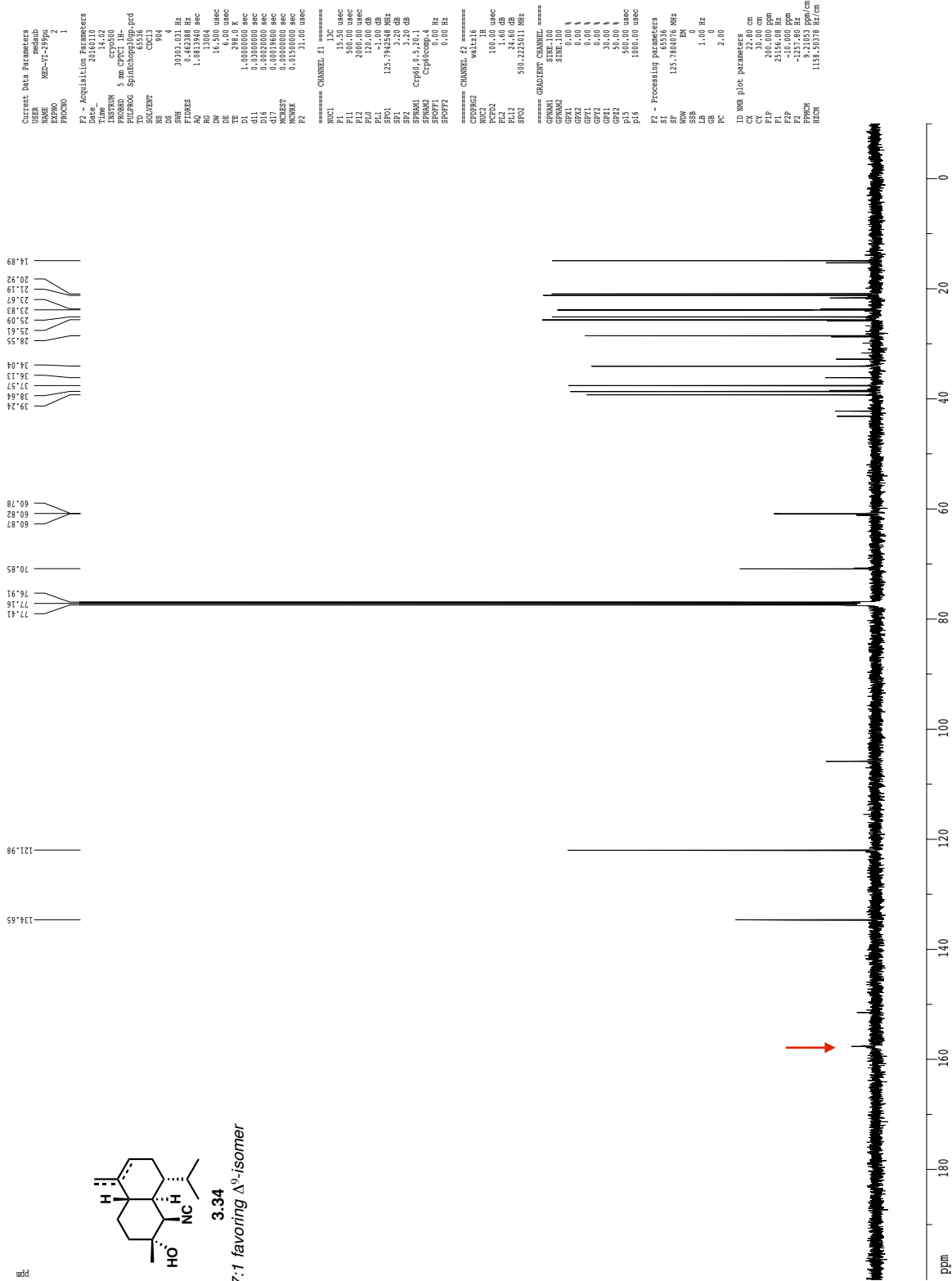


Z-restored spin-echo ¹³C spectrum with ¹H decoupling



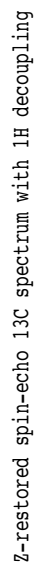


Z-restored spin-echo ^{13}C spectrum with ^1H decoupling

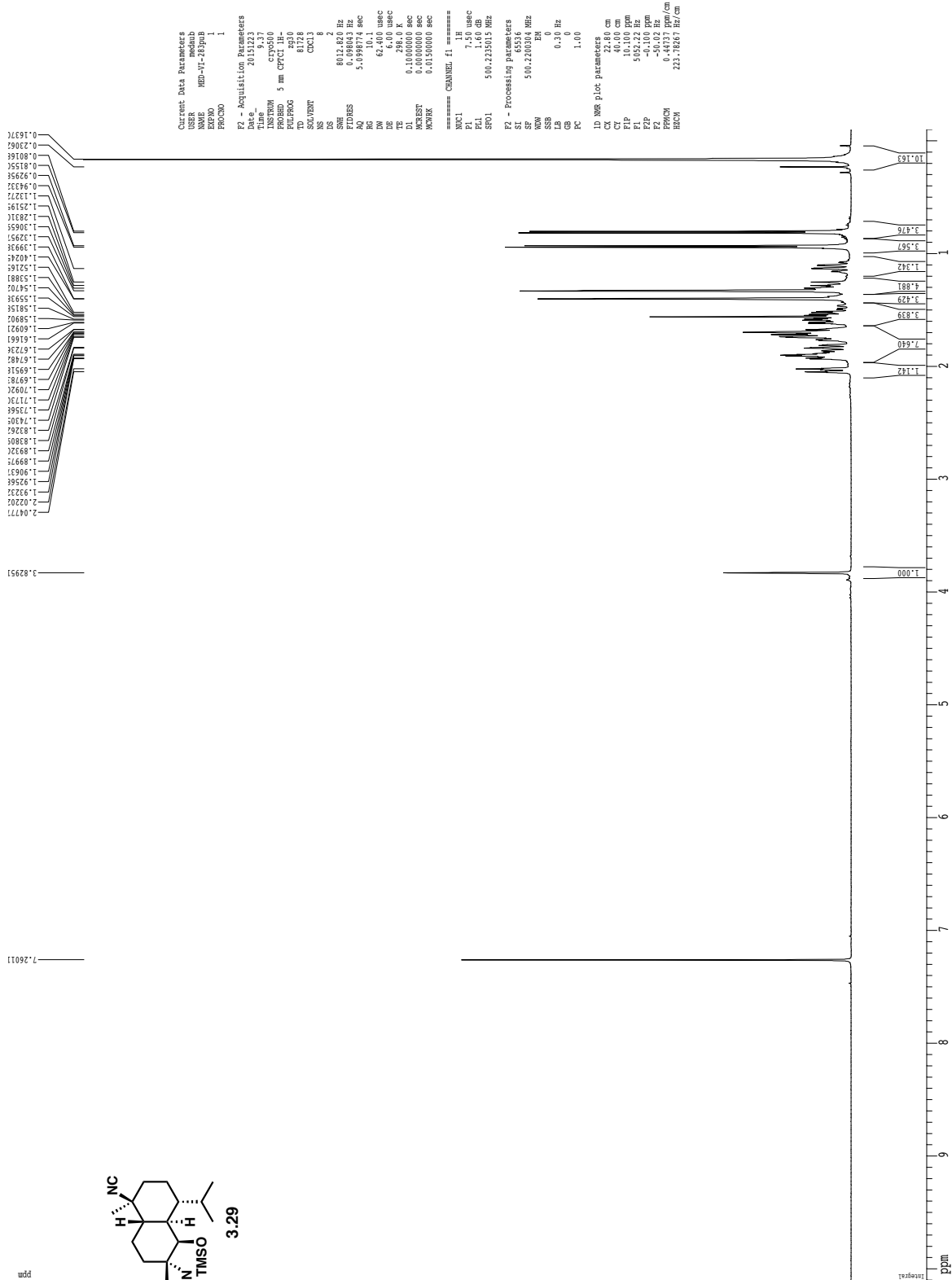
Z-restored spin-echo ^{13}C spectrum with ^1H decoupling

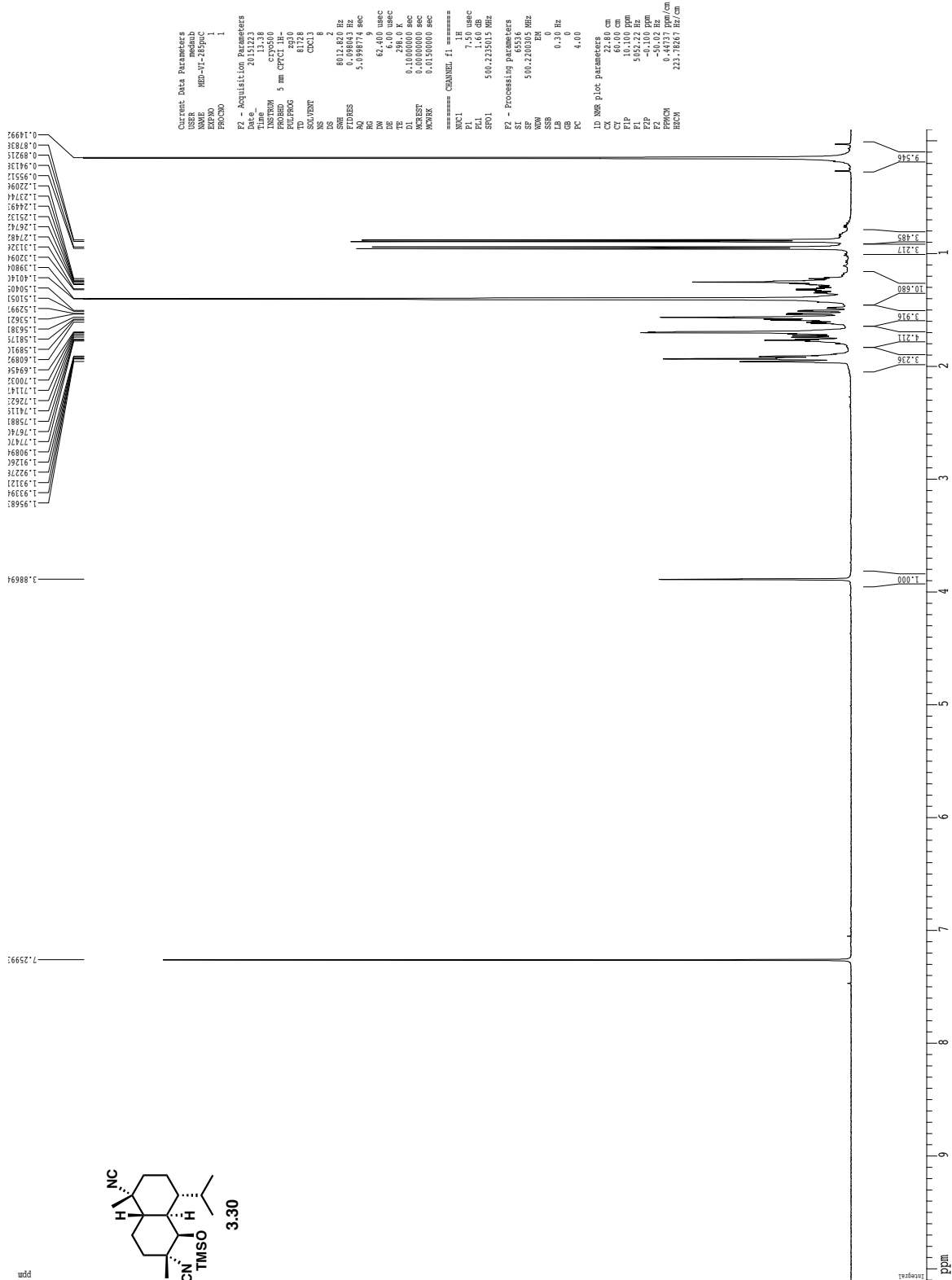
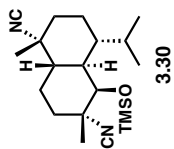
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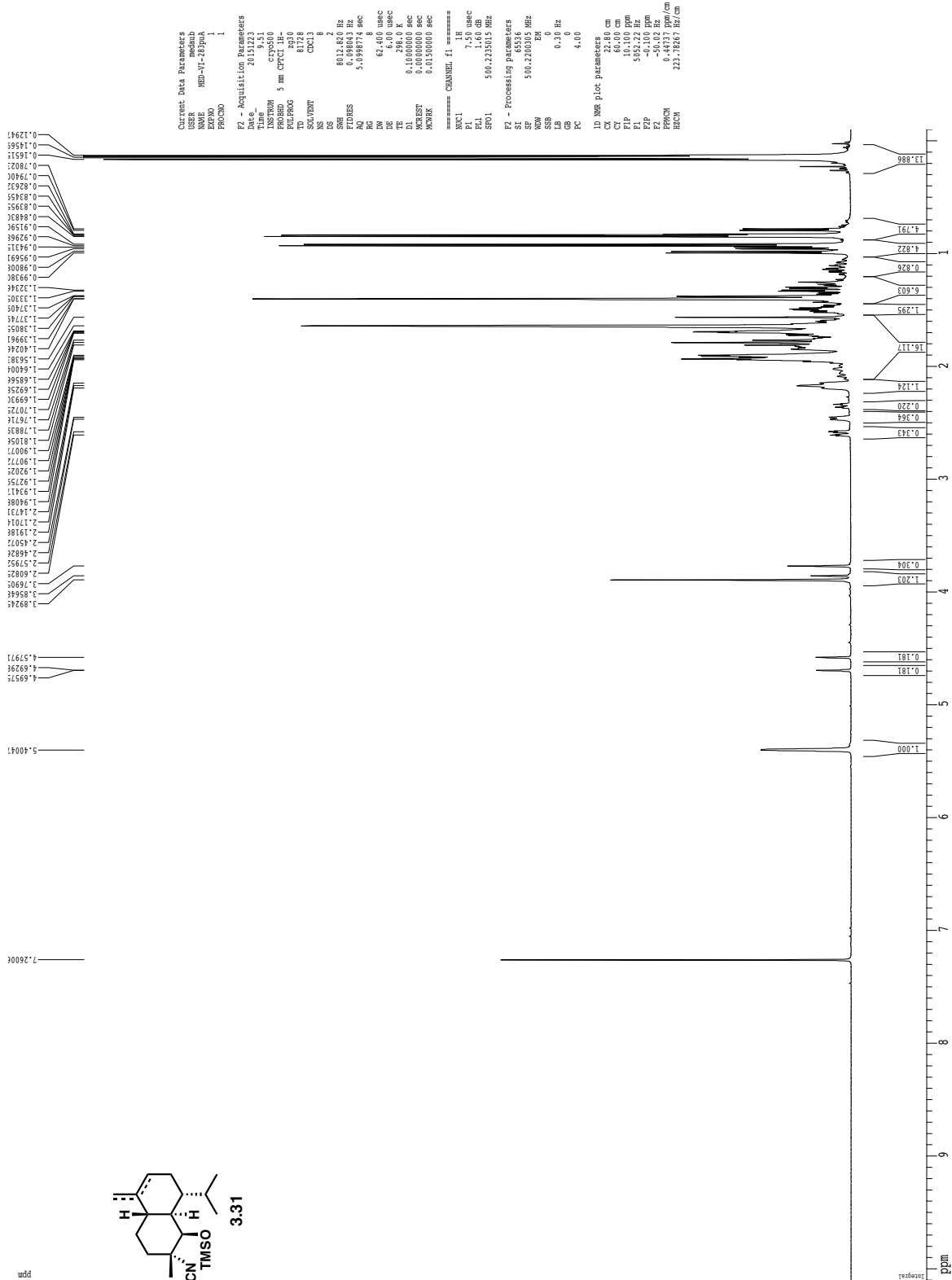


