Development of Lewis Acid Catalyzed Asymmetric Ring Expansion Reactions and Catalysis of Etherification Reactions with sp3 Electrophiles

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and

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A dissertation
by
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For my parents, who taught me to always be passionate
about what you believe in.

Development of Lewis Acid Catalyzed Asymmetric Ring Expansion Reactions

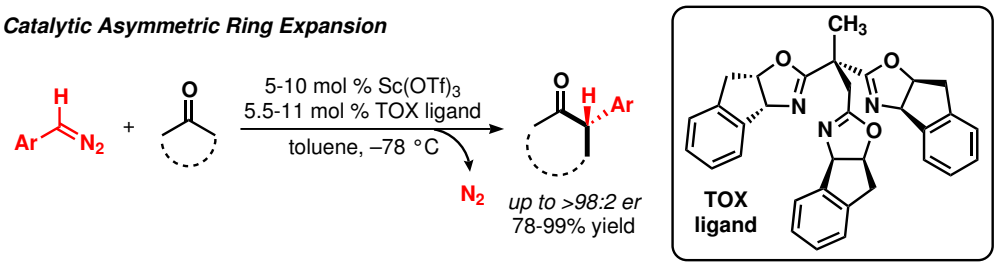
Victor L. Rendina

Thesis Advisor: Jason S. Kingsbury

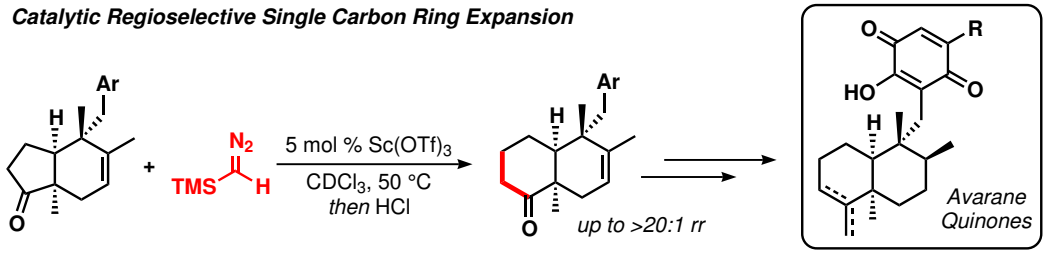
Abstract

■ **Chapter 1.** Over the past 100 years, ring expansion chemistry with non-stabilized diazoalkanes has grown slowly. While the intrinsic hazards and stigma associated with the use of diazoalkanes has been a serious impediment to more widespread development, a number of groups have made significant advances over the years. This chapter aims to provide a brief historical account of the most significant developments related to diazoalkane-based ring expansion methods.

■ **Chapter 2.** The construction of stereogenic centers adjacent to ketones remains a challenging synthetic problem for chemists. Deficiencies with regard to reaction scope, efficiency, and generality remain. In contrast to the majority of other methods in the literature, stereoselective insertion of diazoalkanes provides a pathway to directly access enantiomerically enriched α-substituted cycloalkanones. In this chapter, an account of how we developed the first catalytic asymmetric diazoalkane-based ring expansion reactions is presented. Ring expansion of unfunctionalized cycloalkanones with diazoalkanes efficiently affords α-aryl substituted cycloalkanones with high enantiopurity. Additionally, this work led to the synthesis of new chiral bis(oxazoline) ligands and the discovery of a rapid method to assay the concentration of diazoalkane solutions.



■ **Chapter 3.** Single-carbon ring expansion is a powerful synthetic disconnection, allowing chemists to construct or purchase the lower homologue of a ring system before expanding to the target ring size. Starting from a smaller ring size can often allow access to a broader array of transformations that proceed with greater stereoselection. In our approach to a class of natural products bearing a *cis*-decalin core, we successfully implemented a catalytic regioselective single-carbon ring expansion reaction in the context of an advanced synthetic intermediate. This chapter describes the experimental details behind the first catalytic single carbon cyclopentanone homologations and how we extended the method to more complex substrates.



Catalysis of Etherification Reactions with sp^3 Electrophiles

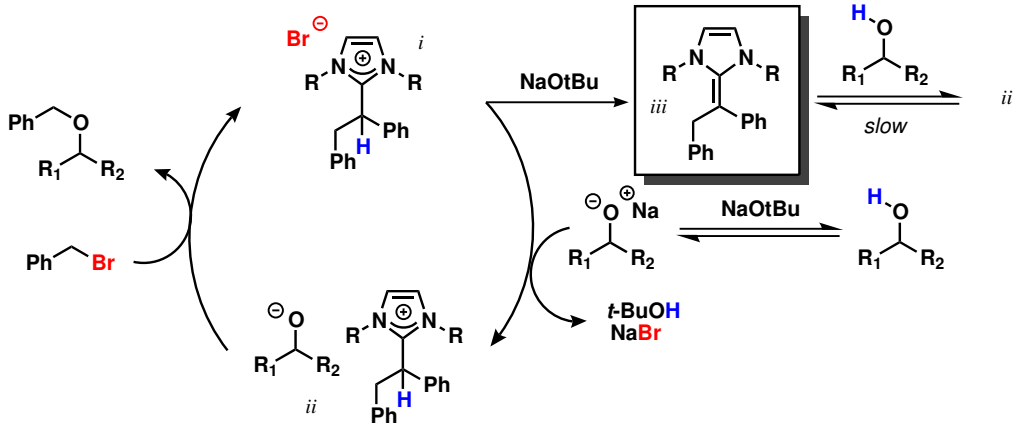
Victor L. Rendina

Thesis Advisors: Marc L. Snapper, Amir H. Hoveyda

Abstract

■ **Chapter 4.** Catalytic activation of sp^2 hybridized electrophiles by nucleophilic catalysts has been studied extensively and proceeds through a well-defined mechanistic pathway. In constrast, activation of sp^3 hybridized electrophiles in a similar fashion with small-molecule organocatalysts remains an elusive endeavor for chemists. This chapter describes preliminary studies towards this lofty goal and how we discovered a new class of imidazole-based catalysts. Thorough mechanistic studies with the newly discovered catalysts ultimately proved that the reactions proceeded through a pathway that does not involve electrophile activation. However, inexpensive and commercially available imidazolium salts were found to catalyze Williamson etherification reactions under mild conditions through a mechanism that involves an unusual imidazolium alkoxide ion-pair.

Imidazolium Catalyzed Williamson Etherification



Contents

Acknowledgements

I would like to first acknowledge Professor T. V. RajanBabu of The Ohio State University, for my development as an organic chemist undoubtedly began in his laboratories as a young undergraduate student. Professor RajanBabu, through his lectures and our discussions, instilled within me a great sense of scientific virtue and rigor that I will carry with me for the rest of my life. It was through his suggestion that I ended up applying for graduate school at Boston College.

At Boston College I have been fortunate to have worked with a number of distinguished faculty members. Professor Jason Kingsbury has been, and continues to be a strong source of support as I move forward with my career. As an advisor, Jason gave me a tremendous amount of intellectual freedom and provided the environment and encouragement for my ideas to grow. He has an incredible sense of compassion for his students and has always wanted the best for us. Professor Kian Tan, through his own actions, taught me the importance of determination and hard work. Professor Lawrence Scott has always been available to assist me with chemistry or publications to no benefit of his own, and for that I am grateful. Professor Marc Snapper has a brilliant and unique perspective on chemistry and learning from his approach has been an important part of my development as a scientist. Professor Amir Hoveyda has a contagious sense of enthusiasm for chemistry and I feel fortunate to have worked with him.

I would also like to thank all of the graduate and undergraduate students who have made my time at Boston College more enjoyable. I have been very fortunate to have met several people in particular through this process who have enriched my life in many ways. Hilan Kaplan is an exceptionally skilled and passionate scientist who I have learned a great deal from through our discussions and from working together. Hilan has been an incredible friend and we had a lot of fun together in the Kingsbury lab. I was also lucky to have the opportunity to work with Bowman Potter, who has become a great friend as well. My time

spent in the Snapper lab was more enjoyable because of Bowman, and his dedication was inspirational towards the end of my graduate career. In the Kingsbury and Snapper labs we never had a lot of resources, but with both Hilan and Bowman, we were able to work as a close team and accomplish far more than what we ever could have done individually.

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List of Abbreviations

$[\alpha]$	specific rotation
Å	angstrom
ϕ	diameter
Ac	acetyl
acac	acetylacetonyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Ar	aryl (substituted aromatic ring)
$B(Ar^F)_4$	tetrakis[(3,5-trifluoromethyl)phenyl]borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
bm	broad medium (IR)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bis(oxazoline)
brsm	based on recovered starting material
bs	broad strong (IR)
Bu	butyl
bw	broad weak (IR)
calcd	calculated
CAN	cerium(IV) ammonium nitrate
conv	conversion
d	day(s); doublet (NMR)

dba	dibenzylideneacetone
DCA	dichloroethane
DCC	dicyclohexylcarbodiimide
dd	doublet of doublets (NMR)
ddd	doublet of doublet of doublets (NMR)
dddd	doublet of doublet of doublet of doublets (NMR)
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DPEN	1,2-diphenyl-1,2-diaminoethane
dr	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv	equivalent(s)
er	enantiomeric ratio
ESI+	electrospray ionization (positive ion mode)
Et	ethyl
g	grams(s)
GC	gas chromatography
h	hour(s)
hfac	hexafluoroacetylacetone

HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
i-Pr	isopropyl
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazolium
IR	infrared spectroscopy
J	coupling constant in Hz (NMR)
L	liter(s)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	molarity (mol / L); molecular formula (HRMS)
m	*meta*
m	milli; multiplet (NMR); medium (IR)
m-CPBA	*meta*-chloroperbenzoic acid
MAD	methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
n	normal (unbranched alkyl chain)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonanace
o	*ortho*

ORTEP	Oak Ridge thermal ellipsoid plot
p	*para*
p	pentet (NMR)
PCC	pyridinium chlorochromate
PDMS	phenyldimethylsilyl
PDMSD	phenyldimethylsilyldiazomethane
Pent	pentyl
Ph	phenyl
PHOX	phosphinooxazoline
PPTS	pyridinium *para*-toluenesulfonate
PPY	4-pyrrolidinopyridine
Pr	propyl
PyBOX	2,6-bis(oxazolinyl)pyridine
q	quartet (NMR)
qd	quartet of doublets (NMR)
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
rr	regioisomeric ratio
s	singlet (NMR); strong (IR)
SAMP	(*S*)-1-amino-2-(methoxylmethyl)pyrrolidine
sept	septet (NMR)
SFC	supercritical fluid chromatography
t	tertiary alkyl chain
t	triplet (NMR)
TBAF	tetra-*n*-butylammonium fluoride

TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets (NMR)
temp	temperature
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMHD	2,2,6,6-tetramethylheptane-3,5-dionate
TMS	trimethylsilyl
TMSD	trimethylsilyldiazomethane
TOX	tris(oxazoline)
Ts	*para*-toluenesulfonyl
tt	triplet of triplets (NMR)
v/v	volume / volume
w	weak (IR)
w/w	weight / weight

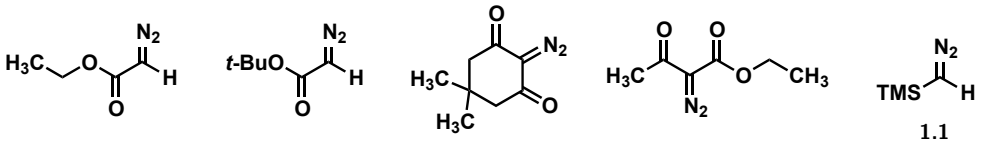
Chapter

1

History of Ring Expansion Reactions with Non-stabilized Diazoalkanes

1.1 Introduction

The synthesis of the first diazoalkanes dates back over 100 years and began with the preparation of ethyl diazoacetate by Curtius,[1] followed later with the synthesis of diazomethane by Pechmann.[2] Diazo compounds have since become an exceptionally versatile and important building block in synthetic organic chemistry. The ambiphilic nature of the diazo functional group has provided access to a wide array of transformations (e.g. C−H, N−H, and O−H insertion, ylide formation, cyclopropanation, 1,3-dipolar cycloadditions) and their use has been extensively reviewed.[3] Although it is generally accepted that diazo compounds are toxic and unstable,[4] their lability is largely correlated with the electronic properties of the flanking functional groups. Diazoalkanes with neighboring electron-withdrawing groups (carbonyl, phosphoryl, sulfonyl) are typically more stable and several such diazoalkanes have become commercially available (Figure 1.1). With the exception of TMSD (**1.1**), all of the commercially available diazo compounds are stabilized by an electron-withdrawing carbonyl moiety. The relatively stable α-diazocarbonyl compounds, although less reactive, are still utilized in many of the same transformations as their more reactive noncarbonyl-stabilized counterparts.[5]



1.1

Figure 1.1: Commercially available diazoalkanes.

[1] Curtius, T. Ueber die Einwirkung von salpetriger Säure auf salzsauren Glycocoläther. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230-2231.

[2] Pechmann, H. V. Ueber Diazomethan. *Ber. Dtsch. Chem. Ges.* **1891**, *27*, 1888-1891.

[3] For lead references refer to: (a) Regitz, M.; Maas, G. *Diazo Compounds−Properties and Synthesis*; Academic Press: Orlando, 1986. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

[4] For a very thorough discussion of diazomethane safety see: Proctor, L. D.; Warr, A. J. Development of a Continuous Process for the Industrial Generation of Diazomethane. *Org. Process Res. Dev.* **2002**, *6*, 884-892.

[5] Ye, T.; McKervey, M. A. Organic Synthesis with α-Diazo Carbonyl Compounds. *Chem. Rev.* **1994**, *94*, 1091-1160.

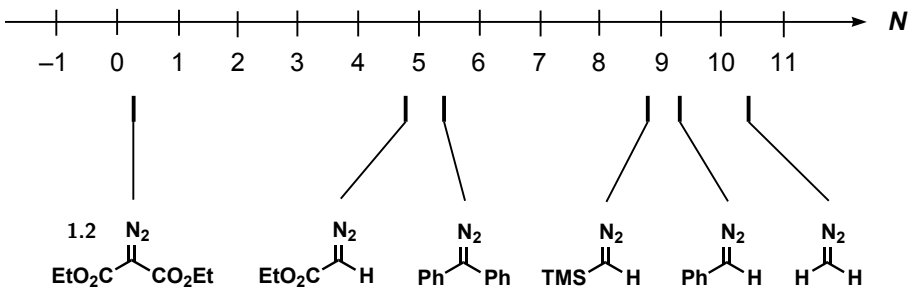


Figure 1.2: Nucleophilicity parameters of several diazoalkanes.

The nucleophilicity, and thus reactivity, of the diazo functional group is highly dependent upon the adjacent functional groups and has been found to span a fairly broad range of values. Careful kinetics experiments carried out by Mayr and coworkers established a series of relative diazoalkane nucleophilicity parameters (Figure 1.2).[6] At the most reactive end of the spectrum, the nucleophilicity of diazomethane was found to be comparable to the enamine functional group. While at the other end of the reactivity spectrum, diethyl 2-diazomalonate (**1.2**) was found to have a nucleophilicity similar to styrene. Using this scale as a general guideline, diazoalkanes can be classfied into two primary categories. Those referred to as stabilized diazoalkanes are diazo compounds adjacent to a carbonyl, phosphoryl, or sulfonyl moeity ($N<5$). The content of this thesis will focus primarily on the utility of the more reactive non-stabilized diazoalkanes, those typically bearing adjacent alkyl or aryl substituents ($N>5$). The relative instability and toxicity of non-stabilized diazoalkanes has limited their synthetic value, however, the recent development of mild methods for their preparation has facilitated a renewed interest in methodologies based on these unique molecules.[7]

This chapter will present a brief historical account of the most significant developments in non-stabilized diazoalkane chemistry, with a specific focus on ring expansion methodology.

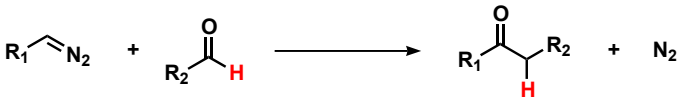
[6] Bug, T.; Hartnagel, M.; Schlierf, C.; Mayr, H. How Nucleophilic Are Diazo Compounds? *Chem. Eur. J.* **2003**, *9*, 4068-4076.

[7] For a recent review see: Maas, G. New Syntheses of Diazo Compounds. *Angew. Chem. Int. Ed.* **2009**, *48*, 8186-8195.

The discussion opens with some of the first reactions of diazoalkanes, discovered more than a century ago, and ultimately culminates in the discovery of mild and catalytic methods for ring expansion first disclosed by our research group nearly 125 years later.

1.2 History of Diazoalkane Ring Expansion Reactions

The reaction of diazoalkanes with carbonyl-containing compounds dates back to observations made by Buchner and Curtius as early as 1885.[8] Although others examined this novel reactivity pattern,[9] Schlotterbeck is largely credited with discovering the reaction of aldehydes with diazoalkanes in 1907.[10] Schlotterbeck was able to confirm through careful experimentation that various aliphatic aldehydes afforded the corresponding methyl ketones when treated with diazomethane. The reaction of aldehydes with diazomethane to form methyl ketones later became known as the Buchner-Curtius-Schlotterbeck reaction (Scheme 1.1).[11] Application of this method to ketone substrates and eventually cyclic ketones did not come until several decades later and required a critical new discovery.



Scheme 1.1: The Buchner-Curtius-Schlotterbeck Reaction

1.2.1 *Protic Solvent Promoted Reactions*

In 1928 Meerwein recorded one of the first reactions of diazomethane with a ketone, promoted by the presence of a protic solvent.[12] When acetone was treated with diazomethane no reaction occurred, however, in the presence of water or alcohols dimethylethylene oxide and 2-butanone were readily produced (Scheme 1.2). This important new discovery could

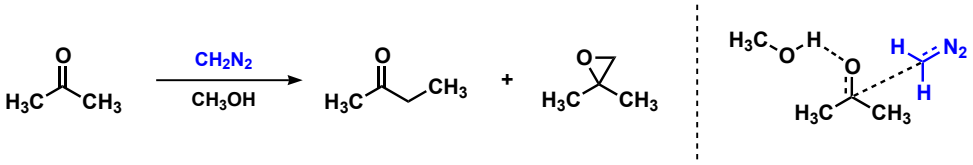
[8] Buchner, E.; Curtius, T. Synthese von Ketonsäureäthern aus Aldehyden und Diazoessigäther. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2377-2379.

[9] (a) Pechmann, H. V.; Frobenius, L. Nachträgliches Über Aromatische Diazoverbindungen. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 170-176. (b) Meyer, H. Über die Einwirkung von Diazomethan auf Aldehydsäuren und Aldehyde. *Monatsh. Chem.* **1905**, *26*, 1295-1301.

[10] (a) Schlotterbeck, F. Umwandlung von Aldehyden in Ketone durch Diazomethan. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 479-483. (b) Schlotterbeck, F. Umwandlung von Aldehyden in Ketone durch Diazomethan. II. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2559-2564.

[11] Eistert, B. In *Newer Methods of Preparative Organic Chemistry,* English ed.; New York, 1948; p 521.

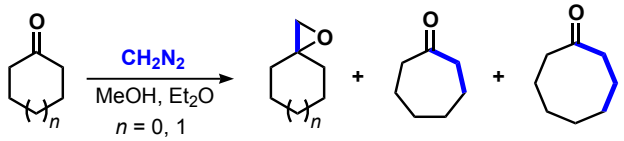
[12] (a) Meerwein, H.; Burneleit, W. Über die Einwirkung von Diazomethan auf Ketone in Gegenwart von Katalysatoren. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 1840-1847. (b) Meerwein, H. Verfahren zur Umsetzung Organischer Verbindungen mit Diazomethan. German Patent 579,309, June 26, 1933.



Scheme 1.2: Discovery of protic solvent catalysis.

be rationalized by invoking a model based on general acid catalysis. Assuming the reaction mechanism proceeds through an initial slow addition of diazomethane to the carbonyl, protic solvents can facilitate this addition by hydrogen bonding to the incipient alkoxide, thereby enhancing the electrophilicity of the carbonyl acceptor.

Following Meerwein's crucial discovery of protic solvent catalysis, Mosettig[13] reported the first carbocyclic ring expansions.[14] Cyclohexanone, when combined with excess diazomethane in ethereal solvents, was completely unreactive.[15] Upon the addition of methanol, nitrogen gas evolved vigorously and the production of cycloheptanone, cyclooctanone, and an epoxide isomeric with cycloheptanone were observed (Scheme 1.3). When the same reaction was carried out starting with cyclopentanone (n = 0), cycloheptanone and cyclooctanone were again the primary products. Residual cyclopentanone and cyclohexanone were not detected, thus indicating complete consumption of the starting material and subsequent



Scheme 1.3: First example of carbocyclic ring expansions with diazomethane.

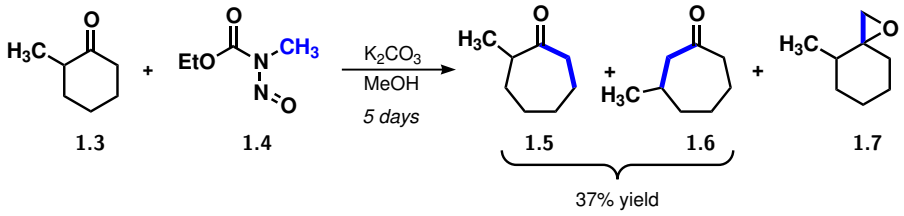
[13] Mosettig, E.; Burger, A. Ring Enlargement With Diazomethane in the Hydroaromatic Series. *J. Am. Chem. Soc.* **1930**, *52*, 3456-3463.

[14] Heller had observed the production of dihydroxyquinoline from isatin several years prior to Mosettig's work. (a) Heller, G. Neue Übergänge aus der Indol- in die Chinolin-Reihe. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 741-745. (b) Heller, G. Neue Übergänge aus der Indol- in die Chinolin-Reihe II. (Nach Versuchen von Rudolph Fuchs, Paul Jacobsohn, Martin Raschig und Elsbeth Schütze). *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 704-710.

[15] A later report indicated that cyclohexanone would undergo ring expansion with diazoethane in the absence of protic catalysis to produce 2-methylcycloheptanone as the primary product. Giraitis, A. P.; Bullock, J. L. Reactions of Cyclohexanone With Diazoethane. *J. Am. Chem. Soc.* **1937**, *59*, 951-951.

homologation of the intermediate cyclohexanone. Addition of diazomethane to cyclopentanone increases torsional strain by introducing an additional sp^3 hybridized center within the confined ring system. Cyclohexanone is generally regarded as more reactive due to the staggered nature of all bonds upon addition of diazomethane.[16] This early example serves to illustrate three fundamental challenges with the diazoalkane carbonyl homologation reaction: (1) controlling the ring size is difficult when the products are more reactive than the starting materials – the products generated possess an identical functional group ready for further reaction (2) formation of oxirane byproducts is often unavoidable (3) an excess of diazomethane is typically used because the reagent decomposes in the reaction timeframe.

Mosettig's first reactions, and subsequent ring expansions,[17] were limited to symmetrical cycloalkanones. It was not until nearly a decade later that Adamson and Kenner reported the homologation of 2-methylcyclohexanone with diazomethane (Scheme 1.4).[18] Generation of diazomethane *in situ* from *N*-nitrosomethylurethane[12] (**1.4**) in the presence of 2-methylcyclohexanone (**1.3**) produced both possible regioisomers of the ring expanded products ($\longrightarrow$ **1.5** + **1.6**) in a combined 37% yield along with an equivalent yield of epoxide **1.7**. The 2– and 3-substituted cycloheptanones were separated and positively identified by selective formation of a bisulfite adduct, however, the regioisomeric ratio was not clearly



Scheme 1.4: First ring expansion of a 2-substituted cycloalkanone.

[16] Gutsche, C. D. The Reaction of Diazomethane and Its Derivatives with Aldehydes and Ketones. *Org. React.* **1954**, *8*, 364-403.

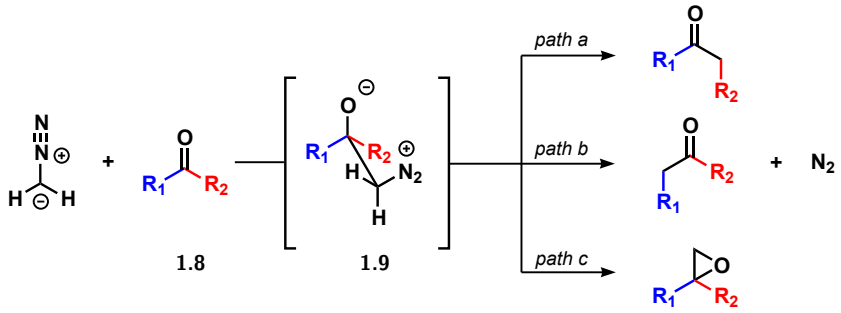
[17] Several medium ring cycloalkanones were prepared on kilogram scale following Meerwein's procedures (reference 12b). Kohler, E. P.; Tishler, M.; Potter, H.; Thompson, H. T. The Preparation of Cyclic Ketones by Ring Enlargement. *J. Am. Chem. Soc.* **1939**, *61*, 1057-1061.

[18] Adamson, D. W.; Kenner, J. Reactions of Aliphatic Diazo-compounds with Carbonyl Derivatives. *J. Chem. Soc.* **1939**, 181-189.

reported.

In 1949, Gutsche began to carefully examine the regiochemical outcome when various 2-aryl substituted cyclohexanones were homologated with diazomethane.[19] The accepted mechanism at the time, based primarily on qualitative data,[16] is depicted below in Scheme 1.5. Initial rate limiting addition of the diazoalkane nucleophile, followed by concerted collapse of betaine intermediate **1.9**,[20] could lead to three possible products. Gutsche hypothesized that by modifying the electronics at R_1 and R_2 in ketone **1.8**, the more electron rich group would migrate preferentially. The results of his findings, along with the corresponding Hammett ρ values[21] are summarized in Table 1.1.

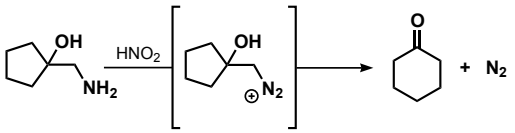
It was anticipated based on this electronic argument that entry 5 (G = *p*-Cl) would show the highest levels of regioselectivity, with preferential migration of the less substituted



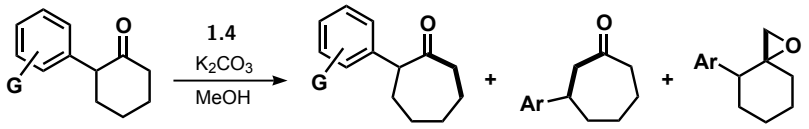
Scheme 1.5: Mechanism for the diazoalkane carbonyl homologation reaction.

[19](a) Gutsche, C. D. Ring Enlargements I. The Ring Enlargement of 2-Chlorocyclohexanone and 2-Phenylcyclohexanone. *J. Am. Chem. Soc.* **1949**, *71*, 3513-3517. (b) Gutsche, C. D.; Strohmayer, H. F.; Chang, J. M. Ring Enlargements VI. The Diazomethane-Carbonyl Reaction: Product Ratios from the Reactions of Diazomethane with Various Substituted 2-Phenylcyclohexanons. *J. Org. Chem.* **1958**, *23*, 1-5.

[20]Intermediate **1.9** resembles the same intermdiate believed to exist in the Tiffeneau-Demjanov reaction. For a review see: Smith, P. A. S.; Baer, D. R. The Demjanov and Tiffeneau-Demjanov Ring Expansions. *Org. React.* **1960**, *11*, 157-180.



[21]Hammett, L. P. The Effect of Structure upon the Reactions of Organic Compounds. Benzene Derivatives. *J. Am. Chem. Soc.* **1937**, *59*, 96-103.



1.10 **1.11** **1.12** **1.13**

entry	G	ρ	**1.11** (%)	**1.12** (%)	**1.13** (%)	rr (**1.11**:**1.12**)
1	H	0	59	14	21	4.2:1
2	p-CH_3	−0.170	55	20	21	2.8:1
3	p-OCH_3	−0.268	57	21	14	2.7:1
4	2,3,4-OCH_3	-	40	28	18	1.4:1
5	p-Cl	+0.227	45	20	26	2.2:1

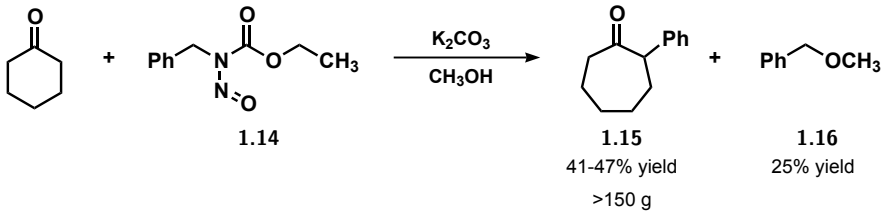
Table 1.1: Early regiochemical investigations by Gutsche and coworkers.

carbon. Entry 4 (G = 2,3,4-OCH_3) was expected to show the lowest levels of regiocontrol, or potentially an inversion of selectivity, favoring migration of the aryl substituted carbon. Unfortunately, the data were inconclusive and attempts were made to rationalize the results. The highest level of regioselectivity was observed for entry 1 (G = H), not entry 5 (G = p-Cl). The lowest level of selectivity was observed in entry 4 as expected, but regardless, there appeared to be little difference between the values in each entry. Gutsche proposed that three factors were important to determine which bond will migrate from betaine intermediate **1.9**: (1) the relative electron-releasing ability of R_1, R_2, and oxygen, (2) the strain involved in the transition state, (3) and the steric and electronic environment around the diazonium. Gutsche concluded that the reactions were largely insensitive to electronic perturbations of the aromatic ring and the observed selectivities must be the result of counterbalancing each of these factors. In general though, there was a strong intrinsic regiochemical preference for migration of the less substituted group, regardless of the electronic perturbations.[22]

Gutsche also examined a variety of aryl-substituted diazo compounds and reported some of the first examples of protic solvent catalyzed reactions with substituted diazoalkanes

[22]The Baeyer-Villiger oxidation typically displays the oppposite regiochemical preference for differentially substituted ketones. Krow, G. R. The Baeyer-Villiger Oxidation of Ketones and Aldehydes. In *Organic Reactions;* Paquette, L. A., Ed.; Wiley: New York, 1993; Vol. 43; p 251.

(Scheme 1.6).[23] Although a number of examples were reported, the most striking example was the large scale preparation of 2-phenylcycloheptanone (**1.15**) by the *in situ* generation of phenyldiazomethane from ethyl *N*-nitroso-*N*-benzylcarbamate (**1.14**).[23b] The yield was moderate, however, over 150 grams of product were obtained in a single run. In addition to the desired product, methyl benzyl ether (**1.16**) was also obtained in a 25% yield, highlighting one of the serious complications with protic solvent based catalysis.



Scheme 1.6: Large scale preparation of 2-phenylcycloheptanone.

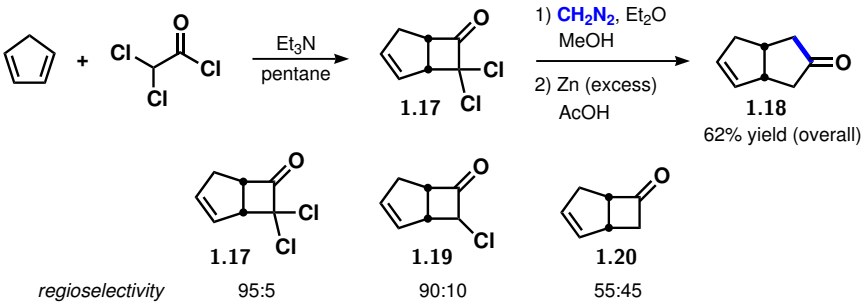
Expanding upon Gutsche's studies directed at elucidating regiochemical preferences, Greene later found that α,α-dichlorocyclobutanones afforded products resulting from preferential migration of the more electron rich C−C bond (Scheme 1.7, **1.17** $\longrightarrow$ **1.18**).[24] Common epoxide byproducts were not observed, presumably due to the ring strain involved in constructing a [2.3] spirocyclic system.[25] Greene also noted a significant rate acceleration for the electron deficient cyclobutanones, consistent with a rate limiting intial addition step. The rate enhancement could be attributed to carbonyl-π electron donation into the adjacent C−Cl σ^* orbital and increased polarization of the C−O bond through inductive effects. In this system, the electronics of the cyclobutanone had a significant impact on the observed regioselectivity. The des-chloro cyclobutanone **1.20** resulted in a 55:45 mixture

[23](a) Gutsche, C. D.; Johnson, H. E. Ring Enlargements. III. Ring Enlargement of Cyclohexanone with Ethyl *N*-Nitroso-*N*-Benzylcarbamates Carrying Methyl and Methoxyl Substituents on the Phenyl Nucleus. *J. Am. Chem. Soc.* **1955**, *77*, 109-112. (b) Gutsche, C. D.; Johnson, H. E. 2-Phenylcycloheptanone. *Org. Synth.* **1955**, *35*, 91. (c) Gutsche, C. D.; Jason, E. F. Ring Enlargements. V. The Preparation of 2-Arylcycloheptanones and 2-Aryl-2-cycloheptenones. *J. Am. Chem. Soc.* **1956**, *78*, 1184-1187.

[24]Greene, A. E.; Depres, J. P. A Versatile Three-Carbon Annelation. Synthesis of Cyclopentanones and Cyclopentanone Derivatives from Olefins. *J. Am. Chem. Soc.* **1979**, *101*, 4003-4005.

[25]Jaz made a similar observation with the ring expansion of cyclobutanone. Jaz, J.; Davreux, J. P. Reactions Des Diazoalcanes Sur Les Cyclanones I. Action Du Diazomethane Sur La Cyclobutanone. *Bull. Chim. Soc. Belg.* **1965**, *74*, 370-379.

of regioisomers, slightly favoring the production of **1.18**.[26] With a single chlorine (**1.19**), a 90:10 ratio was observed. The highest selectivity was observed with **1.17**, affording predominantly the β-ketone **1.18** in a 95:5 regioisomeric ratio after reductive dehalogenation.

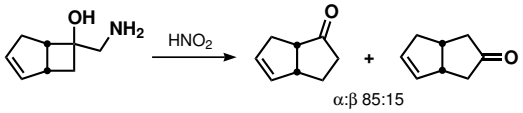


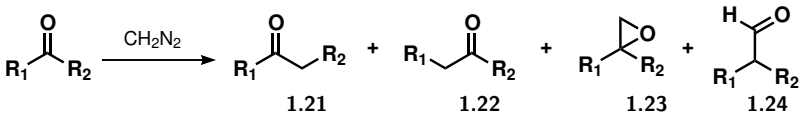
Scheme 1.7: High levels of regiocontrol with α,α-dichlorocyclobutanones.

1.2.2 *Lewis-acid Promoted Reactions*

While usage of a protic solvent was the premier means of accelerating diazoalkane ring expansions for more than half a century, serious deficiencies limited the preparative value of these transformations. As discussed in the previous section, early reactions suffered from low reaction rates, O−H insertion byproducts, multiple homologations, regiochemical issues, and low efficiencies with more sterically demanding or more substituted diazoalkanes. Early mechanistic data suggested that the initial carbonyl addition event to form the diazonium betaine intermediate was rate limiting ($\longrightarrow$ **1.9**, Scheme 1.5, page 8). To increase reaction efficiency, a stronger protic acid could theoretically serve as a better activator, however, strong Brønsted acids have long been known to rapidly decompose diazoalkanes.[16] Further development of this reaction would require the discovery of a new class of promoter.

[26] Unexpectedly, the Tiffeneau-Demjanov rearrangement of **1.20** produced primarily the α-ketone product in an 85:15 ratio (determined by IR spectroscopy). Roberts, J. D.; Gorham, W. F. Syntheses of Some Bicyclo [3.3.0]octane Derivatives. *J. Am. Chem. Soc.* **1952**, *74*, 2278-2282.





entry[a]	R_1	R_2	time	promoter	% conv.[b]	**1.21**:**1.22**:**1.23**:**1.24**[c]
1	Ph	CH_3	4 d	CH_3OH	55.8	4 : 69 : 27 : 0
2	Ph	CH_3	2 min	$BF_3 \cdot Et_2O$	36.3	22 : 78 : 0 : 0
3	Bn	CH_3	3 d	CH_3OH	65.4	32.5 : 20.5 : 47 : 0
4	Bn	CH_3	2 min	$BF_3 \cdot Et_2O$	36.5	78.5 : 21.5 : 0 : 0
5	Pr	CH_3	3 d	CH_3OH	25.0	33 : 34 : 33 : 0
6	Pr	CH_3	4 min	$BF_3 \cdot Et_2O$	19.0	50.5 : 49.5 : 0 : 0
7	*i*-Pr	CH_3	1 d	CH_3OH	4.9	65.5 : 34.5 : 0 : 0
8	*i*-Pr	CH_3	2 min	$BF_3 \cdot Et_2O$	6.8	46 : 22.5 : 0 : 31.5
9	*t*-Bu	CH_3	–	CH_3OH	0	nd
10	*t*-Bu	CH_3	2 min	$BF_3 \cdot Et_2O$	0.8	44 : 15.5 : 0 : 40.5

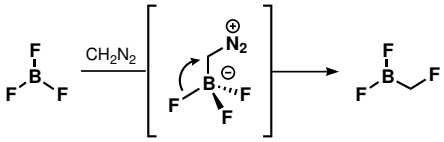
[a] *Conditions:* Run with CH_3OH as solvent or Et_2O as solvent with 1.0 equiv $BF_3 \cdot Et_2O$. [b] Determined by mass of recovered starting material. [c] Determined by gas chromatography.

Table 1.2: Regiochemical investigations by House and coworkers.

Recognizing that protic solvents were problematic and cognizant of the mechanistic data, House was able to develop the first Lewis acid promoted reactions of diazomethane with ketones.[27] A previous report had indicated that diazomethane would undergo rapid decomposition to form polymethylene and fluoromethyl boron difluoride when treated with boron trifluoride.[28] In spite of this outcome, by pre-mixing $BF_3 \cdot Et_2O$ and a solution of the appropriate ketone prior to the addition of diazomethane, House was able to record dramatic increases in reaction efficiency over protic solvent based reactions (Table 1.2). Products that previously took days to form when methanol was used as the promoter were now accessible within minutes. Reaction of diazomethane with pinacolone was completely unsuccessful in methanol (entry 9), but proceeded smoothly with stoichiometric $BF_3 \cdot Et_2O$ in diethyl ether

[27] House, H. O.; Grubbs, E. J.; Gannon, W. F. The Reaction of Ketones with Diazomethane. *J. Am. Chem. Soc.* **1960**, *82*, 4099-4106.

[28] Goubeau, J.; Rohwedder, K. H. Die Reaktion von Diazomethan mit Bortrifluorid in der Gasphase. *Liebigs Ann. Chem.* **1957**, *604*, 168-178.

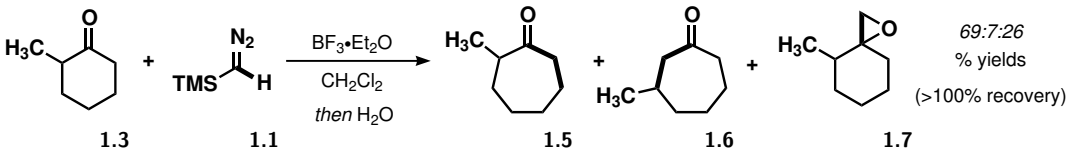


as solvent (entry 10). Formation of the expected epoxide byproducts was also not detected in any case. However, formation of aldehydes from the epoxides through a Lewis acid mediated rearrangement pathway was observed in cases of very hindered ketones. House undertook a careful study of the regiochemical outcome, and compared that directly with data obtained from methanol promoted reactions. For acyclic ketones, a moderate preference was observed for migration of the less sterically demanding side. These observations were consistent with Gutsche's regiochemical studies reported earlier for aryl-substituted cycloalkanones.[19] In House's studies, reactions were run to low levels of conversion to avoid complications arising from multiple homologation events. Regardless of that limitation, a significant improvement to the reaction kinetics opened the door to further investigations and an expanded substrate scope. The use of Lewis acids also paved the way for ring expansion reactions with the less nucleophilic carbonyl-stabilized diazoalkanes, allowing facile access to ring-expanded β-keto ester products.[29]

The next major advance in diazoalkane-based ring expansion chemistry came with Shiori's introduction of trimethylsilyldiazomethane (**1.1**) in 1980.[30] With early reactions plagued by problems of over homologation, the new reagent served to mitigate these issues by generating a bulky α-silyl ketone after the single homologation, effectively shielding the carbonyl functionality from further reaction. The α-keto trimethylsilyl group was readily cleaved upon aqueous workup, providing a traceless form of protection *in situ*. The lower nucleophilicity of TMSD relative to diazomethane necessitated the use of a Lewis acid promoter (Figure 1.2, page 3). Shiori found that the highest efficiencies were obtained when $BF_3 \cdot Et_2O$, previously described by House,[27] was used in conjunction with a non-coordinating solvent like dichloromethane. Attempts to use ethereal solvents resulted in lower chemical yields of the target compounds.

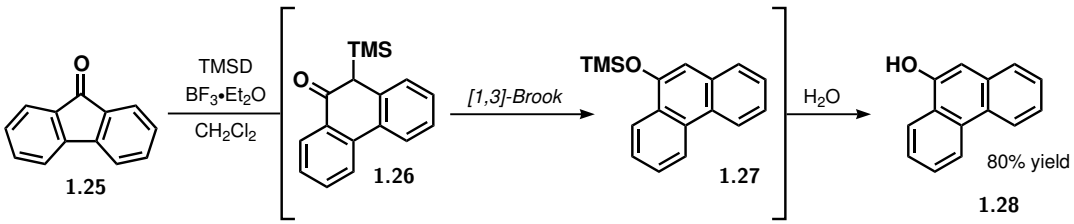
[29] Tai, W. T.; Warnhoff, E. W. β-Keto Esters From Reaction of Ethyl Diazoacetate With Ketones. *Can. J. Chem.* **1964**, *42*, 1333-1340.

[30] Hashimoto, N.; Aoyama, T.; Shioiri, T. New Methods and Reagents in Organic Synthesis. 10. Trimethylsilyldiazomethane ($TMSCHN_2$). A New, Stable, and Safe Reagent for the Homologation of Ketones. *Tetrahedron Lett.* **1980**, *21*, 4619-4622.



Scheme 1.8: Use of trimethylsilyldiazomethane (TMSD) as an alternative to diazomethane.

When 2-methylcyclohexanone (**1.3**, Scheme 1.8) was treated with 1.5 equivalents of $BF_3 \cdot Et_2O$ and 1.5 equivalents of TMSD (**1.1**) in dichloromethane for 4 hours at −15 °C, 2– and 3-methylcycloheptanone ($\longrightarrow$ **1.5** + **1.6**) were produced with nearly 10:1 regioselectivity. The 2-methyl regioisomer **1.5**, resulting from migration of the less substituted carbon, was recovered in a 69% yield. This represents a marked improvement over Adamson and Kenner's previous efforts, which netted a 37% combined yield of 2– and 3-methylcyclohexanone after 5 days with methanol as the promoter.[31] The regioselectivity also agreed with previous reports in the literature, showing an intrinsic preference for migration of the less substituted carbon regardless of the promoter or diazoalkane. When fluorenone (**1.25**, Scheme 1.9) was subjected to the standard conditions, the initially formed α-keto silane **1.26** underwent facile Brook rearrangement[32] to the aromatic silyl enol ether **1.27**. Refluxing in water afforded the deprotected phenol **1.28** in an overall 80% yield. At the time that TMSD was introduced, it was praised for its greater safety profile over diazomethane. While it is true that TMSD has greater thermal stability and has since become commercially available, it should be regarded as highly toxic and great care must



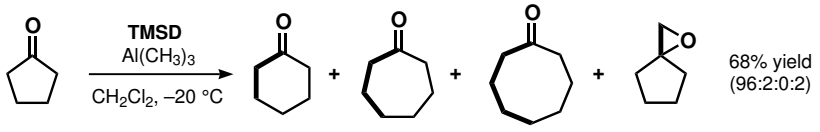
Scheme 1.9: Facile 1,3-Brook rearrangement of α-keto silane intermediate **1.26**.

[31] No regioisomeric ratio was clearly reported, see reference 18 for details.

[32] Concerted 1,3-migration of silicon from carbon to oxygen. Brook, A. G. Some Molecular Rearrangements of Organosilicon Compounds. *Acc. Chem. Res.* **1974**, *7*, 77-84.

be exercised in its use.[33] At least two chemists were recently killed from lung failure after exposure to TMSD.[34]

Although the introduction of TMSD offered significant advantages over diazomethane based homologations, there was still room to improve the product distributions and discover more efficient promoters. Yamamoto and coworkers began to evaluate the efficacy of various aluminum-based Lewis acids.[35,36] When cyclopentanone was treated with TMSD (**1.1**) under Shioiri's standard conditions,[30] an overall 35% yield was obtained with a poor product distribution (64% cyclohexanone, 23% cycloheptanone, 10% cyclooctanone, 3% epoxide). By switching to trimethylaluminum (Scheme 1.10), a substantially higher 68% overall yield was obtained with an improved product distribution (96% cyclohexanone). In a comparable manner to boron-based Lewis acids, alkylaluminum compounds were previously reported to afford decomposition products when treated with diazomethane.[37] Yamamoto found that it was essential to pre-mix the ketone and aluminum reagent for productive reactions to occur.



Scheme 1.10: Improved product distributions with aluminum-based Lewis acids.

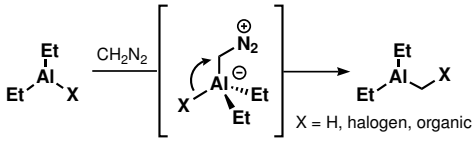
[33]For a note on the safety of TMSD see: Shioiri, T.; Aoyama, T.; Mori, S. Trimethylsilyldiazomethane. *Org. Synth.* **1990**, *68*, 1.

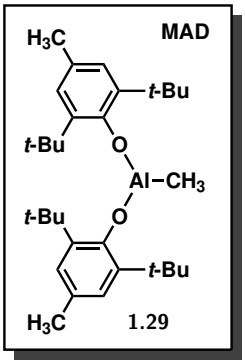
[34]Kemsley, J. N. Firm Fined For Chemist's Death. *Chem. Eng. News* **2011**, *89*, 15.

[35](a) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. Selective Homologation of Ketones and Aldehydes with Diazoalkanes Promoted by Organoaluminum Reagents. *Synthesis.* **1994**, 1283-1290. (b) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. Organoaluminum-Promoted Homologation of Ketones with Diazoalkanes. *J. Org. Chem.* **1994**, *59*, 4725-4726.

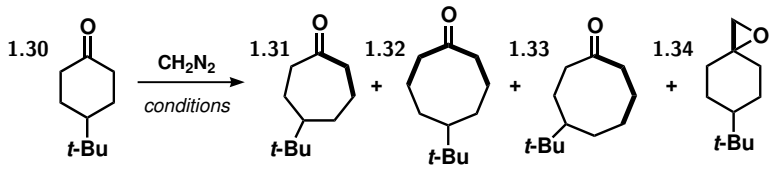
[36]An earlier report by Müller and Bauer discussed the use $AlCl_3$. Müller, E.; Bauer, M. Untersuchungen an Diazomethanen, XVI. Katalysierte Homologisierung cycloaliphatischer und aliphatischer Ketone mit Diazoalkanen. *Liebigs Ann. Chem.* **1962**, *654*, 92-111.

[37]Hoberg, H. Preparation and Rearrangement of Allylalanes. *Angew. Chem. Int. Ed.* **1966**, *5*, 513-514.





While trimethylaluminum was highly effective with TMSD (Scheme 1.10), reactions with diazomethane afforded less desirable product distributions. To improve reaction efficiency and broaden scope, Yamamoto began modifying the steric and electronic environment around the aluminum center. When MAD (**1.29**) was utilized as the promoter,[38] excellent yields with minimal side products derived from overhomologation or epoxidation were observed (Table 1.3). Homologation of 4-*tert*-butylcyclohexanone (**1.30**) proceeded cleanly with MAD, affording a 95% combined yield of all products with the desired singly homologated cycloheptanone **1.31** accounting for 84% of the recovered material (entry 4).

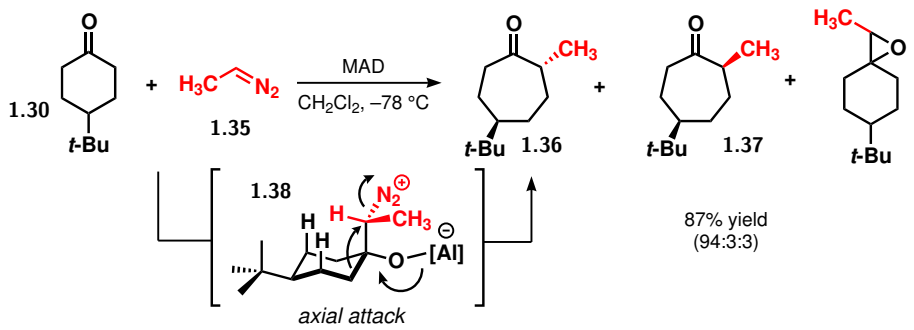


entry	promoter	solvent	temp. (°C)	yield (%)	**1.31**:**1.32**:**1.33**:**1.34**
1	CH_3OH	Et_2O	0	63	50 : 25 : 25 : 0
2	*i*-Bu_3Al	CH_2Cl_2	−78	68	54 : 22 : 22 : 2
3	$(CH_3)_3Al$	CH_2Cl_2	−78	70	66: 15 : 15 : 4
4	MAD (**1.29**)	CH_2Cl_2	−78	95	84 : 3 : 3 : 10

Table 1.3: Highly selective reactions with bulky aluminum Lewis acids.

In an effort to further expand the reaction scope, Yamamoto and coworkers also explored insertion reactions with a number of substituted diazoalkanes. With substituted diazoalkanes and substrates containing an existing prochiral or stereogenic center, Yamamoto reported some of the first diastereoselective diazo insertion reactions. When 4-*tert*-butylcyclohexanone (**1.30**) was combined with diazoethane (**1.35**) in the presence of 1.2 equivalents of MAD (**1.29**), a highly efficient union produced predominantly the *trans*-

[38] Readily prepared *in situ* by pre-mixing trimethylaluminum and 2 equivalents of BHT. See reference 35 for details.



Scheme 1.11: Diastereoselective insertion of diazoethane into 4-*tert*-butylcyclohexanone.

cycloheptanone **1.36** in an isolated 82% yield (87% combined) with >30:1 diastereoselectivity (Scheme 1.11).[39] The high diastereoselectivity may be accounted for by a model involving axial approach of diazoethane in an orientation that places the diazo α-proton over the six-membered ring (**1.38**). A least motion collapse of the anti-periplanar C−C bond, assuming no free rotation once the diazoalkane has added, correctly predicts the major diastereomer. Applying the same analysis with an equatorial approach of the diazo nucleophile leads to the minor *cis* diastereomer ($\longrightarrow$ **1.37**).

1.2.3 *Catalysis of Diazoalkane Ring Expansions*

Early work by House[27] and Shiori[30] demonstrated that diazoalkane insertion reactions may be effectively promoted by stoichiometric quantities of $BF_3 \cdot Et_2O$. In Yamamoto's later work with aluminum-based Lewis acids, turnover was never observed, presumably due to the high oxophilicity of aluminum.[35] For over a decade, Yamamoto's work would remain state of the art.[40] Regardless of the lack of catalytic turnover, Yamamoto's work illustrated some of the most selective and highest yielding diazoalkane ring expansion reactions recorded to date.

[39] The *cis*/*trans* configuration of 2-methyl-5-*tert*-butylcycloheptanone was established by equilibration in methanolic $NaOCH_3$.

[40] Johnson and coworkers observed some catalytic turnover with fluoroboric acid or boron trifluoride in the context of α,β-unsatured ketone substrates. Johnson, W. S.; Neeman, M.; Birkeland, S. P.; Fedoruk, N. A. The Acid-catalyzed Reaction of Diazomethane with Some α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **1962**, *84*, 989-992.

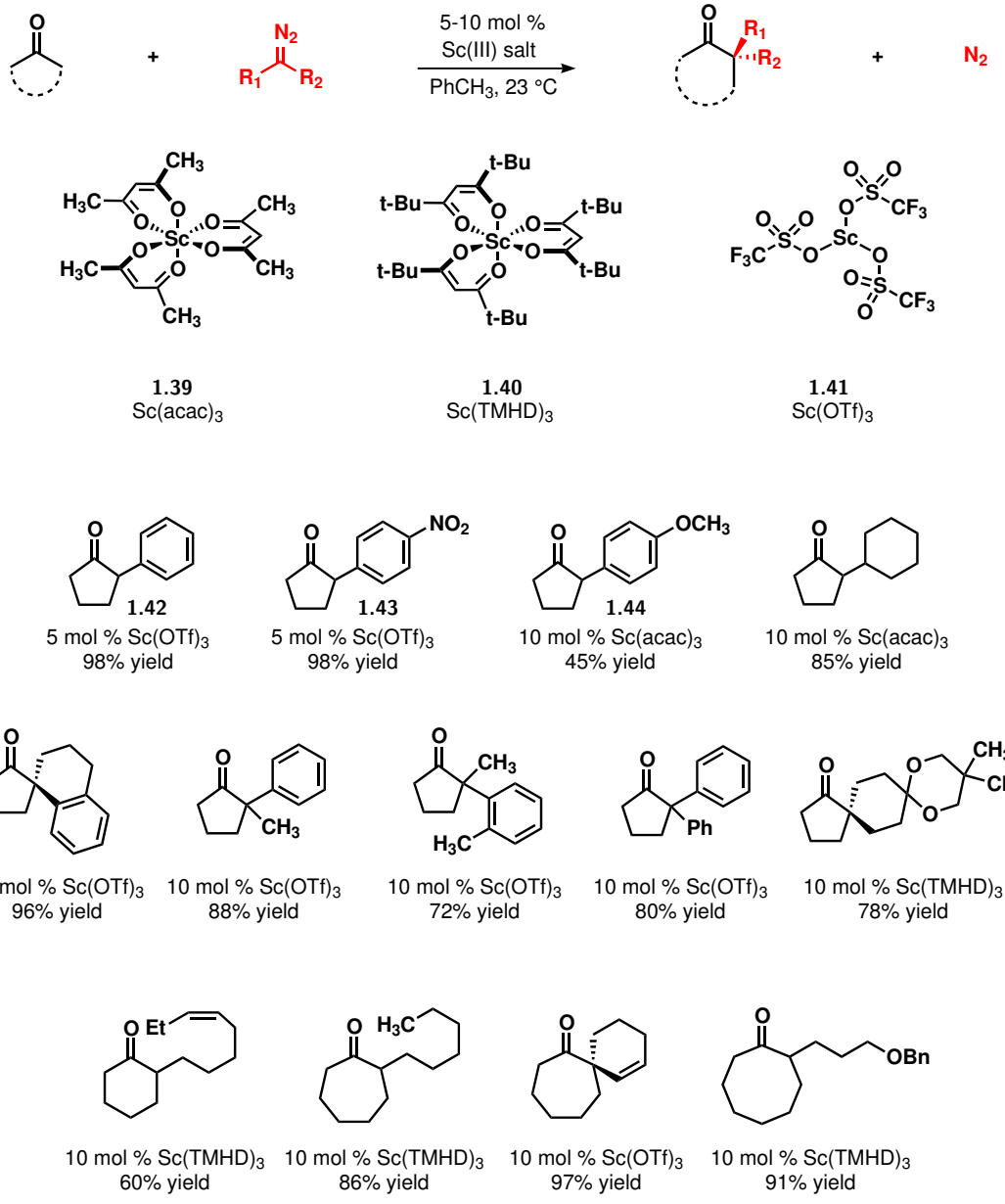
In 2006, work in the Kingsbury research group opened with a search for a broadly applicable and catalytic non-stabilized diazoalkane ring expansion reaction.[41] A wide array of potential aluminum– and boron-based catalysts were evaluated first based on literature precedents, but catalytic turnover was not observed in all cases tested.[42] A survey of potential H-bond donors (alcohols, biphenols, diols, ureas, thioureas, etc. . .) was also carried out, again with the same discouraging results. A screen of lanthanide triflates was conducted and led to a highly rewarding discovery. When cyclobutanone was exposed to phenyldiazomethane in the presence of 5 mol % $Sc(OTf)_3$, a rapid union occured to deliver the target compound 2-phenylcyclopentanone in a near quantitative yield ($\longrightarrow$ **1.42**, Scheme 1.12). The new scandium-catalyzed reaction also did not produce any of the common epoxide byproducts, but instead proceeded cleanly, producing the desired product and nitrogen gas as the only stoichiometric byproduct. At the time, no special precautions were taken to dry the commercial scandium salt, so a control reaction was conducted to rule out protic catalysis. Exposure of cyclobutanone and phenyldiazomethane to 1 mol % triflic acid in toluene at 23 °C did not produce any of the desired homologation product, but instead lead exclusively to diazoalkane decomposition.[43]

Pleased with this new discovery, the substrate scope with aryl-substituted diazoalkanes and cyclobutanone was examined in greater detail. Steric modification of the diazoalkane was readily tolerated, as both α-tertiary and α-quaternary centers were readily produced. Switching to an electron poor aromatic (p-NO_2) had little effect on the isolated yield ($\longrightarrow$ **1.43**, 98% yield). The more electron rich p-OCH_3 susbstituted diazoalkane required a less Lewis acidic $Sc(acac)_3$ (**1.39**) catalyst and still afforded a diminished yield

[41] Moebius, D. C.; Kingsbury, J. S. Catalytic Homologation of Cycloalkanones with Substituted Diazomethanes. Mild and Efficient Single-Step Access to α-Tertiary and α-Quaternary Carbonyl Compounds. *J. Am. Chem. Soc.* **2009**, *131*, 878-879.

[42] Moebius, D. C. Development of Sc(III)-Catalyzed Homologation of Ketones by Non-Stabilized Diazomethanes. Ph.D. Dissertation, Boston College, Chestnut Hill, MA, 2011.

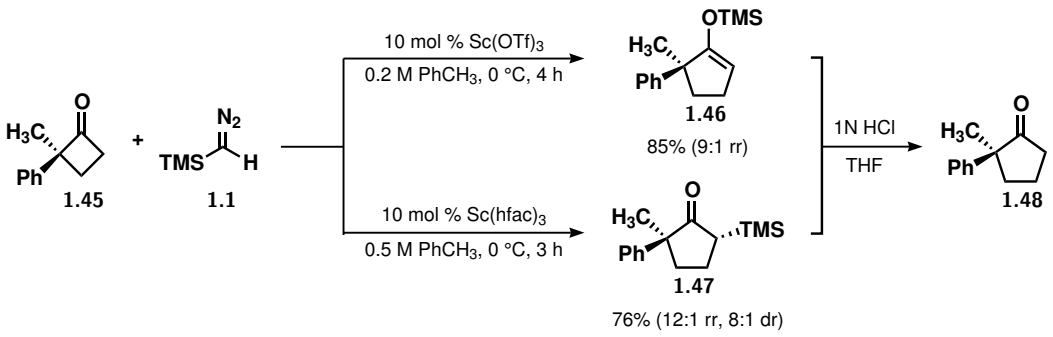
[43] The material recovered consisted of an approximately 1:1 *E:Z* mixture of stilbene.



Scheme 1.12: Efficient catalysis of diazoalkane insertions with scandium (III) salts.

of the product($\longrightarrow$ **1.44**, 45% yield).[44] The *p*-OCH_3 substituted phenyldiazomethane is highly unstable and known to decompose at temperatures as low as -80 °C.[45] To further broaden the utility of the newly discovered scandium catalysis, an examination of more reactive alkyl-substituted diazoalkanes was carried out. The highest yields were obtained with the weaker and more sterically hindered Lewis acid $Sc(TMHD)_3$ (**1.40**). Moderate to high yields were obtained for a number of different ring sizes and diazo substitution patterns.

The substrates first tested under catalytic conditions were all symmetrical cycloalkanones. In a subsequent report, differentially substituted cycloalkanones were examined in the context of regioselective single-carbon homologations (Scheme 1.13).[46] When α,α-disubstituted cyclobutanone **1.45** was treated with TMSD in the presence of 10 mol % scandium triflate, silyl enol ether **1.46** was obtained in an 85% isolated yield as a single compound (9:1 regioselectivity from crude ^{1}H NMR spectroscopy). In constrast to previously discussed methods, the intermediate silyl enol ether could be purified by chromatography



Scheme 1.13: Regioselective scandium catalyzed single carbon ring expansion.

[44] Milder Lewis acids (**1.39** or **1.40**) were substituted in reactions with more labile diazoalkanes because of the ability of Lewis acids to promote diazo decomposition. See reference 35a and references within for details.

[45] Fulton, J. R.; Aggarwal, V. K.; De Vicente, J. The Use of Tosylhydrazone Salts as a Safe Alternative for Handling Diazo Compounds and Their Applications in Organic Synthesis. *Eur. J. Org. Chem.* **2005**, *2005*, 1479-1492.

[46] Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. Catalytic and Regioselective Ring Expansion of Arylcyclobutanones with Trimethylsilyldiazomethane. Ligand-Dependent Entry to β-Ketosilane or Enolsilane Adducts. *Org. Lett.* **2010**, *12*, 3598-3601.

and isolated, providing access to a synthetically useful functional handle. Dilute acid hydrolysis in THF delivered the cyclopentanone **1.48** in high yield. Monitoring of the reaction *in situ* with ReactIR revealed a dual role for $Sc(OTf)_3$, first catalyzing a rapid insertion of TMSD to produce **1.47**. The initial insertion product was then gradually converted to **1.46** through a 1,3-Brook[32] rearrangement. By switching the catalyst to the milder $Sc(hfac)_3$, the reaction was effectively terminated at **1.47**, allowing the β-keto silane to be isolated in a 76% yield.

The seminal report from the Kingsbury group in 2009[41] disclosed the first *catalytic* ring expansion reactions with substituted diazoalkanes.[47] Subsequent studies showed that the new conditions were amenable to regioselective single-carbon ring expansions, as well as regioselective aldehyde homologations.[48] The new scandium-catalyzed reactions offered significant advantages over previous methods. Not only were the reactions catalytic, the conditions were milder and the product distributions were more favorable. Ring expansion products could be obtained in relatively short reaction times and in high yields with high levels of regiocontrol.

[47] The Maruoka group reported substoichiometric carbonyl-stabilized diazoalkane insertion reactions with boron and aluminum Lewis acids around the same time. (a) Hashimoto, T.; Naganawa, Y.; Maruoka, K. Stereoselective Construction of Seven-Membered Rings with an All-Carbon Quaternary Center by Direct Tiffeneau–Demjanov-type Ring Expansion. *J. Am. Chem. Soc.* **2009**, *131*, 6614-6617. (b) Hashimoto, T.; Naganawa, Y.; Maruoka, K. Desymmetrizing Asymmetric Ring Expansion of Cyclohexanones with α-Diazoacetates Catalyzed by Chiral Aluminum Lewis Acid. *J. Am. Chem. Soc.* **2011**, *133*, 8834-8837.

[48] Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. Diverse Alkanones by Catalytic Carbon Insertion into the Formyl C-H Bond. Concise Access to the Natural Precursor of Achyrofuran. *Org. Lett.* **2009**, *11*, 3202-3205.

1.3 Conclusion and Outlook

While the hazards of diazoalkanes may deter many chemists from using these powerful reagents, work is already underway to find creative ways of generating these compounds for use *in situ*.[49] As methodologies mature and their potential is realized, chemists will no longer be able to ignore diazoalkanes when thinking about strategies to access new molecules. Ring expansion of ketones is only one small area where diazoalkanes find use, and significant advances have been made over the past 125 years. Someday chemists may be able to insert a fully substituted carbon atom adjacent a carbonyl with complete regio– and stereochemical control using exceptionally low catalyst loadings. In the two chapters that follow, further advances to ring expansion chemistry are presented that begin to address that ultimate goal. Chapter 2 will discuss progress made toward the development of a highly enantioselective homologation reaction with monoarylated diazomethanes. Chapter 3 presents advances made with regioselective single-carbon methylene insertion that now allow catalytic reactions to be performed on complex targets with regioselectivities of >20:1 in certain cases.

[49]For lead references see reference 45 and Kirmse, W. Reactive Intermediates from *N*-Aziridinylimines. *Eur. J. Org. Chem.* **1998**, *1998*, 201-212.

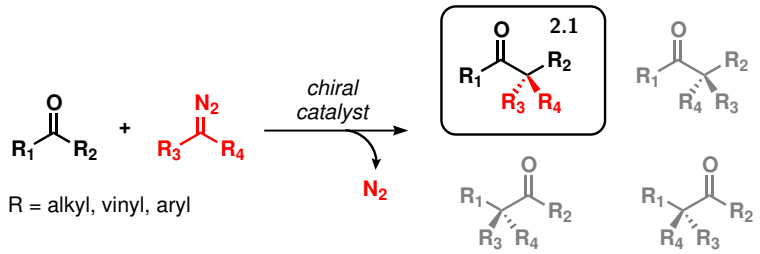
Chapter

2

Development of Sc(III)-Catalyzed Asymmetric Homologation of Cycloalkanones with Non-Stabilized Diazoalkanes

2.1 Introduction

In previous work, we had demonstrated that scandium (III) salts function as highly effective catalysts for the diazoalkane carbonyl homologation reaction.[1] Given the success of these early reactions, we were eager to begin developing a general catalytic enantioselective version of the reaction. In the ideal transformation, a generic ketone, when combined with a chiral scandium catalyst and diazoalkane would undergo a regio– and stereoselective union to deliver a new homologated ketone ($\longrightarrow$ **2.1**, Scheme 2.1). We believed it would be logical to start by extending the ring expansion of symmetrical cycloalkanones to stereoselective insertion reactions.[2] By starting from symmetrical cycloalkanones of the appropriate



Scheme 2.1: General catalytic regio– and enantioselective diazoalkane insertion.

ring size,[3] the classic problems of regiochemical control could be removed and issues with overhomologation could be minimized initially. The ultimate goal of the project was to develop general methods for the construction alkyl, vinyl, and aryl bearing stereogenic centers

[1] See chapter 1 for a more thorough discussion. (a) Moebius, D. C.; Kingsbury, J. S. Catalytic Homologation of Cycloalkanones with Substituted Diazomethanes. Mild and Efficient Single-Step Access to α-Tertiary and α-Quaternary Carbonyl Compounds. *J. Am. Chem. Soc.* **2009**, *131*, 878-879. (b) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. Diverse Alkanones by Catalytic Carbon Insertion into the Formyl C-H Bond. Concise Access to the Natural Precursor of Achyrofuran. *Org. Lett.* **2009**, *11*, 3202-3205. (c) Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. Catalytic and Regioselective Ring Expansion of Arylcyclobutanones with Trimethylsilyldiazomethane. Ligand-Dependent Entry to β-Ketosilane or Enolsilane Adducts. *Org. Lett.* **2010**, *12*, 3598-3601.

[2] Rendina, V. L.; Moebius, D. C.; Kingsbury, J. S. An Enantioselective Synthesis of 2-Aryl Cycloalkanones by Sc-Catalyzed Carbon Insertion. *Org. Lett.* **2011**, *13*, 2004-2007.

[3] The order of reactivity for the ring expansion of cycloalkanones with diazomethane based on literature precedents and qualitative observations is: cyclobutanone $\approx$ cyclohexanone $>$ cycloheptanone $>$ cyclopentanone. Gutsche, C. D. The Reaction of Diazomethane and Its Derivatives with Aldehydes and Ketones. *Org. React.* **1954**, *8*, 364-403.

adjacent to the carbonyl functionality.

We felt confident that by combining scandium (III) salts with the correct chiral ligand, the catalyst ligand complex would efficiently direct the stereochemical outcome of the newly forged C−C bonds. A survey of the Cambridge Structural Database[4] revealed four crystal structures containing chiral ligands bound to scandium triflate. Among the most well characterized and widely studied are the scandium PyBOX complexes reported by the Evans' group (**2.2** and **2.3**, Figure 2.1).[5] Both structures show scandium bound with an additional water molecule (omitted from the line drawings for clarity), bringing the coordination number to seven. Two additional scandium triflate structures, one based on a proline-derived *N*-oxide ligand (**2.4**)[6] and one based on a BINOL ligand framework[7] were reported in 2009 and 2010, respectively. A wider search revealed a fifth chiral scandium complex, containing $ScBr_3$ complexed with a bipyridine-based ligand (**2.5**).[8]

Three of the four structures in Figure 2.1 contain a seven coordinate pentagonal bipyramidal metal geometry. Scandium (III), because of its filled valence shell and lack of *d* electrons, tends to adopt coordination geometries that are based primarily on steric constraints rather than traditional orbital overlap based geometries observed for the transition metals.[9] The literature clearly shows precedents for scandium to form well-defined and com-

[4]Cambridge Structural Database (WebCSD). http://webcsd.ccdc.cam.ac.uk.proxy.bc.edu (accessed Jan 25, 2013).

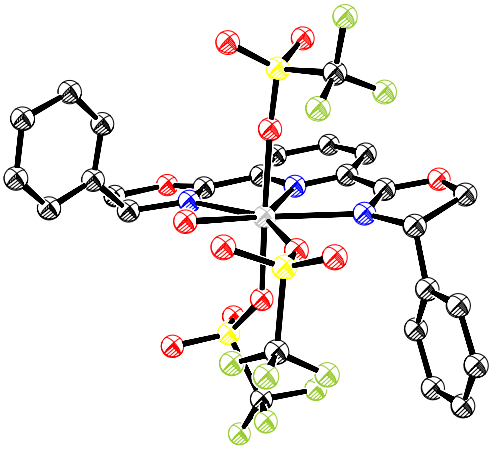
[5](a) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. Highly Enantioselective Syntheses of Homopropargylic Alcohols and Dihydrofurans Catalyzed by a Bis(oxazolinyl)pyridine–Scandium Triflate Complex. *J. Am. Chem. Soc.* **2001**, *123*, 12095-12096. (b) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. Enantioselective Indole Friedel-Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine–Scandium(III) Triflate Complexes. *J. Am. Chem. Soc.* **2003**, *125*, 10780-10781.

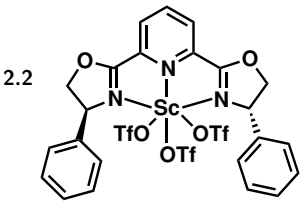
[6]Liu, Y.; Shang, D.; Zhou, X.; Liu, X.; Feng, X. Enantioselective Friedel-Crafts Alkylation of Indoles with Alkylidene Malonates Catalyzed by *N*,*N*-Dioxide-Scandium(III) Complexes: Asymmetric Synthesis of *β*-Carbolines. *Chem. Eur. J.* **2009**, *15*, 2055-2058.

[7]Di Bari, L.; Di Pietro, S.; Pescitelli, G.; Tur, F.; Mansilla, J.; Saá, J. M. $[Ln(binolam)_3] \cdot (OTf)_3$, a New Class of Propeller-Shaped Lanthanide(III) Salt Complexes as Enantioselective Catalysts: Structure, Dynamics and Mechanistic Insight. *Chem. Eur. J.* **2010**, *16*, 14190-14201.

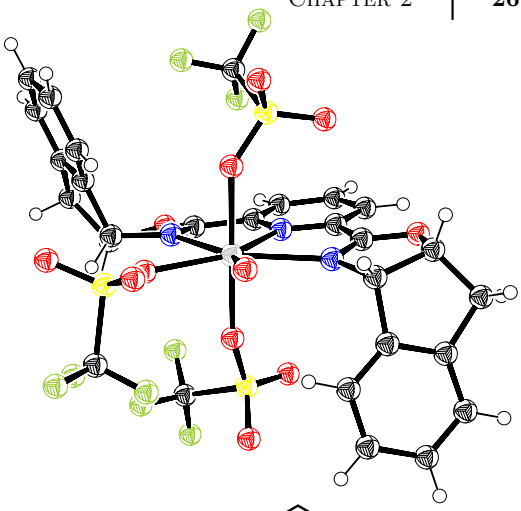
[8]Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. Catalytic Asymmetric Hydroxymethylation of Silicon Enolates Using an Aqueous Solution of Formaldehyde with a Chiral Scandium Complex. *J. Am. Chem. Soc.* **2004**, *126*, 12236-12237.

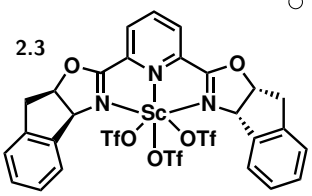
[9]Wu, J. Enantioselective Lanthanide-Catalyzed Mukaiyama Aldol, Carbonyl-Ene, Sakurai-Hosomi, and Quinone Diels-Alder Reactions. Ph.D. Dissertation, Harvard University, Cambridge, MA, 2005.



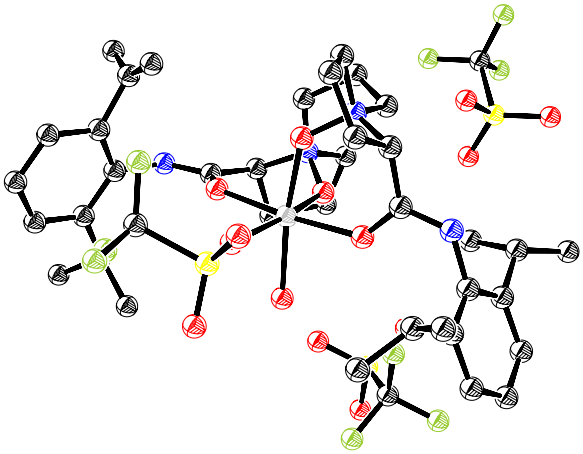


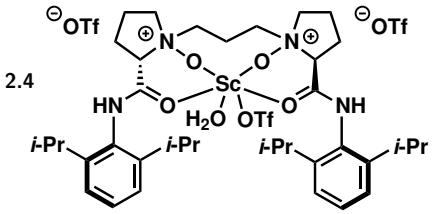
Evans **2001**[5a]



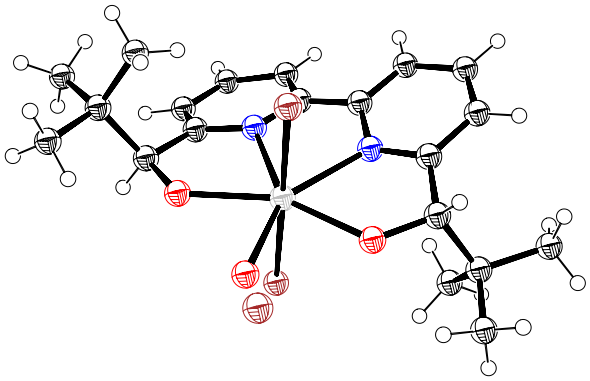


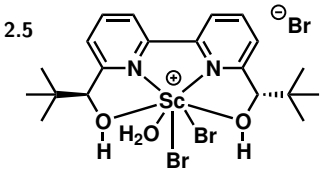
Evans **2003**[5b]





Feng **2009**[6]





Kobayashi **2004**[8]

Figure 2.1: Crystal structures of selected chiral scandium complexes.

petent chiral catalysts. Chiral scandium complexes have been used to catalyze a number of asymmetric C−C bond forming reactions.[10]

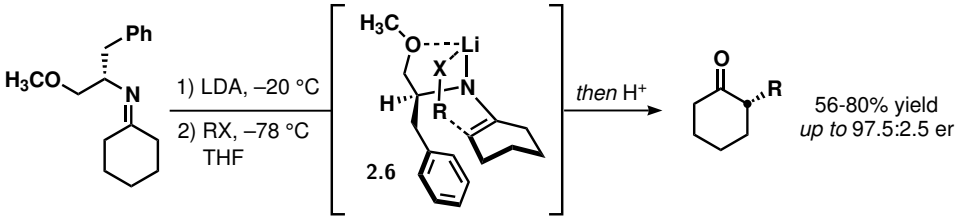
In the sections that follow, an account of how we developed the first catalytic asymmetric diazoalkane carbon insertion reactions is presented. The crystallographic data from the literature suggests a logical starting point for the development of a new method based on chiral scandium complexes. Ligand constructs known to form competent catalysts with Sc(III) salts would be among the first screened for asymmetric induction. Before discussing experimental details, a brief background on alternative methods for the synthesis of α-substituted cycloalkanones is given.

[10]For reviews see: (a) Kobayashi, S. Scandium Triflate in Organic Synthesis. *Eur. J. Org. Chem.* **1999**, 15-27. (b) Mikami, K.; Terada, M.; Matsuzawa, H. "Asymmetric" Catalysis by Lanthanide Complexes. *Angew. Chem. Int. Ed.* **2002**, *41*, 3512-3554. (c) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. L. Rare-Earth Metal Triflates in Organic Synthesis. *Chem. Rev.* **2002**, *102*, 2227-2302.

2.2 Methods for Asymmetric α-Functionalization of Cycloalkanones

2.2.1 *Construction of α-Tertiary Centers*

One of the most common methods for C−C bond construction involves the α-functionalization of ketone enolates. Some of the first sucessful methods for α-functionalized of cycloalkanes in a stereocontrolled fashion relied extensively on the pre-formation of chiral imines or hydrazones. In 1976, Meyers and coworkers reported a highly enantioselective synthesis of 2-alkyl substituted cyclohexanones through the formation of a lithio-chelated enamine nucleophile (**2.6**, Scheme 2.2).[11] Upon treatment with an alkyl electrophile, a stereoselective trap of the electrophile lead to products in up to 97.5:2.5 er after careful imine hydrolysis. The introduction of a chelating methyl ether moiety rigidified the proposed metalloenamine intermediate **2.6** and led to much higher levels of stereocontrol than previous reports with imines that lacked an additional chelating group.[12]



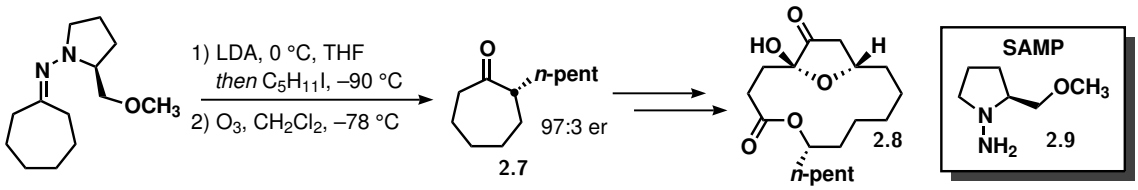
Scheme 2.2: Meyers auxiliary based approach for α-alkylation.

Around the time of Meyers work, the Enders group introduced the proline derived chiral auxiliary (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP, **2.9**, Scheme 2.3), which contained a very similar chelating functional group.[13] The SAMP auxiliary and related

[11] Meyers, A. I.; Williams, D. R.; Druelinger, M. Enantioselective Alkylation of Cyclohexanone via Chiral Lithio-Chelated Enamines. *J. Am. Chem. Soc.* **1976**, *98*, 3032-3033.

[12] (a) Mea-Jacheet, D.; Horeau, A. Asymmetric Synthesis and Optical purity of 2-Methylcyclohexanone. *Bull. Soc. Chim. Fr.* **1968**, 4571-4573. (b) Kitamoto, M.; Hiroi, K.; Terashima, S. Stereochemical Studies. XXIX. Asymmetric Synthesis of 2-Alkylcyclohexanones via Optically Active Lithioenamines. *Chem. Pharm. Bull.* **1974**, *22*, 459-464.

[13] Enders, D.; Eichenauer, H. Asymmetric Synthesis of α-Substituted Ketones by Metalation and Alkylation of Chiral Hydrazones. *Angew. Chem. Int. Ed.* **1976**, *15*, 549-551.



Scheme 2.3: Application of Ender's SAMP auxiliary in total synthesis.

derivatives have been widely utilized for their often very high and predictable levels of stereoinduction and for their mild and varied means of cleavage.[14] In the context of a cycloheptanone substrate, the Holmes group sucessfully applied a SAMP hydrazone alkylation strategy to their enantioselective synthesis of (−)-gloeosporone (⟶ **2.8**, Scheme 2.3).[15] Cleavage of the auxiliary was achieved by treatment with ozone at low temperature, delivering the target cycloheptanone **2.7** in 97:3 er.

More modern strategies have focused on the use of chiral catalysts to control stereochemistry, which foregoes the need to pre-install a costly chiral auxiliary in the substrate. The formation of an α-tertiary center requires control over either the installation of the α-substituent through an asymmetric alkylation event or control over installation of the α-hydrogen. Aside from stoichiometric auxiliary-based approaches, catalytic methods for enolate alkylation based on phase transfer catalysts[16] and chiral lithium enolates[17] have also been demonstrated. Alternative approaches have examined catalytic methods for the installation of an α-hydrogen through an enantioselective enolate protonation event.[18] Achieving stereocontrol while delivering a group as small as a proton has been a significant challenge

[14]For a recent review see: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. The SAMP-/RAMP-Hydrazone Methodology in Asymmetric Synthesis. *Tetrahedron* **2002**, *58*, 2253-2329.

[15]Curtis, N. R.; Holmes, A. B.; Looney, M. G.; Pearson, N. D.; Slim, G. C. Synthesis of (−)-Gloeosporone. *Tetrahedron Lett.* **1991**, *32*, 537-540.

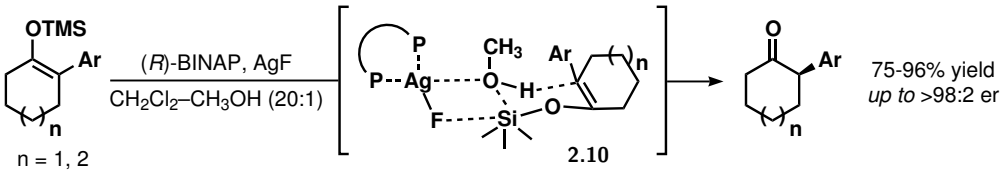
[16]Dolling, U. H.; Davis, P.; Grabowski, E. J. J. Efficient Catalytic Asymmetric Alkylations. 1. Enantioselective Synthesis of (+)-Indacrinone *via* Chiral Phase-Transfer Catalysis. *J. Am. Chem. Soc.* **1984**, *106*, 446-447.

[17]Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. Catalytic Asymmetric Benzylation of Achiral Lithium Enolates Using a Chiral Ligand for Lithium in the Presence of an Achiral Ligand. *J. Am. Chem. Soc.* **1994**, *116*, 8829-8830.

[18]For a review see: Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. Enantioselective Protonation. *Nature Chem.* **2009**, *1*, 359-369.

and the subject of considerable research.

In 2005, the Yanagisawa group introduced an asymmetric protonation method utilizing a simple catalyst system derived from commercially available silver fluoride and (*R*)-BINAP.[19] Starting from a pre-formed silyl enol ether, face selective delivery of the proton from methanol was proposed to proceed through a silver fluoride BINAP complex that delivered methanol while concomitantly deprotecting the silyl ether (**2.10**, Scheme 2.4). High yields and near perfect enantioselectivities were observed across a range of 2-aryl substituted cyclic substrates. The Yamamoto group also demonstrated a very similar asymmetric protonation reaction with a comparable substrate scope using a non-commercial chiral phosphoric acid catalyst.[20]



Scheme 2.4: Yanagisawa's asymmetric protonation of silyl enol ethers.

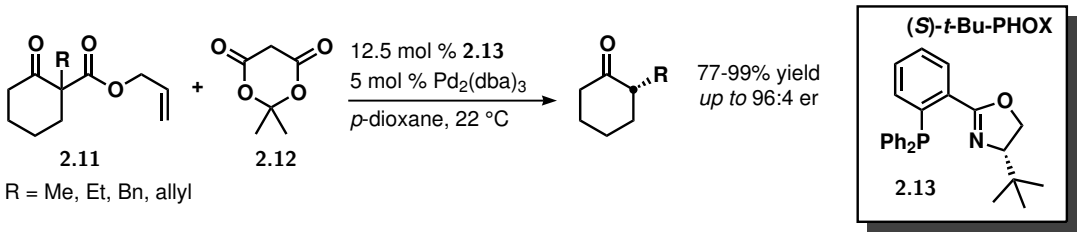
The Stoltz group has also examined enantioselective protonation reactions in the context of palladium enolates.[21] When a racemic allyl β-ketoester (**2.11**, Scheme 2.5) is combined with Pd(0) in the presence of PHOX ligand **2.13**, oxidative addition to the allyl group followed by decarboxylation furnishes a chiral palladium enolate intermediate. By adding a superstoichiometric amount of Meldrum's acid (**2.12**, 2.5 equiv), the reaction can be effectively interrupted before reductive elimination to deliver α-tertiary substituted cycloalkanones in high yields and enantioselectivities. The catalytic cycle is closed by ulti-

[19] Yanagisawa, A.; Touge, T.; Arai, T. Enantioselective Protonation of Silyl Enolates Catalyzed by a Binap · AgF Complex. *Angew. Chem. Int. Ed.* **2005**, *44*, 1546-1548.

[20] Cheon, C. H.; Yamamoto, H. A Brønsted Acid Catalyst for the Enantioselective Protonation Reaction. *J. Am. Chem. Soc.* **2008**, *130*, 9246-9247.

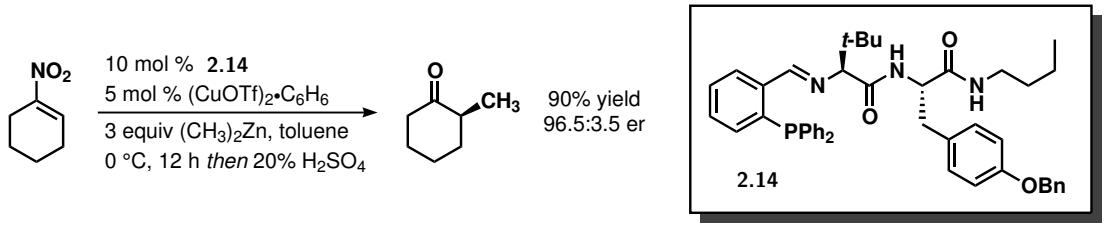
[21] (a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. Catalytic Enantioselective Decarboxylative Protonation. *J. Am. Chem. Soc.* **2006**, *128*, 11348-11349. (b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. Homogeneous Pd-Catalyzed Enantioselective Decarboxylative Protonation. *Org. Lett.* **2008**, *10*, 1039-1042.

mately delivering the allyl fragment to the Meldrum's acid enolate, regenerating the Pd(0) catalyst.



Scheme 2.5: Stoltz's asymmetric protonation of Pd-enolates.

Another strategy, not based on enolate alkylation or asymmetric protonation, was developed by the Hoveyda group. Enantioselective conjugate addition of alkylzinc reagents to nitroalkenes catalyzed by a chiral copper complex, followed by acidic Nef hydrolysis, affords α-tertiary substituted cycloalkanones (Scheme 2.6).[22] The hydrolysis, carried out in a subsequent step with 20% aqueous sulfuric acid, leads to minimal racemization of the products. Notably, the method was amenable to the synthesis of a variety of ring sizes and high levels of enantioselectivity were observed from 5 to 12 membered rings.

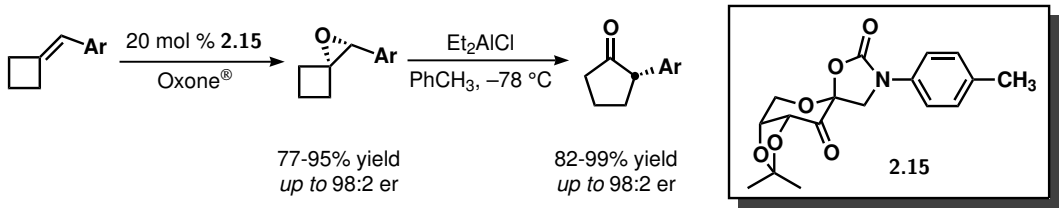


Scheme 2.6: Hoveyda's conjugate addition to nitroalkenes.

The Shi group introduced a two-step protocol to access optically active 2-aryl cyclopentanones using an enantioselective epoxidation of cyclobutylidene olefins (Scheme 2.7).[23] Treatment of trisubstituted cyclobutylidene olefins with catalyst **2.15** in the presence of

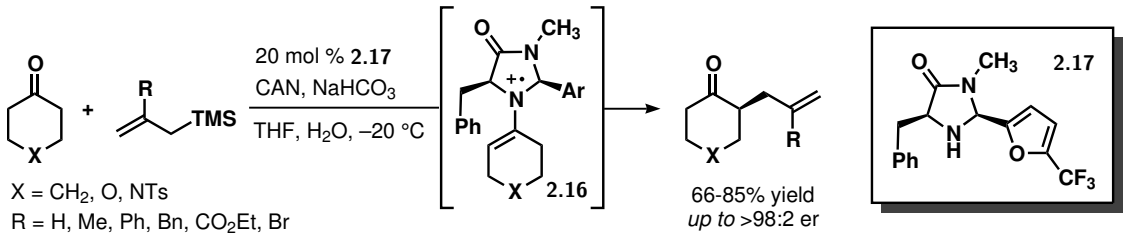
[22] Luchaco-Cullis, C. A.; Hoveyda, A. H. Cu-Catalyzed Enantioselective Conjugate Addition of Alkylzincs to Cyclic Nitroalkenes: Catalytic Asymmetric Synthesis of Cyclic α-Substituted ketones. *J. Am. Chem. Soc.* **2002**, *124*, 8192-8193.

[23] Shen, Y.-M.; Wang, B.; Shi, Y. Enantioselective Synthesis of 2-Aryl Cyclopentanones by Asymmetric Epoxidation and Epoxide Rearrangement. *Angew. Chem. Int. Ed.* **2006**, *45*, 1429-1432.



Scheme 2.7: Shi's asymmetric epoxidation / rearrangement strategy.

Oxone® delivered the intermediate chiral epoxides in high yields and enantioselectivities. Upon exposure of the epoxides to Et_2AlCl, a facile and highly selective rearrangement to the 2-aryl substituted cyclopentanones occurred. Shi also showed that by simply adding lithium iodide during the Lewis-acid mediated rearrangement, the opposite enantiomer of the cyclopentanones could be obtained with high stereochemical fidelity. This obviates the need to synthesize the opposite enantiomer of catalyst **2.15**, which can often be challenging if the source of chirality is ultimately derived from a chiral pool molecule. This method was extended to the synthesis of α-quaternary cyclopentanones by starting from tetrasubstituted cyclobutylidene olefins.[24]



Scheme 2.8: Asymmetric allylation with MacMillan's SOMO catalysis.

In 2010 MacMillian reported an intriguing new organocatalytic allylation method (Scheme 2.8).[25] Treatment of unfunctionalized cycloalkanones with **2.17** and CAN facilitates access to a unique three electron π-system (**2.16**) through a single electron oxidation event. Face-

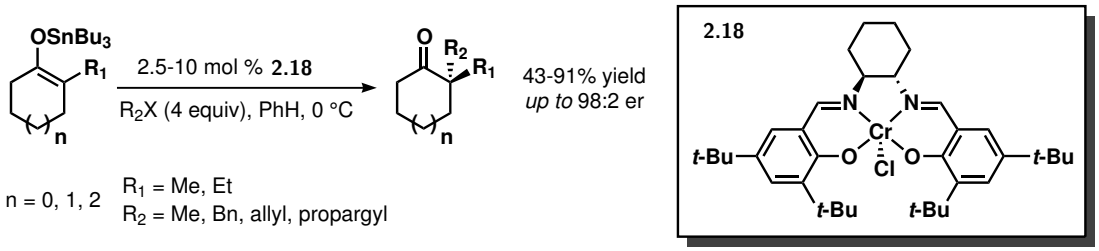
[24]Shen, Y.-M.; Wang, B.; Shi, Y. Enantioselective Synthesis of 2-Alkyl-2-Aryl Cyclopentanones by Asymmetric Epoxidation of Tetrasubstituted Cyclobutylidene Olefins and Epoxide Rearrangement. *Tetrahedron Lett.* **2006**, *47*, 5455-5458.

[25]Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; MacMillan, D. W. C. Direct and Enantioselective α-Allylation of Ketones *via* Singly Occupied Molecular Orbital (SOMO) Catalysis. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20648-20651.

selective radical coupling with substituted allyl trimethylsilanes lead directly to α-tertiary substituted chiral cycloalkanones with excellent enantioselectivity.

2.2.2 *Construction of α-Quaternary Centers*

The construction of quaternary centers, especially those possessing all-carbon substituents, presents a significant and ongoing challenge for synthetic chemists.[26] In their seminal work, Doyle and Jacobsen demonstrated a highly enantioselective catalytic asymmetric alkylation of tin enolates to form products bearing all-carbon quaternary centers (Scheme 2.9).[27] Tetrasubstituted tin enolates underwent smooth conversion to the α-quaternary cycloalkanones upon treatment with chromium salen complex **2.18** and an appropriate alkyl electrophile. Cycloalkanones of varying ring sizes were isolated in moderate to high yields with excellent levels of stereocontrol over the newly constructed C−C bond. Trisubstituted tin enolates that would lead to α-tertiary products decomposed under the reaction conditions and afforded products in low yields and modest enantioselectivities.

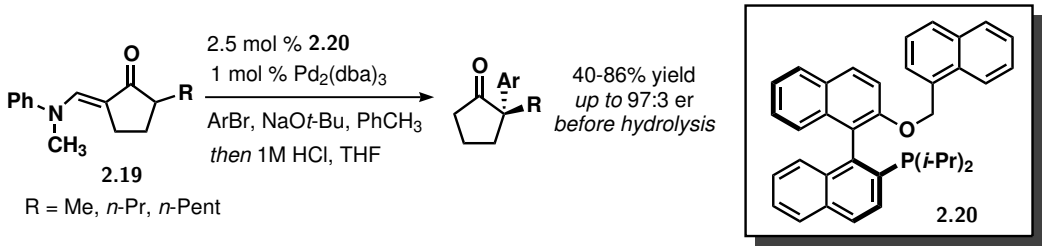


Scheme 2.9: Jacobsen's asymmetric alkylation of tin enolates.

[26] For a reviews on methods for all-carbon quaternary center construction see: (a) Trost, B. M.; Jiang, C. Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters. *Synthesis* **2006**, 369-396. (b) Douglas, C. J.; Overman, L. E. Catalytic Asymmetric Synthesis of All-Carbon Quaternary Stereocenters. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367.

[27] Doyle, A. G.; Jacobsen, E. N. Enantioselective Alkylations of Tributyltin Enolates Catalyzed by Cr(salen)Cl: Access to Enantiomerically Enriched All-Carbon Quaternary Centers. *J. Am. Chem. Soc.* **2005**, *127*, 62-63.

The Buchwald[28] and Hartwig[29] groups introduced similar cross-coupling strategies to access all-carbon quaternary centers containing an aromatic substituent. In Buchwald's approach, a two step sequence involving formylation and condensation to prepare an α' blocked vinylogous amide (**2.19**, Scheme 2.10) was necessary to prevent enolization and coupling from occuring on the left half of the molecule. Hartwig focused on indanone and tetralone substrates lacking enolizable α' protons (Scheme 2.11). Both methods utilized sodium *tert*-butoxide to generate a sodium enolate that transmetallated to a chiral Pd(II) or Ni(II) intermediate and ultimately underwent a stereoselective reductive elimination to forge the new C−aryl bond. Buchwald then cleaved the vinylogous amide protecting group through a dilute acid mediated retro-Claisen condensation. The primary differences between the two methods were in the choice of chiral ligand and aryl coupling partner. Buchwald later expanded the substrate scope to include vinyl electrophiles.[30]



Scheme 2.10: Buchwald's asymmetric arylation of α'-blocked cycloalkanones.

The Trost[31] and Stoltz[32] groups both developed palladium mediated enolate allylation

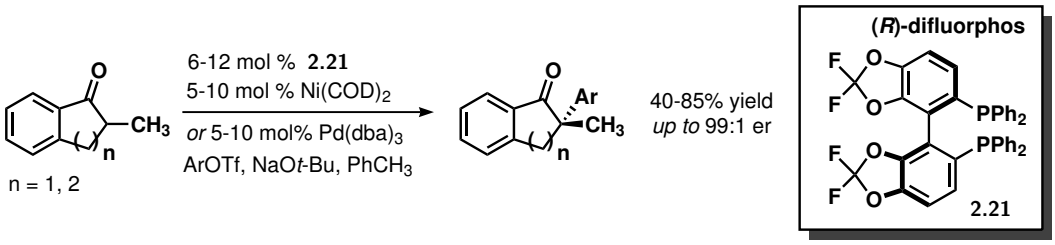
[28](a) Åhman, J.; Wolfe, J. P.; Troutman, M. V; Palucki, M.; Buchwald, S. L. Asymmetric Arylation of Ketone Enolates. *J. Am. Chem. Soc.* **1998**, *120*, 1918-1919. (b) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. An Improved Catalyst for the Asymmetric Arylation of Ketone Enolates. *J. Am. Chem. Soc.* **2002**, *124*, 1261-1268.

[29]Liao, X.; Weng, Z.; Hartwig, J. F. Enantioselective α-Arylation of Ketones with Aryl Triflates Catalyzed by Difluorphos Complexes of Palladium and Nickel. *J. Am. Chem. Soc.* **2008**, *130*, 195-200.

[30]Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. Catalytic Asymmetric Vinylation of Ketone Enolates. *Org. Lett.* **2001**, *3*, 1897-1900.

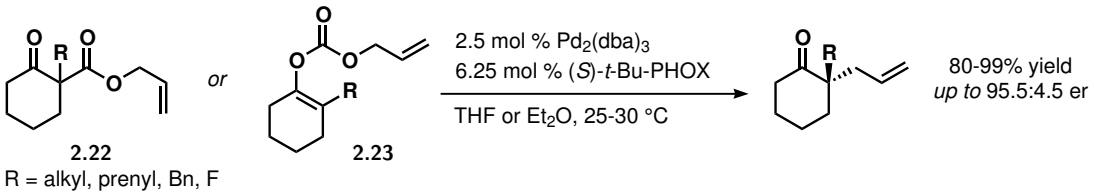
[31]Trost, B. M.; Schroeder, G. M. Palladium-Catalyzed Asymmetric Allylic Alkylation of Ketone Enolates. *J. Am. Chem. Soc.* **2004**, *121*, 6759-6760.

[32](a) Behenna, D. C.; Stoltz, B. M. The Enantioselective Tsuji Allylation. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. Deracemization of Quaternary Stereocenters by Pd-Catalyzed Enantioconvergent Decarboxylative Allylation of Racemic β-Ketoesters. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924-6927.



Scheme 2.11: Hartwig's asymmetric arylation of α'-blocked cycloalkanones.

methods that generate α-keto all-carbon quaternary centers. In Stoltz's work, starting from either the β-keto allyl ester (**2.22**, Scheme 2.12) or allyl enol carbonate (**2.23**) lead to the same intermediate chiral Pd(II) enolate. Reductive elimination with the allyl fragment furnished α-quaternary allyl substituted cycloalkanones in high yields with excellent levels of enantioselectivity. The mechanistic insight gained through the development of this process lead Stoltz to extend this metholodology to allow for the synthesis of α-tertiary centers through asymmetric protonation as discussed previously.[21]



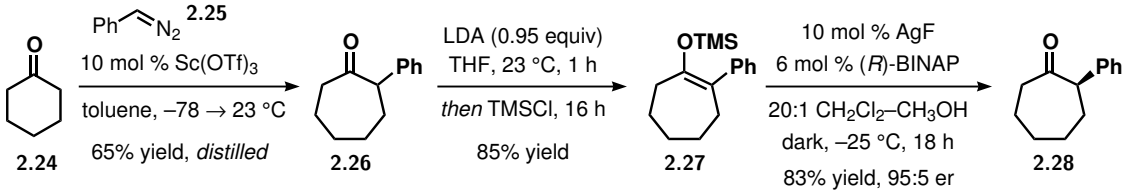
Scheme 2.12: Stoltz's asymmetric allylation of Pd-enolates.

With the exception of MacMillan's notable allylation reactions,[25] all of the previous examples required a multi-step sequence to install functional group handles that would be utilized in the key stereodefining reaction and then ultimately removed to access the target cycloalkanone products. We envisioned developing a general strategy to directly access a broad range of chiral α-substituted cycloalkanones in a single carbon insertion step with aryl–, vinyl–, and alkyl-substituted diazoalkanes. The versatility and prevalence of the ketone functional group justifies the development of methods complementary to those aforementioned.

2.3 Discovery of a Catalyst System for Asymmetric α-Arylation

We initially decided to target the enantioselective α-arylation of cycloalkanones for two primary reasons. The Brewer group had recently introduced a mild and operationally simple method for the synthesis of aryl-substituted diazoalkanes based on a modified Swern oxidation procedure.[33] A simple protocol for preparing the requisite diazoalkanes, coupled with the relative stability of aryl-substituted diazoalkanes,[34] made α-arylation an ideal proving ground for the first asymmetric insertion reactions.

In advance of looking at any catalytic asymmetric reactions, we wanted to run a control experiment to determine if the products of our reaction would retain their stereochemical information in the presence of scandium triflate. The Shi group reported earlier that α-aryl cyclopentanones readily racemize on silica gel, presumably through a rather facile enolization pathway.[23] We began by preparing an optically active sample of (*R*)-2-phenylcycloheptanone according to a three step sequence using the asymmetric protonation chemistry developed by Yanagisawa (Scheme 2.13).[19] Scandium-catalyzed homologation of



Scheme 2.13: Preparation of optically active 2-phenylcycloheptanone.

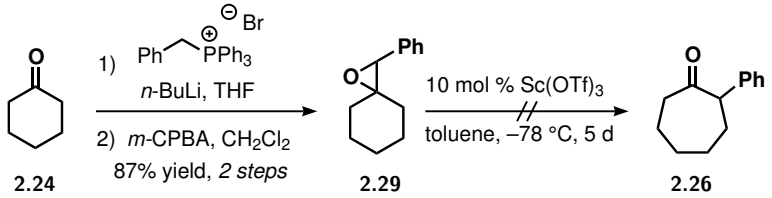
cyclohexanone with phenyldiazomethane (**2.25**) afforded racemic 2-phenylcycloheptanone (**2.26**) in a 65% distilled yield. Dropwise addition of 0.95 equivalents of LDA to **2.26** followed by trapping with TMSCl selectively delivered the thermodynamic enol silane **2.27** in 85% yield. Asymmetric protonation according to the reported conditions provided access

[33](a) Javed, M. I.; Brewer, M. Diazo Preparation *via* Dehydrogenation of Hydrazones with Activated DMSO. *Org. Lett.* **2007**, *9*, 1789-1792. (b) Javed, M. I.; Brewer, M. Diphenyldiazomethane. *Org. Synth.* **2008**, *85*, 189-195.

[34]For the relative reactivity of substituted diazoalkanes see Figure 1.2 on page 3.

(*R*)-2-phenylcycloheptanone (**2.28**) in 83% yield and 95:5 er in our hands.[35] Exposure of **2.28** to phenyldiazomethane, $Sc(OTf)_3$, or the combination of the two (toluene, 0 °C, 6 h) resulted in no loss of enantiopurity (95:5 er by chiral SFC analysis). This promising initial result indicated that chiral homologation products should be configurationally stable under conditions of scandium catalysis. Scheme 2.13 also underscores the benefits of eliminating the three step sequence that must precede asymmetric protonation, as products like **2.28** could be accessible in a single asymmetric homologation step.

We also wanted to run a simple mechanistic control to determine if the scandium-catalyzed reactions proceeded through a pathway involving an epoxide intermediate. House had previously shown that epoxides formed in Lewis acid mediated ring expansion reactions readily underwent rearrangement to the corresponding aldehydes.[36] We had never detected any epoxide or aldehyde byproducts in any scandium catalyzed ring expansion reactions (by ^{1}H NMR), but regardless, we carried out the experiment shown in Scheme 2.14. Epoxide **2.29** was obtained through standard chemistry in an 87% yield over two steps from cyclohexanone. Subjecting epoxide **2.29** to 10 mol % $Sc(OTf)_3$ at −78 °C for 5 days resulted in <2% conversion, clearly indicating that it was improbable the scandium catalyzed homologation reactions involved an epoxide intermediate. The most plausible mechanism was that previously discussed in the literature, a concerted collapse of a diazonium betaine to directly deliver the observed ring expanded products (Scheme 1.5, page 8).[3]



Scheme 2.14: Mechanistic probe of plausible epoxide rearrangement pathway.

[35]The Yanagisawa group reported a 95% yield and 98.5:1.5 er for the preparation of **2.28**. See reference 19 for details.

[36]House, H. O.; Grubbs, E. J.; Gannon, W. F. The Reaction of Ketones with Diazomethane. *J. Am. Chem. Soc.* **1960**, *82*, 4099-4106.

2.3.1 *Optimized Conditions for Consistent Reactivity*

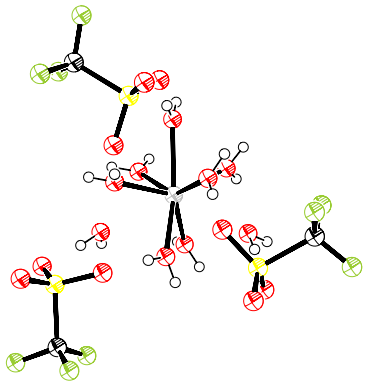


Figure 2.2: Crystal structure of $Sc(H_2O)_9(OTf)_3$.

The newly discovered scandium catalyzed homologation reactions often gave variable and unpredictable results that appeared to depend on the source of $Sc(OTf)_3$ and batch of diazoalkane solution. In order to obtain meaningful results when optimizing conditions for asymmetric reactions, the reaction variability would first need to be understood and mitigated. At the time this project began, no special protocols were in place to purify any of the reaction components. The $Sc(OTf)_3$ was often used as received and the aryl-diazoalkanes were prepared by directly following the reported Brewer procedure.[33] In order to mimimize reaction variability, efforts were undertaken to rigorously purify and dry *all* reaction components: solvents, $Sc(OTf)_3$, ketones, diazoalkanes, and ligands.

Scandium triflate is a deliquescent solid that rapidly absorbs significant quantities of atmospheric moisture. Crystallographic data from the literature has shown $Sc(OTf)_3$ to bind up to nine water molecules (Figure 2.2).[37] Although $Sc(OTf)_3$ is known to retain catalytic activity even in aqueous media,[38] we had anecdotal evidence that suggested drier conditions lead to higher reaction efficiencies for diazoalkane insertion reactions.[39] When Kobayashi first introduced $Sc(OTf)_3$ in 1993, he reported drying the salt at 200 °C under high vacuum

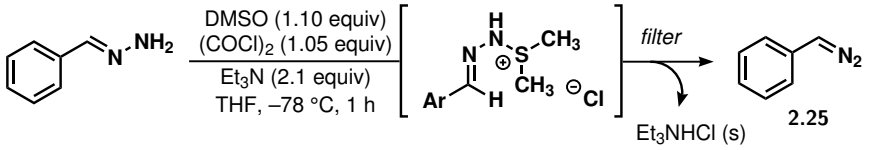
[37] Abbasi, A.; Lindqvist-Reis, P.; Eriksson, L.; Sandström, D.; Lidin, S.; Persson, I.; Sandström, M. Highly Hydrated Cations: Deficiency, Mobility, and Coordination of Water in Crystalline Nonahydrated Scandium(III), Yttrium(III), and Lanthanoid(III) Trifluoromethanesulfonates. *Chem. Eur. J.* **2005**, *11*, 4065-4077.

[38] Kobayashi, S.; Hachiya, I. Lanthanide Triflates as Water-Tolerant Lewis Acids. Activation of Commercial Formaldehyde Solution and Use in the Aldol Reaction of Silyl Enol Ethers with Aldehydes in Aqueous Media. *J. Org. Chem.* **1994**, *59*, 3590-3596.

[39] Reaction rates can be approximated visually by the evolution of nitrogen gas and the loss of the characteristic diazoalkane color.

before use.[40] We took this drying method one step further and dried commercial $Sc(OTf)_3$ under high vacuum at 200 °C with inline P_2O_5 for 24 hours before taking the salt into an inert atmosphere glove box using rigorous Schlenk techniques.

Diazoalkane solutions were originally prepared according to the general procedure reported by Brewer.[33] In a typical experimental procedure, a solution of the hydrazone and triethylamine were added dropwise to a cold solution of chlorodimethylsulfonium chloride, formed *in situ* from oxalyl chloride and DMSO (Scheme 2.15). After stirring for an hour at −78 °C, the reaction mixture was filtered to remove insoluble triethylammonium chloride and carefully concentrated to remove THF. The neat diazoalkane was then dissolved in toluene and stored at −78 °C. Following this procedure gave fairly pure diazoalkane solutions, but we wanted to be sure to remove all traces of Lewis basic impurities. We modified the procedure to include an aqueous workup which removed any residual triethylamine and DMSO. The oxidation was run for one hour in a 9:1 Et_2O:CH_2Cl_2 solvent mixture and immediately poured into a separatory funnel containing an ice cold 50% solution of aqueous NH_4Cl. The NH_4Cl layer was drained and the organics were washed with H_2O and saturated $NaHCO_3$ before drying over solid K_2CO_3. Filtration, concentration, and finally dissolution in toluene afforded exceptionally pure diazoalkane solutions.



Scheme 2.15: Original preparation of aryl-substituted diazoalkanes by Brewer.

Unfortunately, by performing an aqueous workup on the diazoalkanes, we inadvertently introduced an additional problem. Occasionally we would observe the formation of a white precipitate in some of the diazoalkane solutions after prolonged storage at −78 °C. After numerous unsuccessful attempts to isolate and characterize the white precipitate, we realized

[40] Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. Scandium Trifluoromethanesulfonate ($Sc(OTf)_3$). A Novel Reusable Catalyst in the Diels-Alder Reaction. *Tetrahedron Lett.* **1993**, *34*, 3755-3758.

that it was residual water from inefficient drying of diazoalkane solution after workup. Although K_2CO_3 was not the most efficient dessicant, the highest yields of diazoalkane were obtained with solutions dried over K_2CO_3. The residual water was ultimately best removed by carefully gravity filtering the diazoalkane solution at −78 °C in a cold-jacketed dropping funnel, then storing the clear solution over 3Å molecular sieves.

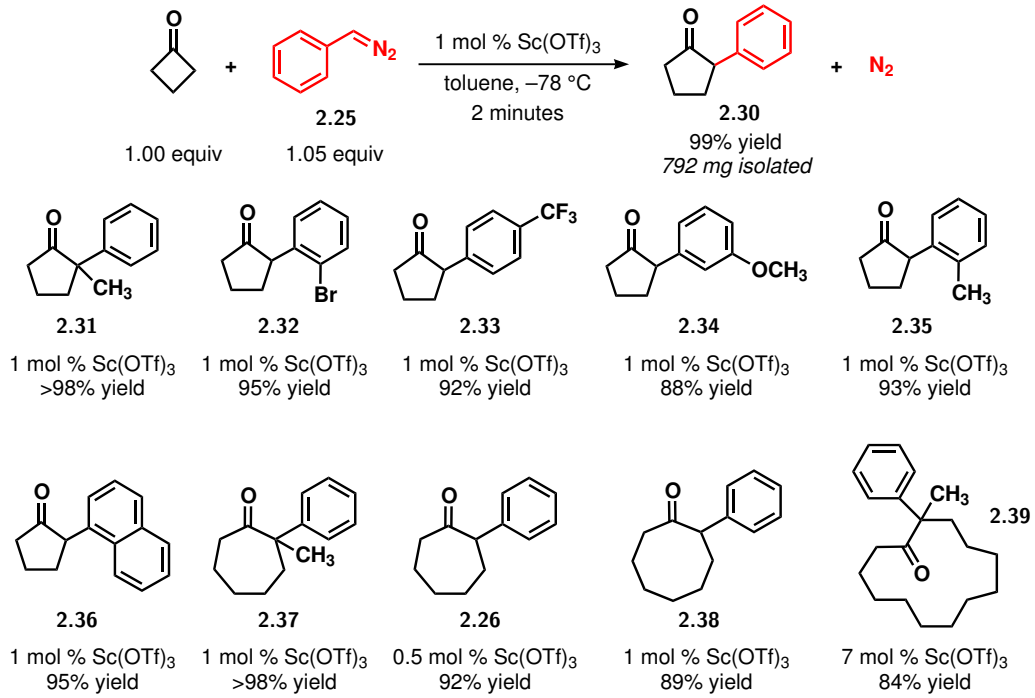
With rigorously dried $Sc(OTf)_3$, pure and dry diazoalkane solutions, distilled ketones, and solvents passed through an alumina column and stored over 3Å molecular sieves,[41] dramatic increases in reaction efficiency were observed.[42] More importantly though, reactions worked in a predictable and reproducible manner. When we had prepared racemic 2-phenylcycloheptanone (**2.26**) previously, the reaction was run with 10 mol % $Sc(OTf)_3$ and 1.1 equivalents of phenyldiazomethane (**2.25**) for 16 hours (Scheme 2.13, page 36). After workup and attempted purification by silica gel chromatography, the desired product was obtained in a quantitative yield but was contaminated with overhomologation byproducts.[43] Careful Kügelrohr distillation delivered analytically pure material in a modest 65% yield. Under the new drier conditions, running the reaction for 15 minutes with 0.5 mol % $Sc(OTf)_3$, 1.0 equivalents of phenyldiazomethane, and 1.2 equivalents of cyclohexanone, a 92% isolated yield was obtained after silica gel chromatography. By modifying the stoichiometry, no further purification away from overhomologation byproducts was necessary. The reaction rates were so high, an 18 gauge exit needle was needed to relieve excess pressure generated by the copious amounts of nitrogen gas evolved.

The newly optimized conditions were successfully applied to a number of ring expansion reactions with aryl-substituted diazoalkanes (Scheme 2.16).[42] Good scope with regard to the diazoalkane and ketone ring size were demonstrated. Reactions catalyzed by low loadings

[41] Williams, D. B. G.; Lawton, M. Drying of Organic Solvents: Quantitative Evaluation of the Efficiency of Several Desiccants. *J. Org. Chem.* **2010**, *75*, 8351-8354.

[42] Rendina, V. L.; Kaplan, H. Z.; Kingsbury, J. S. Highly Efficient and Enantioselective α-Arylation of Cycloalkanones by Scandium-Catalyzed Diazoalkane-Carbonyl Homologation. *Synthesis* **2012**, *44*, 686-693.

[43] Not isolated, but double insertion was detected by low resolution mass spectrometry. $C_{20}H_{23}O$ $[M+H]^+$: 279.1749.



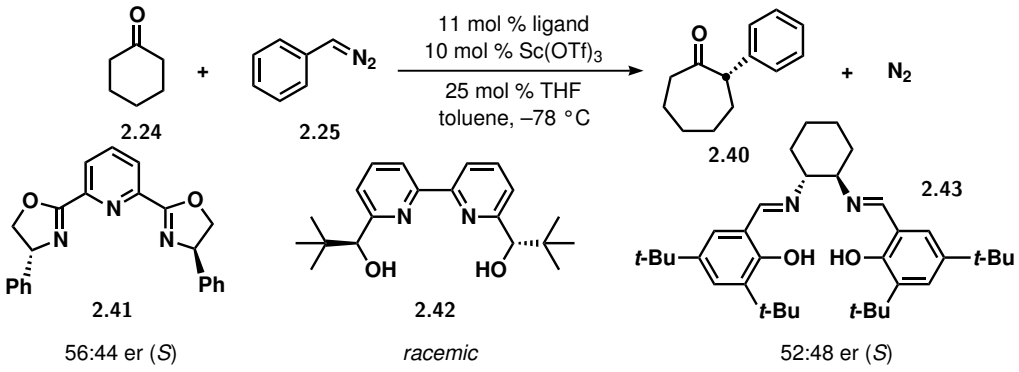
Scheme 2.16: Highly efficient insertion reactions with aryl-diazoalkanes.

of $Sc(OTf)_3$ (0.5–7 mol %) were complete in <1 hour and gave high yields in all cases tested. In addition to being reliable and efficient, the reactions could be scaled to afford gram quantities of homologation products ($\longrightarrow$ **2.30**). With reliable protocols in place and an understanding that water was the culprit of previous reproducibility issues, we were prepared to examine asymmetric insertion reactions.

2.3.2 *Early Results with Bis(oxazoline) Ligands*

We began by evaluating the PyBOX[5] and bipyridine diol[8] ligand frameworks previously reported to form competent chiral scandium complexes (Scheme 2.17). In an inert atmosphere glove box, $Sc(OTf)_3$ was stirred in toluene with a slight excess of the ligand for 1.5 hours to pre-form the ligand-metal complex. During complexation, 25 mol % THF was added as a cosolvent to help solubilize the scandium salt. The catalyst mixture was removed from the glove box, connected to a nitrogen manifold, and stirred with cyclohexanone for 15 minutes.

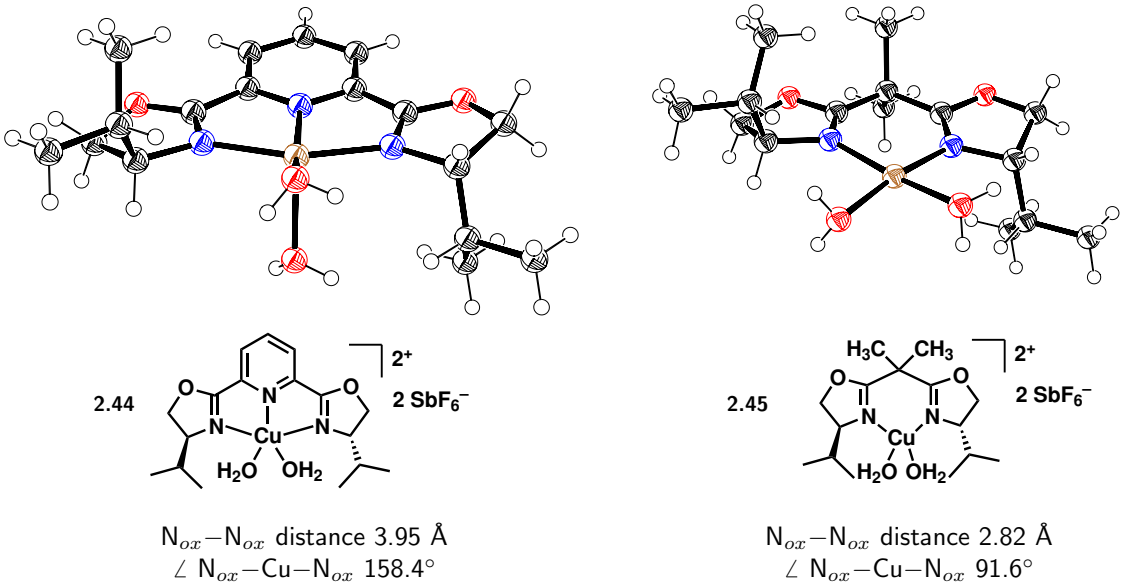
After cooling to −78 °C, phenyldiazomethane (**2.25**) was added in a single portion and the reactions were stirred until no further evolution of nitrogen gas was observed. An aliquot of the reaction mixture was purified by preparative thin-layer chromatography and analyzed for optical purity by chiral SFC analysis in comparison with authentic racemic material. Commercially available PyBOX ligand **2.41** delivered **2.40** in a measurable 56:44 er. The bipyridine diol ligand **2.42** afforded racemic product. We also tested a commercially available Salen[44] ligand which produced nearly racemic product. Ligands **2.42** and **2.43** were likely not stable under the reaction conditions, as diazoalkanes are known to undergo O−H insertion reactions.[45] Etherification of the two O−H groups would decrease the binding affinity of the ligand and metal, leading to background reaction by uncomplexed scandium.



Scheme 2.17: Initial ligand screening.

Previous experiments had shown that Lewis basic impurities could dramatically affect reaction efficiency. Reactions run with PyBOX ligand **2.41** visually progressed more slowly than those without the ligand present. We believed that by excising the bridging pyridine ring, we could decrease the Lewis basicity of the ligand while simultaneously bringing the ligand blocking groups closer to the metal center. The well known bis(oxazoline) ligand

[44] Larrow, J. F.; Jacobsen, E. N. Asymmetric Processes Catalyzed by Chiral (Salen)Metal Complexes. *Topics Organomet. Chem.* **2004**, *6*, 123-152.
[45] See the discussion in Chapter 1 for examples.



$N_{ox}-N_{ox}$ distance 3.95 Å
∠ $N_{ox}-Cu-N_{ox}$ 158.4°

$N_{ox}-N_{ox}$ distance 2.82 Å
∠ $N_{ox}-Cu-N_{ox}$ 91.6°

Figure 2.3: Comparison of copper PyBOX and BOX complexes. Counterions omitted for clarity.

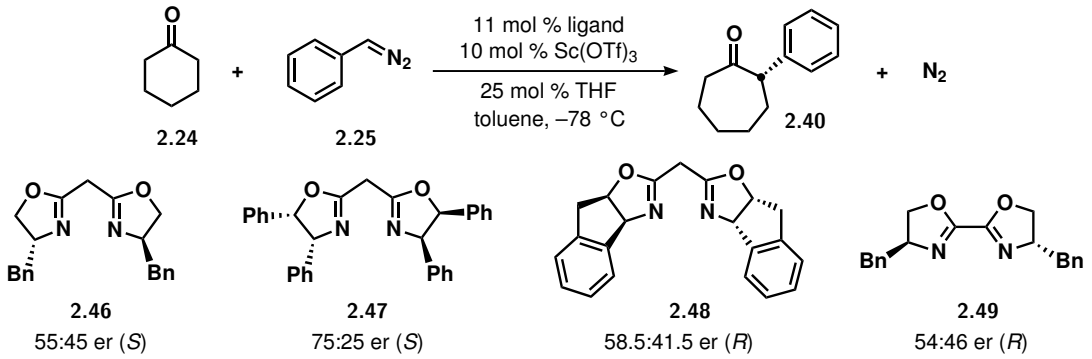
class retains the blocking group structure of the PyBOX ligands, but contains a methylene bridge between the two oxazoline units. While scandium PyBOX crystal structures have been reported, there are no examples of scandium bis(oxazoline) structures. In contrast, a preponderance of bis(oxazoline) copper complexes have been reported.[46] Figure 2.3 shows a direct comparison between copper PyBOX[47] and copper BOX[48] hexafluoroantimonate salts containing the same valine-derived oxazoline units. The BOX complex (right, **2.45**) shows a smaller through space $N_{ox}-N_{ox}$ distance (1.13 Å shorter) and a significantly compressed $N_{ox}-Cu-N_{ox}$ internal angle relative to the corresponding PyBOX complex (left, **2.44**).

We quickly tested several readily available BOX ligands, hoping the different steric and

[46] Nineteen Cu(II) bis(oxazoline) crystal structures were discussed by Desimoni in a 2006 review. Desimoni, G.; Faita, G.; Jørgensen, K. A. C_2-Symmetric Chiral Bis(oxazoline) Ligands in Asymmetric Catalysis. *Chem. Rev.* **2006**, *106*, 3561-3651.

[47] Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. C_2-Symmetric Copper (II) Complexes as Chiral Lewis Acids. Scope and Mechanism of Catalytic Enantioselective Aldol Additions of Enolsilanes to (Benzyloxy)acetaldehyde. *J. Am. Chem. Soc.* **1999**, *121*, 669-685.

[48] Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. Reversal in Enantioselectivity of *tert*-Butyl Versus Phenyl-Substituted Bis(oxazoline) Copper(II) Catalyzed Hetero Diels-Alder and Ene Reactions. Crystallographic and Mechanistic Studies. *Tetrahedron Lett.* **1999**, *40*, 2879-2882.



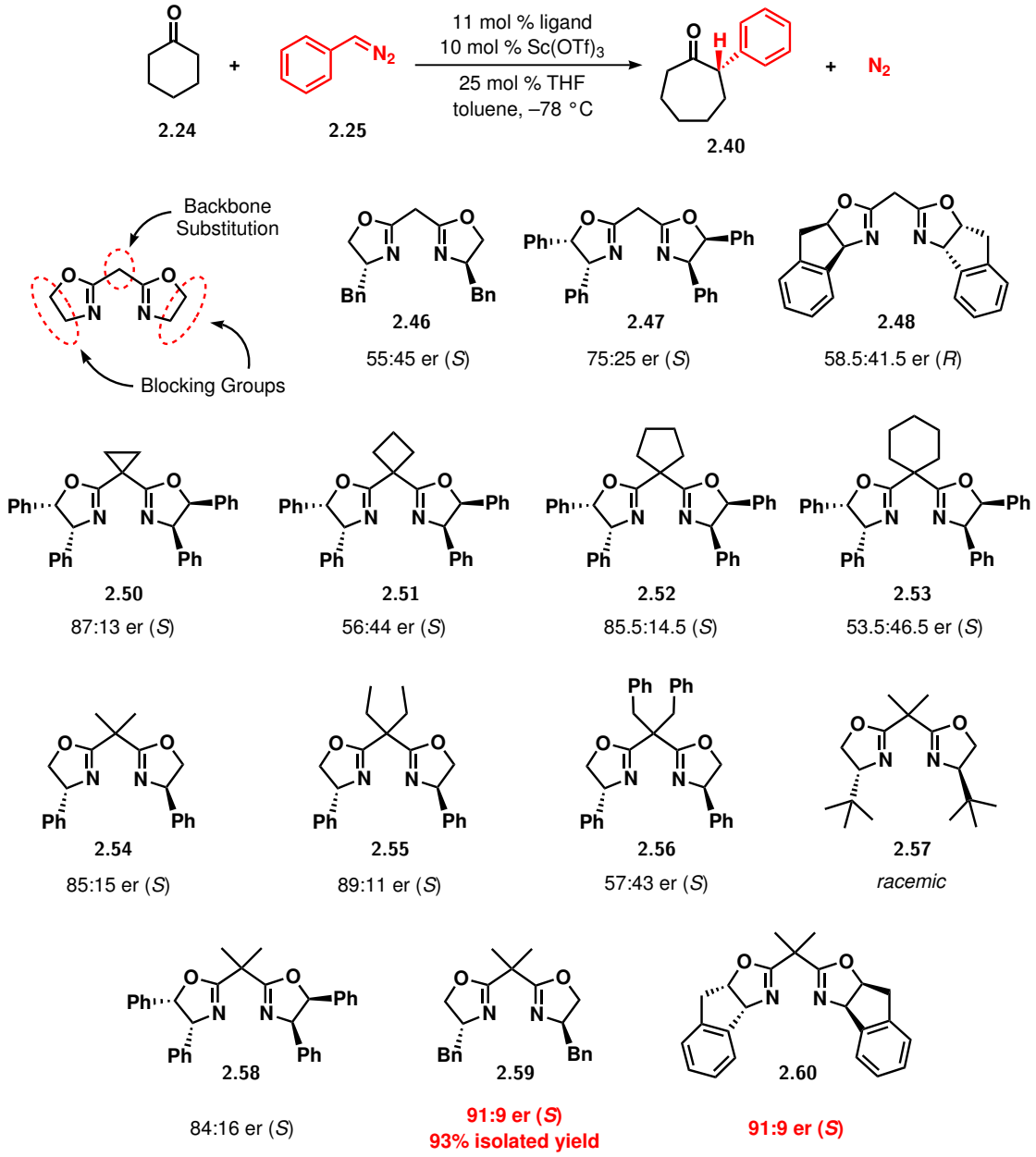
Scheme 2.18: Screen of commercially available bis(oxazoline) ligands.

electronic properties would translate into increased levels of stereoinduction (Scheme 2.18). We were pleased to see that ligand **2.47** provided much higher levels of selectivity. Different blocking groups (**2.46**, **2.48**) and bis(oxazoline) **2.49** resulted in lower selectivity. Excited by this promising lead, we initiated a broader screen of BOX ligands (Scheme 2.19). The bis(oxazoline) framework contains three diversity sites for C_2-symmetric ligands, making it a highly tunable and privileged ligand class.[46] We wanted to simultaneously optimize with regard to both backbone substitution and the amino alcohol derived blocking groups.[49]

Examination of the results in Scheme 2.19 showed that backbone substitution was integral to obtaining high levels of induction. Ligands lacking geminal substitution on the bridging methylene are known to tautomerize, which could adversely impact the ligand-metal binding. We prepared a series of ligands containing cyclic backbone substitution to probe the effect of bite angle on enantioselectivity. Davies and coworkers had prepared a similar series of BOX ligands and observed a strong dependence of enantioselectivity on ligand bite angle in copper catalyzed Diels-Alder reactions.[50] Ligand **2.50**, containing a

[49]For a lead reference on the benefits of multi-factor optimization see: Lendrem, D.; Owen, M.; Godbert, S. DOE (Design of Experiments) in Development Chemistry: Potential Obstacles. *Org. Process Res. Dev.* **2001**, *5*, 324-327.

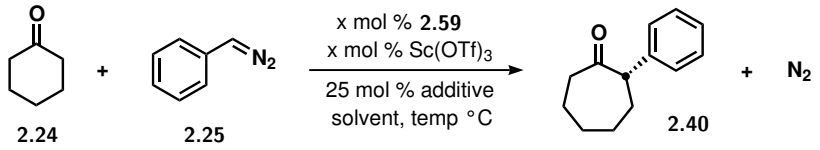
[50](a) Davies, I. W. I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoevena, T. R.; Reidera, P. J.; Verhoeven, T. R.; Reider, P. J. The Influence of Ligand Bite Angle on the Enantioselectivity of Copper(II)-Catalysed Diels-Alder Reactions. *Chem. Commun.* **1996**, 1753-1754. (b) Davies, I. W.; Deeth, R. J.; Larsen, R. D.; Reider, P. J. A CLFSE/MM Study on the Role of Ligand Bite-Angle in Cu(II)-Catalyzed Diels-Alder Reactions. *Tetrahedron Lett.* **1999**, *40*, 1233-1236.



Scheme 2.19: Wider screen of bis(oxazoline) ligands reveals two optimum ligands.

three-membered ring backbone, showed the highest selectivity (87:13 er) among the series, consistent with the results obtained by Davies. However, no clear trend emerged from these data. Ligand **2.51** showed a significant drop in selectivty (55:45 er), which was regained again with ligand **2.52** (85.5:14.5 er). Purity of the ligand may have been a determining factor, as ligand **2.51** was not as easy to crystallize cleanly as the others in the series. Some of the ligands in Scheme 2.19 have also been observed to crystallize as a solvate complex with water. Changing the blocking group to a single phenyl ring on each half and placing geminal methyl groups on the backbone afforded comparable levels of selectivity (ligand **2.54**, 85:15 er). Installing geminal ethyl groups on the backbone increased the selectivity slightly (**2.55**, 89:11 er), but with geminal benzyl groups the selectivity dropped (**2.56**, 57:43 er). Running with *tert*-leucine derived BOX **2.57** gave completely racemic material. Curiously, phenylalanine derived BOX **2.59** and indanyl BOX **2.60** gave an identical 91:9 er. Material from the reaction with ligand **2.59** was isolated in an excellent 93% yield.

We hoped at this point that we could spend time further refining and optimizing the reaction conditions with commercially available BOX ligand **2.59** to improve the selectivity beyond 91:9 er. Significant effort was invested in optimizing the reaction with regard to stoichiometry, solvent, temperature, and even various additives (Table 2.1). Reactions run in CH_2Cl_2 afforded lower selectivities, but the values were consistent regardless of changes with respect to stoichiometry (entries 1–6). Using coordinating solvents either shut down the reaction in the case of CH_3CN (entry 7), or gave lower levels of selectivity in the case of Et_2O (entry 8). Entry 10, run in toluene at -90 °C, showed the highest selectivity at 92.5:7.5 er. The freezing point of toluene (-95 °C) and the practicality of running reactions at temperatures lower than -78 °C prevented us from looking at even lower temperatures. We looked at various additives other than THF hoping that the appropriate additive could help solubilize or stabilize the chiral catalyst. Adding 25 mol % CH_3CN, Et_2O, or DME effectively had no impact on the selectivity (entries 11–13). Addition of 2,6-lutidine or pyridine had a detrimental effect on both reaction kinetics and the observed



entry[a]	mol % $Sc(OTf)_3$	mol % **2.59**	equiv **2.24**	solvent	additive	temp (°C)	er (R/S)[b]	yield (%)[c]
1	10	11	1.1	CH_2Cl_2	THF	−78	84.5:15.5 (S)	99
2[d]	10	11	1.2	CH_2Cl_2	3Å sieves	−78	84:16 (S)	99
3[d]	10	11	1.2	CH_2Cl_2	4Å sieves	−78	84.5:15.5 (S)	>98
4	10	11	1.5	CH_2Cl_2	THF	−78	83.5:16.5 (S)	>98
5	10	11	2.0	CH_2Cl_2	THF	−78	83.5:16.5 (S)	98
6	10	11	4.0	CH_2Cl_2	THF	−78	83:17 (S)	95
7	10	11	1.2	CH_3CN	–	−78	nd	nr
8	10	11	1.2	Et_2O	–	−78	75:25 (S)	nd
9	10	11	1.2	toluene	THF	−78	91:9 (S)	93
10	10	11	1.2	toluene	THF	−90	**92.5:7.5 (*S*)**	nd
11	10	11	1.2	toluene	CH_3CN	−78	90.5:9.5 (S)	nd
12	10	11	1.2	toluene	Et_2O	−78	90.5:9.5 (S)	nd
13	10	11	1.2	toluene	DME	−78	91:9 (S)	nd
14	10	11	1.2	toluene	2,6-lutidine	−78	72.5:27.5 (S)	nd
15	10	11	1.2	toluene	pyridine	−78	57.5:42.5 (S)	nd
16	10	11	1.2	toluene	NaOTf	−78	90.5:9.5 (S)	nd
17	10	11	1.2	toluene	–	−78	90:10 (S)	nd
18	5	5.5	1.2	toluene	THF	−78	90.5:9.5 (S)	nd
19	20	22	1.2	toluene	THF	−78	90.5:9.5 (S)	nd

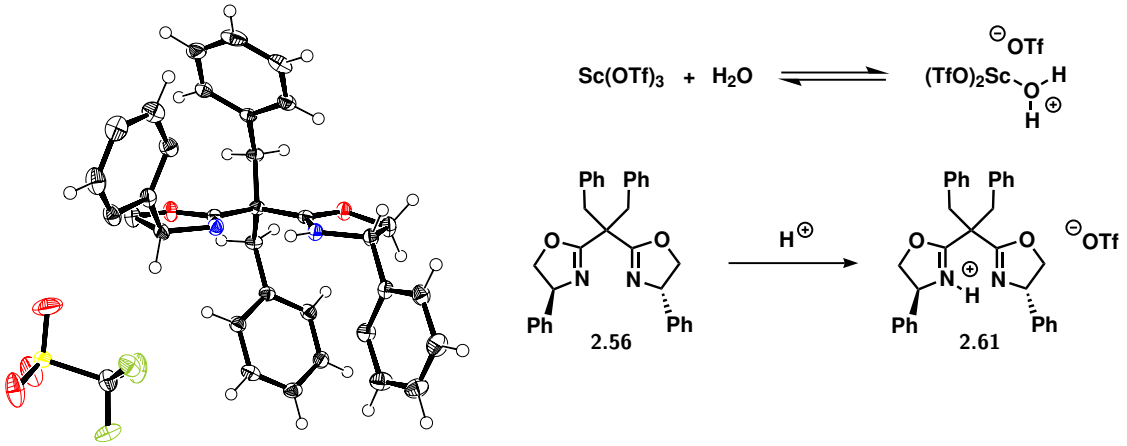
[a] *Conditions:* 0.1 M in solvent with 25 mol % additive, 1.0 equiv phenyldiazomethane (**2.25**). Ligand **2.59** and $Sc(OTf)_3$ pre-complexed for 1.5 hrs at 23 °C. Stirred 15 min with cyclohexanone (**2.24**) before cooling. [b] Determined by chiral SFC analysis in comparison with authentic racemic material. [c] Isolated yield after silica gel chromatography. [d] Run with 18 mg of powdered sieves and 25 mol % THF.

Table 2.1: Attempts to optimize reaction conditions with bis(oxazoline) ligand **2.59**.

enantioselectivity (entries 14, 15). This may help rationalize why reactions with PyBOX ligand **2.41** were sluggish and only moderately selective. We also found that although THF appeared to help solubilize the catalyst mixture, it was unnecessary to obtain high levels of selectivity (entry 17). By pre-mixing the catalyst suspension with cyclohexanone for 15 minutes, the reaction mixture became homogeneous and afforded comparable levels of enantioselectivity (90:10 er). Dropping the catalyst loading to 5 mol % had no effect on the enantioselectivity and increasing the catalyst loading to 20 mol % gave an identical result (entries 18, 19).

2.3.3 *Optimal Conditions for Medium Ring Arylation*

After struggling to obtain higher selectivities through extensive optimization, we wanted to glean more information about the catalyst-ligand complex. ^{1}H NMR analysis of scandium BOX mixtures showed significant line broadening and multiple additional signals, consistent with a poorly defined and fluxional catalyst structure. By constrast, ^{1}H NMR analysis of scandium PyBOX mixtures showed cleanly resolved signals slightly offset from the uncomplexed ligand, consistent with a well defined monomeric catalyst species in solution. Attempts to obtain a solid state structure of scandium BOX complexes lead to a number of bis(oxazoline) triflate salt structures ($\longrightarrow$ **2.61**, Scheme 2.20). It is plausible that residual



Scheme 2.20: Formation of a triflate salt with attempts to crystallize scandium bis(oxazoline) complexes.

water on the Sc(OTf)$_3$, ligand, or in the solvents, caused water to exchange for one of the triflate ligands, producing a Brønsted acid.[51] The crystal structures of scandium PyBOX complexes contain a bound inner-sphere water which could indicate a higher Brønsted basicity of the BOX ligand framework. The increased basicity serves to funnel the Brønsted

[51] Kobayashi, S.; Nagayama, S.; Busujima, T. Lewis Acid Catalysts Stable in Water. Correlation between Catalytic Activity in Water and Hydrolysis Constants and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands. *J. Am. Chem. Soc.* **1998**, *120*, 8287-8288.

acid equilibrium to **2.61**. It is also plausible the the BOX triflate salt was simply less soluble than the corresponding PyBOX triflate salt. A control experiment with 10 mol % **2.61** indicated that it was not a competent catalyst. These data are also consistent with experiments that showed undried $Sc(OTf)_3$ gave variable and significantly lower levels of enantioselectivity.

As discussed in the introduction, the PyBOX[5] and bipyridine diol structures[8] from the literature revealed a 7-coordinate scandium metal center. Evans' well-studied scandium PyBOX catalyzed reactions all relied on a model that invoked a two-point binding interaction between the substrate and metal, thus filling the available coordination sites.[52] We were concerned that the BOX ligand left too much open space around the metal center and multiple equivalents of ketone could be bound during turnover. The NMR experiments also seemed to suggest there was a relatively weak interaction between the ligand and scandium. By installing another coordinating functional group in the ligand, we hypothesized that we could increase the binding affinity for the ligand and fill more space in the coordination sphere. Our hope was that this would force the substrate into a single binding site around the metal center and ultimately lead to a more selective reaction. The most simple way to accomplish this would be to append the third coordinating group to the backbone of

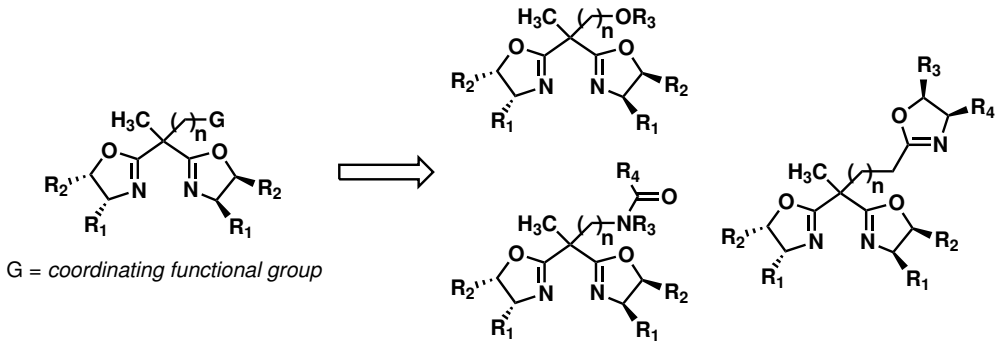
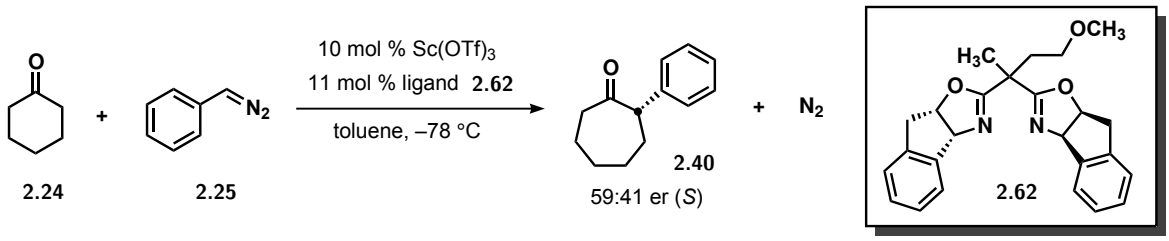


Figure 2.4: Several possibilities for the installation of a third coordinating group.

[52]For a lead reference see: Evans, D. A.; Fandrick, K. R.; Song, H. J.; Scheidt, K. A.; Xu, R. Enantioselective Friedel-Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine-Scandium(III) Triflate Complexes. *J. Am. Chem. Soc.* **2007**, *129*, 10029-10041.

the BOX ligand, breaking the C_2 symmetry. Figure 2.4 illustrates several early ideas we considered.

The first ligand we were able to access was the methyl ether substituted bis(oxazoline) **2.62** (Scheme 2.21). Ligand **2.62** was prepared through an iterative alkylation strategy, first adding methyl iodide and then bromoethyl methyl ether to the unsubstituted BOX framework. We were disappointed to see a significant drop in enantioselectivity (59:41 er), but regardless, we were still motivated to pursue alternative ligands to thoroughly test our hypothesis. The Lewis basicity of cyclohexanone and diethyl ether, as measured by the BF_3 affinity scale, are 76.36 ± 0.82 and 78.77 ± 0.38 $\frac{kJ}{mol}$ respectively.[53] The relatively close Lewis basicities of the pendant ether functionality and cyclohexanone could allow the cyclohexanone (present in 12 catalyst equivalents) to effectively compete for the additional coordination site.

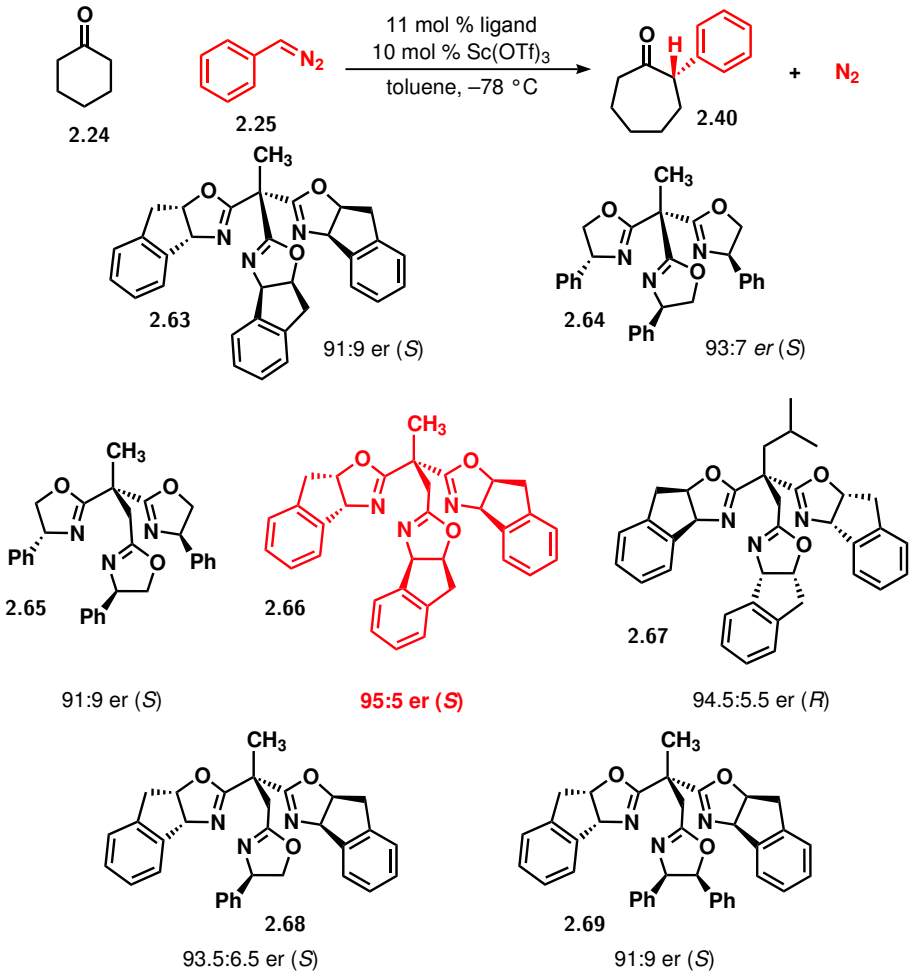


Scheme 2.21: First attempt to use a BOX ligand with third coordinating group.

To increase the binding ability of the third coordinating group we were drawn to the C_3-symmetric tris(oxazoline) ligands reported by Bellemin-Laponnaz and Gade in 2002.[54] The C_3-symmetric TOX ligands **2.63** and **2.64** were synthesized according to the reported procedures and tested under our standard reaction conditions (Scheme 2.22). The indanyl

[53] Calculated from the enthalpy of interaction between $BF_{3(g)}$ and the Lewis base. Laurence, C.; Gal, J. F. *Lewis Basicity and Affinity Scales: Data and Measurement*; John Wiley & Sons: West Sussex, 2010; pp 85-109.

[54] (a) Bellemin-Laponnaz, S.; Gade, L. H. Three 2-Oxazolinyl Rings on One Quaternary Carbon Atom: Preparation of a Novel Tripodal Tris(oxazolinyl) Ligand and the Tetrameric Molecular Structure of its CuI Complex. *Chem. Commun.* **2002**, 1286-1287. (b) Gade, L. H.; Bellemin-Laponnaz, S. S. Exploiting Threefold Symmetry in Asymmetric Catalysis: The Case of Tris(oxazolinyl)ethanes ("trisox"). *Chem. Eur. J.* **2008**, *14*, 4142-4152.



Scheme 2.22: Screen of C_3-symmetric and pseudo C_3-symmetric tris(oxazoline) ligands.

TOX ligand **2.63** afforded the same selectivity observed with the parent BOX ligand **2.60** (91:9 er). We were excited to see a slight increase in selectivity with phenylglycine-derived TOX ligand **2.64** (93:7 er). We also prepared several pseudo C_3-symmetric TOX ligands first introduced by Tang in 2002.[55] The phenyl blocking group (ligand **2.65**) delivered a 91:9 er, while the indanyl ligand **2.66** finally gave a synthetically viable 95:5 er. We wanted to probe the effect of changing the backbone substitution and nature of the third coordinating group

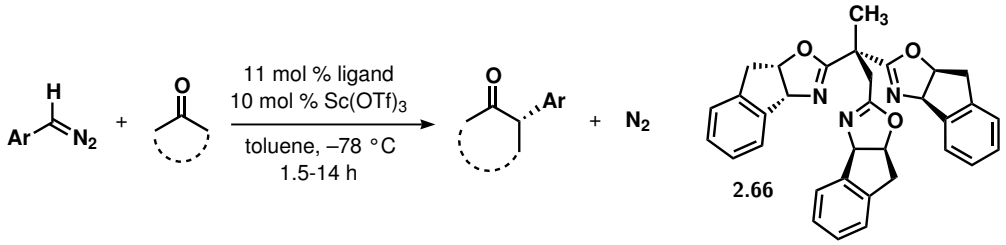
[55](a) Zhou, J.; Tang, Y. Sidearm Effect: improvement of the Enantiomeric Excess in the Asymmetric Michael Addition of Indoles to Alkylidene Malonates. *J. Am. Chem. Soc.* **2002**, *124*, 9030-9031. (b) Zhou, J.; Tang, Y. The Development and Application of Chiral Trisoxazolines in Asymmetric Catalysis and Molecular Recognition. *Chem. Soc. Rev.* **2005**, *34*, 664-676.

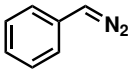
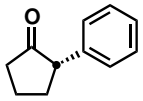
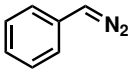
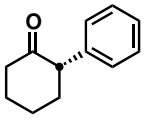
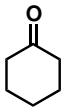
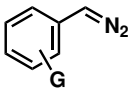
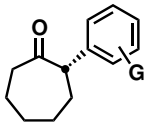
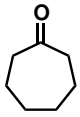
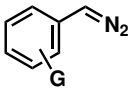
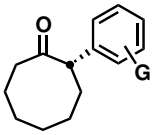
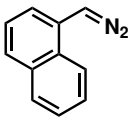
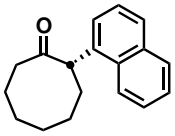
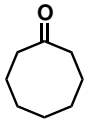
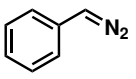
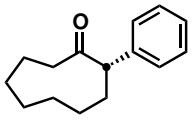
within the context of the pseudo C_3-symmetric ligand framework. Adding an isobutyl group to the backbone (ligand **2.67**) afforded nearly identical selectivity (94.5:5.5 er) as ligand **2.66**, suggesting the ligand likely binds in a tripodal fashion, placing the alkyl chain away from the site of reaction.[56] The nature of the third coordinating group was important to obtaining high selectivity. Without the indanyl blocking group (ligands **2.68** and **2.69**) selectivity dropped.

With high levels of enantioselectivity for the model substrate now attainable using ligand **2.66**, we started to evaluate the reaction scope with regard to cycloalkanone and diazoalkane (Table 2.2). Homologation of cyclobutanone with phenyldiazomethane delivered **2.70** in a lower 85.5:14.5 er (entry 1). The product was purified through an aqueous workup and hexane extraction because of the tendency for α-aryl cyclopentanones to racemize on silica.[23] As anticipated, the reaction with cyclopentanone gave a complex mixture of products derived from overhomologation (entry 2). The desired insertion product **2.71** was significantly more reactive than the starting cyclopentanone.[3,57] Alkyl and halogen groups on the diazoalkane were well tolerated, providing **2.73** and **2.75** in nearly identical selectivity to **2.40** (entries 4 and 5). We were very pleased to see that homologation of cycloheptanone delivered products with even higher selectivity than that observed with cyclohexanone (entries 6–9). The yield in entry 9 was slightly depressed due to the lower nucleophilicity of diazoalkane **2.80**, which caused the reaction to progress slowly and not reach full conversion even after 14 hours. Use of more hindered *ortho*-substituted nucleophiles **2.82** and **2.84** resulted in diminished reactivity with TOX ligand **2.66** at the cold temperatures needed to ensure high enantiocontrol. In these cases, however, the parent BOX ligand **2.60** restored a rapid and smooth merger of the reactants presumably due to a less crowded Sc coordination

[56] For a tripodal structure of TOX bound $ScCl_3$ (not found in the CSD search) see: Gade, L. H.; Marconi, G.; Dro, C.; Ward, B. D.; Poyatos, M.; Bellemin-Laponnaz, S.; Wadepohl, H.; Sorace, L.; Poneti, G. Shaping and Enforcing Coordination Spheres: The Implications of C_3 and C_1 Chirality in the Coordination Chemistry of 1,1,1-Tris(oxazolinyl)ethane ("Trisox"). *Chem. Eur. J.* **2007**, *13*, 3058-3075.

[57] Maruoka, K.; Concepcion, A. B.; Yamamoto, H. Selective Homologation of Ketones and Aldehydes with Diazoalkanes Promoted by Organoaluminum Reagents. *Synthesis* **1994**, 1283-1290.



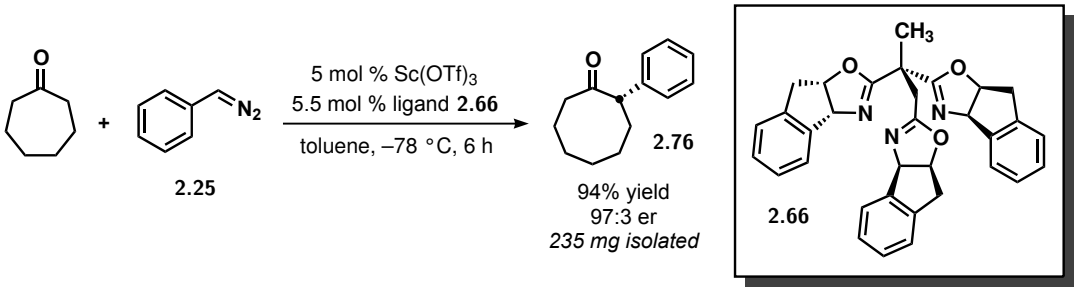
entry	electrophile	nucleophile	ligand	diazoalkane yield (%)[a]	insertion product	yield (%)[b]	er[c]
1[d]		 **2.25**	**2.66**	75	 **2.70**	>98	85.5:14.5
2		 **2.25**	**2.66**	75	 **2.71**	<2	nd
							
3		**2.25** G = H	**2.66**	75	**2.40** G = H	94	95:5
4		**2.72** G = *p*-CH_3	**2.66**	80	**2.73** G = *p*-CH_3	96	94:6
5		**2.74** G = *m*-Br	**2.66**	68	**2.75** G = *m*-Br	>98	94.5:5.5
							
6		**2.25** G = H	**2.66**	75	**2.76** G = H	99	98:2
7		**2.72** G = *p*-CH_3	**2.66**	80	**2.77** G = *p*-CH_3	>98	98.5:1.5
8		**2.78** G = *m*-OCH_3	**2.66**	64	**2.79** G = *m*-OCH_3	>98	97:3
9		**2.80** G = *p*-CF_3	**2.66**	73	**2.81** G = *p*-CF_3	78	98:2
10		**2.82** G = *o*-Br	**2.60**	74	**2.83** G = *o*-Br	85	92.5:7.5
11		**2.84** G = *o*-CH_3	**2.60**	63	**2.85** G = *o*-CH_3	97	93.5:6.5
12		 **2.86**	**2.60**	63	 **2.87**	94	93:7
13[e]		 **2.25**	**2.66**	75	 **2.88**	>98	93:7

[a] Yield over two steps from the aldehyde based on ^{19}F NMR titration with *o*-$FC_6H_4CO_2H$. [b] Isolated yield after silica gel chromatography. [c] By chiral SFC analysis in comparison with authentic racemic material. [d] Purified by extraction into hexanes. [e] Run at −45 °C.

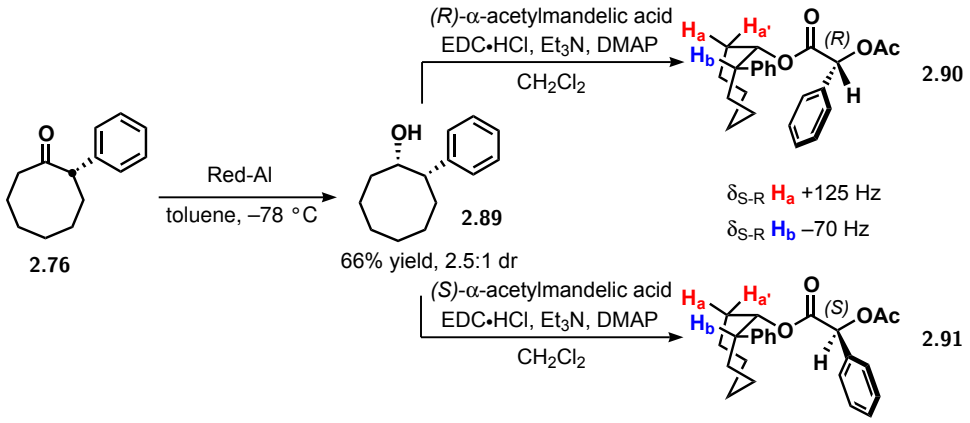
Table 2.2: Scope of asymmetric α-arylation by diazoalkane ring expansion.

sphere (**2.83** and **2.85**, 93:7 er, entries 10 and 11). The same trend was observed when 1-naphthyldiazomethane (**2.86**) was used to prepare aryloctanone **2.87** (93:7 er, entry 12). Reaction of cyclooctanone proceeded slowly, but full conversion and a 93:7 er was obtained after 14 hours at −45 °C (entry 13). Depending on the ring size, the stoichiometry was modified to maximize conversion and minimize overhomologation. For entries 3–5, overhomologation of the cycloheptanone products had been observed in previous studies, therefore the diazoalkane was used as the limiting reagent. A slight excess (1.2 equivalents) of cyclohexanone was added to ensure the diazoalkane was completely consumed before having an opportunity to react with the products. In entries 6–13, overhomologation was not a concern and an excess of the diazoalkane was used (1.2–1.4 equivalents) to ensure high conversion. Reactions with larger cycloalkanones and *ortho*-substituted diazoalkanes proceeded slower than 6– and 4-membered ring expansions, which lead to slight decomposition of the diazoalkane in the reaction time frame.

The asymmetric homologation reactions could be scaled to provide preparative quantities of enantioenriched products. We could also drop the catalyst loading to 5 mol % and still obtain high yields and selectivies in a reasonable timeframe by increasing the reaction concentration. After 6 hours, aryl octanone **2.76** was isolated in 94% yield (235 mg) and 97:3 er with 5 mol % $Sc(OTf_3)$ and 5.5 mol % ligand **2.66** (Scheme 2.23). Attempts to drop the catalyst loading further resulted in incomplete conversion even after prolonged reaction



Scheme 2.23: Scale-up of cycloheptanone homologation with lower catalyst loading.



Scheme 2.24: NMR-based proof of absolute stereochemistry for **2.76**.

times. With 2.5 mol % $Sc(OTf)_3$, **2.76** was recovered in a 50% distilled yield (5 mmol scale) and 95:5 er after 22 hours.

The absolute stereochemistry of **2.40** (entry 3, Table 2.2) was assumed to be (*S*) by comparing optical rotation data with that reported in the asymmetric protonation literature.[58] In order to develop a stereochemical model we needed to confirm the absolute stereochemistry of our medium ring cycloalkanones. While **2.76** was obtained as a solid, attempts to crystallize it directly or various derivatives was largely unsuccessful. We decided to reduce **2.76** and attempt an NMR based stereoproof using α-acetylmandelate esters (Scheme 2.24).[59] A sample of optically enriched **2.76** (>95:5 er) was reduced with Red-Al in toluene at −78 °C to deliver the *cis*-cyclooctanol **2.89** in 2.5:1 dr and a 66% isolated yield of the major diastereomer.[60] Initial attempts to use K-selectride resulted in a more diastereoselective reduction, but the recovered cyclooctanol was completely racemic. Coupling with (*R*)– and (*S*)-α-acetylmandelic acid provided sufficient quantities of α-acetylmandelate esters **2.90** and **2.91** for NMR analysis. The chemical shifts of the protons in both diastereomers were

[58] The absolute stereochemistry given in reference 19 was determined by "analogy".

[59] Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. On the Use of the *O*-Methylmandelate Ester for Establishment of Absolute Configuration of Secondary Alcohols. *J. Org. Chem.* **1986**, *51*, 2370-2374.

[60] Racemic material was converted to the *p*-NO_2 benzoate ester and crystallized to confirm the relative stereochemistry. See the experimental section and appendix for details.

assigned through the COSY and HSQC 2D spectra because of overlapping resonances. The protons indicated as H_a are diastereotopic and careful analysis of the spectra was required to ensure the correct signals in **2.90** and **2.91** were being compared. Regardless of how the data are analyzed, the proton signals associated with the carbon bearing H_a and $H_{a'}$ show a significant upfield shift in the *R* ester, consistent with an anisotropic shielding effect from the ester conformation shown in structure **2.90**. Likewise, the proton labelled H_b was shielded in the *S* ester **2.91**. The data used to make the determination are given in Table 2.3. From these data, absolute stereochemistry for the secondary alcohol was assigned as *S*, confirming that the α-aryl stereochemistry was also *S*.

proton	δ_S (ppm)	δ_R (ppm)	$\delta_{S-R}(ppm)$	Hz	group
H_a	1.87	1.62	+0.25	+125	**A**
$H_{c'}$	1.78	1.58	+0.20	+100	**A**
$H_{a'}$	1.94	1.74	+0.20	+100	**A**
H_c	1.64	1.52	+0.12	+60	**A**
$H_{d'}$	2.06	2.11	−0.05	−25	**B**
H_b	2.96	3.10	−0.14	−70	**B**
H_d	1.69	1.83	−0.14	−70	**B**

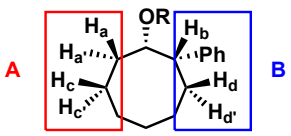
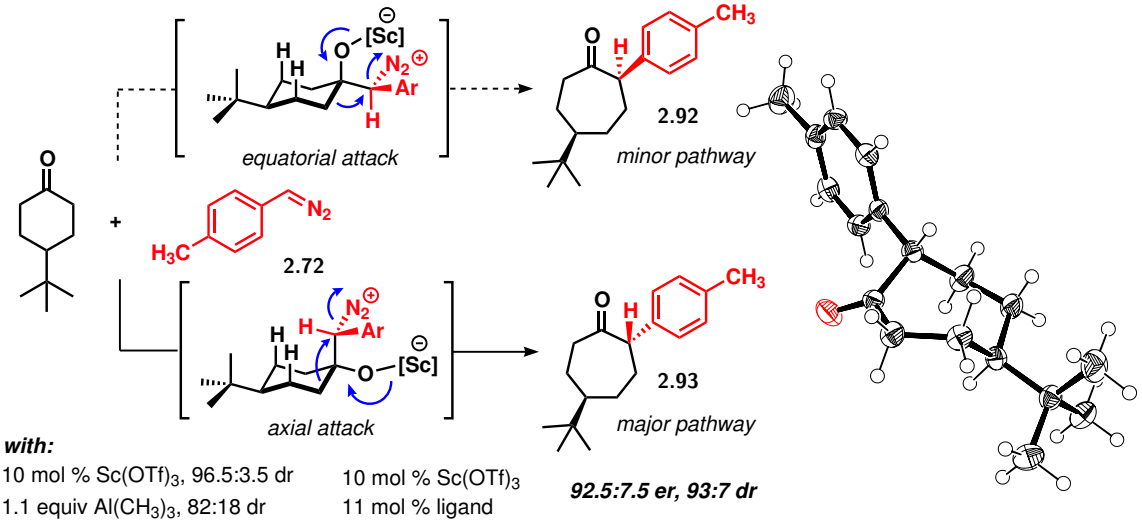


Table 2.3: Data used to determine the absolute stereochemistry of **2.76**.

Before proposing a stereochemical model, we also wanted to gather information about the approach trajectory of the diazoalkane nucleophile. We designed a diastereoselective homologation reaction similar to the experiment performed by Yamamoto in 1994 (Scheme 1.11, page 17).[57] Treatment of 4-*tert*-butylcyclohexanone with diazo **2.72** in the presence of 10 mol % $Sc(OTf)_3$ lead to the highly diastereoselective formation of *trans* insertion product (±)-**2.93** (96.5:3.5 dr, by achiral GC analysis, Scheme 2.25). Crystallization of the major diastereomer confirmed the *trans* relative stereochemistry. Consistent with the reported data in the literature, the observed diastereoselectivity with stoichiometric trimethylaluminum was lower (82:18 dr).[57] With 10 mol % $Sc(OTf)_3$ and ligand **2.66**, an enantio– and diastereoselective reaction delivered **2.93** in 93:7 dr with 92.5:7.5 er for the major diastereomer. The diastereoselectivity can be rationalized by invoking a model with an axial approach of



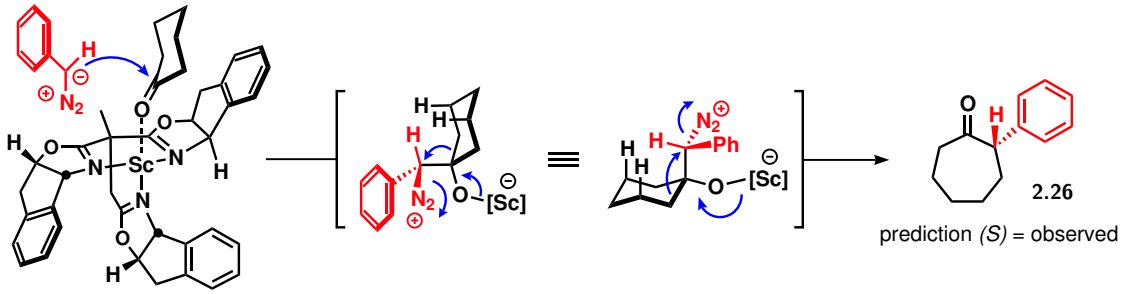
Scheme 2.25: Diastereo– and enantioselective insertion reactions with 4-*tert*-butylcyclohexanone.

the diazoalkane. The diazoalkane likely approaches in an orientation that places the proton over the 6-membered ring to minimize penalizing steric interactions between the aryl group and ring. The principle of least motion states that *"those elementary reactions will be favored that involve the least change in atomic position and electronic configuration"*.[61] Assuming that the betaine intermediate undergoes a least motion collapse directly from the drawn conformation and without C−C bond rotation, the observed diastereomer can be correctly predicted. A 120° rotation after the diazoalkane has added would lead to the other diastereomer. However, it would introduce significant torsional strain. Adding the other enantioface of the diazoalkane in the same orientation (Ar and N_2 swapped, H over ring) still predicts to the same relative stereochemistry.

A stereochemical model to predict the absolute stereochemistry was designed based on the aforementioned principles (Scheme 2.26). The enantioselectivity of the reaction is most likely derived from control over the orientation with which the diazoalkane adds to the symmetric cycloalkanone substrate. The counterions (omitted for clarity) and ligand

[61] Tee, O. S. Application of the Principle of Least Motion to Organic Reactions. A Generalized Approach. *J. Am. Chem. Soc.* **1969**, *91*, 7144-7149.

2.66 establish a chiral pocket that forces the diazoalkane to enter over the open side of the ligand (from left). The diazoalkane adds in an orientation such that the aryl group is directed away out the back of the chiral pocket and the proton is positioned over the cycloalkanone ring. The newly formed C−C bond resides initially in an axial position, and then concerted collapse with expulsion of nitrogen gas delivers the *S* product. This prediction was in agreement with the observed selectivity.



Scheme 2.26: Stereochemical model correctly predicts the (*S*) enantiomer of product.

2.4 Additional Developments

2.4.1 *Synthesis of a Novel π-Extended Bis(oxazoline) Ligand*

Chiral vicinal amino alcohols, both natural and fully synthetic, represent an exceptionally important class of small molecules. Amino alcohols have long been utilized in asymmetric catalysis as ligands themselves[62] or as precursors to various ligand classes.[63] As chemists continue to expand the scope of available catalytic enantioselective transformations, the need for new and rationally designed synthetic amino alcohols is justified. The *cis*-substituted amino indanol **2.94** (Figure 2.5), for instance, was first developed as a subunit of the orally active HIV protease inhibitor indinavir[64] (Crixivan®). Davies, Senanayake, and others in process research at Merck went on to establish the derived oxazolidinone **2.95** and bis(oxazoline) ligands[65] such as **2.60** as highly effective and tunable chiral controllers

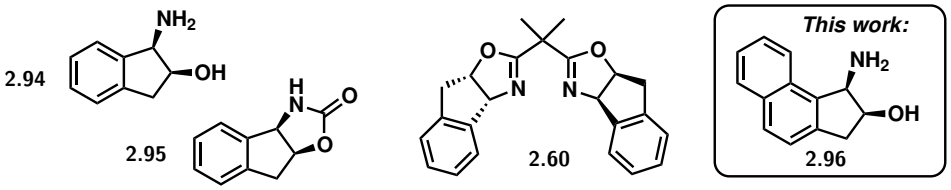


Figure 2.5: *cis*-Amino indanol **2.94** and derivatives.

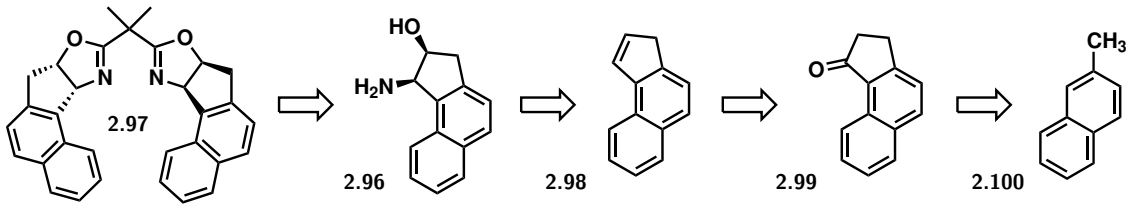
[62](a) Oguni, N.; Omi, T. Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by a Small Amount of Chiral 2-Amino-1-Alcohols. *Tetrahedron Lett.* **1984**, *25*, 2823-2824. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. Catalytic Asymmetric Induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes. *J. Am. Chem. Soc.* **1986**, *108*, 6071-6072. (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. Enantioselective Addition of Dialkylzincs to Aldehydes Promoted by Chiral Amino Alcohols. Mechanism and Nonlinear Effect. *J. Am. Chem. Soc.* **1989**, *111*, 4028-4036.

[63]Yoon, T. P.; Jacobsen, E. N. Privileged Chiral Catalysts. *Science* **2003**, *299*, 1691-1693.

[64]Senanayake, C. H. Applications of *cis*-1-Amino-2-indanol in Asymmetric Synthesis. *Aldrichimica Acta* **1998**, *31(1)*, 3-15.

[65]For pioneering studies with BOX ligands see: (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. Asymmetric Catalytic Cyclopropanation of Olefins: Bis-Oxazoline Copper Complexes. *Tetrahedron Lett.* **1990**, *31*, 6005-6008. (b) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. C_2-Symmetric 4,4,5,5'-Tetrahydrobi(oxazoles) and 4,4',5,5'-Tetrahydro-2,2'-methylenebis[oxazoles] as Chiral Ligands for Enantioselective Catalysis. *Helv. Chim. Acta.* **1991**, *74*, 232-240. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. Bis(oxazolines) as Chiral Ligands in Metal-Catalyzed Asymmetric Reactions. Catalytic, Asymmetric Cyclopropanation of Olefins. *J. Am. Chem. Soc.* **1991**, *113*, 726-728. (d) Corey, E. J.; Imai, N.; Zhang, H. Y. Designed Catalyst for Enantioselective Diels-Alder Addition from a C_2-Symmetric Chiral Bis(oxazoline)-Fe(III) Complex. *J. Am. Chem. Soc.* **1991**, *113*, 728-729.

for catalytic Diels-Alder reactions.[50,66] The superiority of these systems relative to those based on phenylglycinol draws from the fact that the indane ring prevents free rotation about the C−Ph bond, enforcing conformational rigidity.[67] Our success with BOX and TOX ligands derived from amino indanol **2.94** inspired us to develop a new π-extended amino alcohol (**2.96**) to address some of the enantioselectivity issues with smaller ring homologations (entry 1, Table 2.2, page 53).[68] We hypothesized that the lower selectivity observed for 4 $\longrightarrow$ 5 ring expansions was the result of more conformational freedom of the smaller cycloalkanone within the chiral pocket. By extending the ligand blocking groups, we hoped to minimize this flexibility and increase enantioselectivity in the arguably more synthetically useful cyclobutanone homologations.[28]



Scheme 2.27: Retrosynthetic analysis for new π-extended bis(oxazoline) ligand.

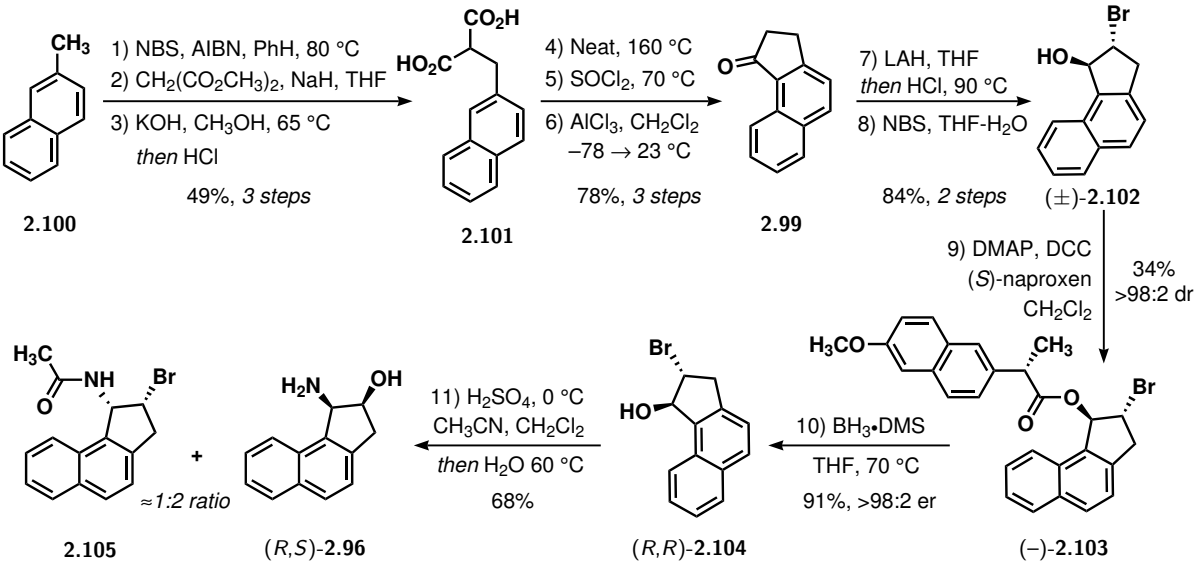
Scheme 2.27 shows a retrosynthesis for the new π-extended BOX ligand **2.97**. The required 3*H*-benz[*e*]indene (**2.98**) was a known material, but it forms in low yield as a byproduct of the pyrolysis of 2'-methyl-biphenyl-2,3-dicarboxylic anhydride.[69] As such, it seemed appropriate to target **2.98** more efficiently by a simple reduction-elimination

[66](a) Davies, I. W.; Senanayake, C. H.; Castonguay, L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. Highly Diastereoselective Diels-Alder Reaction Mediated by a Chiral Auxiliary Derived from Amino Indanol: The Role of Conformation on Diastereoselectivity. *Tetrahedron Lett.* **1995**, *36*, 7619-7622. (b) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. Application of Indane-derived C_2-Symmetric Bis(oxazolines) in Two-point Binding Asymmetric Diels-Alder Reactions. *Tetrahedron Letters* **1996**, *37*, 1725-1726. (c) Davies, I. W.; Gerena, L.; Cai, D.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. A Conformational Toolbox of Oxazoline Ligands. *Tetrahedron Lett.* **1997**, *38*, 1145-1148.

[67]Sibi, M. P.; Ji, J. Practical and Efficient Enantioselective Conjugate Radical Additions. *J. Org. Chem.* **1997**, *62*, 3800-3801. See references 50 and 66 also.

[68]Rendina, V. L.; Goetz, S. A.; Neitzel, A. E.; Kaplan, H. Z.; Kingsbury, J. S. Scalable Synthesis of a New Enantiomerically Pure π-Extended Rigid Amino Indanol. *Tetrahedron Lett.* **2012**, *53*, 15-18.

[69]Brown, R.; Eastwood, F.; Smith, C. Pyrolytic Generation of Aryne and Exocyclic Carbene Species: Trapping by an Adjacent *o*-Tolyl Group. *Aust. J. Chem.* **1992**, *45*, 1315-1320.



Scheme 2.28: Forward synthetic path for π-extended amino alcohol **2.96**.

sequence on the known ketone **2.99**. In opening attempts to prepare **2.99** in one flask from acryloyl chloride and naphthalene by tandem $AlCl_3$-mediated Friedel-Crafts acylation and Nazarov cyclization,[70] tedious column chromatography was needed and the yield was only modest. Other literature procedures called for expensive starting materials and did not scale well in our hands.[71] Therefore, an alternative route was developed from inexpensive 2-methylnaphthalene (**2.100**, Scheme 2.28).

The path of synthesis begins from **2.100** with radical monobromination, displacement of the crude bromide with the sodium salt of dimethyl malonate, and basic hydrolysis to afford the homobenzylic diacid **2.101** in a 49% yield over three steps.[72] Cationic cyclization[71c] to

[70] Dietrich, U.; Hackmann, M.; Rieger, B.; Klinga, M.; Leskelä, M. Control of Stereoerror Formation with High-Activity "Dual-Side" Zirconocene Catalysts: A Novel Strategy To Design the Properties of Thermoplastic Elastic Polypropenes. *J. Am. Chem. Soc.* **1999**, *121*, 4348-4355.

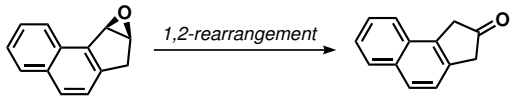
[71] (a) Hulin, B.; Koreeda, M. A Convenient, Mild Method for the Cyclization of 3– and 4-Arylalkanoic Acids *via* Their Trifluoromethanesulfonic Anhydride Derivatives. *J. Org. Chem.* **1984**, *49*, 207-209. (b) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. Enantioselective Total Synthesis of a Potent Antitumor Antibiotic, Fredericamycin A. *J. Am. Chem. Soc.* **2001**, *123*, 3214-3222. (c) Wu, X.; Nilsson, P.; Larhed, M. Microwave-Ehanced Carbonylative Generation of Indanones and 3-Acylaminoindanones. *J. Org. Chem.* **2005**, *70*, 346-349.

[72] An, Q.; Li, G.; Tao, C.; Li, Y.; Wu, Y.; Zhang, W. A General and Efficient Method to Form Self-Assembled Cucurbit[*n*]uril Monolayers on Gold Surfaces. *Chem. Commun.* **2008**, 1989-1991.

give **2.99** was possible in one step using molten H_3PO_4/P_2O_5, but the yield was variable (30–76%) due to competitive oligomerization. In practice, we found it preferable to accomplish the transformation by the sequence: (1) thermal decarboxylation, (2) chlorination, and (3) Friedel-Crafts ring closure (**2.101** $\longrightarrow$ **2.99**, 78% yield, three steps). In just six steps requiring no purification of intermediates, ketone **2.99** can be obtained on decagram scale in an overall 37% yield and >95% purity as judged by ^{1}H NMR analysis. Reduction and acid-mediated elimination in the same vessel provides the target hydrocarbon 3*H*-benz[*e*]indene (**2.98**) in an 85% yield as a white crystalline solid after simple filtration through a pad of silica gel. An initial plan to use the Jacobsen epoxidation[73] for the control of absolute stereochemistry was complicated by the propensity for the racemic epoxide (from *m*-CPBA/$NaHCO_3$ or DMDO) to undergo spontaneous ring opening/1,2-rearrangement to the homobenzylic cyclopentanone.[74] Alternative strategies based on catalytic enantioselective dihydroxylation[75] or diboration[76] could be applicable, but experimentation with racemic material quickly established chiral esters of bromohydrin **2.102** as highly crystalline. Thus, indene oxidation with NBS in THF-water (99% yield) and coupling with (*S*)-naproxen under standard conditions gave a mixture of diasteromeric esters from which (–)-**2.103** crystallized in a 34% yield as a single diastereomer. Naproxen was selected as a resolving agent because of the trivial means by which multigram quantities of enantiopure material can be obtained from over-the-counter pain relief tablets. The absolute configuration of (–)-**2.103**

[73] Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. The Mechanistic Basis for Electronic Effects on Enantioselectivity in the (salen)Mn(III)-Catalyzed Epoxidation Reaction. *J. Am. Chem. Soc.* **1998**, *120*, 948-954.

[74] Rearrangement of the epoxide readily occurred under a variety of reaction conditions.



[75] (a) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sanceau, J. Y.; Bennani, Y. Asymmetric Dihydroxylation of Olefins with a Simple Chiral Ligand. *J. Org. Chem.* **1993**, *58*, 1991-1993. (b) Malla Reddy, S.; Srinivasulu, M.; Venkat Reddy, Y.; Narasimhulu, M.; Venkateswarlu, Y. Catalytic Asymmetric Dihydroxylation of Olefins using Polysulfone-based Novel Microencapsulated Osmium Tetroxide. *Tetrahedron Lett.* **2006**, *47*, 5285-5288.

[76] Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. Rh-Catalyzed Enantioselective Diboration of Simple Alkenes: Reaction Development and Substrate Scope. *J. Org. Chem.* **2005**, *70*, 9538-9544.

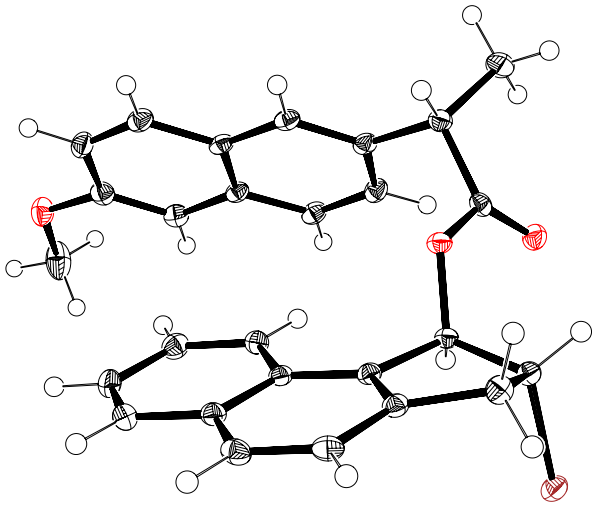
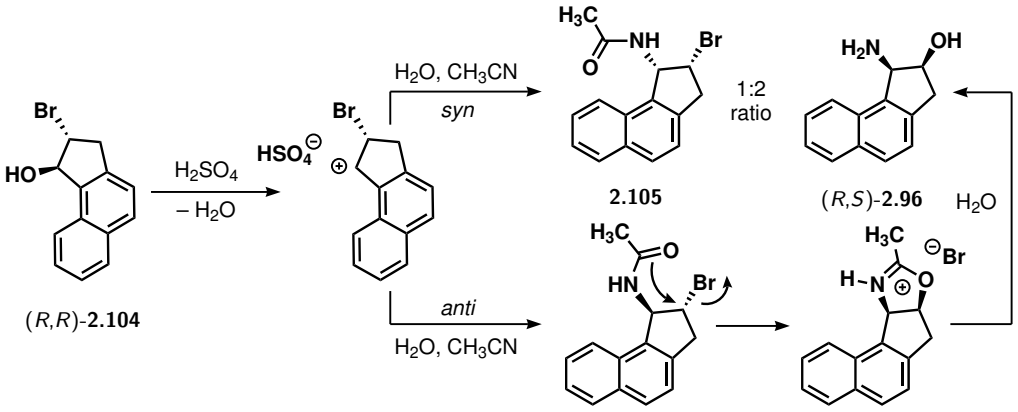


Figure 2.6: X-ray structure of (–)-**2.103** confirms the absolute stereochemistry.

was unequivocally assigned by X-ray diffraction (Figure 2.6).

Among several different hydrolytic conditions tested, cleavage of the resolving agent was best achieved by borane reduction to give the desired (*R*,*R*) bromohydrin **2.104** in a 91% yield with >98:2 er by chiral SFC analysis. The choice of reductive cleavage necessitated the only chromatographic purification in the entire sequence. While hydrolytic cleavage would have been preferrable, competitive bromide elimination was prohibitive. Attempts to move unpurified **2.104** forward were not successful. The purified bromohydrin was then subjected to a Ritter reaction[77] to afford (*R*,*S*)-**2.96** cleanly in a 68% yield after an acid/base extraction procedure. The modest yield was accounted for by the recovery of *cis*-acetamide **2.105** (in a >2:1 ratio in favor of amino alcohol **2.96**). The byproduct likely forms as a result of non-stereospecific trapping of the benzylic cation by acetonitrile and subsequent failure to undergo intramolecular closure to the intermediate oxazoline (Scheme 2.29). The added stability gained by transient bromonium ion formation, a key feature for

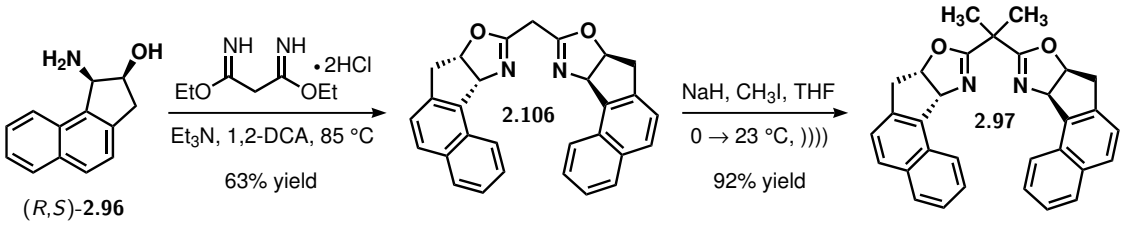
[77]Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. Application of a Ritter-type Reaction to the Synthesis of Chiral Indane-derived C_2-Symmetric Bis(oxazolines). *Tetrahedron Lett.* **1996**, *37*, 813-814.



Scheme 2.29: Mechanistic rationale for formation of acetamide **2.104**.

stereocontrol in this reaction, was offset by enhanced delocalization of the cation within the naphthalene ring. Co-production of acetamide **2.105**, together with the aforementioned facile rearrangement of epoxy-**2.98**,[74] lends support to this hypothesis. Noteworthy is that acetamide hydrolysis does not occur in the absence of the vicinal hydroxyl functionality.[78]

Our experience with the synthesis of bis(oxazolinyl)methanes had shown that the diethoxyimidate method of Davies *et al.*[50a] allows expedient access to the unsubstituted BOX framework. Coupling of amino alcohol **2.96** with commercially available diethyl malonimidate dihydrochloride furnishes BOX ligand **2.106** in 63% yield as a white flocculent solid after washing with hexanes and methanol (Scheme 2.30). Deprotonation with sodium hydride and subsequent trapping with methyl iodide lead to the target *gem*-dimethylated ligand **2.97** in a 92% yield after a hexanes wash.



Scheme 2.30: Transformation of amino alcohol **2.96** to corresponding BOX ligand.

[78] Bruice, T. C.; Marquardt, F. H. Hydroxyl Group Catalysis. IV. The Mechanism of Intramolecular Participation of the Aliphatic Hydroxyl Group in Amide Hydrolysis. *J. Am. Chem. Soc.* **1962**, *84*, 365-370.

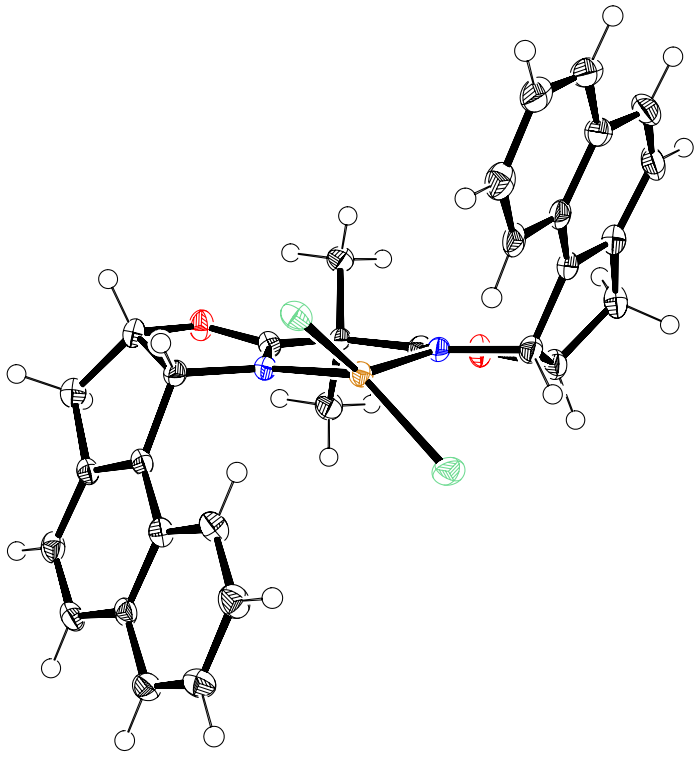


Figure 2.7: X-ray structure of $CuCl_2$·**2.97** complex.

We were eager to test the newly prepared BOX ligand **2.97** in our asymmetric homologation chemistry. The new ligand was sparingly soluble in toluene and in all homologation cases tested, racemic products were obtained. The ligand was likely unable to complex with scandium because of the poor solubility in toluene, however, when we tested the same reactions in CH_2Cl_2, racemic products were again obtained. For further proof of structure and to confirm that **2.97** could act as a viable chiral ligand, we turned to copper(II) salts. Suitable single crystals of $CuCl_2$·**2.97** were obtained by vapor diffusion of pentane into a saturated dichloromethane solution. X-ray diffraction revealed a four-coordinate distorted square planar 17-electron complex flanked by sizeable naphthalene units (Figure 2.7). Importantly, there was considerable homology between this structure and the analogous $CuCl_2$·(indanyl-

box) catalyst with regard to the disposition of groups around the copper(II) center.[79] While **2.97** appears to form a competent complex with copper(II), whether or not the extended blocking groups translate into higher levels of selectivity in asymmetric reactions remains to be seen.

2.4.2 *Development of a Fluorine NMR Titration Protocol*

During the course of our studies, we required a rapid and accurate method to assay the active diazoalkane concentration in toluene stock solutions. Although a number of methods have been reported in the literature, none offered a simple procedure that could be executed quickly and with small quantities of the diazoalkane reagent. Those based on acid-mediated decomposition and collection of evolved nitrogen gas require large quantities of the diazoalkane and elaborate experimental setups.[33] Spectrophotometric methods require preparation of calibration standards and calculation of extinction coefficients for compounds that can readily decompose at room temperature or by light-induced pathways.[80] Esterification with excess benzoic acid and titration of the unreacted carboxylic acid is time-consuming, requiring preparation and calibration of stock base solutions in order to obtain accurate results.[81] Esterification with benzoic acid and calculation of concentration on the basis of the unpurified yield of the benzoate ester is also possible, but at times will provide concentration results of questionable accuracy due to common diazoalkane impurities.[82]

Previously, our preferred method involved quenching a known volume of the diazoalkane solution with excess benzoic acid and isolating the corresponding benzoate ester by chro-

[79] Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. On the Intermediates in Chiral Bis(oxazoline)copper(II)-Catalyzed Enantioselective Reactions–Experimental and Theoretical Investigations. *Chem. Eur. J.* **2002**, *8*, 1888-1898.

[80] Gassman, P. G.; Greenlee, W. J. Dideuteriodiazomethane. *Org. Synth.* **1973**, *53*, 38.

[81] Arndt, F. Diazomethane. *Org. Synth.* **1935**, *15*, 3.

[82] Bimolecular decomposition pathways to produce azine or olefin impurities are common for noncarbonylstabilized diazoalkanes. (a) Overberger, C. G.; Anselme, J. The Thermal and the Photolytic Decomposition of 1-Phenyldiazoethane. *J. Org. Chem.* **1964**, *29*, 1188-1190. (b) Abelt, C. J.; Pleier, J. M. Stereoselective Azine Formation in the Decomposition of Phenyldiazomethanes. *J. Am. Chem. Soc.* **1989**, *111*, 1795-1799. (c) Smith, L. I.; Howard, K. L. Diphenyldiazomethane. *Org. Synth.* **1944**, *24*, 53.

matography. The isolated yield of the benzoate ester could then be used to calculate the amount of active diazoalkane in the aliquot. This method was not only time intensive, but inherently flawed. Assuming the diazoalkane quantitatively converted to the benzoate ester, the method was still subject to mechanical losses during purification and transfer steps.[83] A new method, using commercially available 2-fluorobenzoic acid and quantitative ^{19}F NMR spectroscopy was developed to address some of these shortcomings.[84] The new protocol required minimal experimental time and could be performed safely at low temperature with only micromolar quantities of the diazoalkane.

In a typical experimental procedure, an accurately weighed quantity of excess 2-fluorobenzoic acid was dissolved in 700 μL of $CDCl_3$,[85] enough solvent to prepare a single NMR sample. After cooling to -78 °C, which causes the solution to freeze, a 100 μL aliquot of the diazoalkane solution was added rapidly in a single portion.[86] Upon warming of the mixture to room temperature, the reaction was complete as indicated by the absence of the characteristic diazoalkane color and lack of further nitrogen gas evolution. The reaction mixture was swirled gently to ensure homogeneity and then transferred without rinsing to a standard NMR tube for analysis. The ^{19}F NMR data were recorded with an extended relaxation delay of 10 seconds (d1 = 10). The fluorine T_1 values for 2-fluorobenzoic acid and benzyl 2-fluorobenzoate were determined to be 1.14 ± 0.03 and 1.73 ± 0.06 seconds respectively. Relaxation delays of 10 seconds were sufficiently long (>5 x T_1) to ensure integral accuracies of ±1%.[87] The difference in ^{19}F NMR chemical shift between the unreacted 2-fluorobenzoic acid and 2-fluorobenzoate esters was approximately 1.0 ppm. The

[83] Wernerova, M.; Hudlicky, T. On the Practical Limits of Determining Isolated Product Yields and Ratios of Stereoisomers: Reflections, Analysis, and Redemption. *Synlett* **2010**, 2701-2707.

[84] Rendina, V. L.; Kingsbury, J. S. Titration of Nonstabilized Diazoalkane Solutions by Fluorine NMR. *J. Org. Chem.* **2012**, *77*, 1181-1185.

[85] It was found that 2-fluorobenzoic acid dissolved slowly in $CDCl_3$, and preparation of a stock solution was generally more convenient. See the experimental section for details.

[86] A 1.00 mL syringe with calibration marks every 0.01 mL used. The procedure was sufficiently reproducible with this size syringe; howevery, if more accurate results were desired a 250 μL syringe was substituted.

[87] Saito, T.; Nakaie, S.; Kinoshita, M.; Ihara, T.; Kinugasa, S.; Nomura, A.; Maeda, T. Practical Guide for Accurate Quantitative Solution State NMR Analysis. *Metrologia* **2004**, *41*, 213-218.

spectra were referenced relative to hexafluorobenzene (δ −164.9 ppm) as an internal standard; however, the use of a reference standard was not necessary due to the uniform upfield shift of the esters. Conversion, and ultimately concentration, was calculated on the basis of integration of the two fluorine signals (Equation 2.5).

$$I_{\text{ester}} = \text{integration of ester} \tag{2.1}$$

$$I_{\text{acid}} = \text{integration of acid} \tag{2.2}$$

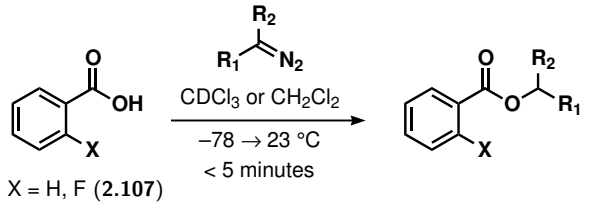
$$m_{\text{acid}} = \text{amount of acid (mmol)} \tag{2.3}$$

$$V_{\text{aliquot}} = \text{volume of aliquot (mL)} \tag{2.4}$$

$$\textit{concentration}\ (\text{M}) = \frac{\left(\frac{I_{\text{ester}}}{I_{\text{ester}}+I_{\text{acid}}}\right) \times m_{\text{acid}}}{V_{\text{aliquot}}} \tag{2.5}$$

Table 2.4 summarizes our findings for titration of various alkyl, aryl, and vinyl diazoalkane solutions. In every case, the reaction quickly and cleanly produced the corresponding 2-fluorobenzoate esters. Noteworthy of the assay is its high reproducibility. Data in Table 2.4 are reported as the average of three trials ± standard deviations. Prior to the discovery of 2-fluorobenzoic acid, attempts were made to use ^{1}H NMR spectroscopy with several substituted benzoic acid derivatives. Although the use of 2,6-dimethoxybenzoic acid was successful in certain cases, it did not prove to be a general solution because of problems with overlapping resonances. Recourse to ^{19}F NMR spectroscopy has avoided this complication in all cases tested thus far.

Results for esterification with benzoic acid and weighing of the unpurified benzoate ester after a basic aqueous workup are also provided in Table 2.4 for comparison. With the exception of methyl benzoate (entry 1), isolation of the benzoate esters leads to concentration values that exceed those obtained with the new procedure. The volatility of methyl benzoate was likely responsible for the lower value obtained in entry 1. Certain diazoalkanes can undergo decomposition upon prolonged storage or warming, and nonvolatile impurities can be



X = H, F (**2.107**)

entry	diazoalkane	2-fluorobenzoic acid (M)	benzoic acid (M)
1	**2.108**	0.49 ± 0.05	0.34
2	**2.109**	0.133 ± 0.003	0.40
3	**2.110**	0.43 ± 0.01	1.26
4	**2.25**	1.16 ± 0.03	1.23
5	**2.84**	1.19 ± 0.01	1.33
6	**2.82**	0.62 ± 0.01	0.68
7	**2.72**	0.60 ± 0.01	0.64
8	**2.80**	0.56 ± 0.02	0.69
9	**2.78**	0.227 ± 0.002	0.29
10	**2.74**	0.826 ± 0.006	1.05
11	**2.86**	0.57 ± 0.02	0.64
12	**2.111**	0.53 ± 0.02	0.55
13	**2.112**	0.310 ± 0.009	0.38

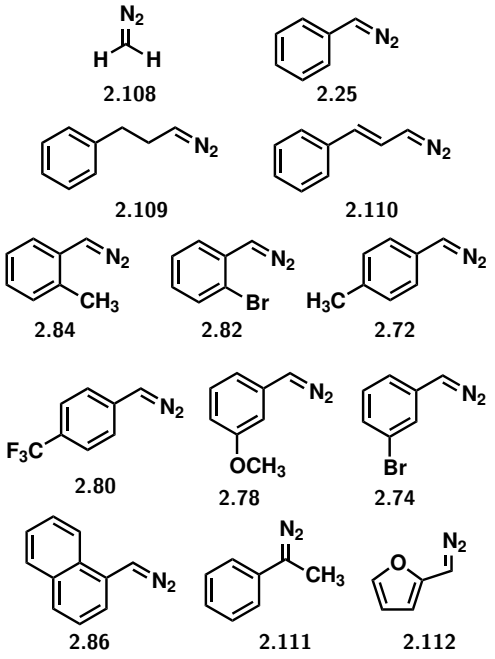
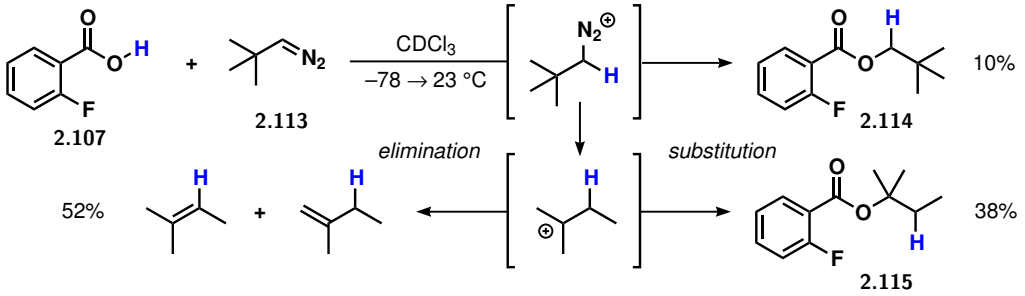


Table 2.4: Scope of titration with 2-fluorobenzoic acid and comparison to the gravimetric benzoate ester method.

introduced during preparative procedures.[82] Either of these complications can account for the higher concentration values observed with the gravimetric benzoylation method. The new titration procedure does not require isolation of the esters and was not affected by the presence of typical impurities.

The accuracy of this method, and all methods based on esterification, rely on quantitative conversion of the diazoalkanes to their corresponding esters. The concentration of unreacted phenyldiazomethane (**2.25**) was quickly analyzed in triplicate by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. The concentration was determined to be 1.25 ± 0.02 M by this method, in reasonable agreement with the value in Table 2.4 (entry 4). In certain cases, diazonium ions formed after the initial protonation event can undergo spontaneous rearrangement or elimination, ultimately leading to



Scheme 2.31: Production of elimination byproducts not observable by ^{19}F NMR.

byproducts that would not be observed by ^{19}F NMR spectroscopy.[88] When 1-diazo-2,2-dimethylpropane (**2.113**) was subjected to 2-fluorobenzoic acid, rapid rearrangement to the tertiary carbocation occured affording predominantly ester **2.115** and two elimination byproducts (Scheme 2.31). The expected ester **2.114**, resulting from direct substitution, only accounted for 10% of the product distribution. For diazoalkanes that undergo elimination, the use of ^{19}F NMR spectroscopy alone does not provide accurate concentration values. The concentration of **2.113** could still be determined from the combined ^{1}H and ^{19}F NMR data, although likely not with the same level of accuracy and precision as diazoalkanes which cleanly afford a single ester product.

[88] Curtin, D. Y.; Gerber, S. M. The Reaction of Aliphatic Diazo Compounds with Acids. *J. Am. Chem. Soc.* **1952**, *74*, 4052-4056.

2.5 Conclusion

In conclusion, this chapter has described a number of projects, not solely limited to diazoalkane ring expansion chemistry. Advances were first made in the procedures for racemic $Sc(OTf)_3$-catalyzed homologation reactions. By carefully purifying and drying all reaction components, catalyst loadings as low as 0.5 mol % were readily tolerated and reactions consistently afforded high chemical yields. With a conscientious and rigorous approach to reaction development, the first examples of catalytic asymmetric diazoalkane ring expansions were demonstrated. High enantioselectivities in the context of α-aryl medium-ring cycloalkanones were observed. The lower selectivities with smaller cycloalkanones prompted the development of a new π-extended amino alcohol and the corresponding bis(oxazoline) ligands. A scalable and inexpensive route was designed and provided the new amino alcohol in 4 steps from known compounds with one chromatography step. Finally, the need for a safe and convenient means to assay diazoalkane solution concentrations lead to the development of a quantitative ^{19}F NMR titration protocol.

Future work in this area will certainly focus on extending the substrate scope of asymmetric homologation reactions. We have taken the first steps towards developing a unified method for the construction of α-keto stereogenic centers. By modifying the diazoalkane nucleophile, access to α-aryl, –vinyl, and –alkyl all-carbon quaternary stereogenic centers could be within reach. The stigma and hazards of handling diazoalkane reagents may hamper future efforts, and research should concentrate on finding suitable methods to generate the diazoalkanes *in situ*. Without the need to prepare or store the hazardous diazoalkane reagents, this chemistry could find much broader appeal among the chemical community. The fact that the reaction rapidly builds significant molecular complexity in a single convergent step justifies its further development.

2.6 Experimental Data

2.6.1 *General Information*

Any practitioner seeking to repeat or adapt experiments reported herein must exercise caution and be cognizant that all diazoalkanes are likely *toxic* and *shock-sensitive*.[89] Diazomethane, a lethal yellow gas at ambient temperature, has been the culprit of several unpredictable and violent explosions.[90] Most diazomethane explosions have taken place during solvent free distillation, and the danger is largely a function of the reagent's volatility.[91] All of higher molecular weight aryldiazoalkanes prepared in this study exist as either viscous oils or solids at room temperature, significantly reducing the risk of explosion. However, the diazoalkanes are best handled in a well-ventilated fume hood as toluene stock solutions, and care must be taken to store and use stock solutions at -78 °C under inert atmosphere. Only one diazoalkane explosion has ever occured in our laboratories, and it was during an attempted vacuum distillation of phenyldiazomethane behind a blast shield.[92] In no situation should distillation be used, nor will be necessary, to purify any of the aryldiazoalkanes mentioned below.

General Procedures

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an atmosphere of nitrogen passed through a tower of finely powdered Drierite®in dry, degassed solvent with standard Schlenk or vacuum-line techniques. Particularly air-sensitive manipulations were performed in an MBraun Unilab nitrogen atmosphere glove box. Flash

[89] Lewinn, E. B. Diazomethane Poisoning: Report of A Fatal Case With Autopsy. *Am. J. Med. Sci.* **1949**, *218*, 543-548.
[90] De Boer, T. J.; Backer, H. J. Diazomethane. *Org. Synth.* **1956**, *36*, 16.
[91] Proctor, L. D.; Warr, A. J. Development of a Continuous Process for the Industrial Generation of Diazomethane. *Org. Process Res. Dev.* **2002**, *6*, 884-892.
[92] Fulton, J. R.; Aggarwal, V. K.; De Vicente, J. The Use of Tosylhydrazone Salts as a Safe Alternative for Handling Diazo Compounds and Their Applications in Organic Synthesis. *Eur. J. Org. Chem.* **2005**, 1479-1492.

column chromatography was performed according to the procedure of Still *et al.*[93] with ZEOPrep 60 Eco 40-63 μm silica gel. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F254 plates purchased from EMD Chemicals. TLC plates were visualized by exposure to ultraviolet light and/or ceric ammonium molybdate, *p*-anisaldehyde, or potassium permanganate stains. Preparative thin-layer chromatography was performed on 500 micron (20 x 20 cm) Analtech silica gel GF plates.

Materials

Benzene, toluene, tetrahydrofuran (THF), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were dispensed under UHP argon from a Glass Contour solvent purification system custom manufactured by SG Waters, LLC (Nashua, NH). Deuterated chloroform ($CDCl_3$), deuterated acetonitrile (CD_3CN), deuterated DMSO (DMSO-d_6), and deuterated 1,1,2,2-tetrachloroethane (TCE-d_2) were purchased from Cambridge Isotope Labs and used as received. Toluene and CH_2Cl_2 used for homologation reactions was stored over 3Å sieves in an inert atmosphere glove box after thoroughly degassing. Scandium triflate (99%) was purchased from Aldrich and then finely powdered and dried at 200 °C over P_2O_5 for 24 hours under high vacuum (approximately 0.1 mm Hg) before taking in an inert atmosphere glove box with rigorous Schlenk techniques. All ligands used in this study were either purchased from Aldrich, prepared according to literature procedures, or synthesized according to the procedures below then dried over P_2O_5 under high vacuum just below their melting points for at least 24 hours before taking in a glove box. Molecular sieves (3Å, 4-8 mesh) were purchased from Aldrich and activated by drying under vacuum (approx. 30 mmHg) at 250 °C for at least 6 hours prior to use. 2-Fluorobenzoic acid was purchased from Aldrich, sublimed at 100 °C under high vacuum (approximately 1 mm Hg), and dried *in vacuo* over P_2O_5 at room temperature for 24 h

[93] Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.

before use. 2,2'-Azobis(isobutyronitrile) (AIBN) was purchased from Aldrich and recrystallized from methanol. Oxalyl chloride ($(COCl)_2$) was purchased from Alfa Aesar and fractionally distilled under nitrogen. Dimethylsulfoxide (DMSO) was purchased from Aldrich and vacuum distilled from calcium hydride. Triethylamine (Et_3N) was purchased from Aldrich and freshly distilled from calcium hydride before use. *N*-Bromosuccinimide (NBS) was purchased from Acros Organics, recrystallized from H_2O, dried over P_2O_5, and stored cold away from light. Cyclobutanone was prepared according to the literature procedure[94] then fractionally distilled and stored over 3Å sieves. Cyclohexanone and cycloheptanone (Aldrich) were distilled from calcium chloride and stored over 3Å sieves. Cyclooctanone, 4-*tert*-butylcyclohexanone, and cyclododecanone (Aldrich) were sublimed under high vacuum then stored as a 1M stock solution in toluene over 3Å sieves in an inert atmosphere glove box. All aldehydes and ketones used for the synthesis of diazoalkanes were purified by distillation or recrystallization according to the reported procedures.[95] Naproxen sodium (CVS generic brand) was purchased CVS pharmacy (Allston, MA) and used as received. Hydrazine hydrate, 4-nitrobenzoyl chloride, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride ($EDC \cdot HCl$), (*R*)– and (*S*)-α-acetylmandelic acid, Red-Al, and K-selectride, dimethyl malonate, 2-methylnaphthalene, phosphorous pentoxide (P_2O_5), lithium aluminum hydride ($LiAlH_4$), thionyl chloride ($SOCl_2$), aluminum chloride ($AlCl_3$), 4-(dimethylamino)pyridine (DMAP), *N*,*N*'-dicyclohexylcarbodiimide (DCC), anhydrous 1,2-dichloroethane (1,2-DCA), diethyl malonimidate dihydrochloride, and copper (II) chloride ($CuCl_2$) were purchased from Aldrich and used as received. Borane-dimethyl sulfide ($BH_3 \cdot DMS$) was purchased from Alfa Aesar and used without further purification. Methyl iodide (CH_3I) was purchased from Acros Organics and used without further purification. Concentrated hydrochloric acid (HCl), concentrated sulfuric acid (H_2SO_4), potassium hydroxide (KOH), sodium hydroxide (NaOH), ammonium chloride (NH_4Cl), anhydrous sodium sulfate (Na_2SO_4), magnesium

[94] Krumpolc, M.; Rocek, J. Cyclobutanone. *Org. Synth.* **1981**, *60*, 20.

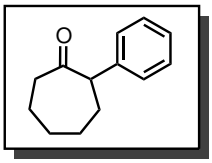
[95] Armarego, W. L. F.; Chai, C. L. *Purification of Laboratory Chemicals*, 5th ed.; Butterworth-Heinemann: Oxford, 2003.

sulfate ($MgSO_4$), Celite® 545, methanol (CH_3OH), ethyl acetate (EtOAc), and hexanes were purchased from Fisher Scientific and used as received.

Instrumentation

Infrared spectra were recorded on a Bruker Alpha-p spectrometer. Bands are reported as strong (s), medium (m), weak (w), broad strong (bs), broad medium (bm), and broad weak (bw). Optical rotation data were recorded on a Rudolph research Autopol IV automatic polarimeter and has been reported as the average of five readings. Melting points were recorded on a Digimelt MPA160 SRS and are uncorrected. Sonication was performed with a Misonix® Sonicator 3000 equipped with a Laude external circulator. ^{1}H NMR spectra were recorded on a Varian VNMRS (500 MHz), VNMRS (400 MHz), or INOVA (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26, DMSO-d_6: δ 2.50). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublets of doublets, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian VNMRS (125 MHz), VNMRS (100 MHz), or INOVA (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.16, CD_3CN: δ 118.26, DMSO-d_6: δ 39.52, TCE-d_2: δ 73.78). ^{19}F NMR spectra were recorded on a Varian VNMRS 470 MHz spectrometer with complete carbon decoupling and are referenced with hexafluorobenzene as an internal standard (C_6F_6 in $CDCl_3$: δ −164.9). Supercritical fluid chromatography (SFC) data were obtained on a Berger Instruments system using Daicel CHIRALPAK® AS-H or AD-H columns (ϕ 4.6 mm, 25 cm length). Gas chromatography (GC) analysis was performed on an Agilent Technologies 7890A system equipped with a flame ionization detector and HP-5 column (30 m x 0.320 mm x 0.25 μm). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility.

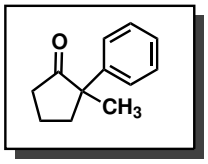
2.6.2 *Experimental Procedures and Characterization Data*



Representative procedure for racemic homologations:

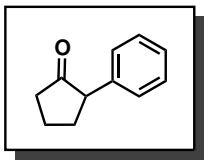
2-phenylcycloheptanone (**2.26**). In an inert atmosphere glovebox scandium triflate (6.2 mg, 0.012 mmol, 0.48 mol %) was suspended in 0.4 mL of toluene. The suspension was moved to a nitrogen manifold, and cyclohexanone (311 μL, 3.00 mmol, 1.19 equiv) was added in a single portion. The solution was stirred for 5 minutes at room temperature then cooled to −78 °C. Phenyldiazomethane **2.25** (2.10 mL, 2.52 mmol, 1.20 M in toluene, 1.00 equiv) was added, and the reaction mixture was warmed to 0 °C. An 18 gauge exit needle was used to relieve excess pressure generated by the copious amounts of nitrogen gas evolved. After 15 minutes, the pale yellow solution was diluted with 30 mL of ether, washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (8% ethyl acetate in hexanes v/v) afforded the desired compound **2.26** as a colorless oil (436 mg, 91.9%) that solidified just below room temperature.

$R_f = 0.20$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.29 (m, 2H), 7.27-7.21 (m, 3H), 3.73 (dd, J = 11.3, 4.1 Hz, 1H), 2.70 (ddd, J = 13.3, 13.3, 3.1 Hz, 1H), 2.57-2.49 (m, 1H), 2.20-2.11 (m, 1H), 2.10-1.91 (m, 4H), 1.72-1.58 (m, 1H), 1.54-1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.6, 140.5, 128.6, 128.0, 127.0, 58.9, 42.8, 32.1, 30.1, 28.7, 25.4; IR (neat) 3028 (w), 2929 (m), 2855 (w), 1702 (s), 1495 (w), 1452 (m), 719 (w), 698 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{13}H_{17}O$ $[M+H]^+$: 189.1279; Found 189.1277.

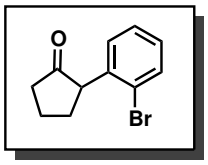


2-methyl-2-phenylcyclopentanone (**2.31**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (24.6 mg, 0.0500 mmol, 1.00 mol %) suspended in 16.1 mL of CH_2Cl_2, cyclobutanone (411 μL, 5.50 mmol, 1.10 equiv), and **2.111** (11.4 mL, 5.0 mmol, 0.44 M in toluene, 1.00 equiv). Purification by column chromatography afforded **2.31** as a colorless oil (857 mg, 98.3%).

R_f = 0.33 (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (m, 4H), 7.25-7.21 (m, 1H), 2.58-2.53 (m, 1H), 2.37-2.33 (m, 2H), 2.05-1.84 (m, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 220.77, 142.75, 128.69, 126.78, 126.41, 53.23, 38.22, 37.76, 25.16, 18.86; IR (neat) 2965 (bm), 2870 (bw), 1735 (s), 1496 (m), 1445 (m), 1156 (m), 1056 (m), 760 (m), 670 (m), 545 (bm) cm^{-1}; HRMS (ESI+) Calcd. for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123; Found 175.1128.

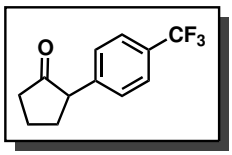


2-phenylcyclopentanone (**2.30**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (24.6 mg, 0.0500 mmol, 1.00 mol %) suspended in 6.2 mL of CH_2Cl_2, cyclobutanone (392 μL, 5.25 mmol, 1.05 equiv), and **2.25** (3.76 mL, 5.00 mmol, 1.33 M in toluene, 1.00 equiv). Purification by column chromatography afforded **2.30** as a white solid (794 mg, 99.2%), mp 37-39 °C. R_f = 0.33 (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (m, 2H), 7.27-7.23 (m, 1H), 7.21-7.18 (m, 2H), 3.33 (dd, J = 11.7, 8.8 Hz, 1H), 2.55-2.44 (m, 2H), 2.30 (ddd, J = 19.5, 10.7, 8.8 Hz, 1H), 2.21-2.08 (m, 2H), 1.99-1.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 218.20, 138.57, 128.73, 128.27, 127.03, 55.45, 38.58, 31.89, 21.00; IR (neat) 2961 (bw), 1737 (s), 1495 (m), 1452 (m), 1269 (bw), 1141 (m), 756 (m), 698 (s), 535 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{11}H_{13}O$ $[M+H]^+$: 161.0966; Found 161.0960.



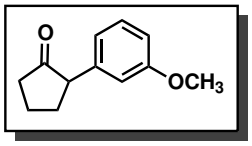
2-(2-bromophenyl)cyclopentanone (**2.32**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol %) suspended in 0.4 mL of CH_2Cl_2, cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2.82** (1.6 mL, 1.0 mmol, 0.64 M in toluene, 1.0 equiv). Purification by column chromatography afforded **2.32** as a white solid (228 mg, 95.4%), mp 50-53 °C. R_f = 0.35 (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.0, 1.5 Hz, 1H), 7.27 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 7.11 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.07 (dd, J = 7.6, 1.7 Hz, 1H), 3.80-3.74 (m, 1H), 2.60-2.49 (m, 2H), 2.41-2.32 (m, 1H), 2.22-2.15 (m, 1H), 2.08-1.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.54, 138.90,

133.20, 129.80, 128.67, 127.89, 125.23, 56.32, 38.74, 31.92, 21.03; IR (neat) 2964 (bm), 2879 (bw), 1740 (s), 1474 (m), 1438 (m), 1163 (m), 1146 (m),1022 (m), 825 (w), 754 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{11}H_{12}BrO$ $[M+H]^+$: 239.0072; Found 239.0079.



2-(4-trifluoromethylphenyl)cyclopentanone (**2.33**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol %) suspended in 1.1 mL of CH_2Cl_2, cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2.80** (943 μL, 1.00 mmol, 1.06 M in toluene, 1.00 equiv). Purification by column chromatography afforded **2.33** as a white solid (209 mg, 91.6%), mp 33-35 °C.

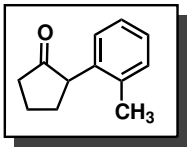
R_f = 0.30 (20% ethyl acetate hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 3.39 (dd, J = 12.0, 8.8 Hz, 1H), 2.58-2.47 (m, 2H), 2.31 (ddd, J = 19.3, 10.5, 8.5 Hz, 1H), 2.24-2.08 (m, 2H), 2.02-1.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.98, 142.41, 129.35 (q, $J_{C\text{-}F}$ = 32.2 Hz), 128.64, 125.63 (q, $J_{C\text{-}F}$ = 4.1 Hz), 124.31 (q, $J_{C\text{-}F}$ = 272.0 Hz), 55.19, 38.44, 31.57, 20.94; IR (neat) 2967 (bw), 2883 (bw), 1743 (m), 1619 (w), 1326 (s), 1163 (m), 1120 (bs), 1069 (m), 840 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{12}H_{12}F_3O$ $[M+H]^+$: 229.0840; Found 229.0848.



2-(3-methoxyphenyl)cyclopentanone (**2.34**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol %) suspended in 1.1 mL of CH_2Cl_2, cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2.78** (943 μL, 1.00 mmol, 1.06 M in toluene, 1.00 equiv). Purification by column chromatography afforded **2.34** as a colorless oil (167 mg, 87.8%).

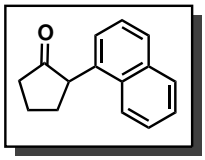
R_f = 0.24 (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, J = 7.8, 7.8 Hz, 1H), 6.81-6.77 (m, 2H), 6.75 (dd, J = 2.2, 2.2 Hz, 1H), 3.80 (s, 3H), 3.30 (dd, J = 11.7, 9.0 Hz, 1H), 2.54-2.43 (m, 2H), 2.30 (ddd, J = 19.5, 11.0, 9.0 Hz, 1H), 2.20-2.07 (m, 2H), 1.98-1.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.95, 159.85, 140.10, 129.68, 120.58, 114.30, 112.26, 55.39, 55.32, 38.57, 31.85, 20.98; IR (neat) 2961 (bm), 2875 (bw),

1739 (s), 1601 (m), 1583 (m), 1490 (m), 1245 (bm), 1159 (m), 1041 (bm), 779 (bm), 695 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{12}H_{15}O_2$ $[M+H]^+$: 191.1072; Found 191.1081.



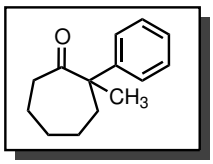
2-(2-methylphenyl)cyclopentanone (**2.35**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol %) suspended in 1.2 mL of CH_2Cl_2, cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2.84** (769 μL, 1.00 mmol, 1.30 M in toluene, 1.00 equiv). Purification by column chromatography afforded **2.35** as a colorless oil (162 mg, 93.0%).

$R_f = 0.36$ (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.13 (m, 3H), 7.01-6.99 (m, 1H), 3.53 (dd, J = 11.7, 8.0 Hz, 1H), 2.54-2.45 (m, 2H), 2.33 (ddd, J = 19.5, 10.8, 8.9 Hz, 1H), 2.32 (s, 3H), 2.22-2.15 (m, 1H), 2.09-1.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 218.81, 137.68, 136.90, 130.67, 127.46, 127.01, 126.40, 53.12, 38.82, 31.82, 21.17, 20.04; IR (neat) 2963 (bm), 2879 (bw), 1740 (s), 1493 (w), 1461 (bw), 1146 (m), 756 (m), 727 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123; Found 175.1122.



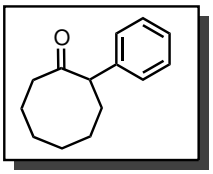
2-(napthalen-1-yl)cyclopentanone (**2.36**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol %) suspended in 0.3 mL of CH_2Cl_2, cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2.86** (1.7 mL, 1.0 mmol, 0.58 M in toluene, 1.0 equiv). Purification by column chromatography afforded **2.36** as a white solid (200 mg, 95.1%), mp 93-95 °C.

$R_f = 0.27$ (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2H), 7.77 (d, J = 8.3 Hz, 1H), 7.53-7.47 (m, 2H), 7.43 (dd, J = 8.3, 7.3 Hz, 1H), 7.25 (dd, J = 7.3, 1.0 Hz, 1H), 4.08 (dd, J = 8.8, 8.8 Hz), 2.68-2.56 (m, 2H), 2.52-2.43 (m, 1H), 2.28-2.17 (m, 2H), 2.13-2.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 218.73, 135.58, 134.23, 132.20, 129.10, 127.78, 126.20, 125.78, 125.62, 125.18, 123.75, 52.44, 39.13, 32.56, 21.30; IR (neat) 2964 (bw), 1738 (s), 1510 (w), 1400 (m), 1142 (m), 1114 (m), 798 (m), 778 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{15}O$ $[M+H]^+$: 211.1123; Found 211.1129.



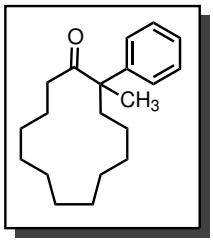
2-methyl-2-phenylcycloheptanone (**2.37**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol %), cyclohexanone (114 μL, 1.10 mmol, 1.10 equiv), and **2.111** (2.3 mL, 1.0 mmol, 0.44 M in toluene, 1.0 equiv). Purification by column chromatography afforded **2.37** as a colorless oil (206 mg, quantitative).

R_f = 0.43 (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34- 7.30 (m, 2H), 7.25-7.20 (m, 3H), 2.55 (ddd, J = 13.7, 11.2, 2.7 Hz, 1H), 2.34-2.28 (m, 1H), 2.22-2.17 (m, 2H), 1.99-1.91 (m, 1H), 1.88-1.80 (m, 2H), 1.57-1.39 (m, 2H), 1.35 (s, 3H), 1.33-1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.16, 145.09, 128.83, 126.74, 126.09, 55.97, 41.05, 36.77, 30.78, 27.10, 26.68, 24.49; IR (neat) 2930 (bm), 2858 (bw), 1702 (s), 1495 (w), 1458 (m), 764 (m), 700 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{19}O$ $[M+H]^+$: 203.1436; Found 203.1443.



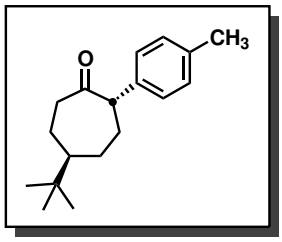
2-phenylcyclooctanone (**2.38**). Prepared according to the representative procedure above using $Sc(OTf)_3$ (24.6 mg, 0.0500 mmol, 1.00 mol %) suspended in 5.8 mL of toluene, cycloheptanone (710 μL, 6.00 mmol, 1.20 equiv), and **2.25** (4.17 mL, 5.00 mmol, 1.20 M in toluene, 1.00 equiv). Purification by column chromatography afforded **2.38** as a white solid (903 mg, 89.2%), mp 36-38 °C.

R_f = 0.33 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.28 (m, 4H), 7.26-7.20 (m, 1H), 3.79 (dd, J = 12.3, 2.7 Hz, 1H), 2.61 (ddd, J = 12.5, 12.5, 4.3 Hz, 1H), 2.42- 2.30 (m, 1H), 2.29-2.22 (m, 1H), 2.04-1.86 (m, 3H), 1.83-1.70 (m, 2H), 1.65-1.55 (m, 2H), 1.53-1.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.57, 139.49, 128.64, 127.91, 127.12, 57.53, 40.40, 31.67, 26.98, 26.88, 26.85, 24.76; IR (neat) 2927 (s), 2855 (w), 1698 (s), 1494 (w), 1449 (m), 700 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{19}O$ $[M+H]^+$: 203.1436; Found: 203.1439.



2-methyl-2-phenylcyclotridecanone (**2.39**). Prepared according to to the representative procedure above using $Sc(OTf)_3$ (24.6 mg, 0.0500 mmol, 7.00 mol %), however, rather then suspending the $Sc(OTf)_3$ in solvent, cyclododecanone (145 mg, 0.715 mmol, 1.00 equiv) was introduced to the $Sc(OTf)_3$ as a solution in 1.8 mL of CH_2Cl_2. The rest of the procedure was carried out as usual with **2.111** (1.8 mL, 0.79 mmol, 0.44 M in toluene, 1.1 equiv). Purification by column chromatography afforded **2.39** as a colorless semi-solid (191 mg, 83.8%).

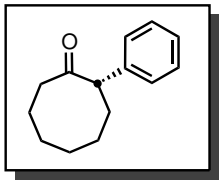
R_f = 0.43 (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.29 (m, 2H), 7.27-7.20 (m, 3H), 2.37 (ddd, J = 18.3, 9.0, 4.2 Hz, 1H), 2.24 (ddd, J = 12.9, 12.9, 3.2 Hz, 1H), 1.98 (dddd, J = 18.3, 4.6, 4.6, 4.6 Hz, 1H), 1.90 (ddd, J = 13.2, 13.2, 5.6 Hz, 1H), 1.84-1.76 (m, 1H), 1.61-1.54 (m, 1H), 1.51-1.39 (m, 2H), 1.38-1.22 (m, 11H), 1.36 (s, 3H), 1.21-1.14 (m, 1H), 1.14-1.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.65, 145.55, 128.73, 126.79, 126.50, 56.04, 36.86, 36.13, 27.56, 26.92, 26.64, 25.84, 25.72, 25.22, 24.75, 24.24, 22.26, 22.13; IR (neat) 2930 (bs), 2860 (bm), 1706 (s), 1495 (m), 1463 (m), 1445 (m), 763 (m), 700 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{20}H_{31}O$ $[M+H]^+$: 287.2375; Found 287.2376.



(±)-*trans*-5-*tert*-butyl-2-*p*-tolylcycloheptanone (**2.93**). Scandium triflate (49.2 mg, 0.10 mmol, 10 mol %) was suspended in 8 mL of toluene. To the stirred suspension, 4-*tert*-butylcyclohexanone (185 mg, 1.20 mmol, 1.20 equiv) was transferred *via* cannula in 2 mL of toluene without rinsing. After stirring for 10 minutes at room temperature, the clear solution was cooled to −78 °C and *p*-tolylphenyldiazomethane (1.5 mL, 1.0 mmol, 0.66 M in toluene, 1.0 equiv) was added *via* syringe. After 1 hour the pale yellow reaction mixture was diluted with 25 mL of Et_2O then washed with 25 mL of water and 25 mL of brine. The organics were dried over anhydrous Na_2SO_4 and concentrated to a faint yellow crude solid. Purification by flash column chromatography (10% ethyl acetate in hexanes) afforded

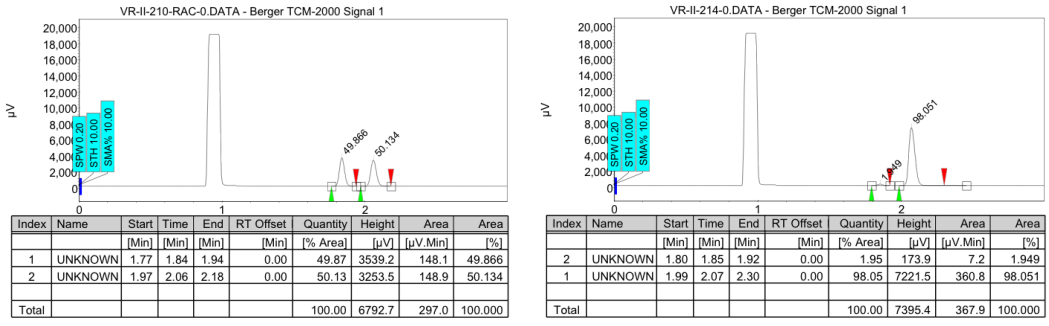
the *trans* diastereomer (±)-**2.93** as a white solid (227 mg, 87.8%), mp 90-92 °C. Suitable crystals for X-ray analysis were grown by slow evaporation of a supersaturated hexanes solution. GC analysis of the crude reaction mixture showed a 96.5:3.5 dr (HP-5, 150 °C hold 5 min, ramp 5 °C/min to 200 °C; t_R = 16.9 min (minor), 17.4 min (major)).

R_f = 0.30 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16-7.09 (m, 4H), 3.67 (dd, J = 11.9, 3.5 Hz, 1H), 2.68 (ddd, J = 16.2, 13.1, 3.3 Hz, 1H), 2.49 (ddd, J = 9.2, 6.3, 2.7 Hz, 1H), 2.32 (s, 3H), 2.23-2.13 (m, 2H), 2.12-2.04 (m, 1H), 2.01-1.90 (m, 1H), 1.49-1.38 (m, 1H), 1.26-1.12 (m, 2H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.10, 137.14, 136.66, 129.36, 127.74, 58.60, 52.16, 41.73, 33.67, 32.00, 29.76, 27.80, 26.94, 21.15; IR (neat) 2953 (bm), 2864 (bw), 1695 (s), 1513 (w), 1366 (w), 1235 (w), 828 (w), 797 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{18}H_{27}O$ $[M+H]^+$: 259.2062; Found: 259.2062.



