THE INTRAMOLECULAR BUCHNER REACTION OF α-DIAZO-β-KETONITRILES: DEVELOPMENT AND APPLICATION TO THE TOTAL SYNTHESIS OF (+)-SALVILEUCALIN B

Thesis by

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To Mom, Dad, Mark and Leah

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ABSTRACT

Since its discovery in 1896, the Buchner reaction has fascinated chemists for more than a century. The highly reactive nature of the carbene intermediates allows for facile dearomatization of stable aromatic rings, and provides access to a diverse array of cyclopropane and seven-membered ring architectures. The power inherent in this transformation has been exploited in the context of a natural product total synthesis and methodology studies.

The total synthesis work details efforts employed in the enantioselective total synthesis of (+)-salvileucalin B. The fully-substituted cyclopropane within the core of the molecule arises from an unprecedented intramolecular Buchner reaction involving a highly functionalized arene and an α-diazo-β-ketonitrile. An unusual retro-Claisen rearrangement of a complex late-stage intermediate was discovered on route to the natural product.

The unique reactivity of α-diazo-β-ketonitriles toward arene cyclopropanation was then investigated in a broader methodological study. This specific di-substituted diazo moiety possesses hitherto unreported selectivity in intramolecular Buchner reactions. This technology was enables the preparation of highly functionalized norcaradienes and cyclopropanes, which themselves undergo various ring opening transformations to afford complex polycyclic structures.

Finally, an enantioselective variant of the intramolecular Buchner reaction is described. Various chiral copper and dirhodium catalysts afforded moderate stereoinduction in the cyclization event.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
C	cytosine
c	concentration of sample for measurement of optical rotation

^{13}C	carbon-13 isotope
^{14}C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
de	diastereomeric excess

DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)

FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
HATU	2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)

L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular seives

m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
t-Oct	*tert*-octyl (1,1,3,3-tetramethylbutyl)
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
pK_a	acid dissociation constant
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl

psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
s	selectivity factor = $k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase
Su	succinimide
t	triplet
T	thymine
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid

temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

Chapter 1

The Intramolecular Buchner Reaction

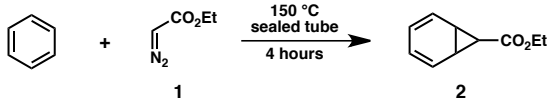
1.1 INTRODUCTION

The cyclopropane motif is of indisputable importance to the field of chemistry.[1] In addition to the prevalence of three membered rings wide array of chemical entities,[2] cyclopropanes have been realized as valuable synthetic intermediates capable of undergoing myriad transformations.[3] The synthesis of cyclopropanes has thus captured the interest of chemists for more than a century. Since the first known synthesis of cyclopropane by Freund in 1882,[4] numerous strategies have been developed to access this moiety.[5] One involves the generation of metal carbenoids from diazo compounds; this method accesses reactive intermediates that participate in formal 2+1 cycloadditions reactions to afford cyclopropane products.[5f]

The first synthesis of a diazo compound is attributed to Curtius in 1883, who reported the diazotization of natural α-amino acids to afford ethyl diazoacetate (EDA).[6] In 1896, Buchner and Curtius investigated the thermolysis of ethyl diazoacetate in

benzene, which they proposed resulted in the formation of the corresponding norcaradiene (Scheme 1.1).[7] This transformation is now known as the Buchner reaction, and since this seminal discovery numerous chemists have contributed to the development of cyclopropanation with diazo compounds throughout the 20th century.[8] The remarkable diversity of cyclopropane structures that can be prepared from the reaction of diazo reagents with alkenes or arenes speaks to the power of this transformation.[5f]

Scheme 1.1. *Buchner's initial report on the reaction of EDA and benzene*



1 2

The use of transition metals to catalyze the cyclopropanation reactions of diazo compounds has transformed this area of research.[9] For more than half of the preceding century the utility of diazo reagents for intermolecular cyclopropanation was limited by the harsh reaction conditions required for de-diazotization and the poor selectivity exhibited by the resulting carbenes.[10] Although the first metal-catalyzed decomposition of ethyl diazoacetate dates back to 1906,[11] it wasn't until the 1960's and 1970's that the methodology involving homogeneous catalysts gained wider adoption in synthetic contexts.[12]

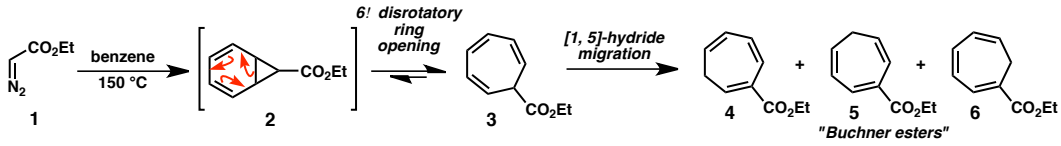
This chapter will focus on specifically the methodological development of the intramolecular arene cyclopropanation, and highlight the power of the transformation in selected total synthesis reports. The ensuing chapters will detail the applicability of intramolecular arene cyclopropanation in a total synthesis work and methodology study.

1.2 THE INTRAMOLECULAR BUCHNER REACTION†

1.2.1 Historical Development of the Buchner Reaction

In 1896, Buchner and Curtius reported the reaction between benzene and ethyl diazoacetate.[7] Although Buchner originally proposed the product of this reaction was norcaradiene **2**, Doering and co-workers,[13] with the assistance of modern NMR techniques, subsequently characterized the products as a mixture of cycloheptatrienes **4**–**6** (Scheme 1.2).[14] Since this discovery, the non-catalyzed and metal-mediated variants of this reaction have become important methods for the preparation of seven-membered rings.[10a]

Scheme 1.2. *The Buchner reaction*

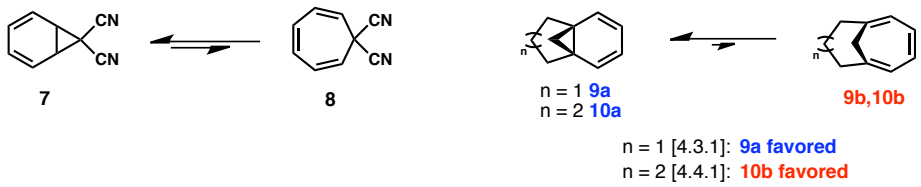


We now understand that cycloheptatriene (CHT) **3** arises from reversible 6π disrotatory electrocyclic ring opening of the initially formed norcaradiene **2**, and that compounds **2** and **3** exist in a dynamic equilibrium that heavily favors **3**.[15] Under the thermal conditions, 1,5-hydride migration results in isomerization of **3** to a thermodynamic mixture of cycloheptatrienes **4**–**6**.[16] The original report by Buchner[7,17] and subsequent findings by Doering[13] have sparked volumes of research on the norcaradiene–

† This review was written in collaboration Dr. Sergiy Levin, a former postdoctoral researcher in the Reisman group. For a published version, see: Reisman, S. E.; Nani, R. R.; Levin, S. *Synlett* **2011**, 2437.

cycloheptatriene equilibrium.[15,18] In simple, unconstrained systems the equilibrium lies toward the cycloheptatriene species.[19] However, several elegant studies have determined that a variety of steric[20] and electronic[21] factors may alter this equilibrium to instead favor the norcaradiene. Ciganek was the first to report that the incorporation of two π-accepting electron-withdrawing groups at the C7 position (e.g. 7,7-dicyanonorcaradiene, **7**, Figure 1.1) result in the stabilization of the norcaradiene valence tautomer. Geometric contraints can also affect the norcaradiene-CHT equilibrium. For example, Vogel and co-workers prepared and compared the ^{1}H NMR spectra of two closely related compounds, **9** and **10**.[22] Illustrating the influence of geometric constraints on the equilibrium, they found that for the ten-carbon system, norcaradiene **9a** predominates; on the other hand, the analogous eleven-carbon framework favors the ring-opened cycloheptatriene **10b**.

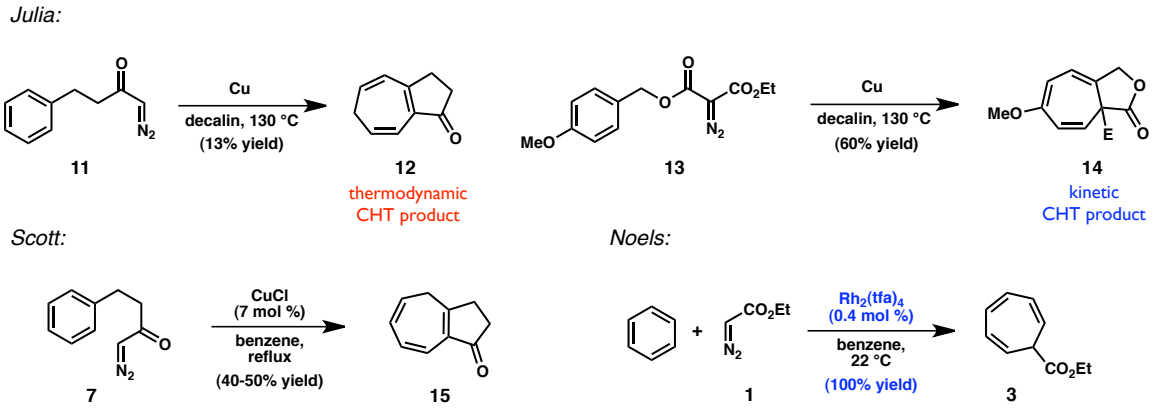
Figure 1.1. *Substituent effects on the norcaradiene-cycloheptatriene equilibrium*



Early synthetic applications of the thermal and photochemical *intermolecular* Buchner reaction were plagued by poor yields and the formation of isomeric cycloheptatriene products that were difficult to separate.[10a,b] Critical improvements in selectivity were achieved when the *intramolecular* Buchner reaction was investigated in combination with the use of heterogenous copper catalysts.

Julia *et al*. first reported the intramolecular cyclopropanation of α-diazoketones in 1970 (Scheme 1.3).[23] Despite the variable yields obtained and harsh conditions employed, the utility of the transformation to generate novel bicycle rings systems was recognized. In 1973, Scott reported that CuCl catalyzes the intramolecular Buchner reaction of phenyldiazobutane **11** to give, following 1,5-hydride migration, cross-conjugated dihydroazulenone **15** (Scheme 1.3).[24] Due to the labile nature of the cycloheptatriene species, however, the forcing conditions required even in the presence of copper catalysts precluded isolation of the kinetic products.

Scheme 1.3. *Seminal examples of metal-catalyzed Buchner reactions*



The problems associated with thermal and catalytic Buchner reactions prior to 1980 were solved with the introduction of dirhodium catalysts. In their initial report, Noels and Hubert demonstrated that $Rh_2(tfa)_4$ catalyzes the reaction between ethyl diazoacetate (**1**) and benzene to afford the kinetic cycloheptatriene product **3** in quantitative yield (Scheme 1.3).[25] The reaction with various substituted benzene compounds also afforded the ring-expanded product in high yields and good positional

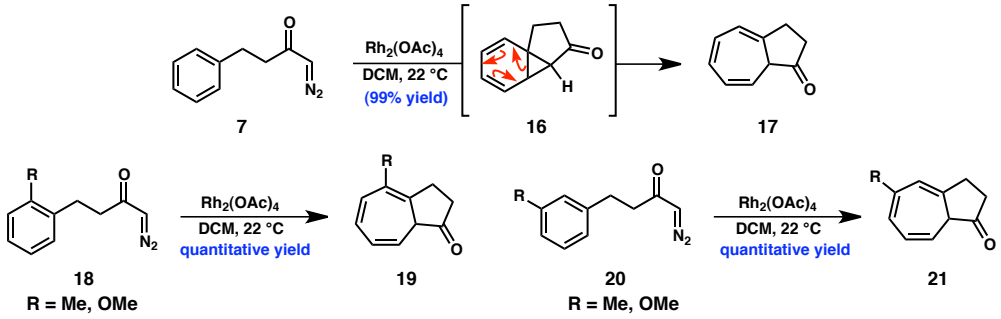
selectivity. The pitfalls endemic to the heterogeneous copper-catalyzed Buchner reaction were efficiently mitigated by the use of dirhodium catalysts, and this discovery greatly facilitated further study of this transformation. As they are the most widely employed catalysts for the Buchner reaction, development and application of Cu and Rh-catalyzed arene cyclopropanation will be reviewed in the following two sections.[26]

1.2.2 Methodological Investigations

1.2.2.1 Dirhodium Catalysts

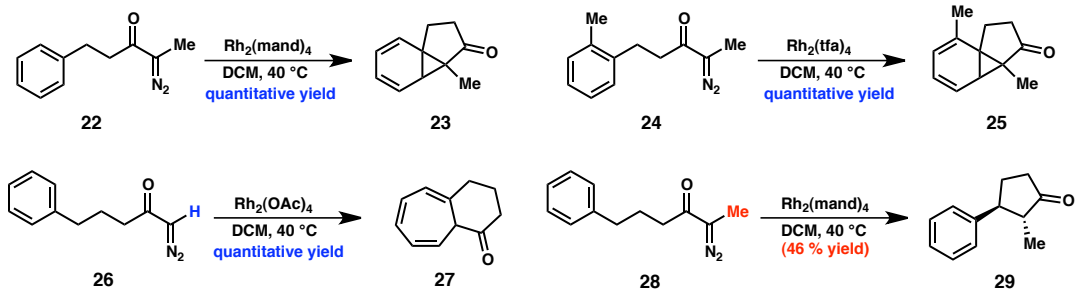
The synthetic utility of the *intramolecular* Buchner reaction was greatly improved with the advent of dirhodium(II) catalysts. Pioneering work by McKervey, Padwa, and others established the effects of arene substitution, diazo structure and catalyst electronics on the selectivity of the cyclopropanation. McKervey was first to examine the 1-diazo-4-phenylbut-2-one systems with dirhodium tetracarboxylate catalysts, and reported markedly improved yields versus the copper catalysts utilized by Julia and Scott (**7**, Scheme 1.4).[27]

Scheme 1.4. *The intramolecular Buchner reaction 1-diazo-4-phenylbut-2-ones*



A range of arene substitution is tolerated, and it was further discovered that cyclopropanation occurs generally at the site distal to *m*- or *o*-substituents (**18** and **20**, respectively).[28] Subsequent studies focused on how parameters such as the diazo substitution pattern and tether length between the arene and carbonyl influenced the yield of the intramolecular Buchner reaction. To examine the impact of diazo substitution on the intramolecular cyclization, 2-diazo-5-phenyl*pent*-3-one **22** and **24** were synthesized (Scheme 1.5).[29] Substrates **22** and **24** mirrored the reactivity of the analogous 1-diazo-4-phenyl*but*-2-one (**7** and **18**), affording products that favor the norcaradiene tautomer. Extension of the tether length in α-diazoketone compounds **26** and **28** revealed the sensitivity of the Buchner reaction to subtle structural changes. Whereas α-diazoketone **26** undergoes intramolecular cyclopropanation to yield cycloheptatriene **27**, α-diazo-β-alkylketone **28** only produces C-H insertion product **29** in modest yield.

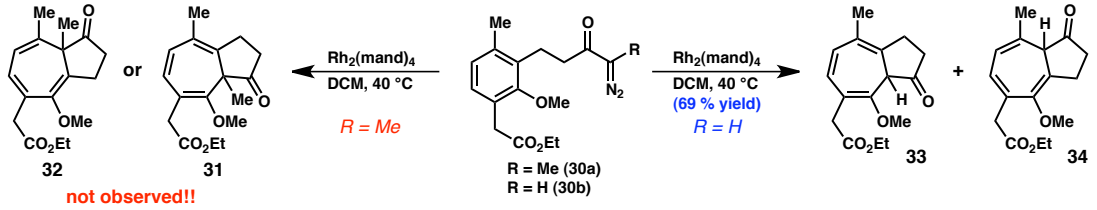
Scheme 1.5. *Investigations of diazo substitution and tether length*



Further limitations of the intramolecular Buchner reaction were revealed in Kennedy's work on 2,6-di-substituted arene compounds **30a,b**.[30] Whereas α-diazoketone **30b** readily cyclopropanates the pendant arene, α-diazo-β-alkylketone **30a** only affords a

mixture of dimeric products and neither of the cycloheptatriene isomers are observed (**31/32**, Scheme 1.6). Despite these pitfalls, the ability of metal carbenoids derived from α-diazoketones such as **30** to smoothly dearomatize arenes under mild conditions affirmed the great potential of the intramolecular Buchner reaction to synthesize complex bicycle structures.

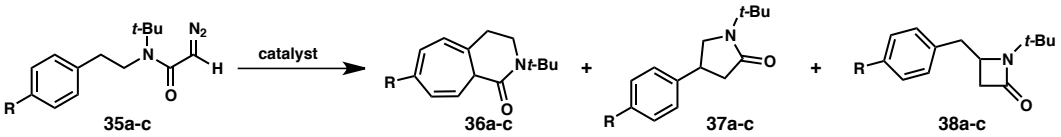
Scheme 1.6. *Investigations of arene and diazo substitution*



In a series of reports,[31] Padwa, Doyle and coworkers made significant contributions to the development of the intramolecular Buchner reaction. Their findings established that the ligand and arene electronics exert a significant impact on the chemoselectivity of intramolecular rhodium carbenoid transformations.[32] A series of intramolecular competition experiments for rhodium carbenoids was undertaken, with the goal of determining reactivity trends for electronically differentiated ligands. Based on these extensive studies, reactivity trends for Rh^{II} carbenoids derived from $Rh_2(pfb)_4$ were established: formal aryl C–H insertion > tertiary aliphatic C–H insertion > olefin cyclopropanation ca. = Buchner reaction > secondary C–H insertion. This is in contrast to the electron rich $Rh_2(cap)_4$ catalyst, which provided the following reactivity trend: olefin cyclopropanation > formal aryl C–H insertion > tertiary C–H insertion > secondary C–H insertion > Buchner reaction.[33]

Compounds **35a-c** were synthesized to examine the effect of arene electronics on the intramolecular Buchner reaction. Using $Rh_2(OAc)_4$ as the catalyst, diazoacetamide **35a** yielded a 2:1 ratio of cycloheptatriene **36a** to benzylic C–H insertion **37a** (Table 1.1). However, exposure of nitroarene **35c** to the various dirhodium catalysts resulted in predominantly C-H insertion product **37c**, regardless of ligand choice. In this case the nitro group appears to inhibit the intramolecular Buchner reaction more than the competing C-H insertion, but an inductive deactivation of the benzylic protons is nonetheless present due to appearance of β-lactam **38c**. For electron neutral- and rich-arenes (**35a,b**), the ligand electronics on dirhodium were found to override the chemoselectivity dictated by arene substitution. Whereas more electron poor catalysts favor cyclopropanation, electron-releasing ligands promote insertion into the benzylic C-H bond to form γ-lactams **37a,b**.

Table 1.1. *Catalyst and substrate effects on chemoselectivity*



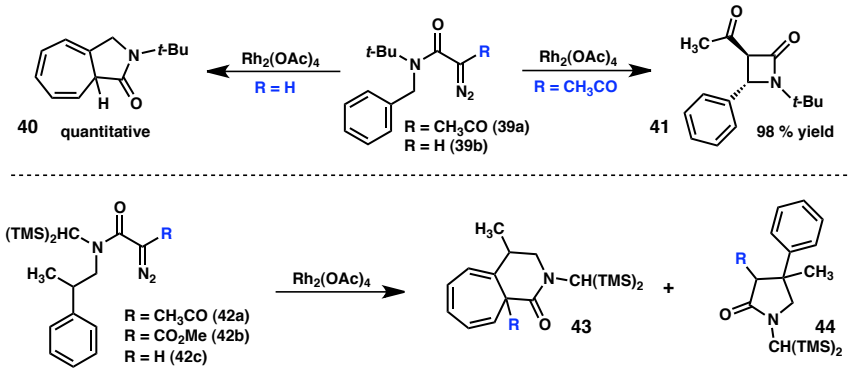
35a-c 36a-c 37a-c 38a-c

*Relative Amounts of **36:37:38***

	Catalyst	Total Yield	36a	37a	38a
R = H (35a)	$Rh_2(pfb)_4$	80%	95	5	-
	$Rh_2(OAc)_4$	85%	68	32	-
	$Rh_2(cap)_4$	82%	3	97	-
	$Rh_2(acam)_4$	80%	23	77	-
			36b	37b	38b
R = OMe (35b)	$Rh_2(pfb)_4$	93%	93	7	-
	$Rh_2(OAc)_4$	90%	76	24	-
	$Rh_2(cap)_4$	81%	14	86	-
	$Rh_2(acam)_4$	80%	36	64	-
			36c	37c	38c
$R = NO_2$ (35c)	$Rh_2(pfb)_4$	92%	27	60	13
	$Rh_2(OAc)_4$	80%	8	77	15
	$Rh_2(acam)_4$	92%	0	97	3

The impact of carbene substituents was also interrogated (Scheme 1.7). It was found that, irrespective of tether length, α-diazoacetamides **39b** and **42c** (R = H) underwent intramolecular cyclopropanation to afford cycloheptatrienes **40** and **43c**.[31a,34] Consistent with the work of McKervey, introduction of an ester or ketone substituent completely alters the chemoselectivity of the cyclization, providing the C-H insertion products **44a** and **44b** in excellent yield. Remarkably, α-diazo-β-acetamidoketone **39a** prefers four-membered ring formation to form β-lactam **41** entirely to the alternative Buchner reaction.

Scheme 1.7. *Effect of diazo substitution: divergent reactivity*



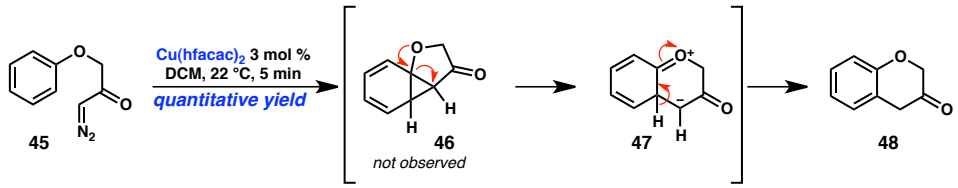
R	Yield 43	Yield 44
CH_3CO	-	100%
CO_2Me	-	100%
H	32%	68%

1.2.2.2 Copper Catalysts

Copper catalysts have recently re-emerged as effective promoters of the intramolecular Buchner reaction. In particular, the use of solubilizing ligands has enabled further development beyond the heterogeneous catalysts employed since the early 20th

century. The discovery and application of homogeneous copper catalysts for alkene cyclopropanation expanded greatly after the seminal reports of by Nozaki[12b,c] and Moser[12d,e] in the late 1960's. However, the intramolecular Buchner reaction of an α-diazo

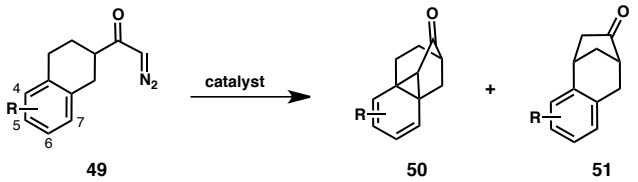
Scheme 1.8. *Homogeneous copper catalysis of the intramolecular Buchner reaction*



ketone using a soluble copper catalyst was not reported until 1984, when Saba disclosed that $Cu(hfacac)_2$ catalyzed cyclization of **45** (Scheme 1.8).[35] As evidenced by this example, for simple α-diazoketones the reaction rate and efficiency with soluble Cu^{II} salts rivals that of the dirhodium catalysts.

Although less frequently utilized for intramolecular arene cyclopropanation, in certain cases copper catalysts have exhibited superior chemoselectivity over complementary dirhodium catalysts. In the study of the intramolecular reaction of tetralin 2-diazo ketone **49** (Table 1.2), Mander evaluated the selectivity of both catalyst systems.[36] These studies revealed that the yields of arene cyclopropanation are highly dependent on both the catalyst and the arene substitution pattern. In general, rhodium catalysts provided mixtures of norcaradiene **50** and cyclopentanone **51**, sometimes favoring **51**. Alternatively, copper catalysts provided lower overall yields, but delivered better selectivity for the norcaradiene (Table 1.2, entries 2, 4, 6).

Table 1.2. *Mander's studies of tetralin 2-diazomethyl ketones*

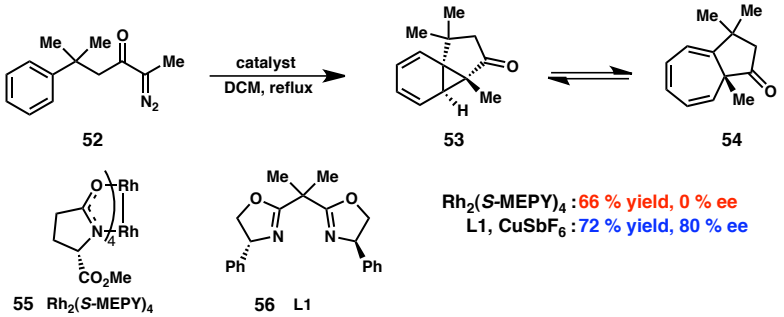


49 50 51

Entry	R	Catalyst	Yield of 50 (%)	Yield of 51 (%)
1	H	$Rh_2(OAc)_4$	39	41
2	H	$Cu(acac)_2$	56	6
3	5-MeO	$Rh_2(OAc)_4$	34	41
4	5-MeO	$Cu(acac)_2$	56	12
5	6-MeO	$Rh_2(OAc)_4$	71	14
6	6-MeO	$Cu(acac)_2$	61	17
7	7-MeO	$Rh_2(OAc)_4$	46	44
8	7-MeO	$Cu(acac)_2$	64	3

Chiral copper catalysts have also been demonstrated to promote enantioselective Buchner reactions. In a series of reports,[37] Maguire and coworker's have established that for substrates such as **52**, superior asymmetric induction is achieved with a copper-bisoxazoline versus various chiral dirhodium species (Scheme 1.9).[38] Furthermore, the use of a highly active cationic copper species allowed for the reaction to be carried out in refluxing dichloromethane, a significant improvement from high temperatures required in heterogeneous copper-catalyzed diazo transformations.

Scheme 1.9. *Stereoinduction in the copper-catalyzed Buchner reaction*



52 53 54

55 Rh_2(*S*-MEPY)$_4$ 56 L1

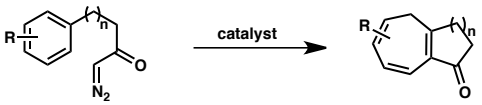
1.2.3 Summary

This section has described the history of the intramolecular Buchner reaction and key methodological studies that contributed greatly to the progress of the transformation. From the collective research of several laboratories the following reactivity trends have emerged:[12a,33] (1) rhodium catalysts promote Buchner reactions at lower temperatures than copper catalysts;[25,39] (2) in systems where C-H insertion is disfavored, rhodium catalysts typically provide higher yields than copper catalysts;[27,29] (3) for rhodium catalysts, electron-deficient ligands favor arene cyclopropanation, whereas electron-rich ligands favor C-H insertion;[31d] (4) *ortho*-substituted aryldiazobutane substrates undergo arene cyclopropanation at the less substituted site;[29] (5) doubly stabilized diazo substrates (e.g. α-diazo-β-keto esters) generally favor C-H insertion over arene cyclopropanation.[40]

1.3 THE INTRAMOLECULAR BUCHNER REACTION IN TOTAL SYNTHESIS

Whereas intramolecular alkene cyclopropanation has been often employed in the synthesis of natural products, the intramolecular Buchner reaction has found far fewer applications in this area. Nonetheless, this facile method of dearomatization has been recognized as a powerful method for carbon-carbon bond formation, and thus the Buchner reaction has been utilized in total synthesis endeavors. Following the early reports of copper and rhodium catalysis, a number of research groups have applied intramolecular variants of the Buchner reaction to the preparation of polycyclic systems

Scheme 1.10. *Commonly studied intramolecular Buchner substrates*



57a: n = 1
57b: n = 2

58a: n = 1
58b: n = 2

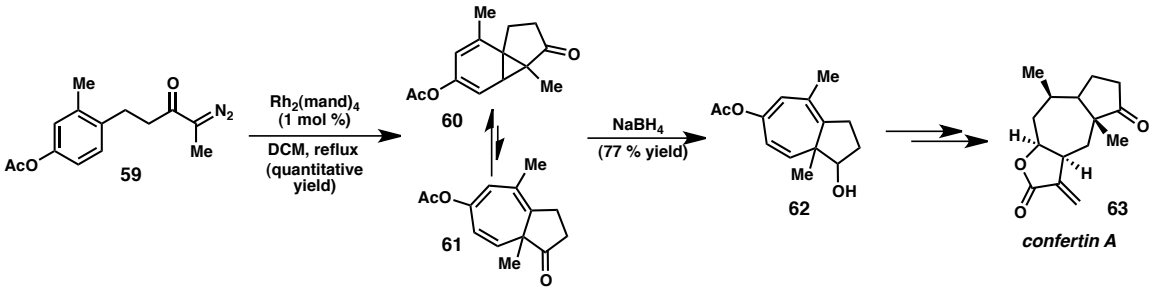
containing seven-membered rings.[5f] The vast majority of studies reported to date have focused on compounds with two-carbon tethers between the α-diazocarbonyl and the arene (e.g. **57a**, Scheme 1.10);[29,41] however, some heteroatom linkers have also been pursued.[42] These studies have primarily utilized arenes bearing electron-releasing substituents, as electron-deficient arenes are typically poor substrates for arene cyclopropanation.[31d,43]

The interest in aryldiazobutanone substrates such as **57a** is fueled in part by the large number of sesquiterpene natural products with bicycle [5.3.0] decane core structures (e.g. **58a**, Scheme 1.10), to which this synthetic methodology provides a convenient entry.[44] Moreover, these substrates do not usually exhibit substantial levels of competing benzylic C-H insertion; as a result, higher yields of the cycloheptatriene products (**58a**) are observed when compared to the Buchner reactions of the corresponding aryldiazopentane systems (e.g. **57b**).

In an early demonstration of the utility of the Rh-catalyzed intramolecular Buchner reaction, McKervey and Kennedy reported that exposure of α-diazo ketone **59** to catalytic Rh_2(mandelate)$_4$ quantitatively provided a mixture of norcaradiene **60** and cycloheptatriene **61** (Scheme 1.11).[30] Although norcaradiene **60** was the major species observed by ^{1}H NMR spectroscopy, chemoselective reduction of the equilibrating mixture allowed for isolation of cycloheptatriene **62** in 77% yield as a mixture of

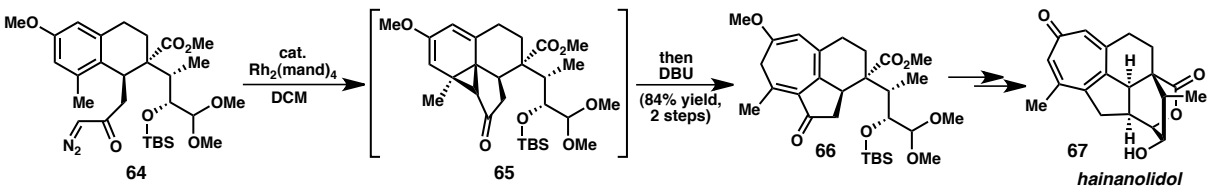
diastereomers. Cycloheptatriene **62** was subsequently advanced in several steps to (±)-confertin A (**63**).

Scheme 1.11. *Totals synthesis of (±)-confertin A*



In their synthesis of hainanolidol (**67**), Mander and co-workers employed an intramolecular arene cyclopropanation reaction to access a 5,7-fused ring system in a considerably more complex setting (Scheme 1.12).[45] Treatment of α-diazo ketone **64** with catalytic Rh_2(mandelate)$_4$ resulted in arene cyclopropanation followed by electrocyclic ring opening to give an unstable cycloheptatriene. Immediate exposure to DBU resulted in isomerization of the olefin to give the more stable and thermodynamically preferred enone **66**. Tricycle **66** was advanced in seven steps to hainanolidol (**67**).[46]

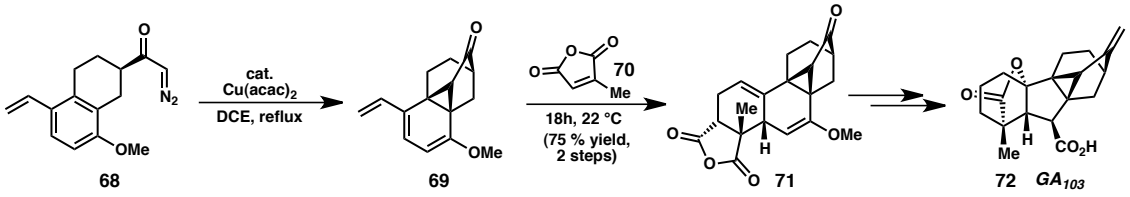
Scheme 1.12. *Total synthesis of hainanolidol (**67**)*



In contrast to the numerous studies targeting the formation of bicycle [5.3.0] decanes by intramolecular arene cyclopropanation, there are far fewer examples of reactions that provide the corresponding bicycle 5.4.0 undecanes. This is likely due to the increased propensity for metal-carbenoid insertion into the activated benzylic C-H bonds of the corresponding substrates (e.g. **57b**, Scheme 1.10).[47] For aryldiazobutane substrates, the strain incurred during cyclobutanone formation disfavors C-H insertion processes; alternatively, it is well known that C-H insertion to give five-membered rings is highly favorable.[48] The competition between C-H insertion and arene cyclopropanation is clearly illustrated by Mander and co-workers' studies of tetralin 2-diazomethyl ketones discussed in section 1.2.2.2 (Table 1.2). Of note, due to the geometric constraints of these systems, the norcaradiene valence tautomer **50** is favored.

Mander subsequently utilized this methodology as part of a cascade reaction sequence in an elegant total synthesis of gibberellin GA103 (**72**, Scheme 1.13).[49] Treatment of α-diazo ketone **68** with $Cu(acac)_2$ in refluxing dichloroethane provided unstable norcaradiene **69**, which was trapped in situ by addition of 3-methylfuran-2,5-dione (**70**) to deliver polycycle **71**. This remarkable sequence proceeded in 75% yield over two steps. Polycycle **71** was subsequently elaborated in 12 steps to GA_{103}.

Scheme 1.13. *An arene cyclopropanation/Diels-Alder cascade reaction in Mander's synthesis of GA_{103} (**72**)*



1.4 CONCLUSION

The Buchner reaction, and products thereof, have fascinated chemistry for more than a century. The discovery of transition metal catalysts greatly increased the applicability in the synthesis of complex molecules via arene dearomatization. As highlighted in this chapter, the intramolecular Buchner reaction has proven to be a useful transformation in the context of natural product total synthesis. Although these synthetic endeavors have driven methodological advances in arene cyclopropanation, there are still challenges with regard to chemoselectivity and stereoselectivity.

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Chapter 2

An Introduction to Salvileucalin B

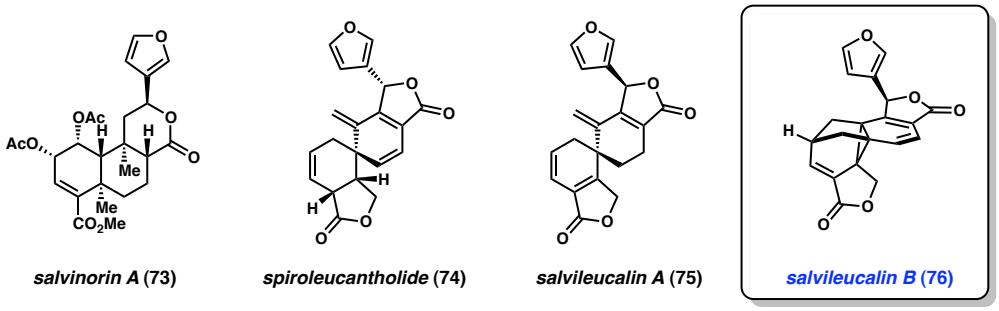
2.1 INTRODUCTION

2.1.1 Natural Products from the Salvia Genus of Plants

Plants of the *Salvia* genus have a rich history in traditional medicine. Indeed, the name *Salvia* derives from the Latin word *salvare*, which means, "to heal." Isolation studies targeting *Salvia* plants have yielded a wealth of structurally intriguing, biologically active natural products, including the potent hallucinogen salvinorin A (**73**, Figure 2.1).[1] Recently, studies aimed at identifying novel diterpenoids as potential medicinal leads resulted in the isolation of three new compounds from *Salvia leucantha*,[2] all displaying rearranged frameworks of the typical neoclerodane skeleton. Of particular interest to us was the compound salvileucalin B (**76**), which exhibits promising cytotoxicity against A549 (human lung adenocarcinoma) and HT-29 (human colon adenocarcinoma) cells.[2b] Salvileucalin B is a unique member of the clerodane family in

that it contains a tricyclo[3.2.1.$0^{2,7}$] octane carbon framework, the first neoclerodane diterpenoid isolated to possess this structural feature.

Figure 2.1. *Salvileucalin B and related rearranged neoclerodane diterpenoids*



salvinorin A **(73)** ***spiroleucantholide*** **(74)** ***salvileucalin A*** **(75)** ***salvileucalin B*** **(76)**

2.1.2 Isolation and Structural Characterization of Salvileucalin B

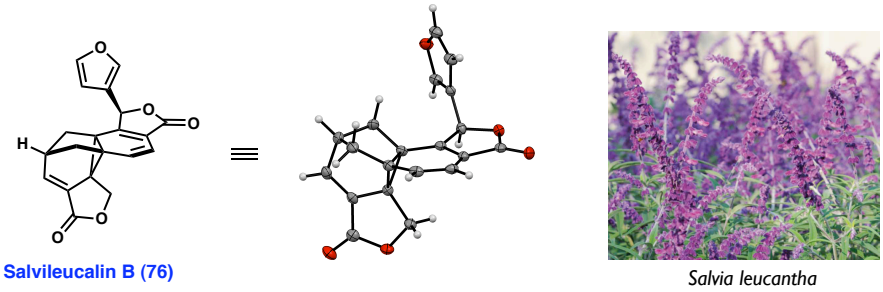
In 2008, Aoyagi *et al*. isolated a novel cytotoxic diterpenoid from the aerial parts of *Salvia leucantha*, more commonly known as the Mexican sage bush. Salvileucalin B (**76**) was isolated in a quantity of 18 mg as an amorphous, colorless powder from 18.66 kg of air-dried plant matter. The connectivity of the natural product was determined by one- and two-dimensional NMR spectroscopy, and the structure was ultimately obtained by X-ray crystallographic analysis (Figure 2.2). The absolute stereochemistry was deduced by comparison of the experimental and theoretical IR and VCD spectra.

2.1.3 Proposed Biosynthesis

The isolation report by Aoyagi *et al*. proposes a biosynthetic pathway for formation of salvileucalin B (**76**, Scheme 2.1). The first intermediate **77**, consisting of a salvigenane skeleton,[3] is suggested to undergo ring contraction to afford spirocycle **79**.

Lactone **77** is itself hypothesized to have evolved from a neoclerodane diterpene by a ring expansion of the standard clerodane framework.[4] Following a series of oxidations that afford salvileucalin A (**75**), an additional desaturation event is hypothesized to generate key intermediate **82**, which then undergoes an intramolecular Diels–Alder reaction (IMDA) to provide salvileucalin B (**76**).

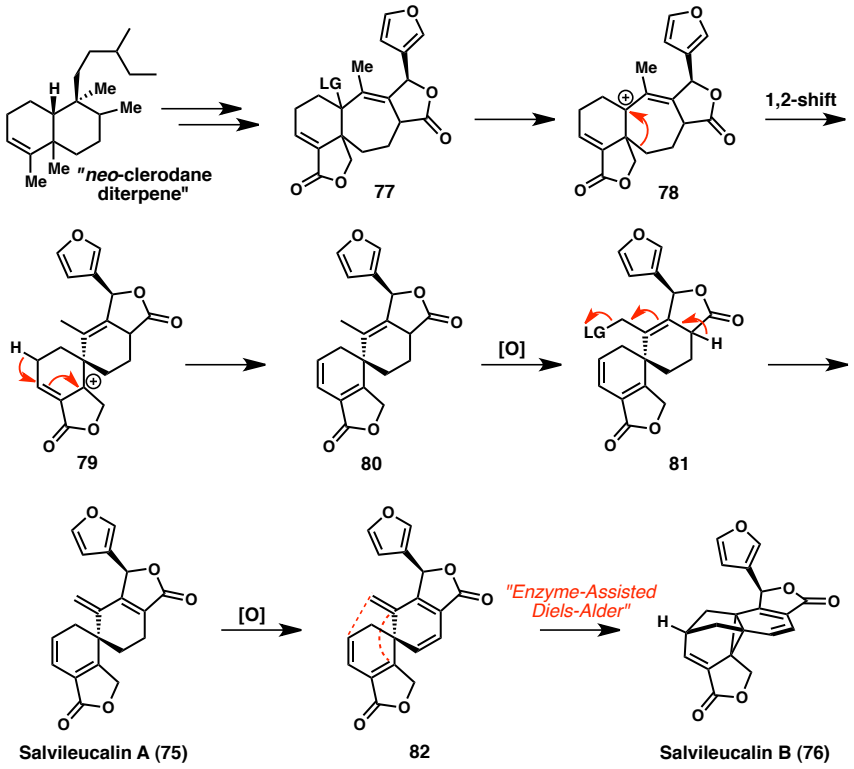
Figure 2.2. *Crystal structure of salvileucalin B*



A key question in the proposed biosynthesis of salvileucalin B (**76**) is whether the Diels–Alder step involves enzyme catalysis. The existence of "Diels–Alderases" (enzymes that catalyze a concerted [4+2] reaction) is still a controversial topic in the chemistry community today.[5] There are many cyclohexene-containing natural products that have been characterized as Diels–Alder cycloadducts,[6] and in certain cases evidence for enzymatic catalysis of this transformation has been advanced.[7] Although speculative in nature, the intramolecular cycloaddition to form the caged core of salvileucalin B has garnered some support by both empirical and theoretical evidence. Despite the poor orientation of the Δ^9-double bond and the diene, the 5-vinyl-1,3-cyclohexadiene motif has been demonstrated to undergo intramolecular [4+2] cycloaddition to generate strained, caged polycyclic structures.[8] Additionally, in 2011, Chen *et al*. reported that a

thermal intramolecular Diels–Alder reaction of α,β-unsaturated ester **83** yielded the propellane core of salvileucalin B (Scheme 2.2).[9] The forcing conditions required for intramolecular cycloaddition of 5-vinyl-1,3-cyclohexadienes, however, likely preclude an unassisted transformation from occurring under typical biological conditions. Nevertheless, these data suggest an intramolecular [4+2] reaction to provide the densely fused polycycle of salvileucalin B is feasible, despite the geometric constraints of the system.

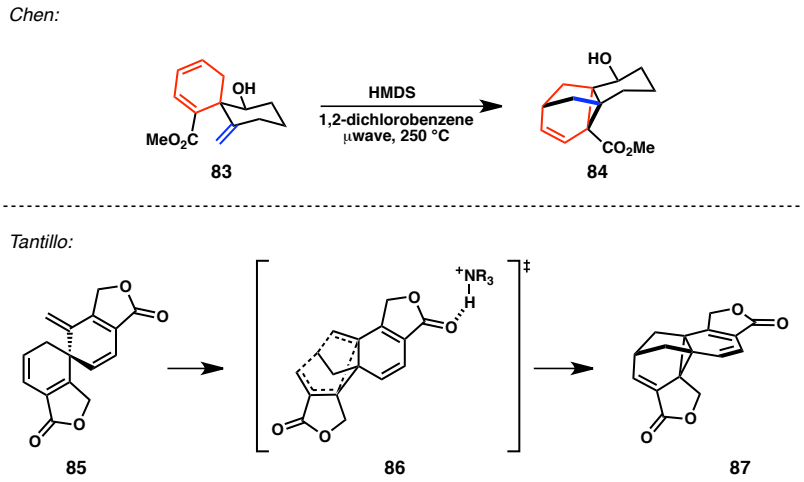
Scheme 2.1. *Biosynthetic hypothesis for salvileucalin B*



Computational simulation by Tantillo and coworkers on the non-catalyzed intramolecular [4+2] of **85** estimated the activation energy to be approximately >25

kcal/mol, making the transformation highly unlikely in a biologically reasonable temperature regime. Coordination of the "northern lactone" to positively charged amino acid residues (e.g., guanidinium, imidazolium, ammonium), however, led to significant reductions in the activation barrier ranging from ~2 to 6 kcal/mol.[10] Although this activation barrier is near the high end for typical enzyme catalyzed reactions,[11] the computations nonetheless demonstrate reasonable non-covalent interactions that could result in reduced energetic boundaries in the IMDA reaction to form salvileucalin B.

Scheme 2.2. *Experimental and theoretical evidence for IMDA*



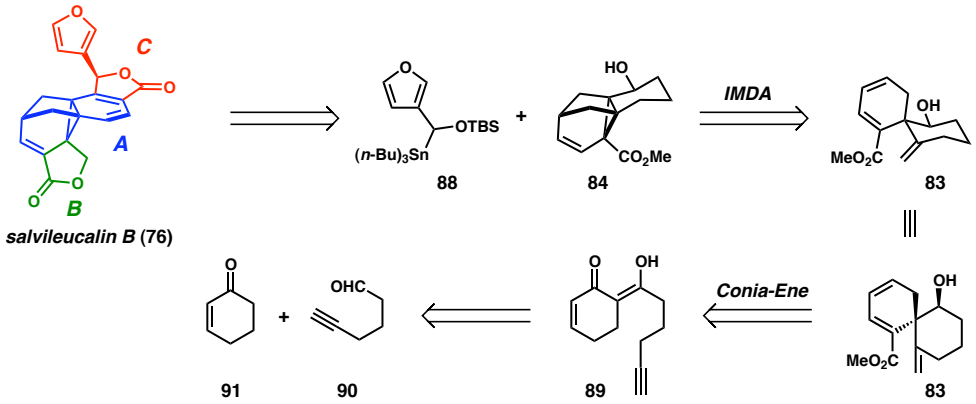
2.2 PREVIOUS TOTAL SYNTHESES OF SALVILEUCALIN B

Prior to our work on salvileucalin B there were no completed total syntheses reported. After our disclosure of the total synthesis of **76**, Chen and coworkers' published a route to a functionalized core of the natural product. This section summarizes their synthetic efforts.

2.2.1 Chen's Progress Towards Salvileucalin B

In 2011 Chen and coworkers' reported a synthetic approach to salvileucalin B that showcased a biomimetic intramolecular Diels–Alder reaction.[9] As part of their strategy, the researchers sought to develop a flexible route that would allow for late-stage incorporation of the two lactones in order to evaluate the biological activity of salvileucalin B and analogues. To fulfill this objective they divided the natural product into three domains, A, B, and C (Scheme 2.3).

Scheme 2.3. *Chen's retrosynthetic analysis of salvileucalin B*

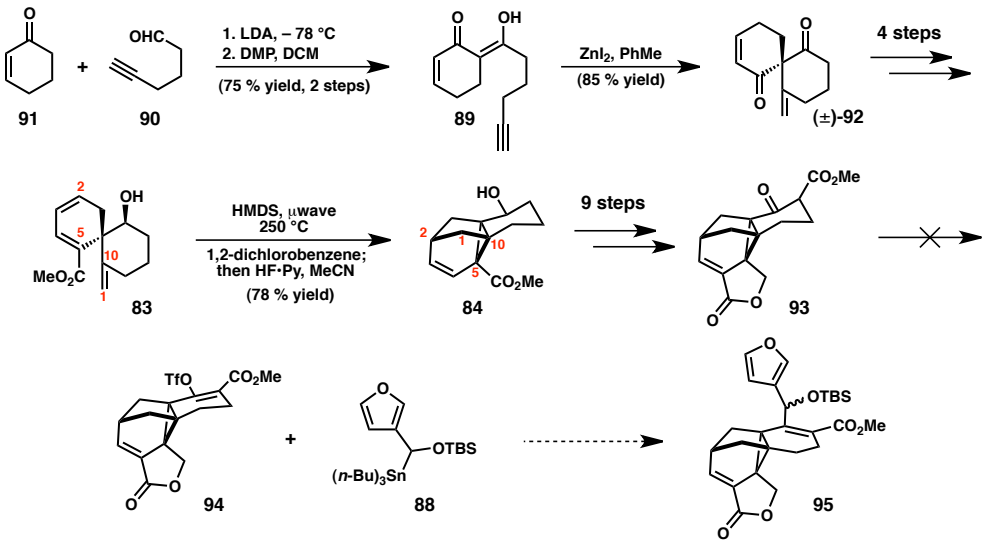


Incorporation of the two lactone subunits (domains B and C) was expected to be achieved by elaboration of the α,β-unsaturated ester and cross-coupling of an appropriately functionalized furan. This convergent entrance to the B and C domains was anticipated to permit access to variable functionality around the norcaradiene core. Cyclopropane **84** was thus targeted as the key intermediate, which was envisioned to arise from an intramolecular Diels–Alder reaction of spirocycle **83**. As discussed in section 2.1.3, this step was inspired by Aoyagi and coworkers' biosynthetic hypothesis of

the formation of the polycyclic framework of the natural product. Bicycle **83** was expected to originate from cyclohexenone **89**, which itself can be further simplified into basic starting materials.

The synthesis commenced with the aldol condensation of cyclohexenone and aldehyde **90**, which afforded diketone **89** after oxidation (Scheme 2.4). Conia–ene cyclization[12] of alkyne **89** promoted by ZnI_2 provided the racemic spirocycle **92** in high yield. A sequence of functional group manipulations yielded the 5-vinyl-1,3-cyclohexadiene motif (**83**) required to test the intramolecular cycloaddition. In the event, microwave heating to 250 °C afforded the fully substituted allylic cyclopropane **84** in 78 % yield.

Scheme 2.4. *Intramolecular [4+2] and further elaboration*

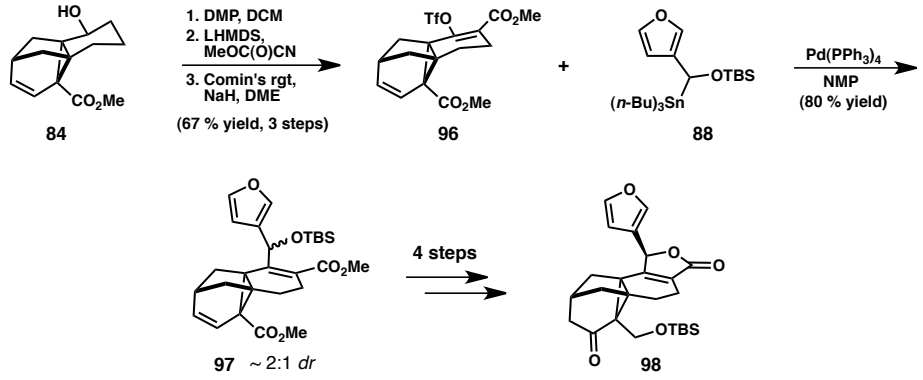


With the A domain of the natural product in hand, efforts were focused on appending the two lactones onto this central unit. A lengthy sequence furnished β-

ketoester **93**, now a single step away from conversion to an enol species capable of the ensuing cross coupling. A variety of conditions were investigated to promote this transformation, however, none afforded the desired product (**94**). Control experiments determined the alkenyl γ-lactone moiety decomposed during these reactions.

The failure of **93** to undergo further elaboration prompted Chen and coworkers' to delay introduction of the B domain lactone. To this end, alcohol **84** was transformed into enol triflate **96** via a sequence of oxidation, α-acylation with Mander's reagent,[13] and conversion of the ketone to the enol triflate (**96**). Diester **96** underwent smooth Stille coupling with stannane **88** to produce α,β-unsaturated ester **97** in good yield, albeit as a mixture of diastereomers. After separation of the correct epimer, an additional four steps yielded the desired northern lactone and appropriate functionality for synthesis of the B domain. Ketone **98** was the most advanced structure reported, and no further work on this synthetic route has been reported at the present time.

Scheme 2.5. *Stille coupling and synthesis of domain C*



2.3 SUMMARY

Isolation chemists have discovered an abundance of structurally intriguing diterpenoid natural products from plants of the *Salvia* genus. Salvileucalin B (**76**) is one of the newer members of this class, and is quite remarkable owing to the presence of a stable norcaradiene embedded within its structure. The fascinating structure and intriguing biosynthetic proposal has recently captured the attention of several different groups, and at the commencement of our studies no partial or full total syntheses existed.

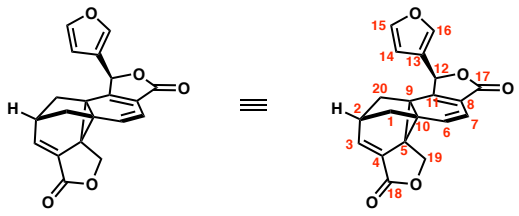
2.4 INTRODUCTION TO SYNTHETIC EFFORTS[†]

2.4.1 Structure and Synthetic Challenges

Salvileucalin B (**76**) represents a formidable challenge to modern synthetic methods (Figure 2.3), with an unprecedented structure bearing several notable features that merit attention when considering a synthetic strategy. The structure of **76** is striking in that it contains a stable norcaradiene core embedded within a caged polycyclic skeleton.[14] Construction of this unusual motif requires the formation of a fully substituted cyclopropane, which remains a challenging transformation despite extensive research in the area of cyclopropanation chemistry. Furthermore, the core of salvileucalin B is decorated with two γ-lactones, two tertiary carbon stereocenters, and the furan moiety.

[†] This work was performed in collaboration with Dr. Sergiy Levin, a former postdoctoral scholar in the Reisman group. Parts of this Chapter have appeared in previous publications: (a) Levin, S.; Nani, R. R.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780. (b) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774.

Figure 2.3. *Salvileucalin B*



Salvileucalin B (76)

The remarkable structure of **76** presented a unique opportunity to investigate the chemistry of norcaradienes and highly functionalized cyclopropanes, and thus inspired us to undertake efforts toward salvileucalin B. At the outset of our studies, there were no previous approaches to salvileucalin B in the literature, and only one other synthetic study has been published to date.[9] This chapter outlines our work toward the completion of this project, which has culminated in the only total synthesis of this diterpenoid yet reported.

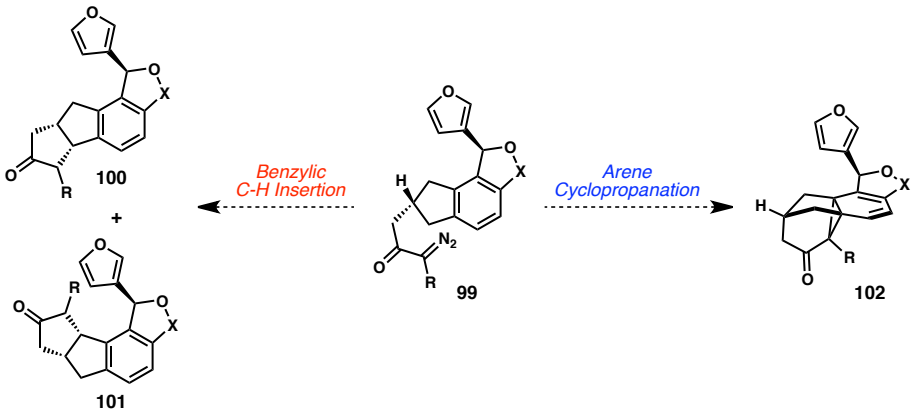
2.4.2 Outline and Context of Approach

In considering a synthesis of **76**, we were intrigued by the possibility of employing a late-stage intramolecular cyclopropanation reaction of a tricyclic arene such as **99** to directly form the norcaradiene core (Scheme 2.6). Since the initial report by Buchner and Curtius in 1885 detailing the thermolysis of ethyl diazoacetate in benzene,[15] the cyclopropanation of arenes has been the focus of numerous investigations. Thermal Buchner reactions generally provide the ring-opened cycloheptatriene products as mixtures of isomers.[16] With the advent of transition metal-catalyzed decomposition of stabilized diazo compounds,[17] several methodological studies have demonstrated that

isomerically pure cycloheptatrienes can be isolated in synthetically useful yields from an appropriate diazo precursor and arene with use of copper[18] and rhodium[19] catalysts. Despite the prevalence of cycloheptane containing natural products, the Buchner reaction is still under-utilized in total synthesis endeavors.[20]

Access to **102** via cyclopropanation of **99** requires the chemoselective intramolecular reaction of a metal-carbenoid (derived from the α-diazo carbonyl of **99**) with the arene π-system, in preference to highly favorable C–H insertion reactions at the adjacent, activated benzylic proton sites. In addition, cyclopropanation to give **102** requires formation of a fully substituted cyclopropane. In this context, the cyclopropanation of **99** provides an interesting case study of the factors influencing benzylic C–H insertion versus arene cyclopropanation. Futhermore, due on the geometric constraints of the polycyclic system, the norcaradiene of **102** was not expected to undergo electrocyclic ring opening to the corresponding cycloheptatriene.[21]

Scheme 2.6. *Chemoselectivity considerations in the key step*

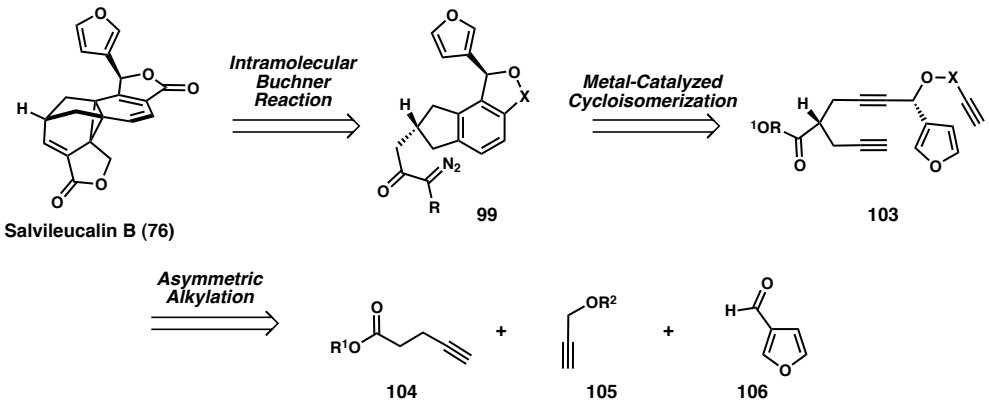


2.5 FIRST GENERATION APPROACH

2.5.1 Retrosynthetic Analysis

In our retrosynthetic analysis of salvileucalin B (**76**), we sought to design a route that would allow for incorporation of the two lactones in the final stages of the synthesis (Scheme 2.7). The rationale for late-stage lactone installation was based on several considerations. Generally, electron-poor aryl rings are less reactive substrates in arene cyclopropanation,[22] and it was expected the presence of the northern lactone would substantially deactivate the benzene moiety. Moreover, the presence of the northern lactone raises the potential for chemoselectivity issues when manipulating the southern lactone. The southern lactone was expected to arise from the Buchner reaction product of acylic diazo ketone **99** via manipulation of the ketone and R groups. Although the use of a cyclic diazo lactone might provide a more expedient method to access the southern lactone, examples of such a diazo compound participating in a Buchner reaction are rare.[23] The identity of the X and R functional groups that would allow for successful execution of the proposed arene cyclopropanation event and subsequent elaboration to the two lactones was critical to the synthetic plan. We initially sought to evaluate two systems, in which X = CH_2 or SiR_2; in each, the aryl ring of **99** was expected to be electronically well suited for the Buchner reaction. However, we also recognized that the norcaradiene products would require late stage functionalization to install the northern lactone. In terms of R, it was envisioned that an ester or related moiety could provide an appropriate handle for elaboration to the southern lactone.

Scheme 2.7. *Retrosynthetic analysis of salvileucalin B*

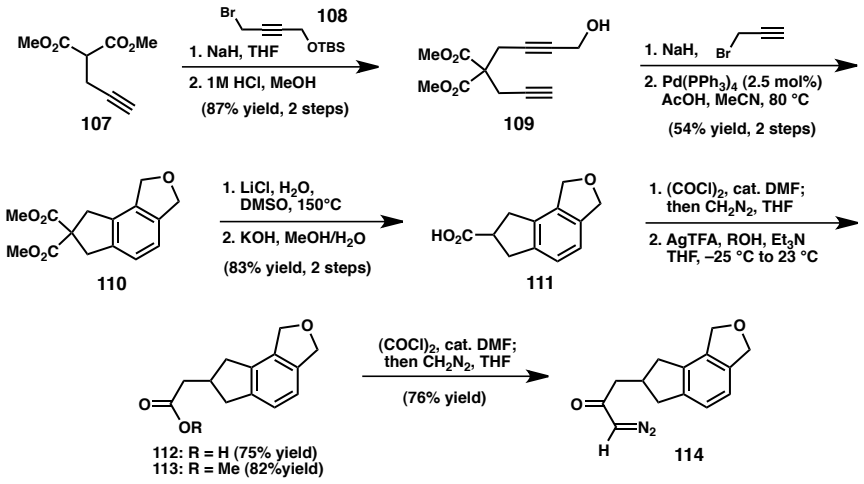


Having established tricycle **99** as a late-stage target, we envisioned that the [5,6,5] ring system could be rapidly assembled via a metal-catalyzed cycloisomerization of an appropriately functionalized triyne (**103**). This acyclic unit, in turn, could be arise from the union of the three simple building blocks **104**, **105**, and **106**.

2.5.2 Synthesis and Evaluation of a Model System

To assess the feasibility of constructing the norcaradiene core of **76** by arene cyclopropanation, our initial synthetic efforts focused on rapidly accessing an appropriate model substrate.[24] To this end, we initially identified terminal diazo ketone **114 as** a suitable compound for investigating different catalysts, solvents, and other reaction parameters (Scheme 3.3). Whereas an enantioselective synthesis of **114** would require an asymmetric alkylation reaction to prepare triyne **103**, for the purpose of rapidly accessing the α-diazo carbonyl compounds of interest, the compounds in this study were prepared as racemates.

Scheme 2.8. *Synthesis of α-diazo ketone* ***114***

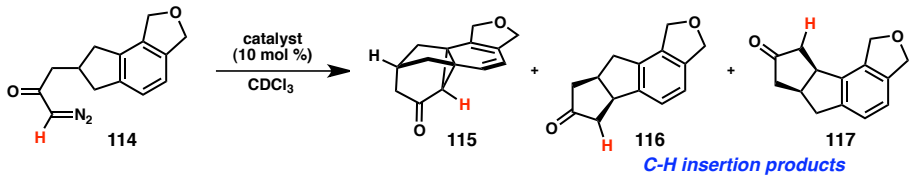


Thus, our model studies commenced with the alkylation of commercially available dimethyl propargyl malonate (**107**) with TBS-protected propargyl bromide **108**,[25] followed by acid-mediated cleavage of the silyl ether to give diyne **109** in 87% yield (Scheme 2.8). Alkylation of **109** with propargyl bromide provided the corresponding triyne, which, after exposure to $Pd(PPh_3)_4$ in the presence of AcOH, smoothly delivered tricycle **110** in 78% yield (54% yield over the two-step sequence).[26] Krapcho dealkoxycarbonylation[27] of tricycle **110** was followed by saponification with potassium hydroxide to give carboxylic acid **111**. Subsequent conversion to the acid chloride and homologation following the Arndt–Eistert protocol[28] furnished carboxylic acid **112** in 75% yield. The α-diazo ketone **113** was prepared in good yield by treatment of the acid chloride derived from carboxylic acid **112** with an ethereal solution of diazomethane.

With α-diazo ketone **114** in hand, a number of metal catalysts were evaluated for their ability to promote the formation of norcaradiene **115** (Table 2.1). Whereas Rh^{II}

catalysts favored the formation of C–H insertion products (entries 4–6), $Cu(acac)_2$ provided more promising levels of cyclopropanation (entry 7). There are several reports of Rh^{II} catalysts providing good yields of Buchner products; however, these systems generally lack benzylic protons, or geometrically disfavor C–H insertion.[29] In systems where C–H insertion is geometrically favorable, Cu^{II} catalysts provide improved selectivity for cyclopropanation.[18c]

Table 2.1. *Catalysts Screened for Cyclopropanation of α-diazo ketone* ***114***



Entry	Catalyst	Temp (°C)	Norcaradiene Yield (%)
1	$Pd(OAc)_2$	22	no rxn
2	Co^{II}(salen)	22	no rxn
3[a]	$[Ir(cod)Cl]_2$	50	decomp
4	$Rh_2(OAc)_4$	22	14
5	$Rh_2(cap)_4$	22	1
6	$Rh_2(tfa)_4$	22	5
7[a]	$Cu(acac)_2$	120	30
8[a]	$Cu(tfacac)_2$	120	50 (73)[c]
9[a]	$Cu(hfacac)_2$	120	40
10[a]	$Cu(TMHD)_2$	120	28
11[a]	$Cu(TBS)_2$	120	11

[a] Run in a microwave for 5 minutes. [b] Determined by ^{1}H NMR analysis of crude reaction mixture, using an internal standard. [c] Isolated yield, slow addition, DCE reflux.

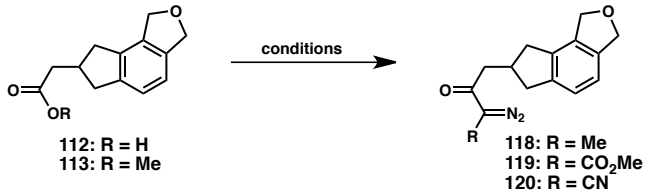
Further screening of several Cu^{II} catalysts revealed that the yields of norcaradiene **115** were highly catalyst dependent, with relatively electron-poor Cu^{II} salts providing the best results (entries 8,9). Although conducting the reactions in a microwave reactor proved useful in the context of catalyst screening, improved yields were obtained for

substrate **115** by using a slow addition protocol. Thus, syringe pump addition of **114** to a solution of $Cu(tfacac)_2$ in dichloroethane at reflux cleanly provided norcaradiene **115** in 73% isolated yield. Notably, the ^1H NMR spectrum of **115** shows no evidence of the corresponding cycloheptatriene at room temperature. In spite of the known propensity of simple norcaradienes to heavily favor the cycloheptatriene valence tautomer,[30] the behavior of **115** is not entirely surprising. The electrocyclic ring-opening of norcaradiene **115** would produce two bridgehead olefins within a strained [4.3.1]bicycle, and is therefore anticipated to be highly unfavorable. Studies have shown that sterically[31] or electronically[32] biased, as well as geometrically constrained norcaradienes[21] (such as that found in **115**) can be stable at room temperature.

2.5.3 Reactivity of Di–Substituted α-Diazo Ketones

Although we were pleased with our ability to prepare norcaradiene **115**, more functionalized norcaradienes were required to facilitate the implementation of an endgame strategy toward salvileucalin B **(76)**. This conclusion was driven in part by our inability to derivatize norcaradiene compound **115** (R = H) a deprotonation/trapping sequence.[33] In particular, it was envisioned that use of di-substituted α-diazo ketones (e.g. **118-120**, R ≠ H, Table 2.2) would provide a cyclopropane with appropriate functionality for conversion to the required γ-lactone. To this end, additional α-diazo carbonyl compounds were prepared from either carboxylic acid **112** or methyl ester **113**, each easily accessible from **112** by simply modifying the conditions of the Arndt–Eistert homologation.[28]

Table 2.2. *Synthesis of α-diazo ketones* ***118–120***



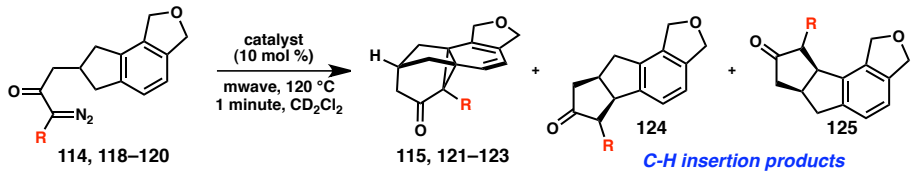
Starting Tricycle	Product	Conditions/Yield (%)
112	118	(i) $(COCl)_2$; (ii) $CH_3CH_2N_2$, CH_2Cl_2 (63 % yield, 2 steps)
112	119	$(imid)_2CO$ then $HCO_2CH_2CO_2K/MgCl_2$ (56% yield); (ii) *p*-ABSA, Et_3N, MeCN (63% yield)
113	120	(i) $LiCH_2CN$, THF, –78 °C (ii) $(imid)SO_2N_3$, pyr, MeCN (50% yield, 2 steps)

To prepare α-diazo ketone **118**, carboxylic acid **112** was converted to the corresponding acid chloride and treated with diazoethane (generated in situ from *N*-ethyl-*N*-nitrosourea). α-Diazo-β-ketoester **119** was prepared from acid **112** by a two-step procedure consisting of conversion to the ketoester,[34] followed by diazo transfer with *p*-ABSA. Alternatively, α-diazo β-ketonitrile **120** was prepared by treatment of methyl ester **113** with α-lithio-acetonitrile followed by diazo transfer with *N*-imidazole sulfonyl azide[35] in the presence of pyridine (Table 2.2).

As evidenced by entries 2 and 3 (Table 2.3) slight structural changes dramatically impact the intramolecular Buchner reaction. Unfortunately, the use of α-diazoethyl ketone **118** or α-diazo-β-ketoester **119** in conjunction with a variety of either rhodium or copper catalysts provided only trace quantities of the corresponding norcaradiene products. Instead, the major products were a mixture of isomeric cyclopentanones resulting from C-H insertion, even when copper catalysts were used. The significant drop in yield observed when switching from the α-diazomethyl ketone to α-diazoethyl ketone,

which are similar in their electronic properties but differ in their steric profile, suggested that less sterically encumbered substrates may provide improved yields of norcaradiene **123**. A survey of carbon-containing moieties that satisfy this requirement but also bear suitable functionality for elaboration to the lactone produced the nitrile as an excellent candidate.[36] Although intermolecular arene cyclopropanation with dicyanodiazomethane was known,[37] there had been no previous reports of a nitrile-containing diazocarbonyl compound undergoing an *intramolecular* Buchner reaction.

Table 2.3. *Impact of diazo substitution on norcaradiene yield*



Entry	R	Catalyst	Norcaradiene Yield (%)
1	H	$Cu(tfacac)_2$	73[a]
2	Me	$Cu(acac)_2$	7[a]
3	CO_2Me	$Cu(hfacac)_2$	2[a]
4	CN	$Cu(tfacac)_2$	6[b]
5	CN	$Cu(acac)_2$	3[b]
6	CN	$Cu(TMHD)_2$	4[b]
7	CN	$Cu(TBS)_2$	14[b]
8	CN	$Cu(hfacac)_2$	53[b]
9	CN	$Cu(hfacac)_2$	64[a]

[a] Isolated yield. [b] Determined by ^1H NMR analysis of crude reaction mixture, using an internal standard.

After extensive screening with α-diazo-β-ketonitrile **120**, it was found that various Cu^{II} salts revealed promising yields of the cyclopropane product (**123**, R = CN), albeit in very low yields. Whereas $Cu(acac)_2$ and $Cu(TBS)_2$ provided **123** in poor yields, we were pleased to find that $Cu(hfacac)_2$ could afford norcaradiene **123** in 53% assay

yield after brief microwave heating. Notably, α-diazo-β-ketonitriles require high temperatures to undergo de-diazotization with copper catalysts; in the case of **120** → **123**, the best yields were observed when heated for short periods to 120 °C using microwave irradiation. Norcaradiene **123** represents the first example of a fully substituted cyclopropane that is formed through an intramolecular arene cyclopropanation reaction. More importantly, the highly serviceable yield obtained in the arene cyclopropanation of α-diazo-β-ketonitrile **120** allowed for facile throughput of material for elaboration to the requisite lactone.

2.6 EXPERIMENTAL SECTION

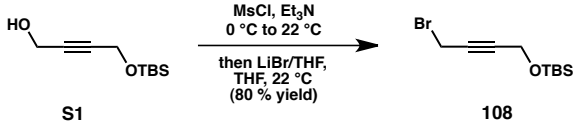
2.6.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), acetonitrile (MeCN), toluene and benzene were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves, MeOH was distilled over magnesium oxide and dichloroethane (DCE) was distilled over calcium hydride. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed either as described by Still et al. (Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.) using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. Microwave experiments were performed using a Biotage Initiator® microwave reactor. 1H and 13C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to internal CHCl3 (1H, δ = 7.26) or CDHCl2 (1H, δ = 5.32), and CDCl3 (13C, δ = 77.0) or CD2Cl2 (13C, δ = 53.8). Data for 1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer

Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Zorbax RX-SIL 5μm column (9.4 x 250 mm). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 220 nm. Analytical HPLC was performed on an Agilent 1290 Infinity Eclipse Plus C_{18} 1.8μm column (2.1 x 50 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

2.6.2 Preparative Procedures and Spectroscopic Data

Preparation of Bromide 108

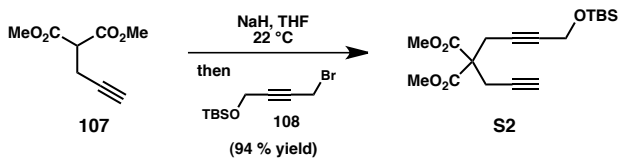


S1 108

A 1 L flame-dried flask was charged with the mono-TBS protected diol (**S1**, 16.1 g, 79.0 mmol) under N_2, followed by THF (300 mL) and Et_3N (20.5 mL, 135.0 mmol). The resulting solution was cooled to 0 °C in an ice bath, and MsCl (9.3 mL, 120.0 mmol) was added dropwise. The resulting thick white slurry was warmed to 22 °C over 30 minutes. In a separate flask, LiBr (35.0 g, 400.0 mmol) was charged under N2 and dissolved in THF (250 mL). The mesylate/THF slurry was filtered directly into the clear yellow LiBr/THF solution at 22 °C. After 30 minutes TLC analysis indicated complete consumption of starting material. The reaction was diluted with Et_2O (300 mL), filtered,

and washed with brine (50 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (10% EtOAc/hexanes) to afford bromide **108** (16.5 g, 80% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) d 4.36 (t, *J* = 2.1 Hz, 2H), 3.94 (t, *J* = 2.1 Hz, 2H), 0.90 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) d 85.5, 79.7, 77.3, 76.8, 51.8, 25.8, 18.3, 14.5, -5.7; IR (NaCl/thin film): 2955, 2929, 2896, 2857 cm^{-1}; HRMS (EI+) calc'd for $C_{10}H_{19}OBrSi$ [M+·] 264.0387, found 264.0368.

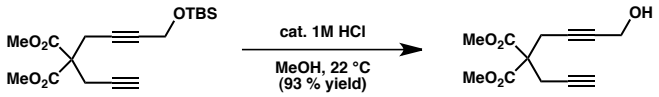
Preparation of Diester S2



A 500 mL flame-dried flask was charged with NaH (1.3 g, 60% dispersion mineral oil, 31.9 mmol), followed by THF (150 mL) under N_2. The suspension was cooled to 0 °C in an ice bath, and propargyl dimethyl malonate (**107**, 4.34 mL, 29.0 mmol) was added dropwise over 10 minutes. After stirring for 25 minutes (cessation of bubbling), bromide **108** (7.48 g, 29.0 mmol) in THF (100 mL) was added to the suspension at 0 °C. The reaction was warmed to 22 °C and stirred for 13 hours, after which time TLC analysis indicated consumption of the starting materials. Water (300 mL) was added, followed by extraction with 2 x 250 mL of Et_2O. The organic layer was dried ($MgSO_4$) and concentrated to yield **S2** (9.27 g, 94% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (t, *J* = 2.1 Hz, 2H), 3.72 (s, 6H), 2.98 (t, *J* = 2.1 Hz, 2H), 2.93 (d, *J* = 2.7 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 82.2, 78.8, 78.3, 77.3, 76.8, 71.6, 56.4, 53.0, 51.6, 25.7, 22.9,

22.6, 18.2, -5.3; IR (NaCl/thin film): 3292, 3001, 2956, 2931, 2897, 2858, 1744 cm^{-1}; HRMS (ES+) calc'd for $C_{18}H_{28}O_5Si$ $[M+H]^+$ 353.1779, found 353.1771.

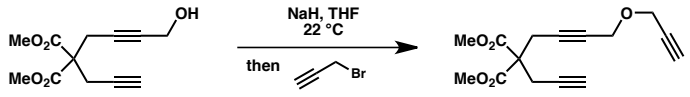
Preparation of Alcohol 109



S2 **109**

A 250 mL flask open to air was charged with **S2** (9.27 g, 26.3 mmol), followed by MeOH (80 mL) and aq. HCl (1M, 0.5 mL, 0.5 mmol) at 22 °C. The clear colorless solution was stirred for 3 hours, then concentrated and purified by flash chromatography (0→20% MeOH/DCM), affording **109** (5.88 g, 93% yield) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (dt, *J* = 6.1, 2.1 Hz, 2H), 3.74 (s, 6H), 2.99 (t, *J* = 2.0 Hz, 2H), 2.94 (d, *J* = 2.6 Hz, 2H), 2.23 (t, *J* = 6.2 Hz, 1H), 2.03 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 82.0, 79.7, 78.2, 71.8, 56.4, 53.1, 50.9, 22.9, 22.7; IR (NaCl/thin film): 3483, 3288, 3008, 2957, 2871, 2848, 1739 cm^{-1}; HRMS (ES+) calc'd for $C_{12}H_{14}O_5$ $[M+H]^+$ 239.0914, found 239.0913.

Preparation of Triyne S3

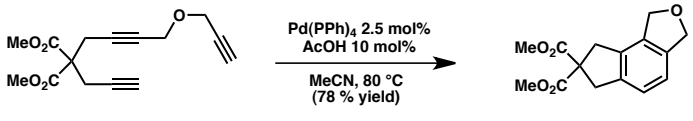


109 **S3**

A 500 mL flame-dried flask was charged with NaH (1.09 g, 60% dispersion mineral oil, 27.1 mmol), followed by THF (100 mL) under N_2. In a separate flask **109** (5.88 g, 24.6 mmol) was azeotroped 3x with benzene, and diluted with THF (75 mL). To

the NaH/THF suspension, pre-cooled to 0 °C, was added the THF solution of **109** via cannula. This brown mixture was stirred for 30 minutes at 0 °C, after which time propargyl bromide (80 wt% toluene, 3.2 mL, 29.5 mmol) was added in one portion. The resulting brown/black slurry was warmed to 22 °C and stirred for 22 hours. After TLC analysis indicated consumption of the starting materials, water (500 mL) was added, and the reaction extracted with 2 x 250 mL Et_2O. The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (0→25% EtOAc/hexanes) to afford **S3** (4.67 g, 69% yield) as an orange/brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (t, *J* = 2.1 Hz, 2H), 4.21 (d, *J* = 2.4 Hz, 2H), 3.77 (s, 6H), 3.04 (t, *J* = 2.1 Hz, 2H), 2.98 (d, *J* = 2.6 Hz, 2H), 2.44 (t, *J* = 2.4 Hz, 1H), 2.03 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 81.4, 78.9, 78.5, 78.3, 77.3, 76.8, 74.9, 71.8, 56.7, 56.5, 56.1, 53.2, 23.0, 22.8; IR (NaCl/thin film): 3286, 2955, 2916, 2850, 1738 cm^{-1}; HRMS (ES+) calc'd for $C_{15}H_{16}O_5$ $[M+H]^+$ 277.1071, found 277.1070.

Preparation of Arene 110

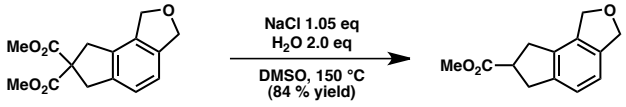


S3 **110**

A 250 mL flask was charged with triyne **S3** (4.67 g, 16.9 mmol), followed by MeCN (150 mL) under N_2. Acetic acid (100 mL, 1.7 mmol) was added, followed by $Pd(PPh_3)_4$ (490 mg, 0.42 mmol) in one portion at 22 °C. The flask was fitted with a condensor, and the clear orange/red solution was heated to 80 °C. After 30 minutes the reaction was complete (TLC analysis) and subsequently cooled to 22 °C. The solvent was

removed via rotary evaporation, and the crude oil was purified by flash chromatography (0→25% EtOAc/hexanes) to afford **110** (3.65 g, 78% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 5.08 (s, 2H), 5.04 (s, 2H), 3.75 (s, 6H), 3.61 (s, 2H), 3.49 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 139.3, 138.2, 134.9, 132.9, 123.1, 119.5, 73.6, 72.4, 60.6, 53.0, 40.2, 38.9; IR (NaCl/thin film): 3436, 3003, 2954, 2916, 2850, 1733 cm^{-1}; HRMS (ES+) calc'd for $C_{15}H_{16}O_5$ [M-H]+ 275.0925, found 275.0917.

Preparation of Ester S4

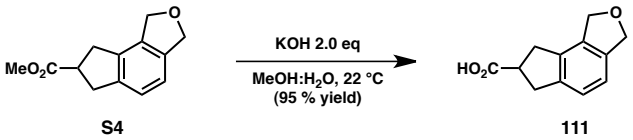


110 **S4**

A 250 mL flask open to air was charged with diester **110** (6.43 g, 23.0 mmol), NaCl (1.44 g, 25.0 mmol), water (840 mL, 47.0 mmol) and DMSO (65 mL) at 22 °C. The flask was fitted with a condensor and heated to 150 °C with vigorous stirring. Upon heating, the reaction darkened from light yellow to brown, and after 30 minutes at 150 °C was black. After heating for 12 hours TLC analysis indicated consumption of starting material, and the reaction was cooled to 22 °C. The reaction was diluted with hexanes/Et_2O (700 mL, 7:3) and washed with 2 x 300 mL water. The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (0→30% EtOAc/hexanes) to afford **S4** (4.2 g, 84% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.10 (s, 2H), 5.04 (s, 2H), 3.43 – 3.35 (tt, *J* = 9.0, 8.0 1H), 3.30 – 3.20 (m, 2H), 3.16 (dd, *J* = 16.1, 7.7 Hz, 1H), 3.09

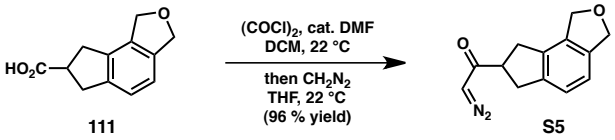
(dd, *J* = 16.1, 9.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 141.0, 137.8, 135.0, 134.6, 123.2, 119.1, 73.7, 72.5, 52.0, 43.7, 35.8, 34.4; IR (NaCl/thin film): 3468, 3022, 2948, 2848, 1729 cm^{-1}; HRMS (ES+) calc'd for $C_{13}H_{14}O_3$ $[M-H]^+$ 217.0870, found 217.0859.

Preparation of Carboxylic Acid 111



A 250 mL flask open to air was charged with monoester **S4** (4.5 g, 21.0 mmol), MeOH (100 mL), water (10 mL), and KOH (2.3 g, 42.0 mmol) at 22 °C. After 4.5 hours the reaction was judged to be complete by TLC, and the reaction volume was reduced to approximately 50 mL total via rotary evaporation. The carboxylate solution was diluted with Et_2O (150 mL) and washed with 1M HCl. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, yielding **111** (4.0 g, 95% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 3.48 – 3.40 (tt, *J* = 9.0, 7.5 Hz, 1H), 3.34 – 3.23 (m, 2H), 3.20 (dd, *J* = 16.2, 7.4 Hz, 1H), 3.13 (dd, *J* = 16.1, 9.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.90, 140.85, 137.69, 134.88, 134.39, 123.27, 119.22, 73.62, 72.44, 43.51, 35.60, 34.20; IR (NaCl/thin film): 3436, 3152, 2998, 2948, 2867, 2746, 2638, 1726 cm^{-1}; HRMS (ES+) calc'd for $C_{12}H_{11}O_3$ [M-H]+ 203.0714, found 203.0703.

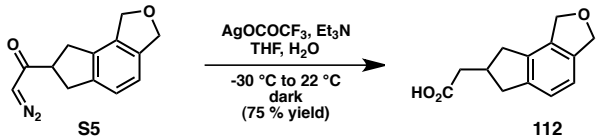
Preparation of Diazo Ketone S5



A flame-dried 250 mL flask containing acid **111** (3.0 g, 13.8 mmol) was charged with DCM (100 mL) under N_2. To the resulting slurry was added 1 drop of DMF, followed by oxalyl chloride (2.33 mL, 27.6 mmol) at 22 °C. Within 15 minutes the solids dissolved, yielding a clear brown solution. After 2 hours the DCM was removed under reduced pressure, followed by azeotroping with 2 x 50 mL anhydrous benzene. ^{1}H NMR analysis of an aliquot confirmed clean conversion of the starting acid **111** to the acid chloride. The resulting murky brown oil was diluted with THF (100 mL) under N_2. Diazomethane (~50-60 mmol, solution in Et_2O) was briefly dried over KOH (5 minutes) and carefully decanted at 0 °C into a 500 mL Erlenmeyer flask. The acid chloride/THF solution was then carefully transferred via cannula to excess diazomethane at 0 °C with gentle stirring, resulting in steady gas evolution. After 30 minutes the starting material was completely consumed (TLC analysis), and the reaction was concentrated under reduced pressure. The crude brown oil was purified by flash chromatography (0→40% EtOAc/hexanes), yielding diazo ketone **S5** (3.0 g, 96% yield) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.31 (bs, 1H), 5.09 (s, 2H), 5.04 (s, 2H), 3.37 (m, 1H), 3.27 – 3.10 (m, 3H), 3.03 (dd, *J* = 16.1, 8.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.00, 140.89, 137.87, 135.05, 134.53, 123.24, 119.21, 73.67, 72.49, 53.97 (br), 49.64 (br), 35.74, 34.22; IR (NaCl/thin film): 3496,

3081, 3027, 2938, 2900, 2849, 2104, 1635 cm^{-1}; HRMS (ES+) calc'd for $C_{13}H_{12}N_2O_2$ $[M+H]^+$ 229.0972, found 229.0973.

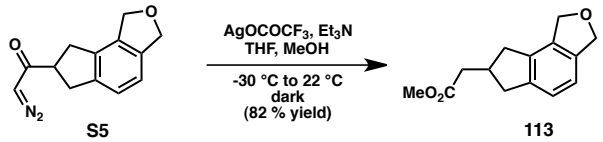
Preparation of Carboxylic Acid 112



A 250 mL flask was charged with diazo ketone **S5** (3.0 g, 13.2 mmol), THF (55 mL), and water (5.5 mL) and purged with N_2. The flask was covered in foil and cooled to -30 °C. To a N_2 purged 5 mL conical flask protected from light was added silver trifluoroacetate (290 mg, 1.32 mmol), followed by Et_3N (5.5 mL, 40.0 mmol) with vigorous stirring at 22 °C. (Note: vigorous stirring during Et_3N addition is critical to ensure dissolution of silver salt. Lack of stirring can result in a brown silver clump and incomplete dissolution. When dissolved one obtains a clear tan solution). The Et_3N/Ag solution was added in one portion to the clear yellow diazo ketone solution at -30 °C. The reaction was slowly warmed over 4 hours (starting material consumed by TLC), after which the reaction was quenched with 300 mL 1M HCl. The product was extracted with 2 x 250 mL Et_2O, the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The brown solid was purified by flash chromatography (0→50% EtOAc/hexanes), affording **112** (2.16 g, 75% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 6.8 Hz, 1H), 5.11 (s, 2H), 5.07 – 5.00 (m, 2H), 3.19 (dd, *J* = 15.6, 7.9 Hz, 1H), 3.07 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.95 (septet, *J* = 7.5 Hz, 1H), 2.69 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.64 – 2.43 (m, 3H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 178.1, 142.0, 137.4, 135.5, 135.1, 123.4, 118.9, 73.7, 72.6, 39.6, 38.5, 37.1, 36.1; IR (NaCl/thin film): 3026, 2935, 2848, 2909, 2680, 1728, 1706 cm^{-1}; HRMS (ES+) calc'd for $C_{13}H_{13}O_3$ $[M–H]^-$ 217.0865, found 217.0872.

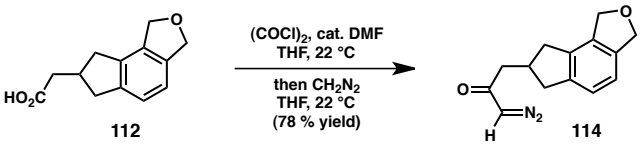
Preparation of Ester 113



A 50 mL flame-dried flask was charged with diazo ketone **S5** (107 mg, 0.47 mmol), THF (5 mL), and MeOH (500 μL) and purged with N_2. The flask was covered in foil and cooled to -30 °C. To a N_2 purged 5 mL conical flask protected from light was added silver trifluoroacetate (10 mg, 0.047 mmol), followed by Et_3N (196 μL, 1.41 mmol) with vigorous stirring at 22 °C. (Note: vigorous stirring during Et_3N addition is critical to ensure dissolution of silver salt. Lack of stirring can result in a brown silver clump and incomplete dissolution. When dissolved one obtains a clear tan solution). The Et3N/Ag solution was added in one portion to the clear yellow diazo ketone solution at -30 °C. The reaction was slowly warmed over 4 hours (starting material consumed by TLC), after which time became was a clear red/brown solution. The reaction was quenched with 1 mL of 1M HCl, and diluted with 50 mL Et_2O. The aqueous layer was cut and back-extracted with 20 mL Et_2O, and the combined organics were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude brown oil was purified (0→25% EtOAc/hexanes), yielding **113** (89 mg, 82% yield) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 5.10 (m,

2H), 5.07 – 4.98 (m, 2H), 3.70 (s, 3H), 3.16 (dd, *J* = 15.6, 7.9 Hz, 1H), 3.04 (dd, *J* = 15.7, 7.9 Hz, 1H), 2.99 – 2.88 (m, 1H), 2.65 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.57 – 2.47 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 142.0, 137.4, 135.6, 135.0, 123.3, 118.7, 73.6, 72.5, 51.5, 39.7, 38.5, 37.1, 36.3; IR (NaCl/thin film): 3470, 3020, 2949, 2903, 2845, 1736 cm^{-1}; HRMS (FAB+) calc'd for $C_{14}H_{15}O_3$ [M+H]-H_2 231.1025, found 231.1021.

Preparation of Diazo Ketone 114

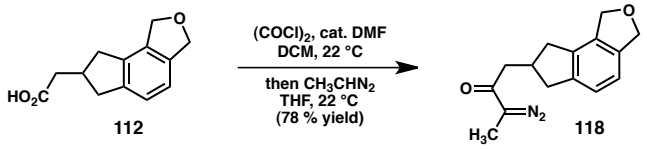


112 114

A flame-dried 50 mL flask containing acid **112** (154 mg, 0.71 mmol) was charged with THF (10 mL) under N_2. To the solution was added 1 drop of DMF, followed by oxalyl chloride (120 μL, 1.41 mmol) at 22 °C. After gas evolution had ceased (20 minutes), the dark yellow solution was concentrated under reduced pressure and azeotroped with 3 x 10 mL benzene. ^{1}H NMR analysis of an aliquot confirmed clean conversion of the starting acid **112** to the acid chloride. The resulting murky brown oil was diluted with THF (20 mL) under N_2. Diazomethane (15 mL, ~0.4M solution in Et_2O) was briefly dried over KOH (5 minutes) and carefully decanted at 0 °C into a 100 mL flask under N_2. The solution of the acid chloride in THF was then carefully transferred via cannula over 5 minutes to the diazomethane at 0 °C with gentle stirring, resulting in steady gas evolution. After 30 minutes the starting material was completely consumed (TLC analysis), and the concentrated under reduced pressure. The crude yellow oil was

purified by flash chromatography (0→40% EtOAc/hexanes), yielding diazo ketone **114** (126 mg, 78% yield) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 5.26 (bs, 1H), 5.09 (s, 2H), 5.06 – 4.98 (m, 2H), 3.15 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.07 – 2.92 (m, 2H), 2.64 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.57 – 2.45 (m, 3H). IR (NaCl/thin film): 3082, 2933, 2890, 2845, 2010, 1637 cm^{-1}; HRMS (ES+) calc'd for $C_{14}H_{14}N_2O_2$ $[M+H]^+$ 243.1128, found 243.1126.

Preparation of Diazo Ketone 118

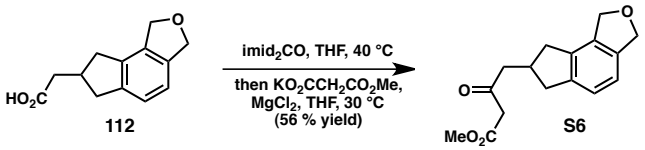


A flame-dried 50 mL flask containing acid **112** (97 mg, 0.44 mmol) was charged with CH_2Cl_2 (5 mL) under N_2. To this solution was added 1 drop of DMF, followed by oxalyl chloride (74 μL, 0.88 mmol) at 22 °C. After 1 hour the reaction mixture was concentrated under reduced pressure. ^{1}H NMR analysis confirmed clean conversion of the starting acid **112** to the acid chloride. The resulting murky brown oil was diluted with THF (9 mL) under N_2, and cannulated into a freshly prepared ethereal diazoethane solution (20 mL, ~ 10 mmol) at 0 °C. The reaction mixture was warmed to 22 °C over 12 h. The reaction mixture was concentrated under reduced pressure (with acetic acid in the trap to quench any unreacted diazoethane). The crude dark yellow oil was purified by flash chromatography (0→50% EtOAc/hexanes), yielding diazo ketone **118** (70 mg, 63% yield) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.09 (s, 2H), 5.01 (s, 2H), 3.16 (dd, *J* = 15.5, 7.4 Hz, 1H), 3.10 – 2.89

(m, 2H), 2.72 – 2.57 (m, 2H), 2.51 (dd, = 15.1, 6.0 Hz, 1H), 2.17 – 2.04 (br. s, 1H* methyl rotamer), 2.00 – 1.92 (br. s, 2H* methyl rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 142.0, 137.4, 135.6, 135.1, 123.3, 118.7, 73.6, 72.5, 62.5, 43.1, 38.6, 37.1, 36.2, 8.0. IR (NaCl/thin film): 2916, 2848, 2068, 1631 cm^{-1}; HRMS (ES+) calc'd for $C_{15}H_{17}N_2O_2$ $[M+H]^+$ 257.1290, found 257.1284.

Preparation of diazoethane: *N*-ethyl-*N*-nitrosourea (1.7 g, 15 mmol) in diethyl ether (20 mL) was slowly added to a stirred 60% aqueous KOH solution (20 mL) at 0 °C. When gas evolution ceased (15 min), the ethereal layer was separated and briefly dried with KOH (5 min) at 0 °C. **Warning**: Diazoethane is a highly toxic volatile compound.

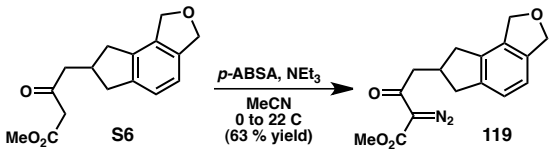
Preparation of β-Ketoester S6



A flame-dried 25 mL round-bottom flask equipped with stir bar and reflux condenser was charged with potassium monomethyl malonate (156 mg, 1.00 mmol) and $MgCl_2$ (70 mg, 0.74 mmol). This flask was evacuated and backfilled with nitrogen 3 times. THF (2 mL) was added and the suspension was heated to 65 °C for 3 h, followed by 30 °C for 2 h. A separate 15 mL flame-dried round-bottom flask was charged with acid **112** (160 mg, 0.73 mmol) in THF (1 mL) and carbonyl diimidazole (140 mg, 0.88 mmol) was added as a suspension in THF (2 mL). The flask was fitted with a reflux condenser and the solution was heated at 40 °C for 1 hour. The resulting acyl imidazole solution was added dropwise via syringe to the magnesium malonate suspension at 30 °C

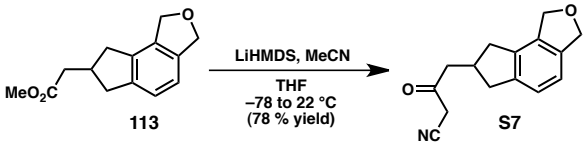
(NOTE: a white precipitate forms rapidly, and vigorous stirring is necessary to avoid clumping). After 40 h the white suspension was cooled to 0 °C and quenched by the addition of 1M HCl (5 mL). The reaction was extracted into EtOAc (3 x 10 mL), washed with water (ca. 15 mL), saturated aqueous NaCl (ca. 15 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration under reduced pressure yielded a crude oil, which was purified by flash chromatography (0→40% EtOAc/hexanes), yielding β-ketoester **S6** (113 mg, 56% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, compound exists as a 10:1 mixture of ketone : enol tautomers, only major ketone peaks are reported) δ 7.10 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 5.09 (apparent s, 2H), 5.07 – 4.93 (m, 2H), 3.75 (s, 1H), 3.47 (s, 2H), 3.17 (dd, J = 15.7, 7.9 Hz, 1H), 3.06 (dd, J = 15.7, 7.9 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.82 – 2.73 (m, 2H), 2.58 (dd, J = 15.6, 7.1 Hz, 1H), 2.46 (dd, J = 15.7, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$ compound exists as a 10:1 mixture of ketone : enol tautomers, ketone tautomer is designated by *, enol tautomer is denoted by §) δ ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9*, 177.3§, 172.9§, 167.5*, 142.1§, 142.0*, 137.41*, 137.38§, 135.6§, 135.5*, 135.1*, 123.3*, 118.8*, 89.7§, 73.7*, 72.5*, 52.4*, 51.1§, 49.2*, 48.7*, 40.7§, 38.5*, 38.4§, 37.2§, 37.1*, 36.9§, 34.9*. IR (NaCl/thin film): 2840, 1744, 1712 cm^{-1}; HRMS (ES+) calc'd for $C_{16}H_{17}O_4$ $[M+H]^+$ 275.1283, found 275.1266.

Preparation of Diazo β-Ketoester 119



To a flame-dried 15 mL round-bottom flask was added β-ketoester **S6** (160 mg, 0.58 mmol), *p*-ABSA (182 mg, 0.76 mmol) and dry MeCN (5 mL). The reaction mixture was cooled to 0 °C and triethylamine (180 μL, 1.3 mmol) was added in one portion. The reaction mixture was allowed to warm up to 22 °C over the period of 12 h, after which time TLC analysis showed complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure and treated with 3:1 pentane:EtOAc (ca 10 mL). The slurry was filtered and the filtrate was concentrated under vacuum. The crude white solid was purified by flash chromatography (3:1 pentane:EtOAc) yielding diazoketone **119** (110 mg, 63% yield) as a white solid. NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.09 (s, 2H), 5.02 (apparent s, 2H), 3.83 (s, 3H), 3.16 (dd, *J* = 15.5, 7.4 Hz, 1H), 3.09 – 3.05 (m, 2H), 3.04 – 2.96 (m, 2H), 2.66 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.53 (dd, *J* = 15.3, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 161.7, 142.2, 137.25, 135.8, 135.0, 123.3, 118.6, 76.0, 73.7, 72.5, 52.2, 45.8, 38.6, 37.1, 35.8. IR (NaCl/thin film): 2953, 2900, 2846, 2135, 1722, 1655 cm^{-1}; HRMS (ES+) calc'd for $C_{16}H_{15}N_2O_4$ $[M–H]^-$ 299.1037, found 299.1028.

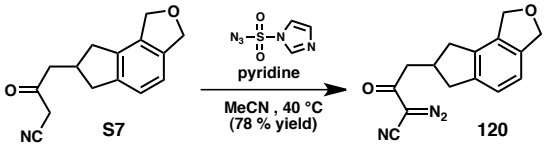
Preparation of β-Ketonitrile S7



A flame-dried 25 mL round-bottom flask was charged with LiHMDS (1M solution in THF, 750 μL, 0.75 mmol) and THF (2 mL), and cooled to –78 °C. MeCN (45 μL, 0.86 mmol) was added dropwise and solution was stirred at –78 °C for 30 min. A

solution of ester **113** (83 mg, 0.36 mmol) in THF (5 mL) was added dropwise and resulting solution was stirred at –78 °C for 30 min and subsequently warmed to 22 °C. TLC analysis showed complete consumption of starting material. Et_2O (20 mL) was added and reaction was quenched by the addition of aqueous saturated NH_4Cl (3 mL). The organic layer was washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude yellow oil was purified by flash chromatography (0→40% EtOAc/hexanes) to yield β-ketonitrile **S7 (**79 mg, 91% yield) as a yellow oil. NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.09 (appar. s, 2H), 5.06 – 4.93 (m, 2H), 3.47 (s, 2H), 3.19 (dd, *J* = 15.7, 7.8 Hz, 1H), 3.08 (dd, *J* = 15.8, 7.9 Hz, 1H), 3.03 – 2.91 (m, 1H), 2.91 – 2.77 (m, 2H), 2.59 (dd, *J* = 15.7, 6.9 Hz, 1H), 2.47 (dd, *J* = 15.8, 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 141.5, 137.5, 135.1, 135.1, 123.3, 118.9, 113.7, 73.6, 72.4, 47.7, 38.3, 36.9, 34.7, 32.2. IR (NaCl/thin film): 2943, 2911, 2847, 2260, 1730 cm^{-1}; HRMS (ES+) calc'd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1181, found 242.1176.

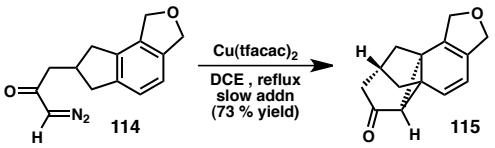
Preparation of Diazo β-Ketonitrile 120



Pyridine (1.13 mL, 14.0 mmol) was added to a solution of imidazole-1-sulfonyl azide[35] (581 mg, 3.36 mmol) and β-ketonitrile **S7** (675 mg, 2.80 mmol) in MeCN (25 mL). Reaction mixture was stirred at 40 °C for 7 h, after which time TLC analysis confirmed consumption of the starting β-ketonitrile **S7**. The reaction mixture was

concentrated under reduced pressure and the crude residue was purified by flash chromatography (0→50% EtOAc/hexanes), yielding diazo β-ketonitrile **120** (460 mg, 62% yield) as a white solid. NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 5.08 (s, 2H), 5.01 (s, 2H), 3.18 (dd, J = 15.6, 7.5 Hz, 1H), 3.13 – 2.92 (m, 2H), 2.92 – 2.74 (m, 2H), 2.66 (dd, J = 15.7, 6.8 Hz, 1H), 2.54 (dd, J = 15.1, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 141.5, 137.6, 135.12, 135.07, 123.4, 119.0, 108.3, 73.7, 72.5, 57.5, 44.9, 38.4, 37.0, 35.8. IR (NaCl/thin film): 2896, 2847, 2222, 2129, 1674 cm^{-1}; HRMS (ES+) calc'd for $C_{15}H_{14}NO_2$ $[M–N_2+H]^+$ 240.1019, found 240.1016.

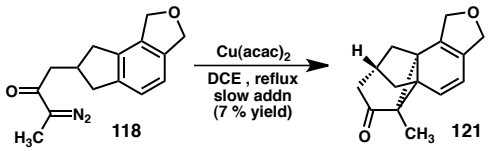
Cyclopropanation of Diazoketone 115



A flame-dried 250 mL three-neck round bottom flask, equipped with stir bar, water-cooled condenser and septa, was charged with a solution of $Cu(tfacac)_2$ (54 mg, 0.15 mmol) in DCE (20 mL) and was heated to reflux under nitrogen. After 15 min a solution of **114** (0.70 g, 2.9 mmol) in DCE (40 mL) was added at the rate of 0.8 mL/min (syringe pump). Upon completion of the addition, heating was continued for an additional 20 min. TLC analysis confirmed consumption of the starting diazoketone **114**, and reaction mixture was concentrated under reduced pressure. The crude brown oil was purified by flash chromatography (0→40% EtOAc/hexanes), yielding norcaradiene **115** (450 mg, 73% yield) as yellow oil, which slowly turns into yellow solid upon storage at -

20 °C. NMR (500 MHz, $CDCl_3$) δ 6.27 (d, *J* = 9.4 Hz, 1H), 6.01 (d, *J* = 9.4 Hz, 1H), 5.05 – 4.85 (m, 1H), 4.85 – 4.58 (m, 3H), 2.35 – 2.25 (m, 1H), 2.18 (d, *J* = 3.0 Hz, 2H), 2.08 – 2.00 (m, 2H), 1.99 (dd, *J* = 12.2, 5.2 Hz, 1H), 1.94 (d, *J* = 12.1 Hz, 1H), 1.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 133.3, 129.4, 128.1, 118.4, 75.2, 75.1, 43.8, 43.2, 39.2, 38.2, 35.6, 34.0, 27.4. IR (NaCl/thin film): 2932, 2863, 1690, cm^{-1}; HRMS (ES+) calc'd for $C_{14}H_{15}O_2$ $[M+H]^+$ 215.1072, found 215.1068.

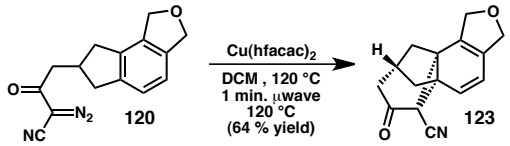
Cyclopropanation of Diazoketone 121



A flame-dried 50 mL three-neck round bottom flask, equipped with stir bar, water-cooled condenser and septa, was charged with the solution of $Cu(acac)_2$ (2.6 mg, 0.01 mmol) in DCE (10 mL) and was heated to reflux under nitrogen. After 10 min, a solution of **118** (50 mg, 0.20 mmol) in DCE (20 mL) was added at a rate of 10 mL/hour (syringe pump). Upon completion of the addition, the solution was heated at reflux for additional 60 min. TLC analysis confirmed consumption of the starting diazoketone **118**, and reaction mixture was concentrated under reduced pressure. The crude brown oil was purified by preparative HPLC chromatography (20→50% EtOAc/hexanes), yielding norcaradiene **121** (3 mg, 7% yield) as white solid. NMR (500 MHz, $CDCl_3$) δ δ 6.16 (d, *J* = 9.4 Hz, 1H), 6.04 (d, *J* = 9.5 Hz, 1H), 4.91 – 4.59 (m, 4H), 2.27 – 2.25 (m, 2H), 2.25 – 2.18 (m, 1H), 2.07 – 2.00 (m, 2H), 1.98 – 1.94 (m, 2H), 0.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 131.59, 131.54, 126.5, 120.6, 75.4, 75.0, 46.6, 45.0, 40.5, 36.9,

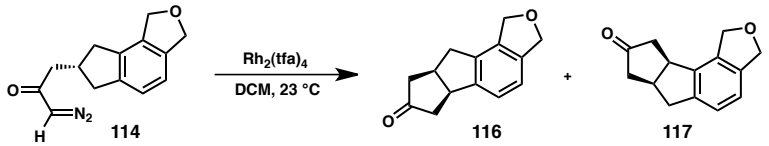
35.2, 31.1, 26.7, 7.0. IR (NaCl/thin film): 2927, 2850, 1738 (weak) 1682, cm^{-1} HRMS (ES+) calc'd for $C_{15}H_{17}O_2$ $[M+H]^+$ 229.1229, found 229.1223.

Cyclopropanation of Diazo β-Ketonitrile 123



A microwave reaction vessel equipped with a stir bar was charged with a solution of diazo β-ketonitrile **120** (53 mg, 0.2 mmol) in CH_2Cl_2 (10 mL). $Cu(hfacac)_2$ (9.5 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) was added via syringe through the septa of the sealed vial. The vial was placed in the microwave reactor and heated to 120 °C for 1 minute (ramp from 22 °C to 120 °C required 2 min). TLC analysis confirmed consumption of the starting material. The solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography (0→100% EtOAc/hexanes), yielding norcaradiene **123** (30 mg, 64% yield) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.41 (d, J = 9.5 Hz, 1H), 6.27 (d, J = 9.5 Hz, 1H), 5.02 – 4.84 (m, 2H), 4.84 – 4.69 (m, 2H), 2.46 – 2.40 (m, 1H), 2.39 – 2.30 (m, 2H), 2.24 – 2.15 (m, 3H), 2.11 (d, J = 12.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 134.7, 130.0, 124.4, 123.0, 111.8, 75.0, 74.6, 51.1, 47.0, 43.4, 36.0, 34.6, 29.7, 26.3. IR (NaCl/thin film): 2963, 2850, 2234, 1691, cm^{-1}; HRMS (ES+) calc'd for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1019, found 240.1025.

Isolation of C-H Insertion of Byproducts of α-Diazoketone 114



A flame-dried 50 mL round bottom flask, equipped with stir bar and septa, was charged with $Rh_2(tfa)_4$ (2 mg, 0.003 mmol) and DCM (10 mL). A solution of **114** (15 mg, 0.06 mmol) in DCM (2 mL) was slowly added to the above solution at over the period of 5 minutes. Gas evolution was observed. The resulting solution was stirred for an additional 2 hours. TLC analysis confirmed consumption of the starting diazoketone **114**, and reaction mixture was concentrated under reduced pressure. ^{1}H NMR analysis of the crude reaction mixture indicated approximately 40% combined yield of two isomeric C-H insertion products (~8:1 ratio of C-H insertion to cyclopropanation). The crude residue was loaded on preparative TLC plate and developed in 1:1 EtOAc/hexanes. UV active band with Rf ~ 0.6 was cut out and extracted into EtOAc. Further purification was achieved by preparative HPLC chromatography (20% EtOAc/hexanes), yielding two C-H insertion products (±)-**116** (2 mg, 7% yield) and (±)-**117** (1.5 mg, 5% yield) as white solids. Relative stereochemistry was assigned by NOE experiments. **116** (less polar product): ^{1}H NMR (600 MHz, CDCl3) δ 7.16 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 5.14 (d, J = 12.1 Hz, 1H), 5.08 (s, 2H), 5.03 (d, J = 12.1 Hz, 1H), 3.93 – 3.79 (m, 1H), 3.30 – 3.17 (m, 2H), 2.84 (app. d, J = 13.7 Hz, 1H), 2.65 (ddd, J = 19.0, 9.6, 1.6 Hz, 1H), 2.58 (ddd, J = 18.9, 8.8, 1.3 Hz, 1H), 2.41 (ddd, J = 18.9, 3.8, 1.1 Hz, 1H), 2.08 (ddd, J = 18.8, 7.3, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 218.6, 141.8, 138.5, 138.2, 135.7, 124.4, 119.9, 73.3, 71.8, 44.9, 43.9, 41.8, 39.7, 38.5. IR (NaCl/thin film):

2916, 2849, 1731, 1462 cm-1; HRMS (ES+) calc'd for C14H13O2+ [M – H]+ 213.0910, found 213.0914.

117 (more polar product): ^{1}H NMR (600 MHz, CDC3) δ 7.10 (s, 2H), 5.13 – 5.08 (m, 2H), 5.05 (s, 2H), 3.88 (td, J = 7.3, 1.9 Hz, 2H), 3.24 (pd, J = 7.2, 1.9 Hz, 1H), 3.15 (dd, J = 16.1, 7.4 Hz, 1H), 2.73 (ddd, J = 19.0, 9.4, 1.7 Hz, 1H), 2.68 (d, J = 1.9 Hz, 1H), 2.59 – 2.54 (m, 2H), 1.97 (dd, J = 18.9, 8.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 218.8, 144.6, 138.4, 136.0, 123.6, 119.6, 73.6, 72.5, 65.9, 45.6, 43.9, 43.6, 39.8, 36.9. IR (NaCl/thin film): 2917, 2849, 1737, 1465 cm-1; HRMS (ES+) calc'd for C14H13O2 + [M – H]+ 213.0910, found 213.0913.

2.7 NOTES AND REFERENCES

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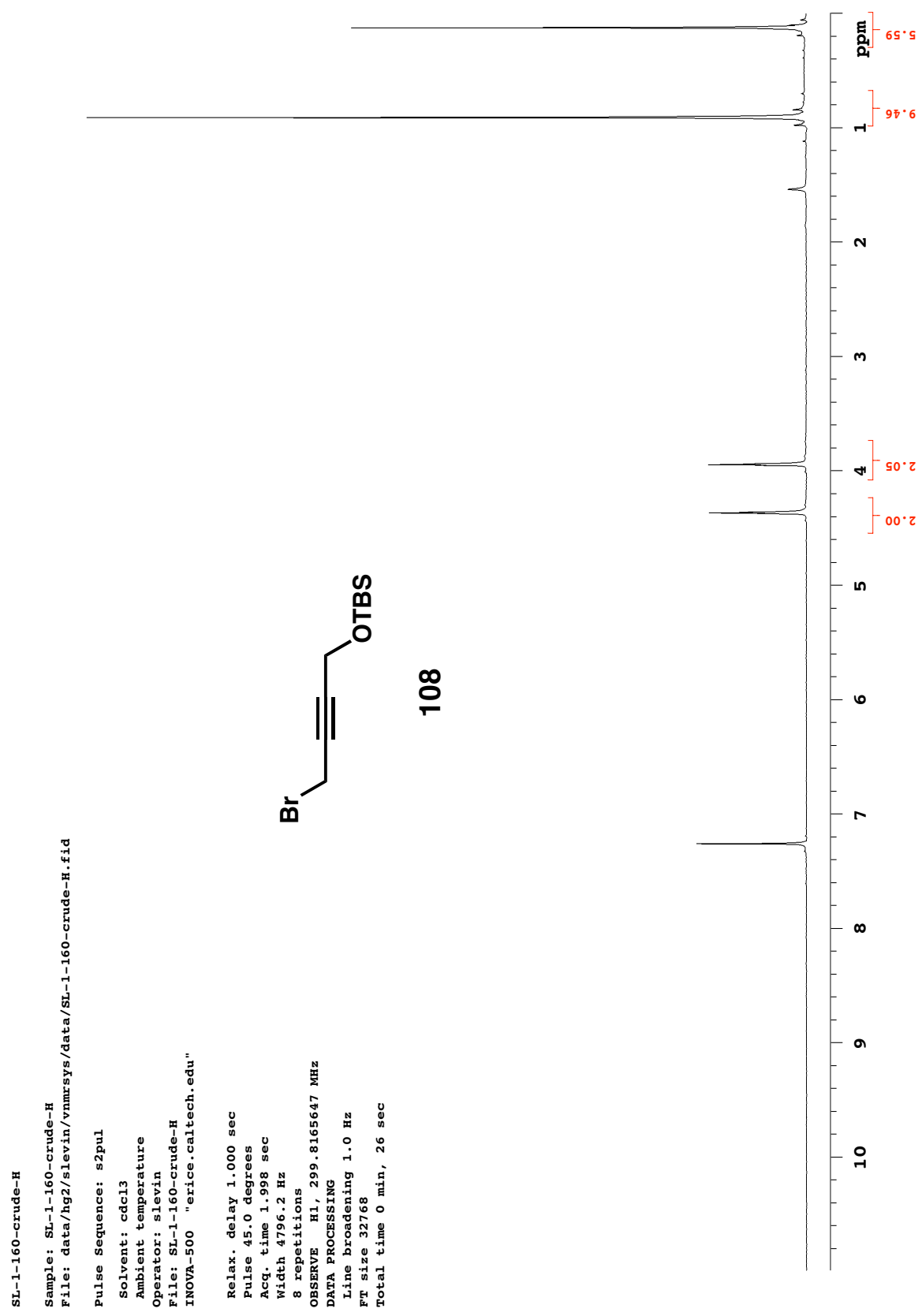
Appendix 1

Spectra Relevant to Chapter 2:

An Introduction to Salvileucalin B


SL-1-160-crude-H
Sample: SL-1-160-crude-H
File: data/hg2/slevin/vnmrsys/data/SL-1-160-crude-H.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: slevin
File: SL-1-160-crude-H
INOVA-500 "erice.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4796.2 Hz
8 repetitions
OBSERVE H1, 299.8165647 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 0 min, 26 sec
Br
OTBS
108
ppm
10
9
8
7
6
5
4
3
2
1
2.00
2.05
9.46
5.59

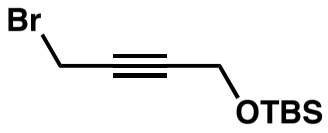
bromide

Sample: RRN-2-propargylBr
File: data/indy/slevin/vnmrsys/data/RRN-2-propargylBr/CARBON01.fid

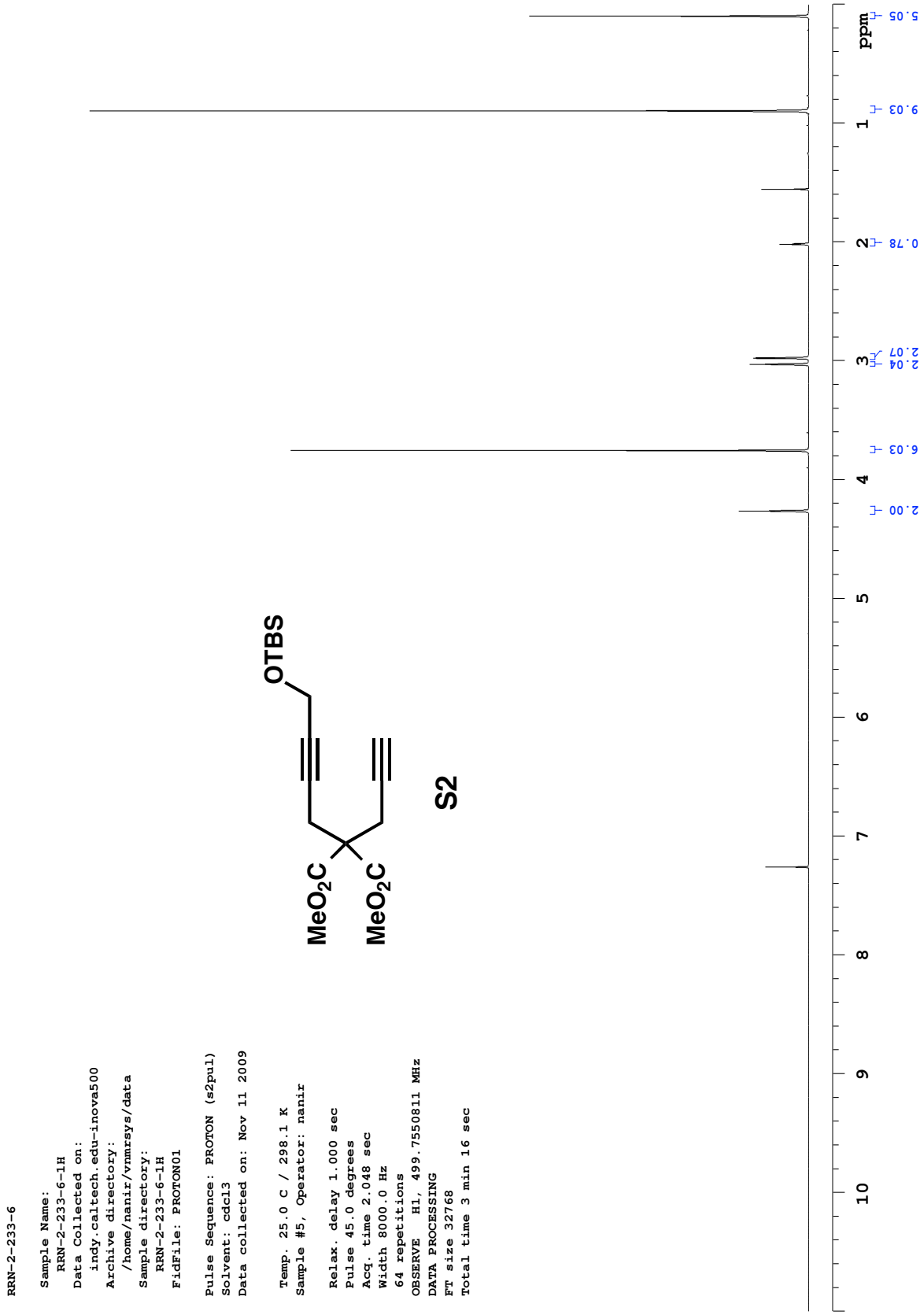
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, Operator: slevin
File: CARBON01
INOVA-500 "erice.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6635141 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 35 min, 38 sec



108


RRN-2-233-6
Sample Name:
RRN-2-233-6-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-233-6-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 11 2009
Temp. 25.0 C / 298.1 K
Sample #5, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7550811 MHz
DATA PROCESSING
FT size 32768
Total time 3 min 16 sec
OTBS
MeO2C
MeO2C
S2
ppm
10
9
8
7
6
5
4
3
2
1
5.05
9.03
0.78
2.07
2.04
6.03
2.00

RRN-2-234-6

Sample Name:
RRN-2-234-6
Data Collected on:
indy.caltech.edu-inova500
Archive directory:

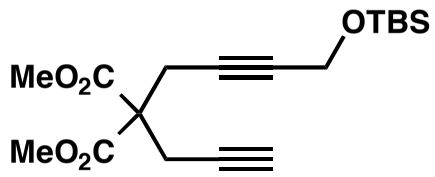
Sample directory:

FidFile: Carbon_02

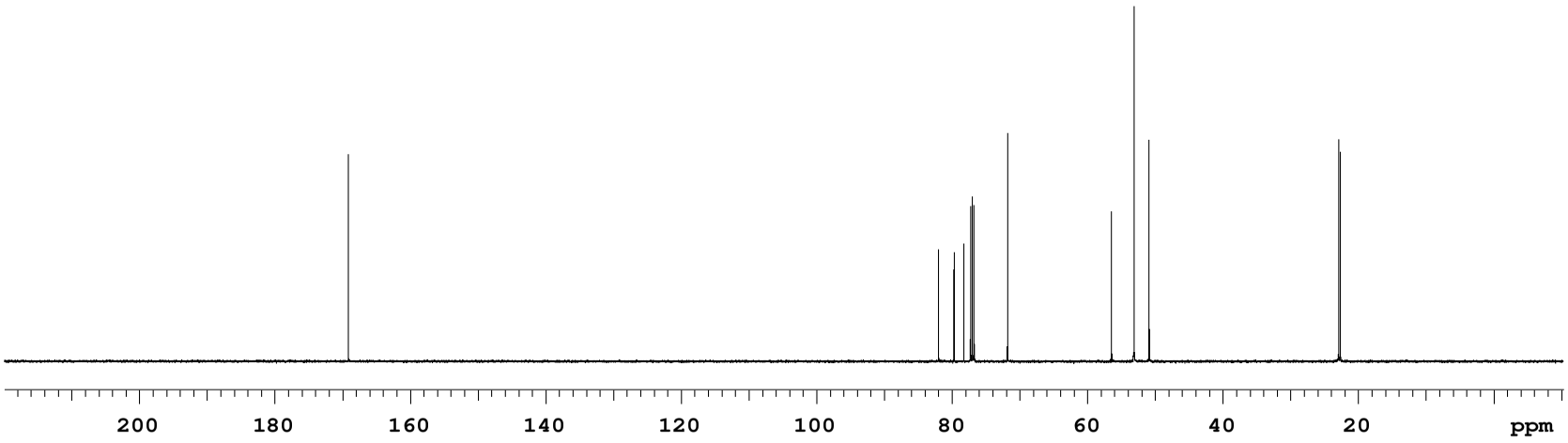
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Oct 9 2009

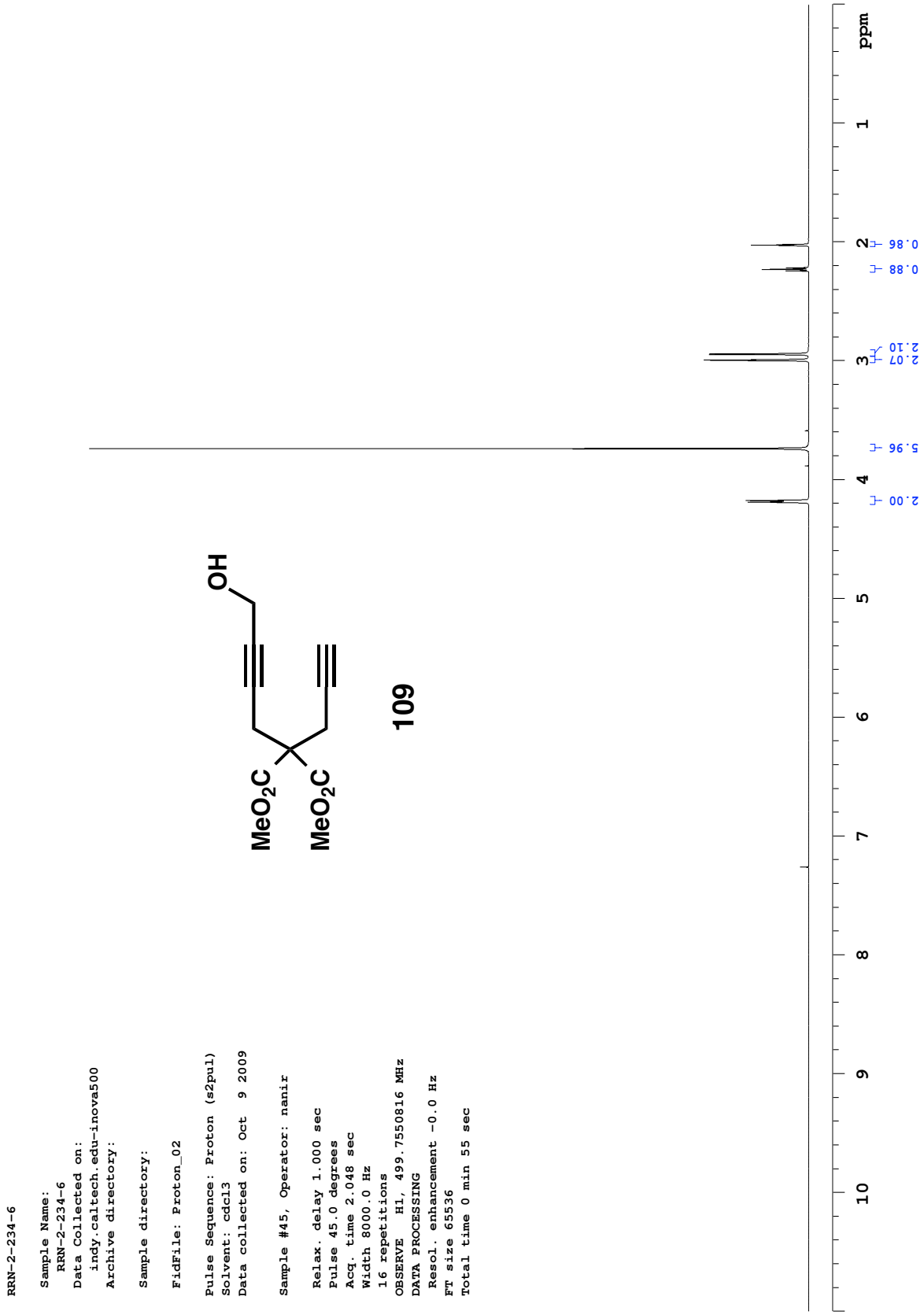
Sample #45, Operator: nanir

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
512 repetitions
OBSERVE C13, 125.6635228 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min



S2




RRN-2-234-6
Sample Name:
RRN-2-234-6
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: Proton_02
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Oct 9 2009
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550816 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 55 sec
OH
MeO2C
MeO2C
109
ppm
0.86
0.88
2.07
2.10
5.96
2.00

RRN-2-234-6

Sample Name:
RRN-2-234-6
Data Collected on:
indy.caltech.edu-inova500
Archive directory:

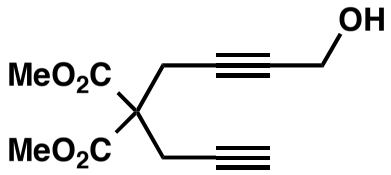
Sample directory:

FidFile: Carbon_02

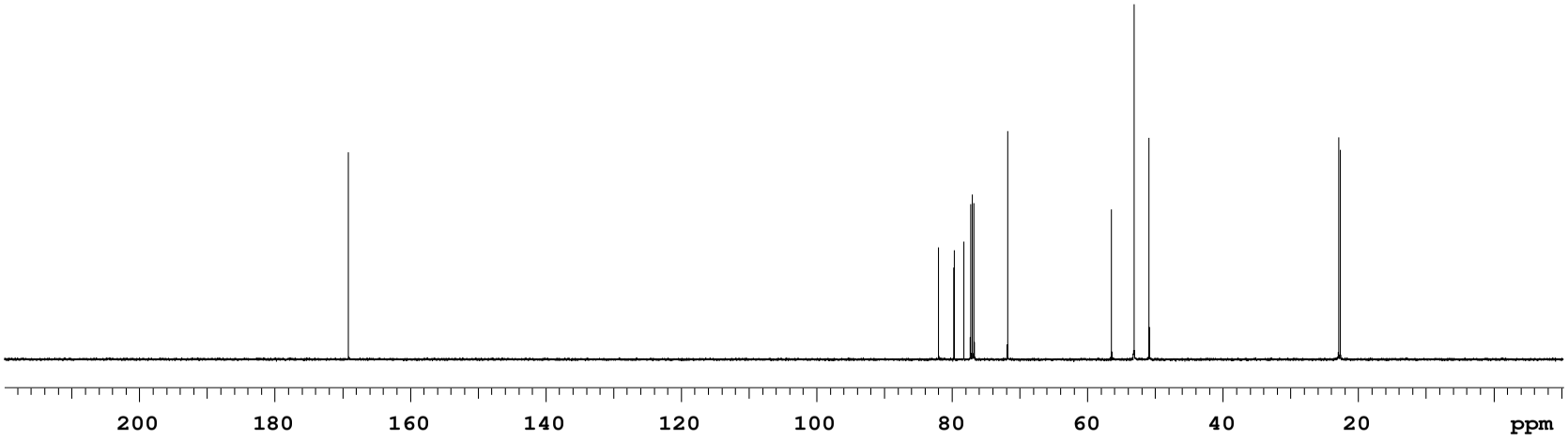
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Oct 9 2009

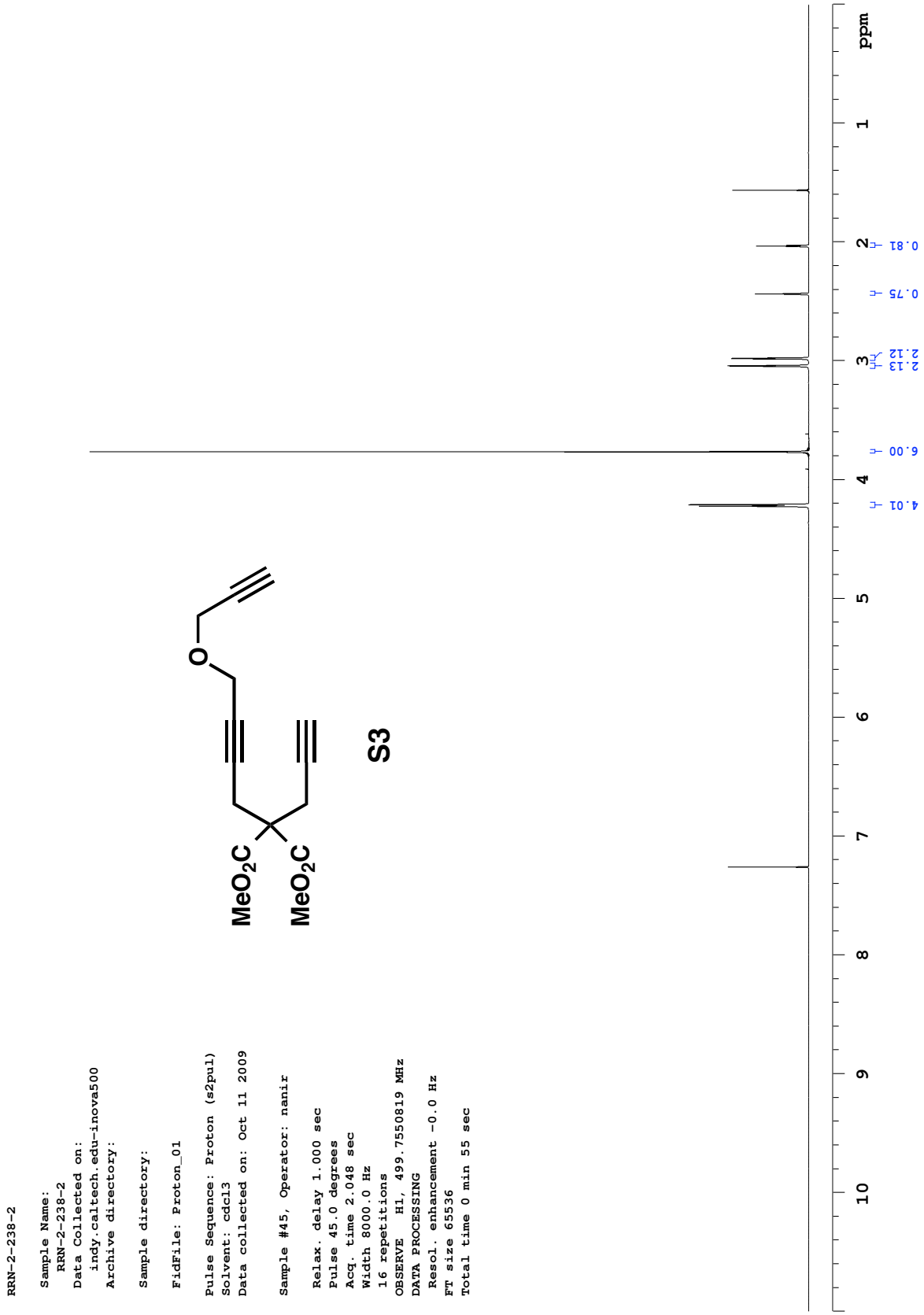
Sample #45, Operator: nanir

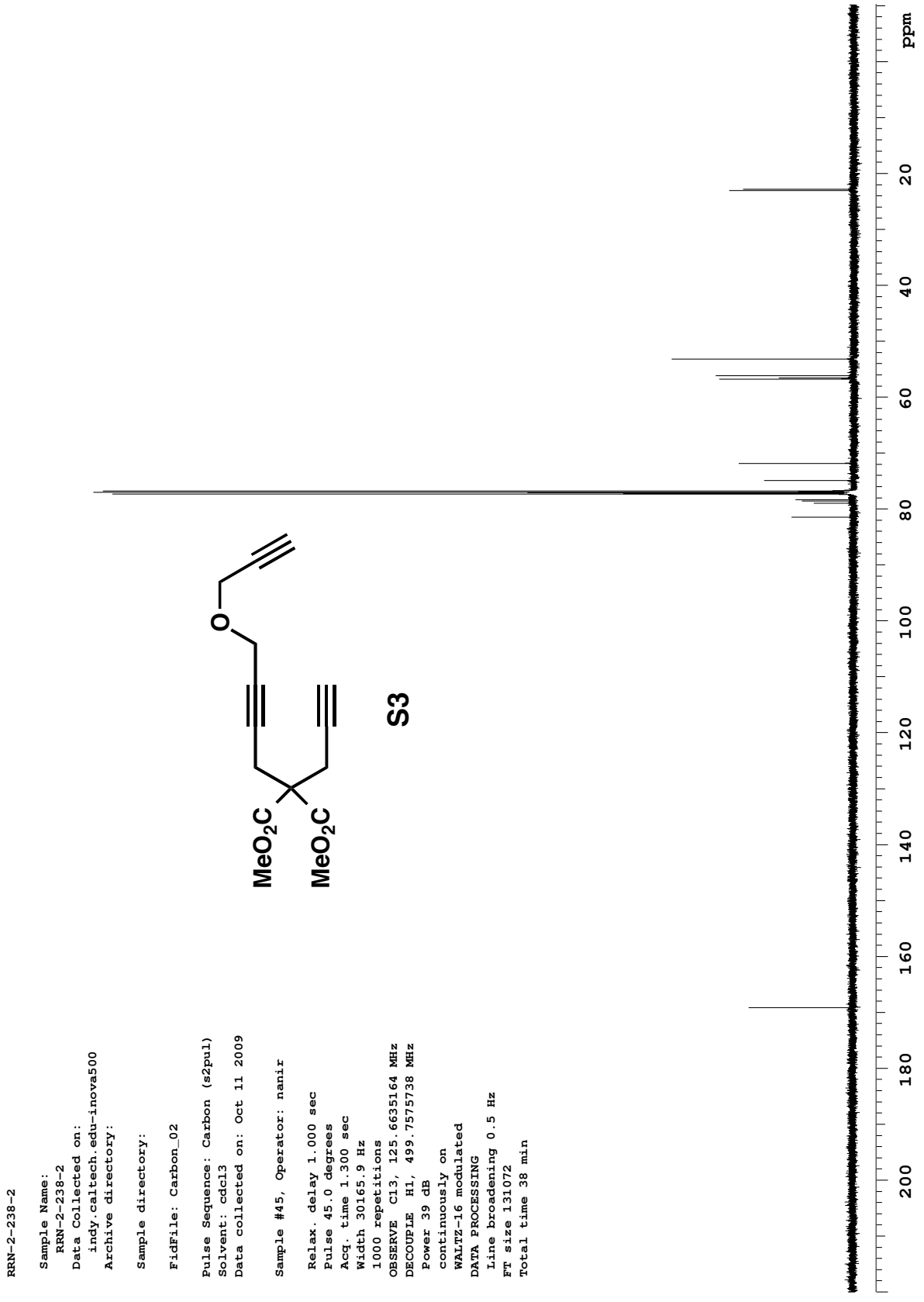
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
512 repetitions
OBSERVE C13, 125.6635228 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min

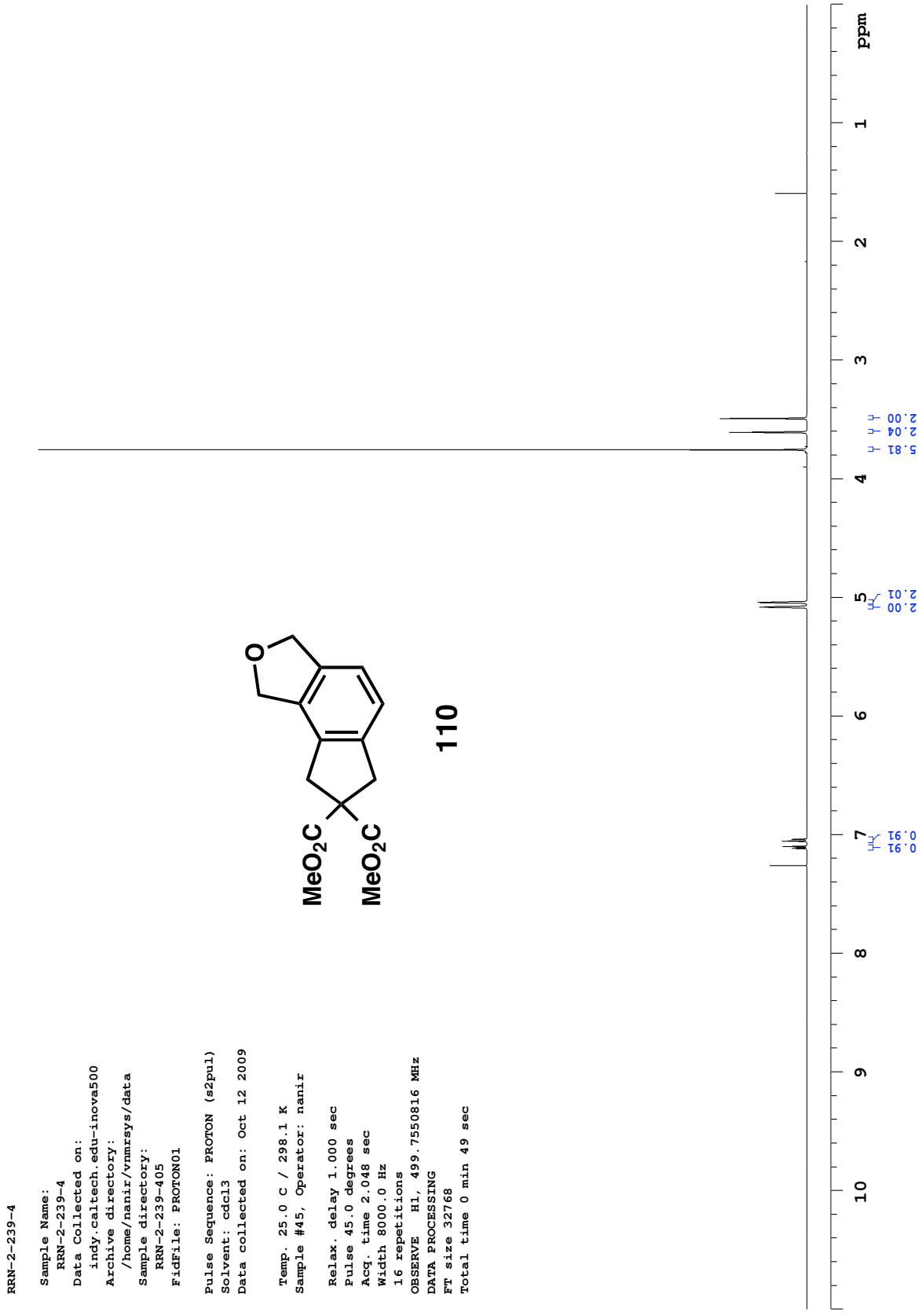


109




RRN-2-238-2
Sample Name:
RRN-2-238-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: Proton_01
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Oct 11 2009
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550819 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 55 sec
MeO2C
MeO2C
O
S3
ppm
10
9
8
7
6
5
4
3
2
1
4.01
6.00
2.13
2.12
0.75
0.81


RRN-2-238-2
Sample Name:
RRN-2-238-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
Sample directory:
FidFile: Carbon_02
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Oct 11 2009
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
1000 repetitions
OBSERVE C13, 125.6635164 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 38 min
O
MeO2C
MeO2C
S3
200
180
160
140
120
100
80
60
40
20
ppm


RRN-2-239-4
Sample Name:
RRN-2-239-4
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-239-405
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 12 2009
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550816 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 49 sec
O
MeO2C
MeO2C
110
ppm
10
9
8
7
6
5
4
3
2
1
0.91
0.91
2.00
2.01
5.81
2.00
2.04

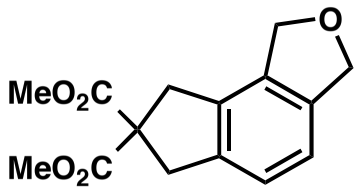
arene

Sample: RRN-2-239-4
File: indy/nanir/vnmrsys/data/RRN-2-239-405/CARBON01.fid

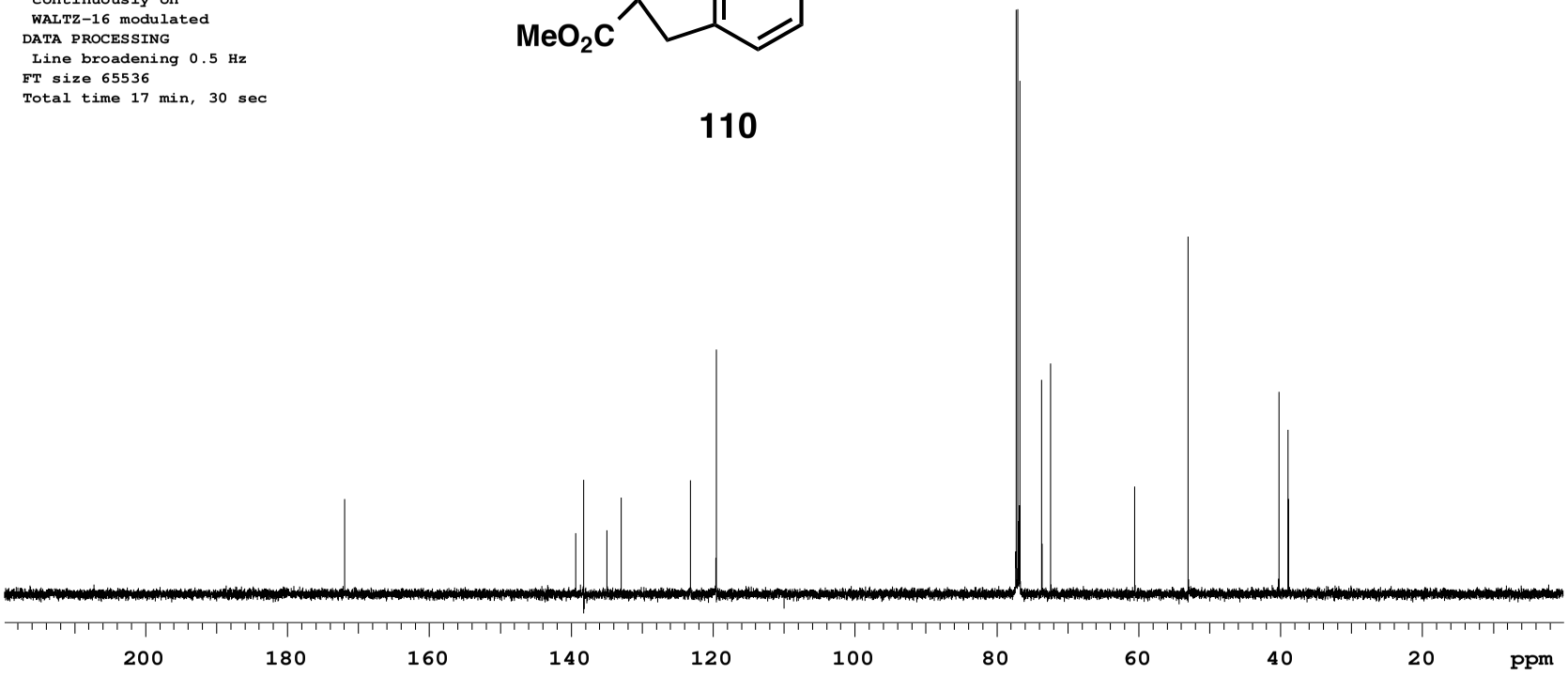
Pulse Sequence: s2pul

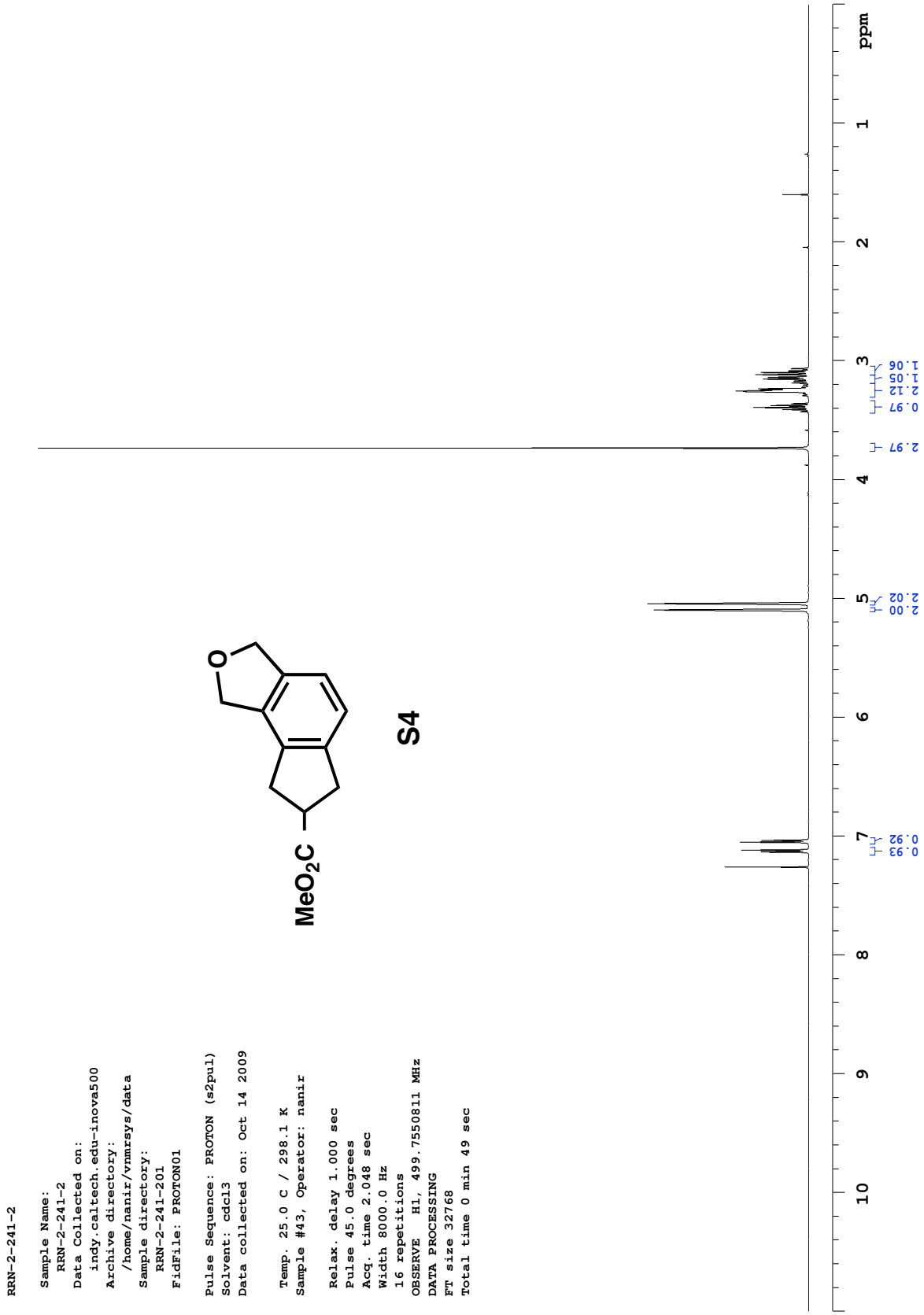
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
File: CARBON01
INOVA-500 "urbino.caltech.edu"

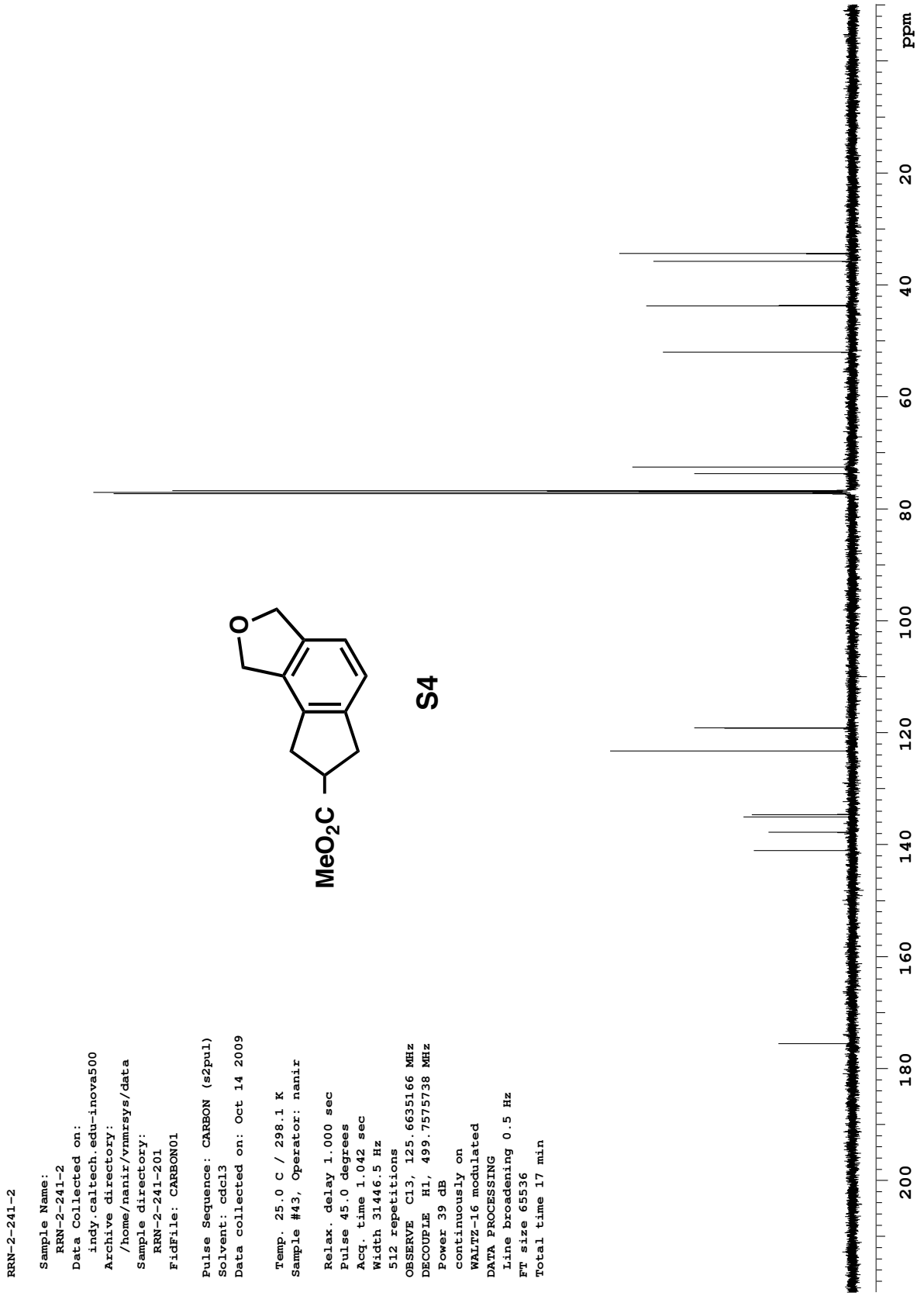
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6635166 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min, 30 sec

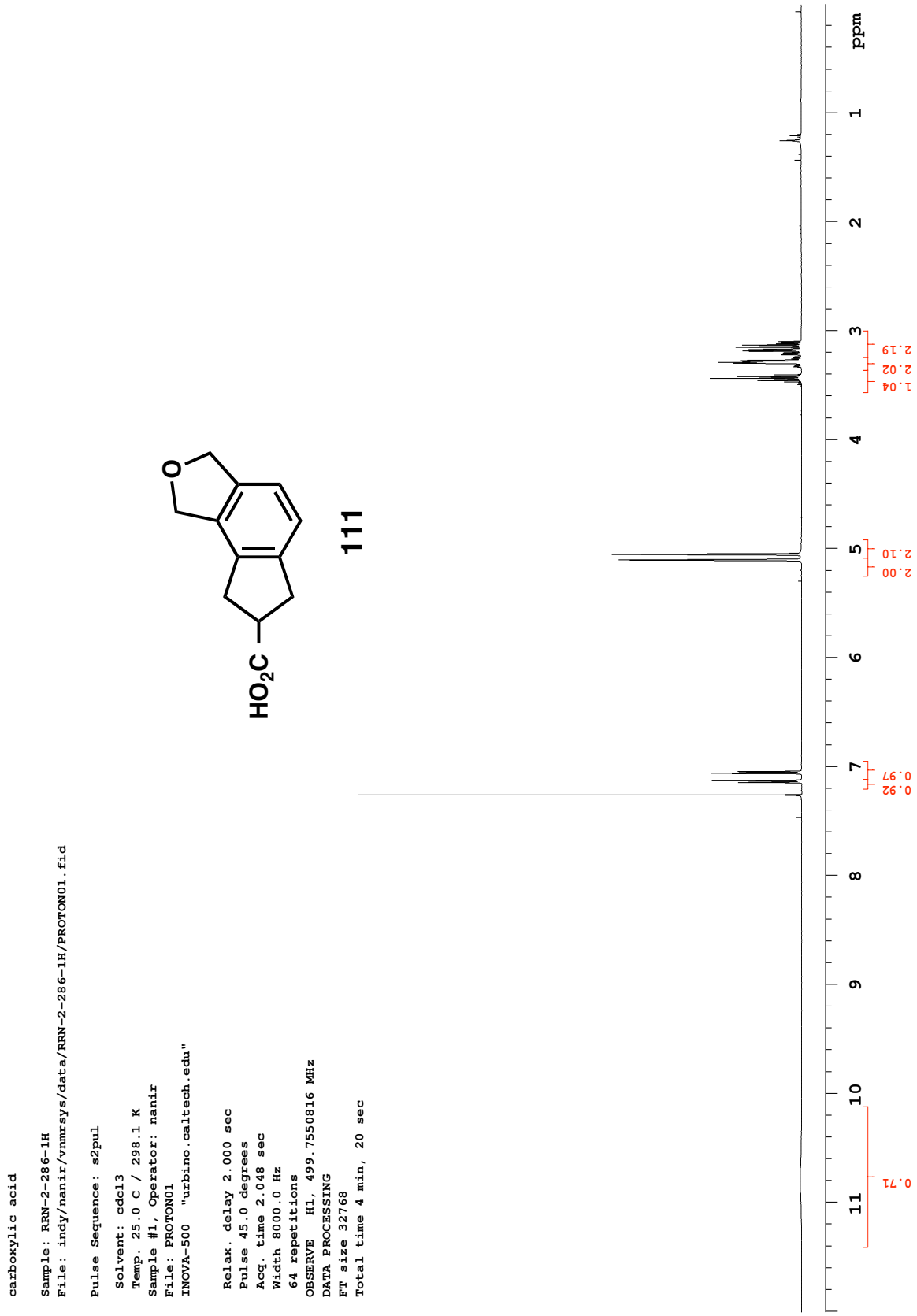


110




RRN-2-241-2
Sample Name:
RRN-2-241-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-241-201
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 14 2009
Temp. 25.0 C / 298.1 K
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550811 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 49 sec
O
MeO2C
S4
ppm
10
9
8
7
6
5
4
3
2
1
0.93
0.92
2.00
2.02
2.97
0.97
2.12
1.05
1.06


RRN-2-241-2
Sample Name:
RRN-2-241-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-241-201
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 14 2009
Temp. 25.0 C / 298.1 K
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6635166 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
O
MeO2C
S4
200
180
160
140
120
100
80
60
40
20
ppm

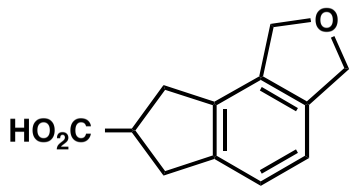

carboxylic acid
Sample: RRN-2-286-1H
File: indy/nanir/vnmrsys/data/RRN-2-286-1H/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, Operator: nanir
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7550816 MHz
DATA PROCESSING
FT size 32768
Total time 4 min, 20 sec
O
HO2C
111
ppm
0.71
2.19
2.02
1.04
2.10
2.00
0.92
0.97

carboxylic acid

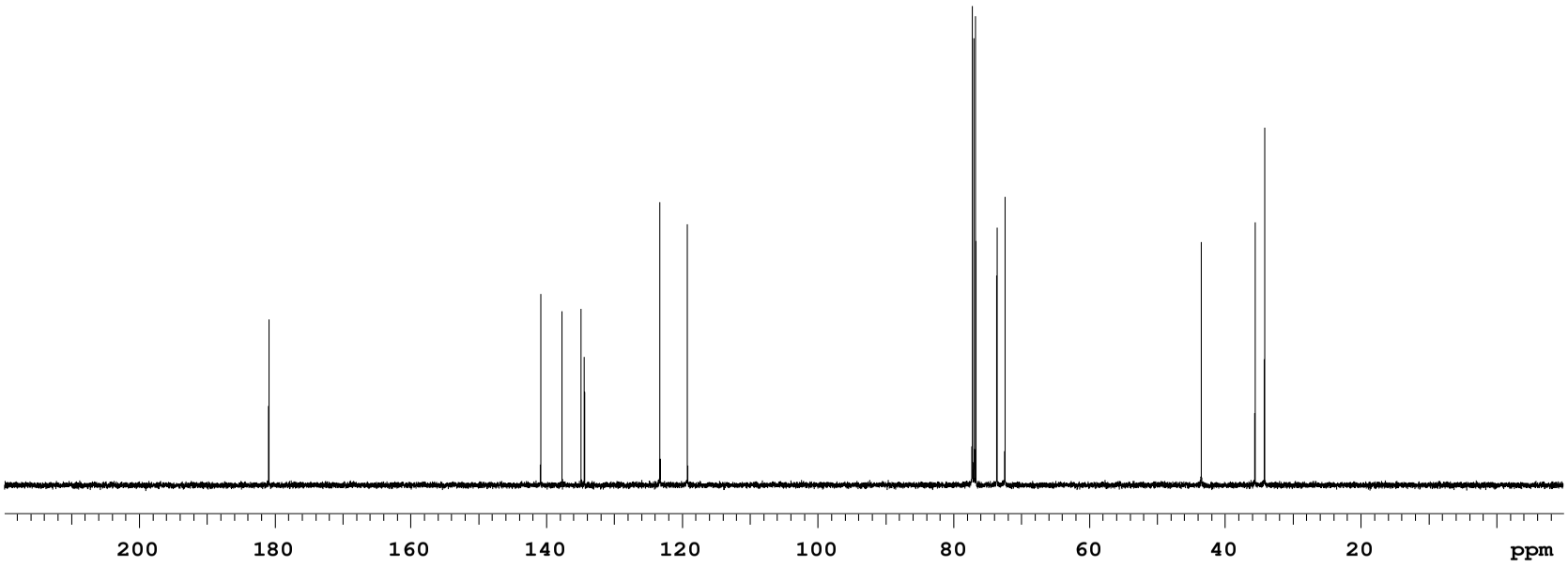
Sample: RRN-2-286-13C
File: indy/nanir/vnmrsys/data/RRN-2-286-13C/CARBON01.fid

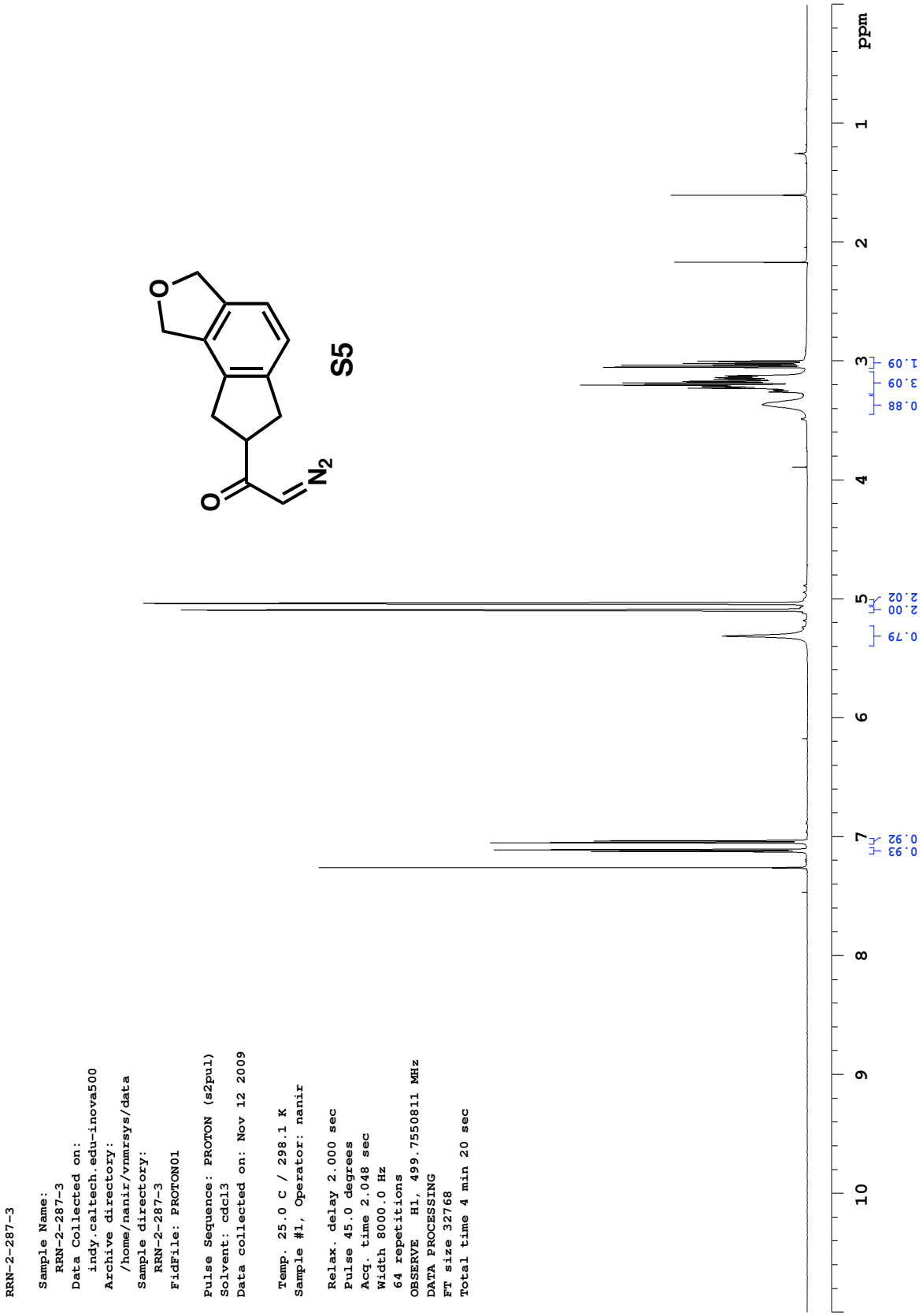
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Sample #2, Operator: nanir
File: CARBON01
INOVA-500 "urbino.caltech.edu"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.042 sec
 Width 31446.5 Hz
 1000 repetitions
OBSERVE C13, 125.6635204 MHz
DECOUPLE H1, 499.7575738 MHz
 Power 39 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 34 min, 11 sec



111




RRN-2-287-3
Sample Name:
RRN-2-287-3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-287-3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 12 2009
Temp. 25.0 C / 298.1 K
Sample #1, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7550811 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 20 sec
S5
O
O
N2
ppm
1
2
3
4
5
6
7
8
9
10
1.09
3.09
0.88
2.00
2.02
0.79
0.93
0.92

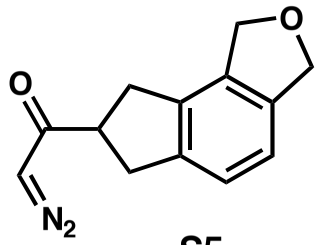
RRN-2-287-3

Sample Name:
RRN-2-287-3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-287-3
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 12 2009

Temp. 25.0 C / 298.1 K
Sample #1, Operator: nanir

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
2000 repetitions
OBSERVE C13, 125.6635166 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 8 min



S5

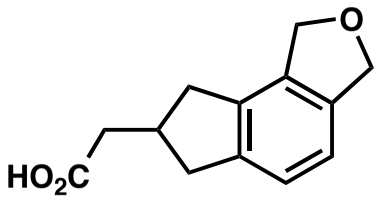
SL-3-007-500-H

Sample: SL-3-007-500-H
File: indy/slevin/vnmrsys/data/SL-3-007-500-H/PROTON01.fid

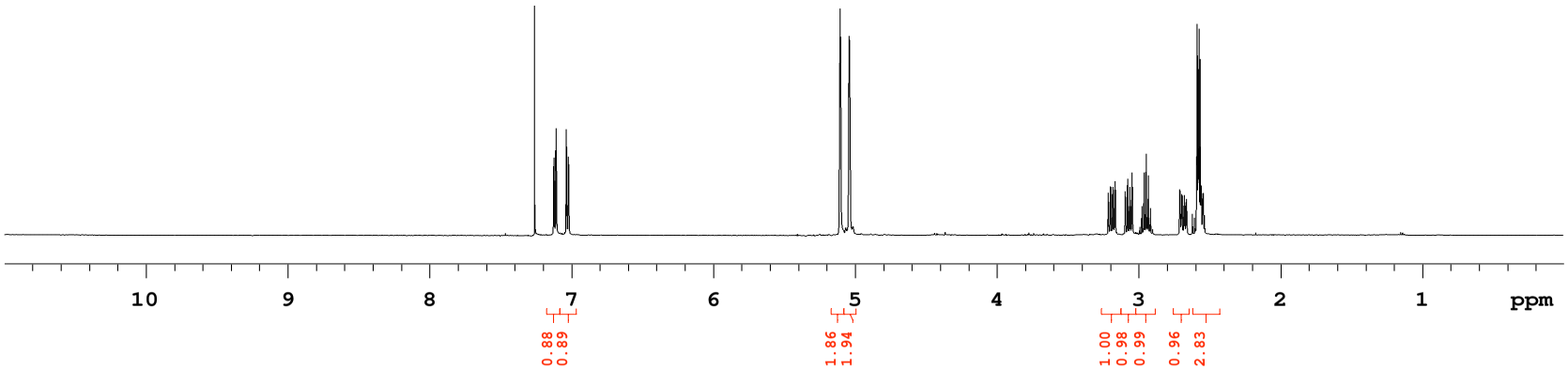
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #48, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7550814 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 24 sec



112



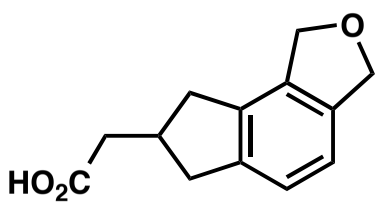
SL-3-007-125-C13

Sample: SL-3-007-125-C13
File: indy/slevin/vnmrsys/data/SL-3-007-125-C13/CARBON01.fid

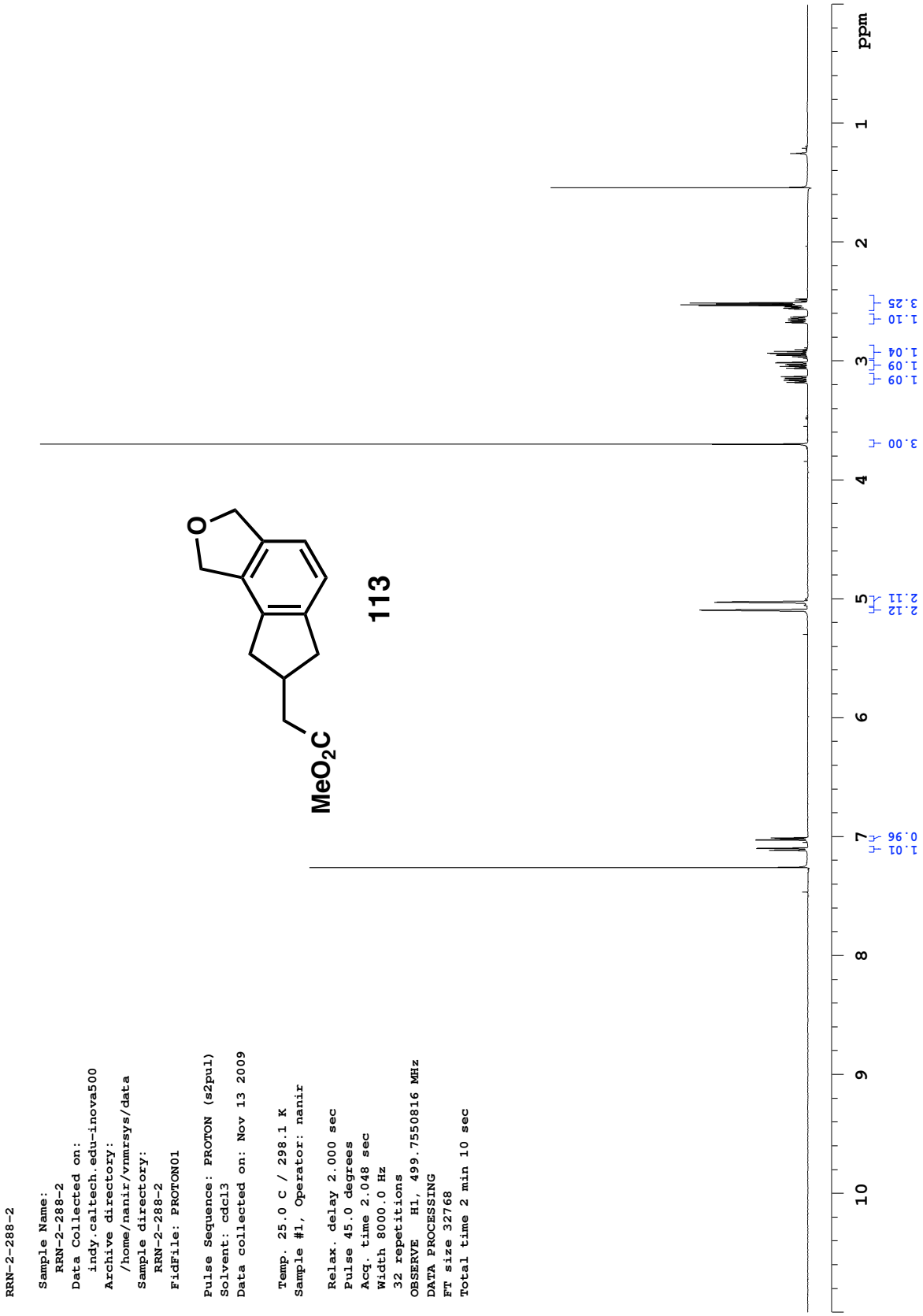
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #48, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 50 min, 56 sec



112


RRN-2-288-2
Sample Name:
RRN-2-288-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-288-2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 13 2009
Temp. 25.0 C / 298.1 K
Sample #1, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7550816 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 10 sec
O
MeO2C
113
ppm
10
9
8
7
6
5
4
3
2
1
0.96
1.01
2.11
2.12
3.00
1.09
1.09
1.04
1.10
3.25

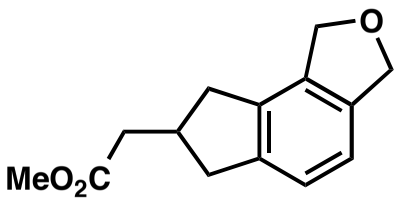
RRN-2-288-2

Sample Name:
RRN-2-288-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-288-2
FidFile: CARBON01

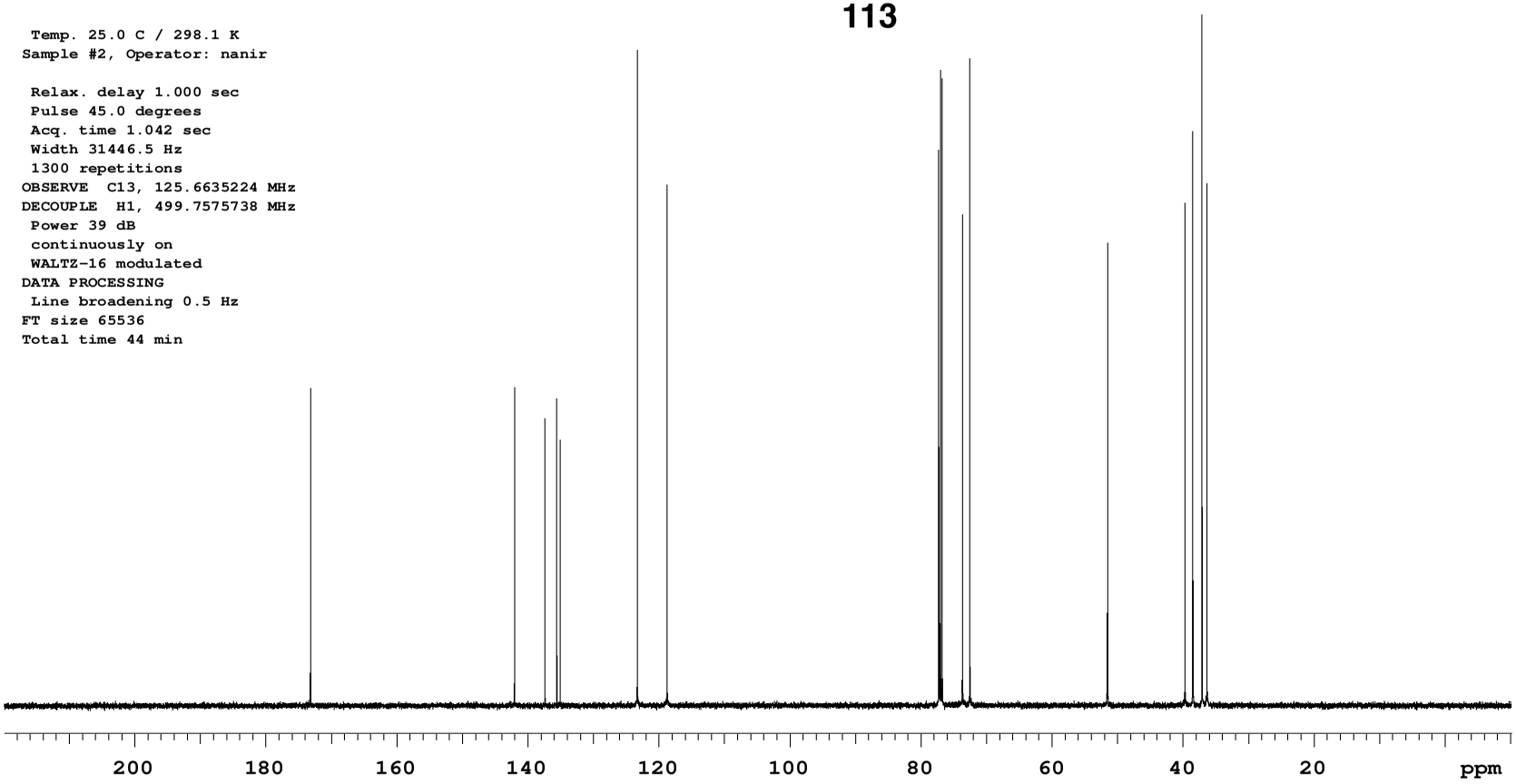
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 13 2009