¹H spectrum

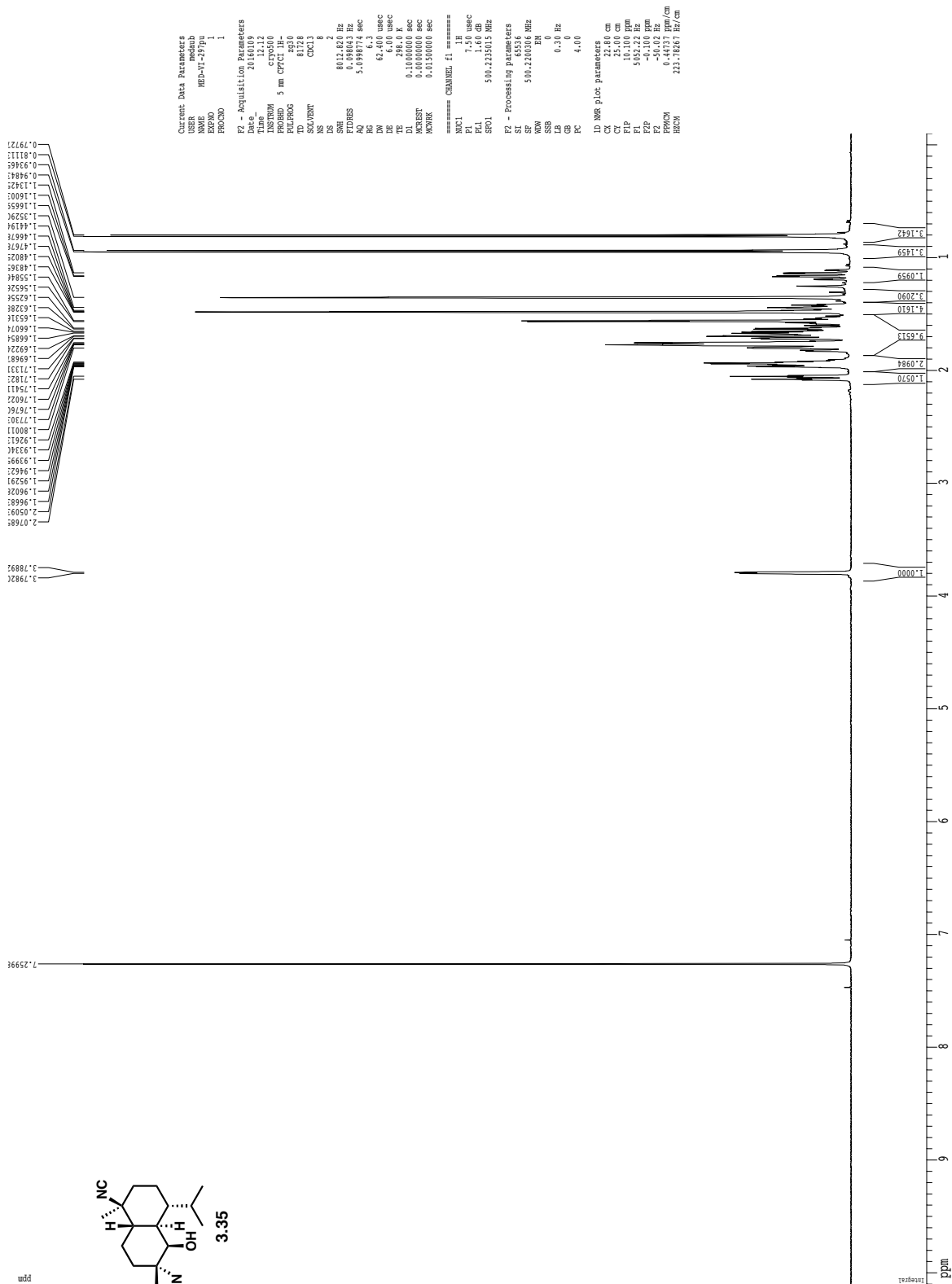




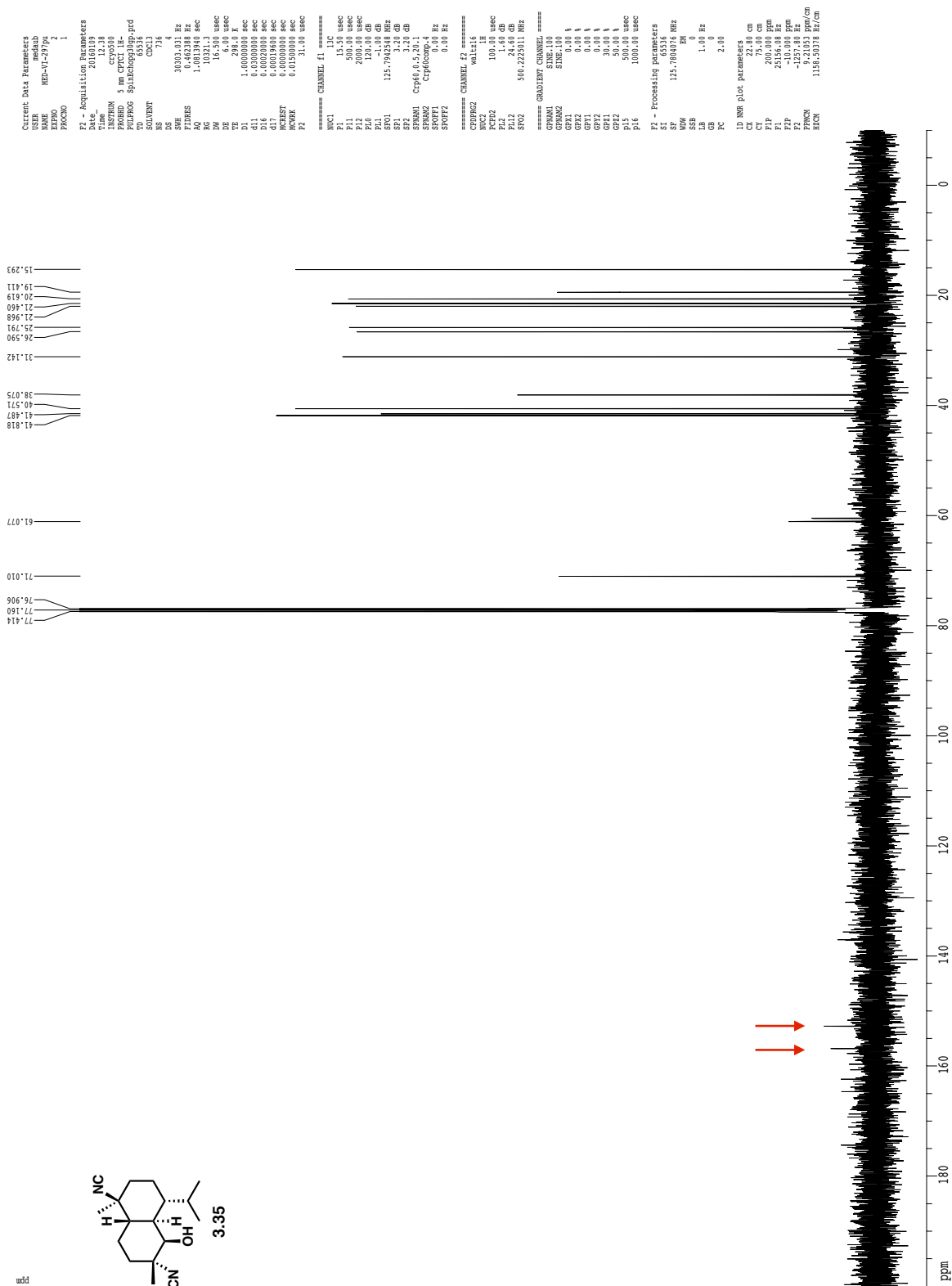
1H spectrum

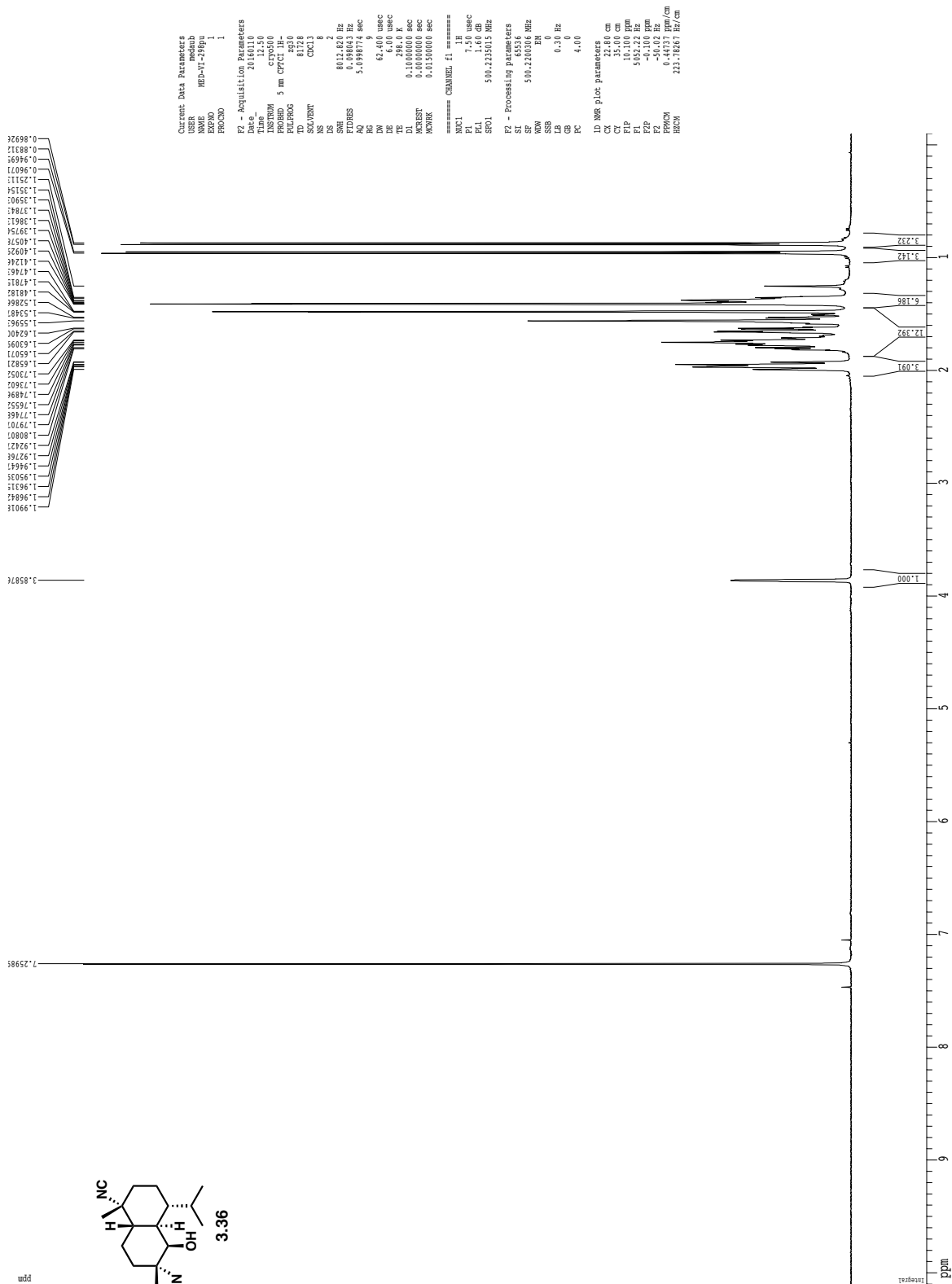
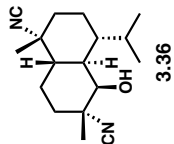


¹H spectrum



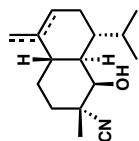
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



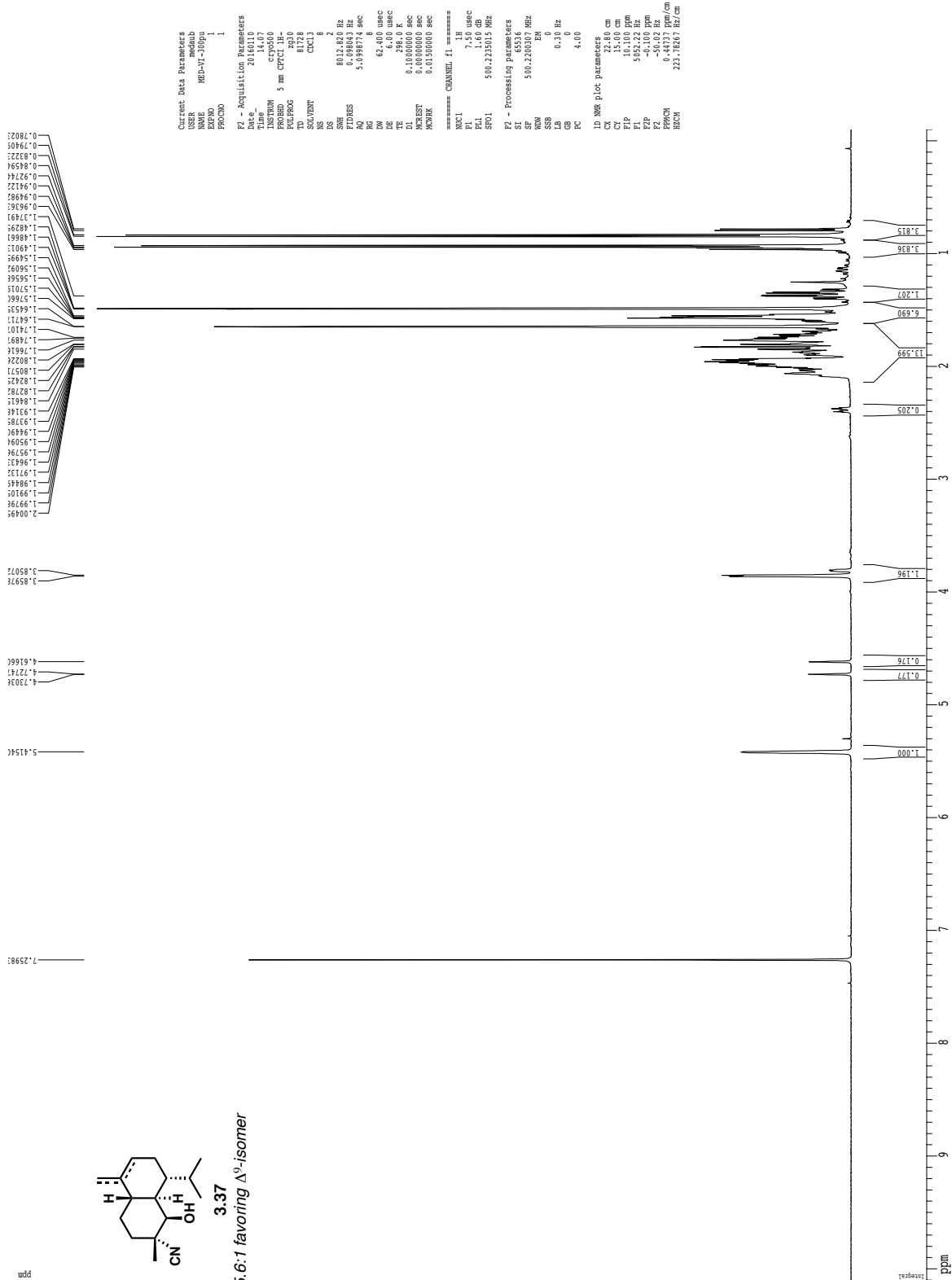


¹H spectrum

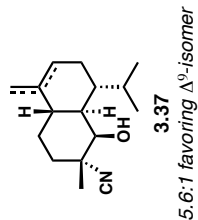
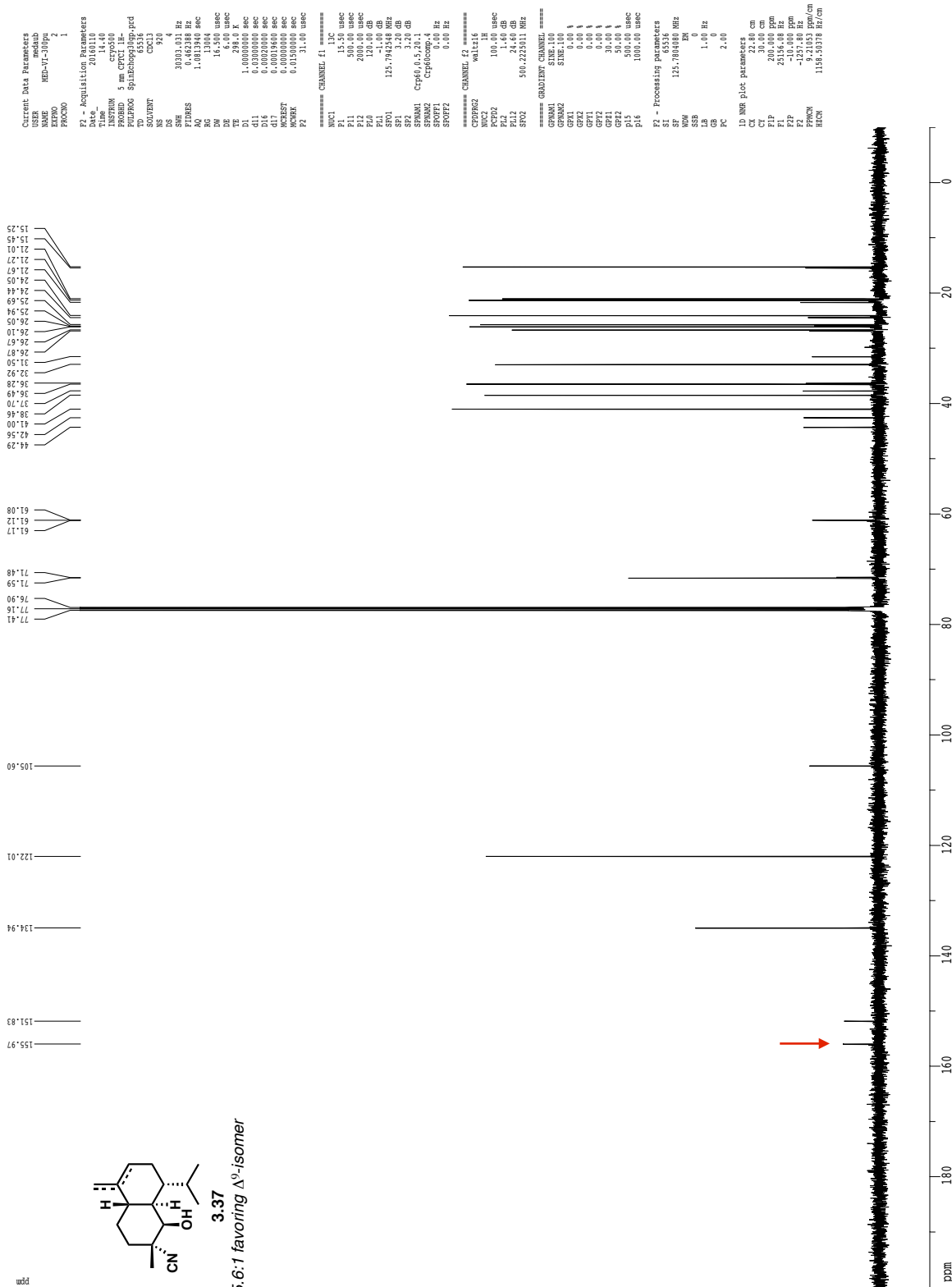
ppm



5.6:1 favoring Δ⁹-isomer

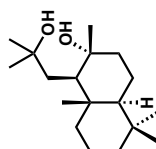


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

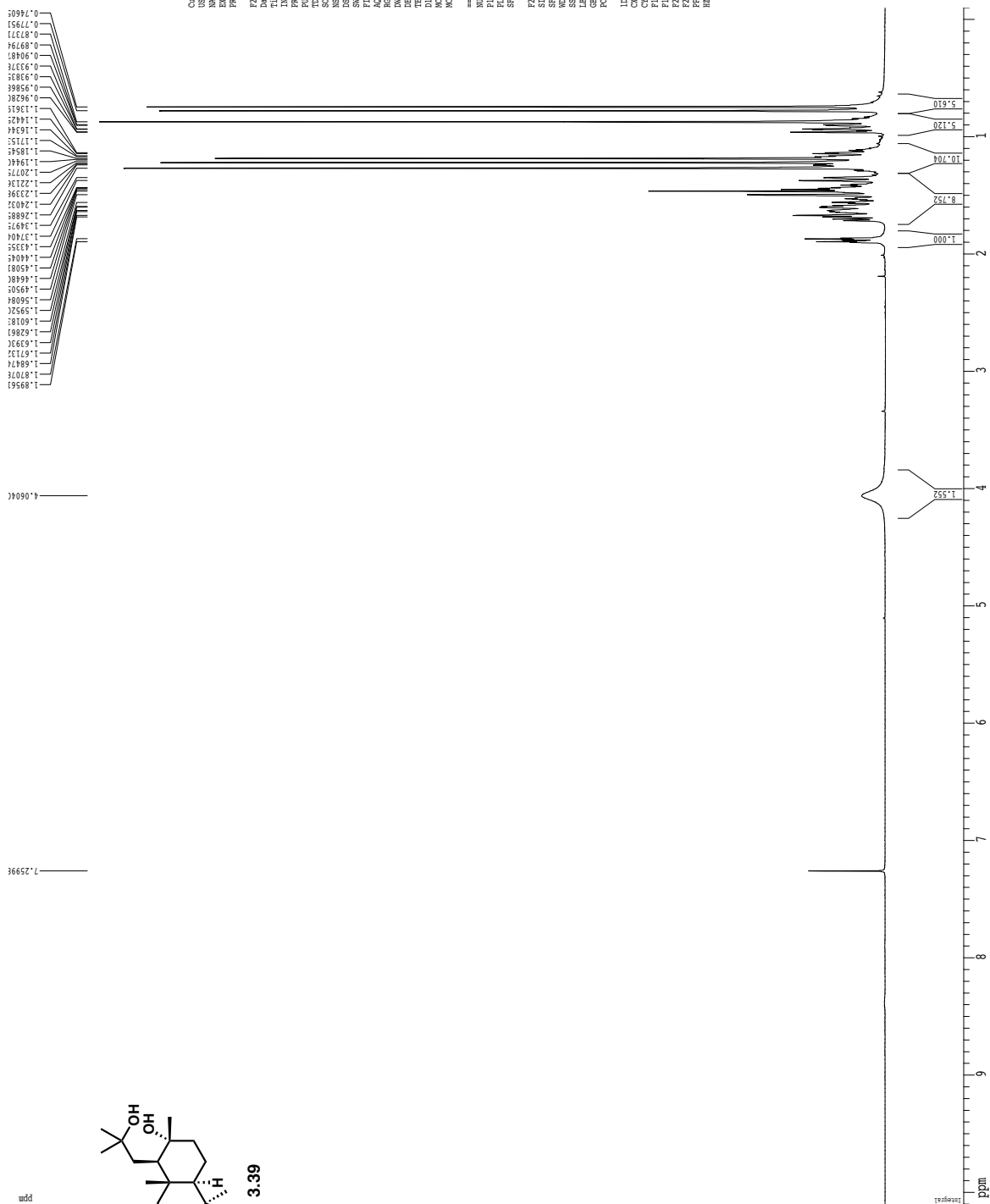


¹H spectrum

ppm



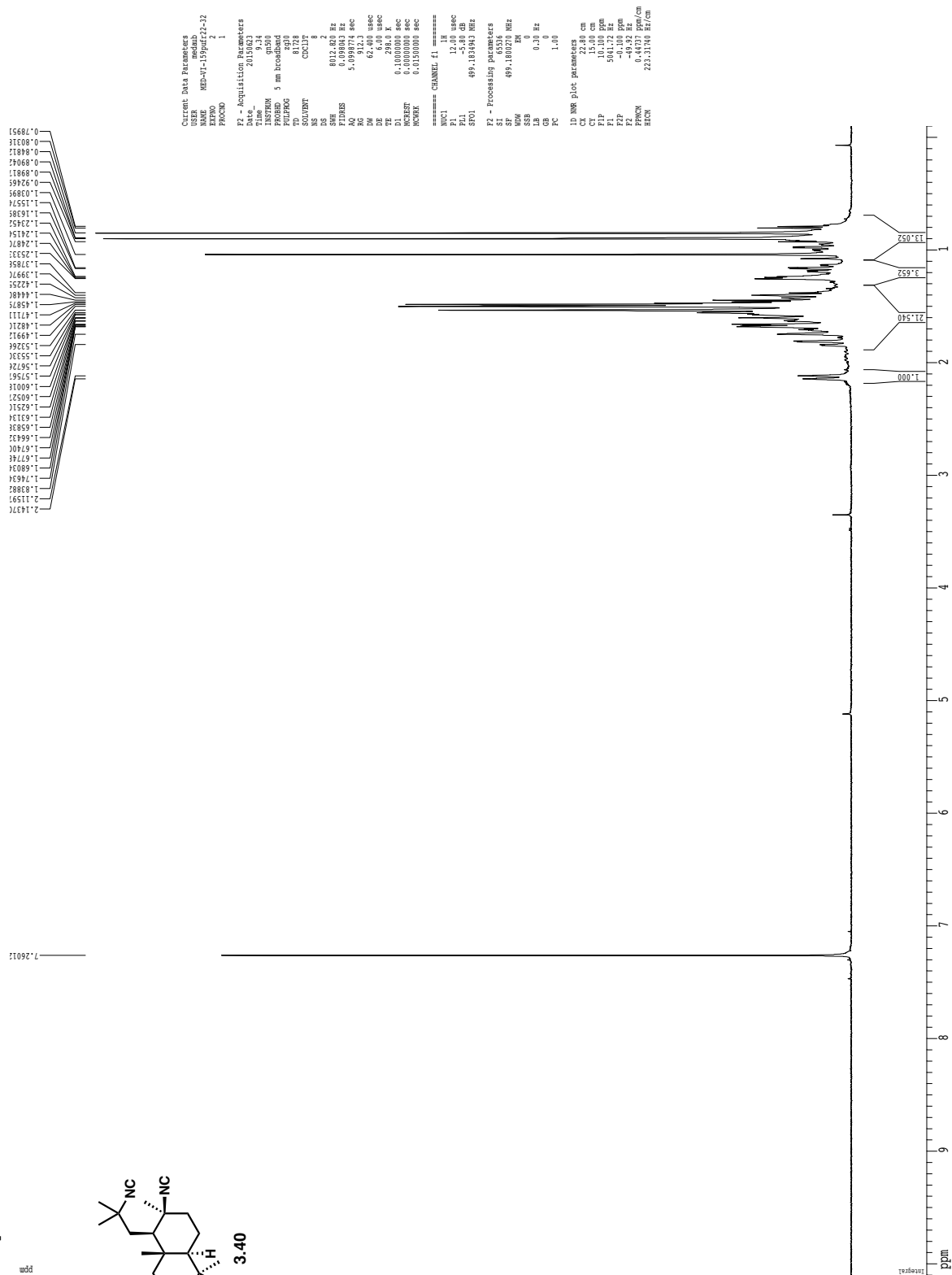
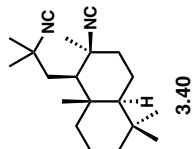
3.39