Representative procedure for asymmetric homologations:

(*S*)-2-phenylcyclooctanone (**2.76**). In an inert atmosphere glove box scandium triflate (30.4 mg, 0.0618 mmol, 5.00 mol %) was weighed into a 25 mL scintillation vial. Ligand **2.66** (35.0 mg, 0.0679 mmol, 5.50 mol %) was transferred to the vial containing scandium triflate with 6.2 mL of toluene. The suspension was sealed with a rubber septum and stirred for 1.5 hours then removed from the glove box and to a nitrogen manifold. Cycloheptanone (146 μL, 1.24 mmol, 1.00 equiv) was added to the cloudy gray suspension and stirred for 15 minutes at which point the reaction mixture became clear and homogeneous. The reaction was cooled to −78 °C and phenyldiazomethane **2.25** (1.20 mL, 1.48 mmol, 1.20 M in toluene, 1.20 equiv) was added in a single portion. After 6 hours the cold reaction mixture was quickly poured into 20 mL of water and diluted with 30 mL of Et_2O. The organic layer was washed with 20 mL water, 20 mL of brine, dried over anhydrous Na_2SO_4, and concentrated to a crude yellow oil. Purification by column chromatography (10% ethyl acetate in hexanes) yielded **2.76** as a white solid (235 mg, 94.0%) with 97:3 er (AS-H, 50 °C, 150 psi, 3.0 mL/min, 4% MeOH, λ = 220 nm; t_R = 1.85 min (minor), 2.07 min (major)). Characterization data were in agreement with those tabulated above for the racemic compound. $[\alpha]_D^{20} = -138.8$ (c 1.26, $CHCl_3$).



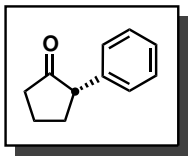
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	1.77	1.84	1.94	0.00	49.87	3539.2	148.1	49.866
2	UNKNOWN	1.97	2.06	2.18	0.00	50.13	3253.5	148.9	50.134
Total						100.00	6792.7	297.0	100.000

VR-II-210-RAC-0 -- AcqDate: 6/4/2010 3:51:10 AM
Description: AS-H, 50C, 150 psi, 3.0 ml/min, 4% MeOH, 220 nm, Sample EtOAc

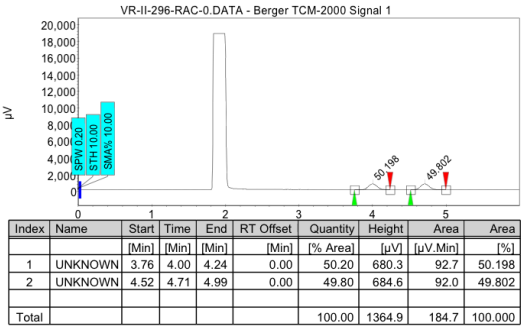
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
2	UNKNOWN	1.80	1.85	1.92	0.00	1.95	173.9	7.2	1.949
1	UNKNOWN	1.99	2.07	2.30	0.00	98.05	7221.5	360.8	98.051
Total						100.00	7395.4	367.9	100.000

VR-II-214-0 -- AcqDate: 6/4/2010 9:35:13 PM
Description: AS-H, 50C, 150 psi, 3.0 ml/min, 4% MeOH, 220 nm, Sample EtOAc

Figure 2.8: SFC trace for (*S*)-2-phenylcyclooctanone (**2.76**)

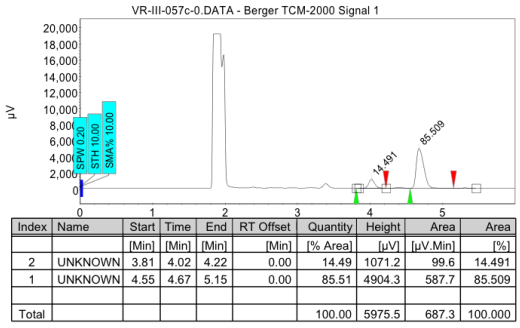


(*S*)-2-phenylcyclopentanone (**2.70**). Run for 1.5 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.66** (8.5 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cyclobutanone (16 μL, 0.18 mmol, 1.2 equiv), and **2.25** (203 μL, 0.15 mmol, 0.74 M in toluene, 1.0 equiv). The crude reaction mixture was not purified by column chromatography,[96] but instead poured into 15 mL of pentane and filtered through a cotton plug. The organics were washed with 10 mL of water, 10 mL of brine, and dried over Na_2SO_4. Concentration under high vacuum afforded a crude yellow oil that was taken up in 1.5 mL of hexanes and again filtered through a cotton plug. Concentration afforded **2.70** as a pale yellow oil (26.2 mg, quantitative) with 85.5:14.5 er (AS-H, 50 °C, 150 psi, 1.5 mL/min, 2% MeOH, λ = 220 nm; t_R = 4.02 min (minor), 4.67 min (major)). Characterization data were in agreement with those tabulated above for the racemic compound.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	3.76	4.00	4.24	0.00	50.20	680.3	92.7	50.198
2	UNKNOWN	4.52	4.71	4.99	0.00	49.80	684.6	92.0	49.802
Total						100.00	1364.9	184.7	100.000

VR-II-296-RAC-0 -- AcqDate: 9/13/2010 6:55:38 PM
Description: AS-H, 50C, 150 psi, 1.5 ml/min, 2% MeOH, 220 nm, Sample EtOAc

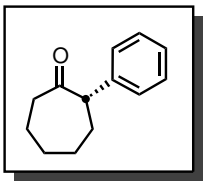


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
2	UNKNOWN	3.81	4.02	4.22	0.00	14.49	1071.2	99.6	14.491
1	UNKNOWN	4.55	4.67	5.15	0.00	85.51	4904.3	587.7	85.509
Total						100.00	5975.5	687.3	100.000

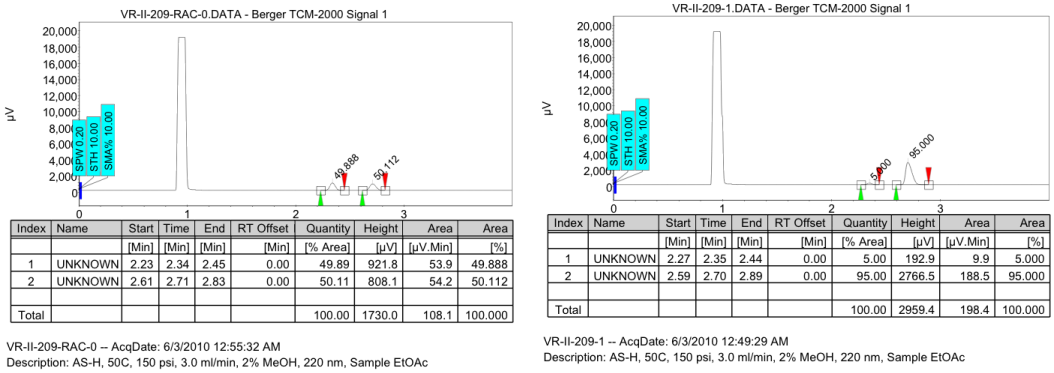
VR-III-057c-0 -- AcqDate: 11/19/2010 6:38:13 PM
Description: AS-H, 50C, 150 psi, 1.5 ml/min, 2% MeOH, 220 nm, Sample EtOAc

Figure 2.9: SFC trace for (*S*)-2-phenylcyclopentanone (**2.70**)

[96] Tertiary α-aryl cyclopentanones are known to racemize on silica gel. See reference 23 for details.



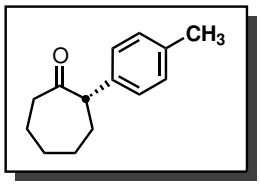
(*S*)-2-phenylcycloheptanone (**2.40**). Run for 1.5 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.66** (8.5 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cyclohexanone (19 μL, 0.18 mmol, 1.2 equiv), and **2.25** (203 μL, 0.15 mmol, 0.74 M in toluene, 1.0 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.40** as a colorless oil (26.5 mg, 94.0%) with 95:5 er (AS-H, 50 °C, 150 psi, 3.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 2.35 min (minor), 2.70 min (major)). Characterization data were in agreement with those tabulated above for the racemic compound. $[\alpha]_D^{20} = -138.2$ (c 0.80, $CHCl_3$).



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	2.23	2.34	2.45	0.00	49.89	921.8	53.9	49.888
2	UNKNOWN	2.61	2.71	2.83	0.00	50.11	808.1	54.2	50.112
Total						100.00	1730.0	108.1	100.000

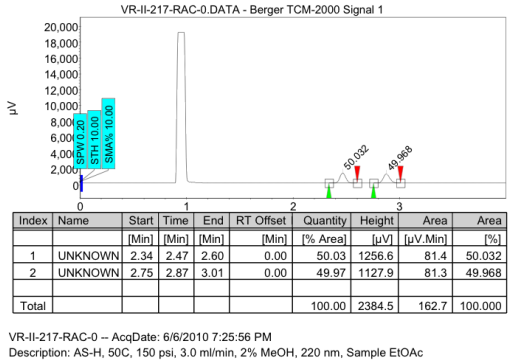
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	2.27	2.35	2.44	0.00	5.00	192.9	9.9	5.000
2	UNKNOWN	2.59	2.70	2.89	0.00	95.00	2766.5	188.5	95.000
Total						100.00	2959.4	198.4	100.000

Figure 2.10: SFC trace for (*S*)-2-phenylcycloheptanone (**2.40**)

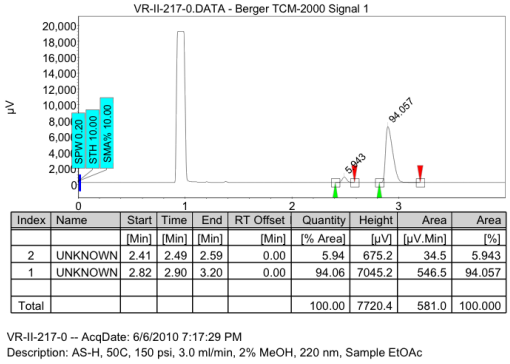


(*S*)-2-(4-methylphenyl)cycloheptanone (**2.73**). Run for 1.5 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.66** (8.5 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cyclohexanone (19 μL, 0.18 mmol, 1.2 equiv), and **2.72** (227 μL, 0.15 mmol, 0.66 M in toluene, 1.0 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.73** as a colorless oil (29.2 mg, 96.4%) with 94:6 er (AS-H, 50 °C, 150 psi, 3.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 2.49 min (minor), 2.90 min (major)).

$[\alpha]_D^{20} = -154.5$ (c 0.47, $CHCl_3$); $R_f = 0.18$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16-7.10 (m, 4H), 3.69 (dd, J = 11.3, 4.1 Hz, 1H), 2.73-2.64 (m, 1H), 2.55-2.47 (m, 1H), 2.32 (s, 3H), 2.18-2.08 (m, 1H), 2.08-1.89 (m, 4H), 1.70-1.56 (m, 1H), 1.52-1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.77, 137.46, 136.61, 129.35, 127.80, 58.56, 42.71, 32.04, 30.18, 28.63, 25.51; IR (neat) 3022 (bw), 2927 (bm), 2856 (w), 1702 (s), 1513 (m), 1454 (bm), 1163 (w), 1129 (w), 825 (w), 789 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{19}O$ $[M+H]^+$: 203.1436; Found 203.1445.

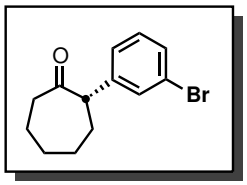


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	2.34	2.47	2.60	0.00	50.03	1256.6	81.4	50.032
2	UNKNOWN	2.75	2.87	3.01	0.00	49.97	1127.9	81.3	49.968
Total						100.00	2384.5	162.7	100.000



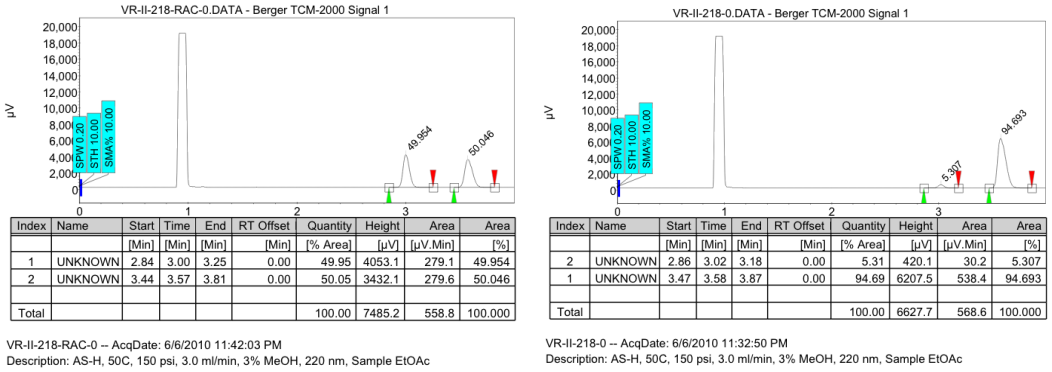
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
2	UNKNOWN	2.41	2.49	2.59	0.00	5.94	675.2	34.5	5.943
1	UNKNOWN	2.82	2.90	3.20	0.00	94.06	7045.2	546.5	94.057
Total						100.00	7720.4	581.0	100.000

Figure 2.11: SFC trace for (*S*)-2-(4-methylphenyl)cycloheptanone (**2.73**)



(*S*)-2-(3-bromophenyl)cycloheptanone (**2.75**). Run for 3 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.66** (8.5 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cyclohexanone (19 μL, 0.18 mmol, 1.2 equiv), and **2.74** (125 μL, 0.15 mmol, 1.20 M in toluene, 1.0 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.75** as a colorless oil (41.1 mg, quantitative) with 94.5:5.5 er (AS-H, 50 °C, 150 psi, 3.0 mL/min, 3% MeOH, λ = 220 nm; t_R = 3.02 min (minor), 3.58 min (major)).

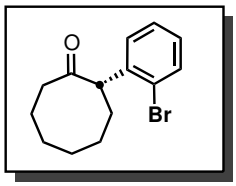
$[\alpha]_D^{20} = -102.7$ (c 1.05, $CHCl_3$); $R_f = 0.27$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.34 (m, 2H), 7.20-7.12 (m, 2H), 3.70 (dd, J = 11.2, 3.7 Hz, 1H), 2.69-2.60 (m, 1H), 2.59-2.51 (m, 1H), 2.14-1.86 (m, 5H), 1.72-1.59 (m, 1H), 1.54-1.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.67, 142.80, 131.11, 130.10, 130.07, 126.83, 122.63, 58.57, 43.06, 32.19, 29.87, 28.82, 25.10; IR (neat) 2928 (m), 2855 (w), 1702 (s), 1593 (w), 1566 (w), 1475 (w), 1454 (w), 1129 (w), 1074 (w), 937 (w), 779 (w), 690 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{13}H_{16}BrO$ $[M+H]^+$: 269.0364; Found: 269.0401.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	2.84	3.00	3.25	0.00	49.95	4053.1	279.1	49.954
2	UNKNOWN	3.44	3.57	3.81	0.00	50.05	3432.1	279.6	50.046
Total						100.00	7485.2	558.8	100.000

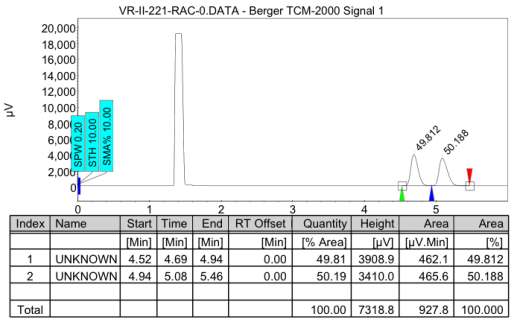
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
2	UNKNOWN	2.86	3.02	3.18	0.00	5.31	420.1	30.2	5.307
1	UNKNOWN	3.47	3.58	3.87	0.00	94.69	6207.5	538.4	94.693
Total						100.00	6627.7	568.6	100.000

Figure 2.12: SFC trace for (*S*)-2-(3-bromophenyl)cycloheptanone (**2.75**)



(*S*)-2-(2-bromophenyl)cyclooctanone (**2.83**). Run for 14 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.60** (5.9 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2.82** (370 μL, 0.21 mmol, 0.57 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.83** as a colorless oil (35.9 mg, 85.0%) with 92.5:7.5 er (AS-H, 50 °C, 150 psi, 2.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 4.65 min (major), 5.09 min (minor)).

$[\alpha]_D^{20} = -1.9$ (c 0.99, $CHCl_3$); R_f = 0.21 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54-7.48 (m, 2H), 7.34-7.28 (m, 1H), 7.12-7.05 (m, 1H), 4.67 (dd, J = 11.5, 3.3 Hz, 1H), 2.74 (ddd, J = 14.9, 7.4, 3.1 Hz, 1H), 2.49-2.40 (m, 1H), 2.39-2.25 (m, 1H), 2.15-2.04 (m, 1H), 2.03-1.88 (m, 2H), 1.86-1.66 (m, 3H), 1.65-1.52 (m, 2H), 1.37-1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.99, 139.78, 132.55, 130.04, 128.33, 127.68, 124.54, 52.89, 44.67, 35.56, 28.61, 25.74, 25.08, 23.87; IR (neat) 3063 (bw), 2927 (bm), 2856 (bw), 1705 (s), 1467 (m), 1440 (m), 1326 (w), 1157 (w), 1021 (m), 743 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{18}BrO$ $[M+H]^+$: 281.0541; Found: 281.0571.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	4.52	4.69	4.94	0.00	49.81	3908.9	462.1	49.812
2	UNKNOWN	4.94	5.08	5.46	0.00	50.19	3410.0	465.6	50.188
Total						100.00	7318.8	927.8	100.000

VR-II-221-RAC-0 -- AcqDate: 6/7/2010 2:40:15 AM
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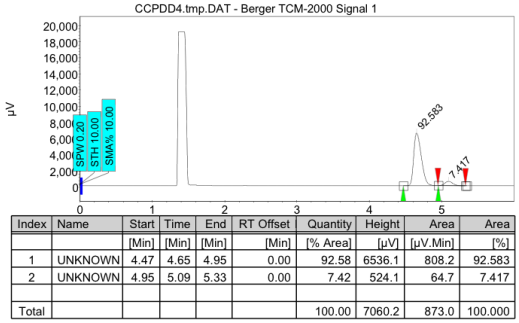
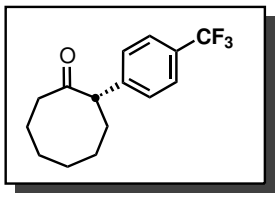


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	4.47	4.65	4.95	0.00	92.58	6536.1	808.2	92.583
2	UNKNOWN	4.95	5.09	5.33	0.00	7.42	524.1	64.7	7.417
Total						100.00	7060.2	873.0	100.000

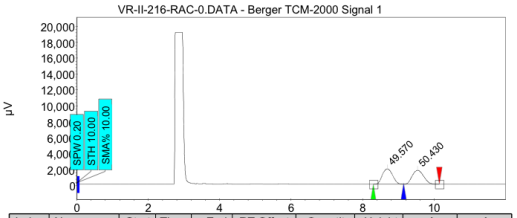
VR-II-221-0 -- AcqDate: 6/7/2010 2:31:51 AM
Description: AS-H, 50C, 150 psi, 2.0 ml/min, 2% MeOH, 220 nm, Sample EtOAc

Figure 2.13: SFC trace for (*S*)-2-(2-bromophenyl)cyclooctanone (**2.83**)



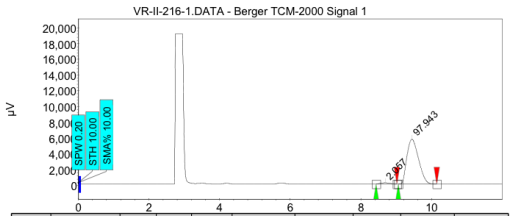
(*S*)-2-(4-trifluromethylphenyl)cyclooctanone (**2.81**). Run for 14 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.66** (8.5 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2.80** (320 μL, 0.21 mmol, 0.66 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.81** as a colorless oil (31.7 mg, 78.3%) with 98:2 er (AD-H, 50 °C, 150 psi, 1.0 mL/min, 3% MeOH, λ = 220 nm; t_R = 8.69 min (minor), 9.44 min (major)).

$[\alpha]_D^{20} = -93.52$ (c 0.88, $CHCl_3$); $R_f = 0.18$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 3.92 (dd, J = 12.1, 2.9 Hz, 1H), 2.55 (ddd, J = 12.5, 12.5, 3.7 Hz, 1H), 2.38- 2.22 (m, 2H), 2.10-1.97 (m, 2H), 1.96-1.86 (m, 1H), 1.84-1.69 (m, 2H), 1.64-1.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.72, 143.67 (q, $J_{C\text{-}F}$ = 1.5 Hz), 129.40 (q, $J_{C\text{-}F}$ = 32.2 Hz), 128.44, 125.50 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.30 (q, $J_{C\text{-}F}$ = 271.5 Hz), 56.73, 41.40, 32.97, 27.22, 26.44, 26.18, 24.75; IR (neat) 2935 (bw), 2860 (bw), 1703 (m), 1617 (w), 1466 (w), 1447 (w), 1419 (w), 1325 (s), 1163 (m), 1122 (m), 1069 (m), 1019 (m), 838 (bw) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{18}F_3O$ $[M+H]^+$: 271.1310; Found: 271.1341.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	8.30	8.69	9.15	0.00	49.57	1904.0	627.0	49.570
2	UNKNOWN	9.15	9.54	10.15	0.00	50.43	1726.3	637.9	50.430
Total						100.00	3630.3	1264.8	100.000

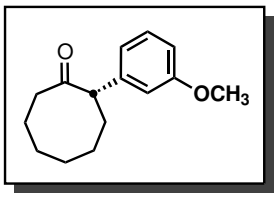
VR-II-216-RAC-0 -- AcqDate: 6/7/2010 3:08:44 AM
Description: AD-H, 50C, 150 psi, 1.0 ml/min, 3% MeOH, 220 nm, Sample EtOAc



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
2	UNKNOWN	8.43	8.69	9.02	0.00	2.06	151.1	45.6	2.057
1	UNKNOWN	9.06	9.44	10.15	0.00	97.94	5688.2	2169.0	97.943
Total						100.00	5839.3	2214.6	100.000

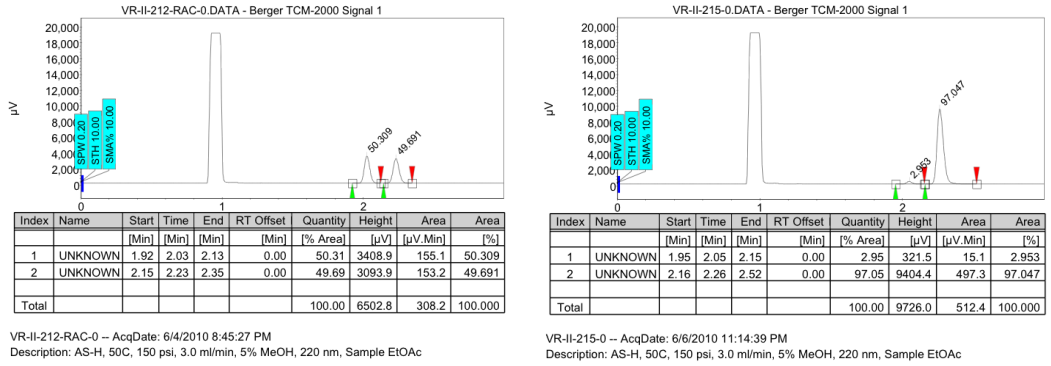
VR-II-216-1 -- AcqDate: 6/7/2010 3:24:28 AM
Description: AD-H, 50C, 150 psi, 1.0 ml/min, 3% MeOH, 220 nm, Sample EtOAc

Figure 2.14: SFC trace for (*S*)-2-(4-trifluromethylphenyl)cyclooctanone (**2.81**)



(*S*)-2-(3-methoxyphenyl)cyclooctanone (**2.79**). Run for 3 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.66** (8.5 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2.78** (200 μL, 0.21 mmol, 1.0 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.79** as a colorless oil (35.1 mg, quantitative) with 97:3 er (AS-H, 50 °C, 150 psi, 2.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 2.05 min (minor), 2.26 min (major)).

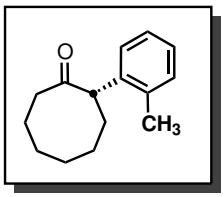
$[\alpha]_D^{20} = -116.3$ (c 0.99, $CHCl_3$); $R_f = 0.16$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.18 (m, 1H), 6.94-6.88 (m, 2H), 6.80-6.75 (m, 1H), 3.80 (s, 3H), 3.75 (dd, J = 12.5, 2.7 Hz, 1H), 2.62 (ddd, J = 11.7, 4.7 Hz, 1H), 2.41-2.29 (m, 1H), 2.29-2.21 (m, 1H), 2.03- 1.84 (m, 3H), 1.82-1.69 (m, 2H), 1.64-1.53 (m, 2H), 1.53-1.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.41, 159.79, 140.98, 129.53, 120.21, 113.81, 112.41, 57.60, 55.31, 40.25, 31.44, 27.10, 26.87, 26.80, 24.74; IR (neat) 2929 (s), 2856 (w), 1697 (s), 1598 (m), 1583 (m), 1491 (m), 1465 (m), 1286 (s), 1048 (m), 767 (w), 696 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1542; Found: 233.1560.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	1.92	2.03	2.13	0.00	50.31	3408.9	155.1	50.309
2	UNKNOWN	2.15	2.23	2.35	0.00	49.69	3093.9	153.2	49.691
Total						100.00	6502.8	308.2	100.000

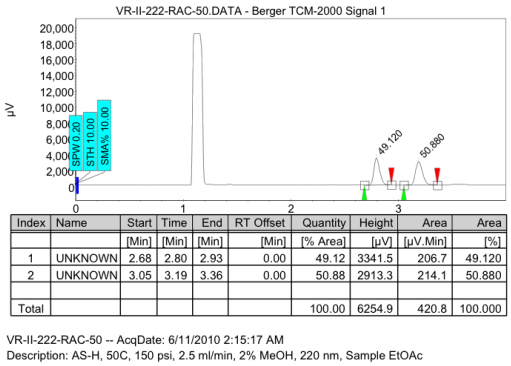
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	1.95	2.05	2.15	0.00	2.95	321.5	15.1	2.953
2	UNKNOWN	2.16	2.26	2.52	0.00	97.05	9404.4	497.3	97.047
Total						100.00	9726.0	512.4	100.000

Figure 2.15: SFC trace for (*S*)-2-(3-methoxyphenyl)cyclooctanone (**2.79**)



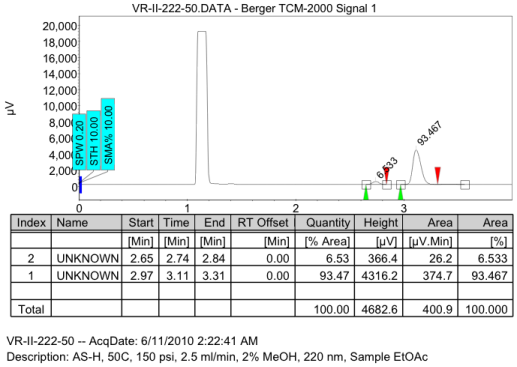
(*S*)-2-(2-methylphenyl)cyclooctanone (**2.85**). Run for 14 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.60** (5.9 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2.84** (180 μL, 0.21 mmol, 1.2 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.85** as a colorless oil (31.3 mg, 96.6%) with 93.5:6.5 er (AS-H, 50 °C, 150 psi, 2.5 mL/min, 2% MeOH, λ = 220 nm; t_R = 2.74 min (minor), 3.11 min (major)).

$[\alpha]_D^{20} = -98.1$ (c 1.26, $CHCl_3$); $R_f = 0.21$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.41 (m, 1H), 7.23-7.17 (m, 1H), 7.16-7.10 (m, 2H), 4.06 (dd, J = 12.1, 2.7 Hz, 1H), 2.72 (ddd, J = 13.1, 11.7, 4.3 Hz, 1H), 2.46-2.35 (m, 1H), 2.40 (s, 3H), 2.33-2.23 (m, 1H), 2.01- 1.87 (m, 3H), 1.84-1.71 (m, 2H), 1.67-1.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.22, 138.06, 136.47, 130.63, 127.04, 126.83, 126.33, 53.04, 40.77, 32.02, 27.21, 27.15, 27.04, 24.91, 20.21; IR (neat) 3096 (w), 3020 (w), 2927 (bs), 2856 (w), 1697 (s), 1488 (w), 1464 (m), 1446 (m), 1325 (m), 1160 (w), 1123 (w), 845 (w), 755 (bm), 730 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{21}O$ $[M+H]^+$: 217.1591; Found: 217.1592.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	2.68	2.80	2.93	0.00	49.12	3341.5	206.7	49.120
2	UNKNOWN	3.05	3.19	3.36	0.00	50.88	2913.3	214.1	50.880
Total						100.00	6254.9	420.8	100.000

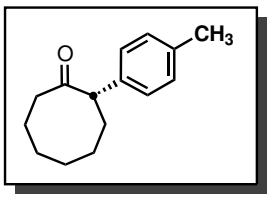
VR-II-222-RAC-50 -- AcqDate: 6/11/2010 2:15:17 AM
Description: AS-H, 50C, 150 psi, 2.5 ml/min, 2% MeOH, 220 nm, Sample EtOAc



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
2	UNKNOWN	2.65	2.74	2.84	0.00	6.53	366.4	26.2	6.533
1	UNKNOWN	2.97	3.11	3.31	0.00	93.47	4316.2	374.7	93.467
Total						100.00	4682.6	400.9	100.000

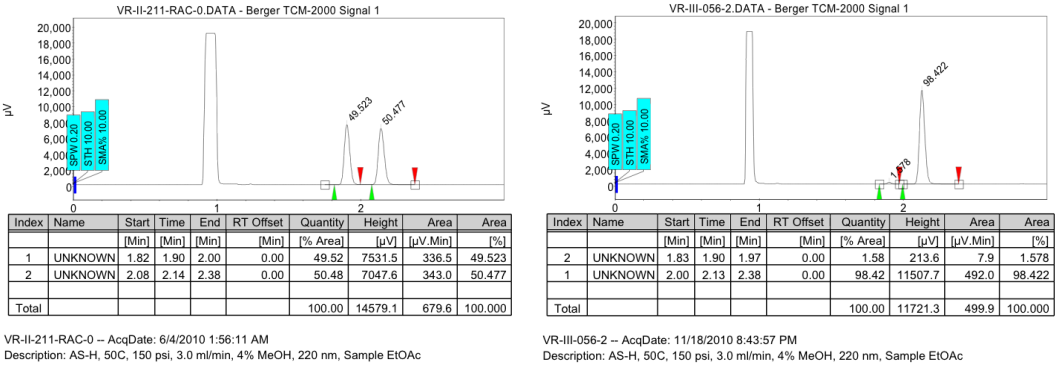
VR-II-222-50 -- AcqDate: 6/11/2010 2:22:41 AM
Description: AS-H, 50C, 150 psi, 2.5 ml/min, 2% MeOH, 220 nm, Sample EtOAc

Figure 2.16: SFC trace for (*S*)-2-(2-methylphenyl)cyclooctanone (**2.85**)



(*S*)-2-(4-methylphenyl)cyclooctanone (**2.77**). Run for 3 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.66** (8.5 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2.72** (320 μL, 0.21 mmol, 0.66 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.77** as a colorless oil (32.5 mg, quantitative) with 98.5:1.5 er (AS-H, 50 °C, 150 psi, 3.0 mL/min, 4% MeOH, λ = 220 nm; t_R = 1.90 min (minor), 2.13 min (major)).

$[\alpha]_D^{20} = -148.9$ (c 0.98, $CHCl_3$); $R_f = 0.37$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 3.74 (dd, J = 12.3, 2.7 Hz, 1H), 2.61 (ddd, J = 12.7, 11.7, 4.5 Hz, 1H), 2.42-2.29 (m, 1H), 2.31 (s, 3H), 2.26- 2.20 (m, 1H), 2.00-1.85 (m, 3H), 1.81-1.70 (m, 2H), 1.63-1.54 (m, 2H), 1.53-1.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.75, 136.78, 136.44, 129.37, 127.76, 57.26, 40.16, 31.46, 27.13, 26.92, 26.82, 24.78, 21.13; IR (neat) 3021 (bw), 2926 (bs), 2856 (bm), 1698 (s), 1513 (m), 1465 (w), 1446 (w), 1159 (w), 818 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{21}O$ $[M+H]^+$: 217.1592; Found: 217.1599.



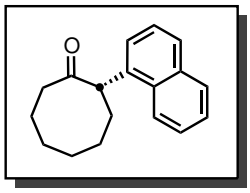
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	1.82	1.90	2.00	0.00	49.52	7531.5	336.5	49.523
2	UNKNOWN	2.08	2.14	2.38	0.00	50.48	7047.6	343.0	50.477
Total						100.00	14579.1	679.6	100.000

VR-II-211-RAC-0 -- AcqDate: 6/4/2010 1:56:11 AM
Description: AS-H, 50C, 150 psi, 3.0 ml/min, 4% MeOH, 220 nm, Sample EtOAc

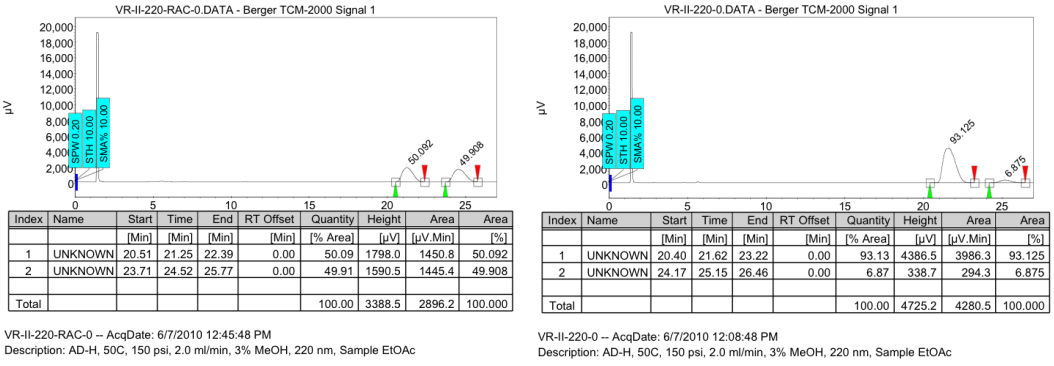
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
2	UNKNOWN	1.83	1.90	1.97	0.00	1.58	213.6	7.9	1.578
1	UNKNOWN	2.00	2.13	2.38	0.00	98.42	11507.7	492.0	98.422
Total						100.00	11721.3	499.9	100.000

VR-III-056-2 -- AcqDate: 11/18/2010 8:43:57 PM
Description: AS-H, 50C, 150 psi, 3.0 ml/min, 4% MeOH, 220 nm, Sample EtOAc

Figure 2.17: SFC trace for (*S*)-2-(4-methylphenyl)cyclooctanone (**2.77**)



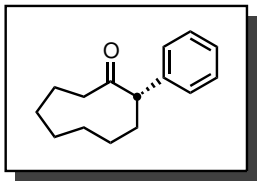
(*S*)-2-(napthalen-1-yl)cyclooctanone (**2.87**). Run for 14 hours at −78 °C according to the representative procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.60** (5.9 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2.86** (396 μL, 0.21 mmol, 0.53 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.87** as a pale yellow solid (35.5 mg, 93.9%) with 93:7 er (AD-H, 50 °C, 150 psi, 2.0 mL/min, 3% MeOH, λ = 220 nm; t_R = 21.52 min (major), 25.15 min (minor)). mp 97- 100 °C. $[\alpha]_D^{20}$ = +48.3 (c 0.82, $CHCl_3$); R_f = 0.20 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33-8.28 (m, 1H), 7.87-7.83 (m, 1H), 7.79-7.74 (m, 1H), 7.64-7.60 (m, 1H), 7.60-7.54 (m, 1H), 7.51-7.45 (m, 2H), 4.65 (dd, J = 12.1, 2.6 Hz, 1H), 2.82 (ddd, J = 12.3, 12.3, 3.9 Hz, 1H), 2.68-2.55 (m, 1H), 2.30 (ddd, J = 12.9, 5.7, 3.7 Hz, 1H), 2.11-1.94 (m, 3H), 1.90-1.79 (m, 2H), 1.78-1.63 (m, 2H), 1.61-1.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.91, 135.62, 134.07, 131.86, 129.01, 127.75, 126.46, 125.70, 125.59, 124.63, 123.68, 52.49, 39.88, 31.66, 27.41, 27.30, 26.91, 24.92; IR (neat) 3042 (w), 2924 (bm), 2898 (bw), 1689 (s), 1510 (w), 1397 (w), 1117 (m), 800 (m), 780 (bs) cm^{-1}; HRMS (ESI+) Calcd. for $C_{18}H_{21}O$ $[M+H]^+$: 253.1592; Found: 253.1622.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	20.51	21.25	22.39	0.00	50.09	1798.0	1450.8	50.092
2	UNKNOWN	23.71	24.52	25.77	0.00	49.91	1590.5	1445.4	49.908
Total						100.00	3388.5	2896.2	100.000

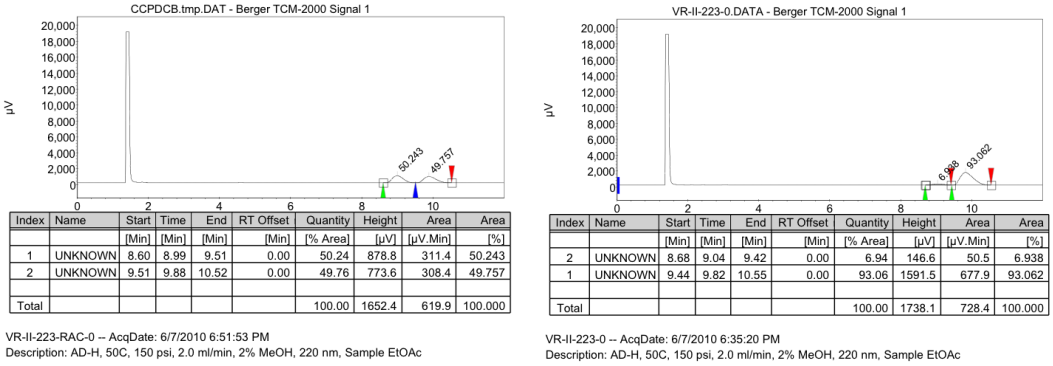
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	20.40	21.62	23.22	0.00	93.13	4386.5	3986.3	93.125
2	UNKNOWN	24.17	25.15	26.46	0.00	6.87	338.7	294.3	6.875
Total						100.00	4725.2	4280.5	100.000

Figure 2.18: SFC trace for (*S*)-2-(napthalen-1-yl)cyclooctanone (**2.87**)



(*S*)-2-(4-phenyl)cyclononanone (**2.88**). Run for 14 hours at −45 °C according to the general procedure with scandium triflate (7.4 mg, 0.015 mmol, 10 mol %), ligand **2.66** (8.5 mg, 0.016 mmol, 11 mol %), toluene (1.5 mL), cyclooctanone (18.9 mg, 0.15 mmol, 1.0 equiv) in 0.15 mL of toluene, and **2.25** (284 μL, 0.21 mmol, 0.74 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **2.88** as a colorless oil (33.0 mg, quantitative) with 93:7 er (AD-H, 50 °C, 150 psi, 2.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 9.04 min (minor), 9.82 min (major)).

$[\alpha]_D^{20} = -43.9$ (c 0.94, $CHCl_3$); $R_f = 0.25$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29- 7.14 (m, 5H), 3.88 (dd, J = 11.9, 2.7 Hz, 1H), 2.46-2.34 (m, 1H), 2.34-2.24 (m, 2H), 1.95-1.34 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.28, 139.72, 128.68, 128.02, 127.12, 58.94, 41.80, 31.78, 25.97, 25.68, 25.49, 24.22, 24.02; IR (neat) 3061 (bw), 3026 (bw), 2926 (bm), 1702 (s), 1495 (w), 1451 (m), 698 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{21}O$ $[M+H]^+$: 217.1592; Found: 217.1589.



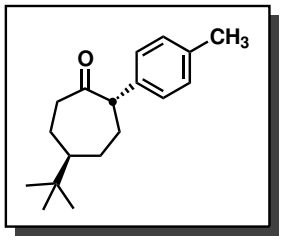
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	8.60	8.99	9.51	0.00	50.24	878.8	311.4	50.243
2	UNKNOWN	9.51	9.88	10.52	0.00	49.76	773.6	308.4	49.757
Total						100.00	1652.4	619.9	100.000

VR-II-223-RAC-0 -- AcqDate: 6/7/2010 6:51:53 PM
Description: AD-H, 50C, 150 psi, 2.0 ml/min, 2% MeOH, 220 nm, Sample EtOAc

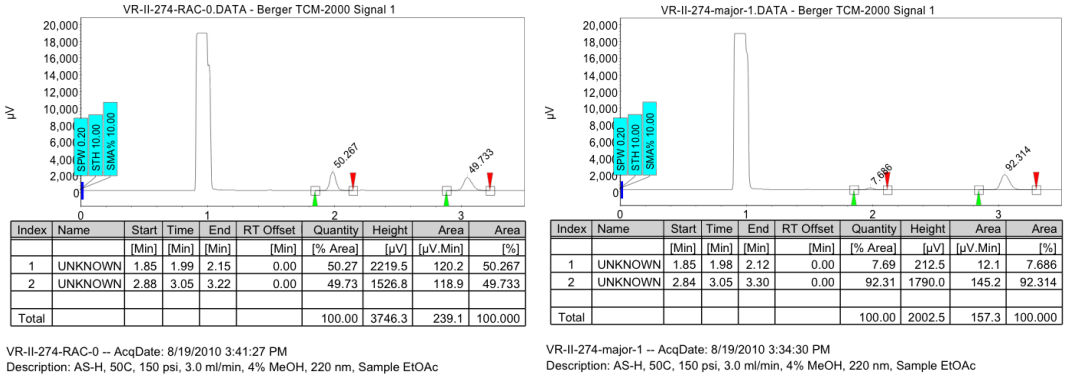
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
2	UNKNOWN	8.68	9.04	9.42	0.00	6.94	146.6	50.5	6.938
1	UNKNOWN	9.44	9.82	10.55	0.00	93.06	1591.5	677.9	93.062
Total						100.00	1738.1	728.4	100.000

VR-II-223-0 -- AcqDate: 6/7/2010 6:35:20 PM
Description: AD-H, 50C, 150 psi, 2.0 ml/min, 2% MeOH, 220 nm, Sample EtOAc

Figure 2.19: SFC trace for (*S*)-2-(4-phenyl)cyclononanone (**2.88**)



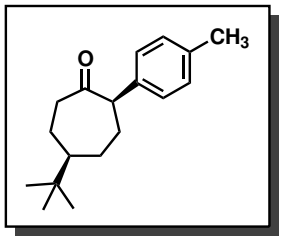
(2*S*,5*R*)-5-(*tert*-butyl)-2-*p*-tolylcycloheptanone (2.93). Run for 3 hours at −78 °C on 0.15 mmol scale according to the representative procedure. Purification by flash column chromatography (8% ethyl acetate in hexanes v/v) afforded the title compound as a white solid (31.0 mg, 79.9%) with 92.5:7.5 er (AS-H, 50 °C, 150 psi, 3.0 mL/min, 4% MeOH, λ = 220 nm; t_R = 1.98 min (minor), 3.05 min (major)). GC analysis of the crude reaction mixture showed a 93:7 dr (HP-5, 150 °C hold 5 min, ramp 5 °C/min to 200 °C; t_R = 16.9 min (minor), 17.4 min (major)). Characterization data were in agreement with those tabulated above for the racemic compound. $[\alpha]_D^{20} = -117.6$ (c 1.03, $CHCl_3$).



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	1.85	1.99	2.15	0.00	50.27	2219.5	120.2	50.267
2	UNKNOWN	2.88	3.05	3.22	0.00	49.73	1526.8	118.9	49.733
Total						100.00	3746.3	239.1	100.000

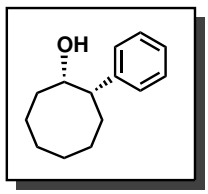
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	1.85	1.98	2.12	0.00	7.69	212.5	12.1	7.686
2	UNKNOWN	2.84	3.05	3.30	0.00	92.31	1790.0	145.2	92.314
Total						100.00	2002.5	157.3	100.000

Figure 2.20: SFC trace for (2*S*,5*R*)-5-(*tert*-butyl)-2-*p*-tolylcycloheptanone (**2.93**)



(±)-*cis*-5-*tert*-butyl-2-*p*-tolylcycloheptanone (**2.92**). To a stirred solution of 4-*tert*-butylcyclohexanone (154 mg, 1.00 mmol) in 6.7 mL of CH_2Cl_2, trimethylaluminum (0.27 mL, 0.55 mmol, 2.0 M in toluene) was added at −78 °C. After stirring for an additional 5 minutes, *p*-tolylphenyldiazomethane (0.76 mL, 0.50 mmol, 0.66 M in toluene) was introduced in a single portion. After 30 minutes at −78 °C, the reaction mixture was warmed to room temperature and slowly quenched by dropwise addition of water. The solution was diluted with 10 mL of water and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to a crude yellow solid. Purification by preparative thin layer chromatography (2.5% ethyl acetate in hexanes v/v) afforded sufficient quantities of the minor *cis* diastereomer (±)-**2.92** for characterization. GC analysis of the crude reaction mixture showed an 81.5:18.5 dr (HP-5, 150 °C hold 5 min, ramp 5 °C/min to 200 °C; t_R = 16.9 min (minor), 17.4 min (major)).

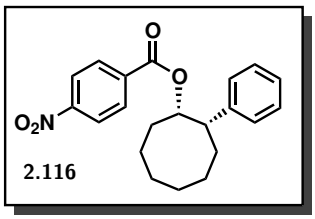
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 3.77 (dd, J = 5.9, 5.9 Hz, 1H), 2.73-2.65 (m, 1H), 2.62-2.53 (m, 1H), 2.32 (s, 3H), 2.30-2.21 (m, 1H), 2.14-2.06 (m, 1H), 2.01-1.89 (m, 2H), 1.48-1.32 (m, 3H), 0.87 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.64, 137.27, 136.46, 129.31, 128.24, 57.10, 49.56, 41.85, 33.73, 30.30, 27.63, 26.75, 25.14, 21.18; IR (neat) 2953 (bs), 2926 (bs), 2864 (bm), 1705 (m), 1514 (w), 1467 (bw), 1454 (bw), 1367 (w), 803(w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{18}H_{27}O$ $[M+H]^+$: 259.2062; Found: 259.2074.



(±)-*cis*-2-phenylcyclooctanol (**2.89**). To a stirred solution of ketone **2.38** (202 mg, 1.00 mmol) in 2.0 mL of THF, K-selectride (5.0 mL, 5.0 mmol, 1.0 M in THF) was added dropwise at −78 °C. The reaction mixture was allowed to slowly warm to room temperature. After 24 hours, the pale yellow solution was cooled to 0 °C and quenched by adding 500 μL of water followed by 6.0 mL of 3N aqueous NaOH. While stirring vigorously, 6.0 mL of 35% H_2O_2 was added

dropwise carefully. The reaction mixture was warmed to room temperature an allowed to stir for an additional 3 hours. The aqueous layer was extracted 3 times with 20 mL of Et_2O, washed with 50 mL of brine, and dried over anhydrous Na_2SO_4. Concentration afforded a crude colorless oil that was purified by flash column chromatography (18% ethyl acetate in hexanes) to afford the desired product (±)-**2.89** as a colorless oil (148 mg, 72.5%, 98.2% brsm) along with the starting ketone (52.8 mg, 26.1%). ^{1}H NMR analysis of the crude reaction mixture showed >98:2 diastereoselectivity.

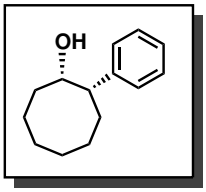
R_f = 0.32 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.31 (m, 2H), 7.29-7.20 (m, 3H), 3.91-3.86 (m, 1H), 3.07 (ddd, J = 10.2, 2.7, 2.7 Hz, 1H), 2.28-2.17 (m, 1H), 1.89-1.73 (m, 5H), 1.73-1.54 (m, 6H), 1.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.35, 128.65, 126.51, 74.04, 47.95, 32.25, 27.98, 27.65, 27.65, 27.08, 26.07, 22.56; IR (neat) 3431 (bm), 3025 (w), 2918 (bs), 2857 (bm), 1492 (w), 1471 (m), 1031 (m), 749 (m), 701 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{24}NO$ $[M+NH_4]^+$: 222.1858; Found: 222.1865.



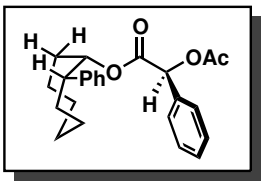
(±)-*cis*-2-phenylcyclooctyl 4-nitrobenzoate (**2.116**). To a solution of (±)-**2.89** (145 mg, 0.71 mmol) in 3.5 mL of CH_2Cl_2, DMAP (8.6 mg, 0.071 mmol) and Et_3N (148 μL, 1.06 mmol) were added. The solution was cooled to 0 °C and 4-nitrobenzoyl chloride (197 mg, 1.06 mmol) was added in a single portion. The reaction was allowed to warm to room temperature and stirred on for 12 hours. The yellow suspension was diluted with 25 mL of CH_2Cl_2, washed with 15 mL of 1 N HCl and then dried over anhydrous Na_2SO_4. Concentration afforded a crude yellow solid that was purified by flash column chromatography (15% ethyl acetate in hexanes v/v) to afford the title compound as a white solid (231.8 mg, 92.6%). mp 93-94 °C. Suitable crystals for X-ray analysis were grown by slow evaporation from a 5% (v/v) solution of Et_2O in hexanes.

R_f = 0.47 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, J = 9.0 Hz, 2H), 8.10 (d, J = 8.8 Hz, 2H), 7.31-7.26 (m, 4H), 7.24-7.19 (m, 1H), 5.54 (ddd, J =

9.6, 3.7, 3.7 Hz, 1H), 3.31 (ddd, J = 10.8, 3.3, 3.3 Hz, 1H), 2.43-2.32 (m, 1H), 2.18-2.08 (m, 1H), 2.06-1.70 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.83, 150.51, 143.94, 136.31, 130.65, 128.54, 128.30, 126.63, 123.59, 78.04, 46.70, 29.95, 28.99, 27.25, 26.96, 26.83, 23.41; IR (neat) 3028 (bw), 2926 (bm), 2858 (bw), 1719 (s), 1607 (w), 1527 (s), 1347 (m), 1274 (s), 1118 (m), 1102 (m), 719 (m), 702 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{21}H_{27}N_2O_4$ $[M+NH_4]^+$: 371.1971; Found: 371.1979.



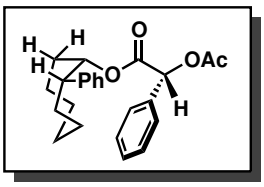
(1*S*,2*S*)-2-phenylcyclooctanol (**2.89**). To a stirred solution of ketone **2.76** (102 mg, 0.50 mmol) in 5.4 mL of toluene, Red-Al (747 μL, 2.45 mmol, 65% w/w in toluene) was added *via* syringe pump over 30 minutes at −78 °C. The reaction mixture was allowed to warm to room temperature slowly and stirred for an additional 16 hours. The clear solution was cooled to 0 °C and quenched with water until evolution of hydrogen gas ceased. The entire reaction mixture was poured into 15 mL of 1 N HCl and extracted three times with 15 mL of Et_2O. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to deliver a crude colorless oil. Purification by flash column chromatography (18% ethyl acetate in hexanes v/v) afforded the desired product as a colorless oil (68.6 mg, 66.3%). ^{1}H NMR analysis of the crude reaction mixture showed a 2.5:1 mixture of *cis* to *trans* diastereomers. Characterization data were identical to that reported above for the racemic material.



(*S*)-((1*S*,2*S*)-2-phenylcyclooctyl)-α-acetyl mandelate (**2.91**). A 1-dram vial was charged with (1*S*,2*S*)-2-phenylcyclooctanol **2.89** (16 mg, 0.078 mmol), (*S*)-α-acetylmandelic acid (17 mg, 0.086 mmol), EDC · HCl (18 mg, 0.094 mmol), and DMAP (4.8 mg, 0.039 mmol). Bench-top CH_2Cl_2 (1.0 mL) was added followed by triethylamine (13 μL, 0.094 mmol). The vial was sealed with a screw-cap and stirred for 18 hours. The reaction was quenched with 1 mL of water. The aqueous layer was removed and the remaining organics were washed with 1 mL of saturated $NaHCO_3$, 1 mL of brine, and finally dried over

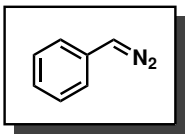
anhydrous Na_2SO_4. Purification directly by preparative thin layer chromatography (15% ethyl acetate in hexanes v/v) afforded sufficient quantities of the title compound for NMR analysis.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44-7.35 (m, 5H), 7.05-7.01 (m, 1H), 6.97-6.93 (m, 2H), 6.73-6.70 (m, 2H), 5.85 (s, 1H), 5.24-5.20 (m, 1H), 2.96 (ddd, J = 10.5, 2.9, 2.9 Hz, 1H), 2.14 (s, 3H), 2.10-2.01 (m, 1H), 1.99-1.91 (m, 1H), 1.90-1.83 (m, 1H), 1.82-1.73 (m, 2H), 1.72-1.57 (m, 7H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.43, 168.06, 143.95, 134.11, 129.29, 128.89, 128.23, 128.11, 128.07, 126.07, 77.93, 74.91, 46.01, 30.31, 29.22, 27.65, 26.81, 26.52, 22.82, 20.88; IR (neat) 2922 (bw), 2859 (bw), 1739 (s), 1453 (w), 1371 (m), 1230 (s), 1209 (s), 1177 (s), 1051 (bm), 750 (m), 695 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{24}H_{32}NO_4$ $[M+NH_4]^+$: 398.2331; Found: 398.2330.



(*R*)-((1*S*,2*S*)-2-phenylcyclooctyl)-α-acetyl mandelate (**2.90**). Prepared in an analogous fashion to the diastereomer above (**2.91**) with (*R*)-α-acetylmandelic acid. The following characterization data were obtained:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.36 (m, 1H), 7.35-7.33 (m, 4H), 7.28-7.24 (m, 2H), 7.21-7.17 (m, 3H), 5.86 (s, 1H), 5.22 (ddd, J = 9.0, 3.7, 3.7 Hz, 1H), 3.10 (ddd, J = 10.8, 3.4, 3.4 Hz, 1H), 2.14 (s, 3H), 2.13-2.08 (m, 1H), 1.87-1.80 (m, 1H), 1.79-1.70 (m, 2H), 1.70-1.49 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.24, 168.11, 144.04, 134.23, 129.08, 128.75, 128.62, 128.28, 127.61, 126.44, 77.69, 74.74, 46.44, 29.75, 29.35, 27.18, 26.88, 26.53, 22.83, 20.83; IR (neat) 2921 (bm), 2853 (bw), 1739 (s), 1452 (w), 1371 (m), 1228 (s), 1209 (s), 1176 (s), 1051 (bm), 967 (bw), 750 (m), 694 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{24}H_{32}NO_4$ $[M+NH_4]^+$: 398.2331; Found: 398.2339.

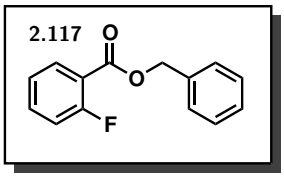


Representative procedure for preparation of aryl diazoalkanes:

phenyldiazomethane (**2.25**). Benzaldehyde (1.05 g, 9.89 mmol) was weighed directly into a pressure tube then stirred vigorously while hydrazine hydrate (4 mL) was added slowly. The pressure tube was sealed and heated to 90 °C for 12 hours. The reaction mixture was poured into 10 mL of brine, extracted with CH_2Cl_2 (3 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated to a colorless oil in a 250 mL round bottom flask. The crude hydrazone was flushed with argon and kept cold (−20 °C) until use in the oxidation step. In a separate flask, dimethyl sulfoxide (780 μL, 10.9 mmol, 1.10 equiv) in 10 mL of CH_2Cl_2 was cooled to −78 °C and oxalyl chloride (910 μL, 10.4 mmol, 1.05 equiv) was added dropwise *via* syringe pump over 15 minutes. The oxidant solution was stirred for an additional 15 minutes. During this time, the crude hydrazone was dissolved in 90 mL of Et_2O, cooled to −78 °C and triethylamine (2.9 mL, 20.8 mmol, 2.1 equiv) was added to the stirred solution. The oxidant, kept cold at −78 °C, was transferred *via* cannula to the solution of hydrazone and triethylamine which immediately formed a pink solution. After 45 minutes the reaction mixture was quickly extracted in a separatory funnel with ice cold 50% aq. NH_4Cl (100 mL), H_2O (100 mL), and saturated $NaHCO_3$. The organics were dried by rapidly swirling over K_2CO_3 on an ice bath for 1 minute. The clear red solution was filtered through a sintered glass funnel and then immediately concentrated under high vacuum (0.1 mm Hg) on a brine/ice bath to yield the title compound as a red oil. The resulting oil was cooled to −78 °C and transferred to a 10 mL volumetric flask with toluene. If the diazo solution was turbid or cloudy it was gravity filtered through a cotton plug in a cold jacketed dropping funnel held at −78 °C. The clear toluene solution was stored over 3Å sieves (4-8 mesh) at −78 °C and titrated with 2-fluorobenzoic acid according the the procedure below to give a concentration of 0.74 M (0.87 g, 7.4 mmol, 75% yield).[97]

[97] Characterization data were obtained from the 2-fluorobenzoate esters for each diazoalkane due to the hazards associated with handling neat diazo compounds.

Note: The above procedure was applicable to all aryl diazoalkanes prepared in this study except **2.86**. The 1-naphthyl hydrazone was sparingly soluble in Et_2O, thus resulting in low conversion to the diazoalkane. Running the entire procedure in CH_2Cl_2 facilitated smooth and complete conversion of the hydrazone.

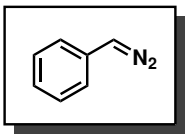


Representative procedure for titration of diazoalkane solutions: **benzyl 2-fluorobenzoate** (**2.117**). A stock solution of 2-fluorobenzoic acid in $CDCl_3$ was prepared by weighing 1.2591 grams directly into a 25.00 mL volumetric flask. The flask was diluted to the total volume with $CDCl_3$, affording a 0.3595 M solution. The stock solution was sealed with a ground glass stopper and stored in the dark.[98] In an oven-dried 1-dram glass vial, the 2-fluorobenzoic acid solution (700 μL, 0.252 mmol, 0.359 M in $CDCl_3$, excess) was added and cooled to -78 °C, causing the solution to freeze. A 100 μL aliquot of phenyldiazomethane (**2.25**) in toluene was added in a single portion, and the reaction was allowed to warm to room temperature. Upon reaching room temperature, the reaction was complete as judged by the absence of color and gas evolution. Approximately 5 μL of hexafluorobenzene was added as an internal standard for spectrum calibration. The homogeneous colorless solution was transferred *via* glass pipette to an NMR tube for analysis. ^{19}F NMR data (8 scans) were recorded with a relaxation delay time of 10 seconds (d1 = 10), and integration of the two signals ($\delta = -111$ acid, $\delta = -112$ ester) showed the aliquot to contain 0.117 mmol of diazoalkane based on 46.4% conversion of the acid to the corresponding ester. The procedure was repeated in triplicate to give a concentration value of 1.16 $\pm$ 0.03 M. The gravimetric benzoate ester method (see below for procedure) gave a comparable concentration of 1.23 M. For characterization purposes, the three samples from the ^{19}F NMR titration procedure were transferred to a separatory funnel with 25 mL of Et_2O. The organic layer was washed

[98] Alternatively, an accurately weighed sample of 2-fluorobenzoic acid could be used. We have found that 2-fluorobenzoic acid dissolves slowly in chloroform and therefore preparing a stock solution was generally more convenient.

with 1N NaOH (2 x 15 mL) and saturated NaCl (15 mL), dried over Na_2SO_4, filtered, and then concentrated. The product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes v/v) to afford the desired ester **2.117** as a colorless oil.

R_f = 0.36 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.55-7.50 (m, 1H), 7.49-7.45 (m, 2H), 7.41-7.37 (m, 2H), 7.37-7.32 (m, 1H), 7.20 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.14 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.2 (d, $J_{C\text{-}F}$ = 260.5 Hz), 135.9, 134.7 (d, $J_{C\text{-}F}$ = 9.3 Hz), 132.3 (d, $J_{C\text{-}F}$ = 0.9 Hz), 128.7, 128.4, 128.2, 124.1 (d, $J_{C\text{-}F}$ = 3.7 Hz), 118.8 (d, $J_{C\text{-}F}$ = 9.8 Hz), 117.1 (d, $J_{C\text{-}F}$ = 22.3 Hz), 67.0; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.26 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 4.4, 4.4 Hz, 1F); IR (neat) 3066, 3034, 2954, 1714, 1612, 1488, 1455, 1292, 1247, 1120, 1075, 1030, 752, 693 cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{12}FO_2$ $[M+H]^+$: 231.0821; Found 231.0817.



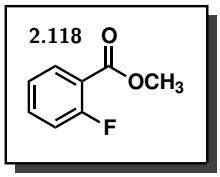
Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	47.04	52.96	47.04	1.18_4
2	46.42	53.58	46.42	1.16_8
3	44.82	55.18	44.82	1.12_8
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	1.16 0.03

Table 2.5: Titration results for phenyldiazomethane (**2.25**)

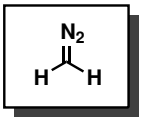
General procedure for titration by isolation of the unpurified benzoate ester: Benzoic acid (150 mg, 1.23 mmol, excess) was dissolved in 3 mL of CH_2Cl_2 and cooled to −78 °C. A 300 μL aliquot of the diazoalkane solution was added in a single portion, and the reaction mixture was allowed to warm to room temperature. After standing at room temperature for 30 minutes the reaction mixture was transferred to a separatory funnel with 25 mL of Et_2O. The organic layer was washed with 1N NaOH (2 x 15 mL) and saturated NaCl (15 mL), dried over Na_2SO_4, filtered, and then concentrated. The crude ester was dried under

high vacuum (approx. 1 mm Hg) for 12 hours and weighed to determine yield. Analytically pure samples for new compounds were obtained by purification on silica gel (ethyl acetate in hexanes). Characterization data for the following benzoate esters have been reported previously:

- **Methyl benzoate** Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Chem. Commun.* **2011**, *47*, 2946-2948.
- **Benzyl benzoate** Tejel, C.; Ciriano, M. A.; Passarelli, V. *Chem. Eur. J.* **2011**, *17*, 91-95.
- **3-Phenylpropyl benzoate** Iranpoor, N.; Firouzabadi, H. Khalili, D.; Motevalli, S. *J. Org. Chem.* **2008**, *73*, 4882-4887.
- **Cinnamyl benzoate, 1-Phenylethyl benzoate** Weng, S.; Ke, C.; Chen, F.; Lyu, Y.; Lin, G. *Tetrahedron.* **2011**, *67*, 1640-1648.
- **2-Methylbenzyl benzoate, 3-Methoxybenzyl benzoate** Iranpoor, N.; Firouzabadi, H.; Khalili, D. *Org. Biomol. Chem.* **2010**, *8*, 4436-4443.
- **4-Methylbenzyl benzoate** Kwok, M.; Choi, W.; He, H. S.; Toy, P. H. *J. Org. Chem.* **2003**, *68*, 9831-9834.
- **Naphthalen-1-ylmethyl benzoate** Kesharwani, T.; Larock, R. C. *Tetrahedron.* **2008**, *64*, 6090-6102.
- **Furan-2-ylmethyl benzoate** Chen, P.; Chou, C. *Tetrahedron.* **1997**, *53*, 17115-17126.

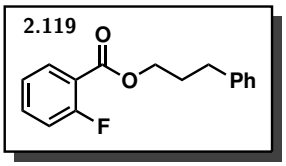


methyl 2-fluorobenzoate (**2.118**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 0.49 ± 0.05 M. The gravimetric benzoate ester method gave a concentration of 0.34 M. colorless oil; R_f = 0.28 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.54-7.49 (m, 1H), 7.21 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.14 (ddd, J = 11.0, 8.3, 1.2 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.0 (d, $J_{C\text{-}F}$ = 259.6 Hz), 134.5 (d, $J_{C\text{-}F}$ = 9.3 Hz), 132.2 (d, $J_{C\text{-}F}$ = 0.9 Hz), 124.0 (d, $J_{C\text{-}F}$ = 4.2 Hz), 118.7 (d, $J_{C\text{-}F}$ = 9.8 Hz), 117.0 (d, $J_{C\text{-}F}$ = 22.3 Hz), 52.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.73 (dddd, $J_{F\text{-}H}$ = 5.5, 5.5, 5.5, 5.5 Hz, 1F); IR (neat) 3000, 2955, 1719, 1613, 1489, 1457, 1435, 1301, 1262, 1125, 1086, 756, 693 cm^{-1}; HRMS (ESI+) Calcd. for $C_8H_8FO_2$ $[M+H]^+$: 155.0508; Found 155.0513.

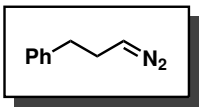


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	17.54	82.46	17.54	0.44_1
2	21.43	78.57	21.43	0.53_9
3	19.94	80.06	19.94	0.50_2
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	0.49 0.05

Table 2.6: Titration results for diazomethane (**2.108**)

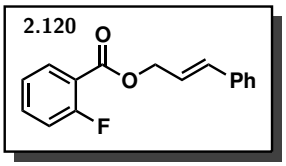


3-phenylpropyl 2-fluorobenzoate (**2.119**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 0.133 ± 0.003 M. The gravimetric benzoate ester method gave a concentration of 0.40 M. colorless oil; R_f = 0.31 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.55-7.50 (m, 1H), 7.32-7.28 (m, 2H), 7.24-7.18 (m, 4H), 7.15 (ddd, J = 11.0, 8.3, 1.0 Hz, 1H), 4.36 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 7.3 Hz, 2H), 2.13-2.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.6 (d, $J_{C\text{-}F}$ = 3.6 Hz), 162.1 (d, $J_{C\text{-}F}$ = 260.0 Hz), 141.3, 134.5 (d, $J_{C\text{-}F}$ = 9.2 Hz), 132.2 (d, $J_{C\text{-}F}$ = 0.9 Hz), 128.6, 126.2, 124.1 (d, $J_{C\text{-}F}$ = 4.1 Hz) 119.1 (d, $J_{C\text{-}F}$ = 9.7 Hz), 117.1 (d, $J_{C\text{-}F}$ = 22.6 Hz), 64.7, 32.3, 30.4; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.49 (dddd, $J_{F\text{-}H}$ = 6.6, 6.6, 4.4, 4.4 Hz, 1F); IR (neat) 3027, 2955, 2927, 1713, 1612, 1488, 1455, 1294, 1249, 1157, 1126, 1082, 1032, 754, 698 cm^{-1}; HRMS (ESI+) Calcd. for $C_{16}H_{16}FO_2$ $[M+H]^+$: 259.1134; Found 259.1135.

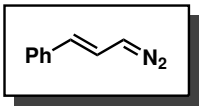


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	5.27	94.73	5.27	0.132_6
2	5.17	94.83	5.17	0.130_1
3	5.43	94.57	5.43	0.136_6
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	0.133 0.003

Table 2.7: Titration results for (3-diazopropyl)benzene (**2.109**)



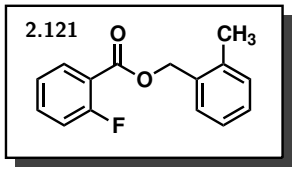
cinnamyl 2-fluorobenzoate (**2.120**). Impurities present in the diazoalkane solution complicated the isolation of **2.120**. An authentic sample for characterization was prepared by Steglich esterification.[99] The fluorobenzoate ester method gave an average concentration of 0.43 ± 0.01 M. The gravimetric benzoate ester method gave a concentration of 1.26 M. colorless oil; R_f = 0.31 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.56-7.50 (m, 1H), 7.44-7.41 (m, 2H), 7.36-7.31 (m, 2H), 7.29-7.25 (m, 1H), 7.21 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.15 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 6.77 (d, J = 15.9 Hz, 1H), 6.41 (dt, J = 15.9, 6.4 Hz, 1H), 5.01 (dd, J = 6.4, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1 (d, $J_{C\text{-}F}$ = 3.6 Hz), 162.0 (d, $J_{C\text{-}F}$ = 260.2 Hz), 136.2, 134.6 (d, $J_{C\text{-}F}$ = 8.7 Hz), 134.4, 132.2, 128.6, 128.1, 126.7, 124.0 (d, $J_{C\text{-}F}$ = 3.6 Hz), 123.0, 118.8 (d, $J_{C\text{-}F}$ = 9.7 Hz), 117.0 (d, $J_{C\text{-}F}$ = 22.5 Hz), 65.8; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.39 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3059, 3027, 2943, 1715, 1612, 1488, 1454, 1289, 1247, 1157, 1122, 1075, 1032, 964, 910, 754, 690 cm^{-1}; HRMS (ESI+) Calcd. for $C_{16}H_{17}FNO_2$ $[M+NH_4]^+$: 274.1243; Found 274.1231.



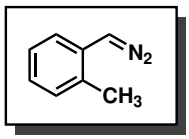
Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	17.38	82.62	17.38	0.43_7
2	17.26	82.74	17.26	0.43_4
3	16.52	83.48	16.52	0.41_6
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	0.43 0.01

Table 2.8: Titration results for (*E*)-(3-diazoprop-1-en-1-yl)benzene (**2.110**)

[99] Neises, B.; Steglich, W. Simple Method for the Esterification of Carboxylic Acids. *Angew. Chem. Int. Ed.* **1978**, *17*, 522-524.

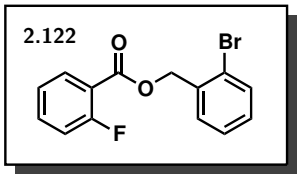


2-methylbenzyl 2-fluorobenzoate (**2.121**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 1.19 ± 0.01 M. The gravimetric benzoate ester method gave a concentration of 1.33 M. colorless oil; R_f = 0.28 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.54-7.49 (m, 1H), 7.47-7.43 (m, 1H), 7.29-7.18 (m, 4H), 7.14 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 5.40 (s, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.2 (d, $J_{C\text{-}F}$ = 260.1 Hz), 137.2, 134.6 (d, $J_{C\text{-}F}$ = 9.4 Hz), 133.8, 132.3 (d, $J_{C\text{-}F}$ = 0.9 Hz), 130.5, 129.4, 128.7, 126.2, 124.0 (d, $J_{C\text{-}F}$ = 4.2 Hz), 118.8 (d, $J_{C\text{-}F}$ = 9.7 Hz), 117.1 (d, $J_{C\text{-}F}$ = 22.3 Hz), 65.6, 19.0; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.23 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3025, 2957, 1716, 1613, 1488, 1456, 1292, 1248, 1123, 1077, 755, 691 cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{14}FO_2$ $[M+H]^+$: 245.0978; Found 245.0989.

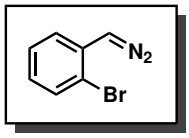


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	47.79	52.21	47.79	1.20_2
2	46.88	53.12	46.88	1.18_0
3	47.34	52.66	47.34	1.19_1
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	1.19 0.01

Table 2.9: Titration results for 1-(diazomethyl)-2-methylbenzene (**2.84**)

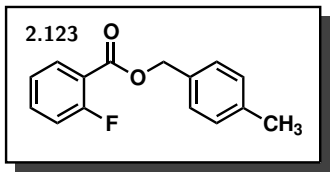


2-bromobenzyl 2-fluorobenzoate (**2.122**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 0.62 ± 0.01 M. The gravimetric benzoate ester method gave a concentration of 0.68 M. white solid; mp 39-41 °C; R_f = 0.27 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.60 (dd, J = 7.8, 1.2 Hz, 1H), 7.58-7.52 (m, 2H),7.35 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.24-7.19 (m, 2H), 7.16 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 5.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0 (d, $J_{C\text{-}F}$ = 3.2 Hz), 162.2 (d, $J_{C\text{-}F}$ = 260.5 Hz), 135.2, 134.8 (d, $J_{C\text{-}F}$ = 9.2 Hz), 133.0, 132.4 (d, $J_{C\text{-}F}$ = 0.9 Hz), 129.9, 129.8, 127.7, 124.2 (d, $J_{C\text{-}F}$ = 3.7 Hz), 123.3, 118.6 (d, $J_{C\text{-}F}$ = 9.7 Hz), 117.2 (d, $J_{C\text{-}F}$ = 22.1 Hz), 66.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.06 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3071, 2952, 1717, 1612, 1488, 1455, 1291, 1247, 1158, 1120, 1029, 748, 691 cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{11}BrFO_2$ $[M+H]^+$: 308.9926; Found 308.9923.

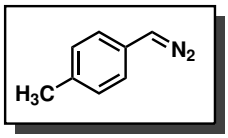


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	24.42	75.58	24.42	0.61_4
2	24.46	75.54	24.46	0.61_5
3	25.11	74.89	25.11	0.63_2
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	0.62 0.01

Table 2.10: Titration results for 1-bromo-2-(diazomethyl)benzene (**2.82**)

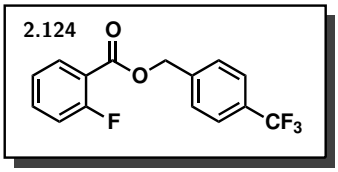


4-methylbenzyl 2-fluorobenzoate (**2.123**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 0.60 ± 0.01 M. The gravimetric benzoate ester method gave a concentration of 0.64 M. colorless oil; $R_f = 0.31$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.54-7.48 (m, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.21-7.11 (m, 4H), 5.35 (s, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.2 (d, $J_{C\text{-}F}$ = 260.5 Hz), 138.2, 134.6 (d, $J_{C\text{-}F}$ = 9.3 Hz), 132.9, 132.3 (d, $J_{C\text{-}F}$ = 1.0 Hz), 129.4, 128.4, 124.0 (d, $J_{C\text{-}F}$ = 3.7 Hz), 118.9 (d, $J_{C\text{-}F}$ = 9.7 Hz), 117.1 (d, $J_{C\text{-}F}$ = 22.4 Hz), 67.0, 21.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.38 (dddd, $J_{F\text{-}H}$ = 6.6, 6.6, 6.6, 6.6 Hz, 1F); IR (neat) 3027, 2951, 1725, 1613, 1488, 1456, 1295, 1250, 1123, 1078, 807, 757 cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{14}FO_2$ $[M+H]^+$: 245.0978; Found 245.0971.

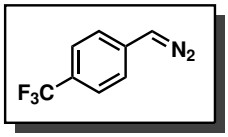


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	24.39	75.61	24.39	0.61_4
2	23.46	76.54	23.46	0.59_0
3	23.79	76.21	23.79	0.59_9
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	0.60 0.01

Table 2.11: Titration results for 1-(diazomethyl)-4-methylbenzene (**2.72**)

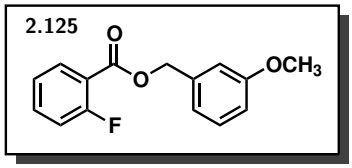


4-(trifluoromethyl)benzyl 2-fluorobenzoate (**2.124**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 0.56 ± 0.02 M. The gravimetric benzoate ester method gave a concentration of 0.69 M. white solid; mp 45-47 °C. R_f = 0.25 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.56-7.52 (m, 1H), 7.22 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.16 (ddd, $J_{C\text{-}F}$ = 10.8. 9.3, 1.0 Hz, 1H), 5.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2 (d, $J_{C\text{-}F}$ = 4.2 Hz), 162.2 (d, $J_{C\text{-}F}$ = 260.5 Hz), 139.3 (d, $J_{C\text{-}F}$ = 0.9 Hz), 135.0 (d, $J_{C\text{-}F}$ = 9.3 Hz), 132.4, 130.6 (q, $J_{C\text{-}F}$ = 32.6 Hz), 128.2, 125.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.2 (d, $J_{C\text{-}F}$ = 3.7 Hz), 124.2 (q, $J_{C\text{-}F}$ = 272.2 Hz), 118.4 (d, $J_{C\text{-}F}$ = 9.8 Hz), 117.2 (d, $J_{C\text{-}F}$ = 22.3 Hz), 66.1; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −65.82 (s, 3F), −111.92 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3086, 2956, 1722, 1614, 1489, 1457, 1326, 1295, 1251, 1164, 1124, 1067, 824, 757 cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{11}F_4O_2$ $[M+H]^+$: 299.0695; Found 299.0682.

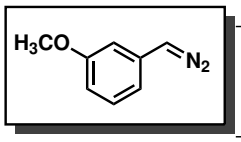


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	22.88	77.12	22.88	0.57_6
2	13.20	45.86	22.35	0.56_2
3	21.14	78.86	21.14	0.53_2
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	0.56 0.02

Table 2.12: Titration results for 1-(diazomethyl)-4-(trifluoromethyl)benzene (**2.80**)

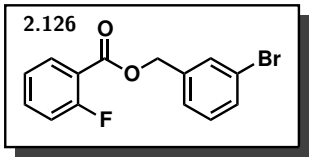


3-methoxybenzyl 2-fluorobenzoate (**2.125**). Impurities present in the diazoalkane solution complicated the isolation of **2.125**. An authentic sample for characterization was prepared by Steglich esterification.[99] The fluorobenzoate ester method gave an average concentration of 0.227 ± 0.002 M. The gravimetric benzoate ester method gave a concentration of 0.29 M. colorless oil; R_f = 0.21 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.55-7.50 (m, 1H), 7.32-7.28 (m, 1H), 7.20 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.15 (ddd, J = 10.9, 8.5, 1.1 Hz, 1H), 7.06-7.00 (m, 2H), 6.88 (dd, J = 8.3, 2.7 Hz, 1H), 5.37 (s, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.1 (d, $J_{C\text{-}F}$ = 260.0 Hz), 159.8, 137.4, 134.7 (d, $J_{C\text{-}F}$ = 8.8 Hz), 132.3, 129.7, 124.0 (d, $J_{C\text{-}F}$ = 4.2 Hz), 120.2, 118.7 (d, $J_{C\text{-}F}$ = 9.6 Hz), 117.1 (d, $J_{C\text{-}F}$ = 22.1 Hz), 113.8, 113.5, 66.8, 55.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.23 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3002, 2954, 2837, 1717, 1612, 1488, 1455, 1373, 1291, 1247, 1156, 1121, 1077, 1050, 867, 754, 690 cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{17}FNO_3$ $[M+NH_4]^+$: 278.1192; Found 278.1182.

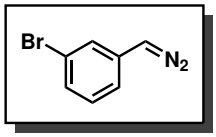


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	9.03	90.97	9.03	0.227_7
2	9.08	90.92	9.08	0.229_0
3	8.89	91.11	8.89	0.224_2
Stock Solution	0.3602 M 0.252 mmol		Average Std. Deviation	0.227 0.002

Table 2.13: Titration results for 1-(diazomethyl)-3-methoxybenzene (**2.78**)

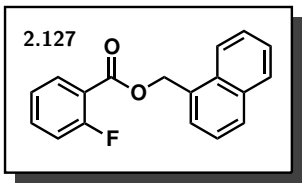


3-bromobenzyl 2-fluorobenzoate (**2.126**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 0.826 ± 0.006 M. The gravimetric benzoate ester method gave a concentration of 1.05 M. white solid; mp 30-32 °C; R_f = 0.35 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.62-7.60 (m, 1H), 7.57-7.51 (m, 1H), 7.49-7.45 (m, 1H), 7.41-7.37 (m, 1H), 7.28-7.24 (m, 1H), 7.22 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.16 (ddd, $J_{C\text{-}F}$ = 10.8, 8.3, 1.0 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.2 (d, $J_{C\text{-}F}$ = 260.5 Hz), 138.1, 134.9 (d, $J_{C\text{-}F}$ = 9.2 Hz), 132.3 (d, $J_{C\text{-}F}$ = 1.0 Hz), 131.4, 131.1, 130.3, 126.7, 124.2 (d, $J_{C\text{-}F}$ = 4.2 Hz), 122.7, 118.5 (d, $J_{C\text{-}F}$ = 9.6 Hz), 117.2 (d, $J_{C\text{-}F}$ = 22.6 Hz), 66.0; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −111.98-−112.08 (m, 1F); IR (neat) 3067, 2952, 1716, 1612, 1487, 1455, 1291, 1246, 1120, 1071, 753, 689 cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{11}BrFO_2$ $[M+H]^+$: 308.9926; Found 308.9918.

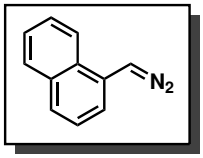


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	32.91	67.09	32.91	0.829_8
2	32.48	67.52	32.48	0.819_0
3	32.93	67.07	32.93	0.830_3
Stock Solution	0.3602 M 0.252 mmol		Average Std. Deviation	0.826 0.006

Table 2.14: Titration results for 1-bromo-3-(diazomethyl)benzene (**2.74**)

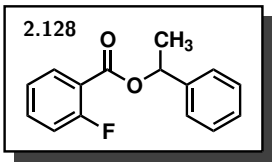


naphthalen-1-ylmethyl 2-fluorobenzoate (**2.127**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 0.57 ± 0.02 M. The gravimetric benzoate ester method gave a concentration of 0.64 M. white solid; mp 40-43 °C; R_f = 0.25 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (d, J = 8.6 Hz, 1H), 7.93 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.92-7.86 (m, 2H), 7.67 (d, J = 6.6 Hz, 1H), 7.59 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.56-7.46 (m, 3H), 7.16 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.12 (ddd, J = 10.8, 9.3, 1.0 Hz, 1H), 5.85 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3 (d, $J_{C\text{-}F}$ = 4.1 Hz), 162.2 (d, $J_{C\text{-}F}$ = 260.5 Hz), 134.7 (d, $J_{C\text{-}F}$ = 9.2 Hz), 133.9, 132.3, 131.8, 131.4, 129.5, 128.8, 127.6, 126.7, 126.1, 125.4, 124.1 (d, $J_{C\text{-}F}$ = 4.1 Hz), 123.8, 118.8 (d, $J_{C\text{-}F}$ = 9.2 Hz), 117.1 (d, $J_{C\text{-}F}$ = 22.6 Hz), 65.5; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.26 (dddd, $J_{F\text{-}H}$ = 7.4, 7.4, 5.2, 5.2 Hz, 1F); IR (neat) 3054, 2960, 1724, 1613, 1488, 1456, 1295, 1248, 1122, 1076, 756 cm^{-1}; HRMS (ESI+) Calcd. for $C_{18}H_{17}FNO_2$ $[M+NH_4]^+$: 298.1243; Found 298.1248.

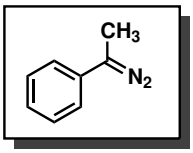


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	22.09	77.91	22.09	0.55_6
2	23.37	76.63	23.37	0.58_8
3	22.47	77.53	22.47	0.56_5
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	0.57 0.02

Table 2.15: Titration results for 1-(diazomethyl)naphthalene (**2.86**)

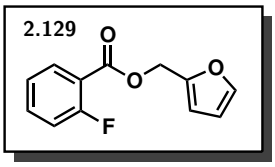


1-phenylethyl 2-fluorobenzoate (**2.128**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions. The fluorobenzoate ester method gave an average concentration of 0.53 ± 0.02 M. The gravimetric benzoate ester method gave a concentration of 0.55 M. colorless oil; R_f = 0.37 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.54-7.49 (m, 1H), 7.48-7.44 (m, 2H), 7.40-7.35 (m, 2H), 7.33-7.28 (m, 1H), 7.20 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.14 (ddd, J= 10.8, 8.3, 1.0 Hz, 1H), 6.15 (q, J = 6.6 Hz, 1H), 1.68 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8 (d, $J_{C\text{-}F}$ = 3.2 Hz), 162.2 (d, $J_{C\text{-}F}$ = 260.1 Hz), 141.7, 134.5 (d, $J_{C\text{-}F}$ = 9.3 Hz), 132.3, 128.7, 128.0, 126.2, 124.0 (d, $J_{C\text{-}F}$ = 4.2 Hz), 119.2 (d, $J_{C\text{-}F}$ = 9.6 Hz), 117.1 (d, $J_{C\text{-}F}$ = 22.6 Hz), 73.6, 22.7; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.27 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3035, 2982, 2932, 1710, 1613, 1488, 1455, 1291, 1248, 1126, 1061, 1030, 754, 697, 540 cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{17}FNO_2$ $[M+NH_4]^+$: 262.1243; Found 262.1247.

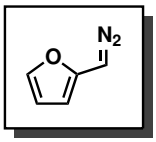


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	20.39	79.61	20.39	0.51_4
2	21.98	78.02	21.98	0.55_4
3	20.74	79.26	20.74	0.52_3
Stock Solution	0.3602 M 0.252 mmol		Average Std. Deviation	0.53 0.02

Table 2.16: Titration results for (1-diazoethyl)benzene (**2.111**)



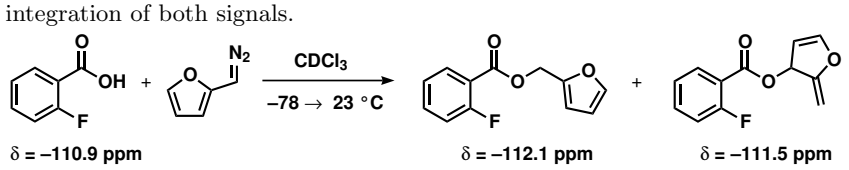
furan-2-ylmethyl 2-fluorobenzoate (**2.129**). Prepared and isolated according to the representative procedure for titration of diazoalkane stock solutions.[100] The fluorobenzoate ester method gave an average concentration of 0.310 ± 0.009 M. The gravimetric benzoate ester method gave a concentration of 0.38 M. pale yellow oil; R_f = 0.24 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.54-7.49 (m, 1H), 7.45 (dd, J = 2.0, 1.0 Hz, 1H), 7.19(ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.13 (ddd, J = 10.7, 8.3, 0.7 Hz, 1H), 6.51-6.49 (m, 1H), 6.39 (dd, J = 3.4, 1.9 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 163.9 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.1 (d, $J_{C\text{-}F}$ = 260.5 Hz), 149.3, 143.4, 134.7 (d, $J_{C\text{-}F}$ = 9.2 Hz), 132.2, 124.0 (d, $J_{C\text{-}F}$ = 4.1 Hz), 118.5 (d, $J_{C\text{-}F}$ = 9.7 Hz), 117.0 (d, $J_{C\text{-}F}$ = 22.1 Hz), 111.0, 110.7, 58.7; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.40 (dddd, $J_{F\text{-}H}$ = 6.6, 6.6, 4.4, 4.4 Hz, 1F); IR (neat) 3124, 2956, 1719, 1613, 1488, 1455, 1292, 1246, 1118, 1070, 918, 819, 751, 599 cm^{-1}; HRMS (ESI+) Calcd. for $C_{12}H_{13}FNO_3$ $[M+NH_4]^+$: 238.0879; Found 238.0876.

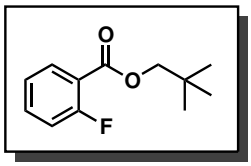


Trial	Ester Integration	Acid Integration	Percent Conversion (%)	Diazoalkane Concentration (M)
1	11.90	88.10	11.90	0.299_4
2	12.50	87.50	12.50	0.314_5
3	12.52	87.48	12.52	0.315_0
Stock Solution	0.3595 M 0.252 mmol		Average Std. Deviation	0.310 0.009

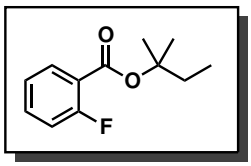
Table 2.17: Titration results for 2-(diazomethyl)furan (**2.112**)

[100]The titration reaction with 2-(diazomethyl)furan (**2.112**) produced two distinct products on the ^{19}F NMR spectrum in a 6.5:1 ratio. We believe the additional product was the result of S_N' addition, however attempts to isolate the compound led to decomposition. The titre reported is the result of integration of both signals.

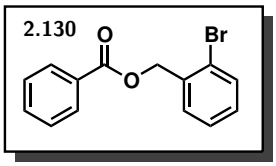




neopentyl 2-fluorobenzoate (**2.114**). An authentic sample for comparison purposes was prepared according to the Steglich esterification procedure.[99] colorless oil; R_f = 0.39 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.55-7.49 (m, 1H), 7.21 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.14 (ddd, J = 11.0, 8.3, 1.0 Hz, 1H), 4.03 (s, 2H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 164.68 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.1 (d, $J_{C\text{-}F}$ = 260.1 Hz), 134.4 (d, $J_{C\text{-}F}$ = 9.2 Hz), 132.2 (d, $J_{C\text{-}F}$ = 0.9 Hz), 124.0 (d, $J_{C\text{-}F}$ = 3.6 Hz), 119.1 (d, $J_{C\text{-}F}$ = 9.7 Hz), 117.1 (d, $J_{C\text{-}F}$ = 22.5 Hz), 74.8, 31.5, 26.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.18 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 4.4, 4.4 Hz, 1F); IR (neat) 2959, 2871, 1713, 1613, 1456, 1296, 1126, 1083, 754, 691 cm^{-1}; HRMS (ESI+) Calcd. for $C_{12}H_{16}FO_2$ $[M+H]^+$: 211.1134; Found 211.1137.

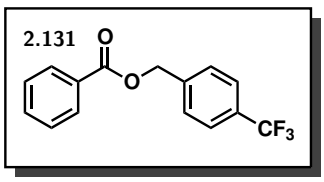


***tert*-amyl 2-fluorobenzoate** (**2.115**). An authentic sample for comparison purposes was prepared according to the Steglich esterification procedure.[99] colorless oil; R_f = 0.44 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.50-7.44 (m, 1H), 7.17 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.10 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 1.91 (q, J = 7.6 Hz, 2H), 1.57 (s, 6H), 0.98 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 163.7 (d, $J_{C\text{-}F}$ = 3.7 Hz), 162.0 (d, $J_{C\text{-}F}$ = 259.1 Hz), 133.9 (d, $J_{C\text{-}F}$ = 8.7 Hz), 132.0 (d, $J_{C\text{-}F}$ = 0.9 Hz), 123.9 (d, $J_{C\text{-}F}$ = 3.7 Hz), 120.7 (d, $J_{C\text{-}F}$ = 9.7 Hz), 117.0 (d, $J_{C\text{-}F}$ = 22.5 Hz), 84.5, 33.9, 25.8, 8.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −113.25 (dddd, $J_{F\text{-}H}$ = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 2976, 2933, 1708, 1613, 1487, 1369, 1126, 838, 755 cm^{-1}; HRMS (ESI+) Calcd. for $C_{12}H_{16}FO_2$ $[M+H]^+$: 211.1134; Found 211.1129.



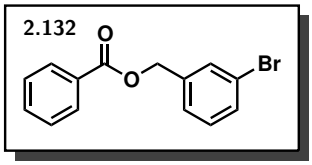
2-bromobenzyl benzoate (**2.130**). Benzoic acid (150 mg, 1.23 mmol, excess) was dissolved in 3 mL of CH_2Cl_2 and cooled to −78 °C. A 300 μL aliquot of the diazoalkane solution was added in a single portion, and the reaction mixture was allowed to warm to room temperature. After standing at room temperature for 30 minutes the reaction mixture was transferred to a separatory funnel with 25 mL of Et_2O. The organic layer was washed with 1N NaOH (2 x 15 mL) and saturated NaCl (15 mL), dried over Na_2SO_4, filtered, and then concentrated. The crude ester was dried under high vacuum (approx. 1 mm Hg) for 12 hours and weighed to determine yield. An analytically pure sample was obtained by purification on silica gel (ethyl acetate in hexanes) to afford **2.130** as a white solid, mp 33-35 °C.

$R_f = 0.30$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12-8.09 (m, 2H), 7.61 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.58 (tt, $J = 7.3$, 1.5 Hz, 1H), 7.51 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.48-7.44 (m, 2H), 7.34 (ddd, $J = 7.6$, 7.6, 1.2 Hz, 1H), 7.22 (ddd, $J = 7.6$, 7.6, 1.5 Hz, 1H), 5.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 135.6, 133.3, 133.0, 130.1, 130.0, 129.9, 129.9, 128.6, 127.7, 123.6, 66.4; IR (neat) 3034, 2956, 1717, 1450, 1374, 1264, 1176, 1096, 1069, 1025, 748, 706 cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{15}BrNO_2$ $[M+NH_4]^+$: 308.0286; Found 308.0278.

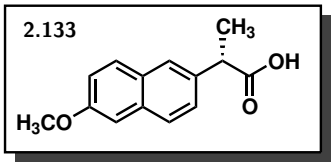


4-(trifluoromethyl)benzyl benzoate (**2.131**). Prepared and isolated according to the general procedure for titration of diazoalkanes by the gravimetric benzoate ester method. white solid; mp 29-30 °C; $R_f = 0.30$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10-8.07 (m, 2H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.61-7.55 (m, 3H), 7.49-7.44 (m, 2H), 5.43 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 140.2 (q, $J_{C\text{-}F} = 1.4$ Hz), 133.4, 130.6 (q, $J_{C\text{-}F} = 32.1$ Hz), 129.9, 129.9, 128.6, 128.2, 125.7 (q, $J_{C\text{-}F} = 3.7$ Hz), 124.2 (q, $J_{C\text{-}F} = 272.1$ Hz), 65.8; IR (neat) 3065 (bw), 2949 (bw), 1720 (s), 1452 (w), 1323 (s), 1266 (bs), 1163 (m), 1106 (bs), 1064 (s), 1018 (m), 824 (m), 708 (s), 593 (m) cm^{-1}; HRMS (ESI+)

Calcd. for $C_{15}H_{12}F_3O_2$ $[M+H]^+$: 281.0789; Found 281.0776.



3-bromobenzyl benzoate (**2.132**). Prepared and isolated according to the general procedure for titration of diazoalkanes by the gravimetric benzoate ester method. colorless oil; $R_f = 0.38$ (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10-8.06 (m, 2H), 7.61-7.56 (m, 2H), 7.49-7.44 (m, 3H), 7.39-7.36 (m, 1H), 7.28-7.24 (m, 1H), 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 138.4, 133.3, 131.5, 131.2, 130.3, 130.0, 129.8, 128.6, 126.8, 122.8, 65.8; IR (neat) 3062 (bw), 3042 (bw), 2952 (bw), 1716 (s), 1601 (m), 1571 (m), 1450 (m), 1263 (bs), 1175 (m), 1095 (bs), 1068 (s), 1026 (m), 776 (m), 707 (bs) cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{12}BrO_2$ $[M+H]^+$: 291.0021; Found 291.0031.



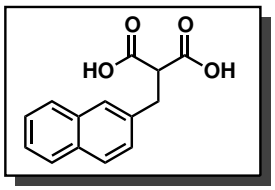
Procedure for isolation of (S)-naproxen from pills:

(*S*)-naproxen (**2.133**). With a ceramic mortar and pestle, 150 generic naproxen sodium pills (220 mg/ea, 33.0 g, 131 mmol) were ground to a fine powder. The resulting light blue powder was suspended in 750 mL of methanol, stirred vigorously for 1 hour, then filtered through Celite® 545 and concentrated *in vacuo* to afford naproxen sodium as a white solid. The crude naproxen sodium was dissolved in 1000 mL of H_2O then 500 mL of CH_2Cl_2 was added. With stirring, concentrated HCl was added slowly until the aqueous solution pH was < 2. The product was extracted with CH_2Cl_2 (3 x 500 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford pure **2.133** as a white solid (28.4 g, 94.3%). Characterization data were in agreement with the literature values.[101]

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71-7.67 (m, 3H), 7.41 (dd, $J = 8.5$, 1.7 Hz, 1H), 7.14 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.11 (d, $J = 2.7$ Hz, 1H), 3.91 (s, 3H), 3.87 (q, $J = 7.2$ Hz, 1H), 1.59 (d, 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.23, 157.86, 135.04, 133.97, 129.45,

[101] Smith, C. R.; RajanBabu, T. V. Catalytic Asymmetric Synthesis Using Feedstocks: An Enantioselective Route to 2-Arylpropionic Acids and 1-Arylethyl Amines *via* Hydrovinylation of Vinyl Arenes. *J. Org. Chem.* **2009**, *74*, 3066-3072.

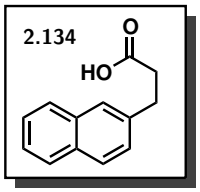
129.04, 127.38, 126.33, 126.28, 119.19, 105.74, 55.46, 45.33, 18.31; HRMS (ESI+) Calcd. for $C_{14}H_{15}O_3$ $[M+H]^+$: 231.1021; Found 231.1029.



2-(naphthalen-2-ylmethyl)malonic acid (**2.101**). (a) A 2 L two-neck flask equipped with a reflux condenser and glass stopper was flame dried under vacuum, back-filled with argon, and charged with 2-methylnaphthalene (35.6 g, 250 mmol, 1.00 equiv). Benzene (500 mL) was added, followed by NBS (46.7 g, 262 mmol, 1.05 equiv) and AIBN (2.05 g, 12.5 mmol, 0.05 equiv). The flask was evacuated and back-filled with argon three times, protected from light with aluminum foil, and carefully brought to reflux. After 12 hours, the flask was cooled to room temperature and the contents were filtered into a separatory funnel, rinsing with 250 mL of ethyl acetate. The organics were washed with saturated $Na_2S_2O_3$ (500 mL), saturated $NaHCO_3$ (500 mL), and saturated NaCl (500 mL), dried over Na_2SO_4, filtered, and concentrated to give a crude tan solid that was immediately dissolved in dry THF (125 mL) and used in the subsequent step without further purification.
(b) Sodium hydride (11.0 g, 276 mmol, 1.10 equiv, 60.2% in oil) was suspended in THF and cooled to 0 °C. Dimethyl malonate (30.0 mL, 262 mmol, 1.05 equiv) was added dropwise over a 30 minute period and the reaction was stirred for an additional 30 minutes at 0 °C. The crude solid from (a) in THF was added in a single portion causing the immediate formation of a white precipitate. The cloudy white suspension was warmed to room temperature and stirred for an additional 2 hours. Et_2O (500 mL) was added and the reaction mixture was filtered through a pad of Celite® 545. Concentration afforded a crude orange oil that was used in the next step without further purification.
(c) The oil obtained in step (b) was dissolved in methanol (500 mL). KOH (56.1 g, 1.00 mol, 4.00 equiv) was slowly added as a solid. The reaction mixture was heated to reflux for 18 hours, cooled to 0 °C, and then diluted with Et_2O (500 mL). The solid was collected on a sintered glass funnel, washed with Et_2O (500 mL) and hexanes (1000 mL), then dissolved

in 250 mL H_2O and cooled to 0 °C. Concentrated HCl was added to adjust the pH to <2. The product was extracted with ethyl acetate (3 x 500 mL), washed with H_2O (250 mL), and saturated NaCl (250 mL), dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. Hexane (500 mL) was added causing the immediate precipitation of an off-white solid. The solid was collected by filtration to afford the title compound (29.6 g, 48.5%, 3 steps), mp 148-151 °C (dec.).

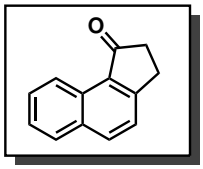
^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.76 (broad s, 2H), 7.88-7.85 (m, 1H), 7.84-7.81 (m, 2H), 7.72 (s, 1H), 7.50-7.44 (m, 2H), 7.42 (dd, J = 8.3, 1.7 Hz, 1H), 3.70 (t, J = 7.8 Hz, 1H), 3.20 (d, J = 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.29, 136.25, 133.03, 131.85, 127.78, 127.50, 127.42, 127.40, 126.95, 126.08, 125.54, 53.37, 34.44; IR (neat) 3265 (bw), 3053 (bw), 2867 (bw), 1756 (bs), 1697 (m), 1656 (bs), 1435 (m), 1306 (bm), 1219 (m), 1140 (bs), 899 (s), 863 (m), 834 (m), 812 (s), 738 (s), 691 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{14}H_{13}O_4$ $[M+H]^+$: 245.0814; Found 245.0819.



3-(naphthalen-2-yl)propanoic acid (**2.134**). Neat diacid **2.101** (5.09 g, 20.8 mmol) was heated to 160 °C until no further evolution of gas was observed (approx. 1.5 hours). After cooling to room temperature **2.134** was recovered as an off-white solid (4.11 g, 98.6%), mp 131-134 °C. Characterization data were in agreement with the literature values.[102]

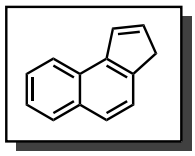
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84-7.79 (m, 3H), 7.67 (s, 1H), 7.51-7.44 (m, 2H), 7.36 (dd, J = 8.6, 1.7 Hz, 1H), 3.15 (t, J = 7.6 Hz, 2H), 2.80 (t, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.38, 137.74, 133.70, 132.32, 128.34, 127.76, 127.66, 127.00, 126.59, 126.20, 125.59, 35.64, 30.83; HRMS (ESI+) Calcd. for $C_{13}H_{11}O$ $[M-OH]^+$: 183.0810; Found 183.0816.

[102]Newcomb, L. F.; Haque, T. S.; Gellman, S. H. Searching for Minimum Increments of Hydrophobic Collapse: Flexible Dinaphthyl Carboxylates. *J. Am. Chem. Soc.* **1995**, *117*, 6509-6519.



2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (**2.99**). Unpurified monoacid **2.134** (23.9 g, 119 mmol, 1.00 equiv) was dissolved in $SOCl_2$ (87.0 mL, 1.20 mol, 10.0 equiv) and heated to 70 °C for 2.5 hours. After cooling to room temperature, excess $SOCl_2$ was removed *in vacuo* to afford the desired acid chloride as a white solid that was used immediately without further purification. To the same flask, CH_2Cl_2 (595 mL) was added and the resulting solution was cooled to −78 °C. $AlCl_3$ (17.4 g, 131 mmol, 1.10 equiv) was added under a stream of nitrogen. The reaction mixture was warmed to room temperature, stirred for an additional hour, and then quenched by the careful addition of crushed ice chips. Aqueous 1N HCl (500 mL) was added and the solution was transferred to a separatory funnel. The product was extracted with CH_2Cl_2 (3 x 300 mL), dried over $MgSO_4$, filtered through a pad of Celite® 545 topped with a thin layer of silica gel, and concentrated to afford the desired cyclopentanone **2.99** as a white solid (16.6 g, 76.4%, two steps), mp 101-103 °C.

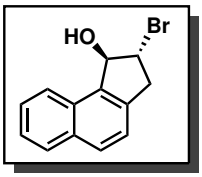
^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.17 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.69-7.65 (m, 1H), 7.58-7.54 (m, 1H), 7.53 (d, J = 8.3 Hz, 1H), 3.25-3.21 (m, 2H), 2.84-2.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.46, 158.44, 135.67, 132.60, 131.00, 129.42, 128.85, 128.09, 126.58, 124.06, 123.95, 36.92, 26.19; IR (neat) 2915 (bw), 1690 (bs), 1436 (m), 1302 (m), 1167 (m), 1103 (m), 835 (s), 770 (s), 639 (m), 577 (m), 542 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{13}H_{11}O$ $[M+H]^+$: 183.0810; Found 183.0818.



3*H*-benz[*e*]indene (**2.98**). In a drybox, $LiAlH_4$ (2.92 g, 76.9 mmol, 0.499 equiv) was weighed into a 500 mL round bottom flask equipped with a magnetic stirbar. Upon removal from the drybox, 308 mL of THF was added, and the resulting gray suspension was cooled to 0 °C. Under a stream of nitrogen, ketone **2.99** (28.05 g, 154 mmol, 1.00 equiv) was added in a single portion. The reaction mixture was warmed to room temperature, stirred for an additional 1.5 hours, then re-cooled to 0 °C. H_2O was added dropwise until no further evolution of hydrogen gas was

apparent. Aqueous 1 N HCl (385 mL, 385 mmol, 2.50 equiv) was then added, and the biphasic reaction mixture was brought to reflux and stirred vigorously for 12 hours. The reaction mixture was transferred to a separatory funnel and the product was extracted with Et_2O (3 x 500 mL). The combined organics were washed with saturated NaCl (1000 mL), dried over Na_2SO_4, filtered, and concentrated to afford a crude yellow oil. The crude oil was filtered through a plug of silica with hexanes as the eluant to afford the desired product as a white crystalline solid (21.8 g, 85.1%), mp 33-35 °C.

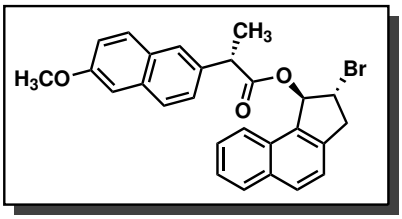
R_f = 0.33 (hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.61-7.51 (m, 3H), 6.81-6.79 (m, 1H), 3.63-3.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.36, 141.10, 134.41, 132.70, 129.68, 128.49, 127.96, 125.69, 125.01, 124.88, 123.94, 122.56, 40.49; IR (neat) 3019 (bw), 2896 (bw), 2882 (bw), 1516 (w), 1327 (m), 1191 (w), 1169 (w), 954 (m), 803 (s), 779 (m), 738 (w), 705 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{13}H_{11}$ $[M+H]^+$: 167.0861; Found 167.0864.



(±)-2-bromo-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol (2.102). To an ice-cold solution of olefin **2.98** (1.00 g, 6.02 mmol, 1.00 equiv) in a 1:1 (v/v) solvent mixture of THF:H_2O (10 mL total), NBS (1.12 g, 6.32 mmol, 1.05 equiv) was added slowly as a solid. The reaction was protected from light with aluminum foil and aged at 0 °C with vigorous stirring for a total of 3 hours. The resulting yellow reaction mixture was quenched with 5 mL of sodium thiosulfate, warmed to room temperature, and transferred to a separatory funnel. The product was extracted with CH_2Cl_2 (3 x 15 mL) and concentrated to afford a white solid. The crude white solid was taken up in 30 mL of ethyl acetate, washed with 25 mL of 1N NaOH, dried over Na_2SO_4, filtered, and concentrated to afford the title compound as a white solid (1.56 g, 98.7%), mp 135-138 °C.

R_f = 0.35 (28% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (d, J = 8.5

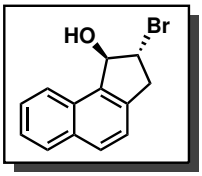
Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.59-7.55 (m, 1H), 7.52-7.48 (m, 1H), 7.38 (d, J = 8.5 Hz, 1H), 5.89 (dd, J = 6.5, 3.2 Hz, 1H), 4.57 (ddd, J = 7.1, 4.2, 3.2 Hz, 1H), 3.91 (dd, J = 17.1, 6.8 Hz, 1H), 3.40 (dd, J = 17.1, 4.1 Hz, 1H), 2.23 (d, J = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.57, 136.08, 133.45, 130.50, 130.18, 128.80, 127.13, 125.84, 123.89, 122.92, 84.01, 54.45, 42.06; IR (neat) 3297 (bm), 3189 (bm), 2948 (w), 2844 (w), 1429 (m), 1331 (m), 1090 (s), 814 (s), 800 (s), 743 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{13}H_{10}Br$ [M-OH]$^+$: 244.9966; Found 244.9967.



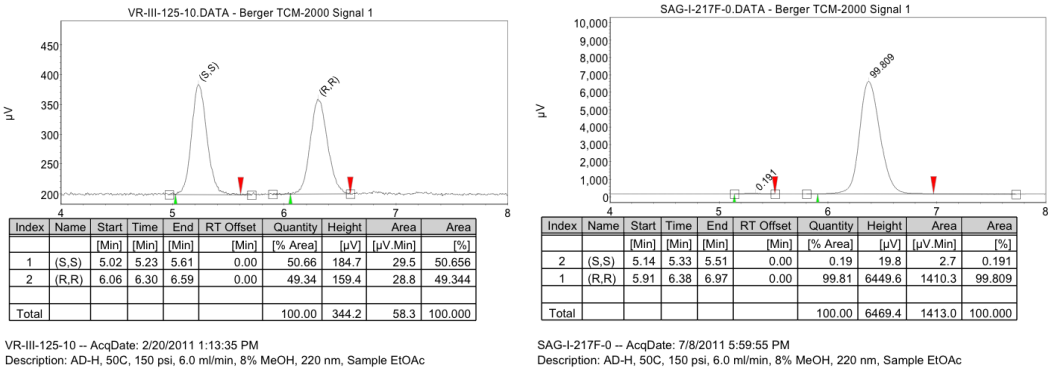
(−)-naproxen ester (**2.103**). To a solution of DCC (8.49 g, 41.1 mmol, 1.05 equiv) in CH_2Cl_2 (200 mL), DMAP (479 mg, 3.92 mmol, 0.100 equiv) was added followed by (*S*)-naproxen **2.133** (9.46 g, 41.1 mmol, 1.05 equiv). Bromohydrin **2.102** (10.3 g, 39.2 mmol, 1.00 equiv) was added as a solid. After 4 hours, the reaction mixture was filtered through Celite® 545 and concentrated to a white solid. Recrystallization from approximately 10:1 (v/v) ethyl acetate:hexanes provided needles (hot filtration to remove residual DCU was required). The solid was washed with ice-cold ethyl acetate (50 mL) and then hexanes (100 mL) to give the title compound as a single diastereomer (6.30 g, 33.8%), mp 153-155 °C.

$[\alpha]_D^{20} = -71.3$ (c 1.02, $CHCl_3$); R_f = 0.24 (15% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.64-7.56 (m, 3H), 7.37 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 8.5, 2.0 Hz, 1H), 7.31 (ddd, J = 8.1, 6.8, 1.0 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.14-7.10 (m, 2H), 6.90 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H), 6.76 (d, J = 1.2 Hz, 1H), 4.62 (ddd, J = 6.3, 2.0, 2.0 Hz, 1H), 3.95 (dd, J = 17.6, 6.3 Hz, 1H), 3.94 (s, 3H), 3.85 (q, J = 7.1 Hz, 1H), 3.43 (dd, J = 17.6, 2.0 Hz, 1H), 1.61 (d, J = 7.1 Hz, 3H); ^{13}C NMR (TCE, 125 MHz) δ 174.47, 157.45, 140.49, 134.81, 133.50, 132.69, 131.85, 130.89, 129.74, 129.22, 128.61, 128.34, 127.15, 126.88, 126.10, 125.84, 125.63, 123.28, 122.73, 118.89, 105.51, 84.30, 55.37, 50.31, 45.06, 43.05, 18.08; IR (neat) 2995 (w), 2931 (w), 1734 (s), 1602

(m), 1222 (s), 1665 (s), 1144 (s), 1090 (m), 962 (m), 860 (m), 816 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{27}H_{23}BrO_3$ $[M]^{+\cdot}$: 474.0831; Found 474.0830.



(1*R*,2*R*)-2-bromo-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol (2.104). To a suspension of ester **2.103** (1.00 g, 2.11 mmol, 1.0 equiv) in THF (1.0 mL), $BH_3 \cdot DMS$ (0.26 mL, 2.8 mmol, 1.3 equiv) was added. The reaction was heated to 70 °C, at which point the cloudy white suspension became a homogeneous clear solution. After 16 hours, the reaction was cooled to 0 °C and H_2O (2 mL) was added slowly. The mixture was transferred to a separatory funnel, diluted with additional H_2O (75 mL), and the product was extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to a colorless oil. Purification by flash column chromatography (25% ethyl acetate in hexanes v/v) afforded the desired product as a white solid (506 mg, 91.2%) with >98% ee by comparision with authentic racemic material (AD-H, 50 °C, 150 psi, 6.0 mL/min, 8% MeOH, λ = 220 nm; t_R = 5.33 min (minor), 6.38 min (major)), mp 117-119 °C. $[\alpha]_D^{20} = -88.9$ (c 1.02, $CHCl_3$). Other characterization data were identical to the racemic sample.



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		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	(S,S)	5.02	5.23	5.61	0.00	50.66	184.7	29.5	50.656
2	(R,R)	6.06	6.30	6.59	0.00	49.34	159.4	28.8	49.344
Total						100.00	344.2	58.3	100.000

VR-III-125-10 -- AcqDate: 2/20/2011 1:13:35 PM
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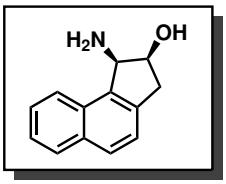
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
2	(S,S)	5.14	5.33	5.51	0.00	0.19	19.8	2.7	0.191
1	(R,R)	5.91	6.38	6.97	0.00	99.81	6449.6	1410.3	99.809
Total						100.00	6469.4	1413.0	100.000

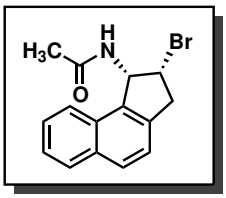
SAG-I-217F-0 -- AcqDate: 7/8/2011 5:59:55 PM
Description: AD-H, 50C, 150 psi, 6.0 ml/min, 8% MeOH, 220 nm, Sample EtOAc

Figure 2.21: SFC trace for (1*R*,2*R*)-2-bromo-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol (**2.104**)



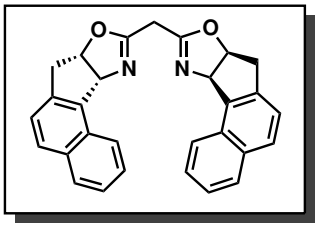
(1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-2-ol (**2.96**). A solution of bromohydrin **2.104** (228 mg, 0.867 mmol, 1.00 equiv) in a 1:1 (v/v) solvent mixture of CH_2Cl_2:CH_3CN (1.7 mL total) was cooled to 0 °C. Concentrated H_2SO_4 (70 μL, 1.3 mmol, 1.5 equiv) was introduced dropwise over one hour. The reaction was aged for an hour at 0 °C and one additional hour at room temperature. H_2O (3.5 mL) then was added, and the reaction was heated to 60 °C for 16 hours. The entire contents of the flask were transferred to a separatory funnel, rinsing with both CH_2Cl_2 and H_2O. The aqueous layer was washed with CH_2Cl_2 (2 x 25 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated to afford acetamide byproduct **2.105** as a yellow solid. The acidic aqueous layer was adjusted to a pH of 11 by the addition of 1 M NaOH. The product was extracted with CH_2Cl_2 (3 x 25 mL), dried over Na_2SO_4, filtered, and concentrated to afford the title compound as a pure white solid (118 mg, 68.3%), mp 117-120 °C.

$[\alpha]_D^{20}$ = +259.6 (c 1.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.57-7.53 (m, 1H), 7.49-7.45 (m, 1H), 7.35 (d, J = 8.3 Hz, 1H), 4.74 (broad s, 1H), 4.58-4.51 (m, 1H), 4.38 (broad d, J = 7.6 Hz, 1H), 3.33 (dd, J = 16.0, 7.3 Hz, 1H), 2.99 (dd, J = 16.0, 6.8 Hz, 1H), 1.59 (broad s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.92, 138.47, 133.32, 130.14, 129.12, 129.06, 126.73, 125.26, 123.81, 123.33, 71.54, 55.70, 40.50; IR (neat) 3310 (w), 3048 (bm), 2836 (bm), 2726 (bm), 1592 (bm), 1340 (m), 1090 (s), 989 (m), 922 (m), 807 (s), 739 (s), 624 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1075; Found 200.1081.



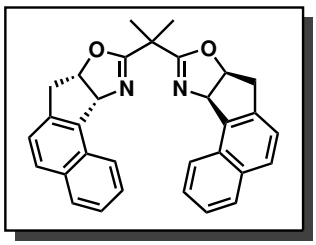
bromo acetamide (**2.105**). This byproduct was obtained from a racemic Ritter reaction according to the procedure above. Further purification of the crude yellow solid by flash column chromatography (50% ethyl acetate in hexanes v/v) afforded an analytically pure white solid (m.p. 200 °C dec.) with the following characterization data:

R_f = 0.37 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.56-7.47 (m, 2H), 7.36 (d, J = 8.3 Hz, 1H), 6.13 (dd, J = 10.0, 6.4 Hz, 1H), 5.90 (broad d, J = 9.6 Hz, 1H), 5.01 (ddd, J = 7.1, 6.3, 6.3 Hz, 1H), 3.64 (dd, J = 16.6, 7.1 Hz, 1H), 3.50 (dd, J = 16.6, 6.3 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.84, 138.57, 134.72, 133.34, 129.99, 129.85, 128.85, 127.28, 125.89, 123.64, 122.56, 55.59, 53.44, 42.46, 23.44; IR (neat) 3282 (bm), 3055 (bw), 2948 (bw), 2848 (w), 1645 (s), 1539 (bm), 1368 (m), 1304 (m), 1275 (m), 815 (s), 777 (m), 682 (m), 596 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{15}BrNO$ $[M+H]^+$: 304.0337; Found 304.0336.



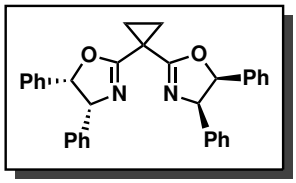
unsubstituted bis(oxazoline) (**2.106**). Amino alcohol **2.96** (393 mg, 1.97 mmol, 2.00 equiv) and diethyl malonimidate dihydrochloride (228 mg, 0.987 mmol, 1.0 equiv) were suspended in 1,2-DCA (5 mL). The reaction mixture was heated to reflux and after 1 hour Et_3N (140 μL, 0.987 mmol, 1.00 equiv) was added. After refluxing for an additional 3.5 hours the reaction mixture was cooled to room temperature and rinsed into a separatory funnel containing 50 mL of H_2O. The product was extracted with CH_2Cl_2 (3 x 50 mL), dried over Na_2SO_4, and concentrated to afford a pale yellow solid. ^{1}H NMR analysis of the unpurified solid indicated 75% conversion. The product mixture was therefore resubjected according to the aforementioned conditions with 76.0 mg imidate salt and 34 μL Et_3N. After workup and concentration, the crude solid was washed with 100 mL of hexanes and 15 mL of MeOH to afford the desired product as a pure white, flocculent solid (268 mg, 63.1%), mp 300 °C (decomp.). $[\alpha]_D^{20}$ = +577.1 (c 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.57-7.53 (m, 2H), 7.48-7.44 (m, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.00 (d, J = 8.0 Hz, 2H), 5.51-5.46 (m, 2H), 3.54 (dd, J = 18.0, 7.1 Hz, 2H), 3.35 (d, J = 18.0 Hz, 2H), 3.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.18, 137.07, 136.92, 133.25, 130.19, 129.58,

128.38, 126.95, 125.68, 124.87, 123.20, 83.59, 76.50, 40.84, 29.12; IR (neat) 3050 (w), 2988 (w), 2916 (w), 1660 (bs), 1433 (m), 1381 (m), 1348 (m), 1166 (s), 1001 (s), 798 (s), 766 (s), 734 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{29}H_{23}N_2O_2$ $[M+H]^+$: 431.1760; Found 431.1764.



bis(oxazoline) ligand (**2.97**). Unsubstituted bis(oxazoline) **2.106** (254 mg, 0.591 mmol, 1.00 equiv) was suspended in THF (6 mL) and cooled to 0 °C. NaH (70.5 mg, 1.77 mmol, 2.99 equiv, 60.2% in oil) was added as a solid in a single portion. The suspension was stirred at 0 °C for 1 hour, and then CH_3I (110 μL, 1.77 mmol, 2.99 equiv) was introduced dropwise. The reaction mixture was warmed to room temperature, stirred for 30 minutes, and sonicated at 60 W continuously for 80 minutes. The suspension was transferred to a separatory funnel and diluted slowly with H_2O (20 mL). The product was extracted with CH_2Cl_2 (3 x 30 mL), dried over $MgSO_4$, filtered, and concentrated to a white solid. The solid was transferred to a sintered glass Hirsch funnel and washed with 50 mL of hexanes before being dried *in vacuo* to afford ligand **2.97** as a flocculent white solid (250 mg, 92.1%), mp 260-261 °C.

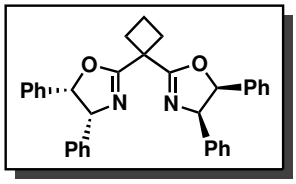
$[\alpha]_D^{20}$ = +601.0 (c 0.40, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.31 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.55 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.47 (ddd, J = 8.1, 6.8, 1.2 Hz 2H), 7.35 (d, J = 8.3 Hz, 2H), 5.95 (d, J = 8.0 Hz, 2H), 5.37 (ddd, J = 8.1, 7.1, 1.6 Hz, 2H), 3.45 (dd, J = 17.8, 7.1 Hz, 2H), 3.18 (dd, J = 17.8, 1.6 Hz, 2H), 1.38 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 °C, 125 MHz) δ 169.26, 137.68, 136.92, 133.37, 130.61, 129.34, 128.27, 126.61, 125.56, 125.42, 123.20, 83.20, 76.51, 40.80, 38.88, 24.06; IR (neat) 3050 (bw), 2977 (bw), 2913 (bw), 1650 (s), 1228 (m), 1146 (s), 1113 (s), 1019 (s), 810 (s), 773 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{31}H_{27}N_2O_2$ $[M+H]^+$: 459.2072; Found 459.2067.



Representative procedure for preparation of bis(oxazoline) ligands with modified bite angles:

bis(oxazoline) ligand (**2.50**). 2,2'-Methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] (75.0 mg, 0.164 mmol, 1.00 equiv) was suspended in THF and cooled to 0 °C. NaH (15.9 mg, 0.399 mmol, 2.49 equiv, 60.2% in oil) was added in a single portion under a stream of nitrogen. 1,2- dibromoethane (21 μL, 0.24 mmol, 1.5 equiv) was added dropwise and the reaction mixture was warmed to room temperature. The reaction was stirred at room temperature for 16 hours then poured into H_2O (10 mL). The product was extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated to a white solid. Purification by flash column chromatography (44:55:1 hexanes: ethyl acetate: NH_4OH v/v/v) afforded the desired product as a white solid (42.8 mg, 55.2%), mp 166-168 °C.

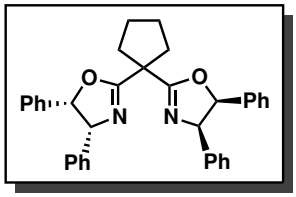
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04-6.94 (m, 20H), 5.96 (d, J = 10.3 Hz, 2H), 5.60 (d, J = 10.3 Hz, 2H), 1.84-1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.21, 137.81, 136.48, 127.97, 127.73, 127.70, 127.46, 127.01, 126.70, 86.20, 74.01, 19.05, 15.93; IR (neat) 3063 (bw), 2927 (bw), 1662 (s), 1454 (m), 1353 (bm), 1164 (m), 1103 (m), 974 (bm), 909 (bm), 727 (bs), 695 (s), 584 (bm) cm^{-1}; HRMS (ESI+) Calcd. for $C_{33}H_{29}N_2O_2$ $[M+H]^+$: 485.2229; Found 485.2216.



bis(oxazoline) ligand (**2.51**). Prepared according to the procedure above on 0.262 mmol scale with 1,3-diiodopropane and purified by flash column chromatography (54:45:1 hexanes: ethyl acetate: NH_4OH v/v/v) to afford the desired product as a white solid (45.0 mg, 34.7%), mp 142-145 °C.

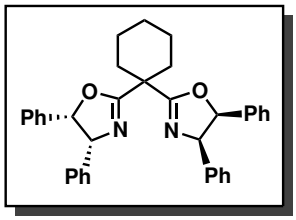
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04-7.00 (m, 10H), 6.99-6.94 (m, 10H), 6.01 (d, J = 10.0 Hz, 2H), 5.66 (d, J = 10.0, 2H), 3.12-3.04 (m, 2H), 2.96-2.87 (m, 2H), 2.30 (ddd, J = 15.9, 7.8, 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.20, 137.73, 136.46, 128.04, 127.77, 127.76,

127.52, 127.07, 126.75, 86.64, 74.09, 43.09, 30.76, 17.23; IR (neat) 3063 (bw), 2950 (bw), 1655 (s), 1496 (m), 1454 (m), 1332 (bm), 1122 (bm), 1076 (m), 966 (bm), 910 (bm), 929 (s), 696 (s), 584 (bm) cm^{-1}; HRMS (ESI+) Calcd. for $C_{34}H_{31}N_2O_2$ $[M+H]^+$: 499.2389; Found 499.2387.



bis(oxazoline) ligand (**2.52**). Prepared according to the procedure above on 0.164 mmol scale with 1,4-diiodobutane and purified by flash column chromatography (59:40:1 hexanes: ethyl acetate: NH_4OH v/v/v) to afford the desired product as a white solid (62.2 mg, 75.9%), mp 167-169 °C.

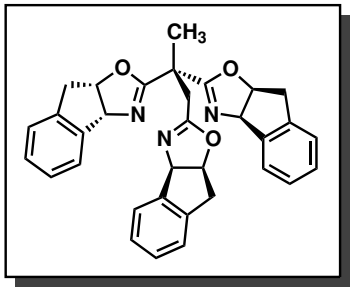
^1H NMR (500 MHz, $CDCl_3$) δ 7.03-7.00 (m, 10H), 6.97-6.94 (m, 10H), 5.96 (d, J = 10.3 Hz, 2H), 5.60 (d, J = 10.3 Hz, 2H), 2.77-2.68 (m, 2H), 2.64-2.55 (m, 2H), 2.04-1.93 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.97, 137.80, 136.50, 128.02, 127.75, 127.72, 127.48, 127.02, 126.73, 86.45, 73.96, 50.17, 36.08, 25.49; IR (neat) 3063 (bw), 2956 (bw), 1651 (m), 1496 (m), 1453 (m), 1318 (bm), 1212 (bm), 1154 (m), 995 (bm), 909 (m), 726 (bs), 695 (s), 583 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{35}H_{33}N_2O_2$ $[M+H]^+$: 513.2542; Found 513.2553.



bis(oxazoline) ligand (**2.53**). Prepared according to the procedure above on 0.131 mmol scale with 1,5-diiodopentane and purified by flash column chromatography (59:40:1 hexanes: ethyl acetate: NH_4OH v/v/v) to afford the desired product as a white solid (60.1 mg, 90.2%), mp 153-156 °C.

^1H NMR (500 MHz, $CDCl_3$) δ 7.04-7.00 (m, 10H), 7.00-6.91 (m, 10H), 5.95 (d, J = 10.3 Hz, 2H), 5.65 (d, J = 10.3 Hz, 2H), 2.52-2.38 (m, 4H), 1.96-1.76 (m, 4H), 1.64 (ddd, J = 11.7, 5.6, 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.44, 137.87, 136.57, 128.09, 127.72, 127.68, 127.44, 126.95, 126.72, 85.83, 74.11, 44.41, 32.91, 25.61, 23.00; IR (neat) 3063 (bw), 2936 (bm), 1650 (m), 1496 (m), 1453 (m), 1318 (bm), 1206 (bm), 1124 (m), 976 (bm), 908 (m), 728 (bs), 695 (s), 582 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{36}H_{35}N_2O_2$

$[M+H]^+$: 527.2699; Found 527.2699.



Representative procedure for preparation of pseudo C3-symmetric tris(oxazoline) ligands:

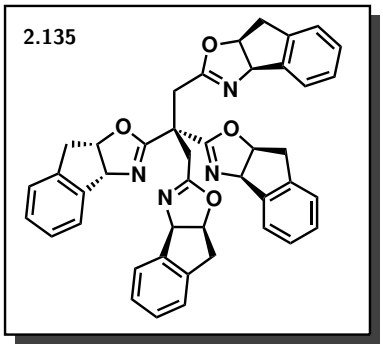
tris(oxazoline) ligand (**2.66**). To a stirred suspension of the parent unsubstituted bis(oxazoline) ligand[103] (1.16 g, 3.50 mmol) in 15 mL THF, NaH (146 mg, 3.67 mmol, 1.05 equiv, 60.2% in oil) was added in a single portion. The reaction mixture was heated to 50 °C for 15 minutes then allowed to cool to room temperature. In a separate 1 dram vial, methyl iodide (497 mg, 3.50 mmol, 1.00 equiv) was weighed and dissolved in 1.5 mL of THF. The solution of methyl iodide was transferred *via* cannula to the peach-colored reaction mixture followed by rinsing with THF (2 x 0.5 mL). The reaction was stirred at room temperature for 30 minutes before adding a second equivalent of NaH (146 mg, 3.67 mmol, 1.05 equiv). After stirring for an additional 30 minutes, (3a*R*,8a*S*)-2-(chloromethyl)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazole[104] (872 mg, 4.20 mmol, 1.20 equiv) was added and the reaction was stirred for 18 hours. The reaction mixture was poured into 50% aqueous NH_4Cl (50 mL), extracted with CH_2Cl_2 (3 x 50 mL) and dried over Na_2SO_4. Concentration delivered a crude yellow foam that was purified by silica gel chromatography (94:5:1 ethyl acetate: methanol: NH_4OH v/v/v). Trituration of the resulting solid with 10 mL MeOH followed by vacuum drying for 20 hours at 80 °C over P_2O_5 afforded **2.66** as a white solid (1.33 g, 75.6% yield), mp 117-120 °C.

$[\alpha]_D^{20} = +378$ (c 1.02, $CHCl_3$); $R_f = 0.40$ (5% MeOH, 1% NH_4OH in ethyl acetate); ^1H

[103] [3a*R*-[2(3'a*R**,8'a*S**),3'aβ,8'aβ]]-(+)-2,2'-Methylenebis[3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole] is now commercially available but could alternatively be prepared in a single step from (1*R*, 2*S*)-1-amino-2-indanol according to the literature procedure. Carloni, S.; Borzatta, V.; Tanzi, G.; Sartori, G.; Maggi, R. Catalysts Based on Metal Complexes for the Synthesis of Optically Active Chrysanthemic Acid. U.S. Patent 2008/0021237 A1, January 24, 2008.

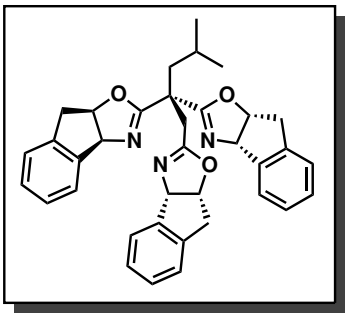
[104] Prepared in two steps from chloroacetonitrile and (1*R*, 2*S*)-1-amino-2-indanol according to known procedures. Ye, M. C.; Li, B.; Zhou, J.; Sun, X. L.; Tang, Y. Modular Synthesis of Chiral Homo– and Heterotrisoxazolines. Improving the Enantioselectivity in the Asymmetric Michael Addition of Indole to Benzylidene Malonate. *J. Org. Chem.* **2005**, *70*, 6108-6110.

NMR (500 MHz, $CDCl_3$) δ 7.52-7.48 (m, 1H), 7.45-7.42 (m, 1H), 7.34-7.30 (m, 1H), 7.28-7.12 (m, 9H), 5.57 (d, J = 8.0 Hz, 1H), 5.48 (d, J = 7.9 Hz, 1H), 5.26 (ddd, 7.9, 7.9, 1.8 Hz, 1H), 5.18 (d, J = 8.0 Hz, 1H), 5.12 (ddd, J = 8.0, 8.0, 1.7 Hz, 1H), 4.08 (ddd, J = 8.0, 6.9, 1.5 Hz, 1H), 3.35-3.24 (m, 2H), 3.11-2.90 (m, 3H), 2.84-2.74 (m, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN, 50 °C) δ 167.88, 167.78, 164.54, 143.69, 143.28, 143.14, 141.60, 141.34, 141.24, 128.15, 126.44, 126.43, 126.38, 126.36, 126.33, 126.31, 84.35, 83.54, 77.64, 77.55, 41.83, 40.52, 40.49, 40.35, 35.50, 21.68; IR (neat): 2969 (bw), 2919 (bw), 1661 (s), 1647 (s), 1478 (m), 1456 (m), 1425 (m), 1220 (m), 1160(s), 1097 (s), 997 (s), 856 (m), 756 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{33}H_{30}N_3O_3$ $[M+H]^+$: 516.2297; Found: 516.2275.



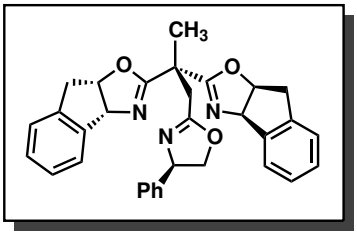
tetra(oxazoline) ligand (**2.135**). Isolated during the preparation of **2.66**. Homologation of cyclohexanone with 10 mol % $Sc(OTf)_3$ and 11 mol % **2.135** afforded a 68.5:31.5 er. white solid, mp 135-140 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.37 (m, 4H), 7.23-7.14 (m, 10H), 7.11-7.07 (m, 2H), 5.34 (d, J = 7.6 Hz, 2H), 5.26 (d, J = 7.6 Hz, 2H), 4.76 (ddd, J = 8.1, 6.7, 1.5 Hz, 2H), 4.51 (ddd, J = 8.6, 7.0, 1.7 Hz, 2H), 3.22-3.13 (m, 6H), 3.02 (d, J = 17.8 Hz, 2H), 2.95 (dd, J = 17.8, 7.3 Hz, 2H), 2.39 (d, J = 18.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.44, 164.14, 142.42, 141.91, 140.09, 139.70, 128.23, 128.14, 127.25, 127.24, 125.68, 125.58, 125.14, 125.08, 83.19, 82.31, 76.52, 76.32, 43.15, 39.75, 39.40, 30.87; IR (neat) 3025 (bw), 2919 (bm), 1650 (s), 1479 (m), 1459 (m), 1427 (m), 1163 (m), 1002 (bs), 908 (m), 927 (bs), 644 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{43}H_{37}N_4O_4$ $[M+H]^+$: 673.2815; Found 673.2800.



tris(oxazoline) ligand (**2.67**). Prepared according to the representative procedure above to afford **2.67** as a white solid, mp 192-194 °C.

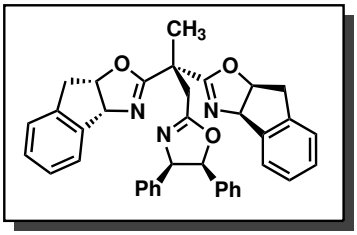
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.48 (m, 1H), 7.45-7.42 (m, 1H), 7.34-7.32 (m, 1H), 7.28-7.21 (m, 5H), 7.20-7.14 (m, 4H), 5.53 (d, J = 7.8 Hz, 1H), 5.48 (d, J = 7.8 Hz, 1H), 5.25 (d, J = 7.8 Hz, 1H), 5.17 (ddd, J = 8.6, 7.1, 1.7 Hz, 1H), 5.03 (ddd, J = 7.6, 6.6, 1.2 Hz, 1H), 4.47 (ddd, J = 8.1, 6.9, 1.5 Hz, 1H) 3.25-3.14 (m, 2H), 3.09-2.99 (m, 2H), 2.93- 2.79 (m, 4H), 1.89 (dd, J = 14.7, 6.6 Hz, 1H), 1.83 (dd, J = 14.2, 6.1 Hz, 1H), 1.66-1.56 (m, 1H), 0.73 (d, J = 6.6 Hz, 3H), 0.38 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.40, 167.33, 164.19, 142.32, 142.02, 141.67, 140.35, 139.89, 139.75, 128.30, 128.26, 127.39, 127.30, 127.27, 125.75, 125.67, 125.54, 125.23, 125.09, 125.01, 83.44, 83.03, 82.48, 76.68, 76.50, 76.36, 44.18, 40.23, 39.88, 39.68, 39.30, 31.36, 23.84, 23.61, 23.02; IR (neat) 3021 (w), 2950 (bm), 1656 (bs), 1458 (m), 1278 (m), 1194 (m), 1151 (m), 1007 (s), 847 (bm), 747 (bs), 598 (m) cm^{-1} ; HRMS (ESI+) Calcd. for $C_{36}H_{36}N_3O_3$ $[M+H]^+$: 558.2757; Found 558.2763.



tris(oxazoline) ligand (**2.68**). Prepared according to the representative procedure above to afford **2.68** as a white solid, mp 69-73 °C.

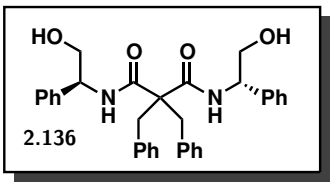
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.46 (m, 2H), 7.29-7.16 (m, 9H), 7.10-7.08 (m, 2H), 5.59- 5.52 (m, 2H), 5.32-5.26 (m, 2H), 4.86 (ddd, J = 10.3, 8.3, 0.0 Hz, 1H), 3.64 (dd, J = 10.0, 8.6 Hz, 1H), 3.56 (dd, J = 8.1, 8.1 Hz, 1H), 3.35-3.26 (m, 2H), 3.06-2.95 (m, 4H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.62, 167.25, 164.87, 142.42, 141.99, 141.77, 140.34, 139.76, 128.63, 128.48, 128.37, 127.48, 127.42, 127.25, 126.59, 125.74, 125.71, 125.22, 125.08, 83.60, 83.57, 76.71, 76.61, 73.98, 69.53, 40.89, 39.79, 39.65, 34.82, 21.12; IR (neat) 3068 (bw), 2939 (bw), 1649 (s), 1162 (m), 1097 (bm), 989 (m), 907

(m), 727 (bs), 644 (m), 613 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{32}H_{30}N_3O_3$ $[M+H]^+$: 504.2287; Found 504.2309.



tris(oxazoline) ligand (**2.69**). Prepared according to the representative procedure above to afford **2.69** as a white solid, mp 104-107 °C.

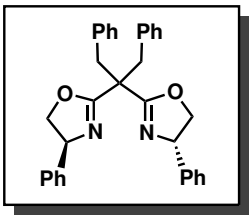
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.28-7.26 (m, 1H), 7.24-7.20 (m, 1H), 7.11- 7.06 (m, 1H), 7.01-6.96 (m, 3H), 6.95-6.91 (m, 3H), 6.81-6.78 (m, 1H), 6.74-6.71 (m, 2H), 6.70- 6.66 (m, 2H), 5.60-5.53 (m, 2H), 5.33-5.28 (m, 2H), 5.21 (d, J = 10.5 Hz, 1H), 4.82 (d, J = 10.5 Hz, 1H), 3.32 (dd, J = 17.8, 6.8 Hz, 1H), 3.26-3.16 (m, 3H), 3.01 (d, J = 17.6 Hz, 1H), 2.95 (d, J = 17.8 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.71, 167.21, 164.96, 141.80, 141.78, 140.17, 139.78, 137.79, 136.87, 128.52, 128.34, 127.81, 127.51, 127.45, 127.10, 127.09, 126.77, 126.31, 125.75, 125.53, 125.26, 125.21, 84.50, 83.72, 83.62, 76.80, 76.65, 74.09, 40.98, 39.79, 39.68, 35.19, 21.33; IR (neat) 3066 (bw), 2937 (bw), 1648 (s), 1455 (m), 1299 (bm), 1162 (m), 1098 (m), 991 (bm), 908 (m), 727 (bs), 697 (s), 645 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{38}H_{34}N_3O_3$ $[M+H]^+$: 580.2600; Found 580.2626.



amido alcohol (**2.136**). Dibenzylmalonic acid (1.21 g, 4.27 mmol, 1.00 equiv) and DMF (66 μL, 0.85 mmol, 0.20 equiv) were suspended in 4.3 mL of CH_2Cl_2 and cooled to 0 °C. Oxalyl chloride (0.74 mL, 8.5 mmol, 2.0 equiv) was added dropwise and the reaction mixture was allowed to stir for four hours. In a separate vessel, (*S*)-phenylglycinol (1.17 g, 8.54 mmol, 2.00 equiv) and Et_3N (3.0 mL, 21 mmol, 4.7 equiv) were dissolved in 10 mL of CH_2Cl_2. The now formed acid chloride in CH_2Cl_2 was transferred dropwise to the solution of amino alcohol via cannula, followed by rinsing with CH_2Cl_2 (2 x 2.5 mL). The reaction mixture was allowed to stir for 16 hours then transferred to a separatory funnel. The organic layer was washed with aqueous 1N HCl (25 mL), saturated

$NaHCO_3$ (25 mL), and saturated NaCl (25 mL), back extracting with 25 mL of CH_2Cl_2 from each aqueous wash. The combined organics were dried over Na_2SO_4, filtered, and concentrated to deliver a crude solid. The crude solid was suspended in boiling hexanes (25 mL) and then collected by filtration on a sintered glass funnel to afford the desired product as a white solid (1.88 g, 84.3%), mp 127-131 °C.

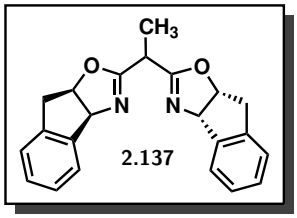
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 7.3 Hz, 2H), 7.27-7.13 (m, 12H), 7.11-7.07 (m, 4H), 7.01-6.96 (m, 4H), 5.04-5.00 (m, 2H), 3.70 (d, J = 5.1 Hz, 4H), 3.46 (d, J = 14.4 Hz, 2H), 3.33 (d, J = 14.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.61, 138.58, 136.31, 129.72, 128.76, 128.54, 127.74, 127.13, 126.90, 66.11, 59.12, 56.02, 43.81; IR (neat) 3332 (bw), 3062 (w), 3030 (w), 2932 (bw), 2876 (bw), 1660 (bm), 1636 (bm), 1515 (bm), 1454 (m), 1237 (bw), 1029 (bm), 908 (m), 729 (s), 697 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{33}H_{35}N_2O_4$ $[M+H]^+$: 523.2597; Found 523.2611.



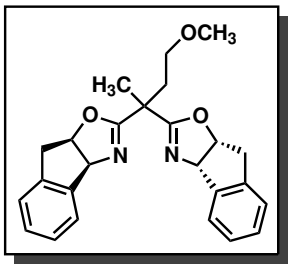
bis(oxazoline) ligand (**2.56**). Prepared from amido alcohol **2.136** according to the literature procedure[105] to afford **2.56** as a white solid, mp 115-117 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.34 (m, 4H), 7.32-7.24 (m, 12H), 7.03-6.99 (m, 4H), 5.18 (dd, J = 9.0, 9.0 Hz, 2H), 4.63 (dd, J = 10.3, 8.3 Hz, 2H), 4.03 (dd, J = 8.6, 8.6 Hz, 2H), 3.55 (d, J = 14.2 Hz, 2H), 3.48 (d, J = 14.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.93, 141.95, 136.93, 130.76, 128.64, 128.34, 127.54, 126.94, 126.93, 75.08, 69.74, 48.86, 39.38; IR (neat) 3086 (bw), 3029 (bw), 2897 (bw), 1650 (m), 1493 (m), 1453 (m), 1174 (m), 1013 (m), 907 (m), 927 (bs), 696 (s), 535 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{33}H_{31}N_2O_2$ $[M+H]^+$: 487.2386; Found 487.2375.

[105] Evans, D. A.; Woerpel, K. A.; Nosse, B.; Schall, A.; Shinde, Y.; Jezek, E.; Haque, M. M.; Chhor, R. B.; Reiser, O. Synthesis of (−)-(*S*,*S*)-Bis(4-isopropyloxazoline). *Org. Synth.* **2006**, *83*, 97-102.



bis(oxazoline) ligand (**2.137**). The corresponding unsubstituted bis(oxazoline) ligand **2.48**[103] (2.50 g, 7.57 mmol, 1.00 equiv) and NaH (317 mg, 7.95 mmol, 1.05 equiv, 60.2% in oil) were suspended in 30 mL of THF. The suspension was heated to 50 °Cfor 15 minutes, producing a clear colorless solution. The reaction mixture was cooled to room temperature and methyl iodide (1.07 g, 7.57 mmol, 1.00 equiv) was added. After allowing to stir for an additional hour at room temperature, the reaction was quenched by pouring into H_2O (50 mL). The product was extracted with CH_2Cl_2 (3 x 100 mL), washed with saturated NaCl (300 mL), dried over Na_2SO_4, filtered, and concentrated to a crude solid. Recrystallization from ethyl acetate (2 crops) delivered the desired product as a white solid (2.12 g, 81.2%). Characterization data were in agreement with the literature values.[106]
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50-7.45 (m, 2H), 7.27-7.21 (m, 6H), 5.57-5.51 (m, 2H), 5.33-5.26 (m, 2H), 3.45 (q, J = 7.3 Hz, 1H), 3.38-3.31 (m, 2H), 3.09-3.01 (m, 2H), 1.38 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.99, 167.98, 141.84, 141.76, 139.78, 139.72, 128.50, 128.48, 127.45, 127.46, 125.64, 125.61, 125.22, 83.42, 83.33, 76.55, 39.75, 39.70, 34.15, 14.82; HRMS (ESI+) Calcd. for $C_{22}H_{21}N_2O_2$ $[M+H]^+$: 345.1603; Found 345.1601.



bis(oxazoline) ligand (**2.62**). To a suspension of methylated bis(oxazoline) **2.137** (344 mg, 1.00 mmol, 1.00 equiv), NaH (59.8 mg, 1.50 mmol, 1.50 equiv, 60.2% in oil) was added as a solid under a stream of nitrogen. The reaction mixture was heated to 50 °C for 30 minutes then cooled to room temperature before introducing 2-bromoethyl methyl ether (282 μL, 3.00 mmol, 3.00 equiv) dropwise. The suspension was stirred for an additional 18 hours then poured into 50 mL of 50% (v/v) aqueous NH_4Cl. The

[106] Foltz, C.; Enders, M.; Bellemin-Laponnaz, S.; Wadepohl, H.; Gade, L. H. Using a Tripod as a Chiral Chelating Ligand: Chemical Exchange Between Equivalent Molecular Structures in Palladium Catalysis with 1,1,1-Tris(oxazolinyl)ethane ("Trisox"). *Chem. Eur. J.* **2007**, *13*, 5994-6008.

product was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with saturated NaCl (150 mL). The saturated NaCl layer was extracted one additional time with CH_2Cl_2 (50 mL) and all organic extracts were combined and dried over Na_2SO_4, filtered, and concentrated to afford a yellow solid. The resulting solid was triturated with boiling Et_2O (5 mL), then washed on a sintered glass filter with pentane (3 x 10 mL) to deliver **2.62** as a pale yellow solid (325 mg, 80.8%), mp 150-152 °C.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51-7.47 (m, 2H), 7.27-7.21 (m, 6H), 5.55-5.51 (m, 2H), 5.27-5.23 (m, 2H), 3.34-3.27 (m, 2H), 3.25-3.19 (m, 1H), 3.14-3.08 (m, 1H), 3.05-2.96 (m, 2H), 2.94 (s, 3H), 2.16-2.12 (m, 2H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.44, 168.29, 142.04, 141.90, 139.83, 139.78, 128.40, 128.35, 127.41, 127.36, 125.71, 125.69, 125.15, 125.08, 83.35, 83.15, 76.52, 76.44, 68.56, 58.24, 40.89, 39.65, 39.59, 35.72, 21.30; IR (neat) 3065 (bw), 2969 (bw), 2809 (w), 1642 (s), 1479 (w), 1458 (bw), 1118 (bs), 990 (m), 907 (m), 729 (bs) cm^{-1}; HRMS (ESI+) Calcd. for $C_{25}H_{27}N_2O_3$ $[M+H]^+$: 403.2022; Found 403.2029.

2.6.3 *NMR Spectral Data*

Figure 2.22: ^{1}H NMR of 2-phenylcycloheptanone (**2.26**)

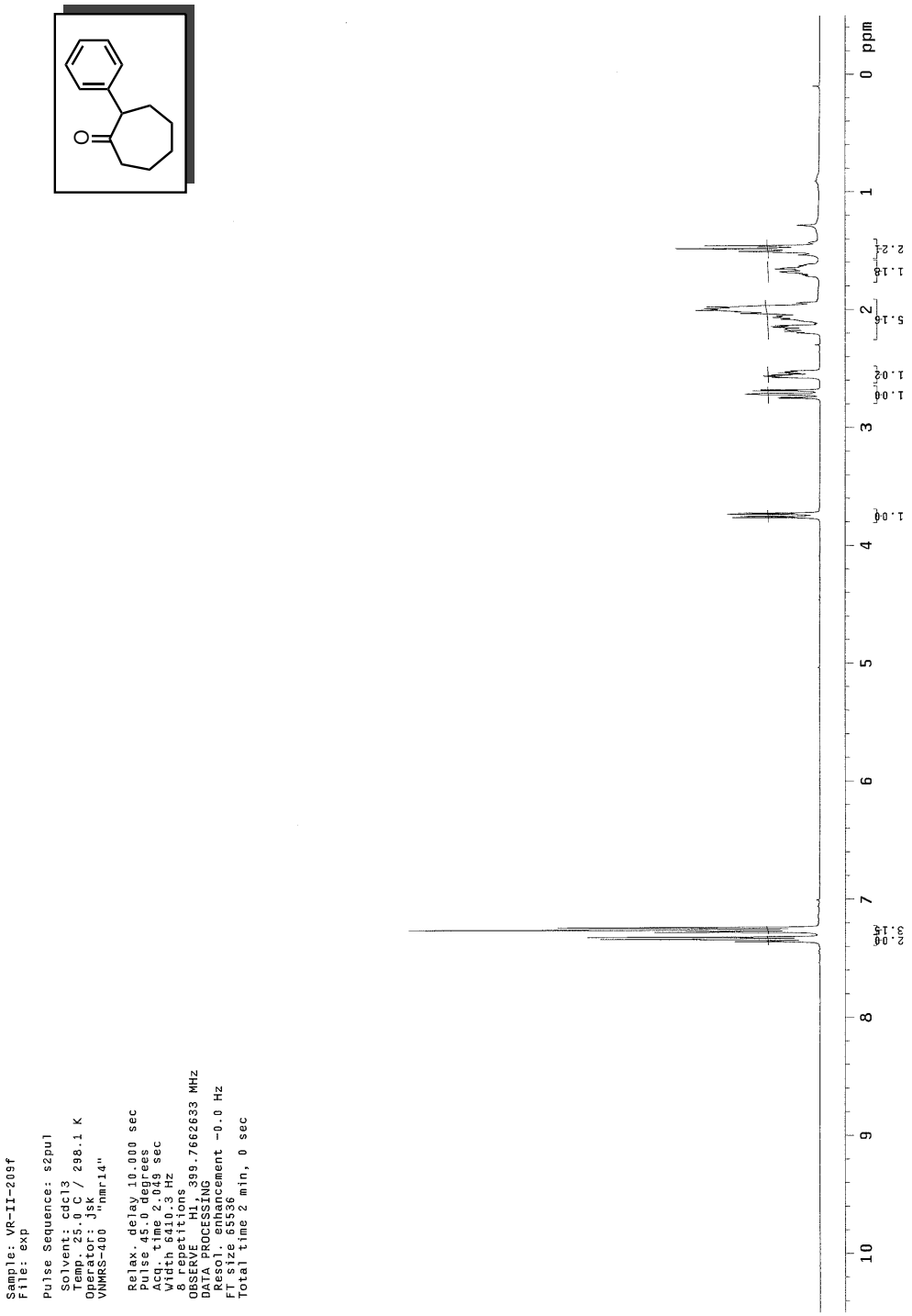


Figure 2.23: ^{13}C NMR of 2-phenylcycloheptanone (**2.26**)

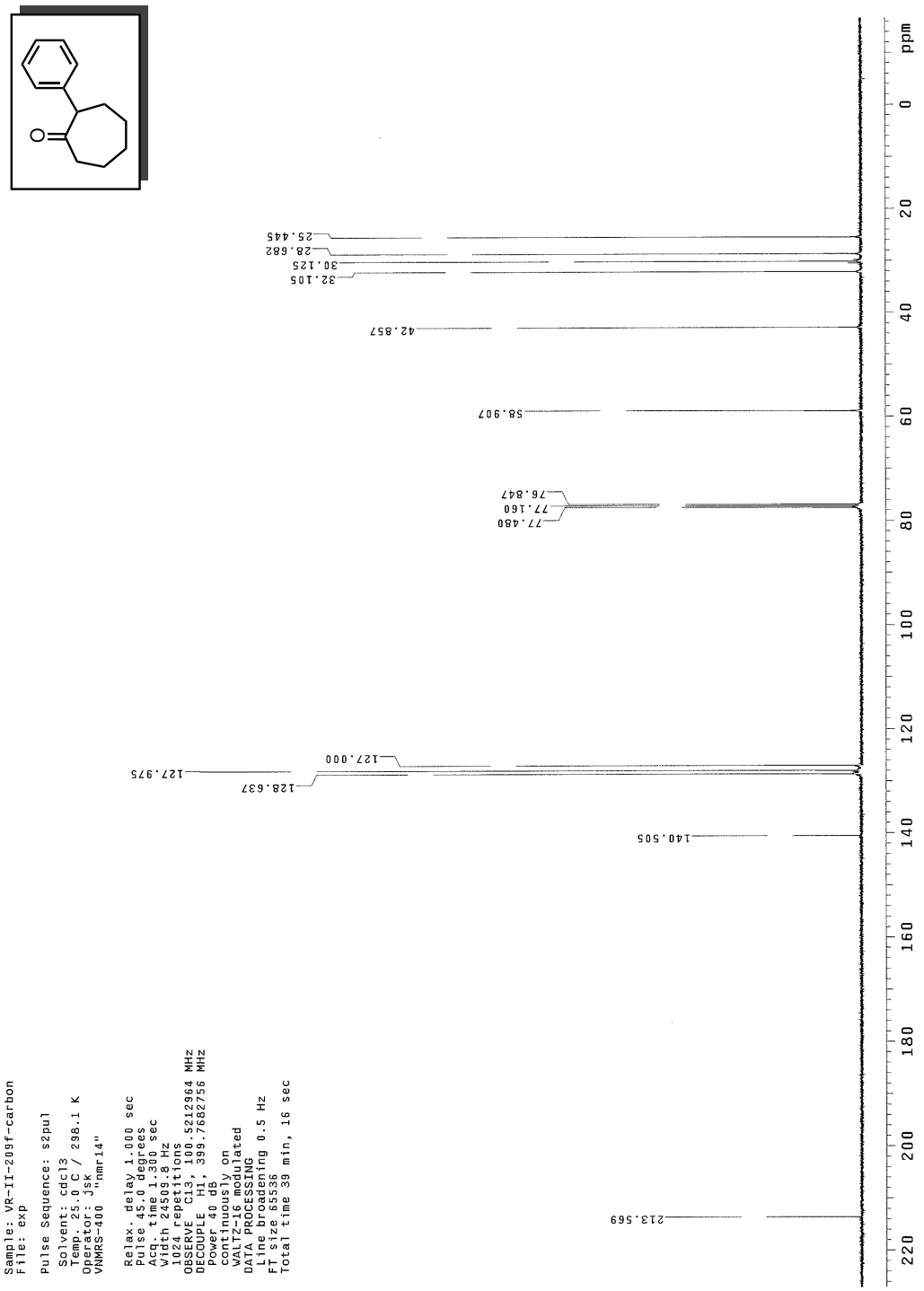


Figure 2.24: ^{1}H NMR of 2-methyl-2-phenylcyclopentanone (**2.31**)

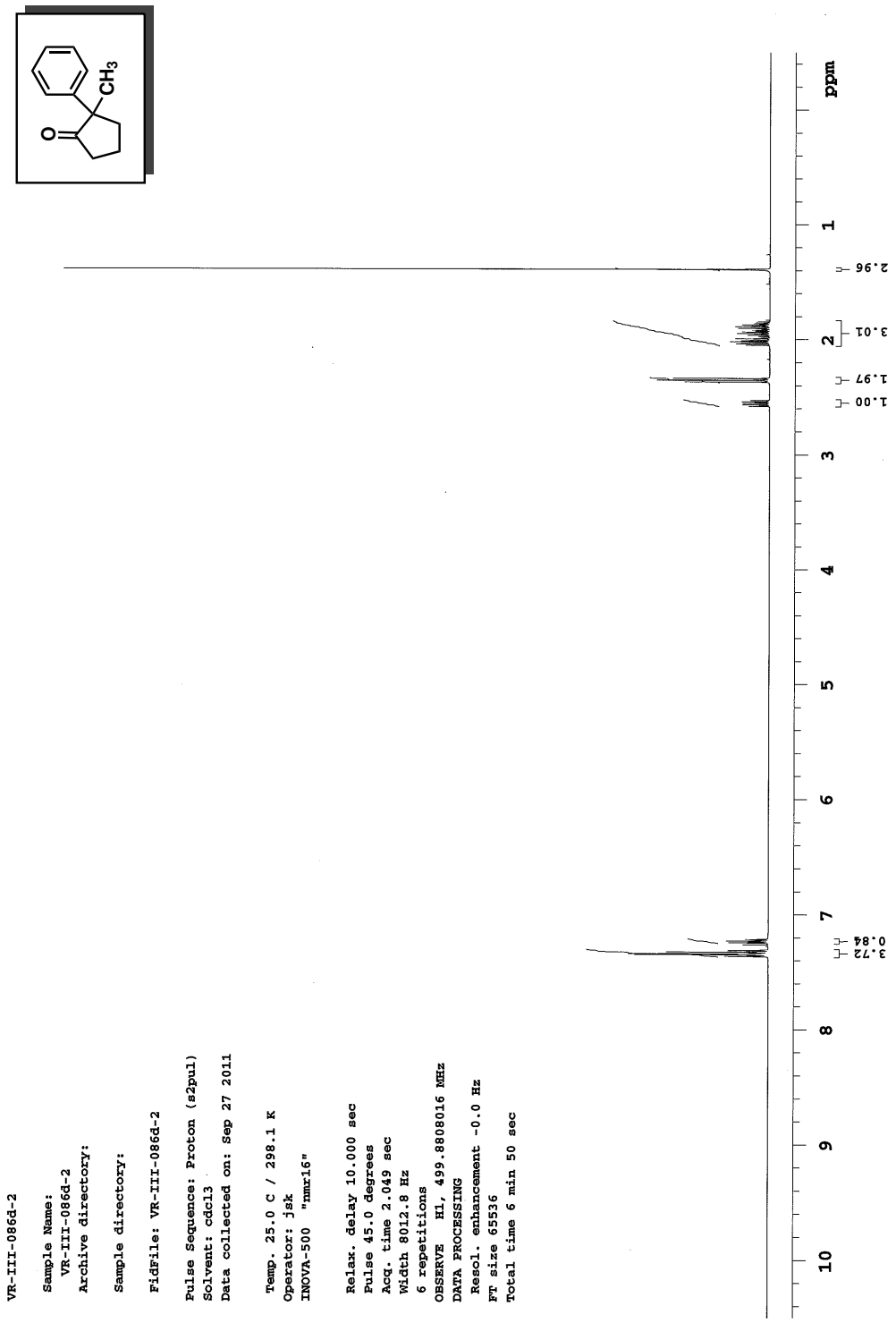


Figure 2.25: ^{13}C NMR of 2-methyl-2-phenylcyclopentanone (**2.31**)

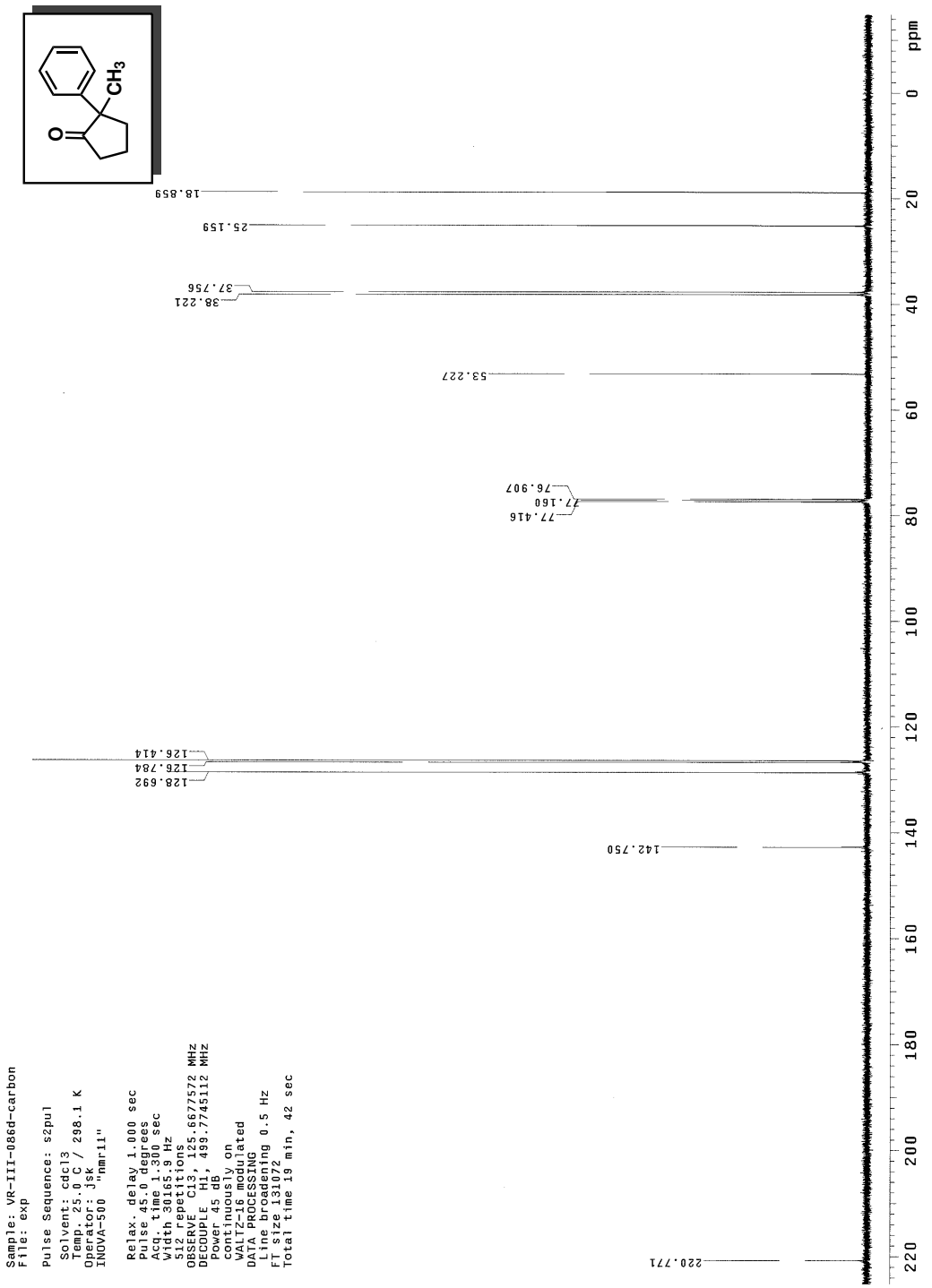


Figure 2.26: ^{1}H NMR of 2-phenylcyclopentanone (**2.30**)

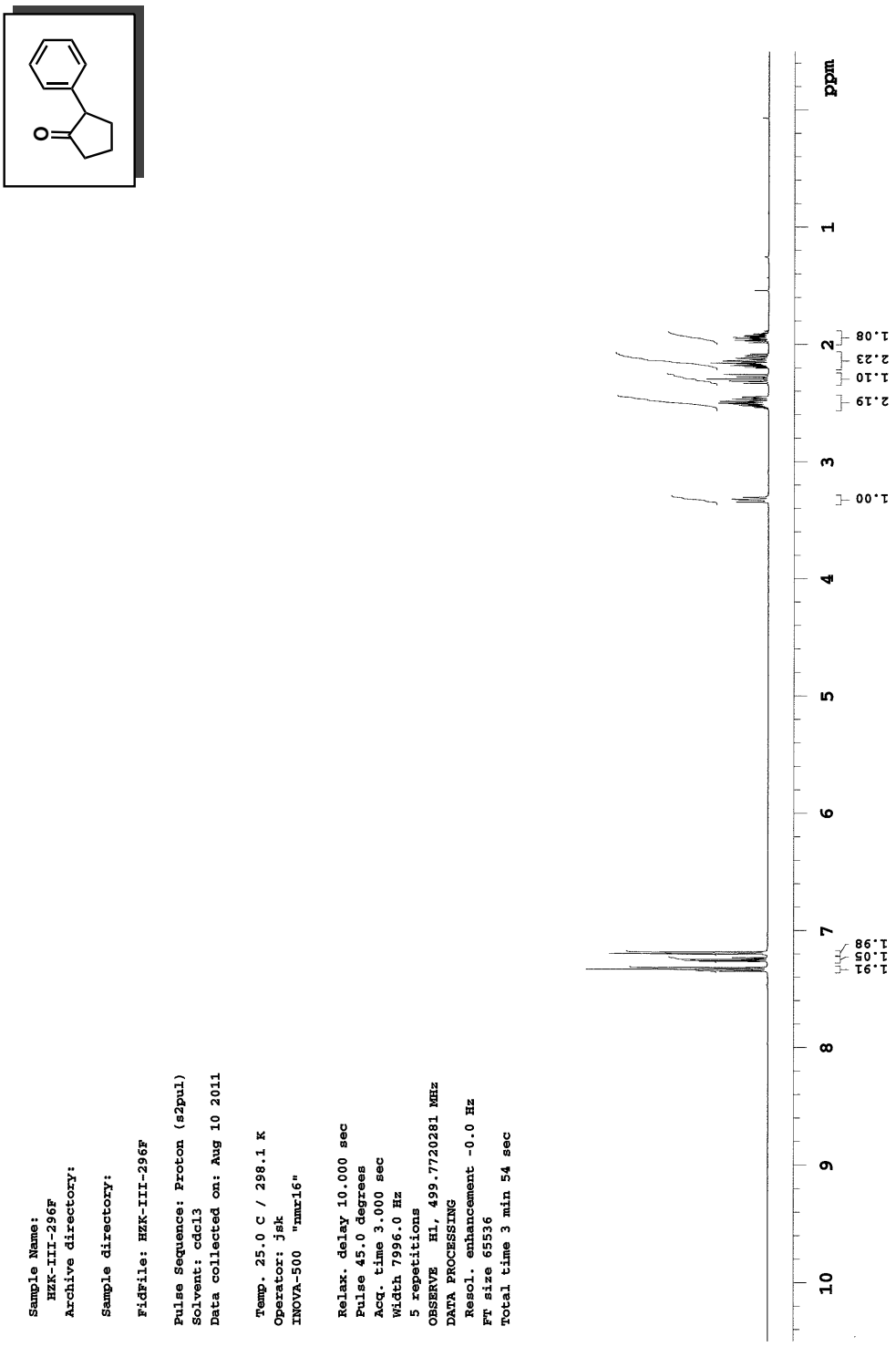


Figure 2.27: ^{13}C NMR of 2-phenylcyclopentanone (**2.30**)

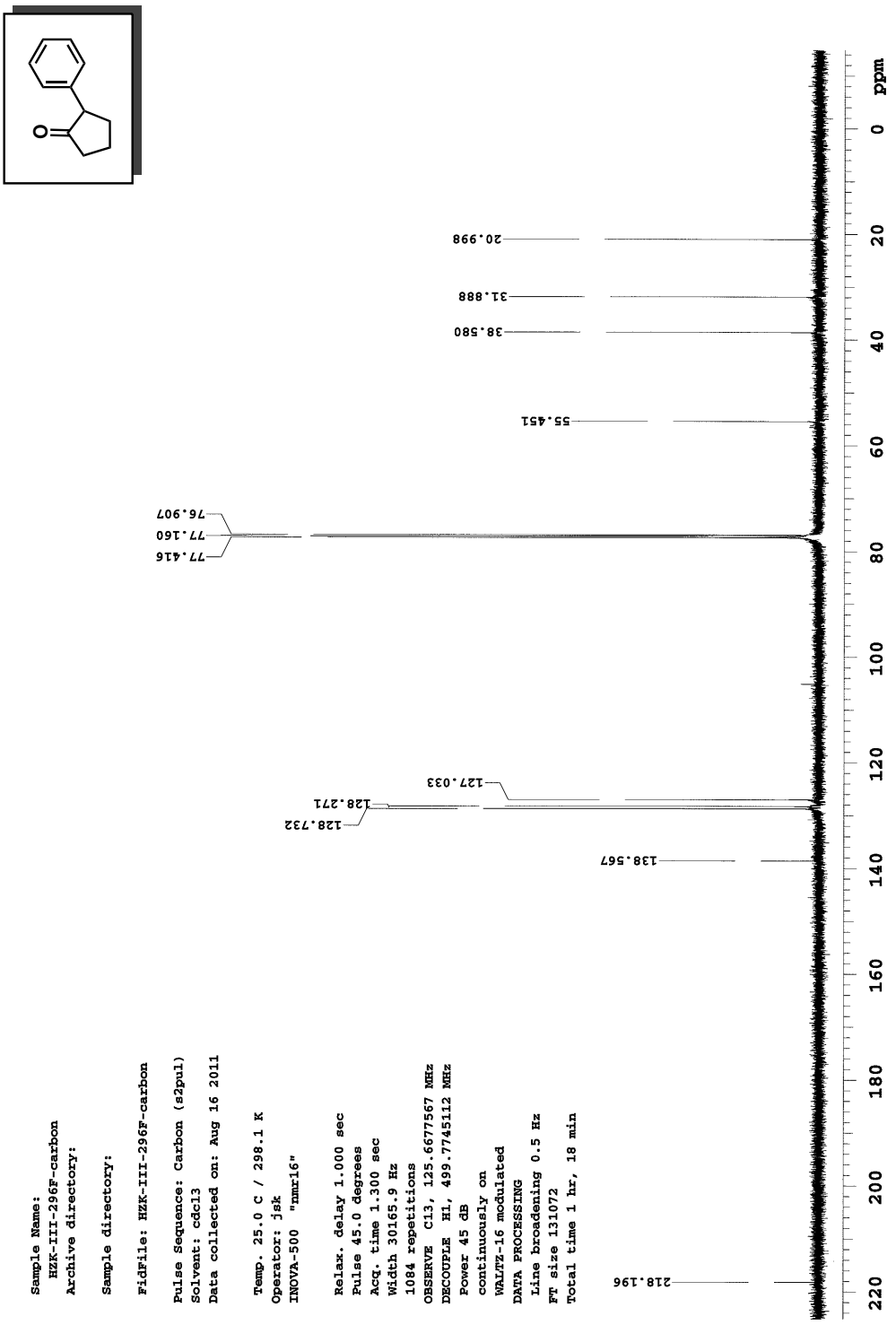


Figure 2.28: ^{1}H NMR of 2-(2-bromophenyl)cyclopentanone (**2.32**)

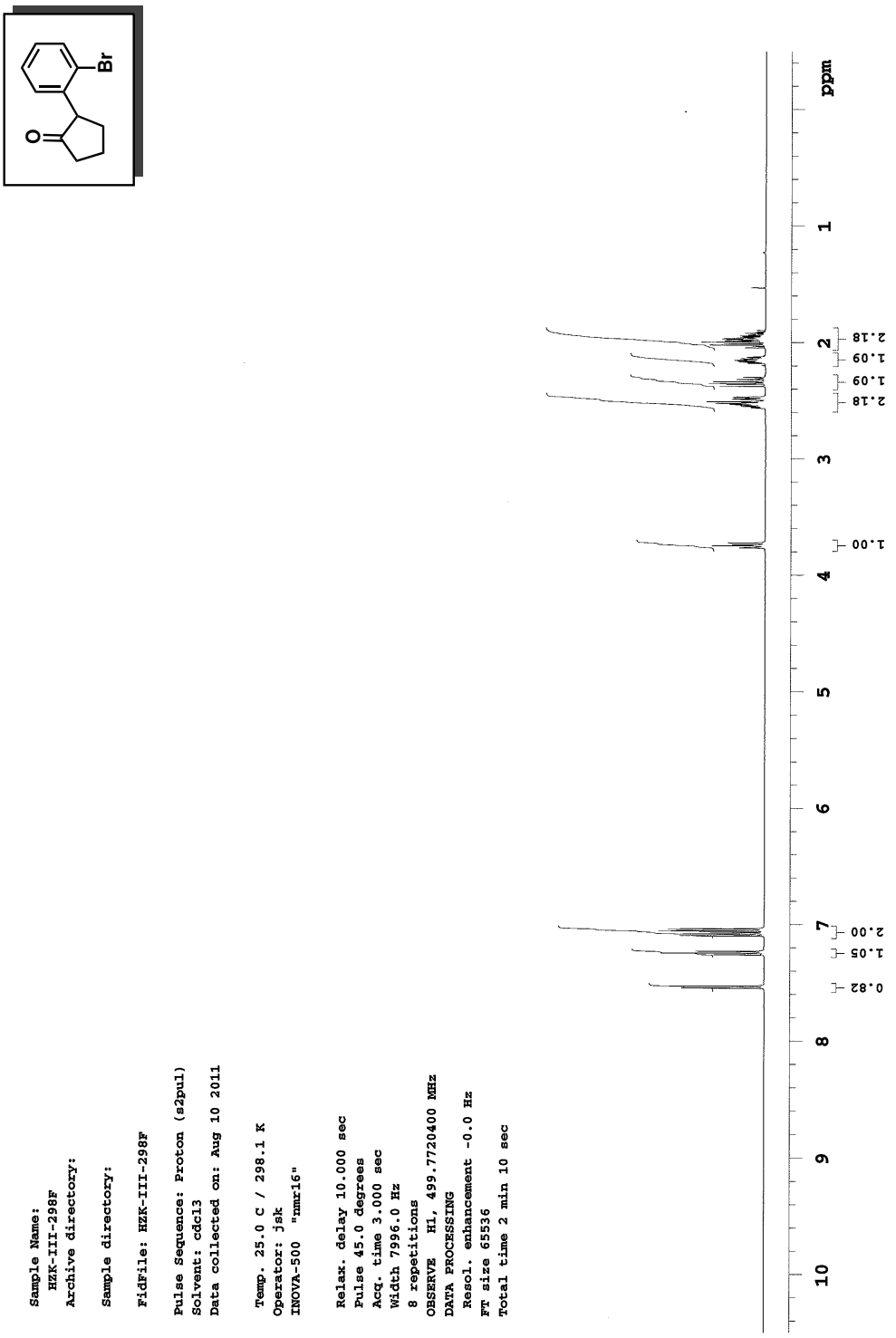


Figure 2.29: ^{13}C NMR of 2-(2-bromophenyl)cyclopentanone (**2.32**)

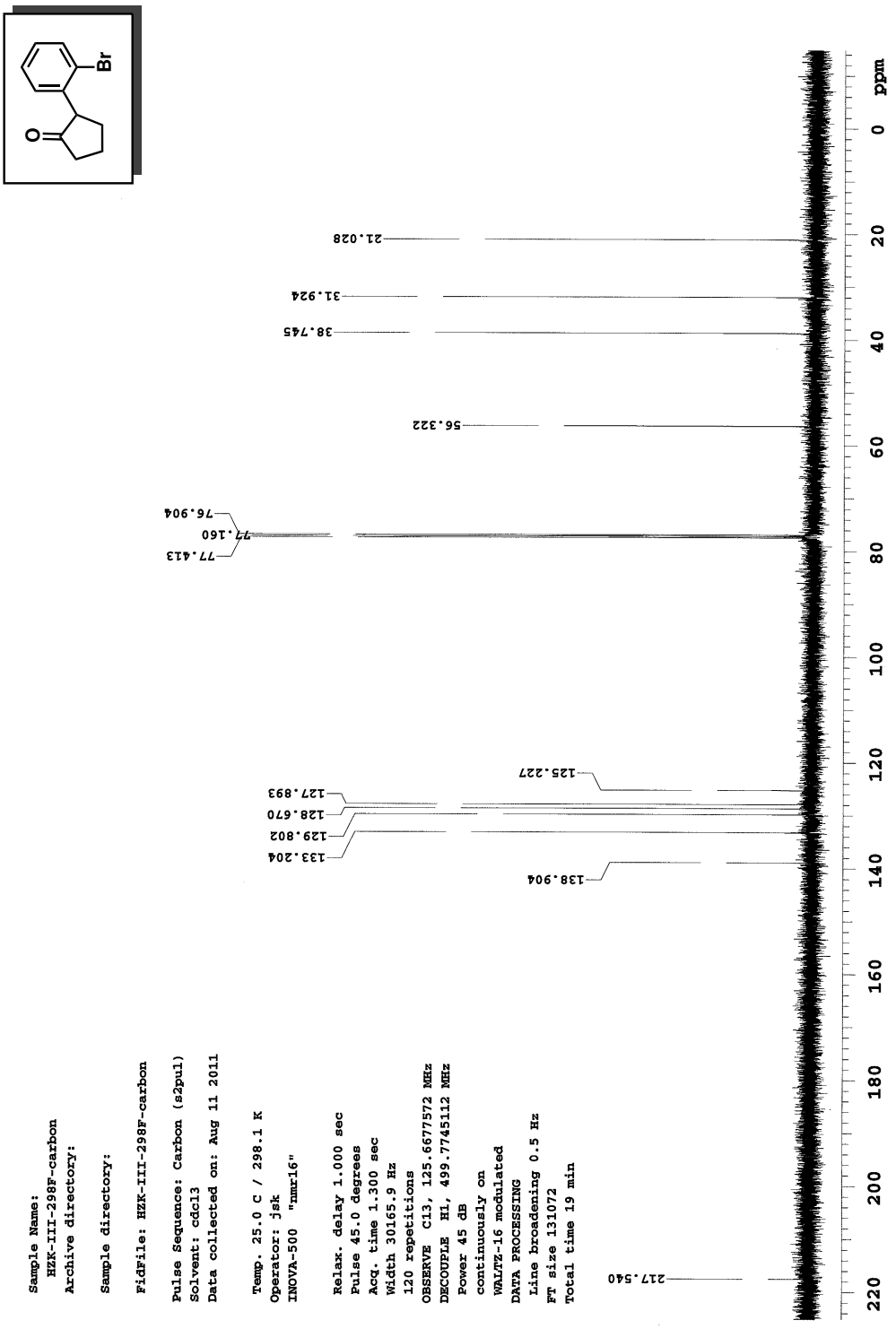


Figure 2.30: ^{1}H NMR of 2-(4-trifluoromethylphenyl)cyclopentanone (**2.33**)

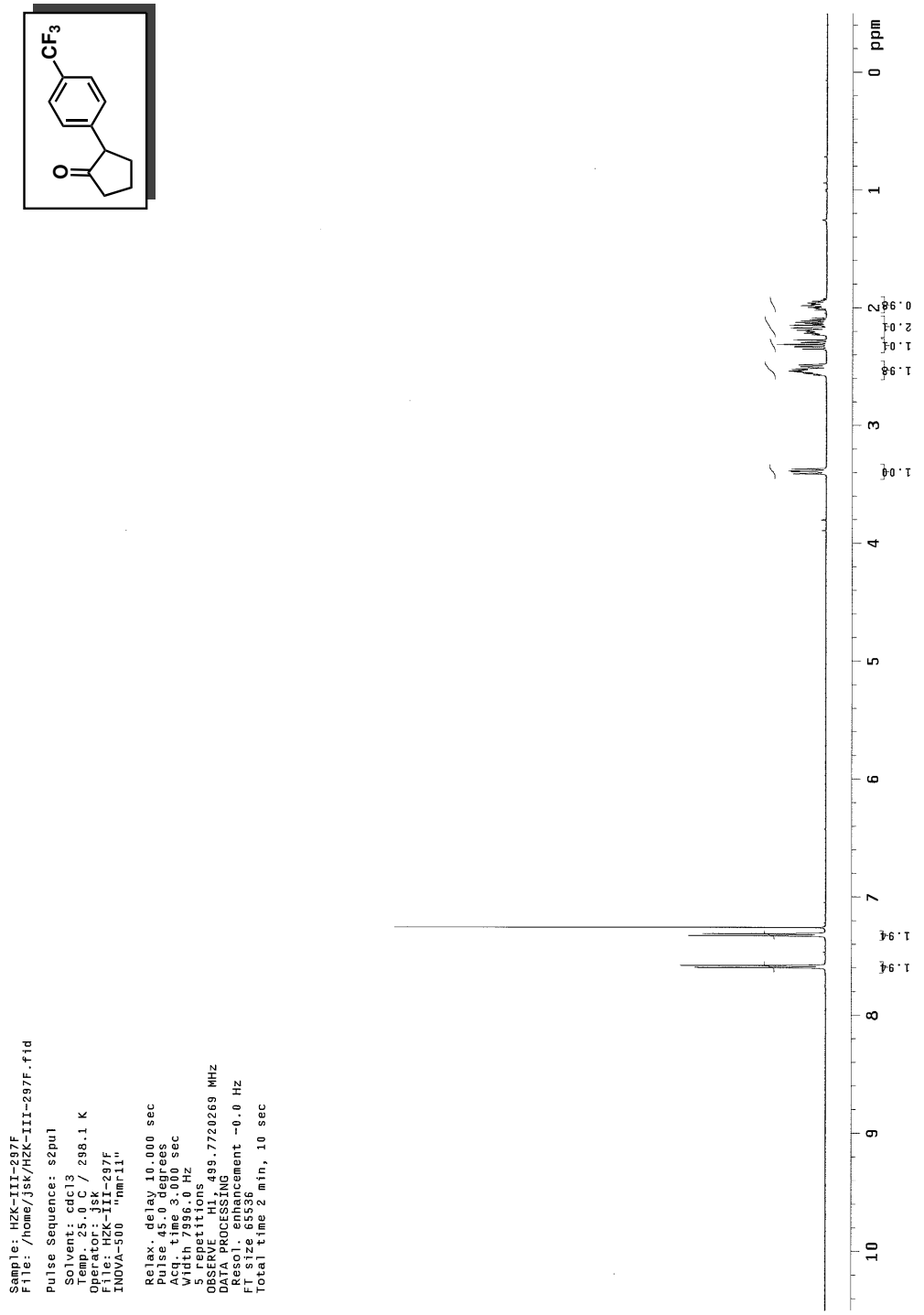


Figure 2.31: ^{13}C NMR of 2-(4-trifluoromethylphenyl)cyclopentanone (**2.33**)

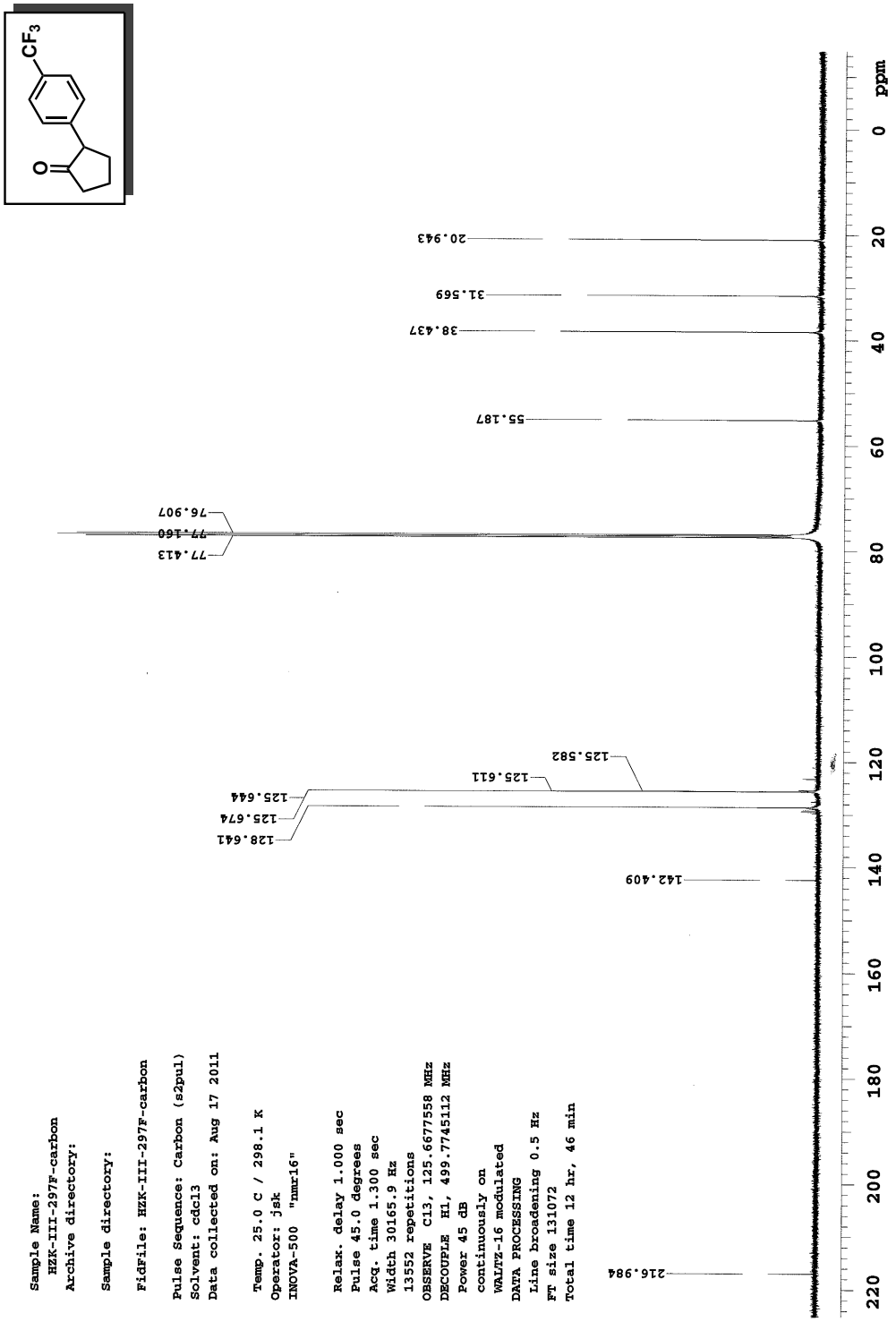


Figure 2.32: ^{1}H NMR of 2-(3-methoxyphenyl)cyclopentanone (**2.34**)

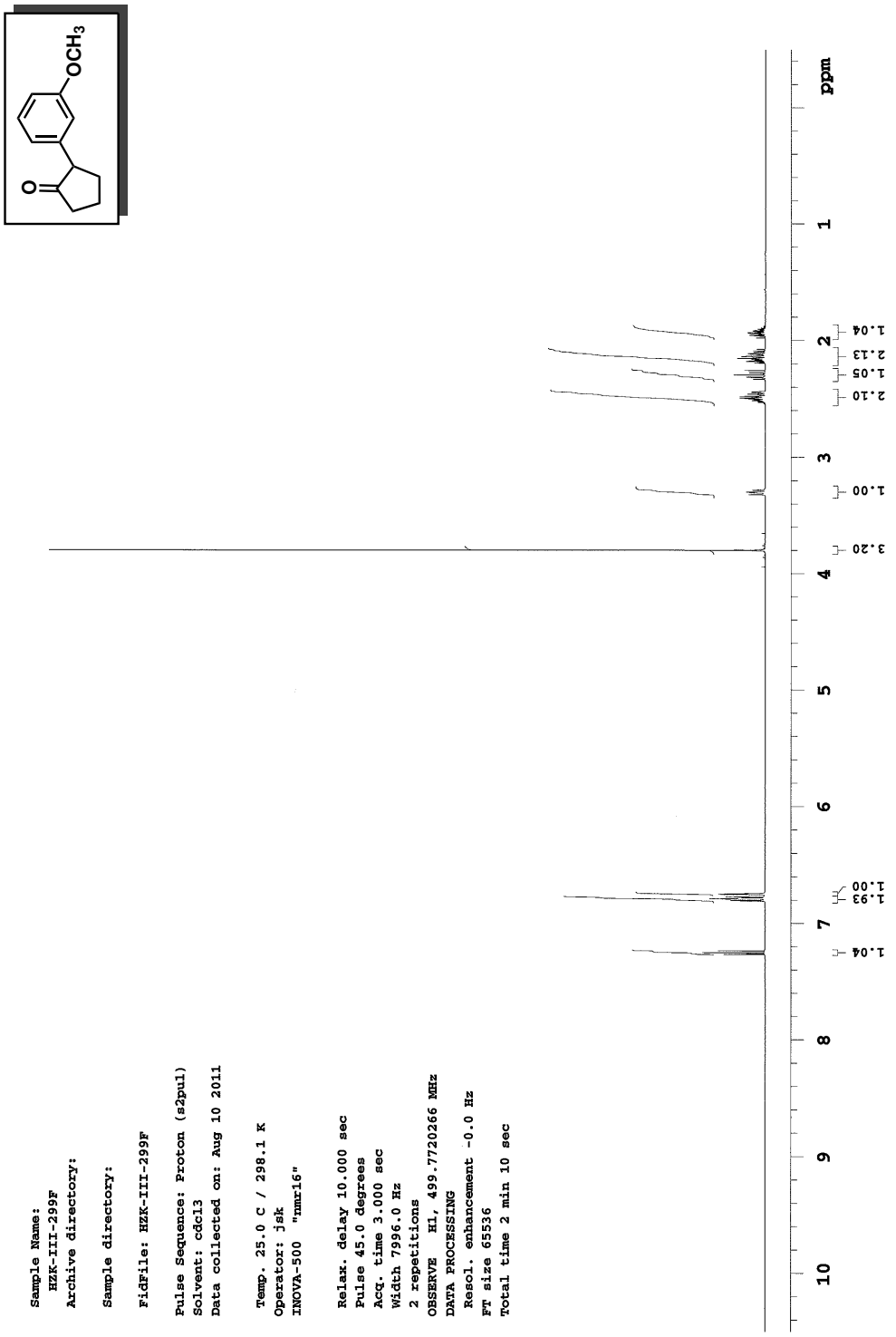


Figure 2.33: ^{13}C NMR of 2-(3-methoxyphenyl)cyclopentanone (**2.34**)

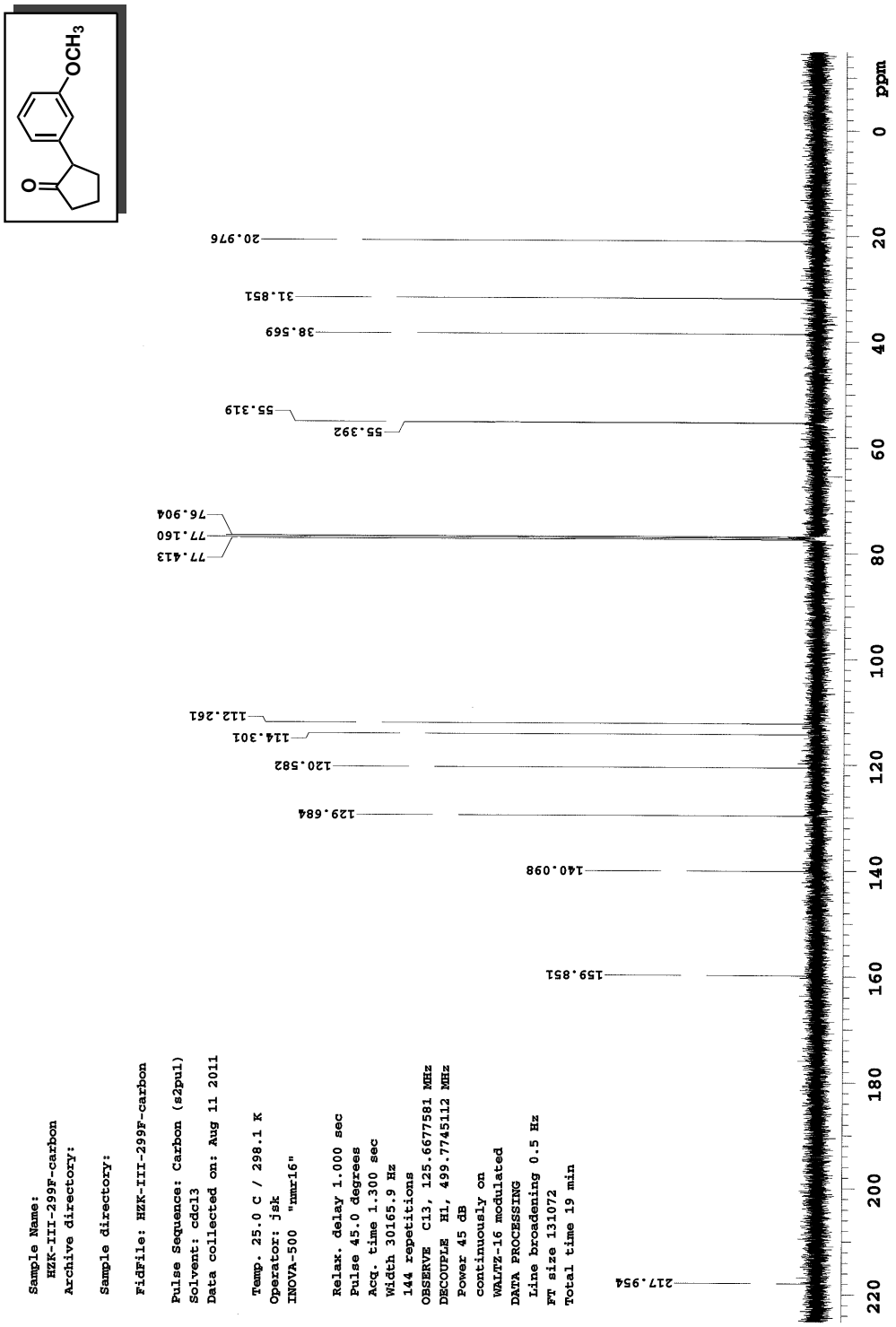


Figure 2.34: ^{1}H NMR of 2-(2-methylphenyl)cyclopentanone (**2.35**)

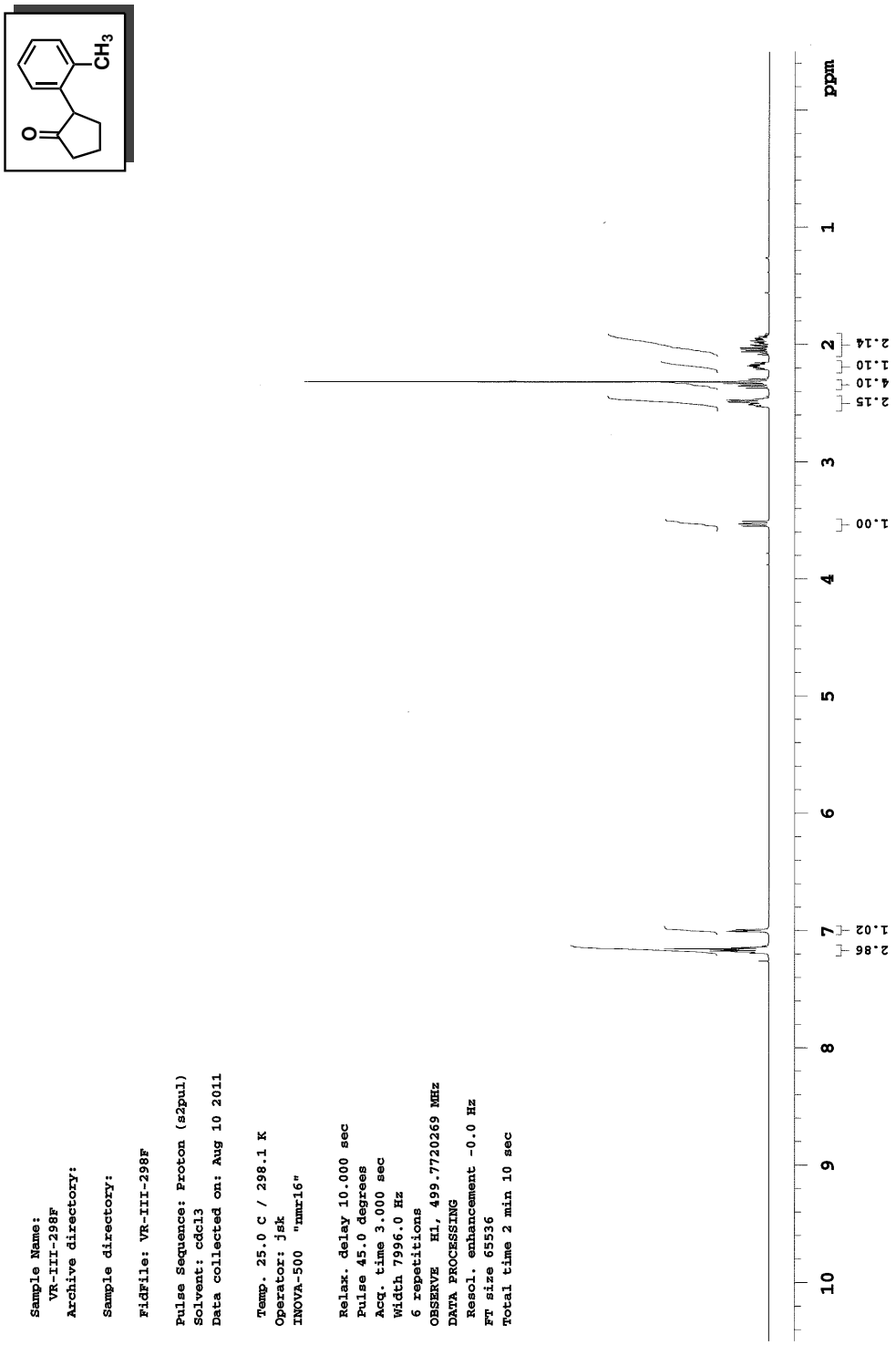


Figure 2.35: ^{13}C NMR of 2-(2-methylphenyl)cyclopentanone (**2.35**)

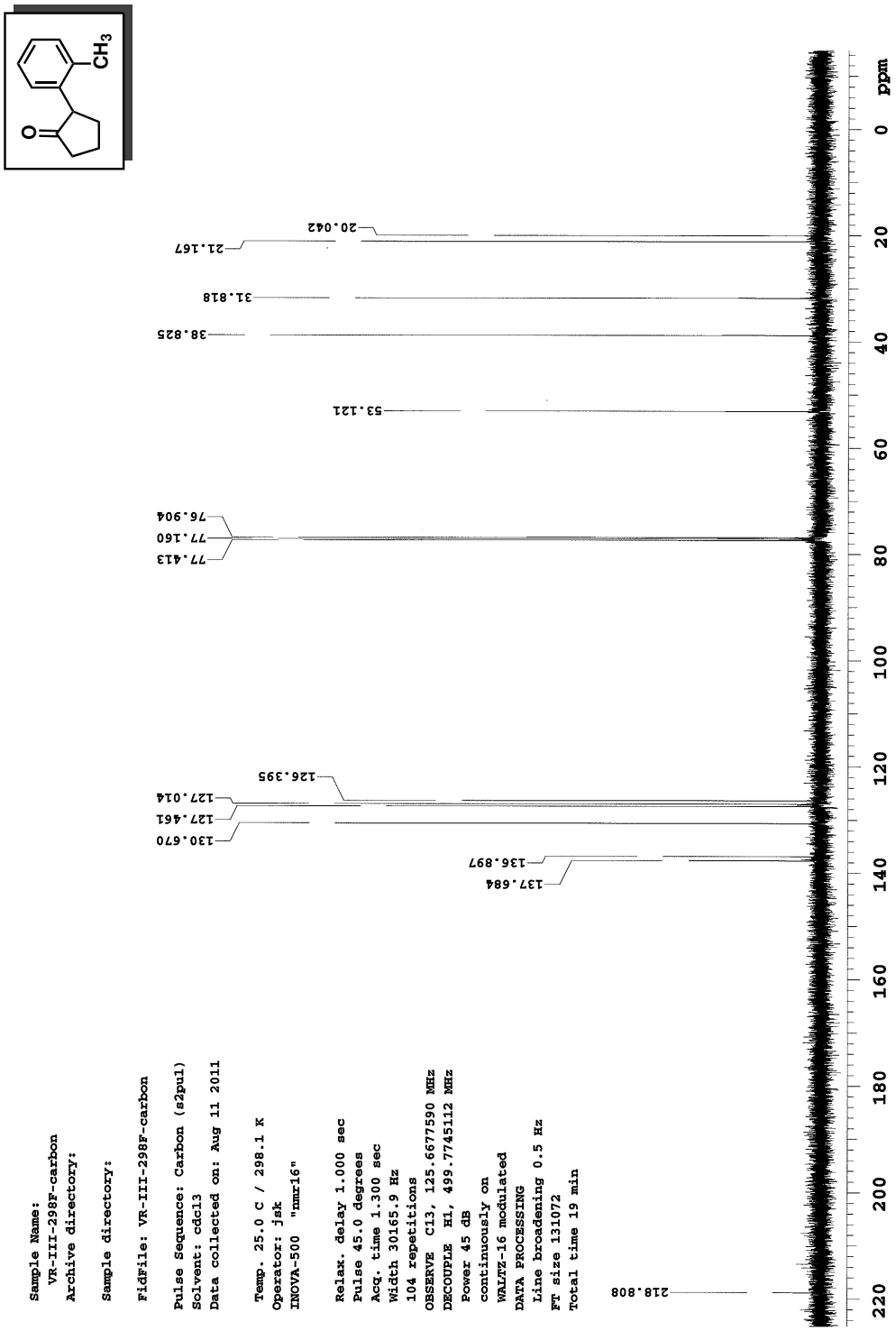


Figure 2.36: ^{1}H NMR of 2-(napthalen-1-yl)cyclopentanone (**2.36**)

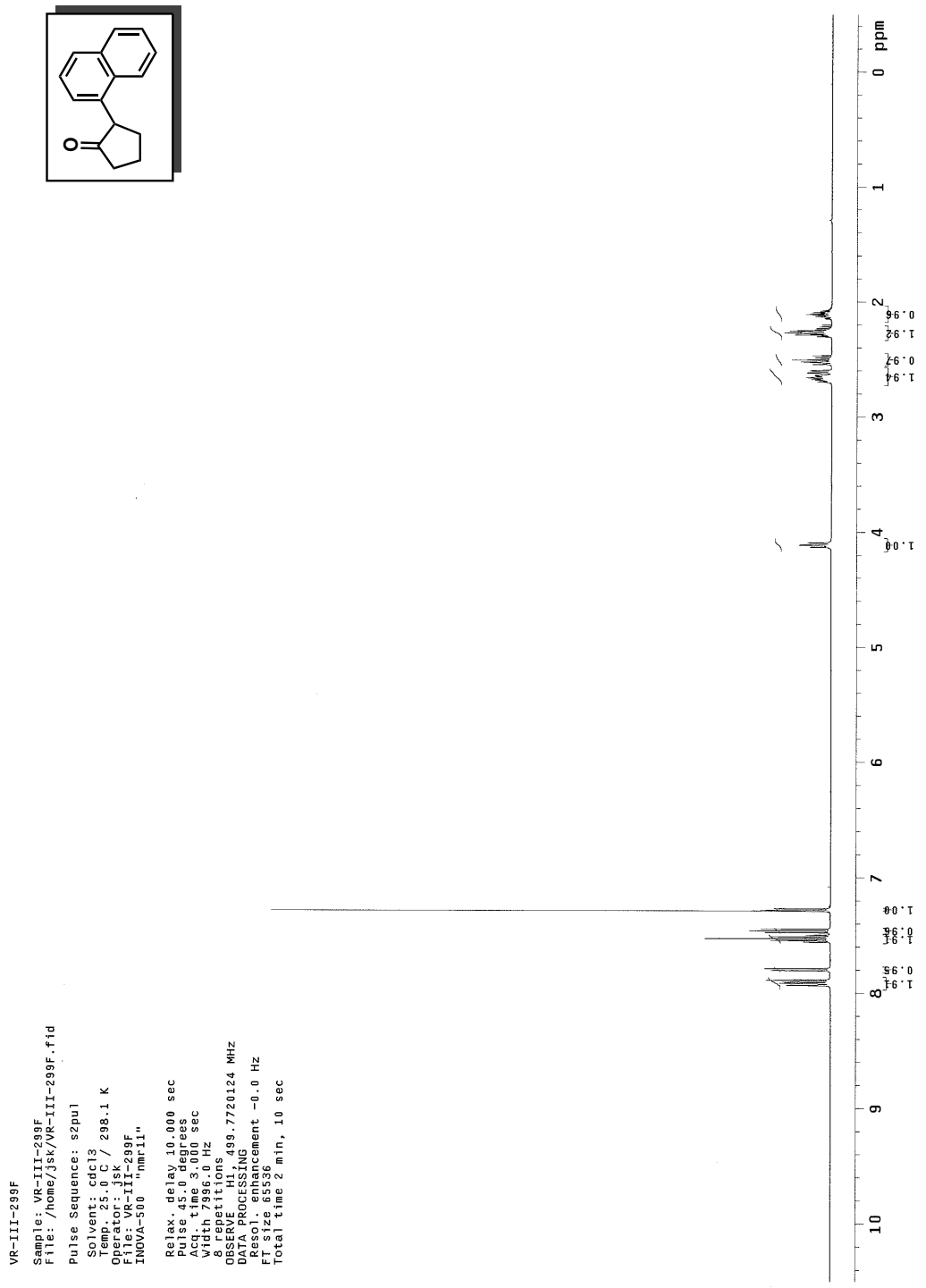


Figure 2.37: ^{13}C NMR of 2-(napthalen-1-yl)cyclopentanone (**2.36**)

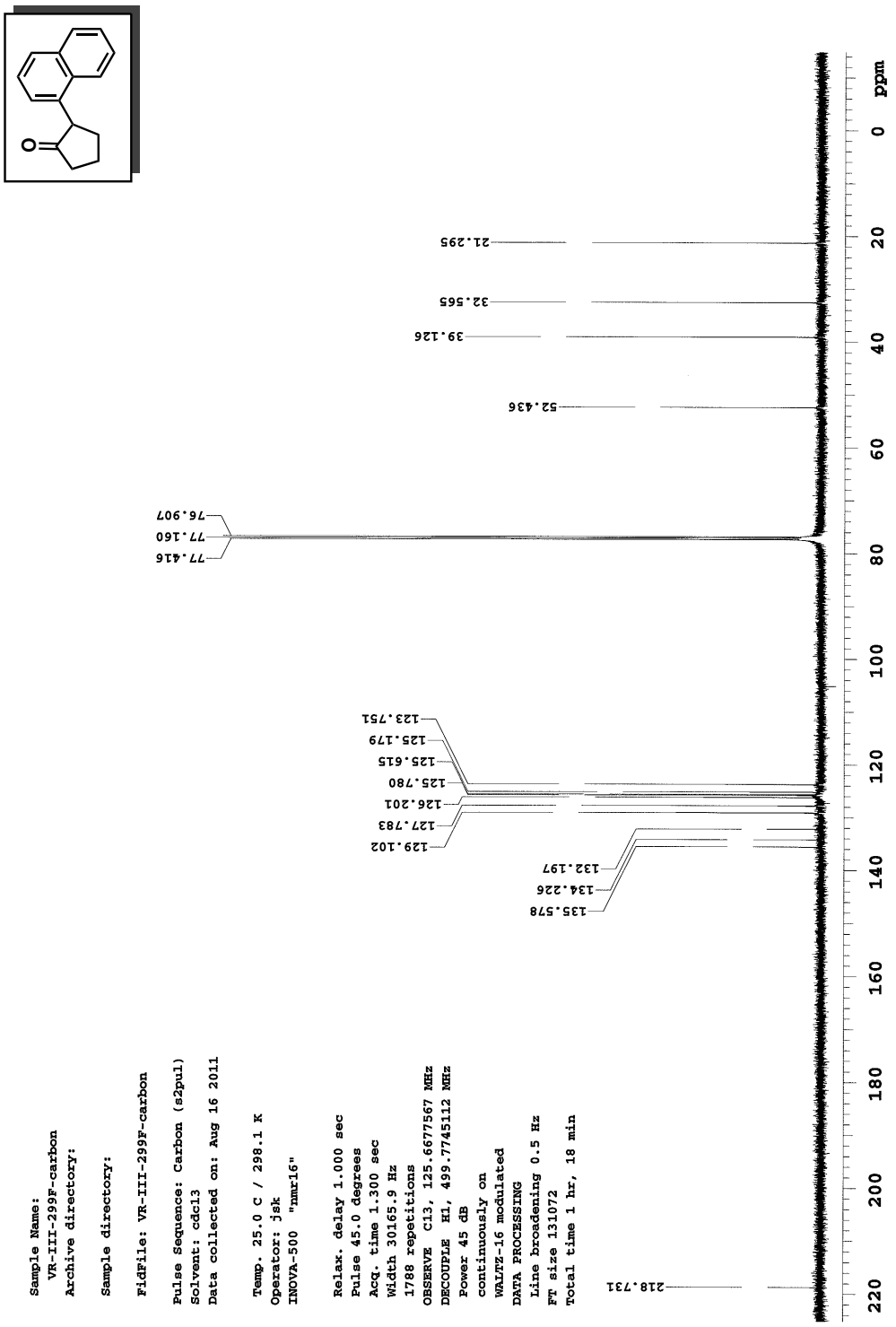


Figure 2.38: ^{1}H NMR of 2-methyl-2-phenylcycloheptanone (**2.37**)

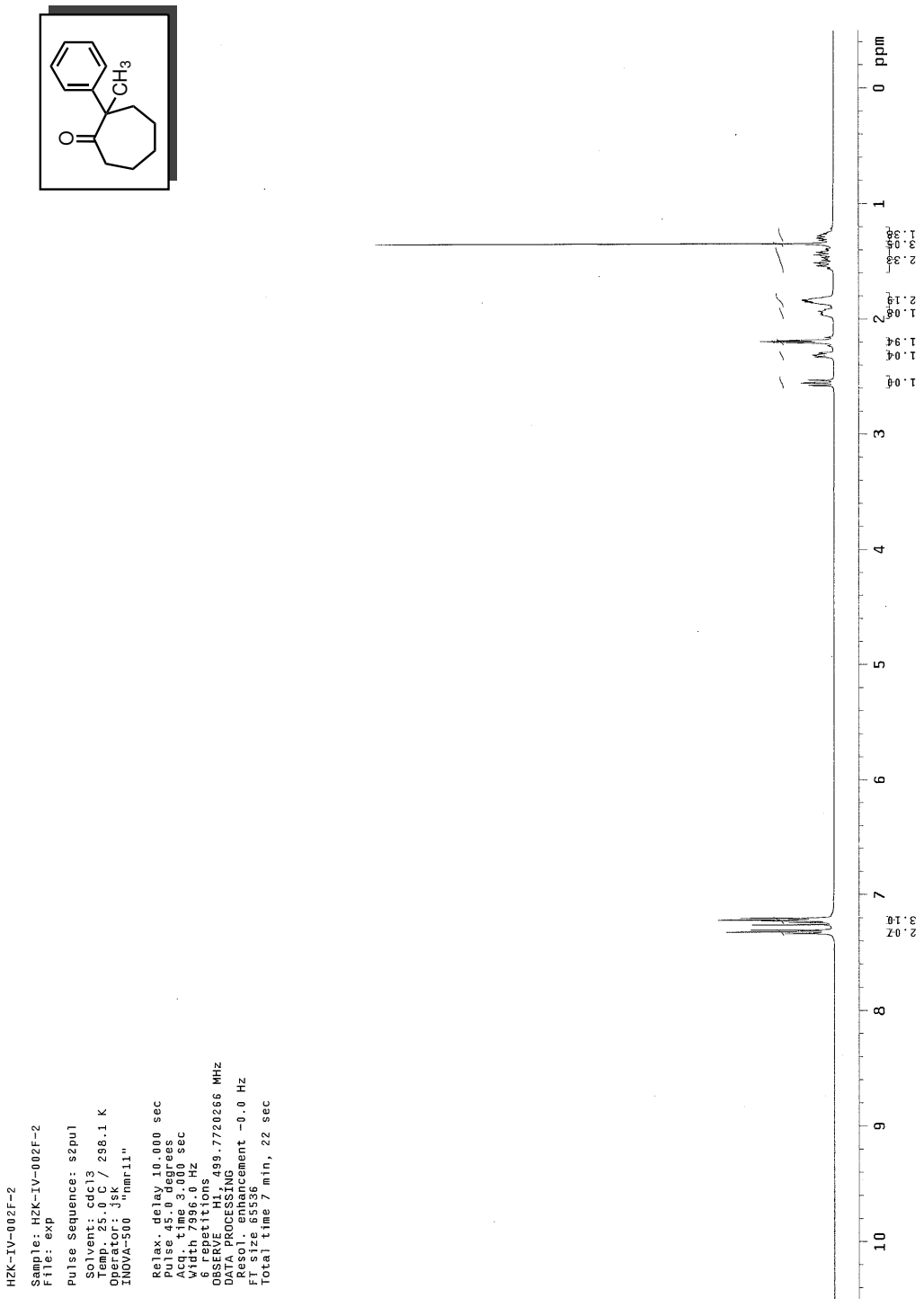


Figure 2.39: ^{13}C NMR of 2-methyl-2-phenylcycloheptanone (**2.37**)

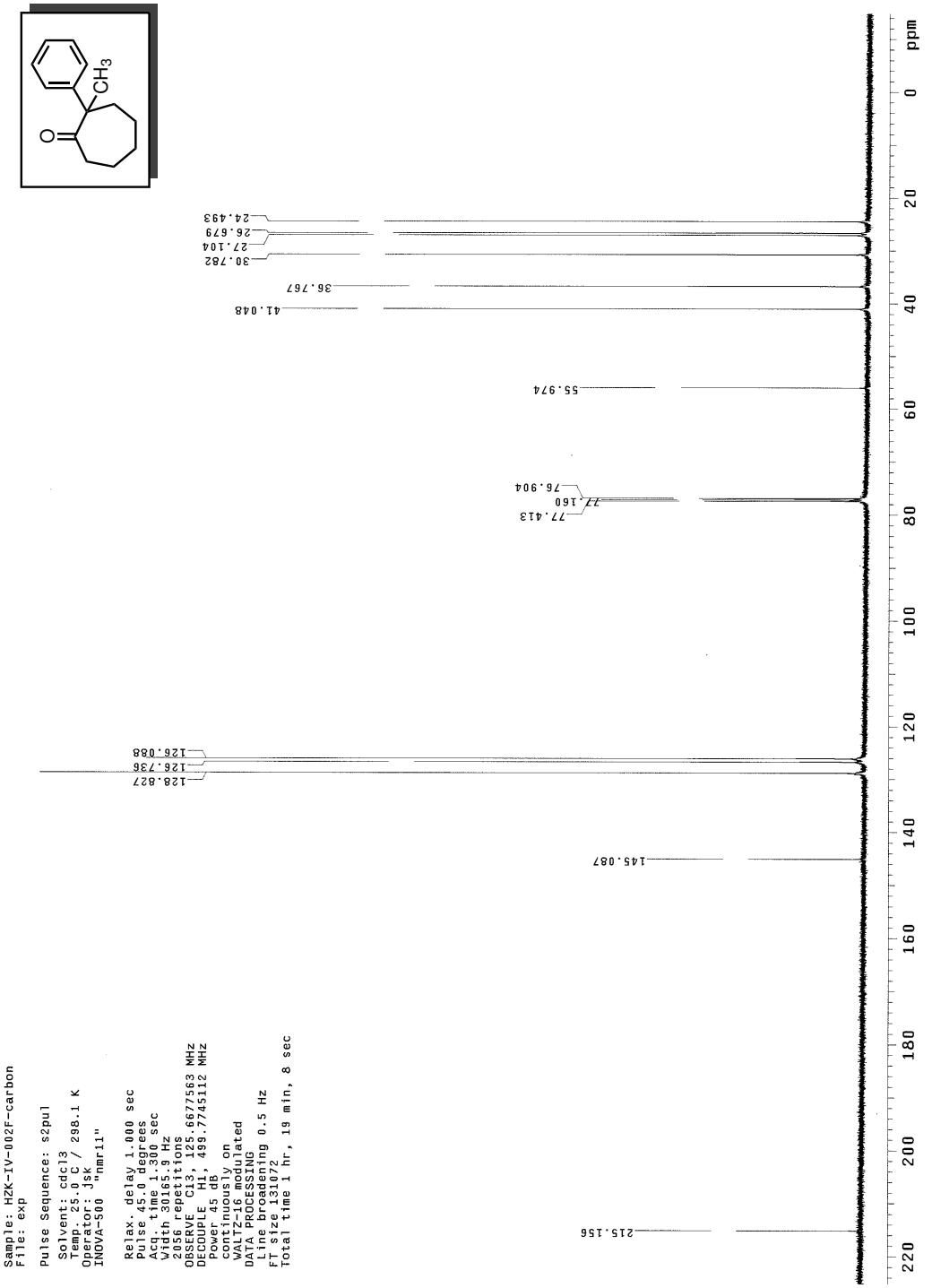


Figure 2.40: ^{1}H NMR of 2-phenylcyclooctanone (**2.38**)

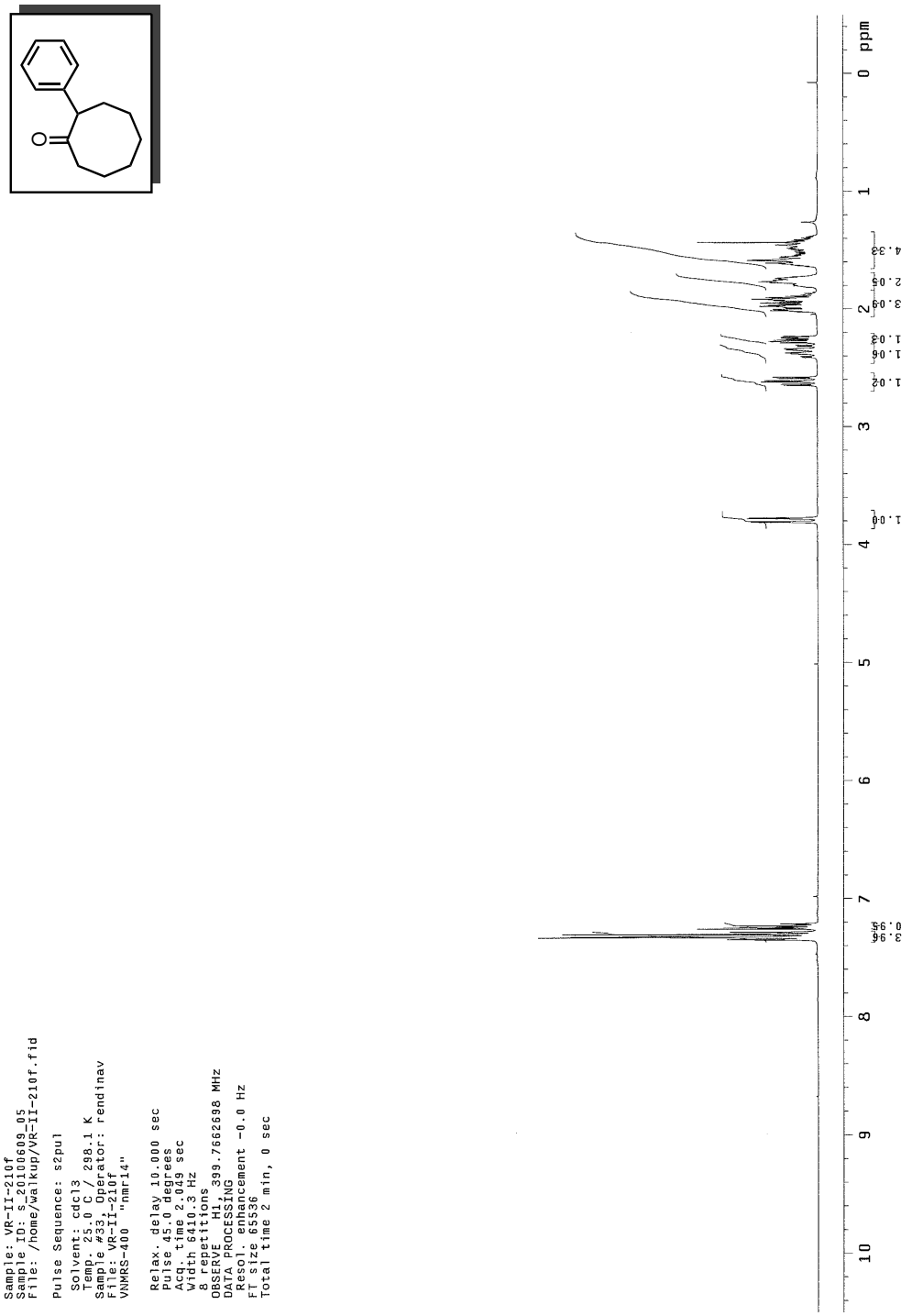


Figure 2.41: ^{13}C NMR of 2-phenylcyclooctanone (**2.38**)

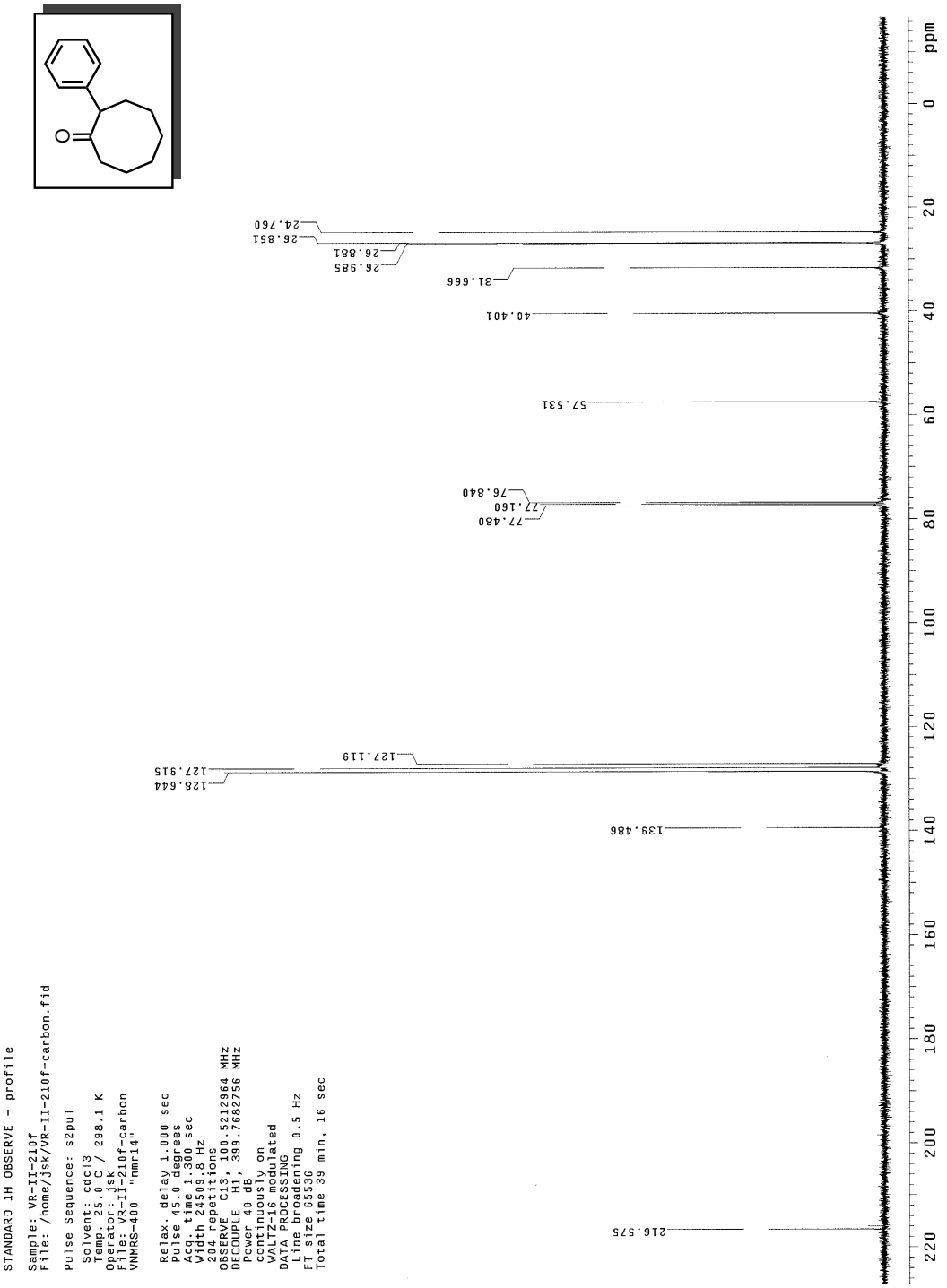


Figure 2.42: ^{1}H NMR of 2-methyl-2-phenylcyclotridecanone (**2.39**)

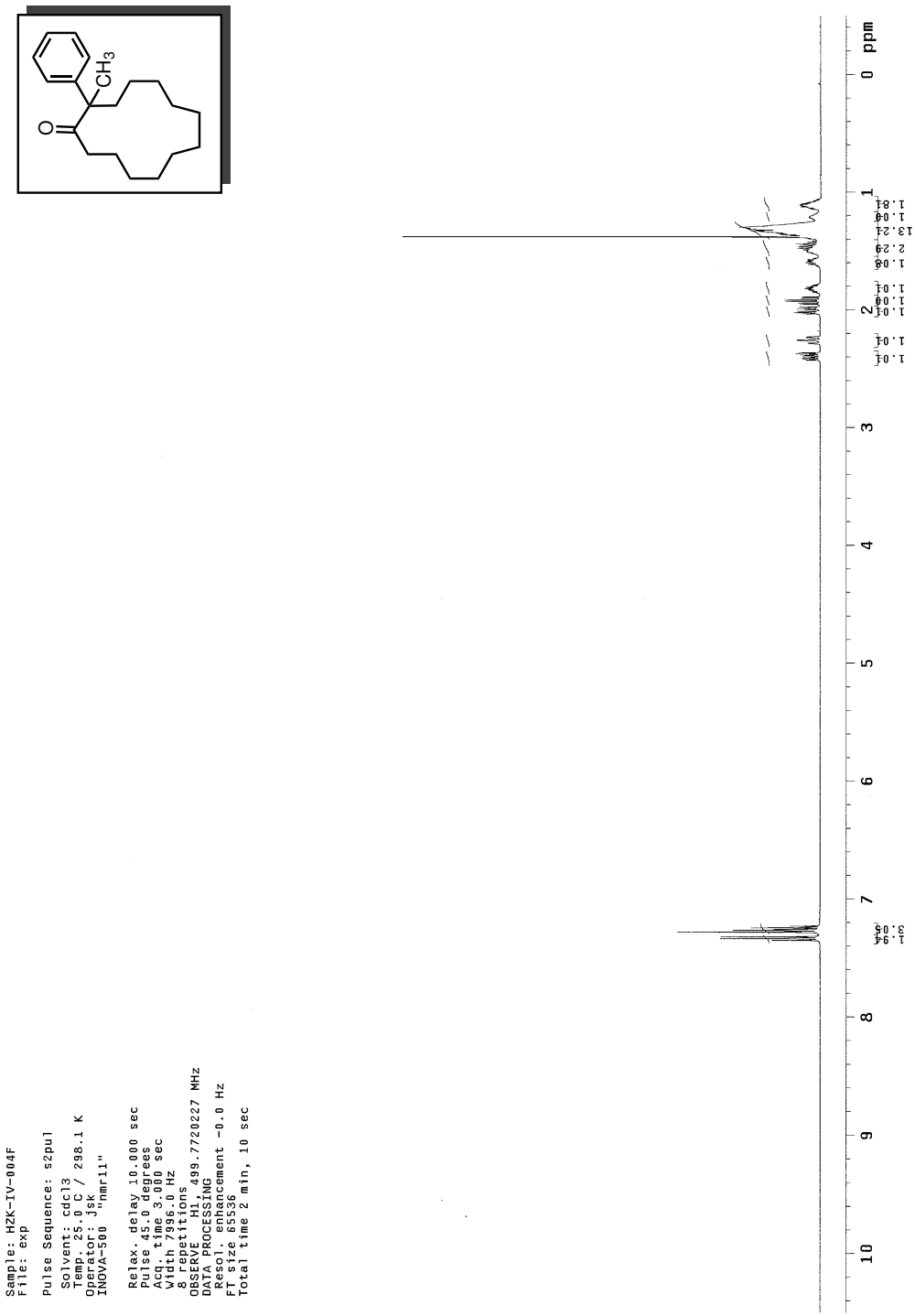


Figure 2.43: ^{13}C NMR of 2-methyl-2-phenylcyclotridecanone (**2.39**)