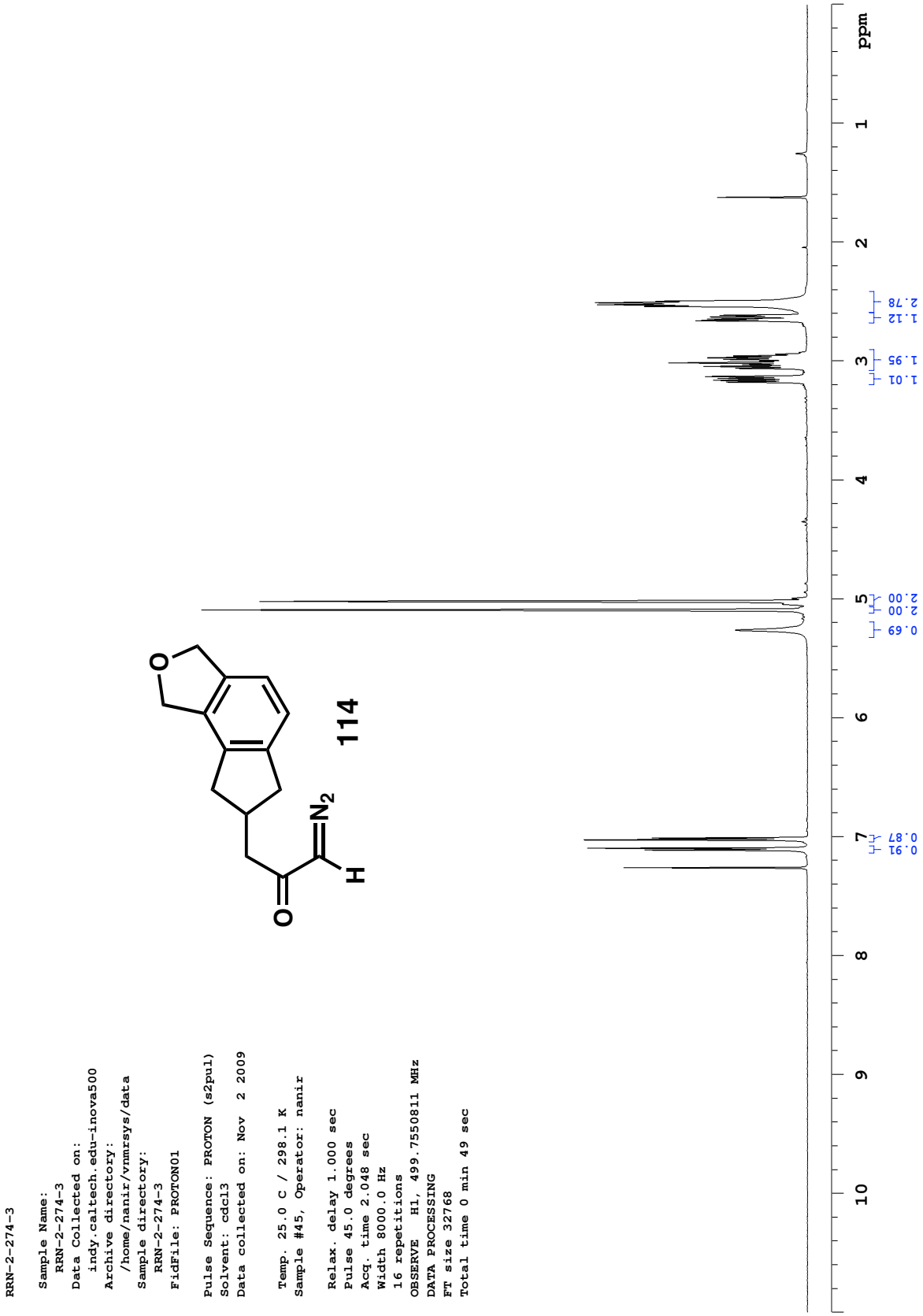
Temp. 25.0 C / 298.1 K
Sample #2, Operator: nanir

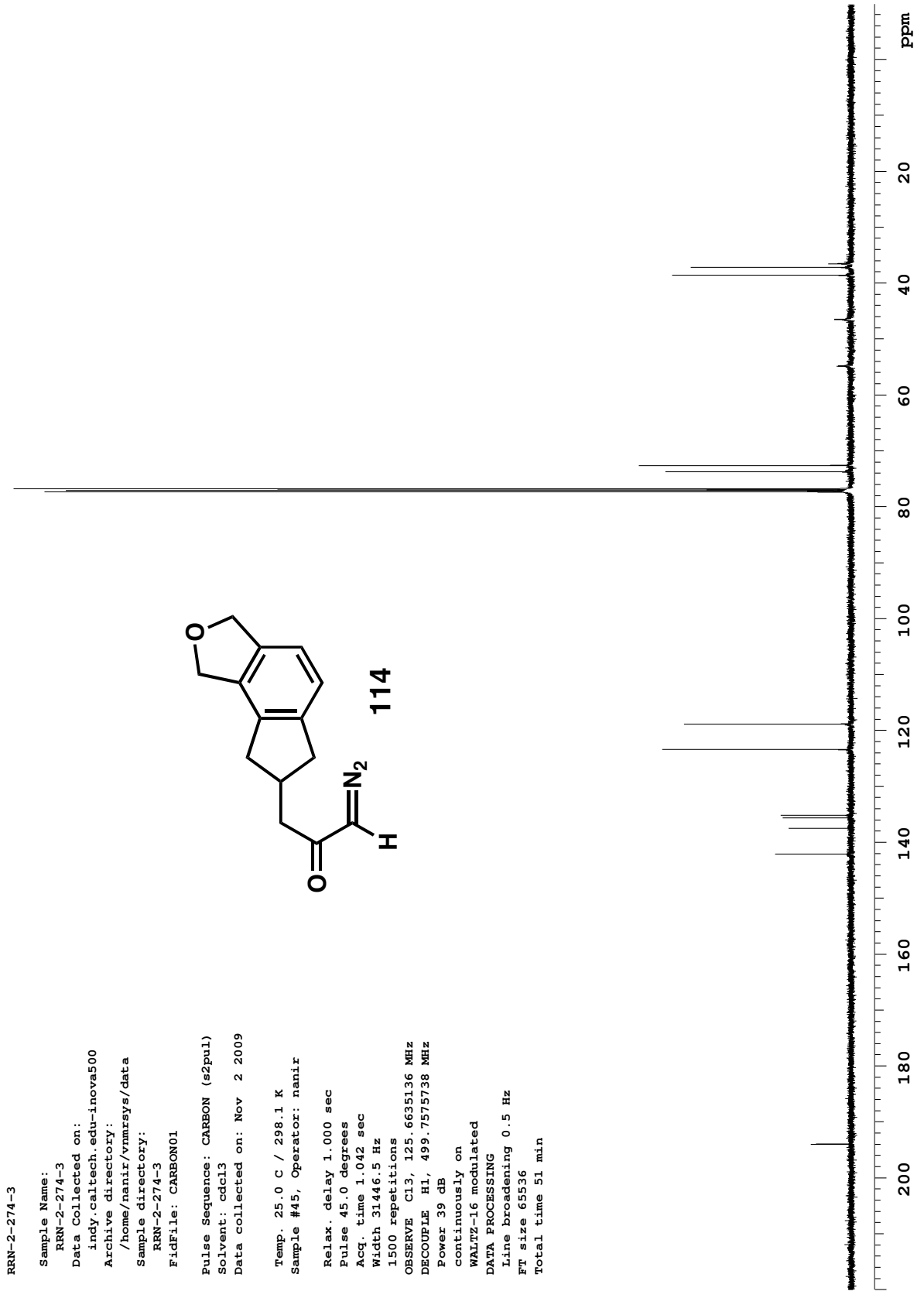
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6635224 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 44 min

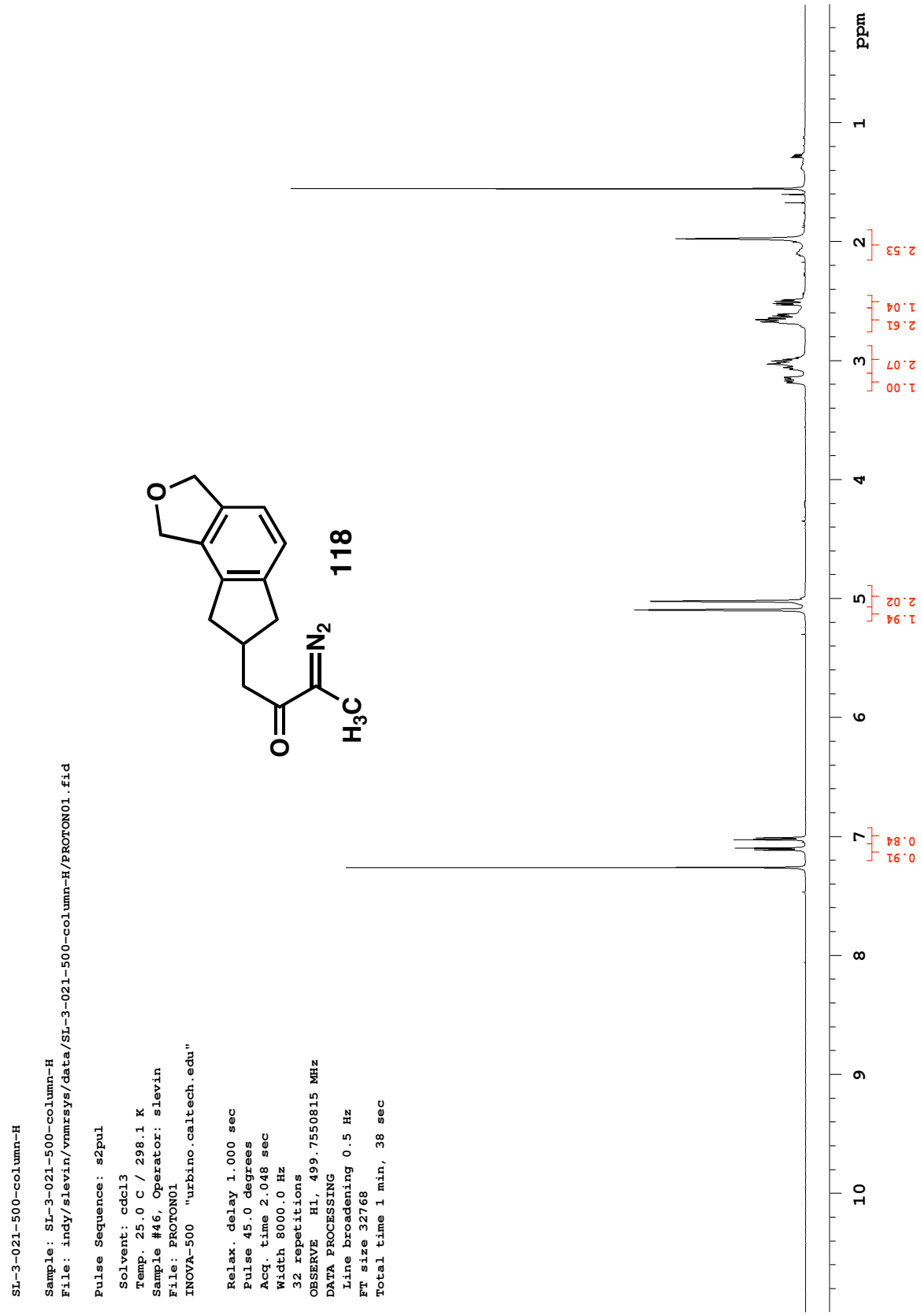


113




RRN-2-274-3
Sample Name:
RRN-2-274-3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-274-3
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 2 2009
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550811 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 49 sec
O
N2
H
O
114
ppm
1
2
3
4
5
6
7
8
9
10
2.78
1.12
1.95
1.01
2.00
2.00
0.69
0.91
0.87


RRN-2-274-3
Sample Name:
RRN-2-274-3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-274-3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 2 2009
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
O
N2
H
O
114
200
180
160
140
120
100
80
60
40
20
ppm


SL-3-021-500-column-H
Sample: SL-3-021-500-column-H
File: indy/slevin/vnmrsys/data/SL-3-021-500-column-H/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7550815 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 1 min, 38 sec
O
N2
H3C
O
118
ppm
10
9
8
7
6
5
4
3
2
1
0.91
0.84
1.94
2.02
1.00
2.07
2.61
1.04
2.53

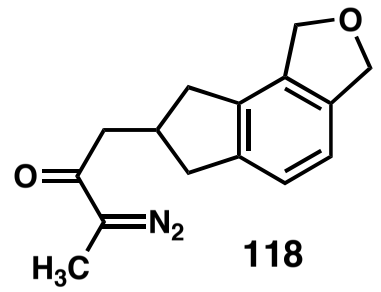
SL-3-021-125-column-13C

Sample: SL-3-021-125-column-13C
File: indy/slevin/vnmrsys/data/SL-3-021-125-column-13C/CARBON01.fid

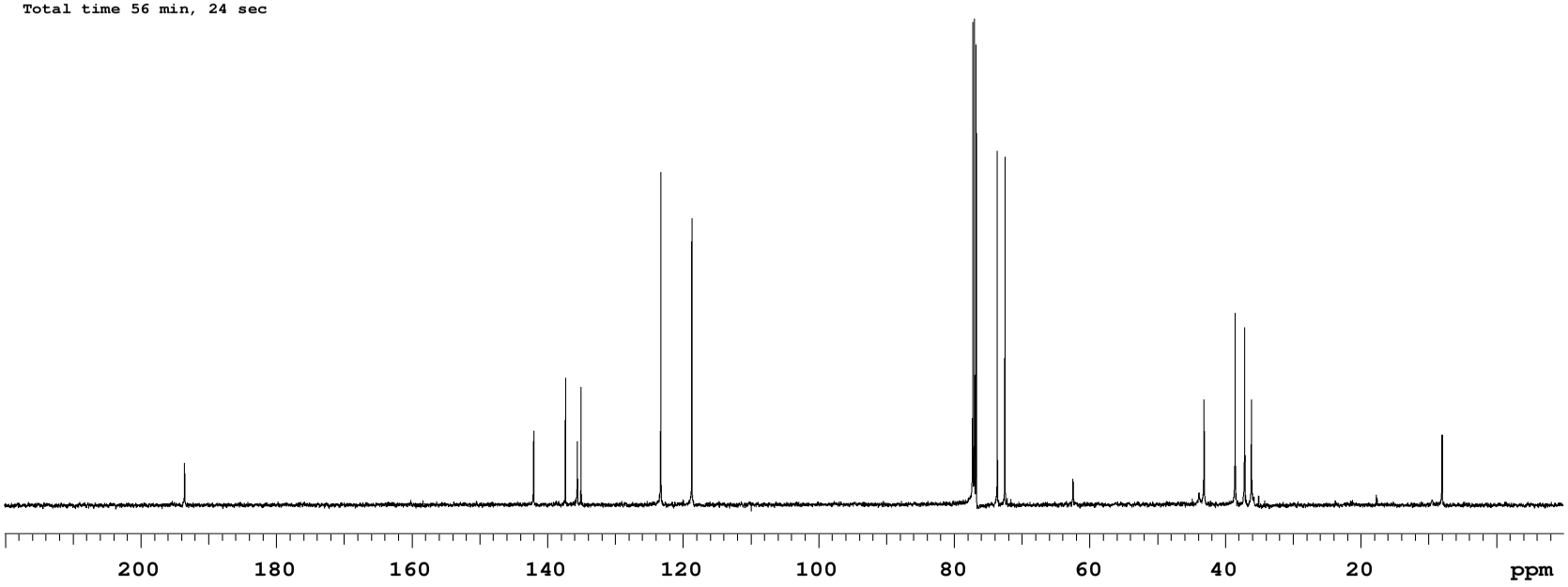
Pulse Sequence: s2pul

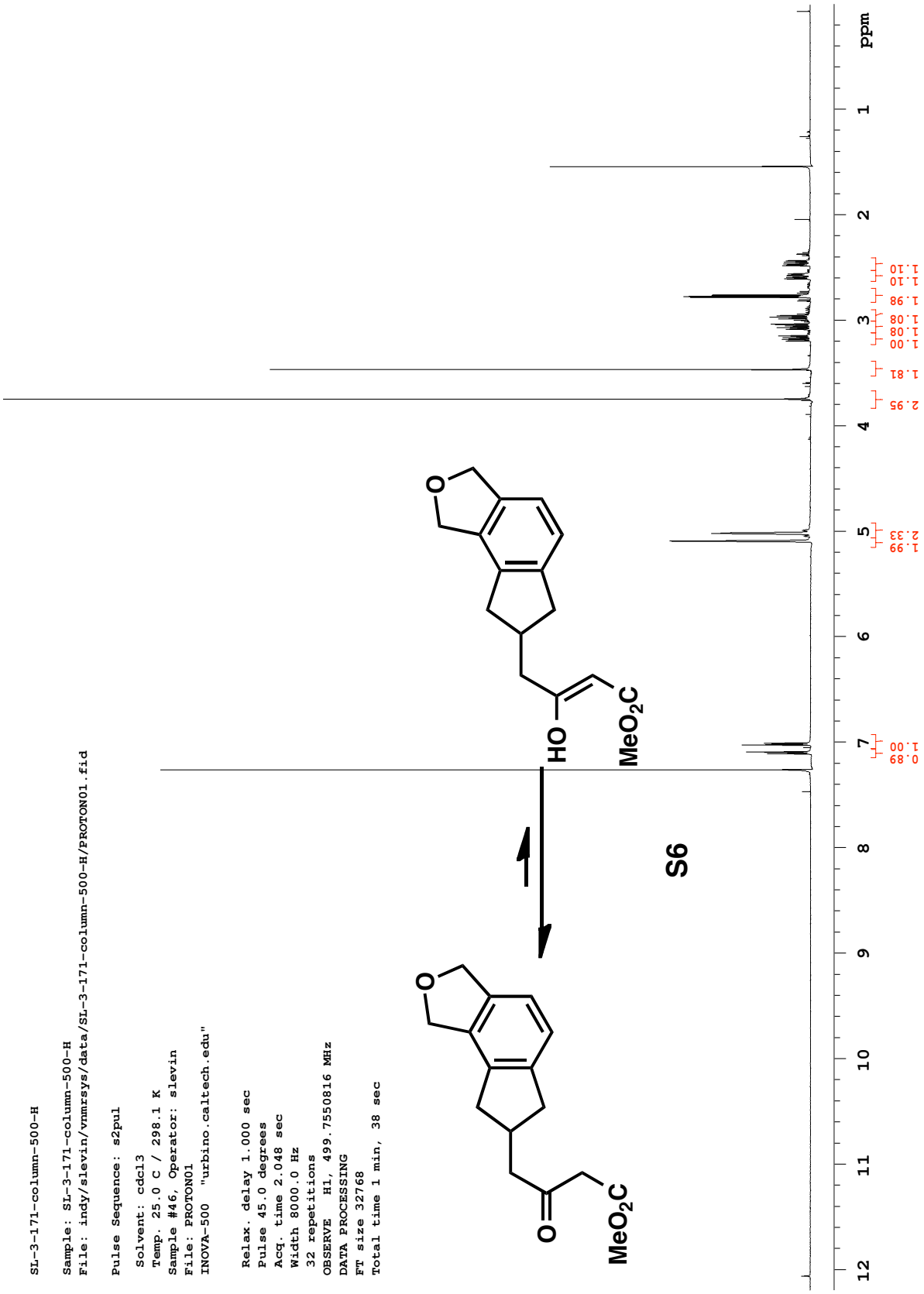
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #47, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"

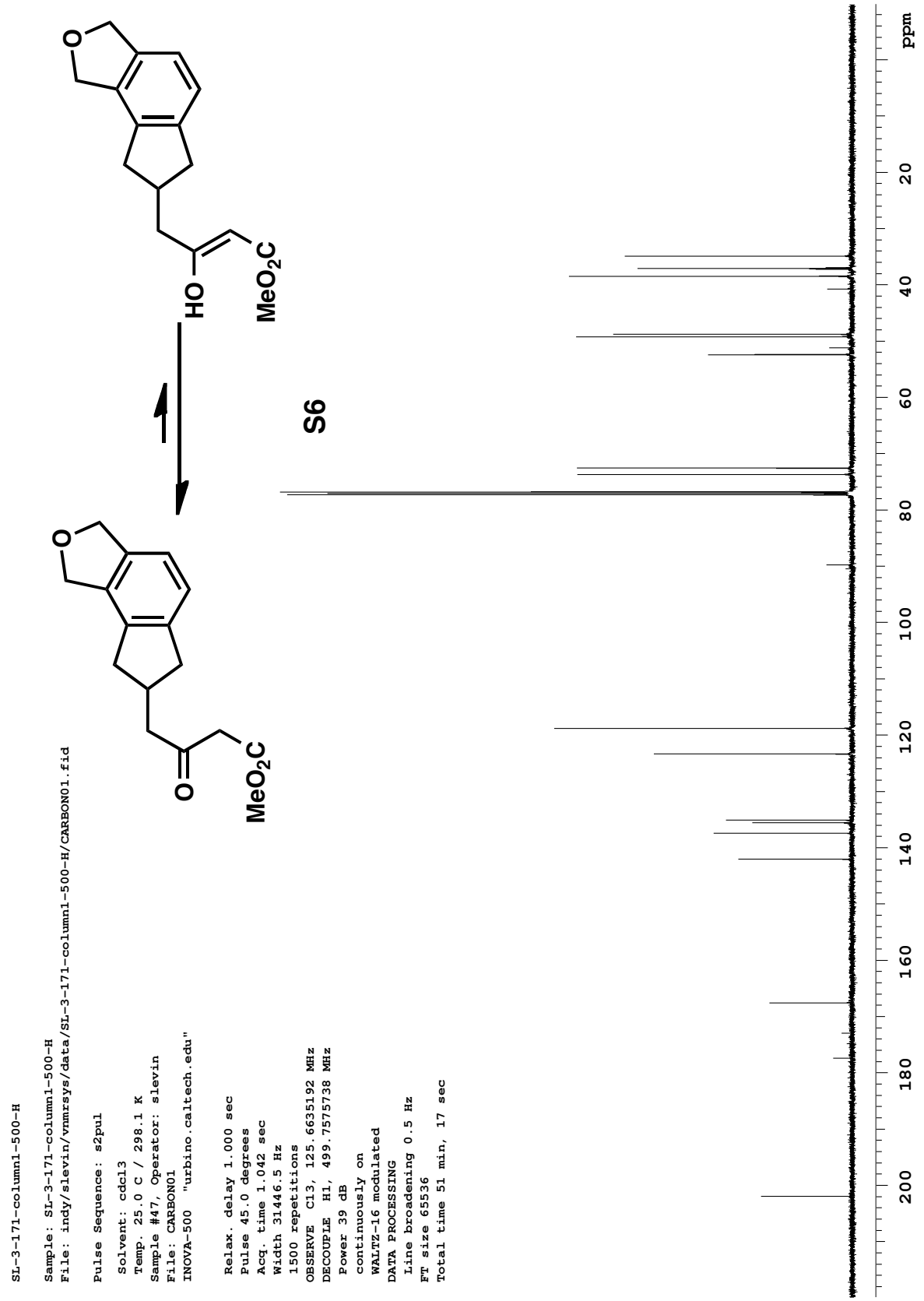
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1650 repetitions
OBSERVE C13, 125.6635240 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 56 min, 24 sec



118




SL-3-171-column-500-H
Sample: SL-3-171-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-171-column-500-H/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7550816 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 38 sec
HO
MeO2C
O
O
MeO2C
S6
ppm
1 2 3 4 5 6 7 8 9 10 11 12
0.89
1.00
1.99
2.33
2.95
1.81
1.00
1.08
1.08
1.98
1.10
1.10


SL-3-171-column1-500-H
Sample: SL-3-171-column1-500-H
File: indy/slevin/vnmrsys/data/SL-3-171-column1-500-H/CARBON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #47, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6635192 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min, 17 sec
O
HO
MeO2C
O
MeO2C
S6
200
180
160
140
120
100
80
60
40
20
ppm

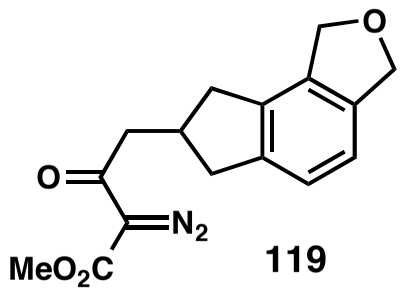
SL-1-217-500-column-H

Sample: SL-1-217-500-column-H
File: indy/slevin/vnmrsys/data/SL-1-217-500-column-H/PROTON01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #47, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550812 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec



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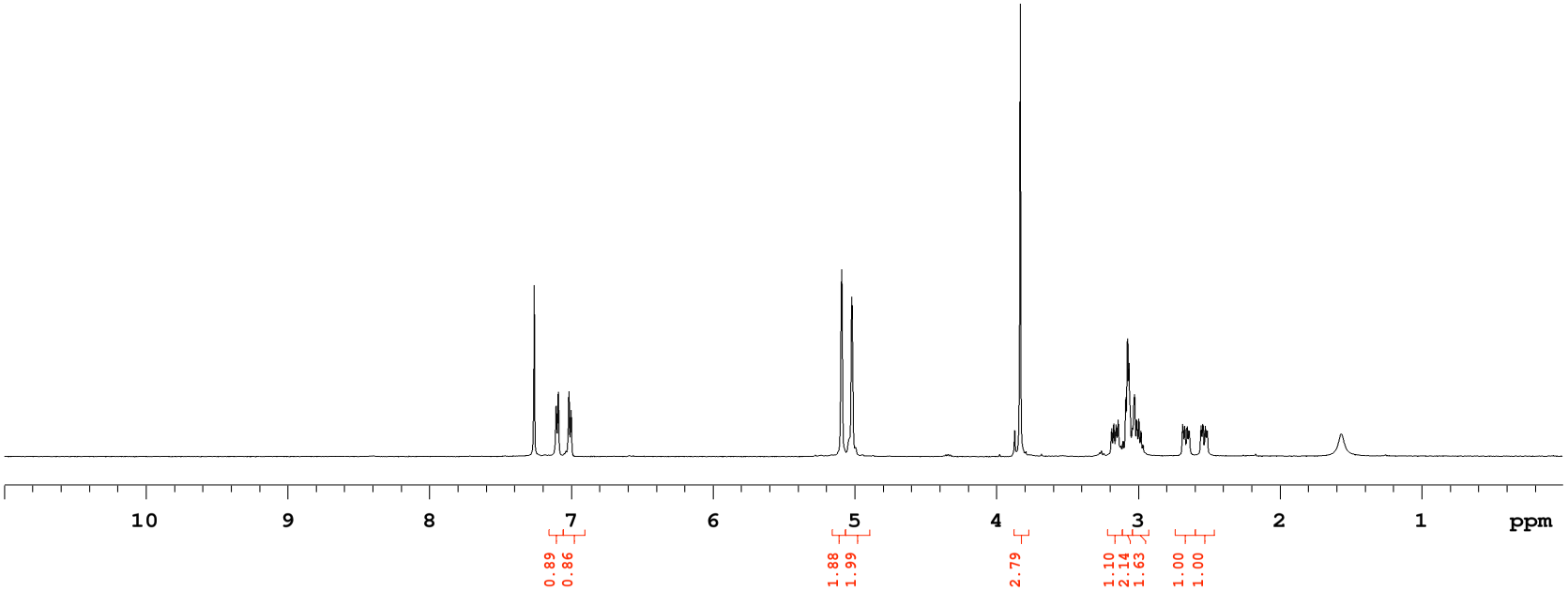


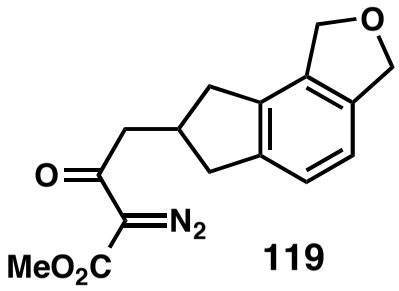
SL-1-217-125-C13

Sample: SL-1-217-125-C13
File: indy/slevin/vnmrsys/data/SL-1-217-125-C13/CARBON01.fid

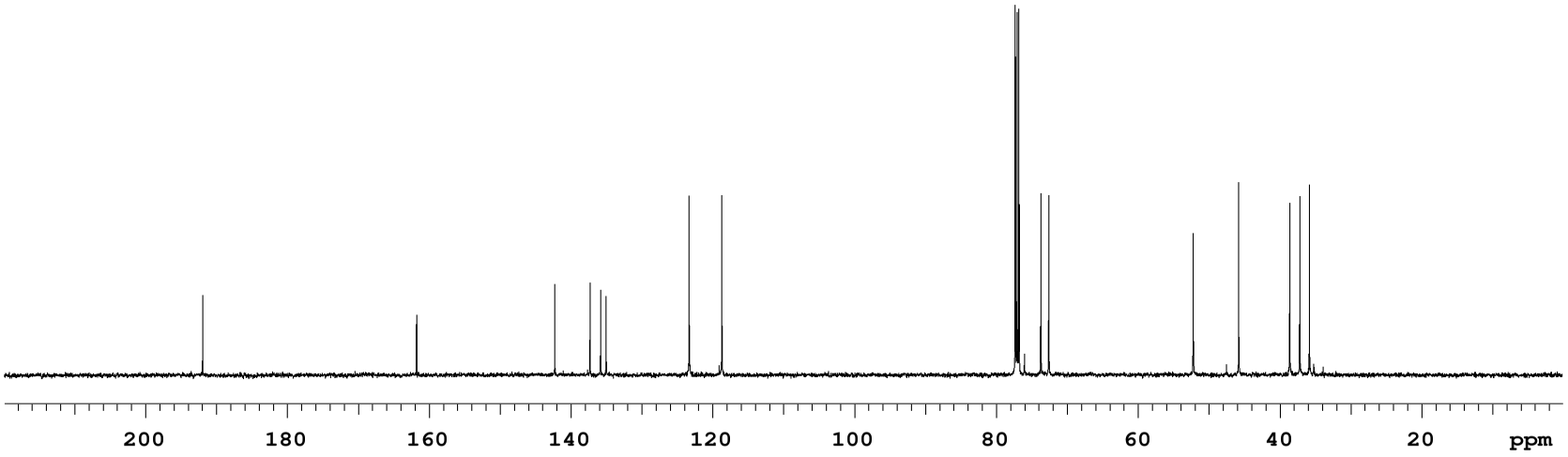
Pulse Sequence: s2pul

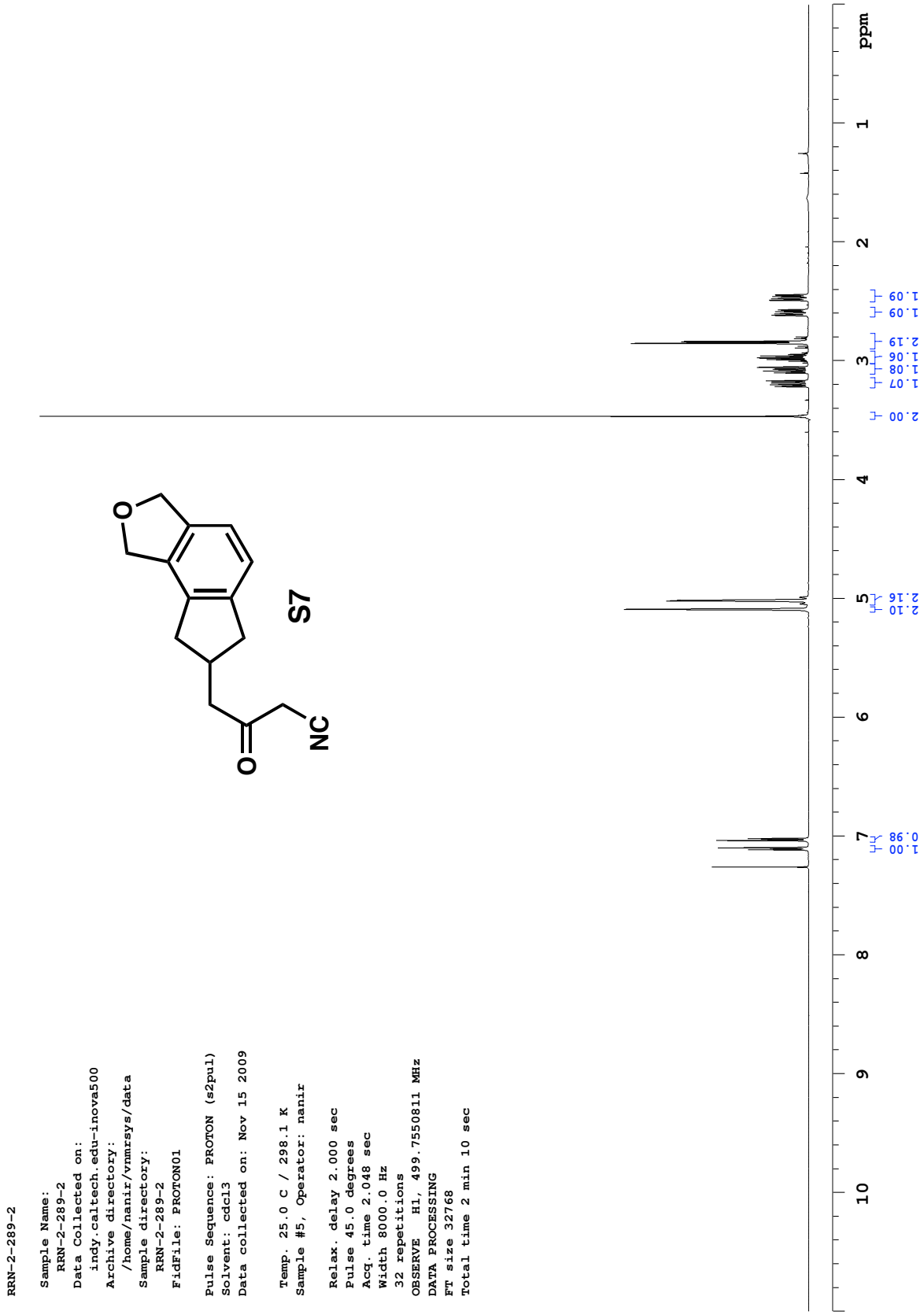
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 34 min, 11 sec



119




RRN-2-289-2
Sample Name:
RRN-2-289-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-289-2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 15 2009
Temp. 25.0 C / 298.1 K
Sample #5, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7550811 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 10 sec
O
O
NC
S7
ppm
1
2
3
4
5
6
7
8
9
10
1.09
1.09
2.19
1.06
1.08
1.07
2.00
2.16
2.10
0.98
1.00

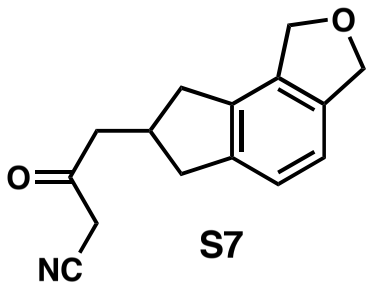
nitrile

Sample: RRN-2-289-2-13C
File: indy/nanir/vnmrsys/data/RRN-2-289-2-13C/CARBON01.fid

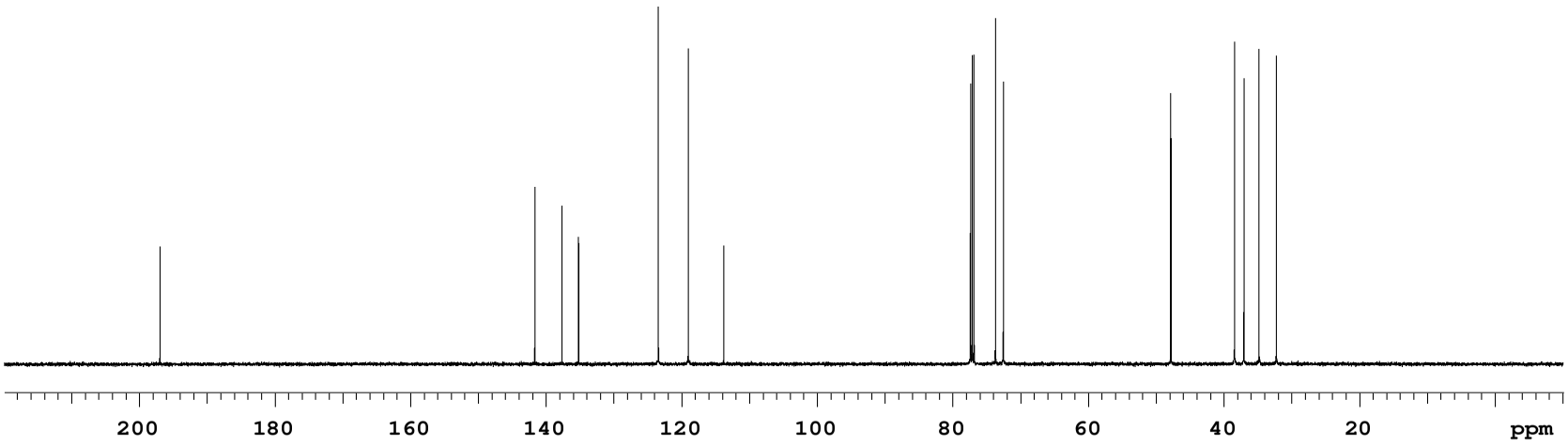
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #6, Operator: nanir
File: CARBON01
INOVA-500 "urbino.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min, 11 sec



S7




SL-3-127-crude-500-H
Sample: SL-3-127-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-127-column-500-H/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550812 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec
O
O
N2
NC
120
ppm
1
2
3
4
5
6
7
8
9
10
1.01
1.94
1.98
1.01
1.00
1.95
1.95
0.87
0.88

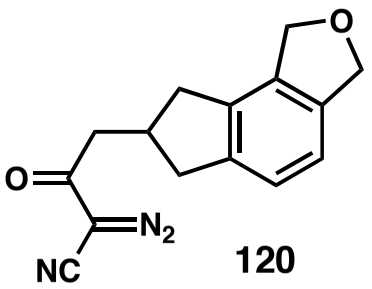
SL-3-127-crude-500-H

Sample: SL-3-127-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-127-column-500-H/CARBON01.fid

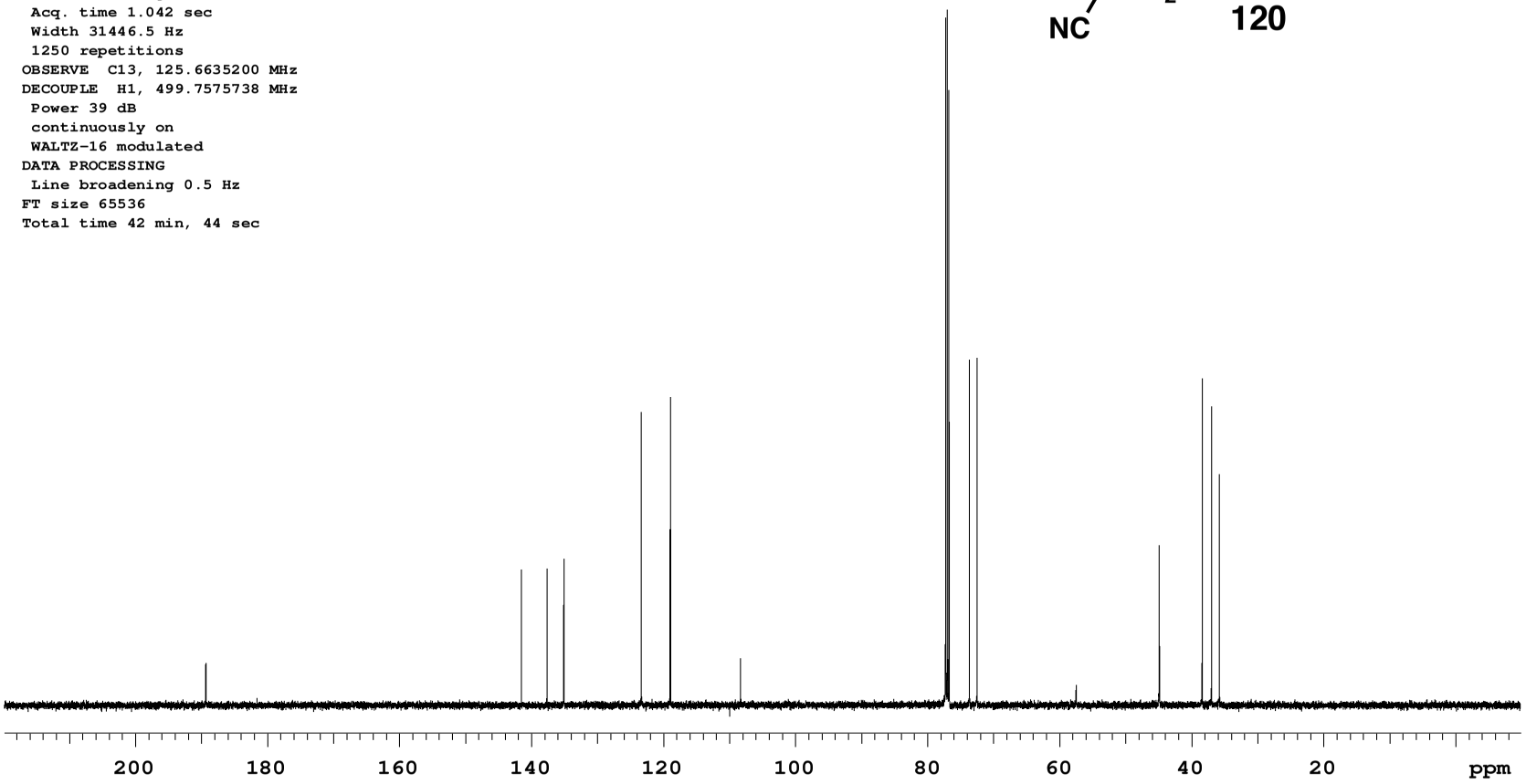
Pulse Sequence: s2pul

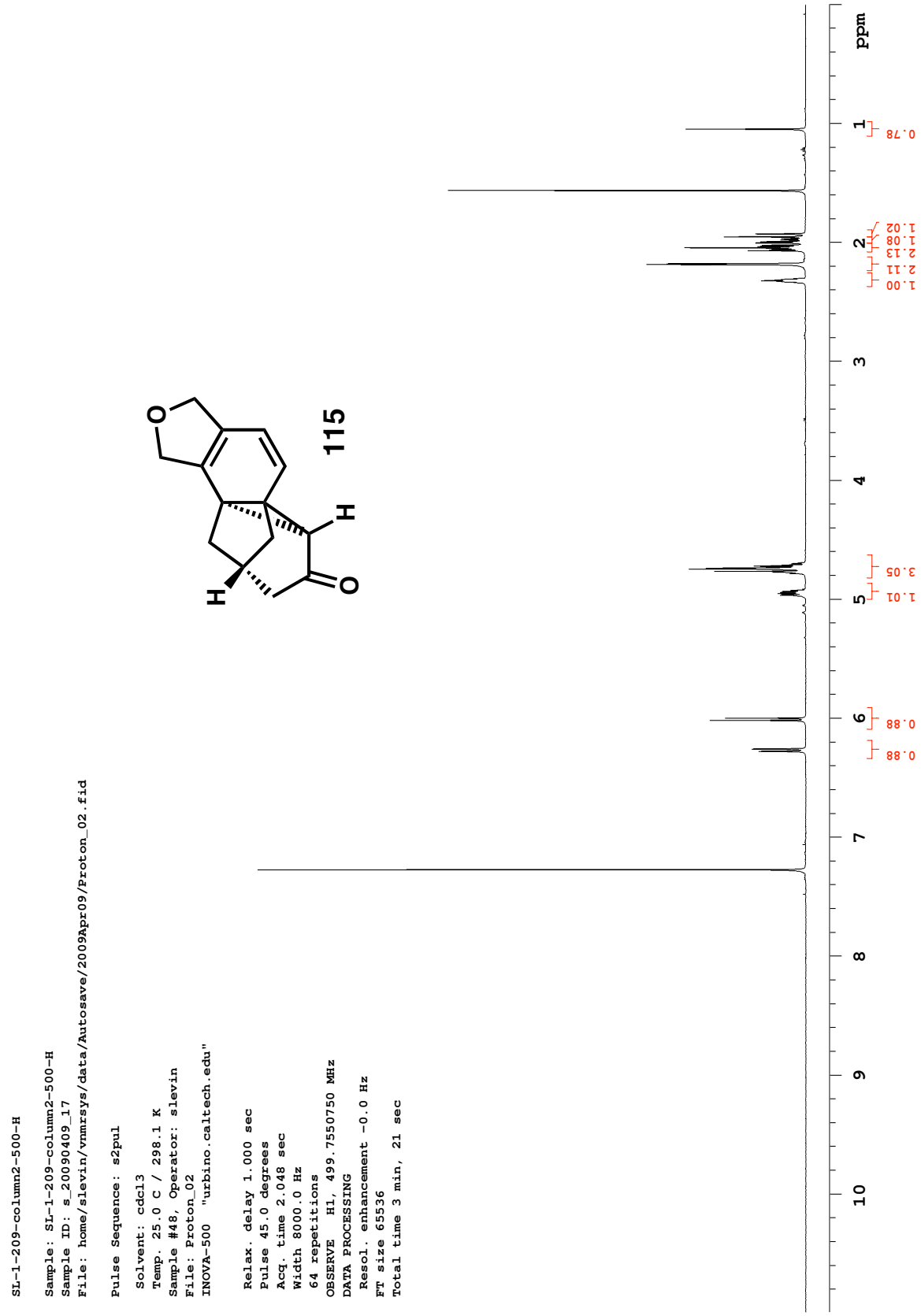
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1250 repetitions
OBSERVE C13, 125.6635200 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 42 min, 44 sec



120




SL-1-209-column2-500-H
Sample: SL-1-209-column2-500-H
Sample ID: s_20090409_17
File: home/slevin/vnmrsys/data/Autosave/2009Apr09/Proton_02.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #48, Operator: slevin
File: Proton_02
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7550750 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 3 min, 21 sec
O
H
H
O
115
ppm
1
2
3
4
5
6
7
8
9
10
0.78
1.00
2.11
2.13
1.08
1.02
1.01
3.05
0.88
0.88

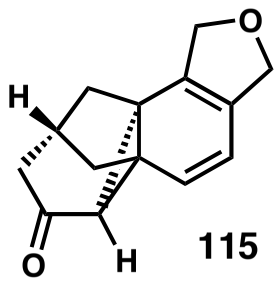
SL-1-209-125-13C

Sample: SL-1-209-prepTLC-F2-500-H
Sample ID: s_20090409_26
File: home/slevin/vnmrsys/data/Autosave/2009Apr10/Carbon_01.fid

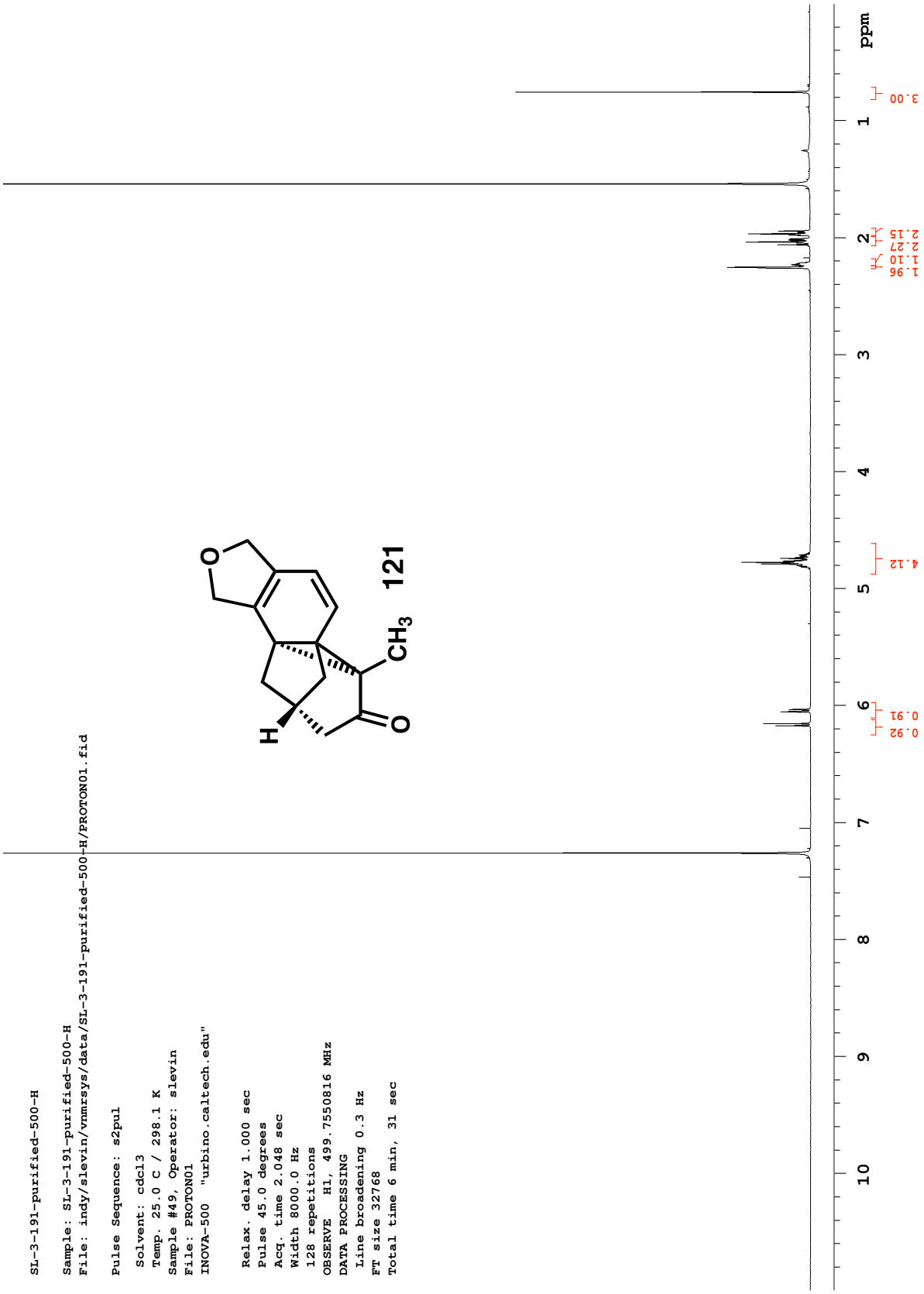
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #41, Operator: slevin
File: Carbon_01
INOVA-500 "urbino.caltech.edu"

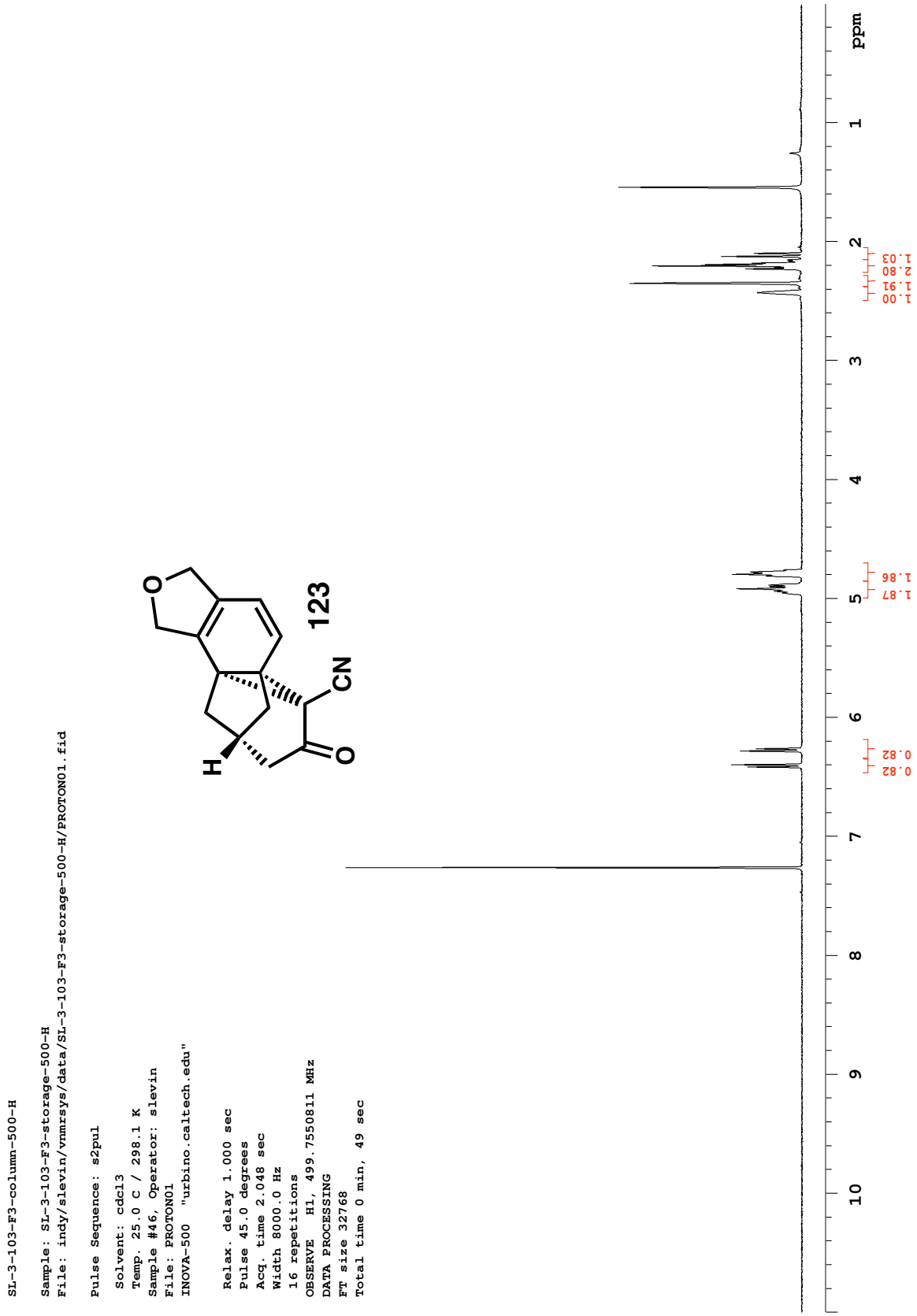
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
7000 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 4 hr, 29 min, 22 sec



115


SL-3-191-purified-500-H
Sample: SL-3-191-purified-500-H
File: indy/slevin/vnmrsys/data/SL-3-191-purified-500-H/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #49, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7550816 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 6 min, 31 sec
O
H
O
CH3
121
ppm
10
9
8
7
6
5
4
3
2
1
0.92
0.91
4.12
1.96
1.10
2.27
2.15
3.00

SL-3-191-1-125-13C
Sample: SL-3-191-1-125-13C
File: data/indy/slevin/vnmrsys/data/SL-3-191-1-125-13C/CARBON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: CARBON01
INOVA-500 "erice.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.000 sec
Width 31446.5 Hz
14100 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 8 hr, 11 min, 48 sec
O
H
O
CH3
121
200
180
160
140
120
100
80
60
40
20
ppm
*


SL-3-103-F3-column-500-H
Sample: SL-3-103-F3-storage-500-H
File: indy/slevin/vnmrsys/data/SL-3-103-F3-storage-500-H/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550811 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec
O
H
O
CN
123
ppm
1
2
3
4
5
6
7
8
9
10
0.82
0.82
1.87
1.86
1.00
1.91
2.80
1.03

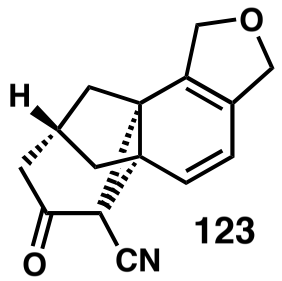
SL-3-103-pHPLC-500-H

Sample: SL-3-103-pHPLC-500-H
File: indy/slevin/vnmrsys/data/SL-3-103-pHPLC-500-H01/CARBON01.fid

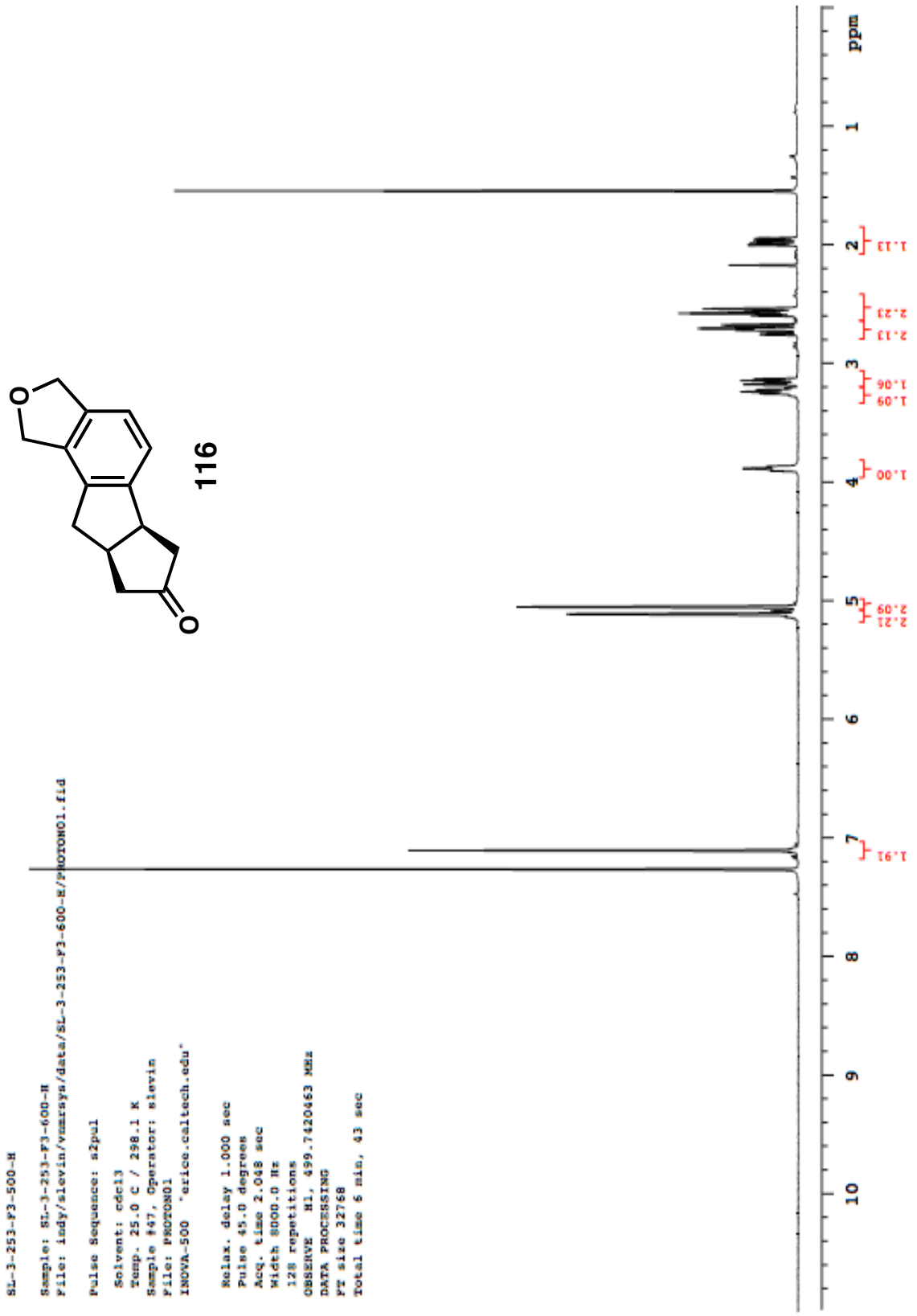
Pulse Sequence: s2pul

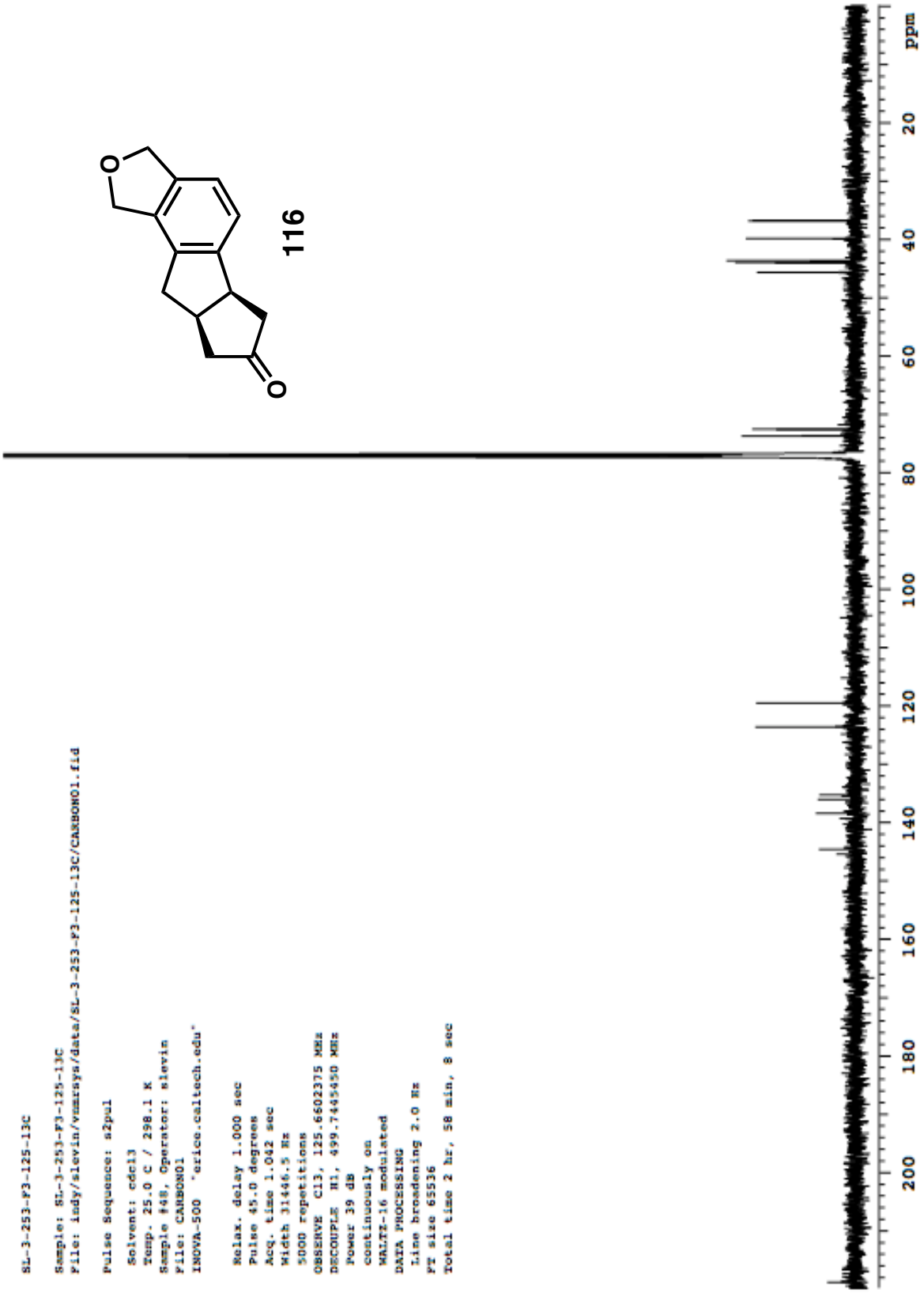
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #47, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"

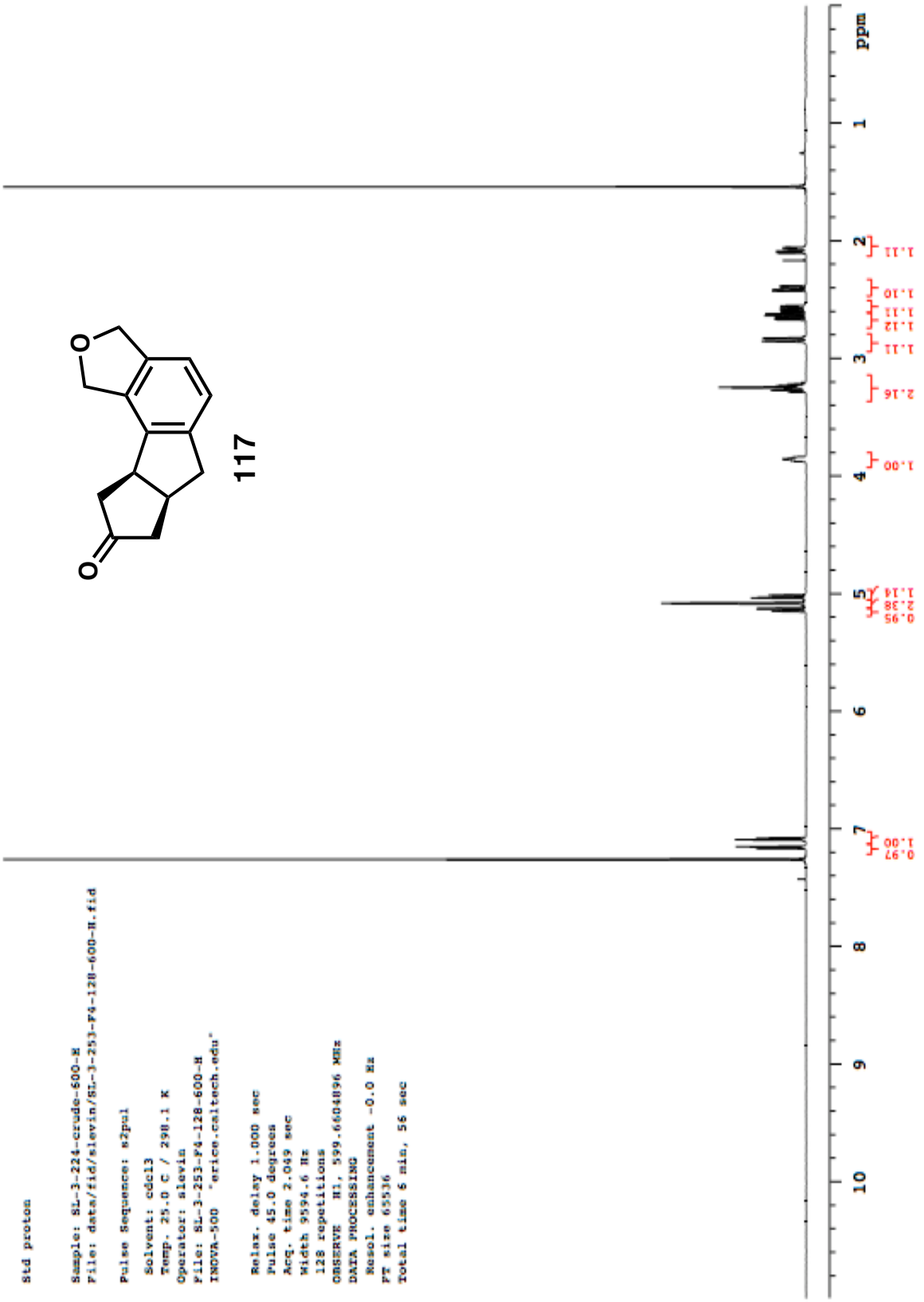
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13900 repetitions
OBSERVE C13, 125.6635158 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 7 hr, 55 min, 10 sec

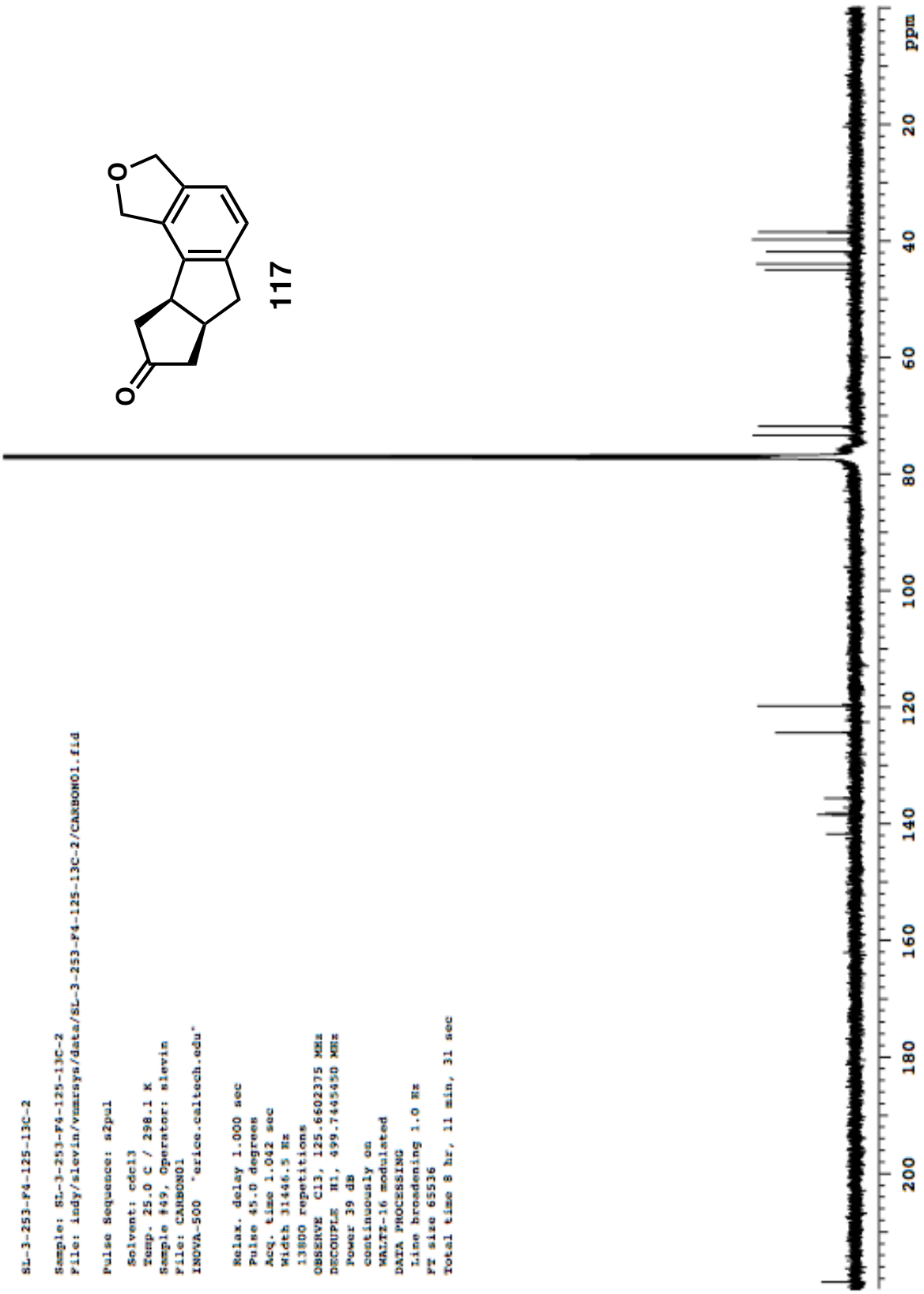


123


SL-3-253-P3-500-H
Sample: SL-3-253-P3-600-H
File: indy/slevin/vnmrsys/data/SL-3-253-P3-600-H/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #47, Operator: slevin
File: PROTON01
INOVA-500 "erice.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7420463 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 43 sec
116
ppm
1.13
2.23
2.13
1.09
1.06
1.00
2.21
2.09
1.91


SL-3-253-P3-125-13C
Sample: SL-3-253-P3-125-13C
File: indy/slevin/vmrsraya/data/SL-3-253-P3-125-13C/CARBON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #48, Operator: slevin
File: CARBON01
INOVA-500 "erice.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6602375 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 2 hr, 58 min, 8 sec
O
O
116
200
180
160
140
120
100
80
60
40
20
ppm


Std proton
Sample: SL-3-224-crude-600-H
File: data/fid/slevin/SL-3-253-F4-128-600-H.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: slevin
File: SL-3-253-F4-128-600-H
INOVA-500 "erice.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 9594.6 Hz
128 repetitions
OBSERVE H1, 599.6604896 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 6 min, 56 sec
O
O
117
ppm
1
2
3
4
5
6
7
8
9
10
1.11
1.10
1.11
1.12
1.11
2.16
1.00
0.95
2.38
1.14
0.97
1.00


SL-3-253-F4-125-13C-2
Sample: SL-3-253-F4-125-13C-2
File: indy/slevin/vnmrsys/data/SL-3-253-F4-125-13C-2/CARBON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #49, Operator: slevin
File: CARBON01
INOVA-500 "erice.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13800 repetitions
OBSERVE C13, 125.66023375 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 8 hr, 11 min, 31 sec
O
O
117
200
180
160
140
120
100
80
60
40
20
ppm

Chapter 3

Enantioselective Total Synthesis of Salvileucalin B

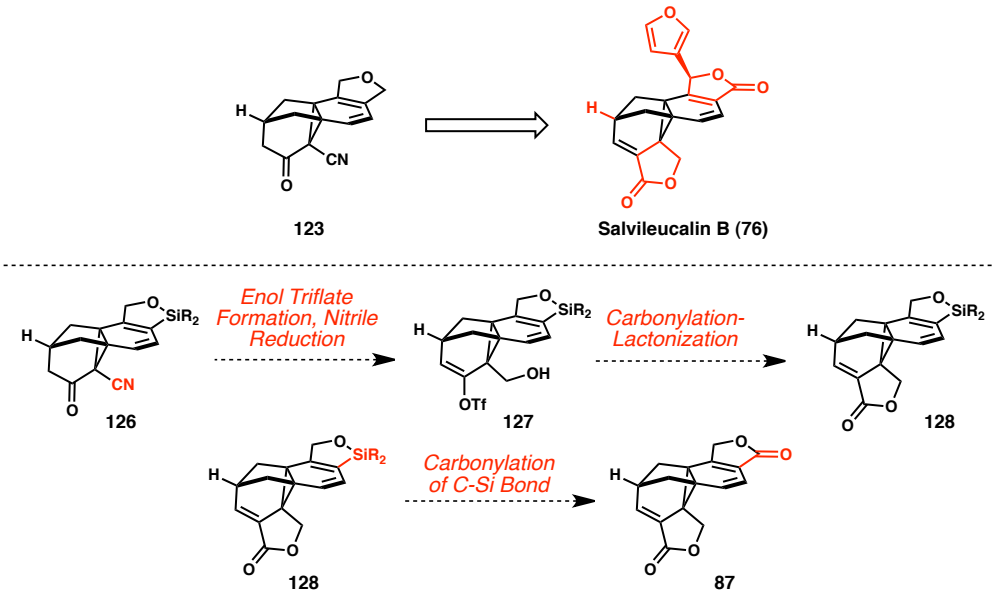
3.1 INTRODUCTION

3.1.1 Strategy for Lactone Synthesis

Having successfully established the feasibility of generating a fully substituted norcaradiene by arene cyclopropanation, our attention turned to applying this key reaction in a fully functionalized system that would enable the synthesis of salvileucalin B. Specifically, this would require: 1) enantioselective synthesis of a cycloisomerization substrate containing the pendant furan, 2) installation of the northern lactone, and 3) construction of the southern lactone. The southern lactone was expected to arise from a sequence involving enol triflate formation, nitrile reduction, and carbonylative lactonization (Scheme 3.1).[1] In contrast, however, it was unclear at the time how the northern lactone would be introduced. As discussed in the previous chapter, early incorporation of the northern lactone was expected to detrimentally impact the arene

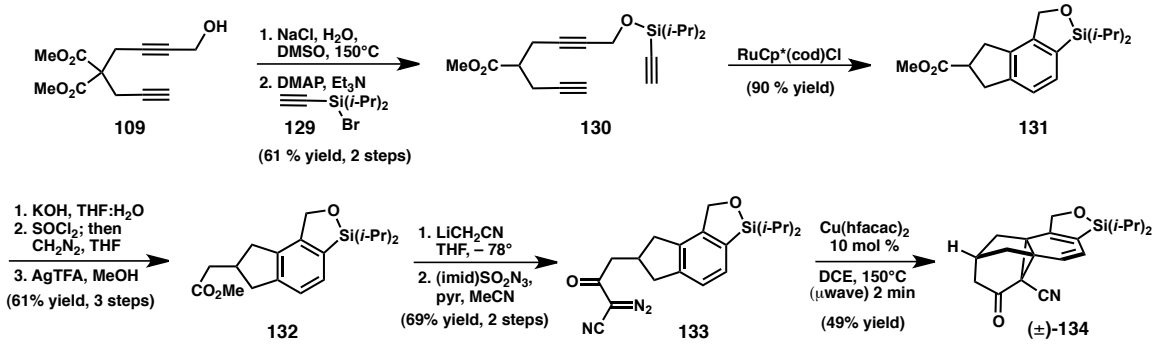
cyclopropanation, as electron-poor benzenes are poor Buchner substrates. Furthermore, the northern lactone was expected to be vulnerable to the reduction chemistry we envisioned using in the synthesis of the southern lactone. Alternatively, we imagined that a cyclic silyl ether moiety (e.g. **128**) could act as a stable lactone precursor. The silicon substitution was not expected to negatively perturb the arene electronics for the Buchner reaction. Furthermore, we anticipated conversion of the C-Si bond to the northern lactone would be possible, given the range of silicon cross-coupling technologies available. Despite the broad use of silicon-based reagents in cross coupling, carbonylations of C–Si bonds such as those in **128** are much more rare. Nonetheless, we were encouraged by a report by Kumada and coworkers in 1979, which disclosed the palladium-promoted carbonylation of vinyl silicates to give α,β-unsaturated esters.[2] Although stoichiometric, this finding suggests the desired transformation is mechanistically feasible.

Scheme 3.1. *Strategy for installation of both lactones*



Diazo-β-ketonitrile **133** was obtained by a short synthetic sequence from **109**, which began with Krapcho dealkoxycarbonylation[3] followed by silylation with alkynylsilyl bromide **129**[4] to give triyne **130** (Scheme 3.2). Exposure of **130** to 1 mol % of RuCp*(cod)Cl smoothly provided arene **131** in 90% yield.[5] Notably, the cycloisomerization of **130** clearly indicates that the benefit of a "Thorpe–Ingold" effect from the gem-diester moiety is not required for cyclization.[6] This result lends support for proposed future work on an enantioselective route, which will require the cyclization of a chiral substrate bearing a tertiary center at C2.

Scheme 3.2. *Cyclopropanation of silyl analogue* ***134***



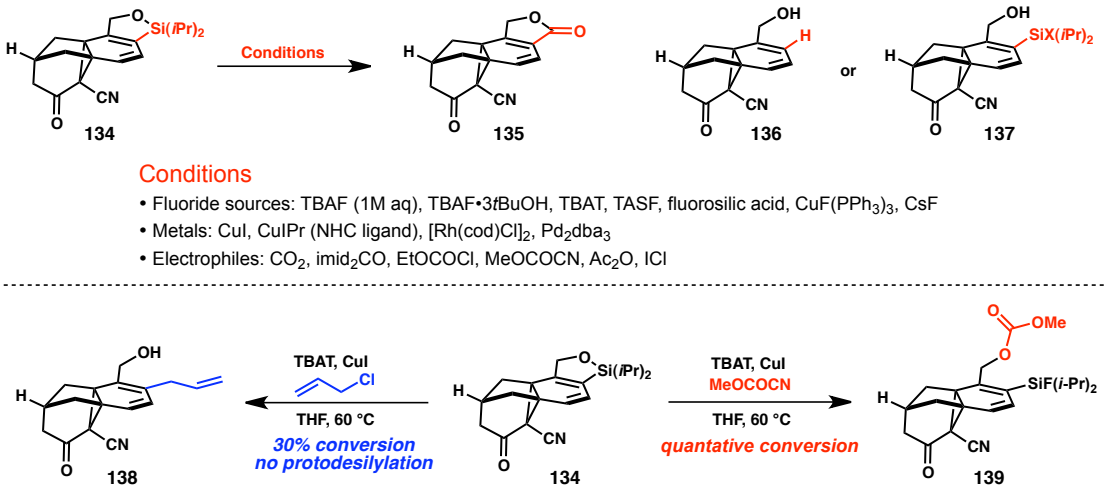
Homologation of arene **131** proceeded as before with use of the Arndt–Eistert protocol[7] to provide methyl ester **132**, which was converted in two steps to α-diazo β-ketonitrile **133**. Heating a solution of **133** in the presence of 10 mol % $Cu(hfacac)_2$ to 150 °C under microwave irradiation for 2 min provided cyclopropane **134** in 49% yield (Scheme 3.2). In this case, the use of the microwave reactor significantly improved the efficiency of the reaction; heating under similar conditions in an oil bath to 80 °C for 6 h provided less than 5% yield of the desired cyclopropanation product.

Strategically, the proposed carbonylation of the C–Si bond of **128** was to be attempted as the last synthetic step, as the reduction chemistry to prepare **127** was expected to be incompatible with the presence of the northern lactone. For practical reasons, however, we elected to investigate the carbonylation chemistry on β-ketonitrile **134**, since it was more readily available. The strategy involved the following sequence: activation of the silicon atom, transmetalation to yield an alkenyl metal species, and either capture with an acyl electrophile or migratory insertion into carbon monoxide. Although precedent existed for the elementary steps of this proposal,[8] to our knowledge, the specific use of carbon monoxide or acyl electrophiles had not been reported. We therefore viewed the development of the proposed transformation as an avenue to address a fundamental gap in silicon reagent-based cross coupling chemistry. An extensive methodological campaign was undertaken, and a variety of fluoride sources, metals and electrophiles were examined.

The results of the attempted carbonylation approach are summarized in Scheme 3.3. A multitude of different fluoride reagents was screened, in combination with various transition metals and carbonyl-containing electrophiles. None of the desired lactone product was ever isolated, and when conversion of the silyl ether occurred, only the protodesilyated (**136**) or ring-opened (**137**) compounds were observed. The sole successful reaction that resulted in productive cleavage of the C–Si bond of was the allylation of **134**, effected by TBAT and copper iodide in the presence of allyl chloride. Notably, no protodesilyation was observed, a problem that frequently plagued the attempted carbonylation. Unfortunately, when we employed the exact conditions with methyl cyanoformate as the electrophile, only full conversion to the acylated fluorosilane

product **139** was observed. We suspect that rather than alkoxide-directed transmetalation from silicon to copper, the oxyanion reacts irreversibly with methyl cyanoformate to produce **139** and prevent further reaction.

Scheme 3.3. *Carbonylation attempts*



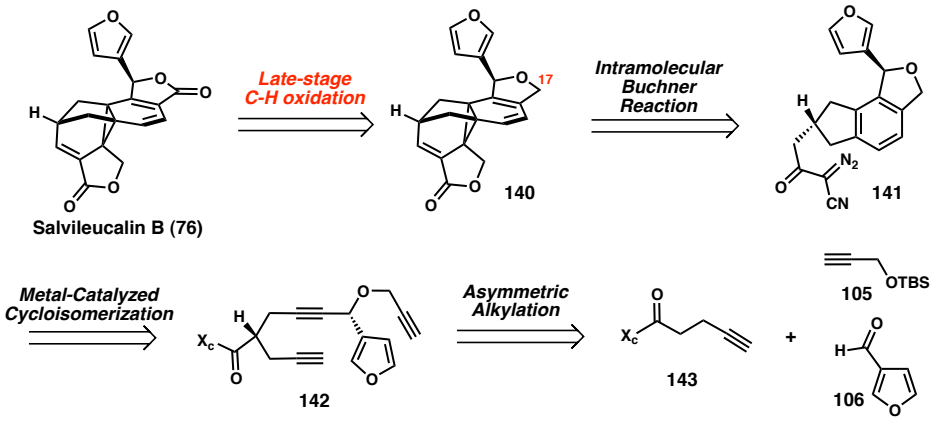
3.2 SECOND GENERATION APPROACH

3.2.1 Modification of Route

In light of our inability to effect a single step formation of the northern lactone from cyclic silyl ethers, we reconsidered our synthetic plan to access this moiety. We ultimately took inspiration from a serendipitous observation on the instability of **115** (see chapter 2); we found that the *iso*-dihydrofuran moiety **115** is prone to oxidation to the furan upon prolonged exposure to air. On the basis of these observations, it was hypothesized that the required lactone of **76** may be accessible by chemoselective allylic C–H oxidation at C(17) of *iso*-dihydrofuran **140** to the α,β-unsaturated lactone of the

natural product (Scheme 3.4). Although viewed as a potentially risky final step (*vide infra*), the revised retrosynthesis was highly attractive due to the great similarity to our previously developed route, for which the intermediates only lack the furan unit. Thus, norcaradiene **140** was expected to arise from arene cyclopropanation of α-diazo-β-ketonitrile **141**, the *des*-furan version of which had been previously accessed via cycloisomerization of triyne **142**.

Scheme 3.4. *Revised retrosynthetic analysis of salvileucalin B*

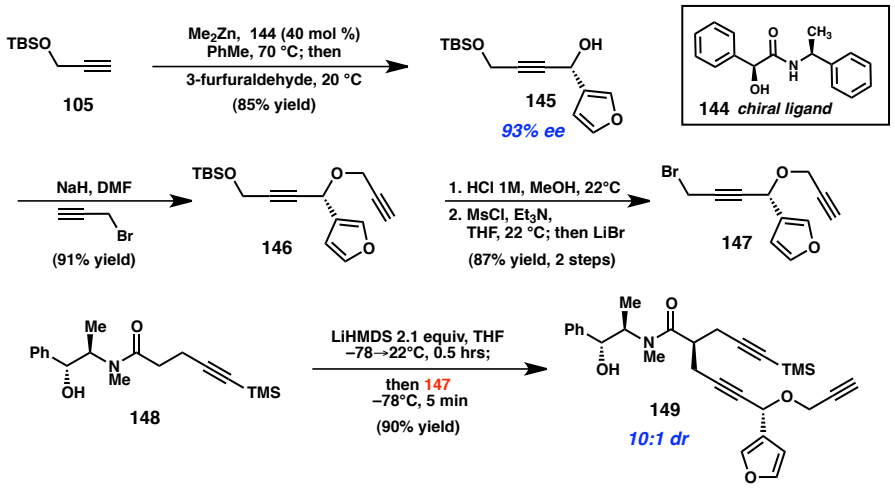


In spite of the anticipated advantages, we were not without some significant trepidation with regard to the final oxidation. Aside the potentially reactive diene and *exo*-methylene lactone, the main concern was the susceptibility of the furan to undergo oxidative transformations. It is known that furans can react with a range of oxidants, including molecular oxygen, peracids, hydrogen peroxide, and high-valent transition metals.[9] Nevertheless, we viewed the allylic C-17 protons as the most activated and sterically accessible hydrogens, and thus proceeded with our plan to target **140**.

3.2.2 Forward Synthesis

In order to access *des*-oxy salvileucalin **140** (Scheme 3.4) in an enantioselective fashion, we opted to employ asymmetric alkylation technology in the synthesis of triyne **149** (Scheme 3.5). In the forward sense, enantioselective 1,2-addition of the zinc acetylide derived from **105** to 3-furaldehyde (**106**) was promoted by chiral mandelamide ligand **144** to provide alcohol **145** in 85% yield and 93% ee.[10] Alcohol **145** was converted to the corresponding propargyl bromide (**147**) in a three-step sequence involving O-propargylation, deprotection of the silyl ether, and Finkelstein-type bromination.[11]

Scheme 3.5. *Enantioselective synthesis of triyne* ***149***

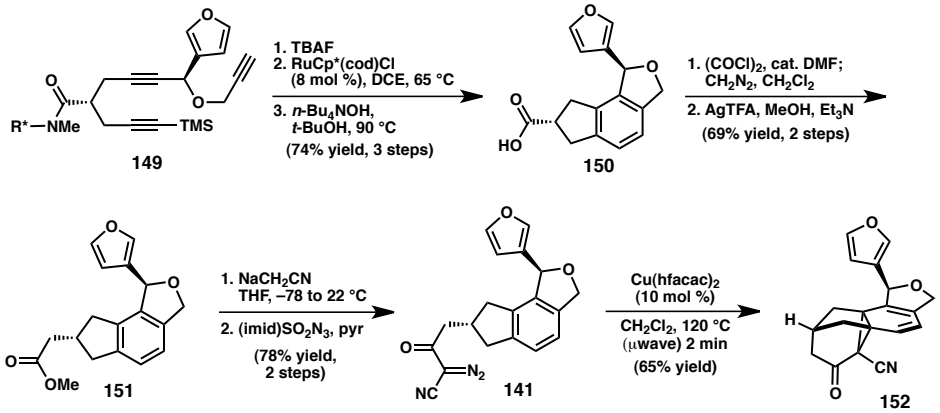


Alkylation of pseudoephedrine amide **148** with propargyl bromide **147** using the conditions developed by Myers and co-workers[12] provided triyne **149** in excellent yield and 10:1 dr (Scheme 3.5). Simultaneous cleavage of the alkynyl silane and saponification of the amide in substrate **149** could be achieved using 5 equiv of *n*-Bu_4NOH in aqueous *t*-BuOH at 90 °C; however, under these conditions, the carboxylic acid was isolated with

erosion of the dr (4:1). Efforts to identify conditions under which the amide could be hydrolyzed without competitive epimerization proved unsuccessful.

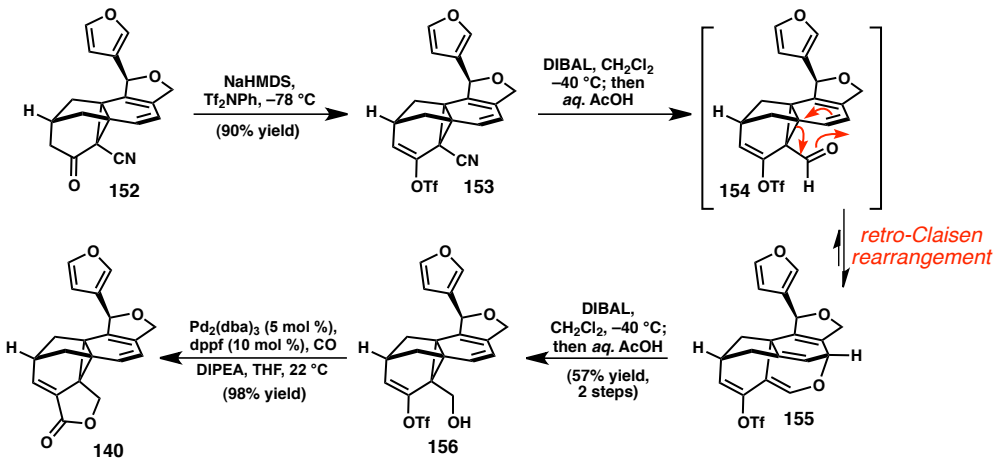
On the other hand, desilylation of alkyne **149** using TBAF followed by exposure of the triyne to a dichloromethane solution of RuCp*(cod)Cl catalyst smoothly effected the cycloisomerization (Scheme 3.6). At this stage, cleavage of the amide was realized without epimerization to furnish carboxylic acid **150** in 74% yield (over three steps) as a 10:1 mixture of diastereomers. With this sequence, gram quantities of tricycle **150** were easily prepared. Conversion of **150** to the α-diazoketone was followed by Arndt–Eistert homologation[7] in the presence of methanol to provide ester **151**. Treatment of ester **151** with the sodium salt of acetonitrile delivered the β-ketonitrile, which underwent diazo transfer with 1*H*-imidazole-1-sulfonyl azide[13] to give key diazo substrate **141**. We were pleased to find that exposure of α-diazo-β-ketonitrile **141** to 10 mol % $Cu(hfacac)_2$ under our previously optimized conditions[14] provided norcaradiene **152** in 65% yield. The structure of **152** was confirmed by single-crystal X-ray diffraction.

Scheme 3.6. *Synthesis of norcaradiene* ***152***



In order to advance norcaradiene **152** to **140**, our synthetic plan required a three-step sequence involving conversion to the enol triflate, chemoselective reduction of the nitrile to a hydroxymethyl group, and Pd-catalyzed intramolecular carbonylative cyclization.[1,15] To this end, ketone **152** was treated with NaHMDS at –78 °C and trapped with *N*-phenylbis(trifluoromethanesulfonimide) to provide the corresponding enol triflate **153** in 90% yield (Scheme 3.7). The enol triflate was treated with excess DIBAL at –40 °C and quenched with dilute aqueous acetic acid; however, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed that the major product was not the desired aldehyde **154**. After further analysis, the major product was tentatively assigned as vinyl ether **155**, the product of a retro-Claisen rearrangement.

Scheme 3.7. *Synthesis of norcaradiene* ***140***



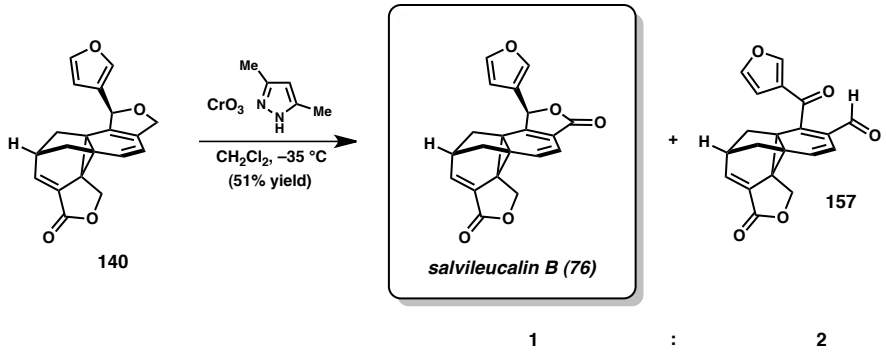
Elegant studies by Boeckman and co-workers[16] previously demonstrated that similar ring-opening Claisen rearrangements are reversible. Although the equilibrium heavily favors vinyl ether **155** (aldehyde **154** was not detected by ^{1}H NMR spectroscopy),

it was hypothesized that kinetic trapping of the presumed aldehyde **154** may be possible using an appropriate reducing agent. We were pleased to find that exposure of vinyl ether **155** to DIBAL at –40 °C resulted in rapid reduction to deliver primary alcohol **156**, which was isolated in 57% yield over two steps. Less Lewis acidic reductants such as $LiBH_4$ reacted with slower rates and resulted in lower yields of **156** due to competitive cleavage of the enol triflate. This observation is consistent with Boeckman and co-workers' finding that Lewis acids accelerate the retro-Claisen rearrangement.[16a] Vinyl ether **155** is sensitive to both light and oxygen; the moderate yield is attributed to some decomposition of **155** during workup. Attempts to promote the sequential reductions in a one-pot process by hydrolysis of the intermediate imine with a slight excess of protic acid followed by addition of a second DIBAL aliquot proved unfruitful. Subjection of triflate **156** to standard Pd-catalyzed carbonylation conditions[1] provided lactone **140** in excellent yield.

With access to the entire carbon skeleton of **76**, what remained was the allylic oxidation of the *iso*-dihydrofuran of **140** to the required lactone.[17] Allylic oxidations to provide 2-(5*H*)-furanones from *iso*-dihydrofurans are known in the literature,[18] although typically not with substrates containing other oxidation-sensitive functionality. Subjection of **140** to reagents such as SeO_2 and chromium(IV) species resulted in either undesired oxidation to the *bis*-furan or over-oxidation to ketoaldehyde **157**. After considerable experimentation, it was found that exposure of **140** to chromium trioxide–3,5-dimethylpyrazole complex[19] at –35 °C provided a 1:2 mixture of **76** and the isomeric ketoaldehyde **157**. The characterization data obtained for synthetic **76** were fully consistent with Takeya and co-workers' reported data for the natural compound.[20]

Although the yield of **76** was moderate, the implementation of this late-stage C–H oxidation circumvented the need for extraneous protecting-group and redox manipulations and thus represents a strategic advantage.[21]

Scheme 3.8. *Completion of first total synthesis of (+)-salvileucalin B*



3.3 CONCLUSIONS

In conclusion, the first total synthesis of (+)-salvileucalin B has been accomplished in 18 steps (longest linear sequence) from commercially available materials. These studies resulted in the development of a copper-catalyzed arene cyclopropanation reaction to access a norcaradiene bearing a fully substituted cyclopropane ring.

3.4 EXPERIMENTAL SECTION

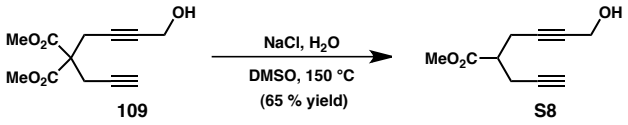
3.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), acetonitrile (MeCN), toluene and benzene were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves, MeOH was distilled over magnesium oxide and dichloroethane (DCE) was distilled over calcium hydride. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed either as described by Still et al. (Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.) using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. Microwave experiments were performed using a Biotage Initiator® microwave reactor. 1H and 13C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to internal CHCl3 (1H, δ = 7.26) or CDHCl2 (1H, δ = 5.32), and CDCl3 (13C, δ = 77.0) or CD2Cl2 (13C, δ = 53.8). Data for 1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer

Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Zorbax RX-SIL 5μm column (9.4 x 250 mm). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 220 nm. Analytical HPLC was performed on an Agilent 1290 Infinity Eclipse Plus C_{18} 1.8μm column (2.1 x 50 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

3.4.2 Substrate Preparation

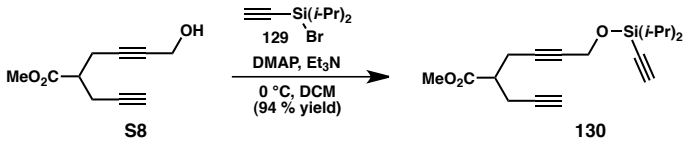
Preparation of S8



A 250 mL flask open to air was charged with diester **109** (4.95 g, 20.8 mmol), NaCl (1.30 g, 22.3 mmol), water (740 μL, 41.1 mmol) and DMSO (80 mL). The flask was fitted with a condenser and heated to 150 °C with vigorous stirring. Upon heating, the reaction darkened from light yellow to brown, and after 30 min at 150 °C was black. After heating for 11 h TLC analysis indicated consumption of the starting material, and reaction was cooled to 22 °C. The reaction was diluted with CH_2Cl_2 (500 mL) and washed with aqueous NaCl (2 x 250 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (0→80% EtOAc/hexanes) to afford

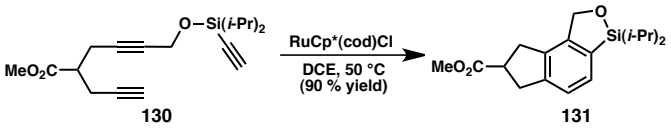
S8 (2.44 g, 65% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (dt, *J* = 6.1, 2.1 Hz, 2H), 3.74 (s, 3H), 2.76 (tt, *J* = 7.1, 5.9 Hz, 1H), 2.70 – 2.65 (m, 2H), 2.65 – 2.53 (m, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.48 (t, *J* = 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 81.5, 80.7, 80.3, 70.5, 52.1, 50.7, 42.9, 42.8, 20.1, 20.0, 19.8, 19.7. IR (NaCl/thin film): 3292, 2953, 2916, 1727. HRMS (FAB) calc'd for $C_{10}H_{13}O_3$ $[M+H]^+$ 181.0865, found 181.0860.

Preparation of Triyne 130



A freshly prepared solution of bromo(ethynyldiisopropyl)silane **129** (17.3 mmol) in CH_2Cl_2 (100 mL) was slowly added to a solution of alcohol **S8** (2.44 g, 13.5 mmol), triethylamine (3.80 mL, 27.3 mmol) and DMAP (330 mg, 2.7 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was allowed to warm up to 22 °C over a period of 24 h. The solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography (0→40% EtOAc/hexanes), yielding triyne **130** (4.03 g, 94% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (t, *J* = 2.1 Hz, 2H), 3.73 (s, 3H), 2.80 – 2.70 (m, 1H), 2.70 – 2.56 (m, 4H), 2.47 (s, 1H), 2.00 (t, *J* = 2.1 Hz, 1H), 1.12 – 0.96 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 95.5, 83.8, 81.5, 80.6, 80.4, 70.4, 53.0, 52.1, 43.2, 20.3, 20.0, 16.9, 16.8, 12.8. IR (NaCl/thin film): 2948, 2867, 2033, 1741, cm^{-1}; HRMS (ES+) calc'd for $C_{18}H_{26}O_3Si$ $[M+H]^+$ 319.1724, found 319.1719.

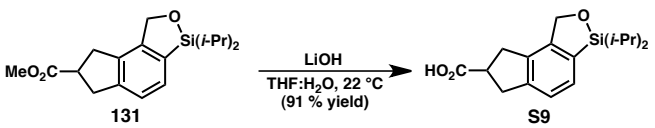
Preparation of Ester 131



130 131

A flame-dried 250 mL three-neck round bottom flask, equipped with condenser and magnetic stir bar, was charged with a degassed (3 freeze-pump-thaw cycles) solution of triyne **130** (4.00 g, 12.6 mmol) in dichloroethane (40 mL). A solution of RuCp*(cod)Cl (55.0 mg, 144 μmol) in DCE (10 mL) was prepared in a glove-box and slowly added to the triyne solution at 22 °C. **Warning**: Reaction is highly exothermic. Use of chilled (0 °C) water condenser is required. Upon completion of the catalyst addition the reaction was heated at 50 °C for 30 min. After cooling to 22 °C the solution was concentrated under reduced pressure, crude oil was purified by flash chromatography (0→15% EtOAc/hexanes) to afford **131** (3.61 g, 90% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 7.3 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 5.11 – 4.92 (m, 2H), 3.74 (s, 3H), 3.39 (quintet, J = 8.6 Hz, 1H), 3.35 – 3.18 (m, 2H), 3.18 – 2.98 (m, 2H), 1.29 – 1.13 (m, 2H), 1.13 – 0.90 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 146.6, 143.5, 134.6, 130.6, 129.7, 123.0, 71.1, 52.0, 43.1, 36.1, 33.9, 17.0, 17.0, 13.1, 13.1. IR (NaCl/thin film): 2944, 2864, 1738 cm^{-1}; HRMS (ES+) calc'd for $C_{18}H_{27}O_3Si$ $[M+H]^+$ 319.1729, found 319.1717.

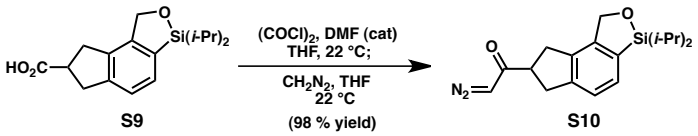
Preparation of Acid S9



131 S9

To a solution of ester **131** (1.70 g, 5.34 mmol) in THF (40 mL) at 22 °C was added solution of LiOH (0.26 g, 11 mmol) in H_2O (20 mL). The resulting heterogeneous mixture was stirred vigorously for 60 min, after which time the reaction became homogeneous. TLC analysis indicated consumption of starting material. The reaction was diluted with CH_2Cl_2 (250 mL) and washed with aqueous 1M HCl (ca. 100 mL), saturated aqueous NaCl (ca. 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure afford acid **S9** (1.59 g, 98% yield) as a yellow oil which was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 5.09 – 4.99 (m, 2H), 3.44 (tt, *J* = 9.3, 8.0 Hz 1H), 3.38 – 3.26 (m, 2H), 3.21 – 3.06 (m, 2H), 1.24 – 1.14 (m, 2H), 1.01 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1, 146.5, 143.30, 134.4, 130.7, 129.8, 123.0, 71.1, 43.0, 36.0, 33.7, 17.0, 13.1, 13.1. IR (NaCl/thin film): 3023, 2944, 2864, 1734, 1707 cm^{-1}. HRMS (ES+) calc'd for $C_{17}H_{23}O_3Si$ $[M - H]^-$ 303.1422, found 303.1427.

Preparation of Diazo Ketone S10

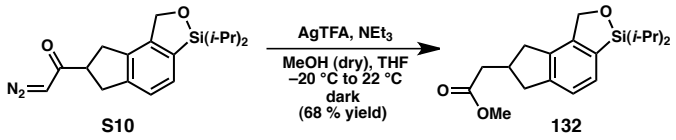


S9 S10

A flame-dried 25 mL flask containing acid **S9** (131 mg, 0.430 mmol) was charged with THF (5 mL) under N_2. To the resulting solution was added 1 drop of DMF, followed by oxalyl chloride (73 μL, 0.86 mmol) at 22 °C. Within 10 min gas evolution stopped and solvent was removed under the reduced pressure, followed by azeotroping with 3 x 10 mL anhydrous benzene to remove traces of residual HCl. ^{1}H NMR analysis confirmed clean conversion of the starting acid **S9** to the acid chloride. The resulting yellow oil was

diluted with THF (10 mL) under N_2. Diazomethane (~5-6 mmol, solution in Et_2O) was briefly dried over KOH (5 min) and carefully decanted at 0 °C into a 50 mL Erlenmeyer flask. The acid chloride/THF solution was then transferred via Teflon cannula to excess diazomethane at 0 °C with gentle stirring, resulting in steady gas evolution. The solution was warmed to 22 °C over the period of 10 h. TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure (with AcOH in the trap to quench any unreacted CH_2N_2). The crude yellow oil was purified by flash chromatography (4:1 EtOAc/hexanes), yielding diazo ketone **S10** (130 mg, 98% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 5.32 (br. s, 1H), 5.12 – 4.92 (m, 2H), 3.37 (br. s, 1H), 3.28 (dd, *J* = 16.1, 7.7 Hz, 1H), 3.20 (dd, *J* = 16.0, 9.2 Hz, 1H), 3.10 (dd, *J* = 15.7, 7.6 Hz, 1H), 3.00 (dd, *J* = 15.8, 9.0 Hz, 1H), 1.32 – 1.13 (m, 2H), 1.03-0.97 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 146.6, 143.4, 134.5, 130.7, 129.8, 123.0, 71.2, 54.0, 49.1, 36.0, 33.8, 17.0, 13.10, 13.08. IR (NaCl/thin film): 2942, 2863, 2104, 1641 cm^{-1}. HRMS (ES+) calc'd for $C_{18}H_{25}N_2O_2Si$ $[M+H]^+$ 329.1685, found 329.1676.

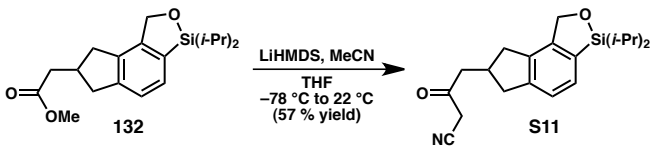
Preparation of Methyl Ester 132



A 25 mL flame-dried flask was charged with diazo ketone **S10** (87 mg, 0.27 mmol). Dry benzene (10 mL) was added and evaporated under vacuum. The azeotropic procedure was repeated two additional times. The resulting material was dried under high

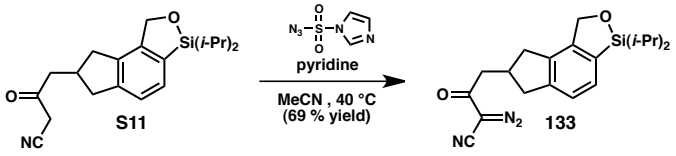
vacuum for 30 min then dissolved in THF (3 mL) and dry MeOH (300 μL) was added. The flask was covered in foil and cooled to –20 °C. A solution of silver trifluoroacetate (6.0 mg, 0.03 mmol) in Et_3N (110 μL, 0.80 mmol) was added in one portion to the diazo ketone solution at –20 °C. (Note: vigorous stirring during Et_3N addition is critical to ensure dissolution of silver salt. Lack of stirring can result in a brown silver clump and incomplete dissolution. When dissolved one obtains a clear tan solution). The reaction was slowly warmed over 4 h to 22 °C (starting material consumption was confirmed by TLC). The reaction was diluted with diethylether (15 mL) quenched with 1M HCl (2 mL). The aqueous layer was extracted with 20 mL Et_2O, and the combined organics were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude brown oil was purified by flash chromatography (8:1 EtOAc/hexanes), yielding ester **132** (60 mg, 68% yield) as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.3 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 5.14 – 4.89 (m, 2H), 3.70 (s, 3H), 3.18 (dd, J = 15.9, 7.9 Hz, 1H), 3.01 (dd, J = 15.5, 8.0 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.68 (dd, J = 15.9, 7.4 Hz, 1H), 2.58 – 2.49 (m, 2H), 2.50 (dd, J = 15.9, 6.9 Hz, 1H), 1.35 – 1.11 (m, 2H), 1.11 – 0.82 (m, 12H); IR (NaCl/thin film): 2943, 2864, 1739 cm^{-1}; HRMS (ES+) calc'd for $C_{19}H_{29}O_3Si$ $[M+H]^+$ 333.1886, found 333.1875.

Preparation of β-Ketonitrile S11



A flame-dried 25 mL flask was charged with LiHMDS (1M solution in THF, 780 μL, 0.78 mmol) and THF (2 mL), and cooled to –78 °C. MeCN (48 μL, 0.90 mmol) was added dropwise and solution was stirred at –78 °C for 30 min. Ester **132** (120 mg, 0.36 mmol) in THF (3 mL) was added dropwise and resulting solution was left at –78 °C for 60 min then warmed to 22 °C. TLC analysis showed complete consumption of starting material. Et_2O (50 mL) was added and the reaction was quenched by the addition of aqueous saturated NH_4Cl (ca. 20 mL). The organic layer dried $MgSO_4$ and concentrated under reduced pressure. The crude yellow oil was purified by flash chromatography (0→40% EtOAc/hexanes) to yield β-ketonitrile **S11 (**105 mg, 90% yield) as a colorless oil. NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 5.10 – 4.86 (m, 2H), 3.48 (s, 2H), 3.22 (dd, *J* = 15.9, 7.9 Hz, 1H), 3.05 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.04 – 2.92 (m, 1H), 2.92 – 2.80 (m, 2H), 2.62 (dd, *J* = 15.9, 7.1 Hz, 1H), 2.43 (dd, *J* = 15.5, 6.7 Hz, 1H), 1.30 – 1.11 (m, 2H), 1.12 – 0.77 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 146.7, 144.0, 135.1, 130.4, 129.6, 123.1, 113.6, 71.2, 48.0, 38.7, 36.4, 34.2, 32.2, 17.00, 16.99, 16.97, 13.1. IR (NaCl/thin film): 2943, 2864, 2261, 1732 cm^{-1}; HRMS (ES+) calc'd for $C_{20}H_{28}NO_2Si$ $[M+H]^+$ 342.1889, found 342.1881.

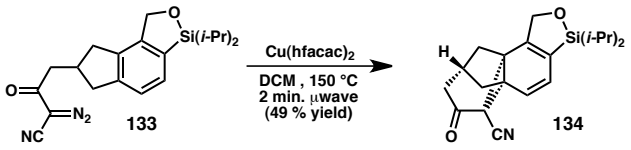
Preparation of Diazo β-Ketonitrile 133



Pyridine (120 mL, 1.5 mmol) was added to a solution of imidazole-1-sulfonyl azide (61 mg, 0.35 mmol) and β-ketonitrile **S11** (100 mg, 0.29 mmol) in MeCN (6 mL).

Reaction mixture was stirred at 40 °C for 12 h, after which time TLC analysis confirmed consumption of the starting β-ketonitrile **S11**. The solvent was removed under reduced pressure and crude residue was purified by flash chromatography (0→20% EtOAc/hexanes), yielding α-diazo-β-ketonitrile **133** (85 mg, 79% yield) as a yellow oil. NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 5.15 – 4.86 (m, 2H), 3.21 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.12 – 2.93 (m, 2H), 2.93 – 2.76 (m, 2H), 2.69 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.60 – 2.41 (m, 1H), 1.28 – 1.15 (m, 2H), 1.04 – 0.96 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 146.7, 144.0, 135.1, 130.5, 129.6, 123.1, 108.4, 71.2, 57.5, 45.1, 38.8, 36.4, 35.3, 17.0, 13.1); IR (NaCl/thin film): 2942, 2864, 2222, 2128, 1678cm^{-1}; HRMS (ES+) calc'd for $C_{20}H_{26}NO_2Si$ $[M–N_2+H]^+$ 340.1738, found 340.1718.

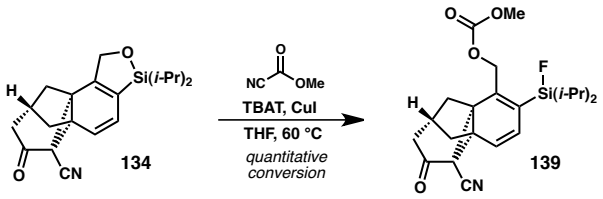
Cyclopropanation of α-Diazo-β-Ketonitrile 133



A 5 mL microwave vial equipped with a stir bar was charged with α-diazo-β-ketonitrile **133** (10.0 mg, 0.027 mmol) in CH_2Cl_2 (2 mL). $Cu(hfacac)_2$ (1.3 mg, 0.03 mmol) in CH_2Cl_2 (0.7 mL) was added via syringe through the septa of the sealed vial. The vial was placed into the microwave reactor and heated to 150 °C for 2 min (ramp from 22 °C to 120 °C required 2 min). TLC analysis confirmed consumption of the starting material. The solvent was concentrated under reduced pressure, and the crude residue was purified by flash chromatography (1:3 EtOAc/hexanes), yielding

norcaradiene **134** (4.5 mg, 49% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 9.1 Hz, 1H), 6.18 (dd, *J* = 9.2, 0.9 Hz, 1H), 4.91 (dd, *J* = 16.6, 0.6 Hz, 1H), 4.72 (d, *J* = 16.6 Hz, 1H), 2.55 – 2.36 (m, 1H), 2.36 – 2.28 (m, 2H), 2.19 (d, *J* = 3.0 Hz, 2H), 2.17 (d, *J* = 5.2 Hz, 1H), 2.10 (d, *J* = 12.7 Hz, 1H), 1.23 – 1.07 (m, 2H), 1.06 –1.00 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 149.1, 128.9, 128.1, 122.1, 111.9, 72.6, 51.0, 48.3, 43.4, 36.0, 34.5, 30.0, 26.1, 17.04, 16.98, 16.7, 16.6, 13.0, 12.9. IR (NaCl/thin film): 2943, 2864, 2239, 2128, 1699 cm^{-1}; HRMS (ES+) calc'd for $C_{20}H_{26}NO_2Si$ $[M+H]^+$ 340.1733, found 340.1720.

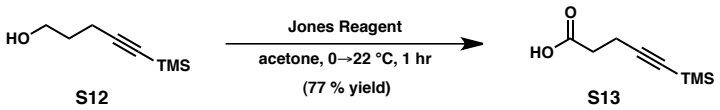
Preparation of Fluorosilane 139



A 1 mL microwave vial equipped with a stir bar was charged with α-keto-α-cyanocyclopropane **134** (2.5 mg, 0.007 mmol), CuI (1.7 mg, 0.009 mmol), and tetra-*n*-butylammonium difluorotriphenylsilicate (6.0 mg, 0.011 mmol). The vial was sealed and flushed with nitrogen, and Mander's reagent (0.8 mL, 0.009 mmol) in THF (1.0 mL) was added via syringe through the septa of the sealed vial. The vial was heated to 60 °C for 2 hours, at which point TLC analysis confirmed consumption of the starting material. The reaction was filtered and the solvent was concentrated under reduced pressure. The crude residue was purified by preparative thin-layer chromatography (1:2 EtOAc/hexanes), yielding norcaradiene **139**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (d, *J* = 9.4 Hz, 1H), 6.24 (d, *J* = 9.4 Hz, 1H), 5.09 (d, *J* = 12.7 Hz, 1H), 4.95 (d, *J* = 12.7 Hz, 1H), 3.80 (s, 3H),

2.34 (m, 3H), 2.29 (m, 2H), 2.19 (m, 2H), 1.24 (m, 2H), 1.12 (dd, J = 7.2, 1.6 Hz, 6H), 1.05 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.58, 155.35, 138.91, 129.17, 123.20, 111.83, 109.98, 68.13, 55.15, 51.34, 49.72, 43.40, 36.40, 35.45, 29.54, 25.41, 16.71, 16.46, 13.00, 12.38. IR (NaCl/thin film): 2937, 2848, 2239, 1743, 1694, 1343, 1034 cm^{-1}; HRMS (FAB+) calc'd for $C_{22}H_{29F}O_4NSi$ $[M+H]^+$ 418.1850, found 418.1860.

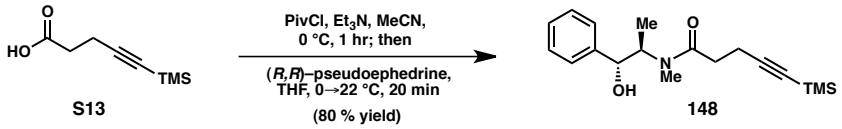
Preparation of Carboxylic Acid S13



To a 250 mL round-bottom flask containing acetone (15 mL) at 0 °C was added Jones reagent (21.4 mL, 64 mmol, approximately 3M). Alcohol **S12** (4.55 g, 29.1 mmol) in acetone (50 mL) was added dropwise via cannula to the vigorously stirred Jones reagent solution at 0 °C over 35 minutes. Upon completion of the addition the resulting thick green slurry was warmed to 22 °C, and stirred for 1 hour. After consumption of the starting material (TLC analysis), the reaction was quenched with isopropanol (2 mL). The reaction was filtered through a plug of celite and washed with 10 x 20 mL portions of acetone. The combined filtrates were concentrated *in vacuo*, and the resulting residue was partitioned between Et_2O and water. The aqueous layer was separated, back-extracted twice with Et_2O, and then basified with solid potassium carbonate and sodium bicarbonate such that the pH did not exceed 10 (Note: a pH exceeding 10 can result in silyl cleavage, the product of which is difficult to separate from **S13**). The basic aqueous layer was washed once with Et_2O, then acidified to pH 1 with aqueous 1M HCl and extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$,

filtered, and concentrated *in vacuo* to provide 3.85 g (77% yield) of acid **S13** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 – 2.50 (m, 4H), 0.13 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.65, 104.52, 85.69, 77.25, 76.75, 33.16, 15.49, -0.00. IR (NaCl/thin film): 3017, 2928, 2858, 2173 cm^{-1}; HRMS (EI+) calc'd for $C_7H_{11}O_2Si$ [M–CH_3] 155.0528, found 155.0555.

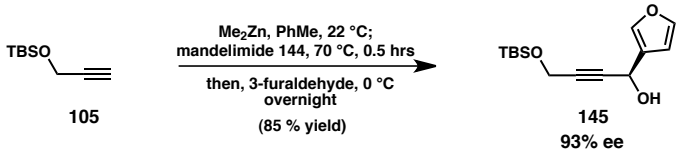
Preparation of Amide 148



To a flame-dried 500 mL round-bottom flask under N_2 containing acid **S13** (3.18 g, 18.7 mmol) was added MeCN (80 mL). After cooling to 0 °C, triethylamine (6.5 mL, 46.8 mmol) and pivaloyl chloride (2.35 mL, 19.0 mmol) were added successively, resulting in the formation of a thick yellow slurry, which was stirred for 1 hour at the same temperature. In a separate flask, (*R,R*)-pseudoephedrine was dissolved in THF (80 mL) under N_2, and transferred via cannula to the mixed anhydride at 0 °C. The reaction was warmed to 22 °C over 1.5 hours, and quenched with water and aqueous 1M HCl after consumption of starting material (TLC analysis). The volatiles were concentrated *in vacuo*, and the residue was partitioned between EtOAc and brine. The aqueous layer was separated and backextracted once with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0 → 50% EtOAc/hexanes) to provide 4.75 g (80% yield) of amide **148** as a light yellow oil. $[\alpha]^{25}_{D}$ –76.1° (*c* 0.96, CH_2Cl_2); ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor peaks, 500 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 10H), 4.58 (t, *J* =

7.6 Hz, 2H), 4.49 (s, 1H), 4.03* (dd, *J* = 8.7, 6.9 Hz, 1H), 2.92* (s, 3H), 2.85 (s, 3H), 2.74 (m, 1H), 2.65 – 2.44 (m, 7H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.99* (d, *J* = 6.8 Hz, 3H), 0.15* (s, 9H), 0.14 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.26, 172.16*, 142.19, 141.06*, 128.73, 128.47*, 128.40, 127.75, 126.88, 126.42, 106.53*, 105.94, 85.03, 84.78*, 77.20*, 76.41, 75.48*, 58.29*, 58.16, 33.41, 32.74*, 32.47*, 26.83*, 16.13*, 15.92, 15.37*, 14.43, 0.12*, 0.06. IR (NaCl/thin film): 3392, 3064, 3031, 2959, 2899, 2176 cm^{-1}; HRMS (FAB+) calc'd for $C_{18}H_{28}NO_2Si$ [M+H] 318.1889, found 318.1896.

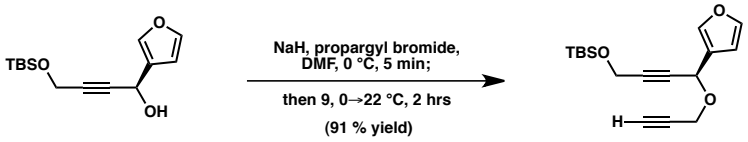
Preparation of Propargyl Alcohol 145



To a flame-dried 1L flask under N_2 were added PhMe (110 mL), alkyne **105** (25.6 mL, 126 mmol) and Me_2Zn (100 mL, 120 mmol, 1.2M in PhMe) successively at 22 °C. The clear solution was stirred for 30 minutes at 22 °C. To a separate flame-dried 500 mL flask was added the mandelimide **144** (3.06 g, 12 mmol) and PhMe (110 mL), followed by heating to 70 °C to effect complete dissolution of the solids. This clear solution was transferred via cannula to the zinc-acetylide solution at 22 °C. After heating at 70 °C for 30 minutes the reaction was cooled to 0 °C and neat 3-furaldehyde (**106**, 2.60 mL, 30 mmol) was added dropwise. The reaction was allowed to warm to 22 °C over 12 hours. After consumption of starting material (TLC analysis) the reaction (yellow slurry) was cooled to 0 °C and quenched carefully with aqueous 1M HCl (125 mL) until vigorous bubbling ceased (CAUTION! Methane gas evolves). The aqueous layer was separated

and back-extracted three times with PhMe. The combined organics layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 30% EtOAc/hexanes) to provide 6.9 g (85% yield, 93% ee) of alcohol **145** as a light yellow oil. The enantiomeric excess was determined by chiral HPLC analysis (OD-H, 1 mL/min, 10% IPA in hexanes, λ = 220 nm). $[\alpha]^{25}_{D}$ +7.5° (*c* 1.78, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.40 (t, *J* = 1.7 Hz, 1H), 6.51 (dd, *J* = 1.8, 0.9 Hz 1H), 5.43 (br s, 1H), 4.39 (d, *J* = 1.8 Hz, 2H), 0.91 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.55, 140.12, 126.24, 109.11, 83.88, 83.85, 57.29, 51.65, 25.76, 18.25, –5.18. IR (NaCl/thin film): 3367, 2955, 2930, 2886, 2858 cm^{-1}; HRMS (FAB+) calc'd for $C_{14}H_{21}O_3Si$ [M+H]-H_2 265.1260, found 265.1265.

Preparation of propargyl ether 146

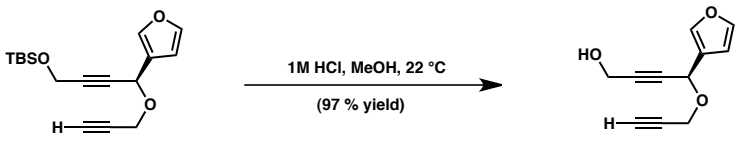


145 146

To a flame-dried 250 mL flask in a glovebox was added sodium hydride (95%, 388 mg, 15.3 mmol). The flask was removed from the box and placed under N_2 on the bench. DMF (45 mL) was charged to the flask, and the grey suspension was cooled to 0 °C. Propargyl bromide (80% wt PhMe, 4.9 mL, 43.8 mmol) was added to the NaH slurry, immediately after which alcohol **145** (3.89 g, 14.6 mmol) in DMF (30 mL) was transferred to the reaction via cannula. The orange suspension was warmed to 22 °C and allowed to stir for 2 hours. After consumption of starting material (TLC analysis) the reaction was quenched with saturated aqueous NH_4Cl and the aqueous layer extracted

five times with hexane. The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 10% EtOAc/hexanes) to provide 4.0 g (91% yield) of propargyl ether **146** as a light yellow oil. $[\alpha]^{25}_D$ +60.4° (*c* 1.55, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.40 (t, *J* = 1.7 Hz, 1H), 6.50 (dd, *J* = 1.8, 0.6 Hz, 1H), 5.43 – 5.41 (m, 1H), 4.40 (d, *J* = 1.7 Hz, 2H), 4.34 (dd, *J* = 15.7, 2.4 Hz, 1H), 4.25 (dd, *J* = 15.7, 2.4 Hz, 1H), 2.45 (t, *J* = 2.4 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.52, 141.11, 123. 38, 109.53, 85.49, 80.92, 79.15, 74.86, 62.53, 54.91, 51.66, 25.76, 18.25, –5.18. IR (NaCl/thin film): 3297, 3146, 2955, 2929, 2893, 2857, 2114 cm^{-1}; HRMS (EI+) calc'd for $C_{17}H_{24}O_3Si$ [M+•] 304.1495, found 304.1446.

Preparation of alcohol S14

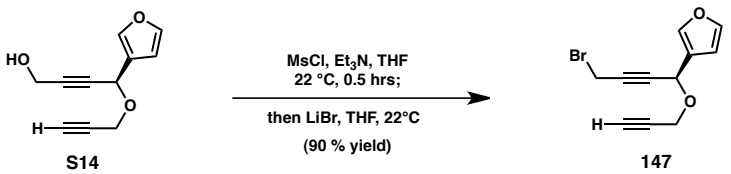


146 **S14**

To a 250 mL flask containing propargyl ether **146** (4.00 g, 13.2 mmol) was added aqueous 1M HCl (400 μL). The clear yellow reaction was stirred open to air at 22 °C for 4 hours, at which point TLC analysis indicated full consumption of starting material. The reaction was neutralized and dried with solid $NaHCO_3$ and Na_2SO_4, filtered, concentrated and purified by silica gel chromatography (0 → 40% EtOAc/hexanes) to provide 2.43 g (97% yield) of alcohol **S14** as a yellow oil. $[\alpha]^{25}_D$ +78.3° (*c* 3.40, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.41 (t, *J* = 1.7 Hz, 1H), 6.50 (dd, *J* = 1.8, 0.7 Hz, 1H), 5.43 (br s, 1H), 4.37 (dd, *J* = 6.2, 1.6 Hz, 2H), 4.33 (dd, *J* = 15.7, 2.4 Hz,

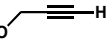
1H), 4.24 (dd, *J* = 15.7, 2.4 Hz, 1H), 2.47 (t, *J* = 2.4 Hz, 1H), 1.58 (t, *J* = 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.60, 141.12, 123.01, 109.37, 84.97, 81.78, 78.95, 75.10, 62.38, 54.88, 50.73. IR (NaCl/thin film): 3400, 3292, 3148, 2914, 2861, 2117 cm^{-1}; HRMS (EI+) calc'd for $C_{11}H_{10}O_2$ [M+•] 190.0630, found 190.0614

Preparation of bromide 147

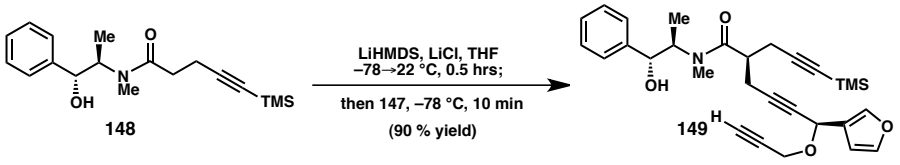


S14 147

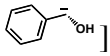
To a flame-dried 1 L flask under N_2 containing alcohol **S14** (3.33 g, 17.5 mmol) was added THF (300 mL), MsCl (1.50 mL, 19.3 mmol) and Et_3N (2.93 mL, 21.0) at 22 °C. Upon addition of Et_3N a slurry immediately resulted, and this was stirred for 35 minutes. In a separate flame-dried 1 L flask LiBr (6.09 g, 70.1 mmol) was dissolved in THF (50 mL). The mesylate solution was transferred via a fritted funnel to the flask containing LiBr/THF with a THF (50 mL) wash. The resulting murky orange solution was stirred under N_2 at 22 °C for 12 hours, after which time most of the THF was concentrated *in vacuo*, and the residue was diluted with brine and extracted three times with hexane. The combined organics layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 10% EtOAc/hexanes) to provide 4.0 g (90% yield) of bromide **147** as a light yellow oil. $[\alpha]^{25}_D$ +73.5° (*c* 1.57, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.41 (t, *J* = 1.7 Hz, 1H), 6.50 (dd, *J* = 1.7, 0.7 Hz, 1H), 5.44 (br s, 1H), 4.32 (dd, *J* = 15.7, 2.4 Hz, 1H), 4.24 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.98 (d, *J* = 1.9 Hz, 2H), 2.48 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 143.66, 141.20, 122.89, 109.42, 83.13, 81.71, 78.93, 75.13, 62.43, 55.04, 13.72. IR (NaCl/thin film): 3293, 3148, 3007, 2957, 2904, 2856, 2117 cm^{-1}; HRMS (EI+) calc'd for cationic fragment C_8H_6OBr [M– ] 196.9602, found 196.9637.

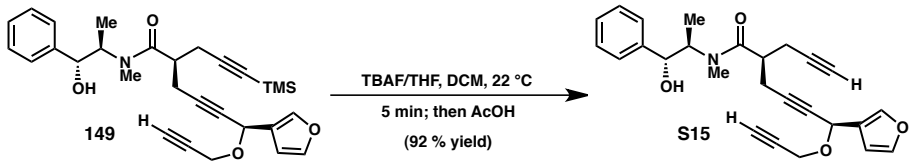
Preparation of triyne 149



To a flame-dried 250 mL flask in a glovebox was added LHMDS (97%, 3.28 g, 19.6 mmol) and LiCl (1.72 g, 40.5 mmol). The flask was sealed and placed under N_2 on the bench. THF (10 mL) was added at 22 °C, and the thin slurry was cooled to –78 °C. To a 100 mL flask containing amide **148** (3.00 g, 9.45 mmol) THF (60 mL) was charged, and the solution was cannula transferred to the LHMDS/LiCl solution at –78 °C. The light copper colored solution was warmed to 22 °C, and held at this temperature for 30 minutes. The reaction was re-cooled to –78 °C, and bromide **147** (1.71g, 6.75 mmol) in THF (20 mL) was cannula transferred to the amide enolate with a 10 mL THF wash. After 10 minutes the reaction was judged complete by TLC, and was quenched with aqueous saturated NH_4Cl and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 40% EtOAc/hexanes) to provide 3.29 g (90% yield) of triyne **149** as a light yellow oil. $[\alpha]^{25}_D$ –4.2° (*c* 3.25, CH_2Cl_2); ^{1}H NMR (2.5:1 rotamer ratio, asterisk denotes minor peaks, 500 MHz, $CDCl_3$) δ 7.55* (s, 1H), 7.49 – 7.48 (m, 1H), 7.41 – 7.26 (m, 12H), 6.51* (dd, *J* = 1.7, 0.6 Hz, 1H)), 6.46 (dd, *J* = 1.7, 0.6 Hz, 1H), 5.37* (br s,

1H), 5.32 (br s, 4H), 4.62 – 4.51 (m, 3H), 4.34 – 4.25 (m, 3H), 4.18 (dd, *J* = 15.7, 2.4 Hz, 2H), 3.75 – 3.60 (br s, 2H), 3.35* (app qnt, *J* = 7.4 Hz, 1H), 3.14 (app qnt, *J* = 7.4 Hz, 1H), 2.98 (s, 3H), 2.96* (s, 3H), 2.64 – 2.48 (m, 8H), 2.45 – 2.42 (m, 2H), 1.06 – 1.01 (m, 6H), 0.15 (s, 9H), 0.08* (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.67, 173.91*, 143.53, 143.49*, 141.84, 141.32, 141.13*, 141.04, 128.73, 128.39*, 128.34, 127.76, 126.84, 126.60, 123.61*, 123.58, 109.58*, 109.42, 103.98*, 103.69, 86.81, 86.34*, 85.17*, 84.20, 79.35*, 79.14, 78.25, 78.11*, 75.89, 75.40*, 74.88, 74.83*, 62.62*, 62.49, 58.42*, 58.26, 54.78, 54.65*, 40.93, 40.27*, 32.62, 30.70, 29.65*, 27.44, 23.26*, 23.13, 22.15*, 21.71, 16.02*, 14.30, -0.02*, -0.08. IR (NaCl/thin film): 3400, 3294, 3146, 3062, 3029, 2959, 2901, 2856, 2281, 2228, 2174, 2115, 1625 cm^{-1}; HRMS (EI+) calc'd for cationic fragment $C_{22}H_{28}NO_3Si$ [M– ] 382.1833, found 382.1819.

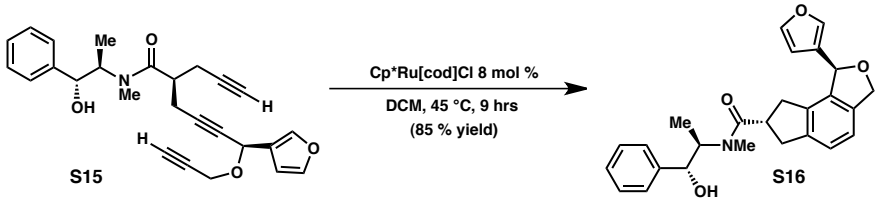
Preparation of triyne S15



To a 100 mL flask containing triyne **149** (3.42 g, 6.98 mmol) was added DCM (50 mL). TBAF (1M THF, 7.12 mL, 7.12 mmol) was charged to the yellow solution at 22 °C, resulting in an immediate color change to light brown. After 5 minutes TLC analysis indicated complete consumption of starting material, and the reaction was quenched with acetic acid (450 μL). The solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography (0 → 40% EtOAc/hexanes) to provide 2.77 g (92% yield) of triyne **S15** as a light yellow oil. $[\alpha]^{25}_{D}$ –8.1° (*c* 1.75, CH_2Cl_2); ^{1}H NMR (2.5:1 rotamer

ratio, asterisk denotes minor peaks, 500 MHz, $CDCl_3$) δ 7.55 – 7.54* (m, 1H), 7.48 (dt, *J* = 1.5, 0.8 Hz, 1H), 7.40 – 7.25 (m, 12H), 6.50* (d, *J* = 1.1 Hz, 1H), 6.46 (dd, *J* = 1.7, 0.6 Hz, 1H), 5.36* (br s, 1H), 5.32 (br s, 1H), 4.64 (s, 1H), 4.57 (d, *J* = 8.4 Hz, 2H), 4.33 – 4.24 (m, 2H), 4.24 – 4.15 (m, 3H), 3.61 (br s, 1H), 3.31* (app qnt, *J* = 7.0 Hz, 1H), 3.15 (app qnt, *J* = 7.3 Hz, 1H), 2.96 (s, 3H), 2.95* (s, 3H), 2.70 – 2.39 (m, 12H), 2.04 (t, *J* = 2.6 Hz, 1H), 1.96* (t, *J* = 2.6 Hz, 1H), 1.04* (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.44, 173.64*, 143.53, 143.48*, 141.64, 141.27, 141.20*, 141.01, 128.72, 128.36, 127.82, 126.78*, 126.61, 123.63*, 123.56, 109.56, 109.40, 85.05*, 83.98, 81.48*, 81.38, 79.33*, 79.11, 78.35, 78.18*, 77.20*, 75.86, 75.40*, 74.89, 74.83*, 70.29, 70.01*, 62.61*, 62.46, 58.21*, 57.64, 54.78, 54.66*, 40.76, 40.06*, 32.15, 27.51*, 21.95*, 21.70*, 21.62, 21.59, 15.84*, 14.22. IR (NaCl/thin film): 3394, 3290, 2977, 2913, 2848, 2590, 2228, 2114, 1622 cm^{-1}; HRMS (EI+) calc'd for $C_{26}H_{27}NO_4$ [M+•] 417.1940, found 417.1939.

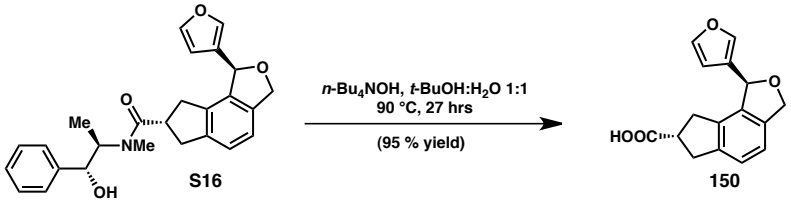
Preparation of arene S16



To a flame-dried 500 mL flask containing triyne **S15** (2.70 g, 6.47 mmol) was added DCM (100 mL). In a glovebox, Cp*Ru[cod]Cl (50 mg, 0.13 mmol) was dissolved in DCM (10 mL), and the clear brown catalyst solution was added in one portion to the triyne at 45 °C. After 2 hours an additional 50 mg of catalyst (2 mol %) was charged as a DCM solution, and this was repeated two times until the starting material was completely

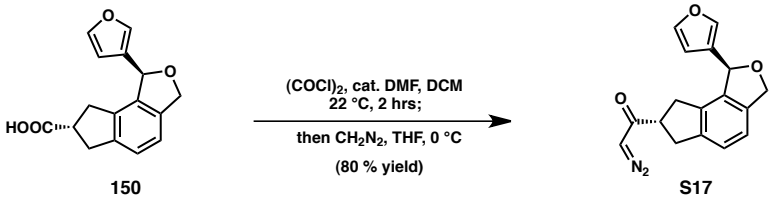
consumed (HPLC analysis, 4 x 2 mol % catalyst additions total). The solvent was then concentrated *in vacuo*, and the residue was purified by silica gel chromatography (0 → 50% EtOAc/hexanes) to provide 2.3 g (85% yield) of arene **S16** as a yellow oil. $[\alpha]^{25}_{D}$ – 9.7° (*c* 0.86, CH_2Cl_2); ^{1}H NMR (2.2:1 rotamer ratio, asterisk denotes minor peaks, 500 MHz, $CDCl_3$) δ 7.49* (s, 1H), 7.45 (s, 1H), 7.43* (t, *J* = 1.5 Hz, 1H), 7.37 (t, *J* = 1.7 Hz, 1H), 7.36 – 7.22 (m, 10H), 7.16 – 7.11 (m, 2H), 7.09 – 7.04 (m, 2H), 6.27* (d, *J* = 1.1 Hz, 1H), 6.22 (d, *J* = 1.2 Hz, 1H), 6.12 (br s, 2H), 5.22 (dd, *J* = 11.9, 1.7 Hz, 2H), 5.10 (d, *J* = 11.9 Hz, 2H), 4.64 – 4.59 (m, 1H), 4.57 (d, *J* = 8.6 Hz, 1H), 4.49 (s, 1H), 4.07 – 3.97 (m, 1H), 3.53* (app qnt, *J* = 8.5 Hz, 1H), 3.40 (app tt, *J* = 8.9, 7.0 Hz 1H), 3.26 – 3.04 (m, 5H), 2.94* (s, 3H), 2.93 – 2.89 (m, 1H), 2.88 (s, 3H), 2.73* (dd, *J* = 16.3, 8.9 Hz, 1H), 2.64 (dd, *J* = 16.3, 9.0 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.03* (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.89, 175.40*, 143.59, 143.55*, 142.35, 141.70, 141.12*, 140.74, 140.69, 137.92, 137.85*, 136.48*, 136.42, 136.27*, 135.70, 128.74, 128.48*, 128.35, 127.63, 126.75, 126.29, 125.66*, 125.57, 123.76, 123.65*, 119.20, 119.01*, 109.44*, 109.32, 77.20*, 77.16, 76.46, 75.46*, 72.77, 58.47, 58.19*, 41.77, 41.60*, 36.42*, 35.96, 34.13*, 33.66, 32.71, 27.23*, 15.52*, 14.34. IR (NaCl/thin film): 3391, 3131, 3058, 3028, 2916, 2849, 1622 cm^{-1}; HRMS (EI+) calc'd for $C_{26}H_{27}NO_4$ [M+•] 417.1940, found 417.1959.

Preparation of acid 150



To a 500 mL flask open to air was added arene **S16** (2.45 g, 5.87 mmol), *t*-BuOH (70 mL), and water (70 mL). To this colorless clear solution was added *n*-Bu_4NOH (1.5 M in H_2O, 11.74 mL, 17.61 mmol), and the reaction was heated to 90 °C for 27 hours. At this time HPLC analysis indicated a 99:1 ratio of starting material to product, and the clear yellow reaction was cooled to 0 °C and quenched with an aqueous 5:1 mixture of $NaH_2PO_4/NaHSO_4$ (approximately pH=2.5). After a reaction pH of < 3 was achieved, most of the *t*-BuOH was concentrated *in vacuo*. The mixture was then extracted with EtOAc until HPLC analysis confirmed no remaining product in the aqueous layer. The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and purified by silica gel chromatography (0 → 70% EtOAc/hexanes) to provide 1.50 g (95% yield) of acid **150** as a 10:1 ratio of inseparable diastereomers. $[\alpha]^{25}_D$ +96.1° (*c* 1.95, CH_2Cl_2); ^1H NMR (10:1 diastereomer ratio, asterisk denotes minor peaks 500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.44* (s, 1H), 7.38 (t, *J* = 1.5 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.23* (d, *J* = 1.5 Hz, 1H), 6.22 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.13 (s, 2H), 5.22 (d, *J* = 12.1 Hz, 2H), 5.10 (d, *J* = 11.8 Hz, 2H), 3.38 – 3.17 (m, 6H), 3.01 (dd, *J* = 16.8, 6.5 Hz, 2H), 2.83 (dd, *J* = 16.4, 8.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.07, 180.84*, 143.71, 141.43, 141.40*, 140.74, 140.65*, 138.06*, 138.03, 136.50, 136.39*, 135.28, 125.30, 123.88, 119.38, 109.27*, 109.21, 77.19*, 77.15, 72.66, 43.70*, 43.17, 35.48*, 35.42, 33.76*, 33.34. IR (NaCl/thin film): 3122, 3076, 3027, 2951, 2853, 2744, 2655, 2565, 1731, 1705 cm^{-1}; HRMS (FAB+) calc'd for $C_{16}H_{13}O_4$ [M+H]-H_2 269.0814, found 269.0816.

Preparation of diazo ketone S17

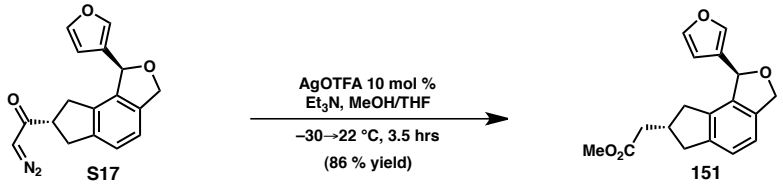


150 S17

To a flame-dried 250 mL flask containing acid **150** (1.47 g, 5.44 mmol, 10:1 ratio diastereomers) was added DCM (60 mL), 1 drop of DMF, and $(COCl)_2$ (933 μL, 10.9 mmol) at 22 °C. A clear deep red solution resulted, and steady gas evolution occurred for 15 minutes. After 2 hours the solvent was concentrated *in vacuo*, and the red residue was placed under argon. NMR analysis confirmed complete conversion of the acid to the acid chloride. The acid chloride was then dissolved in THF (70 mL), and in a separate Erlenmeyer flask 250 mL of an ethereal diazomethane solution was dried briefly over KOH at 0 °C. This was carefully decanted into a separate oven-dried Erlenmeyer at 0 °C, and placed under nitrogen. The acid chloride/THF solution was cannula transferred over 10 minutes to the yellow diazomethane (excess) solution at 0 °C, which resulted in a steady gas evolution. The murky brown reaction was held for 20 minutes at the same temperature, after which time TLC analysis indicated full consumption of the starting material. The reaction was quenched with AcOH until bubbling subsided, and the volatiles were concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 → 30% EtOAc/hexanes) to provide 1.28 g (80% yield) of diazo ketone **S17** as a yellow solid. The product was determined to be a 10:1 mixture of separable diastereomers. The major diastereomer was separated from a small sample (preparative HPLC) for characterization. $[\alpha]^{25}_{D}$ +175.7° (*c* 0.98, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.38 (dd, *J* = 2.4, 1.0 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.08

(d, *J* = 7.6 Hz, 1H), 6.22 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.12 (br s, 1H), 5.25 (br s, 1H), 5.22 (dd, *J* = 12.1, 1.9 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 3.33 – 3.08 (m, 3H), 2.95 (dd, *J* = 16.4, 6.1 Hz, 1H), 2.73 (dd, *J* = 16.4, 9.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.10, 143.68, 141.51, 140.70, 138.16, 136.61, 135.43, 125.47, 123.87, 119.37, 109.26, 77.12, 72.71, 53.90, 49.20, 35.53, 33.39. IR (NaCl/thin film): 3090, 2942, 2913, 2848, 2228, 2104, 1635 cm^{-1}; HRMS (FAB+) calc'd for $C_{17}H_{13}N_2O_3$ [M+H]-H_2 293.0926, found 293.0932.

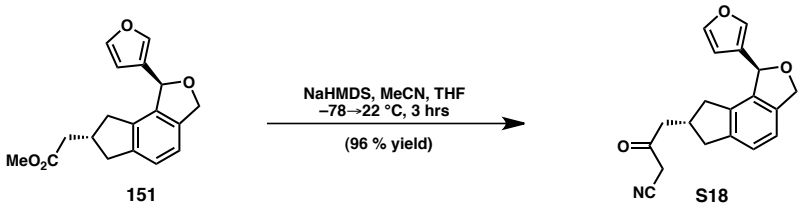
Preparation of methyl ester 151



To a flame-dried 250 mL flask containing diazo ketone **S17** (1.22 g, 4.14 mmol, 10:1 ratio diastereomers) was added THF (110 mL) and MeOH (12.0 mL). The flask was covered in foil and cooled to -30 °C. To a N_2 purged 25 mL conical flask protected from light was added silver trifluoroacetate (91 mg, 0.414 mmol), followed by Et_3N (1.73 mL, 12.42 mmol) with vigorous stirring at 22 °C. (Note: vigorous stirring during Et_3N addition is critical to ensure dissolution of silver salt. Lack of stirring can result in a brown silver clump and incomplete dissolution. When dissolved a clear tan solution is obtained). The Et_3N/AgOTFA solution was added in one portion to the clear yellow diazo ketone solution at -30 °C. The reaction was slowly warmed to 23 °C over 3.5 hours (starting material consumed by TLC), after which time clear red/brown solution was present with a silver mirror. The reaction was quenched with 1 mL of aqueous 1M HCl,

and diluted with 50 mL Et_2O. The aqueous layer was separated and back-extracted twice Et_2O, and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude brown residue was purified (0→30% EtOAc/hexanes), yielding 1.07 g (86% yield) of methyl ester **151** as a white solid. The product was determined to be a 10:1 mixture of separable diastereomers. The major diastereomer was separated from a small sample (preparative HPLC) for characterization. $[\alpha]^{25}_{D}$ +97.1° (*c* 0.92, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 1H), 7.37 (t, *J* = 1.8 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.22 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.11 (br s, 1H), 5.21 (dd, *J* = 11.9, 1.5 Hz, 1H), 5.09 (d, *J* = 11.9 Hz, 1H), 3.67 (s, 3H), 3.13 (dd, *J* = 15.8, 7.8 Hz, 1H), 2.84 (apt spt, *J* = 7.0 Hz, 1H), 2.74 (dd, *J* = 16.1, 8.0 Hz, 1H), 2.63 (dd, *J* = 15.8, 6.4 Hz, 1H), 2.43 (d, *J* = 7.4 Hz, 2H), 2.36 (dd, *J* = 16.0, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.17, 143.65, 142.62, 140.63, 137.79, 136.65, 136.39, 125.58, 124.06, 118.97, 109.32, 77.21, 72.70, 51.53, 39.78, 38.37, 36.29, 35.93. IR (NaCl/thin film): 3438, 3142, 3121, 2996, 2953, 2894, 2840, 1723 cm^{-1}; HRMS (FAB+) calc'd for $C_{17}H_{13}N_2O_3$ [M+H]-H_2 297.1127, found 297.1126.

Preparation of ketonitrile S18



151 S18

To a flame-dried 100 mL flask containing methyl ester **151** (1.05 g, 3.52 mmol, 10:1 ratio diastereomers) was added THF (50 mL). To a separate flame-dried 250 mL flask in the glovebox was added NaHMDS (1.42 g, 7.75 mmol). The flask was then

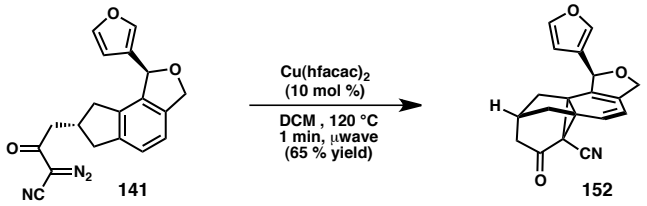
sealed and put under N_2 on the bench. THF (25 mL) was charged to the NaHMDS, and the light yellow solution was cooled to –78 °C. Anhydrous MeCN (440 μL, 8.45 mmol) was added via syringe to the NaHMDS solution, and stirred at –78 °C for 20 minutes. The methyl ester **151** solution was transferred via cannula to the sodio-acetonitrile solution with a 10 mL THF wash. The reaction was allowed to warm to 0 °C over 1.5 hours, at which point TLC analysis indicated complete consumption of starting material. The reaction was quenched with aqueous saturated NH_4Cl, and diluted with brine and Et_2O. The aqueous layer was separated and back-extracted twice with Et_2O. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified (0→45% EtOAc/hexanes) to provide 1.04 g (96% yield) of keto nitrile **S18** as an approximate 10:1 mixture of inseparable diastereomers. $[\alpha]^{25}_D$ +92.5° (*c* 2.25, CH_2Cl_2); ^{1}H NMR (10:1 diastereomer ratio, asterisk denotes minor peaks 500 MHz, $CDCl_3$) δ 7.43* (d, *J* = 1.1 Hz, 1H), 7.42 (s, 1H), 7.38 (t, *J* = 1.7 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.21 (dd, *J* = 1.8, 0.6 Hz, 2H), 6.12* (s, 1H), 6.10 (s, 1H), 5.21 (dd, *J* = 11.9, 1.5 Hz, 2H), 5.09 (d, *J* = 11.9 Hz, 2H), 3.42 (s, 2H), 3.40* (s, 2H), 3.17 (dd, *J* = 15.8, 7.8 Hz, 2H), 2.92 – 2.82 (m, 2H), 2.80 – 2.74 (m, 6H), 2.56 (dd, *J* = 15.8, 6.0 Hz, 2H), 2.30 (dd, *J* = 16.2, 5.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.76, 196.69*, 143.65, 143.59*, 142.23*, 142.10, 140.55, 137.91, 137.80*, 136.68, 136.62*, 136.10*, 135.86, 125.71*, 125.46, 124.06, 123.94*, 119.13, 119.08*, 113.63, 109.22, 77.20*, 77.12, 72.71*, 72.62, 47.76, 47.39*, 38.21, 38.13*, 36.33*, 36.14, 34.91*, 34.26, 32.14. IR (NaCl/thin film): 3139, 3076, 3025, 2942, 2913, 2847, 2259, 2183, 1729 cm^{-1}; HRMS (FAB+) calc'd for $C_{19}H_{16}NO_3$ [M+H]-H_2 306.1130, found 306.1137.

Preparation of diazo keto nitrile 141

To a 500 mL flask containing keto nitrile **S18** (975 mg, 3.18 mmol, approximately 10:1 ratio diastereomers) and imidazole sulfonyl azide (715 mg, 4.13 mmol) was added MeCN (100 mL). The headspace was purged with N_2, and pyridine (1.41 mL, 17.50 mmol) was added in one portion, resulting in a hazy yellow solution. The reaction was heated to 40 °C, and after 1 hour became orange in color. After heating an additional 13 hours the TLC analysis indicated full consumption of starting material. The volatiles were removed *in vacuo*, and the residue was purified by flash chromatography (0→30% EtOAc/hexanes), yielding 858 mg (81% yield) of diazo keto nitrile **141** (yellow oil) as a 10:1 mixture of inseparable diastereomers. $[\alpha]^{25}_{D}$ +87.0° (*c* 2.80, CH_2Cl_2); ^{1}H NMR (10:1 diastereomer ratio, asterisk denotes minor peaks 500 MHz, CDCl3) δ 7.43 (s, 2H), 7.38 (t, *J* = 1.7 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.21 (dd, *J* = 1.7, 0.7 Hz, 2H), 6.11 (br s, 2H), 5.22 (dd, *J* = 11.9, 1.5 Hz, 2H), 5.10 (d, *J* = 11.9 Hz, 2H), 3.17 (dd, *J* = 15.8, 7.9 Hz, 2H), 2.98 – 2.85 (m, 2H), 2.81 – 2.69 (m, 6H), 2.63 (dd, *J* = 15.8, 6.1 Hz, 2H), 2.37 (dd, *J* = 16.2, 6.0 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 189.22, 143.61, 142.18*, 142.01, 140.56, 140.54*, 137.95, 137.82*, 136.68, 136.59*, 136.08*, 135.81, 125.65*, 125.48, 124.03, 123.90*, 119.12, 119.07*, 109.23, 108.30*, 77.20*, 77.10, 72.69*, 72.61, 57.46, 44.88, 44.56*, 38.20, 38.11*, 36.40*, 36.12, 35.81*, 35.23. IR (NaCl/thin film): 3487, 3330, 3131, 3073, 3024, 2943, 2904, 2846, 2459, 2249,

2221, 2129, 1883, 1673 cm^{-1}; HRMS (FAB+) calc'd for $C_{19}H_{14}N_3O_3$ [M+H]-H_2 332.1035, found 332.1028.

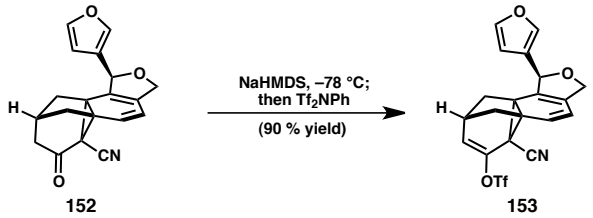
Preparation of Norcaradiene 152



A 20 mL microwave vial was charged with $Cu(hfacac)_2$ (14.9 mg, 0.03 mmol), sealed, and purged with N_2. To a flame-dried 25 mL flask containing diazo β-ketonitrile **141** (100 mg, 0.30 mmol, 10:1 mixture diastereomers) was charged DCM (15 mL). The diazo solution was then transferred via syringe into the sealed microwave vial. The vial was placed into the microwave reactor and heated to 120 °C for 1 minute (the desired temperature was reached in 1.5 minutes). TLC analysis confirmed consumption of the starting material, and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (gradient elution, 0 → 60% EtOAc/Hexanes), yielding norcaradiene **152** (60 mg, 65% yield, single diastereomer) as a white solid. m.p. 197-199 °C; $[\alpha]^{25}_D$ + 185.8° (*c* 0.18, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.5, 0.8 Hz, 1H), 7.42 (td, *J* = 1.7, 0.6 Hz, 1H), 6.45 (d, *J* = 9.4 Hz, 1H), 6.34 (dd, *J* = 1.7. 0.8 Hz, 1H), 6.31 (d, *J* = 9.4 Hz, 1H), 5.98 (t, *J* = 4.9 Hz, 1H), 4.91 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.88 (dd, *J* = 12.5, 4.5 Hz, 1H), 2.32 – 2.20 (m, 3H), 2.14 (d, *J* = 12.8 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.73 (d, *J* = 13.3 Hz, 1H), 1.68 (ddd, *J* = 13.4, 5.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 144.0, 140.9, 135.8, 131.1, 125.4, 125.4, 123.0, 112.0, 109.2, 79.3, 73.6, 51.6, 46.9, 43.24, 35.7, 34.5, 29.9, 26.2; IR (NaCl/thin film): 2937, 2848,

2239, 1694, 1343, 1034 cm^{-1}; HRMS (FAB+) calc'd for $C_{19}H_{16}O_5N$ $[M+H]^+$ 306.1130 found 306.1136.

Preparation of Vinyl Triflate 153

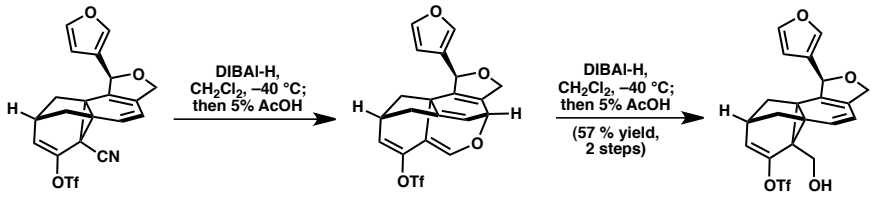


152 153

To a solution of β-ketonitrile **152** (30.0 mg, 0.10 mmol) in THF (20 mL) cooled to –78 °C was added NaHMDS (20.0 mg, 0.11 mmol) in THF (1 mL). The resulting orange solution was stirred under N_2 for 30 minutes, after which time Tf_2NPh (43.0 mg, 0.12 mmol) in THF 1 mL) was added in one portion. After 40 minutes the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ at –78 °C and warmed up to 23 °C. The resulting mixture was diluted with saturated aqueous NaCl (20 mL) and extracted with diethyl ether (3 x 40 mL). The combined ethereal solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient elution, 0 → 50% Hexanes/ EtOAc) to give 39 mg (90% yield) of **153** as a yellow oil. $[\alpha]^{25}_D$ + 168.4° (*c* 2.50, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.40 (td, *J* = 1.7, 0.6 Hz, 1H), 6.41 (d, *J* = 9.4 Hz, 1H), 6.33 (ddd, *J* = 1.7, 0.9, 0.4 Hz, 1H), 6.17 (d, *J* = 9.4 Hz, 1H), 5.99 (d, *J* = 8.3 Hz, 1H), 5.91 (t, *J* = 5.0 Hz, 1H), 4.89 (m, 2H), 2.59 (dtt, *J* = 8.3, 4.9, 0.5 Hz, 1H), 1.78 (dd, *J* = 12.5, 5.0 Hz, 1H), 1.53 (d, *J* = 12.9 Hz, 1H), 1.40 (dd, *J* = 12.9, 5.0 Hz, 1H), 1.10 (d, *J* = 12.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 140.9, 137.0, 135.4, 128.6, 125.2, 123.4, 123.2, 118.6 (q, *J* = 318 Hz), 115.5, 111.8, 109.1, 79.3, 73.8,

44.4, 39.7, 31.1, 29.4, 27.6, 16.7; IR (NaCl/thin film): 2935, 2854, 2240, 1654, 1506, 1425, 1212 cm^{-1}; HRMS (ES+) calc'd for $C_{20}H_{15}F_3NO_5S$ $[M+H]^+$ 438.0623, found 438.0641.

Preparation of Vinyl Triflate 156



153 155 156

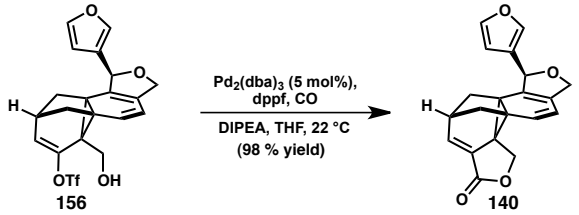
To a flame-dried flask under N_2 containing a solution of vinyl triflate **153** (25.0 mg, 0.06 mmol) in DCM (10 mL) was added DIBAL-H (24.0 mg, 0.17 mmol) in DCM (1 mL) at –30 °C. After 30 minutes, reaction was complete (TLC analysis) and was quenched with 5% aqueous AcOH (5 mL) (**Warning**: H_2 evolution). The reaction mixture was warmed up to room temperature and stirred vigorously for 30 minutes (clear biphasic mixture resulted). The organic layer was separated and stirred with dilute aqueous $NaHCO_3$ solution (5 mL, 1:1 H_2O: aqueous saturated $NaHCO_3$) to remove traces of AcOH. This organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield 27.0 mg crude rearranged product **155** as pale yellow oil, which turns darker upon standing. (**Warning**: rearranged product **155** is extremely unstable and should be used for the next step immediately; it should be kept under argon and away from light as often as possible during workup). A small portion of the rearranged product **155** was purified by preparative HPLC for analytical purposes to give rearranged product **155** as a clear oil (retention time 4.6 minutes, 15% EtOAc/Hexanes), which was immediately dissolved in CD_2Cl_2 under argon for NMR

analysis. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.41 (br s, 1H), 7.40 (app t, *J* = 1.7 Hz, 1H), 6.50 (s, 1H), 6.27 (dt, *J* = 1.7, 0.7 Hz, 1H), 5.78 (br d, *J* = 4.1 Hz, 1H), 5.75 (d, *J* = 7.4 Hz, 1H), 5.53 (dt, *J* = 4.0, 2.0 Hz, 1H), 5.50 (t, *J* = 2.2 Hz, 1H), 4.59 (dt, *J* = 13.5, 1.7 Hz, 1H), 4.53 (dt, *J* = 13.5, 1.7 Hz, 1H), 2.71 (td, *J* = 7.0, 4.1 Hz, 1H), 2.32 (br d, *J* = 17.8 Hz, 1H), 2.16 – 2.02 (m, 2H), 1.73 (dd, *J* = 10.4, 4.2 Hz, 1H); A completely clean ^{13}C NMR could not be obtained on the purified material due to the rapid decomposition. ^{13}C NMR, HSQC and HMBC spectra could be obtained, however, on mostly pure compound directly from the workup. ^{13}C NMR (125 MHz, CD2Cl2) δ 144.16, 141.98, 141.48, 140.43, 139.16, 135.15, 130.34, 123.91, 120.28, 118.90 (q, J = 320 Hz), 116.43, 109.70, 108.83, 85.38, 74.53, 69.95, 57.85, 41.31, 36.26, 33.88; HRMS (EI+) calc'd for $C_{20}H_{15}F_3O_6S$ $[M^-]^+$ 440.0541, found 440.0523.

The rearranged product **155** was dissolved in benzene and concentrated under reduced pressure, dried under vacuum for 10 minutes, backfilled with Ar, dissolved in dry DCM (10 mL). The resulting solution was cooled to –30 °C and treated with DIBAL-H (24.0 mg, 0.17 mmol) in DCM (1 mL). After 15 minutes, reaction was complete (TLC analysis) and was carefully quenched (H_2 evolution) with 5% aqueous AcOH (5 mL). When gas evolution ceased, the reaction mixture was warmed up to room temperature and stirred vigorously for 30 minutes (a clear biphasic mixture formed). The organic layer was separated and stirred with dilute aqueous $NaHCO_3$ solution (5 mL, 1:1 H_2O saturated aqueous $NaHCO_3$) to remove traces of AcOH. This organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield crude yellow oil. This residue was purified by preparative HPLC (40% Hexanes/EtOAc, retention time 4 minutes) to give 14.3 mg (57% yield, two steps) of **156** as a clear oil.

$[\alpha]^{25}_D$ + 81.1° (*c* 3.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 1.4, 0.9 Hz, 1H), 7.38 (td, *J* = 1.7, 0.5 Hz, 1H), 6.38 (ddd, *J* = 1.8, 0.9, 0.4 Hz, 1H), 6.15 (d, *J* = 9.5 Hz, 1H), 6.12 (d, *J* = 9.5 Hz, 1H), 5.95 (d, *J* = 8.2 Hz, 1H), 5.90 (dd, *J* = 9.2, 4.0 Hz, 1H), 4.87 (dd, *J* = 12.3, 5.6 Hz, 1H), 4.75 (dd, *J* = 12.3, 3.7 Hz, 1H), 3.68 (dd, *J* = 12.8, 5.2 Hz, 1H), 3.58 (dd, *J* = 12.8, 6.6 Hz, 1H), 2.38 (dt, *J* = 8.9, 4.5 Hz, 1H), 1.56 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.48 (dd, *J* = 6.7, 5.3 Hz, 1H), 1.44 (d, *J* = 11.9 Hz, 1H), 1.23 (dd, *J* = 12.3, 4.8 Hz, 1H), 1.02 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.62, 143.55, 140.4, 132.3, 130.7, 125.8, 125.6, 121.0, 118.4 (q, *J* = 317.5 Hz), 116.1, 109.3, 80.1, 73.7, 56.0, 39.4, 34.1, 32.70, 30.8, 27.5, 24.2; IR (NaCl/thin film): 3436, 2930, 2895, 2855, 1653, 1505, 1417, 1208 cm^{-1}; HRMS (FAB+) calc'd for $C_{20}H_{18}F_3O_6S$ $[M+H]^+$ 443.0776, found 443.0792.

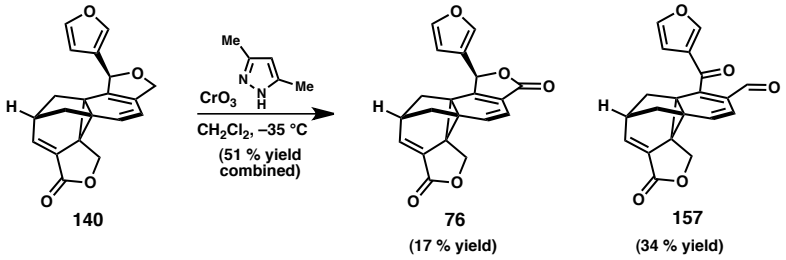
Preparation of Lactone 140



To an oven-dried 20-mL vial, equipped with a stir bar, septum and CO balloon, was added solution of vinyl triflate **156** (7.0 mg, 16 μmol) in dry THF (4 mL). CO was allowed to bubble through the solution for 5 minutes. Triethylamine (9.0 μL, 64 μmol) was added, followed by dppf (1.6 mg, 1.6 μmol) in THF (0.4 mL) and $Pd_2(dba)_3$ in THF (0.8 mL). The resulting yellow solution was gently warmed up to 40 °C under CO atmosphere. After 40 minutes the reaction was complete (LCMS analysis) and was passed through short pug of silica-gel, which was washed with EtOAc (3 x 5 mL). The

resulting filtrate was concentrated under reduced pressure, and the crude residue was purified by preparative HPLC (40% EtOAc/Hexanes, retention time 3.9 minutes) to give 5.2 mg (98% yield) of **140** as a clear oil, which solidifies when stored. $[\alpha]^{25}_{D}$ + 91.4° (*c* 2.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 1.3, 1.0 Hz, 1H), 7.39 (td, *J* = 1.7, 0.5 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.30 (ddd, *J* = 1.9, 0.8, 0.4 Hz, 1H), 6.23 (d, *J* = 9.4 Hz, 1H), 6.05 (d, *J* = 9.4 Hz, 1H), 5.85 (t, *J* = 4.4 Hz 1H), 4.90 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.81 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.94 (d, *J* = 10.2 Hz, 1H), 3.90 (d, *J* = 10.2 Hz, 1H), 2.73 (dt, *J* = 7.0, 4.8 Hz, 1H), 1.64 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.28 (dd, *J* = 12.4, 4.8 Hz, 1H), 1.23 (d, *J* = 12.0 Hz, 1H), 0.84 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 143.8, 140.7, 132.7, 131.0, 129.8, 125.4, 124.9, 124.7, 119.5, 109.1, 79.8, 74.0, 66.9, 39.6, 34.5, 31.6, 29.8, 27.8, 23.6; IR (NaCl/thin film):2956, 2927, 2852, 1761, 1653, 1506, 1231, 1156 cm^{-1}; HRMS (EI+) calc'd for $C_{20}H_{16}O_4$ $[M^{\cdot}]^+$ 320.1049, found 320.1052.

Preparation of Salvileucalin B (76)



In a glove box a stirred suspension of finely grinded CrO_3 (27.0 mg, 0.27 mmol)[1] in DCM (7 mL) at –35 °C was charged with a solution of 1,3-dimethylpyrazole (52.0 mg, 0.54 mmol) in DCM (4 mL). After 30 minutes complete dissolution of the CrO_3 was

[1] CrO_3 was dried under vacuum over P_2O_5 for 12 hours.

observed. To this clear dark orange solution (CrO_3•DMP complex) was added solution of **140** (8.6 mg, 0.03 mmol) in DCM (2 mL). After 3 hours dark brown solution was allowed to warm up to 23 °C and loaded directly onto a 50 g silica column (no solvent evaporation). Elution with Hexanes/EtOAc (1:2) afforded crude mixture of salvileucalin B (**76**) and keto-aldehyde **157** as a yellow oil. Further purification was achieved by preparative HPLC (2:3 EtOAc/Hexanes) to yield 1.5 mg (17% yield) of salvileucalin B (**76**) as a clear oil and ketoaldehyde **157** 3.0 mg (34% yield) as yellow oil.

Synthetic Salvileucalin B (**76**): $[\alpha]^{25}_D$ + 40.8° (*c* 0.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.45 (d, *J* = 14.4 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 1H), 6.63 (d, *J* = 9.5 Hz, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 6.22 (s, 1H), 6.10 (s, 1H), 3.96 (d, *J* = 10.5 Hz, 1H), 3.79 (d, *J* = 10.5 Hz, 1H), 2.85 (dt, *J* = 6.9, 4.7 Hz, 1H), 1.72 (dd, *J* = 12.2, 4.7 Hz, 1H), 1.37 (dd, *J* = 12.4, 4.8 Hz, 1H), 1.33 (d, *J* = 12.3 Hz, 1H), 1.00 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 168.1, 154.2, 144.5, 142.2, 134.3, 126.3, 123.8, 122.6, 119.2, 118.0, 108.3, 75.9, 66.3, 42.4, 36.6, 31.5, 29.6, 27.3, 25.7; IR (NaCl/thin film): 2952, 2913, 2848, 1754, 1352, 1295, 1233; HRMS (EI+) calc'd for $C_{20}H_{14}O_5$ $[M^-]^+$ 334.0841, found 334.0840.

Keto-Aldehyde **157**: $[\alpha]^{25}_D$ – 210.1° (*c* 0.24, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.44 (s, 1H), 7.15 (d, *J* = 7.0 Hz, 1H), 6.63 (d, *J* = 9.5 Hz, 1H), 6.23 (d, *J* = 9.5 Hz, 1H), 6.21 (s, 1H), 6.10 (s, 1H), 3.96 (d, *J* = 10.5 Hz, 1H), 3.79 (d, *J* = 10.5 Hz, 1H), 2.84 (dt, *J* = 9.2, 4.6 Hz, 1H), 1.71 (dd, *J* = 12.2, 4.7 Hz, 1H), 1.36 (dd, *J* = 12.4, 4.8 Hz, 1H), 1.33 (d, *J* = 12.3 Hz, 1H), 1.00 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.4, 187.3, 168.1, 149.5, 146.7, 145.6, 134.5, 133.0, 128.8, 125.7, 123.7, 119.4, 108.3, 66.5, 42.9, 40.1, 31.0, 29.90, 28.7, 27.2; IR (NaCl/thin film): 3030, 2957, 2928, 2851,

2754, 1760, 1683, 1657, 1557, 1233 cm^{-1}; HRMS (ESI) calc'd for $C_{20}H_{15}O_5$ $[M+H]^+$ 335.0914, found 335.0920.