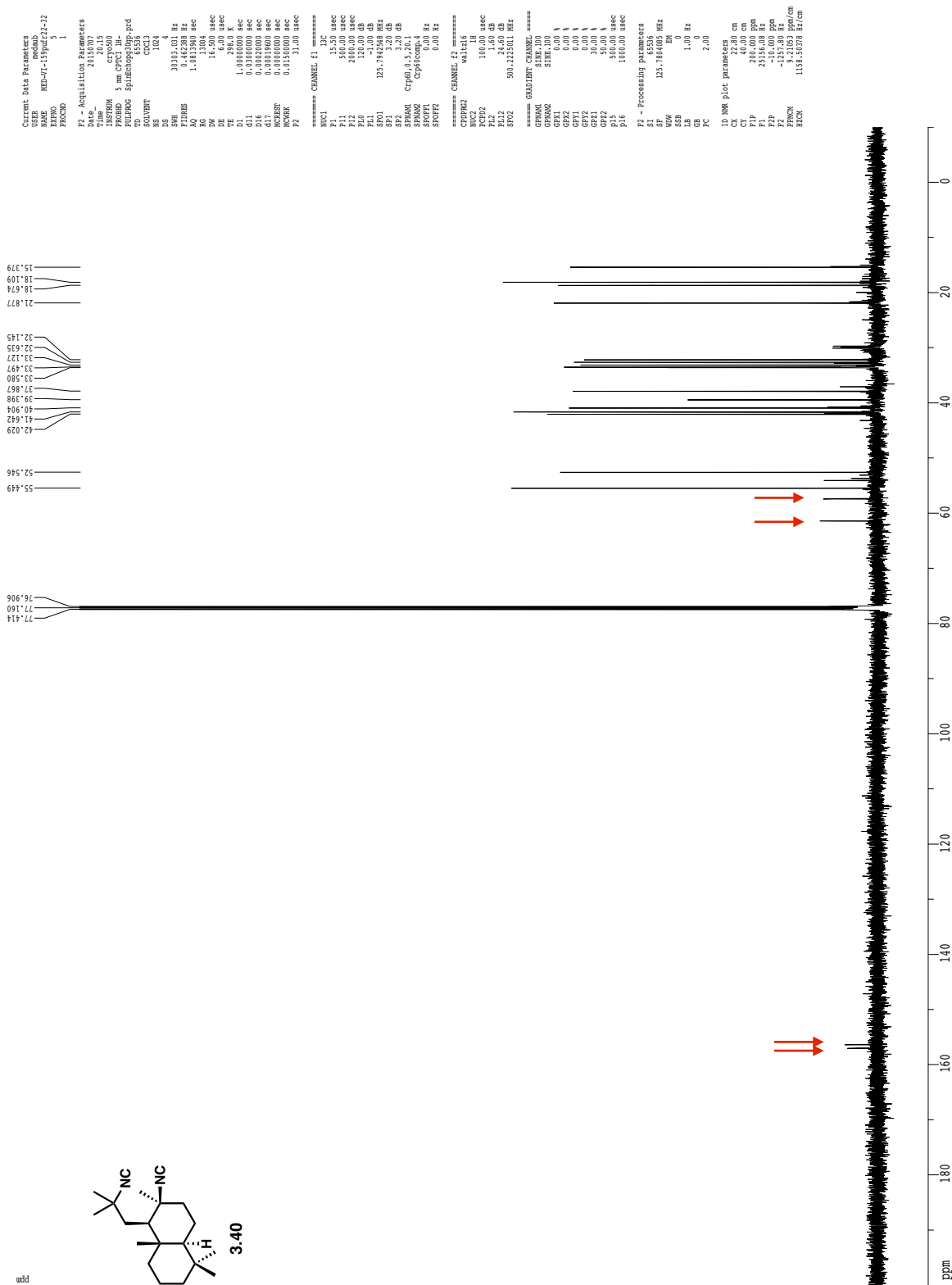
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 EXPNO 1
 PROCNO 1
 F2 - Acquisition Parameters
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 PRG2 81728
 TO COC13T
 SOLVENT
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 SFE 8012.820 Hz
 FIDRES 0.098043 Hz
 AQ 5.0998774 sec
 RG 655
 DW 62.400 usec
 DE 6.00 usec
 TE 298.2 K
 T1 0.10000000 sec
 T1RHO 0.00000000 sec
 MCHST 0.00000000 sec
 MCHRK 0.01500000 sec
 ===== CHANNEL f1 =====
 NUC1 1H
 P1 12.00 usec
 PL1 -5.80 dB
 SFO1 499.1359943 MHz
 F2 - Processing parameters
 SI 65514
 SF 499.1359943 MHz
 NS 8
 DS 2
 SSB 0
 LB 0.30 Hz
 GB 0
 CB 0
 PC 1.00
 ID NMR plot parameters
 CX 22.80 cm
 CY 22.80 cm
 CZ 45.00 cm
 FFP 10.100 ppm
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 F2 -4.100 ppm
 F3 0.00000000 Hz
 FWHM 0.44737 ppm/cm
 HCM 223.31740 Hz/cm

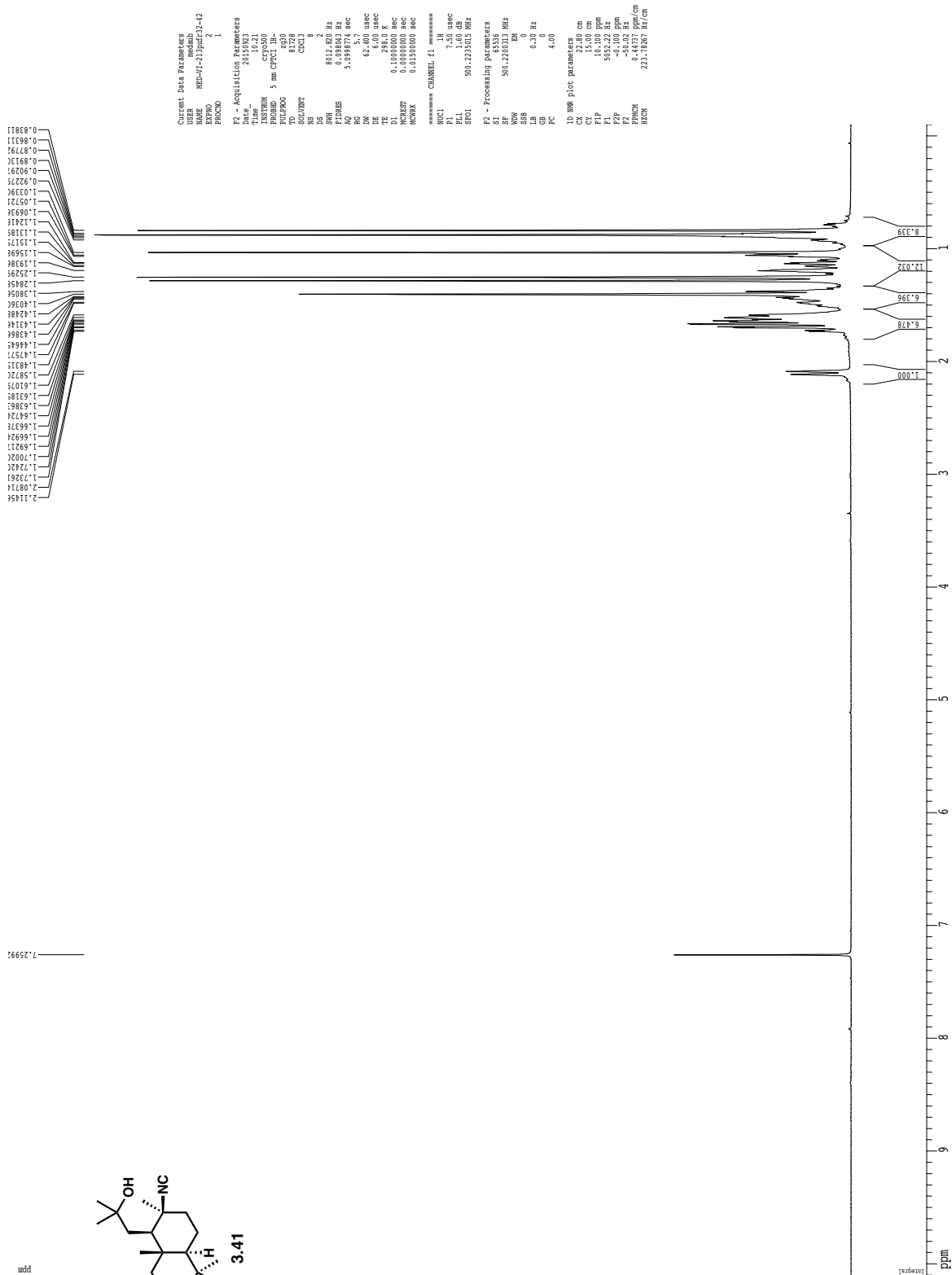
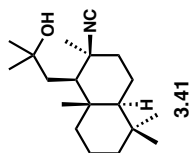
¹³C spectrum with ¹H decoupling



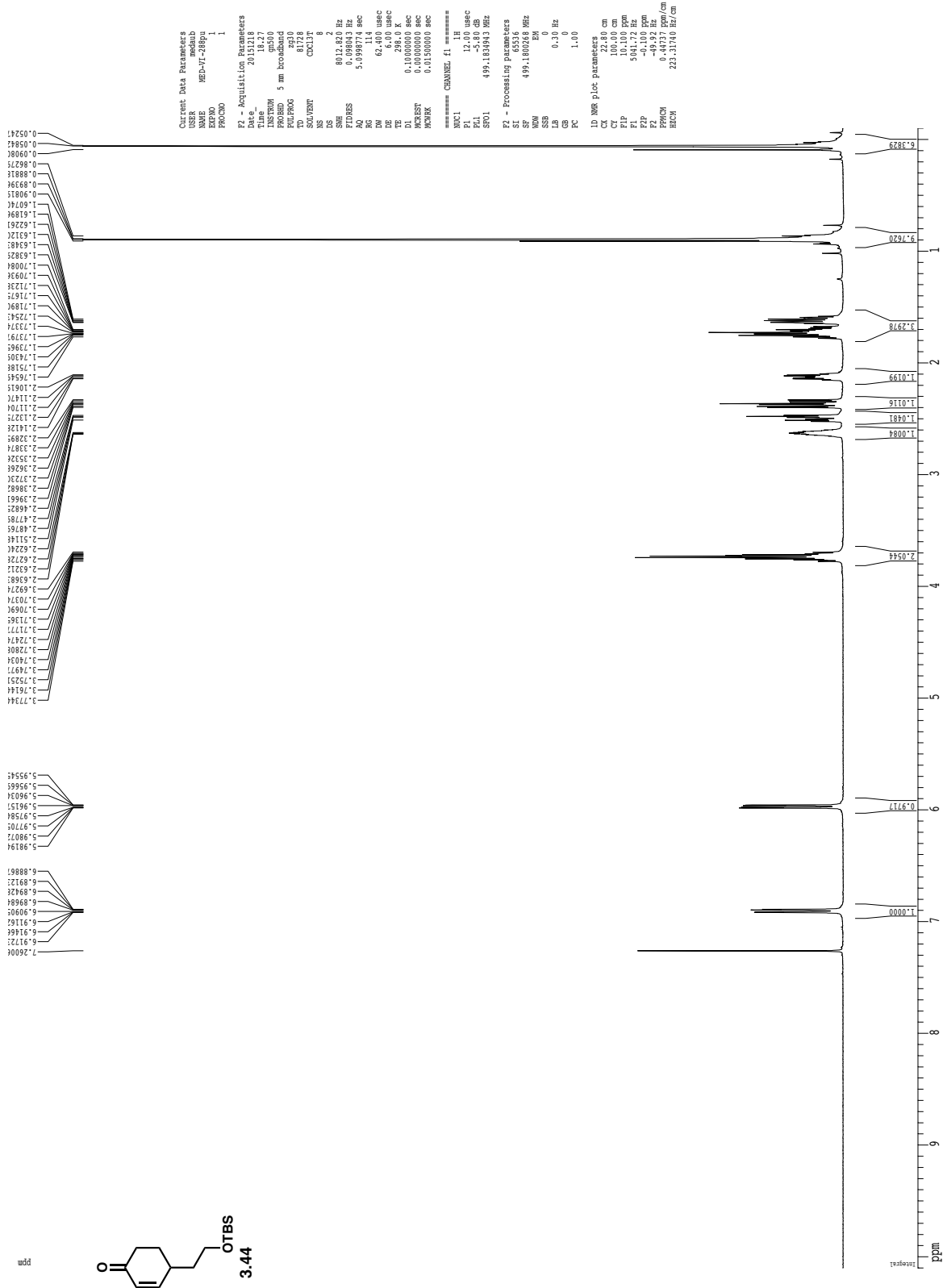


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

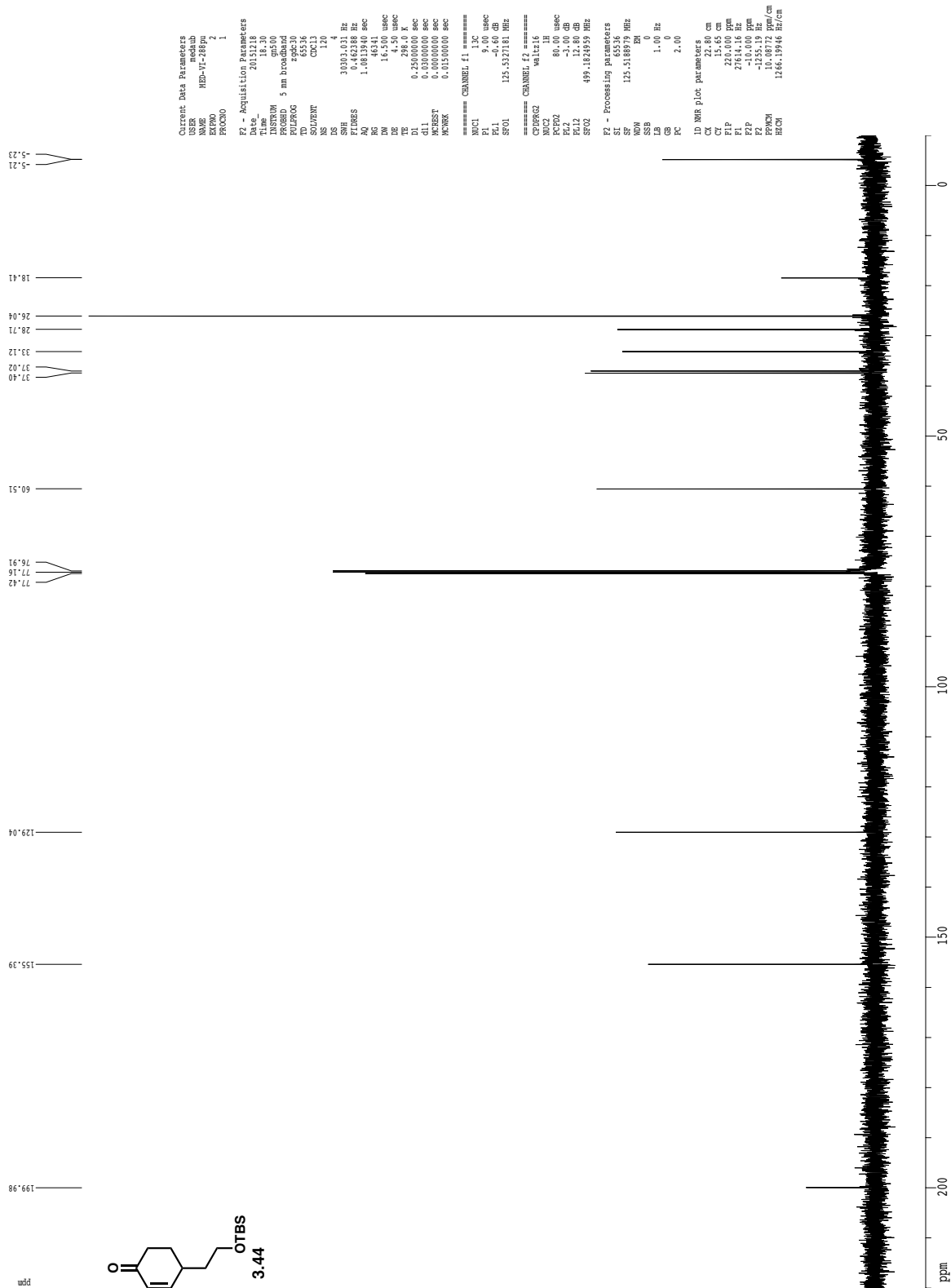


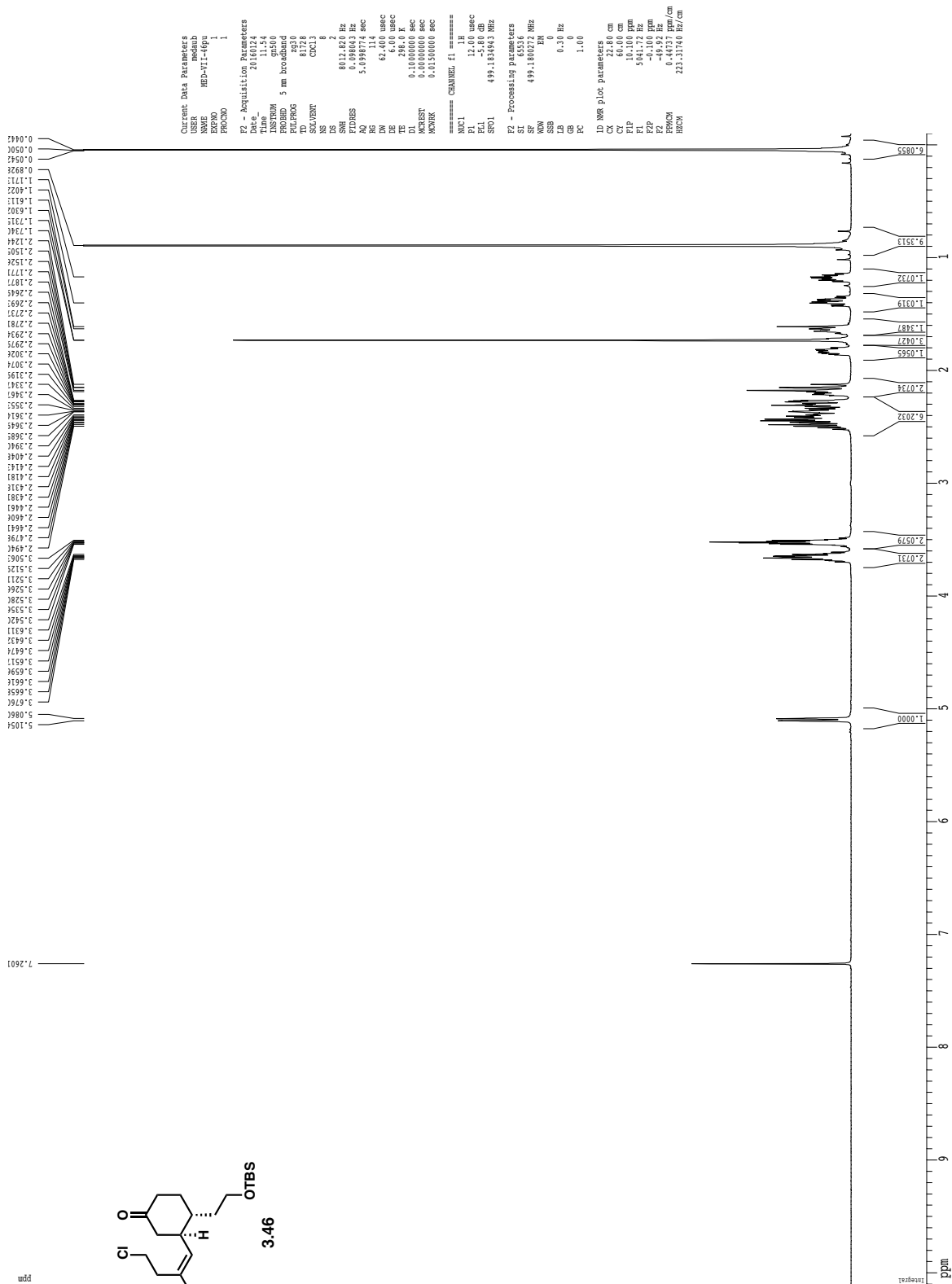
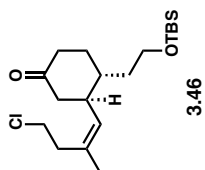


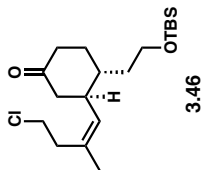
¹H spectrum



¹³C spectrum with ¹H decoupling





[illegible]

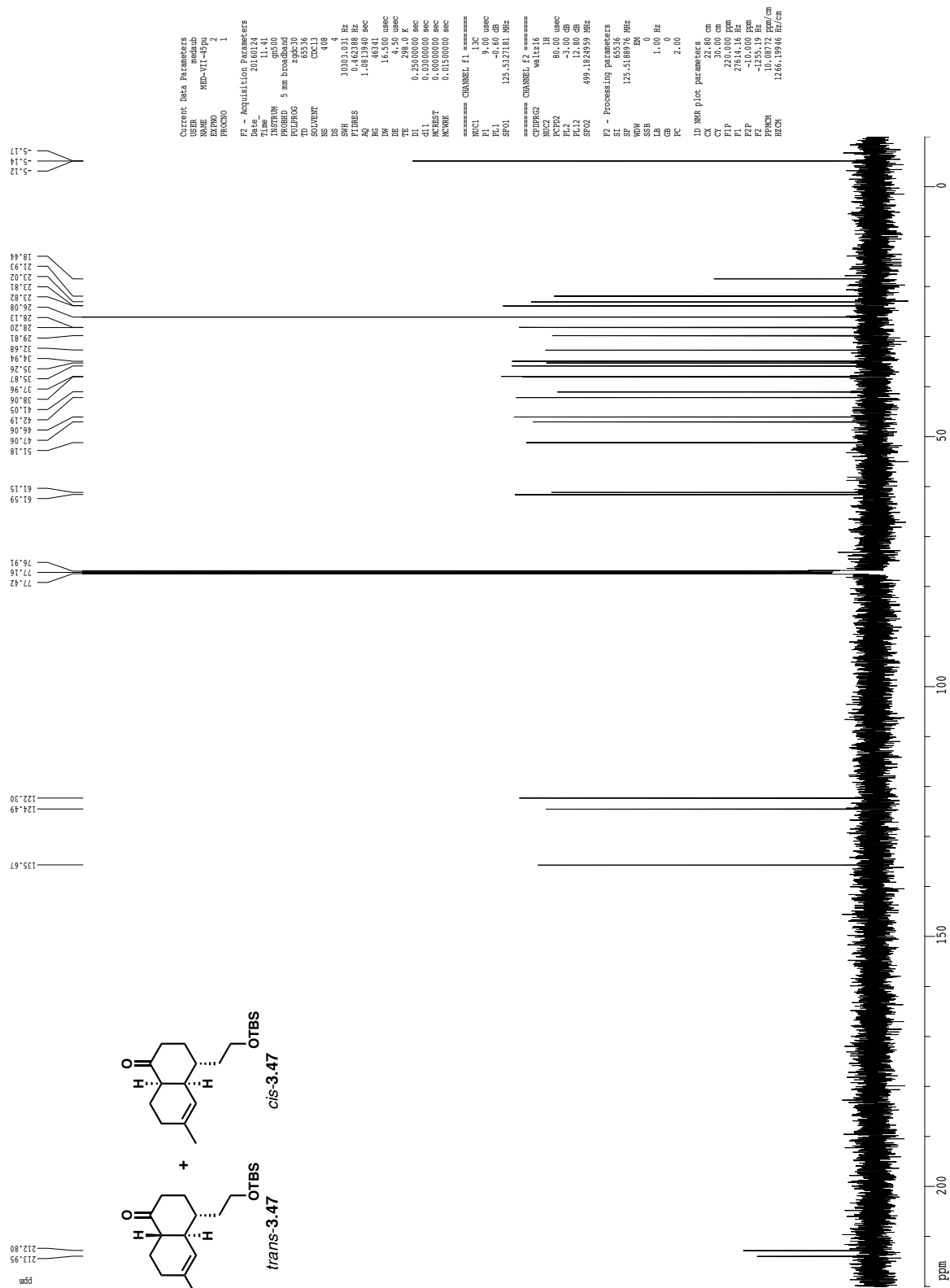
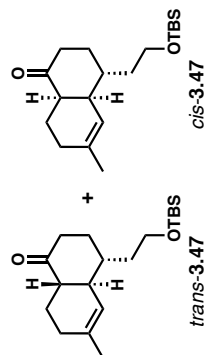