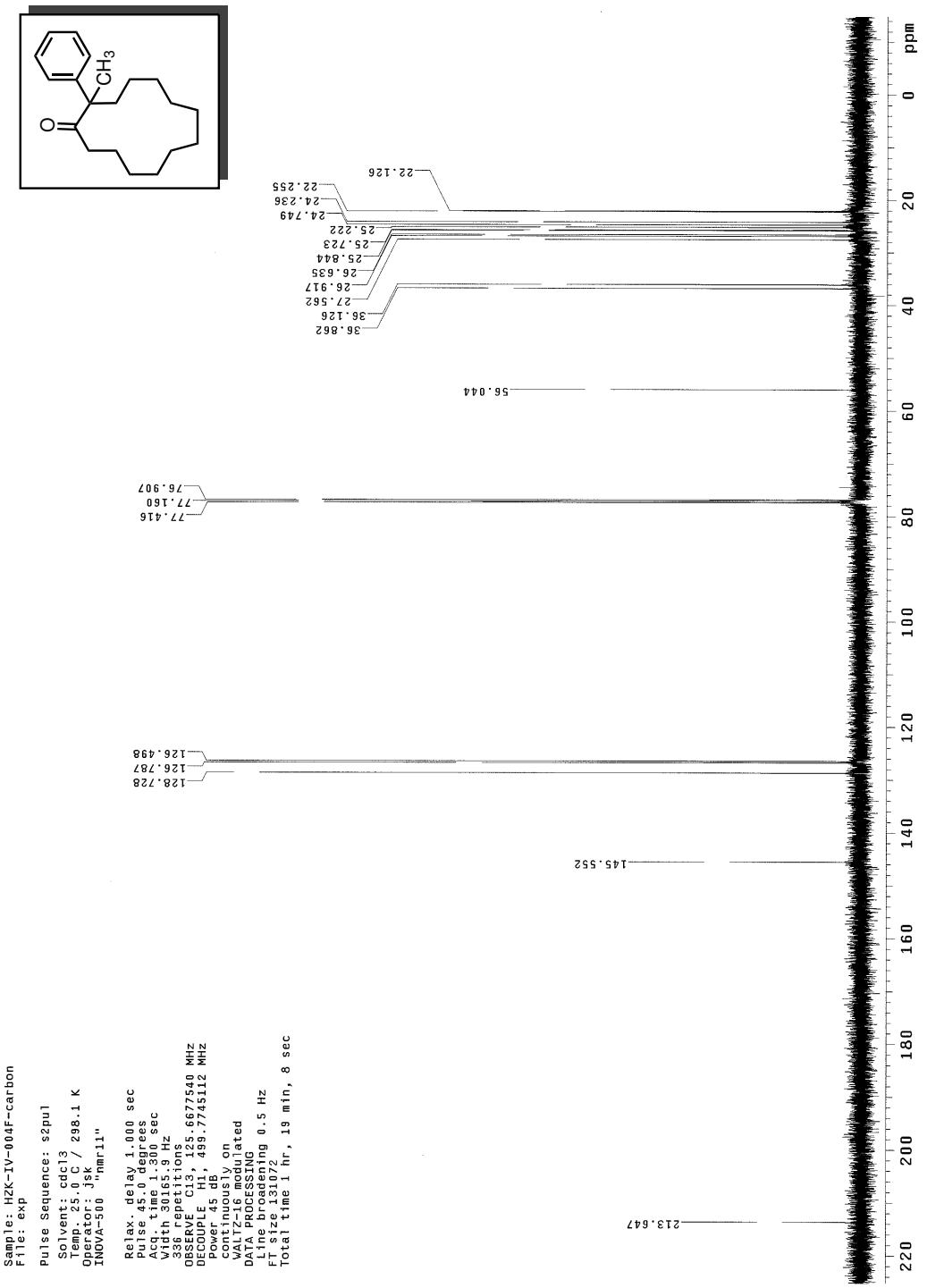


Figure 2.44: ^{1}H NMR of (±)-*trans*-5-*tert*-butyl-2-*p*-tolylcycloheptanone (**2.93**)

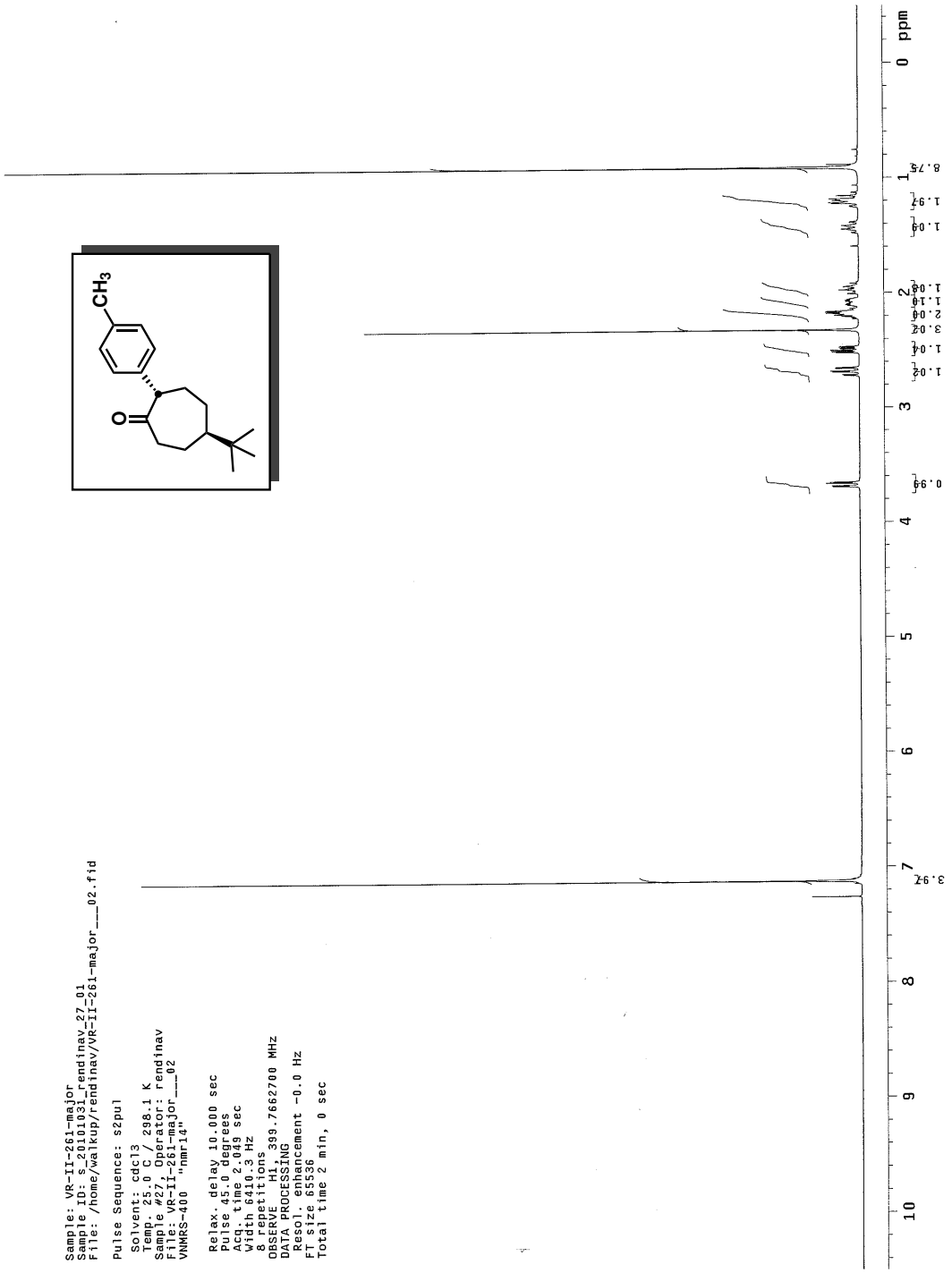


Figure 2.45: ^{13}C NMR of (±)-*trans*-5-*tert*-butyl-2-*p*-tolylcycloheptanone (**2.93**)

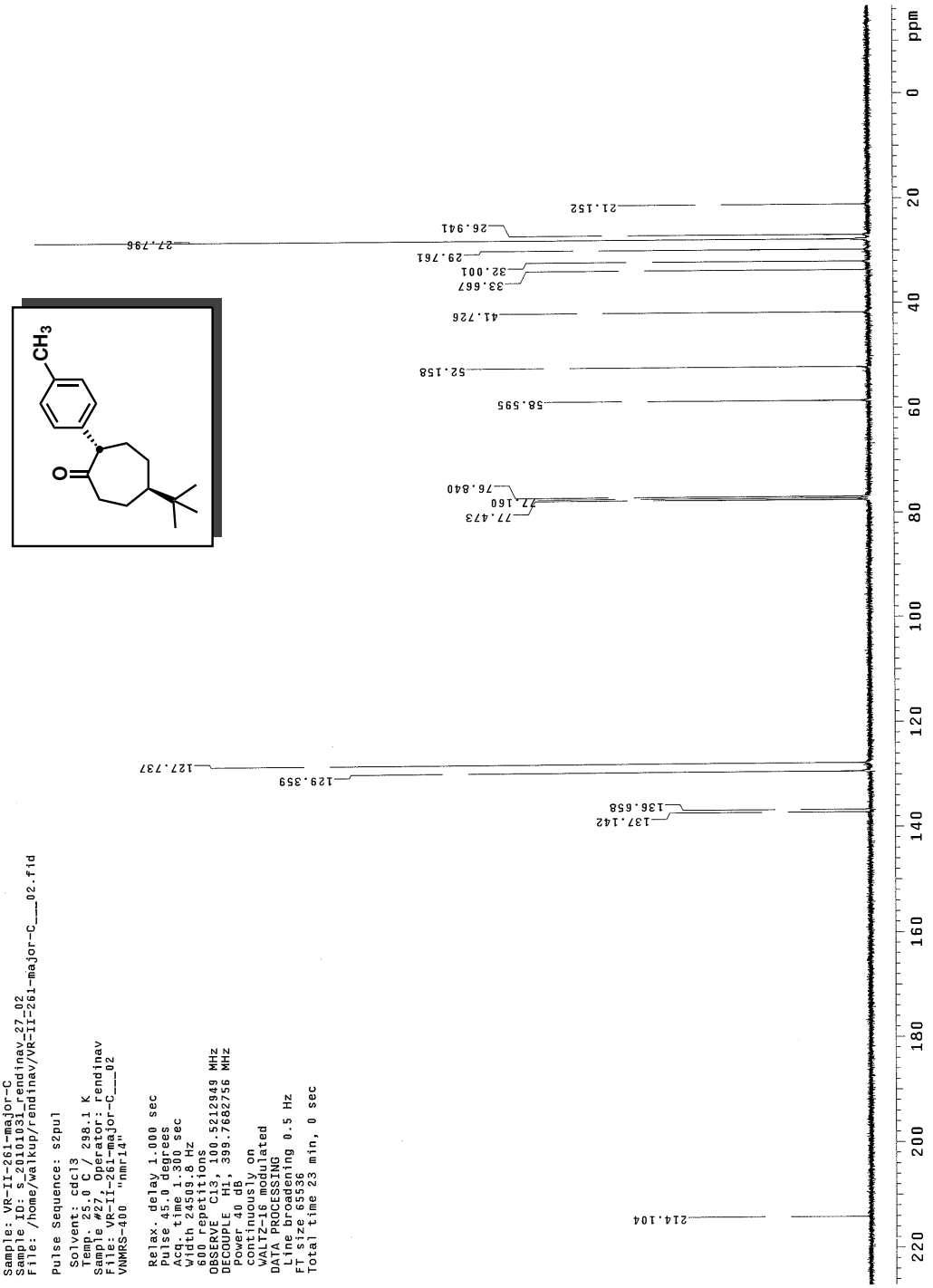


Figure 2.46: ^{1}H NMR of (*S*)-2-(4-methylphenyl)cycloheptanone (**2.73**)

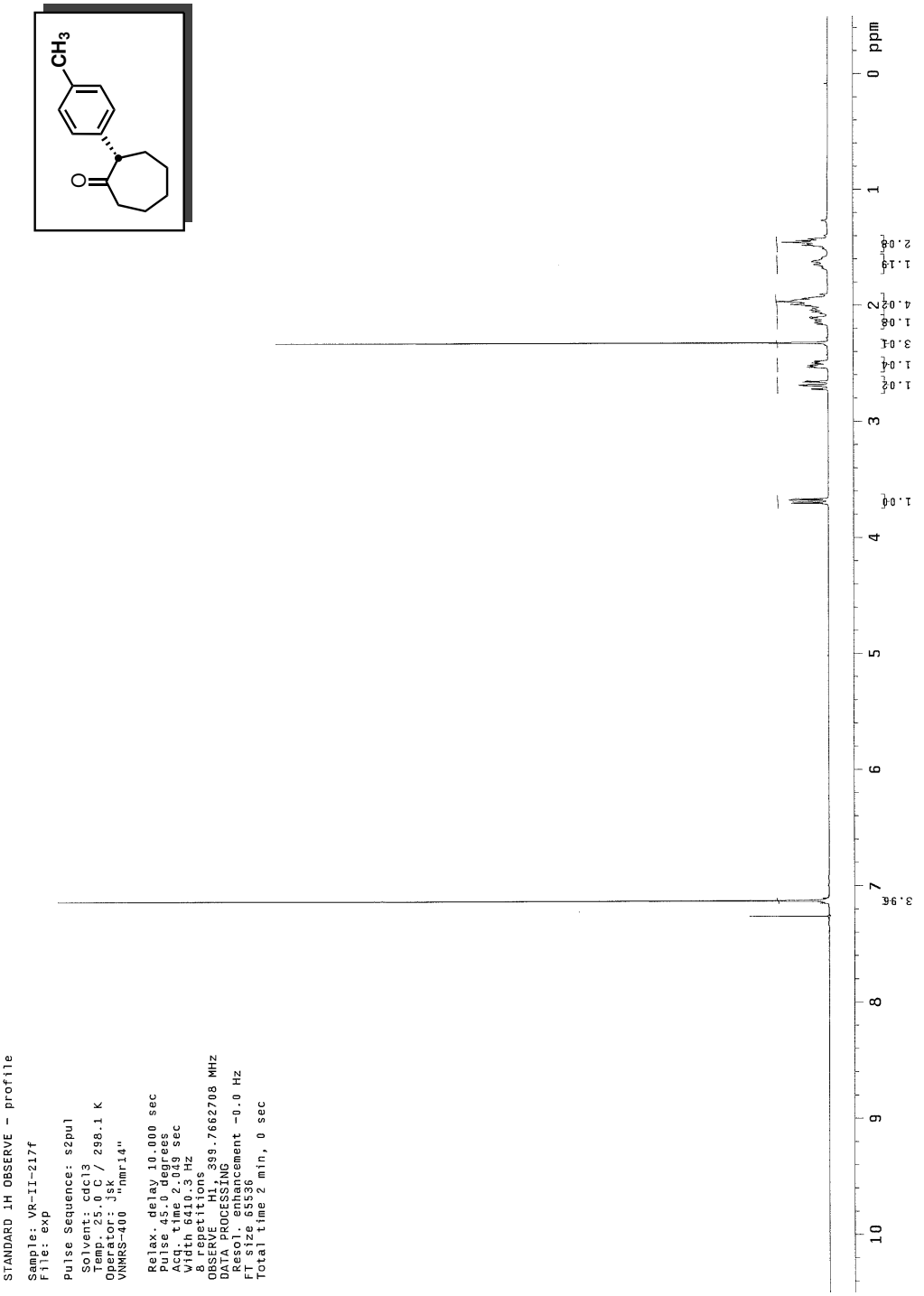


Figure 2.47: ^{13}C NMR of (*S*)-2-(4-methylphenyl)cycloheptanone (**2.73**)

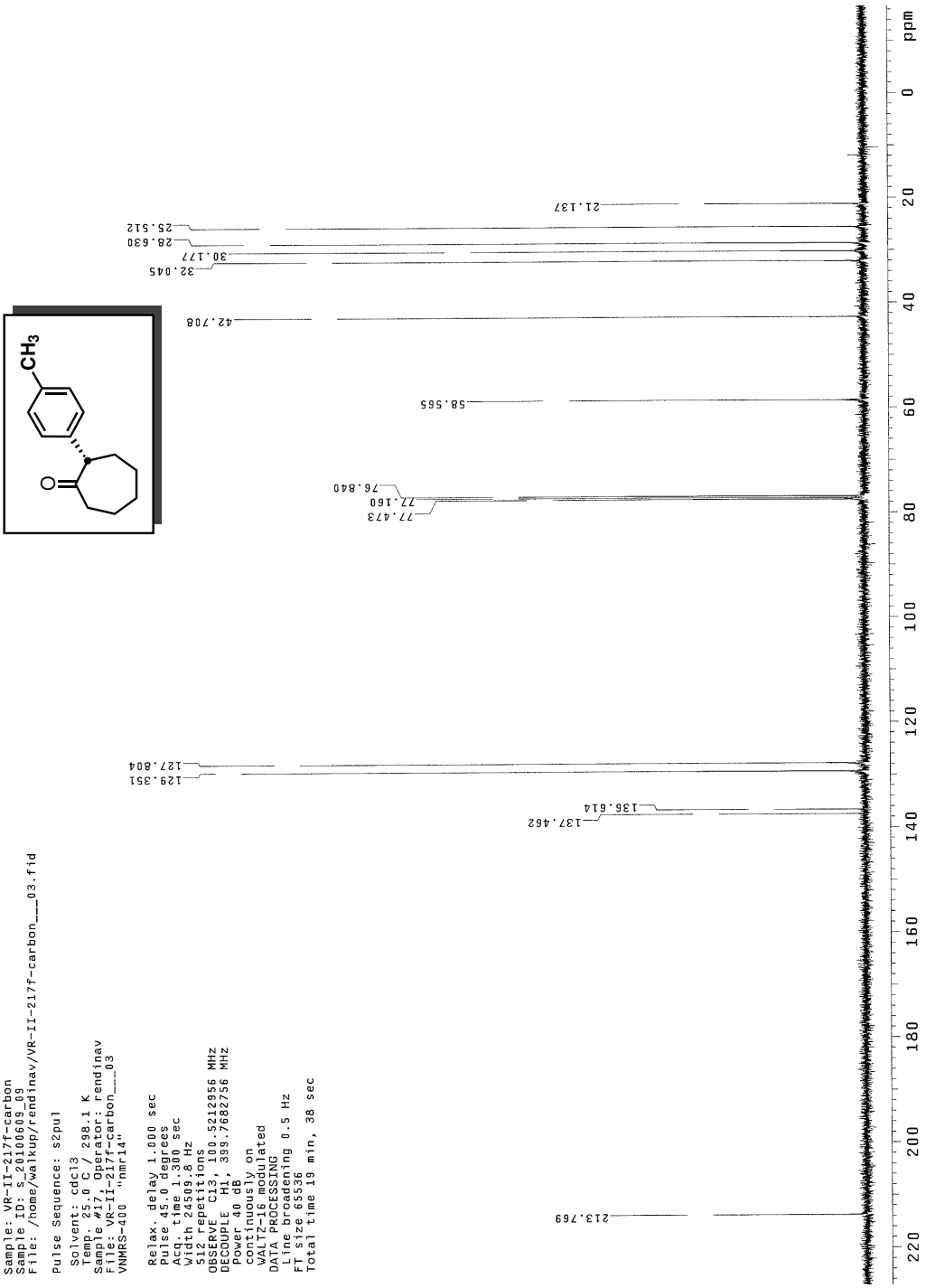


Figure 2.48: ^{1}H NMR of (*S*)-2-(3-bromophenyl)cycloheptanone (**2.75**)

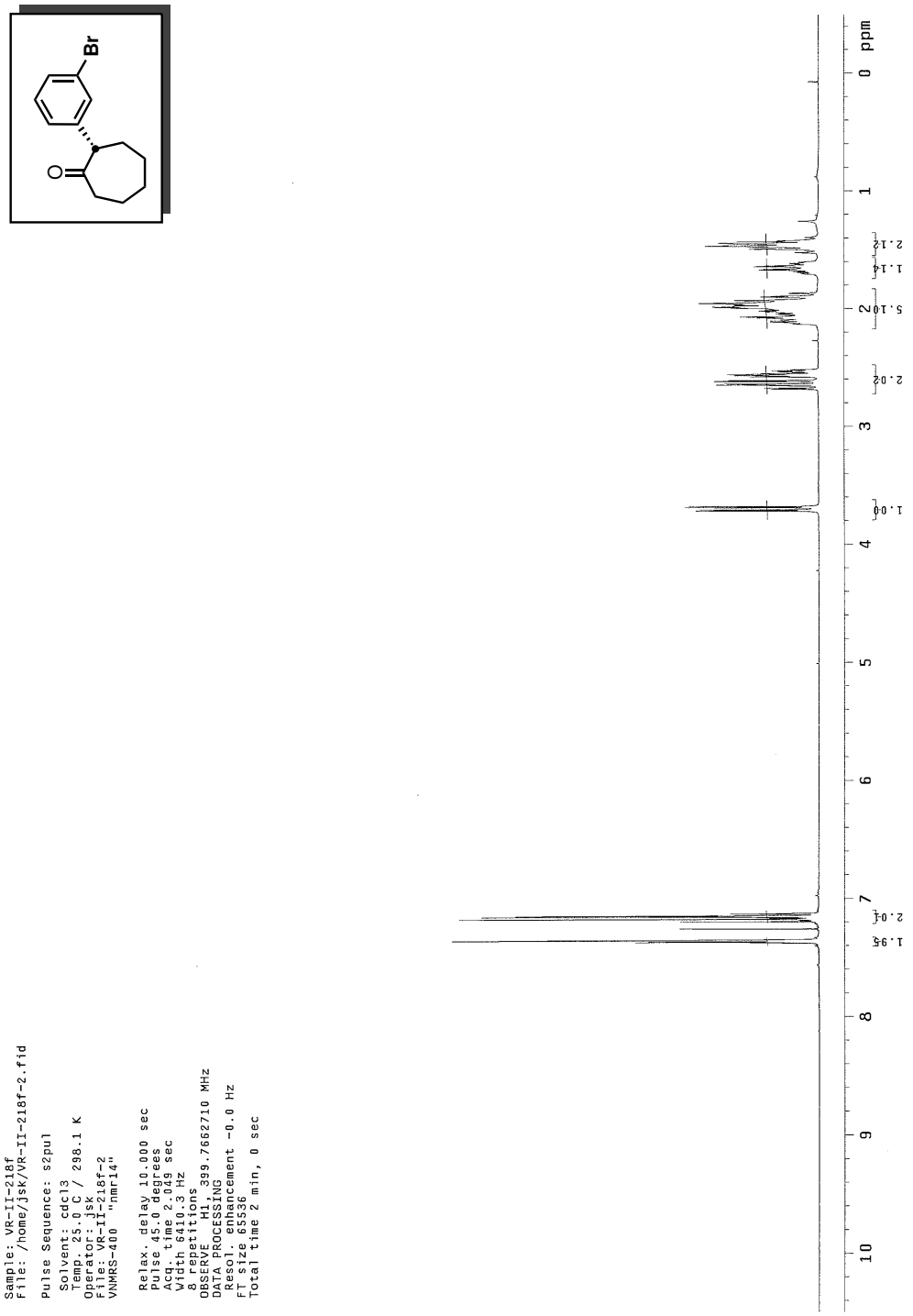


Figure 2.49: ^{13}C NMR of (*S*)-2-(3-bromophenyl)cycloheptanone (**2.75**)

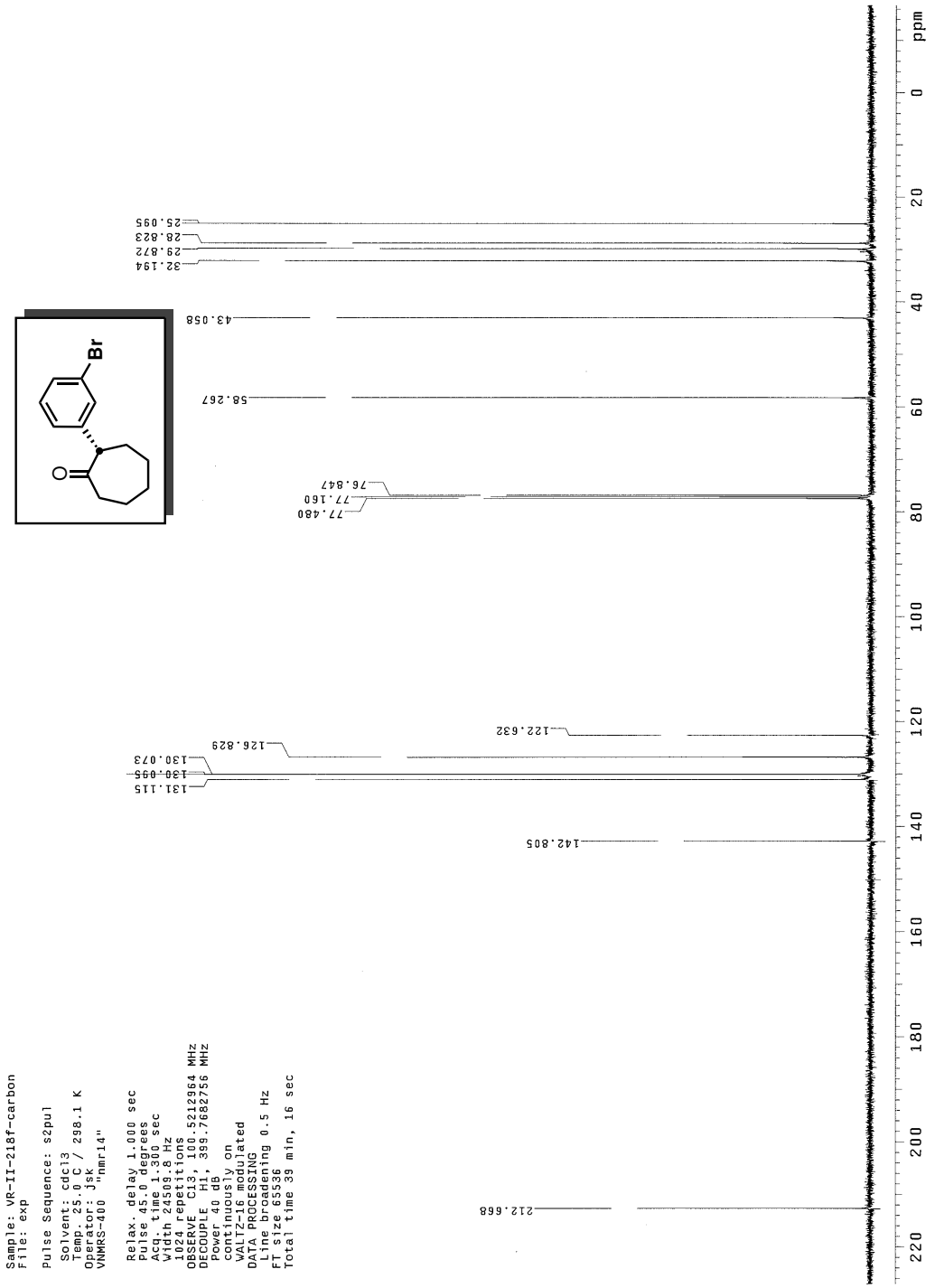


Figure 2.50: ^{1}H NMR of (*S*)-2-(2-bromophenyl)cyclooctanone (**2.83**)

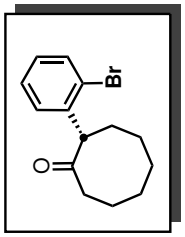


Figure 2.51: ^{13}C NMR of (*S*)-2-(2-bromophenyl)cyclooctanone (**2.83**)

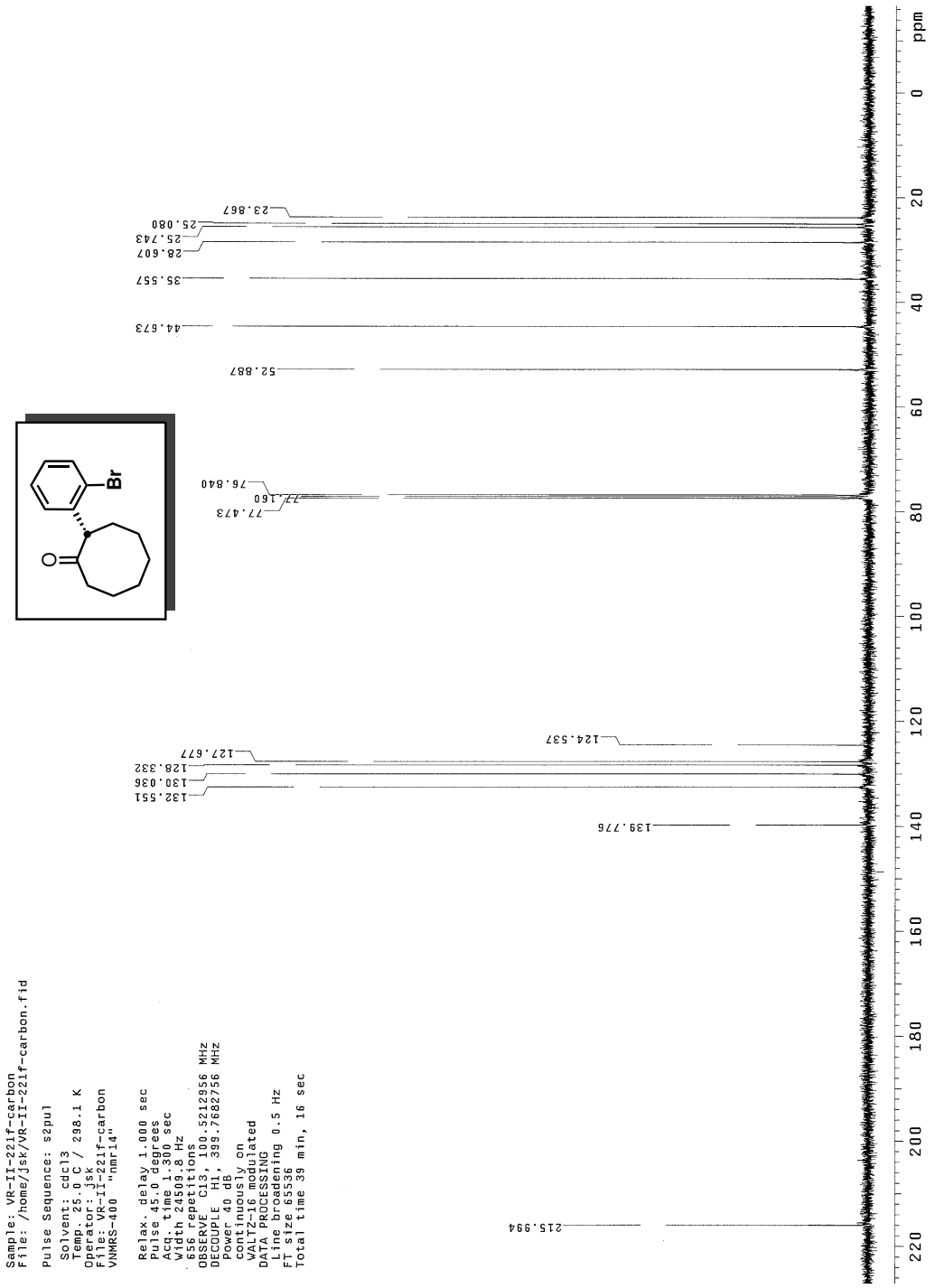


Figure 2.52: ^{1}H NMR of (*S*)-2-(4-trifluromethylphenyl)cyclooctanone (**2.81**)

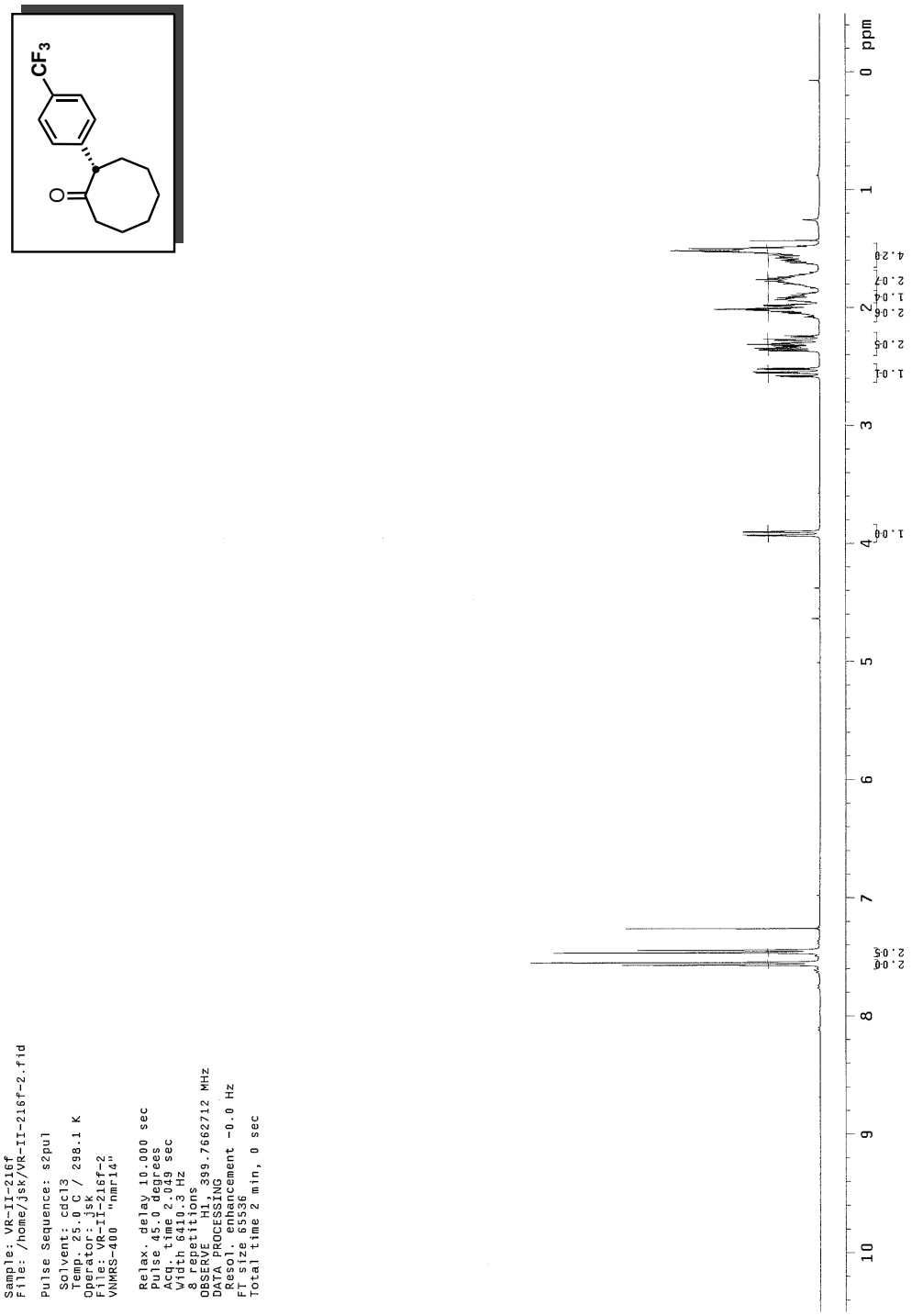


Figure 2.53: ^{13}C NMR of (*S*)-2-(4-trifluromethylphenyl)cyclooctanone (**2.81**)

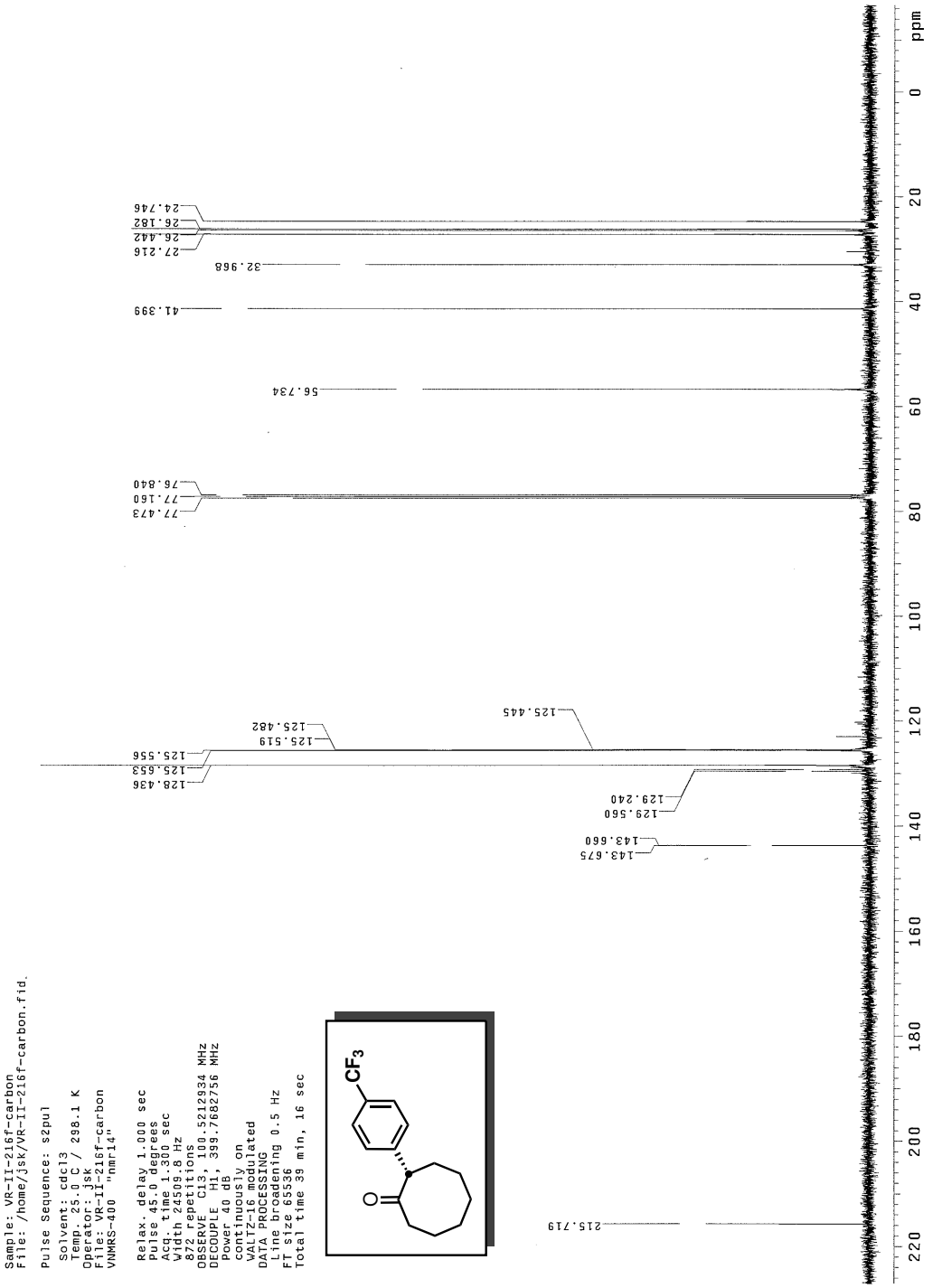


Figure 2.54: ^{1}H NMR of (*S*)-2-(2-methylphenyl)cyclooctanone (**2.85**)

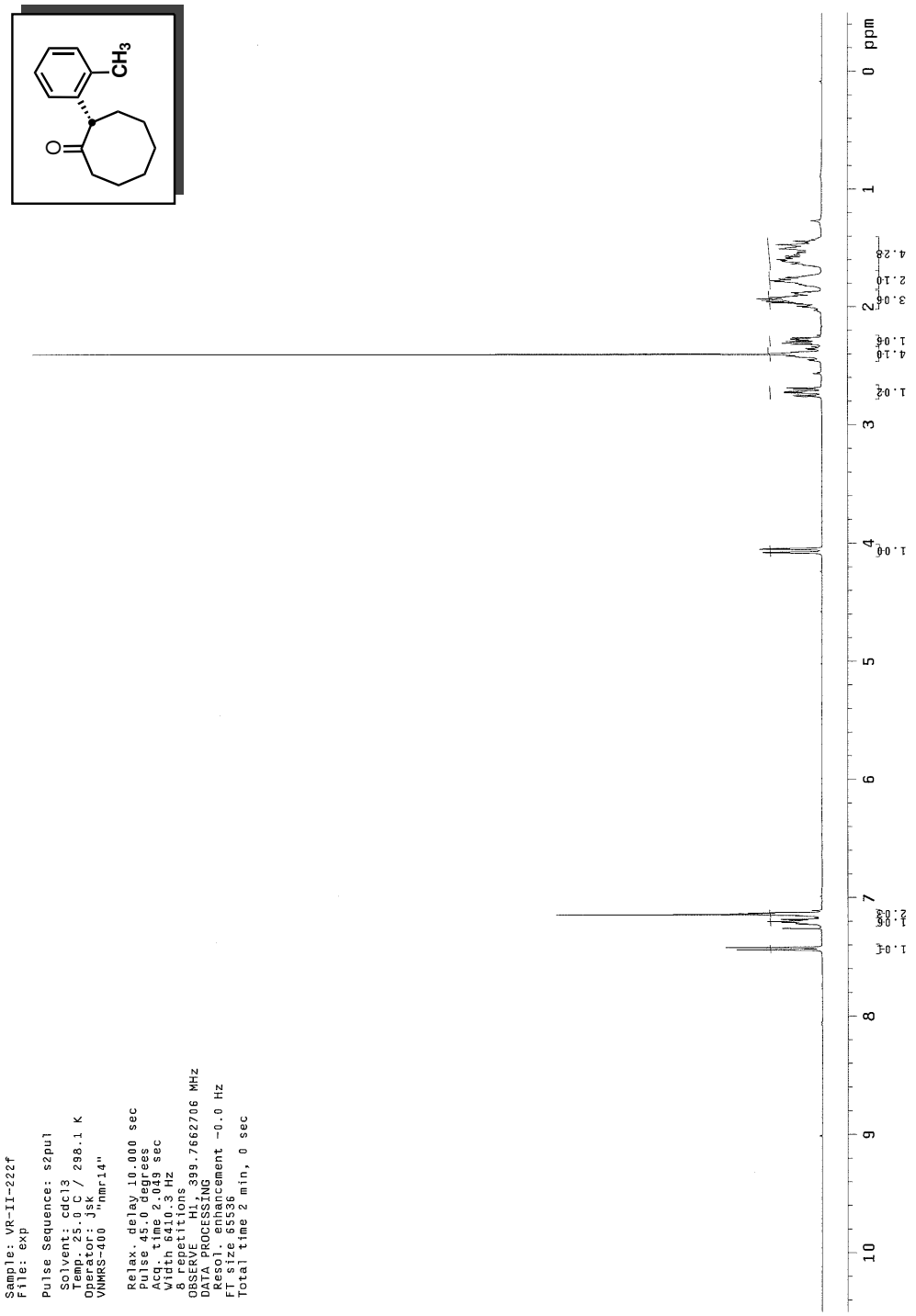


Figure 2.55: ^{13}C NMR of (*S*)-2-(2-methylphenyl)cyclooctanone (**2.85**)

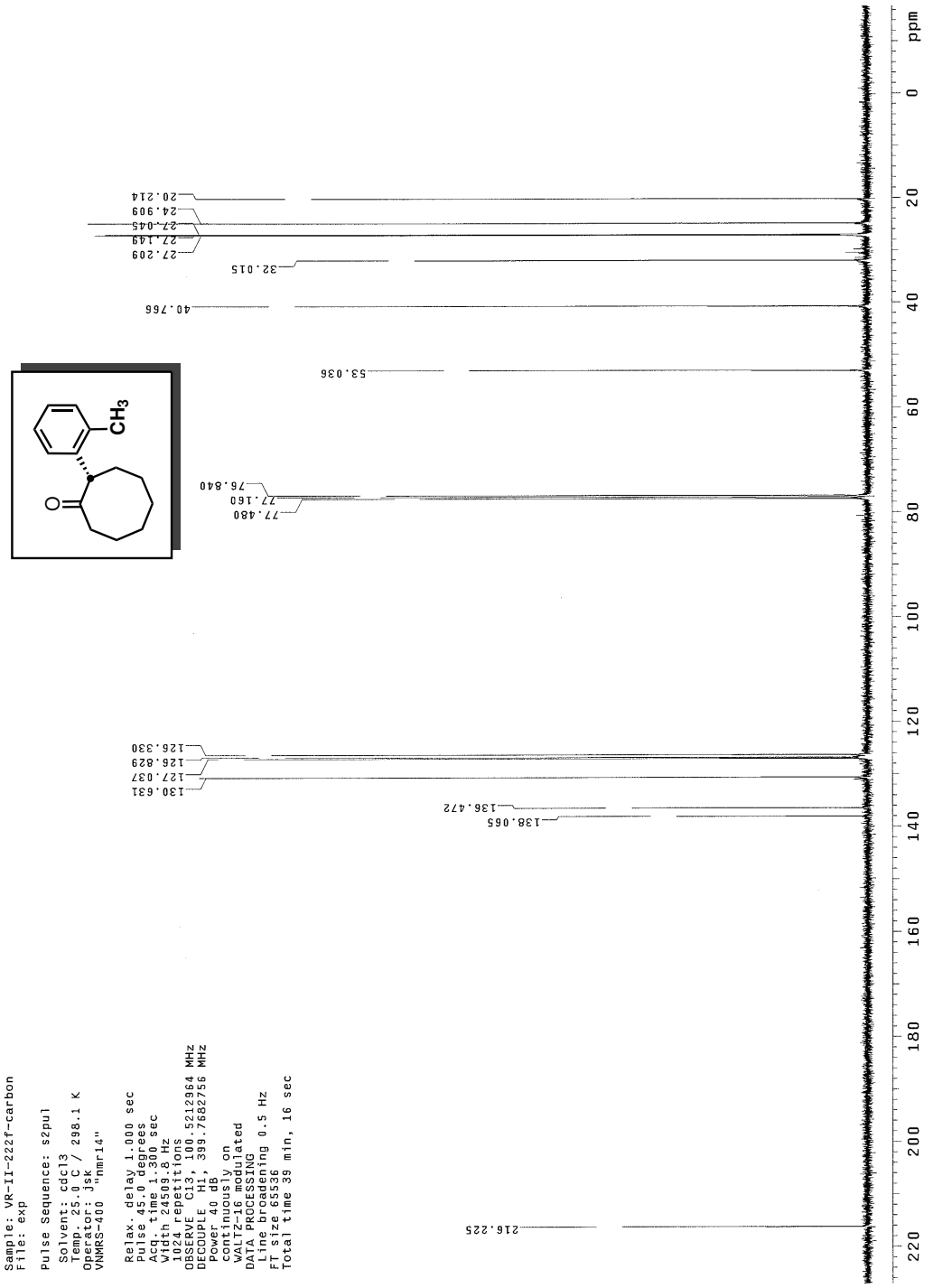


Figure 2.56: ^{1}H NMR of (*S*)-2-(2-methylphenyl)cyclooctanone (**2.85**)

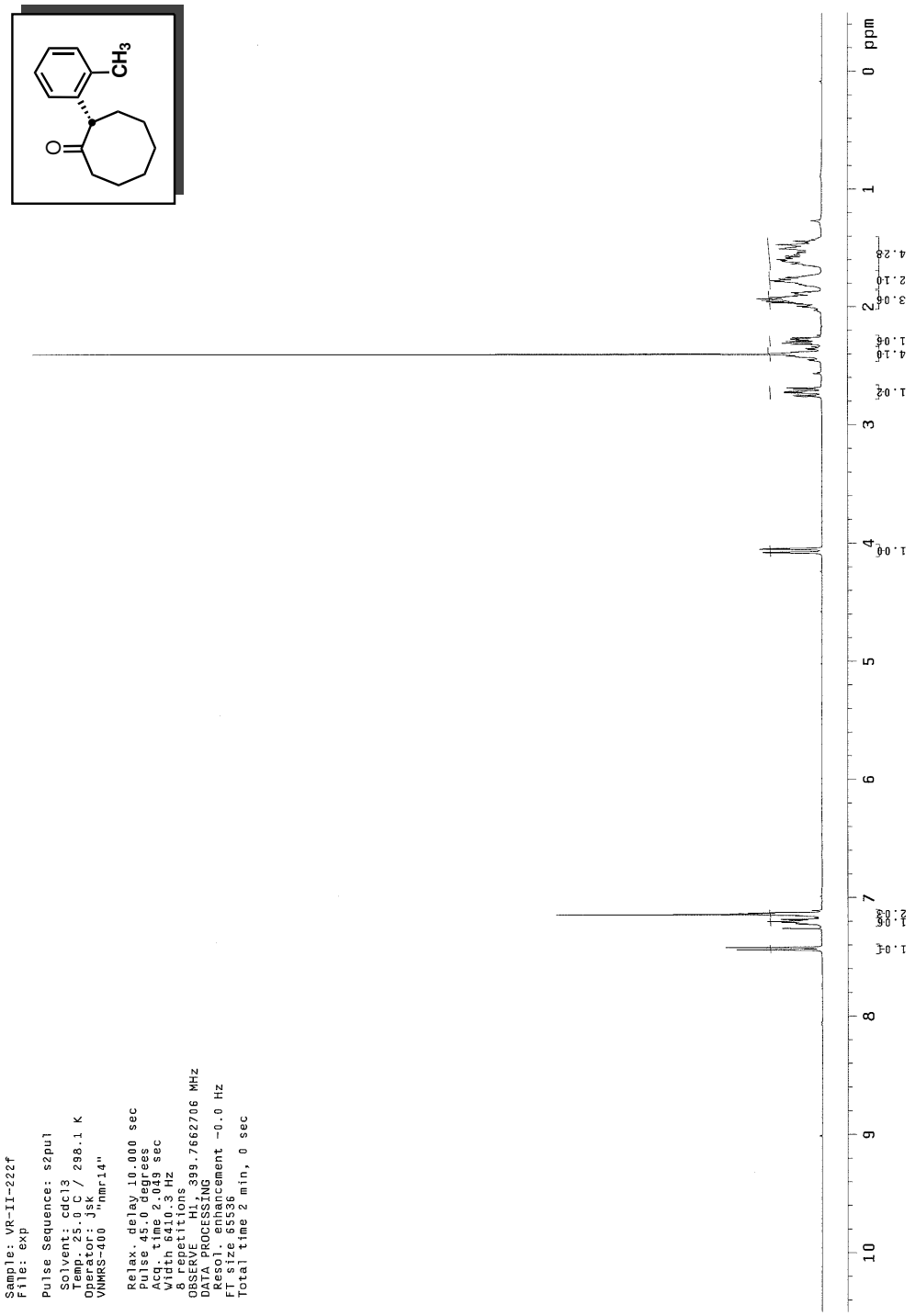


Figure 2.57: ^{13}C NMR of (*S*)-2-(2-methylphenyl)cyclooctanone (**2.85**)

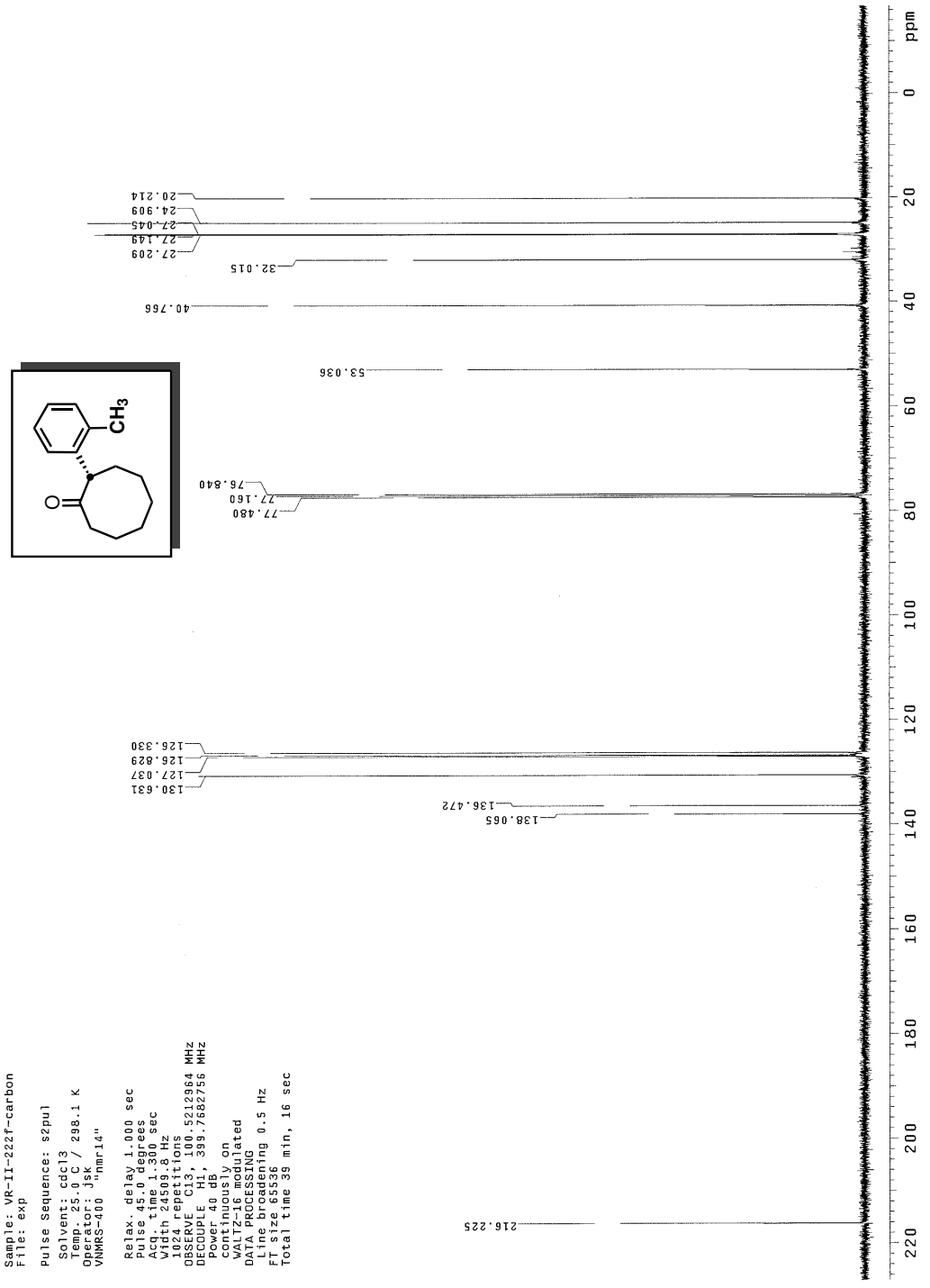


Figure 2.58: ^{1}H NMR of (*S*)-2-(4-methylphenyl)cyclooctanone (**2.77**)

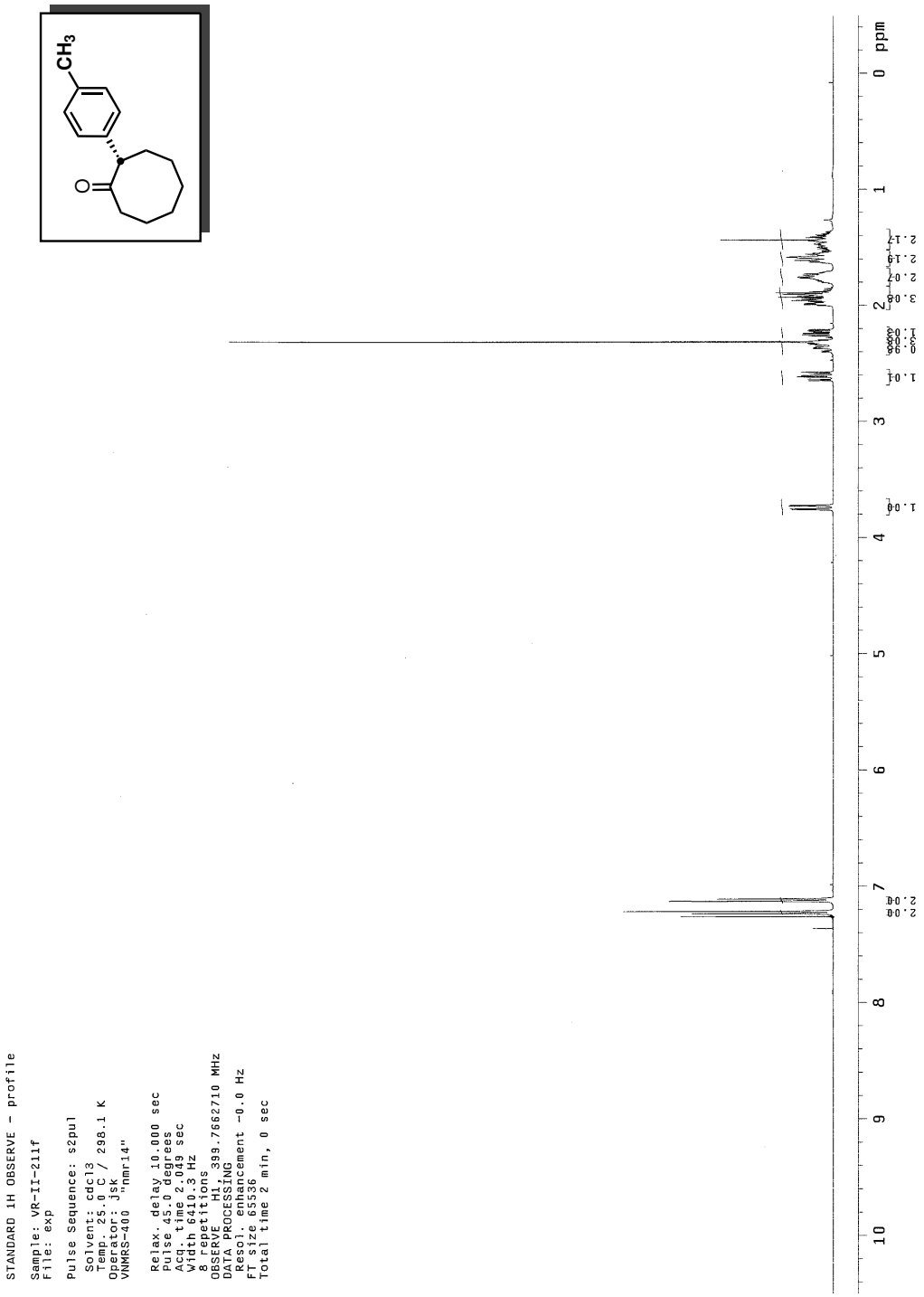


Figure 2.59: ^{13}C NMR of (*S*)-2-(4-methylphenyl)cyclooctanone (**2.77**)

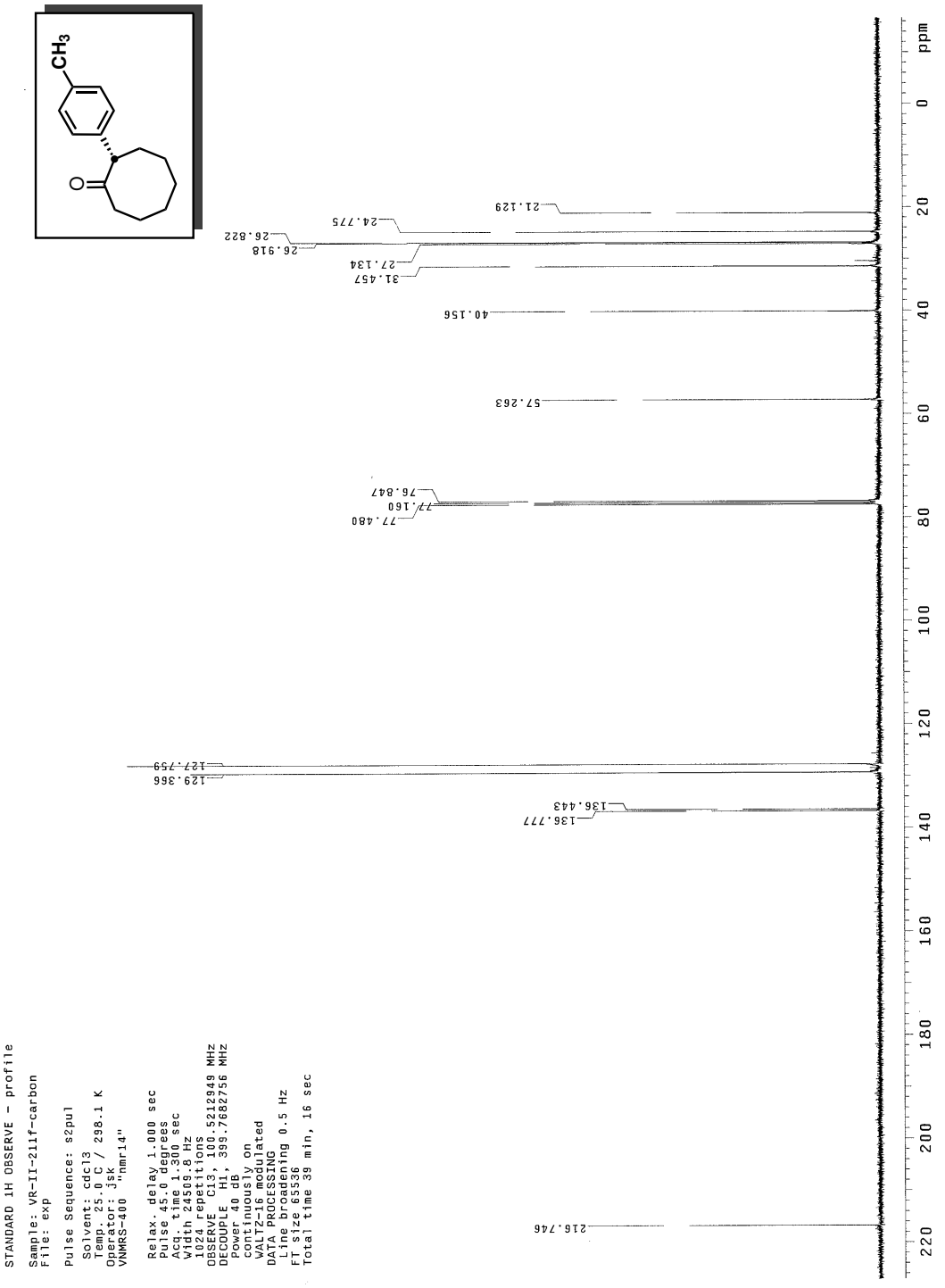


Figure 2.60: ^{1}H NMR of (*S*)-2-(napthalen-1-yl)cyclooctanone (**2.87**)

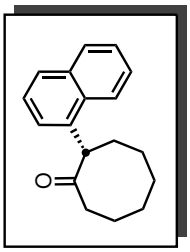


Figure 2.61: ^{13}C NMR of (*S*)-2-(napthalen-1-yl)cyclooctanone (**2.87**)

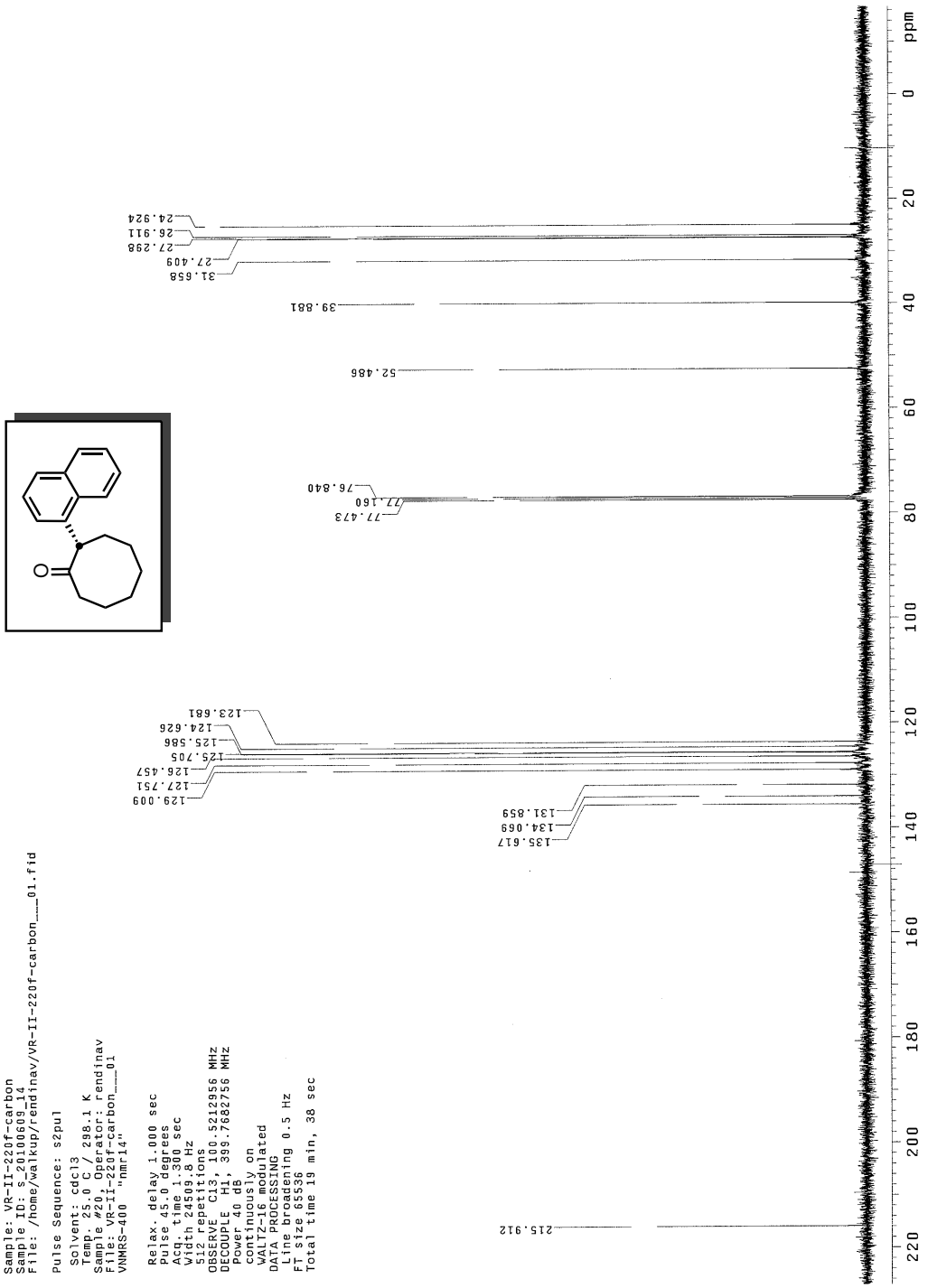


Figure 2.62: ^{1}H NMR of (*S*)-2-(4-phenyl)cyclononanone (**2.88**)

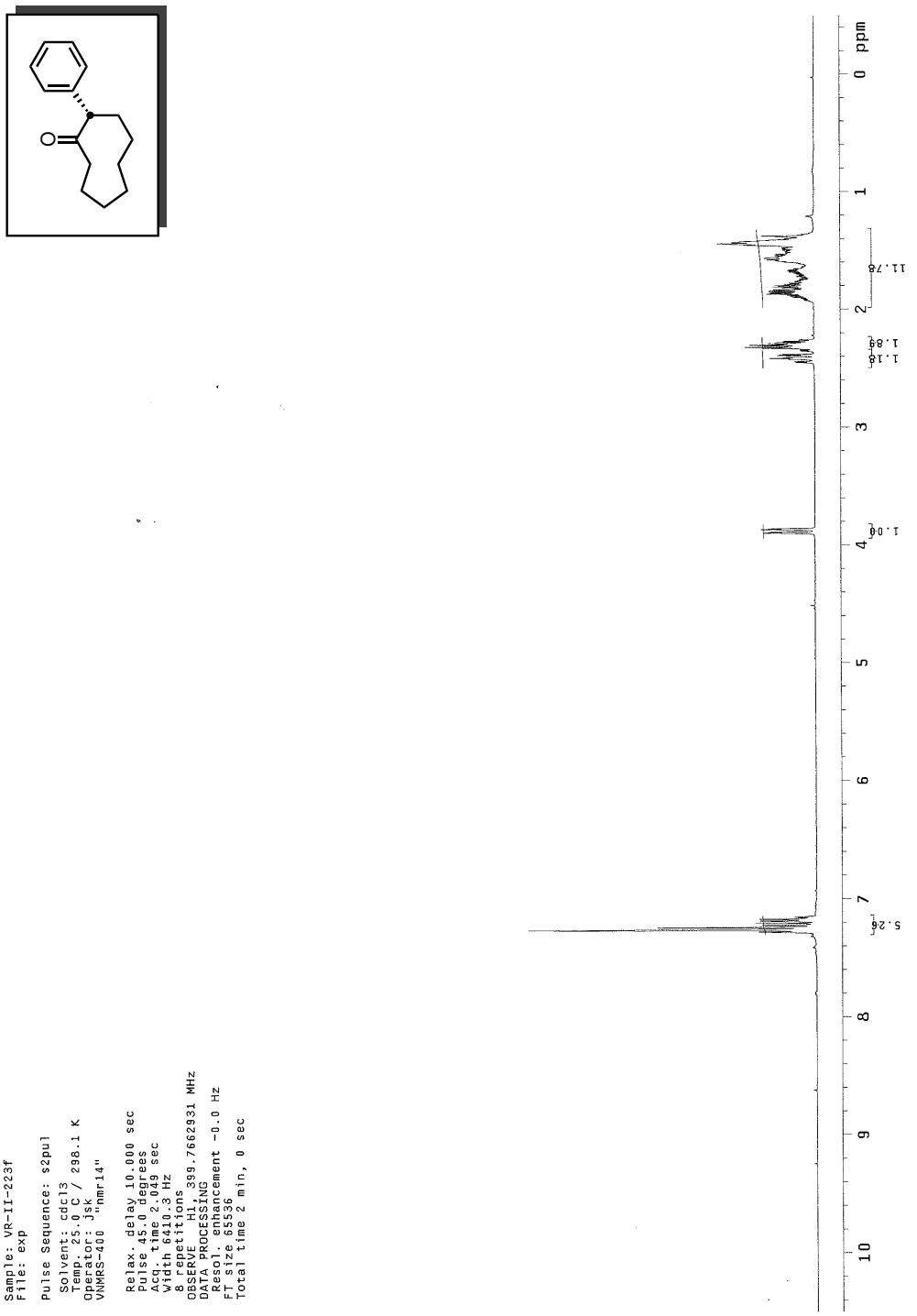


Figure 2.63: ^{13}C NMR of (*S*)-2-(4-phenyl)cyclononanone (**2.88**)

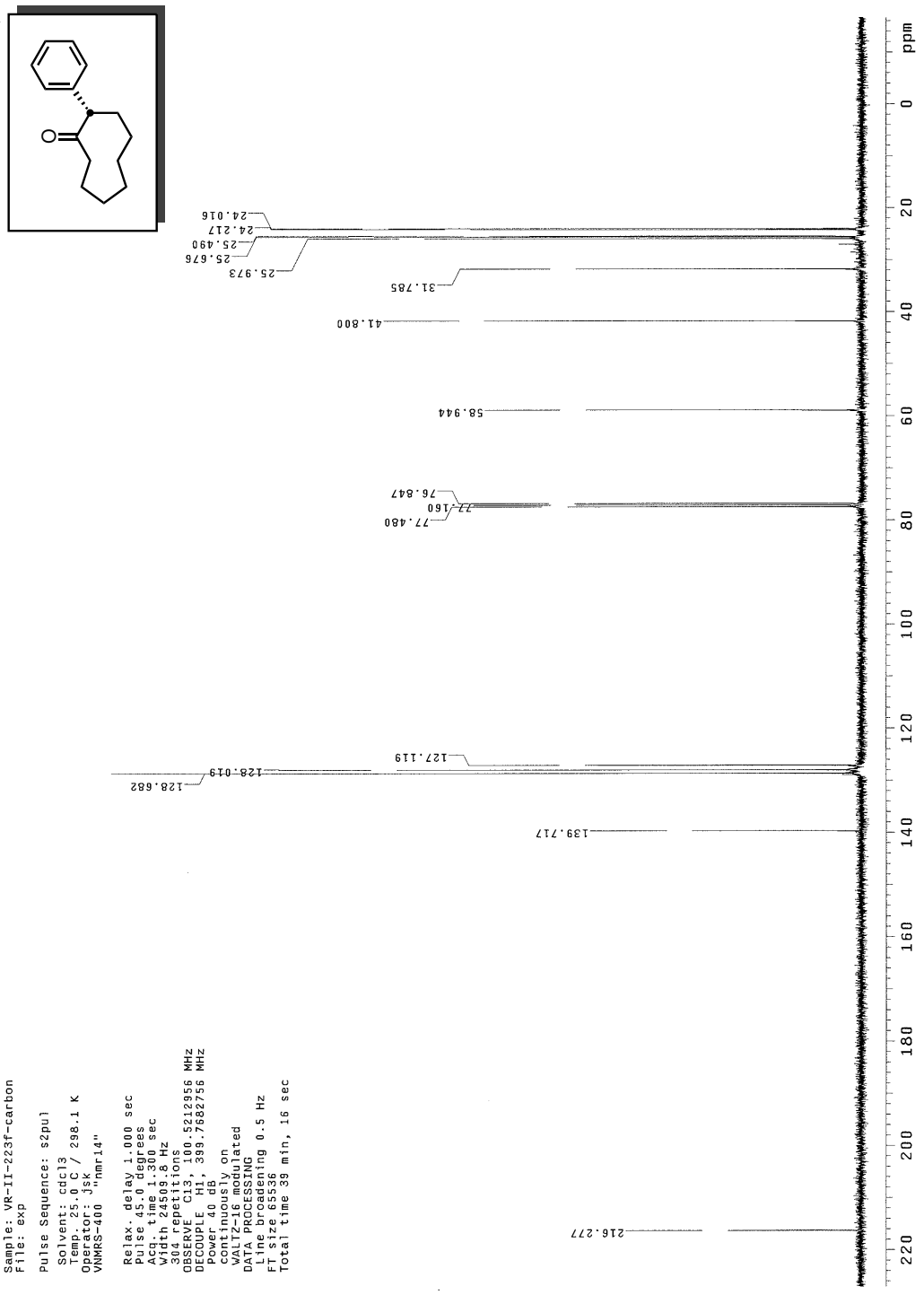


Figure 2.64: ^{1}H NMR of (±)-*cis*-2-phenylcyclooctanol (**2.89**)

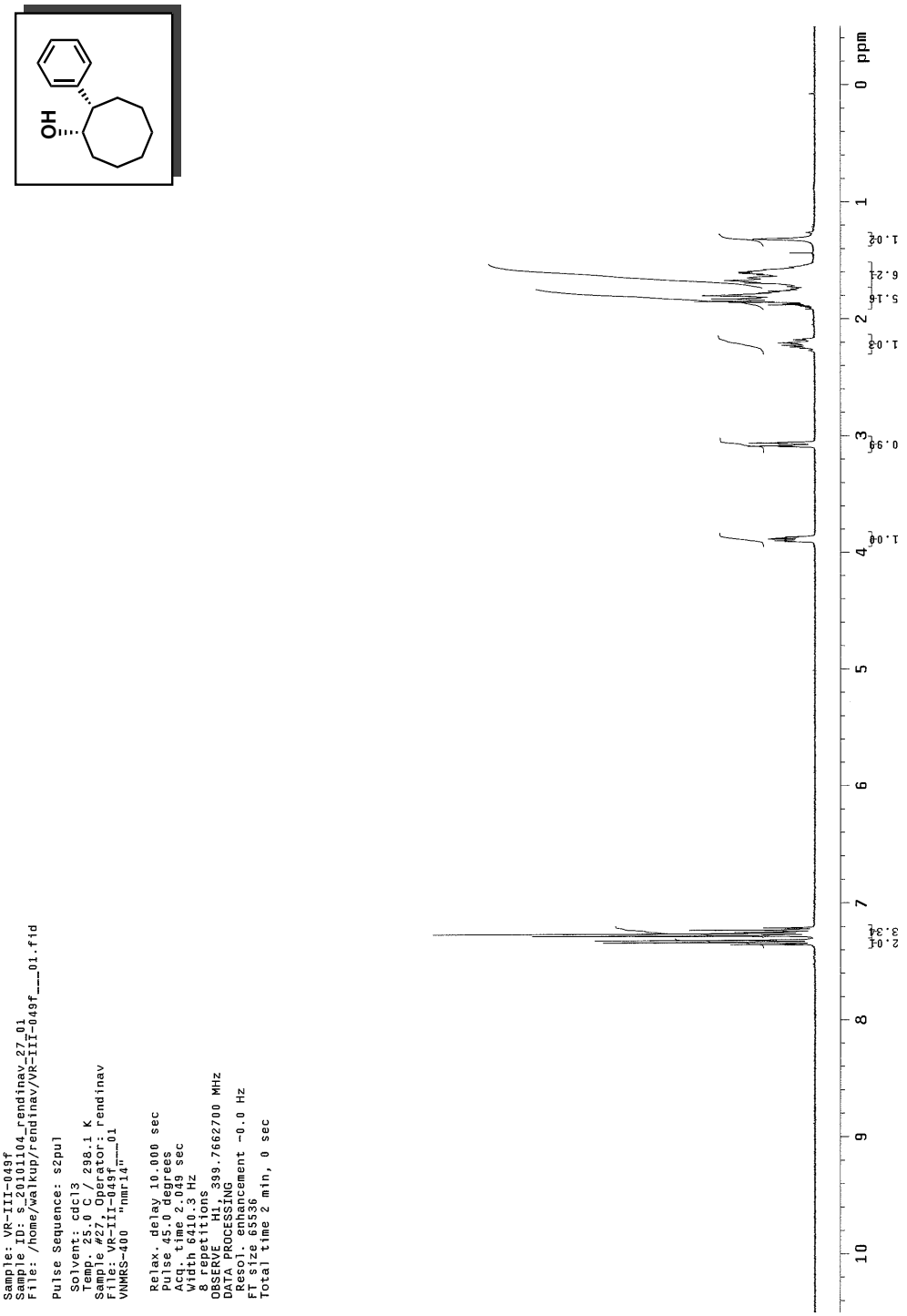


Figure 2.65: ^{13}C NMR of (±)-*cis*-2-phenylcyclooctanol (**2.89**)

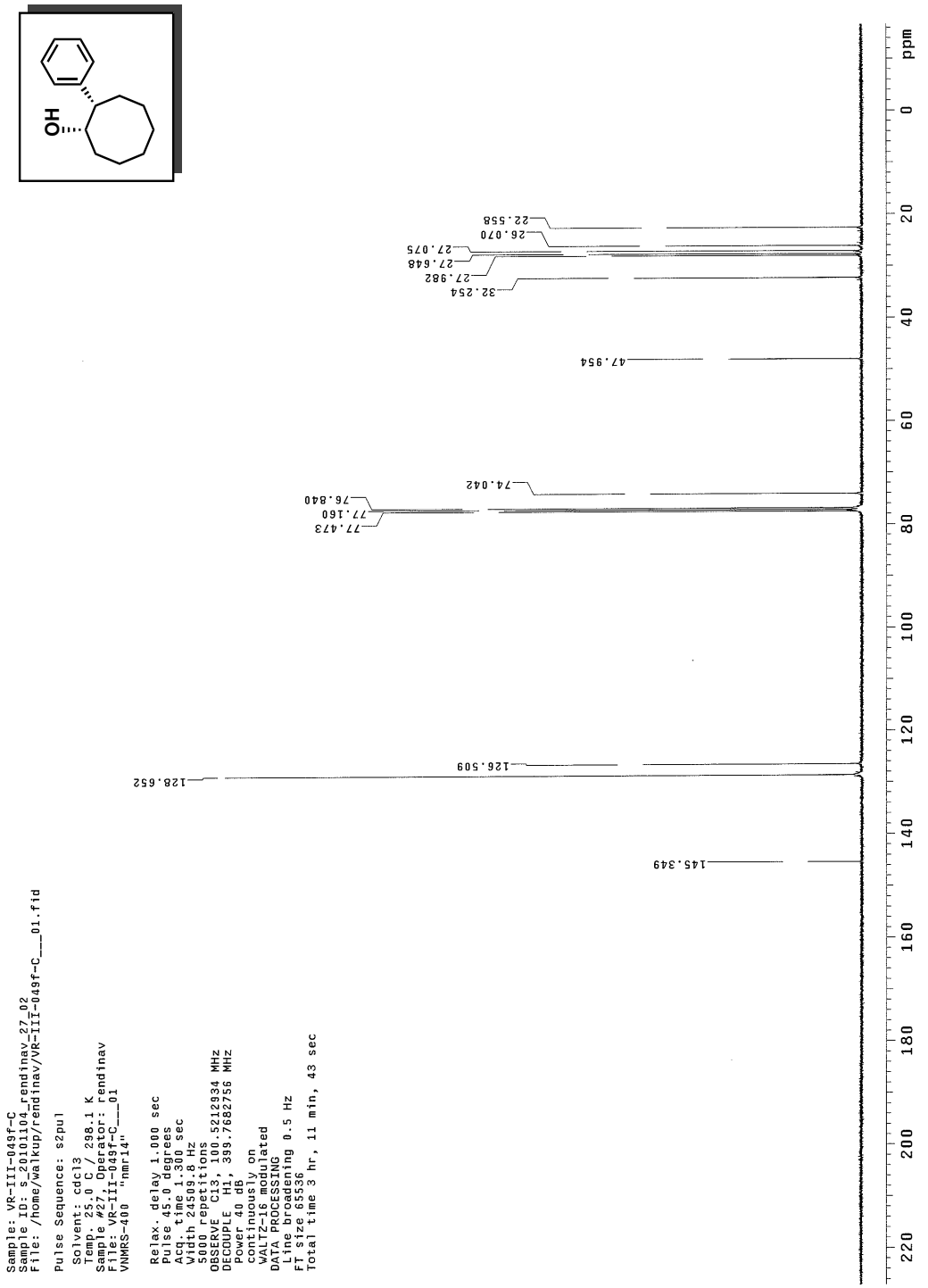


Figure 2.66: ^{1}H NMR of (±)-*cis*-2-phenylcyclooctyl 4-nitrobenzoate (**2.116**)

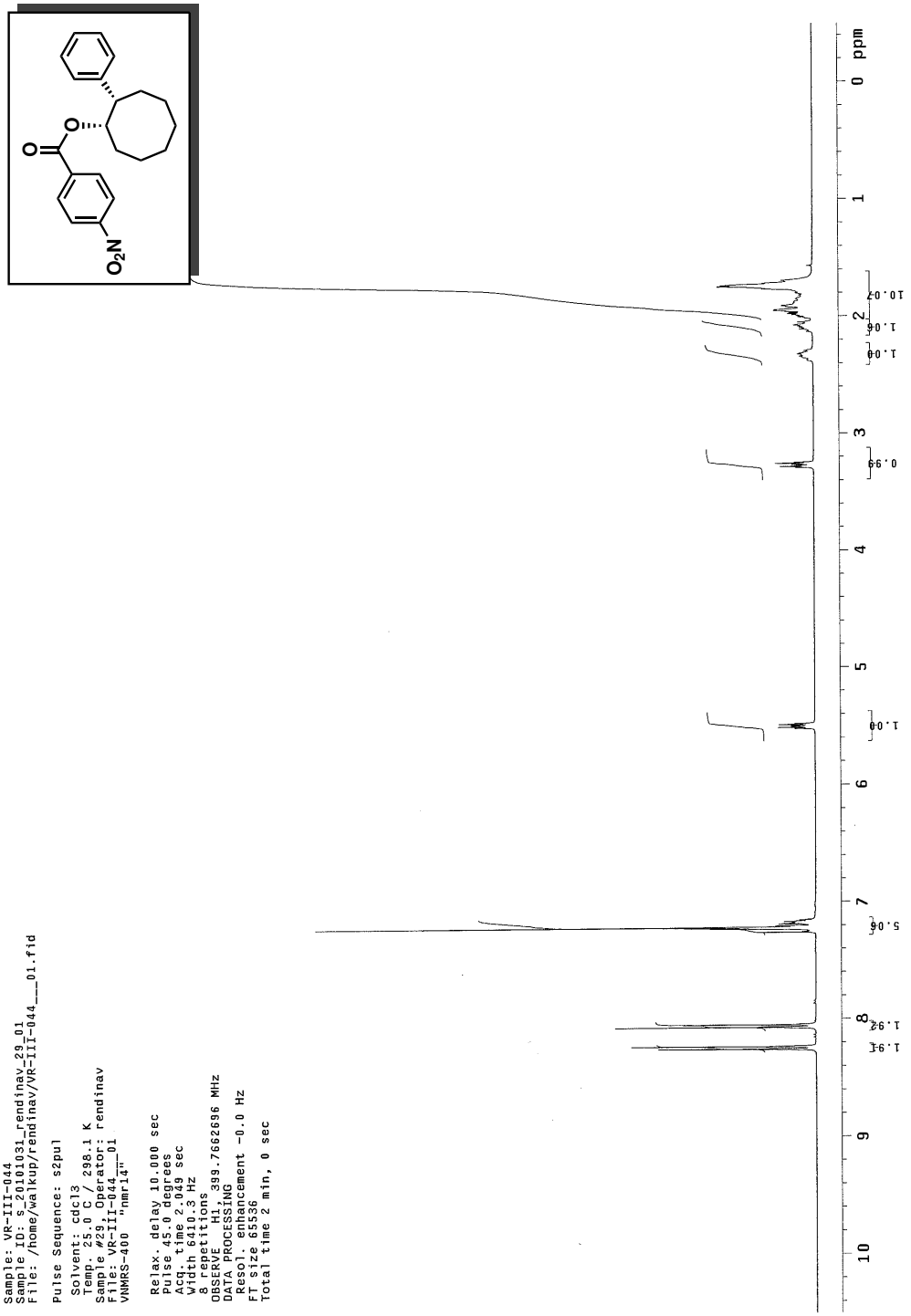


Figure 2.67: ^{13}C NMR of (±)-*cis*-2-phenylcyclooctyl 4-nitrobenzoate (**2.116**)

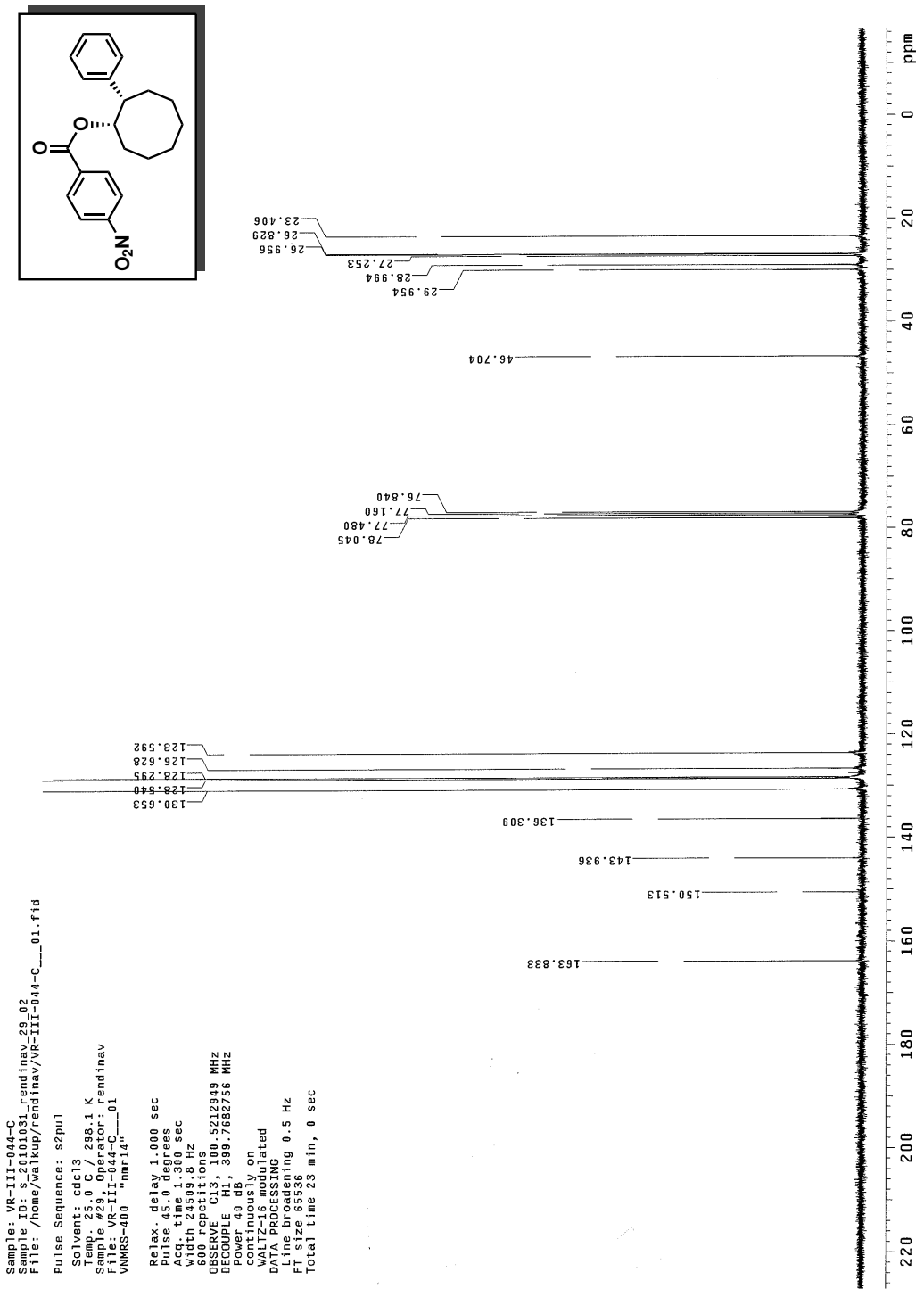


Figure 2.68: ^{1}H NMR of (*S*)-((1*S*,2*S*)-2-phenylcyclooctyl)-α-acetyl mandelate (**2.91**)

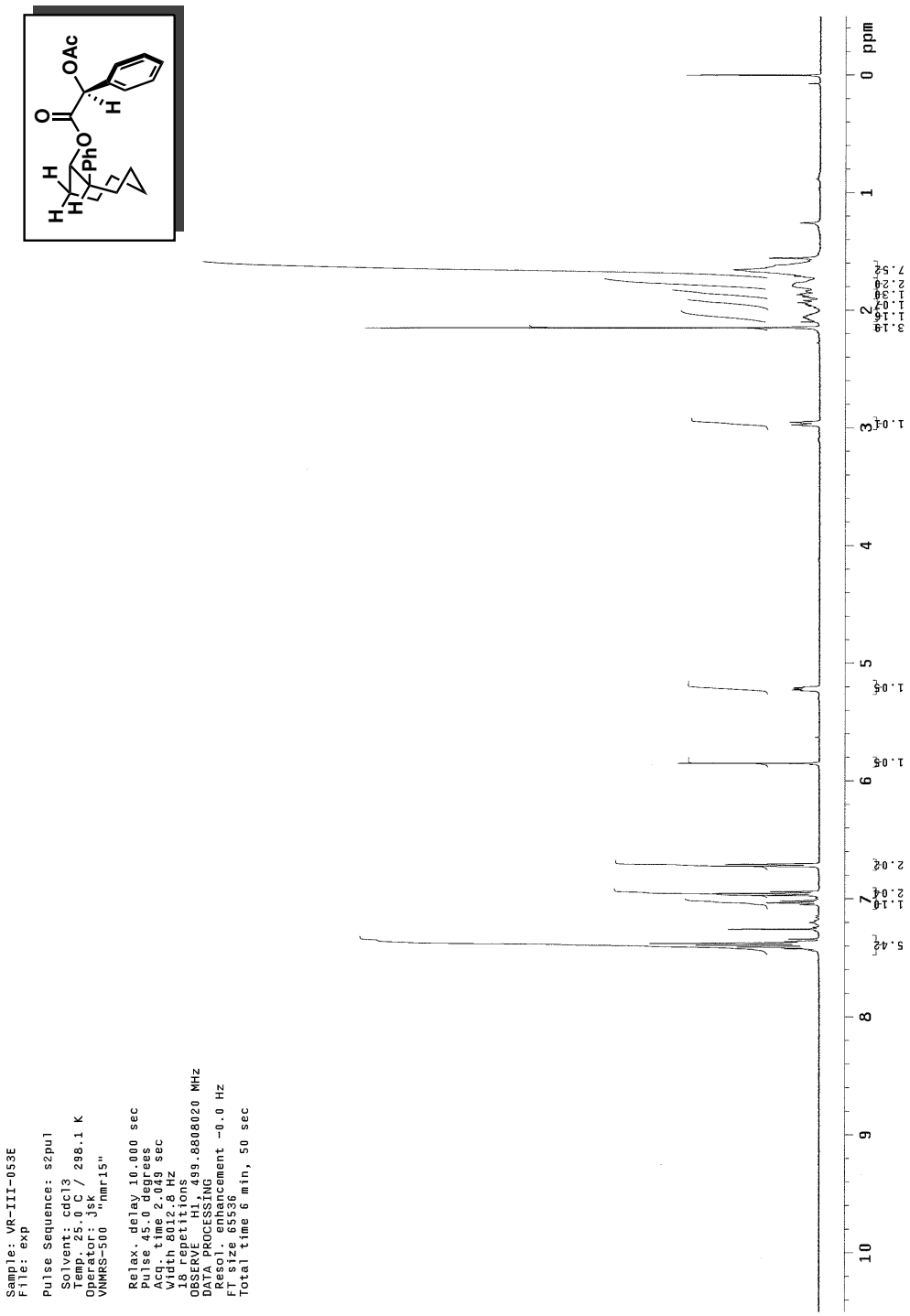


Figure 2.69: ^{13}C NMR of (*S*)-((1*S*,2*S*)-2-phenylcyclooctyl)-α-acetyl mandelate (**2.91**)

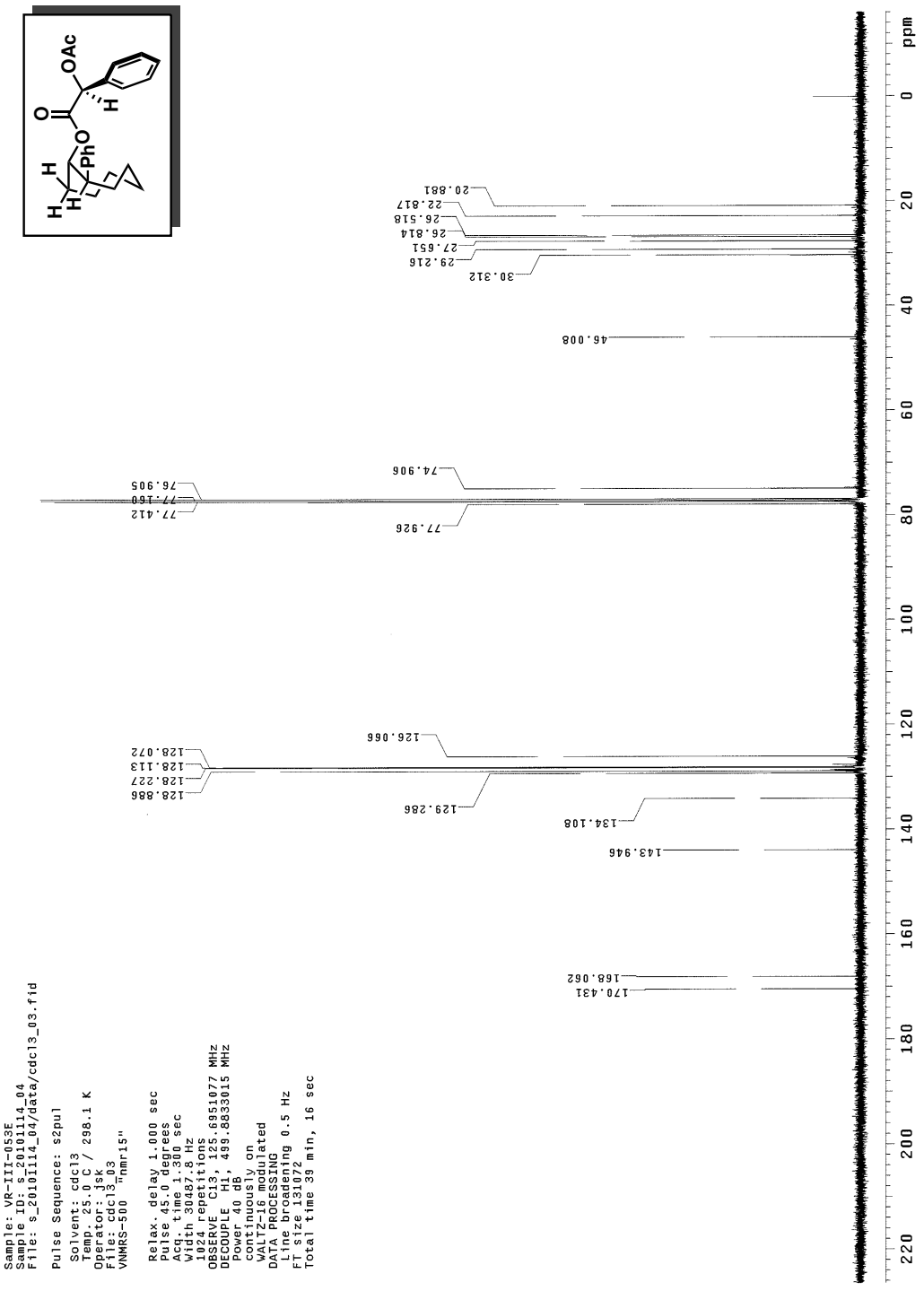


Figure 2.70: ^{19}F NMR of 2-fluorobenzoic acid (**2.107**)

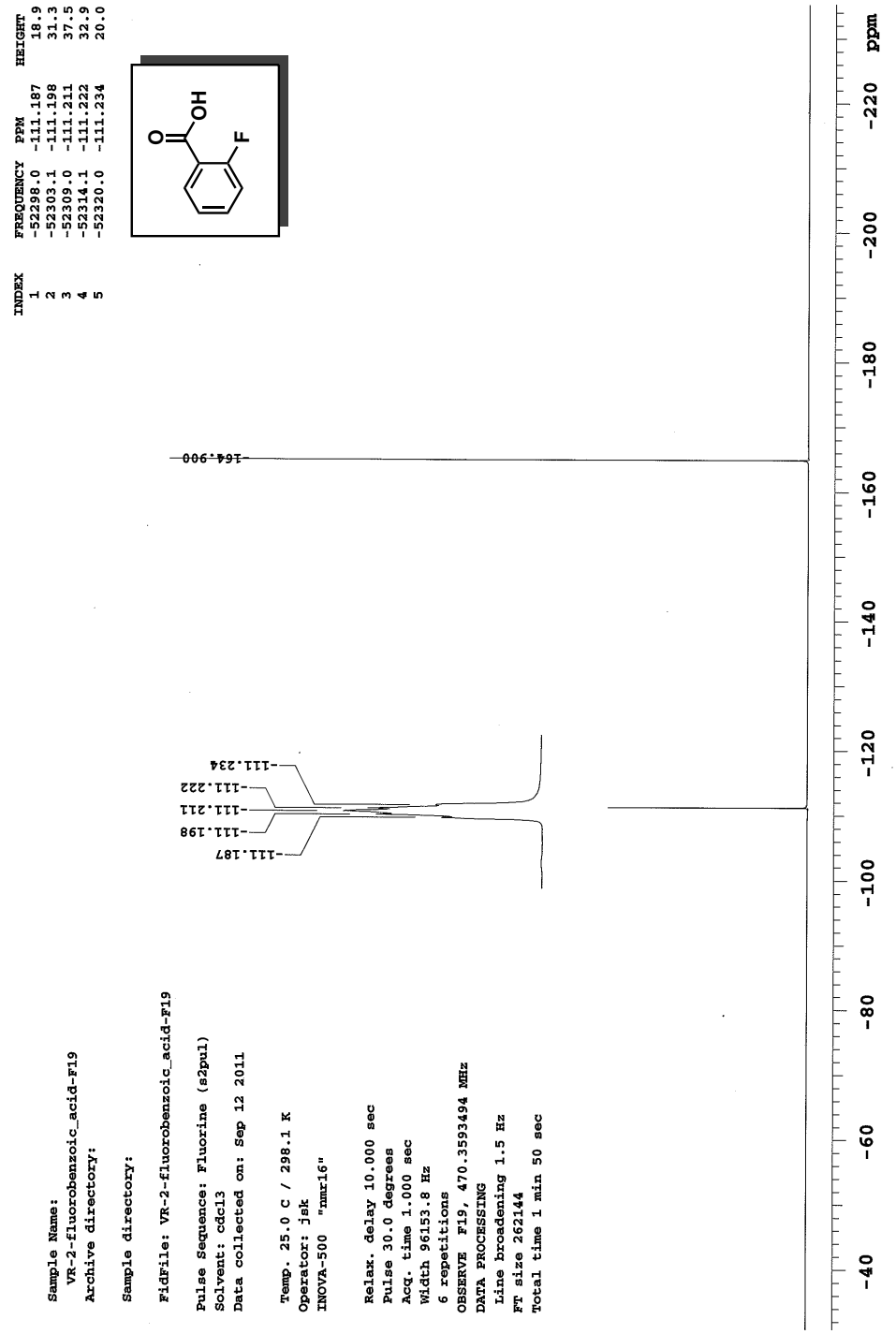


Figure 2.71: ^{1}H NMR of benzyl 2-fluorobenzoate (**2.117**)

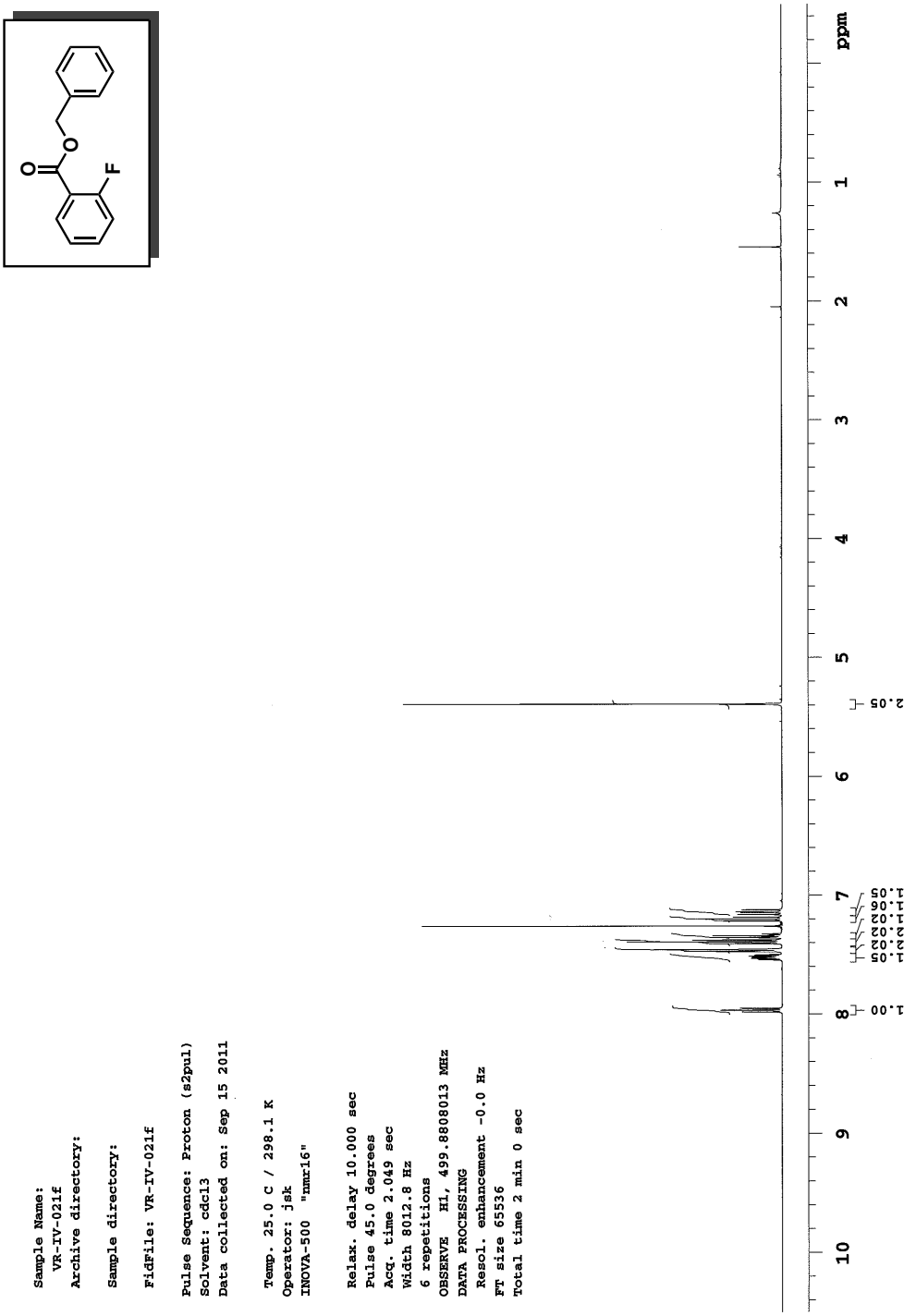


Figure 2.72: ^{13}C NMR of benzyl 2-fluorobenzoate (**2.117**)

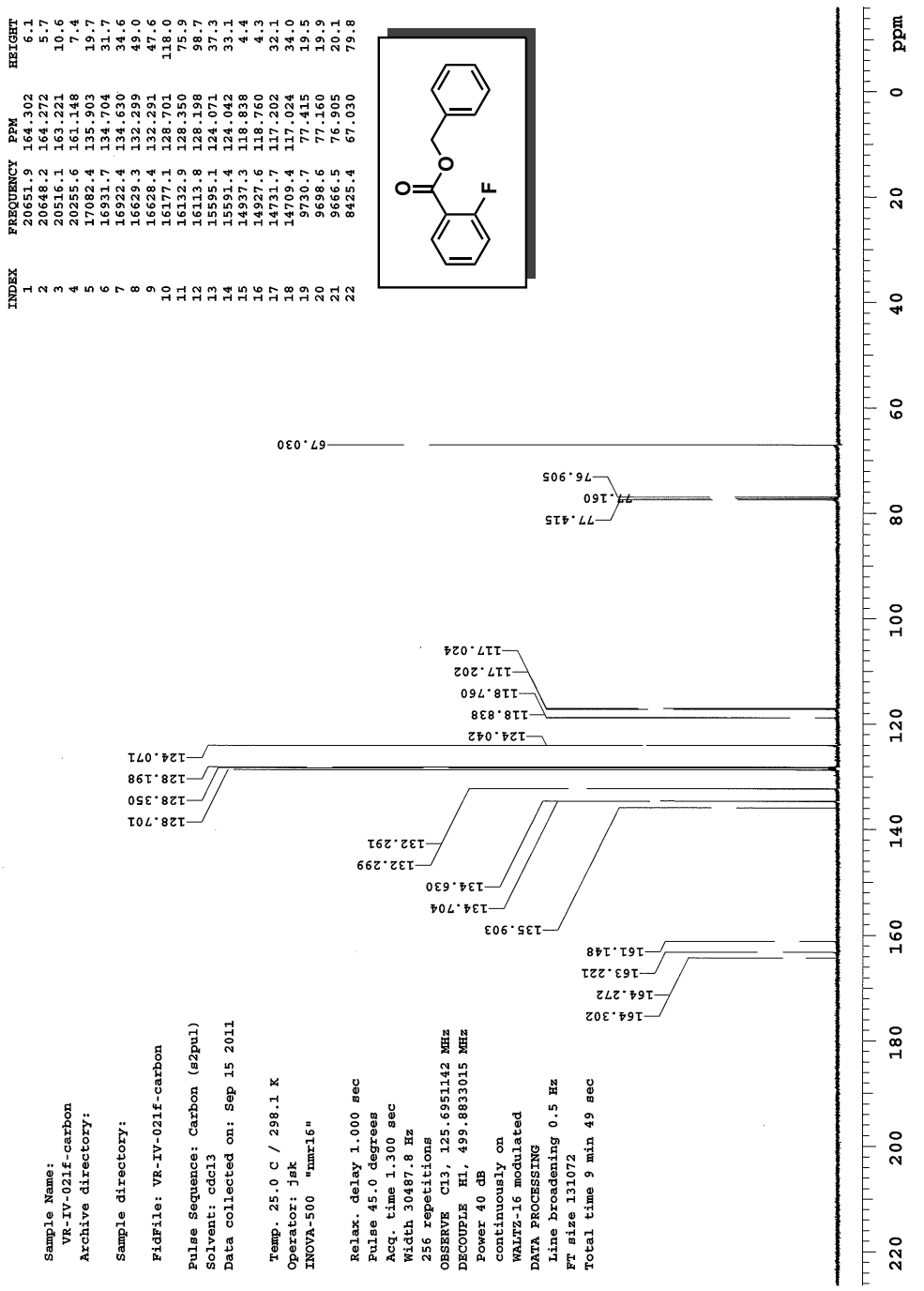


Figure 2.73: ^{19}F NMR of benzyl 2-fluorobenzoate (**2.117**)

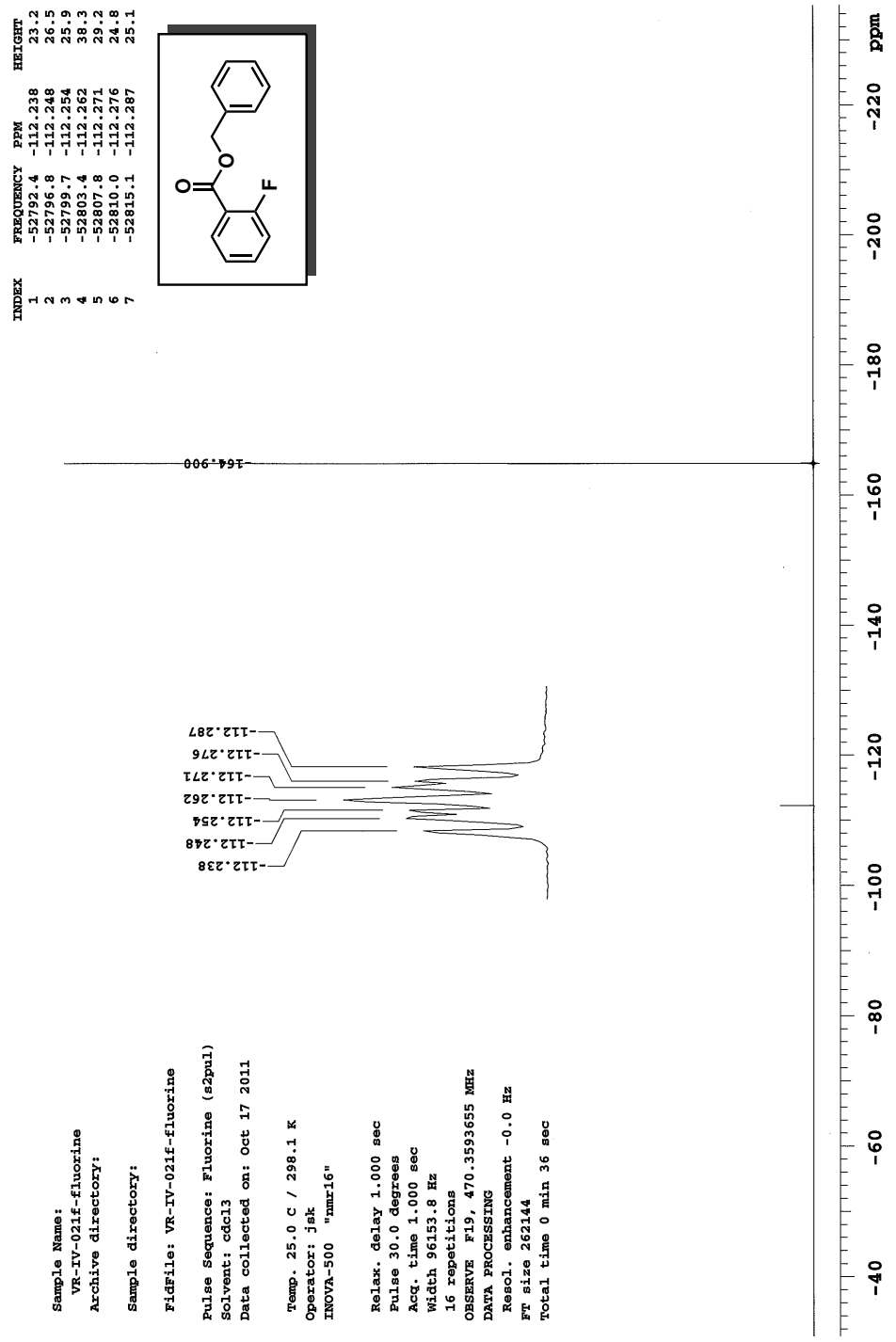


Figure 2.74: ^{1}H NMR of methyl 2-fluorobenzoate (**2.118**)

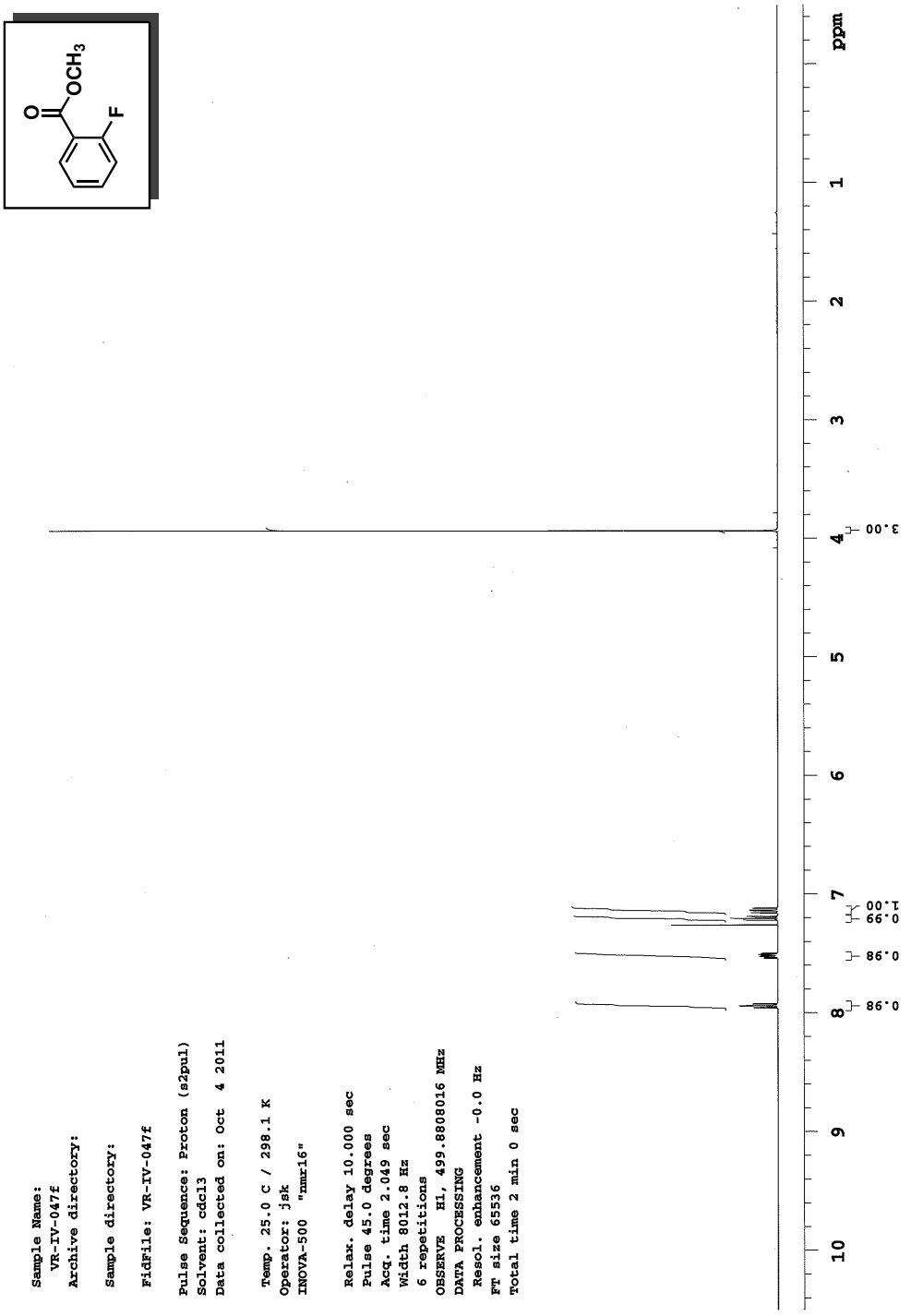


Figure 2.75: ^{13}C NMR of methyl 2-fluorobenzoate (**2.118**)

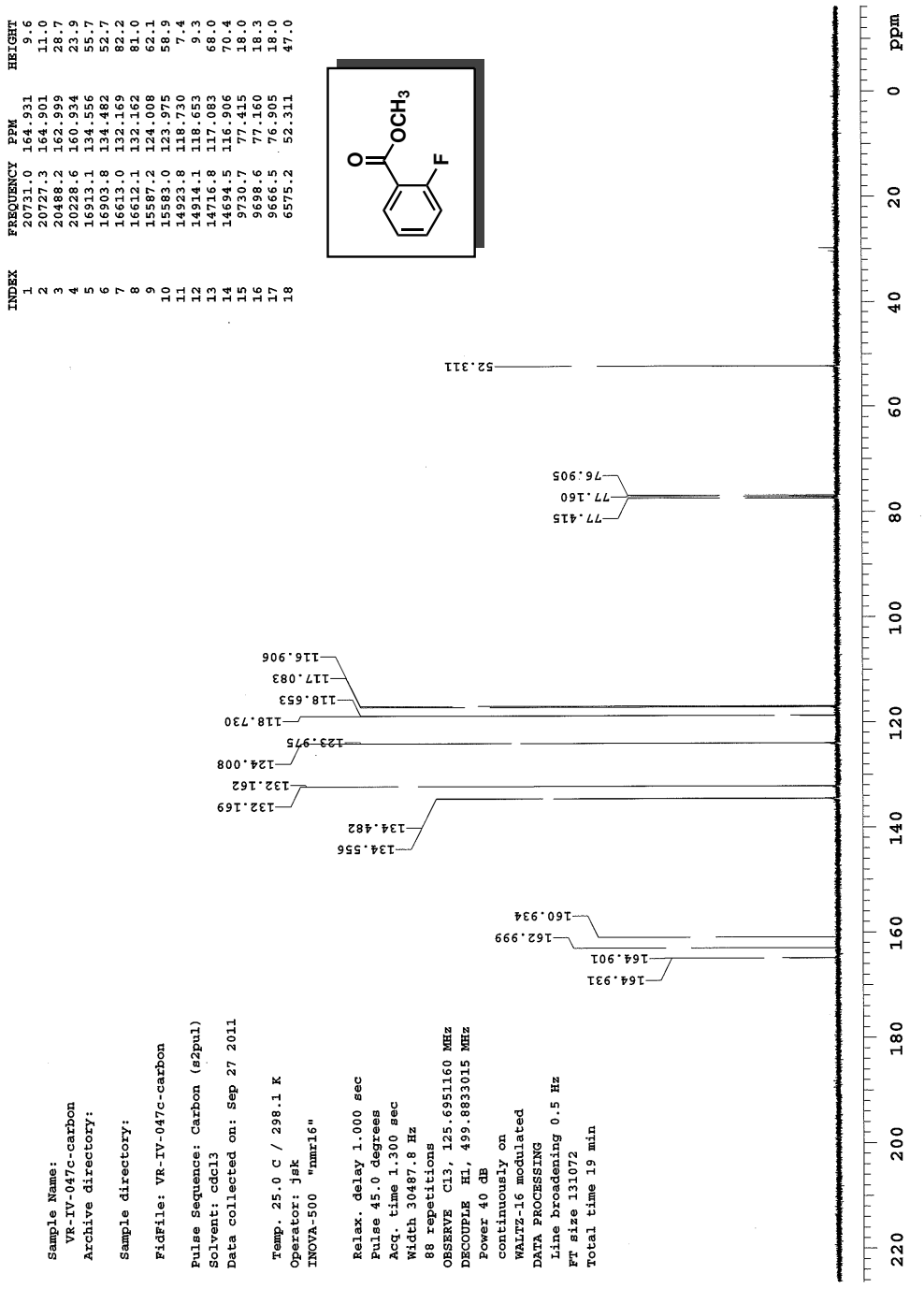


Figure 2.76: ^{19}F NMR of methyl 2-fluorobenzoate (**2.118**)

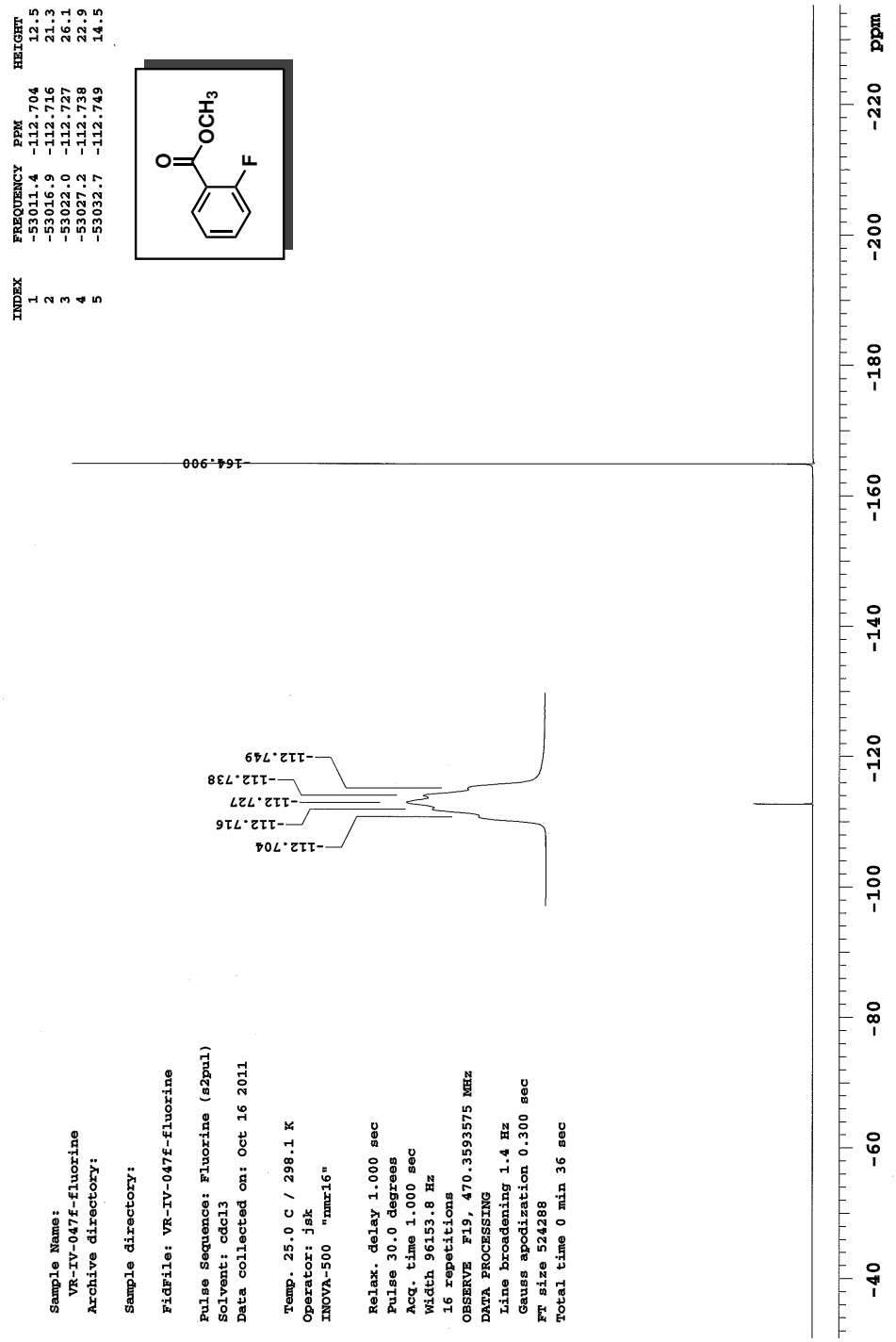


Figure 2.77: ^{1}H NMR of 3-phenylpropyl 2-fluorobenzoate (**2.119**)

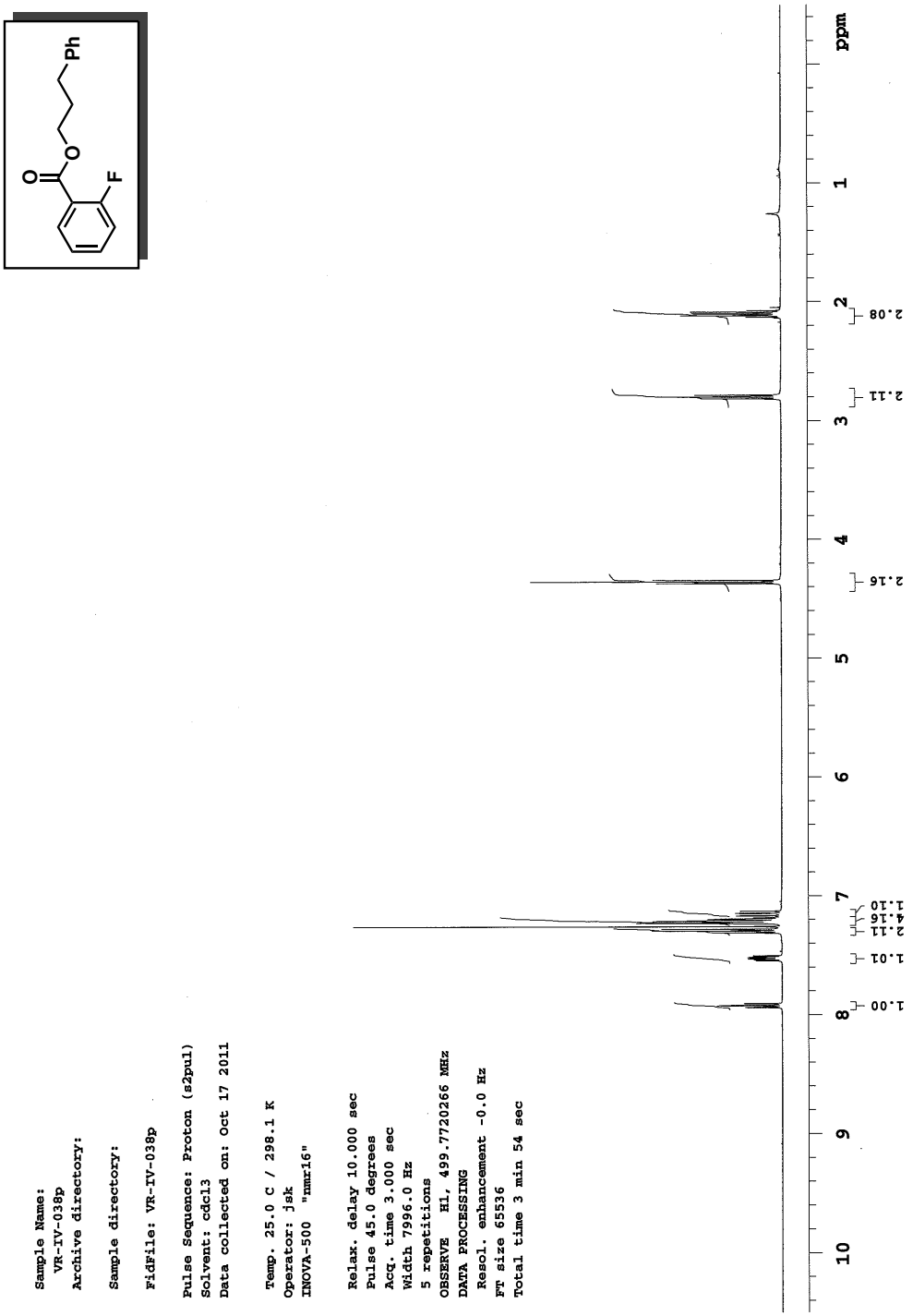


Figure 2.78: ^{13}C NMR of 3-phenylpropyl 2-fluorobenzoate (**2.119**)

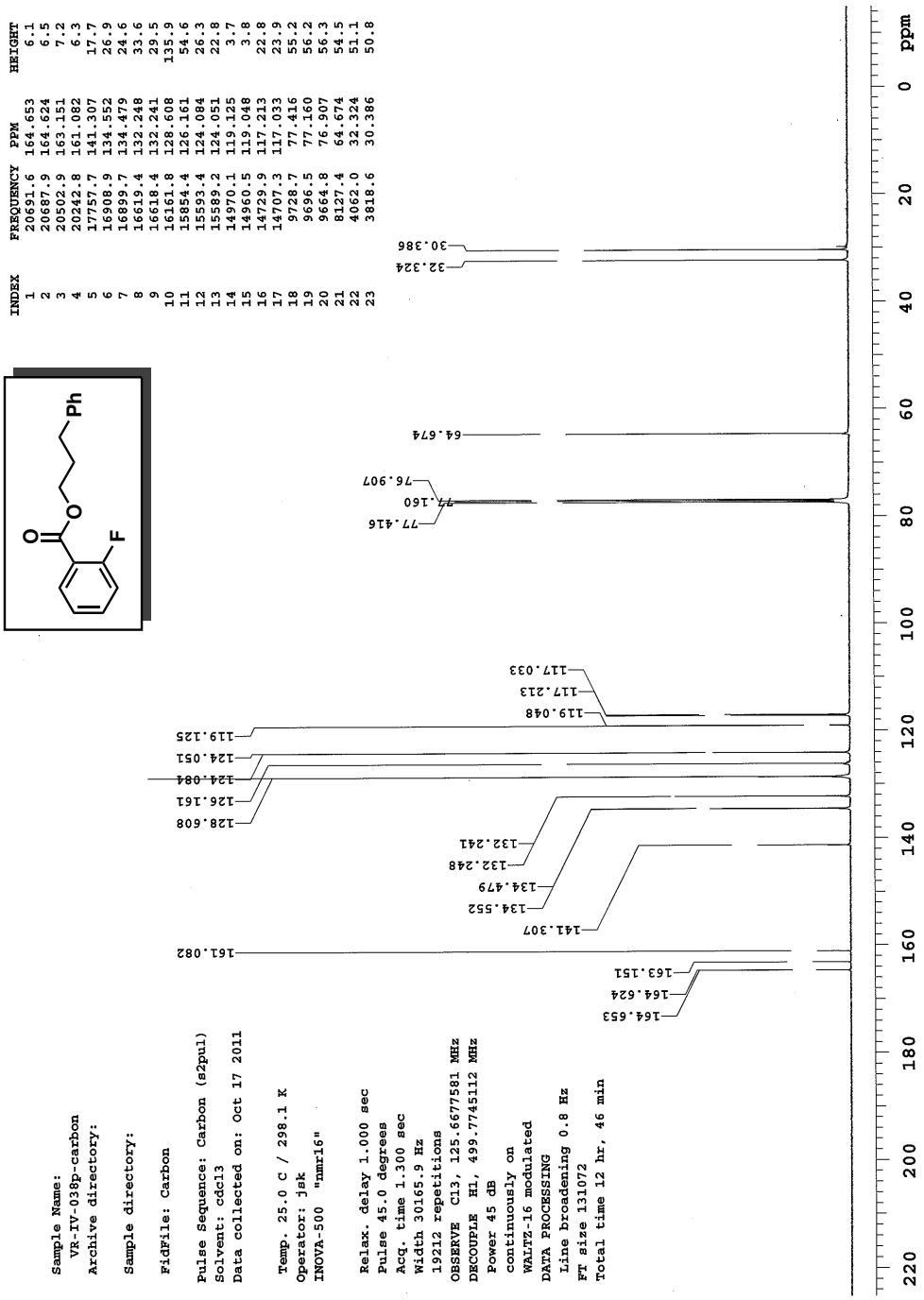


Figure 2.79: ^{19}F NMR of 3-phenylpropyl 2-fluorobenzoate (**2.119**)

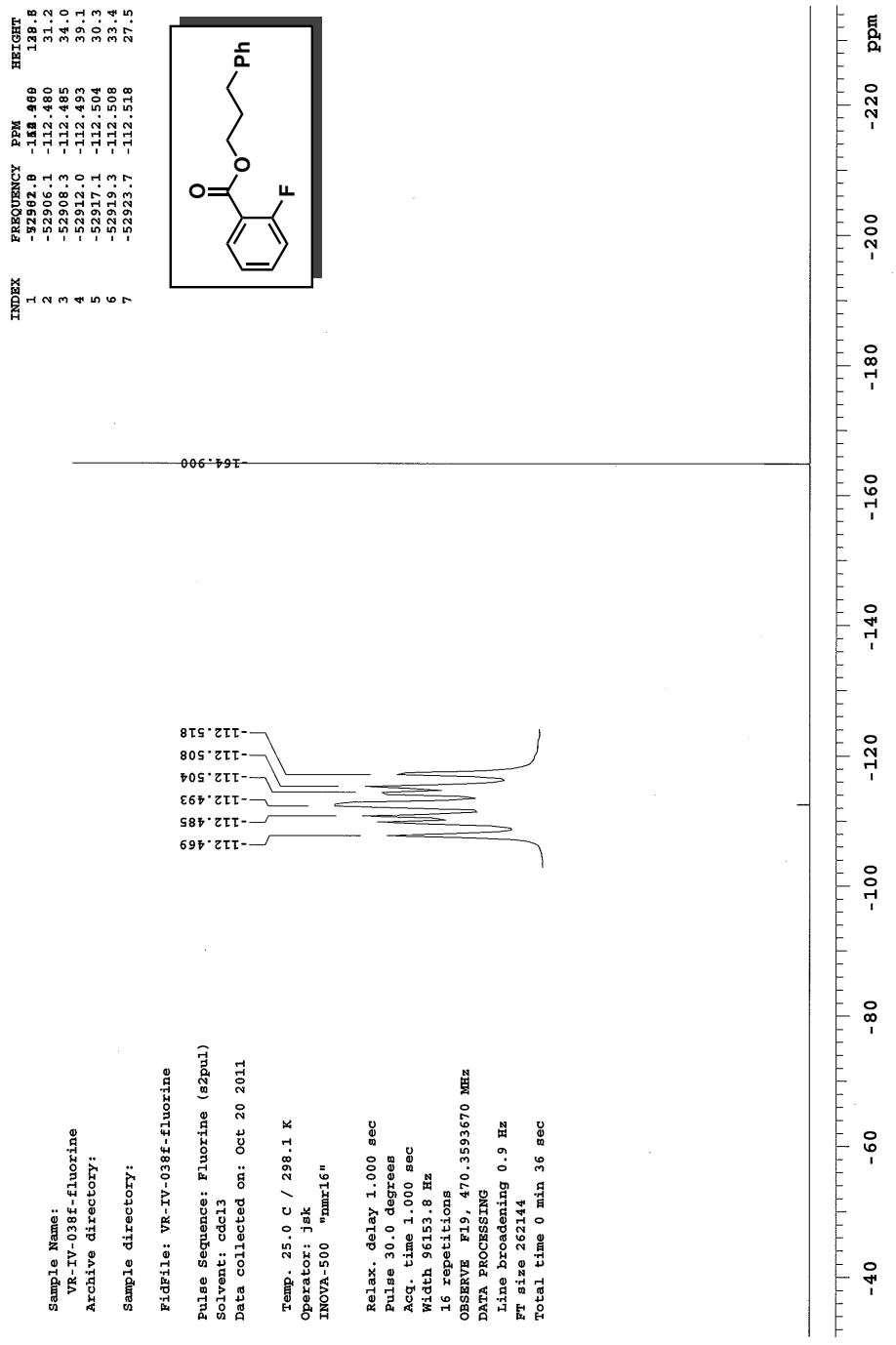


Figure 2.80: ^{1}H NMR of cinnamyl 2-fluorobenzoate (**2.120**)

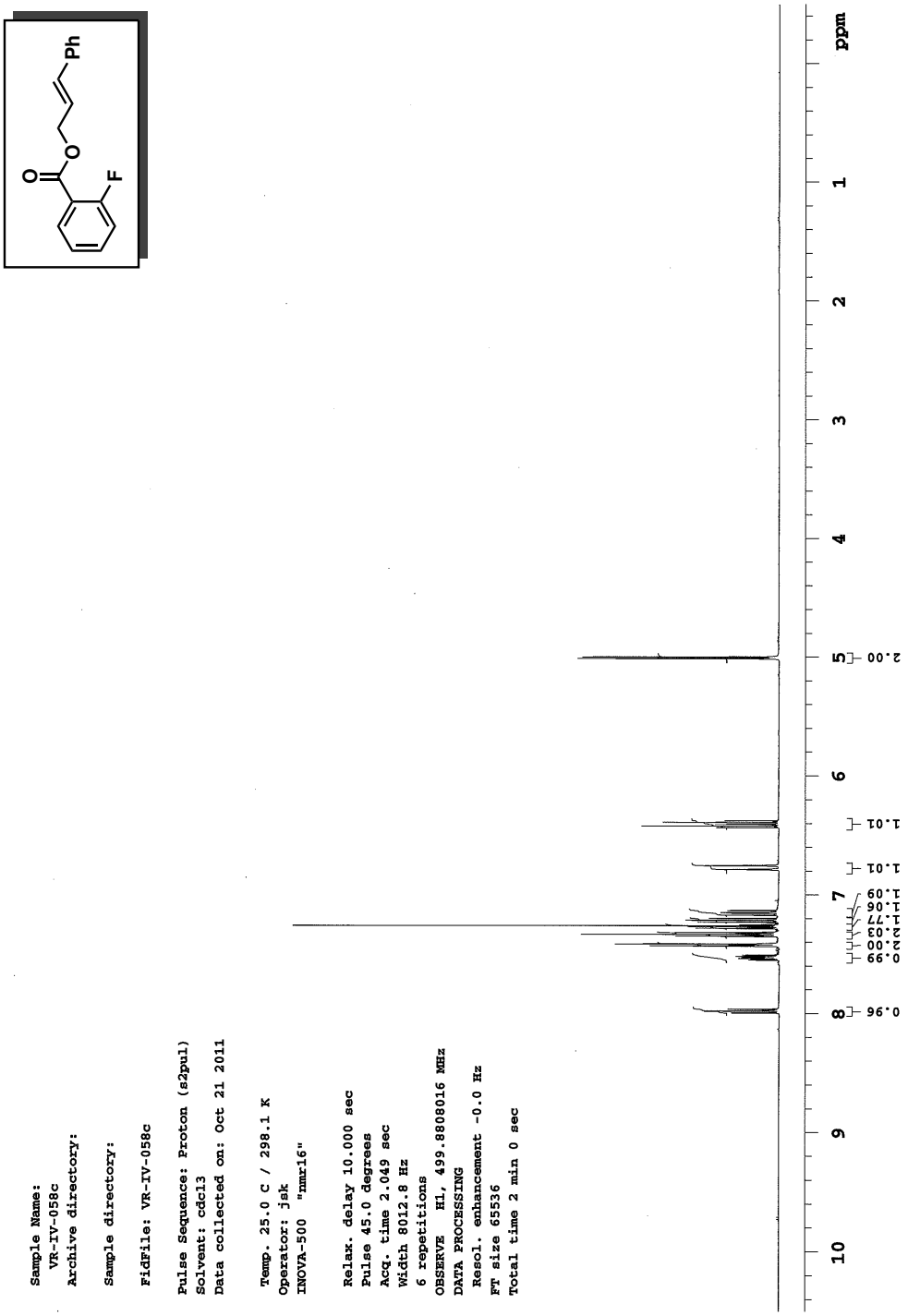


Figure 2.81: ^{13}C NMR of cinnamyl 2-fluorobenzoate (**2.120**)

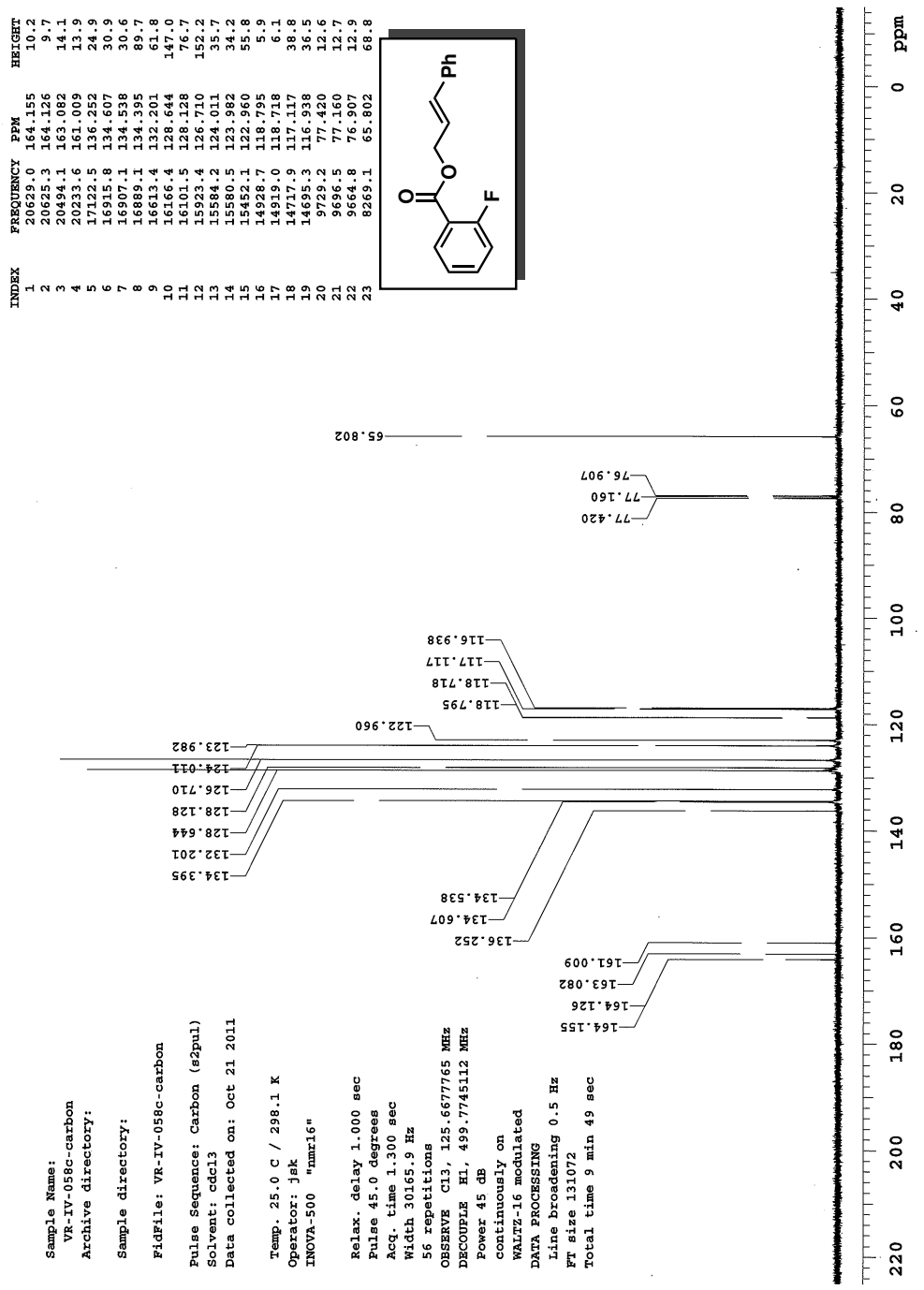


Figure 2.82: ^{19}F NMR of cinnamyl 2-fluorobenzoate (**2.120**)

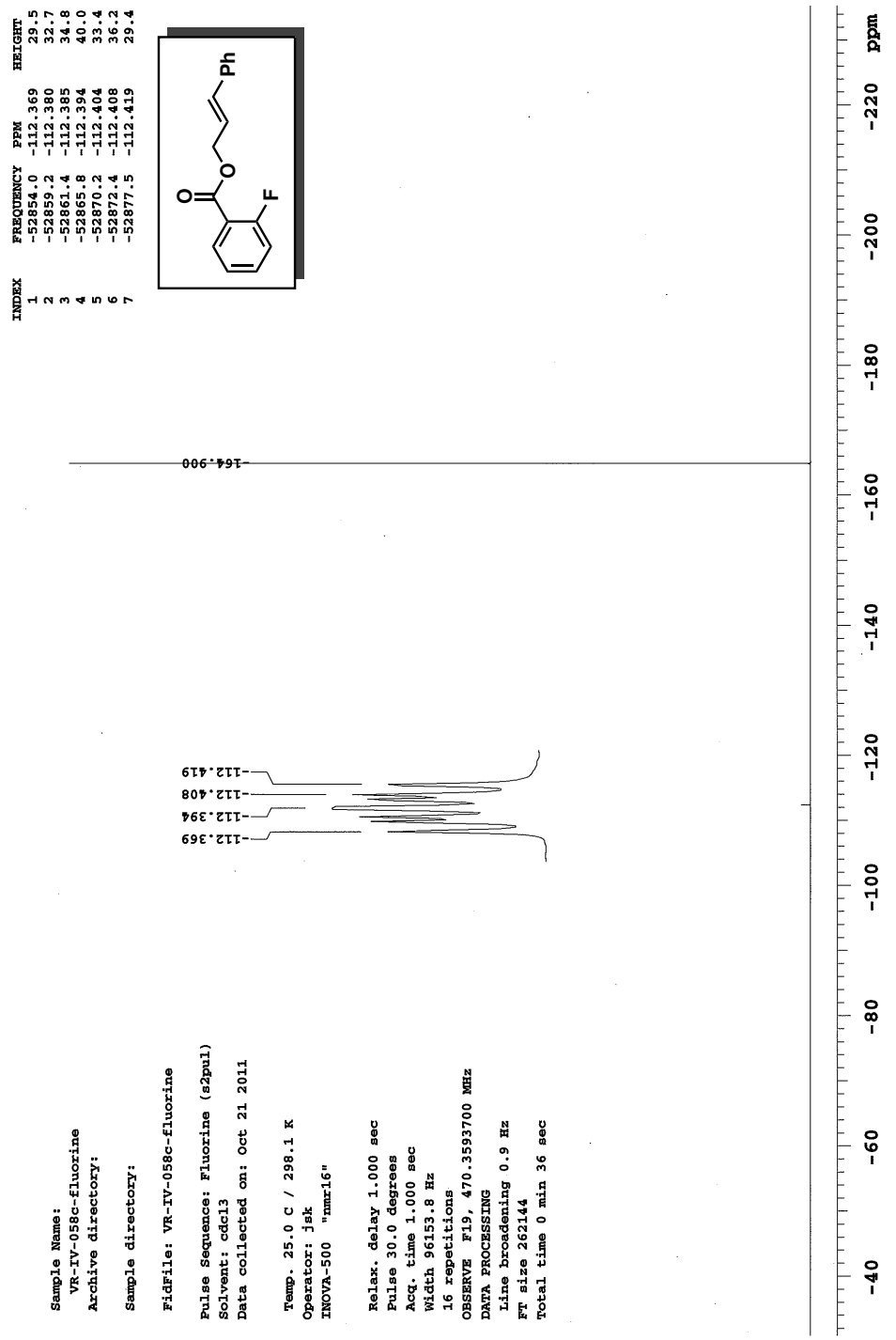


Figure 2.83: ^{1}H NMR of 2-methylbenzyl 2-fluorobenzoate (**2.121**)

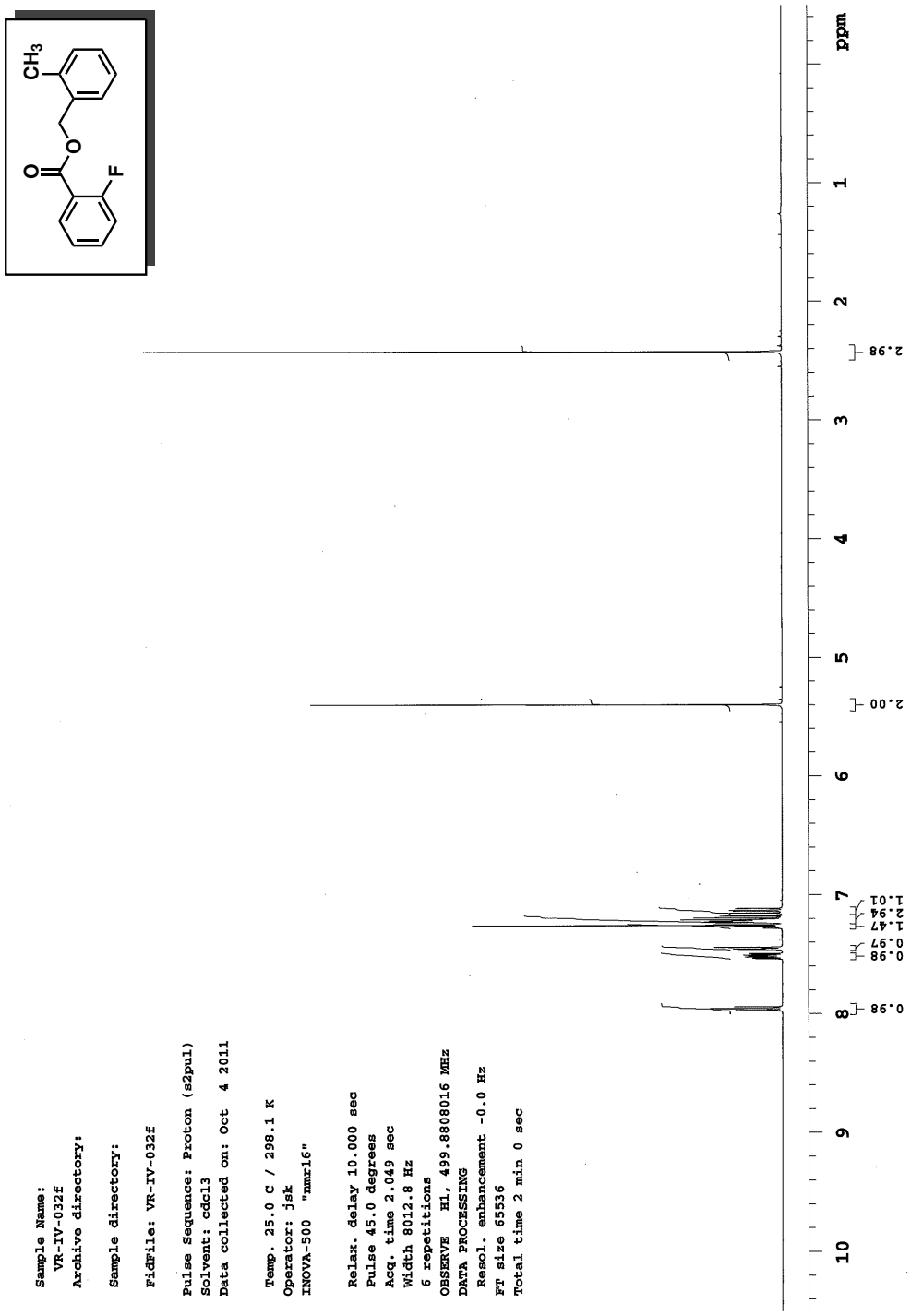


Figure 2.84: ^{13}C NMR of 2-methylbenzyl 2-fluorobenzoate (**2.121**)

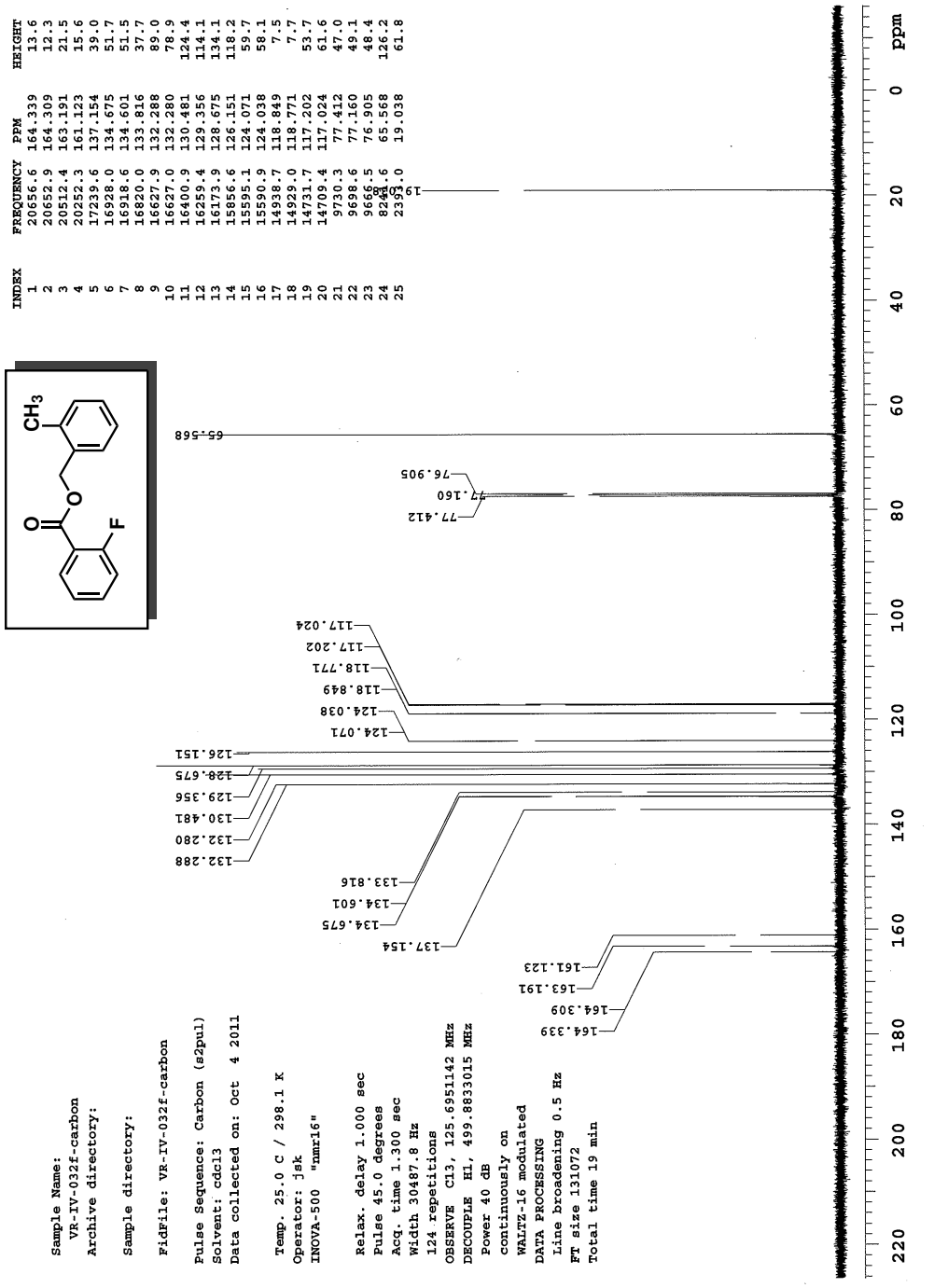


Figure 2.85: ^{19}F NMR of 2-methylbenzyl 2-fluorobenzoate (**2.121**)

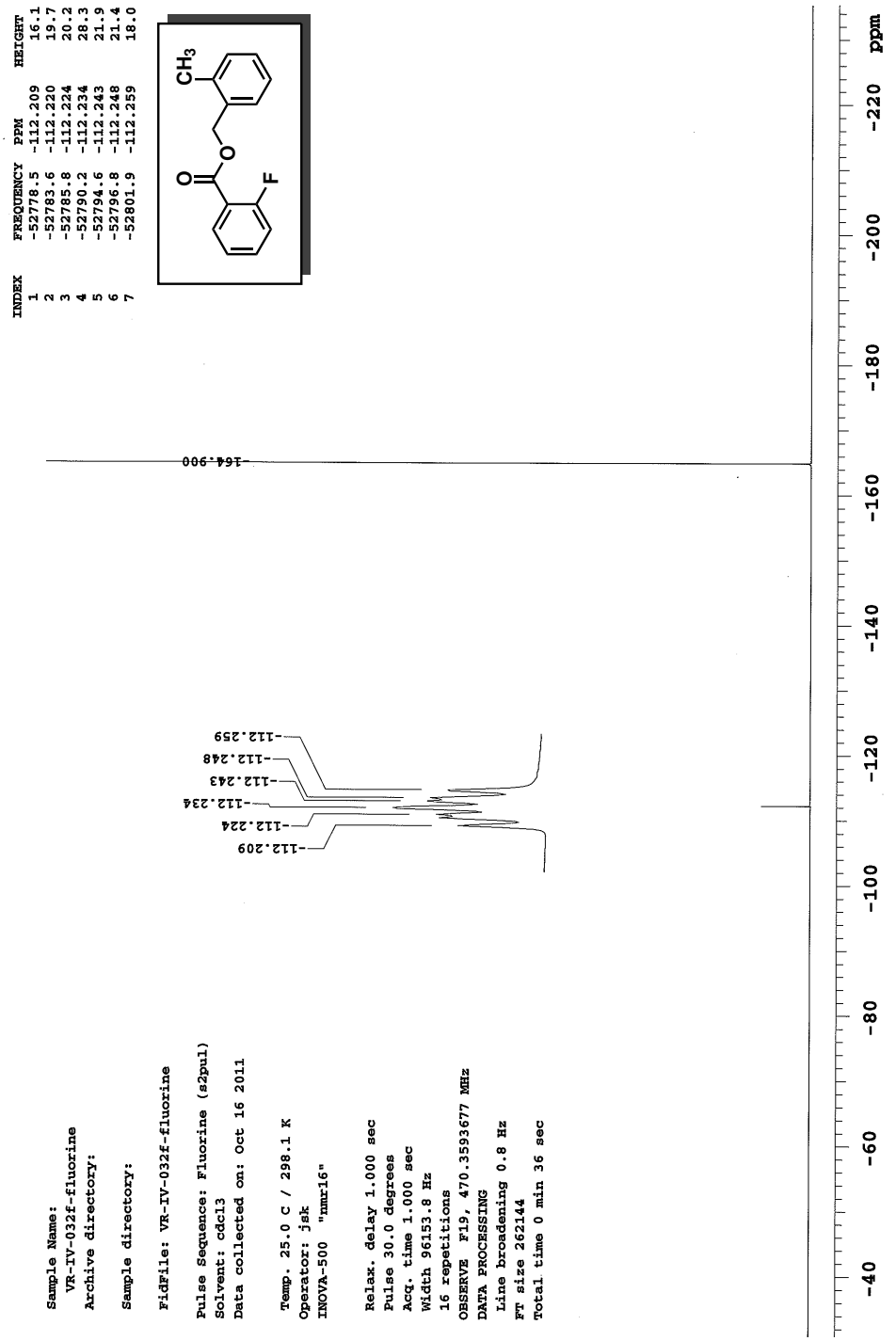


Figure 2.86: ^{1}H NMR of 2-bromobenzyl 2-fluorobenzoate (**2.122**)

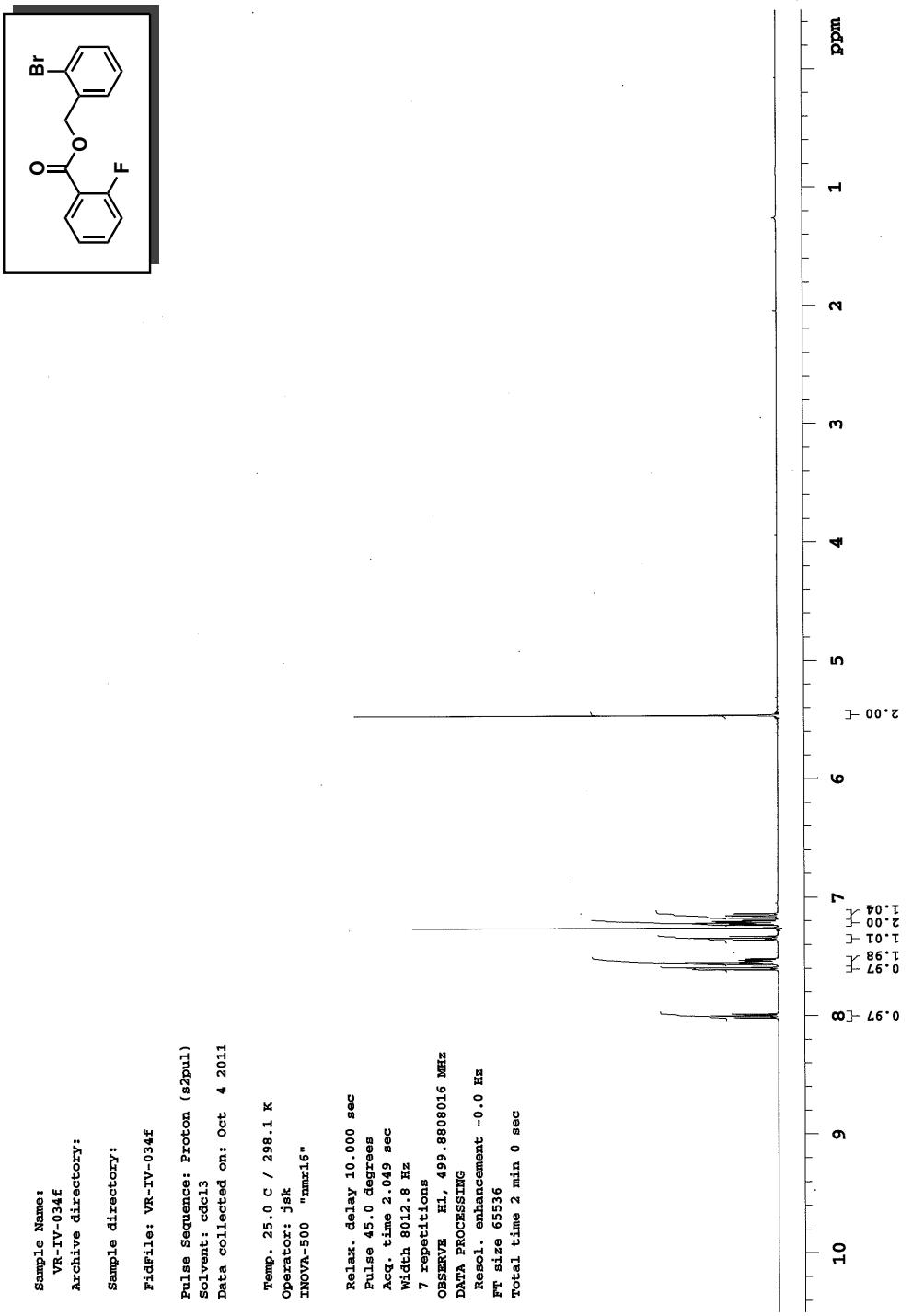


Figure 2.87: ^{13}C NMR of 2-bromobenzyl 2-fluorobenzoate (**2.122**)

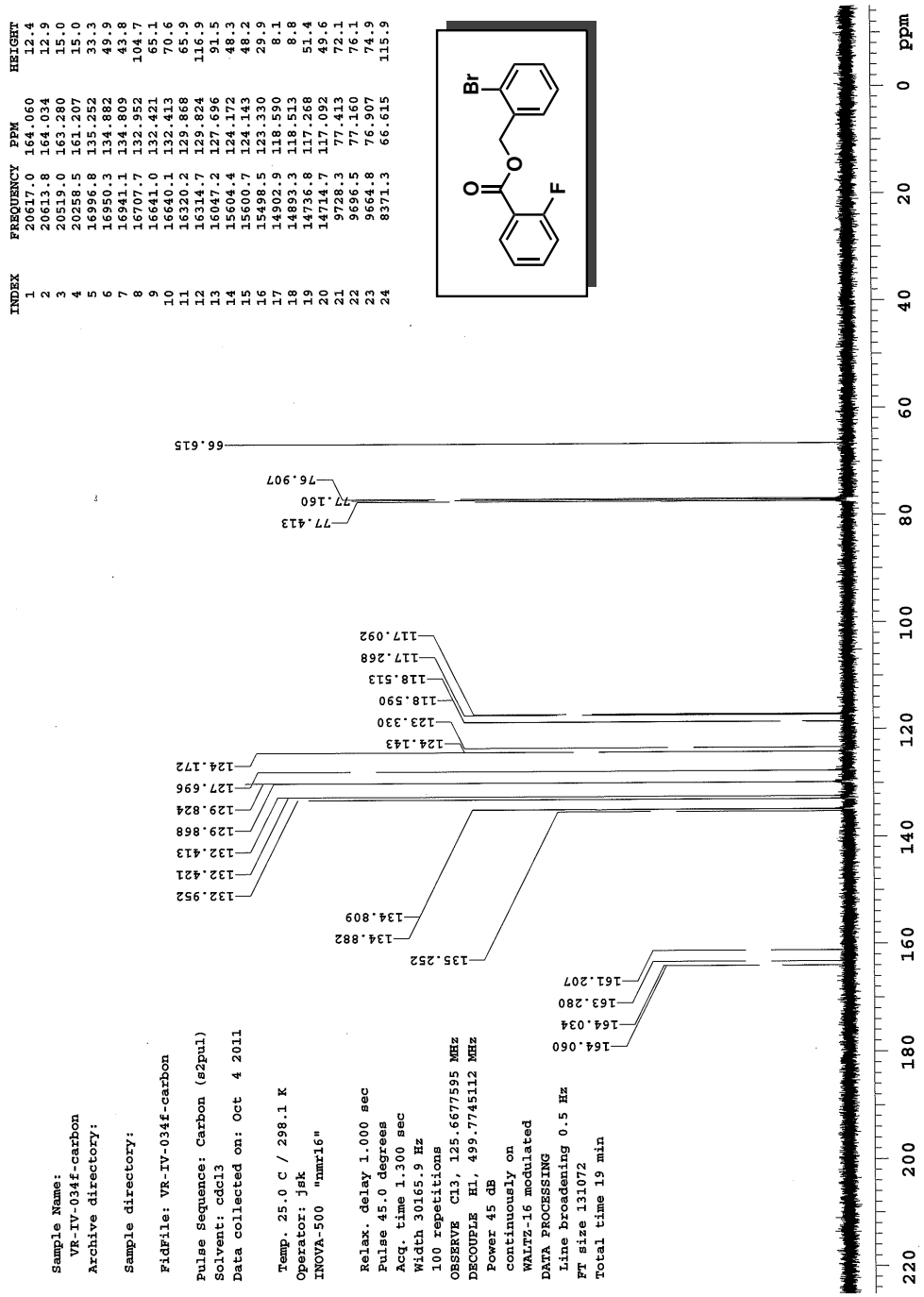


Figure 2.88: ^{19}F NMR of 2-bromobenzyl 2-fluorobenzoate (**2.122**)

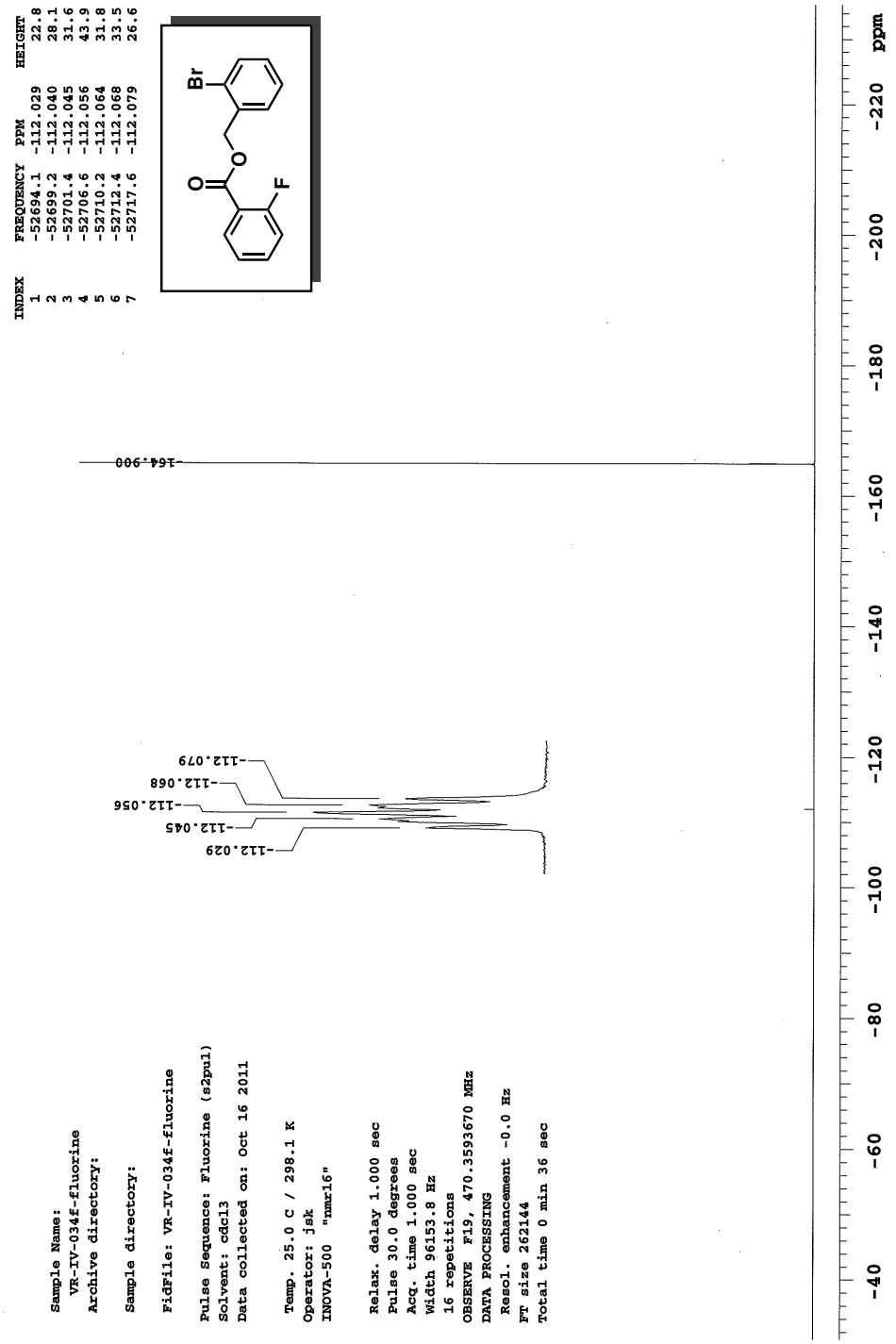


Figure 2.89: ^{1}H NMR of 4-methylbenzyl 2-fluorobenzoate (**2.123**)

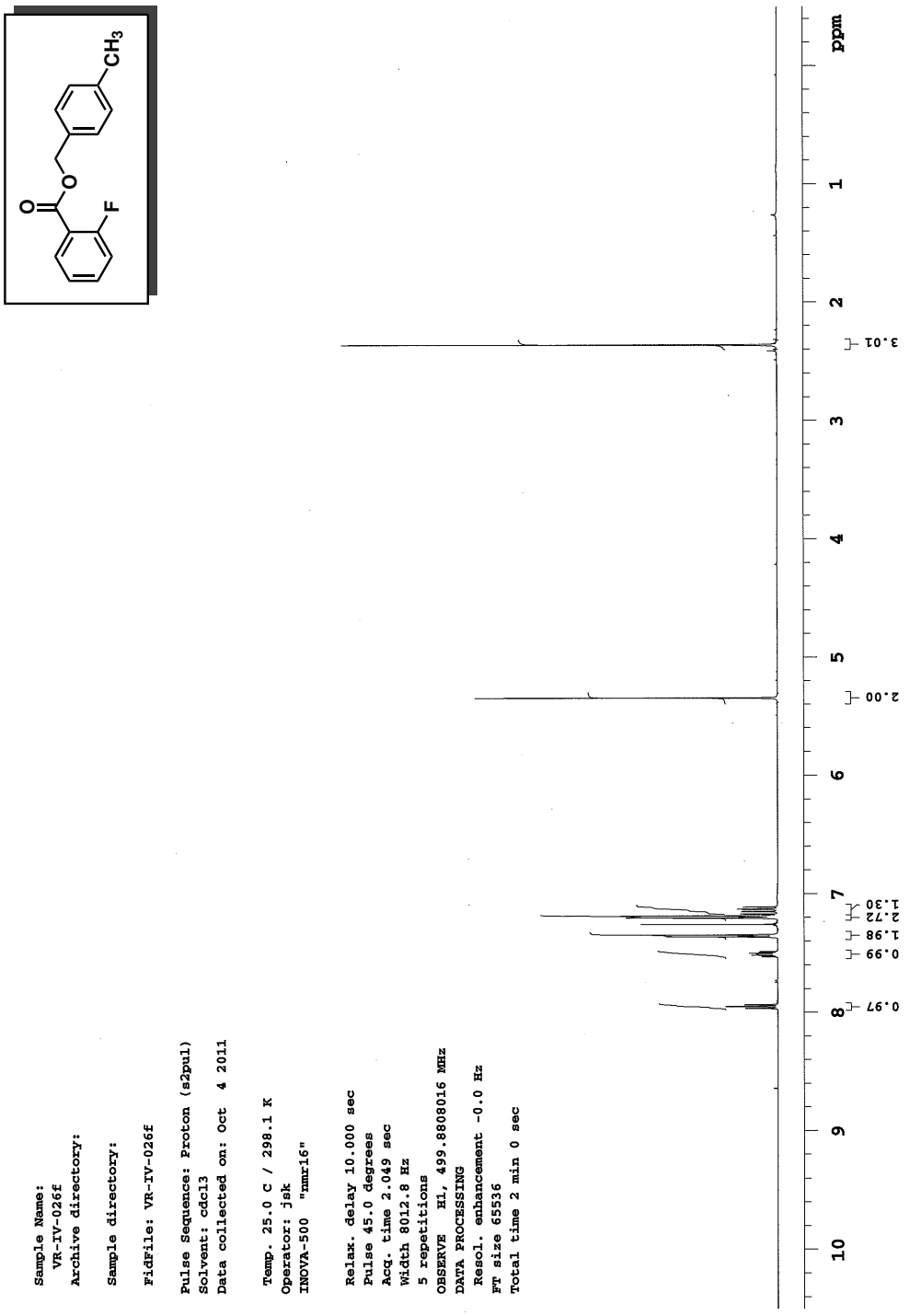


Figure 2.90: ^{13}C NMR of 4-methylbenzyl 2-fluorobenzoate (**2.123**)

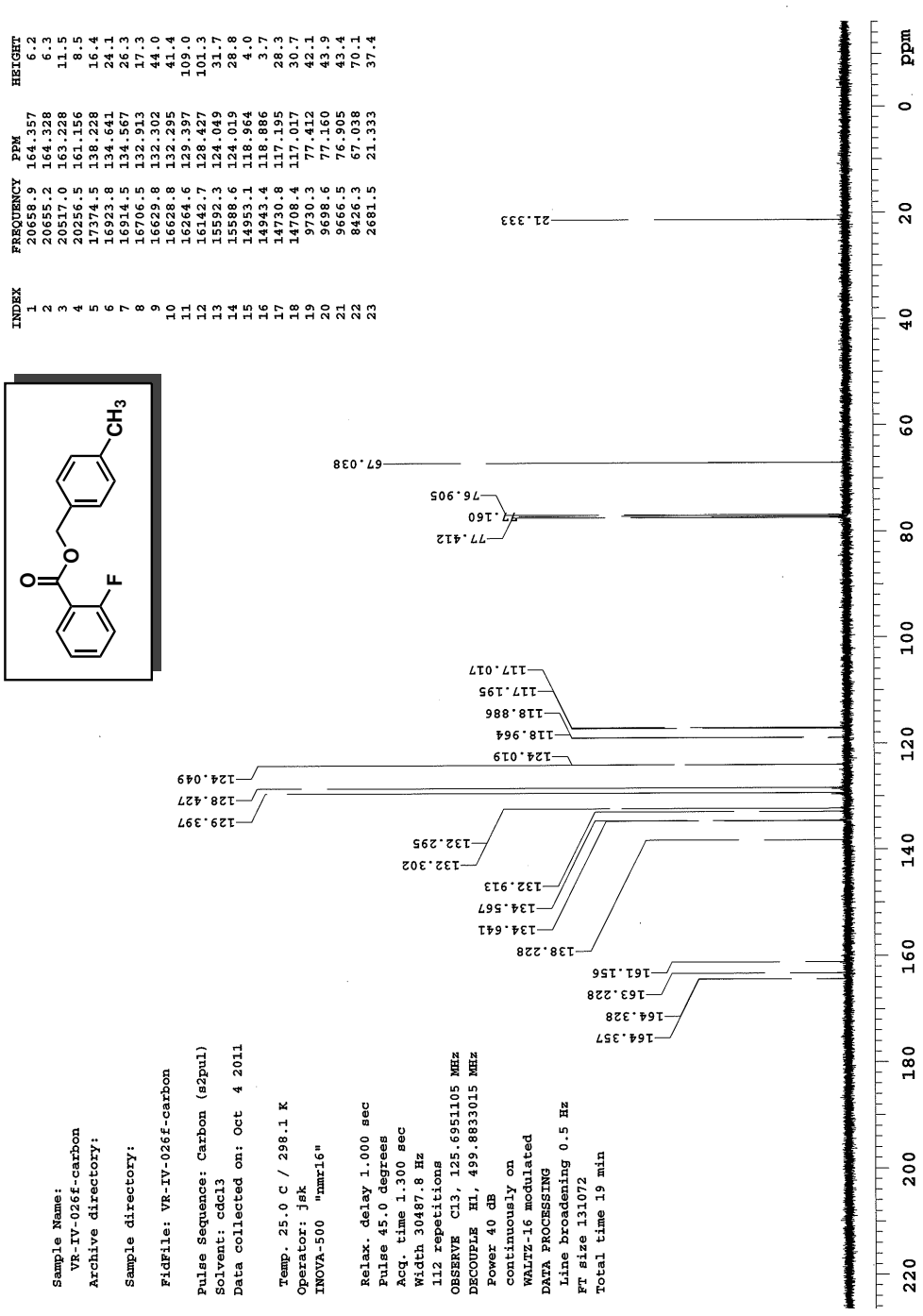


Figure 2.91: ^{19}F NMR of 4-methylbenzyl 2-fluorobenzoate (**2.123**)

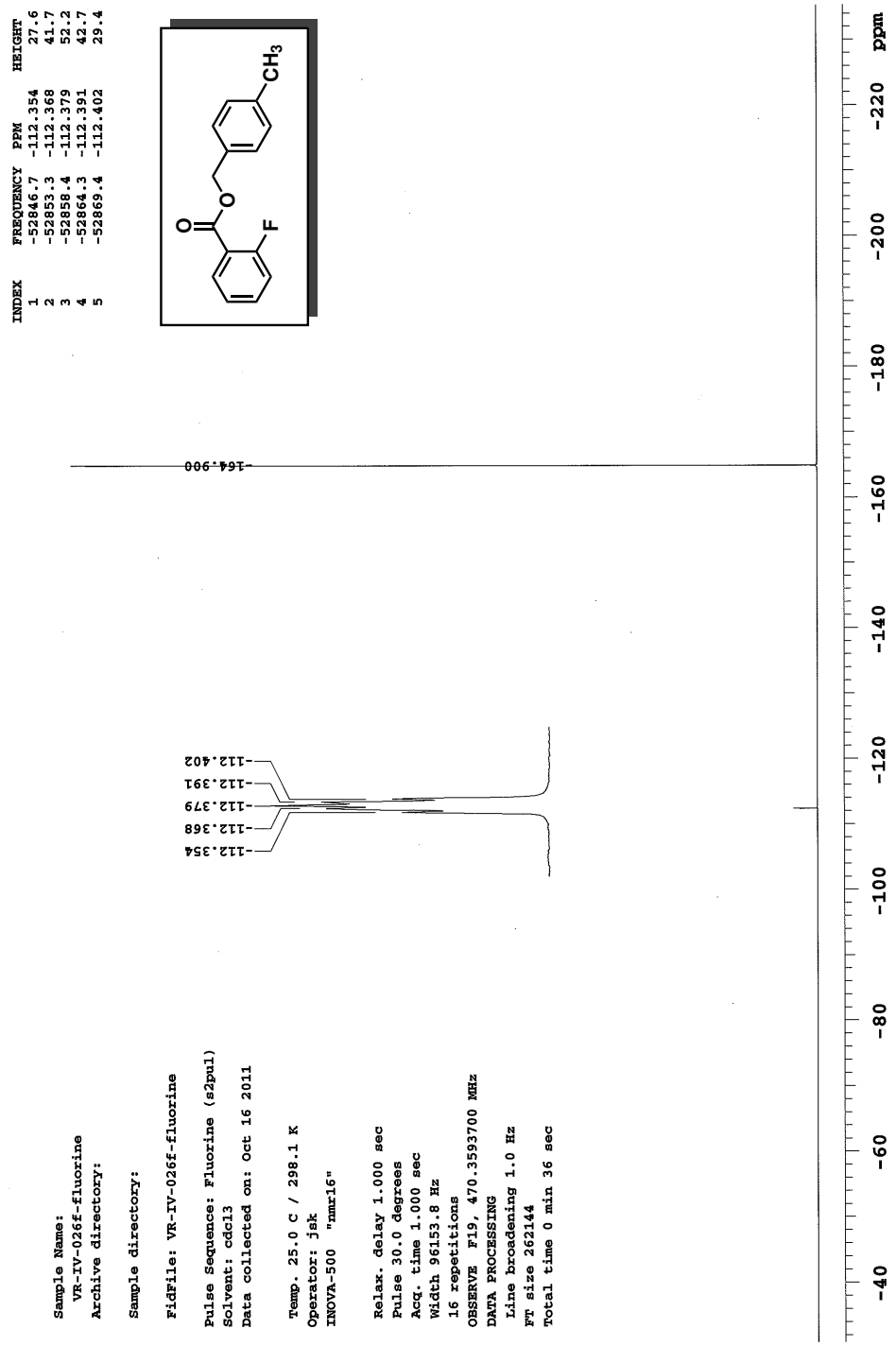


Figure 2.92: ^{1}H NMR of 4-(trifluoromethyl)benzyl 2-fluorobenzoate (**2.124**)

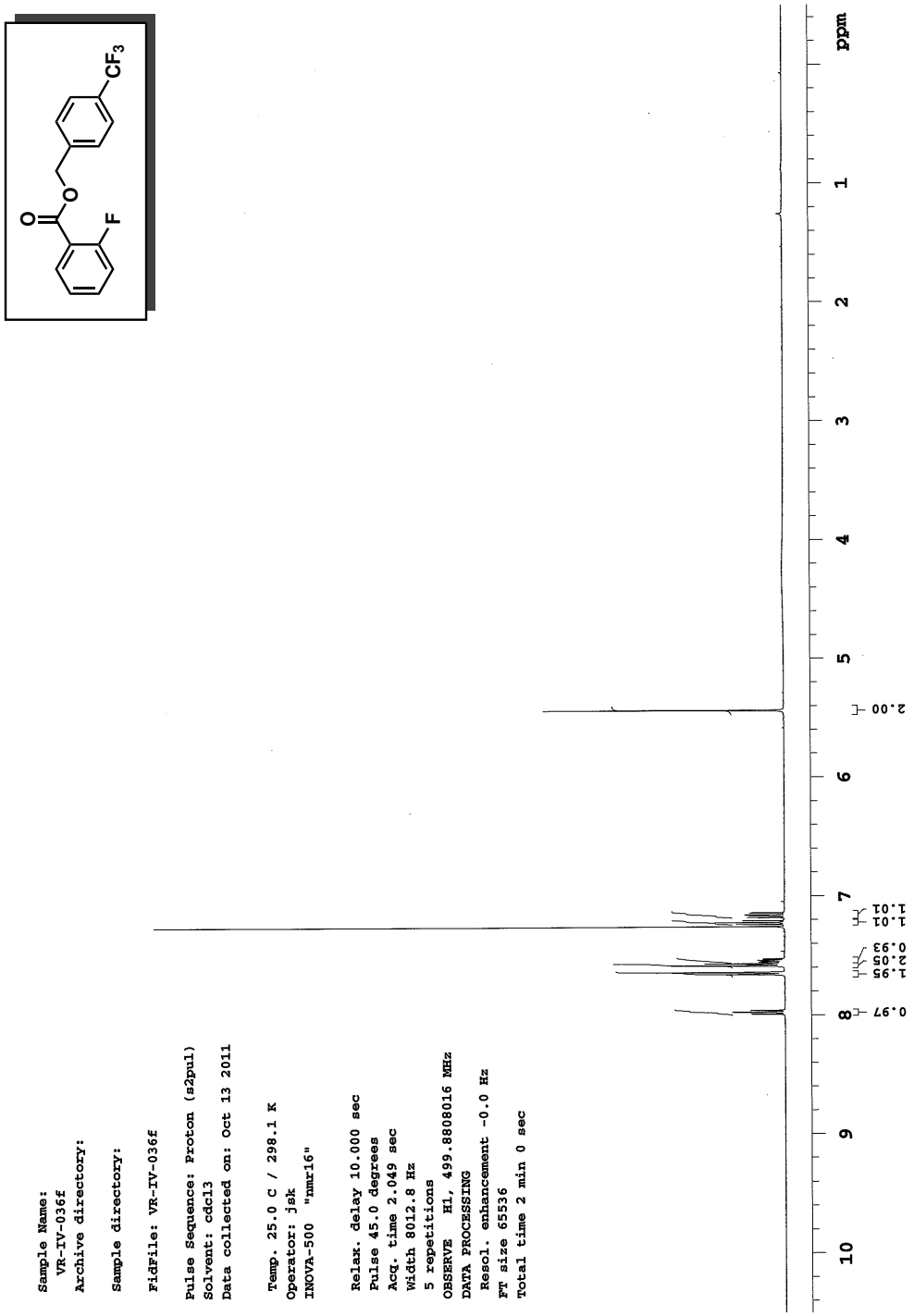


Figure 2.93: ^{13}C NMR of 4-(trifluoromethyl)benzyl 2-fluorobenzoate (**2.124**)

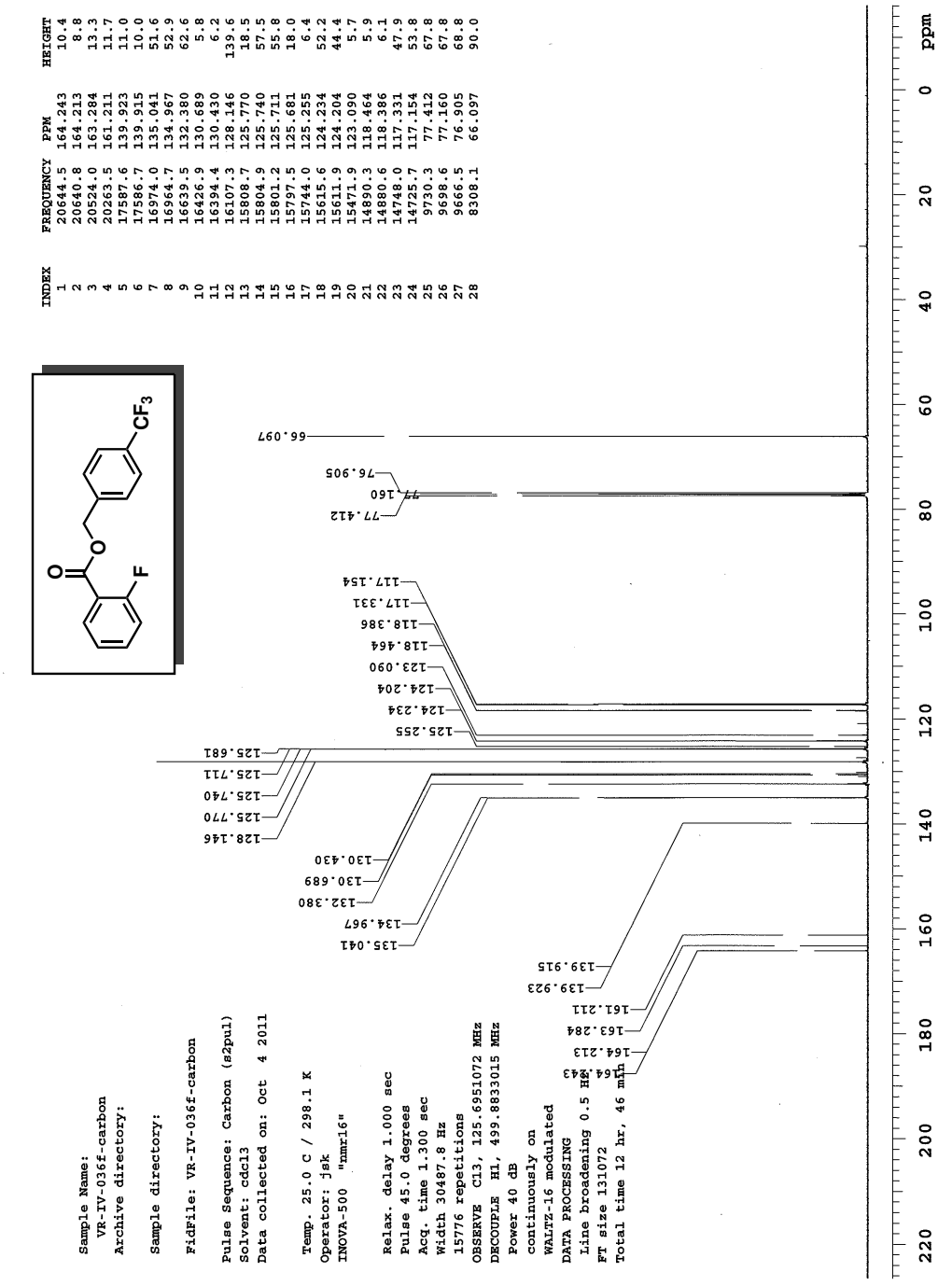


Figure 2.94: ^{19}F NMR of 4-(trifluoromethyl)benzyl 2-fluorobenzoate (**2.124**)

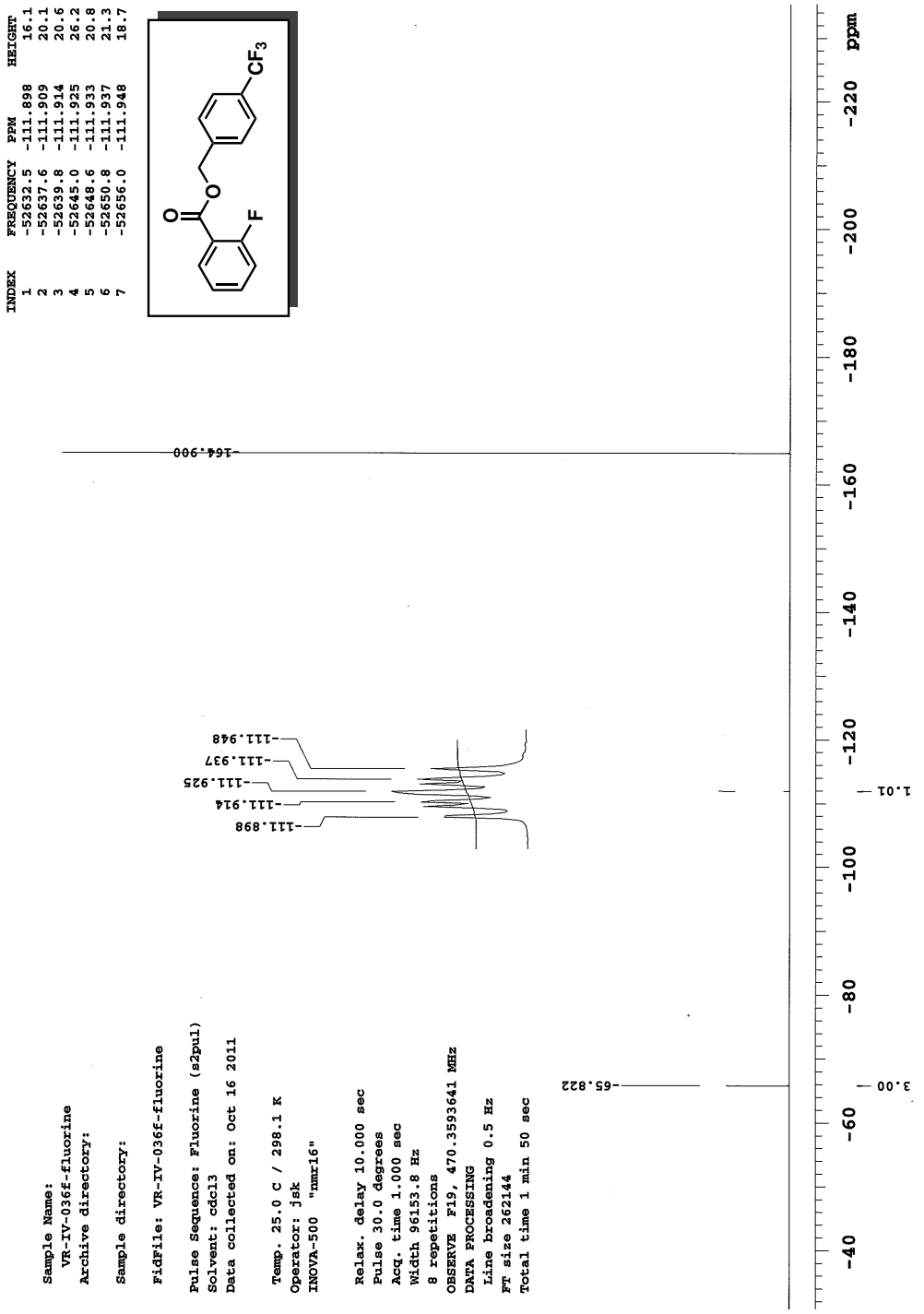


Figure 2.95: ^{1}H NMR of 3-methoxybenzyl 2-fluorobenzoate (**2.125**)

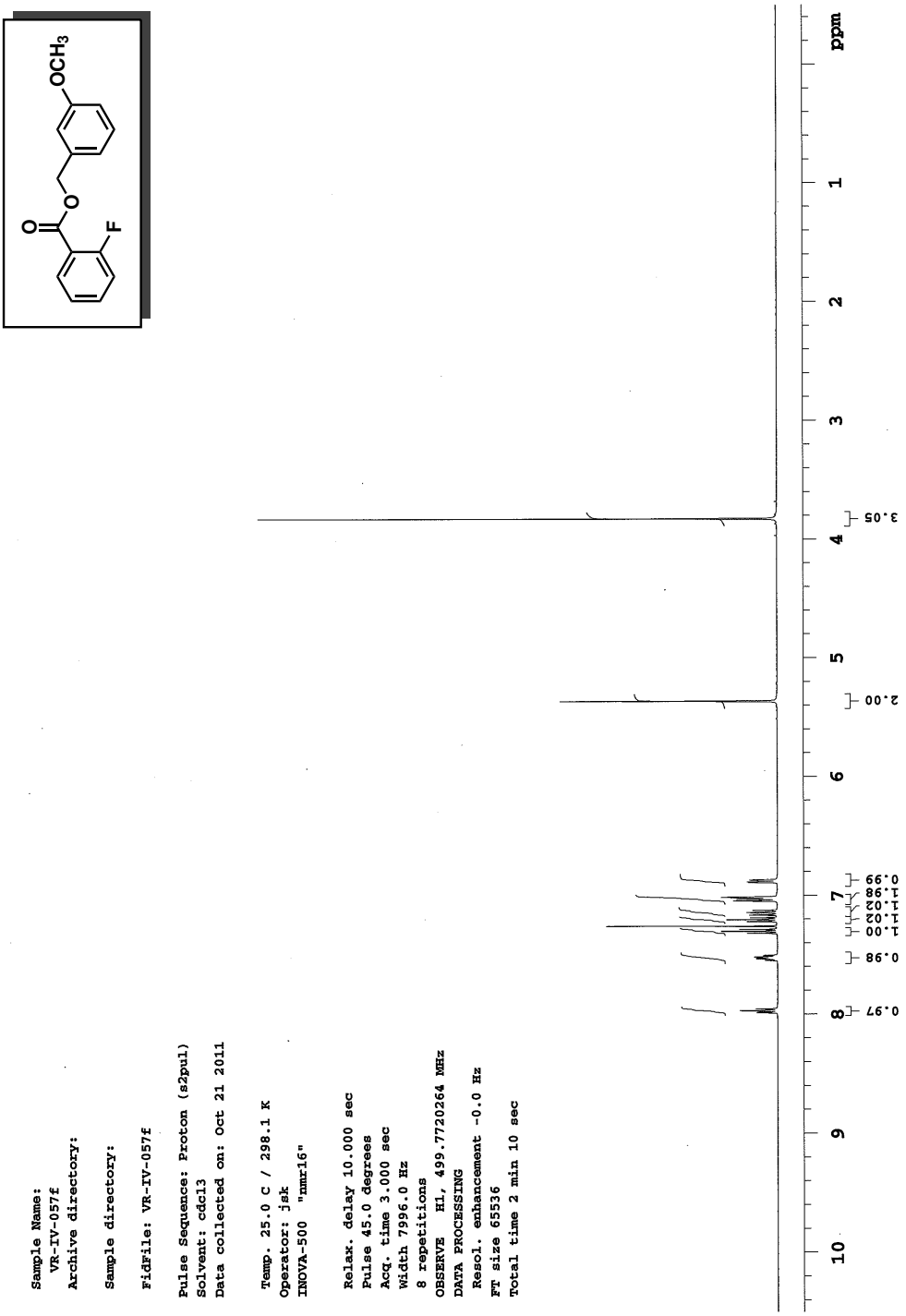


Figure 2.96: ^{13}C NMR of 3-methoxybenzyl 2-fluorobenzoate (**2.125**)

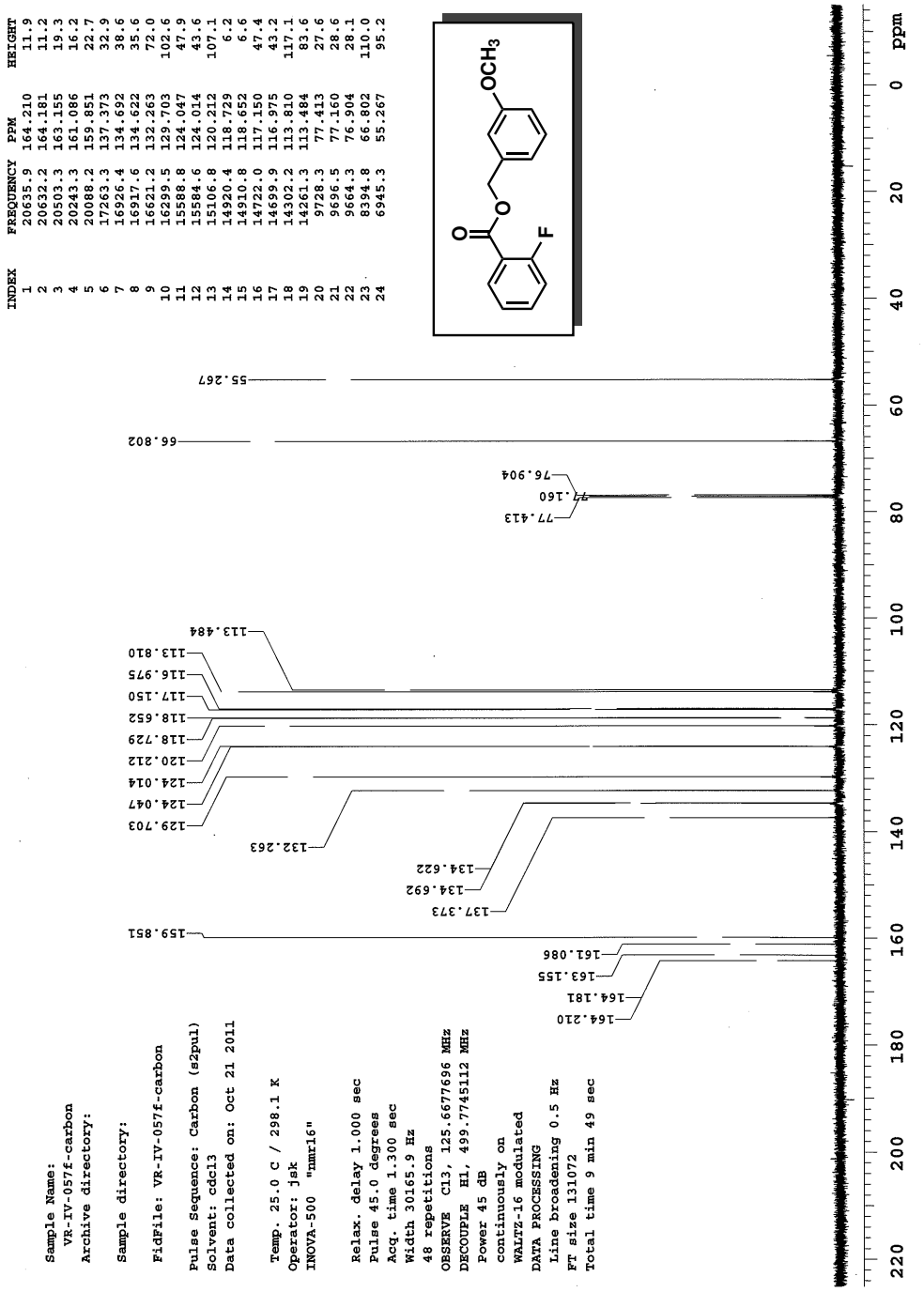


Figure 2.97: ^{19}F NMR of 3-methoxybenzyl 2-fluorobenzoate (**2.125**)

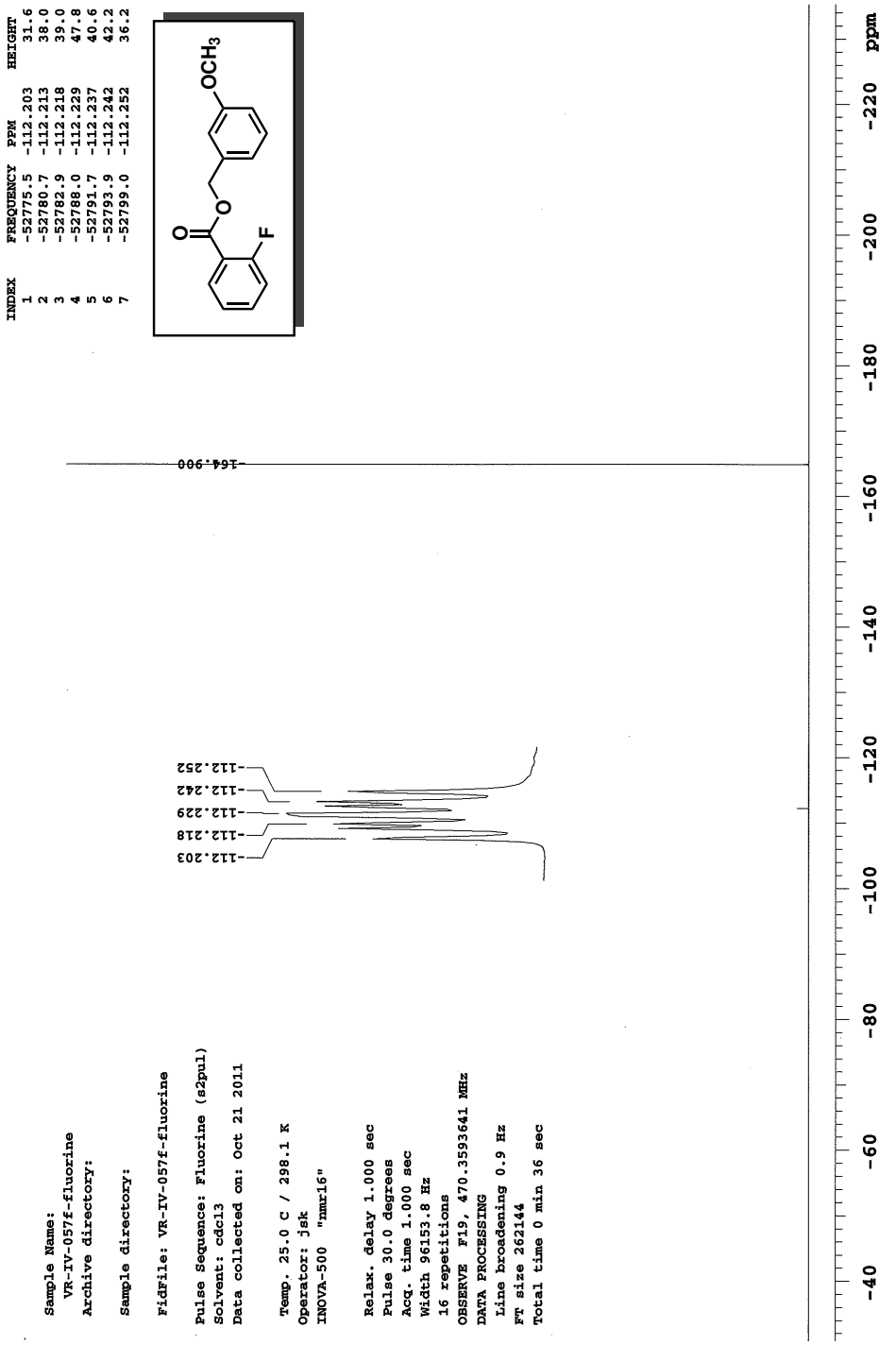


Figure 2.98: ^{1}H NMR of 3-bromobenzyl 2-fluorobenzoate (**2.126**)

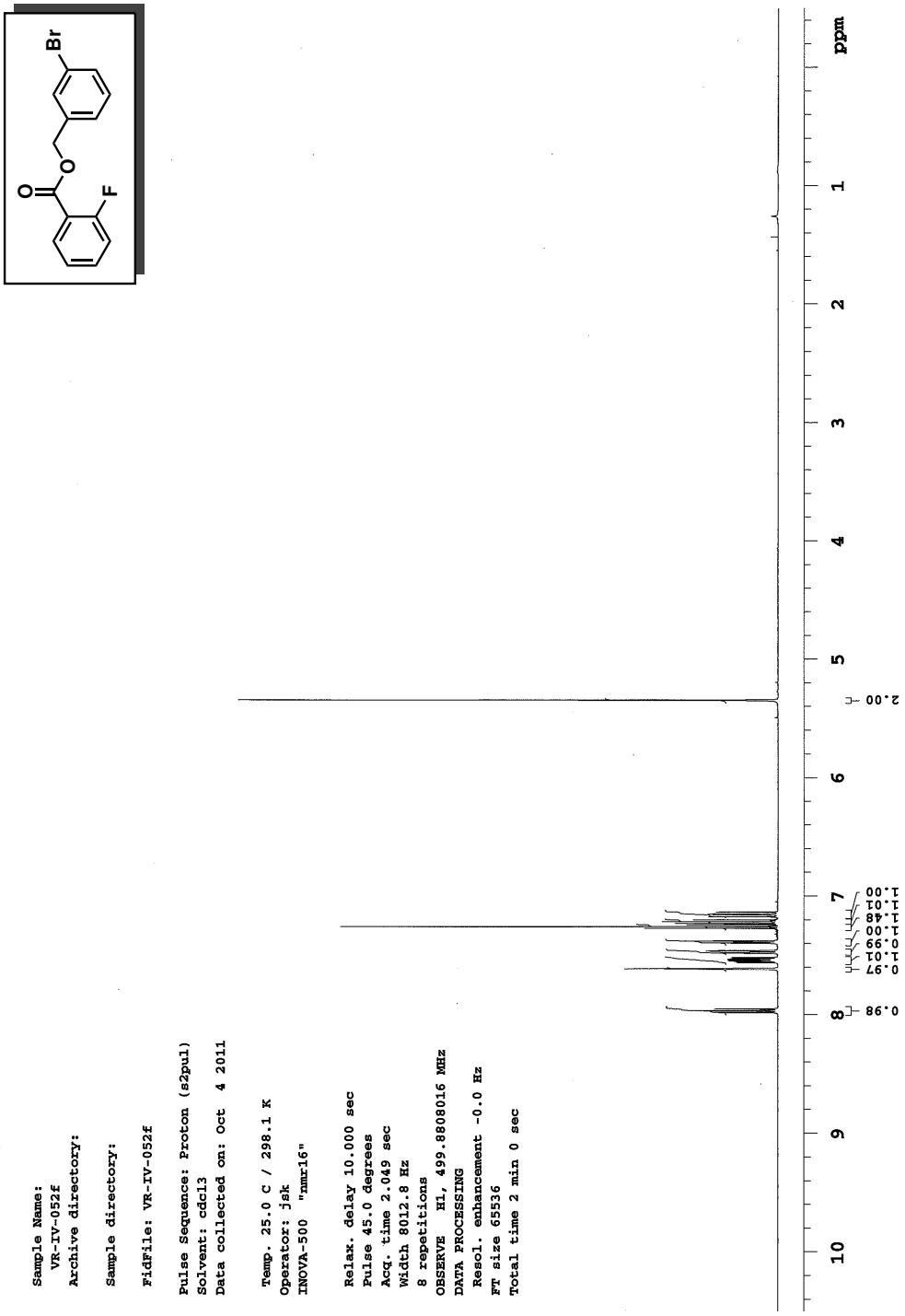


Figure 2.99: ^{13}C NMR of 3-bromobenzyl 2-fluorobenzoate (**2.126**)

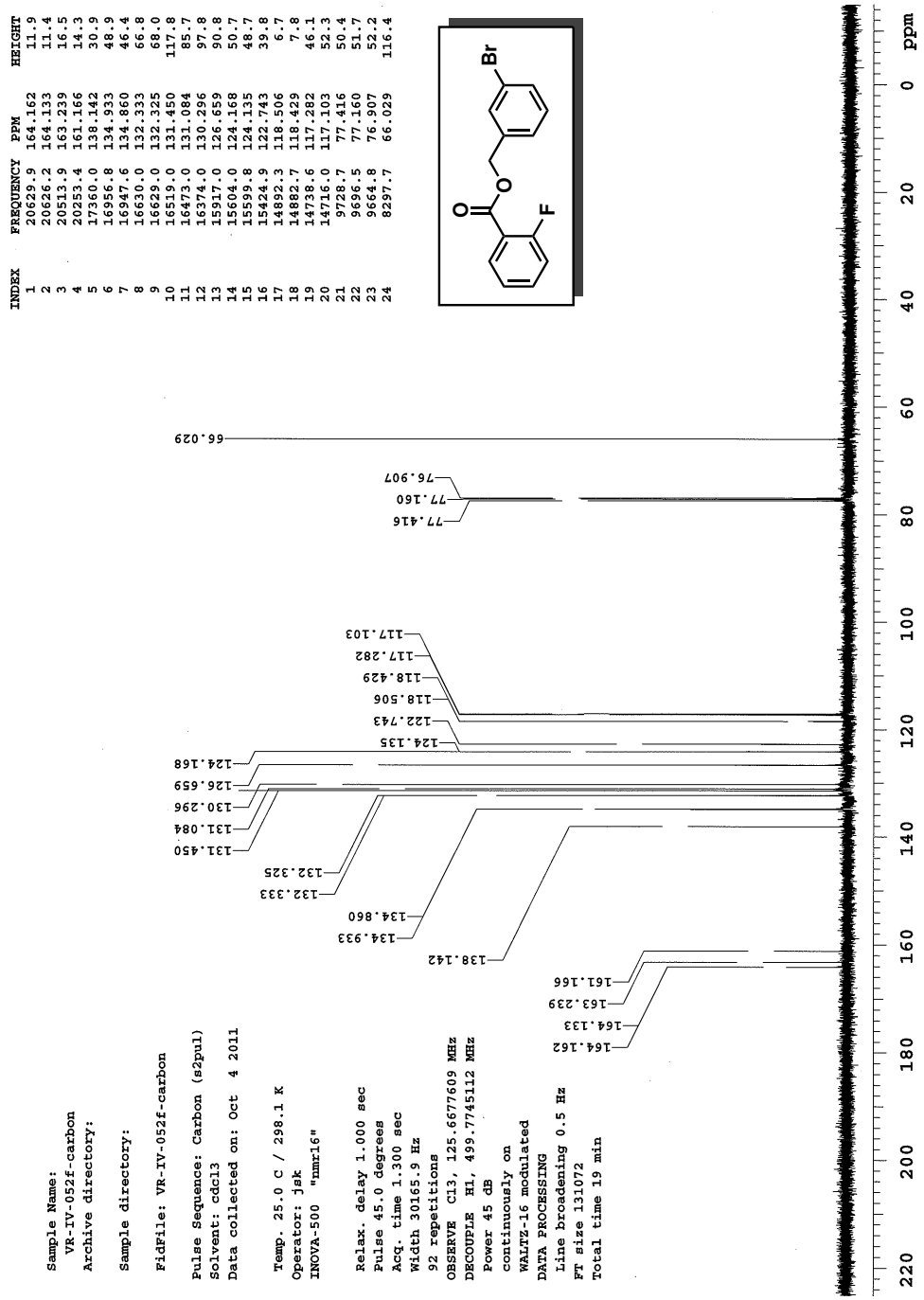


Figure 2.100: ^{19}F NMR of 3-bromobenzyl 2-fluorobenzoate (**2.126**)

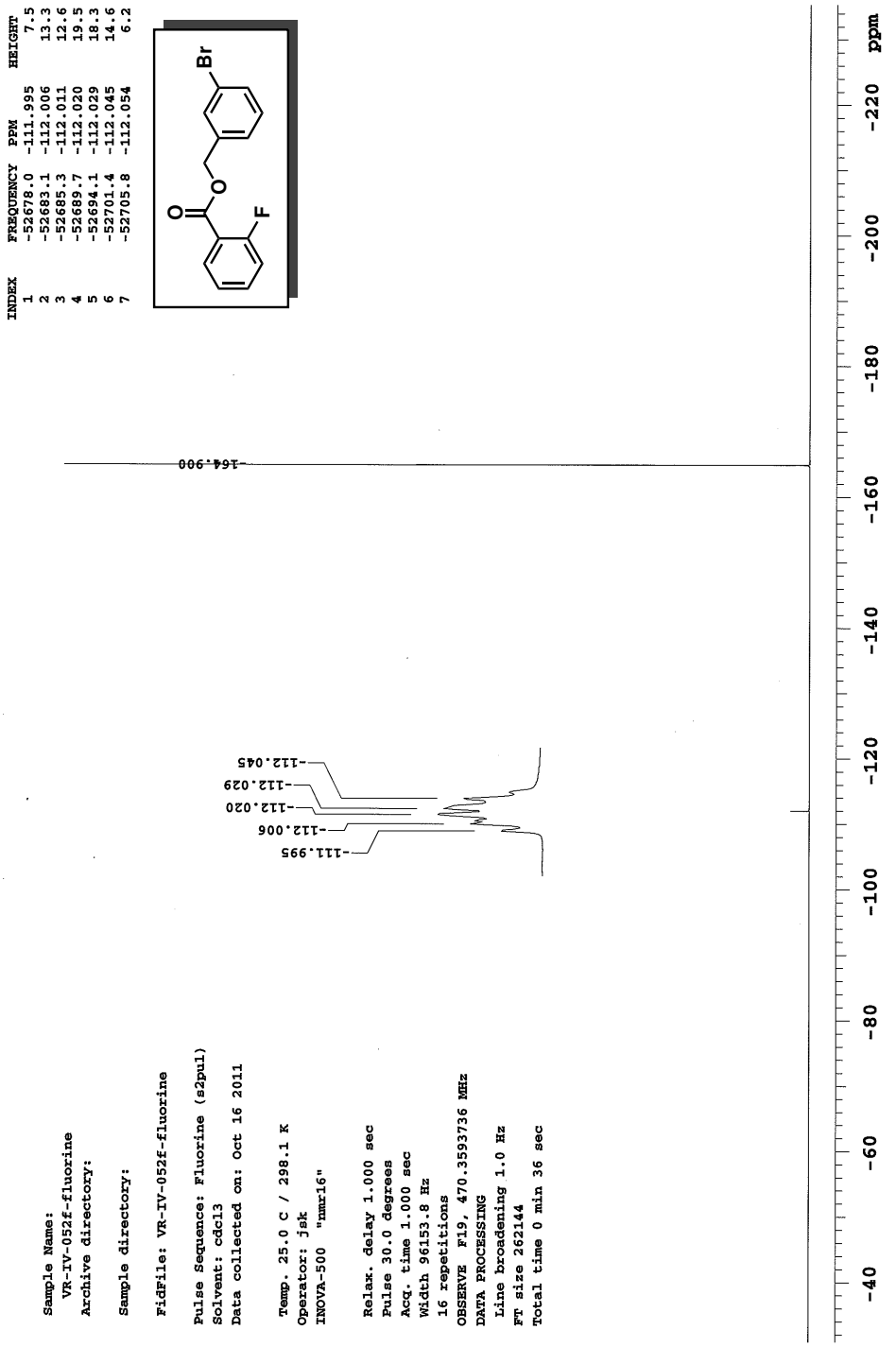


Figure 2.101: ^{1}H NMR of naphthalen-1-ylmethyl 2-fluorobenzoate (**2.127**)

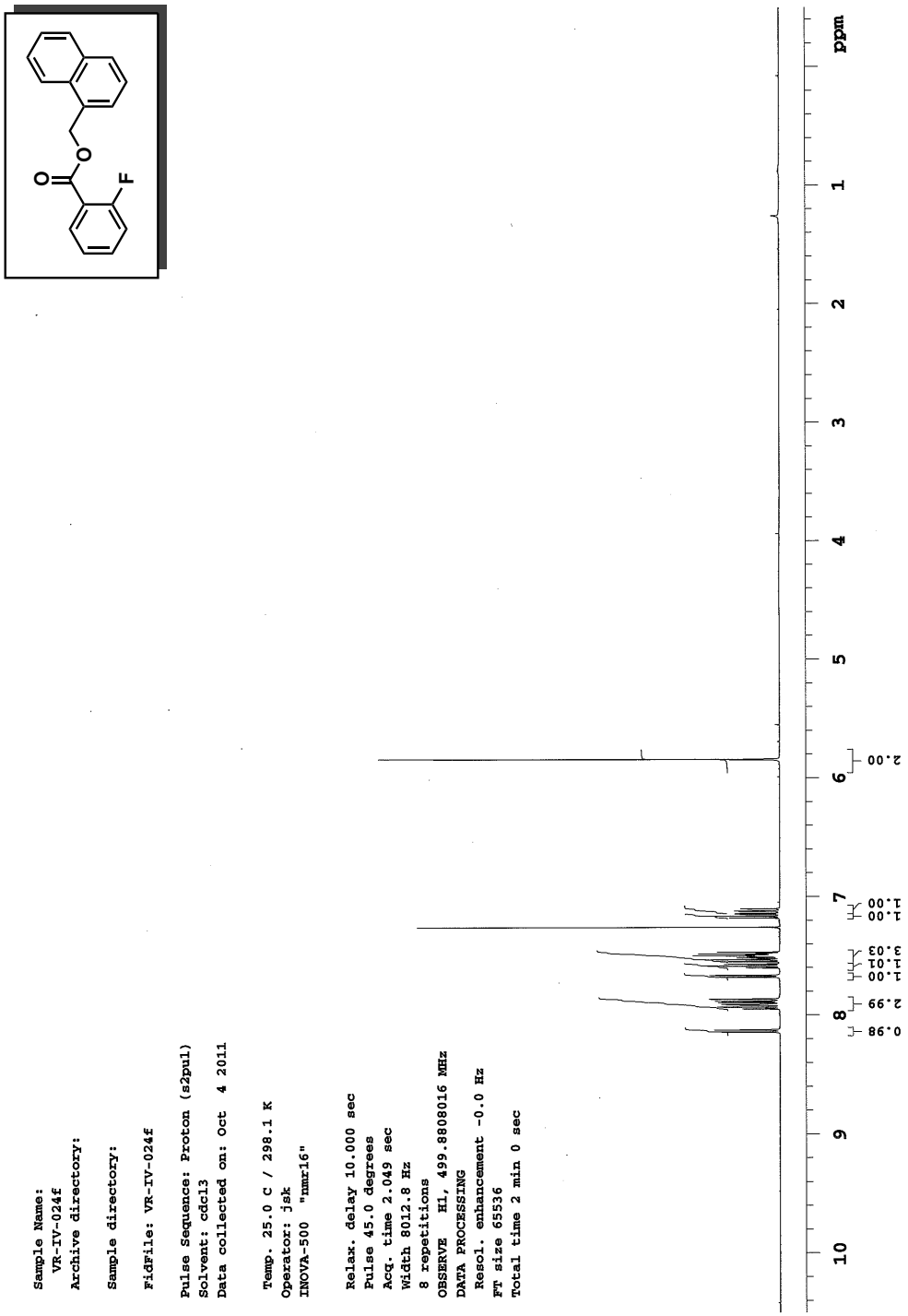


Figure 2.102: ^{13}C NMR of naphthalen-1-ylmethyl 2-fluorobenzoate (**2.127**)

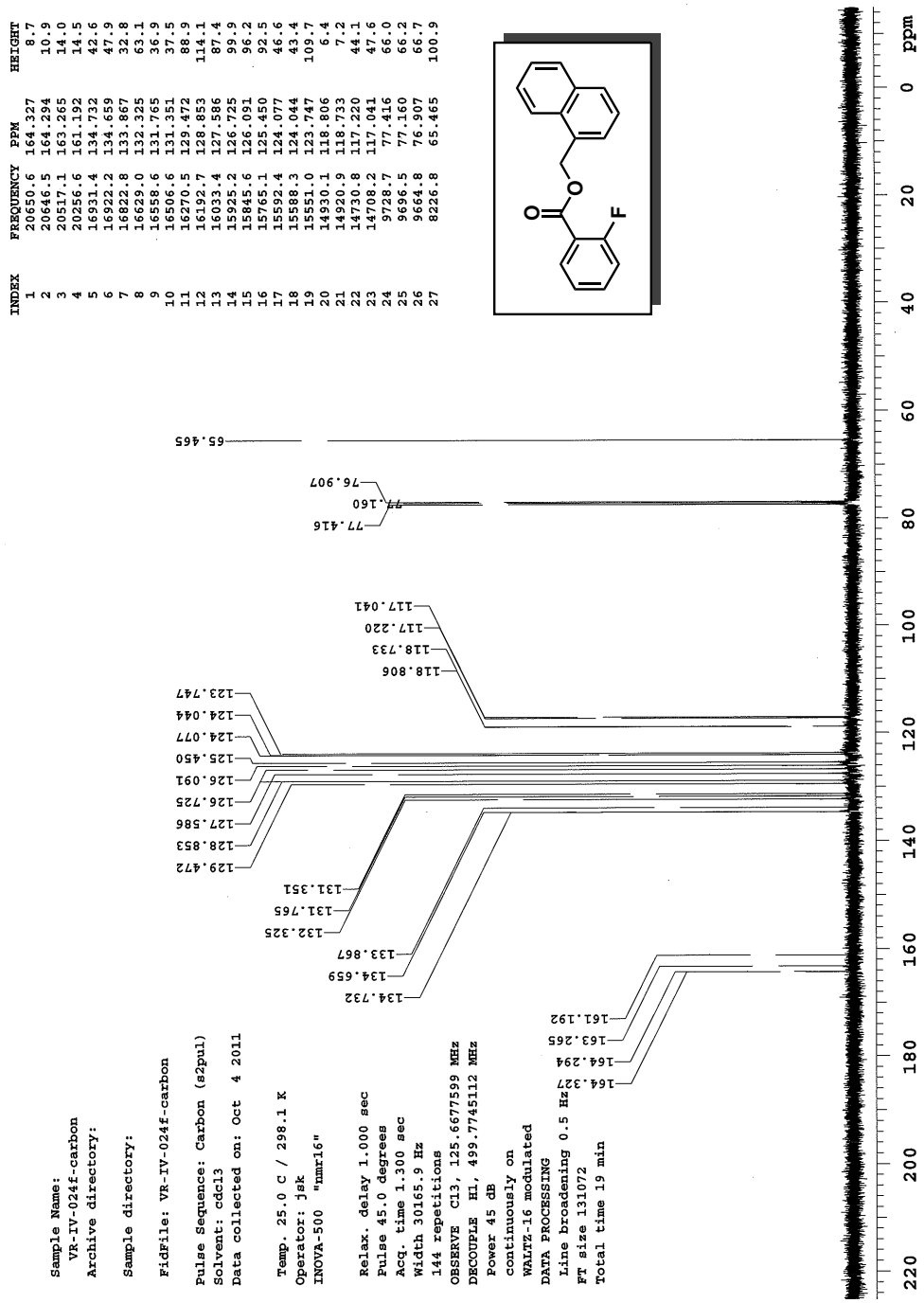


Figure 2.103: ^{19}F NMR of naphthalen-1-ylmethyl 2-fluorobenzoate (**2.127**)

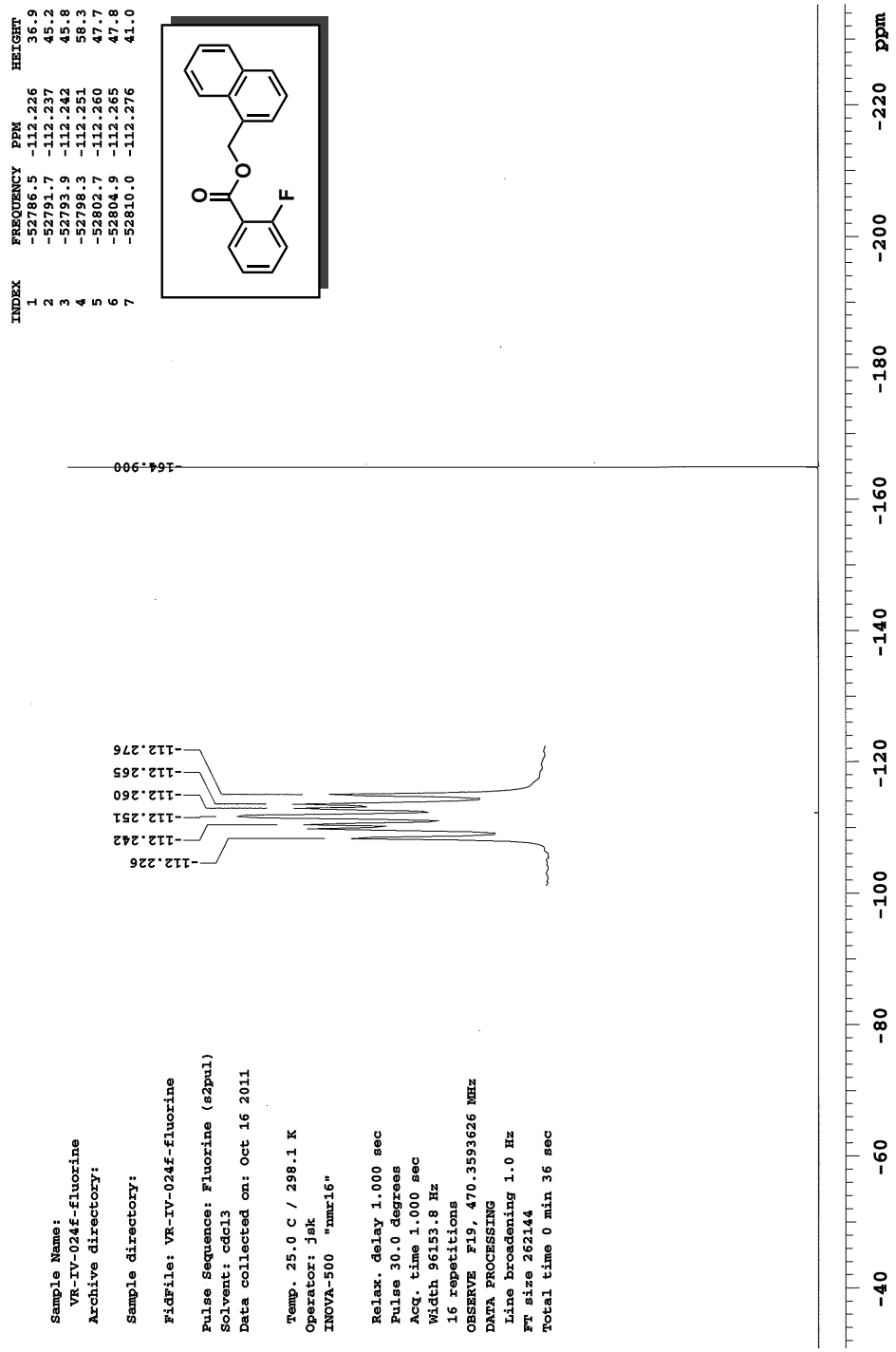


Figure 2.104: ^{1}H NMR of 1-phenylethyl 2-fluorobenzoate (**2.128**)

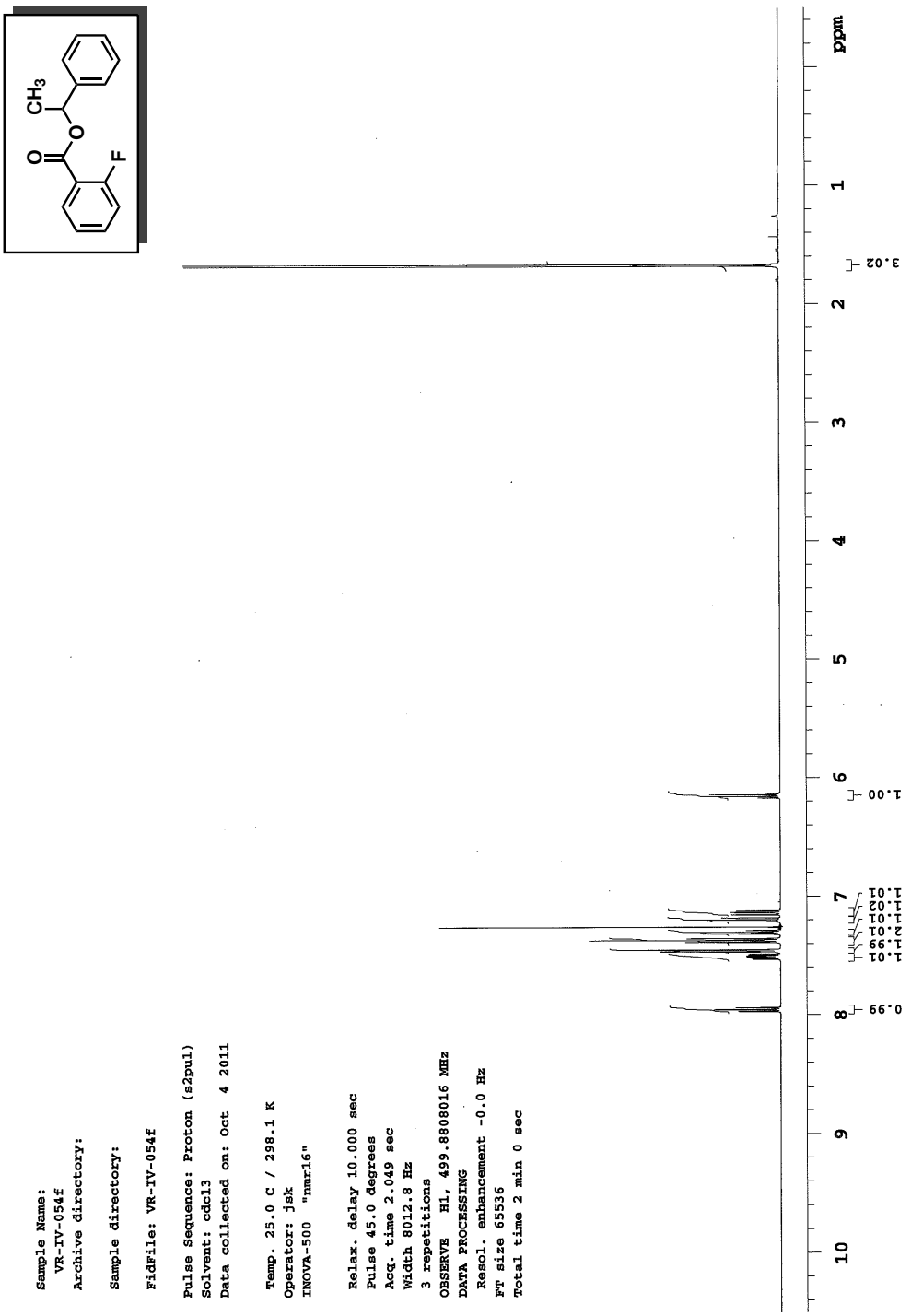


Figure 2.105: ^{13}C NMR of 1-phenylethyl 2-fluorobenzoate (**2.128**)