3.5 NOTES AND REFERENCES

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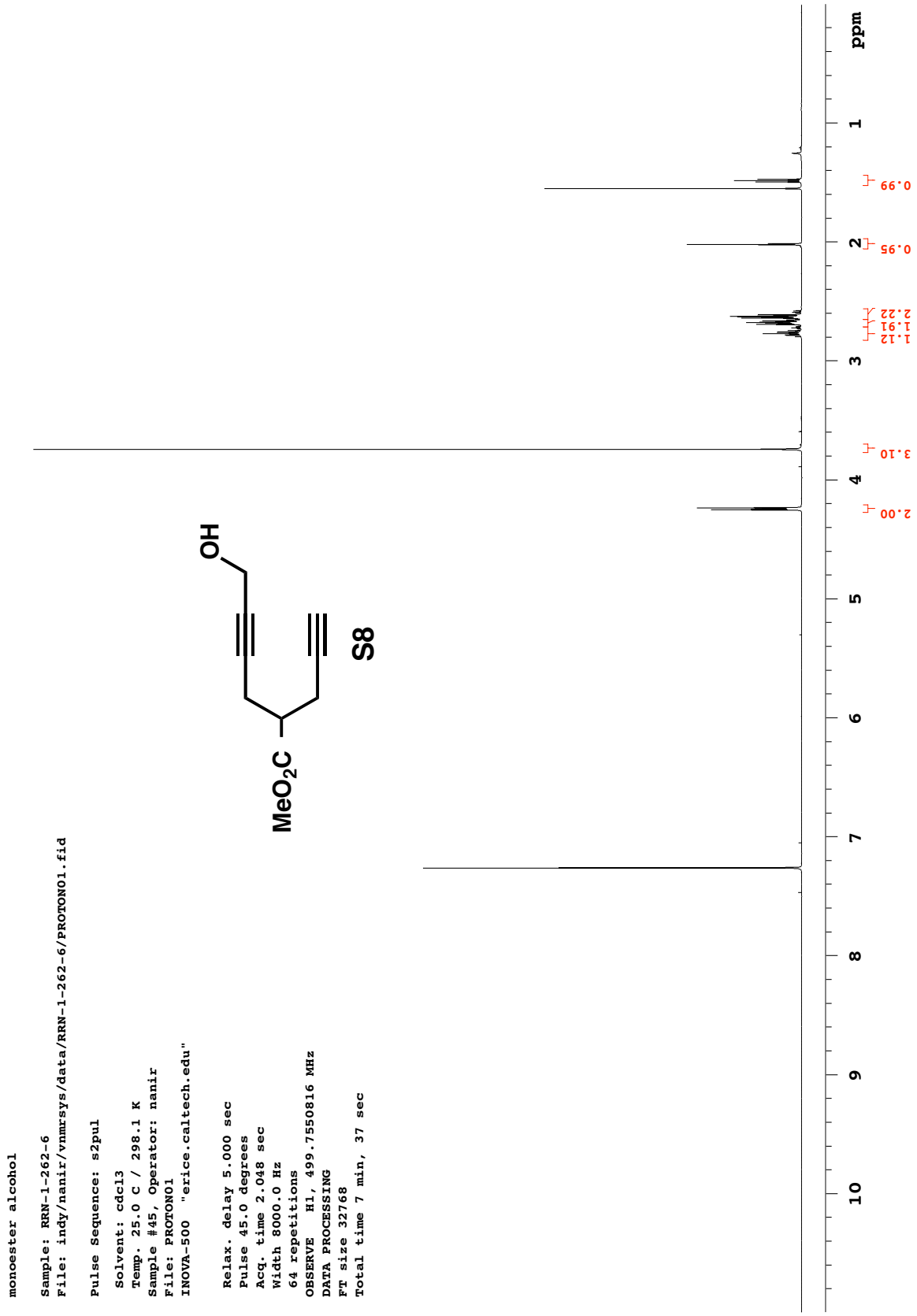
Appendix 2

Spectra Relevant to Chapter 3:

Enantioselective Total Synthesis of Salvileucalin B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Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7550816 MHz
DATA PROCESSING
FT size 32768
Total time 7 min, 37 sec
OH
MeO2C
S8
ppm
0.99
0.95
1.12
1.91
2.22
3.10
2.00

monoester alcohol

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Sample #40, Operator: nanir
File: CARBON01
INOVA-500 "erice.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
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512 repetitions
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Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
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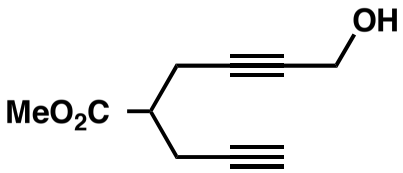
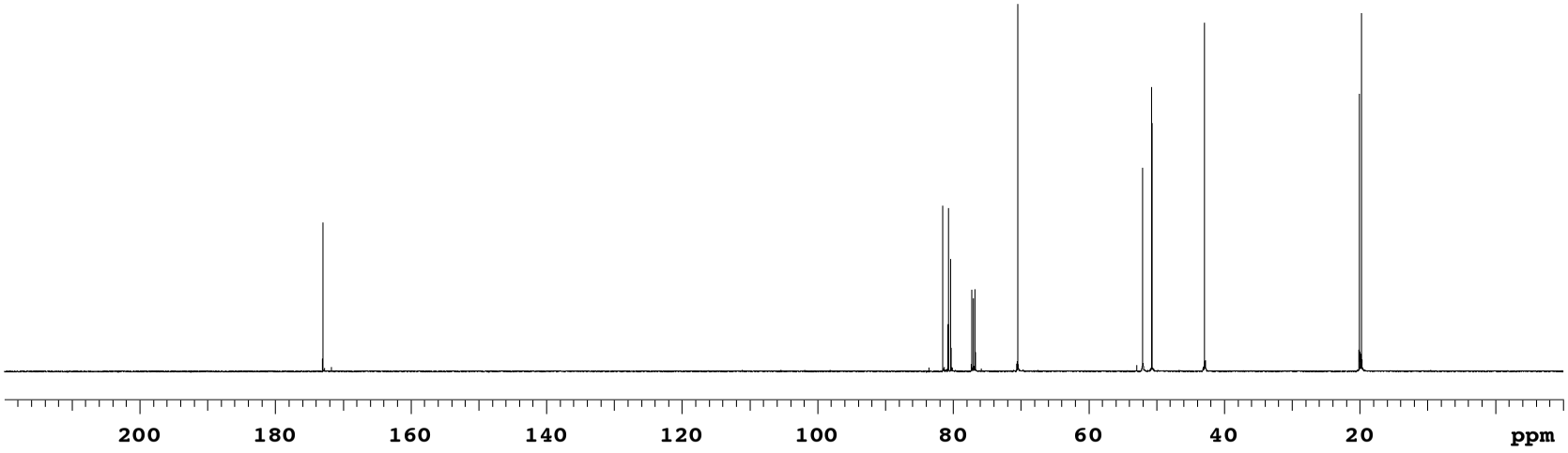
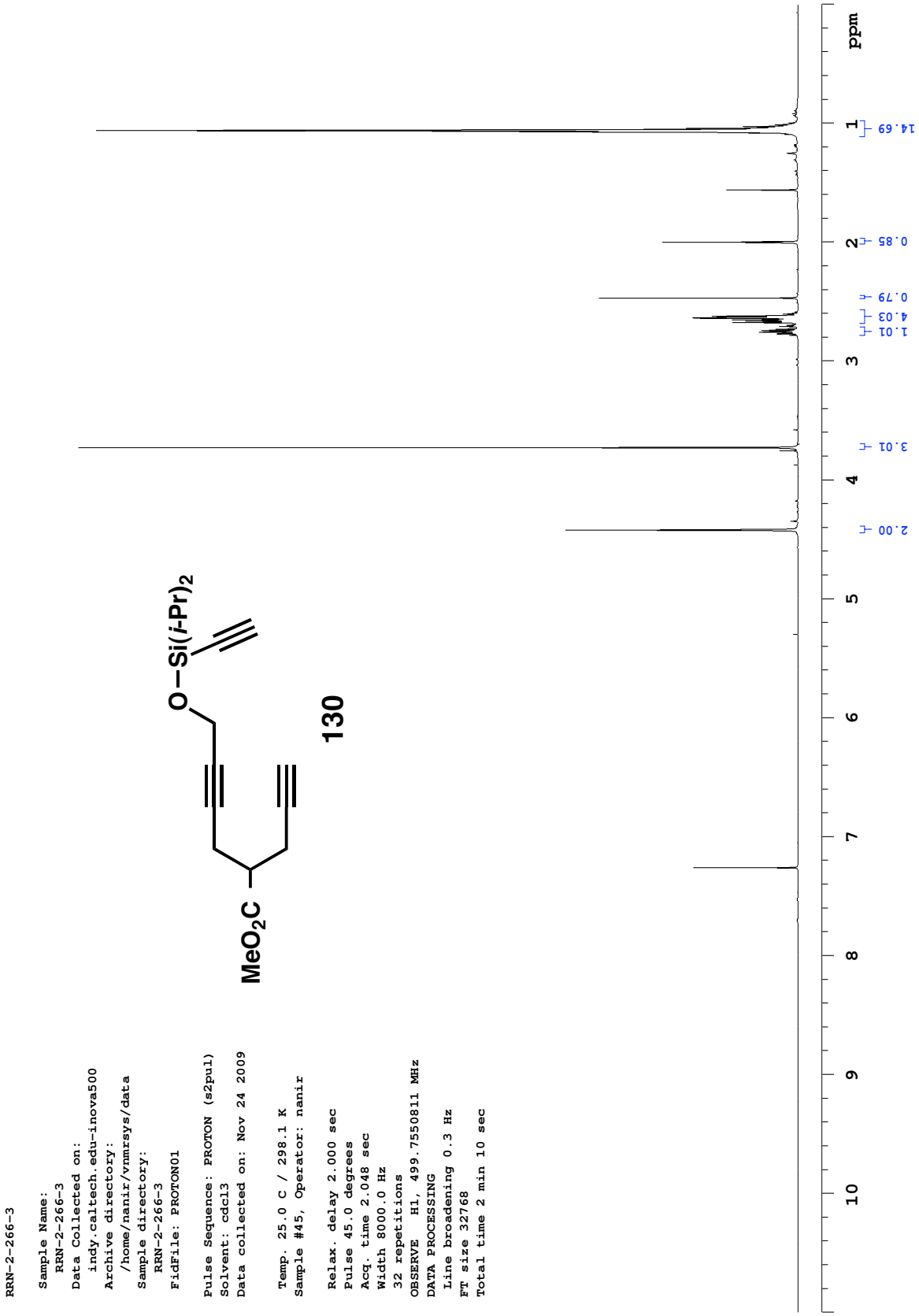


S8

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Sample directory:
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Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
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Temp. 25.0 C / 298.1 K
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Pulse 45.0 degrees
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Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7550811 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 2 min 10 sec
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ppm
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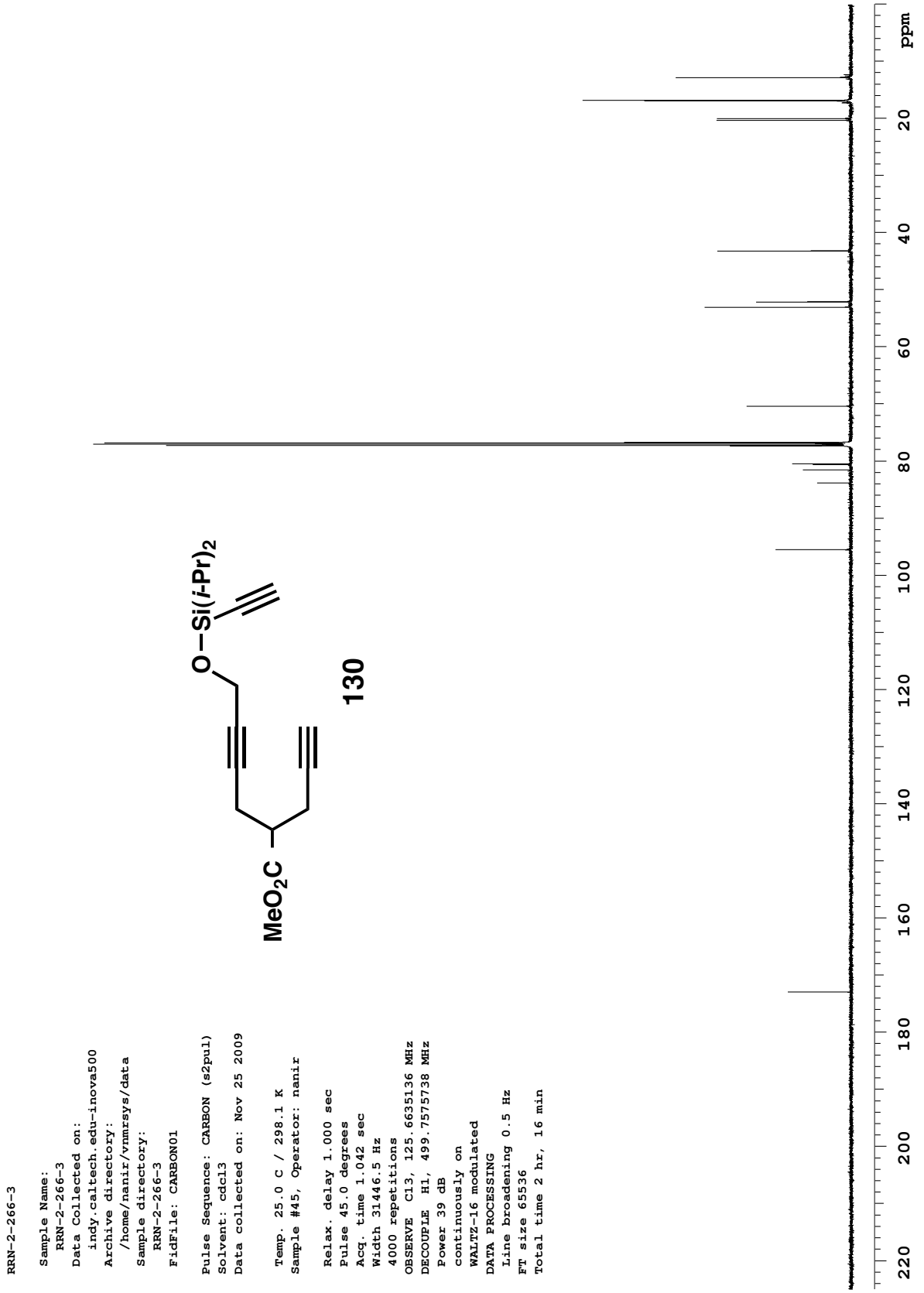
4.03
1.01
3.01
2.00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DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 16 min
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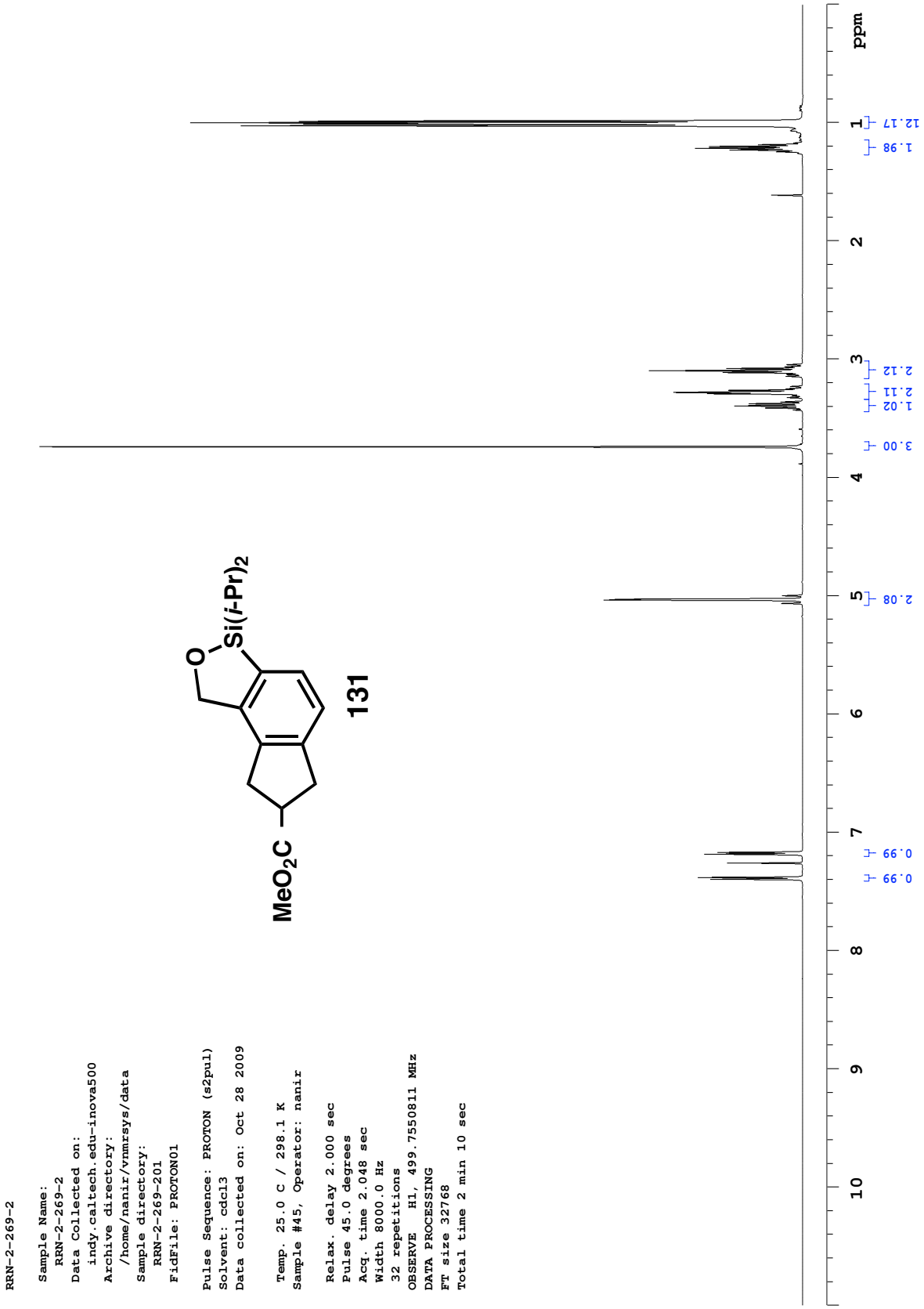
160
140
120
100
80
60
40
20
ppm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Solvent: cdcl3
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Width 8000.0 Hz
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OBSERVE H1, 499.7550811 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 10 sec
O
Si(i-Pr)2
MeO2C
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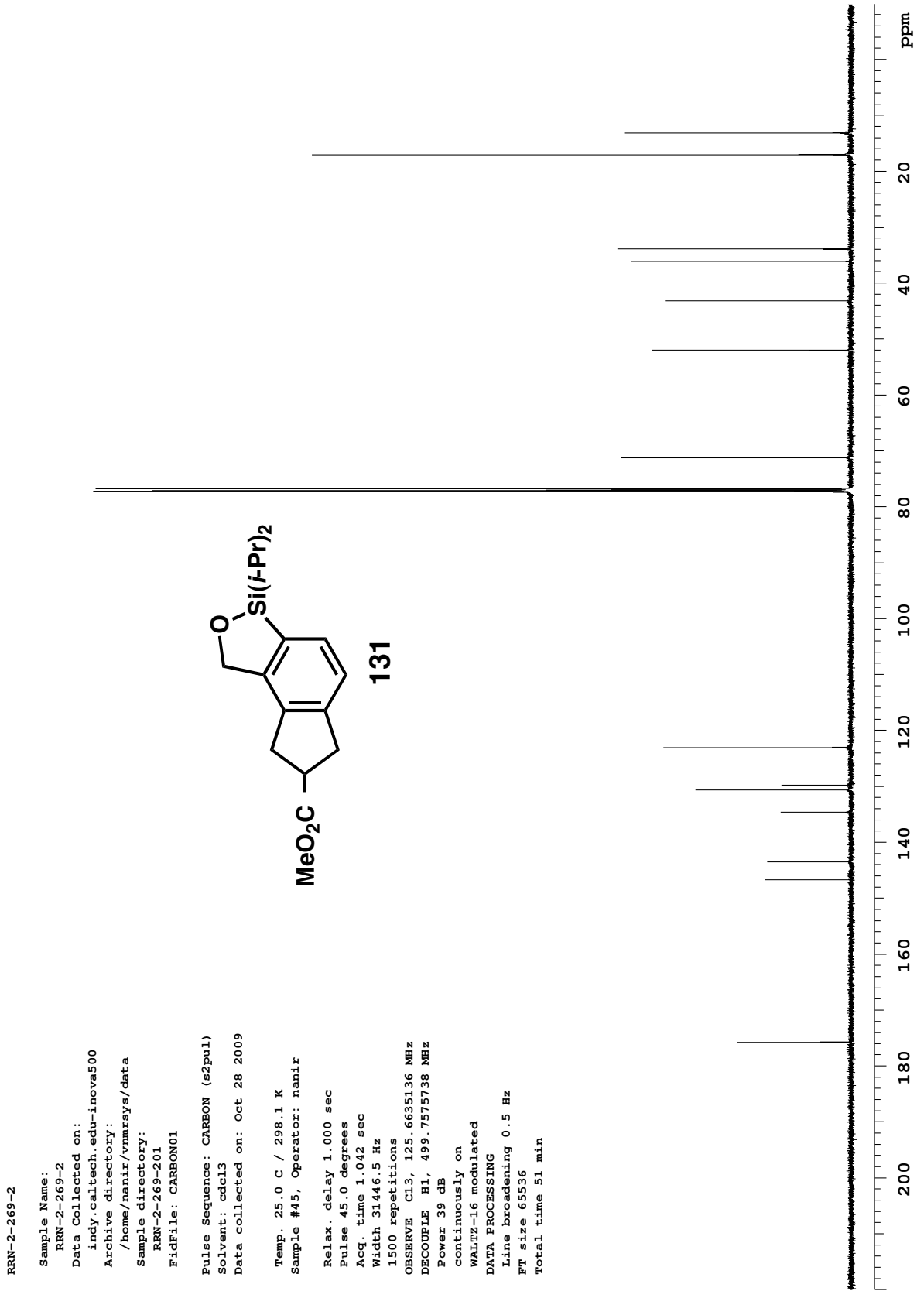
ppm
12.17
1.98
2.12
2.11
1.02
3.00
2.08
0.99
0.99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Sample directory:
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Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 28 2009
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
O
Si(i-Pr)2
MeO2C
131
200
180
160
140
120
100
80
60
40
20
ppm

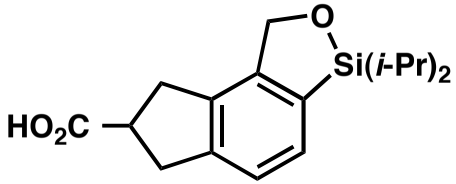
RRN-2-272-6

Sample: RRN-2-272-6
File: home/slevin/vnmrsys/data/RRN-2-272-6.fid

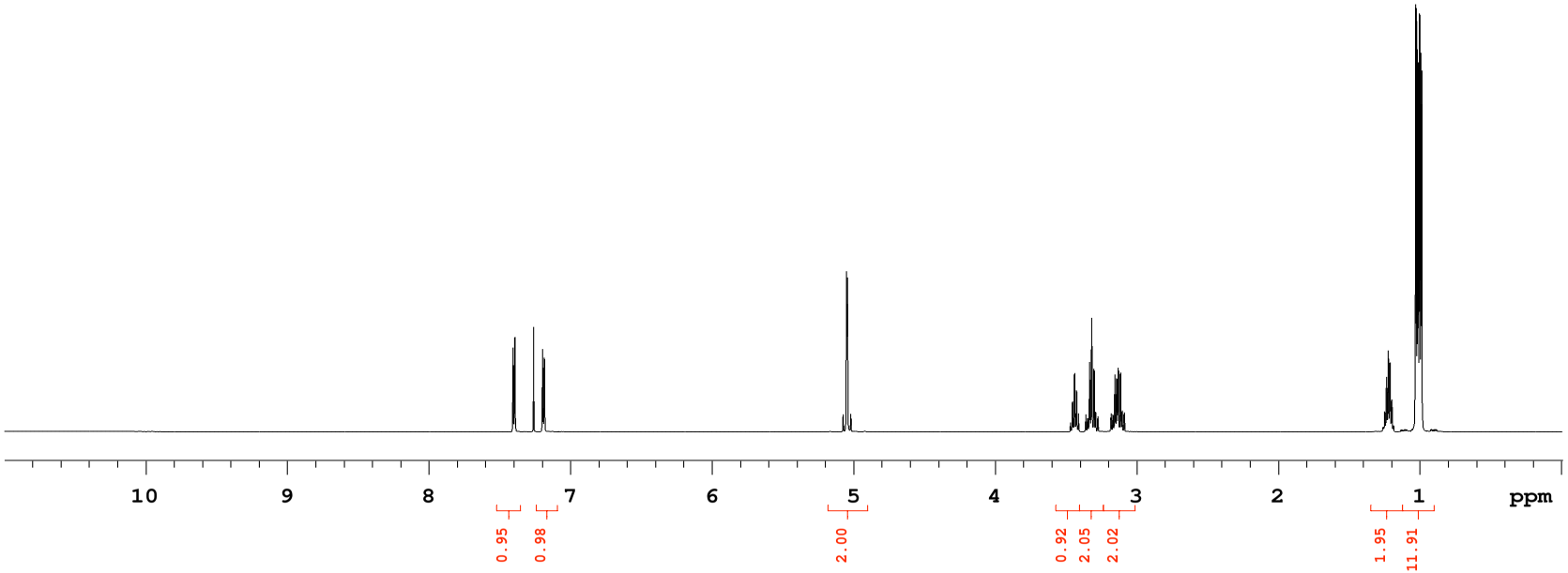
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: slevin
File: RRN-2-272-6
INOVA-500 "urbino.caltech.edu"

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6613025 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 1 min, 13 sec



S9



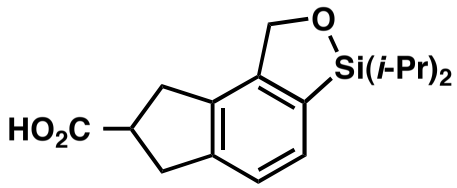
RRN-2-272-3

Sample Name:
RRN-2-272-3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-2-272-3
FidFile: CARBON01

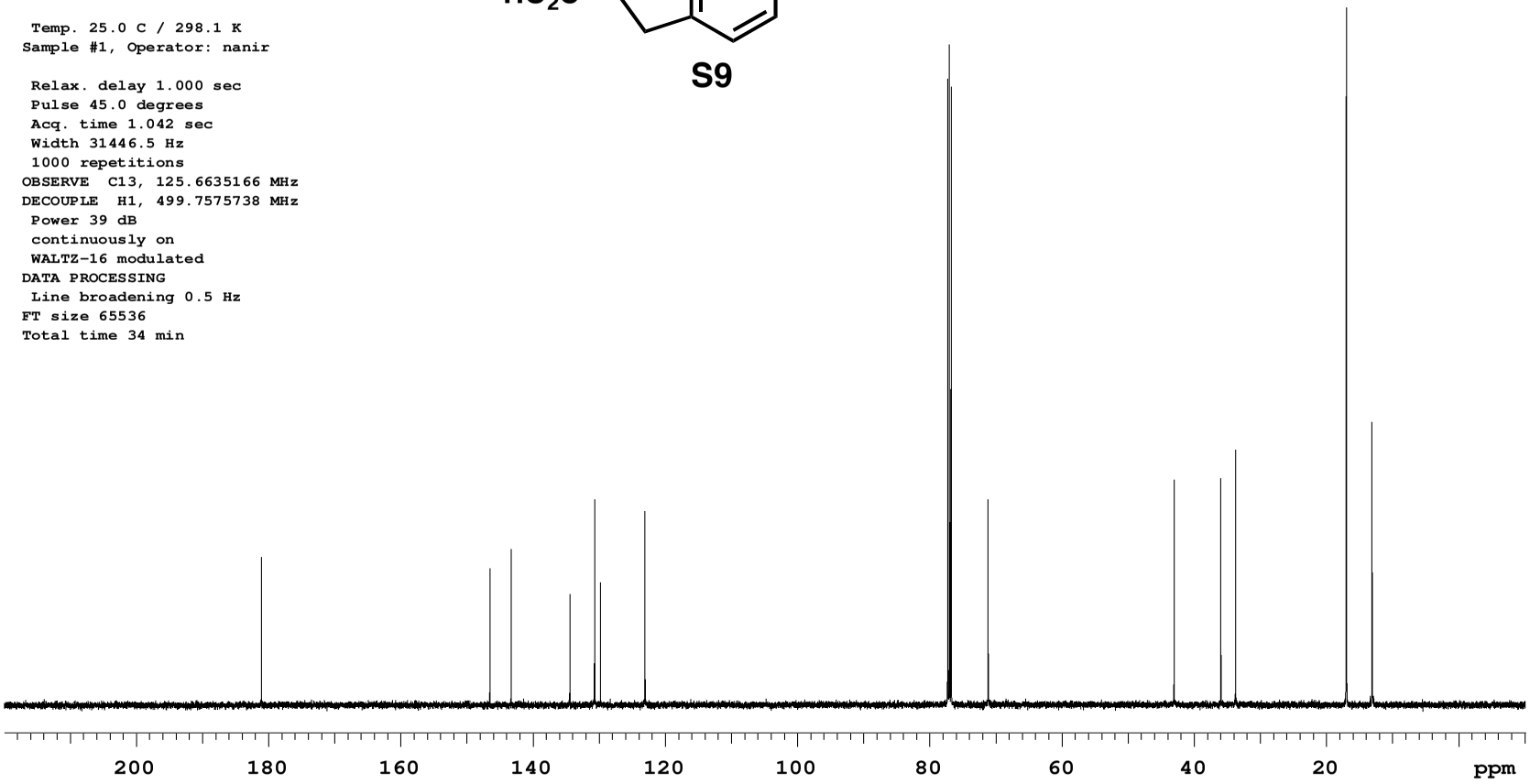
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 23 2009

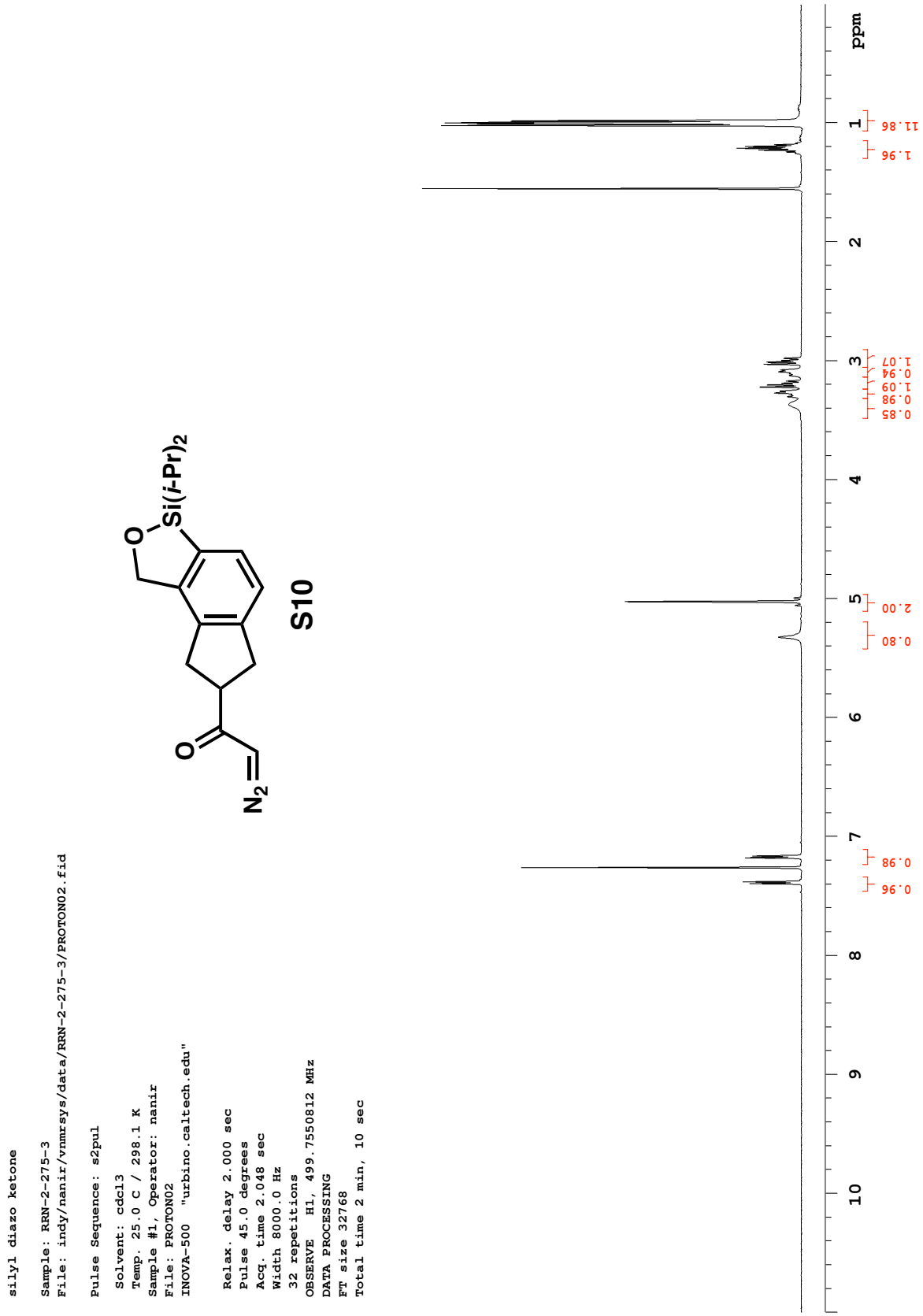
Temp. 25.0 C / 298.1 K
Sample #1, Operator: nanir

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6635166 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min



S9




silyl diazo ketone
Sample: RRN-2-275-3
File: indy/nanir/vnmrsys/data/RRN-2-275-3/PROTON02.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, Operator: nanir
File: PROTON02
INOVA-500 "uxbino.caltech.edu"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7550812 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 10 sec
O
Si(i-Pr)2
O
N2
S10
ppm
11.86
1.96
0.85
0.98
1.09
0.94
1.07
2.00
0.80
0.98
0.96

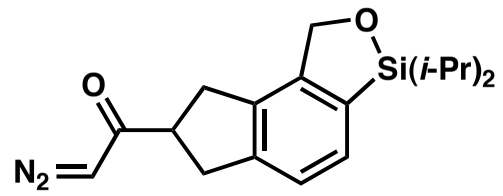
silyl diazo ketone

Sample: RRN-2-275-2
File: indy/nanir/vnmrsys/data/RRN-2-275-2/CARBON01.fid

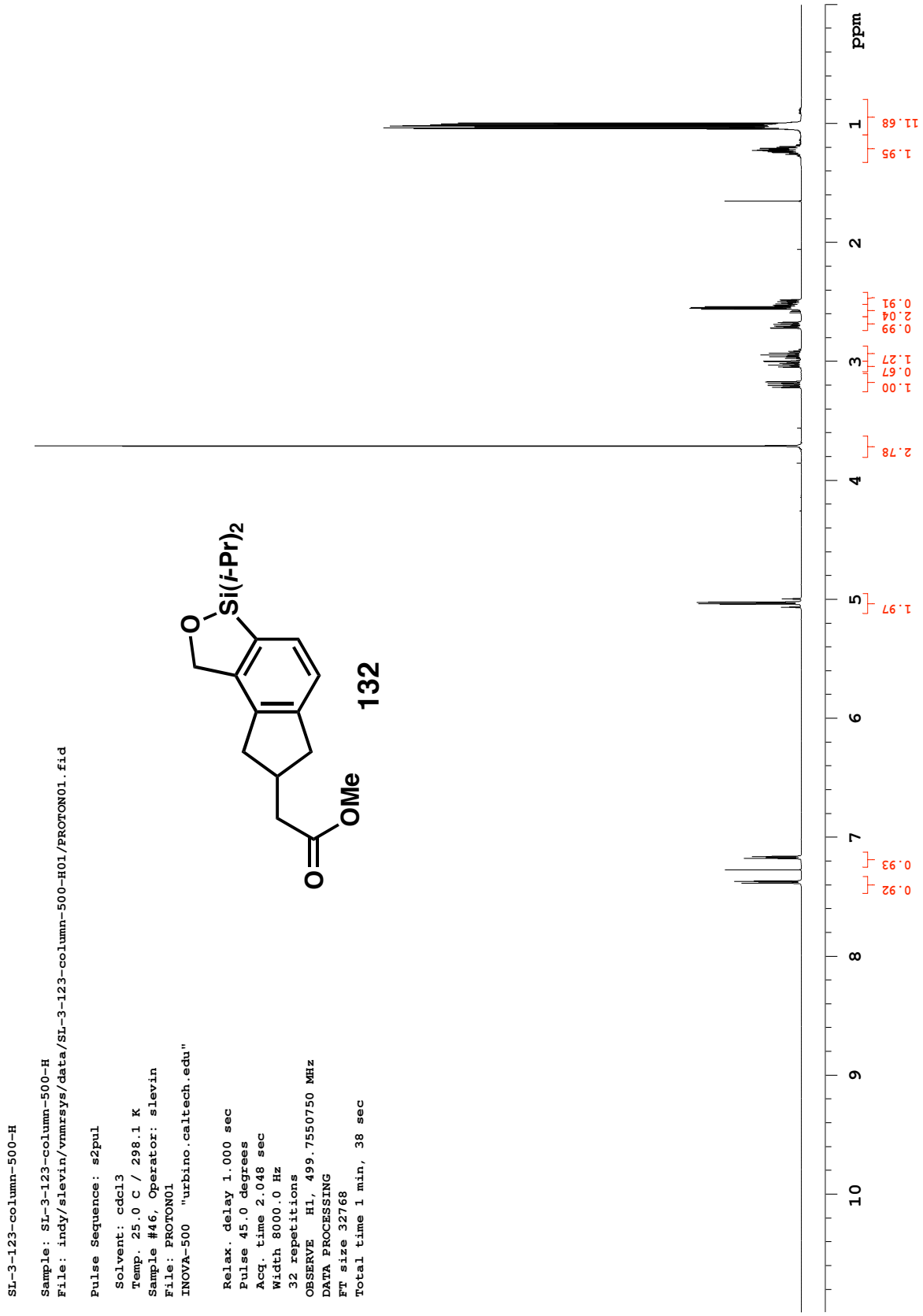
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, Operator: nanir
File: CARBON01
INOVA-500 "urbino.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 51 min, 17 sec



S10


SL-3-123-column-500-H
Sample: SL-3-123-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-123-column-500-H01/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7550750 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 38 sec
Si(i-Pr)2
O
OMe
O
132
ppm
10
9
8
7
6
5
4
3
2
1
0.92
0.93
1.97
2.78
1.00
0.67
1.27
0.99
2.04
0.91
1.95
11.68

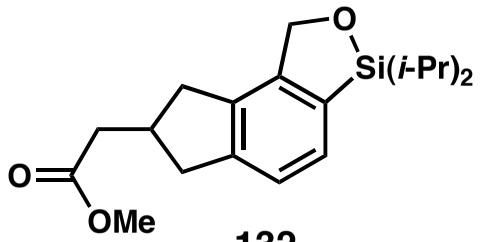
SL-3-123-column-500-H

Sample: SL-3-123-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-123-column-500-H01/CARBON01.fid

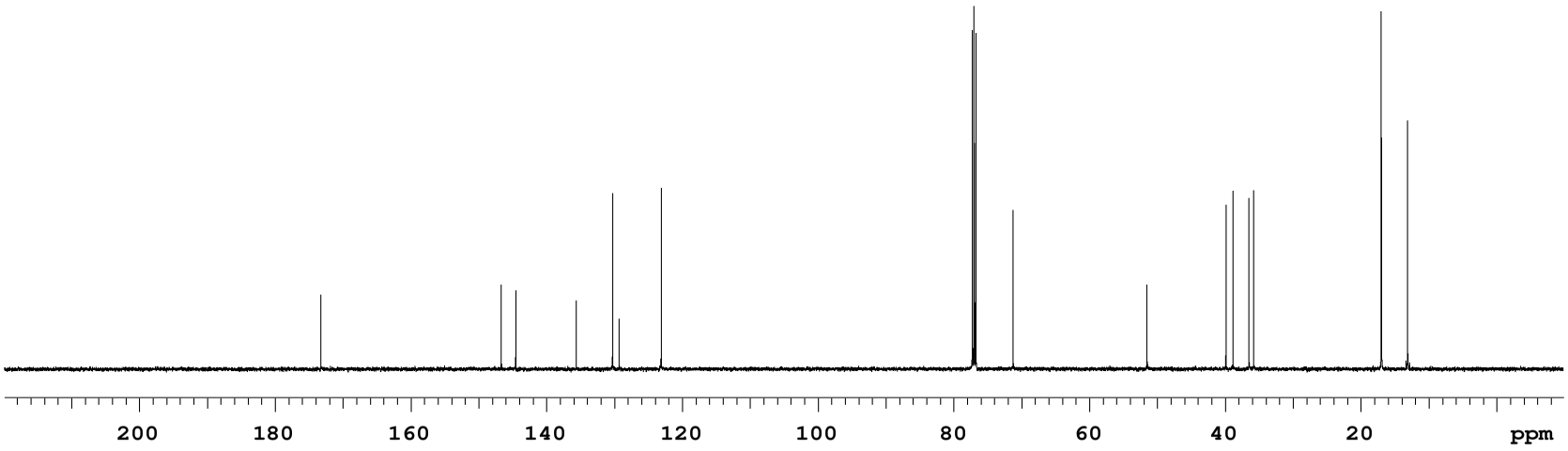
Pulse Sequence: s2pul

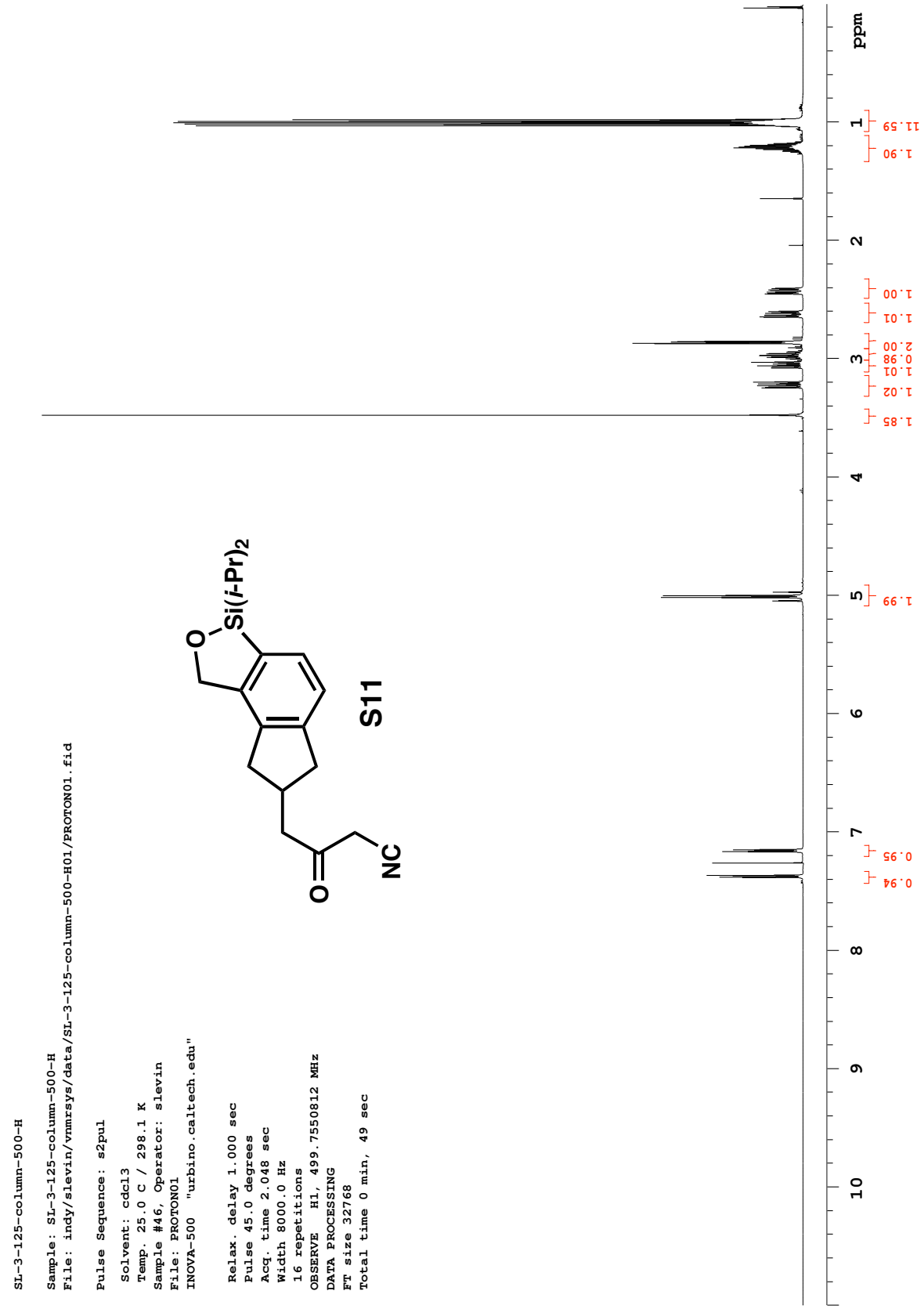
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6635171 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min, 17 sec



132




SL-3-125-column-500-H
Sample: SL-3-125-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-125-column-500-H01/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7550812 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec
Si(i-Pr)2
O
O
NC
S11
ppm
10
9
8
7
6
5
4
3
2
1
11.59
1.90
1.00
1.01
2.00
0.98
1.01
1.02
1.85
1.99
0.95
0.94

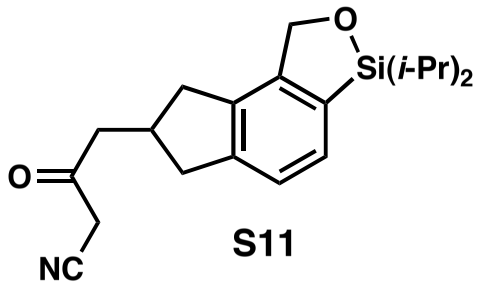
SL-3-125-column-500-H

Sample: SL-3-125-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-125-column-500-H01/CARBON01.fid

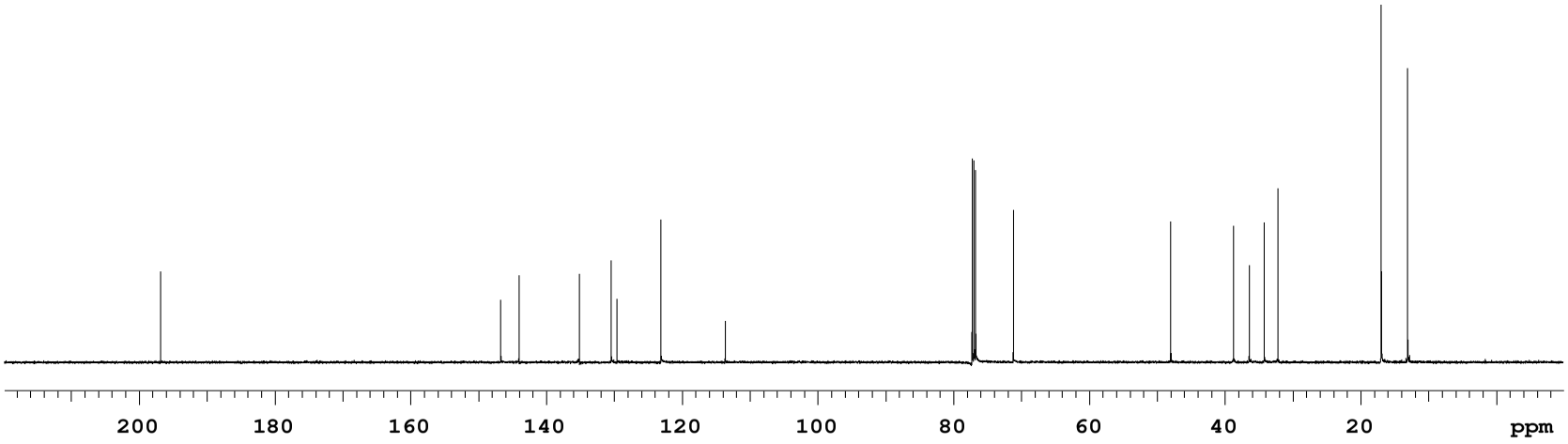
Pulse Sequence: s2pul

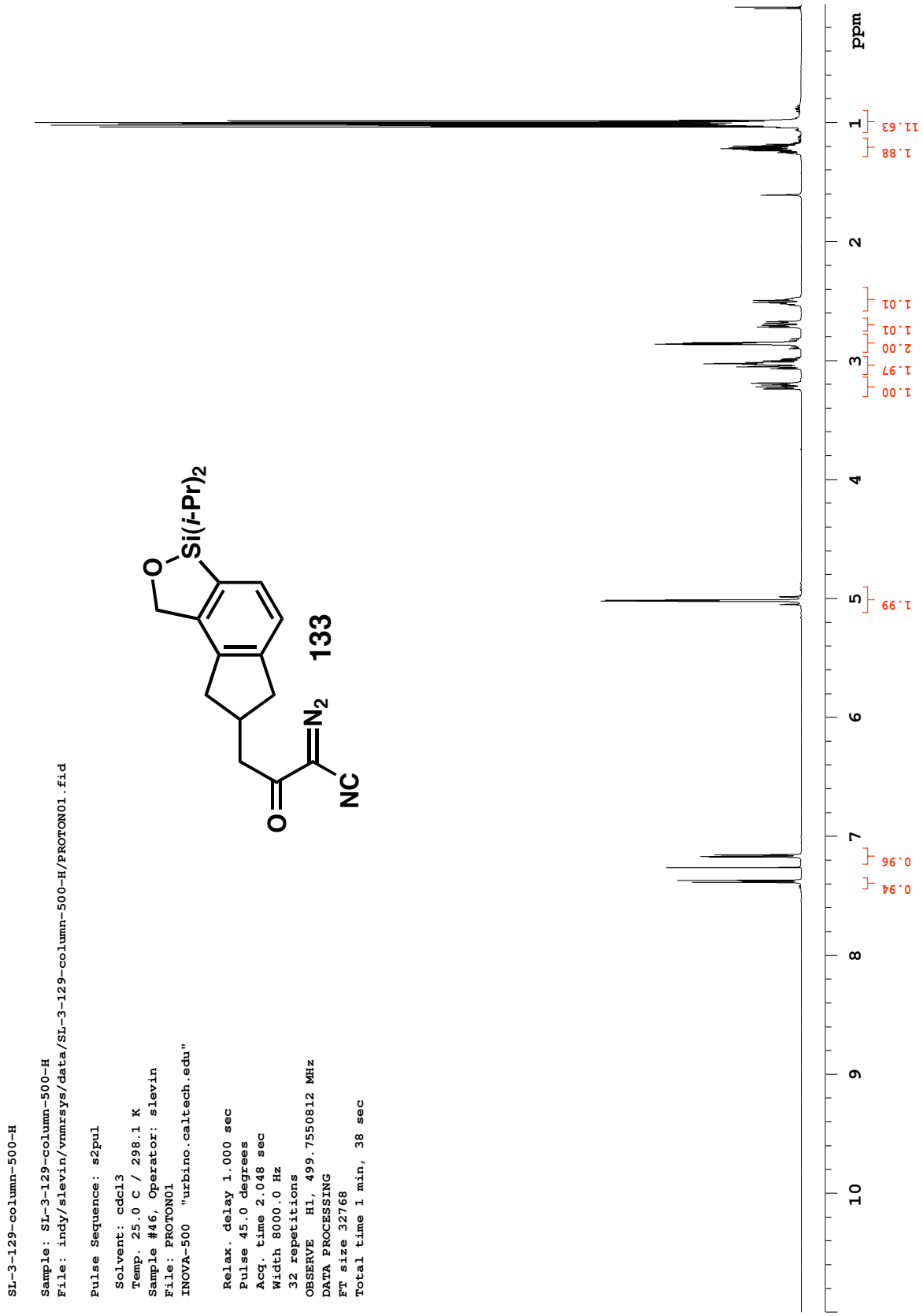
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"

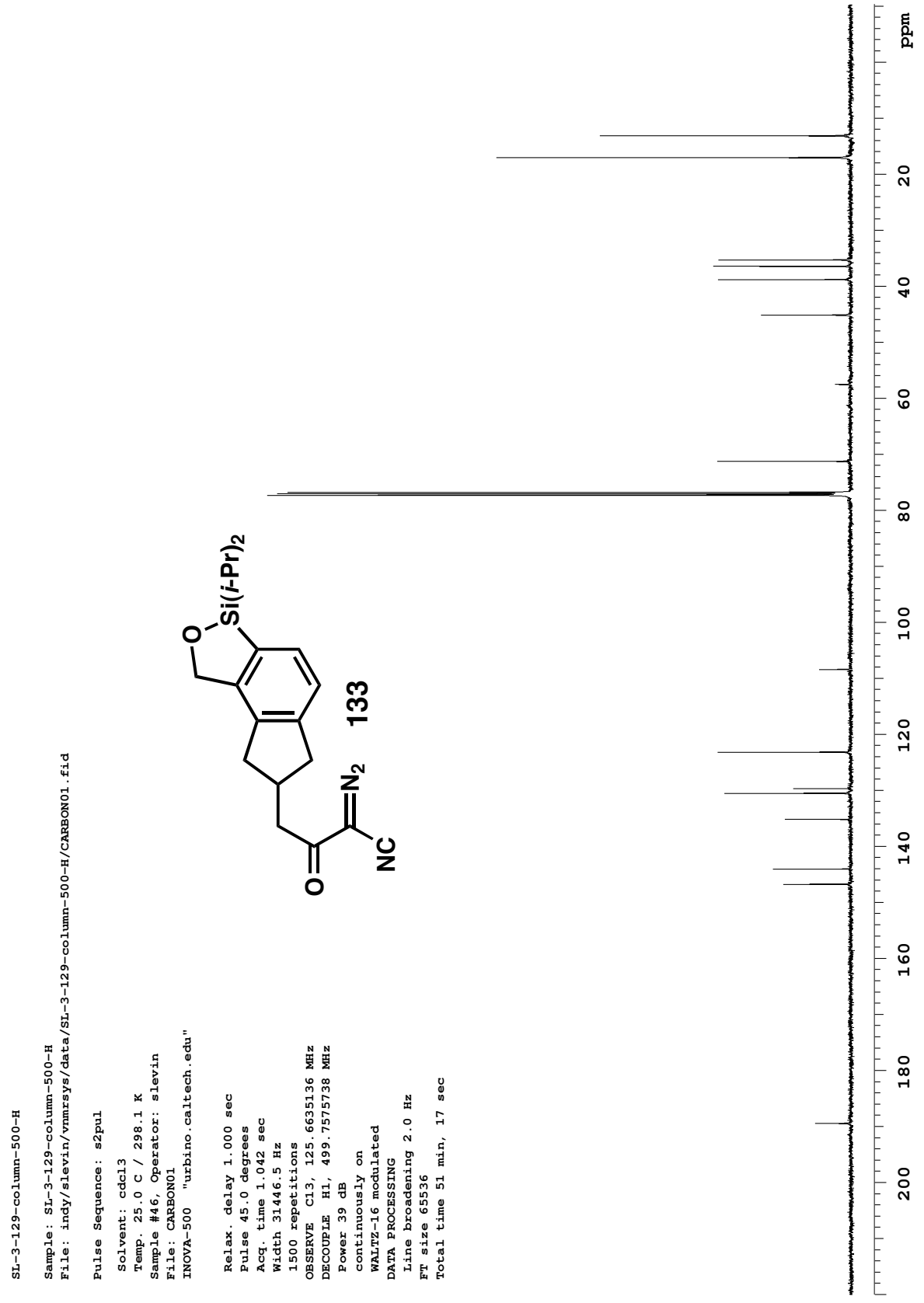
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1250 repetitions
OBSERVE C13, 125.6635196 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 42 min, 44 sec

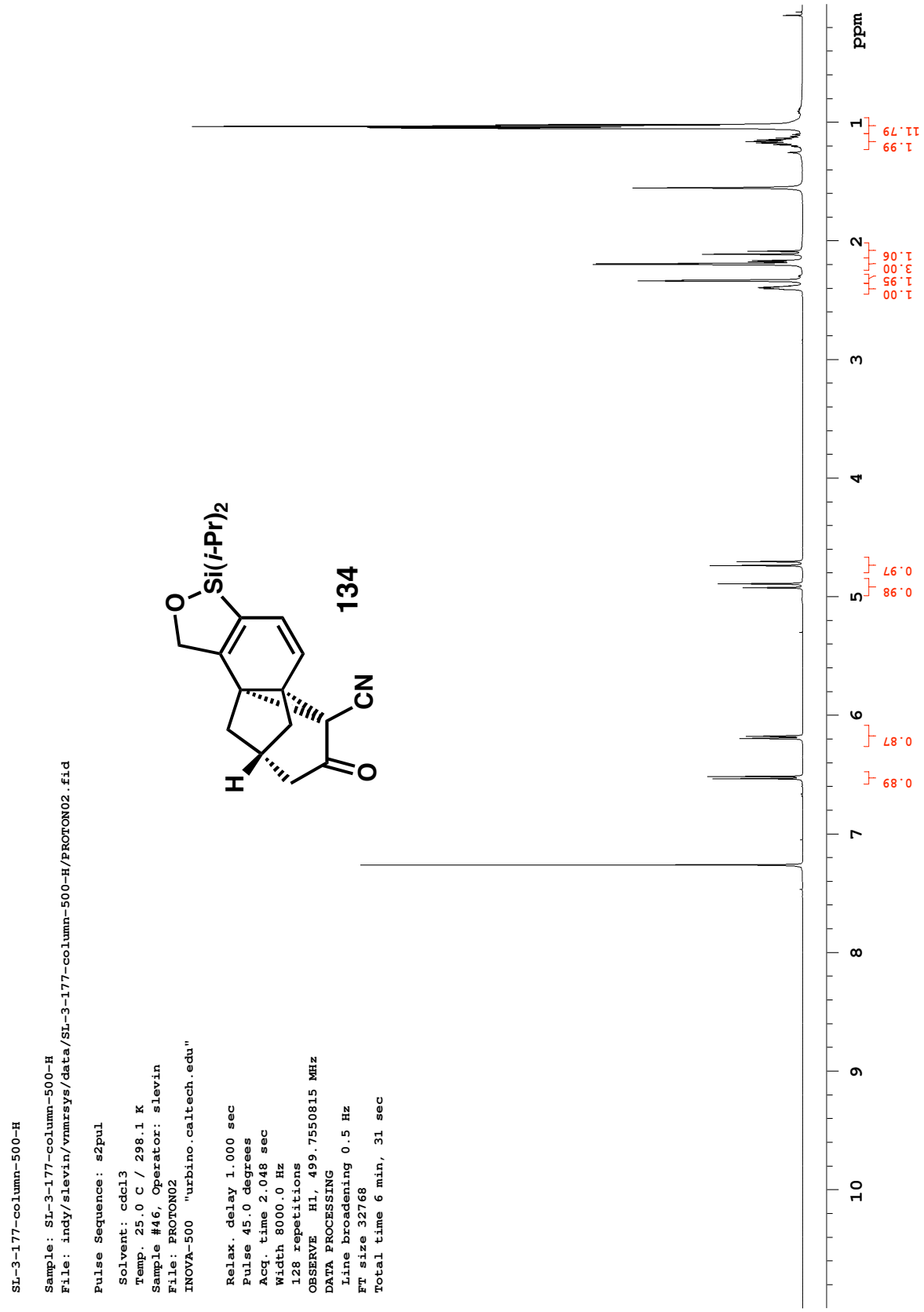


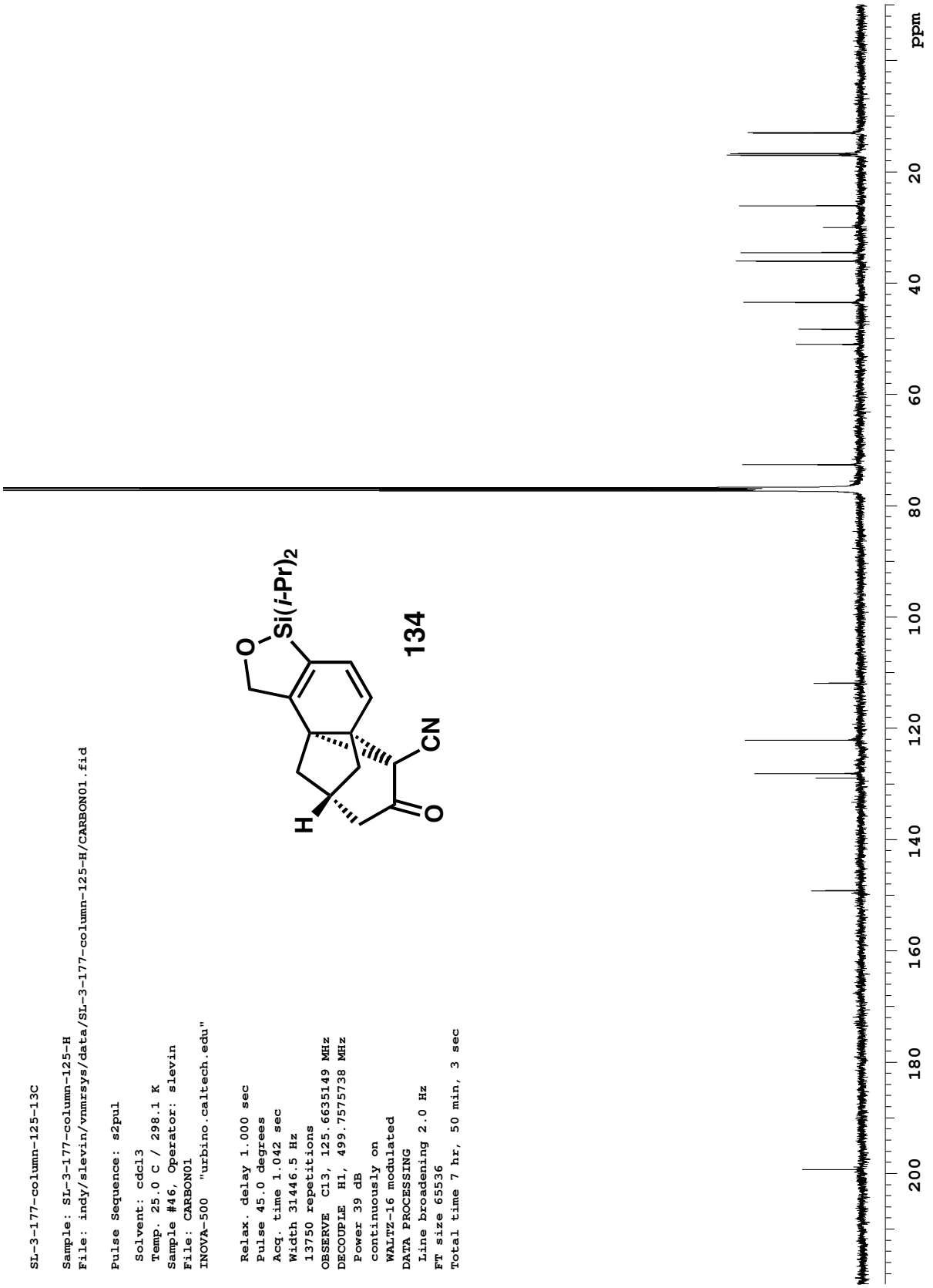
S11

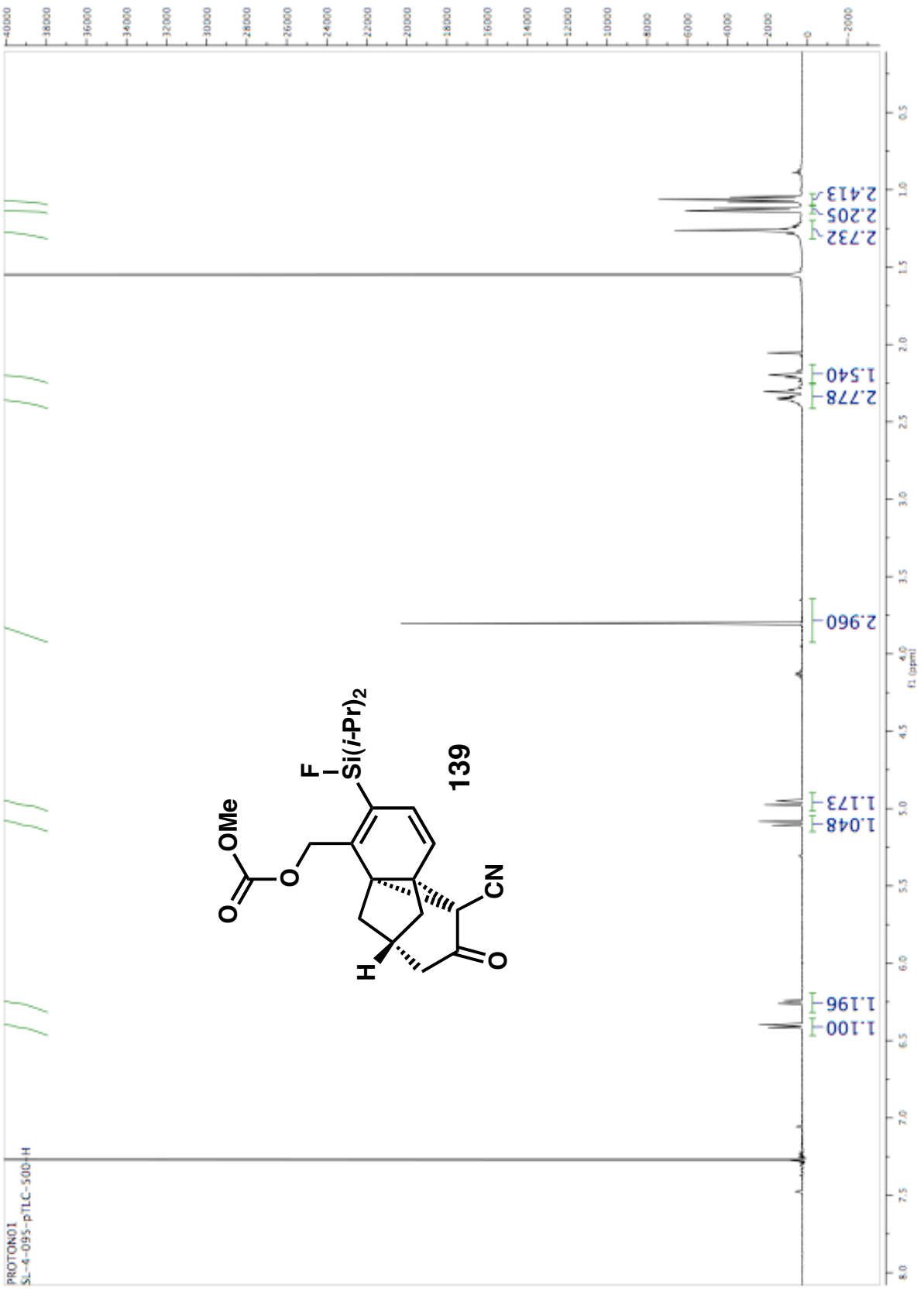


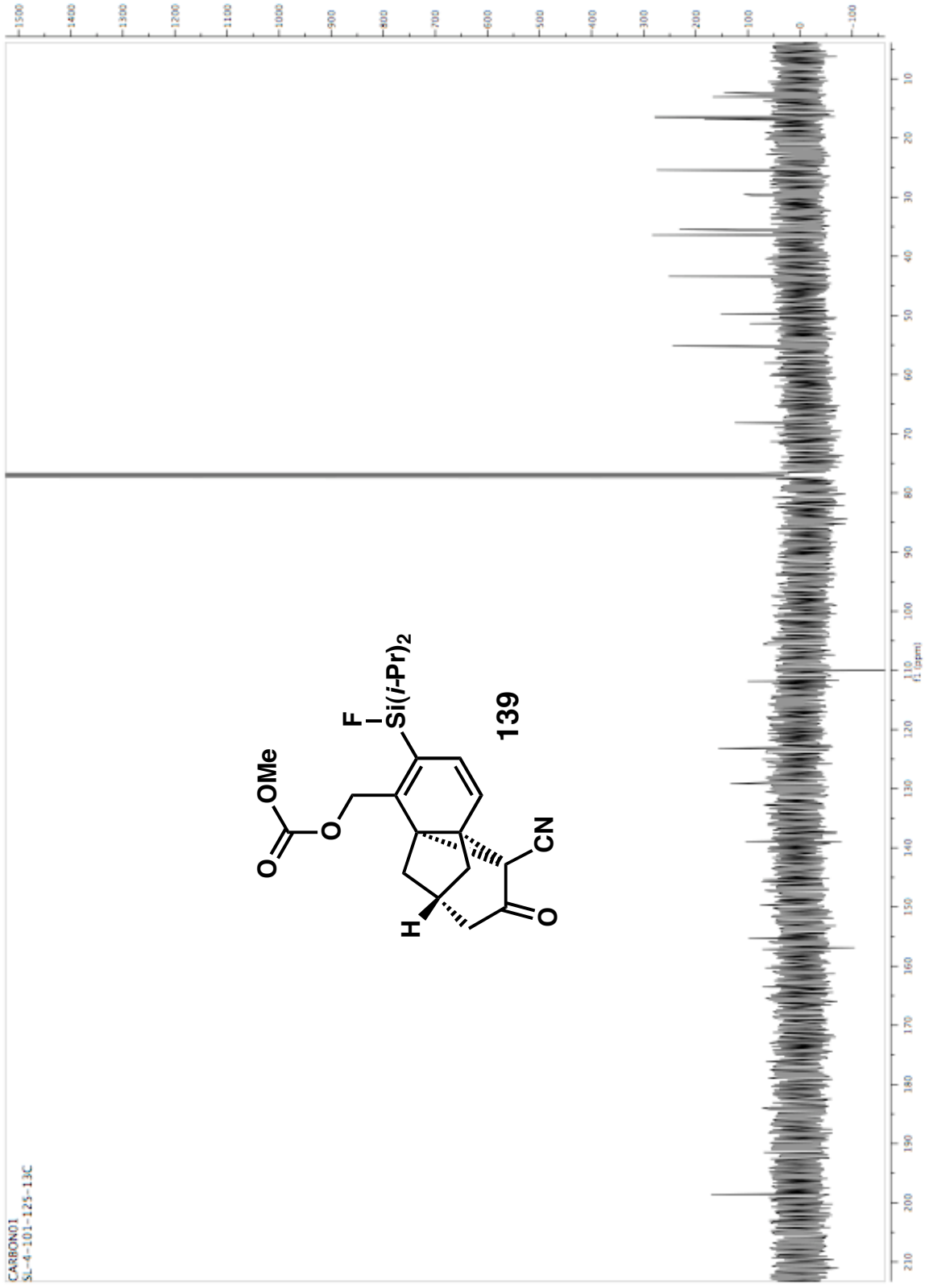

SL-3-129-column-500-H
Sample: SL-3-129-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-129-column-500-H/PROTON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: PROTON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7550812 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 38 sec
Si(i-Pr)2
O
O
N2
NC
133
ppm
1
2
3
4
5
6
7
8
9
10
11.63
1.88
1.01
1.01
2.00
1.97
1.00
1.99
0.96
0.94

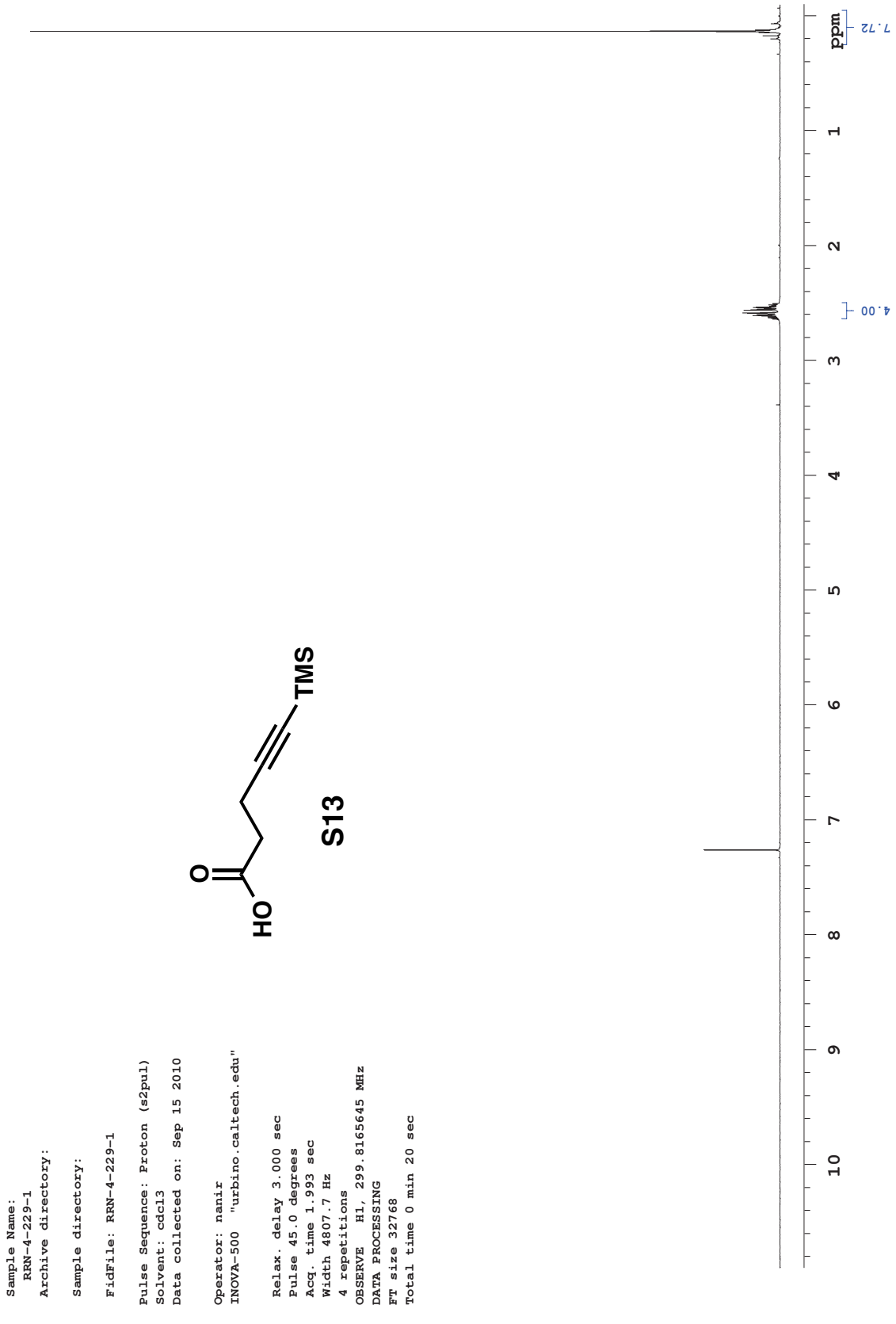

SL-3-129-column-500-H
Sample: SL-3-129-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-129-column-500-H/CARBON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6635136 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 51 min, 17 sec
O
Si(i-Pr)2
O
N2
NC
133
200
180
160
140
120
100
80
60
40
20
ppm

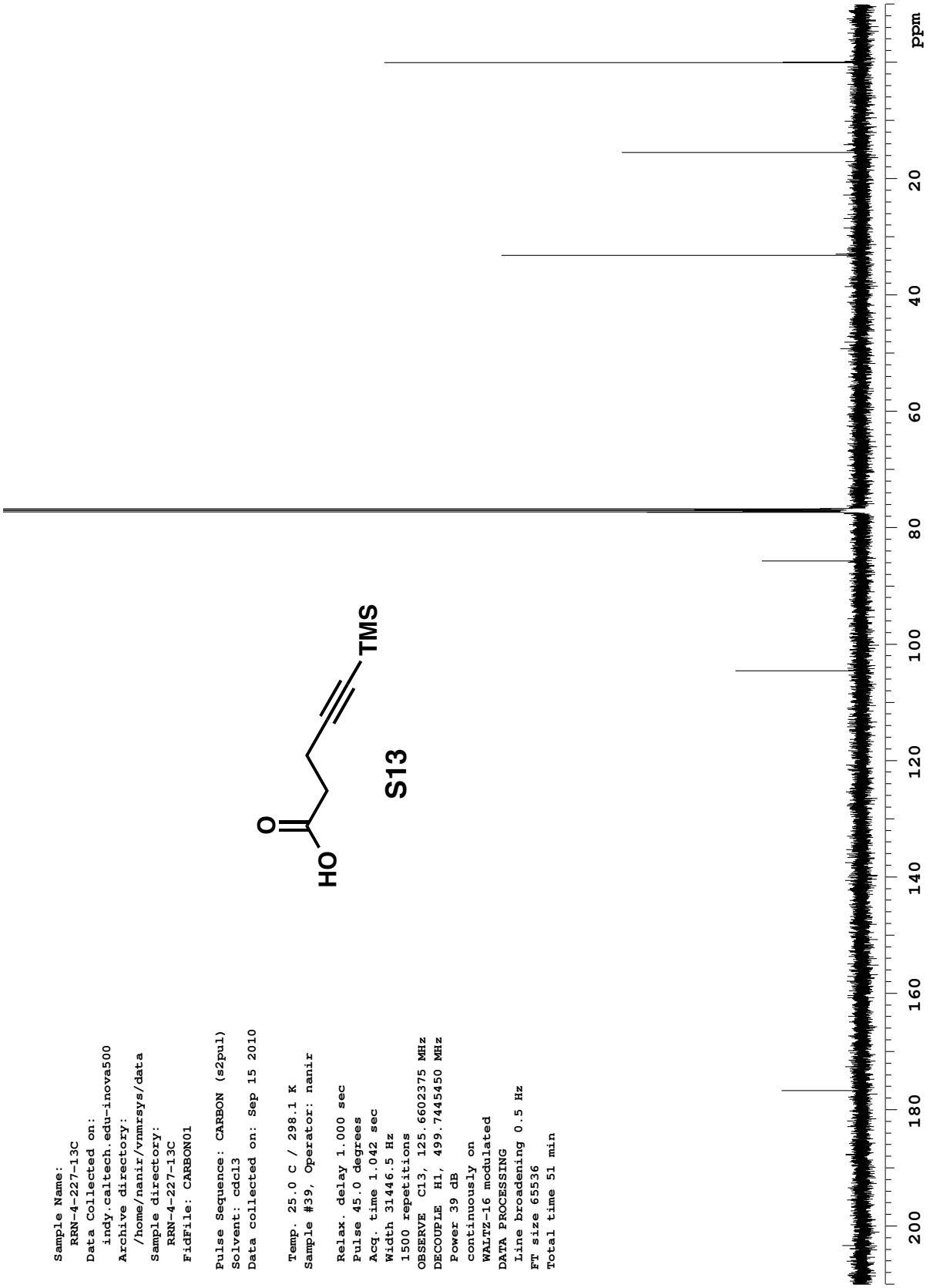

SL-3-177-column-500-H
Sample: SL-3-177-column-500-H
File: indy/slevin/vnmrsys/data/SL-3-177-column-500-H/PROTON02.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: PROTON02
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7550815 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 6 min, 31 sec
Si(i-Pr)2
O
H
O
CN
134
ppm
1
2
3
4
5
6
7
8
9
10
11.79
1.99
1.06
3.00
1.95
1.00
0.97
0.98
0.87
0.89

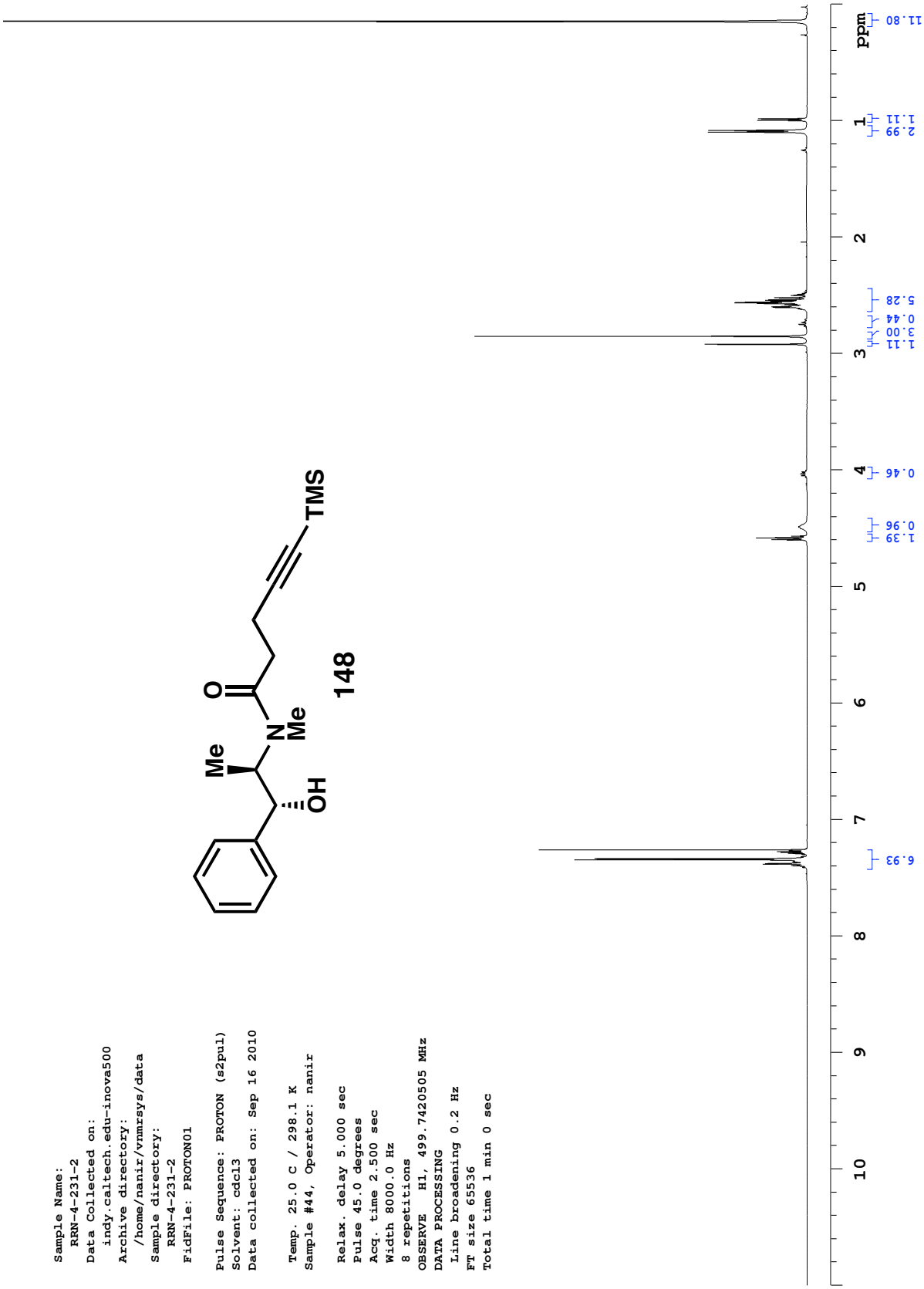

SL-3-177-column-125-13C
Sample: SL-3-177-column-125-H
File: indy/slevin/vnmrsys/data/SL-3-177-column-125-H/CARBON01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
File: CARBON01
INOVA-500 "urbino.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13750 repetitions
OBSERVE C13, 125.6635149 MHz
DECOUPLE H1, 499.7575738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 7 hr, 50 min, 3 sec
O
Si(i-Pr)2
CN
H
O
134
200
180
160
140
120
100
80
60
40
20
ppm

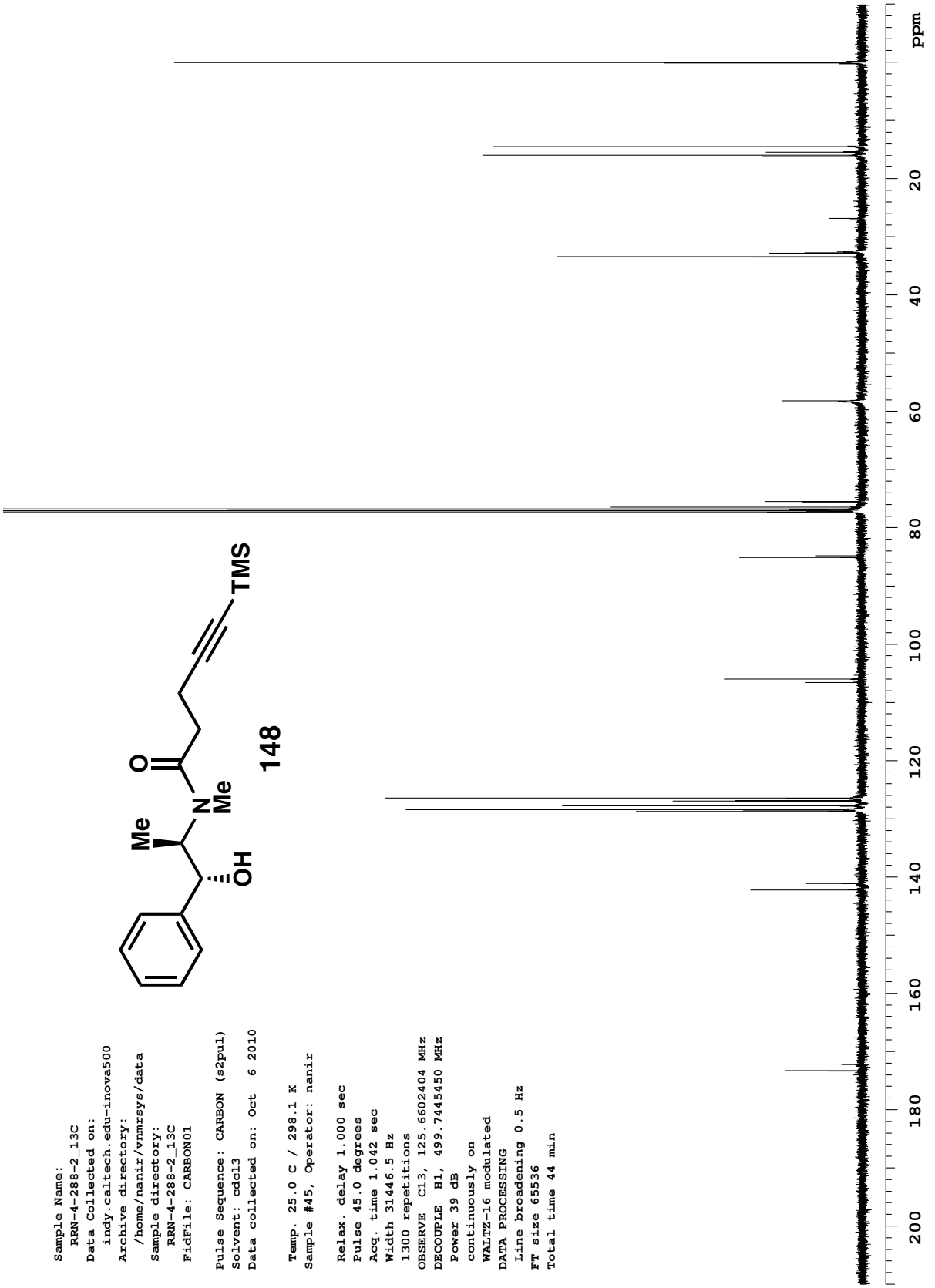

2.413
2.205
2.732
1.540
2.778
2.960
1.173
1.048
1.196
1.100
139
F
Si(i-Pr)2
OMe
O
O
CN
O
H
PROTON01
SL-4-095-pTLC-500+H
f1 (ppm)

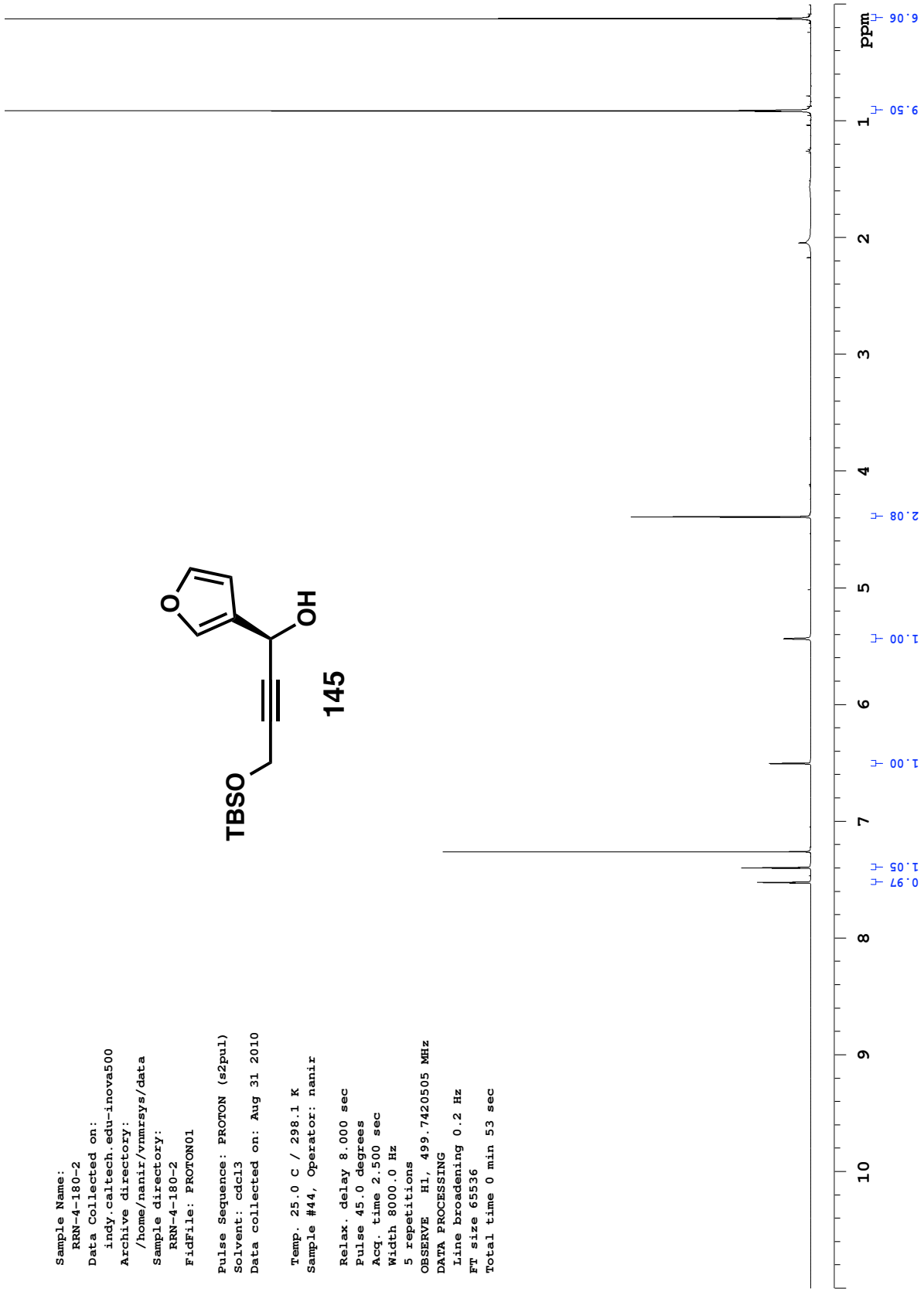

CARBON01
SL-4-101-125-13C
f1 (ppm)
OMe
O
O
F
Si(i-Pr)2
CN
O
H
139

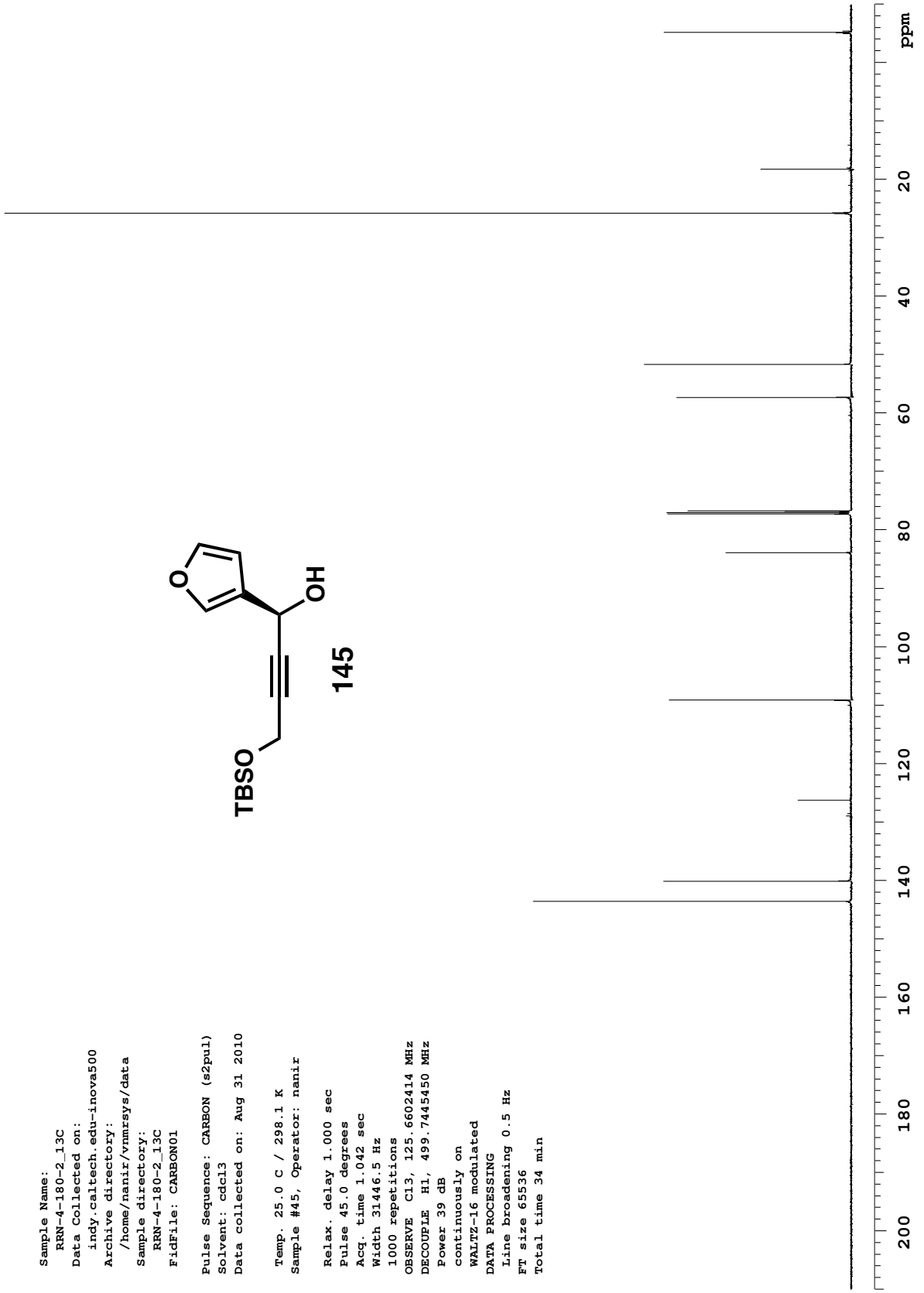

Sample Name:
RRN-4-229-1
Archive directory:
Sample directory:
FidFile: RRN-4-229-1
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Sep 15 2010
Operator: nanir
INOVA-500 "uzbino.caltech.edu"
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.993 sec
Width 4807.7 Hz
4 repetitions
OBSERVE H1, 299.8165645 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 20 sec
HO
O
TMS
S13
ppm
7.72
4.00


Sample Name:
RRN-4-227-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-227-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 15 2010
Temp. 25.0 C / 298.1 K
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6602375 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
HO
O
TMS
S13
200
180
160
140
120
100
80
60
40
20
ppm

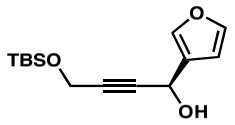

Sample Name:
RRN-4-231-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-231-2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 16 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
Me
OH
N
Me
O
TMS
148
ppm
11.80
6.93
1.39
0.96
0.46
5.28
0.44
3.00
1.11
2.99
1.11


Sample Name:
RRN-4-288-2_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-288-2_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 6 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6602404 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 44 min
Me
N
Me
O
OH
TMS
148
200
180
160
140
120
100
80
60
40
20
ppm


Sample Name:
RRN-4-180-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-180-2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: nanir
Relax. delay 8.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
5 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 53 sec
O
OH
TBSO
145
ppm
6.06
9.50
2.08
1.00
1.00
1.05
0.97

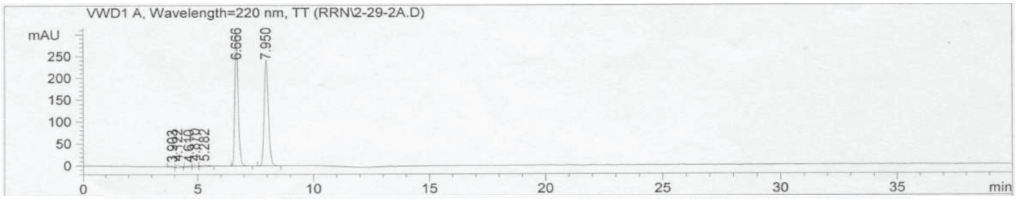

Sample Name:
RRN-4-180-2_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-180-2_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6602414 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
O
OH
TBSO
145
200
180
160
140
120
100
80
60
40
20
ppm

Chromatograms of racemic and enantiomerically enriched propargyl alcohol 9



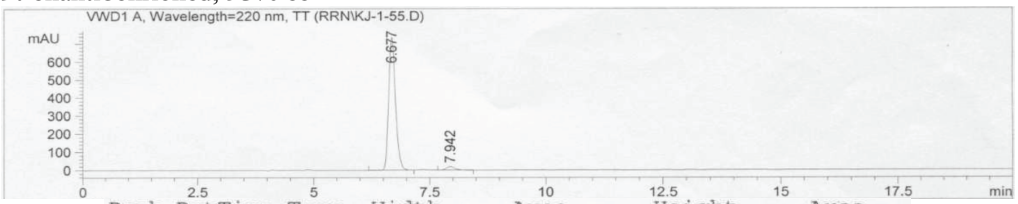
9

9: racemic



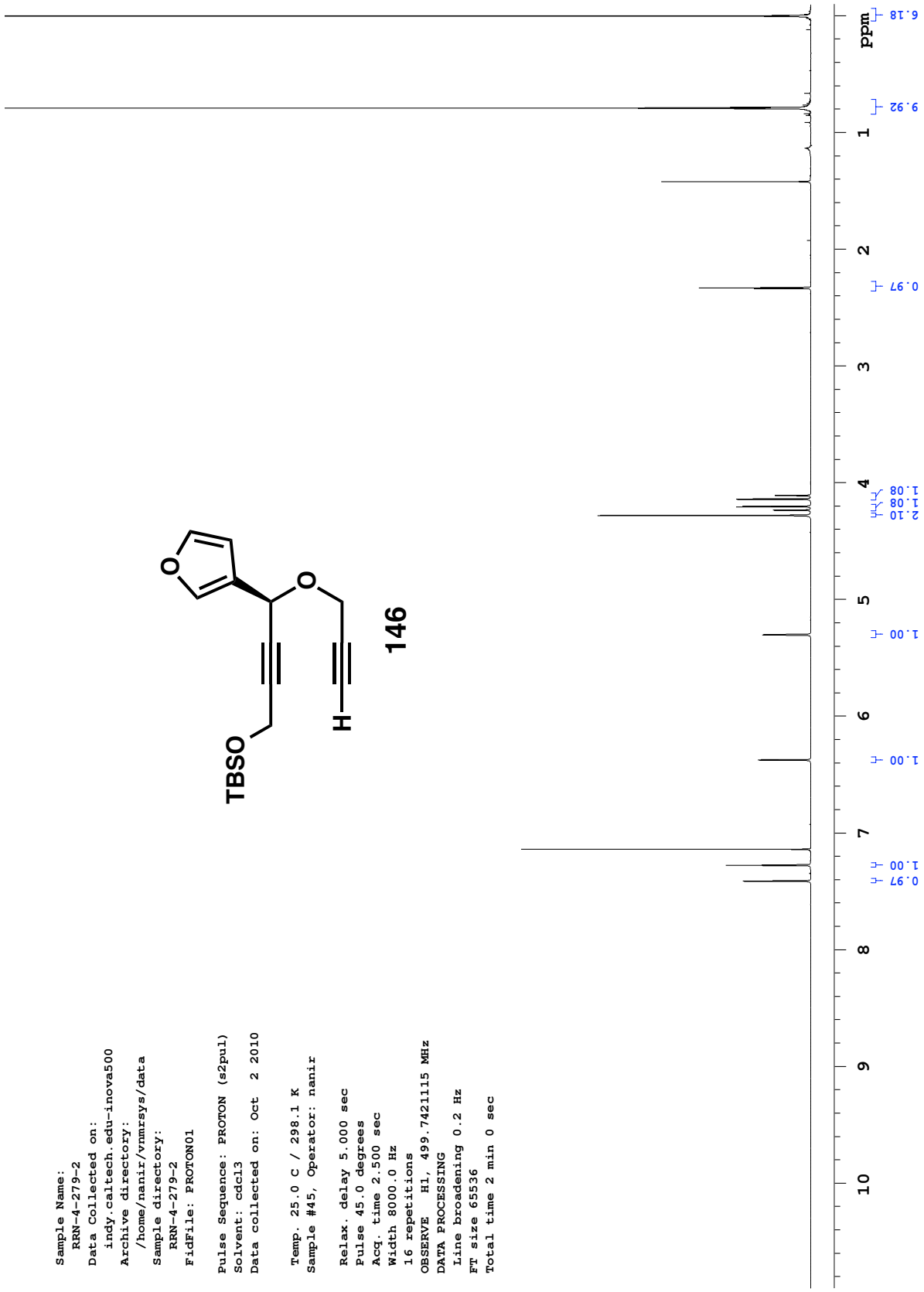
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.903	BP	0.1998	33.27868	2.74223	0.5267
2	4.122	VB	0.1546	68.28712	6.20676	1.0808
3	4.610	BV	0.2080	47.00773	2.92367	0.7440
4	4.870	VV	0.1402	51.05111	5.03297	0.8080
5	5.282	VB	0.2295	57.73202	3.26651	0.9138
6	6.666	PB	0.1531	3023.55933	302.17783	47.8553
7	7.950	VP	0.1916	3037.20996	241.98224	48.0714

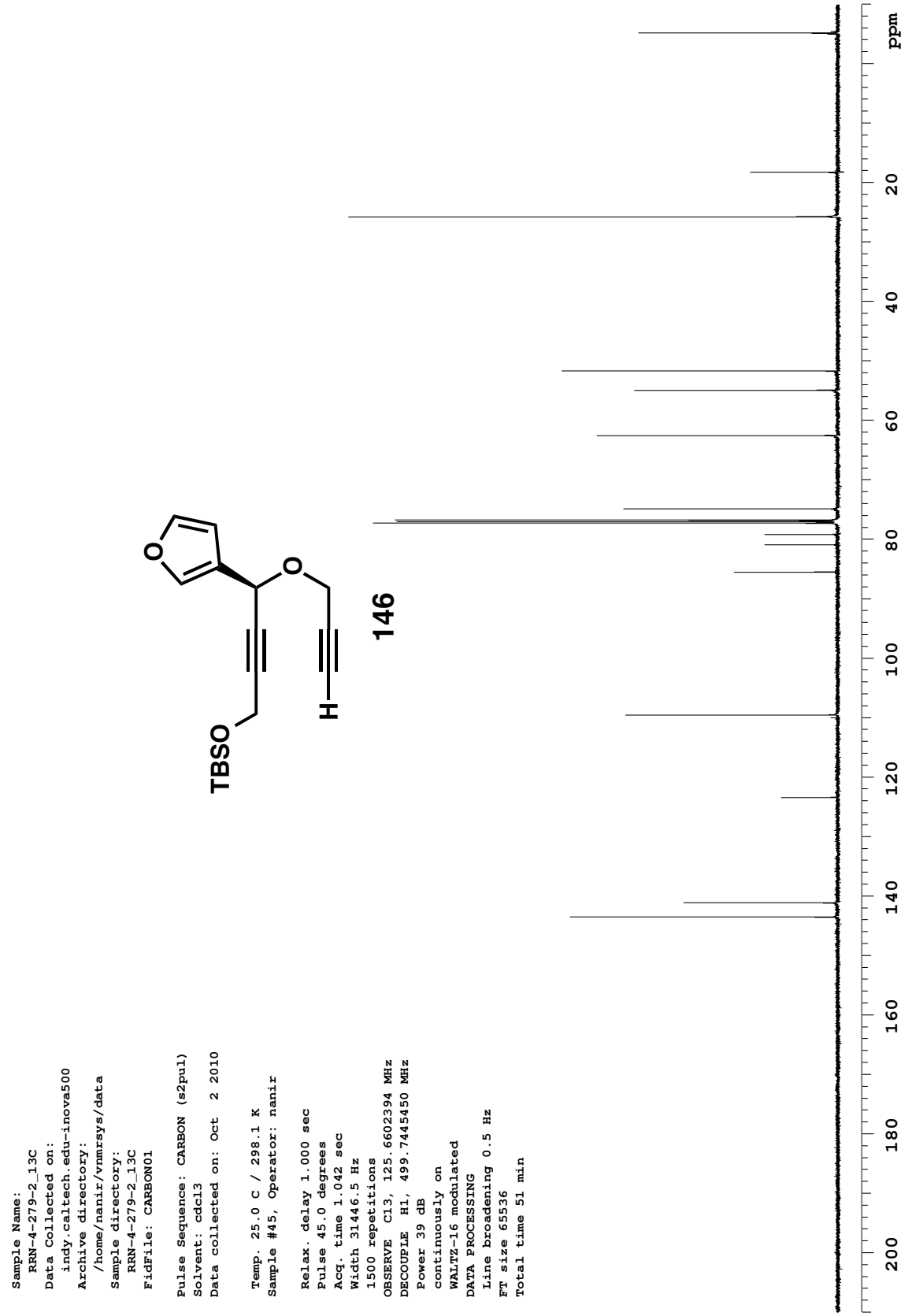
9: enantioenriched, 93% ee

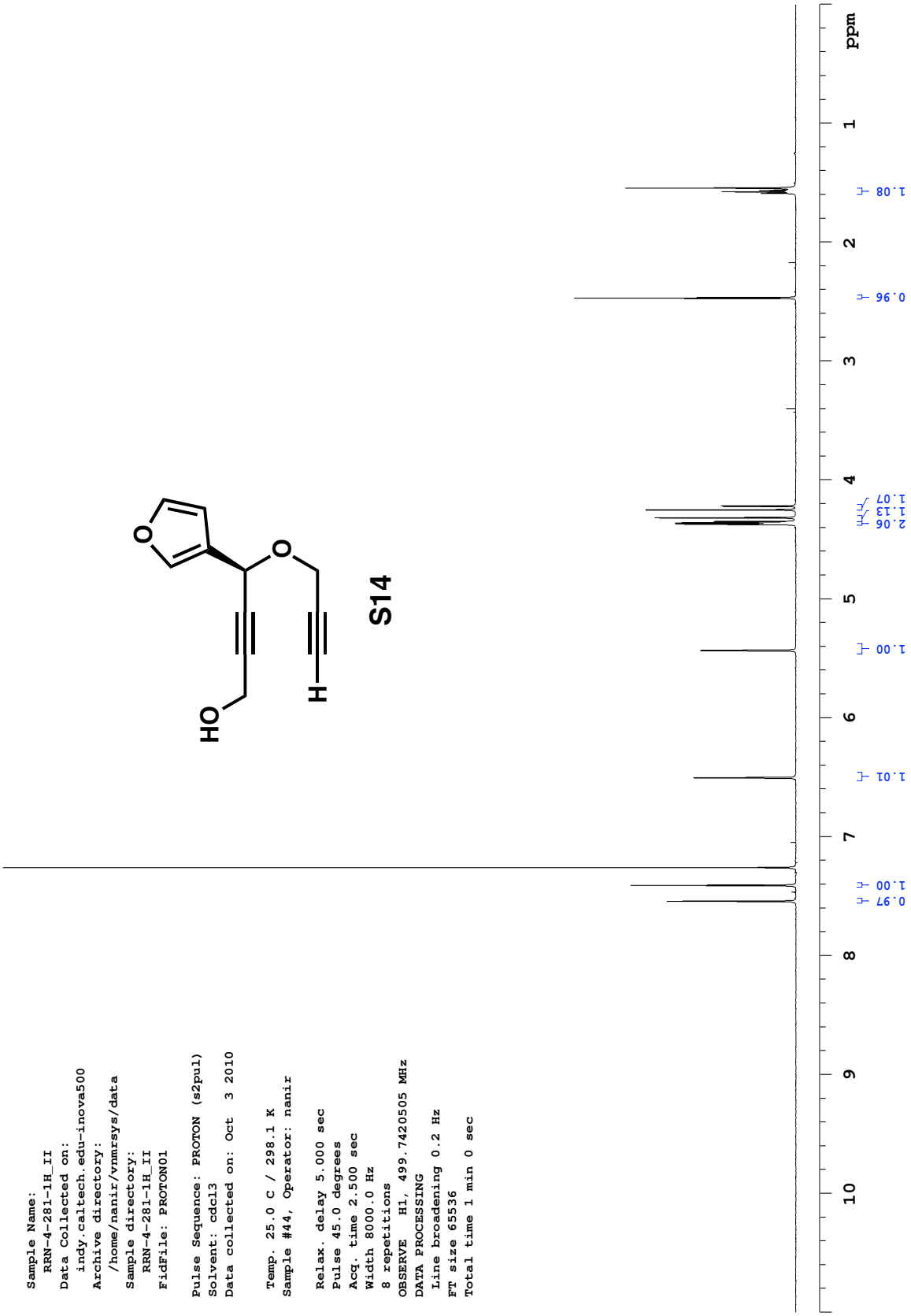


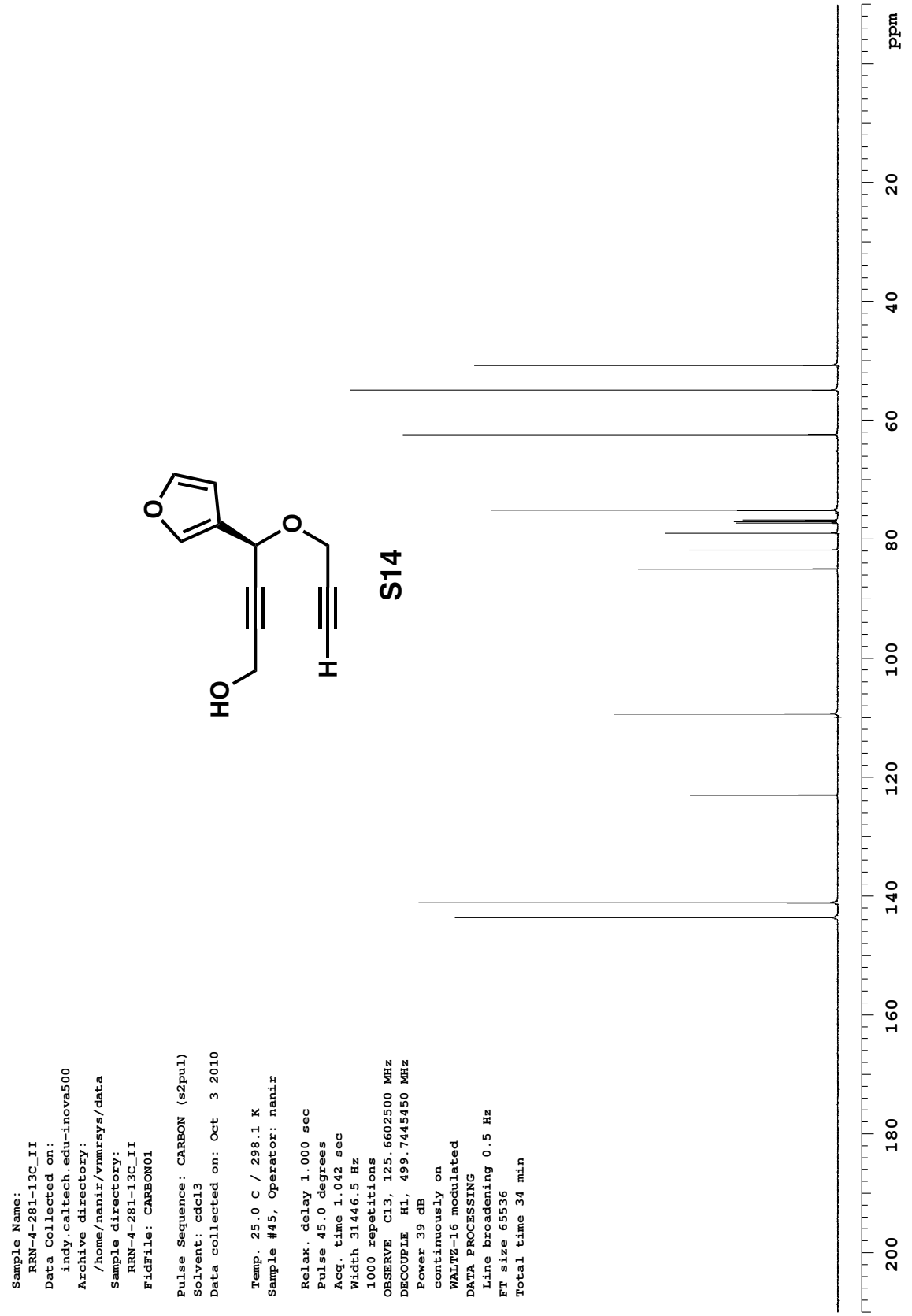
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.677	BV	0.1566	7498.69678	736.95380	96.7791
2	7.942	VB	0.1945	249.56261	19.49618	3.2209

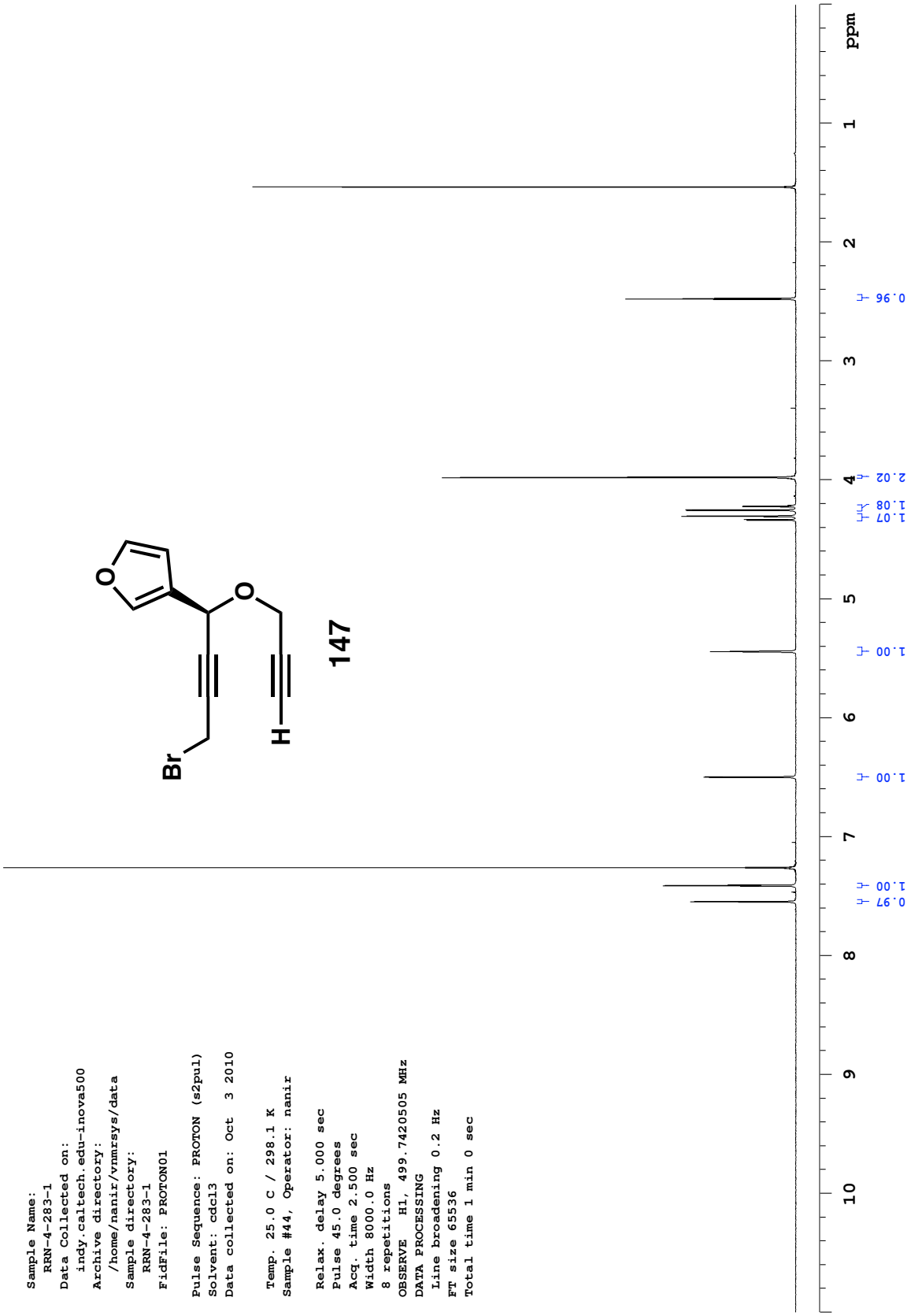
!

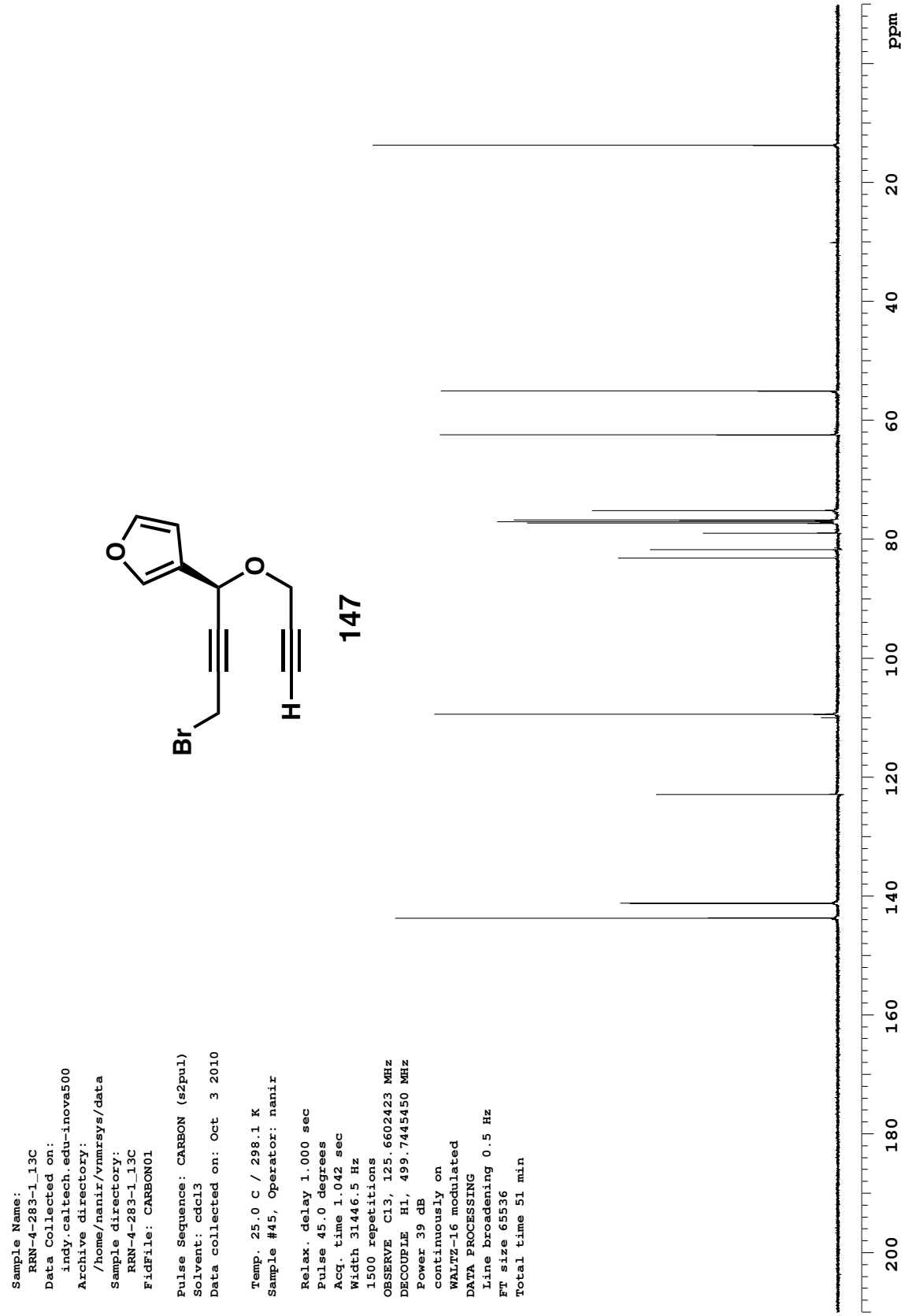

Sample Name:
RRN-4-279-2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-279-2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 2 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7421115 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 0 sec
TBSO
H
146
O
O
ppm
6.18
9.92
0.97
1.08
1.08
2.10
1.00
1.00
0.97
1.00

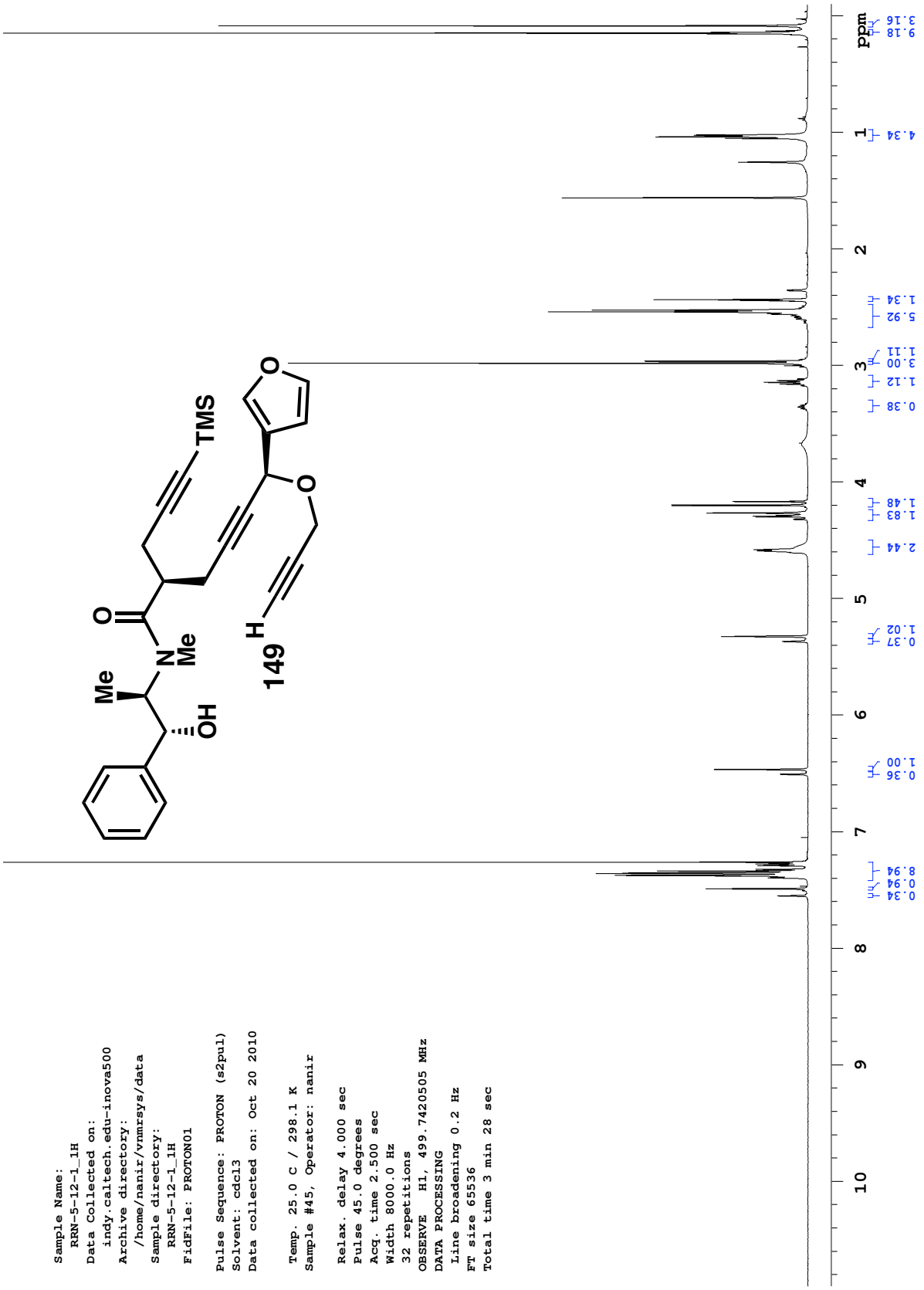

Sample Name:
RRN-4-279-2_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-279-2_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 2 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6602394 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
TBSO
O
O
H
146
200
180
160
140
120
100
80
60
40
20
ppm


Sample Name:
RRN-4-281-1H_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-281-1H_II
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 3 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
HO
O
O
H
S14
ppm
1.08
0.96
2.06
1.13
1.07
1.00
1.01
0.97
1.00

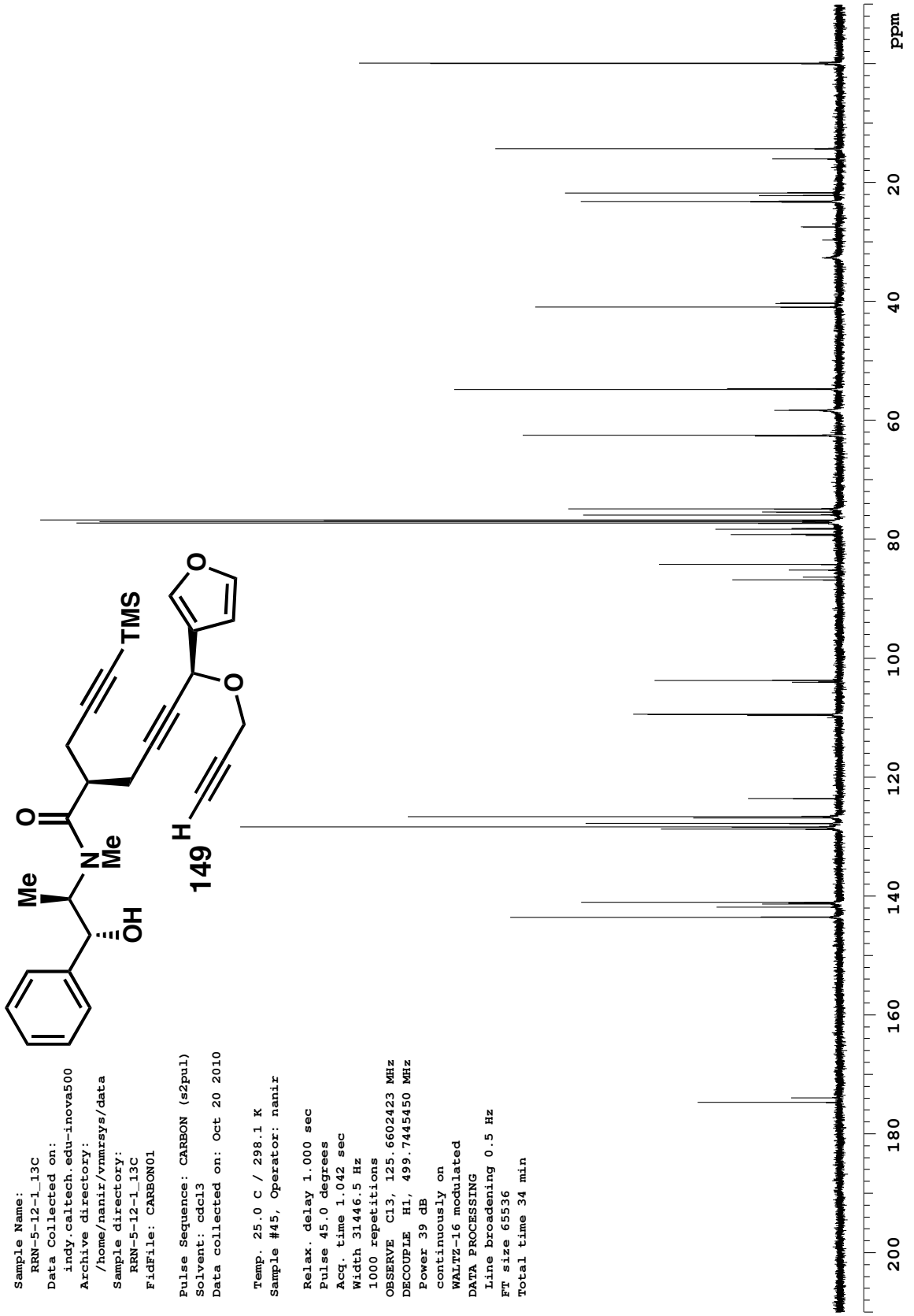

Sample Name:
RRN-4-281-13C_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-281-13C_II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 3 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6602500 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
HO
O
O
H
S14
200
180
160
140
120
100
80
60
40
20
ppm

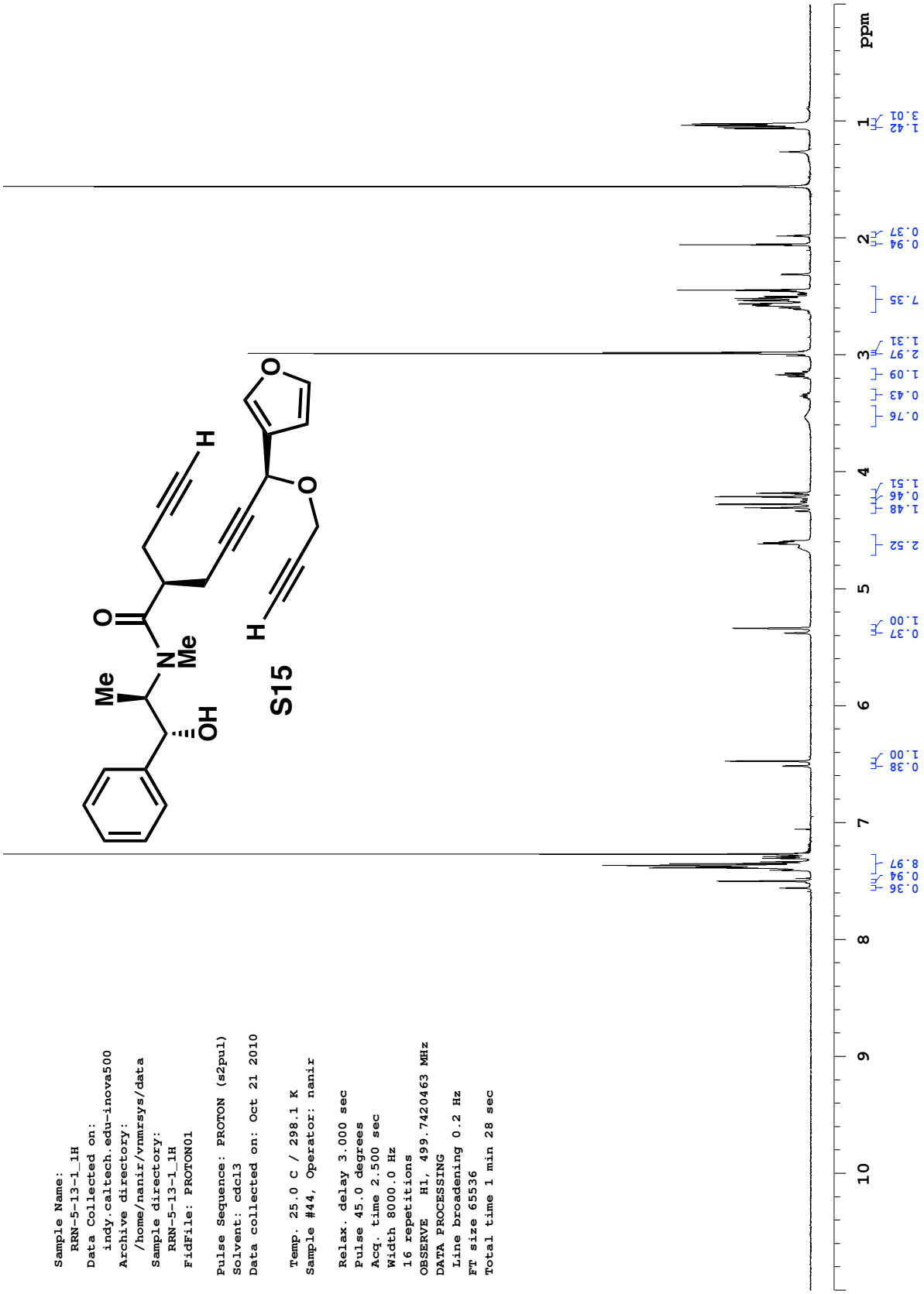

Sample Name:
RRN-4-283-1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-283-1
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 3 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
O
O
Br
H
147
ppm
0.96
2.02
1.07
1.08
1.00
1.00
0.97
1.00

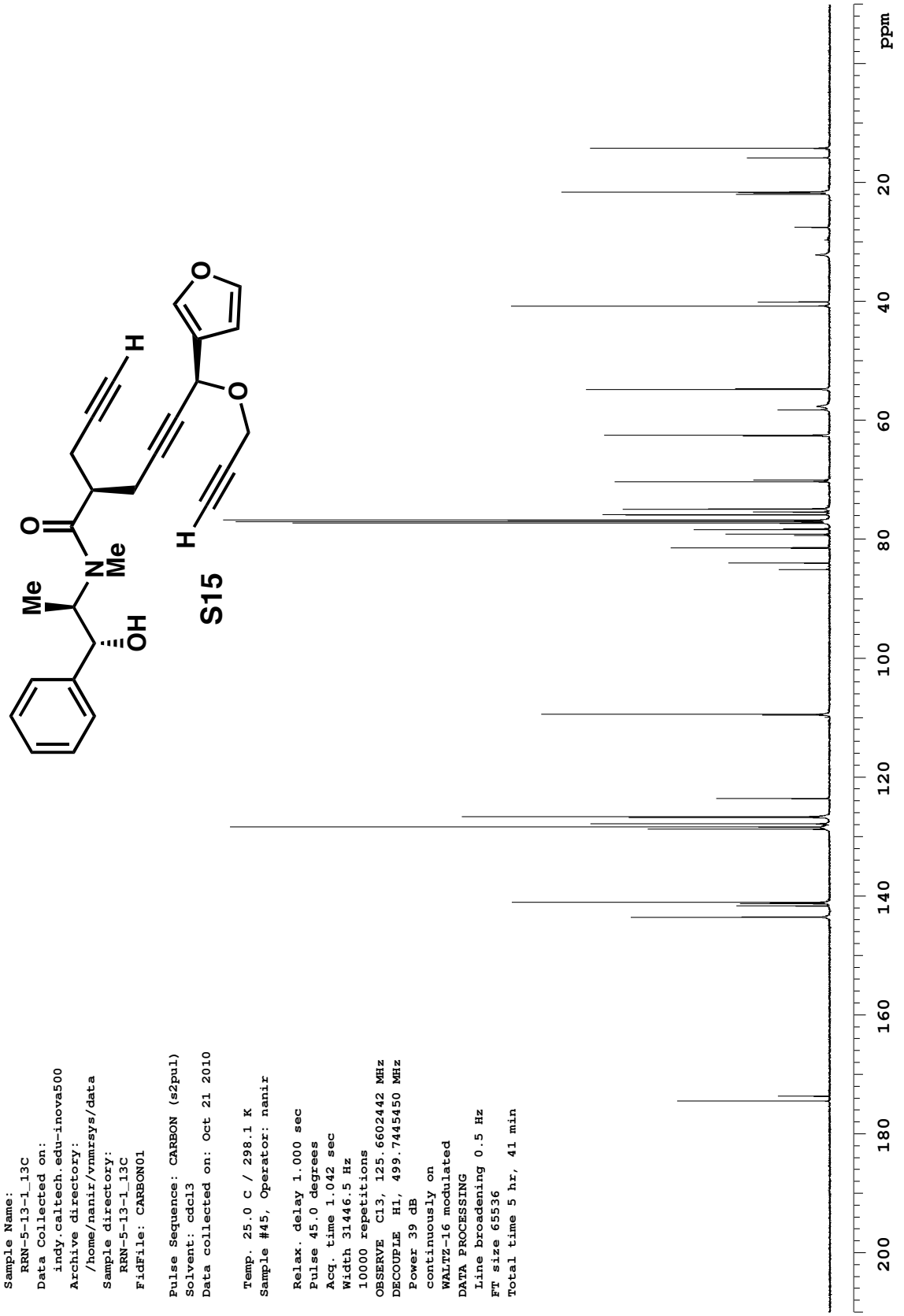

Sample Name:
RRN-4-283-1_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-283-1_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 3 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6602423 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
O
O
Br
H
147
200
180
160
140
120
100
80
60
40
20
ppm

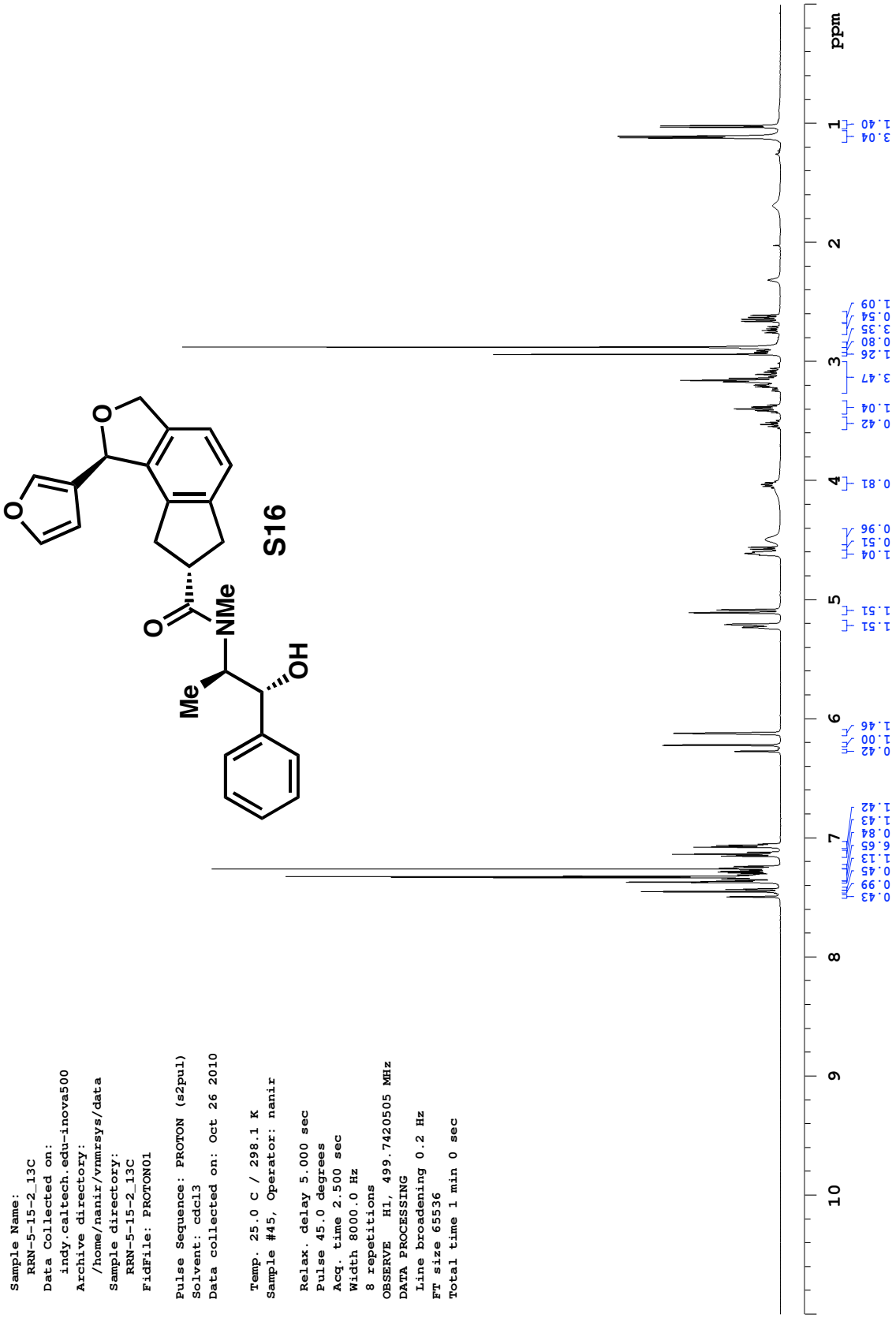


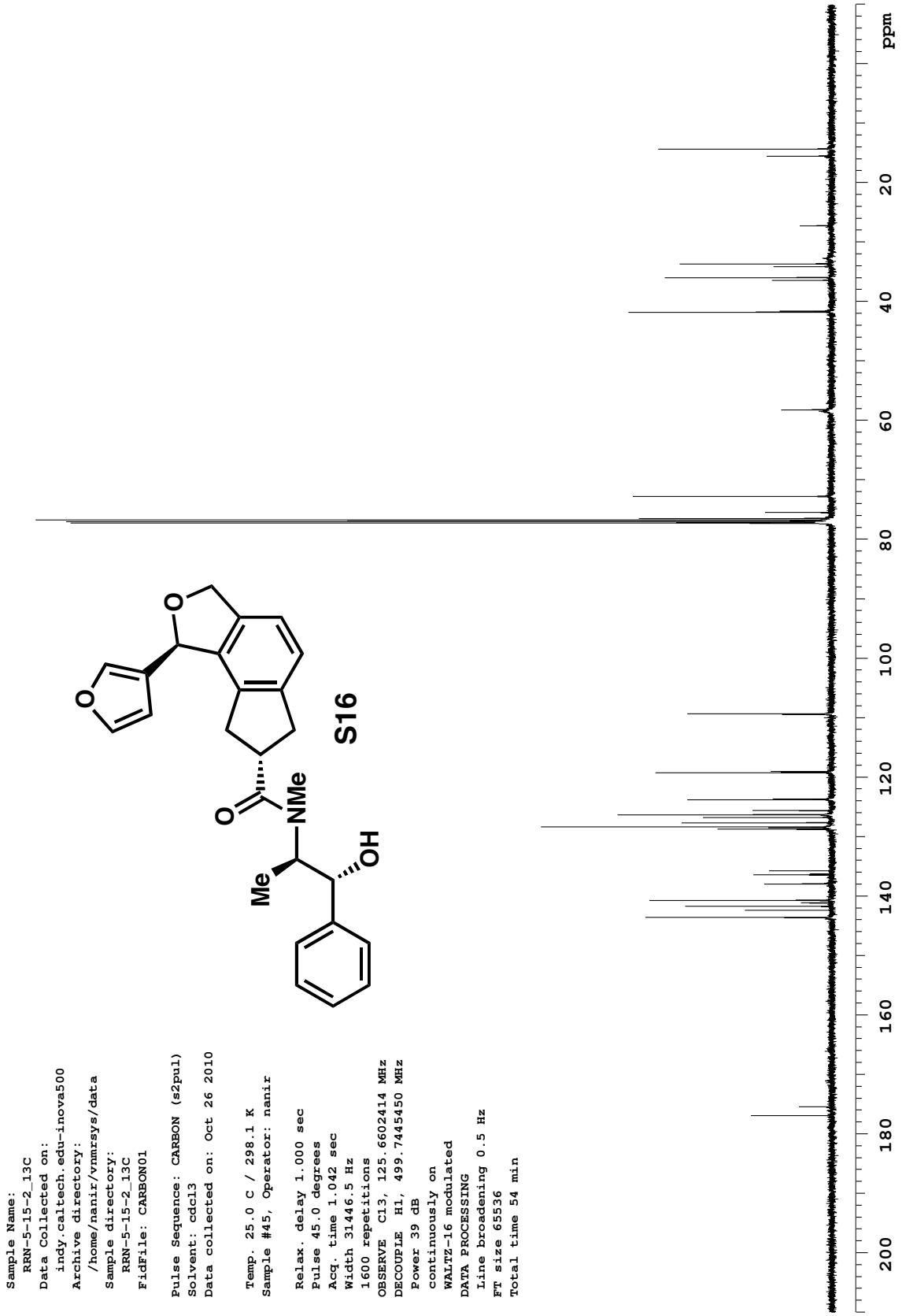

```
Sample Name:
  RRN-5-12-1_1H
Data Collected on:
  indy.caltech.edu-inova500
Archive directory:
  /home/nanir/vnmrsys/data
Sample directory:
  RRN-5-12-1_1H
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 20 2010

 Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir

Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE  H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 28 sec
```

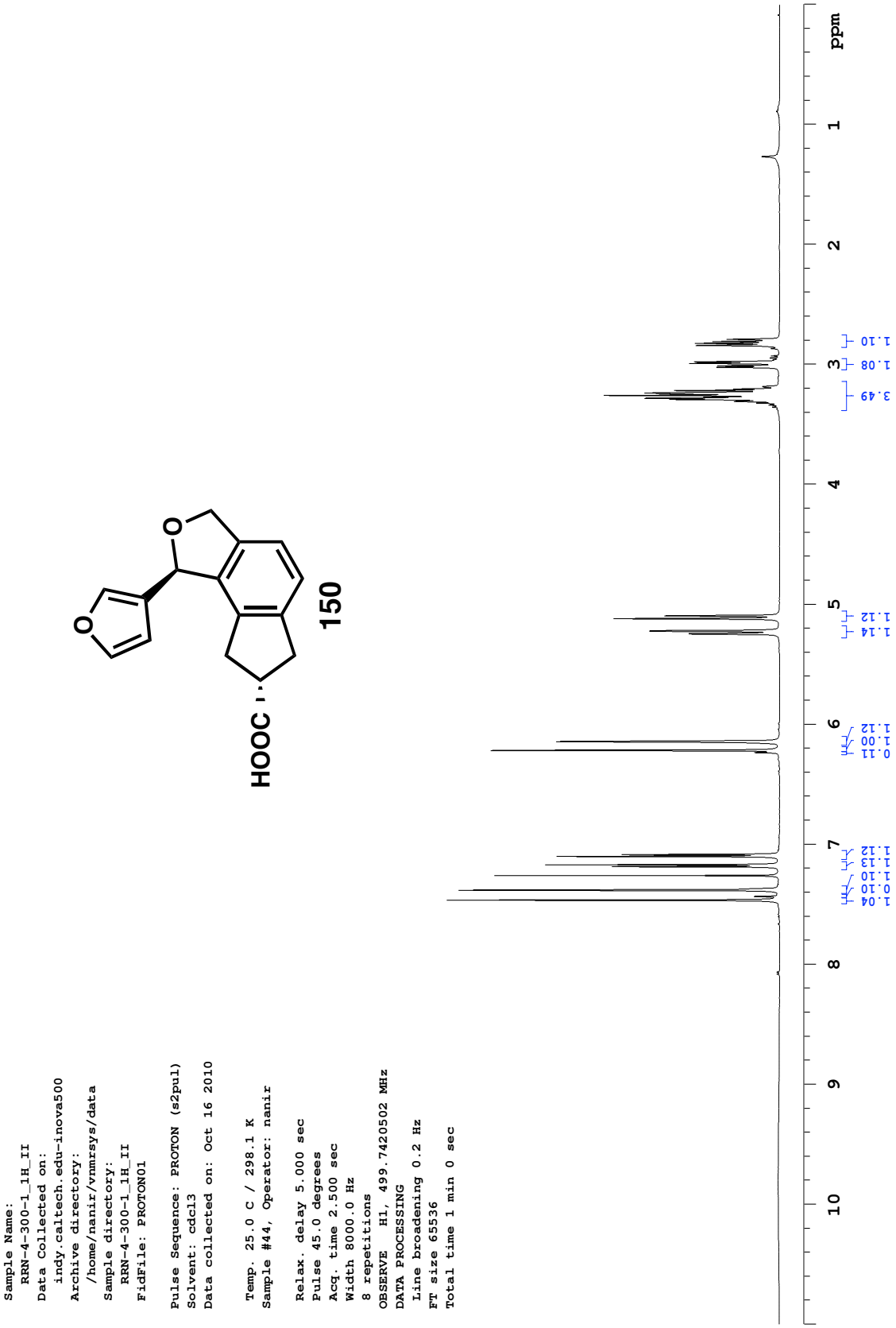

Sample Name:
RRN-5-12-1_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-12-1_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 20 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6602423 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 34 min
Me
O
N
Me
OH
TMS
O
O
H
149
ppm
200
180
160
140
120
100
80
60
40
20

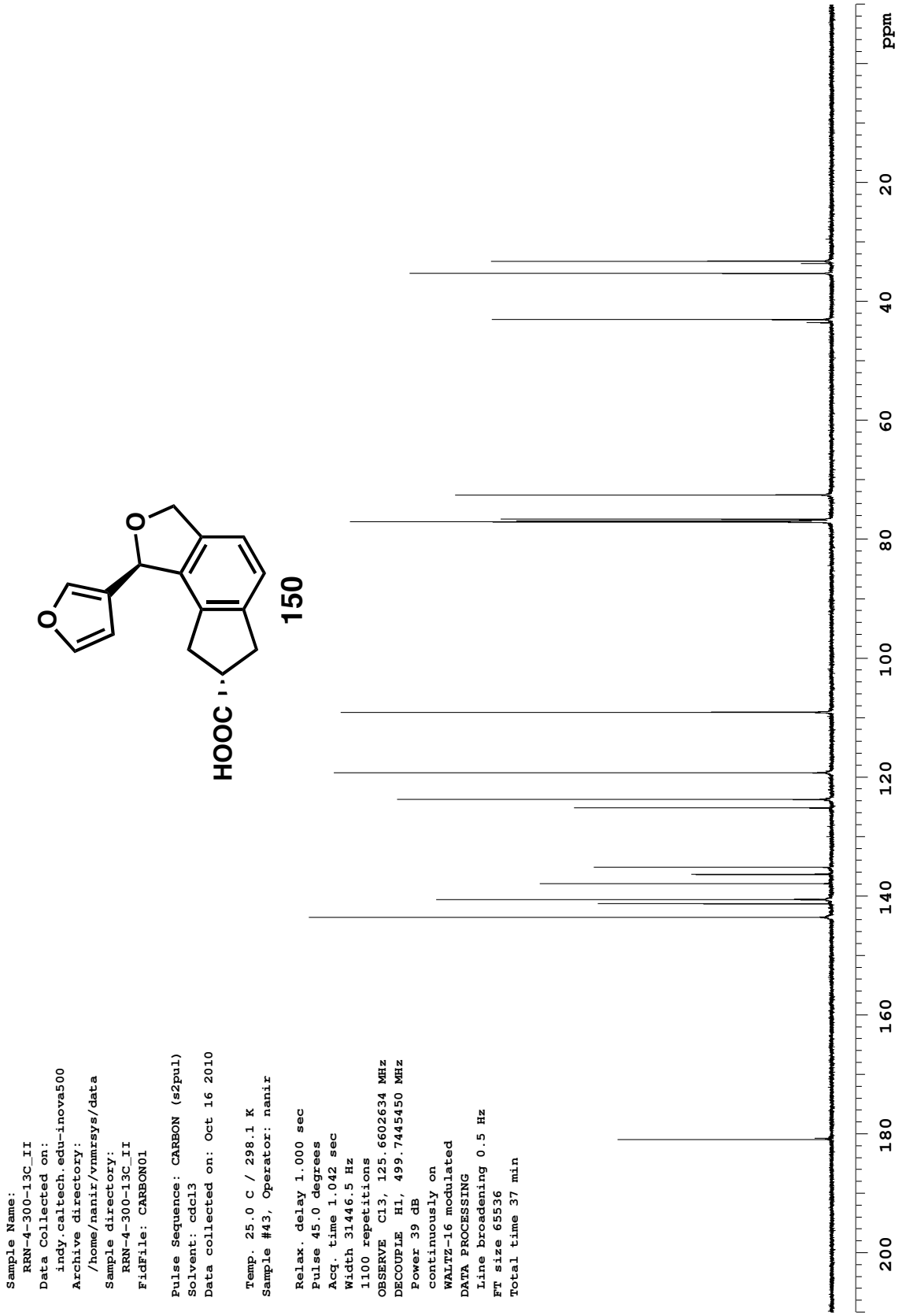

Sample Name:
RRN-5-13-1_1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-13-1_1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 21 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7420463 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
Me
N
Me
O
OH
O
O
H
H
S15
ppm
1.42
3.01
0.94
0.37
7.35
1.31
2.97
1.09
0.43
0.76
1.48
0.46
1.51
2.52
0.37
1.00
0.38
1.00
0.36
0.94
8.97

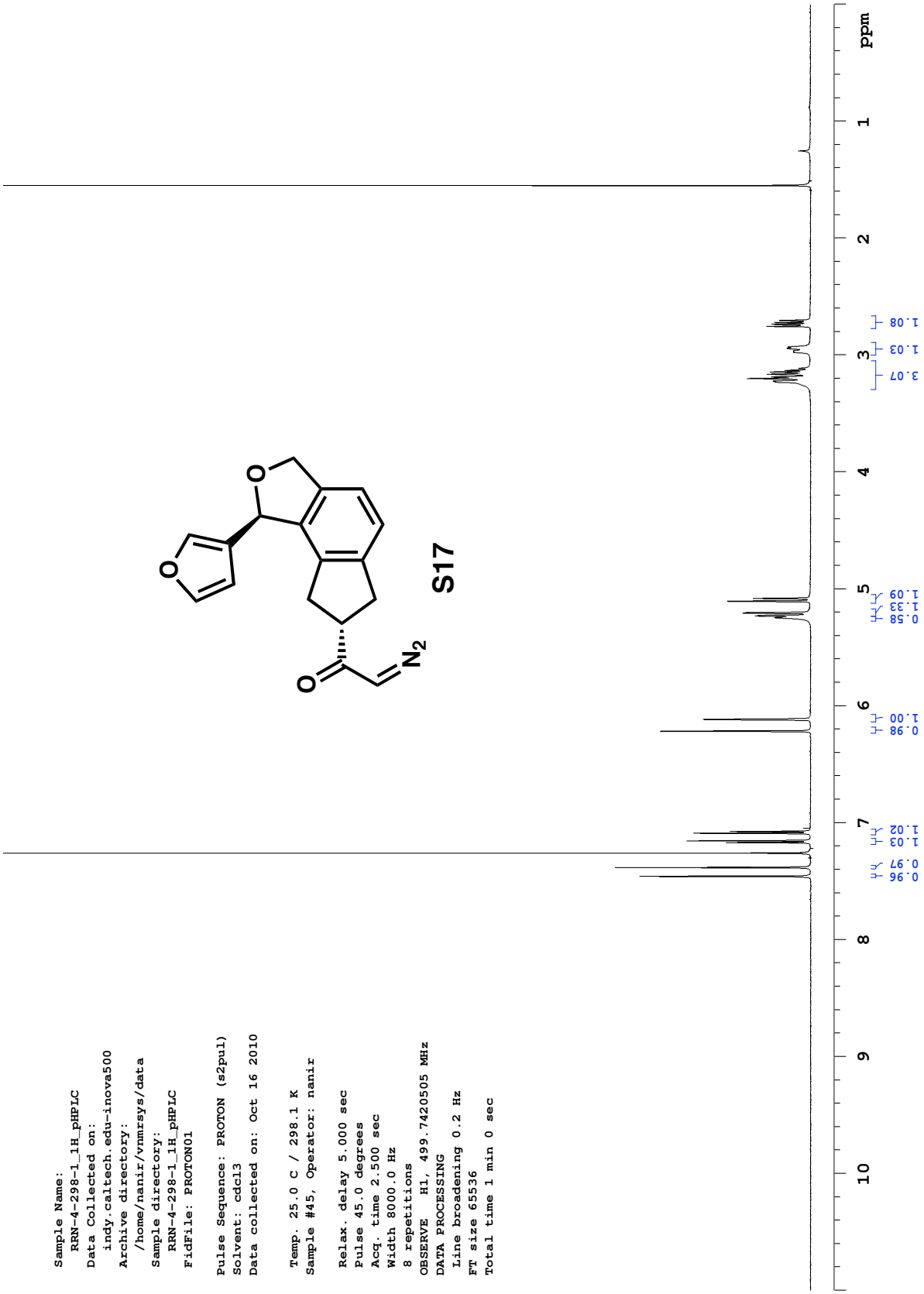

Sample Name:
RRN-5-13-1_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-13-1_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 21 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
10000 repetitions
OBSERVE C13, 125.6602442 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 5 hr, 41 min
Me
N
Me
O
OH
H
O
O
H
S15
200
180
160
140
120
100
80
60
40
20
ppm

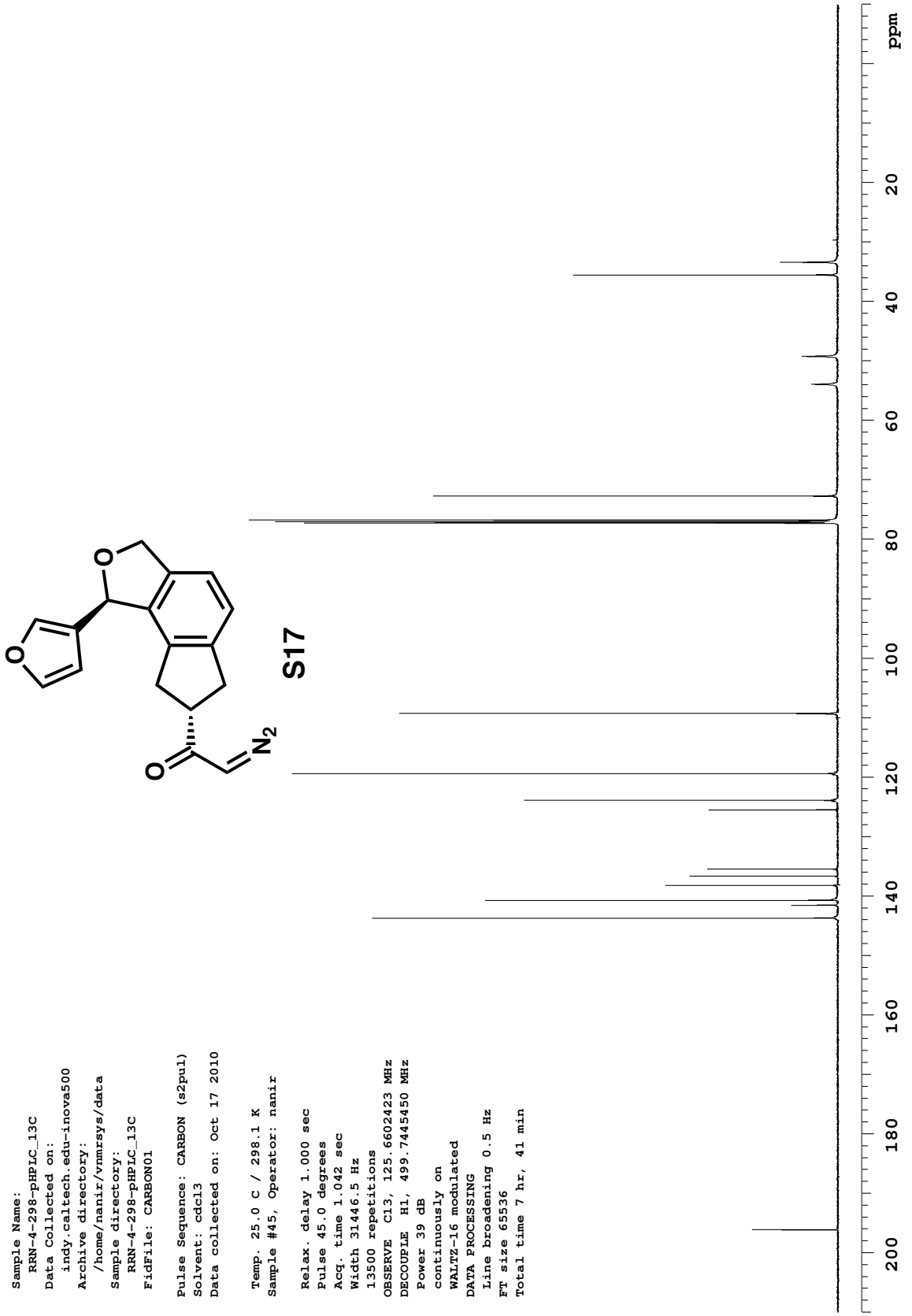

Sample Name:
RRN-5-15-2_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-15-2_13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 26 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
S16
O
NMe
Me
OH
ppm
1 2 3 4 5 6 7 8 9 10
3.04
1.40
1.09
0.54
3.35
0.80
1.26
3.47
0.42
1.04
0.81
0.96
0.51
1.04
1.51
1.51
0.42
1.00
1.46
1.42
1.43
0.84
6.65
1.13
0.45
0.99
0.43

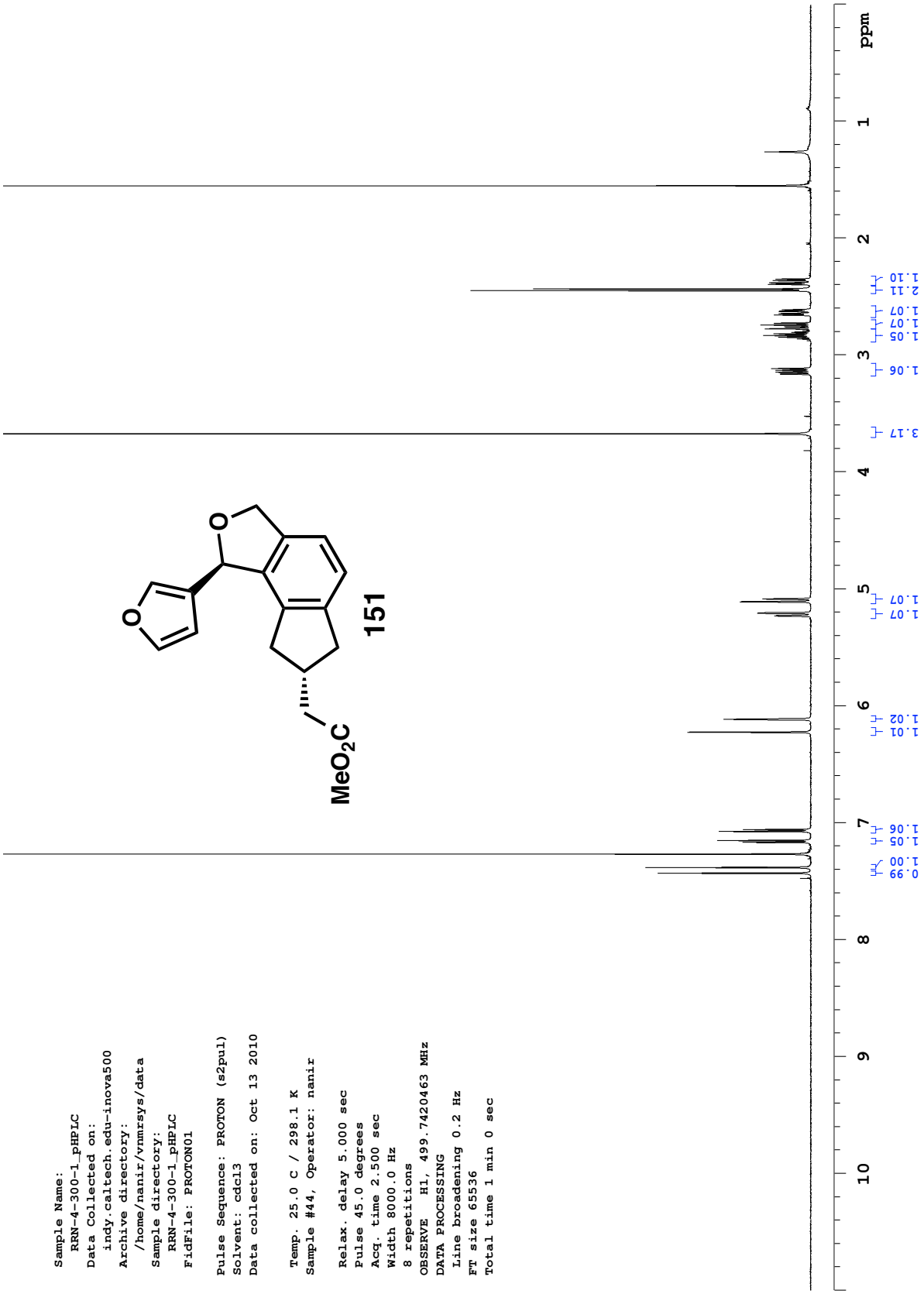

Sample Name:
RRN-5-15-2_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-15-2_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 26 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6602414 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 54 min
O
O
O
NMe
Me
OH
S16
200
180
160
140
120
100
80
60
40
20
ppm

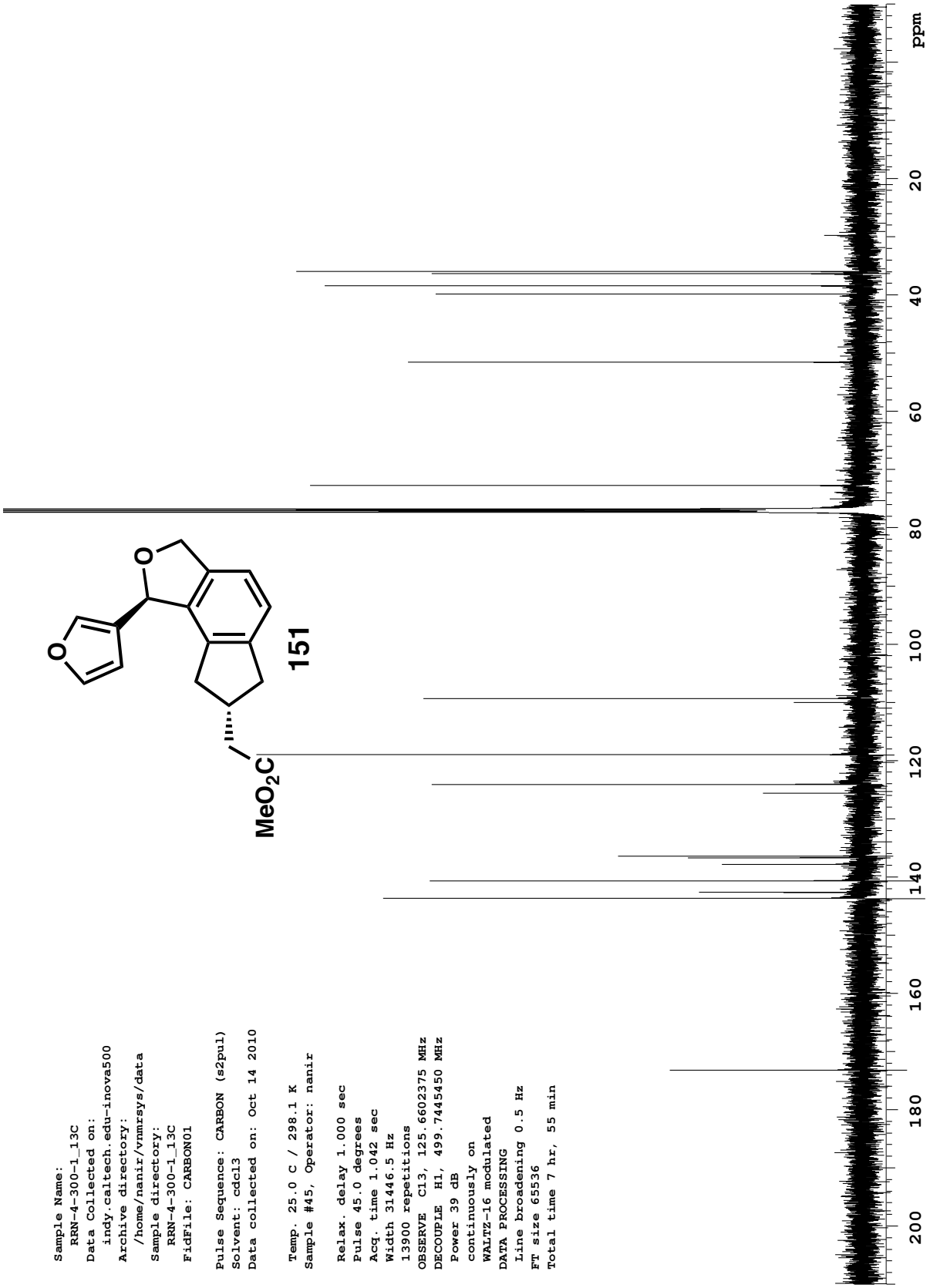

Sample Name:
RRN-4-300-1_1H_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-300-1_1H_II
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 16 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420502 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
HOOC
150
ppm
1.10
1.08
3.49
1.14
1.12
0.11
1.00
1.12
1.12
1.13
1.10
0.10
1.04

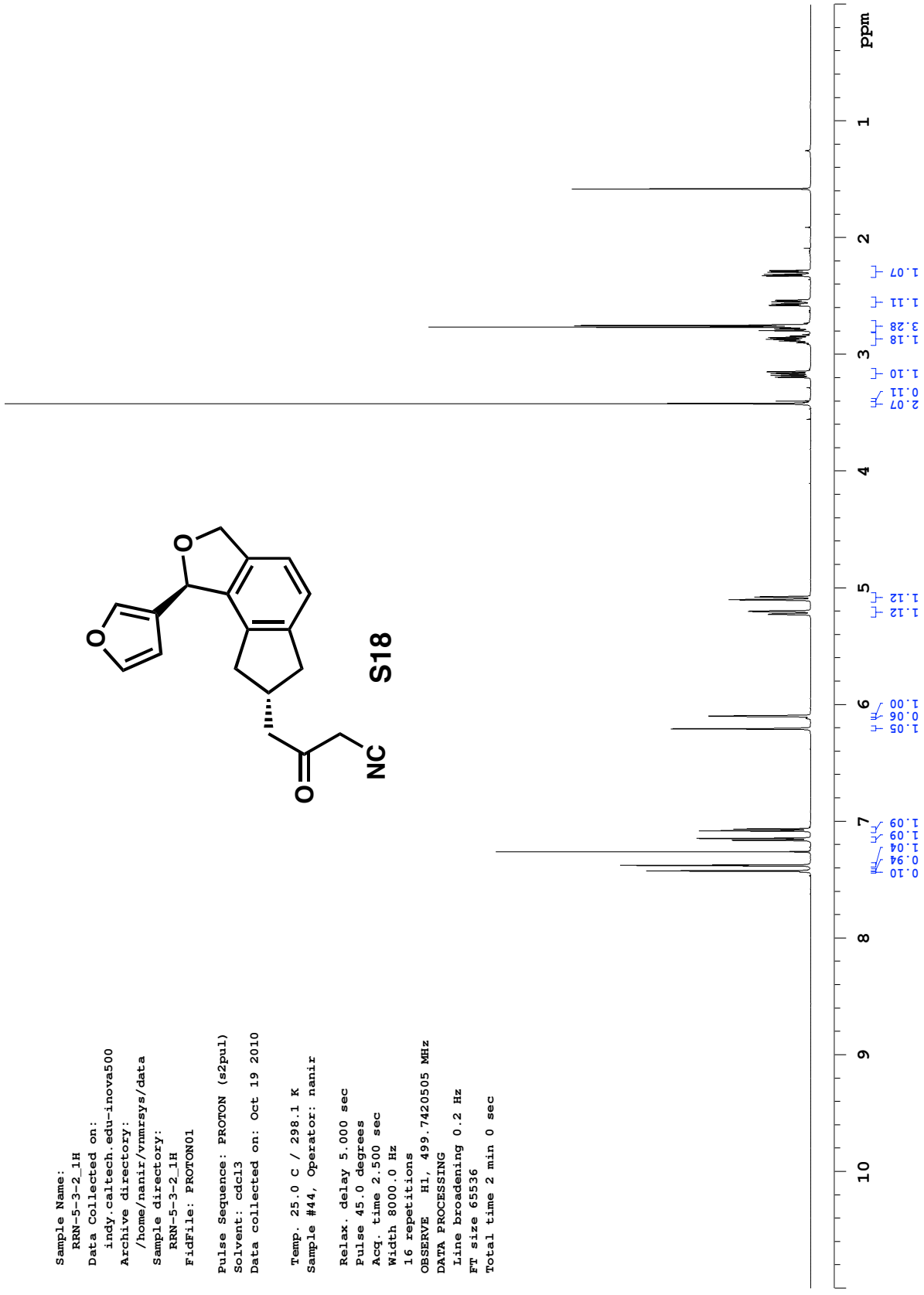

Sample Name:
RRN-4-300-13C_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-300-13C_II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 16 2010
Temp. 25.0 C / 298.1 K
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1100 repetitions
OBSERVE C13, 125.6602634 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 37 min
HOOC
150
200
180
160
140
120
100
80
60
40
20
ppm

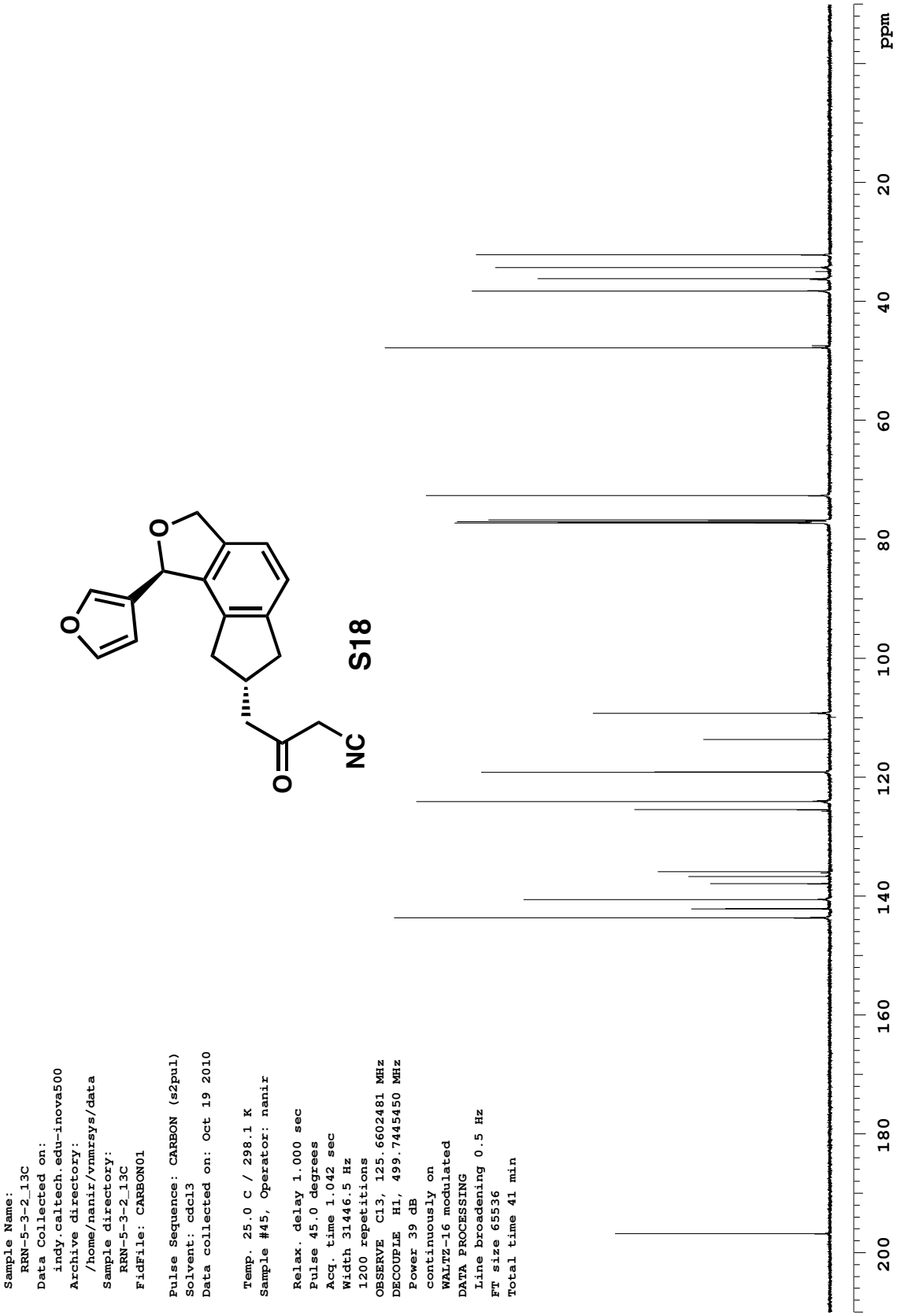

Sample Name:
RRN-4-298-1_1H_pHPLC
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-298-1_1H_pHPLC
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 16 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
O
O
O
N2
S17
ppm
1
2
3
4
5
6
7
8
9
10
1.08
1.03
3.07
0.58
1.33
1.09
0.98
1.00
1.03
1.02
0.96
0.97

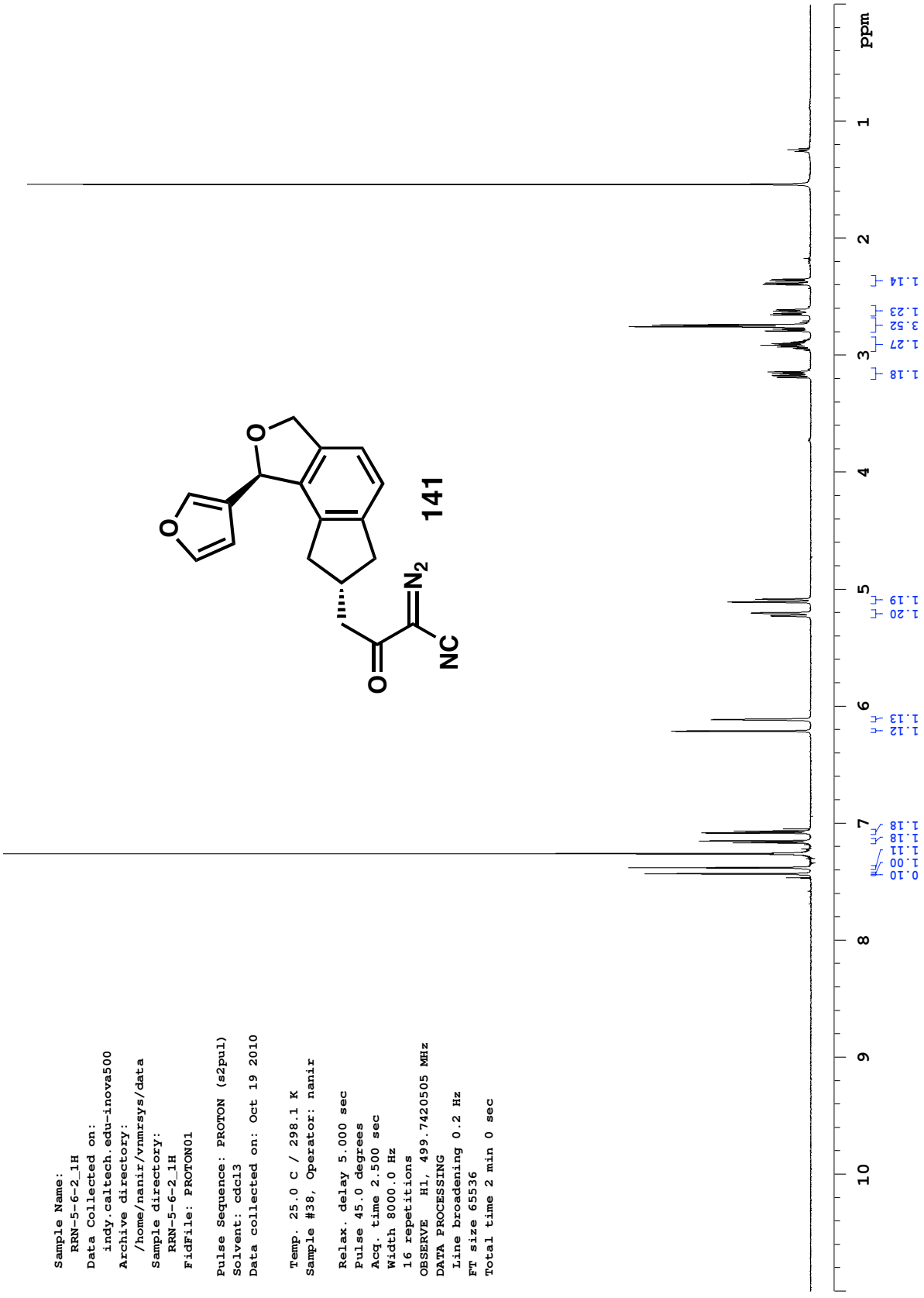

Sample Name:
RRN-4-298-pHPLC_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-298-pHPLC_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 17 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13500 repetitions
OBSERVE C13, 125.6602423 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 41 min
O
O
O
N2
S17
200
180
160
140
120
100
80
60
40
20
ppm

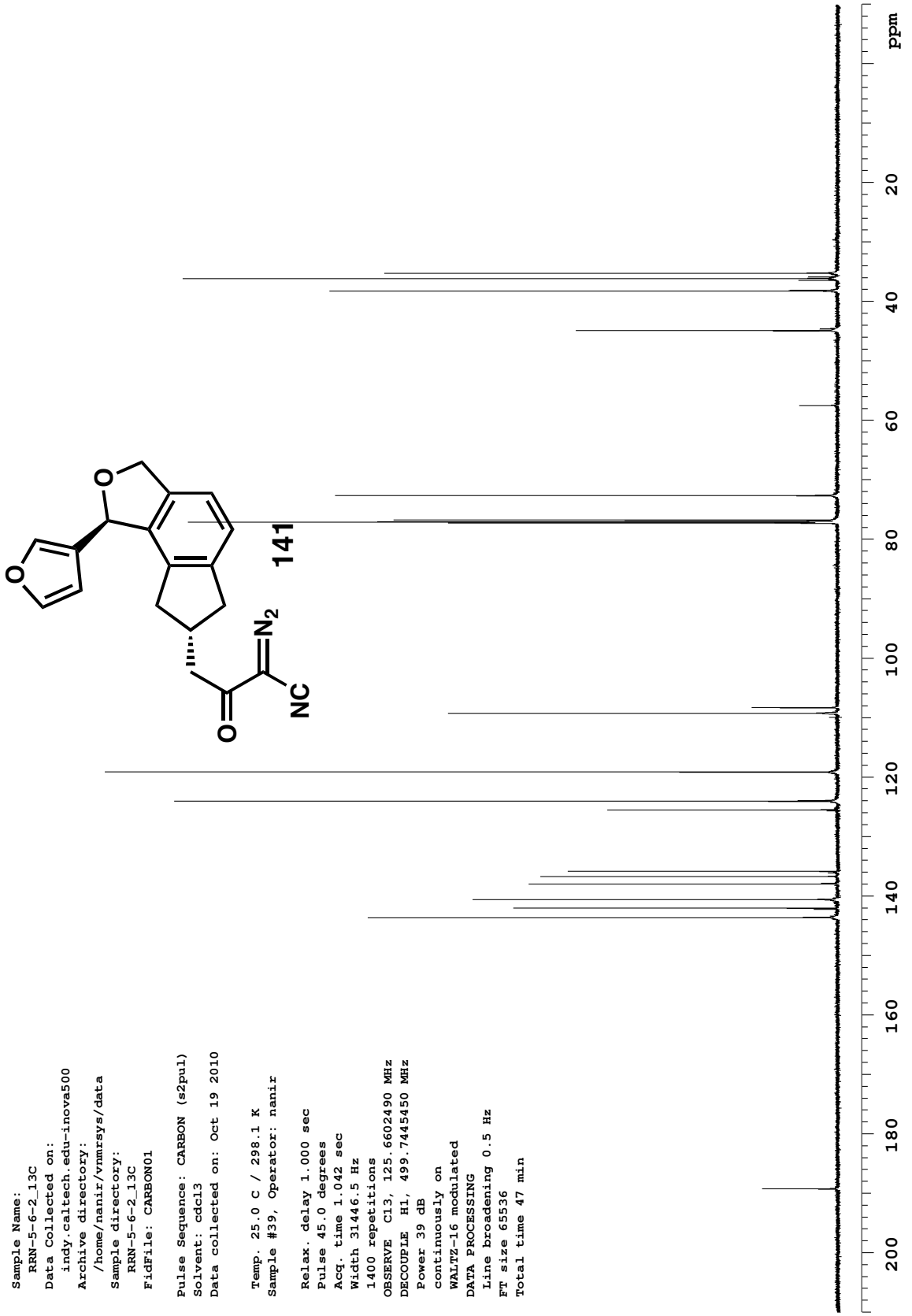

Sample Name:
RRN-4-300-1_pHPLC
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-300-1_pHPLC
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 13 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7420463 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 0 sec
MeO2C
151
ppm
1 2 3 4 5 6 7 8 9 10
0.99
1.00
1.05
1.06
1.02
1.01
1.07
1.07
3.17
1.06
1.05
1.07
1.07
2.11
1.10