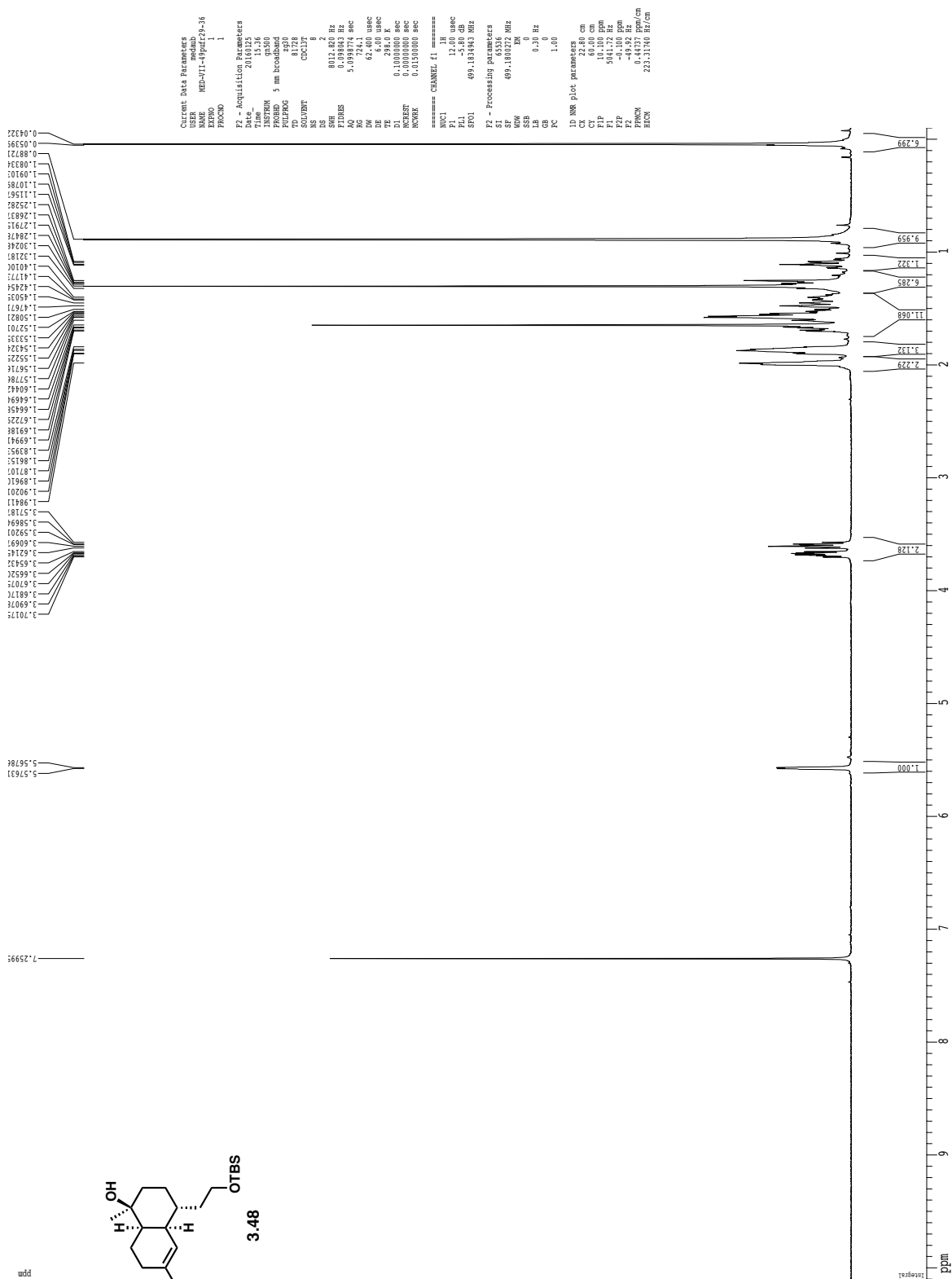
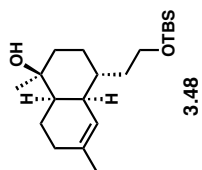
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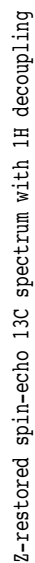


Current Data Parameters		P2 - Acquisition Parameters		P2 - Processing parameters		1D NMR plot parameters	
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PROG	zgpg30	PROG	zgpg30	PROG	zgpg30	PROG	zgpg30
SOLVENT	CDCl3	SOLVENT	CDCl3	SOLVENT	CDCl3	SOLVENT	CDCl3
NUC1	1H	NUC1	1H	NUC1	1H	NUC1	1H
CHNMR1	1H	CHNMR1	1H	CHNMR1	1H	CHNMR1	1H
RF1	12.00 uSec	RF1	12.00 uSec	RF1	12.00 uSec	RF1	12.00 uSec
NUC2	13C	NUC2	13C	NUC2	13C	NUC2	13C
RF2	499.183493 Hz	RF2	499.183493 Hz	RF2	499.183493 Hz	RF2	499.183493 Hz
NUC3	15N	NUC3	15N	NUC3	15N	NUC3	15N
RF3	499.180271 MHz	RF3	499.180271 MHz	RF3	499.180271 MHz	RF3	499.180271 MHz
NUC4	19F	NUC4	19F	NUC4	19F	NUC4	19F
RF4	0.00 Hz	RF4	0.00 Hz	RF4	0.00 Hz	RF4	0.00 Hz
GB	1.00	GB	1.00	GB	1.00	GB	1.00
PC	1.00	PC	1.00	PC	1.00	PC	1.00
CHX	22.40 cm	CHX	22.40 cm	CHX	22.40 cm	CHX	22.40 cm
CCX	16.00 cm	CCX	16.00 cm	CCX	16.00 cm	CCX	16.00 cm
FF1	5041.72 Hz	FF1	5041.72 Hz	FF1	5041.72 Hz	FF1	5041.72 Hz
FF2	-1.00 ppm	FF2	-1.00 ppm	FF2	-1.00 ppm	FF2	-1.00 ppm
FF3	0.00 Hz	FF3	0.00 Hz	FF3	0.00 Hz	FF3	0.00 Hz
FF4	0.00 Hz	FF4	0.00 Hz	FF4	0.00 Hz	FF4	0.00 Hz
FF5	0.00 Hz	FF5	0.00 Hz	FF5	0.00 Hz	FF5	0.00 Hz
FF6	0.00 Hz	FF6	0.00 Hz	FF6	0.00 Hz	FF6	0.00 Hz
FF7	0.00 Hz	FF7	0.00 Hz	FF7	0.00 Hz	FF7	0.00 Hz
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FF11	0.00 Hz	FF11	0.00 Hz	FF11	0.00 Hz	FF11	0.00 Hz
FF12	0.00 Hz	FF12	0.00 Hz	FF12	0.00 Hz	FF12	0.00 Hz
FF13	0.00 Hz	FF13	0.00 Hz	FF13	0.00 Hz	FF13	0.00 Hz
FF14	0.00 Hz	FF14	0.00 Hz	FF14	0.00 Hz	FF14	0.00 Hz
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FF16	0.00 Hz	FF16	0.00 Hz	FF16	0.00 Hz	FF16	0.00 Hz
FF17	0.00 Hz	FF17	0.00 Hz	FF17	0.00 Hz	FF17	0.00 Hz
FF18	0.00 Hz	FF18	0.00 Hz	FF18	0.00 Hz	FF18	0.00 Hz
FF19	0.00 Hz	FF19	0.00 Hz	FF19	0.00 Hz	FF19	0.00 Hz
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FF22	0.00 Hz	FF22	0.00 Hz	FF22	0.00 Hz	FF22	0.00 Hz
FF23	0.00 Hz	FF23	0.00 Hz	FF23	0.00 Hz	FF23	0.00 Hz
FF24	0.00 Hz	FF24	0.00 Hz	FF24	0.00 Hz	FF24	0.00 Hz
FF25	0.00 Hz	FF25	0.00 Hz	FF25	0.00 Hz	FF25	0.00 Hz
FF26	0.00 Hz	FF26	0.00 Hz	FF26	0.00 Hz	FF26	0.00 Hz
FF27	0.00 Hz	FF27	0.00 Hz	FF27	0.00 Hz	FF27	0.00 Hz
FF28	0.00 Hz	FF28	0.00 Hz	FF28	0.00 Hz	FF28	0.00 Hz
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FF30	0.00 Hz	FF30</					

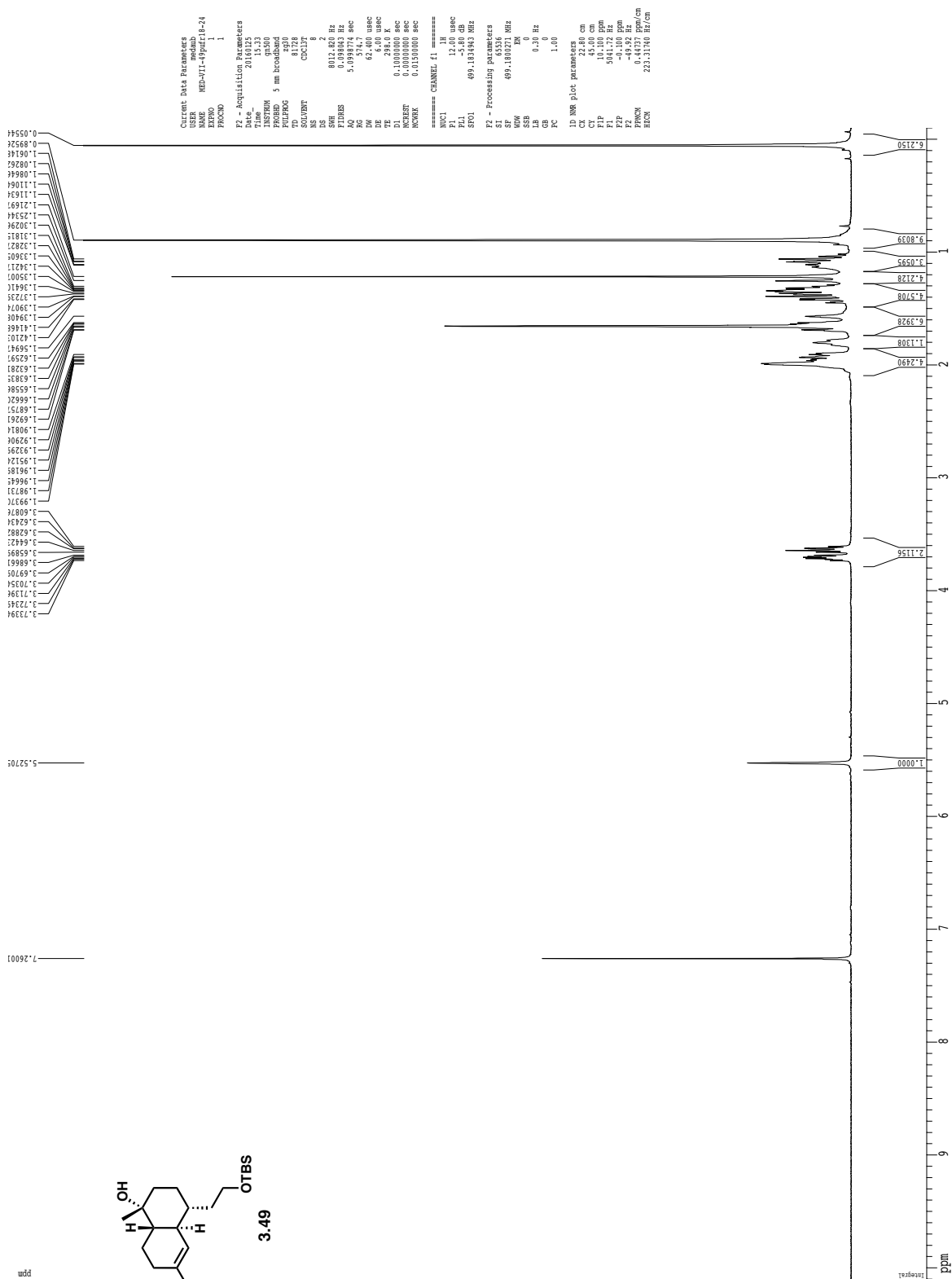
¹³C spectrum with 1H decoupling

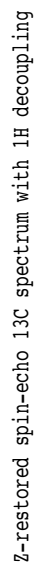




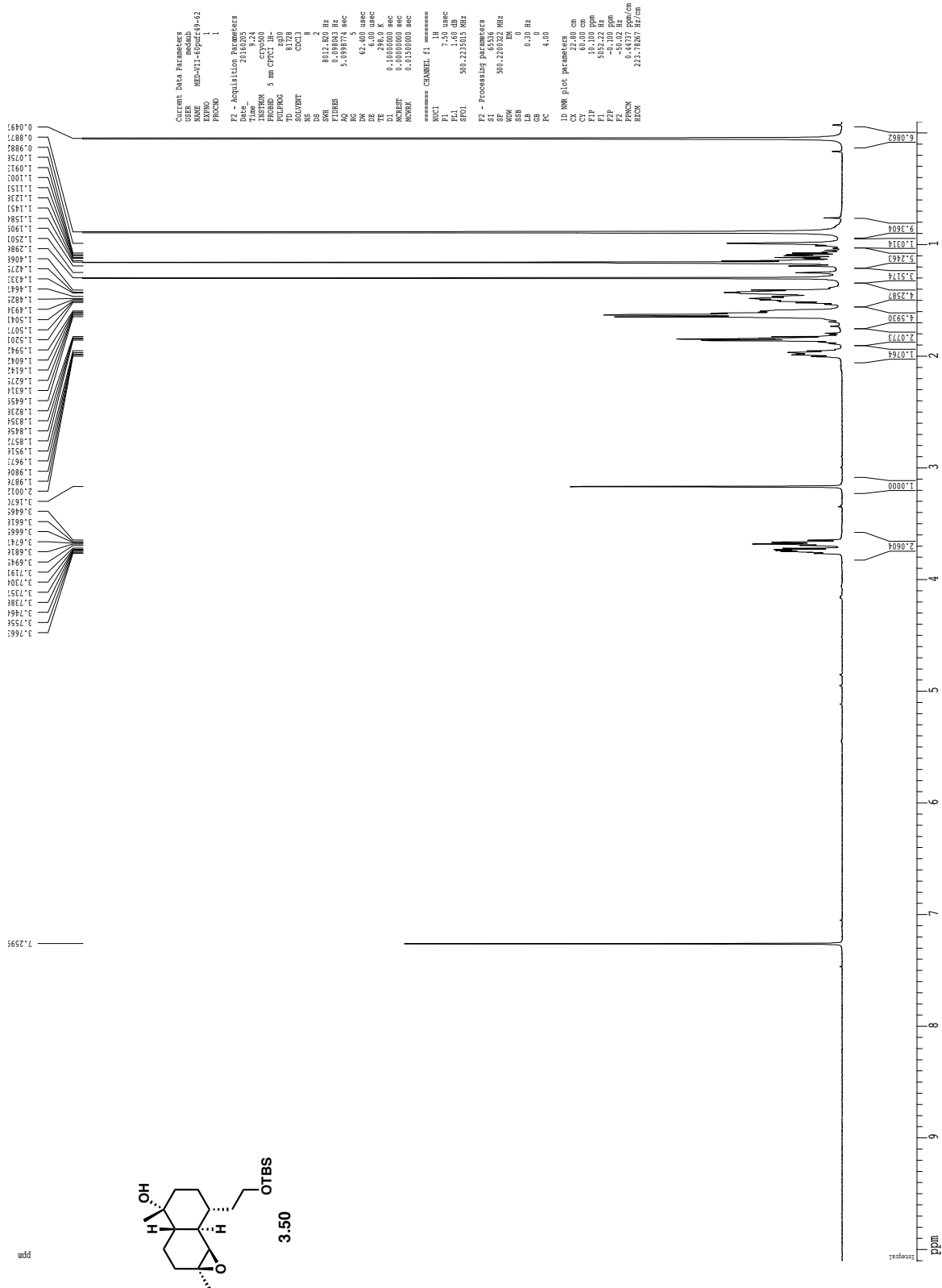


¹H spectrum

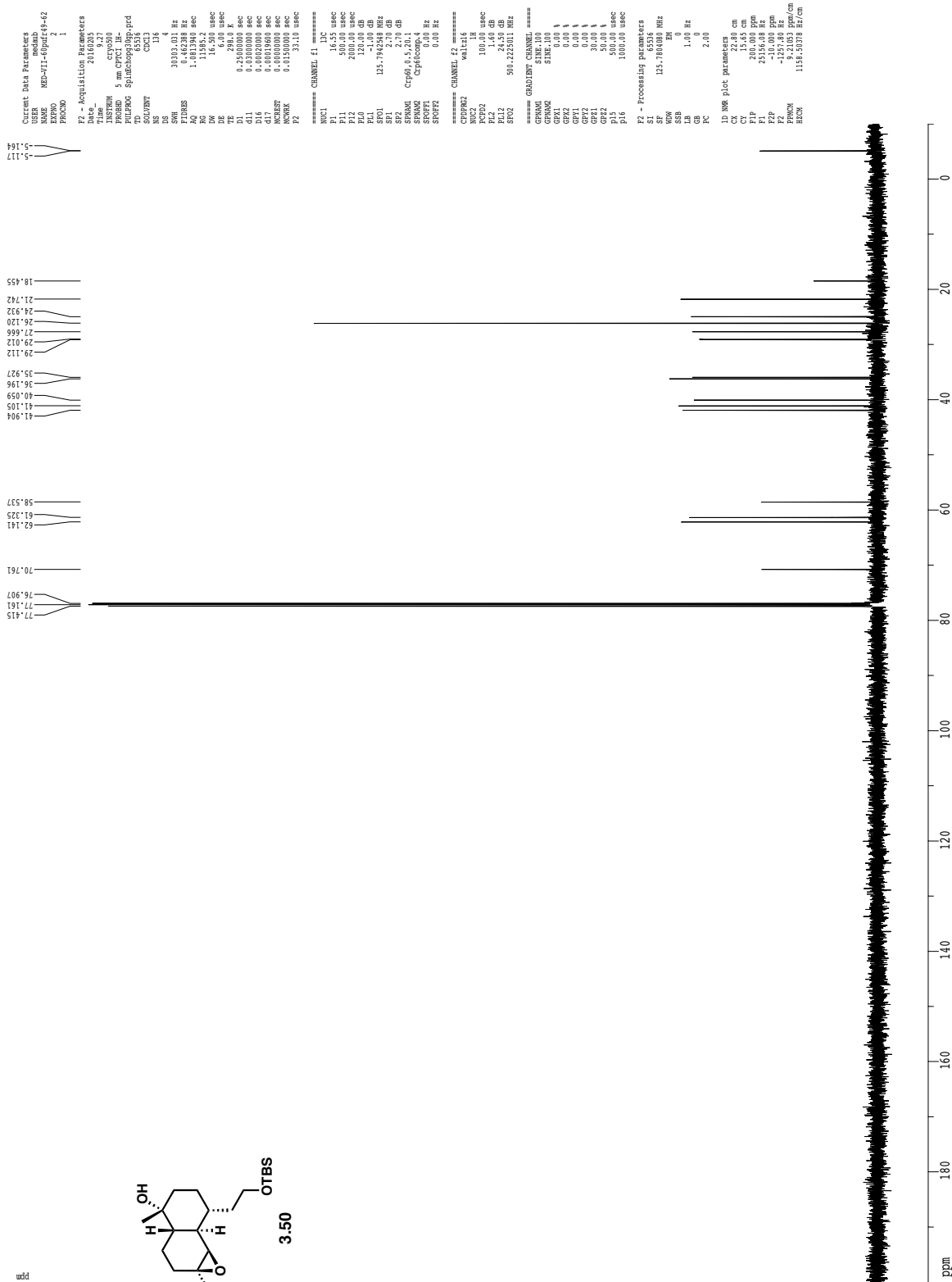


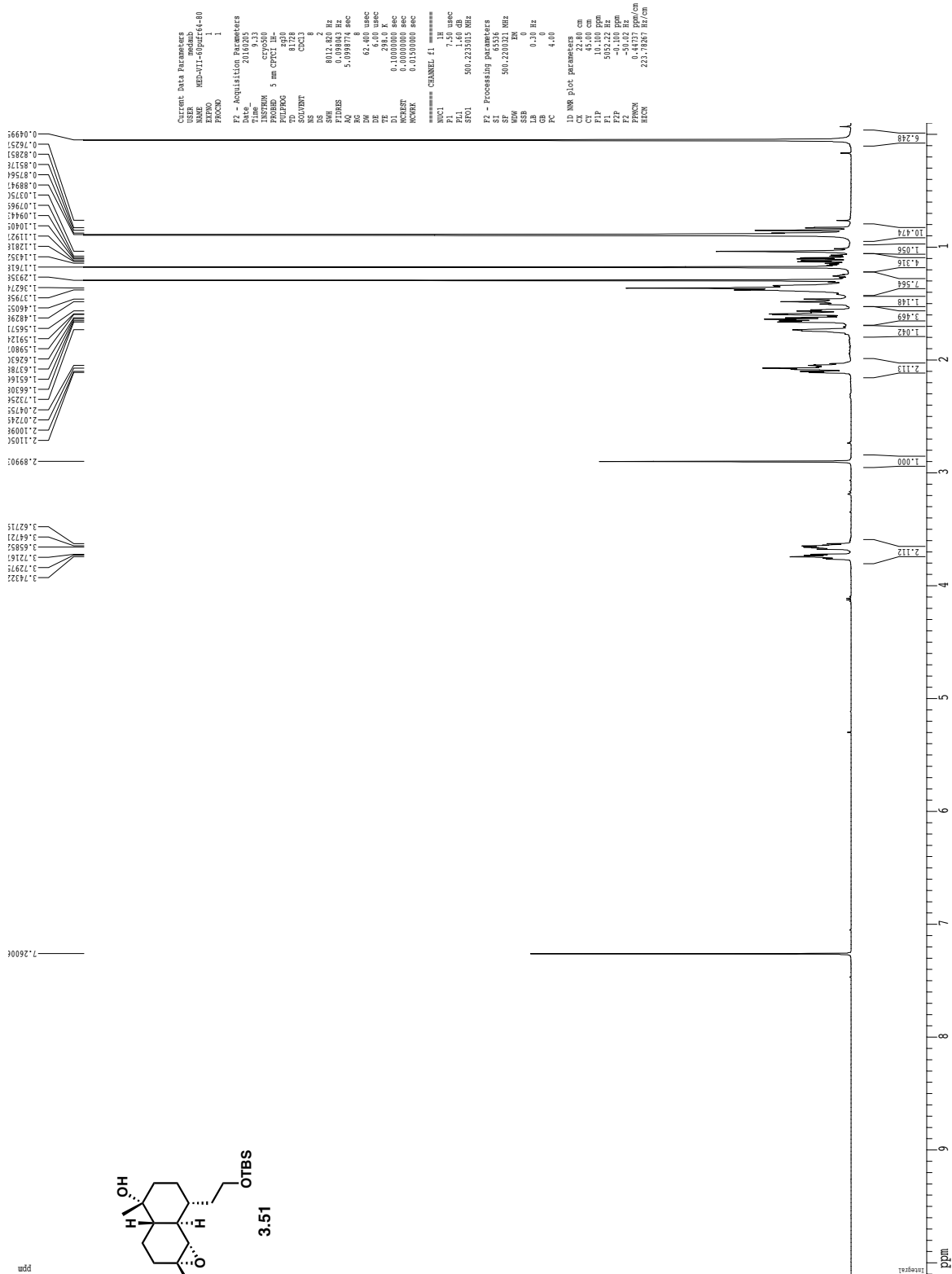
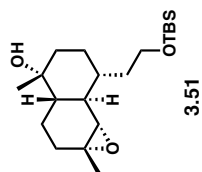