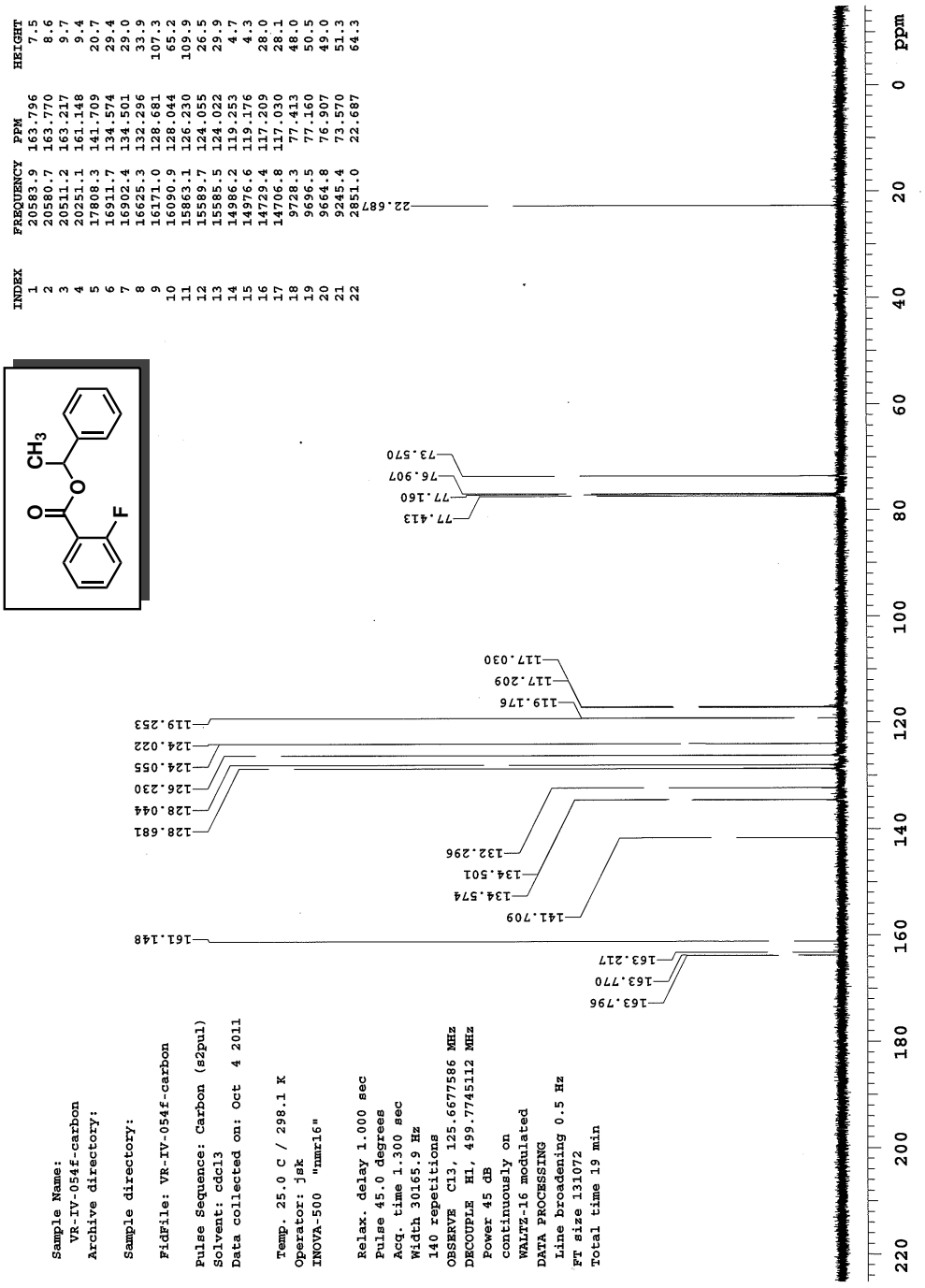


Figure 2.106: ^{19}F NMR of 1-phenylethyl 2-fluorobenzoate (**2.128**)

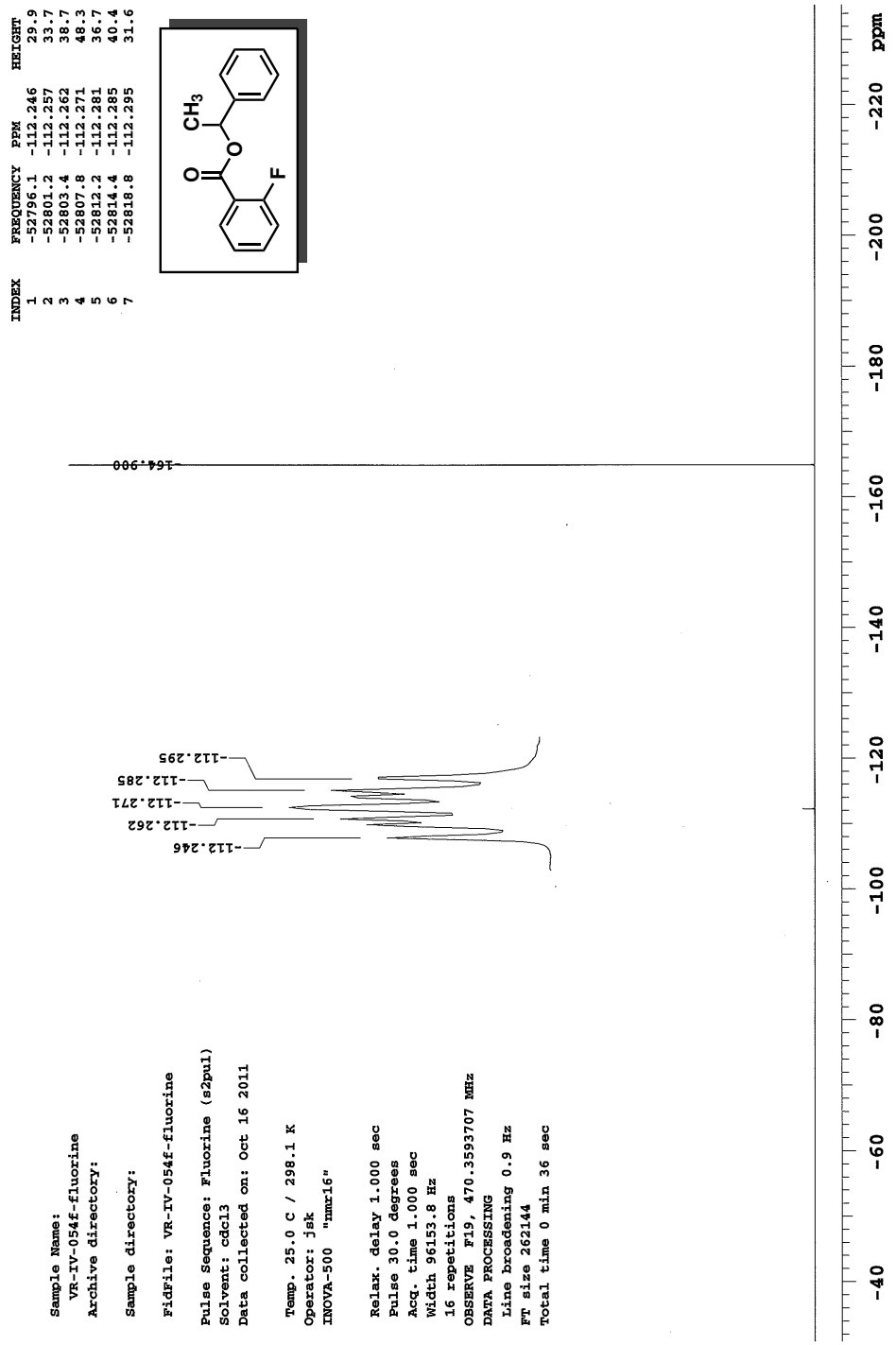


Figure 2.107: ^{1}H NMR of furan-2-ylmethyl 2-fluorobenzoate (**2.129**)

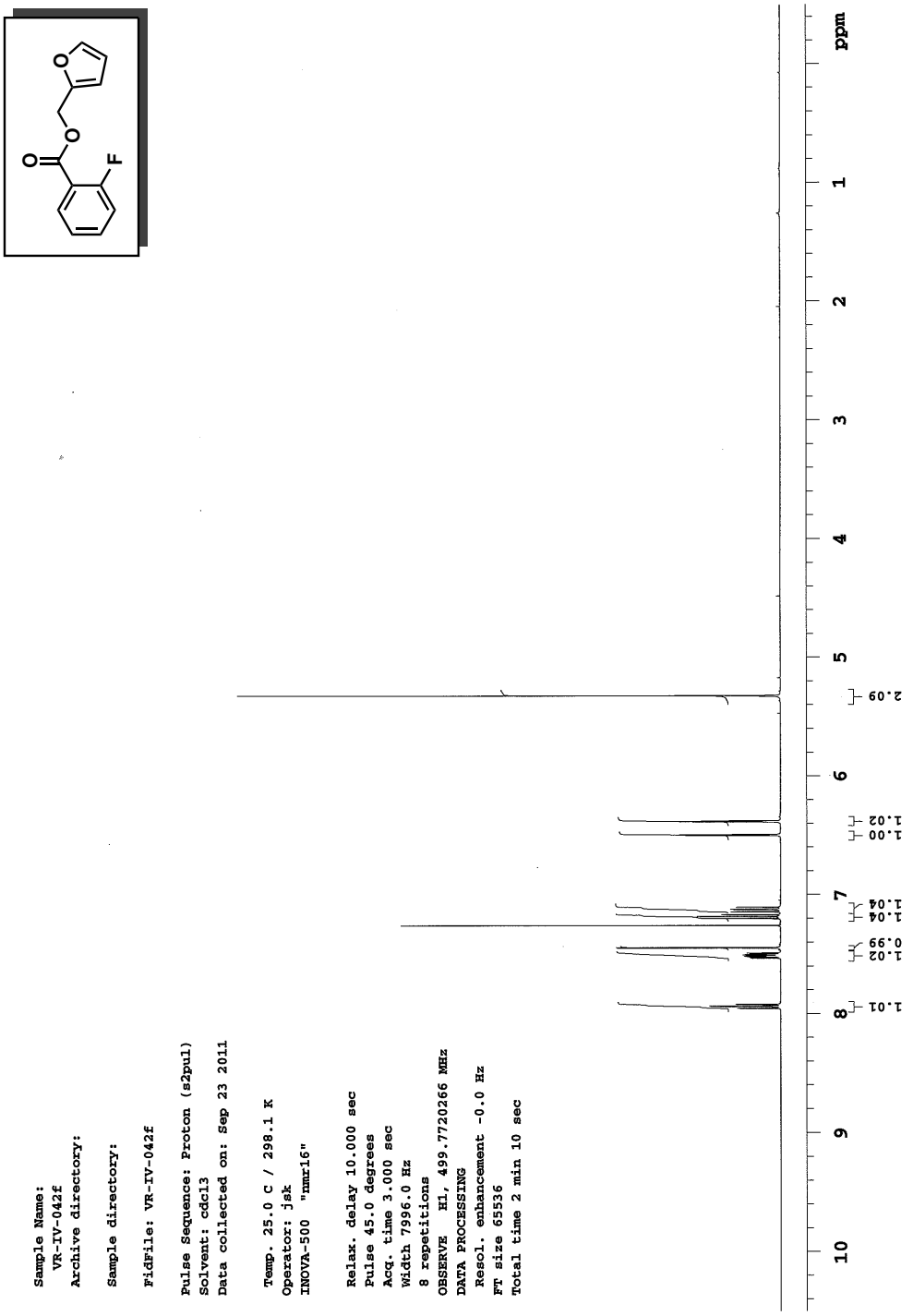


Figure 2.108: ^{13}C NMR of furan-2-ylmethyl 2-fluorobenzoate (**2.129**)

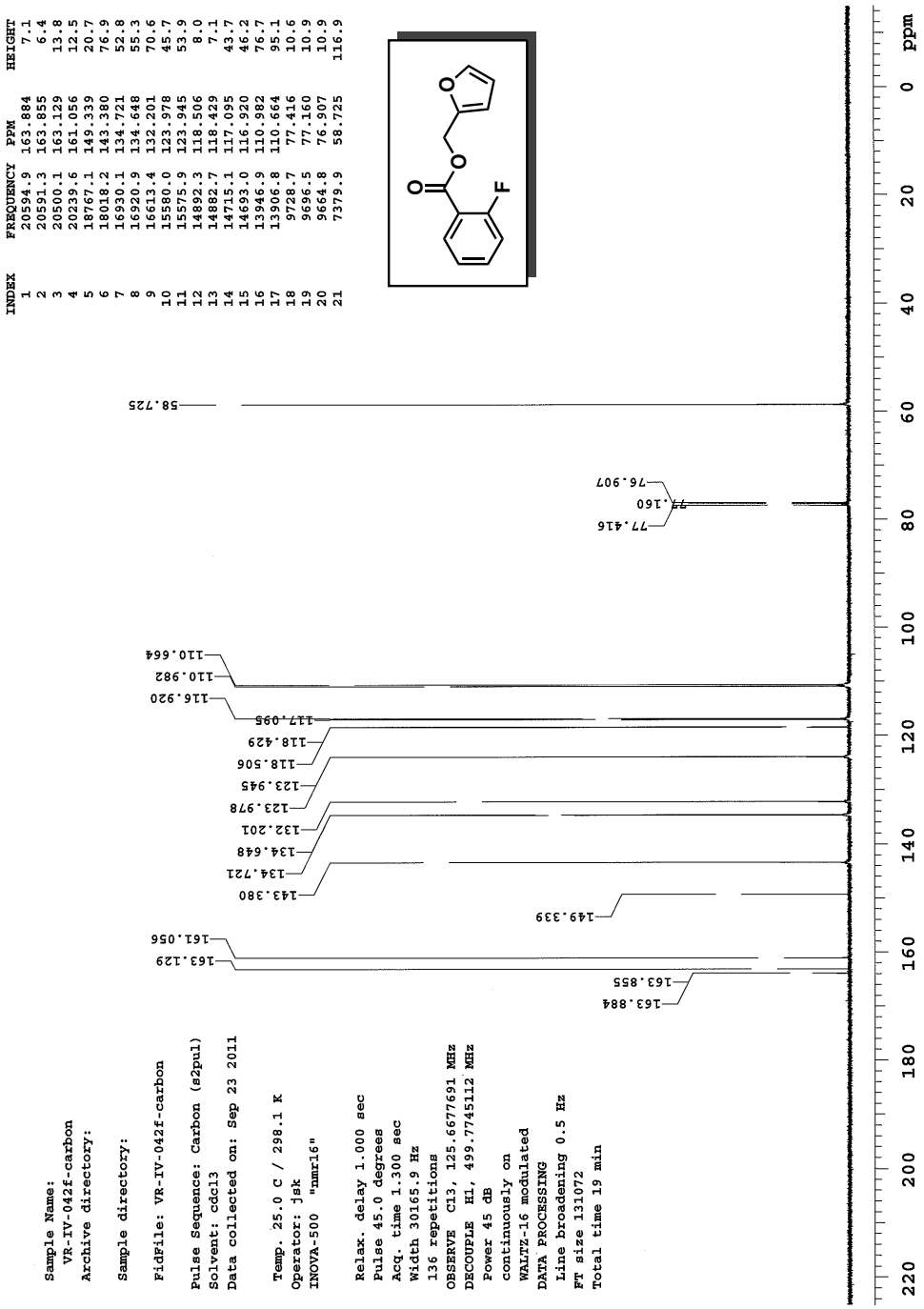


Figure 2.109: ^{19}F NMR of furan-2-ylmethyl 2-fluorobenzoate (**2.129**)

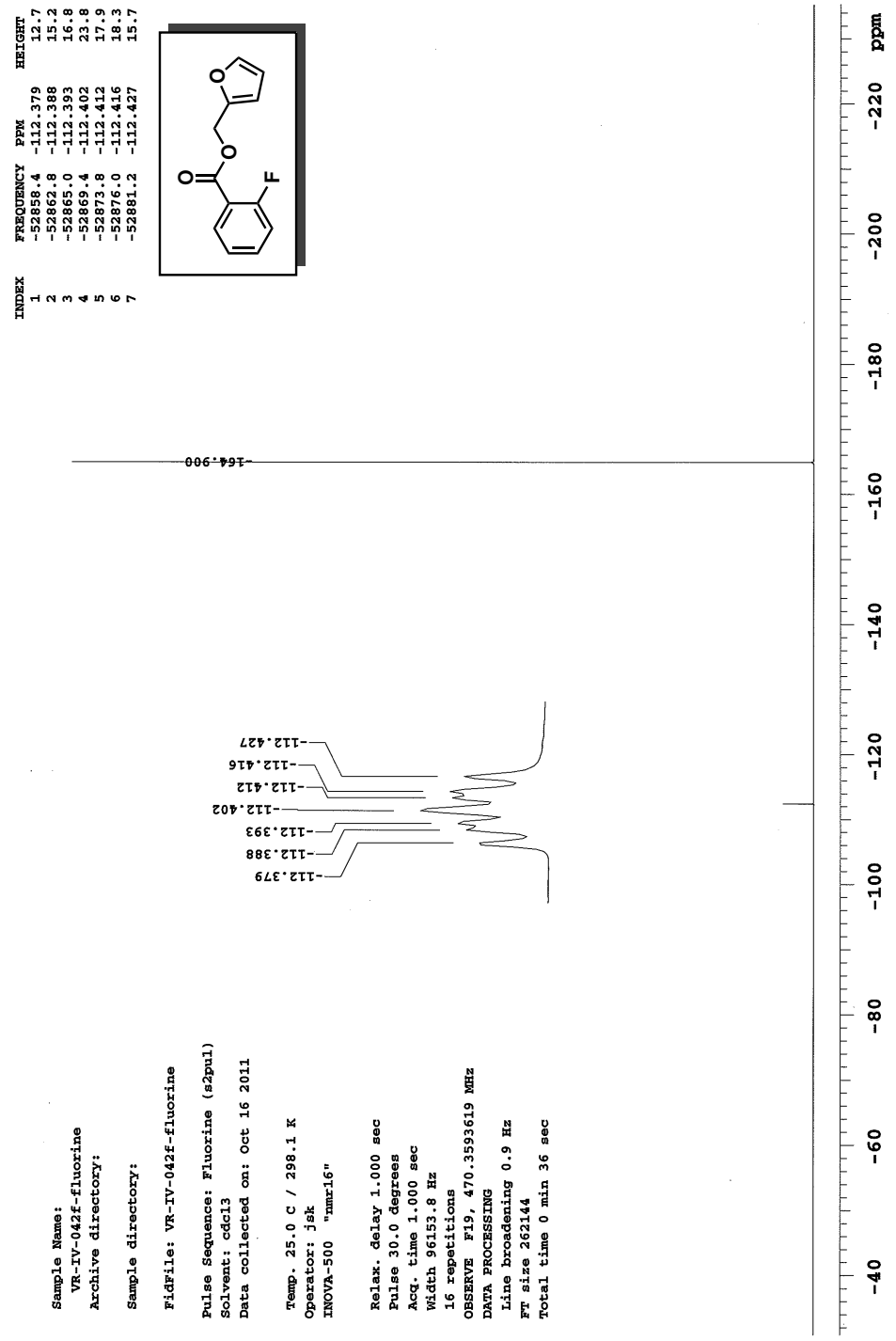


Figure 2.110: ^{1}H NMR of 2-bromobenzyl benzoate (**2.130**)

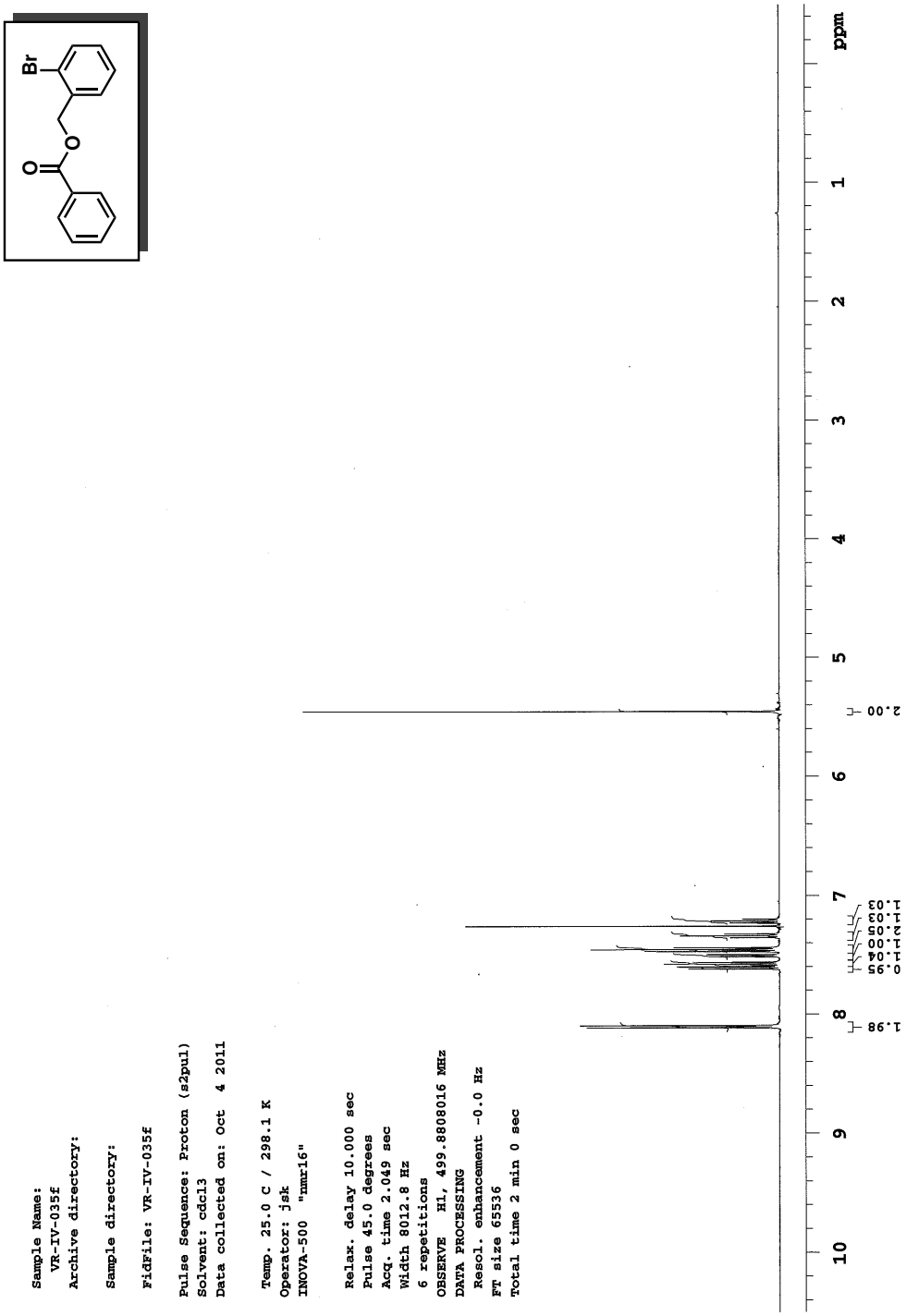


Figure 2.111: ^{13}C NMR of 2-bromobenzyl benzoate (**2.130**)

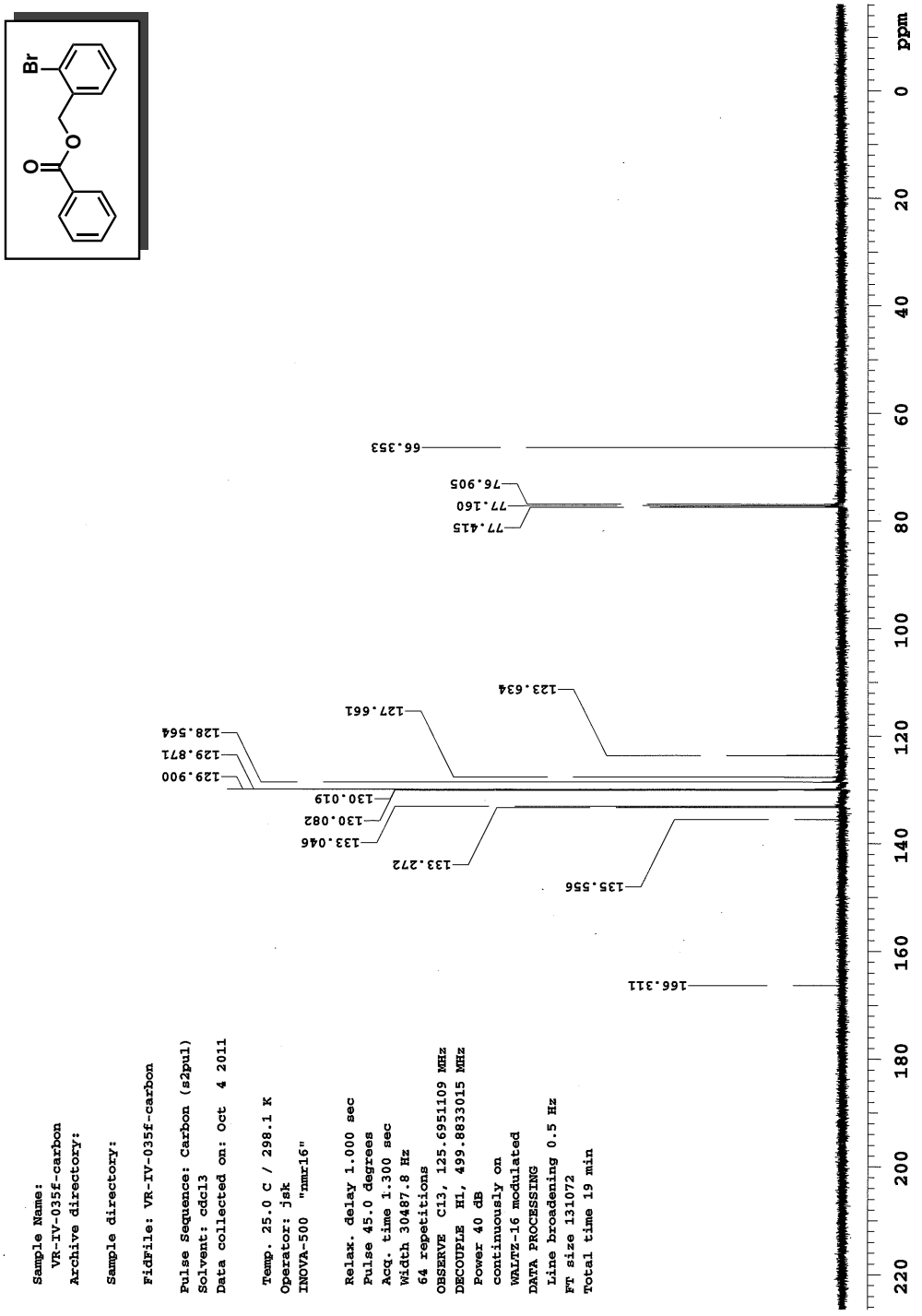


Figure 2.112: ^{1}H NMR of 4-(trifluoromethyl)benzyl benzoate (**2.131**)

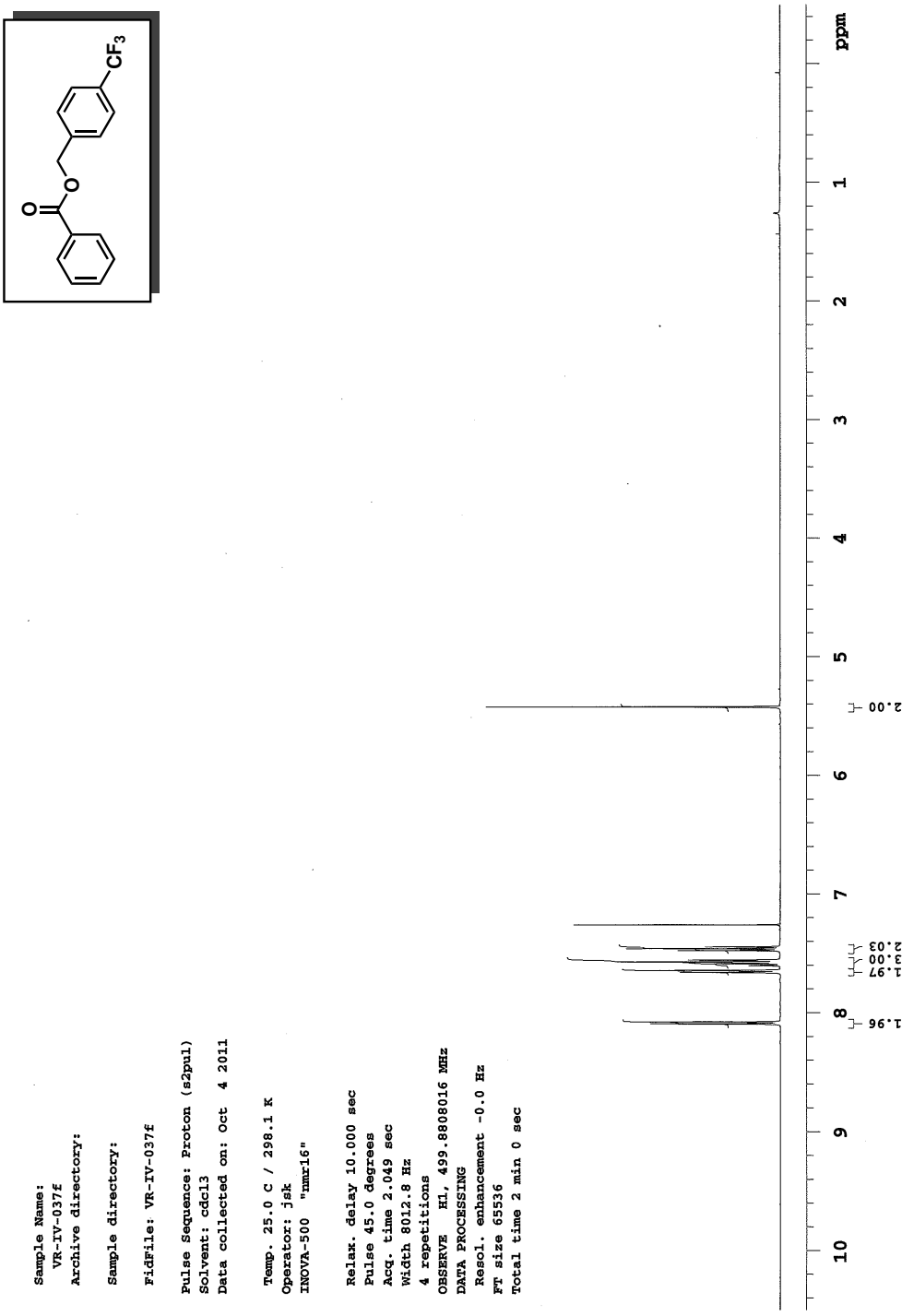


Figure 2.113: ^{13}C NMR of 4-(trifluoromethyl)benzyl benzoate (**2.131**)

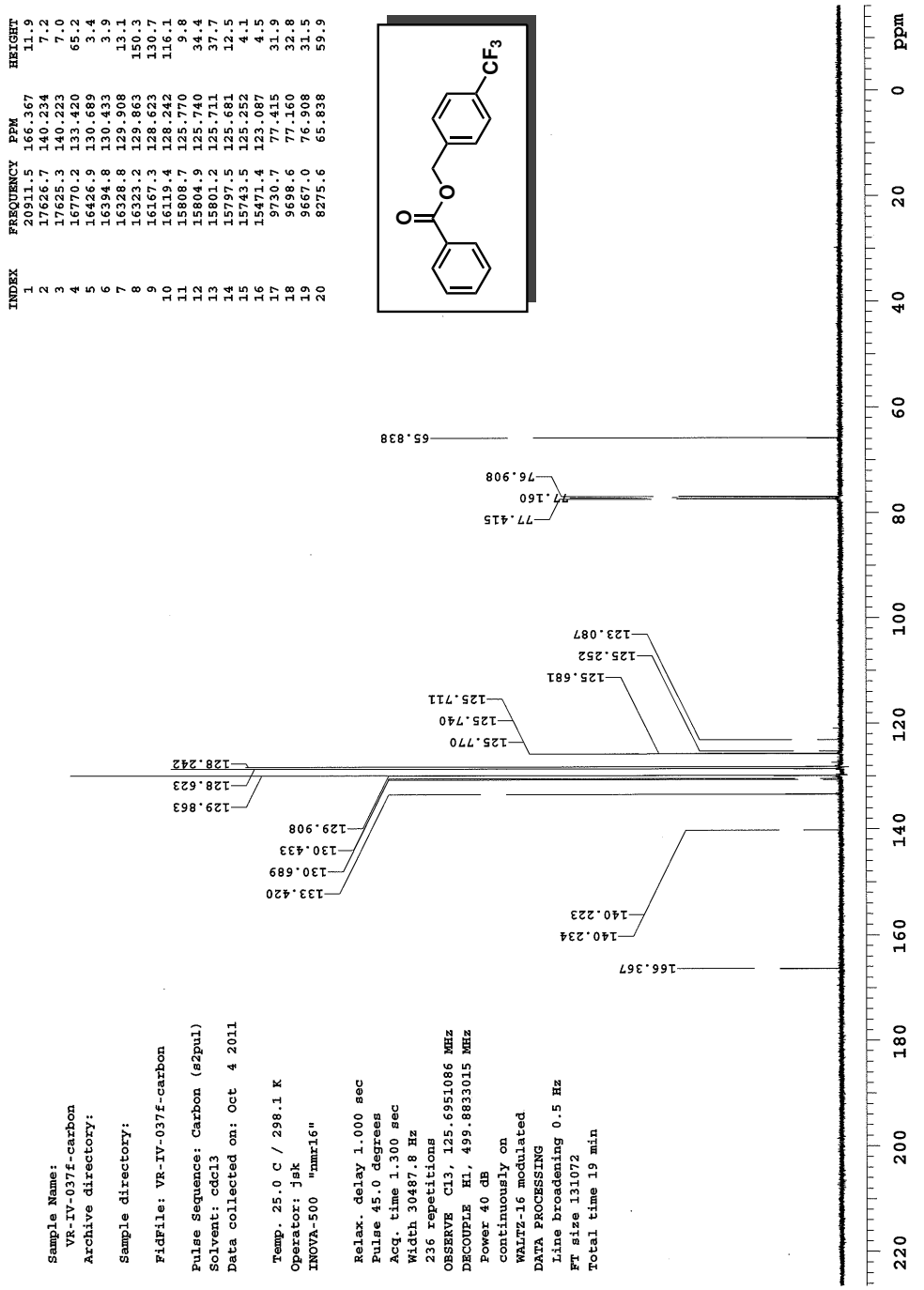


Figure 2.114: ^{1}H NMR of 3-bromobenzyl benzoate (**2.132**)

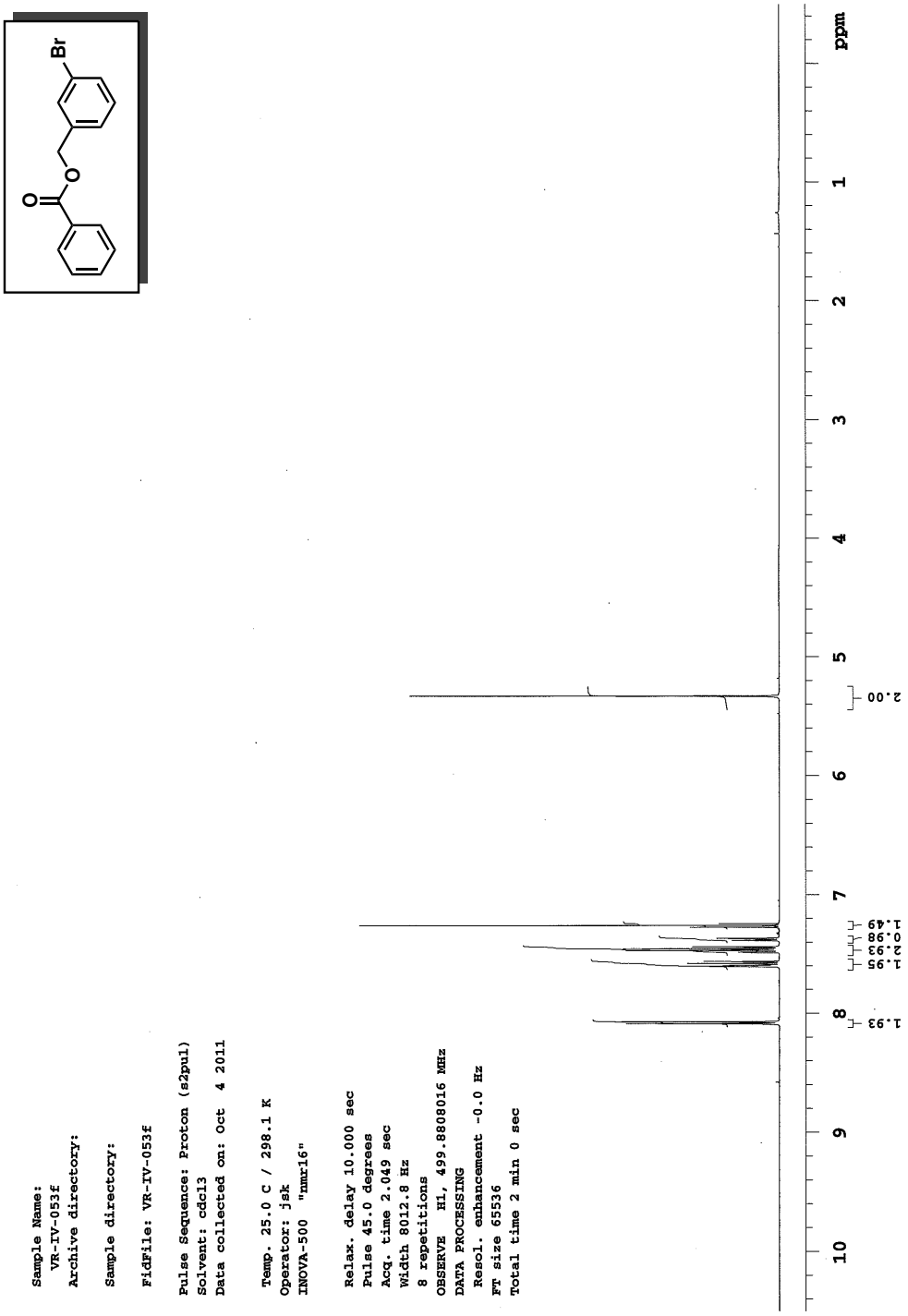


Figure 2.115: ^{13}C NMR of 3-bromobenzyl benzoate (**2.132**)

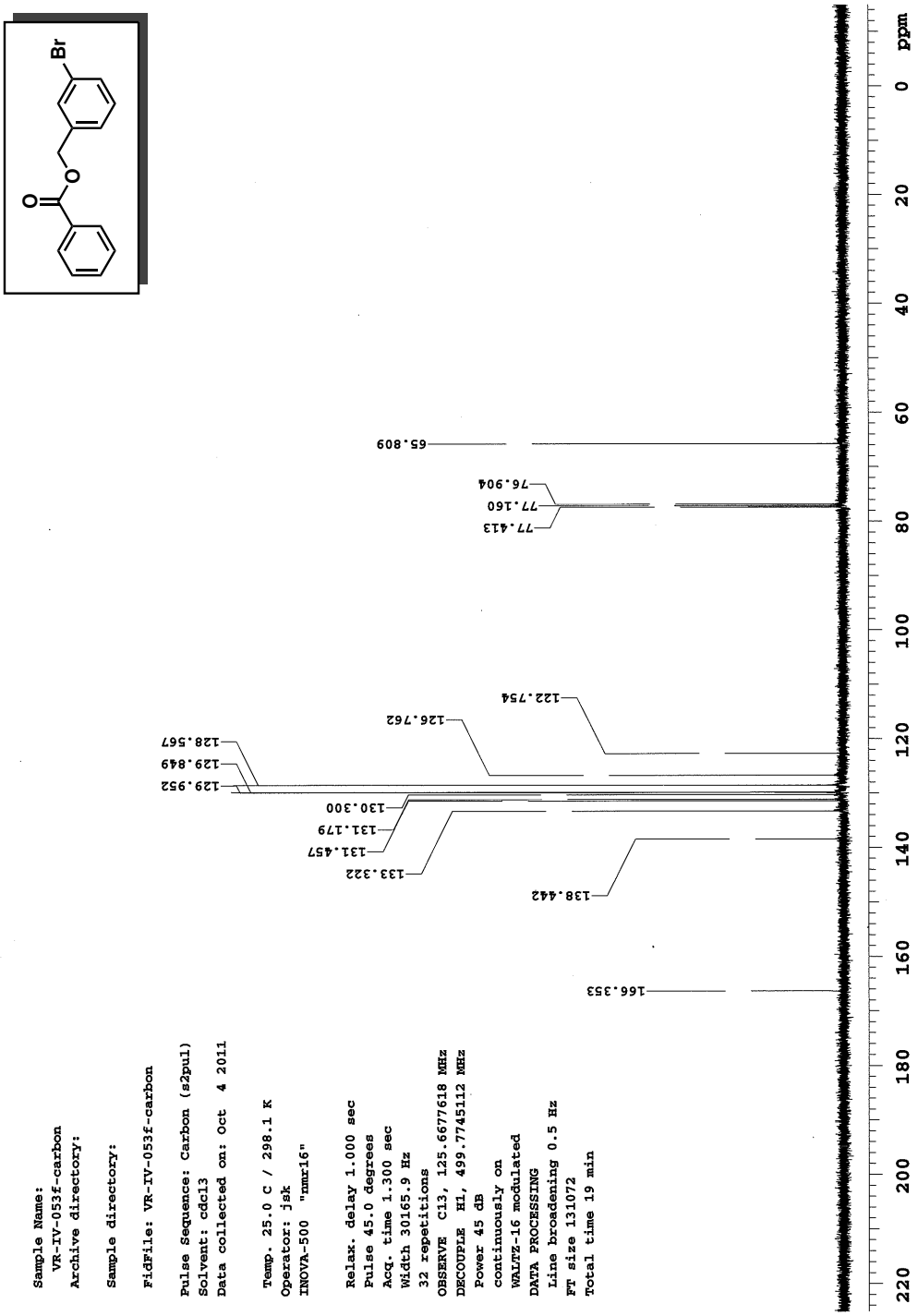


Figure 2.116: ^{1}H NMR of neopentyl 2-fluorobenzoate (**2.114**)

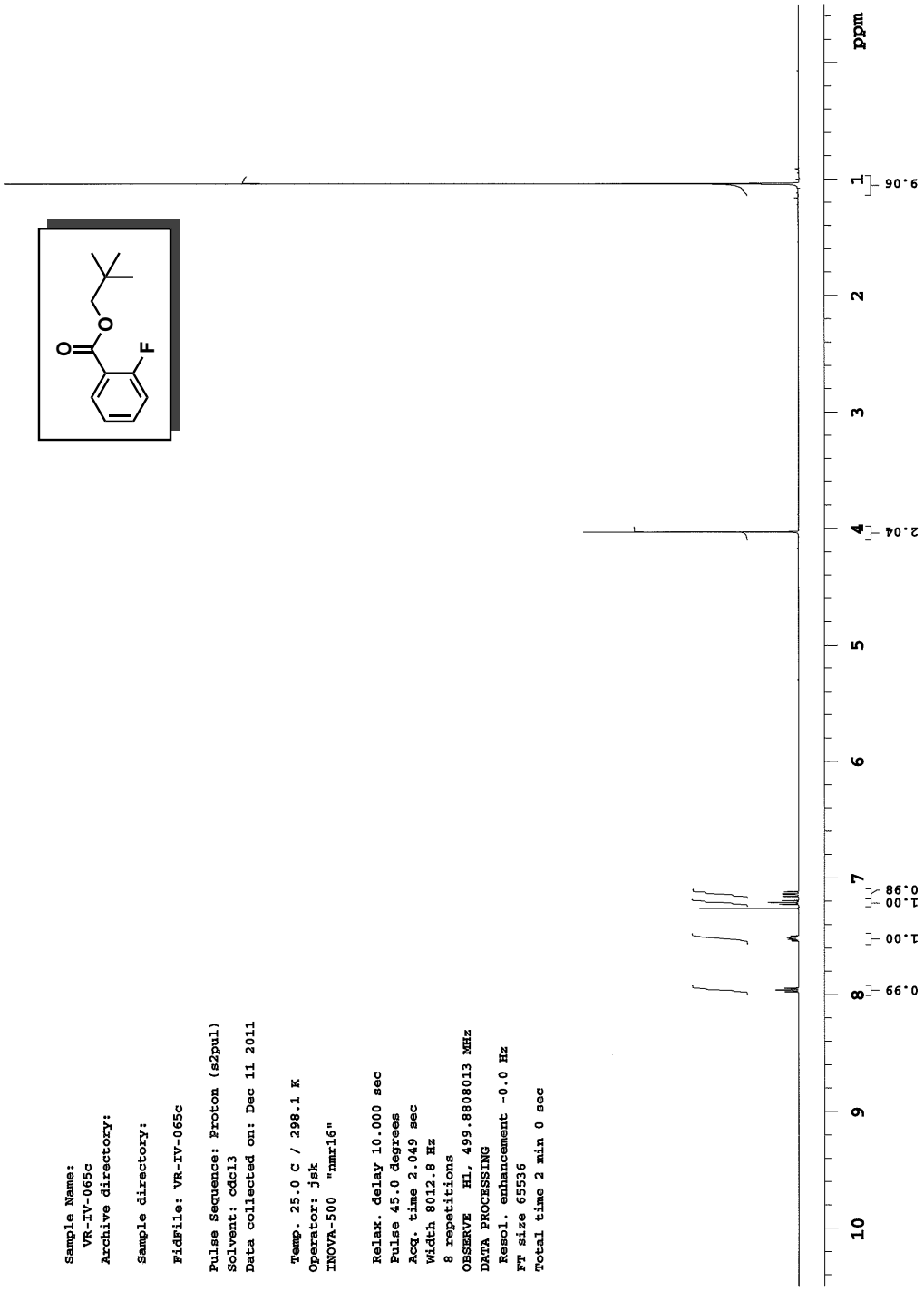


Figure 2.117: ^{13}C NMR of neopentyl 2-fluorobenzoate (**2.114**)

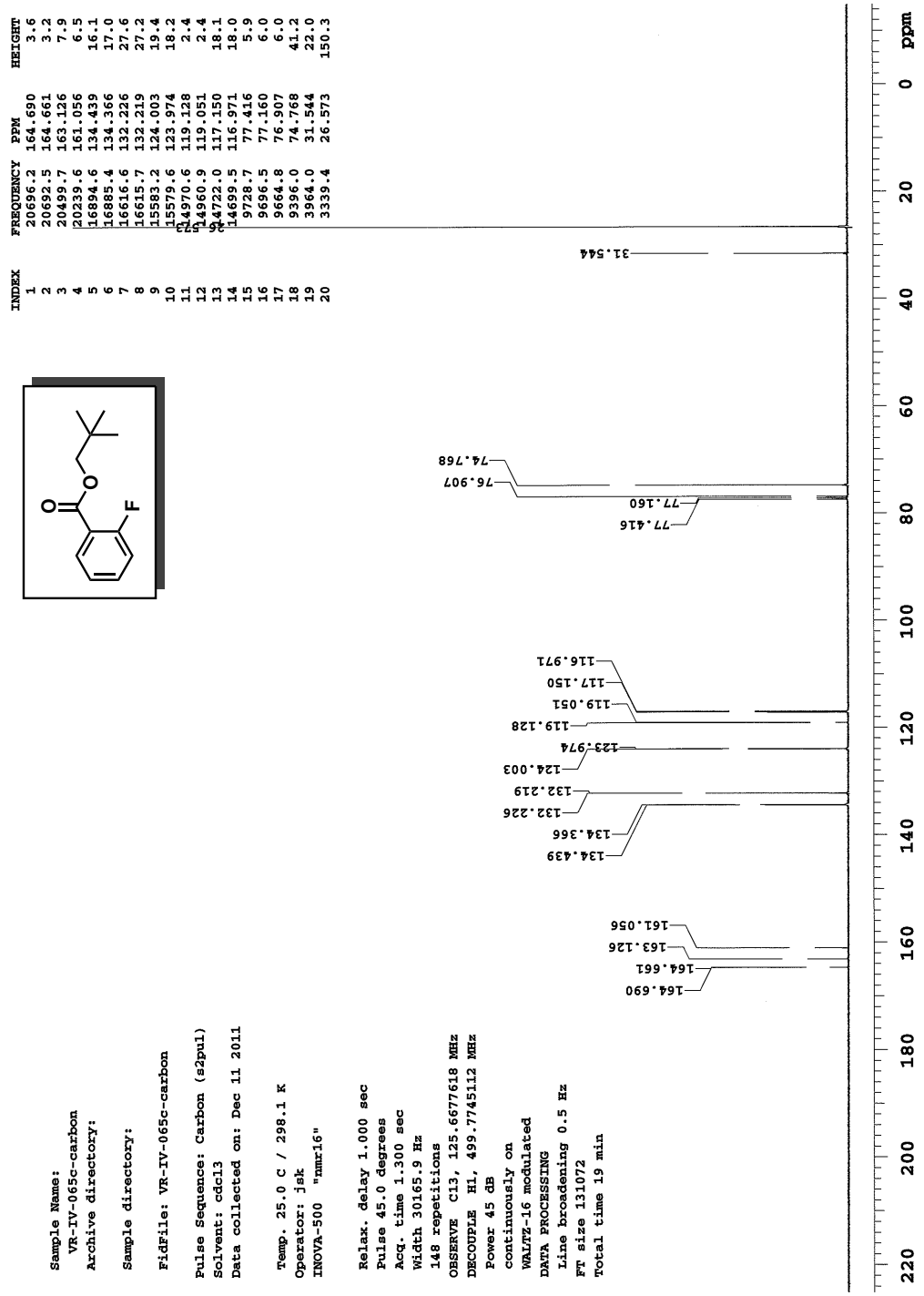


Figure 2.118: ^{19}F NMR of neopentyl 2-fluorobenzoate (**2.114**)

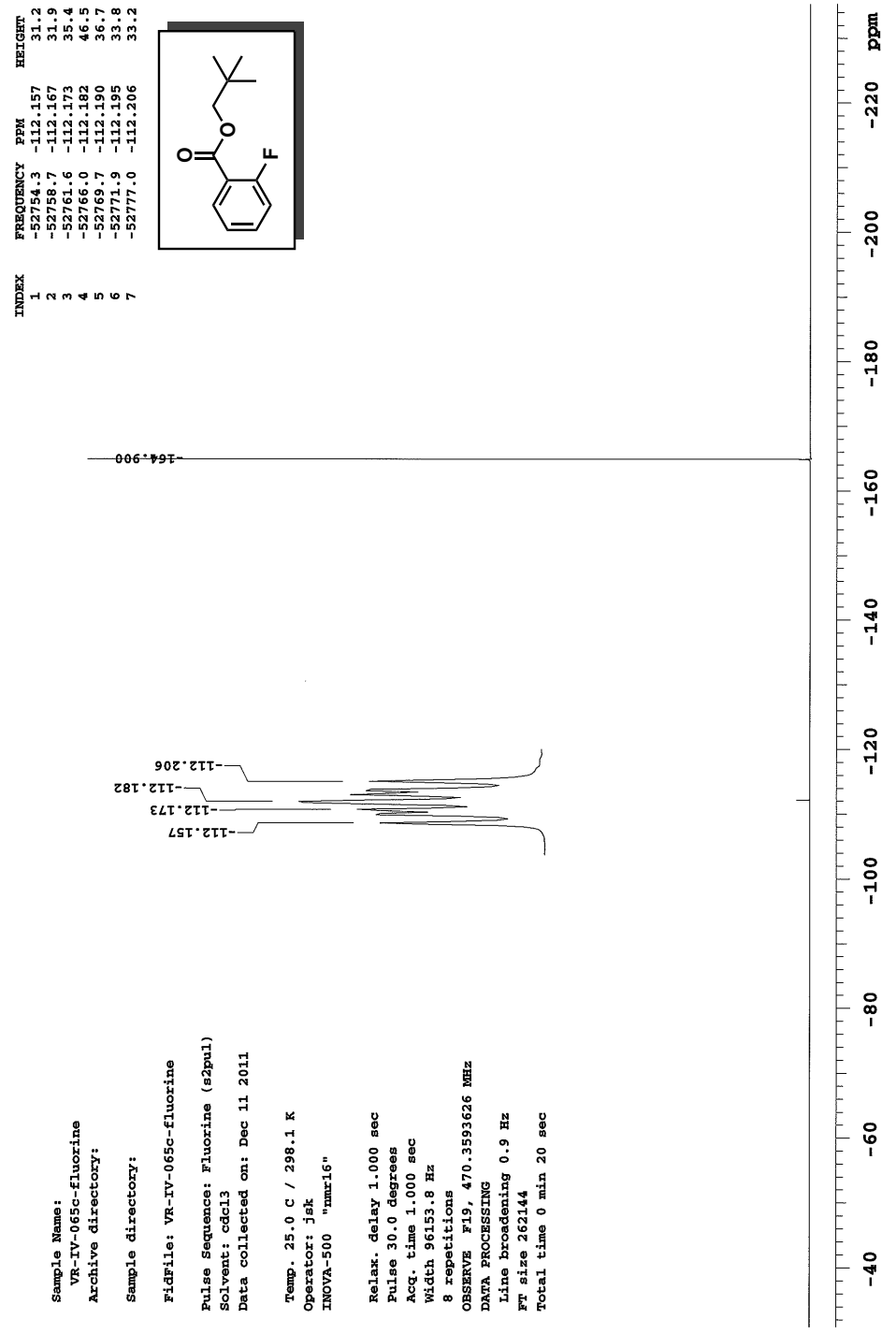


Figure 2.119: ^{1}H NMR of *tert*-amyl 2-fluorobenzoate (**2.115**)

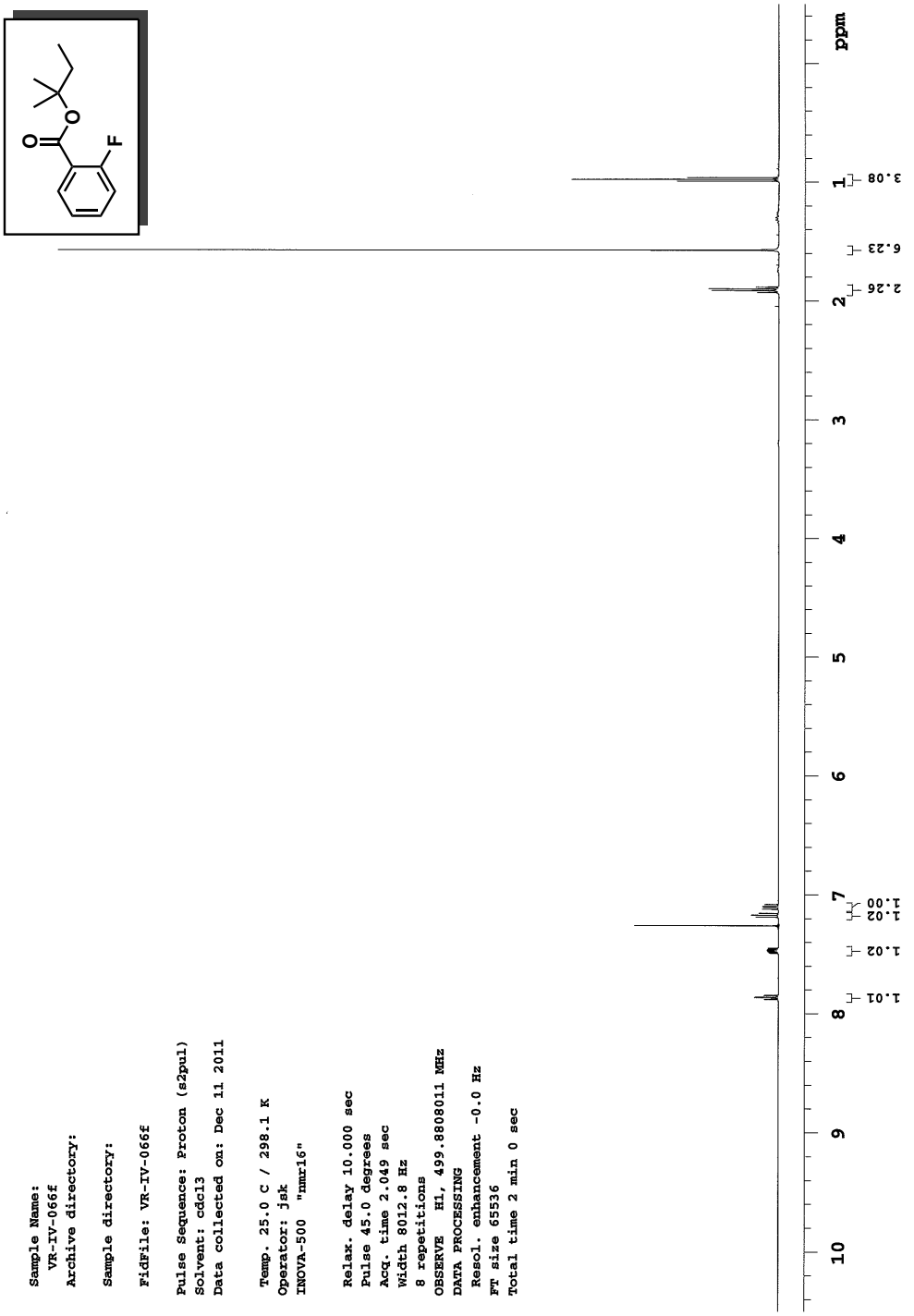


Figure 2.120: ^{13}C NMR of *tert*-amyl 2-fluorobenzoate (**2.115**)

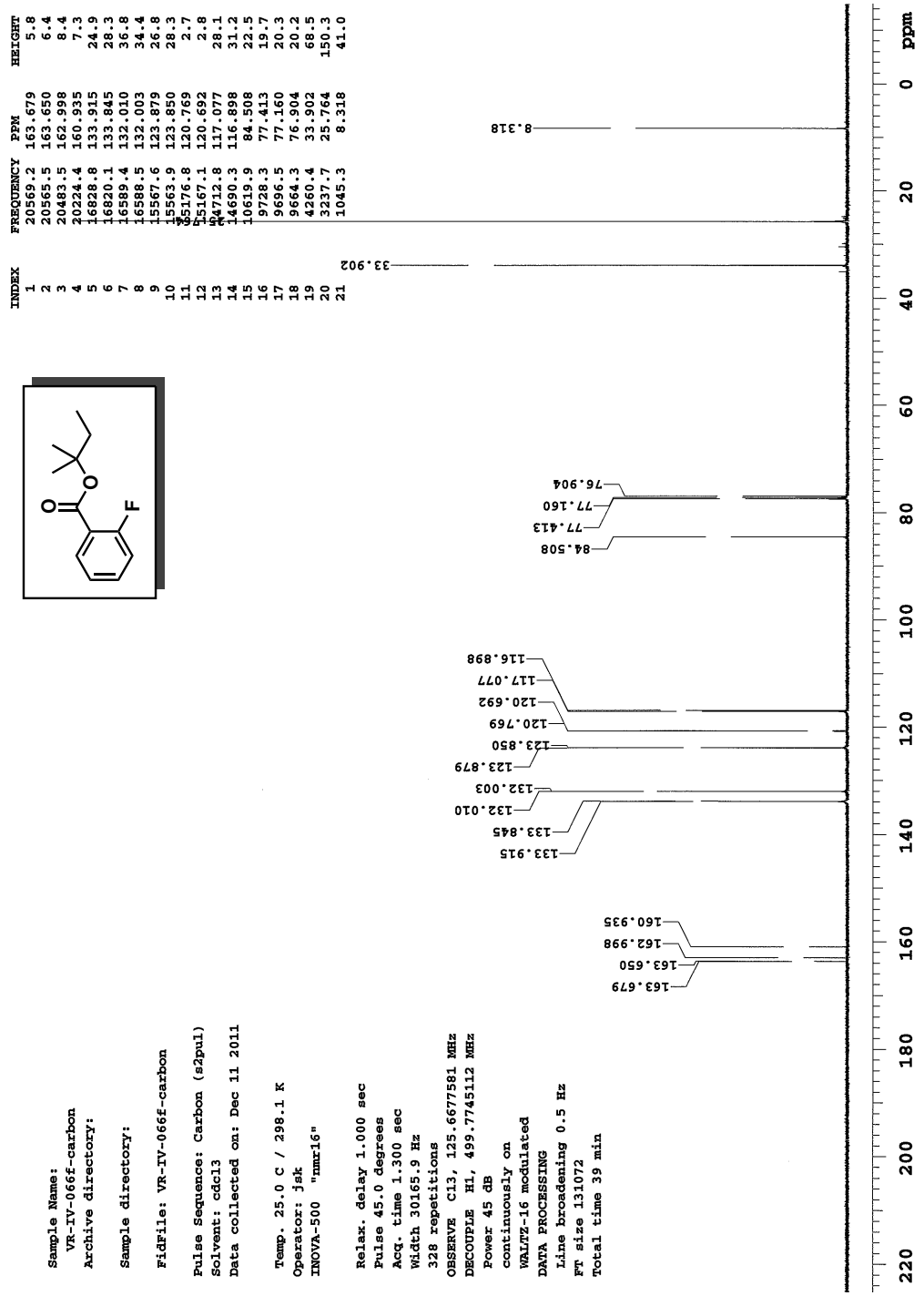


Figure 2.121: ^{19}F NMR of *tert*-amyl 2-fluorobenzoate (**2.115**)

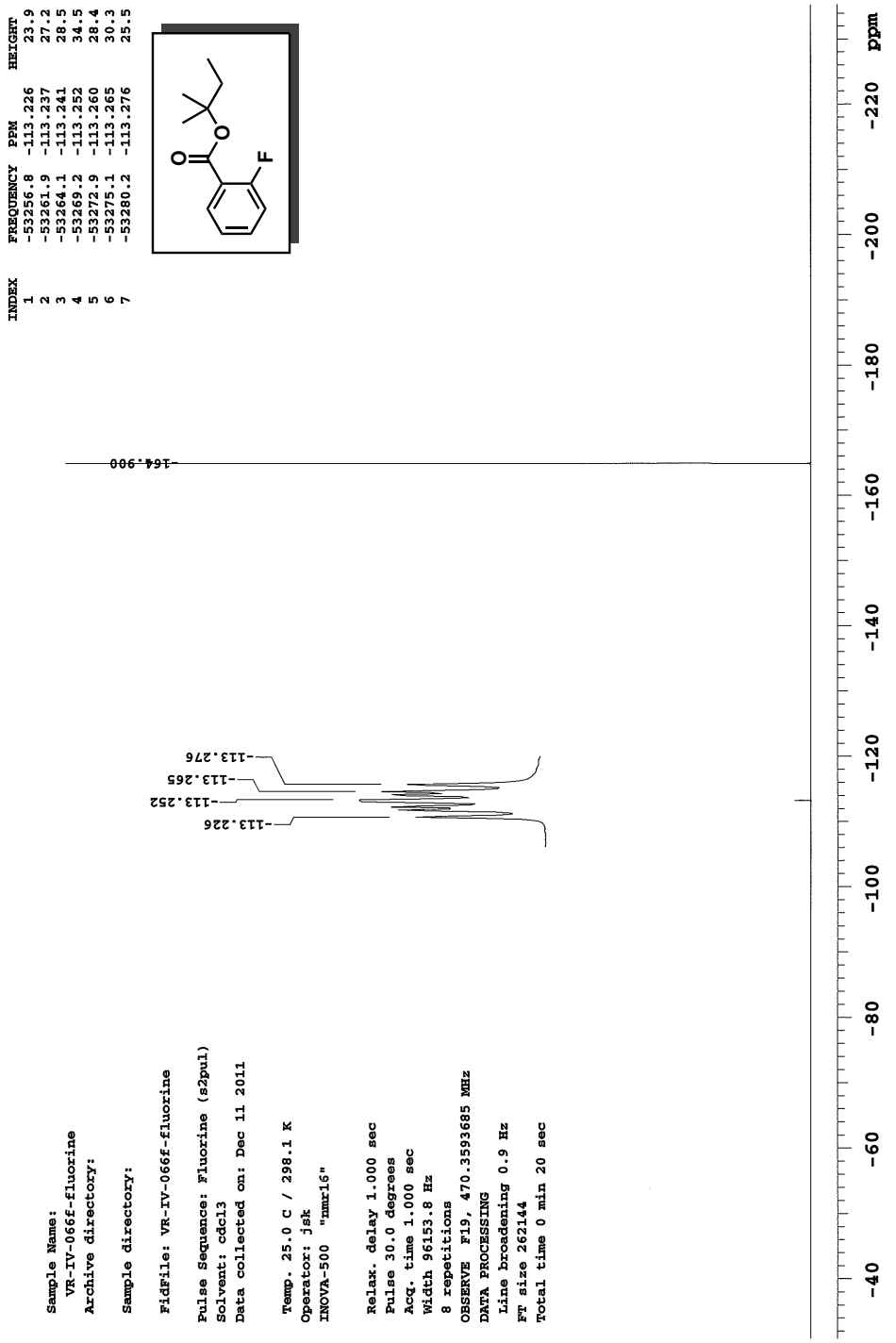


Figure 2.122: ^{1}H NMR of (*S*)-naproxen (**2.133**)

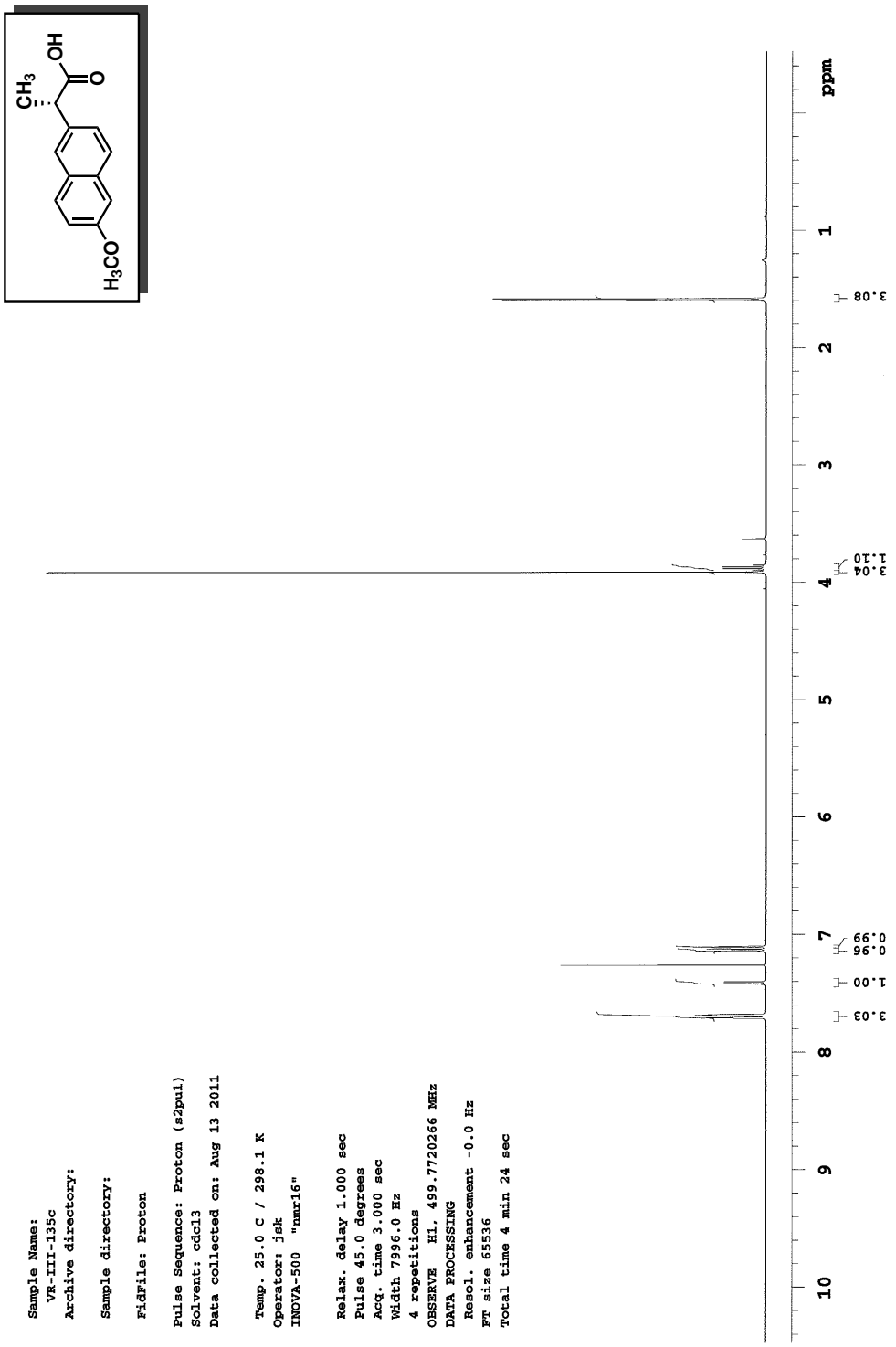


Figure 2.123: ^{1}H NMR of 2-(naphthalen-2-ylmethyl)malonic acid (**2.101**)

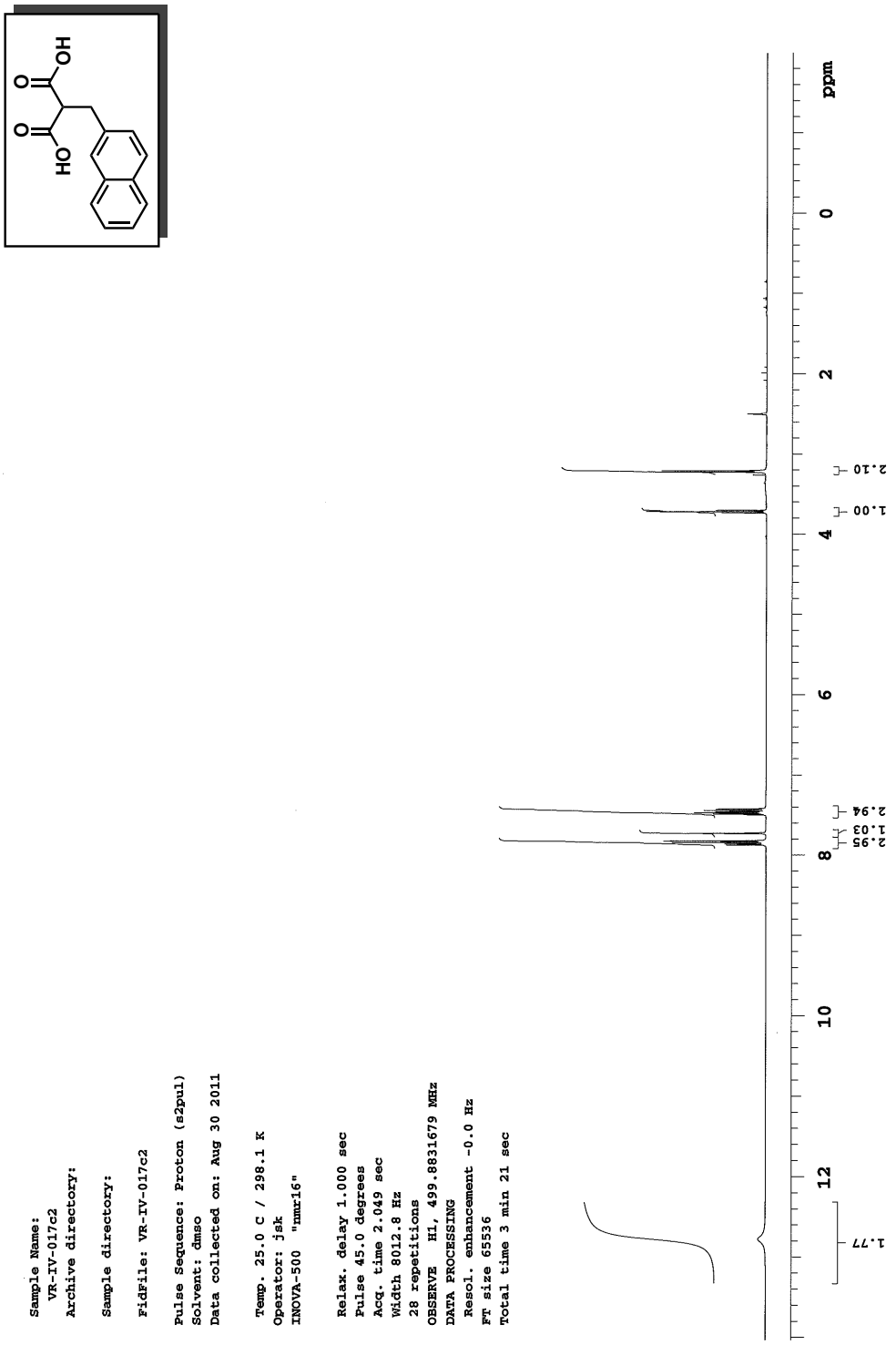


Figure 2.124: ^{13}C NMR of 2-(naphthalen-2-ylmethyl)malonic acid (**2.101**)

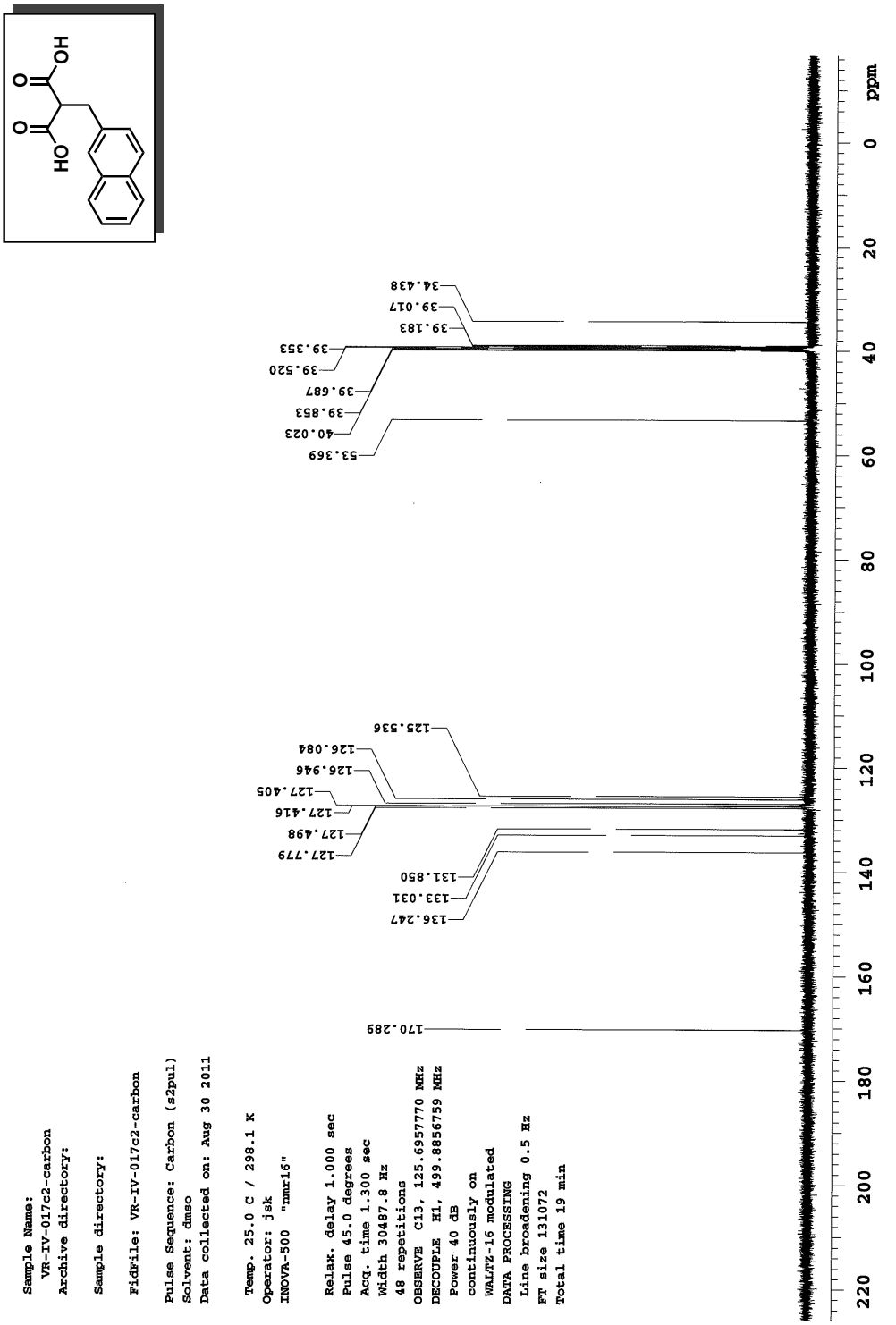


Figure 2.125: ^{1}H NMR of 3-(naphthalen-2-yl)propanoic acid (**2.134**)

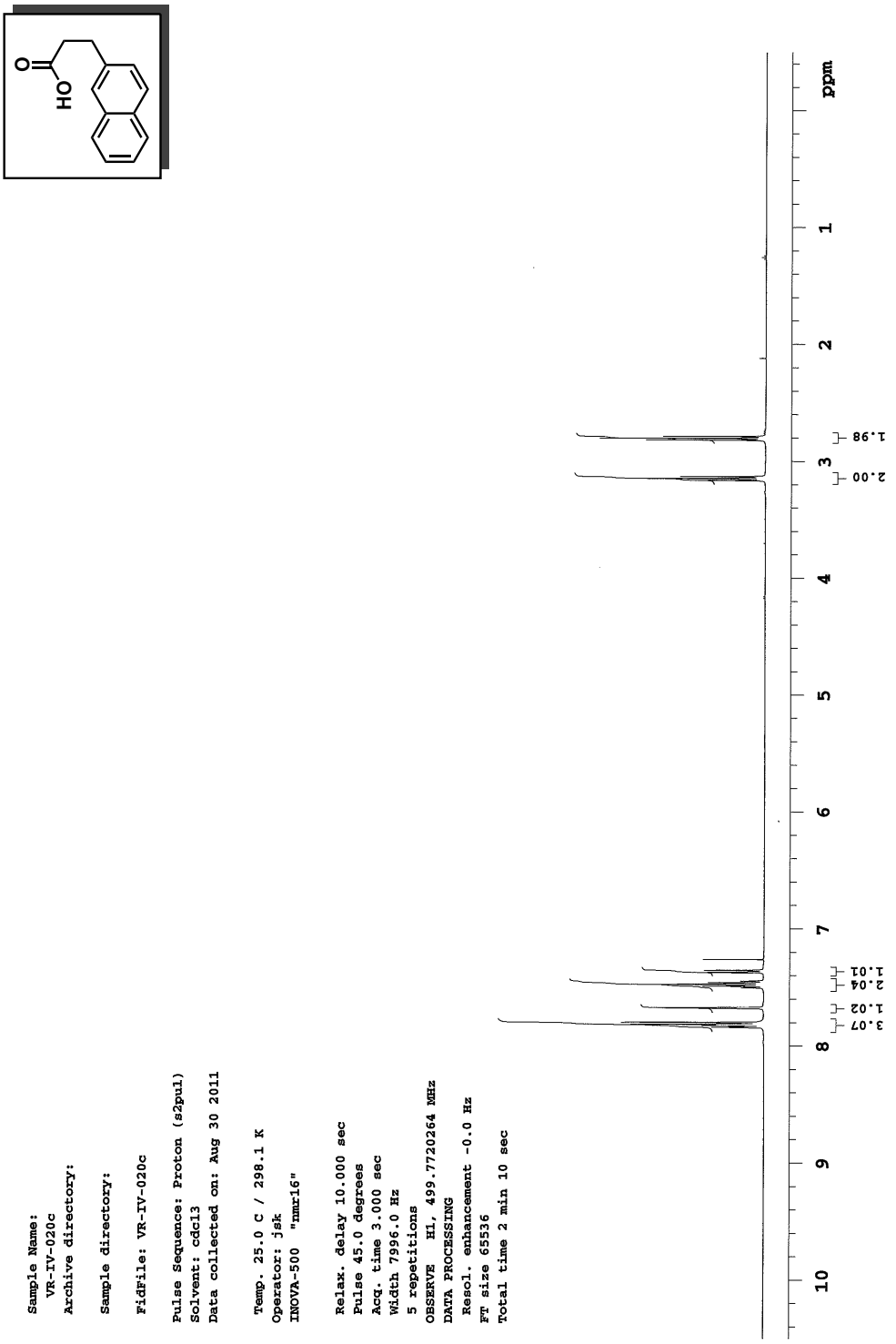


Figure 2.126: ^{13}C NMR of 3-(naphthalen-2-yl)propanoic acid (**2.134**)

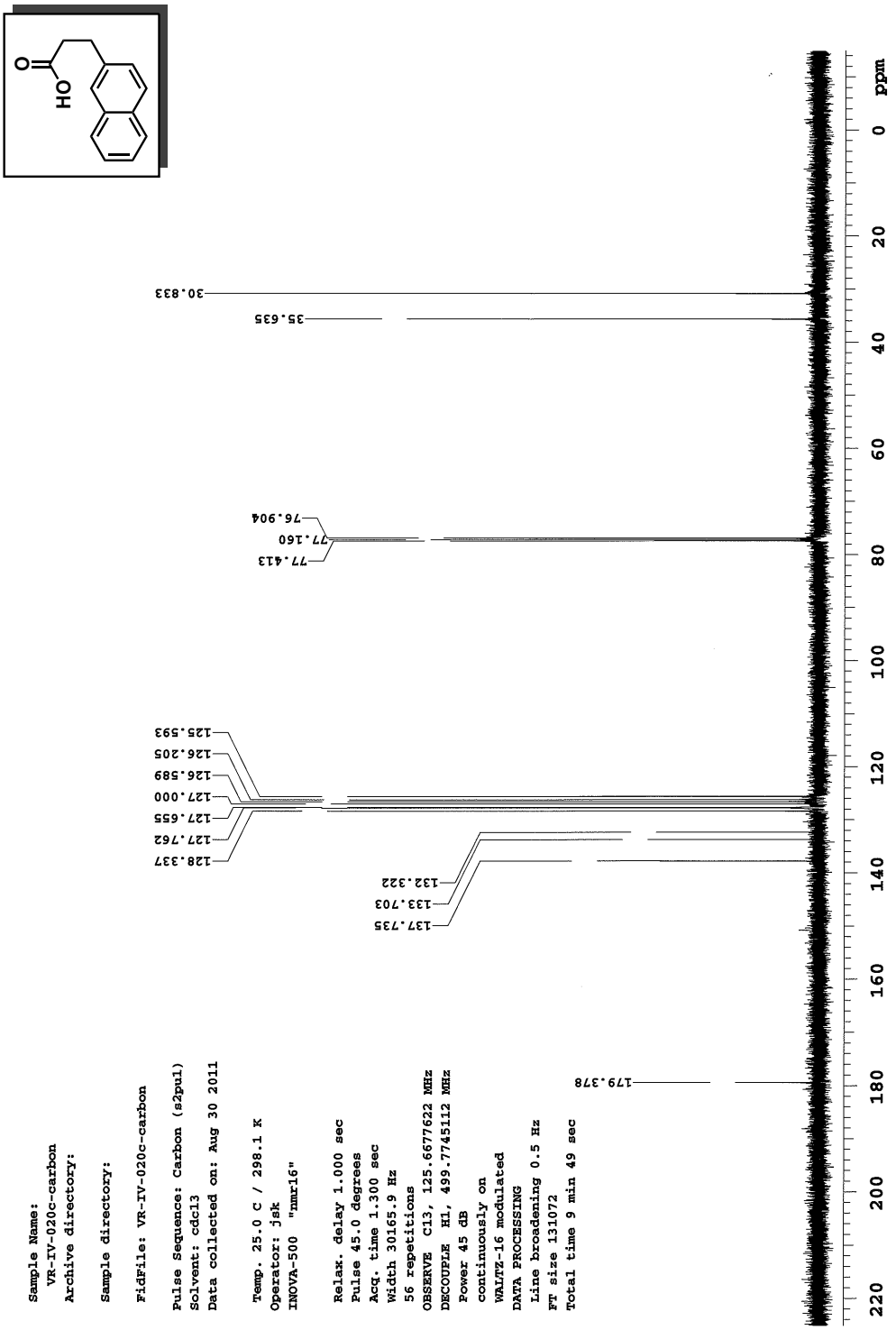


Figure 2.127: ^{1}H NMR of 2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (**2.99**)

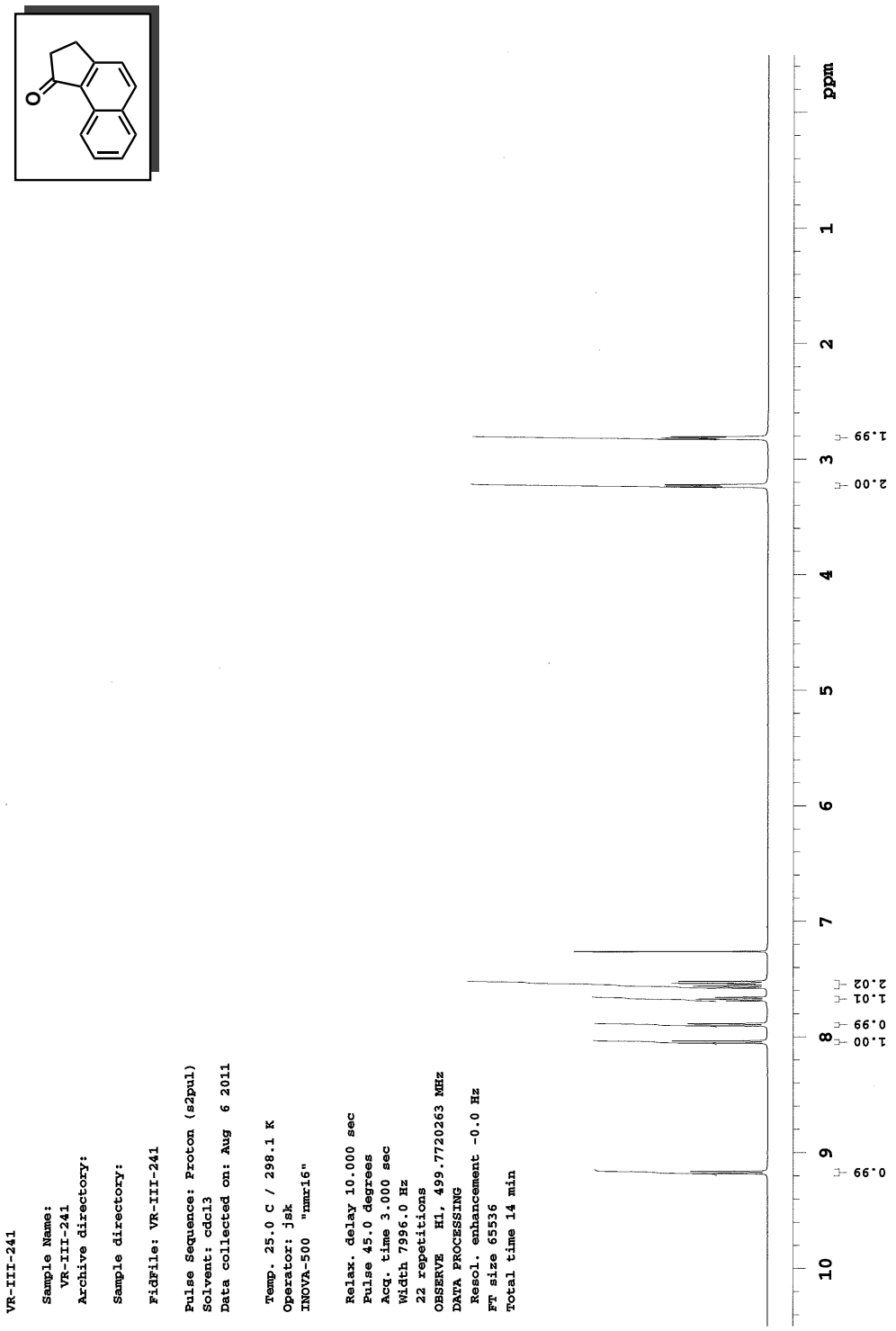


Figure 2.128: ^{13}C NMR of 2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one (**2.99**)

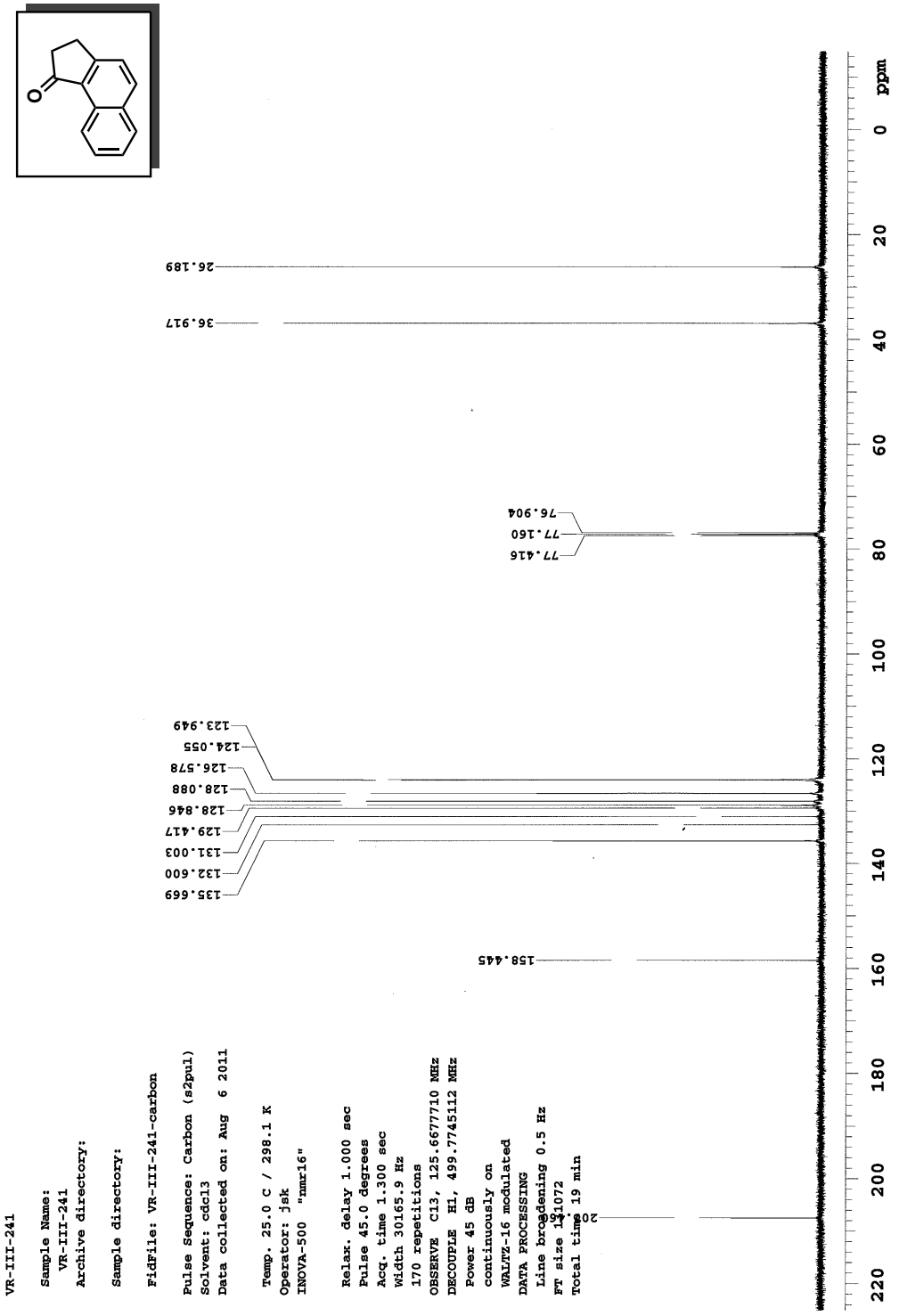


Figure 2.129: ^{1}H NMR of 3*H*-benz[*e*]indene (**2.98**)

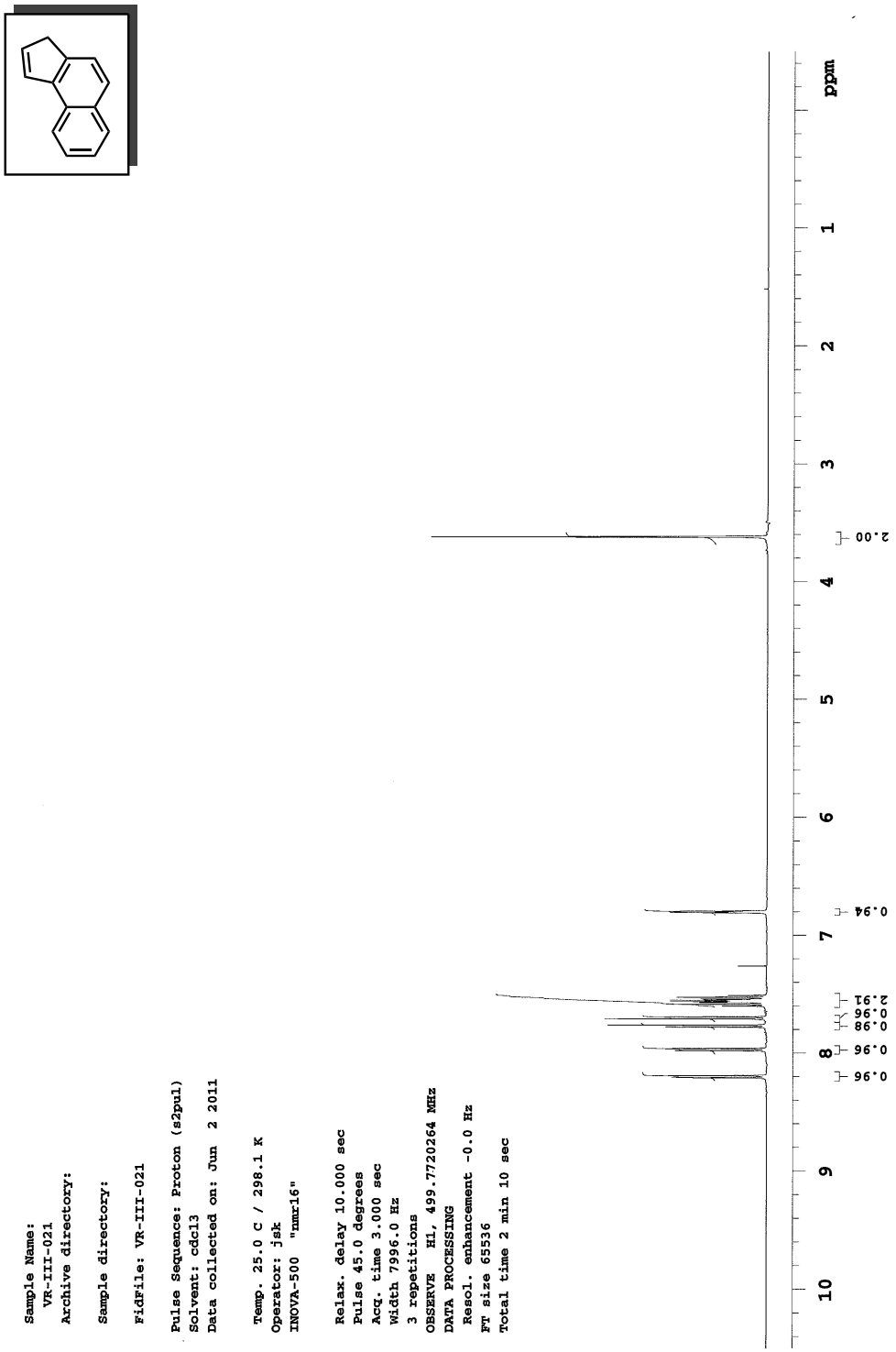


Figure 2.130: ^{13}C NMR of 3*H*-benz[*e*]indene (**2.98**)

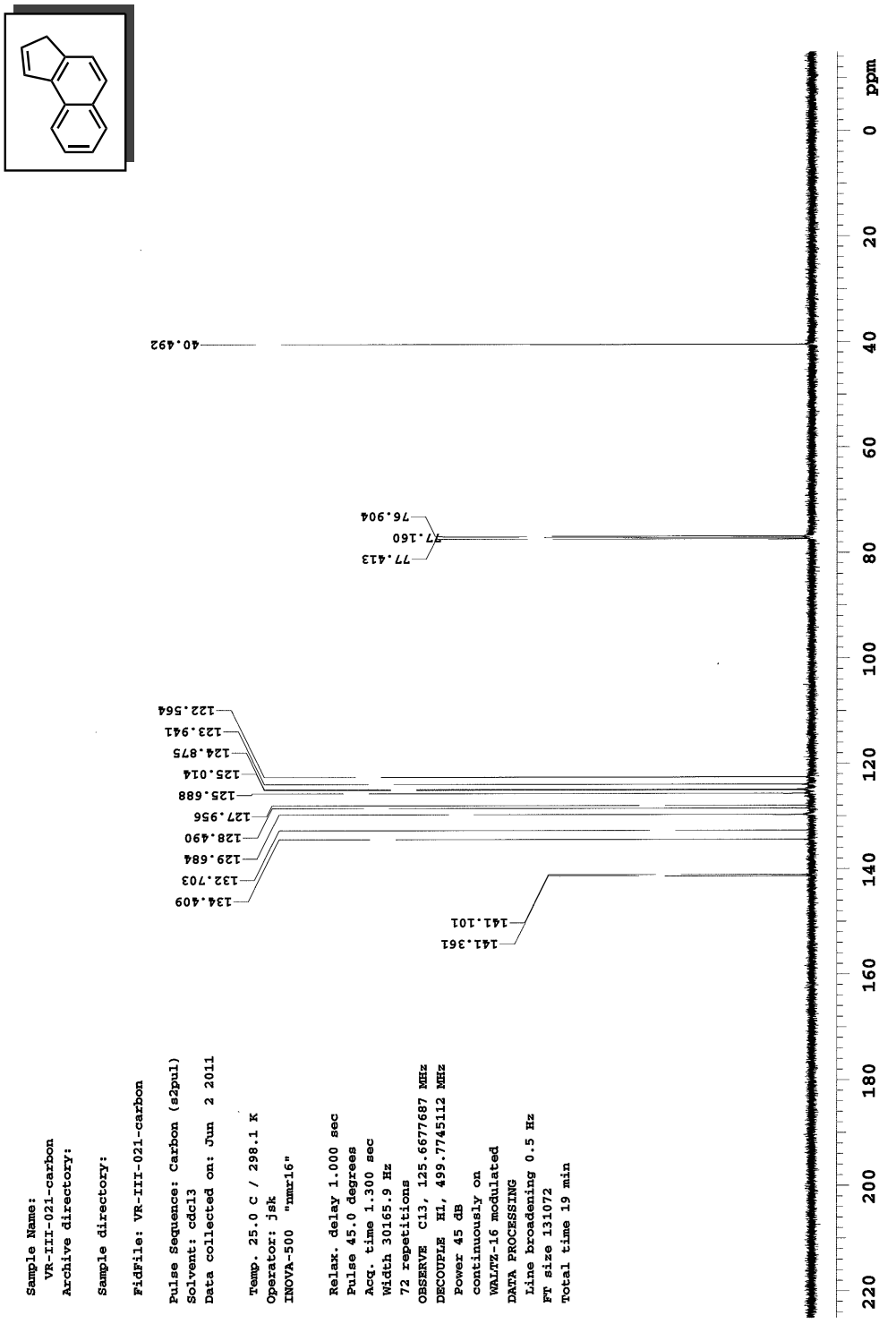


Figure 2.131: ^{1}H NMR of (±)-2-bromo-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol (**2.102**)

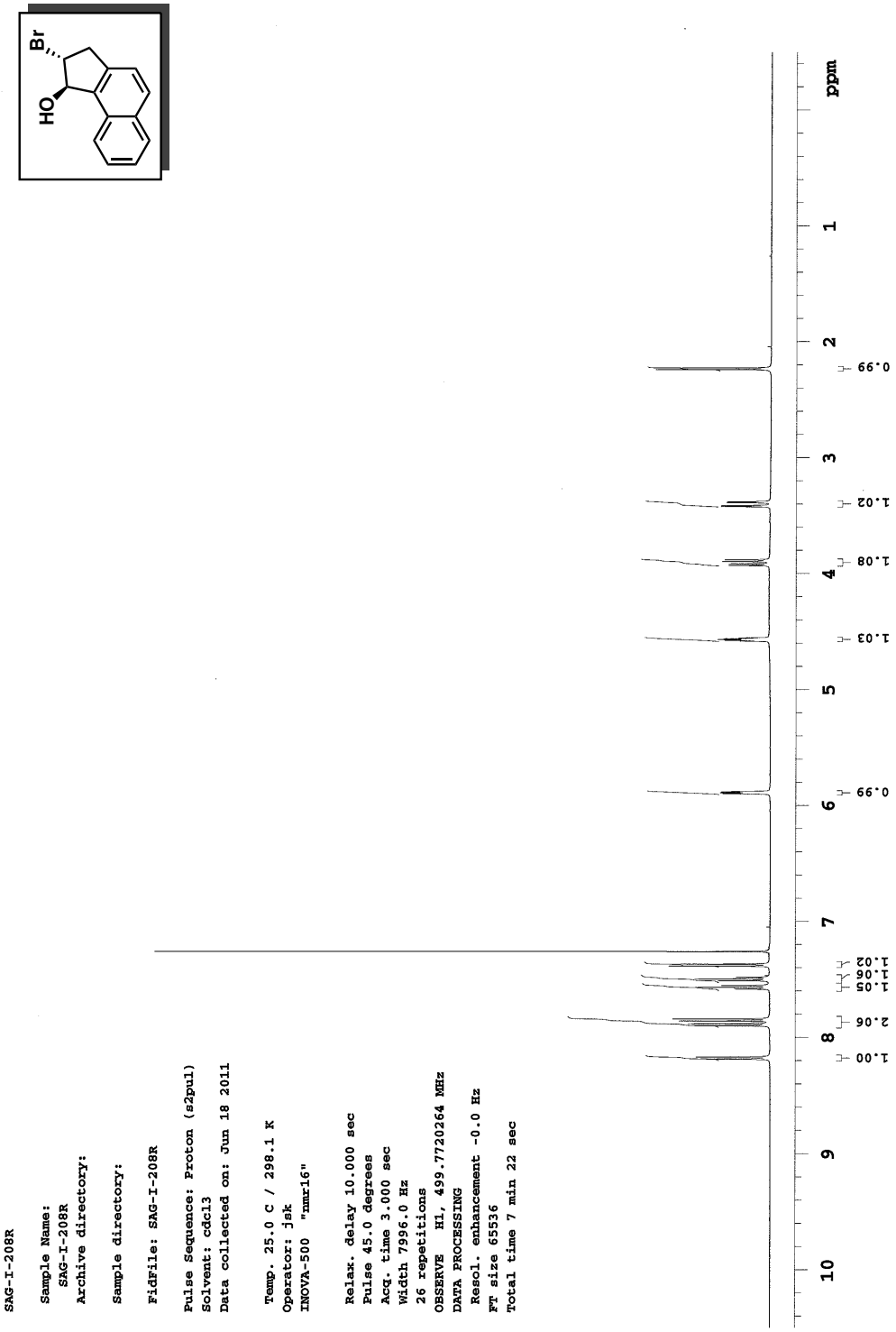


Figure 2.132: ^{13}C NMR of (±)-2-bromo-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-ol (**2.102**)

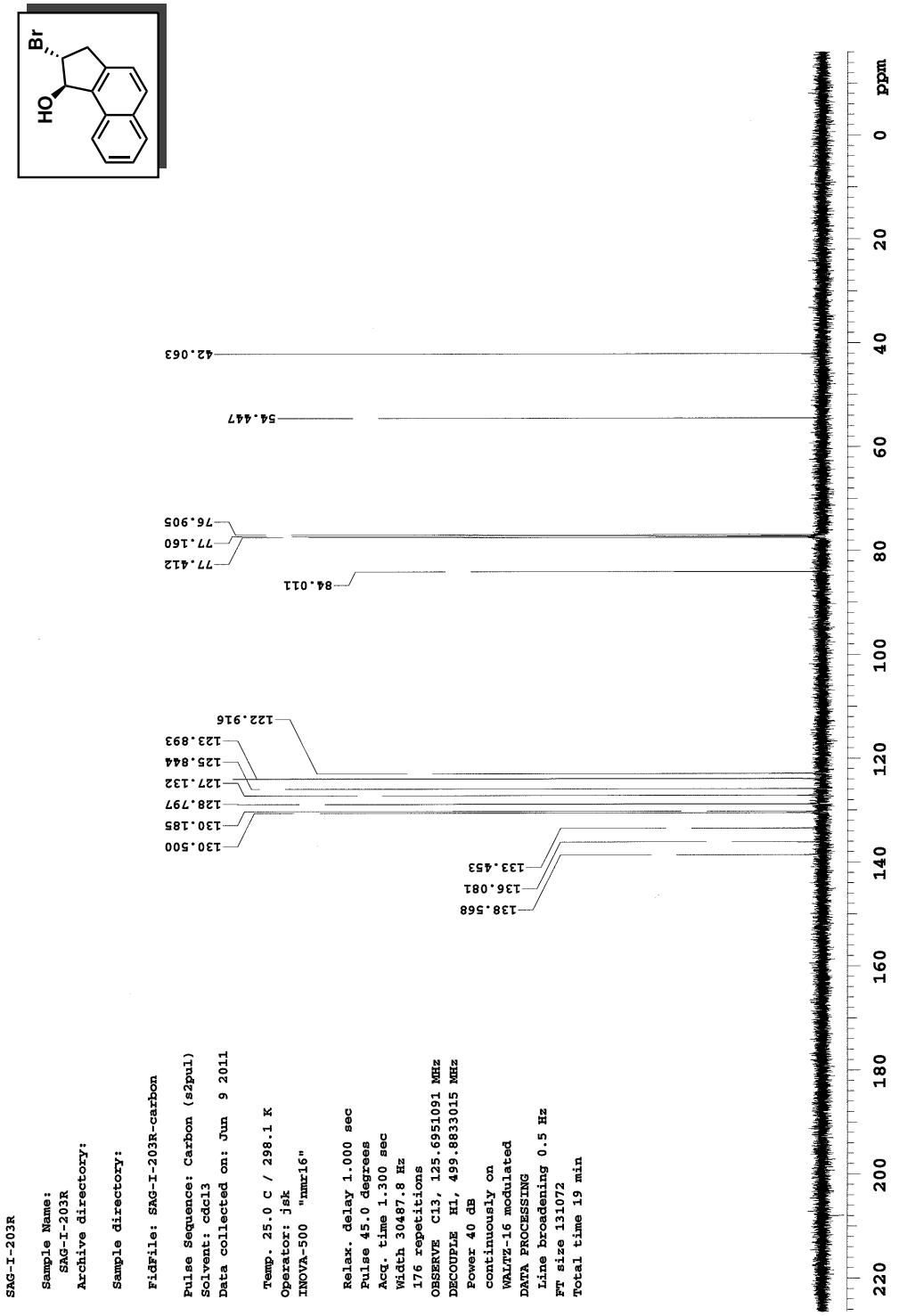


Figure 2.133: ^{1}H NMR of (−)-naproxen ester (**2.103**)

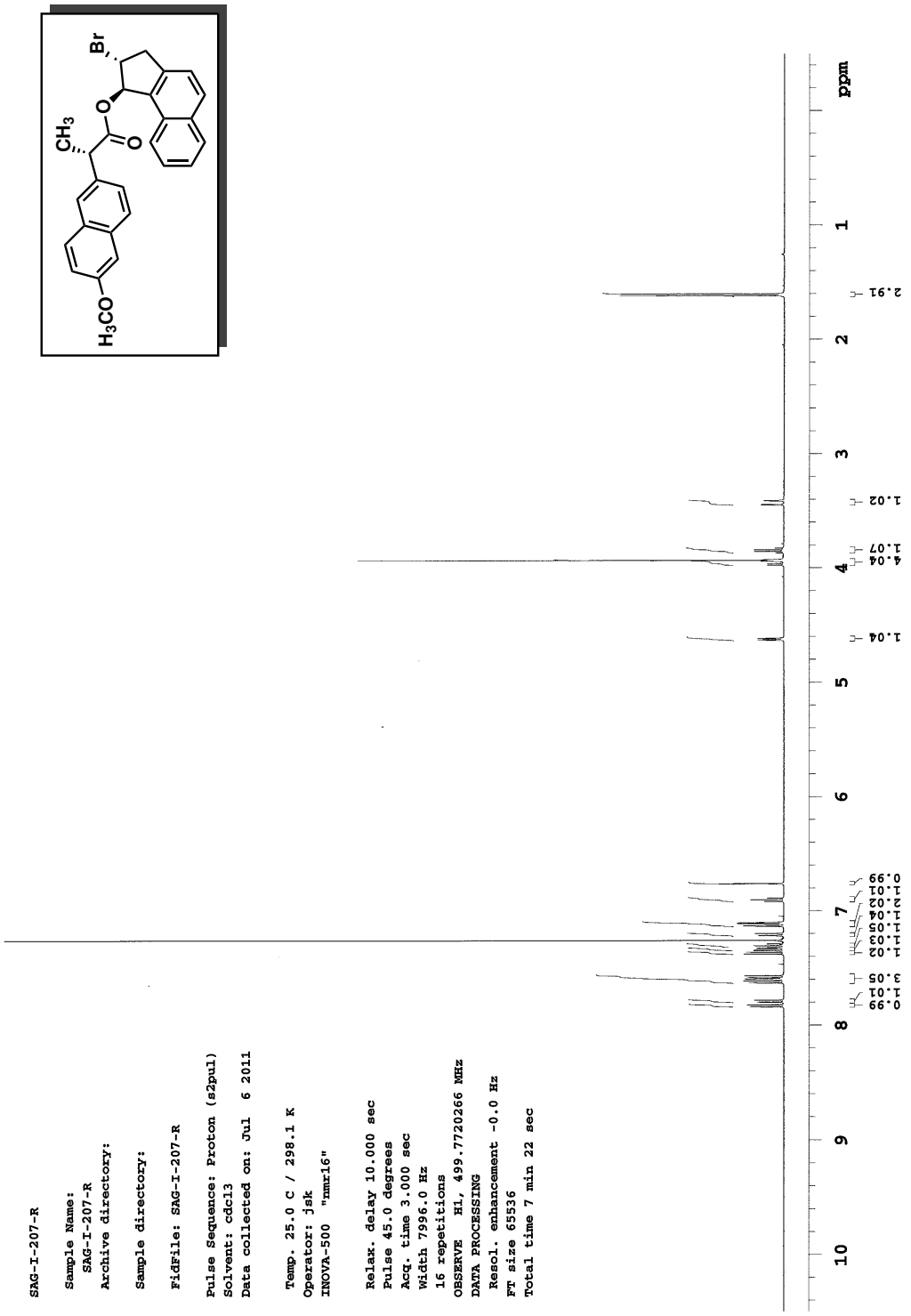


Figure 2.134: ^{13}C NMR of (−)-naproxen ester (**2.103**)

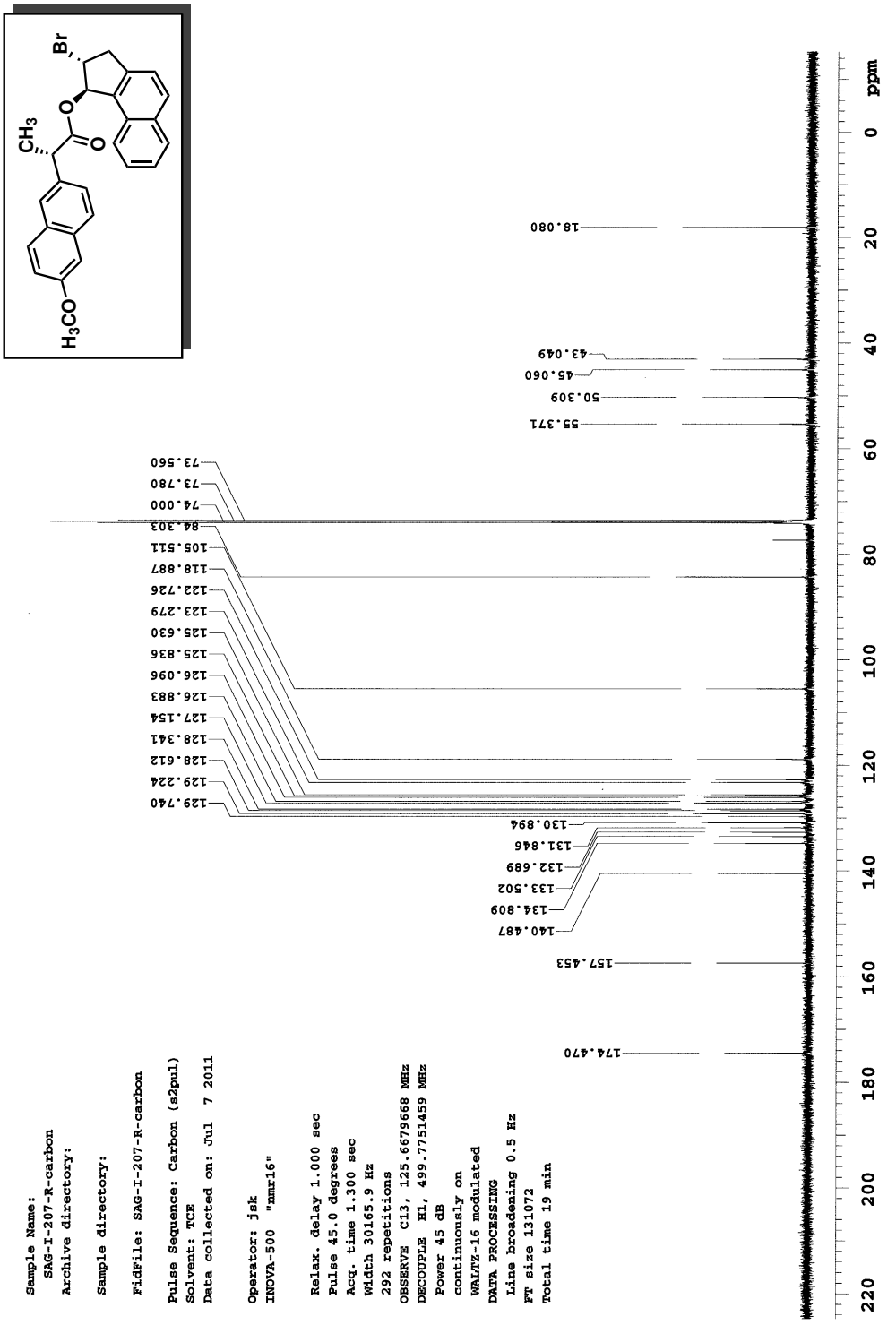


Figure 2.135: ^{1}H NMR of (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-2-ol (**2.96**)

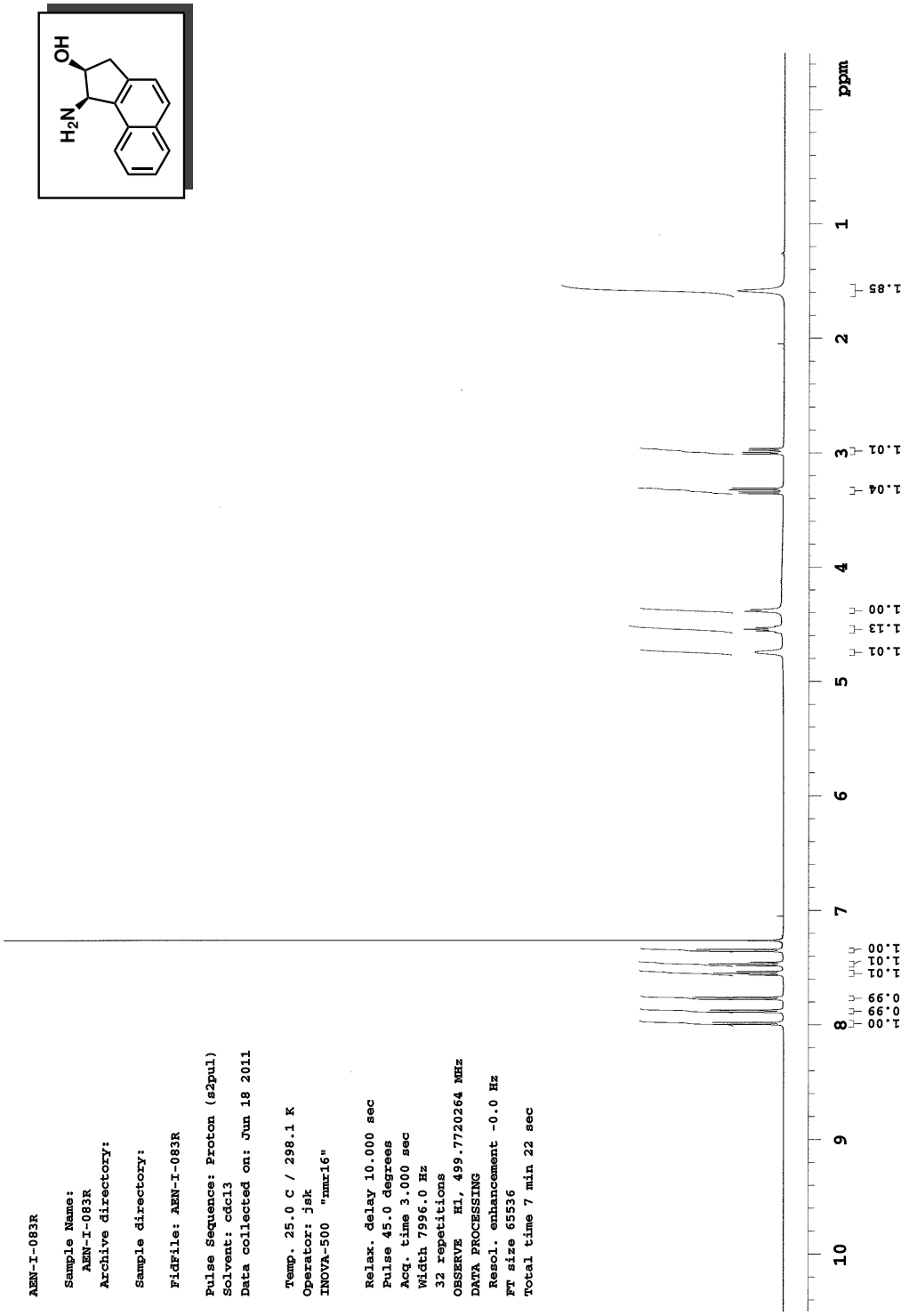


Figure 2.136: ^{13}C NMR of (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-2-ol (**2.96**)

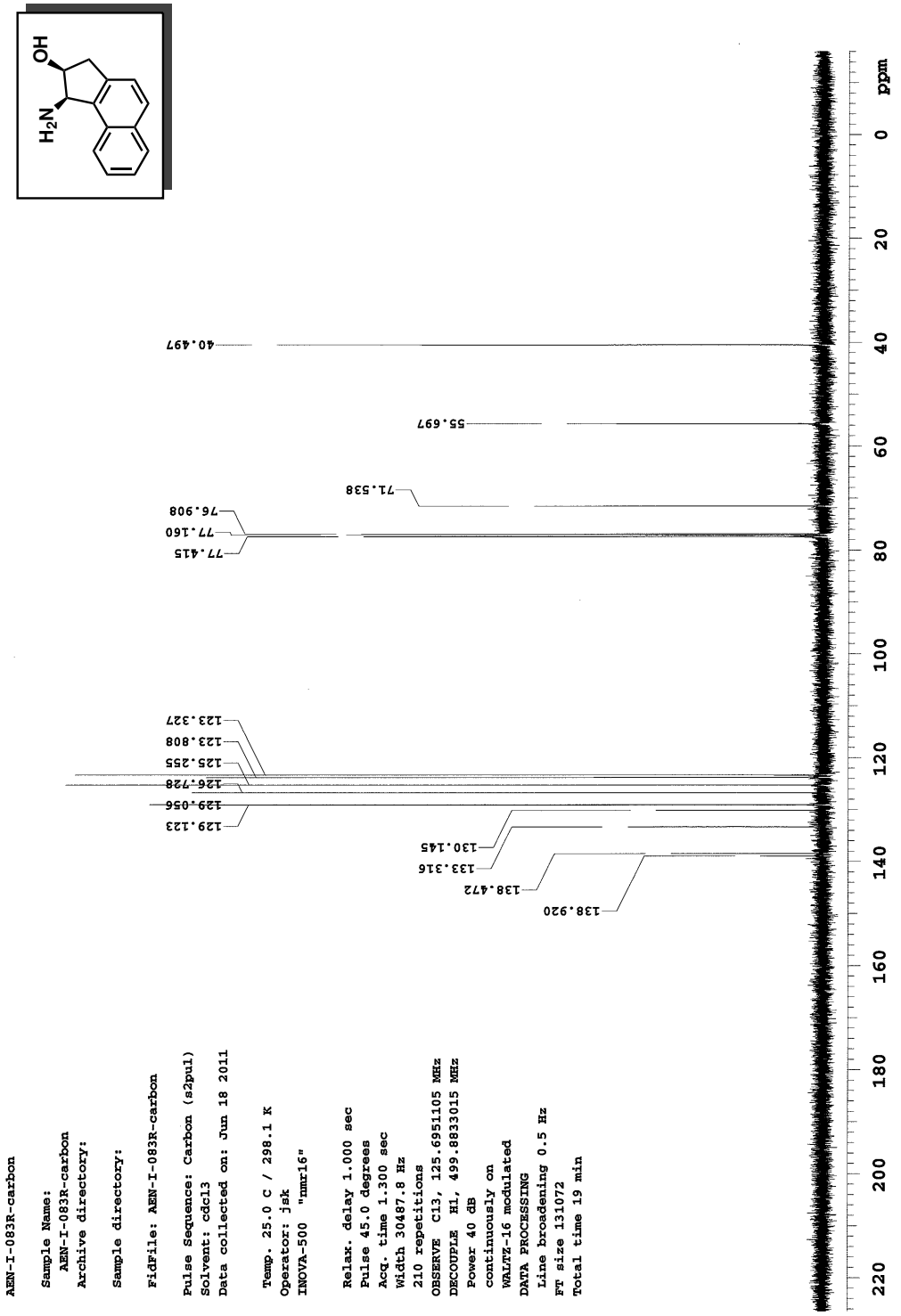


Figure 2.137: ^{1}H NMR of bromo acetamide (**2.105**)

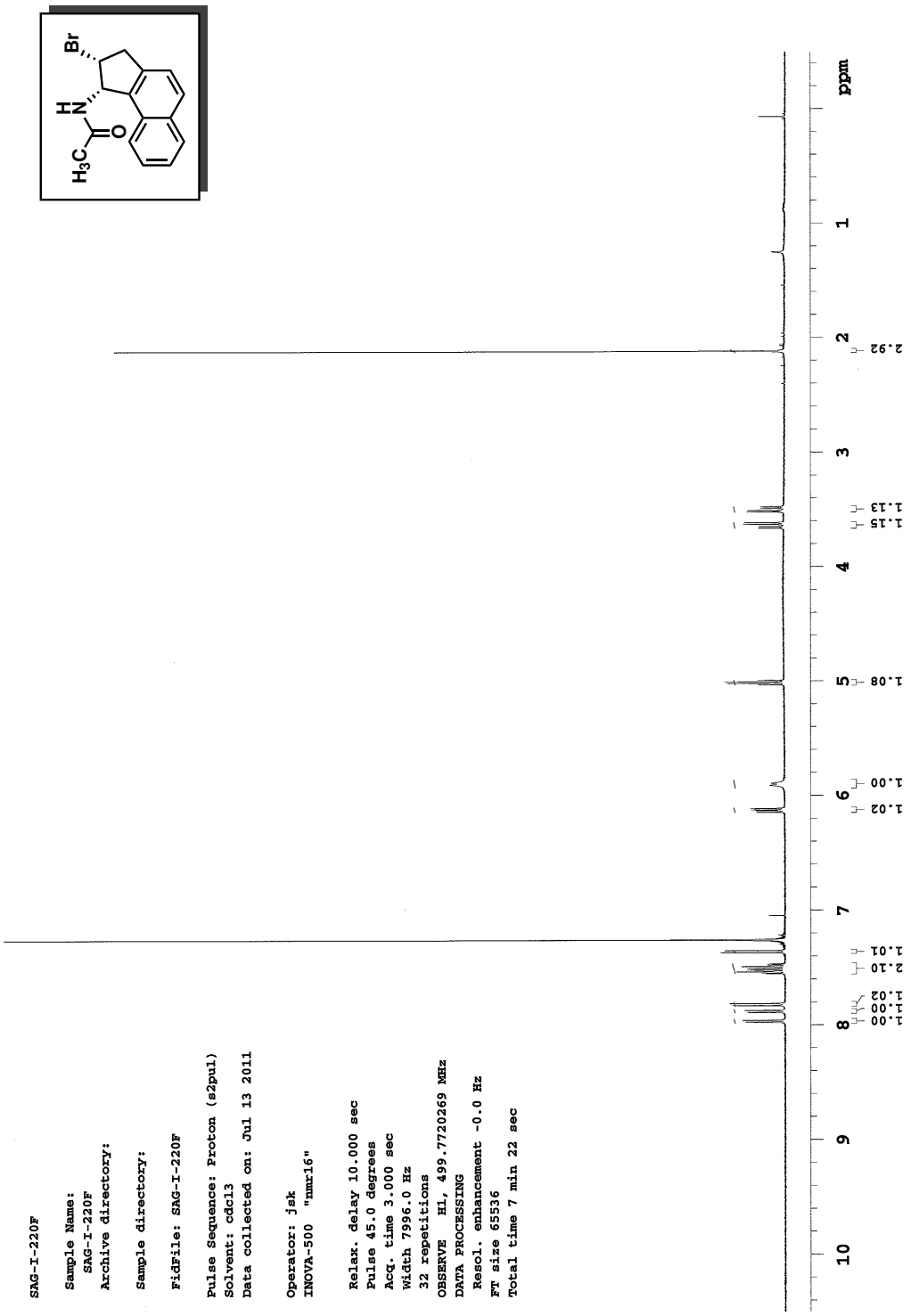


Figure 2.138: ^{13}C NMR of bromo acetamide (**2.105**)

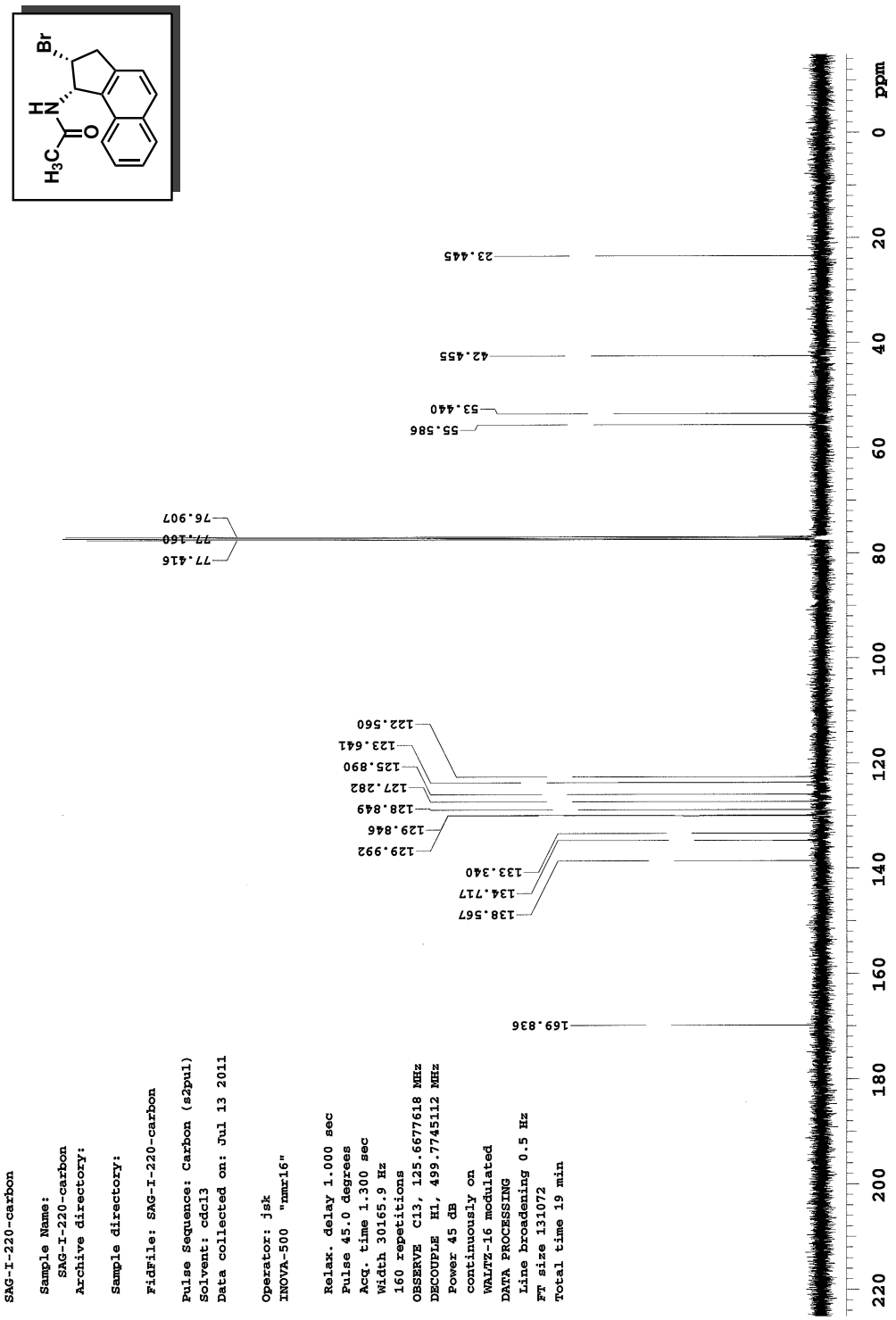


Figure 2.139: ^{1}H NMR of unsubstituted bis(oxazoline) (**2.106**)

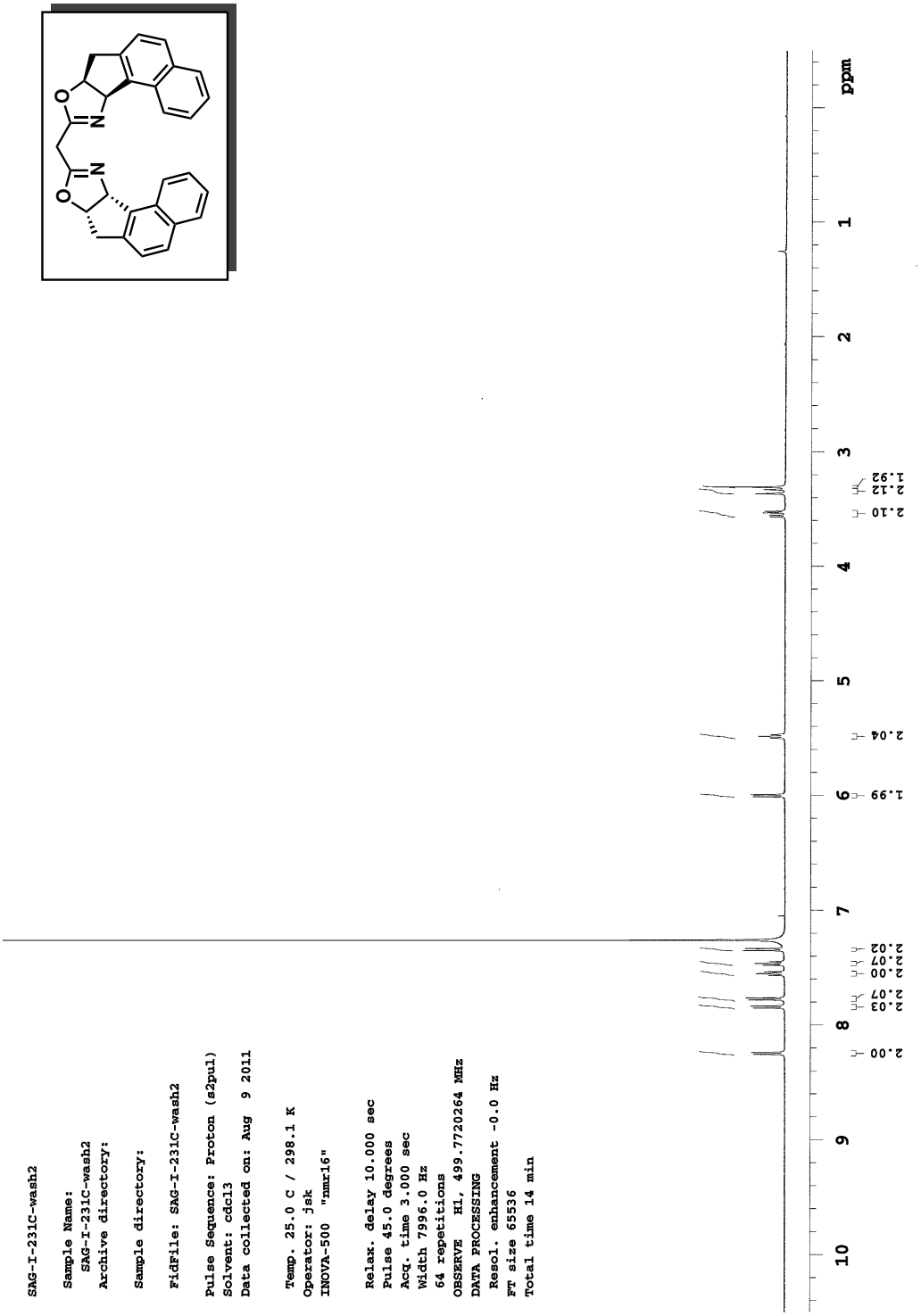


Figure 2.140: ^{13}C NMR of unsubstituted bis(oxazoline) (**2.106**)

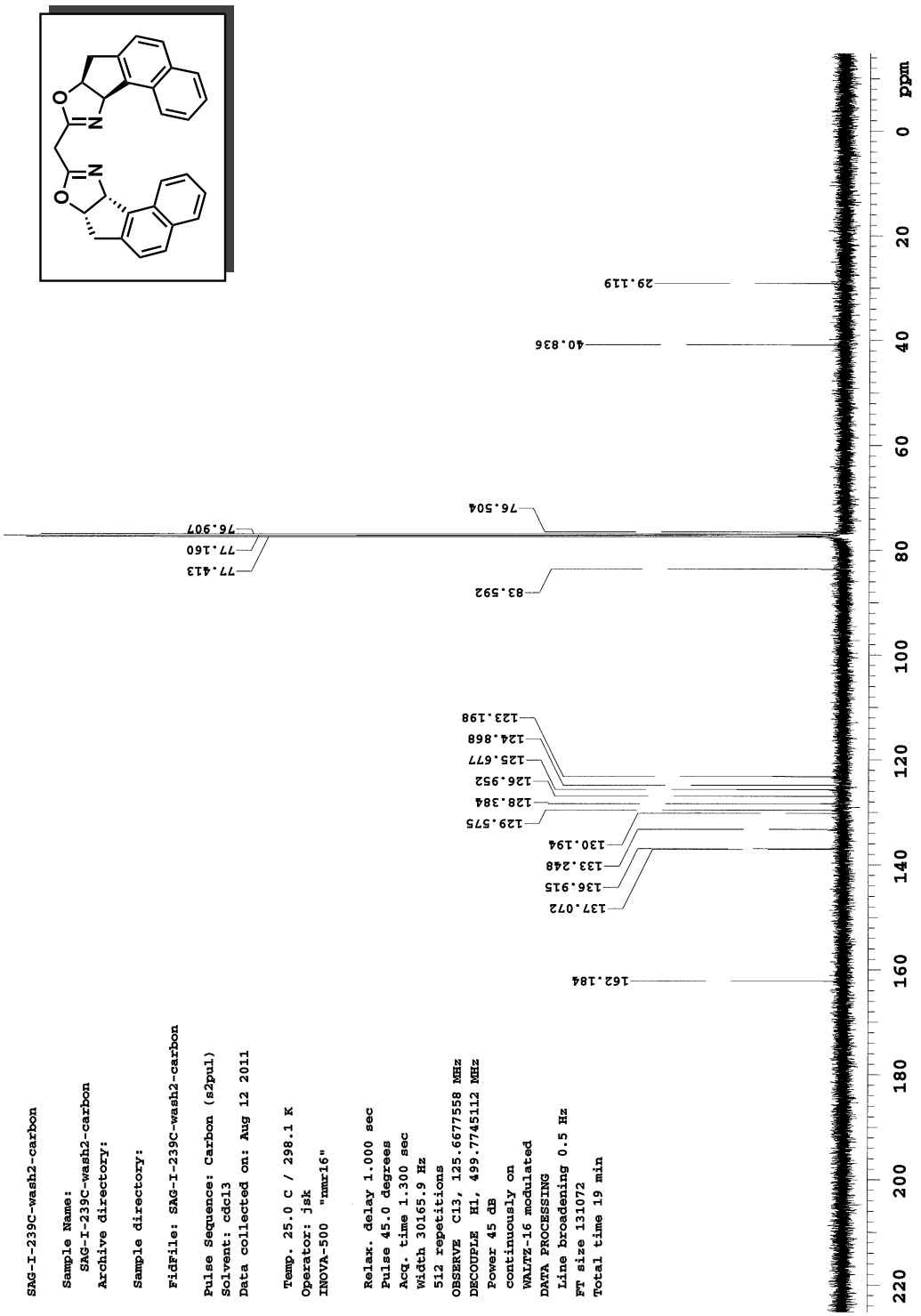


Figure 2.141: ^{1}H NMR of bis(oxazoline) ligand (**2.97**)

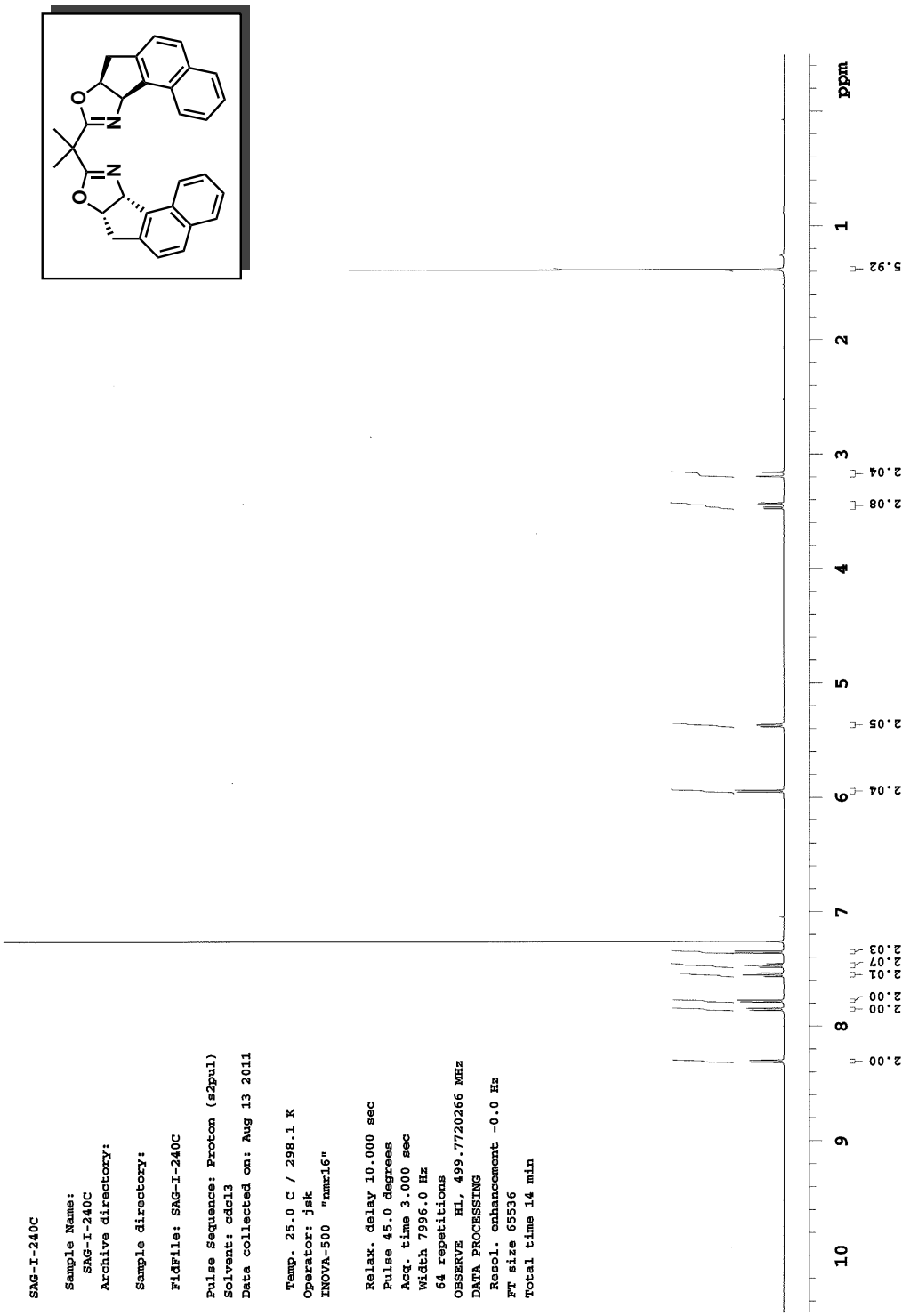


Figure 2.142: ^{13}C NMR of bis(oxazoline) ligand (**2.97**)

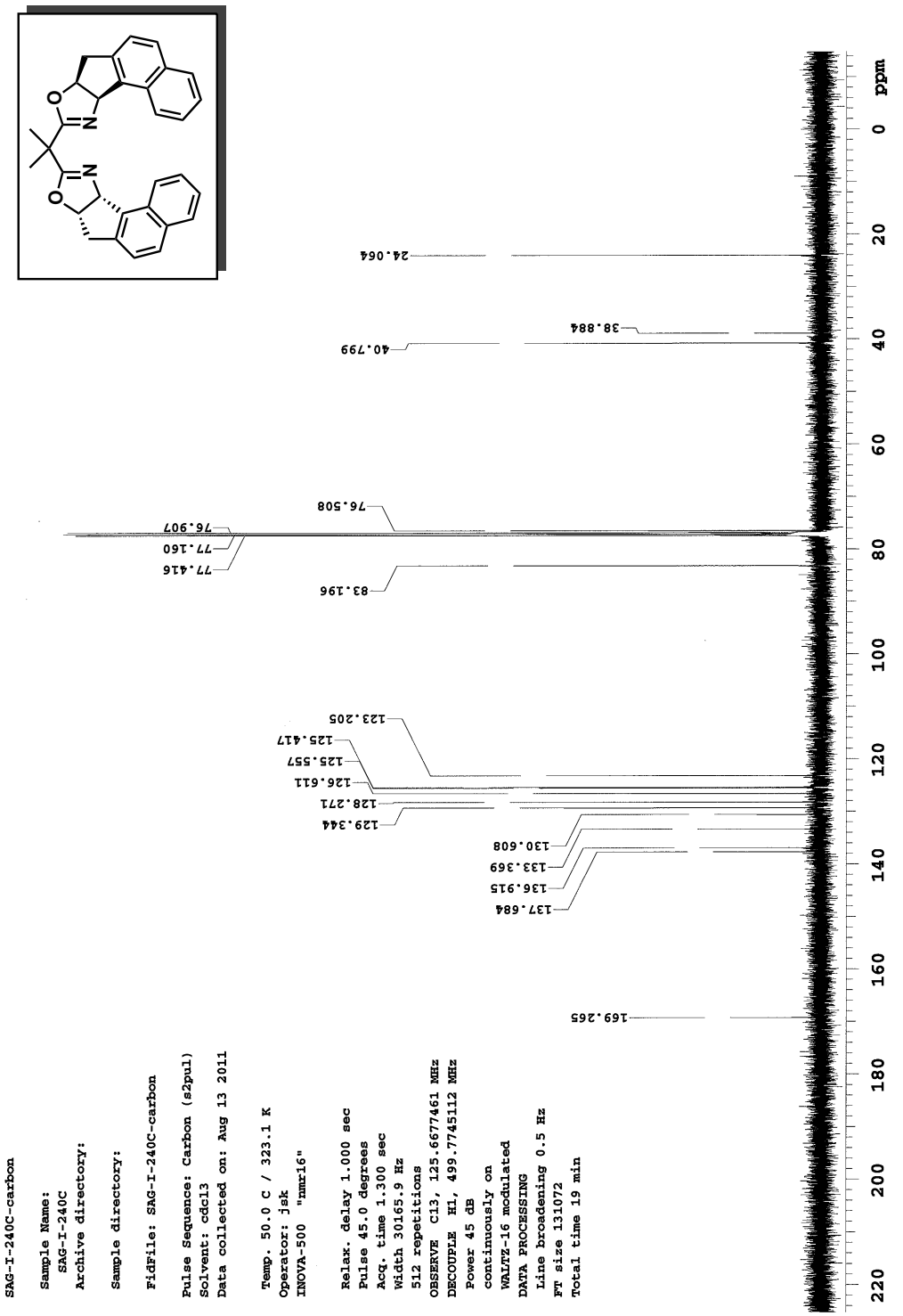


Figure 2.143: ^{1}H NMR of bis(oxazoline) ligand (**2.50**)

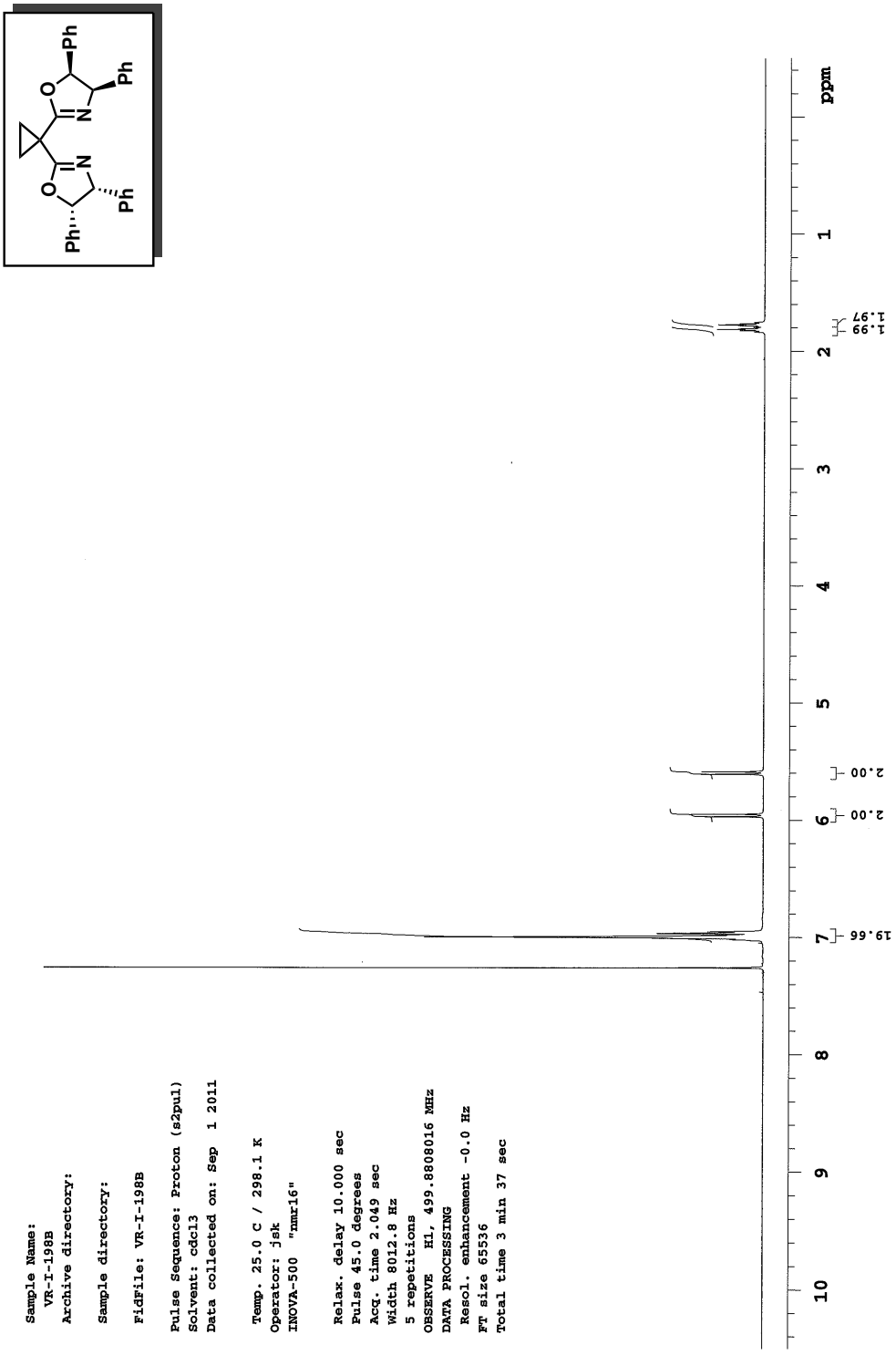


Figure 2.144: ^{13}C NMR of bis(oxazoline) ligand (**2.50**)

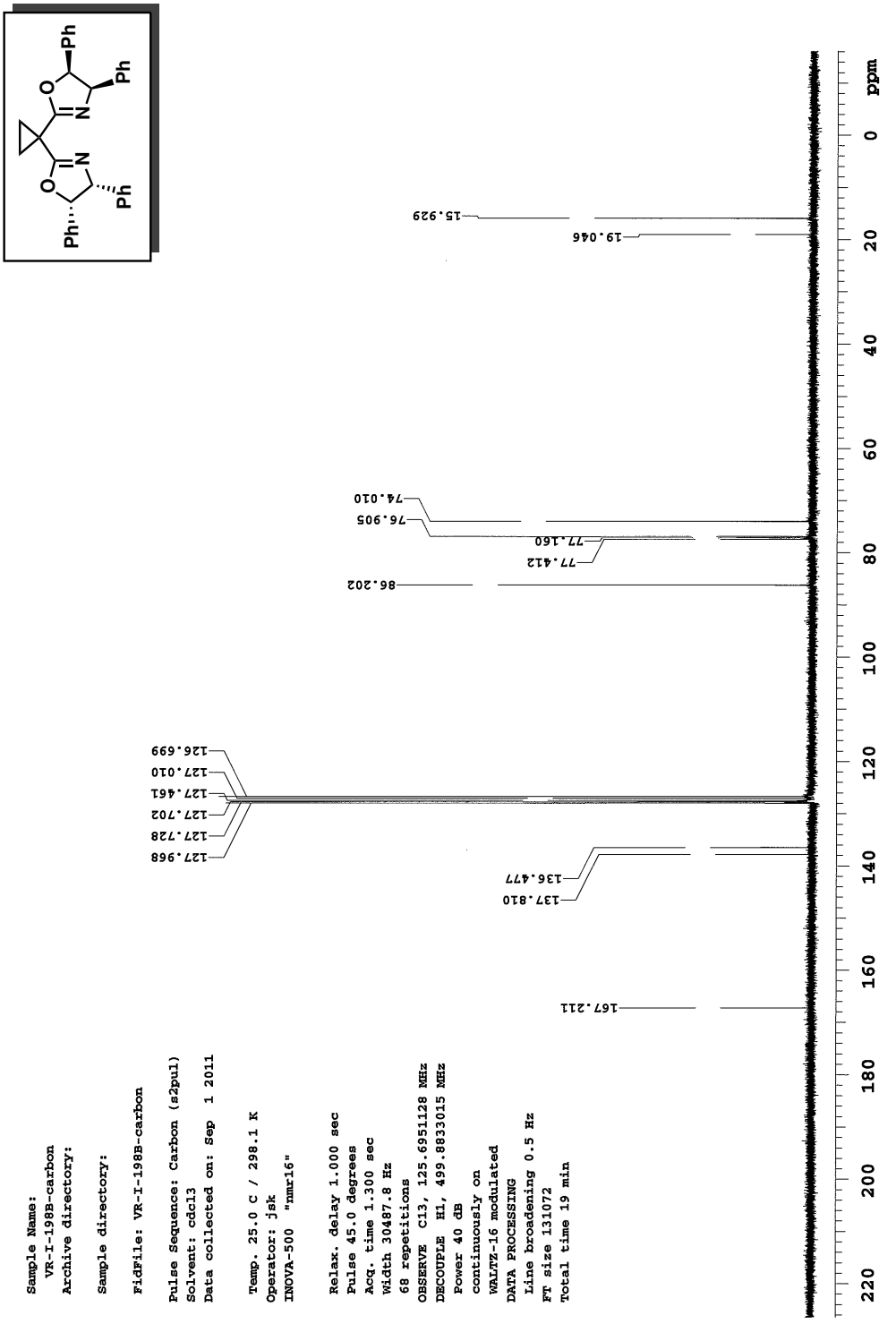


Figure 2.145: ^{1}H NMR of bis(oxazoline) ligand (**2.51**)

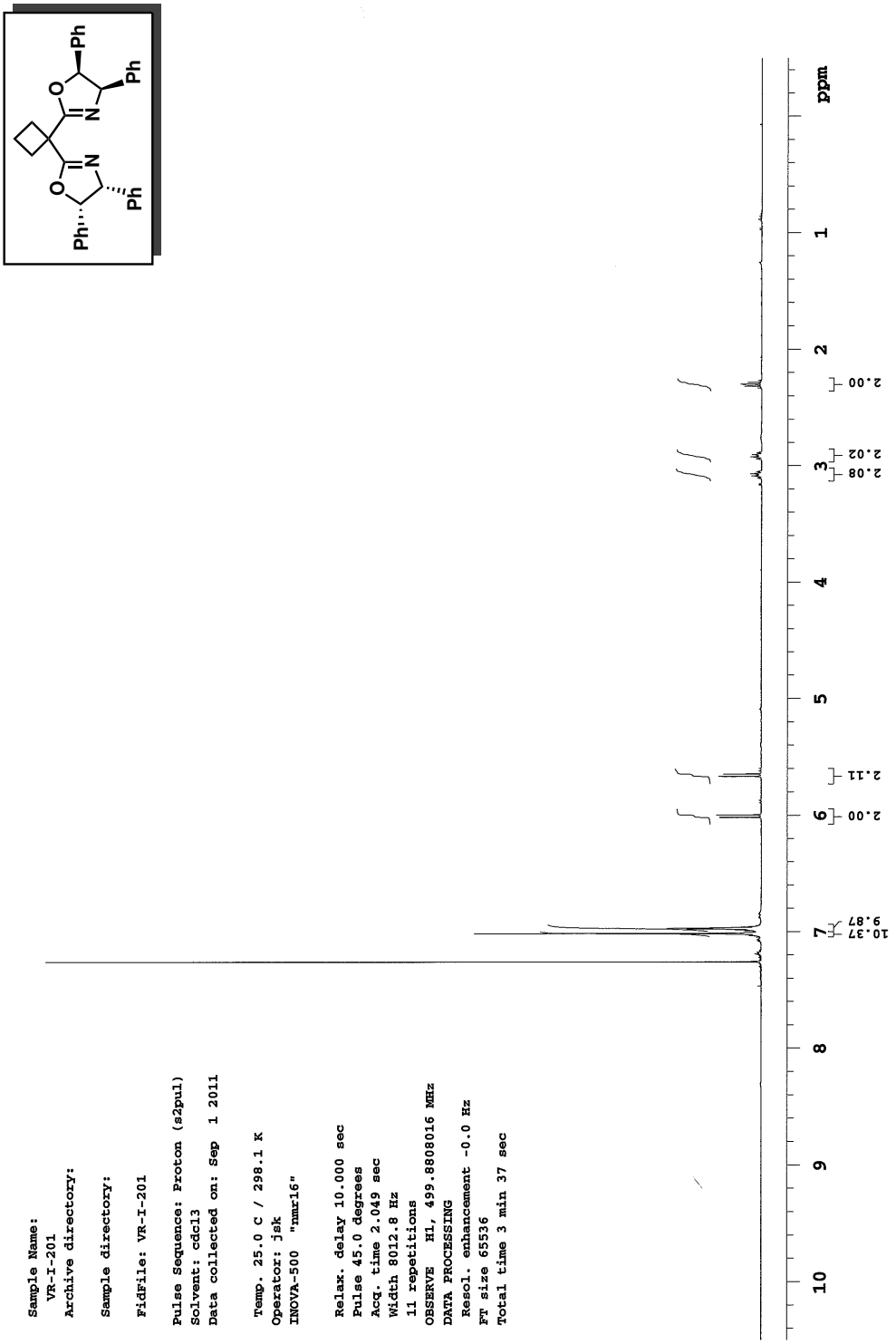


Figure 2.146: ^{13}C NMR of bis(oxazoline) ligand (**2.51**)

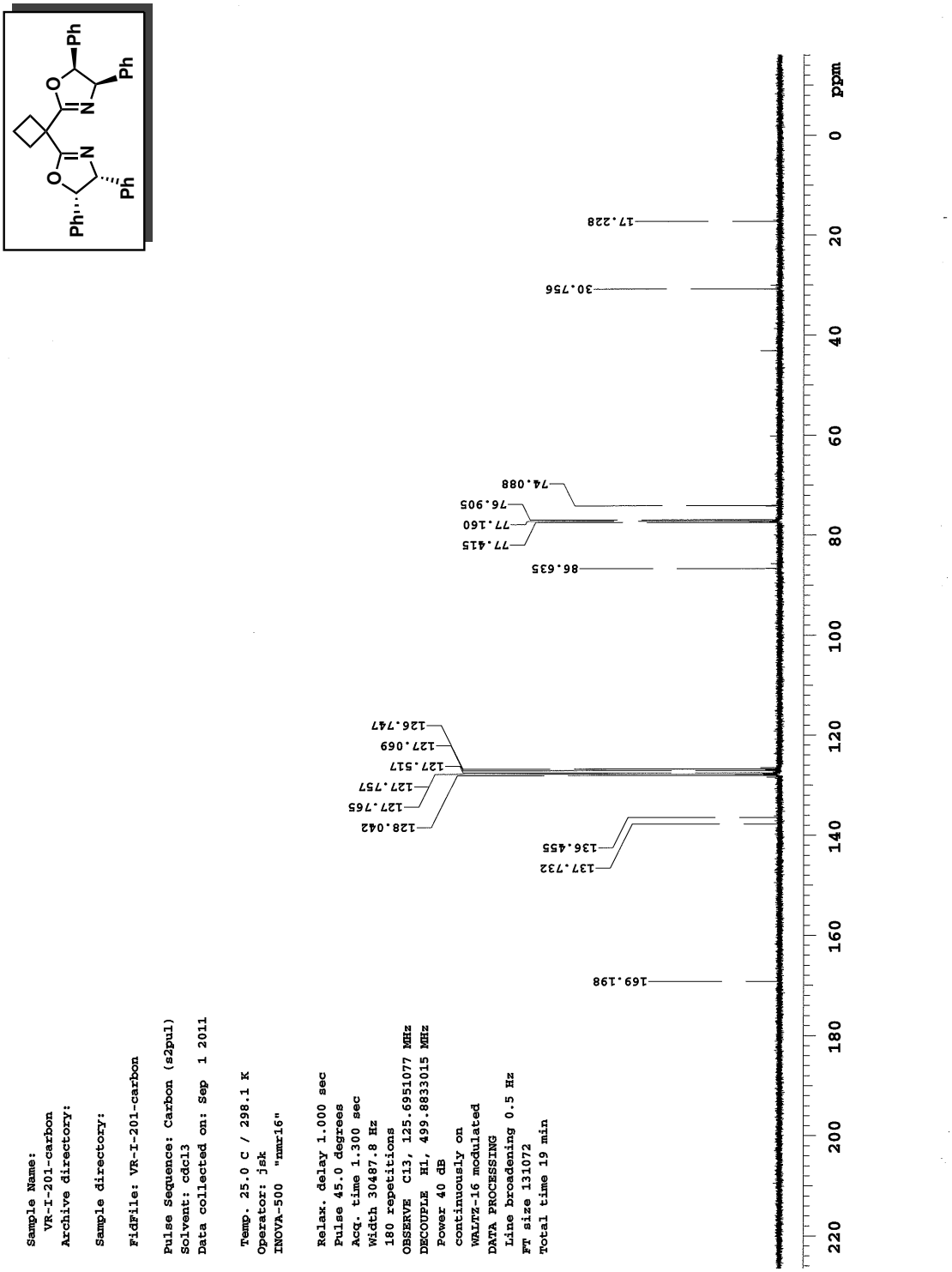


Figure 2.147: ^{1}H NMR of bis(oxazoline) ligand (**2.52**)

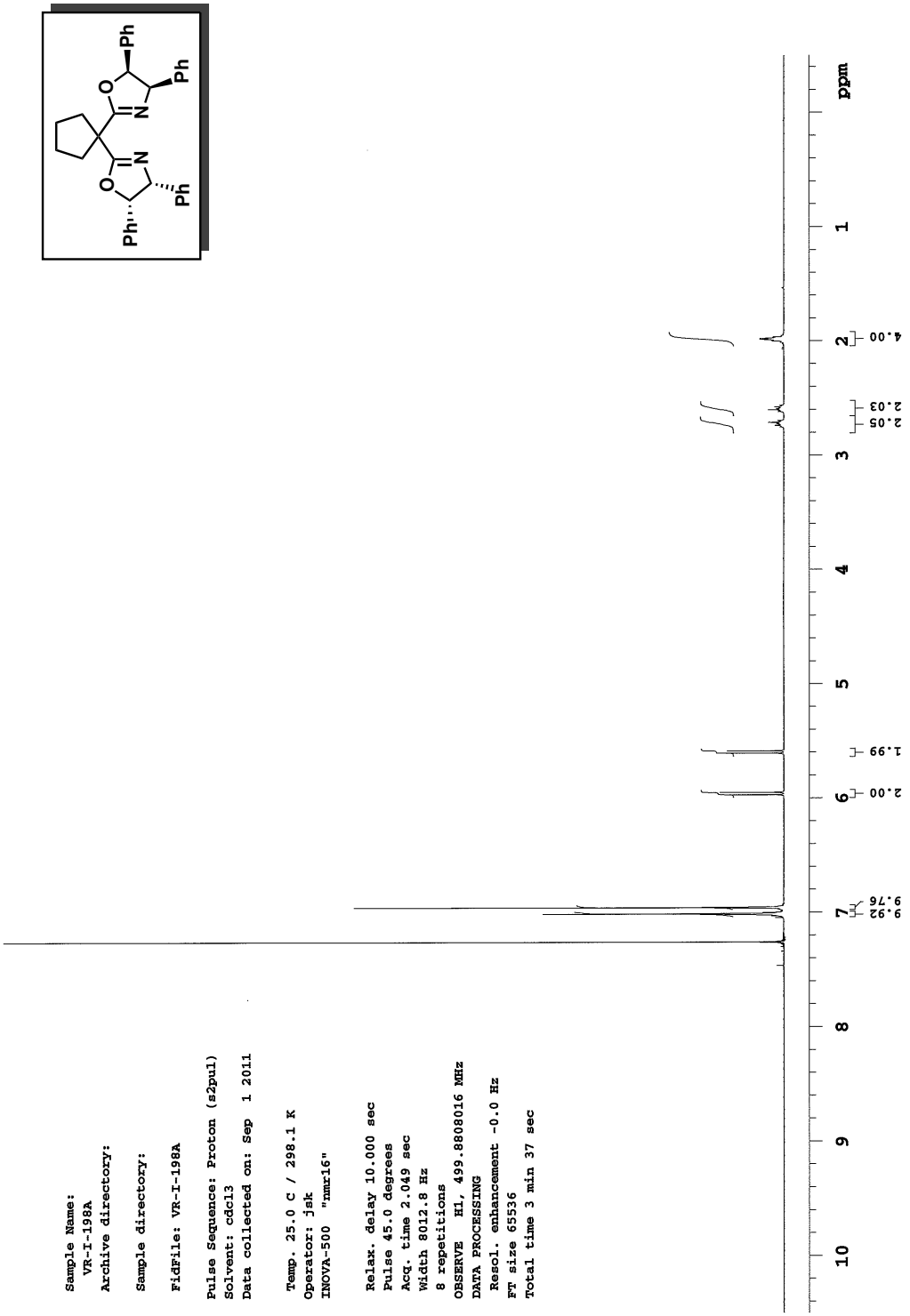


Figure 2.148: ^{13}C NMR of bis(oxazoline) ligand (**2.52**)

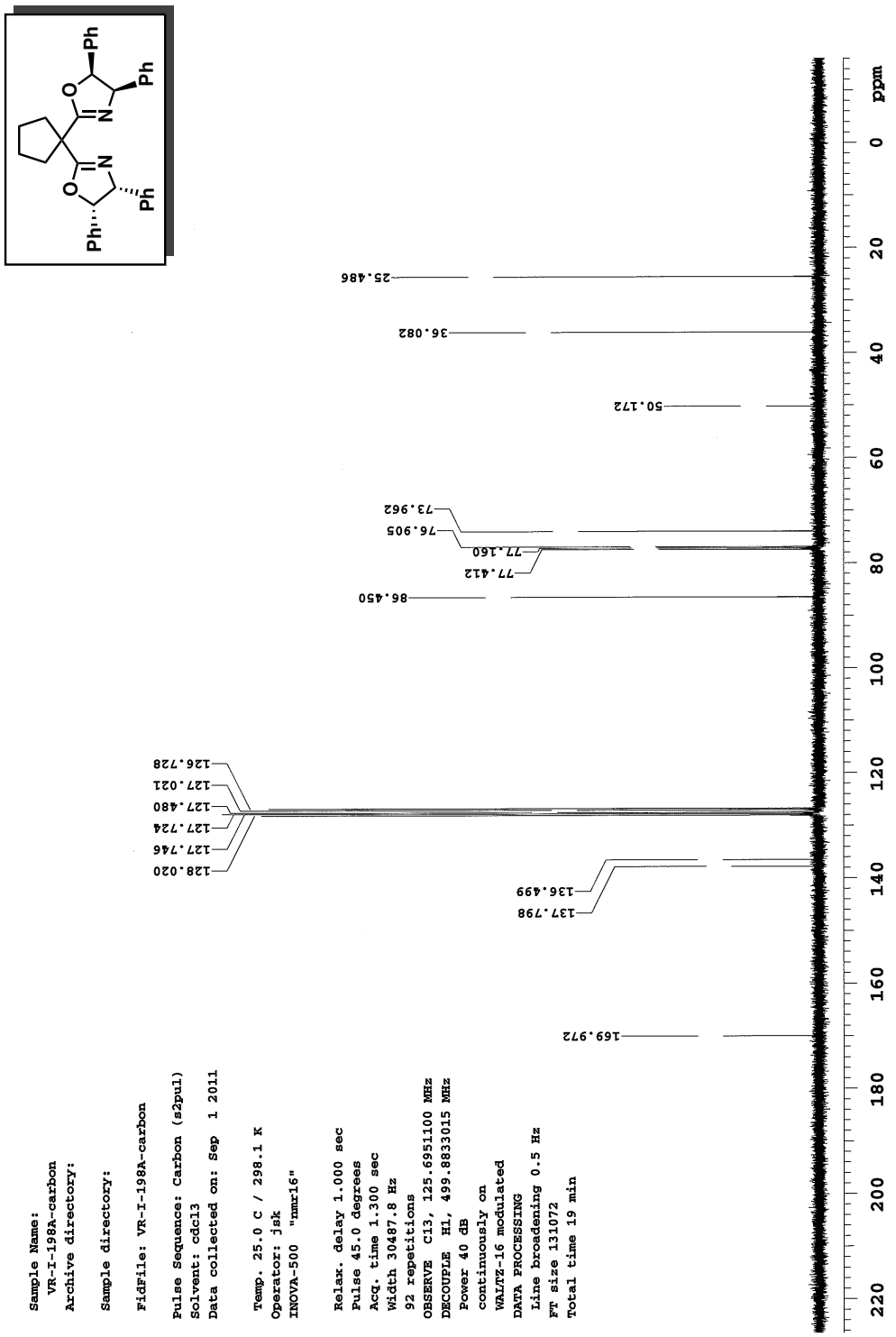


Figure 2.149: ^{1}H NMR of bis(oxazoline) ligand (**2.53**)

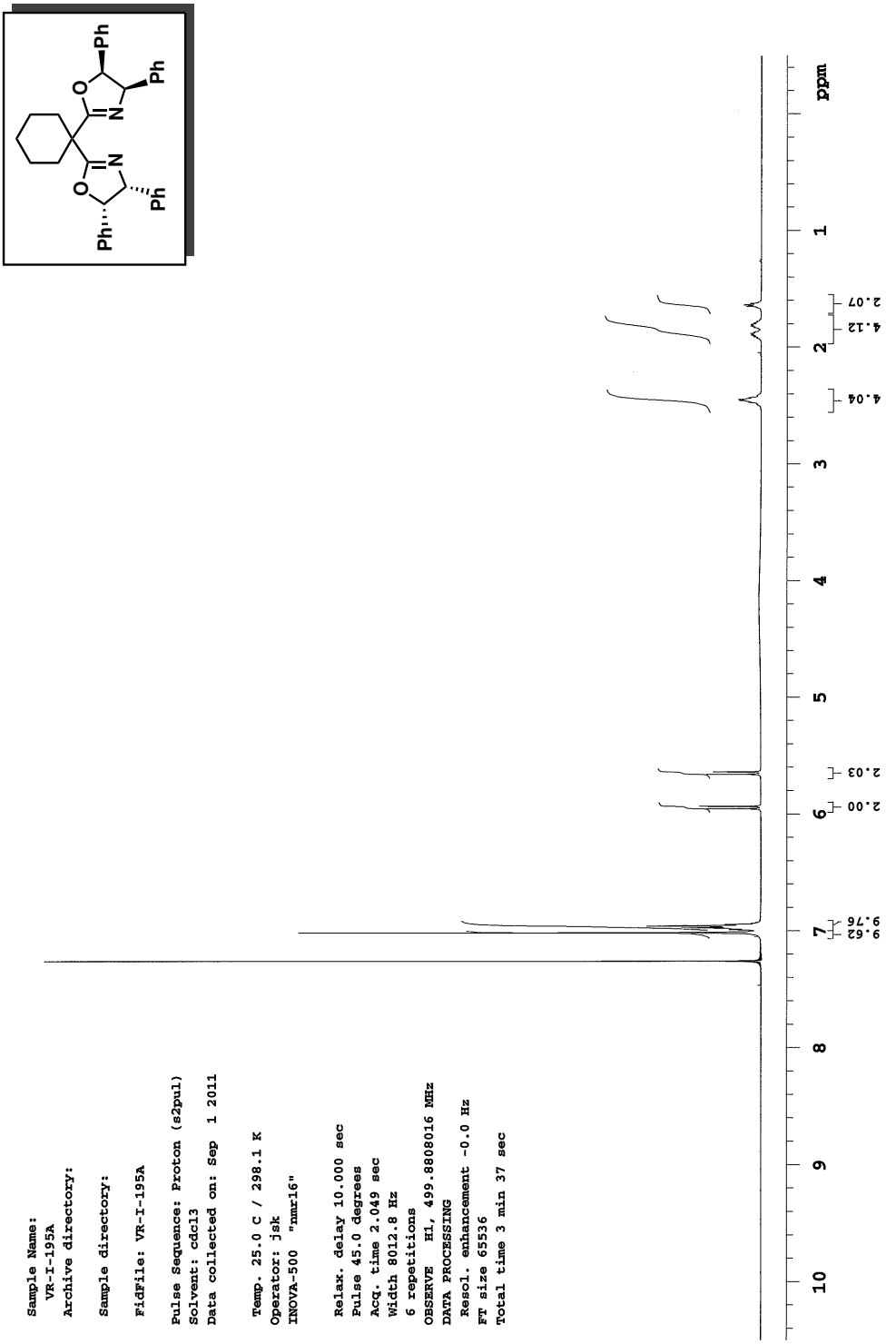


Figure 2.150: ^{13}C NMR of bis(oxazoline) ligand (**2.53**)

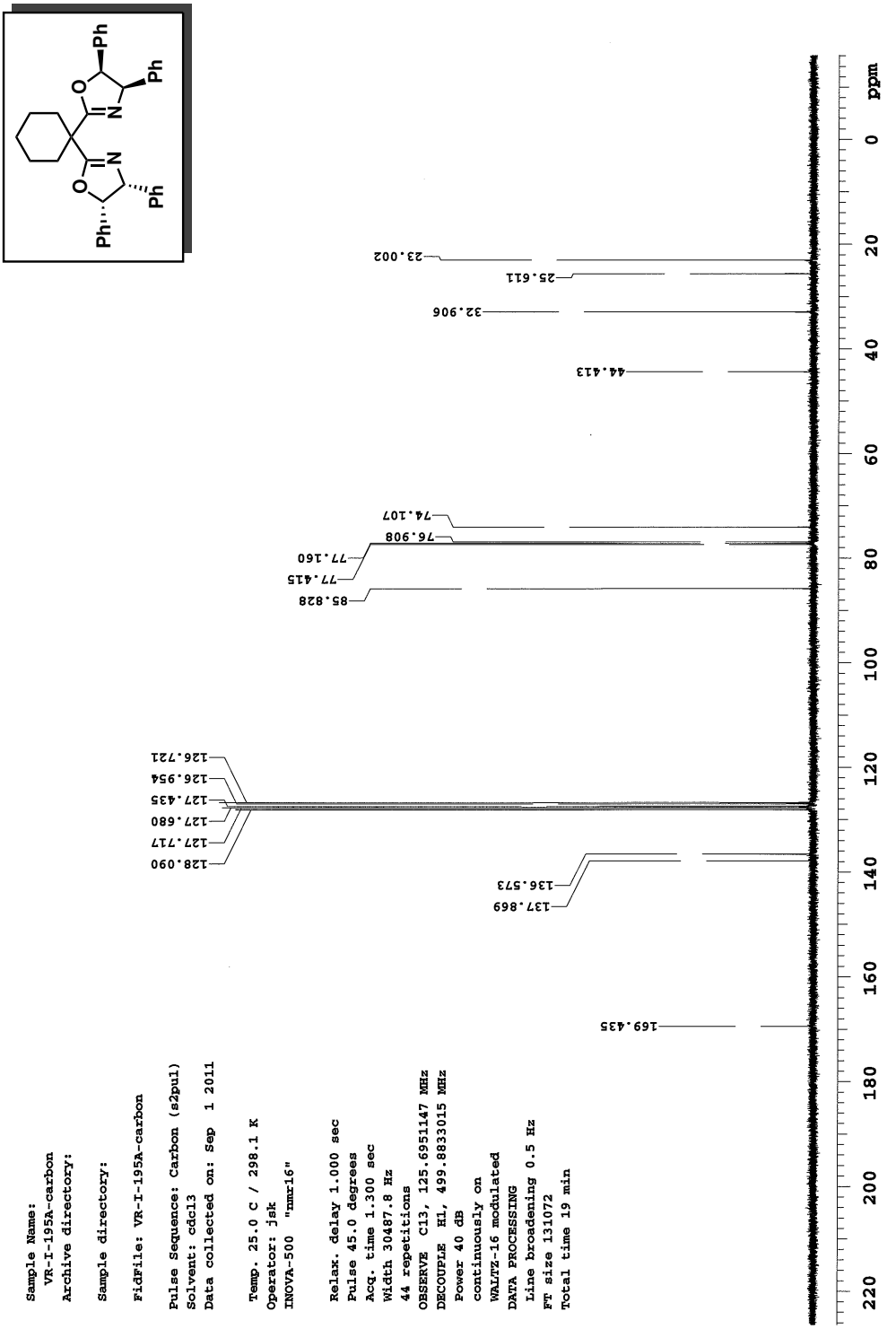


Figure 2.151: ^{1}H NMR of tetra(oxazoline) ligand (**2.135**)

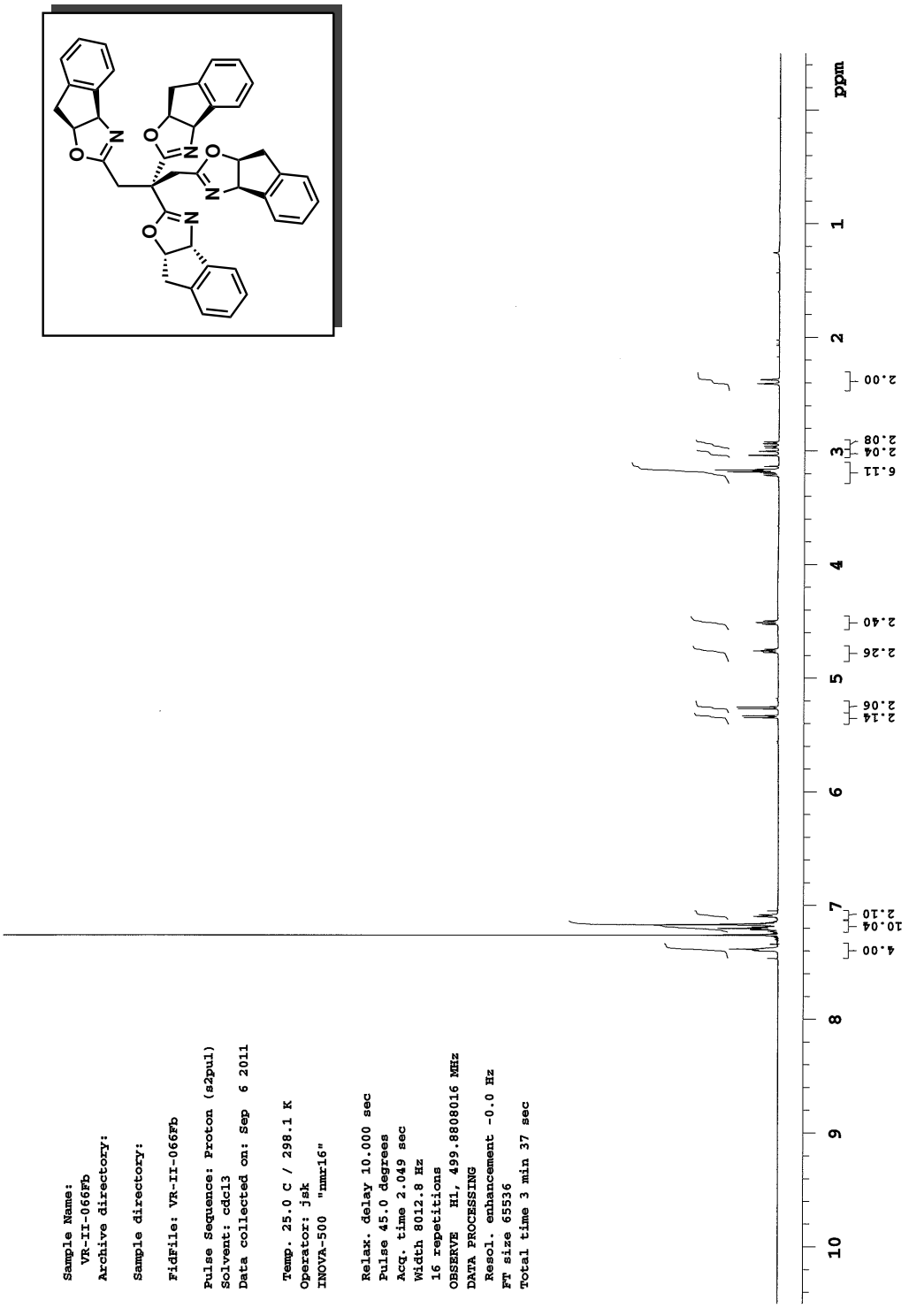


Figure 2.152: ^{13}C NMR of tetra(oxazoline) ligand (**2.135**)

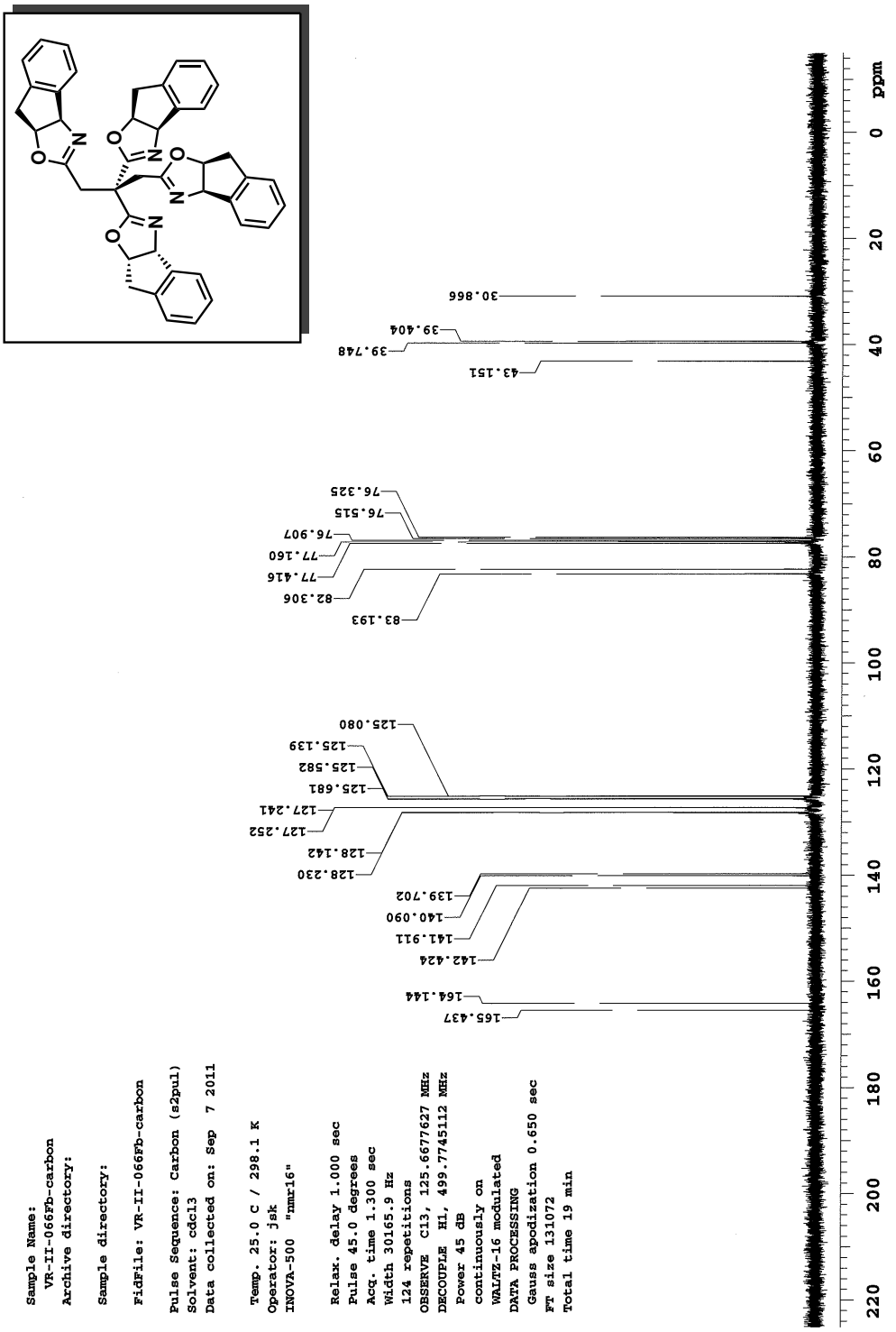


Figure 2.153: ^{1}H NMR of tris(oxazoline) ligand (**2.67**)

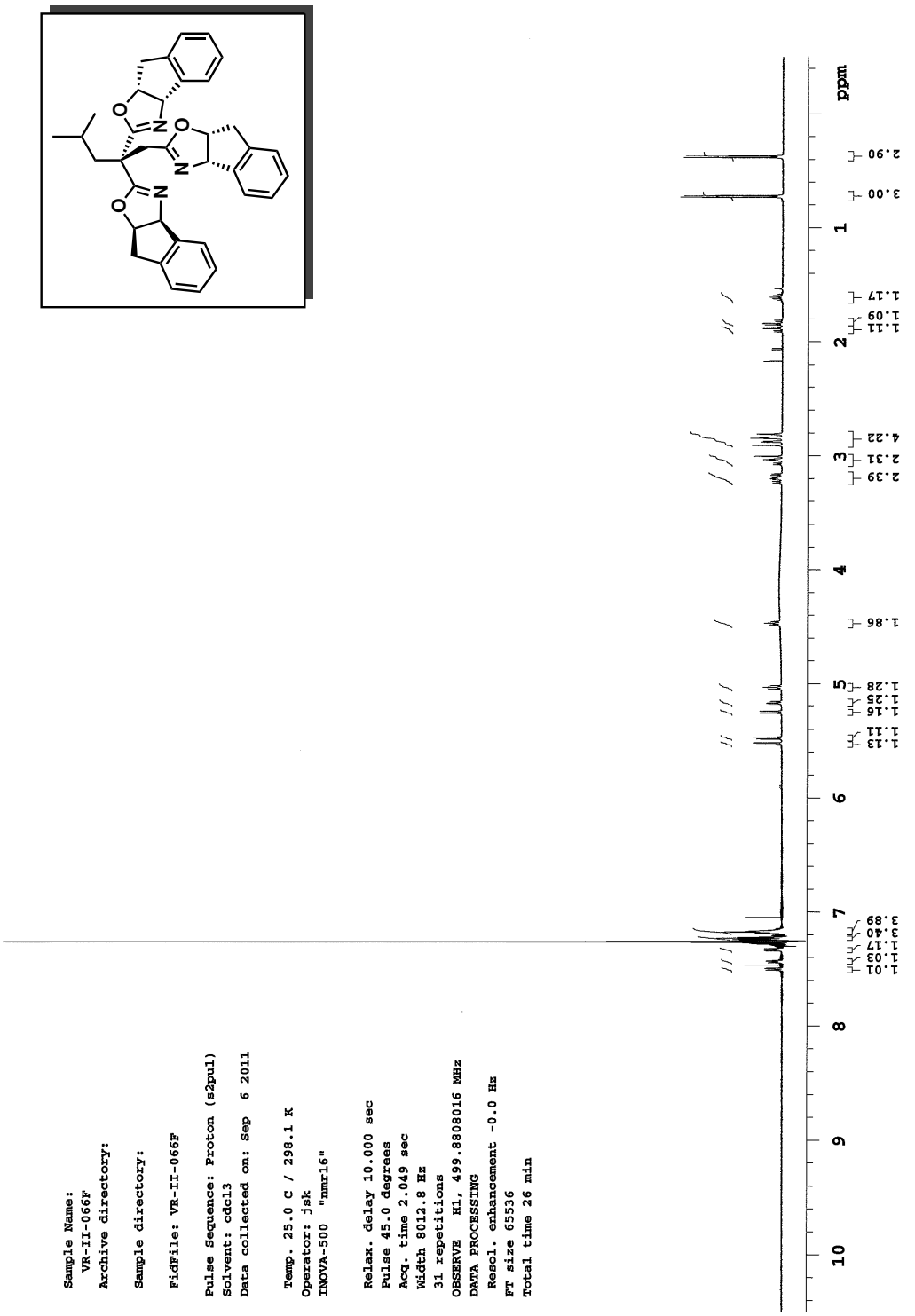


Figure 2.154: ^{13}C NMR of tris(oxazoline) ligand (**2.67**)

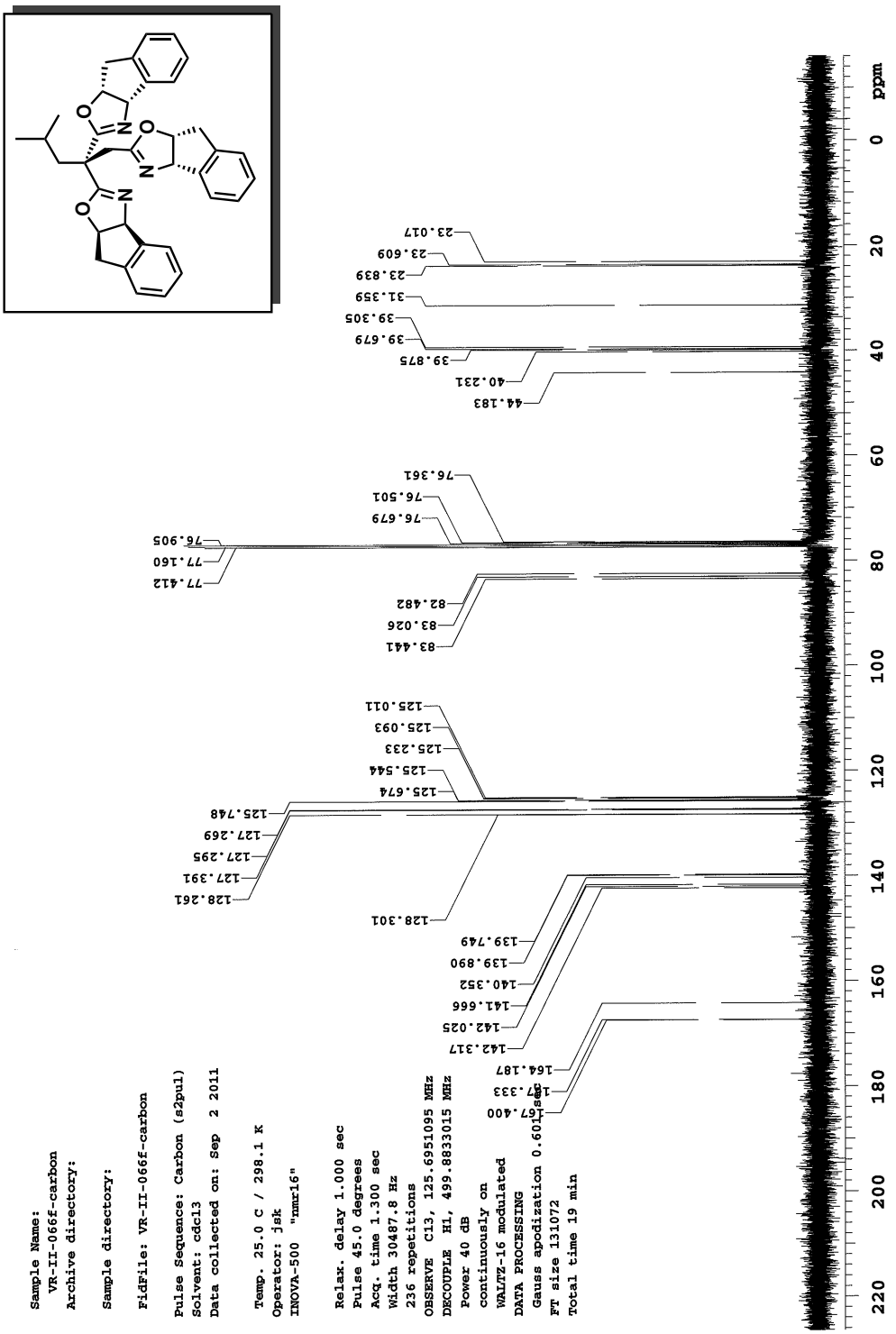


Figure 2.155: ^{1}H NMR of tris(oxazoline) ligand (**2.68**)

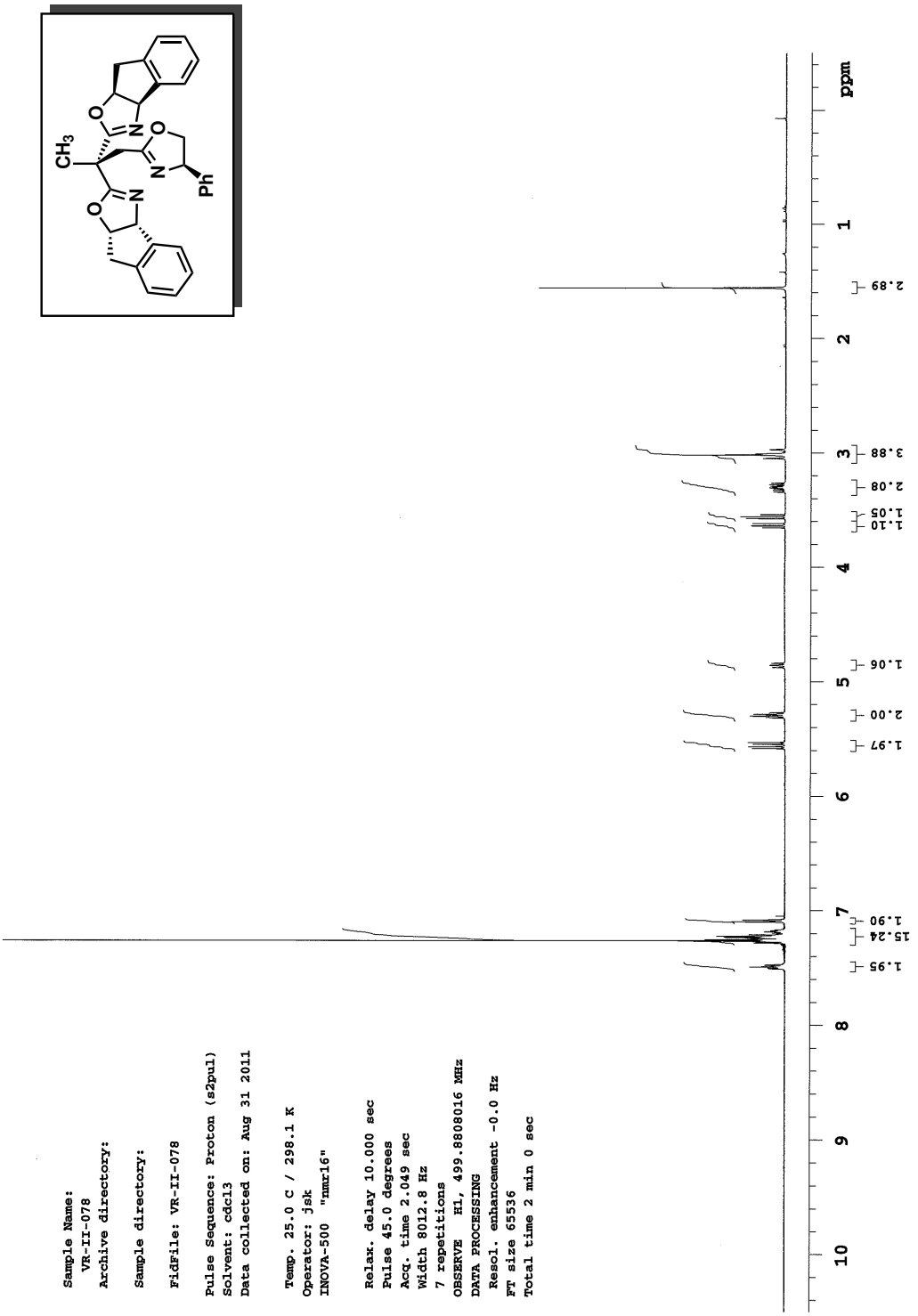


Figure 2.156: ^{13}C NMR of tris(oxazoline) ligand (**2.68**)

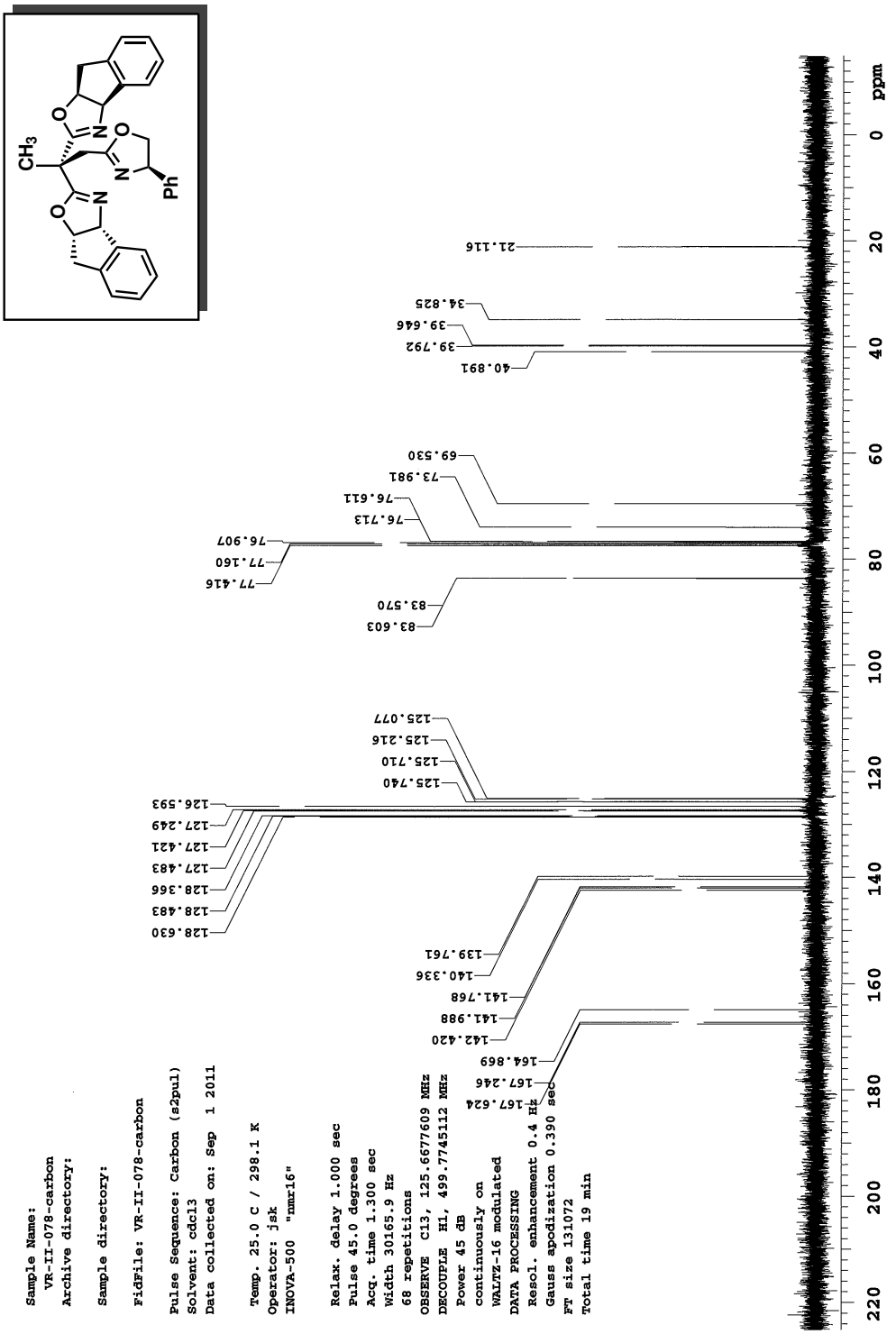


Figure 2.157: ^{1}H NMR of tris(oxazoline) ligand (**2.69**)

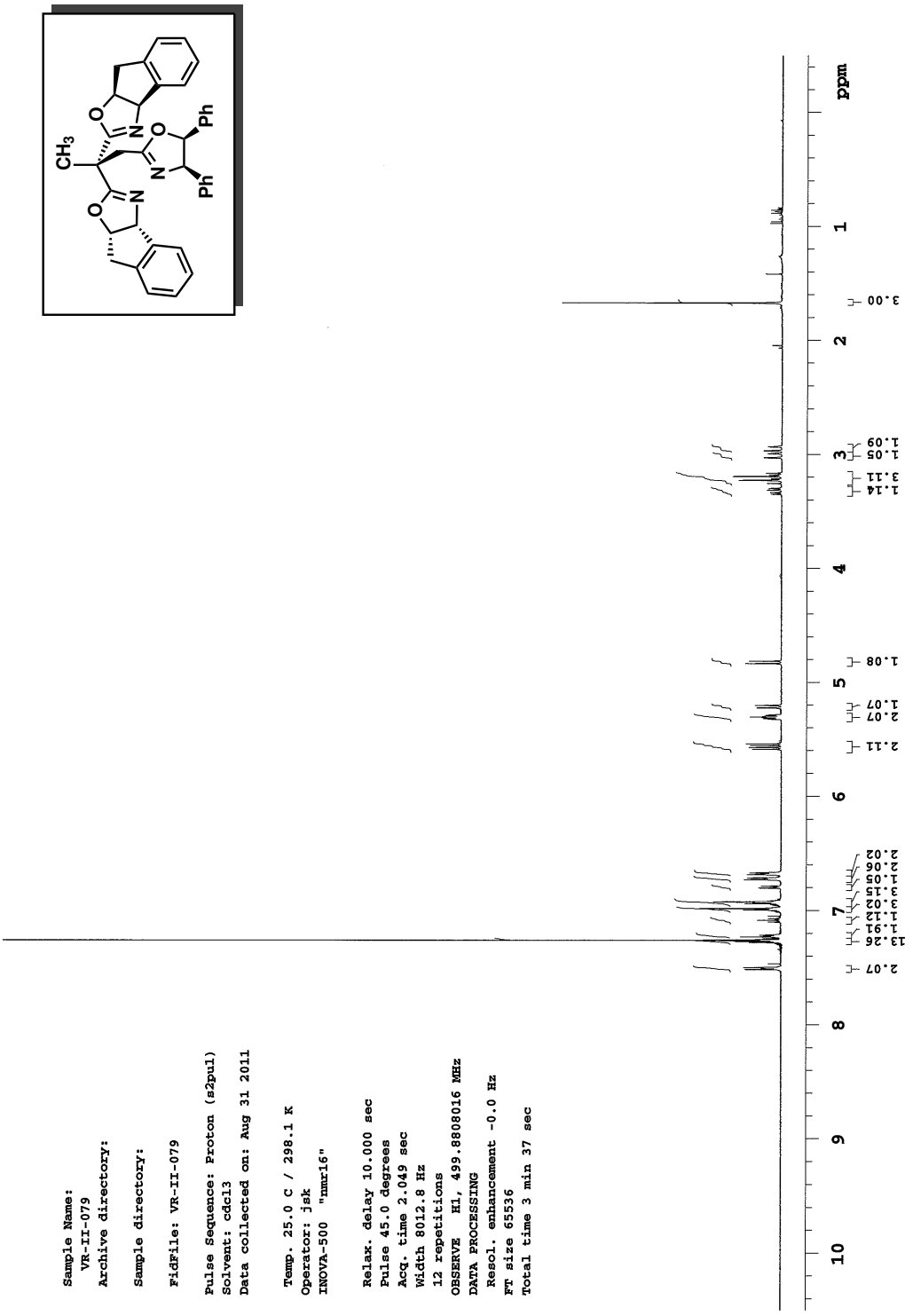


Figure 2.158: ^{13}C NMR of tris(oxazoline) ligand (**2.69**)

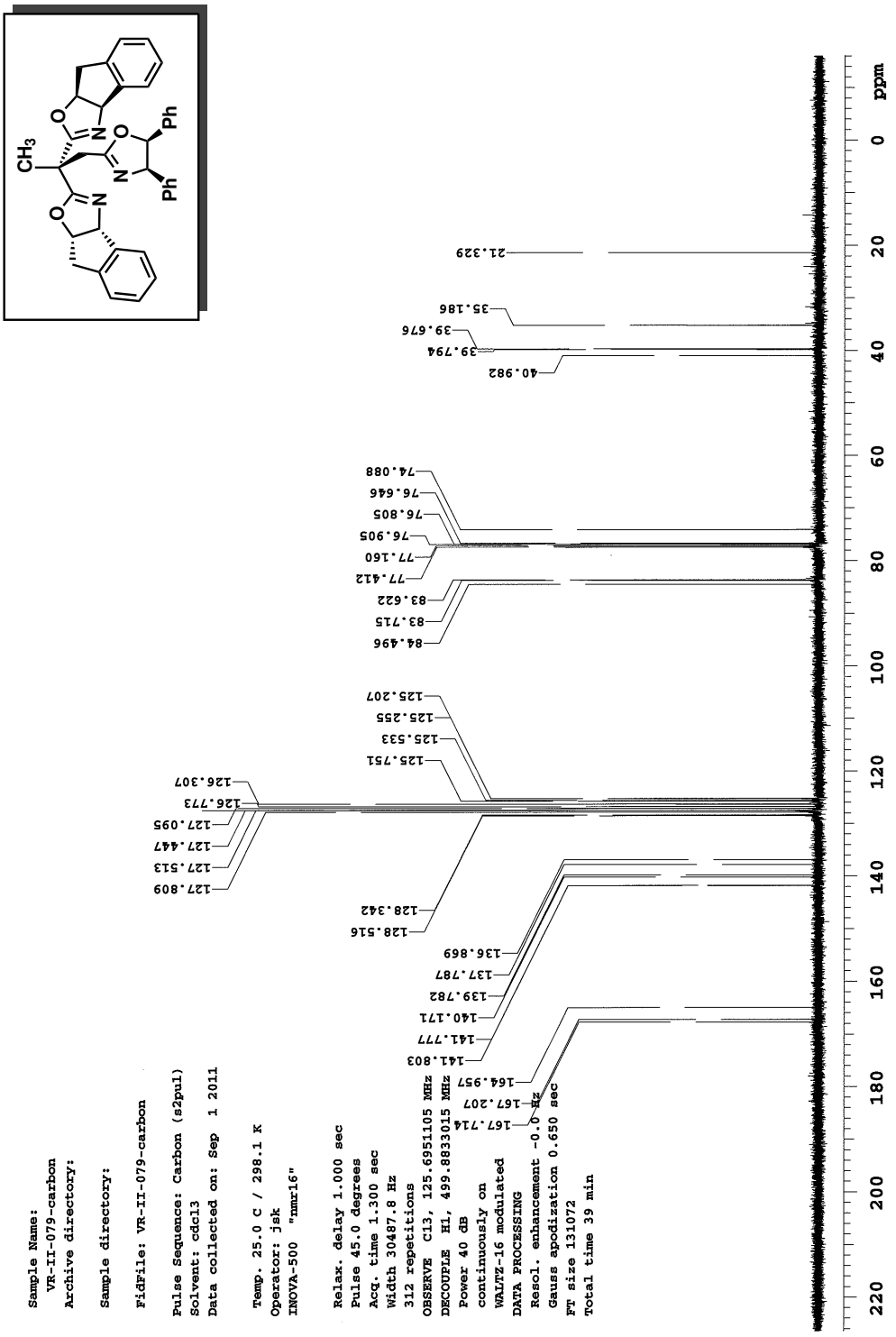


Figure 2.159: ^{1}H NMR of amido alcohol (**2.136**)

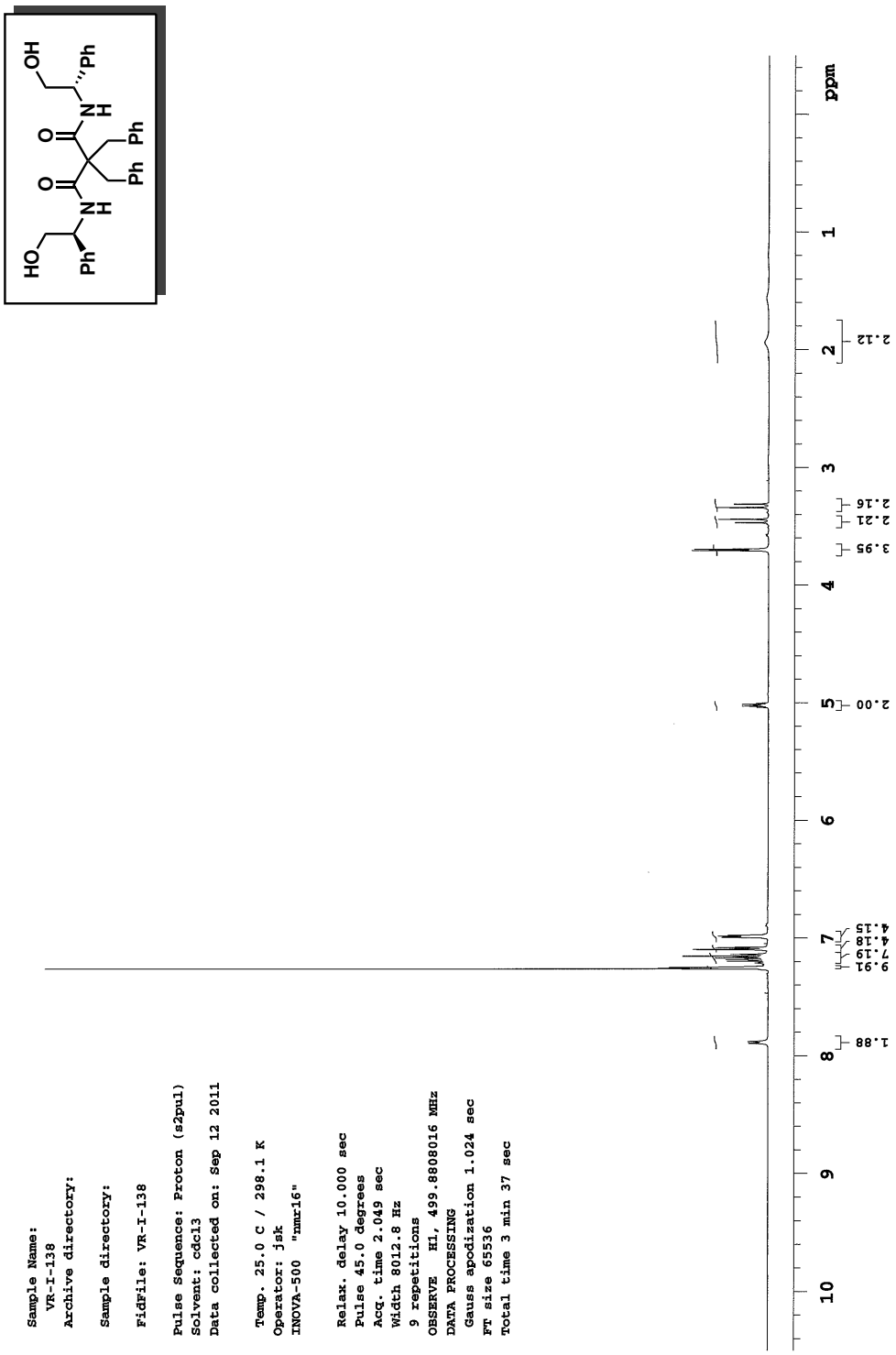


Figure 2.160: ^{13}C NMR of amido alcohol (**2.136**)

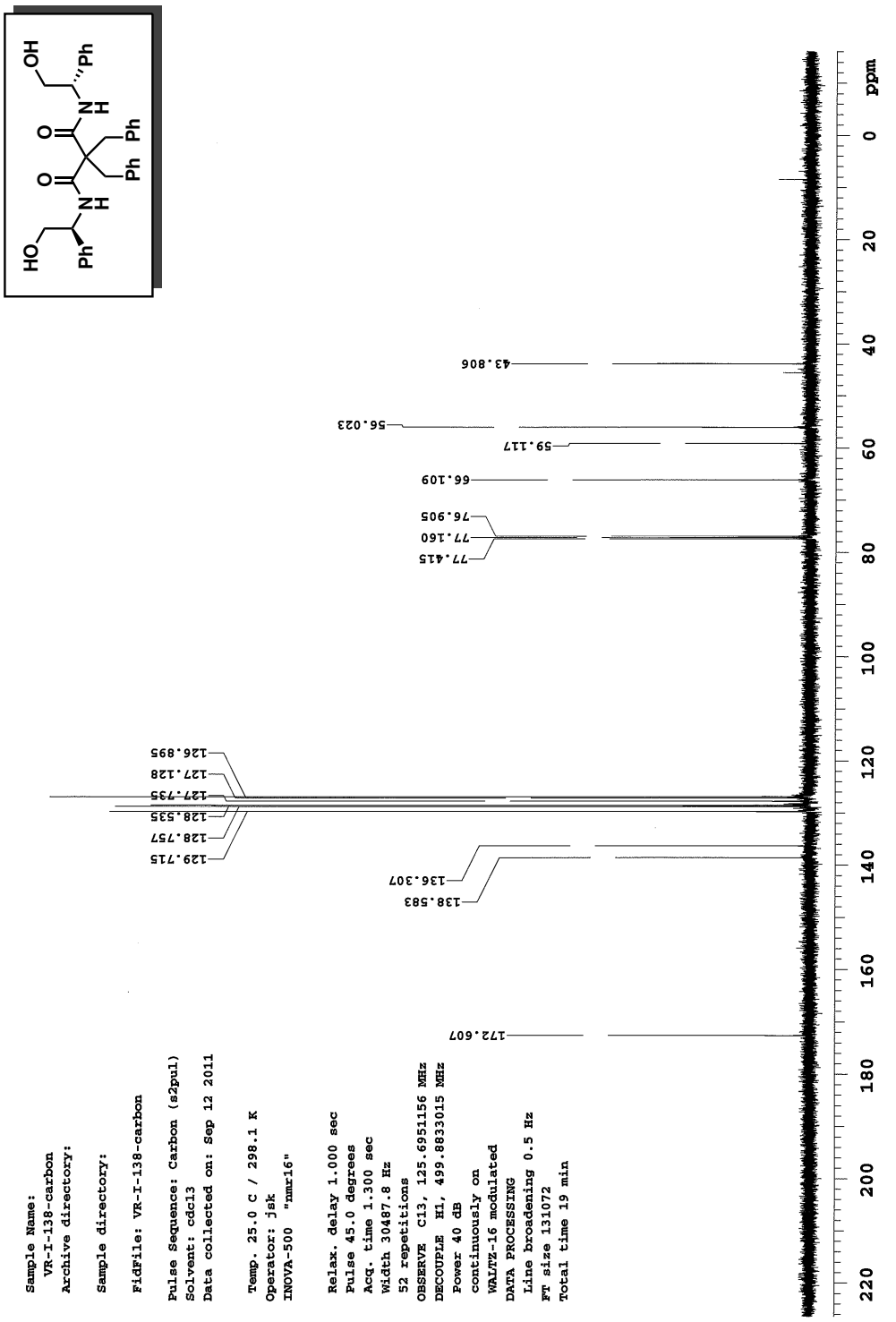


Figure 2.161: ^{1}H NMR of bis(oxazoline) ligand (**2.56**)

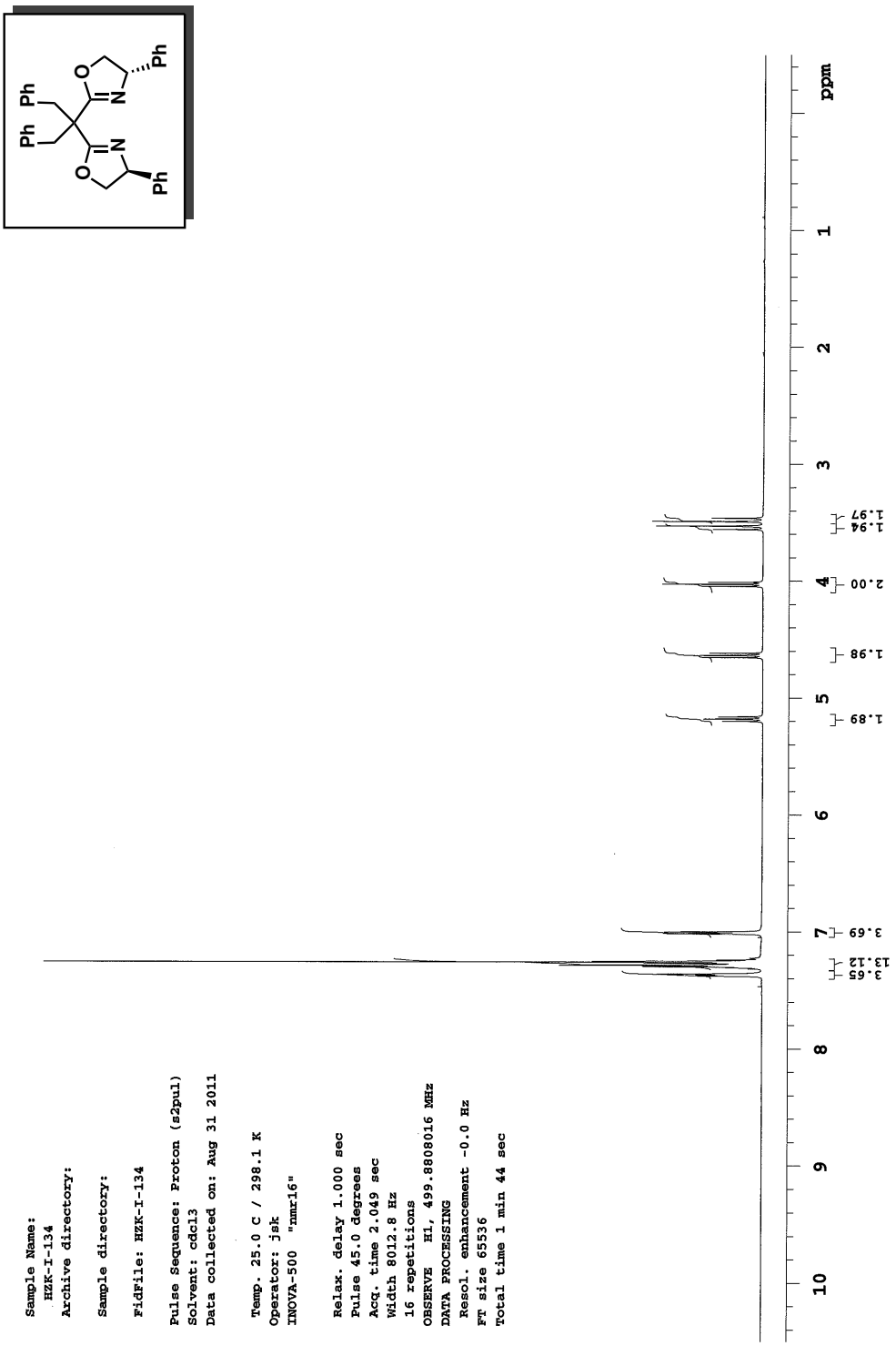


Figure 2.162: ^{13}C NMR of bis(oxazoline) ligand (**2.56**)

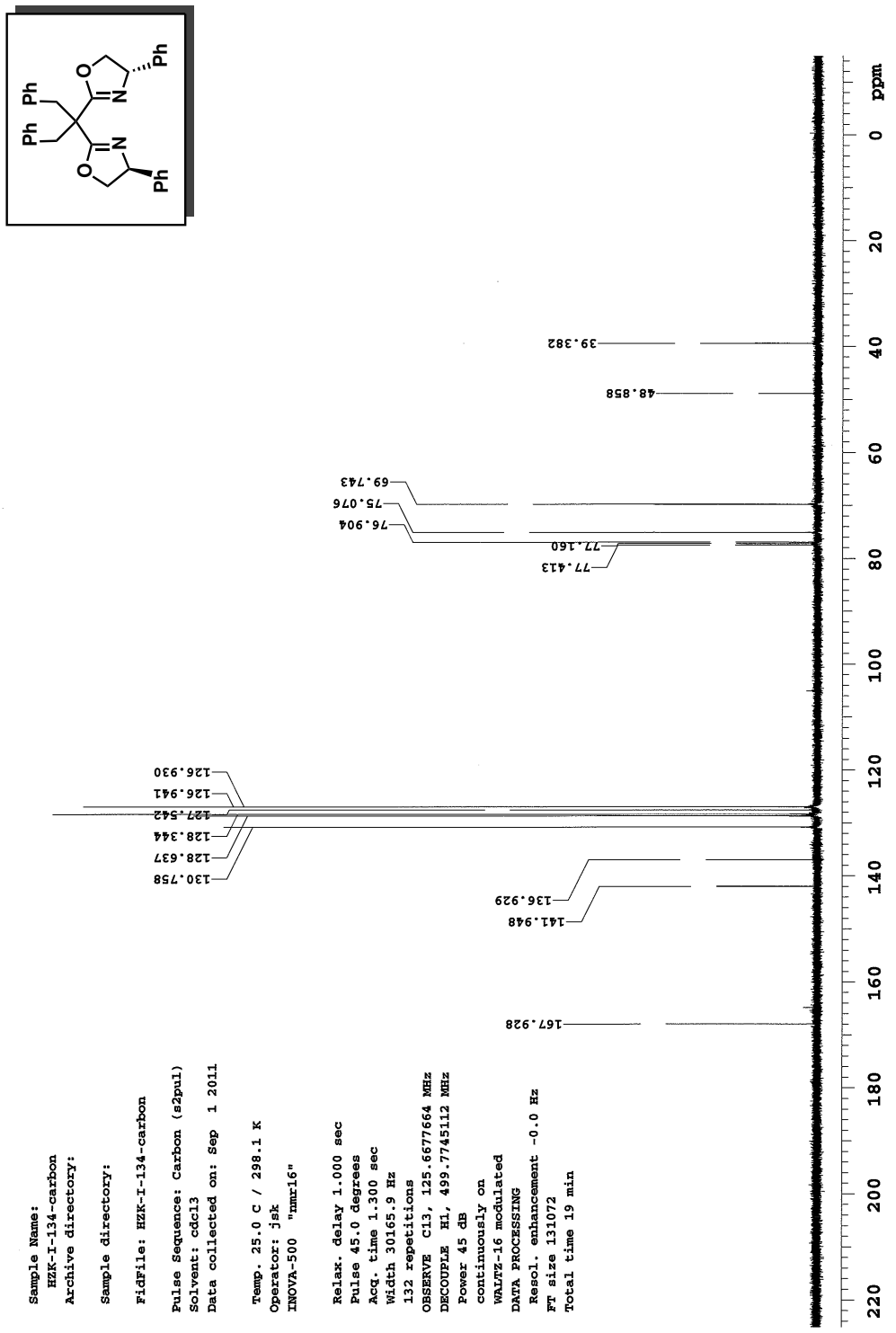


Figure 2.163: ^{1}H NMR of bis(oxazoline) ligand (**2.62**)

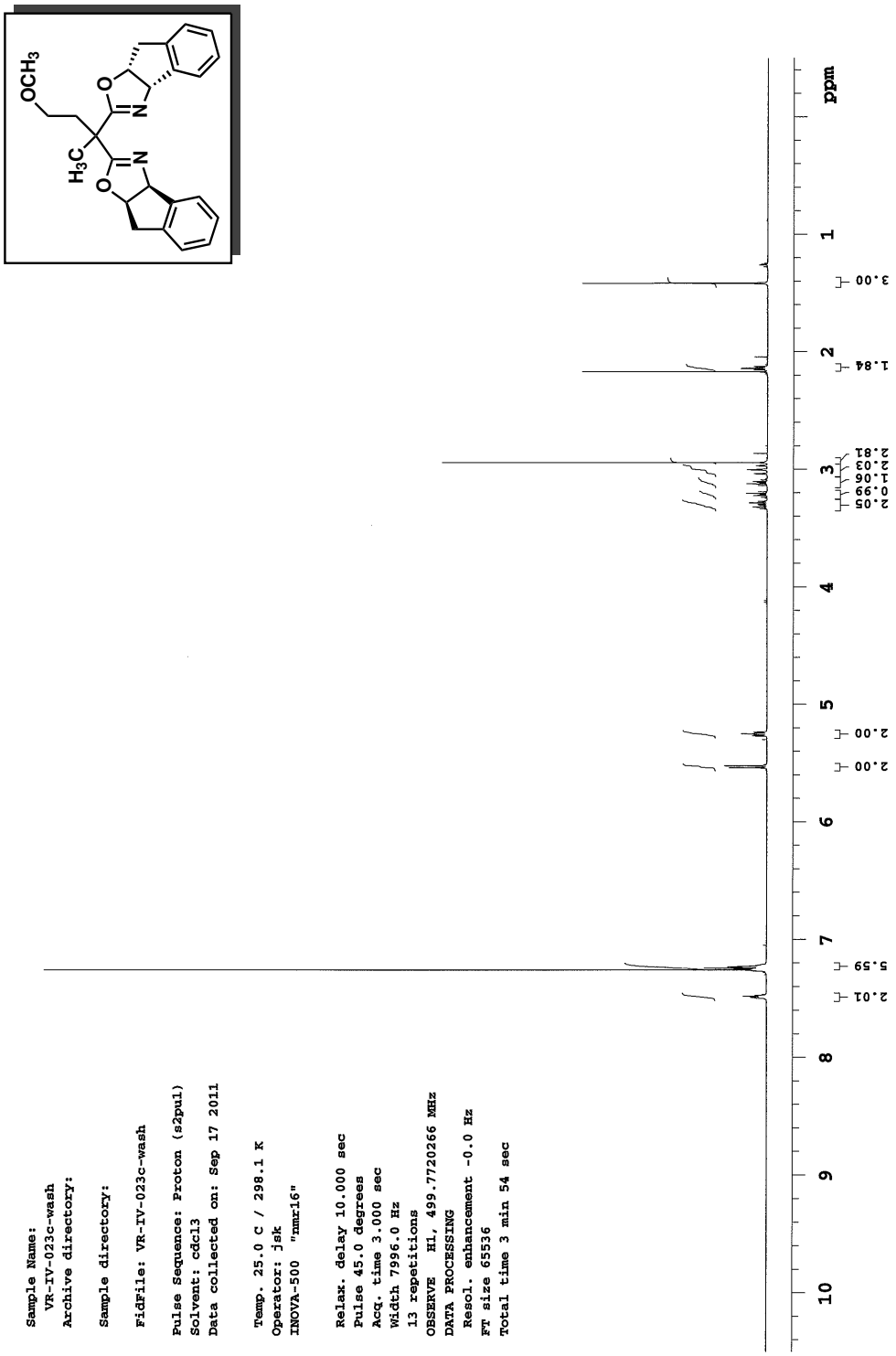
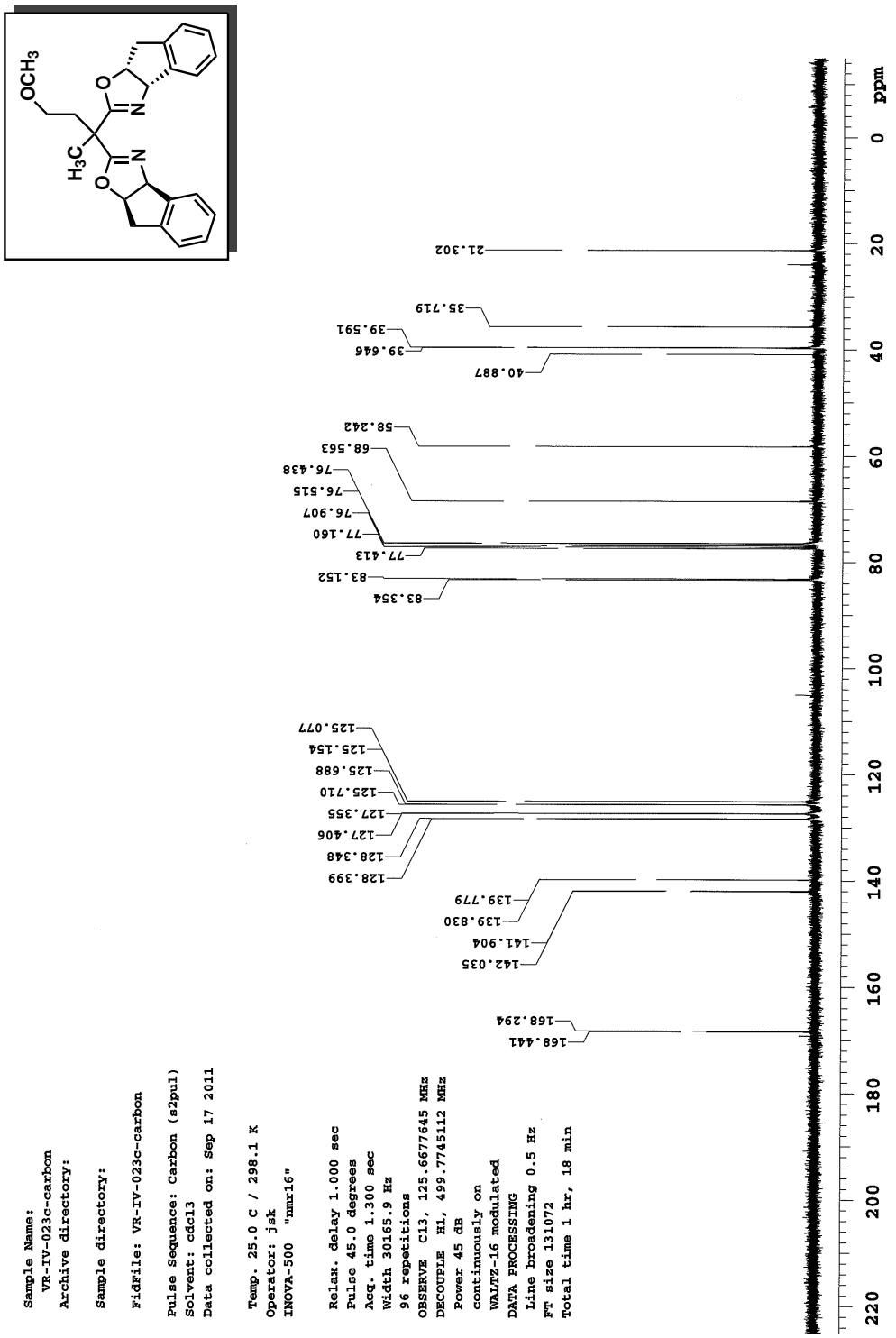


Figure 2.164: ^{13}C NMR of bis(oxazoline) ligand (**2.62**)



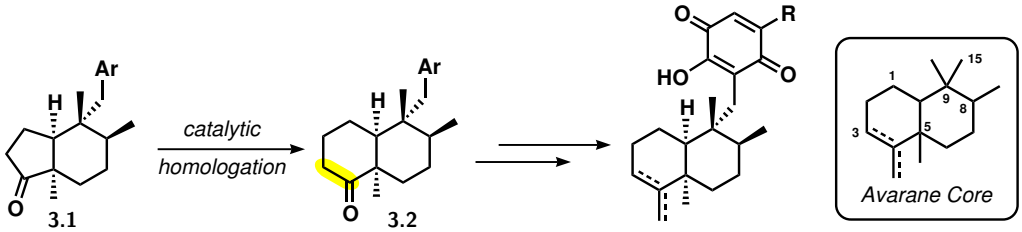
Chapter

3

Extension of Catalytic Single Carbon Ring Expansion to Complex Molecule Synthesis

3.1 Introduction

Natural product total synthesis often provides the impetus for developing new organic methodologies and can function as a proving ground for evaluating the utility of existing synthetic tools.[1] Our group recently disclosed methodology for catalytic and regioselective single carbon ring expansion of α,α-substituted cyclobutanones with trimethylsilyldiazomethane.[2] To prove the generality of our new mild and catalytic approach, we aimed to apply this strategic ring expansion reaction in the context of natural product synthesis. Several biologically active sesquiterpenoid quinone natural products bearing a *cis*-fused decalin core were selected, and we set out with the intent of developing a general strategy to access the *cis*-decalin carbon framework common to the avarane[3] family of natural products (Scheme 3.1). By designing a route in which the pendant aryl group could be tuned, a number of different natural products and their analogs could be accessed through single carbon homologation of a cyclopentanone intermediate (**3.1** $\longrightarrow$ **3.2**).