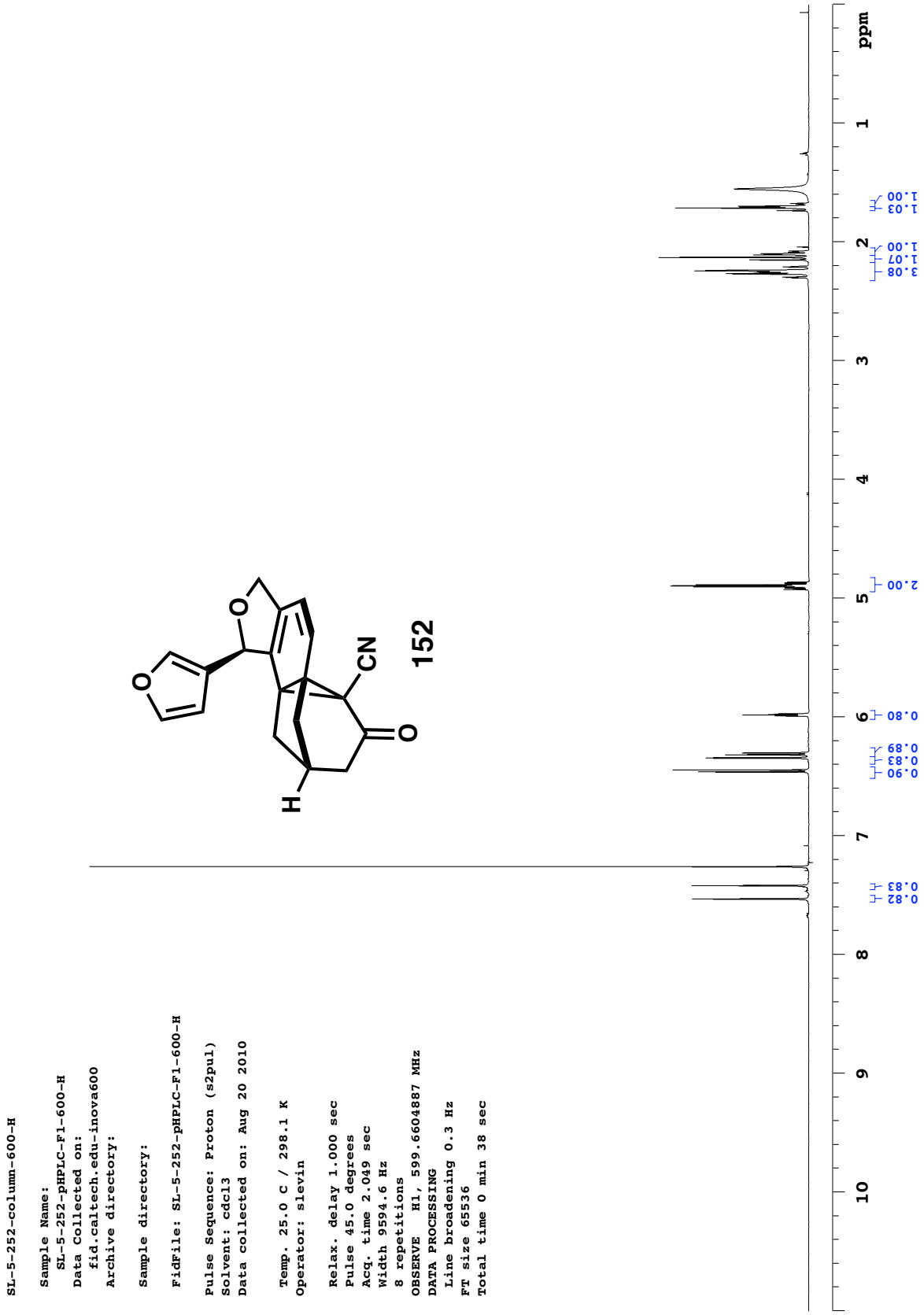

Sample Name:
RRN-4-300-1_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-4-300-1_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 14 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13900 repetitions
OBSERVE C13, 125.6602375 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 55 min
MeO2C
151
ppm
200
180
160
140
120
100
80
60
40
20


Sample Name:
RRN-5-3-2_1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-3-2_1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 19 2010
Temp. 25.0 C / 298.1 K
Sample #44, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 0 sec
O
O
O
NC
S18
ppm
1
2
3
4
5
6
7
8
9
10
1.07
1.11
3.28
1.18
1.10
0.11
2.07
1.12
1.12
1.05
0.06
1.00
0.10
0.94
1.04
1.09
1.09


Sample Name:
RRN-5-3-2_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-3-2_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 19 2010
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6602481 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 41 min
O
O
O
NC
S18
200
180
160
140
120
100
80
60
40
20
ppm


Sample Name:
RRN-5-6-2_1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-6-2_1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 19 2010
Temp. 25.0 C / 298.1 K
Sample #38, Operator: nanir
Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 0 sec
O
O
O
N2
NC
141
ppm
1 2 3 4 5 6 7 8 9 10
1.14
1.23
3.52
1.27
1.18
1.19
1.20
1.12
1.13
1.18
1.18
1.11
1.00
0.10


Sample Name:
RRN-5-6-2_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-6-2_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 19 2010
Temp. 25.0 C / 298.1 K
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1400 repetitions
OBSERVE C13, 125.6602490 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 47 min
O
O
O
N2
NC
141
200
180
160
140
120
100
80
60
40
20
ppm


SL-5-252-column-600-H
Sample Name:
SL-5-252-pHPLC-F1-600-H
Data Collected on:
fid.caltech.edu-inova600
Archive directory:
Sample directory:
FidFile: SL-5-252-pHPLC-F1-600-H
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 20 2010
Temp. 25.0 C / 298.1 K
Operator: slevin
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 9594.6 Hz
8 repetitions
OBSERVE H1, 599.6604887 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 0 min 38 sec
O
O
CN
O
H
152
ppm
1
2
3
4
5
6
7
8
9
10
0.82
0.83
2.00
0.80
0.89
0.83
0.90
1.03
1.00
3.08
1.07
1.00

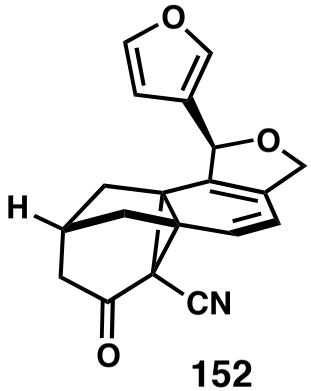
SL-5-249-column-125-13C

Sample Name:
SL-5-249-F1-pHPLC-500-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/slevin/vnmrsys/data
Sample directory:
SL-5-249-F1-pHPLC-500-13C
FidFile: CARBON01

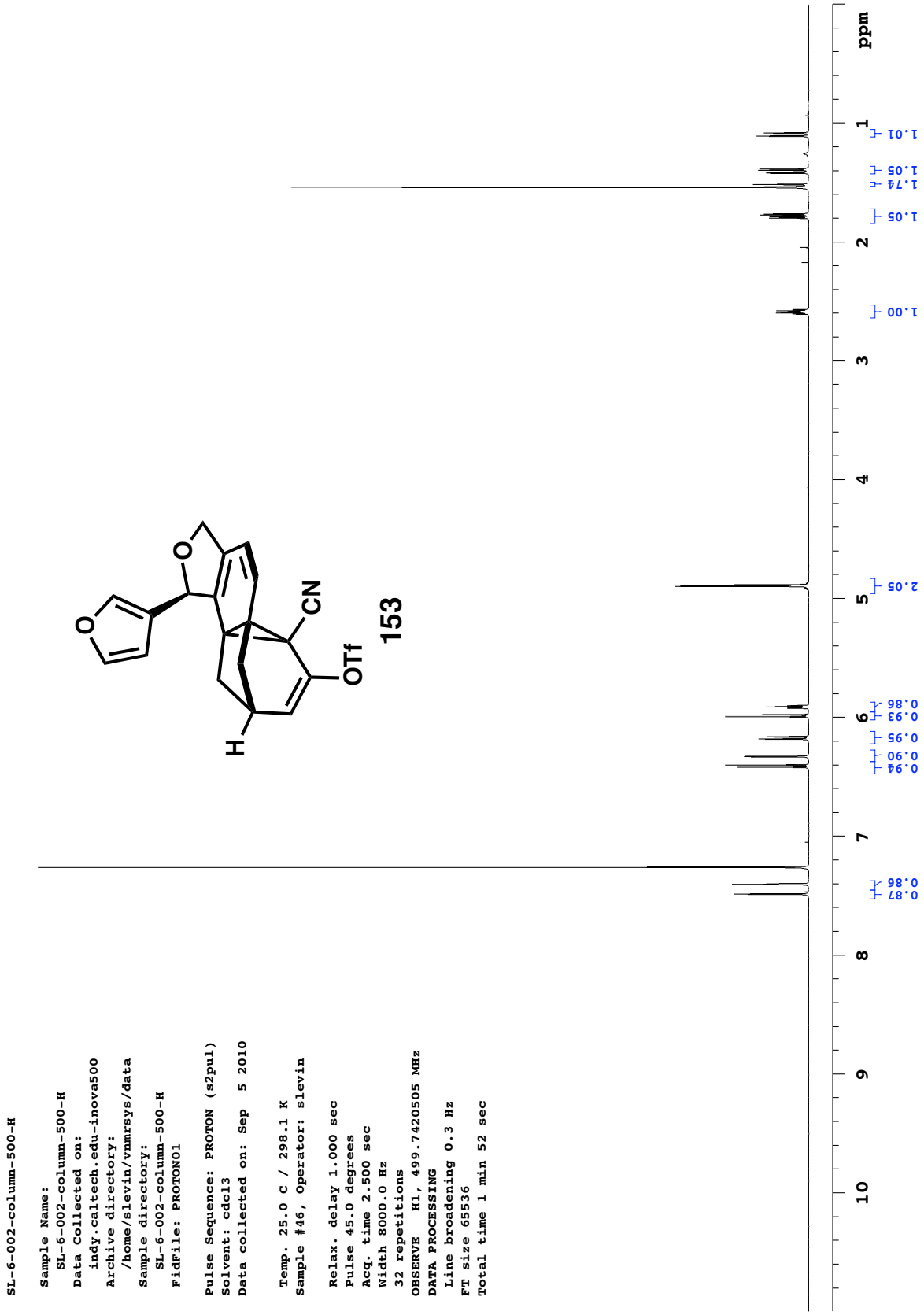
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 23 2010

Temp. 25.0 C / 298.1 K
Sample #48, Operator: slevin

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13500 repetitions
OBSERVE C13, 125.6602389 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 41 min



152


SL-6-002-column-500-H
Sample Name:
SL-6-002-column-500-H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/slevin/vnmrsys/data
Sample directory:
SL-6-002-column-500-H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 5 2010
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 1 min 52 sec
O
O
CN
OTf
H
153
ppm
1.01
1.05
1.74
1.05
1.00
2.05
0.86
0.93
0.95
0.90
0.94
0.87
0.86

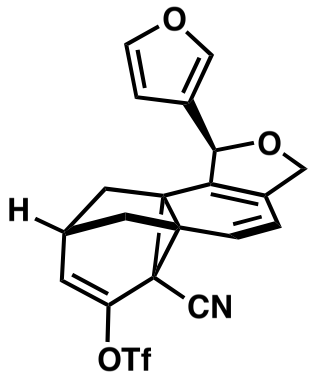
SL-6-002-column-125-13C

Sample Name:
SL-6-002-column-125-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/slevin/vnmrsys/data
Sample directory:
SL-6-002-column-125-13C
FidFile: CARBON01

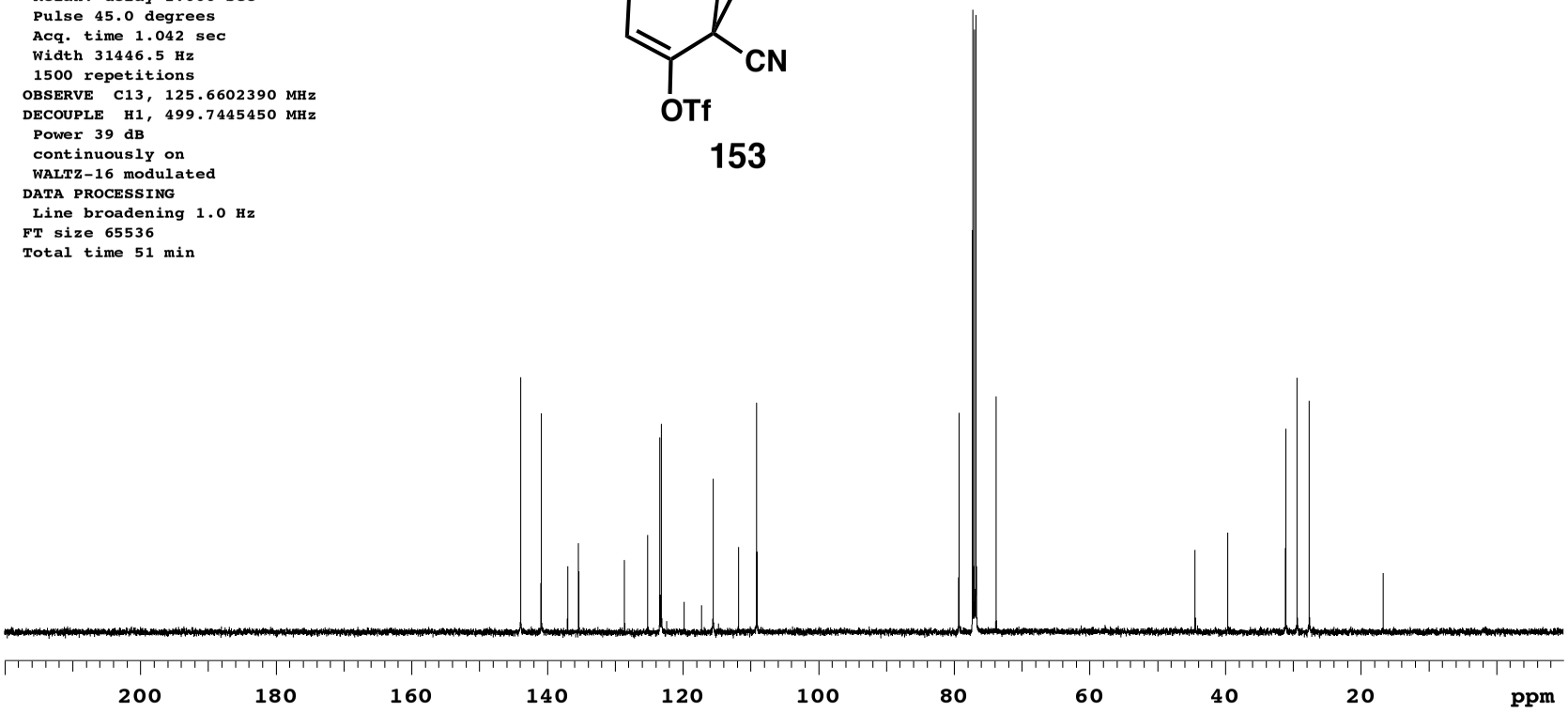
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 5 2010

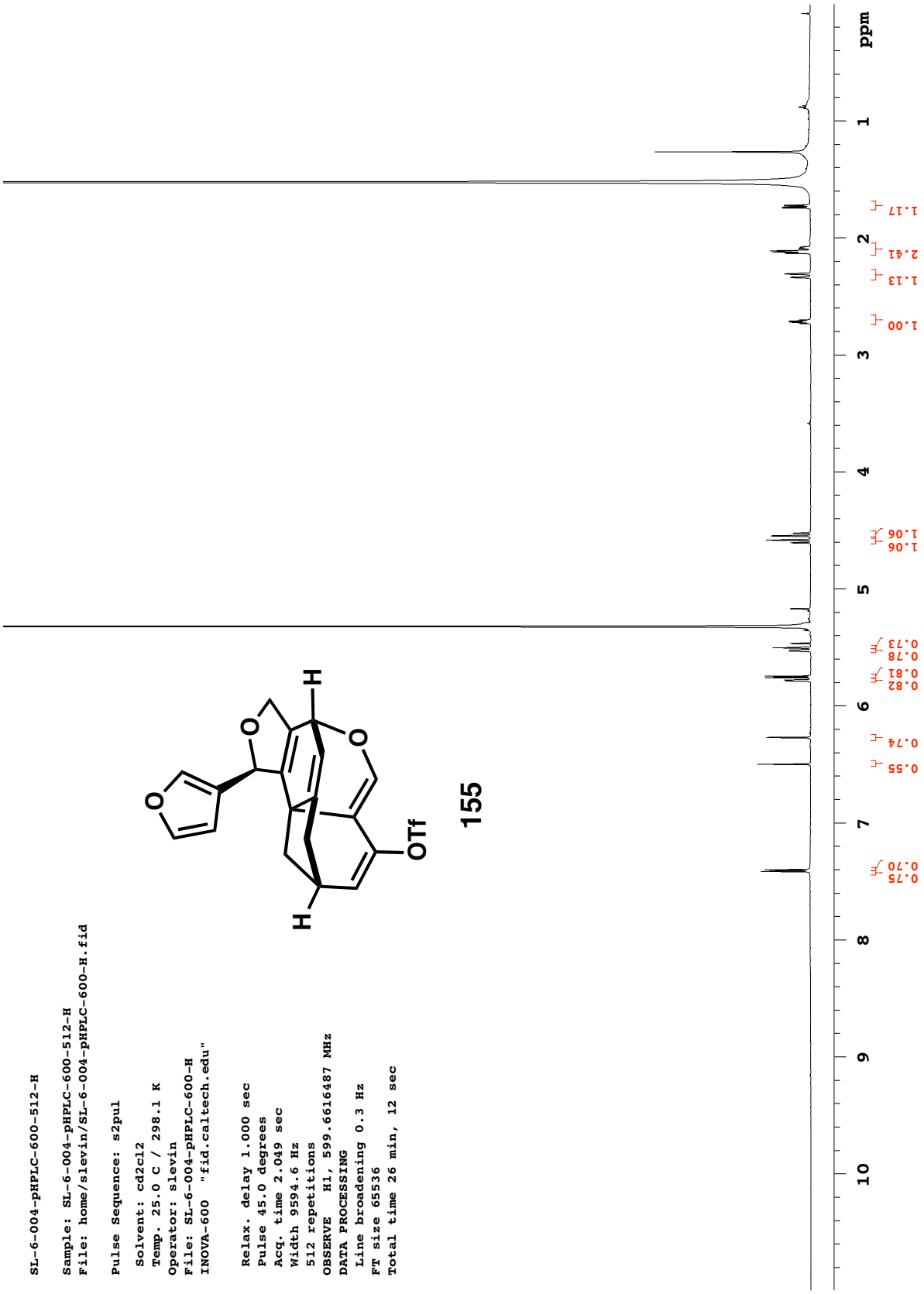
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6602390 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 51 min



153




SL-6-004-pHPLC-600-512-H
Sample: SL-6-004-pHPLC-600-512-H
File: home/slevin/SL-6-004-pHPLC-600-H.fid
Pulse Sequence: s2pul
Solvent: cd2cl2
Temp. 25.0 C / 298.1 K
Operator: slevin
File: SL-6-004-pHPLC-600-H
INOVA-600 "fid.caltech.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 9594.6 Hz
512 repetitions
OBSERVE H1, 599.6616487 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 26 min, 12 sec
O
O
O
H
H
OTf
155
ppm
1
2
3
4
5
6
7
8
9
10
1.17
2.41
1.13
1.00
1.06
1.06
0.73
0.78
0.82
0.81
0.74
0.55
0.75
0.70

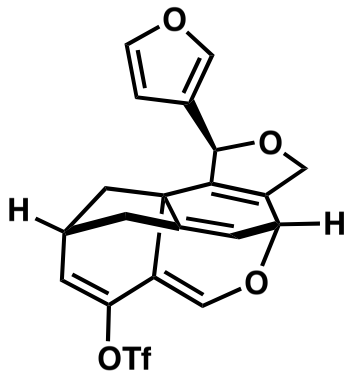
SL-6-085-crude-500-H

Sample Name:
SL-6-085-crude-500-H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/slevin/vnmrsys/data
Sample directory:
SL-6-085-crude-500-H
FidFile: CARBON01

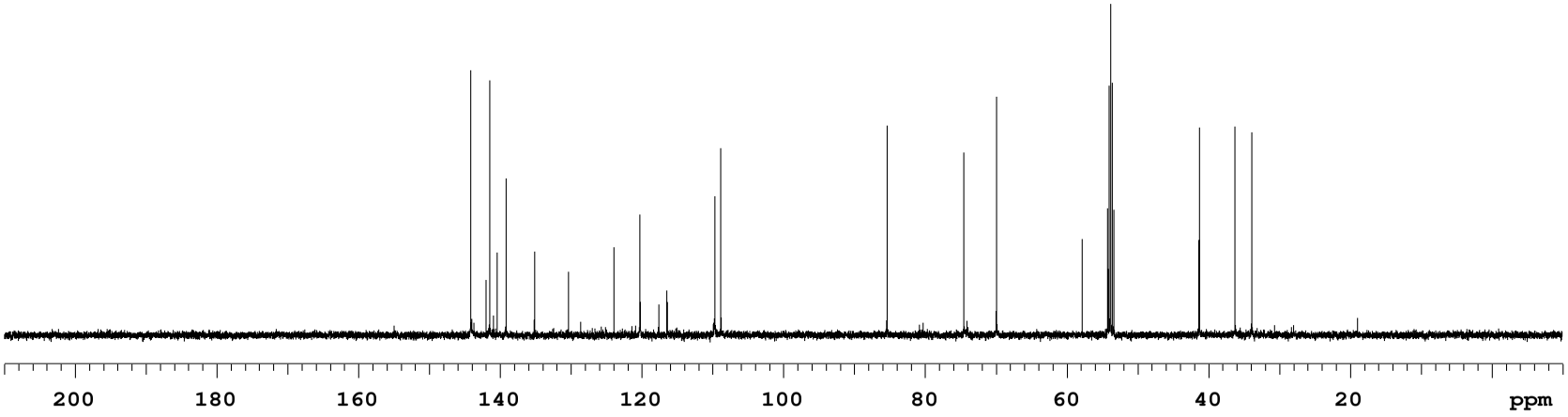
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 9 2010

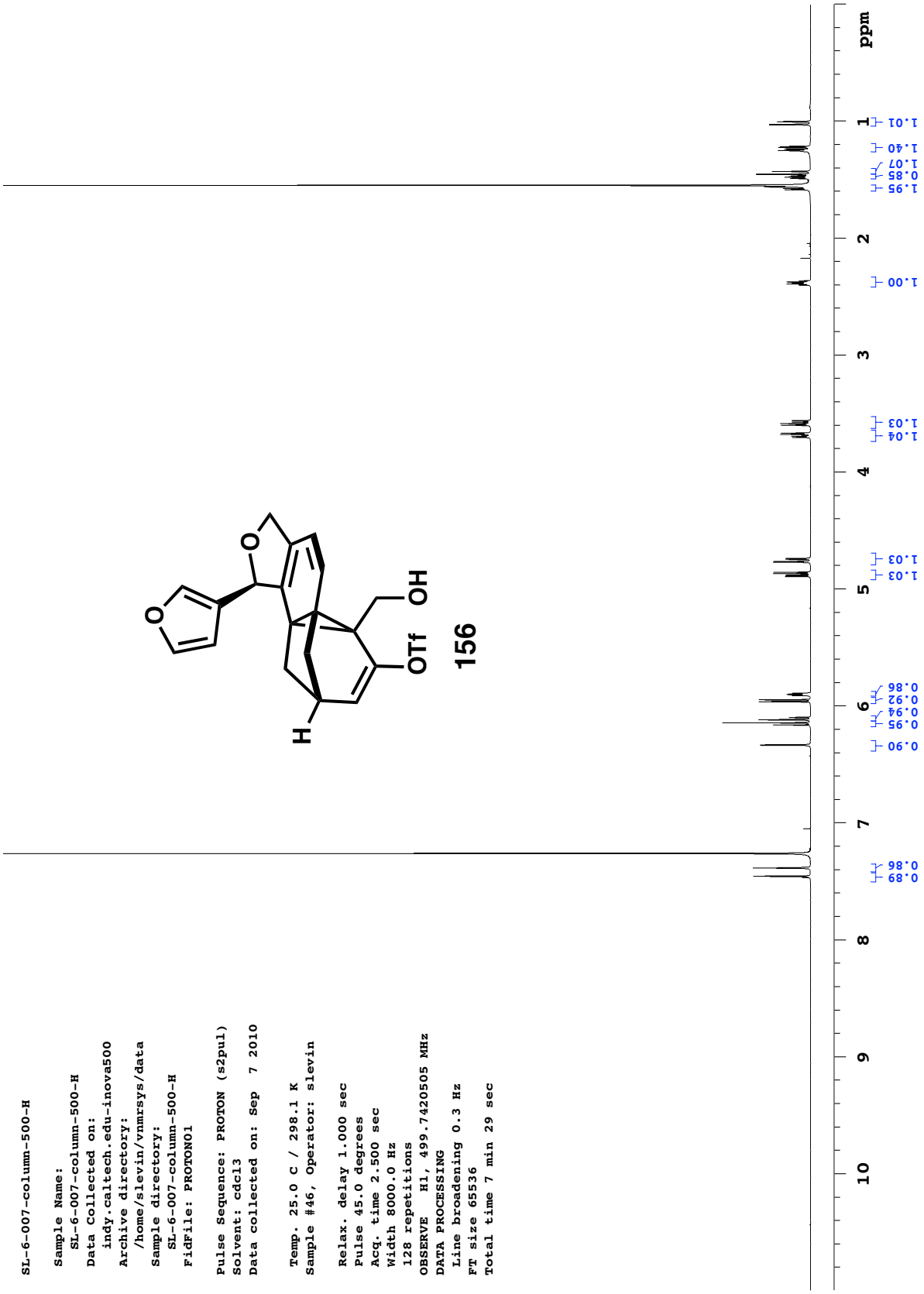
Temp. 25.0 C / 298.1 K
Sample #47, Operator: slevin

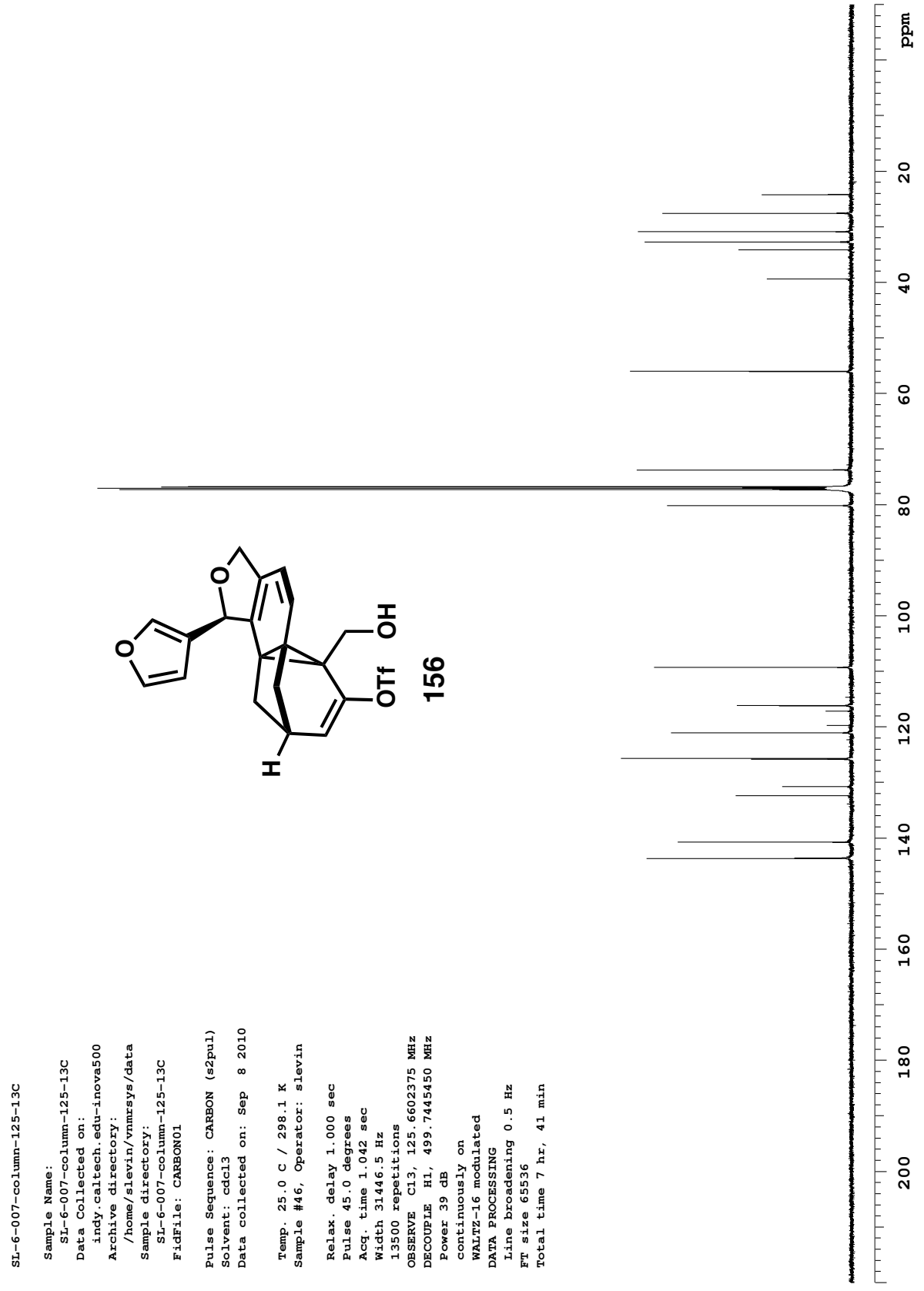
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
320 repetitions
OBSERVE C13, 125.6604283 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 8 min

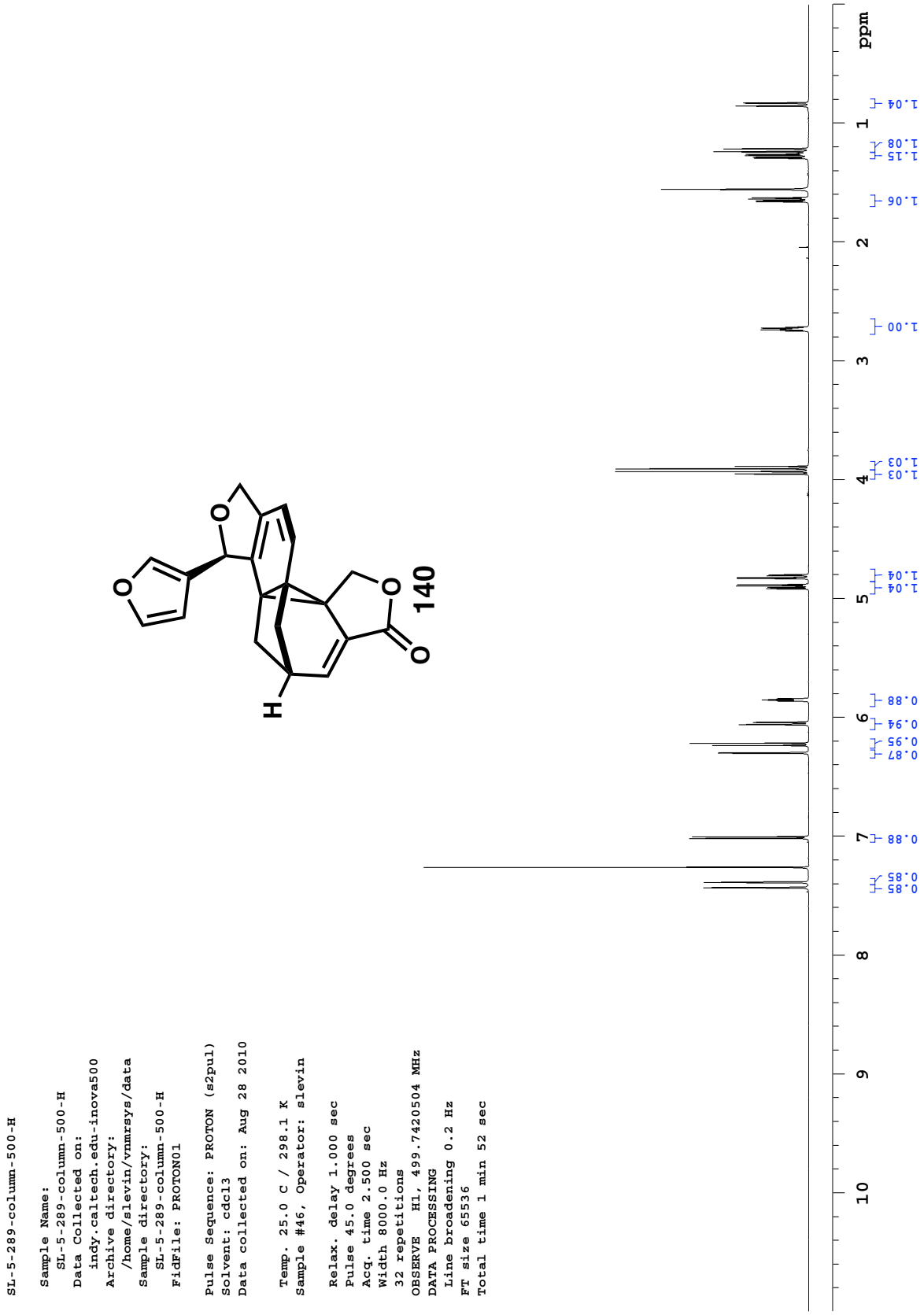


155




SL-6-007-column-500-H
Sample Name:
SL-6-007-column-500-H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/slevin/vnmrsys/data
Sample directory:
SL-6-007-column-500-H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 7 2010
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.7420505 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 7 min 29 sec
O
O
OH
OTf
H
156
ppm
1.01
1.40
1.07
0.85
1.95
1.00
1.04
1.03
1.03
0.86
0.92
0.94
0.95
0.90
0.89
0.86


SL-6-007-column-125-13C
Sample Name:
SL-6-007-column-125-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/slevin/vnmrsys/data
Sample directory:
SL-6-007-column-125-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 8 2010
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13500 repetitions
OBSERVE C13, 125.6602375 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 41 min
O
O
OTf
OH
H
156
200
180
160
140
120
100
80
60
40
20
ppm


SL-5-289-column-500-H
Sample Name:
SL-5-289-column-500-H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/slevin/vnmrsys/data
Sample directory:
SL-5-289-column-500-H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 28 2010
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
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FT size 65536
Total time 1 min 52 sec
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O
O
O
H
140
ppm
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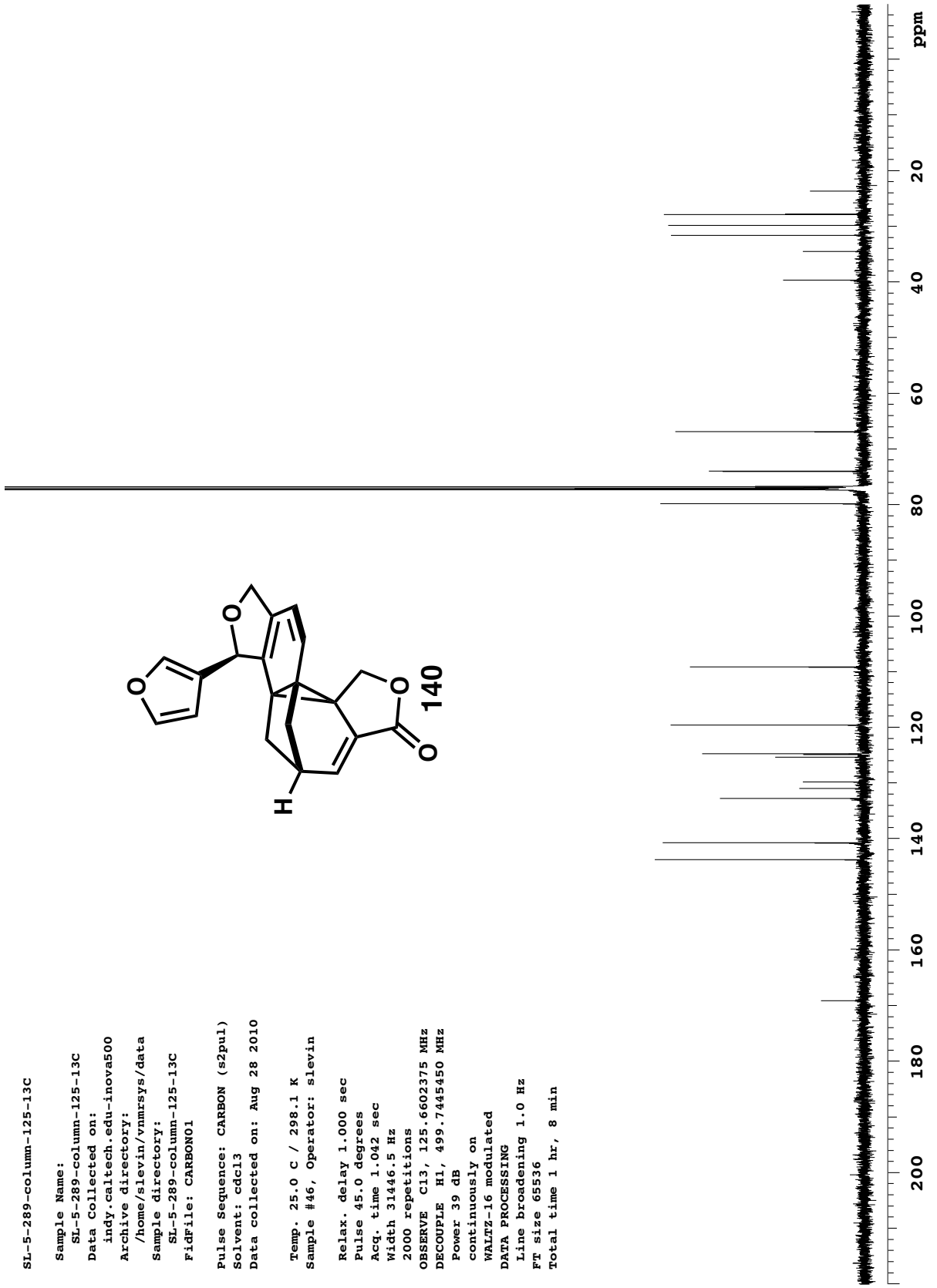
1.15
1.08
1.06
1.00
1.03
1.03
1.04
1.04
0.88
0.94
0.95
0.87
0.88
0.85
0.85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Solvent: cdcl3
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Pulse 45.0 degrees
Acq. time 1.042 sec
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2000 repetitions
OBSERVE C13, 125.6602375 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
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H
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200
180
160
140
120
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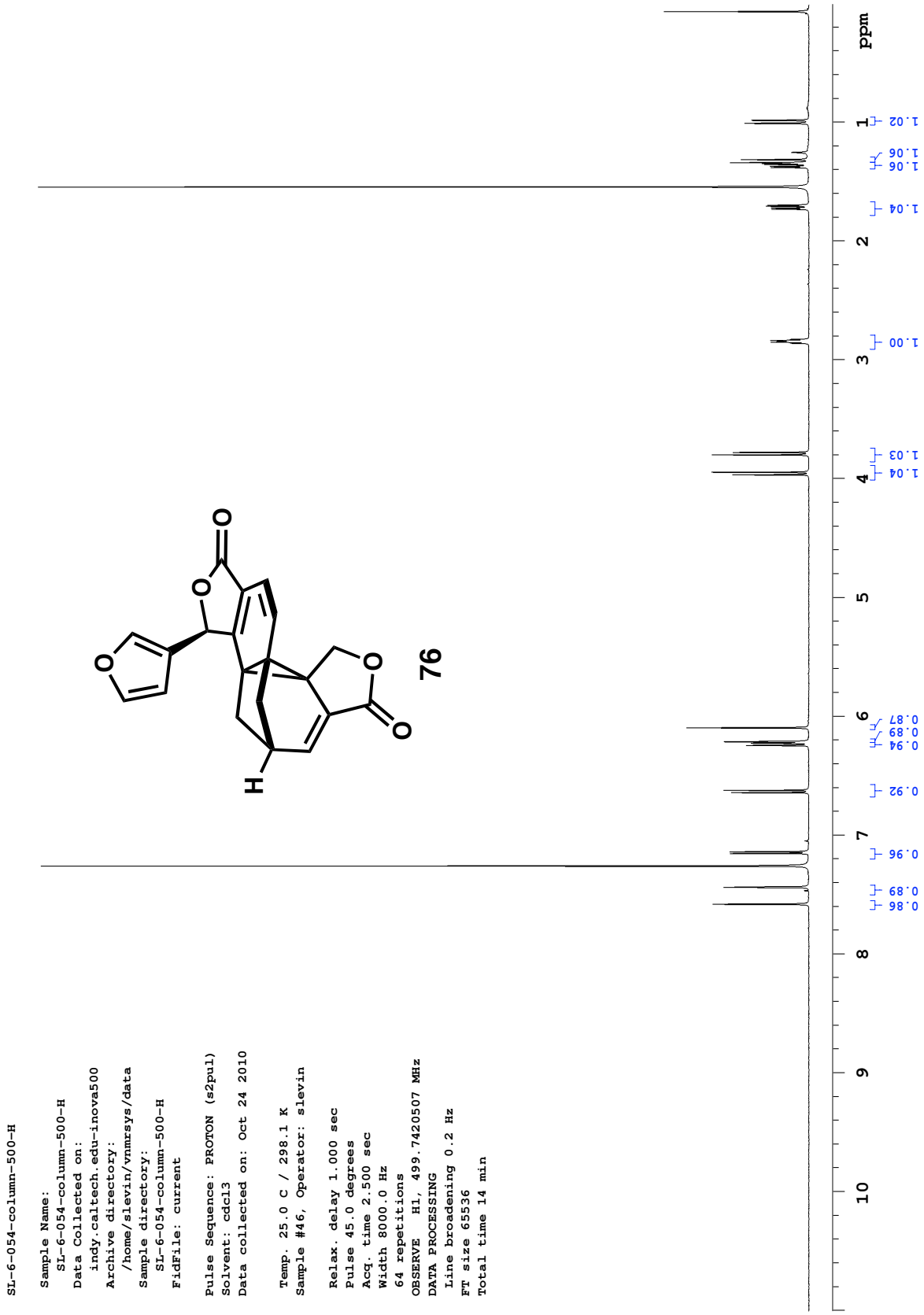
80
60
40
20
ppm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Archive directory:
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Sample directory:
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FidFile: current
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 24 2010
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7420507 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 14 min
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O
O
O
H
76
ppm
1
2
3
4
5
6
7
8
9
10
1.02
1.06
1.04
1.00
1.03
1.04
0.87
0.89
0.94
0.92
0.96
0.89
0.86

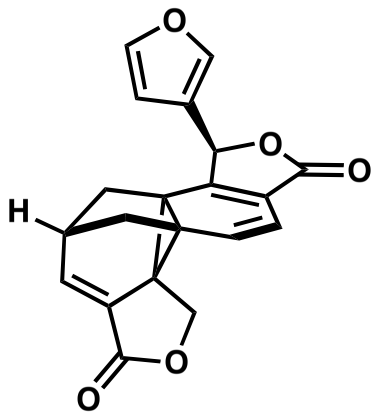
SL-6-067-column-125-13C

Sample Name:
SL-6-067-column-125-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/slevin/vnmrsys/data
Sample directory:
SL-6-067-column-125-13C
FidFile: CARBON01

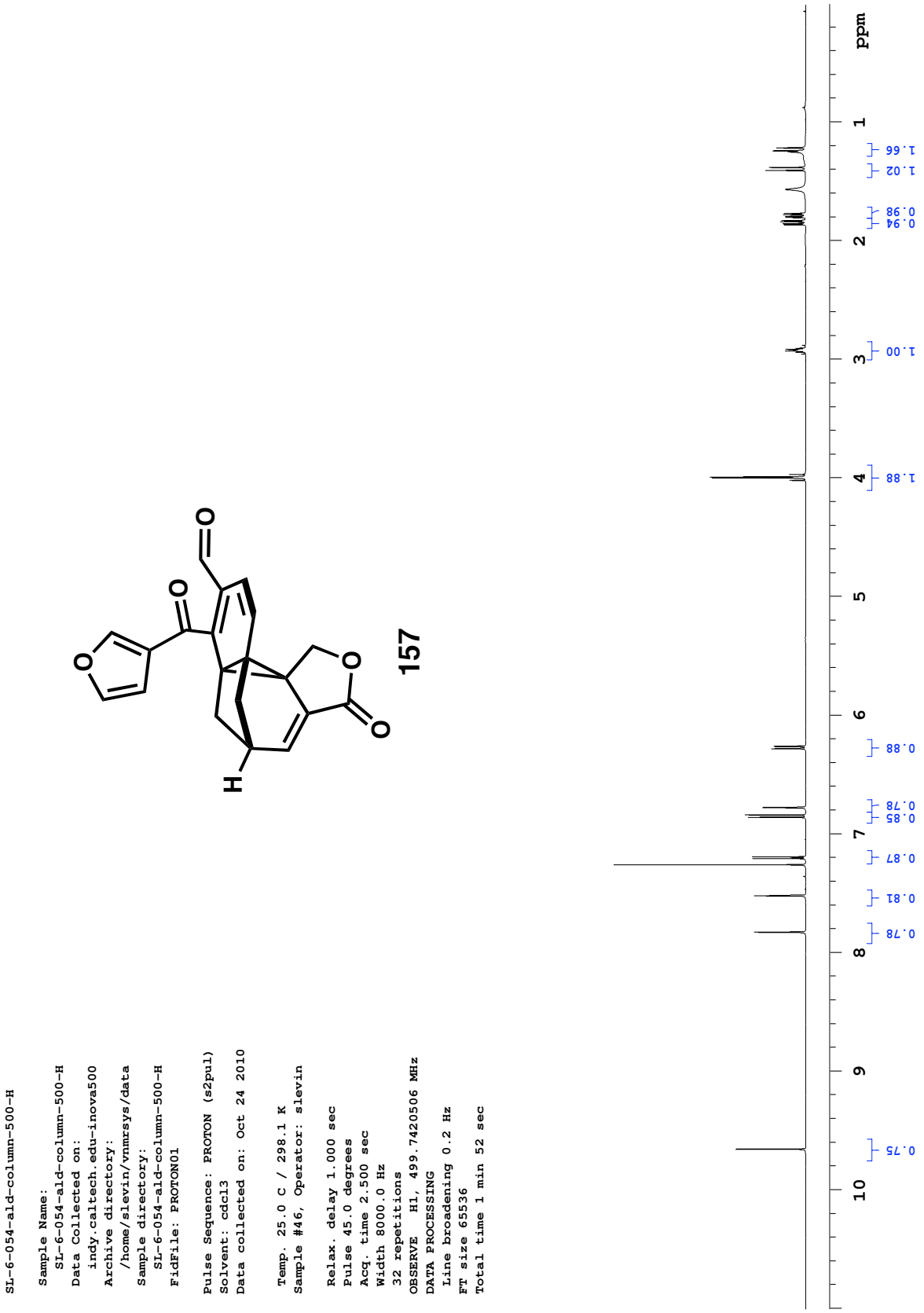
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 1 2010

Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
13500 repetitions
OBSERVE C13, 125.6602385 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 7 hr, 41 min



76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Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 24 2010
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin
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Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7420506 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
O
O
O
O
H
157
ppm
1.66
1.02
0.98
0.94
1.00
1.88
0.88
0.78
0.85
0.87
0.81
0.78
0.75

SL-6-054-ald-column-500-H

Sample Name:
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Data Collected on:
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Sample directory:
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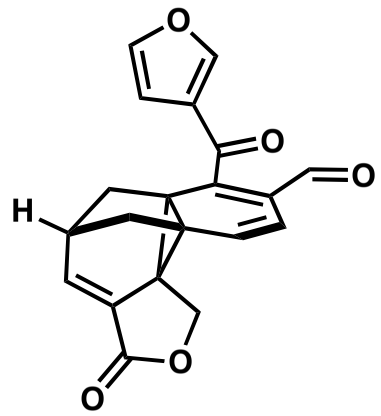
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 24 2010

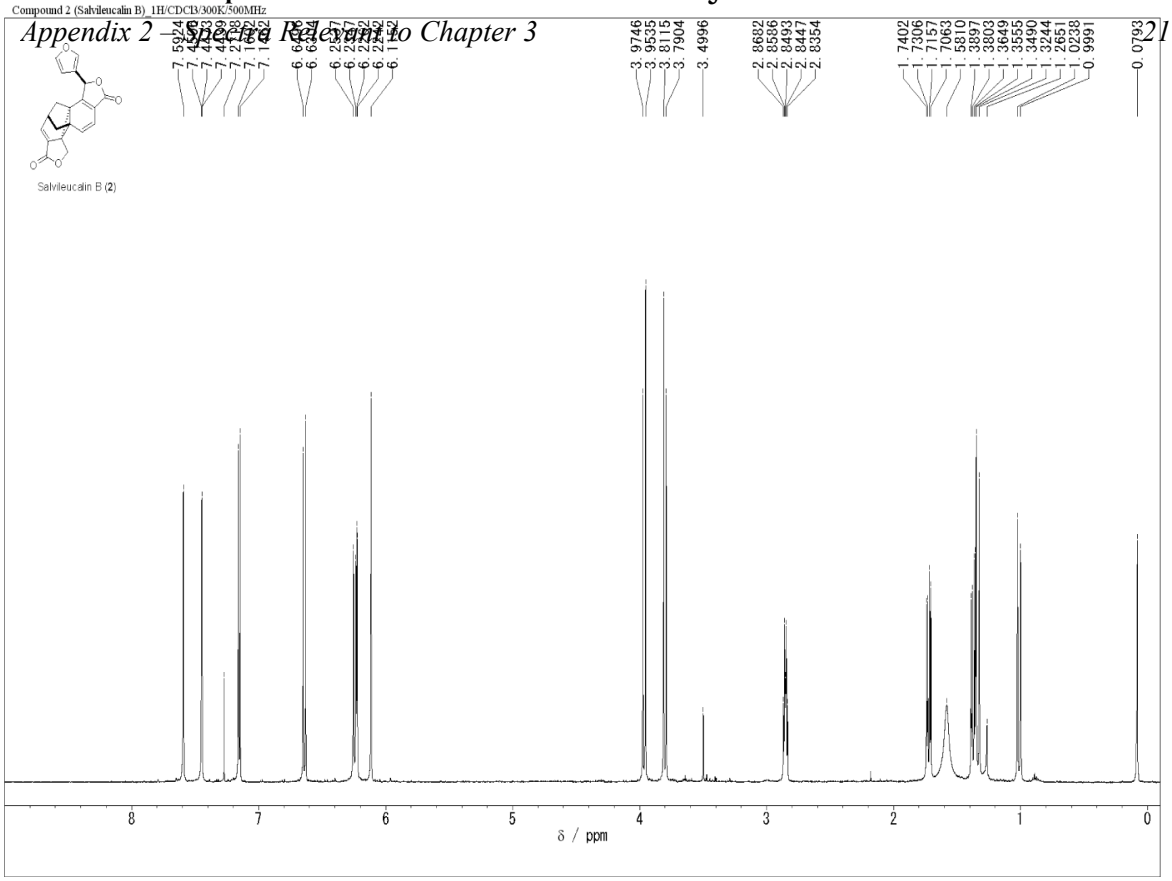
Temp. 25.0 C / 298.1 K
Sample #46, Operator: slevin

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1550 repetitions
OBSERVE C13, 125.6602385 MHz
DECOUPLE H1, 499.7445450 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 52 min

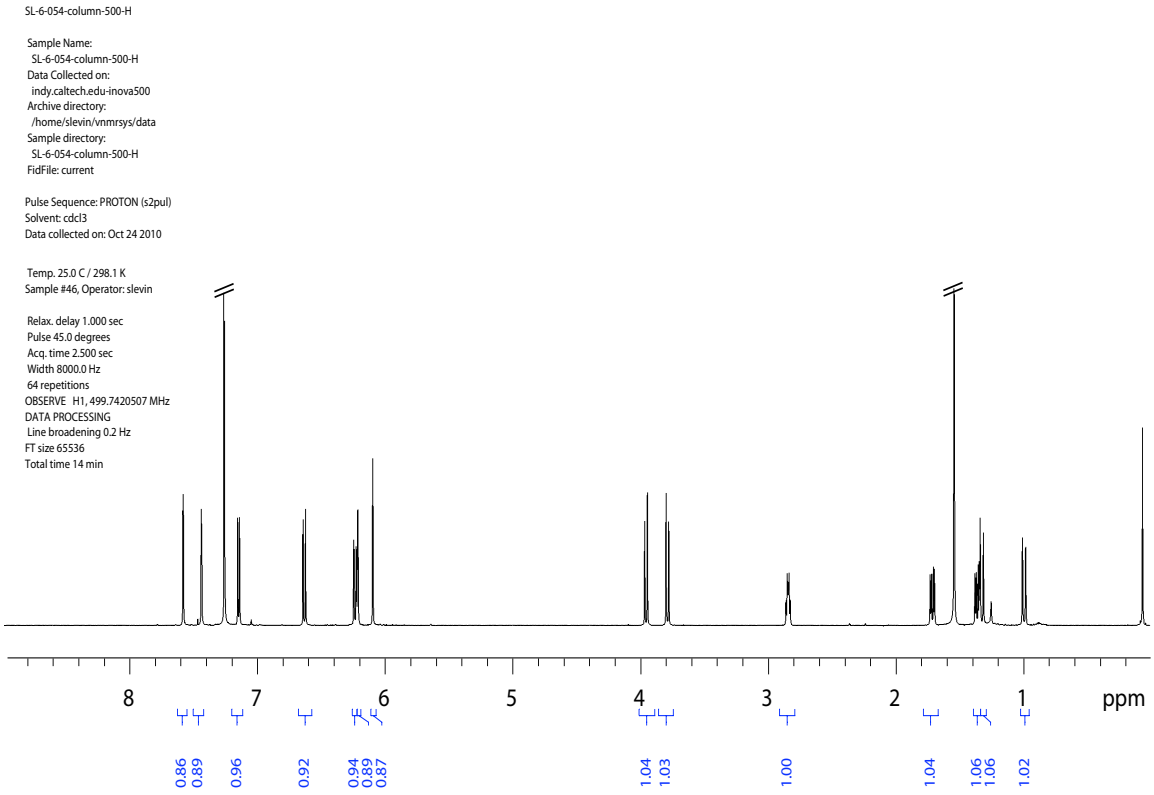


157

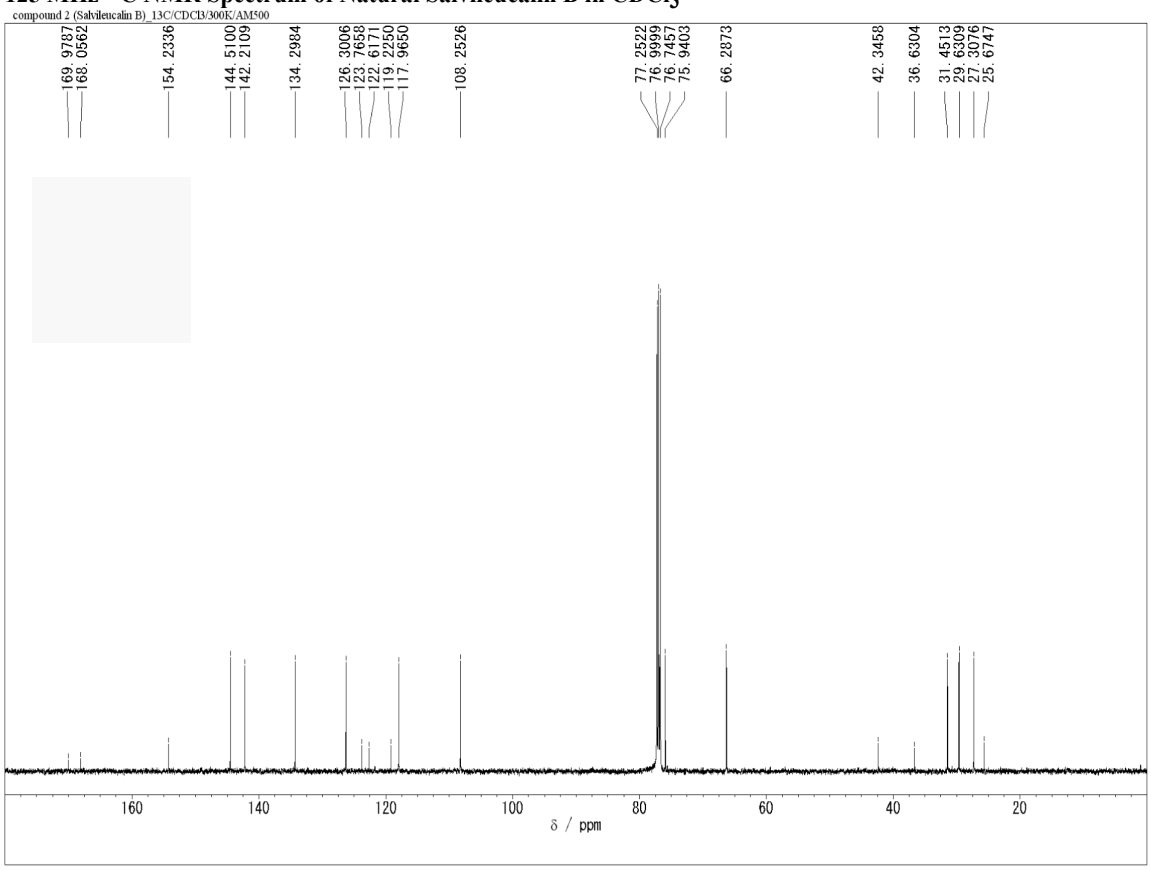
500 MHz ^{1}H NMR Spectrum of Natural Salvileucalin B in $CDCl_3$



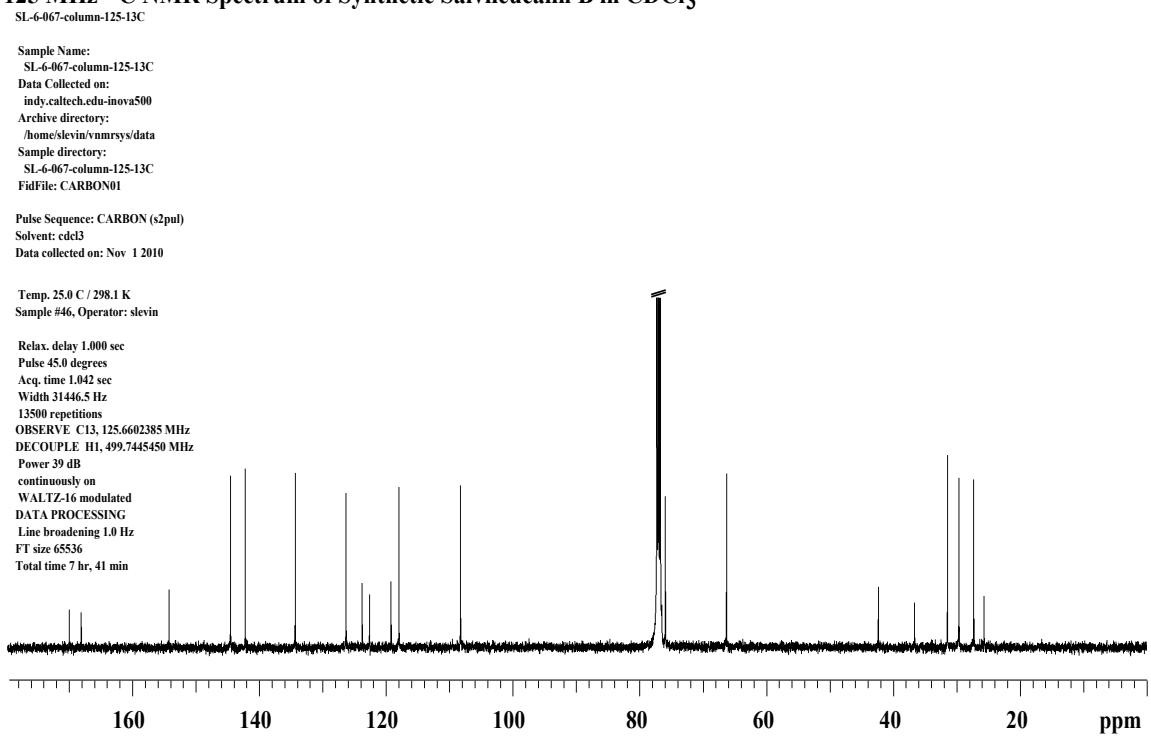
500 MHz ^{1}H NMR Spectrum of Synthetic Salvileucalin B in $CDCl_3$



125 MHz ^{13}C NMR Spectrum of Natural Salvileucalin B in $CDCl_3$



125 MHz ^{13}C NMR Spectrum of Synthetic Salvileucalin B in $CDCl_3$



Chapter 4[†]

Intramolecular Cyclopropanations of α-Diazo-β-Ketonitriles

4.1 INTRODUCTION

Transition metal-catalyzed cycloaddition reactions between diazo compounds and alkenes or arenes are widely employed for the preparation of cyclopropanes,[1] versatile synthetic intermediates that can be elaborated to cyclopropane-containing natural products or pharmaceuticals.[2] In addition, the ~28 kcal/mol of ring strain associated with the three-membered ring endows these compounds with the ability to participate in a variety of transformations that proceed by C–C bond scission. These reactions include sigmatropic processes such as vinyl-cyclopropane rearrangements[3] and rate-accelerated Cope and retro-Claisen rearrangements,[4] nucleophilic displacement reactions,[2a,5] and a variety of cycloaddition reactions.[5c,6] As a result of their synthetic utility, the development of new catalytic cyclopropanation reactions has been the subject of intense study by a

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[†] This chapter is based on a recently published report. See: Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7304.

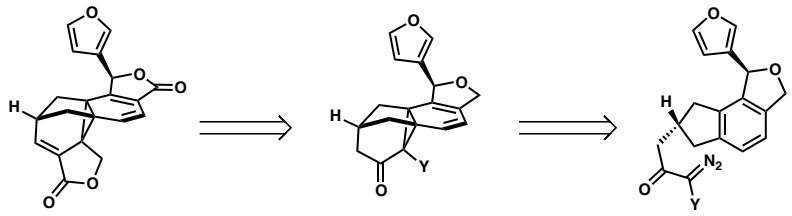
number of prominent researchers.[7] Despite remarkable advances in the state-of-the-art over the past several decades, certain cyclopropane substitution patterns nonetheless remain challenging to access by metal-catalyzed diazo cycloaddition chemistry. In particular, efforts to prepare highly substituted cyclopropanes by the cycloaddition between di-substituted diazo groups and highly substituted olefins or arenes are often complicated by competing C-H insertion processes.[8] Thus, in order to gain access to the full complement of cyclopropane structural patterns, continued efforts to expand the scope of cyclopropanation reactions are required.

4.2 BACKGROUND

4.2.1 Cyclopropanation Studies in the Salvileucalin B Synthesis

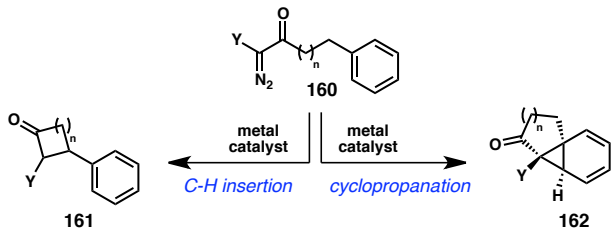
Our own foray into the area of cyclopropanation research grew out of a total synthesis program focused on the preparation of the natural product salvileucalin B (**76**).[9] Salvileucalin B is an unusual diterpenoid that contains a stable norcaradiene embedded within its carbocyclic framework. Retrosynthetically, we envisioned constructing the norcaradiene of **76** by an intramolecular Buchner-type reaction[10] of an appropriately functionalized α-diazo-carbonyl compound (**158**, Scheme 4.1). To enable elaboration of norcaradiene **158** to **76**, it was deemed critical to utilize a di-substituted diazo substrate that possessed a functional handle for installation of the γ-lactone (e.g. **159**, Y ≠ H).

Scheme 4.1. *Retrosynthetic analysis of salvileucalin B*



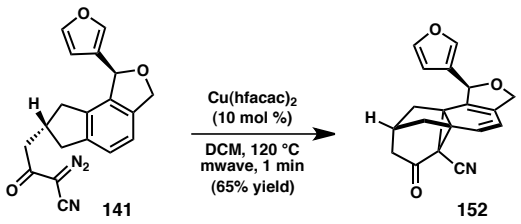
However, a survey of the literature describing *intra*molecular Buchner-type reactions of diazo compounds revealed that subtle changes in the substrate can dramatically affect the yields of the norcaradiene products.[11] For example, in systems bearing three atoms between the arene and diazo group (Figure 4.1, **160**, n = 1), cyclopropanation is typically favored, since C-H insertion would produce a four-membered ring.[11d] On the other hand, C-H insertion processes become competitive in substrates containing four-atom linkers (**160**, n = 2), since five-membered ring formation is facile. The diazo substitution also critically influences the ratio of arene cyclopropanation to C-H insertion.[11d] Whereas terminal α-diazoketones (**160**, Y = H) are excellent substrates for arene cyclopropanation, the corresponding α-diazo-β-ketoesters (**160**, Y = CO_2R) strongly favor C-H insertion or carbene dimerization.[12] Finally, the metal catalyst and ligand framework also significantly influence the ratio of cyclopropanation to C-H insertion.[11c,d]

Figure 4.1. *Divergent reactivity: C-H insertion vs. cyclopropanation*



Consistent with the reactivity trends described above, there were no prior examples of intramolecular Buchner reactions to generate fully substituted cyclopropanes at the outset of our research. Moreover, there were no examples of intramolecular Buchner reactions using acceptor–acceptor (A–A) substituted diazo substrates possessing a four-atom linker, such as the α-diazo-β-ketoester (**160**, Y = CO_2Me) we envisioned utilizing in the synthesis of salvileucalin B. After extensive experimentation, we found that the α-diazo-β-ketonitrile moiety was unique among A–A substituted diazo substrates in its ability to undergo arene cyclopropanation, a discovery that lead to the successful synthesis of **76** via the Cu-catalyzed cyclopropanation of **141** (Scheme 4.2).[9b,c,13] Inspired by this novel reactivity and mindful of an apparent gap in the existing technology, we recognized that this transformation could potentially be of broad utility well beyond our synthetic studies toward salvileucalin B. Thus, we initiated a program aimed at investigating the cyclopropanation reactions of α-diazo-β-ketonitriles, the results of which are described herein.

Scheme 4.2. *Cu-catalyzed cyclopropanation of* ***141***

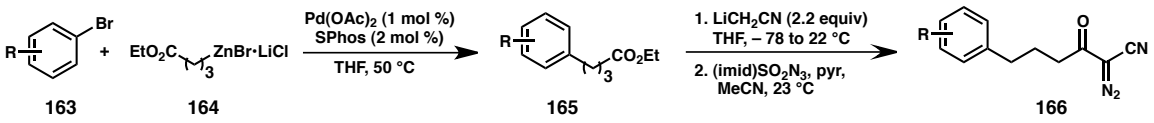


4.3 INTRAMOLECULAR CYCLOPROPANATION OF α-DIAZO-β-KETONITRILES

4.3.1 Substrate Preparation and Catalyst Screening

Our initial efforts focused on studying the reactivity of simple arylhexanone systems toward Buchner-type cyclopropanation. The α-diazo-β-ketonitriles (**166**) were easily prepared in three steps from aryl bromides **163** by Negishi cross coupling with organozinc **164**,[14] homologation to the ketonitrile,[9b] and diazo transfer[15] (Scheme 4.3). This sequence allows facile access to a variety of arene substitution patterns from a range of commercially available aryl bromide starting materials.

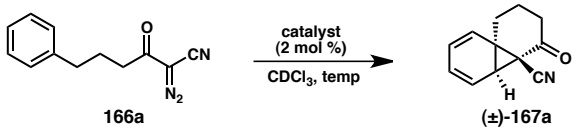
Scheme 4.3. *Substrate preparation*



Using the parent phenyl substrate **166a**, a screen of metal complexes revealed that while $Cu(hfacac)_2$ provided norcaradiene **167a** in 54% yield, several dirhodium tetracarboxylate salts proved more effective (Table 4.1, entries 7–9, and 11). Of the Rh^{II}

catalysts investigated, the more electron-deficient catalysts provided higher yields of **167a** (entries 7–9). This trend is consistent with that reported by Padwa and coworkers, whose studies on the Buchner reactions of terminal diazo ketones determined that $Rh_2(pfb)_4$ favors cyclopropanation, while $Rh_2(cap)_4$ favors C-H insertion.[11d] The commercially available bridging carboxylate-containing catalyst $Rh_2(esp)_2$ developed by Du Bois[16] also cleanly provided **167a**.

Table 4.1. *Catalyst Screen*



166a (±)-167a

Entry	Catalyst	Temperature (°C)	Norcaradiene Yield (%)
1	$Cu(hfacac)_2$	90	24
2	$Cu(hfacac)_2$[b]	90	54
3	$Cu(acac)_2$	120	4
4	$Co^{II}(salen)$	22	0
5	$Co^{II}(salen)$	120	0
6	$[Ir(cod)Cl]_2$	120	0
7	$Rh_2(pfb)_4$	22	65 (70)[c]
8	$Rh_2(tfa)_4$	22	54
9	$Rh_2(OAc)_4$	22	60 (65)[c]
10	$Rh_2(cap)_4$	22	2
11	$Rh_2(esp)_2$	22	58 (70)[c]

[a] Yield determined by ^1H NMR analysis versus an internal standard. [b] 5 mol % of catalyst was employed. [c] Isolated yield, substrate was added by syringe pump to catalyst at – 40 °C.

Taken together, these findings stand in contrast to our studies on the cyclopropanation of tetrasubstituted arene **141** (Scheme 4.2), which determined that $Cu(hfacac)_2$ was optimal while Rh^{II} catalysts performed poorly.[9b] We attribute this dichotomy in reactivity to the sensitivity of Rh^{II} catalysts to the steric profile of the substrate. Compound **141** is a particularly challenging substrate, since the geometric

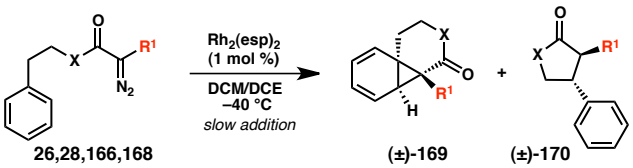
constraints require cyclopropanation at the equivalent of a tetrasubsituted alkene, with the additional steric encumbrance of an *ortho*-substituent. Thus, the Rh-carbenoid derived from **141** encounters increased steric hindrance in the cyclopropation transition state, which destabilizes this pathway relative to the more sterically accessible C-H insertion pathways.

On the other hand, our findings, as well as those of Mander and coworkers,[11e] suggest that Cu carbenoids are less sensitive to substrate sterics and typically provide higher chemoselectivity for cyclopropanation over C-H insertion. However, the Cu-catalyzed reactions also require higher temperatures to initiate de-diazotization; the harsher reaction conditions can result in lower overall yields and the need for higher catalyst loadings, despite the often-improved chemoselectivity. Ultimately, these studies determined that for simple, sterically unencumbered arenes such as **166**, the best yields are obtained by slow addition of α-diazo-β-ketonitrile **166** to a solution of either $Rh_2(esp)_2$ or $Rh_2(pfb)_4$ as the catalyst (entries 7 and 11). All subsequent studies were conducted using the slow addition protocol and one of these two catalysts, as indicated.

4.3.2 Control Experiments and Reaction Scope

Our studies toward salvileucalin B revealed a profound effect by the diazo substitution on the product distribution of the reaction.[9b] To systematically study this effect, a series of A–A diazo substrates was prepared (Table 4.2).

Table 4.2. *Influence of diazo substitution on chemoselectivity*

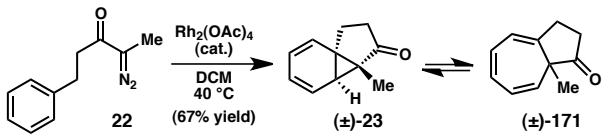


Entry	R^1	X	Yield 169 (%)	Yield 170 (%)
1	H (26)	CH_2	>95	ND
2	Me (28)	CH_2	ND	43
3	COMe (168a)	CH_2	ND	32
4	CO_2Me (168b)	CH_2	ND	45
5	NO_2 (168c)	CH_2	ND	28
6	CN (166a)	CH_2	70	ND
7	CO_2Me (168d)	NMe	ND	50

[a] ND = not detected.

Consistent with previous work in our group and by others, the terminal diazo compound (**26**, R^1 = H) was found to cleanly undergo arene cyclopropanation, delivering norcaradiene **27** in quantitative yield (entry 1). However, even the relatively minor perturbation of changing R^1 from proton to methyl drastically affected the chemoselectivity, with the reaction now favoring C-H insertion to give cyclopentanone **29** (entry 2). The propensity of **28** to undergo C-H insertion is in stark contrast to the corresponding 4-diazo-1-phenylpentan-3-one (**22**) – a compound containing one fewer methylene in the linker – which when treated with catalytic $Rh_2(OAc)_4$, is reported to provide an equilibrating mixture of norcaradiene **23** and cycloheptatriene **171** in 67% yield (Scheme 4.4). This divergent reactivity clearly reflects the preference for five- over four-membered ring formation.

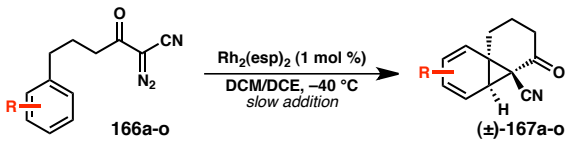
Scheme 4.4. *Kennedy and coworkers' arene cyclopropanation of 4-diazo-1-phenylpentan-3-one*

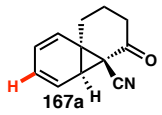
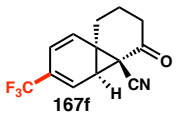
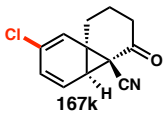
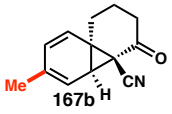
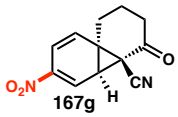
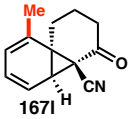
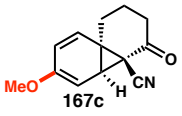
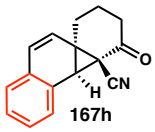
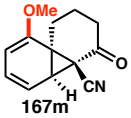
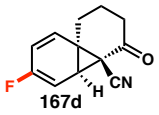
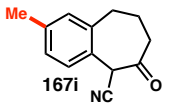
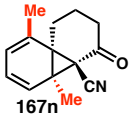
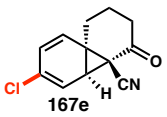
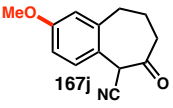
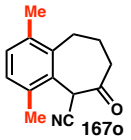


A further investigation of substrates revealed that, in general, di-substituted diazo compounds containing four-atom linkers favor C-H insertion over arene cyclopropanation (Table 4.2). Thus, treatment of a variety of A–A substituted substrates (R^1 = COMe, CO_2Me, NO_2) with catalytic $Rh_2(esp)_2$ provides modest yields of cyclopentanone **170**; in these cases, no norcaradiene is detected in the crude reaction mixture. The mass balance was determined by ^1H NMR and LCMS to be a mixture of dimerization products. Of the di-substituted diazo substrates evaluated here, α-diazo-β-ketonitrile **166a** was *uniquely* effective in providing the norcaradiene product (**167a**).[17]

In addition to studying the effect of diazo substitution, the influence of arene substitution on the yield of cyclopropanation was also evaluated (Table 4.3). Substrates bearing electron-donating groups (EDGs) in the *ortho*, *meta*, or *para* positions react efficiently with low catalyst loadings. However, in the case of *m*-substituted substrates (entries 9, 10), the resulting norcaradienes readily undergo C-C bond scission and rearomatization to produce the benzo-fused cycloheptanone products **167i** and **167j**.[18] In contrast, norcaradienes with *p*- or *o*-EDGs (entries 2, 3, 12, and 13) are more stable and can be isolated when the reaction is quenched with pyridine (to attenuate the Lewis acidity of the residual rhodium) and chromatographically purified using Florisil.

Table 4.3. *Scope of norcaradiene formation*



Entry	Yield (%)[a]	Entry	Yield (%)[a]	Entry	Yield (%)[a]
1	 167a 70 70[b]	6	 167f 36 64[b]	11	 167k 66
2	 167b 80	7	 167g 20 50[b]	12	 167l 81
3	 167c 90	8	 167h 31 40[b]	13	 167m 47
4	 167d 67	9	 167i 93	14	 167n <5 24[b]
5	 167e 63 72[b]	10	 167j 81	15	 167o 50 58[b]

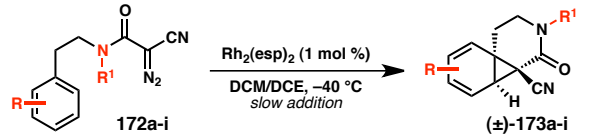
[a] Isolated yield. [b] Conducted at 0 °C using $Rh_2(pfb)_4$ (1 mol %) as catalyst.

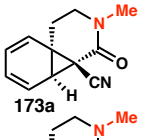
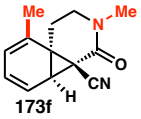
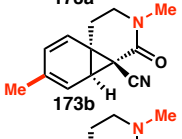
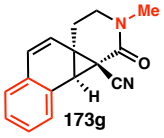
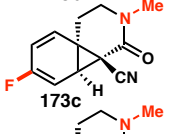
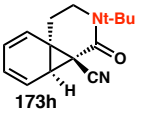
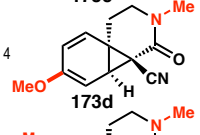
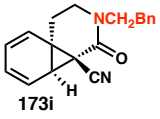
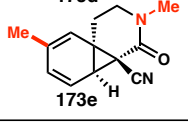
Substrates bearing electron-withdrawing substituents also undergo arene cyclopropanation to provide stable norcaradienes; however, these systems are less reactive and the products are typically generated in lower yields using $Rh_2(esp)_2$ under the standard reaction conditions (entries 5–7).[19] Notably, for these substrates, use of the more reactive $Rh_2(pfb)_4$ catalyst provided better yields of the norcaradiene products. The use of $Rh_2(pfb)_4$ also delivered higher yields of the norcaradienes from more sterically encumbered substrates (entries 8, 14, 15). Only when using $Rh_2(pfb)_4$ with these more hindered α-diazo-β-ketonitrile systems do we observe detectable quantities of C-H insertion products (~5–10%). For unsymmetrical substrates (9–13, 15), the arene

cyclopropanation reaction occurs regioselectively at the less hindered site.[11b,20] The exception is naphthyl substrate **166h**, which provides a modest yield of tetracycle **167h** due to competitive formation of the positional isomer and dimerization product. The electronic nature of the *m*- or *o*-substituent does not exert a significant effect with regard to regioselectivity (see entries 9–13).

A series of the analogous α-diazo-β-cyanoamides were also prepared and studied (Table 4.4). For these substrates, the norcaradiene products are stable and isolable regardless of the substitution pattern or purification method. Similar reactivity trends to those for the α-diazo-β-ketonitriles were observed; however, the yields of norcaradiene products were typically lower due to increased formation of carbene dimerization products.

Table 4.4. *Buchner reaction of α-diazo-β-cyanoamides.*



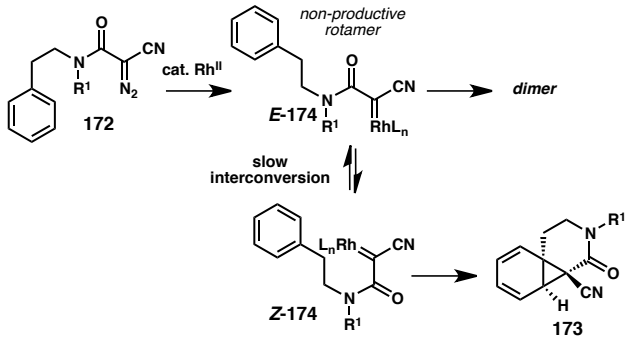
Entry		Yield (%)[a]	Entry		Yield (%)[a]
1	 173a	70	6	 173f	20
2	 173b	42	7	 173g	48
3	 173c	61	8	 173h	80
4	 173d	83	9	 173i	93
5	 173e	57			

[a] Isolated yield.

It has been hypothesized by Wee[12b,21] and others[12a,22] that metal-carbenoids generated from amide-linked diazo substrates (**172**) exist as two slowly interconverting rotamers, **(*Z*)-174** and **(*E*)-174** (Scheme 4.5). Only **(*Z*)-174** is geometrically capable of arene cyclopropanation; if rotation around the amide bond is slow relative to the rate of the competing dimerization process, then the population of **(*E*)-174** could contribute to increased dimer formation while lowering the overall yield of norcaradiene **173**.

Two substrates were designed to probe this hypothesis. *N*-Substitution with a *tert*-butyl group (**172h**) was expected to increase the population of productive rotamer **(*Z*)-174** (R^1 = *t*-Bu), and thereby afford higher yields of norcaradiene. Consistent with this hypothesis, norcaradiene **173h** was isolated in 80% yield (Table 4.4, entry 8), an improvement relative to the 70% yield obtained for **173a**. Moreover, the symmetric di-phenethyl substrate **172i** – in which the amide conformers are identical – provides norcaradiene **173i** in excellent yield (entry 9).

Scheme 4.5. *Effects of amide rotamers on arene cyclopropanation*

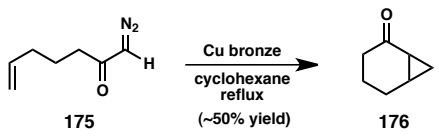


4.3.3 Intramolecular Cyclopropanation with Alkenes

Given the unique reactivity of α-diazo-β-ketonitriles for arene cyclopropanation, we sought to explore the analogous reactions of highly substituted alkenes. In contrast to the intramolecular Buchner reaction, intramolecular alkene cyclopropanation has been extensively investigated for the synthesis of natural and unnatural cyclopropanes. This area of diazo chemistry began in earnest in 1961, when Stork reported the first intramolecular metal-catalyzed cyclopropanation of a α-diazoketone (**175**, Scheme 4.6).[23] Since this work, the metal-catalyzed intramolecular cyclopropanation of alkenes with α-diazocarbonyl compounds has found widespread application in the synthesis of bicyclic structures with a range of substitution patterns and ring sizes.[1a-e,24]

The intramolecular cyclopropanation reaction represents a powerful tool in the construction of complex molecular architectures. The cyclization event rapidly converts simple linear starting materials into bicyclic products adaptable for further transformation. The excellent stereocontrol inherent in the cyclization process imparts a distinct advantage over the analogous *intermolecular* reaction, where control of diastereoselectively is a major consideration. This section examines selected examples of the title reaction in the context of total synthesis.

Scheme 4.6. *The First Catalytic Intramolecular Cyclopropanation of a Diazo Compound*



175 176

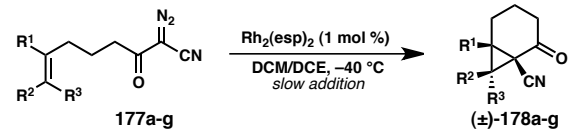
The intramolecular 2+1 cycloaddition of alkenes with α-diazocarbonyl compounds to form bicyclic systems typically proceeds in good yield and is tolerant of a wide range of tether patterns and alkene/arene substitution.[1c,11f,24] Although the transition metal-catalyzed cyclopropanation of alkenes has been thoroughly studied, certain substrate classes are still problematic for the transformation. In particular, diazo compounds that bear four-atom linkers are especially susceptible to C-H insertion events to form cyclopentanones such as **170** (Table 4.2). The intramolecular cyclization of alkenes with di-substituted diazo compounds containing four-atom tethers is highly substrate dependent, and examples of both C-H insertion[17c,25] and cyclopropanation[4f,8c,26] exist. Furthermore, the *intramolecular* cyclopropanation of tri- and tetrasubstituted olefins with A–A substituted carbenoids remains under-developed. To our knowledge, there are very few examples of intramolecular metal-catalyzed cyclopropanation reactions of tri- and tetrasubstituted[8a,22] alkenes using disubstituted diazo substrates.[8a,27]

We were therefore pleased to find that the intramolecular cycloaddition of alkenyl α-diazo-β-ketonitriles proceeds smoothly under mild conditions (Table 4.5). In the case of tetrasubstituted alkene substrates **177b** and **177e–g**, the corresponding cyclopropane products contain three vicinal all-carbon quaternary centers, and are formed in good yields as single diastereomers.[28]

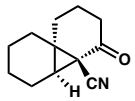
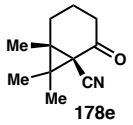
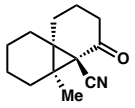
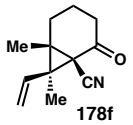
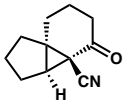
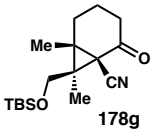
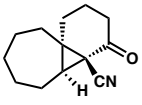
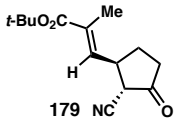
Notably, the alkene cyclopropanation reactions are much less sensitive to water or parameters such as concentration, substrate addition rate, and temperature, than those of the corresponding aryl systems. Of all the alkenyl substrates tested in this report, only the unsaturated ester **177h** (R^1 = H, R^2 = CO_2t-Bu, R^3 = Me) failed to provide the desired cyclopropane, affording instead the C-H insertion product **179** (entry 8).[29] To our

knowledge, this is the first example of tetrasubstituted alkenes undergoing intramolecular cyclopropanation with A–A substituted carbenoids, and we anticipate that this diastereoselective reaction to prepare bi- and tricyclic compounds will find application in a variety of synthetic contexts.

Table 4.5. *Cyclopropanation of various alkenes*



177a-g (±)-178a-g

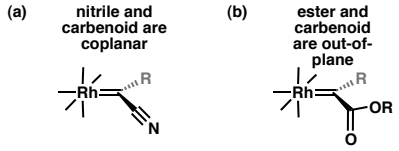
Entry		Yield (%)[a]	Entry		Yield (%)[a]
1	 178a	82	5	 178e	90
2	 178b	76	6	 178f	79
3	 178c	93	7	 178g	93
4	 178d	92	8	 179	40

[a] Isolated yield.

The unique propensity of α-diazo-β-ketonitriles toward arene and alkene cyclopropanation warrants some discussion. A significant difference between rhodium carbenoids derived from α-diazo-β-ketonitriles and α-diazo-β-ketoesters or other A–A substituted diazo compounds is the linear geometry of nitrile. Ester or ketone substituted carbenoids are proposed to adopt out-of-plane conformations in which the π-system of

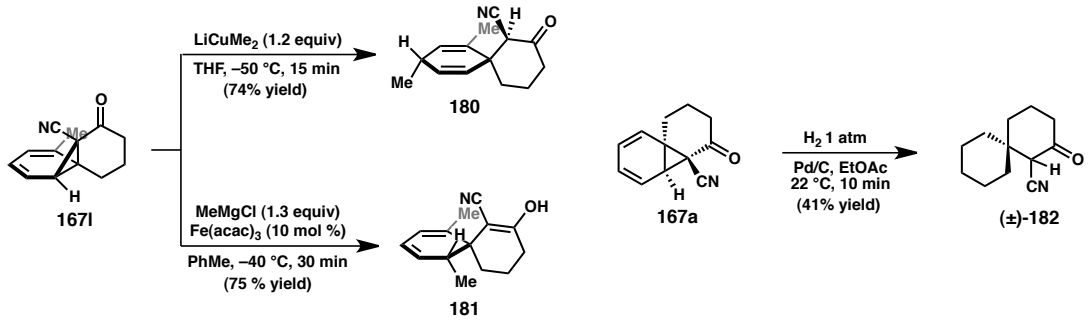
the carbonyl and the vacant 2p orbital of the carbenoid are orthogonal, preventing delocalization (Figure 4.2, b).[30] Alternatively, the nitrile is intrinsically coplanar with the Rh-carbenoid; this conformational effect likely enhances the electrophilicity of the carbenoid (Figure 4.2, a). That more electrophilic carbenoids favor cyclopropanation over C-H insertion is consistent with Padwa's reports on the ligand effects of dirhodium catalysts, which demonstrated that more electron deficient Rh complexes improve the ratio of cyclopropanation to C-H insertion.[11d] Moreover, the relatively small steric profile of the nitrile likely minimizes destabilizing nonbonding interactions between the Rh-carbenoid and the arene/alkene during the cyclopropanation transition structure, while the out-of-plane conformations of esters or ketones sterically obstruct the approach of the arene/alkene to the carbenoid. Charette and coworkers recently proposed these effects to account for the unique reactivity to cyano-substituted carbenoids for asymmetric intermolecular cyclopropanation reactions.[31] Similarly, Fox and coworkers propose that 5- and 6-membered *cyclic* Rh-carbenoids are constrained such that the carbonyl is more coplanar with the carbenoid, which minimizes steric interactions during intermolecular cyclopropanation reactions, allowing them to out-compete β-hydride migration.[32]

Figure 4.2. *Conformational considerations of acceptor substituted carbenoids*



The remarkable reactivity of α-diazo-β-ketonitriles enables the preparation of highly substituted cyclopropanes with unprecedented chemical architectures, and we anticipated that these compounds could participate in a variety of ring-opening reactions. For example, A–A substituted vinyl cyclopropanes are known to undergo S_N2 and S_N2'-type ring-opening reactions.[5a,b] We were therefore pleased to find that treatment of norcaradiene **167l** with lithium dimethylcuprate in THF results in S_N2' addition to provide spirofused bicyclic diene **180**,[33] which is isolated as a single diastereomer (Scheme 4.7).[34] Alternatively, **167l** undergoes clean S_N2 addition when treated with methylmagnesium chloride in the presence of catalytic $Fe(acac)_3$ to deliver the isomeric compound **181** as a single diastereomer.[5e] Finally, we found that hydrogenation of **167a** with 1 atm of H_2 over Pd/C rapidly afforded the saturated spirocycle **182** in 41 % yield, constituting an orthogonal method to these bicyclic architechtures.

Scheme 4.7. *Various transformations of norcaradiene* ***167***

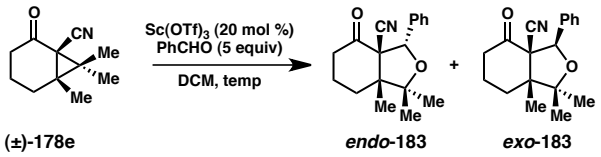


These transformations provide access to spirofused bicycles with complementary substitution patterns, and also highlight the utility of 7-cyano-7-keto-norcaradienes as substrates for stereocontrolled C-C bond formation. Furthermore, this demonstrates an

additional advantaged conferred by the cyano group, as this in concert with the ketone stabilizes the norcaradiene form and allows access to the cyclopropane for ring-opening reactions not possible for structures that favor the cycloheptatriene valence tautomer.

There is also extensive literature describing the transformations of *donor*-acceptor (D–A) cyclopropanes.[5c,6a,6c] For example, D–A cyclopropanes are useful synthons to access 2,5-disbustituted tetrahydrofurans via Lewis acid-mediated aldehyde cycloaddition reactions.[6d,26c] Although cyclopropanes such as **178e** lack a traditional donor groups (such as an arene, alkoxy, or amino substituent), we hypothesized that stabilization of the developing tertiary carbocation would enable cycloaddition.[35] We were pleased to find that treatment of **178e** with catalytic $Sc(OTf)_3$ and excess benzaldehyde provides tetrahydrofuran **183** in excellent yield, albeit as as a mixture of *endo* and *exo* diastereomers (Table 4.6).

Table 4.6. *Cycloaddition of "donor"–acceptor cyclopropane* ***178e*** *with benzaldehyde*



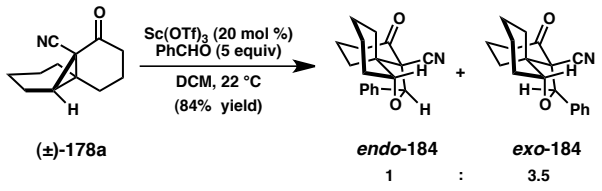
3+2 experiments.

entry	Temp (°C)	Combined Yield (%)	*endo*-183 : *exo*-183	Yield Major (%)
1	– 20	80	3.4 : 1	61
2	40	85	1 : 3.3	65

[a] Isolated yield.

Interestingly, the diastereoselectivity of the reaction was heavily dependent on the reaction temperature. At low temperatures, *endo*-diastereomer **183** is favored and can be isolated in 61% yield. Alternatively, when the reaction is conducted in refluxing dichloromethane, the thermodynamically more stable *exo*-product predominates (65% isolated yield). Indeed, control experiments revealed that re-exposure of ***endo*-183** to the reaction conditions results in equilibration to the same 3.3:1 *exo*/*endo* ratio as observed at 40 °C. Although aldehyde cycloaddition reactions of D–A cyclopropanes have been extensively studied by Johnson, Kerr, and others, examples of this transformation without a true donor component (e.g. phenyl, vinyl, alkoxy, etc.) are less common.[6c,35-36] Similarly, we discovered that cyclopropane **178a** – bearing a secondary alkyl group as the "donor" – also cleanly reacts with benzaldehyde under standard conditions to give a mixture of diastereomeric tricycles in good yield (Scheme 4.8). These studies clearly demonstrate the high reactivity of the α-cyano-α-ketocyclopropanes in aldehyde cycloaddition reactions.[37]

Scheme 4.8. *Cycloaddition of "donor"–acceptor cyclopropane* ***178a*** *with benzaldehyde*



4.4 CONCLUSIONS

In conclusion, the intramolecular cyclopropanation of α-diazo-β-ketonitriles has been investigated. Of particular importance, α-diazo-β-ketonitriles are shown to demonstrate unique reactivity in their propensity to undergo arene cyclopropanation; other similar A–A substituted diazo substrates fail to deliver the Buchner-type product, favoring instead C-H insertion processes. In addition, α-diazo-β-ketonitriles undergo highly efficient intramolecular cyclopropanation of tri- and tetrasubstituted alkenes, which in the latter case provides access to products containing three contiguous all-carbon quaternary centers. These types of highly functionalized cyclopropane products with other A–A motifs are challenging to prepare by cycloaddition chemistry. We have also demonstrated that the α-cyano-α-ketocyclopropane products serve as excellent substrates for S_N2, S_N2', and aldehyde cycloaddition reactions. The development and application of enantio- and diastereoselective intramolecular cyclopropanation reactions of α-diazo-β-ketonitriles is the subject of ongoing research in our laboratory.

4.5 EXPERIMENTAL SECTION

4.5.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. *N*-Methyl-2-phenylacetamide was purchased from Acros Organics. Scandium triflate ($Sc(OTf)_3$), iron acetylacetonate ($Fe(acac)_3$), palladium acetate ($Pd(OAc)_2$) and all rhodium and copper catalysts were purchased from either Strem or Sigma-Aldrich. Cobalt and iridium catalysts were purchased from Strem. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al. (Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. **1978**, *43*, 2923) using silica gel (partical size 0.032-0.063) purchased from Silicycle or Florisil (100 – 200 mesh) purchased from Sigma-Aldrich. ^1H and ^{13}C NMR spectra were recorded on a Varian 300 MR (at 300 MHz and 75 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer

Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 mm) or an Agilent Zorbax RX-SIL 5μm column (9.4 x 250 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

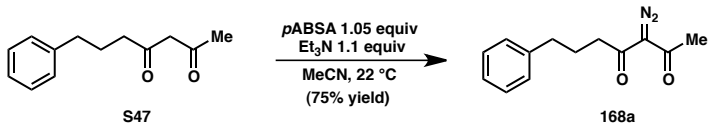
4.5.2 Preparative Procedures and Spectroscopic Data

Catalyst Screen: General Procedure for Diazoketone 166a (Table 4.1)

Method A (Entries 1-6): A sealed 1 mL microwave vial equipped with a stir bar was flushed with N_2 and charged with a stock solution of a-diazo-b-ketonitrile **166a** (0.005 mmol) and 1,2,4,5-tetrachlorobenzene (0.005 mmol) in $CDCl_3$ (400 μL), followed by the catalyst (0.0001 mmol) in $CDCl_3$ (100 μL). The solution was heated in a Biotage Initiator microwave reactor to the indicated temperature for 1 min (ramp time required 2 min). TLC analysis confirmed consumption of the starting material. The solution was transferred to a NMR tube and the yield of cyclopropane **167a** was determined relative to the ratio of **166a**:1,2,4,5-tetrachlorobenzene in the stock solution.

Method B (Entries 7–11): A sealed 1 mL vial equipped with a stir bar was flushed with N_2 and charged with a stock solution of a-diazo-b-ketonitrile **166a** (0.005 mmol) and 1,2,4,5-tetrachlorobenzene (0.005 mmol) in $CDCl_3$ (400 μL), followed by the rhodium catalyst (0.0001 mmol) in $CDCl_3$ (100 μL). The solution was stirred for 2 hours under nitrogen. TLC analysis confirmed consumption of the starting material. The solution was transferred to an NMR tube and the yield of cyclopropane **167a** was determined relative to the ratio of **166a**:1,2,4,5-tetrachlorobenzene in the stock solution.

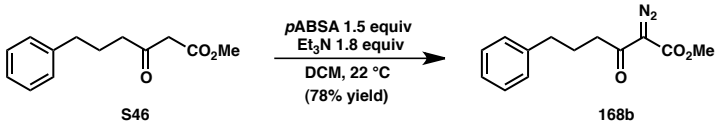
Preparation of 3-diazo-7-phenylheptane-2,4-dione (168a)



A 50 mL round bottom flask was charged with diketone **S47**[‡] (0.71 g, 3.48 mmol) and para-acetamidobenzenesulfonyl azide (0.87 g, 1.66 mmol). The headspace was swept with nitrogen and MeCN (12 mL) was charged, followed by cooling to 0 °C in an ice bath. Triethylamine (0.53 mL, 3.82 mmol) was added in one portion and a slurry quickly resulted. The reaction was allowed to warm to room temperature over 1 hour, at which point TLC analysis indicated complete consumption of the starting material. The reaction was quenched with 2M NaOH and extracted with DCM. The organic layer was cut, acidified to pH = 5 with 5% aqueous acetic acid, washed with brine and dried over sodium sulfate. The solvent was concentrated under reduced pressure, and the crude residue was purified by flash chromatography (0→20% EtOAc/hexanes), yielding diazo diketone **168a** (0.60 g, 75% yield) as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (m, 2H), 7.19 (m, 3H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 3H), 2.43 (s, 3H), 2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 190.54 (broad), 188.31 (broad), 141.18, 128.35, 128.33, 125.97, 83.95, 39.64, 34.90, 28.50, 25.42; FTIR (NaCl, thin film) 3061, 3026, 2936, 2860, 2117, 1682, 1651, 1496, 1454, 1372, 1286, 1228 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{13}O_3$ $[M–H]^-$ $–N_2$ 201.0921, found 201.0918.

[‡] Zhang, Y.; Jiao, J.; Flowers, R. A., II; *J. Org. Chem.* **2006**, *71*, 4516.

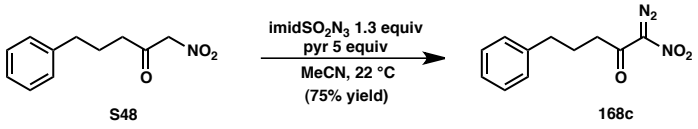
Preparation of methyl 2-diazo-3-oxo-6-phenylhexanoate (168b)



S46 168b

A 25 mL round bottom flask was charged with β-ketoester **S46** (0.25 g, 1.13 mmol) and para-acetamidobenzenesulfonyl azide (0.40 g, 1.66 mmol). The headspace was swept with nitrogen and DCM (20 mL) was charged, followed by cooling to 0 °C in an ice bath. Triethylamine (0.29 mL, 2.06 mmol) was added in one portion and a clear yellow solution resulted. The reaction was allowed to warm to room temperature slowly overnight, during which time a flocculent white precipitate occurred. After TLC analysis indicated complete consumption of the starting material, the reaction was quenched with 2M NaOH. The organic layer was cut, acidified to pH = 5 with 5% aqueous acetic acid, washed with brine and dried over sodium sulfate. The solvent was concentrated under reduced pressure, and the crude residue was purified by flash chromatography (0→20% EtOAc/hexanes), yielding α-diazo-β-ketoester **168b** (0.22 g, 94% yield) as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (m, 2H), 7.19 (m, 3H), 3.82 (s, 3H), 2.88 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H), 1.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 192.27, 161.56, 141.49, 128.32, 128.17, 125.74, 75.60, 51.98, 39.46, 35.06, 25.75; FTIR (NaCl, thin film) 3026, 2952, 2858, 2135, 1731, 1603, 1496, 1435, 1375, 1311, 1223 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{13}N_2O_3$ $[M–H]^-$ 245.0932, found 245.0929.

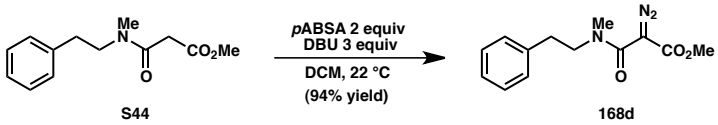
Preparation of 1-diazo-1-nitro-5-phenylpentan-2-one (168c)



S48 168c

To a 20 mL vial was added the nitro ketone **S48** (115 mg, 0.56 mmol) followed by acetonitrile (2 mL) and imidazole sulfonyl azide (127 mg, 0.80 mmol). Pyridine (210 mg, 2.78 mmol) was charged and dark red mixture was stirred at 22 °C under an air atmosphere. After 30 seconds a white precipitate occurred. After TLC analysis indicated consumption of the starting material (2 hours) the solvent of the dark red mixture was removed by rotary evaporation under reduced pressure. The crude residue was purified by flash chromatography (0→15% EtOAc/hexanes), yielding the α-diazo-β-ketonitro compound **168c** (97 mg, 75% yield) as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (m, 2H), 7.20 (m, 3H), 3.04 (t, J = 7.3 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 186.57, 140.96, 128.39, 126.08, 112.15 (broad), 40.11, 34.84, 25.07; FTIR (NaCl, thin film) 3026, 2938, 2860, 2139, 1664, 1509, 1453, 1317, 1235, 1167 cm^{-1}; HRMS (FAB+) calc'd for $C_{11}H_{12}N_3O_3$ $[M+H]^+$ 234.0879, found 234.0868.

Preparation of methyl 2-diazo-3-(methyl(phenethyl)amino)-3-oxopropanoate (168d)

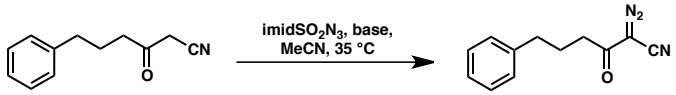


S44 168d

A 25 mL round bottom flask was charged with β-ketoamide **S44** (0.27 g, 1.18 mmol) and para-acetamidobenzenesulfonyl azide (0.56 g, 2.36 mmol). The headspace was swept with nitrogen and DCM (5 mL) was charged, followed by cooling to 0 °C in an ice bath. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.52 mL, 3.53 mmol) was added in one portion and a clear yellow solution resulted. The reaction was allowed to warm to room temperature slowly overnight. After TLC analysis indicated complete consumption of the

starting material, the reaction was quenched with 2M NaOH. The organic layer was cut, acidified to pH = 5 with 5% aqueous acetic acid, washed with brine and dried over sodium sulfate. The solvent was concentrated under reduced pressure, and the crude residue was purified by flash chromatography (0→40% EtOAc/hexanes), yielding α-diazo-β-amido ester **168d** (0.29 g, 94% yield) as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (m, 2H), 7.22 (m, 3H), 3.79 (s, 3H), 3.60 (m, 2H), 2.98 (s, 3H), 2.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 162.63, 161.18, 138.46, 128.73, 128.49, 126.48, 66.11, 59.69, 52.14, 51.50 (broad), 36.43 (broad), 33.74; FTIR (NaCl, thin film) 3026, 2952, 2861, 2223, 1715, 1629, 1483, 1435, 1400, 1301, 1082 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{16}N_3O_3$ $[M+H]^+$ 262.1186, found 262.1184.

General procedure 1 for the synthesis of α-diazo-β-keto nitriles.[§]



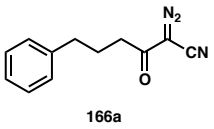
S15 166a

To a 20 mL vial was added the keto nitrile substrate **S15** (0.26 mmol, 1.00 equiv) followed by acetonitrile (2 mL) and either imidazole sulfonyl azide or the corresponding HCl salt (0.29 mmol, 1.10 equiv). Pyridine (1.135 mmol, 5 equiv) was charged and the light yellow mixture was heated to 35 °C sealed under an air atmosphere. After 10 minutes a white precipitate occurred. After TLC analysis indicated consumption of the starting material (typically 3 to 6 hours) the solvent of the dark red mixture was removed by rotary evaporation under reduced pressure. The crude residue was purified by silica

[§] Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797.

gel chromatography to afford the α-diazo-β-keto nitriles products, eluting as a distinct yellow band on the column.

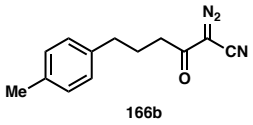
2-Diazo-3-oxo-6-phenylhexanenitrile (166a)



166a

The reaction was run on 3.70 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 500 mg (64% yield) of **166a** as a bright yellow oil, which solidified on standing to a bright yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (m, 2H), 7.20 (m, 3H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.85, 140.65, 128.43, 128.39, 128.39, 128.37, 126.16, 108.32, 57.20, 38.59, 34.75, 25.59; FTIR (NaCl, thin film) 3062, 3027, 2936, 2863, 2222, 2127, 1682, 1497, 1454, 1372, 1212 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+ - N_2$ 186.0913, found 186.0924.

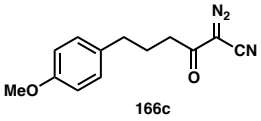
2-Diazo-3-oxo-6-(*p*-tolyl)hexanenitrile (166b)



166b

The reaction was run on 0.44 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 82 mg (83% yield) of **166b** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 2.63 (m, 4H), 2.33 (s, 3H), 2.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.91, 137.54, 135.62, 129.10, 128.26, 108.34, 57.17, 38.62, 34.30, 25.70, 20.93; FTIR (NaCl, thin film) 3192, 2923, 2861, 2221, 2126, 1677, 1515, 1454, 1372, 1212, 1180 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{12}NO_2$ $[M+H]^+ - N_2$ 200.1070, found 200.1071.

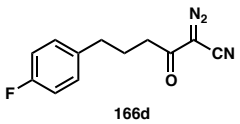
2-Diazo-6-(4-methoxyphenyl)-3-oxohexanenitrile (166c)



166c

The reaction was run on 0.92 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 164 mg (74% yield) of **166c** as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09 (m, 2H), 6.84 (m, 2H), 3.79 (s, 3H), 2.62 (t, J = 7.4 Hz, 4H), 1.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.90, 157.91, 132.66, 129.26, 113.78, 108.33, 57.15, 55.14, 38.54, 33.81, 25.80; FTIR (NaCl, thin film) 3002, 2935, 2833, 2221, 2126, 1675, 1610, 1512, 1454, 1245, 1177 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{13}N_3O_2$ $[M+H]^+$ 243.1008, found 243.1015.

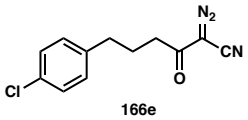
2-Diazo-6-(4-fluorophenyl)-3-oxohexanenitrile (166d)



166d

The reaction was run on 1.08 mmol scale for 4 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 200 mg (77% yield) of **166d** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (m, 2H), 6.98 (m, 2H), 2.64 (m, 4H), 2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.73, 161.34 (d, $J_{C\text{-}F}$ = 243.8 Hz), 136.30 (d, $J_{C\text{-}F}$ = 3.2 Hz), 129.71 (d, $J_{C\text{-}F}$ = 7.8 Hz), 115.17 (d, $J_{C\text{-}F}$ = 21.0 Hz), 108.30, 57.24, 38.45, 33.91, 25.69; FTIR (NaCl, thin film) 2930, 2862, 2222, 2126, 1676, 1600, 1508, 1218 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{10}FN_3O$ $[M\ \ ]^+$ 231.0808, found 231.0817.

6-(4-Chlorophenyl)-2-diazo-3-oxohexanenitrile (166e)

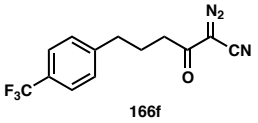


166e

The reaction was run on 0.91 mmol scale for 4 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 110 mg (50% yield) of **166e** as a bright yellow oil. ^{1}H NMR

($CDCl_3$, 300 MHz) δ 7.26 (m, 2H), 7.10 (m, 2H), 2.63 (m, 4H), 2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.71, 139.12, 131.95, 129.74, 128.58, 108.30, 57.30, 38.49, 34.13, 25.50; FTIR (NaCl, thin film) 2935, 2863, 2222, 2128, 1676, 1492, 1407, 1373, 1180 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_9ClN_3O$ $[M–H]^-$ 246.0440, found 246.0437.

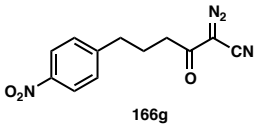
2-Diazo-3-oxo-6-(4-(trifluoromethyl)phenyl)hexanenitrile (166f)



166f

The reaction was run on 0.60 mmol scale for 4 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 111 mg (67% yield) of **166f** as a bright yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56 (m, 2H), 7.30 (m, 1H), 2.74 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.3 Hz, 2H), 2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.58, 144.84 (q, $J_{C\text{-}F}$ = 1.3 Hz), 128.71, 128.59 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.42 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.20 (q, $J_{C\text{-}F}$ = 271.7 Hz), 108.27, 57.36, 38.47, 34.60, 25.29; FTIR (NaCl, thin film) 2934, 2869, 2224, 2129, 1681, 1618, 1417, 1327, 1163 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_9F_3N_3O$ $[M–H]^-$ 280.0703, found 280.0698.

2-Diazo-6-(4-nitrophenyl)-3-oxohexanenitrile (166g)

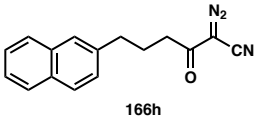


166g

The reaction was run on 0.26 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 39 mg (57% yield) of **166g** as a bright yellow solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.15 (m, 2H), 7.34 (m, 2H), 2.78 (t, J = 7.9 Hz, 2H), 2.66 (t, J = 7.2 Hz, 2H), 2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.35, 148.57, 146.55, 129.17, 123.75, 108.21, 57.45, 38.34, 34.60, 25.04; FTIR (NaCl, thin film) 3109, 3077, 2937,

2866, 2222, 2130, 1677, 1598, 1515, 1364, 1182 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_9N_2O_3$ $[M–H]^-$ $–N_2$ 229.0619, found 229.0629.

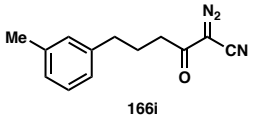
2-Diazo-6-(naphthalen-2-yl)-3-oxohexanenitrile (166h)



166h

The reaction was run on 0.57 mmol scale for 4 hr. The crude material was purified by silica gel chromatography (85:15 Hexanes:EtOAc) to give 120 mg (80% yield) of **166h** as a bright yellow solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.81 (m, 3H), 7.64 (s, 1H), 7.46 (m, 2H), 7.33 (dd, *J* = 8.4, 1.7 Hz, 1H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.80, 138.14, 133.44, 132.05, 128.09, 127.54, 127.37, 126.98, 126.59, 125.99, 125.32, 108.32, 57.22, 38.58, 34.91, 25.48; FTIR (NaCl, thin film) 3027, 2954, 2913, 2867, 2223, 2128, 1674, 1597, 1455, 1400, 1273 cm^{-1}; HRMS (FAB+) calc'd for $C_{16}H_{13}N_3O$ $[M\ \ ]^+$ 263.1059, found 263.1069.

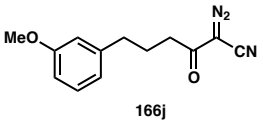
2-Diazo-3-oxo-6-(*m*-tolyl)hexanenitrile (166i)



166i

The reaction was run on 0.81 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 159 mg (86% yield) of **166i** as a bright yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.19 (t, *J* = 7.5 Hz, 1H), 7.00 (m, 4H), 2.63 (m, 4H), 2.33 (s, 2H), 2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.94, 140.60, 138.05, 129.21, 128.35, 126.91, 125.40, 108.34, 57.19, 38.67, 34.70, 25.64, 21.33; FTIR (NaCl, thin film) 3020, 2924, 2862, 2221, 2126, 1677, 1608, 1456, 1371, 1211, 1182 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO$ $[M+H]^+$ $–N_2$ 200.1070, found 200.1071.

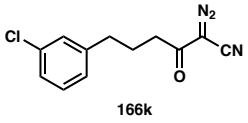
2-Diazo-6-(3-methoxyphenyl)-3-oxohexanenitrile (166j)



166j

The reaction was run on 0.38 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 72 mg (79% yield) of **166j** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (t, *J* = 7.8, 1H), 6.75 (m, 3H), 3.80 (s, 3H), 2.64 (m, 4H), 2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.84, 159.63, 142.27, 129.41, 120.74, 114.08, 111.45, 108.32, 57.19, 55.07, 38.56, 34.76, 25.45; FTIR (NaCl, thin film) 3002, 2940, 2836, 2221, 2125, 1682, 1601, 1583, 1488, 1454, 1371, 1258 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+ - N_2$ 216.1019, found 216.1016.

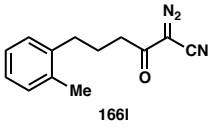
6-(3-Chlorophenyl)-2-diazo-3-oxohexanenitrile (166k)



166k

The reaction was run on 0.61 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (85:15 Hexanes:EtOAc) to give 120 mg (80% yield) of **166k** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (m, 3H), 7.05 (m, 1H), 2.64 (m, 4H), 2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.60, 142.73, 134.19, 129.71, 128.46, 126.56, 126.39, 108.26, 57.29, 38.43, 34.39, 25.31; FTIR (NaCl, thin film) 3062, 2937, 2865, 2221, 2127, 1678, 1597, 1574, 1475, 1372, 1205 cm^{-1}; HRMS (FAB+) calc'd for $C_{12}H_{11}N_3OCl$ $[M+H]^+$ 248.0591, found 248.0585.

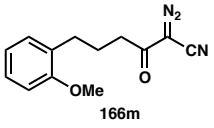
2-Diazo-3-oxo-6-(*o*-tolyl)hexanenitrile (166l)



166l

The reaction was run on 1.54 mmol scale for 3 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 277 mg (80% yield) of **166l** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (m, 4H), 2.67 (m, 4H), 2.32 (s, 3H), 1.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.78, 138.90, 135.88, 130.25, 128.81, 126.26, 125.95, 108.33, 57.15, 38.88, 32.23, 24.29, 19.13; FTIR (NaCl, thin film) 3016, 2945, 2868, 2221, 2127, 1682, 1493, 1461, 1371, 1168 cm^{-1}; HRMS (FAB+) calc'd for $C_{13}H_{14}N_3O$ $[M+H]^+$ 228.1173, found 228.1148.

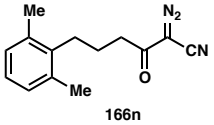
2-Diazo-6-(2-methoxyphenyl)-3-oxohexanenitrile (166m)



166m

The reaction was run on 0.35 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 66 mg (78% yield) of **166m** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 7.12 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.89 (td, *J* = 7.4, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.83 (s, 3H), 2.68 (t, *J* = 7.4 Hz, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.00 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 190.13, 157.40, 130.01, 129.06, 127.47, 120.39, 110.20, 108.41, 56.98, 55.12, 38.91, 29.26, 24.20; FTIR (NaCl, thin film) 3002, 2938, 2836, 2221, 2126, 1677, 1600, 1586, 1494, 1464, 1370, 1243, 1179 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+ – N_2$ 216.1019, found 216.1020.

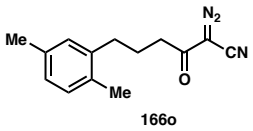
2-Diazo-6-(2,6-dimethylphenyl)-3-oxohexanenitrile (166n)



166n

The reaction was run on 2.79 mmol scale for 16 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 525 mg (78% yield) of **166n** as a bright yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (m, 3H), 2.77 (t, *J* = 7.1 Hz, 2H), 2.69 (m, 2H), 2.36 (s, 6H), 1.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.69, 137.75, 135.99, 128.13, 125.92, 108.36, 57.12, 39.43, 28.85, 23.27, 19.68; FTIR (NaCl, thin film) 3016, 2955, 2221, 2127, 1677, 1467, 1369, 1189 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{14}NO$ $[M\text{-}H]^-$ $-N_2$ 212.1081, found 212.1091.

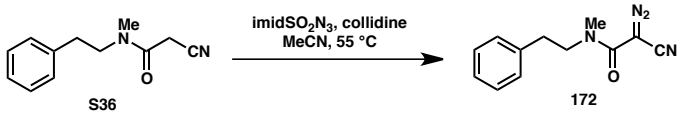
2-Diazo-6-(2,5-dimethylphenyl)-3-oxohexanenitrile (166o)



166o

The reaction was run on 0.73 mmol scale for 4 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 150 mg (86% yield) of **166o** as a bright yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.05 (d, *J* = 8.1 Hz, 1H), 6.96 (m, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.64 (m, 2H), 2.32 (s, 3H), 2.29 (s, 3H), 1.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.83, 138.72, 135.34, 132.68, 130.17, 129.64, 126.92, 108.34, 57.13, 38.91, 32.24, 24.41, 20.85, 18.66; FTIR (NaCl, thin film) 2919, 2868, 2220, 2129, 1672, 1503, 1454, 1376, 1180 cm^{-1}; HRMS (FAB+) calc'd for $C_{14}H_{16}N_3O$ $[M+H]^+$ 242.1293, found 242.1284.

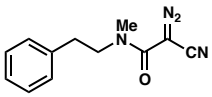
General procedure 2 for the synthesis of α-diazo-cyanoacetamides.



S36 172

To a 20 mL vial was added the cyanoacetamide substrate **S36** (1.63 mmol, 1.00 equiv) followed by acetonitrile (5 mL) and either imidazole sulfonyl azide[3] or the corresponding HCl salt (1.79 mmol, 1.10 equiv). 2,4,6-Collidine (8.15 mmol, 5.0 equiv) was charged and the light yellow mixture was heated to 55 °C sealed under an air atmosphere. A white precipitate occurred after 3 hours. After TLC analysis indicated consumption of the starting material (typically 24 hours) the solvent of the dark red mixture was removed by rotary evaporation under reduced pressure. The crude residue was purified by silica gel chromatography to afford the α-diazo-cyanoacetamides products, eluting as a distinct yellow band on the column.

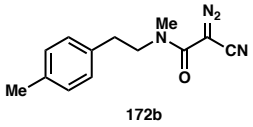
2-Cyano-2-diazo-*N*-methyl-*N*-phenethylacetamide (172a)



172a

The reaction was run on 1.63 mmol scale for 24 hr. The crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to give 273 mg (73% yield) of **172a** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (m, 2H), 7.24 (m, 3H), 3.64 (m, 2H), 3.03 (s, 3H), 2.90 (t, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.90, 137.77 (broad), 128.76, 128.63, 126.72, 109.89, 52.56 (broad), 51.89, 36.31 (broad), 34.08 (broad); FTIR (NaCl, thin film) 3026, 2930, 2860, 2213, 2120, 1636, 1631, 1481, 1453, 1399, 1216 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{13}N_2O$ $[M+H]^+ – N_2$ 201.1022, found 201.1019.

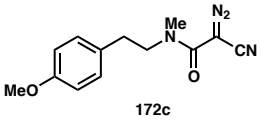
2-Cyano-2-diazo-*N*-methyl-*N*-(4-methylphenethyl)acetamide (172b)



172b

The reaction was run on 0.787 mmol scale for 24 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 140 mg (74% yield) of **172b** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 (s, 4H), 3.62 (m, 2H), 3.03 (s, 3H), 2.86 (t, *J* = 7.6 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.83, 136.22, 134.57 (broad), 129.26, 128.61, 109.88, 52.50 (broad), 51.95, 36.24 (broad), 33.62 (broad), 20.92; FTIR (NaCl, thin film) 2923, 2859, 2213, 2120, 1636, 1399, 1214 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}N_2O$ $[M+H]^+ - N_2$ 215.1179, found 215.1172.

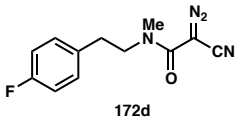
2-Cyano-2-diazo-*N*-(4-methoxyphenethyl)-*N*-methylacetamide (172c)



172c

The reaction was run on 3.01 mmol scale for 18 hr. The crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to give 530 mg (68% yield) of **172c** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (m, 2H), 6.86 (m, 2H), 3.79 (s, 3H), 3.61 (m, 2H), 3.03 (s, 3H), 2.84 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.83, 158.33, 129.74, 114.00, 109.91, 55.15, 52.53 (broad), 52.04, 36.26 (broad), 33.18 (broad); FTIR (NaCl, thin film) 3030, 2995, 2934, 2835, 2214, 2121, 1636, 1612, 1513, 1481, 1399, 1302, 1247, 1178 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}N_2O_2$ $[M+H]^+ - N_2$ 231.1128, found 231.1119.

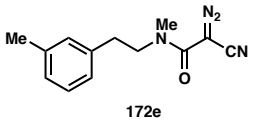
2-Cyano-2-diazo-*N*-(4-fluorophenethyl)-*N*-methylacetamide (172d)



172d

The reaction was run on 4.10 mmol scale for 24 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 624 mg (62% yield) of **172d** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (m, 2H), 7.01 (m, 2H), 3.61 (m, 2H), 3.04 (s, 3H), 2.88 (t, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 162.58, 160.63, 158.87, 133.35 (broad), 130.17 (d, $J_{C\text{-}F}$ = 8.0 Hz), 115.47, 115.30, 109.81, 52.49 (broad), 51.74, 36.19 (broad), 33.14 (broad); FTIR (NaCl, thin film) 3069, 3040, 2934, 2860, 2215, 2122, 1633, 1510, 1482, 1398, 1219 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{12}N_2FO$ $[M+H]^+ - N_2$ 219.0928, found 219.0936.

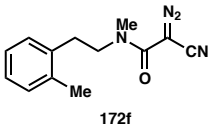
2-Cyano-2-diazo-*N*-methyl-*N*-(3-methylphenethyl)acetamide (172e)



172e

The reaction was run on 2.92 mmol scale for 24 hr. The crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to give 476 mg (67% yield) of **172e** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (m, 1H), 7.05 (m, 3H), 3.63 (m, 2H), 3.04 (s, 3H), 2.86 (t, J = 7.7 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.82, 138.18, 137.61 (broad), 129.49, 128.45, 127.36, 125.67, 109.82, 52.46 (broad), 51.88, 36.23 (broad), 33.92 (broad), 21.21; FTIR (NaCl, thin film) 3014, 2928, 2863, 2214, 2120, 1634, 1482, 1398, 1215 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}N_2O$ $[M+H]^+ - N_2$ 215.1179, found 215.1171.

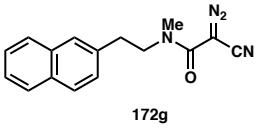
2-Cyano-2-diazo-*N*-methyl-*N*-(2-methylphenethyl)acetamide (172f)



172f

The reaction was run on 0.74 mmol scale for 24 hr. The crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to give 95 mg (53% yield) of **172f** as a bright yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (m, 4H), 3.59 (t, *J* = 7.7 Hz, 2H, 2H), 3.07 (s, 3H), 2.91 (t, *J* = 7.7 Hz, 2H, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.94, 136.12, 135.99 (broad), 130.48, 129.53, 126.94, 126.25, 109.87, 52.55 (broad), 50.72, 36.45 (broad), 31.35 (broad), 29.66, 19.19; FTIR (NaCl, thin film) 3014, 2928, 2863, 2214, 2120, 1634, 1482, 1398, 1215 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}N_2O$ $[M+H]^+ – N_2$ 215.1179, found 215.1171.

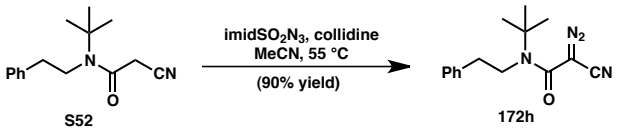
2-Cyano-2-diazo-*N*-methyl-*N*-(2-(naphthalen-2-yl)ethyl)acetamide (172g)



172g

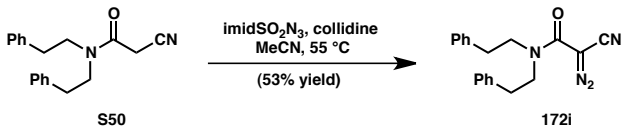
The reaction was run on 1.98 mmol scale for 18 hr. The crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to give 390 mg (71% yield) of **172g** as a bright yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (m, 3H), 7.68 (s, 1H), 7.47 (m, 2H), 7.37 (m, 1H), 3.73 (m, 2H), 3.06 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.94, 135.24 (broad), 133.46, 132.23, 128.33, 127.58, 127.44, 127.30 (broad), 126.99, 126.14, 125.61, 109.90, 52.58 (broad), 51.83, 36.40 (broad), 34.26 (broad); FTIR (NaCl, thin film) 3051, 3019, 2932, 2859, 2213, 2120, 1636, 1481, 1399, 1309, 1220, 1083 cm^{-1}; HRMS (MM) calc'd for $C_{16}H_{15}N_2O$ $[M+H]^+ – N_2$ 251.1179, found 215.1171.

Preparation of *N*-(*t*-butyl)-2-cyano-2-diazo-*N*-phenethylacetamide (172h)



Compound **172h** was synthesized according to general procedure 2. The reaction was run on 0.13 mmol scale for 18 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 31 mg (90% yield) of **172h** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (m, 5H), 3.67 (m, 2H), 2.95 (m, 2H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.83, 137.59, 128.83, 128.71, 126.92, 110.67, 59.71, 54.61, 47.28, 37.88, 28.98; FTIR (NaCl, thin film) 3027, 2975, 2928, 2211, 2120, 1633, 1454, 1386, 1364, 1181 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{19}N_2O$ $[M+H]^+ - N_2$ 243.1492, found 243.1490.

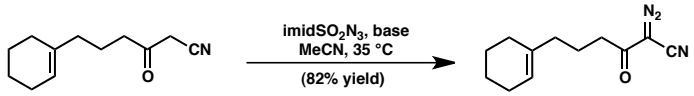
Preparation of 2-cyano-2-diazo-*N*,*N*-diphenethylacetamide (172i)



Compound **172i** was synthesized according to general procedure 2. The reaction was run on 0.68 mmol scale for 24 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 115 mg (53% yield) of **172i** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (m, 4H), 7.22 (m, 6H), 3.56 (t, J = 7.7 Hz, 4H), 2.87 (t, J = 7.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.63, 137.76 (broad), 128.78, 128.63, 126.73, 110.09, 52.99, 50.44, 34.55 (broad); FTIR (NaCl, thin film)

3025, 2929, 2859, 2212, 2120, 1638, 1453, 1419, 1217 cm^{-1}; HRMS (MM) calc'd for $C_{19}H_{19}N_2O$ $[M+H]^+ – N_2$ 291.1492, found 291.1483.

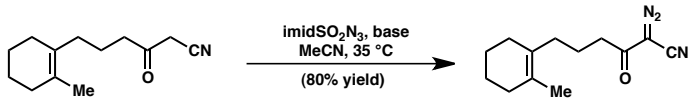
Preparation of 6-(cyclohex-1-en-1-yl)-2-diazo-3-oxohexanenitrile (177a)



S57 177a

Compound **177a** was synthesized according to general procedure 1. The reaction was run on 1.05 mmol scale for 3 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 179 mg (82% yield) of **177a** as a bright yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.42 (dt, J = 2.6, 1.2 Hz, 1H), 2.58 (t, J = 7.3 Hz, 2H), 1.99 (m, 4H), 1.89 (m, 3H), 1.81 (m, 2H), 1.60 (m, 2H), 1.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 190.20, 136.07, 122.36, 108.41, 57.05, 38.65, 36.95, 27.79, 25.11, 22.76, 22.30, 22.05; FTIR (NaCl, thin film) 2928, 2835, 2221, 2126, 1682, 1438, 1367, 1211 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{15}NO$ $[M–H]^- – N_2$ 188.1081, found 188.1077.

Preparation of 2-diazo-6-(2-methylcyclohex-1-en-1-yl)-3-oxohexanenitrile (177b)

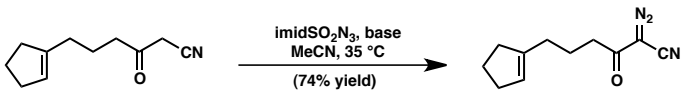


S60 177b

Compound **177b** was synthesized according to general procedure 1. The reaction was run on 0.54 mmol scale for 6 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 98 mg (80% yield) of **177b** as a bright yellow oil. This compound was subjected to preparative HPLC (SiO_2 column, 5%

EtOAc/Hexanes, 5 mL/min) to achieve higher isomeric purity. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as a >95:5 mixture of alkene isomers, only major **177b** peaks are reported) δ 2.58 (t, *J* = 7.4 Hz, 2H), 2.04 (t, *J* = 7.7 Hz, 2H), 1.90 (m, 4H), 1.75 (m, 2H), 1.59 (s, 3H), 1.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a >95:5 mixture of alkene isomers, only major **177b** peaks are reported) δ 190.23, 128.39, 127.62, 108.44, 56.97, 39.06, 32.27, 31.77, 29.24, 23.32, 23.22, 22.63, 19.05; FTIR (NaCl, thin film) 2925, 2858, 2221, 2127, 1684, 1437, 1368, 1238 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{16}NO$ $[M–H]^-$ $–N_2$ 202.1237, found 202.1233.

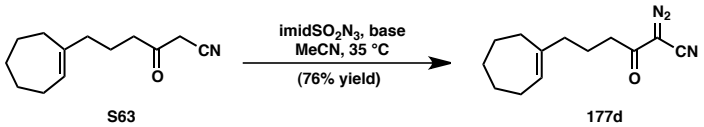
Preparation of 6-(cyclopent-1-en-1-yl)-2-diazo-3-oxohexanenitrile (177c)



S55 177c

Compound **177c** was synthesized according to general procedure 1. The reaction was run on 1.16 mmol scale for 10 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 174 mg (74% yield) of **177c** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.35 (m, 1H), 2.59 (t, *J* = 7.4 Hz, 2H), 2.28 (m, 2H), 2.19 (m, 2H), 2.11 (m, 2H), 1.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 190.13, 142.92, 124.69, 108.41, 57.10, 38.89, 34.68, 32.34, 30.12, 23.30, 22.20; FTIR (NaCl, thin film) 2934, 2838, 2221, 2123, 1675, 1438, 1367, 1179 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{12}NO$ $[M–H]^-$ $–N_2$ 174.0924, found 174.0919.

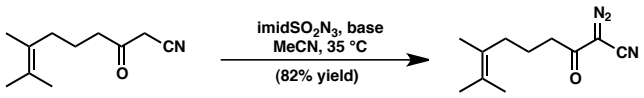
Preparation of 6-(cyclohept-1-en-1-yl)-2-diazo-3-oxohexanenitrile (177d)



S63 177d

Compound **177d** was synthesized according to general procedure 1. The reaction was run on 1.15 mmol scale for 10 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 200 mg (76% yield) of **177d** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.56 (tt, J = 6.4, 1.2 Hz, 1H), 2.59 (t, J = 7.3 Hz, 2H), 2.07 (m, 4H), 2.01 (t, J = 7.3 Hz, 2H), 1.78 (m, 2H), 1.72 (m, 2H), 1.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 190.21, 142.84, 127.41, 108.39, 57.07, 39.09, 38.61, 32.44, 32.30, 28.17, 27.13, 26.69, 22.26; FTIR (NaCl, thin film) 2920, 2847, 2221, 2127, 1676, 1446, 1366, 1211, 1180 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{18}NO$ $[M+H]^+$ $-N_2$ 204.1383, found 204.1375.

Preparation of 2-diazo-7,8-dimethyl-3-oxonon-7-enenitrile (177e)

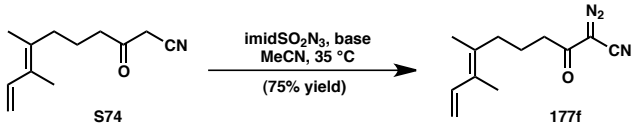


S66 177e

Compound **177e** was synthesized according to general procedure 1. The reaction was run on 0.36 mmol scale for 3 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 500 mg (64% yield) of **177e** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.58 (t, J = 7.4 Hz, 2H), 2.08 (m, 2H), 1.76 (m, 2H), 1.64 (m, 6H), 1.63 (q, J = 1.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 190.19, 126.11, 125.57, 108.43, 56.96, 38.95, 33.25, 22.57, 20.51, 20.14, 18.07; FTIR (NaCl, thin

film) 2987, 2918, 2861, 2222, 2128, 1676, 1451, 1372, 1216 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{16}NO$ $[M+H]^+ - N_2$ 178.1227, found 178.1228.

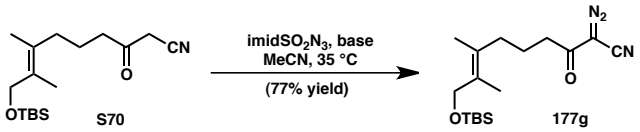
Preparation of (*E*)-2-diazo-7,8-dimethyl-3-oxodeca-7,9-dienenitrile (177f)



S74 177f

Compound **177f** was synthesized according to general procedure 1. The reaction was run on 0.414 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 67 mg (75% yield) of **177f** as a bright yellow oil. ^1H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 6.81 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.15 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.02 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.62 (t, *J* = 7.3 Hz, 2H), 2.21 (m, 2H), 1.80 (m, 83H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 189.95, 135.69, 133.64, 127.96, 112.07, 108.40, 57.10, 39.02, 34.56, 22.42, 18.15, 13.39; FTIR (NaCl, thin film) 2954, 2916, 2872, 2220, 2124, 1675, 1374, 1219 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{15}N_3O$ $[M\bullet]^+$ 217.1215, found 217.1219.

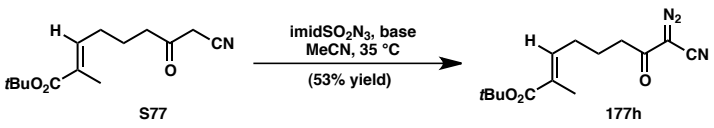
Preparation of a-diazo-b-ketonitrile (177g)



S70 177g

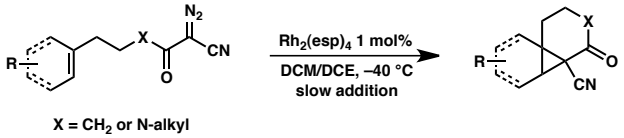
Compound **177g** was synthesized according to general procedure 1. The reaction was run on 0.64 mmol scale for 5 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 500 mg (77% yield) of **177g** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 4.14 (s, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.09 (m, 2H), 1.77 (m, 2H), 1.68 (m, 6H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 190.05, 129.63, 128.79, 108.38, 63.75, 57.04, 39.02, 33.76, 25.94, 22.20, 18.38, 17.64, 15.47, -5.25; FTIR (NaCl, thin film) 2954, 2928, 2856, 2221, 2128, 1679, 1471, 1361, 1251 cm^{-1}; HRMS (MM) calc'd for $C_{17}H_{30}NO_2Si$ $[M+H]^+ - N_2$ 308.2040, found 308.2038.

Preparation of a-diazo-b-ketonitriles (177h)



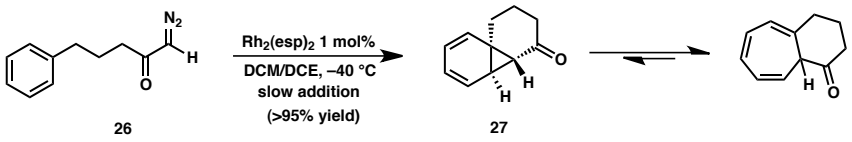
Compound **177h** was synthesized according to general procedure 1. The reaction was run on 0.757 mmol scale for 12 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 111 mg (53% yield) of **177h** as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.59 (tq, *J* = 7.5, 1.5 Hz, 1H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.21 (m, 2H), 1.84 (m, 2H), 1.79 (s, 3H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.62, 167.13, 138.79, 130.46, 108.26, 80.10, 57.25, 38.71, 28.00, 27.59, 23.00, 12.40; FTIR (NaCl, thin film) 2977, 2932, 2222, 2129, 1703, 1678, 1456, 1367, 1289, 1160 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{20}NO_3$ $[M+H]^+ - N_2$ 250.1438, found 250.1443.

General procedure 3 for synthesis norcaradienes 167,173 and cyclopropanes 178



In a glovebox an oven-dried 20 mL vial containing a stirbar was charged with bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] ($Rh_2(esp)_2$, 0.001 mmol, 0.01 equiv) and anhydrous DCM (3 mL). The diazo compound (0.1 mmol, 1 equiv) was dried azeotropically with benzene, and dissolved with DCM (2.0 mL) in a high recovery vial. The catalyst and diazo solution were cooled to –40 °C in appropriately sized well plates by a NesLab chiller. A Free Slate® robotic system (http://www.freeslate.com), equipped with a needle-bearing robotic arm and a backing solvent line containing 1,2-dichloroethane, was utilized to perform a slow addition of the diazo species to the rhodium catalyst. In a typical experiment 5 mL of the diazo/DCM solution was withdrawn by the robotic arm needle, positioned over the stirring catalyst solution, and dispensed at a rate of 70 mL/sec with a 10 mL DCE backing solvent wash. A 30 second delay occurred before initiation of another addition cycle. This loop was repeated until the entirety of the diazo solution was transferred to the catalyst (~3 hours), and the reaction was allowed to warm to rt, sealed and removed from the glovebox. The solvent was removed by rotary evaporation under reduced pressure, and the crude residue was purified by silica gel chromatography or Florisil (for more sensitive norcaradienes) to afford the norcaradiene (or cyclopropane) products. For certain norcaradiene substrates upon purification the ring opened aromatized product was isolated.

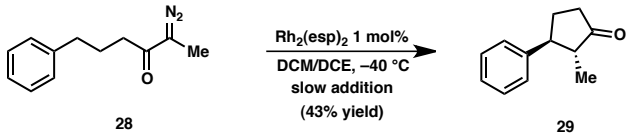
Preparation of cycloheptatriene (27)



26 27

Compound **27** was synthesized according to general procedure 3. The reaction was run with 28 mg (0.15 mmol) of a-diazoketone **26**,[4] and the solvent was removed *in vacuo* to afford 23.5 mg (>95% yield) of **27** as a white solid, of greater than 95% purity by ^{1}H NMR. The spectral data is consistent with that reported in the literature.[4] Product **27** was unstable to either Florisil or silica gel chromatography.

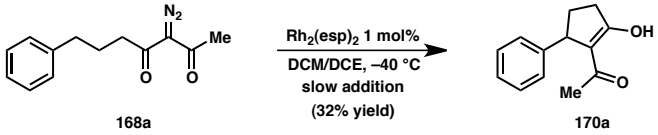
Preparation of *trans*-2-methyl-3-phenylcyclopentanone (29)



28 29

Compound **29** was synthesized according to general procedure 3. The reaction was run with 22 mg (0.11 mmol) of a-diazo methyl ketone **28**,[4] and the crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) followed by preparative HPLC (9:1 Hexanes:EtOAc) to afford 8.2 mg (43% yield) of **29** as a white solid. The spectral data is consistent with that reported in the literature.[4]

Preparation of 1-(2-hydroxy-5-phenylcyclopent-1-en-1-yl)ethanone (170a)

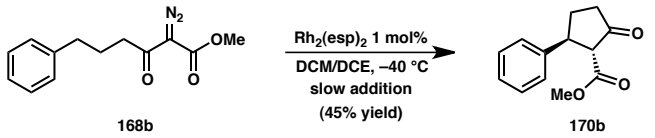


168a 170a

Compound **170a** was synthesized according to general procedure 3. The reaction was run with 27 mg (0.12 mmol) of a-diazo-b-keto ketone **168a**, and the crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) followed by preparative HPLC (85:15 Hexanes:EtOAc, SiO_2 column, 5 mL/min) to afford 7.6 mg (32% yield) of **170a** as a colorless oil. The *trans* stereochemical relationship in the ketone tautomer product was assigned based coupling constant analysis and comparison to related systems.[**] ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as a 3:1 mixture of enol : keto tautomers, enol tautomer designated by *, keto tautomer denoted by §) δ 7.31 (m, 2H*, 2H§), 7.20 (m, 3H*, 3H§), 4.07 (dd, *J* = 8.3, 4.8 Hz, 1H*), 3.93 (td, *J* = 11.2, 6.4 Hz, 1H§), 3.55 (d, *J* = 11.2 Hz, 1H§), 2.59 (m, 1H*, 1H§), 2.44 (m, 2H*, 2H§), 2.30 (s, 3H§), 2.00 (m, 1H§), 1.83 (m, 1H*), 1.69 (s, 3H*); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 3:1 mixture of enol : keto tautomers, enol tautomer designated by *, keto tautomer denoted by §) δ 211.26§, 203.13*, 202.06§, 180.91*, 145.47*, 141.92§, 128.76§, 128.73*, 127.01§, 127.00*, 126.98§, 126.50*, 113.34*, 69.89§, 44.77*, 43.82§, 39.35§, 35.12*, 31.38*, 31.30§, 28.40§, 21.52*; FTIR (NaCl, thin film) 3026, 2963, 1742, 1711, 1651, 1614, 1493, 1385, 1235, 1122 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{13}O_2$ $[M+H]^+$ 201.0920, found 201.0912.

[**] Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M.; Twohig, M. F.; *J. Chem. Soc., Perkin Trans. 1* **1990**, 1047.

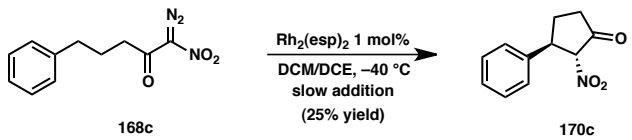
Preparation of *trans*-methyl 2-oxo-5-phenylcyclopentanecarboxylate (170b)



168b 170b

Compound **170b** was synthesized according to general procedure 3. The reaction was run with 25 mg (0.10 mmol) of a-diazo-b-keto ester **168b** , and the crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) followed by preparative HPLC (8:2 Hexanes:EtOAc) to afford 10 mg (45% yield) of **170b** as a white solid. The *trans* stereochemical relationship in the product was assigned based coupling constant analysis and compared to related systems.[4] ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as a >10:1 mixture of keto : enol tautomers, only major keto peaks are reported) δ 7.35 (m, 2H), 7.27 (m, 3H), 3.82 (td, *J* = 12.0, 5.9 Hz, 1H), 3.72 (s, 3H), 3.37 (dd, *J* = 12.0, 1.0 Hz, 1H), 2.60 (m, 1H), 2.47 (m, 2H), 2.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a >10:1 mixture of ketone : enol tautomers, only major keto peaks are reported) δ 210.56, 169.10, 140.90, 128.84, 127.25, 126.80, 62.27, 52.57, 46.10, 38.72, 28.98; FTIR (NaCl, thin film) 3029, 2952, 1757, 1726, 1496, 1336, 1277, 1111 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}O_3$ $[M+H]^+$ 217.0870, found 217.0874.

Preparation of *trans*-2-nitro-3-phenylcyclopentanone (170c)

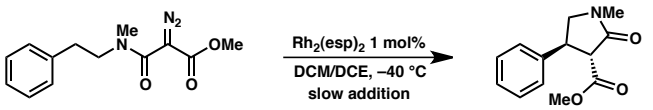


168c 170c

Compound **170c** was synthesized according to general procedure 3. The reaction was run with 19 mg (0.082 mmol) of a-diazo-b-keto nitro compound **168c** , and the crude

material was purified by silica gel chromatography (7:3 EtOAc:hexanes) followed by preparative HPLC (1:1 Hexanes:EtOAc) to afford 4.2 mg (25% yield) of **170c** as a colorless oil. The *trans* stereochemical relationship in the product was assigned based coupling constant analysis and compared to related systems.[4] ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as a >20:1 mixture of keto : enol tautomers, only major keto peaks are reported) δ 7.38 (m, 2H), 7.33 (m, 1H), 7.28 (m, 2H), 5.24 (d, *J* = 12.0 Hz, 1H), 4.13 (td, *J* = 12.2, 6.8 Hz, 1H), 2.65 (m, 3H), 2.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a >20:1 mixture of ketone : enol tautomers, only major keto peaks are reported) δ 202.34, 137.65, 129.23, 128.22, 126.64, 95.49, 47.13, 36.54, 25.96; FTIR (NaCl, thin film) 3031, 2952, 2916, 1768, 1550, 1496, 1370, 1115 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found 206.0823.

Preparation of *trans*-methyl 1-methyl-2-oxo-4-phenylpyrrolidine-3-carboxylate (170d)

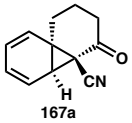


168d 170d

Compound **170d** was synthesized according to general procedure 3. The reaction was run with 32.0 mg (0.122 mmol) of a-diazo-b-amido ester **168d**, and the crude material was purified by silica gel chromatography (7:3 EtOAc:hexanes) followed by recrystallization from hexanes/EtOAc to afford 14.3 mg (50% yield) of **170d** as a white solid. The *trans* stereochemical relationship in the product was assigned based coupling

constant analysis and compared to related systems.[††] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 2H), 7.29 (m, 1H), 7.23 (m, 2H), 4.00 (q, *J* = 8.4 Hz, 1H), 3.80 (dd, *J* = 9.8, 8.5 Hz, 1H), 3.78 (s, 3H), 3.60 (d, *J* = 8.5 Hz, 1H), 3.42 (dd, *J* = 9.8, 7.6 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 169.95, 168.72, 140.17, 128.98, 127.50, 126.86, 55.79, 54.73, 52.74, 41.37, 29.95; FTIR (NaCl, thin film) 3027, 2952, 2883, 1740, 1696, 1496, 1432, 1260, 1166 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1125, found 234.1124.

Norcaradiene (167a)

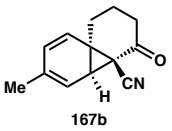


167a

The reaction was run with 23.0 mg (0.108 mmol) of a-diazo-b-keto nitrile **166a**, and the crude material was purified by chromatography using Florisil as the stationary phase (6:4 Hexanes:EtOAc) to afford 14.0 mg (70% yield) of **167a** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.45 (m, 1H), 6.39 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.22 (ddq, *J* = 8.9, 6.0, 0.9 Hz, 1H), 6.07 (dd, *J* = 9.2, 1.0 Hz, 1H), 3.54 (d, *J* = 6.1 Hz, 1H), 2.54 (dddd, *J* = 18.7, 6.6, 4.4, 0.7 Hz, 1H), 2.45 (ddd, *J* = 18.7, 10.1, 7.2 Hz, 1H), 2.33 (ddd, *J* = 14.3, 11.4, 4.9 Hz, 1H), 2.19 (dt, *J* = 14.3, 4.8 Hz, 1H), 1.90 (m, 1H), 1.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.40, 127.50, 126.52, 126.27, 122.18, 112.63, 43.74 (broad), 35.49, 27.83, 17.63; FTIR (NaCl, thin film) 3047, 2949, 2858, 2239, 1689, 1427, 1326, 1276, 1174 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{10}NO$ $[M-H]^-$ 184.0768, found 184.0776.

[††] Choi, M. K-W.; Yu, Y-W.; Che, C-M.; *Org. Lett.* **2005**, *7*, 1081.

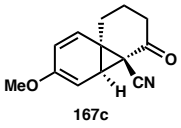
4-Methyl norcaradiene (167b)



167b

The reaction was run with 18.0 mg (0.0800 mmol) of a-diazo-b-keto nitrile **166b**, and the crude material was purified by chromatography using Florisil as the stationary phase (6:4 Hexanes:EtOAc) to afford 12.5 mg (80% yield) of **167b** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.24 (dd, *J* = 9.5, 1.3 Hz, 1H), 6.03 (d, *J* = 9.4 Hz, 1H), 5.90 (d, *J* = 5.9 Hz, 1H), 3.41 (d, *J* = 5.9 Hz, 0H), 2.50 (m, 1H), 2.40 (ddd, *J* = 18.7, 10.3, 7.2 Hz, 1H), 2.29 (ddd, *J* = 14.1, 11.6, 4.9 Hz, 1H), 2.15 (dt, *J* = 14.2, 4.6 Hz, 1H), 1.97 (d, *J* = 1.5 Hz, 3H), 1.87 (m, 1H), 1.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.38, 136.39, 129.92, 126.78, 117.04, 112.89, 40.87 (broad), 35.41, 27.47, 21.44, 17.53; FTIR (NaCl, thin film) 3034, 2917, 2859, 2239, 1787, 1450, 1326, 1289, 1166 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{12}NO$ $[M-H]^-$ 198.0924, found 198.0934.

4-Methoxy norcaradiene (167c)

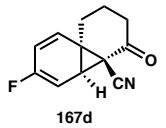


167c

The reaction was run with 31.0 mg (0.127 mmol) of a-diazo-b-keto nitrile **166c**, and the crude material was purified by chromatography using Florisil as the stationary phase (1:1 Hexanes:EtOAc) to afford 24.7 mg (90% yield) of **167c** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.19 (dd, *J* = 9.9, 2.1 Hz, 1H), 6.08 (d, *J* = 9.8, 1H), 5.12 (d, *J* = 6.4 Hz, 1H), 3.64 (s, 3H), 3.49 (d, *J* = 5.6 Hz, 1H), 2.49 (ddd, *J* = 19.1, 6.5, 4.1 Hz, 1H), 2.38 (ddd, *J* = 19.1, 10.5, 7.2 Hz, 1H), 2.26 (ddd, *J* = 14.2, 11.7, 4.9 Hz, 1H), 2.16 (dt, *J* = 14.2, 4.5 Hz, 1H), 1.88 (m, 1H), 1.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.08, 157.12, 129.05, 125.64, 113.06, 90.34, 55.08, 45.00 (broad), 40.39 (broad), 35.40, 27.27, 17.54; FTIR (NaCl, thin film) 3011, 2945, 2853,

2238, 1683, 1650, 1584, 1447, 1422, 1242, 1177 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1019, found 216.1015.

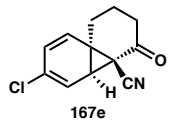
4-Fluoro norcaradiene (167d)



167d

The reaction was run with 17.0 mg (0.0736 mmol) of a-diazo-b-keto nitrile **166d**, and the crude material was purified by silica gel chromatography (1:1 Hexanes:EtOAc) to afford 10.0 mg (67% yield) of **167d** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.34 (td, J = 9.5, 2.1 Hz, 1H), 6.19 (dd, J = 9.7, 5.2 Hz, 1H), 5.83 (dddd, J = 9.0, 7.0, 2.0 Hz, 1H), 3.76 (m, 1H), 2.52 (m, 2H), 2.36 (ddd, J = 15.1, 10.8, 4.7 Hz, 1H), 2.19 (dt, J = 14.5, 5.0 Hz, 1H), 1.96 (m, 1H), 1.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.46, 160.05 (d, $J_{C\text{-}F}$ = 252.4 Hz), 129.52 (d, $J_{C\text{-}F}$ = 9.9 Hz), 120.74 (d, $J_{C\text{-}F}$ = 32.9 Hz), 102.79 (d, $J_{C\text{-}F}$ = 24.7 Hz), 49.91 (broad), 35.46, 27.72, 18.04; FTIR (NaCl, thin film) 3076, 2952, 2863, 2240, 1690, 1660, 1427, 1327, 1207, 1170 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_9FNO$ $[M-H]^-$ 202.0674, found 202.0666.

4-Chloro norcaradiene (167e)

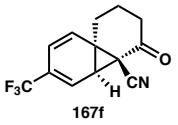


167e

The reaction was run with 21.5 mg (0.0870 mmol) of a-diazo-b-keto nitrile **166e**, and the crude material was purified by silica gel chromatography (1:1 Hexanes:EtOAc) to afford 12.0 mg (63% yield) of **167e** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.39 (dd, J = 9.5, 1.7 Hz, 1H), 6.25 (m, 1H), 6.13 (d, J = 9.5 Hz, 1H), 3.59 (d, J = 6.6 Hz, 1H), 2.55 (ddd, J = 18.7, 6.7, 4.5 Hz, 1H), 2.47 (ddd, J = 18.7, 9.9, 7.2 Hz, 1H), 2.33 (ddd, J = 14.4, 11.2, 4.8 Hz, 1H), 2.19 (dt, J = 14.4, 4.8 Hz, 1H), 1.94 (m, 1H), 1.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.02, 133.06, 128.84,

128.52, 119.08, 112.33, 46.17 (broad), 35.46, 35.46, 27.47, 17.74; FTIR (NaCl, thin film) 3066, 2951, 2858, 2240, 1691, 1411, 1325, 1179 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_9ClNO$ $[M-H]^-$ 218.0378, found 218.0377.

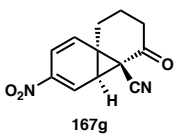
4-Trifluoromethyl norcaradiene (167f)



167f

The reaction was run with 28.0 mg (0.100 mmol) of a-diazo-b-keto nitrile **166f**, and the crude material was purified by silica gel chromatography (1:1 Hexanes:EtOAc) to afford 9.0 mg (36% yield) of **167f** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.69 (m, 1H), 6.52 (dd, *J* = 9.6, 1.4 Hz, 1H), 6.27 (dd, *J* = 9.6, 1.1 Hz, 1H), 3.52 (d, *J* = 6.3 Hz, 1H), 2.58 (ddd, *J* = 18.8, 6.5, 4.4 Hz, 1H), 2.49 (ddd, *J* = 18.8, 10.2, 7.1 Hz, 1H), 2.38 (ddd, *J* = 14.4, 11.3, 4.9 Hz, 1H), 2.22 (dt, *J* = 14.4, 4.7 Hz, 1H), 1.95 (m, 1H), 1.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 198.59, 130.38 (q, *J* = 32.3 Hz), 128.70, 122.60 (q, *J* = 5.3 Hz), 122.55 (q, *J* = 272.2 Hz), 121.68 (q, *J* = 2.5 Hz), 111.44, 40.94 (broad), 35.52, 27.41, 25.12, 17.55; FTIR (NaCl, thin film) 3057, 2952, 2928, 2242, 1701, 1374, 1308, 1181 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_9F_3NO$ $[M-H]^-$ 252.0642, found 252.0635.

4-Nitro norcaradiene (167g)

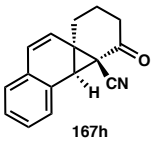


167g

The reaction was run with 22.0 mg (0.0850 mmol) of a-diazo-b-keto nitrile **166g**, and the crude material was purified by silica gel chromatography (1:1 Hexanes:EtOAc) to afford 4.2 mg (20% yield) of **167g** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43 (m, 1H), 7.37 (dd, *J* = 9.4, 1.8 Hz, 1H), 6.40 (d, *J* = 9.5 Hz, 1H), 4.06 (d, *J* = 7.5 Hz, 1H), 2.64 (m, 2H), 2.51 (ddd, *J* = 14.8, 10.3, 4.6 Hz,

1H), 2.27 (ddd, *J* = 14.7, 6.2, 4.4 Hz, 1H), 2.05 (m, 1H), 1.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.74, 148.22, 128.21, 123.68, 122.26, 111.66, 69.01 (broad), 56.12 (broad), 35.61, 30.68, 28.18, 18.31; FTIR (NaCl, thin film) 3083, 2925, 2853, 2242, 1699, 1521, 1344, 1181 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_9N_2O_3$ $[M-H]^-$ 229.0619, found 229.0623.

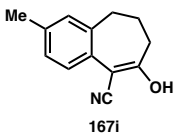
5-Oxo-4b,4c,5,6,7,8-hexahydrobenzo[2,3]cyclopropa[1,2-*a*]naphthalene-4c-carbonitrile (167h)



167h

The reaction was run with 25.0 mg (0.0950 mmol) of a-diazo-b-keto nitrile **166h**, and the crude material was purified by chromatography using Florisil as the stationary phase (6:4 Hexanes:EtOAc) to afford 6.9 mg (31% yield) of **167h** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 (m, 1H), 7.33 (m, 3H), 6.79 (d, *J* = 9.6 Hz, 1H), 6.08 (dd, *J* = 9.6, 1.3 Hz, 1H), 3.82 (s, 1H), 2.62 (ddd, *J* = 18.8, 6.2, 3.5 Hz, 1H), 2.42 (ddd, *J* = 18.7, 11.0, 7.4 Hz, 1H), 2.29 (m, 2H), 1.92 (m, 1H), 1.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.72, 131.76, 129.63, 129.44, 128.93, 128.65, 128.47, 127.12, 124.89, 113.06, 42.18, 38.26, 35.50, 27.84, 27.06, 17.28; FTIR (NaCl, thin film) 3042, 2947, 2888, 2239, 1686, 1455, 1326, 1284, 1172, 1120 cm^{-1}; HRMS (MM) calc'd for $C_{16}H_{13}NO$ $[M-H]^-$ 234.0924, found 234.0922.

8-Hydroxy-3-methyl-6,7-dihydro-5*H*-benzo[7]annulene-9-carbonitrile (167i)

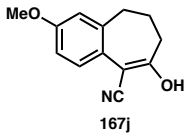


167i

The reaction was run with 38.0 mg (0.167 mmol) of a-diazo-b-keto nitrile **166i**, and the crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to afford 31.1 mg (93% yield) of **167i** as a white solid. ^{1}H NMR

(CD_3CN, 500 MHz, compound exists as a 1.5:1 mixture of enol : keto tautomers, only major enol peaks are reported) δ 8.17 (br s, 1H), 7.22 (m, 1H), 7.09 (s, 1H), 7.05 (m, 1H), 2.63 (t, J = 6.9 Hz, 3H), 2.28 (m, 2H), 2.17 (m, 5H); ^{13}C NMR (CD_3CN, 126 MHz, compound exists as a 1.5:1 mixture of enol : keto tautomers, only major enol peaks are reported) δ 172.39, 140.77, 137.84, 131.89, 131.01, 128.43, 128.20, 118.66, 87.13, 32.56, 32.38, 31.92, 21.08; FTIR (NaCl, thin film, keto and enol stretches reported) 3139, 2937, 2863, 2216, 1629, 1495, 1392, 1243 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{12}NO$ $[M-H]^-$ 198.0924, found 198.0923.

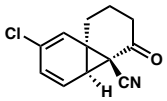
8-Hydroxy-3-methoxy-6,7-dihydro-5*H*-benzo[7]annulene-9-carbonitrile (167j)



167j

The reaction was run with 20.0 mg (0.0823 mmol) of a-diazo-b-keto nitrile **166j**, and the crude material was purified by silica gel chromatography (4:6 Hexanes:EtOAc) to afford 14.4 mg (81% yield) of **167j** as a white solid. ^1H NMR (CD_3CN, 500 MHz, compound exists as a 1.5:1 mixture of enol : keto tautomers, only major enol peaks are reported) δ 7.98 (s, 1H), 7.25 (d, J = 8.3 Hz, 1H), 6.85 (s, 1H), 6.81 (m, 1H), 3.78 (s, 3H), 2.64 (t, J = 6.8 Hz, 2H), 2.28 (m, 2H), 2.17 (m, 2H); ^{13}C NMR (CD_3CN, 126 MHz, compound exists as a 1.5:1 mixture of enol : keto tautomers, only major enol peaks are reported) δ 171.75, 159.51, 142.47, 129.69, 126.46, 118.74, 115.88, 112.69, 86.69, 55.87, 32.76, 32.23, 31.73; FTIR (NaCl, thin film, keto and enol stretches reported) 3206, 2938, 2868, 2210, 1725, 1631, 1608, 1497, 1376, 1259 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{12}NO_2$ $[M–H]^-$ 214.0874, found 214.0883.

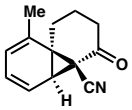
3-Chloro norcaradiene (167k)



167k

The reaction was run with 25.0 mg (0.101 mmol) of a-diazo-b-keto nitrile **166k**, and the crude material was purified by chromatography using Florisil as the stationary phase (1:1 Hexanes:EtOAc) to afford 14.6 mg (66% yield) of **167k** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.47 (dd, *J* = 9.3, 1.5 Hz, 1H), 6.29 (dd, *J* = 9.3, 6.2 Hz, 1H), 6.13 (s, 1H), 3.58 (d, *J* = 6.1 Hz, 1H), 2.50 (m, 2H), 2.33 (ddd, *J* = 14.4, 11.1, 4.8 Hz, 1H), 2.22 (dt, *J* = 14.4, 4.9 Hz, 1H), 1.94 (m, 1H), 1.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.18, 132.13, 129.93, 124.66, 123.05, 112.39, 45.98 (broad), 35.47, 27.73, 17.81; FTIR (NaCl, thin film) 3063, 2945, 2888, 2242, 1684, 1628, 1409, 1321, 1271, 1173 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{10}ClNO$ [M]$^{+}$ 219.0451, found 219.0449.

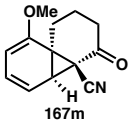
2-Methyl norcaradiene (167l)



167l

The reaction was run with 23.0 mg (0.101 mmol) of a-diazo-b-keto nitrile **166l**, and the crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to afford 16.3 mg (81% yield) of **167l** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.35 (dd, *J* = 9.3, 6.2 Hz, 1H), 6.17 (m, 1H), 6.07 (ddd, *J* = 9.3, 5.7, 0.9 Hz, 1H), 3.48 (d, *J* = 5.7 Hz, 1H), 2.56 (ddd, *J* = 19.3, 6.9, 2.6 Hz, 1H), 2.38 (m, 2H), 2.15 (dt, *J* = 14.2, 3.9 Hz, 1H), 2.06 (s, 3H), 1.88 (m, 1H), 1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.79, 134.35, 127.86, 123.43, 119.26, 112.52, 46.87, 38.58, 35.05, 24.76, 24.72, 20.55, 16.57; FTIR (NaCl, thin film) 3057, 2959, 2897, 2235, 1678, 1445, 1325, 1299, 1191 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{12}NO$ [M-H]$^{-}$ 198.0924, found 198.0928.

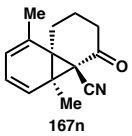
2-Methoxy norcaradiene (167m)



167m

The reaction was run with 19 mg (0.078 mmol) of a-diazo-b-keto nitrile **166m**, and the crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to afford 8.0 mg (47% yield) of **167m** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.39 (ddd, *J* = 9.2, 7.0, 0.8 Hz, 1H), 5.77 (dd, *J* = 9.2, 5.5 Hz, 1H), 5.43 (d, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 3.44 (d, *J* = 5.5 Hz, 1H), 2.56 (m, 1H), 2.50 (dddd, *J* = 19.0, 6.5, 3.4, 0.7 Hz, 1H), 2.37 (ddd, *J* = 19.0, 10.9, 7.4 Hz, 1H), 2.07 (dt, *J* = 14.5, 4.2 Hz, 1H), 1.86 (m, 1H), 1.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.33, 155.44, 128.63, 112.61, 112.53, 96.10, 55.79, 44.44, 39.02, 35.41, 23.98, 22.62, 16.94; FTIR (NaCl, thin film) 2954, 2928, 2888, 2236, 1685, 1560, 1389, 1267, 1234, 1185 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1019, found 216.1020.

2,6-Dimethyl norcaradiene (167n)

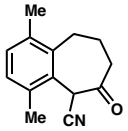


167n

The reaction was run according to a variation of general procedure 7. $Rh_2(pfb)_4$ was used in place of $Rh_2(esp)_2$, and the reaction was run at rt instead of – 40 °C in the glovebox. 100 mg (0.415 mmol) of a-diazo-b-keto nitrile **166n**, and the crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) followed by recrystallization from ethyl acetate/hexanes to afford 21.2 mg (24% yield) of **167n** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.58 (d, *J* = 10.1 Hz, 1H), 6.52 (dd, *J* = 10.2, 6.7 Hz, 1H), 6.10 (d, *J* = 6.7 Hz, 1H), 2.75 (dddd, *J* = 18.6, 8.7, 5.4, 0.8 Hz, 1H), 2.61 (m, 2H), 2.36 (ddd, *J* = 16.1, 8.3, 3.7 Hz, 1H), 2.04 (m, 1H), 2.00 (s, 3H), 1.92 (m, 1H), 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 202.49, 132.01, 128.11, 125.96, 115.73, 39.98, 26.35, 21.20, 20.22, 19.86; FTIR (NaCl, thin film) 3012, 2951, 2873, 2233, 1723, 1692,

1448, 1323, 1269, 1215 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{16}NO$ $[M+H]^+$ 214.1226, found 214.1235.

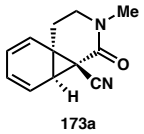
1,4-Dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-5-carbonitrile (167o)



167o

The reaction was run with 31.5 mg (0.130 mmol) of a-diazo-b-keto nitrile **166o**, and the crude material was purified by silica gel chromatography (2% MeOH/DCM) to afford 14.3 mg (50% yield) of **167o** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz, compound exists as a 1:1 mixture of enol : keto tautomers, only major keto peaks are reported) δ 7.13 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 4.75 (s, 1H), 3.11 (ddd, *J* = 15.0, 4.5, 3.3 Hz, 1H), 2.84 (td, *J* = 14.6, 4.7 Hz, 1H), 2.60 (m, 2H), 2.38 (s, 6H), 2.21 (m, 1H), 1.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1:1 mixture of enol : keto tautomers) δ 201.81, 172.70, 137.84, 137.53, 134.57, 134.44, 134.24, 133.15, 131.52, 130.85, 129.78, 129.15, 128.40, 128.17, 116.59, 115.62, 84.13, 46.47, 38.44, 31.08, 29.24, 26.70, 26.33, 25.09, 20.23, 20.21, 20.06, 19.70; FTIR (NaCl, thin film) 3167, 2969, 2864, 2211, 1628, 1588, 1449, 1368, 1331, 1265, 1156 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{14}NO$ $[M–H]^-$ 212.1081, found 212.1073.

Amido norcaradiene (173a)

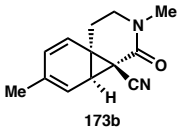


173a

The reaction was run with 25.0 mg (0.109 mmol) of a-diazo-b-amido nitrile **172a**, and the crude material was purified by silica gel chromatography (8:2 EtOAc:hexanes) to afford 15.3 mg (70% yield) of **172a** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.54 (m, 2H), 6.28 (t, *J* = 7.5 Hz, 1H), 6.11 (d, *J* = 8.0 Hz, 1H), 4.06 (d, *J* = 7.1 Hz, 1H), 3.33 (m, 2H), 3.07 (s, 3H), 2.62 (ddd, *J* = 15.2, 10.1, 5.6 Hz, 1H),

2.37 (dt, *J* = 14.4, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.70, 127.91, 127.51, 124.54, 123.59, 113.55, 63.49 (broad), 45.37, 36.05, 27.43, 25.75 (broad); FTIR (NaCl, thin film) 3044, 2932, 2878, 2240, 1651, 1504, 1442, 1402, 1344 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{11}N_2O$ $[M-H]^-$ 199.0877, found 199.0881.

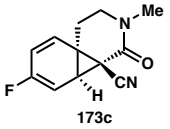
4-Methyl amido norcaradiene (173b)



173b

The reaction was run with 22 mg (0.091 mmol) of a-diazo-b-amido nitrile **172b**, and the crude material was purified by silica gel chromatography (8:2 EtOAc:hexanes) to afford 8.0 mg (42% yield) of **173b** as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.28 (d, *J* = 9.0 Hz, 1H), 6.01 (d, *J* = 9.0 Hz, 1H), 5.94 (d, *J* = 6.5 Hz, 1H), 3.61 (d, *J* = 6.5 Hz, 1H), 3.26 (m, 2H), 3.03 (s, 3H), 2.54 (ddd, *J* = 14.2, 10.5, 6.8 Hz, 1H), 2.24 (dt, *J* = 14.2, 3.8 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.94, 136.38, 129.61, 124.81, 119.11, 113.60, 51.55 (broad), 44.84, 35.93, 26.47, 21.86; FTIR (NaCl, thin film) 3030, 2937, 2883, 2240, 1646, 1501, 1451, 1344 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}N_2O$ $[M+H]^+$ 215.1179, found 215.1174.

4-Fluoro amido norcaradiene (173c)

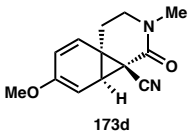


173c

The reaction was run with 33.0 mg (0.134 mmol) of a-diazo-b-amido nitrile **172c**, and the crude material was purified by silica gel chromatography (8:2 EtOAc:hexanes) to afford 17.8 mg (61% yield) of **173c** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.41 (ddd, *J* = 12.6, 8.6, 2.1 Hz, 1H), 6.20 (dd, *J* = 8.5, 5.5 Hz, 1H), 6.10 (td, *J* = 8.3, 2.1 Hz, 1H), 4.65 (m, 1H), 3.47 (ddd, *J* = 13.0, 6.4, 4.5 Hz, 1H), 3.32 (ddd, *J* = 13.0, 8.5, 4.4 Hz, 1H), 3.09 (s, 3H), 2.67 (m, 1H), 2.44 (m, 1H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 163.85, 161.31, 159.31, 124.99 (d, *J* = 10.1 Hz), 116.41 (d, *J* = 30.0 Hz), 113.96, 112.01 (broad), 83.34 (broad), 46.31, 36.30, 33.02 (broad), 28.59; FTIR (NaCl, thin film) 3071, 2947, 2888, 2241, 1651, 1501, 1454, 1404, 1342, 1151 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{11}FN_2O$ $[M+H]^+$ 219.0928, found 219.0918.

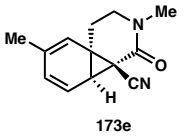
4-Methoxy amido norcaradiene (173d)



173d

The reaction was run with 25.5 mg (0.100 mmol) of a-diazo-b-amido nitrile **172d**, and the crude material was purified by silica gel chromatography (8:2 EtOAc:hexanes) to afford 19.1 mg (83% yield) of **173d** as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.15 (dd, *J* = 9.5, 2.1 Hz, 1H), 6.06 (d, *J* = 9.5 Hz, 1H), 5.28 (br d, *J* = 7.3 Hz, 1H), 3.68 (br s, 1H), 3.65 (s, 3H), 3.28 (m, 2H), 3.03 (s, 3H), 2.51 (m, 1H), 2.24 (dt, *J* = 14.1, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.76, 156.75, 126.67, 122.44 (broad), 113.70, 95.14 (broad), 54.97, 44.73, 35.80, 26.08, 22.13 (broad); FTIR (NaCl, thin film) 3050, 2936, 2240, 1650, 1501, 1446, 1402, 1240 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}N_2O_2$ $[M+H]^+$ 231.1128, found 231.1121.

3-Methyl amido norcaradiene (173e)

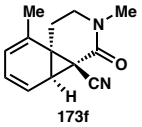


173e

The reaction was run with 32.0 mg (0.132 mmol) of a-diazo-b-amido nitrile **172e**, and the crude material was purified by silica gel chromatography (8:2 EtOAc:hexanes) to afford 16.0 mg (57% yield) of **173e** as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.30 (d, *J* = 9.0 Hz, 1H), 6.17 (dd, *J* = 8.5, 6.6 Hz, 1H), 5.76 (s, 1H), 3.55 (d, *J* = 6.3 Hz, 1H), 3.25 (m, 2H), 3.02 (s, 3H),

2.51 (ddd, *J* = 14.2, 11.1, 6.5 Hz, 1H), 2.23 (dt, *J* = 14.2, 3.2 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.00, 135.66, 130.15, 122.65, 121.25, 113.58, 57.00 (broad), 49.30 (broad), 44.78, 35.91, 26.57, 21.89; FTIR (NaCl, thin film) 3030, 2937, 2883, 2240, 1646, 1501, 1443, 1342, 1240 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}N_2O$ [M+H]$^+$ 215.1179, found 215.1175.

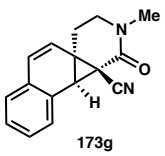
2-Methyl amido norcaradiene (173f)



173f

The reaction was run with 20 mg (0.083 mmol) of a-diazo-b-amido nitrile **172f**, and the crude material was purified by silica gel chromatography (7:3 EtOAc:hexanes) followed by preparative HPLC (85:15 EtOAc:Hexanes, SiO_2 column, 5 mL/min) to afford 3.6 mg (20% yield) of **173f** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.30 (dd, *J* = 9.2, 6.3 Hz, 1H), 6.15 (m, 1H), 6.04 (ddd, *J* = 9.2, 5.8, 0.8 Hz, 1H), 3.29 (d, *J* = 5.8 Hz, 1H), 3.23 (m, 1H), 3.18 (ddd, *J* = 13.5, 6.4, 2.1 Hz, 1H), 3.01 (s, 3H), 2.53 (td, *J* = 13.2, 6.3 Hz, 1H), 2.17 (ddd, *J* = 13.9, 4.1, 2.0 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (CD_2Cl_2, 126 MHz) δ 165.38, 132.52, 127.24, 123.67, 119.26, 112.81, 45.23, 43.97, 38.33, 35.81, 23.72, 20.56, 16.55; FTIR (NaCl, thin film) 3049, 2932, 2884, 2241, 1648, 1502, 1447, 1403, 1344, 1271 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}N_2O$ [M+H]$^+$ 215.1179, found 215.1169.

Benzo amido norcaradiene (173g)

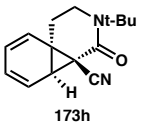


173g

The reaction was run with 21.5 mg (0.77 mmol) of a-diazo-b-amido nitrile **172g**, and the crude material was purified by silica gel chromatography

(8:2 EtOAc:hexanes) to afford 9.3 mg (48% yield) of **173g** as a yellow solid. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.47 (m, 1H), 7.35 (m, 3H), 6.79 (d, *J* = 9.7 Hz, 1H), 6.08 (dd, *J* = 9.6, 1.3 Hz, 1H), 3.68 (s, 1H), 3.36 (td, *J* = 13.3, 4.5 Hz, 1H), 3.22 (ddd, *J* = 13.7, 6.2, 1.7 Hz, 1H), 3.02 (s, 3H), 2.48 (td, *J* = 13.7, 6.2 Hz, 1H), 2.25 (ddd, *J* = 13.9, 4.4, 1.7 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 126 MHz) δ 164.60, 132.25, 130.23, 129.73, 129.20, 129.12, 128.72, 128.04, 124.53, 114.30, 44.64, 39.55, 36.28, 36.12, 25.82, 19.89; FTIR (NaCl, thin film) 3016, 2918, 2888, 2238, 1644, 1504, 1443, 1342, 1269 cm^{-1}; HRMS (MM) calc'd for $C_{16}H_{15}N_2O$ $[M+H]^+$ 251.1179, found 251.1169.

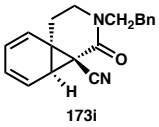
Amido norcaradiene (173h)



173h

The reaction was run with 26.5 mg (0.100 mmol) of a-diazo-b-amido nitrile **172h**, and the crude material was purified by silica gel chromatography (6:4 EtOAc:hexanes) to afford 19.4 mg (80% yield) of **173h** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.61 (m, 2H), 6.33 (t, *J* = 7.5 Hz, 1H), 6.15 (m, 1H), 4.58 (d, *J* = 7.9 Hz, 1H), 3.55 (ddd, *J* = 13.0, 6.0, 4.4 Hz, 1H), 3.27 (ddd, *J* = 13.2, 9.4, 4.0 Hz, 1H), 2.61 (ddd, *J* = 13.8, 9.2, 4.3 Hz, 1H), 2.41 (m, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.39, 128.71, 128.39, 125.08, 123.69, 114.31, 82.20 (broad), 58.76, 41.29, 35.16 (broad), 30.52, 28.02; FTIR (NaCl, thin film) 2977, 2918, 2885, 2243, 1633, 1447, 1358, 1225 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{19}N_2O$ $[M+H]^+$ 243.1492, found 243.1480.