¹H spectrum

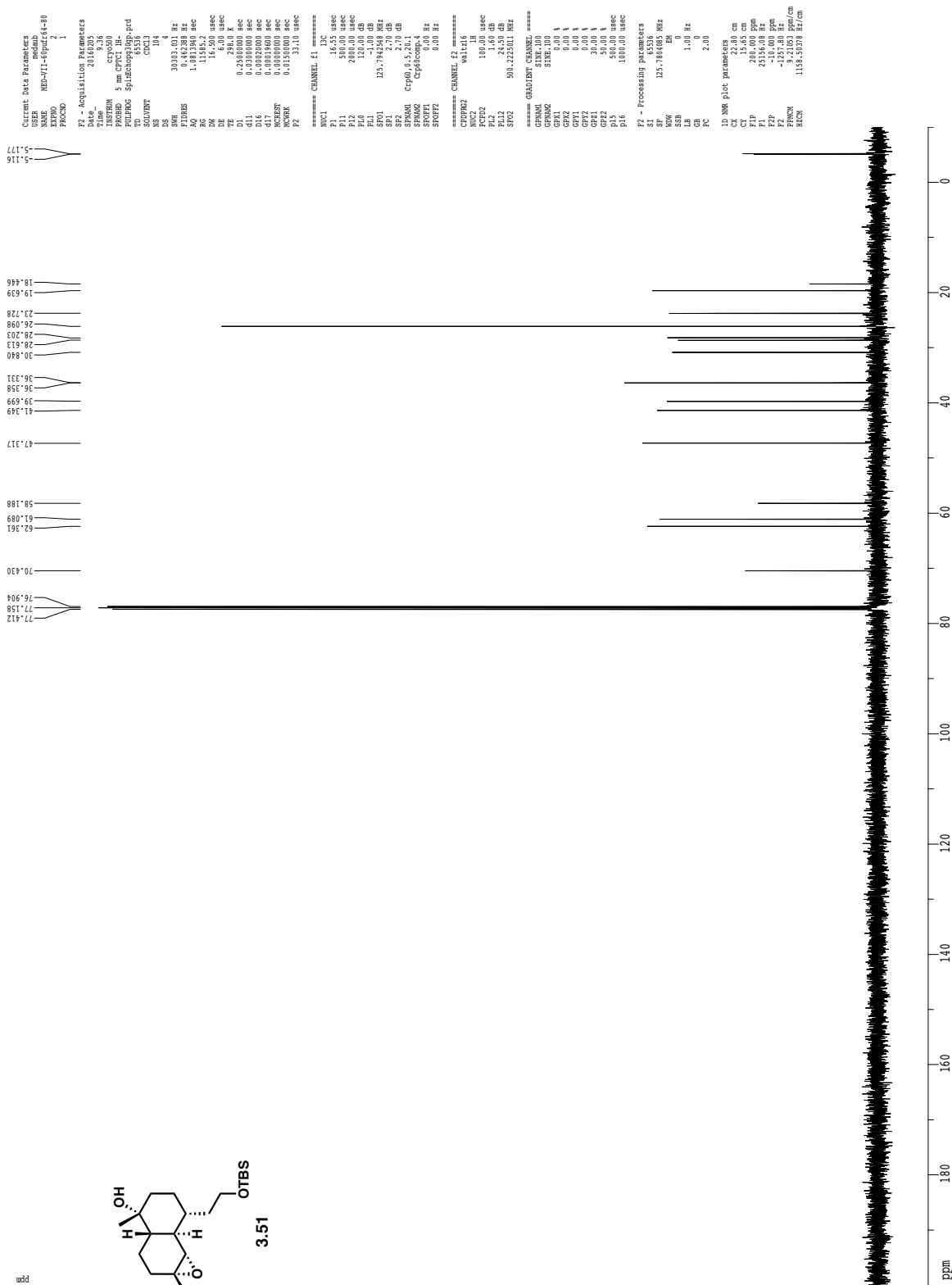


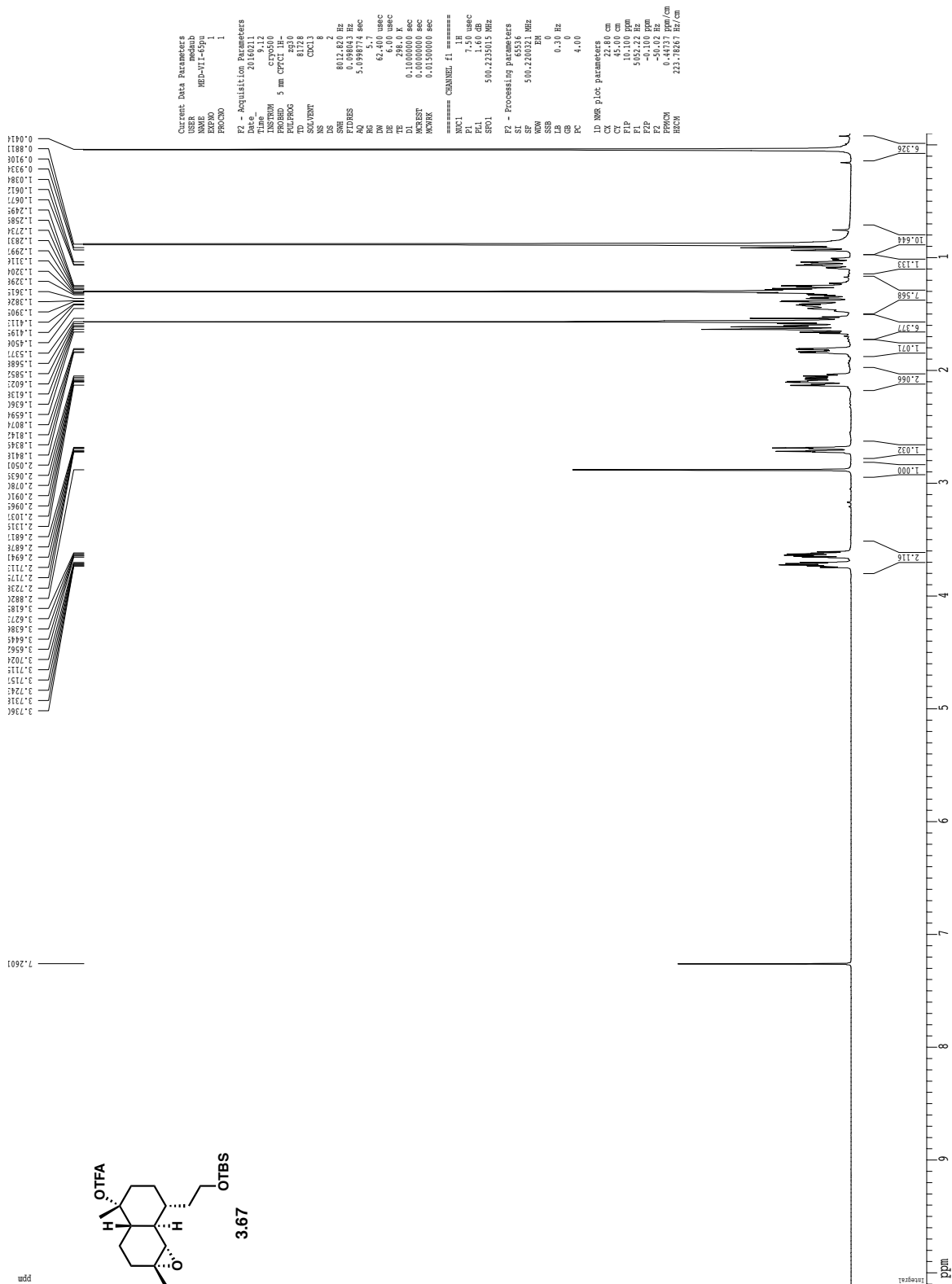
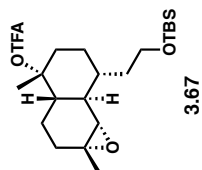
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



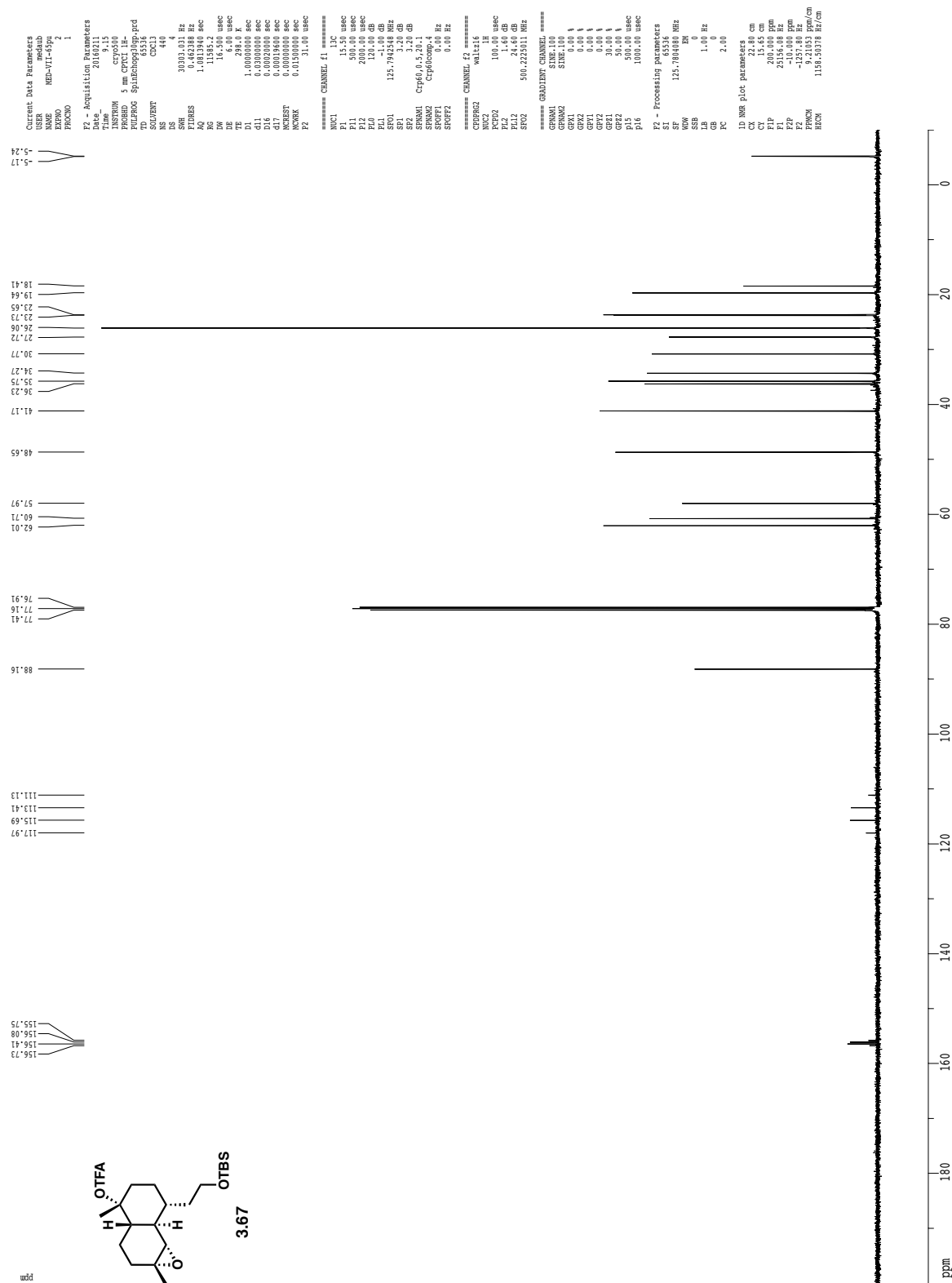


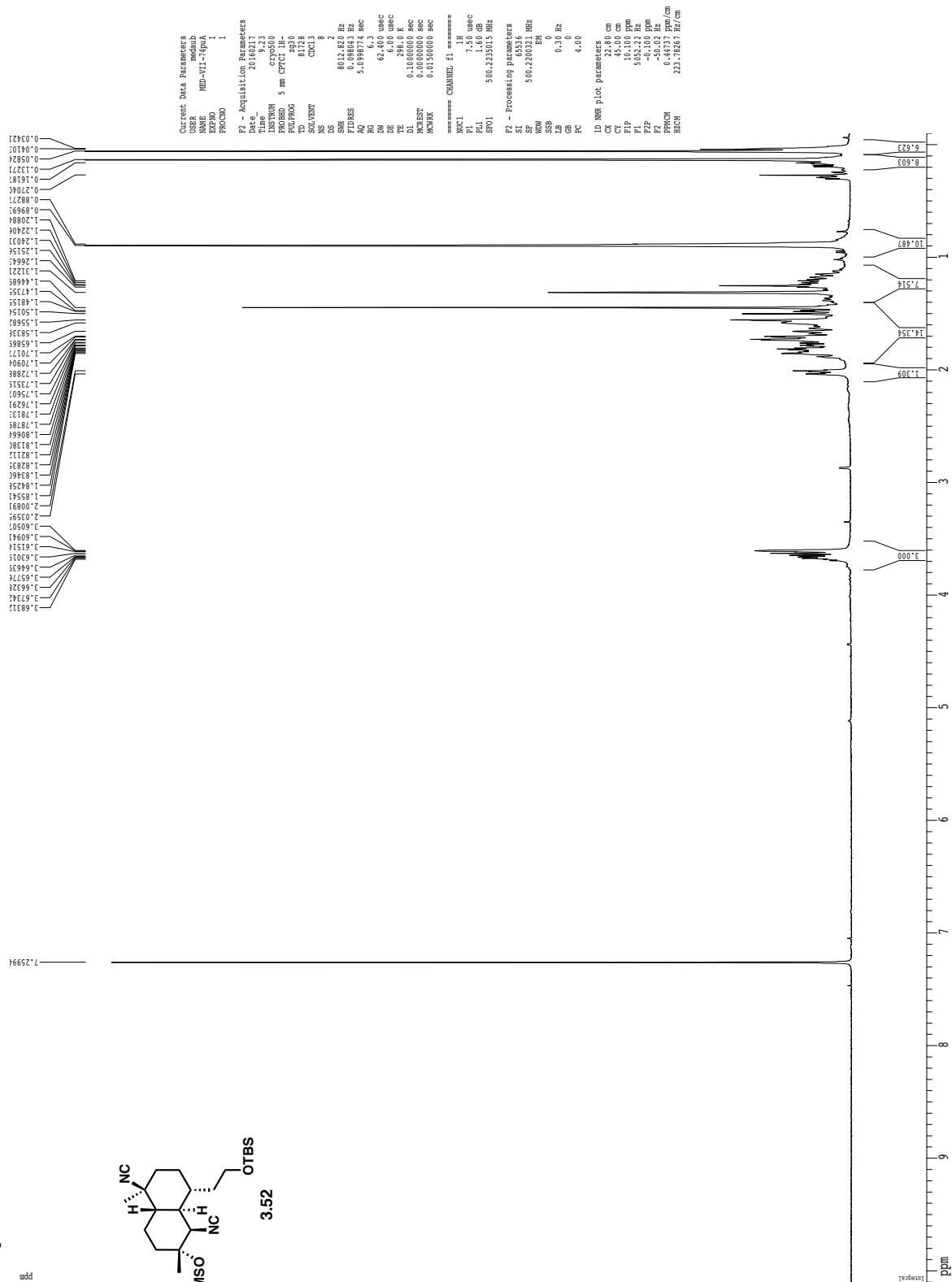
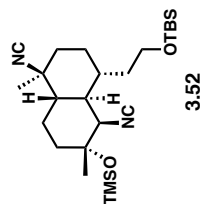
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