Scheme 3.1: Access to *cis*-decalin natural products by single-carbon ring expansion.

This chapter will discuss progress made towards sesquiterpene quinone natural products with an emphasis on ring expansion methodology development. Improvements have been

[1] For a review on the impact of total synthesis on the field of organic chemistry see: Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century. *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122.

[2] Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. Catalytic and Regioselective Ring Expansion of Arylcyclobutanones with Trimethylsilyldiazomethane. Ligand-Dependent Entry to β-Ketosilane or Enolsilane Adducts. *Org. Lett.* **2010**, *12*, 3598-3601.

[3] (a) Marcos, I. S.; Conde, A.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G. Quinone/Hydroquinone Sesquiterpenes. *Mini-Rev. Org. Chem.* **2010**, *7*, 230-254. (b) Thomson, R. H. *Naturally Occuring Quinones IV: Recent Advances*, 4th ed.; Chapman & Hall: New York, 1997.

made to our original reaction conditions for cyclobutanones, such that the arguably more challenging cyclopentanone[4] substrates are now readily homologated to the corresponding cyclohexanones with high yields and regioselectivities. Methods developed in our group showcase the first examples of catalytic ring expansions with trimethylsilyldiazomethane and represent a significant improvement over existing protocols. A history of previous single carbon homologation methods with diazoalkanes was presented in chapter 1. Examples of diazoalkane-based single carbon homologation in complex molecule synthesis are presented in the section that follows.

[4]The order of reactivity for the ring expansion of cycloalkanones with diazomethane based on literature precedents and qualitative observations is: cyclobutanone ≈ cyclohexanone > cycloheptanone > cyclopentanone. Gutsche, C. D. The Reaction of Diazomethane and Its Derivatives with Aldehydes and Ketones. *Org. React.* **1954**, *8*, 364-403.

3.2 Diazoalkane Single Carbon Homologation in Complex Molecules

Single-carbon ring expansion is a powerful synthetic disconnection and has been successfully implemented in a number of complex molecule syntheses. As discussed in Chapter 1, diazoalkane based ring expansions have made significant advances over the years. More recent methodologies, based on the findings of Shioiri[5] and Yamamoto,[6] have made their way into the total syntheses of several natural and synthetic biologically active complex molecules. Chemists will often construct or purchase the lower homologue of a ring system, utilize known methods to build up complexity, and then implement a key ring expansion event to access the target ring size. In the section that follows, several examples of sucessful single-carbon homologation in the context of complex substrates will be presented.

Polycyclic ether marine natural products, especially those belonging to the brevotoxin family, have been linked to cases of neurotoxic shellfish poising.[7] The discovery of these molecules and their corresponding biological effects lead to the development of new synthetic strategies to access the *trans*-fused 6– to 9-membered polycyclic ether framework common to these natural products.[8] In 1997, Mori and coworkers published a strategy based on iterative ring expansion of the corresponding 6-membered lower homologue to access 7-membered oxepane rings.[9] Table 3.1 shows the results of a Lewis acid screen on model substrate

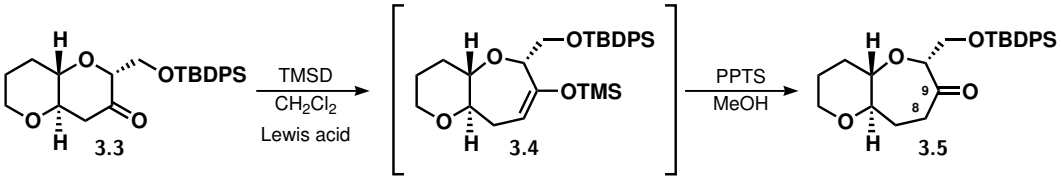
[5]Hashimoto, N.; Aoyama, T.; Shioiri, T. New Methods and Reagents in Organic Synthesis. 10. Trimethylsilyldiazomethane ($TMSCHN_2$). A New, Stable, and Safe Reagent for the Homologation of Ketones. *Tetrahedron Lett.* **1980**, *21*, 4619-4622.

[6](a) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. Selective Homologation of Ketones and Aldehydes with Diazoalkanes Promoted by Organoaluminum Reagents. *Synthesis.* **1994**, 1283-1290. (b) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. Organoaluminum-Promoted Homologation of Ketones with Diazoalkanes. *J. Org. Chem.* **1994**, *59*, 4725-4726.

[7]Watkins, S. M.; Reich, A.; Fleming, L. E.; Hammond, R. Neurotoxic Shellfish Poisoning. *Mar. Drugs.* **2008**, *6*, 431-55.

[8]Nicolaou, K. C.; Yang, Z.; Shi, G.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. Total Synthesis of Brevetoxin A. *Nature.* **1998**, *392*, 264-269.

[9](a) Mori, Y.; Yaegashi, K.; Furukawa, H. Stereoselective Synthesis of the 6,7,6- and 6,7,7-Ring Systems of Polycyclic Ethers by 6-endo Cyclization and Ring Expansion. *Tetrahedron.* **1997**, *53*, 12917-12932. (b) Mori, Y. Yaegashi, K.; Furukawa, H. Oxiranyl Anions in Organic Synthesis: Application to the Synthesis of Hemibrevetoxin B. *J. Am. Chem. Soc.* **1997**, *119*, 4557-4558. (c) Mori, Y.; Nogami, K.; Hayashi, H.; Noyori, R. Sulfonyl-Stabilized Oxiranyllithium-Based Approach to Polycyclic Ethers. Convergent Synthesis of the ABCDEF-Ring System of Yessotoxin and Adriatoxin. *J. Org. Chem.* **2003**, *68*, 9050-9060.



entry	Lewis acid	conditions	**3.5** (%)	8-keto isomer (%)	rr
1	Et_2AlCl	−78 °C, 2h	40	7	5.7:1
2	Me_3Al	−78 °C, 1.5h	48	32	1.5:1
3	$BF_3 \cdot Et_2O$	−20 °C, 1h	56	11	5.1:1
4	$BF_3 \cdot Et_2O$	−78 °C, 1h	76	5	15:1

Table 3.1: Lewis acid and condition screen for polyether model substrate.

3.3. The highest yields and regioselectivites were observed with the Shioiri[5] conditions at −78 °C (entry 4). Preferential migration of the anticipated less substituted bond, followed by 1,3-Brook rearrangement[10] yielded **3.4**, which was deprotected with PPTS to afford the target oxepane **3.5** in 76% yield over two steps.[11]

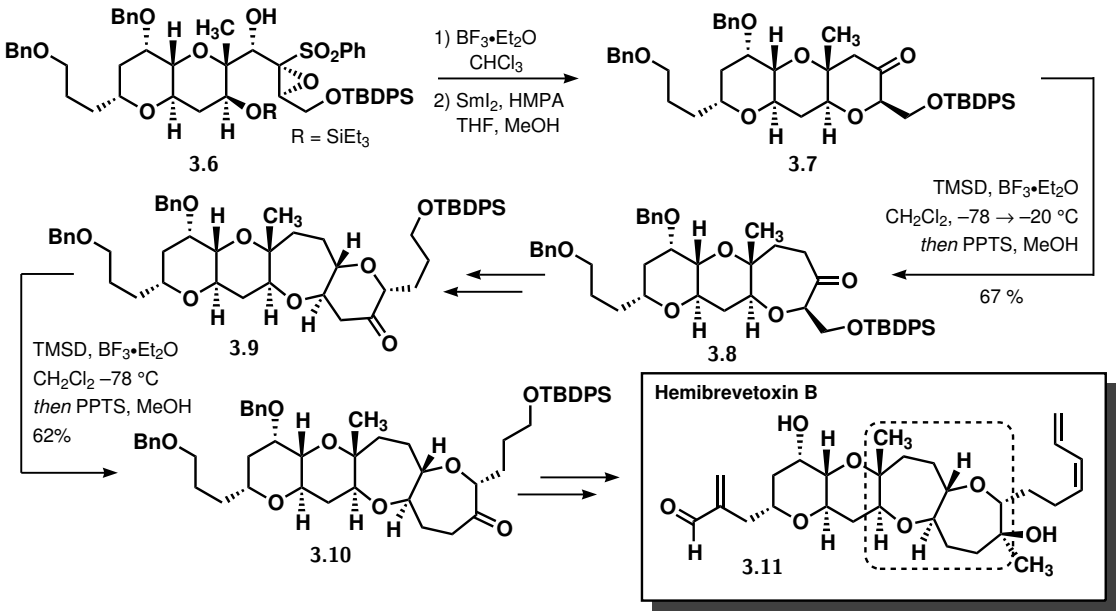
Satisfied with these model studies, Mori utilized this ring expansion strategy in a formal synthesis of hemibrevetoxin B (Scheme 3.2). Lewis acid mediated ring closure of **3.6** and deoxygenation afforded cyclohexanone homologation substrate **3.7**. Single carbon ring expansion under highly optimized conditions yielded the first 7-membered ether **3.8** in a 67% yield. After a series of manipulations, **3.9** was obtained and subsequently homologated to introduce the second 7-membered ring. Mori was able to sucessfully implement two regioselective single-carbon ring expansion events and secure intermediate **3.10**, which could then be elaborated to the target product ($\longrightarrow$ **3.11**).

In Pazos' 2009 synthesis of isolaurepan, a similar homologation strategy was employed to produce the oxepane ring system found in the desired target (Scheme 3.3).[12] Treatment

[10]Brook, A. G. Some Molecular Rearrangements of Organosilicon Compounds. *Acc. Chem. Res.* **1974**, *7*, 77-84.

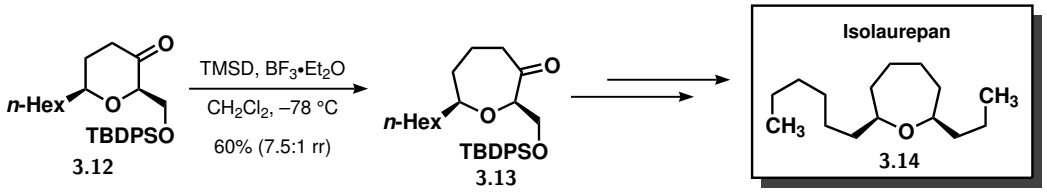
[11]For a more complete discussion of regioselectivity preferences see Chapter 1.

[12]Pazos, G.; Pérez, M. Gándara, Z.; Gómez, G.; Fall, Y. A New, Enantioselective Synthesis of (+)-Isolaurepan. *Tetrahedron Lett.* **2009**, *50*, 5285-5287.



Scheme 3.2: Mori's formal synthesis of hemibrevetoxin B featuring iterative ring expansions.

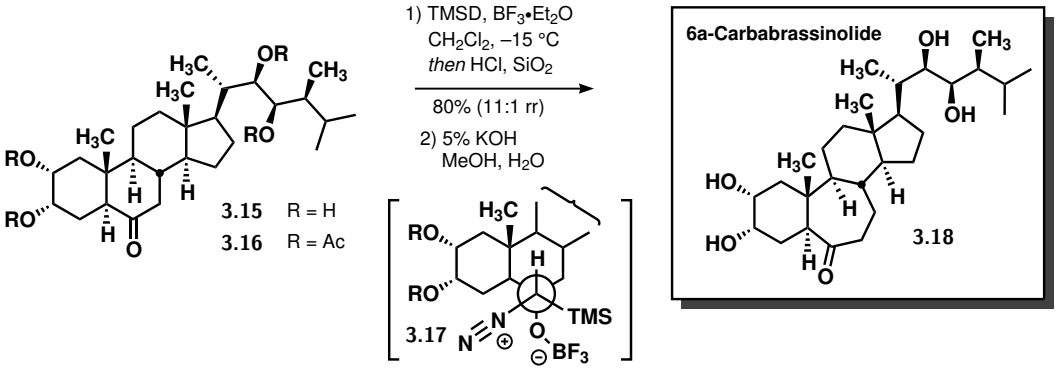
of α-tertiary substituted cyclohexanone **3.12** with $BF_3 \cdot Et_2O$ and TMSD afforded cycloheptanone **3.13** in a respectable 60% isolated yield. Again, preferential migration of the less substituted carbon atom was observed to deliver a 7.5:1 mixture of regioisomers. The late stage homologation product **3.13** was then advanced to the target isolaurepan (**3.14**) with four additional steps.



Scheme 3.3: Pazos' total synthesis of isolaurepan.

In Seto's synthesis of 6a-carbabrassinolide, a regioselective ring expansion facilitated concise access to the target steroid derivative (Scheme 3.4).[13] Global acetate protection

[13]Seto, H.; Fujioka, S.; Koshino, H.; Hayasaka, H.; Shimizu, T.; Yoshida, S.; Watanabe, T. Synthesis and Biological Activity of 6a-Carbabrassinolide: B-Ring Homologation of 6-Oxo-Steroid to 6-Oxo-7a-Homosteroid with Trimethylsilyldiazomethane-Boron Trifluoride Etherate. *Tetrahedron Lett.* **1999**, *40*, 2359-2362.



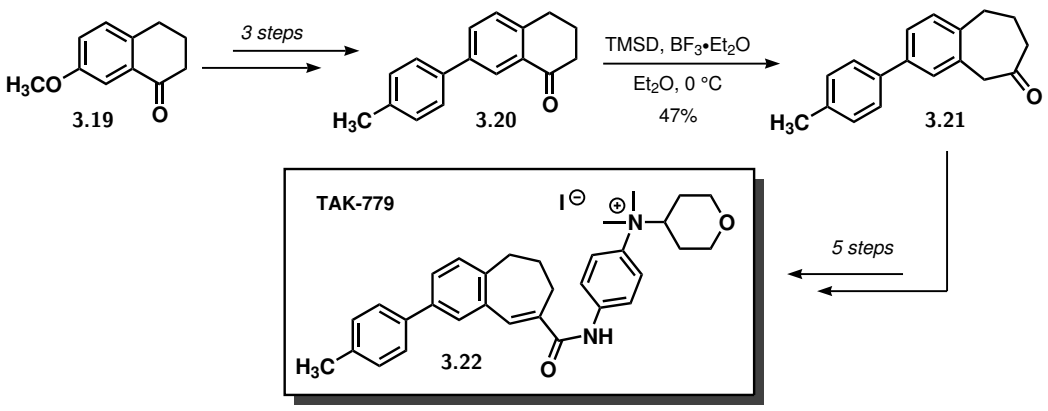
Scheme 3.4: Seto's synthesis of 6a-Carbabrassinolide.

(**3.15** $\longrightarrow$ **3.16**) prevents formation of methyl ethers by O-H insertion. Seto proposes that the diazoalkane adds to place the bulky TMS group away from the ring fusion and with the proton oriented inside of the ring system (**3.17**). This simple model, based on minimization of steric interactions, correctly predicts the regiochemical outcome in the previous two examples as well. Seto obtains the desired heptanone in 11:1 regioselectivity and an excellent 80% yield. Base-mediated global acetate deprotection delivered 6a-carbabrassinolide (**3.18**).

In Smalley's approach to the novel antiviral compound TAK-779 (Scheme 3.5), a deca-gram scale highly regioselective single carbon ring expansion was employed to form the crucial benzofused 7-membered carbocycle.[14] Starting from inexpensive and commercially available 7-methoxy-1-tetralone (**3.19**), biaryl tetralone **3.20** was quickly accessed through a three step sequence. Ring expansion with $BF_3 \cdot Et_2O$ and TMSD afforded the desired suberone **3.21** in multi-gram quantities as a single regioisomer by ^{1}H NMR spectroscopy. The high preference for migration of the aryl bond can be rationalized by an electronic orbital overlap argument. Diazoalkane insertion reactions with aldehydes typically afford ketone products, formed by preferential migration of the carbonyl C-H bond.[15] The spheri-

[14]Smalley, T. L. A Ring Expansion Strategy in Antiviral Synthesis: A Novel Approach to TAK-779. *Synthetic Commun.* **2004**, *34*, 1973-1980.

[15]For a lead reference on aldehyde homologations with diazoalkanes see: Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. Diverse Alkanones by Catalytic Carbon Insertion into the Formyl C-H Bond. Concise Access to the Natural Precursor of Achyrofuran. *Org. Lett.* **2009**, *11*, 3202-3205.



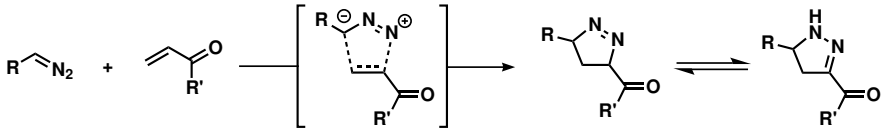
Scheme 3.5: Smalley's approach to TAK-779 with highly regioselective ring expansion.

cal, non-directional nature of the hydrogen *s* orbital allows for facile migration. In Smalley's example, the migrating carbon center is sp^2 hybridized, resulting in a less directional orbital that can overlap more readily with the C−N σ^* orbital. This migration preference was also consistent with a previous report by House that showed a strong preference for phenyl versus alkyl migration with diazomethane and $BF_3 \cdot Et_2O$.[16] The synthesis was completed in 5 additional steps, providing scalable access to TAK-779 (**3.22**).

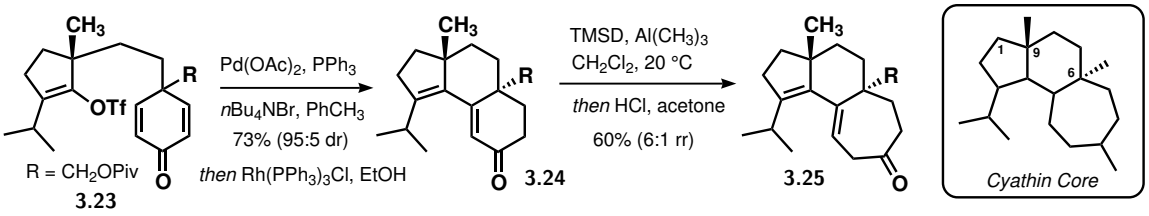
The reaction of diazomethane with α,β-unsaturated carbonyl compounds under classical protic conditions has been shown to produce pyrazoline products arising from 1,3-dipolar cycloaddtions.[17] Limited examples of α,β-unsaturated carbonyl substrates undergoing ring expansion in the presence of Lewis acid catalysts have been reported. It was not until the introduction of Lewis acids for diazoalkane ring expansion that these types of substrates were accessible.[18] In Drège's synthesis of the cyathin terpenoid framework, an intramolecular Heck reaction (**3.23** $\longrightarrow$ **3.24**, Scheme 3.6) set the stage for a rare α,β-unsaturated

[16] See Table 1.2 on page 12 and: House, H. O.; Grubbs, E. J.; Gannon, W. F. The Reaction of Ketones with Diazomethane. *J. Am. Chem. Soc.* **1960**, *82*, 4099-4106.

[17] See reference 4 for further details.



[18] Johnson, W. S.; Neeman, M.; Birkeland, S. P.; Fedoruk, N. A. The Acid-catalyzed Reaction of Diazomethane with Some α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **1962**, *84*, 989-992.



Scheme 3.6: Drège's approach to the cyathin terpenoid carbon framework.

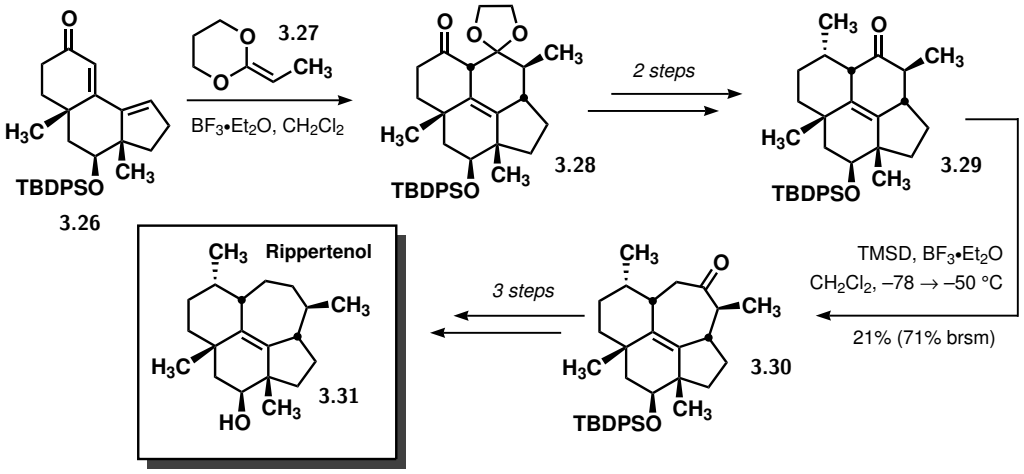
cyclohexenone ring expansion.[19] Under the Yamamoto[6] conditions, cyclohexenone **3.24** was smoothly converted to the desired cycloheptanone **3.25** in a 60% isolated yield with 6:1 regioselectivity.

In arguably one of the most challenging single carbon homologations to date, the Snyder group attempted to homologate an exceptionally crowded α,α'-disubstituted cyclohexanone during their synthesis of Rippertenol (Scheme 3.7).[20] A Lewis acid mediated inverse demand Diels-Alder reaction between electron deficient diene **3.26** and ketene acetal **3.27** afforded the carbon framework of the six membered ring ($\longrightarrow$ **3.28**) that would later be subjected to single carbon homologation. Two further steps, Lombardo-Takai olefination with an acidic workup and hydrogenation, unmasked the ketone for ring expansion (**3.28** $\longrightarrow$ **3.29**). Extensive screening lead to modified Shioiri[5] conditions as the optimium means to obtain cycloheptanone **3.30**, although it was only recovered in 21% yield under highly optimized conditions. The regiochemical outcome was not anticipated, however, it was of little consequence as the ketone was removed in subsequent steps. To avoid epimerization of the adjacent methyl stereocenter, a two-step reduction radical deoxgenation strategy followed by silyl deprotection delivered the target natural product **3.31**.

The Synder synthesis of rippertenol and other examples that have been presented il-

[19](a) Drège, E.; Morgant, G.; Desmaële, D. Asymmetric Synthesis of the Tricyclic Core of Cyathin Diterpenoids via Intramolecular Heck Reaction. *Tetrahedron Lett.* **2005**, *46*, 7263-7266. (b) Drège, E.; Tominiaux, C.; Morgant, G.; Desmaële, D. Synthetic Studies on Cyathin Terpenoids: Enantioselective Synthesis of the Tricyclic Core of Cyathin through Intramolecular Heck Cyclisation. *Eur. J. Org. Chem.* **2006**, 4825-4840.

[20]Snyder, S. A.; Wespe, D. A.; von Hof, J. M. A Concise, Stereocontrolled Total Synthesis of Rippertenol. *J. Am. Chem. Soc.* **2011**, *133*, 8850-8853.

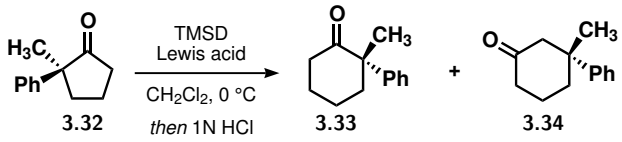


Scheme 3.7: Synder's total synthesis of rippertenol.

lustrate a need for more mild and catalytic methods to accomplish single carbon ring expansions. Although a number of the syntheses showcase successful and high yielding ring expansions, none of the examples are catalytic. The sections that follow will detail our work to develop and successfully implement the first mild and catalytic ring expansion methodology in the context of complex molecule synthesis.

3.3 Model Optimization Studies for Cyclopentanone Ring Expansions

Previous studies from our group on scandium catalyzed single carbon ring expansion were focused on α-quaternary cyclobutanones,[2] and we were intent on utilizing this methodology in the context of an advanced α-quaternary substituted cyclopentanone intermediate. We therefore chose to concentrate our studies first on a suitable model system, 2-methyl-2-phenyl cyclopentanone (**3.32**), which was prepared on gram scale by methods developed in our group for substituted carbon insertion.[21] To establish a benchmark for our testing, we



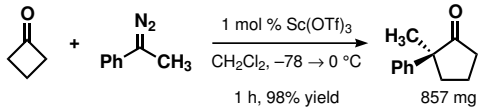
entry[a]	promoter	conversion (%)	yield **3.33** (%)	rr (**3.33**:**3.34**)
1[b]	$BF_3 \cdot Et_2O$	94	80	>100:1
2[c]	$Al(CH_3)_3$	13	< 2	–

[a]Conversion, yield, and regioselectivity were determined by GC analysis with hexamethylbenzene as an internal standard. [b]Run with 1.5 equivalents of $BF_3 \cdot Et_2O$ and TMSD. [c]Run with 1.2 equivalents of $Al(CH_3)_3$ and 1.1 equivalents TMSD.

Table 3.2: Establishing a point of comparison to previous methods.

first evaluated the efficacy of the Shioiri[5] conditions (Table 3.2, entry 1). We were surprised to see such high levels of regiocontrol with good yields of the desired cyclohexanone **3.33**. We then tested Yamamoto's[6] conditions, which resulted in substantially lower conversion and a poor yield of the desired product (entry 2). The Shioiri conditions worked well in this context, but regardless required superstoichiometric amounts of $BF_3 \cdot Et_2O$ to achieve high levels of conversion. For this model substrate 1.5 equivalents was sufficient, but some of the previously mentioned studies on more complex molecules required more than 4 equivalents. The presence of Lewis basic functional groups other than the target ketone can interact

[21]See Chapter 2 for experimental details.



with the Lewis acid promoter and shut down the reaction.

We then attempted to translate the previously reported conditions to our model cyclopentanone substrate. Initial attempts resulted in highly irreproducible reactions, rarely affording complete conversion. Even two identical reactions run side by side under presumably the same conditions gave dramatically different outcomes. Occasionally, reactions were successful, giving hope that we could discover or control all the variables to produce a more reliable reaction profile. We decided to approach the problem in two directions: (1) control all the environmental variables by running with freshly purified reagents under dry conditions in a glove box, (2) monitor the reaction progress with an advanced analytical technique to obtain the maximum possible information.

Attempts to use ReactIR to monitor the reaction did not generate any usable data and was operationally difficult to set up rigorously anhydrous reactions. ReactIR was abandoned quickly in favor of ^{1}H NMR spectroscopy, which proved to be operationally simpler and provided better quality data. Reactions could be set up in a glove box and transferred to a J-Young tube for analysis. In a glove box, rigorously vacuum dried $Sc(OTf)_3$ was combined with cyclopentanone **3.32** in $CDCl_3$ and allowed to stir for 15 minutes before adding 1.5 equivalents of TMSD. The heterogeneous yellow reaction mixture was transferred to a J-Young NMR tube, where a slow stream of nitrogen gas evolution began. ^{1}H NMR data were recorded at 30 minute intervals and showed complete conversion after 450 minutes (7.5 hours) at room temperature. After an additional 8 hours, no further change was observed in the spectrum, and the mixture was then subjected to a dilute acid hydrolysis. The products of the reaction were primarily **3.33** and **3.34** in an 8:1 ratio by ^{1}H NMR spectroscopy. This promising result was promptly repeated with an identical setup and gratifyingly afforded identical results.

With these two successful reactions, we still needed to determine the cause of the previously irreproducible reactions. When the reactions were worked up, they were first rinsed into a separatory funnel with benchtop Et_2O, which immediately caused the rapid de-

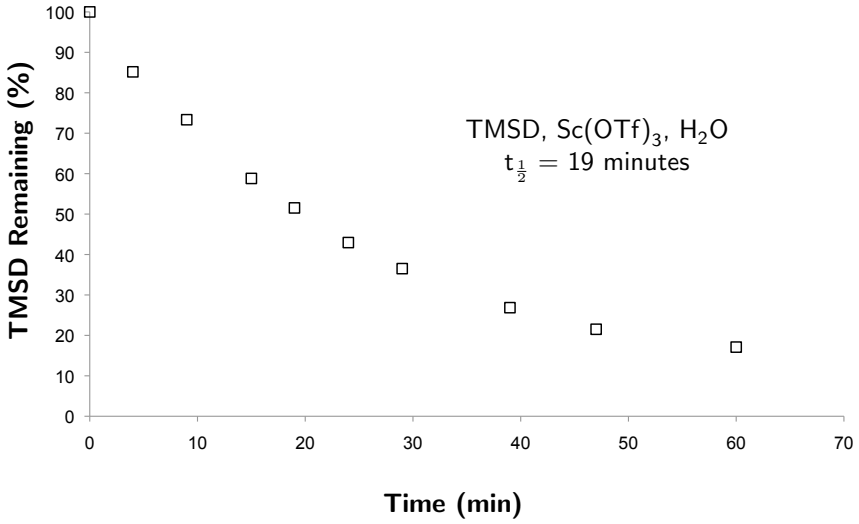


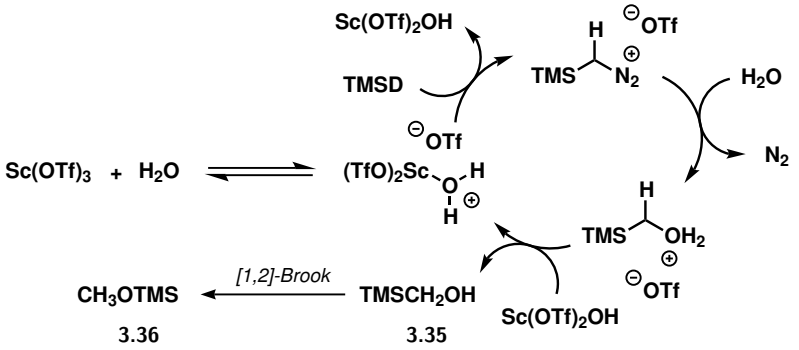
Figure 3.1: Decomposition of TMSD with $Sc(OTf)_3$ and H_2O.

struction of any remaining diazoalkane. We had also observed that monitoring the reaction progress by thin layer chromatography in certain cases also destroyed the diazoalkane. Trace amounts of water were previously found to have a profound impact on both reaction kinetics and selectivity for asymmetric ring expansion reactions with chiral scandium catalysts.[22] We rationalized that trace amounts of water present in any of the reaction components, or adventitious atmospheric water, may have been responsible for the inconsistent reactivity. An experiment was carried out to test this hypothesis. When TMSD was mixed with 5 equivalents of water, an insignificant change in the concentration[23] was observed after 24 hours at room temperature. The same experiment with TMSD and 10 mol % $Sc(OTf)_3$ also showed minimal change,[24] but when an equivalent of water was added the diazoalkane began to rapidly decompose (Figure 3.1). In less than 20 minutes, half of the original diazoalkane had been destroyed. The proposed pathway of decomposition is illustrated in Scheme 3.8.

[22]Rendina, V. L.; Moebius, D. C.; Kingsbury, J. S. An Enantioselective Synthesis of 2-Aryl Cycloalkanones by Sc-Catalyzed Carbon Insertion. *Org. Lett.* **2011**, *13*, 2004-2007.

[23]Determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

[24]This result was somewhat surprising given that Lewis acids are known to promote the decomposition of diazoalkanes. See reference 6a and references within.



Scheme 3.8: Proposed pathway for diazoalkane decomposition with hydrated scandium triflate.

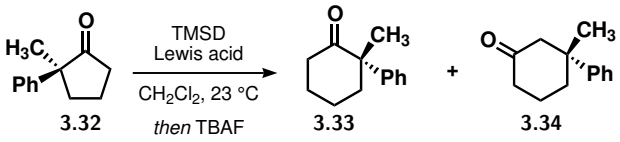
Although $Sc(OTf)_3$ is a water tolerant Lewis acid and is prepared from aqueous triflic acid,[25] presumably an equilibrium can be established with water which generates small quantities of acid.[26] Brønsted acids have long been known to facilitate rapid decomposition of diazoalkanes, first by protonation and then by subsequent substitution with the conjugate base or an appropriate nucleophile.[27] In this case, water displaces nitrogen followed by a proton transfer to regenerate the Brønsted acid. Trimethylsilyl methanol (**3.35**) was not observed by ^{1}H NMR spectroscopy, instead a 1,2-Brook rearrangement[10] likely occurred to produce methoxytrimethylsilane ($\longrightarrow$ **3.36**).

With a reliable reaction protocol in hand, we began to evaluate other variables to discover an optimized set of conditions. We first investigated other scandium (III) salts and several other lanthanide triflates to ensure that we were optimizing the best catalyst. Results of the catalyst screen are summarized in Table 3.3. The highest yield of the major regioisomer **3.33** was obtained with $Sc(OTf)_3$ (entry 1). Other less Lewis acidic scandium salts (entries 2–5) resulted in lower levels of conversion with comparable levels of regiocontrol. We were intrigued by the high levels of regiocontrol observed with $Yb(OTf)_3$ (entry

[25]Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. Scandium Trifluoromethanesulfonate ($Sc(OTf)_3$). A Novel Reusable Catalyst in the Diels-Alder Reaction. *Tetrahedron Lett.* **1993**, *34*, 3755-3758.

[26]Kobayashi, S.; Nagayama, S.; Busujima, T. Lewis Acid Catalysts Stable in Water. Correlation between Catalytic Activity in Water and Hydrolysis Constants and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands. *J. Am. Chem. Soc.* **1998**, *120*, 8287-8288.

[27]For a lead reference on the reaction of diazoalkanes with acids see: Rendina, V. L.; Kingsbury, J. S. Titration of Nonstabilized Diazoalkane Solutions by Fluorine NMR. *J. Org. Chem.* **2012**, *77*, 1181-1185.



entry[a]	catalyst	time (h)	conversion (%)	yield[b] (%)	rr (**3.33**:**3.34**)
1	$Sc(OTf)_3$	16	>98	88	7.4:1
2	$Sc(Cl)_3(thf)_3$	24	22	–	5.6:1
3	$Sc(hfac)_3$	24	35	–	8:1
4	$ScBr_3$	16	< 2	–	–
5	$Sc(acac)_3$	16	< 2	–	–
6	$Y(OTf)_3$	24	< 10	–	–
7	$Yb(OTf)_3$	24	80	70	55:1

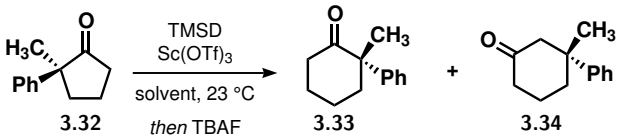
[a]Conditions: 0.05 mmol scale, 10 mol % catalyst, 2 equivalents TMSD, 0.1 M in CH_2Cl_2. Conversion, yield, and regioselectivity were determined by GC analysis with hexamethylbenzene as an internal standard after treatment with 2 equivalents TBAF (1M in THF) and filtration through silica gel. [b]Combined yield of both regioisomers.

Table 3.3: Screen of Lewis acid catalysts.

7). This less potent and larger Lewis acid may enforce a more selective initial addition of the diazoalkane, leading to the substantially higher regioselectivity. Later attempts to use the stronger Lewis acid $Yb(NTf_2)_3$ to increase reaction conversion resulted in rapid decomposition of the diazoalkane and low conversion to the homologated products. We decided to continue optimizing $Sc(OTf)_3$ because of its higher activity and the ease that reactions could be monitored by ^{1}H NMR spectroscopy. Ytterbium (III) salts are paramagnetic and complicated monitoring by NMR.

Table 3.4 shows the results of a solvent screen with catalytic $Sc(OTf)_3$. Entries 1–4 all showed high levels of conversion and similar levels of regiocontrol, despite significant differences in polarity. Even hexanes (entry 4), where the catalyst was completely heterogeneous, proceeded to high conversion. Running in ethereal or Lewis basic solvents (entries 5–7) not surprisingly supressed catalyst efficiency.[28] The higher regiocontrol observed in Et_2O suggested that filling the coordination sphere around scandium may produce a more selective

[28]A similar observation was made by Shioiri when using $BF_3 \cdot Et_2O$ as a promoter. Methylene chloride was selected as the optimum solvent. See reference 5 for details.



3.32 3.33 3.34

entry[a]	solvent	conversion (%)	yield[b] (%)	yield **3.33** (%)	rr (**3.33**:**3.34**)
1	CH_2Cl_2	>98	88	78	7.4:1
2	toluene	>98	95	79	5:1
3	$CHCl_3$	>98	91	79	7:1
4	hexanes	94	86	75	6.8:1
5	Et_2O	77	70	65	14.7:1
6	THF	27	10	8	3.2:1
7	CH_3CN	62	28	25	8.2:1

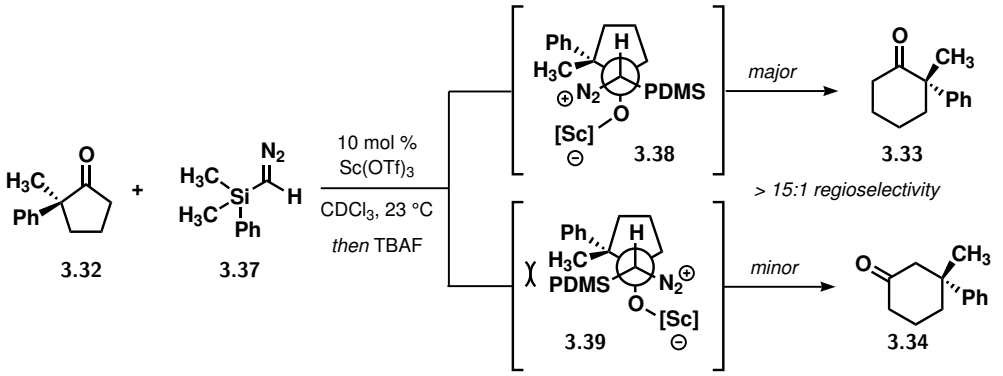
[a]Conditions: 0.05 mmol scale, 10 mol % $Sc(OTf)_3$, 2 equivalents TMSD, 0.1 M in solvent, 16 h. Conversion, yield, and regioselectivity were determined by GC analysis with hexamethylbenzene as an internal standard after treatment with 2 equivalents TBAF (1M in THF) and filtration through silica gel. [b]Combined yield of both regioisomers.

Table 3.4: Solvent screen with $Sc(OTf)_3$.

catalyst. A single experiment examining regioselectivity as a function of conversion seemed to indicate that binding of the product silyl enol ether resulted in higher selectivity as the reaction progressed. The large discrepancy between conversion and yield in CH_3CN (entry 7) was determined to be the result of overhomologation to produce the cycloheptanone.

With a successful preliminary result (Table 3.3, entry 1, page 294), we still wanted to see if the yield of the major regioisomer could be enhanced by increasing the regioisomeric ratio. We prepared the sterically more demanding phenyldimethylsilyldiazomethane[29] (**3.37**, Scheme 3.9) and rationalized that higher levels of regioselectivity would be observed based on the preference for the diazoalkane to add such that the bulky silicon group would be oriented away from the more substituted side of the ketone. The intermediate **3.38** avoids this costly steric interaction and leads to the observed major regioisomer **3.33** in >15:1 selectivity, doubling the previously observed selectivity with TMSD. For simpler model substrates, employing **3.37** could provide access to an easily isolable and synthetically useful more stable silyl enol ether with high levels of regiocontrol.

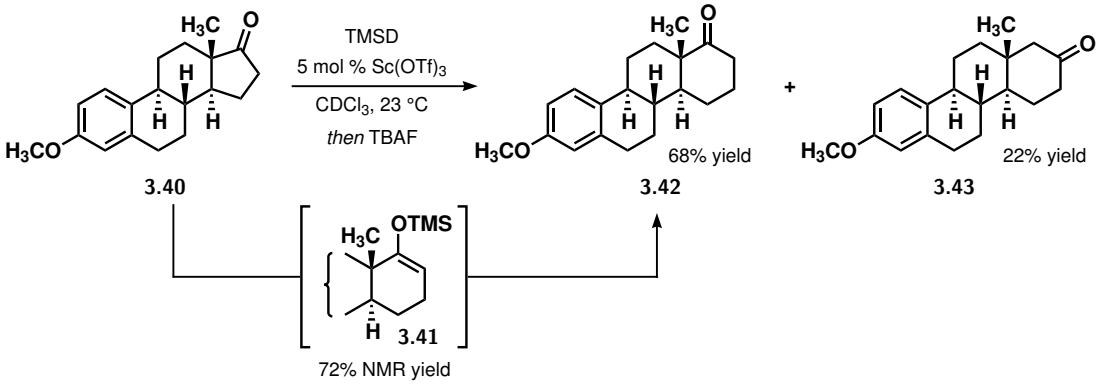
[29]Shioiri, T.; Aoyama, T.; Mori, S. Trimethylsilylyldiazomethane. *Org. Synth.* **1990**, *68*, 1.



Scheme 3.9: Higher levels of regiocontrol with a more sterically hindered diazoalkane.

Pleased with the performance of the $Sc(OTf)_3$ TMSD system thus far, we did not want to spend excessive time optimizing model substrate **3.32**. Our synthetic strategy would ultimately involve homologation of a *cis*-fused 6,5-ring system (Scheme 3.1, page 281), and we wanted to evaluate a more representative model. Commercially available estrone 3-methyl ether (**3.40**) was subjected to two equivalents of TMSD and 5 mol % $Sc(OTf)_3$ in deuterochloroform for 24 hours (Scheme 3.10). Complete conversion and a 72% yield of enol silane **3.41** was observed by ^{1}H NMR spectroscopy before deprotection with TBAF. Purification by column chromatography afforded the major regioisomer **3.42** in an acceptable 68% isolated yield along with 22% of **3.43**.

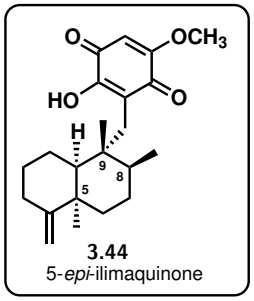
With all of these results and information in hand, we were ready to start looking at



Scheme 3.10: Single carbon homologation of estrone 3-methyl ether.

more complex substrates. The following section will discuss our progress towards several sesquiterpene quinone natural products, with a focus on the key ring expansion step.

3.4 Application to the Total Synthesis of 5-*epi*-Ilimaquinone



3.44
5-*epi*-ilimaquinone

We initially decided to concentrate our efforts on the synthesis of 5-*epi*-ilimaquinone (**3.44**), first isolated from the marine sponge *Fenestraspongia* by Faulkner and coworkers in 1985.[30] Access to 5-*epi*-ilimaquinone, never prepared before by total synthesis, would additionally faciliate access to several other related aminoquinone derivatives. The section that follows will discuss two synthetic generations, culminating in the successful implementation of catalytic single carbon ring expansion through careful experimentation and application of findings discussed in the previous section.

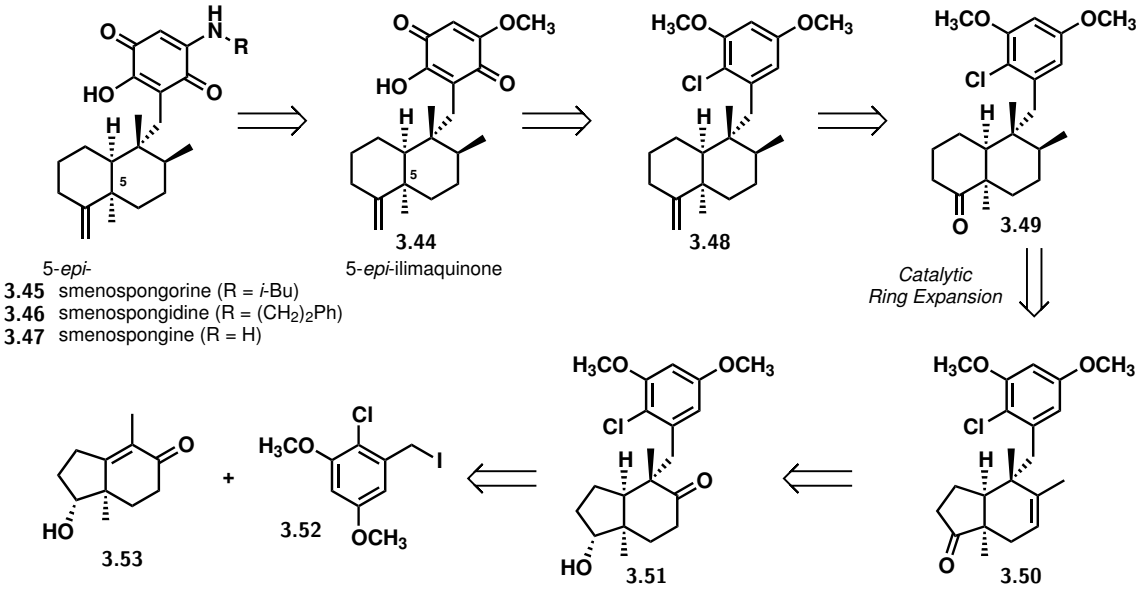
3.4.1 *First Generation Synthesis*

The retrosynthetic analysis for 5-*epi*-ilimaquinone (**3.44**) is depicted in Scheme 3.11. We had also originally planned to target several other natural aminoquinone derivatives (**3.45**, **3.46**, **3.47**), which could theoretically be prepared in a single substitution step from **3.44** with the appropriate amine. A late-stage oxidation of aryl intermediate **3.48**, similar to that found in Snapper's synthesis of (−)-illimaquinone, could provide the sensitive quinone moiety found in the final targets.[31] Intermediate **3.48** could be accessed by olefination of **3.49**, which would be dervived from **3.50** following the key ring expansion event and hydrogenation to set the C-8 β-methyl stereocenter. Intermediate **3.50** could be prepared from **3.51** following olefination and oxidation steps. The pendant aryl group in **3.51** could be attached by a dissolved metal reductive alyklation with reduced Hajos-Parrish ketone **3.53** and aryl iodide **3.52**, introducing both the *cis* ring junction and C-9 quaternary center.

We began by preparing reduced Hajos-Parrish ketone **3.53** according to a modified lit-

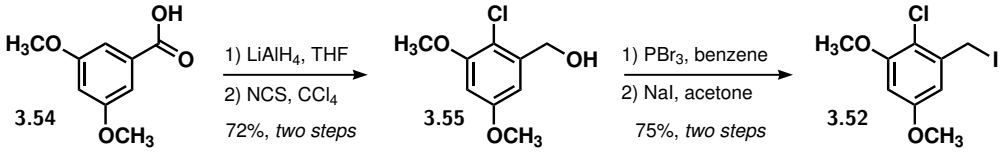
[30] Originally isolated as a 2:3 mixture with (–)-ilimaquinone. Carté, B.; Rose, C. B.; Faulkner, D. J. 5-*epi*-Ilimiquinone, a Metabolite of the Sponge *Fenestraspongia* Sp. *J. Org. Chem.* **1985**, *50*, 2785-2787.

[31] Bruner, S. D.; Radeke, H. S.; Tallarico, J. A.; Snapper, M. L. Total Synthesis of (-)-Ilimaquinone. *J. Org. Chem.* **1995**, *60*, 1114-1115.



Scheme 3.11: Retrosynthetic analysis for 5-*epi*-ilimaquinone and related aminoquinones.

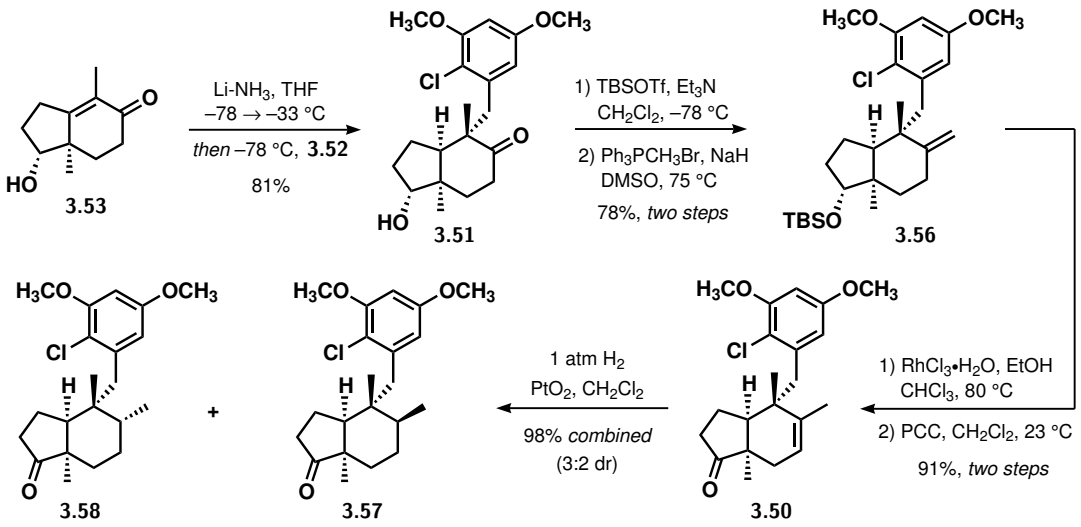
erature protocol,[32] which was obtained with >98% ee after a single recrystallization. Electrophile **3.52** was selected because of its prior use in the total synthesis of (−)-ilimaquinone by the Snapper group.[33] Starting from commercially available 3,5-dimethoxybenzoic acid (**3.54**), reduction and chlorination afforded chloroalcohol **3.55** (Scheme 3.12). Standard bromination conditions allowed access to the benzyl bromide which was stable enough to be purified by silica gel chromatography. By employing Finkelstein conditions, the more reactive benzyl iodide (**3.52**) could be isolated cleanly after simple filtration and concentration.



Scheme 3.12: First generation electrophile synthesis.

[32]See the experimental section for details. Shigehisa, H.; Mizutani, T.; Tosaki, S.; Ohshima, T.; Shibasaki, M. Formal Total Synthesis of (+)-Wortmannin Using Catalytic Asymmetric Intramolecular Aldol Condensation Reaction. *Tetrahedron* **2005**, *61*, 5057-5065.

[33]The Snapper group utilized the corresponding aryl bromide. See reference 31 for details.



Scheme 3.13: First generation forward synthesis.

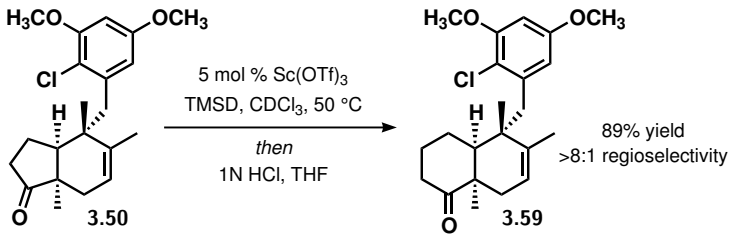
With fragments **3.52** and **3.53** in hand, we were prepared to couple them in a single dissolved metal reductive alkylation step. In previous examples, 6,6 ring systems were known to form exclusively *trans* decalin ring systems.[34] Key to our synthetic strategy was the precedents for formation of a *cis* ring junction within the context of 6,5 ring systems.[35] However, previous examples in the literature did not study the diastereoselectivity in these systems when trapping an electrophile to form an all carbon quaternary center. Exposure of **3.53** to lithium metal in ammonia formed a cup-shaped enolate intermediate after protonation at the ring fusion, facilitating a substrate controlled highly diastereoselective trap of electrophile **3.52** ($\longrightarrow$ **3.51**, Scheme 3.13). The *cis* ring fusion and stereochemistry

[34]The stereochemical outcome of these reactions was extensively studied by Stork. (a) Stork, G.; Darling, S. D. Stereochemistry of the Lithium-Ammonia Reduction of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **1960**, *82*, 1512-1513. (b) Stork, G.; Rosen, P.; Goldman, N. L. The α-Alkylation of Enolates From the Lithium-Ammonia Reduction of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **1961**, *83*, 2965-2966. (c) Stork, G.; Darling, S. D. The Stereochemistry of the Lithium-Ammonia Reduction of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **1964**, *86*, 1761-1768. (d) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V; Tsuji, J. Alkylation and Carbonation of Ketones by Trapping the Enolates from the Reduction of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **1965**, *87*, 275-286.

[35]Two examples are known in the literature: (a) Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. Total Synthesis of (−)-Austalide B. A Generic Solution to Elaboration of the Pyran/p-Cresol/Butenolide Triad. *J. Am. Chem. Soc.* **1994**, *116*, 11323-11334. (b) Renoud-Grappin, M.; Vanucci, C.; Lhommet, G. Diastereoselective Synthesis of a Limonoid Model Related to the Insect Antifeedant Genudin. *J. Org. Chem.* **1994**, *59*, 3902-3905.

of the newly forged all carbon quaternary center were later unambiguously confirmed by X-ray crystallography. Ketoalcohol **3.51** was protected[36] and olefinated to deliver **3.56** in 76% yield over two steps. Attempts to hydrogenate **3.56**, the free alcohol, or ketone to set the C-8 β-methyl stereocenter were less than satisfactory with a variety of standard heterogeneous hydrogenation catalysts. We reasoned that moving the olefin into the ring system and farther away from the congested C-9 quaternary center could favorably affect the outcome of further hydrogenation efforts. Rhodium mediated isomerization[37] with concomitant silyl deprotection followed by PCC oxidation provided cyclopentanone **3.50** in a 91% yield over two steps. Hydrogenation over Adams' catalyst delivered epimeric cyclopentanones **3.57** and **3.58** in an unoptimized 3:2 dr slightly favoring the desired β-methyl epimer. We turned our attention next to the key ring expansion event with two potential cyclopentanone substrates in hand (**3.50** and **3.57**).

We were pleased to see that the conditions optimized previously for model systems translated exceptionally well to cyclopentanone **3.50** with very little modification (Scheme 3.14). Exposure of **3.50** to 10 mol % $Sc(OTf)_3$ and 1.5 equivalents of TMSD in $CDCl_3$ showed only 33% conversion after 18 hours at room temperature. Simply heating the reaction mixture to 50 °C resulted in 88% conversion in an additional 9 hours and complete conversion with a further 10 hours of heating. After dilute acid hydrolysis, the regioselec-

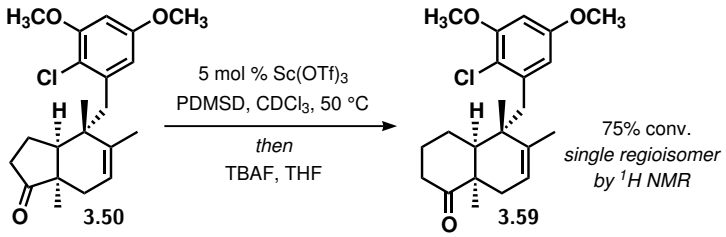


Scheme 3.14: Successful ring expansion of cyclopentanone **3.50**.

[36] Olefination of unprotected **3.51** resulted recovery of an unexpected product, likely the result of an intramolecular 1,5-hydride shift. See section 3.4.3 (page 309) for further details.

[37] Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. Total Synthesis and Biological Evaluation of the Nakijiquinones. *J. Am. Chem. Soc.* **2001**, *123*, 11586-11593.

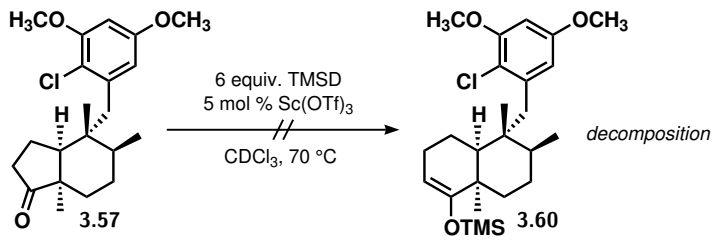
tivity by ^{1}H NMR spectroscopy was approximately 6:1, favoring the desired regioisomer (**3.59**). Dropping the catalyst loading to 5 mol % and increasing the concentration allowed the desired cyclohexanone to be recovered in an 89% isolated yield (>8:1 regioselectivity, 16 h, 50 °C) after protodesilylation. We also attempted to use the bulkier PDMSD with **3.50**, which had previously performed better in the context of model studies (Scheme 3.9, page 296). After heating for 24 hours at 50 °C the reaction mixture was analyzed by ^{1}H NMR spectroscopy and showed a single regioisomer; however, the conversion had only reached 75% during this time period ($\longrightarrow$ **3.59**, Scheme 3.15). The larger diazoalkane afforded the higher levels of regioselectivity expected from model studies, but the reaction efficiency suffered. Content with the use of TMSD, we attempted to press forward with **3.59** in hand. Unfortunately, all attempts to hydrogenate **3.59** were unsucessful.[38]



Scheme 3.15: Higher regiocontrol but lower efficiency with PDMSD.

When β-methyl cyclopentanone **3.57** was subjected to similar homologation conditions optimized above for **3.50** (5 mol % $Sc(OTf)_3$, 2 equivalents TMSD), we were disappointed to see a complete lack of reactivity. Heating the reaction mixture to 50 °C did nothing to drive a productive reaction, instead simply accelerated decomposition of the diazoalkane. The starting cyclopentanone was returned unchanged. In another experiment with 6 equivalents of TMSD, heating to 70 °C lead to complete decomposition of the diazoalkane and starting material (Scheme 3.16). Not even a trace amount of the characteristic enol silane **3.60** could be detected. A control experiment containing a mixture of β– and α-methyl cyclopentanones

[38] A complete discussion of attempts to further transform **3.59** and related compounds will be included as part of the Ph.D. dissertation of Hilan Z. Kaplan.



Scheme 3.16: Complete decomposition with forcing conditions.

3.57 and **3.58** was run with two equivalents of TMSD and 5 mol % $Sc(OTf)_3$ at 50 °C overnight. We were able to observe complete conversion of the α epimer **3.58** by ^{1}H NMR, but the β epimer remained completely untouched. This control indicated that our reaction was working properly and something particular about the β epimer was preventing the homologation reaction from occuring.

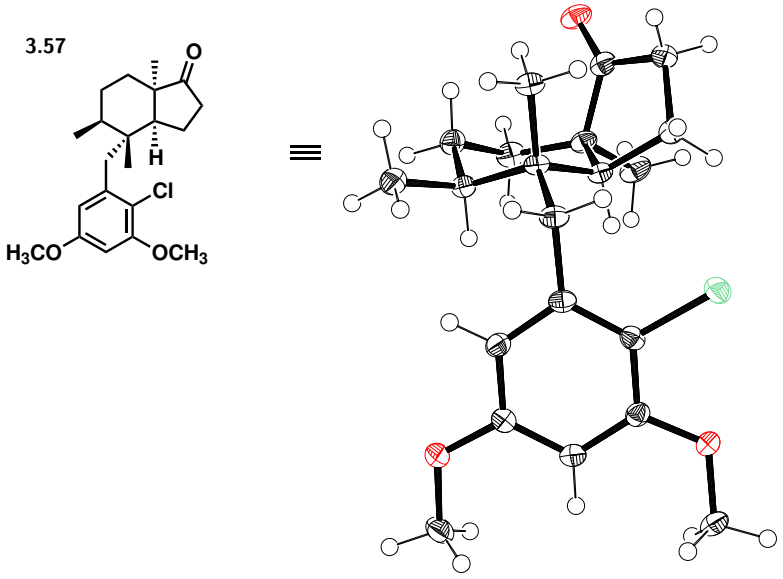


Figure 3.2: ORTEP diagram of β-methyl hydrogenation product.

Looking at the solid state structure of β-methyl cyclopentanone **3.57** revealed a likely rationale for why this substrate failed to undergo homologation even under strongly forcing conditions (Figure 3.2). Access to the π^* orbital of the carbonyl was exceptionally hindered

by angular methyl groups on both sides of the molecule. The α face of the carbonyl was effectively blocked by the adjacent methyl group and the β face was shielded by the axial methyl group on the C-9 quaternary center. The solid state structure of the α-methyl cyclopentanone **3.58** revealed a different chair conformation where the β face of the carbonyl was now more accessible (Figure 3.3). Although the solid state structure may not accurately represent the solution phase structure as there may be more conformational liberty in solution, these structural features shed light on why **3.58** readily underwent homologation, whereas **3.57** was completely inert.

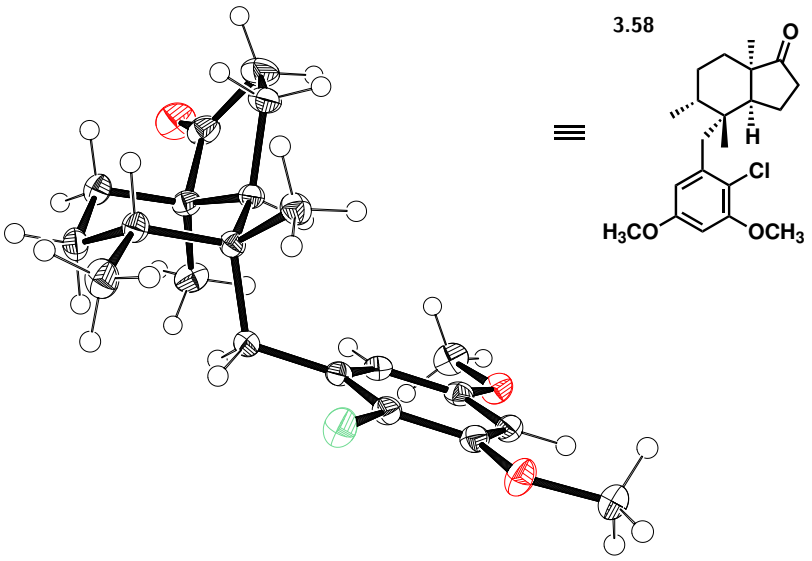


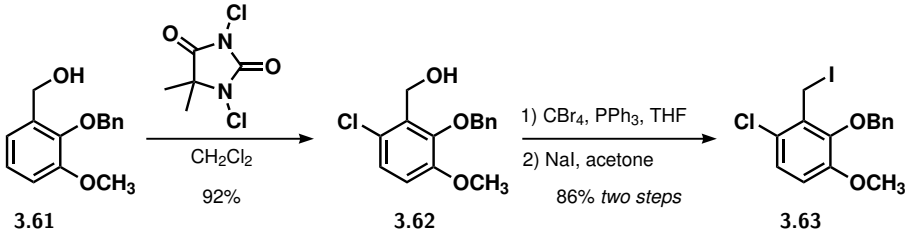
Figure 3.3: ORTEP diagram of α-methyl hydrogenation product.

3.4.2 *Second Generation Synthesis*

The first generation dissolved metal reductive alkylation (**3.53** + **3.52** $\longrightarrow$ **3.51**, Scheme 3.13, page 300) and subsequent single carbon homologation reactions with trisubstituted ene-one **3.50** performed exceptionally well. However, we ran into a number of unexpected difficulties when attempting to further transform cyclohexanone **3.59**. Installing the C-8

β-methyl stereogenic center appeared to be an insurmountable problem.[38] In an attempt to address these issues, a second generation route was designed. The synthetic strategy remained largely the same for the second generation route. A dissolved metal reductive alkylation event would build a significant portion of the carbon framework and set the key *cis* ring fusion. Ring expansion with TMSD would then provide access to the decalin core found in the final target. The major difference in the second generation was the selection of electrophile.

We wanted to incorporate functionality into the electrophile that could be unmasked later and provide a means to direct a homogeneous hydrogenation catalyst to the β-face of the molecule.[39] A similar directed hydrogenation strategy was employed by Terashima to set the C-8 methyl stereogenic center in his synthesis of (+)-arenarol, a natural product containing a very similar *cis*-decalin carbon framework.[40] We began by preparing electrophile **3.63** (Scheme 3.17), which contained an orthogonally protected phenol that we planned to use later as a directing group and ultimately as a functional handle for quinone oxidation.[41] Starting from benzyl alcohol **3.61**, regioselective chlorination with 1,3-dichloro-



3.61 **3.62** **3.63**

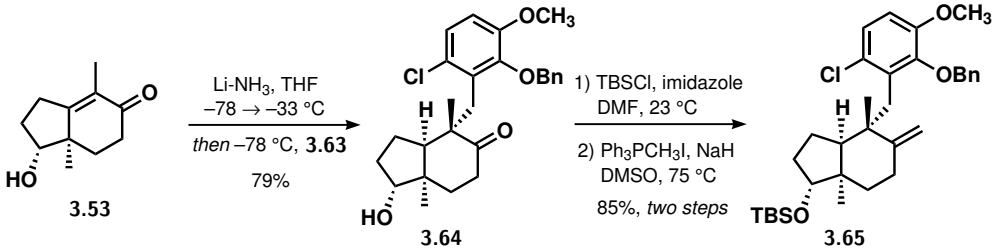
Scheme 3.17: Second generation electrophile synthesis.

[39]Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-Directable Chemical Reactions. *Chem. Rev.* **1993**, *93*, 1307-1370.

[40]Kawano, H.; Masanori, I.; Tadashi, K.; Terashima, S. Studies Toward the Synthesis of Popolohuanone E: Synthesis of Natural (+)-Arenarol Related to the Proposed Biogenetic Precursor of Popolohuanone E. *Tetrahedron Lett.* **1997**, *38*, 7769-7772.

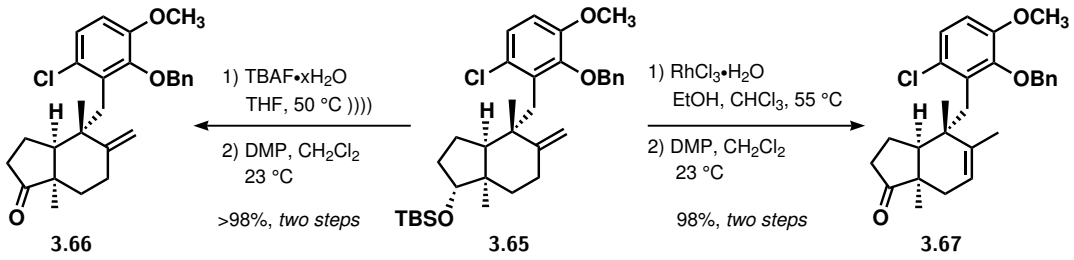
[41]Early model studies on the oxidation of free phenols with Fremy's salt were very promising. Wehrli, P. A.; Pigott, F. Oxidation with the Nitrosodisulfonate Radical. I. Preparation and Use of Disodium Nitrosodisulfonate: Trimethyl-*p*-Benzoquinone. *Org. Synth.* **1972**, *52*, 83. For a review see: Zimmer, H.; Lankin, D. C.; Horgan, S. W. Oxidations with Potassium Nitrosodisulfonate (Fremy's Radical). The Teuber Reaction. *Chem. Rev.* **1971**, *72*, 229-246.

5,5-dimethylhydantoin delivered the desired aryl-chloride **3.62** in 92% yield.[42] Bromination under Appel conditions,[43] followed by displacement of the bromide with sodium iodide provided decagram-scale access to the desired second generation electrophile **3.63** in an 86% yield over two steps.



Scheme 3.18: Second generation forward synthesis.

We then proceeded with the dissolved metal reductive alkylation of electrophile **3.63** and reduced Hajos-Parrish ketone **3.53**. The reductive alkylation smoothly delivered the desired keto-alcohol **3.64** in 79% yield after column chromatography (Scheme 3.18). Silyl protection under standard conditions and Wittig olefination afforded **3.65** in 85% yield over two steps. At this stage in the previous generation synthesis we isomerized the 1,1-disubstituted exocyclic olefin to help facilitate a poorly diastereoselective hydrogenation over Adam's catalyst (Scheme 3.13, page 300). By diverging the material at this point and bringing forward both the 1,1-disubstituted olefin and the trisubstituted olefin, we could

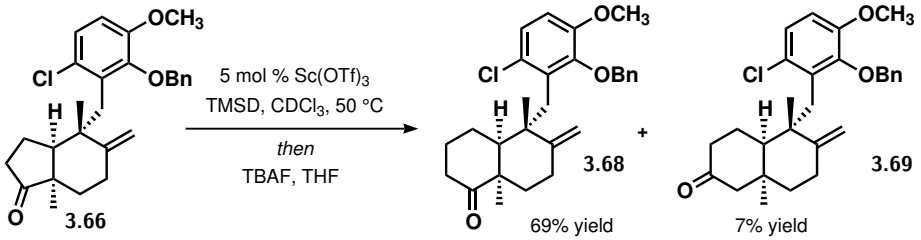


Scheme 3.19: Divergent approach in second generation synthesis.

[42] Auerbach, J.; Weissman, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. *N*-Bromosuccinimide / Dibromodimethylhydantoin in Aqueous Base: A Practical Method for the Bromination of Activated Benzoic Acids. *Tetrahedron Lett.* **1993**, *34*, 931-934.

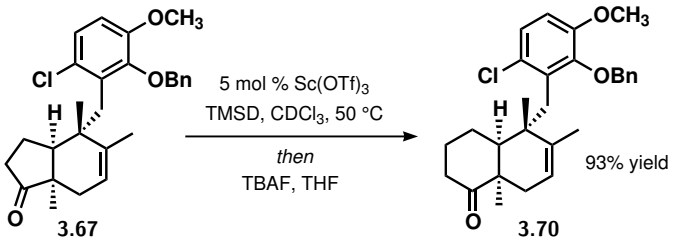
[43] Appel, R. Tertiary Phosphane/Tetrachloromethane, a Versatile Reagent for Chlorination, Dehydration, and P–N Linkage. *Angew. Chem. Int. Ed.* **1975**, *14*, 801-811.

have more substrates to test in the homologation reaction and subsequent hydrogenation (Scheme 3.19). Direct deprotection of **3.65** with TBAF followed by Dess-Martin oxidation provided access to the exocyclic 1,1-disubstituted cyclopentanone **3.66** in quantitative yield over two steps. Rhodium mediated isomerization and deprotection of **3.65** followed by Dess-Martin oxidation afforded the trisubtituted olefin **3.67** in 98% yield over two steps. Attempts were not made to hydrogenate either **3.66** or **3.67** prior to the homologation event because of our previous challenges with β-methyl cyclopentanone **3.57**.



Scheme 3.20: Homologation of **3.66** gives diminished selectivity and yields.

We then focused on the key ring expansion event with two additional cyclopentanone substrates in hand (**3.66**, **3.67**). We were pleased again to see that both substrates readily underwent homologation with mild warming of the reaction mixture, reaching full conversion in less than 24 hours. Exocyclic cyclopentanone **3.66** delivered a slightly diminished 69% isolated yield of the desired major regioisomer **3.68**, along with a 7% isolated yield of the minor regioisomer **3.69** (Scheme 3.20, approx. 7:1 rr by crude ^{1}H NMR). Isomerized cyclopentanone **3.67** afforded an excellent 93% isolated yield of the target homologated



Scheme 3.21: Excellent yield with the homologation of **3.67**.

product **3.70** (Scheme 3.21). The homologation reaction of **3.67** tracked well with the results obtained in the first generation route with **3.50** (89% isolated, >8:1 rr). These results illustrate how seemingly subtle changes to the molecule can have a fairly striking effect on the outcome of the homologation reaction.

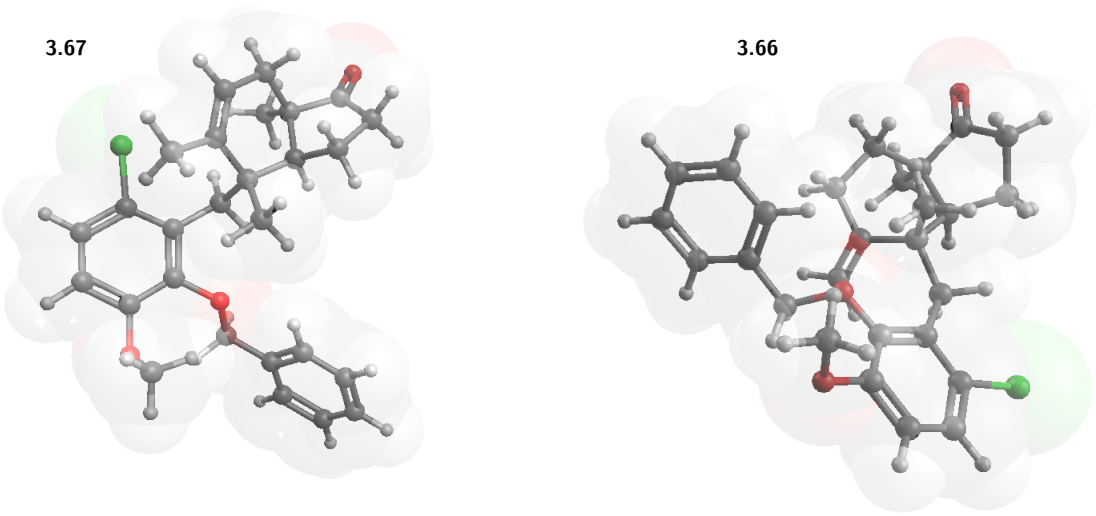


Figure 3.4: Modeling of cyclopentanones **3.66** and **3.67** reveals different chair conformations.

Modeling of cyclopentanones **3.66** and **3.67** *in silico* revealed that the position of the olefin significantly impacts the preferred chair conformation of the molecule.[44] The endocyclic olefin cyclopentanone **3.67** (left, Figure 3.4) adopts a half-chair conformation that places both the C-9 appended aryl group and α-keto methyl in a distorted 1,3-diaxial orientation. The exocyclic olefin cyclopentanone **3.66** (right, Figure 3.4) prefers a twist-boat conformation where the C-9 aryl moiety rests in an equatorial disposition and the α-keto methyl remains axial. The change in conformation translates to a modified steric environment around the ketone, which in turn affects the outcome of the homologation reactions.

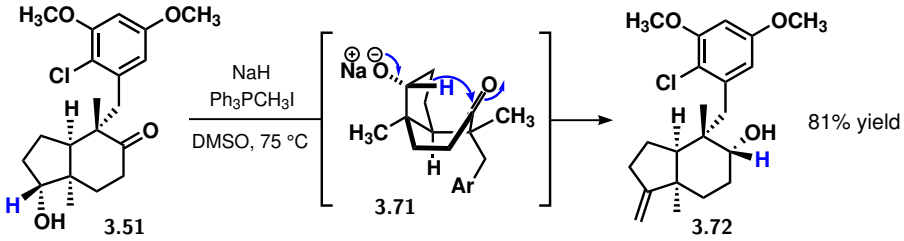
The homologation reactions performed exceptionally well, and we were especially pleased to see that reactions worked consistently. The reliability and scalability of the reaction

[44]Optimized geometries were calculated with Gaussian '09 - B3LYP 3-21G / Avogadro 1.03

allowed ample quantities of material to be moved forward. Again significant hardships were encountered when attempting to further transform both **3.68** and **3.70**. A complete discussion is beyond the scope of this chapter and will be discussed elsewhere.[38]

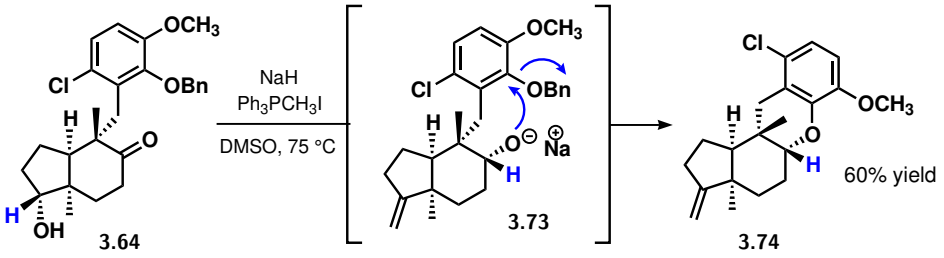
3.4.3 *An Unexpected 1,5-Hydride Shift*

During the course of our studies we observed an unexpected molecular rearrangement when attempting to directly olefinate the *cis*-fused keto alcohol products derived from dissolved metal reductive alkylation. When keto-alcohol **3.51** was subjected to Wittig methylenation conditions, an ene-carbinol isomeric with the anticipated product was isolated in an 81% yield ($\longrightarrow$ **3.72**, Scheme 3.22). The observed product, whose connectivity was rigorously established by TOCSY NMR data, was the result of what we believed to be a transannular 1,5-hydride migration followed by cyclo*pentanone* methylenation. This type of internal redox event has been observed previously in a number conformationally biased bicyclic systems.[45] We speculated that the two quaternary carbon centers, arranged 1,3 around the cyclohexanone, would suffer from a 1,3-diaxial interaction in either chair conformer.



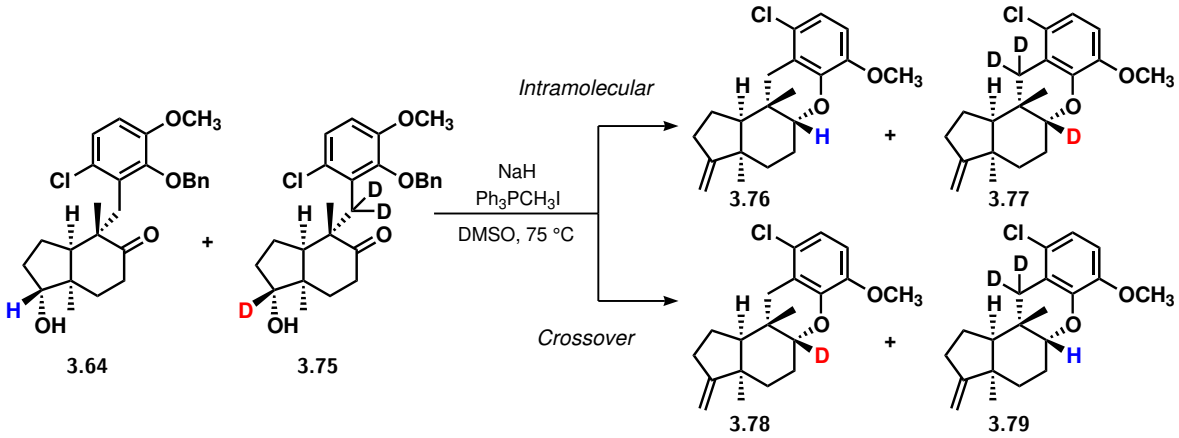
Scheme 3.22: Unexpected molecular rearrangement during Wittig olefination.

[45](a) Dvornik, D.; Edwards, O. E. Ajaconine: An Intramolecular Cannizzaro-type Reaction and the Location of the Undefined Oxygen. *Proc. Chem. Soc.* **1958**, 280-281. (b) Acklin, W.; Prelog, V. Die Bestimmung der absoluten Konfiguration von 8-Methyl-hydrindan-Derivaten durch asymmetrische Synthese. Eine intramolekulare 1,5-Hydrid-Verschiebung in der *cis*-Hydrindan-Reihe. *Helv. Chim. Acta.* **1959**, *42*, 1239-1247. (c) Parker, W.; Stevenson, J. R. A Transannular 2,6-Hydride Shift in the Bicyclo[3,3,1]nonane System. *J. Chem. Soc. Chem. Comm.* **1969**, 1289-1290. (d) Wicha, J.; Caspi, E. Transformations of Steroidal Neopentyl Systems. VII. Mechanism of the Transformation of (19*R*)-Hydroxy-19a-methyl-(5α)-3-ones to 19-Keto-19a-methyl-(5α)-3α-hydroxy Analogs. *J. Org. Chem.* **1973**, *38*, 1280-1283. (e) Shepherd, J. M.; Singh, D.; Wilder Jr., P. An Alkali Induced 1,4-Hydride Shift in endo-Tricyclo[5.2.1.0]decyl Ketols. *Tetrahedron Lett.* **1974**, *15*, 2743-2746. (f) Warnhoff, E. W. A Base-induced Transannular 1,4-Hydride Shift in a Cyclohexanone. *J. Chem. Soc. Chem. Comm.* **1976**, 517-518.



Scheme 3.23: Further molecular rearrangement with second generation electrophile.

Under the reaction conditions, a boat conformation (**3.71**) that helps alleviate some of the penalizing 1,3 interactions could be energetically accessible and allow the migrating hydrogen to come in close proximity of the carbonyl π^* orbital. In the second generation synthesis we also observed a similar molecular rearrangement with unprotected keto-alcohol **3.64** (Scheme 3.23). Instead of isolating the analogous rearranged ene-carbinol, further transformation of **3.73** led to the unusual tetracyclic olefin **3.74** which could be recovered in a 60% isolated yield. All analytical data were consistent with structure **3.74** and no other major products were isolated from the reaction mixture.



Scheme 3.24: Design of crossover experiment to test intramolecular hydride shift.

To test if the hydride shift occured through an intramolecular process we designed a simple crossover experiment (Scheme 3.24). Subjecting a 1:1 molar mixture of **3.64** and **3.75** to Wittig conditions should result in exclusive formation of **3.76** and **3.77** if the

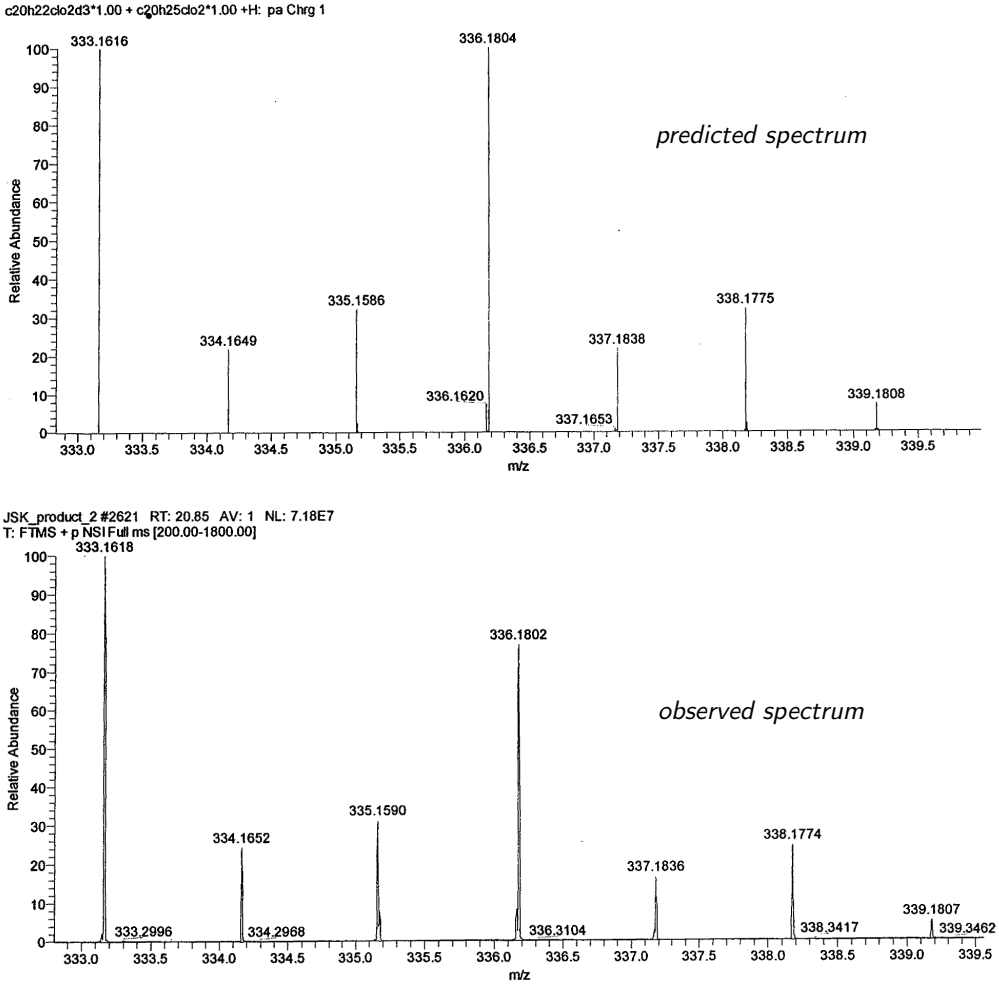


Figure 3.5: Predicted mass spectrum for **3.76** + **3.77** and observed spectrum.

process proceeds through a clean intramolecular reaction. In the event that the mechanism involves a bimolecular process, the crossover products **3.78** and **3.79** should also be observed. We began by preparing a sample of doubly-labelled keto-alcohol **3.75**, which required the synthesis of labelled versions of the second generation electrophile **3.63** and reduced Hajos-Parrish ketone **3.53**.[46] With the requisite material in hand, we subjected **3.64** and **3.75** to the standard Wittig conditions. High resolution mass spectroscopic data were then recorded on the reaction mixture (Figure 3.5) and confirmed that the process does

[46]See the experimental section for details.

indeed occur through an exclusively intramolecular pathway. The predicted mass spectrum for **3.76** and **3.77**, which accounts for the natural isotopic distribution pattern, was identical to the experimental spectrum. The crossover product masses for **3.78** ($C_{20}H_{25}DClO_2$, 334.1679 $[M+H]^+$) and **3.79** ($C_{20}H_{24}D_2ClO_2$, 335.1741 $[M+H]^+$) were not detected. Although there is a mass hit in the experimental spectrum at 334.1652, the peak corresponds to the expected $[M + H + 1]^+$ peak for **3.76** and the resolution of the instrument was high enough to distinguish between 334.1652 and 334.1679. In the event that the masses overlapped in the spectrum, the ratio between peak heights was still in agreement with the expected natural isotopic distribution for the intramolecular products. These data are a nice complement to the examples in the literature, since the previously reported cases did not thoroughly investigate the reaction mechanism.[45]

3.5 Conclusion

In summary, we have succesfully demonstrated the first examples of catalytic single-carbon homologation with α-quaternary cyclopentanone substrates. In model systems, high levels of regioselectivity can be obtained by either using $Yb(OTf)_3$ as the catalyst, or by employing the more sterically demanding diazoalkane PDMSD (up to >50:1 rr). Rigorously controlling environmental variables led to procedures that allow these reactions to be carried out reliably. The precautions discussed in Chapter 2 with regard to dry reaction conditions proved to be integral to the success of single-carbon homologations as well. When extending the method to more complex substrates, moderate to high yields with good levels of regiocontrol were observed (69-93% yield, >8:1 rr). Of the previous examples in the literature, the new reactions catalyzed by low loadings of $Sc(OTf)_3$ were among the highest yielding and most selective. We are confident that these newly developed conditions could find other applications in the future.

3.6 Experimental Data

3.6.1 *General Information*

General Procedures

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an atmosphere of argon passed through a tower of finely powdered Drierite® in dry, degassed solvent with standard Schlenk or vacuum-line techniques. Particularly air-sensitive manipulations were performed in an MBraun Unilab nitrogen atmosphere glove box. Flash column chromatography, driven by compressed air, was performed according to the procedure of Still *et al.*[47] with ZEOPrep 60 Eco 40-63 μm silica gel. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F254 plates purchased from EMD Chemicals. TLC plates were visualized by exposure to ultraviolet light and/or exposure to ceric ammonium molybdate, *p*-anisaldehyde, or potassium permanganate stains.

Materials

Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), benzene, acetonitrile (CH_3CN), and *N*,*N*-dimethylformamide (DMF) were dispensed under UHP argon from a Glass Contour solvent purification system custom manufactured by SG Waters, LLC (Nashua, NC). Pyridine, phosphorus tribromide (PBr_3), *N*-chlorosuccinimide (NCS), sodium iodide (NaI), methyltriphenylphosphonium bromide (Ph_3PCH_3Br), boron trifluoride etherate ($BF_3 \cdot OEt_2$), dimethyl sulfoxide (DMSO), trimethylaluminum ($AlMe_3$), methanol, *tert*-butyldimethylsilyl triuoromethanesulfonate (TBSOTf), tert-butyldimethylsilyl chloride (TBSCl), triethylamine (Et_3N), imidazole, D-phenylalanine (D-Phe), pyridinium p-toluenesulfonate (PPTS), deuterochloroform ($CDCl_3$), carbon tetrachloride (CCl_4), 1,3-dichloro-5,5-dimethylhydantoin, and acetone were purified and dried according to the re-

[47] Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.

ported procedures.[48] Estrone 3-methyl ether, potassium carbonate (K_2CO_3), 3,5- dimethoxybenzoic acid, *n*-butyllithium (*n*-BuLi) in hexanes, sodium borohydride ($NaBH_4$), lithium aluminum hydride ($LiAlH_4$), lithium aluminum deuteride ($LiAlD_4$), sodium borodeuteride ($NaBD_4$), sodium hydride (NaH), ethanol (EtOH), chloroform ($CHCl_3$), sodium chlorite ($NaClO_2$), pyridinium chlorochromate (PCC), platinum(IV)oxide (PtO_2), 10% wt/wt palladium on carbon (Pd/C), lithium wire, sodium chunks, tetra-*n*-butylammonium fluoride hydrate ($TBAF \cdot xH_2O$), hydrogen peroxide in water (30% wt/wt), and Celite® 545 were purchased from Sigma-Aldrich and used without further purification. Sodium chloride (NaCl), ammonium chloride (NH_4Cl), sodium bicarbonate ($NaHCO_3$), potassium carbonate (K_2CO_3), sodium hydroxide (NaOH), sodium sulfate (Na_2SO_4), sodium thiosulfate ($Na_2S_2O_3$), sodium dihydrogen phosphate (NaH_2PO_4), and magnesium sulfate ($MgSO_4$) were purchased from Fisher Scientific and used without further purification. Methyltriphenylphosphonium iodide was prepared from triphenylphosphine (Aldrich), and methyl iodide (Aldrich) by stirring in benzene for 2 hours, filtering, washing with hexanes, and drying over P_2O_5 before use. Molecular sieves (3Å, 4-8 mesh) were purchased from Aldrich and activated by drying under vacuum (approx. 30 mm Hg) at 250 °C for at least 6 hours prior to use. Rhodium chloride hydrate ($RhCl_3 \cdot H_2O$) was purchased from Pressure Chemical Co. and used without further purification. Anhydrous ammonia was purchased from Airgas Inc. and distilled from sodium metal prior to use. Dess-Martin Periodinane was prepared according to the reported literature procedure.[49] Scandium triflate ($Sc(OTf)_3$) (99%) was purchased from Sigma-Aldrich, finely powdered, and then dried at 200 °C over P_2O_5 for 24 hours under high vacuum (0.1 mm Hg). The dried scandium triflate was taken into a dry box using rigorous Schlenk techniques.[50] Trimethylsilyldiazomethane (TMSD) and phenyldimethylsilyldiazomethane (PDMSD) were prepared according to the reported liter-

[48] Armarego, W. L. F.; Chai, C. L. *Purification of Laboratory Chemicals*, 5th ed.; Butterworth-Heinemann: Oxford, 2003.

[49] Meyer, S. D.; Schreiber, S. L. Acceleration of the Dess-Martin Oxidation by Water. *J. Org. Chem.* **1994**, *59*, 7549-7552.

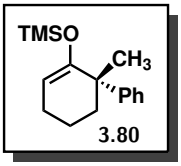
[50] For information on handling scandium triflate, refer to the previous chapter.

ature procedure[29] and were stored over 3Å molecular sieves at −40 °C in a drybox. Note: TMSD is both non-explosive and non-mutagenic, however it is extremely toxic and should be handled with the appropriate precautions.

Instrumentation

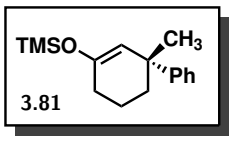
Infrared spectra were recorded on a Bruker Alpha-p spectrometer. Bands are reported as strong (s), medium (m), weak (w), broad strong (bs), broad medium (bm), and broad weak (bw). Optical rotation data were recorded on a Rudolph research Autopol IV automatic polarimeter and is reported as the average of five readings. Melting points were recorded on a Digimelt MPA160 SRS and are uncorrected. Sonication was performed with a Misonix® Sonicator 3000 equipped with a Laude external circulator. ^{1}H NMR spectra were recorded on a Varian VNMRS (500 MHz), INOVA (500 MHz), or VNMRS (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian VNMRS (125 MHz), INOVA (125 MHz), or VNMRS (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.16, DMSO-d_6: δ 39.52). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility. Supercritical fluid chromatography (SFC) data were obtained on a Berger Instruments system using a Daicel CHIRALPAK AS-H column (ϕ 4.6 mm, 25 cm length). Gas chromatography (GC) analysis was performed on an Agilent Technologies 7890A system equipped with a flame ionization detector and HP-5 column (30 m x 0.320 mm x 0.25 μm).

3.6.2 *Experimental Procedures and Characterization Data*



trimethyl(6-methyl-6-phenylcyclohex-1-enyloxy)silane (**3.80**). In a drybox, $Yb(OTf)_3$ (19.2 mg, 0.0310 mmol, 0.100 equiv) was weighed directly into a 1.5 mL vial. A solution of ketone **2.31** (54.0 mg, 0.310 mmol, 1.0 equiv) in 1.55 mL of CH_2Cl_2 was then transferred directly to the solid $Yb(OTf)_3$. TMSD (251 μL, 0.630 mmol, 2.00 equiv, 2.47 M in hexanes) was introduced dropwise, and the reaction mixture was allowed to stir for 27 hours in the drybox. The vessel was then removed from the drybox, and the reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL). The product was extracted with Et_2O (3 x 10 mL), and the combined organics were washed with saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (100% hexanes) afforded the desired enol silane **3.80** as a colorless oil (61.8 mg, 76.5%).

R_f = 0.35 (100% hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.35 (m, 2H), 7.30-7.26 (m, 2H), 7.19-7.14 (m, 1H), 4.93 (dd, J = 3.9, 3.9 Hz, 1H), 2.12-2.07 (m, 2H), 1.88 (ddd, J = 13.2, 6.6, 2.9 Hz, 1H), 1.71 (ddd, J = 13.2, 11.3, 2.9 Hz, 1H), 1.49-1.42 (m, 1H), 1.45 (s, 3H), 1.38-1.27 (m, 1H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.39, 148.23, 127.81, 127.14, 125.58, 103.74, 43.96, 41.17, 26.20, 24.74, 19.08, 0.51; IR (neat) 2961 (bm), 2932 (bm), 2838 (w), 1657 (m), 1248 (s),1182 (s), 1152 (w), 843 (s), 759 (m), 698 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{16}H_{25}OSi$ $[M+H]^+$: 261.1675; Found 261.1671.

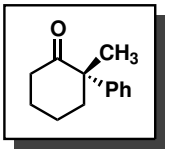


trimethyl(3-methyl-3-phenylcyclohex-1-enyloxy)silane (**3.81**). Authentic material for comparison purposes was prepared according to the literature procedure.[51]

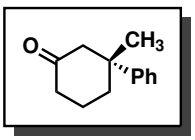
R_f = 0.38 (3% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.40-7.37 (m, 2H), 7.31-7.27 (m, 2H), 7.19-7.15 (m, 1H), 4.95-4.94 (m, 1H), 2.08-1.98 (m, 2H), 1.83-1.77 (m, 1H), 1.66-1.54 (m, 2H), 1.48-1.41 (m, 1H), 1.40 (s, 3H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$,

[51]Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934-946.

125 MHz) δ 150.68, 150.43, 128.02, 126.79, 125.65, 113.50, 40.12, 39.05, 30.33, 29.96, 19.72, 0.63; IR (neat) 2958 (bm), 2933 (bm), 1661 (m), 1251 (m), 1196 (s) 894 (m), 843 (s), 760 (m), 699 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{16}H_{25}OSi$ $[M+H]^+$: 261.1675; Found 261.1662.

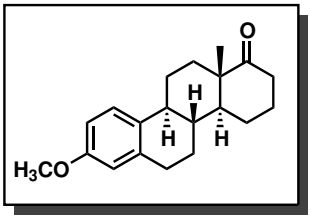


2-methyl-2-phenyl-cyclohexanone (**3.33**). To a solution of silyl enol ether **3.80** (57.1 mg, 0.219 mmol, 1.00 equiv) in 1.1 mL of THF, TBAF (1.0 mL, 1.0 mmol, 4.8 equiv, 1.0 M solution in THF) was added. After 40 minutes at 23 °C, the reaction mixture was poured into H_2O (20 mL). The product was extracted with ethyl acetate (3 x 15 mL), and the combined organics were washed with saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was then passed through a plug of silica gel eluting with ethyl acetate and then concentrated to afford the desired product **3.33** as a yellow oil (46.2 mg, quantitative).
R_f = 0.48 (10% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.33 (m, 2H), 7.26- 7.22 (m, 1H), 7.24 (tt, J = 6.8, 1.2 Hz, 1H), 7.20-7.17 (m, 2H), 2.72-2.66 (m, 1H), 2.42-2.28 (m,2H), 2.00-1.93 (m, 1H), 1.78-1.67 (m, 4H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214. 17, 143.42, 129.11, 126.69, 126.22, 54.51, 40.05, 38.30, 28.59, 22.00; IR (neat) 2934 (bm), 2863 (bm), 1708 (s), 1495 (w), 1448 (w), 759 (w), 702 (m), 551 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{13}H_{17}O$ $[M+H]^+$: 189.1279; Found 189.1284.



3-methyl-3-phenyl-cyclohexanone (**3.34**). To a solution of silyl enol ether **3.81** (46.3 mg, 0.178 mmol, 1.00 equiv) in 0.9 mL of THF, TBAF (0.40 mL, 0.43 mmol, 2.4 equiv, 1.0 M solution in THF) was added. After 40 minutes at 23 °C, the reaction mixture was poured into H_2O (20 mL). The product was extracted with ethyl acetate (3 x 15 mL), and the combined organics were washed with saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was then passed through a plug of silica gel eluting with ethyl acetate and then concentrated to afford the desired product **3.34** as a yellow oil.

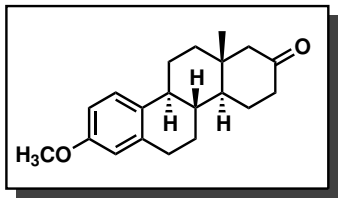
R_f = 0.30 (10% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.31 (m, 4H), 7.23- 7.18 (m, 1H), 2.88 (d, J = 14.2 Hz, 1H), 2.44 (d, J = 14.4 Hz, 1H), 2.34-2.29 (m, 2H), 2.22-2.16 (m, 1H), 1.96-1.84 (m, 2H), 1.72-1.63 (m, 1H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.58, 147.57, 128.65, 126.31, 125.70, 53.21, 42.94, 40.92, 38.07, 29.90, 22.14; IR (neat) 2957 (bm), 2872 (bm), 1710 (s), 1498 (w), 1422 (m), 1228 (m), 1031 (bw), 764 (m), 700 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{13}H_{17}O$ $[M+H]^+$: 189.1279; Found 189.1279.



homologated estrone 3-methyl ether major (**3.42**). In a drybox, $Sc(OTf)_3$ (3.7 mg, 0.0075 mmol, 0.050 equiv) was weighed directly into a 1.5 mL vial equipped with a magnetic stirbar. A solution of estrone 3-methyl ether (42.6 mg, 0.150 mmol, 1.00 equiv) in $CDCl_3$ (0.53 mL) was transferred directly to the solid $Sc(OTf)_3$. The cloudy gray suspension was stirred for 15 minutes at which point TMSD (121 μL, 0.300 mmol, 2.00 equiv, 2.47 M in hexanes) was introduced dropwise. The entire reaction mixture (including any residual solids) was transferred via glass pipette to a J. Young NMR tube, and the vial was rinsed with an additional 0.2 mL of $CDCl_3$. The reaction tube was removed from the drybox, connected to a nitrogen manifold, and allowed to stand for 24 hours at 23 °C. 1,3,5-trimethoxybenzene (11.0 mg, 0.654 mmol) was added, and ^{1}H NMR analysis indicated a 72% yield of the major enol silane. The reaction mixture was poured into H_2O (5 mL), and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics dried over Na_2SO_4, filtered, and concentrated. The crude residue was then dissolved in 1 mL of THF, TBAF $\cdot$ xH_2O (168 mg, excess) was added as a solid, and the reaction mixture was allowed to stir for 30 minutes at 23 °C. The reaction mixture was then poured into H_2O (5 mL) and the product was extracted with Et_2O (3 x 5 mL), and the combined organics were passed through a plug of silica gel rinsing with ethyl acetate (10 mL) and concentrated. Purification by column chromatography (15% ethyl acetate in hexanes v/v) afforded the

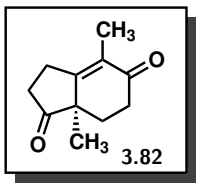
desired homologated estrone derivative **3.42** as a white solid (30.4 mg, 67.9%), mp 136-138 °C.

R_f = 0.30 (15% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (dd, J = 8.8, 0.5 Hz, 1H), 6.72 (dd, J = 8.9, 2.9 Hz, 1H), 6.63 (d, 2.9 Hz, 1H), 3.78 (s, 3H), 2.88-2.83 (m, 2H), 2.67 (ddd, J = 14.2, 14.2, 6.8 Hz, 1H), 2.38 (dddd, 11.5, 4.2, 4.2, 4.2 Hz, 1H), 2.28-2.21 (m, 2H), 2.16-2.05 (m, 2H), 1.99-1.93 (m, 1H), 1.89 (ddd, J = 13.9, 3.4, 3.4 Hz, 1H), 1.73 (ddd, J = 13.7, 13.7, 3.9 Hz, 1H), 1.69-1.58 (m, 1H), 1.55-1.39 (m, 4H), 1.34-1.25 (m, 1H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.45, 157.69, 137.76, 132.60, 126.48, 113.59, 111.77, 55.33, 50.44, 48.54, 43.17, 38.99, 37.32, 32.66, 30.24, 26.78, 26.07, 26.03, 23.08, 17.02; IR (neat) 2930 (bs), 2863 (bm), 1703 (s), 1610 (w), 1502 (m), 1429 (bm), 1254 (m), 1237 (m), 1040 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{20}H_{27}O_2$ $[M+H]^+$: 299.2011; Found 299.1999.

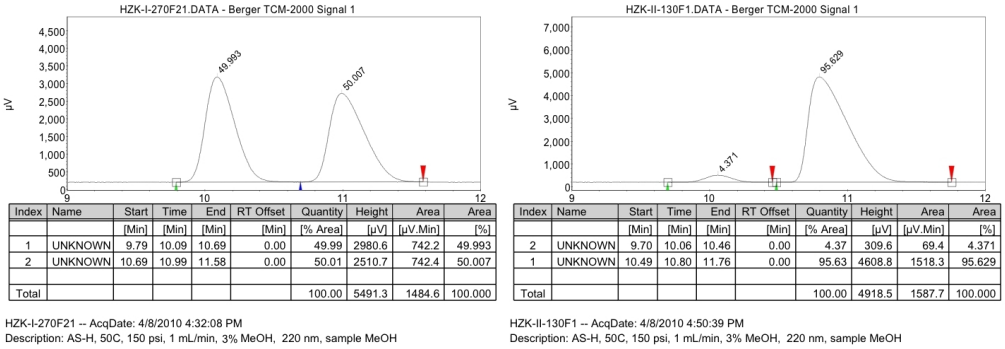


homologated estrone 3-methyl ether minor (**3.43**). Isolated as the minor regioisomer in the procedure for compound **3.42**. Purification by column chromatography (15% ethyl acetate in hexanes v/v) afforded the minor regioisomer as a white solid (9.9 mg, 22%), mp 176-180 °C.

R_f = 0.17 (15% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (d J = 8.3 Hz, 1H), 6.73 (dd, J = 8.8, 2.9 Hz, 1H), 6.64 (d, J = 2.9 Hz, 1H), 3.78 (s, 3H), 2.89-2.83 (m, 2H), 2.47-2.21 (m, 5H), 2.23 (d, J = 13.7 Hz, 1H), 2.16-2.09 (m, 1H), 2.14 (d, J = 13.4, 2.4 Hz, 1H), 1.67-1.42 (m, 5H), 1.41-1.24 (m, 2H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.83, 157.74, 137.95, 132.58, 126.45, 113.64, 111.84, 56.93, 55.38, 48.12, 43.72, 41.38, 41.33, 39.66, 38.38, 30.20, 26.76, 26.50, 25.72, 17.88; IR (neat) 2922 (bs), 2861 (bm), 1709 (s), 1612 (w), 1501 (m), 1256 (s), 1038 (m), 810 (w), 79 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{20}H_{27}O_2$ $[M+H]^+$: 299.2011; Found 299.2015.



Hajos-Parrish ketone (**3.82**). A 40 mL vial (95 mm x 25 mm) equipped with a magnetic stirbar and a rubber septum was charged with 2-methyl-2-(3- oxopentyl)cyclopentane-1,3-dione[52] (2.00 g, 10.2 mmol, 1.00 equiv), D-Phe (505 mg, 3.06 mmol, 0.300 equiv), and PPTS (1.28 g, 5.09 mmol, 0.499 equiv). DMSO (0.73 mL) was added with a syringe, and the resulting suspension was stirred for 5 minutes at room temperature. The vial was then sonicated (60 W) continuously at 50 °C for 24 hours. 20 minutes into the reaction period at 50 °C, the reaction mixture was observed to be dark yellow and homogeneous. The crude reaction mixture was directly loaded onto a flash column and eluted with 50% Et_2O in pentane (v/v) to afford the desired product **3.82** as a colorless oil (1.61 g, 88.6%) with 91% ee (AS-H, 50 °C, 150 psi, 1.0 mL/min, 3% MeOH, λ = 220 nm; t_R = 10.06 min (minor), 10.80 min (major)).
R_f = 0.50 (60% Et_2O in pentane v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.96-2.87 (m, 1H), 2.85-2.73 (m, 2H), 2.60-2.37 (m, 3H), 2.07 (ddd, J = 13.4, 5.1, 2.2 Hz, 1H), 1.85 (ddd, J = 13.9, 13.9, 5.9 Hz, 1H), 1.78 (d, J = 1.2 Hz, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.74, 197.99, 162.55, 129.95, 48.99, 35.54, 32.92, 28.94, 24.60, 21.38, 10.89; HRMS (ESI+) Calcd. for $C_{11}H_{15}O_2$ $[M+H]^+$: 179.1072; Found 179.1076.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	9.79	10.09	10.69	0.00	49.99	2980.6	742.2	49.993
2	UNKNOWN	10.69	10.99	11.58	0.00	50.01	2510.7	742.4	50.007
Total						100.00	5491.3	1484.6	100.000

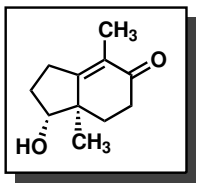
HZK-I-270F21 -- AcqDate: 4/8/2010 4:32:08 PM
Description: AS-H, 50C, 150 psi, 1 mL/min, 3% MeOH, 220 nm, sample MeOH

Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
2	UNKNOWN	9.70	10.06	10.46	0.00	4.37	309.6	69.4	4.371
1	UNKNOWN	10.49	10.80	11.76	0.00	95.63	4608.8	1518.3	95.629
Total						100.00	4918.5	1587.7	100.000

HZK-II-130F1 -- AcqDate: 4/8/2010 4:50:39 PM
Description: AS-H, 50C, 150 psi, 1 mL/min, 3% MeOH, 220 nm, sample MeOH

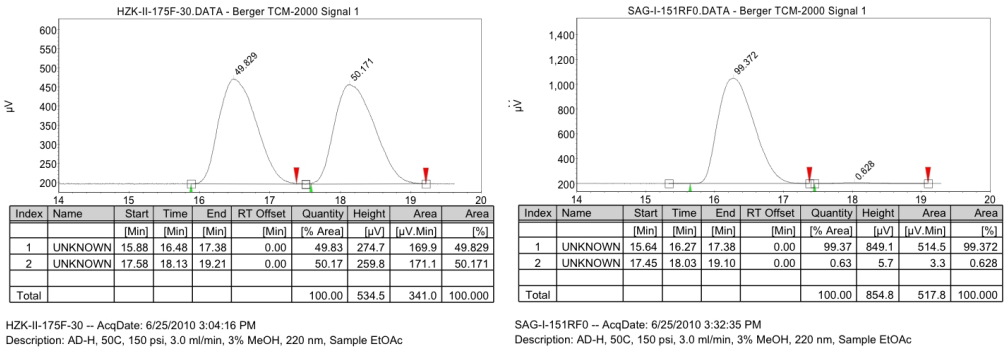
Figure 3.6: SFC trace for Hajos-Parrish ketone (**3.82**)

[52] Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1990**, *Coll. Vol.* *7*, 363.



Hajos-Parrish keto-alcohol (**3.53**). Hajos-Parrish ketone **3.82** (3.49 g, 19.6 mmol, 1.00 equiv) was dissolved in 70 mL of EtOH, and the resulting homogeneous solution was cooled to −25 °C. Sodium borohydride (0.233 g, 6.16 mmol, 0.314 equiv) was added as a solid, and the mixture was closely monitored by TLC. After 20 minutes, the reaction was judged to be complete and was quenched by the addition of saturated aqueous NaCl (30 mL) and H_2O (20 mL). The reaction mixture was poured into a separatory funnel and the product was extracted with Et_2O (3 x 50 mL). The combined organics were washed with saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (85% Et_2O in pentane v/v) afforded the desired product as a white solid (3.34 g, 94.5%). Enantioenrichment was achieved by recrystallization from hot Et_2O and hexanes (approx. 3:1 v/v) to afford the optically pure product **3.53** (2.14 g, 60.6%) with 99% ee (AS-H, 50 °C, 150 psi, 3.0 mL/min, 3% MeOH, $\lambda = 220$ nm; $t_R = 16.27$ min (major), 18.03 min (minor)).

$R_f = 0.38$ (60% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.83 (ddd, J = 13.2, 7.3, 5.9 Hz, 1H), 2.62-2.52 (m, 2H), 2.46-2.36 (m, 2H), 2.19-2.11 (m, 1H), 2.07 (ddd, J = 12.7, 5.4, 2.0 Hz, 1H), 1.88-1.74 (m, 2H), 1.66 (dd, J = 1.2 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.96, 168.10, 129.09, 81.05, 45.15, 34.11, 33.41, 29.60, 25.76, 15.34, 10.80; HRMS (ESI+) Calcd. for $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1229; Found 181.1220.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	15.88	16.48	17.38	0.00	49.83	274.7	169.9	49.829
2	UNKNOWN	17.58	18.13	19.21	0.00	50.17	259.8	171.1	50.171
Total						100.00	534.5	341.0	100.000

HZK-II-175F-30 -- AcqDate: 6/25/2010 3:04:16 PM
Description: AD-H, 50C, 150 psi, 3.0 ml/min, 3% MeOH, 220 nm, Sample EtOAc

Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
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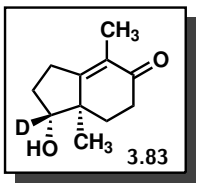
1	UNKNOWN	15.64	16.27	17.38	0.00	99.37	849.1	514.5	99.372
2	UNKNOWN	17.45	18.03	19.10	0.00	0.63	5.7	3.3	0.628
Total						100.00	854.8	517.8	100.000

SAG-I-151RF0 -- AcqDate: 6/25/2010 3:32:35 PM
Description: AD-H, 50C, 150 psi, 3.0 ml/min, 3% MeOH, 220 nm, Sample EtOAc

Figure 3.7: SFC trace for Hajos-Parrish keto-alcohol (**3.53**)



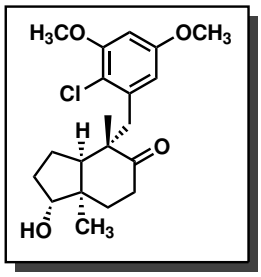
(±)-d_1-Hajos-Parrish keto-alcohol (3.83). Racemic Hajos-Parrish ketone **3.82**[53] (100 mg, 0.563 mmol, 1.00 equiv) was dissolved in 2.0 mL of EtOH, and the resulting homogeneous solution was cooled to −25 °C. Sodium borodeuteride (7.4 mg, 0.18 mmol, 0.31 equiv) was added as a solid, and the mixture was closely monitored by TLC. After 20 minutes, the reaction was judged to be complete and was quenched by the addition of saturated aqueous NaCl (10 mL) and H_2O (10 mL). The reaction mixture was poured into a separatory funnel and the product was extracted with Et_2O (3 x 15 mL). The combined organics were washed with saturated aqueous NaCl (25 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (85% Et_2O in pentane v/v) afforded the desired product as a white solid (113 mg, quantitative), mp 67-73 °C

R_f = 0.36 (85% Et_2O in pentane v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.61-2.52 (m, 2H), 2.45-2.35 (m, 2H), 2.17-2.11 (m, 1H), 2.07 (ddd, J = 12.9, 5.4, 1.6 Hz, 1H), 1.86-1.74 (m, 2H), 1.66 (s, 3H), 1.60 (s, 1H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.07, 168.37, 128.98, 80.48 (t, J = 20.7 Hz), 45.03, 34.01, 33.39, 29.40, 25.76, 15.31, 10.76; IR (neat) 3415 (bm), 2922 (bm), 1641 (s), 1354 (m), 1326 (m), 1298 (w), 1171 (m), 1126 (m), 1044 (bm) cm^{-1}; HRMS (ESI+) Calcd. for $C_{11}H_{16}DO_2$ $[M+H]^+$: 182.1291; Found 182.1298.

General procedure for dissolved metal reductive alkylation: A flame-dried, 2-neck, 25 mL round bottom flask equipped with a cold finger condenser, septum, and a magnetic stir bar was charged with lithium wire (5.8 mg, 0.83 mmol, 3.0 equiv), and the entire apparatus was flame-dried again. After backfilling with argon, the apparatus was cooled to −78 °C, and ammonia (3.6 mL) was freshly distilled from sodium metal into the reaction flask, dissolving the lithium wire and forming a deep blue solution. A solution of enone **3.53** (50.0 mg, 0.277 mmol, 1.00 equiv) in 2.0 mL of THF was then added to the dissolved metal solution over 30 minutes *via* syringe pump. Upon completion of the addition, the reaction

[53]Prepared in an identical fashion to **3.82** with DL-phenylalanine.

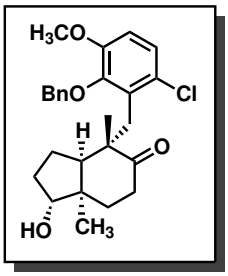
mixture was warmed to −25 °C and stirred at this temperature for 1 hour. The solution was then re-cooled to −78 °C and diluted with 1.2 mL of THF. In a separate flask, a solution of the appropriate electrophile (1.39 mmol, 5.0 equiv) in 1.6 mL THF was pre-cooled to −78 °C and then added as rapidly as possible to the blue solution *via* syringe. Almost immediately, the deep blue color bleached to white, and stirring was continued at − 78 °C for 8 hours. The reaction mixture was then warmed slowly to room temperature, and the ammonia was allowed to evaporate from the reaction mixture. During this time, pressure generated from the vaporization of ammonia was liberated through an exit needle or through an external bubbler. The basic solution was acidified by the addition of 20 mL of saturated aqueous NH_4Cl. The mixture was poured into a separatory funnel, and the product was extracted with Et_2O (3 x 20 mL). The combined organics were washed with H_2O (15 mL), saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude product. Purification was carried out by flash column chromatography on silica gel (ethyl acetate in hexanes). *Note:* This reaction must be carried out under an atmosphere of argon gas, as the use of nitrogen gas results in reaction with lithium metal to form considerable amounts of lithium nitride (Li_3N).



(−)-keto-alcohol (**3.51**). Carried out according to the general procedure for dissolved metal reductive alkylation with enone **3.53** (56.2 mg, 0.312 mmol, 1.00 equiv) and iodide **3.52** (488 mg, 1.56 mmol, 5.00 equiv). The electrophile was not pre-cooled, however, due to a lack of solubility below room temperature. Purification by flash column chromatography (50% ethyl acetate in hexanes v/v) afforded the desired product **3.51** as a white solid (92.6 mg, 80.9%), mp 165-168 °C.

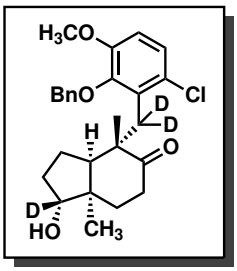
$[\alpha]_D^{20} = -27.64$ (c 1.13, $CHCl_3$); $R_f = 0.33$ (60% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.37 (d, J = 2.7 Hz, 1H), 6.15 (d, J = 2.7 Hz, 1H), 3.86-3.79 (m, 4H), 3.74 (s, 3H), 3.51 (d, J = 13.9 Hz, 1H), 3.0 (d, J = 13.9 Hz, 1H), 2.87 (ddd, J = 15.2, 9.3, 5.6 Hz,

1H), 2.38- 2.30 (m, 1H), 2.22 (ddd, J = 11.0, 8.3, 0 Hz, 1H), 2.07-1.99 (m, 1H), 1.97-1.76 (m, 3H), 1.34 (s, 3H), 1.17 (dddd, J = 9.3, 9.3, 9.3, 9.3 Hz, 1H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.37, 158.20, 155.88, 137.45, 115.56, 107.95, 98.29, 81.39, 56.29, 55.79, 55.55, 52.32, 42.94, 41.50, 35.43, 32.59, 31.43, 26.82, 23.71, 19.71; IR (neat) 3448 (bm), 2958 (bm), 2878 (m), 1697 (s), 1590 (s), 1455 (s), 1330 (s), 1203 (s), 1163 (s), 1084 (m), 979 (m), 753 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{20}H_{28}ClO_4$ $[M+H]^+$: 367.1676; Found 367.1684.



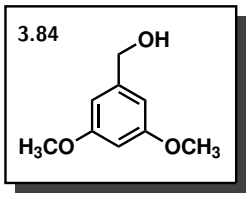
(−)-keto-alcohol (**3.64**). Carried out according to the general procedure for dissolved metal reductive alkylation with enone **3.53** (499 mg, 2.77 mmol, 1.00 equiv) and iodide **3.63** (5.40 mg, 13.9 mmol, 5.00 equiv). Purification by flash column chromatography (40 to 70% ethyl acetate in hexanes v/v) afforded the desired product **3.64** as a white solid (968 mg, 78.9%), mp 45-50 °C.

$[\alpha]_D^{20} = -32.50$ (c 0.86, $CHCl_3$); $R_f = 0.33$ (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.31 (m, 5H), 7.05 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.04 (d, J = 11.2 Hz, 1H), 4.89 (d, J = 11.5 Hz, 1H), 3.83 (s, 3H), 3.71 (ddd, J = 6.1, 6.1, 6.1 Hz, 1H), 3.42 (d, J = 13.7 Hz, 1H), 2.87 (d, J = 13.7 Hz, 1H), 2.65 (dddd, J = 13.7 Hz, 5.4, 5.4, 5.4 Hz, 1H), 2.10 (dd, J = 11.7, 8.1 Hz, 1H), 2.04-1.90 (m, 2H), 1.83-1.74 (m, 1H), 1.73-1.62 (m, 1H), 1.56-1.47 (m, 2H), 1.47-1.38 (m, 1H), 1.17 (s, 3H), 1.08-0.93 (m, 1H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.79, 151.12, 147.91, 137.57, 130.44, 128.75, 128.57, 128.34, 127.24, 124.37, 111.91, 81.00, 75.17, 57.00, 56.07, 51.83, 42.27, 37.15, 35.00, 32.25, 31.45, 27.15, 23.91, 19.08; IR (neat) 3430 (bw), 2956 (bm), 2872 (bm), 1697 (s), 1576 (w), 1463 (bs), 1375 (m), 1275 (s), 1214 (bm), 1077 (bm), 974 (bs), 798 (m), 749 (s), 697 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{26}H_{32}ClO_4$ $[M+H]^+$: 443.1989; Found 443.2005.



(±)-d_3-keto-alcohol (**3.75**). Carried out according to the general procedure for dissolved metal reductive alkylation with enone **3.83** (193 mg, 1.06 mmol, 1.00 equiv) and iodide **3.95** (2.08 g, 5.31 mmol, 5.00 equiv). Purification by flash column chromatography (30 to 60% ethyl acetate in hexanes v/v) afforded the desired product **3.75** as a white solid (398 mg, 84.1%), mp 44-51 °C.

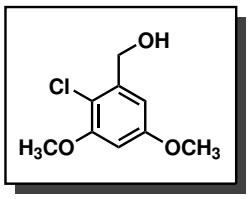
R_f = 0.33 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.30 (m, 5H), 7.04 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.03 (d, J = 11.2 Hz, 1H), 4.89 (d, J = 11.2 Hz, 1H), 3.83 (s, 3H), 2.63 (ddd, J = 16.6, 6.4, 6.4 Hz, 1H), 2.09 (dd, J = 11.7, 8.1 Hz, 1H), 2.03-1.90 (m, 2H), 1.81-1.74 (m, 1H), 1.72-1.47 (m, 3H), 1.45-1.38 (m, 1H), 1.16 (s, 3H), 1.03-0.92 (m, 1H), 0.79 (s, 3H); 13 C NMR ($CDCl_3$, 125 MHz) δ 214.80, 151.12, 147.92, 137.58, 130.38, 128.74, 128.56, 128.33, 127.22, 124.36, 111.94, 80.50 (t, J = 21.9 Hz), 75.16, 56.98, 56.07, 51.68, 42.14, 35.00, 32.21, 31.36, 27.12, 23.89, 19.02; IR (neat) 3449 (bw), 3063 (bw), 2956 (bm), 2870 (bm), 1698 (m), 1574 (w), 1461 (bs), 1374 (m), 1293 (m), 1267 (m), 1097 (bm), 974 (bs), 798 (m), 749 (bm), 698 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{26}H_{29}D_3ClO_4$ $[M+H]^+$: 446.2177; Found 446.2190.



(3,5-dimethoxyphenyl)methanol (**3.84**). In a drybox, $LiAlH_4$ (2.08 g, 54.9 mmol, 1.00 equiv) was weighed into a 250 mL round bottom flask equipped with a magnetic stirbar. After removing the flask from the drybox, 50 mL of THF was added, and the resulting grey suspension was cooled to 0 °C. In a separate flask, 3,5-dimethoxybenzoic acid (10.0 g, 54.9 mmol. 1.00 equiv) was suspended in 60 mL of THF. The slurry of 3,5-dimethoxybenzoic acid was added to the $LiAlH_4$ suspension via syringe, and the reaction mixture was allowed to warm slowly to room temperature and stir for 12 hours. The dark grey solution was then re-cooled to 0 °C, and H_2O (5 mL) was slowly added to quench the excess $LiAlH_4$. The resulting thick slurry was warmed to room temperature and diluted with 50 mL of 1

N HCl. The reaction mixture was poured into a separatory funnel and the product was extracted with Et_2O (3 x 60 mL). The combined organics were washed with H_2O (2 x 100 mL), saturated aqueous NaCl (100 mL), dried over Na_2SO_4, filtered, and concentrated to give **3.84** as a white solid that was used without any further purification (9.00 g, 97.5%), mp 45-48 °C.

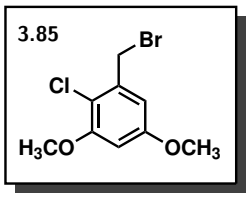
R_f = 0.16 (30% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.53 (d, J = 2.1 Hz, 2H), 6.39 (t, J = 2.1 Hz, 1H), 4.64 (d, J = 6.1 Hz, 2H), 3.80 (s, 6H), 1.66 (t, J = 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.92, 143.53, 104.57, 99.51, 65.11, 55.33; IR (neat) 3346 (bm), 2938 (bm), 2838 (m), 1594 (s), 1458 (s), 1428 (s), 1317 (m), 1202 (s), 1148 (s), 1058 (s), 1034 (s), 829 (s), 688 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_9H_{13}O_3$ $[M+H]^+$: 169.0865; Found 169.0863.



(2-chloro-3,5-dimethoxyphenyl)methanol (**3.55**). To a solution of **3.84** (10.4 g, 62.0 mmol, 1.00 equiv) in 310 mL of CCl_4 was added *N*- chlorosuccinimide (7.86 g, 58.9 mmol, 0.950 equiv) as a solid. The solution was then refluxed for 48 hours. The reaction mixture was cooled to room temperature and concentrated to remove CCl_4. The resulting residue was suspended in 200 mL of Et_2O and filtered through a sintered glass frit. The filtrate was then washed with saturated aqueous $NaHCO_3$ (100 mL), saturated aqueous NH_4Cl (100 mL), H_2O (100 mL), and saturated aqueous NaCl (100 mL). The extract was then dried over Na_2SO_4, filtered, and concentrated. The crude solid was recrystallized from hot Et_2O and hexanes (approx. 5:1 v/v) to afford the desired product **3.55** as a white crystalline solid (9.00 g, 71.7%), mp 88-90 °C.

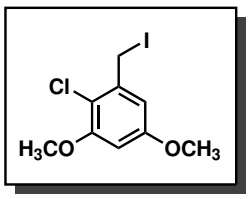
R_f = 0.24 (30% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.68 (d, J = 2.8 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 4.77 (d, J = 6.7 Hz, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 1.95 (t, 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.22, 155.76, 140.22, 112.26, 104.22, 99.04, 63.03, 56.33, 55.68; IR (neat) 3282 (bm), 2937 (m), 2838 (m), 1590 (s), 1454

(s), 1420 (s), 1330 (s), 1198 (s), 1084 (s), 1030 (s), 952 (m), 831 (s), 680 (m), 604 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_9H_{12}ClO_3$ $[M+H]^+$: 203.0475; Found 203.0470.



1-(bromomethyl)-2-chloro-3,5-dimethoxybenzene (**3.85**). Benzyl alcohol **3.55** (2.80 g, 13.8 mmol, 1.00 equiv) was dissolved in 46 mL of benzene, and the resulting homogeneous solution was cooled to 4 °C. PBr_3 (0.49 mL, 5.1 mmol, 0.37 equiv) was added dropwise, then the reaction mixture was warmed to room temperature and stirred for 2.5 hours. The reaction was quenched by the addition of 50 mL of H_2O and transferred into a separatory funnel. The product was extracted with Et_2O (3 x 50 mL) and the combined organics were washed with H_2O (50 mL), saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated to afford the desired product **3.85** as a white solid that was used without further purification (3.01 g, 82.1%), mp 100-102 °C.

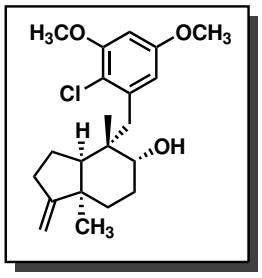
R_f = 0.37 (15% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.58 (d, J = 2.8 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 4.57 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.94, 156.25, 136.90, 114.59, 106.69, 100.26, 56.41, 55.71, 31.06; IR (neat) 3097 (w), 2975 (m), 1585 (s), 1470 (s), 1432 (s), 1334 (s), 1200 (s), 1165 (s), 1082 (s), 1030 (s), 951 (s), 819 (s), 721 (m), 673 (s) 610 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_9H_{11}{}^{79}Br^{37}ClO_2$ $[M+H]^+$: 266.9601; Found 266.9601.



2-chloro-1-(iodomethyl)-3,5-dimethoxybenzene (**3.52**). To a solution of benzyl bromide **3.85** (502 mg, 1.89 mmol, 1.00 equiv) in 3.2 mL of acetone at room temperature, NaI (566 mg, 3.78 mmol, 2.00 equiv) was added as a solid. The resulting suspension was stirred for 12 hours in the dark. The reaction mixture was poured into 50% aqueous $Na_2S_2O_3$ (15 mL), and the product was extracted with Et_2O (3 x 15 mL). The combined organics were washed with saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered, and concentrated to afford the desired product **3.52** as a white solid that was used without further purification

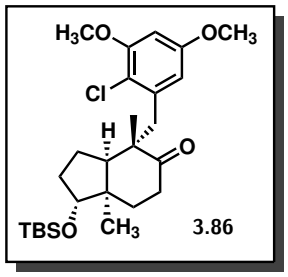
(539 mg, 91.3%), mp 127-129 °C.

R_f = 0.37 (15% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.54 (d, J = 2.7 Hz, 1H), 6.44 (d, J = 2.7 Hz, 1H), 4.50 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.87, 156.39, 138.31, 114.16, 105.99, 99.86, 56.41, 55.72, 3.05; IR (neat) 3058 (w), 2939 (w), 1586 (s), 1469 (s), 1418 (m), 1332 (s), 1204 (s), 1156 (s), 1076 (s), 1030 (m), 951 (m), 818 (m), 675 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_9H_{11}ClIO_2$ $[M+H]^+$: 312.9492; Found 312.9490.



(±)-exocyclic ene-ol (**3.72**). In a drybox, NaH (35.1 mg, 1.46 mmol, 7.02 equiv) was weighed into a 2-neck, 25 mL round bottom flask equipped with a magnetic stirbar. After removing the flask from the drybox, a reflux condenser was installed. 1.5 mL of DMSO was added, and the suspension was heated to 75 °C for 1 hour. During this time, the reaction became homogeneous, forming a teal-colored, clear solution. This solution was cooled to room temperature, and a solution of Ph_3PCH_3I (764 mg, 1.88 mmol, 9.04 equiv) in 2.6 mL of DMSO was added over 30 minutes via syringe pump. Upon addition of the salt, the reaction mixture became bright yellow. After completion of the addition, the mixture was stirred for an additional 30 minutes at room temperature, at which point a solution of racemic keto-alcohol **3.51** (76.3 mg, 0.208 mmol, 1.00 equiv) in 0.58 mL of DMSO was added dropwise. The reaction mixture was then heated to 75 °C and stirred for 16 hours. The resulting amber solution was cooled to room temperature and acidified by the addition of 5 mL of saturated aqueous NH_4Cl. The reaction mixture was diluted with H_2O (15 mL), poured into a separatory funnel, and the product was extracted with Et_2O (3 x 15 mL). The combined organics were washed with H_2O (15 mL), saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (40% Et_2O in pentane v/v) afforded compound **3.72** as a white solid (61.3 mg, 80.8%), mp 117-119 °C.

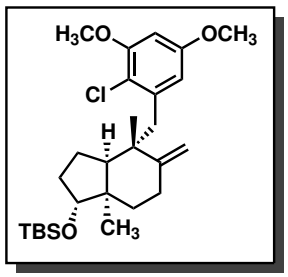
$R_f = 0.33$ (60% Et_2O in pentane v/v); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.69 (d, $J = 2.7$ Hz, 1H), 6.38 (d, $J = 2.7$ Hz, 1H), 4.75-4.71 (m, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.61-3.57 (m, 1H), 2.97-2.89 (m, 2H), 2.57-2.47 (m, 1H), 2.42-2.32 (m, 1H), 2.09-1.90 (m, 2H), 1.82-1.65 (m, 4H), 1.57-1.50 (m, 1H), 1.49 (d, $J = 4.6$ Hz, 1H), 1.11 (s, 3H), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.86, 158.13, 155.71, 139.15, 115.83, 108.95, 101.44, 97.62, 72.48, 56.27, 55.57, 51.66, 45.02, 41.99, 38.36, 31.34, 30.57, 27.79, 25.55, 23.26, 18.40; IR (neat) 3556 (bw), 2949 (bm), 1588 (s), 1454 (s), 1287 (m), 1201 (s), 1161 (s), 1082 (m), 1034 (s), 907 (m), 730 (s), 632 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{21}H_{28}ClO_2$ $[M\text{-}OH]^+$: 347.1778; Found 347.1766.



(−)-keto-*tert*-butyldimethylsilyl ether (**3.86**). To a solution of keto- alcohol **3.72** (170 mg, 0.464 mmol, 1.00 equiv) in 11.6 mL of CH_2Cl_2, Et_3N (129 μL, 0.928 mmol, 2.00 equiv) was added. The solution was cooled to −78 °C and treated dropwise with TBSOTf (160 μL, 0.696 mmol, 1.50 equiv) *via* syringe. The solution was stirred for 2.5 hours at −78 °C, after which the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). After warming to room temperature, the mixture was poured into a separatory funnel and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with H_2O (10 mL), saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (15% ethyl acetate in hexanes v/v) afforded the desired silyl ether **3.86** as a white solid (178 mg, 79.9%), mp 136-138 °C.

$[\alpha]_D^{20} = -30.54$ (c 0.96, $CHCl_3$); $R_f = 0.32$ (15% ethyl acetate in hexanes v/v); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.37 (d, $J = 2.9$ Hz, 1H), 6.18 (d, $J = 2.7$ Hz, 1H), 3.84 (s, 3H), 3.76-3.72 (m, 4H), 3.50 (d, $J = 14.2$ Hz, 1H), 2.98 (d, $J = 14.2$ Hz, 1H), 2.78 (ddd, $J = 17.1$, 8.3, 5.6 Hz, 1H), 2.33 (ddd, $J = 16.7$, 8.1, 5.6 Hz, 1H), 2.15 (ddd, $J = 11.3$, 8.3, 0 Hz, 1H), 1.98-1.73 (m, 4H), 1.53-1.43 (m, 1H), 1.23 (s, 3H), 1.15-1.05 (m, 1H), 0.92-0.90

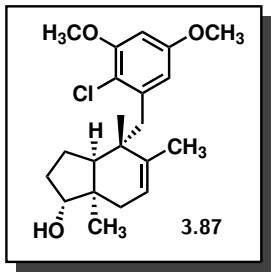
(m, 12H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.75, 158.18, 155.86, 137.64, 115.61, 107.99, 98.30, 81.05, 56.29, 55.55, 55.36, 52.46, 43.11, 41.36, 35.66, 32.50, 31.96, 26.70, 26.00, 24.91, 19.76, 18.24, −4.19, −4.76; IR (neat) 2995 (s), 2857 (m), 1704 (s), 1591 (s), 1459 (s), 1332 (m), 1164 (s), 1081 (m), 835 (s), 775 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{26}H_{42}ClO_4Si$ $[M+H]^+$: 481.2541; Found 481.2530.



(+)-*tert*-butyldimethylsilyl ether-alkene (**3.56**). In a drybox, NaH (32.6 mg, 1.36 mmol, 7.39 equiv) was weighed into a 2-neck, 25 mL round bottom flask equipped with a magnetic stirbar. After removing the flask from the drybox, a reflux condenser was installed. DMSO (1.5 mL) was added, and the suspension was heated to 75 °C for 1 hour. During this time, the reaction became homogeneous, forming a teal-colored, clear solution. This solution was cooled to room temperature, and a solution of Ph_3PCH_3Br (624 mg, 1.75 mmol, 9.51 equiv) in 2.4 mL of DMSO was added over 30 minutes *via* syringe pump. Upon addition of the salt solution, the reaction mixture became bright yellow. After completion of the addition, the mixture was stirred for an additional 30 minutes at room temperature, at which point a solution of ketone **3.86** (93.4 mg, 0.184 mmol, 1.00 equiv) in 0.56 mL of DMSO and 0.50 mL of THF was added dropwise. The reaction mixture was then heated to 75 °C and stirred for 16 hours. The resulting amber solution was cooled to room temperature and acidified by the addition of 5 mL of saturated aqueous NH_4Cl. The reaction mixture was diluted with H_2O (15 mL), poured into a separatory funnel, and the product was extracted with Et_2O (3 x 15 mL). The combined organics were washed with H_2O (15 mL), saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (5% Et_2O in pentane v/v) afforded the desired olefin **3.56** as a white solid (95.0 mg, quantitative), mp 97-98 °C.

$[\alpha]_D^{20}$ = +32.36 (c 1.00, $CHCl_3$); R_f = 0.33 (50% Et_2O in pentane v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.35 (d, J = 2.7 Hz, 1H), 6.21 (d, J = 2.7 Hz, 1H), 4.93 (s, 1H), 4.42 (s, 1H),

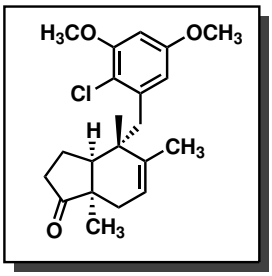
3.85 (s, 3H), 3.73 (s, 3H), 3.55 (dd, J = 5.9, 1.5 Hz, 1H), 3.25 (d, J = 13.5 Hz, 1H), 3.01 (d, J = 13.4 Hz, 1H), 2.71 (ddd, J = 13.7, 13.7, 5.4 Hz, 1H), 2.24-2.18 (m, 1H), 2.09-2.02 (m, 1H), 1.98-1.89 (m, 1H), 1.84-1.74 (m, 1H), 1.47-1.22 (m, 7H), 0.92 (s, 9H), 0.81 (s, 3H), 0.5 (s, 3H), 0.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.51, 155.43, 151.32, 139.52, 115.84, 111.96, 108.01, 97.80, 84.33, 56.26, 55.42, 55.00, 45.96, 44.34, 41.51, 33.80, 31.57, 29.91, 26.68, 26.10, 23.31, 22.42, 18.34, −4.27, −4.69; IR (neat) 2953 (s), 2930 (s), 2856 (m), 1590 (s), 1455 (s), 1371 (m), 1285 (m), 1255 (m), 1202 (m), 1163 (s), 1074 (s), 1004 (m), 833 (s), 722 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{27}H_{44}ClO_3Si$ $[M+H]^+$: 479.2748; Found 479.2733.



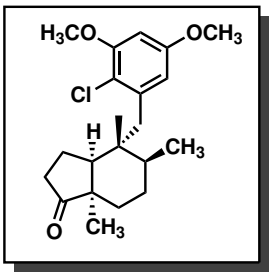
(−)-trisubstituted ene-ol (**3.87**). Exocyclic alkene **3.56** (1.00 g, 2.09 mmol, 1.00 equiv) and $RhCl_3 \cdot H_2O$ (87.3 mg, 0.417 mmol, 0.200 equiv) were weighed into a 100 mL round bottom flask equipped with a magnetic stirbar and dissolved in 21 mL of $CHCl_3$ and 21 mL of EtOH. The resulting deep red solution was refluxed for a period of 2.5 days, during which time the solution got darker and a metallic precipitate formed. The reaction mixture was concentrated, and the crude residue was purified by flash column chromatography (60% Et_2O in pentane v/v) to afford the desired product **3.87** as a white solid (749 mg, 98.2%), mp 44-48 °C.

$[\alpha]_D^{20} = -130.65$ (c 0.39, $CHCl_3$); R_f = 0.36 (50% Et_2O in pentane v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.45 (d, J = 2.7 Hz, 1H), 6.38 (d, J = 2.7 Hz, 1H), 5.58-5.62 (m, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.56 (ddd, J = 8.8, 6.1, 6.1 Hz, 1H), 3.19 (d, J = 12.9 Hz, 1H), 2.75 (d, J = 13.2 Hz, 1H), 2.12-1.95 (m, 3H), 1.85 (dddd, J = 6.1, 6.1, 6.1, 6.1 Hz, 1H), 1.73-1.66 (m, 1H), 1.46 (s, 3H), 1.42-1.32 (m, 2H), 1.16 (s, 3H), 1.09-0.99 (m, 1H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.02, 155.65, 141.40, 139.51, 122.22, 116.08, 108.25, 97.96, 82.56, 56.29, 55.95, 55.53, 43.45, 42.90, 39.97, 34.98, 31.60, 26.58, 25.23, 22.14, 21.50; IR (neat) 3407 (bm), 2956 (m), 2873 (m), 1590 (s), 1455 (s), 1329 (m), 1202 (m), 1162 (s), 1118 (m),

1036 (m), 811 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{21}H_{30}ClO_3$ $[M+H]^+$: 365.1884; Found 365.1879.



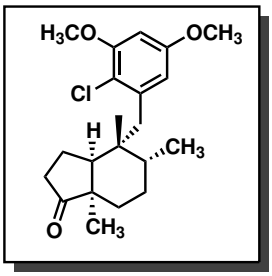
(−)-trisubstituted ene-one (**3.50**). Alcohol **3.87** (610 mg, 1.67 mmol, 1.00 equiv) and Celite® 545 (720 mg) were weighed into a 25 mL round bottom flask equipped with a magnetic stirbar and suspended in 8.4 mL of CH_2Cl_2. PCC (721 mg, 3.34 mmol, 2.00 equiv) was then added as a solid, causing a black discoloration, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with 50 mL of Et_2O, filtered through Celite® 545 on a sintered glass frit, and concentrated. The crude residue was purified by flash column chromatography (25% Et_2O in pentanes v/v) to afford the desired ketone **3.50** as a white solid (561 mg, 92.6%), mp 130-135 °C. $[\alpha]_D^{20} = -99.36$ (c 1.68, $CHCl_3$); $R_f = 0.29$ (20% Et_2O in pentane v/v); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.41 (d, $J = 2.7$ Hz, 1H), 6.40 (d, $J = 2.7$ Hz, 1H), 5.51-5.47 (m, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.24 (d, $J = 13.2$ Hz, 1H), 2.80 (d, $J = 13.2$ Hz, 1H), 2.35-2.25 (m, 2H), 2.25-2.15 (m, 2H), 1.99-1.91 (m, 2H), 1.54-1.52 (m, 3H), 1.41-1.32 (m, 4H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 223.25, 158.10, 155.82, 139.81, 138.97, 120.87, 116.05, 108.61, 97.88, 56.30, 55.54, 53.45, 47.24, 42.34, 40.94, 36.15, 31.39, 26.91, 23.98, 21.51, 21.27; IR (neat) 2964 (m), 2937 (m), 2839 (w), 1737 (s), 1590 (s), 1455 (s), 1330 (m), 1205 (m), 1163 (s), 1086 (m), 1036 (m) cm^{-1} ; HRMS (ESI+) Calcd. for $C_{21}H_{28}ClO_3$ $[M+H]^+$: 363.1727; Found 363.1726.



(±)-β-methyl ketone (**3.57**). To a solution of racemic trisubstituted ene-one **3.50** (18.6 mg, 0.0513 mmol, 1.00 equiv) in 0.3 mL of CH_2Cl_2 at room temperature, PtO_2 (1.2 mg, 0.00513 mmol, 0.10 equiv) was added as a solid. With vigorous stirring, the suspension was purged for 1 minute with hydrogen from a balloon, during which time the brown PtO_2 turned black, signifying reduction to the active Pt(0). The reaction was stirred for 3.5 hours under a positive pressure of hydrogen and then filtered through

Celite® 545. After removal of solvent, ^{1}H NMR analysis of the crude mixture showed incomplete conversion, so the material was resubjected to the reaction conditions. After another 6 hours of stirring under hydrogen atmosphere, the suspension was again filtered and concentrated. Purification by flash column chromatography (15% Et_2O, 75% pentane, 10% CH_2Cl_2 v/v/v) afforded the desired β-methyl product **3.57** as a white solid (12.1 mg, 64.6%), mp 131-133 °C. X-ray quality single crystals were obtained by crystallization from hot Et_2O and hexanes (approx. 5:1 v/v).

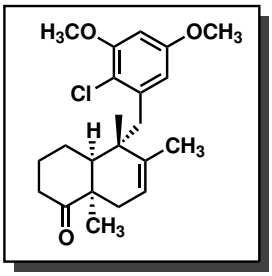
R_f = 0.43 (30% Et_2O in pentane v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.42 (d, J = 2.9 Hz, 1H), 6.41 (d, J = 2.7 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.02 (d, J = 13.7 Hz, 1H), 2.63 (d, J = 13.7 Hz, 1H), 2.32-2.23 (m, 1H), 2.09-1.97 (m, 3H), 1.88 (d, J = 7.6 Hz, 1H) 1.79-1.70 (m, 1H), 1.53-1.45 (m, 1H), 1.33-1.27 (m, 1H), 1.20-1.04 (m, 2H), 1.00 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H), 0.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 222.16, 158.01, 155.88, 138.93, 116.17, 108.63, 97.80, 56.33, 55.55, 49.60, 49.39, 42.14, 41.71, 37.07, 34.74, 30.23, 27.81, 27.41, 21.05, 17.37, 15.89; IR (neat) 2961 (m), 2926 (m), 1732 (s), 1589 (s), 1454 (s), 1329 (m), 1202 (s), 1164 (s), 1087 (m), 1038 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{21}H_{30}ClO_3$ $[M+H]^+$: 365.1884; Found 365.1895.



(±)-α-methyl ketone (**3.58**). Isolated from the hydrogenation reaction above to afford the α-methyl diastereomer **3.58** as a white solid (6.3 mg, 33.7%), mp 147-149 °C. X-ray quality single crystals were obtained by crystallization from hot Et_2O and hexanes (approx. 5:1 v/v).

R_f = 0.31 (15% Et_2O, 10% CH_2Cl_2 in pentane v/v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.46 (d, J = 2.9 Hz, 1H), 6.40 (d, J = 2.9 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.07 (d, J = 13.4 Hz, 1H), 2.82 (d, J = 13.7 Hz, 1H), 2.41 (ddd, J = 19.3, 8.5, 2.4 Hz, 1H), 2.28 (ddd, J = 10.5, 7.0, 0 Hz, 1H), 2.19-2.10 (m, 1H), 1.87-1.74 (m, 2H), 1.74-1.65 (m, 1H), 1.51 (m, 3H), 1.38 (s, 3H), 1.27-1.21 (m, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$,

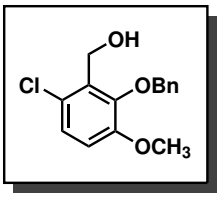
125 MHz) δ 222.87, 158.05, 156.01, 139.90, 116.15, 109.01, 97.26, 56.32, 55.58, 49.76, 48.71, 39.01, 37.49, 35.86, 35.01, 28.95, 26.32, 23.85, 22.18, 20.86, 16.19; IR (neat) 2963 (m), 2877 (m), 1732 (s), 1590 (s), 1455 (s), 1327(m), 1201 (s), 1162 (s), 1092 (m), 1035 (m), 732 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{21}H_{30}ClO_3$ $[M+H]^+$: 365.1884; Found 365.1885.



(+)-ene-decalone (**3.59**). In a drybox, $Sc(OTf)_3$ (5.2 mg, 0.011 mmol, 0.052 equiv) was weighed directly into a 1.5 mL vial equipped with a magnetic stirbar. A solution of ketone **3.50** (76.6 mg, 0.211 mmol, 1.00 equiv) in $CDCl_3$ (0.8 mL) was transferred directly to the solid $Sc(OTf)_3$. The cloudy gray suspension was stirred for 15 minutes at which point TMSD (215 μL, 0.422 mmol, 2.00 equiv, 1.96 M in hexanes) was introduced dropwise. The entire reaction mixture (including any residual solids) was transferred *via* glass pipette to a J. Young NMR tube, and the vial was rinsed with an additional 0.2 mL of $CDCl_3$. The reaction tube was removed from the drybox, connected to a nitrogen manifold, and placed in an oil bath pre- heated to 50 °C. After 16 hours of heating, the reaction was cooled to room temperature. ^{1}H NMR analysis indicated complete conversion and an approximate 8.5:1 ratio of regioisomeric silyl products. The reaction mixture was rinsed from the NMR tube with Et_2O (5 mL) and concentrated to give a crude yellow oil. The crude mixture was immediately dissolved in 4 mL of 1:1 (v/v) 1N HCl: THF and stirred for 2 hours. The reaction mixture was poured into saturated $NaHCO_3$ (20 mL) and the products were extracted with Et_2O (3 x 20 mL). The combined organics were washed with saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (18% ethyl acetate in hexanes v/v) provided the desired homologated ketone **3.59** as a colorless oil (71.1 mg, 88.9%) as well as the minor regioisomer as a colorless oil (8.6 mg, 10.8%).

$[\alpha]_D^{20} = +4.12$ (c 1.33, $CHCl_3$); $R_f = 0.35$ (18% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.46 (d, $J = 2.7$ Hz, 1H), 6.39 (d, $J = 2.7$ Hz, 1H), 5.54-5.51 (m, 1H), 3.87 (s,

3H), 3.74 (m, 3H), 3.215 (d, J = 14.4 Hz, 1H), 2.83 (d, J = 14.4 Hz, 1H), 2.63-2.56 (m , 1H), 2.48-2.44 (m, 1H), 2.12 (ddd, J = 8.1, 4.9, 0 Hz, 1H), 2.09-2.03 (m, 1H), 1.93-1.86 (m, 1H), 1.81-1.72 (m, 4H), 1.64-1.53 (m, 2H), 1.34 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.38, 158.10, 155.76, 139.31, 138.47, 121.64, 115.92, 107.47, 97.82, 56.29, 55.52, 49.03, 48.89, 42.66, 40.15, 36.66, 32.58, 26.44, 24.27, 24.05, 23.22, 20.19; IR (neat) 2963 (m), 2940 (m), 1701 (s), 1590 (s), 1454 (s), 1330 (m), 1203 (s), 1163 (s), 1087 (m), 1036 (w), 830 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_{22}H_{30}ClO_3$ $[M+H]^+$: 377.1884; Found 377.1891.

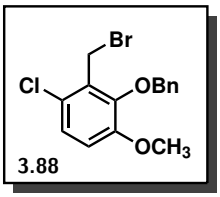


(2-(benzyloxy)-6-chloro-3-methoxyphenyl)methanol (**3.62**). Benzyl protected reduced *o*-vanillin[54] (35.5 g, 145 mmol, 1.00 equiv) was weighed into a 500 mL round bottom flask equipped with a magnetic stirbar and dissolved in 290 mL of CH_2Cl_2. The solution was cooled to 0 °C, and 1,3-dichloro-5,5- dimethylhydantoin (34.4 g, 174 mmol, 1.20 equiv) was added as a solid. The reaction mixture was then stirred for 12 hours at 4 °C. The resulting slurry was diluted with saturated aqueous $Na_2S_2O_3$ (150 mL), and the product was extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (300 mL), H_2O (300 mL), saturated aqueous NaCl (300 mL), dried over $MgSO_4$, filtered, and concentrated. The crude solid was recrystallized from hot hexanes and ethyl acetate (approx. 10:1 v/v) to afford the desired product **3.62** as a white crystalline solid (34.5 g, 85.8%), mp 80-83 °C. The mother liquor was then purified by column chromatography (40% ethyl acetate in hexanes v/v) to provide more of the desired compound as a white solid (2.51 g, 6.2%).

R_f = 0.30 (40% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46-7.43 (m, 2H), 7.41- 7.33 (m, 3H), 7.11 (d, J = 7.1 Hz, 1H), 6.85 (d, J = 6.8 Hz, 1H), 5.09 (s, 2H), 4.72 (d, J = 7.1 Hz, 2H), 3.89 (s, 3H), 2.02 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.88, 147.42, 137.15, 132.84, 128.76, 128.71, 128.58, 125.96, 125.04, 112.95,

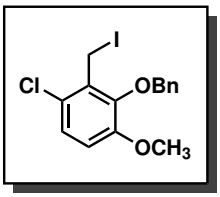
[54]Prepared in two steps from *o*-vanillin according to the literature procedure: Speicher, A.; Holz, J. *Tetrahedron Lett.* **2010**, *51*, 2986-2989.

75.93, 58.27, 56.24; IR (neat) 3373 (bw), 3007 (bw), 2839 (w), 1579 (w), 1472 (s), 1439 (m), 1370 (m), 1272 (s), 1221 (s), 1080 (m), 1002 (bs), 802 (m), 745 (m), 695 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{15}ClO_3$ $[M]^{+\cdot}$: 278.0710; Found 278.0695.



2-(benzyloxy)-3-(bromomethyl)-4-chloro-1-methoxybenzene (**3.88**). Benzyl alcohol **3.62** (14.3 g, 51.3 mmol, 1.00 equiv) and CBr_4 (22.1 g, 66.7 mmol, 1.30 equiv) were weighed into a 250 mL round bottom flask equipped with a magnetic stirbar and dissolved in 103 mL of THF. The solution was cooled to 0 °C and PPh_3 (17.5 g, 66.7 mmol, 1.30 equiv) was added as a solid. The reaction mixture was then warmed to room temperature, and after 10 minutes diluted with water (50 mL), poured into a separatory funnel, and the product was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (30% ethyl acetate in hexanes v/v) afforded the product **3.88** as a white solid (15.4 g, 87.7%), mp 65-67 °C.

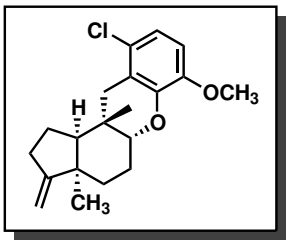
R_f = 0.25 (5% Et_2O in pentane v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55-7.52 (m, 2H), 7.43-7.33 (m, 3H), 7.14 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 5.17 (s, 2H), 4.65 (s, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.94, 147.46, 137.29, 130.58, 128.67, 128.60, 128.56, 128.41, 126.36, 125.09, 113.49, 75.16, 56.24, 25.51; IR (neat) 3030 (bw), 2837 (bw), 1579 (w), 1474 (s), 1437 (m), 1372 (w), 1272 (s), 1236 (m), 1075 (m), 978 (bm), 802 (m), 696 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{18}BrClNO_2$ $[M+NH_4]^+$: 358.0209; Found 358.0212.



2-(benzyloxy)-4-chloro-3-(iodomethyl)-1-methoxybenzene (**3.63**). Benzyl bromide **3.88** (34.1 g, 99.8 mmol, 1.00 equiv) was weighed into a 250 mL round bottom flask equipped with a magnetic stirbar and dissolved in 166 mL of freshly distilled acetone. NaI (29.9 g, 198 mmol, 1.98 equiv) was then added as a solid, and the resulting suspension was stirred for 12 hours at room temperature in the dark. The mixture was filtered through Celite® 545 rinsing

with ethyl acetate (3 x 150 mL) and concentrated. The crude residue was dissolved in 200 mL of ethyl acetate and poured into a separatory funnel. The organics were washed with 50% aqueous $Na_2S_2O_3$ (150 mL), dried over Na_2SO_4, and concentrated to afford the desired product **3.63** as a pale yellow solid that was used without further purification (38.0 g, 98.1%), mp 72-75 °C.

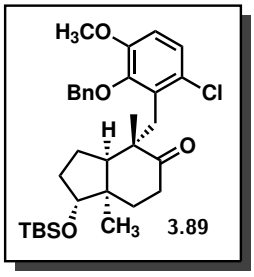
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56-7.52 (m, 2H), 7.43-7.34 (m, 3H), 7.08 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H), 4.55 (s, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.88, 146.77, 137.34, 131.75, 128.62, 128.41, 128.33, 125.87, 125.09, 112.84, 74.04, 56.18, −2.65; IR (neat) 3006 (bw), 2974 (bw), 2839 (w), 1575 (m), 1471 (s), 1460 (s), 1430 (s), 1366 (s), 1267 (s), 1223 (bs), 1099 (s), 1064 (s), 964 (s), 883 (m), 797 (s), 747 (s), 693 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{18}ClINO_2$ $[M+NH_4]^+$: 406.0071; Found 406.0075.



(±)-decahydrocyclopenta[*a*]xanthene (**3.74**). In a drybox, NaH (37.9 mg, 1.58 mmol, 7.00 equiv) was weighed into a 2-neck, 10 mL round bottom flask equipped with a magnetic stirbar. After removing the flask from the drybox, a reflux condenser was installed. 1.7 mL of DMSO was added, and the suspension was heated to 75 °C for 1 hour. During this time, the reaction became homogeneous, forming a teal-colored, clear solution. This solution was cooled to room temperature, and a solution of Ph_3PCH_3I (825 mg, 2.03 mmol, 9.00 equiv) in 2.8 mL of DMSO was added over 30 minutes *via* syringe pump. Upon addition of the salt, the reaction mixture became bright yellow. After completion of the addition, the mixture was stirred for an additional 30 minutes at room temperature, at which point a solution of racemic **3.64** (99.2 mg, 0.224 mmol, 1.00 equiv) in 0.62 mL of DMSO was added dropwise. The reaction mixture was then heated to 75 °C and stirred for 16 hours. The resulting amber solution was cooled to room temperature and acidified by the addition of 5 mL of saturated aqueous NH_4Cl. The reaction mixture was

diluted with H_2O (15 mL), poured into a separatory funnel, and the product was extracted with Et_2O (3 x 15 mL). The combined organics were washed with H_2O (15 mL), saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (10% ethyl acetate in hexanes v/v) afforded the unexpected compound **3.74** as a white solid (59.5 mg, 60.2%), mp 87-89 °C.

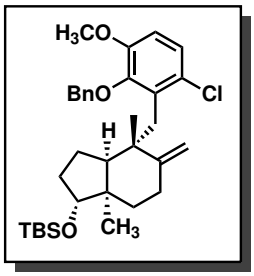
R_f = 0.26 (10% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.86 (d, J = 8.6 Hz, 1H), 6.66 (d, J = 8.6 Hz, 1H), 4.80 (dd, J = 1.7, 1.7 Hz, 1H), 4.76 (dd, J = 2.2, 2.2 Hz, 1H), 4.04 (dd, J = 6.1, 6.1 Hz, 1H), 3.84 (s, 3H), 2.98 (d, J = 17.6 Hz, 1H), 2.47-2.37 (m, 2H), 2.29 (d, J = 17.6 Hz, 1H), 1.90-1.82 (m, 1H), 1.81-1.73 (m, 3H), 1.69-1.57 (m, 3H), 1.19 (s, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.44, 147.30, 143.75, 126.18, 120.11, 119.58, 109.90, 102.77, 79.33, 56.37, 53.18, 44.08, 34.39, 33.40, 31.80, 30.90, 29.50, 24.52, 24.35, 24.19; IR (neat) 3071 (w), 2951 (bm), 2916 (bm), 1649 (w), 1578 (m), 1476 (bs), 1308 (m), 1253 (m), 1230 (s), 1097 (m), 1051 (m), 799 (m), 782 (m), 673 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{20}H_{26}ClO_4$ $[M+H]^+$: 333.1621; Found 333.1619.



(−)-keto-*tert*-butyldimethylsilyl ether (**3.89**). To a solution of keto- alcohol **3.64** (1.03 g, 2.32 mmol, 1.00 equiv) in 12 mL of DMF were added imidazole (474 mg, 6.97 mmol, 3.00 equiv) and TBSCl (1.05 g, 6.97 mmol, 3.00 equiv) sequentially as solids. After stirring 5 hours at room temperature, 5 mL of methanol was added and the reaction was stirred for an additional 15 minutes. The reaction mixture was then poured into saturated NH_4Cl (20 mL) and the product was extracted with Et_2O (5 x 10 mL). The combined organics were washed with 1 N HCl (30 mL), H_2O (30 mL), saturated aqueous NaCl (30 mL), dried over Na_2SO_4, filtered, and concentrated to afford the desired product **3.89** as a viscous oil that was used without further purification (1.14 g, 88.4%).

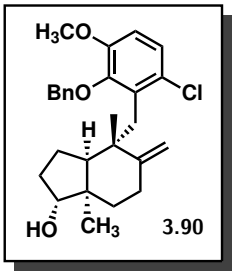
$[\alpha]_D^{20}$ = −31.95 (c 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.32 (m, 5H), 7.04 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 5.02 (d, J = 11.2 Hz, 1H), 4.91 (d, J =

11.0 Hz, 1H), 3.83 (s, 3H), 3.66 (dd, J = 7.3, 5.9 Hz, 1H), 3.42 (d, J = 13.4 Hz, 1H), 2.86 (d, J = 13.4 Hz, 1H), 2.61 (ddd, J = 17.4, 5.9, 5.9 Hz, 1H), 2.07-1.97 (m, 2H), 1.84-1.77 (m, 1H), 1.77-1.67 (m, 2H), 1.52- 1.44 (m, 1H), 1.44-1.36 (m, 1H), 1.10 (s, 3H), 0.91 (s, 9H), 0.80 (s, 3H), 0.03-0.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.05, 151.19, 147.94, 137.56, 130.67, 128.79, 128.55, 128.32, 127.28, 124.39, 111.91, 80.62, 75.12, 56.89, 56.09, 52.03, 42.41, 37.09, 35.24, 32.13, 32.06, 27.20, 26.01, 25.26, 19.14, 18.24, −4.21, −4.77; IR (neat) 2956 (bs), 2876 (bm), 1705 (s), 1465 (bs), 1377 (bw), 1277 (s), 1214 (m), 1115 (bm), 1060 (s), 981 (bm), 836 (s), 775 (s), 698 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{32}H_{46}ClO_4Si$ $[M+H]^+$: 557.2854; Found 557.2836.



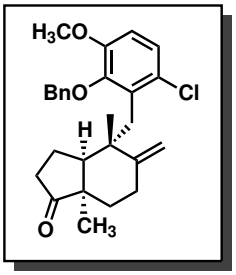
(+)-tert-butyldimethylsilyl ether-alkene (**3.65**). In a drybox, NaH (92.6 mg, 3.86 mmol, 7.00 equiv) was weighed into a 2-neck, 25 mL round bottom flask equipped with a magnetic stirbar. After removing the flask from the drybox, a reflux condenser was installed. 4.2 mL of DMSO was added, and the suspension was heated to 75 °C for 1 hour. During this time, the reaction became homogeneous, forming a teal-colored, clear solution. This solution was cooled to room temperature, and a solution of Ph_3PCH_3I (2.01 mg, 4.96 mmol, 9.00 equiv) in 6.8 mL of DMSO was added over 30 minutes *via* syringe pump. Upon addition of the salt solution, the reaction mixture became bright yellow. After completion of the addition, the mixture was stirred for an additional 30 minutes at room temperature, at which point a solution of ketone **3.89** (307 mg, 0.551 mmol, 1.00 equiv) in 1.5 mL of DMSO and 1.5 mL of THF was added dropwise. The reaction mixture was then heated to 75 °C and stirred for 16 hours. The resulting amber solution was cooled to room temperature and acidified by the addition of 5 mL of saturated aqueous NH_4Cl. The reaction mixture was diluted with H_2O (15 mL), poured into a separatory funnel, and the product was extracted with Et_2O (3 x 20 mL). The combined organics were washed with H_2O (25 mL), saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered, and

concentrated. Purification by flash column chromatography (20% Et_2O in pentane v/v) afforded the desired compound **3.65** as a white solid (296 mg, 96.7%), mp 98-105 °C.
$[\alpha]_D^{20} = +15.37$ (c 1.05, $CHCl_3$); $R_f = 0.33$ (3% Et_2O in pentane v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43-7.29 (m, 5H), 7.04 (d, $J = 8.8$ Hz, 1H) 6.73 (d, $J = 8.8$ Hz, 1H), 4.98-4.81 (m, 2H), 4.75-4.71 (m, 1H), 4.35-4.30 (m, 1H), 3.84 (s, 3H), 3.51 (dd, $J = 5.9$, 2.0 Hz, 1H), 3.36 (d, J = 13.2 Hz, 1H), 2.76-2.65 (m, 1H), 2.73 (d, $J = 12.9$ Hz, 1H), 2.05-1.93 (m, 2H), 1.93-1.84 (m, 1H), 1.77-1.68 (m, 1H), 1.43-1.34 (m, 1H), 1.30-1.20 (m, 1H), 1.20-1.09 (m, 2H), 1.14 (s, 3H), 0.92 (s, 9H), 0.82 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.93, 151.25, 148.43, 137.74, 133.02, 128.62, 128.49, 128.10, 127.82, 124.31, 111.03, 110.56, 83.86, 75.02, 56.04, 55.78, 45.67, 43.81, 38.05, 33.26, 31.72, 30.03, 26.65, 26.12, 23.10, 22.71, 18.32, −4.26, −4.69; IR (neat) 2954 (bs), 2933 (bs), 2856 (bm), 1463 (s), 1438 (m), 1371 (bw), 1277 (bm), 1074 (bs), 1006 (m), 836 (s), 740 (m), 697 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{33}H_{48}ClO_3Si$ $[M+H]^+$: 555.3061; Found 555.3084.



(+)-1,1-disubstituted ene-ol (**3.90**). To a solution of *tert*-butyldimethylsilyl ether **3.65** (1.27 g, 2.29 mmol, 1.00 equiv) in 5.7 mL of THF was added TBAF · xH_2O (10.5 g, 37.5 mmol, 16.4 equiv) as a solid. The resulting suspension was then sonicated (60 W) continuously at 50 °C for 12 hours, during which time the reaction mixture became homogenous. The reaction mixture was directly loaded onto a plug of silica gel and eluted with ethyl acetate to afford the desired compound **3.90** as a solid that was used without further purification (1.01 g, quantitative), mp 122-125 °C.
$[\alpha]_D^{20} = +34.99$ (c 0.96, $CHCl_3$); $R_f = 0.48$ (50% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.30 (m, 5H), 7.04 (d, $J = 8.8$ Hz, 1H), 6.73 (d, $J = 8.8$ Hz, 1H), 4.97-4.85 (m, 2H), 4.77-4.74 (m, 1H), 4.37-4.33 (m, 1H), 3.84 (s, 3H), 3.56 (ddd, $J = 5.6$, 4.2, 1.2 Hz, 1H), 3.33 (d, J = 12.9 Hz, 1H), 2.75-2.63 (m, 1H), 2.73 (d, $J = 13.2$ Hz, 1H), 2.04-1.92 (m, 3H), 1.81-1.72 (m, 1H), 1.46-1.38 (m, 1H), 1.37-1.27 (m, 2H), 1.20 (s,

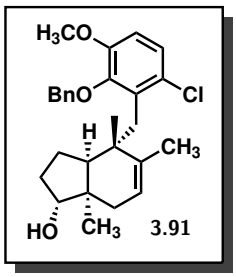
3H), 1.19-1.12 (m, 1H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.56, 151.18, 148.45, 137.83, 132.73, 128.53, 128.47, 128.07, 127.77, 124.25, 111.06, 110.79, 83.99, 75.10, 56.02, 55.30, 45.32, 43.56, 37.89, 33.02, 30.71, 29.79, 26.45, 22.60, 21.87; IR (neat) 3377 (bw), 3058 (bw), 2917 (bw), 2848 (bw), 1647 (bw), 1479 (m), 1295 (bm), 1063 (bs), 925 (bm), 737 (s), 688 (bs) cm^{-1}; HRMS (ESI+) Calcd. for $C_{27}H_{34}ClO_3$ $[M+H]^+$: 441.2196; Found 441.2174.



(+)-1,1-disubstituted ene-one (3.66). Alcohol **3.90** (1.01 g, 2.29 mmol, 1.00 equiv) was weighed into a 50 mL round bottom flask equipped with a magnetic stirbar and dissolved in 23 mL of wet CH_2Cl_2. The solution was cooled to 4 °C and DMP (2.91 g, 6.87 mmol, 3.00 equiv) was added as a solid. The reaction mixture was stirred for 12 hours at 4 °C, at which point additional DMP (2.02 g, 4.58 mmol, 2.00 equiv) and 50 μL of H_2O were added. The reaction was warmed to room temperature and stirred for an additional hour. The reaction mixture was poured into 1 N NaOH (100 mL), and the product was extracted with CH_2Cl_2 (3 x 25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (20% ethyl acetate in hexanes v/v) afforded the desired compound **3.66** as a white foam (1.00 g, quantitative), mp 95-98 °C.

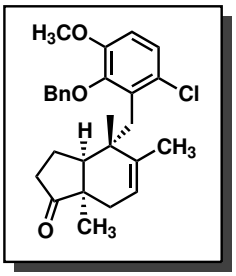
$[\alpha]_D^{20}$ = +11.12 (c 1.17, $CHCl_3$); R_f = 0.27 (20% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.30 (m, 5H), 7.06 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 4.98-4.86 (m, 2H), 4.80-4.77 (m, 1H), 4.43-4.39 (m, 1H), 3.86 (s, 3H), 3.34 (d, J = 12.9 Hz, 1H), 2.74 (d, J = 12.9 Hz, 1H), 2.71-2.60 (m, 1H), 2.38 (dd, J = 19.3, 8.5 Hz, 1H), 2.11-1.96 (m, 2H), 1.92-1.81 (m, 2H), 1.52-1.42 (m, 1H), 1.35 (ddd, J = 13.4, 13.4, 3.9 Hz, 1H), 1.23 (s, 3H), 1.20-1.12 (m, 1H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 222.21, 151.19, 150.50, 148.50, 137.64, 132.08, 128.64, 128.54, 128.27, 127.63, 124.34, 111.32, 111.24, 75.30, 57.35, 56.03, 48.82, 43.20, 38.17, 35.51, 30.61, 29.22, 21.81, 21.58, 21.49; IR (neat) 2935 (bm), 2856 (bw), 1734 (s), 1575 (w), 1464 (bs), 1406 (m), 1277 (s), 1234 (bm), 1072

(m), 978 (bm), 896 (bm), 798 (m), 698 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{27}H_{32}ClO_3$ $[M+H]^+$: 439.2040; Found 439.2024.

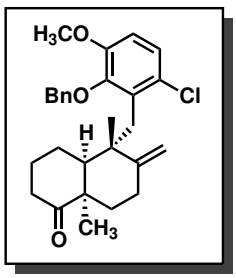


(−)-trisubstituted ene-ol (**3.91**). Silyl ether-alkene **3.65** (263 mg, 0.473 mmol, 1.00 equiv) and $RhCl_3 \cdot H_2O$ (14.7 mg, 0.0702 mmol, 0.148 equiv) were weighed into 5 mL 2-neck round bottom flask equipped with a magnetic stirbar and a reflux condenser and dissolved in 1.2 mL of EtOH and 1.2 mL of $CHCl_3$. The resulting deep red solution then was heated to 55 °C for 15 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude residue was purified by column chromatography (25% ethyl acetate in hexanes) to afford the desired compound **3.91** as a clear oil that was used directly in the next step (208 mg, quantitative).

$[\alpha]_D^{20} = -103.49$ (c 0.85, $CHCl_3$); $R_f = 0.38$ (30% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45-7.41 (m, 2H), 7.39-7.30 (m, 3H), 7.07 (d, $J = 8.8$ Hz, 1H), 6.75 (d, $J = 8.8$ Hz, 1H), 5.35-5.32 (m, 1H), 4.94 (d, $J = 11.0$ Hz, 1H), 4.88 (d, $J = 11.0$ Hz, 1H), 3.86 (s, 3H), 3.52 (ddd, $J = 6.1, 6.1, 0$ Hz, 1H), 3.24 (d, $J = 12.9$ Hz, 1H), 2.75 (d, $J = 12.9$ Hz, 1H), 2.07-2.01 (m, 1H), 1.92-1.85 (m, 1H), 1.84-1.76 (m, 2H), 1.67 (dddd, $J = 15.3, 7.6, 7.6, 2.0$ Hz, 1H), 1.47-1.43 (m, 3H), 1.39-1.30 (m, 2H), 1.14 (s, 3H), 1.11-1.02 (m, 1H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.49, 148.35, 140.37, 137.71, 133.32, 128.45, 128.40, 128.09, 127.78, 124.63, 121.62, 111.00, 82.91, 74.81, 56.01, 55.17, 42.96, 42.51, 36.88, 34.60, 31.52, 26.91, 24.69, 22.15, 21.29; IR (neat) 3389 (bw), 3064 (bw), 2955 (bm), 2873 (bm), 1574 (w), 1464 (bs), 1373 (m), 1276 (s), 1178 (m), 1074 (bm), 981 (bm), 797 (m), 697 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{27}H_{33}ClO_3$ $[M+H]^+$: 441.2196; Found 441.2182.



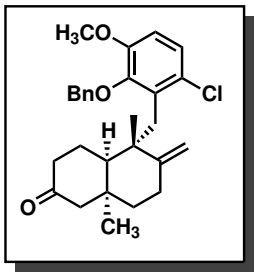
(−)-trisubstituted ene-one (**3.67**). Alcohol **3.91** (208 mg, 0.473 mmol, 1.00 equiv) was weighed into a 10 mL round bottom flask equipped with a magnetic stirbar and dissolved in 4.7 mL of wet CH_2Cl_2. DMP (602 mg, 1.42 mmol, 3.00 equiv) was then added as a solid and the reaction mixture was stirred for 1.5 hours at room temperature. The reaction mixture was poured into 1 N NaOH (20 mL), and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (12% ethyl acetate in hexanes v/v) afforded the desired compound **3.67** as a colorless oil (203 mg, 97.8%, 2 steps). $[\alpha]_D^{20} = -84.42$ (c 0.95, $CHCl_3$); $R_f = 0.33$ (15% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.30 (m, 5h), 7.09 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.29-5.26 (m, 1H), 4.96 (d, J = 11.0 Hz, 1H), 4.90 (d, J = 11.2 Hz, 1H), 3.87 (s, 3H), 3.20 (d, J = 13.2, Hz, 1H), 2.77 (d, J = 13.0 Hz, 1H), 2.32 (dd, J = 18.6, 7.6 Hz, 1H), 2.18 (dd, J = 11.7, 6.4 Hz, 1H), 2.13- 2.05 (m, 1H), 2.05-1.98 (m, 1H), 1.91-1.83 (m, 1H), 1.72 (dddd, J = 18.1, 2.0, 2.0, 2.0 Hz, 1H), 1.50-1.45 (m, 3H), 1.34 (dddd, J = 12.2, 12.2, 12.2, 8.5 Hz, 1H), 1.25 (s, 3H), 0.94 (s, 3H); 13C NMR ($CDCl_3$, 125 MHz) δ 223.13, 151.52, 148.33, 139.33, 137.56, 132.77, 128.51, 128.40, 128.22, 127.75, 124.73, 119.92, 111.18, 74.92, 56.03, 54.11, 47.07, 41.61, 37.68, 36.04, 30.82, 25.03, 23.58, 21.89, 21.05; IR (neat) 2966 (bm), 2935 (bw), 1736 (s), 1464 (bs), 1372 (m), 1277 (s), 1242 (bm), 1076 (m), 984 (bm), 798 (m), 698 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{27}H_{34}ClO_3$ $[M+H]^+$: 439.2040; Found 439.2037.



(+)-1,1-disubstituted ene-decalone major (**3.68**). In a drybox, $Sc(OTf)_3$ (4.2 mg, 0.0086 mmol, 0.050 equiv) was weighed directly into a J. Young NMR tube. A solution of ketone **3.66** (75.2 mg, 0.171 mmol, 1.00 equiv) in 0.48 mL of $CDCl_3$ was transferred directly to the solid $Sc(OTf)_3$. The cloudy gray suspension was allowed to stand

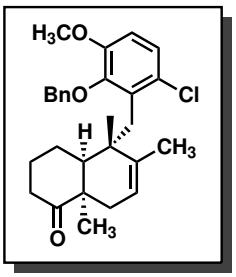
for 15 minutes at which point TMSD (174 μL, 0.342 mmol, 2.00 equiv, 2.47 M in hexanes) was introduced dropwise. The reaction tube was removed from the drybox, connected to a nitrogen manifold, and allowed to stand at room temperature for 12 hours. The reaction mixture was then warmed to 50 °C for 48 hours. ^{1}H NMR analysis indicated roughly 98% conversion and an approximate 5:1 ratio of regioisomeric silyl products. The reaction mixture was poured into H_2O (5 mL), and the products were extracted with Et_2O (20 mL). The organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. The enol-silane products were then purified away from a trace amount of starting material by column chromatography (7% ethyl acetate in hexanes v/v). The purified product mixture was then dissolved in 2 mL of THF, TBAF $\cdot$ xH_2O (95.8 mg, 0.342 mmol, 2.00 equiv) was added as a solid, and the reaction mixture was allowed to stir for 10 minutes at room temperature. The solution was concentrated and purified by column chromatography (15 to 25% ethyl acetate in hexanes v/v) to afford the desired homologated ketone **3.68** as a white solid (53.4 mg, 68.8%), mp 88-92 °C.

$[\alpha]_D^{20}$ = +8.23 (c 0.65, $CHCl_3$); R_f = 0.34 (15% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.30 (m, 5H), 7.05 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 4.97 (d, J = 11.0 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.77-4.74 (m, 1H), 4.46-4.43 (m, 1H), 3.86 (s, 3H), 3.37 (d, J = 12.9 Hz, 1H), 2.82 (d, J = 12.9 Hz, 1H), 2.63 (ddd, J = 13.9, 4.4, 4.4 Hz, 1H), 2.45-2.37 (m, 1H), 2.33-2.26 (m, 1H), 2.12 (ddd, J = 14.6, 5.1, 5.1 Hz, 1H), 1.95-1.76 (m, 4H), 1.59-1.49 (m, 1H), 1.38-1.31 (m, 2H), 1.33 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.60, 151.80, 151.31, 148.28, 137.69, 132.98, 128.55, 128.25, 127.59, 124.43, 111.07, 110.30, 75.16, 56.00, 55.82, 50.90, 44.72, 39.92, 37.07, 32.57, 29.70, 24.24, 24.16, 22.82; IR (neat) 3087 (bw), 2938 (bm), 2861 (bm), 1698 (s), 1575 (w), 1462 (s), 1438 (m), 1372 (m), 1276 (s), 1214 (bm), 980 (bm), 798 (m), 698 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{28}H_{34}ClO_3$ $[M+H]^+$: 453.2196; Found 453.2209.



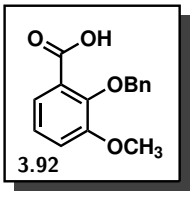
(+)-1,1-disubstituted ene-decalone minor (**3.69**). The minor regioisomer **3.69** was isolated from the reaction above as a colorless oil (6.5 mg, 8.4%).

$[\alpha]_D^{20}$ = +25.56 (c 0.59, $CHCl_3$); R_f = 0.25 (15% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.32 (m, 5H), 7.6 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.01 (d, J = 10.2, 1H), 5.01 (d, J = 10.2 Hz, 1H), 4.89 (d, J = 11.2 Hz, 1H), 4.76-4.72 (m, 1H), 4.43-4.39 (m, 1H), 3.86 (s, 3H), 3.38 (d, J = 12.9 Hz, 1H), 2.88 (d, J = 13.2 Hz, 1H), 2.67-2.58 (m, 1H), 2.24 (d, J = 13.9, 1H), 2.24- 2.18 (m, 2H), 2.08 (ddd, J = 14.6, 4.4, 4.4 Hz, 1H), 2.03-1.96 (m, 1H), 1.97 (d, J = 13.7, 1H), 1.76-1.69 (m, 1H), 1.52-1.44 (m, 2H), 1.31-1.24 (m, 1H), 1.18 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.83, 151.32, 151.06, 148.34, 137.92, 132.92, 128.55, 128.48, 128.19, 127.63, 124.42, 111.14, 110.74, 75.12, 56.20, 56.05, 53.03, 44.95, 40.33, 40.24, 39.50, 34.10, 31.46, 29.98, 26.03, 23.18; IR (neat) 3086 (bw), 2936 (bm), 2853 (bm), 1716 (s), 1464 (s), 1438 (bm), 1373 (bw), 1275 (s), 1215 (bm), 1102 (bm), 985 (bm), 798 (m), 698 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{28}H_{34}ClO_3$ $[M+H]^+$: 453.2196; Found 453.2218.



(−)-trisubstituted ene-decalone (**3.70**). In a drybox, $Sc(OTf)_3$ (6.5 mg, 0.015 mmol, 0.045 equiv) was weighed directly into a 1.5 mL vial equipped with a magnetic stirbar. A solution of ketone **3.67** (128 mg, 0.292 mmol, 1.00 equiv) in $CDCl_3$ (0.53 mL) was transferred directly to the solid $Sc(OTf)_3$. The cloudy gray suspension was stirred for 15 minutes at which point TMSD (236 μL, 0.583 mmol, 2.00 equiv, 2.47 M in hexanes) was introduced dropwise. The entire reaction mixture (including any residual solids) was transferred *via* glass pipette to a J. Young NMR tube, and the vial was rinsed with an additional 0.2 mL of $CDCl_3$. The reaction tube was removed from the drybox, connected to a nitrogen manifold, and placed in an oil bath pre-heated to 50 °C. After 16 hours of heating, the reaction was cooled to room temperature. ^{1}H NMR analysis indicated

complete conversion. The reaction mixture was poured into H_2O (5 mL), and the product was extracted with Et_2O (20 mL). The organics were washed with saturate aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was then dissolved in 2 mL of THF, TBAF $\cdot$ xH_2O (164 mg, 0.584 mmol, 2.00 equiv) was added as a solid, and the reaction mixture was allowed to stir for 10 minutes at 23 °C. The solution was concentrated and purified by column chromatography (15% ethyl acetate in hexanes v/v) to afford the desired homologated ketone **3.70** as a colorless oil (124 mg, 93.4%).
$[\alpha]_D^{20} = -32.35$ (c 0.83, $CHCl_3$); $R_f = 0.57$ (30% ethyl acetate in hexanes v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.39 (m, 2H), 7.38-7.30 (m, 3H), 7.09 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.36-5.32 (m, 1H), 4.96 (d, J = 10.7 Hz, 1H), 4.88 (d, J = 10.7 Hz, 1H), 3.88 (s, 3H), 3.14 (d, J = 13.7 Hz, 1H), 2.99 (d, J = 13.9 Hz, 1H), 2.50 (ddd, J = 14.6, 12.6, 6.8, 1H), 2.46-2.40 (m, 1H), 2.39-2.35 (m, 1H), 2.27-2.21 (m, 1H), 1.93-1.86 (m, 1H), 1.78-1.72 (m, 1H), 1.68-1.66 (m, 3H), 1.64-1.58 (m, 1H), 1.35 (s, 3H), 1.34-1.18 (m, 2H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.42, 151.57, 148.21, 139.89, 137.28, 133.52, 128.72, 128.56, 128.29, 127.58, 124.82, 119.27, 111.02, 74.83, 55.97, 51.23, 49.70, 42.12, 37.94, 37.23, 32.88, 24.73, 24.47, 23.74, 20.49; IR (neat) 3030 (bw), 2955 (bm), 2861 (bm), 1698 (s), 1574 (m), 1462 (bs), 1371 (m), 1276 (s), 1214 (bm), 1080 (bs), 979 (bs), 924 (bm), 797 (s), 732 (bs), 697 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{28}H_{34}ClO_3$ $[M+H]^+$: 453.2196; Found 453.2210.

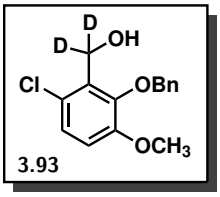


2-(benzyloxy)-3-methoxybenzoic acid (**3.92**). Benzyl protected *o*-vanillin[55] (3.40 g, 14.0 mmol, 1.00 equiv) was weighed into a 50 mL round bottom flask equipped with a magnetic stirbar and dissolved in 14 mL of CH_3CN. NaH_2PO_4 (5.6 mL of a 0.67 M solution in H_2O, 3.80 mmol, 0.271 equiv) was then added followed by H_2O_2 (1.4 mL of a 30% wt/wt solution in H_2O, 14.7 mmol, 1.05 equiv). The reaction flask was placed in a water bath, and $NaClO_2$ (2.37 g, 21.0

[55]Prepared in a single step from *o*-vanillin according to the literature method. See reference 54 for details.

mmol, 1.50 equiv) in 21 mL of water was added dropwise over 2 hours. Upon completion of the addition, the reaction was allowed to stir, open to the air, for 12 hours at room temperature. The reaction mixture was poured into 1 N HCl (100 mL) and transferred to a separatory funnel. The product was extracted with CH_2Cl_2 (3 x 50 mL) and the organics were washed with 50% aqueous $Na_2S_2O_3$ (200 mL). The aqueous phase was back-extracted with additional CH_2Cl_2 (2 x 100 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated to afford the desired product **3.92** as white solid that was used without further purification (3.34 g, 92.3%), mp 81-83 °C.

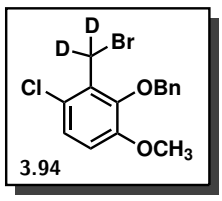
^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.40 (s, 1H), 7.70 (dd, J = 7.6, 2.0 Hz, 1 H), 7.45-7.37 (m, 5H), 7.21-7.15 (m, 2H), 5.27 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 167.50, 153.25, 146.29, 137.60, 128.16, 128.03, 127.80, 127.78, 124.21, 121.22, 115.72, 74.59, 56.02; IR (neat) 3017 (bw), 1697 (bs), 1579 (m), 1471 (m), 1459 (m), 1312 (s), 1287 (m), 1260 (s), 1204 (s), 1172 (m), 1089 (m), 1052 (s), 974 (s), 866 (m), 750 (bs), 697 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{15}O_4$ $[M+H]^+$: 259.0970; Found 259.0969.



***d*$_2$-(2-(benzyloxy)-6-chloro-3-methoxyphenyl)methanol** (**3.93**). (a) In a drybox, $LiAlD_4$ (605 mg, 14.4 mmol, 1.00 equiv) was weighed into a 250 mL round bottom flask equipped with a magnetic stirbar. After removing the flask from the drybox, 100 mL of THF was added, and the resulting grey suspension was cooled to 0 °C. In a separate flask, acid **3.92** (3.73 g, 14.4 mmol. 1.00 equiv) was suspended in 44 mL of THF. The slurry of **3.92** was added to the $LiAlD_4$ suspension via cannula, and the reaction mixture was allowed to warm slowly to room temperature and stir for 20 hours. The dark grey solution was then re-cooled to 0 °C, and H_2O (50 mL) was slowly added to quench the excess $LiAlD_4$. The resulting thick slurry was warmed to room temperature and diluted with 100 mL of 1 N HCl. The reaction mixture was poured into a separatory funnel and the product was extracted with Et_2O (3 x 100 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL),

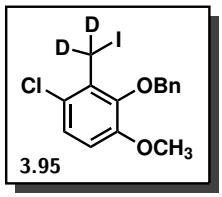
saturated aqueous NaCl (250 mL), dried over Na_2SO_4, filtered, and concentrated. (b) The crude solid was dissolved in 29 mL of CH_2Cl_2 and the solution was cooled to 4 °C. 1,3-dichloro-5,5-dimethylhydantoin (3.41 g, 17.3 mmol, 1.20 equiv) was added as a solid, and the reaction mixture was then stirred for 20 hours at 4 °C. The resulting slurry was diluted with saturated aqueous $Na_2S_2O_3$ (20 mL), and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (30 mL), H_2O (30 mL), saturated aqueous NaCl (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography (30% ethyl acetate in hexanes v/v) to afford the desired compound **3.93** as a white solid (3.55 g, 85.1%, 2 steps), mp 81-83 °C.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47-7.43 (m, 2H), 7.42-7.33 (m, 3H), 7.11 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 5.09 (s, 2H), 3.89 (s, 3H), 2.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.81, 147.35, 137.10, 132.67, 128.70, 128.66, 128.51, 125.90, 124.98, 112.88, 75.87, 56.17; IR (neat) 3364 (bm), 3034 (w), 2943 (bw), 1576 (m), 1468 (bs), 1439 (s), 1368 (s), 1299 (m), 1236 (bs), 1082 (m), 1046 (s), 964 (bs), 844 (m), 801 (bs), 691 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{17}D_2ClNO_3$ $[M+NH_4]^+$: 298.1179; Found 298.1177.



***d*$_2$-2-(benzyloxy)-3-(bromomethyl)-4-chloro-1-methoxybenzene** (**3.94**). Benzyl alcohol **3.93** (2.98 g, 10.6 mmol, 1.00 equiv) and CBr_4 (4.57 g, 13.8 mmol, 1.30 equiv) were weighed into a 50 mL round bottom flask equipped with a magnetic stirbar and dissolved in 21 mL of THF. The solution was cooled to 0 °C and PPh_3 (3.62 g, 13.8 mmol, 1.30 equiv) was added as a solid. The reaction mixture was then warmed to room temperature, and after 10 minutes diluted with water (20 mL), poured into a separatory funnel, and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (30% ethyl acetate in hexanes v/v) afforded the product **3.94** as a white solid (3.40 g, 93.4%), mp 62-65 °C.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55-7.51 (m, 2H), 7.43-7.34 (m, 3H), 7.12 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.16 (s, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.90, 147.42, 137.27, 130.42, 128.64, 128.53, 128.39, 126.29, 125.06, 113.47, 75.13, 56.21; IR (neat) 3031 (w), 2944 (bw), 1577 (m), 1468 (s), 1438 (m), 1267 (s), 1237 (s), 1097 (s), 971 (s), 948 (s), 918 (m), 892 (m), 804 (s), 765 (s), 691 (s), 572 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{16}D_2BrClNO_2$ $[M+NH_4]^+$: 360.0335; Found 360.0334.



***d*$_2$-2-(benzyloxy)-4-chloro-3-(iodomethyl)-1-methoxybenzene** (**3.95**). Benzyl bromide **3.94** (3.06 g, 8.90 mmol, 1.00 equiv) was weighed into a 50 mL round bottom flask equipped with a magnetic stirbar and dissolved in 15 mL of freshly distilled acetone. NaI (2.67 g, 17.8 mmol, 2.00 equiv) was then added as a solid, and the resulting suspension was stirred for 12 hours at room temperature in the dark. The mixture was filtered through Celite® 545 rinsing with ethyl acetate (3 x 10 mL) and concentrated. The crude residue was dissolved in 30 mL of ethyl acetate and poured into a separatory funnel. The organics were washed with 50% aqueous NaS_2O_3 (20 mL), dried over Na_2SO_4, and concentrated to afford the desired product **3.95** as a pale yellow solid that was used without further purification (3.44 g, 98.8%), mp 74-76 °C.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56-7.53 (m, 2H), 7.43-7.34 (m, 3H), 7.08 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.88, 146.78, 137.35, 131.66, 128.64, 128.42, 128.34, 125.86, 125.10, 112.86, 74.05, 56.19; IR (neat) 3005 (bw), 2837 (bw), 1573 (m), 1467 (s), 1437 (m), 1367 (m), 1296 (m), 1266 (s), 1235 (s), 1095 (s), 971 (bs), 877 (m), 802 (s), 744 (s), 692 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{16}D_2ClINO_2$ $[M+NH_4]^+$: 408.0196; Found 408.0182.

3.6.3 *NMR Spectral Data*

Figure 3.8: ^{1}H NMR of trimethyl(6-methyl-6-phenylcyclohex-1-enyloxy)silane (**3.80**)

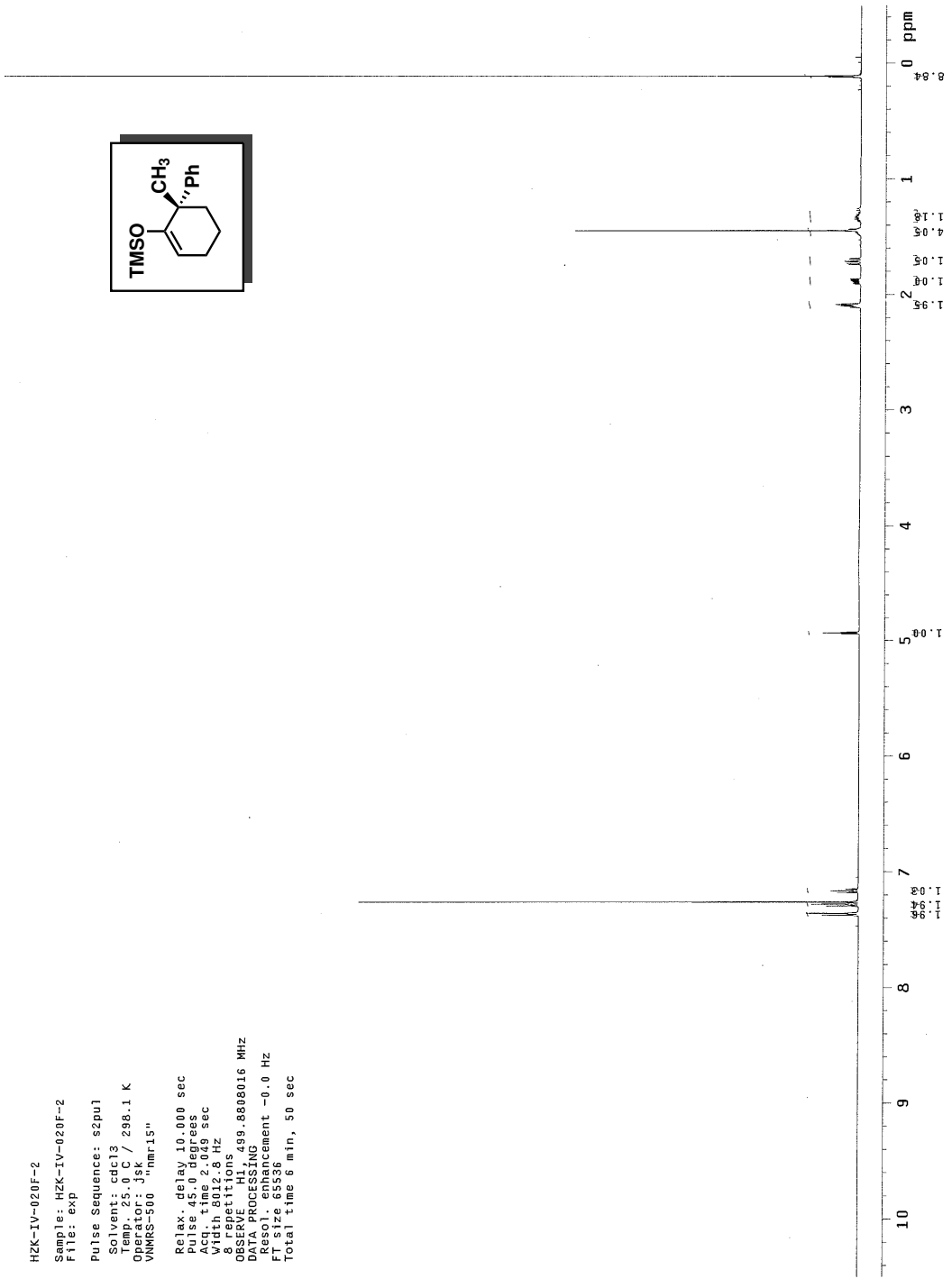


Figure 3.9: ^{13}C NMR of trimethyl(6-methyl-6-phenylcyclohex-1-enyloxy)silane (**3.80**)

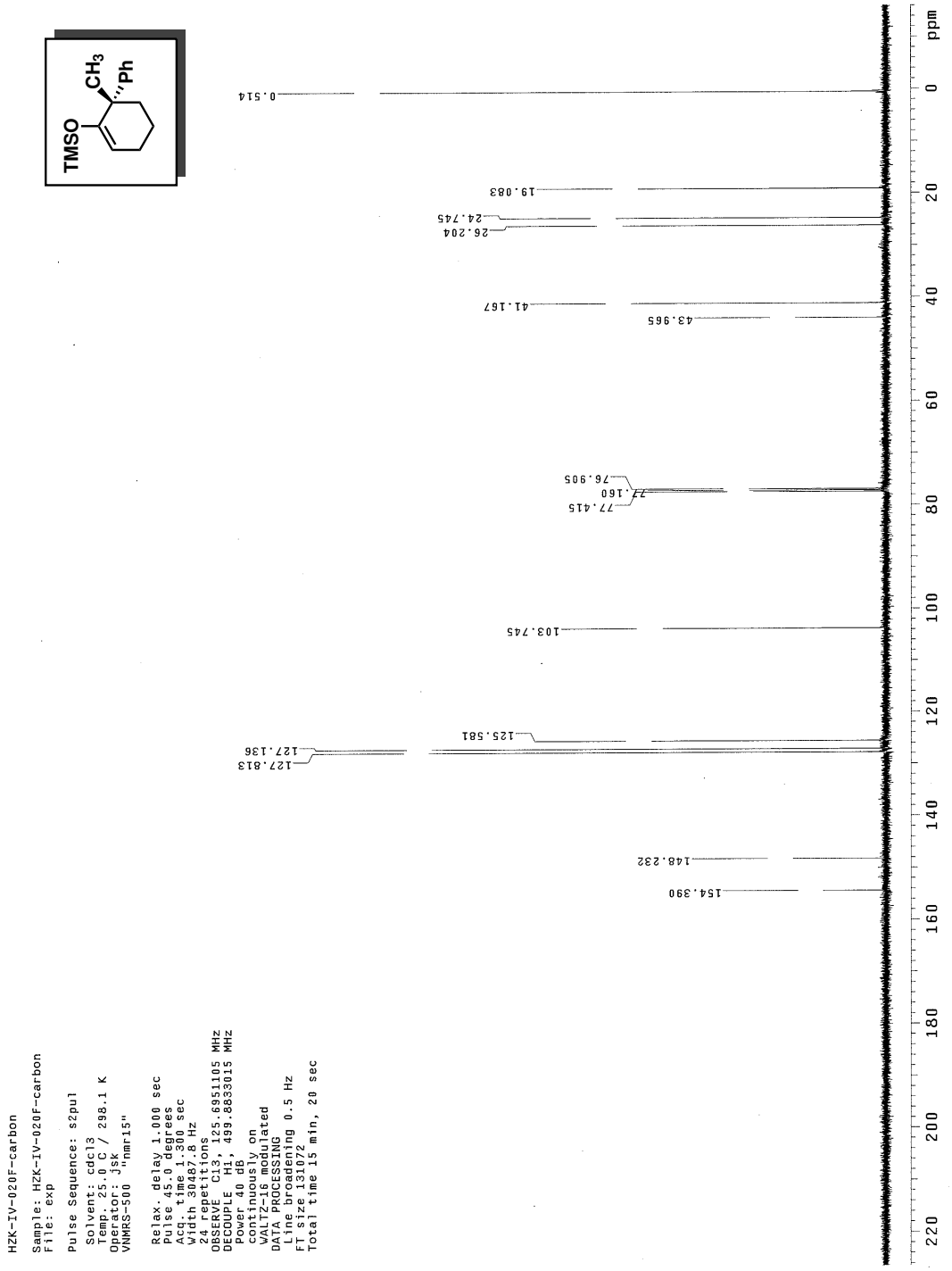


Figure 3.10: ^{1}H NMR of trimethyl(3-methyl-3-phenylcyclohex-1-enyloxy)silane (**3.81**)

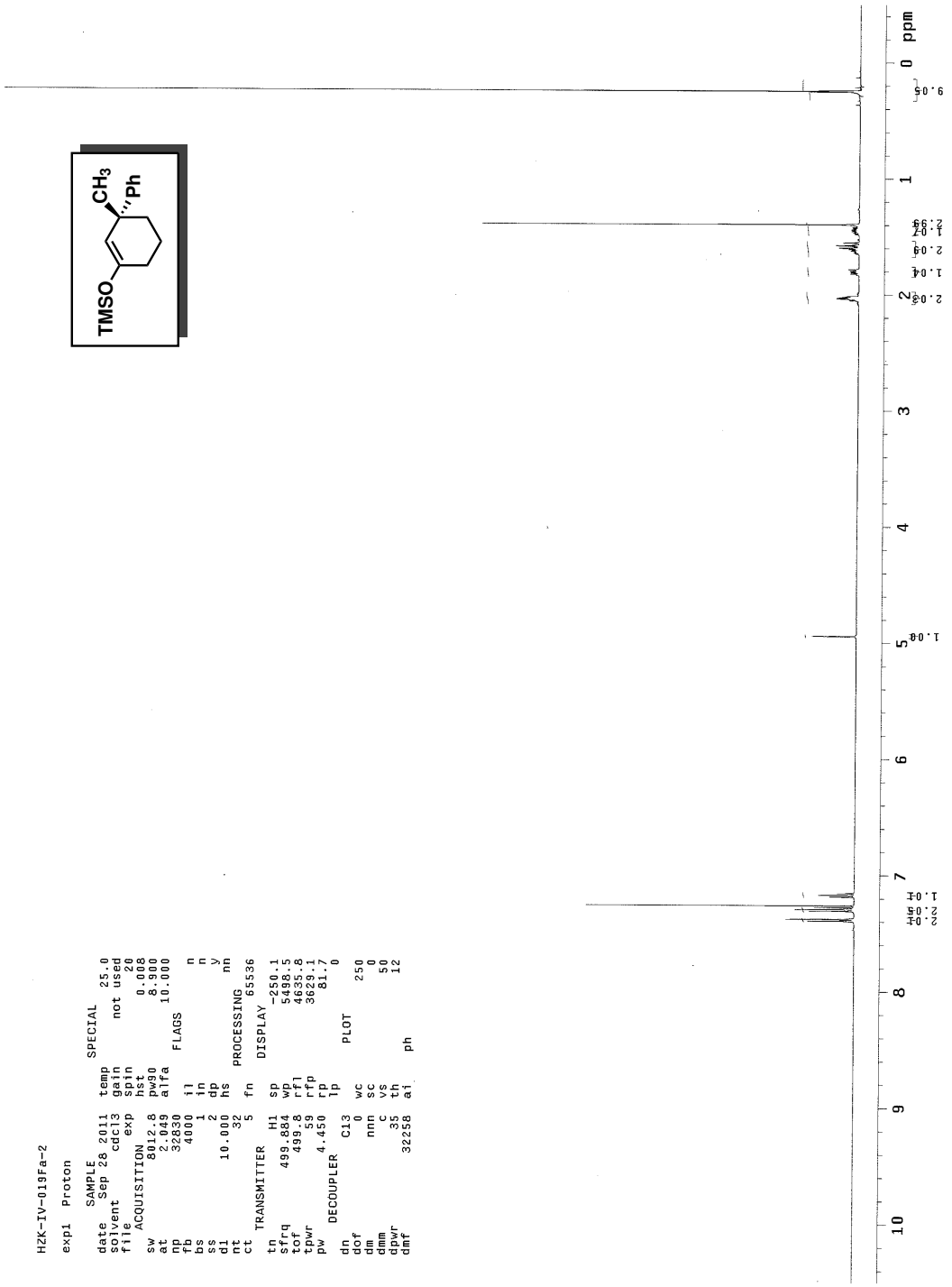


Figure 3.11: ^{13}C NMR of trimethyl(3-methyl-3-phenylcyclohex-1-enyloxy)silane (**3.81**)

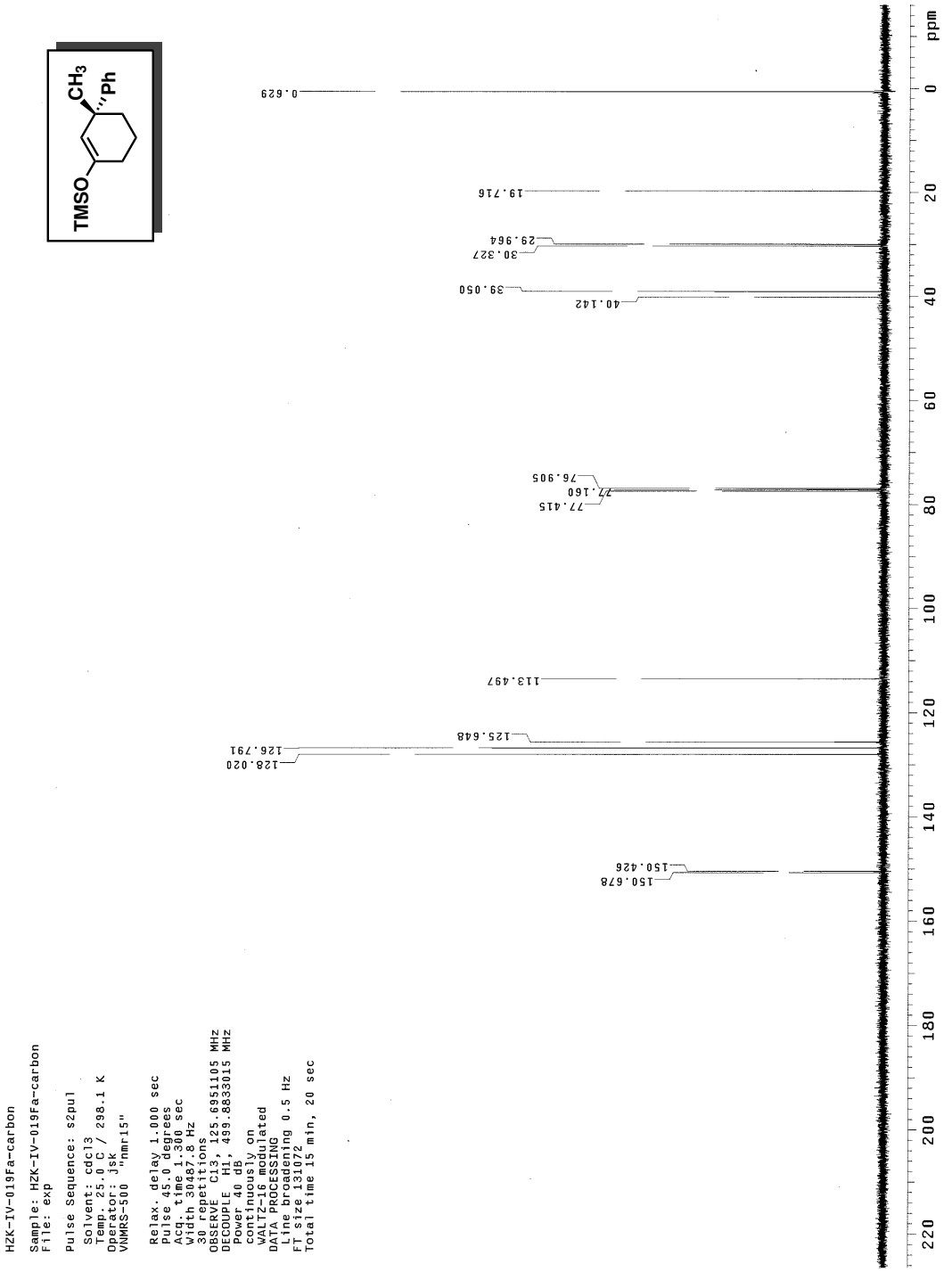


Figure 3.12: ^{1}H NMR of 2-methyl-2-phenyl-cyclohexanone (**3.33**)

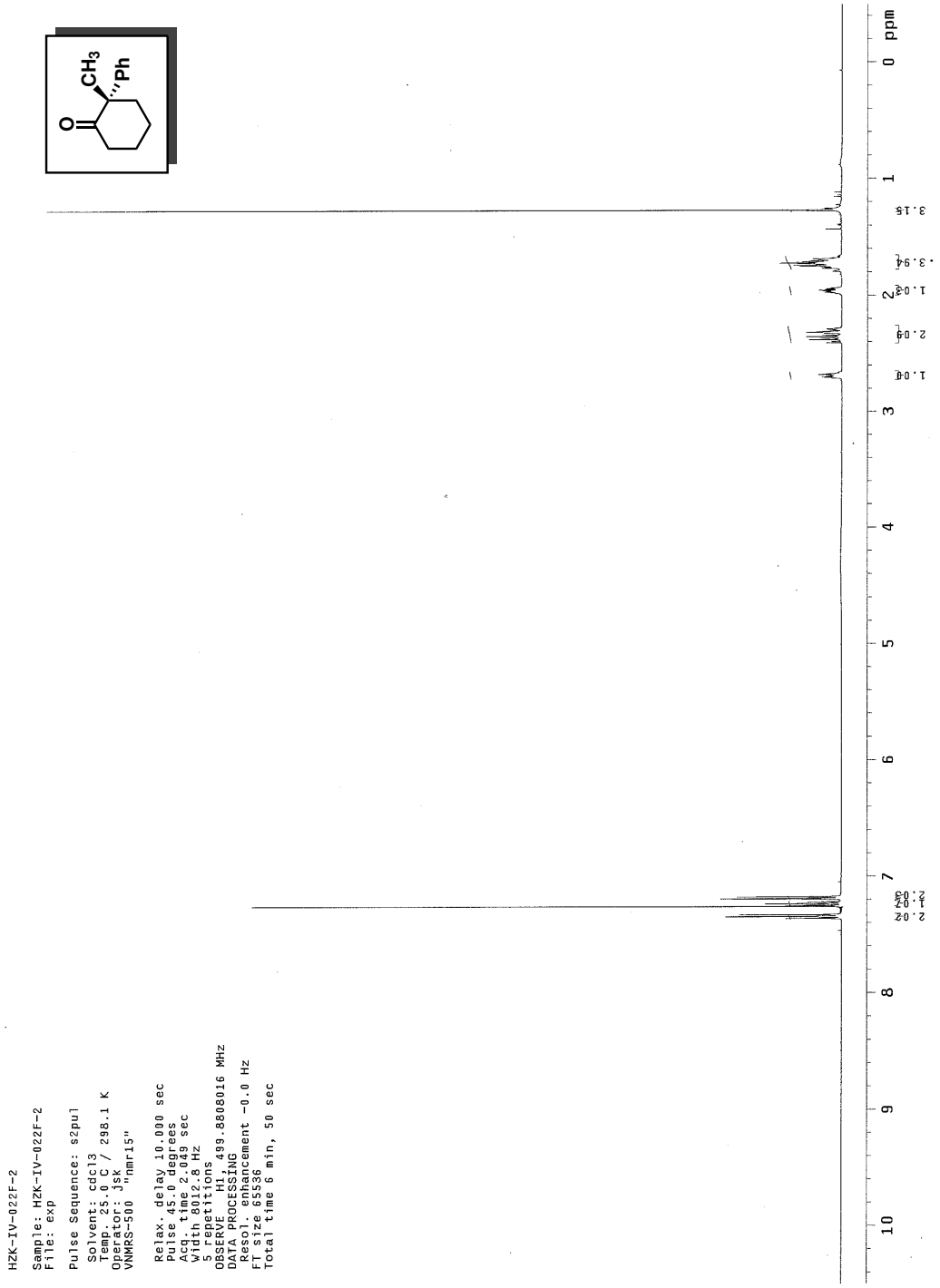


Figure 3.13: ^{13}C NMR of 2-methyl-2-phenyl-cyclohexanone (**3.33**)

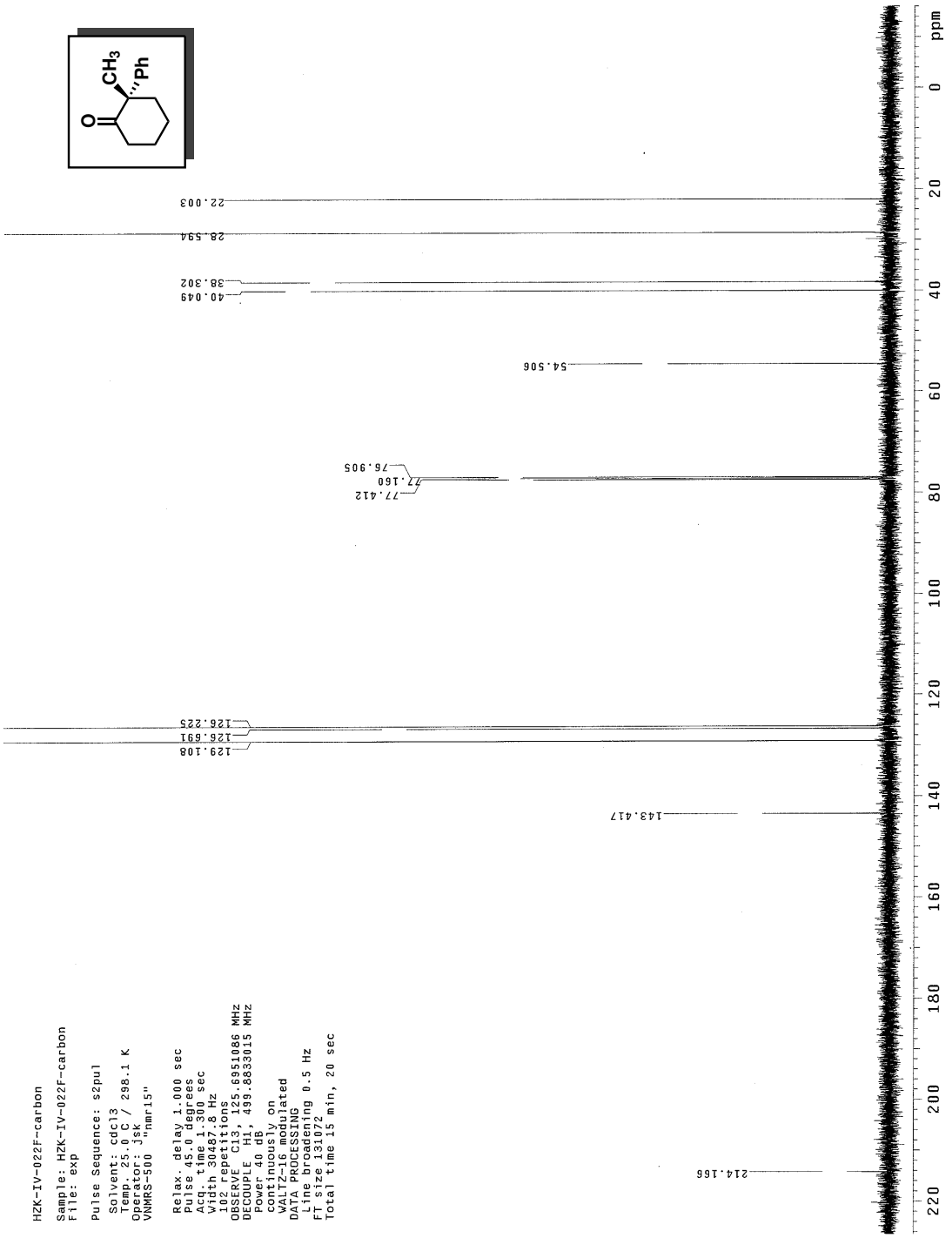


Figure 3.14: ^{1}H NMR of 3-methyl-3-phenyl-cyclohexanone (**3.34**)

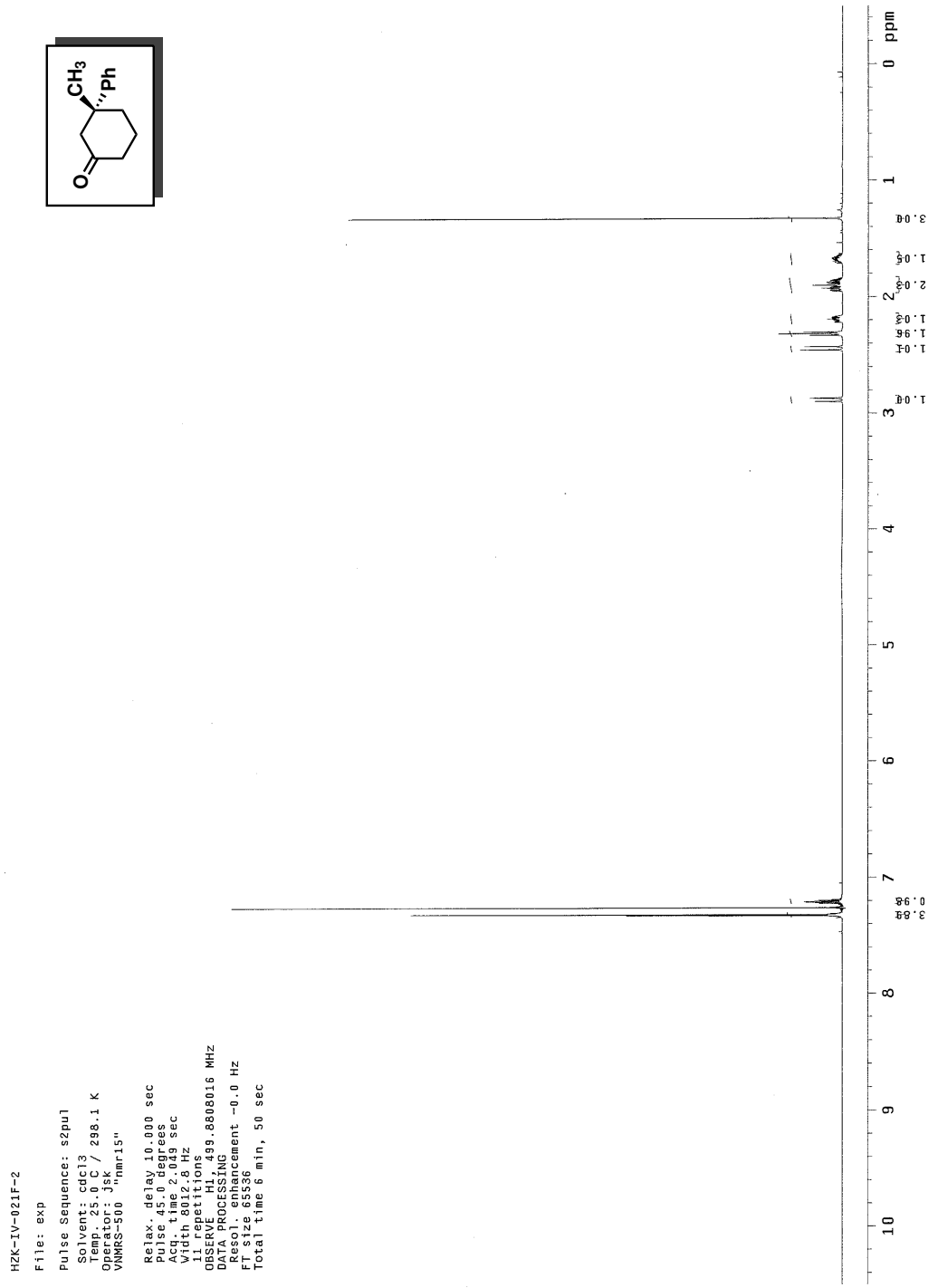


Figure 3.15: ^{13}C NMR of 3-methyl-3-phenyl-cyclohexanone (**3.34**)

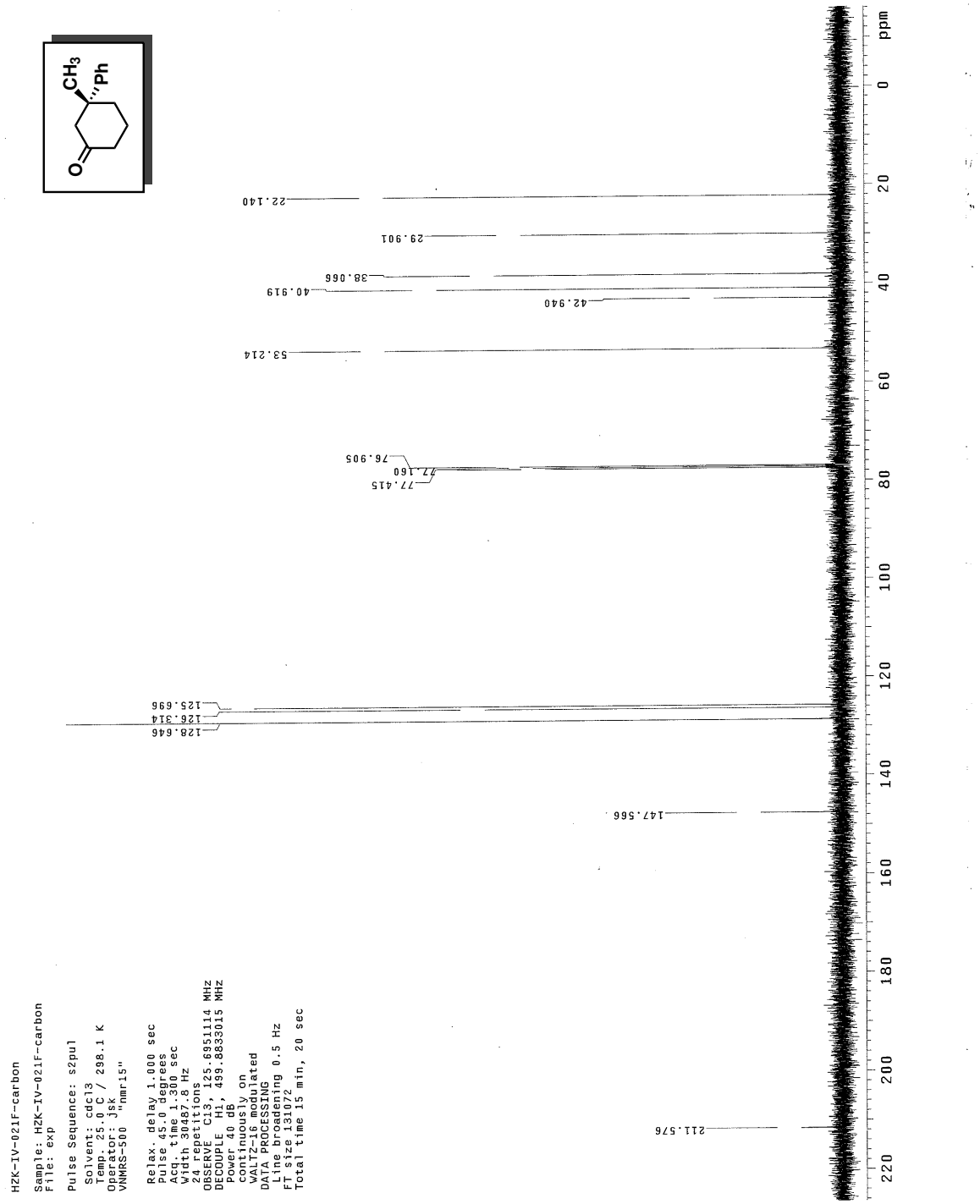


Figure 3.16: ^{1}H NMR of homologated estrone 3-methyl ether major (**3.42**)

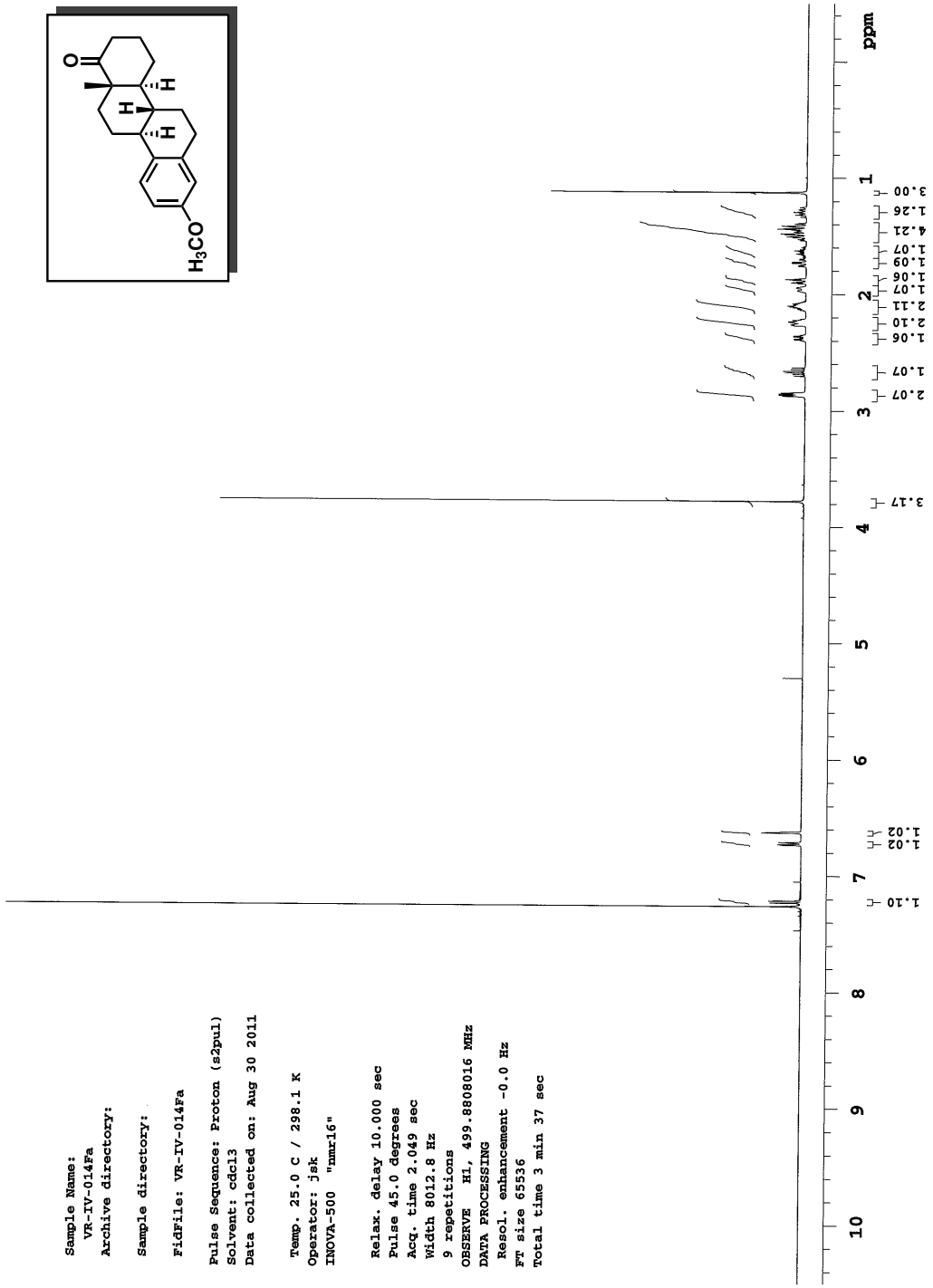


Figure 3.17: ^{13}C NMR of homologated estrone 3-methyl ether major (**3.42**)

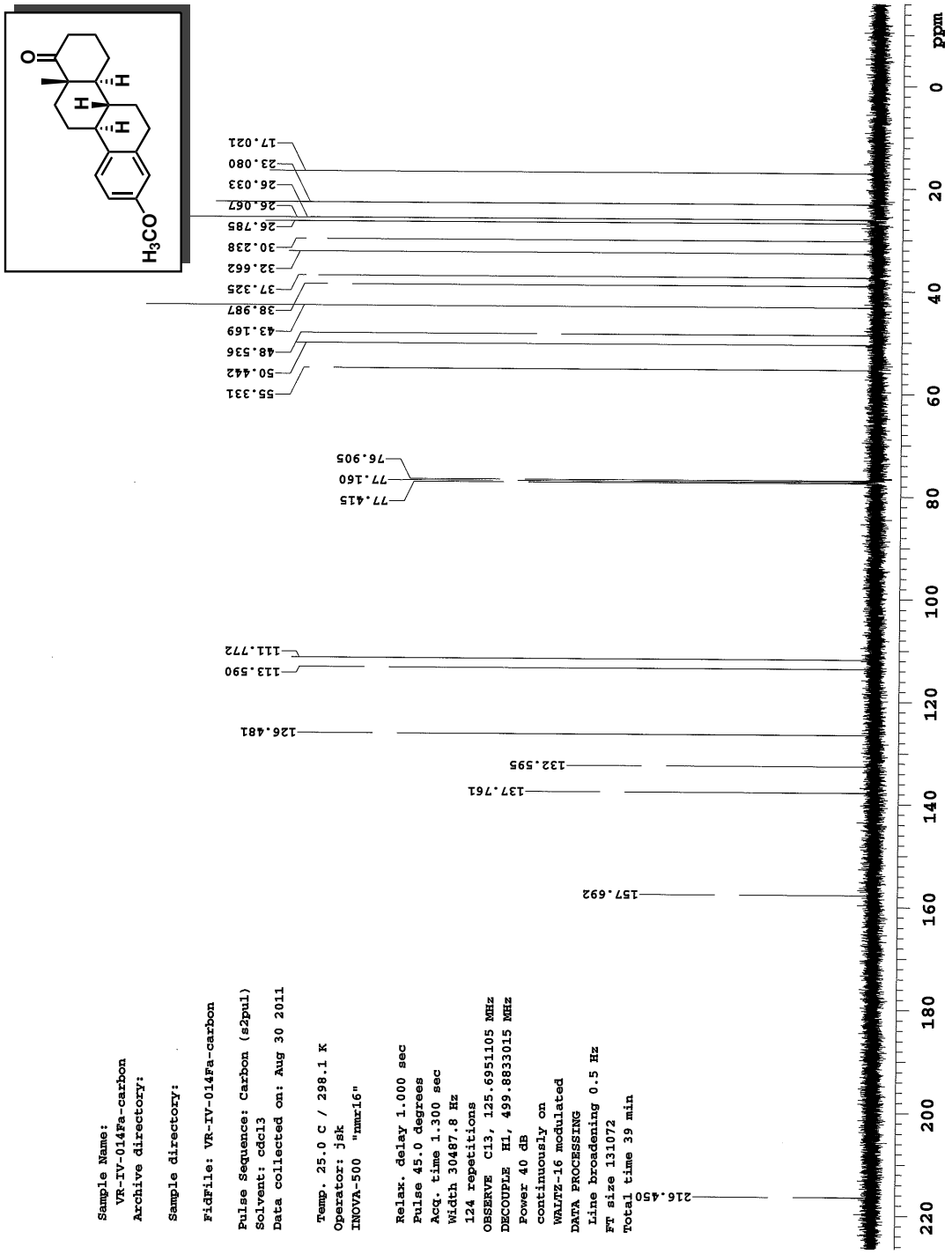


Figure 3.18: ^{1}H NMR of homologated estrone 3-methyl ether minor (**3.43**)