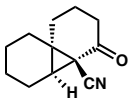
Amido norcaradiene (173i)



173i

The reaction was run with 27.0 mg (0.0850 mmol) of a-diazo-b-amido nitrile **172i**, and the crude material was purified by silica gel chromatography (6:4 EtOAc:hexanes) to afford 24.2 mg (93% yield) of **173i** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (m, 2H), 7.24 (m, 3H), 6.51 (m, 2H), 6.23 (t, *J* = 7.3 Hz, 1H), 6.06 (d, *J* = 8.0 Hz, 1H), 3.80 (m, 2H), 3.61 (ddd, *J* = 13.5, 7.6, 6.1 Hz, 1H), 3.07 (ddd, *J* = 13.1, 5.4, 4.2 Hz, 1H), 2.96 (m, 3H), 2.42 (m, 1H), 2.19 (td, *J* = 14.3, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.64, 128.86, 128.63, 127.95, 127.56, 126.66, 124.49, 123.67, 113.51, 64.02 (broad), 50.72, 44.70, 33.66, 27.65, 26.13 (broad); FTIR (NaCl, thin film) 3025, 2929, 2859, 2241, 1646, 1495, 1454 cm^{-1}; HRMS (MM) calc'd for $C_{19}H_{19}N_2O$ $[M+H]^+$ 291.1492, found 291.1482.

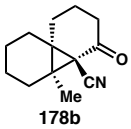
4-Oxodecahydrocyclopropa[1,2:1,3]dibenzene-4a-carbonitrile (178a)



178a

The reaction was run with 20.2 mg (0.0931 mmol) of a-diazo-b-keto nitrile **177a**, and the crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to afford 14.4 mg (82% yield) of **178a** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.42 (dddd, *J* = 19.1, 6.2, 2.4, 0.9 Hz, 1H), 2.33 (dd, *J* = 8.1, 1.9 Hz, 1H), 2.08 (m, 4H), 1.90 (m, 3H), 1.76 (m, 1H), 1.63 (m, 3H), 1.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.77, 116.51, 36.68, 35.30, 34.89, 29.49, 28.33, 28.29, 20.37, 20.34, 20.32, 16.63; FTIR (NaCl, thin film) 2942, 2916, 2848, 2228, 1682, 1557, 1455 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{14}NO$ $[M-H]^-$ 188.1081, found 188.1080.

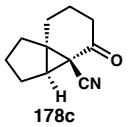
4b-Methyl-4-oxodecahydrocyclopropa[1,2:1,3]dibenzene-4a-carbonitrile (178b)



178b

The reaction was run with 29.0 mg (0.125 mmol) of a-diazo-b-keto nitrile **177b**, and the crude material was purified by silica gel chromatography (75:25 Hexanes:EtOAc) to afford 19.4 mg (76% yield) of **178b** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.45 (m, 1H), 2.18 (ddd, *J* = 14.8, 6.8, 5.1 Hz, 1H), 2.06 (m, 2H), 1.86 (m, 6H), 1.62 (m, 2H), 1.37 (m, 2H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.36, 118.06, 38.71, 38.67, 38.62, 35.07, 31.41, 31.33, 29.08, 22.63, 20.86, 20.55, 20.43; FTIR (NaCl, thin film) 2942, 2878, 2227, 1696, 1448, 1322, 1266 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{16}NO$ $[M-H]^-$ 202.1237, found 202.1245.

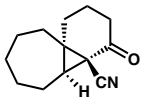
4-Oxooctahydro-1*H*-cyclopenta[1,3]cyclopropa[1,2]benzene-3b-carbonitrile (178c)



178c

The reaction was run with 50 mg (0.25 mmol) of a-diazo-b-keto nitrile **177c**, and the crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to afford 40 mg (93% yield) of **178c** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.40 (m, 2H), 2.23 (m, 3H), 2.06 (m, 4H), 1.87 (m, 3H), 1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 198.67, 116.14, 47.77, 38.34, 35.99, 35.76, 33.18, 27.29, 25.16, 22.34, 19.40; FTIR (NaCl, thin film) 2936, 2866, 2233, 1698, 1466, 1326, 1303, 1179, 1080 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{14}NO$ $[M+H]^+$ 176.1070, found 176.1076.

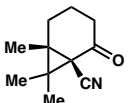
4-Oxodecahydro-1*H*-benzo[1,3]cyclopropa[1,2]annulene-4a-carbonitrile (178d)



178d

The reaction was run with 61 mg (0.26 mmol) of a-diazo-b-keto nitrile **177d**, and the crude material was purified by silica gel chromatography (75:25 Hexanes:EtOAc) to afford 50 mg (92% yield) of **178d** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.40 (m, 1H), 2.22 (m, 4H), 2.05 (ddd, *J* = 14.7, 6.7, 1.3 Hz, 1H), 1.78 (m, 7H), 1.48 (m, 2H), 1.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.30, 116.15, 40.46, 40.22, 35.38, 33.88, 33.62, 31.45, 27.58, 27.39, 27.34, 25.59, 17.22; FTIR (NaCl, thin film) 2925, 2852, 2234, 1694, 1465, 1325, 1291, 1138 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383, found 204.1391.

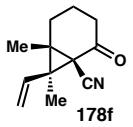
6,7,7-Trimethyl-2-oxobicyclo[4.1.0]heptane-1-carbonitrile (178e)



178e

The reaction was run with 35.0 mg (0.171 mmol) of a-diazo-b-keto nitrile **177e**, and the crude material was purified by silica gel chromatography (1:1 Hexanes:EtOAc) to afford 27.2 mg (90% yield) of **178e** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.51 (m, 1H), 2.03 (m, 1H), 1.86 (m, 4H), 1.46 (s, 3H), 1.41 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.26, 117.34, 39.55, 39.43, 38.79, 35.70, 27.05, 22.81, 21.18, 20.30, 19.46; FTIR (NaCl, thin film) 3005, 2953, 2878, 2848, 2231, 1698, 1455, 1323, 1279, 1093 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{16}NO$ $[M+H]^+$ 178.1226, found 178.1218.

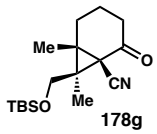
Vinylcyclopropyl ketone (178f)



178f

The reaction was run with 31.0 mg (0.143 mmol) of a-diazo-b-keto nitrile **177f**, and the crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to afford 21.4 mg (79% yield) of **178f** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.97 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.41 (dd, *J* = 10.9, 0.7 Hz, 1H), 5.37 (dd, *J* = 17.2, 0.7 Hz, 1H), 2.55 (m, 1H), 2.09 (m, 1H), 1.89 (m, 4H), 1.48 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.21, 136.16, 119.05, 116.81, 42.82, 39.31, 38.81, 36.59, 27.16, 22.55, 21.12, 16.01; FTIR (NaCl, thin film) 3091, 2992, 2952, 2878, 2232, 1703, 1455, 1323, 1274, 1162 cm^{-1}; HRMS (FAB+) calc'd for $C_{12}H_{16}NO$ $[M+H]^+$ 190.1232, found 190.1252.

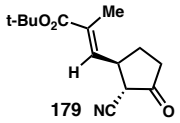
Cyclopropyl ketone (178g)



178g

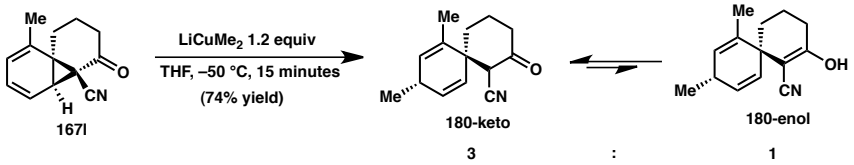
The reaction was run with 35.0 mg (0.104 mmol) of a-diazo-b-keto nitrile **177g**, and the crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to afford 29.7 mg (93% yield) of **178g** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.79 (d, *J* = 10.7 Hz, 1H), 3.72 (d, *J* = 10.7 Hz, 1H), 2.49 (m, 1H), 2.04 (m, 1H), 1.85 (m, 4H), 1.49 (s, 3H), 1.29 (m, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.59, 116.70, 65.67, 42.54, 38.87, 38.71, 34.04, 27.42, 25.73, 22.88, 19.84, 18.17, 14.93, -5.51, -5.55; FTIR (NaCl, thin film) 2953, 2929, 2884, 2856, 2232, 1701, 1472, 1257, 1095 cm^{-1}; HRMS (MM) calc'd for $C_{17}H_{29}NO_2Si$ $[M-H]^-$ 306.1895, found 306.1907.

Cyclopentanone (179)



The reaction was run with 44 mg (0.16 mmol) of a-diazo-b-keto nitrile **177h**, and the crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to afford 16 mg (40% yield) of **179** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, exists as an 85:15 equilibrating mixture of *trans* : *cis* diastereomers, only major *trans* peaks are reported) δ 6.48 (dq, *J* = 9.6, 1.5 Hz, 1H), 3.39 (tdd, *J* = 12.0, 9.6, 6.3 Hz, 1H), 3.07 (d, *J* = 12.0 Hz, 1H), 2.58 (m, 1H), 2.43 (ddd, *J* = 19.3, 11.9, 8.8 Hz, 1H), 2.28 (dddd, *J* = 13.3, 8.8, 6.2, 1.4 Hz, 1H), 1.94 (d, *J* = 1.5 Hz, 3H), 1.80 (dtd, *J* = 13.3, 12.0, 8.7 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 204.74, 166.31, 136.76, 133.69, 115.54, 81.06, 45.70, 41.57, 36.63, 28.01, 27.54, 13.10; FTIR (NaCl, thin film) 3275, 2978, 2933, 2247, 1762, 1706, 1368, 1293, 1253, 1153 cm^{-1}; HRMS (FAB+) calc'd for $C_{14}H_{20}NO_3$ $[M+H]^+$ 250.1443, found 250.1439.

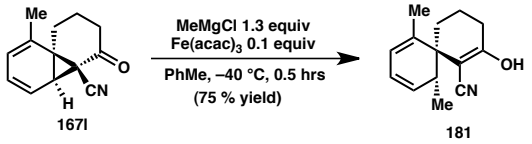
Preparation of 7,9-dimethyl-2-oxospiro[5.5]undeca-7,10-diene-1-carbonitrile (180)



To an oven-dried 25 mL flask was added cuprous iodide (74 mg, 0.39 mmol). The flask was sealed, flushed with nitrogen, and charged with THF (6 mL). The CuI/THF slurry was cooled to – 10 °C and methyllithium (1.2 M Et_2O, 550 mL, 0.66 mmol) was added fast dropwise to the rapidly stirred mixture. Within 30 seconds the CuI dissolved, affording a pale yellow solution. In a separate flask norcaradiene **167l** (55 mg, 0.28 mmol) was dissolved in THF (5 mL) and cooled to – 78 °C. The Me_2CuLi/THF solution

was cannula transferred dropwise to the norcaradiene at – 78 °C. The initially bright yellow reaction transformed into a murky orange mixture upon the completion of the cuprate addition. After stirring for an additional 15 minutes, TLC analysis indicated consumption of the starting material and the reaction was quenched with excess aqueous NH_4Cl. The reaction was warmed to 22 °C and 2 drops of aqueous NH_4OH were added. The mixture was extracted twice with ethyl acetate, and the combined organics washed with brine and dried over Na_2SO_4. The solvent was removed by rotary evaporation under reduced pressure, and the crude residue was purified by flash chromatography (0→15→40% EtOAc/hexanes), yielding diene **180** (44 mg, 74% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz, compound exists as a 3:1 mixture of ketone : enol tautomers, keto tautomer designated by *, enol tautomer denoted by §) δ 5.99 (br s, 1H§), 5.94 (m, 1H*), 5.70 (m, 1H§), 5.66 (m, 1H*), 5.60 (m, 2H§), 5.49 (dd, J = 10.2, 1.9 Hz, 1H*), 3.82 (s, 1H*), 2.89 (m, 1H*), 2.82 (m, 1H§), 2.60 (m, 1H*), 2.37 (m, 1H*), 2.26 (m, 3H§), 2.20 (m, 1H*), 2.04 (m, 2H*), 1.84 (m, 3H*), 1.82 (m, 2H§), 1.70 (s, 3H§), 1.67 (m, 1H*), 1.52 (m, 1H§), 1.05 (d, J = 7.4 Hz, 3H*), 1.03 (d, J = 7.3 Hz, 1H§); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 3:1 mixture of ketone : enol tautomers, keto tautomer designated by *, enol tautomer denoted by §) δ 200.12*, 166.83§, 135.22*, 133.00§, 131.66*, 130.92*, 130.26§, 130.05§, 129.34§, 122.75*, 117.08§, 114.67*, 90.87§, 52.43*, 47.63*, 40.70§, 40.19*, 35.09*, 33.55§, 31.36*, 31.17§, 27.66§, 22.02§, 21.50*, 21.17*, 19.12§, 18.18*, 17.85§; FTIR (NaCl, thin film) 3330, 3022, 2958, 2925, 2871, 2248, 2203, 1725, 1448, 1340, 1203, 1171 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{16}NO$ $[M-H]^-$ 214.1237, found 214.1228.

Preparation of 2-hydroxy-7,11-dimethylspiro[5.5]undeca-1,7,9-triene-1-carbonitrile (181)



167l 181

Procedure adapted from the work of Furstner et al.[‡‡] To an oven-dried 25 mL flask was norcaradiene **167l** (44 mg, 0.24 mmol) and $Fe(acac)_3$ (8.3 mg, 0.024 mmol). The flask was sealed, flushed with nitrogen, and charged with toluene (6 mL). Dissolution of the highly crystalline norcaradiene **167l** was achieved by vigorous stirring of the mixture for 10 minutes at 22 °C. The clear red solution was cooled to – 50 °C, and methylmagnesium chloride (3.0M THF, 102 mL, 0.31 mmol) was added dropwise. The brown solution was stirred for 0.5 hours at that temperature, after which TLC analysis indicated consumption of the starting material. The reaction was quenched with 2 equivalents of acetic acid in THF and warmed to 22 °C. The mixture was extracted twice with ethyl acetate, and the combined organics washed with water, brine and dried over Na_2SO_4. The solvent was removed by rotary evaporation under reduced pressure, and the crude residue was purified by flash chromatography (0→20% EtOAc/hexanes), yielding diene **181** (36 mg, 75% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz, compound exists as a >10:1 mixture of enol : ketone tautomers, only major enol peaks are reported) δ 6.00 (s, 1H), 5.83 (m, 1H), 5.79 (m, 1H), 5.48 (d, J = 9.2 Hz, 1H), 2.86 (m, 1H), 2.25 (t, J = 6.5 Hz, 2H), 1.81 (s, 3H), 1.71 (m, 3H), 1.57 (m, 1H), 1.02 (d, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a >10:1 mixture of enol : ketone tautomers,

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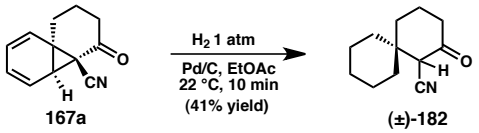
[‡‡] Sherry, B. D.; Furstner, A. *Chem. Commun.* **2009**, 7116.

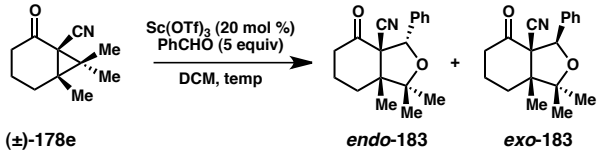
only major enol peaks are reported) δ 168.74, 141.93, 130.38, 124.08, 121.54, 117.12, 89.51, 43.58, 38.17, 27.89, 24.10, 21.79, 18.57, 15.06; FTIR (NaCl, thin film) 3350, 3038, 2963, 2234, 2203, 1728, 1447, 1381, 1309, 1208, 1154 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{16}NO$ $[M-H]^-$ 214.1237, found 214.1241.

Preparation of 2-oxospiro[5.5]undecane-1-carbonitrile 182



To 10 mL flask was added palladium on carbon (10 mg, 10 wt %, 0.008 mmol). The flask was sealed, flushed with nitrogen, and charged with an EtOAc (3 mL) solution of norcaradiene **167a** (20 mg, 0.108 mmol). The suspension was sparged with hydrogen gas for 1 minute, and kept under 1 atm of H_2. After stirring for an additional 15 minutes, TLC analysis indicated consumption of the starting material, and the reaction was filtered through celite. The pad was washed thoroughly with EtOAc, the solvent removed by rotary evaporation under reduced pressure, and the crude residue purified by flash chromatography (0→40% EtOAc/hexanes), yielding spirocycle **182** (8.5 mg, 41% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 3.34 (s, 1H), 2.64 (ddd, J = 14.1, 6.5, 5.7 Hz, 1H), 2.33 (dddd, J = 14.0, 8.9, 6.2, 1.1 Hz, 1H), 2.19 (m, 1H), 1.89 (m, 2H), 1.54 (m, 11H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.02, 115.50, 54.79, 42.75, 39.54, 35.74, 31.65, 30.86, 25.33, 21.33, 21.20, 20.96; FTIR (NaCl, thin film) 2929, 2855, 2243, 1725, 1448, 1320, 1050 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{17}NO$ $[M-H]^-$ + Na^+ 213.1135, found 213.1143.

Preparation of 1,1,7α-trimethyl-4-oxo-3-phenyloctahydroisobenzofuran-3α-carbonitrile (183) and diastereomer



Procedure adapted from the work of Johnson et al.[§§] To an oven-dried 1 dram vial under nitrogen was added scandium(III) triflate (28 mg, 0.058 mmol) followed by DCM (1 mL). In a separate flask cyclopropane **178e** (51 mg, 0.29 mmol) and benzaldehyde (147 mL, 1.5 mmol) were dissolved in DCM (5 mL), and this solution was added in one portion to the $Sc(OTf)_3$ at 22 °C (6 mL DCM total, 0.05 M). The murky reaction was heated to 40 °C, at which time the catalyst dissolved and a clear yellow solution resulted. After stirring for 10 minutes at that temperature, TLC analysis indicated consumption of the starting material. The reaction was cooled to 22 °C, directly transferred onto a silica plug, and eluted with excess diethyl ether. The solvent was removed by rotary evaporation under reduced pressure, and ^{1}H NMR analysis of the crude indicated a 1 : 3.3 ratio of *endo* : *exo* products. The crude residue was purified by flash chromatography (0→15→30% EtOAc/hexanes), yielding *endo*-ketone **183** (18 mg, 20% yield) and *exo*-ketone **183** (53 mg, 65% yield) both as white solids. ***Endo* diastereomer 183:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 5H), 5.64 (s, 1H), 2.10 (m, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.65 (m, 2H), 1.58 (m, 4H), 1.42 (s, 3H), 1.32 (s, 3H), 1.14 (ddd, J = 15.9, 12.8, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.91, 135.96, 128.56, 128.43, 126.26, 120.68, 87.10, 84.24, 67.25, 54.78, 40.35, 32.19, 22.70, 22.64, 20.18, 18.79; FTIR (NaCl, thin

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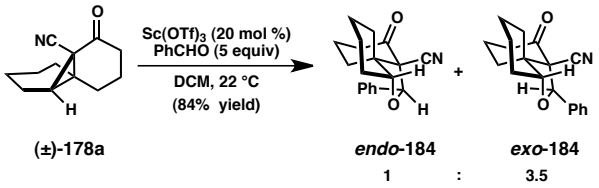
[§§] Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122.

film) 2961, 2883, 2238, 1713, 1451, 1424, 1392, 1213, 1109 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{21}NO_2$ $[M-H]^-$ 282.1500, found 282.1508. ***Exo* diastereomer 183:** ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33 (m, 5H), 5.60 (s, 1H), 2.71 (m, 2H), 2.13 (m, 2H), 2.02 (m, 1H), 1.77 (m, 1H), 1.57 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.20, 136.96, 128.69, 128.41, 125.98, 116.52, 87.28, 80.85, 69.02, 55.88, 37.85, 31.12, 26.46, 24.35, 21.63, 19.62; FTIR (NaCl, thin film) 2999, 2961, 2882, 2238, 1710, 1451, 1424, 1393, 1242, 1110 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{21}NO_2$ $[M-H]^-$ 282.1500, found 282.1504.

Preparation of 7-oxo-6-phenyldecahydro-1*H*-dibenzo[*b*,*c*]furan-6a-carbonitrile (184) and diastereomer



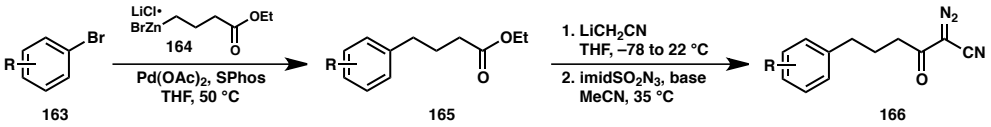
(±)-178a *endo*-184 : *exo*-184

1 : 3.5

Procedure adapted from the work of Johnson et al.[15] To an oven-dried 1 dram vial under nitrogen was added scandium(III) triflate (7.8 mg, 0.015 mmol). In a separate flask cyclopropane **178a** (15 mg, 0.080 mmol) and benzaldehyde (42 mL, 0.40 mmol) were dissolved in DCM (530 mL, 0.15 M), and this solution was added in one portion to the $Sc(OTf)_3$ at 22 °C. The clear yellow solution was stirred at 22 °C for 24 hours, at which time TLC analysis indicated consumption of the starting material. The reaction directly transferred onto a silica plug, and eluted with excess diethyl ether. The solvent was removed by rotary evaporation under reduced pressure, and ^1H NMR analysis of the crude indicated a 1 : 3.5 ratio of *endo* : *exo* products. The crude residue was purified by

flash chromatography (0→15→30% EtOAc/hexanes), yielding *endo*-ketone **184** (5 mg, 21% yield) and *exo*-ketone **184** (15 mg, 63% yield) both as white solids. ***Endo* diastereomer 184:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 5H), 5.55 (s, 1H), 3.72 (dd, *J* = 12.1, 3.9 Hz, 1H), 2.08 (m, 2H), 2.02 (m, 1H), 1.93 (m, 2H), 1.79 (m, 3H), 1.69 (m, 1H), 1.64 (ddd, *J* = 14.0, 3.0, 1.8 Hz, 1H), 1.50 (m, 3H), 0.91 (ddd, *J* = 15.7, 13.9, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 202.01, 136.01, 128.62, 128.55, 126.00, 118.96, 87.20, 85.21, 68.11, 53.51, 40.36, 28.74, 24.42, 23.13, 22.75, 20.53, 20.02; FTIR (NaCl, thin film) 2944, 2870, 2239, 1710, 1452, 1345, 1234, 1155, 1070 cm^{-1}; HRMS (MM) calc'd for $C_{19}H_{20}NO_2$ $[M-H]^-$ 294.1500, found 294.1507. ***Exo* diastereomer 184:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (m, 3H), 7.21 (m, 2H), 5.58 (s, 1H), 4.00 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.79 (m, 1H), 2.66 (m, 1H), 2.12 (m, 3H), 1.89 (m, 4H), 1.75 (m, 1H), 1.67 (m, 2H), 1.50 (qt, *J* = 13.4, 4.4 Hz, 1H), 1.39 (qt, *J* = 13.4, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.21, 137.46, 128.65, 128.63, 125.40, 114.92, 86.44, 82.73, 70.81, 55.65, 37.70, 28.69, 24.80, 23.06, 22.57, 21.35, 20.35; FTIR (NaCl, thin film) 2944, 2870, 2245, 1713, 1452, 1318, 1240, 1152, 1072 cm^{-1}; HRMS (MM) calc'd for $C_{19}H_{20}NO_2$ $[M-H]^-$ 294.1500, found 294.1500.

General procedure for the synthesis of α-diazo-β-ketonitriles

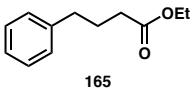


General procedure 4 for the cross coupling of aryl halides and 4-Ethoxy-4-oxobutylzinc bromide (164).

Adapted from the work of Knochel et al.[***] A dry and argon flushed 20 mL Schlenk-tube is charged with the aryl bromide (**1163**, 2.50 mmol, 1 equiv), $Pd(OAc)_2$ (0.25 mmol, 0.01 equiv), S-Phos (0.50 mmol, 0.02 equiv) and THF (2.5 mL). After stirring the reaction mixture for 5 min, 4-Ethoxy-4-oxobutylzinc bromide (**164**, 3 mmol, 1.2 equiv, 0.40 M in THF) is added (mildly exothermic), affording a light yellow solution. The reaction mixture was heated to 50 °C for 2 hours, during which time the color had progressed to dark brown/black. Then, the reaction mixture was cooled to room temperature and quenched with a saturated aqueous NH_4Cl solution, and extracted with 1:1 v/v hexanes/ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and the solvent was removed by rotary evaporation under reduced pressure. The crude residue was purified by silica gel chromatography to afford the aryl-butanoate products.

[***] Manolikakes, G.; Hernandez, C. M.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422.

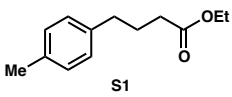
Ethyl 4-phenylbutanoate (165)



165

The reaction was run on 3.75 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 560 mg (78% yield) of **165** as a colorless oil. The spectral data is consistent with that reported in the literature.[†††]

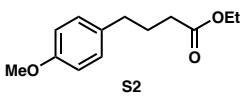
Ethyl 4-(*p*-tolyl)butanoate (S1)



S1

The reaction was run on 3.75 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 470 mg (60% yield) of **S1** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (m, 4H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.93 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.48, 138.27, 135.31, 128.98, 128.30, 60.17, 34.63, 33.61, 26.61, 20.94, 14.20; FTIR (NaCl, thin film) 2977, 2924, 2858, 1733, 1515, 1373, 1243, 1145 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1380, found 207.1389.

Ethyl 4-(4-methoxyphenyl)butanoate (S2)



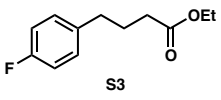
S2

The reaction was run on 3.25 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 600 mg (85% yield) of **S2** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09 (m, 2H), 6.83 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.59 (t, *J*

[†††] Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920.

= 7.6 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.92 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.53, 157.81, 133.46, 129.34, 113.73, 60.20, 55.20, 34.19, 33.59, 26.76, 14.22.; FTIR (NaCl, thin film) 2980, 2936, 2860, 2835, 1732, 1612, 1583, 1513, 1464, 1373, 1300, 1246 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{19}O_3$ $[M+H]^+$ 223.1329, found 223.1339.

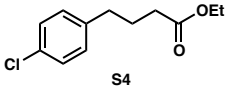
Ethyl 4-(4-fluorophenyl)butanoate (S3)



S3

The reaction was run on 3.25 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 590 mg (84% yield) of **S3** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (m, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.62 (*J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.93 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.37, 161.33 (d, $J_{C\text{-}F}$ = 243.5 Hz), 137.00 (d, $J_{C\text{-}F}$ = 3.3 Hz), 129.77 (d, $J_{C\text{-}F}$ = 7.9 Hz), 115.07 (d, $J_{C\text{-}F}$ = 21.1 Hz), 60.29, 34.27, 33.51, 26.63, 26.62, 14.22; FTIR (NaCl, thin film) 3039, 2981, 2937, 2868, 1732, 1600, 1510, 1374, 1221 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{15}FO_2$ $[M\ \ ]^+$ 210.1056, found 210.1049.

Ethyl 4-(4-chlorophenyl)butanoate (S4)

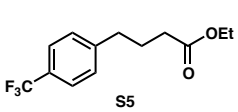


S4

The reaction was run on 3.25 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 586 mg (78% yield) of **S4** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (m, 2H), 7.11 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.92 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,

126 MHz) δ 173.28, 139.82, 131.65, 129.78, 128.42, 60.29, 34.41, 33.46, 26.38, 14.21; FTIR (NaCl, thin film) 3022, 2979, 2933, 2866, 1730, 1491, 1374, 1176 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{15}ClO_2$ [M]$^+$ 226.0761, found 226.0718.

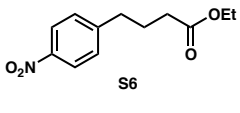
Ethyl 4-(4-(trifluoromethyl)phenyl)butanoate (S5)



S5

The reaction was run on 3.25 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 560 mg (66% yield) of **S5** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 7.7 Hz, 2H), 2.32 (t, *J* = 7.3 Hz, 2H), 1.97 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.18, 145.53 (q, $J_{C\text{-}F}$ = 1.4 Hz), 128.76, 128.35 (q, $J_{C\text{-}F}$ = 32.3 Hz), 125.28 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.30 (q, $J_{C\text{-}F}$ = 271.7 Hz), 60.36, 34.90, 33.46, 26.19, 14.20; FTIR (NaCl, thin film) 3044, 2982, 2940, 2871, 1735, 1618, 1418, 1375, 1326, 1163 cm^{-1}; HRMS (EI+) calc'd for $C_{13}H_{15}F_3O_2$ [M]$^+$ 260.1024, found 260.1035.

Ethyl 4-(4-nitrophenyl)butanoate (S6)

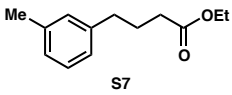


S6

The reaction was run on 3.75 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 633 mg (70% yield) of **S6** as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (m, 2H), 7.34 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.76 (t, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.99 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.95, 149.29, 146.43, 129.23, 123.66, 60.43, 34.91, 33.36, 25.98, 14.20;

FTIR (NaCl, thin film) 2980, 2939, 2869, 1733, 1604, 1517, 1345, 1247, 1180 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{14}NO_4$ $[M–H]^-$ 236.0928, found 236.0941.

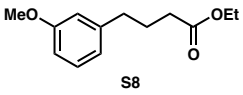
Ethyl 4-(*m*-tolyl)butanoate (S7)



S7

The reaction was run on 5.85 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 1080 mg (90% yield) of **S7** as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.17 (m, 1H), 7.00 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.32 (m, 5H), 1.95 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.47, 141.31, 137.82, 129.24, 128.19, 126.62, 125.42, 60.17, 35.01, 33.64, 26.52, 21.33, 14.19; FTIR (NaCl, thin film) 2979, 2929, 2863, 1733, 1608, 1456, 1373, 1240, 1178 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1380, found 207.1390.

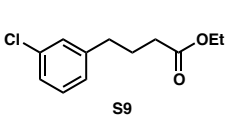
Ethyl 4-(3-methoxyphenyl)butanoate (S8)



S8

The reaction was run on 3.75 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 717 mg (85% yield) of **S8** as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.20 (m, 1H), 6.76 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.95 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.40, 159.57, 143.00, 129.25, 120.82, 114.14, 111.19, 60.18, 55.03, 35.10, 33.57, 26.37, 14.19; FTIR (NaCl, thin film) 2977, 2937, 2868, 2835, 1734, 1601, 1583, 1489, 1456, 1373, 1258, 1151 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{19}O_3$ $[M+H]^+$ 223.1329, found 223.1327.

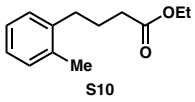
Ethyl 4-(3-methoxyphenyl)butanoate (S9)



S9

The reaction was run on 3.63 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 655 mg (80% yield) of **S9** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (m, 3H), 7.06 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.95 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.10, 143.38, 134.01, 129.52, 128.49, 126.58, 126.06, 60.21, 34.66, 33.38, 26.16, 14.15; FTIR (NaCl, thin film) 3057, 2980, 2933, 2863, 1732, 1598, 1573, 1477, 1374, 1203 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{16}O_2Cl$ $[M+H]^+$ 227.0839, found 227.0830.

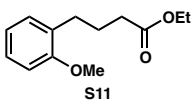
Ethyl 4-(*o*-tolyl)butanoate (S10)



S10

The reaction was run on 8.20 mmol scale for 4 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 1.40 g (83% yield) of **S10** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (m, 4H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.65 (m, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.33 (s, 3H), 1.92 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.45, 139.62, 135.90, 130.17, 128.92, 126.05, 125.88, 60.24, 33.93, 32.52, 25.31, 19.19, 14.22; FTIR (NaCl, thin film) 2977, 2939, 2870, 1733, 1494, 1463, 1372, 1246, 1183 cm^{-1}; HRMS (FAB+) calc'd for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1380, found 207.1386.

Ethyl 4-(2-methoxyphenyl)butanoate (S11)

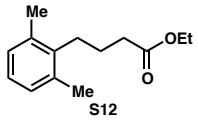


S11

The reaction was run on 3.75 mmol scale for 2 hr. The crude material

was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 742 mg (75% yield) of **S11** as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (td, *J* = 8.1, 1.8 Hz, 1H), 7.12 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.88 (td, *J* = 7.4, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.92 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.68, 157.40, 129.94, 129.75, 127.14, 120.27, 110.12, 60.10, 55.11, 33.88, 29.47, 24.99, 14.21; FTIR (NaCl, thin film) 3064, 2977, 2938, 2835, 1732, 1601, 1587, 1494, 1464, 1373, 1242 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{19}O_3$ $[M+H]^+$ 223.1329, found 223.1331.

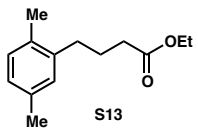
Ethyl 4-(2,6-dimethylphenyl)butanoate (S12)



S12

The reaction was run on 6.23 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 800 mg (58% yield) of **S12** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 (m, 4H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.65 (m, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.33 (s, 6H), 1.79 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.31, 138.34, 136.00, 128.05, 125.70, 60.23, 34.40, 29.06, 24.15, 19.67, 14.20; FTIR (NaCl, thin film) 3066, 2957, 1732, 1586, 1467, 1373, 1245, 1192 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1536, found 221.1527.

Ethyl 4-(2,5-dimethylphenyl)butanoate (S13)

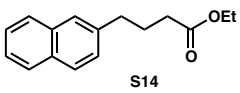


S13

The reaction was run on 5.85 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9.5:0.5 Hexanes:EtOAc) to give 1440 mg (70% yield) of **S13** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.03

(d, *J* = 7.6 Hz, 1H), 6.94 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.61 (m, 2H), 2.37 (t, *J* = 7.4 Hz, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 1.90 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.51, 139.46, 135.25, 132.70, 130.09, 129.75, 126.71, 60.25, 34.00, 32.54, 25.42, 20.92, 18.72, 14.24; FTIR (NaCl, thin film) 3041, 2978, 2938, 2868, 1732, 1503, 1458, 1373, 1194 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{20}O_2$ $[M+H]^+$ 220.1463, found 220.1469.

Ethyl 4-(naphthalen-2-yl)butanoate (S14)



S14

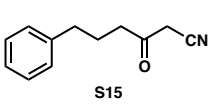
The reaction was run on 3.33 mmol scale for 2 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 800 mg (90% yield) of **S14** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (m, 3H), 7.62 (s, 1H), 7.44 (m, 2H), 7.33 (dd, *J* = 8.4, 1.7 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.82 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.05 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.43, 138.86, 133.51, 132.00, 127.91, 127.54, 127.36, 127.18, 126.54, 125.87, 125.15, 60.22, 35.21, 33.59, 26.34, 14.20; FTIR (NaCl, thin film) 3047, 2977, 2933, 2863, 1730, 1699, 1505, 1369, 1179 cm^{-1}; HRMS (EI+) calc'd for $C_{16}H_{18}O_2$ $[M+H]^+$ 242.1307, found 242.1300.

General procedure 5 for the synthesis of keto nitriles.

In a glovebox a flame-dried 50 mL flask was charged with solid LHMDS (5.25 mmol, 2.20 equiv). This flask was sealed on the benchtop under N_2 THF (10 mL) was charged, dissolving the LHMDS. After cooling to –78 °C, acetonitrile (6.21 mmol, 2.6 equiv) was added in one portion. The hazy light yellow solution was stirred for 0.5 hours at this

temperature. After this time a solution of the ester (**165**, 2.39 mmol, 1.0 equiv) in 15 mL of THF was added fast drop-wise via cannula to the lithio-acetonitrile solution at –78 °C. The reaction became orange during the addition of the ester. After completion of the transfer, the reaction was slowly warmed to 0 °C over 1 hour. At this point TLC analysis indicated complete consumption of starting material, and was quenched with a saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and the solvent was removed by rotary evaporation under reduced pressure. The crude residue was purified by silica gel chromatography to afford the keto nitriles products.

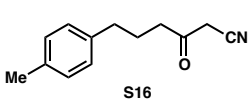
3-Oxo-6-phenylhexanenitrile (S15)



S15

The reaction was run on 2.58 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 429 mg (89% yield) of **S15** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (m, 2H), 7.22 (m, 1H), 7.16 (m, 2H), 3.39 (s, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H), 1.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.28, 140.74, 128.44, 128.36, 126.14, 113.71, 41.11, 34.50, 31.92, 24.58; FTIR (NaCl, thin film) 3026, 2943, 2863, 2260, 1729, 1497, 1453, 1403, 1373, 1308 cm^{-1}; HRMS (ESI–) calc'd for $C_{12}H_{12}NO$ [M–H]$^-$ 186.0924, found 186.0921.

3-Oxo-6-(*p*-tolyl)hexanenitrile (S16)

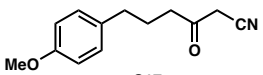


S16

The reaction was run on 1.00 mmol scale for 1 hr. The crude

material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 158 mg (79% yield) of **S16** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (m, 2H), 7.05 (m, 2H), 3.38 (s, 2H), 2.60 (m, 4H), 2.32 (s, 3H), 1.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.26, 137.61, 135.73, 129.18, 128.30, 113.67, 41.17, 34.11, 31.95, 24.73, 20.97; FTIR (NaCl, thin film) 3019, 2943, 2921, 2863, 2260, 1729, 1514, 1457, 1403, 1373, 1308 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO$ $[M–H]^-$ 200.1081, found 200.1085.

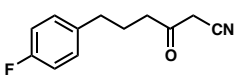
6-(4-Methoxyphenyl)-3-oxohexanenitrile (S17)



S17

The reaction was run on 2.16 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 280 mg (60% yield) of **S17** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07 (m, 2H), 6.84 (m, 2H), 3.79 (s, 3H), 3.38 (s, 2H), 2.59 (m, 4H), 1.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.33, 157.94, 132.74, 129.29, 113.84, 113.72, 55.19, 41.10, 33.61, 31.91, 24.85; FTIR (NaCl, thin film) 3036, 3010, 2952, 2922, 2835, 2258, 1716, 1615, 1585, 1515, 1372, 1347, 1300, 1251 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO_2$ $[M–H]^-$ 216.1030, found 216.1038.

6-(4-Fluorophenyl)-3-oxohexanenitrile (S18)

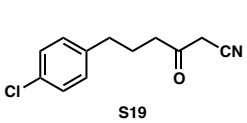


S18

The reaction was run on 2.38 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 380 mg (78% yield) of **S18** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (m, 2H), 6.98 (m, 2H), 3.41 (s, 2H), 2.62 (m, 4H), 1.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.32, 161.38 (d, $J_{C\text{-}F}$ = 243.5 Hz), 136.47 (d, $J_{C\text{-}F}$ = 3.8 Hz),

129.64 (d, $J_{C\text{-}F}$ = 7.7 Hz), 115.04 (d, $J_{C\text{-}F}$ = 20.8 Hz), 113.77, 40.96, 33.61, 31.90, 24.64, 24.63; FTIR (NaCl, thin film) 3040, 2946, 2867, 2261, 1731, 1600, 1510, 1454, 1403, 1307, 1219 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{11}FNO$ $[M–H]^-$ 204.0830, found 204.0830.

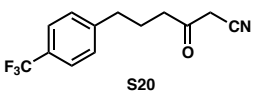
6-(4-Chlorophenyl)-3-oxohexanenitrile (S19)



S19

The reaction was run on 1.97 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 250 mg (57% yield) of **S19** as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.26 (m, 2H), 7.09 (m, 2H), 3.41 (s, 2H), 2.62 (m, 4H), 1.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.09, 139.24, 131.83, 129.69, 128.53, 113.67, 41.00, 33.84, 31.98, 24.46; FTIR (NaCl, thin film) 3027, 2946, 2866, 2260, 1729, 1696, 1492, 1455, 1406, 1373, 1306, 1090 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{11}ClNO$ $[M–H]^-$ 220.0535, found 220.0549.

3-Oxo-6-(4-(trifluoromethyl)phenyl)hexanenitrile (S20)

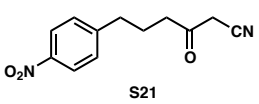


S20

The reaction was run on 1.61 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 250 mg (61% yield) of **S20** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 3.42 (s, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 1.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.05, 145.02 (q, $J_{C\text{-}F}$ = 1.5 Hz), 128.66, 128.41 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.34 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.23 (q, $J_{C\text{-}F}$ = 272.0 Hz), 113.69, 40.98, 34.31, 31.99, 24.27; FTIR (NaCl, thin

film) 3044, 2940, 2872, 2261, 1727, 1617, 1459, 1407, 1340, 1248, 1114 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{11}F_3NO$ $[M–H]^-$ 254.0798, found 254.0813.

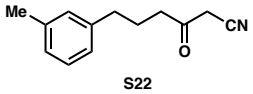
6-(4-Nitrophenyl)-3-oxohexanenitrile (S21)



S21

The reaction was run on 1.00 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (6:4 Hexanes:EtOAc) to give 124 mg (54% yield) of **S21** as a yellow solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.14 (m, 2H), 7.33 (m, 2H), 3.47 (s, 2H), 2.75 (t, J = 7.7 Hz, 2H), 2.66 (t, J = 7.1 Hz, 2H), 1.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 196.80, 148.75, 146.51, 129.17, 123.75, 113.60, 40.94, 34.43, 32.05, 24.11; FTIR (NaCl, thin film) 2952, 2920, 2870, 2258, 1728, 1597, 1507, 1347 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{11}N_2O_3$ $[M–H]^-$ 231.0775, found 231.0785.

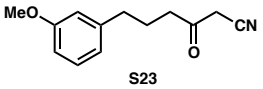
3-Oxo-6-(*m*-tolyl)hexanenitrile (S22)



S22

The reaction was run on 2.04 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 329 mg (80% yield) of **S22** as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.18 (t, J = 7.5 Hz, 1H), 7.03 (m, 1H), 6.97 (m, 2H), 3.39 (s, 2H), 2.61 (m, 4H), 2.33 (s, 3H), 1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.29, 140.67, 138.09, 129.20, 128.36, 126.91, 125.39, 113.70, 41.18, 34.45, 31.93, 24.62, 21.35; FTIR (NaCl, thin film) 3017, 2944, 2920, 2863, 2260, 1731, 1607, 1588, 1487, 1455, 1403, 1306 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{16}NO$ $[M+H]^+$ 202.1226, found 202.1225.

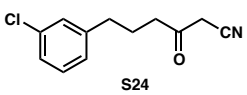
6-(3-Methoxyphenyl)-3-oxohexanenitrile (S23)



S23

The reaction was run on 1.00 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 175 mg (81% yield) of **S23** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (t, *J* = 7.8 1H), 6.75 (m, 2H), 6.70 (m, 1H), 3.80 (s, 3H), 3.40 (s, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.21, 159.69, 142.36, 129.48, 120.77, 114.21, 113.67, 111.38, 55.12, 41.12, 34.55, 31.96, 24.48; FTIR (NaCl, thin film) 3002, 2943, 2836, 2260, 1729, 1601, 1583, 1487, 1455, 1312, 1260 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{16}NO_2$ $[M+H]^+$ 218.1176, found 218.1182.

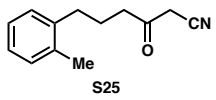
6-(3-chlorophenyl)-3-oxohexanenitrile (S24)



S24

The reaction was run on 1.68 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 310 mg (84% yield) of **S24** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (m, 3H), 7.04 (m, 1H), 3.44 (s, 2H), 2.61 (m, 4H), 1.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.04, 142.85, 134.15, 129.74, 128.42, 126.57, 126.34, 113.66, 41.00, 34.17, 31.99, 24.32; FTIR (NaCl, thin film) 3060, 2946, 2867, 2260, 1731, 1697, 1572, 1475, 1403, 1305 cm^{-1}; HRMS (FAB+) calc'd for $C_{12}H_{12}NClO$ $[M\ ]^+$ 221.0607, found 221.0608.

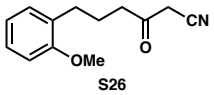
3-Oxo-6-(*o*-tolyl)hexanenitrile (S25)



S25

The reaction was run on 2.09 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 311 mg (75% yield) of **S25** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (m, 4H), 3.42 (s, 2H), 2.64 (m, 4H), 2.33 (s, 3H), 1.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.30, 138.98, 135.88, 130.24, 128.77, 126.20, 125.87, 113.77, 41.33, 31.94, 31.85, 23.28, 19.09; FTIR (NaCl, thin film) 3017, 2946, 2920, 2260, 1732, 1603, 1493, 1462, 1403, 1372, 1306 cm^{-1}; HRMS (FAB+) calc'd for $C_{13}H_{15}NO$ [M]$^{+}$ 201.1154, found 201.1149.

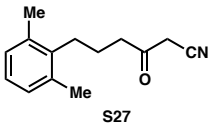
6-(2-Methoxyphenyl)-3-oxohexanenitrile (S26)



S26

The reaction was run on 1.00 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 165 mg (76% yield) of **S26** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (td, *J* = 7.8, 1.7 Hz, 1H), 7.09 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.89 (td, *J* = 7.4, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.2, 1.0 Hz, 1H), 3.82 (s, 3H), 3.39 (s, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 1.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.46, 157.40, 130.04, 129.14, 127.53, 120.49, 113.79, 110.36, 55.23, 41.37, 31.80, 28.99, 23.41; FTIR (NaCl, thin film) 3002, 2941, 2837, 2260, 1729, 1599, 1586, 1493, 1464, 1290, 1243 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{16}NO_2$ [M+H]$^{+}$ 218.1176, found 218.1178.

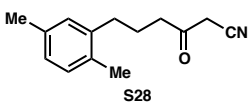
6-(2,6-Dimethylphenyl)-3-oxohexanenitrile (S27)



S27

The reaction was run on 3.18 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 600 mg (88% yield) of **S27** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.02 (m, 3H), 3.45 (s, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.65 (m, 2H), 2.34 (s, 6H), 1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.14, 137.83, 136.04, 128.18, 125.96, 113.75, 41.91, 31.97, 28.65, 22.44, 19.75; FTIR (NaCl, thin film) 3019, 2953, 2941, 2260, 1732, 1585, 1470, 1403, 1306, 1092 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{16}NO$ [M-H]$^-$ 214.1237, found 214.1243.

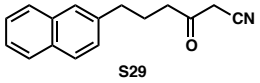
6-(2,5-Dimethylphenyl)-3-oxohexanenitrile (S28)



S28

The reaction was run on 2.02 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 341 mg (78% yield) of **S28** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (d, *J* = 7.6 Hz, 1H), 6.95 (m, 1H), 6.93 (s, 1H), 3.40 (s, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 2.61 (m, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 1.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.23, 138.80, 135.37, 132.74, 130.25, 129.68, 126.97, 113.71, 41.48, 32.03, 31.92, 23.49, 20.88, 18.71; FTIR (NaCl, thin film) 2944, 2868, 2260, 1732, 1504, 1462, 1403, 1306, 1082 cm^{-1}; HRMS (EI+) calc'd for $C_{14}H_{17}NO$ [M]$^+$ 215.1310, found 215.1339.

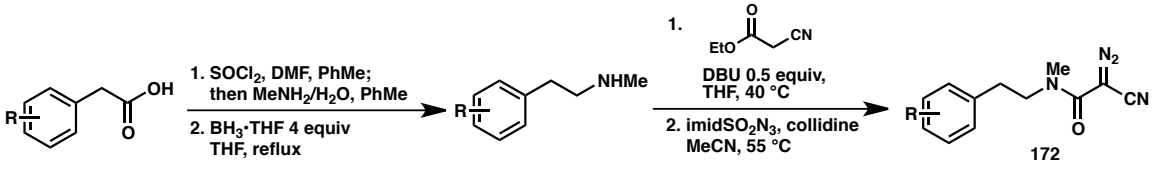
6-(naphthalen-2-yl)-3-oxohexanenitrile (S29)



S29

The reaction was run on 1.53 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 295 mg (82% yield) of **S29** as a wispy white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (m, 3H), 7.60 (m, 1H), 7.47 (m, 2H), 7.31 (dd, *J* = 8.4, 1.7 Hz, 1H), 3.34 (s, 2H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.22, 138.25, 133.42, 132.00, 128.10, 127.55, 127.33, 126.95, 126.53, 126.03, 125.33, 113.68, 41.04, 34.59, 31.87, 24.37; FTIR (NaCl, thin film) 3052, 2944, 2848, 2260, 1731, 1633, 1597, 1456, 1399, 1245, 1085 cm^{-1}; HRMS (FAB+) calc'd for $C_{16}H_{15}NO$ [M]$^{+}$ 237.1154, found 237.1157.

General procedure for the synthesis of α-diazo-β-amidonitriles



General procedure 6 for the synthesis of 2-arylacetamides.

Adapted from the procedure of Haney et al.[‡‡‡] To a 100 mL round bottom flask was charged (2-methylphenyl) acetic acid (3.47 mmol, 1.00 equiv) followed by anhydrous toluene (10 mL). DMF (0.31 mL, 1.15 equiv) and thionyl chloride (0.30 mL, 1.2 equiv) were added successively, resulting in a clear yellow solution, which was heated to 40 °C

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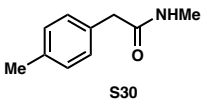
‡‡‡ Ulysse, G. L.; Yang, Q.; McLaws, M. D.; Keefe, D. K.; Guzzo, P. R.; Haney, B. P.; *Organic Process Research & Development* **2010** *14* (1), 225.

for 30 minutes. The resulting acid chloride solution was transferred to an addition funnel, and added in a rapid dropwise fashion to a vigorously stirred, pre-cooled (0 °C) 40% wt methylamine/water solution. A heterogeneous biphasic mixture resulted, and upon completion of the acid chloride addition was warmed to 22 °C for 30 minutes. LC/MS analysis indicated complete consumption of the starting 2-arylacetic acid. The reaction was quenched with water, and extracted with ethyl acetate (3 X 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine, and subsequently dried over sodium sulfate. The solvent was removed by rotary evaporation under reduced pressure to yield a crude residue of sufficient purity for the ensuing reduction step. Recrystallization from hexanes/ethyl acetate was in certain cases employed to improve product purity.

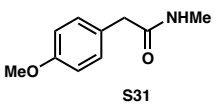
_N_-Methyl-2-(_p_-tolyl)acetamide (S30)



S30

The reaction was run on 3.47 mmol scale to afford 450 mg (80% yield) of **S30** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (m, 2H), 7.13 (m, 2H), 5.32 (br s, 1H), 3.54 (s, 2H), 2.75 (d, J = 4.9 Hz, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.83, 136.90, 131.77, 129.59, 129.30, 43.17, 26.36, 20.98. FTIR (NaCl, thin film) 3251, 3083, 2962, 2915, 2837, 1653, 1631, 1575, 1512, 1408, 1219, 1166 cm^{-1}; HRMS (MM) calc'd for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.1019, found 180.1011.

2-(4-Methoxyphenyl)-_N_-methylacetamide (S31)

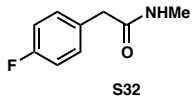


S31

The reaction was run on 27.5 mmol scale to afford, after

recrystallization from hexanes/EtOAc, 2.9 g (60% yield) of **S31** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (m, 2H), 6.86 (m, 2H), 5.58 (br s, 1H), 3.78 (s, 3H), 3.48 (s, 2H), 2.72 (d, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.98, 158.74, 130.49, 126.82, 114.30, 55.23, 42.67, 26.36; FTIR (NaCl, thin film) 3251, 3083, 2962, 2915, 2837, 1653, 1631, 1575, 1512, 1408, 1219, 1166 cm^{-1}; HRMS (MM) calc'd for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.1019, found 180.1011.

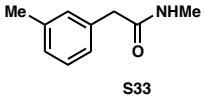
2-(4-Fluorophenyl)-*N*-methylacetamide (S32)



S32

The reaction was run on 15.5 mmol scale to afford 2.1 g (80% yield) of **S32** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (m, 2H), 6.99 (m, 2H), 5.86 (br s, 1H), 3.49 (s, 2H), 2.73 (d, J = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.41, 162.02 (d, $J_{C\text{-}F}$ = 245.6 Hz), 130.85 (d, $J_{C\text{-}F}$ = 7.7 Hz), 130.67 (d, $J_{C\text{-}F}$ = 3.4 Hz), 115.63 (d, $J_{C\text{-}F}$ = 21.6 Hz), 42.54, 26.39; FTIR (NaCl, thin film) 3291, 3092, 2943, 2907, 1648, 1564, 1505, 1410, 1219, 1162 cm^{-1}; HRMS (MM) calc'd for $C_9H_{11}FNO$ $[M+H]^+$ 168.0819, found 168.0827.

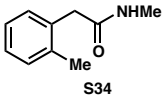
***N*-Methyl-2-(*m*-tolyl)acetamide (S33)**



S33

The reaction was run on 22.2 mmol scale to afford 2.5 g (70% yield) of **S33** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (t, J = 7.5 Hz, 1H), 7.06 (m, 3H), 5.61 (br s, 1H), 3.52 (s, 2H), 2.74 (d, J = 4.8 Hz, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.73, 138.64, 134.75, 130.17, 128.80, 127.99, 126.40, 43.54, 26.39, 21.28; FTIR (NaCl, thin film) 3291, 3083, 2942, 1647, 1559, 1490, 1409, 1339 cm^{-1}; HRMS (MM) calc'd for $C_{10}H_{14}NO$ $[M+H]^+$ 164.1070, found 164.1077.

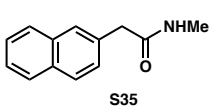
_N_-methyl-2-(_o_-tolyl)acetamide (S34)



S34

The reaction was run on 21.3 mmol scale to afford 2.9 g (83% yield) of **S34** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (m, 4H), 5.35 (br s, 1H), 3.57 (s, 2H), 2.73 (d, J = 4.9 Hz, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.29, 137.21, 133.33, 130.74, 130.49, 127.76, 126.56, 41.66, 26.40, 19.41; FTIR (NaCl, thin film) 3270, 3077, 2914, 1643, 1556, 1406, 1348, 1254 cm^{-1}; HRMS (MM) calc'd for $C_{10}H_{14}NO$ $[M+H]^+$ 164.1070, found 164.1065.

_N_-methyl-2-(naphthalen-2-yl)acetamide (S35)



S35

The reaction was run on 15.0 mmol scale to afford 2.9 g (quantitative yield) of **S35** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (m, 3H), 7.69 (s, 1H), 7.48 (m, 2H), 7.35 (dd, J = 8.4, 1.8 Hz, 1H), 5.68 (br s, 1H), 3.71 (s, 2H), 2.73 (d, J = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.53, 133.43, 132.39, 132.34, 128.68, 128.19, 127.62, 127.51, 127.30, 126.35, 125.96, 43.70, 26.41; FTIR (NaCl, thin film) 3262, 3081, 3052, 2931, 1643, 1567, 1430, 1409, 1333, 1269, 1165 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1070, found 200.1078.

General procedure 7 for the synthesis of 2-cyanoacetamides.

Adapted from the procedure of Priestley et al.[§§§] To a 100 mL round bottom flask fitted with a condenser and flushed with nitrogen was charged *N*-methyl-2-phenylacetamide

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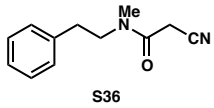
[§§§] Priestley, E. Scott; Cheney, Daniel L.; Wurtz, Nicholas R.; Glunz, Peter W.; PCT Int. Appl. (2007) WO 076431 A1.

(2.53 mmol, 1.00 equiv) followed by anhydrous THF (10 mL). Borane–tetrahydrofuran (10.12 mmol, 1M THF, 4 equiv) was added via syringe to the amide at room temperature. Upon completion of the addition the clear, colorless reaction was heated to reflux for 4 hours. After this time the reaction was cooled in an ice bath, and methanol (3.5 mL) was added cautiously (gas evolution!). 6 M HCl (5 mL) was added fast dropwise, and the mixture was heated to reflux for 30 minutes. The volatiles were then concentrated *in vacuo*, and the resulting mixture was cooled in an ice bath and 50% aqueous NaOH (5 mL) was added (pH > 10). The mixture was then diluted with water and extracted with diethyl ether (3 X 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated, affording a colorless oil. The crude secondary amine was used directly in the subsequent step.

Adapted from the procedure of Price et al.[****] To a 25 mL round bottom flask containing the N-methyl-2-phenethylamine (2.60 mmol, 1.00 equiv) was added DBU (1.30 mmol, 0.5 equiv) and THF (5 mL). Ethyl cyanoacetate (3.88 mmol, 1.5 equiv) was added in one portion, and the clear, deep yellow reaction was stirred at room temperature overnight. After TLC analysis indicated complete consumption of the starting material, the volatiles were concentrated *in vacuo* and the crude residue was purified by column chromatography to afford the 2-cyanoacetamide products.

[****] Price, K. E.; Larrivée-Aboussafy, C.; Lillie, B. M.; McLaughlin, R. W.; Mustakis, J.; Hettenbach, K. W.; Hawkins, J. M.; Vaidyanathan, R.; *Org. Lett.* **2009** *11* (9), 2003.

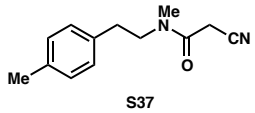
2-Cyano-*N*-methyl-*N*-phenethylacetamide (S36)



S36

The reaction was run on 9.10 mmol scale and the crude material was purified by silica gel chromatography (3:7 hexanes:EtOAc) to afford 1.34 g (72% yield, 2 steps) of **S36** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 7.28 (m, 4H*, 4H§), 7.14 (m, 1H*, 1H§), 3.62 (m, 2H§), 3.50 (t, *J* = 6.6 Hz, 2H*), 3.44 (s, 2H§), 3.03 (s, 3H§), 2.91 (s, 3H*), 2.88 (m, 4H*, 2H§); ^{13}C NMR ($CDCl_3$, 126 MHz; compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 161.66§, 161.33*, 138.25*, 137.46§, 128.98*, 128.62*§, 128.49§, 127.15*, 126.44§, 114.05§, 113.92*, 52.19§, 50.47*, 36.48*, 34.02§, 33.80§, 33.27*, 25.20§, 24.03*; FTIR (NaCl, thin film) 3027, 2928, 2860, 2259, 1657, 1453, 1401, 1175 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{15}N_2O$ $[M+H]^+$ 203.1179, found 203.1177.

2-Cyano-*N*-methyl-*N*-(4-methylphenethyl)acetamide (S37)

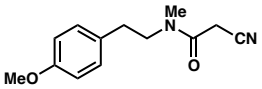


S37

The reaction was run on 2.53 mmol scale and the crude material was purified by silica gel chromatography (3:7 hexanes:EtOAc) to afford 347 mg (63% yield, 2 steps) of **S37** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as a 1.2:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 7.15 (m, 2H*), 7.11 (m, 4H§), 7.03 (m, 2H*), 3.60 (m, 2H§), 3.48 (t, *J* = 6.5 Hz, 2H*), 3.44 (s, 2H§), 3.02 (s, 3H*), 2.91 (s, 3H§), 2.87 (s, 2H*), 2.84 (m, 2H*, 2H§), 2.34 (s, 3H*), 2.32 (s, 3H§); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1.2:1 mixture of rotamers, major rotamer is designated by *, minor rotamer

denoted by [§]) δ 161.67*, 161.34[§], 136.59*, 135.75[§], 135.05[§], 134.26*, 129.45[§], 129.02*, 128.41*, 128.35[§], 114.10*, 114.02[§], 52.08*, 50.35[§], 36.25[§], 33.61*, 33.41*, 32.68[§], 25.06[*], 23.94[§], 20.75*[§]; FTIR (NaCl, thin film) 3027, 2923, 2861, 2259, 1657, 1515, 1452, 1401, 1172 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{17}N_2O$ $[M+H]^+$ 217.1335, found 217.1330.

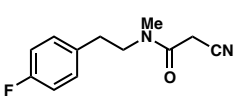
2-Cyano-*N*-(4-methoxyphenethyl)-*N*-methylacetamide (S38)



S38

The reaction was run on 11.4 mmol scale to afford, after chromatography (3:7 hexanes:EtOAc) and recrystallization from hexanes/EtOAc, 1.26 g (47% yield, 2 steps) of **S38** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz; compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by [*], minor rotamer denoted by [§]) δ 7.12 (m, 2H[§]), 7.05 (m, 2H*), 6.87 (m, 2H*), 6.85 (m, 2H[§]), 3.80 (s, 3H*), 3.79 (s, 3H[§]), 3.58 (m, 2H[§]), 3.47 (t, J = 6.5 Hz, 2H*), 3.44 (s, 2H[§]), 3.02 (s, 3H*), 2.90 (s, 3H[§]), 2.90 (s, 2H*), 2.82 (m, 2H*, 2H[§]); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by [*], minor rotamer denoted by [§]) δ 161.47*[§], 158.41*[§], 130.23[§], 129.63*[§], 129.30*, 114.39*, 114.09[§], 113.91*[§], 55.19*, 55.13[§], 52.43*, 50.67[§], 36.54[§], 33.81*, 33.13*, 32.40[§], 25.21[§], 24.10*; FTIR (NaCl, thin film) 3030, 2935, 2836, 2259, 1660, 1611, 1513, 1464, 1401, 1247, 1178 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1285, found 233.1289.

2-Cyano-*N*-(4-fluorophenethyl)-*N*-methylacetamide (S39)

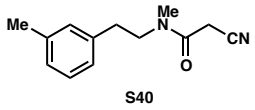


S39

The reaction was run on 8.8 mmol scale and the crude material was

purified by silica gel chromatography (3:7 hexanes:EtOAc) to afford 1.00 g (52% yield, 2 steps) of **S39** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as a 1.5:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 7.15 (m, 2H*, 2H§), 7.02 (m, 2H*, 2H§), 3.59 (m, 2H*), 3.49 (t, J = 6.8 Hz, 2H§), 3.44 (s, 2H*), 3.03 (s, 2H§), 3.02 (s, 3H§), 2.93 (s, 3H*), 2.89 (t, J = 6.8 Hz, 2H§), 2.85 (t, J = 7.4 Hz, 2H*); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1.5:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 161.85§ (d, $J_{C\text{-}F}$ = 246.4 Hz), 161.59* (d, $J_{C\text{-}F}$ = 244.0 Hz), 161.51§, 161.37*, 133.93* (d, $J_{C\text{-}F}$ = 3.4 Hz), 133.12§ (d, $J_{C\text{-}F}$ = 3.4 Hz), 130.21§ (d, $J_{C\text{-}F}$ = 8.1 Hz), 130.12* (d, $J_{C\text{-}F}$ = 8.0 Hz), 115.93§ (d, $J_{C\text{-}F}$ = 21.4 Hz), 115.39* (d, $J_{C\text{-}F}$ = 21.1 Hz), 113.95§, 113.82*, 52.27§ (d, $J_{C\text{-}F}$ = 1.7 Hz), 50.53* (d, $J_{C\text{-}F}$ = 1.4 Hz), 36.57*, 33.91§, 33.36§, 32.51*, 25.25*, 24.28§; FTIR (NaCl, thin film) 3040, 2932, 2866, 2260, 1660, 1600, 1510, 1402, 1220 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{14}FN_2O$ $[M+H]^+$ 221.1085, found 221.1090.

2-Cyano-*N*-methyl-*N*-(3-methylphenethyl)acetamide (S40)

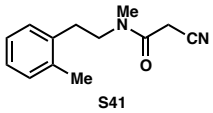


S40

The reaction was run on 11.4 mmol scale and the crude material was purified by silica gel chromatography (4:6 hexanes:EtOAc) to afford 1.35 g (65% yield, 2 steps) of **S40** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 7.20 (m, 1H*, 1H§), 7.10 (d, J = 7.5, 1H*), 7.03 (m, 1H*, 2H§), 6.94 (m, 1H*, 1H§), 3.59 (m, 2H§), 3.48 (t, J = 6.6 Hz, 2H*), 3.45 (s, 2H§), 3.02 (s, 3H*), 2.92 (s, 3H§), 2.91 (s, 2H*), 2.83 (m, 2H*, 2H§), 2.34 (s, 3H*), 2.33 (s, 3H§); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1.1:1 mixture of rotamers, major rotamer is

designated by *, minor rotamer denoted by §) δ 161.67*, 161.22§, 138.89*, 138.26§, 138.21§, 137.42*, 129.54§, 129.47*, 129.01§, 128.49§, 128.02*, 127.30*, 125.67*§, 114.02*, 113.78§, 52.41*, 50.73§, 36.68§, 34.12*, 33.93*, 33.33§, 25.28§, 24.11*, 21.31*§; FTIR (NaCl, thin film) 3017, 2923, 2858, 2259, 1660, 1486, 1457, 1402, 1169 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{17}N_2O$ $[M+H]^+$ 217.1335, found 217.1347.

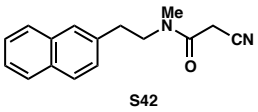
2-Cyano-*N*-methyl-*N*-(2-methylphenethyl)acetamide (S41)



S41

The reaction was run on 11.5 mmol scale and the crude material was purified by silica gel chromatography (3:7 hexanes:EtOAc) to afford, after recrystallization from hexanes/EtOAc, 1.00 g (40% yield, 2 steps) of **S41** as a white solid. ^1H NMR ($CDCl_3$, 500 MHz; compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 7.16 (m, 4H*, 3H§), 7.05 (m, 1H§), 3.56 (m, 2H*), 3.48 (t, J = 6.7 Hz, 2H§), 3.47 (s, 2H*), 3.04 (s, 3H§), 2.96 (s, 3H*), 2.91 (t, J = 6.7 Hz, 2H§), 2.89 (m, 2H*, 2H§), 2.38 (s, 3H*), 2.34 (s, 3H§); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 161.57§, 161.31*, 136.33§, 136.22*, 135.66*, 135.65§, 130.79§, 130.37*, 129.61§, 129.35*, 127.45§, 126.72*, 126.65§, 126.10*, 114.03§, 113.85*, 51.03§, 49.43*, 36.49*, 34.11§, 31.37§, 30.76*, 25.25*, 23.86§, 19.17§, 19.10*; FTIR (NaCl, thin film) 3015, 2946, 2858, 2259, 1654, 1490, 1458, 1400, 1172 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{17}N_2O$ $[M+H]^+$ 217.1335, found 217.1343.

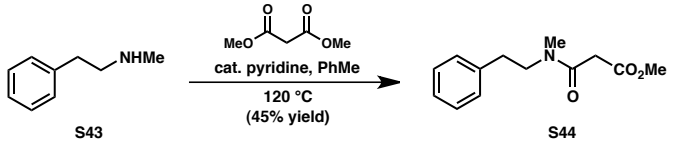
2-Cyano-*N*-methyl-*N*-(2-(naphthalen-2-yl)ethyl)acetamide (S42)



S42

The reaction was run on 13.0 mmol scale and the crude material was purified by silica gel chromatography (3:7 hexanes:EtOAc) to afford 2.00 g (61% yield, 2 steps) of **S42** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as a 1.2:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 7.82 (m, 3H*, 3H§), 7.66 (s, 1H*), 7.61 (s, 1H§), 7.48 (m, 2H*, 2H§), 7.36 (dd, J = 8.4, 1.8 Hz, 1H*), 7.28 (dd, J = 8.4, 1.8 Hz, 1H§), 3.71 (m, 2H*), 3.61 (t, J = 6.8 Hz, 1H§), 3.45 (s, 2H*), 3.06 (m, 2H*, 5H§), 2.96 (s, 2H§), 2.91 (s, 3H*); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1.2:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 161.52§, 161.37*, 135.79*, 134.76§, 133.42*, 133.36§, 132.19§, 132.10*, 128.76§, 128.20*, 128.20§, 127.63*, 127.54*, 127.39*§, 127.37§, 127.31*, 127.08§, 127.01§, 126.53§, 126.48*, 126.06*, 125.94§, 125.47*§, 113.99§, 113.89*, 52.12§, 50.45*, 36.58*, 34.33§, 33.94§, 33.49*, 25.21*, 24.22§; FTIR (NaCl, thin film) 3015, 3019, 2939, 2861, 2259, 1659, 1483, 1401, 1176 cm^{-1}; HRMS (MM) calc'd for $C_{16}H_{17}N_2O$ $[M+H]^+$ 253.1335, found 253.1345.

Preparation of methyl 3-(methyl(phenethyl)amino)-3-oxopropanoate (S44)

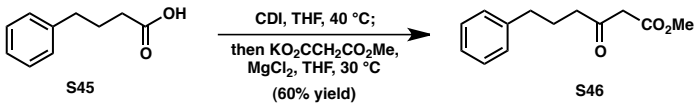


S43 S44

To a 10 mL schlenk tube under an atmosphere of nitrogen was added commercially available *N*-methyl-phenethylamine **S43** (400 mg, 2.96 mmol), dimethyl malonate (510 mL, 4.44 mmol), and toluene (6 mL). Pyridine (12 mL, 0.148 mmol) was

charged and the tube was sealed and heated to 120 °C for 48 hours. The initially murky mixture clarified to a light yellow solution upon achieving reflux. After cooling the reaction was loaded directly onto a silica gel column and purified by flash chromatography (0→60% EtOAc/hexanes) to afford **S44** (0.31 g, 45% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz; compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 7.29 (m, 2H*, 2H§), 7.19 (m, 3H*, 3H§), 3.76 (s, 3H*), 3.71 (s, 3H§), 3.61 (m, 2H*), 3.51 (t, J = 7.2 Hz, 2H§), 3.44 (s, 2H*), 3.15 (s, 2H§), 2.99 (s, 3H§), 2.87 (m, 5H*, 2H§); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1.1:1 mixture of rotamers, major rotamer is designated by *, minor rotamer denoted by §) δ 168.02§, 167.97*, 165.79§, 165.70*, 138.86*, 137.77§, 128.83§, 128.77*, 128.66§, 128.45*, 126.86§, 126.32*, 52.38*, 52.34§, 52.31§, 50.23*, 41.40*, 40.42§, 36.66*, 34.59§, 33.61§, 33.49*; FTIR (NaCl, thin film) 3026, 2949, 1743, 1653, 1490, 1437, 1325, 1257, 1155 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{18}NO_3$ $[M+H]^+$ 236.1281, found 236.1284.

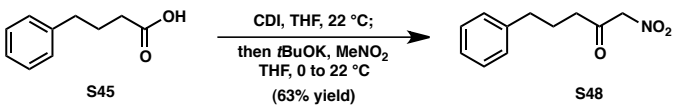
Preparation of methyl 3-oxo-6-phenylhexanoate (S46)



A flame-dried 100 mL round-bottom flask equipped with stir bar and reflux condenser was charged with potassium monomethyl malonate (1.59 g, 10.1 mmol) and $MgCl_2$ (0.64 g, 6.77 mmol). This flask was evacuated and backfilled with nitrogen 3 times. THF (10 mL) was added and the suspension was heated to 65 °C for 3 hr, followed

by 30 °C for 2 h. A separate 50 mL flame-dried round-bottom flask was charged with commercially available 4-phenylbutyric acid **S45** (1.11 g, 6.77 mmol) and carbonyl diimidazole (1.15 g, 7.11 mmol). The flask was fitted with a reflux condenser and THF (10 mL) was added, and the solution was heated at 40 °C for 1 hour. The resulting acyl imidazole solution was added dropwise via cannula to the magnesium malonate suspension at 30 °C (NOTE: a white precipitate forms rapidly, and vigorous stirring is necessary to avoid clumping). After 12 hr the white suspension was cooled to 0 °C and quenched by the addition of 1M HCl (5 mL). The reaction was extracted into EtOAc (3 x 50 mL), washed successively with water, brine, and dried over sodium sulfate. Concentration under reduced pressure yielded a crude oil, which was purified by flash chromatography (0→20% EtOAc/hexanes), yielding β-ketoester **S46** (0.90 g, 60% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as a 10:1 mixture of ketone : enol tautomers, only major ketone peaks are reported) δ 7.29 (m, 2H), 7.17 (m, 3H), 3.73 (s, 3H), 3.43 (s, 2H), 2.63 (t, J = 7.6 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 1.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 10:1 mixture of ketone : enol tautomers, only major ketone peaks are reported) δ 202.37, 167.52, 141.24, 128.37, 128.33, 125.94, 52.26, 48.95, 42.06, 34.70, 24.76; FTIR (NaCl, thin film) 3026, 2951, 2860, 1748, 1715, 1628, 1496, 1453, 1407, 1319, 1258 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{15}O_3$ $[M–H]^-$ 219.1027, found 219.1027.

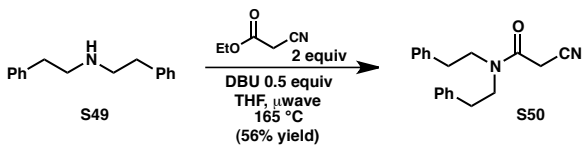
Preparation of 1-nitro-5-phenylpentan-2-one (S48)



S45 S48

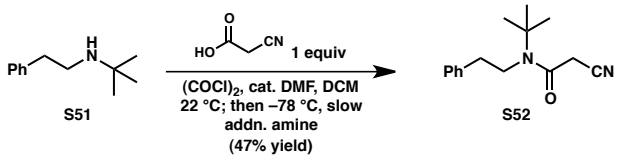
A 250 mL flame-dried round-bottom flask was charged with commercially available 4-phenylbutyric acid **S45** (1.42 g, 8.66 mmol) and carbonyl diimidazole (1.15 mg, 7.11 mmol). THF (45 mL) was introduced, and the clear, colorless solution was stirred at 22 °C for 5 hrs. In a separate 100 mL round-bottom flask potassium *tert*-butoxide (1.12 g, 9.96 mmol) was dissolved in THF (30 mL) and cooled to 0 °C. Nitromethane (4.67 mL, 86.6 mmol) was added dropwise, resulting in a thick white slurry. After warming to room temperature, the slurry was poured directly into the acyl imidazole flask pre-cooled to 0 °C, and the headspace with re-swept with nitrogen. After stirring overnight at room temperature, the orange slurry was quenched with 1M HCl. The volatiles were concentrated and the aqueous was extracted twice with EtOAc. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0→40% EtOAc/hexanes), yielding a-nitroketone **S48** (1.14 g, 63% yield) as a white solid, after recrystallization from EtOAc/hexanes. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (m, 2H), 7.22 (m, 1H), 7.16 (m, 2H), 5.20 (s, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 195.93, 140.61, 128.49, 128.37, 126.20, 83.10, 39.40, 34.45, 24.34; FTIR (NaCl, thin film) 3063, 3019, 2954, 2868, 1727, 1655, 1454, 1397, 1341, 1312, 1198 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{13}N_2O_3$ $[M–H]^-$ 206.0823, found 206.0814.

Preparation of 2-cyano-*N*,*N*-diphenethylacetamide (S50)



To a 5 mL microwave vessel was added *N*,*N*-diphenethylamine **S49**[††††] (1.2 g, 5.33 mmol) and a stirbar, and was sealed with a crimped cap under nitrogen. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.40 mL, 2.67 mmol), THF (3 mL) and ethylcyanoacetate (1.13 mL, 10.66 mmol) were added successively via syringe, and the clear orange solution was heated in a microwave to 165 °C for 45 minutes. After cooling the reaction was extracted with EtOAc, washed with 1M HCl, brine, and dried over sodium sulfate. The solvent was removed by rotary evaporation under reduced pressure, and the crude residue was purified by flash chromatography (0→33% EtOAc/hexanes), yielding acetamide **S50** (1.0 g, 56% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as a 1:1 mixture of rotamers) δ 7.31 (m, 4H), 7.23 (m, 4H), 7.09 (m, 2H), 3.61 (m, 2H), 3.29 (t, *J* = 6.7 Hz, 2H), 2.92 (m, 2H), 2.87 (s, 2H), 2.80 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 1:1 mixture of rotamers) δ 161.59, 138.46, 137.38, 129.03, 128.72, 128.69, 128.58, 127.22, 126.52, 113.96, 50.73, 48.37, 34.53, 33.49, 24.34; FTIR (NaCl, thin film) 3061, 3027, 2926, 2860, 2256, 1660, 1496, 1454, 1428, 1368, 1183 cm^{-1}; HRMS (MM) calc'd for $C_{19}H_{21}N_2O$ $[M+H]^+$ 293.1648, found 293.1660.

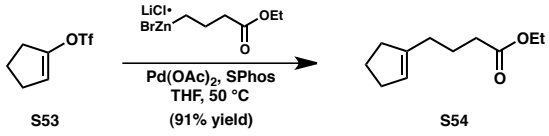
Preparation of *N*-(*t*-butyl)-2-cyano-*N*-phenethylacetamide (S52)



[††††] Synthesized from *N*-phenethyl-2-phenylacetamide (coupling product of 2-phenethylamine and phenylacetic acid), followed by borane reduction according to general procedure 7.

To a 25 mL round bottom flask containing cyanoacetic acid (64 mg, 0.75 mmol) was added DCM (5 mL) and one drop of DMF. Oxalyl chloride (70 mL, 0.83 mmol) was added in one portion, and gas evolution resulted. After 20 minutes the bubbling ceased, and the reaction was cooled to –78 °C, and a solution of amine **S72**[‡‡‡‡] (0.40 g, 2.3 mmol) in DCM (7 mL) was added dropwise to the acid chloride via cannula. The reaction immediately turned yellow upon addition of the amine and progressed to a clear dark orange solution during the addition. The reaction was warmed to 22 °C and stirred for 10 minutes, at which point TLC analysis indicated formation of a new species. The volatiles were concentrated *in vacuo* and the crude residue was purified by column chromatography (0→10→30% EtOAc/hexanes), cyanoamide **S73** (86 mg, 47% yield, unoptimized) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (m, 3H), 7.17 (m, 2H), 3.48 (m, 2H), 3.25 (s, 2H), 2.87 (t, J = 7.6 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.98, 137.45, 129.02, 128.40, 127.14, 114.54, 58.57, 47.70, 37.93, 28.68, 27.46; FTIR (NaCl, thin film) 2973, 2918, 2255, 1653, 1453, 1413, 1394, 1362, 1175 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{21}N_2O$ $[M+H]^+$ 245.1648, found 245.1661.

Preparation of ethyl 4-(cyclopent-1-en-1-yl)butanoate (S54)

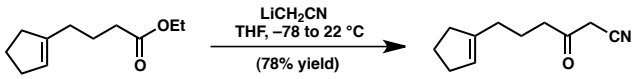


S53 S54

‡‡‡‡ Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A.; *J. Am. Chem. Soc.* **1993**, *115*, 8669.

Compound **S54** was synthesized according to general procedure 4. The reaction was run on 5.10 mmol scale for 0.5 hr. The crude material was purified by silica gel chromatography (95:5 Hexanes:Et_2O) to give 850 mg (91% yield) of **S54** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.33 (m, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.27 (m, 4H), 2.21 (m, 2H), 2.09 (m, 2H), 1.84 (m, 2H), 1.77 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.70, 143.58, 124.06, 60.14, 34.86, 33.96, 32.40, 30.47, 23.38, 23.01, 14.22; FTIR (NaCl, thin film) 2947, 2844, 1737, 1446, 1372, 1242, 1178 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{19}O_2$ $[M+H]^+$ 183.1380, found 183.1371.

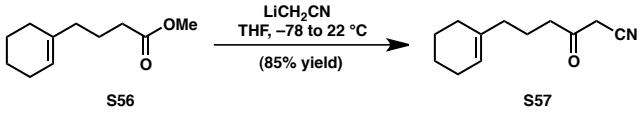
Preparation of 6-(cyclopent-1-en-1-yl)-3-oxohexanenitrile (S55)



S54 S55

Compound **S55** was synthesized according to general procedure 5. The reaction was run on 4.17 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 572 mg (78% yield) of **S55** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.34 (m, 1H), 3.45 (s, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.28 (m, 2H), 2.19 (m, 2H), 2.09 (m, 2H), 1.84 (m, 2H), 1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.45, 143.13, 124.64, 113.77, 41.56, 34.70, 32.35, 32.00, 30.03, 23.32, 21.22; FTIR (NaCl, thin film) 2947, 2844, 2260, 1729, 1444, 1403, 1306, 1085 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{14}NO$ $[M–H]^-$ 176.1081, found 176.1073.

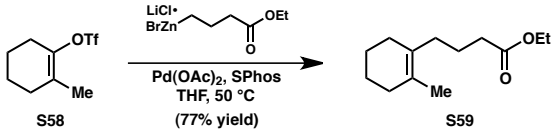
Preparation of 6-(cyclohex-1-en-1-yl)-3-oxohexanenitrile (S57)



S56 S57

Compound **S57** was synthesized according to general procedure 5 from known compound **S56**.[§§§§] The reaction was run on 1.78 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc) to give 290 mg (85% yield) of **S57** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.38 (m, 1H), 3.45 (s, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 1.95 (m, 4H), 1.87 (m, 2H), 1.73 (p, *J* = 7.2 Hz, 2H), 1.59 (m, 2H), 1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.52, 136.33, 122.29, 113.79, 41.38, 36.92, 32.01, 27.85, 25.14, 22.80, 22.35, 21.09; FTIR (NaCl, thin film) 2926, 2934, 2260, 1728, 1438, 1403, 1306, 1091 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{16}NO$ $[M–H]^-$ 190.1237, found 190.1233.

Preparation of ethyl 4-(2-methylcyclohex-1-en-1-yl)butanoate (S59)



S58 S59

Compound **S59** was synthesized according to general procedure 4. Enol triflate **S58** was synthesized according to Isamir et al[*****] and obtained as a 9:1 mixture of **S59** to the enol triflate derived from the thermodynamic enolization of 2-Me cyclohexanone. The reaction was run on 2.95 mmol scale for 3 hr. The crude material was purified by

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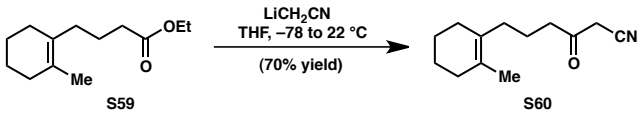
§§§§ Snider, B. B.; *J. Org. Chem.* **1974**, *39*, 255.

***** Martínez, I; Alford, P. E.; Ovaska, T. V.; *Org. Lett.* **2005** *7*, 1133

silica gel chromatography (95:5 Hexanes:EtOAc) to give 600 mg (77% yield) of **S59** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as a 5:1 mixture of alkene isomers, only major **S59** peaks are reported) δ 4.12 (q, *J* = 7.1 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.01 (m, 2H), 1.91 (m, 4H), 1.69 (m, 2H), 1.59 (s, 3H), 1.56 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 5:1 mixture of alkene isomers, only major **S59** peaks are reported) δ 173.84, 128.94, 126.94, 60.15, 34.02, 32.62, 31.82, 29.34, 23.42, 23.37, 23.33, 19.02, 14.25; FTIR (NaCl, thin film) 2927, 2858, 1737, 1447, 1372, 1245, 1155 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{23}O_2$ $[M+H]^+$ 211.1693, found 211.1697.

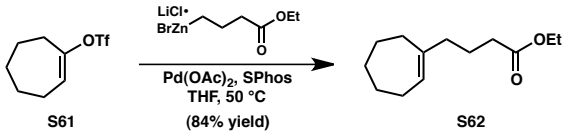
Preparation of 6-(2-methylcyclohex-1-en-1-yl)-3-oxohexanenitrile (S60)



Compound **S60** was synthesized according to general procedure 5. The reaction was run on 1.66 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (8:2 Hexanes:EtOAc), and followed by recrystallization from 99:1 Hexanes:EtOAc, afforded 230 mg (70% yield) of **S60** as a wispy white solid. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as a 93:7 mixture of alkene isomers, only major **S60** peaks are reported) δ 3.44 (s, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.02 (t, *J* = 7.7 Hz, 2H), 1.91 (m, 4H), 1.71 (m, 2H), 1.59 (s, 3H), 1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as a 93:7 mixture of alkene isomers, only major **S60** peaks are reported) δ 197.53, 128.51, 127.49, 113.79, 41.67, 32.14, 31.93, 31.76, 29.24, 23.31, 23.22, 21.71,

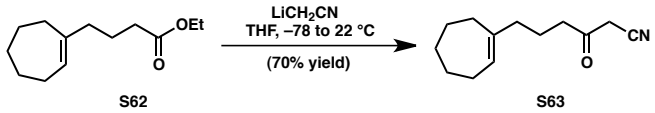
19.09; FTIR (NaCl, thin film) 2924, 2858, 2260, 1730, 1448, 1403, 1371, 1306, 1077 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{18}NO$ $[M–H]^-$ 204.1394, found 204.1387.

Preparation of ethyl 4-(cyclohept-1-en-1-yl)butanoate (S62)



Compound **S62** was synthesized according to general procedure 4. The reaction was run on 5.10 mmol scale for 0.5 hr. The crude material was purified by silica gel chromatography (95:5 Hexanes:Et_2O) to give 900 mg (84% yield) of **S62** as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.53 (tt, J = 6.5, 1.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.26 (m, 2H), 2.05 (m, 4H), 1.98 (m, 2H), 1.70 (m, 4H), 1.44 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.80, 143.50, 126.80, 60.10, 39.50, 33.74, 32.61, 32.52, 28.27, 27.30, 26.81, 23.11, 14.22; FTIR (NaCl, thin film) 2919, 2847, 1737, 1446, 1372, 1244, 1169 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{23}O_2$ $[M+H]^+$ 211.1693, found 211.1691.

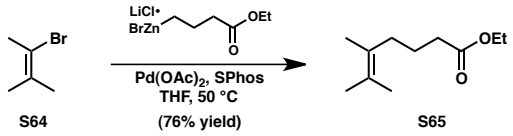
Preparation of 6-(cyclohept-1-en-1-yl)-3-oxohexanenitrile (S63)



Compound **S63** was synthesized according to general procedure 5. The reaction was run on 3.57 mmol scale for 1 hr. The crude material was purified by silica gel

chromatography (8:2 Hexanes:EtOAc) to give 510 mg (70% yield) of **S63** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.52 (tt, *J* = 6.4, 1.2 Hz, 1H), 3.45 (s, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.05 (m, 4H), 1.97 (m, 2H), 1.71 (m, 4H), 1.44 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.54, 143.11, 127.37, 113.78, 41.34, 39.02, 32.50, 32.34, 32.04, 28.21, 27.23, 26.74, 21.29; FTIR (NaCl, thin film) 2919, 2846, 2260, 1729, 1446, 1403, 1306, 1091 cm^{-1}; HRMS (MM) calc'd for $C_{13}H_{18}NO$ $[M–H]^-$ 204.1394, found 204.1397.

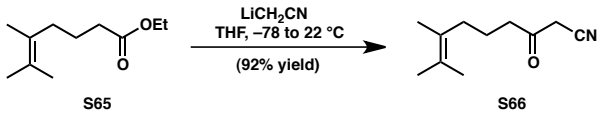
Preparation of ethyl 5,6-dimethylhept-5-enoate (S65)



S64 S65

Compound **S65** was synthesized according to general procedure 4. The reaction was run on 3.63 mmol scale for 2.5 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 510 mg (76% yield) of **S65** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.11 (q, *J* = 7.1 Hz, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.05 (m, 2H), 1.68 (m, 2H), 1.62 (m, 9H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.81, 126.65, 124.91, 60.14, 33.91, 33.60, 23.35, 20.54, 20.11, 18.16, 14.23; FTIR (NaCl, thin film) 2981, 2917, 2862, 1737, 1457, 1372, 1243, 1173 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{21}O_2$ $[M+H]^+$ 185.1536, found 185.1540.

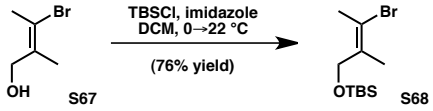
Preparation of 7,8-dimethyl-3-oxonon-7-enenitrile (S66)



S65 S66

Compound **S66** was synthesized according to general procedure 5. The reaction was run on 1.47 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 253 mg (92% yield) of **S66** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.45 (s, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.04 (t, J = 7.6 Hz, 2H), 1.70 (m, 2H), 1.63 (br s, 6H), 1.60 (m, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.55, 126.21, 125.46, 113.80, 41.54, 33.07, 31.92, 21.67, 20.52, 20.18, 18.06; FTIR (NaCl, thin film) 2987, 2918, 2862, 2260, 1730, 1451, 1372, 1306, 1084 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{16}NO$ $[M+H]^+$ 178.1237, found 178.1248.

Preparation of bromo alkene (S68)



S67 S68

To a 250 mL round bottom flask was added allylic alcohol **S67**[†††††] (2.40 g, 14.5 mmol), dichloromethane (100 mL), and imidazole (1.20 g, 1.75 mmol). The clear colorless solution was cooled to 0 °C in an ice bath and *tert*-butyldimethylsilyl chloride (2.40 g, 16.0 mmol) was added in one portion. A mild exotherm occurred and a white

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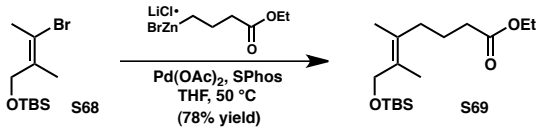
[†††††] Curran, D. P.; Kuo, S. C.; *Tetrahedron* **1987**, *43*, 5653.

solid rapidly precipitated. The reaction was warmed to room temperature and stirred for 16 hr. The reaction was quenched with water and the organic phase was separated and washed successively with 1M HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography (100% hexanes), yielding bromo alkene **S68** (3.50 g, 10:1 *E*:*Z* ratio, 63% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 4.16 (s, 2H), 2.34 (m, 3H), 1.89 (q, *J* = 1.5 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 133.92, 119.61, 62.70, 25.85, 24.94, 20.86, 18.32, -5.32; FTIR (NaCl, thin film) 2954, 2928, 2856, 2884, 1471, 1372, 1254, 1086, 1056 cm^{-1}; HRMS (EI+) calc'd for $C_{11}H_{22}OSi^{81}Br$ $[M+H]^+–H_2$ 279.0603, found 279.0598.

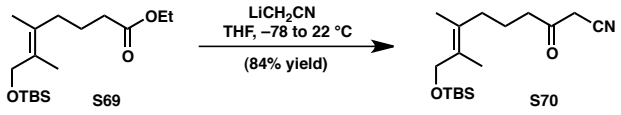
Preparation of ethyl ester (S69)



Compound **S69** was synthesized according to general procedure 4. The reaction was run on 3.25 mmol scale for 4 hr. The crude material was purified by silica gel chromatography (9.5:0.5 Hexanes:EtOAc) to give 800 mg (78% yield) of **S69** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 4.13 (m, 4H), 2.28 (t, *J* = 7.5

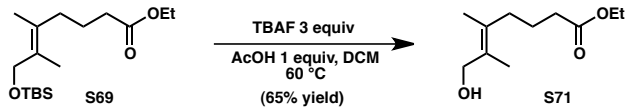
Hz, 2H), 2.06 (m, 2H), 1.68 (m, 8H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 173.71, 129.42, 129.03, 63.87, 60.20, 34.05, 33.96, 25.97, 22.99, 18.42, 17.73, 15.41, 14.24, -5.21; FTIR (NaCl, thin film) 2955, 2929, 2856, 1737, 1471, 1372, 1251, 1163 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{19}O_2$ $[M–OTBS]^+$ 183.1380, found 183.1384.

Preparation of b-ketonitrile (S70)



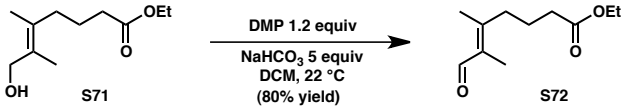
Compound **S70** was synthesized according to general procedure 5. The reaction was run on 2.39 mmol scale for 3 hr. The crude material was purified by silica gel chromatography (9:1 Hexanes:EtOAc) to give 622 mg (84% yield) of **S70** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 4.13 (s, 2H), 3.44 (s, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.07 (m, 2H), 1.74 (m, 2H), 1.68 (m, 3H), 1.66 (m, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 197.39, 129.55, 129.00, 113.76, 63.79, 41.46, 33.49, 31.98, 25.96, 21.24, 18.41, 17.59, 15.60, -5.24; FTIR (NaCl, thin film) 2953, 2928, 2856, 2260, 1732, 1462, 1371, 1254, 1067 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{16}NO$ $[M–OTBS]^+$ 178.1226, found 178.1234.

Preparation of (*E*)-ethyl 7-hydroxy-5,6-dimethylhept-5-enoate (S71)



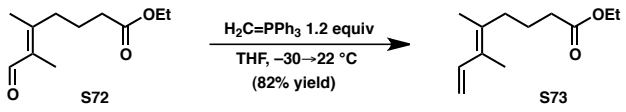
To the ester (**S69**, 1.25 g, 3.98 mmol) in a 100 mL round bottom flask was added in succession DCM (15 mL), acetic acid (0.24 mL, 3.98 mmol) and tetra-*n*-butylammonium fluoride (12 mL, 1M THF solution, 11.9 mmol). The clear, colorless reaction was heated to 60 °C for 18 hours open to air, at which point TLC analysis indicated full consumption of the starting material. The volatiles were concentrated *in vacuo*, and the residue was purified by flash chromatography (0→25→40% EtOAc/hexanes), yielding allylic alcohol **S71** (520 mg, 65% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 4.12 (m, 4H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.07 (m, 2H), 1.73 (m, 8H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 173.63, 132.06, 128.66, 63.98, 60.26, 33.93, 33.92, 22.93, 17.72, 16.21, 14.23; FTIR (NaCl, thin film) 3420, 2977, 2935, 2863, 1734, 1447, 1373, 1160 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{19}O_2$ $[M–OH]^+$ 183.1380, found 183.1382.

Preparation of (*E*)-ethyl 5,6-dimethyl-7-oxohept-5-enoate (S72)



To a 25 mL round bottom flask was added the allylic alcohol (**S71**, 170 mg, 0.865 mmol) followed by DCM (15 mL) and sodium bicarbonate (363 mg, 4.33 mmol). Dess-Martin periodinane (440 mg, 1.04 mmol) was charged and the slurry was stirred vigorously at 22 °C open to air. After 15 minutes TLC analysis indicated full consumption of the starting material. The reaction was diluted with hexanes (10 mL), filtered, and the filtrate was concentrated *in vacuo*. The white solid residue was purified by flash chromatography (0→15% EtOAc/hexanes), yielding enal **S72** (135 mg, 80% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 10.13 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.30 (m, 2H), 2.18 (q, *J* = 1.4 Hz, 3H), 1.79 (m, 2H), 1.74 (q, *J* = 1.4 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 191.47, 172.97, 156.84, 132.61, 60.43, 36.25, 33.78, 22.30, 17.16, 14.19, 10.55; FTIR (NaCl, thin film) 2980, 2936, 2872, 1732, 1667, 1447, 1373, 1172 cm^{-1}; HRMS (MM) calc'd for $C_{11}H_{18}O_3$ $[M–OH]^+$ 199.1329, found 199.1328.

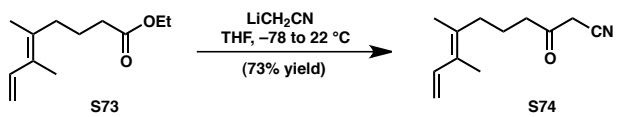
Preparation of (*E*)-ethyl 5,6-dimethylocta-5,7-dienoate (S73)



To an oven-dried 25 mL round bottom flask was added $MePPh_3Br$ (353 mg, 0.990 mmol), and the headspace was purged with N_2. The solid was slurried in THF (5 mL) and the mixture was cooled to –30 °C in a dry ice/acetone bath. *n*-Butyllithium (400 mL,

2.1M hexanes, 0.850 mmol) was added dropwise, resulting in dissolution of the solids and the formation of a clear bright yellow solution. The flask was warmed briefly to 22 °C and re-cooled to –30 °C. In a conical 10 mL round bottom flask a THF (5 mL) solution of enal **S72** (140 mg, 0.707 mmol) was cannula transferred to the phosphorane at –30 °C. During the addition the yellow color of the Wittig reagent dissipated, and upon completion of the transfer the reaction was warmed to 22 °C for 10 minutes. After TLC analysis indicated full consumption of the starting material, the reaction was quenched with 200 mL of acetic acid and diluted with hexanes (20 mL). The white slurry was filtered through celite, and the filtrate was concentrated *in vacuo*. The white solid residue was purified by flash chromatography (0→10% EtOAc/hexanes), yielding diene **S73** (113 mg, 82% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 6.82 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.12 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.99 (dd, *J* = 10.9, 1.6 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.25 (m, 2H), 2.18 (m, 2H), 1.81 (q, *J* = 1.4 Hz, 3H), 1.74 (m, 5H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 173.59, 135.89, 134.36, 127.51, 111.63, 60.24, 34.83, 33.94, 23.20, 18.19, 14.24, 13.31; FTIR (NaCl, thin film) 3088, 2980, 2934, 2869, 1736, 1373, 1173 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{21}O_2$ $[M+H]^+$ 197.1536, found 197.1533.

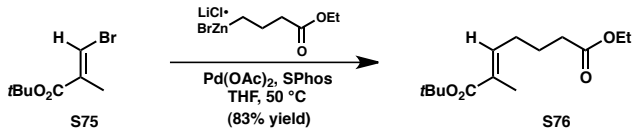
Preparation of (*E*)-7,8-dimethyl-3-oxodeca-7,9-dienenitrile (S74)



S73 S74

Compound **S74** was synthesized according to general procedure 5. The reaction was run on 0.58 mmol scale for 1 hr. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 80 mg (73% yield) of **S74** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 6.80 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.14 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.02 (dd, *J* = 10.9, 1.5 Hz, 1H), 3.44 (s, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 2.18 (m, 2H), 1.80 (q, *J* = 1.4 Hz, 3H), 1.76 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz, compound exists as an inseparable 10:1 *E*:*Z* mixture of alkene isomers, only major peaks are reported) δ 197.24, 135.67, 133.74, 127.89, 113.71, 112.13, 41.50, 34.29, 31.99, 21.49, 18.11, 13.43; FTIR (NaCl, thin film) 3020, 2921, 2871, 2261, 1732, 1446, 1376, 1307 cm^{-1}; HRMS (MM) calc'd for $C_{12}H_{16}NO$ $[M–H]^-$ 190.1237, found 190.1235.

Preparation of (*E*)-1-*tert*-butyl 7-ethyl 2-methylhept-2-enedioate (S76)



Compound **S76** was synthesized according to general procedure 4. Bromo ester **S75** was synthesized according to the procedure of Zhang et al.[‡‡‡‡‡] The reaction was run on 11.3 mmol scale for 0.5 hr. The crude material was purified by silica gel chromatography (9.5:0.5 Hexanes:EtOAc) to give 2.60 g (83% yield) of **S76** as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.62 (tq, *J* = 7.5, 1.5 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H),

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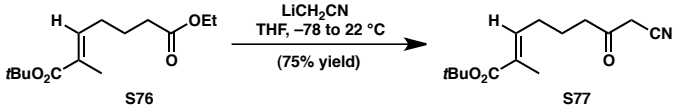
[‡‡‡‡‡] Li, X.; Zeng, X.; *Tett. Lett.* **2006**, *47*, 6839.

2.32 (t, *J* = 7.4 Hz, 2H), 2.19 (q, *J* = 7.4 Hz, 2H), 1.78 (m, 5H), 1.48 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.26, 167.36, 139.61, 130.03, 80.01, 60.30, 33.72, 28.08, 27.91, 23.86, 14.21, 12.38; FTIR (NaCl, thin film) 2978, 2933, 2868, 1734, 1700, 1457, 1368, 1251, 1159 cm^{-1}; HRMS (MM) calc'd for $C_{10}H_{15}O_4$ [M•–*t*Bu]$^-$ 199.0976, found 199.0975.

Preparation of (*E*)-*tert*-butyl 8-cyano-2-methyl-7-oxooct-2-enoate (S77)



Compound **S77** was synthesized according to general procedure 5. The reaction was run on 1.04 mmol scale for 5 minutes at –78 °C, after which time it was immediately quenched with acetic acid (140 mL, 2.28 mmol), and then subjected to the normal workup of procedure 5. The crude material was purified by silica gel chromatography (7:3 Hexanes:EtOAc) to give 195 mg (75% yield) of **S77** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.58 (tq, *J* = 7.5, 1.5 Hz, 1H), 3.45 (s, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.19 (m, 2H), 1.78 (m, 5H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 196.98, 167.22, 138.89, 130.52, 113.63, 80.22, 41.36, 31.99, 28.07, 27.43, 22.13, 12.47; FTIR (NaCl, thin film) 2977, 2933, 2259, 1731, 1699, 1457, 1368, 1291, 1159 cm^{-1}; HRMS (MM) calc'd for $C_{14}H_{22}NO_3$ [M+H]$^+$ 252.1594, found 252.1588.

4.6 NOTES AND REFERENCES

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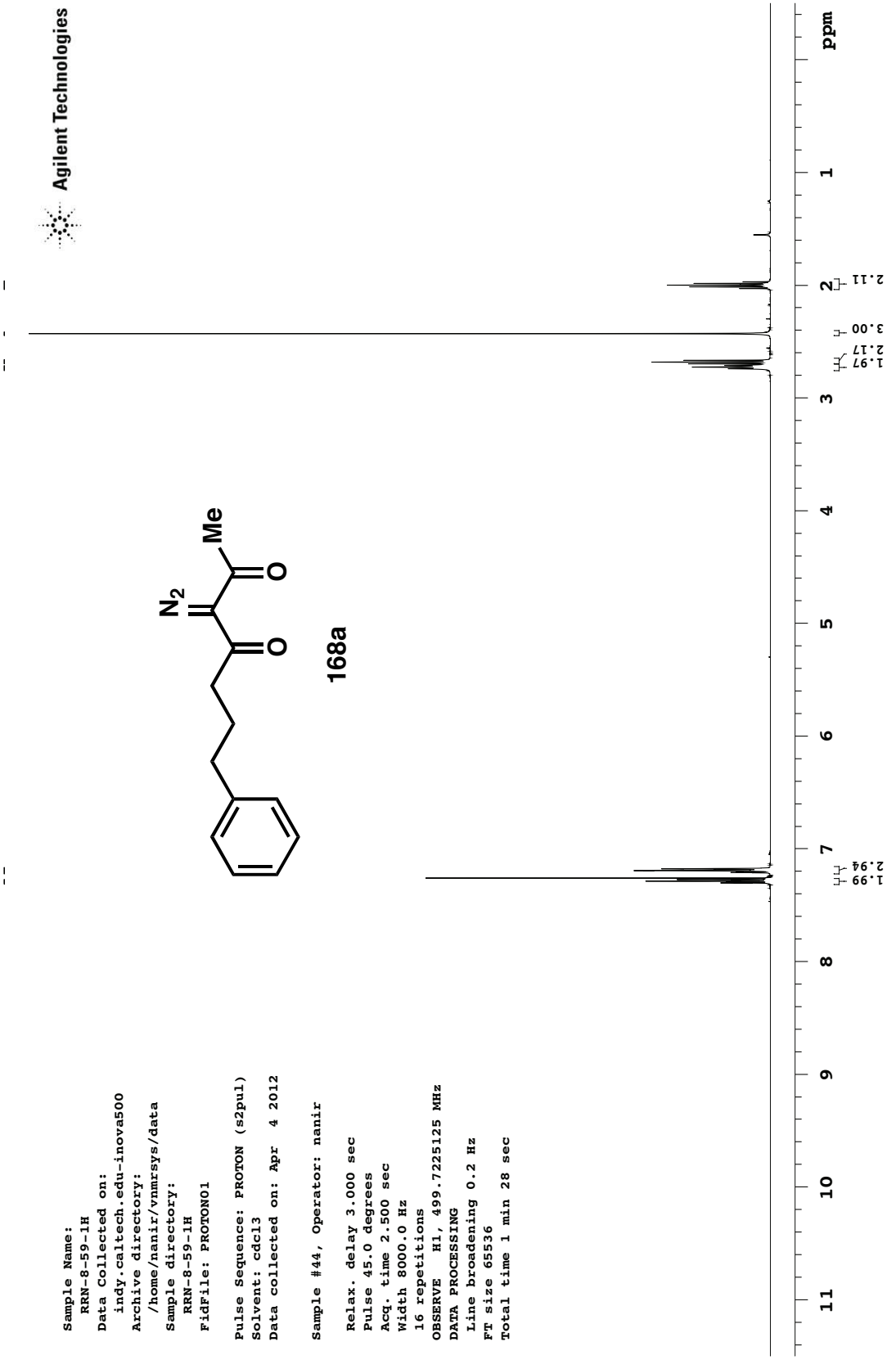
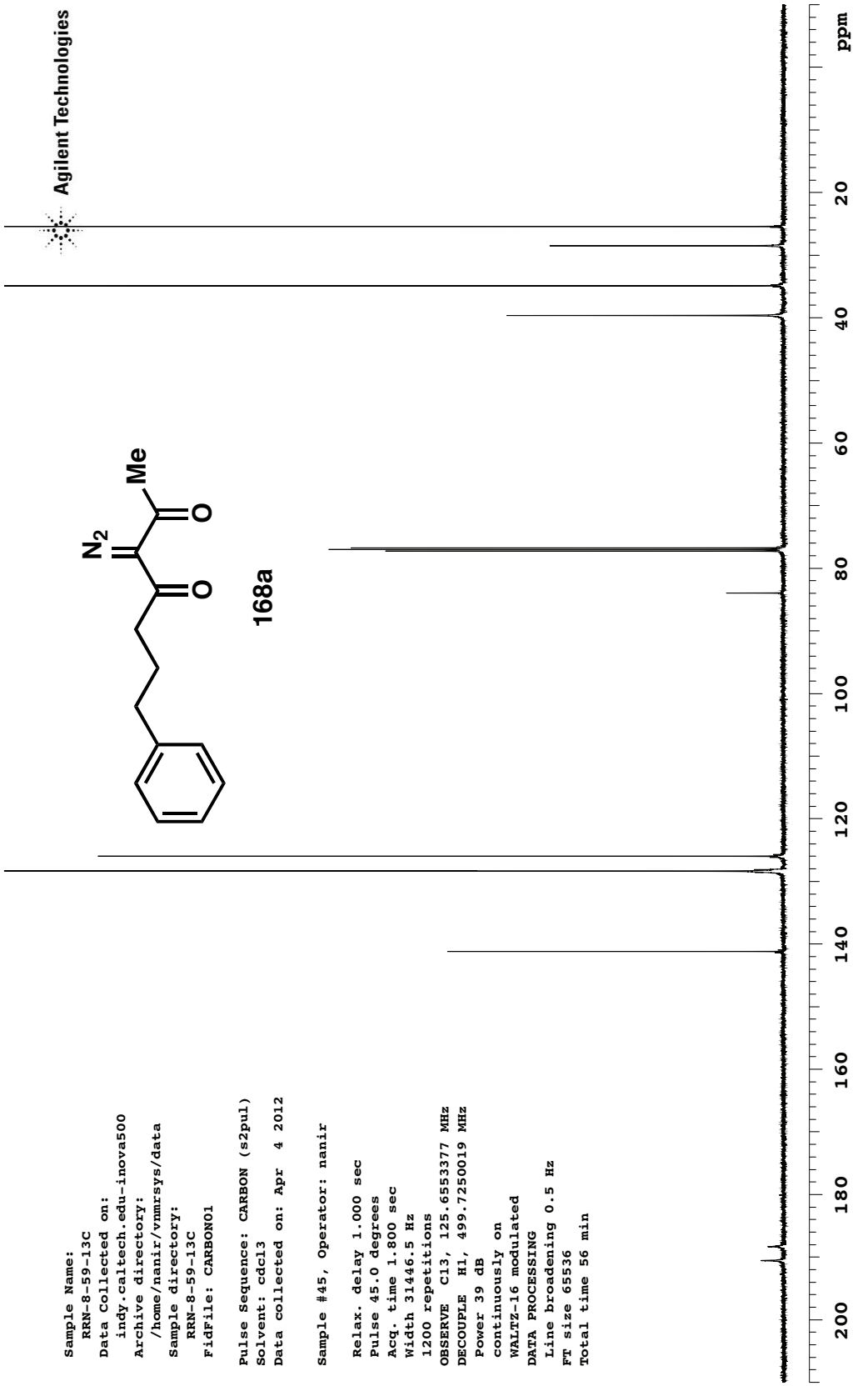
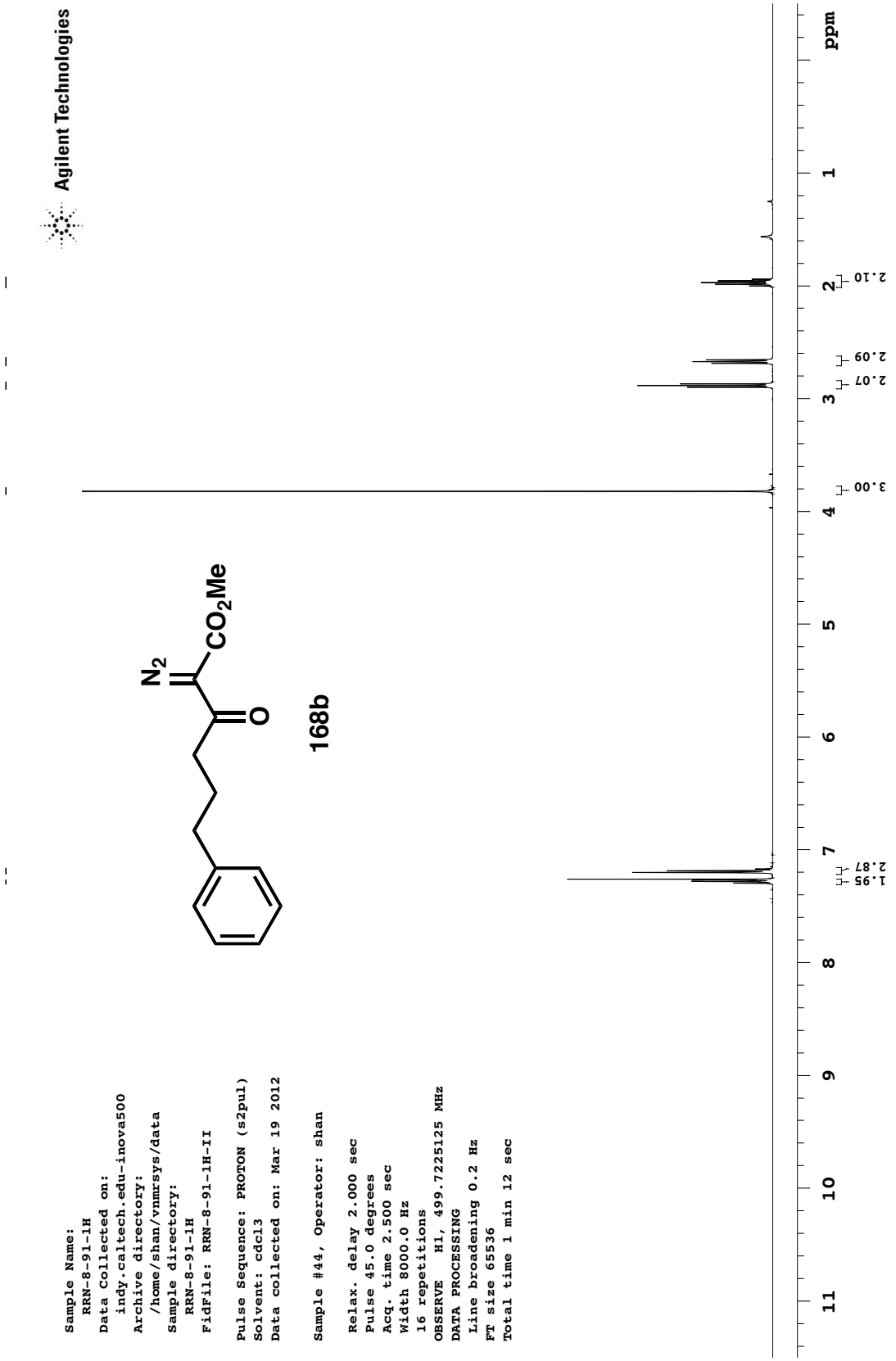
Appendix 3

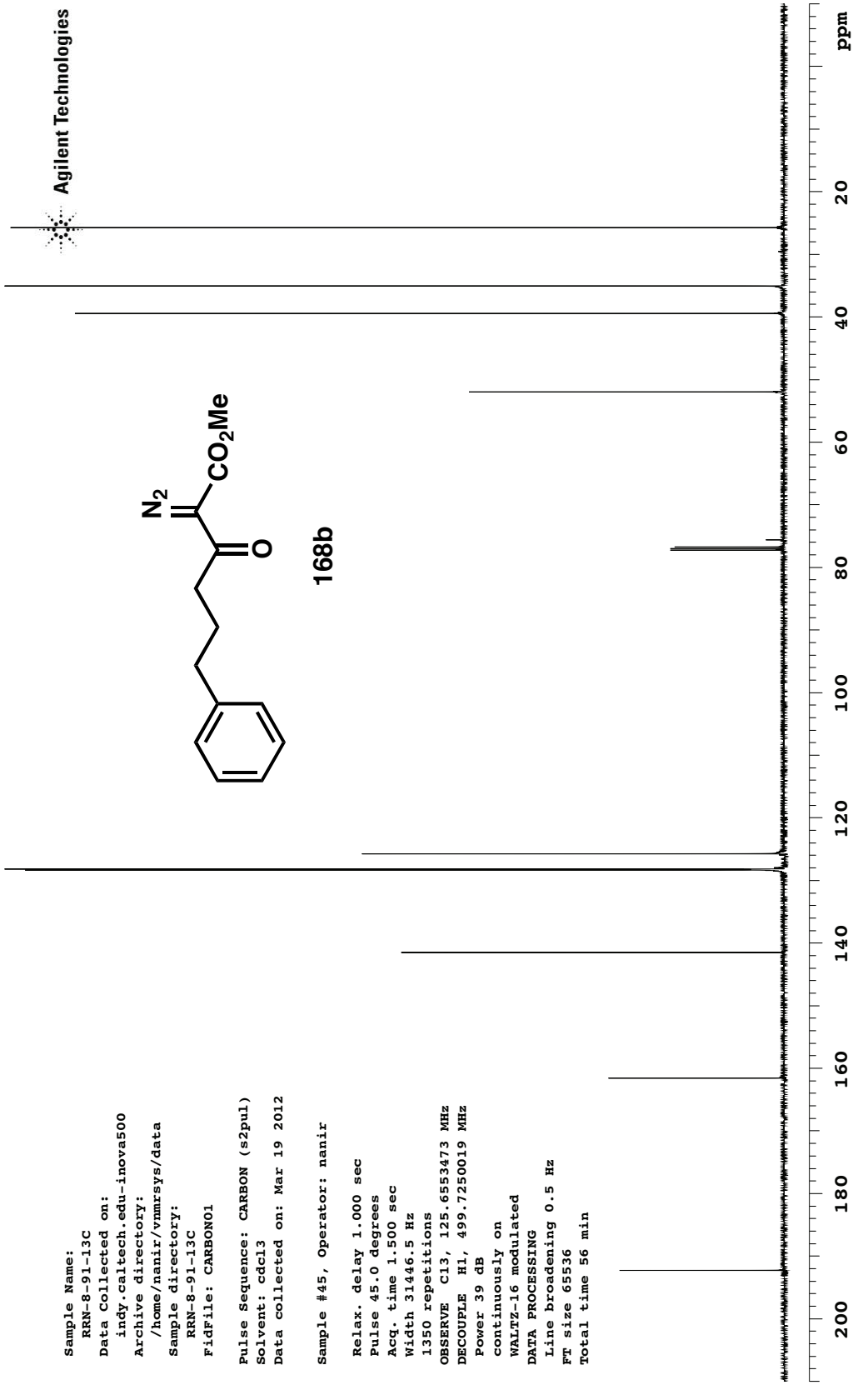
Spectra Relevant to Chapter 4:

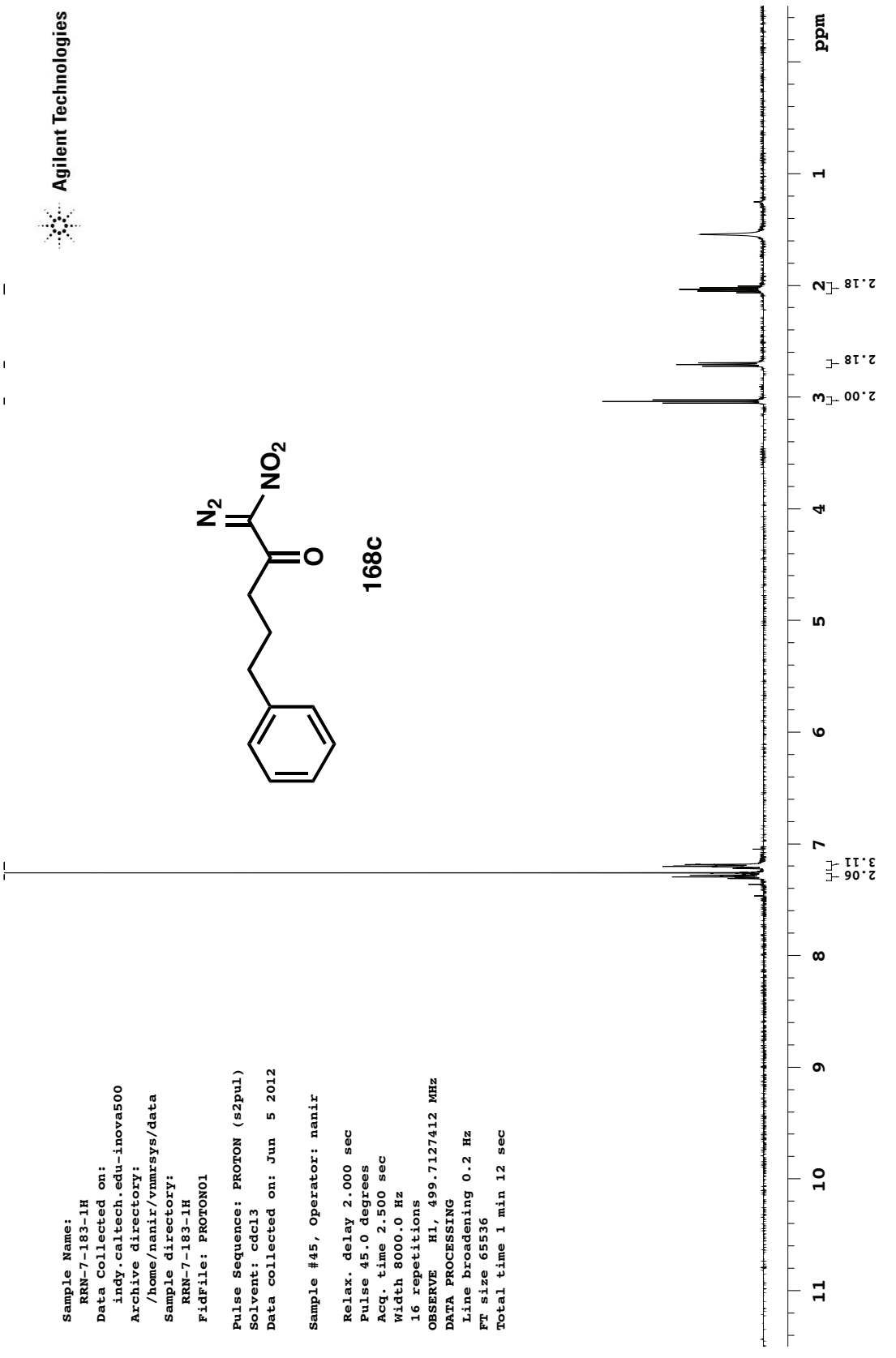
Intramolecular Cyclopropanations of α-Diazo-β-Ketonitriles

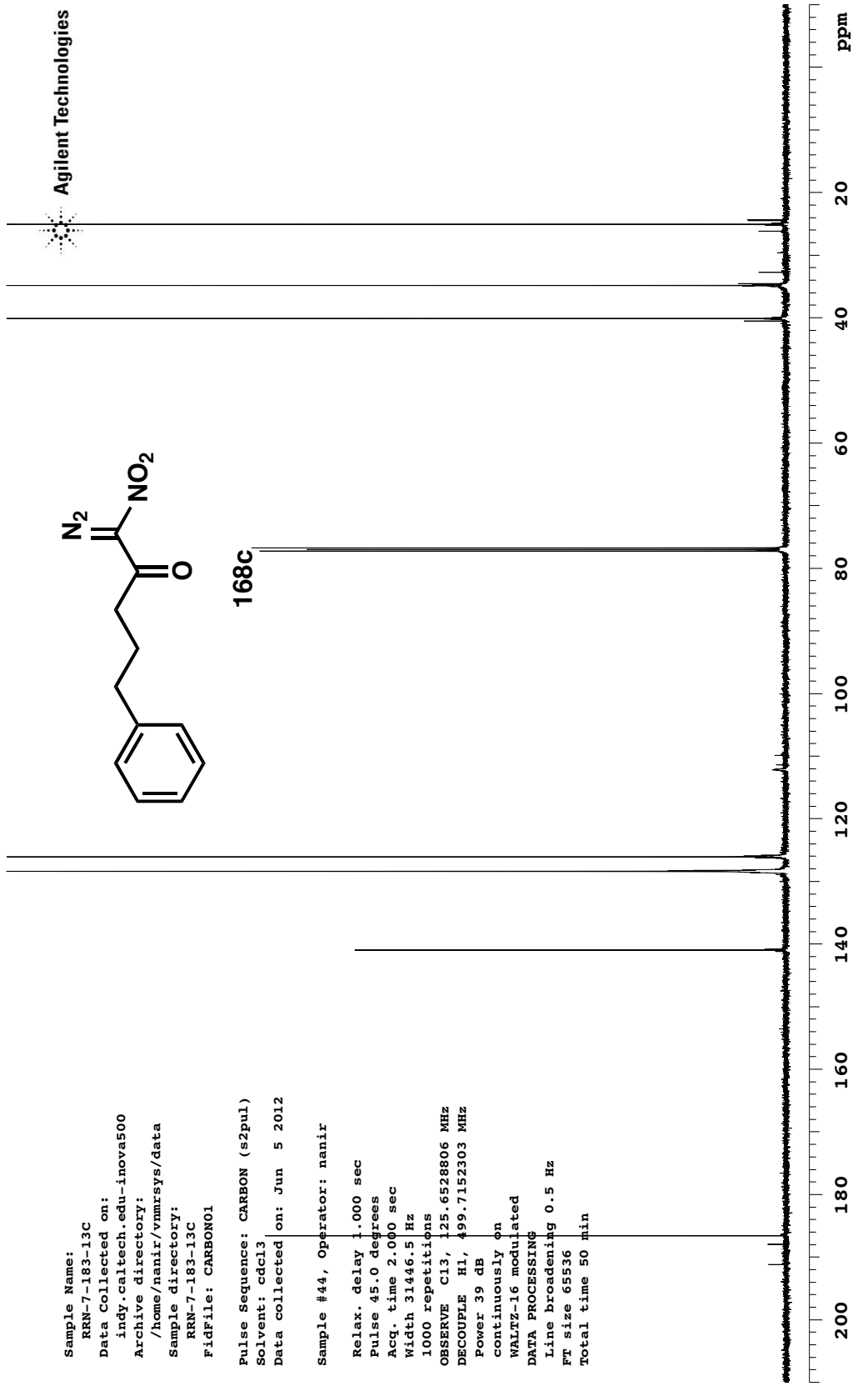

Agilent Technologies
Me
O
O
N_2
O
168a
2.11
3.00
2.17
1.97
1.99
2.94
ppm
Sample Name:
RRN-8-59-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-59-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 4 2012
Sample #44, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
Plotname: --Not assigned--

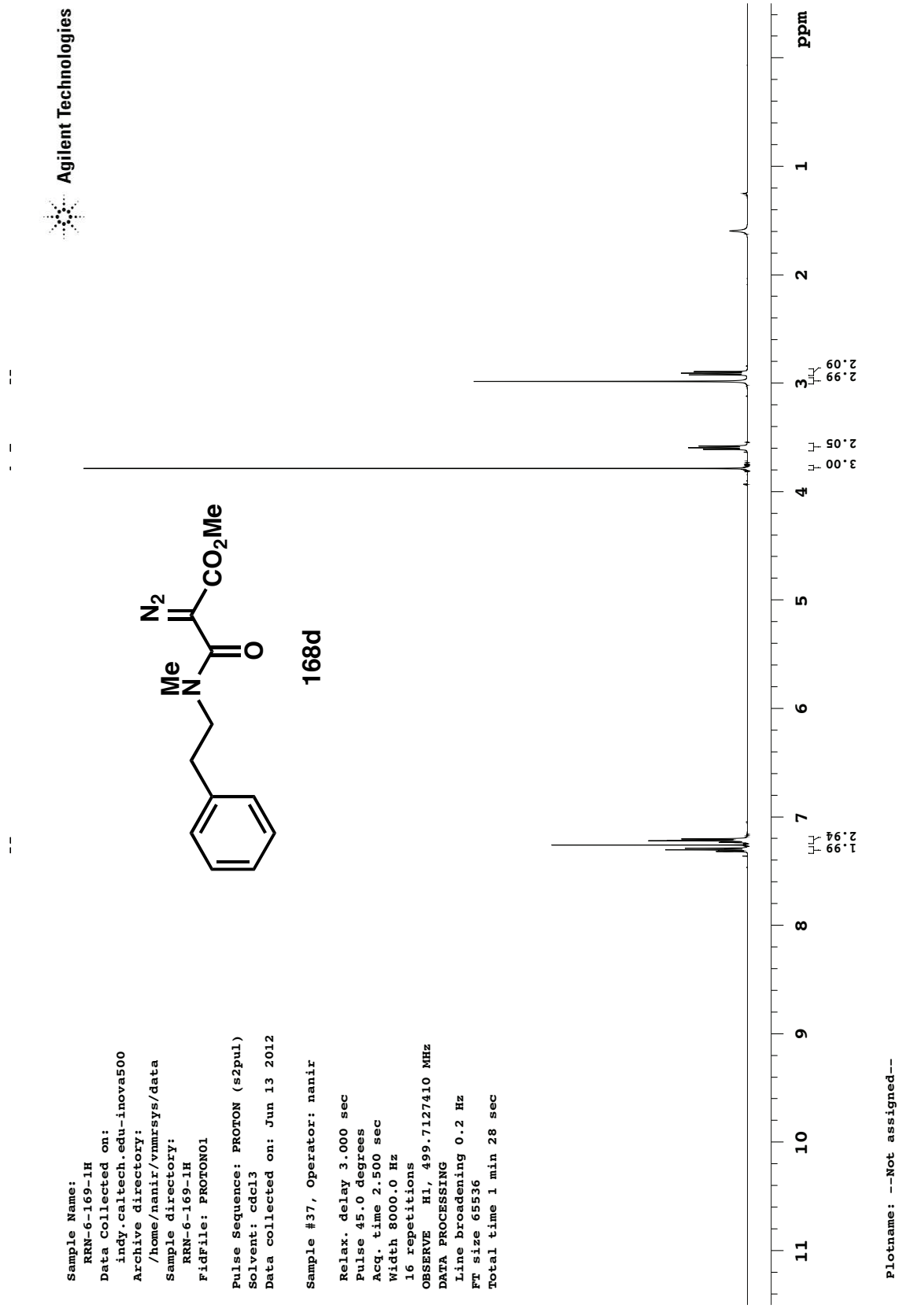

Agilent Technologies
Me
O
O
N_2
168a
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-8-59-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-59-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 4 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6553377 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
Plotname: --Not assigned--


Agilent Technologies
Sample Name:
RRN-8-91-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/shan/vnmrsys/data
Sample directory:
RRN-8-91-1H
FidFile: RRN-8-91-1H-II
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 19 2012
Sample #44, Operator: shan
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
N_2
CO_2Me
O
168b
2.10
2.09
2.07
3.00
1.95
2.87
ppm


Agilent Technologies
N_2
CO_2Me
O
168b
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-8-91-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-91-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 19 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
1350 repetitions
OBSERVE C13, 125.6553473 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
Plotname: --Not assigned--


Agilent Technologies
Sample Name:
RRN-7-183-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-183-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2012
Sample #45, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127412 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
N2
NO2
O
168c
2.06
3.11
2.00
2.18
2.18
ppm
Plotname: --Not assigned--


Agilent Technologies
N_2
NO_2
O
168c
ppm
200
180
160
140
120
100
80
60
40
20
Sample Name:
RRN-7-183-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-183-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6528806 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 50 min
Plotname: --Not assigned--


Agilent Technologies
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RRN-6-169-1H
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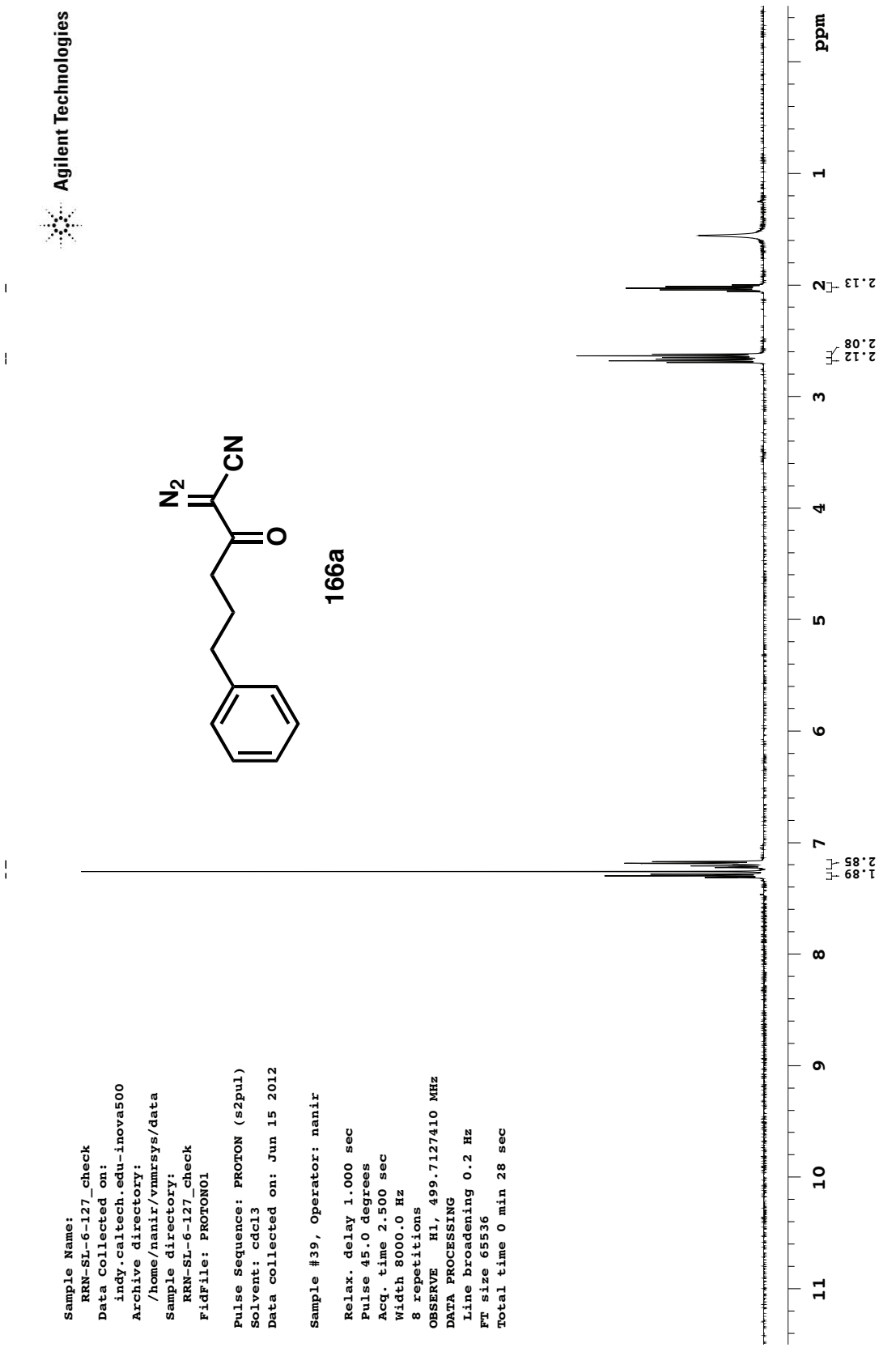
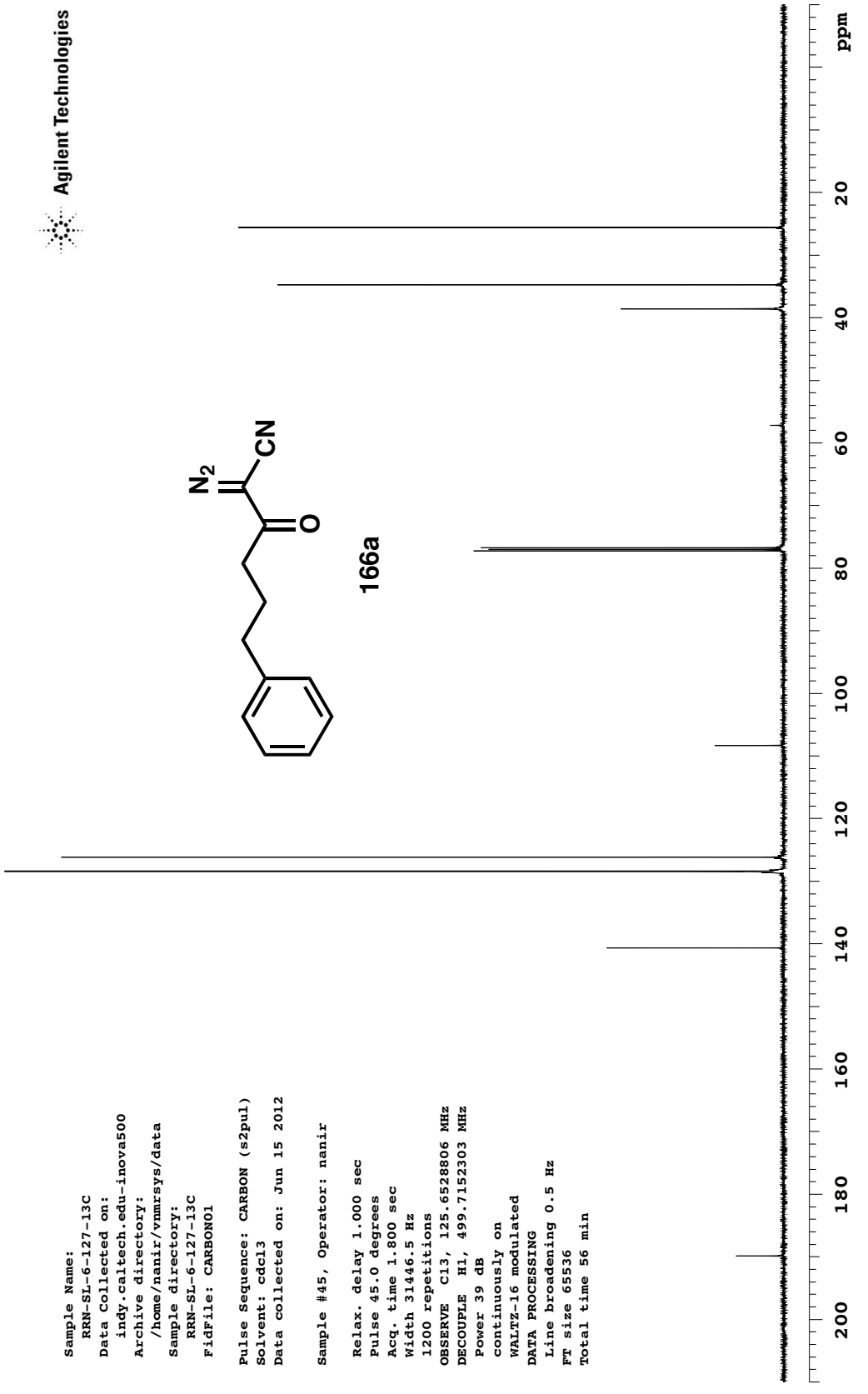
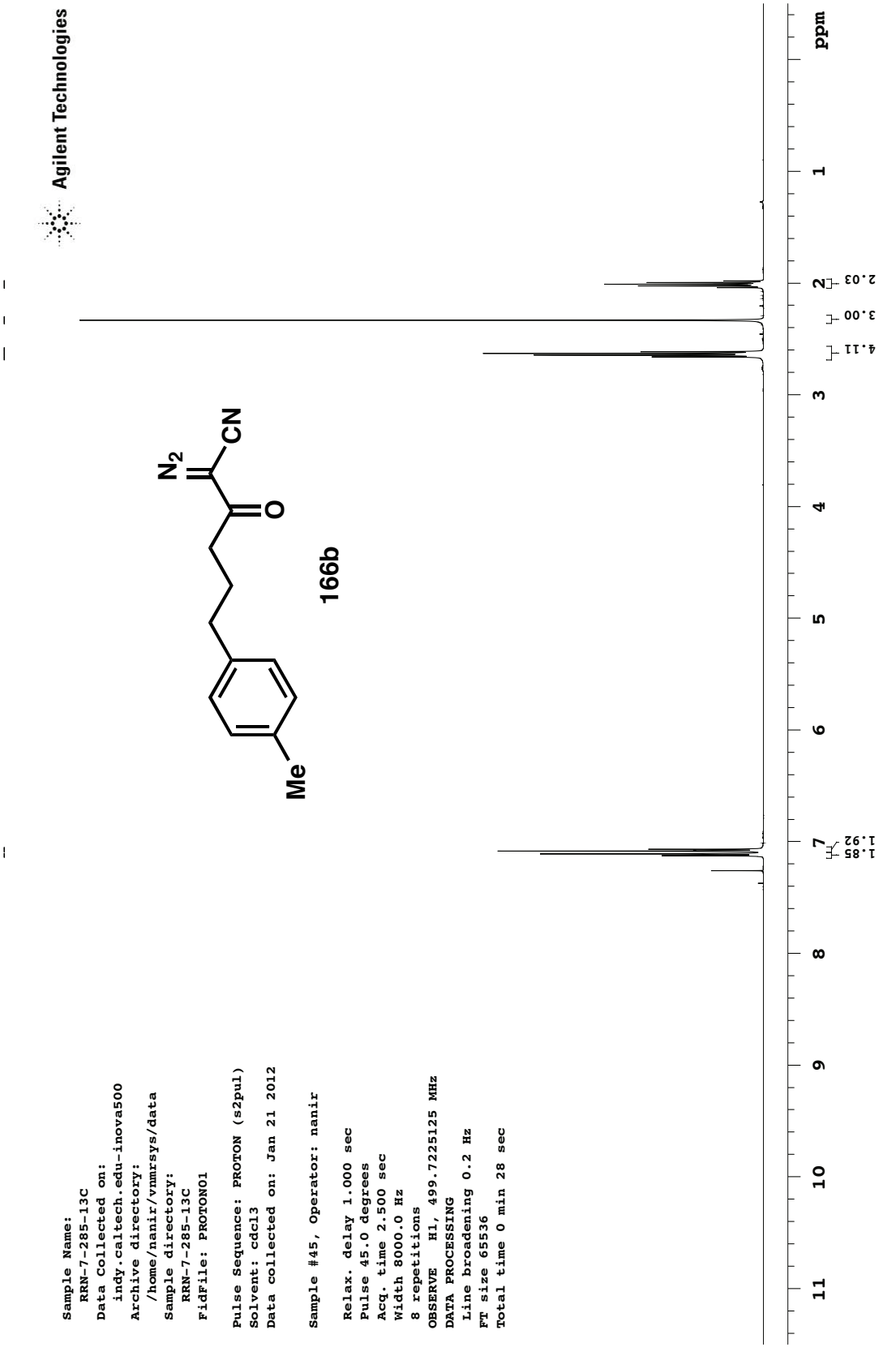
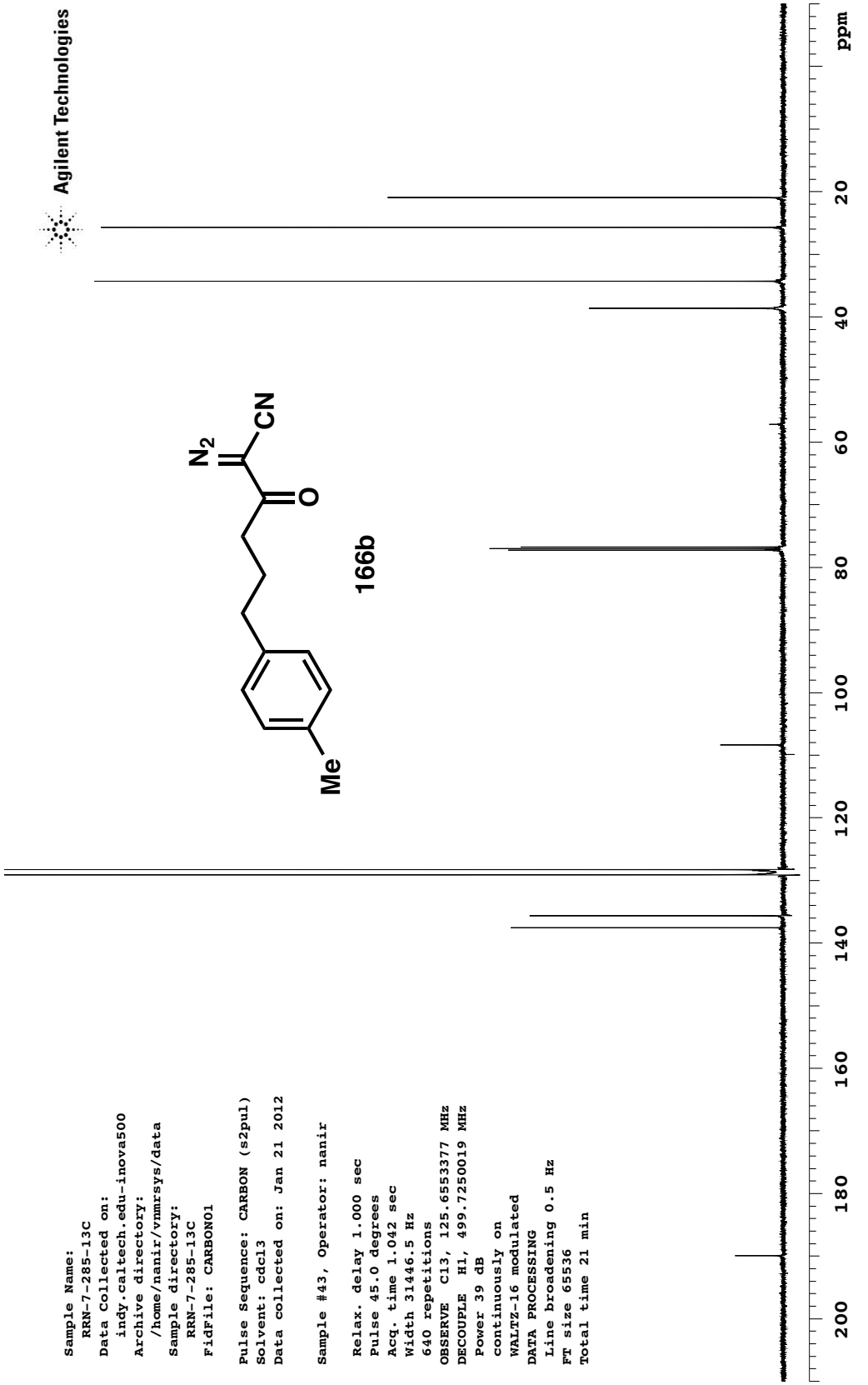
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 13 2012
Sample #37, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
Me
N
O
N2
CO2Me
168d
1.99
2.94
3.00
2.05
2.99
2.09
ppm
Plotname: --Not assigned--

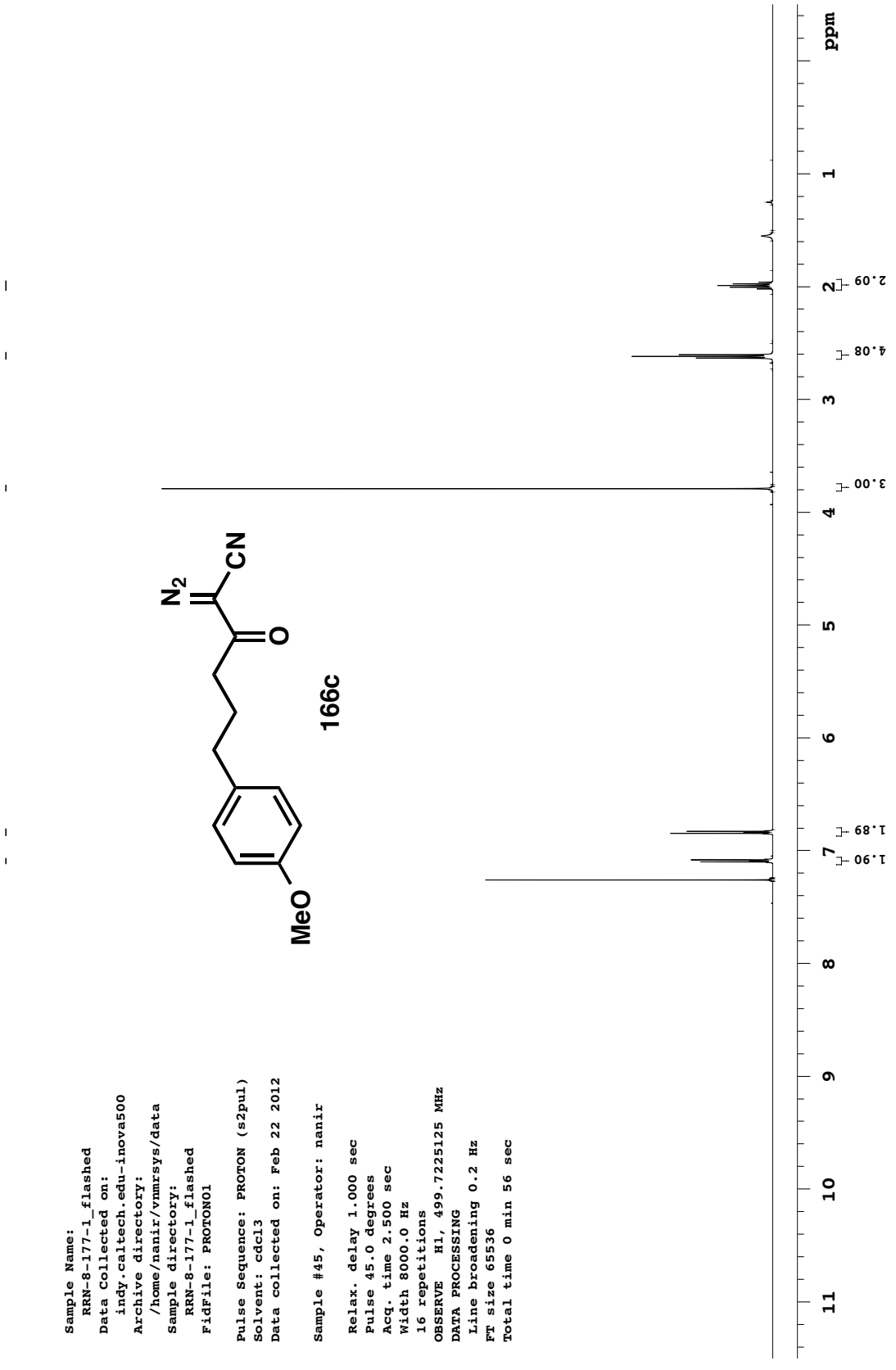
Agilent Technologies
Sample Name:
RRN-6-169-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-169-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 13 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.900 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528777 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
Me
N
N2
CO2Me
O
168d
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

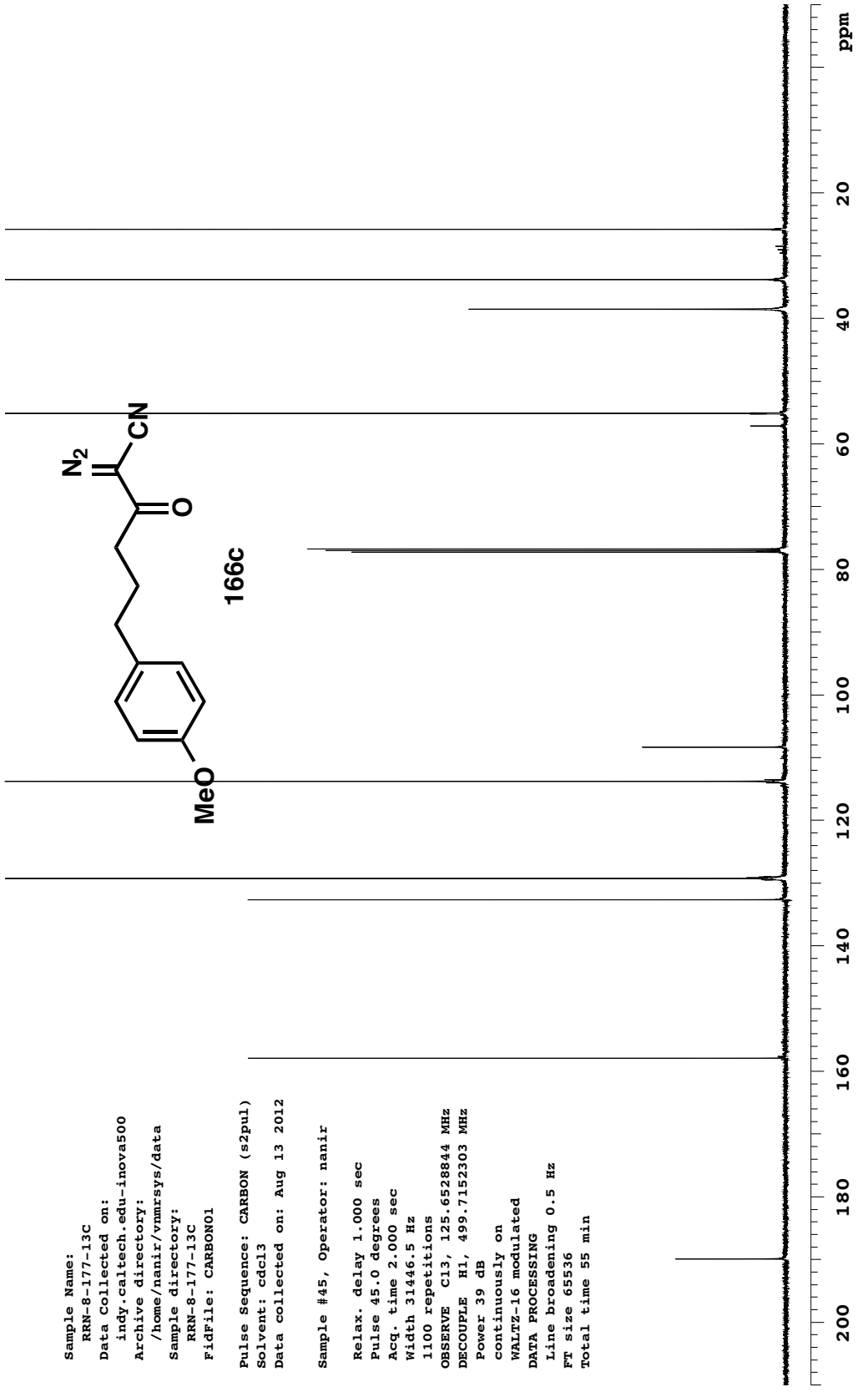

Agilent Technologies
Sample Name:
RRN-SL-6-127_check
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-SL-6-127_check
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 15 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
N2
CN
O
166a
1.89
2.85
2.08
2.12
2.13
ppm
Plotname: --Not assigned--

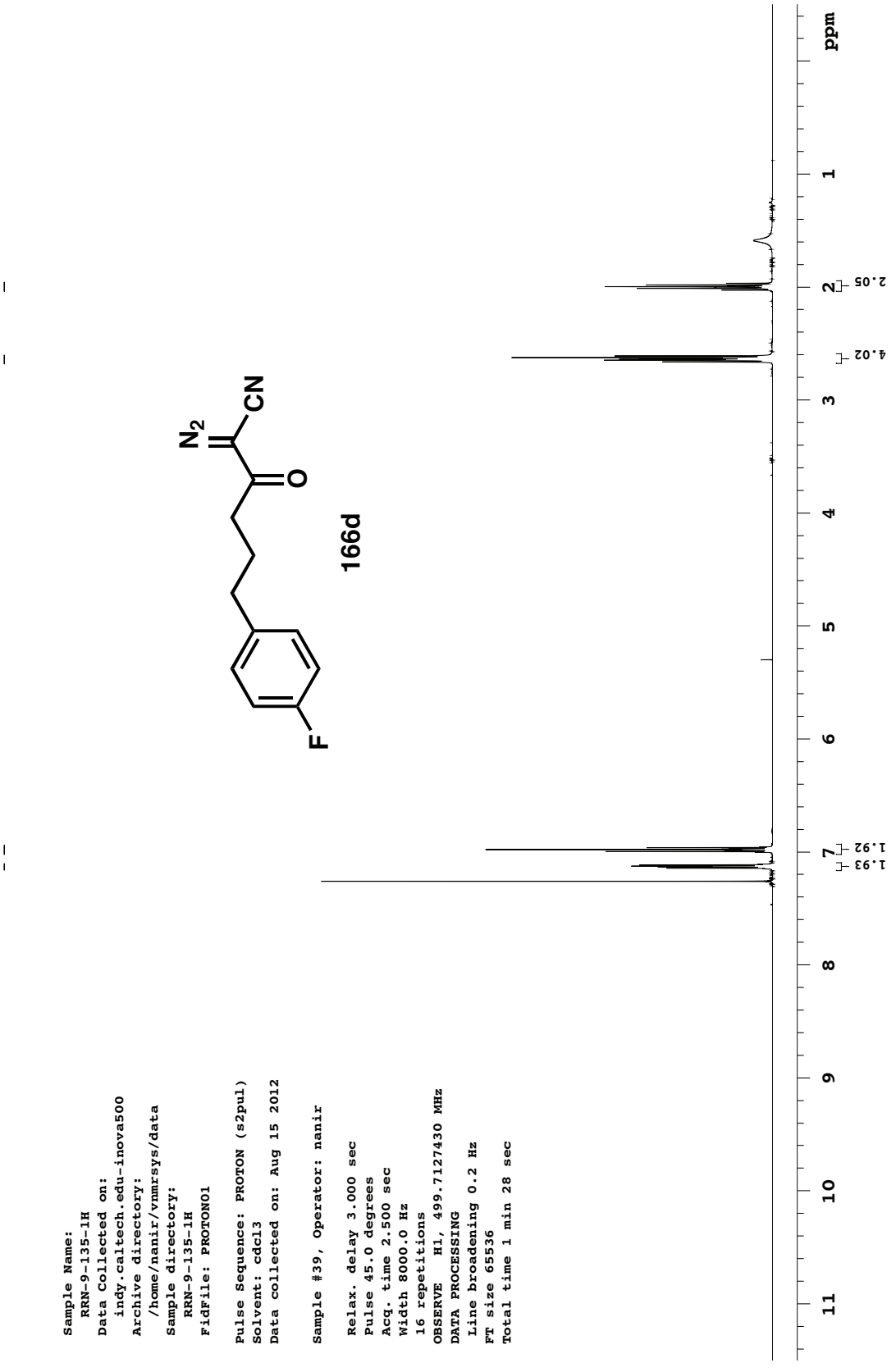

Agilent Technologies
Sample Name:
RRN-SL-6-127-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-SL-6-127-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 15 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528806 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
N2
CN
O
166a
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

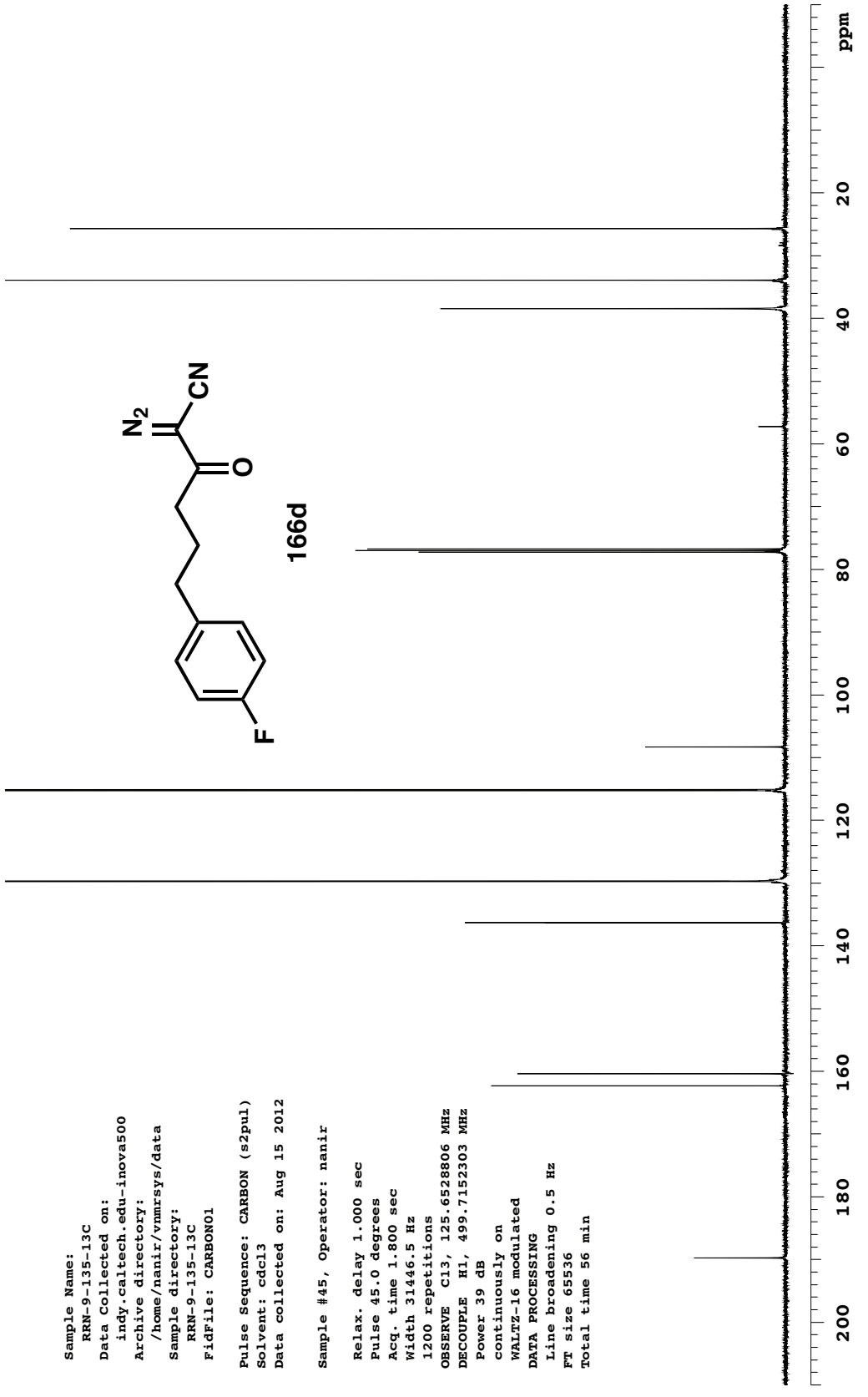

Agilent Technologies
Sample Name:
RRN-7-285-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-285-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
N2
CN
O
Me
166b
2.03
3.00
4.11
1.85
1.92
ppm
Plotname: --Not assigned--

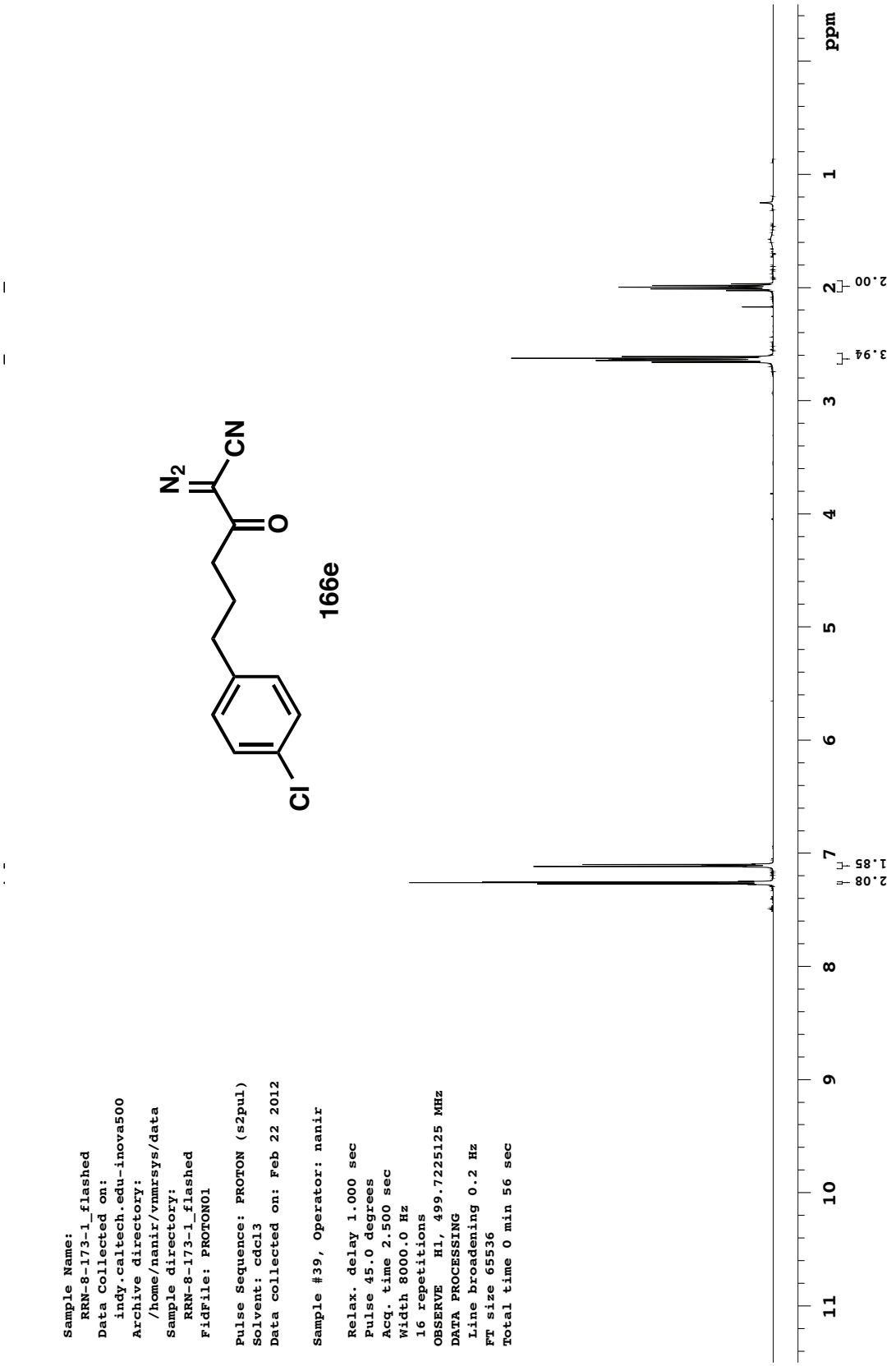

Agilent Technologies
Sample Name:
RRN-7-285-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-285-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2012
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
640 repetitions
OBSERVE C13, 125.6553377 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 21 min
166b
Me
O
CN
N2
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

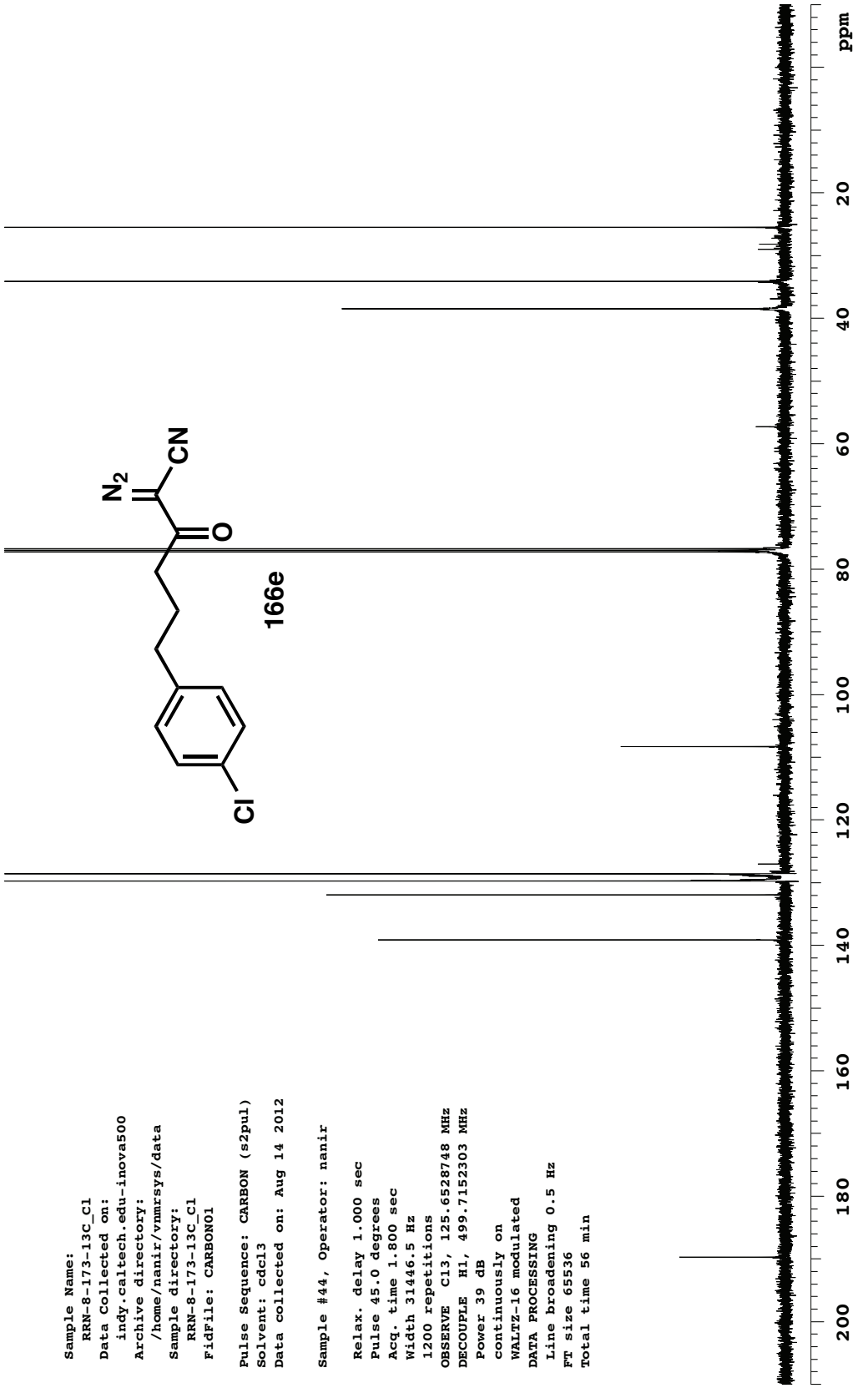

Sample Name:
RRN-8-177-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-177-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 22 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
N2
CN
O
MeO
166c
ppm
11
10
9
8
7
6
5
4
3
2
1
1.90
1.89
3.00
4.08
2.09


Sample Name:
RRN-8-177-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-177-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 13 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
1100 repetitions
OBSERVE C13, 125.6528844 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 55 min
MeO
O
CN
N2
166c
200
180
160
140
120
100
80
60
40
20
ppm

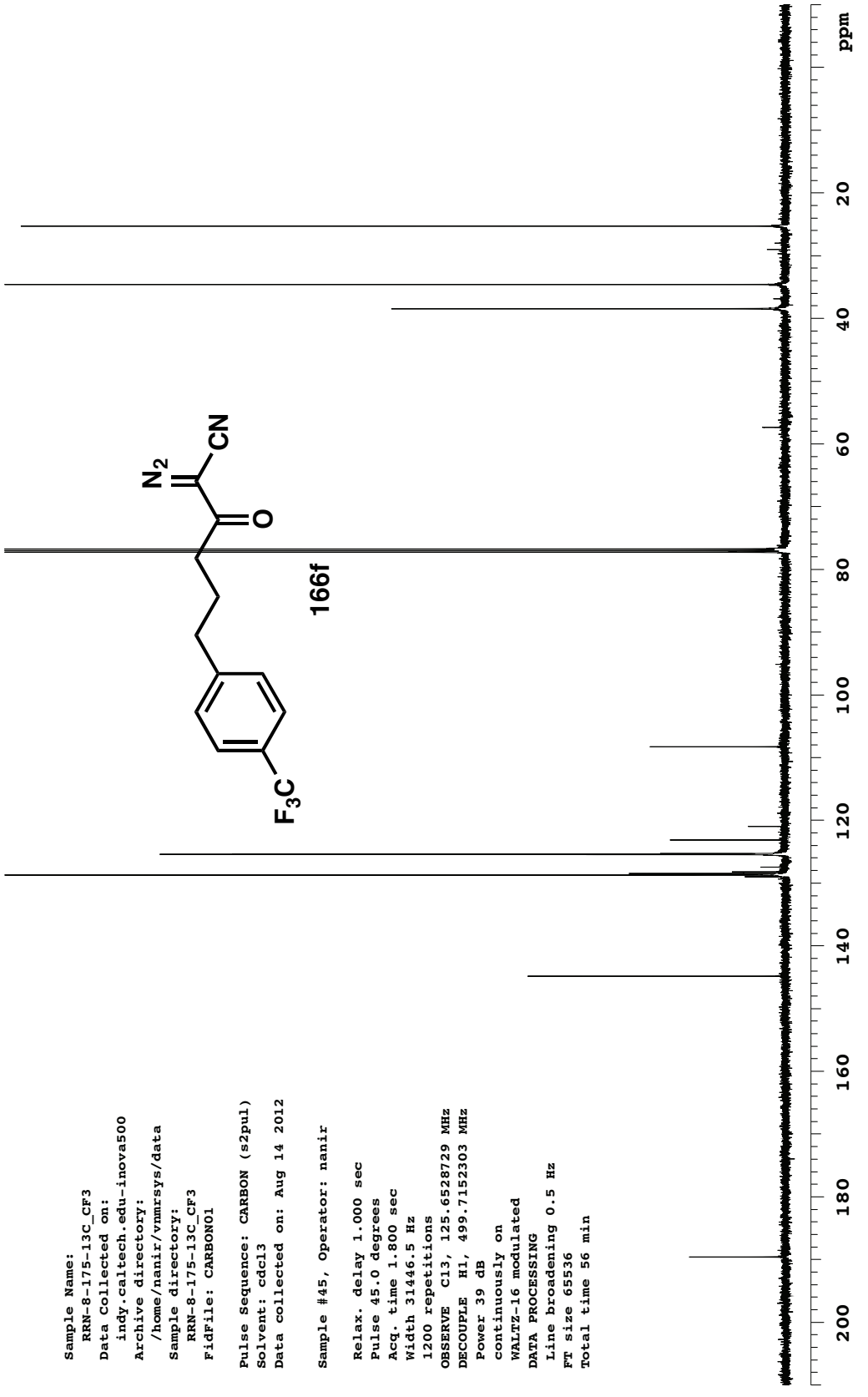

Sample Name:
RRN-9-135-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-135-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 15 2012
Sample #39, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127430 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
N2
CN
O
F
166d
11
10
9
8
7
6
5
4
3
2
1
ppm
1.93
1.92
4.02
2.05

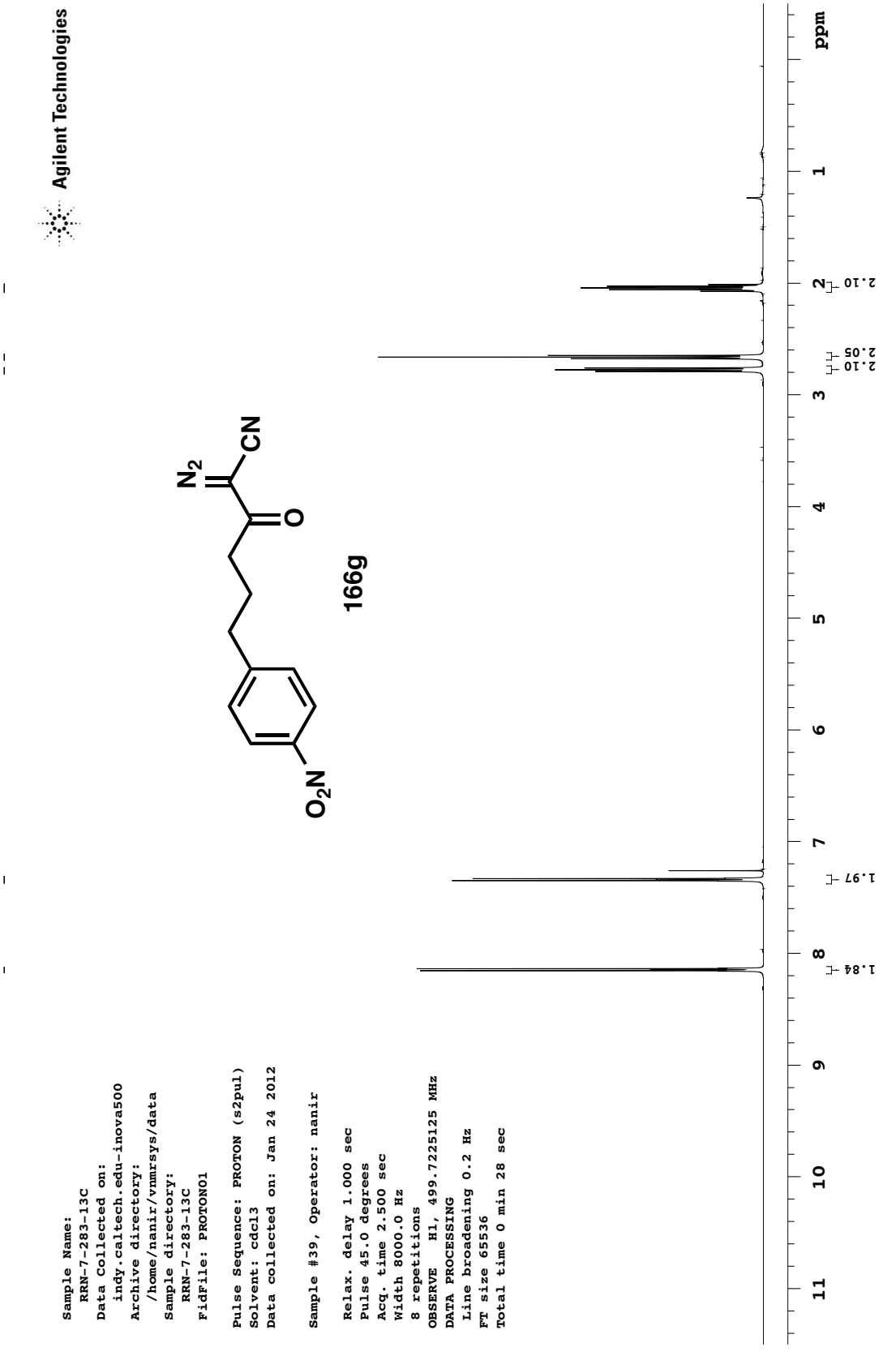

Sample Name:
RRN-9-135-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-135-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 15 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528806 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
N2
CN
O
F
166d
200
180
160
140
120
100
80
60
40
20
ppm

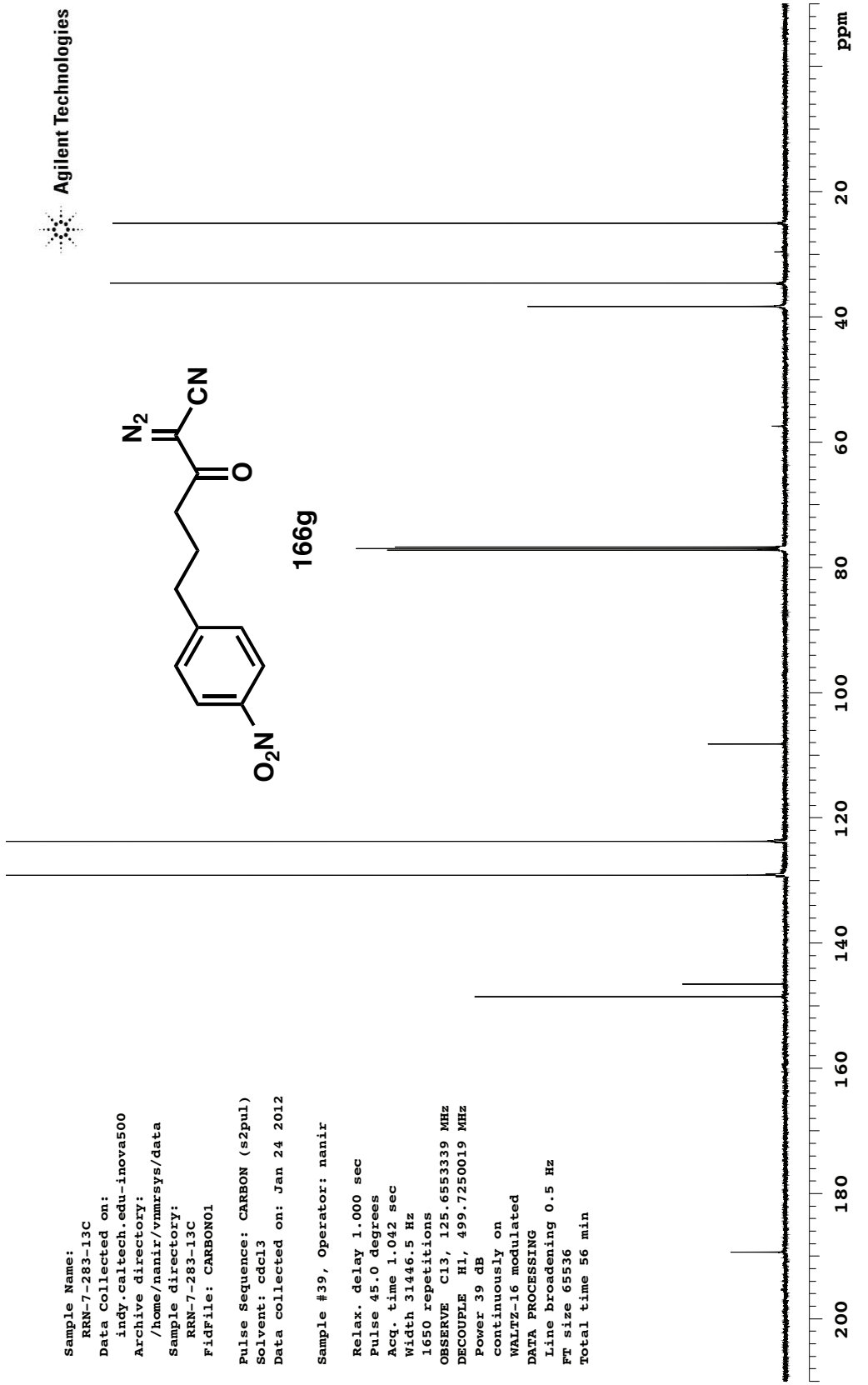

Sample Name:
RRN-8-173-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-173-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 22 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
N2
CN
O
Cl
166e
2.00
3.94
2.08
1.85
ppm