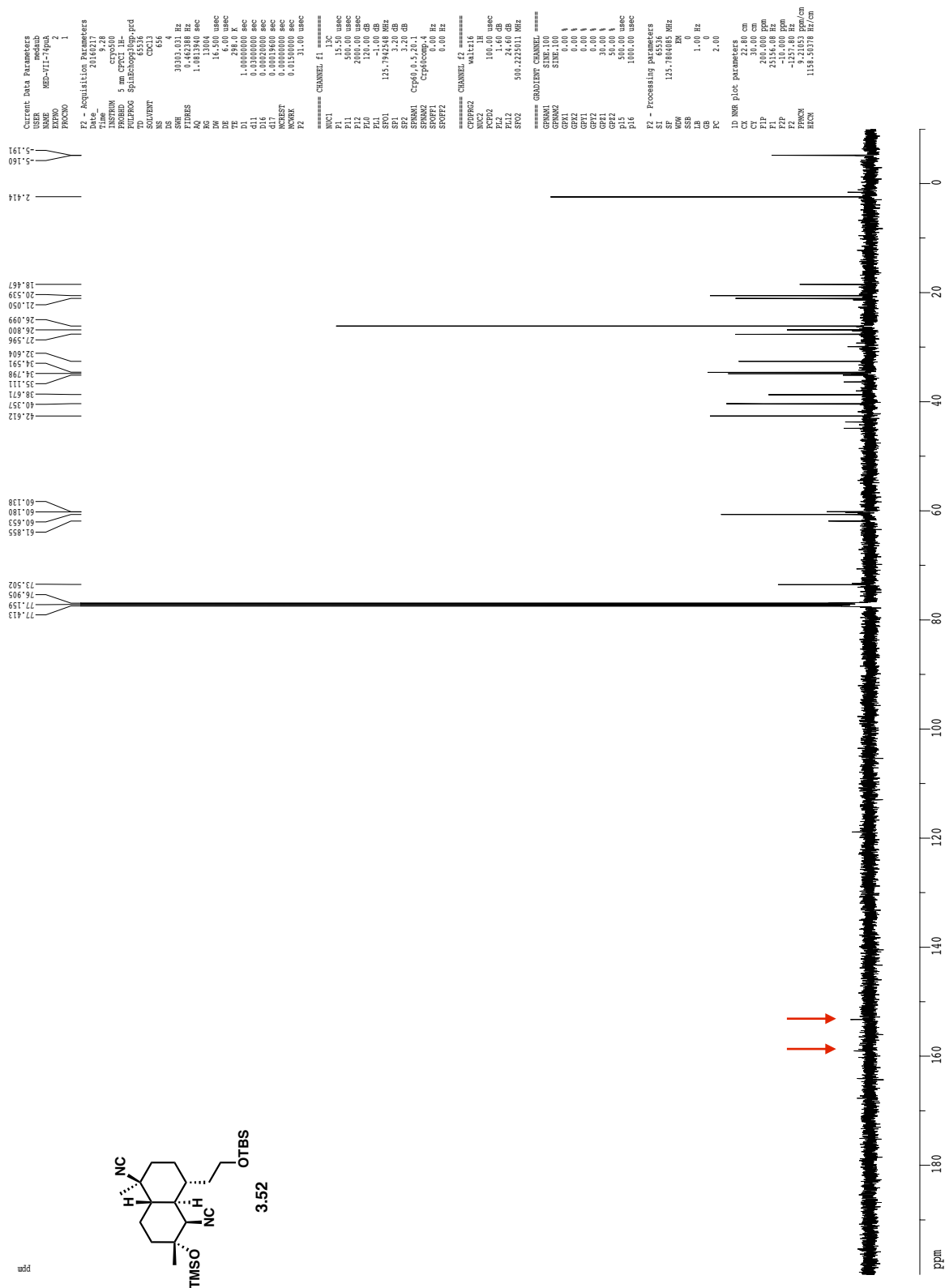


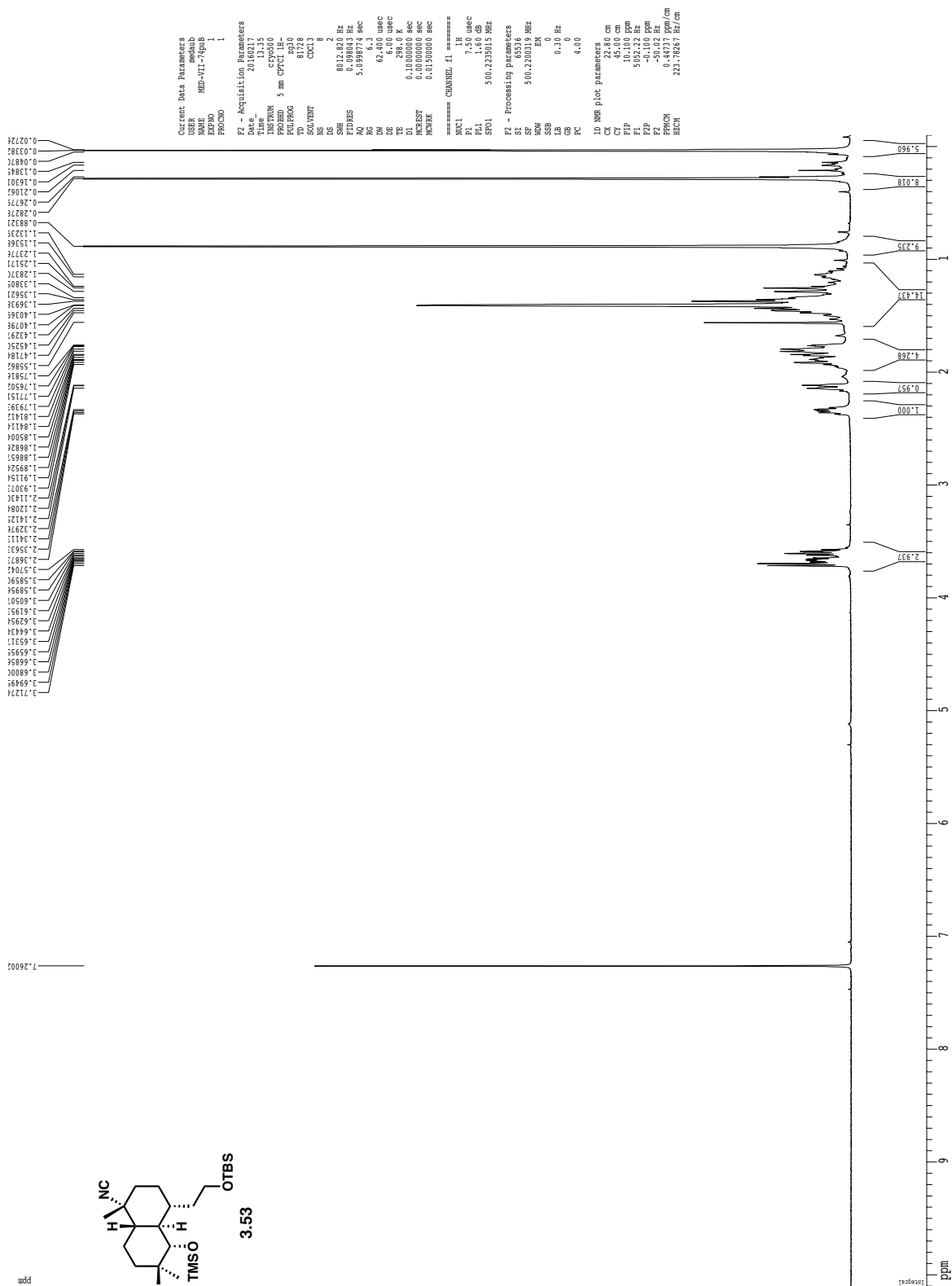
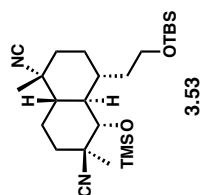
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

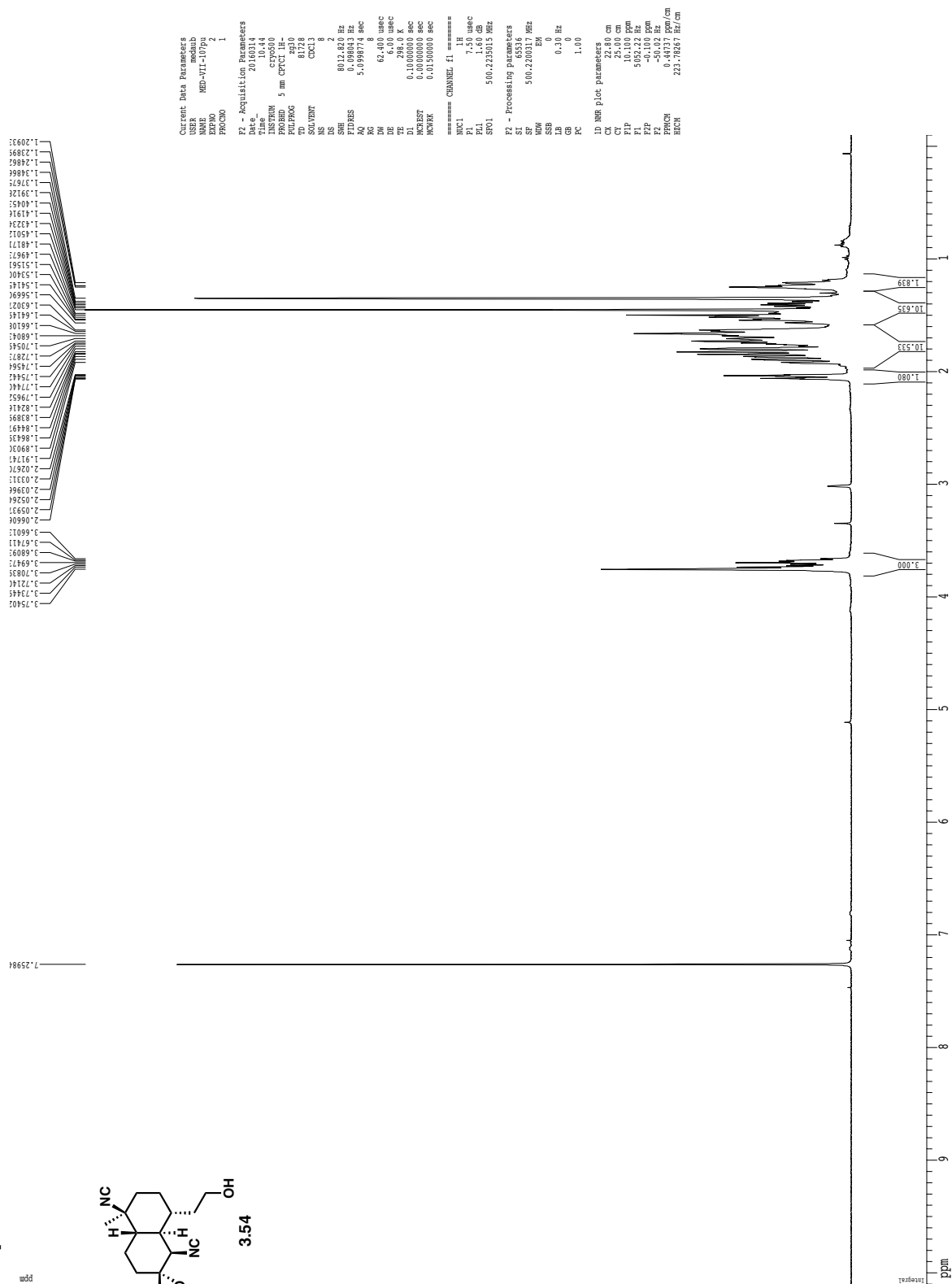
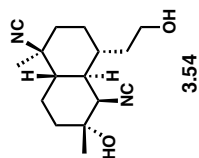




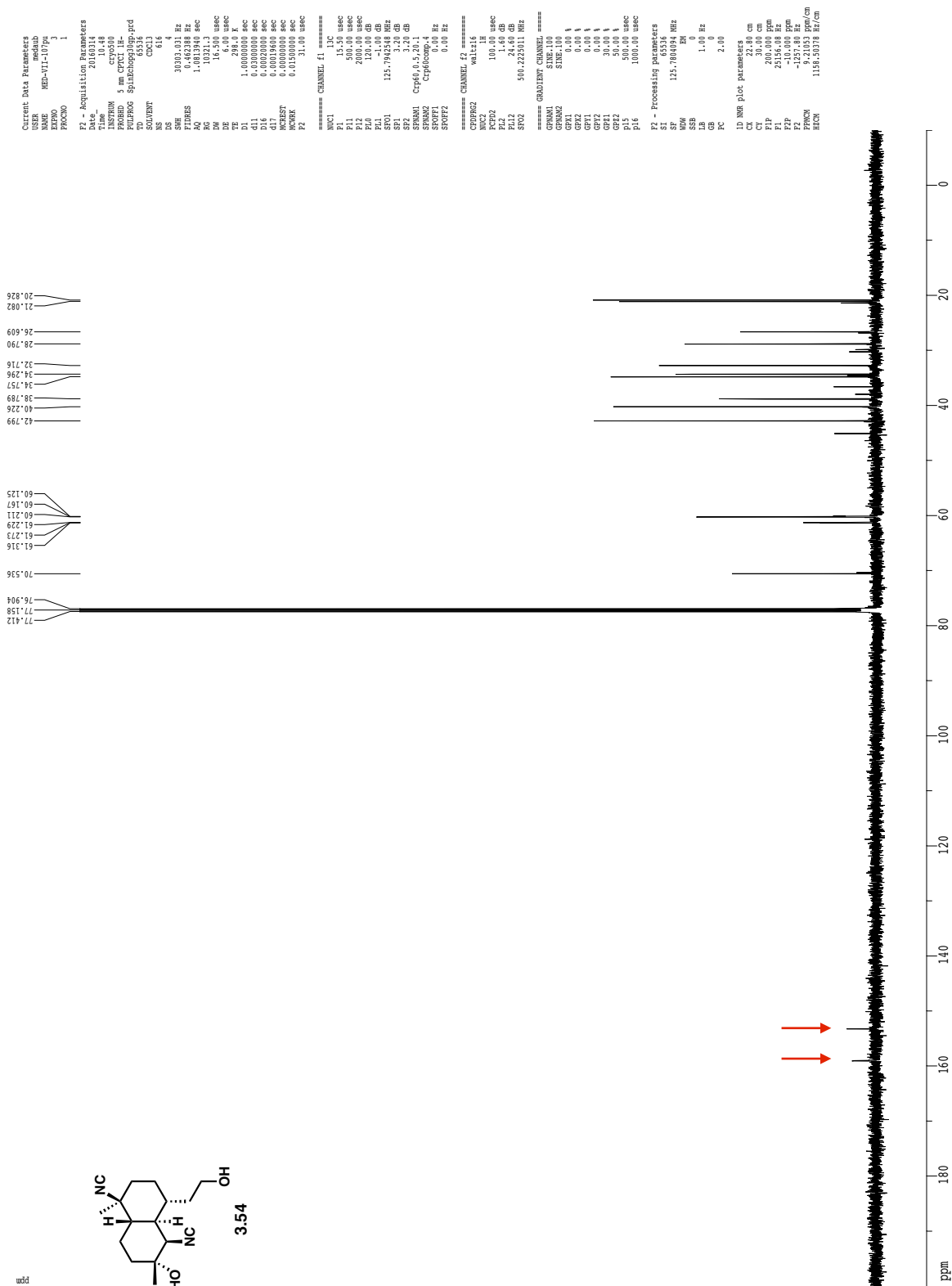
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

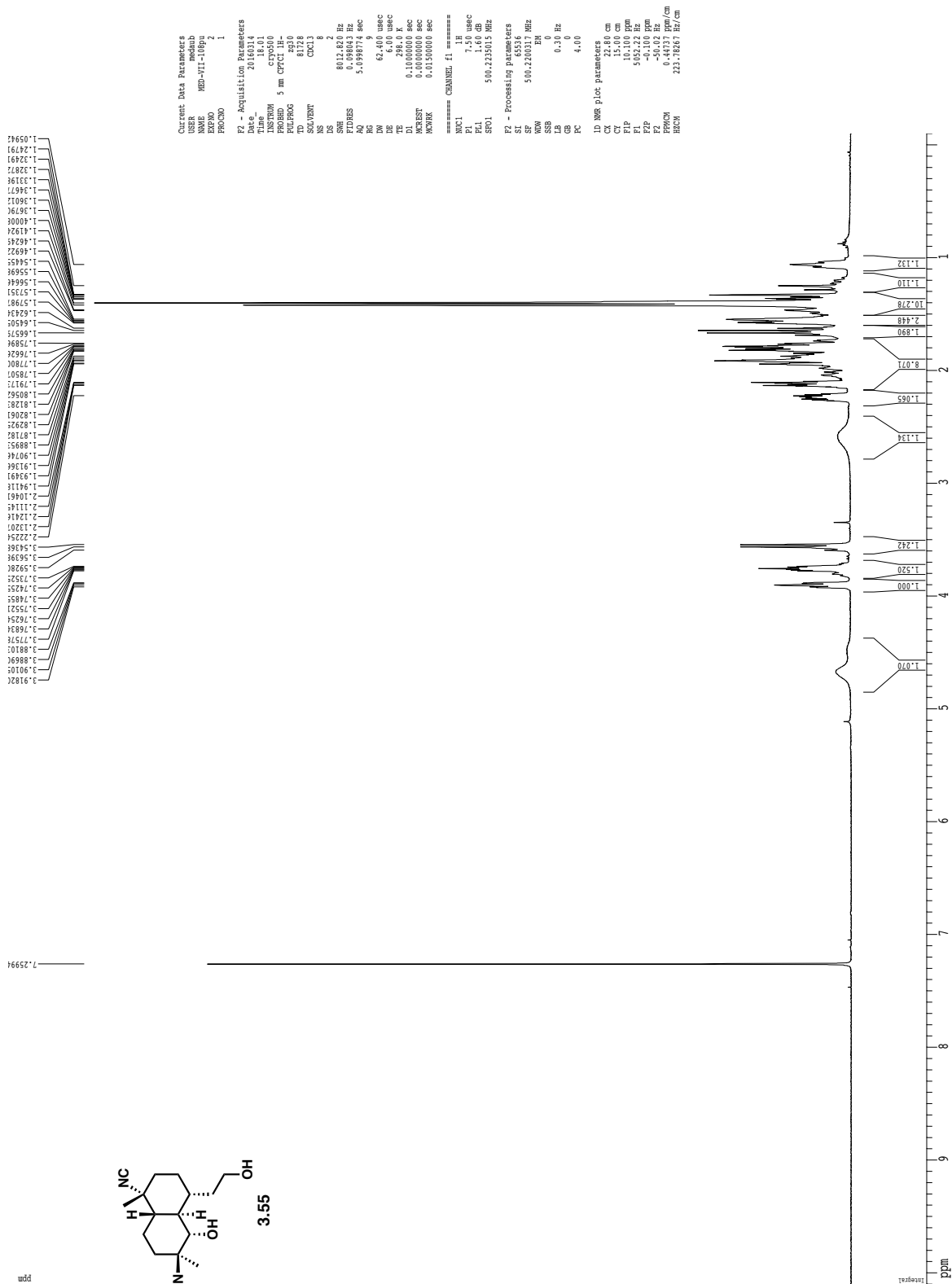
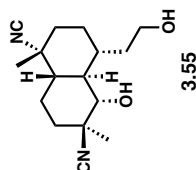




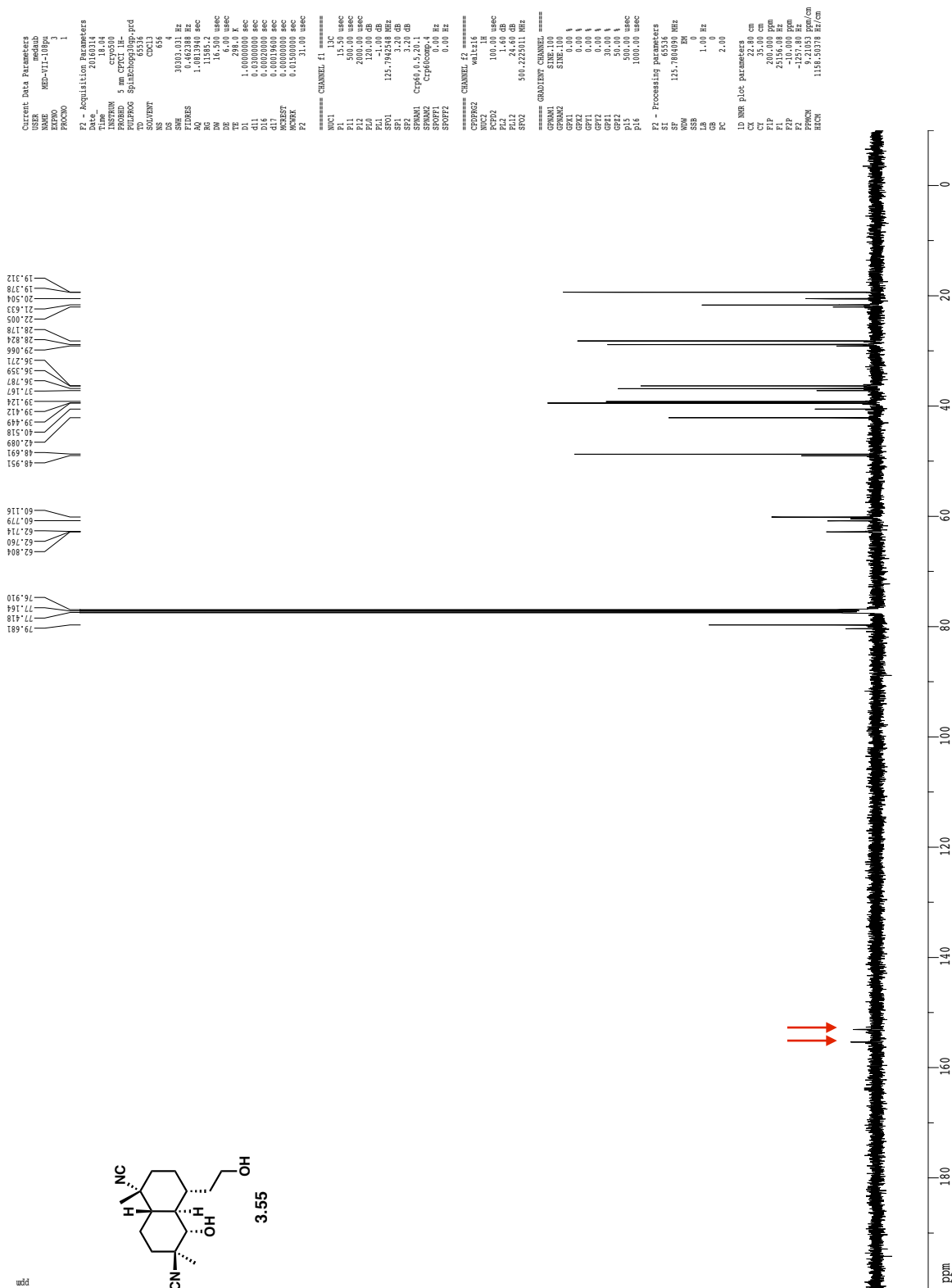


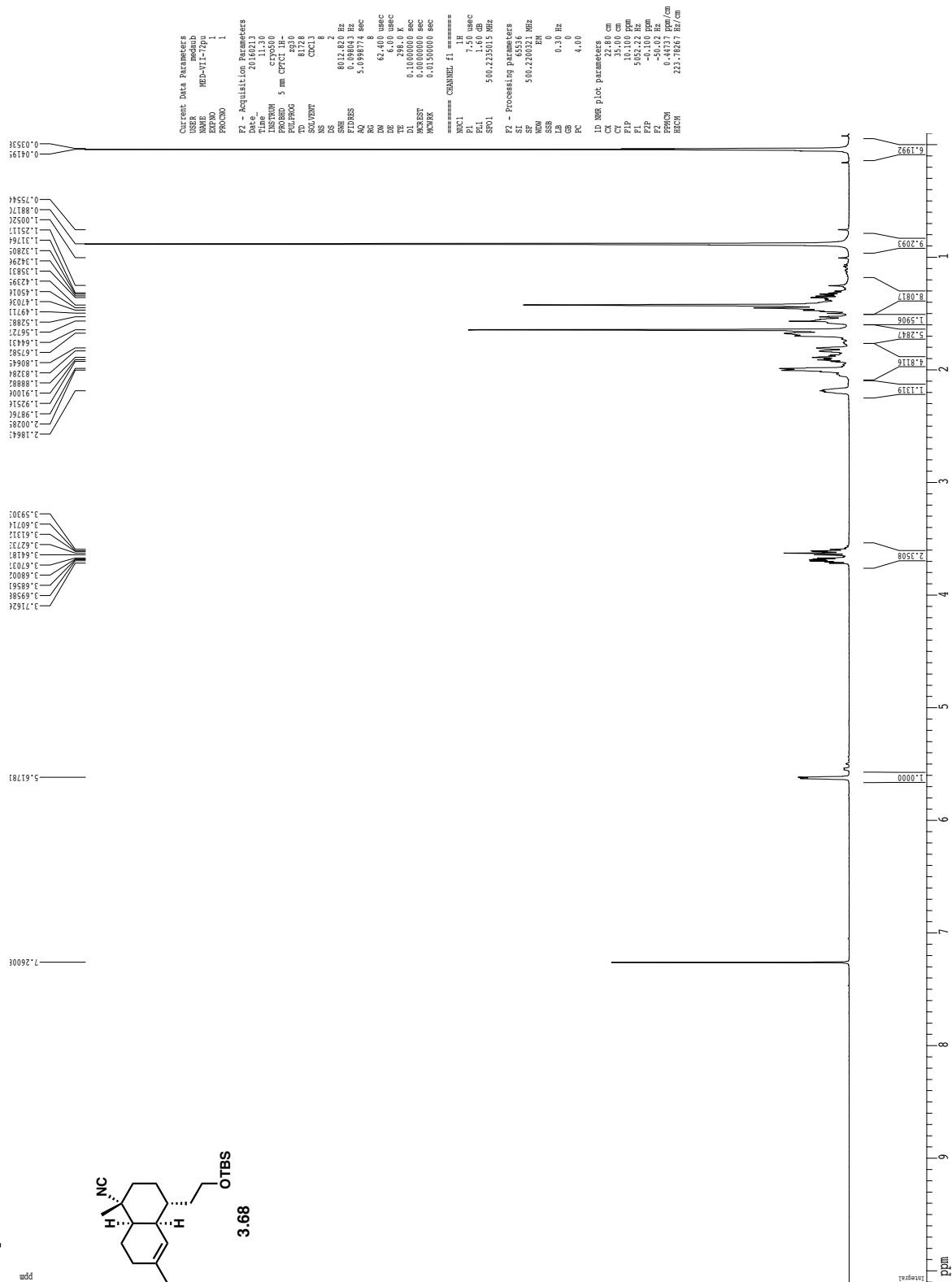
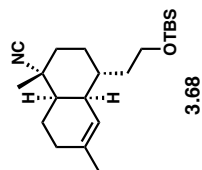
Z-restored spin-echo ^{13}C spectrum with ^1H decoupling