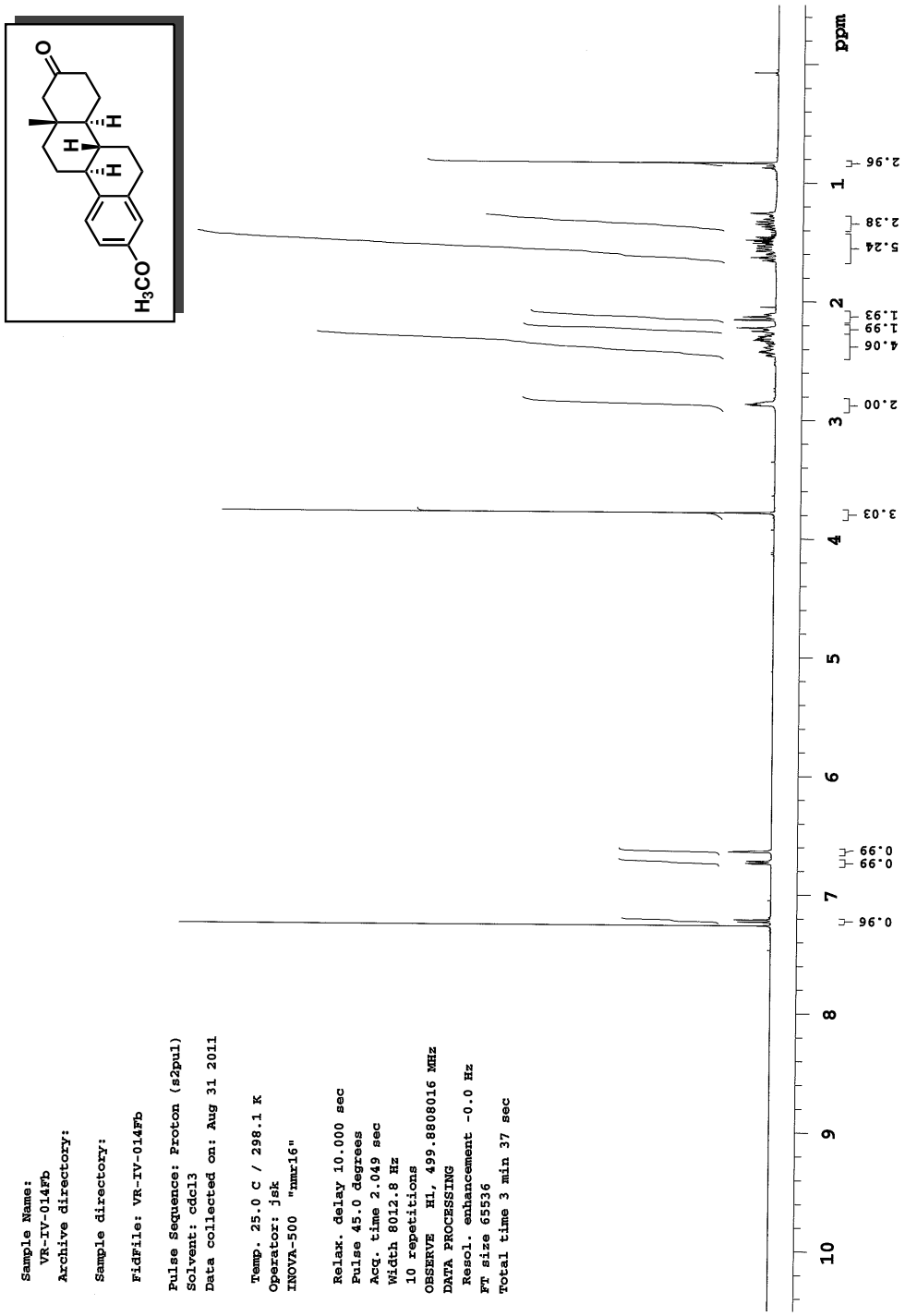


Figure 3.19: ^{13}C NMR of homologated estrone 3-methyl ether minor (**3.43**)

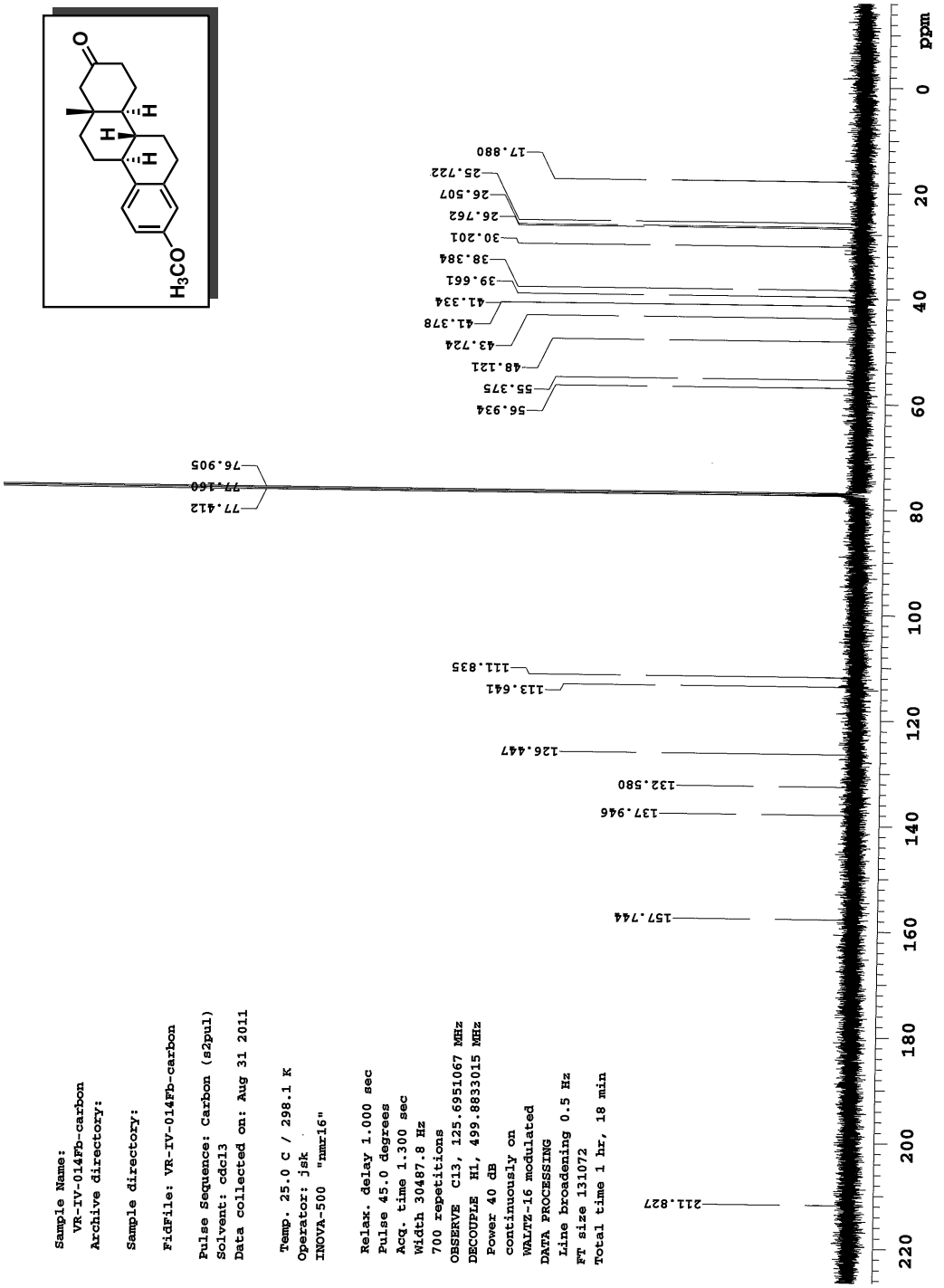


Figure 3.20: ^{1}H NMR of ($\pm$)-d_1-Hajos-Parrish keto-alcohol (**3.83**)

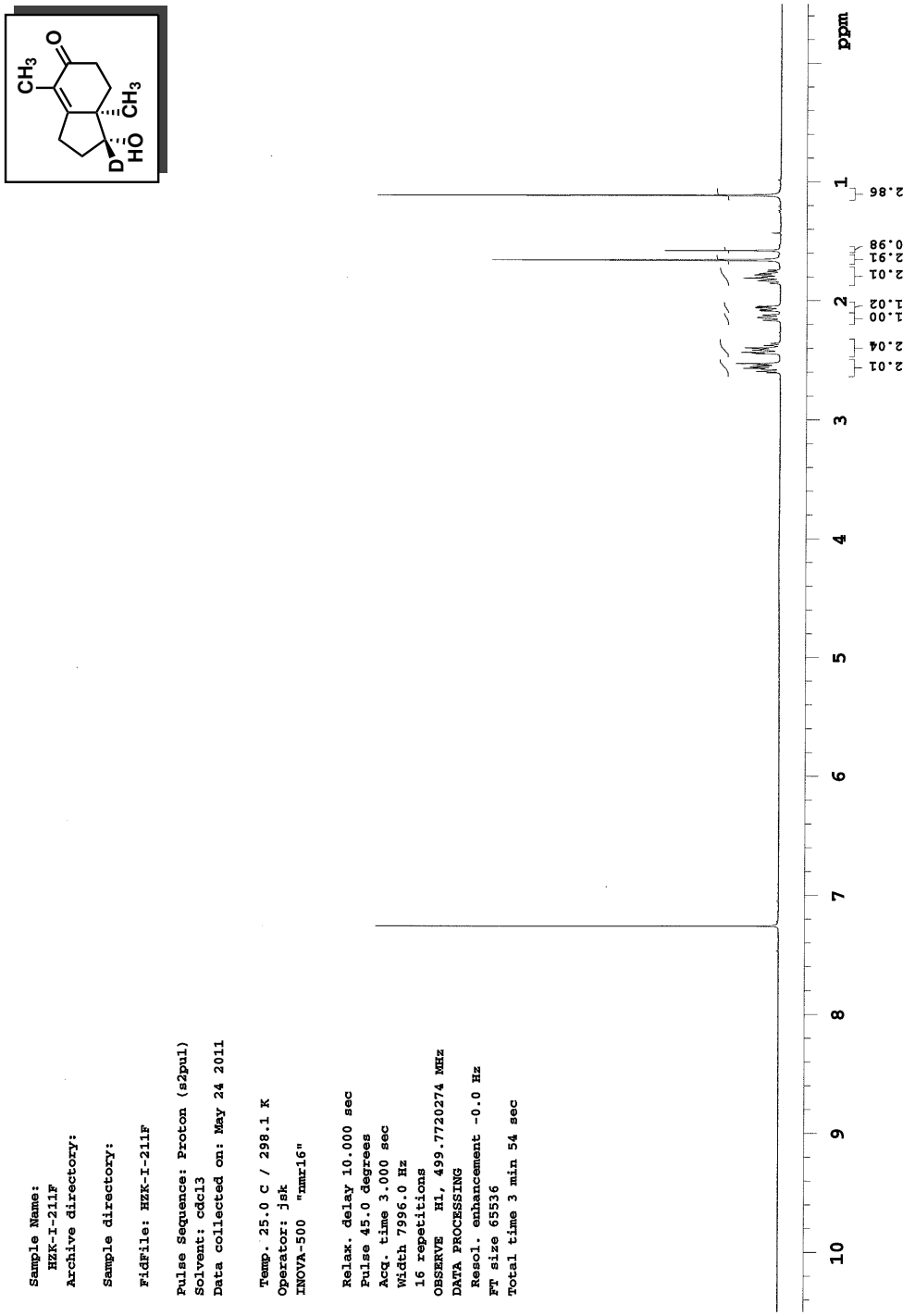


Figure 3.21: ^{13}C NMR of (±)-d_1-Hajos-Parrish keto-alcohol (**3.83**)

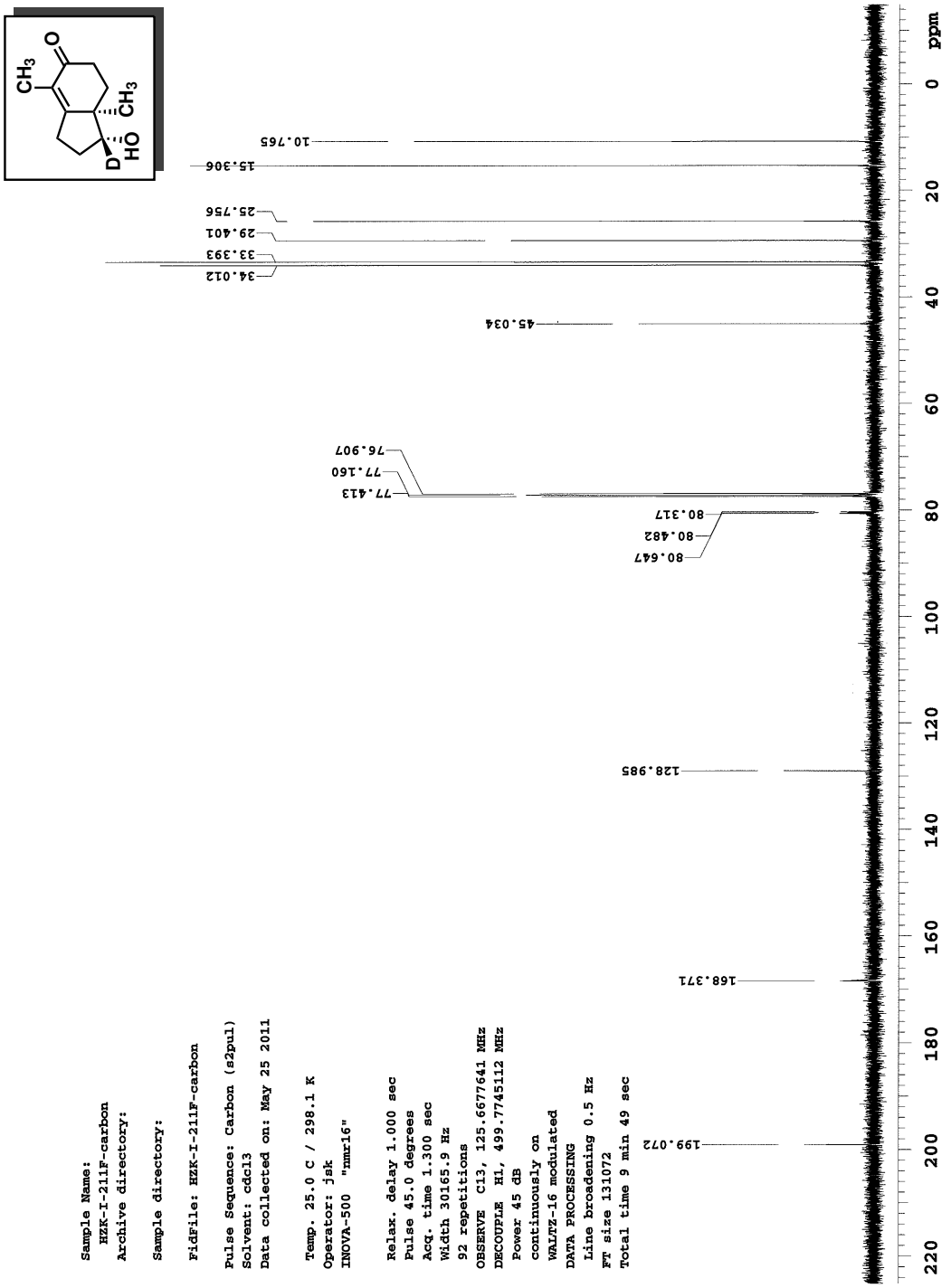


Figure 3.22: ^{1}H NMR of (−)-keto-alcohol (**3.51**)

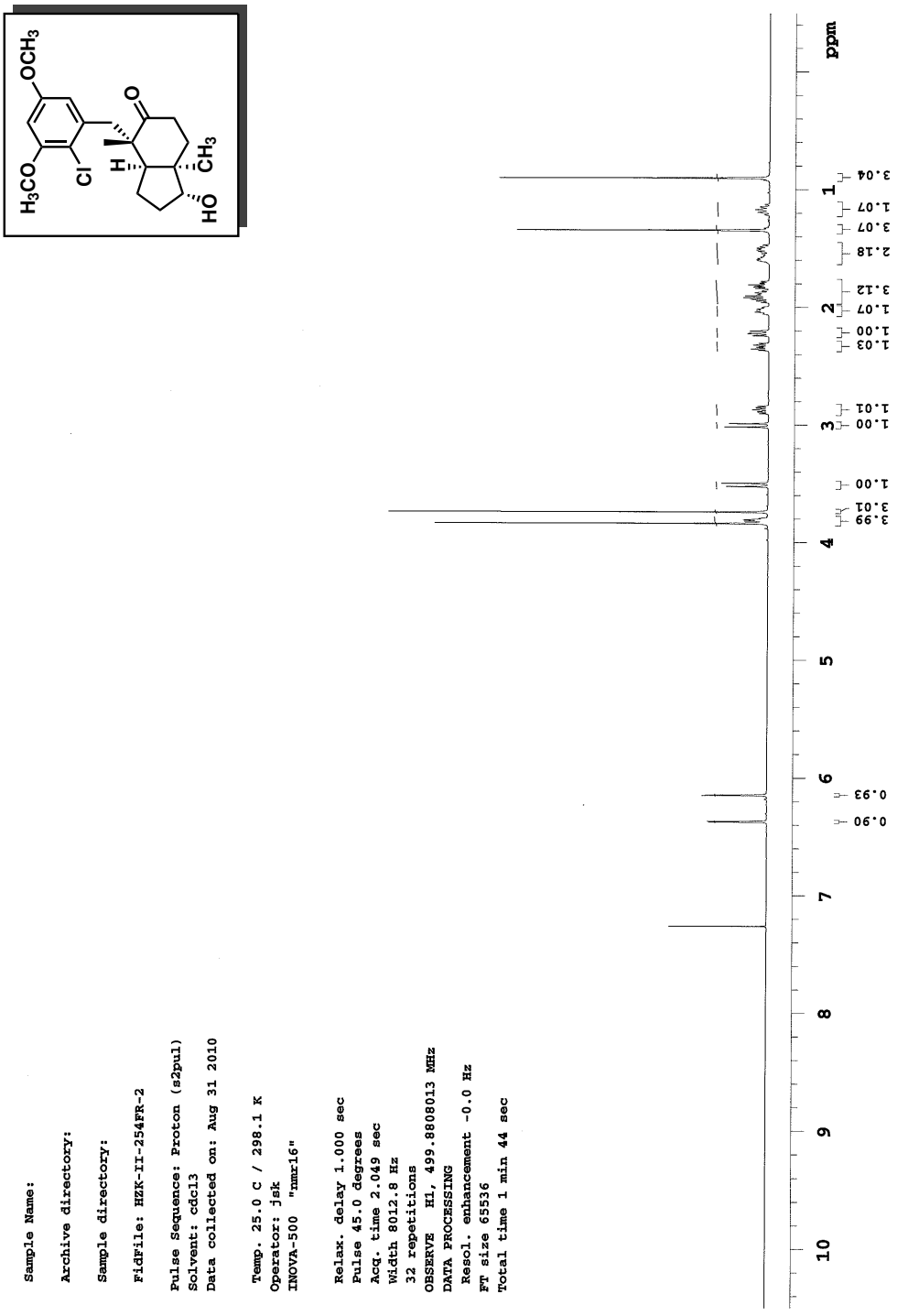


Figure 3.23: ^{13}C NMR of (−)-keto-alcohol (**3.51**)

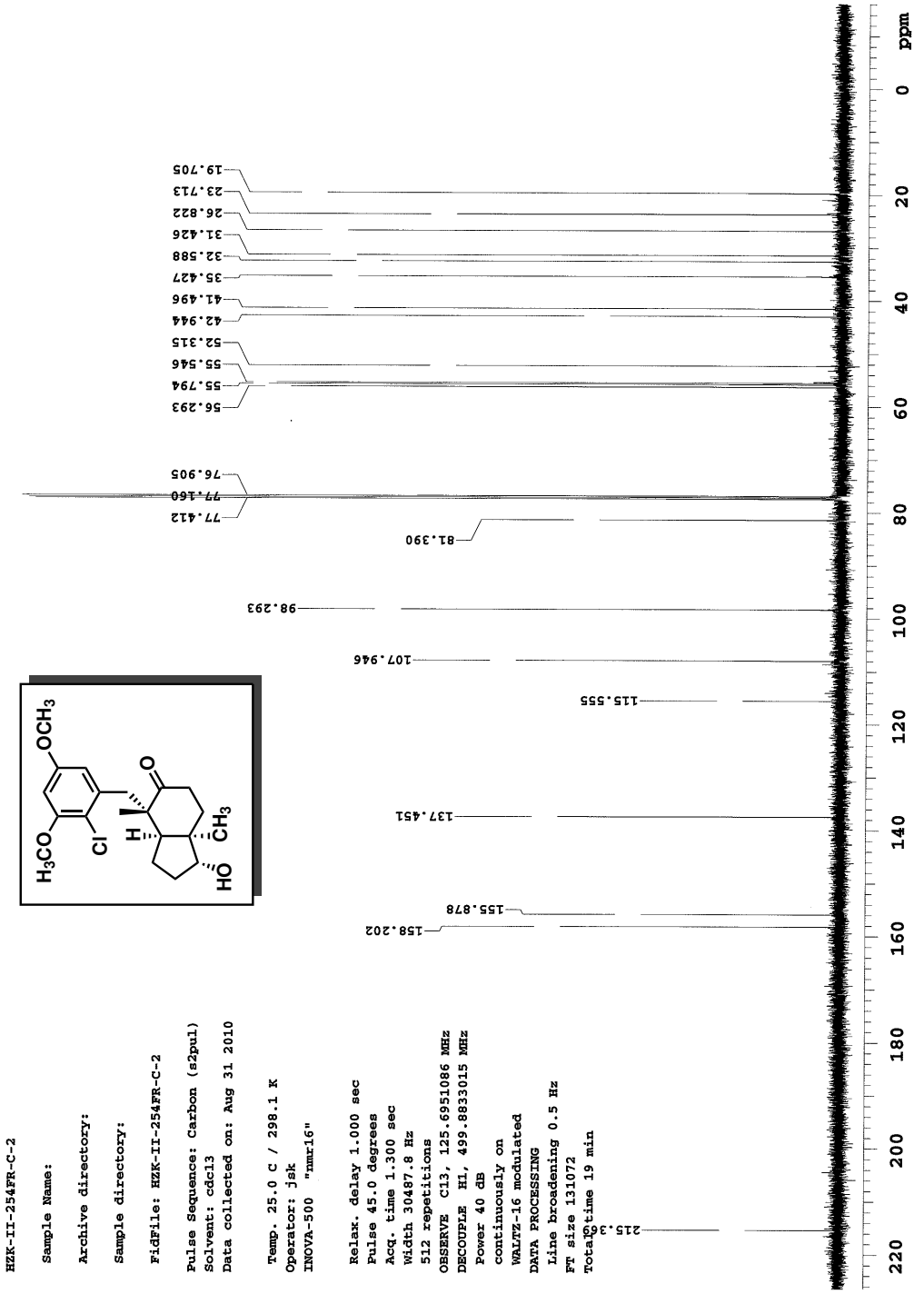


Figure 3.24: ^{1}H NMR of (−)-keto-alcohol (**3.64**)

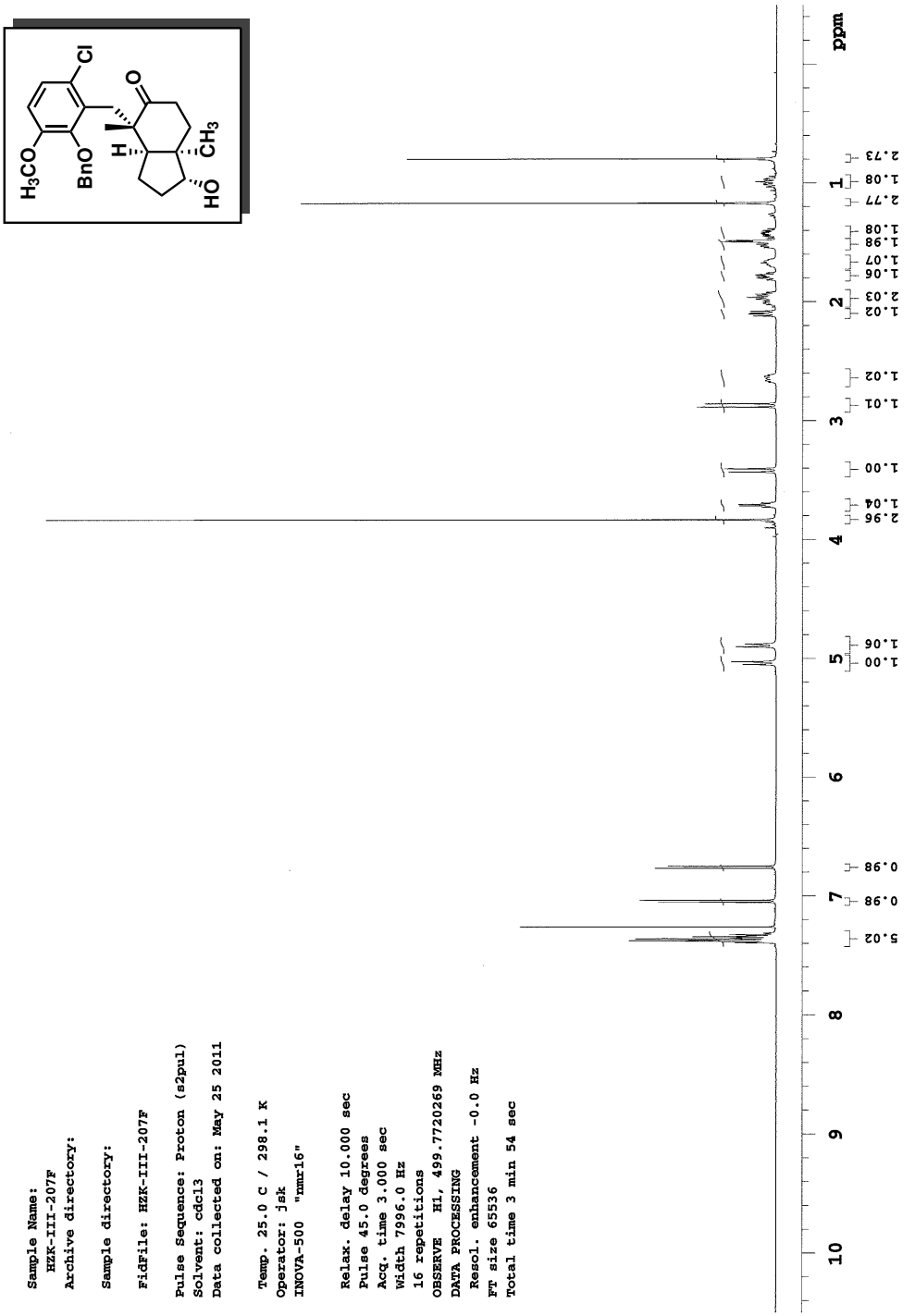


Figure 3.25: ^{13}C NMR of (−)-keto-alcohol (**3.64**)

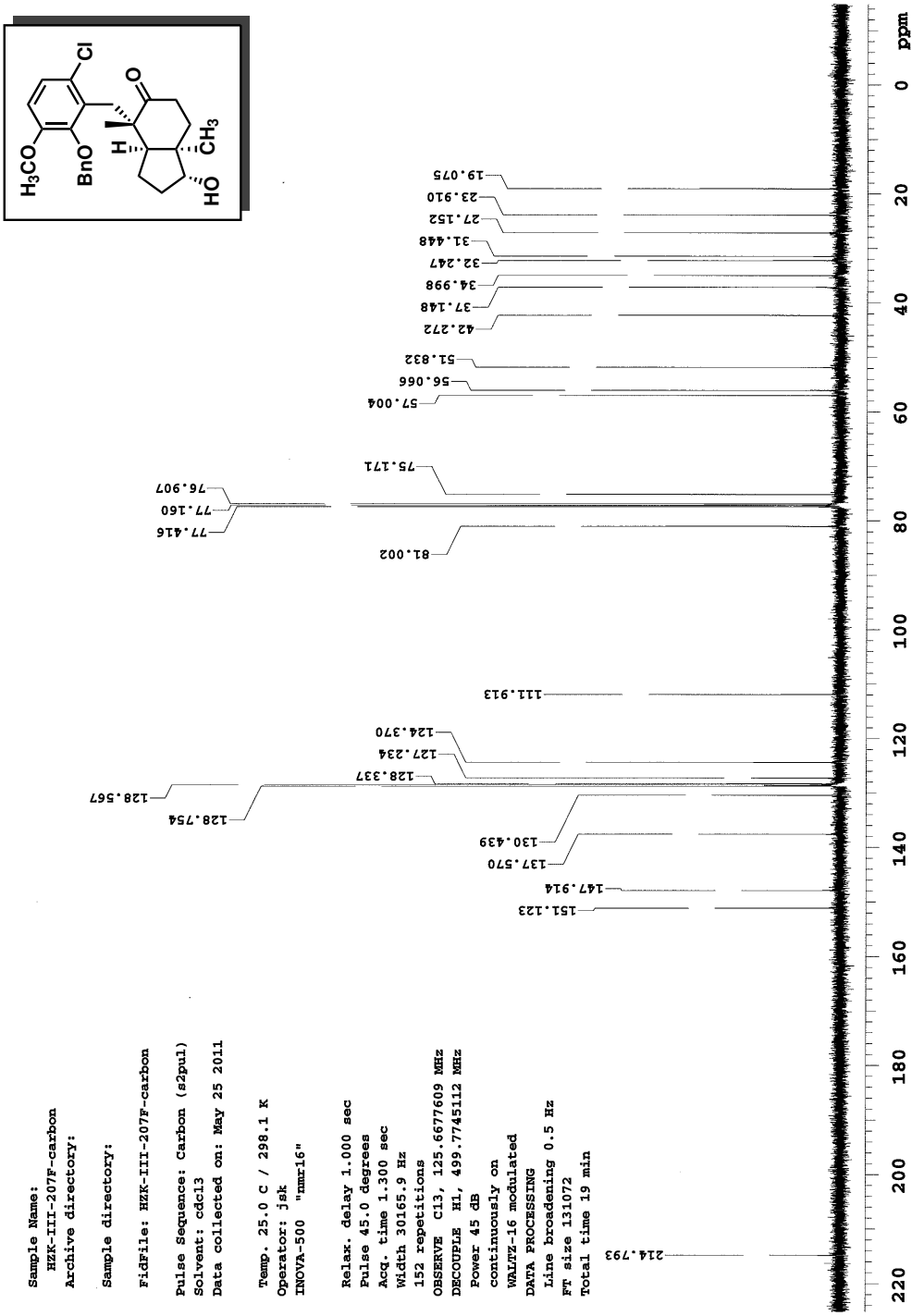


Figure 3.26: ^{1}H NMR of (±)-d_3-keto-alcohol (**3.75**)

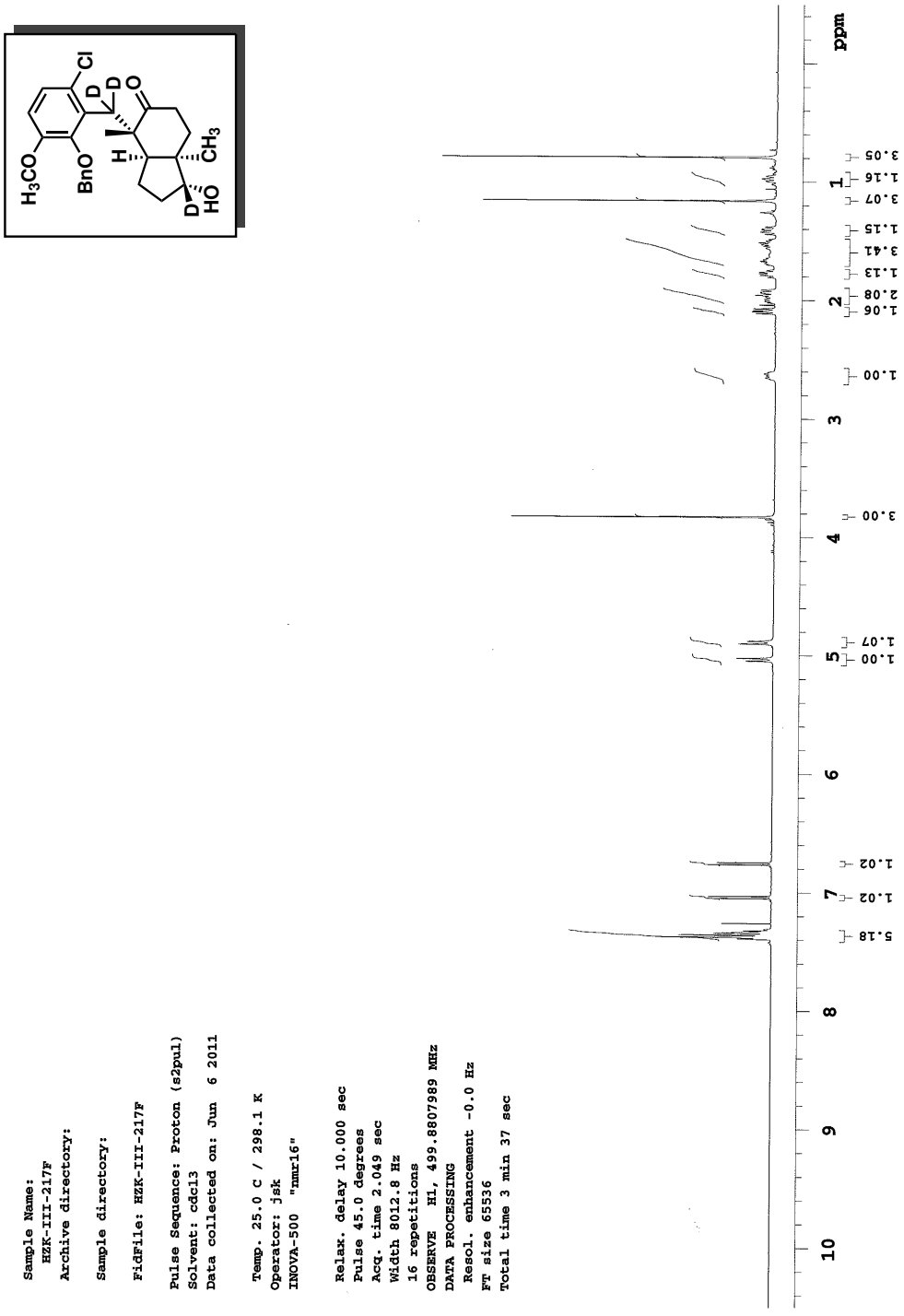


Figure 3.27: ^{13}C NMR of (±)-d_3-keto-alcohol (**3.75**)

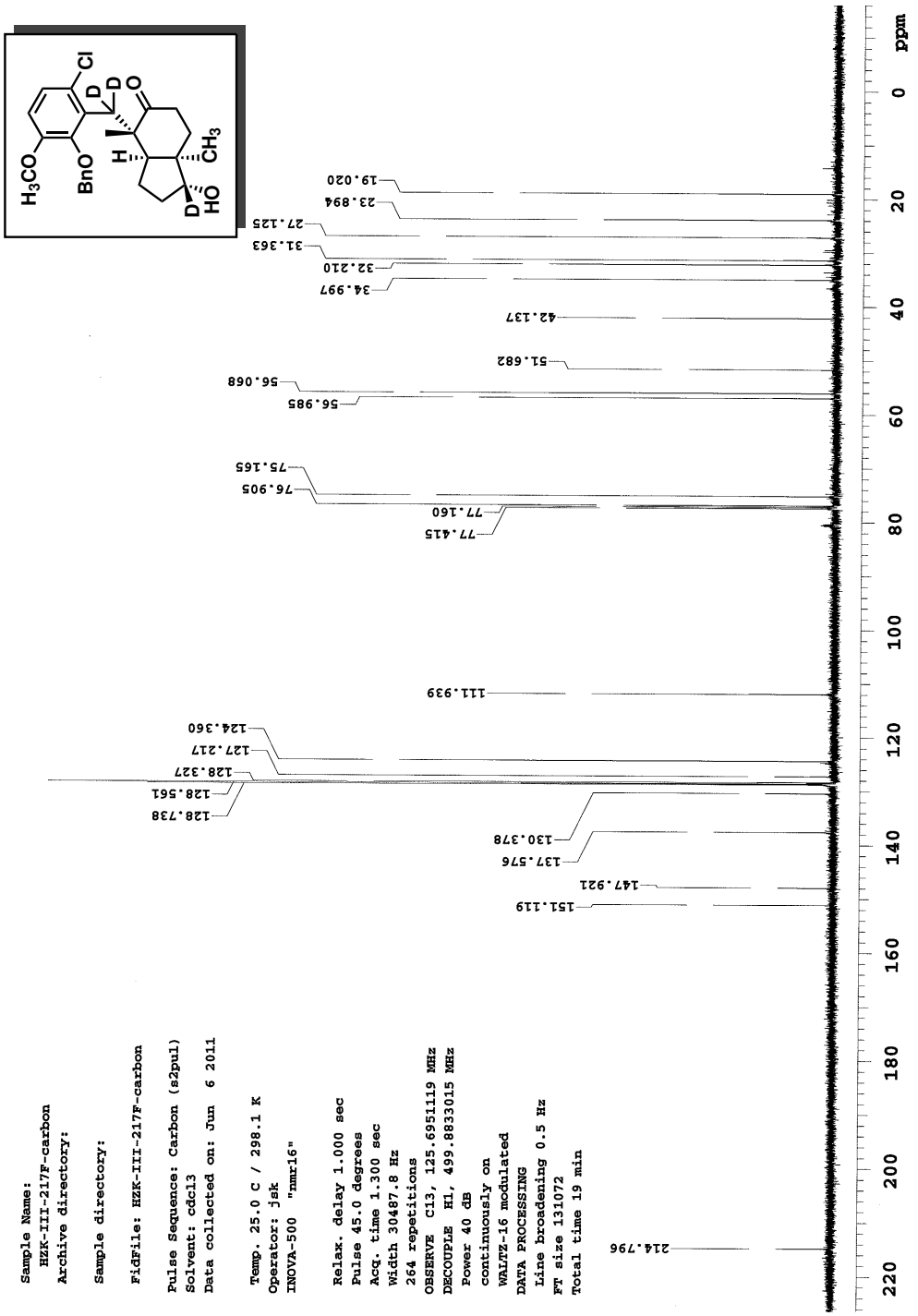


Figure 3.28: ^{1}H NMR of (3,5-dimethoxyphenyl)methanol (**3.84**)

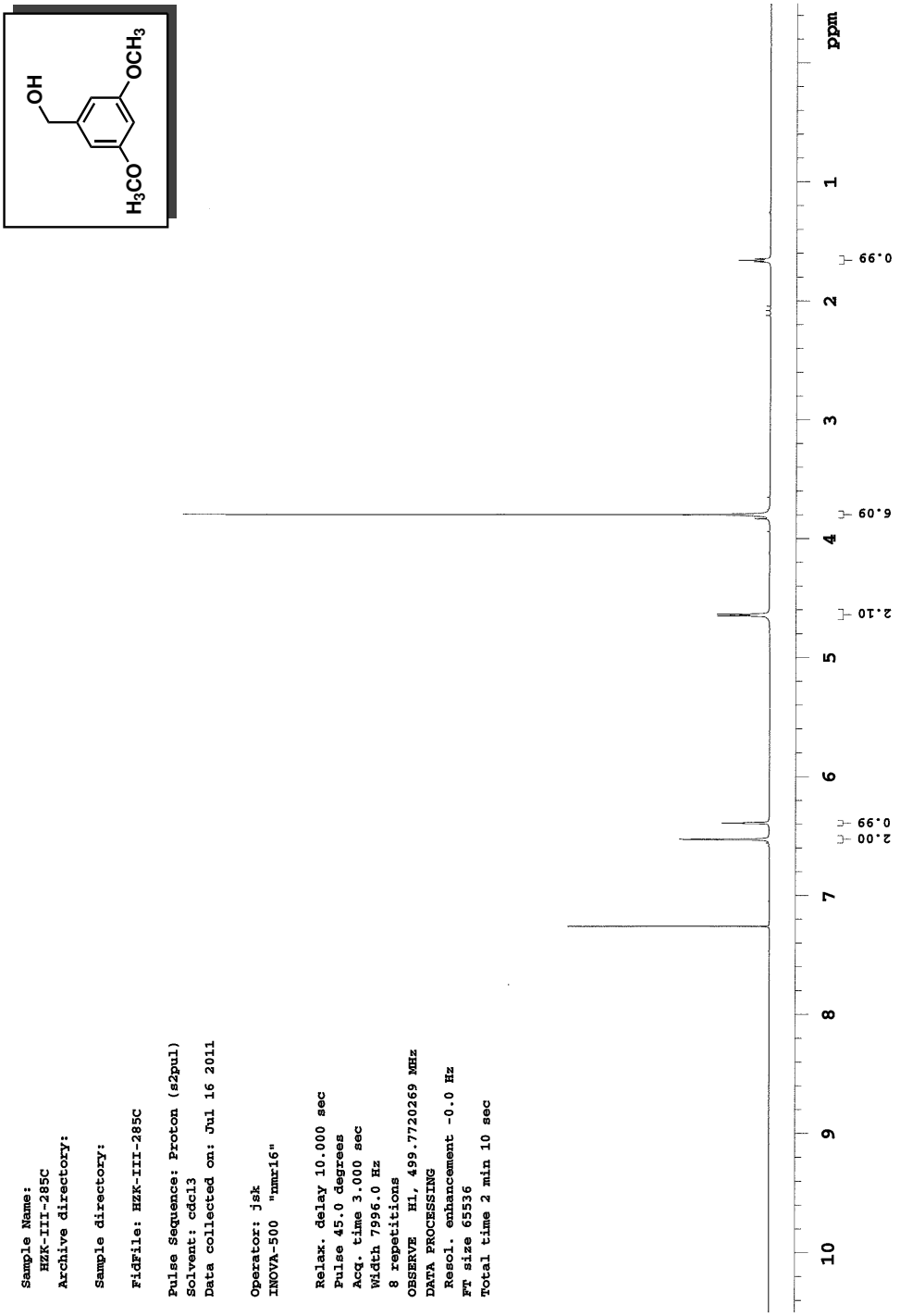


Figure 3.29: ^{13}C NMR of (3,5-dimethoxyphenyl)methanol (**3.84**)

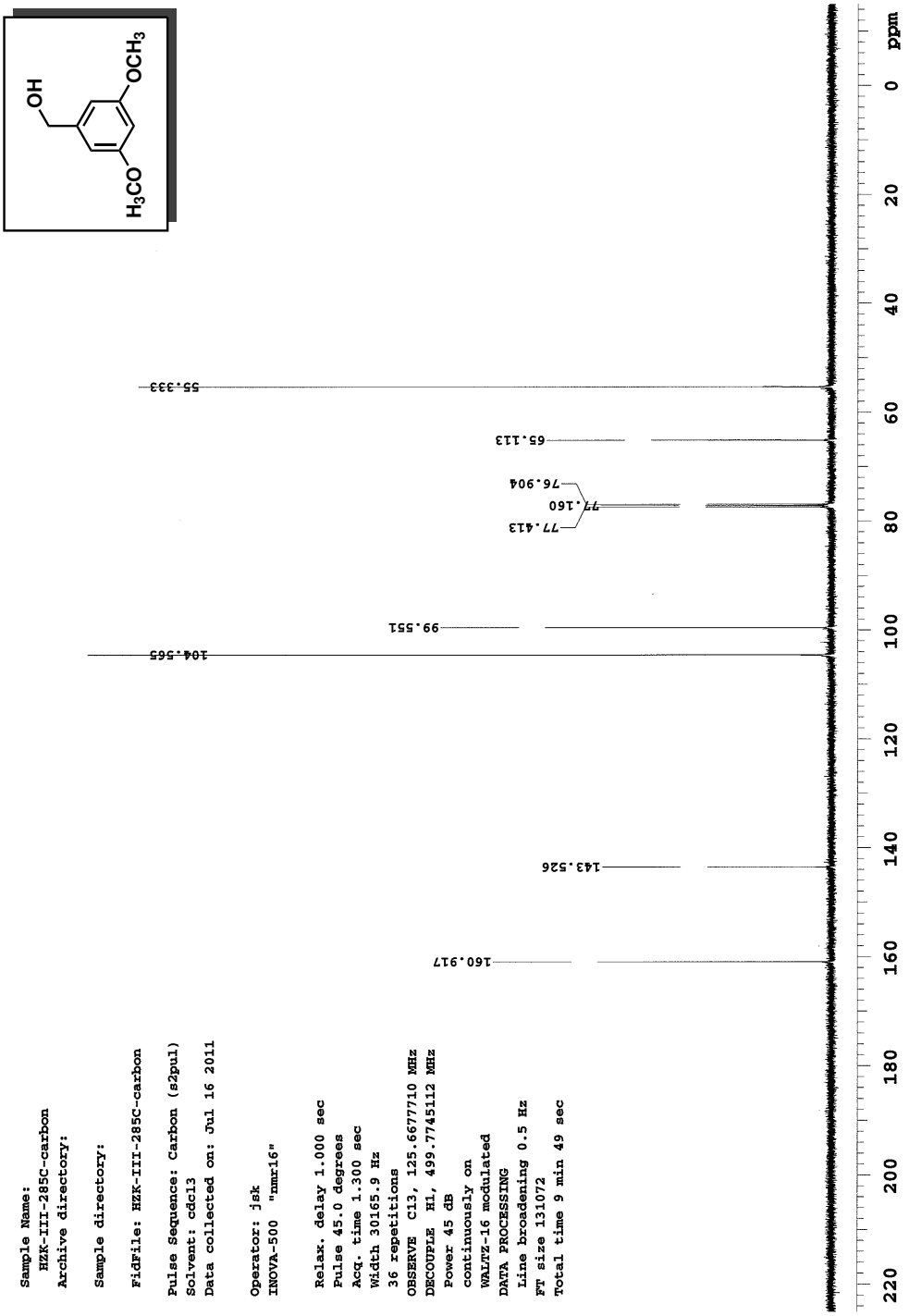


Figure 3.30: ^{1}H NMR of (2-chloro-3,5-dimethoxyphenyl)methanol (**3.55**)

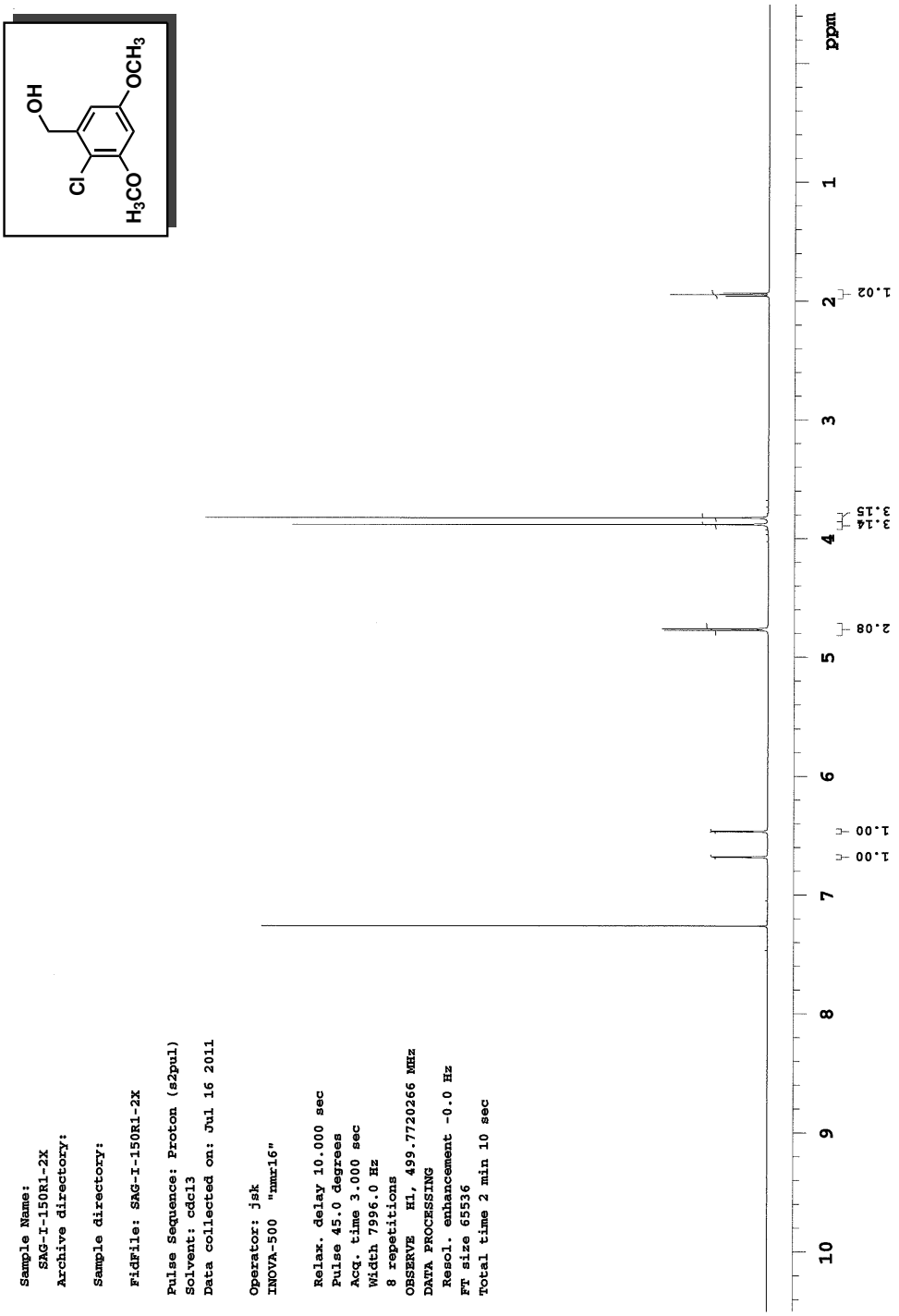


Figure 3.31: ^{13}C NMR of (2-chloro-3,5-dimethoxyphenyl)methanol (**3.55**)

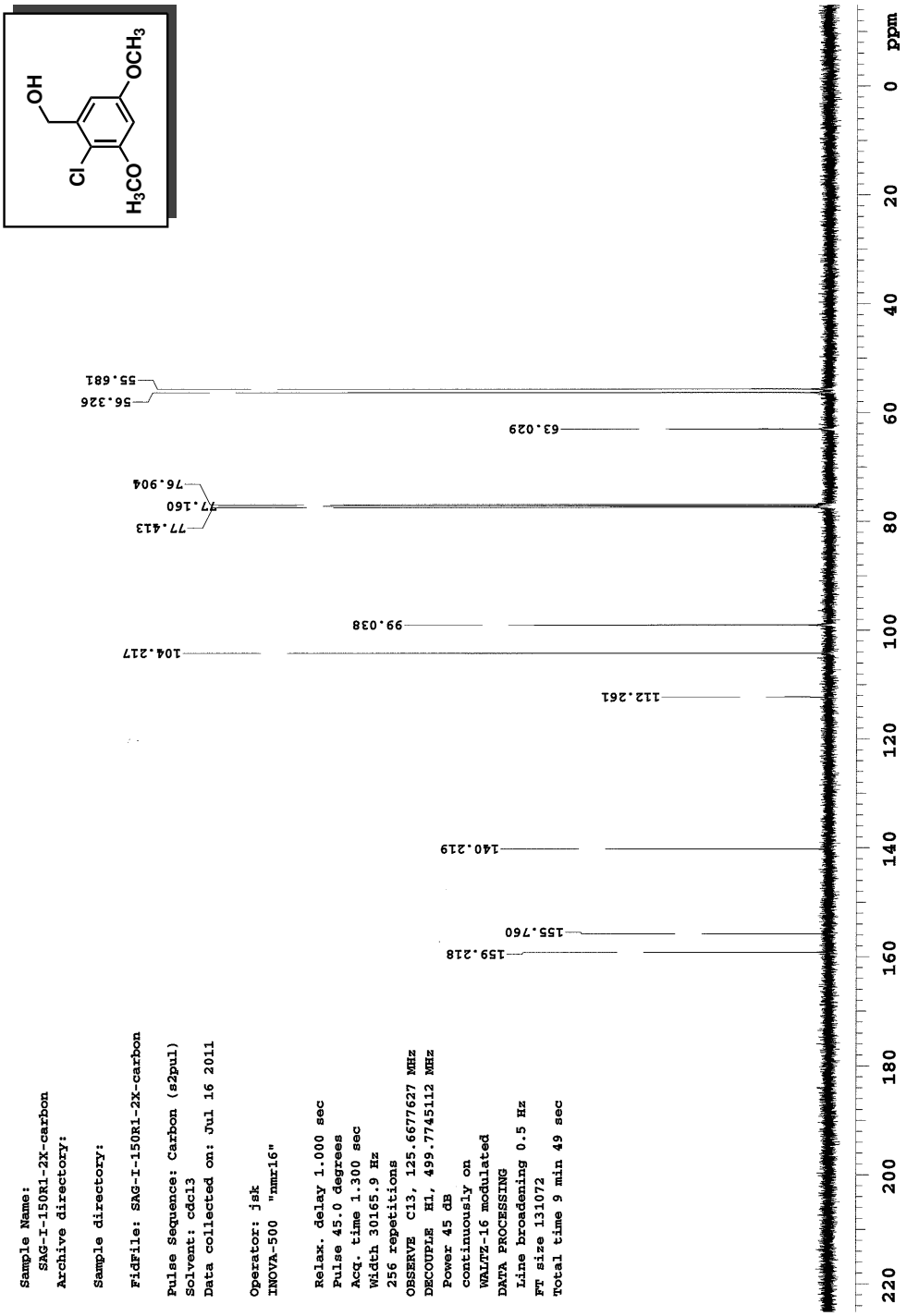


Figure 3.32: ^{1}H NMR of 1-(bromomethyl)-2-chloro-3,5-dimethoxybenzene (**3.85**)

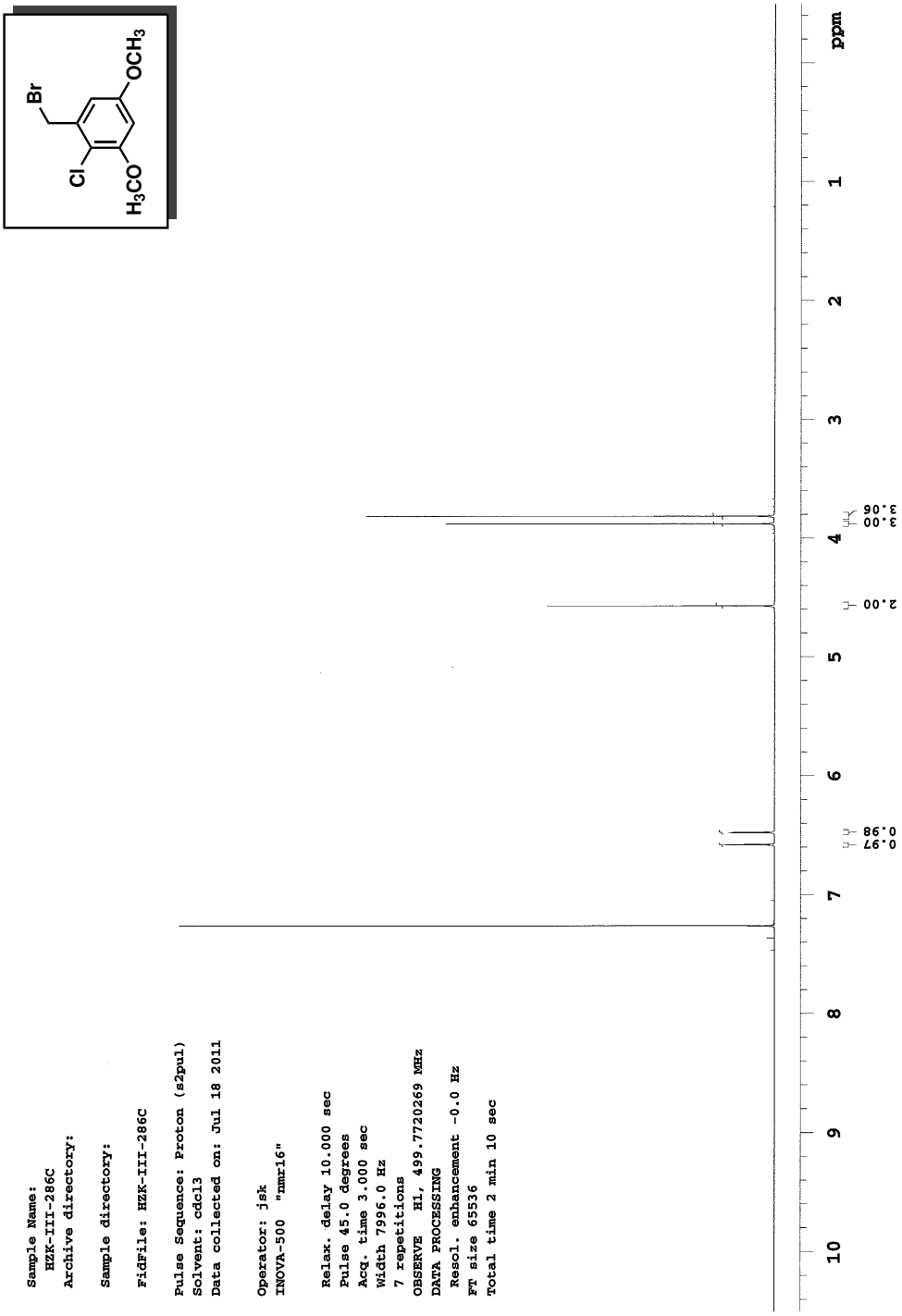


Figure 3.33: ^{13}C NMR of 1-(bromomethyl)-2-chloro-3,5-dimethoxybenzene (**3.85**)

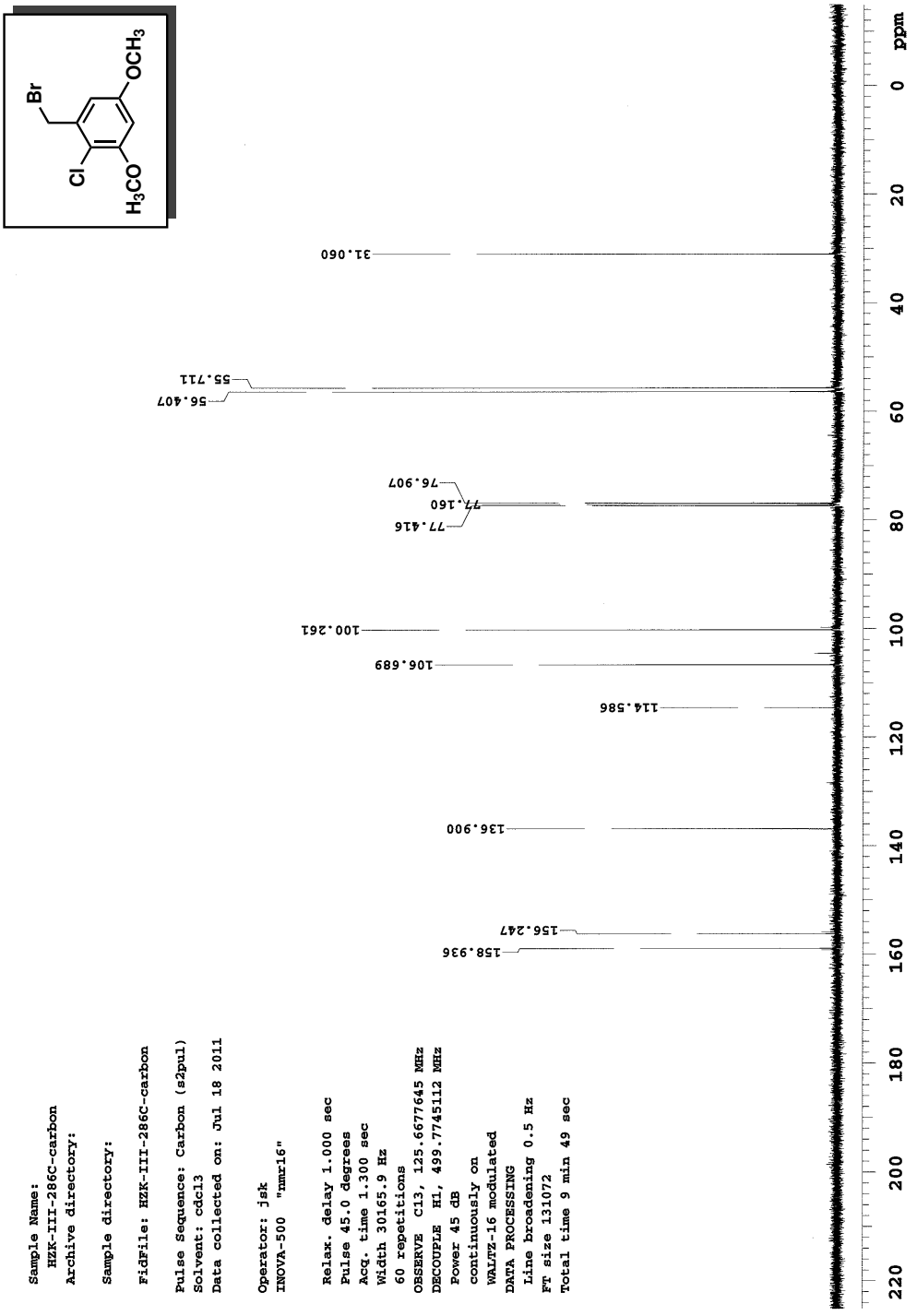


Figure 3.34: ^{1}H NMR of 2-chloro-1-(iodomethyl)-3,5-dimethoxybenzene (**3.52**)

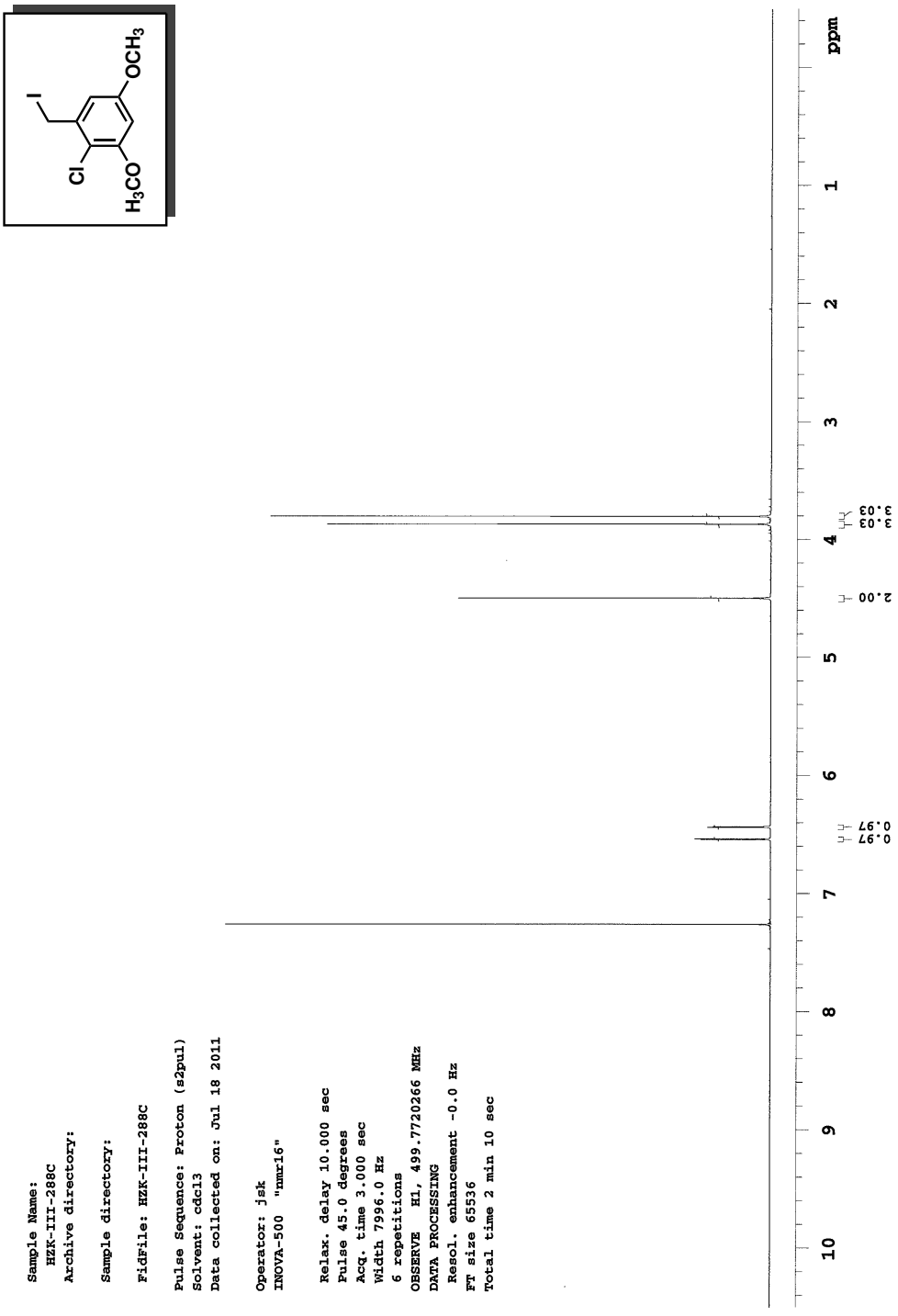


Figure 3.35: ^{13}C NMR of 2-chloro-1-(iodomethyl)-3,5-dimethoxybenzene (**3.52**)

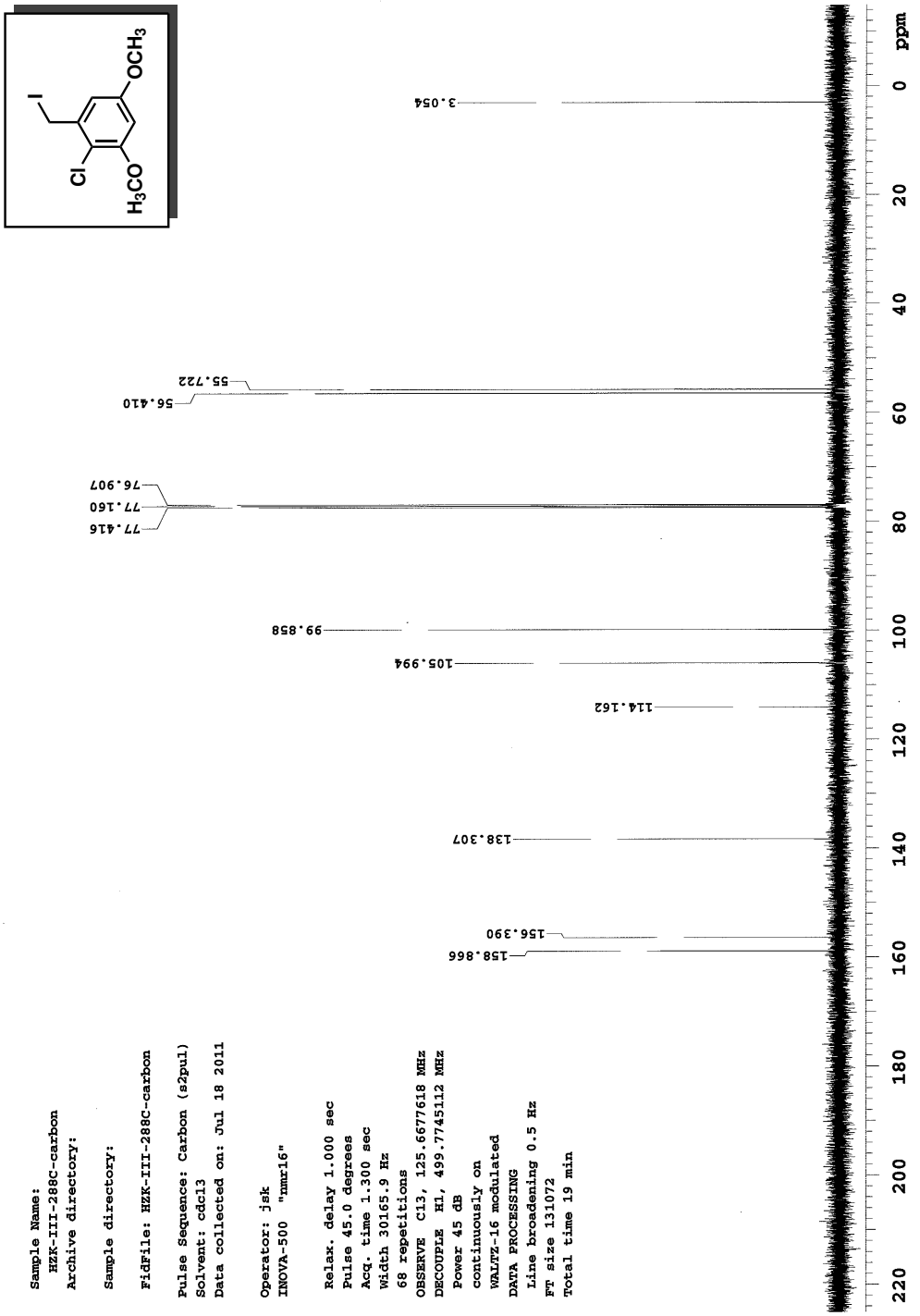


Figure 3.36: ^{1}H NMR of (±)-exocyclic ene-ol (**3.72**)

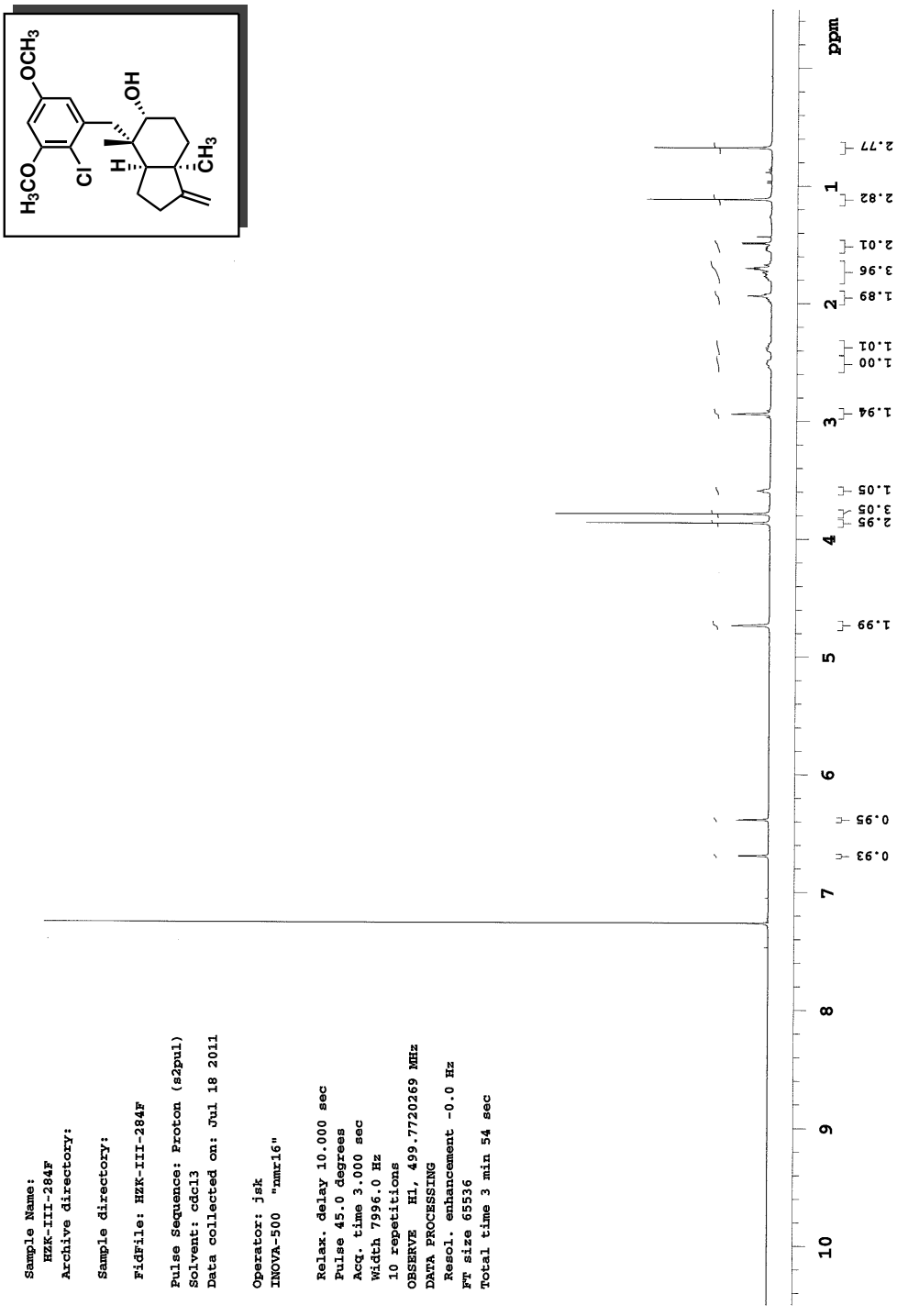


Figure 3.37: ^{13}C NMR of (±)-exocyclic ene-ol (**3.72**)

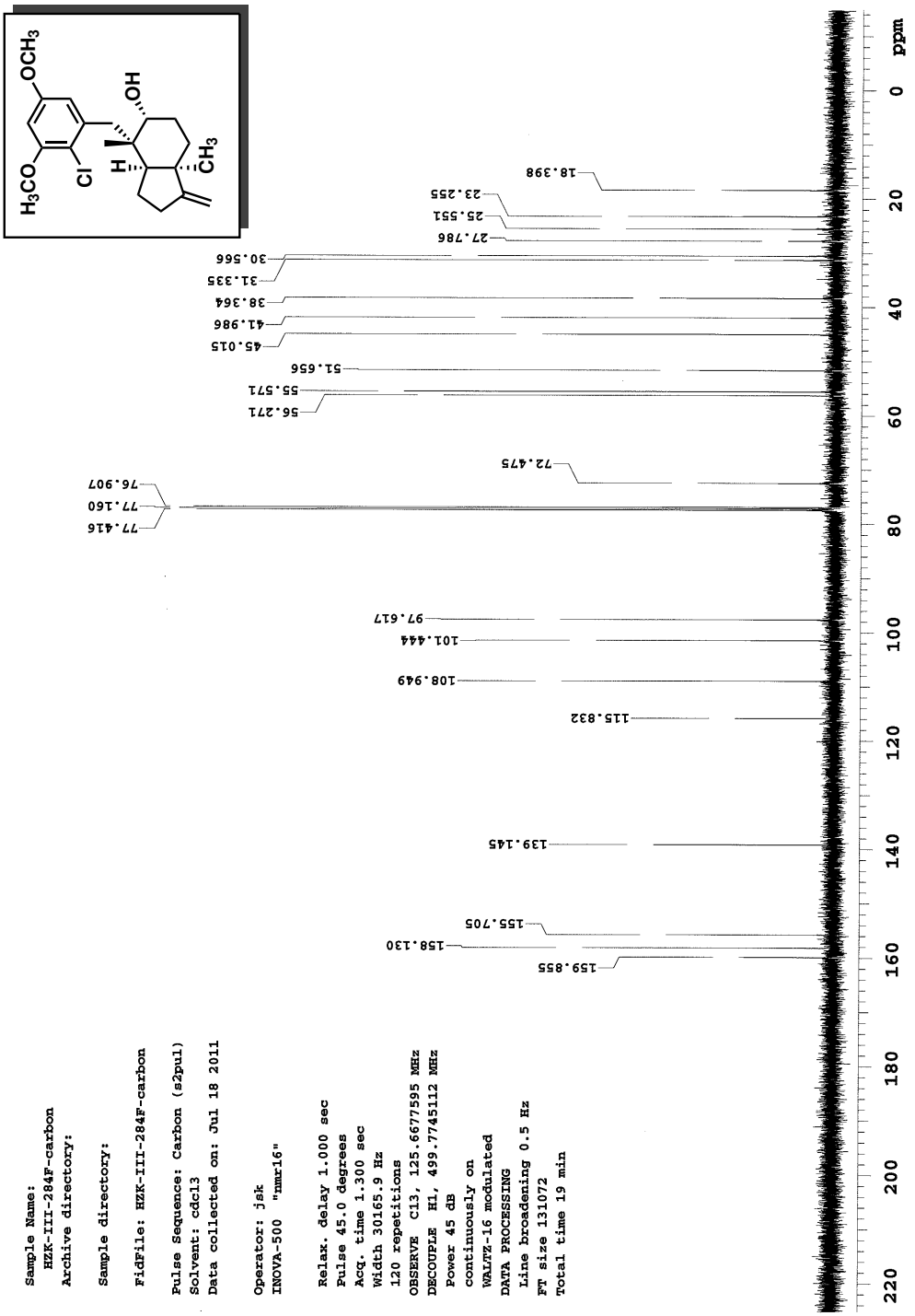
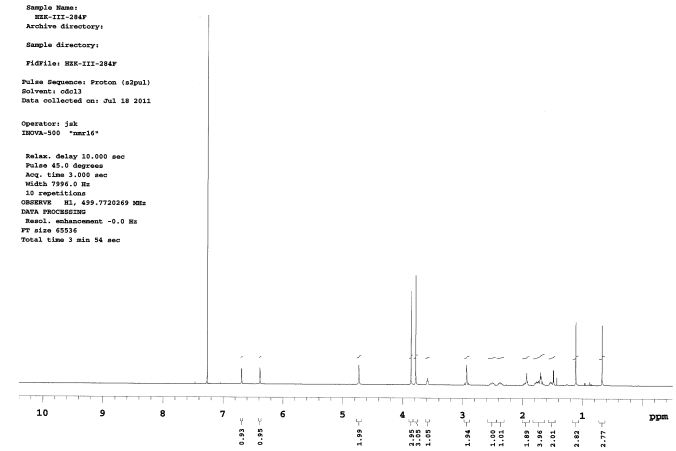
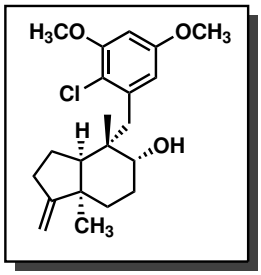
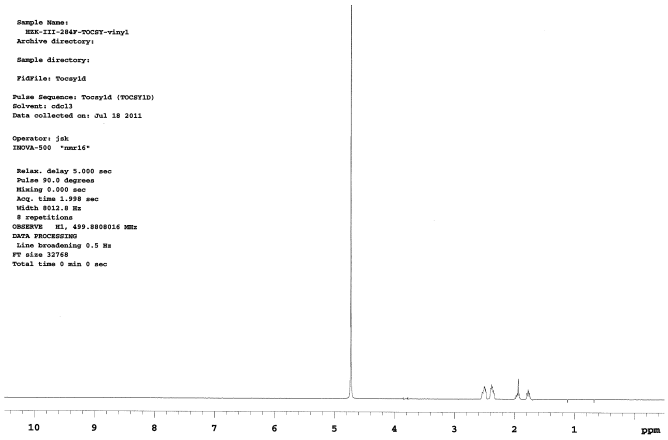


Figure 3.38: 1D TOCSY NMR of (±)-exocyclic ene-ol (**3.72**)

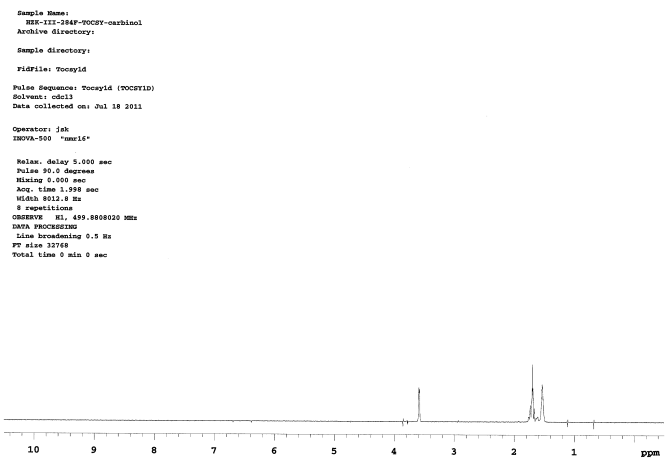






Irradiation of vinyl protons

5H in spin system



Irradiation of carbinol proton

4H in spin system

Figure 3.39: ^{1}H NMR of (−)-keto-*tert*-butyldimethylsilyl ether (**3.86**)

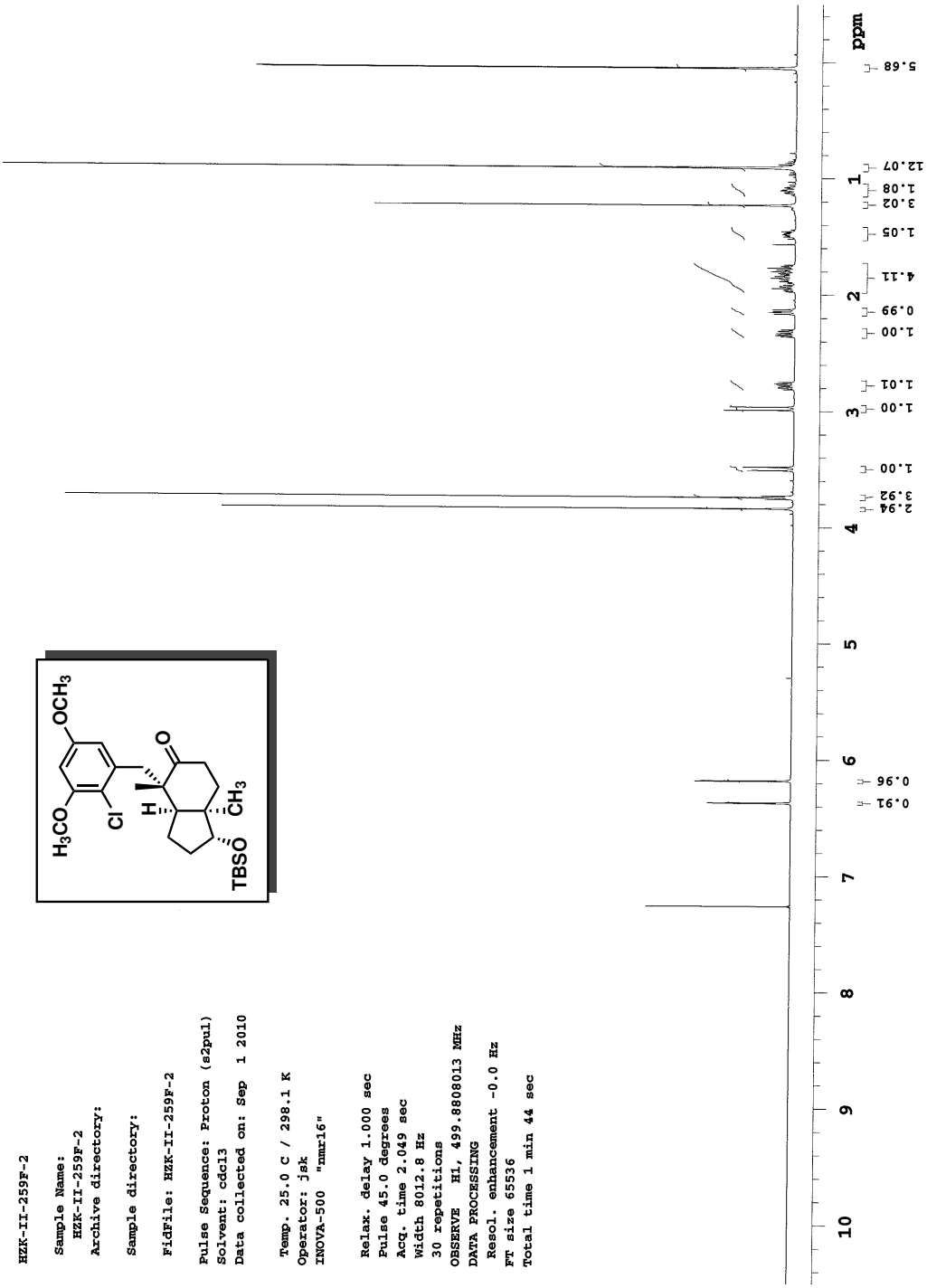


Figure 3.40: ^{13}C NMR of (−)-keto-*tert*-butyldimethylsilyl ether (**3.86**)

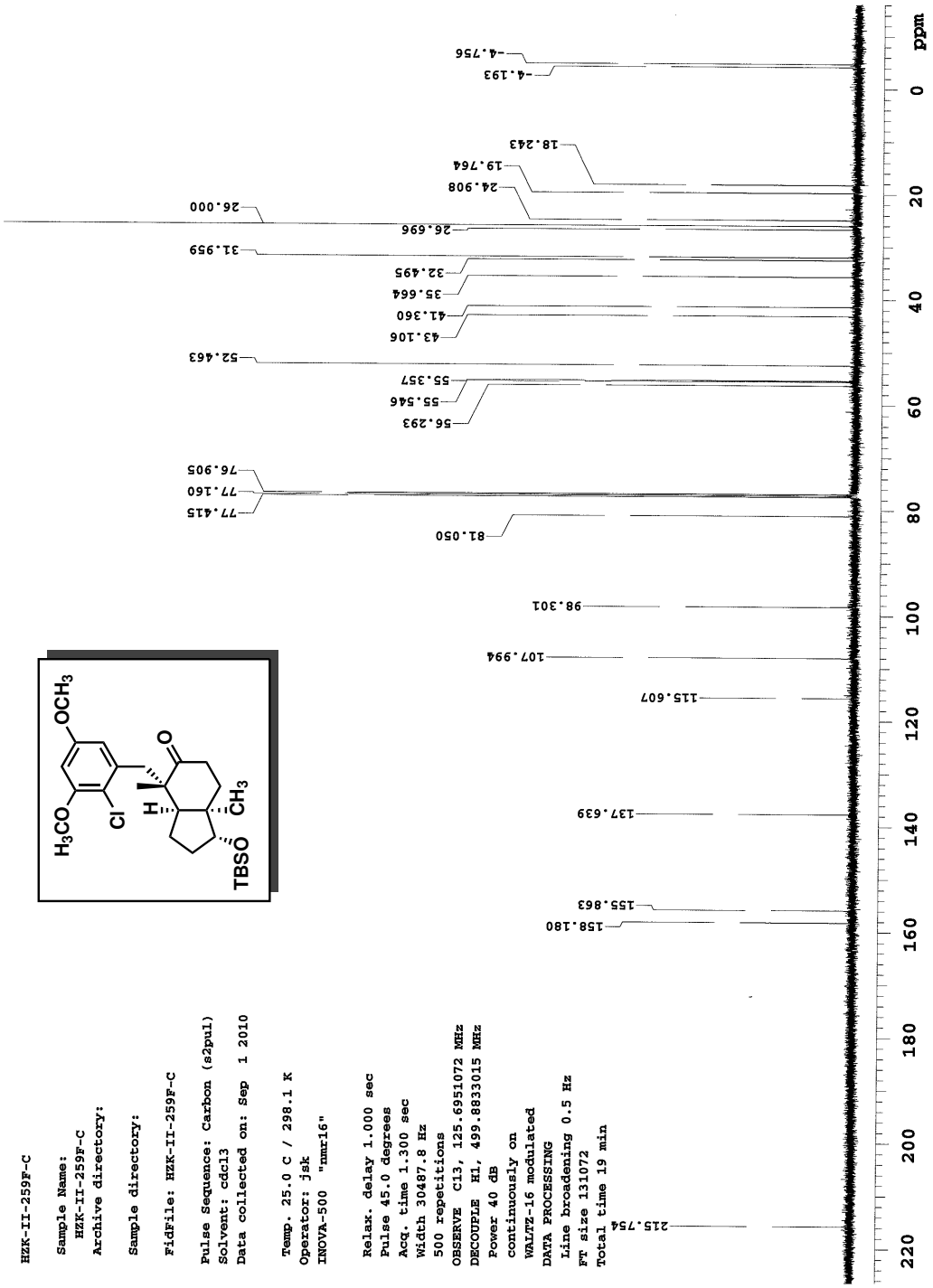


Figure 3.41: ^{1}H NMR of (+)-*tert*-butyldimethylsilyl ether-alkene (**3.56**)

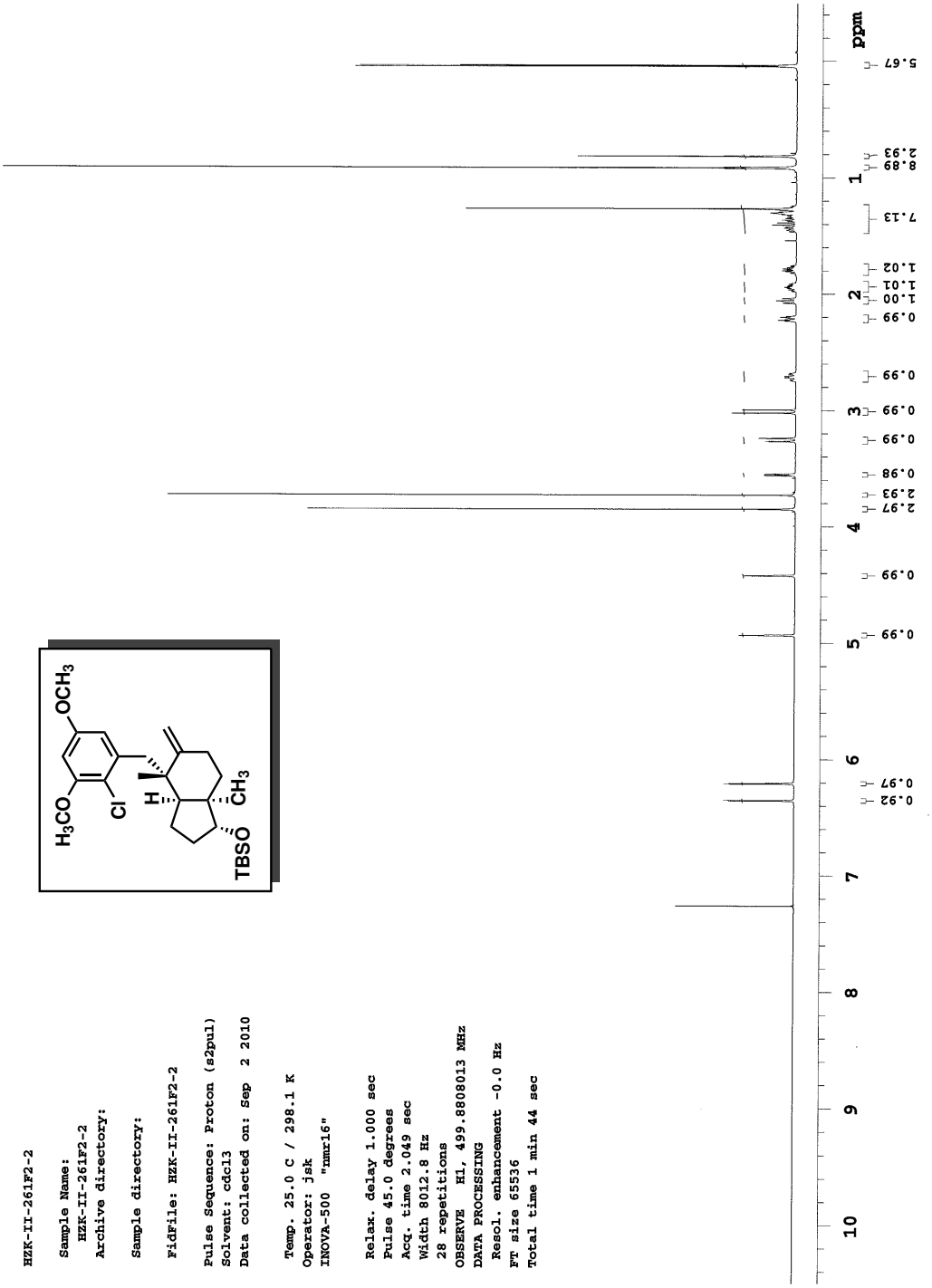


Figure 3.42: ^{13}C NMR of (+)-*tert*-butyldimethylsilyl ether-alkene (**3.56**)

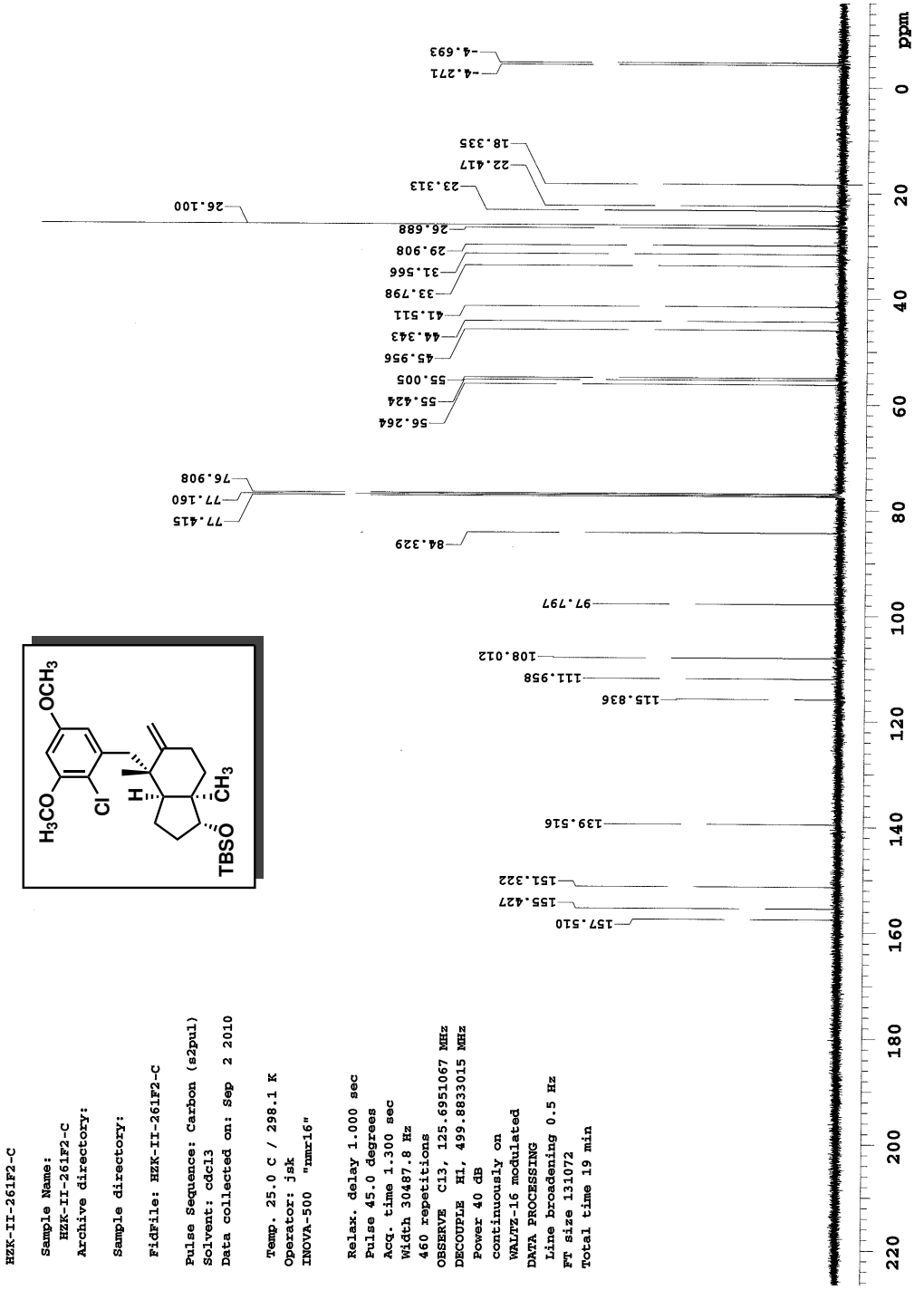


Figure 3.43: ^{1}H NMR of (−)-trisubstituted ene-ol (**3.87**)

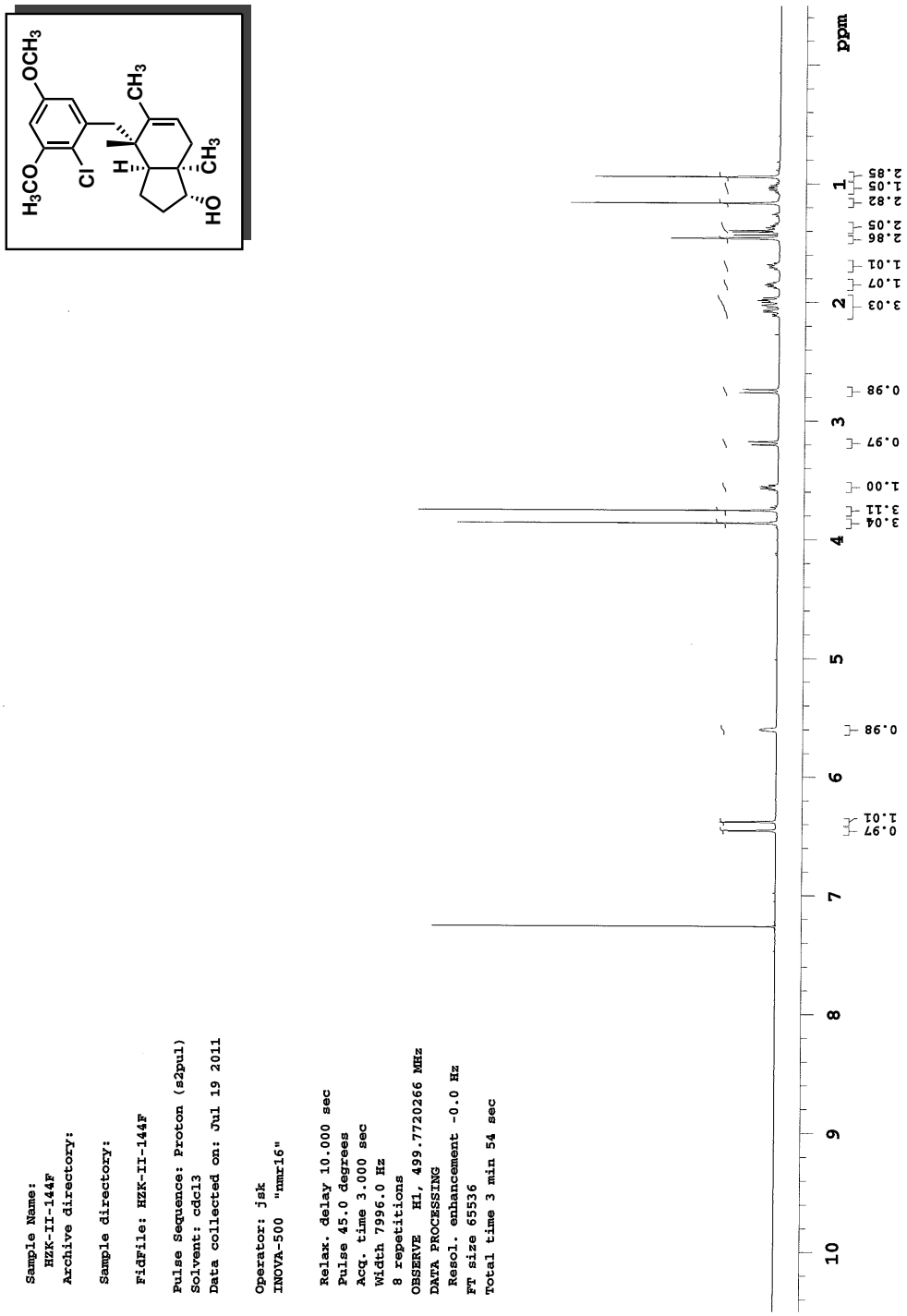


Figure 3.44: ^{13}C NMR of (−)-trisubstituted ene-ol (**3.87**)

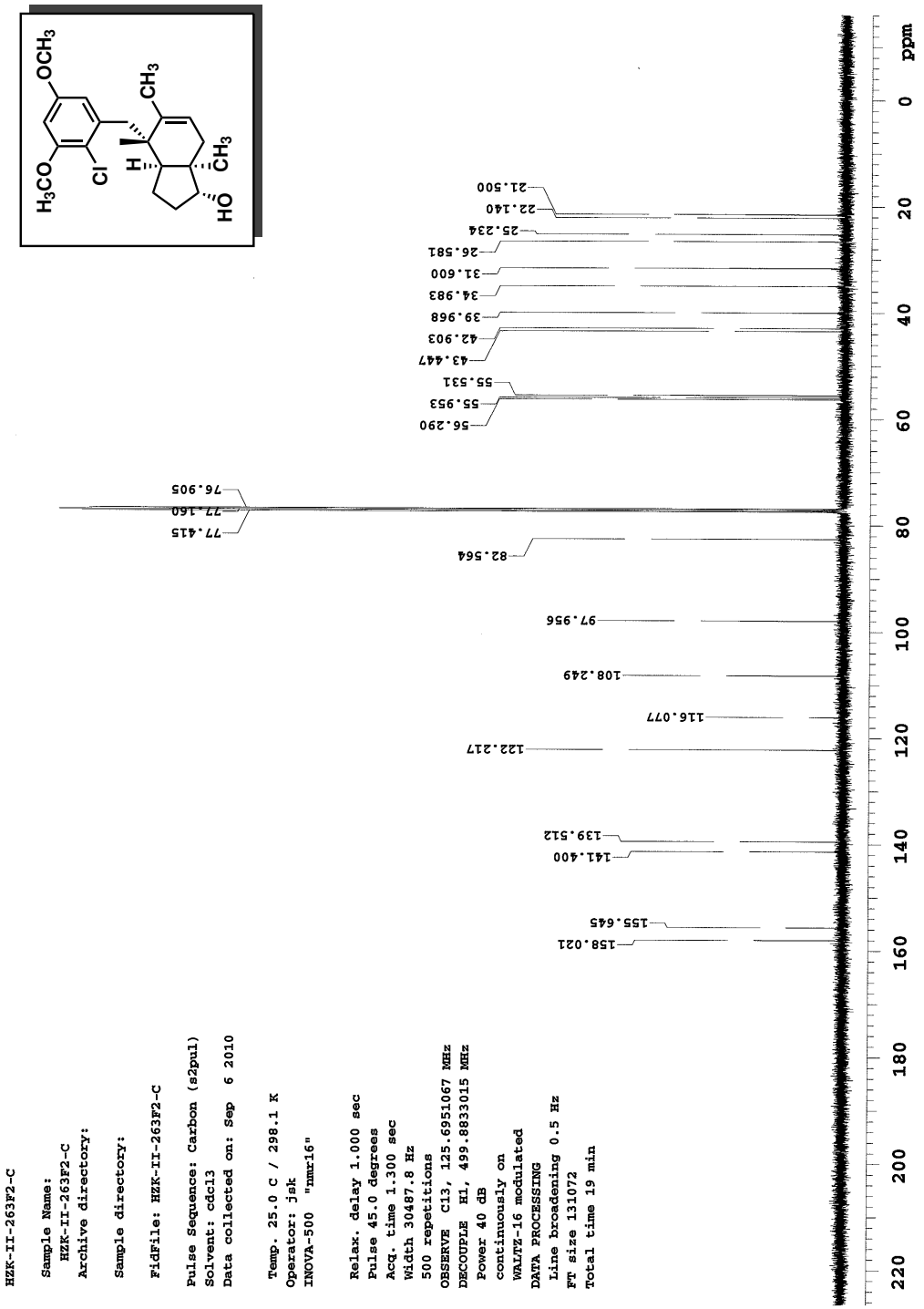


Figure 3.45: ^{1}H NMR of (−)-trisubstituted ene-one (**3.50**)

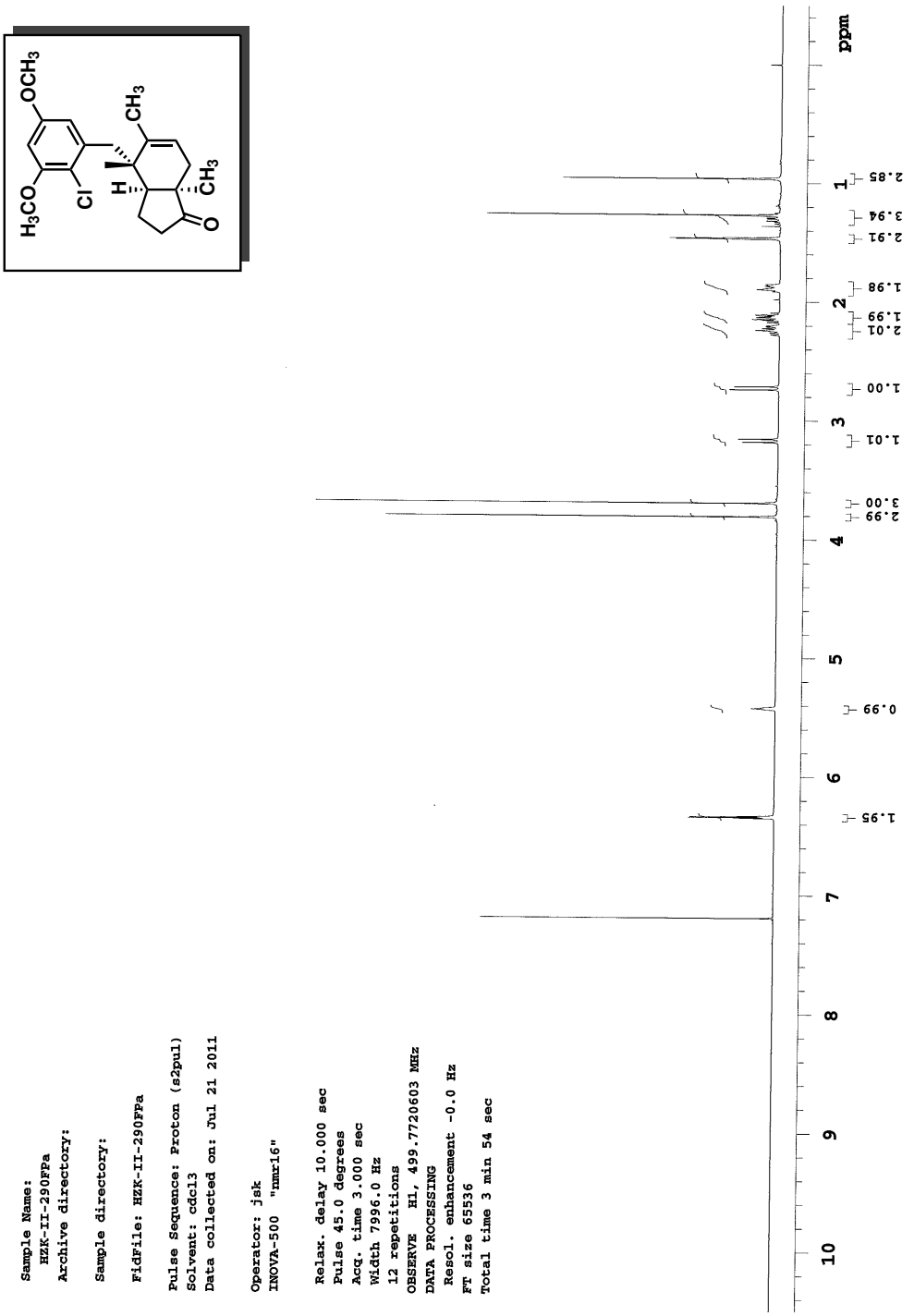


Figure 3.46: ^{13}C NMR of (−)-trisubstituted ene-one (**3.50**)

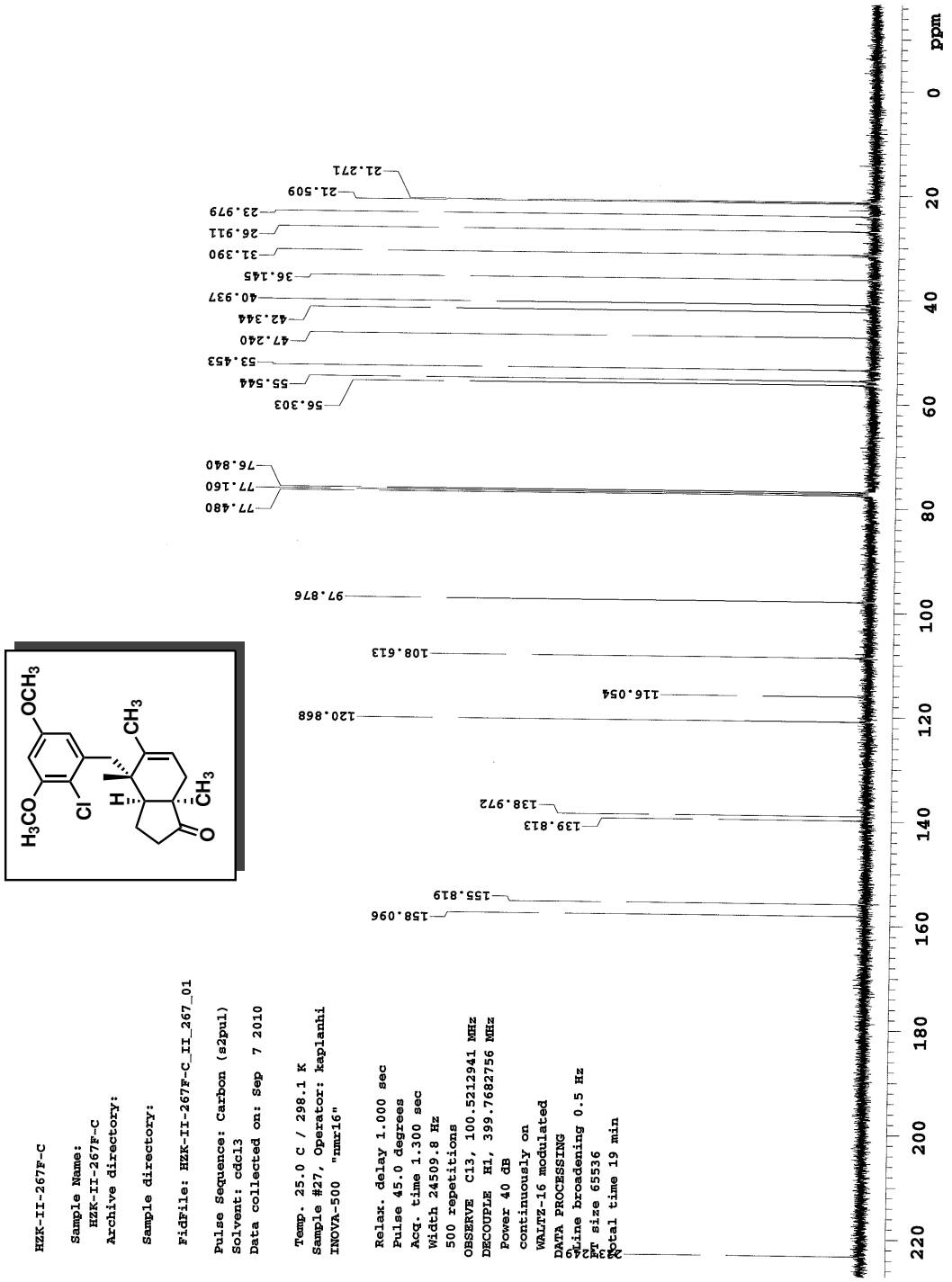


Figure 3.47: ^{1}H NMR of ($\pm$)-β-methyl ketone (**3.57**)

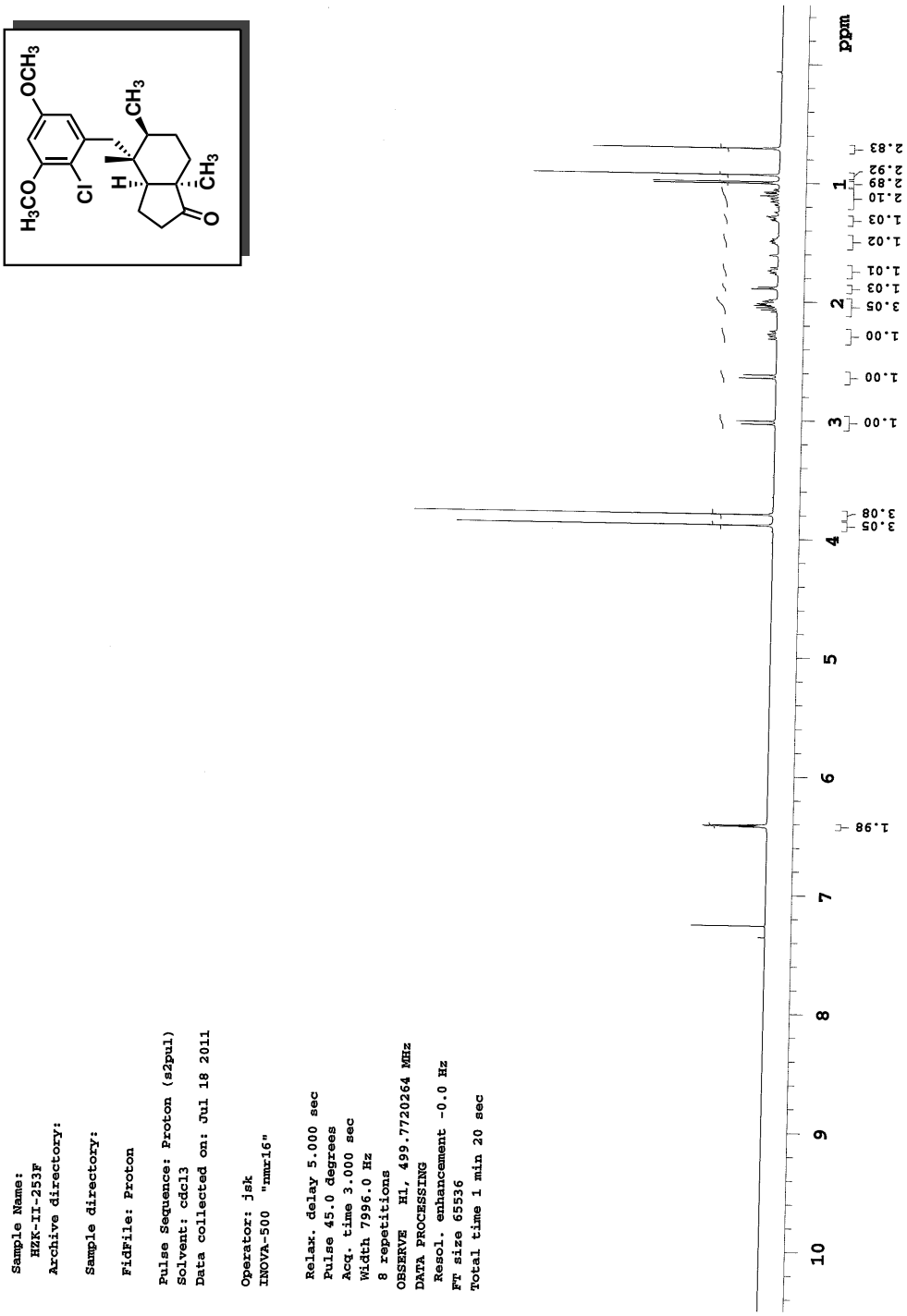


Figure 3.48: ^{13}C NMR of (±)-β-methyl ketone (**3.57**)

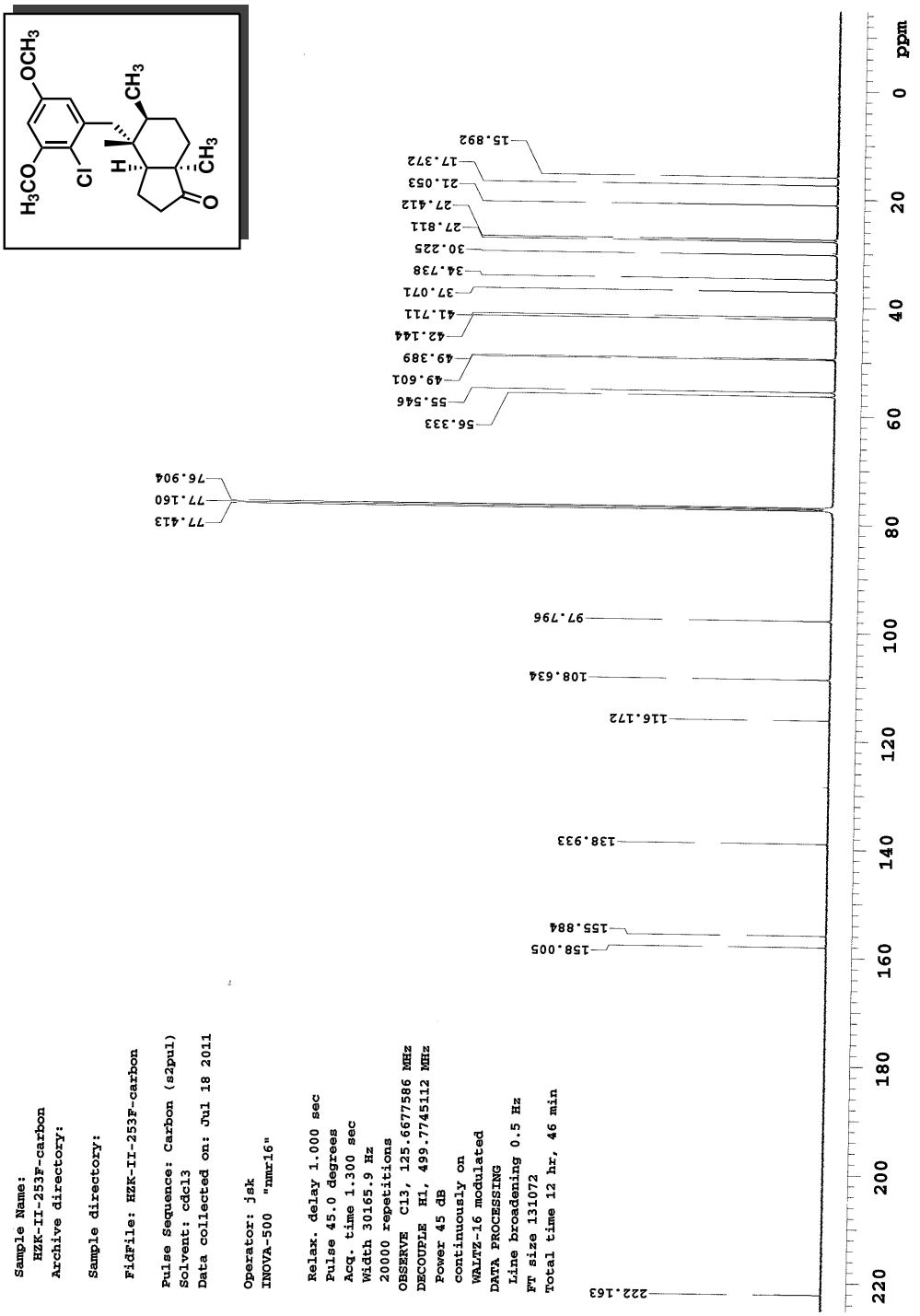


Figure 3.49: ^{1}H NMR of ($\pm$)-α-methyl ketone (**3.58**)

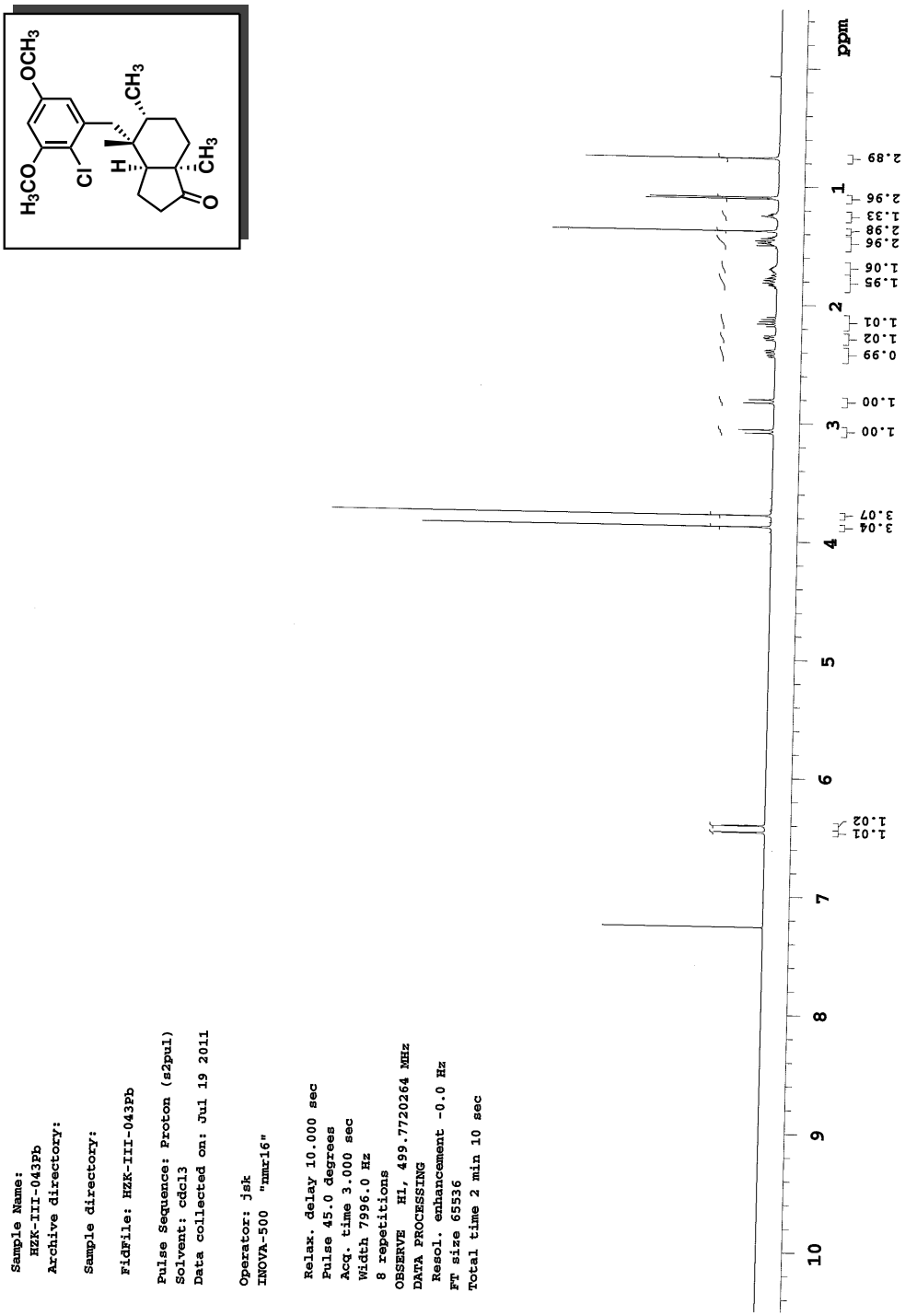


Figure 3.50: ^{13}C NMR of (±)-α-methyl ketone (**3.58**)

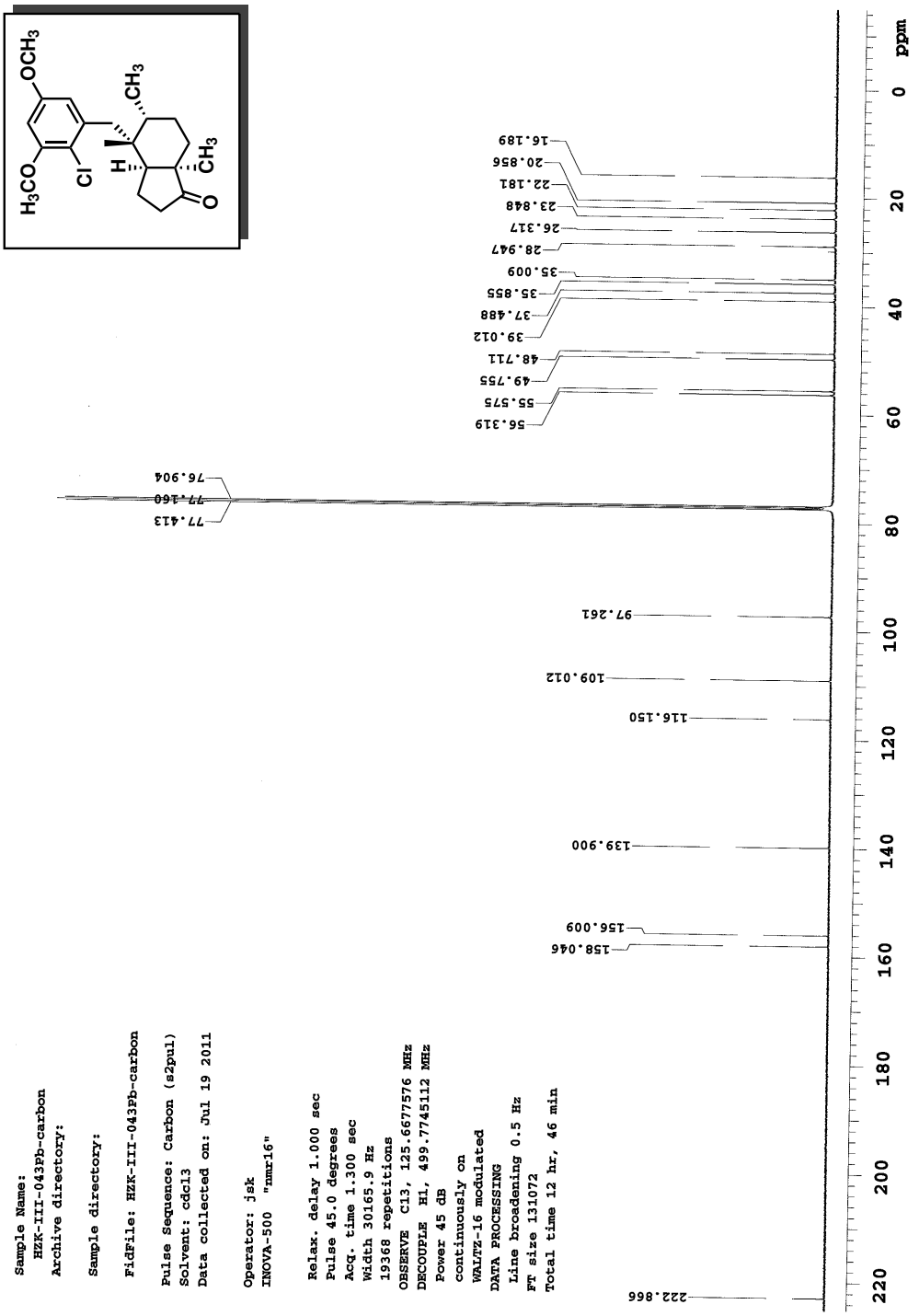


Figure 3.51: ^{1}H NMR of (+)-ene-decalone (**3.59**)

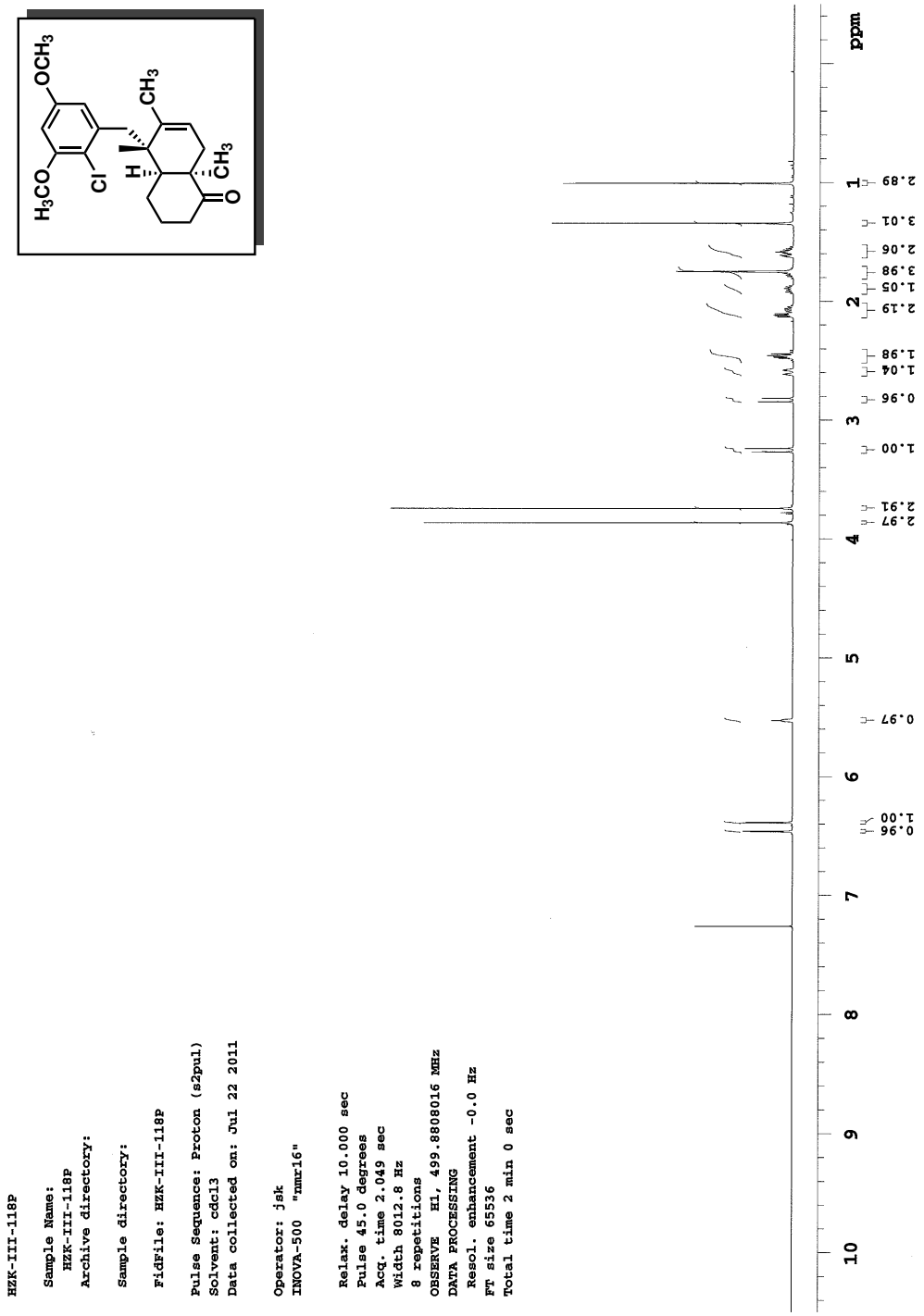


Figure 3.52: ^{13}C NMR of (+)-ene-decalone (**3.59**)

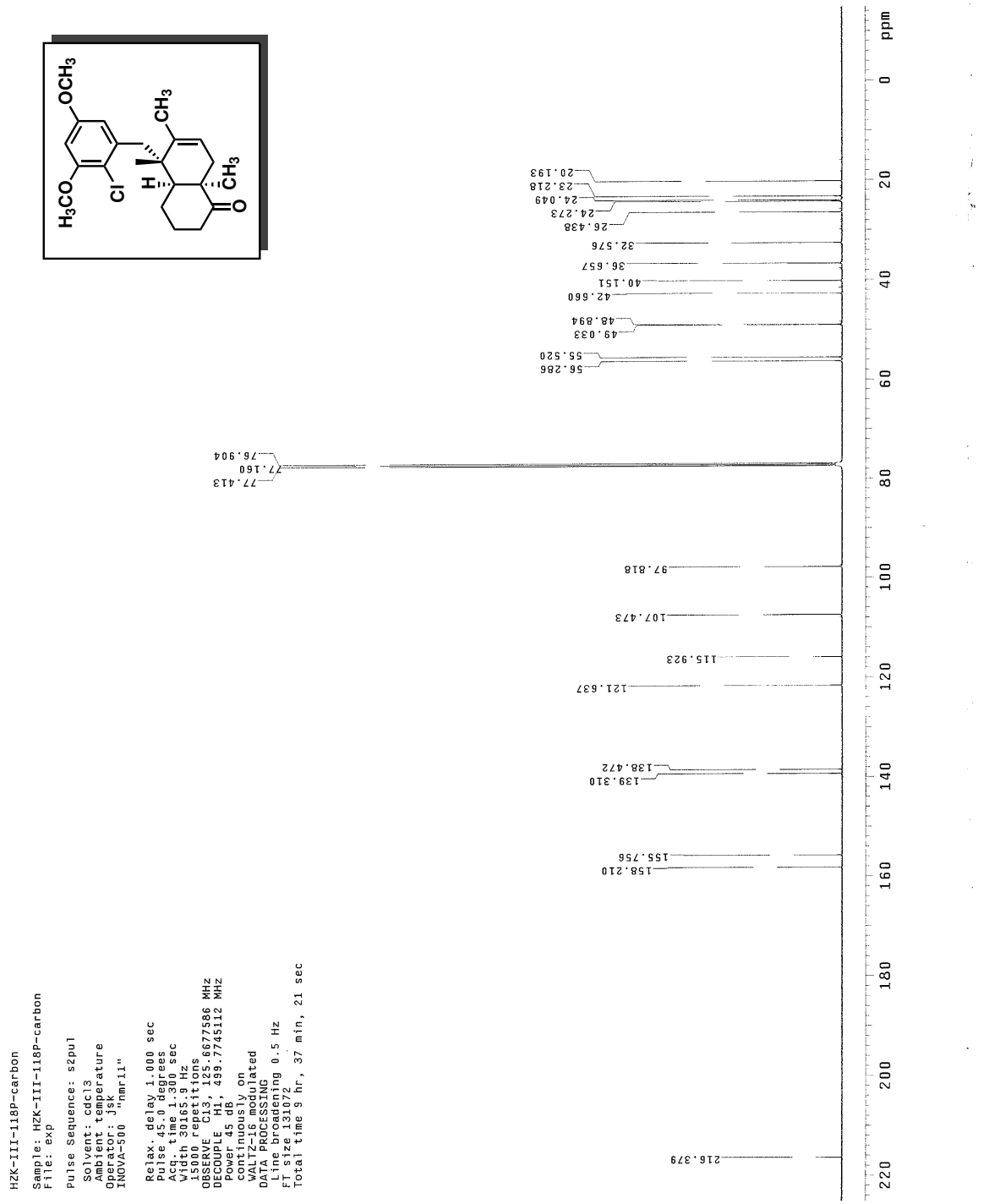


Figure 3.53: ^{1}H NMR of (2-(benzyloxy)-6-chloro-3-methoxyphenyl)methanol (**3.62**)

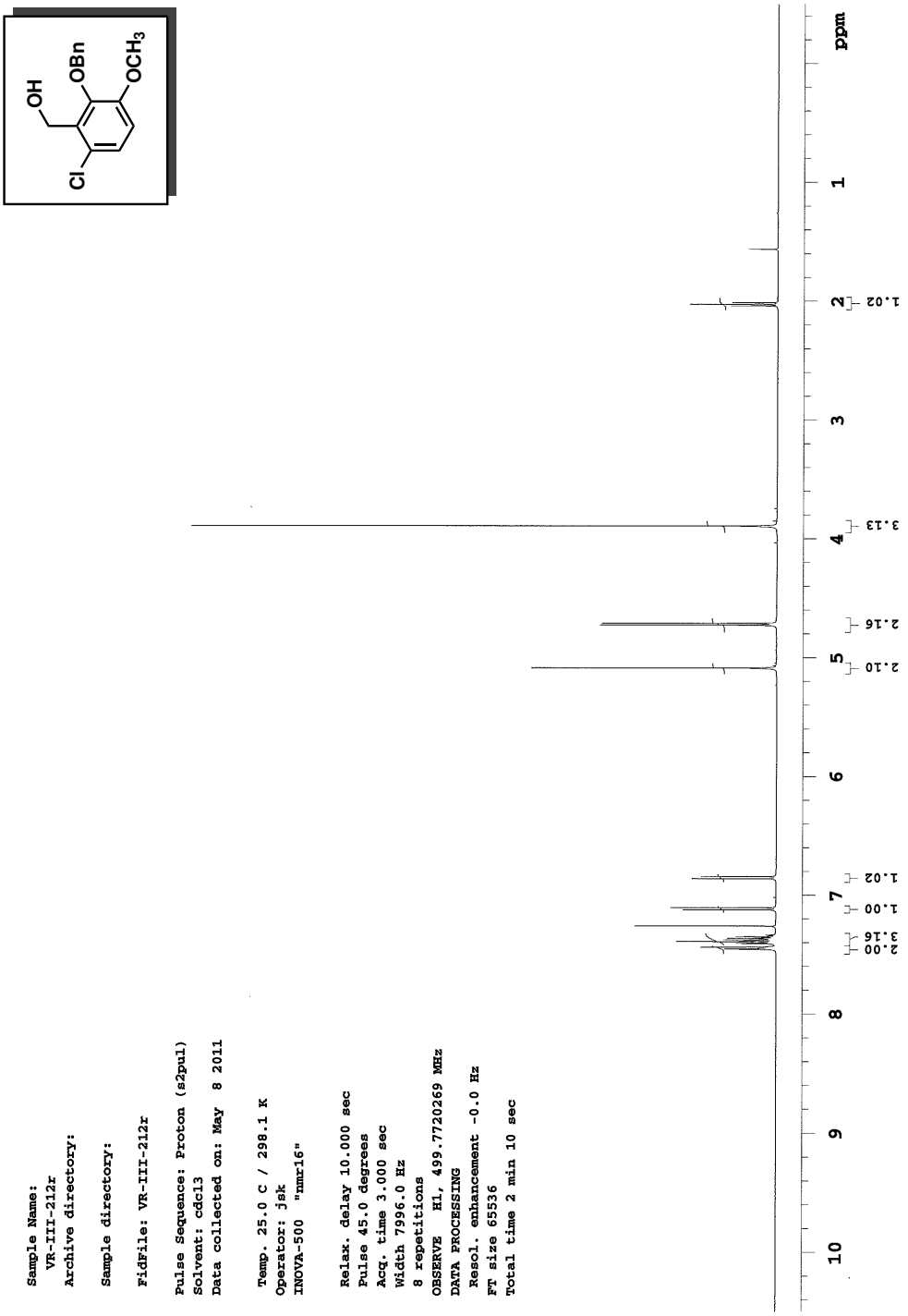


Figure 3.54: ^{13}C NMR of (2-(benzyloxy)-6-chloro-3-methoxyphenyl)methanol (**3.62**)

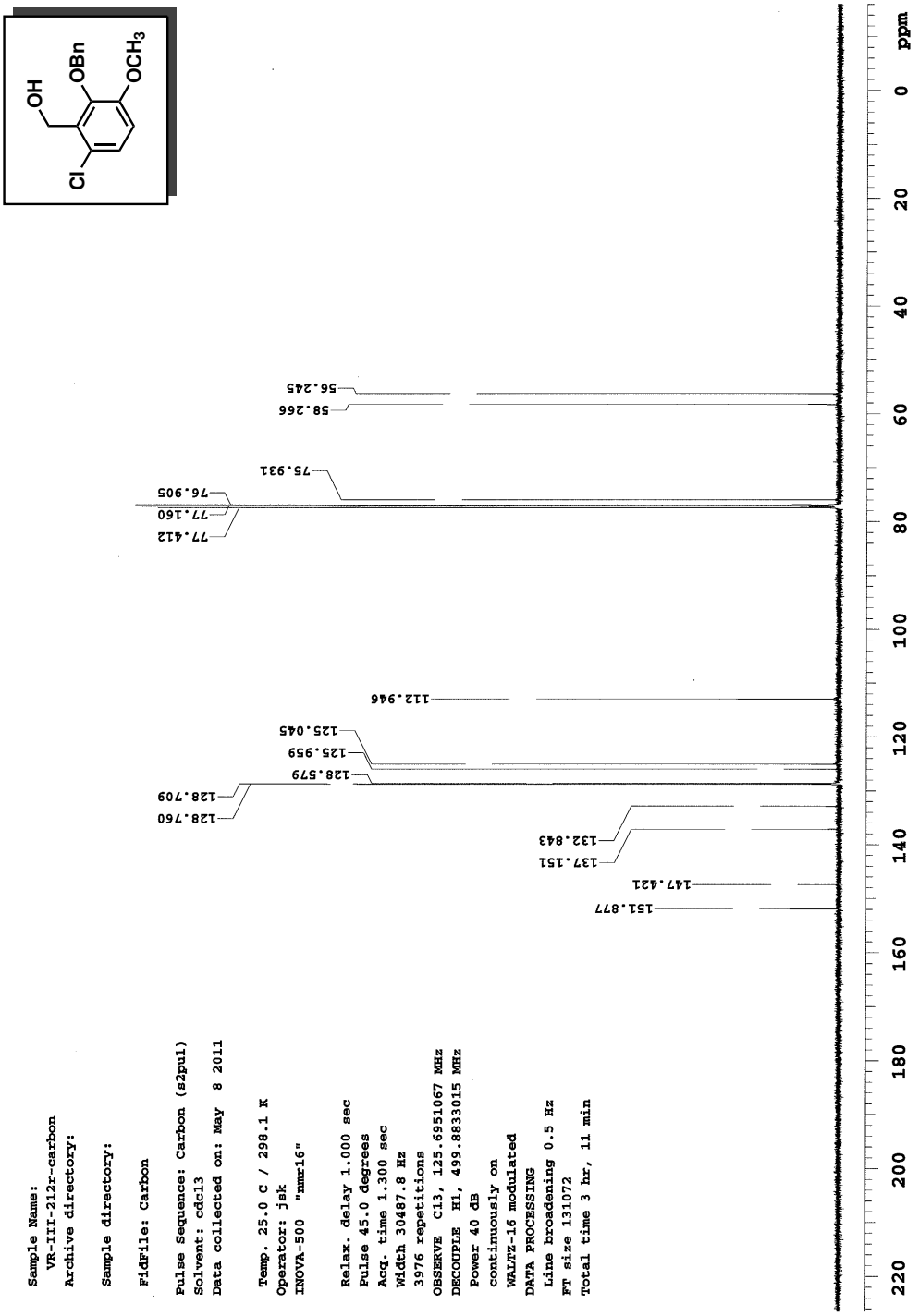


Figure 3.55: ^{1}H NMR of 2-(benzyloxy)-3-(bromomethyl)-4-chloro-1-methoxybenzene (**3.88**)

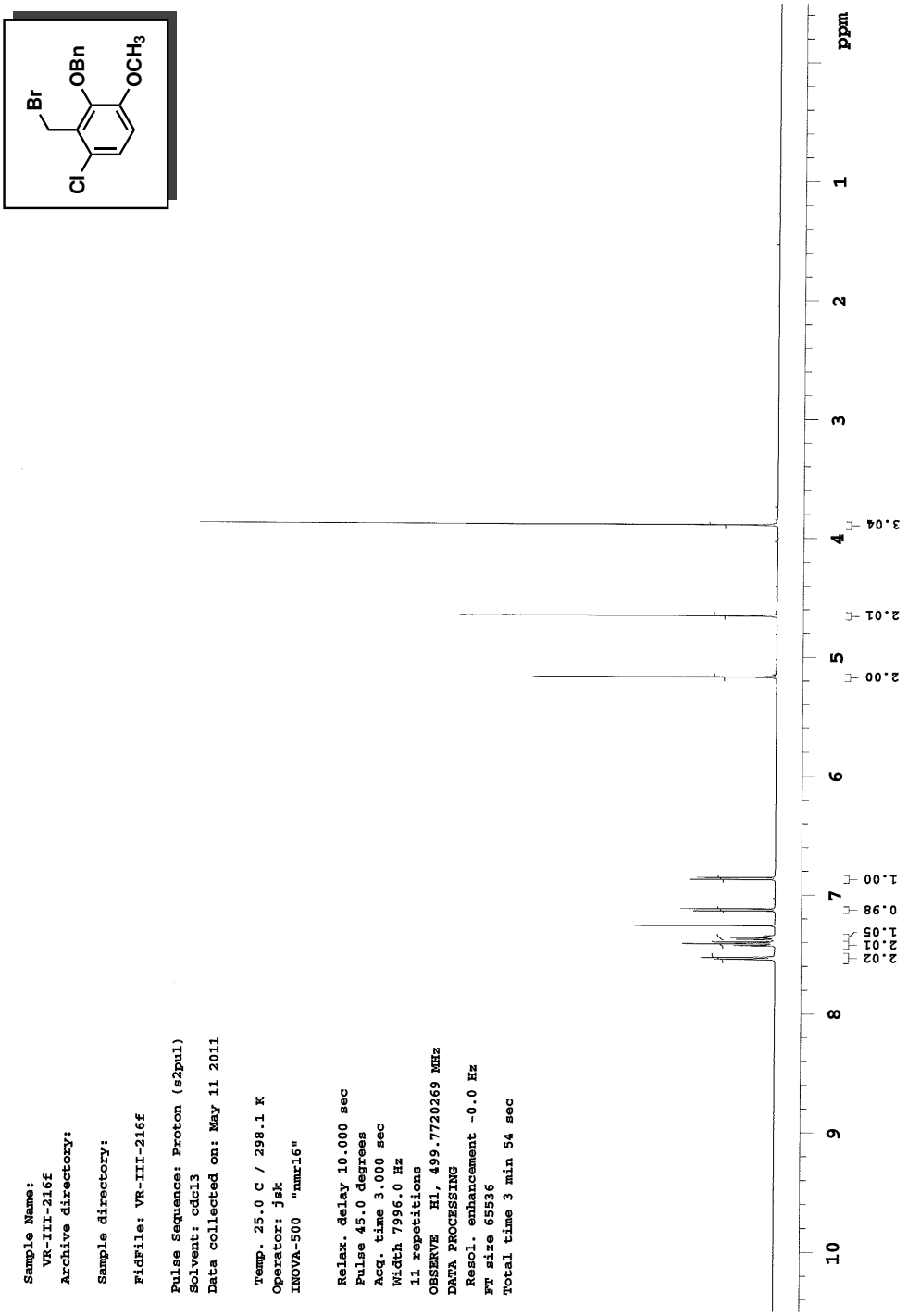


Figure 3.56: ^{13}C NMR of 2-(benzyloxy)-3-(bromomethyl)-4-chloro-1-methoxybenzene (**3.88**)

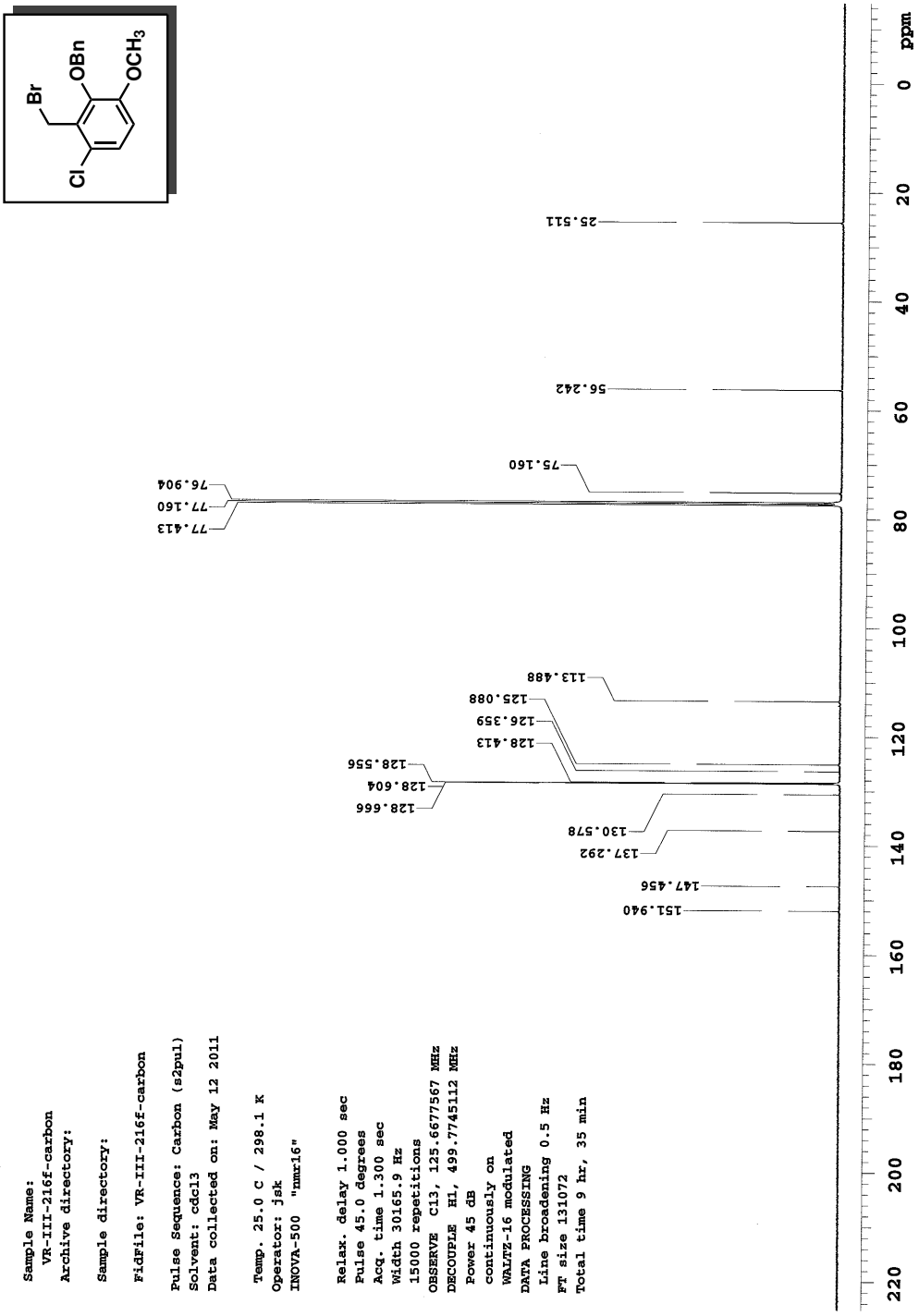


Figure 3.57: ^{1}H NMR of 2-(benzyloxy)-4-chloro-3-(iodomethyl)-1-methoxybenzene (**3.63**)

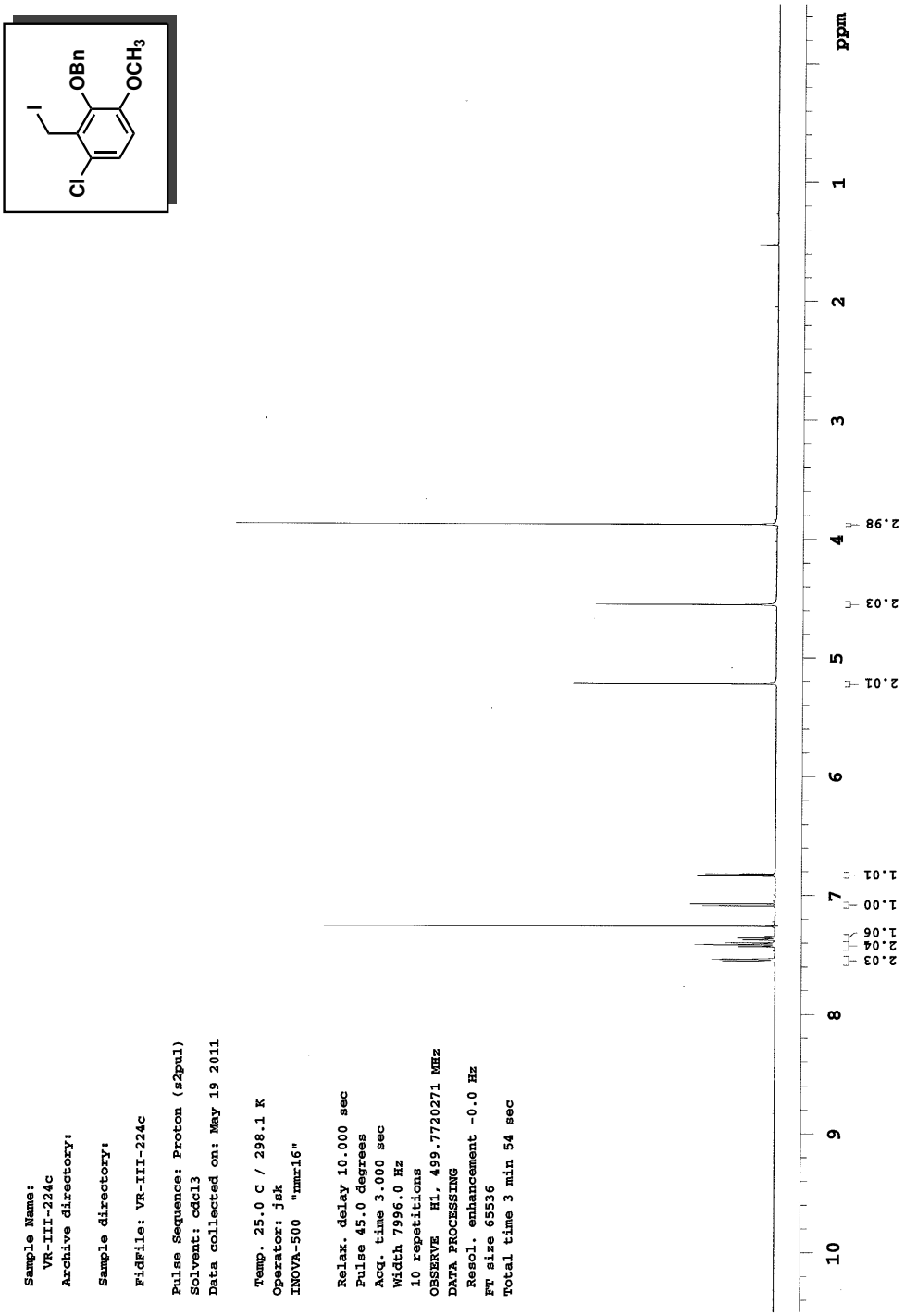


Figure 3.58: ^{13}C NMR of 2-(benzyloxy)-4-chloro-3-(iodomethyl)-1-methoxybenzene (**3.63**)

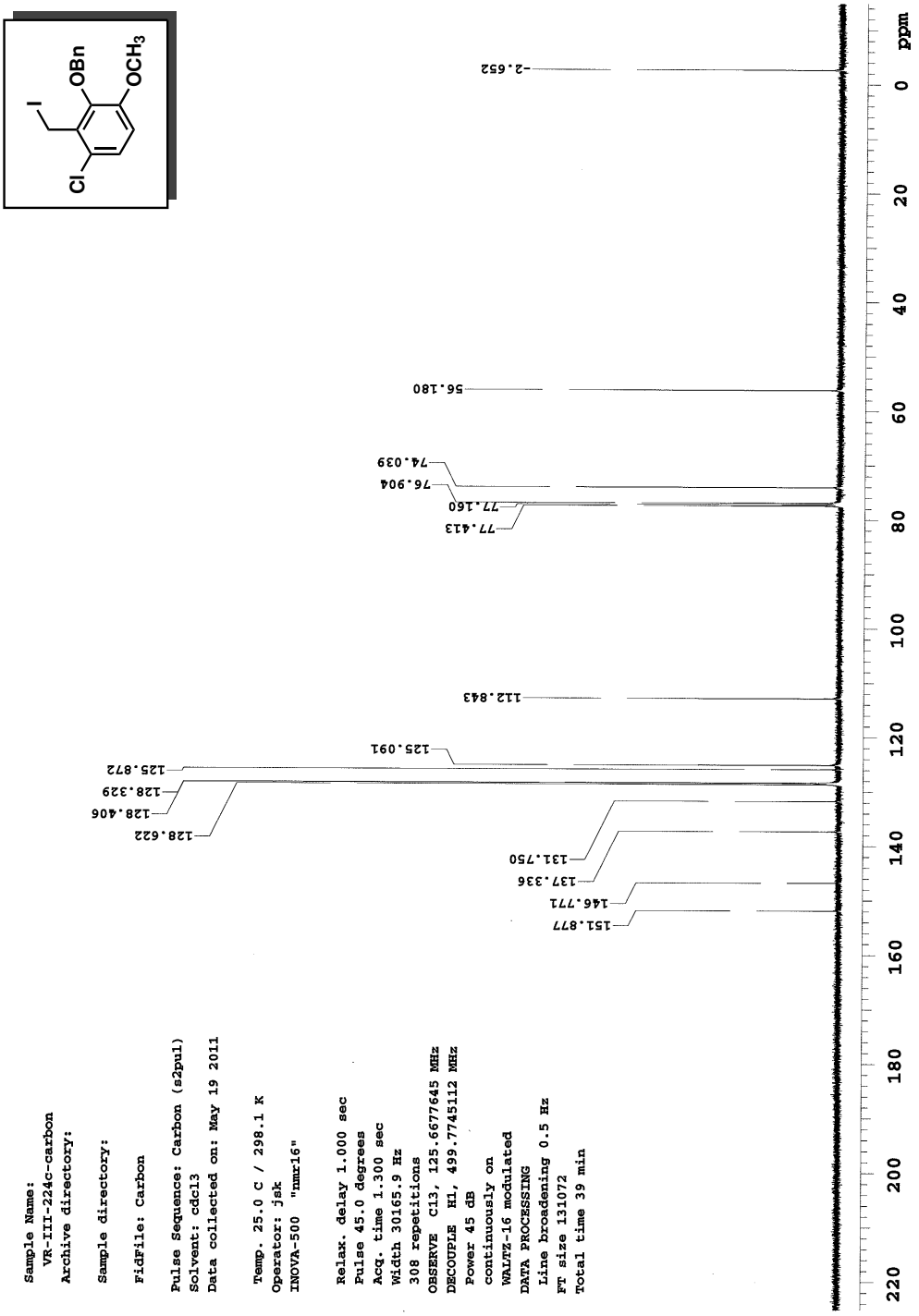


Figure 3.59: ^{1}H NMR of (±)-decahydrocyclopenta[*a*]xanthene (**3.74**)

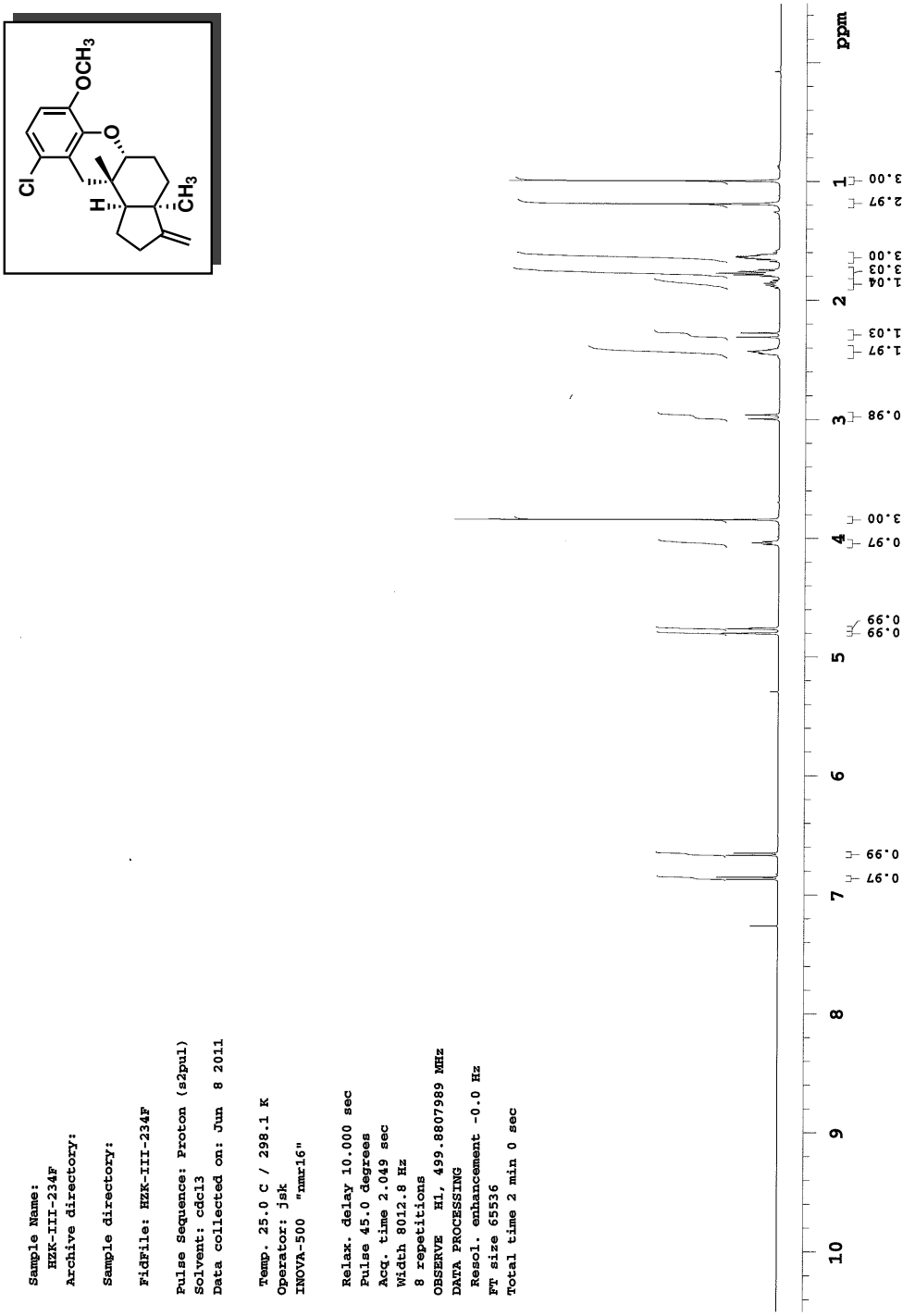


Figure 3.60: ^{13}C NMR of (±)-decahydrocyclopenta[*a*]xanthene (**3.74**)

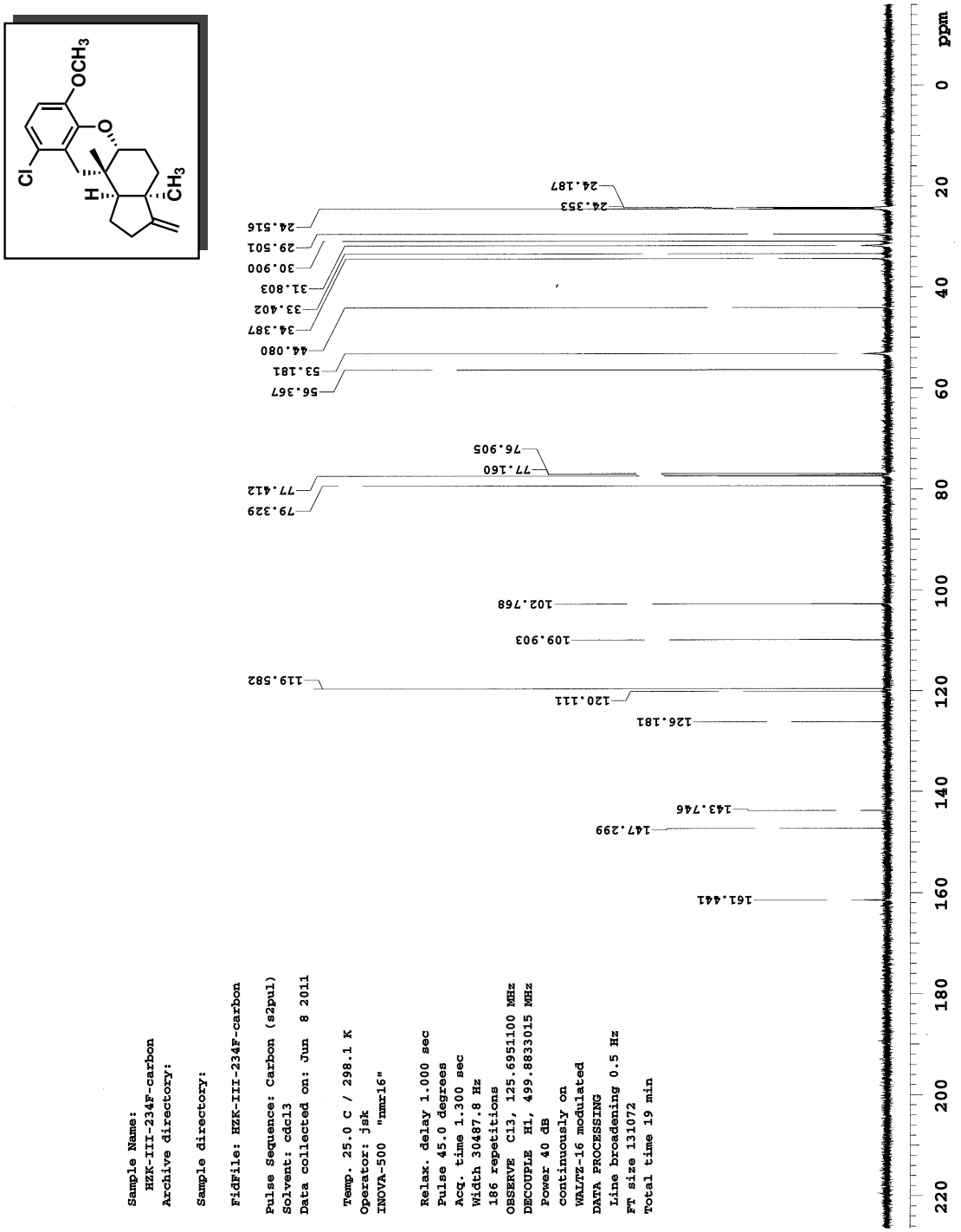


Figure 3.61: ^{1}H NMR of (−)-keto-*tert*-butyldimethylsilyl ether (**3.89**)

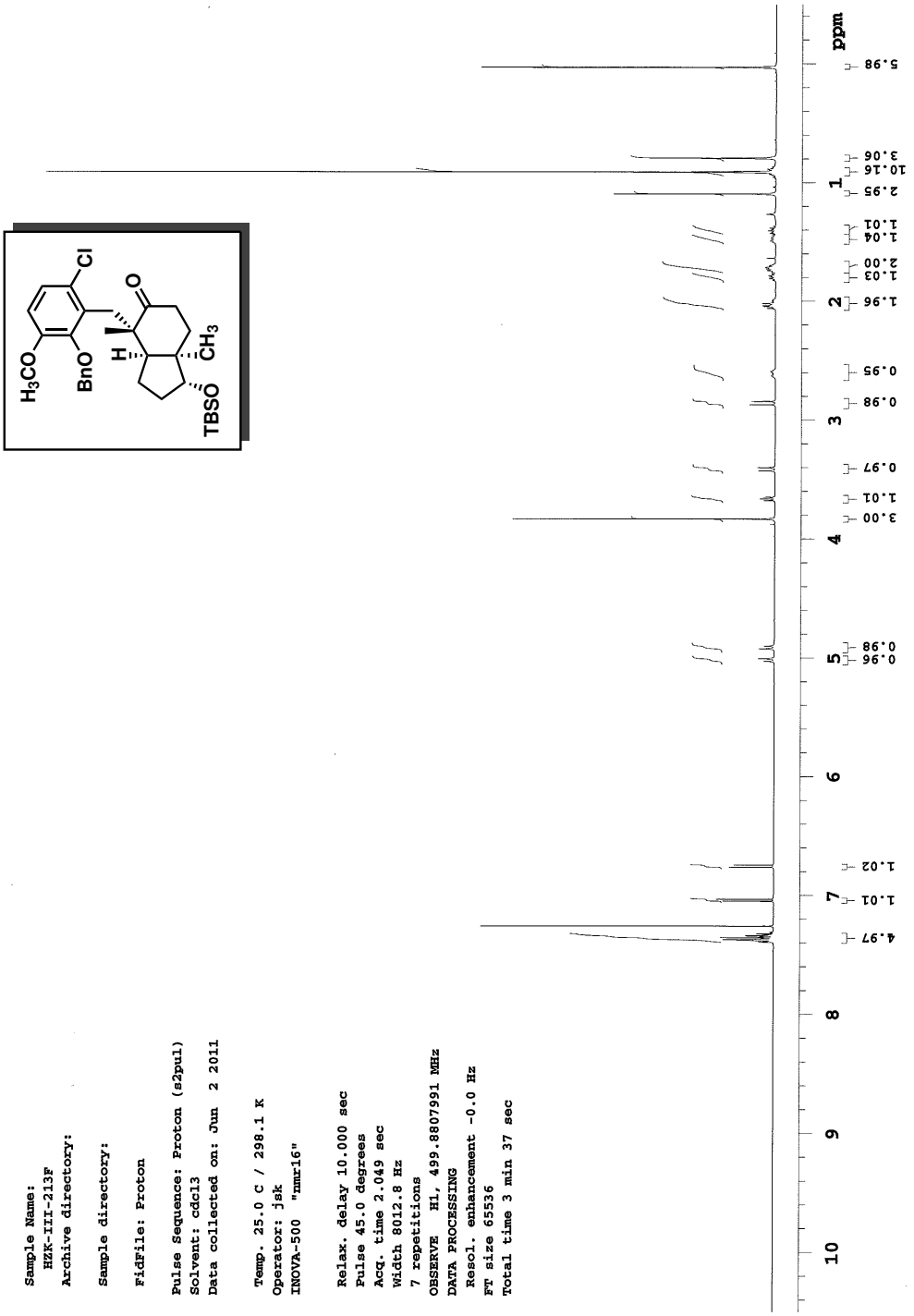


Figure 3.62: ^{13}C NMR of (−)-keto-*tert*-butyldimethylsilyl ether (**3.89**)

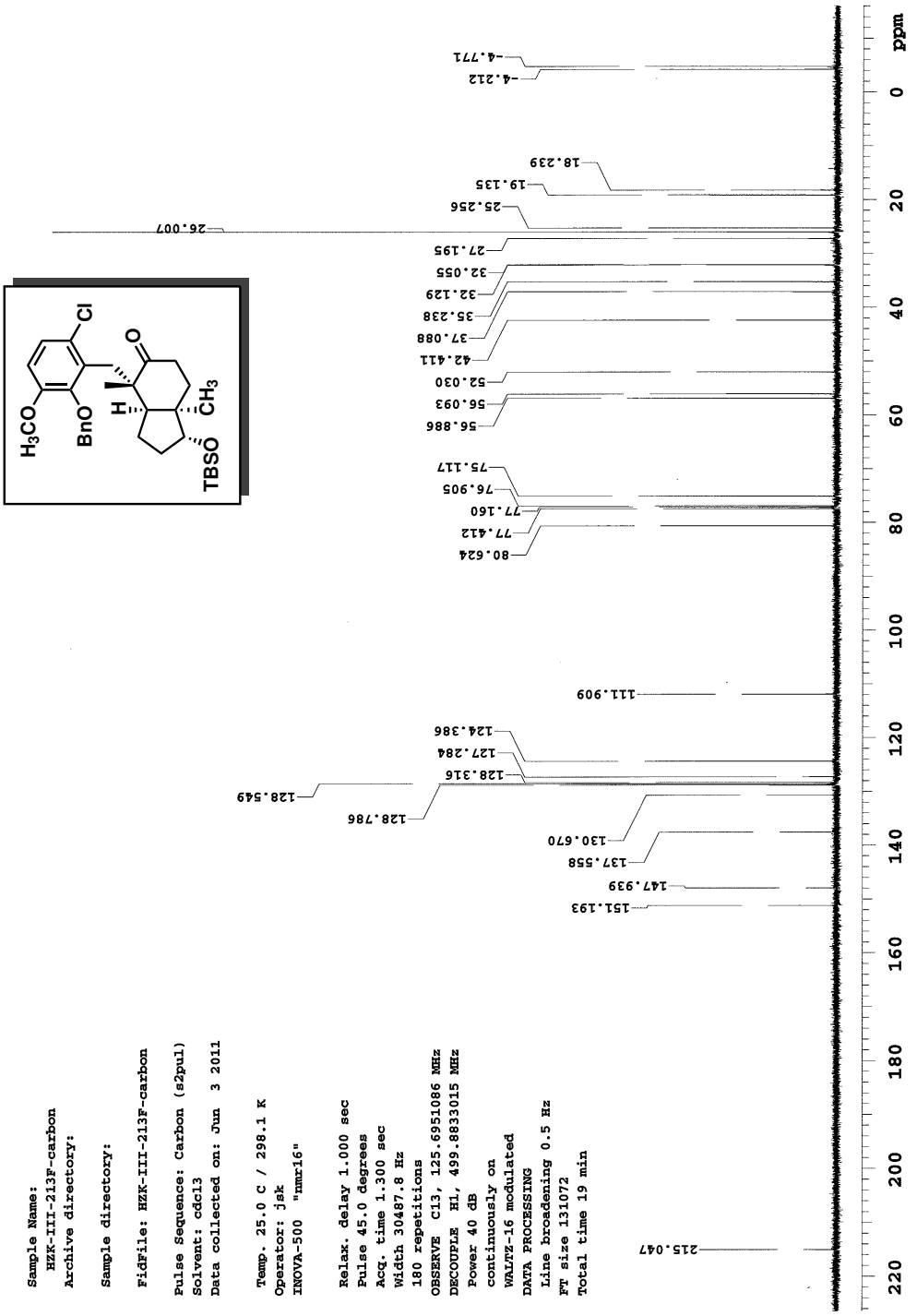


Figure 3.63: ^{1}H NMR of (+)-tert-butyldimethylsilyl ether-alkene (**3.65**)

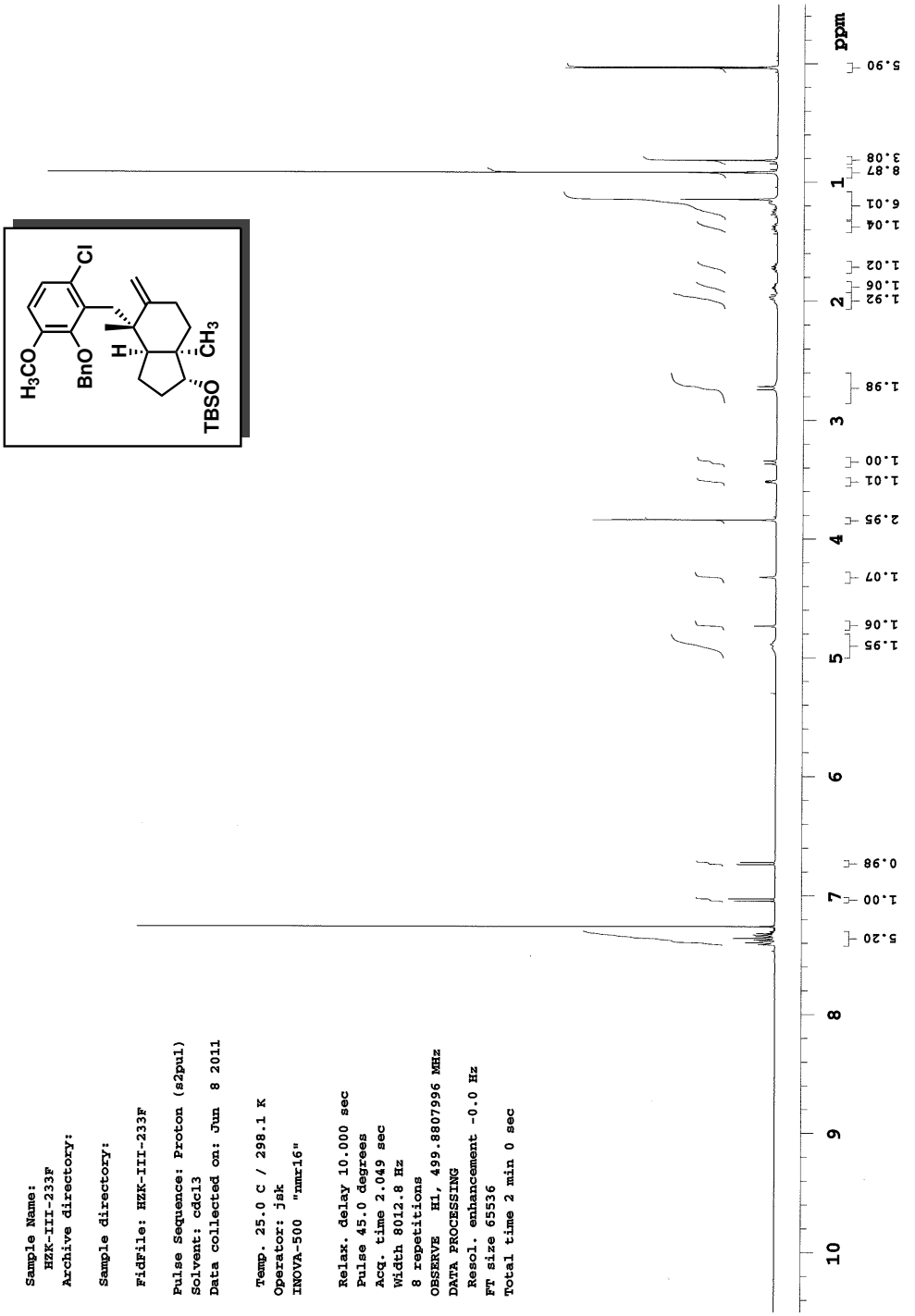


Figure 3.64: ^{13}C NMR of (+)-tert-butyldimethylsilyl ether-alkene (**3.65**)

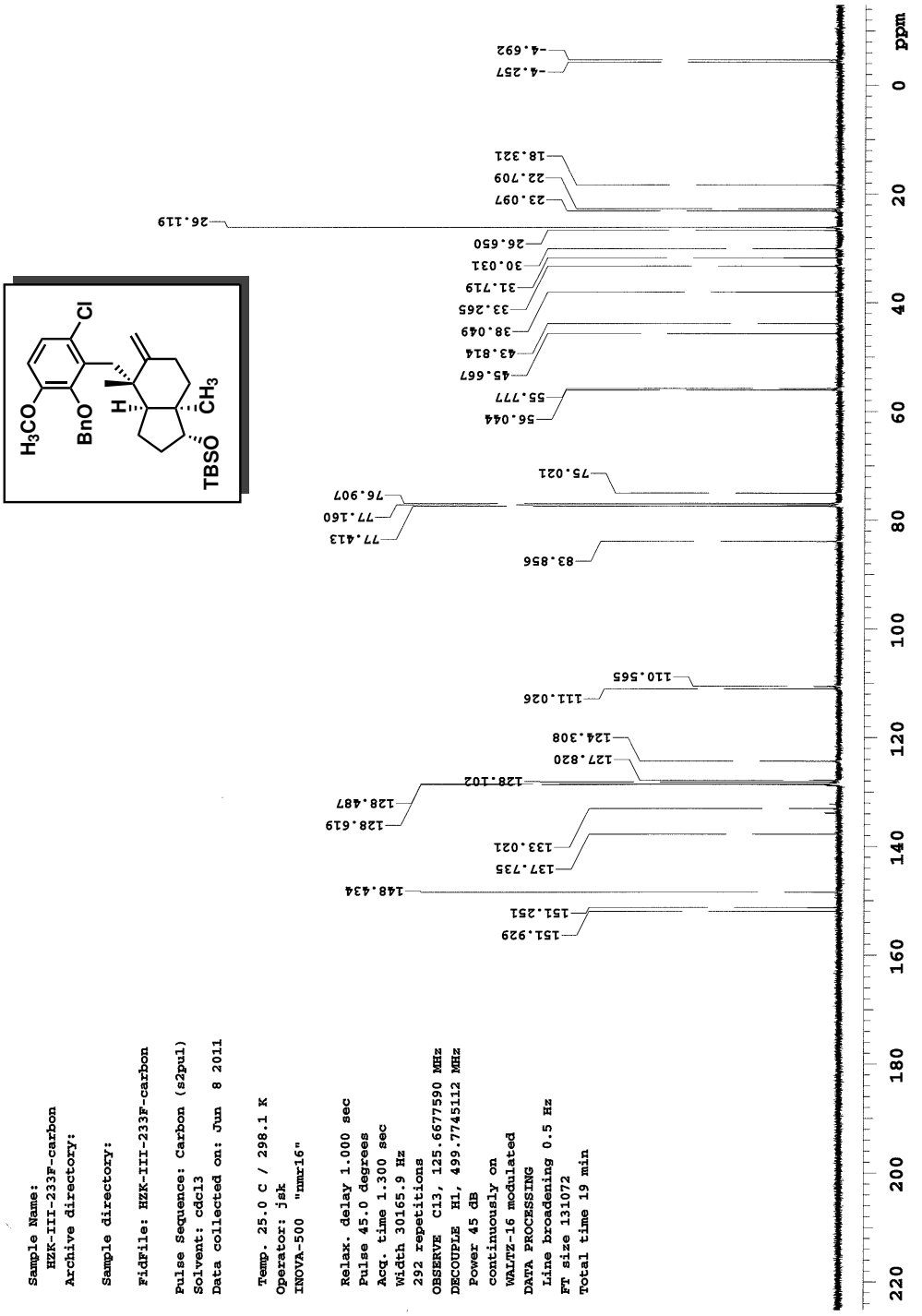


Figure 3.65: ^{1}H NMR of (+)-1,1-disubstituted ene-ol (**3.90**)

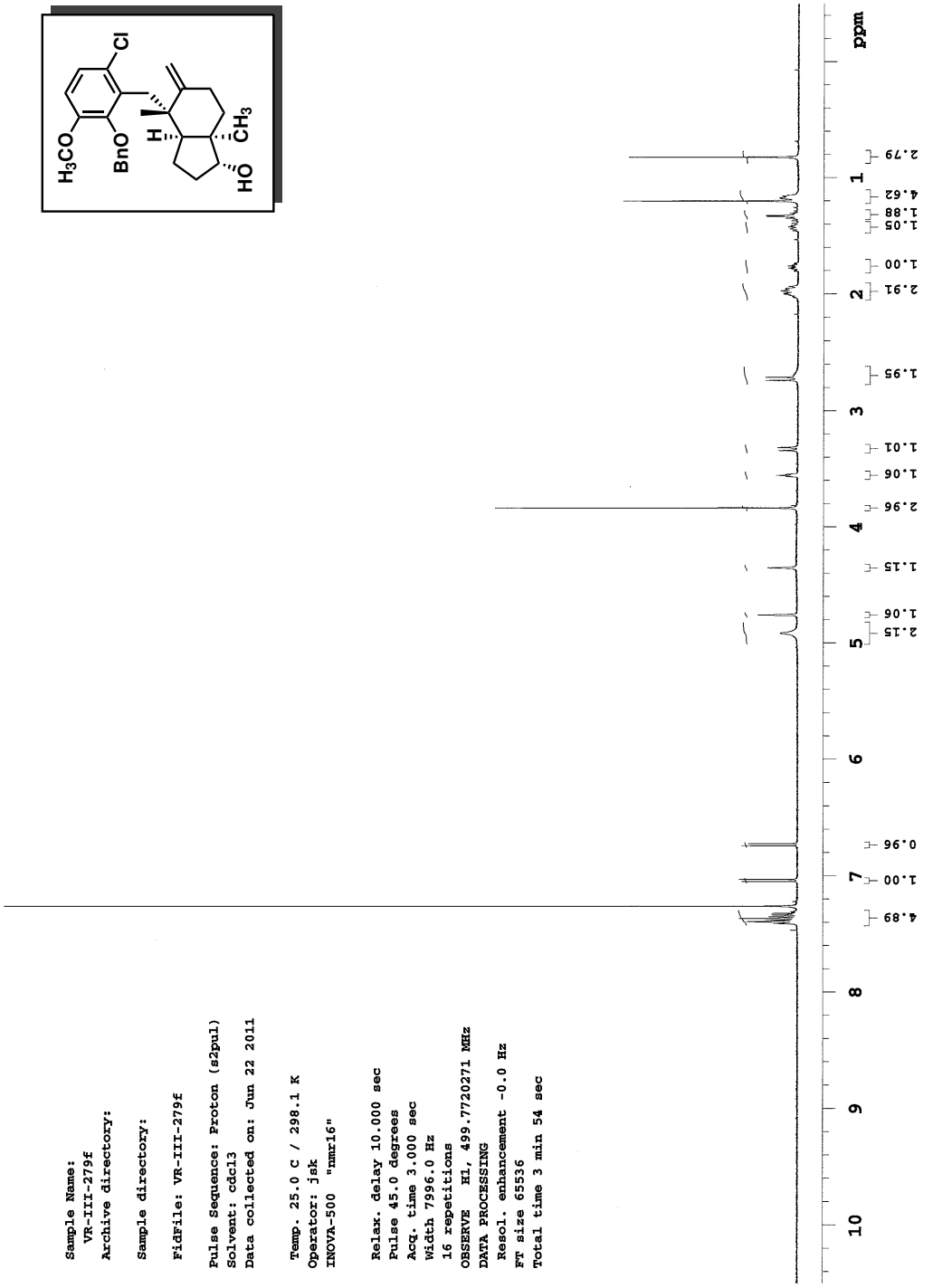


Figure 3.66: ^{13}C NMR of (+)-1,1-disubstituted ene-ol (**3.90**)

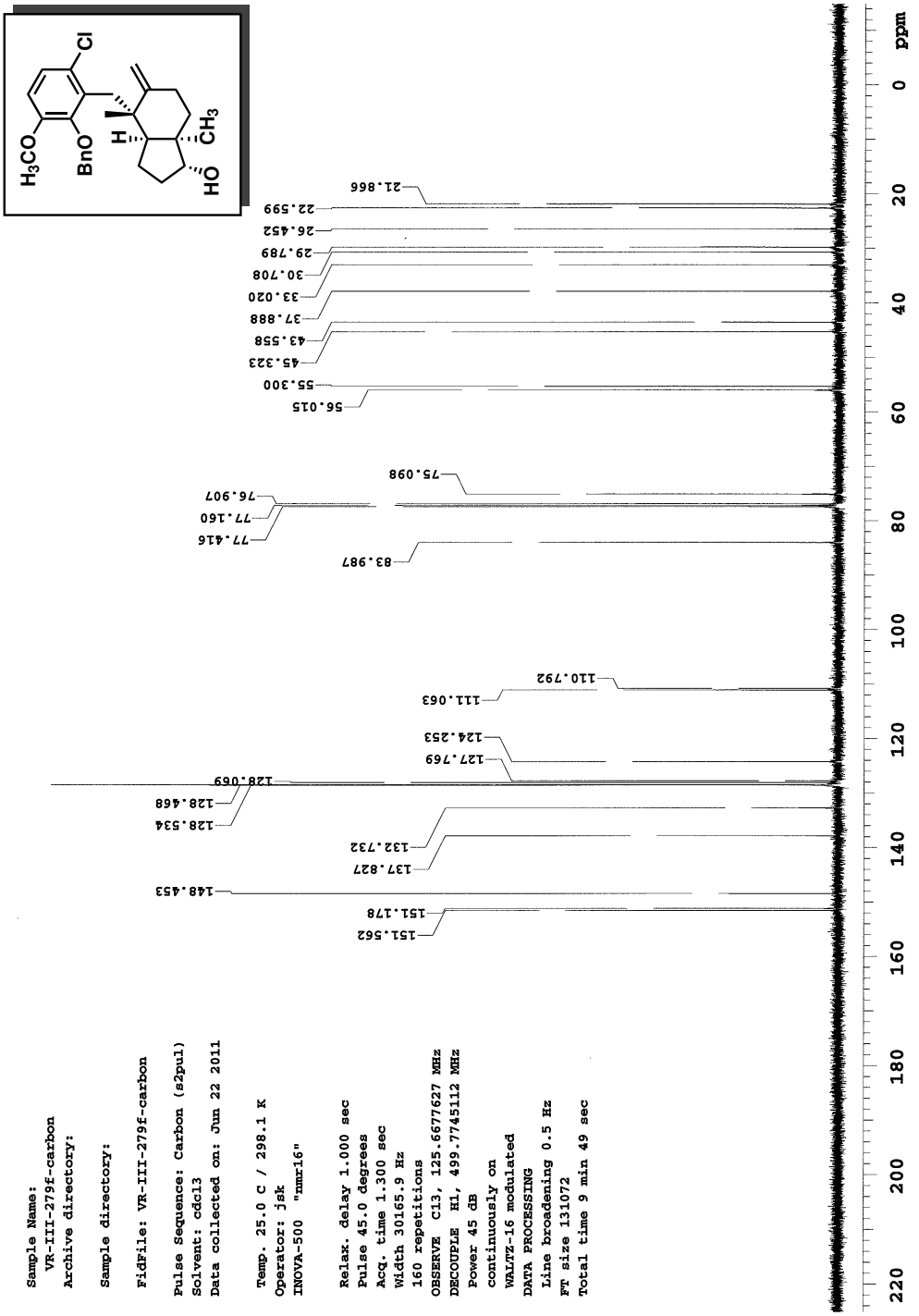


Figure 3.67: ^{1}H NMR of (+)-1,1-disubstituted ene-one (**3.66**)

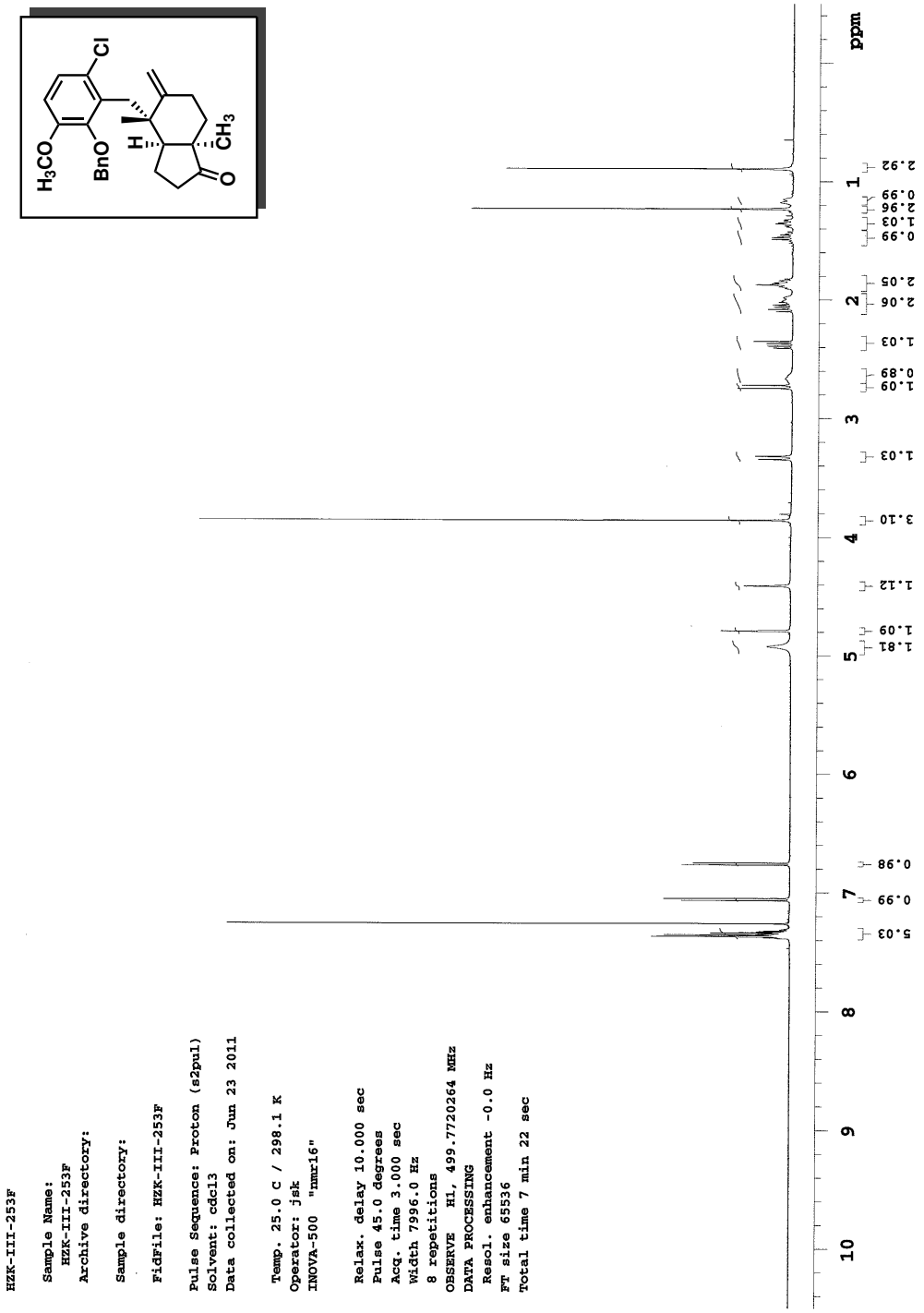


Figure 3.68: ^{13}C NMR of (+)-1,1-disubstituted ene-one (**3.66**)

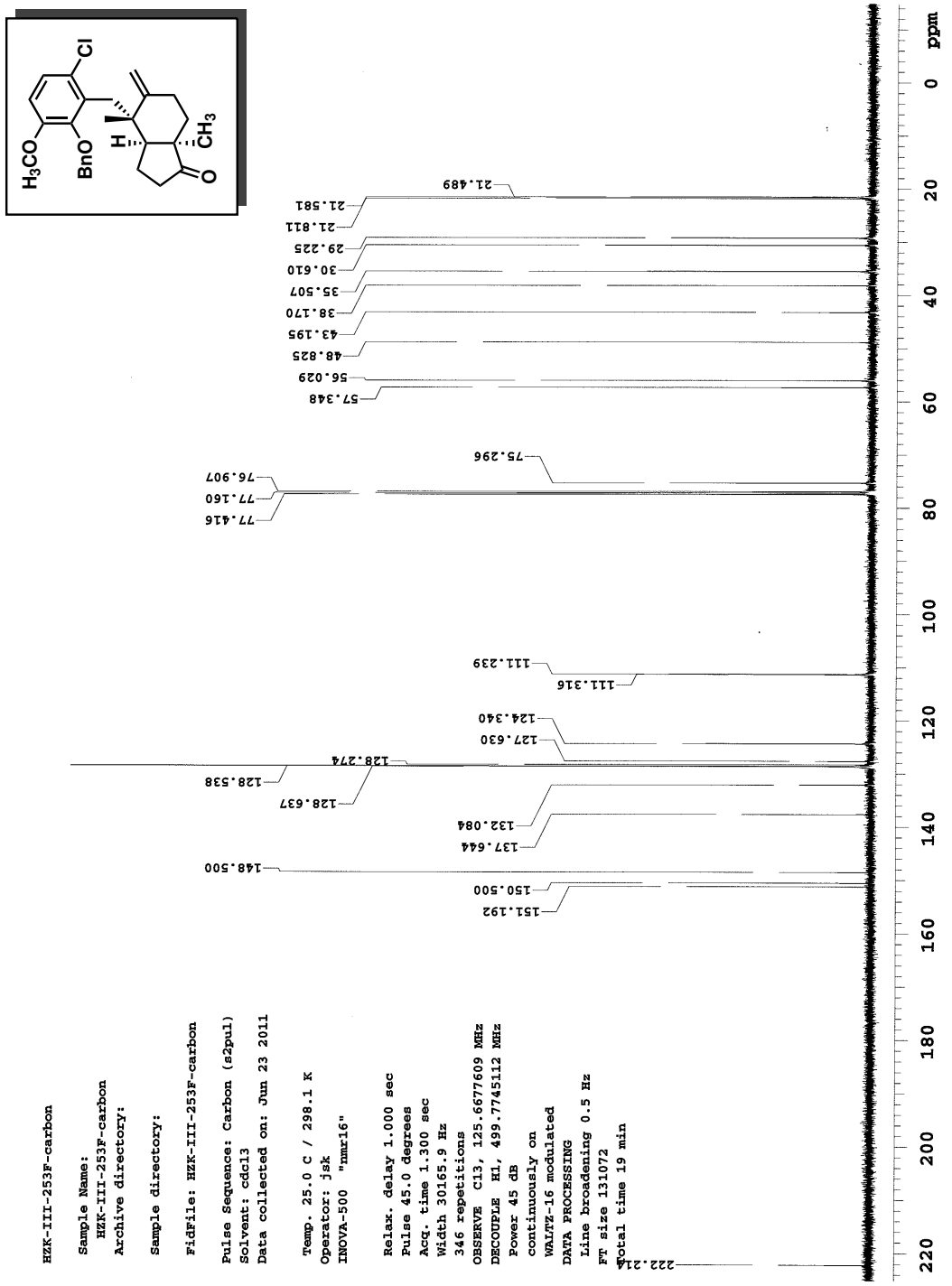


Figure 3.69: ^{1}H NMR of (−)-trisubstituted ene-ol (**3.91**)

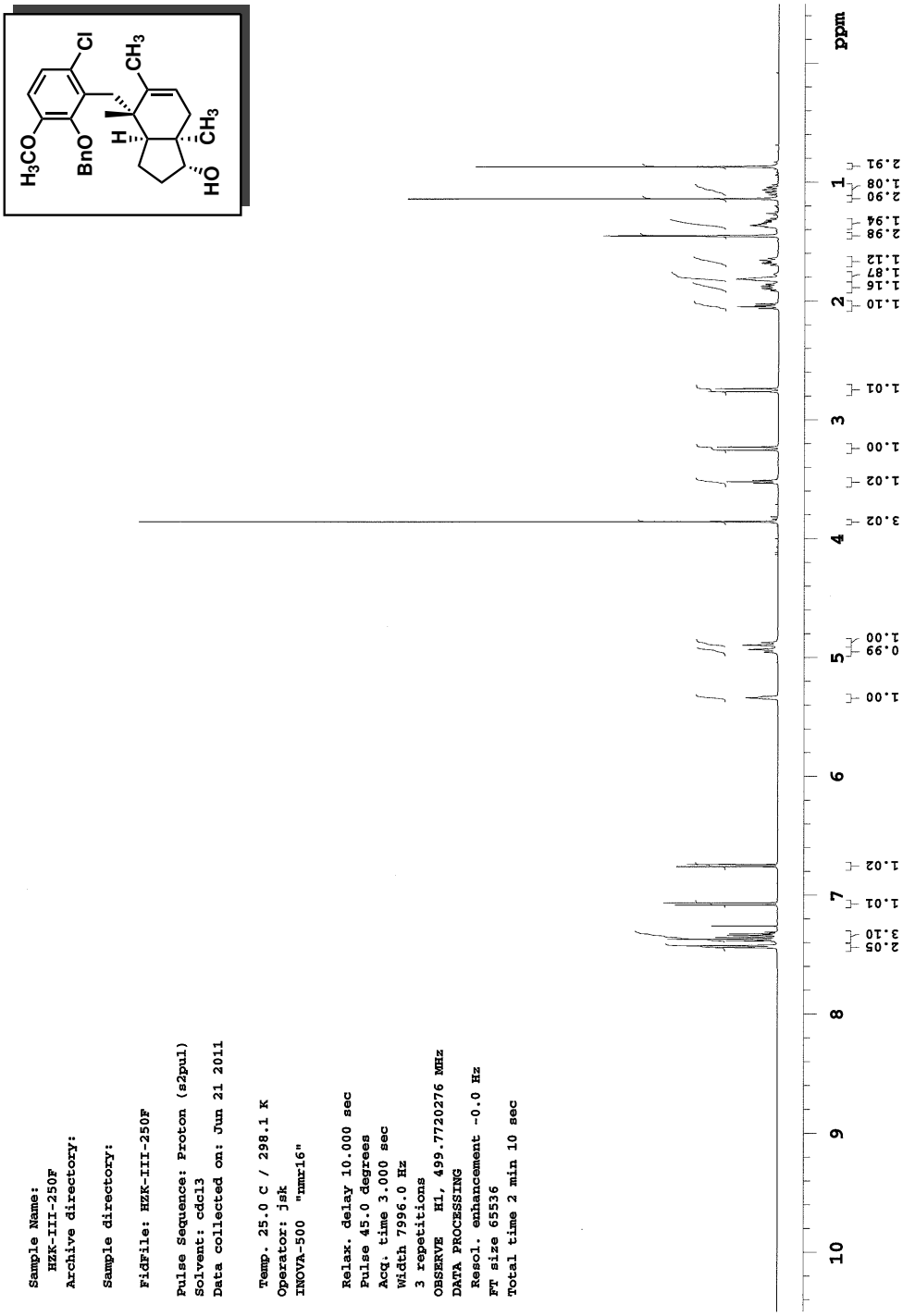


Figure 3.70: ^{13}C NMR of (−)-trisubstituted ene-ol (**3.91**)

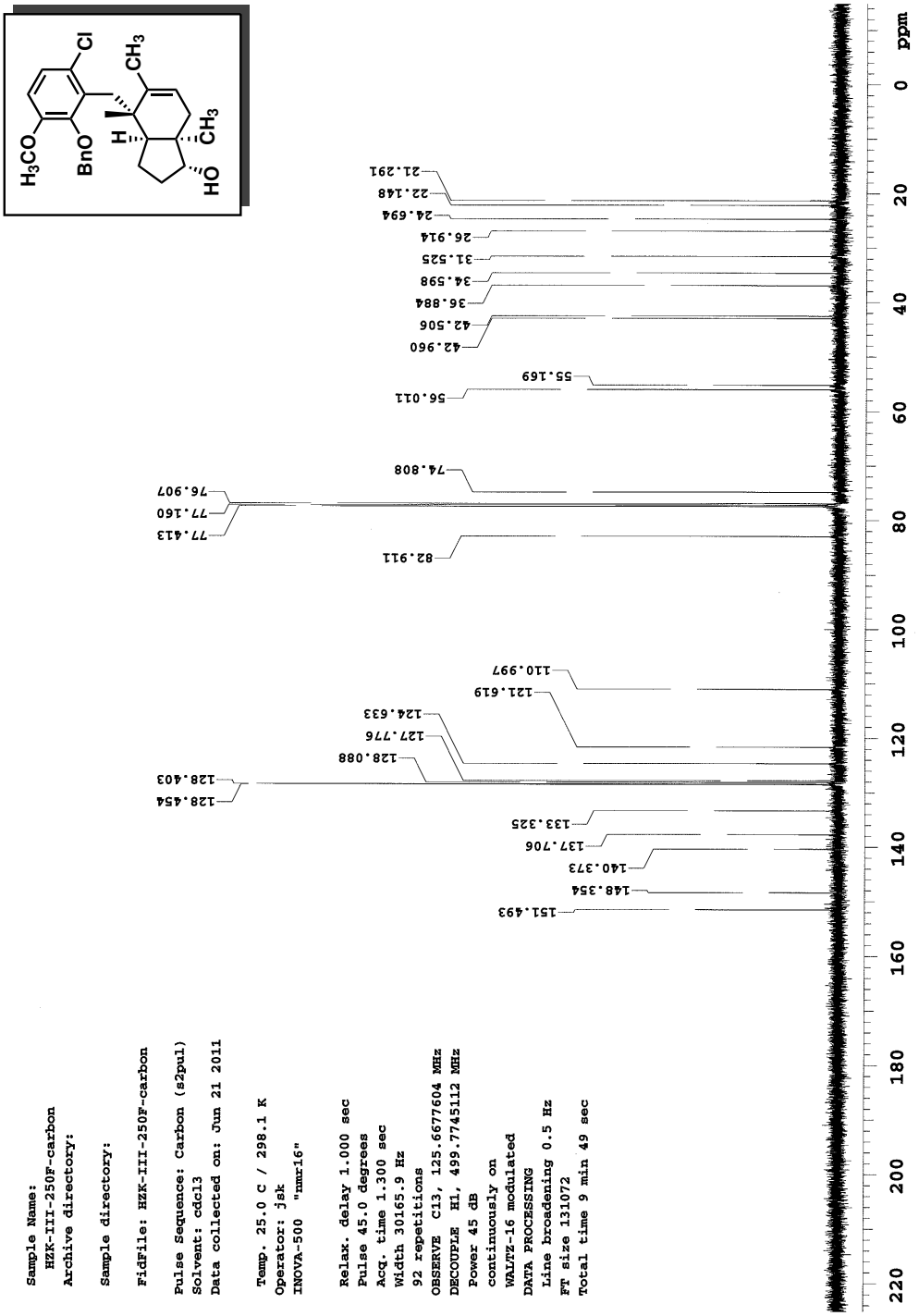


Figure 3.71: ^{1}H NMR of (−)-trisubstituted ene-one (**3.67**)

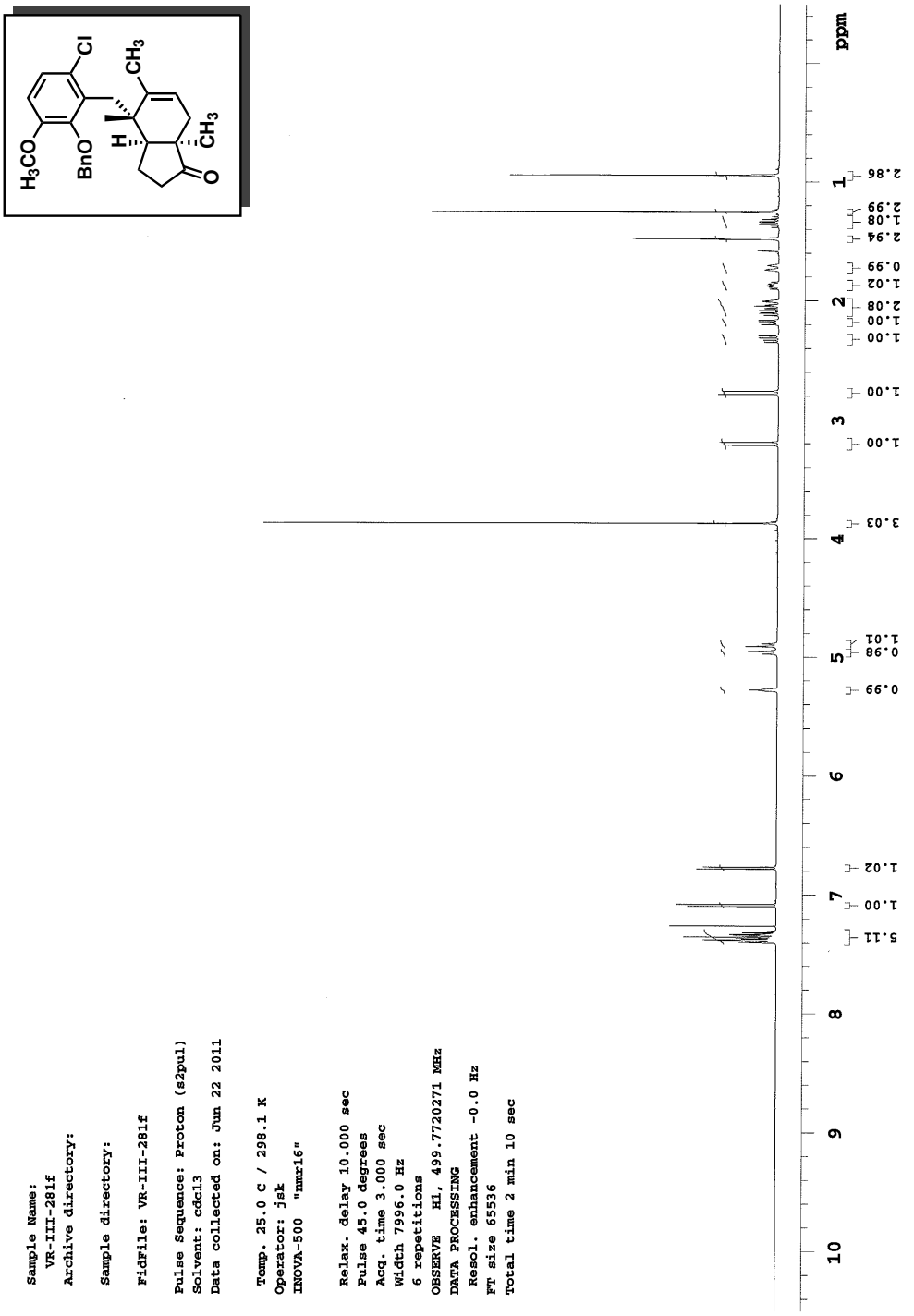


Figure 3.72: ^{13}C NMR of (−)-trisubstituted ene-one (**3.67**)

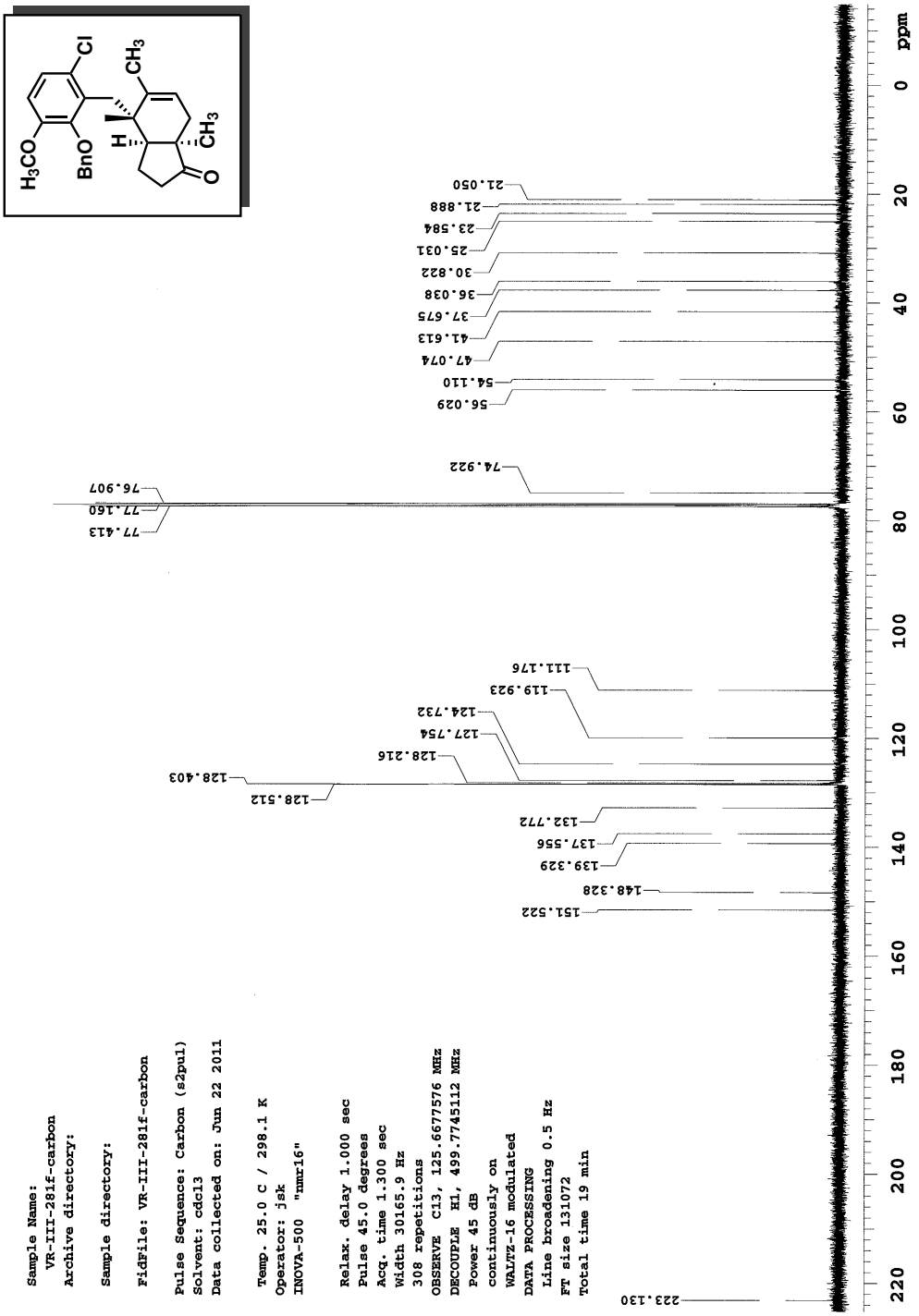


Figure 3.73: ^{1}H NMR of (+)-1,1-disubstituted ene-decalone major (**3.68**)

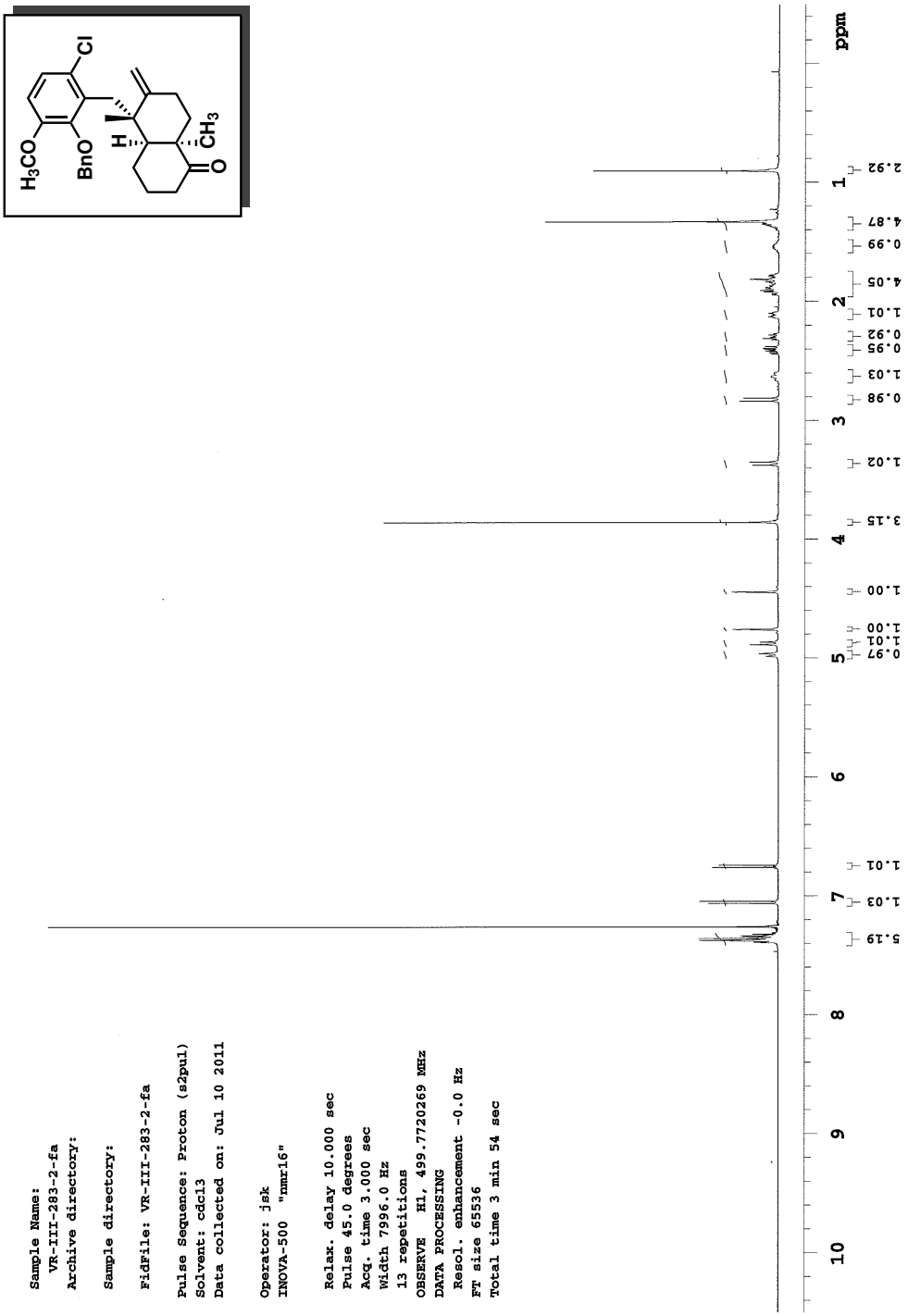


Figure 3.74: ^{13}C NMR of (+)-1,1-disubstituted ene-decalone major (**3.68**)

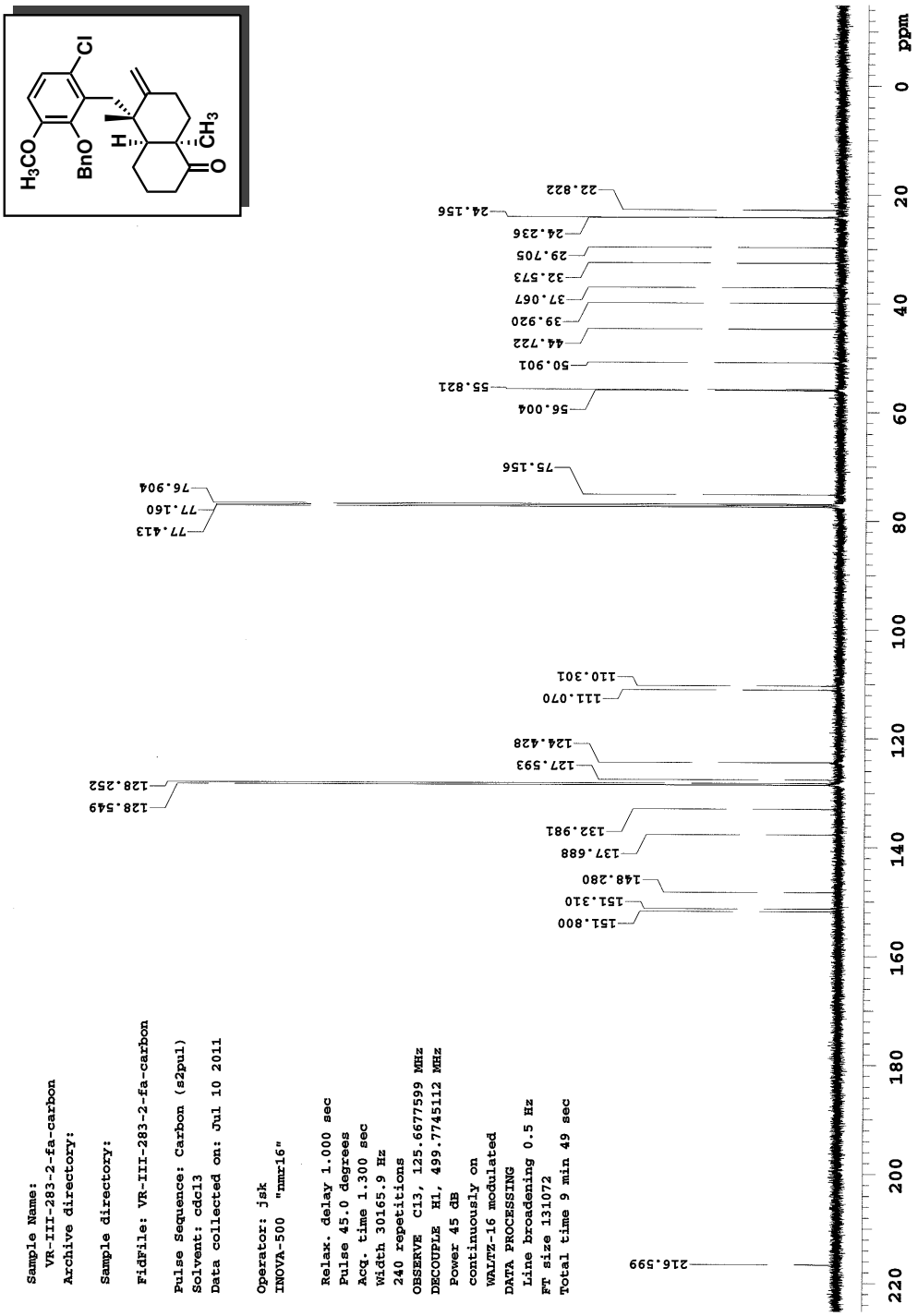


Figure 3.75: ^{1}H NMR of (+)-1,1-disubstituted ene-decalone minor (**3.69**)

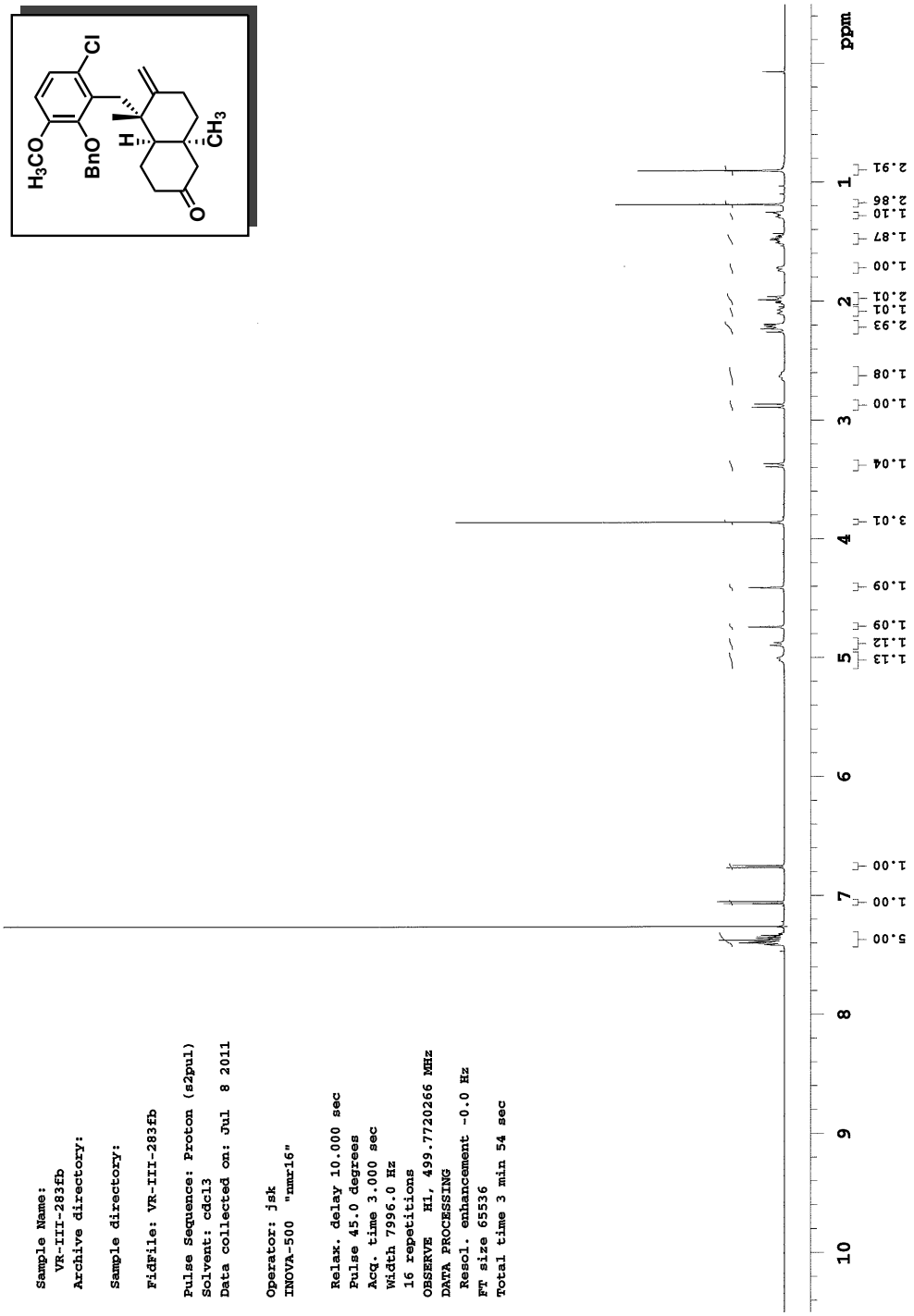


Figure 3.76: ^{13}C NMR of (+)-1,1-disubstituted ene-decalone minor (**3.69**)

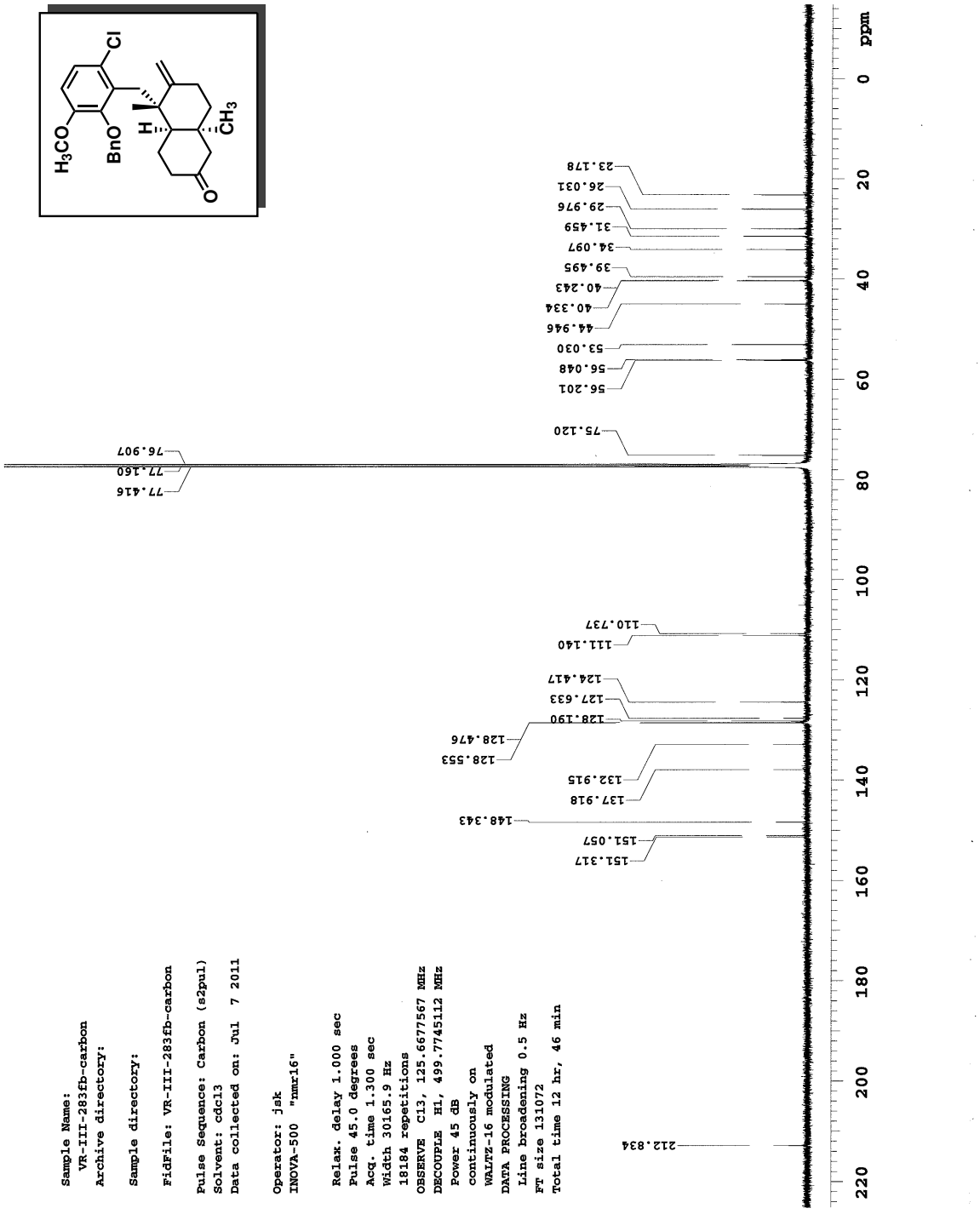


Figure 3.77: ^{1}H NMR of (−)-trisubstituted ene-decalone (**3.70**)