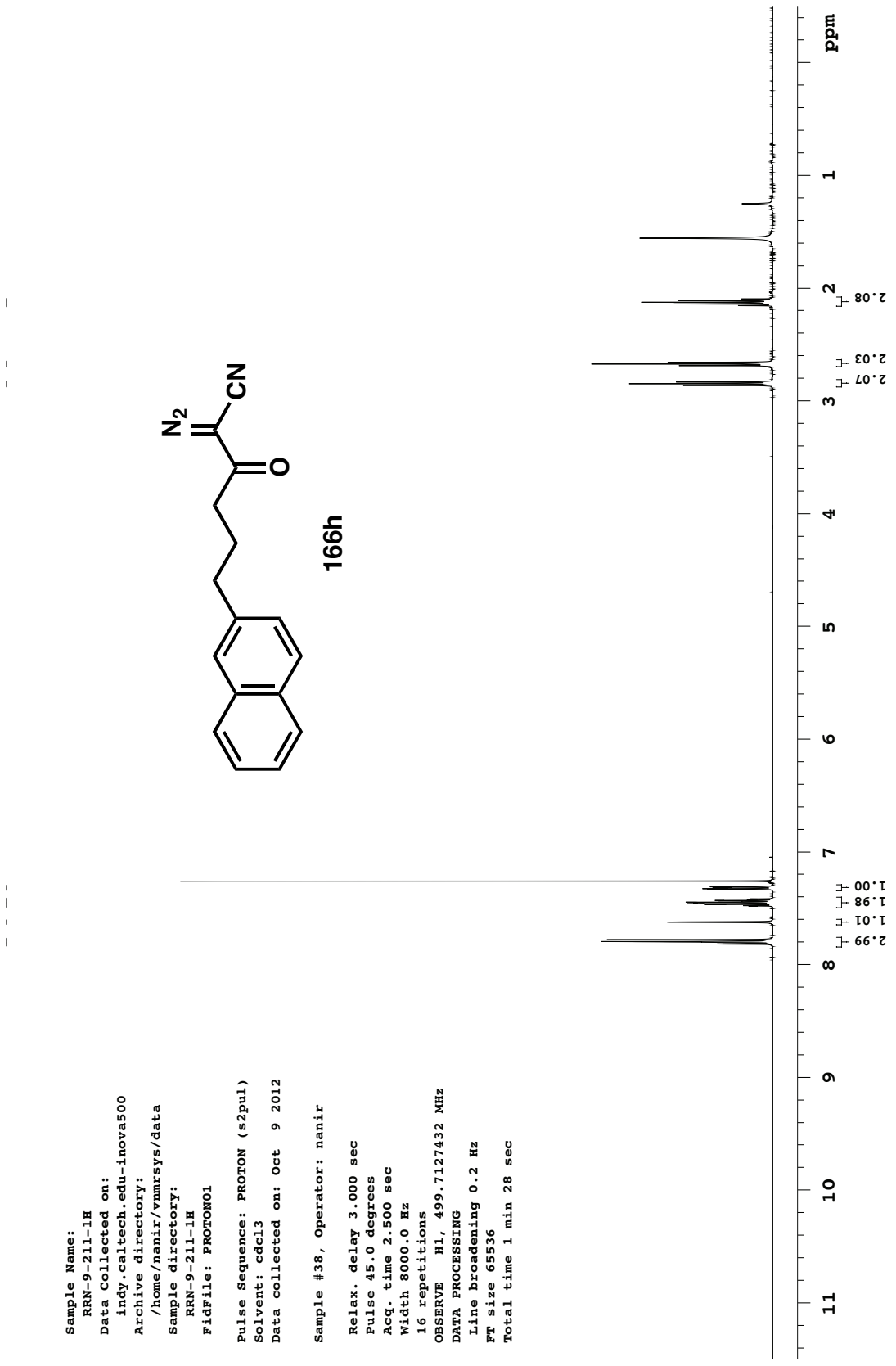

Sample Name:
RRN-8-173-13C_C1
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-173-13C_C1
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 14 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528748 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
166e
N2
CN
O
Cl
200
180
160
140
120
100
80
60
40
20
ppm

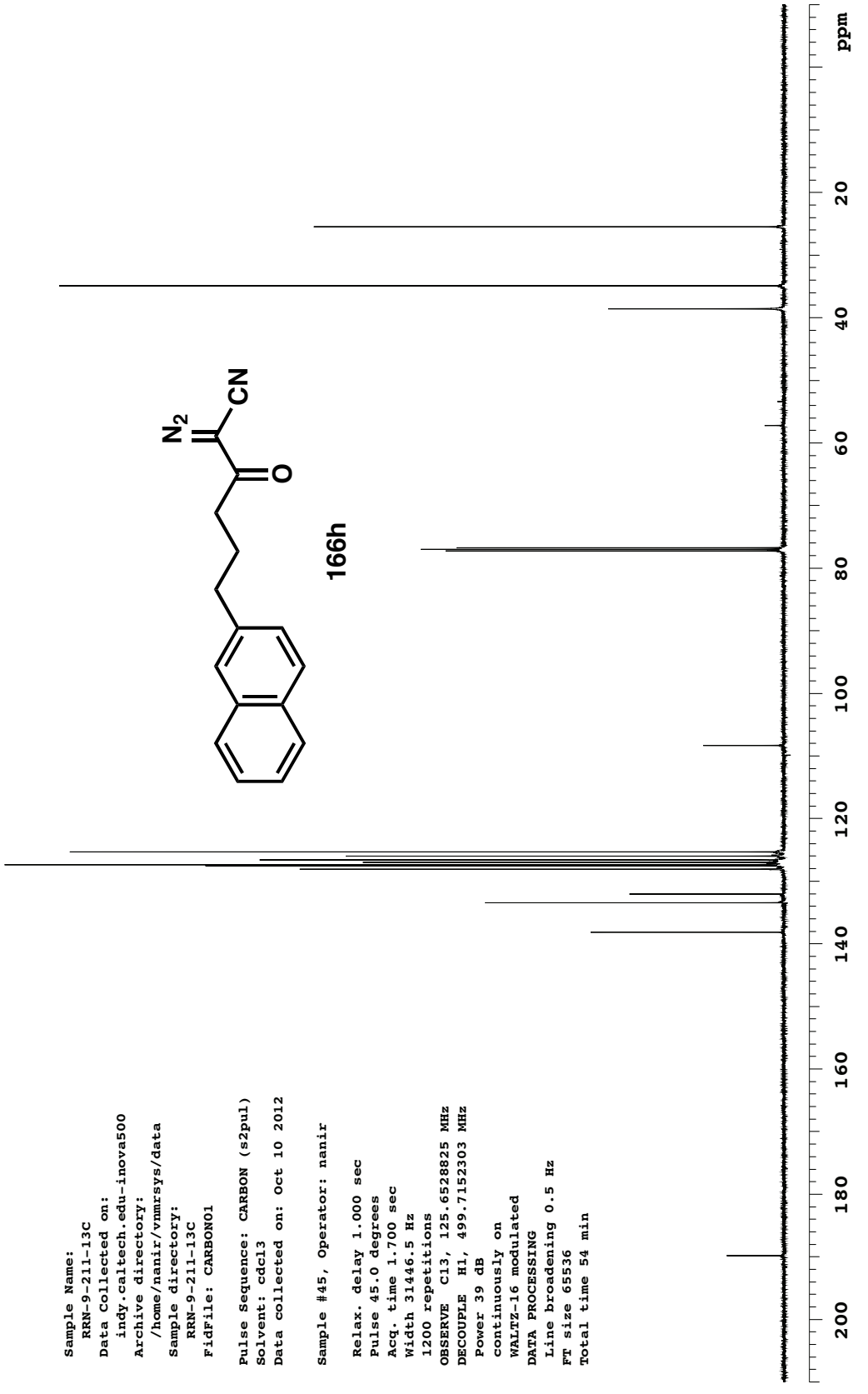

Sample Name:
RRN-8-175-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-175-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 22 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
166f
N_2
CN
O
F_3C
1.84
1.90
2.02
1.99
2.06
ppm

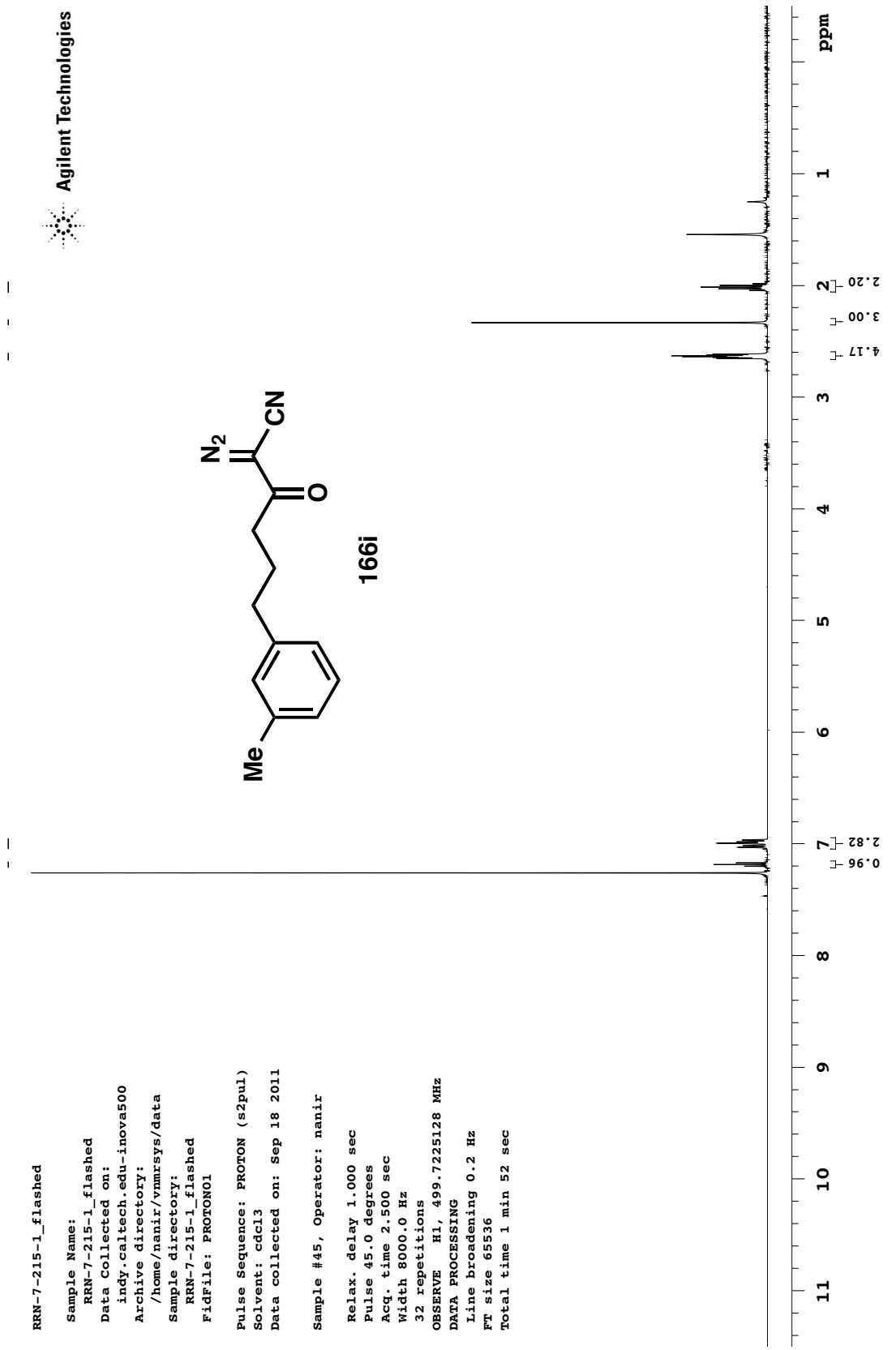

Sample Name:
RRN-8-175-13C_CF3
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-175-13C_CF3
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 14 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528729 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
N2
CN
O
F3C
166f
200
180
160
140
120
100
80
60
40
20
ppm

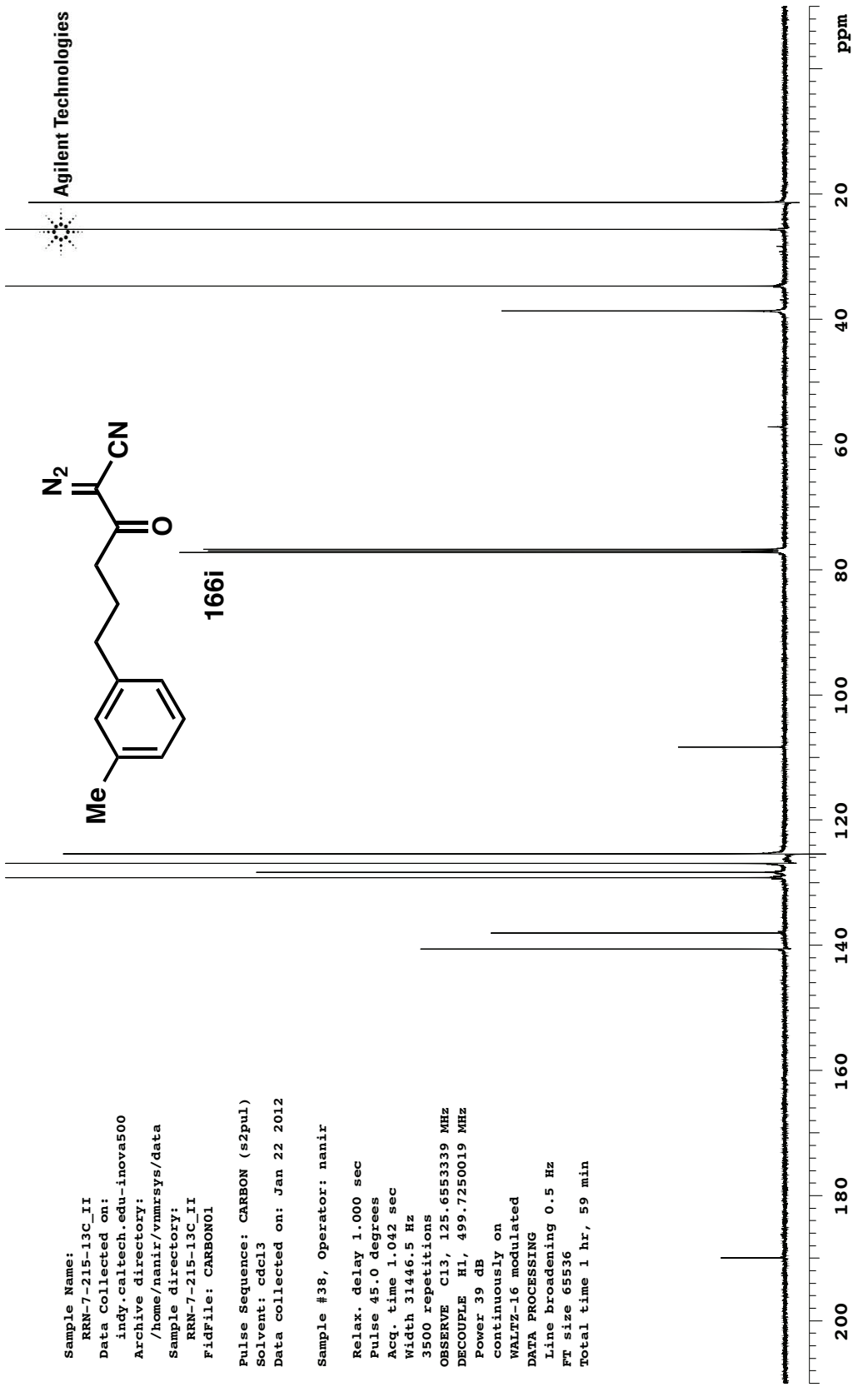

Agilent Technologies
Sample Name:
RRN-7-283-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-283-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 24 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
166g
N2
CN
O
O2N
1.84
1.97
2.10
2.05
2.10
ppm
Plotname: --Not assigned--

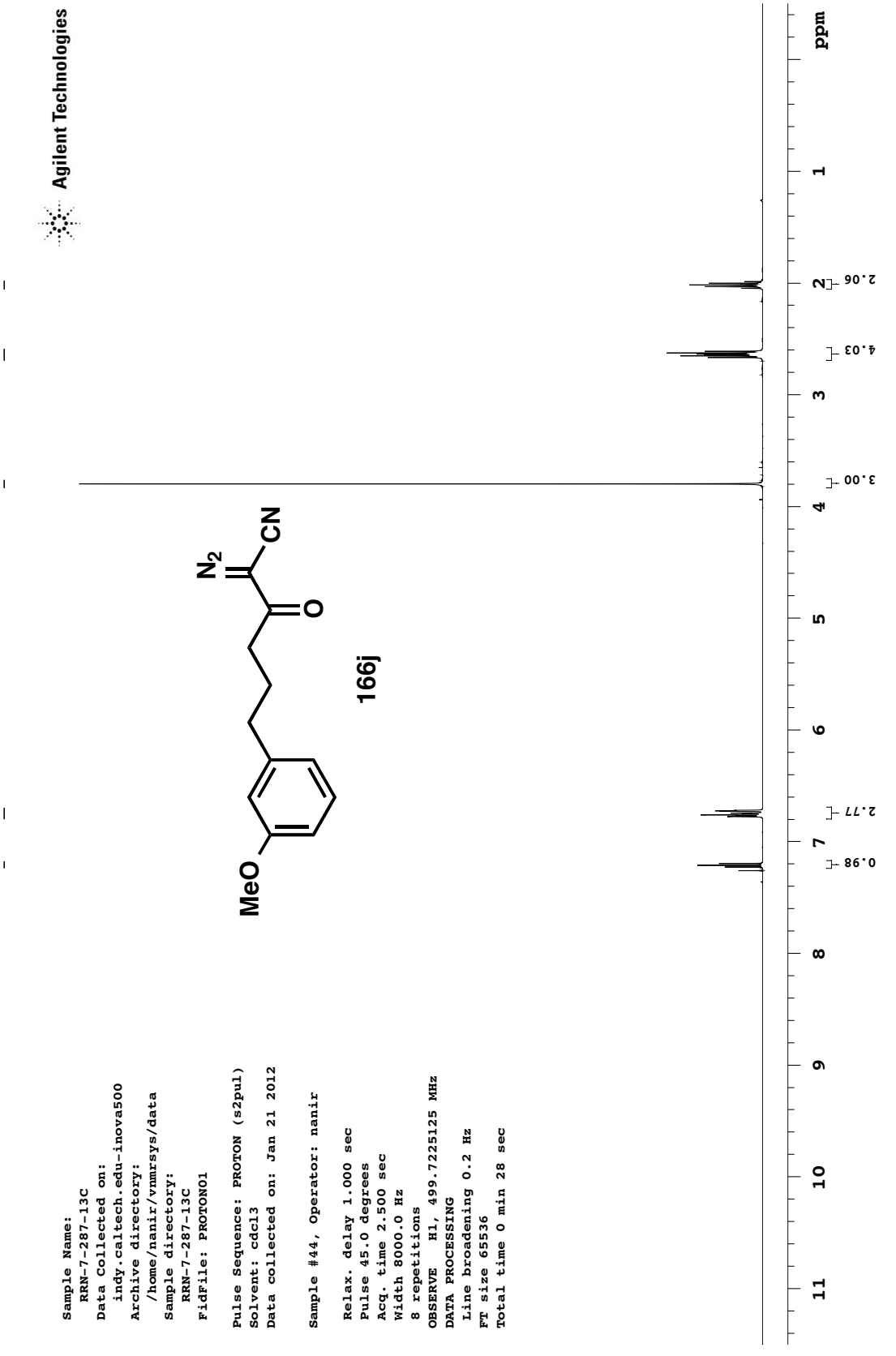

Agilent Technologies
Sample Name:
RRN-7-283-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-283-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 24 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1650 repetitions
OBSERVE C13, 125.6553339 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
166g
ppm
200
180
160
140
120
100
80
60
40
20
Plotname: --Not assigned--

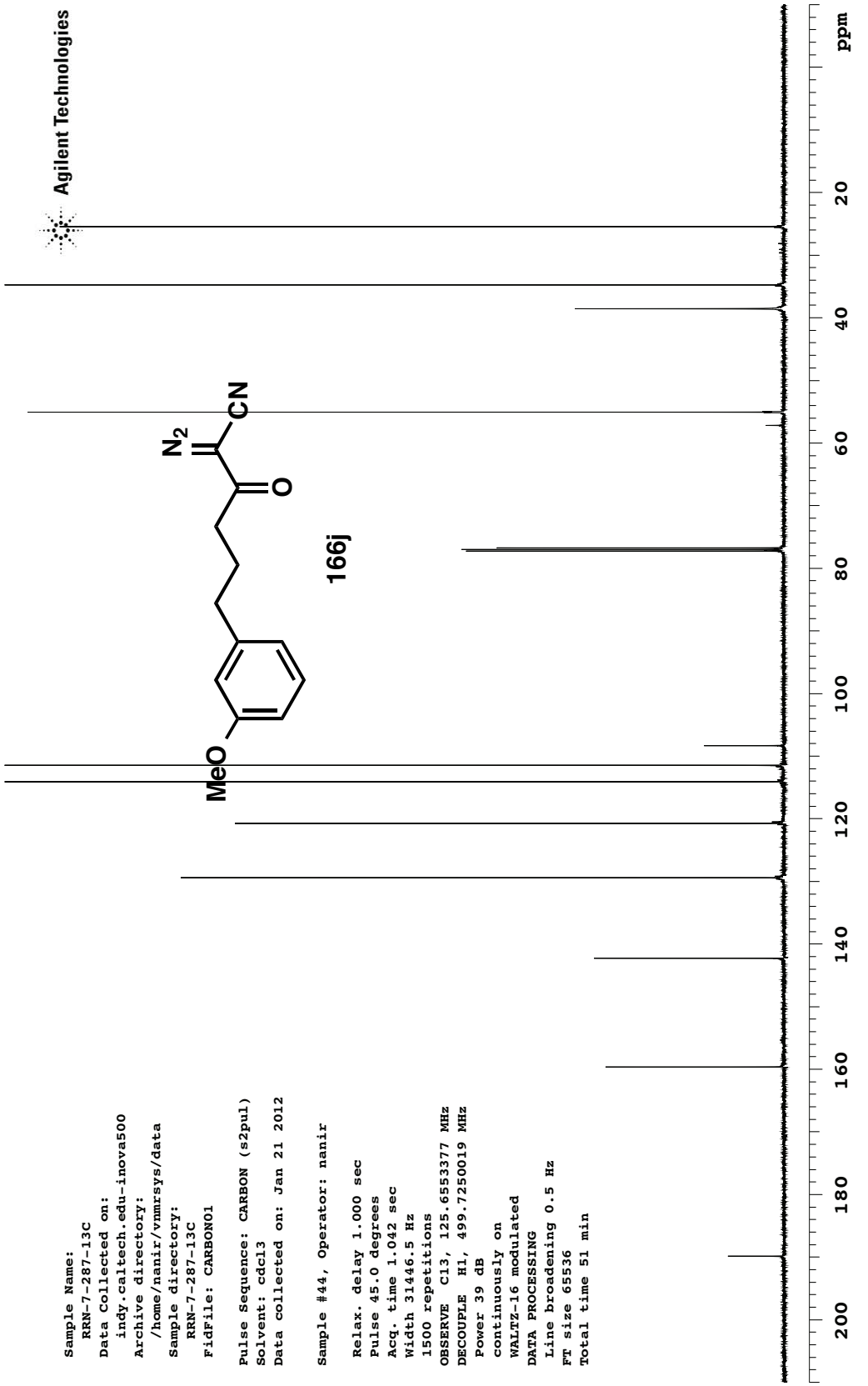

Sample Name:
RRN-9-211-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-211-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 9 2012
Sample #38, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127432 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
N2
CN
O
166h
2.99
1.01
1.98
1.00
2.07
2.03
2.08
ppm

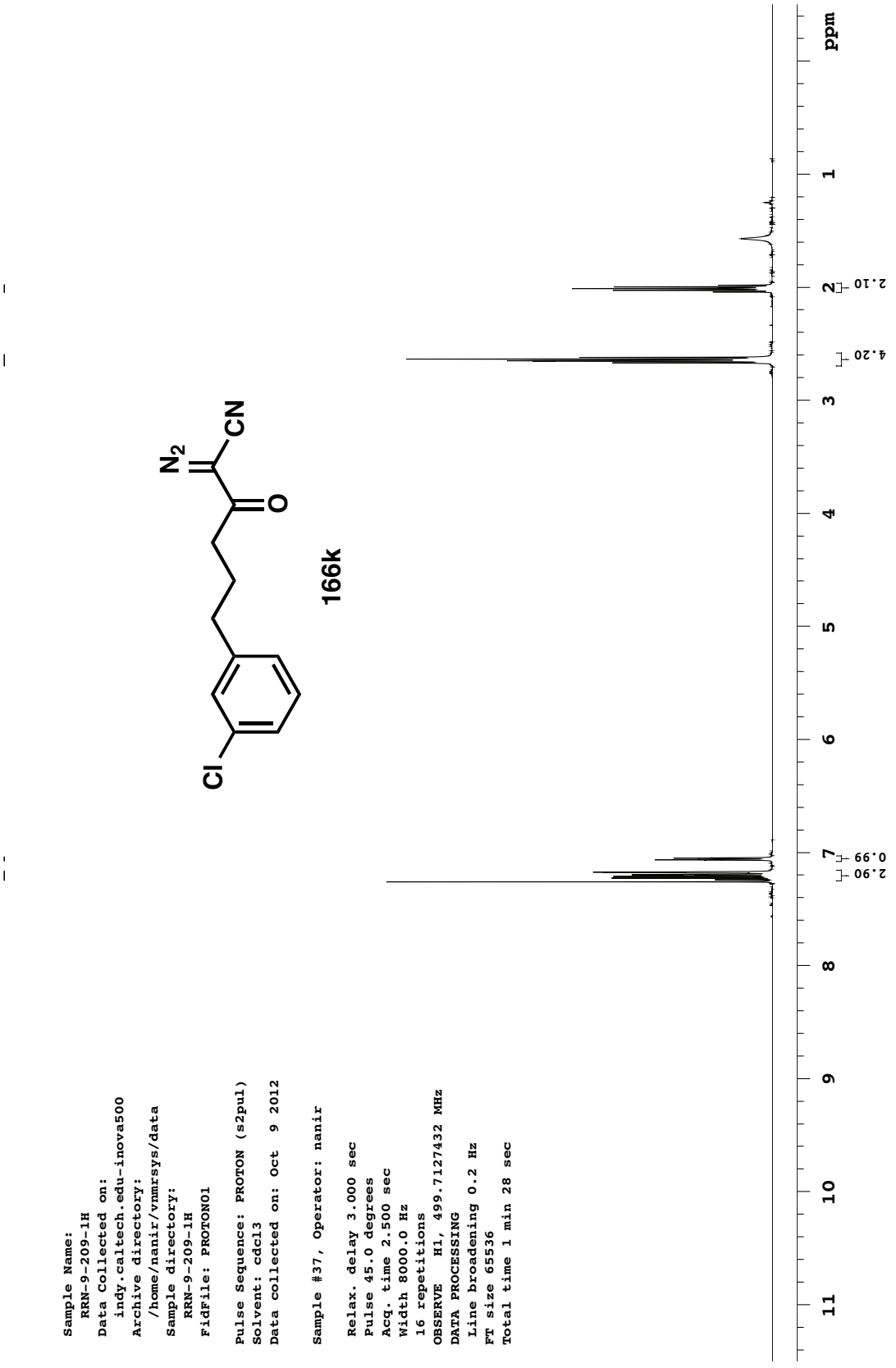

Sample Name:
RRN-9-211-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-211-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 10 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.700 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528825 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 54 min
166h
N2
CN
O
200
180
160
140
120
100
80
60
40
20
ppm

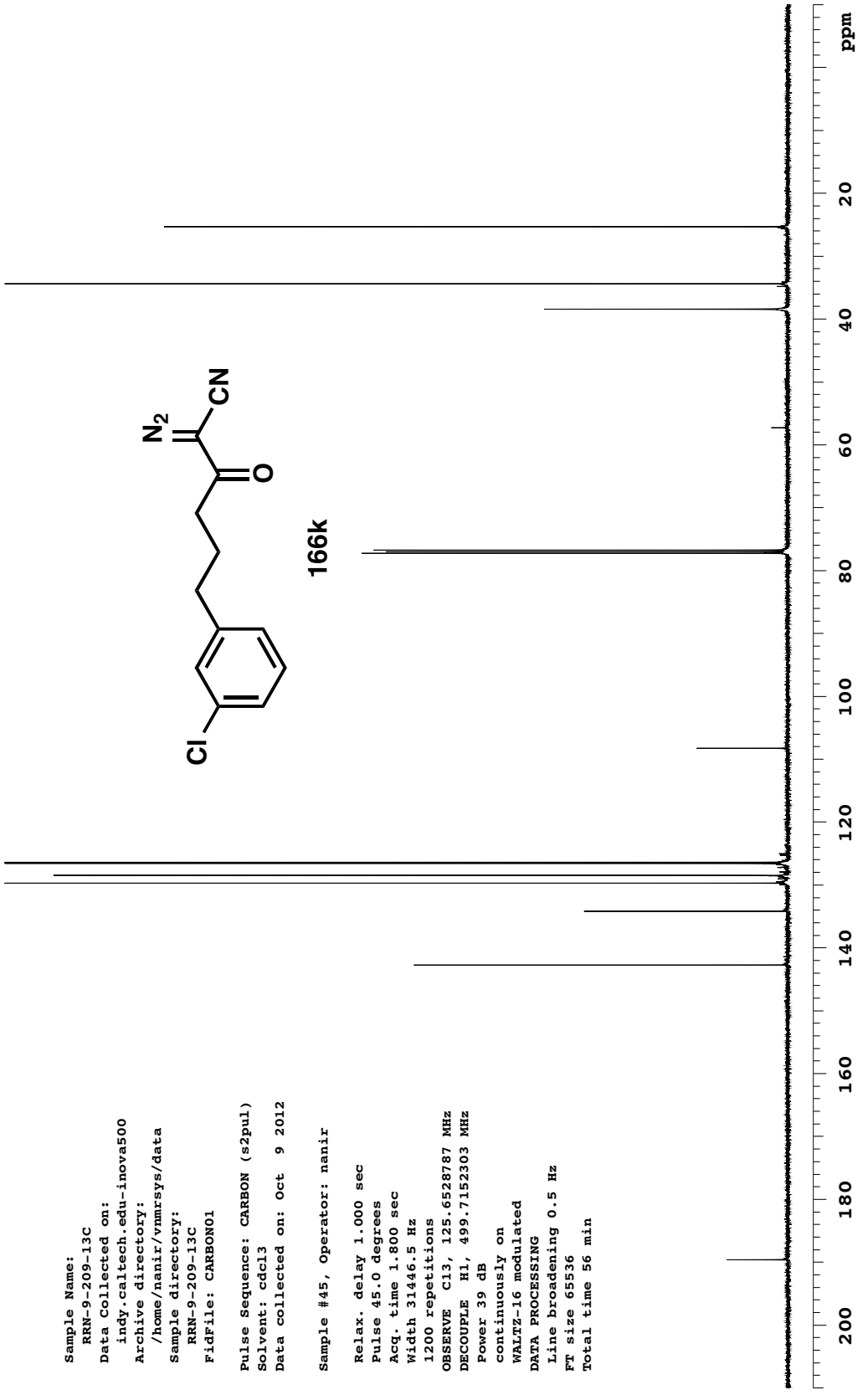

RRN-7-215-1_flashed
Sample Name:
RRN-7-215-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-215-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 18 2011
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
Agilent Technologies
N2
CN
O
Me
166i
11
10
9
8
7
6
5
4
3
2
1
ppm
0.96
2.82
4.17
3.00
2.20
Plotname: --Not assigned--

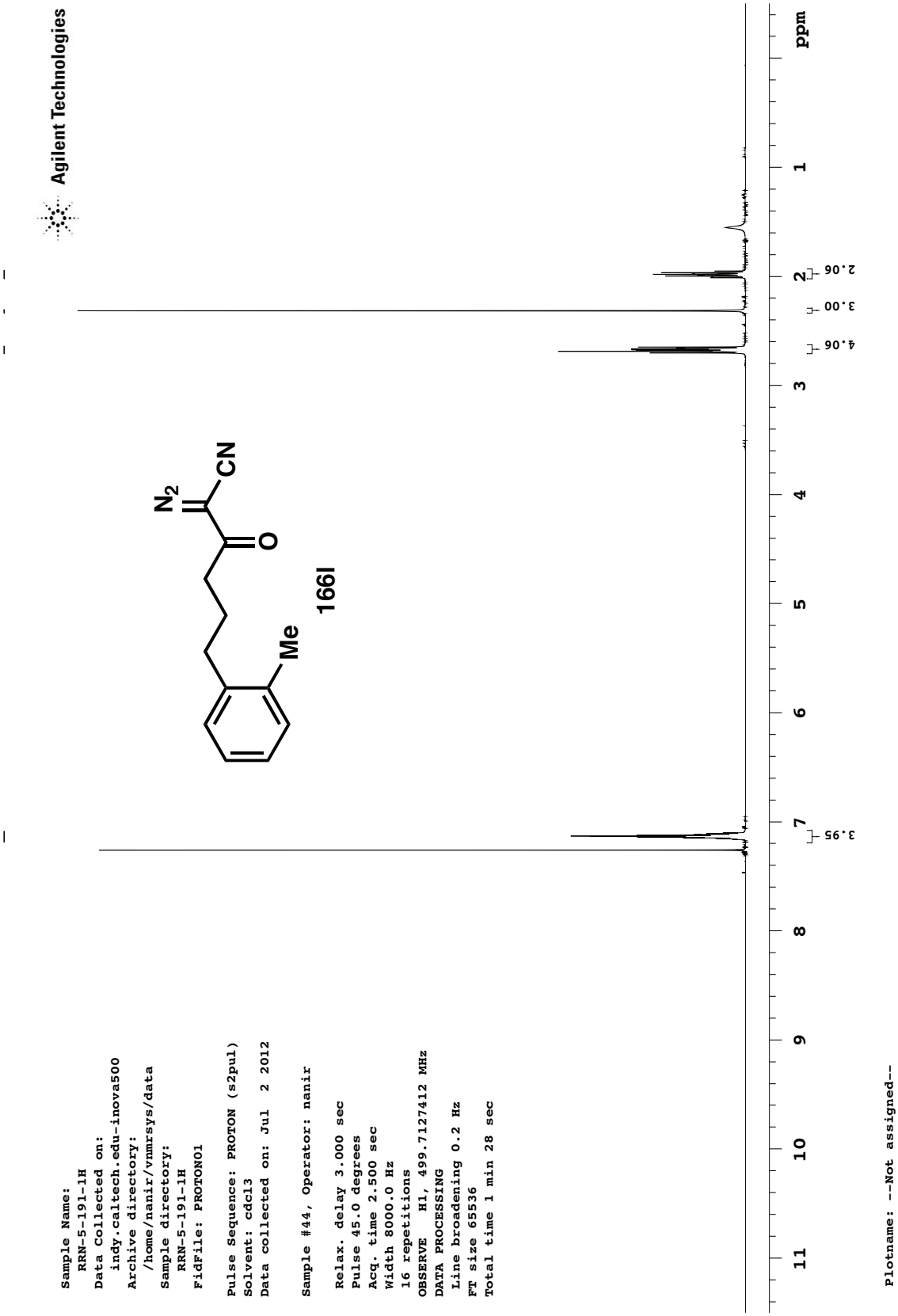

Agilent Technologies
166i
Me
N2
CN
O
ppm
200
180
160
140
120
100
80
60
40
20
Sample Name:
RRN-7-215-13C_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-215-13C_II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 22 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
3500 repetitions
OBSERVE C13, 125.6553339 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 59 min
Plotname: --Not assigned--

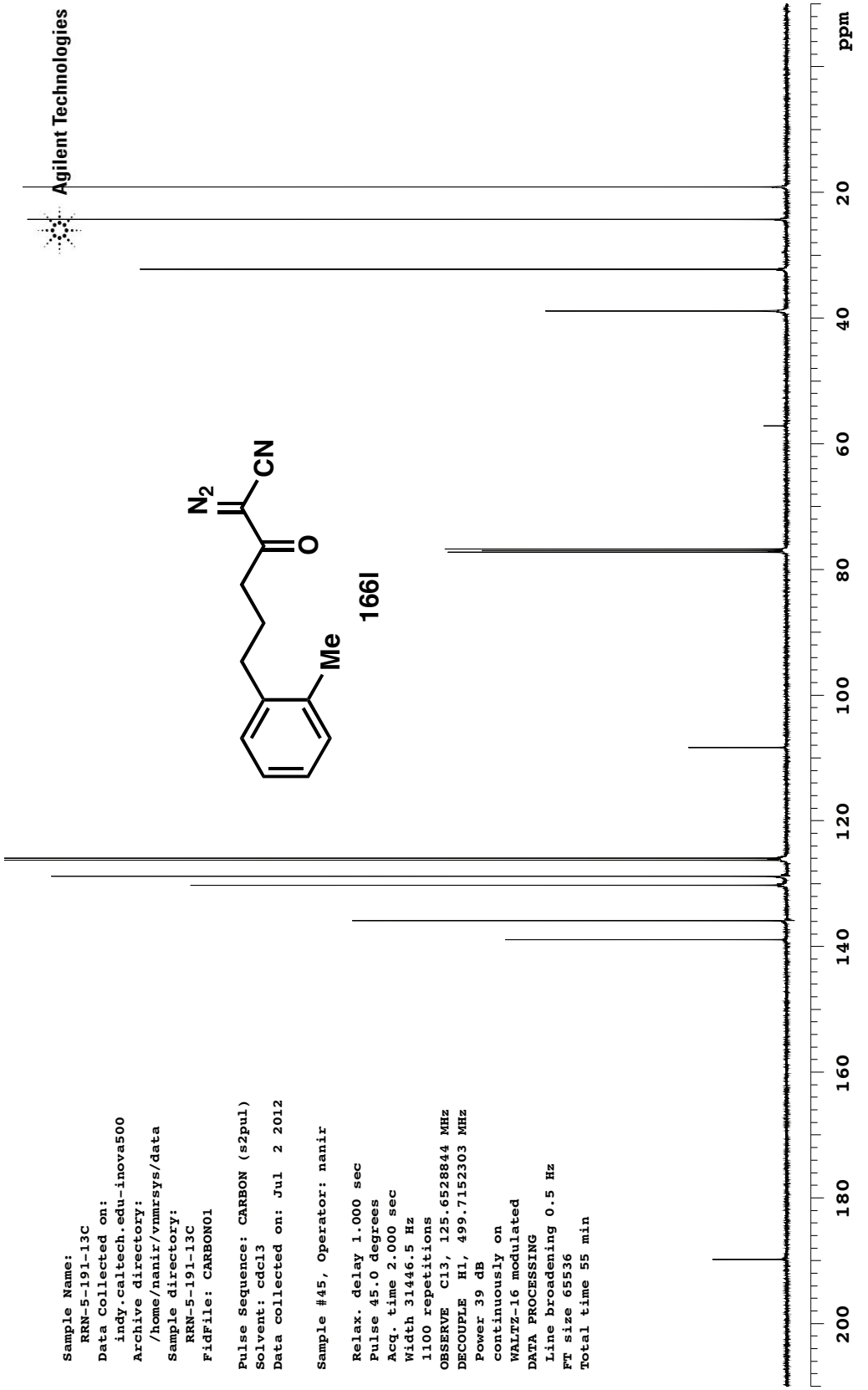

Agilent Technologies
Sample Name:
RRN-7-287-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-287-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
N2
CN
O
MeO
166j
2.06
4.03
3.00
2.77
0.98
ppm
Plotname: --Not assigned--


Agilent Technologies
MeO
N2
CN
O
166j
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-7-287-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-287-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6553377 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
Plotname: --Not assigned--

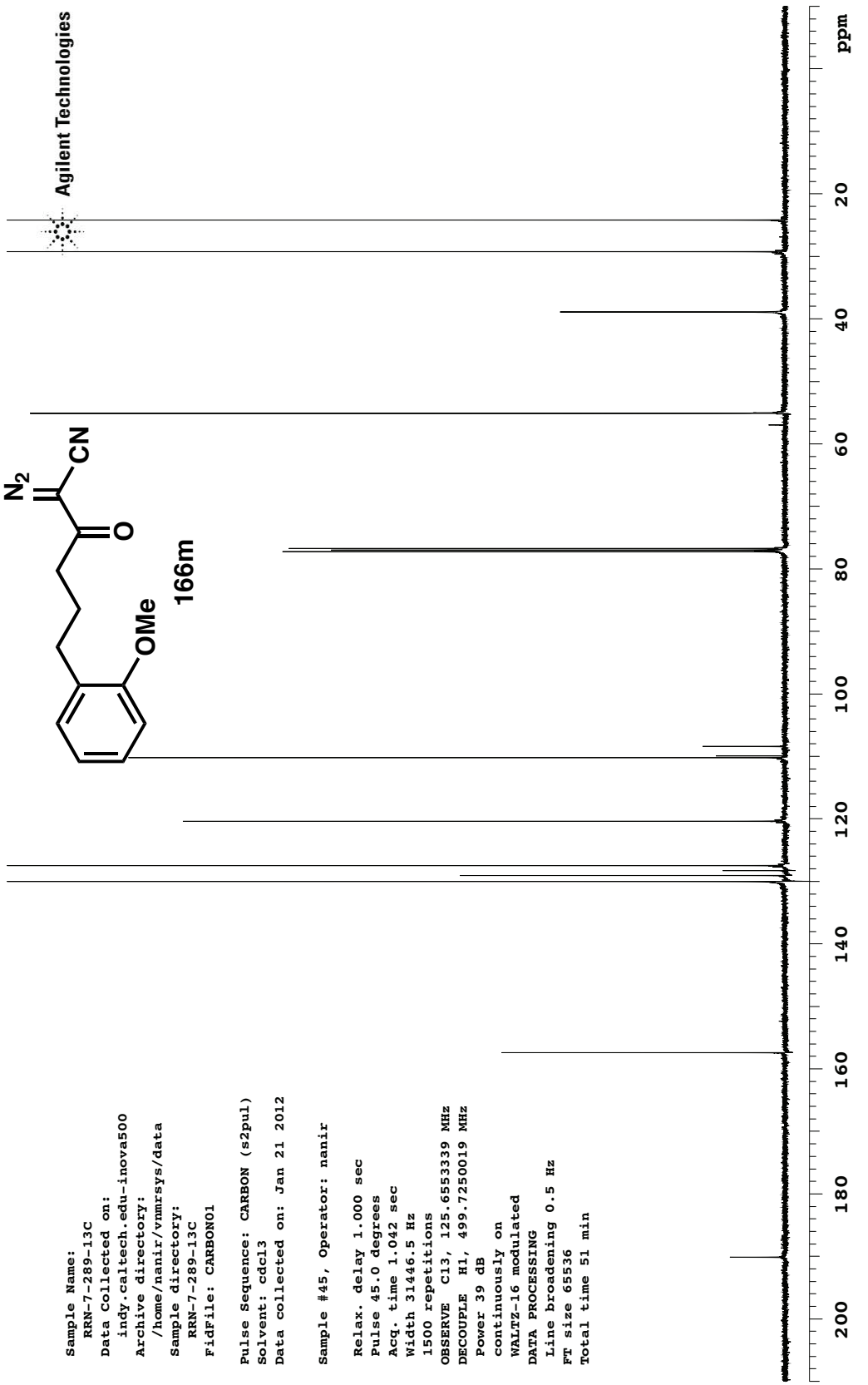

Sample Name:
RRN-9-209-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-209-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 9 2012
Sample #37, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127432 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
N2
CN
O
Cl
166k
2.10
4.20
2.90
0.99
ppm

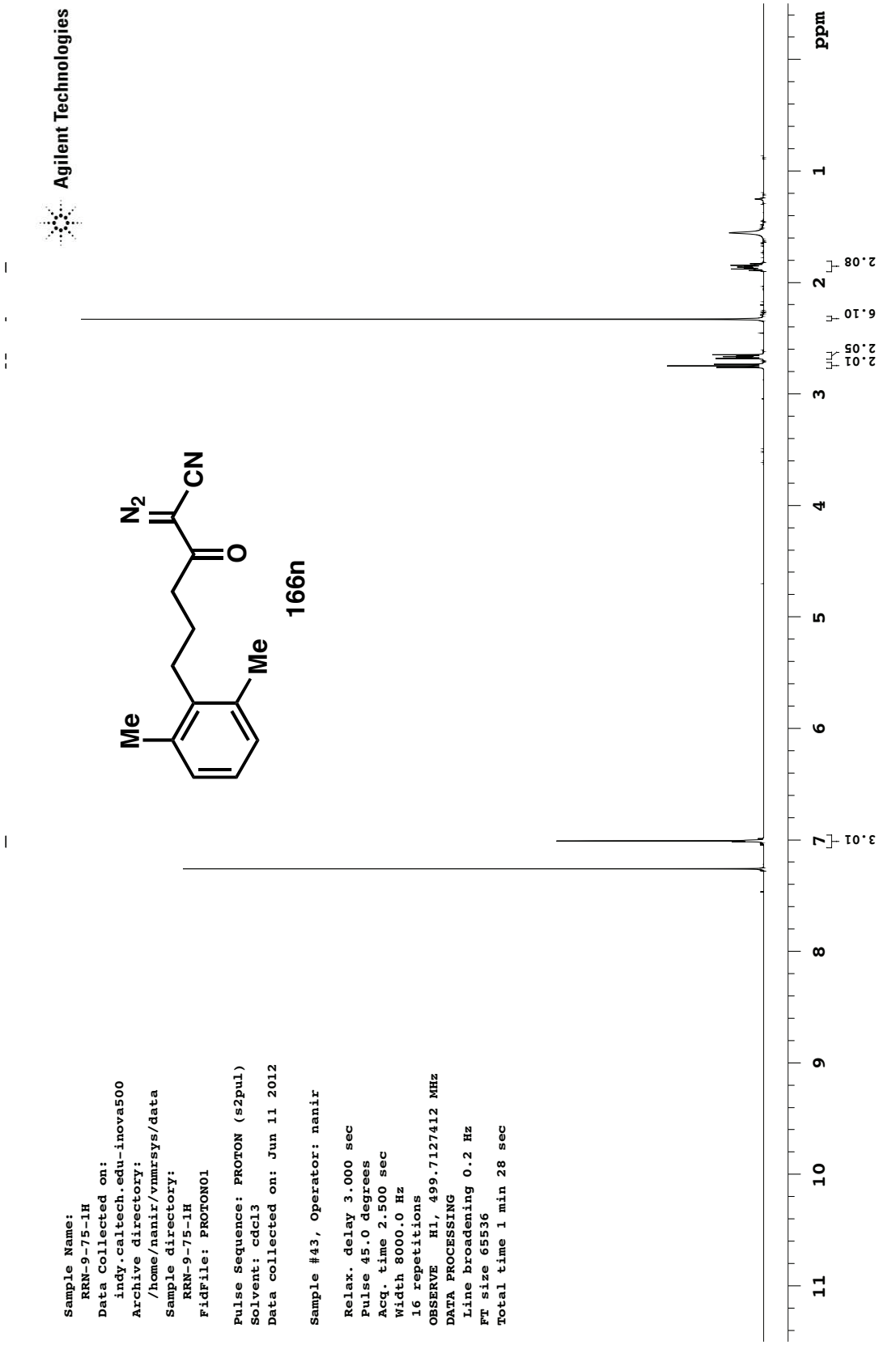

Sample Name:
RRN-9-209-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-209-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 9 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528787 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
166k
N2
CN
O
Cl
200
180
160
140
120
100
80
60
40
20
ppm

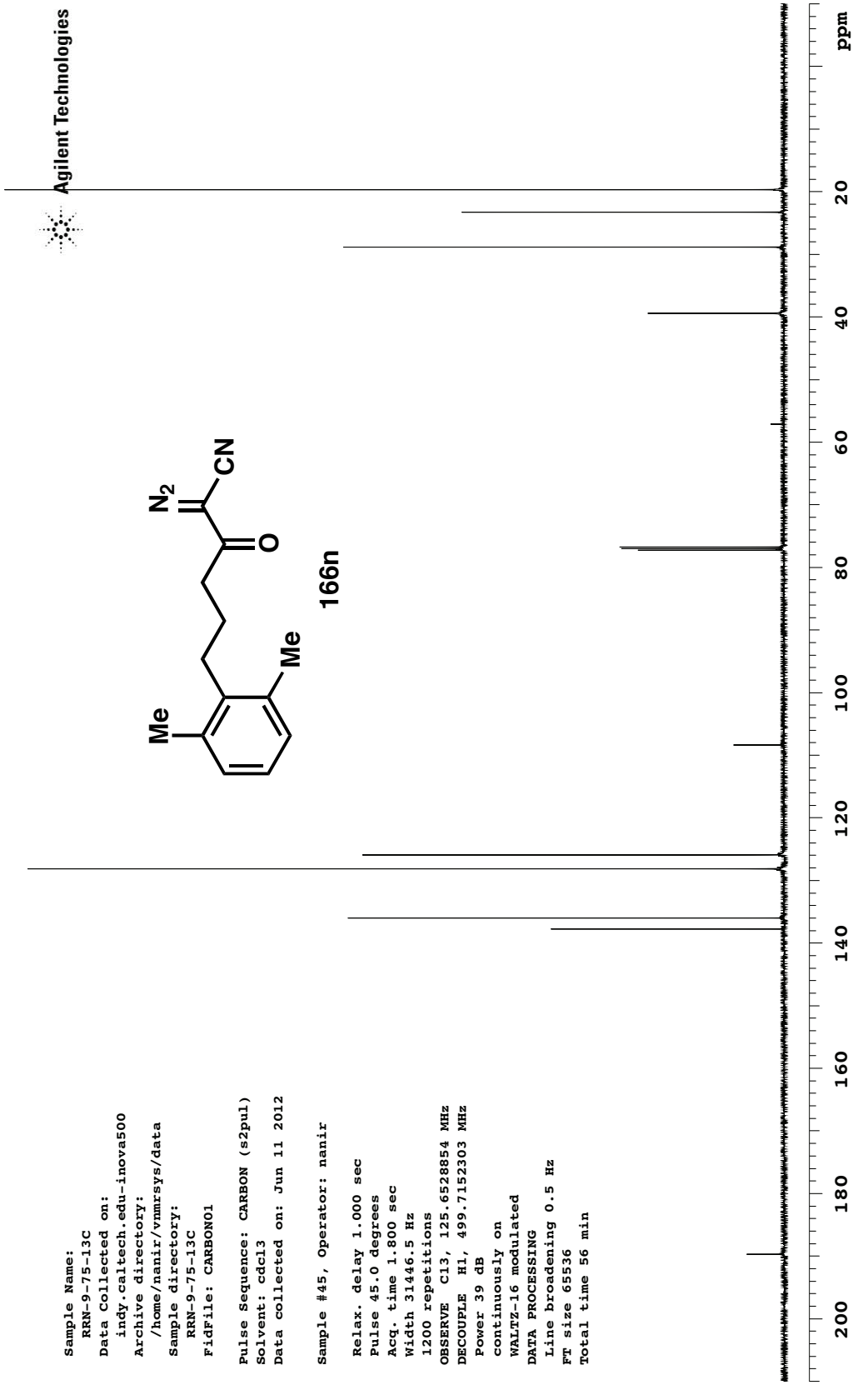

Agilent Technologies
Sample Name:
RRN-5-191-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-191-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 2 2012
Sample #44, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127412 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
N2
CN
O
Me
166l
3.95
2.06
3.00
4.06
ppm
Plotname: --Not assigned--

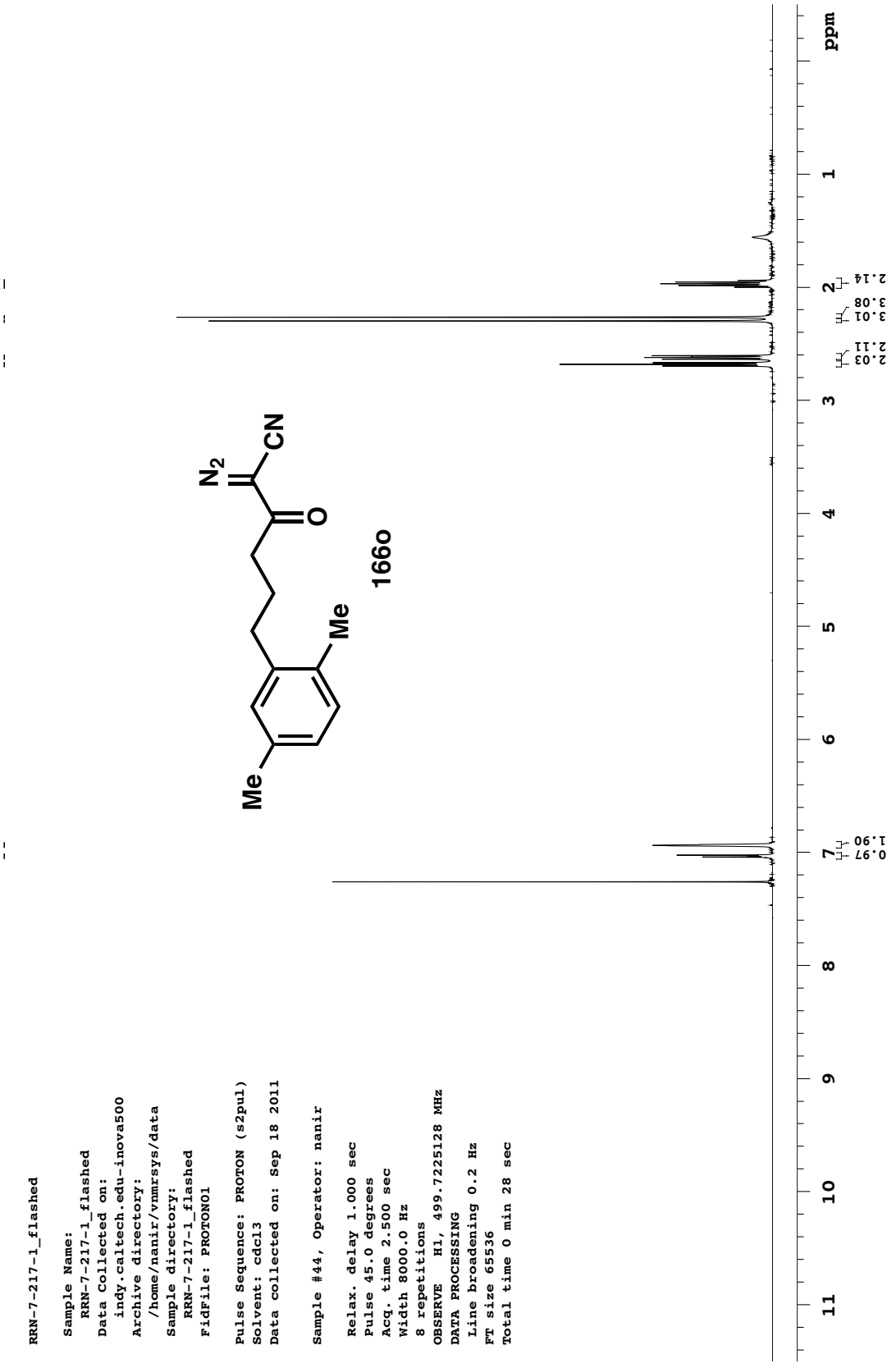

Agilent Technologies
Sample Name:
RRN-5-191-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-191-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 2 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
1100 repetitions
OBSERVE C13, 125.6528844 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 55 min
N2
CN
O
Me
166l
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

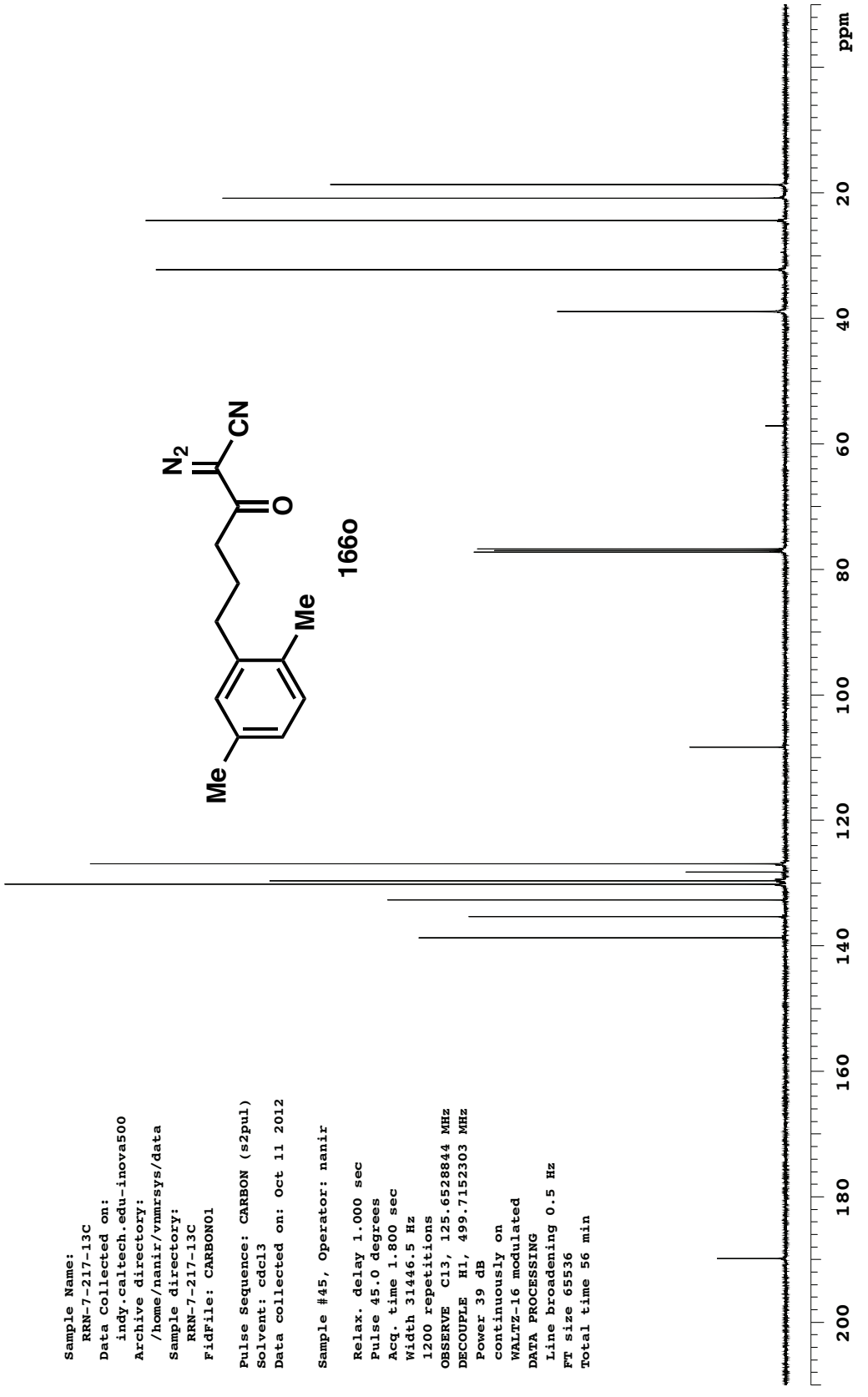
RRN-7-289-1_flashed
Sample Name:
RRN-7-289-1_flashed
Data Collected on:
hg3.caltech.edu-mercury300
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-289-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 22 2011
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
32 repetitions
OBSERVE H1, 300.0862591 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 2 min 11 sec
Agilent Technologies
N2
CN
O
OMe
166m
3.00
4.06
2.05
1.90
0.95
0.94
ppm
Plotname: --Not assigned--

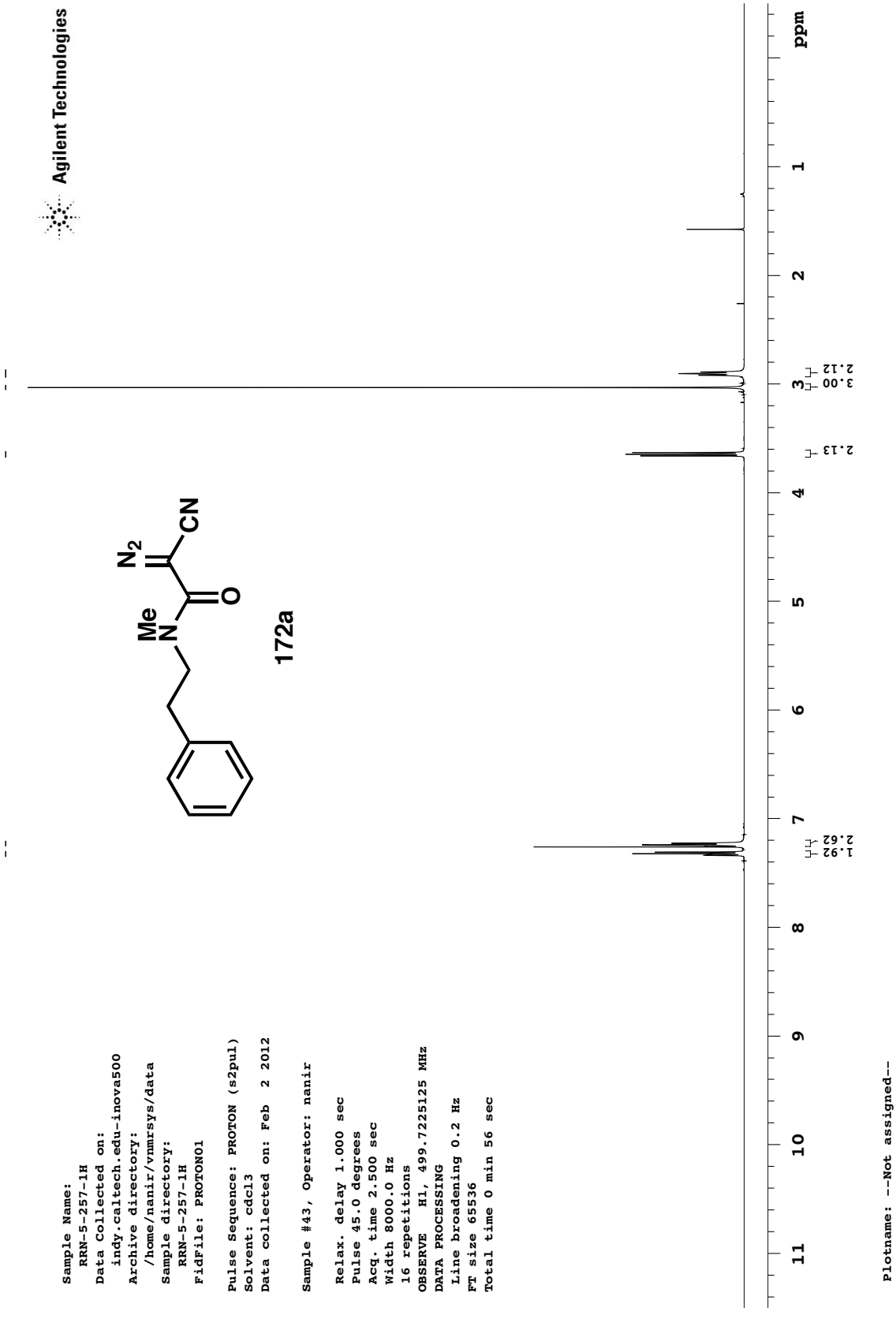

Agilent Technologies
N2
CN
O
OMe
166m
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-7-289-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-289-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6553339 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
Plotname: --Not assigned--

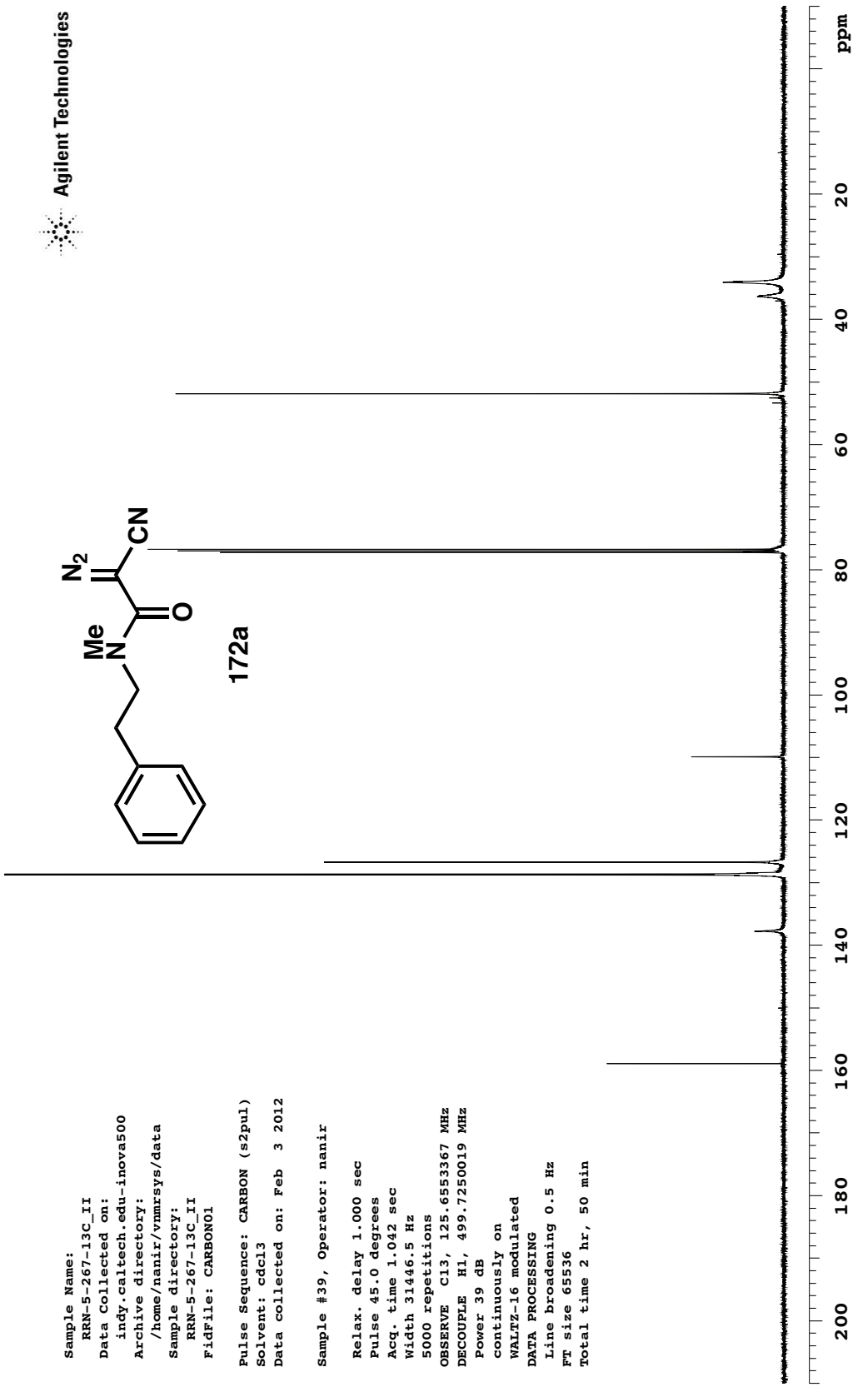

Agilent Technologies
Sample Name:
RRN-9-75-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-75-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 11 2012
Sample #43, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127412 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
N2
CN
O
Me
Me
166n
3.01
2.08
6.10
2.01
2.05
ppm
Plotname: --Not assigned--


Agilent Technologies
Sample Name:
RRN-9-75-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-75-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 11 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528854 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
Me
Me
O
N2
CN
166n
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

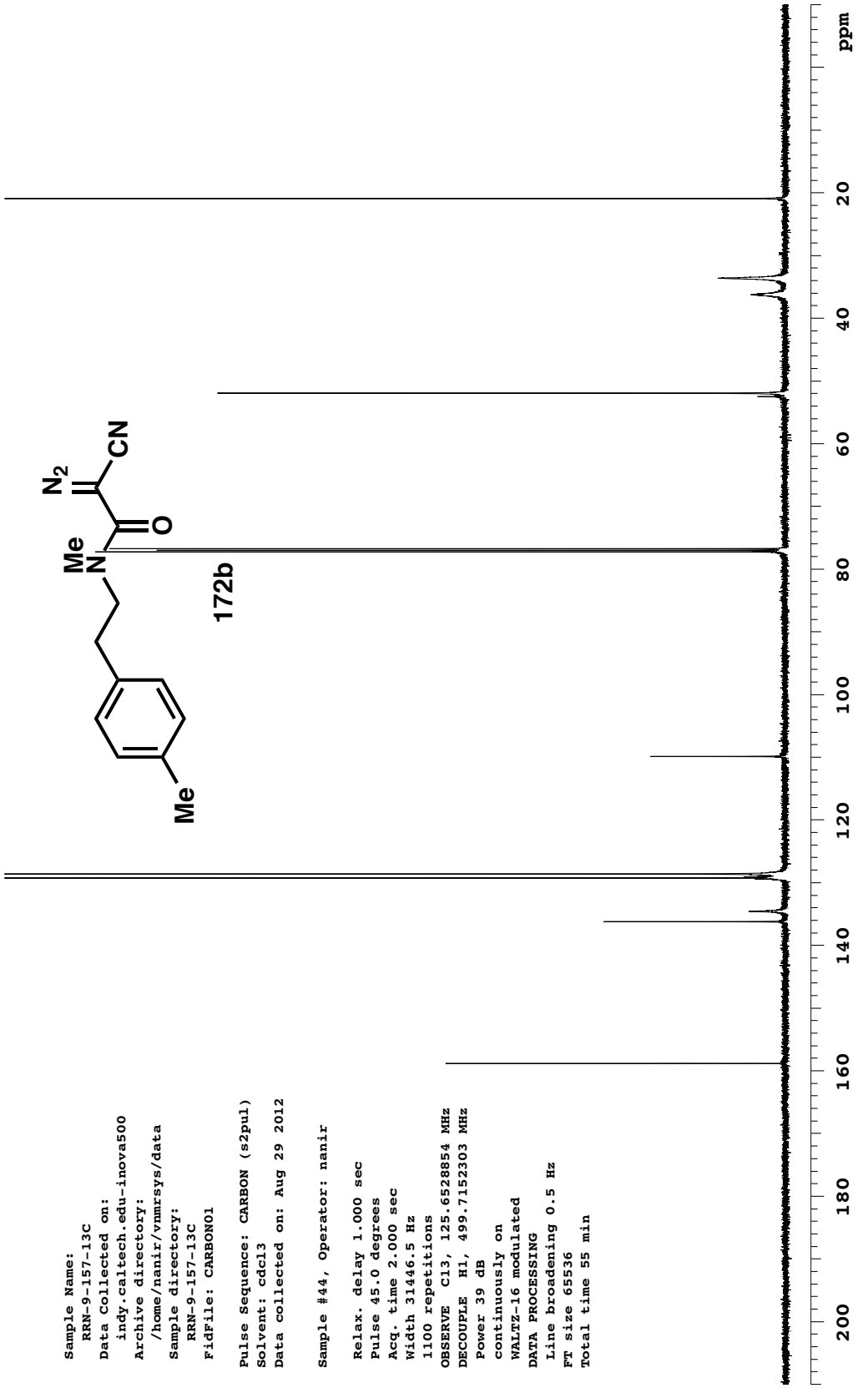

RRN-7-217-1_flashed
Sample Name:
RRN-7-217-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-217-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 18 2011
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
N2
CN
O
Me
Me
166o
ppm
0.97
1.90
2.03
2.11
3.01
3.08
2.14

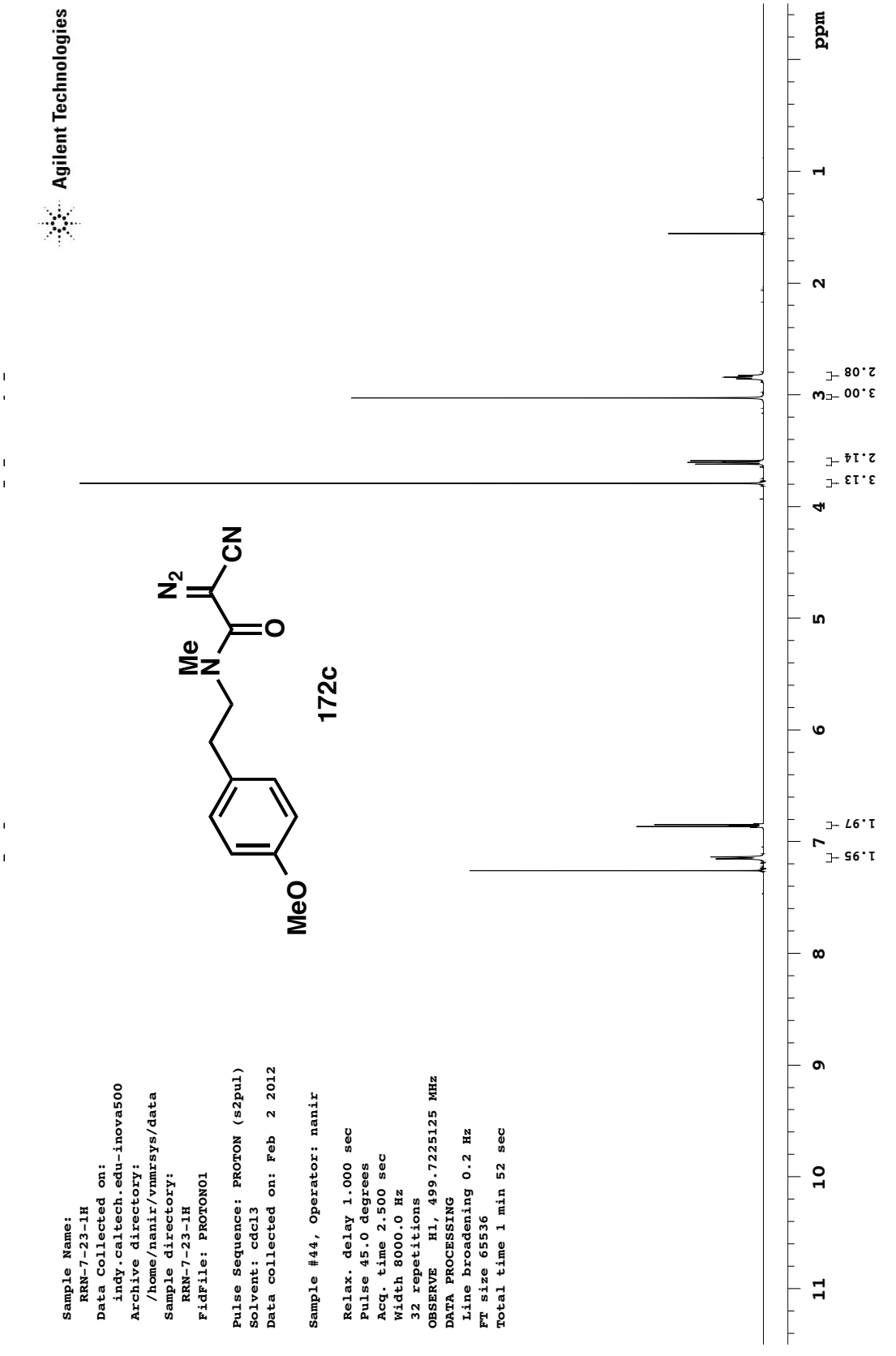

Sample Name:
RRN-7-217-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-217-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 11 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528844 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
N2
CN
O
Me
Me
166o
200
180
160
140
120
100
80
60
40
20
ppm

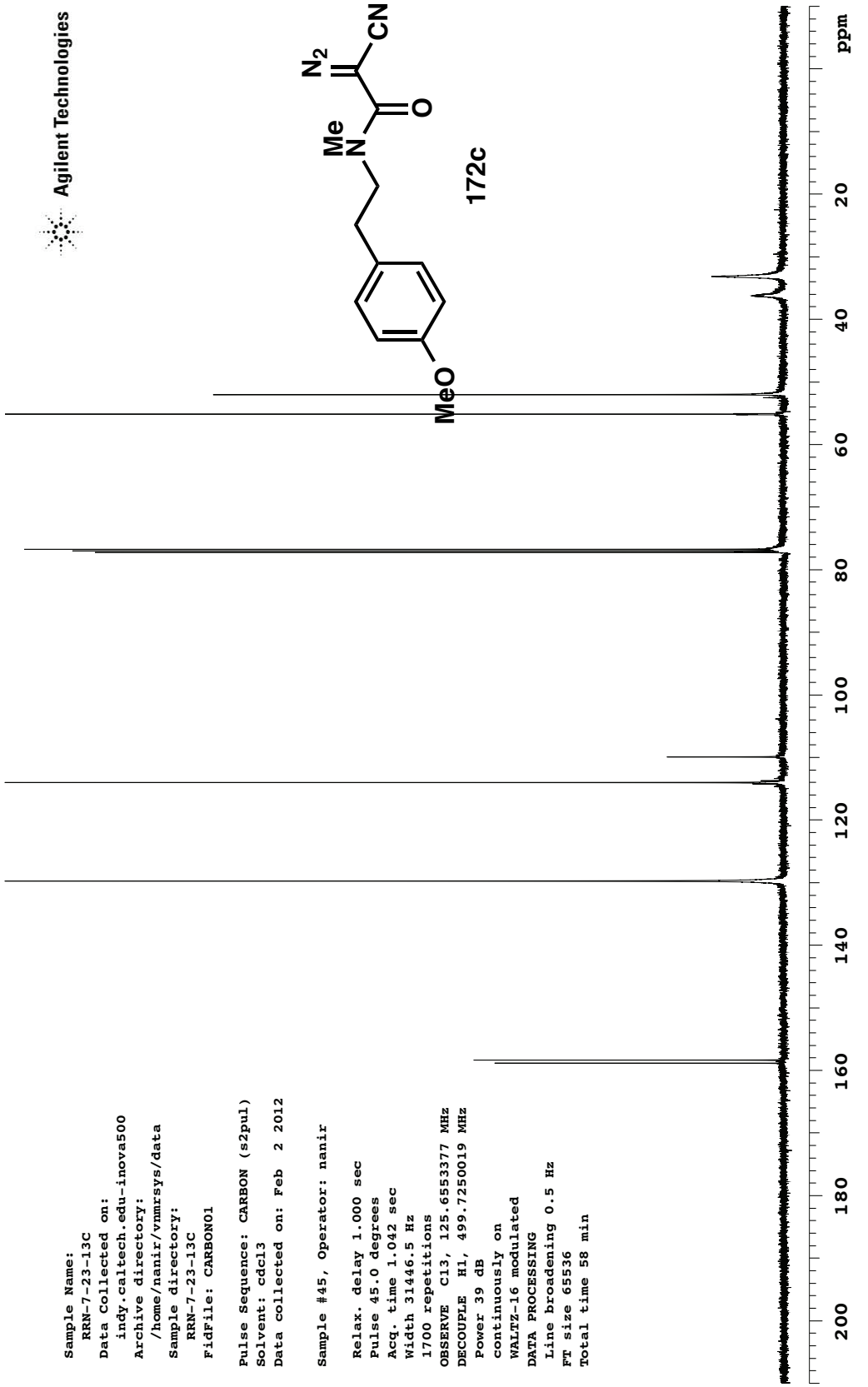

Agilent Technologies
Me
N
O
N2
CN
172a
2.13
3.00
2.12
1.92
2.62
ppm
Sample Name:
RRN-5-257-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-257-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 2 2012
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
Plotname: --Not assigned--

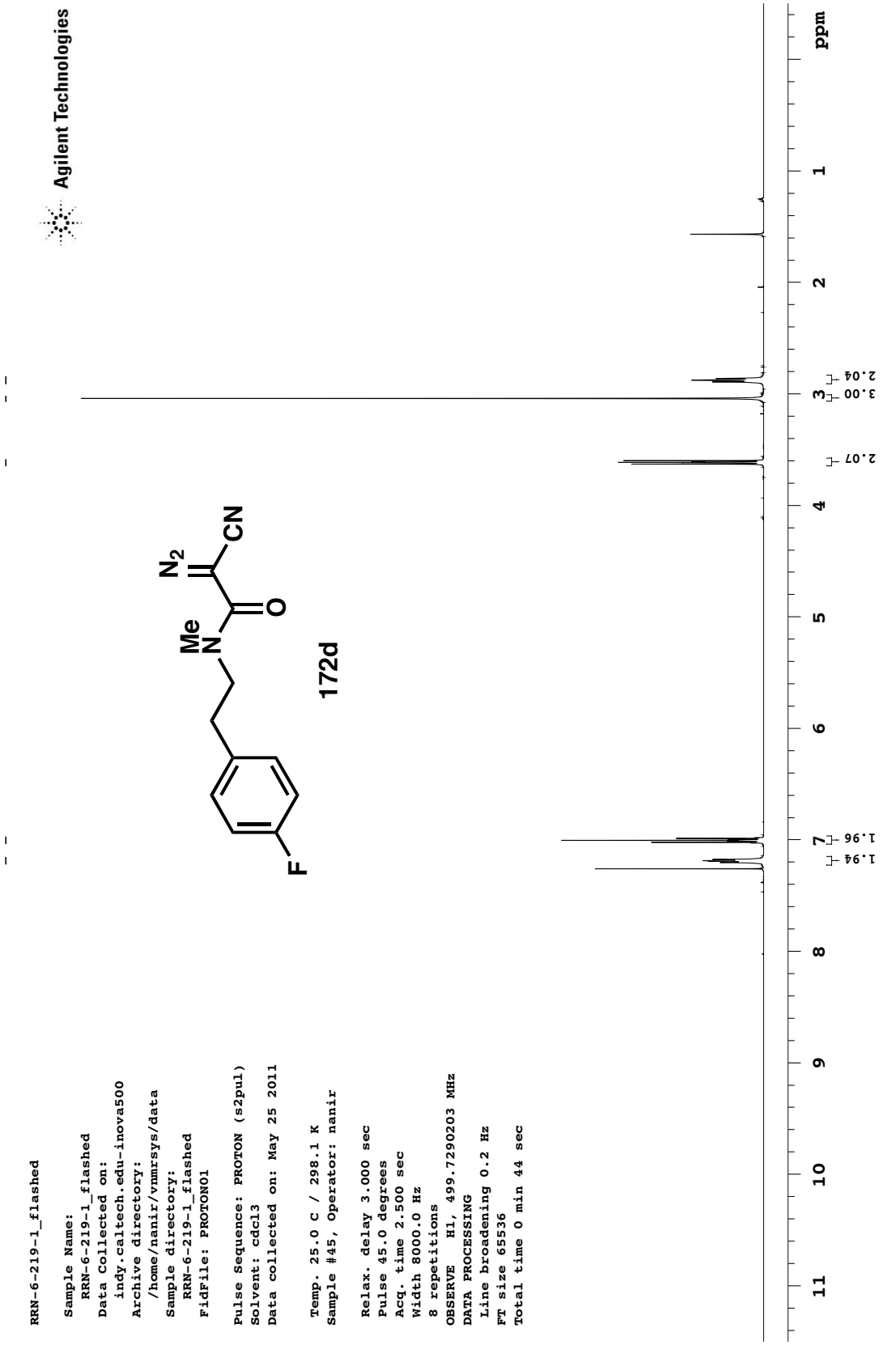

Agilent Technologies
Sample Name:
RRN-5-267-13C_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-5-267-13C_II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 3 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6553367 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 50 min
Me
N
O
N2
CN
172a
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

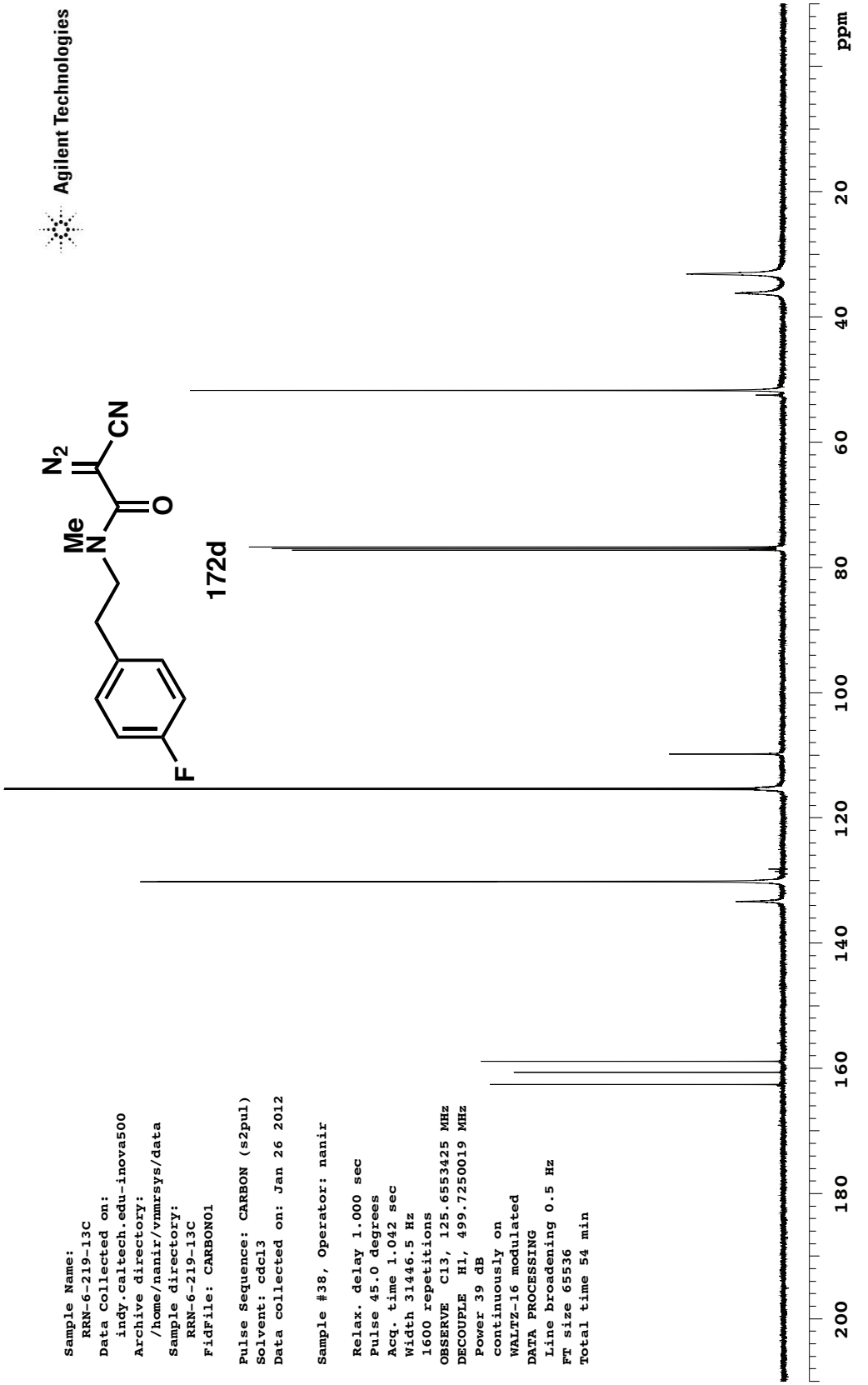

Sample Name:
RRN-9-157-2_HVAC_check
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-157-2_HVAC_check
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 29 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7127430 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
Me
N
Me
O
N2
CN
172b
3.91
2.16
3.00
2.09
3.08
ppm

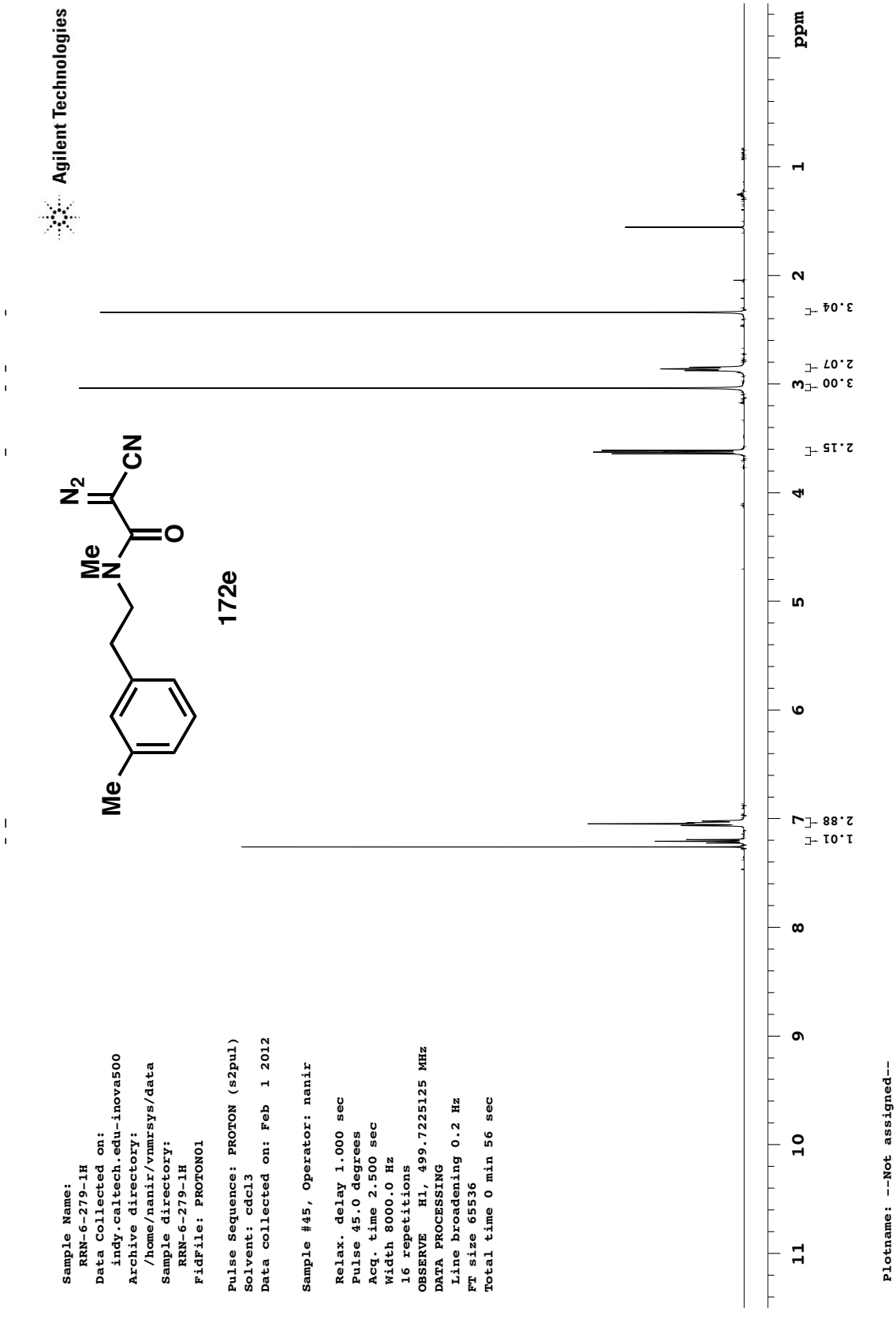

Sample Name:
RRN-9-157-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-157-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 29 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
1100 repetitions
OBSERVE C13, 125.6528854 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 55 min
Me
N
Me
O
N2
CN
172b
200
180
160
140
120
100
80
60
40
20
ppm

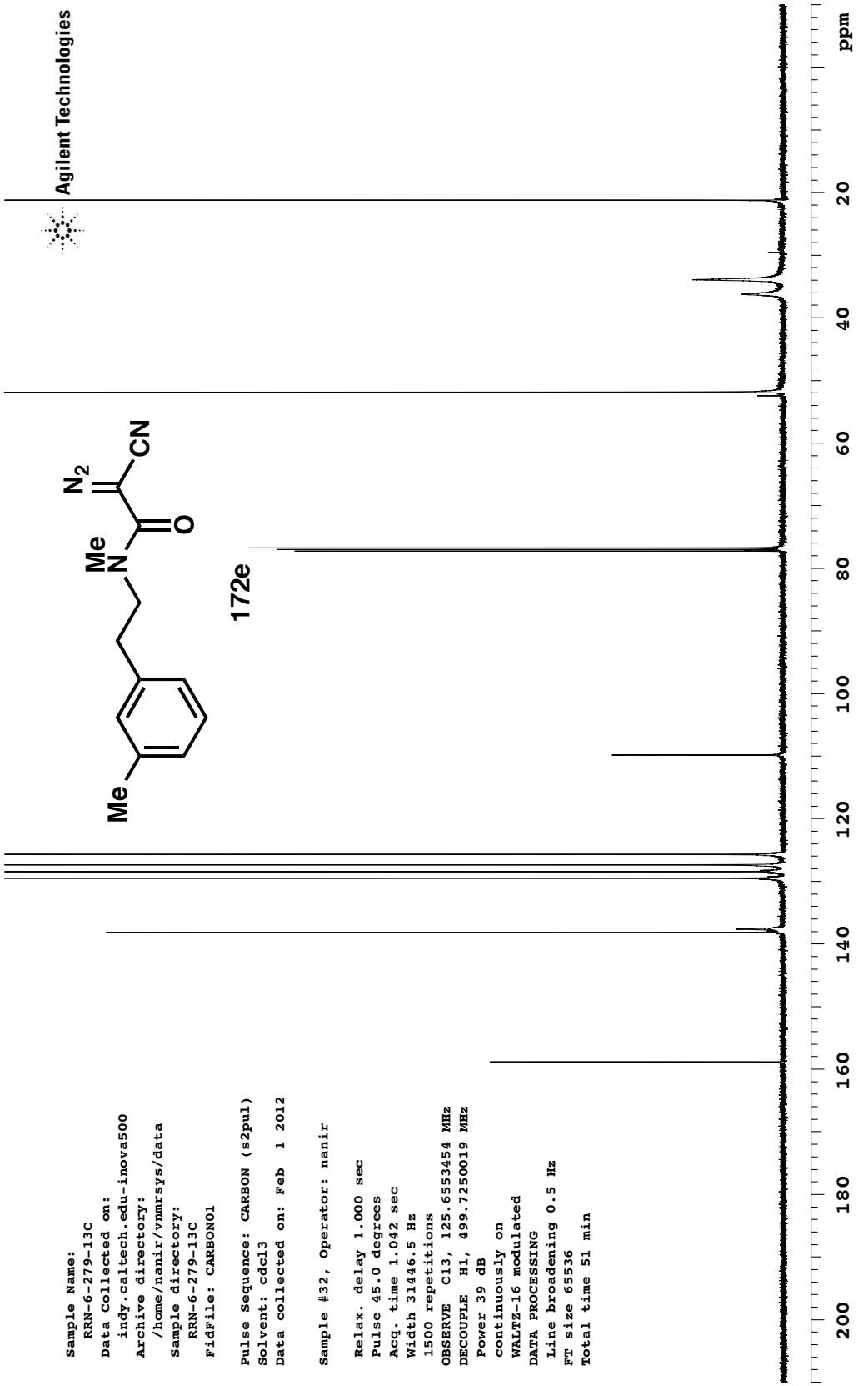

Agilent Technologies
Sample Name:
RRN-7-23-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-23-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 2 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
Me
N
O
N2
CN
MeO
172c
1.95
1.97
3.13
2.14
3.00
2.08
ppm
Plotname: --Not assigned--

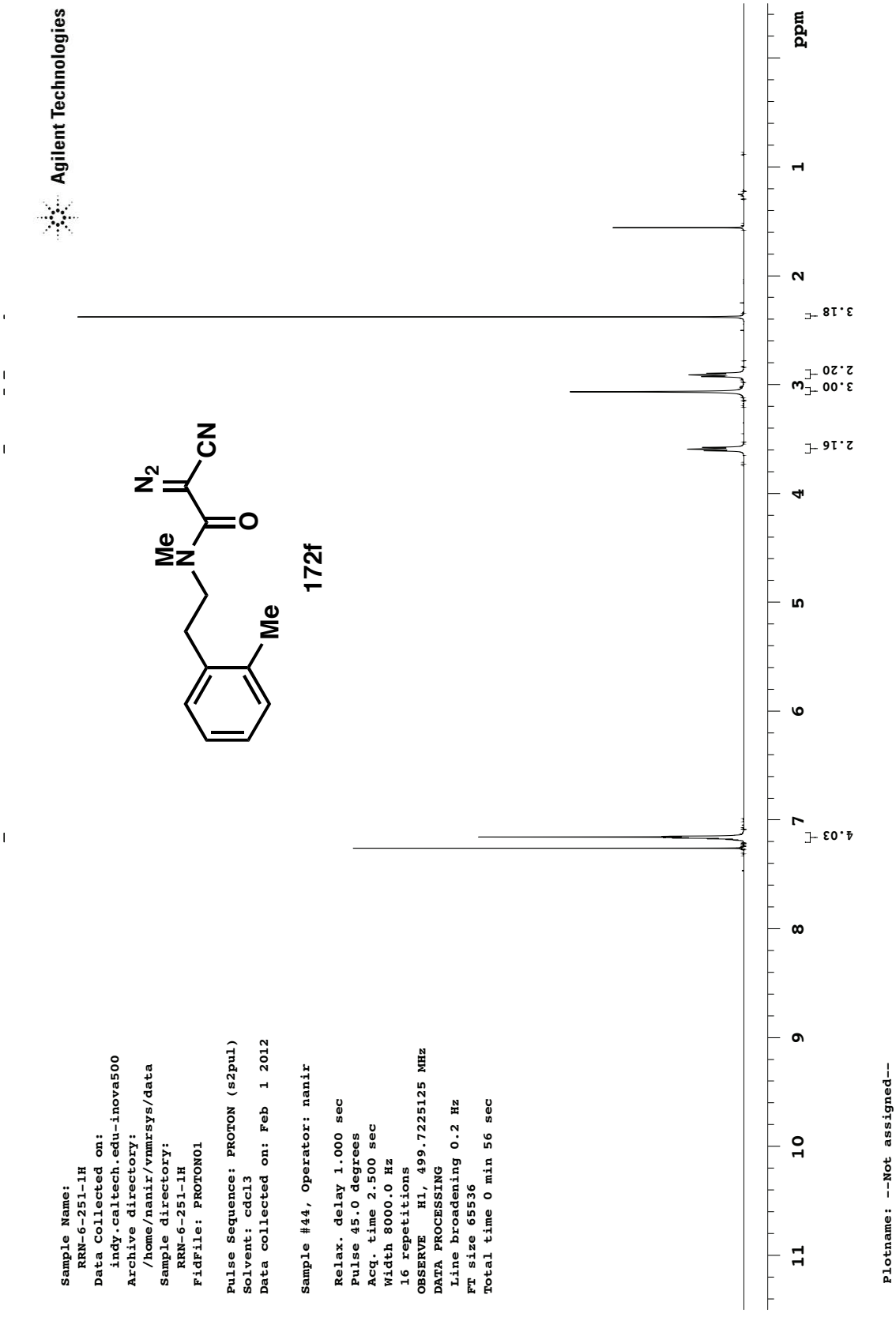

Agilent Technologies
Sample Name:
RRN-7-23-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-23-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 2 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6553377 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
Me
N
O
N2
CN
MeO
172c
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--


Agilent Technologies
RRN-6-219-1_flashed
Sample Name:
RRN-6-219-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-219-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 25 2011
Temp. 25.0 C / 298.1 K
Sample #45, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7290203 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 44 sec
Me
N
O
CN
F
172d
1.94
1.96
2.07
2.04
3.00
ppm
Plotname: --Not assigned--

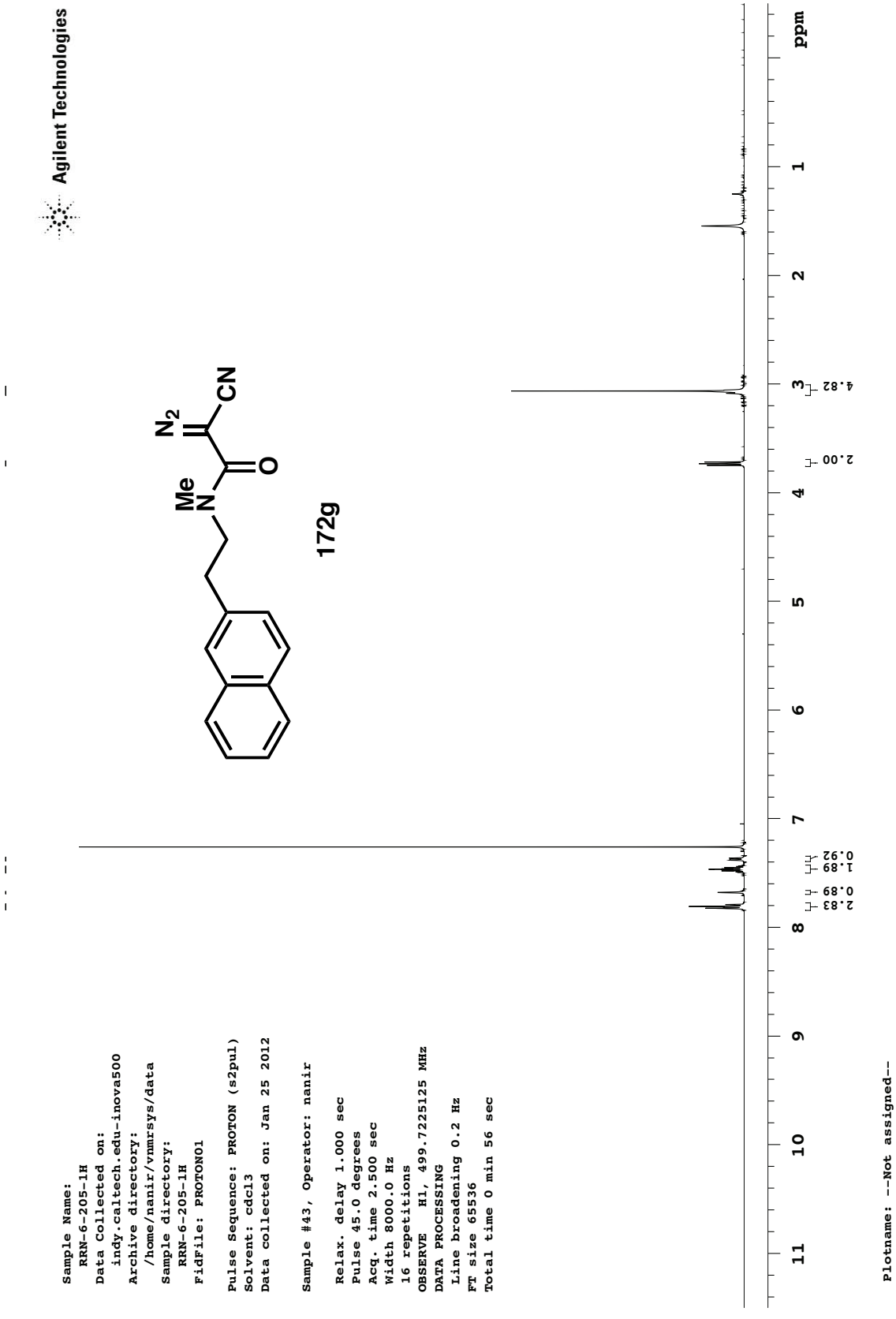

Agilent Technologies
172d
Me
N
O
N2
CN
F
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-6-219-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-219-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 26 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6553425 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 54 min
Plotname: --Not assigned--


Agilent Technologies
Me
N
Me
O
N2
CN
172e
Sample Name:
RRN-6-279-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-279-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 1 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
1.01
2.88
2.15
3.00
2.07
3.04
ppm
Plotname: --Not assigned--

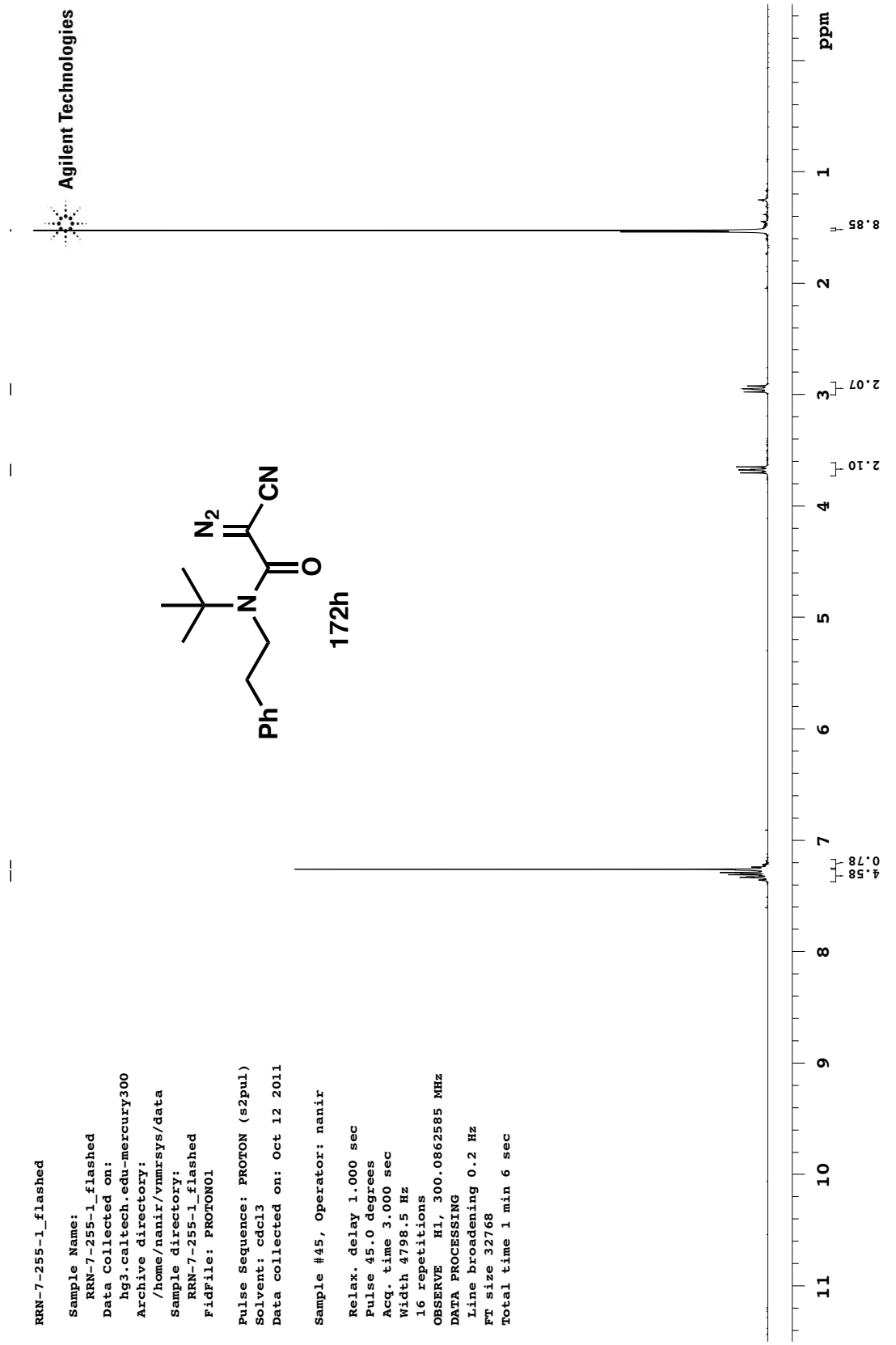

Agilent Technologies
Me
N
Me
O
N2
CN
172e
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-6-279-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-279-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 1 2012
Sample #32, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6553454 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 51 min
Plotname: --Not assigned--


Agilent Technologies
Sample Name:
RRN-6-251-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-251-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 1 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
N2
CN
O
Me
N
Me
172f
4.03
2.16
3.00
2.20
3.18
ppm
Plotname: --Not assigned--

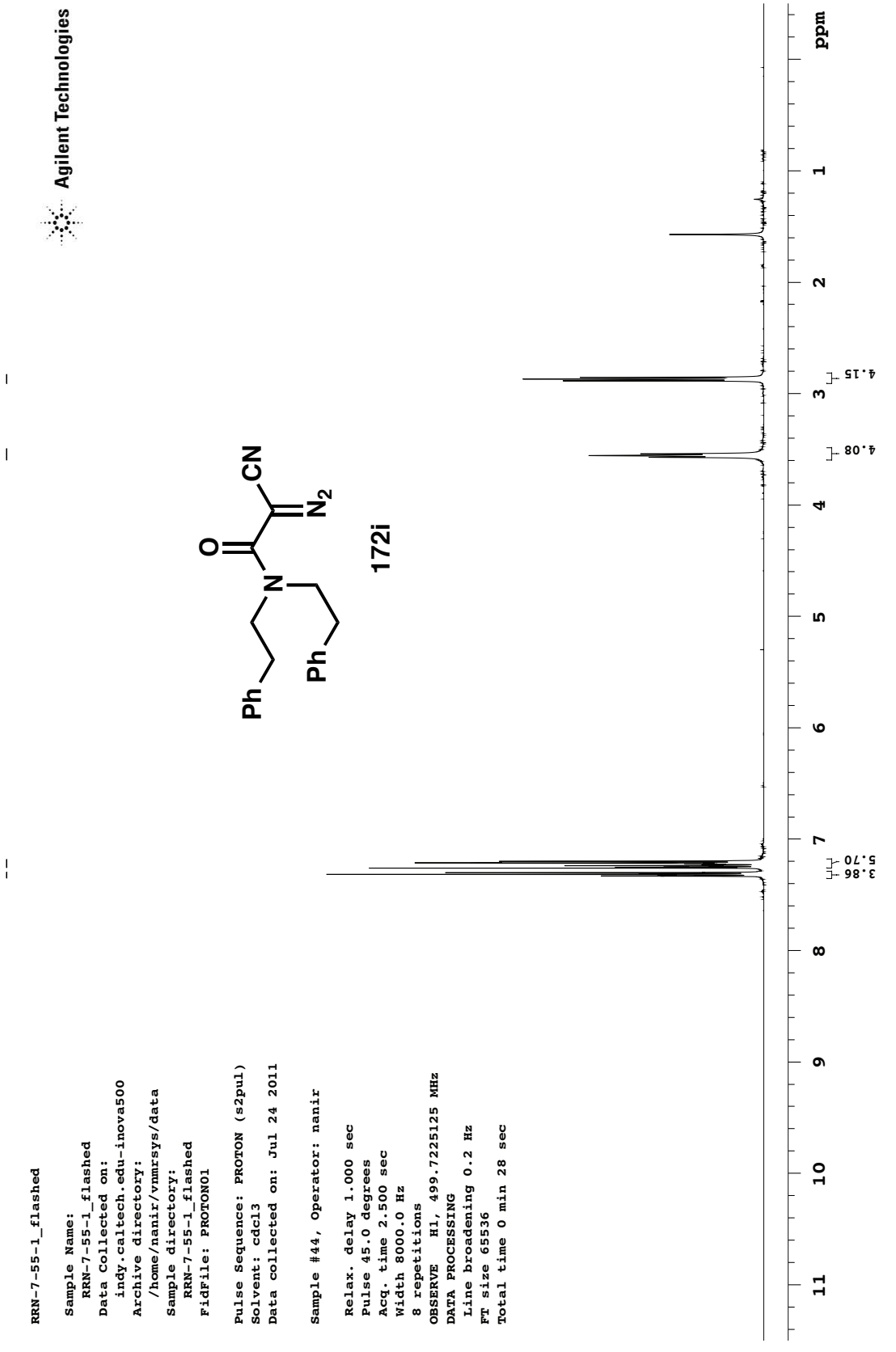
Agilent Technologies
Me
N
O
N2
CN
Me
172f
Sample Name:
RRN-6-251-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-251-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 2 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6553329 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 50 min
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

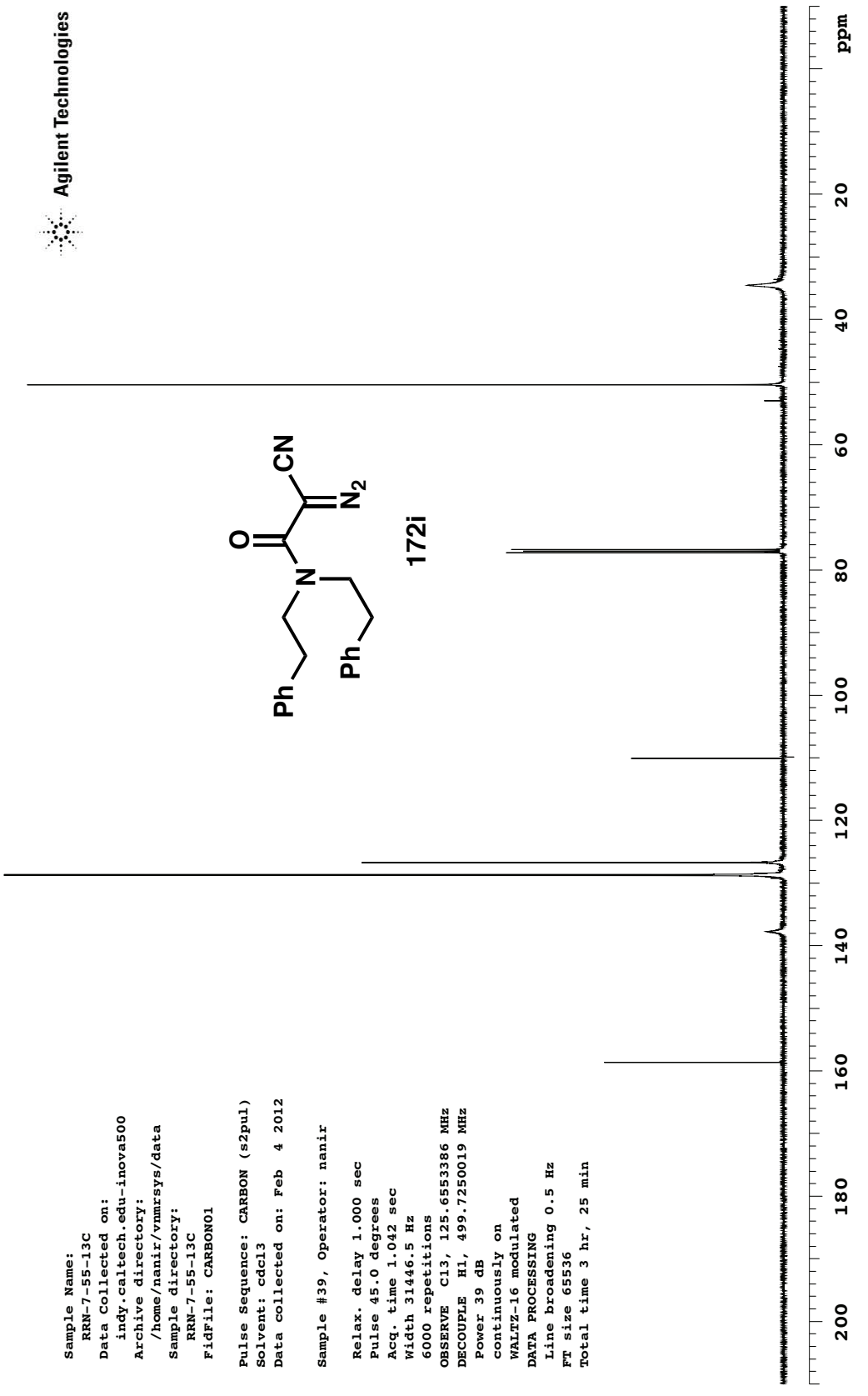

Agilent Technologies
Sample Name:
RRN-6-205-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-205-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 25 2012
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
Me
N
O
N2
CN
172g
2.83
0.89
1.89
0.92
2.00
4.82
ppm
Plotname: --Not assigned--

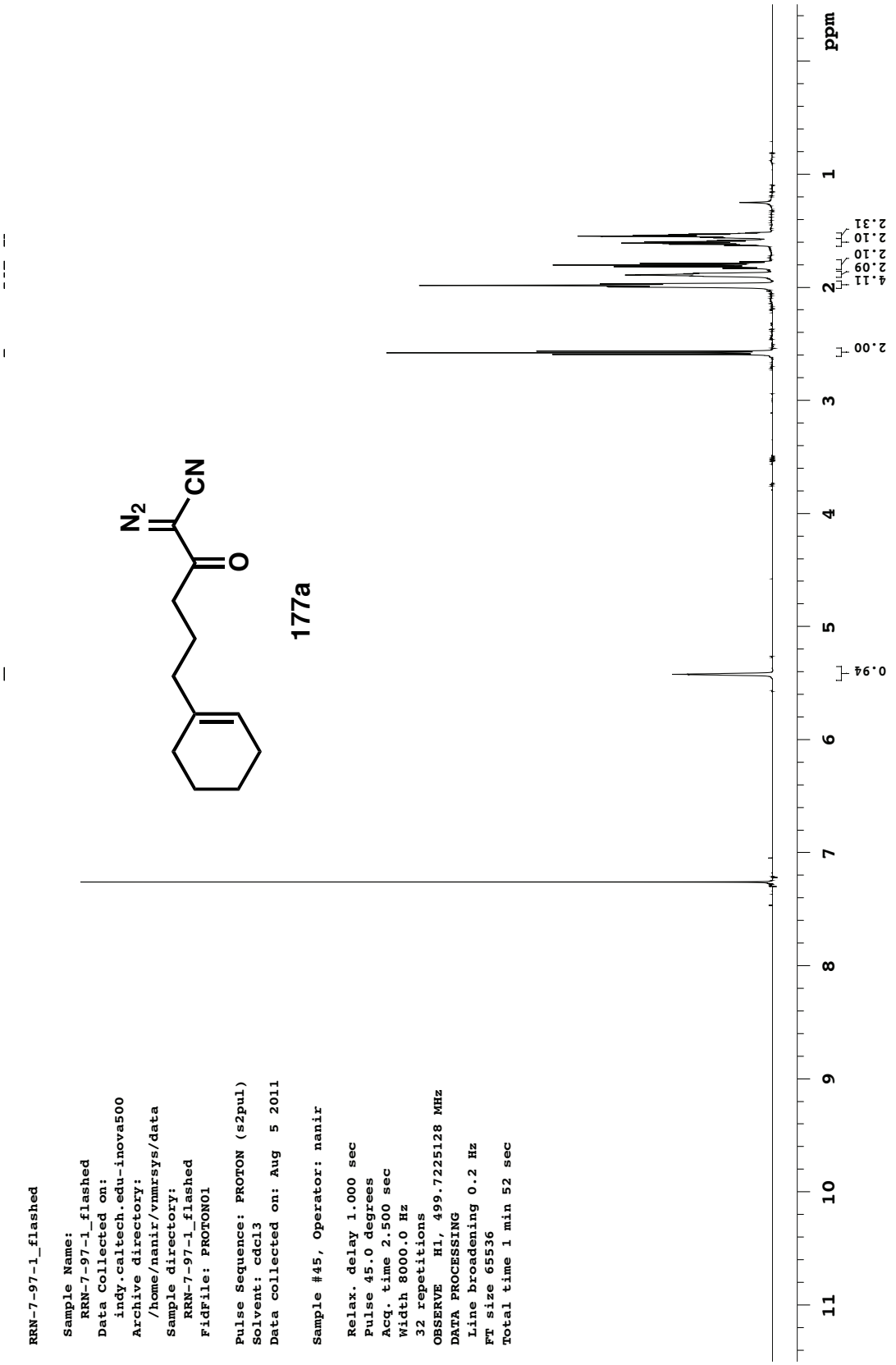
Agilent Technologies
Sample Name:
RRN-6-205-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-6-205-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 25 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6553377 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 54 min
Me
N
O
N2
CN
172g
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

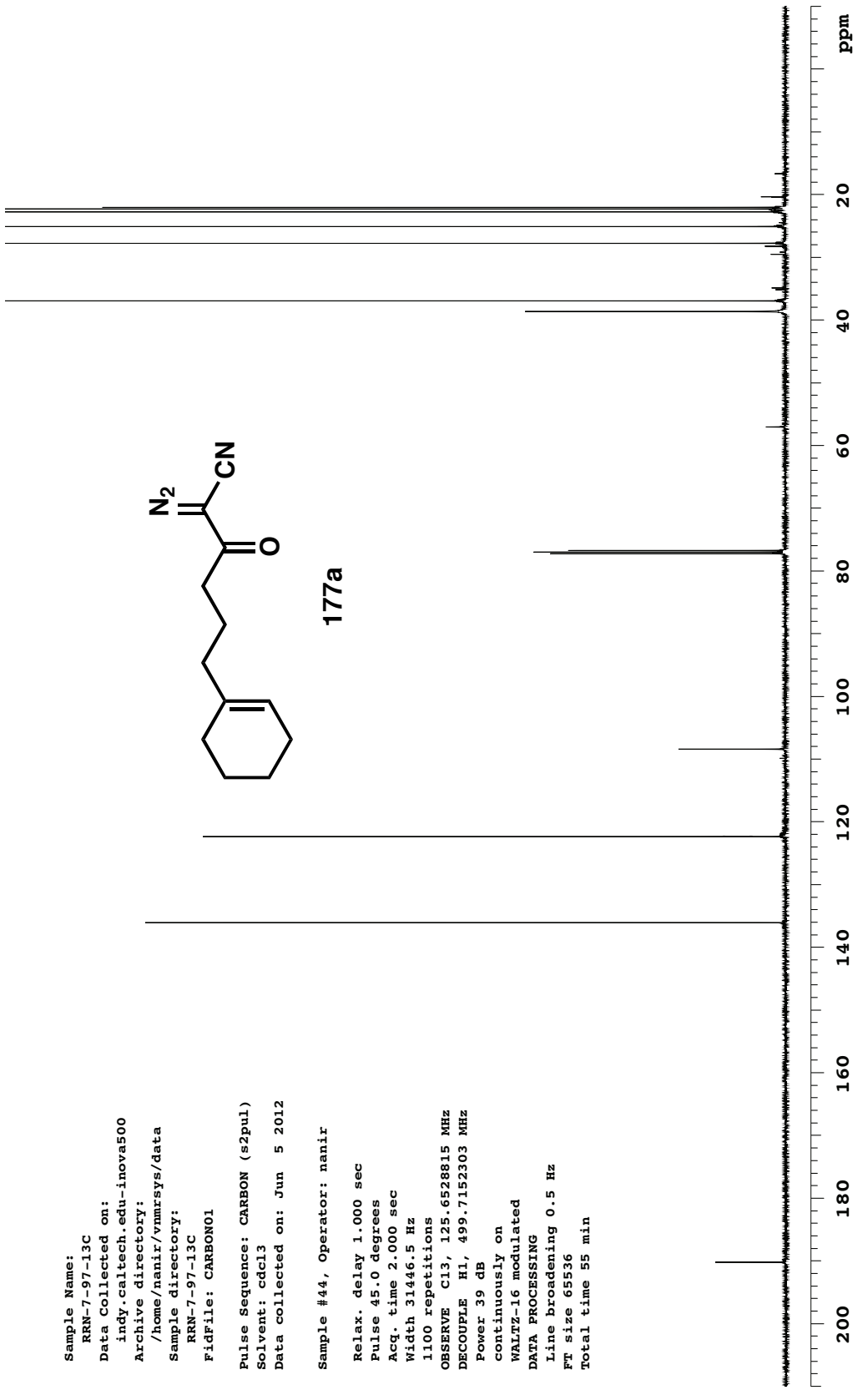

RRN-7-255-1_flashed
Sample Name:
RRN-7-255-1_flashed
Data Collected on:
hg3.caltech.edu-mercury300
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-255-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 12 2011
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
16 repetitions
OBSERVE H1, 300.0862585 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 1 min 6 sec
Agilent Technologies
N2
CN
O
N
Ph
172h
8.85
2.07
2.10
4.58
0.78
ppm
Plotname: --Not assigned--

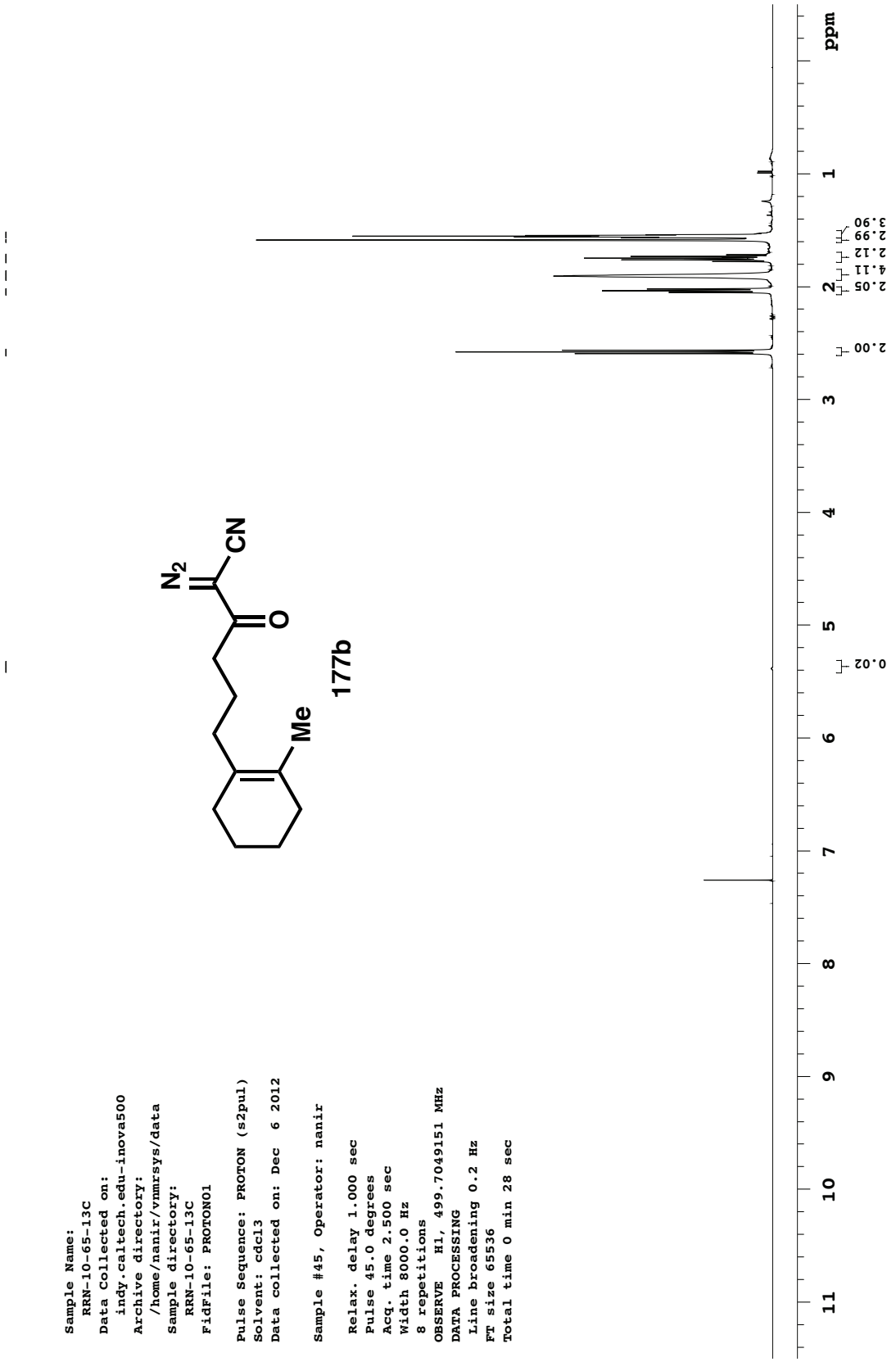
Agilent Technologies
Sample Name:
RRN-7-255-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-255-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 6 2012
Sample #45, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
5000 repetitions
OBSERVE C13, 125.6553300 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 4 hr, 14 min
Ph
N
O
N2
CN
172h
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

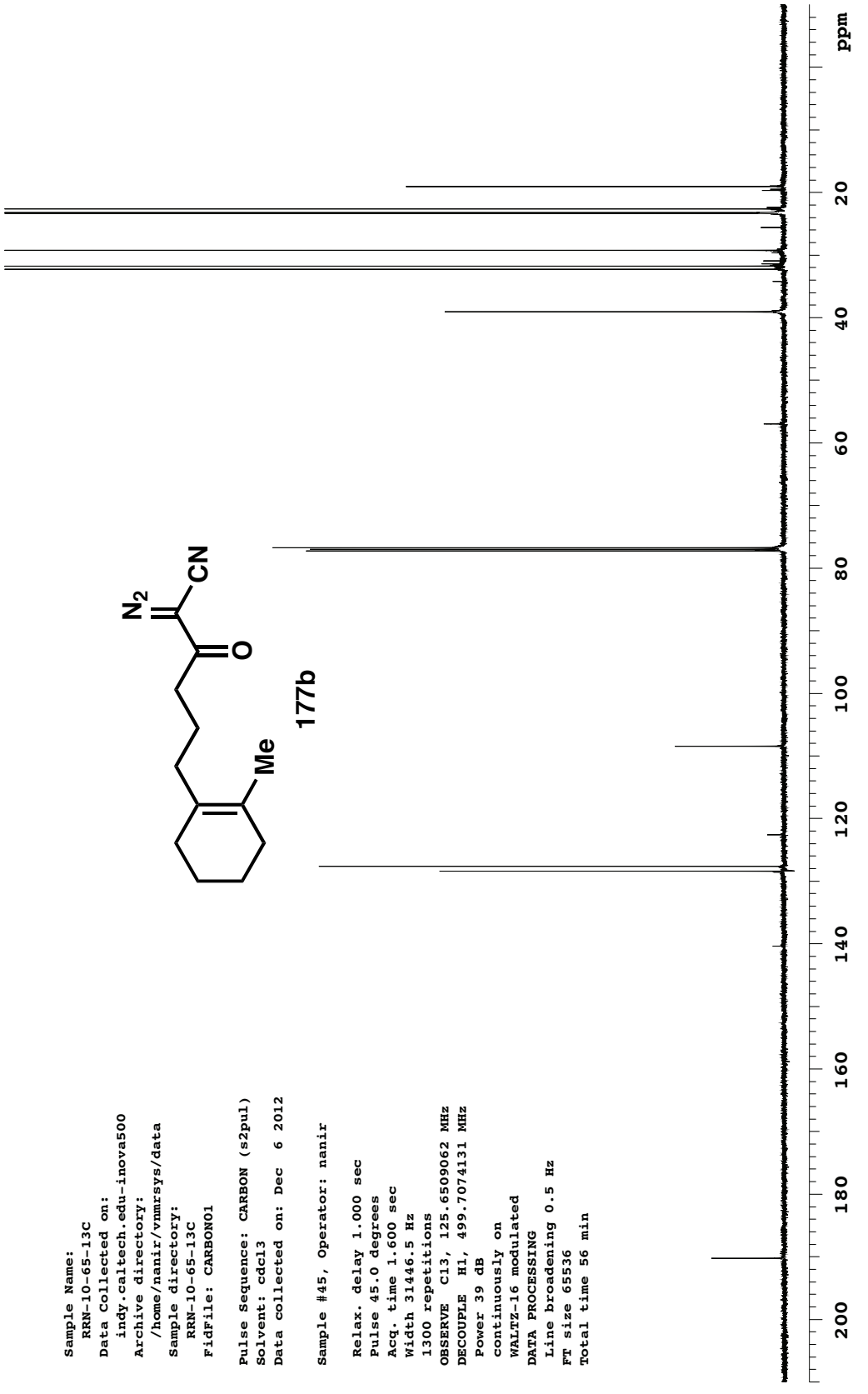

RRN-7-55-1_flashed
Sample Name:
RRN-7-55-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-55-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 24 2011
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
Agilent Technologies
O
CN
N2
N
Ph
Ph
172i
3.86
5.70
4.08
4.15
ppm
Plotname: --Not assigned--

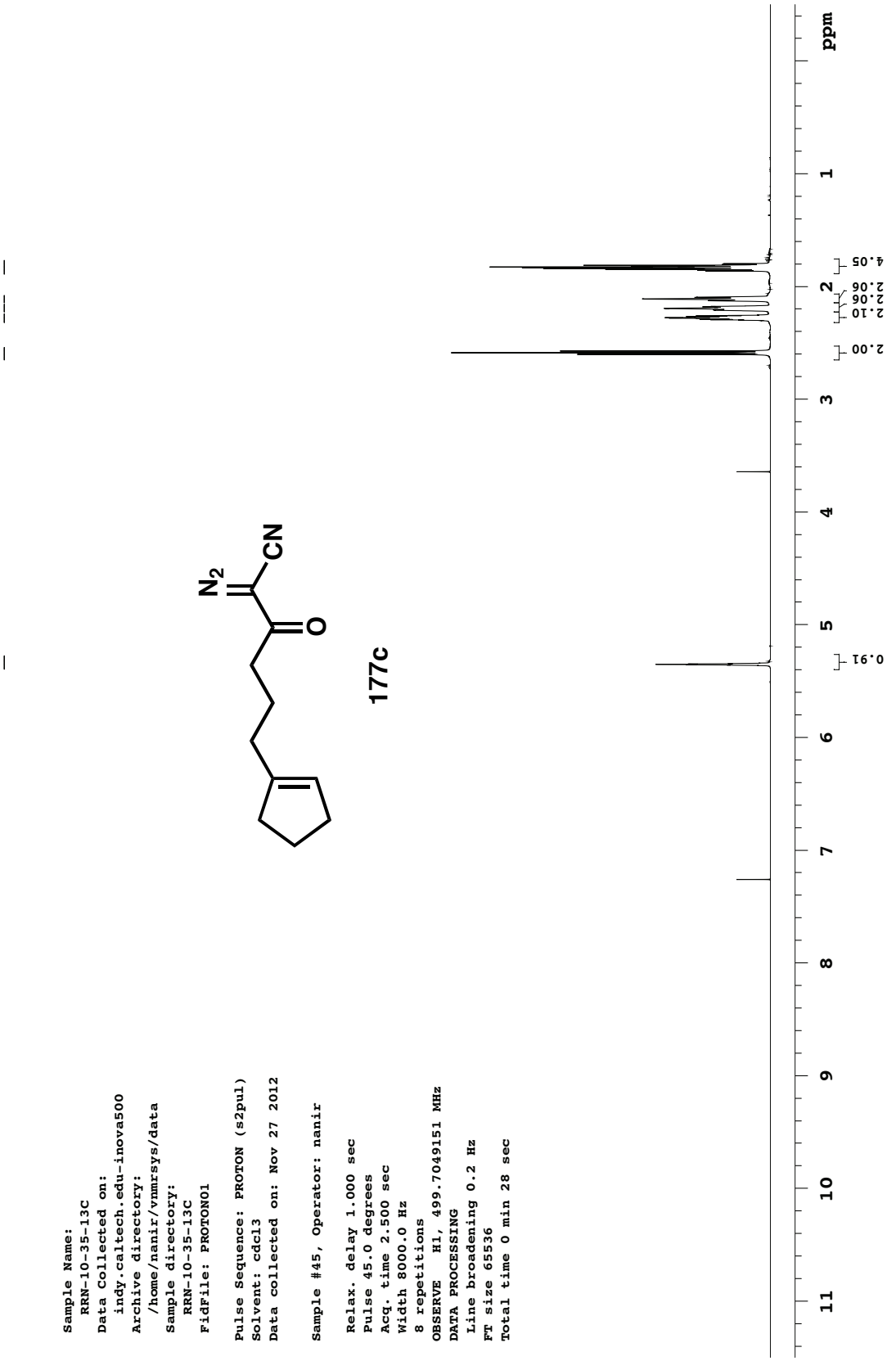

Agilent Technologies
Sample Name:
RRN-7-55-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-55-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 4 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
6000 repetitions
OBSERVE C13, 125.6553386 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 25 min
O
CN
N2
N
Ph
Ph
172i
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

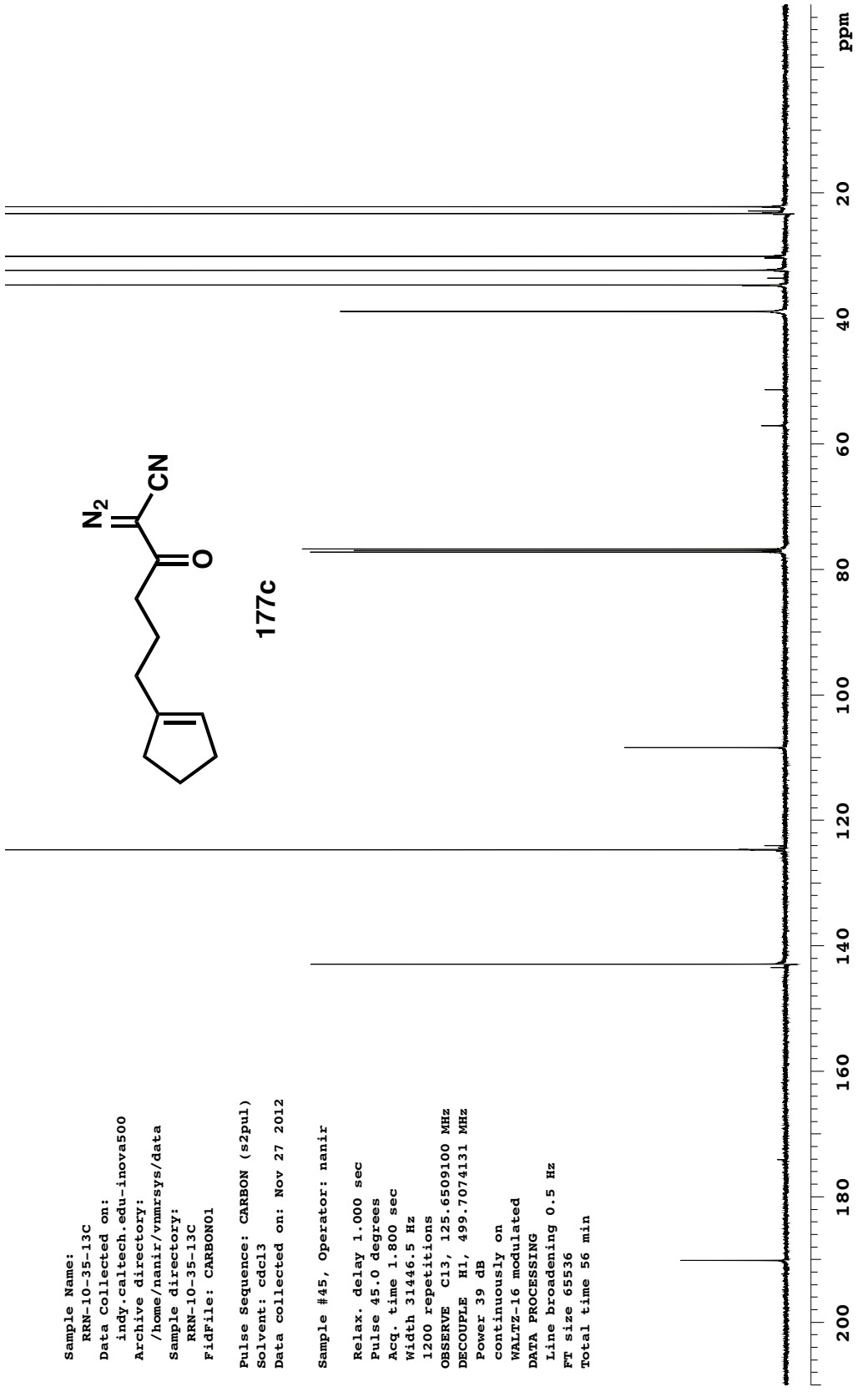

RRN-7-97-1_flashed
Sample Name:
RRN-7-97-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-97-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 5 2011
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225128 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
N2
CN
O
177a
0.94
2.00
4.11
2.09
2.10
2.10
2.31
ppm

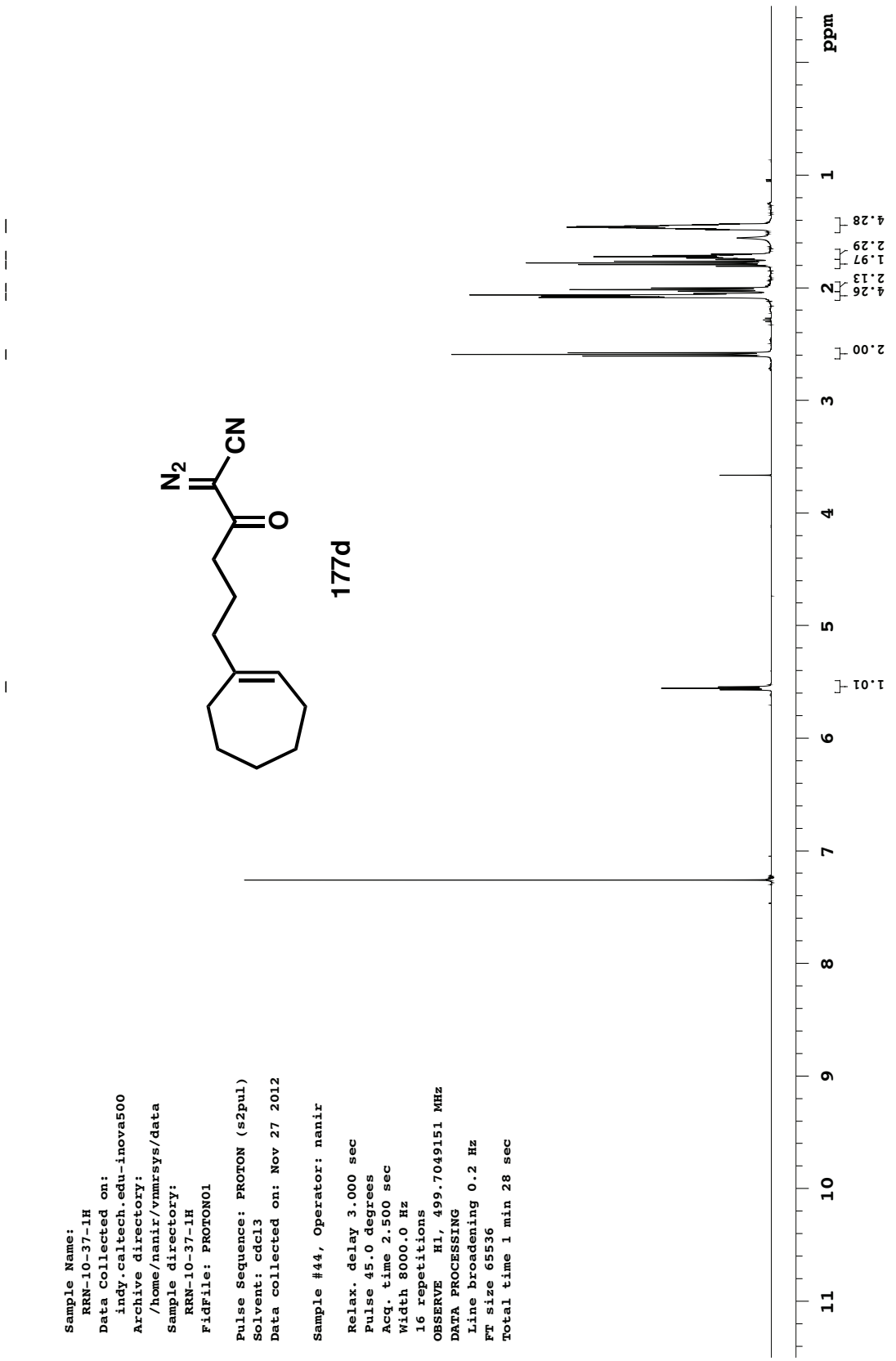

Sample Name:
RRN-7-97-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-97-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
1100 repetitions
OBSERVE C13, 125.6528815 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 55 min
N2
CN
O
177a
200
180
160
140
120
100
80
60
40
20
ppm

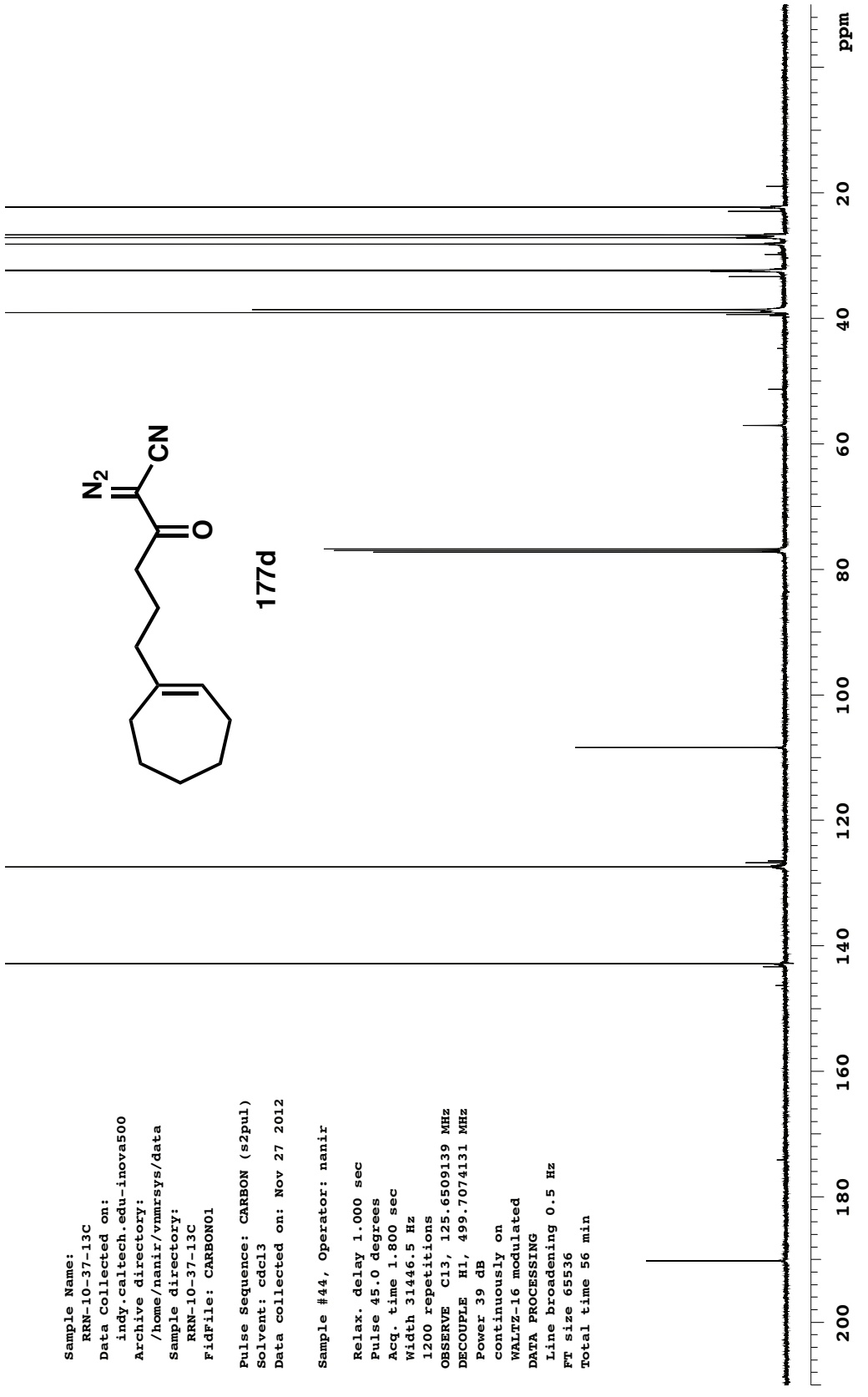

Sample Name:
RRN-10-65-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-65-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 6 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
N2
CN
O
Me
177b
ppm
0.02
2.00
2.05
4.11
2.12
2.99
3.90

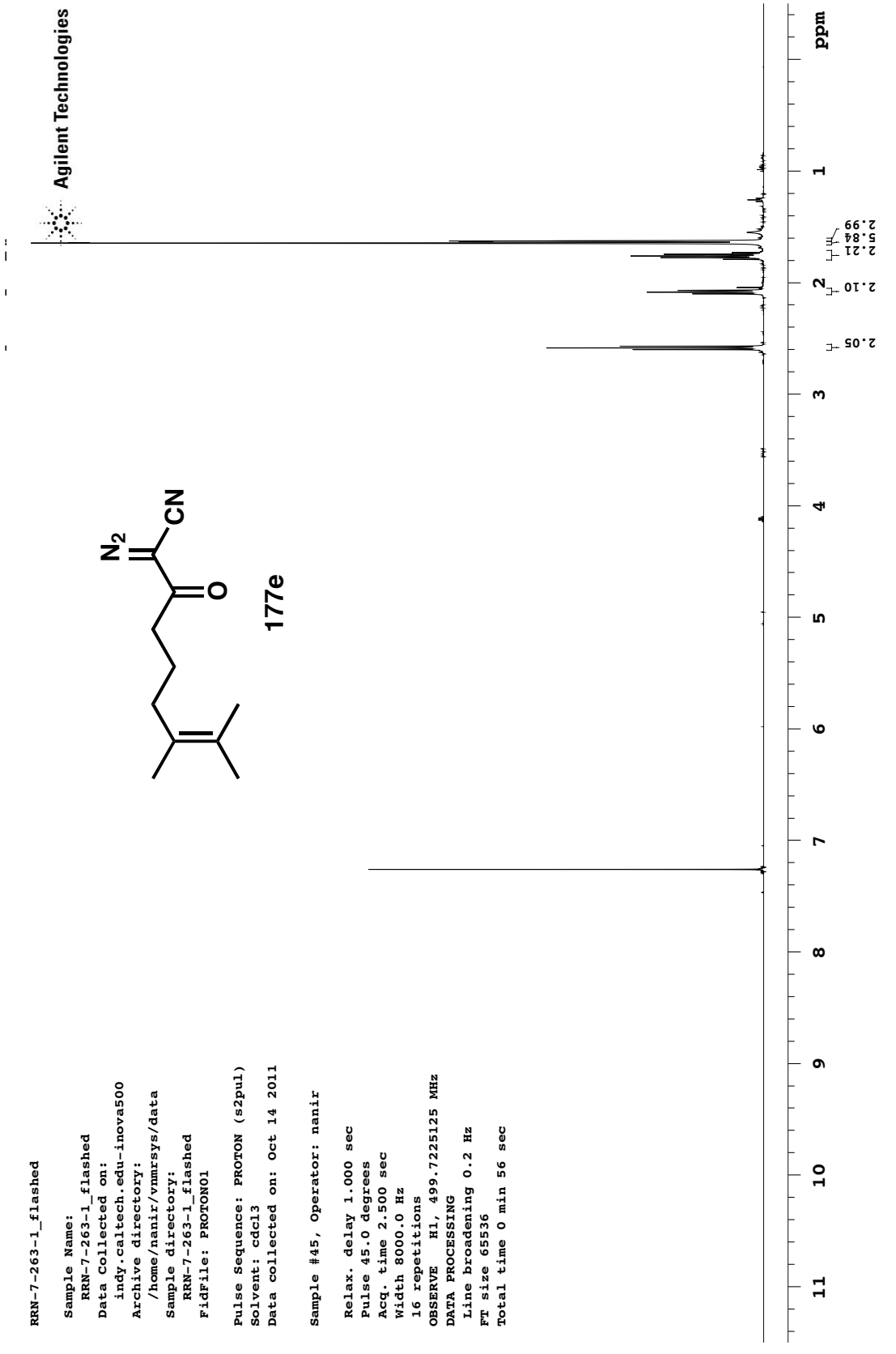

Sample Name:
RRN-10-65-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-65-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 6 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6509062 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
N2
CN
O
Me
177b
200
180
160
140
120
100
80
60
40
20
ppm

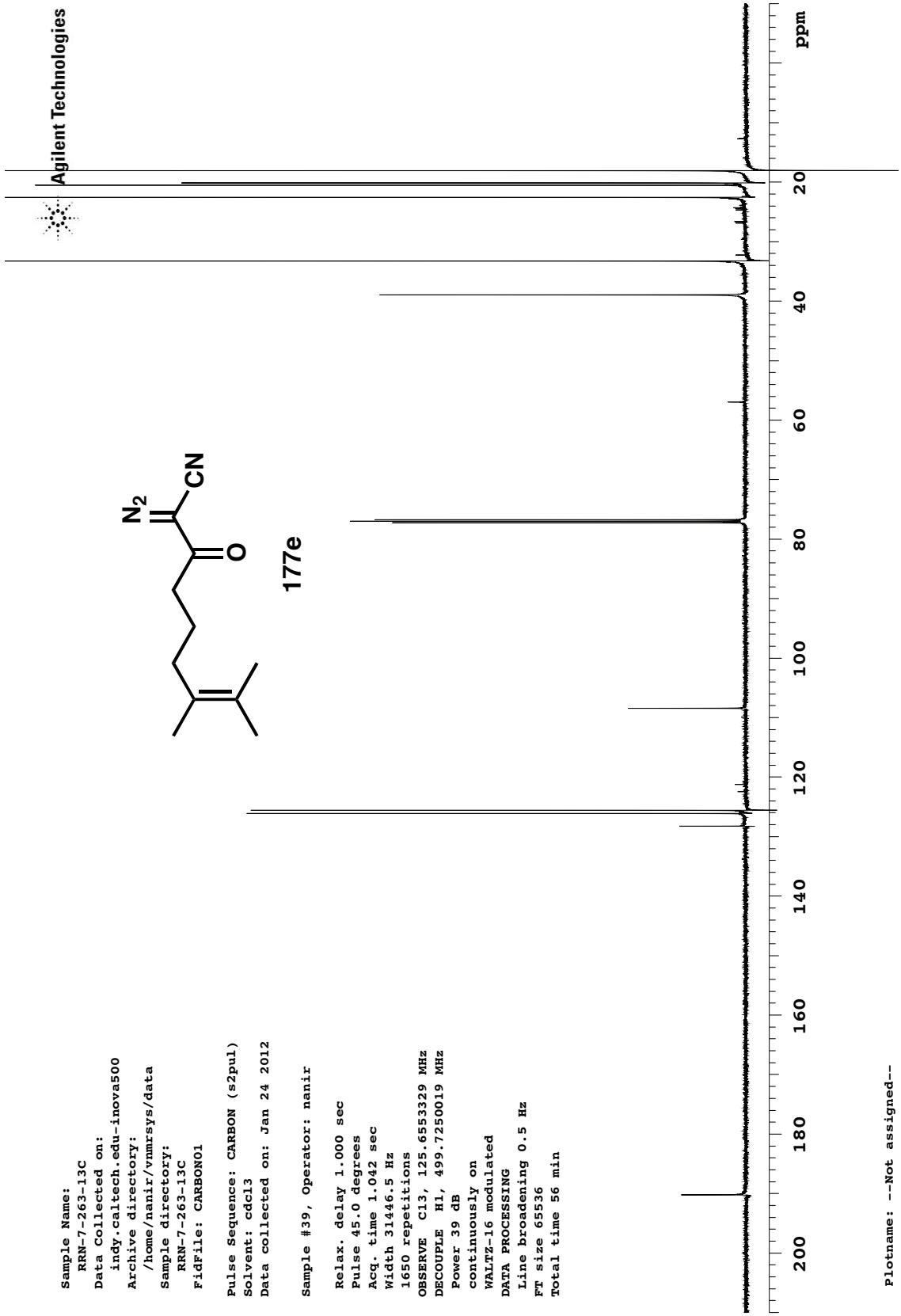

Sample Name:
RRN-10-35-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-35-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 27 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
N2
CN
O
177c
4.05
2.06
2.06
2.10
2.00
0.91
ppm

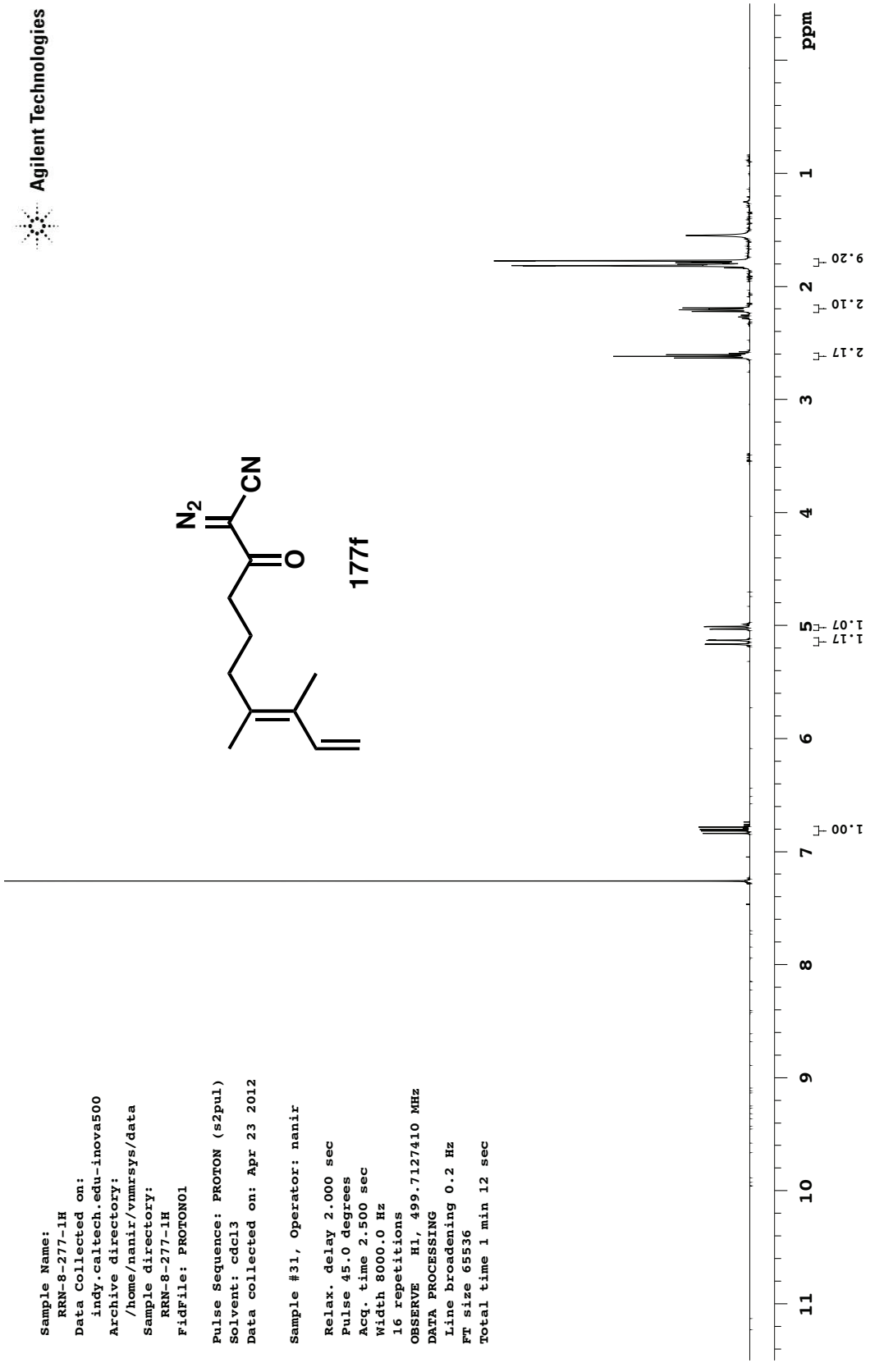

Sample Name:
RRN-10-35-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-35-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 27 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6509100 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
N2
CN
O
177c
200
180
160
140
120
100
80
60
40
20
ppm

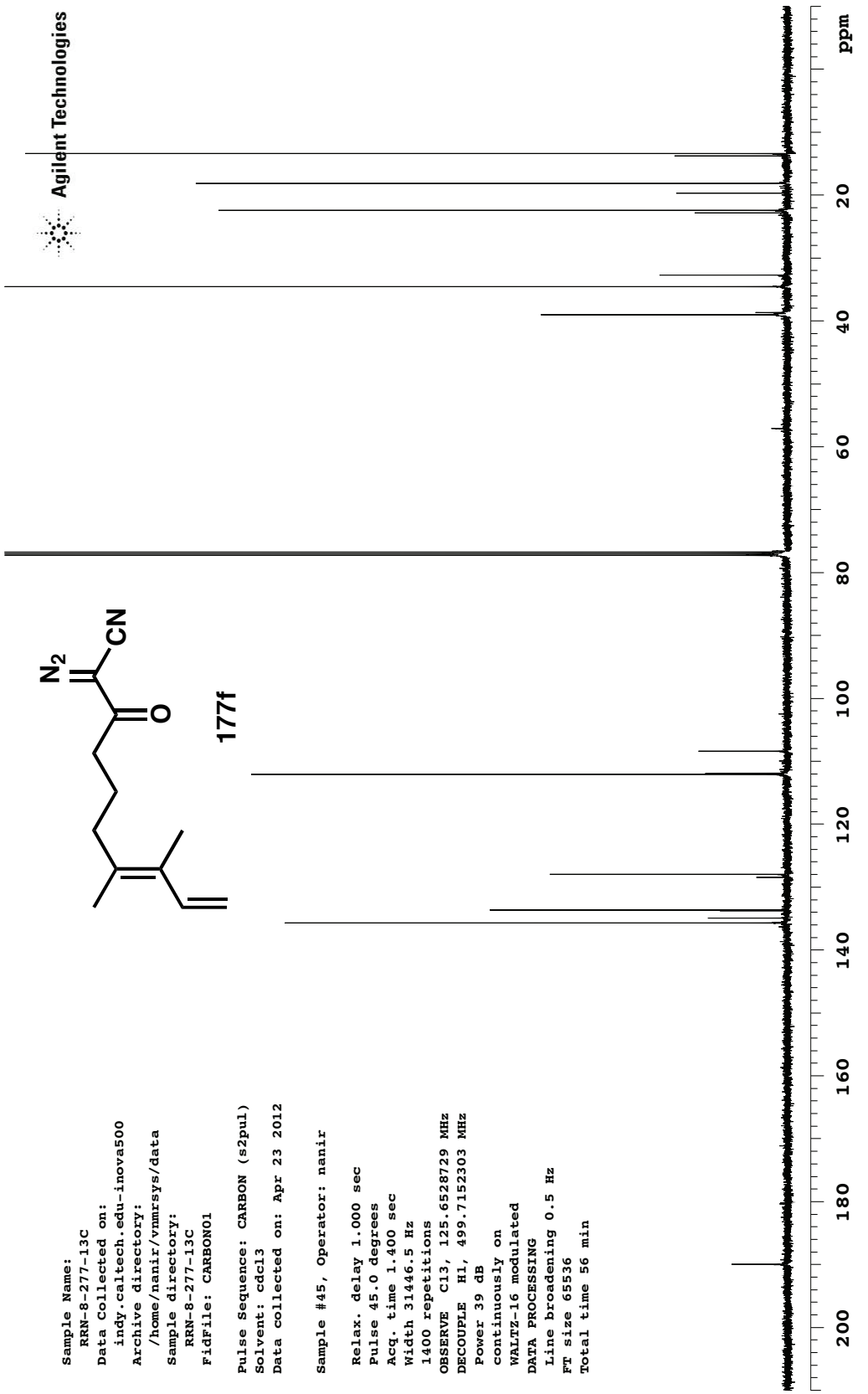

Sample Name:
RRN-10-37-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-37-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 27 2012
Sample #44, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
N2
CN
O
177d
1.01
2.00
4.26
2.13
1.97
2.29
4.28
ppm

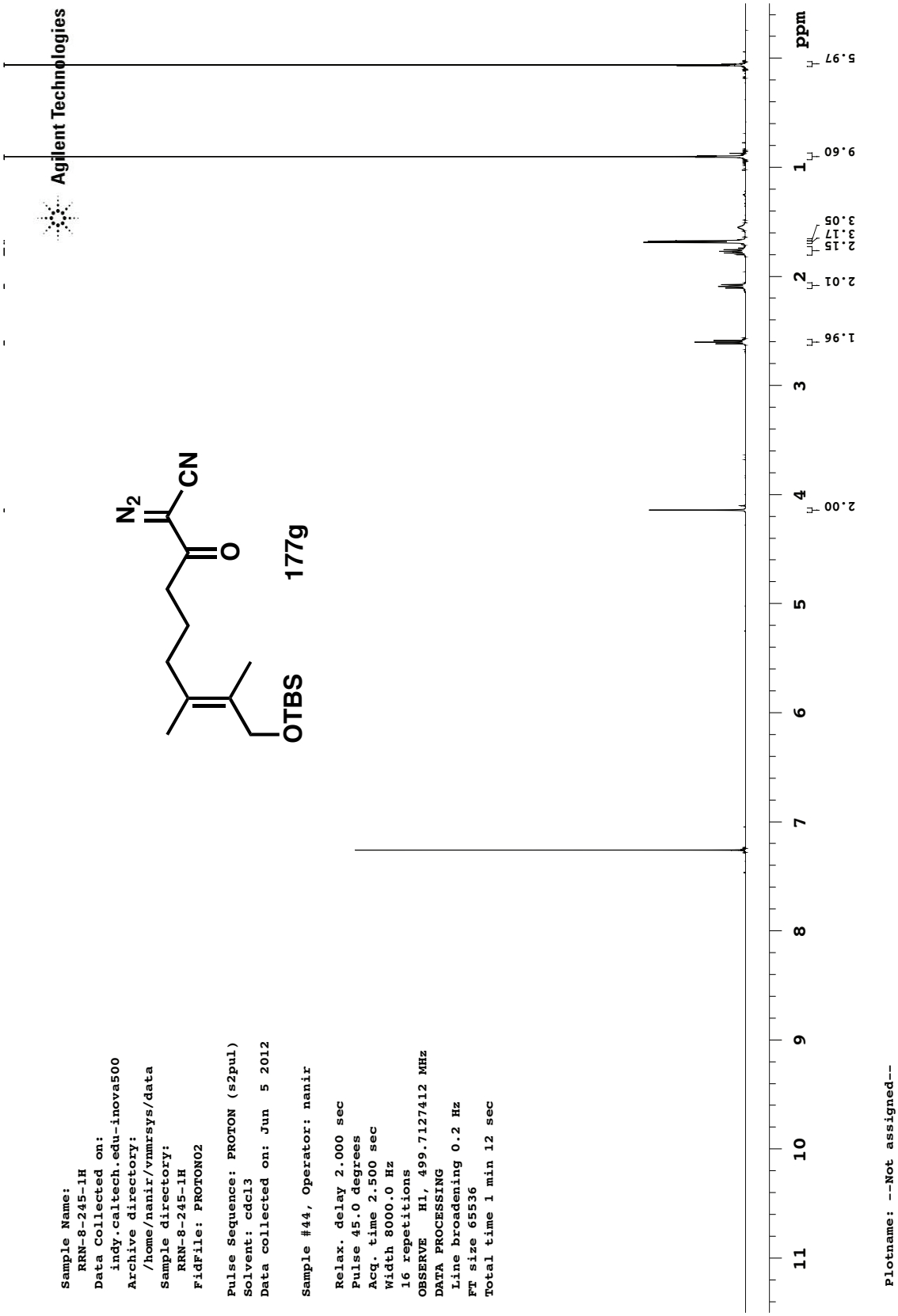

Sample Name:
RRN-10-37-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-37-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 27 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6509139 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
N2
CN
O
177d
200
180
160
140
120
100
80
60
40
20
ppm

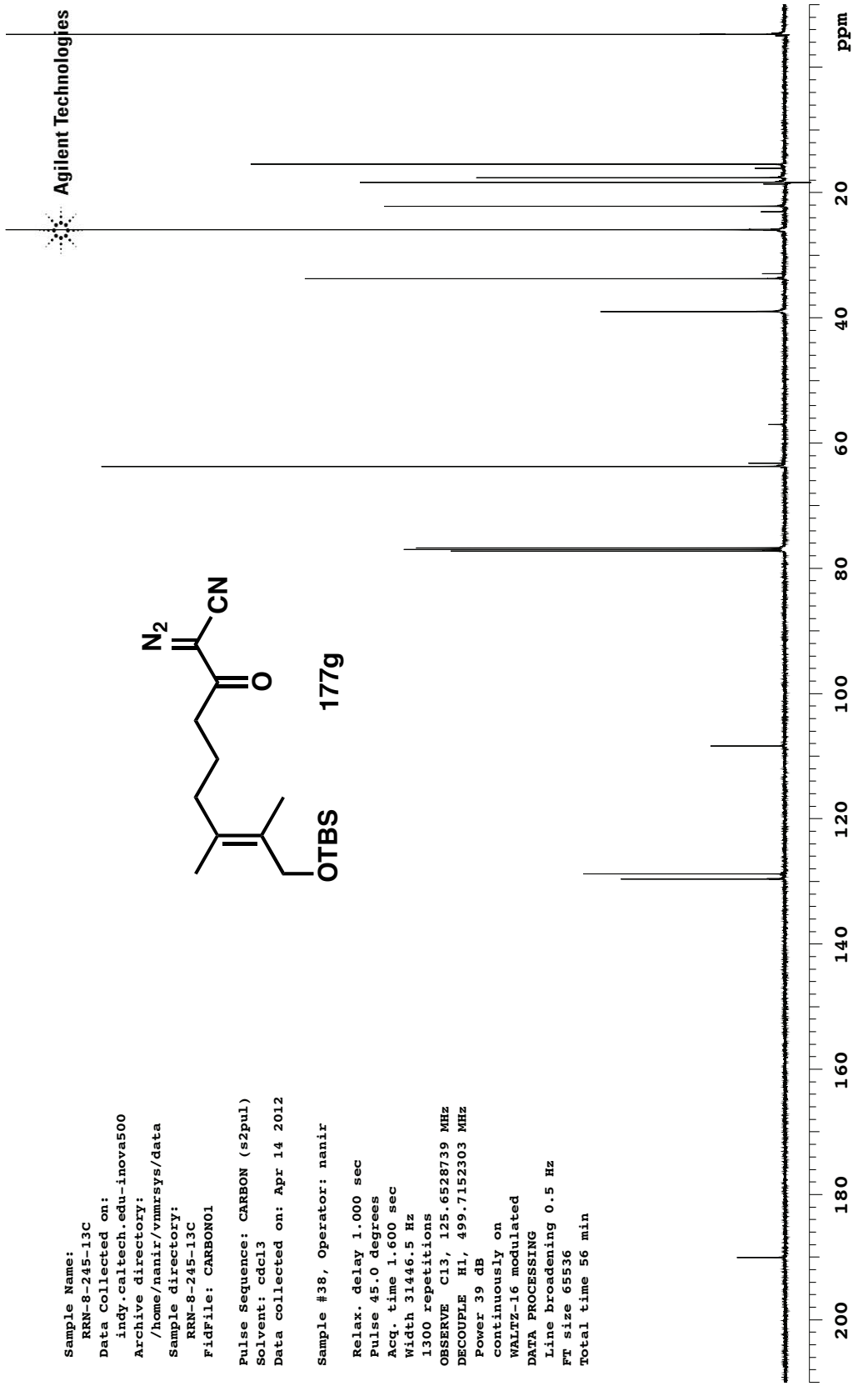

RRN-7-263-1_flashed
Sample Name:
RRN-7-263-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-263-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 14 2011
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
Agilent Technologies
N2
CN
O
177e
2.05
2.10
2.21
5.84
2.99
ppm
Plotname: --Not assigned--

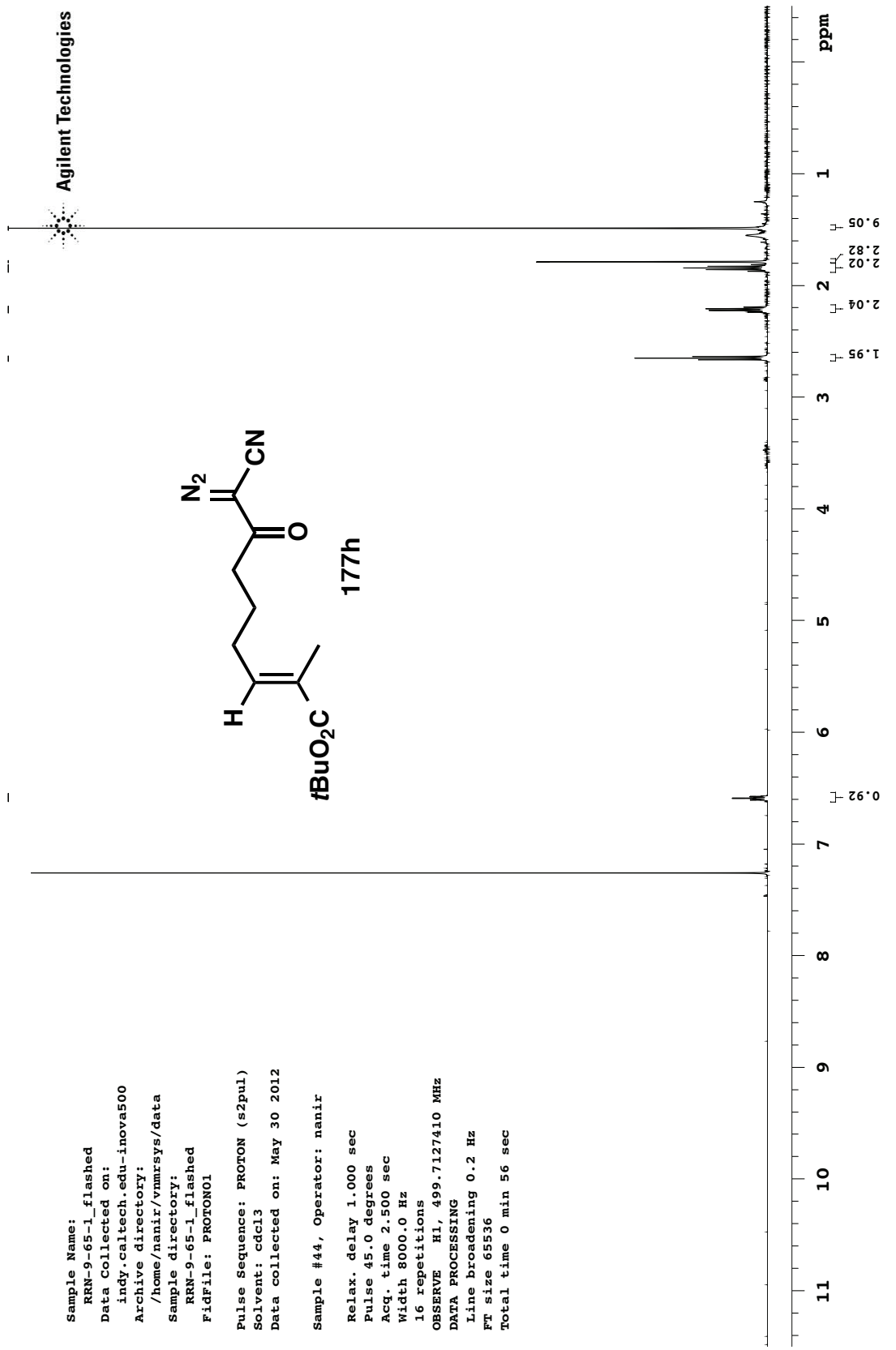

Agilent Technologies
177e
N2
CN
O
ppm
200
180
160
140
120
100
80
60
40
20
Sample Name:
RRN-7-263-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-263-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 24 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1650 repetitions
OBSERVE C13, 125.6553329 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
Plotname: --Not assigned--