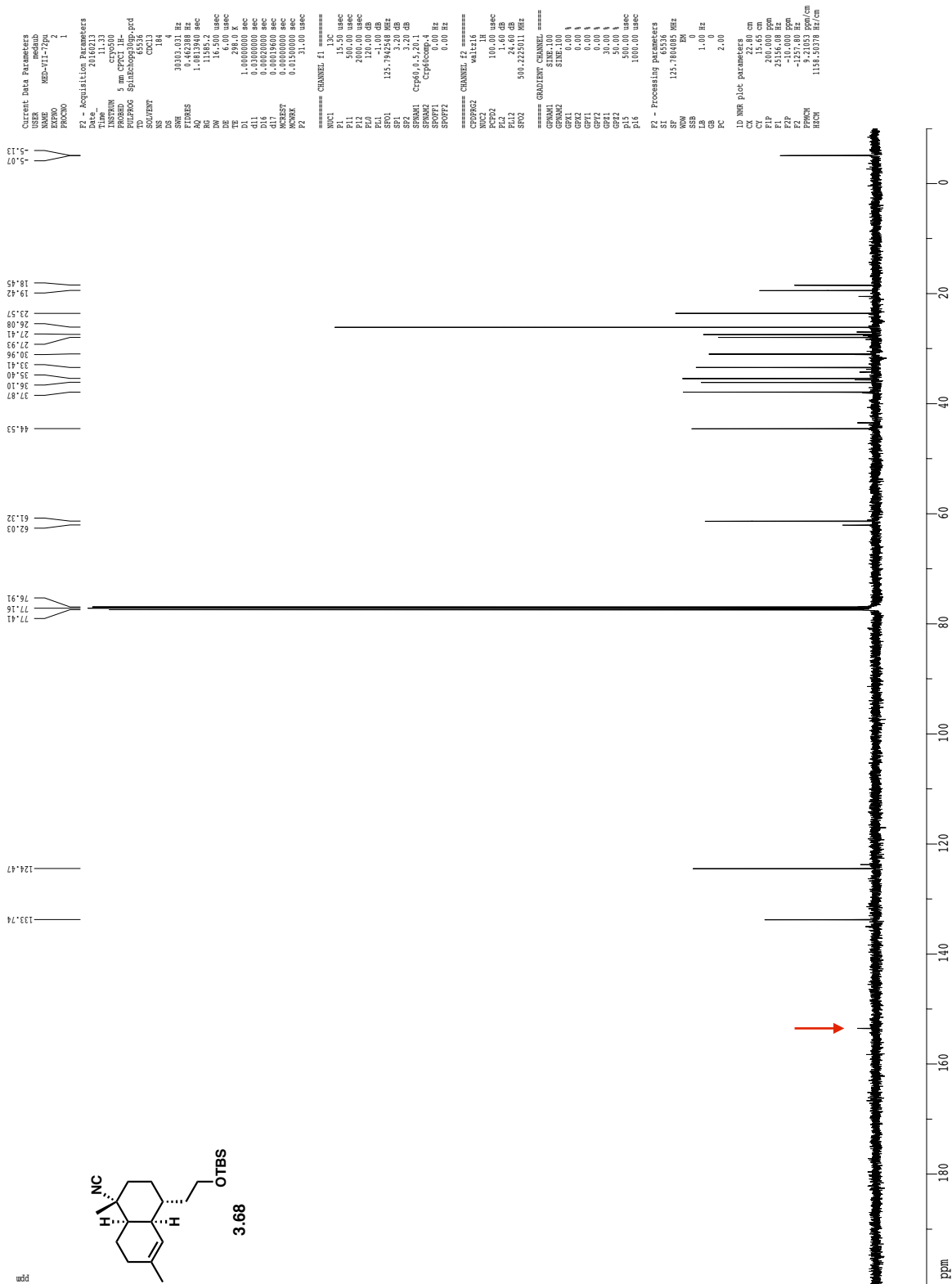


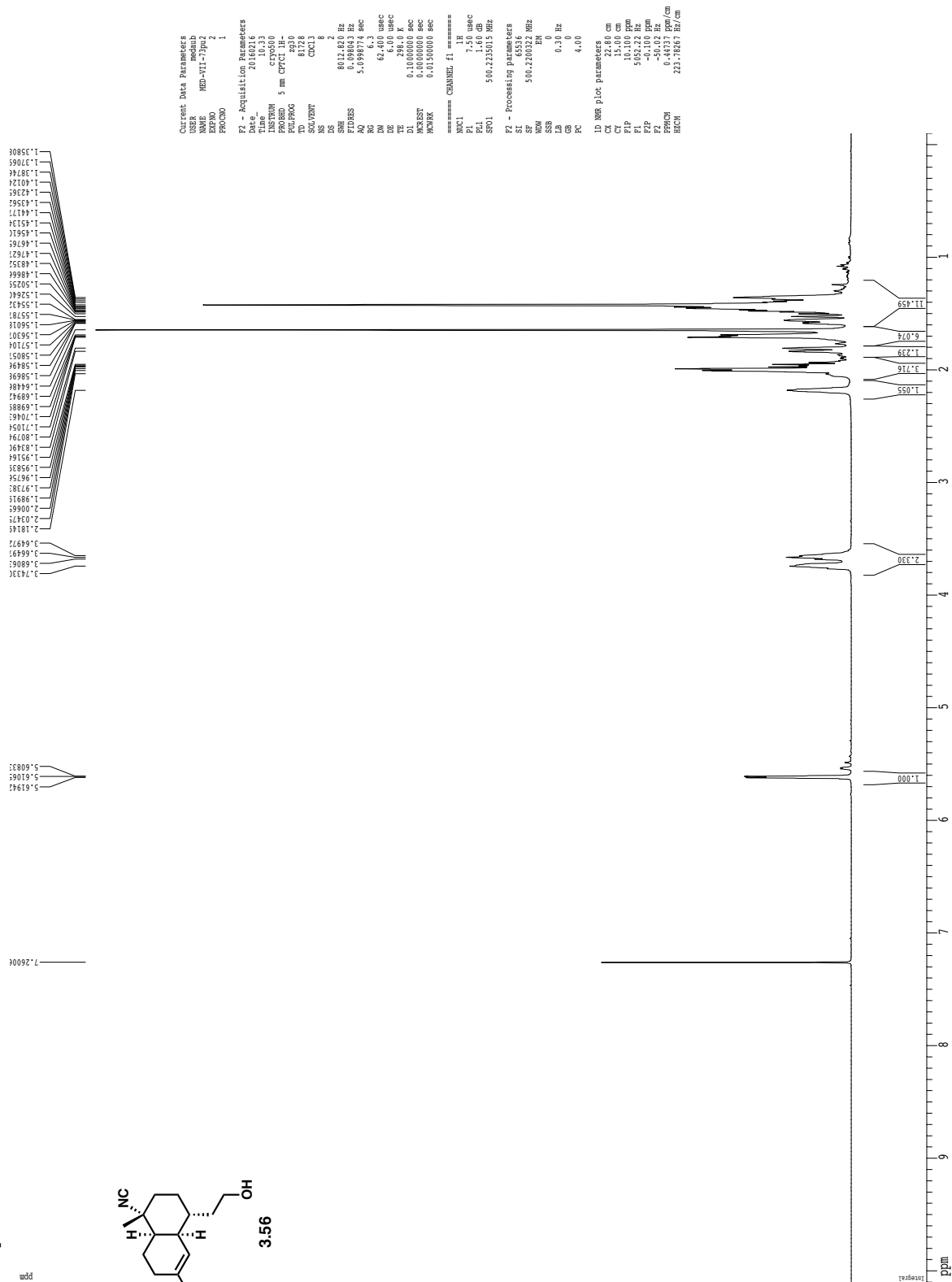
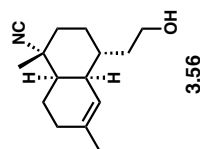
Z-restored spin-echo ¹³C spectrum with ¹H decoupling

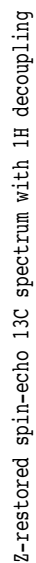


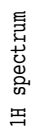


Z-restored spin-echo ¹³C spectrum with ¹H decoupling

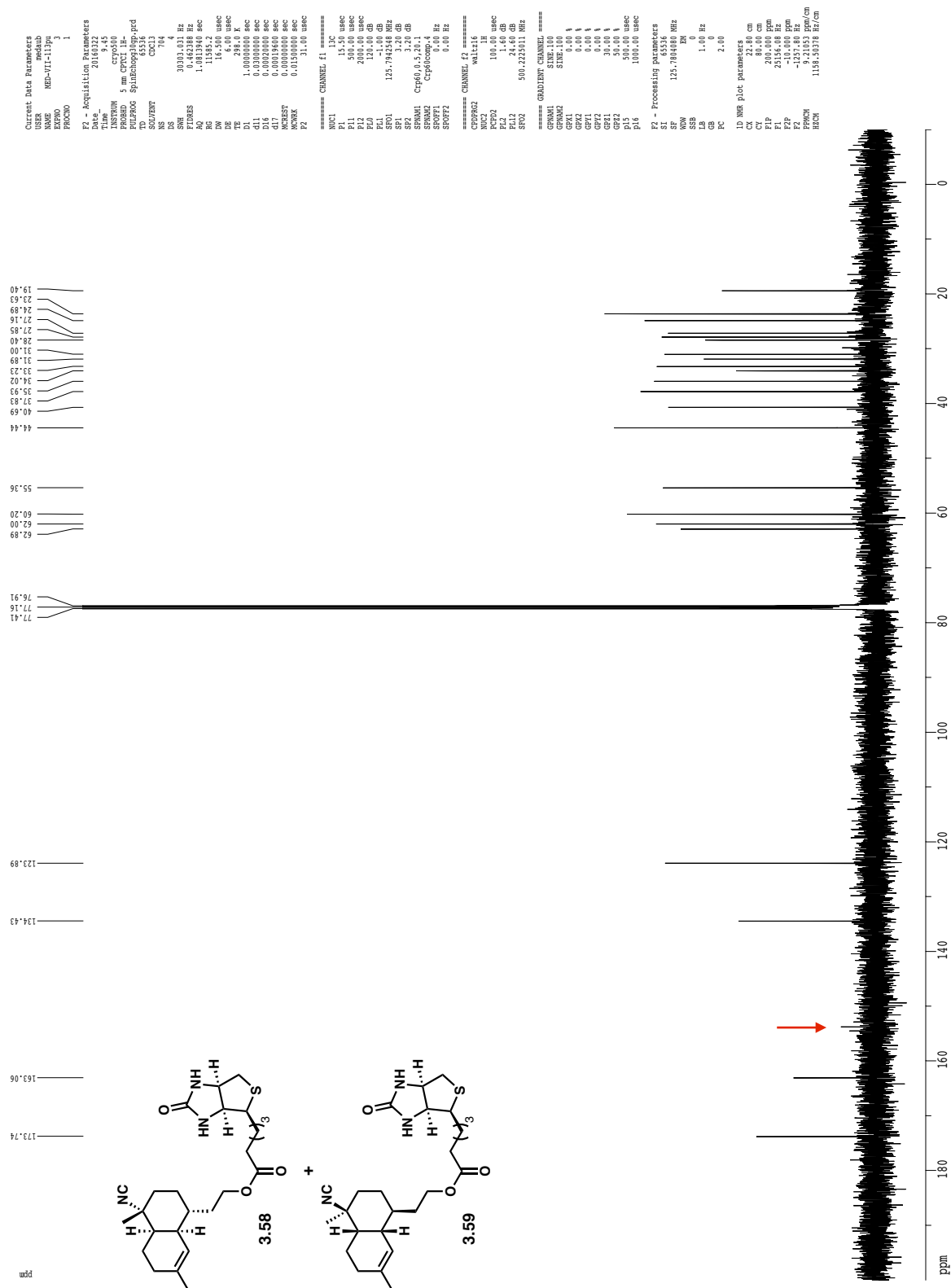








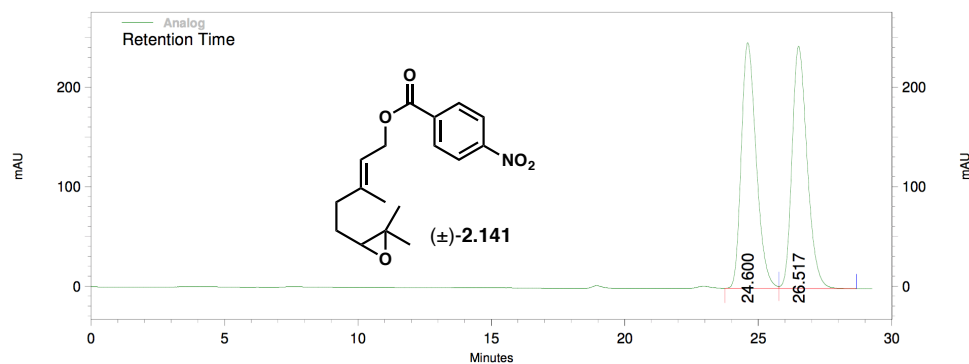
Z-restored spin-echo ¹³C spectrum with ¹H decoupling



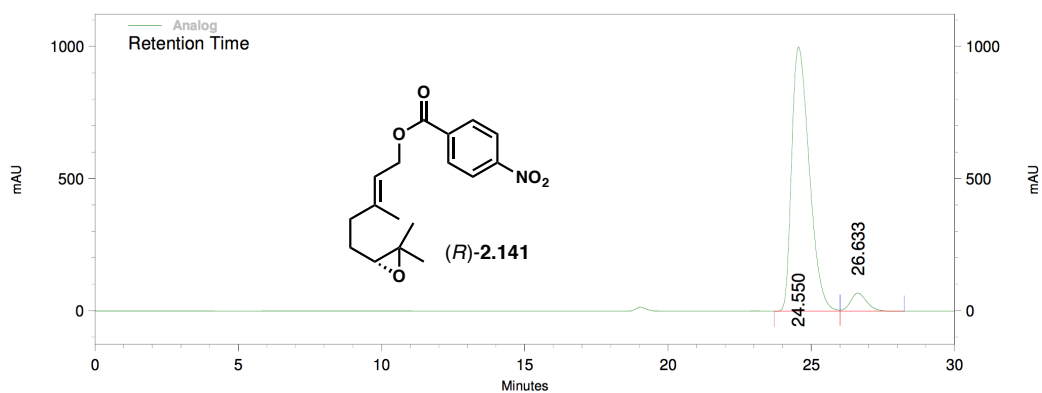


Determination of enantiomeric excess of (*R,E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 4-nitrobenzoate (**2.141**)

Chiralpak AS-H column, 5% *i*PrOH in hexanes, flow rate of 0.5 mL/min



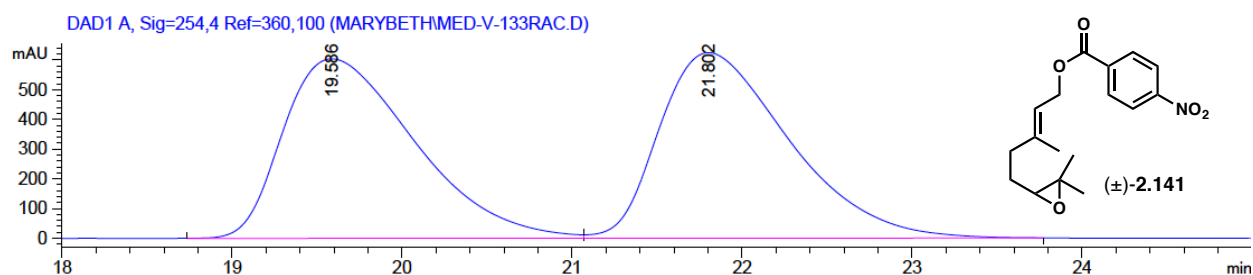
Analog Results				
Name	Retention Time	Area	Area Percent	Integration Codes
	24.600	9573444	49.968	BV
	26.517	9585783	50.032	VI
Totals		19159227	100.000	



Analog Results				
Name	Retention Time	Area	Area Percent	Integration Codes
	24.550	42622032	93.999	BV
	26.633	2721242	6.001	VI
Totals		45343274	100.000	

Determination of enantiomeric excess of (*S,E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 4-nitrobenzoate (**2.141**) prepared using a Shi epoxidation of geraniol

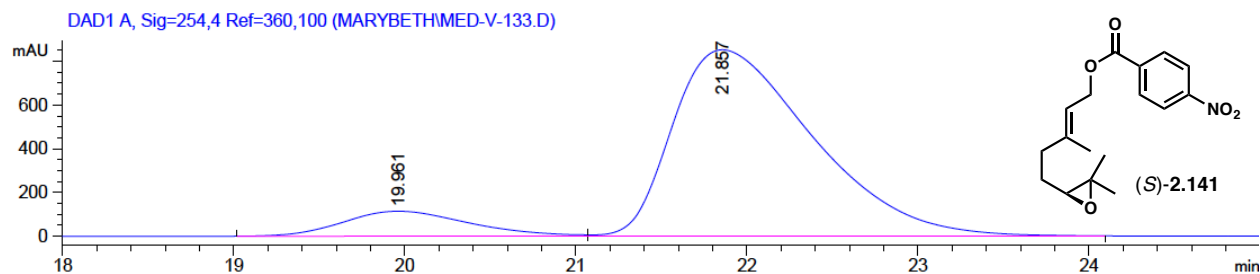
Chiralpak AS-H column, 5% *i*PrOH in hexanes, flow rate of 1 mL/min



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.586	BV	0.8530	3.24618e4	604.06555	49.4941
2	21.802	VB	0.8331	3.31254e4	624.27069	50.5059

Totals : 6.55871e4 1228.33624



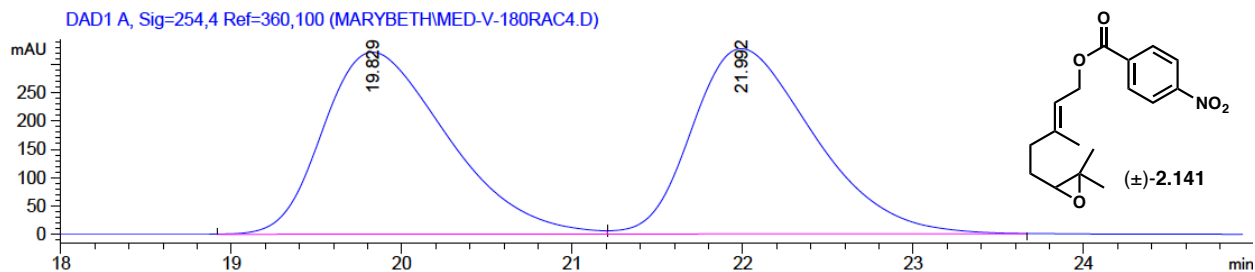
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.961	BV	0.7849	5835.65576	114.06203	10.7424
2	21.857	VB	0.8804	4.84880e4	851.41559	89.2576

Totals : 5.43236e4 965.47762

Determination of enantiomeric excess of (*S,E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 4-nitrobenzoate (**2.141**) prepared using a Sharpless dihydroxylation of geranyl acetate, mesylation, and epoxide formation

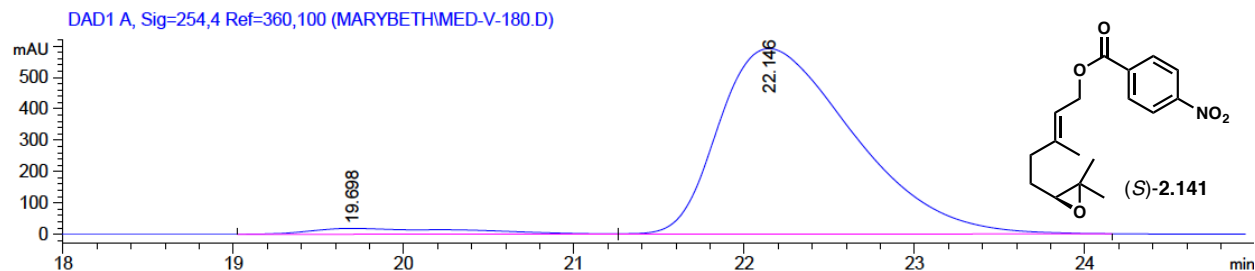
Chiralpak AS-H column, 5% *i*PrOH in hexanes, flow rate of 1 mL/min



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.829	BV	0.7924	1.62995e4	321.01459	50.0756
2	21.992	VB	0.7600	1.62502e4	326.86288	49.9244