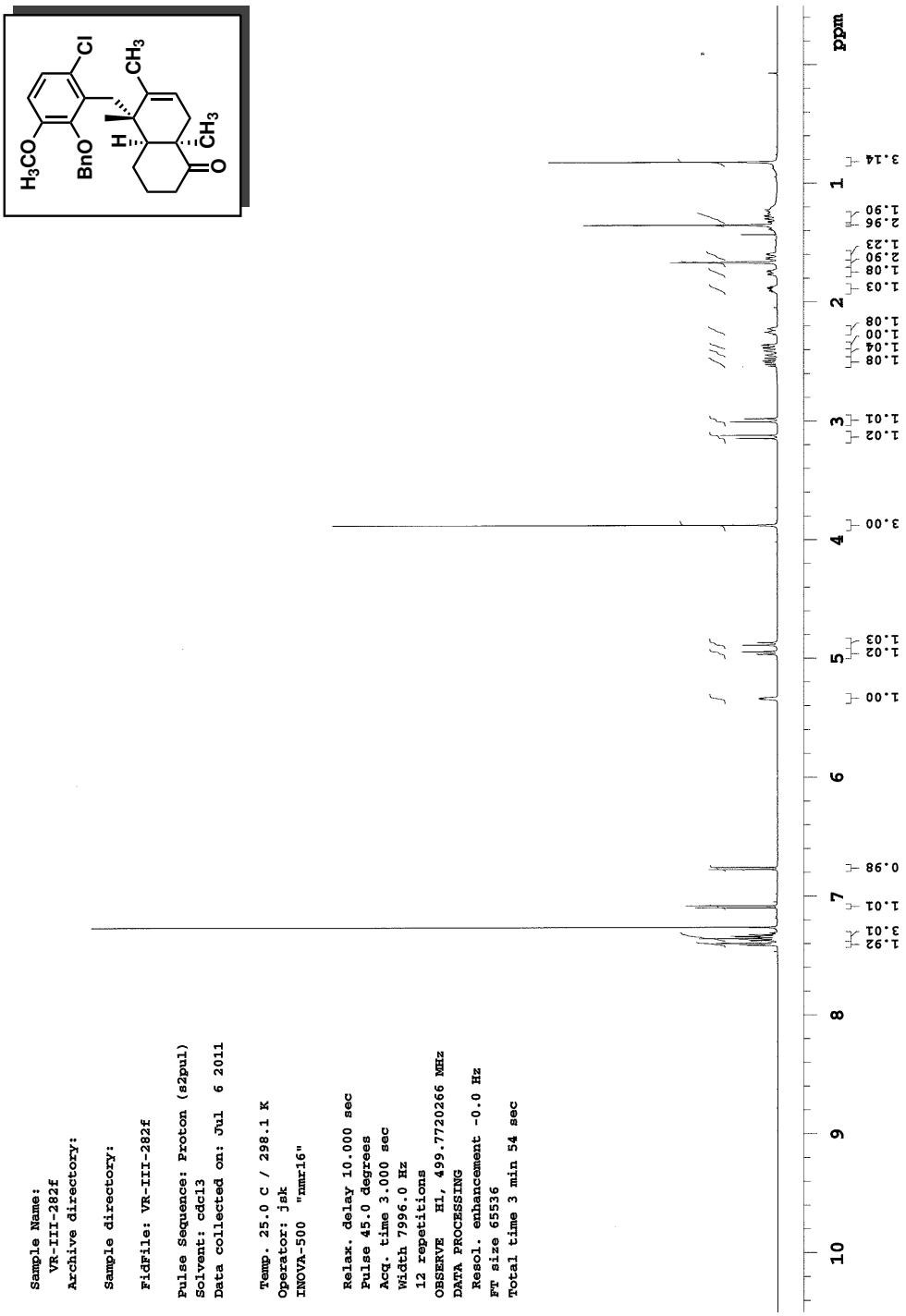


Figure 3.78: ^{13}C NMR of (−)-trisubstituted ene-decalone (**3.70**)

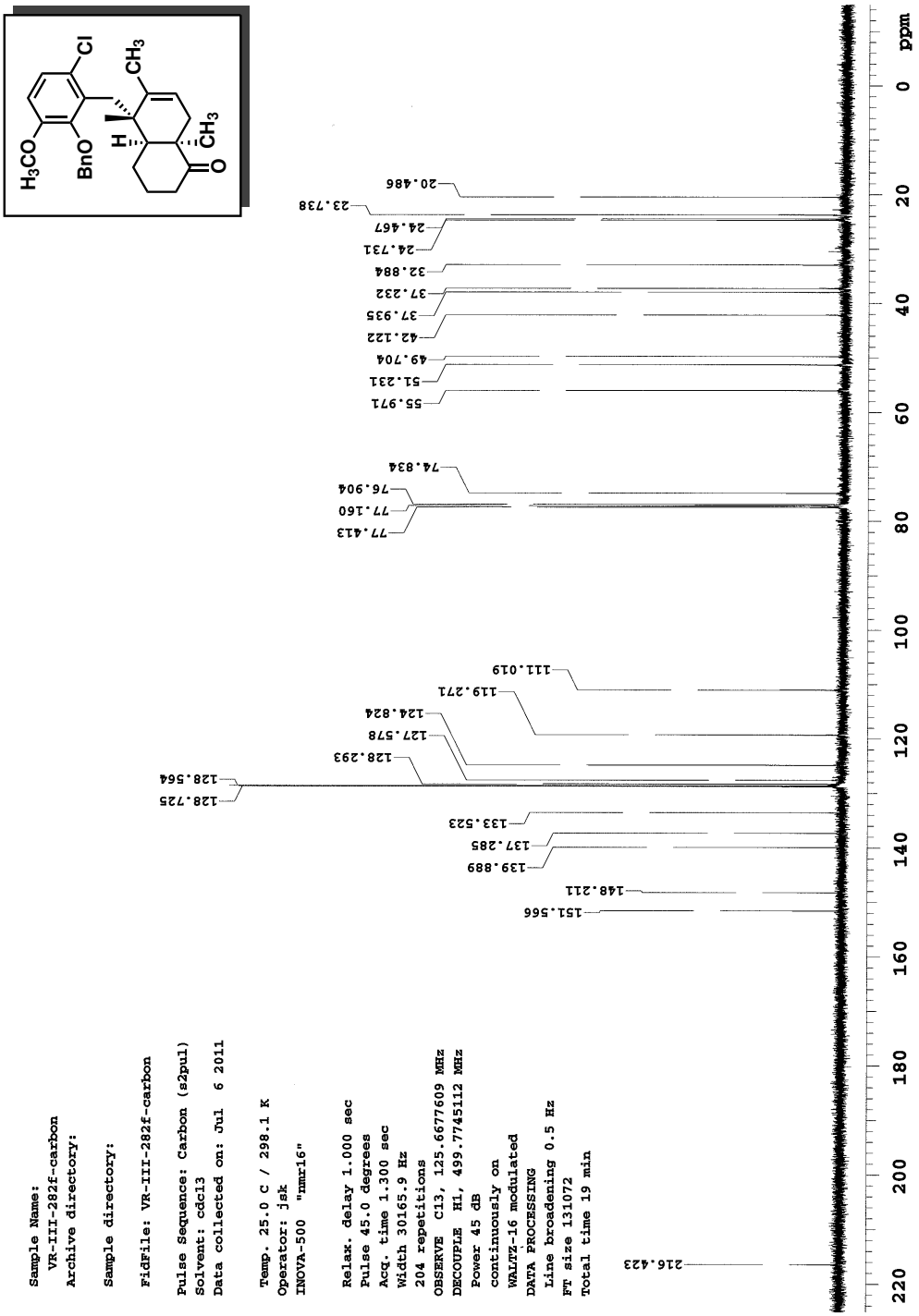


Figure 3.79: ^{1}H NMR of 2-(benzyloxy)-3-methoxybenzoic acid (**3.92**)

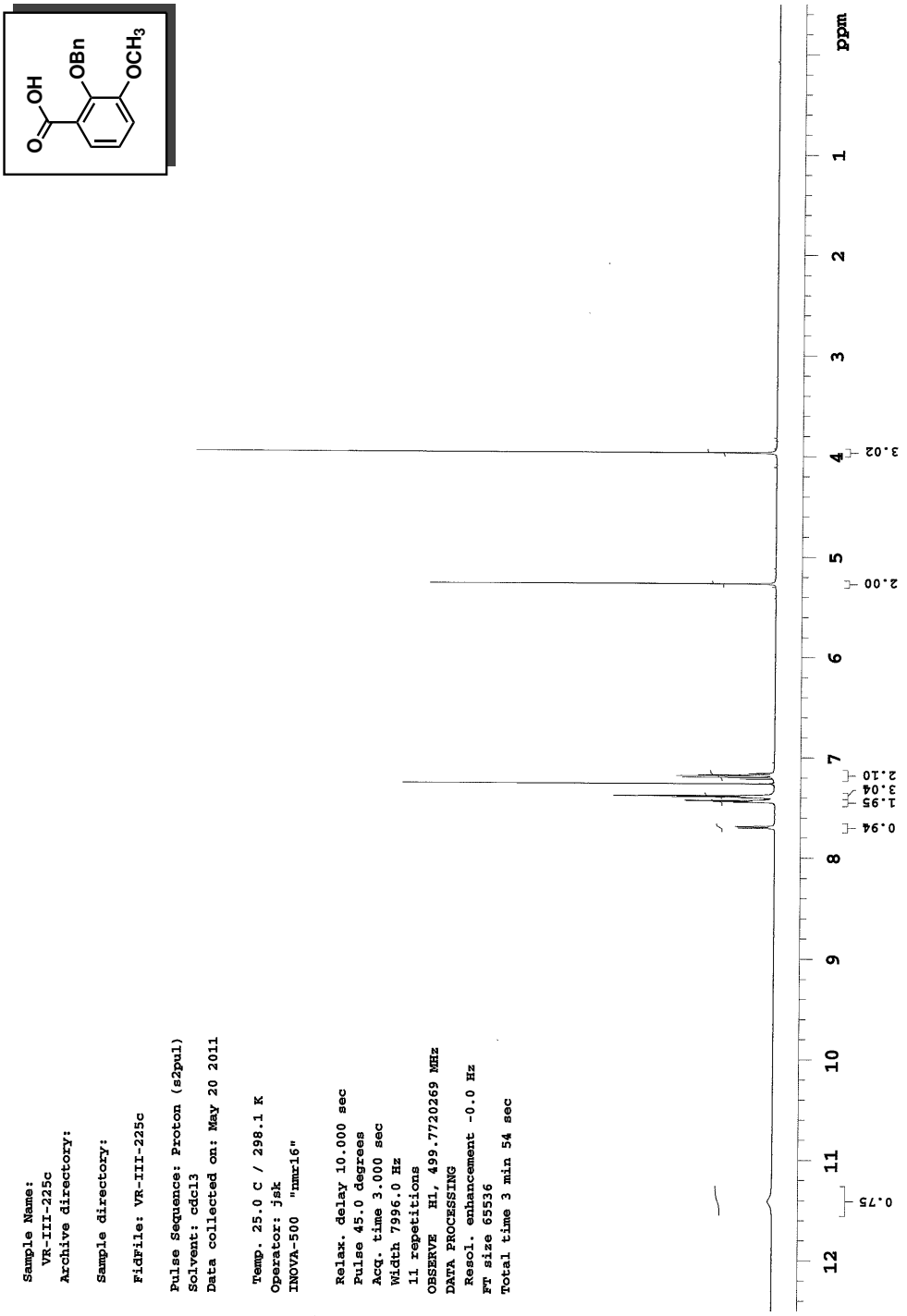


Figure 3.80: ^{13}C NMR of 2-(benzyloxy)-3-methoxybenzoic acid (**3.92**)

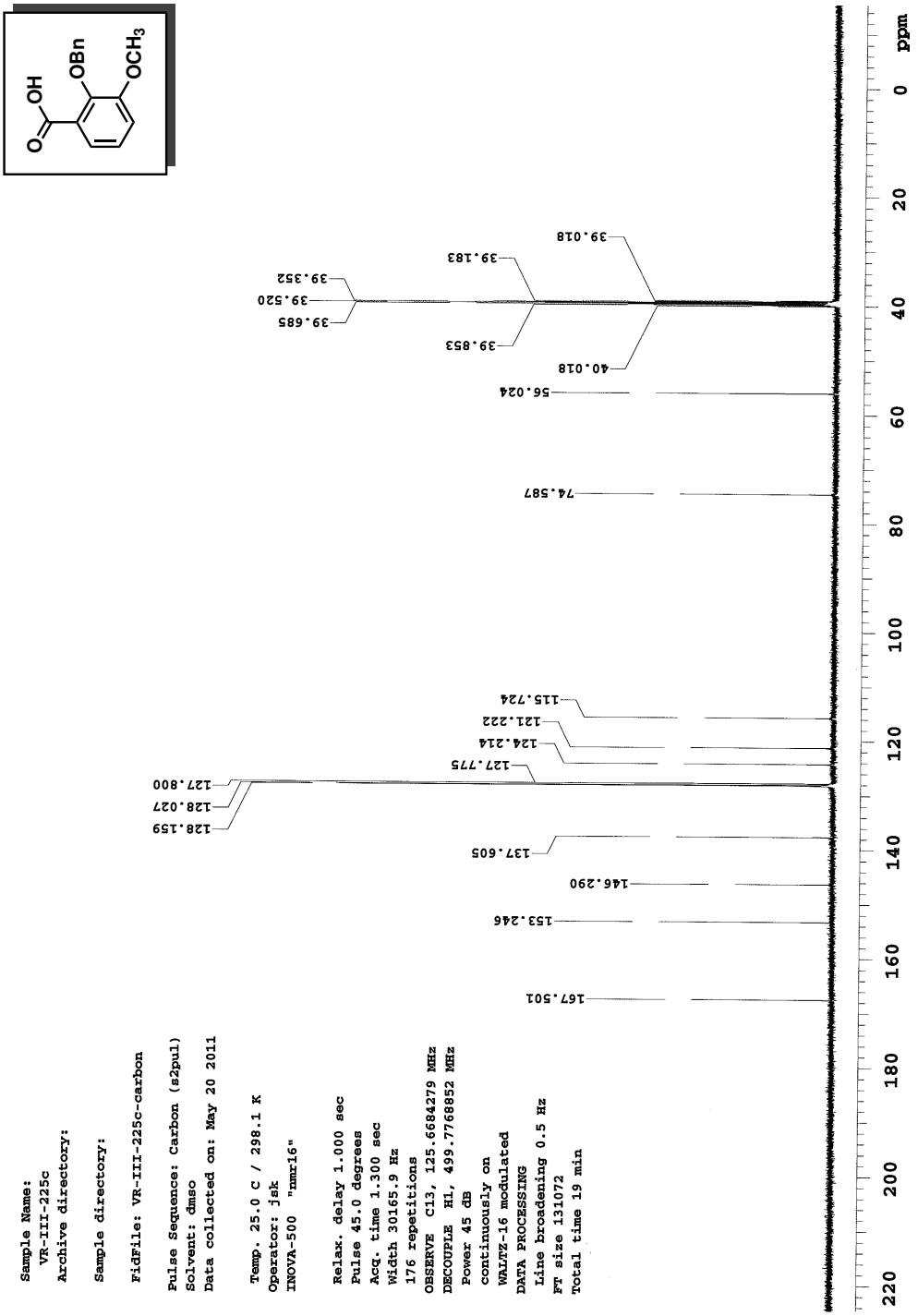


Figure 3.81: ^{1}H NMR of d_2-(2-(benzyloxy)-6-chloro-3-methoxyphenyl)methanol (**3.93**)

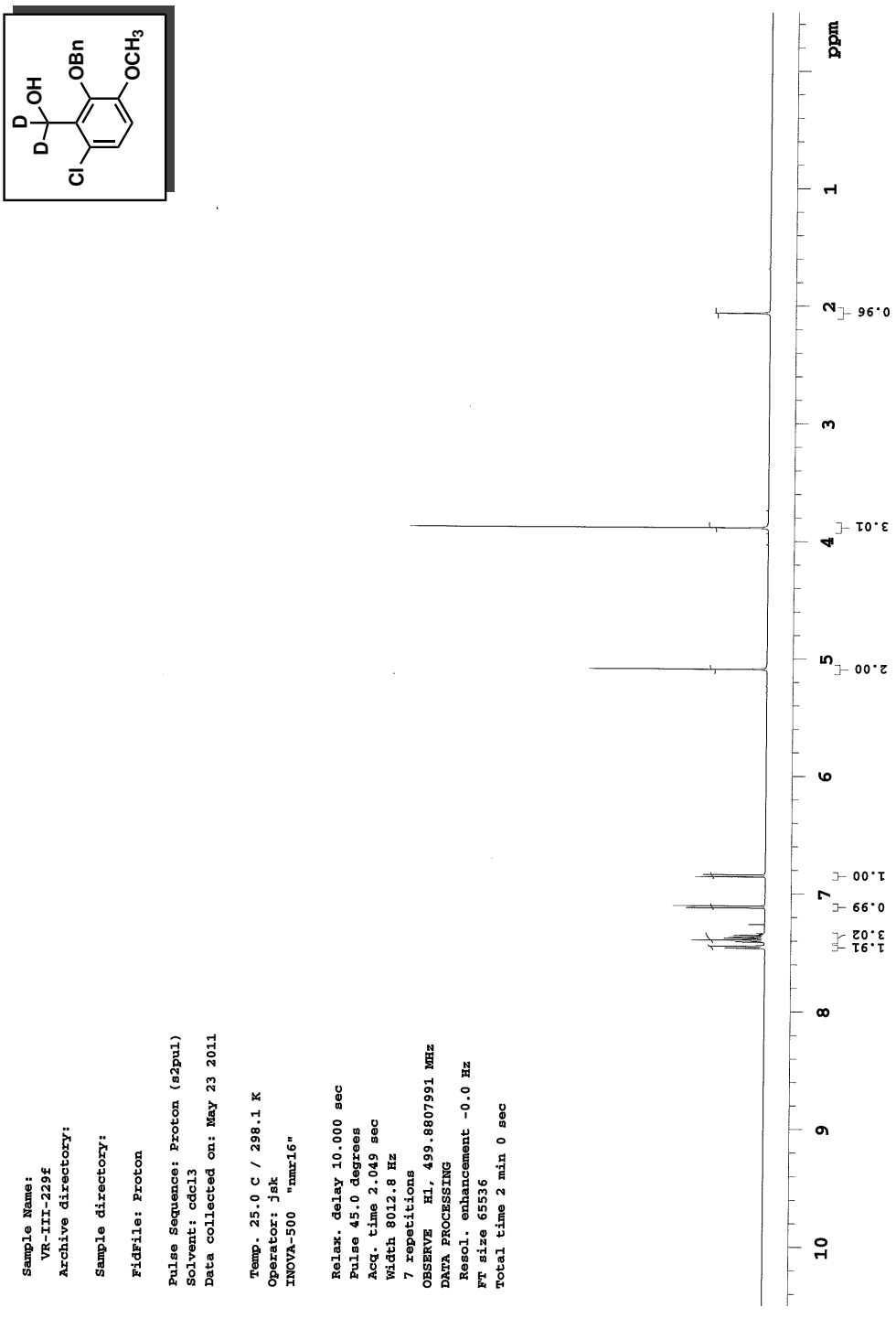


Figure 3.82: ^{13}C NMR of d_2-(2-(benzyloxy)-6-chloro-3-methoxyphenyl)methanol (**3.93**)

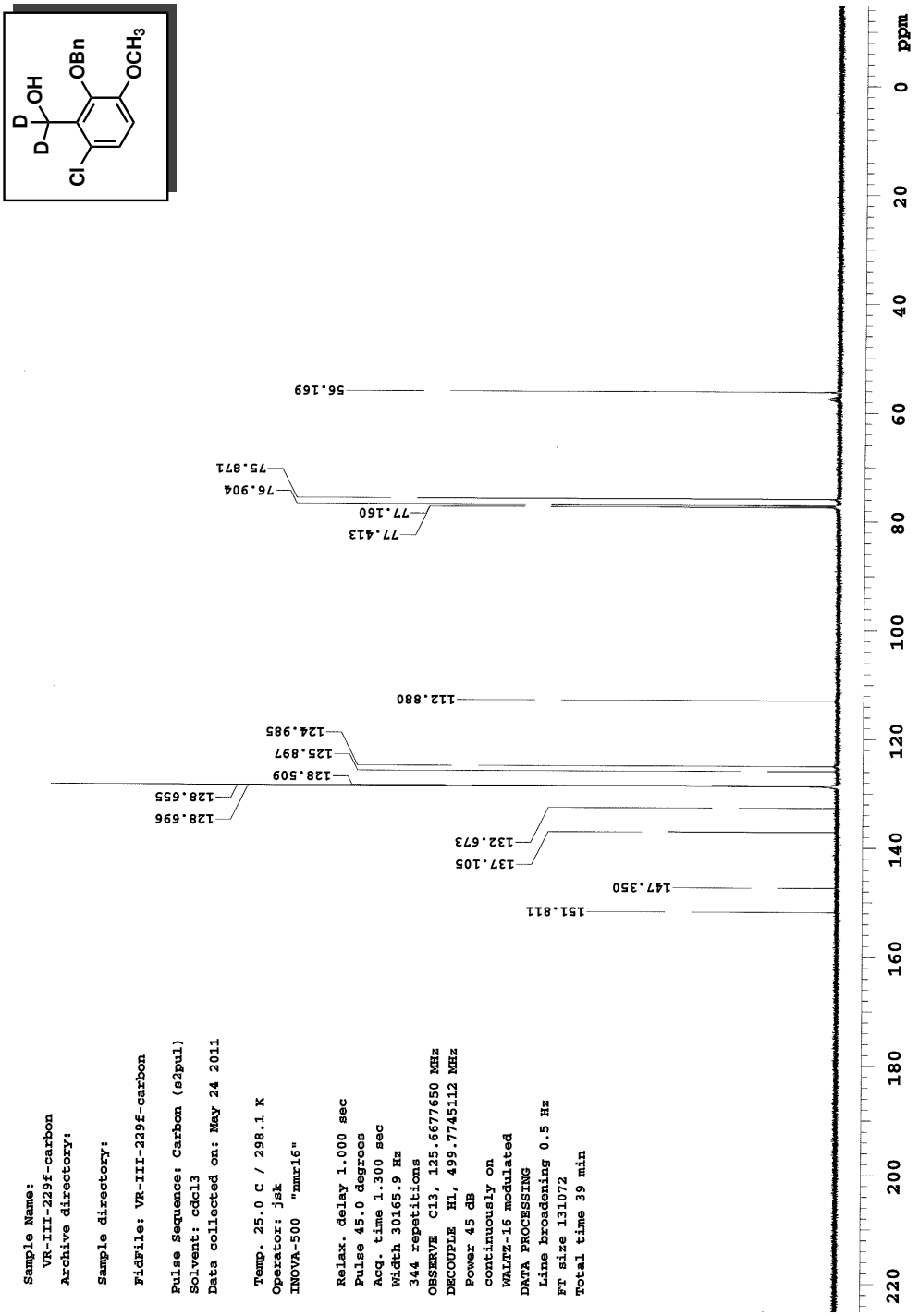


Figure 3.83: ^{1}H NMR of d_2-2-(benzyloxy)-3-(bromomethyl)-4-chloro-1-methoxybenzene (**3.94**)

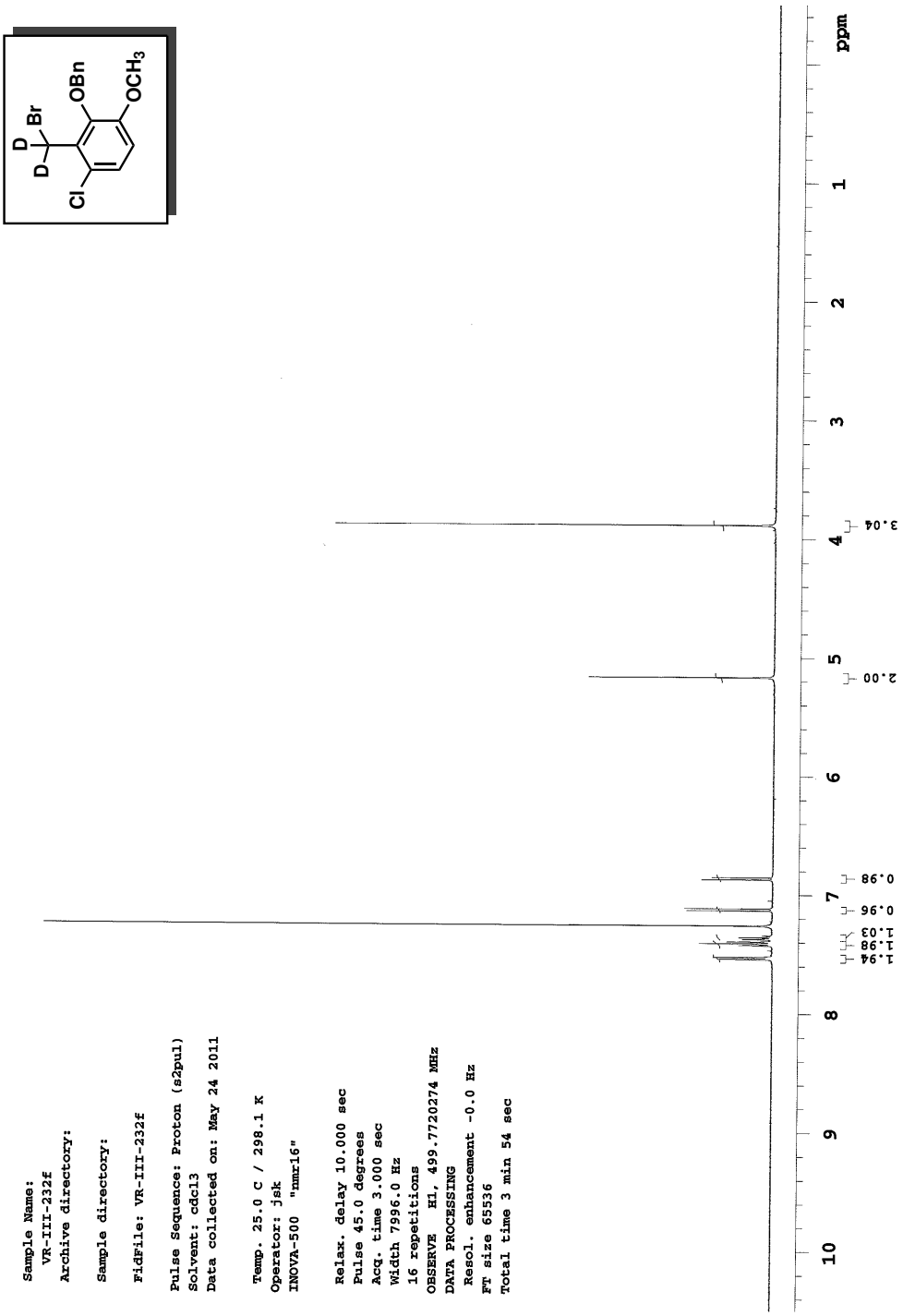


Figure 3.84: ^{13}C NMR of d_2-2-(benzyloxy)-3-(bromomethyl)-4-chloro-1-methoxybenzene (**3.94**)

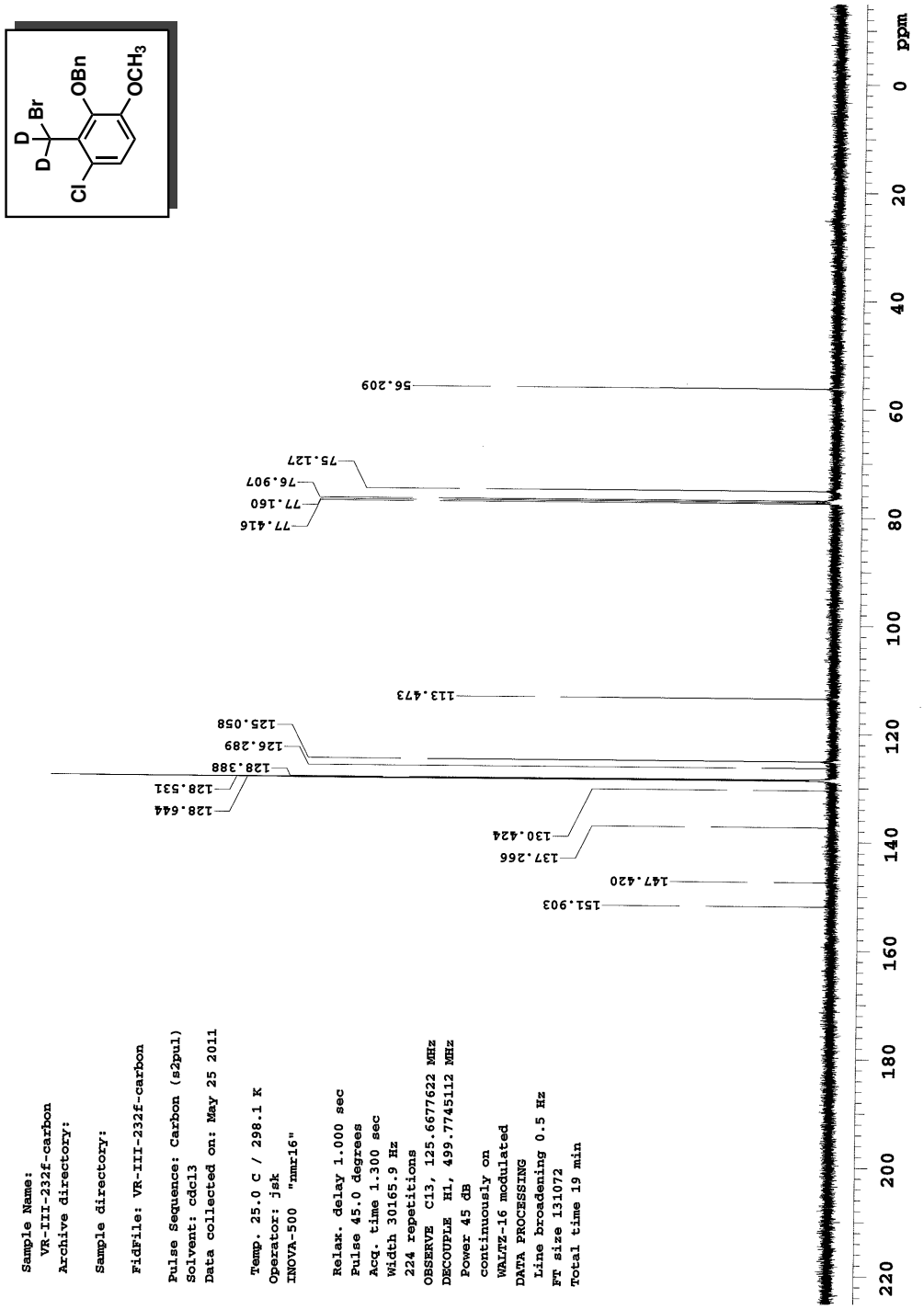


Figure 3.85: ^{1}H NMR of d_2-2-(benzyloxy)-4-chloro-3-(iodomethyl)-1-methoxybenzene (**3.95**)

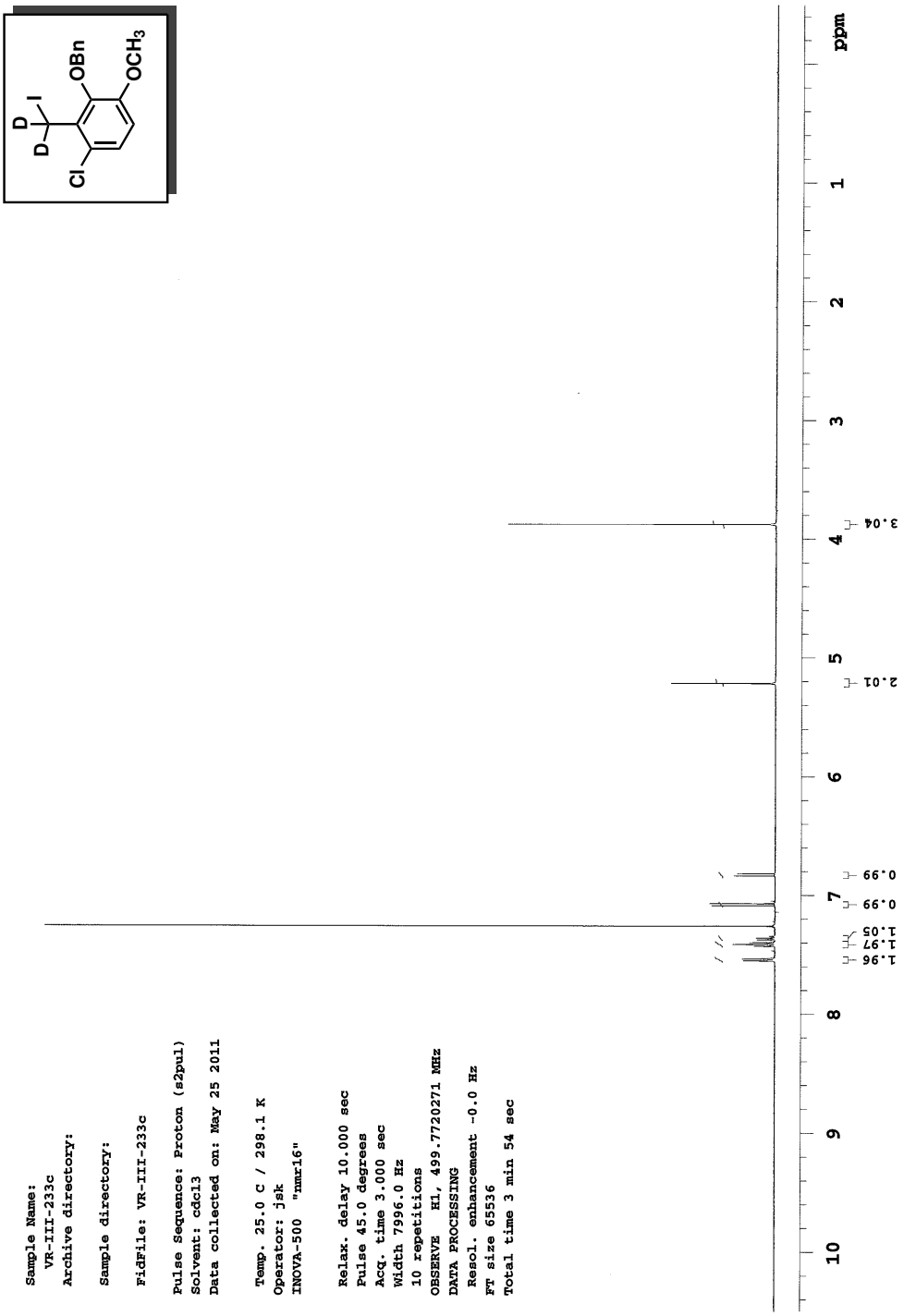
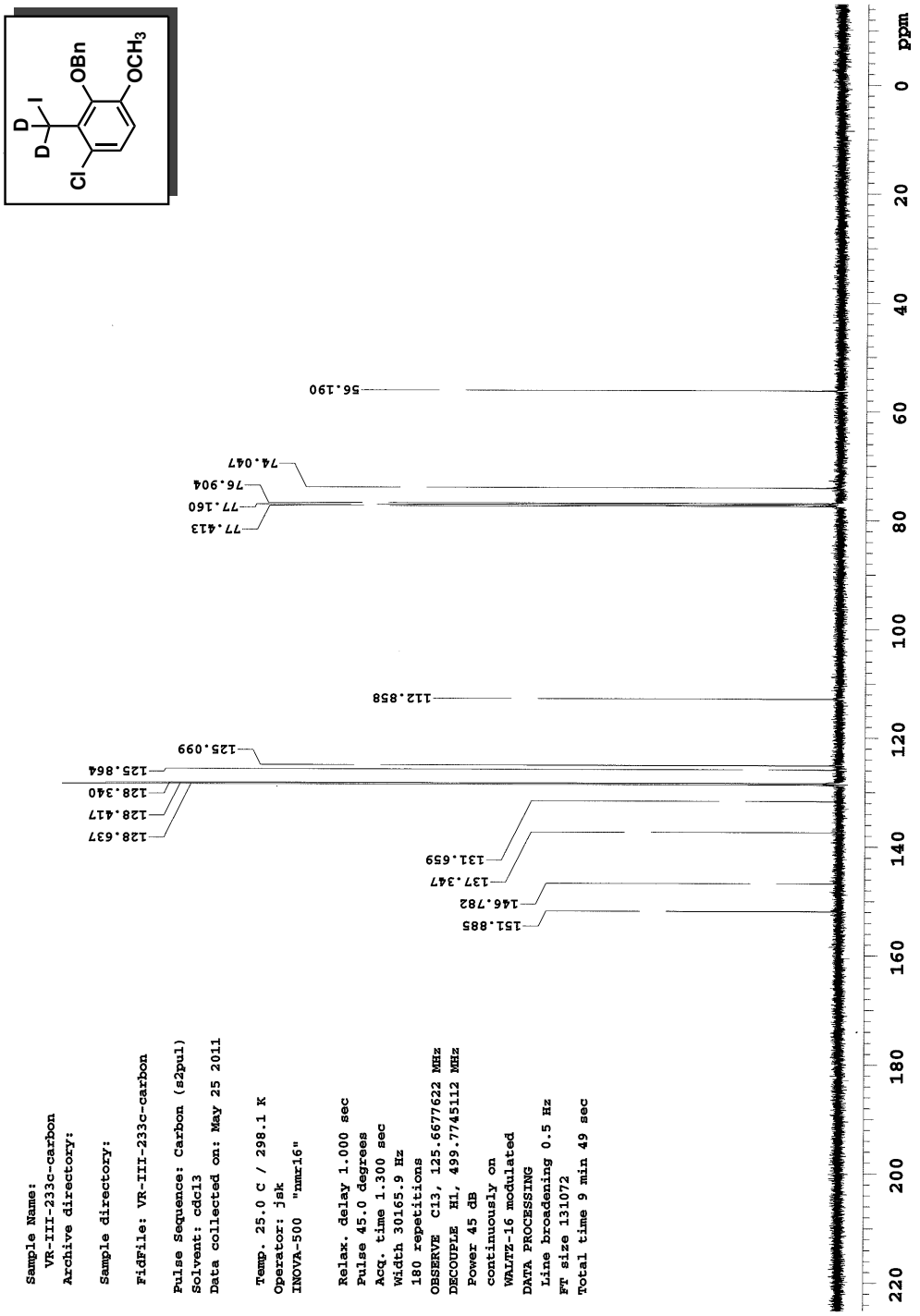


Figure 3.86: ^{13}C NMR of d_2-2-(benzyloxy)-4-chloro-3-(iodomethyl)-1-methoxybenzene (**3.95**)



Chapter

4

Catalysis of Etherification Reactions with sp^3 Electrophiles

4.1 Introduction

The formation of C−O bonds through the activation of sp^2 hybridized electrophiles has been extensively studied. Catalytic methods based on 4-(dialkylamino)pyridines proceed through a well understood nucleophilic activation mechanism.[1] A multitude of catalytic enantioselective methods have subsequently been developed that rely on the nucleophilic activation of sp^2 hybridized electrophiles with chiral Lewis bases.[2] Among the most successful are those based on the DMAP (**4.1**) and PPY (**4.2**) framework introduced by the Fu[3] and Fuji[4] (Scheme 4.1). The Miller group has also found success using an imidaozle ring, part of a chiral tripeptide, as the nucleophilic activating moiety.[5]

With the exception of soluble iodide sources such as TBAI, catalytic nucleophilic activation of sp^3 hybridized electrophiles remains a largely undeveloped area.[6] In biological settings, *S*-adenosyl methionine (SAM) serves as an activator for the methyl group by forming an intermediate sulfonium species.[7] To the best of our knowledge, there are no examples

[1] For mechanistic studies see: (a) Höfle, G.; Steglich, W.; Vorbrüggen, H. 4-Dialkylaminopyridines as Highly Active Acylation Catalysts. *Angew. Chem. Int. Ed.* **1978**, *17*, 569-583. (b) Spivey, A. C.; Arseniyadis, S. Nucleophilic Catalysis by 4-(Dialkylamino)pyridines Revisited–The Search for Optimal Reactivity and Selectivity. *Angew. Chem. Int. Ed.* **2004**, *43*, 5436-5441. (c) Held, I.; Villinger, A.; Zipse, H. The Stability of Acylpyridinium Cations and Their Relation to the Catalytic Activity of Pyridine Bases. *Synthesis* **2005**, *9*, 1425-1430. (d) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. The DMAP-Catalyzed Acetylation of Alcohols–A Mechanistic Study. *Chem. Eur. J.* **2005**, *11*, 4751-4757. (e) Lutz, V.; Glatthaar, J.; Würtele, C.; Serafin, M.; Hausmann, H.; Schreiner, P. R. Structural Analyses of *N*-Acetylated 4-(Dimethylamino)pyridine (DMAP) Salts. *Chem. Eur. J.* **2009**, *15*, 8548-8557.

[2] France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. Nucleophilic Chiral Amines as Catalysts in Asymmetric Synthesis. *Chem. Rev.* **2003**, *103*, 2985-3012.

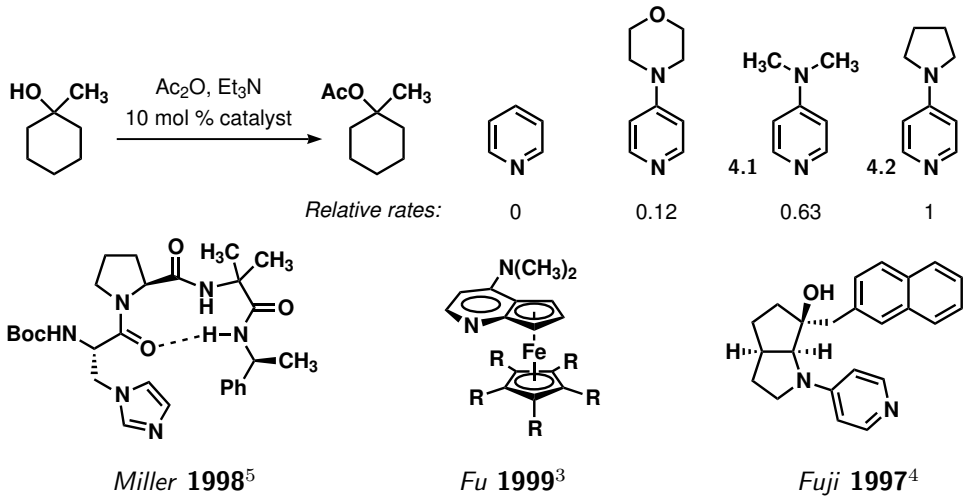
[3] Hodous, B. L.; Ruble, J. C.; Fu, G. C. Enantioselective Addition of Alcohols to Ketenes Catalyzed by a Planar-Chiral Azaferrocene: Catalytic Asymmetric Synthesis of Arylpropionic Acids. *J. Am. Chem. Soc.* **1999**, *121*, 2637-2638.

[4] Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. Nonenzymatic Kinetic Resolution of Racemic Alcohols through an "Induced Fit" Process. *J. Am. Chem. Soc.* **1997**, *119*, 3169-3170.

[5] Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. Kinetic Resolution of Alcohols Catalyzed by Tripeptides Containing the *N*-Alkylimidazole Substructure. *J. Am. Chem. Soc.* **1998**, *120*, 1629-1630.

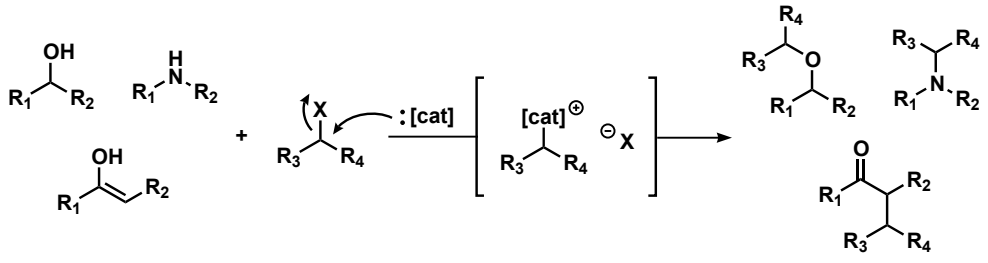
[6] For examples of TBAI in homogeneous alkylation reactions see: (a) Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T. Synthesis on 1,4-Diaminocyclitol Antibiotics. III. Synthesis of 4-Hydroxypurpurosamine B Derivatives. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1529-1531. (b) Nemoto, H.; Takamatsu, S.; Yamamoto, Y. An Improved and Practical Method for the Synthesis of Optically Active Diethyl Tartrate Dibenzyl Ether. *J. Org. Chem.* **1991**, *56*, 1321-1322.

[7] Roje, S. *S*-Adenosyl-L-methionine: Beyond the Universal Methyl Group Donor. *Phytochem.* **2006**, *67*, 1686-1698.



Scheme 4.1: Nucleophilic catalysis with sp^2 hybridized electrophiles.

of catalytic activation of sp^3 electrophiles with Lewis basic small organic molecules for C−O bond forming reactions.[8] Our original intent was to find a suitable nucleophilic activator for electrophiles with leaving groups attached directly to sp^3 hybridized carbons. Discovery of a small molecule catalyst capable of generating more reactive sp^3 electrophiles *in situ*, and possibly even chiral electrophiles from achiral or racemic precursors, could have a broad impact on synthetic chemistry. In the ideal reaction, carbon, nitrogen, oxgen, and other atoms could serve as potential nucleophiles, allowing formation of C−C, C−N, and C−O bonds (Scheme 4.2).



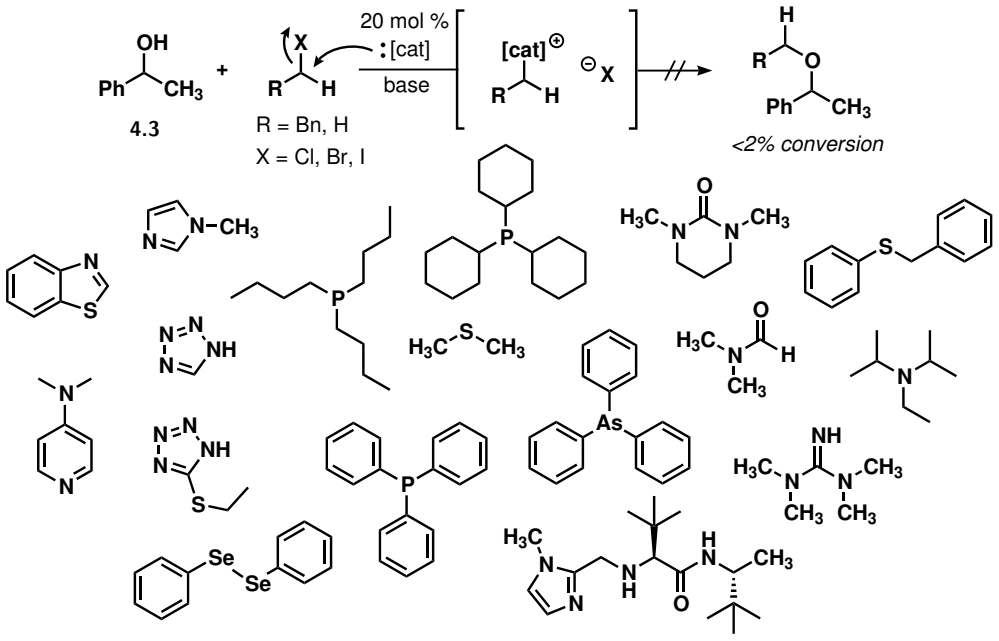
Scheme 4.2: Hypothetical activation of sp^3 hybridized electrophiles for alkylation reactions.

[8] A singular example was found where catalytic dimethylsulfide was used with Ag_2O to enhance the yield of methyl ether formation. No discussion of mechanism was provided. Werz, D. B.; Seeberger, P. H. Total Synthesis of Antigen Bacillus Anthracis Tetrasaccharide–Creation of an Anthrax Vaccine Candidate. *Angew. Chem. Int. Ed.* **2005**, *44*, 6315-6318.

4.2 Discovery of a Catalyzed Reaction

4.2.1 *Initial Lewis-Base Screening*

We began by screening a number of potential Lewis basic additives against mild etherification conditions.[9] In THF as solvent with a variety of weak bases (DIPEA, TMG, K_2CO_3) to help scavenge the equivlent of HX produced, conversion to the target ether was never observed, even at elevated temperatures (Scheme 4.3). Alkylation of either the base or the additive was consistent with the formation of a precipitate in most cases, and the salts formed were not competent electrophiles.[10] A screen of solvents (toluene, CH_2Cl_2, DMF,



Scheme 4.3: Initial screening of Lewis bases affords no product in every case.

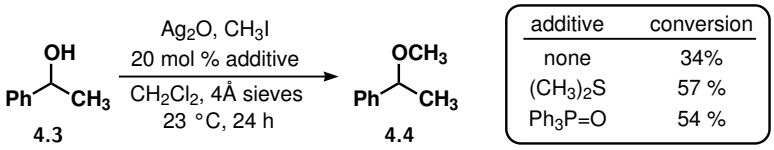
CH_3CN) also did not lead to any productive reaction under the conditions tested. The use

[9] Etherification reactions are typically carried out with the more nucleophilic alkoxide and an alkyl halide. (a) Williamson, A. Ueber die Theorie der Aetherbildung. *Liebigs Ann. Chem.* **1851**, *77*, 37-49. (b) Feuer, H.; Hooz, J. Methods of Formation of the Ether Linkage. In *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; Wiley: New York, 1967; pp 445-498.

[10] An experiment with stoichiometric commercial trimethylsulfonium iodide did not show any methyl ether formation.

of stronger bases such as NaH or KH formed a much more reactive alkoxide nucleophile and even at low temperatures reactions proceeded rapidly to complete conversion without additives, leaving little room for catalysis.

When stoichiometric Ag_2O was employed as the base, a moderate increase in conversion was observed with catalytic dimethylsulfide or triphenylphosphine oxide present in the reaction mixture (**4.3** $\longrightarrow$ **4.4**, Scheme 4.4).[8] The use of Ag_2O helps activate the electrophile by generating a highly insoluble silver halide salt, essentially functioning as a halide-specific Lewis acid.[11] The presence of sulfur or phosphine oxide additives could potentially serve as silver(I) ligands, producing a more soluble silver salt.[12] This may explain why we observed a subtle increase in conversion. We were wary of developing a reaction with stoichiometric silver, and also had concerns that the additive was not actually functioning as a nucleophilic activator.



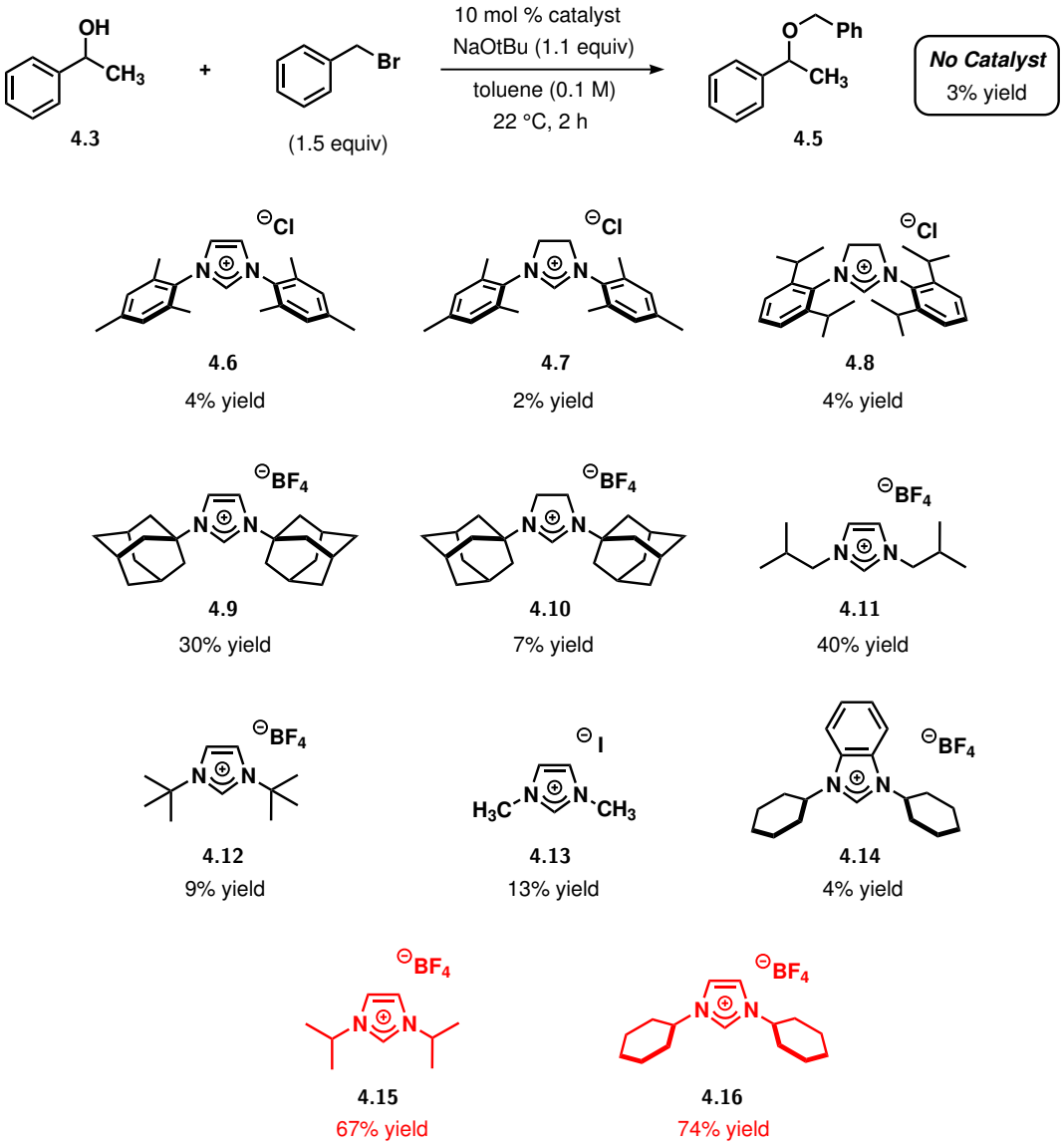
Scheme 4.4: Moderate conversion increase with dimethyl sulfide and triphenylphosphine oxide.

4.2.2 *Discovery of Imidazolium Salt Catalyzed Reactions*

After looking at standard nitrogen, oxygen, sulfur, selenium, and phosphorus centered Lewis bases and failing to observe any serious catalysis, we decided to examine carbon centered *N*-hetereocyclic carbenes. In the presence of a suitable base, imidazolium and imidazolin-

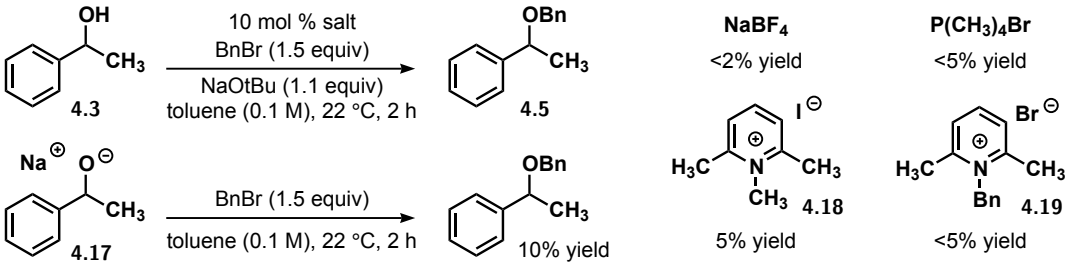
[11] For recent examples of alkylation reactions assisted by Ag_2O see: (a) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. Regioselective Activation of Glycosyl Acceptors by a Diarylborinic Acid-Derived Catalyst. *J. Am. Chem. Soc.* **2011**, *133*, 13926-13929. (b) Chan, L.; Taylor, M. S. Regioselective Alkylation of Carbohydrate Derivatives Catalyzed by a Diarylborinic Acid Derivative. *Org. Lett.* **2011**, *13*, 3090-3093.

[12] Daubinet, A. Design, Synthesis and Evaluation of Silver-Specific Ligands. Ph.D. Dissertation, Rhodes University, Grahamstown, South Africa, 2001.



Scheme 4.5: Screen of imidazolium and imidazolinium salts for catalytic activity.

ium salts could be deprotonated to furnish the NHC.[13] We began by screening a variety of sterically and electronically differentiated commercially available imidazolium and imidazolinium salts (Scheme 4.5). When 1-phenylethanol (**4.3**) was subjected to benzyl bromide and sodium *tert*-butoxide in toluene as solvent, after two hours a 3% yield of the target ether **4.5** was observed by ^{1}H NMR. Salts bearing sterically hindered aryl groups (**4.6**, **4.7**, and **4.8**) did not appear to provide any additional product. We were exceptionally pleased to see a 30% yield with bis-adamantyl imidazolium **4.9**, a ten-fold increase in yield over the uncatalyzed reaction. The corresponding imidazolinium salt **4.10** delivered a marginal 7% yield. The yield again increased to 40% with isobutyl substituted imidazolium **4.11**. The bis-*tert*-butyl (**4.12**) and bis-methyl (**4.13**) imidazolium salts were ineffective. Benzimidazolium **4.14** also provided no advantage over the uncatalyzed background reaction. The highest yields were obtained with bis-isopropyl imidazolium **4.15** (67%) and bis-cyclohexyl imidazolium **4.16** (74%). These data suggested that an unsaturated imidazolium ring and a secondary sp^3 hybridized carbon attached to the nitrogens were key structural features.



Scheme 4.6: Control reactions establish requirement of the imdazolium ring for catalysis.

In order to establish that the imidazolium salt was in fact necessary for catalysis, we ran a series of control experiments (Scheme 4.6). With sodium tetrafluoroborate or tetramethylphosphonium bromide present, less than 5% yield of the product was observed. Other

[13](a) Schönherr, H. J.; Wanzlick, H. W. Chemie Nucleophiler Carbene, XVIII. 1,3,4,5-Tetraphenylimidazoliumperchlorat. *Liebigs Ann. Chem.* **1970**, *731*, 176-179. (b) Arduengo, A. J.; Harlow, R. L.; Kline, M. A Stable Crystalline Carbene. *J. Am. Chem. Soc.* **1991**, *113*, 361-363. (c) Arduengo, A. J.; Dias, H. V. R.; Harlow, R. L.; Kline, M. Electronic Stabilization of Nucleophilic Carbenes. *J. Am. Chem. Soc.* **1992**, *114*, 5530-5534.

cationic heterocylic salts derived from 2,6-lutidine (**4.18** and **4.19**) did not accelerate the reaction. Starting from the sodium alkoxide **4.17**,[14] which was fully soluble in toluene, a slightly higher 10% yield was obtained in the absence of any catalyst. This result indicates that *tert*-butanol present in the reaction mixture had a subtle inhibitory effect, presumably through hydrogen bonding to the nucleophile. These control reactions suggest that the nitrogen hetereocyclic plays a critical role in the reaction. Specifically, imidazolium heterocycles bearing the appropriate alkyl substituents were required to obtain any catalytic activity.

[14]Formed by deprotonation of **4.3** with NaH in THF inside an inert atmosphere glovebox. The $\Delta\delta$ (δ**4.17**$-\delta$**4.3**) of the benzyllic methine proton by ^{1}H NMR in toluene-d_8 was +0.17 ppm after concentration and trituration with toluene.

4.3 Mechanistic Studies

In the sections that follow, a discussion of the mechanism of this transformation will be presented. Several hypotheses were proposed and rigorously tested before finally arriving at a mechanism we believed to be consistent with the complete set of data.

4.3.1 *Preliminary Hypothesis Based on Electrophile Activation*

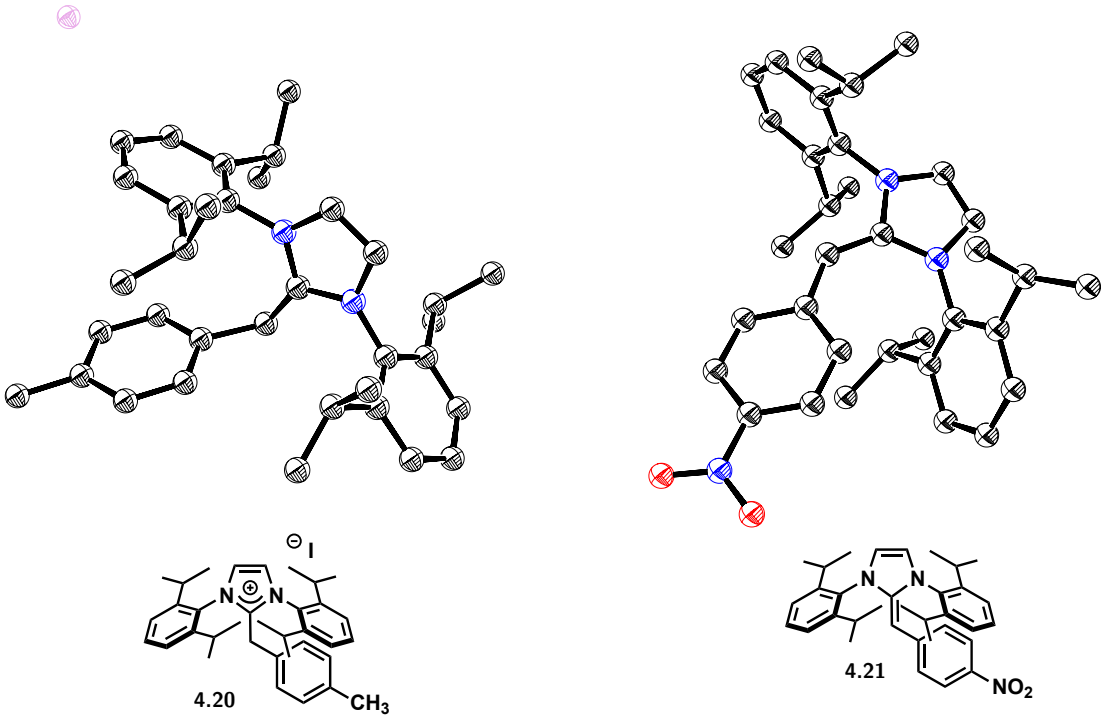
Crystallographic evidence from the literature suggested that carbenes were capable of reacting as nucleophiles with various sp^3 hybridized electrophiles (Figure 4.1).[15] In 2010 and 2011 von Wangelin and coworkers treated aryl substituted imidazolium salts with potassium *tert*-butoxide in THF solutions, forming the carbene, and then subsequently added various halide electrophiles. With an excess of base present (>2 equivalents), the products isolated resembled a deoxy Breslow intermediate,[16] formed by alkylation at the C2 position of the imidazole ring followed by further deprotonation at the benzylic position (**4.21**, right). The newly formed double bond showed a length of 1.39 Å in structure **4.21**, considerably longer than the average C_{sp^2}=C_{sp^2} bond length (1.32 Å),[17] suggesting the bond contains significant charge-separated ylide character. The nucleophilic nature of the benzylic position was confirmed by adding a second equivalent of electrophile, producing doubly alkylated imidazolium salts (not shown). This type of reactivity mirrors that observed for Breslow intermediates in Stetter and benzoin condensation reactions.[18] The protonated

[15] (a) Knappke, C. E. I.; Neudörfl, J. M.; von Wangelin, A. J. On New N-Heterocyclic Carbene Derived Alkylidene Imidazolines. *Org. Biomol. Chem.* **2010**, *8*, 1695-1705. (b) Knappke, C. E. I.; Arduengo, A. J.; Jiao, H.; Neudörfl, J. M.; von Wangelin, A. J. On the Dual Role of *N*-Heterocyclic Carbenes as Bases and Nucleophiles in Reactions with Organic Halides. *Synthesis* **2011**, 3784-3795.

[16] (a) Breslow, R. On the Mechanism of Thiamine Action. IV. Evidence from Studies on Model Systems. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726. (b) A Breslow intermediate was recently isolated: Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J. M.; Schlörer, N. E.; Teles, J. H. Umpolung by N-Heterocyclic Carbenes: Generation and Reactivity of the Elusive 2,2-Diamino Enols (Breslow Intermediates). *Angew. Chem. Int. Ed.* **2012**, *51*, 12370-12374.

[17] Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. Tables of Bond Lengths Determined by X-ray and Neutron Diffraction. Part 1. Bond Lengths in Organic Compounds. *J. Chem. Soc. Perk. T. 2* **1987**, S1-S19.

[18] For a lead reference see: Enders, D.; Balensiefer, T. Nucleophilic Carbenes in Asymmetric Organocatalysis. *Acc. Chem. Res.* **2004**, *37*, 534-541.

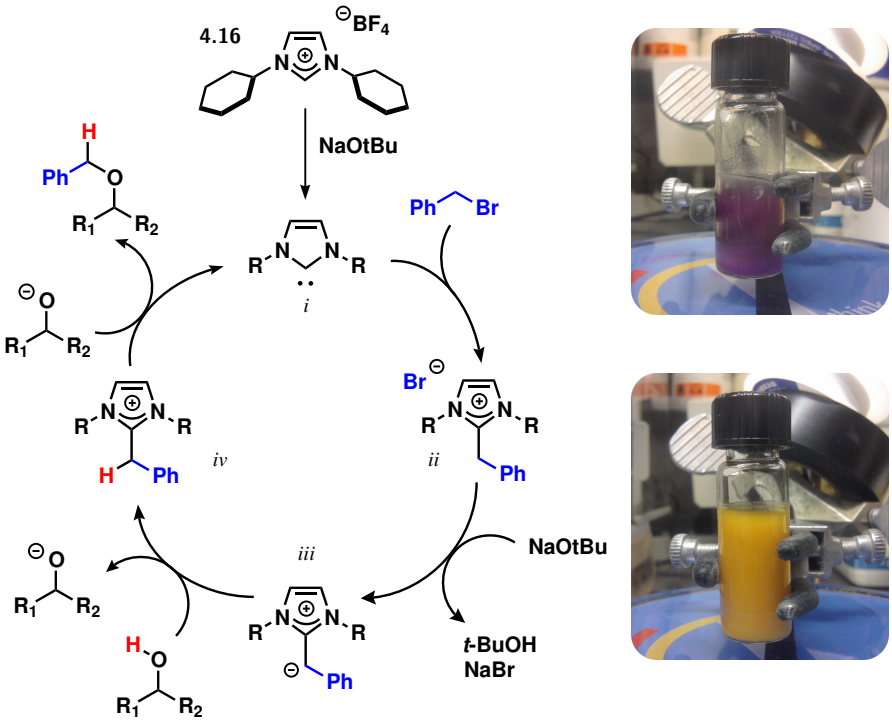


von Wangelin **2010**[15a] *von Wangelin* **2011**[15b]

Figure 4.1: Crystal structures of products from carbenes and sp^3 electrophiles.

imidazolium salt **4.20** (left) was obtained by adding TMSI to a solution containing residual *tert*-butanol from the carbene formation, liberating an equivalent of HI. Direct isolation of **4.20** was complicated by the tendency to rapidly become deprotonated, necessitating an acidic quench after formation of the alkylated species.

We had hoped that in the presence of a suitable nucleophile, an intermediate akin to **4.20** could serve as an activated electrophile. Given the precedents for carbenes to act as nucleophiles towards sp^3 electrophiles, we proposed the catalytic cycle illustrated in Scheme 4.7. Stirring the imidazolium salt **4.16** in toluene with sodium *tert*-butoxide produces the carbene (**4.16** $\longrightarrow$ *i*), entering the catalytic cycle. Addition of benzyl bromide forms the activated electrophile (*i* $\longrightarrow$ *ii*), which can then either directly undergo alkylation and regenerate the carbene (*ii* $\longrightarrow$ *i*), or become deprotonated (*ii* $\longrightarrow$ *iii*) to form a species similar

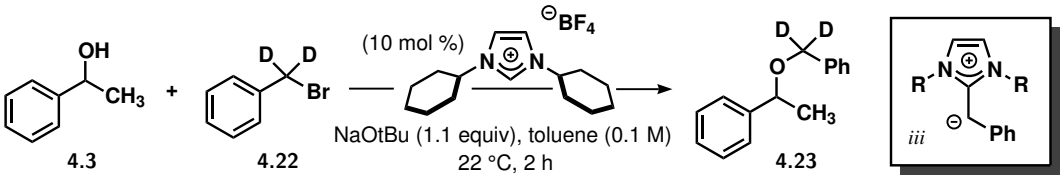


Scheme 4.7: First mechanistic proposal involving NHC activation of the electrophile.

to **4.21**. Reprotonation from from the secondary alcohol would generate an imidazolium alkoxide salt pair (*iii* ⟶ *iv*). The more nucleophilic alkoxide could then attack the activated benzyl bromide, generating the ether product and releasing the carbene for further turnovers. Prior to the addition of the electrophile, we observed the formation of a purple solution (top right), likely indicating formation of the carbene.[19] Upon addition of benzyl bromide to the carbene solution we *immediately* observed the formation of a turbid bright yellow suspension (bottom right). We believed this was consistent with the formation of intermediate *iii* and the precipitation of sodium bromide.

In order to test this mechanistic hypothesis, we designed a series of deuterium labeling

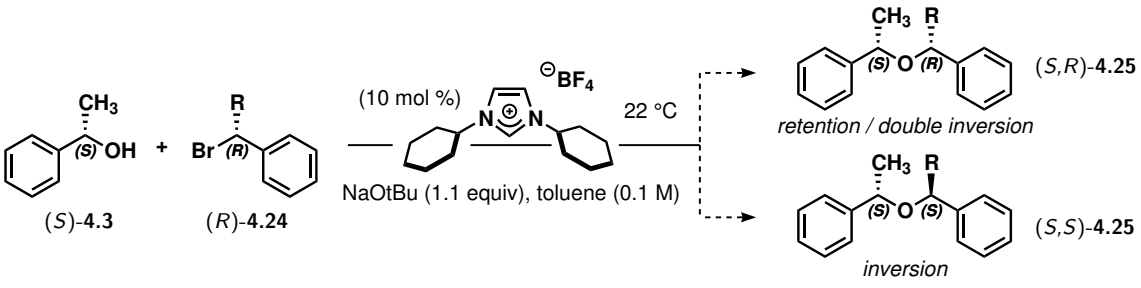
[19]Non-transition metal carbene complexes are known to form colored solutions. (a) Arnold, P. L.; Rodden, M.; Wilson, C. Thermally Stable Potassium *N*-Heterocyclic Carbene Complexes with Alkoxide Ligands, and a Polymeric Crystal Structure with Distorted, Bridging Carbenes. *Chem. Commun.* **2005**, 1743-1745. (b) Willans, C. E. Non-transition Metal *N*-Heterocyclic Carbene Complexes. *Organomet. Chem.* **2010**, *36*, 1-28.



Scheme 4.8: No benzylic proton incorportation observed with d_2-benzyl bromide.

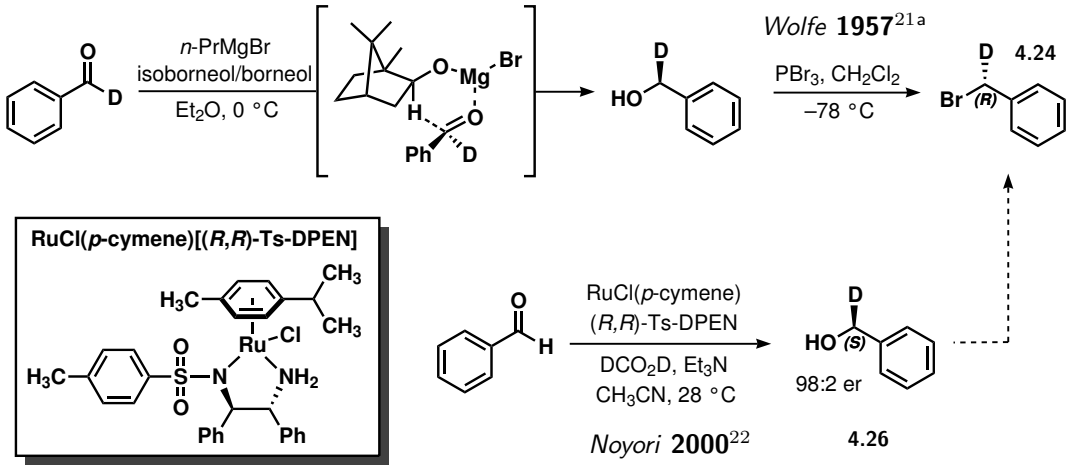
experiments. To probe for the formation of intermediate *iii* in the catalytic cyle, we ran an experiment with d_2-benzyl bromide (**4.22**, Scheme 4.8). Our expectation was that if *iii* was part of the productive catalytic cycle, we would see proton incorporation into the ether product. The recovered product **4.23** showed no incorporation of protons at the benzylic position by ^{1}H NMR spectroscopy, suggesting that *iii* was not part of a productive pathway in the catalytic cycle. Regardless, the formation of *iii* was not integral to this mechanism being operative, as proposed intermediate *ii* could be directly alkylated without proceeding through intermediate *iii*.

We wanted to design an experiment to directly test whether or not the electrophile was being activated through a nucleophilic displacement of the leaving group. In the proposed mechanism, the electrophile would undergo two inversions at the site of the leaving group – once upon addition of the carbene ($i \longrightarrow ii$) and again when the nucleophile attacks ($iv \longrightarrow i$). Starting from a chiral optically pure alcohol and reacting that with a chiral secondary electrophile would give different diastereomers of the product depending on the mechanism (Scheme 4.9). Double inversion of the electrophile, a net retention of the original



Scheme 4.9: Proposed experiment to test for nucleophilic electrophile activation.

configuration, would lead to a different diastereomer than direct S_N2 substitution. Alternatively, a 50:50 mixture of diastereomers would be indicative of an S_N1 pathway. While both (*R*)– and (*S*)-α-methylbenzyl bromide (R = CH_3) were known compounds and could be readily prepared from the commercially available chiral alcohol,[20] attempts to use the more hindered secondary electrophile were unsuccessful. We decided to target d_1-benzyl bromide (R = D) and were presented with the unique challenge of preparing a stereogenic center containing a hydrogen and deuterium.



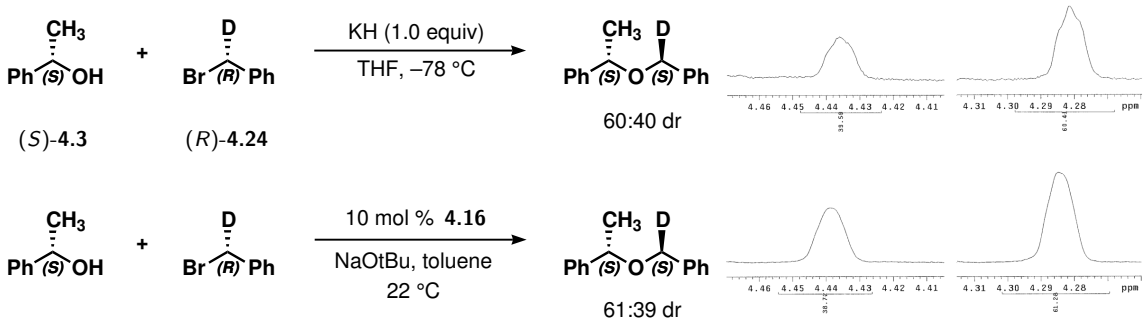
Scheme 4.10: Preparation of optically active d_1-benzyl bromide.

We found one early report discussing the preparation of optically active d_1-benzyl bromide (Scheme 4.10, top).[21] The bromide was obtained after PBr_3 bromination of the optically active benzyl alcohol, prepared through Meerwein-Ponndorf-Verley type reduction with a stoichiometric mixture of borneol and isoborneol. No discussion with regard to absolute stereochemical control was provided. We decided to prepare the benzyl alco-

[20] Chen, Y.; Tang, W. L.; Mou, J.; Li, Z. High-Throughput Method for Determining the Enantioselectivity of Enzyme-Catalyzed Hydroxylations Based on Mass Spectrometry. *Angew. Chem. Int. Ed.* **2010**, *49*, 5278-5283.

[21] (a) Streitweiser, A.; Wolfe, J. R. Stereochemistry of the Primary Carbon. V. Optically Active Benzyl-α-*d* Alcohol. *J. Am. Chem. Soc.* **1957**, *79*, 903-907. (b) Streitweiser, A.; Wolfe, J. R. Stereochemistry of the Primary Carbon. XI. Ethanolysis of Optically Active Benzyl-α-*d* *p*-Toluenesulfonate. *J. Am. Chem. Soc.* **1959**, *81*, 4912-4914.

hol precursor through a more modern asymmetric transfer hydrogenation with deuterated formic acid using the protocol reported by Noyori in 2000 (Scheme 4.10, bottom).[22] The enantiomeric ratio of alcohol **4.26**, after transfer hydrogenation of benzaldehyde, was determined to be 98:2 er by ^{1}H NMR using the Mosher ester method.[23] Bromination at low temperature with PBr_3 delivered the d_1-benzyl bromide **4.24** cleanly after simple Kügelrohr distillation. We were concerned about racemization during this step; however there were no standard methods available to determine the enantiopurity of the bromide.[24] The optical rotation reported in the literature for **4.24** was +0.105° and no discussion of the optical purity was given.[21a] In order for our experiment to be successful we only needed a marginal enrichment, so we moved forward with the bromide.



Scheme 4.11: Data indicates reaction proceeds through an S_N2 mechanism.

As a point of comparison, we exposed optically pure (*S*)-**4.3** to bromide **4.24** and potassium hydride in THF at −78 °C (Scheme 4.11). The material recovered was formed in a 60:40 dr based on integration of the ^{1}H NMR signals for the benzylic hydrogen attached to the deuterated carbon. Assuming the reaction proceeded through a clean S_N2 mechanism

[22] Yamada, I.; Noyori, R. Asymmetric Transfer Hydrogenation of Benzaldehydes. *Org. Lett.* **2000**, *2*, 3425-3427.

[23] Dale, J. A.; Dull, D. L.; Mosher, H. S. α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines. *J. Org. Chem.* **1969**, *34*, 2543-2549.

[24] The use of chiral shift reagents may have been workable, but was not attempted. McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. The Determination of Enantiomeric Purity Using Chiral Lanthanide Shift Reagents. *J. Am. Chem. Soc.* **1974**, *96*, 1038-1054.

under these conditions,[25] the enantiopurity of bromide **4.24** would have been approximately 60:40 er. We then ran the same experiment under our catalyzed conditions and were surprised to see that the ether was formed with a nearly identical 61:39 dr, favoring the same diastereomer as the S_N2 control reaction. These data rule out the possibility of a double inversion mechanism, suggesting that a pathway other than nucleophilic activation of the electrophile was operative.

4.3.2 *Second Hypothesis: Carbenes as Brønsted Bases*

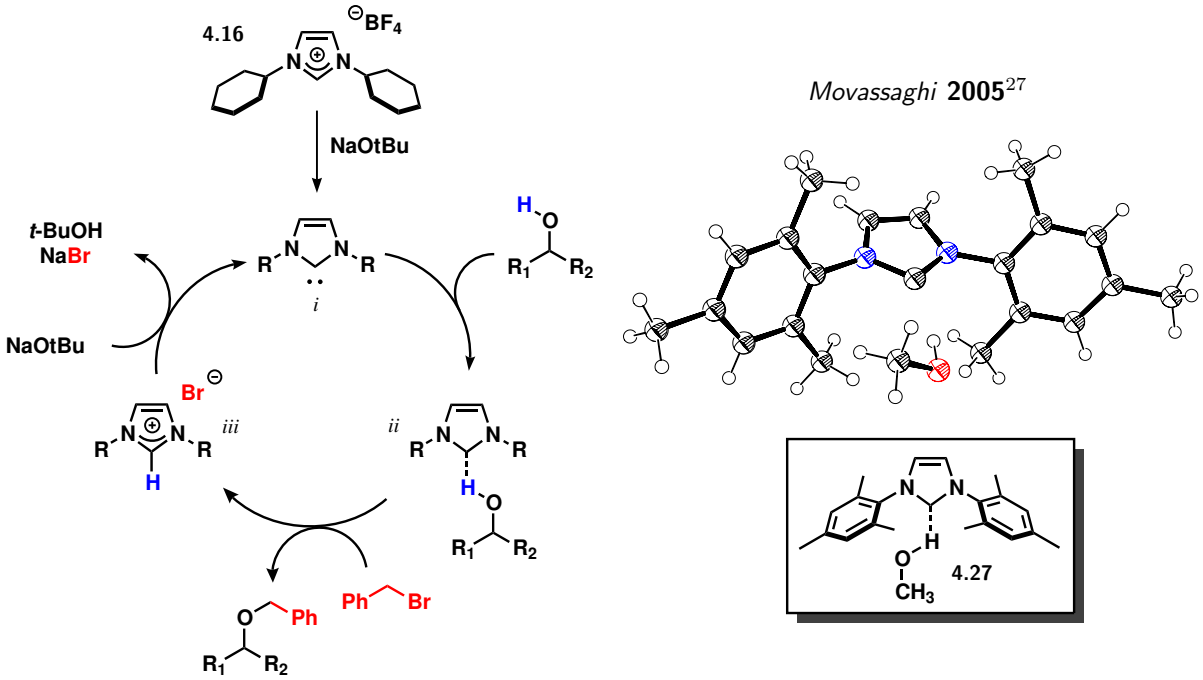
Imidazolium derived carbenes have been described as reasonably strong Brønsted bases, with pK_a values of the conjugate acids ranging anywhere from 16-24 in DMSO.[26] In 2005, the Movassaghi group reported an NHC catalyzed amidation reaction of unactivated esters with amino alcohols.[27] In the proposed mechanism, the amino alcohol was primed for nucleophilic attack by removing the alcohol proton with the NHC, generating a more nucleophilic alkoxide. Careful NMR studies showed that alcohols in the presence of NHCs exhibit a significant downfield shift for the O−H proton. Movassaghi was also able to obtain a solid state structure of IMes complexed with methanol, which showed a nearly linear (∠ C−H−O, 174°) hydrogen bond interaction between the methanol and C2 position of the imidazolylidene ring (**4.27**, Scheme 4.12). The Scheidt group more recently introduced an NHC catalyzed intermolecular *oxa*-Michael reaction, where they also propose a Brønsted base role for the NHC.[28] In a single intramolecular example, Scheidt observed a marginal level of enantioselectivity with a chiral NHC, suggesting that the proton may not be fully

[25] (a) Ashby, E. C.; Bae, D. H.; Park, W. S.; Depriest, R. N.; Su, W. Y. Evidence for Single Electron Transfer in the Reaction of Alkoxides with Alkyl Halides. *Tetrahedron Lett.* **1984**, *25*, 5107-5110. (b) Vollhardt, K. P. C.; Shore, N. E. *Organic Chemistry: Structure and Function*, 6th ed.; W. H. Freeman and Company: New York, 2011.

[26] Alder, R. W.; Allen, P. R.; Williams, S. J. Stable Carbenes as Strong Bases. *J. Chem. Soc. Chem. Comm.* **1995**, 1267-1268.

[27] Movassaghi, M.; Schmidt, M. A. *N*-Heterocyclic Carbene-Catalyzed Amidation of Unactivated Esters with Amino Alcohols. *Org. Lett.* **2005**, *7*, 2453-2456.

[28] Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *N*-Heterocyclic Carbene-Catalyzed Conjugate Additions of Alcohols. *J. Am. Chem. Soc.* **2010**, *132*, 13179-13181.

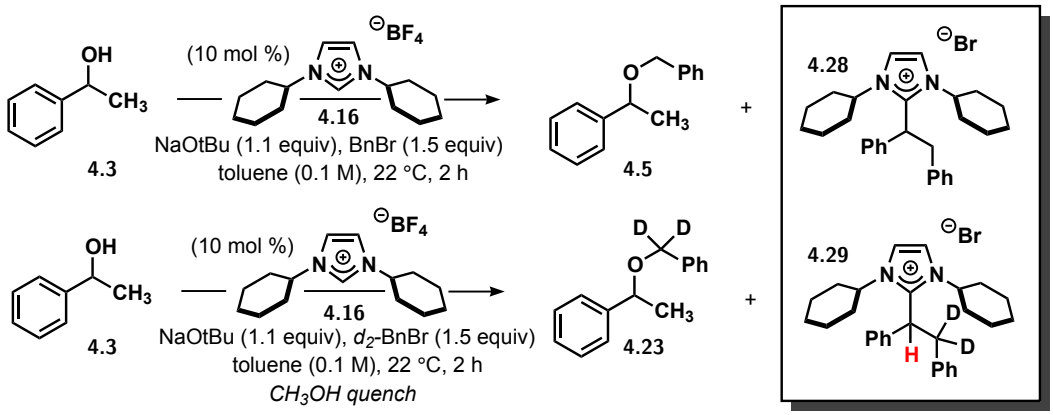


Scheme 4.12: Proposed cycle for carbene as Brønsted base and crystallographic precedents.

transferred to the NHC or the imidazolium alkoxide ion-pair was closely associated.

The proposed catalytic cycle for a Brønsted base mechanism, illustrated in Scheme 4.12, again opens with deprotonation of the imidazolium salt **4.16** to deliver the carbene (**4.16** $\longrightarrow$ *i*). The secondary alcohol enters the catalytic cycle, forming neutral alcohol carbene complex *ii*. The activated alcohol displaces the bromide, forming the ether product and regenerating the imidazolium salt (*ii* $\longrightarrow$ *iii*). The carbene can then be regenerated by deprotonating with an additional equivalent of sodium *tert*-butoxide (*iii* $\longrightarrow$ *i*).

To test this mechanistic hypothesis we were curious if intermediate *iii*, the imidazolium salt, could be recovered after the reaction by reprotonating the carbene. The imidazolium salt **4.16** was virtually insoluble in Et_2O and fully soluble in CH_2Cl_2, so by selective extraction we hoped to cleanly recover the salt. At the conclusion of the reaction we concentrated the mixture and removed any organic soluble materials by washing with Et_2O. The remaining material was dissolved in CH_2Cl_2 and filtered away from sodium bromide. We



Scheme 4.13: Attempts to recover **4.16** lead to the discovery of doubly alkylated salts.

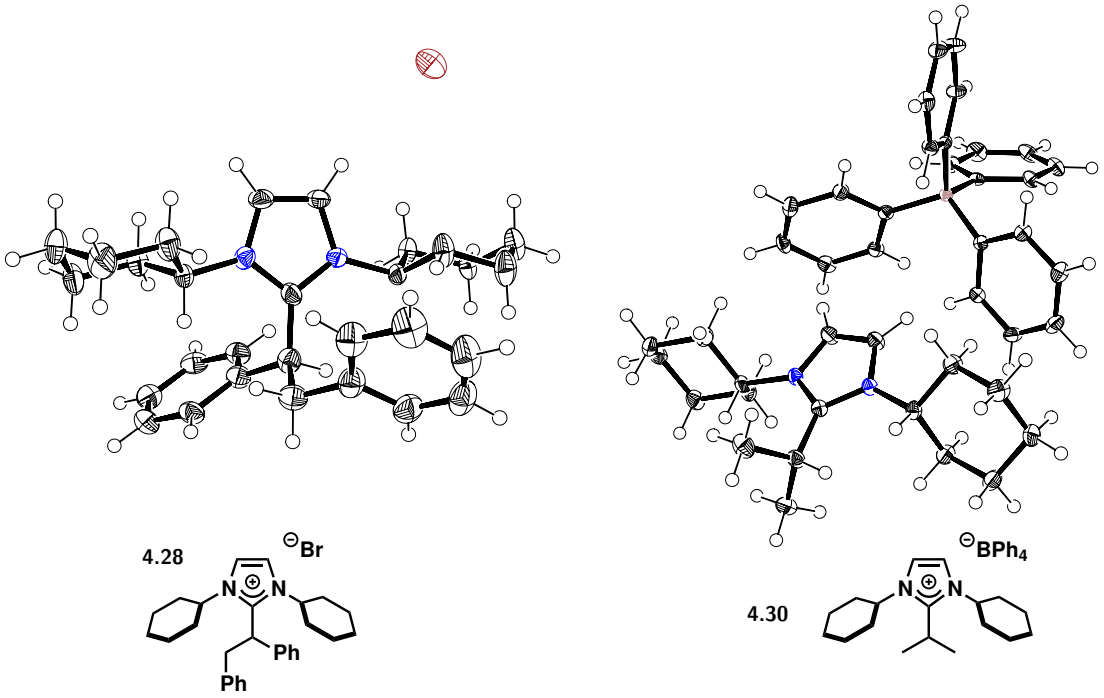
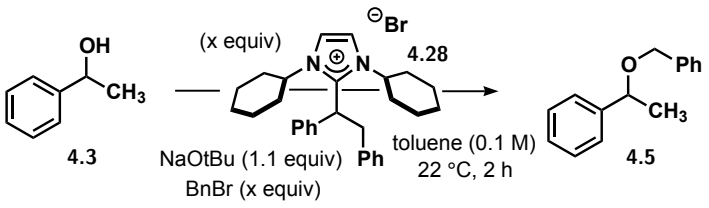


Figure 4.2: Crystal structures of C2 alkylated imidazolium salts prepared during this study.

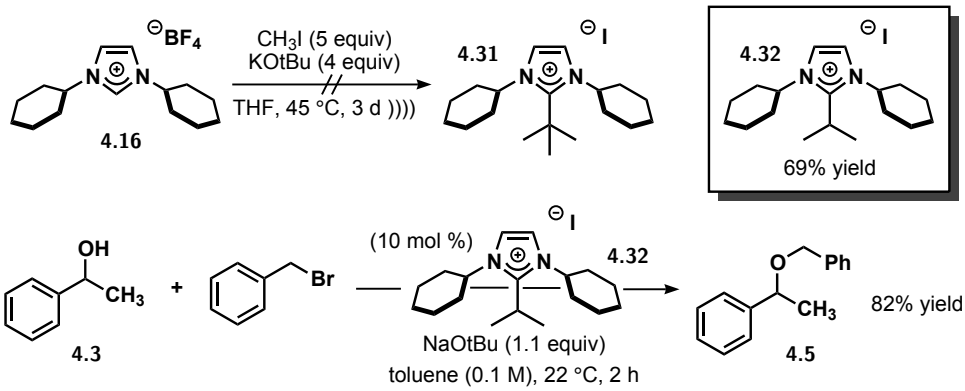
were surprised to see that after concentration of the CH_2Cl_2, the only salt recovered was doubly alkylated imidazolium **4.28** in >90% purity by ^{1}H NMR spectroscopy (Scheme 4.13). The structure of **4.28** was confirmed by careful analysis of the spectral data and ultimately by X-ray crystallography (Figure 4.2, left). In no situation did we ever recover any of the starting imidazolium salt **4.16**. When we ran the same experiment with d_2-benzyl bromide and quenched the reaction with methanol, the recovered salt contained only two deuteriums (**4.29**). A proton was incorporated at the benzylic methine carbon, indicating that it was deprotonated at some point during the reaction. These data seemed to support a mechanism comparable to the original proposal based on a nucleophilic activation role for the carbene (Scheme 4.7, page 440).

We were able to independently synthesize an authentic sample of the doubly alkylated imidazolium salt **4.28** in high yield by adding excess sodium *tert*-butoxide and benzyl bromide to a THF solution of **4.16**. With sufficient quantities of material in hand, we carried out a series of experiments to try to understand the role of the alkylated imidazolium (Scheme 4.14). In the absence of benzyl bromide and with stoichiometric **4.28** none of the desired product was detectable, consistent with the previous experiment which showed the reaction proceeds through an S_N2 pathway (Scheme 4.11, page 443). Transfer of a benzyl group from **4.28** would require a double inversion of the electrophile which was formerly ruled out. With a catalytic amount of **4.28** and 1.5 equivalents of benzyl bromide the yield increased to 70%, a result suspiciously similar to the yield obtained with the parent imidazolium salt **4.16** (74%).



equiv salt **4.28**	equiv BnBr	yield **4.5**
1.0	0	<2%
0.10	1.5	70%

Scheme 4.14: Experiments with C2 alkylated imidazolium salt **4.28**.



Scheme 4.15: Attempted substitution of C2 position with quaternary carbon.

Given that we recovered **4.29** (Scheme 4.13) with a proton incorporated at the benzylic methine position, this data point seemed to suggest a role for an anion adjacent to the imidazolium ring. We attempted to prepare a catalyst with a quaternary carbon attached to the C2 position of the imidazolium to remove any hydrogens. Exposure of **4.16** to 5 equivalents of methyl iodide and 4 equivalents of potassium *tert*-butoxide did not deliver the anticipated quaternary substituted imidazolium salt even with prolonged heating and sonication of the heterogeneous mixture ($\longrightarrow$ **4.31**, Scheme 4.15). Instead, a 69% isolated yield of the isopropyl substituted salt **4.32** was obtained. A solid state structure of the tetraphenyl borate salt (**4.30**, Figure 4.2) showed that significant amount of allylic strain would be generated upon introduction of the *tert*-butyl group, likely explaining why the reaction failed to introduce an additional methyl group.[29] Carrying out the reaction with a catalytic amount of isopropyl substituted imidazolium iodide salt **4.32** delivered the ether product in 82% yield, the highest yield observed up to this point. While this data point does not rule out the possible involvement of the proton adjacent to the imidazolium ring, it does point to a mechanistic pathway that does not require the involvement of a C2 carbene.

[29]The $C_{16}-C_1-N_2-C_{10}$ dihedral angle was 5.2° in the solid state structure. See the appendix for further details.

4.3.3 *Loosely Associated Ion-Pair Mechanism*

The experiments in the previous two sections showed that an intermediate involving a carbene in the catalytic cycle was highly unlikely. Alkylation of the imidazolium ring at the C2 position effectively blocks the formation of a carbene,[30] yet the salts were still competent catalysts. We were still curious if there was a role for the benzylic methine proton adjacent to the imidazolium ring. A study of base loading versus yield of **4.3** revealed a linear increase ($R^2 = 0.99$) in yield up to 1.3 equivalents of base, and a significant drop in yield beyond 1.4 equivalents (Figure 4.3). The reaction was highly sensitive even to subtle changes in the amount of base, suggesting a proton transfer event may be critical in the reaction mechanism.

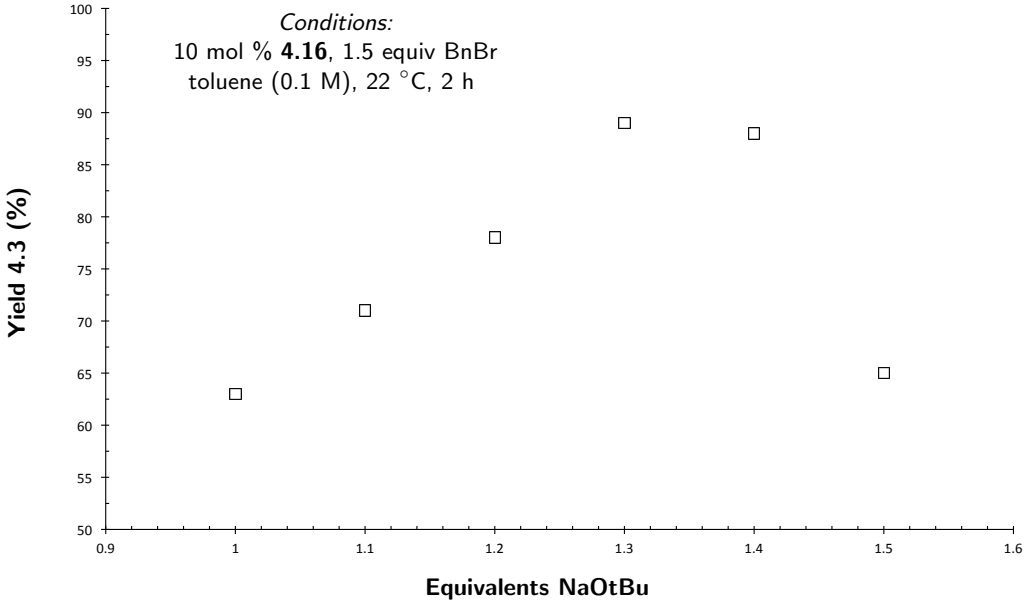
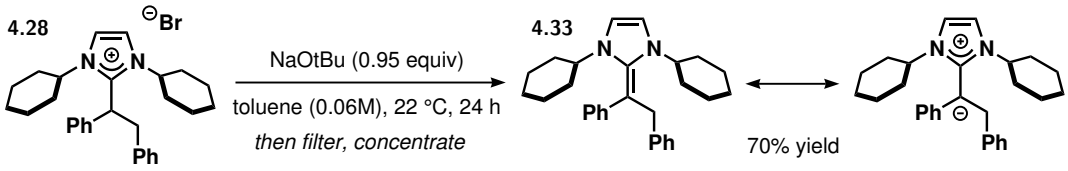


Figure 4.3: Base loading study, equivalents of NaOtBu versus product yield.

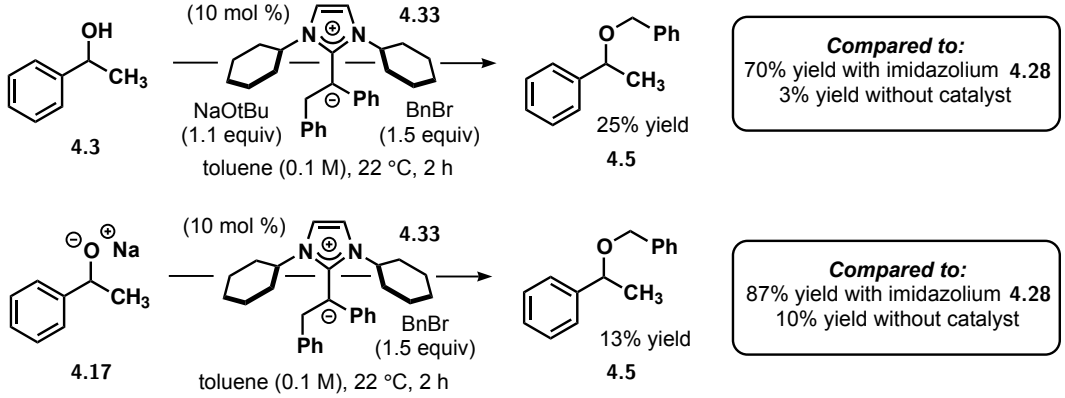
We were able to cleanly deprotonate dibenzylated imidazolium bromide salt **4.28** with sodium *tert*-butoxide in toluene, conditions comparable to our standard reaction conditions

[30] Abnormal carbenes at the C4 or C5 positions of imidazoliums have been reported but we did not believe this was a likely intermediate. Arnold, P. L.; Pearson, S. Abnormal *N*-Heterocyclic Carbenes. *Coordin. Chem. Rev.* **2007**, *251*, 596-609.



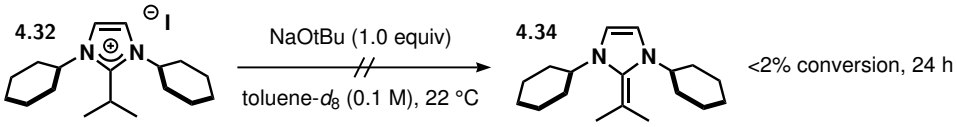
Scheme 4.16: Deprotonation of imidazolium salt **4.28** to afford ylide **4.33**.

(Scheme 4.16). After filtration inside an inert atmosphere glove box to remove any residual **4.28** and sodium bromide, concentration afforded a pure dark green solid in 70% yield ($\longrightarrow$ **4.33**). Dilute toluene or benzene solutions of **4.33** were bright yellow, consistent with some of the earlier color changes observed in the reaction (Scheme 4.7, page 440). The ^{1}H and ^{13}C NMR data for **4.33** showed considerable C_s symmetry, indicative of significant ylide or single bond character. The symmetry could be the result of free rotation, or an orthogonal relationship between the phenyl groups and the imidazole ring.



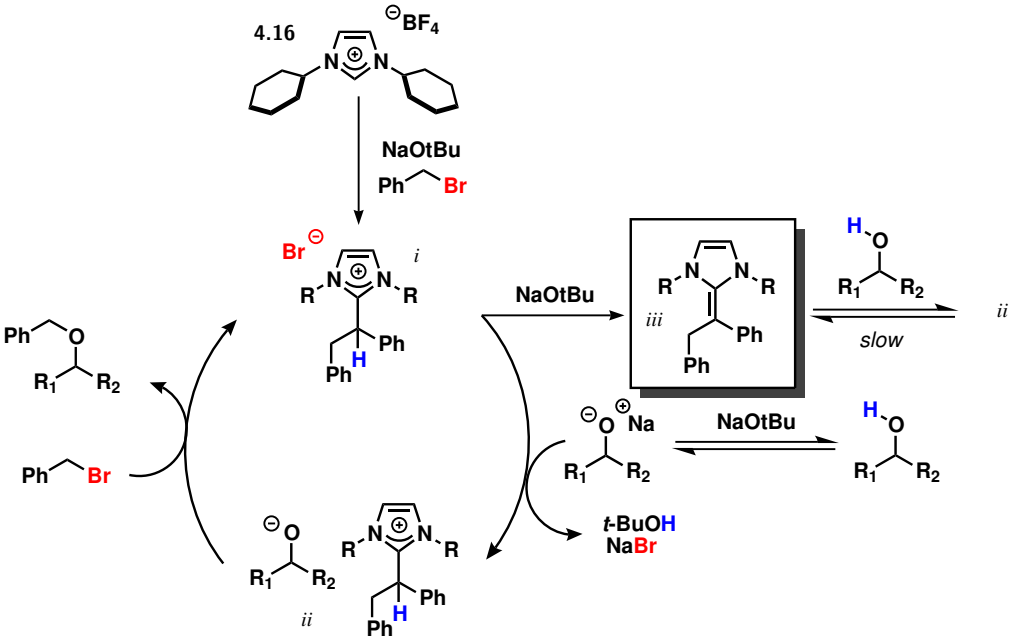
Scheme 4.17: Experiments with ylide **4.33** showed poorer yields than the parent imidazolium salt **4.28**.

To test the catalytic activity of **4.33**, we subjected it to two different experiments. Under standard conditions with 1-phenylethanol, a substantially lower 25% yield of ether **4.5** was observed (Scheme 4.17, top). In contrast, the protonated imidazolium salt **4.28** gave a 70% yield in the same time frame under identical conditions. The 25% yield was still higher than the uncatalyzed background reaction, suggesting that ylide **4.33** could be a resting state of the more active imidazolium catalyst that can slowly re-enter the catalytic cycle



Scheme 4.18: Attempts to form ylide from **4.32** were unsuccessful.

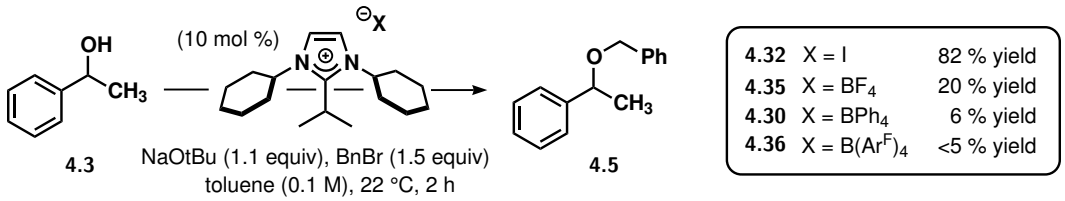
upon protonation. The base loading study was also consistent with this observation. Higher loadings of base lead to a decrease in yield, presumably by funnelling more of the catalyst to the less active deprotonated form. Starting with the sodium alkoxide of 1-phenylethanol delivered the product in a marginal 13% yield, within experimental error of the uncatalyzed background reaction. The same reaction with imidazolium salt **4.28** afforded a significantly augmented 87% yield. When we attempted to form the analogous ylide with **4.32**, <2% conversion occured in 24 hours by ^{1}H NMR ($\longrightarrow$ **4.34**, Scheme 4.18). The slightly higher yield obtained with **4.32** (82% versus 70% with **4.28**) could be attributed to the fact that the isopropyl group methine proton was significantly less acidic and production of the deactivated form of the catalyst was not as facile.



Scheme 4.19: Proposed mechanism consistent with all of the data points.

The experimental evidence points to the mechanistic proposal illustrated in Scheme 4.19. Before entering the catalytic cycle, **4.16** rapidly undergoes double benzylation to produce the active catalyst (**4.16** $\longrightarrow$ *i*). The sodium alkoxide of the secondary alcohol, in equilibrium with sodium *tert*-butoxide, exchanges for the bromide counter-ion causing sodium bromide to precipitate from the reaction mixture (*i* $\longrightarrow$ *ii*). The alkoxide, now paired with a weakly associated and diffuse counter-ion, displaces benzyl bromide to deliver the product and regenerate the catalyst (*ii* $\longrightarrow$ *i*). Alternatively, the catalyst can be deprotonated by sodium *tert*-butoxide to generate the inactive ylide form (*i* $\longrightarrow$ *iii*). The ylide can slowly re-enter the catalytic cycle upon protonation from the secondary alcohol (*iii* $\longrightarrow$ *ii*).

During the course of our studies, we had also prepared a series of catalysts with different counter-ions and were initially perplexed by the results (Scheme 4.20). Catalysts with larger and more weakly coordinating ions lead to diminishing yields of **4.5**. Our hope was that by increasing the solubility of the catalyst, we should see a corresponding increase in the yield. The critical step in the proposed mechanism requires the formation of an imidazolium alkoxide ion-pair (*i* $\longrightarrow$ *ii*). The formation of the integral ion-pair could be driven by the precipitation of sodium bromide, and with other more soluble counter-ions this key exchange may not occur as readily.[31] These observations are consistent with the proposed mechanistic pathway in Scheme 4.19.



Scheme 4.20: Diminishing yields with larger and less coordinating anions.

[31] For a discussion on solubility of weakly coordinated ions in low dielectric media see: Krossing, I.; Raabe, I. Noncoordinating Anions–Fact or Fiction? A Survey of Likely Candidates. *Angew. Chem. Int. Ed.* **2004**, *43*, 2066-2090.

4.4 Transition State Structure Experiments

Previous screening had shown that commercially available aryl-substituted imidazolium salts containing *ortho* substitution were not competent catalysts (Scheme 4.5, page 435). Given the new information about the mechanism, it was plausible that these catalysts were inactive because they could not form the active doubly-alkylated catalyst *in situ*. We pre-

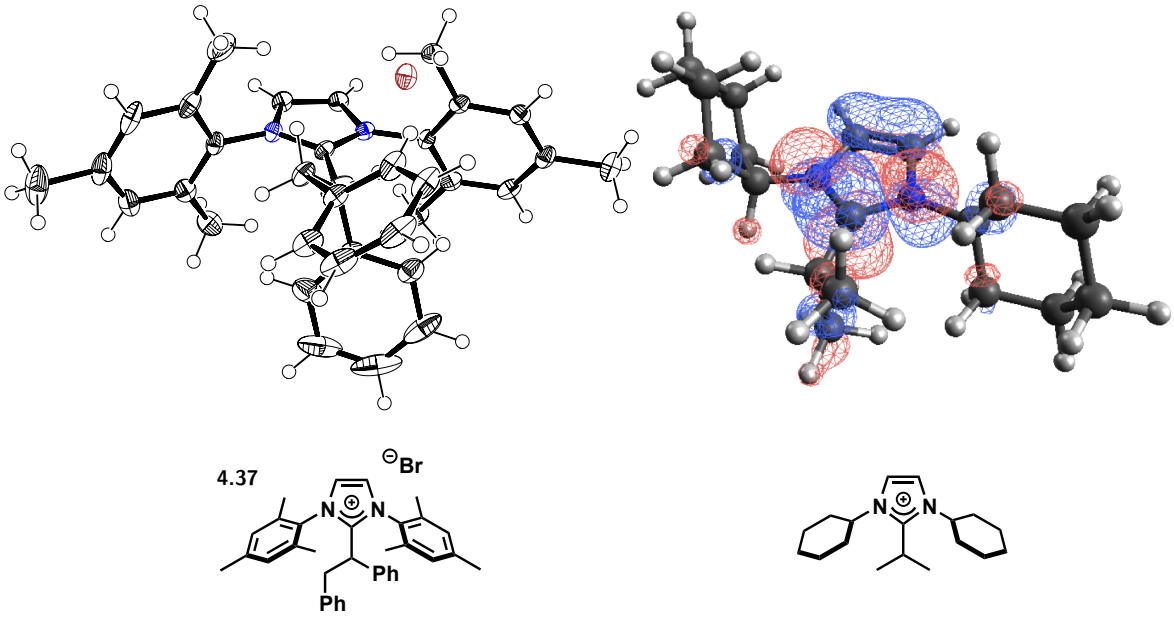
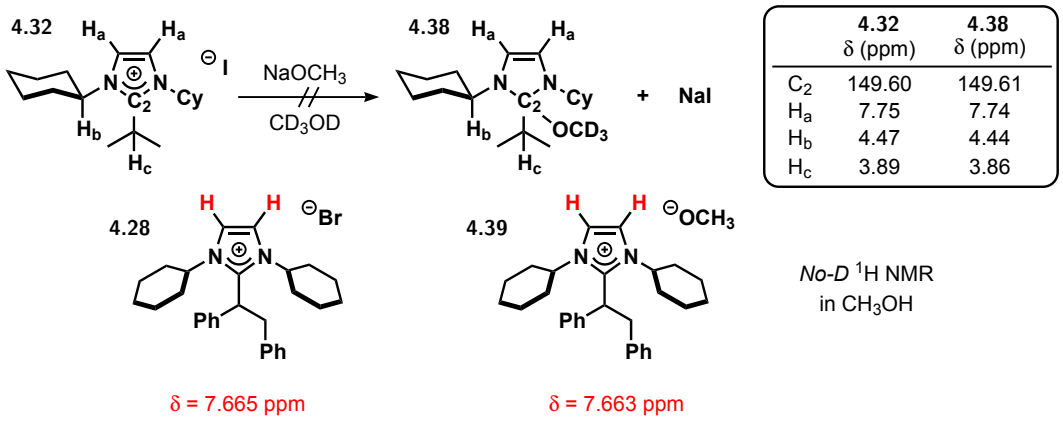


Figure 4.4: Crystal structure of **4.37** (left) and imidazolium LUMO (right) – *Gaussian '03 - AM1*

pared an authentic sample of doubly-benzylated IMes (**4.37**, Figure 4.4, left) and found that even with pre-alkylation, the catalyst was not active. However, the solid state structure of **4.37** led to a hypothesis about the method of interaction between the imidazolium and alkoxide. Low level computation modeling of the imidazolium LUMO showed a large coefficient centered on the C2 position between the two nitrogens (Figure 4.4, right). It was possible that the *ortho* substitution on the aryl groups blocked access to the LUMO, weakening the interaction between the catalyst and alkoxide.[32] While this would generate a

[32] Attempts to prepared other unhindered and electronically modified aryl-imidazolium salts (aryl = phenyl, *p*-OCH_3 phenyl, *p*-NO_2 phenyl) were unsuccessful.



	4.32 δ (ppm)	4.38 δ (ppm)
C_2	149.60	149.61
H_a	7.75	7.74
H_b	4.47	4.44
H_c	3.89	3.86

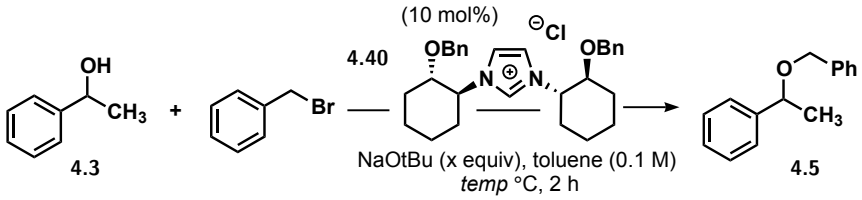
Scheme 4.21: NMR data indicates alkoxide not bound to C2 position.

less nucleophilic alkoxide, we hypothesized that the formation of a neutral C2 adduct could be a solubilizing interaction in the low dielectric solvent.

A covalent interaction between the alkoxide and imidazolium was tested by a series of NMR experiments (Scheme 4.21). Covalent interaction between the imidazolium C2 and alkoxide would dearomatize the ring and lead to significant differences in the chemical shifts relative to the halide salts. Treatment of imidazolium iodide **4.32** with freshly prepared $NaOCH_3$ showed effectively no change in the proton and carbon NMR chemical shifts ($\longrightarrow$ **4.38**). Furthermore, proton NMR data for **4.28** and the corresponding methoxide salt **4.39**[33] exhibited identical proton shifts in methanol for the C4 and C5 hydrogens. These experiments do not completely rule out the possibility of a fleeting covalent interaction in a highly unfavorable equilibrium with the dissociated form. For solubility reasons, methanol was used as the solvent for these experiments. The use of methanol could discourage formation of the neutral dearomatized adduct **4.38** by stabilizing the charge separated form. This appears to be the case with **4.28** and **4.38**, as there is essentially no difference in the proton spectra even with the different counterions.

In an attempt to understand how intimately associated the imidazolium alkoxide ion-pair was, a C_2-symmetric chiral catalyst (**4.40**) was prepared to look for any kinetic resolution

[33]Prepared by adding methanol to ylide **4.33**. See the experimental section for characterization data.



entry[a]	equiv base	temp (°C)	er **4.3**[b]	er **4.5**[b]	k_{rel}	yield **4.5** (%)[c]
1	1.3	22	*na*	*na*	*na*	>98
2	0.75	22	50:50	50:50	1	55
3	0.75	0	52:48	51:49	1.06	46
4	0.75	−78	50:50	50:50	1	9

[a] *Conditions:* 0.1 M in toluene with 10 mol % **4.40**, 1.5 equiv benzyl bromide. Catalyst **4.40** and NaOtBu pre-mixed for 15 minutes at 22 °C before adding benzyl bromide and cooling to the appropriate temperature. [b] Determined by chiral GC analysis in comparison with authentic racemic material. [c] Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Table 4.1: Chiral C_2-symmetric catalyst **4.40** shows no asymmetric induction.

of the secondary alcohol (Table 4.1). We were pleased to see with 1.3 equivalents of sodium *tert*-butoxide the reaction rapidly reached complete conversion (entry 1). Dropping the base loading to 0.75 equivalents delivered the product in 55% yield, consistent with 0.2 equivalents of base consumed during the formation of the doubly-alkylated active catalyst. Unfortunately both the product (**4.5**) and starting material (**4.3**) were racemic (entry 2). Carrying out the reaction at lower temperatures also did not afford material in any detectable levels of enantioselectivity (entries 3 and 4). These data suggest that the ions were weakly associated in a manner that was poorly organized.[34]

Computations on imidazolium methoxide geometries in toluene solution lead to another plausible hypothesis for the how the two ions interact in solution. Geometry optimization calculations seemed to suggest that there was a considerable degree of hydrogen bonding between the C4 imidazolium hydrogen and the alkoxide (Figure 4.5). The C4–H bond length of 1.20 Å was signifcantly elongated relative to the C5–H bond length of just 1.08 Å. The solid state structures of **4.28** (page 446) and **4.37** (page 453) also seemed to show

[34]Several other secondary alcohols were tested and all in all cases racemic starting materials and products were recovered.

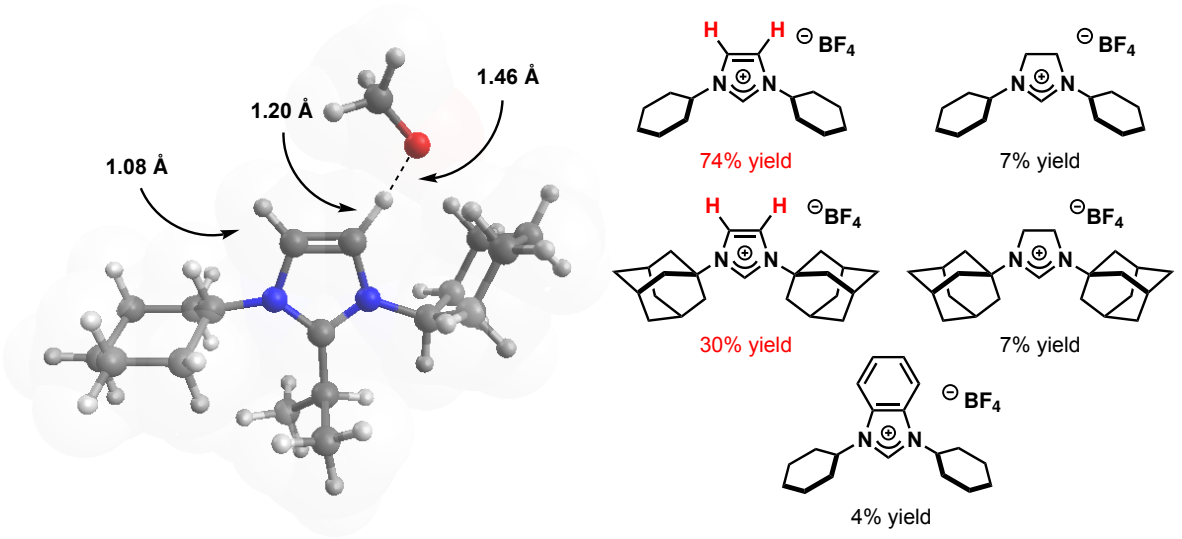
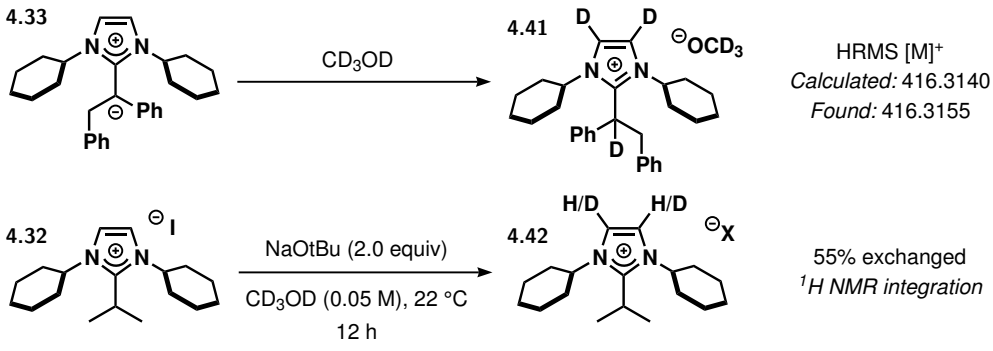


Figure 4.5: Computations suggest role for C4 and C5 protons – *Gaussian '03 - B3LYP/6-31G**

the halide counter-ion associated with a single C4 hydrogen.[35] Reexamining the data for the catalysts illustrated in Figure 4.5 showed a clear trend. The most successful catalysts were those with unsaturated sp^2 hybridized backbones containing two hydrogens. When we recorded NMR data for ylide **4.33** in deuterated methanol we expected to see deuterium incorporated at the benzylic methine position, but we were surprised to see that the signals associated with the C4 and C5 positions also exchanged ($\longrightarrow$ **4.41**, Scheme 4.22, top).

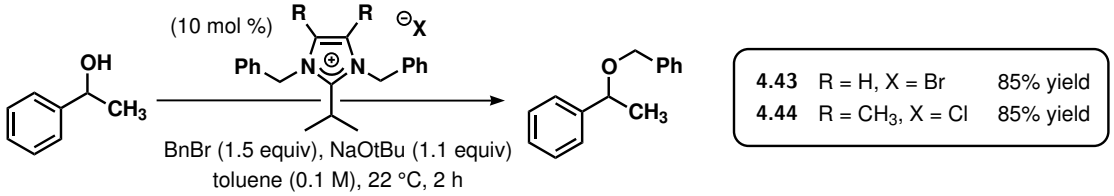


Scheme 4.22: Protons at C4 and C5 positions are exchangable under basic conditions.

[35] Carbon hydrogen bond lengths were not accurately determined in the solid state structures. The orientation of the halide relative to the imidazolium ring may have simply been the result of a preferred crystal packing orientation. See the appendix for details.

Exposure of imidazolium **4.32** to sodium *tert*-butoxide in deuterated methanol showed a slow 55% exchange of *only* the backbone hydrogens in 12 hours ($\longrightarrow$ **4.42**, Scheme 4.22, bottom). Weak C−H···O hydrogen bonds are known to exist and given the propensity for these hydrogens to exchange under basic conditions, we believed this might be a plausible secondary interaction between the catalyst and alkoxide.[36]

While there was good evidence that the hydrogens may be important, we needed to prepare an imidazolium salt with alkyl substitution at the C4 and C5 positions. Synthesizing a penta-substituted imidazolium proved to be a significant challenge, but through the use of microwave chemistry we were able to access 4,5-dimethyl imidazolium **4.44** (Scheme 4.23).[37] The results in Scheme 4.23 clearly show that there was no difference in chemical yield after two hours with methyl substitution or hydrogens on the C4 and C5 positions. These data points confirm that the backbone hydrogens were not an integral catalyst feature and suggest that the alkoxide interaction was predominantly ionic in nature.[38]



Scheme 4.23: Protons at C4 and C5 position not required for catalytic activity.

[36]Taylor, R.; Kennard, O. Crystallographic Evidence for the Existence of C−H···O, C−H···N and C−H···Cl Hydrogen Bonds. *J. Am. Chem. Soc.* **1982**, *104*, 5063-5070.

[37]Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. Efficient Synthesis of Imidazoles from Aldehydes and 1,2-Diketones Using Microwave Irradiation. *Org. Lett.* **2004**, *6*, 1453-1456.

[38]Macchioni, A. Ion Pairing in Transition-Metal Organometallic Chemistry. *Chem. Rev.* **2005**, *105*, 2039-2073.

4.5 Conclusions

Numerous examples of stereoselective reactions catalyzed by chiral ion-pairs have been reported in the literature. Strategies based on phase-transfer catalysis are among the most common and well studied.[39] Chiral crown ethers have also been used under single-liquid phase conditions to sequester potassium ions while remaining closely associated with the substrate to impart stereoselectivity.[40] More recently the Jacobsen group and others have utilized chiral thioureas as "anion-binding" catalysts to generate chiral ion pairs with cationic substrates.[41] Future chiral catalyst designs, based on these mechanistic studies the aforementioned reports from the literature, will likely need to incorporate more functional groups that can engange in well-defined non-covalent secondary interactions (H-bonding, cation-π, π-π, etc...) to create more organized transition states.

In summary, we have laid the groundwork for a new class of cationic organocatalysts that are capable of constructing C−O bonds. Careful mechanistic studies first ruled out the possible involvment of carbenes and lead to the discovery of unusual C2 alkylated imidazolium salts.[15] Further mechanistic experiments showed that the reaction can be catalyzed

[39] For pioneering reports see: (a) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. Efficient Catalytic Asymmetric Alkylations. 1. Enantioselective Synthesis of (+)-Indacrinone *via* Chiral Phase-Transfer Catalysis. *J. Am. Chem. Soc.* **1984**, *106*, 446-447. (b) Corey, E. J.; Xu, F.; Noe, M. C. A Rational Approach to Catalytic Enantioselective Enolate Alkylation Using a Structurally Rigidified and Defined Chiral Quaternary Ammonium Salt Under Phase Transfer Conditions. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415. (c) Ooi, T.; Kameda, M.; Maruoka, K. Molecular Design of a C_2-Symmetric Chiral Phase-Transfer Catalyst for Practical Asymmetric Synthesis of α-Amino Acids. *J. Am. Chem. Soc.* **1999**, *121*, 6519-6520. For reviews see: (d) ODonnell, M. J. The Enantioselective Synthesis of α-Amino Acids by Phase-Transfer Catalysis with Achiral Schiff Base Esters. *Acc. Chem. Res.* **2004**, *37*, 506-517. (e) Ooi, T.; Maruoka, K. Recent Advances in Asymmetric Phase-Transfer Catalysis. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4266.

[40] (a) Cram, D. J.; Sogah, G. D. Y. Chiral Crown Complexes Catalyse Michael Addition Reactions to Give Adducts in High Optical Yields. *J. Chem. Soc. Chem. Comm.* **1981**, 625-628. (b) Aoki, S.; Sasaki, S.; Koga, K. Simple Chiral Crown Ethers Complexed with Potassium *tert*-Butoxide as Efficient Catalysts for Asymmetric Michael Additions. *Tetrahedron Lett.* **1989**, *30*, 7229-7230.

[41] For lead references see: (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. Enantioselective Pictet-Spengler-Type Cyclizations of Hydroxylactams: H-Bond Donor Catalysis by Anion Binding. *J. Am. Chem. Soc.* **2007**, *129*, 13404-13405. (b) Zuend, S. J.; Jacobsen, E. N. Mechanism of Amido-Thiourea Catalyzed Enantioselective Imine Hydrocyanation: Transition State Stabilization *via* Multiple Non-Covalent Interaction. *J. Am. Chem. Soc.* **2009**, *131*, 15358-15374. (c) Knowles, R. R.; Jacobsen, E. N. Attractive Noncovalent Interactions in Asymmetric Catalysis: Links Between Enzymes and Small Molecule Catalysts. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678-20685.

by penta-substituted imidazolium salts, suggesting the catalyst interacts in largely ionic fashion with the substrate. While catalytic Williamson ether reactions are known under phase transfer conditions, our approach requires only a single organic liquid phase.[42] Developing novel chiral imidazolium salts will be the subject of future work in this area and results will be forthcoming.

[42]Tan, S. N.; Dryfe, R. A.; Girault, H. H. Electrochemical Study of Phase-Transfer Catalysis Reactions: The Williamson Ether Synthesis. *Helv. Chim. Acta.* **1994**, *77*, 231-242.

4.6 Experimental Data

4.6.1 *General Information*

General Procedures

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an atmosphere of nitrogen passed through a tower of finely powdered Drierite® in dry, degassed solvent with standard Schlenk or vacuum-line techniques. Particularly air-sensitive manipulations were performed in an MBraun Unilab nitrogen atmosphere glove box. Flash column chromatography was performed according to the procedure of Still *et al.*[43] with SiliCycle® Silia*Flash*® P60 40-63 μm silica gel. Analytical thin-layer chromatography (TLC) was performed using SiliCycle® SiliaPlate 0.25 mm silica gel 60 F254 plates. TLC plates were visualized by exposure to ultraviolet light and/or ceric ammonium molybdate, *p*-anisaldehyde, or potassium permanganate stains.

Materials

Toluene, tetrahydrofuran (THF), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were dispensed under nitrogen from a Glass Contour solvent purification system custom manufactured by SG Waters, LLC (Nashua, NH). Deuterated chloroform ($CDCl_3$), deuterated methanol (CD_3OD), and deuterated DMSO (DMSO-d_6) were purchased from Cambridge Isotope Labs and used as received. Deuterated benzene (C_6D_6) and deuterated toluene (toluene-d_8) were purchased from Cambridge Isotope Labs and distilled under nitrogen from $CaCl_2$. Molecular sieves (3Å, 8-12 mesh) were purchased from W.R. Grace and activated by oven drying at 250 °C for at least 6 hours prior to use. Glyoxal (40% in H_2O, w/w), 2-isopropylimidazole, paraformaldehyde, (1*S*,2*S*)-*trans*-2-benzyloxycyclohexylamine, 1,3-dicyclohexylimidazolium tetrafluoroborate,

[43] Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.

ammonium acetate (NH_4OAc), isobutyraldehyde, phosphorus tribromide (PBr_3), and *N*,*N*-diisopropylethylamine (DIPEA) were purchased from Aldrich and used without further purification. Benzyl bromide and benzyl chloride were purchased from Aldrich, distilled from $CaCl_2$ under reduced pressure, and stored under nitrogen in the dark at −20 °C. Iodomethane was purchased from Aldrich, distilled under nitrogen, and stored over copper wire in the dark at −20 °C. Sodium *tert*-butoxide (NaOtBu) and potassium *tert*-butoxide (KOtBu) were purchased from Aldrich and used as received inside a glove box.[44] 2,3-Butanedione was purchased from Avocado Research Chemicals, fractionally distilled from $MgSO_4$ under nitrogen, and stored in the dark at −20 °C. 1-Phenylethanol was purchased from Aldrich, vacuum distilled from $MgSO_4$, and stored over 3Å sieves (8-12 mesh). Potassium hydride (KH) was purchased from Strem Chemicals (20-25% in oil) and was washed under nitrogen with excess pentane before storing in a glove box. Sodium tetrafluoroborate (Aldrich) and sodium tetraphenylborate (Lancaster) were vacuum dried (22 °C, 18 h, approx. 1 mm Hg) over P_2O_5 before storing in a glove box. Sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate ($NaB(Ar^F)_4$) was prepared according to the literature procedure then vacuum dried (22 °C, 18 h, approx. 1 mm Hg) over P_2O_5 before storing in a dry box.[45] Ammonium chloride (NH_4Cl), concentrated hydrochloric acid (HCl), sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), sodium sulfate (Na_2SO_4), magnesium sulfate ($MgSO_4$), ethyl acetate (EtOAc), glacial acetic acid (AcOH), ammonium hydroxide (NH_4OH), and Celite® 545 were purchased from Fisher Scientific and used as received.

Instrumentation

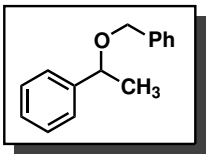
Infrared spectra were recorded on a Bruker Alpha-p spectrometer. Bands are reported as strong (s), medium (m), weak (w), broad strong (bs), broad medium (bm), and broad weak

[44] Control reactions established there was no difference in reaction efficiency between sublimed material and unpurified commercial samples.

[45] Yakelis, N. A.; Bergman, R. G. Safe Preparation and Purification of Sodium Tetrakis[(3,5-trifluoromethyl)phenyl]borate ($NaBArF_{24}$): Reliable and Sensitive Analysis of Water in Solutions of Fluorinated Tetraarylborates. *Organometallics* **2005**, *24*, 3579-3581.

(bw). Optical rotation data were recorded on a Rudolph research Autopol IV automatic polarimeter and has been reported as the average of five readings. Melting points were recorded on a Mel-Temp® II manufactured by Laboratory Devices, Inc. and are uncorrected. Sonication was performed with a Branson 1510 40 kHz bench-top sonicator. Microwave reactions were performed in 10 mL sealed vessels with a CEM Discover® 908005 system. ^{1}H NMR spectra were recorded on a Varian VNMRS or Varian INOVA 500 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26, C_6D_6: δ 7.16, CD_3OD: δ 3.31). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, tt = triplet of triplets, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian VNMRS 125 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (C_6D_6: δ 128.06, $CDCl_3$: δ 77.16, CD_3OD: δ 49.00, DMSO-d_6: δ 39.52). Gas chromatography (GC) analysis was performed on a Hewlett Packard HP 6890 system equipped with a flame ionization detector and HP-5 column (30 m x 0.320 mm x 0.25 μm) or Supelco™ Beta DEX™ 120 column (30 m x 0.25 mm x 0.25 μm). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility.

4.6.2 *Experimental Procedures and Characterization Data*



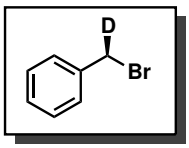
Representative procedure for etherification of secondary alcohols catalyzed by imidazolium salts:

(1-(benzyloxy)ethyl)benzene (**4.5**). In a dry box, NaOtBu (21.1 mg, 0.220 mmol, 1.10 equiv) and imidazolium salt **4.32** (8.0 mg, 0.020 mmol, 10 mol %) were combined in a 1 dram (3.7 mL) vial. The mixture of solids was moved to a nitrogen manifold and toluene (2 mL) was added, forming a white suspension. Benzyl bromide (36 μL, 0.30 mmol, 1.5 equiv) was added followed by 1-phenylethanol (24 μL, 0.20 mmol, 1.0 equiv). The reaction mixture was allowed to stir at room temperature for 2 hours and then quenched by addition of Et_2O (1 mL) containing an accurately weighed quantity of 1,3,5-trimethoxybenzene.[46] The reaction contents were transferred to a 16 x 125 mm test tube containing saturated aqueous NH_4Cl (2 mL) and vigorously stirred for 15 seconds. An aliquot of the upper organic layer was withdrawn and ^{1}H NMR data were obtained with a relaxation delay time of 10 seconds (d1 = 10). Integration of the internal standard and product peaks indicated a yield of 0.16 mmol, 82%. The highest yield obtained with imidazolium salt **4.32** was 0.18 mmol, 89%. An analytically pure sample for comparison purposes was obtained by purification on silica gel (5% ethyl acetate in hexanes v/v) to afford a colorless oil.

R_f = 0.64 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.27 (m, 10H), 4.51 (q, J = 6.6 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 12.0 Hz, 1H), 1.49 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.89, 138.81, 128.64, 128.49, 127.84, 127.64, 127.61, 126.49, 77.37, 70.45, 24.35; IR (neat) 3062 (bw), 3030 (bm), 2975 (bm), 2928 (bm), 2863 (bm), 1494 (m), 1452 (m), 1206 (m), 1095 (bm), 1053 (bm), 1028 (m), 912 (bw), 761 (m), 735 (m), 698 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{20}NO$ $[M+NH_4]^+$:

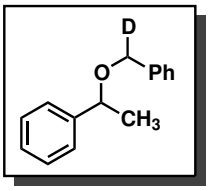
[46] A stock solution containing an accurately weighed quantity of 1,3,5-trimethoxybenzene in Et_2O was freshly prepared prior to workup. The stock solutions typically contained 10.0-15.0 mg of 1,3,5-trimethoxybenzene per mL.

230.1545; Found 230.1540.



(*R*)-α-deuterobenzyl bromide (**4.24**). A solution of (*S*)-α-deuterobenzyl alcohol[47] (750 mg, 6.87 mmol, 1.00 equiv) in 9.2 mL of CH_2Cl_2 was cooled to −78 °C. To the stirred solution, PBr_3 (743 μL, 7.90 mmol, 1.15 equiv) was introduced dropwise *via* syringe. The reaction mixture was stirred for 30 minutes at −78 °C then poured into 25 mL of ice cold H_2O. The product was extracted with CH_2Cl_2 (3 x 15 mL), dried over anhydrous Na_2SO_4 containing K_2CO_3, filtered, and concetrated to a colorless oil. The resulting oil was purified by Kügelrohr distillation under reduced pressure to deliver **4.24** as a colorless oil. The product was taken directly into an inert atmosphere glove box and stored at −40 °C in the dark.

$[\alpha]_D^{20} = +0.160$ (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.38 (m, 2H), 7.37-7.32 (m, 2H), 7.32-7.28 (m, 1H), 4.49 (t, $J_{H\text{-}D} = 1.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.90, 129.18, 128.15, 128.57, 33.48 (t, $J_{C\text{-}D} = 23.3$ Hz); IR (neat) 3086 (bw), 3062 (bw), 3030 (bw), 1494 (m), 1452 (m), 1205 (m), 1163 (bm), 1074 (w), 882 (m), 742 (m), 691 (s) cm^{-1}.

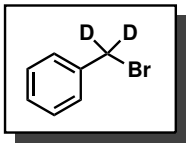


(±)-*d*$_1$-(1-(benzyloxy)ethyl)benzene (**4.25**). In a glove box, KH (10.0 mg, 0.250 mmol, 1.00 equiv) was weighed into a 1 dram glass vial. The vial was removed from the glove box, attached to a nitrogen manifold, and 1.5 mL of THF was added. To the stirred suspension, 1-phenylethanol (30.5 mg, 0.250 mmol, 1.00 equiv) was added and the reaction mixture was stirred for 10 minutes. After cooling to −78 °C, (±)-**4.24** (47.3 mg, 0.275 mmol, 1.10 equiv) dissolved in 1 mL of THF was added in a single portion. The reaction mixture was allowed to warm slowly to room temperature over 3 hours then poured into 15 mL of saturated aqueous NH_4Cl. The product was extracted with Et_2O (3 x 15 mL), dried over anhydrous Na_2SO_4,

[47] Prepared according to the procedure in reference 22. The material was obtained in 98:2 er as the *S* enantiomer by Mosher's ester analysis. δ = 5.31 ppm (major), δ = 5.35 ppm (minor)

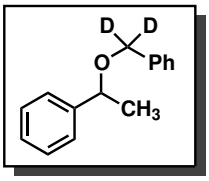
and concentrated to a colorless oil. Purification by silica gel chromatography (5% ethyl acetate in hexanes v/v) provided sufficient material for comparison purposes as a colorless oil. Characterization data below were tabulated for the 1:1 mixture of diastereomers.

R_f = 0.64 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.26 (m, 10H), 4.50 (q, J = 6.4 Hz, 1H), 4.44 (t, $J_{H\text{-}D}$ = 1.5 Hz, 0.5H), 4.28 (t, $J_{H\text{-}D}$ = 1.5 Hz, 0.5H), 1.49 (d, J = 6.4 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.90, 138.74, 128.64, 128.49, 127.86, 127.64, 127.62, 126.48, 77.32, 77.31, 70.11 (t, $J_{C\text{-}D}$ = 21.9 Hz), 70.08 (t, $J_{C\text{-}D}$ = 21.4 Hz), 24.35; IR (neat) 3029 (bw), 2975 (bw), 2928 (bw), 2864 (bw), 1439 (w), 1450 (m), 1207 (w), 1096 (bs), 1057 (m), 1028 (m), 760 (m), 723 (m), 699 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{19}DNO$ $[M+NH_4]^+$: 231.1608; Found 231.1616.



α,α-dideuterobenzyl bromide (**4.22**). Prepared in analogous fashion to **4.24** with α,α-dideuterobenzyl alcohol. Characterization data were in agreement with the previously reported values.[48]

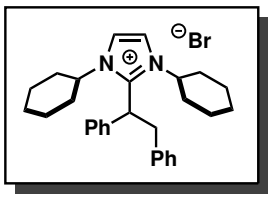
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.38 (m, 2H), 7.37-7.33 (m, 2H), 7.32-7.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.80, 129.13, 128.91, 128.54, 33.24 (p, $J_{C\text{-}D}$ = 23.3 Hz).



***d*$_2$-(1-(benzyloxy)ethyl)benzene** (**4.23**). Prepared according to the procedure for **4.25** with α,α-dideuterobenzyl bromide (**4.22**) to afford a colorless oil.

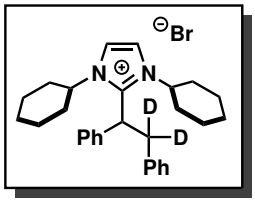
R_f = 0.64 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.28 (m, 10H), 4.52 (q, J = 6.6 Hz, 1H), 1.51 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.90, 138.68, 128.63, 128.49, 127.88, 127.63, 126.48, 77.25, 24.34; IR (neat) 3028 (bw), 2975 (bw), 2928 (bw), 2862 (bw), 1493 (m), 1448 (m), 1370 (w), 1207 (w), 1096 (bs), 1025 (bm), 759 (m), 697 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{15}H_{18}D_2NO$ $[M+NH_4]^+$: 232.1670; Found 232.1664.

[48] Miyashita, A.; Hotta, M.; Saida, Y. Selective sp^3 C–H Bond Activation of Alkylaromatics Promoted by Platinum Complexes. *J. Organomet. Chem.* **1994**, *473*, 353-358.



imidazolium bromide salt (**4.28**). In a glove box 1,3-dicyclohexylimidazolium tetrafluoroborate (320 mg, 1.00 mmol, 1.00 equiv) was combined with KOtBu (241 mg, 2.15 mmol, 2.15 equiv). The mixture of solids was moved to a nitrogen manifold, suspended in THF (20 mL) and placed in a sonication bath for 1 minute to form a clear homogenous solution. Benzyl bromide (250 μL, 2.05 mmol, 2.05 equiv) was introduced dropwise causing the immediate formation of a white precipitate. The yellow reaction mixture was sonicated at 45 °C for 24 hours then cooled to room temperature and filtered through Celite® 545, rinsing with excess CH_2Cl_2. Concentration afforded a pale yellow solid that was recrystallized by slow vapor diffusion of Et_2O into a CH_2Cl_2 solution to provide **4.28** as a white solid (487 mg, 98.7%), mp 166-168 °C.

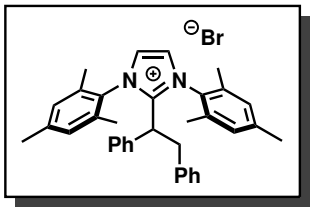
^{1}H NMR (CD_3OD, 500 MHz) δ 7.73 (s, 2H), 7.54-7.48 (m, 2H), 7.44-7.39 (m, 3H), 7.35-7.30 (m, 2H), 7.30-7.25 (m, 1H), 7.18-7.14 (m, 2H), 5.52 (dd, J = 12.7, 4.2 Hz, 1H), 4.15-4.02 (m, 2H), 3.39 (dd, J = 13.2, 4.4 Hz, 1H), 3.45 (t, J = 13.0 Hz, 1H), 2.18-2.10 (m, 2H), 1.96-1.89 (m, 2H), 1.88-1.76 (m, 2H), 1.68-1.60 (m, 2H), 1.59-1.46 (m, 4H), 1.40-1.29 (qd, J = 12.5, 3.7 Hz, 2H), 1.27-1.15 (m, 2H), 1.02-0.84 (m, 2H), 0.52-0.35 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 146.24, 138.71, 138.52, 130.58, 130.32, 130.22, 129.38, 128.64, 128.58, 120.99, 59.50, 43.16, 37.98, 34.60, 33.18, 26.32, 26.26, 25.55; IR (neat) 3027 (bw), 2929 (bm), 2855 (bw), 1573 (bw), 1495 (m), 1450 (m), 1196 (bw), 1030 (bw), 896 (m), 744 (m), 722 (m), 698 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{29}H_{37}N_2$ $[M]^+$: 413.2957; Found 413.2960.



***d*$_2$-imidazolium bromide salt** (**4.29**). An authentic sample for comparison purposes was prepared according the procedure for imidazolium salt **4.28** with α,α-dideuterobenzyl bromide. The material recovered contained approximately 60% proton incorporation at the benzylic methine position by ^{1}H NMR spectroscopy. There also appeared to be some deuterium incorporation on the backbone. The ^{13}C NMR data were difficult to deconvolute

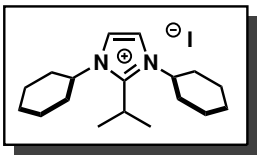
and have been tabulated below for the mixture of compounds.

^{1}H NMR (CD_3OD, 500 MHz) δ 7.72 (s, 2H), 7.53-7.48 (m, 2H), 7.44-7.39 (m, 3H), 7.35-7.25 (m, 3H), 7.17-7.13 (m, 2H), 5.50 (s, 1H), 4.14-4.03 (m, 2H), 2.20-2.11 (m, 2H), 1.97-1.88 (m, 2H), 1.88-1.74 (m, 2H), 1.68-1.60 (m, 2H), 1.60-1.46 (m, 4H), 1.33 (qd, J = 12.5, 3.7 Hz, 2H), 1.26-1.15 (m, 2H), 1.00-0.84 (m, 2H), 0.53-0.34 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 146.20, 146.16, 138.62, 138.51, 138.44, 130.56, 130.29, 130.20, 129.35, 129.34, 128.60, 128.58, 121.01, 120.89, 59.46, 43.00, 34.56, 33.17, 26.30, 26.26, 25.54; HRMS (ESI+) Calcd. for $C_{29}H_{35}D_2N_2$ $[M]^+$: 415.3077; Found 415.3072.



imidazolium bromide salt (**4.37**). Prepared according to the procedure for imidazolium bromide **4.28** on 0.300 mmol scale. The product was recrystallized by slow vapor diffusion of hexanes into a saturated $CHCl_3$ solution at −20 °C to afford **4.37** as a white solid (151 mg, 89.1%), mp 219-223 °C.

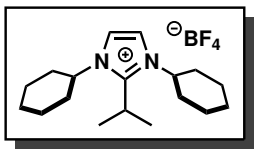
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.29 (s, 2H), 7.20-7.13 (m, 3H), 7.06-6.99 (m, 7H), 6.62-6.58 (m, 2H), 6.47-6.43 (m, 2H), 4.28 (dd, J = 12.5, 3.4 Hz, 1H), 3.26-3.14 (m, 2H), 2.45 (s, 6H), 2.19 (s, 6H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.46, 142.19, 135.65, 135.18, 134.51, 131.05, 130.33, 130.21, 130.15, 129.18, 128.91, 128.57, 128.53, 128.26, 127.10, 126.53, 44.19, 35.95, 21.22, 18.08, 17.41; IR (neat) 3056 (bw), 3022 (bw), 2992 (bw), 2919 (bw), 1605 (w), 1559 (w), 1494 (s), 1453 (m), 1382 (w), 1239 (m), 1034 (bw), 859 (m), 792 (m), 752 (m), 696 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{35}H_{37}N_2$ $[M]^+$: 485.2957; Found 485.2976.



imidazolium iodide salt (**4.32**). In a glove box 1,3-dicyclohexylimidazolium tetrafluoroborate (1.60 g, 5.00 mmol, 1.00 equiv) was combined with KOtBu (2.24 g, 20.0 mmol, 4.00 equiv). The mixture of solids was moved to a nitrogen manifold, suspended in THF (50 mL), and placed in a sonication bath for 1 minute to form a clear homogenous solution. Iodomethane

(1.56 mL, 25.0 mmol, 5.00 equiv) was introduced dropwise causing the immediate formation of a white precipitate. The reaction mixture was sonicated at 45 °C for 3 days then cooled to room temperature and filtered through Celite® 545, rinsing with excess CH_2Cl_2. Concentration afforded a pale yellow solid that was recrystallized by slow vapor diffusion of Et_2O into a $CHCl_3$ solution to provide **4.32** as a faint yellow solid (1.80 g, 89.5%), mp >250 °C (decomp).

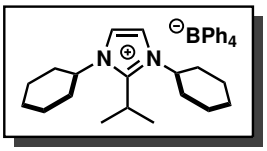
^{1}H NMR (CD_3OD, 500 MHz) δ 7.75 (s, 2H), 4.47 (tt, J = 12.0, 3.8 Hz, 2H), 3.89 (sept, J = 7.4 Hz, 1H), 2.07-2.00 (m, 4H), 1.97-1.91 (m, 4H), 1.84 (qd, J = 12.4, 3.6 Hz, 4H), 1.80-1.74 (m, 2H), 1.65-1.54 (m, 4H), 1.51 (d, J = 7.2 Hz, 6H), 1.42-1.31 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 149.60, 120.57, 59.37, 34.39, 26.24, 25.79, 25.73, 19.99; IR (neat) 3085 (bw), 3053 (bw), 2925 (bs), 2859 (m), 1573 (w), 1501 (m), 1449 (m), 3838 (w), 1252 (m), 1201 (s), 1145 (w), 1100 (m), 1002 (w), 985 (w), 896 (m), 785 (m), 752 (m), 738 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{18}H_{31}N_2$ $[M]^+$: 275.2487; Found 275.2501.



imidazolium tetrafluoroborate salt (**4.35**). In a glove box, imidazolium iodide **4.32** (101 mg, 0.250 mmol, 1.00 equiv) was dissolved in 2.5 mL of CH_2Cl_2. To the stirred solution, $NaBF_4$ (27.4 mg, 0.250 mmol, 1.00 equiv) was added as a solid in a single portion. The suspension was stirred for 2 days then filtered through glass wool and concentrated *in vacuo*. The resulting white solid was suspended in 2 mL of hexanes and concentrated again to afford **4.35** as a white powder (81.0 mg, 89.4%), mp 246-250 °C (decomp).

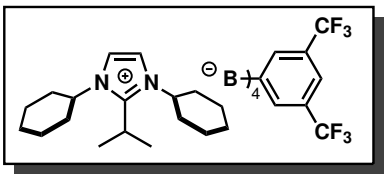
^{1}H NMR (CD_3OD, 500 MHz) δ 7.74 (s, 2H), 4.45 (tt, J = 12.0, 3.9 Hz, 2H), 3.87 (sept, J = 6.9 Hz, 1H), 2.06-2.00 (m, 4H), 1.98-1.90 (m, 4H), 1.89-1.74 (m, 6H), 1.64-1.53 (m, 4H), 1.51 (d, J = 7.3 Hz, 6H), 1.41-1.31 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 149.60, 120.52, 59.38, 34.37, 26.24, 25.78, 25.73, 19.90; IR (neat) 3084 (bw), 3051 (bw), 2926 (bm), 2860 (bm), 1574 (w), 1500 (m), 1450 (m), 1253 (w), 1201 (m), 1144 (bw), 1098 (bm), 1056 (bs), 897 (m), 784 (m), 753 (m), 737 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{18}H_{31}N_2$ $[M]^+$:

275.2487; Found 275.2489.



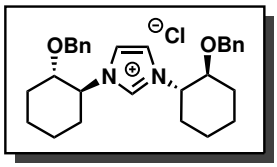
imidazolium tetraphenylborate salt (**4.30**). Prepared according to the procedure for **4.35** on 0.250 mmol scale with $NaBPh_4$ (85.6 mg, 0.250 mmol, 1.00 equiv) to afford **4.30** as a white solid (136 mg, 91.3%), mp 179-182 °C.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46-7.40 (m, 8H), 7.04 (t, J = 7.3 Hz, 8H), 6.90 (t, J = 7.1 Hz, 4H), 6.08 (s, 2H), 3.91 (tt, J = 12.2, 3.4 Hz, 2H), 3.33 (sept, J = 7.1 Hz, 1H), 1.99-1.91 (m, 4H), 1.79-1.69 (m, 6H), 1.51-1.41 (m, 4H), 1.37 (d, J = 7.3 Hz, 6H), 1.36-1.24 (m, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 163.35 (q, $J_{C\text{-}B}$ = 49.4 Hz), 147.65, 135.52, 135.51, 125.22 (q, $J_{C\text{-}B}$ = 2.4 Hz), 121.45, 119.44, 56.94, 32.54, 24.57, 24.24, 23.55, 19.11; IR (neat) 3054 (bw), 2982 (bw), 2928 (bw), 2857 (bw), 1578 (w), 1495 (w), 1477 (bw), 1449 (w), 1223 (w), 1267 (bw), 1189 (w), 1131 (bw), 1096 (bw), 894 (w), 843 (w), 734 (m), 701 (s), 611 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{18}H_{31}N_2$ $[M]^+$: 275.2487; Found 275.2492.

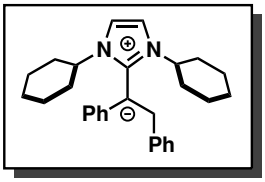


imidazolium tetrakis[(3,5-trifluoromethyl)phenyl]-borate salt (**4.36**). Prepared according to the procedure for **4.35** on 0.250 mmol scale with $NaB(Ar^F)_4$ (222 mg, 0.250 mmol, 1.00 equiv) to afford **4.36** as a white solid (218 mg, 76.6%), mp 152-155 °C.

^{1}H NMR (CD_3OD, 500 MHz) δ 7.69 (s, 2H), 7.63-7.58 (m, 12H), 4.38 (tt, J = 12.0, 3.7 Hz, 2H), 3.77 (sept, J = 7.3 Hz, 1H), 2.02-1.95 (m, 4H), 1.94-1.87 (m, 4H), 1.83-1.70 (m, 6H), 1.57-1.46 (m, 4H), 1.46 (d, J = 7.3 Hz, 6H), 1.36-1.23 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 162.90 (q, $J_{C\text{-}B}$ = 49.8 Hz), 149.56, 135.84, 130.47 (qq, $J_{C\text{-}F\text{-}B}$ = 31.4, 3.3 Hz), 125.79 (q, $J_{C\text{-}F}$ = 271.7 Hz), 120.44, 118.50 (broad), 59.47, 34.36, 26.21, 25.79, 25.69, 19.70; IR (neat) 2947 (bw), 2870 (bw), 1610 (bw), 1495 (bw), 1454 (bw), 1353 (m), 1273 (s), 1159 (bm), 1114 (bs), 887 (m), 838 (m), 715 (m), 682 (m), 668 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{18}H_{31}N_2$ $[M]^+$: 275.2487; Found 275.2491.

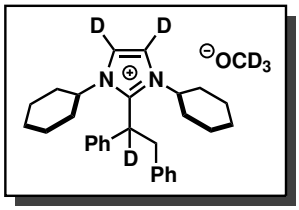


imidazolium chloride salt (**4.40**). A solution of (1*S*,2*S*)-*trans*-2-benzyloxycyclohexylamine (205 mg, 1.00 mmol, 2.00 equiv) in toluene (4 mL) was cooled to 0 °C. Paraformaldehyde (15.0 mg, 0.500 mmol, 1.00 equiv) was added as a solid in a single portion and the reaction mixture was stirred for 20 minutes. Concentrated HCl (41.8 μL, 0.500 mmol, 1.00 equiv, 12 N) and glyoxal (57.1 μL, 0.500 mmol, 1.00 equiv, 40.0% w/w in water) were added at 0 °C then the mixture was warmed to reflux and heated for 46 hours. After cooling to room temperature, 30 mL of saturated aqueous Na_2CO_3 was added. The aqueous layer was washed with EtOAc (3 x 20 mL) and the organic washes were discarded. The product was extracted with CH_2Cl_2 (6 x 30 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated to afford **4.40** as a white solid (205 mg, 85.3%), mp 134-137 °C. $[\alpha]_D^{20} = +110.0$ (c 0.94, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 9.03 (t, J = 1.7 Hz, 1H), 7.63 (d, J = 1.7 Hz, 2H), 7.26-7.21 (m, 6H), 7.04-7.00 (m, 4H), 4.51 (d, J = 12.0 Hz, 2H), 4.19 (ddd, J = 12.2, 10.0, 4.4 Hz, 2H), 4.14 (d, J = 11.7 Hz, 2H), 3.53 (td, J = 10.5, 4.6 Hz, 2H), 2.43-2.36 (m, 2H), 2.11-2.04 (m, 2H), 1.97-1.85 (m, 6H), 1.54-1.27 (m, 6H); ^{13}C NMR (CD_3OD, 125 MHz) δ 139.32, 136.90, 129.40, 128.75, 128.70, 121.76, 121.72, 80.32, 71.44, 65.52, 65.50, 32.26, 32.25, 31.66, 25.60, 24.62; IR (neat) 3033 (bw), 2933 (bm), 2859 (bm), 1554 (bw), 1451 (m), 1361 (bw), 1169 (m), 1095 (bs), 1028 (m), 941 (m), 870 (m), 800 (w), 734 (s), 696 (s), 658 (m) cm^{-1}; HRMS (ESI+) Calcd. for $C_{29}H_{37}N_2O_2$ $[M]^+$: 445.2855; Found 445.2837.



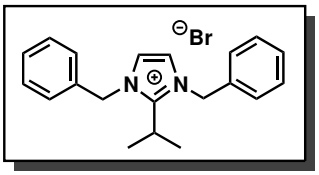
imidazolium ylide (**4.33**). In a glove box, imidazolium salt **4.28** (150 mg, 0.300 mmol, 1.00 equiv) was suspended in 5 mL of toluene. To the stirred suspension, NaOtBu (27.5 mg, 0.286 mmol, 0.95 equiv) was added as a solid in a single portion, causing an immediate yellow coloration. The reaction mixture was stirred for 24 hours then filtered through Celite® 545 and concentrated under high vacuum to afford **4.33** as a sensitive dark green solid (83.2 mg, 70.5%).

^{1}H NMR (C_6D_6, 500 MHz) δ 7.46 (d, J = 7.3 Hz, 2H), 7.27 (dd, J = 8.6, 1.0 Hz, 2H), 7.20-7.16 (m, 2H), 7.12 (dd, J = 7.6, 7.6 Hz, 2H), 7.03-6.99 (m, 1H), 6.77 (tt, J = 7.1, 1.2 Hz, 1H), 6.02 (s, 2H), 4.14 (s, 2H), 3.79 (tt, J = 11.7, 3.4 Hz, 2H), 1.89-1.82 (m, 4H), 1.49-1.42 (m, 4H), 1.30-1.24 (m, 2H), 1.14-1.03 (m, 4H), 0.88-0.76 (m, 6H); ^{13}C NMR (C_6D_6, 125 MHz) δ 152.42, 145.90, 144.31, 128.79, 128.66, 128.37, 128.25, 127.97, 127.87, 125.57, 122.70, 118.33, 113.94, 69.00, 57.15, 38.85, 32.61, 25.87, 25.76; IR (neat) 3132 (bw), 3054 (bw), 3017 (bw), 2926 (bs), 2852 (m), 1671 (bw), 1521 (s), 1485 (s), 1446 (m), 1379 (m), 1269 (s), 1177 (s), 964 (m), 892 (m), 758 (m), 729 (m), 694 (s), 631 (m), 602 (m) cm^{-1}.



***d*$_3$-imidazolium methoxide salt** (**4.41**). A sample of imidazolium ylide **4.33** (approx. 25 mg) was dissolved in 1 mL of CD_3OD to give a clear colorless solution. The solution was concentrated under high vacuum and the resulting colorless oil was re-dissolved in 0.7 mL of CD_3OD for spectral analysis.

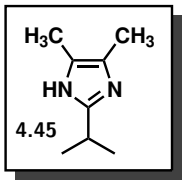
^{1}H NMR (CD_3OD, 500 MHz) δ 7.53-7.49 (m, 2H), 7.45-7.38 (m, 3H), 7.35-7.26 (m, 3H), 7.16-7.13 (m, 2H), 4.13-4.02 (m, 2H), 3.92 (d, J = 13.2 Hz, 1H), 3.44 (d, J = 13.2 Hz, 1H), 2.18-2.11 (m, 2H), 1.96-1.89 (m, 2H), 1.86-1.73 (m, 2H), 1.68-1.61 (m, 2H), 1.59-1.44 (m, 4H), 1.32 (qd, J = 12.5, 3.9 Hz, 2H), 1.25-1.14 (m, 2H), 1.00-0.83 (m, 2H), 0.49-0.35 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 146.22, 138.71, 138.47, 130.62, 130.35, 130.19, 129.46, 128.69, 128.57, 120.62 (t, $J_{C\text{-}D}$ = 22.9 Hz), 59.51, 42.86 (t, $J_{C\text{-}D}$ = 20.1 Hz), 37.89, 34.60 (broad), 33.20, 26.34, 26.27, 25.58; HRMS (ESI+) Calcd. for $C_{29}H_{34}D_3N_2$ $[M]^+$: 416.3140; Found 416.3155.



imidazolium bromide salt (**4.43**). To a suspension of 2-isopropylimidazole (220 mg, 2.00 mmol, 1.00 equiv) and K_2CO_3 (1.10 g, 8.00 mmol, 4.00 equiv) in THF (10 mL), benzyl bromide (977 μL, 8.00 mmol, 4.00 equiv) was added in a single portion. The reaction mixture was refluxed for 20 hours then cooled to room temperature and diluted with 10 mL of 1:1

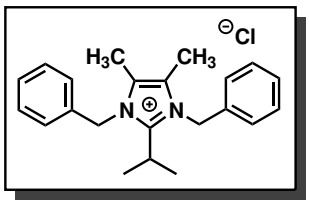
CH_2Cl_2: CH_3OH (v/v). The suspension was filtered through Celite® 545, concentrated, and recrystallized from minimal CH_3CN and EtOAc (approx. 5:1 v/v) to afford **4.43** as a white solid (500 mg, 67.4%), mp 158-160 °C.

^{1}H NMR (CD_3OD, 500 MHz) δ 7.58 (s, 2H), 7.47-7.38 (m, 6H), 7.33-7.29 (m, 4H), 5.58 (s, 4H), 3.77 (sept, J = 7.3 Hz, 1H), 1.29 (d, J = 7.3 Hz, 6H); ^{13}C NMR (CD_3OD, 125 MHz) δ 151.79, 135.57, 130.41, 129.98, 128.56, 124.05, 53.33, 26.70, 19.15; IR (neat) 3062 (bw), 2972 (bw), 2876 (bw), 1579 (w), 1513 (w), 1371 (bw), 1260 (w), 1174 (w), 789 (bw), 728 (s), 697 (bm) cm^{-1}; HRMS (ESI+) Calcd. for $C_{20}H_{23}N_2$ $[M]^+$: 291.1861; Found 291.1874.



2,4,5-substituted imidazole (**4.45**). In a microwave vessel, 2,3-butanedione (104 μL, 1.20 mmol, 1.00 equiv), isobutyraldehyde (110 μL, 1.20 mmol, 1.00 equiv), and NH_4OAc (925 mg, 12.0 mmol, 10.0 equiv) were suspended in glacial AcOH (2.5 mL). The reaction mixture was microwaved at 180 °C for 5 minutes then rapidly cooled to room temperature. The reaction contents were transferred carefully to a solution of saturated aqueous NH_4OH (15 mL) that was chilled to 0 °C. The product was extracted with CH_2Cl_2 (3 x 25 mL), dried over $MgSO_4$, filtered, and concentrated to a pale yellow solid. The solid was dissolved in minimal warm 1:1 Et_2O: hexanes (v/v), cooled to −20 °C, filtered, and washed with hexanes to afford **4.45** as a faint yellow solid (81.0 mg, 48.8%), mp 194-196 °C.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.33 (broad s, 1H), 2.97 (sept, J = 7.1 Hz, 1H), 2.13 (s, 6H), 1.3 (d, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.15, 125.56 (broad), 28.35, 21.98, 10.76; IR (neat) 3157 (bw), 2964 (m), 2916 (bm), 2872 (bm), 1620 (m), 1438 (bs), 1390 (m), 1287 (bm), 1096 (m), 1019 (m), 884 (bw), 735 (w) cm^{-1}; HRMS (ESI+) Calcd. for $C_8H_{15}N_2$ $[M+H]^+$: 139.1235; Found 139.1230.



imidazolium chloride salt (**4.44**). In a microwave vessel, imidazole **4.45** (41.5 mg, 0.300 mmol, 1.00 equiv), DIPEA (78.4 μL, 0.450 mmol, 1.50 equiv), and benzyl chloride (173 μL, 1.50 mmol, 5.00 equiv) were dissolved in CH_3CN (1.5 mL). The reaction mixture was microwaved at 180 °C for 5 minutes then rapidly cooled to room temperature. The solvent was removed *in vacuo* and resulting dark brown oil was dissolved in 50 mL of saturated aqueous K_2CO_3. The aqueous solution was washed with Et_2O (2 x 25 mL), discarding the organic washes. The product was extracted with CH_2Cl_2 (3 x 75 mL), dried over $MgSO_4$, filtered, and concentrated to afford **4.44** as a white solid (36.2 mg, 34.0%), mp 138-140 °C.

^{1}H NMR (CD_3OD, 500 MHz) δ 7.47-7.42 (m, 4H), 7.40-7.36 (m, 2H), 7.13-7.08 (m, 4H), 5.56 (s, 4H), 3.67 (sept, J = 7.3 Hz, 1H), 2.21 (s, 6H), 1.23 (d, J = 7.3 Hz, 6H); ^{13}C NMR (CD_3OD, 125 MHz) δ 150.97, 135.76, 130.44, 129.47, 128.63, 126.84, 49.82, 26.95, 19.61, 8.83; IR (neat) 3032 (bw), 2973 (bm), 2932 (bm), 2876 (bw), 1650 (bw), 1605 (bw), 1510 (m), 1451 (s), 1396 (bm), 1335 (bs), 1279 (bm), 1096 (bm), 865 (m), 729 (s), 696 (s) cm^{-1}; HRMS (ESI+) Calcd. for $C_{22}H_{27}N_2$ $[M]^+$: 319.2174; Found 319.2175.

4.6.3 *NMR Spectral Data*

Figure 4.6: ^{1}H NMR of (1-(benzyloxy)ethyl)benzene (**4.5**)

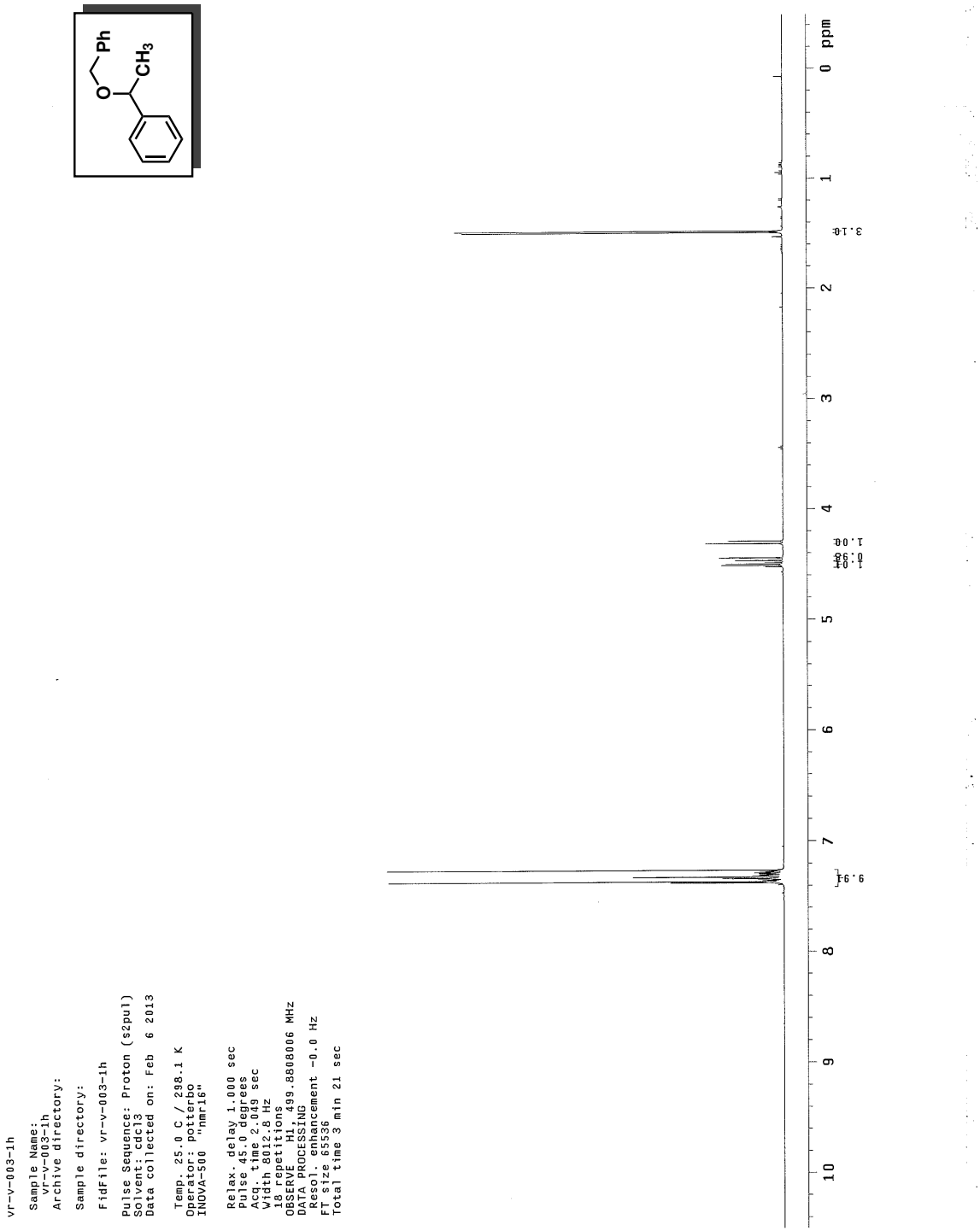


Figure 4.7: ^{13}C NMR of (1-(benzyloxy)ethyl)benzene (**4.5**)

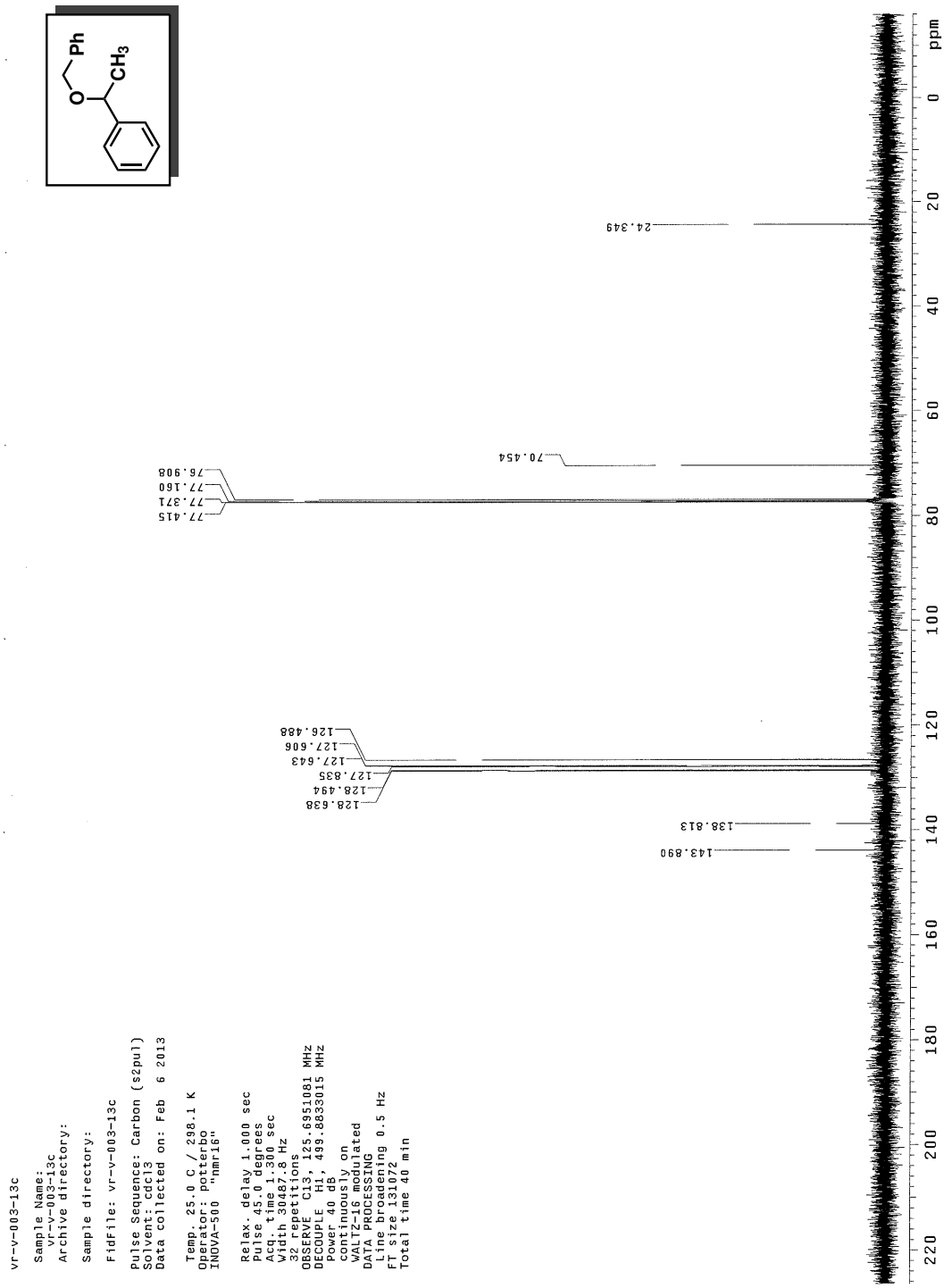


Figure 4.8: ^{1}H NMR of (*R*)-α-deuterobenzyl bromide (**4.24**)

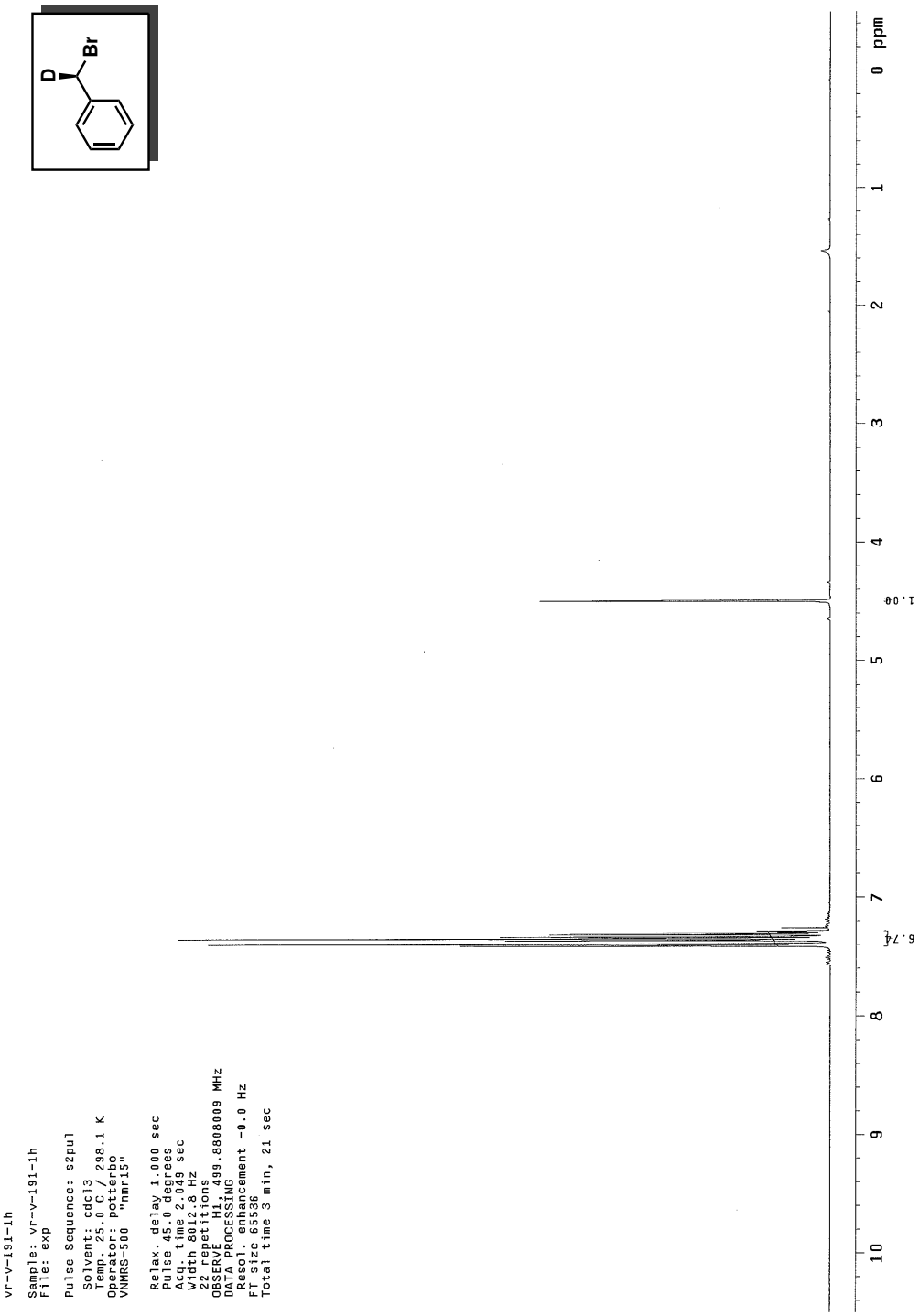


Figure 4.9: ^{13}C NMR of (*R*)-α-deuterobenzyl bromide (**4.24**)

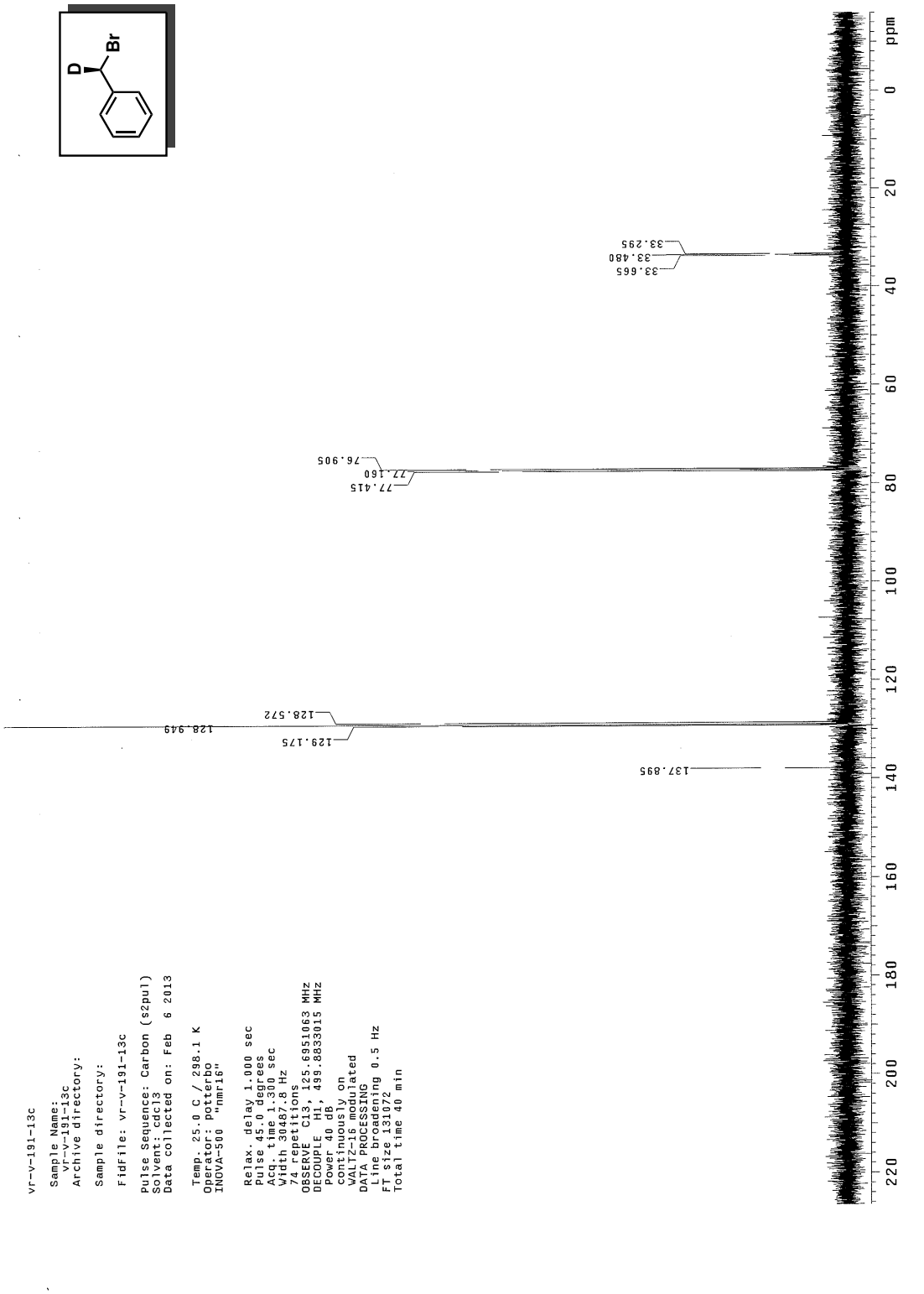


Figure 4.10: ^{1}H NMR of (±)-d_1-(1-(benzyloxy)ethyl)benzene (**4.25**)

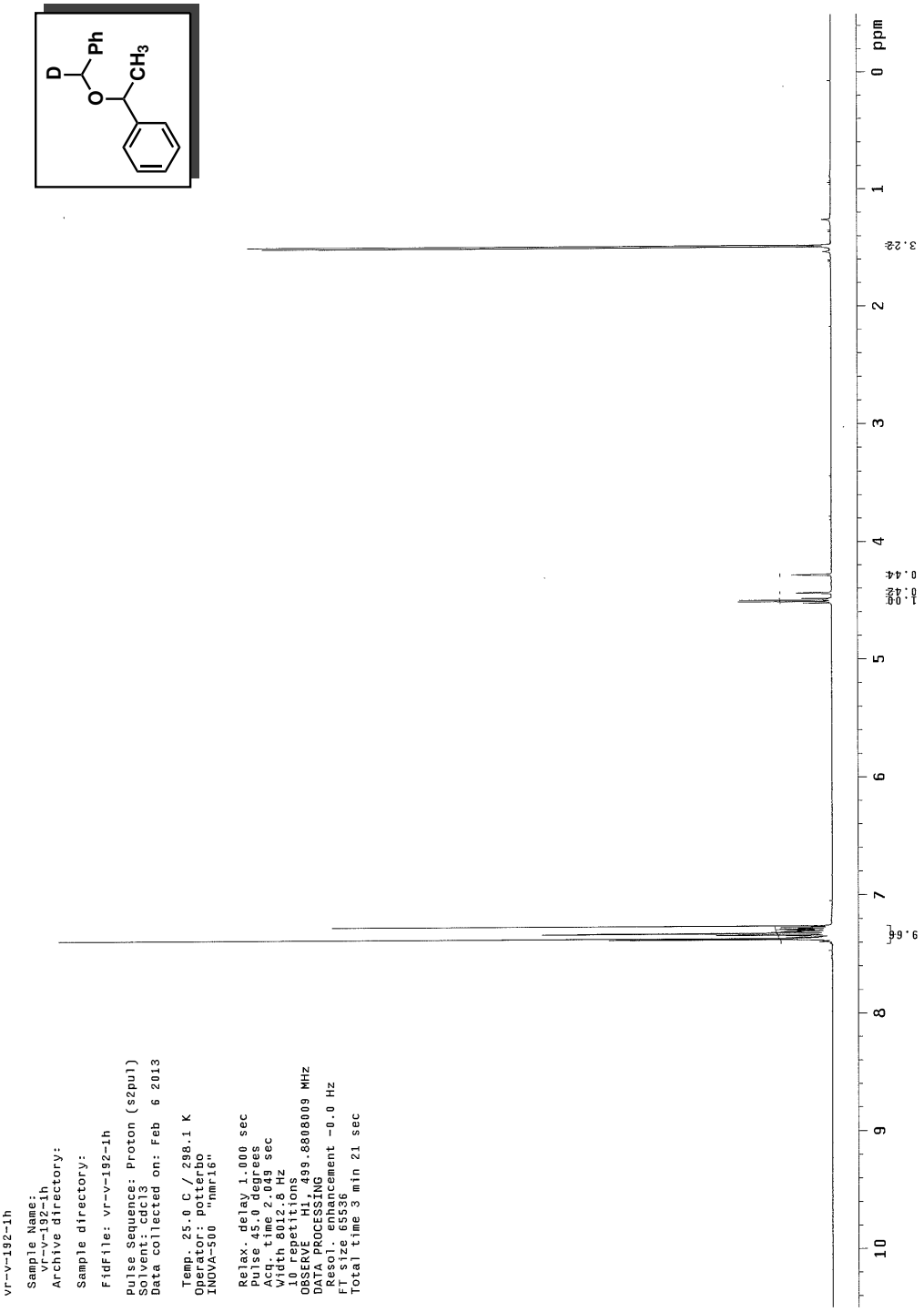


Figure 4.11: ^{13}C NMR of (±)-d_1-(1-(benzyloxy)ethyl)benzene (**4.25**)

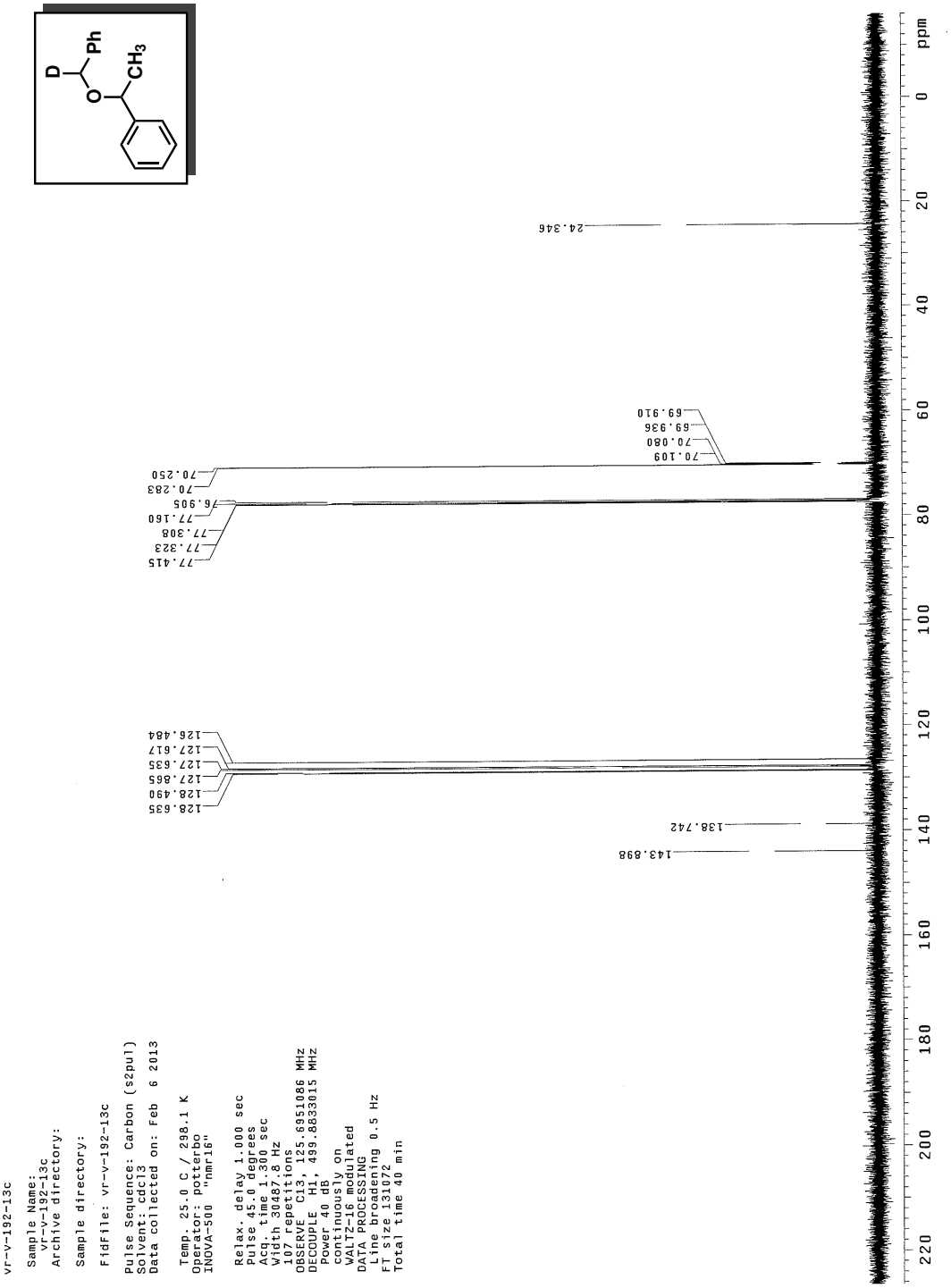


Figure 4.12: ^{1}H NMR of d_2-(1-(benzyloxy)ethyl)benzene (**4.23**)

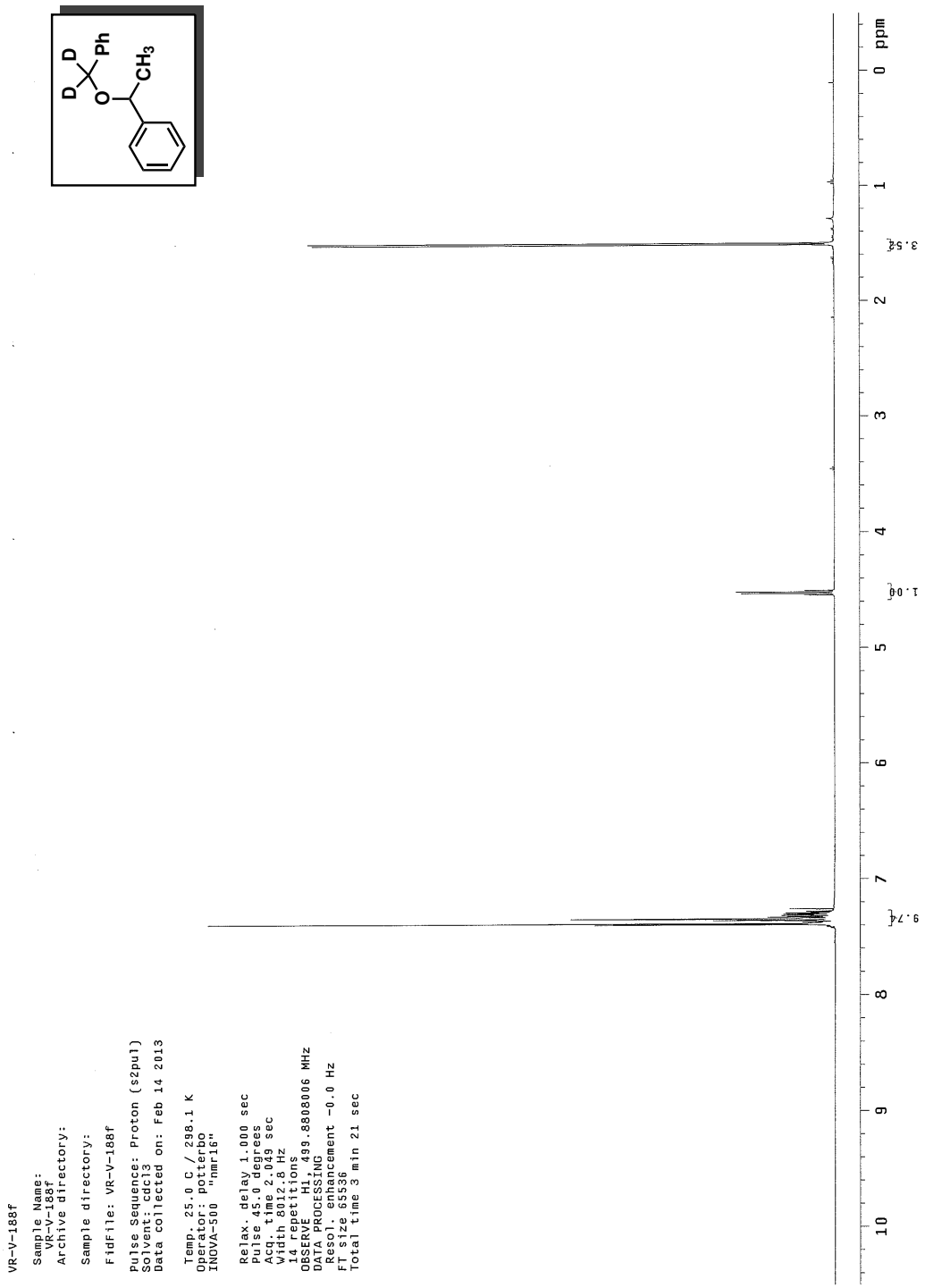


Figure 4.13: ^{13}C NMR of d_2-(1-(benzyloxy)ethyl)benzene (**4.23**)

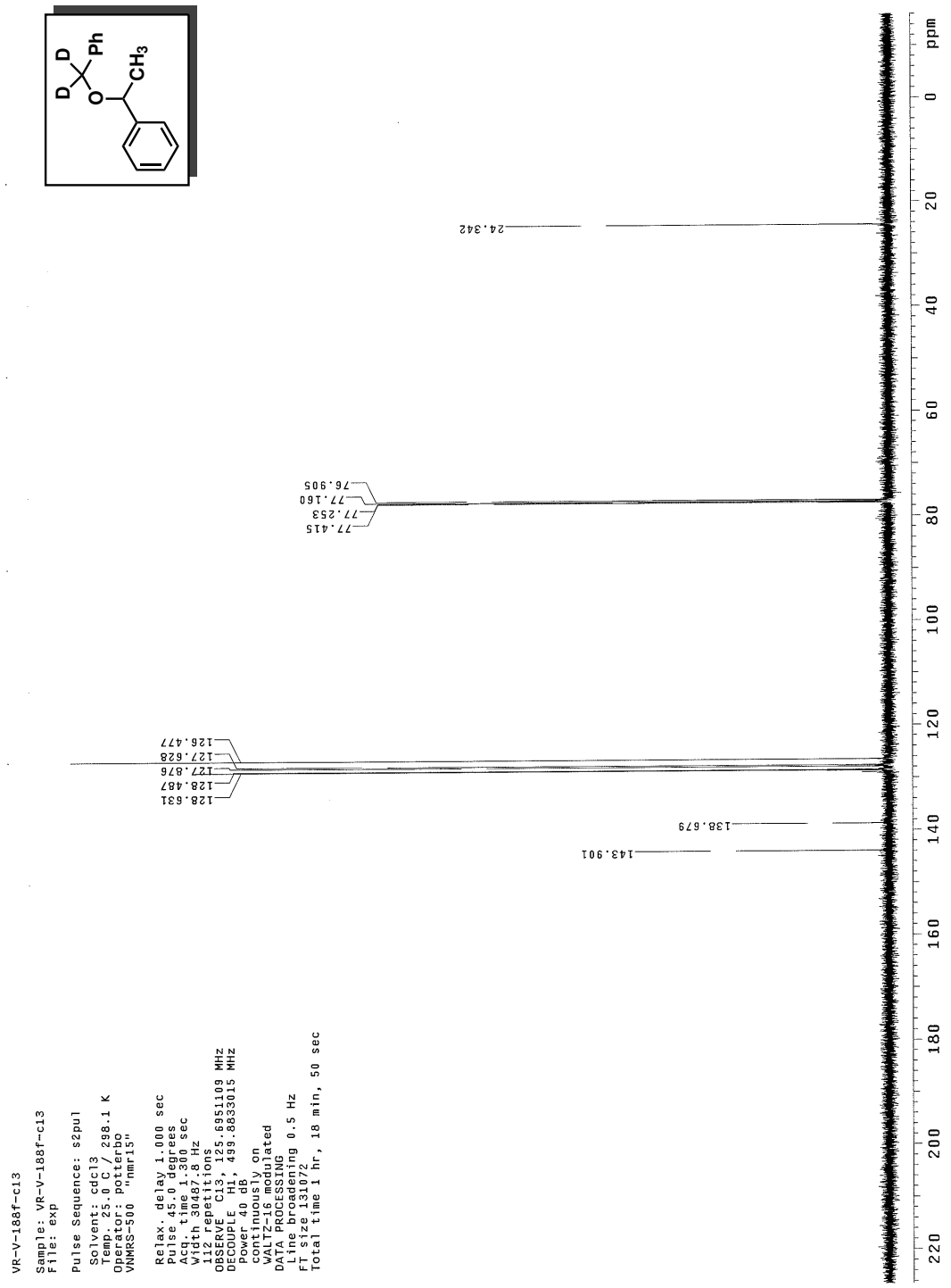


Figure 4.14: ^{1}H NMR of imidazolium bromide salt (**4.28**)

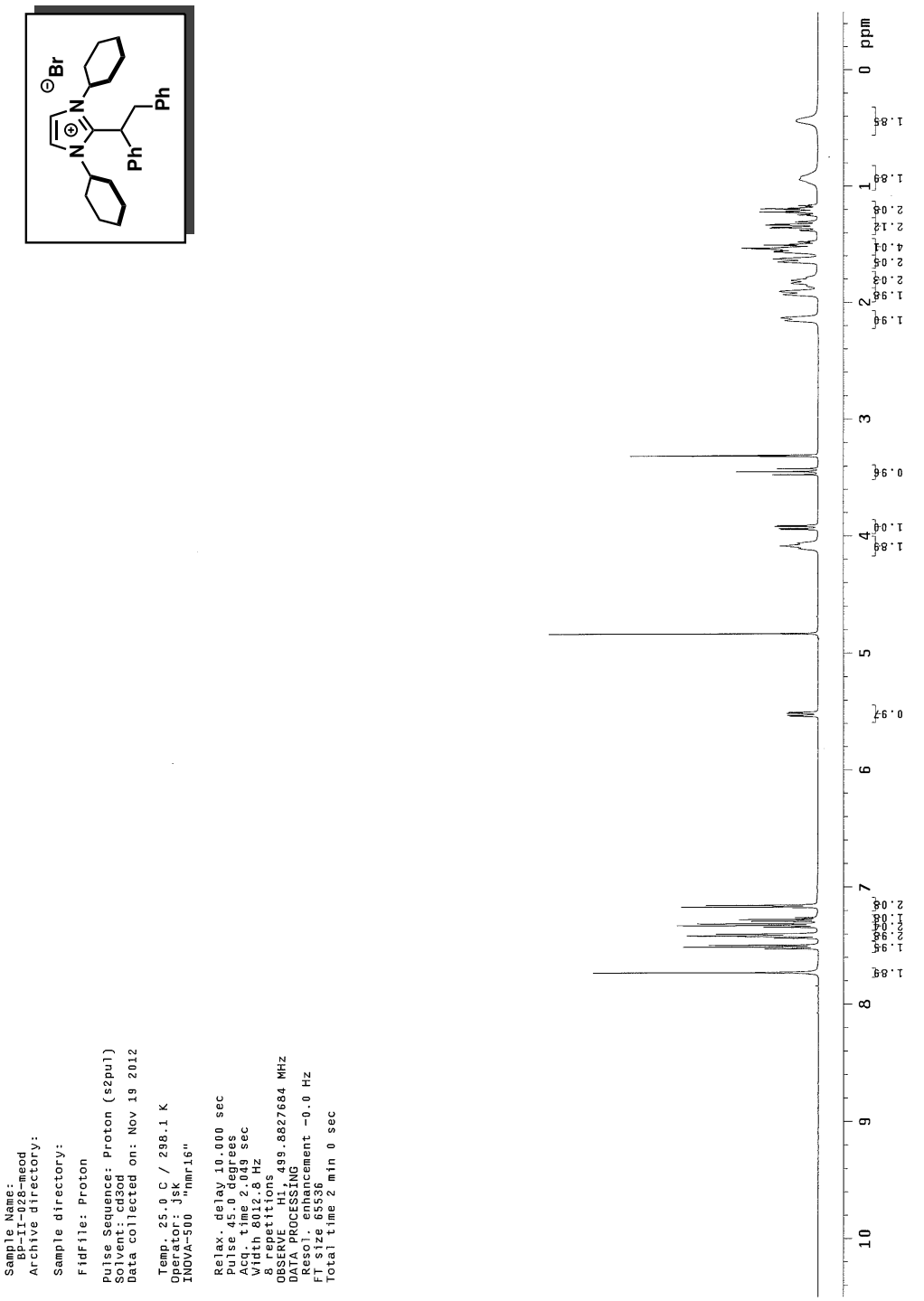


Figure 4.15: ^{13}C NMR of imidazolium bromide salt (**4.28**)

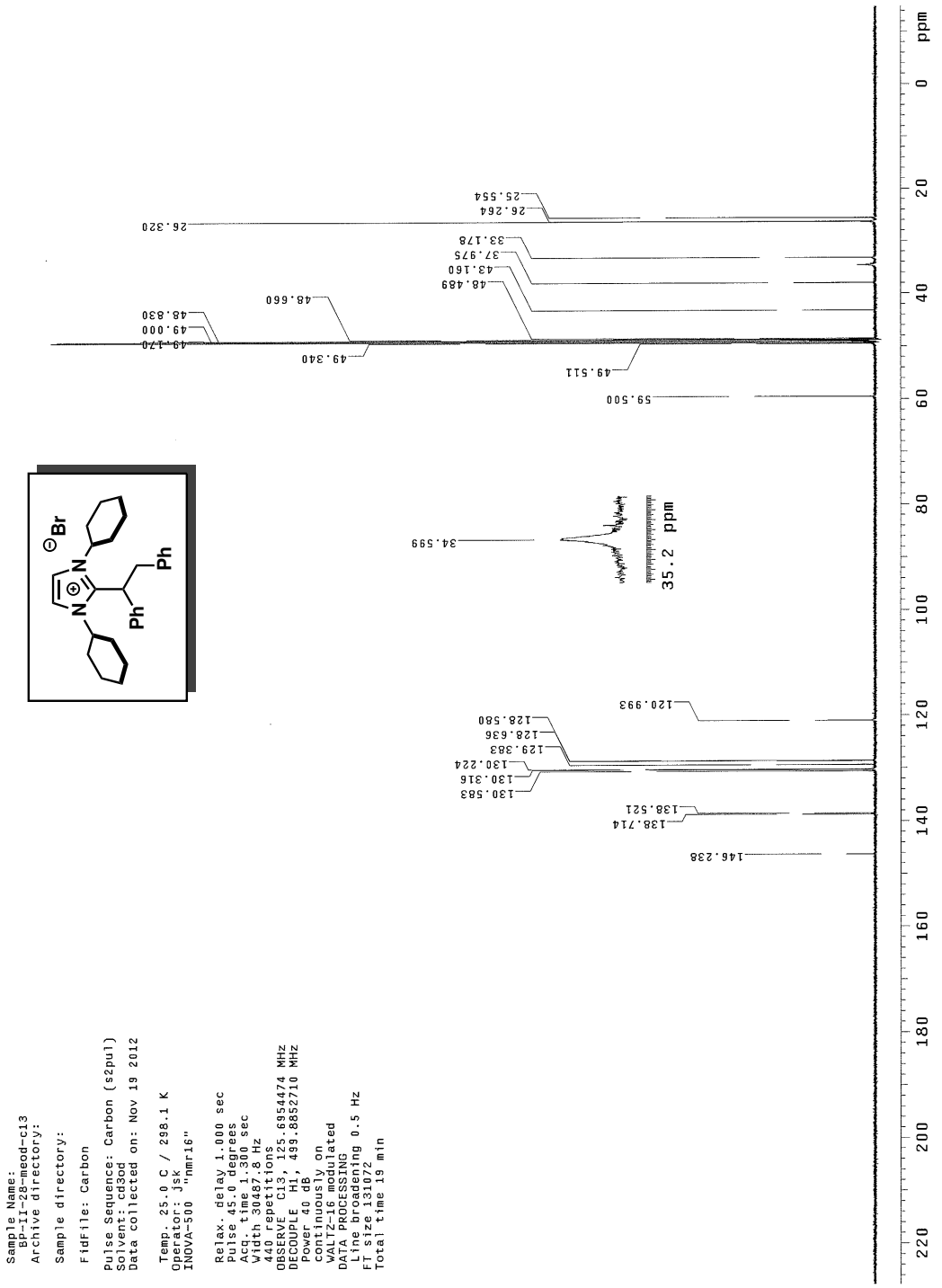


Figure 4.16: HSQC NMR of imidazolium bromide salt (**4.28**)

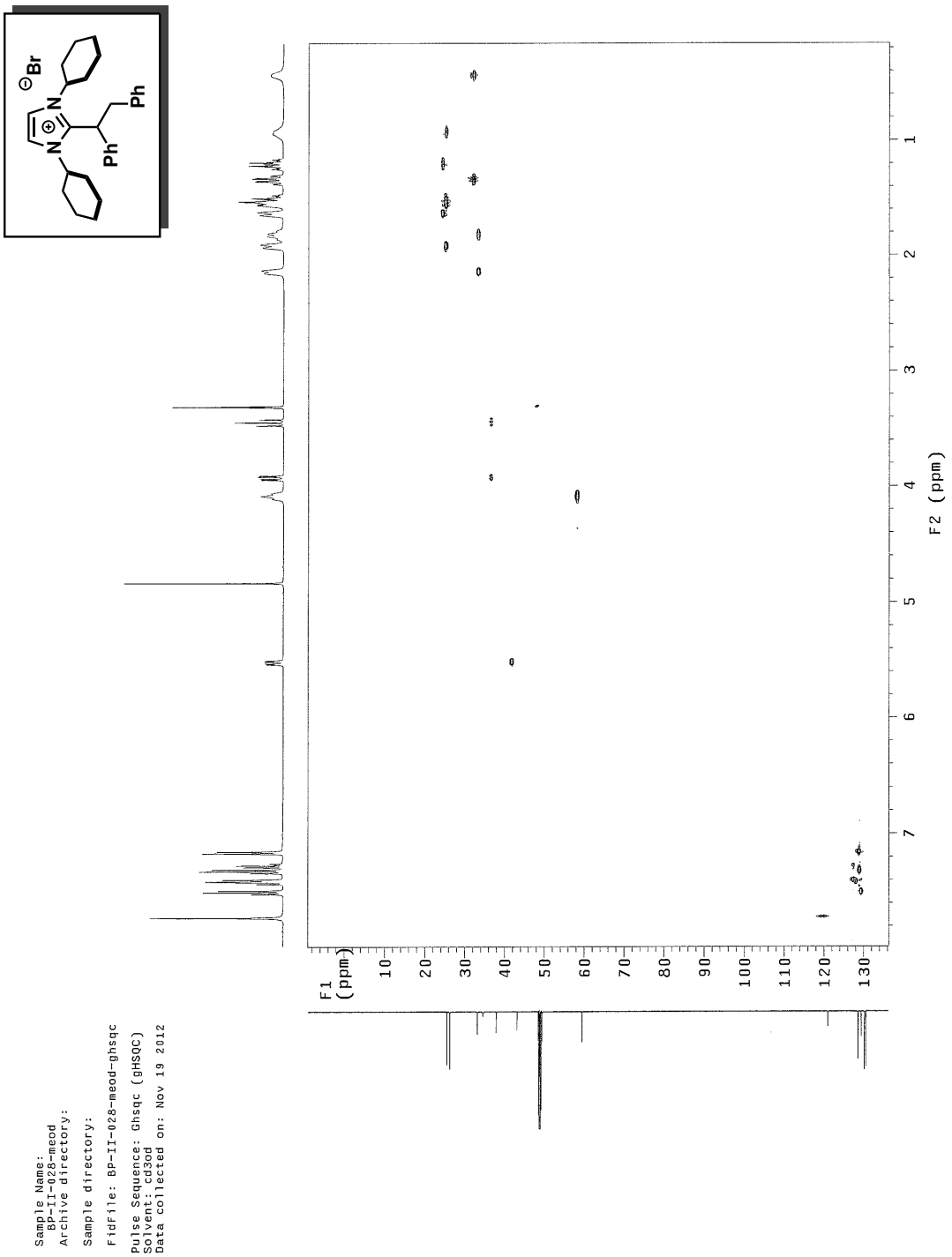


Figure 4.17: ^{1}H NMR of d_2-imidazolium bromide salt (**4.29**)

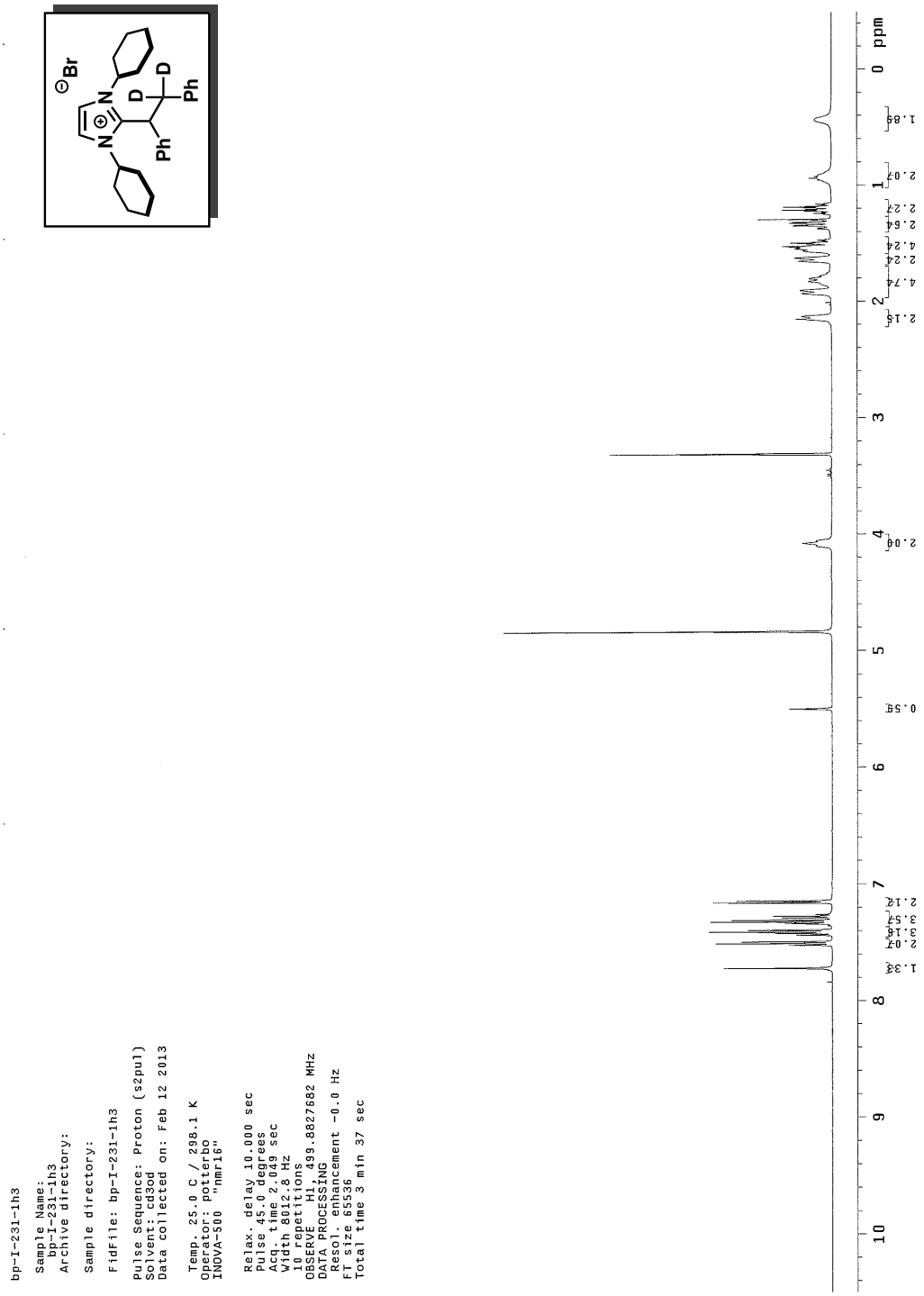


Figure 4.18: ^{13}C NMR of d_2-imidazolium bromide salt (**4.29**)

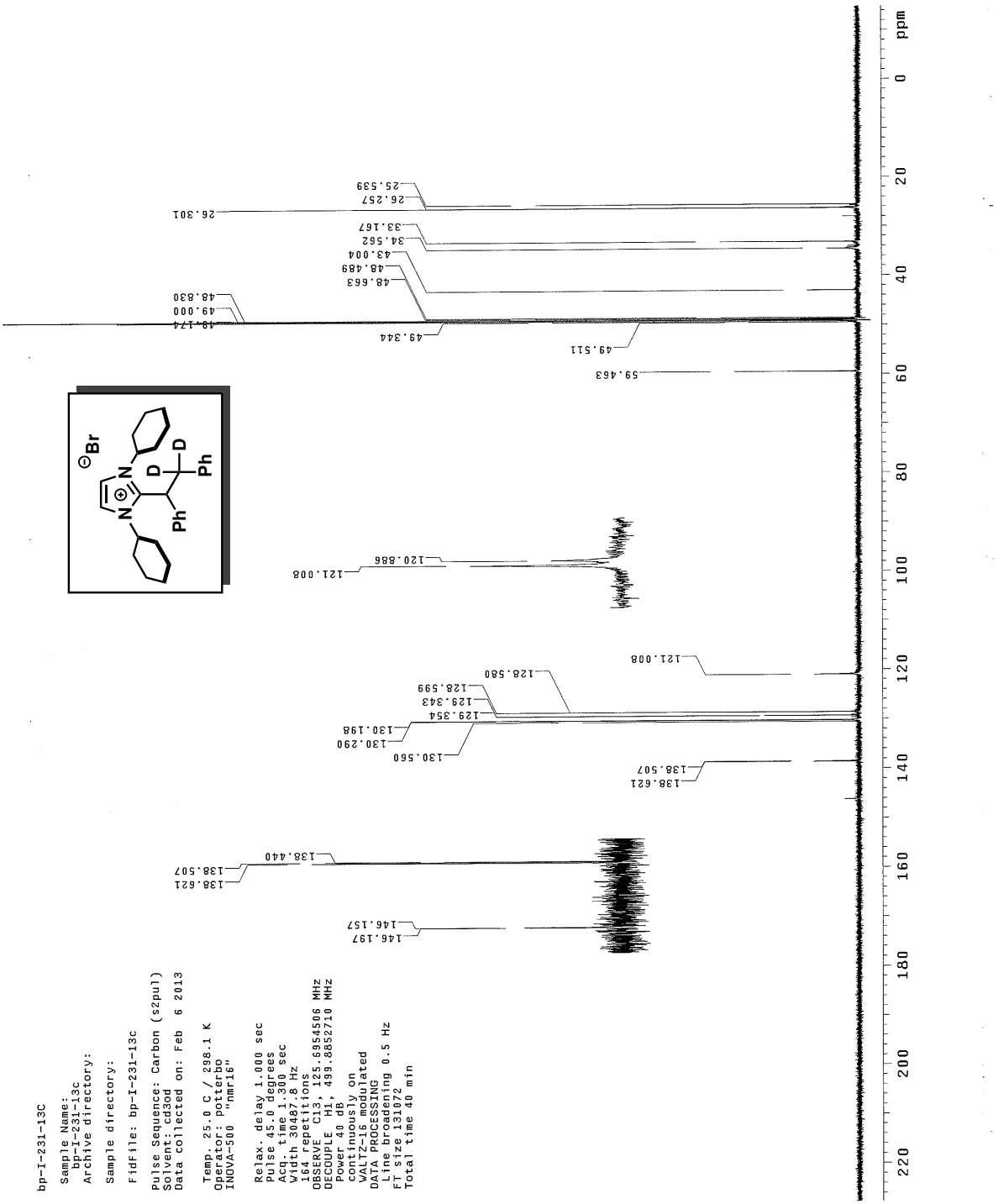


Figure 4.19: ^{1}H NMR of imidazolium bromide salt (**4.37**)

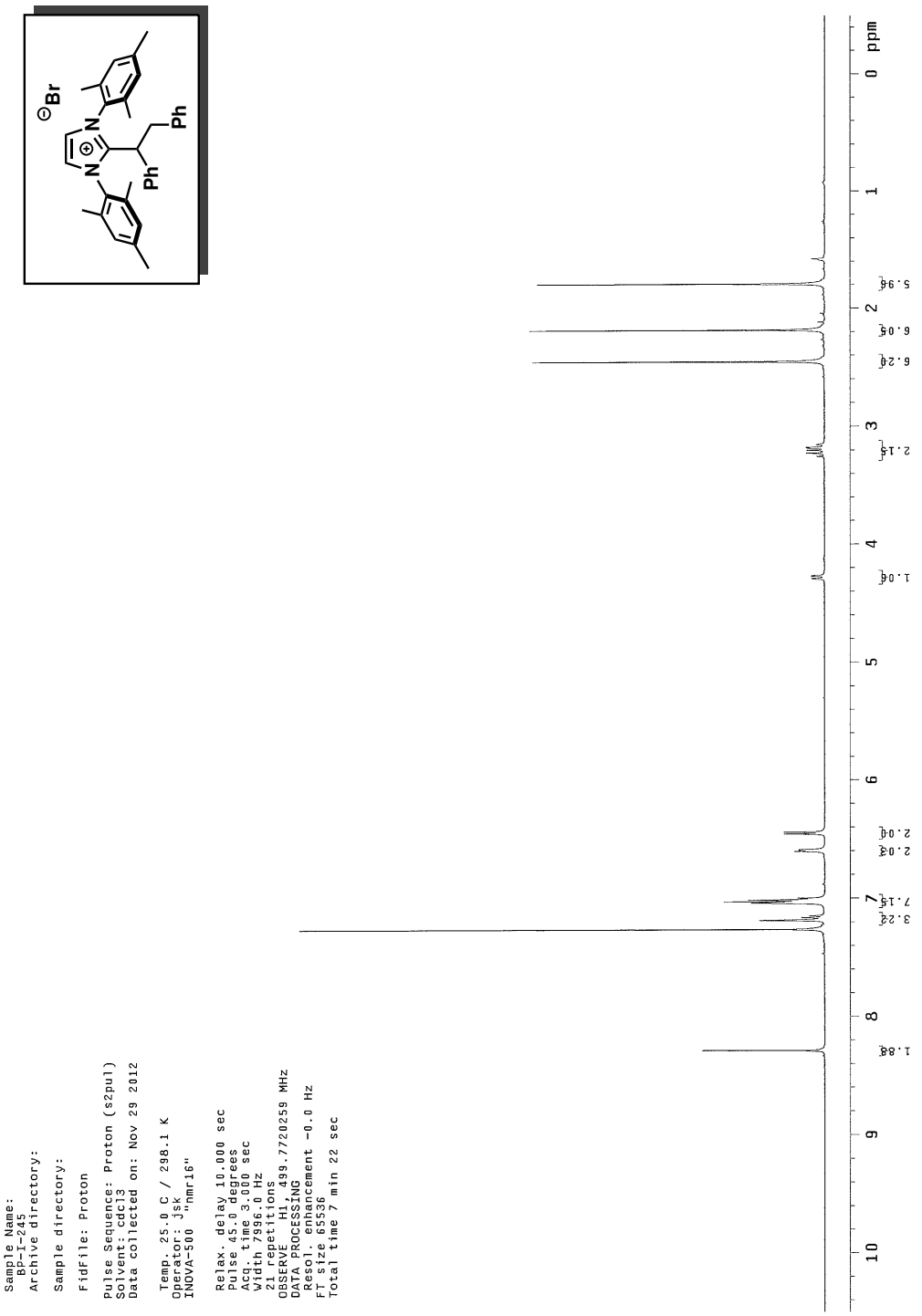


Figure 4.20: ^{13}C NMR of imidazolium bromide salt (**4.37**)

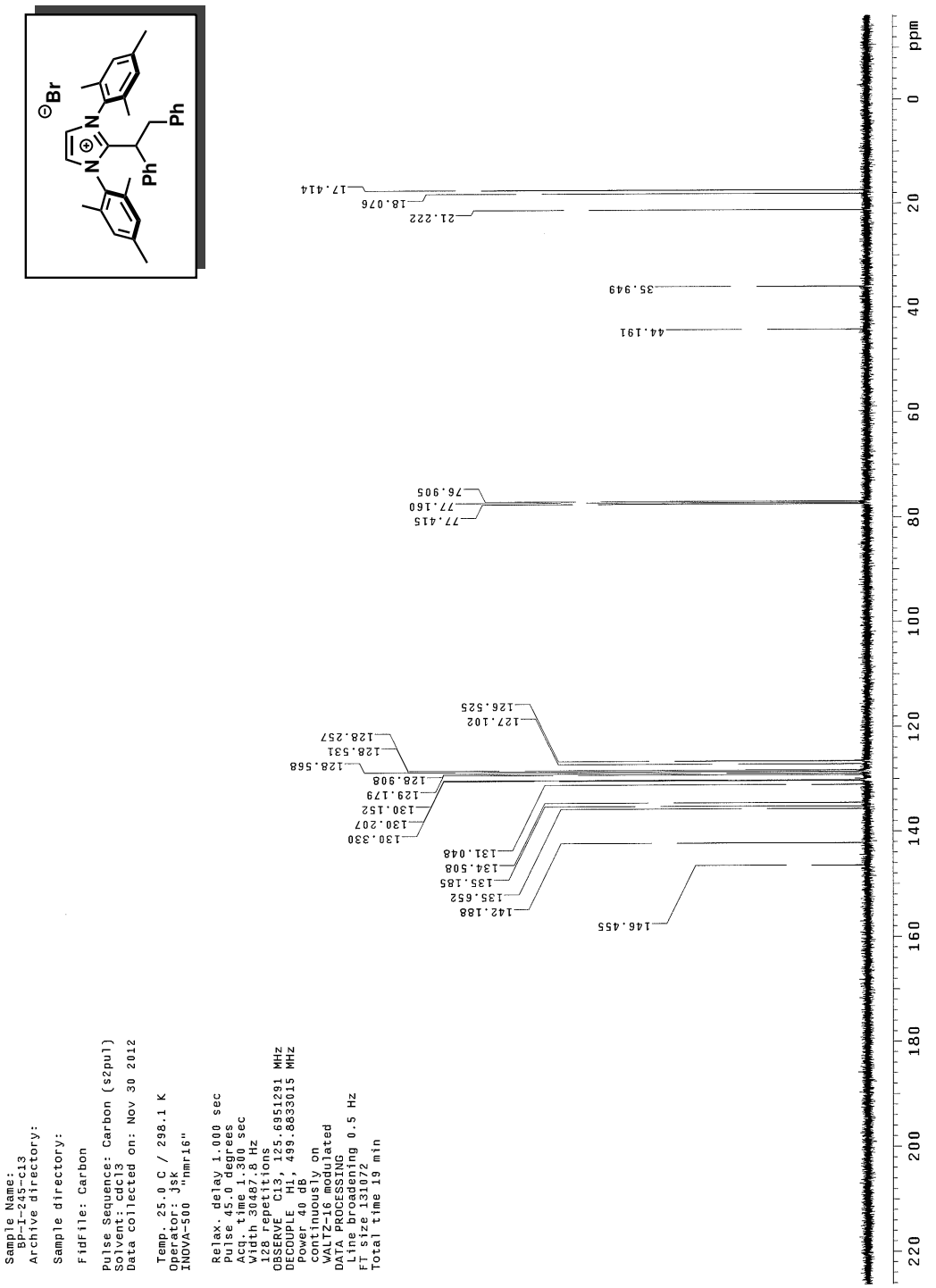


Figure 4.21: ^{1}H NMR of imidazolium iodide salt (**4.32**)

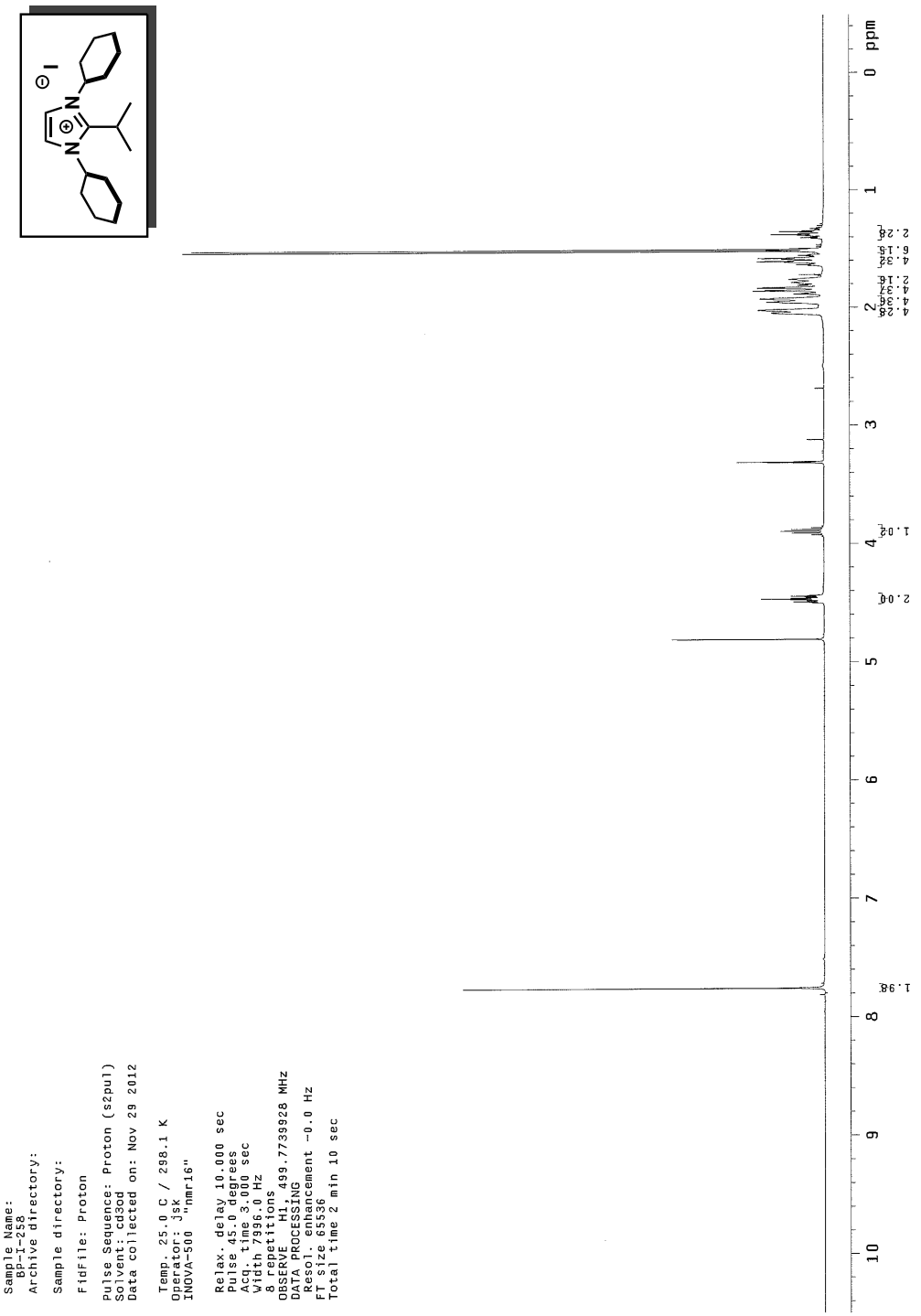


Figure 4.22: ^{13}C NMR of imidazolium iodide salt (**4.32**)

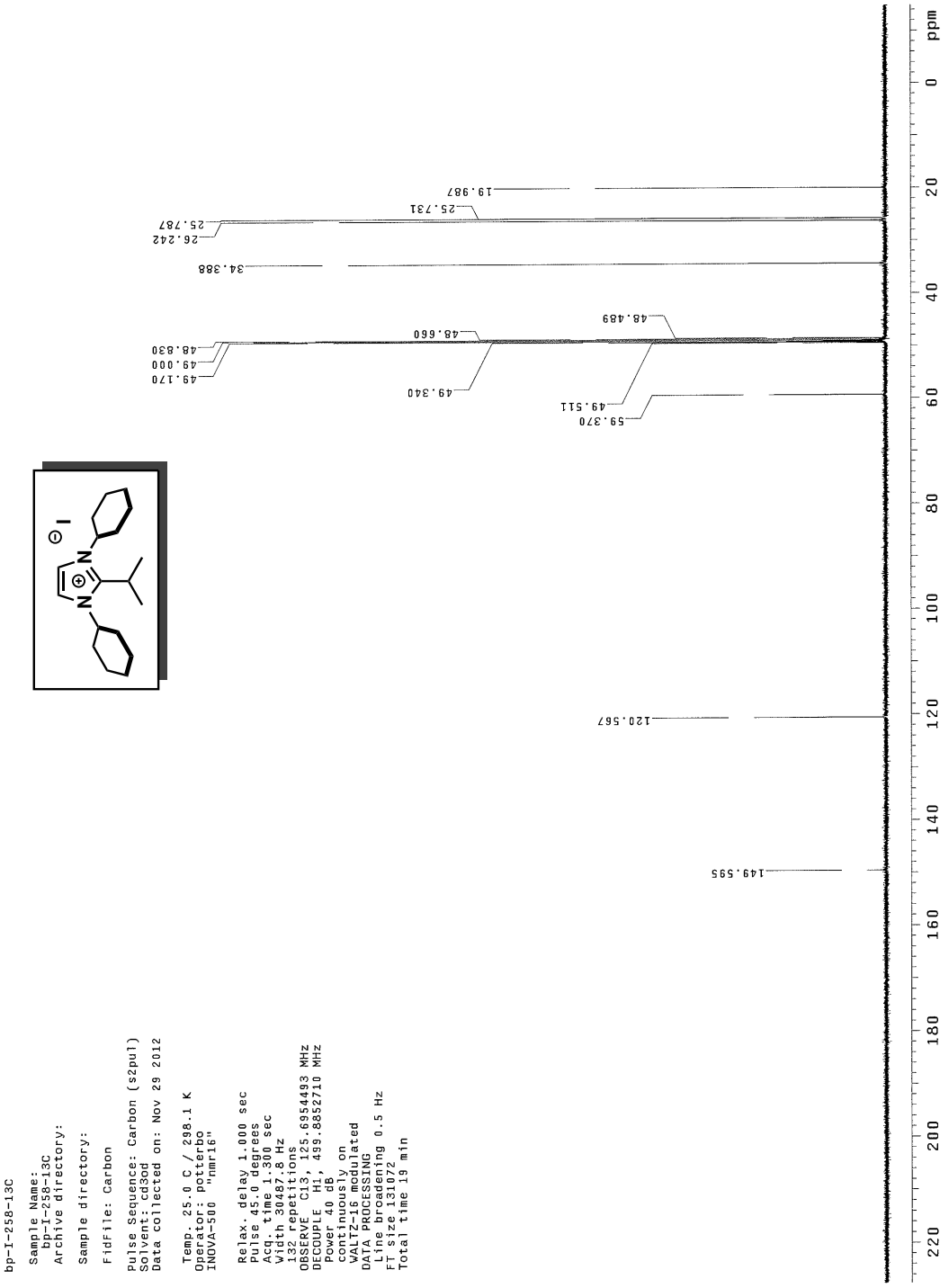


Figure 4.23: ^{1}H NMR of imidazolium tetrafluoroborate salt (**4.35**)

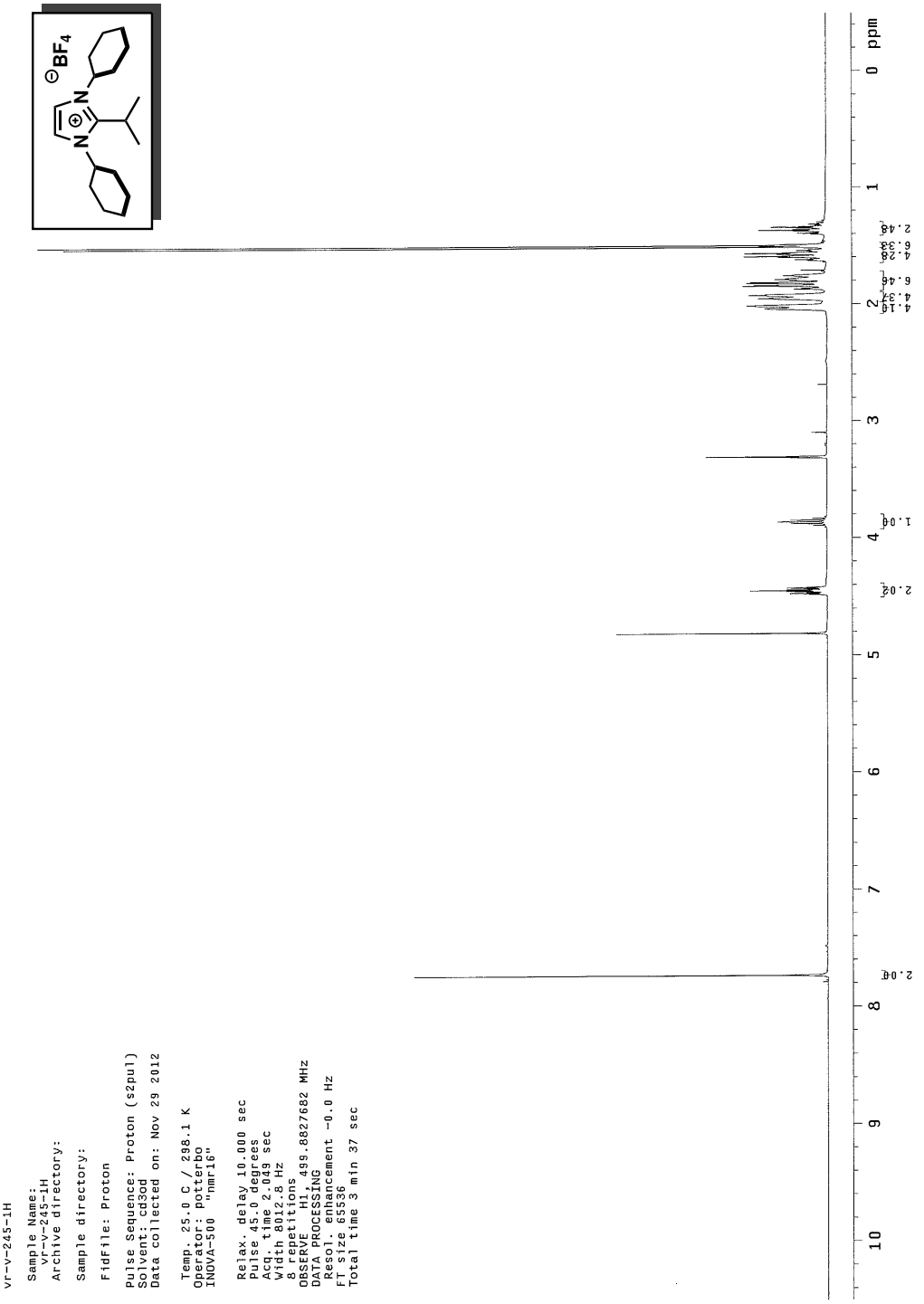


Figure 4.24: ^{13}C NMR of imidazolium tetrafluoroborate salt (**4.35**)