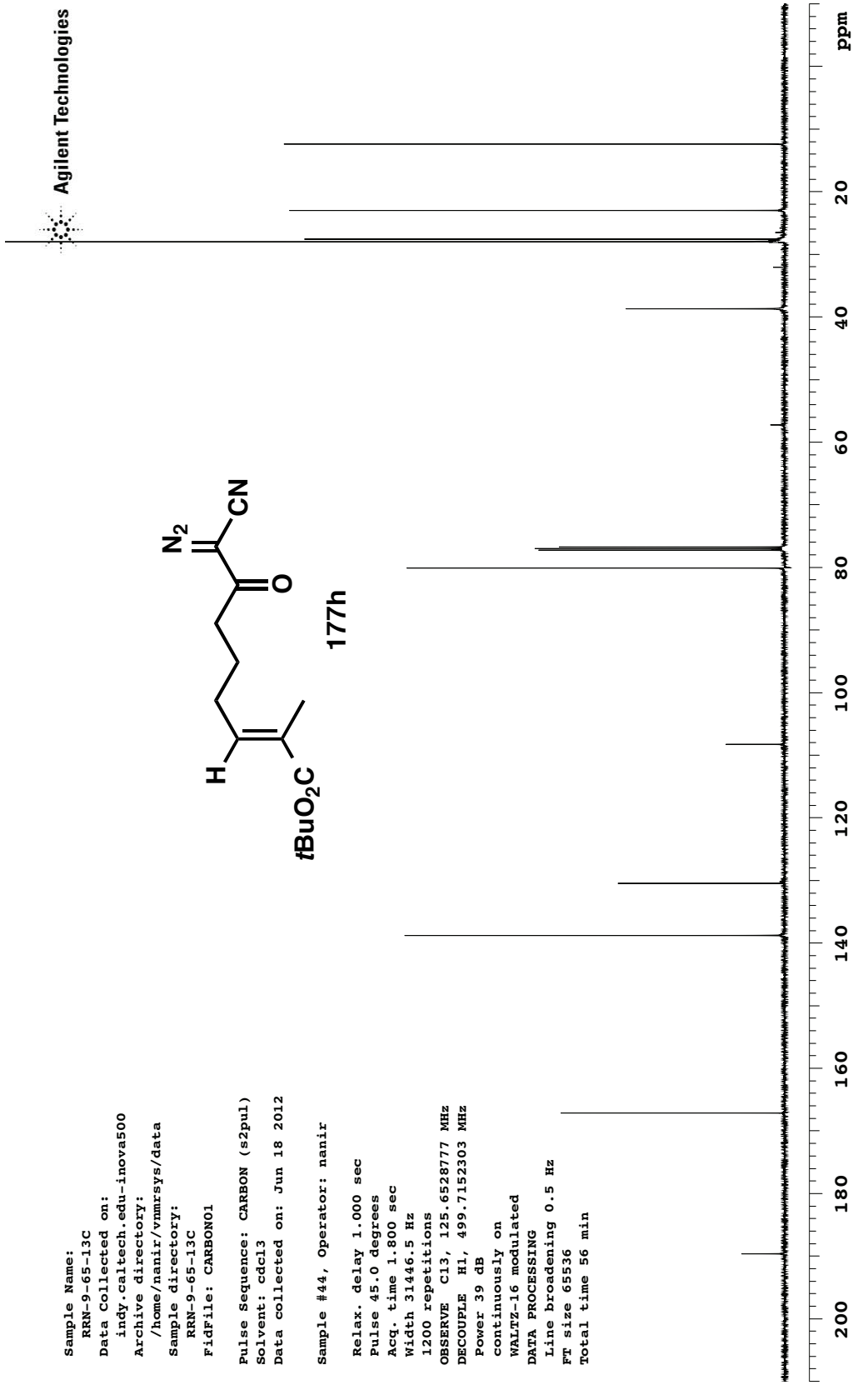

Agilent Technologies
Sample Name:
RRN-8-277-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-277-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 23 2012
Sample #31, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
N2
CN
O
177f
1.00
1.07
1.17
2.17
2.10
9.20
ppm
Plotname: --Not assigned--

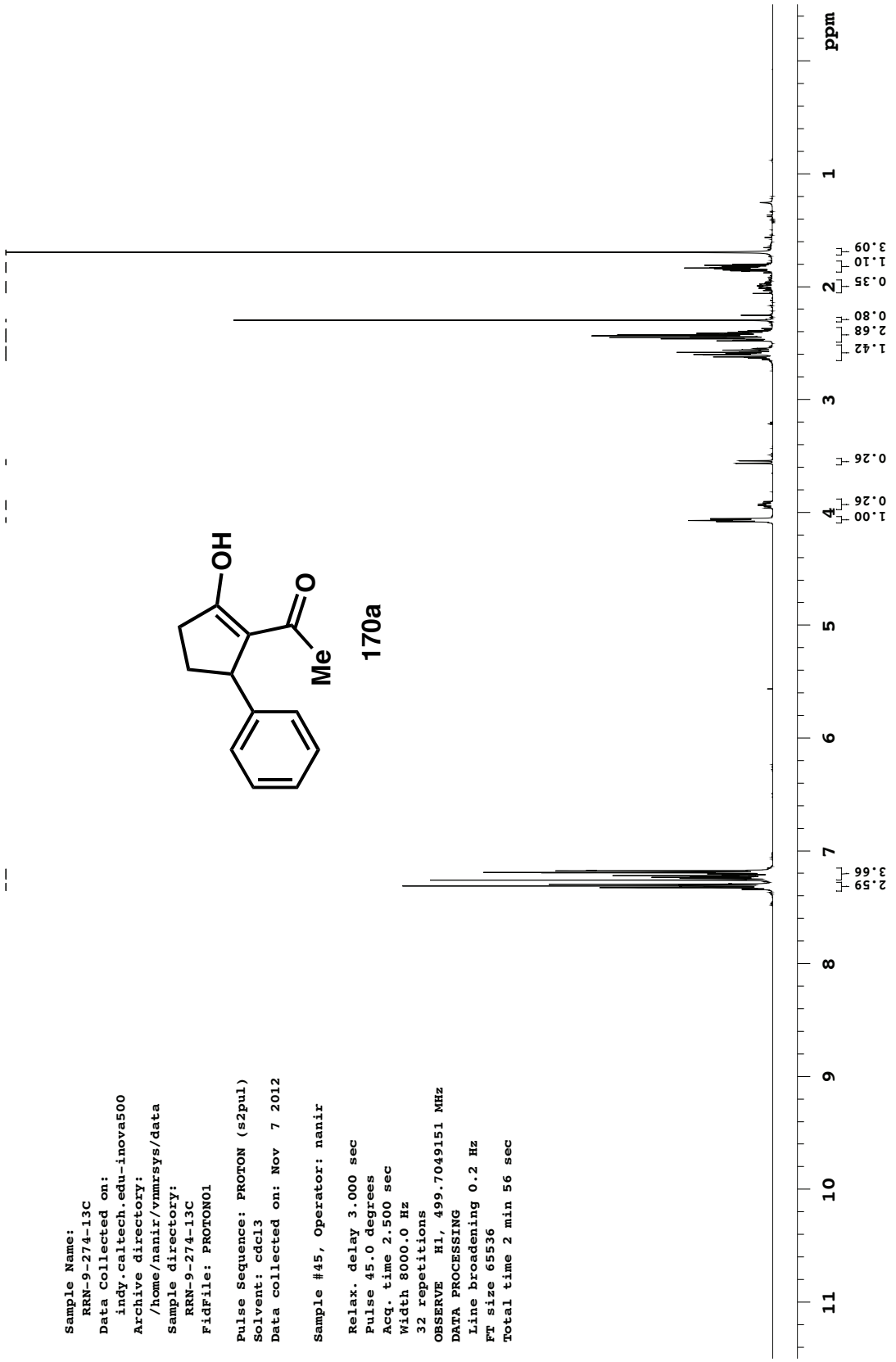

Agilent Technologies
N_2
CN
O
177f
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-8-277-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-277-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 23 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.400 sec
Width 31446.5 Hz
1400 repetitions
OBSERVE C13, 125.6528729 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
Plotname: --Not assigned--

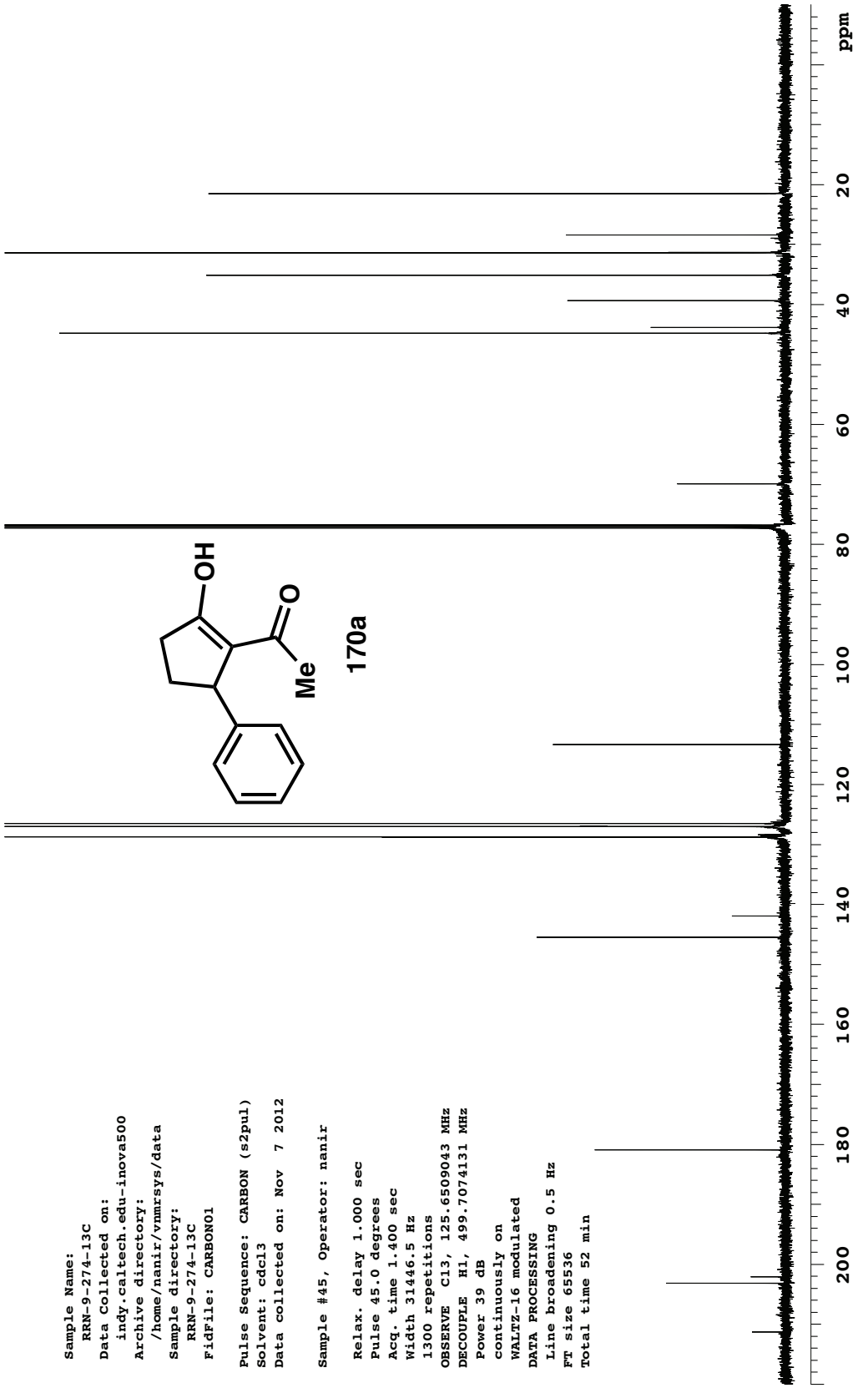

Agilent Technologies
N2
CN
O
OTBS
177g
ppm
5.97
9.60
3.05
3.17
2.15
2.01
1.96
2.00
11
10
9
8
7
6
5
4
3
2
1
Sample Name:
RRN-8-245-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-245-1H
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2012
Sample #44, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127412 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
Plotname: --Not assigned--

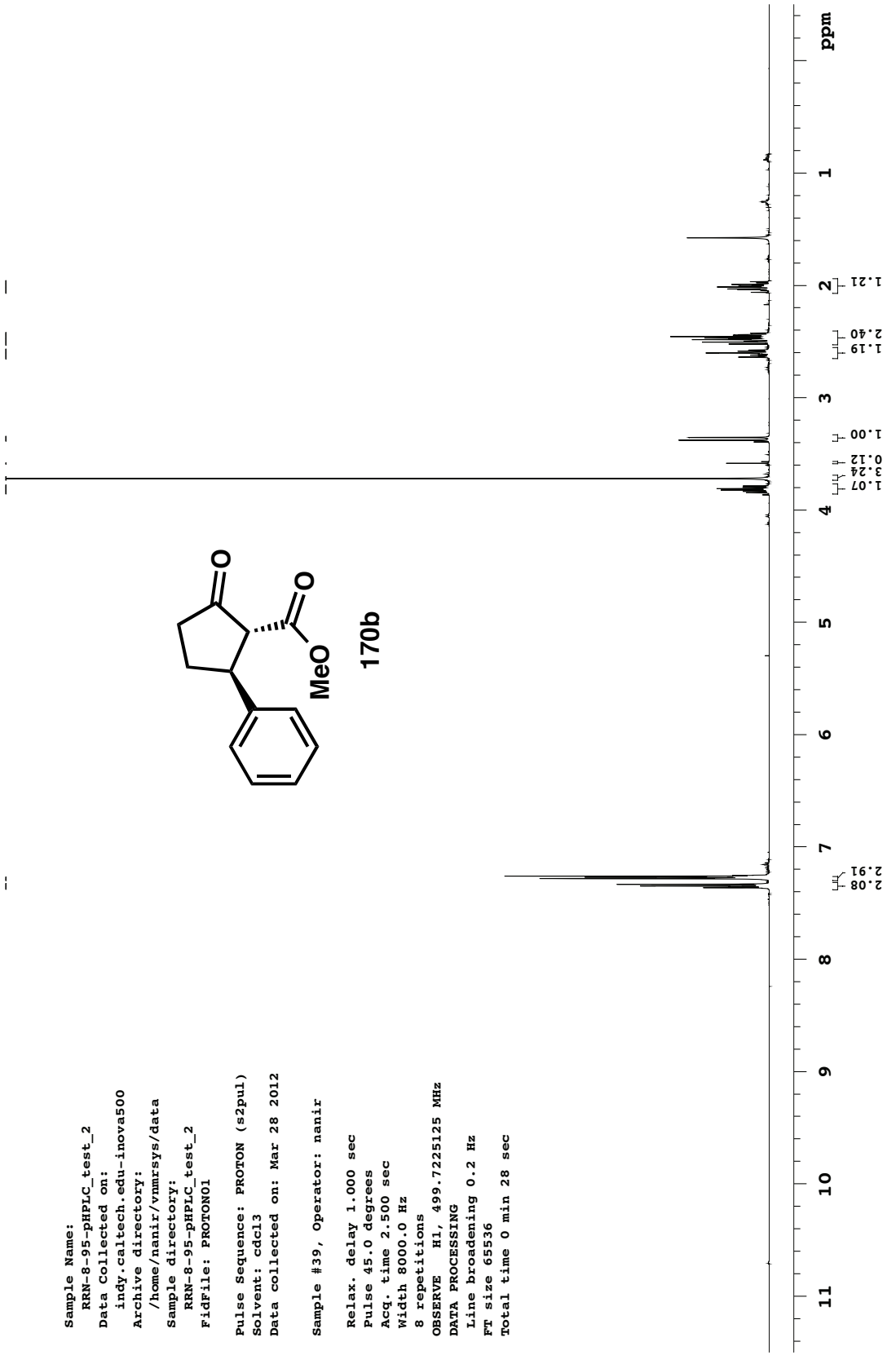

Agilent Technologies
N2
CN
O
OTBS
177g
ppm
200
180
160
140
120
100
80
60
40
20
Sample Name:
RRN-8-245-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-245-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 14 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6528739 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
Plotname: --Not assigned--

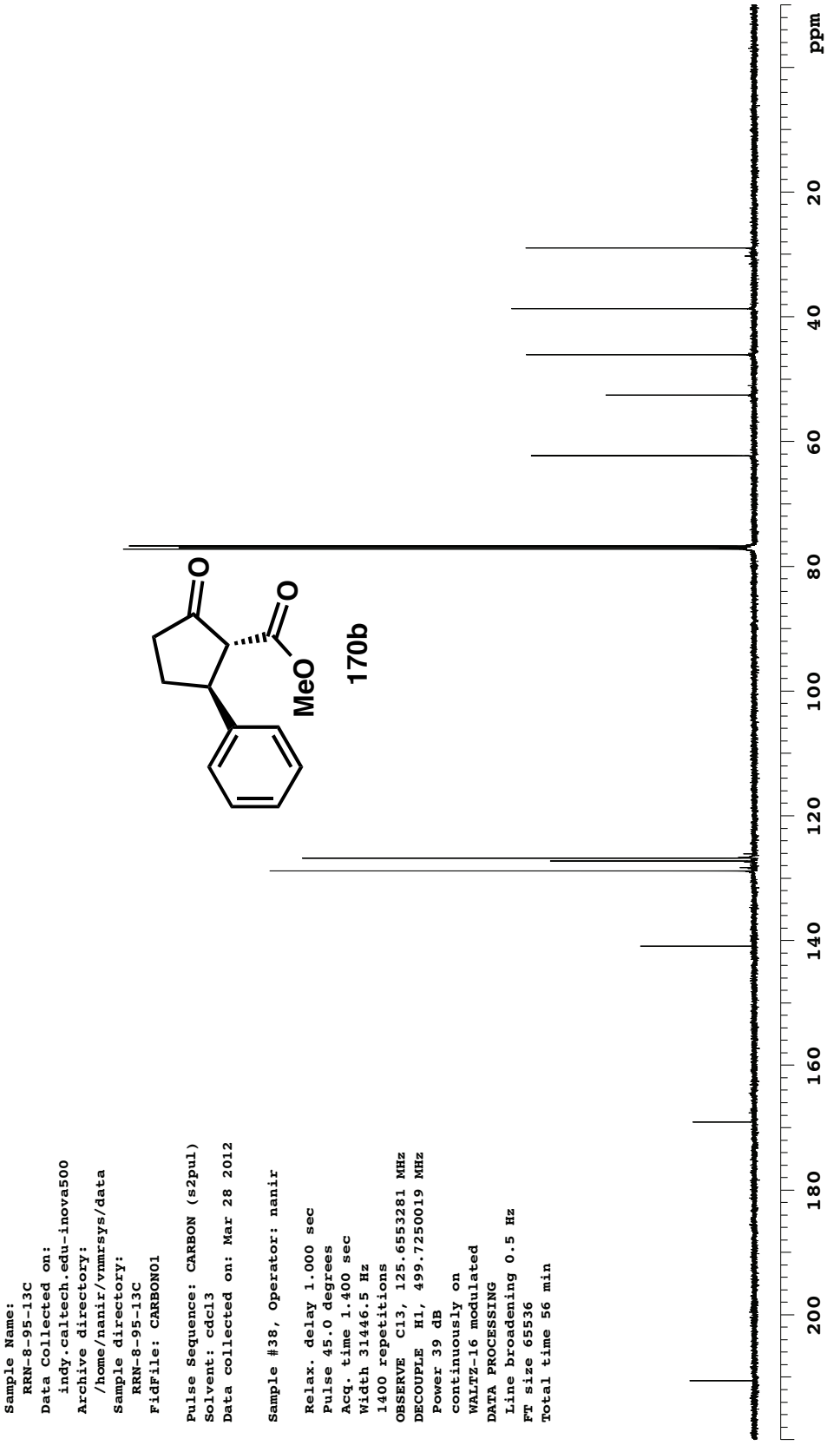

Agilent Technologies
Sample Name:
RRN-9-65-1_flashed
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-65-1_flashed
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 30 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
N2
CN
O
H
tBuO2C
177h
0.92
1.95
2.04
2.02
2.82
9.05
ppm
Plotname: --Not assigned--

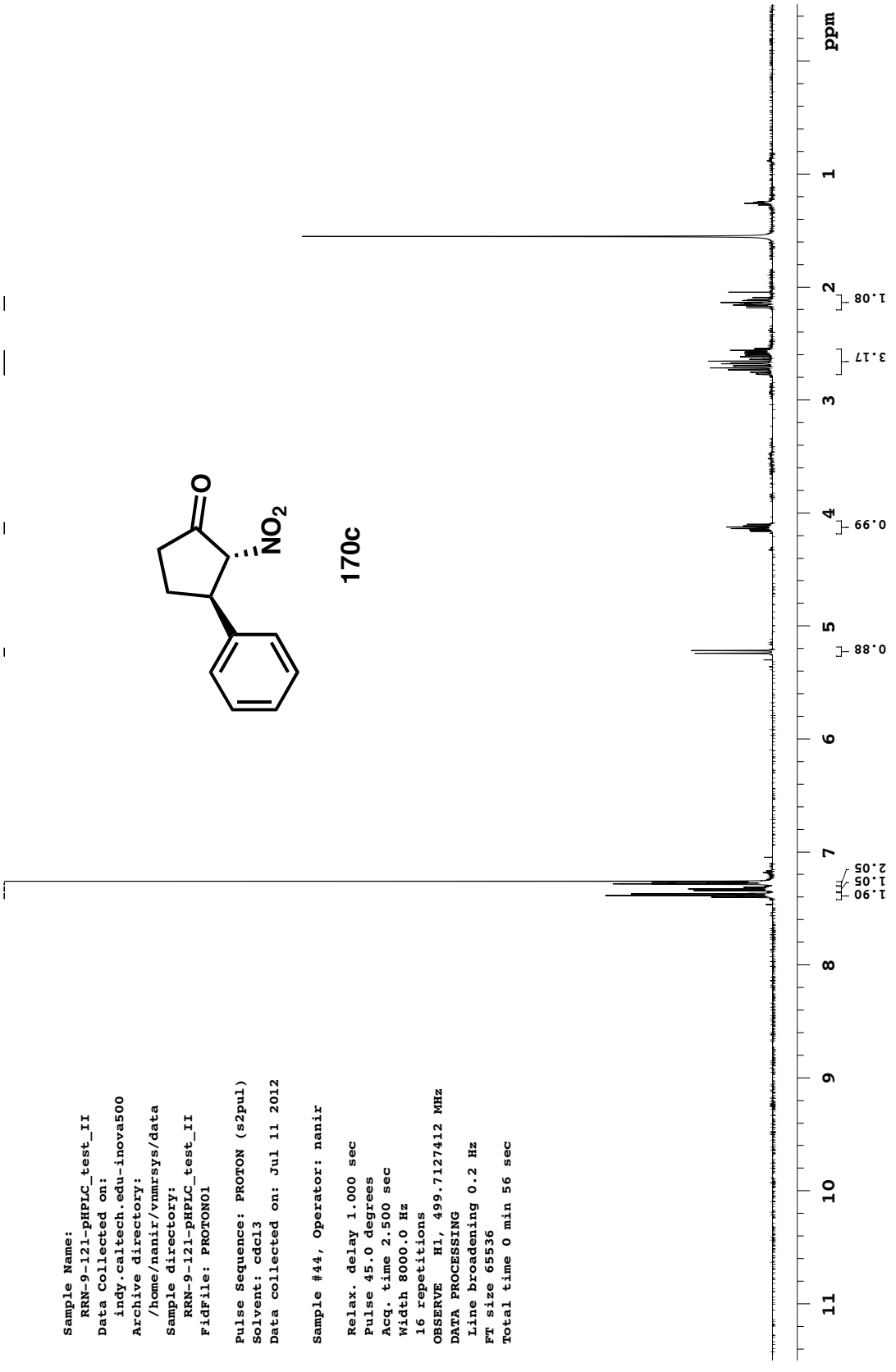

Agilent Technologies
Sample Name:
RRN-9-65-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-65-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 18 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6528777 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
Plotname: --Not assigned--
N2
CN
O
H
tBuO2C
177h
200
180
160
140
120
100
80
60
40
20
ppm

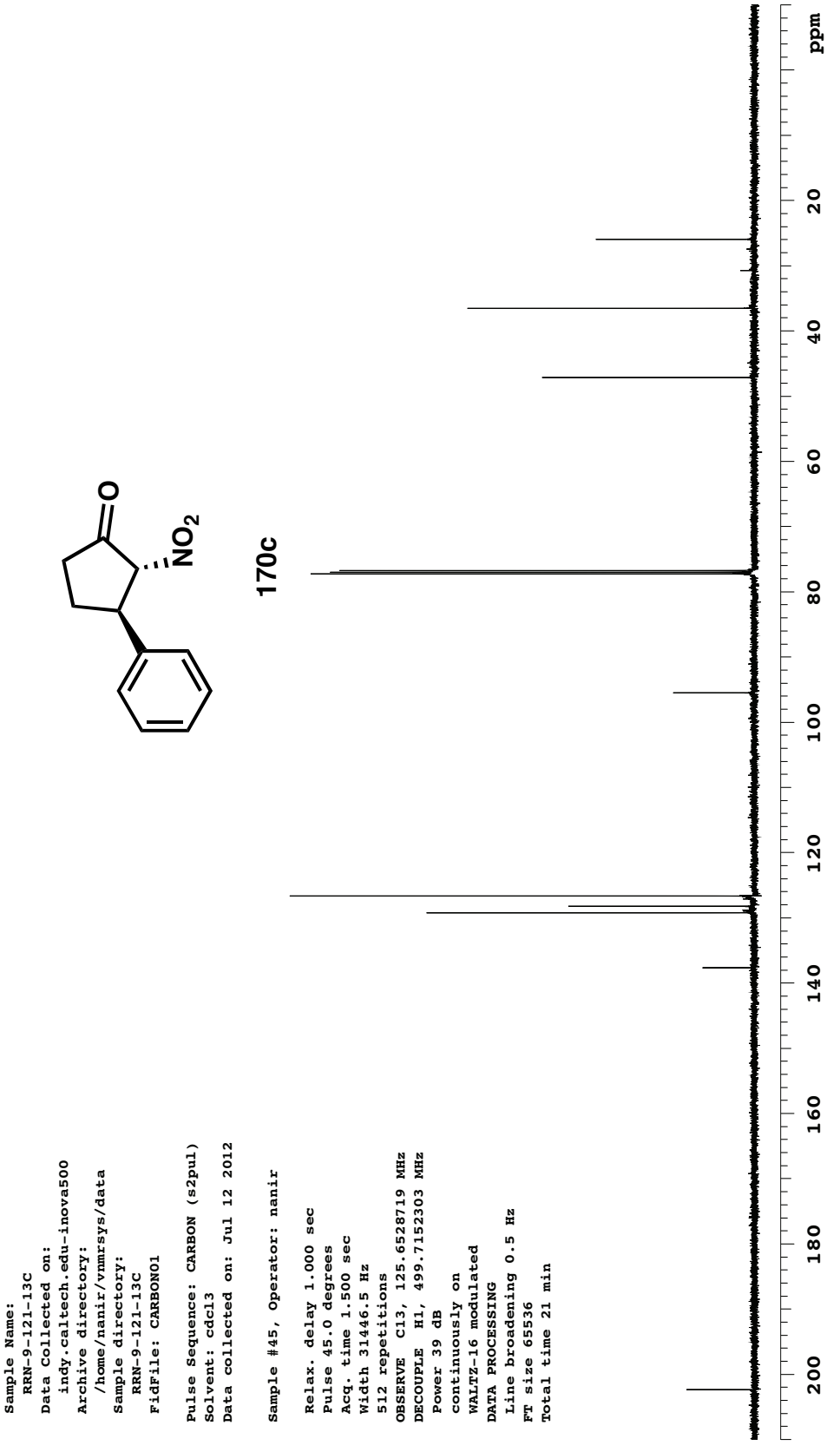

Sample Name:
RRN-9-274-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-274-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 7 2012
Sample #45, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
OH
O
Me
170a
2.59
3.66
1.00
0.26
0.26
1.42
2.68
0.80
0.35
1.10
3.09
11
10
9
8
7
6
5
4
3
2
1
ppm

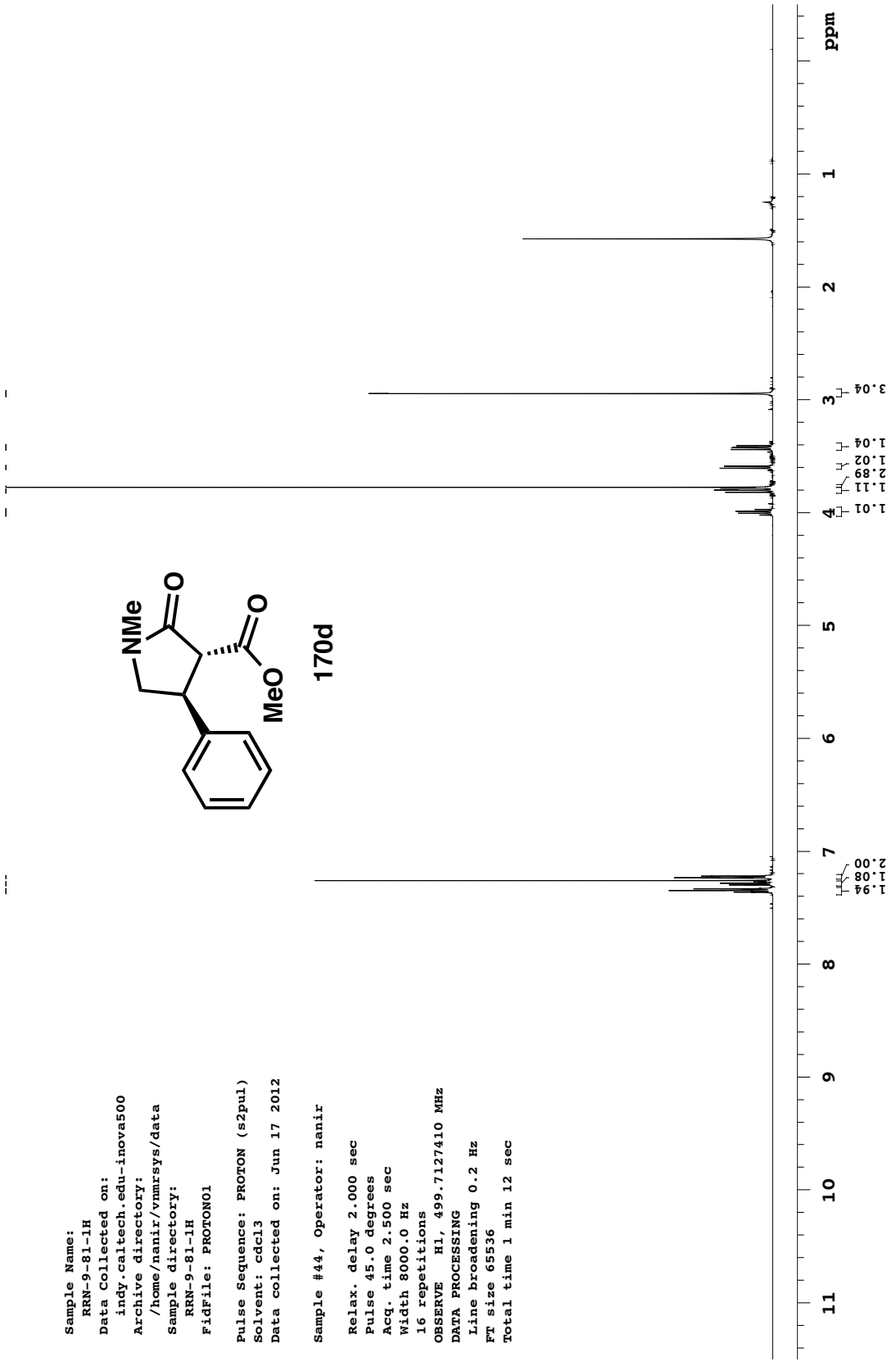

Sample Name:
RRN-9-274-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-274-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 7 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.400 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6509043 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 52 min
OH
O
Me
170a
200
180
160
140
120
100
80
60
40
20
ppm

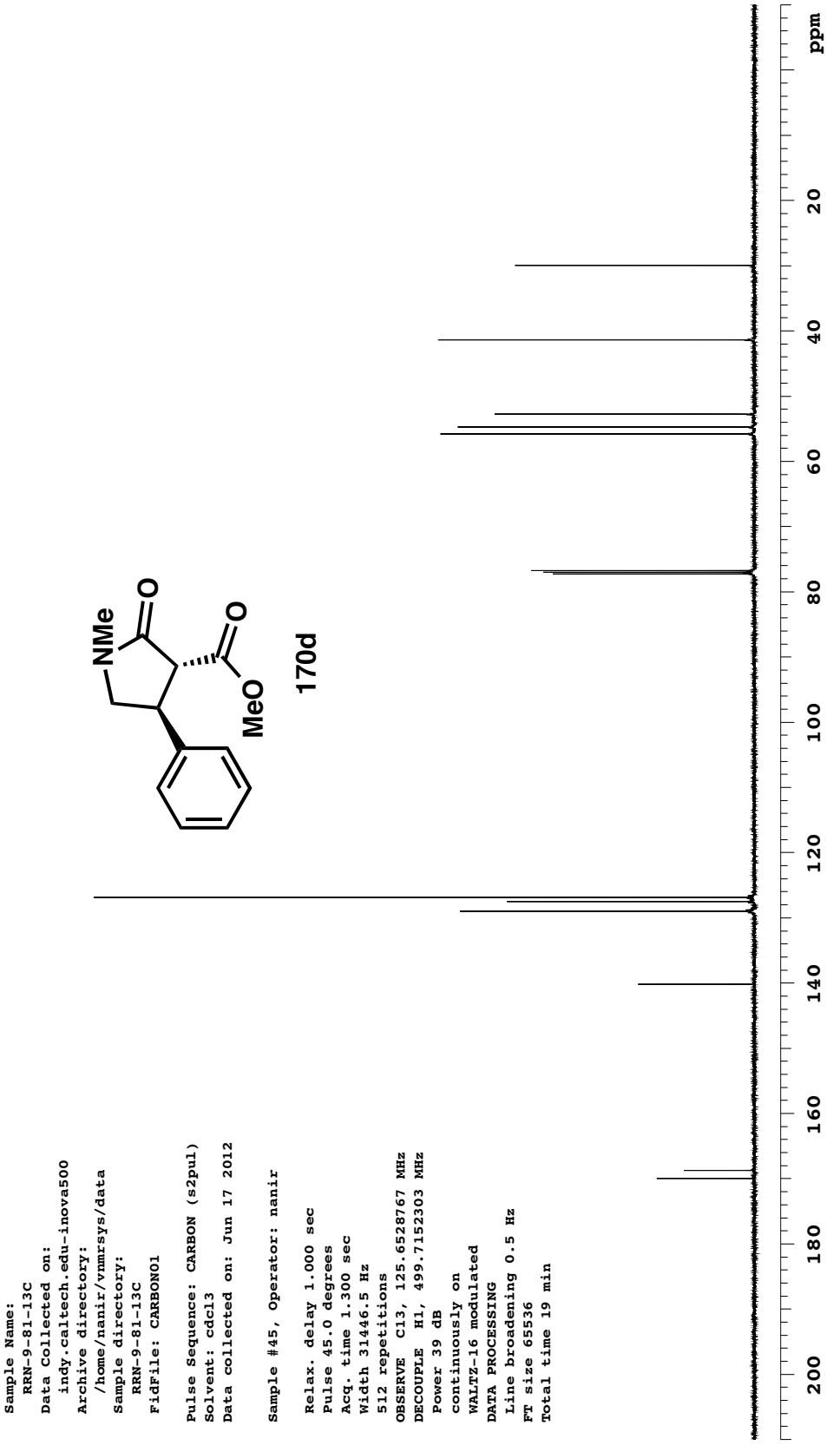

Sample Name:
RRN-8-95-pHPLC_test_2
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-95-pHPLC_test_2
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 28 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
O
O
MeO
170b
2.08
2.91
1.07
3.24
0.12
1.00
1.19
2.40
1.21
ppm

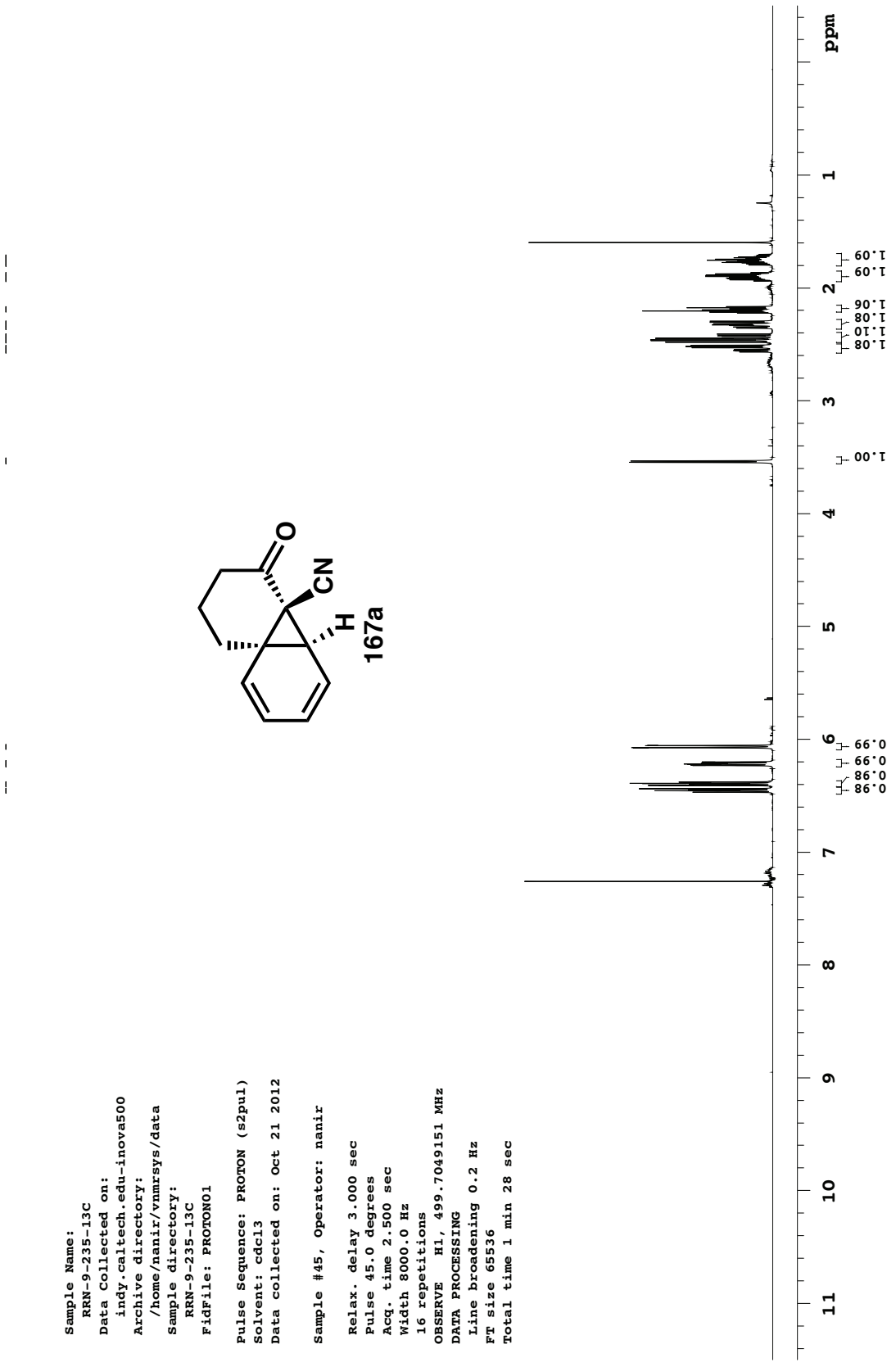

Sample Name:
RRN-8-95-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-95-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 28 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.400 sec
Width 31446.5 Hz
1400 repetitions
OBSERVE C13, 125.6553281 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min
O
O
MeO
170b
200
180
160
140
120
100
80
60
40
20
ppm

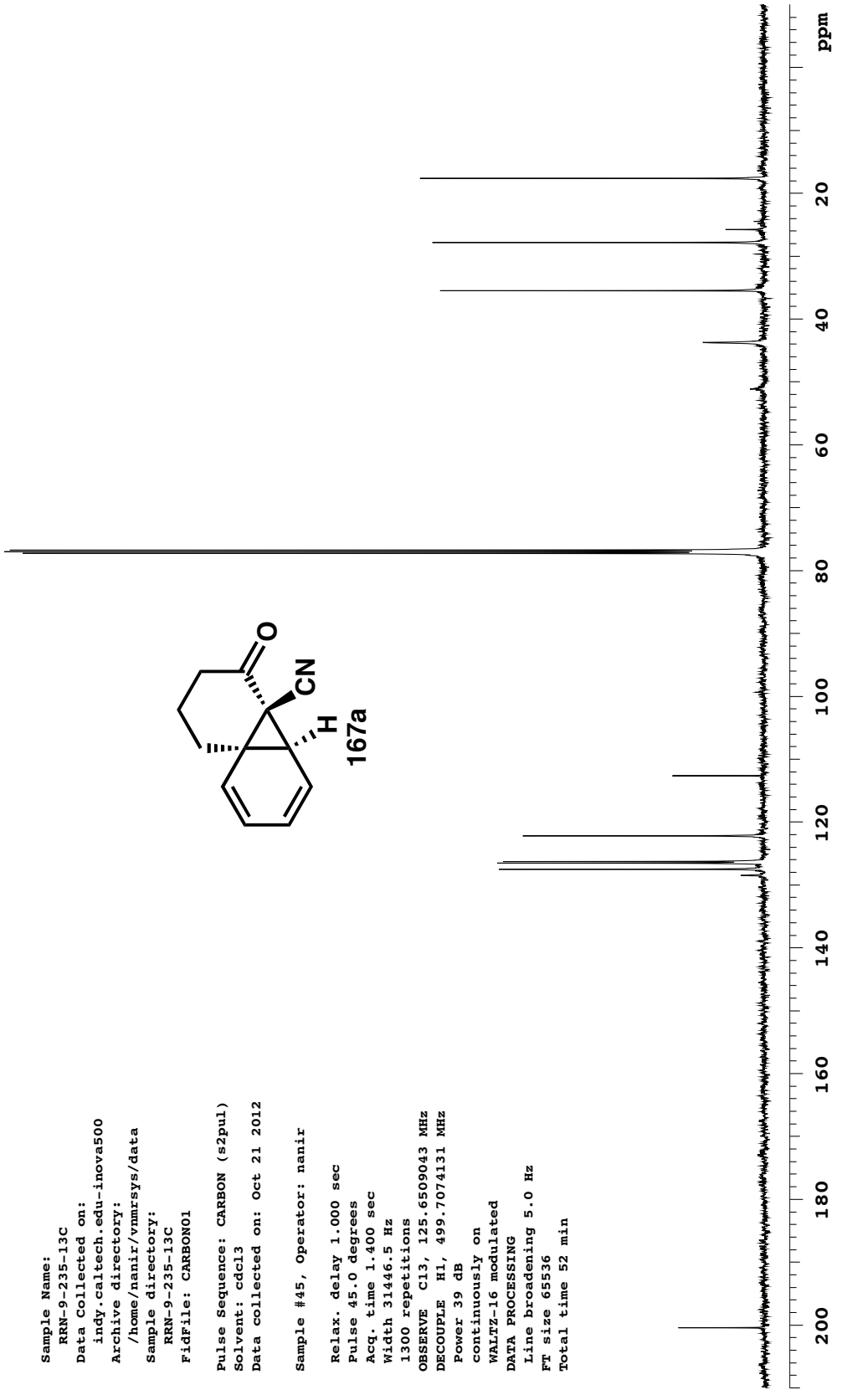

Sample Name:
RRN-9-121-pHPLC_test_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-121-pHPLC_test_II
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 11 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127412 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
O
NO2
170c
1.90
1.05
2.05
0.88
0.99
3.17
1.08
ppm

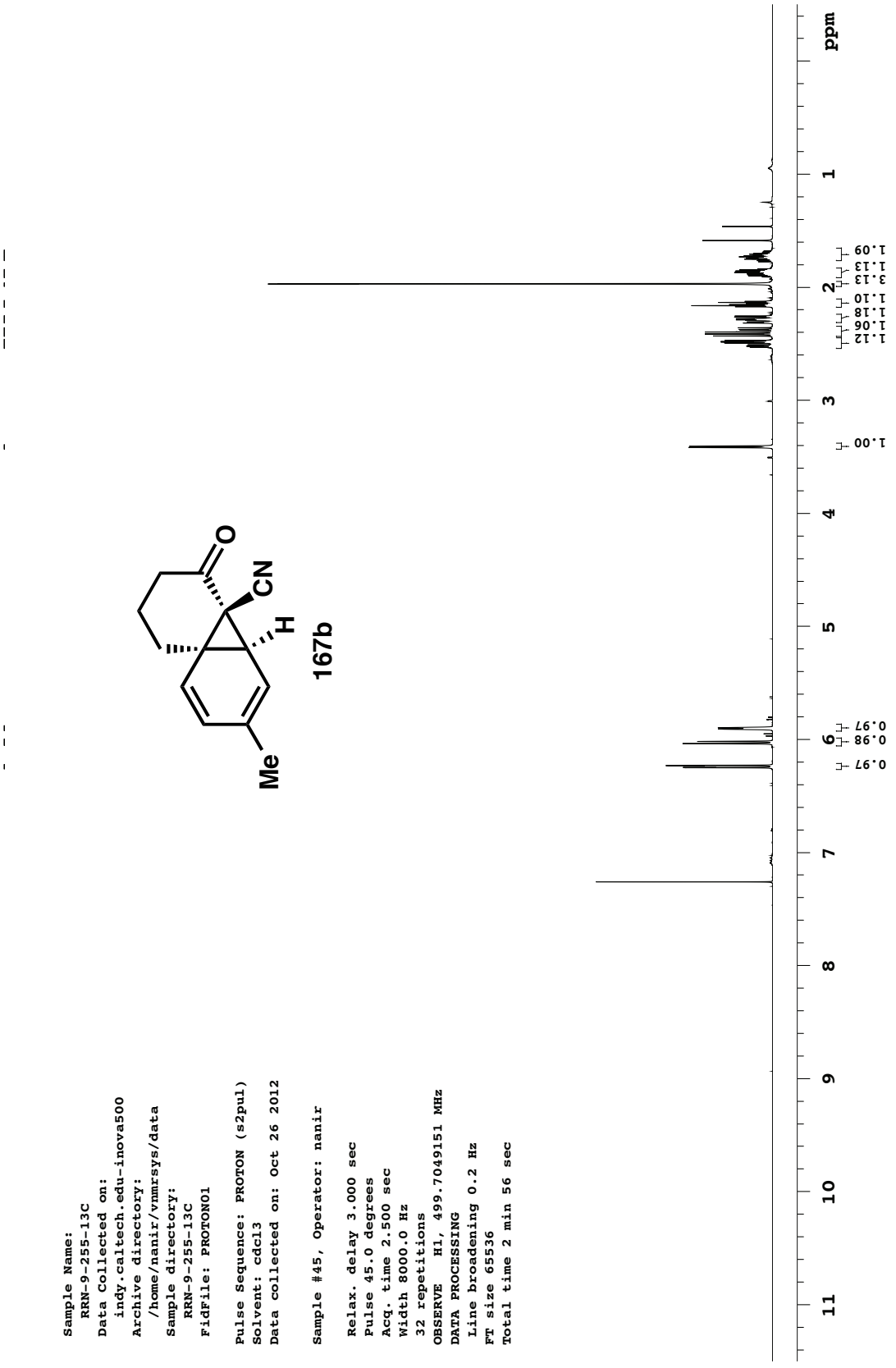

Sample Name:
RRN-9-121-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-121-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 12 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528719 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 21 min
O
NO2
170c
200
180
160
140
120
100
80
60
40
20
ppm

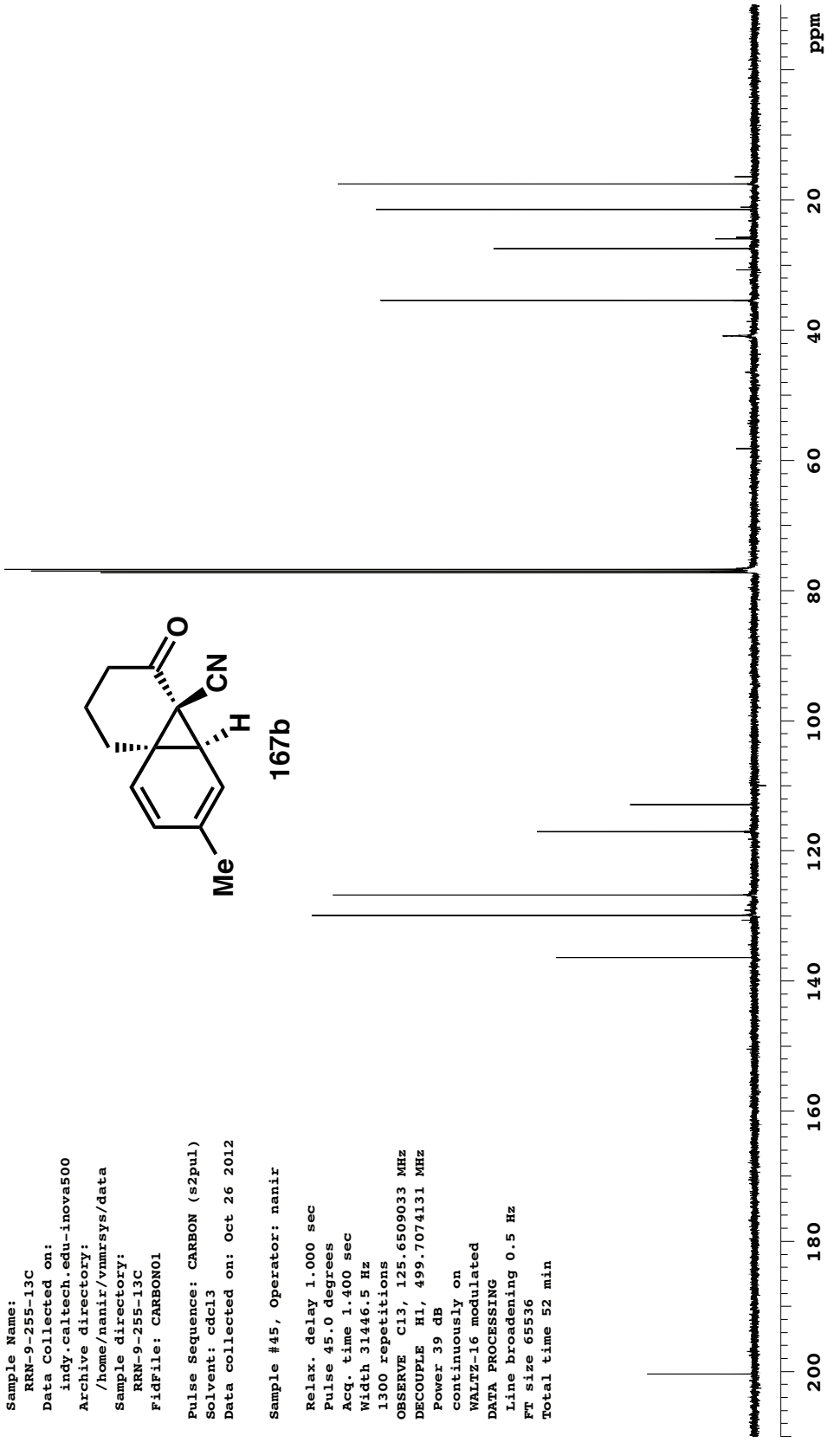

Sample Name:
RRN-9-81-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-81-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 17 2012
Sample #44, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
NMe
O
O
MeO
170d
1.94
1.08
2.00
1.01
1.11
2.89
1.02
1.04
3.04
ppm

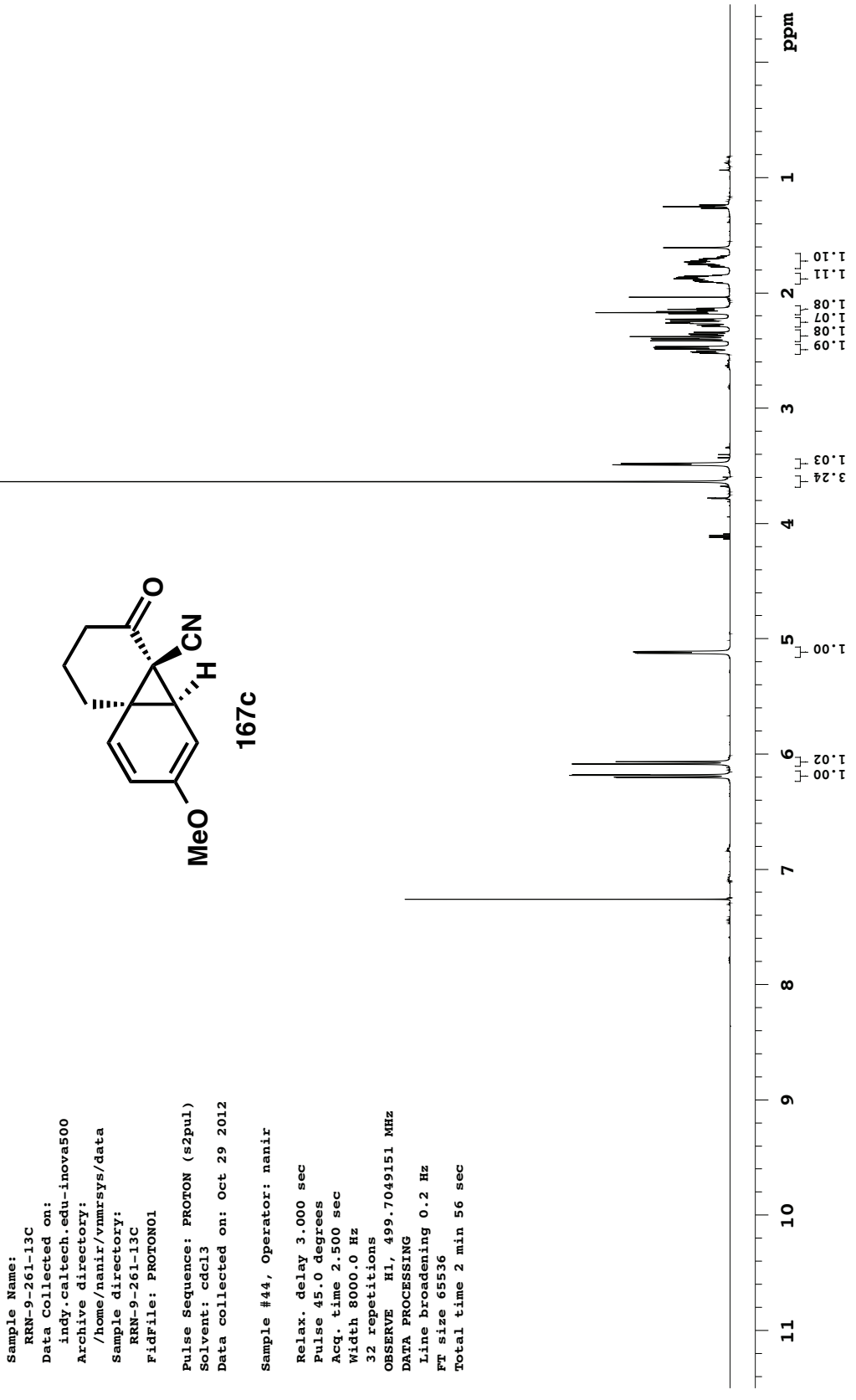

Sample Name:
RRN-9-81-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-81-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 17 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528767 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min
NMe
O
O
MeO
170d
200
180
160
140
120
100
80
60
40
20
ppm

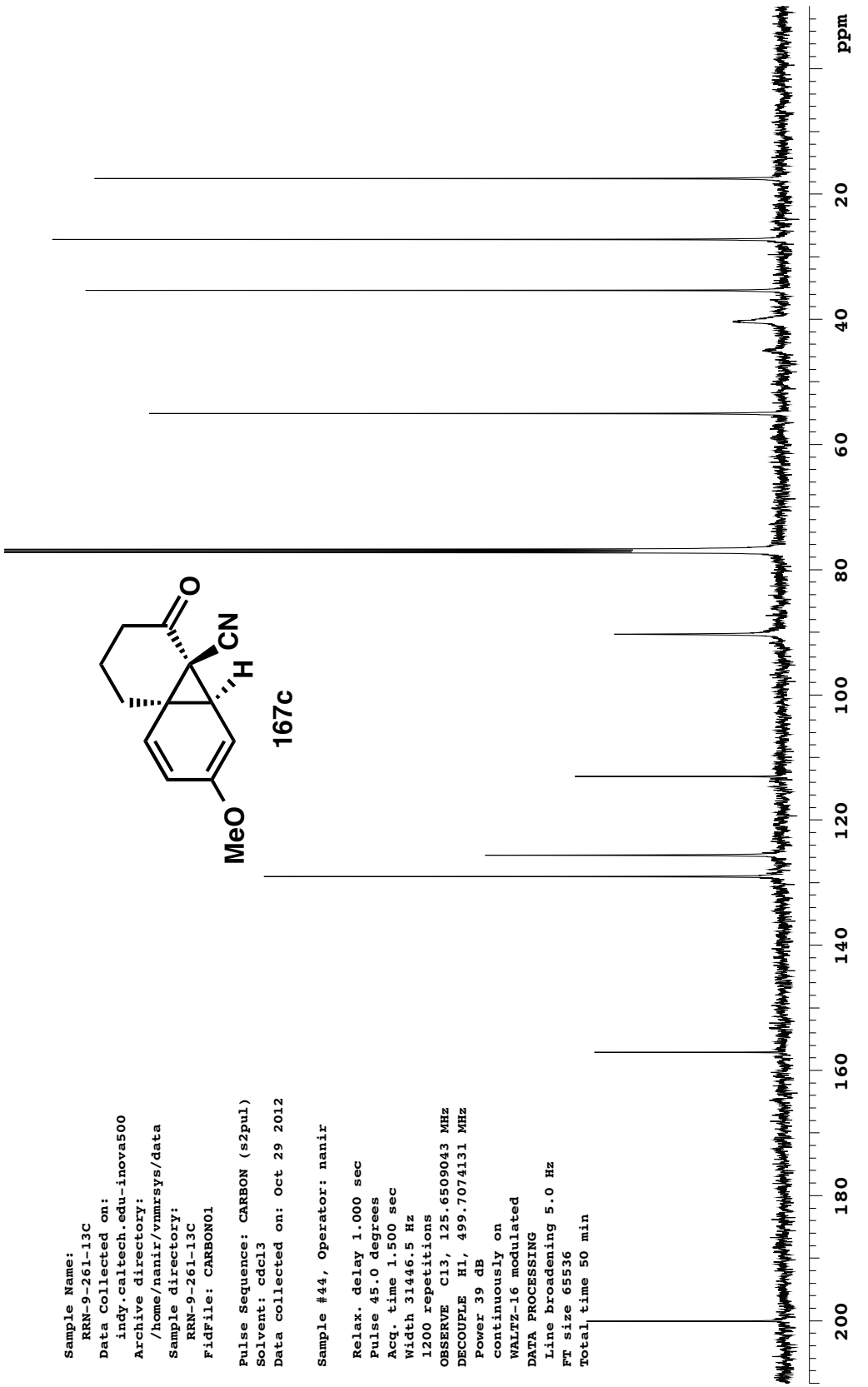

Sample Name:
RRN-9-235-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-235-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 21 2012
Sample #45, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
O
CN
H
167a
ppm
1.00
1.09
1.09
1.06
1.08
1.10
1.08
0.99
0.99
0.86
0.86

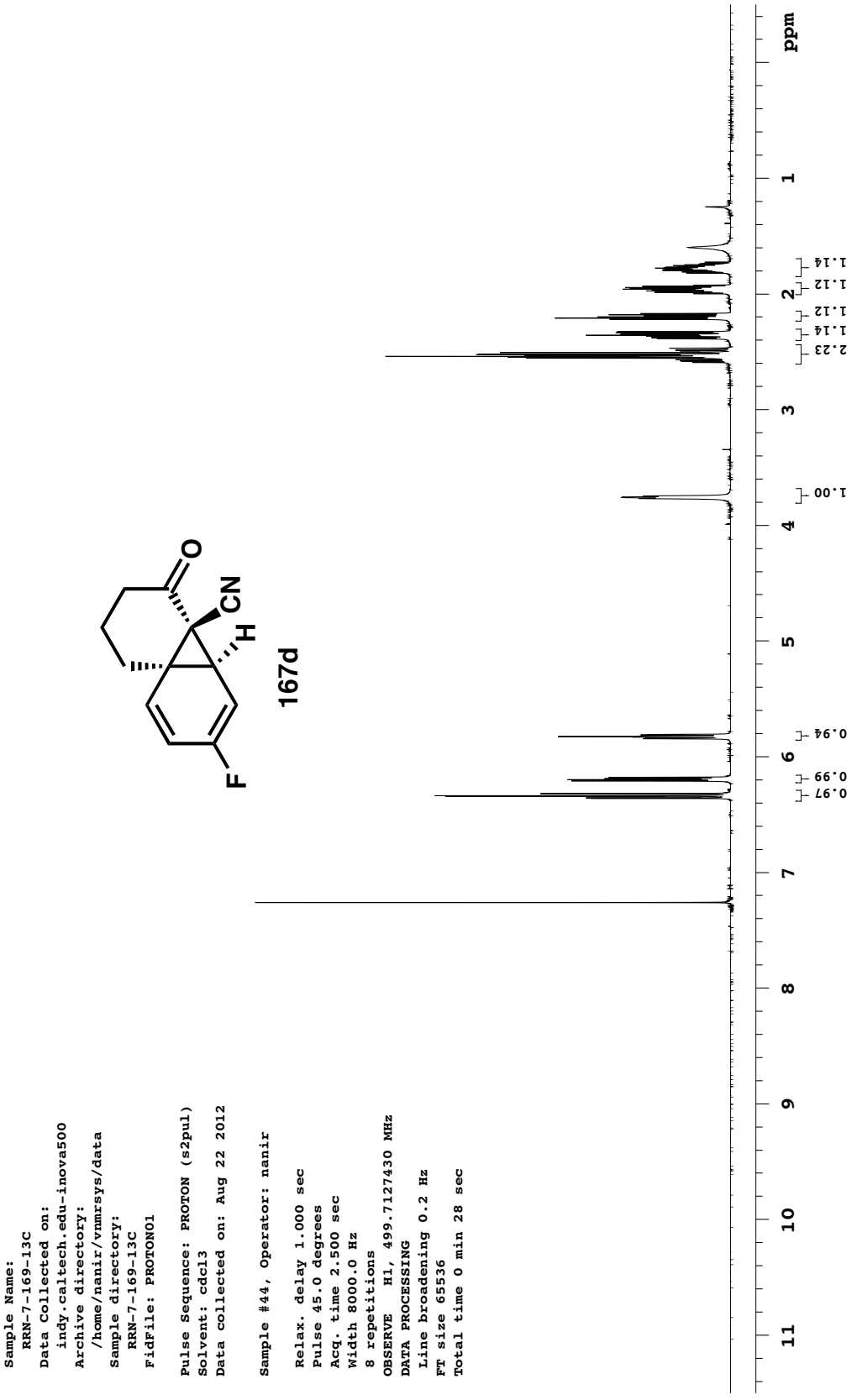

Sample Name:
RRN-9-235-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-235-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 21 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.400 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6509043 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 52 min
O
CN
H
167a
200
180
160
140
120
100
80
60
40
20
ppm

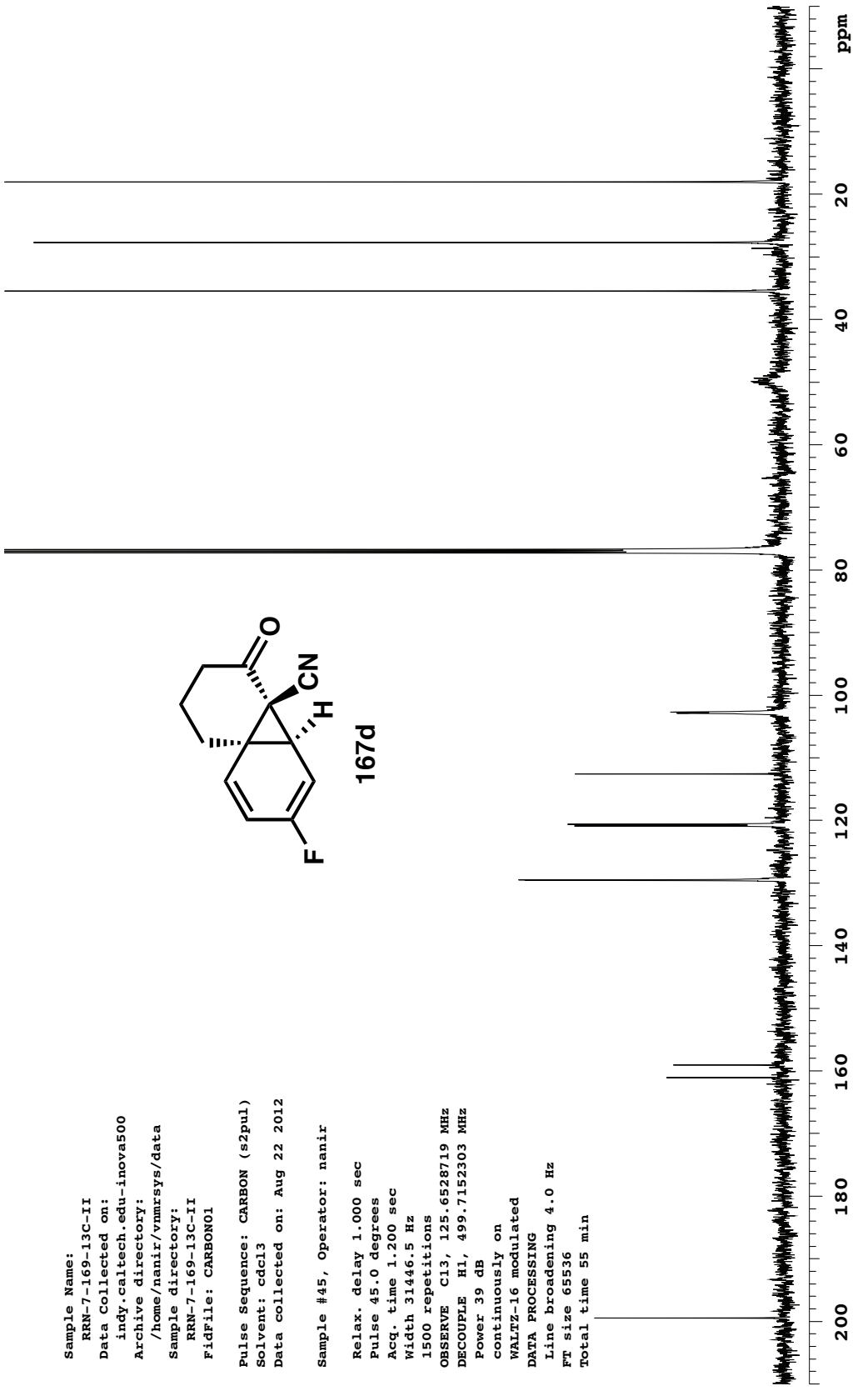

Sample Name:
RRN-9-255-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-255-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 26 2012
Sample #45, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
O
CN
H
Me
167b
ppm
1.00
0.97
0.98
0.97
1.12
1.06
1.18
1.10
3.13
1.13
1.09


Sample Name:
RRN-9-255-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-255-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 26 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.400 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6509033 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 52 min
O
CN
H
Me
167b
200
180
160
140
120
100
80
60
40
20
ppm


Sample Name:
RRN-9-261-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-261-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 29 2012
Sample #44, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
O
CN
H
MeO
167c
1.00
1.02
1.00
3.24
1.03
1.09
1.08
1.07
1.08
1.11
1.10
ppm

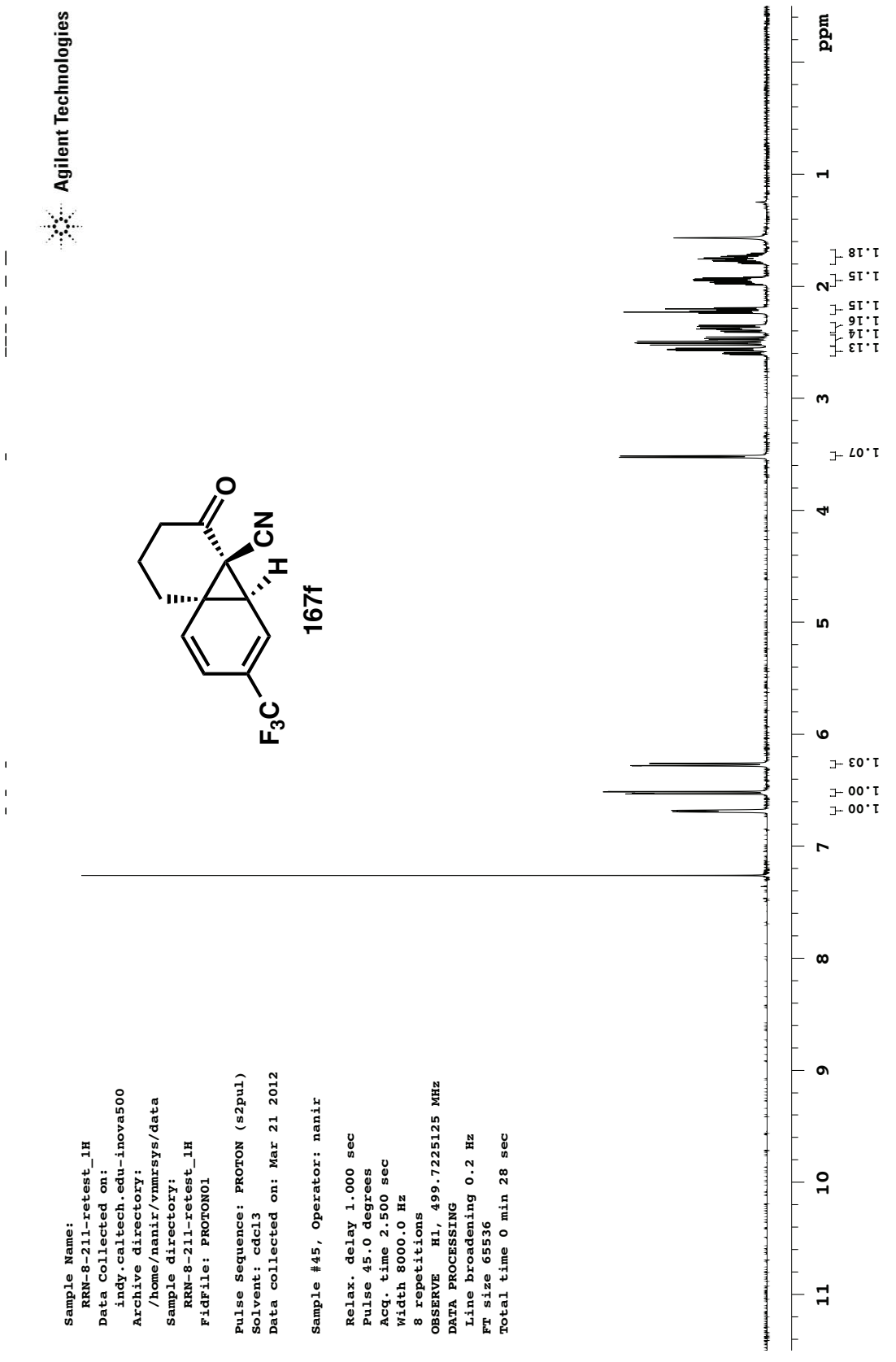

Sample Name:
RRN-9-261-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-261-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 29 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
1200 repetitions
OBSERVE C13, 125.6509043 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 50 min
O
CN
H
MeO
167c
200
180
160
140
120
100
80
60
40
20
ppm

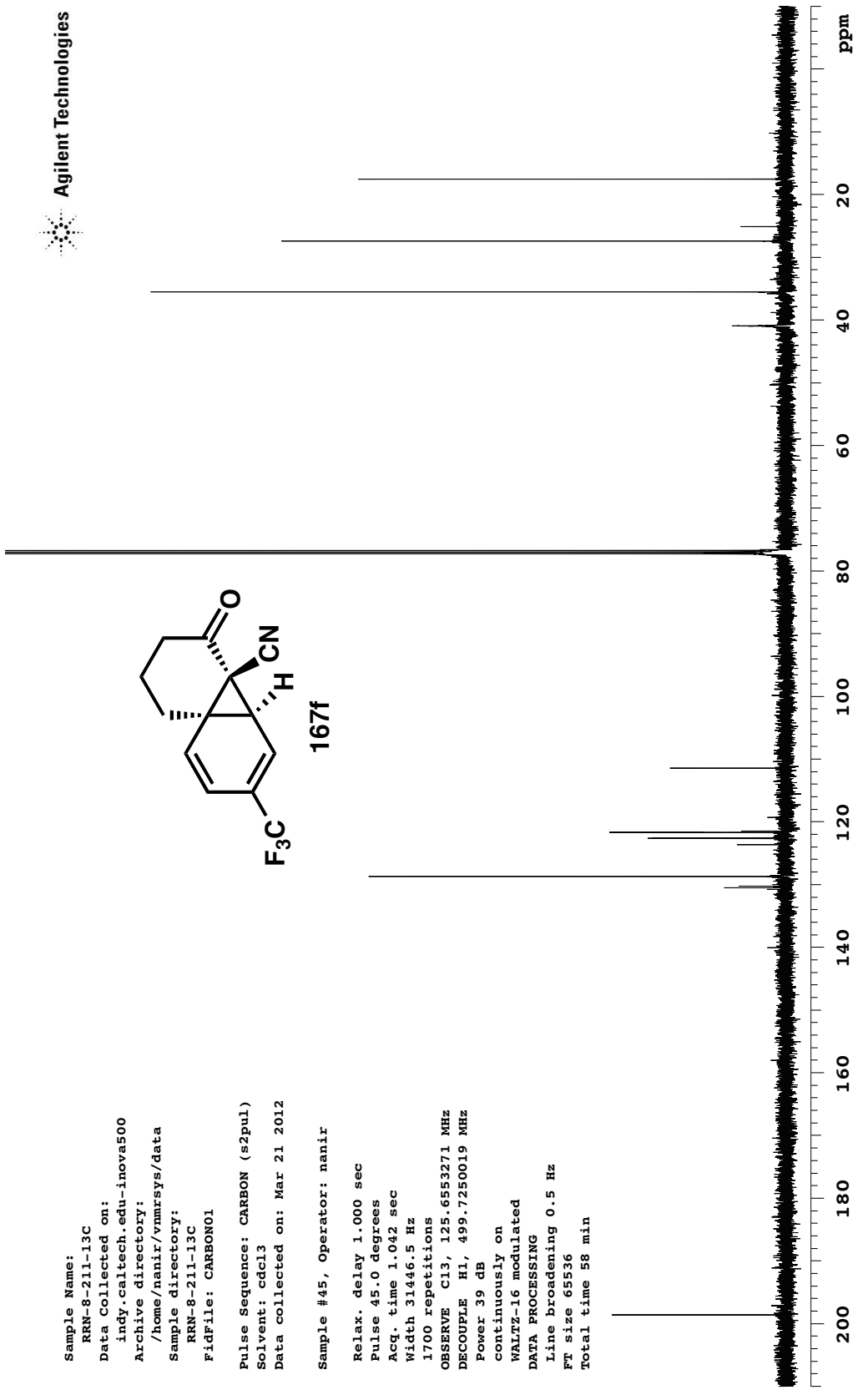

Sample Name:
RRN-7-169-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-169-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 22 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127430 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
O
CN
H
F
167d
1.00
0.94
0.97
0.99
2.23
1.14
1.12
1.12
1.14
1.12
ppm

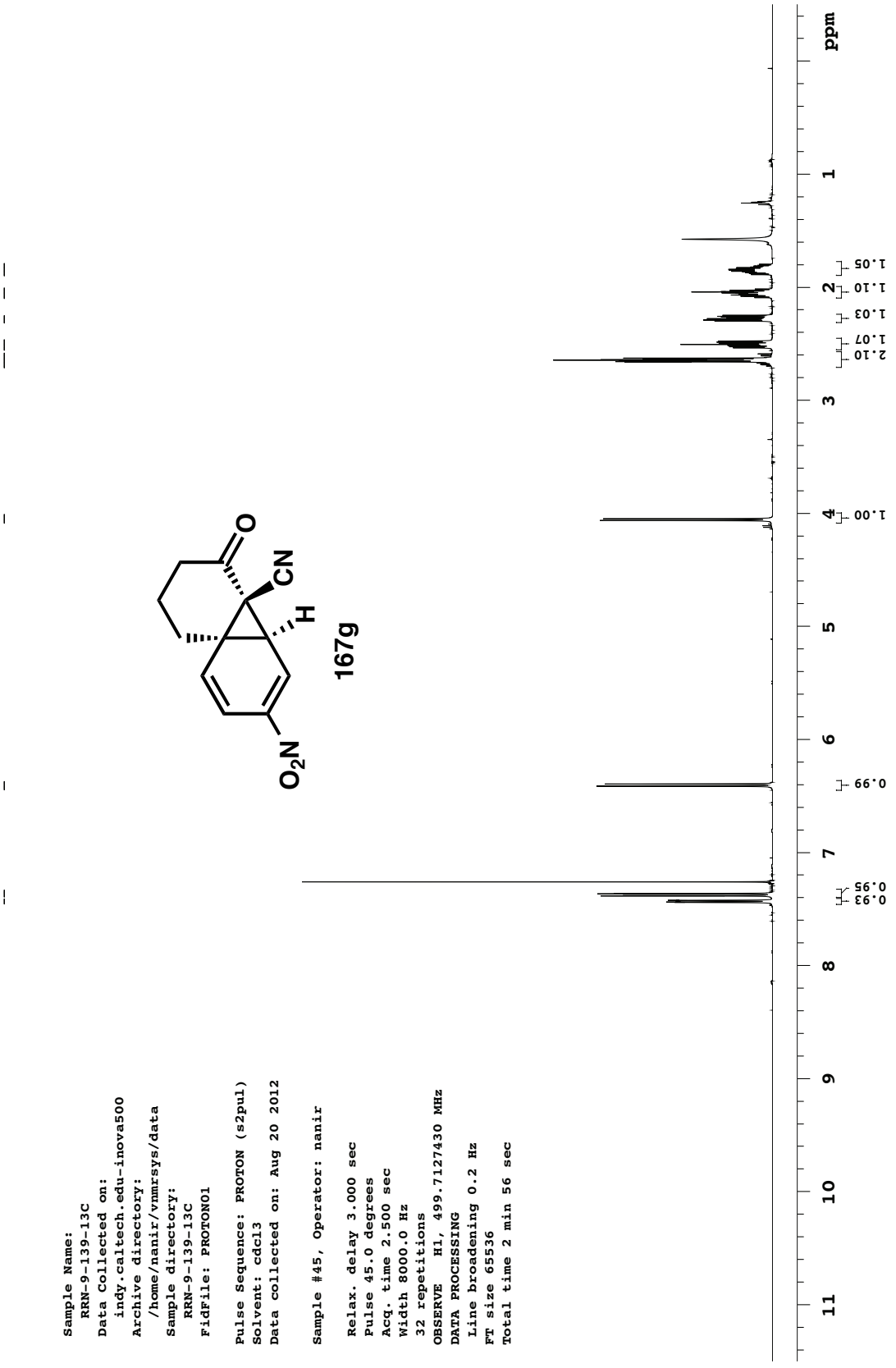

Sample Name:
RRN-7-169-13C-II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-169-13C-II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 22 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.200 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6528719 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 65536
Total time 55 min
O
CN
H
F
167d
200
180
160
140
120
100
80
60
40
20
ppm

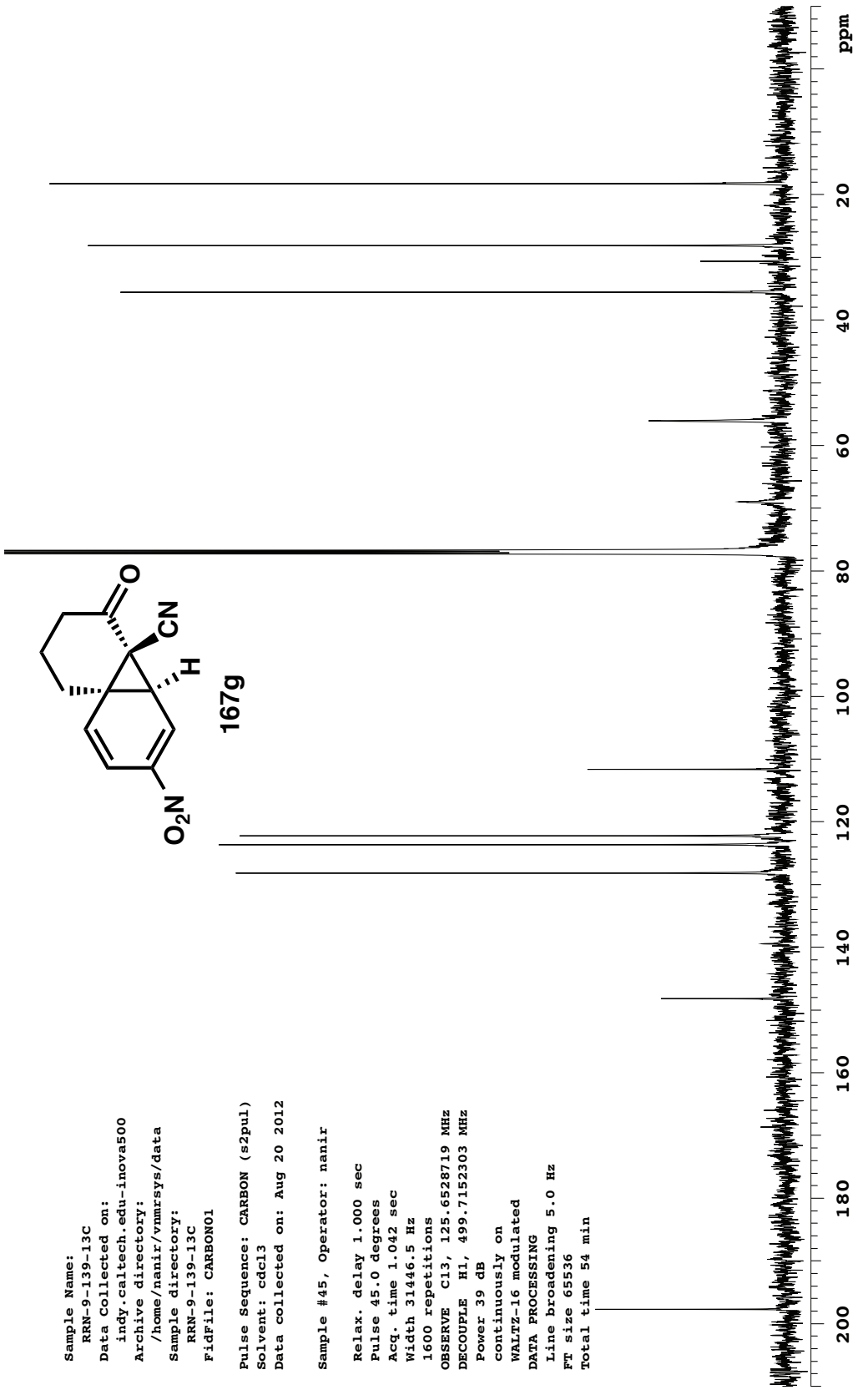
Agilent Technologies
Sample Name:
RRN-8-207-Cl-rex
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-207-Cl-rex
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2012
Sample #31, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
O
CN
H
Cl
167e
1.00
2.14
1.08
1.05
1.07
1.07
0.93
0.92
0.96
ppm
Plotname: --Not assigned--

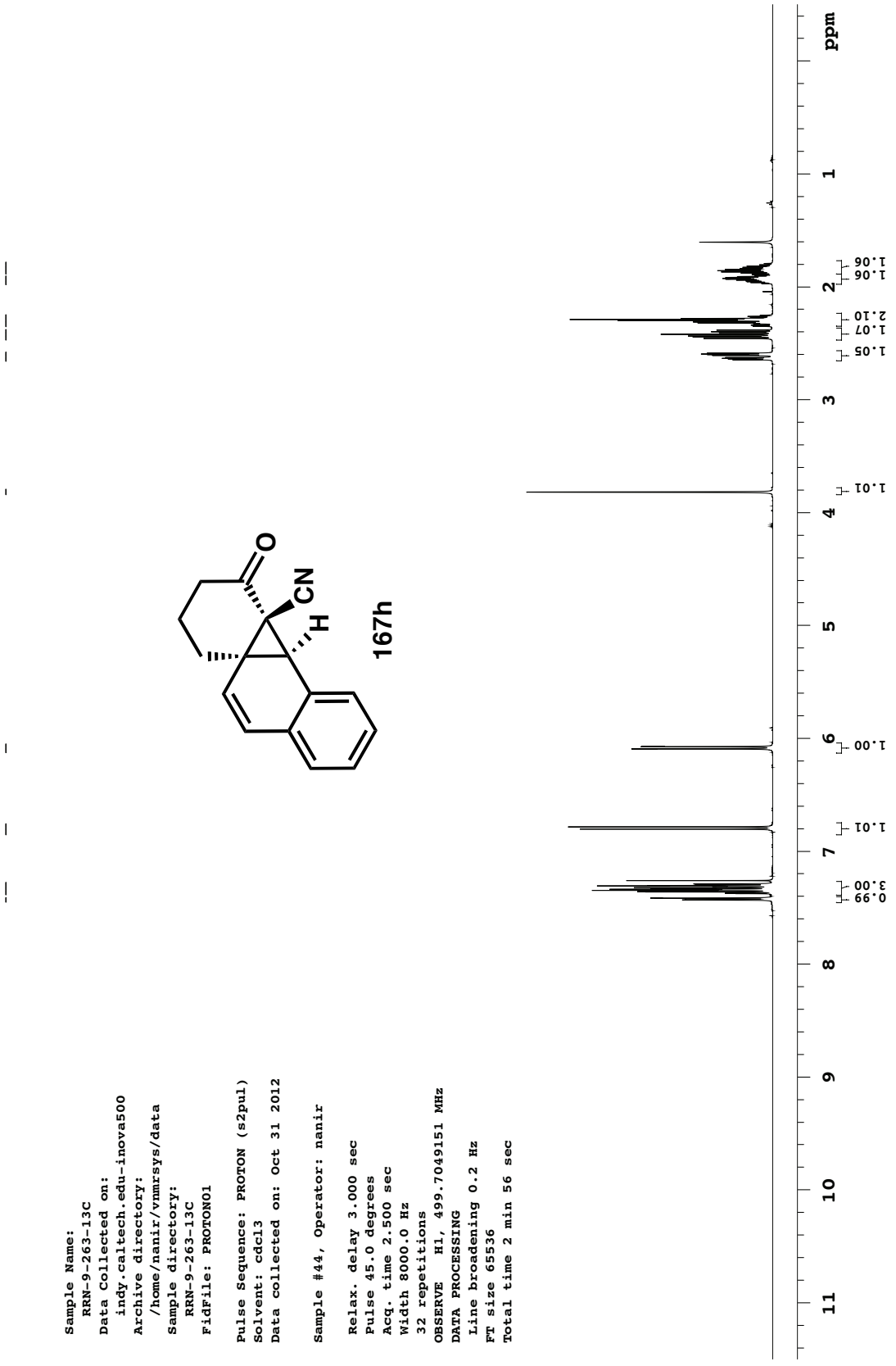
Agilent Technologies
Sample Name:
RRN-8-207-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-207-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6553281 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 58 min
O
CN
H
Cl
167e
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

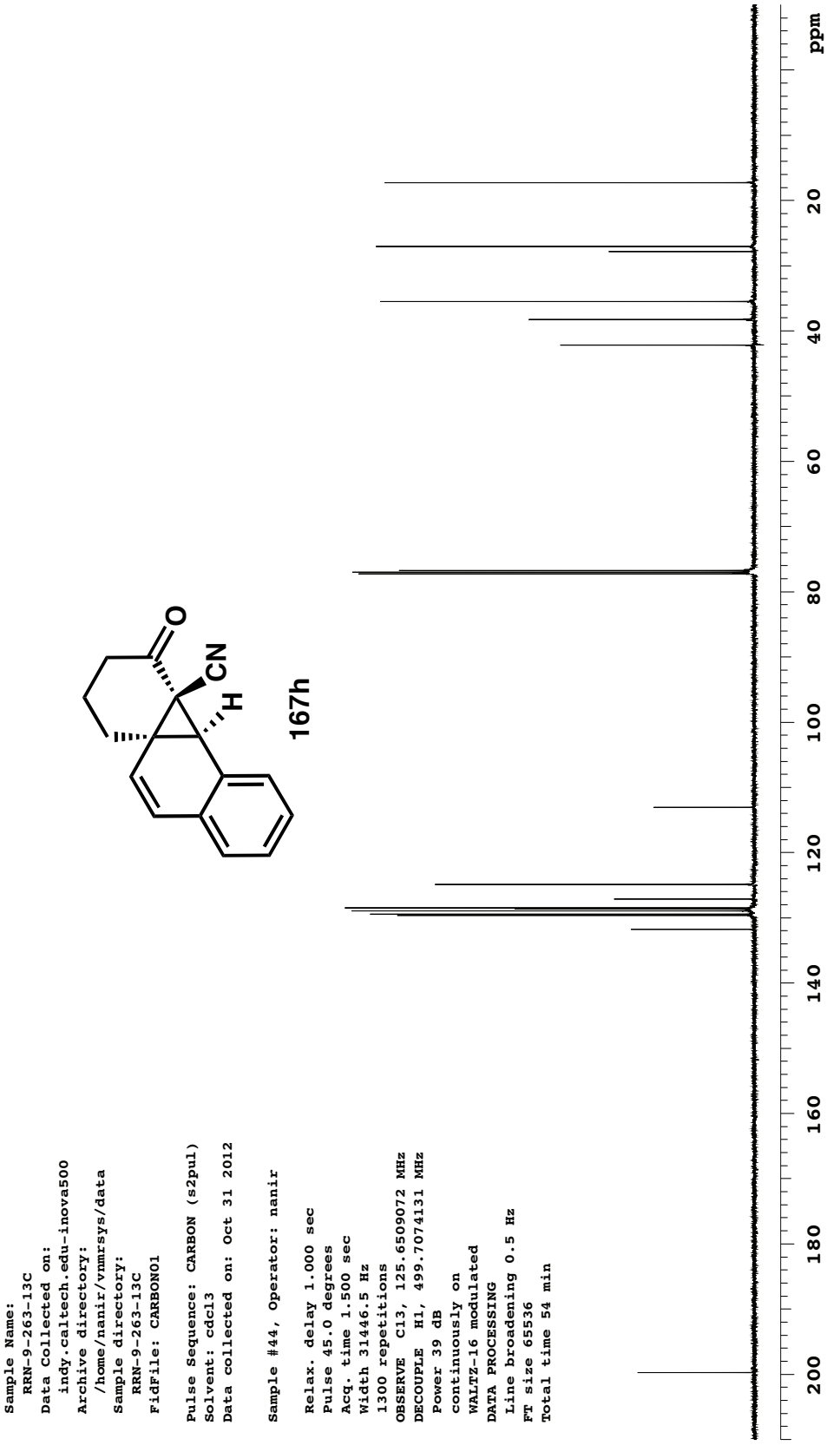

Agilent Technologies
Sample Name:
RRN-8-211-retest_1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-211-retest_1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
O
H
CN
F3C
167f
1.00
1.00
1.03
1.07
1.13
1.14
1.16
1.15
1.15
1.18
ppm
Plotname: --Not assigned--

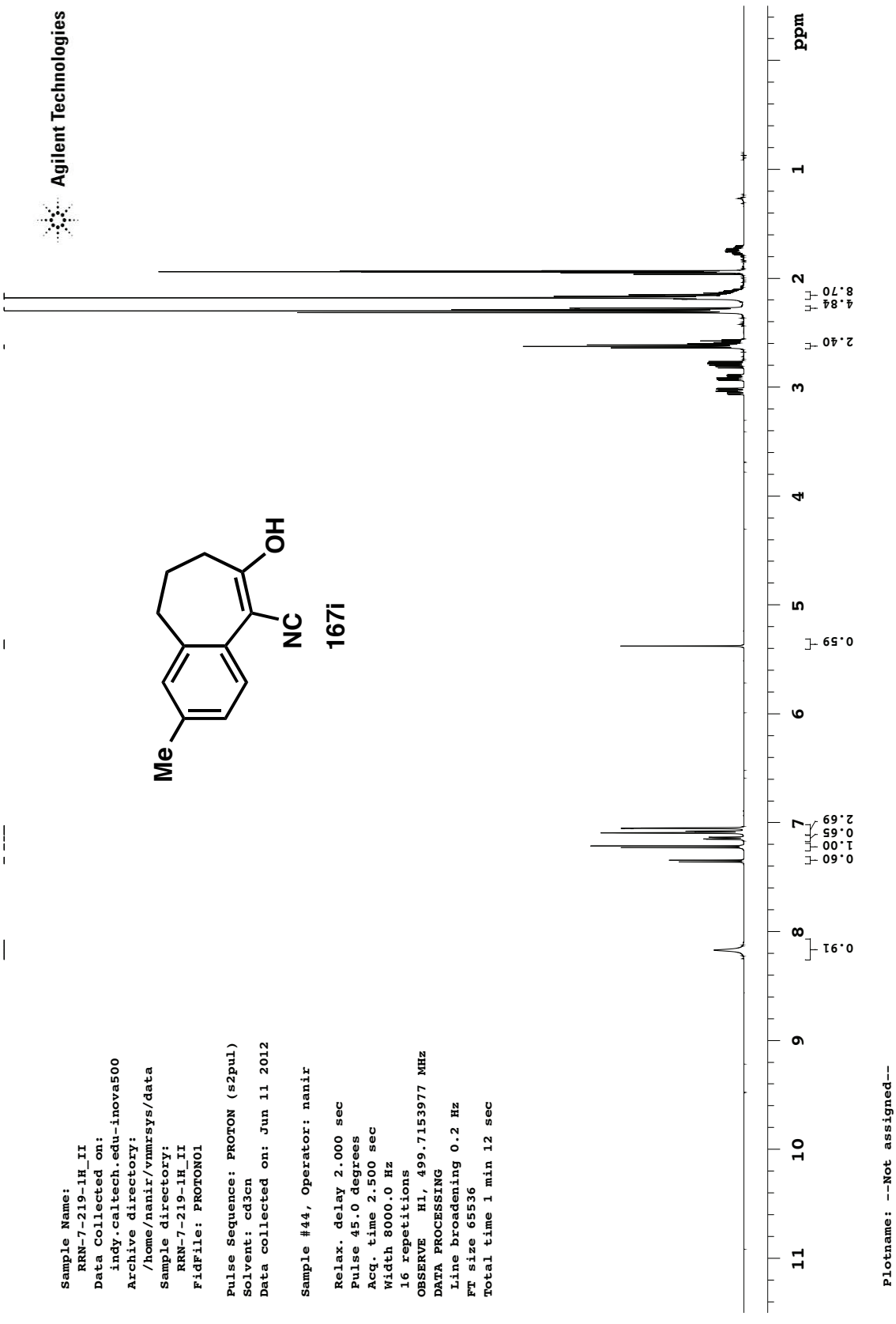

Agilent Technologies
Sample Name:
RRN-8-211-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-211-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6553271 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
O
CN
H
F3C
167f
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

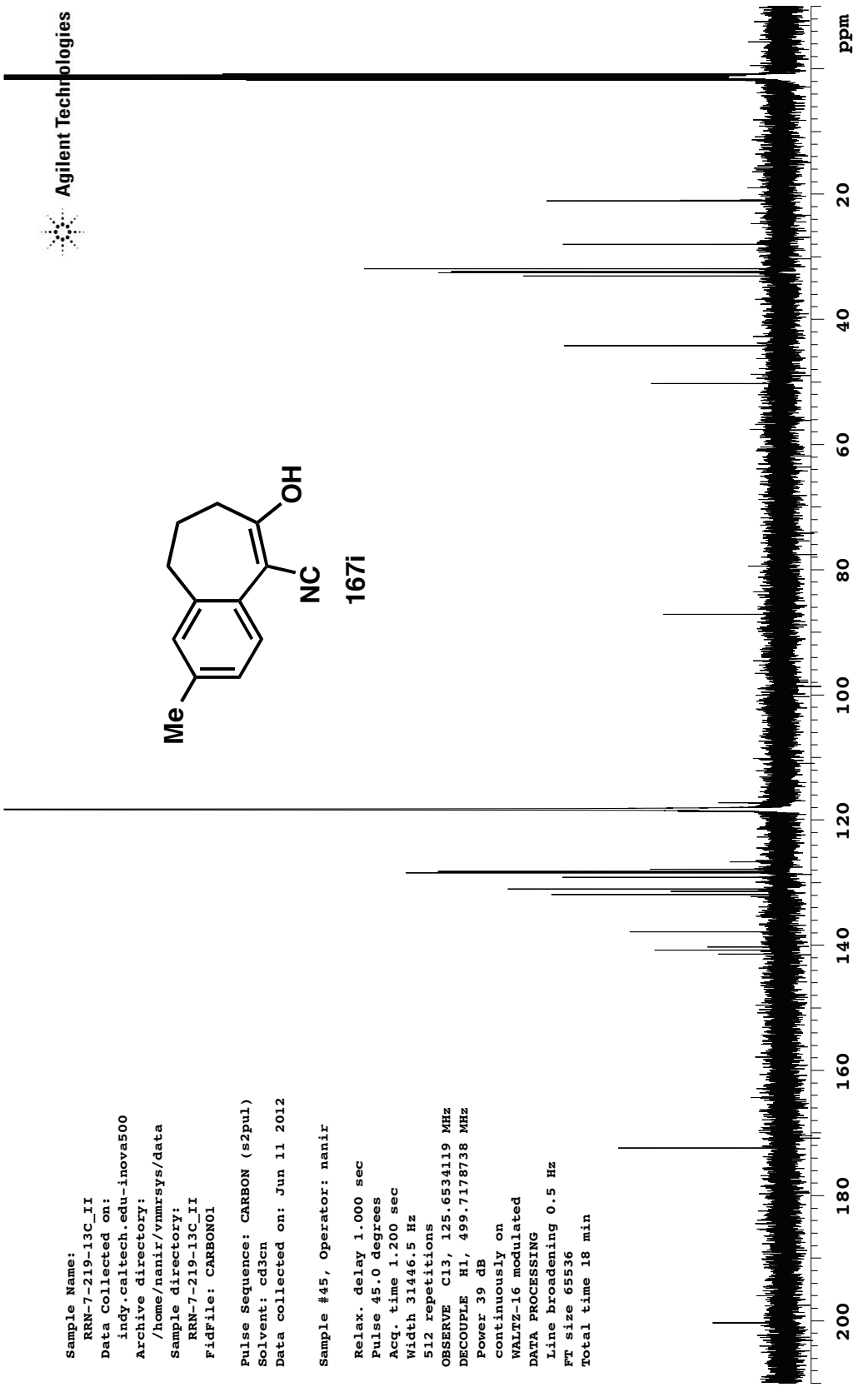

Sample Name:
RRN-9-139-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-139-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 20 2012
Sample #45, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7127430 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
O
CN
H
O2N
167g
0.93
0.95
1.00
0.99
2.10
1.07
1.03
1.10
1.05
ppm

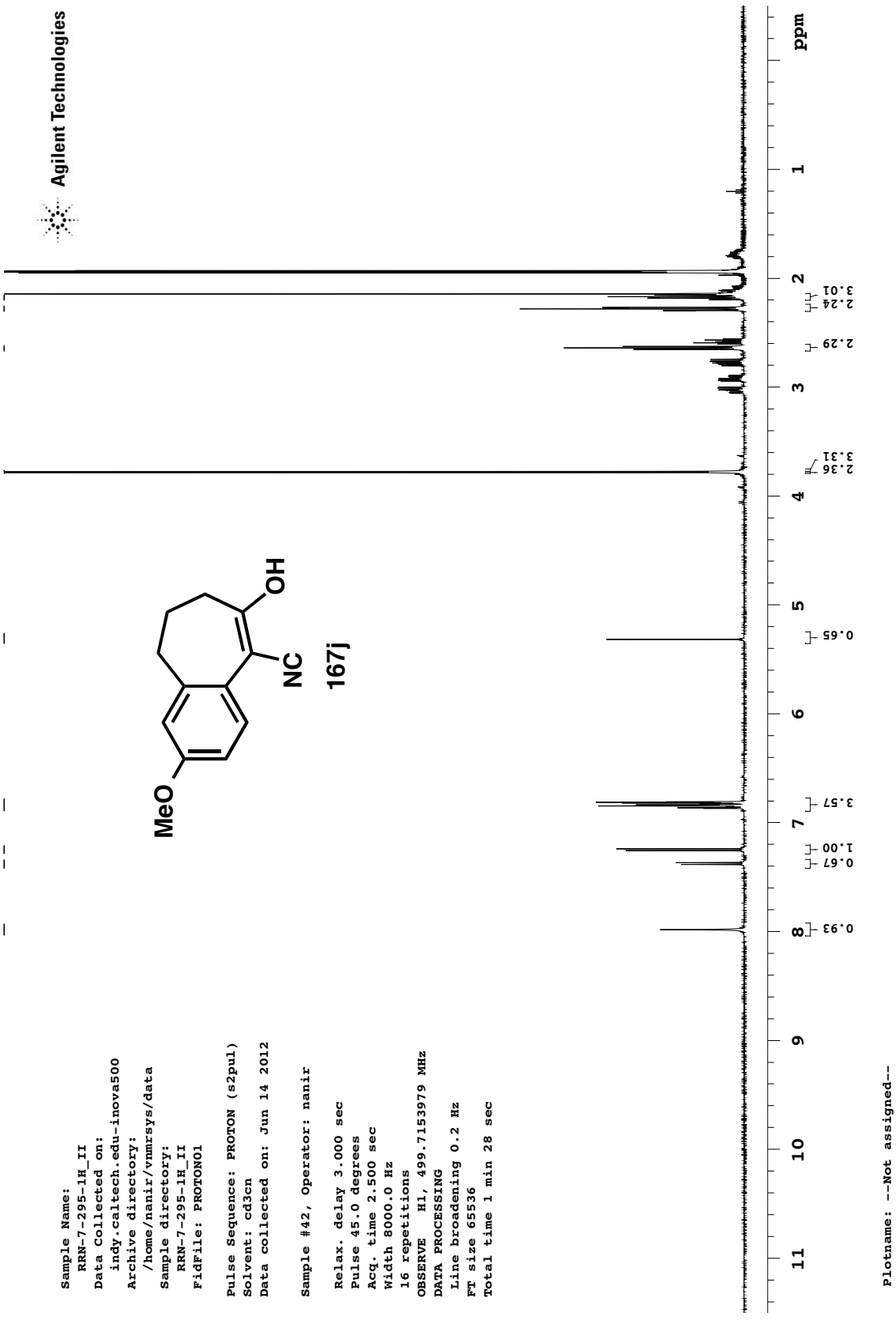

Sample Name:
RRN-9-139-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-139-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 20 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6528719 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 54 min
O
CN
H
O2N
167g
200
180
160
140
120
100
80
60
40
20
ppm

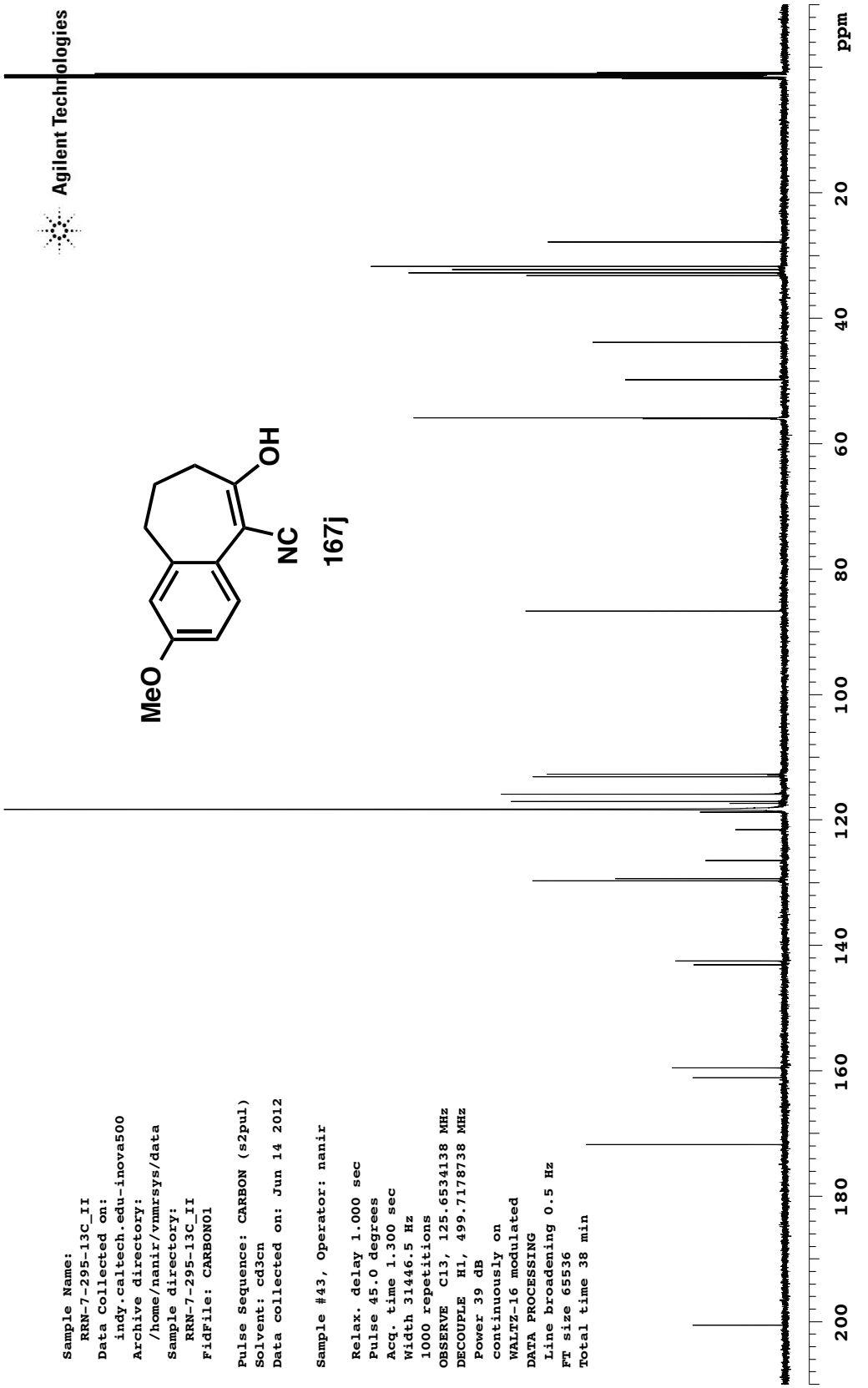

Sample Name:
RRN-9-263-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-263-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 31 2012
Sample #44, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
O
CN
H
167h
ppm
1.06
1.06
2.10
1.07
1.05
1.01
1.00
1.01
0.99
3.00

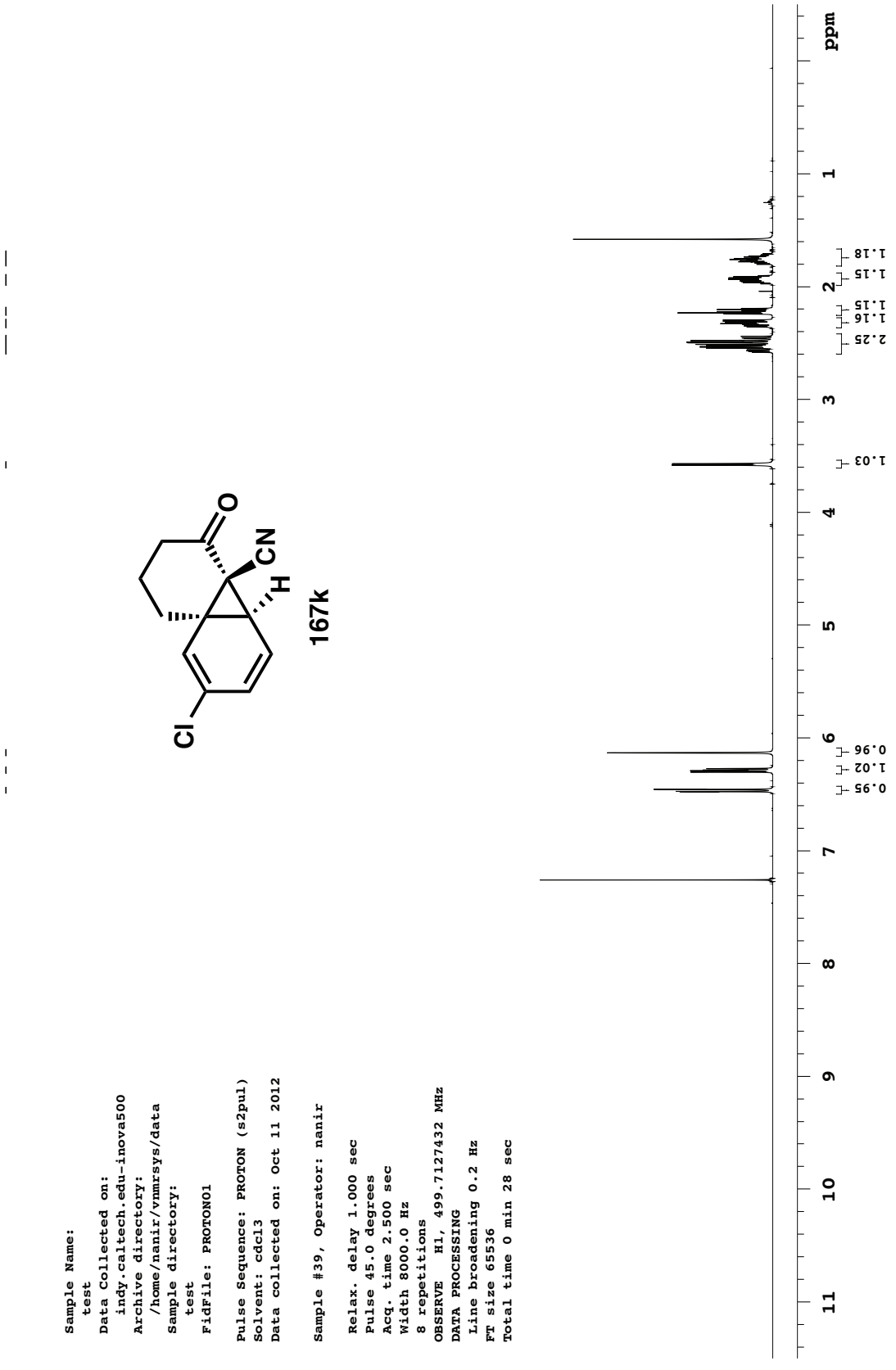

Sample Name:
RRN-9-263-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-263-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 31 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6509072 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 54 min
O
CN
H
167h
200
180
160
140
120
100
80
60
40
20
ppm

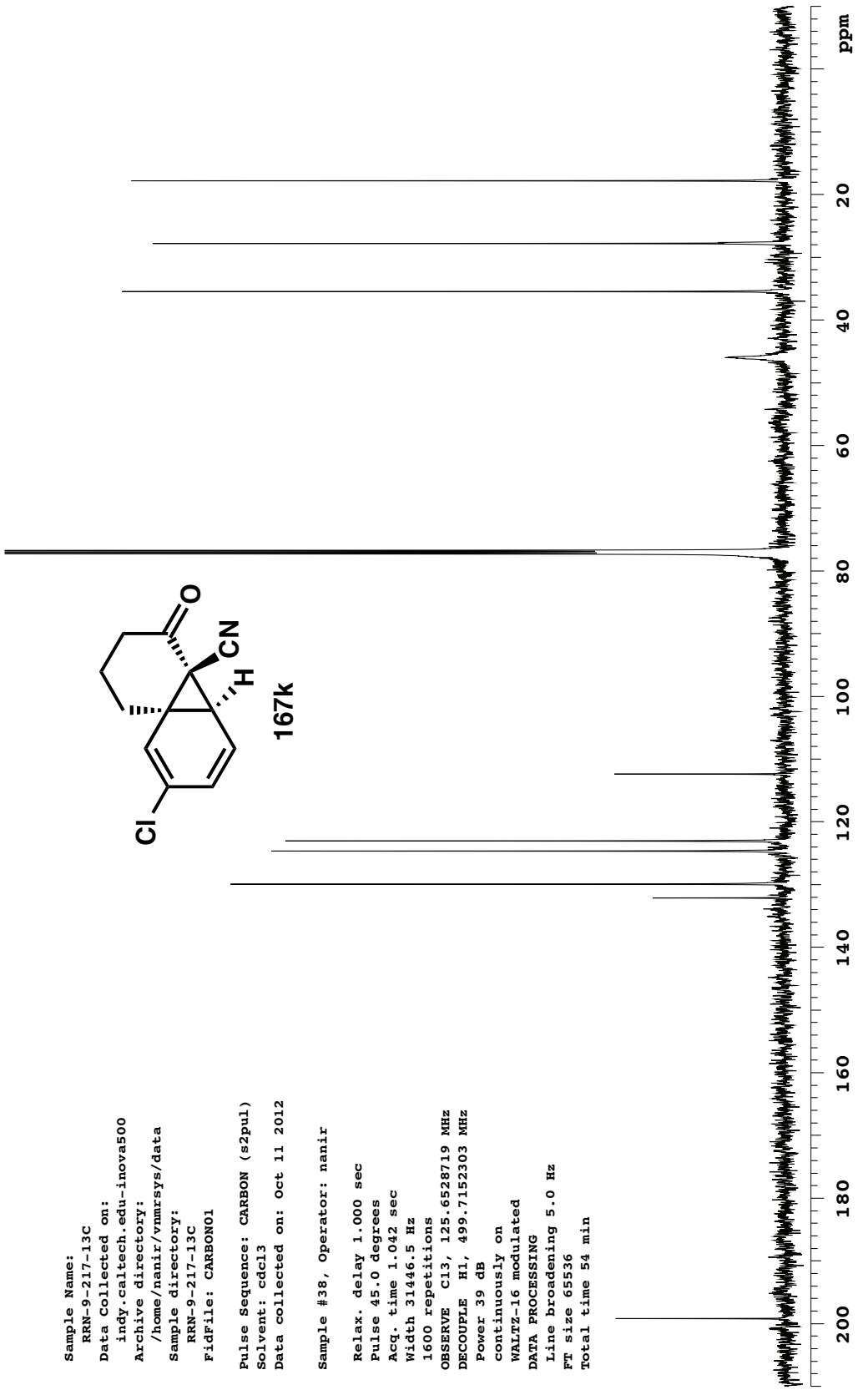

Agilent Technologies
Me
NC
OH
167i
Sample Name:
RRN-7-219-1H_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-219-1H_II
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jun 11 2012
Sample #44, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7153977 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
0.91
0.60
1.00
0.65
2.69
0.59
2.40
4.84
8.70
ppm
Plotname: --Not assigned--

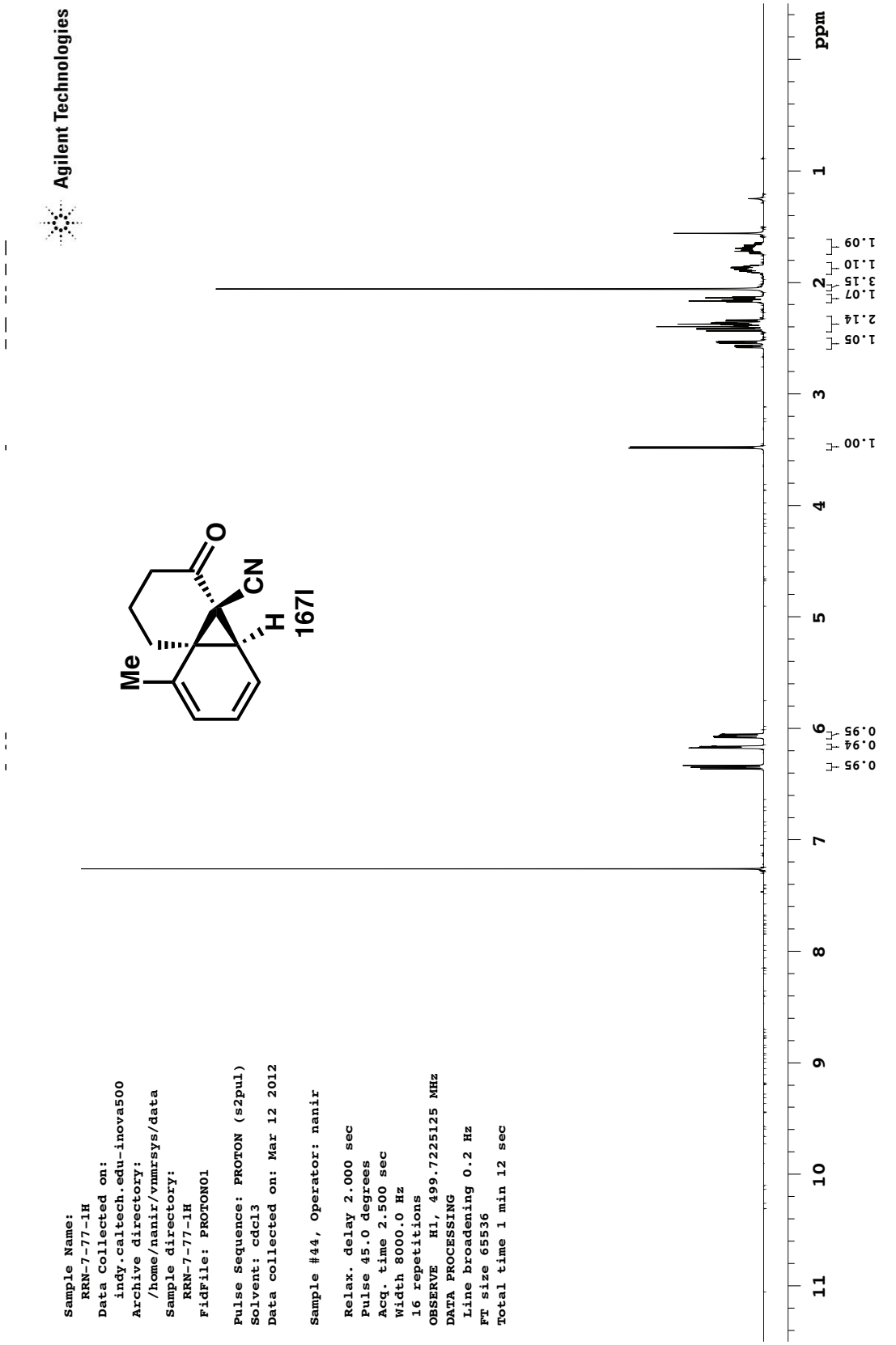

Agilent Technologies
OH
NC
Me
167i
ppm
200
180
160
140
120
100
80
60
40
20
Sample Name:
RRN-7-219-13C_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-219-13C_II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jun 11 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.200 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6534119 MHz
DECOUPLE H1, 499.7178738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 18 min
Plotname: --Not assigned--

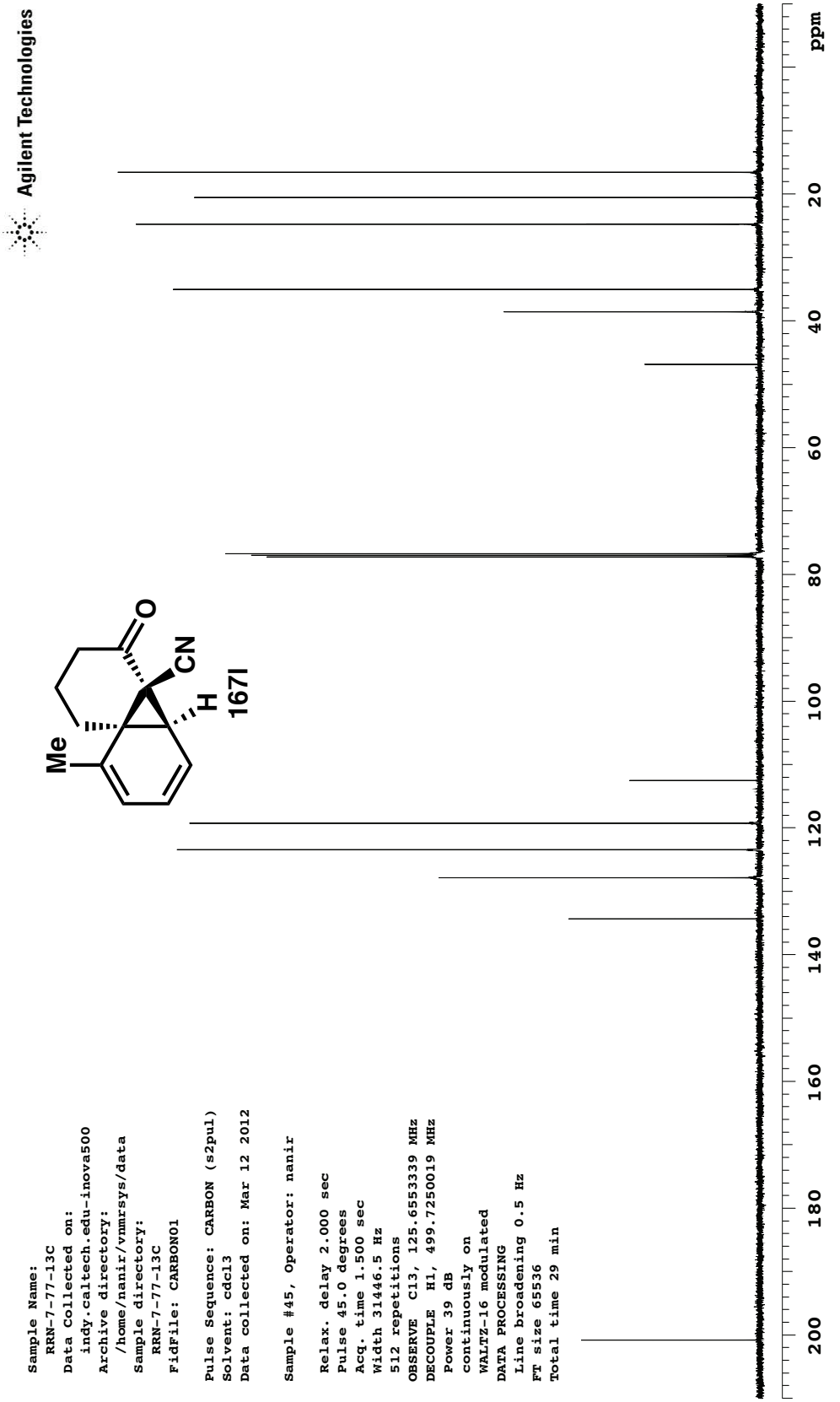

Agilent Technologies
MeO
NC
OH
167j
ppm
0.93
0.67
1.00
3.57
0.65
2.36
3.31
2.29
2.24
3.01
Sample Name:
RRN-7-295-1H_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-295-1H_II
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd3cn
Data collected on: Jun 14 2012
Sample #42, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7153979 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
Plotname: --Not assigned--


Agilent Technologies
MeO
NC
OH
167j
ppm
200
180
160
140
120
100
80
60
40
20
Sample Name:
RRN-7-295-13C_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-295-13C_II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd3cn
Data collected on: Jun 14 2012
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6534138 MHz
DECOUPLE H1, 499.7178738 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min
Plotname: --Not assigned--

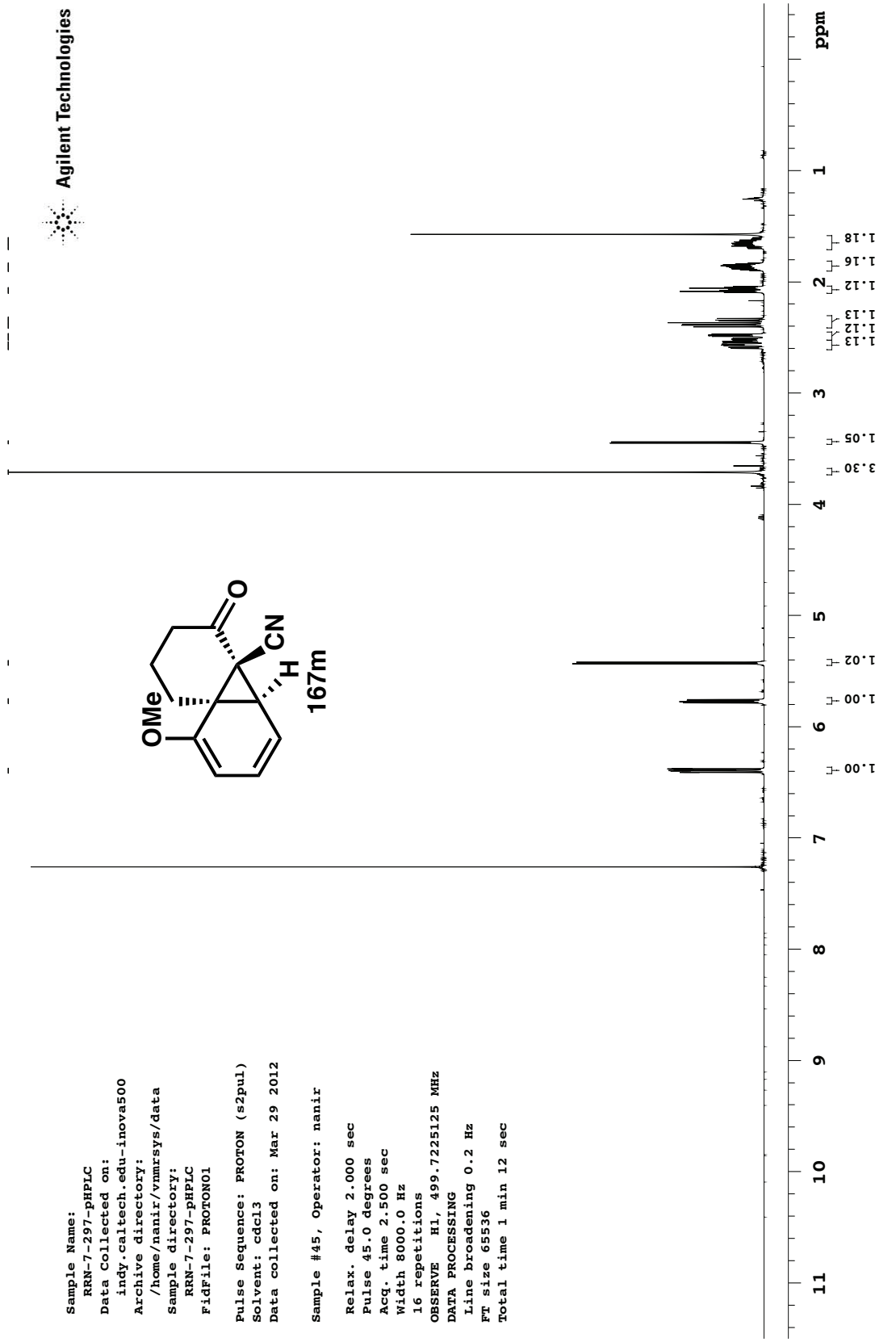

Sample Name:
test
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
test
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 11 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7127432 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
O
CN
H
Cl
167k
0.95
1.02
0.96
1.03
2.25
1.16
1.15
1.15
1.18
ppm


Sample Name:
RRN-9-217-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-217-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 11 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6528719 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 54 min
O
CN
H
Cl
167k
200
180
160
140
120
100
80
60
40
20
ppm

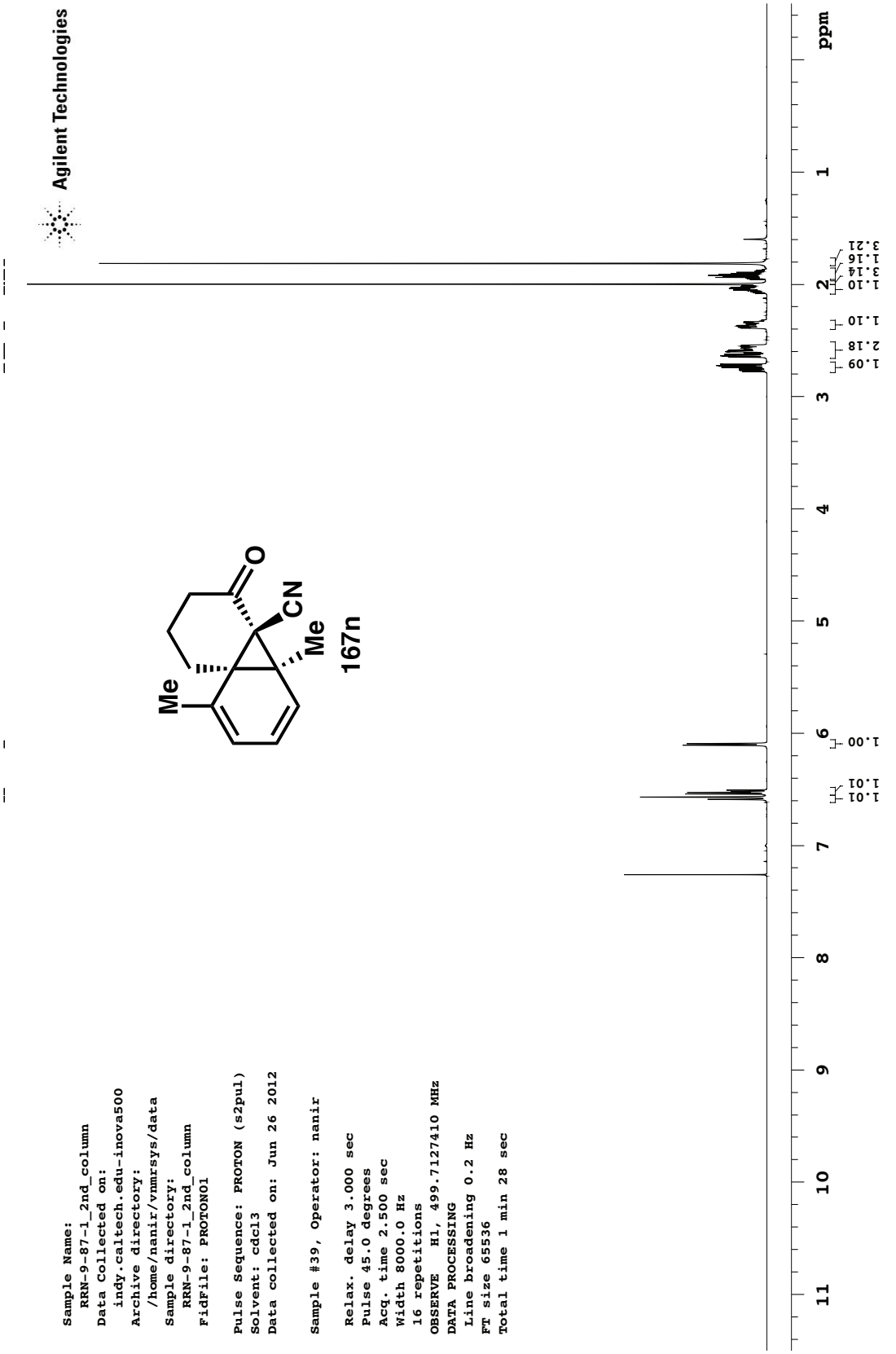

Agilent Technologies
Me
CN
H
O
167l
Sample Name:
RRN-7-77-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-77-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 12 2012
Sample #44, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
0.95
0.94
0.95
1.00
1.05
2.14
1.07
3.15
1.10
1.09
ppm
Plotname: --Not assigned--



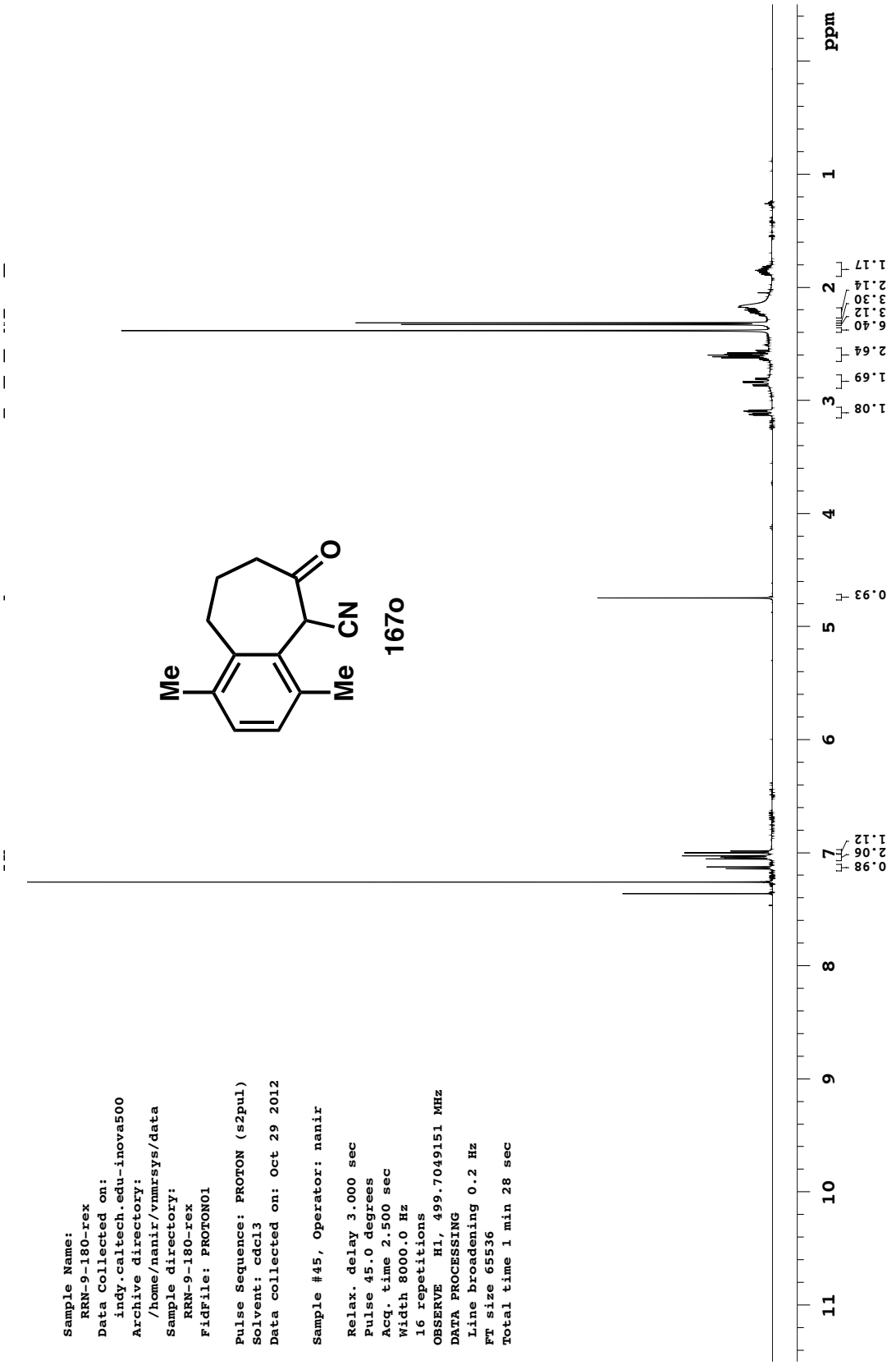

```
Sample Name:
   RRN-7-77-13C
Data Collected on:
   indy.caltech.edu-inova500
Archive directory:
   /home/nanir/vnmrsys/data
Sample directory:
   RRN-7-77-13C
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 12 2012

Sample #45, Operator: nanir

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
512 repetitions
OBSERVE  C13, 125.6553339 MHz
DECOUPLE  H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 29 min

Plotname: --Not assigned--
```

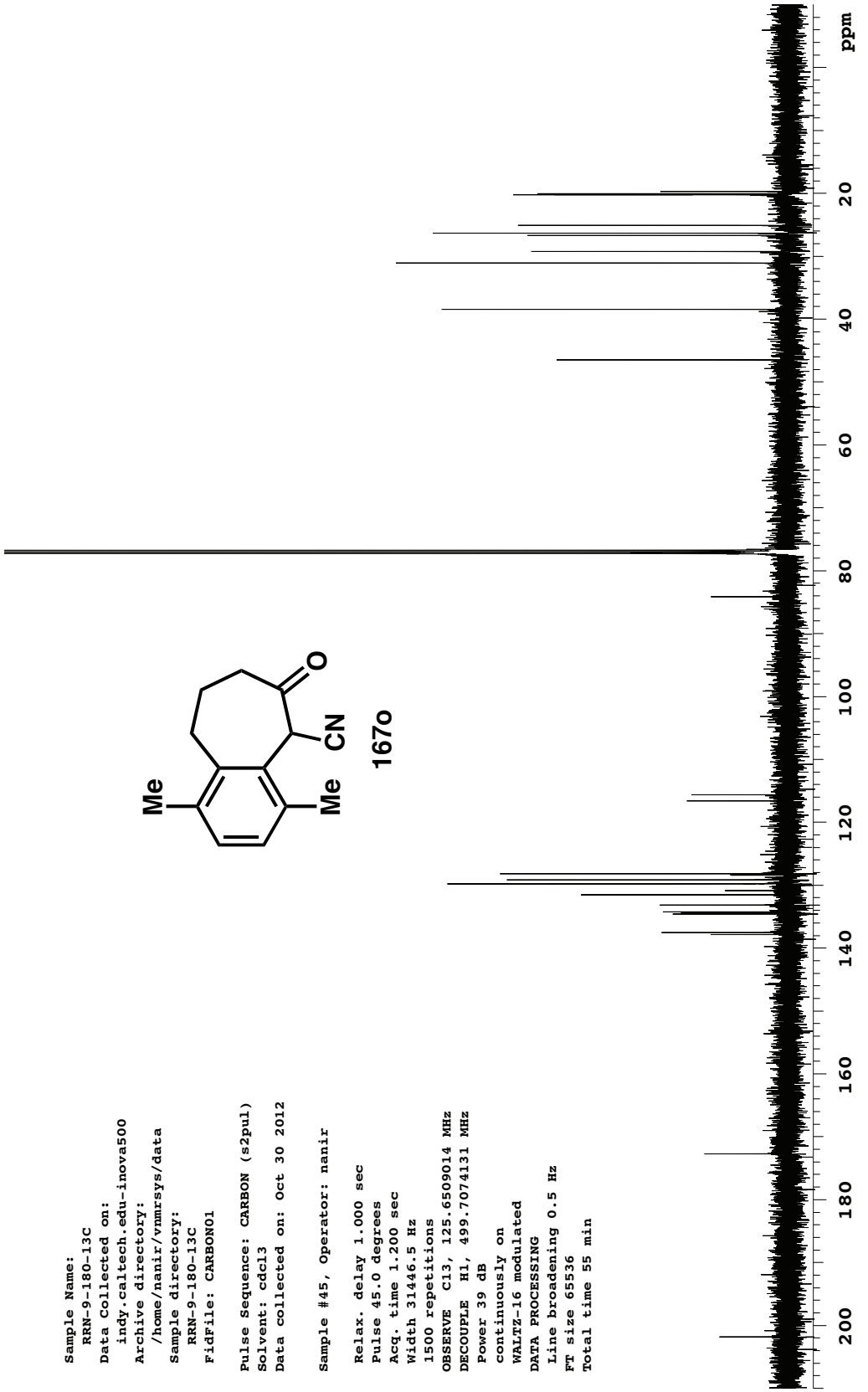

Agilent Technologies
OMe
O
CN
H
167m
1.00
1.00
1.02
1.05
3.30
1.13
1.12
1.13
1.12
1.16
1.18
ppm
Sample Name:
RRN-7-297-pHPLC
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-297-pHPLC
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 29 2012
Sample #45, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
Plotname: --Not assigned--

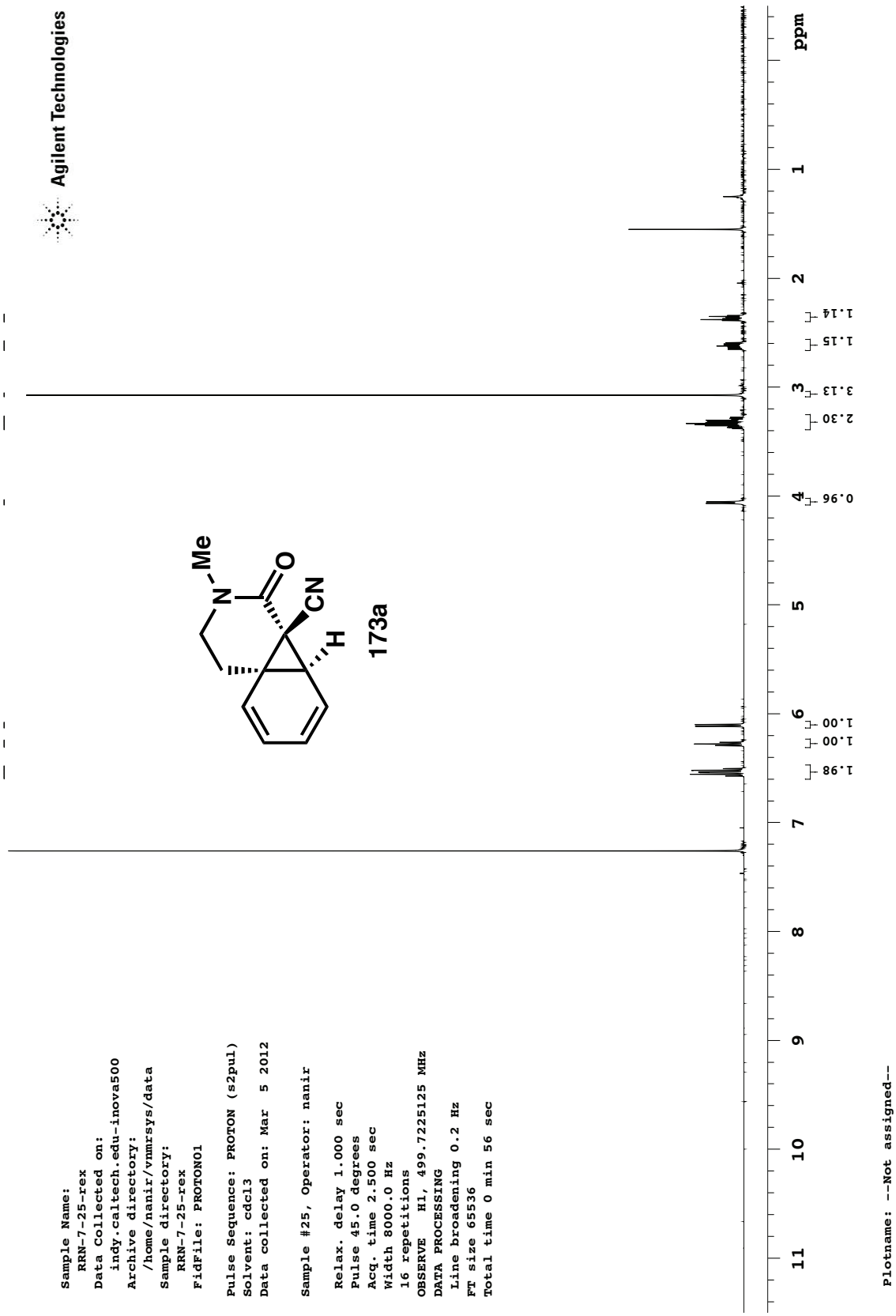
Agilent Technologies
Sample Name:
RRN-7-297-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-297-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 29 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1700 repetitions
OBSERVE C13, 125.6553271 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 58 min
OMe
O
CN
H
167m
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--


Agilent Technologies
Me
CN
O
Me
167n
ppm
1.00
1.01
1.01
1.09
2.18
1.10
1.10
3.14
1.16
3.21
Sample Name:
RRN-9-87-1_2nd_column
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-87-1_2nd_column
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 26 2012
Sample #39, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
Plotname: --Not assigned--

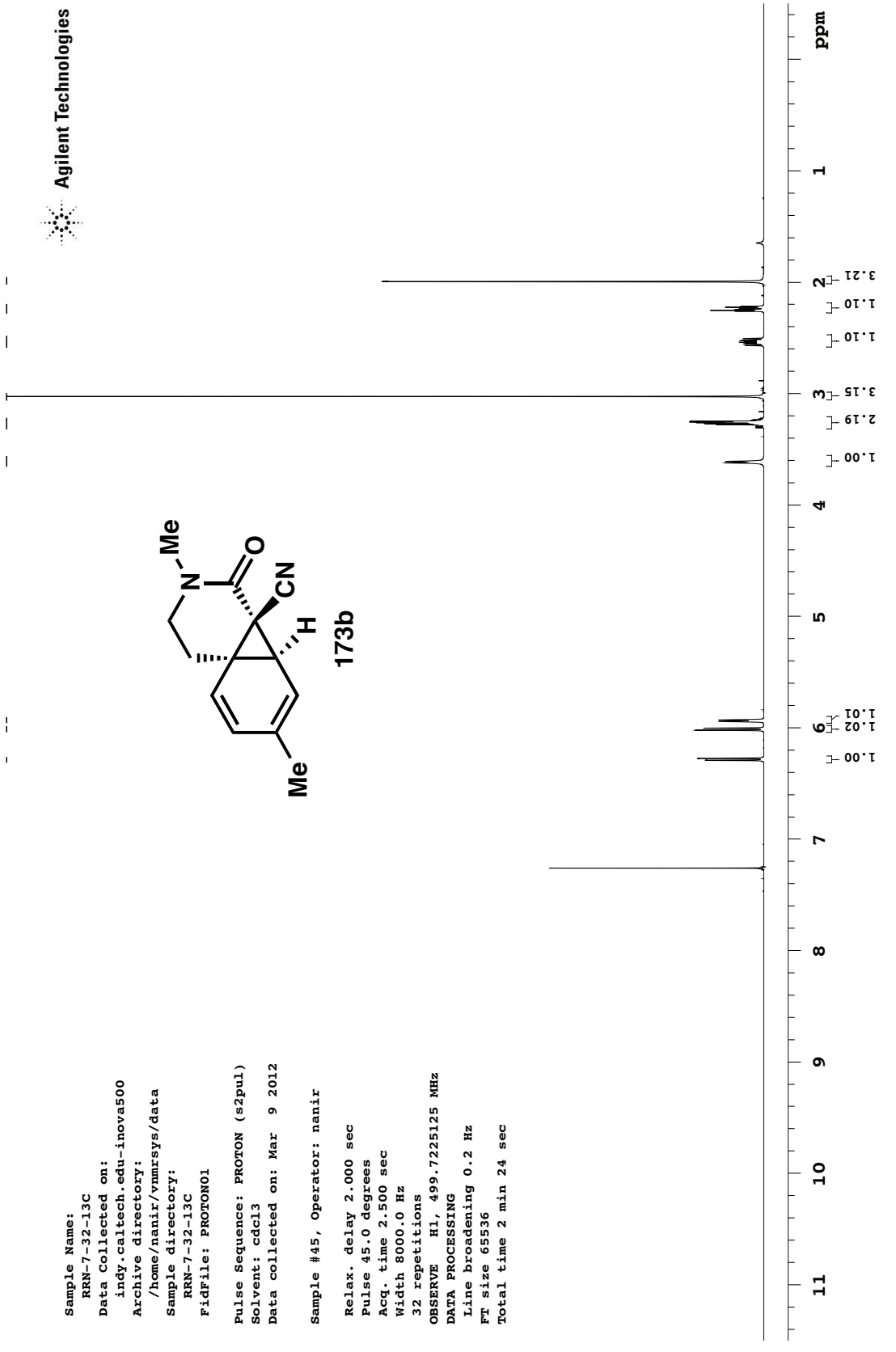
Agilent Technologies
Sample Name:
RRN-9-87-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-87-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 26 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528739 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 21 min
O
CN
Me
Me
167n
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--


Sample Name:
RRN-9-180-rex
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-180-rex
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 29 2012
Sample #45, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
Me
Me
CN
O
167o
ppm
0.98
2.06
1.12
0.93
1.08
1.69
2.64
6.40
3.12
3.30
2.14
1.17

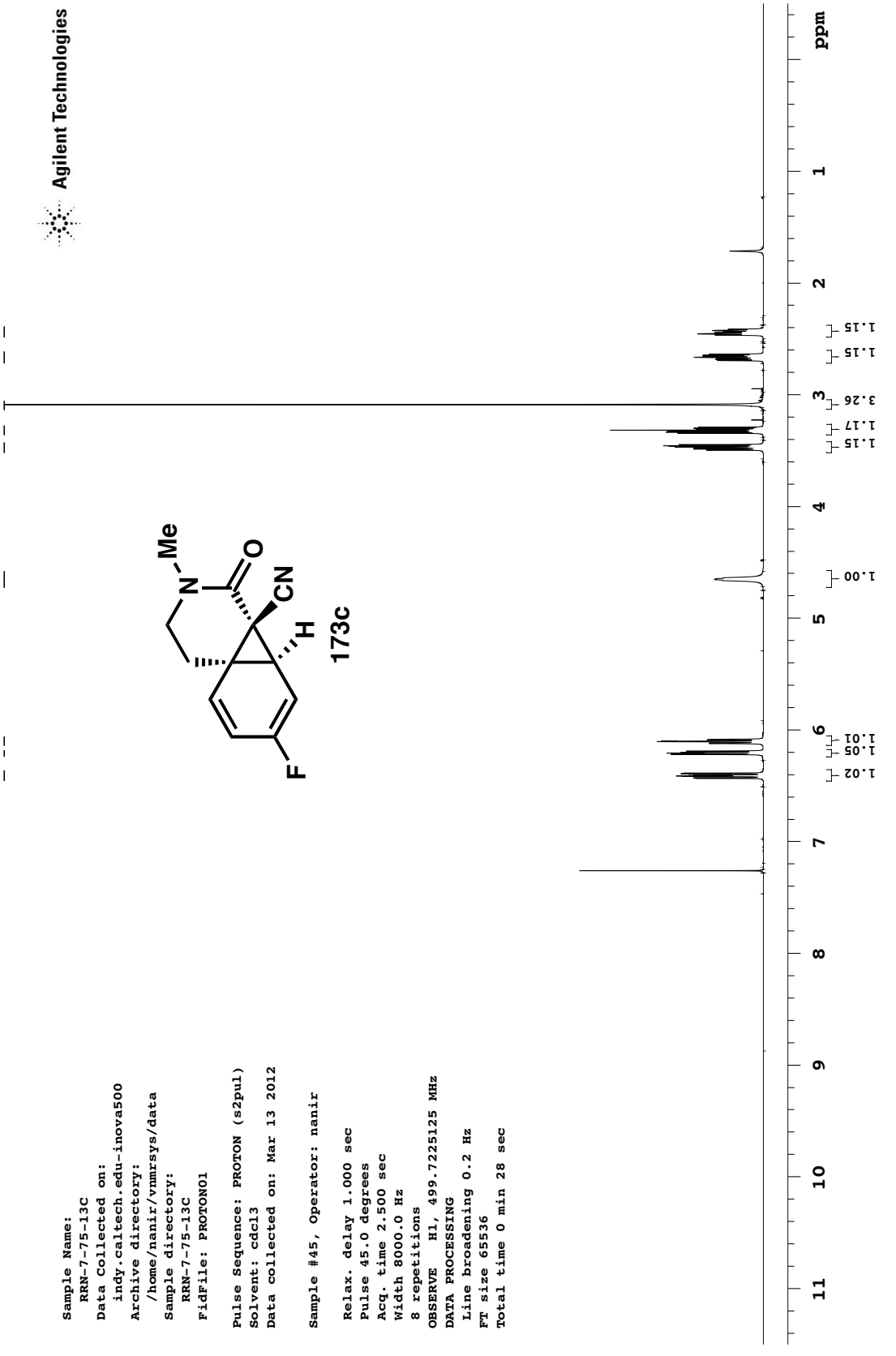

Sample Name:
RRN-9-180-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-180-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 30 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.200 sec
Width 31446.5 Hz
1500 repetitions
OBSERVE C13, 125.6509014 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 55 min
Me
Me
CN
O
167o
200
180
160
140
120
100
80
60
40
20
ppm


Agilent Technologies
Me
N
O
CN
H
173a
ppm
1.98
1.00
1.00
0.96
2.30
3.13
1.15
1.14
Sample Name:
RRN-7-25-rex
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-25-rex
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 5 2012
Sample #25, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec
Plotname: --Not assigned--

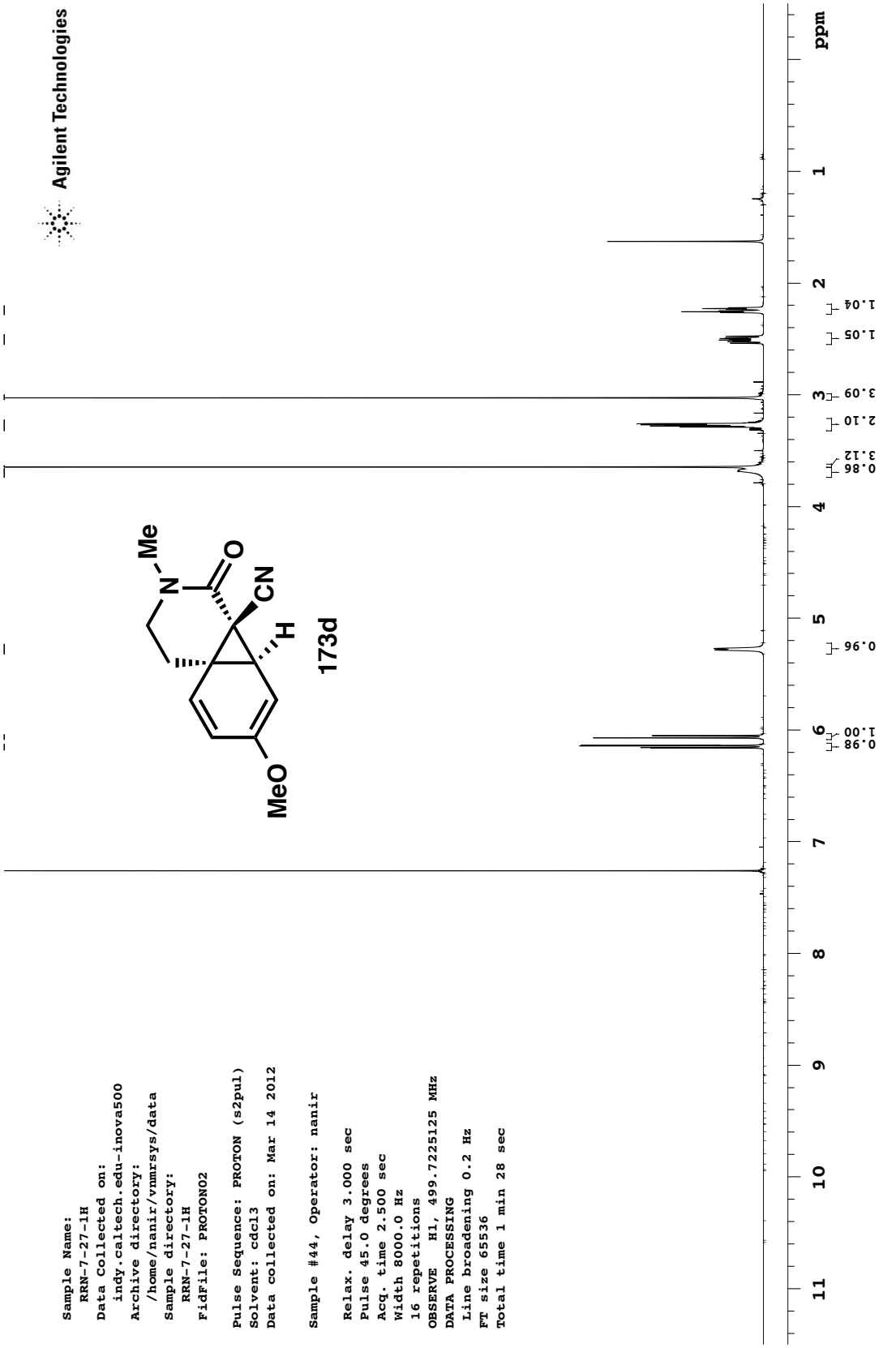
Agilent Technologies
Sample Name:
RRN-7-25-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-25-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 6 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
384 repetitions
OBSERVE C13, 125.6553339 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 19 min
Me
N
O
CN
H
173a
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--


Agilent Technologies
Me
N
O
CN
H
Me
173b
1.00
2.19
3.15
1.10
1.10
3.21
1.00
1.02
1.01
ppm
Sample Name:
RRN-7-32-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-32-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 9 2012
Sample #45, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
Plotname: --Not assigned--

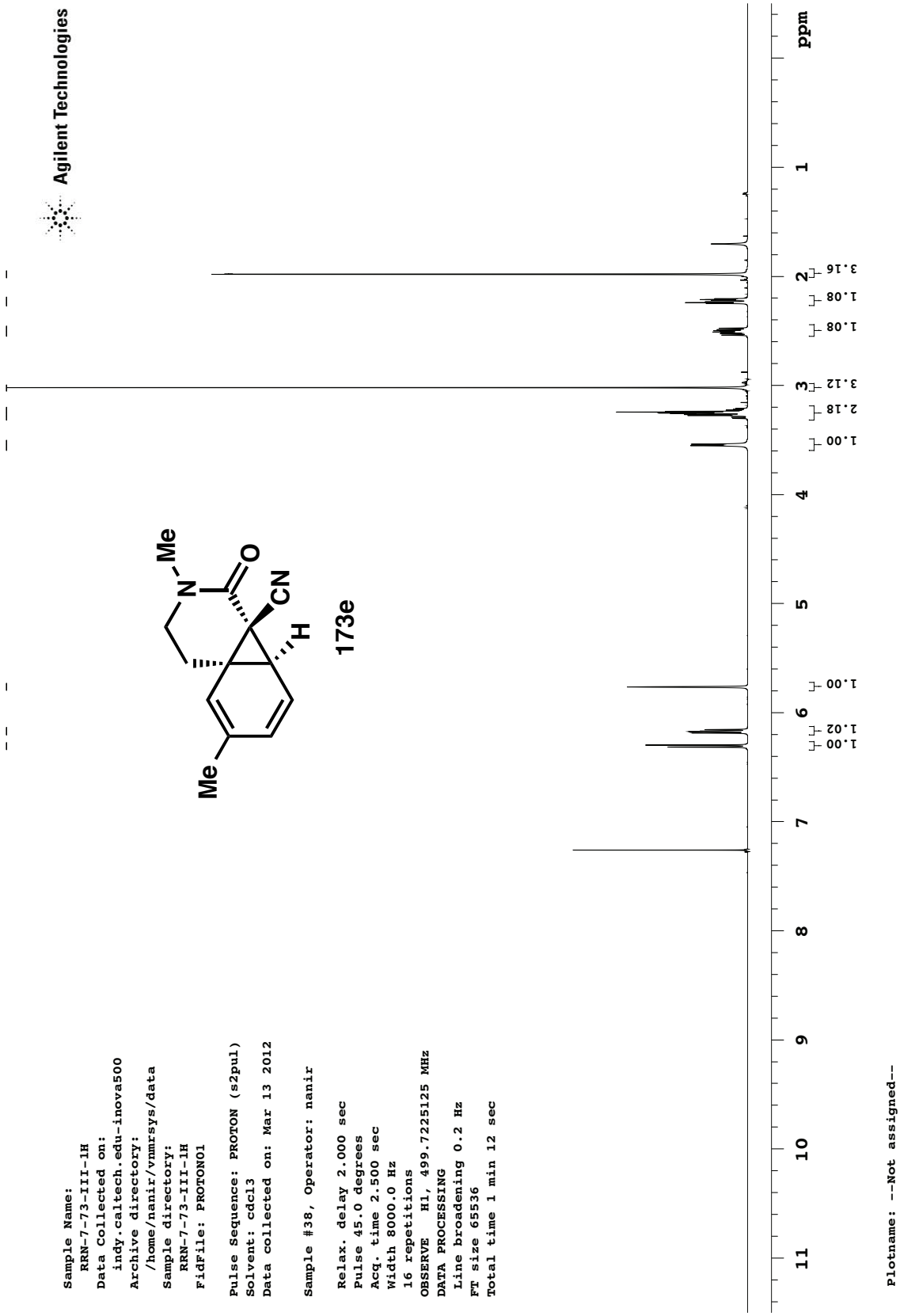
Agilent Technologies
Sample Name:
RRN-7-32-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-32-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 9 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6553291 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 54 min
Me
N
O
CN
H
Me
173b
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

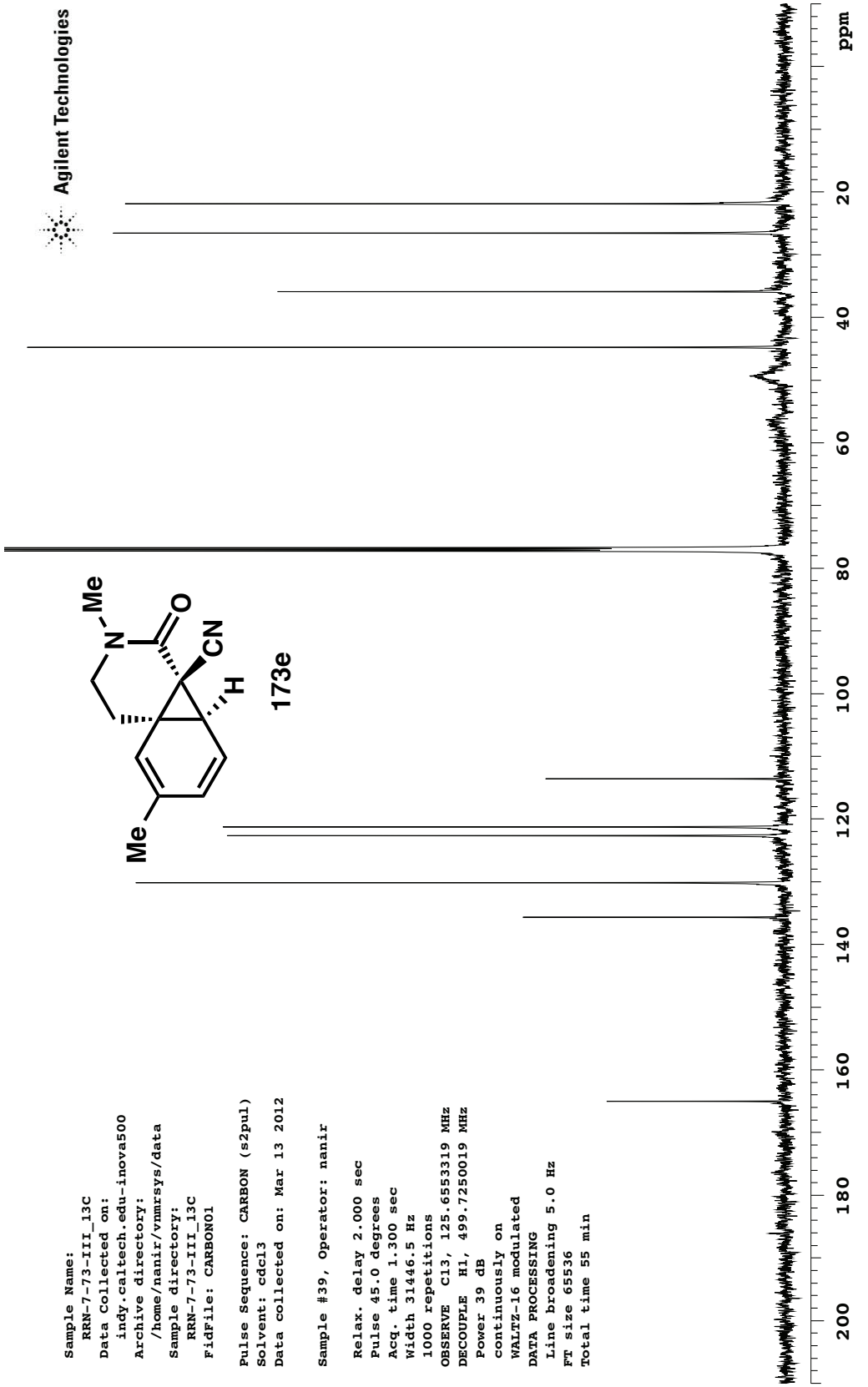

Agilent Technologies
Me
N
O
CN
H
F
173c
1.00
1.02
1.05
1.01
1.15
1.17
1.15
3.26
1.15
1.15
ppm
Sample Name:
RRN-7-75-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-75-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 13 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
Plotname: --Not assigned--

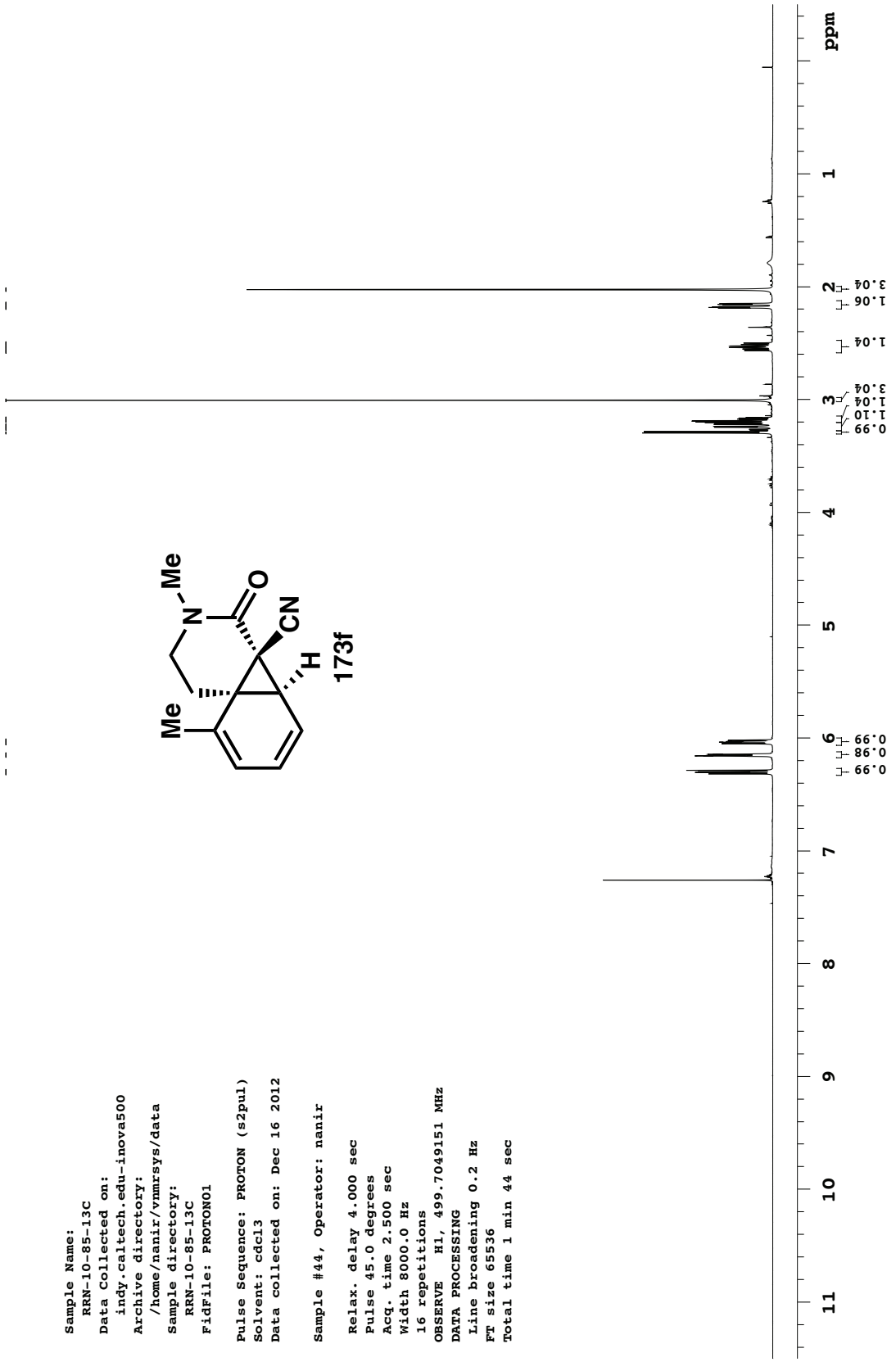
Agilent Technologies
Sample Name:
RRN-7-75-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-75-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 13 2012
Sample #45, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
900 repetitions
OBSERVE C13, 125.6553339 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 65536
Total time 52 min
Me
N
O
CN
H
F
173c
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

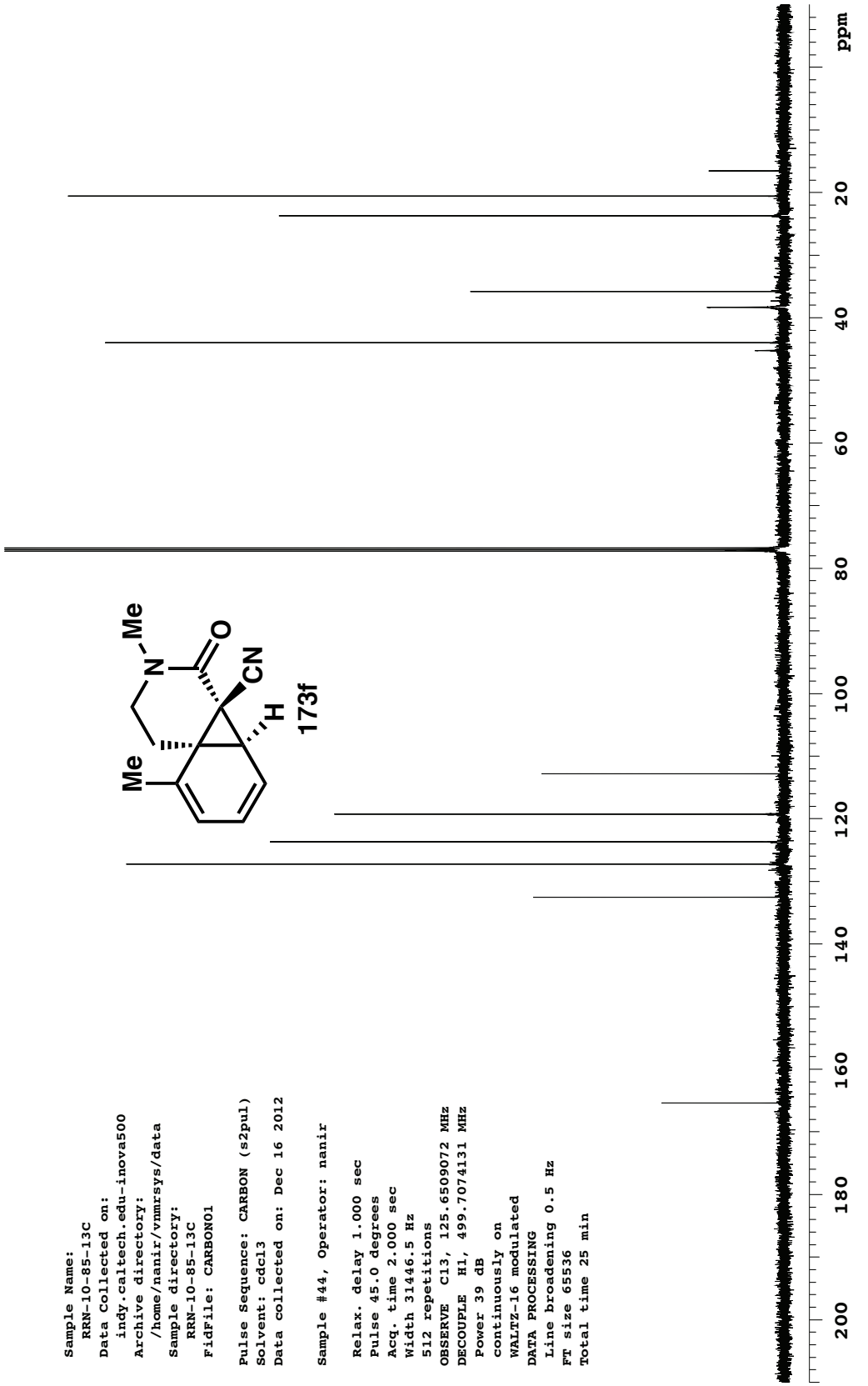

Agilent Technologies
Sample Name:
RRN-7-27-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-27-1H
FidFile: PROTON02
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 14 2012
Sample #44, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
Me
N
O
CN
H
MeO
173d
0.86
3.12
2.10
3.09
1.05
1.04
0.96
0.98
1.00
ppm
Plotname: --Not assigned--

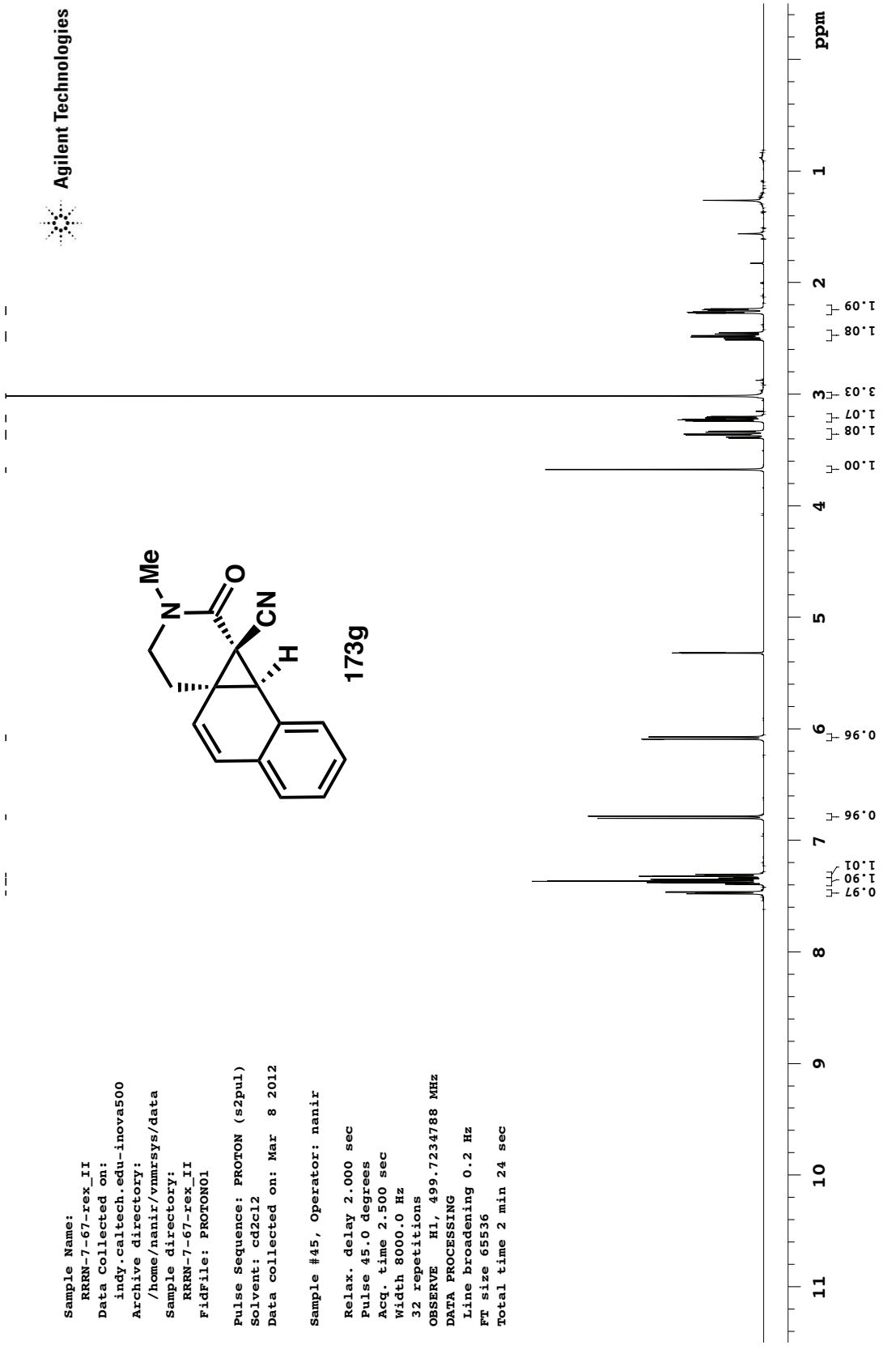
Agilent Technologies
Sample Name:
RRN-7-27-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-27-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 14 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6553377 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 25 min
Me
N
O
CN
H
MeO
173d
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--


Agilent Technologies
Me
N
O
CN
H
Me
173e
3.16
1.08
1.08
3.12
2.18
1.00
1.00
1.02
1.00
ppm
11
10
9
8
7
6
5
4
3
2
1
Sample Name:
RRN-7-73-III-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-73-III-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 13 2012
Sample #38, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
Plotname: --Not assigned--