Totals : 3.25497e4 647.87747



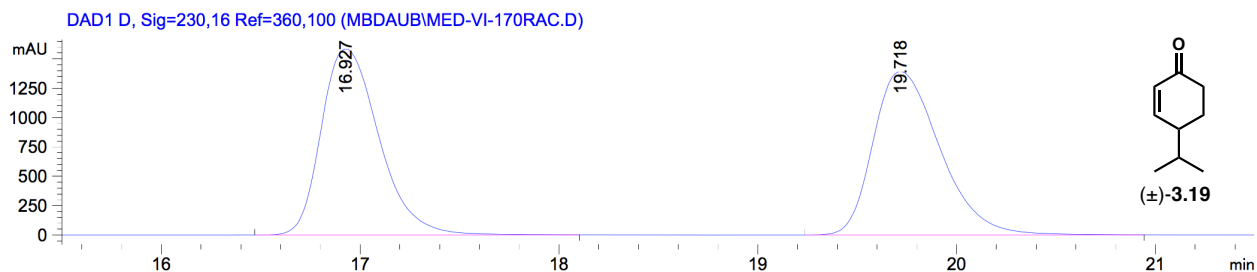
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.698	BV	0.8785	1226.24646	18.76202	3.6365
2	22.146	VB	0.8614	3.24940e4	591.03827	96.3635

Totals : 3.37202e4 609.80029

Determination of enantiomeric excess of (*R*)-cryptone (**3.19**)

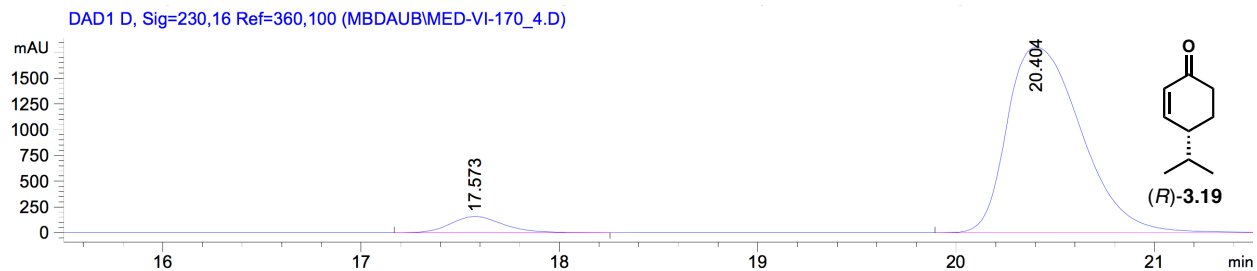
Chiralpak AD-H column, 2% *i*PrOH in hexanes, flow rate of 0.5 mL/min



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.927	BB	0.3153	3.19316e4	1583.48645	49.5504
2	19.718	BB	0.3625	3.25110e4	1391.95129	50.4496

Totals : 6.44426e4 2975.43774



Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.573	BB	0.2838	2905.68164	157.06201	5.8487
2	20.404	BB	0.4093	4.67749e4	1799.40332	94.1513

Totals : 4.96805e4 1956.46533

APPENDIX B: X-Ray Crystallographic Data

X-ray Data Collection, Structure Solution and Refinement:

A colorless crystal of approximate dimensions 0.087 x 0.104 x 0.235 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2¹ program package was used to determine the unit-cell parameters and for data collection (120 sec/frame scan time for a hemisphere of diffraction data). The raw frame data was processed using SAINT² and SADABS³ to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL⁴ program. The systematic absences were consistent with the hexagonal space groups $R3$ and $R\bar{3}$. The non-centrosymmetric space group $R3$ was assigned and later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors⁵ for neutral atoms were used throughout the analysis. Hydrogen atom H(2) was located from a difference-Fourier map and refined (x, y, z and U_{iso}). The remaining hydrogen atoms were included using a riding model.

At convergence, $wR2 = 0.0909$ and $Goof = 1.038$ for 217 variables refined against 4475 data ($0.78 \text{ \AA}$), $R1 = 0.0391$ for those 4030 data with $I > 2.0\sigma(I)$. The absolute structure was assigned by refinement of the Flack⁶ parameter.

Definitions:

$$wR2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$$

$$R1 = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$$

$$Goof = S = [\Sigma[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2} \text{ where } n \text{ is the number of reflections and } p \text{ is the total number of parameters refined.}$$

The thermal ellipsoid plot is shown at the 50% probability level.

¹ APEX2 Version 2014.1-1, Bruker AXS, Inc.; Madison, WI 2014.

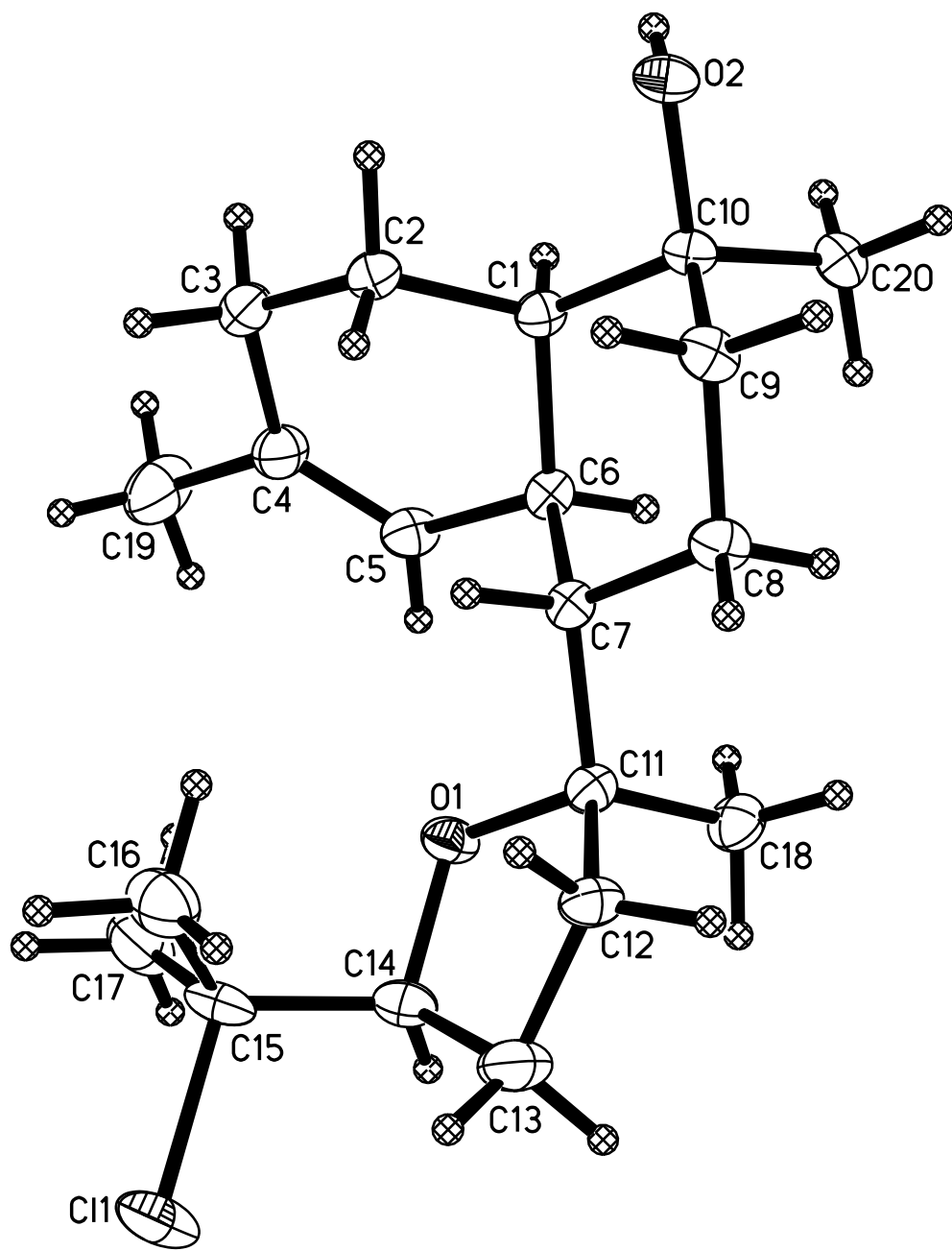
² SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.

³ Sheldrick, G. M. SADABS, Version 2014/4, Bruker AXS, Inc.; Madison, WI 2014.

⁴ Sheldrick, G. M. SHELXTL, Version 2014/6, Bruker AXS, Inc.; Madison, WI 2014.

⁵ International Tables for X-Ray Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

⁶ Parsons, S., Flack, H. D., Wagner, T. Acta Cryst. B69, 249-259, 2013.



Crystal data and structure refinement for **2.102**.

Identification code	cdv36 (Mary Beth Daub)
Empirical formula	C ₂₀ H ₃₃ Cl O ₂
Formula weight	340.91
Temperature	133(2) K
Wavelength	0.71073 Å
Crystal system	Trigonal
Space group	<i>R</i> 3
Unit cell dimensions	a = 29.890(4) Å α = 90°. b = 29.890(4) Å β = 90°. c = 5.8875(7) Å γ = 120°.
Volume	4555.3(13) Å ³
Z	9
Density (calculated)	1.118 Mg/m ³
Absorption coefficient	0.196 mm ⁻¹
F(000)	1674
Crystal color	colorless
Crystal size	0.235 x 0.104 x 0.087 mm ³
Theta range for data collection	1.363 to 27.103°
Index ranges	-35 ≤ h ≤ 38, -38 ≤ k ≤ 38, -7 ≤ l ≤ 7
Reflections collected	14320
Independent reflections	4475 [R(int) = 0.0325]
Completeness to theta = 25.500°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8621 and 0.8081
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4475 / 1 / 217
Goodness-of-fit on F ²	1.038
Final R indices [I > 2σ(I) = 4030 data]	R1 = 0.0391, wR2 = 0.0879
R indices (all data, 0.78Å)	R1 = 0.0458, wR2 = 0.0909
Absolute structure parameter	-0.04(3)
Largest diff. peak and hole	0.231 and -0.176 e.Å ⁻³

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.102**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	8687(1)	7730(1)	1355(1)	39(1)
O(1)	7761(1)	8189(1)	4036(3)	21(1)
O(2)	6829(1)	9742(1)	2200(3)	20(1)
C(1)	7330(1)	9417(1)	4167(4)	17(1)
C(2)	7809(1)	9791(1)	2793(5)	22(1)
C(3)	8295(1)	9986(1)	4236(5)	26(1)
C(4)	8288(1)	9578(1)	5765(5)	26(1)
C(5)	7879(1)	9109(1)	5959(4)	21(1)
C(6)	7367(1)	8933(1)	4790(4)	16(1)
C(7)	7271(1)	8584(1)	2681(4)	16(1)
C(8)	6766(1)	8468(1)	1471(4)	20(1)
C(9)	6742(1)	8954(1)	898(4)	20(1)
C(10)	6814(1)	9279(1)	3008(4)	18(1)
C(11)	7265(1)	8071(1)	3110(4)	18(1)
C(12)	7231(1)	7795(1)	875(4)	22(1)
C(13)	7523(1)	7507(1)	1373(5)	30(1)
C(14)	7920(1)	7841(1)	3176(5)	23(1)
C(15)	8480(1)	8176(1)	2363(5)	26(1)
C(16)	8531(1)	8528(1)	396(5)	36(1)
C(17)	8829(1)	8482(1)	4319(6)	35(1)
C(18)	6845(1)	7710(1)	4770(5)	25(1)
C(19)	8782(1)	9746(1)	7075(7)	42(1)
C(20)	6365(1)	9012(1)	4661(4)	22(1)

Bond lengths [Å] and angles [°] for **2.102**.

Cl(1)-C(15)	1.828(3)
O(1)-C(14)	1.436(3)
O(1)-C(11)	1.450(3)
O(2)-C(10)	1.443(3)
C(1)-C(2)	1.533(4)
C(1)-C(10)	1.543(4)
C(1)-C(6)	1.549(3)
C(2)-C(3)	1.525(4)
C(3)-C(4)	1.507(4)
C(4)-C(5)	1.325(4)
C(4)-C(19)	1.512(4)
C(5)-C(6)	1.513(4)
C(6)-C(7)	1.553(3)
C(7)-C(8)	1.544(4)
C(7)-C(11)	1.545(3)
C(8)-C(9)	1.527(4)
C(9)-C(10)	1.524(3)
C(10)-C(20)	1.521(4)
C(11)-C(18)	1.529(4)
C(11)-C(12)	1.530(4)
C(12)-C(13)	1.528(4)
C(13)-C(14)	1.533(4)
C(14)-C(15)	1.535(4)
C(15)-C(17)	1.516(4)
C(15)-C(16)	1.520(4)
C(14)-O(1)-C(11)	111.20(19)
C(2)-C(1)-C(10)	113.9(2)
C(2)-C(1)-C(6)	109.2(2)
C(10)-C(1)-C(6)	112.5(2)
C(3)-C(2)-C(1)	110.4(2)
C(4)-C(3)-C(2)	113.5(2)
C(5)-C(4)-C(3)	122.6(3)
C(5)-C(4)-C(19)	122.6(3)

C(3)-C(4)-C(19)	114.8(3)
C(4)-C(5)-C(6)	124.6(2)
C(5)-C(6)-C(1)	108.2(2)
C(5)-C(6)-C(7)	114.4(2)
C(1)-C(6)-C(7)	111.23(19)
C(8)-C(7)-C(11)	109.1(2)
C(8)-C(7)-C(6)	110.6(2)
C(11)-C(7)-C(6)	116.2(2)
C(9)-C(8)-C(7)	113.2(2)
C(10)-C(9)-C(8)	111.6(2)
O(2)-C(10)-C(20)	108.1(2)
O(2)-C(10)-C(9)	105.6(2)
C(20)-C(10)-C(9)	112.4(2)
O(2)-C(10)-C(1)	110.0(2)
C(20)-C(10)-C(1)	111.1(2)
C(9)-C(10)-C(1)	109.5(2)
O(1)-C(11)-C(18)	108.1(2)
O(1)-C(11)-C(12)	103.7(2)
C(18)-C(11)-C(12)	111.1(2)
O(1)-C(11)-C(7)	108.53(19)
C(18)-C(11)-C(7)	113.8(2)
C(12)-C(11)-C(7)	111.1(2)
C(13)-C(12)-C(11)	103.7(2)
C(12)-C(13)-C(14)	104.0(2)
O(1)-C(14)-C(13)	106.6(2)
O(1)-C(14)-C(15)	106.5(2)
C(13)-C(14)-C(15)	116.5(2)
C(17)-C(15)-C(16)	111.2(3)
C(17)-C(15)-C(14)	110.7(2)
C(16)-C(15)-C(14)	112.9(2)
C(17)-C(15)-Cl(1)	107.7(2)
C(16)-C(15)-Cl(1)	107.7(2)
C(14)-C(15)-Cl(1)	106.27(19)

Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.102**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	45(1)	44(1)	46(1)	-8(1)	-1(1)	36(1)
O(1)	23(1)	21(1)	23(1)	-3(1)	-4(1)	15(1)
O(2)	28(1)	22(1)	16(1)	0(1)	-2(1)	17(1)
C(1)	19(1)	16(1)	16(1)	-1(1)	-2(1)	9(1)
C(2)	21(1)	17(1)	26(1)	5(1)	2(1)	10(1)
C(3)	21(1)	18(1)	37(2)	3(1)	-1(1)	8(1)
C(4)	22(2)	21(1)	32(2)	-2(1)	-7(1)	10(1)
C(5)	26(1)	21(1)	18(1)	-1(1)	-6(1)	13(1)
C(6)	18(1)	17(1)	12(1)	0(1)	-1(1)	7(1)
C(7)	17(1)	16(1)	14(1)	1(1)	0(1)	8(1)
C(8)	25(1)	22(1)	17(1)	-6(1)	-6(1)	14(1)
C(9)	23(1)	25(1)	15(1)	-4(1)	-5(1)	15(1)
C(10)	20(1)	18(1)	17(1)	1(1)	0(1)	12(1)
C(11)	19(1)	16(1)	17(1)	0(1)	-3(1)	8(1)
C(12)	27(2)	18(1)	23(1)	-4(1)	-4(1)	12(1)
C(13)	36(2)	23(2)	35(2)	-6(1)	-6(1)	19(1)
C(14)	30(2)	23(1)	22(1)	2(1)	0(1)	18(1)
C(15)	36(2)	29(2)	27(1)	-2(1)	2(1)	26(1)
C(16)	41(2)	39(2)	35(2)	10(1)	13(1)	26(2)
C(17)	30(2)	42(2)	42(2)	-10(2)	-4(1)	24(2)
C(18)	26(2)	21(1)	25(1)	5(1)	2(1)	10(1)
C(19)	32(2)	29(2)	58(2)	3(2)	-21(2)	8(2)
C(20)	20(1)	25(2)	23(1)	0(1)	2(1)	13(1)

Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for **2.102**.

	x	y	z	U(eq)
H(2)	6875(14)	9924(14)	3200(60)	33(10)
H(1A)	7344	9595	5625	20
H(2A)	7837	9612	1431	26
H(2B)	7774	10087	2278	26
H(3A)	8599	10118	3218	32
H(3B)	8336	10278	5180	32
H(5A)	7910	8867	6896	25
H(6A)	7087	8728	5916	19
H(7A)	7559	8788	1593	19
H(8A)	6732	8276	50	24
H(8B)	6469	8243	2458	24
H(9A)	7016	9163	-219	24
H(9B)	6404	8854	194	24
H(12A)	6867	7551	463	27
H(12B)	7397	8046	-377	27
H(13A)	7695	7479	-11	36
H(13B)	7286	7156	1962	36
H(14A)	7912	7613	4440	27
H(16A)	8421	8771	889	53
H(16B)	8313	8320	-867	53
H(16C)	8892	8720	-102	53
H(17A)	8715	8711	4949	53
H(17B)	9185	8688	3772	53
H(17C)	8813	8243	5501	53
H(18A)	6874	7402	5022	37
H(18B)	6504	7609	4136	37
H(18C)	6888	7890	6218	37
H(19A)	8744	9460	8030	64
H(19B)	8855	10043	8037	64
H(19C)	9068	9845	6009	64
H(20A)	6042	8928	3885	33

H(20B)	6419	9242	5946	33
H(20C)	6345	8693	5216	33

Torsion angles [°] for **2.102**.

C(10)-C(1)-C(2)-C(3)	169.2(2)
C(6)-C(1)-C(2)-C(3)	-64.0(3)
C(1)-C(2)-C(3)-C(4)	38.4(3)
C(2)-C(3)-C(4)-C(5)	-5.3(4)
C(2)-C(3)-C(4)-C(19)	175.2(3)
C(3)-C(4)-C(5)-C(6)	-3.2(4)
C(19)-C(4)-C(5)-C(6)	176.3(3)
C(4)-C(5)-C(6)-C(1)	-21.5(4)
C(4)-C(5)-C(6)-C(7)	103.1(3)
C(2)-C(1)-C(6)-C(5)	53.7(3)
C(10)-C(1)-C(6)-C(5)	-178.7(2)
C(2)-C(1)-C(6)-C(7)	-72.7(3)
C(10)-C(1)-C(6)-C(7)	54.8(3)
C(5)-C(6)-C(7)-C(8)	-174.4(2)
C(1)-C(6)-C(7)-C(8)	-51.4(3)
C(5)-C(6)-C(7)-C(11)	60.5(3)
C(1)-C(6)-C(7)-C(11)	-176.5(2)
C(11)-C(7)-C(8)-C(9)	-178.1(2)
C(6)-C(7)-C(8)-C(9)	52.9(3)
C(7)-C(8)-C(9)-C(10)	-56.3(3)
C(8)-C(9)-C(10)-O(2)	175.1(2)
C(8)-C(9)-C(10)-C(20)	-67.2(3)
C(8)-C(9)-C(10)-C(1)	56.7(3)
C(2)-C(1)-C(10)-O(2)	-47.4(3)
C(6)-C(1)-C(10)-O(2)	-172.4(2)
C(2)-C(1)-C(10)-C(20)	-167.1(2)
C(6)-C(1)-C(10)-C(20)	67.9(3)
C(2)-C(1)-C(10)-C(9)	68.2(3)
C(6)-C(1)-C(10)-C(9)	-56.8(3)
C(14)-O(1)-C(11)-C(18)	93.5(2)
C(14)-O(1)-C(11)-C(12)	-24.5(3)
C(14)-O(1)-C(11)-C(7)	-142.7(2)
C(8)-C(7)-C(11)-O(1)	174.31(19)
C(6)-C(7)-C(11)-O(1)	-59.9(3)

C(8)-C(7)-C(11)-C(18)	-65.4(3)
C(6)-C(7)-C(11)-C(18)	60.5(3)
C(8)-C(7)-C(11)-C(12)	60.9(3)
C(6)-C(7)-C(11)-C(12)	-173.3(2)
O(1)-C(11)-C(12)-C(13)	32.7(3)
C(18)-C(11)-C(12)-C(13)	-83.2(3)
C(7)-C(11)-C(12)-C(13)	149.1(2)
C(11)-C(12)-C(13)-C(14)	-29.0(3)
C(11)-O(1)-C(14)-C(13)	6.1(3)
C(11)-O(1)-C(14)-C(15)	131.1(2)
C(12)-C(13)-C(14)-O(1)	14.9(3)
C(12)-C(13)-C(14)-C(15)	-103.7(3)
O(1)-C(14)-C(15)-C(17)	61.5(3)
C(13)-C(14)-C(15)-C(17)	-179.7(2)
O(1)-C(14)-C(15)-C(16)	-63.9(3)
C(13)-C(14)-C(15)-C(16)	54.8(3)
O(1)-C(14)-C(15)-Cl(1)	178.21(17)
C(13)-C(14)-C(15)-Cl(1)	-63.1(3)

Hydrogen bonds for **2.102** [$\text{\AA}$ and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(2)#1	0.77(4)	1.97(4)	2.732(2)	171(4)

Symmetry transformations used to generate equivalent atoms:

#1 $-y+5/3, x-y+4/3, z+1/3$