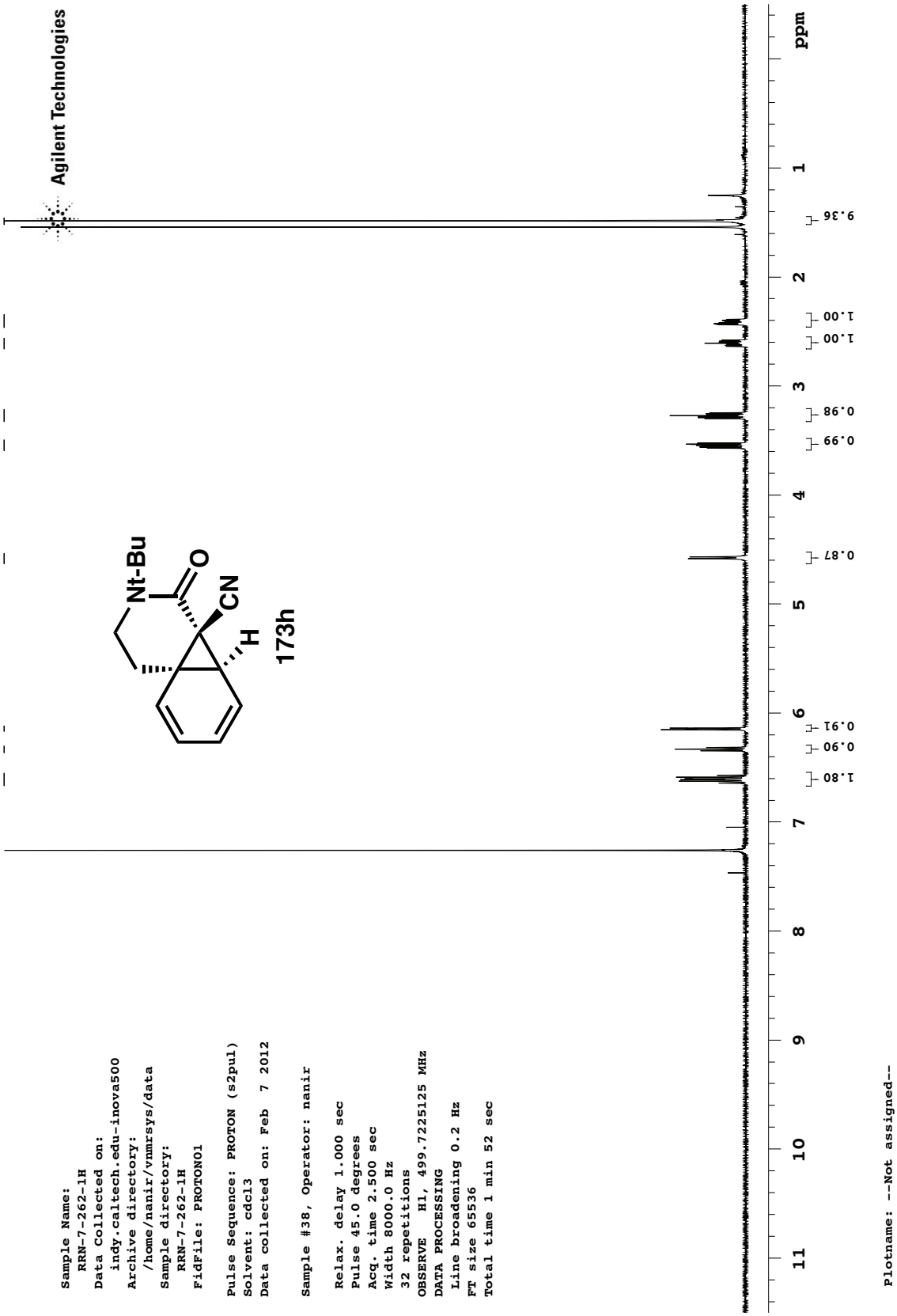

Agilent Technologies
Me
N
O
CN
H
Me
173e
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-7-73-III_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-73-III_13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 13 2012
Sample #39, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6553319 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 55 min
Plotname: --Not assigned--

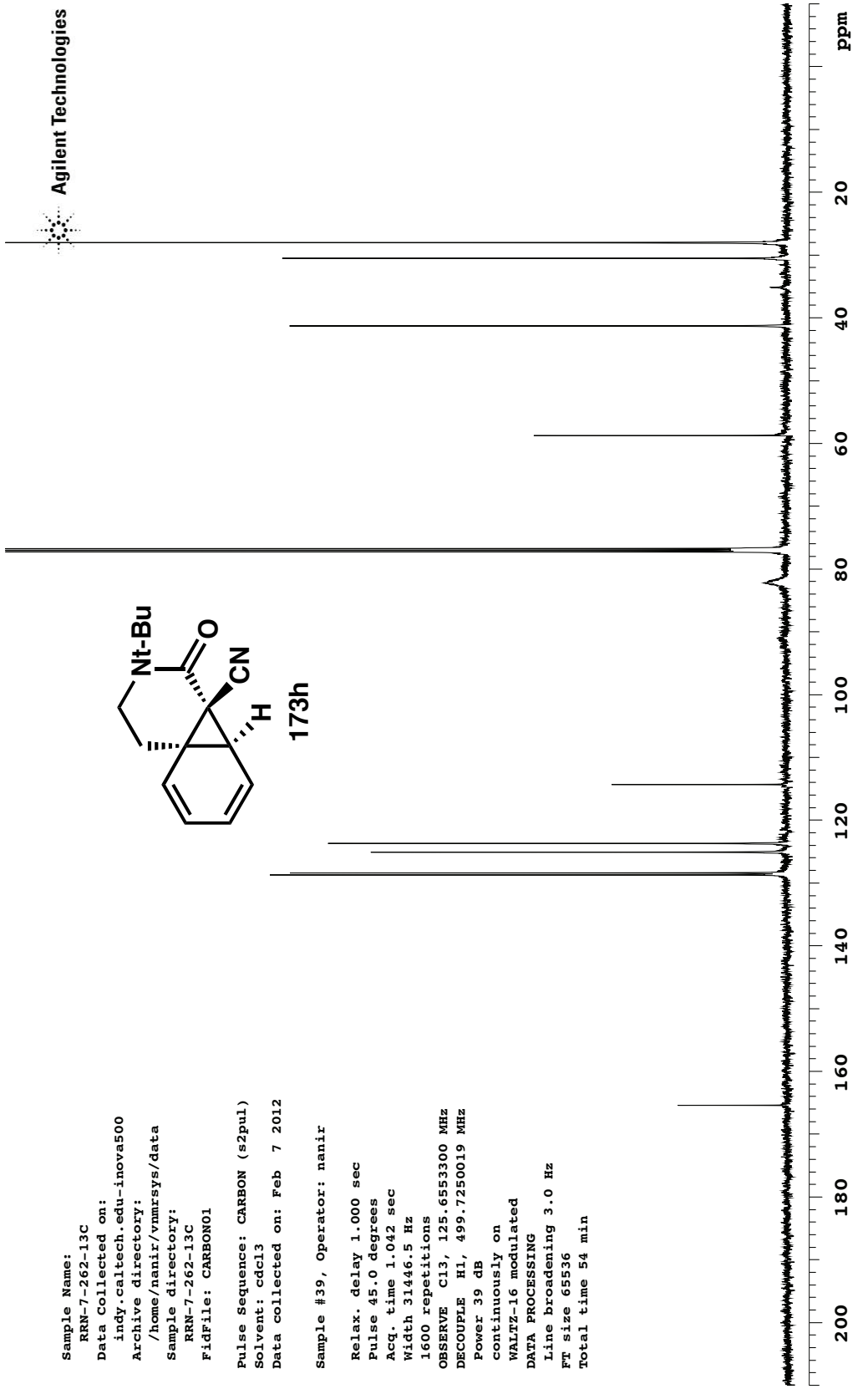

Sample Name:
RRN-10-85-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-85-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 16 2012
Sample #44, Operator: nanir
Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 44 sec
Me
N
Me
O
CN
H
Me
173f
ppm
0.99
0.98
0.99
3.04
1.06
1.04
3.04
1.04
1.10
0.99

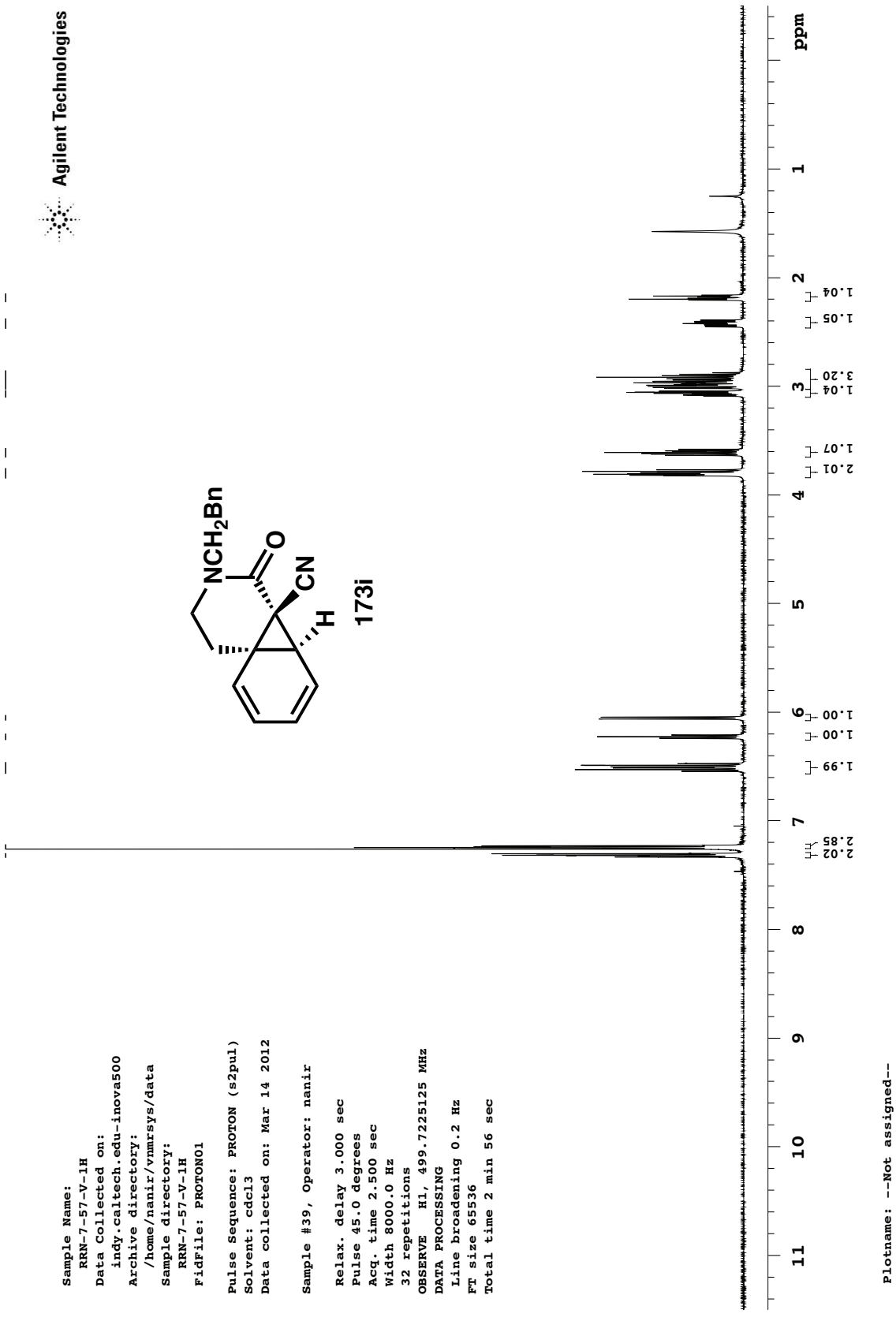

Sample Name:
RRN-10-85-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-85-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 16 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6509072 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 25 min
Me
N
Me
O
CN
H
Me
173f
200
180
160
140
120
100
80
60
40
20
ppm


Agilent Technologies
Me
N
O
CN
H
173g
Sample Name:
RRRN-7-67-rex_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRRN-7-67-rex_II
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cd2cl2
Data collected on: Mar 8 2012
Sample #45, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7234788 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 24 sec
0.97
1.90
1.01
0.96
0.96
1.00
1.08
1.07
3.03
1.08
1.09
ppm
Plotname: --Not assigned--

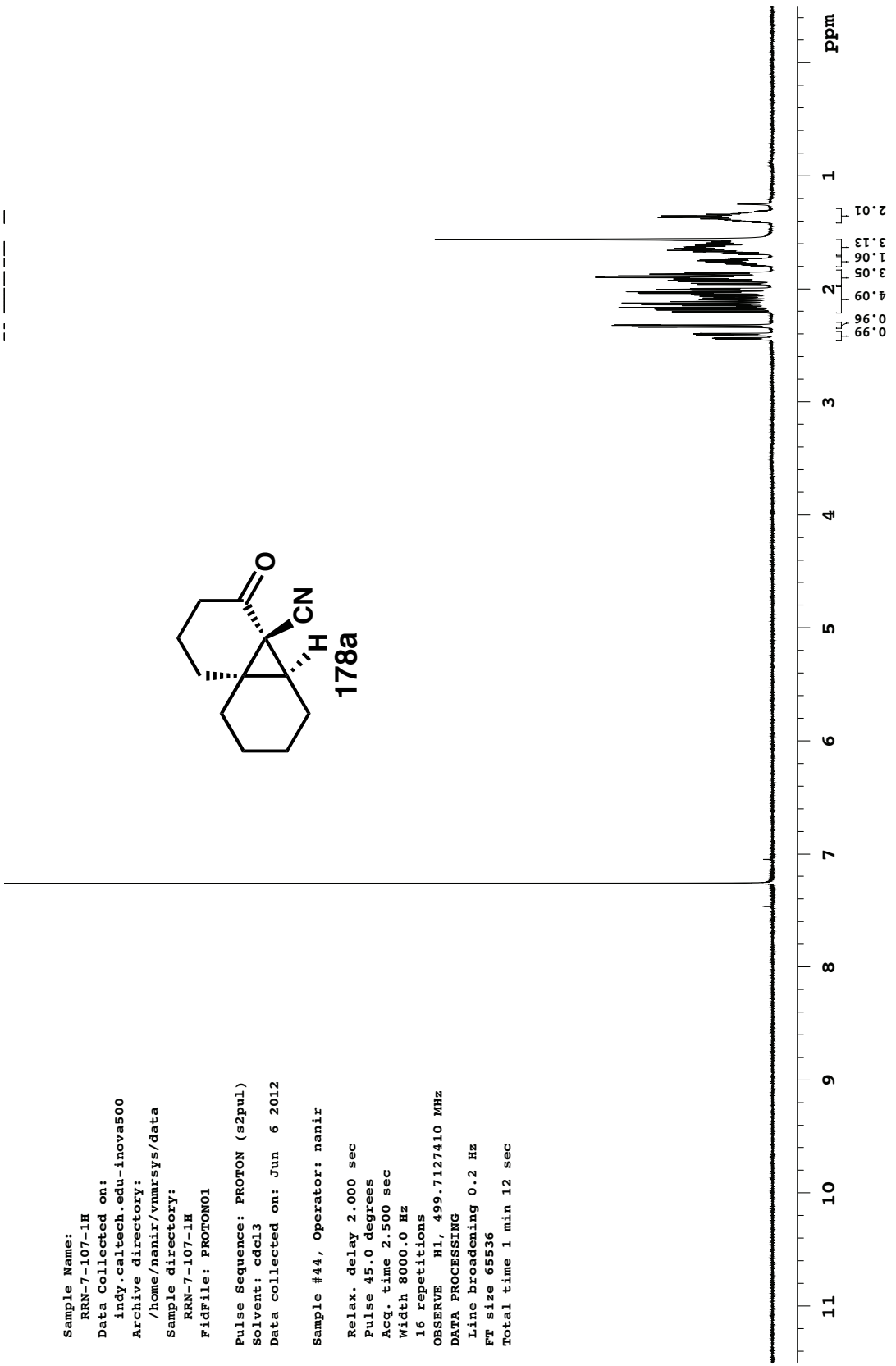
Agilent Technologies
Sample Name:
RRN-7-67-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-67-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cd2cl2
Data collected on: Mar 8 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
640 repetitions
OBSERVE C13, 125.6555202 MHz
DECOUPLE H1, 499.7259614 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 26 min
Me
N
O
CN
H
173g
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

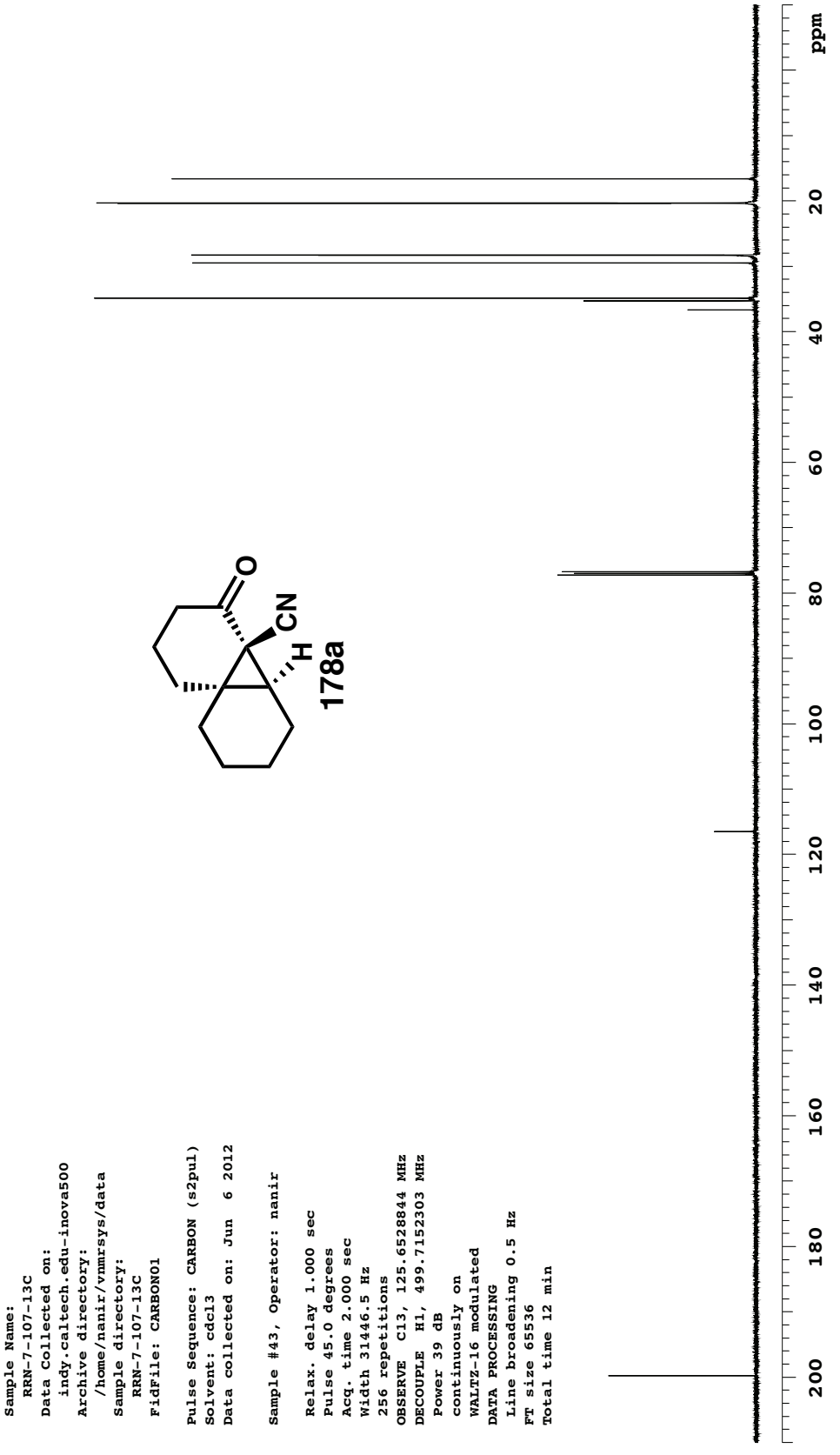

Agilent Technologies
Nt-Bu
O
CN
H
173h
9.36
1.00
1.00
0.98
0.99
0.87
1.80
0.90
0.91
ppm
Sample Name:
RRN-7-262-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-262-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 7 2012
Sample #38, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 52 sec
Plotname: --Not assigned--

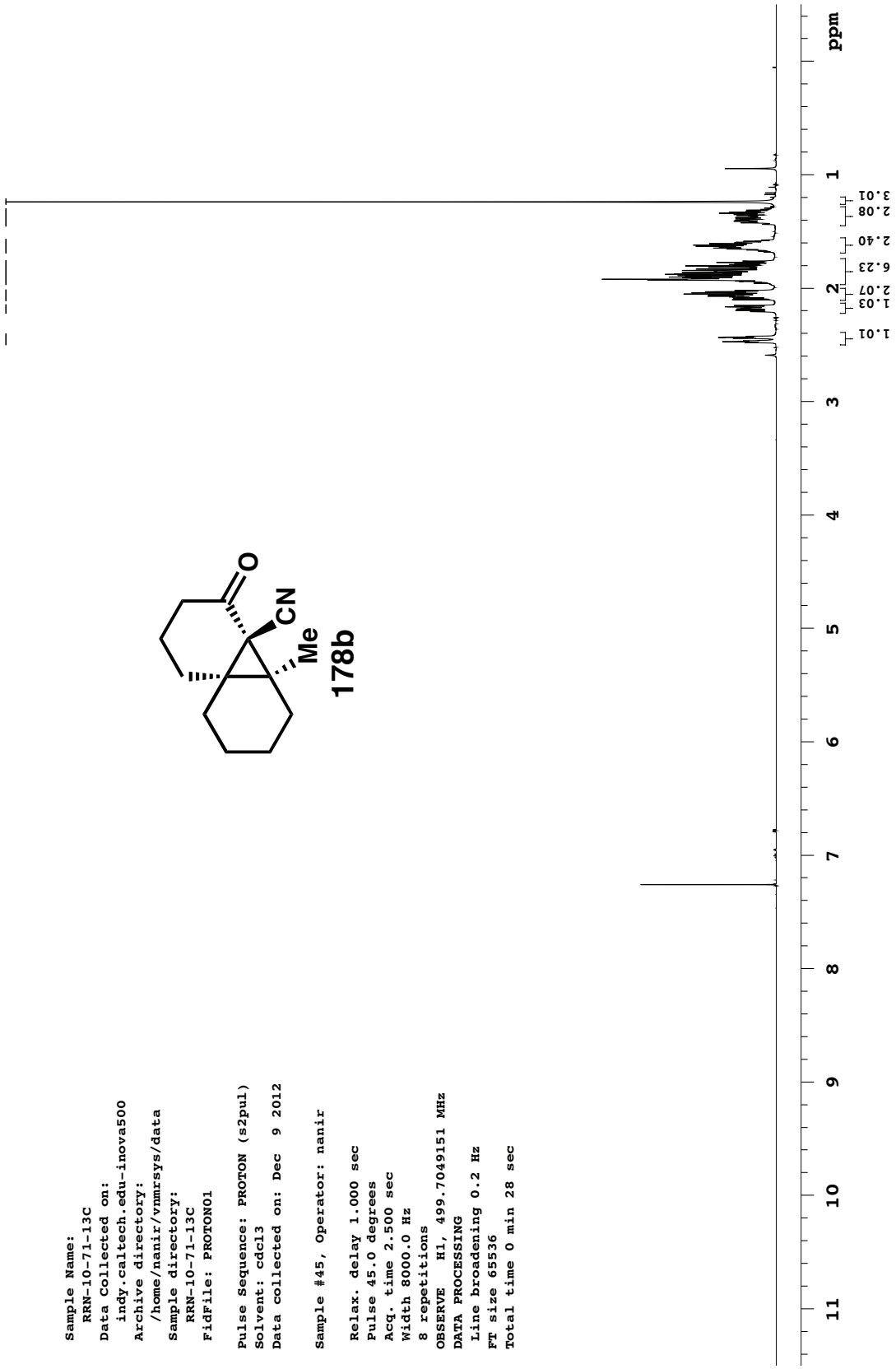

Agilent Technologies
Nt-Bu
O
CN
H
173h
200
180
160
140
120
100
80
60
40
20
ppm
Sample Name:
RRN-7-262-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-262-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Feb 7 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.042 sec
Width 31446.5 Hz
1600 repetitions
OBSERVE C13, 125.6553300 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 65536
Total time 54 min
Plotname: --Not assigned--

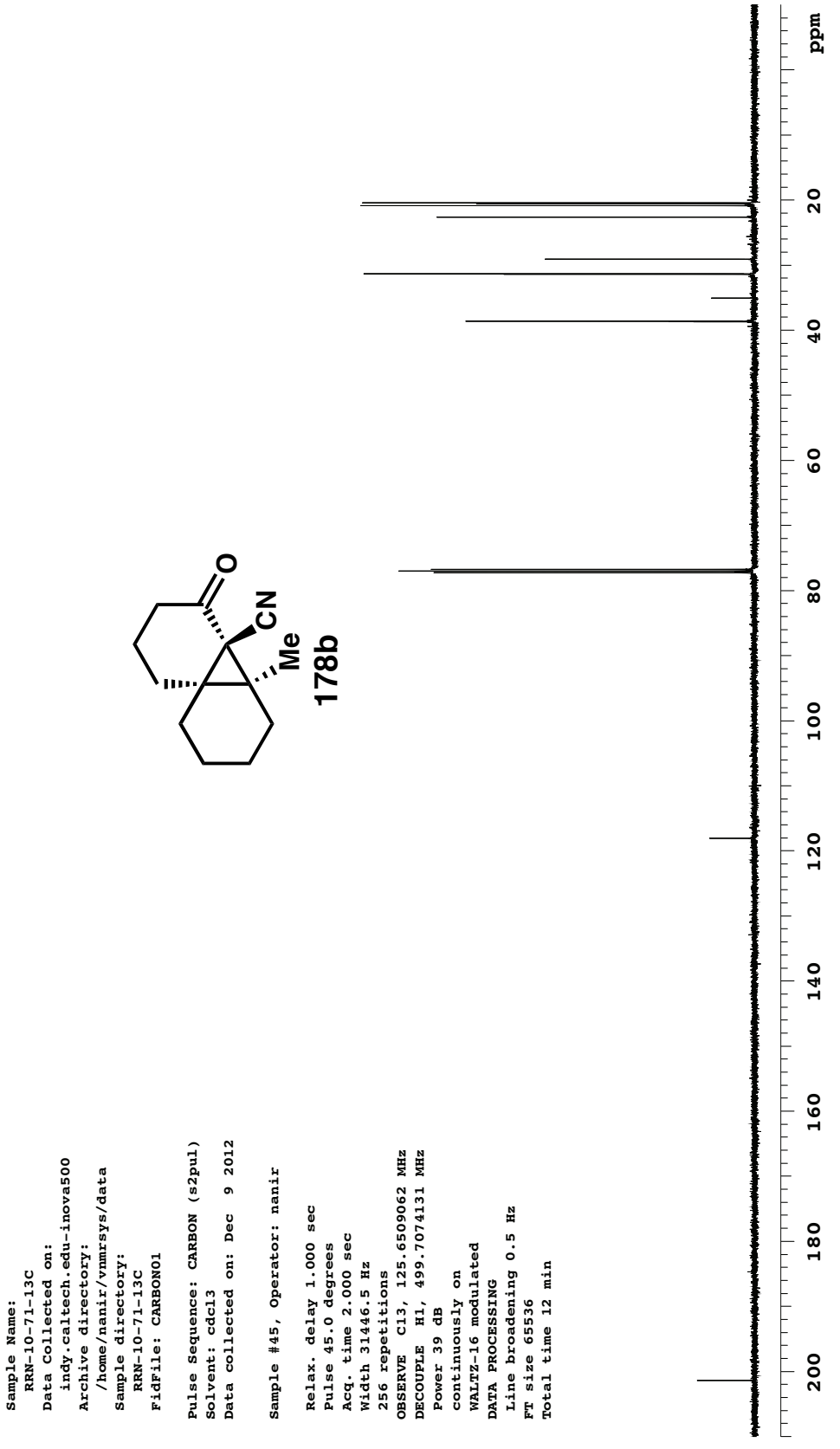

Agilent Technologies
NCH2Bn
O
CN
H
173i
Sample Name:
RRN-7-57-V-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-57-V-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 14 2012
Sample #39, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7225125 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
2.02
2.85
1.99
1.00
1.00
2.01
1.07
1.04
3.20
1.05
1.04
ppm
Plotname: --Not assigned--

Agilent Technologies
Sample Name:
RRN-7-57-V-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-57-V-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 14 2012
Sample #39, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6553310 MHz
DECOUPLE H1, 499.7250019 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 34 min
NCH2Bn
O
CN
H
173i
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

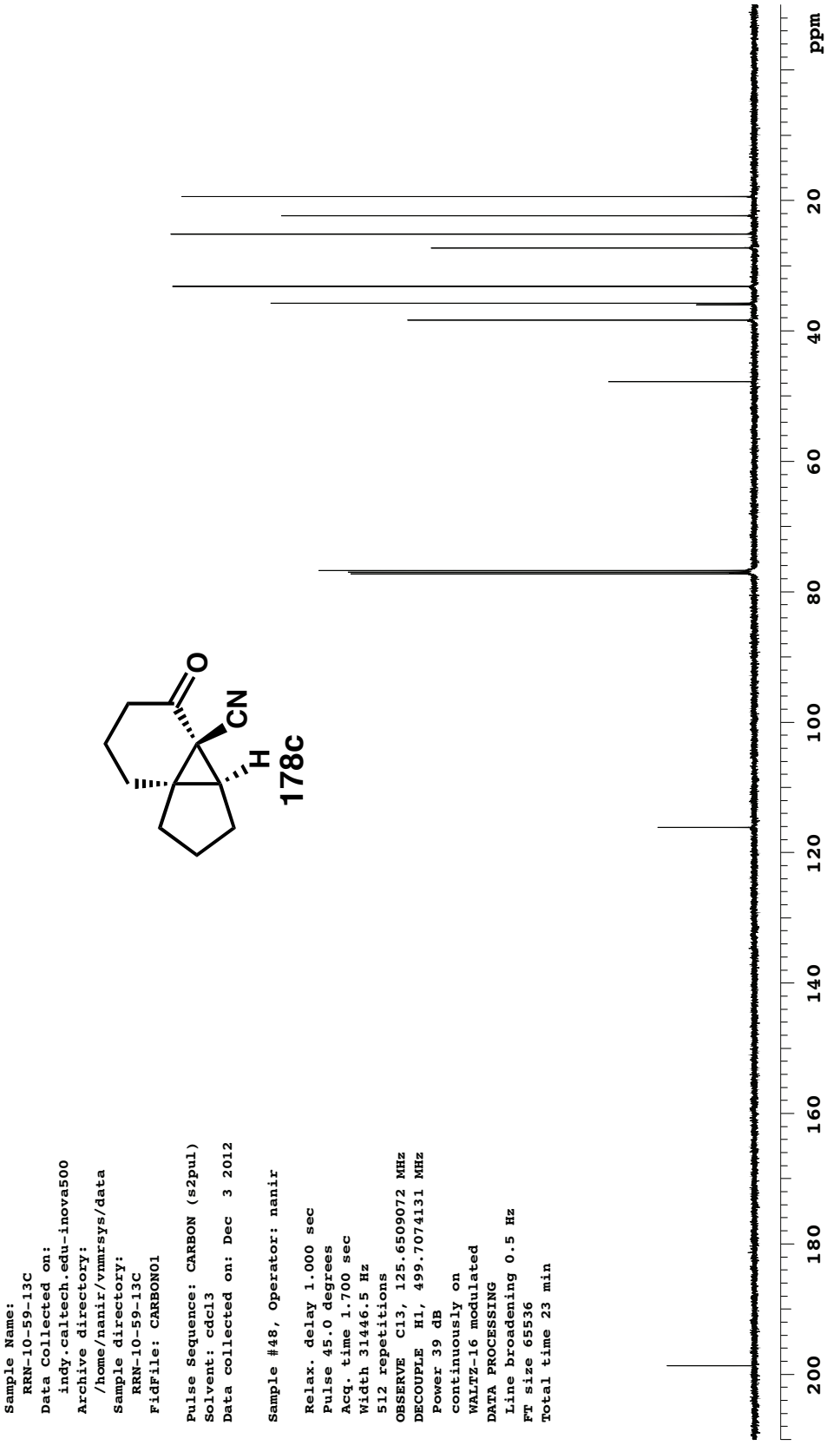

Sample Name:
RRN-7-107-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-107-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 6 2012
Sample #44, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
O
CN
H
178a
ppm
0.99
0.96
4.09
3.05
1.06
3.13
2.01

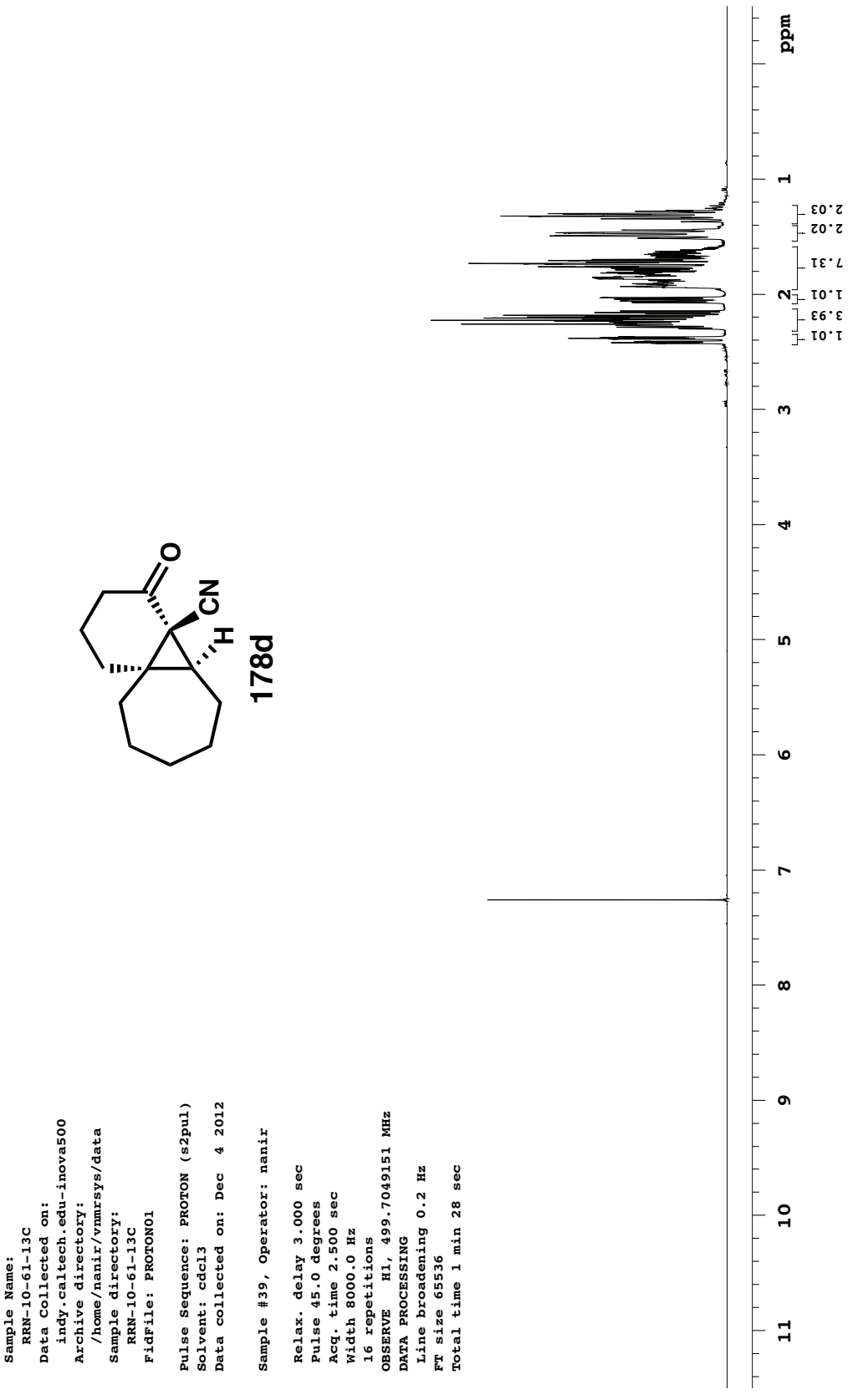

Sample Name:
RRN-7-107-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-7-107-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 6 2012
Sample #43, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6528844 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 12 min
O
CN
H
178a
200
180
160
140
120
100
80
60
40
20
ppm

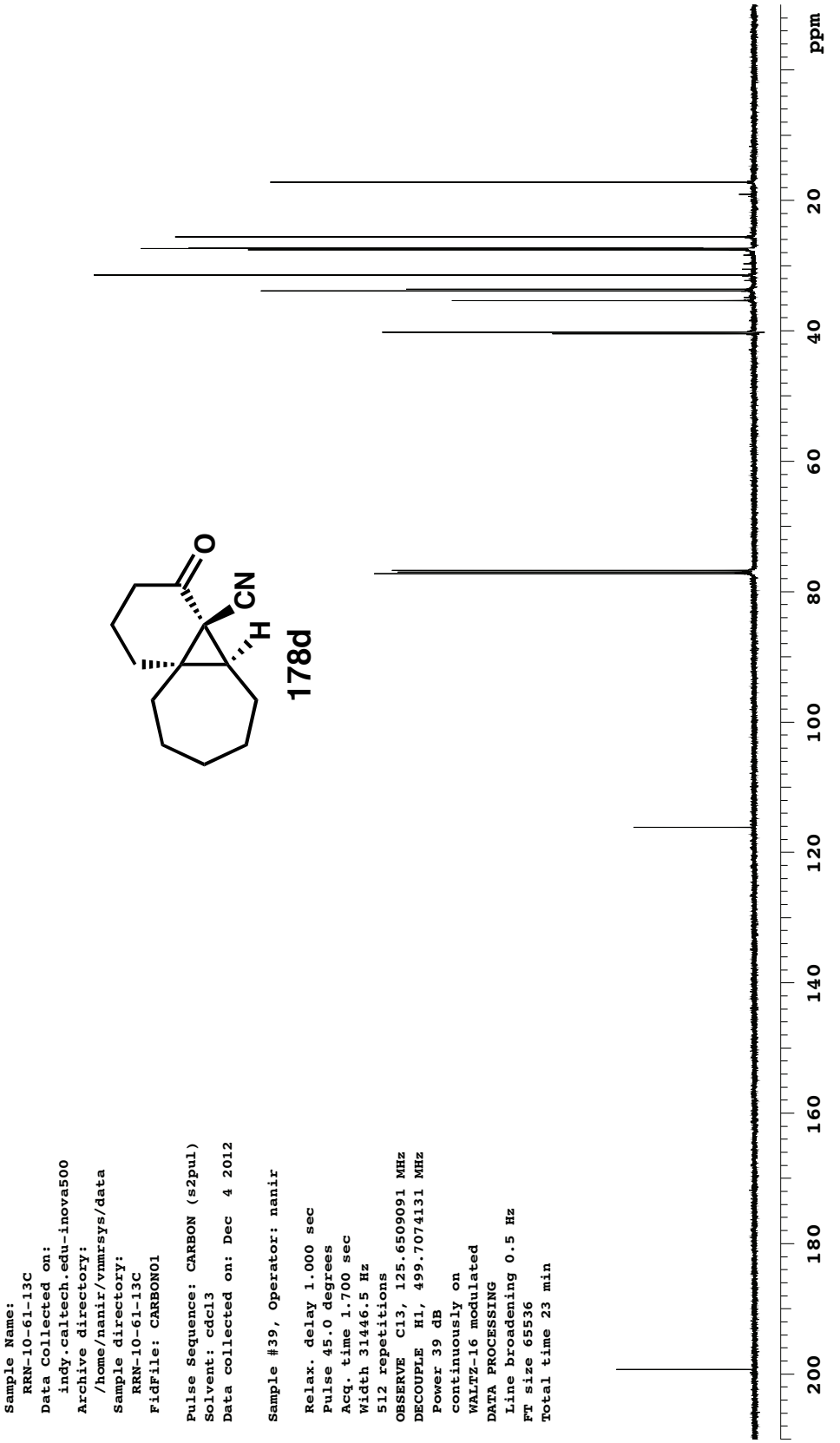

Sample Name:
RRN-10-71-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-71-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 9 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec
O
CN
Me
178b
ppm
1.01
1.03
2.07
6.23
2.40
2.08
3.01

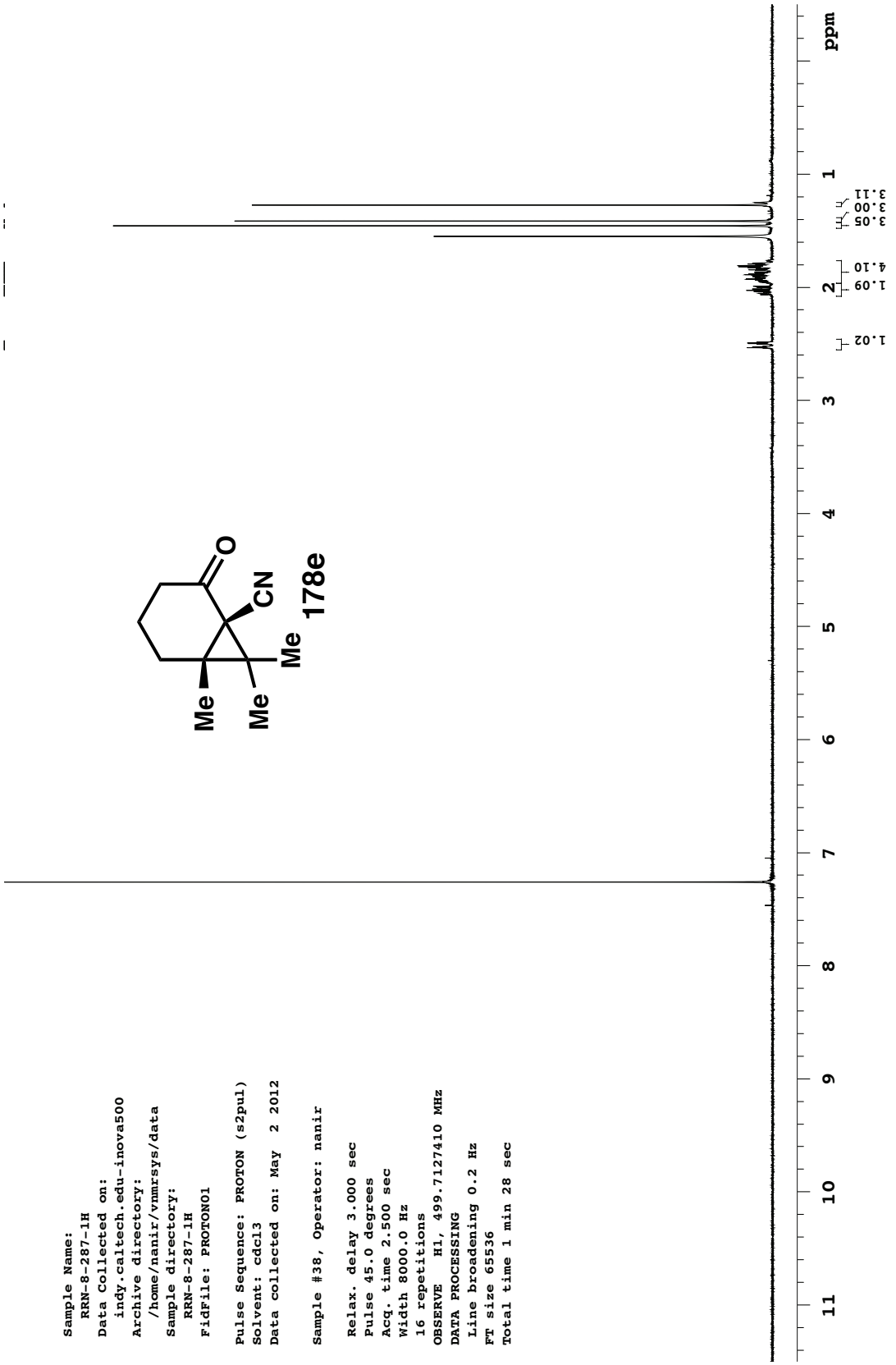

Sample Name:
RRN-10-71-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-71-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 9 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
256 repetitions
OBSERVE C13, 125.6509062 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 12 min
O
CN
Me
178b
200
180
160
140
120
100
80
60
40
20
ppm

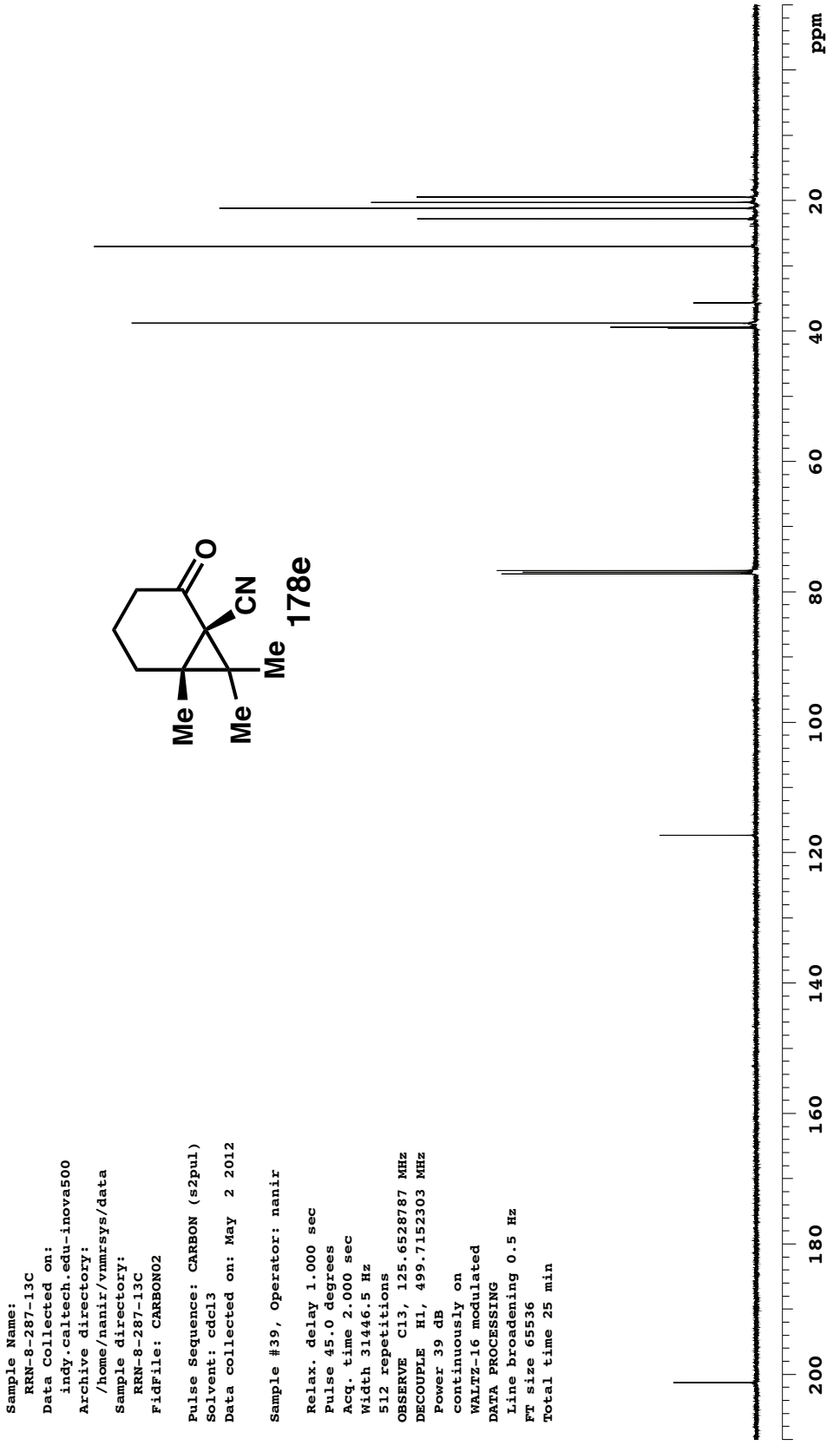
Sample Name:
RRN-10-59-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-59-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 3 2012
Sample #48, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
O
CN
H
178c
2.00
3.09
4.15
3.10
1.33
11
10
9
8
7
6
5
4
3
2
1
ppm

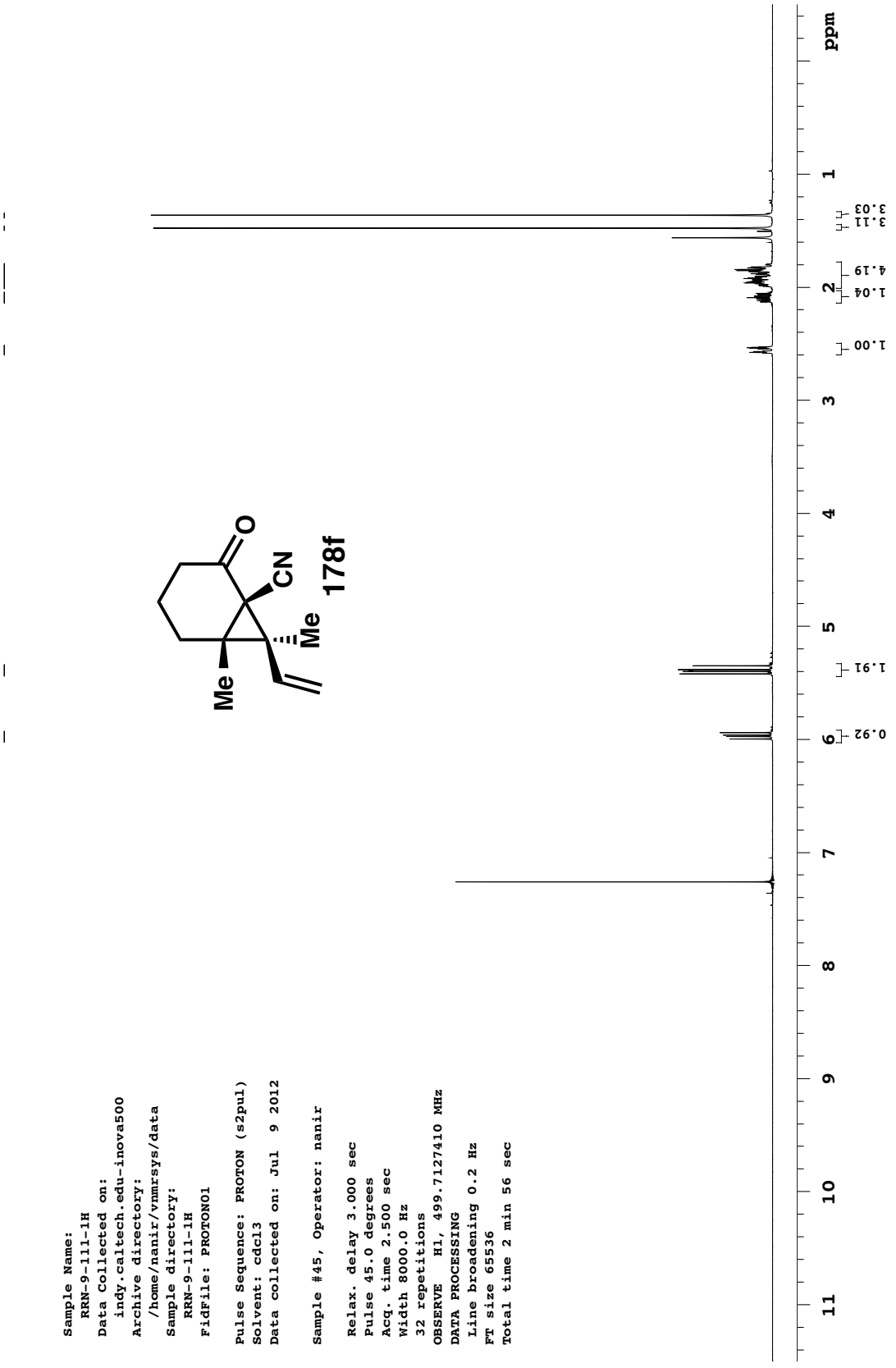

Sample Name:
RRN-10-59-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-59-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 3 2012
Sample #48, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.700 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6509072 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 23 min
O
CN
H
178c
200
180
160
140
120
100
80
60
40
20
ppm

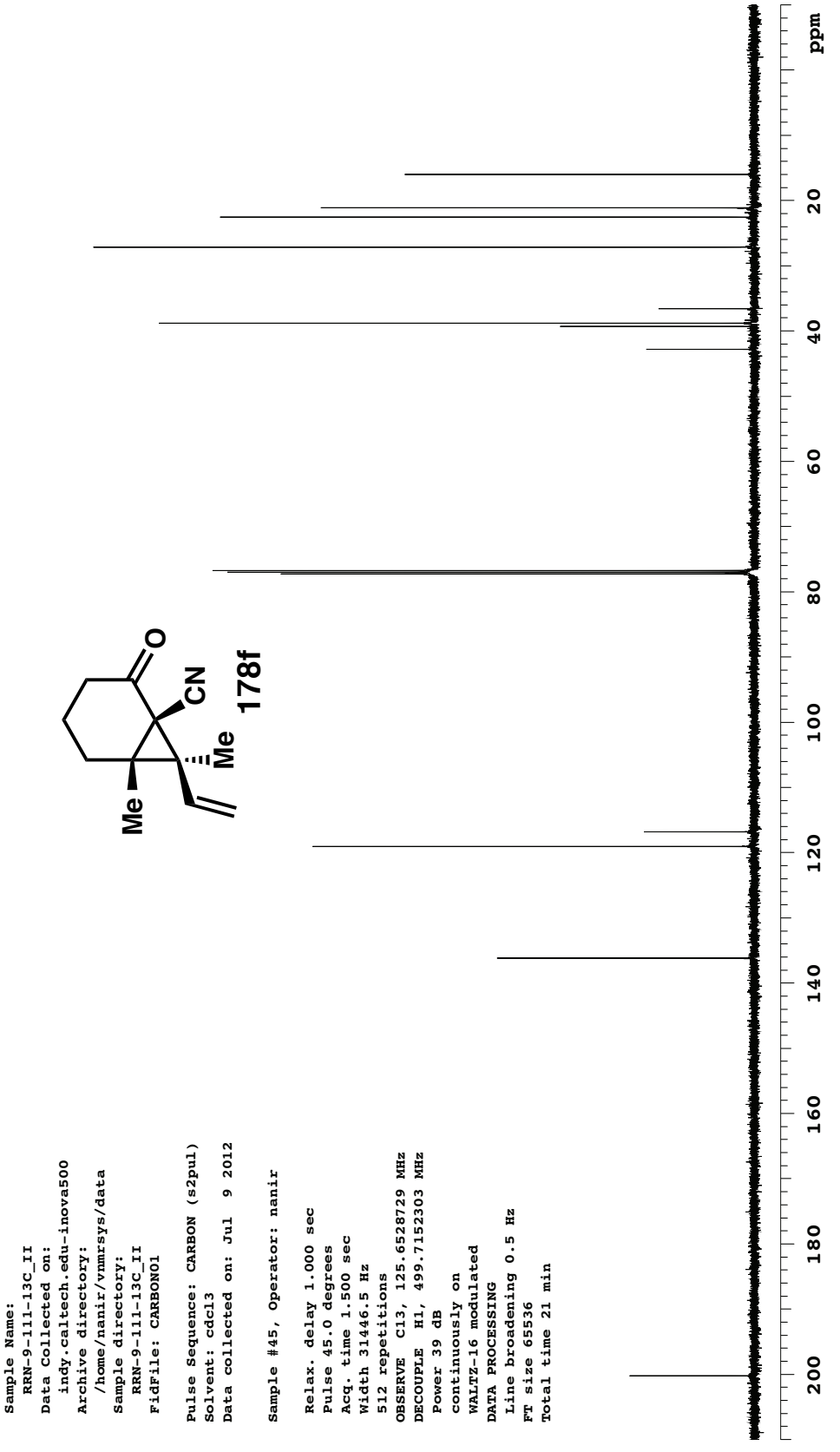

Sample Name:
RRN-10-61-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-61-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 4 2012
Sample #39, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
O
CN
H
178d
1.01
3.93
1.01
7.31
2.02
2.03
11
10
9
8
7
6
5
4
3
2
1
ppm

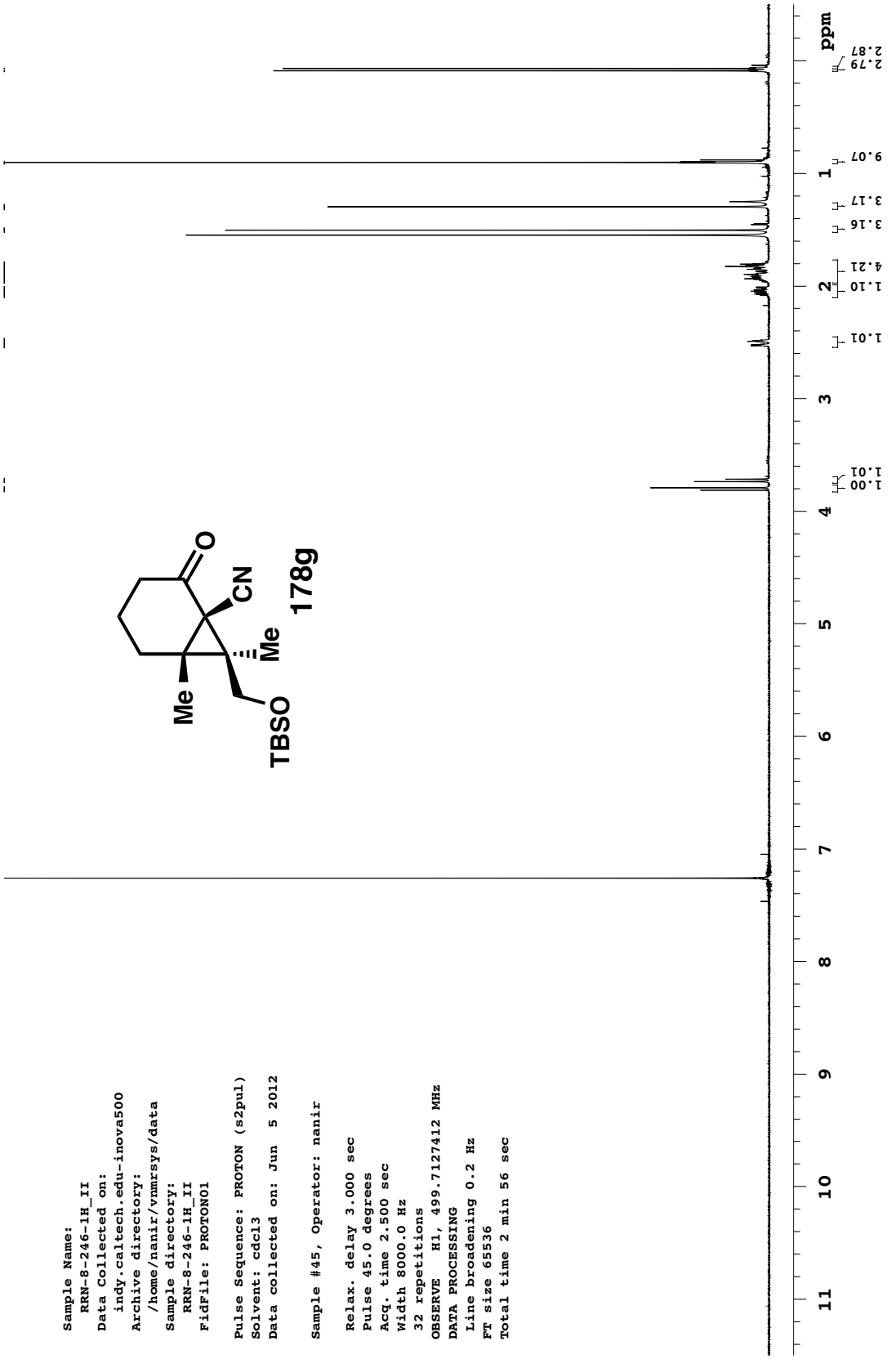

Sample Name:
RRN-10-61-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-61-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 4 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.700 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6509091 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 23 min
O
CN
H
178d
200
180
160
140
120
100
80
60
40
20
ppm

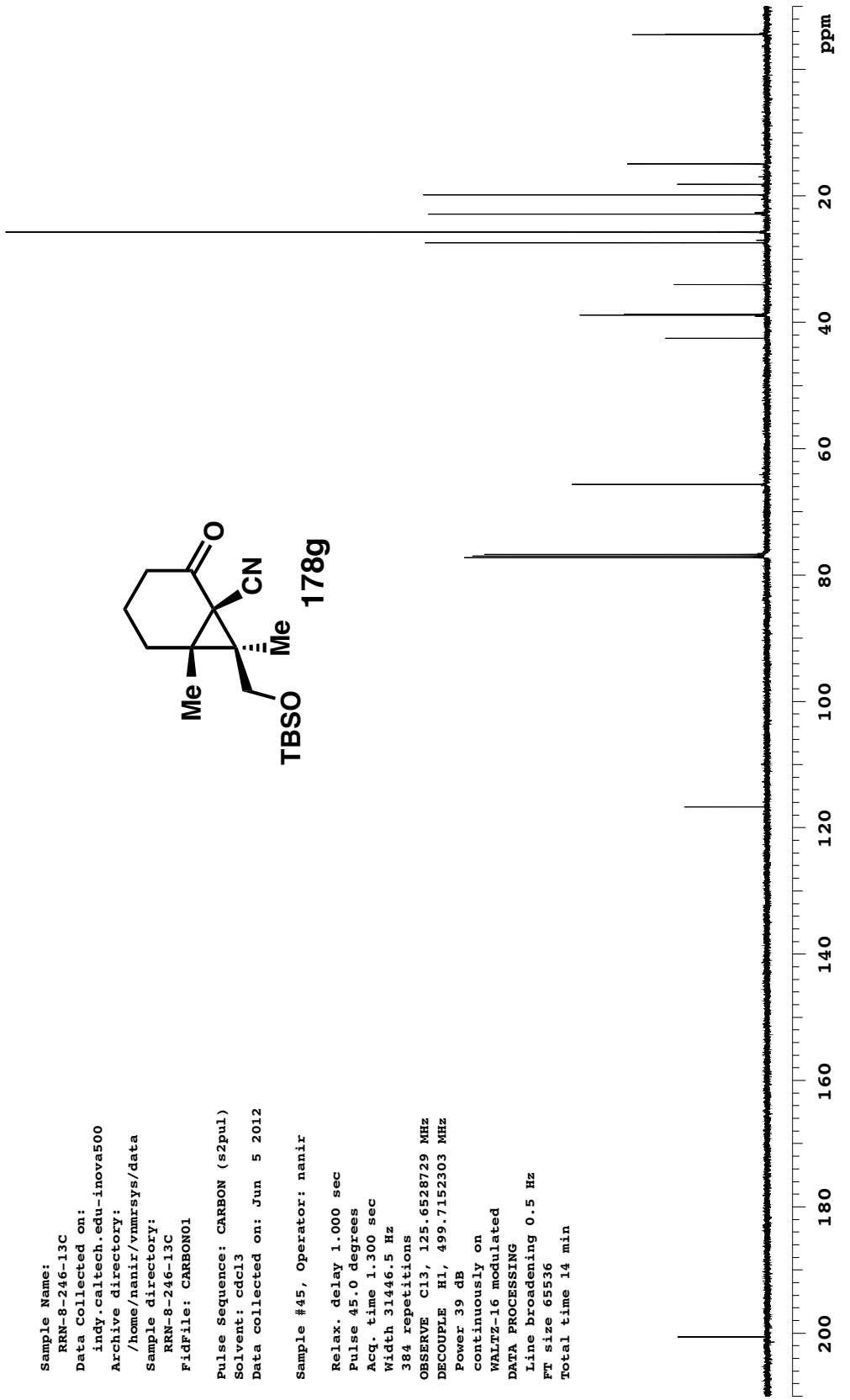

Sample Name:
RRN-8-287-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-287-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 2 2012
Sample #38, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
O
CN
Me
Me
Me
178e
1.02
1.09
4.10
3.05
3.00
3.11
ppm

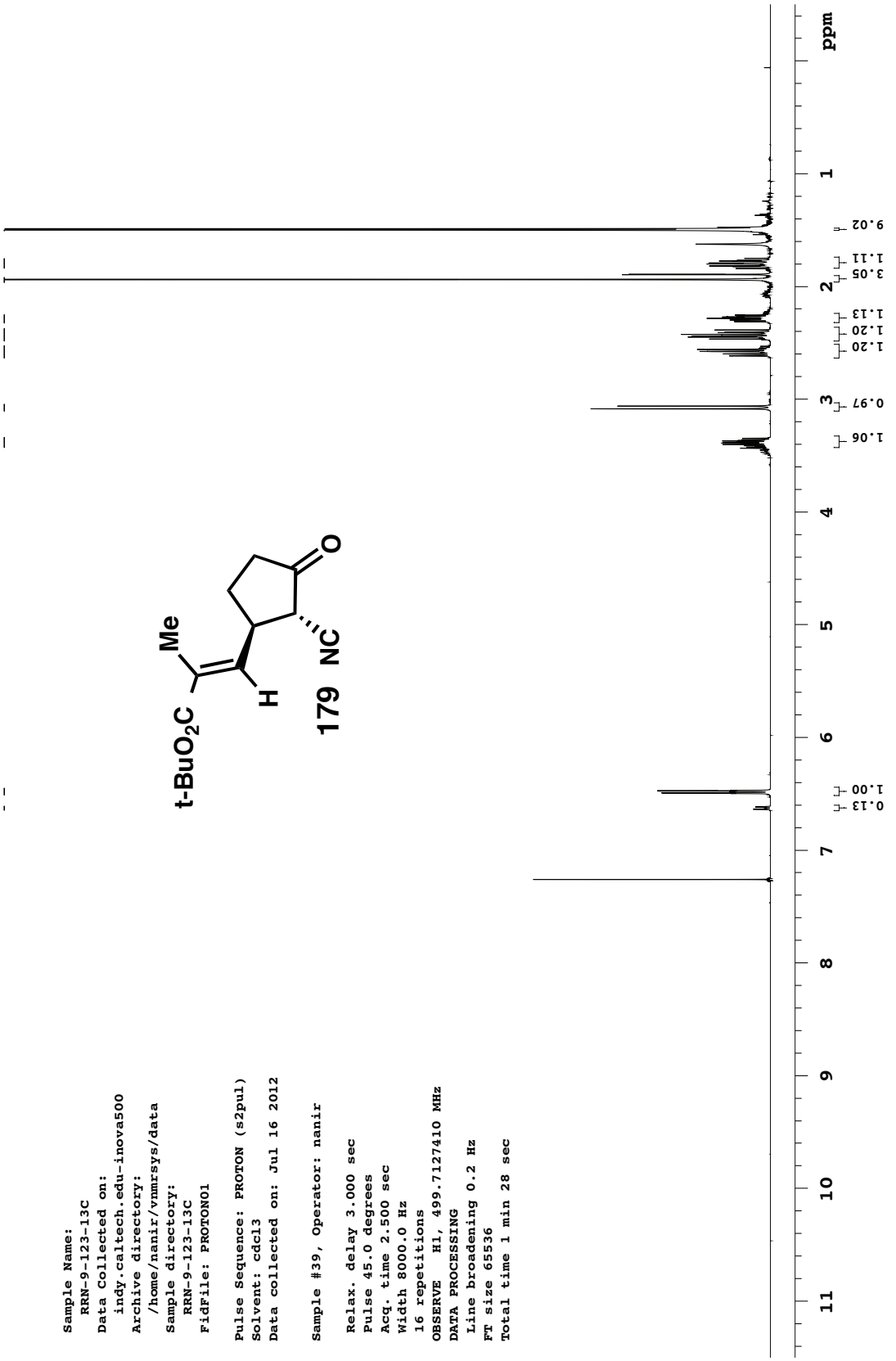

Sample Name:
RRN-8-287-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-287-13C
FidFile: CARBON02
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 2 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528787 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 25 min
O
CN
Me
Me
Me
178e
200
180
160
140
120
100
80
60
40
20
ppm

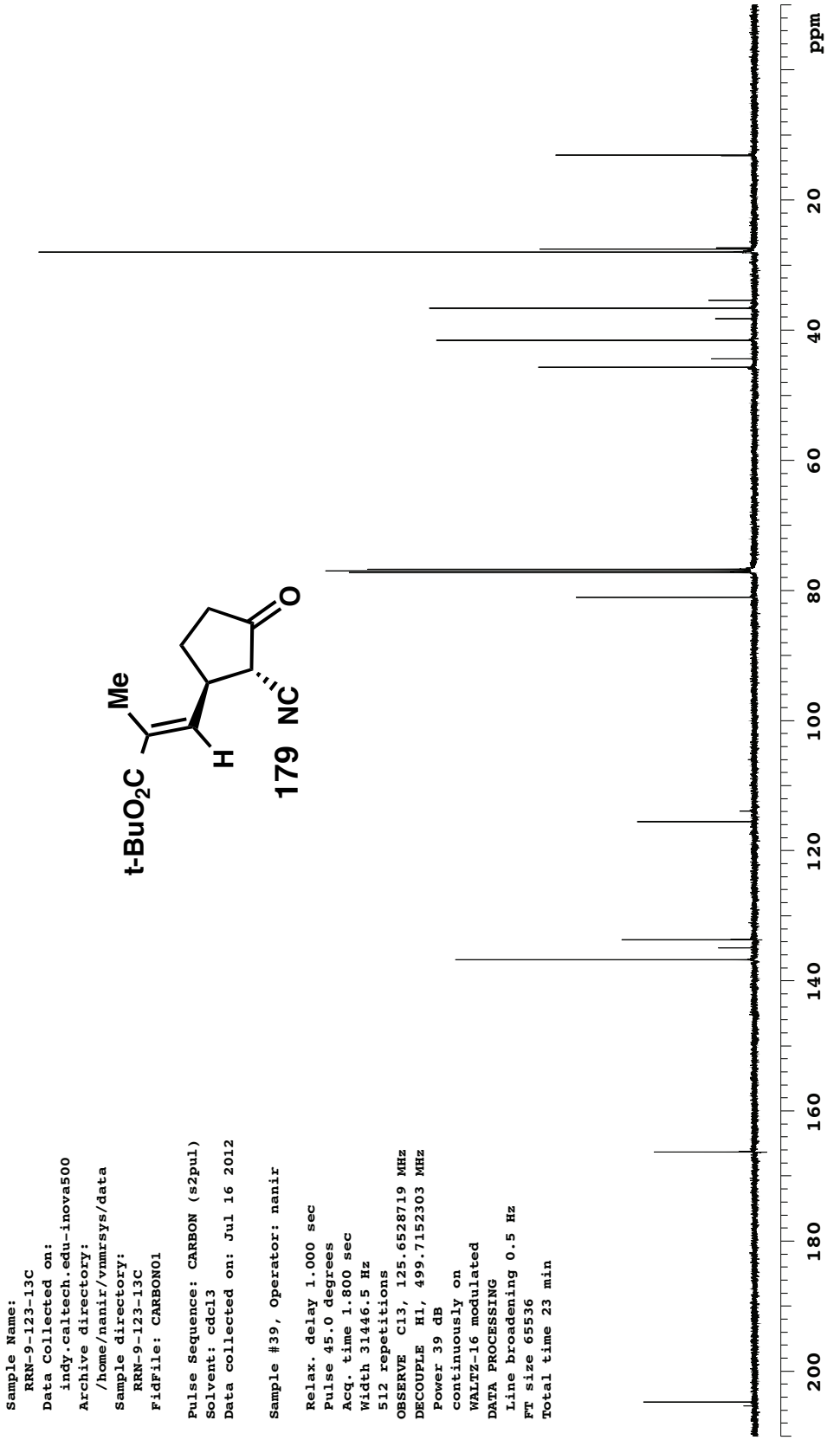

Sample Name:
RRN-9-111-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-111-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 9 2012
Sample #45, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
O
CN
Me
Me
178f
ppm
1.00
1.04
4.19
3.11
3.03
1.91
0.92


Sample Name:
RRN-9-111-13C_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-111-13C_II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 9 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528729 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 21 min
O
CN
Me
Me
178f
200
180
160
140
120
100
80
60
40
20
ppm


Sample Name:
RRN-8-246-1H_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-246-1H_II
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2012
Sample #45, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7127412 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 56 sec
O
CN
Me
Me
TBSO
178g
ppm
2.79
2.87
9.07
3.17
3.16
1.10
4.21
1.01
1.00
1.01


Sample Name:
RRN-8-246-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-8-246-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 5 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31446.5 Hz
384 repetitions
OBSERVE C13, 125.6528729 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 14 min
O
CN
Me
Me
TBSO
178g
200
180
160
140
120
100
80
60
40
20
ppm


Sample Name:
RRN-9-123-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-123-13C
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 16 2012
Sample #39, Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127410 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec
t-BuO2C
Me
H
NC
O
179
ppm
0.13
1.00
1.06
0.97
1.20
1.20
1.13
3.05
1.11
9.02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Archive directory:
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Sample directory:
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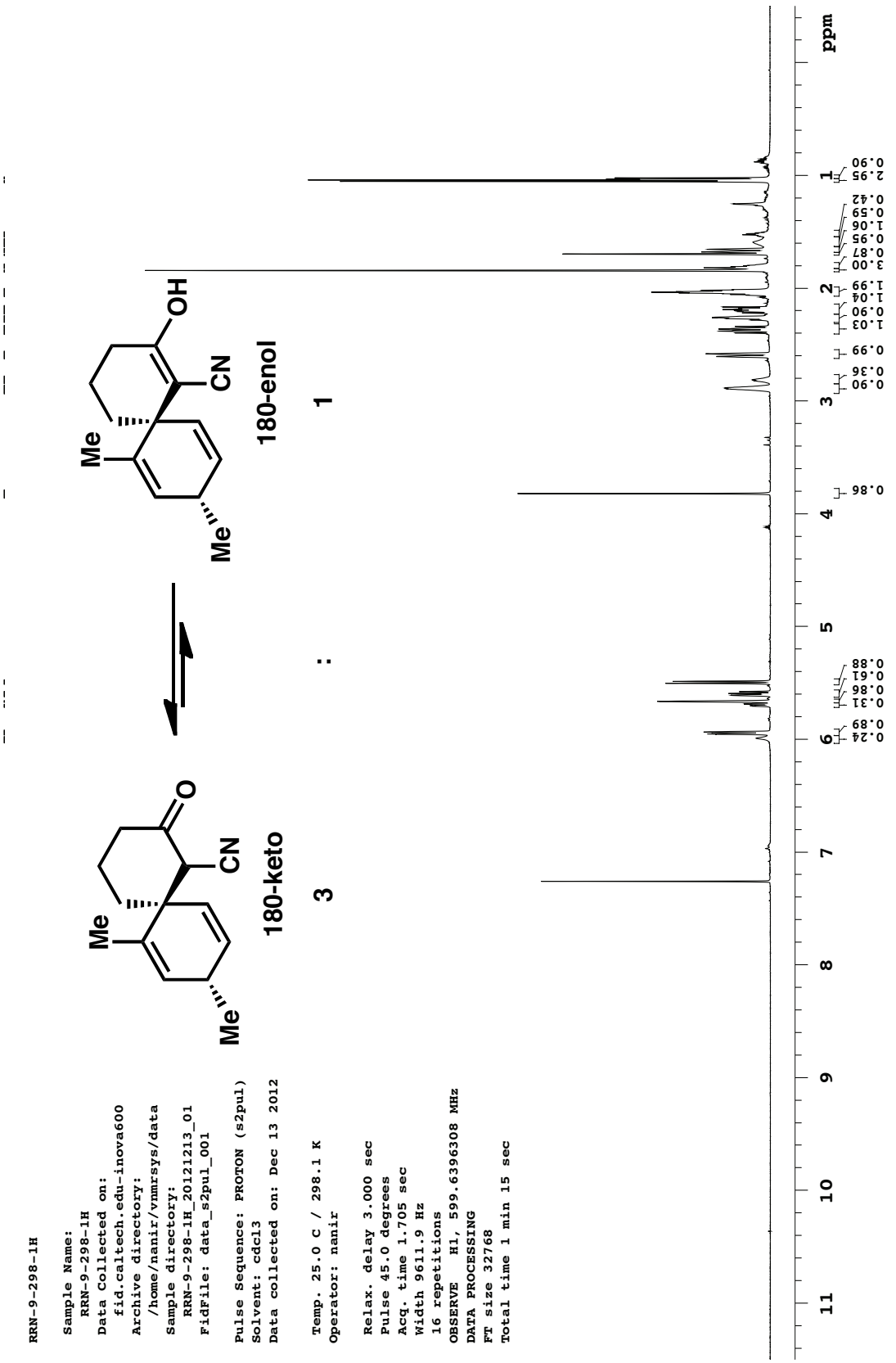
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 16 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528719 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 23 min
t-BuO2C
Me
H
NC
O
179
200
180
160
140
120
100
80
60
40
20
ppm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Archive directory:
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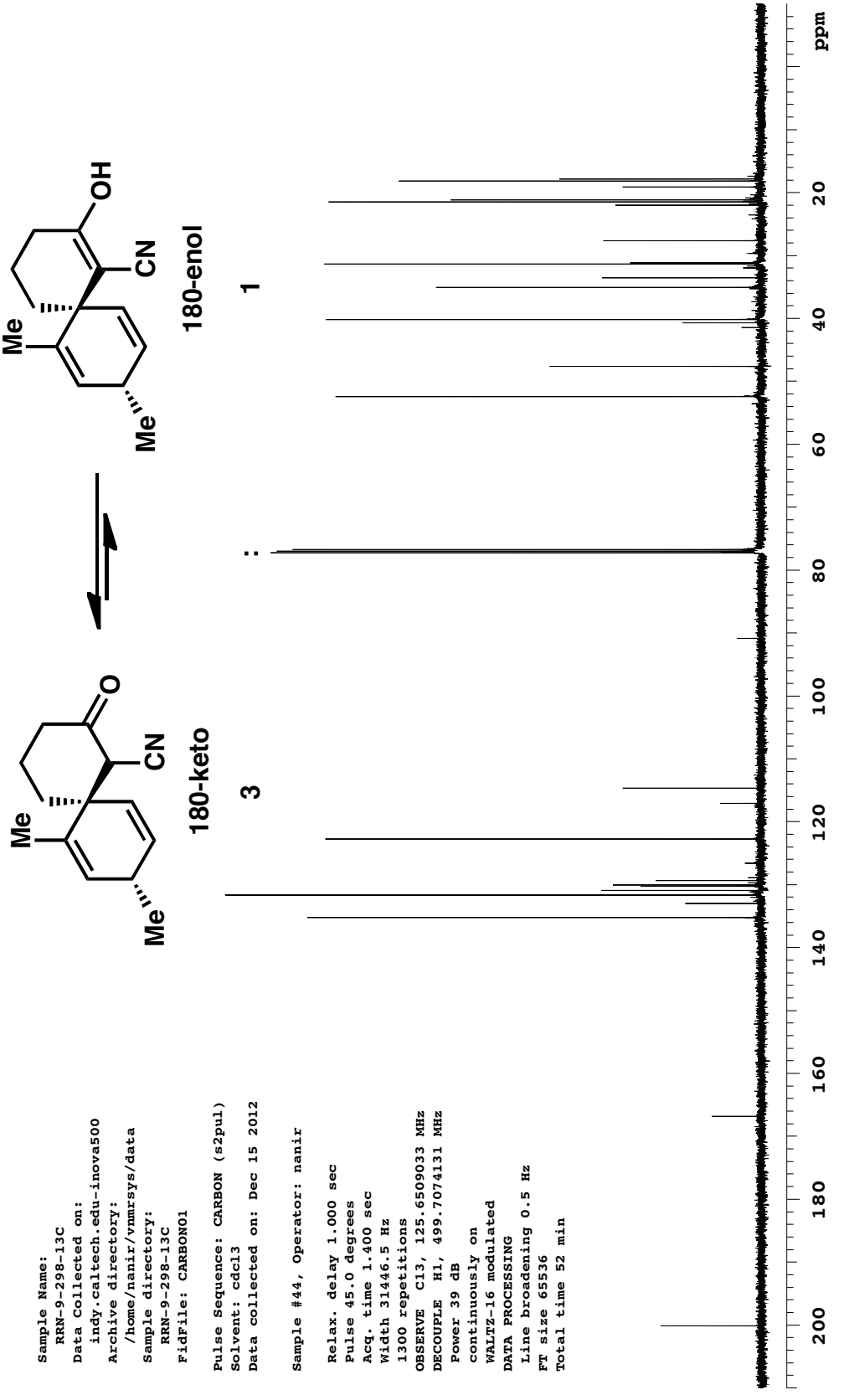
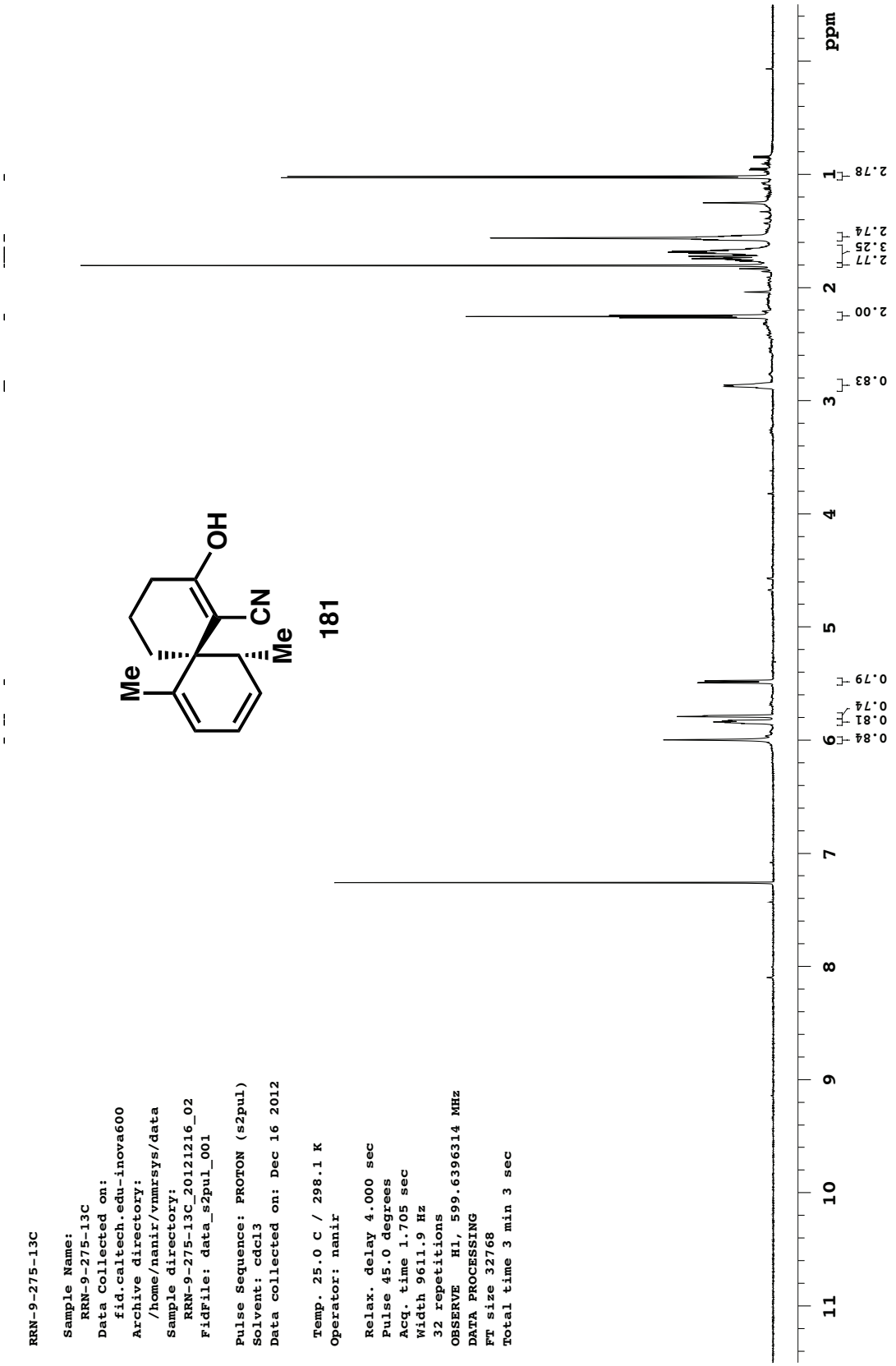
Sample directory:
RRN-9-298-1H_20121213_01
FidFile: data_s2pul_001
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 13 2012
Temp. 25.0 C / 298.1 K
Operator: nanir
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.705 sec
Width 9611.9 Hz
16 repetitions
OBSERVE H1, 599.6396308 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 15 sec
Me
Me
O
CN
180-keto
3
:
1
Me
Me
OH
CN
180-enol
ppm
11
10
9
8
7
6
5
4
3
2
1
0.24
0.89
0.31
0.86
0.61
0.88
0.86
0.90
0.36
0.99
1.03
0.90
1.04
1.99
3.00
0.87
0.95
1.06
0.59
0.42
2.95
0.90


Me
Me
O
CN
180-keto
3
:
Me
Me
OH
CN
180-enol
1
Sample Name:
RRN-9-298-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-298-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 15 2012
Sample #44, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.400 sec
Width 31446.5 Hz
1300 repetitions
OBSERVE C13, 125.6509033 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 52 min
200
180
160
140
120
100
80
60
40
20
ppm


RRN-9-275-13C
Sample Name:
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Data Collected on:
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Archive directory:
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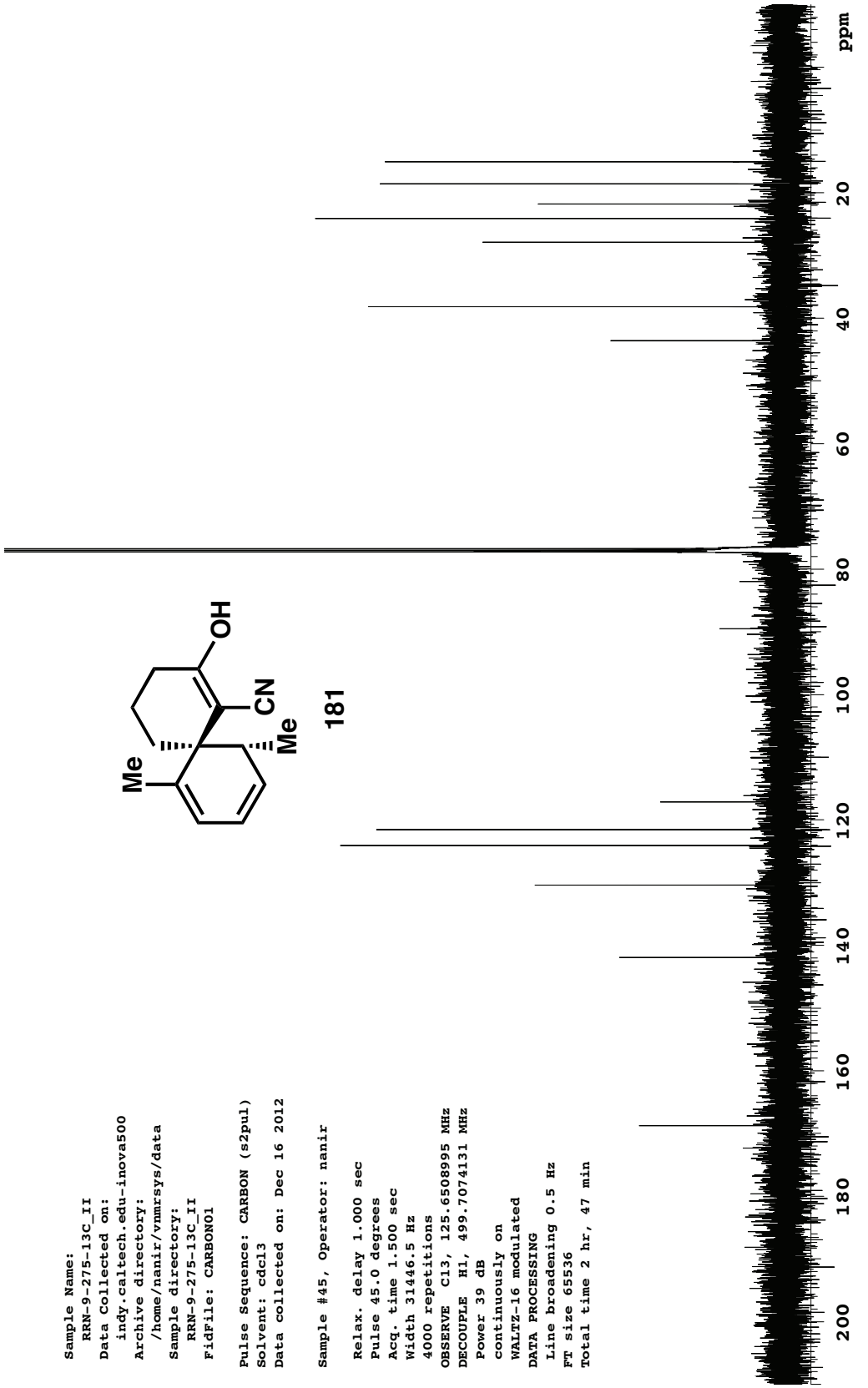
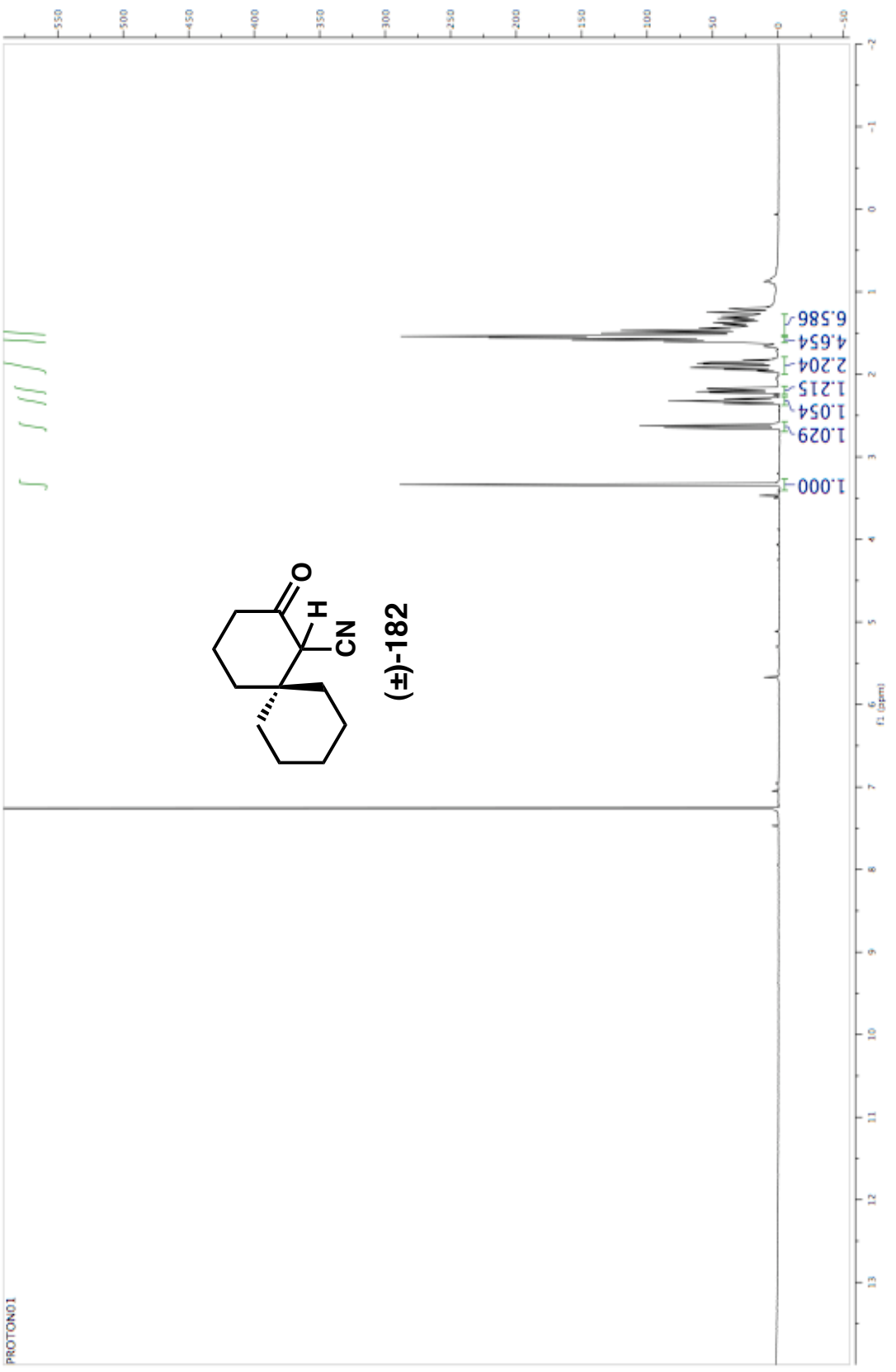
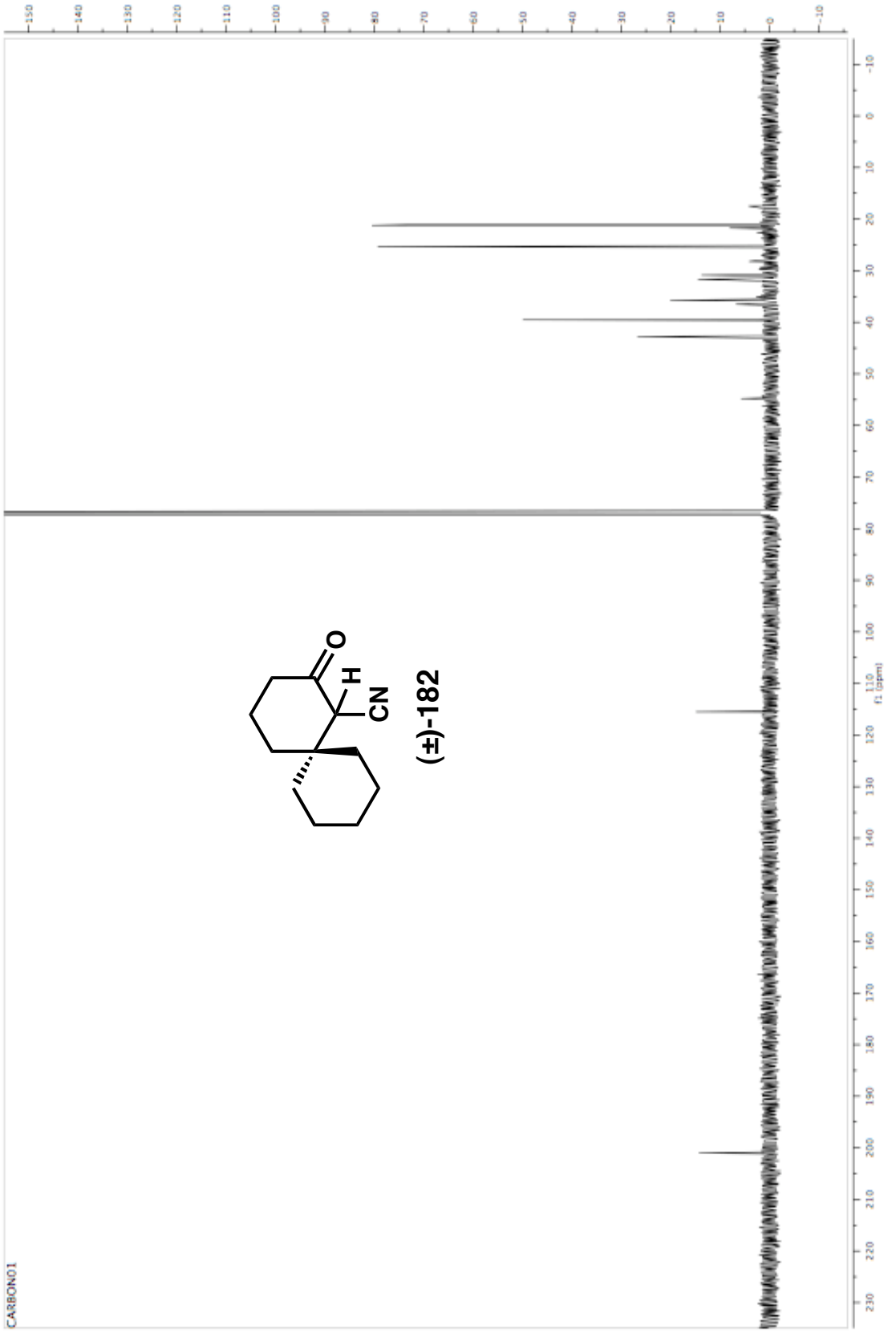
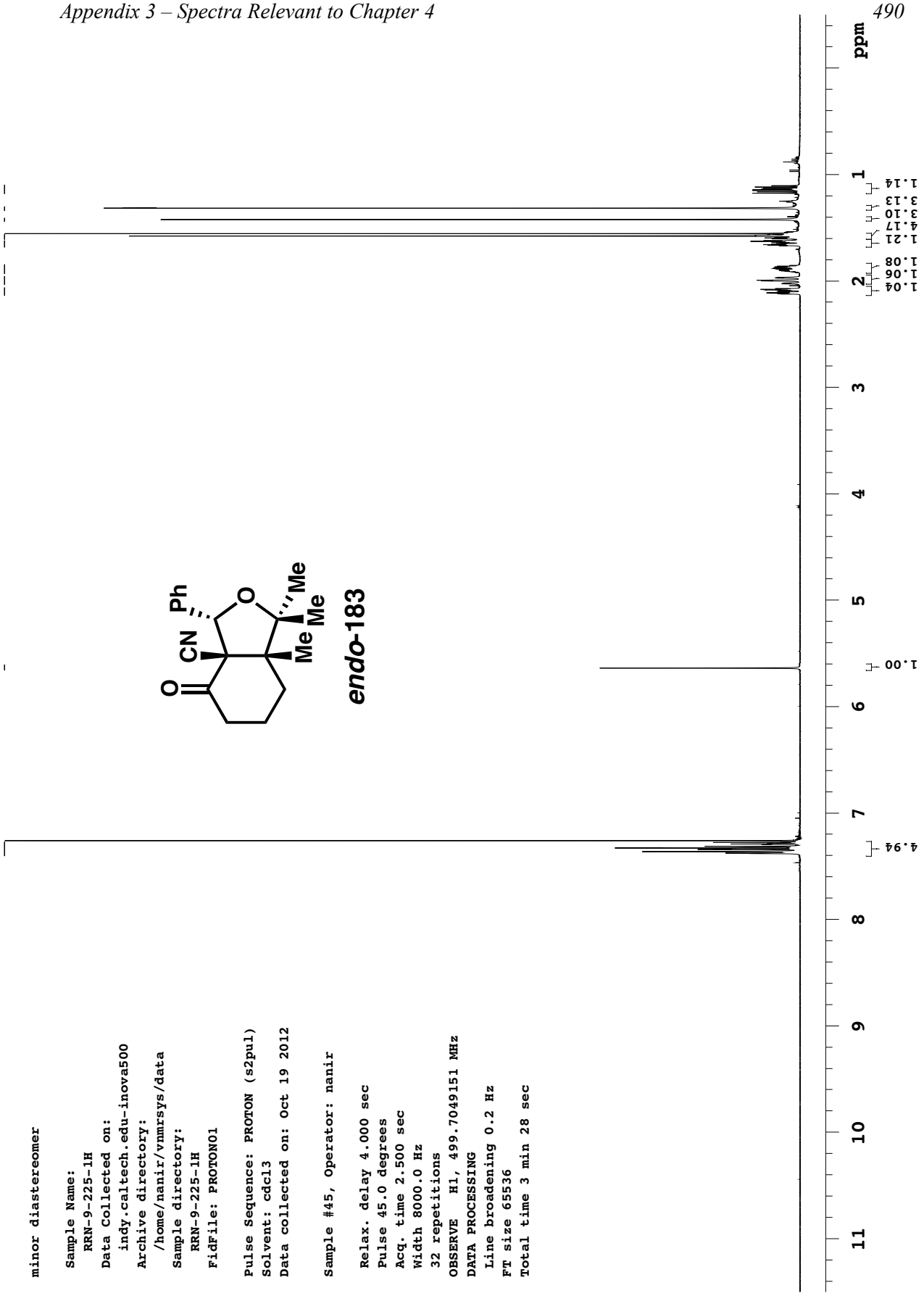
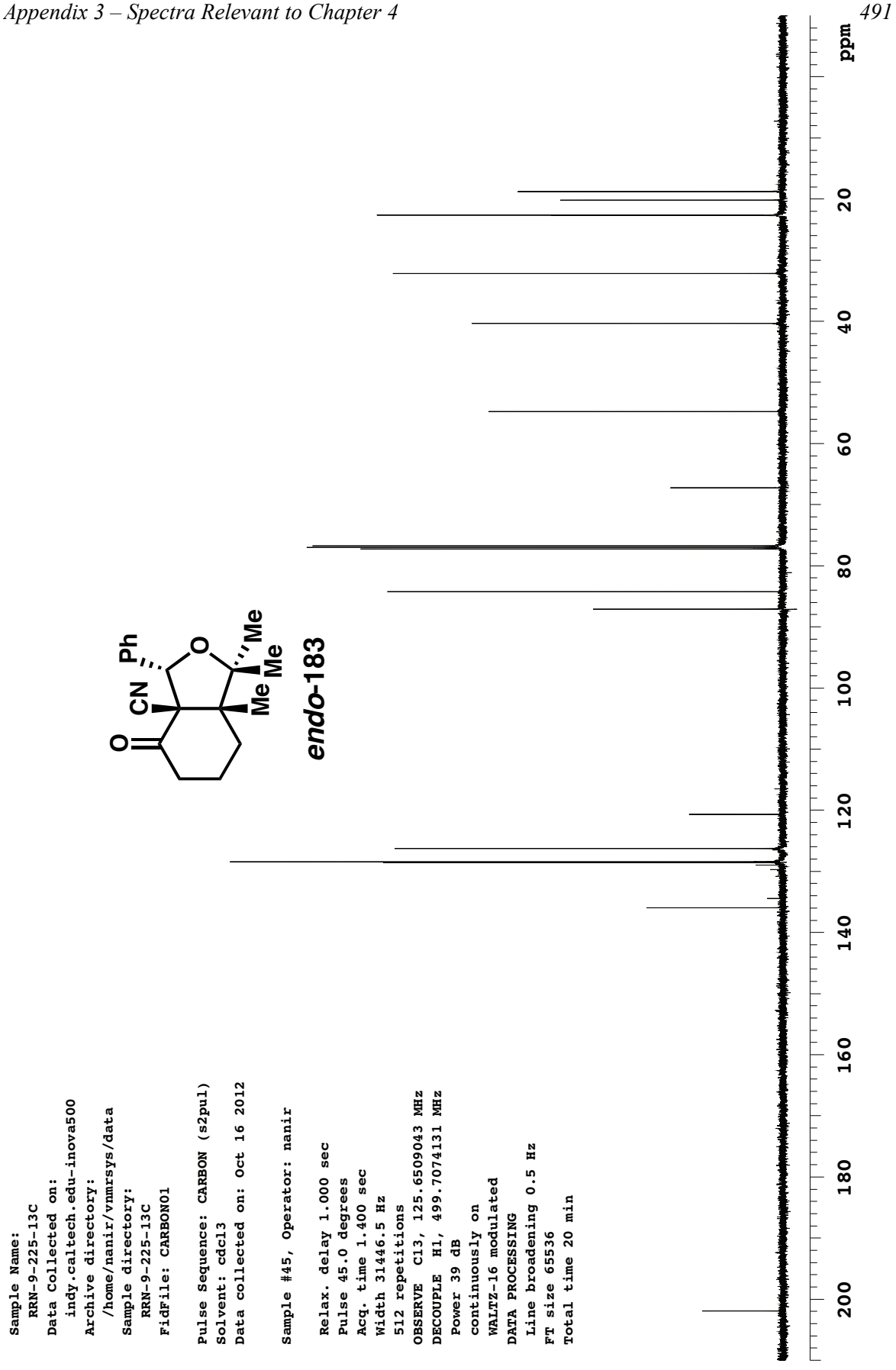
Sample directory:
RRN-9-275-13C_20121216_02
FidFile: data_s2pul_001
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 16 2012
Temp. 25.0 C / 298.1 K
Operator: nanir
Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 1.705 sec
Width 9611.9 Hz
32 repetitions
OBSERVE H1, 599.6396314 MHz
DATA PROCESSING
FT size 32768
Total time 3 min 3 sec
OH
CN
Me
Me
181
2.78
2.77
3.25
2.74
2.00
0.83
0.79
0.84
0.81
0.74
ppm


Sample Name:
RRN-9-275-13C_II
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-275-13C_II
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 16 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
4000 repetitions
OBSERVE C13, 125.6508995 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 47 min
OH
CN
Me
Me
181
200
180
160
140
120
100
80
60
40
20
ppm


(±)-182
O
H
CN
6.586
4.654
2.204
1.215
1.054
1.029
1.000
PROTON01
f1 (ppm)


O
H
CN
(±)-182
CARBON01
f1 (ppm)


minor diastereomer
Sample Name:
RRN-9-225-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-225-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 19 2012
Sample #45, Operator: nanir
Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 28 sec
Ph
CN
O
O
Me
Me
Me
endo-183
ppm
1.00
4.94
1.04
1.06
1.08
1.21
4.17
3.10
3.13
1.14

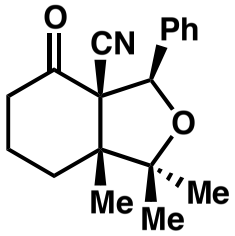

Sample Name:
RRN-9-225-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-225-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 16 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.400 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6509043 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 20 min
O
CN
Ph
O
Me
Me
Me
endo-183
200
180
160
140
120
100
80
60
40
20
ppm

Sample Name:
RRN-9-163-ppt
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-163-ppt
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2012

Sample #44, Operator: nanir

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127430 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 56 sec



***exo*-183**

Sample Name:
RRN-9-163-13C
Data Collected on:
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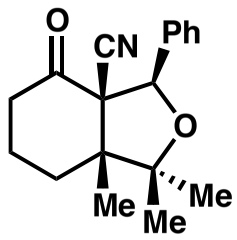
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-9-163-13C
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 2 2012

Sample #45, Operator: nanir

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.500 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6528758 MHz
DECOUPLE H1, 499.7152303 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 21 min



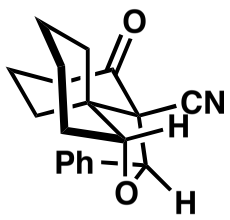
***exo*-183**

Sample Name:
RRN-10-73-2_endo
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-73-2_endo
FidFile: PROTON01

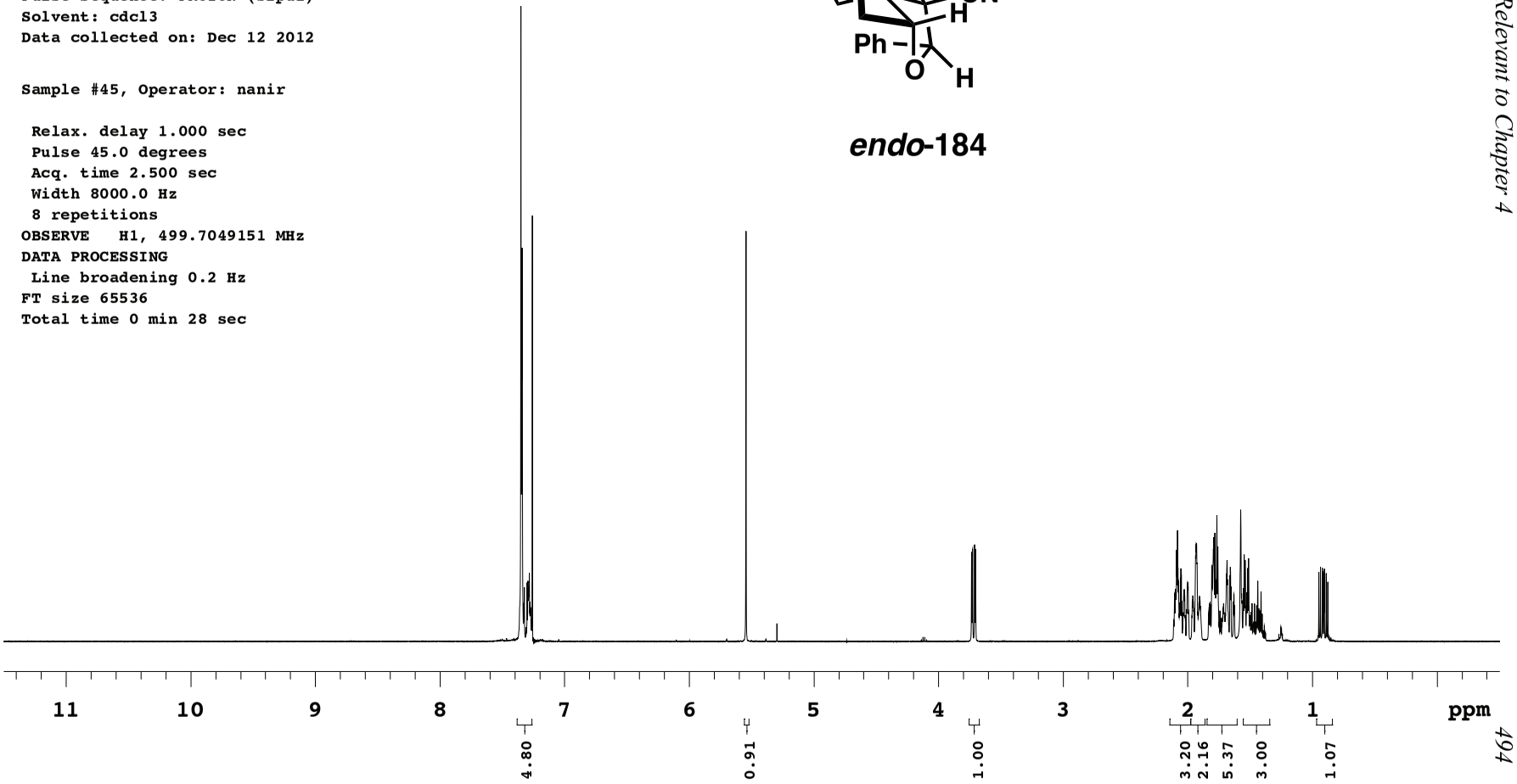
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 12 2012

Sample #45, Operator: nanir

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 28 sec



***endo*-184**

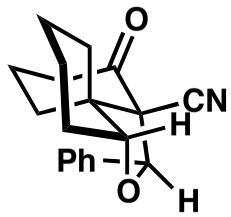


Sample Name:
RRN-10-73-2-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-73-2-13C
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 11 2012

Sample #44, Operator: nanir

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31446.5 Hz
800 repetitions
OBSERVE C13, 125.6509024 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 30 min



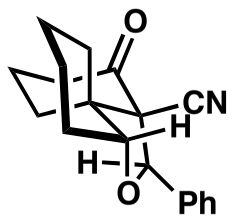
***endo*-184**

Sample Name:
RRN-10-73-3_13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
RRN-10-73-3_13C
FidFile: PROTON01

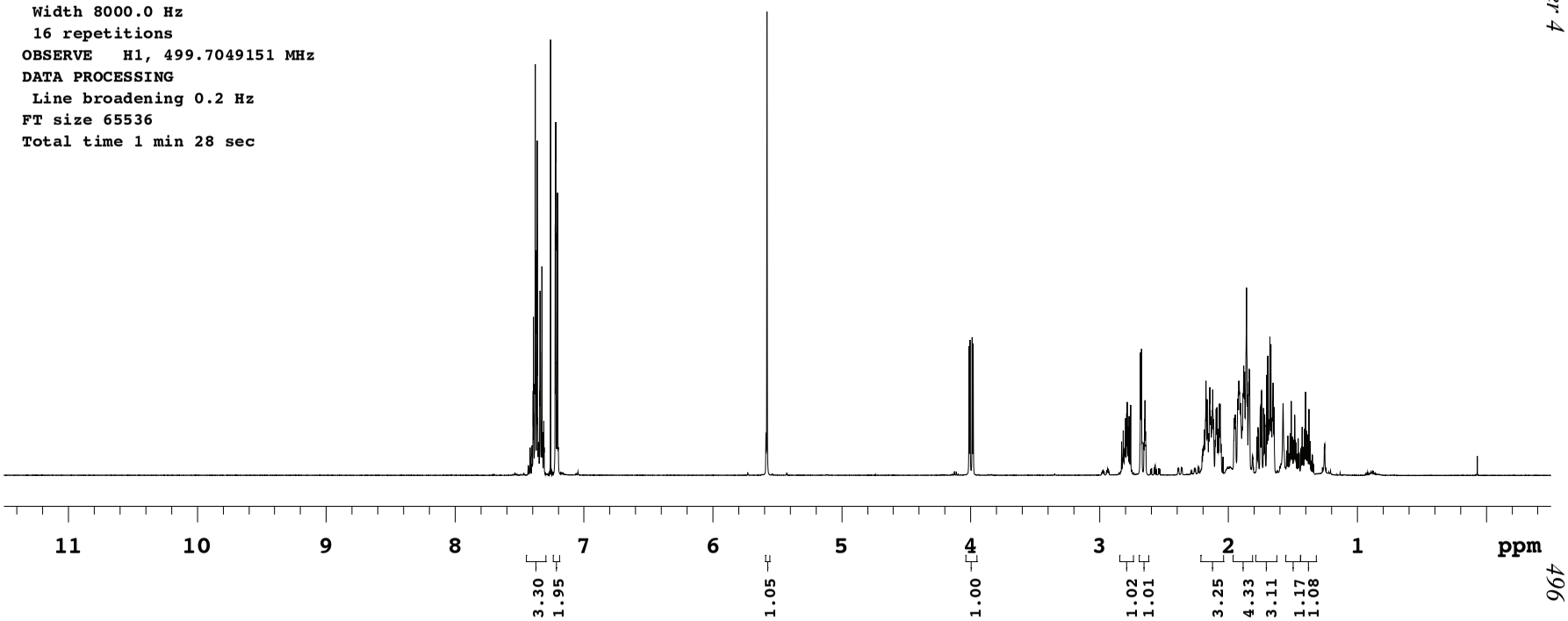
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 16 2012

Sample #45, Operator: nanir

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7049151 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 28 sec



***exo*-184**



Sample Name:
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Data Collected on:
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Archive directory:
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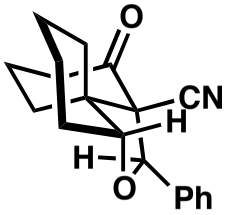
Sample directory:
RRN-10-73-3_13C
FidFile: CARBON01

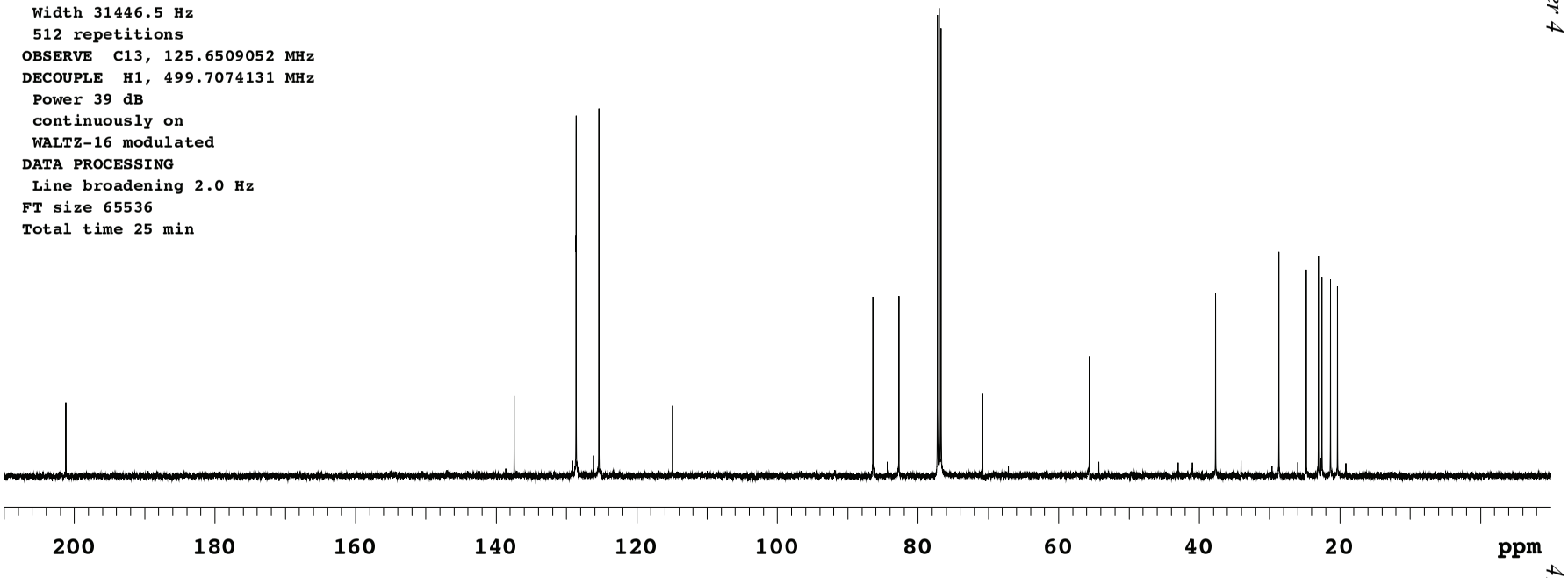
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Dec 16 2012

Sample #45, Operator: nanir

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.000 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6509052 MHz
DECOUPLE H1, 499.7074131 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 25 min



***exo*-184**



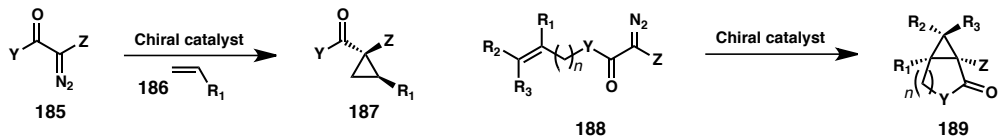
Appendix 4

Progress Toward an Asymmetric Intramolecular Buchner Reaction

A4.1 INTRODUCTION AND BACKGROUND

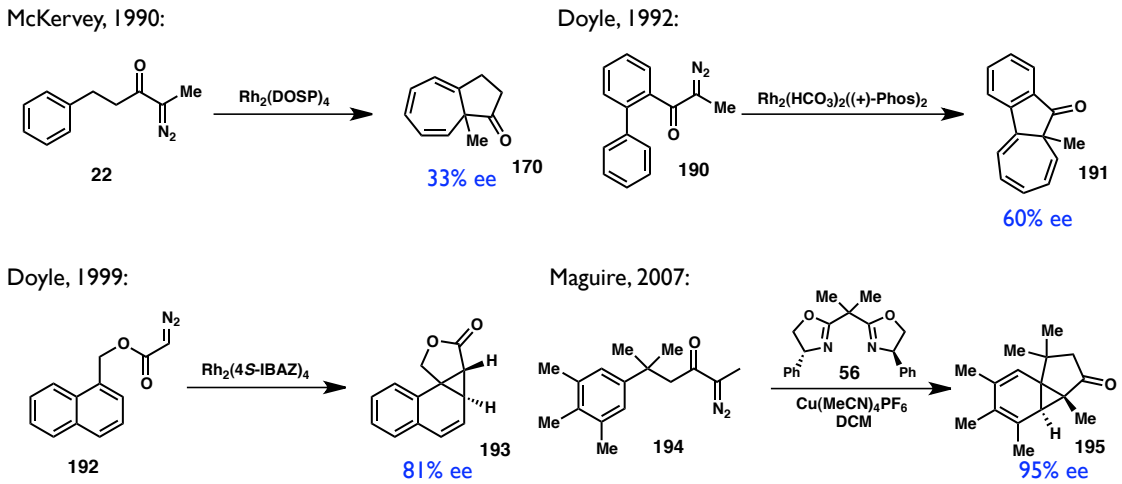
The enantioselective 2+1 cycloaddition between diazo compounds and alkenes comprises an attractive method for the preparation of optically active cyclopropanes.[1] Since the first report of the asymmetric cyclopropanation of styrene by Nozaki and coworkers in 1966,[2] this field has witnessed enormous growth, yielding a wide array of methods to access substituted enantioenriched cyclopropanes (Scheme A4.1).

Scheme A4.1. *Asymmetric inter- and intramolecular alkene cyclopropanation*



Despite the advances made in the area of asymmetric alkene cyclopropanation with diazo compounds, the development of an analogous enantioselective Buchner reaction has proved to be far more elusive. In 1990 McKervey and coworkers reported the first enantioselective intramolecular Buchner cyclization;[3] however, the ee's of the cycloheptatriene products were modest. In the intervening years, only a handful of additional examples have been reported in the past two decades (Scheme A4.2).[4] The introduction of a variety of new chiral dirhodium catalysts by Doyle improved enantioselectivity in asymmetric intramolecular arene cyclopropanation, albeit with very limited substrate scope. The most recent report of an enantioselective intramolecular Buchner reaction comes from the work of Maguire and coworkers'. In a series of reports, they demonstrated that excellent stereocontrol in the Buchner reaction of α-diazoketones such as **194** could be achieved by a combination of copper and chiral bisoxazoline ligands.[4c,5]

Scheme A4.2. *Examples of asymmetric intramolecular arene cyclopropanation*



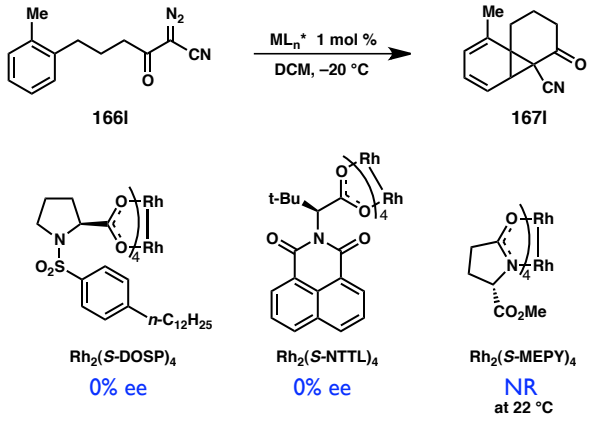
A4.2 TOWARD A GENERAL ASYMMETRIC BUCHNER REACTION

The development of a general enantioselective Buchner reaction constitutes a major challenge in the field of asymmetric catalysis. We recognized the potential utility of intramolecular arene cyclopropanation to access complex bicyclic architectures, and the development of an enantioselective process would likely further the Buchner reaction's appeal in synthetic endeavors.[6] Thus, a screen of chiral catalysts was initiated with various α-diazonitriles previously examined in Chapter 4. The high propensity of α-diazo-β-ketonitriles and related substrates to undergo aromatic cycloaddition versus C-H insertion made these compounds excellent candidates for examining asymmetric induction.[7] The results with various chiral dirhodium and copper catalysts are reported herein.

A4.2.1 Screen of Chiral Dirhodium Catalysts

Chiral dirhodium catalysts were first investigated due to their high levels of activity with α-diazocarbonyl compounds. Furthermore, the past decade has seen great advances in chiral ligand development for dirhodium complexes,[8] and the possibility for screening numerous catalysts existed. We commenced our investigation with α-diazo-β-ketonitrile **166l** in combination with various chiral dirhodium catalyst frameworks (Scheme A4.3). Although excellent conversion was obtained with electron-neutral dirhodium catalysts, no enantioinduction was observed.

Scheme A4.3. *Chiral dirhodium catalyst screen with* ***166l***



We next focused our attention on α-diazo-β-amidonitrile substrate **196** (Scheme A4.4). A screen of various dirhodium catalysts produced the first promising ee's. In particular, the amino acid derived naphthalimide catalysts[9] (Rh_2(*S*-NTTL)$_4$ and Rh_2(*S*-NTPA)$_4$) yielded the stable norcaradiene product **197** in 50 % enantiomeric excess. Before committing to a more systematic screen involving a multitude of dirhodium catalysts, we sought to examine different substrates in combination with the most encouraging catalysts from Scheme A4.4. The choice to probe enantioselectivity by varying substrates was driven in part by the known capriciousness of the asymmetric Buchner reaction in the work of Maguire.

Scheme A4.4. *Chiral dirhodium catalyst screen with* ***196***

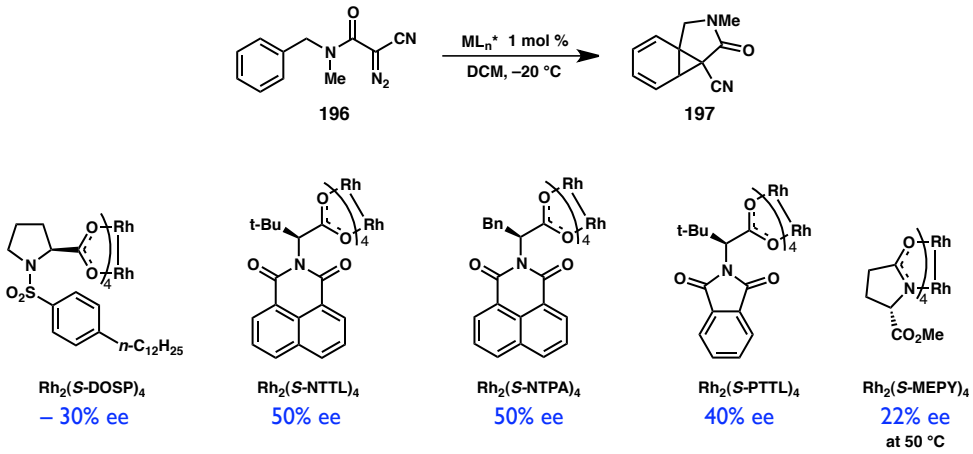
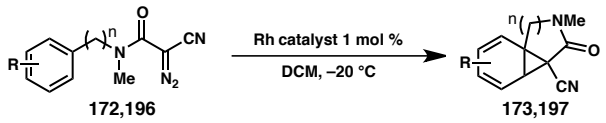


Table A4.1 delineates the screen of the dirhodium catalysts from Scheme A4.4 in combination with four additional amide substrates. Consistent with previous reports, slight structural changes resulted in a dramatic impact on the ee of the norcaradiene product. The 4-methoxy product **199** (n = 1) was created in racemic fashion by the Rh$_2$(*S*-NTTL)$_4$ and Rh$_2$(*S*-NTPA)$_4$ naphthalimide-based catalysts. Remarkably, the 4-methyl product **201** (n = 1) was produced with the best ee observed in this project, wherein Rh$_2$(*S*-NTTL)$_4$ catalyzed the Buchner reaction of α-diazo-β-amidonitrile **196** in 78 % ee. Unfortunately, addition of another methylene unit into the tether attaching the diazo amide and arene (substrates **173a** and **173b**, n = 2) resulted in moderate to poor stereocontrol.

Table A4.1. *Chiral dirhodium catalyst screen with* ***172,196***



	Rh_2(*S*-NTTL)$_4$	Rh_2(*S*-NTPA)$_4$	Rh_2(*S*-PTTL)$_4$	Rh_2(*S*-DOSP)$_4$
197	50% ee	50% ee	40% ee	– 30% ee
199	0% ee	0% ee	–[a]	–
201	78% ee	66% ee	52% ee	– 44% ee
173a	50% ee	–	–	24% ee
173b	2% ee	– 20% ee	– 8% ee	– 2% ee

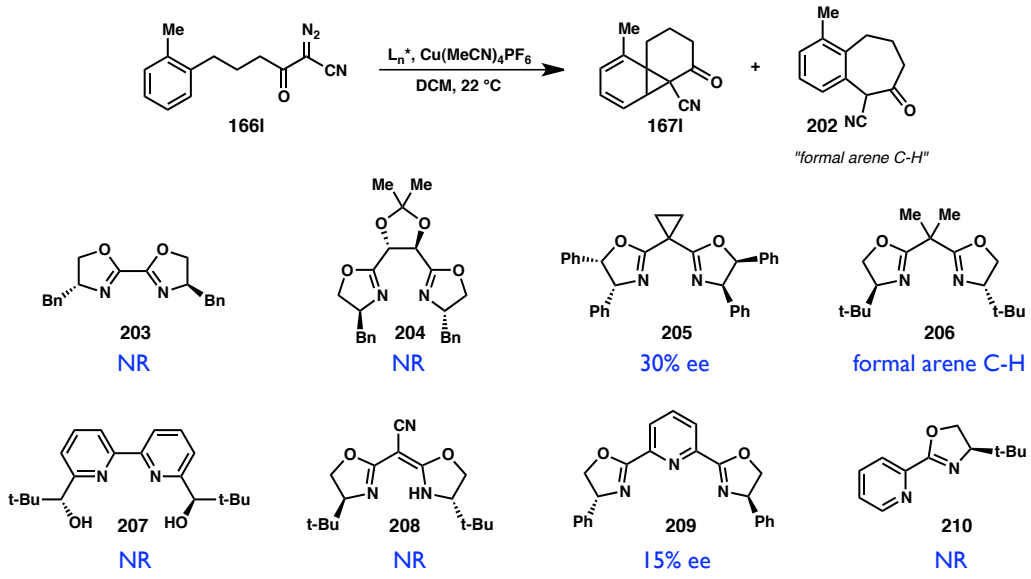
[a]Dashed line indicates catalyst was not run with substrate

A4.2.2 Screen of Chiral Copper Catalysts

Despite the excellent reactivity observed with the chiral dirhodium catalysts, our studies exposed some of the drawbacks of their use in the asymmetric Buchner reaction. Although some promising enantiocontrol was observed, the ee of reaction was wildly variable from substrate to substrate. Furthermore, extensive catalyst screening would have required the individual preparation of each dirhodium catalyst, some ligands of which necessitate multistep syntheses. With the goal of more efficient screening of ligand frameworks in mind, chiral copper catalysts were thus investigated. The *in situ* preparation of the active species, coupled with a large collection of chiral ligands available from the very generous Stoltz group, made this catalyst system ideal for investigating in the context of the enantioselective Buchner reaction.

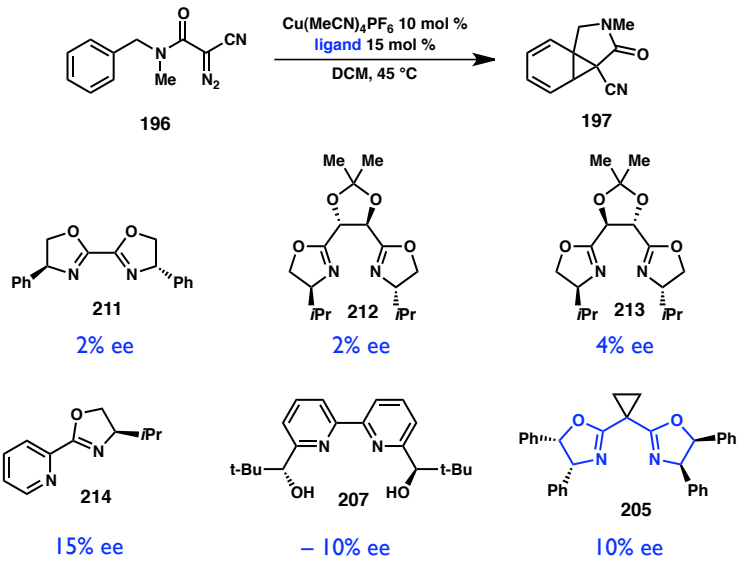
Our studies first commenced with α-diazo-β-ketonitrile **166l** (Scheme A4.5). Because the copper promoted de-diazotization of acceptor–acceptor substituted diazo compounds such as **166l** typically occurs at much high temperatures than with rhodium, only highly reactive cationic copper species were useful in these screens. We thus focused on ligands reported for asymmetric intermolecular alkene cyclopropanation in conjunction with copper.[2,10] Although some promising ee values were obtained with bisoxazoline ligand **205**, this transformation was fraught with problems. The conversion was very low or negligible in most cases, and due to competitive decomposition of the norcaradiene product to arene **202**, the upper temperature range was limited. The poor stereoinduction and unfavorable reactivity thus prompted us to explore chiral copper catalysts with different diazo compounds.

Scheme A4.5. *Cationic copper and chiral ligand screen with* ***166l***



We thus turned our attention again to the α-diazo-β-amidonitrile system. An initial screen of various bidentate nitrogen containing ligands yielded very low levels of stereoinduction (Scheme A4.6). Nevertheless, slightly better conversions were obtained as compared to the ketone system, and the norcaradiene products were stable to the reaction conditions. We proceeded forward with the bisoxazoline framework given the ready available of different members of the ligand class, wherein different parts of the BOX framework were systematically altered.

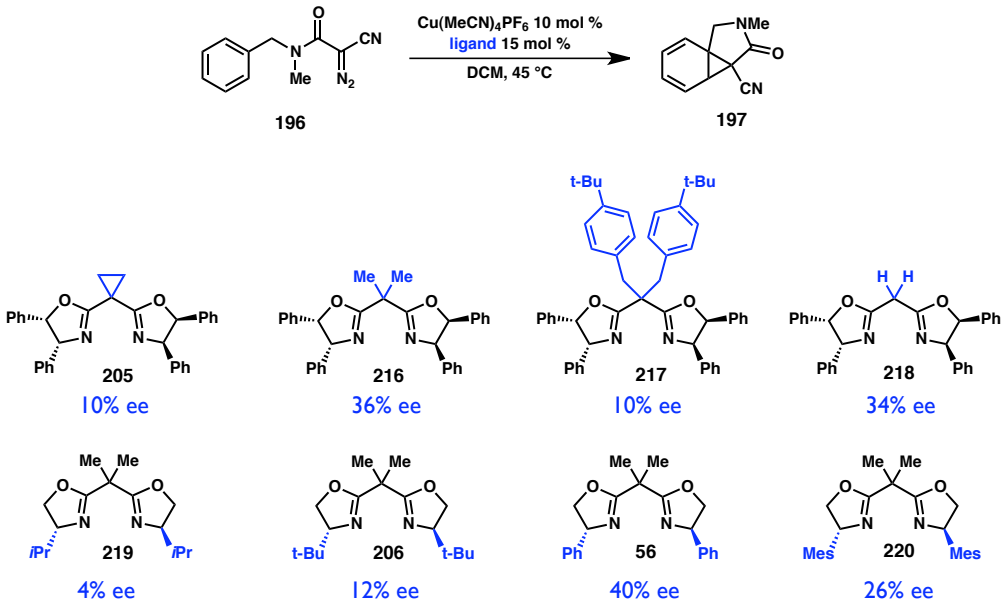
Scheme A4.6. *Cationic copper and chiral ligand screen with* ***196***



The tether carbon of the bisoxazoline ligands was the first variable section investigated (Scheme A4.7). Improved ee values were obtained when moving to the *gem*-dimethyl based ligand **216** from **205**, but no clear trend correlated to the steric bulk of the substituents attached the methylene could be observed. The effect of the substituent attached to the carbon a to the nitrogen within the oxazoline ring was also examined.

While alkyl-based ligands **219** and **206** only afforded the norcaradiene product in poor ee, a large jump was observed when employing the PhBox catalyst **56**. Unfortunately, increasing the substitution of the phenyl ring by employing the mesityl-derived ligand resulted in erosion of enantioselectivity (**220**).

Scheme A4.7. *Cationic copper and chiral ligand screen with* ***196***



A4.3 CONCLUSION

This section summarizes our efforts toward the development of a general enantioselective intramolecular arene cyclopropanation reaction. While some promising enantioselectivities were obtained with chiral dirhodium catalysts, the stereoinduction of the reaction was highly substrate dependent. Future directions should focus on thorough investigation of dirhodium catalysts due to the excellent reactivity of these systems versus copper.

A4.4 NOTES AND REFERENCES

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Chapter 5

Hydrazide-functionalized Resins for Glycomics and Glycoproteomics

5.1 INTRODUCTION AND BACKGROUND[†]

Glycobiology is the study of the structure, biosynthesis, and biology of carbohydrate-modified proteins and lipids.[1] The main goal of this field is to elucidate the purpose of these glycoconjugates, and uncover how these modifications mediate various biological processes. There is no single predominant role of protein- and lipid-linked sugars, and the functions of glycans (i.e. sugars that are bound to the macromolecule) are wide ranging.[2] These capacities span from structural and cell adhesion duties[3] to the modulation of protein properties and trafficking.[4]

Protein glycosylation is the reaction of a carbohydrate with a nucleophilic moiety of a protein. *N*-Linked glycosylation is the attachment of a sugar molecule to a nitrogen

[†] This work was performed in collaboration with Dr. Sergiy Levin, a former postdoctoral scholar in the Reisman group, and Dr. Kyoung-Soon Jang, a current postdoctoral scholar in the Clemons group. This chapter is based on a manuscript in preparation, co-written with Dr. Kyoung-Soon Jang and Prof. Bil Clemons.

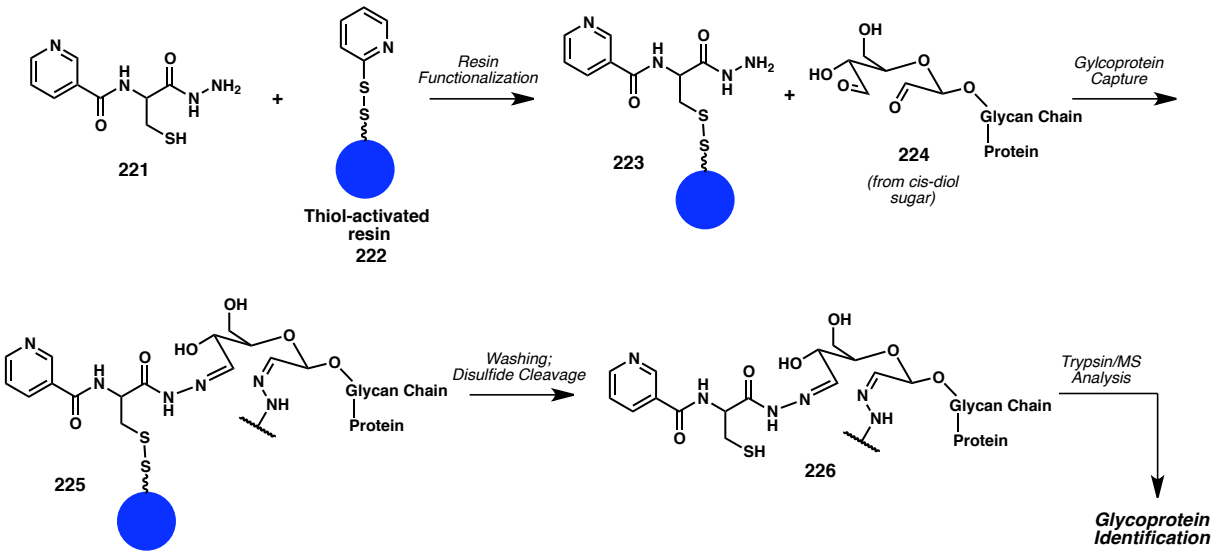
atom of an amino acid residue of the protein. This type of linkage is important for both the structure[4] and function[5] of some eukaryotic proteins. For example, some proteins do not fold correctly unless they are glycosylated first.[6] Also, certain N-linked polysaccharides confer extracellular stability on some secreted glycoproteins.[7] Thus, the determination of the glycosylation identity and pattern for specific proteins is critical for further understanding of the various biological functions mediated by glycans.

The identification of an organisms total glycosylated protein pool, the glycoproteome, requires selectively and efficiently isolating glycoproteins from biological samples. Various enrichment techniques, such as lectin affinity chromatograpy,[8] metabolic tagging/click chemistry,[9] and periodate oxidation/hydrazide chemistry,[10] have been established for studies in eukaryotes. Among these, chemical coupling by hydrazide chemistry is the most generally applicable. Originally introduced by Zhang and colleagues,[10] periodate oxidizes the cis-diol of glycans to aldehydes which can then be coupled to a hydrazide resin to form a stable hydrazone bond. The captured glycoprotein can then be analyzed by mass spectrometry.

The limitation of this method is the requirement of an enzyme to release enriched protein from functionalized resins. Peptide:N-glycosidase F (PNGase F) has been commonly used for this; however, it cannot cleave the equivalent bonds in most bacterial glycoproteins. In lieu of a functional enzyme, we have developed new chemical probes to take advantage of the hydrazide chemistry. Our probes have been designed to possess thiol and cationic moieties in addition to the hydrazide group (Scheme 5.1). The thiol group will be used for conjugation to a thiol-activated solid support, which can be released under reducing conditions after glycoprotein capture. The addition of the

positive charge is expected to improve the ionization signal during MS analysis, as reported in previous literature.[11]

Scheme 5.1. *Probe design for selective glycoprotein capture and identification*



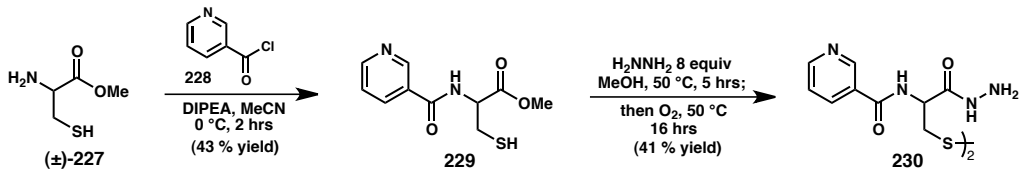
In this study, we demonstrate the novel enrichment technique for efficient identification of bacterial free glycans and glycoproteins as well as eukaryotic glycoproteins. The cationic hydrazide functionalized resins was able to selectively capture bacterial glycoproteins and free oligosaccharides in periplasmic fractions of *C. jejuni*, followed by mass spectrometric analysis. This method provides simple and sensitive ways necessary for comprehensive glycomic and glycoproteomic studies.

5.2 RESULTS AND DISCUSSION

5.2.1 Preparation of Cationic Cysteine Hydrazide and Functionalized Resins

The first goal of the collaborative project was to synthesize *c*ysteine *h*ydrazide *n*icotinamide (*Cyhn*) **221**. This was accomplished in a straightforward two-step sequence (Scheme 5.2). Racemic cysteine methyl ester (**227**) was coupled with the acid chloride of nicotinic acid, affording cysteine methyl ester nicotinamide **229**. Unreacted cysteine methyl ester was removed using solution-phase extraction, and the major impurity of the reaction (acylation of the thiol group of the product) was separated by silica column chromatography. Reaction of the cysteine methyl ester nicotinamide with excess hydrazine hydrate in methanol resulted in the *Cyhn* compound (**216**). The reaction was monitored by LC/MS, and upon complete consumption of the starting material the solution was sparged with oxygen gas to effect dimerization of the *Cyhn* monomer. Precipitation of *Cyhn* dimer resulted during this process, and after concentration and trituration with methanol the *Cyhn* dimer (**230**) was obtained in >95% purity.

Scheme 5.2. *Synthesis of Cyhn dimer* ***230***



In the course of out studies we observed that ester **229** is stable as the free thiol; the *Cyhn* monomer **221**, however, was very susceptible to oxidation to the disulfide. This

feature of hydrazide **221** greatly hampered the attempted isolation and purification of this compound. Alternatively, the *Cyhn* dimer (**230**) existed as a stable solid that could be reliably produced in high purity. The stability and ease of purification of the *Cyhn* dimer was exploited to obtain gram quantities of a *Cyhn* monomer precursor. Prior to the conjugation, the disulfide moiety of the *Cyhn*-dimer was reduced with dithiothreitol (DTT) and the liberated monomer was used *in situ* for conjugation to the activated thiol resins. The pyridyl group serves as a handle for forming a cationic species, facilitating mass spec analysis of various conjugated species. The *Cyhn* compound was conjugated onto commercially available thiol-activated solid supports such as thiopropyl Sepharose™ 6B resins or BcMag™ thiol-activated magnetic beads, resulting in the *Cyhn*-6B or *Cyhn*-BcMag resins, respectively. The prepared *Cyhn* resins were employed to selectively conjugate free oligosaccharides as well as oxidized glycoproteins from mixtures as demonstrated in section 5.2.2.

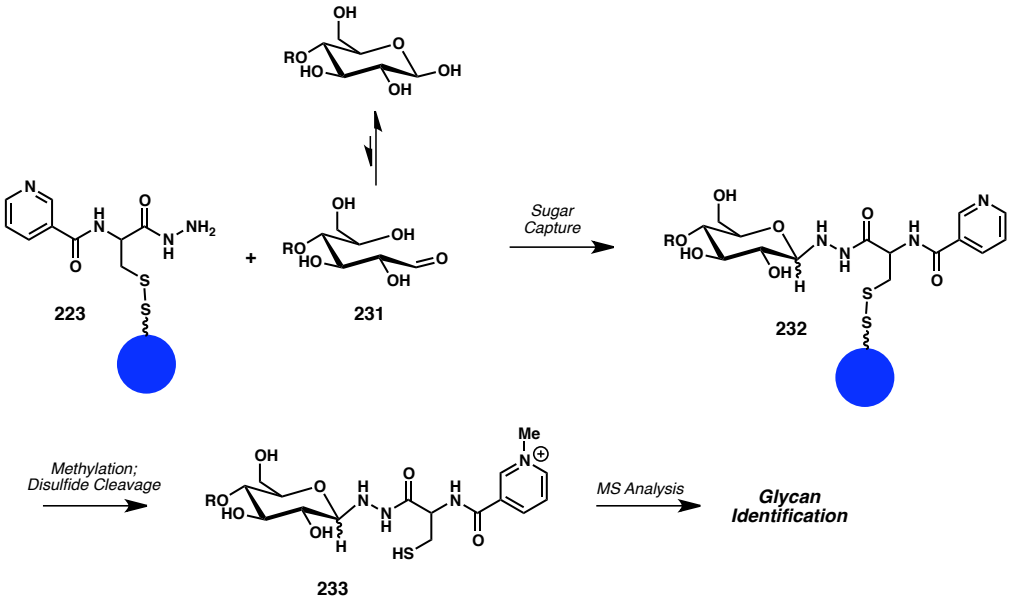
5.2.2 Control Experiments: Sugar Capture and MS Analysis[‡]

To test whether mass spectroscopy would be suitable for analysis of captured sugars and glycoproteins, control experiments with simple saccharides were enacted. The *Cyhn* resins were used to enrich soluble free sugars with reducing ends. The incubation of free oligosaccharides, i.e. commercially available maltopentaose (M5) and maltohexaose (M6), with the *Cyhn*-6B resins showed selective isolation of the reduced glycans; however, it was observed that the *Cyhn*-conjugated glycans ionized as the sodium adduct,

[‡] The experiments and analysis in Section 5.2.2-3 were performed by Dr. Kyoung-Soon Jang of the Clemons group.

not as the protonated pyridinium. Rendering the *Cyhn* with a discrete positive charge via *N*-methylation of the pyridine nitrogen provided a solution (**233**, Scheme 5.3). The mild post-methylation of the glycan-*Cyhn* conjugates allowed a permanent positive charge to the *Cyhn* conjugates, resulting in higher ionization signals during MS analysis (Scheme 5.3). Finally, the *Cyhn*-enrichment followed by post-methylation was able to identify bacterial free heptasaccharide from periplasmic extracts of *C. jejuni*.

Scheme 5.3. *Capture and MS analysis of various saccharides*



5.3 CONCLUSIONS

In this study, we established a novel enrichment tool to investigate the bacterial glycome and glycoproteome. This versatile enrichment technique enabled us to efficiently isolate bacterial periplasmic free oligosaccharides as well as glycoproteins, and subsequent MS analyses allowed the identification of those molecules.

The *Cyhn*-based enrichment technique, developed in this study, showed high efficient capture in both case of bacterial glycoproteins and free glycans. As the pyridine moiety on the *Cyhn* molecule can be used as a UV-chromophore due to its optical activity, the *Cyhn*-conjugation will be able to be utilized for quantitative glycomics in combination with conventional HPLC. The pivotal play using this enrichment technique would allow us to explore the diversity of NLG pathways in a variety of bacterial samples.

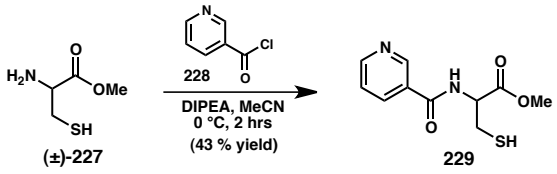
5.4 EXPERIMENTAL SECTION

5.4.1 Materials and Methods

Nicotinic acid, *N*,*N*-dimethylformamide, *N*,*N*-diisopropylethylamine, L-cysteine methyl ester hydrochloride, hydrazine monohydrate, sodium *meta*-periodate, and iodomethane were purchased from Sigma-Aldrich. Thionyl chloride was obtained from Junsei Chemical Co., Ltd. *N*-hydroxysuccinimide (NHS)-fluorescein was obtained from Thermo Fisher Scientific Inc. Thiopropyl Sepharose™ 6B resins and BcMag™ thiol-activated magnetic beads were purchased from GE Healthcare Biosciences (Pittsburgh, PA) and Bioclone Inc. (San Diego, CA), respectively. All other chemicals were of analytical grade.

5.4.2 Preparative Procedures and Spectroscopic Data

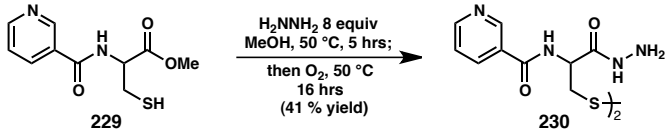
Preparation of Cysteine Methyl Ester Nicotinamide 229



Nicotinic acid (7.9 g, 64.2 mmol) was suspended in 100 mL thionyl chloride (512 mmol). *N*,*N*-Dimethylformamide (0.2 mL, 2.6 mmol) was added to the solution as a catalyst. The reaction mixture was stirred for 1 h at room temperature (RT), during which time the slurry became homogeneous. Upon complete consumption of the nicotinic acid, the thionyl chloride was removed *in vacuo*, and the residue was azeotroped with benzene to remove residual thionyl chloride and HCl. The crude off-white solid (**228**) was suspended in 150 mL of acetonitrile and cooled to 0°C under a nitrogen atmosphere. A

heterogeneous mixture containing cysteine methyl ester hydrochloride **227** (10 g, 58.3 mmol) and *N*,*N*-diisopropylethylamine (8.3 mL, 47.2 mmol) in 200 mL of acetonitrile was transferred in one portion to the nicotinic acid chloride. The resulting thick white slurry was stirred vigorously and allowed to warm to RT over 2 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ and the acetonitrile was concentrated *in vacuo*. The aqueous phase was extracted with dichloromethane (3×100 mL), and the combined organic phases were washed with brine. The organic layer was dried over Na_2SO_4, and then the solvent was removed *in vacuo*. The crude residue was purified using silica column chromatography (50→100% EtOAc:hexanes) affording the cysteine methyl ester nicotinamide **229** as a viscous colorless oil (6.0 g, 25.0 mmol, 43% yield). ^{1}H NMR (500 MHz, $CDCl_3$) d: 9.07 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.77 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.15 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 7.09 (br d, *J* = 7.1 Hz, 1H), 5.09 (dt, *J* = 7.1, 4.0 Hz, 1H), 3.85 (s, 3H), 3.16 (dd, *J* = 9.0, 4.0 Hz, 2H), 1.40 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.37, 165.17, 152.69, 148.24, 135.06, 129.22, 123.46, 53.92, 53.02, 26.78; FTIR (NaCl, thin film) 3309, 3035, 2951, 1740, 1653, 1591, 1539, 1351, 1217 cm^{-1}; HRMS (ESI+) calc'd for $C_{10}H_{12}N_2O_3S$ $[M+H]^+$ 241.0641, found 241.0643.

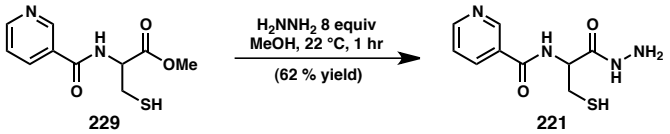
Preparation of cysteine dihydrazide nicotinamide 230



Cysteine methyl ester nicotinamide (**229**, 5.9 g, 24.4 mmol) was dissolved in 100 mL of dry methanol, and then hydrazine monohydrate (9.5 mL, 195.2 mmol) was added.

The solution was stirred at 50°C for 5 hr, and the conversion to cysteine hydrazide nicotimamide (*Cyhn* monomer) was monitored by LC-MS. After the complete consumption of the staring material, the solution was sparged with oxygen gas for 15 minutes, then maintained under an oxygen atmosphere overnight at 50°C. After LC-MS analysis indicated complete conversion to the *Cyhn* disulfide dimer, the volatiles were removed *in vacuo*. The white residue was subjected to hot trituration in refluxing methanol (100 mL), and the precipitated product was filtered and washed with cold methanol. Drying under vacuum (0.1 Torr) afforded the cystine dihydrazide nicotinamide (*Cyhn* dimer) **230** as a white solid (2.4 g, 41% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.42 (s, 1H), 8.99 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.87 (d, *J* = 8.2 Hz, 1H), 8.69 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.17 (app dt, *J* = 7.9, 2.0 Hz, 1H), 7.48 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 4.74 (m, 1H), 4.30 (br s, 2H), 3.22 (dd, *J* = 13.6, 4.9 Hz, 1H), 3.03 (dd, *J* = 13.6, 9.9 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 168.90, 165.04, 151.96, 148.72, 135.26, 129.44, 123.30, 51.34, 39.74; IR (NaCl/thin film) 3281, 3035, 2960, 1633, 1537, 1327; HRMS (ESI-) calc'd for $C_{18}H_{22}N_8O_4S_2$ $[M-H]^-$ 477.1133, found 477.1148.

Preparation of *Cynh* Monomer 221



Cysteine methyl ester nicotinamide (**229**, 80 mg, 0.33 mmol) was dissolved in 400 mL of dry methanol under nitrogen, and then hydrazine monohydrate (67 mL, 1.33 mmol) was added. The solution was stirred at room temperature until conversion to the cysteine hydrazide nicotimamide (*Cyhn* monomer) was achieved by LC-MS. All

manipulations thereafter were performed under an argon atmostphere. The volatiles were then concentrated *in vacuo*, and the residue was slurried in ethanol, filtered, and washed with cold ethanol. Drying under vacuum (0.1 Torr) afforded the cystine hydrazide nicotinamide (*Cyhn* monomer) **221** as a white solid (50 mg, 62% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.35 (s, 1H), 9.05 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.71 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.23 (app dt, *J* = 7.9, 2.0 Hz, 1H), 7.52 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.51 (td, *J* = 9.0, 5.2 Hz, 1H), 4.28 (br s, 2H), 2.90 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.82 (dd, *J* = 13.5, 9.0 Hz, 1H), S*H* not observed; ^{13}C NMR (126 MHz, DMSO-d_6) δ: 169.00, 165.17, 151.98, 148.76, 135.34, 129.55, 123.33, 55.10, 26.00. IR (NaCl/thin film) 3290, 3036, 2960, 1630, 1537, 1328; HRMS (ESI+) calc'd for $C_9H_{12}N_4O_2S$ $[M+H]^+$ 241.0754, found 241.0755.

Preparation of cationic cysteine hydrazide-functionalized resins. To hydrolyze the disulfide bond of the cysteine dihydrzide nicotinamide (*Cyhn* dimer), the *Cyhn* dimer (86 mg, 180 mmol) was suspended in 50% ethanol (1 mL), then one equivalent of dithiothreitol was added to the solution. Each thiopropyl Sepharose™ 6B resins (1 mL, 30 mmol) and BcMag™ thiol-activated magnetic beads (150 mg, 36 mmol) were washed with deionized water, respectively. The resins were suspended in 50% methanol. Five hundred milliliters of the *Cyhn* solution was added in each suspension. The suspensions were placed on rocking incubator at RT overnight. Then, the resins were washed with 50% methanol, followed by water and 20% ethanol. The resulting resins were stored in 20% ethanol at 4°C prior to use.

Enrichment of free glycans and post-methylation of the *Cyhn*-conjugate. To capture free oligosaccharides, reducing glycans (each 50 nmole) were incubated with 10 mL of *Cyhn*-6B resins (ca. 10 nmole) at 100°C for 20 min in 2% (v/v) acetic acid in acetonitrile. After the capturing, the resins were subsequently incubated with 10% of methyl iodide in acetonitrile at RT for 10 h with gentle shaking. The resins were then washed with acetonitrile, followed by deionized water, then released by 50 mL of 10 mM dithiothreitol in 50% methanol for further MALDI-TOF MS analysis.

5.5 NOTES AND REFERENCES

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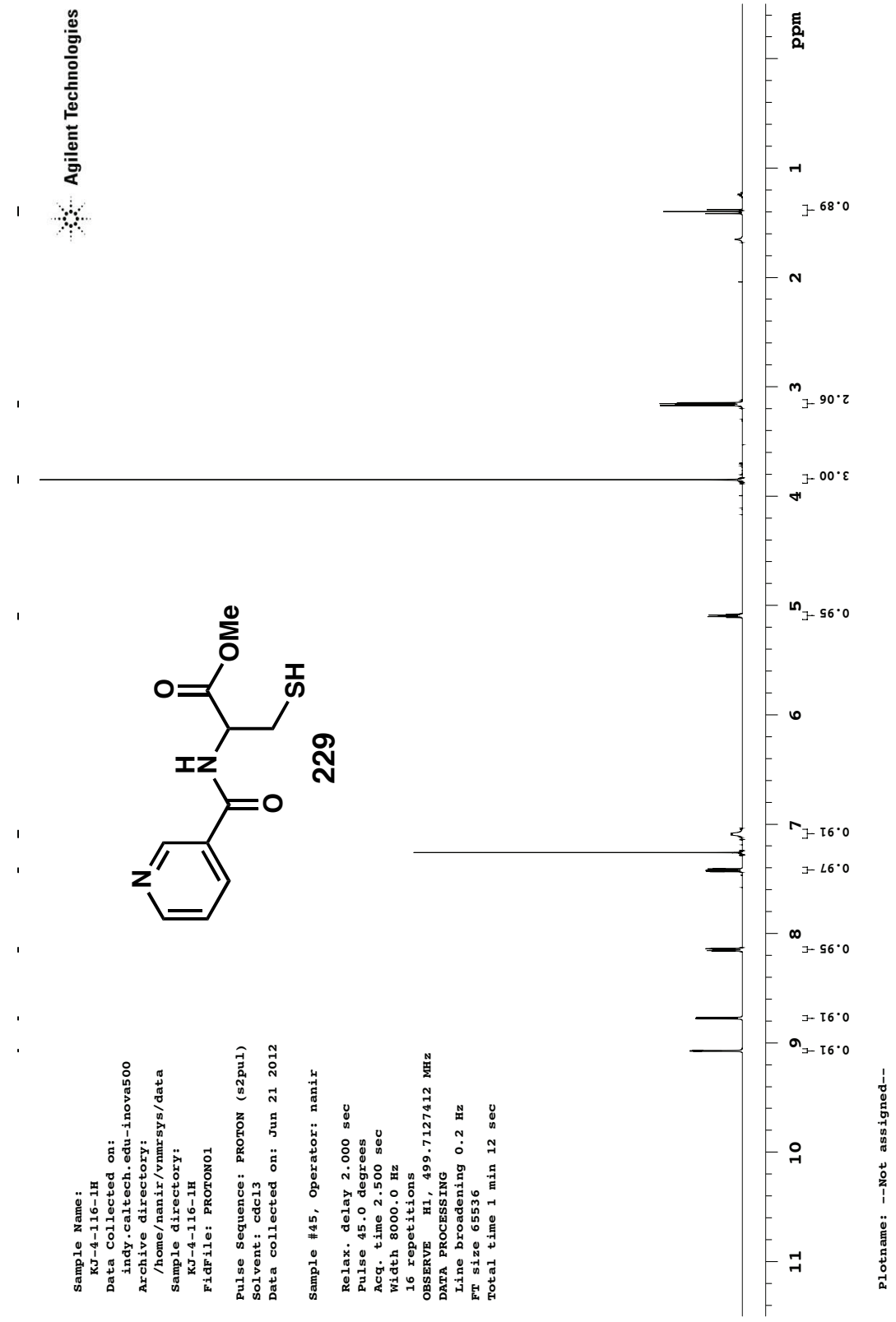
Appendix 5

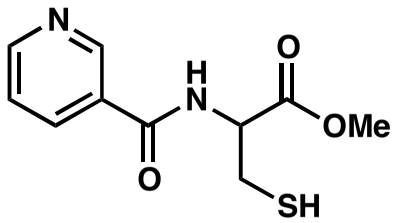
Spectra Relevant to Chapter 5:

Hydrazide-functionalized Resins for Glycomics and Glycoproteomics

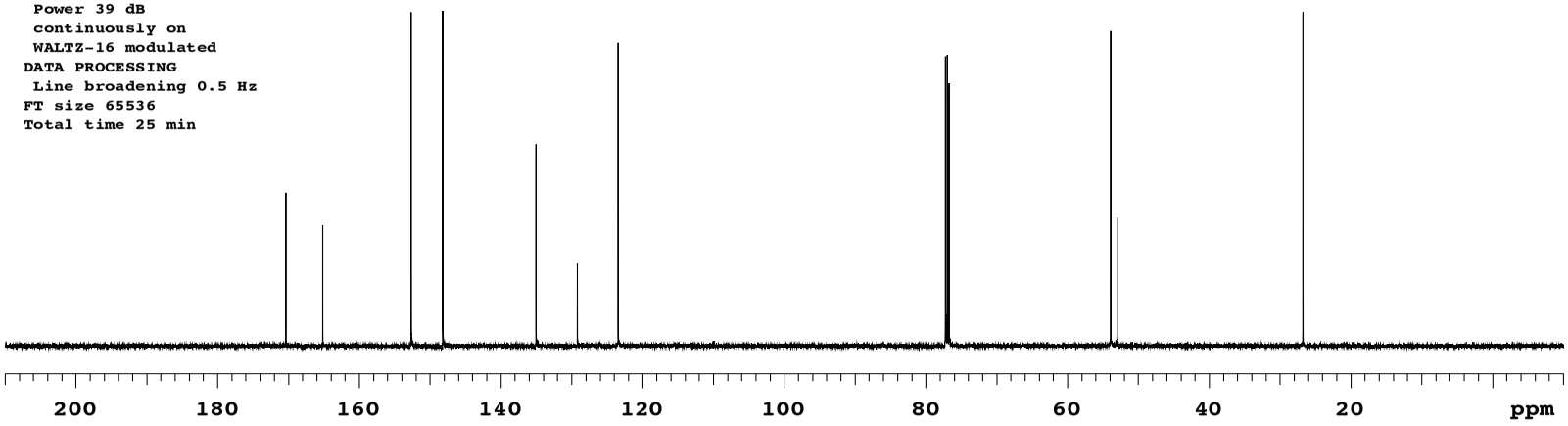

Agilent Technologies
Sample Name:
KJ-4-116-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
KJ-4-116-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 21 2012
Sample #45, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7127412 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
OMe
SH
229
ppm
0.89
2.06
3.00
0.95
0.91
0.97
0.95
0.91
0.91
Plotname: --Not assigned--

Agilent Technologies

```
 Sample Name:
   KJ-4-116-13C
 Data Collected on:
   indy.caltech.edu-inova500
 Archive directory:
   /home/nanir/vnmrsys/data
 Sample directory:
   KJ-4-116-13C
 FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 21 2012

Sample #45, Operator: nanir

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.000 sec
 Width 31446.5 Hz
 512 repetitions
OBSERVE  C13, 125.6528748 MHz
DECOUPLE  H1, 499.7152303 MHz
 Power 39 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 25 min
```



229

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Plotname: --Not assigned--
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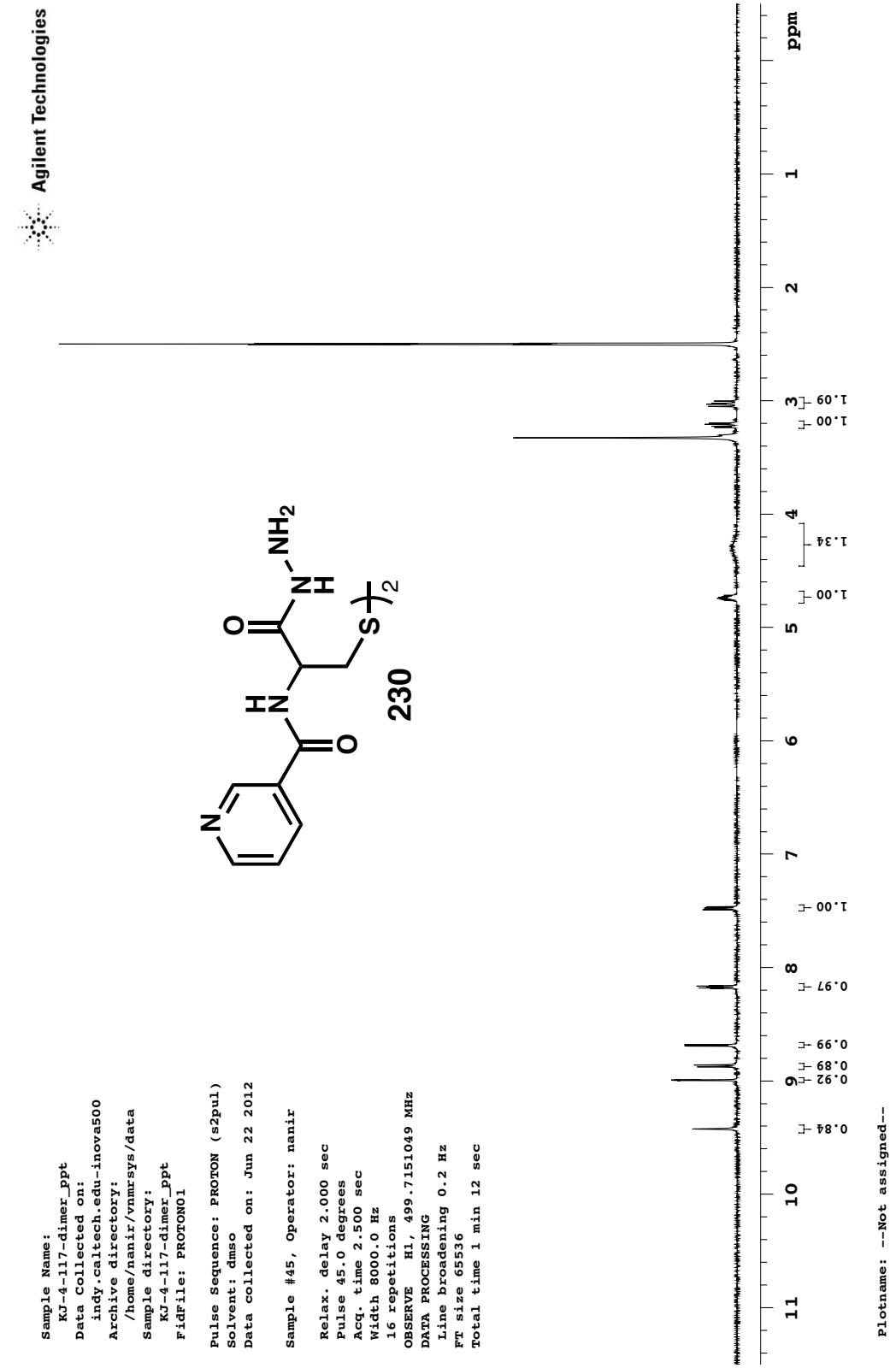
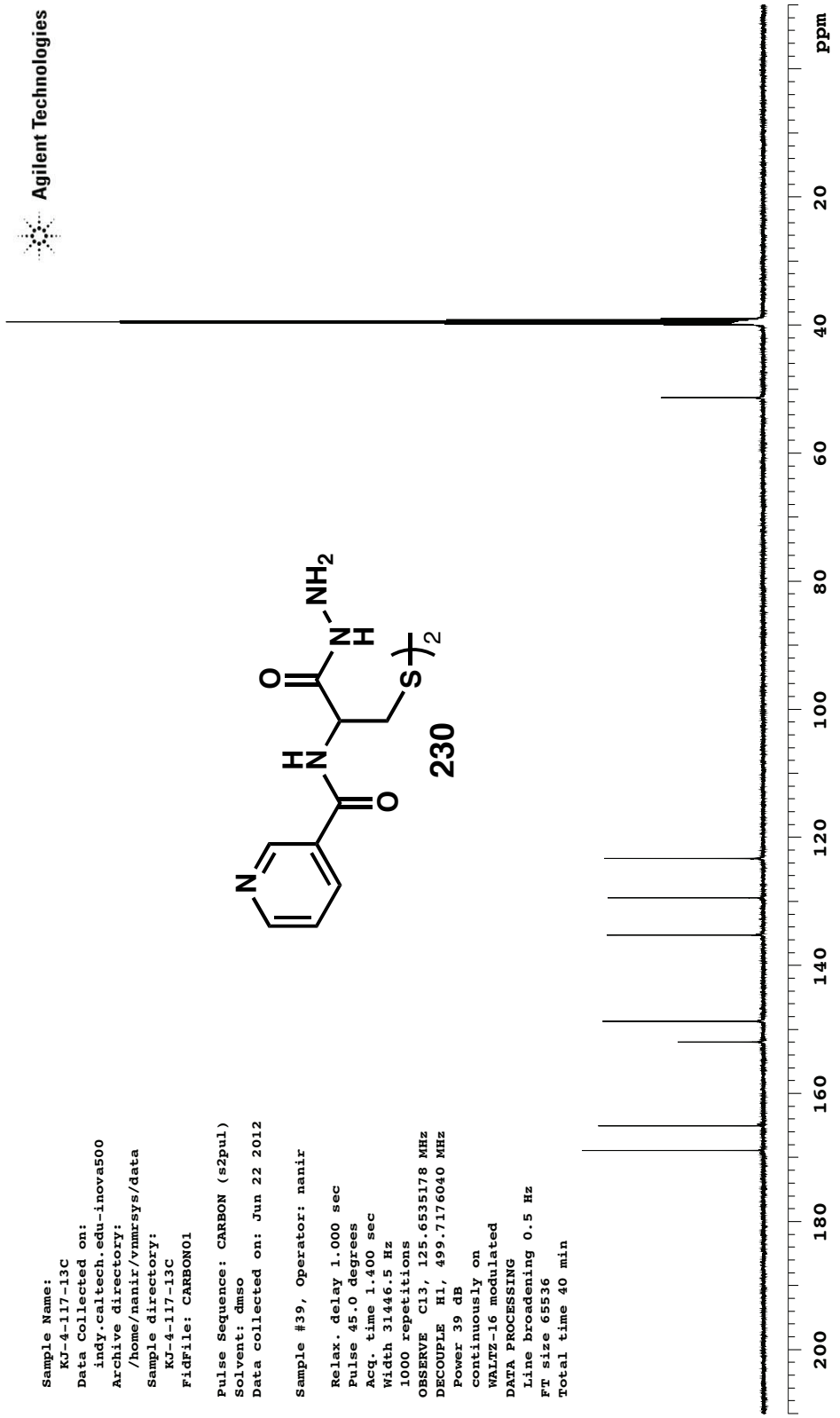
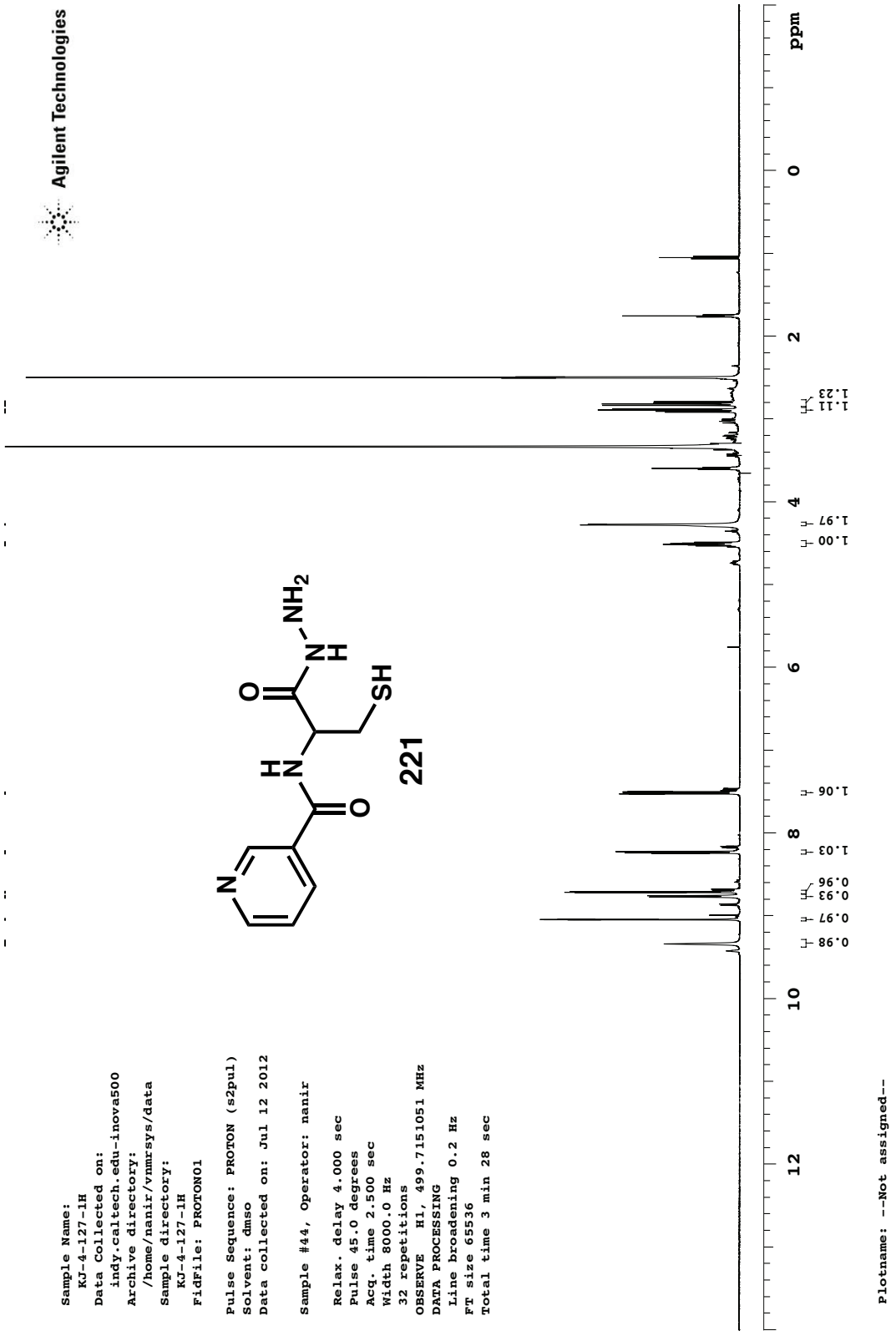

Agilent Technologies
Sample Name:
KJ-4-117-dimer_ppt
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
KJ-4-117-dimer_ppt
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Jun 22 2012
Sample #45, Operator: nanir
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7151049 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min 12 sec
230
ppm
1.09
1.00
1.34
1.00
1.00
0.97
0.99
0.89
0.92
0.84
Plotname: --Not assigned--


Agilent Technologies
Sample Name:
KJ-4-117-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
KJ-4-117-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Jun 22 2012
Sample #39, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.400 sec
Width 31446.5 Hz
1000 repetitions
OBSERVE C13, 125.6535178 MHz
DECOUPLE H1, 499.7176040 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 40 min
230
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--


Agilent Technologies
Sample Name:
KJ-4-127-1H
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
KJ-4-127-1H
FidFile: PROTON01
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Jul 12 2012
Sample #44, Operator: nanir
Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 2.500 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.7151051 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min 28 sec
221
0.98
0.97
0.93
0.96
1.03
1.06
1.00
1.97
1.11
1.23
12
10
8
6
4
2
0
ppm
Plotname: --Not assigned--

Agilent Technologies
Sample Name:
KJ-4-127-13C
Data Collected on:
indy.caltech.edu-inova500
Archive directory:
/home/nanir/vnmrsys/data
Sample directory:
KJ-4-127-13C
FidFile: CARBON01
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Jul 12 2012
Sample #45, Operator: nanir
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 31446.5 Hz
512 repetitions
OBSERVE C13, 125.6535187 MHz
DECOUPLE H1, 499.7176040 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 23 min
O
NH2
H
N
SH
H
N
O
N
221
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: --Not assigned--

ABOUT THE AUTHOR

Roger Rauhauser Nani was born in City Island, Bronx, New York on August 9th, 1984, to Paul M. and Karen R. Nani. He grew up in a small maritime community, and enjoyed spending time sailing and partaking in local neighborhood events with his family. His interest in science was sparked at an early age when he received a chemistry kit, and his curiosity was piqued by the array of colors and appearance of the different chemicals. In 1998, Roger began attending Fordham Preparatory High School. It was in Mr. McNamara's freshman biology class where he recalls a fascination of the scientific method and the various experiments that he engaged in.

His interest in science was fostered throughout high school, and upon enrolling in Boston College in 2002 was prompted to pursue a biochemistry degree. He joined Professor Marc Snapper's laboratory as an undergraduate research in his junior year, and his project focused on the optimization of the synthesis of iron cyclobutadiene complexes for use in total synthesis. Upon graduating in 2006, he accepted a position as an associate chemist in the process group at Amgen, under the supervision of George Moniz.

In the summer of 2008, Roger shipped off to the West Coast to begin his doctoral studies under the guidance of Professor Sarah E. Reisman at the California Institute of Technology. His research there focused on the development of an enantioselective total synthesis of the natural product salvileucalin B, and the subsequent investigations into a unique arene cyclopropanation reaction discovered during the synthesis. In June 2013, Roger will move to Frederick, Maryland, to begin a postdoctoral position in the labs of Dr. Martin Schnermann at the National Cancer Institute. Shortly thereafter, he will be wed to his wonderful fiancé in Larchmont, New York on September 7th.