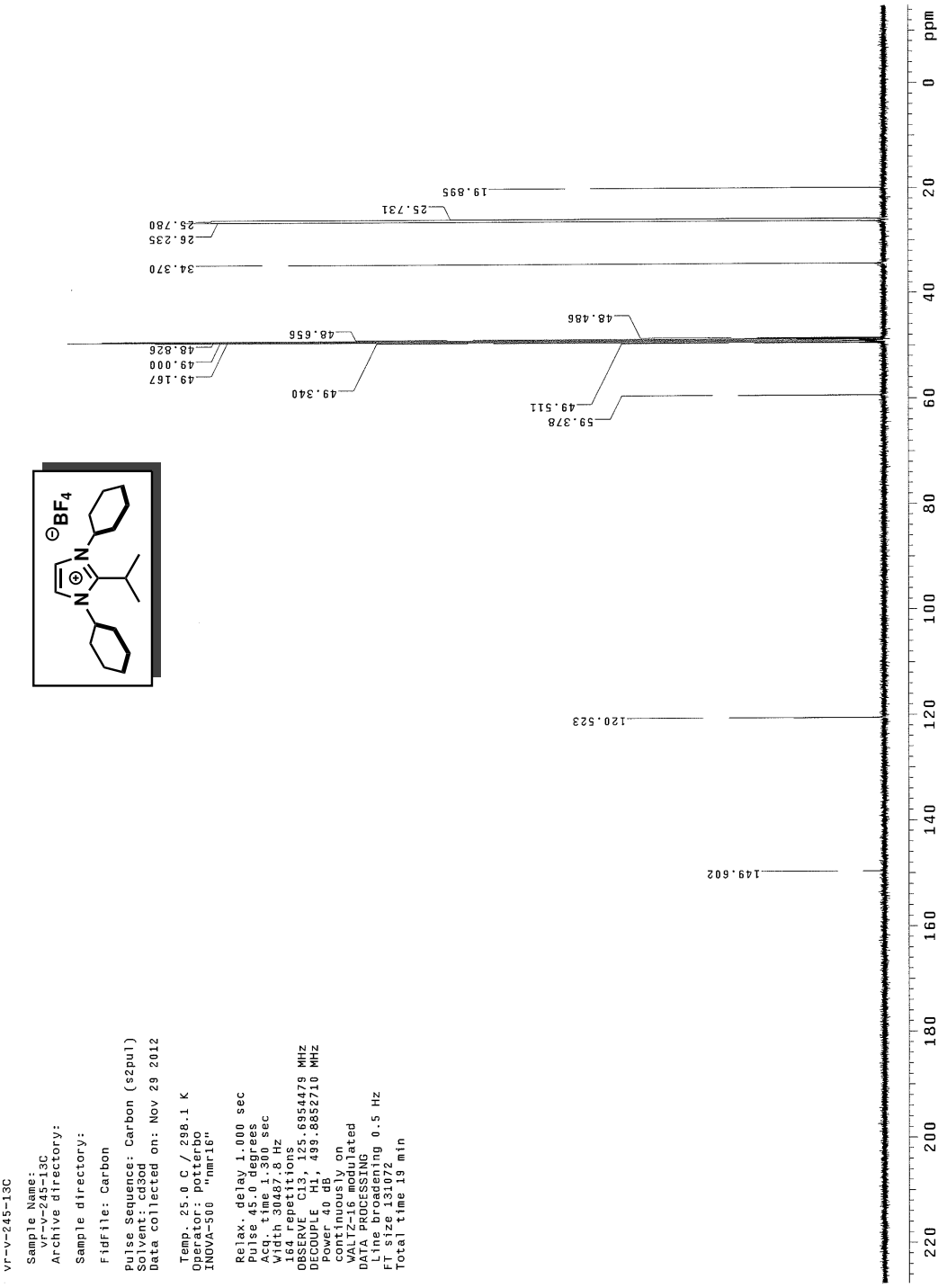


Figure 4.25: ^{1}H NMR of imidazolium tetraphenylborate salt (**4.30**)

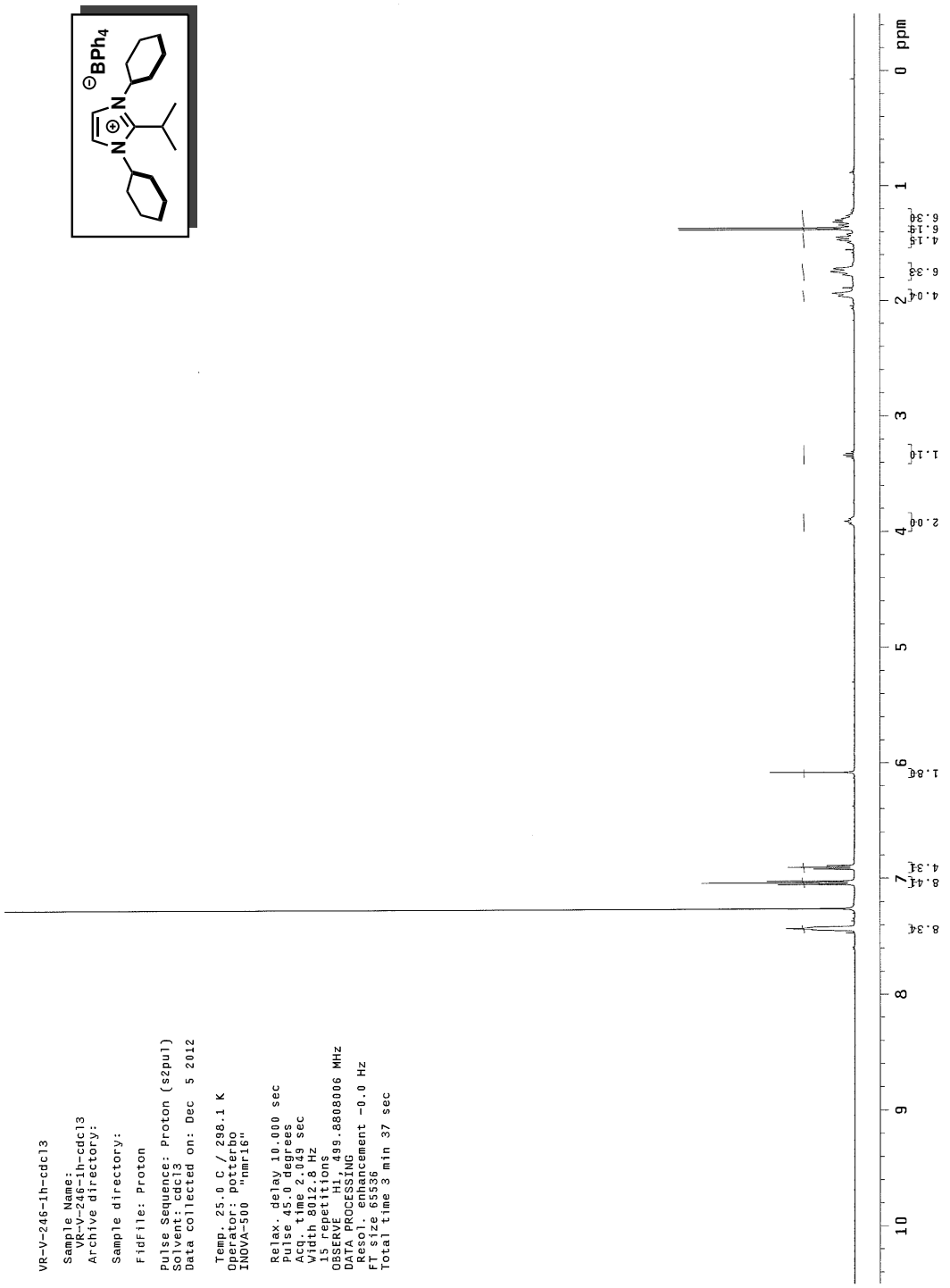


Figure 4.26: ^{13}C NMR of imidazolium tetraphenylborate salt (**4.30**)

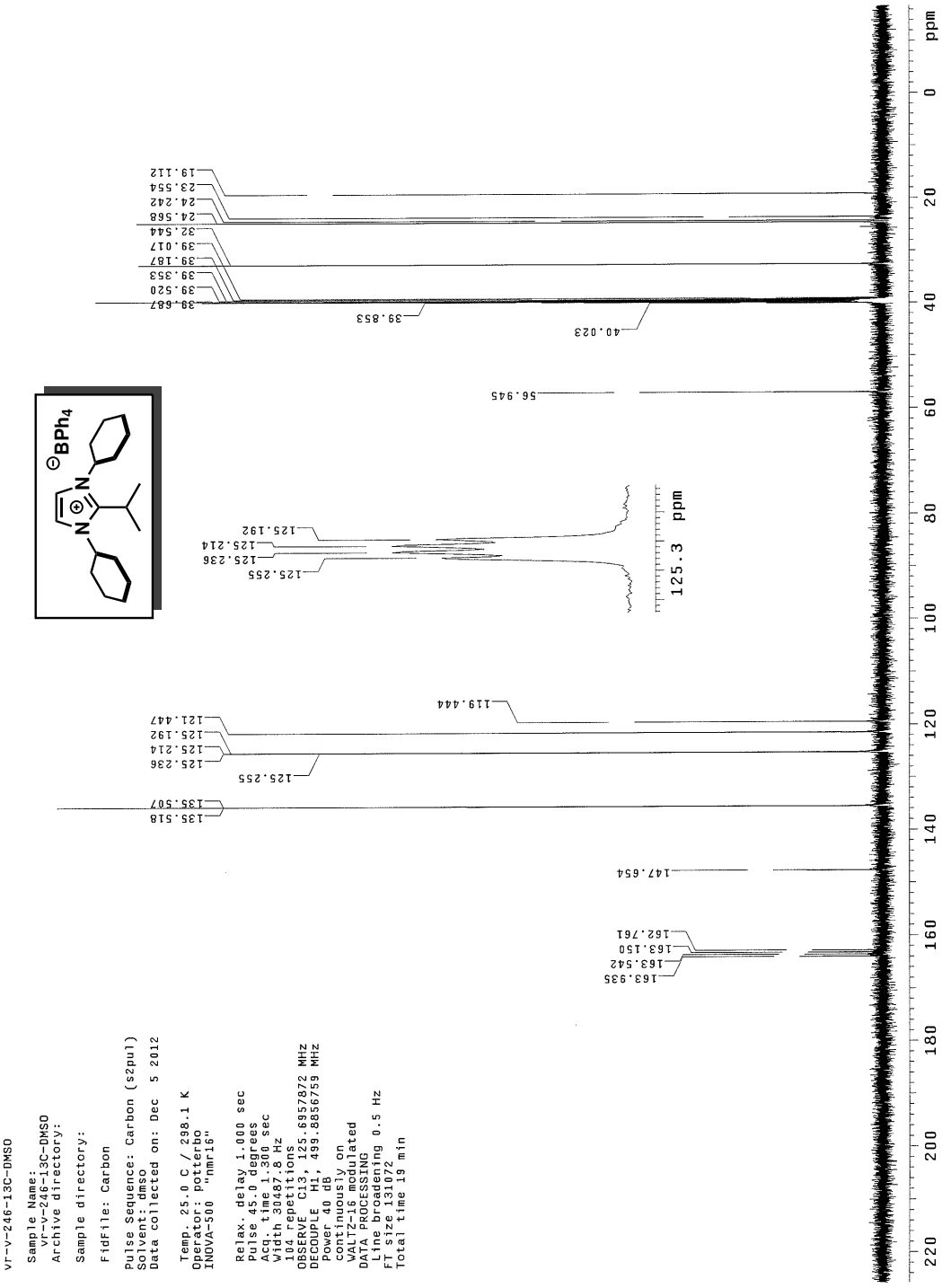


Figure 4.27: ^{1}H NMR of imidazolium tetrakis[(3,5-trifluoromethyl)phenyl]borate salt (**4.36**)

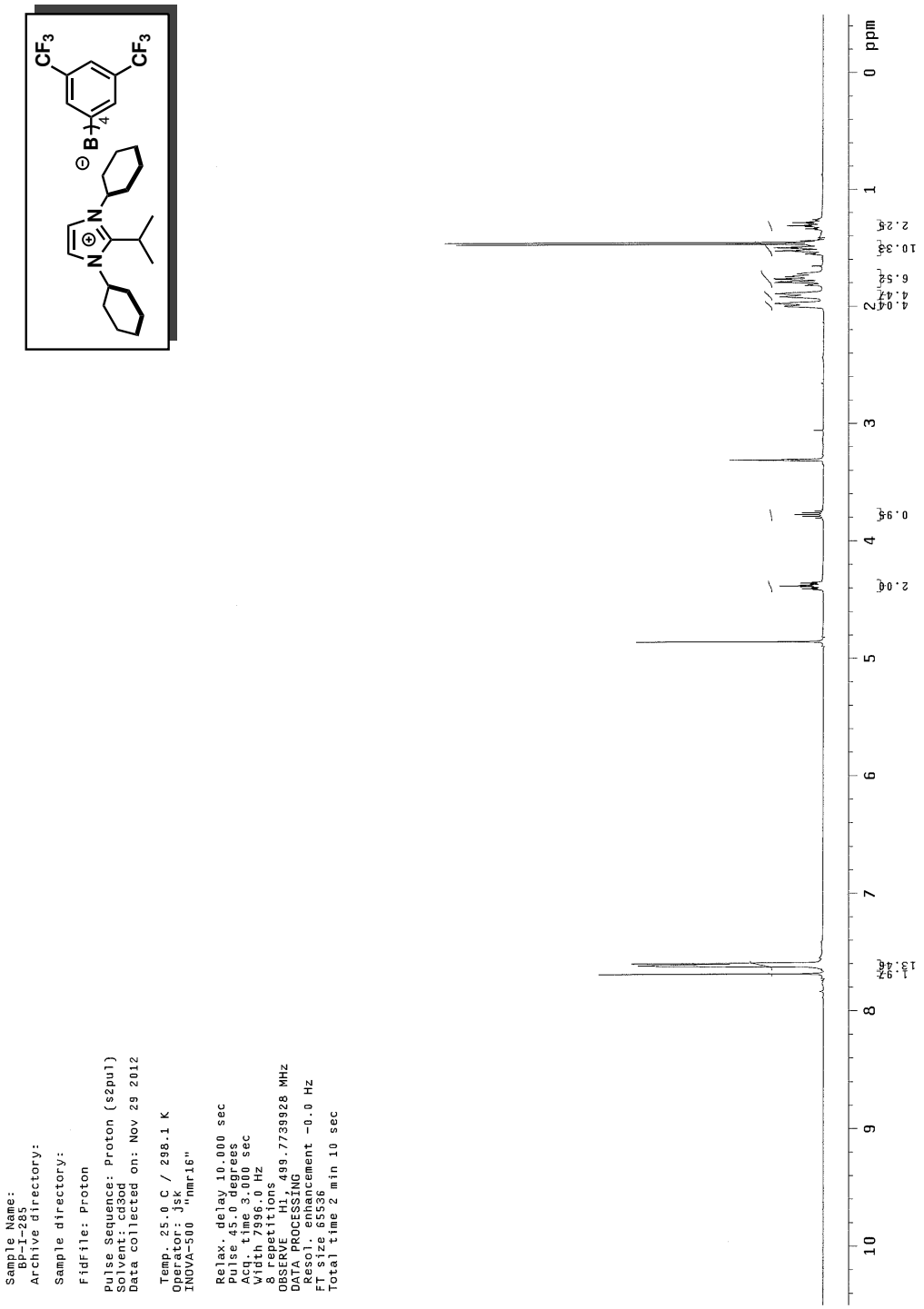


Figure 4.28: ^{13}C NMR of imidazolium tetrakis[(3,5-trifluoromethyl)phenyl]borate salt (**4.36**)

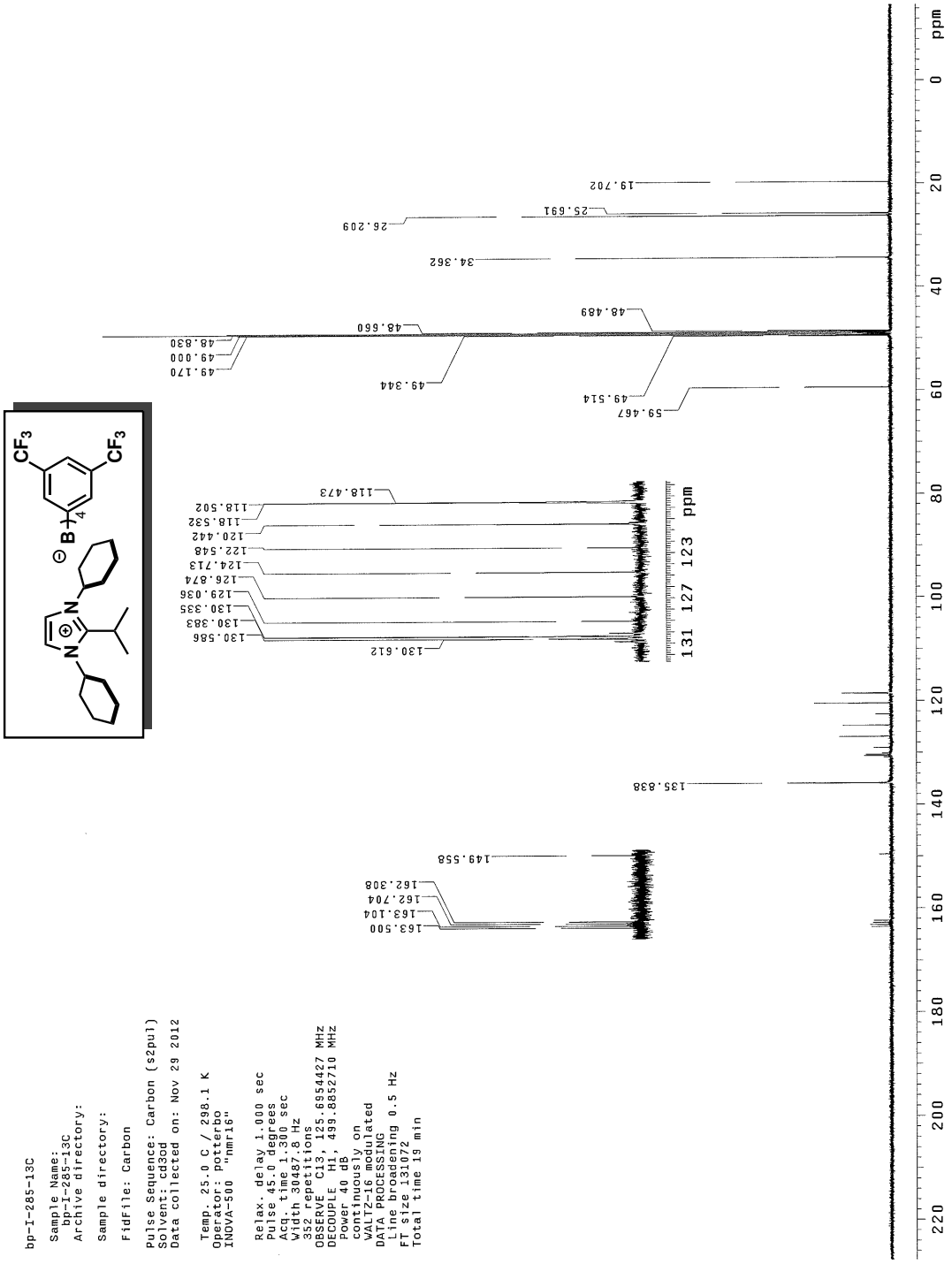


Figure 4.29: ^{1}H NMR of imidazolium chloride salt (**4.40**)

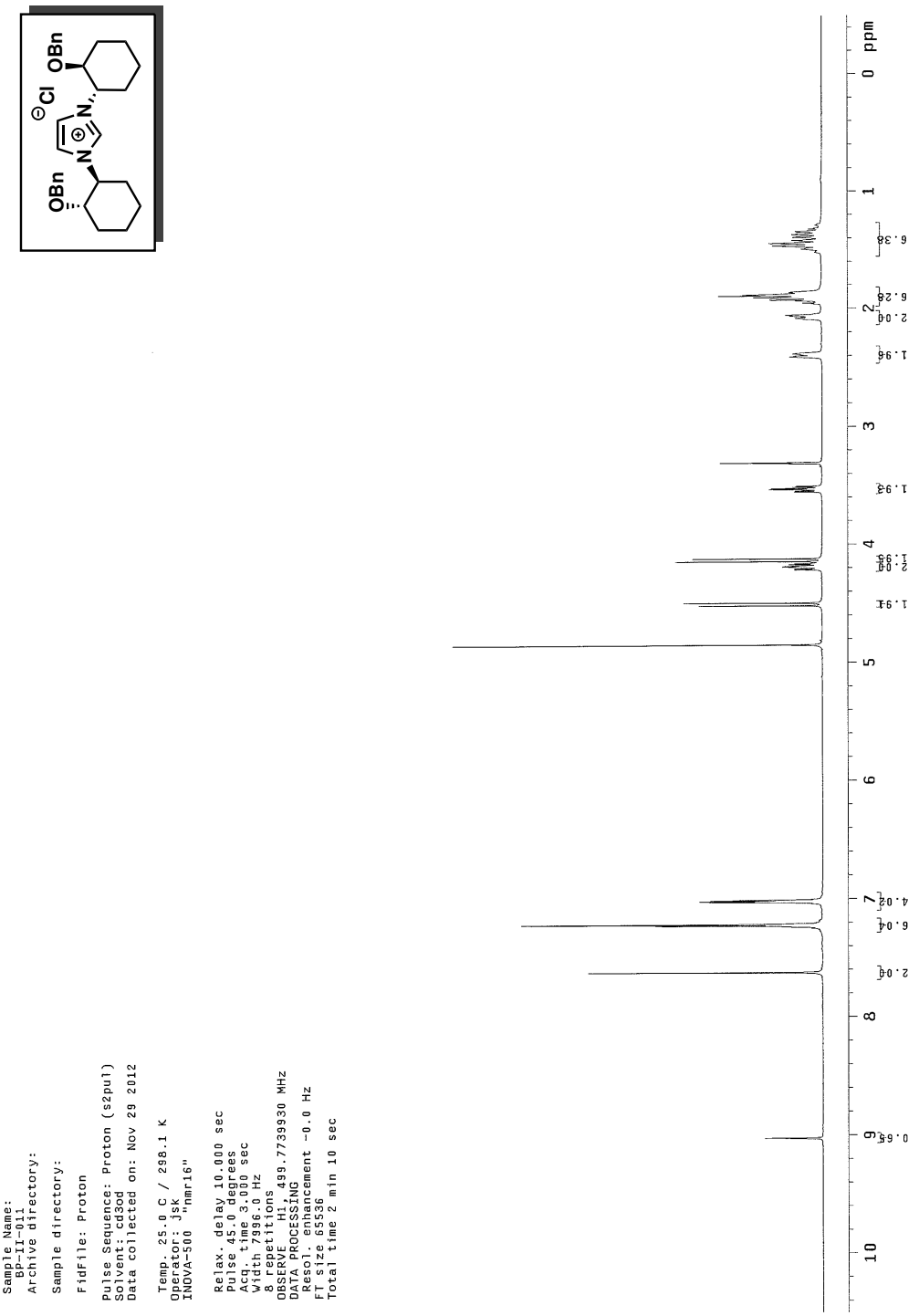


Figure 4.30: ^{13}C NMR of imidazolium chloride salt (**4.40**)

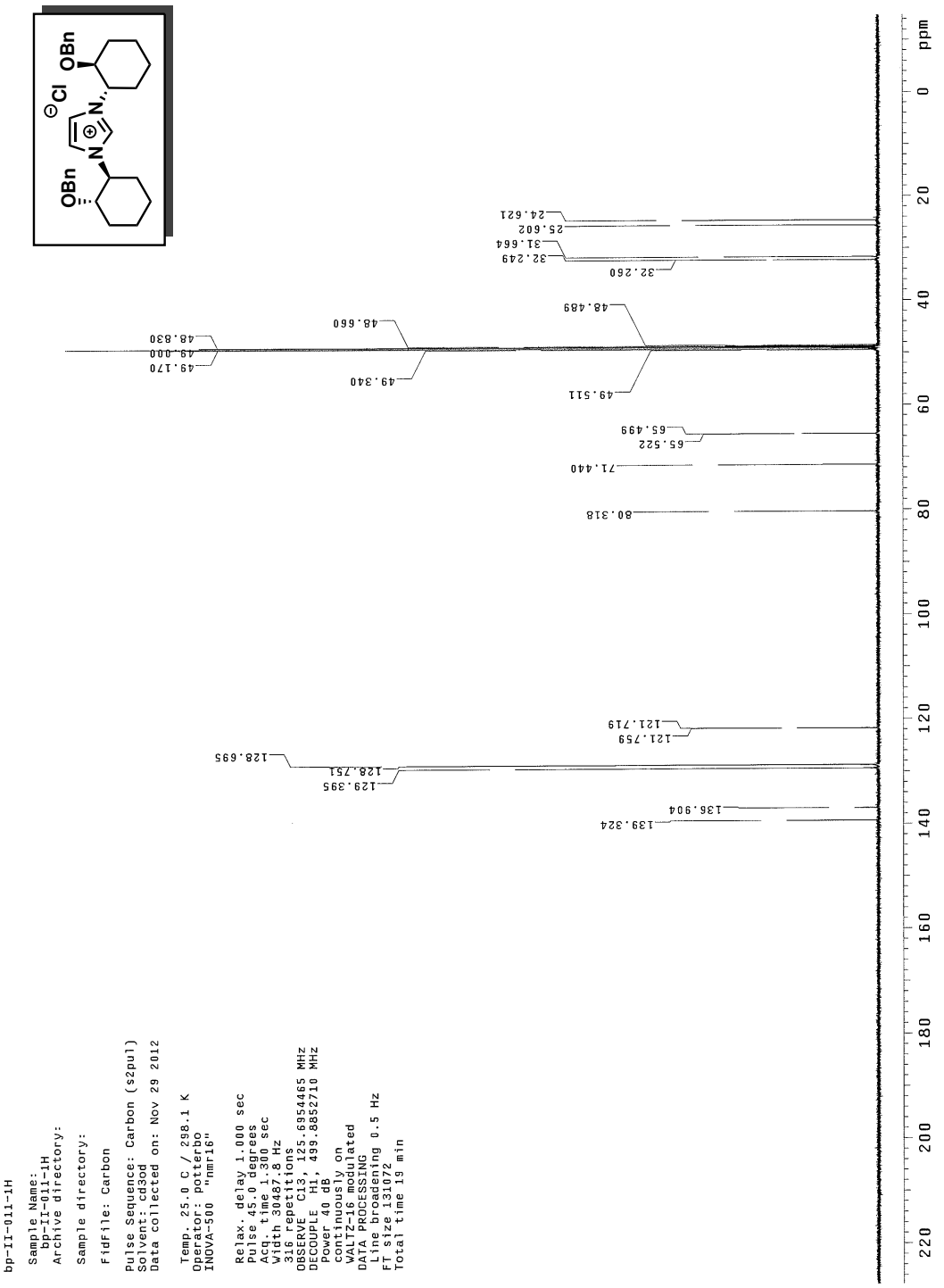


Figure 4.31: ^{1}H NMR of imidazolium ylide (**4.33**)

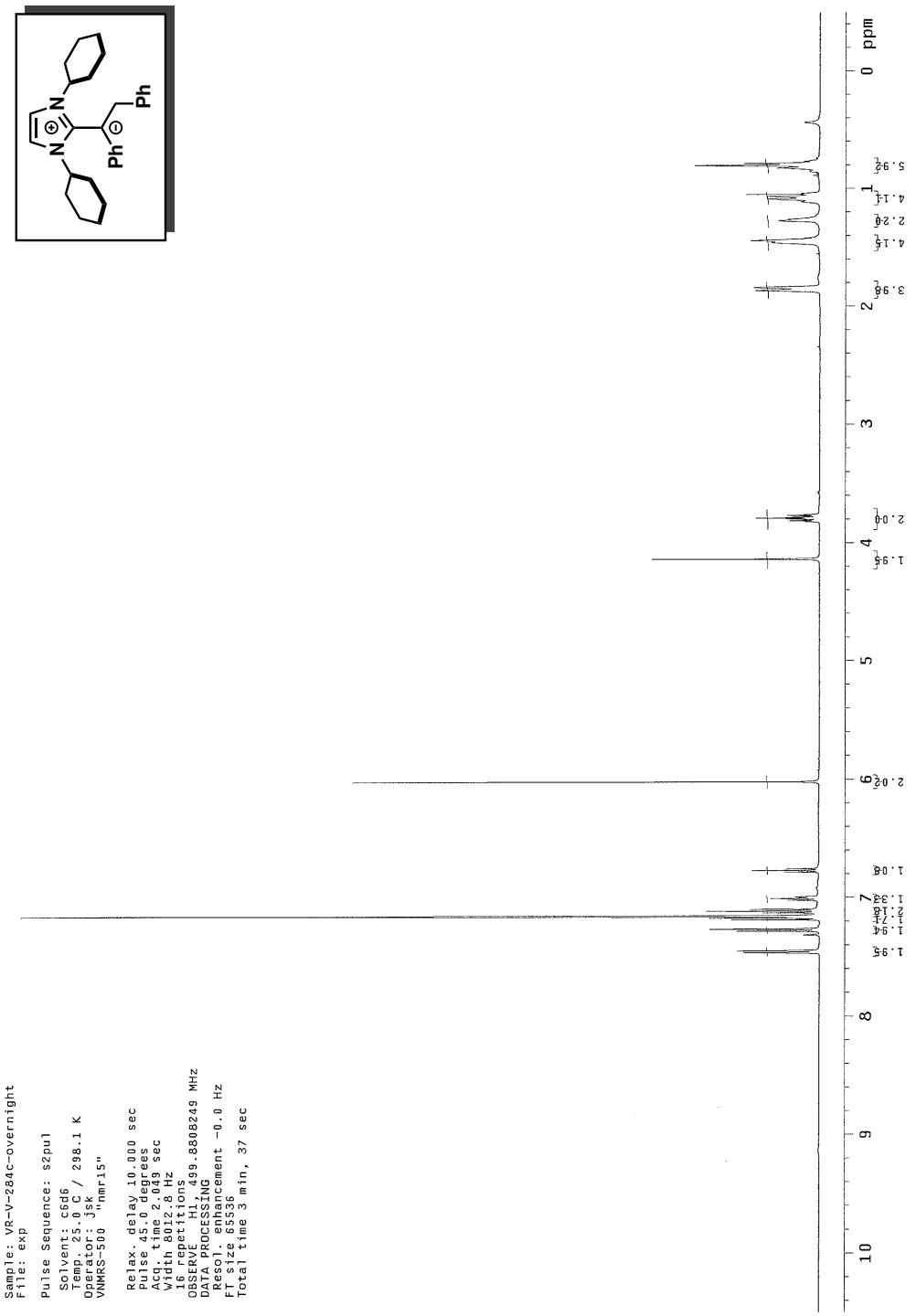


Figure 4.32: ^{13}C NMR of imidazolium ylide (**4.33**)

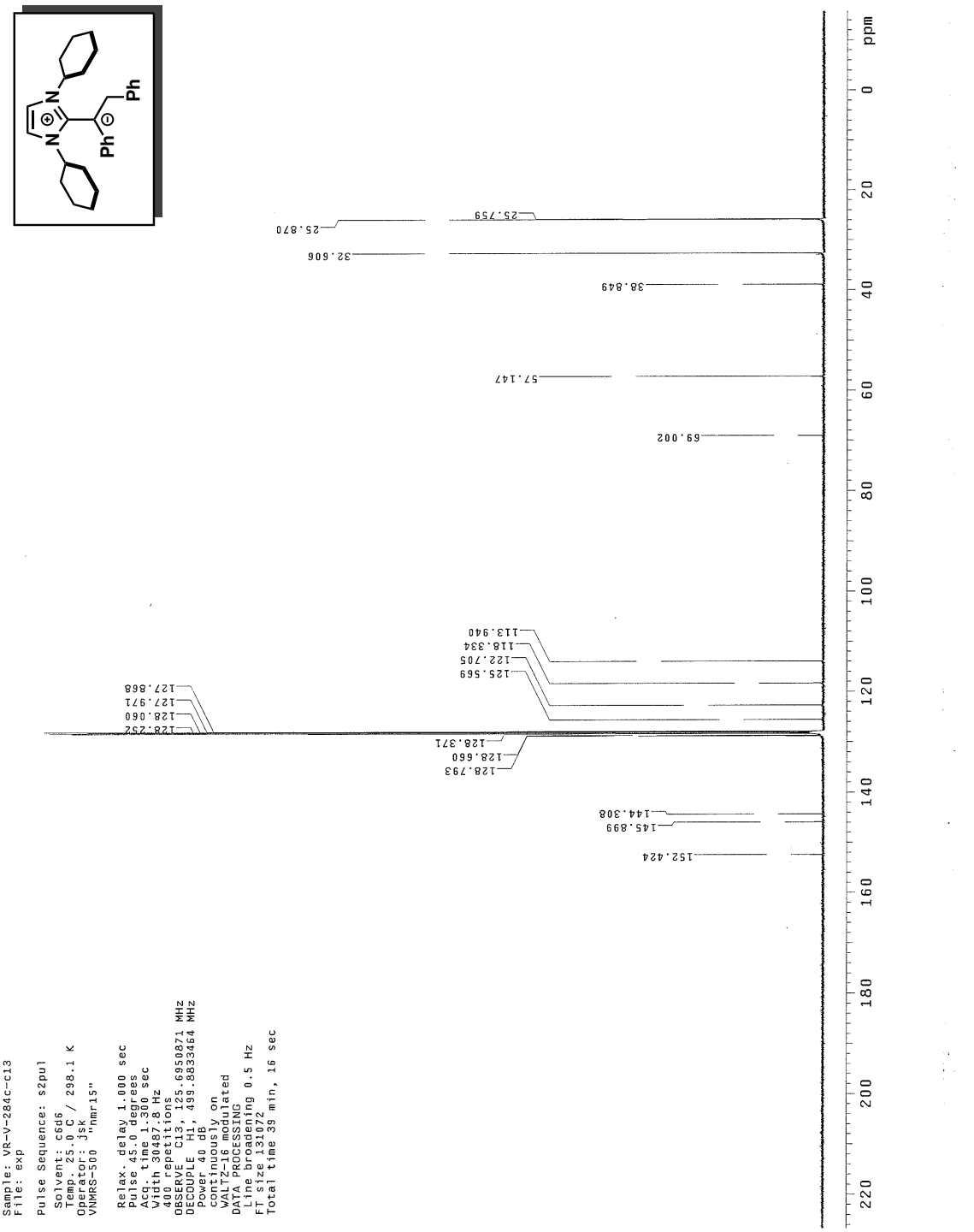


Figure 4.33: HSQC NMR of imidazolium ylide (**4.33**)

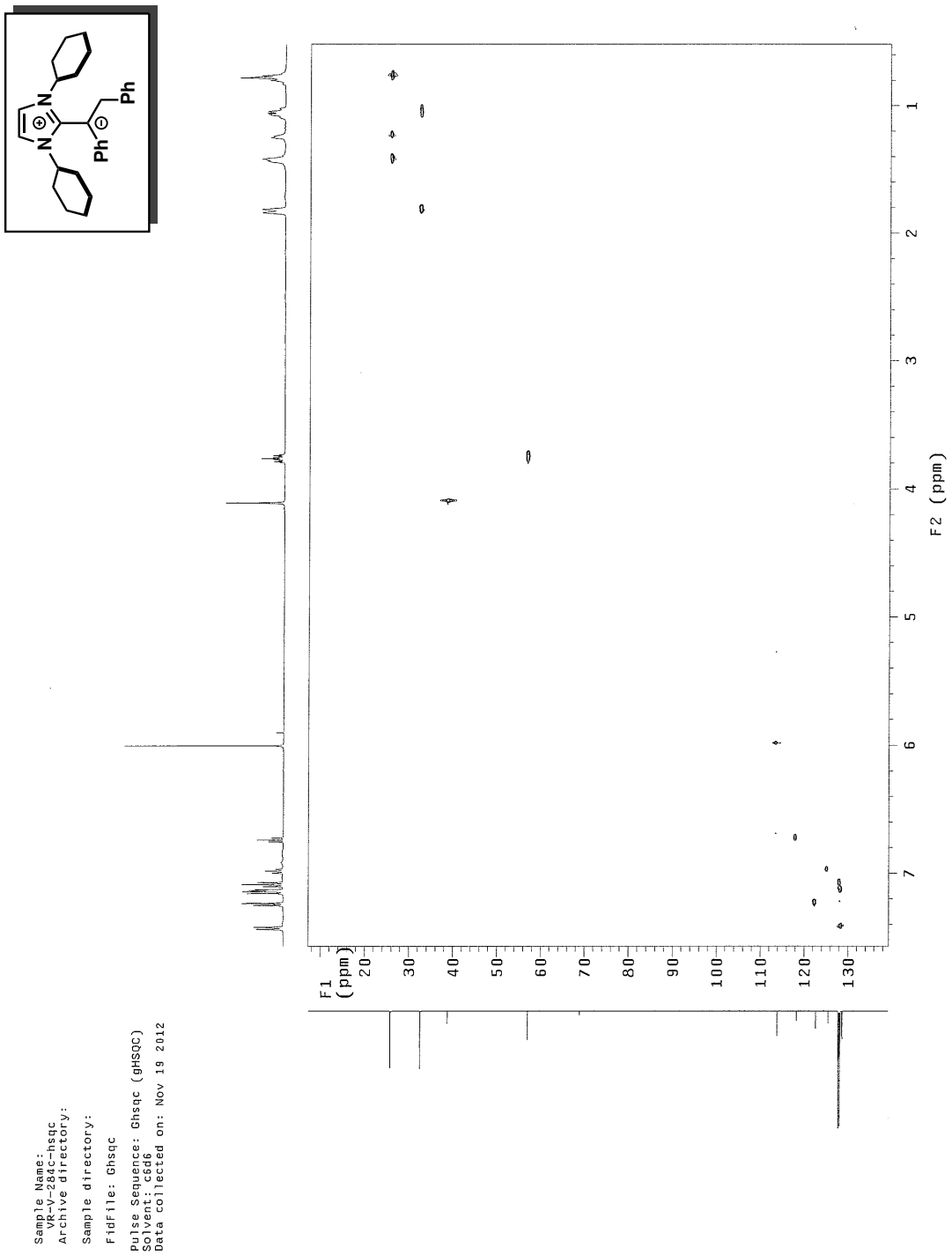


Figure 4.34: ^{1}H NMR of d_3-imidazolium methoxide salt (**4.41**)

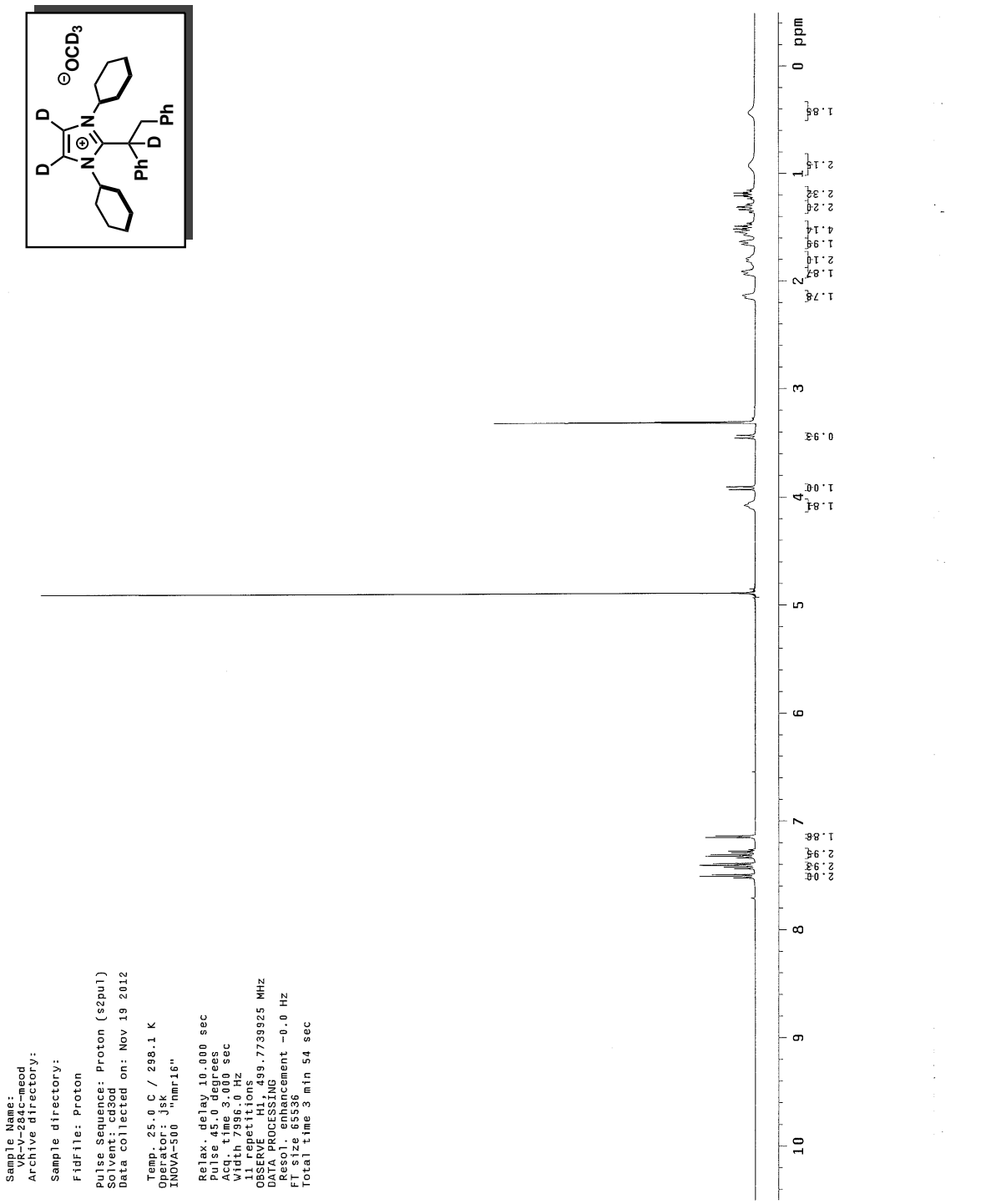


Figure 4.35: ^{13}C NMR of d_3-imidazolium methoxide salt (**4.41**)

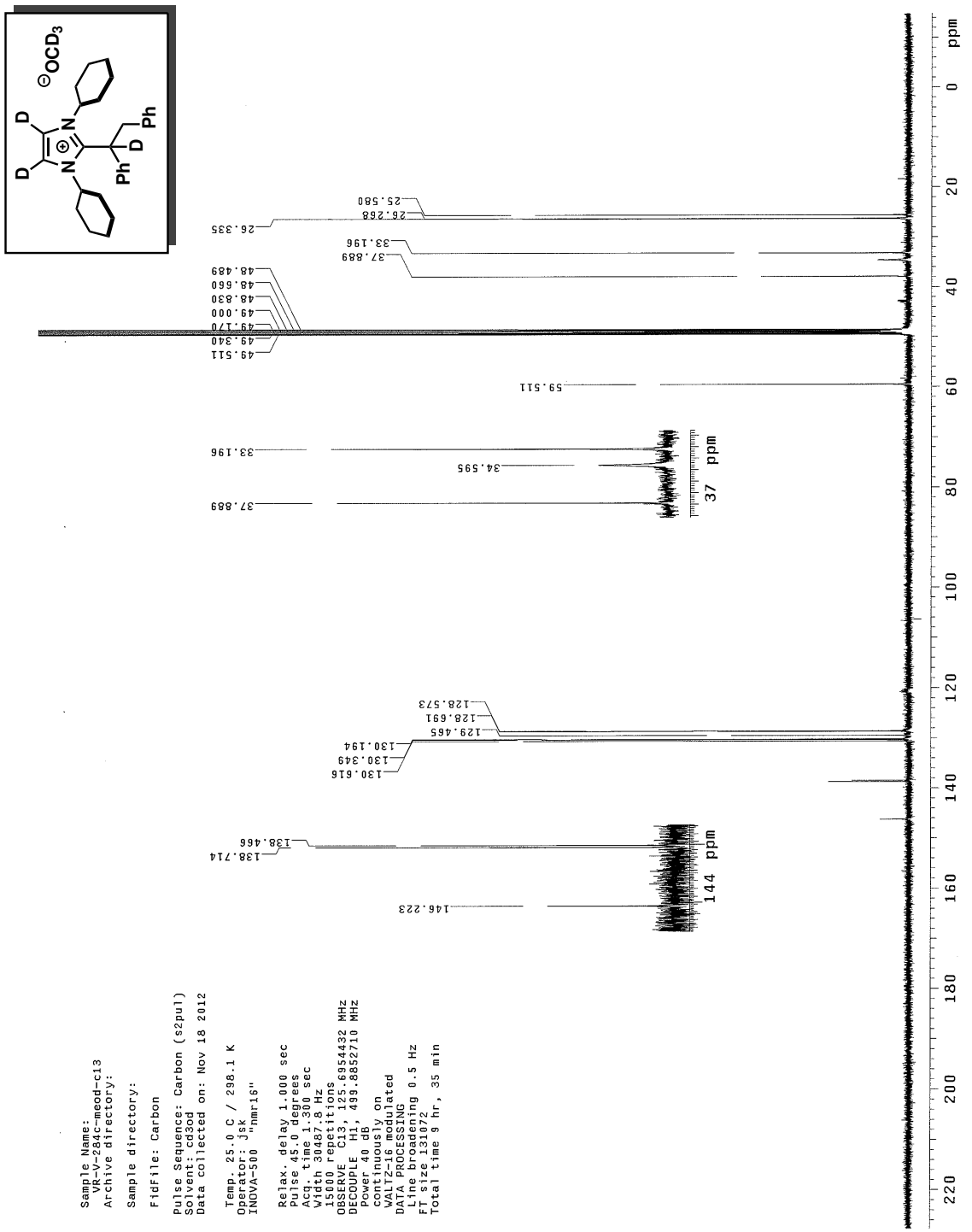


Figure 4.36: ^{1}H NMR of imidazolium bromide salt (**4.43**)

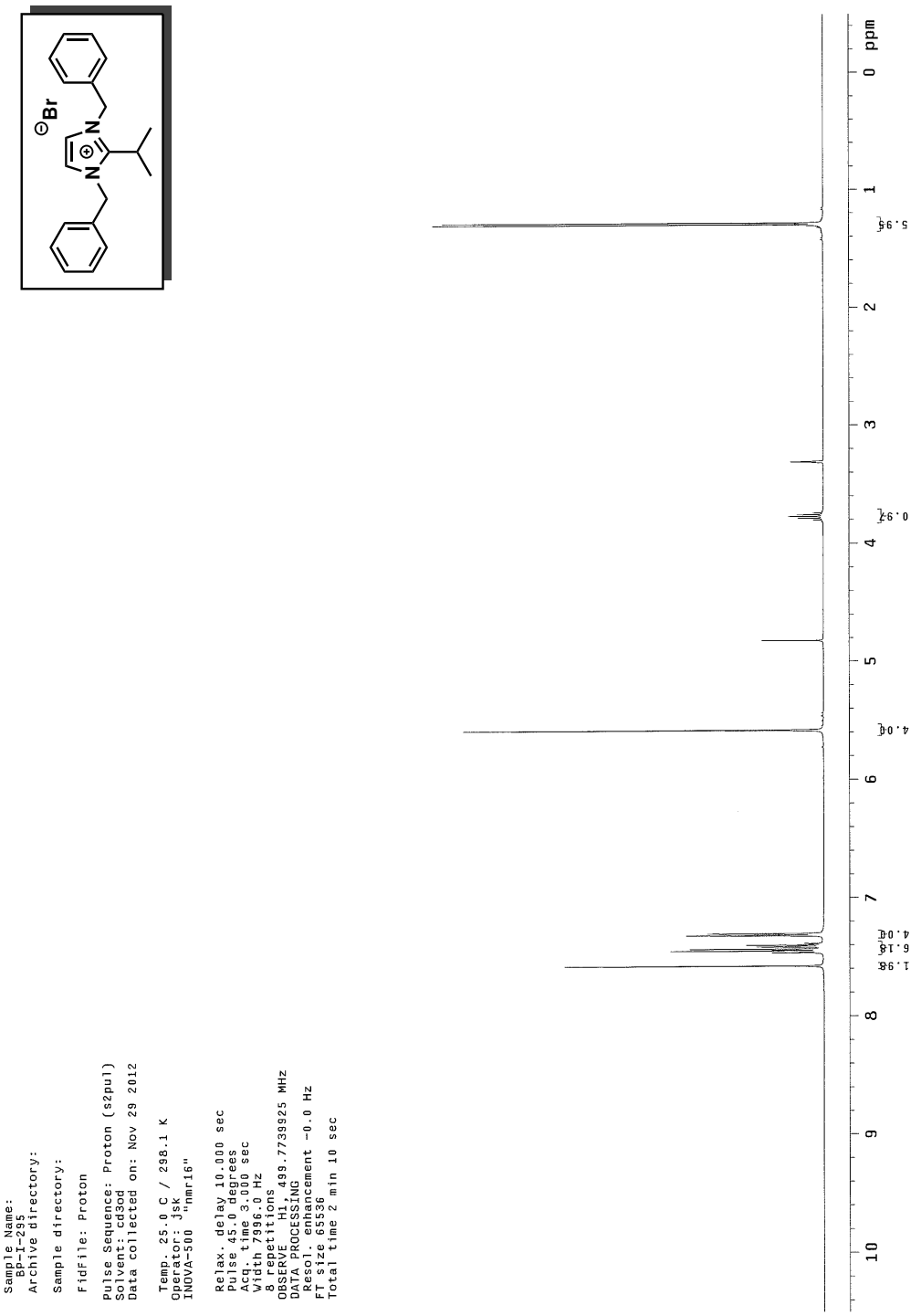


Figure 4.37: ^{13}C NMR of imidazolium bromide salt (**4.43**)

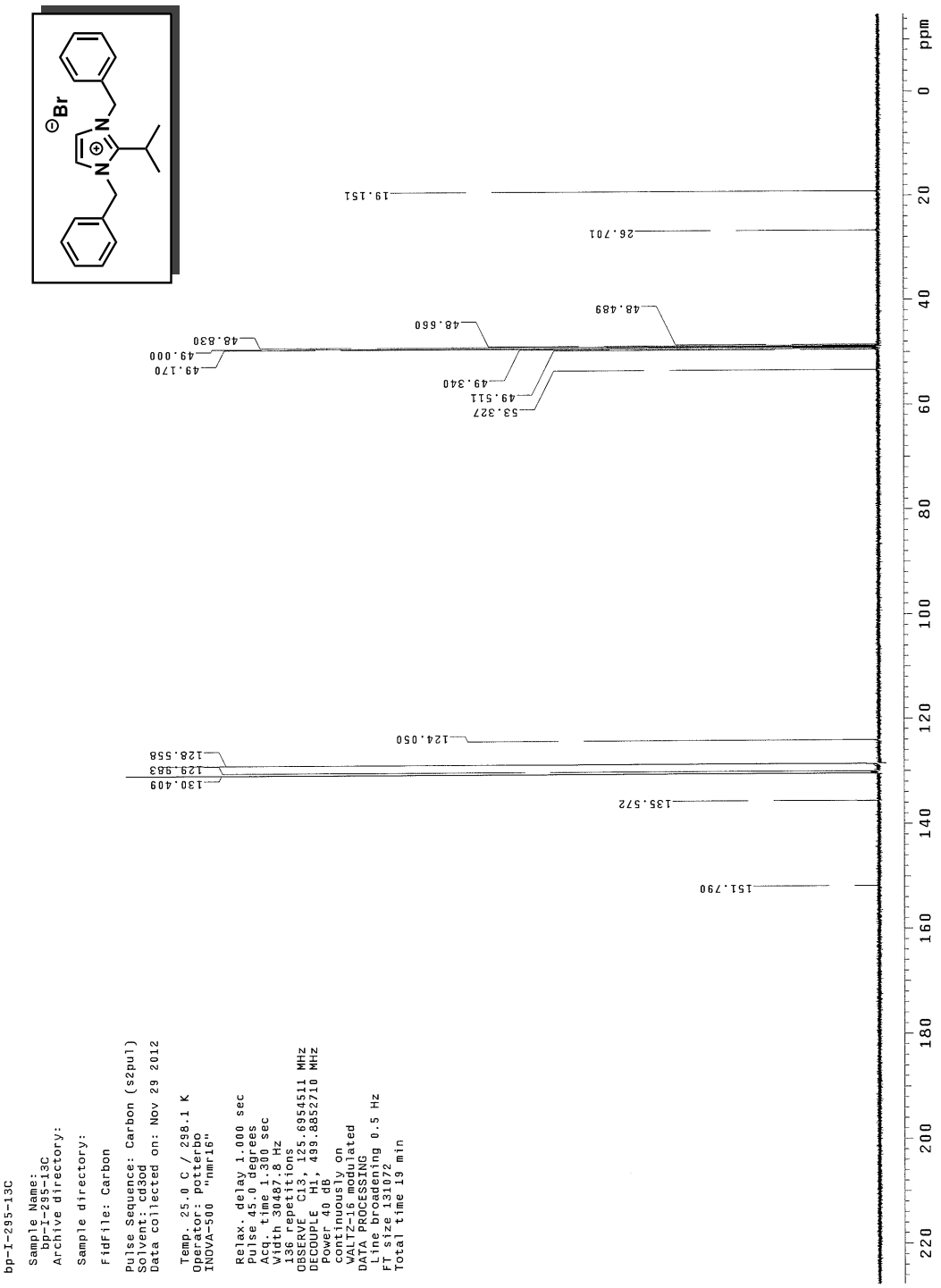


Figure 4.38: ^{1}H NMR of 2,4,5-substituted imidazole (**4.45**)

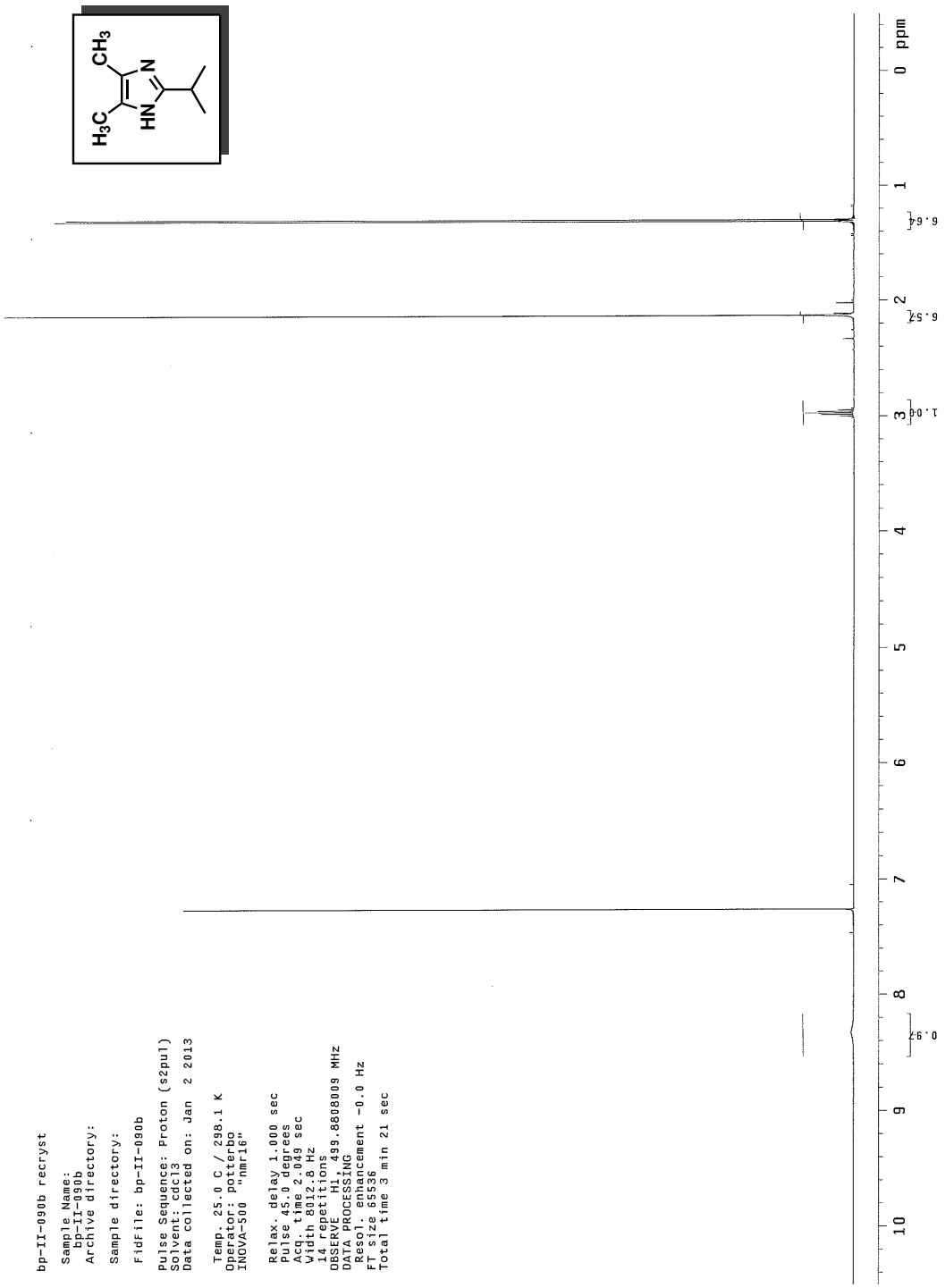


Figure 4.39: ^{13}C NMR of 2,4,5-substituted imidazole (**4.45**)

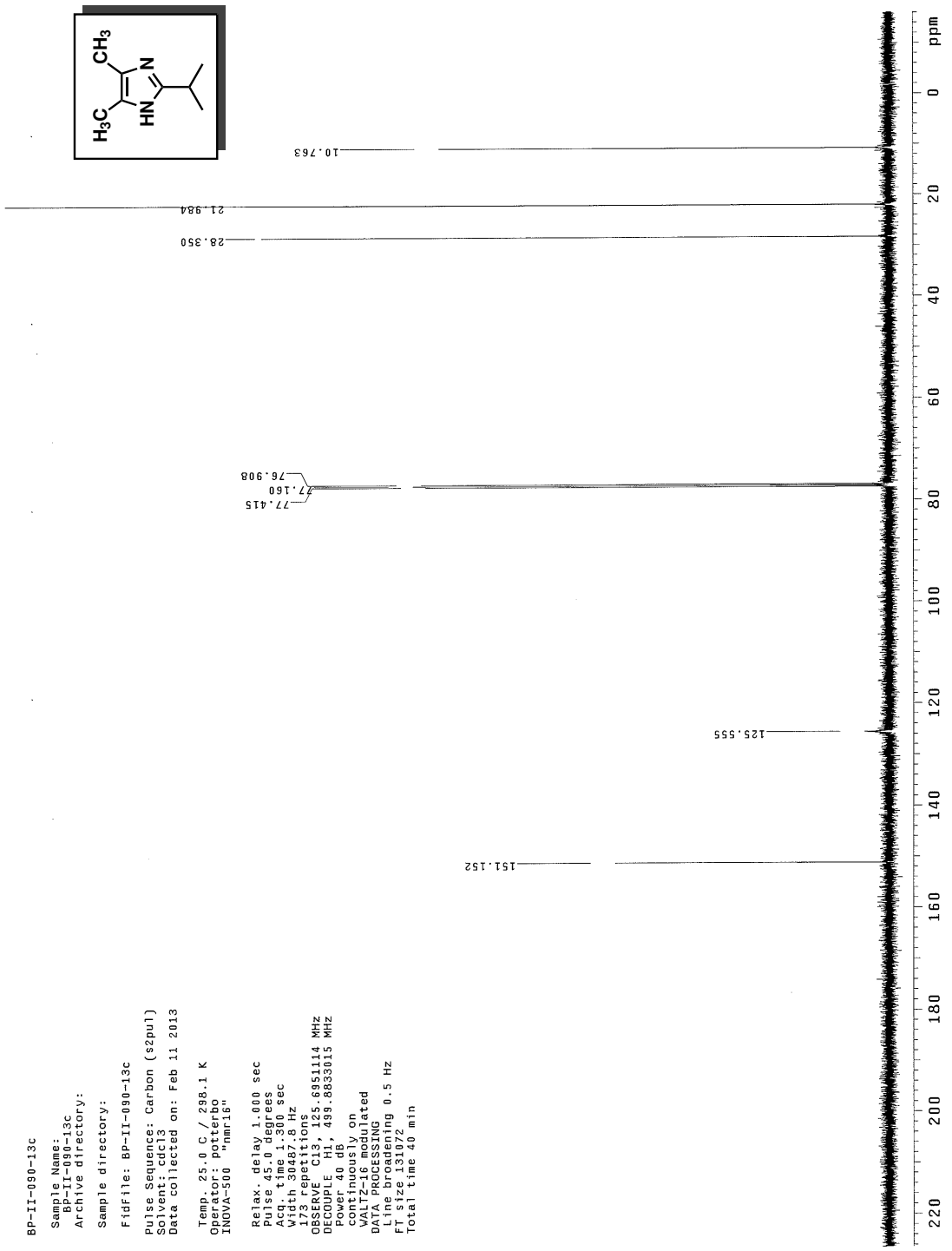


Figure 4.40: ^{1}H NMR of imidazolium chloride salt (**4.44**)

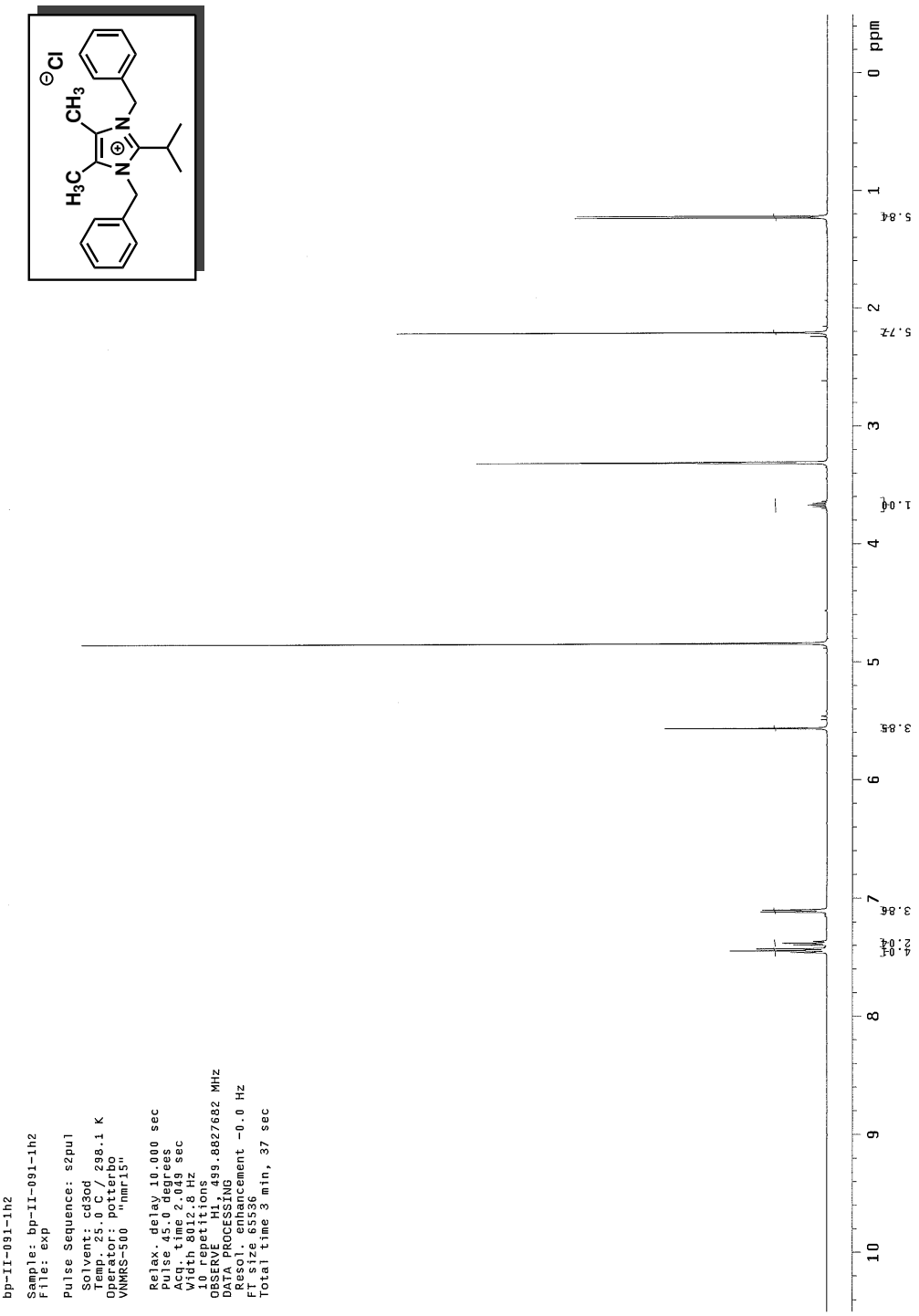
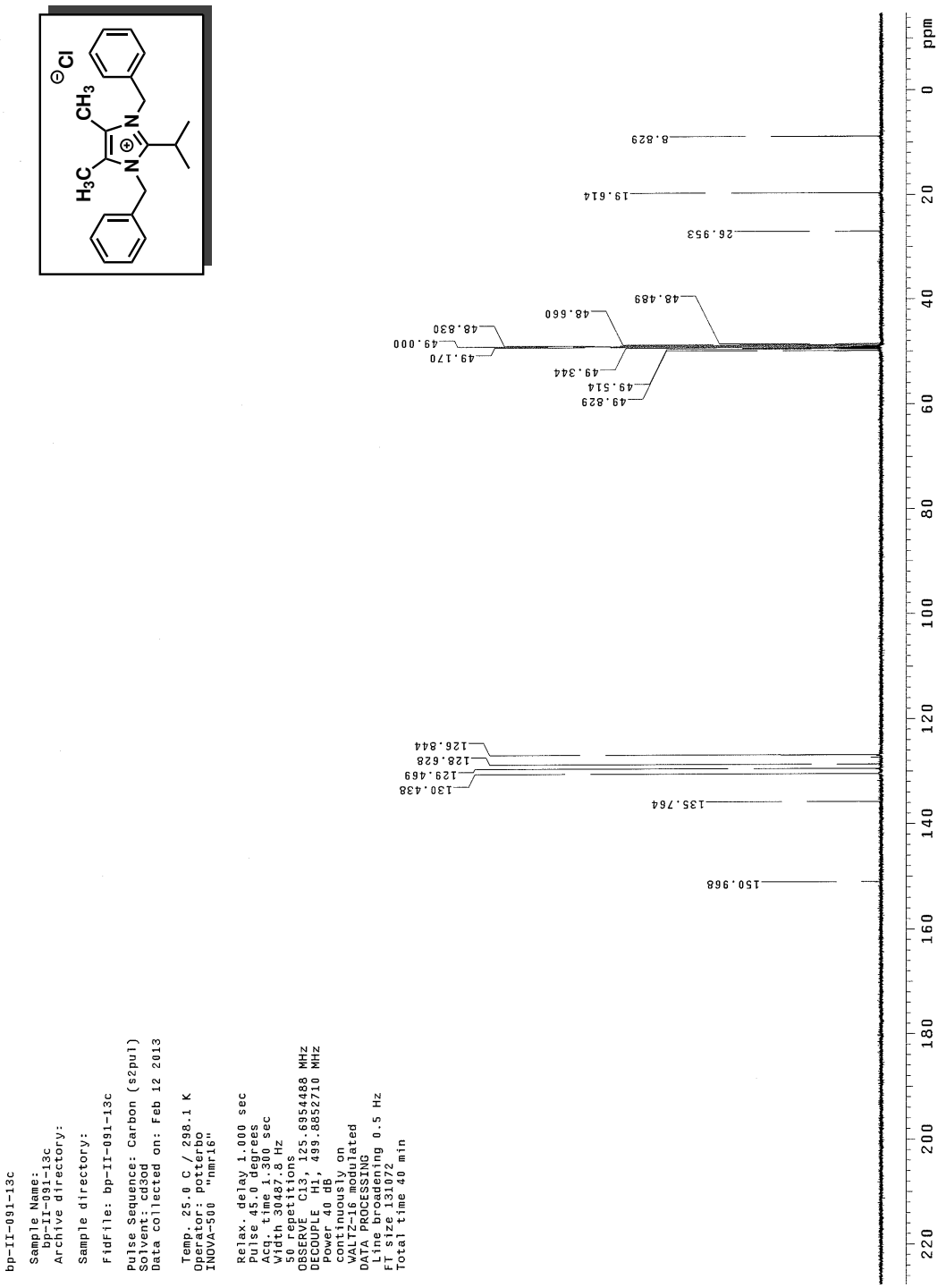


Figure 4.41: ^{13}C NMR of imidazolium chloride salt (**4.44**)



Appendix

A

Appendix A: X-Ray Crystallographic Data

A.1 General Procedure for X-Ray Data Collection

Selected single crystals suitable for X-ray crystallographic analysis were used for structural determination. The X-ray intensity data were measured at 100(2) K (Oxford Cryostream 700) on a Bruker Kappa APEX Duo diffractometer system equipped with a sealed Mo-target X-ray tube ($\lambda = 0.71073$ Å) and a high brightness IμS copper source ($\lambda = 1.54178$ Å). The crystals were mounted on a goniometer head with paratone oil. The detector was placed at a distance of 6.000 cm from the crystal. For each experiment, data collection strategy was determined by APEX software package and all frames were collected with a scan width of 0.5° in ω and ψ with an exposure time of 10 or 20 s/frame.

The frames were integrated with the Bruker SAINT Software package using a narrow frame integration algorithm to a maximum 2θ angle of 56.54° (0.75 Å resolution) for Mo data and 136.50° (0.83 Å resolution) for Cu data. The final cell constants are based upon the refinement of the XYZ-centroids of several thousand reflections above 20 σ(I). Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the empirical method (SADABS). The structures were solved and refined by full-matrix least squares procedures on $|F^2|$ using the Bruker SHELXTL (version 6.12) software package. All hydrogen atoms were included in idealized positions for structure factor calculations except for those forming hydrogen bonds or on a chiral center. Anisotropic displacement parameters were assigned to all non-hydrogen atoms, except those disordered.

A.2 X-Ray Data Tables

A.2.1 *Structural Data for Ketone* **2.93**

Suitable crystals for X-ray analysis were grown by slow evaporation of a supersaturated hexanes solution of racemic material.

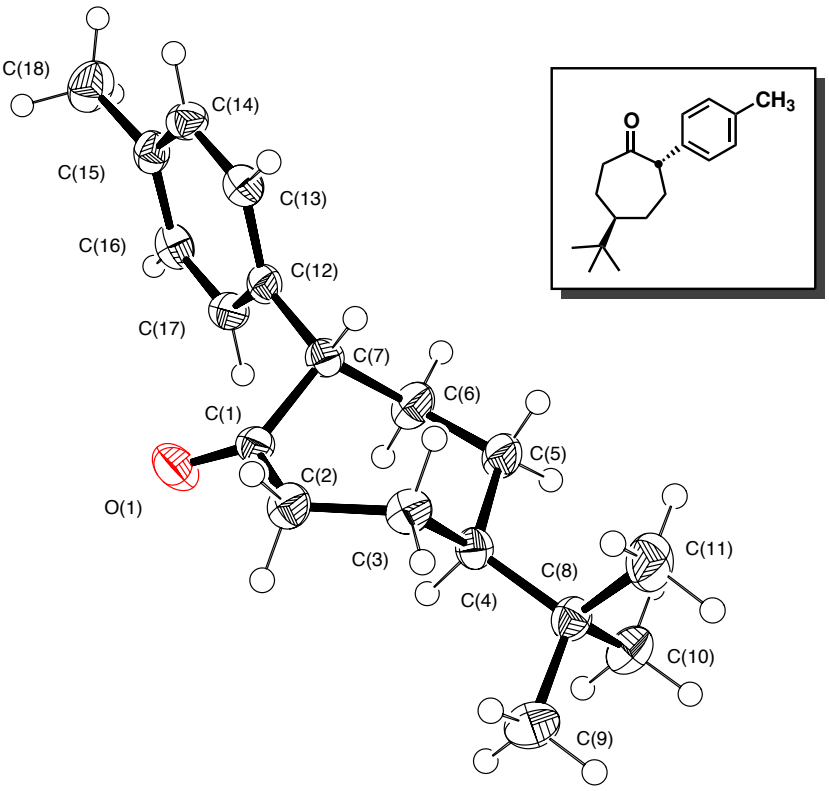


Figure A1: ORTEP drawing of ketone (±)-**2.93** shown at 50% probability

Table A1: Crystal data and structure refinement for (±)-**2.93**

Empirical formula	$C_{18}H_{26}O$
Formula weight	258.39
Temperature	143(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 19.6684(17) Åα = 90°. b = 6.0152(5) Åβ = 90°. c = 26.140(2) Åγ = 90°.
Volume	3092.6(5) Å^3
Z	8
Density (calculated)	1.110 Mg/m^3
Absorption coefficient	0.066 mm^{-1}
F(000)	1136
Crystal size	0.25 x 0.12 x 0.09 mm^3
Theta range for data collection	1.56 to 28.00°.
Index ranges	−23<=h<=25, −7<=k<=7, −34<=l<=33
Reflections collected	46273
Independent reflections	3712 [R(int) = 0.0335]
Completeness to theta = 28.00°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9941 and 0.9837
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3712 / 0 / 173
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0525, wR2 = 0.1434
R indices (all data)	R1 = 0.0694, wR2 = 0.1573
Extinction coefficient	na
Largest diff. peak and hole	0.356 and −0.227 e.Å^{-3}

Table A2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (±)-**2.93**

	x	y	z	U(eq)
O(1)	424(1)	12639(2)	2146(1)	42(1)
C(1)	541(1)	10709(3)	2059(1)	26(1)
C(2)	92(1)	9443(3)	1692(1)	32(1)
C(3)	400(1)	7468(3)	1416(1)	31(1)
C(4)	1068(1)	7957(3)	1134(1)	26(1)
C(5)	1672(1)	7656(3)	1495(1)	36(1)
C(6)	1729(1)	9334(3)	1929(1)	36(1)
C(7)	1130(1)	9475(3)	2312(1)	26(1)
C(8)	1135(1)	6647(3)	624(1)	30(1)
C(9)	569(1)	7416(3)	253(1)	42(1)
C(10)	1812(1)	7186(3)	357(1)	40(1)
C(11)	1083(1)	4156(3)	705(1)	48(1)
C(12)	1341(1)	10598(3)	2806(1)	26(1)
C(13)	1196(1)	9596(3)	3270(1)	28(1)
C(14)	1363(1)	10621(3)	3727(1)	30(1)
C(15)	1676(1)	12680(3)	3739(1)	30(1)
C(16)	1838(1)	13671(3)	3274(1)	31(1)
C(17)	1669(1)	12644(3)	2814(1)	30(1)
C(18)	1832(1)	13845(4)	4236(1)	46(1)

Table A3: Bond lengths (Å) and angles (°) for (±)-**2.93**

O(1)-C(1)	1.2054(19)
C(1)-C(2)	1.510(2)
C(1)-C(7)	1.528(2)
C(2)-C(3)	1.516(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.536(2)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.528(2)
C(4)-C(8)	1.555(2)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.523(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.547(2)
...	

Table A3 continued...

C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(12)	1.514(2)
C(7)-H(7A)	1.0000
C(8)-C(11)	1.517(2)
C(8)-C(10)	1.537(2)
C(8)-C(9)	1.545(2)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-C(13)	1.386(2)
C(12)-C(17)	1.390(2)
C(13)-C(14)	1.384(2)
C(13)-H(13A)	0.9500
C(14)-C(15)	1.383(2)
C(14)-H(14A)	0.9500
C(15)-C(16)	1.391(2)
C(15)-C(18)	1.508(2)
C(16)-C(17)	1.391(2)
C(16)-H(16A)	0.9500
C(17)-H(17A)	0.9500
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
O(1)-C(1)-C(2)	119.60(14)
O(1)-C(1)-C(7)	122.09(14)
C(2)-C(1)-C(7)	118.30(13)
C(1)-C(2)-C(3)	117.65(13)
C(1)-C(2)-H(2A)	107.9
C(3)-C(2)-H(2A)	107.9
C(1)-C(2)-H(2B)	107.9
C(3)-C(2)-H(2B)	107.9
H(2A)-C(2)-H(2B)	107.2
C(2)-C(3)-C(4)	114.83(13)
C(2)-C(3)-H(3A)	108.6
C(4)-C(3)-H(3A)	108.6
C(2)-C(3)-H(3B)	108.6
C(4)-C(3)-H(3B)	108.6
H(3A)-C(3)-H(3B)	107.5
C(5)-C(4)-C(3)	110.28(13)
...	

Table A3 continued...

C(5)-C(4)-C(8)	113.84(12)
C(3)-C(4)-C(8)	112.74(12)
C(5)-C(4)-H(4A)	106.5
C(3)-C(4)-H(4A)	106.5
C(8)-C(4)-H(4A)	106.5
C(6)-C(5)-C(4)	115.99(13)
C(6)-C(5)-H(5A)	108.3
C(4)-C(5)-H(5A)	108.3
C(6)-C(5)-H(5B)	108.3
C(4)-C(5)-H(5B)	108.3
H(5A)-C(5)-H(5B)	107.4
C(5)-C(6)-C(7)	117.59(14)
C(5)-C(6)-H(6A)	107.9
C(7)-C(6)-H(6A)	107.9
C(5)-C(6)-H(6B)	107.9
C(7)-C(6)-H(6B)	107.9
H(6A)-C(6)-H(6B)	107.2
C(12)-C(7)-C(1)	111.09(12)
C(12)-C(7)-C(6)	111.56(12)
C(1)-C(7)-C(6)	108.90(12)
C(12)-C(7)-H(7A)	108.4
C(1)-C(7)-H(7A)	108.4
C(6)-C(7)-H(7A)	108.4
C(11)-C(8)-C(10)	109.29(15)
C(11)-C(8)-C(9)	109.61(15)
C(10)-C(8)-C(9)	106.04(14)
C(11)-C(8)-C(4)	111.97(14)
C(10)-C(8)-C(4)	110.76(13)
C(9)-C(8)-C(4)	108.99(13)
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(8)-C(10)-H(10A)	109.5
C(8)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(8)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(8)-C(11)-H(11A)	109.5
C(8)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(8)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(13)-C(12)-C(17)	117.80(14)
C(13)-C(12)-C(7)	119.78(14)
C(17)-C(12)-C(7)	122.41(14)
C(14)-C(13)-C(12)	120.94(15)
C(14)-C(13)-H(13A)	119.5
C(12)-C(13)-H(13A)	119.5
C(15)-C(14)-C(13)	121.56(15)
C(15)-C(14)-H(14A)	119.2
C(13)-C(14)-H(14A)	119.2
C(14)-C(15)-C(16)	117.79(14)
C(14)-C(15)-C(18)	121.72(16)
C(16)-C(15)-C(18)	120.49(16)
C(17)-C(16)-C(15)	120.68(15)
C(17)-C(16)-H(16A)	119.7
C(15)-C(16)-H(16A)	119.7
C(12)-C(17)-C(16)	121.19(14)
C(12)-C(17)-H(17A)	119.4
C(16)-C(17)-H(17A)	119.4
C(15)-C(18)-H(18A)	109.5
C(15)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(15)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

Table A4: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for (±)-**2.93**

	x	y	z	U(eq)
H(2A)	−74	10502	1430	38
H(2B)	−310	8911	1884	38
H(3A)	65	6902	1165	37
H(3B)	483	6272	1668	37
H(4A)	1057	9569	1040	32
H(5A)	1646	6149	1646	44
H(5B)	2095	7728	1290	44
H(6A)	1792	10825	1776	44
H(6B)	2146	8989	2126	44
H(7A)	977	7929	2393	32
H(9A)	609	6601	−70	63
H(9B)	617	9013	188	63
H(9C)	124	7121	406	63
H(10A)	1843	6347	37	61
H(10B)	2190	6773	582	61

Table A4 continued...

	x	y	z	U(eq)
H(10C)	1833	8782	283	61
H(11A)	1128	3392	376	72
H(11B)	641	3798	857	72
H(11C)	1447	3668	936	72
H(13A)	979	8184	3275	34
H(14A)	1260	9893	4040	36
H(16A)	2066	15063	3270	37
H(17A)	1781	13353	2501	36
H(18A)	1494	15013	4296	69
H(18B)	2286	14511	4217	69
H(18C)	1818	12768	4517	69

Table A5: Torsion angles (°) for (±)-**2.93**

O(1)-C(1)-C(2)-C(3)	153.87(15)
C(7)-C(1)-C(2)-C(3)	−26.5(2)
C(1)-C(2)-C(3)-C(4)	−52.70(19)
C(2)-C(3)-C(4)-C(5)	87.59(17)
C(2)-C(3)-C(4)-C(8)	−143.93(14)
C(3)-C(4)-C(5)-C(6)	−67.65(19)
C(8)-C(4)-C(5)-C(6)	164.48(14)
C(4)-C(5)-C(6)-C(7)	59.7(2)
O(1)-C(1)-C(7)-C(12)	22.7(2)
C(2)-C(1)-C(7)-C(12)	−156.93(13)
O(1)-C(1)-C(7)-C(6)	−100.59(17)
C(2)-C(1)-C(7)-C(6)	79.82(16)
C(5)-C(6)-C(7)-C(12)	161.27(14)
C(5)-C(6)-C(7)-C(1)	−75.76(18)
C(5)-C(4)-C(8)-C(11)	69.06(19)
C(3)-C(4)-C(8)-C(11)	−57.54(19)
C(5)-C(4)-C(8)-C(10)	−53.21(18)
C(3)-C(4)-C(8)-C(10)	−179.80(14)
C(5)-C(4)-C(8)-C(9)	−169.50(14)
C(3)-C(4)-C(8)-C(9)	63.90(17)
C(1)-C(7)-C(12)-C(13)	108.50(16)
C(6)-C(7)-C(12)-C(13)	−129.79(15)
C(1)-C(7)-C(12)-C(17)	−70.50(17)
C(6)-C(7)-C(12)-C(17)	51.21(19)
C(17)-C(12)-C(13)-C(14)	1.2(2)
C(7)-C(12)-C(13)-C(14)	−177.87(14)
C(12)-C(13)-C(14)-C(15)	0.3(2)
C(13)-C(14)-C(15)-C(16)	−1.9(2)
C(13)-C(14)-C(15)-C(18)	177.46(16)
C(14)-C(15)-C(16)-C(17)	2.0(2)
C(18)-C(15)-C(16)-C(17)	−177.37(15)
C(13)-C(12)-C(17)-C(16)	−1.1(2)
C(7)-C(12)-C(17)-C(16)	177.95(14)
C(15)-C(16)-C(17)-C(12)	−0.5(2)

...

Table A5 continued...

Table A6: Anisotropic displacement parameters (Å^{2}x 10^3) for (±)-**2.93**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	48(1)	31(1)	48(1)	−1(1)	−13(1)	10(1)
C(1)	22(1)	31(1)	24(1)	5(1)	3(1)	2(1)
C(2)	20(1)	42(1)	32(1)	−1(1)	2(1)	0(1)
C(3)	26(1)	35(1)	31(1)	0(1)	1(1)	−4(1)
C(4)	24(1)	26(1)	29(1)	−2(1)	1(1)	1(1)
C(5)	26(1)	53(1)	30(1)	−6(1)	−1(1)	12(1)
C(6)	20(1)	58(1)	32(1)	−8(1)	0(1)	3(1)
C(7)	22(1)	30(1)	27(1)	1(1)	−1(1)	2(1)
C(8)	32(1)	27(1)	30(1)	−3(1)	2(1)	−2(1)
C(9)	43(1)	48(1)	34(1)	−2(1)	−7(1)	−5(1)
C(10)	42(1)	48(1)	32(1)	−4(1)	7(1)	−1(1)
C(11)	69(1)	26(1)	50(1)	−5(1)	8(1)	−2(1)
C(12)	19(1)	32(1)	28(1)	−1(1)	0(1)	5(1)
C(13)	23(1)	29(1)	33(1)	1(1)	−1(1)	−1(1)
C(14)	26(1)	38(1)	27(1)	4(1)	1(1)	0(1)
C(15)	23(1)	36(1)	32(1)	−6(1)	−2(1)	3(1)
C(16)	21(1)	29(1)	44(1)	0(1)	0(1)	−2(1)
C(17)	22(1)	37(1)	30(1)	8(1)	4(1)	2(1)
C(18)	47(1)	52(1)	40(1)	−15(1)	−5(1)	−1(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2 \left[h^2 a*^2 U^{11} + ... + 2hka*b*U^{12}\right]$

A.2.2 *Structural Data for Ester* **2.116**

Suitable crystals for X-ray analysis were grown by slow evaporation from a 5% (v/v) solution of Et_2O in hexanes.

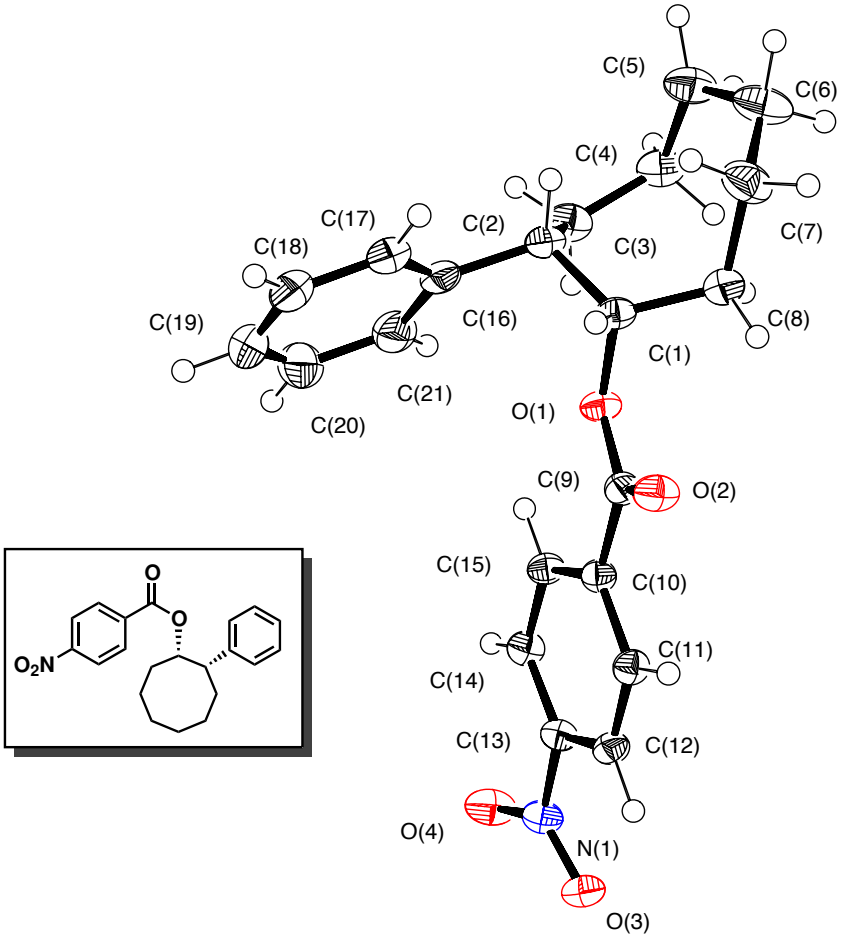


Figure A2: ORTEP drawing of ester **2.116** shown at 50% probability

Table A7: Crystal data and structure refinement for **2.116**

Empirical formula	$C_{21}H_{23}NO_4$
Formula weight	353.40
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P 2(1)/n
Unit cell dimensions	a = 8.4054(10) Åα = 90°.
	b = 6.9528(8) Åβ = 92.883(4)°.
	c = 31.194(4) Åγ = 90°.
Volume	1820.7(4) Å^3
Z	4
Density (calculated)	1.289 Mg/m^3
Absorption coefficient	0.723 mm^{-1}
F(000)	752
Crystal size	0.18 x 0.12 x 0.08 mm^3
Theta range for data collection	5.39 to 67.98°.
Index ranges	−10<=h<=9, −8<=k<=5, −36<=l<=37
Reflections collected	30952
Independent reflections	3302 [R(int) = 0.0240]
Completeness to theta = 67.98°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9444 and 0.8808
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3302 / 3 / 251
Goodness-of-fit on F^2	1.054
Final R indices [I>2sigma(I)]	R1 = 0.0426, wR2 = 0.1054
R indices (all data)	R1 = 0.0432, wR2 = 0.1057
Extinction coefficient	na
Largest diff. peak and hole	0.493 and −0.319 e.Å^{-3}

Table A8: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.116**

	x	y	z	U(eq)
O(1)	8285(1)	8167(1)	1043(1)	24(1)
O(2)	9580(1)	10772(2)	811(1)	31(1)
O(3)	13969(1)	4594(2)	-404(1)	31(1)
O(4)	13354(1)	2223(2)	4(1)	38(1)
N(1)	13281(1)	3919(2)	-100(1)	27(1)
C(1)	7295(2)	9388(2)	1304(1)	25(1)
C(2)	6756(2)	8094(2)	1667(1)	27(1)
C(3)	5660(2)	6435(2)	1517(1)	34(1)
C(4)	3967(2)	6922(3)	1326(1)	34(1)
C(5)	3099(2)	8562(3)	1532(1)	42(1)
C(4X)	3953(10)	6828(14)	1704(3)	34(1)
C(5X)	3099(2)	8562(3)	1532(1)	42(1)
C(6)	3226(2)	10527(3)	1336(1)	45(1)
C(7)	4797(2)	11497(3)	1275(1)	42(1)
C(8)	6013(2)	10364(3)	1022(1)	37(1)
C(9)	9387(2)	9051(2)	821(1)	23(1)
C(10)	10383(2)	7651(2)	586(1)	22(1)
C(11)	11411(2)	8393(2)	289(1)	24(1)
C(12)	12376(2)	7182(2)	67(1)	24(1)
C(13)	12302(2)	5228(2)	149(1)	24(1)
C(14)	11322(2)	4448(2)	448(1)	25(1)
C(15)	10348(2)	5680(2)	665(1)	24(1)
C(16)	8218(2)	7408(2)	1934(1)	32(1)
C(17)	8895(2)	8599(3)	2251(1)	38(1)
C(18)	10270(2)	8049(3)	2489(1)	48(1)
C(19)	10974(2)	6306(3)	2417(1)	52(1)
C(20)	10307(2)	5093(3)	2108(1)	52(1)
C(21)	8938(2)	5637(3)	1866(1)	41(1)

Table A9: Bond lengths (Å) and angles (°) for **2.116**

O(1)-C(9)	1.3344(17)
O(1)-C(1)	1.4654(16)
O(2)-C(9)	1.2085(18)
O(3)-N(1)	1.2291(16)
O(4)-N(1)	1.2246(17)
N(1)-C(13)	1.4742(18)
C(1)-C(8)	1.517(2)
C(1)-C(2)	1.531(2)
C(1)-H(1)	0.971(18)
...	

Table A9 continued...

C(2)-C(16)	1.526(2)
C(2)-C(3)	1.534(2)
C(2)-H(2)	0.984(18)
C(3)-C(4)	1.552(3)
C(3)-H(3A)	0.99
C(3)-H(3B)	0.99
C(4)-C(5)	1.513(3)
C(4)-H(4A)	0.99
C(4)-H(4B)	0.99
C(5)-C(6)	1.503(3)
C(5)-H(5A)	0.99
C(5)-H(5B)	0.99
C(6)-C(7)	1.503(2)
C(6)-H(6A)	0.99
C(6)-H(6B)	0.99
C(7)-C(8)	1.539(2)
C(7)-H(7A)	0.99
C(7)-H(7B)	0.99
C(8)-H(8A)	0.939(15)
C(8)-H(8B)	0.995(15)
C(9)-C(10)	1.4978(19)
C(10)-C(15)	1.393(2)
C(10)-C(11)	1.3966(19)
C(11)-C(12)	1.380(2)
C(11)-H(11)	0.95
C(12)-C(13)	1.385(2)
C(12)-H(12)	0.95
C(13)-C(14)	1.385(2)
C(14)-C(15)	1.386(2)
C(14)-H(14)	0.95
C(15)-H(15)	0.95
C(16)-C(17)	1.390(2)
C(16)-C(21)	1.393(2)
C(17)-C(18)	1.396(3)
C(17)-H(17)	0.95
C(18)-C(19)	1.373(3)
C(18)-H(18)	0.95
C(19)-C(20)	1.378(3)
C(19)-H(19)	0.95
C(20)-C(21)	1.396(3)
C(20)-H(20)	0.95
C(21)-H(21)	0.95
C(9)-O(1)-C(1)	116.79(11)
O(4)-N(1)-O(3)	123.65(12)
O(4)-N(1)-C(13)	118.43(12)
O(3)-N(1)-C(13)	117.93(12)
...	

Table A9 continued...

O(1)-C(1)-C(8)	110.06(12)
O(1)-C(1)-C(2)	105.54(11)
C(8)-C(1)-C(2)	117.60(13)
O(1)-C(1)-H(1)	107.5(10)
C(8)-C(1)-H(1)	106.9(10)
C(2)-C(1)-H(1)	108.9(10)
C(16)-C(2)-C(1)	109.05(12)
C(16)-C(2)-C(3)	112.69(13)
C(1)-C(2)-C(3)	114.39(13)
C(16)-C(2)-H(2)	106.1(10)
C(1)-C(2)-H(2)	106.0(10)
C(3)-C(2)-H(2)	108.1(10)
C(2)-C(3)-C(4)	118.51(14)
C(2)-C(3)-H(3A)	107.7
C(4)-C(3)-H(3A)	107.7
C(2)-C(3)-H(3B)	107.7
C(4)-C(3)-H(3B)	107.7
H(3A)-C(3)-H(3B)	107.1
C(5)-C(4)-C(3)	117.02(15)
C(5)-C(4)-H(4A)	108
C(3)-C(4)-H(4A)	108
C(5)-C(4)-H(4B)	108
C(3)-C(4)-H(4B)	108
H(4A)-C(4)-H(4B)	107.3
C(6)-C(5)-C(4)	117.78(15)
C(6)-C(5)-H(5A)	107.9
C(4)-C(5)-H(5A)	107.9
C(6)-C(5)-H(5B)	107.9
C(4)-C(5)-H(5B)	107.9
H(5A)-C(5)-H(5B)	107.2
C(7)-C(6)-C(5)	122.72(17)
C(7)-C(6)-H(6A)	106.7
C(5)-C(6)-H(6A)	106.7
C(7)-C(6)-H(6B)	106.7
C(5)-C(6)-H(6B)	106.7
H(6A)-C(6)-H(6B)	106.6
C(6)-C(7)-C(8)	116.44(16)
C(6)-C(7)-H(7A)	108.2
C(8)-C(7)-H(7A)	108.2
C(6)-C(7)-H(7B)	108.2
C(8)-C(7)-H(7B)	108.2
H(7A)-C(7)-H(7B)	107.3
C(1)-C(8)-C(7)	113.75(14)
C(1)-C(8)-H(8A)	106.7(13)
C(7)-C(8)-H(8A)	110.7(12)
C(1)-C(8)-H(8B)	105.2(12)
C(7)-C(8)-H(8B)	108.5(12)
H(8A)-C(8)-H(8B)	111.9(17)
O(2)-C(9)-O(1)	124.55(13)
O(2)-C(9)-C(10)	123.48(13)
O(1)-C(9)-C(10)	111.96(12)
C(15)-C(10)-C(11)	119.99(13)
C(15)-C(10)-C(9)	122.38(13)
C(11)-C(10)-C(9)	117.59(13)
C(12)-C(11)-C(10)	120.46(13)
C(12)-C(11)-H(11)	119.8
C(10)-C(11)-H(11)	119.8
C(11)-C(12)-C(13)	118.18(13)
C(11)-C(12)-H(12)	120.9
C(13)-C(12)-H(12)	120.9
C(14)-C(13)-C(12)	122.86(13)
C(14)-C(13)-N(1)	118.67(13)
C(12)-C(13)-N(1)	118.45(13)
C(13)-C(14)-C(15)	118.26(13)
C(13)-C(14)-H(14)	120.9
C(15)-C(14)-H(14)	120.9
C(14)-C(15)-C(10)	120.22(13)
C(14)-C(15)-H(15)	119.9
C(10)-C(15)-H(15)	119.9
C(17)-C(16)-C(21)	117.95(16)
C(17)-C(16)-C(2)	119.48(15)
C(21)-C(16)-C(2)	122.55(15)
C(16)-C(17)-C(18)	120.98(18)
C(16)-C(17)-H(17)	119.5
C(18)-C(17)-H(17)	119.5
C(19)-C(18)-C(17)	120.39(19)
C(19)-C(18)-H(18)	119.8
C(17)-C(18)-H(18)	119.8
C(18)-C(19)-C(20)	119.50(18)
C(18)-C(19)-H(19)	120.3
C(20)-C(19)-H(19)	120.3
C(19)-C(20)-C(21)	120.46(19)
C(19)-C(20)-H(20)	119.8
C(21)-C(20)-H(20)	119.8
C(16)-C(21)-C(20)	120.71(19)
C(16)-C(21)-H(21)	119.6
C(20)-C(21)-H(21)	119.6

Table A10: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **2.116**

	x	y	z	U(eq)
H(1)	7970(20)	10400(30)	1427(5)	30
H(2)	6160(20)	8930(30)	1856(6)	32
H(3A)	5538	5568	1765	41
H(3B)	6215	5695	1298	41
H(4A)	4051	7227	1018	41
H(4B)	3301	5753	1343	41
H(5A)	1956	8219	1531	50
H(5B)	3494	8650	1836	50
H(4C)	3271	5689	1644	41
H(4D)	4092	6959	2020	41
H(5C)	2438	8867	1777	50
H(5D)	2346	7949	1319	50
H(6A)	2667	10462	1049	54
H(6B)	2600	11408	1511	54
H(7A)	5291	11798	1562	50
H(7B)	4586	12735	1126	50
H(8A)	5500(20)	9390(30)	857(6)	45
H(8B)	6590(20)	11280(30)	841(6)	45
H(11)	11445	9741	240	29
H(12)	13072	7676	-137	29
H(14)	11317	3104	502	30
H(15)	9654	5179	869	29
H(17)	8415	9805	2306	45
H(18)	10722	8887	2703	58
H(19)	11914	5938	2578	62
H(20)	10782	3877	2059	62
H(21)	8493	4791	1653	49

Table A11: Torsion angles (°) for **2.116**

C(9)-O(1)-C(1)-C(8)	78.24(16)
C(9)-O(1)-C(1)-C(2)	−153.92(12)
O(1)-C(1)-C(2)-C(16)	61.89(15)
C(8)-C(1)-C(2)-C(16)	−174.94(14)
O(1)-C(1)-C(2)-C(3)	−65.31(15)
C(8)-C(1)-C(2)-C(3)	57.86(18)
C(16)-C(2)-C(3)-C(4)	167.37(14)
C(1)-C(2)-C(3)-C(4)	−67.32(18)
C(2)-C(3)-C(4)-C(5)	−38.0(2)
C(3)-C(4)-C(5)-C(6)	94.4(2)
C(4)-C(5)-C(6)-C(7)	−56.4(3)
C(5)-C(6)-C(7)-C(8)	54.8(3)
...	

Table A11 continued...

O(1)-C(1)-C(8)-C(7)	173.43(13)
C(2)-C(1)-C(8)-C(7)	52.6(2)
C(6)-C(7)-C(8)-C(1)	−100.5(2)
C(1)-O(1)-C(9)-O(2)	−2.5(2)
C(1)-O(1)-C(9)-C(10)	176.73(11)
O(2)-C(9)-C(10)-C(15)	167.47(14)
O(1)-C(9)-C(10)-C(15)	−11.80(19)
O(2)-C(9)-C(10)-C(11)	−10.5(2)
O(1)-C(9)-C(10)-C(11)	170.19(12)
C(15)-C(10)-C(11)-C(12)	1.1(2)
C(9)-C(10)-C(11)-C(12)	179.17(13)
C(10)-C(11)-C(12)-C(13)	−0.5(2)
C(11)-C(12)-C(13)-C(14)	−0.9(2)
C(11)-C(12)-C(13)-N(1)	177.51(12)
O(4)-N(1)-C(13)-C(14)	−9.6(2)
O(3)-N(1)-C(13)-C(14)	169.86(13)
O(4)-N(1)-C(13)-C(12)	171.97(14)
O(3)-N(1)-C(13)-C(12)	−8.57(19)
C(12)-C(13)-C(14)-C(15)	1.5(2)
N(1)-C(13)-C(14)-C(15)	−176.84(12)
C(13)-C(14)-C(15)-C(10)	−0.8(2)
C(11)-C(10)-C(15)-C(14)	−0.4(2)
C(9)-C(10)-C(15)-C(14)	−178.39(12)
C(1)-C(2)-C(16)-C(17)	82.23(16)
C(3)-C(2)-C(16)-C(17)	−149.60(14)
C(1)-C(2)-C(16)-C(21)	−96.12(17)
C(3)-C(2)-C(16)-C(21)	32.0(2)
C(21)-C(16)-C(17)-C(18)	1.0(2)
C(2)-C(16)-C(17)-C(18)	−177.39(15)
C(16)-C(17)-C(18)-C(19)	−0.6(3)
C(17)-C(18)-C(19)-C(20)	−0.4(3)
C(18)-C(19)-C(20)-C(21)	0.8(3)
C(17)-C(16)-C(21)-C(20)	−0.6(2)
C(2)-C(16)-C(21)-C(20)	177.78(15)
C(19)-C(20)-C(21)-C(16)	−0.3(3)

Table A12: Anisotropic displacement parameters (Å^{2}x 10^3) for **2.116**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	26(1)	21(1)	27(1)	−2(1)	9(1)	−3(1)
O(2)	33(1)	20(1)	40(1)	2(1)	13(1)	0(1)
O(3)	30(1)	34(1)	29(1)	−4(1)	10(1)	−4(1)
O(4)	38(1)	21(1)	55(1)	−3(1)	18(1)	−1(1)
N(1)	24(1)	24(1)	32(1)	−5(1)	5(1)	−4(1)
C(1)	27(1)	22(1)	27(1)	−3(1)	8(1)	−1(1)
C(2)	28(1)	25(1)	27(1)	−1(1)	9(1)	0(1)
C(3)	34(1)	25(1)	45(1)	1(1)	11(1)	−4(1)
C(4)	34(1)	29(1)	40(1)	−6(1)	10(1)	−9(1)
C(5)	32(1)	43(1)	51(1)	−2(1)	16(1)	−4(1)
C(4X)	34(1)	29(1)	40(1)	−6(1)	10(1)	−9(1)
C(5X)	32(1)	43(1)	51(1)	−2(1)	16(1)	−4(1)
C(6)	37(1)	35(1)	65(1)	−15(1)	18(1)	0(1)
C(7)	36(1)	32(1)	59(1)	4(1)	12(1)	6(1)
C(8)	34(1)	46(1)	33(1)	8(1)	10(1)	6(1)
C(9)	22(1)	22(1)	24(1)	3(1)	3(1)	−2(1)
C(10)	21(1)	22(1)	24(1)	−1(1)	2(1)	−2(1)
C(11)	26(1)	20(1)	27(1)	2(1)	3(1)	−3(1)
C(12)	24(1)	26(1)	25(1)	2(1)	5(1)	−4(1)
C(13)	21(1)	24(1)	27(1)	−4(1)	4(1)	−2(1)
C(14)	26(1)	19(1)	31(1)	0(1)	3(1)	−4(1)
C(15)	23(1)	24(1)	26(1)	1(1)	5(1)	−4(1)
C(16)	32(1)	37(1)	28(1)	8(1)	12(1)	1(1)
C(17)	36(1)	51(1)	28(1)	0(1)	9(1)	4(1)
C(18)	41(1)	77(2)	27(1)	4(1)	5(1)	3(1)
C(19)	44(1)	75(2)	36(1)	21(1)	6(1)	13(1)
C(20)	50(1)	51(1)	55(1)	22(1)	13(1)	17(1)
C(21)	45(1)	37(1)	40(1)	10(1)	10(1)	6(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2 \left[h^2 a*^2 U^{11} + ... + 2hka*b*U^{12}\right]$

A.2.3 *Structural Data for Bis(oxazoline) Triflate Salt* **2.61**

Suitable crystals for X-ray analysis were grown by layering a $CHCl_3$ solution containing a 1:1 molar mixture of $Sc(OTf)_3$ and **2.56** with hexanes.

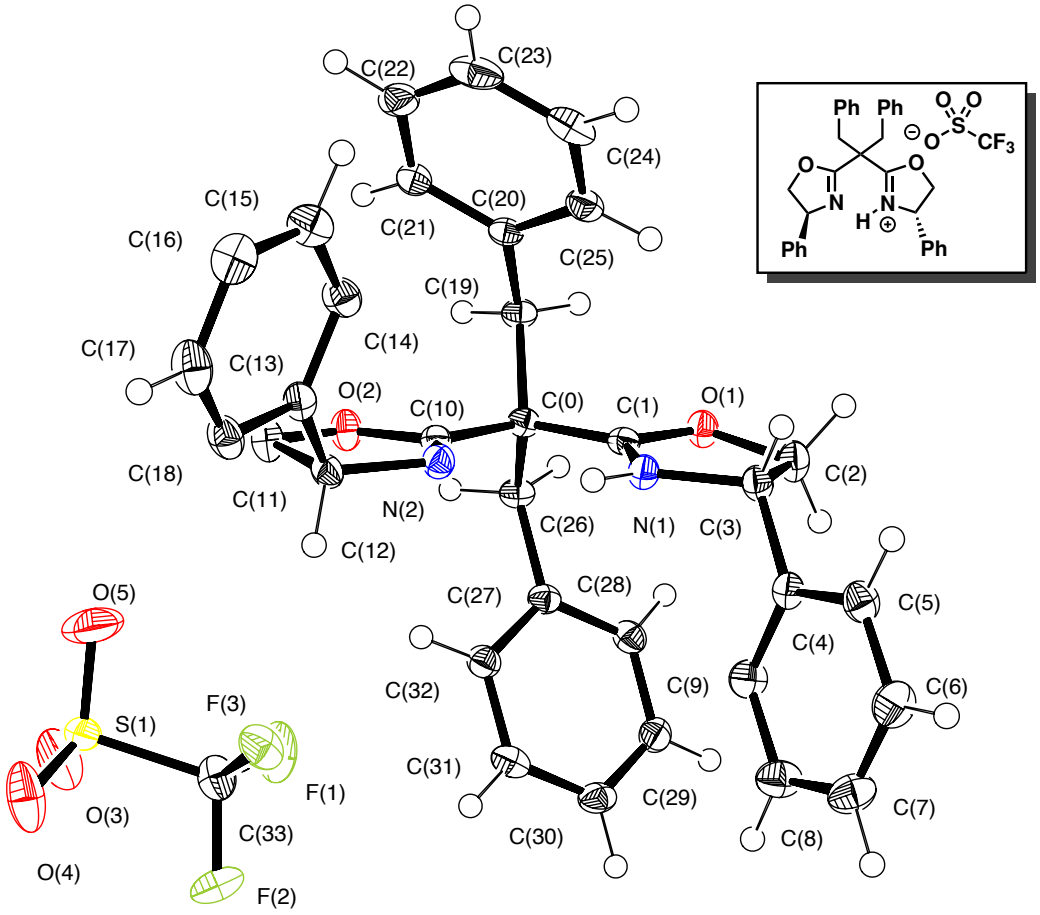


Figure A3: ORTEP drawing of bis(oxazoline) triflate salt **2.61** shown at 50% probability

Table A13: Crystal data and structure refinement for **2.61**

Empirical formula	$C_{35}H_{32}Cl_3F_3N_2O_5S$
Formula weight	756.04
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 1 21/n 1
Unit cell dimensions	a = 12.210(3) Å $\alpha = 90°$.
	b = 15.378(4) Å $\beta = 102.372(3)°$.
	c = 19.087(4) Å $\gamma = 90°$.
Volume	3500.7(14) $Å^3$
Z	4
Density (calculated)	1.434 Mg/m^3
Absorption coefficient	0.382 mm^{-1}
F(000)	1560
Crystal size	0.14 x 0.09 x 0.06 mm^3
Theta range for data collection	2.22 to 28.28°.
Index ranges	−16<=h<=16, −20<=k<=20, −25<=l<=24
Reflections collected	51917
Independent reflections	8620 [R(int) = 0.0382]
Completeness to theta = 28.28°	99.4%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9774 and 0.9484
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8620 / 142 / 566
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0468, wR2 = 0.1153
R indices (all data)	R1 = 0.0549, wR2 = 0.1210
Extinction coefficient	na
Largest diff. peak and hole	0.794 and −0.805 e.$Å^{-3}$

Table A14: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **2.61**

	x	y	z	U(eq)
O(1)	6813(1)	1776(1)	3263(1)	21(1)
O(2)	3126(1)	1848(1)	1796(1)	23(1)
N(1)	6051(1)	3053(1)	2978(1)	18(1)
N(2)	4048(1)	3115(1)	2089(1)	20(1)
C(0)	4980(1)	1708(1)	2504(1)	17(1)
C(1)	5954(1)	2220(1)	2910(1)	17(1)
C(2)	7617(1)	2395(1)	3681(1)	24(1)
C(3)	7149(1)	3308(1)	3433(1)	20(1)
C(4)	7029(1)	3905(1)	4039(1)	19(1)
C(5)	7689(1)	4648(1)	4175(1)	24(1)
C(6)	7607(2)	5186(1)	4744(1)	31(1)
C(7)	6866(2)	4986(1)	5179(1)	32(1)
C(8)	6202(2)	4248(1)	5043(1)	29(1)
C(9)	6283(1)	3708(1)	4474(1)	24(1)
C(10)	4045(1)	2291(1)	2128(1)	17(1)
C(11)	2360(1)	2500(1)	1412(1)	25(1)
C(12)	2934(1)	3379(1)	1655(1)	21(1)
C(13)	3026(1)	3960(1)	1034(1)	20(1)
C(14)	3836(1)	3804(1)	633(1)	24(1)
C(15)	3868(2)	4302(1)	33(1)	28(1)
C(16)	3100(2)	4969(1)	−172(1)	30(1)
C(17)	2301(2)	5136(1)	232(1)	30(1)
C(18)	2262(1)	4634(1)	828(1)	25(1)
C(19)	5369(1)	1118(1)	1936(1)	19(1)
C(20)	5589(1)	1598(1)	1291(1)	18(1)
C(21)	4864(1)	1496(1)	625(1)	24(1)
C(22)	5062(2)	1934(1)	28(1)	30(1)
C(23)	5968(2)	2488(1)	89(1)	33(1)
C(24)	6694(2)	2595(1)	748(1)	29(1)
C(25)	6515(1)	2144(1)	1346(1)	23(1)
C(26)	4571(1)	1102(1)	3056(1)	19(1)
C(27)	4430(1)	1555(1)	3733(1)	18(1)
C(28)	5154(1)	1366(1)	4385(1)	22(1)
C(29)	5022(1)	1766(1)	5015(1)	23(1)
C(30)	4180(1)	2376(1)	5000(1)	24(1)
C(31)	3457(1)	2572(1)	4353(1)	24(1)
C(32)	3572(1)	2159(1)	3723(1)	21(1)
S(1)	−598(1)	3515(1)	2218(1)	25(1)
O(3)	−1124(1)	2759(1)	2450(1)	44(1)
O(4)	−1257(1)	4286(1)	2196(1)	45(1)
O(5)	−48(2)	3371(2)	1647(1)	86(1)
C(33)	572(2)	3704(1)	2968(1)	27(1)
F(1)	1166(9)	3014(5)	3224(4)	40(2)
F(2)	164(7)	4027(3)	3533(3)	33(1)
F(3)	1254(11)	4310(10)	2808(11)	31(2)
F(1X)	1260(7)	3000(5)	2982(12)	65(3)
F(2X)	287(9)	3774(15)	3573(4)	77(3)
F(3X)	1219(11)	4379(10)	2888(11)	31(2)
C(34)	5330(2)	5825(1)	2459(1)	34(1)
Cl(1)	6463(1)	5211(1)	2287(1)	41(1)
Cl(2)	4732(1)	5293(1)	3103(1)	60(1)
Cl(3)	4331(1)	5975(1)	1660(1)	60(1)

...

Table A14 continued...

Table A15: Bond lengths (Å) and angles (°) for **2.61**

O(1)-C(1)	1.3102(18)
O(1)-C(2)	1.4736(19)
O(2)-C(10)	1.3493(18)
O(2)-C(11)	1.458(2)
N(1)-C(1)	1.291(2)
N(1)-C(3)	1.486(2)
N(1)-H(1N)	0.866(15)
N(2)-C(10)	1.268(2)
N(2)-C(12)	1.490(2)
C(0)-C(1)	1.497(2)
C(0)-C(10)	1.506(2)
C(0)-C(19)	1.564(2)
C(0)-C(26)	1.567(2)
C(2)-C(3)	1.550(2)
C(2)-H(2A)	0.983(15)
C(2)-H(2B)	0.987(15)
C(3)-C(4)	1.509(2)
C(3)-H(3)	0.981(14)
C(4)-C(5)	1.390(2)
C(4)-C(9)	1.391(2)
C(5)-C(6)	1.387(2)
C(5)-H(5)	0.959(15)
C(6)-C(7)	1.387(3)
C(6)-H(6)	0.952(16)
C(7)-C(8)	1.388(3)
C(7)-H(7)	0.945(15)
C(8)-C(9)	1.387(2)
C(8)-H(8)	0.961(15)
C(9)-H(9)	0.945(15)
C(11)-C(12)	1.548(2)
C(11)-H(11A)	0.978(15)

...

Table A15 continued...

C(11)-H(11B)	0.985(15)
C(12)-C(13)	1.507(2)
C(12)-H(12)	0.982(14)
C(13)-C(18)	1.393(2)
C(13)-C(14)	1.395(2)
C(14)-C(15)	1.386(2)
C(14)-H(14)	0.970(15)
C(15)-C(16)	1.388(3)
C(15)-H(15)	0.960(15)
C(16)-C(17)	1.389(3)
C(16)-H(16)	0.951(15)
C(17)-C(18)	1.386(3)
C(17)-H(17)	0.946(15)
C(18)-H(18)	0.955(15)
C(19)-C(20)	1.509(2)
C(19)-H(19A)	0.970(14)
C(19)-H(19B)	0.971(14)
C(20)-C(25)	1.394(2)
C(20)-C(21)	1.394(2)
C(21)-C(22)	1.389(2)
C(21)-H(21)	0.947(15)
C(22)-C(23)	1.382(3)
C(22)-H(22)	0.953(15)
C(23)-C(24)	1.385(3)
C(23)-H(23)	0.937(16)
C(24)-C(25)	1.391(2)
C(24)-H(24)	0.933(15)
C(25)-H(25)	0.957(15)
C(26)-C(27)	1.510(2)
C(26)-H(26A)	0.973(14)
C(26)-H(26B)	0.981(14)
C(27)-C(28)	1.395(2)
C(27)-C(32)	1.396(2)
C(28)-C(29)	1.391(2)
C(28)-H(28)	0.944(14)
C(29)-C(30)	1.387(2)
C(29)-H(29)	0.955(15)
C(30)-C(31)	1.388(3)
C(30)-H(30)	0.952(15)
C(31)-C(32)	1.394(2)
C(31)-H(31)	0.946(15)
C(32)-H(32)	0.961(15)
S(1)-O(5)	1.4154(16)
S(1)-O(4)	1.4273(15)
S(1)-O(3)	1.4439(15)
S(1)-C(33)	1.8158(19)

...

Table A15 continued...

C(33)-F(2X)	1.281(8)
C(33)-F(1)	1.319(7)
C(33)-F(3)	1.327(8)
C(33)-F(3X)	1.331(9)
C(33)-F(1X)	1.366(8)
C(33)-F(2)	1.375(5)
C(34)-Cl(3)	1.752(2)
C(34)-Cl(2)	1.759(2)
C(34)-Cl(1)	1.764(2)
C(34)-H(34)	0.991(16)
C(1)-O(1)-C(2)	107.94(12)
C(10)-O(2)-C(11)	105.57(12)
C(1)-N(1)-C(3)	111.83(13)
C(1)-N(1)-H(1N)	119.5(13)
C(3)-N(1)-H(1N)	128.6(13)
C(10)-N(2)-C(12)	106.96(13)
C(1)-C(0)-C(10)	111.76(12)
C(1)-C(0)-C(19)	109.76(12)
C(10)-C(0)-C(19)	109.07(12)
C(1)-C(0)-C(26)	107.26(12)
C(10)-C(0)-C(26)	110.93(12)
C(19)-C(0)-C(26)	107.99(12)
N(1)-C(1)-O(1)	114.85(14)
N(1)-C(1)-C(0)	128.24(14)
O(1)-C(1)-C(0)	116.88(13)
O(1)-C(2)-C(3)	105.12(12)
O(1)-C(2)-H(2A)	107.8(12)
C(3)-C(2)-H(2A)	112.8(12)
O(1)-C(2)-H(2B)	106.9(12)
C(3)-C(2)-H(2B)	113.9(12)
H(2A)-C(2)-H(2B)	109.9(17)
N(1)-C(3)-C(4)	112.63(12)
N(1)-C(3)-C(2)	99.62(12)
C(4)-C(3)-C(2)	114.04(13)
N(1)-C(3)-H(3)	108.0(12)
C(4)-C(3)-H(3)	111.6(11)
C(2)-C(3)-H(3)	110.2(12)
C(5)-C(4)-C(9)	119.70(15)
C(5)-C(4)-C(3)	119.69(14)
C(9)-C(4)-C(3)	120.60(14)
C(6)-C(5)-C(4)	120.03(16)
C(6)-C(5)-H(5)	119.3(13)
C(4)-C(5)-H(5)	120.6(13)
C(7)-C(6)-C(5)	120.14(16)
C(7)-C(6)-H(6)	118.4(14)
C(5)-C(6)-H(6)	121.4(14)

...

Table A15 continued...

C(6)-C(7)-C(8)	119.99(16)
C(6)-C(7)-H(7)	120.3(14)
C(8)-C(7)-H(7)	119.7(14)
C(9)-C(8)-C(7)	119.96(16)
C(9)-C(8)-H(8)	121.1(13)
C(7)-C(8)-H(8)	119.0(13)
C(8)-C(9)-C(4)	120.18(15)
C(8)-C(9)-H(9)	119.9(12)
C(4)-C(9)-H(9)	119.9(12)
N(2)-C(10)-O(2)	119.28(14)
N(2)-C(10)-C(0)	127.66(14)
O(2)-C(10)-C(0)	113.06(12)
O(2)-C(11)-C(12)	104.46(12)
O(2)-C(11)-H(11A)	106.5(12)
C(12)-C(11)-H(11A)	114.5(12)
O(2)-C(11)-H(11B)	106.4(12)
C(12)-C(11)-H(11B)	112.8(12)
H(11A)-C(11)-H(11B)	111.3(17)
N(2)-C(12)-C(13)	112.67(13)
N(2)-C(12)-C(11)	103.22(12)
C(13)-C(12)-C(11)	112.81(13)
N(2)-C(12)-H(12)	108.1(12)
C(13)-C(12)-H(12)	108.4(12)
C(11)-C(12)-H(12)	111.5(12)
C(18)-C(13)-C(14)	118.96(15)
C(18)-C(13)-C(12)	120.23(14)
C(14)-C(13)-C(12)	120.73(14)
C(15)-C(14)-C(13)	120.46(15)
C(15)-C(14)-H(14)	120.5(12)
C(13)-C(14)-H(14)	119.1(12)
C(14)-C(15)-C(16)	120.27(16)
C(14)-C(15)-H(15)	119.3(13)
C(16)-C(15)-H(15)	120.4(13)
C(15)-C(16)-C(17)	119.56(17)
C(15)-C(16)-H(16)	118.6(14)
C(17)-C(16)-H(16)	121.8(14)
C(18)-C(17)-C(16)	120.28(16)
C(18)-C(17)-H(17)	121.2(14)
C(16)-C(17)-H(17)	118.5(14)
C(17)-C(18)-C(13)	120.46(16)
C(17)-C(18)-H(18)	119.5(13)
C(13)-C(18)-H(18)	120.0(13)
C(20)-C(19)-C(0)	114.52(12)
C(20)-C(19)-H(19A)	111.9(12)
C(0)-C(19)-H(19A)	106.9(12)
C(20)-C(19)-H(19B)	108.1(11)
...	

Table A15 continued...

C(0)-C(19)-H(19B)	105.6(11)
H(19A)-C(19)-H(19B)	109.6(16)
C(25)-C(20)-C(21)	118.88(15)
C(25)-C(20)-C(19)	121.16(14)
C(21)-C(20)-C(19)	119.96(14)
C(22)-C(21)-C(20)	120.37(16)
C(22)-C(21)-H(21)	119.6(13)
C(20)-C(21)-H(21)	120.0(13)
C(23)-C(22)-C(21)	120.41(17)
C(23)-C(22)-H(22)	119.4(13)
C(21)-C(22)-H(22)	120.2(14)
C(22)-C(23)-C(24)	119.70(16)
C(22)-C(23)-H(23)	121.8(15)
C(24)-C(23)-H(23)	118.5(15)
C(23)-C(24)-C(25)	120.21(17)
C(23)-C(24)-H(24)	120.7(14)
C(25)-C(24)-H(24)	119.0(14)
C(24)-C(25)-C(20)	120.40(16)
C(24)-C(25)-H(25)	119.1(12)
C(20)-C(25)-H(25)	120.5(12)
C(27)-C(26)-C(0)	114.33(12)
C(27)-C(26)-H(26A)	110.2(11)
C(0)-C(26)-H(26A)	106.4(11)
C(27)-C(26)-H(26B)	110.4(11)
C(0)-C(26)-H(26B)	108.4(11)
H(26A)-C(26)-H(26B)	106.8(16)
C(28)-C(27)-C(32)	118.81(14)
C(28)-C(27)-C(26)	120.00(14)
C(32)-C(27)-C(26)	121.18(14)
C(29)-C(28)-C(27)	120.69(15)
C(29)-C(28)-H(28)	122.5(12)
C(27)-C(28)-H(28)	116.7(12)
C(30)-C(29)-C(28)	120.19(15)
C(30)-C(29)-H(29)	120.1(12)
C(28)-C(29)-H(29)	119.6(12)
C(29)-C(30)-C(31)	119.61(15)
C(29)-C(30)-H(30)	118.9(13)
C(31)-C(30)-H(30)	121.4(13)
C(30)-C(31)-C(32)	120.32(15)
C(30)-C(31)-H(31)	119.0(13)
C(32)-C(31)-H(31)	120.7(13)
C(31)-C(32)-C(27)	120.35(15)
C(31)-C(32)-H(32)	119.7(12)
C(27)-C(32)-H(32)	119.9(12)
O(5)-S(1)-O(4)	117.71(14)
O(5)-S(1)-O(3)	115.20(13)
...	

Table A15 continued...

O(4)-S(1)-O(3)	113.12(9)
O(5)-S(1)-C(33)	102.02(10)
O(4)-S(1)-C(33)	103.53(9)
O(3)-S(1)-C(33)	102.37(9)
F(2X)-C(33)-F(1)	88.1(8)
F(2X)-C(33)-F(3)	117.0(12)
F(1)-C(33)-F(3)	109.1(8)
F(2X)-C(33)-F(3X)	108.7(11)
F(1)-C(33)-F(3X)	112.2(8)
F(3)-C(33)-F(3X)	9(2)
F(2X)-C(33)-F(1X)	109.4(4)
F(1)-C(33)-F(1X)	21.3(7)
F(3)-C(33)-F(1X)	98.5(9)
F(3X)-C(33)-F(1X)	104.1(8)
F(2X)-C(33)-F(2)	17.7(10)
F(1)-C(33)-F(2)	105.2(4)
F(3)-C(33)-F(2)	106.1(10)
F(3X)-C(33)-F(2)	97.6(11)
F(1X)-C(33)-F(2)	126.5(8)
F(2X)-C(33)-S(1)	113.8(5)
F(1)-C(33)-S(1)	116.2(4)
F(3)-C(33)-S(1)	111.0(8)
F(3X)-C(33)-S(1)	114.8(7)
F(1X)-C(33)-S(1)	105.4(8)
F(2)-C(33)-S(1)	108.6(4)
Cl(3)-C(34)-Cl(2)	110.73(12)
Cl(3)-C(34)-Cl(1)	109.59(12)
Cl(2)-C(34)-Cl(1)	109.87(10)
Cl(3)-C(34)-H(34)	107.8(14)
Cl(2)-C(34)-H(34)	109.9(13)
Cl(1)-C(34)-H(34)	108.9(14)

Table A16: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **2.61**

	x	y	z	U(eq)
H(1N)	5523(14)	3385(12)	2746(10)	22
H(2A)	8354(14)	2284(13)	3569(11)	29
H(2B)	7645(17)	2274(13)	4192(8)	29
H(3)	7600(15)	3575(12)	3122(10)	23
H(5)	8214(16)	4788(13)	3883(10)	29
H(6)	8050(17)	5699(12)	4846(12)	37
H(7)	6792(19)	5362(13)	5558(10)	38
H(8)	5694(17)	4117(14)	5350(11)	35
H(9)	5820(16)	3211(11)	4376(11)	28
H(11A)	1642(14)	2412(13)	1551(11)	30
...				

Table A16 continued...

	x	y	z	U(eq)
H(11B)	2297(17)	2386(13)	898(8)	30
H(12)	2534(16)	3698(12)	1969(10)	25
H(14)	4387(15)	3350(12)	786(11)	29
H(15)	4440(16)	4193(14)	−232(11)	34
H(16)	3146(19)	5308(13)	−581(10)	36
H(17)	1793(17)	5600(12)	91(12)	36
H(18)	1701(16)	4749(13)	1097(10)	30
H(19A)	6025(14)	803(12)	2186(10)	23
H(19B)	4757(14)	713(12)	1772(10)	23
H(21)	4248(15)	1110(12)	574(11)	29
H(22)	4578(17)	1848(14)	−430(9)	36
H(23)	6108(19)	2800(14)	−304(10)	39
H(24)	7304(15)	2972(13)	800(12)	35
H(25)	7040(15)	2209(13)	1793(9)	28
H(26A)	3860(13)	855(12)	2807(10)	23
H(26B)	5100(15)	617(11)	3173(10)	23
H(28)	5695(15)	929(11)	4379(11)	26
H(29)	5485(16)	1593(13)	5462(9)	28
H(30)	4096(17)	2636(13)	5438(9)	29
H(31)	2896(15)	2999(12)	4346(11)	29
H(32)	3043(15)	2276(13)	3282(9)	26
H(34)	5608(19)	6406(12)	2639(12)	41

Table A17: Torsion angles (°) for **2.61**

C(3)-N(1)-C(1)-O(1)	1.56(18)
C(3)-N(1)-C(1)-C(0)	179.38(13)
C(2)-O(1)-C(1)-N(1)	3.91(18)
C(2)-O(1)-C(1)-C(0)	−174.17(12)
C(10)-C(0)-C(1)-N(1)	1.8(2)
C(19)-C(0)-C(1)-N(1)	122.91(16)
C(26)-C(0)-C(1)-N(1)	−120.01(16)
C(10)-C(0)-C(1)-O(1)	179.56(12)
C(19)-C(0)-C(1)-O(1)	−59.30(16)
C(26)-C(0)-C(1)-O(1)	57.77(16)
C(1)-O(1)-C(2)-C(3)	−7.33(16)
C(1)-N(1)-C(3)-C(4)	−127.04(14)
C(1)-N(1)-C(3)-C(2)	−5.82(16)
O(1)-C(2)-C(3)-N(1)	7.52(15)
O(1)-C(2)-C(3)-C(4)	127.71(13)
N(1)-C(3)-C(4)-C(5)	−133.27(15)
C(2)-C(3)-C(4)-C(5)	114.13(16)
N(1)-C(3)-C(4)-C(9)	48.3(2)
C(2)-C(3)-C(4)-C(9)	−64.32(19)
C(9)-C(4)-C(5)-C(6)	0.4(2)
...	

Table A17 continued...

C(3)-C(4)-C(5)-C(6)	−178.04(16)
C(4)-C(5)-C(6)-C(7)	−0.2(3)
C(5)-C(6)-C(7)-C(8)	−0.1(3)
C(6)-C(7)-C(8)-C(9)	0.2(3)
C(7)-C(8)-C(9)-C(4)	0.1(3)
C(5)-C(4)-C(9)-C(8)	−0.4(2)
C(3)-C(4)-C(9)-C(8)	178.07(15)
C(12)-N(2)-C(10)-O(2)	0.52(18)
C(12)-N(2)-C(10)-C(0)	179.58(14)
C(11)-O(2)-C(10)-N(2)	4.16(18)
C(11)-O(2)-C(10)-C(0)	−175.03(12)
C(1)-C(0)-C(10)-N(2)	5.0(2)
C(19)-C(0)-C(10)-N(2)	−116.51(17)
C(26)-C(0)-C(10)-N(2)	124.67(16)
C(1)-C(0)-C(10)-O(2)	−175.87(12)
C(19)-C(0)-C(10)-O(2)	62.60(15)
C(26)-C(0)-C(10)-O(2)	−56.22(16)
C(10)-O(2)-C(11)-C(12)	−6.57(16)
C(10)-N(2)-C(12)-C(13)	−126.64(14)
C(10)-N(2)-C(12)-C(11)	−4.65(16)
O(2)-C(11)-C(12)-N(2)	6.78(16)
O(2)-C(11)-C(12)-C(13)	128.67(13)
N(2)-C(12)-C(13)-C(18)	−143.68(15)
C(11)-C(12)-C(13)-C(18)	99.92(17)
N(2)-C(12)-C(13)-C(14)	39.8(2)
C(11)-C(12)-C(13)-C(14)	−76.60(19)
C(18)-C(13)-C(14)-C(15)	−1.0(2)
C(12)-C(13)-C(14)-C(15)	175.54(15)
C(13)-C(14)-C(15)-C(16)	0.7(3)
C(14)-C(15)-C(16)-C(17)	0.3(3)
C(15)-C(16)-C(17)-C(18)	−0.8(3)
C(16)-C(17)-C(18)-C(13)	0.5(3)
C(14)-C(13)-C(18)-C(17)	0.5(2)
C(12)-C(13)-C(18)-C(17)	−176.12(15)
C(1)-C(0)-C(19)-C(20)	−74.00(16)
C(10)-C(0)-C(19)-C(20)	48.74(17)
C(26)-C(0)-C(19)-C(20)	169.38(13)
C(0)-C(19)-C(20)-C(25)	70.98(18)
C(0)-C(19)-C(20)-C(21)	−109.45(16)
C(25)-C(20)-C(21)-C(22)	−0.2(2)
C(19)-C(20)-C(21)-C(22)	−179.78(14)
C(20)-C(21)-C(22)-C(23)	−1.2(2)
C(21)-C(22)-C(23)-C(24)	1.3(3)
C(22)-C(23)-C(24)-C(25)	0.2(3)
C(23)-C(24)-C(25)-C(20)	−1.6(2)
C(21)-C(20)-C(25)-C(24)	1.6(2)
...	

Table A17 continued...

C(19)-C(20)-C(25)-C(24)	−178.81(14)
C(1)-C(0)-C(26)-C(27)	47.83(16)
C(10)-C(0)-C(26)-C(27)	−74.47(16)
C(19)-C(0)-C(26)-C(27)	166.06(13)
C(0)-C(26)-C(27)-C(28)	−111.23(16)
C(0)-C(26)-C(27)-C(32)	69.54(19)
C(32)-C(27)-C(28)-C(29)	0.5(2)
C(26)-C(27)-C(28)-C(29)	−178.76(14)
C(27)-C(28)-C(29)-C(30)	−1.6(2)
C(28)-C(29)-C(30)-C(31)	1.3(2)
C(29)-C(30)-C(31)-C(32)	0.0(2)
C(30)-C(31)-C(32)-C(27)	−1.2(2)
C(28)-C(27)-C(32)-C(31)	0.9(2)
C(26)-C(27)-C(32)-C(31)	−179.87(14)
O(5)-S(1)-C(33)-F(2X)	−173.8(12)
O(4)-S(1)-C(33)-F(2X)	63.5(12)
O(3)-S(1)-C(33)-F(2X)	−54.3(12)
O(5)-S(1)-C(33)-F(1)	−73.7(6)
O(4)-S(1)-C(33)-F(1)	163.6(5)
O(3)-S(1)-C(33)-F(1)	45.8(6)
O(5)-S(1)-C(33)-F(3)	51.7(10)
O(4)-S(1)-C(33)-F(3)	−71.0(10)
O(3)-S(1)-C(33)-F(3)	171.2(10)
O(5)-S(1)-C(33)-F(3X)	60.0(10)
O(4)-S(1)-C(33)-F(3X)	−62.7(10)
O(3)-S(1)-C(33)-F(3X)	179.5(10)
O(5)-S(1)-C(33)-F(1X)	−53.9(7)
O(4)-S(1)-C(33)-F(1X)	−176.6(7)
O(3)-S(1)-C(33)-F(1X)	65.6(7)
O(5)-S(1)-C(33)-F(2)	168.0(3)
O(4)-S(1)-C(33)-F(2)	45.3(3)
O(3)-S(1)-C(33)-F(2)	−72.5(3)

Table A18: Hydrogen bonds (Å and °) for **2.61**

D−H...A	d(D−H)	d(H...A)	d(D...A)	∠(DHA)
N(1)−H(1N)...N(2)	0.866(15)	2.005(18)	2.6627(19)	131.9(17)

Table A19: Anisotropic displacement parameters ($Å^2$x 10^3) for **2.61**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	19(1)	17(1)	26(1)	−2(1)	1(1)	2(1)
O(2)	19(1)	20(1)	28(1)	0(1)	1(1)	−3(1)
N(1)	18(1)	16(1)	20(1)	−1(1)	2(1)	1(1)
N(2)	18(1)	19(1)	21(1)	−2(1)	2(1)	3(1)
C(0)	19(1)	14(1)	19(1)	−1(1)	5(1)	−1(1)
C(1)	18(1)	18(1)	17(1)	−1(1)	6(1)	2(1)
C(2)	19(1)	20(1)	29(1)	−3(1)	−1(1)	1(1)
C(3)	16(1)	19(1)	23(1)	−2(1)	2(1)	−1(1)
C(4)	18(1)	17(1)	21(1)	0(1)	1(1)	0(1)
C(5)	22(1)	21(1)	29(1)	0(1)	5(1)	−4(1)
C(6)	34(1)	21(1)	36(1)	−6(1)	6(1)	−8(1)
C(7)	41(1)	24(1)	30(1)	−8(1)	9(1)	−2(1)
C(8)	35(1)	26(1)	29(1)	−2(1)	13(1)	−2(1)
C(9)	26(1)	18(1)	27(1)	−1(1)	7(1)	−4(1)
C(10)	17(1)	18(1)	17(1)	−2(1)	5(1)	−1(1)
C(11)	19(1)	24(1)	30(1)	2(1)	0(1)	−1(1)
C(12)	16(1)	22(1)	24(1)	−3(1)	4(1)	4(1)
C(13)	18(1)	16(1)	26(1)	−4(1)	2(1)	1(1)
C(14)	23(1)	20(1)	29(1)	−1(1)	6(1)	5(1)
C(15)	30(1)	24(1)	33(1)	−1(1)	10(1)	0(1)
C(16)	35(1)	22(1)	32(1)	5(1)	4(1)	−3(1)
C(17)	26(1)	19(1)	42(1)	4(1)	0(1)	4(1)
C(18)	19(1)	20(1)	34(1)	−3(1)	3(1)	4(1)
C(19)	23(1)	14(1)	20(1)	−2(1)	7(1)	1(1)
C(20)	20(1)	16(1)	20(1)	−2(1)	7(1)	4(1)
C(21)	21(1)	28(1)	24(1)	−5(1)	6(1)	4(1)
C(22)	30(1)	40(1)	21(1)	1(1)	7(1)	17(1)
C(23)	41(1)	32(1)	32(1)	12(1)	22(1)	19(1)
C(24)	29(1)	23(1)	42(1)	3(1)	21(1)	2(1)
C(25)	22(1)	23(1)	26(1)	−3(1)	9(1)	1(1)
C(26)	23(1)	15(1)	20(1)	0(1)	8(1)	0(1)
C(27)	20(1)	17(1)	19(1)	0(1)	7(1)	−2(1)
C(28)	20(1)	22(1)	23(1)	2(1)	7(1)	0(1)
C(29)	21(1)	29(1)	20(1)	1(1)	5(1)	−6(1)
C(30)	27(1)	25(1)	23(1)	−5(1)	12(1)	−8(1)

...

Table A19 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(31)	24(1)	22(1)	29(1)	−1(1)	12(1)	1(1)
C(32)	20(1)	23(1)	21(1)	1(1)	6(1)	1(1)
S(1)	21(1)	30(1)	24(1)	−5(1)	7(1)	−2(1)
O(3)	29(1)	22(1)	78(1)	−1(1)	7(1)	−4(1)
O(4)	26(1)	27(1)	74(1)	11(1)	−8(1)	1(1)
O(5)	54(1)	170(2)	41(1)	−49(1)	28(1)	−28(1)
C(33)	25(1)	24(1)	31(1)	8(1)	4(1)	1(1)
F(1)	39(3)	22(2)	51(3)	8(2)	−11(2)	8(2)
F(2)	54(2)	29(3)	19(2)	−5(2)	12(2)	−5(1)
F(3)	25(3)	25(3)	44(4)	−3(2)	13(2)	−8(2)
F(1X)	28(2)	35(2)	123(8)	35(4)	−3(4)	8(2)
F(2X)	60(3)	147(8)	23(2)	29(4)	2(2)	−23(5)
F(3X)	21(2)	25(2)	43(4)	−1(3)	0(3)	1(2)
C(34)	38(1)	24(1)	36(1)	4(1)	−1(1)	−5(1)
Cl(1)	37(1)	45(1)	41(1)	9(1)	10(1)	−3(1)
Cl(2)	57(1)	52(1)	80(1)	20(1)	39(1)	12(1)
Cl(3)	69(1)	32(1)	60(1)	−6(1)	−29(1)	10(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2 \left[h^2 a *^2 U^{11} + ... + 2hka * b * U^{12}\right]$

A.2.4 *Structural Data for Naproxen Ester* **2.103**

Suitable X-ray quality crystals of **2.103** were grown by slow evaporation of an approximately 10:1:1 (v/v/v) mixture of ethyl acetate, CH_2Cl_2, and hexanes. The structure of **2.103** has been deposited with the Cambridge Crystallographic Data Centre (CCDC #844999).

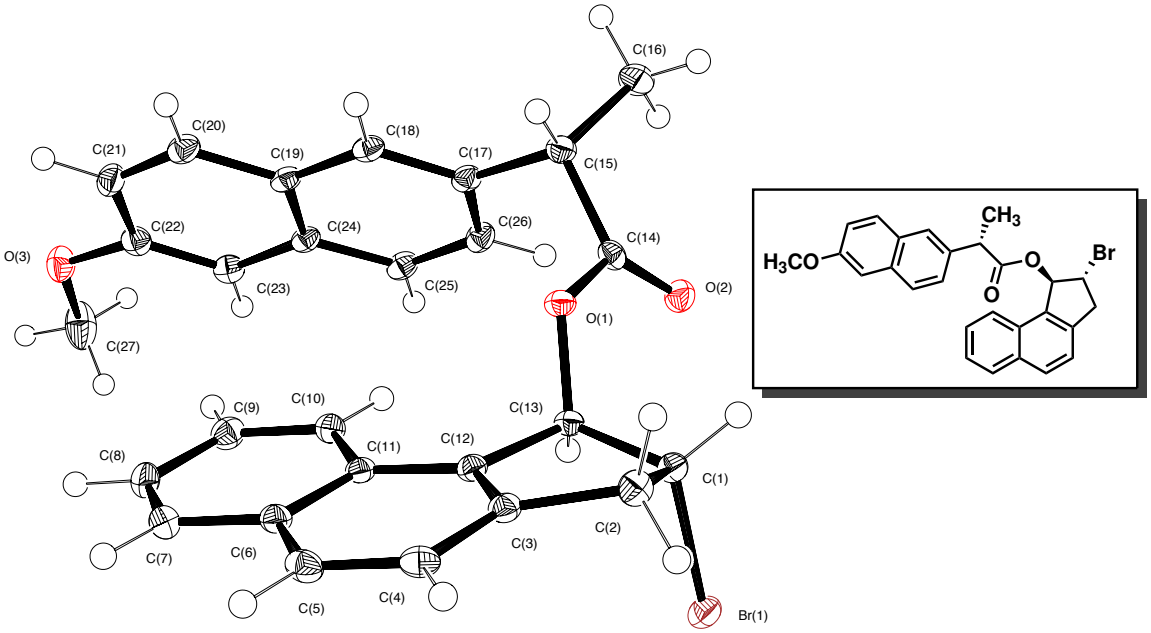


Figure A4: ORTEP drawing of ketone **2.103** shown at 50% probability

Table A20: Crystal data and structure refinement for **2.103**

Empirical formula	$C_{27}H_{23}BrO_3$
Formula weight	475.36
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 6.1357(3) Å $\alpha = 90°$.
	b = 10.2342(5) Å $\beta = 90°$.
	c = 33.8898(17) Å $\gamma = 90°$.
Volume	2128.08(18) $Å^3$
Z	4
Density (calculated)	1.484 Mg/m^3
Absorption coefficient	1.959 mm^{-1}
F(000)	976
Crystal size	0.18 x 0.15 x 0.10 mm^3
Theta range for data collection	2.08 to 28.34°.
Index ranges	−8<=h<=6, −13<=k<=13, −45<=l<=45
Reflections collected	53379
Independent reflections	5206 [R(int) = 0.0212]
Completeness to theta = 28.34°	99.7%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8282 and 0.7194
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5206 / 0 / 280
Goodness-of-fit on F^2	1.125
Final R indices [I>2sigma(I)]	R1 = 0.0195, wR2 = 0.0502
R indices (all data)	R1 = 0.0199, wR2 = 0.0504
Absolute structure parameter	0.020(5)
Extinction coefficient	na
Largest diff. peak and hole	0.370 and −0.469 e.$Å^{-3}$

Table A21: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **2.103**

	x	y	z	U(eq)
Br(1)	1514(1)	5925(1)	7835(1)	17(1)
O(1)	609(2)	7812(1)	6770(1)	14(1)
O(2)	3612(2)	8785(1)	7017(1)	18(1)
O(3)	6160(2)	4085(1)	4788(1)	22(1)
C(1)	−34(3)	7079(1)	7462(1)	15(1)
C(2)	−2447(3)	6689(2)	7454(1)	16(1)
C(3)	−2478(2)	5627(1)	7145(1)	14(1)
C(4)	−4106(2)	4675(1)	7076(1)	16(1)
C(5)	−3846(3)	3825(1)	6768(1)	17(1)
C(6)	−1993(2)	3881(1)	6517(1)	15(1)
C(7)	−1742(3)	3009(1)	6194(1)	18(1)
C(8)	51(3)	3079(2)	5955(1)	19(1)
C(9)	1673(3)	4031(2)	6020(1)	18(1)
C(10)	1494(3)	4883(1)	6332(1)	15(1)
C(11)	−329(3)	4824(1)	6589(1)	13(1)
C(12)	−636(3)	5672(1)	6915(1)	13(1)
C(13)	864(2)	6741(1)	7051(1)	13(1)
C(14)	2279(3)	8670(1)	6759(1)	14(1)
C(15)	2365(3)	9343(1)	6359(1)	15(1)
C(16)	3555(3)	10647(1)	6381(1)	21(1)
C(17)	3479(3)	8364(1)	6085(1)	15(1)
C(18)	2446(3)	7916(1)	5752(1)	15(1)
C(19)	3421(3)	6957(1)	5507(1)	14(1)
C(20)	2381(3)	6489(2)	5161(1)	17(1)
C(21)	3346(3)	5556(1)	4932(1)	19(1)
C(22)	5400(3)	5025(2)	5041(1)	18(1)
C(23)	6463(3)	5456(1)	5372(1)	17(1)
C(24)	5498(3)	6444(1)	5610(1)	14(1)
C(25)	6554(3)	6935(1)	5951(1)	17(1)
C(26)	5578(3)	7873(2)	6181(1)	17(1)
C(27)	8127(3)	3441(2)	4898(1)	33(1)

Table A22: Bond lengths (Å) and angles (°) for **2.103**

Br(1)-C(1)	1.9736(15)
O(1)-C(14)	1.3507(18)
O(1)-C(13)	1.4615(16)
O(2)-C(14)	1.2024(19)
O(3)-C(22)	1.3700(19)
O(3)-C(27)	1.425(2)
...	

Table A22 continued...

C(1)-C(2)	1.533(2)
C(1)-C(13)	1.535(2)
C(1)-H(1A)	1
C(2)-C(3)	1.510(2)
C(2)-H(2A)	0.99
C(2)-H(2B)	0.99
C(3)-C(12)	1.373(2)
C(3)-C(4)	1.415(2)
C(4)-C(5)	1.367(2)
C(4)-H(4A)	0.95
C(5)-C(6)	1.421(2)
C(5)-H(5A)	0.95
C(6)-C(7)	1.419(2)
C(6)-C(11)	1.426(2)
C(7)-C(8)	1.369(2)
C(7)-H(7A)	0.95
C(8)-C(9)	1.411(2)
C(8)-H(8A)	0.95
C(9)-C(10)	1.3741(19)
C(9)-H(9A)	0.95
C(10)-C(11)	1.419(2)
C(10)-H(10A)	0.95
C(11)-C(12)	1.4173(19)
C(12)-C(13)	1.502(2)
C(13)-H(13A)	1
C(14)-C(15)	1.521(2)
C(15)-C(16)	1.523(2)
C(15)-C(17)	1.527(2)
C(15)-H(15A)	1
C(16)-H(16A)	0.98
C(16)-H(16B)	0.98
C(16)-H(16C)	0.98
C(17)-C(18)	1.374(2)
C(17)-C(26)	1.420(2)
C(18)-C(19)	1.418(2)
C(18)-H(18A)	0.95
C(19)-C(20)	1.420(2)
C(19)-C(24)	1.422(2)
C(20)-C(21)	1.364(2)
C(20)-H(20A)	0.95
C(21)-C(22)	1.421(2)
C(21)-H(21A)	0.95
C(22)-C(23)	1.371(2)
C(23)-C(24)	1.423(2)
C(23)-H(23A)	0.95
C(24)-C(25)	1.417(2)
...	

Table A22 continued...

C(25)-C(26)	1.373(2)
C(25)-H(25A)	0.95
C(26)-H(26A)	0.95
C(27)-H(27A)	0.98
C(27)-H(27B)	0.98
C(27)-H(27C)	0.98
C(14)-O(1)-C(13)	115.12(11)
C(22)-O(3)-C(27)	116.71(13)
C(2)-C(1)-C(13)	105.81(12)
C(2)-C(1)-Br(1)	108.65(10)
C(13)-C(1)-Br(1)	105.81(10)
C(2)-C(1)-H(1A)	112.1
C(13)-C(1)-H(1A)	112.1
Br(1)-C(1)-H(1A)	112.1
C(3)-C(2)-C(1)	102.20(12)
C(3)-C(2)-H(2A)	111.3
C(1)-C(2)-H(2A)	111.3
C(3)-C(2)-H(2B)	111.3
C(1)-C(2)-H(2B)	111.3
H(2A)-C(2)-H(2B)	109.2
C(12)-C(3)-C(4)	120.64(13)
C(12)-C(3)-C(2)	111.02(13)
C(4)-C(3)-C(2)	128.34(14)
C(5)-C(4)-C(3)	118.85(14)
C(5)-C(4)-H(4A)	120.6
C(3)-C(4)-H(4A)	120.6
C(4)-C(5)-C(6)	121.63(14)
C(4)-C(5)-H(5A)	119.2
C(6)-C(5)-H(5A)	119.2
C(7)-C(6)-C(5)	121.50(14)
C(7)-C(6)-C(11)	118.70(14)
C(5)-C(6)-C(11)	119.80(13)
C(8)-C(7)-C(6)	120.74(15)
C(8)-C(7)-H(7A)	119.6
C(6)-C(7)-H(7A)	119.6
C(7)-C(8)-C(9)	120.59(14)
C(7)-C(8)-H(8A)	119.7
C(9)-C(8)-H(8A)	119.7
C(10)-C(9)-C(8)	120.24(15)
C(10)-C(9)-H(9A)	119.9
C(8)-C(9)-H(9A)	119.9
C(9)-C(10)-C(11)	120.52(15)
C(9)-C(10)-H(10A)	119.7
C(11)-C(10)-H(10A)	119.7
C(12)-C(11)-C(10)	123.85(13)
C(12)-C(11)-C(6)	116.95(13)
...	

Table A22 continued...

C(10)-C(11)-C(6)	119.18(13)
C(3)-C(12)-C(11)	122.07(13)
C(3)-C(12)-C(13)	110.76(12)
C(11)-C(12)-C(13)	127.14(14)
O(1)-C(13)-C(12)	106.24(11)
O(1)-C(13)-C(1)	112.56(11)
C(12)-C(13)-C(1)	102.85(12)
O(1)-C(13)-H(13A)	111.6
C(12)-C(13)-H(13A)	111.6
C(1)-C(13)-H(13A)	111.6
O(2)-C(14)-O(1)	124.00(13)
O(2)-C(14)-C(15)	125.46(14)
O(1)-C(14)-C(15)	110.20(12)
C(14)-C(15)-C(16)	111.65(12)
C(14)-C(15)-C(17)	105.06(11)
C(16)-C(15)-C(17)	112.98(13)
C(14)-C(15)-H(15A)	109
C(16)-C(15)-H(15A)	109
C(17)-C(15)-H(15A)	109
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(18)-C(17)-C(26)	119.19(14)
C(18)-C(17)-C(15)	120.80(15)
C(26)-C(17)-C(15)	119.98(13)
C(17)-C(18)-C(19)	121.17(15)
C(17)-C(18)-H(18A)	119.4
C(19)-C(18)-H(18A)	119.4
C(18)-C(19)-C(20)	121.88(15)
C(18)-C(19)-C(24)	119.33(13)
C(20)-C(19)-C(24)	118.79(14)
C(21)-C(20)-C(19)	120.69(15)
C(21)-C(20)-H(20A)	119.7
C(19)-C(20)-H(20A)	119.7
C(20)-C(21)-C(22)	120.37(14)
C(20)-C(21)-H(21A)	119.8
C(22)-C(21)-H(21A)	119.8
O(3)-C(22)-C(23)	125.18(16)
O(3)-C(22)-C(21)	114.09(14)
C(23)-C(22)-C(21)	120.73(15)
C(22)-C(23)-C(24)	119.68(16)
C(22)-C(23)-H(23A)	120.2
C(24)-C(23)-H(23A)	120.2
...	

Table A22 continued...

C(25)-C(24)-C(19)	118.66(14)
C(25)-C(24)-C(23)	121.63(15)
C(19)-C(24)-C(23)	119.71(14)
C(26)-C(25)-C(24)	120.69(15)
C(26)-C(25)-H(25A)	119.7
C(24)-C(25)-H(25A)	119.7
C(25)-C(26)-C(17)	120.92(14)
C(25)-C(26)-H(26A)	119.5
C(17)-C(26)-H(26A)	119.5
O(3)-C(27)-H(27A)	109.5
O(3)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
O(3)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5

Table A23: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **2.103**

	x	y	z	U(eq)
H(1A)	169	8023	7528	17
H(2A)	−2929	6355	7714	19
H(2B)	−3382	7435	7377	19
H(4A)	−5358	4628	7240	19
H(5A)	−4931	3182	6721	20
H(7A)	−2830	2370	6144	22
H(8A)	205	2480	5742	23
H(9A)	2893	4084	5849	22
H(10A)	2600	5516	6376	18
H(13A)	2410	6435	7065	15
H(15A)	843	9497	6264	18
H(16A)	2768	11236	6559	31
H(16B)	3628	11037	6118	31
H(16C)	5035	10507	6482	31
H(18A)	1054	8255	5684	18
H(20A)	999	6828	5087	21
H(21A)	2642	5261	4699	22
H(23A)	7837	5096	5442	21
H(25A)	7953	6612	6022	20
H(26A)	6318	8198	6407	20
H(27A)	8508	2793	4697	49
H(27B)	7923	3003	5152	49
H(27C)	9303	4085	4920	49

Table A24: Torsion angles (°) for **2.103**

C(13)-C(1)-C(2)-C(3)	26.23(14)
Br(1)-C(1)-C(2)-C(3)	−87.00(12)
C(1)-C(2)-C(3)-C(12)	−17.68(16)
C(1)-C(2)-C(3)-C(4)	162.81(14)
C(12)-C(3)-C(4)-C(5)	−1.9(2)
C(2)-C(3)-C(4)-C(5)	177.55(14)
C(3)-C(4)-C(5)-C(6)	−0.3(2)
C(4)-C(5)-C(6)-C(7)	−179.09(14)
C(4)-C(5)-C(6)-C(11)	1.3(2)
C(5)-C(6)-C(7)-C(8)	179.80(14)
C(11)-C(6)-C(7)-C(8)	−0.6(2)
C(6)-C(7)-C(8)-C(9)	−0.9(2)
C(7)-C(8)-C(9)-C(10)	1.5(2)
C(8)-C(9)-C(10)-C(11)	−0.6(2)
C(9)-C(10)-C(11)-C(12)	−179.58(14)
C(9)-C(10)-C(11)-C(6)	−0.9(2)
C(7)-C(6)-C(11)-C(12)	−179.73(13)
C(5)-C(6)-C(11)-C(12)	−0.1(2)
C(7)-C(6)-C(11)-C(10)	1.5(2)
C(5)-C(6)-C(11)-C(10)	−178.94(13)
C(4)-C(3)-C(12)-C(11)	3.2(2)
C(2)-C(3)-C(12)-C(11)	−176.36(13)
C(4)-C(3)-C(12)-C(13)	−178.73(13)
C(2)-C(3)-C(12)-C(13)	1.72(16)
C(10)-C(11)-C(12)-C(3)	176.64(13)
C(6)-C(11)-C(12)-C(3)	−2.1(2)
C(10)-C(11)-C(12)-C(13)	−1.1(2)
C(6)-C(11)-C(12)-C(13)	−179.86(13)
C(14)-O(1)-C(13)-C(12)	−159.00(12)
C(14)-O(1)-C(13)-C(1)	89.17(15)
C(3)-C(12)-C(13)-O(1)	−103.41(13)
C(11)-C(12)-C(13)-O(1)	74.55(17)
C(3)-C(12)-C(13)-C(1)	15.03(15)
C(11)-C(12)-C(13)-C(1)	−167.01(14)
C(2)-C(1)-C(13)-O(1)	88.44(14)
Br(1)-C(1)-C(13)-O(1)	−156.36(9)
C(2)-C(1)-C(13)-C(12)	−25.48(14)
Br(1)-C(1)-C(13)-C(12)	89.72(11)
C(13)-O(1)-C(14)-O(2)	−18.5(2)
C(13)-O(1)-C(14)-C(15)	155.10(12)
O(2)-C(14)-C(15)-C(16)	−29.1(2)
O(1)-C(14)-C(15)-C(16)	157.37(13)
O(2)-C(14)-C(15)-C(17)	93.68(17)
O(1)-C(14)-C(15)-C(17)	−79.82(15)

...

Table A24 continued...

C(14)-C(15)-C(17)-C(18)	121.44(14)
C(16)-C(15)-C(17)-C(18)	−116.62(16)
C(14)-C(15)-C(17)-C(26)	−56.50(17)
C(16)-C(15)-C(17)-C(26)	65.44(17)
C(26)-C(17)-C(18)-C(19)	1.2(2)
C(15)-C(17)-C(18)-C(19)	−176.72(13)
C(17)-C(18)-C(19)-C(20)	−179.67(14)
C(17)-C(18)-C(19)-C(24)	0.5(2)
C(18)-C(19)-C(20)-C(21)	−179.37(14)
C(24)-C(19)-C(20)-C(21)	0.5(2)
C(19)-C(20)-C(21)-C(22)	0.9(2)
C(27)-O(3)-C(22)-C(23)	5.1(2)
C(27)-O(3)-C(22)-C(21)	−175.16(15)
C(20)-C(21)-C(22)-O(3)	179.08(14)
C(20)-C(21)-C(22)-C(23)	−1.2(2)
O(3)-C(22)-C(23)-C(24)	179.80(14)
C(21)-C(22)-C(23)-C(24)	0.1(2)
C(18)-C(19)-C(24)-C(25)	−1.6(2)
C(20)-C(19)-C(24)-C(25)	178.56(14)
C(18)-C(19)-C(24)-C(23)	178.31(13)
C(20)-C(19)-C(24)-C(23)	−1.6(2)
C(22)-C(23)-C(24)-C(25)	−178.87(14)
C(22)-C(23)-C(24)-C(19)	1.3(2)
C(19)-C(24)-C(25)-C(26)	1.0(2)
C(23)-C(24)-C(25)-C(26)	−178.89(14)
C(24)-C(25)-C(26)-C(17)	0.7(2)
C(18)-C(17)-C(26)-C(25)	−1.8(2)
C(15)-C(17)-C(26)-C(25)	176.13(14)

Table A25: Anisotropic displacement parameters (Å^{2}x 10^3) for **2.103**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	18(1)	20(1)	13(1)	2(1)	−2(1)	−1(1)
O(1)	14(1)	13(1)	14(1)	3(1)	−1(1)	−1(1)
O(2)	19(1)	18(1)	16(1)	0(1)	−2(1)	−4(1)
O(3)	22(1)	23(1)	21(1)	−7(1)	−1(1)	2(1)
C(1)	17(1)	14(1)	13(1)	0(1)	−1(1)	1(1)
C(2)	14(1)	18(1)	16(1)	0(1)	2(1)	1(1)
C(3)	14(1)	14(1)	13(1)	2(1)	−1(1)	2(1)
C(4)	13(1)	16(1)	18(1)	4(1)	1(1)	1(1)
C(5)	14(1)	15(1)	22(1)	3(1)	−3(1)	−3(1)
C(6)	15(1)	13(1)	15(1)	2(1)	−2(1)	−1(1)
C(7)	22(1)	15(1)	17(1)	0(1)	−2(1)	−3(1)
C(8)	25(1)	18(1)	14(1)	−4(1)	−1(1)	1(1)
C(9)	19(1)	21(1)	16(1)	1(1)	2(1)	2(1)
C(10)	15(1)	14(1)	15(1)	1(1)	0(1)	0(1)
C(11)	14(1)	12(1)	12(1)	2(1)	−2(1)	0(1)
C(12)	13(1)	14(1)	12(1)	2(1)	−2(1)	0(1)
C(13)	14(1)	12(1)	13(1)	2(1)	0(1)	−1(1)
C(14)	15(1)	12(1)	16(1)	−2(1)	2(1)	1(1)
C(15)	15(1)	13(1)	16(1)	1(1)	−2(1)	−1(1)
C(16)	24(1)	16(1)	22(1)	3(1)	0(1)	−6(1)
C(17)	16(1)	16(1)	12(1)	3(1)	2(1)	−2(1)
C(18)	12(1)	17(1)	15(1)	4(1)	−1(1)	−1(1)
C(19)	14(1)	17(1)	12(1)	4(1)	0(1)	−2(1)
C(20)	15(1)	20(1)	17(1)	4(1)	−3(1)	−2(1)
C(21)	19(1)	22(1)	15(1)	0(1)	−3(1)	−4(1)
C(22)	19(1)	17(1)	17(1)	1(1)	3(1)	−3(1)
C(23)	15(1)	19(1)	18(1)	2(1)	1(1)	0(1)
C(24)	14(1)	17(1)	12(1)	3(1)	1(1)	−2(1)
C(25)	13(1)	21(1)	16(1)	3(1)	−2(1)	−1(1)
C(26)	15(1)	20(1)	15(1)	1(1)	−2(1)	−3(1)
C(27)	22(1)	37(1)	39(1)	−18(1)	−4(1)	7(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2 \left[h^2 a*^2 U^{11} + ... + 2hka*b* U^{12}\right]$

A.2.5 *Structural Data for* **2.97** *Copper Chloride Complex*

Bis(oxazoline) ligand **2.97** (25.0 mg, 0.054 mmol, 1.00 equiv) was dissolved in 2 mL of CH_2Cl_2. $CuCl_2$ (25.0 mg, 0.186 mmol, 3.44 equiv) was added as a solid and the suspension was stirred for 1 hour at room temperature. The suspension was filtered through a cotton plug into a 1 dram glass shell vial that was placed into a 25 mL scintillation vial containing 5 mL of pentane. The scintillation vial was sealed with a screw cap for 1 week, after which time suitable orange X-ray quality crystals of $CuCl_2$·**2.97** were obtained. The structure of $CuCl_2$·**2.97** has been deposited with the Cambridge Crystallographic Data Centre (CCDC #845000).

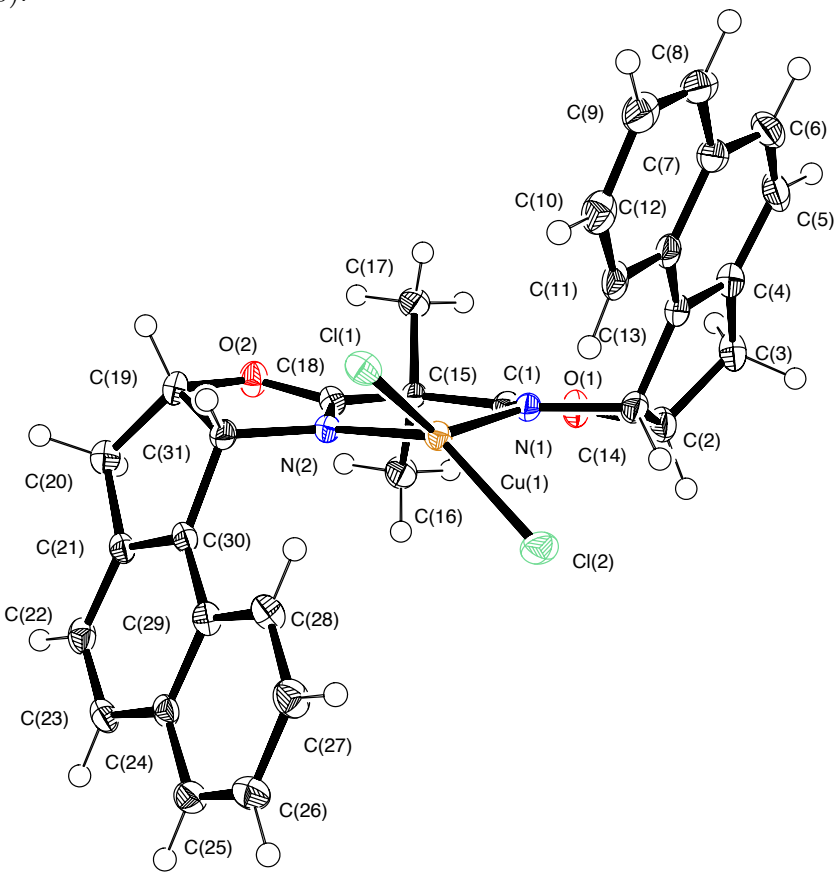


Figure A5: ORTEP drawing of $CuCl_2$·**2.97** shown at 50% probability

Table A26: Crystal data and structure refinement for $CuCl_2$·**2.97**

Empirical formula	$C_{32}H_{28}Cl_4CuN_2O_2$ (contains CH_2Cl_2)
Formula weight	677.90
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P 1
Unit cell dimensions	a = 13.3742(5) Å α = 88.632(2)°. b = 18.7820(7) Å β = 77.873(2)°. c = 25.5722(10) Å γ = 74.830(2)°.
Volume	6058.1(4) $Å^3$
Z	8
Density (calculated)	1.487 Mg/m^3
Absorption coefficient	1.107 mm^{-1}
F(000)	2776
Crystal size	0.12 x 0.10 x 0.07 mm^3
Theta range for data collection	1.12 to 28.70°.
Index ranges	−17<=h<=17, −25<=k<=25, −34<=l<=34
Reflections collected	220519
Independent reflections	58427 [R(int) = 0.0240]
Completeness to theta = 28.70°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9265 and 0.8786
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	58427 / 0 / 2950
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0489, wR2 = 0.1324
R indices (all data)	R1 = 0.0536, wR2 = 0.1371
Absolute structure parameter	0.018(4)
Extinction coefficient	na
Largest diff. peak and hole	2.523 and −1.276 e.$Å^{-3}$

Table A27: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for $CuCl_2 \cdot$**2.97**

	x	y	z	U(eq)
Cu(1)	5923(1)	3980(1)	3895(1)	16(1)
Cl(1)	5758(1)	4665(1)	4622(1)	21(1)
Cl(2)	7639(1)	3375(1)	3750(1)	25(1)
O(1)	5478(2)	3770(1)	2367(1)	23(1)
O(2)	2868(2)	3874(1)	3954(1)	22(1)
N(1)	5899(2)	4040(2)	3124(1)	17(1)
N(2)	4505(2)	3794(1)	4070(1)	16(1)
C(1)	5211(3)	3870(2)	2901(1)	18(1)
C(2)	6575(3)	3810(2)	2190(1)	23(1)
C(3)	6647(3)	4372(2)	1754(1)	26(1)
C(4)	6676(3)	5049(2)	2049(1)	23(1)
C(5)	6614(3)	5757(2)	1839(2)	28(1)
C(6)	6651(3)	6318(2)	2157(2)	30(1)
C(7)	6756(3)	6200(2)	2693(2)	24(1)
C(8)	6752(3)	6788(2)	3033(2)	29(1)
C(9)	6847(3)	6667(2)	3553(2)	30(1)
C(10)	7008(3)	5950(2)	3753(2)	27(1)
C(11)	7034(3)	5363(2)	3428(1)	22(1)
C(12)	6868(3)	5479(2)	2903(1)	21(1)
C(13)	6785(3)	4914(2)	2567(1)	20(1)
C(14)	6805(3)	4122(2)	2692(1)	20(1)
C(15)	4121(2)	3798(2)	3139(1)	16(1)
C(16)	4004(3)	3036(2)	2973(2)	24(1)
C(17)	3327(3)	4425(2)	2926(1)	23(1)
C(18)	3878(3)	3832(2)	3742(1)	18(1)
C(19)	2727(3)	3895(2)	4538(1)	20(1)
C(20)	2285(3)	3253(2)	4762(1)	22(1)
C(21)	3232(3)	2691(2)	4885(1)	18(1)
C(22)	3269(3)	1969(2)	5048(1)	21(1)
C(23)	4188(3)	1518(2)	5143(1)	21(1)
C(24)	5102(3)	1787(2)	5109(1)	18(1)
C(25)	6059(3)	1333(2)	5218(1)	22(1)
C(26)	6917(3)	1597(2)	5197(2)	25(1)
C(27)	6876(3)	2338(2)	5066(2)	25(1)
C(28)	5967(3)	2793(2)	4952(1)	22(1)
C(29)	5067(3)	2529(2)	4958(1)	19(1)
C(30)	4108(3)	2964(2)	4826(1)	17(1)
C(31)	3878(3)	3745(2)	4617(1)	17(1)
Cu(2)	5894(1)	8992(1)	3907(1)	15(1)
Cl(3)	7629(1)	8427(1)	3737(1)	23(1)
Cl(4)	5738(1)	9662(1)	4641(1)	21(1)
O(3)	5346(2)	8809(1)	2396(1)	23(1)
		...		

Table A27 continued...

	x	y	z	U(eq)
O(4)	2833(2)	8869(1)	4007(1)	22(1)
N(3)	5825(2)	9064(1)	3141(1)	16(1)
N(4)	4488(2)	8786(2)	4100(1)	17(1)
C(32)	5128(3)	8894(2)	2928(1)	16(1)
C(33)	6437(3)	8855(2)	2201(1)	21(1)
C(34)	6478(3)	9420(2)	1765(1)	23(1)
C(35)	6476(3)	10105(2)	2060(1)	21(1)
C(36)	6369(3)	10819(2)	1848(1)	24(1)
C(37)	6407(3)	11386(2)	2166(2)	26(1)
C(38)	6564(3)	11258(2)	2696(2)	21(1)
C(39)	6565(3)	11845(2)	3034(2)	26(1)
C(40)	6664(3)	11727(2)	3554(2)	27(1)
C(41)	6824(3)	11013(2)	3755(2)	23(1)
C(42)	6866(3)	10423(2)	3431(1)	20(1)
C(43)	6690(2)	10537(2)	2906(1)	17(1)
C(44)	6616(2)	9972(2)	2570(1)	17(1)
C(45)	6692(3)	9165(2)	2696(1)	18(1)
C(46)	4062(3)	8781(2)	3183(1)	16(1)
C(47)	4032(3)	7988(2)	3042(2)	26(1)
C(48)	3209(3)	9353(2)	2964(1)	24(1)
C(49)	3835(3)	8830(2)	3785(1)	19(1)
C(50)	2716(3)	8889(2)	4592(1)	20(1)
C(51)	2280(3)	8248(2)	4820(1)	23(1)
C(52)	3231(3)	7683(2)	4927(1)	20(1)
C(53)	3271(3)	6957(2)	5096(1)	21(1)
C(54)	4195(3)	6503(2)	5179(1)	21(1)
C(55)	5127(3)	6766(2)	5122(1)	19(1)
C(56)	6088(3)	6304(2)	5223(1)	23(1)
C(57)	6959(3)	6559(2)	5182(2)	28(1)
C(58)	6923(3)	7303(2)	5048(1)	25(1)
C(59)	6002(3)	7757(2)	4942(1)	23(1)
C(60)	5091(3)	7504(2)	4966(1)	18(1)
C(61)	4122(3)	7946(2)	4853(1)	17(1)
C(62)	3889(3)	8728(2)	4654(1)	18(1)
Cu(3)	632(1)	7628(1)	7046(1)	12(1)
Cl(5)	1147(1)	8220(1)	6318(1)	19(1)
Cl(6)	−1074(1)	7793(1)	7024(1)	18(1)
O(5)	3478(2)	6256(1)	7250(1)	21(1)
O(6)	495(2)	7247(1)	8652(1)	20(1)
N(5)	1988(2)	6861(1)	6999(1)	14(1)
N(6)	395(2)	7676(1)	7837(1)	14(1)
C(63)	2464(2)	6654(2)	7382(1)	14(1)
C(64)	3802(3)	6235(2)	6666(1)	19(1)
C(65)	4264(3)	5445(2)	6447(1)	20(1)
C(66)	3386(3)	5279(2)	6232(1)	17(1)
C(67)	3404(3)	4597(2)	6009(1)	19(1)
		...		

Table A27 continued...

	x	y	z	U(eq)
C(68)	2521(3)	4518(2)	5848(1)	19(1)
C(69)	1607(3)	5127(2)	5882(1)	16(1)
C(70)	694(3)	5046(2)	5720(1)	20(1)
C(71)	−172(3)	5641(2)	5741(1)	22(1)
C(72)	−144(3)	6343(2)	5904(1)	22(1)
C(73)	738(3)	6439(2)	6059(1)	19(1)
C(74)	1627(2)	5831(2)	6070(1)	15(1)
C(75)	2533(2)	5884(2)	6259(1)	15(1)
C(76)	2738(2)	6553(2)	6490(1)	15(1)
C(77)	2037(2)	6733(2)	7980(1)	15(1)
C(78)	2757(3)	7070(2)	8248(1)	20(1)
C(79)	2064(3)	5952(2)	8181(2)	22(1)
C(80)	932(3)	7240(2)	8129(1)	15(1)
C(81)	−601(3)	7719(2)	8728(1)	19(1)
C(82)	−837(3)	8293(2)	9176(1)	23(1)
C(83)	−670(3)	8975(2)	8884(1)	19(1)
C(84)	−747(3)	9671(2)	9121(1)	26(1)
C(85)	−669(3)	10253(2)	8809(2)	25(1)
C(86)	−501(3)	10182(2)	8242(2)	21(1)
C(87)	−456(3)	10799(2)	7919(2)	25(1)
C(88)	−312(3)	10729(2)	7370(2)	26(1)
C(89)	−243(3)	10041(2)	7135(2)	23(1)
C(90)	−298(3)	9438(2)	7441(1)	19(1)
C(91)	−423(2)	9486(2)	8001(1)	15(1)
C(92)	−516(2)	8887(2)	8343(1)	15(1)
C(93)	−583(3)	8123(2)	8196(1)	16(1)
Cu(4)	632(1)	2654(1)	7045(1)	13(1)
Cl(7)	1070(1)	3278(1)	6324(1)	21(1)
Cl(8)	−1080(1)	2799(1)	7054(1)	19(1)
O(7)	3560(2)	1366(1)	7200(1)	20(1)
O(8)	611(2)	2220(1)	8635(1)	20(1)
N(7)	2022(2)	1923(1)	6972(1)	15(1)
N(8)	451(2)	2682(1)	7834(1)	14(1)
C(94)	2532(2)	1722(2)	7344(1)	15(1)
C(95)	3846(3)	1347(2)	6611(1)	21(1)
C(96)	4317(3)	551(2)	6405(1)	22(1)
C(97)	3425(3)	356(2)	6218(1)	17(1)
C(98)	3435(3)	−342(2)	6028(1)	20(1)
C(99)	2551(3)	−432(2)	5877(1)	20(1)
C(100)	1647(3)	170(2)	5885(1)	18(1)
C(101)	743(3)	73(2)	5724(1)	22(1)
C(102)	−120(3)	667(2)	5722(1)	24(1)
C(103)	−92(3)	1380(2)	5866(1)	24(1)
C(104)	773(3)	1493(2)	6024(1)	20(1)
C(105)	1659(3)	887(2)	6051(1)	16(1)
C(106)	2571(3)	956(2)	6232(1)	15(1)
		...		

Table A27 continued...

	x	y	z	U(eq)
C(107)	2762(2)	1640(2)	6451(1)	17(1)
C(108)	2118(2)	1735(2)	7943(1)	15(1)
C(109)	2115(3)	935(2)	8088(1)	20(1)
C(110)	2845(3)	2011(2)	8243(1)	19(1)
C(111)	1018(3)	2238(2)	8111(1)	15(1)
C(112)	−503(3)	2667(2)	8728(1)	19(1)
C(113)	−730(3)	3210(2)	9197(1)	21(1)
C(114)	−580(3)	3908(2)	8930(1)	19(1)
C(115)	−631(3)	4578(2)	9189(1)	25(1)
C(116)	−579(3)	5186(2)	8890(2)	25(1)
C(117)	−449(3)	5159(2)	8327(2)	20(1)
C(118)	−424(3)	5796(2)	8020(2)	24(1)
C(119)	−299(3)	5755(2)	7475(2)	27(1)
C(120)	−213(3)	5084(2)	7213(2)	22(1)
C(121)	−264(3)	4465(2)	7502(1)	18(1)
C(122)	−371(2)	4477(2)	8057(1)	16(1)
C(123)	−454(2)	3858(2)	8382(1)	16(1)
C(124)	−516(2)	3104(2)	8215(1)	16(1)
Cu(5)	5547(1)	7168(1)	8804(1)	20(1)
Cl(9)	6562(1)	7958(1)	8780(1)	25(1)
Cl(10)	4077(1)	7745(1)	9385(1)	30(1)
O(9)	6817(2)	6058(1)	7346(1)	22(1)
O(10)	5070(2)	5094(1)	8895(1)	29(1)
N(9)	6030(2)	6843(2)	8047(1)	18(1)
N(10)	5467(2)	6154(2)	9010(1)	19(1)
C(125)	6285(3)	6182(2)	7852(1)	17(1)
C(126)	7097(3)	6751(2)	7168(1)	20(1)
C(127)	6773(3)	6955(2)	6633(2)	30(1)
C(128)	5685(3)	7445(2)	6798(2)	27(1)
C(129)	4922(4)	7687(2)	6473(2)	34(1)
C(130)	3937(4)	8104(2)	6696(2)	40(1)
C(131)	3676(3)	8371(2)	7231(2)	34(1)
C(132)	2663(3)	8823(2)	7460(2)	40(1)
C(133)	2430(3)	9089(2)	7978(2)	44(1)
C(134)	3215(3)	8929(2)	8284(2)	36(1)
C(135)	4210(3)	8481(2)	8081(2)	27(1)
C(136)	4468(3)	8173(2)	7554(2)	24(1)
C(137)	5442(3)	7681(2)	7324(2)	22(1)
C(138)	6358(3)	7316(2)	7595(1)	19(1)
C(139)	6042(2)	5496(2)	8110(1)	15(1)
C(140)	7094(3)	4910(2)	8118(2)	22(1)
C(141)	5390(3)	5197(2)	7786(2)	24(1)
C(142)	5482(2)	5635(2)	8690(1)	18(1)
C(143)	4591(3)	5292(2)	9460(2)	34(1)
C(144)	5039(4)	4656(2)	9809(2)	42(1)
C(145)	5929(4)	4858(3)	9963(2)	44(1)
		...		

Table A27 continued...

	x	y	z	U(eq)
C(146)	6715(5)	4420(3)	10242(2)	60(2)
C(147)	7452(4)	4718(3)	10369(2)	49(1)
C(148)	7494(4)	5440(3)	10251(2)	48(1)
C(149)	8296(4)	5727(3)	10389(2)	51(1)
C(150)	8343(4)	6418(4)	10257(2)	57(2)
C(151)	7605(4)	6883(3)	9973(2)	49(1)
C(152)	6825(3)	6608(3)	9844(2)	36(1)
C(153)	6753(3)	5896(3)	9972(1)	34(1)
C(154)	5957(3)	5569(2)	9840(2)	34(1)
C(155)	5064(3)	5930(2)	9560(1)	25(1)
Cu(6)	5708(1)	2037(1)	8906(1)	21(1)
Cl(11)	6857(1)	2719(1)	8901(1)	34(1)
Cl(12)	4464(1)	2623(1)	9594(1)	31(1)
O(11)	6726(2)	1128(1)	7368(1)	22(1)
O(12)	4842(2)	109(1)	8827(1)	23(1)
N(11)	6049(2)	1828(2)	8123(1)	18(1)
N(12)	5454(2)	1045(2)	9040(1)	19(1)
C(156)	6250(2)	1195(2)	7885(1)	17(1)
C(157)	7029(3)	1825(2)	7226(1)	23(1)
C(158)	6639(3)	2119(2)	6726(2)	31(1)
C(159)	5557(3)	2614(2)	6944(2)	28(1)
C(160)	4747(4)	2915(2)	6658(2)	34(1)
C(161)	3783(3)	3324(2)	6935(2)	34(1)
C(162)	3595(3)	3512(2)	7489(2)	31(1)
C(163)	2599(3)	3938(2)	7776(2)	41(1)
C(164)	2438(3)	4096(2)	8304(2)	40(1)
C(165)	3282(3)	3870(2)	8578(2)	34(1)
C(166)	4259(3)	3454(2)	8312(2)	28(1)
C(167)	4442(3)	3246(2)	7768(2)	28(1)
C(168)	5401(3)	2775(2)	7479(2)	22(1)
C(169)	6354(3)	2344(2)	7698(1)	21(1)
C(170)	6009(2)	494(2)	8108(1)	15(1)
C(171)	5422(3)	199(2)	7741(1)	23(1)
C(172)	7060(3)	−88(2)	8127(1)	21(1)
C(173)	5400(2)	605(2)	8676(1)	17(1)
C(174)	4344(3)	264(2)	9400(2)	25(1)
C(175)	4588(3)	−453(2)	9701(2)	31(1)
C(176)	5525(3)	−405(2)	9906(1)	29(1)
C(177)	6138(4)	−983(2)	10173(2)	35(1)
C(178)	6952(4)	−849(2)	10361(2)	37(1)
C(179)	7216(3)	−170(2)	10304(1)	31(1)
C(180)	8044(4)	−20(3)	10507(2)	39(1)
C(181)	8301(4)	636(3)	10431(2)	35(1)
C(182)	7733(4)	1194(3)	10156(2)	42(1)
C(183)	6892(3)	1078(2)	9960(2)	33(1)
C(184)	6608(3)	410(2)	10028(1)	30(1)
		...		

Table A27 continued...

	x	y	z	U(eq)
C(185)	5753(3)	266(2)	9836(1)	27(1)
C(186)	4962(3)	785(2)	9563(1)	23(1)
Cu(7)	2279(1)	5962(1)	1977(1)	16(1)
Cl(13)	4034(1)	5598(1)	1700(1)	23(1)
Cl(14)	2069(1)	7179(1)	1876(1)	23(1)
O(13)	1490(2)	4025(1)	1757(1)	26(1)
O(14)	−610(2)	5976(1)	2956(1)	22(1)
N(13)	2028(2)	5062(2)	1696(1)	17(1)
N(14)	1021(2)	6057(1)	2572(1)	17(1)
C(187)	1360(3)	4715(2)	1927(1)	18(1)
C(188)	2489(3)	3825(2)	1354(2)	26(1)
C(189)	2278(3)	3529(2)	849(2)	31(1)
C(190)	1985(3)	4206(2)	540(2)	26(1)
C(191)	1486(3)	4289(2)	102(2)	33(1)
C(192)	1292(3)	4950(2)	−140(2)	33(1)
C(193)	1610(3)	5556(2)	31(1)	24(1)
C(194)	1435(3)	6245(2)	−225(2)	31(1)
C(195)	1804(3)	6801(2)	−78(2)	29(1)
C(196)	2365(3)	6706(2)	336(2)	24(1)
C(197)	2514(3)	6063(2)	610(1)	18(1)
C(198)	2131(3)	5474(2)	465(1)	18(1)
C(199)	2268(3)	4785(2)	727(1)	19(1)
C(200)	2705(3)	4586(2)	1228(1)	20(1)
C(201)	351(3)	5000(2)	2330(1)	21(1)
C(202)	−543(3)	5141(3)	2009(2)	33(1)
C(203)	185(4)	4433(2)	2762(2)	36(1)
C(204)	307(3)	5713(2)	2607(1)	19(1)
C(205)	−560(3)	6664(2)	3194(1)	22(1)
C(206)	−780(3)	6612(2)	3804(1)	22(1)
C(207)	306(3)	6400(2)	3925(1)	20(1)
C(208)	554(3)	6177(2)	4422(1)	20(1)
C(209)	1590(3)	5980(2)	4466(1)	21(1)
C(210)	2414(3)	6018(2)	4023(1)	19(1)
C(211)	3497(3)	5806(2)	4060(1)	23(1)
C(212)	4274(3)	5873(2)	3639(2)	27(1)
C(213)	4027(3)	6164(2)	3153(2)	23(1)
C(214)	2979(3)	6370(2)	3104(1)	19(1)
C(215)	2162(3)	6289(2)	3526(1)	17(1)
C(216)	1081(3)	6445(2)	3488(1)	17(1)
C(217)	617(3)	6661(2)	2998(1)	17(1)
Cu(8)	2092(1)	901(1)	1944(1)	19(1)
Cl(15)	3837(1)	511(1)	1689(1)	27(1)
Cl(16)	1849(1)	2122(1)	1853(1)	28(1)
O(15)	1214(2)	−976(1)	1636(1)	32(1)
O(16)	−782(2)	900(2)	2923(1)	26(1)
N(15)	1808(2)	29(2)	1628(1)	20(1)
		...		

Table A27 continued...

	x	y	z	U(eq)
N(16)	849(2)	984(2)	2541(1)	19(1)
C(218)	1131(3)	−315(2)	1846(1)	23(1)
C(219)	2186(3)	−1156(2)	1212(2)	28(1)
C(220)	1910(4)	−1361(2)	698(2)	37(1)
C(221)	1664(3)	−640(2)	419(2)	29(1)
C(222)	1205(4)	−484(3)	−33(2)	38(1)
C(223)	1106(3)	195(2)	−246(2)	34(1)
C(224)	1500(3)	732(2)	−41(1)	24(1)
C(225)	1450(3)	1419(2)	−284(2)	32(1)
C(226)	1913(3)	1909(2)	−110(2)	30(1)
C(227)	2444(3)	1742(2)	314(1)	24(1)
C(228)	2469(3)	1092(2)	576(1)	18(1)
C(229)	1991(3)	576(2)	409(1)	19(1)
C(230)	2023(3)	−121(2)	645(1)	21(1)
C(231)	2453(3)	−406(2)	1140(1)	21(1)
C(232)	163(3)	−56(2)	2283(2)	25(1)
C(233)	−789(3)	88(3)	1996(2)	37(1)
C(234)	97(4)	−660(2)	2700(2)	43(1)
C(235)	125(3)	640(2)	2568(1)	21(1)
C(236)	−726(3)	1576(2)	3170(1)	23(1)
C(237)	−927(3)	1504(2)	3779(1)	24(1)
C(238)	161(3)	1316(2)	3898(1)	19(1)
C(239)	422(3)	1120(2)	4397(1)	20(1)
C(240)	1459(3)	949(2)	4437(1)	22(1)
C(241)	2271(3)	999(2)	3996(1)	19(1)
C(242)	3350(3)	821(2)	4031(2)	24(1)
C(243)	4119(3)	897(2)	3613(2)	29(1)
C(244)	3854(3)	1171(2)	3124(2)	25(1)
C(245)	2812(3)	1344(2)	3071(1)	20(1)
C(246)	2000(3)	1248(2)	3498(1)	17(1)
C(247)	933(3)	1372(2)	3455(1)	18(1)
C(248)	453(3)	1578(2)	2969(1)	19(1)
C(1S)	9881(6)	7224(4)	1229(3)	29(2)
Cl(20)	9338(2)	7938(2)	835(1)	35(1)
Cl(21)	8946(2)	7091(2)	1796(1)	46(1)
C(1T)	9909(7)	7411(6)	1351(4)	29(2)
Cl(50)	9281(3)	8084(2)	953(2)	40(1)
Cl(51)	8998(2)	7284(2)	1923(1)	37(1)
C(2S)	8489(7)	9012(4)	4840(4)	41(2)
Cl(22)	9281(2)	8275(2)	5132(1)	62(1)
Cl(23)	9192(4)	9680(2)	4628(1)	66(1)
C(2T)	8789(13)	8956(7)	4603(9)	68(4)
Cl(52)	9569(5)	9574(3)	4561(2)	57(1)
Cl(53)	9454(4)	8111(2)	4817(2)	68(2)
C(3S)	7706(6)	9280(4)	6424(3)	16(1)
Cl(24)	6674(2)	8852(2)	6467(1)	41(1)

...

Table A27 continued...

	x	y	z	U(eq)
Cl(25)	7417(2)	10129(2)	6112(1)	25(1)
C(3R)	7877(13)	9142(8)	6183(12)	60(6)
Cl(54)	7434(4)	10129(3)	6252(2)	38(1)
Cl(55)	6803(4)	8768(3)	6163(3)	62(1)
C(3T)	8141(13)	9072(10)	6041(10)	61(6)
Cl(84)	7605(4)	9903(3)	6453(2)	53(1)
Cl(85)	7062(5)	8810(3)	5862(3)	71(1)
C(4S)	9819(4)	2271(3)	1127(2)	45(1)
Cl(26)	9502(3)	3141(2)	822(2)	36(1)
Cl(27)	8819(3)	2000(2)	1588(2)	41(1)
Cl(56)	9245(5)	2991(3)	769(2)	55(1)
Cl(57)	8935(4)	2138(3)	1773(2)	53(1)
Cl(86)	9516(4)	3257(3)	999(2)	52(1)
Cl(87)	8613(4)	2062(2)	1391(2)	46(1)
C(5S)	8930(6)	3970(4)	4482(3)	40(2)
Cl(28)	9543(2)	3104(1)	4701(1)	49(1)
Cl(29)	9659(3)	4620(2)	4536(2)	60(1)
C(5T)	8650(19)	4031(11)	4762(14)	121(10)
Cl(88)	9399(8)	3288(5)	5073(4)	132(3)
Cl(89)	9394(4)	4685(2)	4657(2)	43(1)
C(6S)	8174(5)	4048(3)	6059(2)	50(1)
Cl(30)	7142(3)	3772(2)	5862(2)	59(1)
Cl(31)	7548(4)	4913(3)	6404(2)	88(2)
Cl(60)	7079(5)	4014(4)	5740(3)	113(2)
Cl(61)	7743(2)	4803(1)	6503(1)	24(1)
C(7S)	4908(5)	7157(3)	1163(2)	50(1)
Cl(32)	5051(1)	7954(1)	1520(1)	55(1)
Cl(33)	4502(1)	7463(1)	589(1)	41(1)
C(8S)	5427(5)	2558(3)	787(2)	54(1)
Cl(34)	5340(1)	3252(1)	1236(1)	65(1)
Cl(35)	4623(1)	1991(1)	1068(1)	50(1)

Table A28: Bond lengths (Å) and angles (°) for $CuCl_2 \cdot$**2.97**

Cu(1)-N(2)	1.975(3)
Cu(1)-N(1)	1.977(3)
Cu(1)-Cl(1)	2.2239(8)
Cu(1)-Cl(2)	2.2352(9)
O(1)-C(1)	1.340(4)
O(1)-C(2)	1.464(4)
O(2)-C(18)	1.328(4)
O(2)-C(19)	1.466(4)
N(1)-C(1)	1.288(4)
N(1)-C(14)	1.496(4)

...

Table A28 continued...

N(2)-C(18)	1.293(4)
N(2)-C(31)	1.487(4)
C(1)-C(15)	1.496(4)
C(2)-C(3)	1.523(5)
C(2)-C(14)	1.544(5)
C(3)-C(4)	1.506(5)
C(4)-C(13)	1.374(5)
C(4)-C(5)	1.412(5)
C(5)-C(6)	1.363(6)
C(6)-C(7)	1.414(6)
C(7)-C(8)	1.418(5)
C(7)-C(12)	1.427(5)
C(8)-C(9)	1.371(6)
C(9)-C(10)	1.409(6)
C(10)-C(11)	1.387(5)
C(11)-C(12)	1.408(5)
C(12)-C(13)	1.423(5)
C(13)-C(14)	1.509(5)
C(15)-C(18)	1.507(4)
C(15)-C(17)	1.539(4)
C(15)-C(16)	1.557(4)
C(19)-C(20)	1.526(5)
C(19)-C(31)	1.547(4)
C(20)-C(21)	1.505(5)
C(21)-C(30)	1.376(4)
C(21)-C(22)	1.402(4)
C(22)-C(23)	1.363(5)
C(23)-C(24)	1.426(5)
C(24)-C(25)	1.417(5)
C(24)-C(29)	1.428(4)
C(25)-C(26)	1.355(5)
C(26)-C(27)	1.414(5)
C(27)-C(28)	1.374(5)
C(28)-C(29)	1.412(5)
C(29)-C(30)	1.431(5)
C(30)-C(31)	1.526(4)
Cu(2)-N(4)	1.978(3)
Cu(2)-N(3)	1.980(3)
Cu(2)-Cl(4)	2.2258(8)
Cu(2)-Cl(3)	2.2382(9)
O(3)-C(32)	1.336(4)
O(3)-C(33)	1.463(4)
O(4)-C(49)	1.324(4)
O(4)-C(50)	1.472(4)
N(3)-C(32)	1.282(4)
N(3)-C(45)	1.491(4)

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Table A28 continued...

N(4)-C(49)	1.294(4)
N(4)-C(62)	1.491(4)
C(32)-C(46)	1.505(4)
C(33)-C(34)	1.522(5)
C(33)-C(45)	1.543(4)
C(34)-C(35)	1.505(5)
C(35)-C(44)	1.365(4)
C(35)-C(36)	1.418(5)
C(36)-C(37)	1.372(6)
C(37)-C(38)	1.420(5)
C(38)-C(39)	1.418(5)
C(38)-C(43)	1.428(4)
C(39)-C(40)	1.369(6)
C(40)-C(41)	1.405(5)
C(41)-C(42)	1.381(5)
C(42)-C(43)	1.411(5)
C(43)-C(44)	1.417(4)
C(44)-C(45)	1.525(4)
C(46)-C(49)	1.503(4)
C(46)-C(48)	1.539(4)
C(46)-C(47)	1.553(4)
C(50)-C(51)	1.524(5)
C(50)-C(62)	1.560(5)
C(51)-C(52)	1.498(5)
C(52)-C(61)	1.381(5)
C(52)-C(53)	1.413(5)
C(53)-C(54)	1.359(5)
C(54)-C(55)	1.435(5)
C(55)-C(56)	1.419(5)
C(55)-C(60)	1.425(4)
C(56)-C(57)	1.355(6)
C(57)-C(58)	1.422(5)
C(58)-C(59)	1.378(5)
C(59)-C(60)	1.408(5)
C(60)-C(61)	1.428(5)
C(61)-C(62)	1.518(4)
Cu(3)-N(6)	1.980(3)
Cu(3)-N(5)	1.982(3)
Cu(3)-Cl(5)	2.2233(8)
Cu(3)-Cl(6)	2.2333(8)
O(5)-C(63)	1.342(4)
O(5)-C(64)	1.462(4)
O(6)-C(80)	1.342(4)
O(6)-C(81)	1.477(4)
N(5)-C(63)	1.277(4)
N(5)-C(76)	1.490(4)

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Table A28 continued...

N(6)-C(80)	1.277(4)
N(6)-C(93)	1.490(4)
C(63)-C(77)	1.511(4)
C(64)-C(65)	1.520(4)
C(64)-C(76)	1.548(4)
C(65)-C(66)	1.500(4)
C(66)-C(75)	1.374(4)
C(66)-C(67)	1.408(4)
C(67)-C(68)	1.372(5)
C(68)-C(69)	1.427(5)
C(69)-C(70)	1.413(5)
C(69)-C(74)	1.427(4)
C(70)-C(71)	1.375(5)
C(71)-C(72)	1.403(5)
C(72)-C(73)	1.376(5)
C(73)-C(74)	1.421(4)
C(74)-C(75)	1.423(4)
C(75)-C(76)	1.513(4)
C(77)-C(80)	1.510(4)
C(77)-C(79)	1.538(4)
C(77)-C(78)	1.552(4)
C(81)-C(82)	1.518(4)
C(81)-C(93)	1.539(4)
C(82)-C(83)	1.509(5)
C(83)-C(92)	1.364(4)
C(83)-C(84)	1.426(5)
C(84)-C(85)	1.351(5)
C(85)-C(86)	1.425(5)
C(86)-C(87)	1.414(5)
C(86)-C(91)	1.429(4)
C(87)-C(88)	1.381(6)
C(88)-C(89)	1.411(5)
C(89)-C(90)	1.370(5)
C(90)-C(91)	1.408(4)
C(91)-C(92)	1.423(4)
C(92)-C(93)	1.520(4)
Cu(4)-N(7)	1.977(3)
Cu(4)-N(8)	1.982(3)
Cu(4)-Cl(7)	2.2176(8)
Cu(4)-Cl(8)	2.2288(8)
O(7)-C(94)	1.339(4)
O(7)-C(95)	1.473(4)
O(8)-C(111)	1.339(4)
O(8)-C(112)	1.479(4)
N(7)-C(94)	1.277(4)
N(7)-C(107)	1.497(4)

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Table A28 continued...

N(8)-C(111)	1.280(4)
N(8)-C(124)	1.490(4)
C(94)-C(108)	1.513(4)
C(95)-C(96)	1.522(5)
C(95)-C(107)	1.547(4)
C(96)-C(97)	1.505(4)
C(97)-C(106)	1.372(4)
C(97)-C(98)	1.405(4)
C(98)-C(99)	1.369(5)
C(99)-C(100)	1.421(5)
C(100)-C(101)	1.410(5)
C(100)-C(105)	1.427(4)
C(101)-C(102)	1.380(5)
C(102)-C(103)	1.410(5)
C(103)-C(104)	1.369(5)
C(104)-C(105)	1.425(4)
C(105)-C(106)	1.428(4)
C(106)-C(107)	1.517(4)
C(108)-C(111)	1.506(4)
C(108)-C(109)	1.540(4)
C(108)-C(110)	1.550(4)
C(112)-C(113)	1.521(4)
C(112)-C(124)	1.532(4)
C(113)-C(114)	1.504(5)
C(114)-C(123)	1.377(4)
C(114)-C(115)	1.416(5)
C(115)-C(116)	1.369(5)
C(116)-C(117)	1.415(5)
C(117)-C(118)	1.418(5)
C(117)-C(122)	1.439(4)
C(118)-C(119)	1.372(6)
C(119)-C(120)	1.407(5)
C(120)-C(121)	1.372(5)
C(121)-C(122)	1.397(4)
C(122)-C(123)	1.427(4)
C(123)-C(124)	1.516(4)
Cu(5)-N(9)	1.965(3)
Cu(5)-N(10)	1.987(3)
Cu(5)-Cl(10)	2.2319(10)
Cu(5)-Cl(9)	2.2514(9)
O(9)-C(125)	1.333(4)
O(9)-C(126)	1.483(4)
O(10)-C(142)	1.327(4)
O(10)-C(143)	1.466(5)
N(9)-C(125)	1.282(4)
N(9)-C(138)	1.502(4)

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Table A28 continued...

N(10)-C(142)	1.281(4)
N(10)-C(155)	1.489(4)
C(125)-C(139)	1.512(4)
C(126)-C(127)	1.530(5)
C(126)-C(138)	1.532(5)
C(127)-C(128)	1.484(6)
C(128)-C(137)	1.372(5)
C(128)-C(129)	1.427(5)
C(129)-C(130)	1.356(7)
C(130)-C(131)	1.410(7)
C(131)-C(132)	1.410(6)
C(131)-C(136)	1.444(5)
C(132)-C(133)	1.371(8)
C(133)-C(134)	1.406(6)
C(134)-C(135)	1.377(5)
C(135)-C(136)	1.418(6)
C(136)-C(137)	1.404(5)
C(137)-C(138)	1.530(4)
C(139)-C(142)	1.509(4)
C(139)-C(141)	1.531(4)
C(139)-C(140)	1.547(4)
C(143)-C(144)	1.543(6)
C(143)-C(155)	1.543(6)
C(144)-C(145)	1.468(8)
C(145)-C(154)	1.373(6)
C(145)-C(146)	1.457(7)
C(146)-C(147)	1.351(9)
C(147)-C(148)	1.396(8)
C(148)-C(149)	1.426(8)
C(148)-C(153)	1.432(5)
C(149)-C(150)	1.348(9)
C(150)-C(151)	1.444(7)
C(151)-C(152)	1.378(7)
C(152)-C(153)	1.393(7)
C(153)-C(154)	1.458(7)
C(154)-C(155)	1.521(5)
Cu(6)-N(11)	1.982(3)
Cu(6)-N(12)	1.989(3)
Cu(6)-Cl(12)	2.2316(10)
Cu(6)-Cl(11)	2.2419(9)
O(11)-C(156)	1.335(4)
O(11)-C(157)	1.484(4)
O(12)-C(173)	1.342(4)
O(12)-C(174)	1.478(4)
N(11)-C(156)	1.286(4)
N(11)-C(169)	1.503(4)

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Table A28 continued...

N(12)-C(173)	1.285(4)
N(12)-C(186)	1.492(4)
C(156)-C(170)	1.507(4)
C(157)-C(158)	1.520(5)
C(157)-C(169)	1.536(5)
C(158)-C(159)	1.500(6)
C(159)-C(168)	1.367(5)
C(159)-C(160)	1.422(5)
C(160)-C(161)	1.370(7)
C(161)-C(162)	1.423(6)
C(162)-C(163)	1.420(6)
C(162)-C(167)	1.437(5)
C(163)-C(164)	1.349(7)
C(164)-C(165)	1.419(6)
C(165)-C(166)	1.378(6)
C(166)-C(167)	1.408(6)
C(167)-C(168)	1.418(5)
C(168)-C(169)	1.526(5)
C(170)-C(173)	1.500(4)
C(170)-C(171)	1.538(4)
C(170)-C(172)	1.548(4)
C(174)-C(175)	1.528(5)
C(174)-C(186)	1.550(5)
C(175)-C(176)	1.481(6)
C(176)-C(185)	1.372(5)
C(176)-C(177)	1.432(5)
C(177)-C(178)	1.359(7)
C(178)-C(179)	1.406(6)
C(179)-C(180)	1.411(6)
C(179)-C(184)	1.444(6)
C(180)-C(181)	1.362(7)
C(181)-C(182)	1.394(6)
C(182)-C(183)	1.392(6)
C(183)-C(184)	1.400(6)
C(184)-C(185)	1.423(6)
C(185)-C(186)	1.514(5)
Cu(7)-N(13)	1.985(3)
Cu(7)-N(14)	1.989(3)
Cu(7)-Cl(13)	2.2281(9)
Cu(7)-Cl(14)	2.2439(8)
O(13)-C(187)	1.333(4)
O(13)-C(188)	1.472(4)
O(14)-C(204)	1.336(4)
O(14)-C(205)	1.465(4)
N(13)-C(187)	1.281(4)
N(13)-C(200)	1.491(4)

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Table A28 continued...

N(14)-C(204)	1.274(4)
N(14)-C(217)	1.503(4)
C(187)-C(201)	1.494(5)
C(188)-C(189)	1.525(6)
C(188)-C(200)	1.543(4)
C(189)-C(190)	1.488(5)
C(190)-C(199)	1.367(5)
C(190)-C(191)	1.407(6)
C(191)-C(192)	1.363(6)
C(192)-C(193)	1.422(5)
C(193)-C(198)	1.415(5)
C(193)-C(194)	1.422(5)
C(194)-C(195)	1.357(6)
C(195)-C(196)	1.405(5)
C(196)-C(197)	1.372(4)
C(197)-C(198)	1.421(4)
C(198)-C(199)	1.429(4)
C(199)-C(200)	1.517(5)
C(201)-C(204)	1.511(5)
C(201)-C(203)	1.539(5)
C(201)-C(202)	1.552(5)
C(205)-C(206)	1.530(5)
C(205)-C(217)	1.546(5)
C(206)-C(207)	1.499(5)
C(207)-C(216)	1.374(5)
C(207)-C(208)	1.405(4)
C(208)-C(209)	1.366(5)
C(209)-C(210)	1.418(5)
C(210)-C(211)	1.422(5)
C(210)-C(215)	1.431(4)
C(211)-C(212)	1.358(6)
C(212)-C(213)	1.413(5)
C(213)-C(214)	1.386(5)
C(214)-C(215)	1.402(5)
C(215)-C(216)	1.422(4)
C(216)-C(217)	1.512(4)
Cu(8)-N(16)	1.982(3)
Cu(8)-N(15)	2.000(3)
Cu(8)-Cl(15)	2.2127(9)
Cu(8)-Cl(16)	2.2430(9)
O(15)-C(218)	1.334(4)
O(15)-C(219)	1.474(4)
O(16)-C(235)	1.335(4)
O(16)-C(236)	1.457(4)
N(15)-C(218)	1.276(4)
N(15)-C(231)	1.481(4)

...

Table A28 continued...

N(16)-C(235)	1.289(5)
N(16)-C(248)	1.491(4)
C(218)-C(232)	1.500(5)
C(219)-C(220)	1.521(6)
C(219)-C(231)	1.541(4)
C(220)-C(221)	1.507(6)
C(221)-C(230)	1.379(5)
C(221)-C(222)	1.409(6)
C(222)-C(223)	1.360(7)
C(223)-C(224)	1.411(5)
C(224)-C(225)	1.410(6)
C(224)-C(229)	1.430(5)
C(225)-C(226)	1.366(6)
C(226)-C(227)	1.402(5)
C(227)-C(228)	1.374(4)
C(228)-C(229)	1.410(5)
C(229)-C(230)	1.422(5)
C(230)-C(231)	1.527(5)
C(232)-C(235)	1.495(5)
C(232)-C(234)	1.545(5)
C(232)-C(233)	1.561(5)
C(236)-C(237)	1.534(5)
C(236)-C(248)	1.554(5)
C(237)-C(238)	1.500(4)
C(238)-C(247)	1.386(5)
C(238)-C(239)	1.407(4)
C(239)-C(240)	1.364(5)
C(240)-C(241)	1.412(5)
C(241)-C(242)	1.415(5)
C(241)-C(246)	1.432(4)
C(242)-C(243)	1.352(6)
C(243)-C(244)	1.418(6)
C(244)-C(245)	1.382(5)
C(245)-C(246)	1.413(5)
C(246)-C(247)	1.411(4)
C(247)-C(248)	1.515(4)
C(1S)-Cl(20)	1.753(7)
C(1S)-Cl(21)	1.764(7)
C(1T)-Cl(51)	1.753(8)
C(1T)-Cl(50)	1.754(8)
C(2S)-Cl(22)	1.766(7)
C(2S)-Cl(23)	1.766(8)
C(2T)-Cl(52)	1.739(12)
C(2T)-Cl(53)	1.742(12)
C(3S)-Cl(24)	1.753(7)
C(3S)-Cl(25)	1.755(7)

...

Table A28 continued...

C(3R)-Cl(55)	1.766(13)
C(3R)-Cl(54)	1.793(13)
C(3T)-Cl(85)	1.787(13)
C(3T)-Cl(84)	1.799(14)
C(4S)-Cl(56)	1.717(7)
C(4S)-Cl(87)	1.753(7)
C(4S)-Cl(27)	1.761(6)
C(4S)-Cl(26)	1.780(6)
C(4S)-Cl(86)	1.825(7)
C(4S)-Cl(57)	1.873(7)
C(5S)-Cl(28)	1.756(7)
C(5S)-Cl(29)	1.774(7)
C(5T)-Cl(89)	1.755(14)
C(5T)-Cl(88)	1.770(14)
C(6S)-Cl(61)	1.735(6)
C(6S)-Cl(30)	1.762(6)
C(6S)-Cl(31)	1.780(7)
C(6S)-Cl(60)	1.835(8)
C(7S)-Cl(33)	1.707(5)
C(7S)-Cl(32)	1.845(5)
C(8S)-Cl(34)	1.723(5)
C(8S)-Cl(35)	1.744(5)
N(2)-Cu(1)-N(1)	91.65(11)
N(2)-Cu(1)-Cl(1)	97.62(8)
N(1)-Cu(1)-Cl(1)	142.81(8)
N(2)-Cu(1)-Cl(2)	140.60(8)
N(1)-Cu(1)-Cl(2)	93.77(9)
Cl(1)-Cu(1)-Cl(2)	101.20(3)
C(1)-O(1)-C(2)	108.1(3)
C(18)-O(2)-C(19)	108.1(2)
C(1)-N(1)-C(14)	108.0(3)
C(1)-N(1)-Cu(1)	125.9(2)
C(14)-N(1)-Cu(1)	124.7(2)
C(18)-N(2)-C(31)	107.1(3)
C(18)-N(2)-Cu(1)	125.9(2)
C(31)-N(2)-Cu(1)	125.9(2)
N(1)-C(1)-O(1)	116.1(3)
N(1)-C(1)-C(15)	130.3(3)
O(1)-C(1)-C(15)	113.5(3)
O(1)-C(2)-C(3)	110.1(3)
O(1)-C(2)-C(14)	102.9(3)
C(3)-C(2)-C(14)	107.7(3)
C(4)-C(3)-C(2)	103.6(3)
C(13)-C(4)-C(5)	121.0(3)
C(13)-C(4)-C(3)	112.7(3)
C(5)-C(4)-C(3)	126.3(3)

...

Table A28 continued...

C(6)-C(5)-C(4)	119.5(3)
C(5)-C(6)-C(7)	121.1(3)
C(6)-C(7)-C(8)	121.3(3)
C(6)-C(7)-C(12)	120.0(3)
C(8)-C(7)-C(12)	118.7(4)
C(9)-C(8)-C(7)	120.7(3)
C(8)-C(9)-C(10)	120.6(4)
C(11)-C(10)-C(9)	119.8(4)
C(10)-C(11)-C(12)	120.6(3)
C(11)-C(12)-C(13)	123.3(3)
C(11)-C(12)-C(7)	119.3(3)
C(13)-C(12)-C(7)	117.4(3)
C(4)-C(13)-C(12)	120.9(3)
C(4)-C(13)-C(14)	110.2(3)
C(12)-C(13)-C(14)	128.9(3)
N(1)-C(14)-C(13)	113.6(3)
N(1)-C(14)-C(2)	102.9(3)
C(13)-C(14)-C(2)	104.4(3)
C(1)-C(15)-C(18)	112.8(3)
C(1)-C(15)-C(17)	107.6(3)
C(18)-C(15)-C(17)	110.2(3)
C(1)-C(15)-C(16)	110.2(3)
C(18)-C(15)-C(16)	106.0(3)
C(17)-C(15)-C(16)	110.0(3)
N(2)-C(18)-O(2)	117.2(3)
N(2)-C(18)-C(15)	129.8(3)
O(2)-C(18)-C(15)	112.9(3)
O(2)-C(19)-C(20)	108.9(3)
O(2)-C(19)-C(31)	102.6(2)
C(20)-C(19)-C(31)	108.4(3)
C(21)-C(20)-C(19)	104.0(3)
C(30)-C(21)-C(22)	121.1(3)
C(30)-C(21)-C(20)	112.4(3)
C(22)-C(21)-C(20)	126.5(3)
C(23)-C(22)-C(21)	120.0(3)
C(22)-C(23)-C(24)	120.7(3)
C(25)-C(24)-C(23)	121.6(3)
C(25)-C(24)-C(29)	118.6(3)
C(23)-C(24)-C(29)	119.8(3)
C(26)-C(25)-C(24)	121.3(3)
C(25)-C(26)-C(27)	120.4(3)
C(28)-C(27)-C(26)	119.9(3)
C(27)-C(28)-C(29)	121.0(3)
C(28)-C(29)-C(24)	118.7(3)
C(28)-C(29)-C(30)	123.9(3)
C(24)-C(29)-C(30)	117.4(3)

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Table A28 continued...

C(21)-C(30)-C(29)	120.7(3)
C(21)-C(30)-C(31)	110.8(3)
C(29)-C(30)-C(31)	128.4(3)
N(2)-C(31)-C(30)	113.0(3)
N(2)-C(31)-C(19)	103.9(2)
C(30)-C(31)-C(19)	103.6(3)
N(4)-Cu(2)-N(3)	91.70(11)
N(4)-Cu(2)-Cl(4)	96.97(8)
N(3)-Cu(2)-Cl(4)	143.18(8)
N(4)-Cu(2)-Cl(3)	141.75(8)
N(3)-Cu(2)-Cl(3)	93.78(8)
Cl(4)-Cu(2)-Cl(3)	100.90(3)
C(32)-O(3)-C(33)	107.5(3)
C(49)-O(4)-C(50)	108.2(2)
C(32)-N(3)-C(45)	107.3(3)
C(32)-N(3)-Cu(2)	126.0(2)
C(45)-N(3)-Cu(2)	125.5(2)
C(49)-N(4)-C(62)	107.0(3)
C(49)-N(4)-Cu(2)	125.8(2)
C(62)-N(4)-Cu(2)	125.8(2)
N(3)-C(32)-O(3)	117.1(3)
N(3)-C(32)-C(46)	130.2(3)
O(3)-C(32)-C(46)	112.7(3)
O(3)-C(33)-C(34)	110.3(3)
O(3)-C(33)-C(45)	102.7(2)
C(34)-C(33)-C(45)	107.9(3)
C(35)-C(34)-C(33)	103.6(3)
C(44)-C(35)-C(36)	121.4(3)
C(44)-C(35)-C(34)	112.6(3)
C(36)-C(35)-C(34)	126.0(3)
C(37)-C(36)-C(35)	118.9(3)
C(36)-C(37)-C(38)	120.6(3)
C(39)-C(38)-C(37)	121.1(3)
C(39)-C(38)-C(43)	118.4(3)
C(37)-C(38)-C(43)	120.5(3)
C(40)-C(39)-C(38)	121.0(3)
C(39)-C(40)-C(41)	120.6(3)
C(42)-C(41)-C(40)	120.0(3)
C(41)-C(42)-C(43)	120.5(3)
C(42)-C(43)-C(44)	123.7(3)
C(42)-C(43)-C(38)	119.3(3)
C(44)-C(43)-C(38)	117.0(3)
C(35)-C(44)-C(43)	121.5(3)
C(35)-C(44)-C(45)	110.5(3)
C(43)-C(44)-C(45)	128.0(3)
N(3)-C(45)-C(44)	113.2(3)
N(3)-C(45)-C(33)	103.2(3)
C(44)-C(45)-C(33)	103.5(3)
C(49)-C(46)-C(32)	113.2(3)
C(49)-C(46)-C(48)	110.8(3)
C(32)-C(46)-C(48)	108.3(3)
C(49)-C(46)-C(47)	105.1(3)
C(32)-C(46)-C(47)	109.4(3)
C(48)-C(46)-C(47)	110.0(3)
N(4)-C(49)-O(4)	117.6(3)
N(4)-C(49)-C(46)	129.0(3)
O(4)-C(49)-C(46)	113.2(3)
O(4)-C(50)-C(51)	108.6(3)
O(4)-C(50)-C(62)	102.2(2)
C(51)-C(50)-C(62)	108.2(3)
C(52)-C(51)-C(50)	104.1(3)
C(61)-C(52)-C(53)	120.6(3)
C(61)-C(52)-C(51)	112.7(3)
C(53)-C(52)-C(51)	126.6(3)
C(54)-C(53)-C(52)	120.2(3)
C(53)-C(54)-C(55)	120.7(3)
C(56)-C(55)-C(60)	119.1(3)
C(56)-C(55)-C(54)	121.2(3)
C(60)-C(55)-C(54)	119.8(3)
C(57)-C(56)-C(55)	121.0(3)
C(56)-C(57)-C(58)	120.6(3)
C(59)-C(58)-C(57)	119.2(3)
C(58)-C(59)-C(60)	121.7(3)
C(59)-C(60)-C(55)	118.4(3)
C(59)-C(60)-C(61)	124.0(3)
C(55)-C(60)-C(61)	117.6(3)
C(52)-C(61)-C(60)	121.0(3)
C(52)-C(61)-C(62)	110.7(3)
C(60)-C(61)-C(62)	128.3(3)
N(4)-C(62)-C(61)	113.1(3)
N(4)-C(62)-C(50)	103.7(3)
C(61)-C(62)-C(50)	103.6(3)
N(6)-Cu(3)-N(5)	91.10(11)
N(6)-Cu(3)-Cl(5)	142.54(8)
N(5)-Cu(3)-Cl(5)	96.85(8)
N(6)-Cu(3)-Cl(6)	95.15(8)
N(5)-Cu(3)-Cl(6)	142.95(8)
Cl(5)-Cu(3)-Cl(6)	99.96(3)
C(63)-O(5)-C(64)	107.7(2)
C(80)-O(6)-C(81)	107.0(2)
C(63)-N(5)-C(76)	107.8(3)
C(63)-N(5)-Cu(3)	126.3(2)

Table A28 continued...

C(76)-N(5)-Cu(3)	124.70(19)
C(80)-N(6)-C(93)	107.5(3)
C(80)-N(6)-Cu(3)	126.7(2)
C(93)-N(6)-Cu(3)	124.53(19)
N(5)-C(63)-O(5)	117.0(3)
N(5)-C(63)-C(77)	129.8(3)
O(5)-C(63)-C(77)	113.0(3)
O(5)-C(64)-C(65)	111.1(3)
O(5)-C(64)-C(76)	102.8(2)
C(65)-C(64)-C(76)	108.5(3)
C(66)-C(65)-C(64)	103.7(3)
C(75)-C(66)-C(67)	121.6(3)
C(75)-C(66)-C(65)	112.6(3)
C(67)-C(66)-C(65)	125.8(3)
C(68)-C(67)-C(66)	119.2(3)
C(67)-C(68)-C(69)	121.0(3)
C(70)-C(69)-C(74)	119.6(3)
C(70)-C(69)-C(68)	121.1(3)
C(74)-C(69)-C(68)	119.3(3)
C(71)-C(70)-C(69)	120.5(3)
C(70)-C(71)-C(72)	120.4(3)
C(73)-C(72)-C(71)	120.3(3)
C(72)-C(73)-C(74)	121.0(3)
C(73)-C(74)-C(75)	123.8(3)
C(73)-C(74)-C(69)	118.1(3)
C(75)-C(74)-C(69)	118.2(3)
C(66)-C(75)-C(74)	120.5(3)
C(66)-C(75)-C(76)	110.9(3)
C(74)-C(75)-C(76)	128.6(3)
N(5)-C(76)-C(75)	114.4(3)
N(5)-C(76)-C(64)	103.3(2)
C(75)-C(76)-C(64)	103.3(2)
C(80)-C(77)-C(63)	112.8(2)
C(80)-C(77)-C(79)	111.1(3)
C(63)-C(77)-C(79)	106.7(3)
C(80)-C(77)-C(78)	106.8(3)
C(63)-C(77)-C(78)	109.6(3)
C(79)-C(77)-C(78)	109.8(3)
N(6)-C(80)-O(6)	117.1(3)
N(6)-C(80)-C(77)	129.4(3)
O(6)-C(80)-C(77)	113.4(3)
O(6)-C(81)-C(82)	111.3(3)
O(6)-C(81)-C(93)	102.3(2)
C(82)-C(81)-C(93)	108.0(3)
C(83)-C(82)-C(81)	103.4(3)
C(92)-C(83)-C(84)	120.7(3)

...

Table A28 continued...

C(92)-C(83)-C(82)	112.6(3)
C(84)-C(83)-C(82)	126.5(3)
C(85)-C(84)-C(83)	120.0(3)
C(84)-C(85)-C(86)	121.0(3)
C(87)-C(86)-C(85)	120.7(3)
C(87)-C(86)-C(91)	119.9(3)
C(85)-C(86)-C(91)	119.3(3)
C(88)-C(87)-C(86)	120.4(3)
C(87)-C(88)-C(89)	119.3(3)
C(90)-C(89)-C(88)	121.2(3)
C(89)-C(90)-C(91)	120.9(3)
C(90)-C(91)-C(92)	123.7(3)
C(90)-C(91)-C(86)	118.2(3)
C(92)-C(91)-C(86)	118.1(3)
C(83)-C(92)-C(91)	120.9(3)
C(83)-C(92)-C(93)	110.4(3)
C(91)-C(92)-C(93)	128.4(3)
N(6)-C(93)-C(92)	113.8(3)
N(6)-C(93)-C(81)	103.4(2)
C(92)-C(93)-C(81)	103.5(2)
N(7)-Cu(4)-N(8)	90.77(11)
N(7)-Cu(4)-Cl(7)	96.61(8)
N(8)-Cu(4)-Cl(7)	142.15(8)
N(7)-Cu(4)-Cl(8)	144.40(8)
N(8)-Cu(4)-Cl(8)	95.09(8)
Cl(7)-Cu(4)-Cl(8)	99.90(3)
C(94)-O(7)-C(95)	107.2(2)
C(111)-O(8)-C(112)	106.9(2)
C(94)-N(7)-C(107)	107.6(3)
C(94)-N(7)-Cu(4)	126.3(2)
C(107)-N(7)-Cu(4)	124.80(19)
C(111)-N(8)-C(124)	107.0(3)
C(111)-N(8)-Cu(4)	126.5(2)
C(124)-N(8)-Cu(4)	124.95(19)
N(7)-C(94)-O(7)	117.7(3)
N(7)-C(94)-C(108)	129.3(3)
O(7)-C(94)-C(108)	112.5(3)
O(7)-C(95)-C(96)	109.4(3)
O(7)-C(95)-C(107)	103.1(2)
C(96)-C(95)-C(107)	108.6(3)
C(97)-C(96)-C(95)	103.8(3)
C(106)-C(97)-C(98)	121.7(3)
C(106)-C(97)-C(96)	112.3(3)
C(98)-C(97)-C(96)	126.0(3)
C(99)-C(98)-C(97)	119.0(3)
C(98)-C(99)-C(100)	121.5(3)

...

Table A28 continued...

C(101)-C(100)-C(99)	121.1(3)
C(101)-C(100)-C(105)	119.5(3)
C(99)-C(100)-C(105)	119.4(3)
C(102)-C(101)-C(100)	120.4(3)
C(101)-C(102)-C(103)	120.1(3)
C(104)-C(103)-C(102)	120.8(3)
C(103)-C(104)-C(105)	120.4(3)
C(104)-C(105)-C(100)	118.6(3)
C(104)-C(105)-C(106)	123.6(3)
C(100)-C(105)-C(106)	117.8(3)
C(97)-C(106)-C(105)	120.6(3)
C(97)-C(106)-C(107)	111.2(3)
C(105)-C(106)-C(107)	128.3(3)
N(7)-C(107)-C(106)	112.8(3)
N(7)-C(107)-C(95)	103.2(2)
C(106)-C(107)-C(95)	103.3(3)
C(111)-C(108)-C(94)	112.2(2)
C(111)-C(108)-C(109)	110.1(3)
C(94)-C(108)-C(109)	106.3(3)
C(111)-C(108)-C(110)	107.4(3)
C(94)-C(108)-C(110)	110.6(3)
C(109)-C(108)-C(110)	110.2(3)
N(8)-C(111)-O(8)	117.1(3)
N(8)-C(111)-C(108)	129.8(3)
O(8)-C(111)-C(108)	113.1(3)
O(8)-C(112)-C(113)	110.0(3)
O(8)-C(112)-C(124)	101.9(2)
C(113)-C(112)-C(124)	108.2(3)
C(114)-C(113)-C(112)	103.2(3)
C(123)-C(114)-C(115)	121.0(3)
C(123)-C(114)-C(113)	112.5(3)
C(115)-C(114)-C(113)	126.4(3)
C(116)-C(115)-C(114)	119.1(3)
C(115)-C(116)-C(117)	121.7(3)
C(116)-C(117)-C(118)	121.5(3)
C(116)-C(117)-C(122)	119.6(3)
C(118)-C(117)-C(122)	118.9(3)
C(119)-C(118)-C(117)	120.3(3)
C(118)-C(119)-C(120)	120.5(3)
C(121)-C(120)-C(119)	120.2(3)
C(120)-C(121)-C(122)	121.3(3)
C(121)-C(122)-C(123)	124.0(3)
C(121)-C(122)-C(117)	118.7(3)
C(123)-C(122)-C(117)	117.2(3)
C(114)-C(123)-C(122)	121.3(3)
C(114)-C(123)-C(124)	110.1(3)
...	

Table A28 continued...

C(122)-C(123)-C(124)	128.4(3)
N(8)-C(124)-C(123)	113.8(3)
N(8)-C(124)-C(112)	103.6(2)
C(123)-C(124)-C(112)	103.7(2)
N(9)-Cu(5)-N(10)	90.59(12)
N(9)-Cu(5)-Cl(10)	140.46(8)
N(10)-Cu(5)-Cl(10)	95.55(9)
N(9)-Cu(5)-Cl(9)	96.51(9)
N(10)-Cu(5)-Cl(9)	142.50(9)
Cl(10)-Cu(5)-Cl(9)	101.77(4)
C(125)-O(9)-C(126)	106.6(2)
C(142)-O(10)-C(143)	107.4(3)
C(125)-N(9)-C(138)	106.5(3)
C(125)-N(9)-Cu(5)	127.5(2)
C(138)-N(9)-Cu(5)	125.2(2)
C(142)-N(10)-C(155)	106.5(3)
C(142)-N(10)-Cu(5)	125.6(2)
C(155)-N(10)-Cu(5)	125.5(2)
N(9)-C(125)-O(9)	117.8(3)
N(9)-C(125)-C(139)	129.4(3)
O(9)-C(125)-C(139)	112.8(3)
O(9)-C(126)-C(127)	108.9(3)
O(9)-C(126)-C(138)	102.3(3)
C(127)-C(126)-C(138)	107.8(3)
C(128)-C(127)-C(126)	103.0(3)
C(137)-C(128)-C(129)	119.7(4)
C(137)-C(128)-C(127)	113.0(3)
C(129)-C(128)-C(127)	127.3(4)
C(130)-C(129)-C(128)	119.7(4)
C(129)-C(130)-C(131)	121.6(4)
C(132)-C(131)-C(130)	121.8(4)
C(132)-C(131)-C(136)	119.2(4)
C(130)-C(131)-C(136)	119.0(4)
C(133)-C(132)-C(131)	120.9(4)
C(132)-C(133)-C(134)	120.0(4)
C(135)-C(134)-C(133)	121.1(5)
C(134)-C(135)-C(136)	120.4(4)
C(137)-C(136)-C(135)	124.2(3)
C(137)-C(136)-C(131)	117.6(4)
C(135)-C(136)-C(131)	118.2(4)
C(128)-C(137)-C(136)	122.0(3)
C(128)-C(137)-C(138)	109.9(3)
C(136)-C(137)-C(138)	128.2(3)
N(9)-C(138)-C(137)	112.2(3)
N(9)-C(138)-C(126)	103.3(2)
C(137)-C(138)-C(126)	103.1(3)
...	

Table A28 continued...

C(142)-C(139)-C(125)	112.3(3)
C(142)-C(139)-C(141)	111.3(3)
C(125)-C(139)-C(141)	109.1(3)
C(142)-C(139)-C(140)	105.0(3)
C(125)-C(139)-C(140)	109.2(3)
C(141)-C(139)-C(140)	110.0(3)
N(10)-C(142)-O(10)	117.6(3)
N(10)-C(142)-C(139)	128.3(3)
O(10)-C(142)-C(139)	113.6(3)
O(10)-C(143)-C(144)	109.3(3)
O(10)-C(143)-C(155)	102.0(3)
C(144)-C(143)-C(155)	106.2(4)
C(145)-C(144)-C(143)	104.6(4)
C(154)-C(145)-C(146)	118.6(5)
C(154)-C(145)-C(144)	112.8(4)
C(146)-C(145)-C(144)	128.5(5)
C(147)-C(146)-C(145)	119.7(5)
C(146)-C(147)-C(148)	122.8(5)
C(147)-C(148)-C(149)	120.7(4)
C(147)-C(148)-C(153)	120.3(5)
C(149)-C(148)-C(153)	119.0(5)
C(150)-C(149)-C(148)	119.8(4)
C(149)-C(150)-C(151)	121.8(5)
C(152)-C(151)-C(150)	118.3(6)
C(151)-C(152)-C(153)	121.5(4)
C(152)-C(153)-C(148)	119.5(5)
C(152)-C(153)-C(154)	124.2(4)
C(148)-C(153)-C(154)	116.3(4)
C(145)-C(154)-C(153)	122.3(4)
C(145)-C(154)-C(155)	110.2(4)
C(153)-C(154)-C(155)	127.5(4)
N(10)-C(155)-C(154)	112.2(3)
N(10)-C(155)-C(143)	103.4(3)
C(154)-C(155)-C(143)	103.9(3)
N(11)-Cu(6)-N(12)	90.54(11)
N(11)-Cu(6)-Cl(12)	144.77(9)
N(12)-Cu(6)-Cl(12)	96.21(9)
N(11)-Cu(6)-Cl(11)	96.36(8)
N(12)-Cu(6)-Cl(11)	144.97(9)
Cl(12)-Cu(6)-Cl(11)	97.58(4)
C(156)-O(11)-C(157)	106.9(3)
C(173)-O(12)-C(174)	107.1(3)
C(156)-N(11)-C(169)	106.1(3)
C(156)-N(11)-Cu(6)	126.9(2)
C(169)-N(11)-Cu(6)	125.8(2)
C(173)-N(12)-C(186)	106.6(3)
...	

Table A28 continued...

C(173)-N(12)-Cu(6)	124.5(2)
C(186)-N(12)-Cu(6)	126.2(2)
N(11)-C(156)-O(11)	117.9(3)
N(11)-C(156)-C(170)	128.8(3)
O(11)-C(156)-C(170)	113.4(3)
O(11)-C(157)-C(158)	109.1(3)
O(11)-C(157)-C(169)	101.9(3)
C(158)-C(157)-C(169)	107.4(3)
C(159)-C(158)-C(157)	103.3(3)
C(168)-C(159)-C(160)	120.4(4)
C(168)-C(159)-C(158)	112.2(3)
C(160)-C(159)-C(158)	127.3(4)
C(161)-C(160)-C(159)	118.8(4)
C(160)-C(161)-C(162)	122.2(4)
C(163)-C(162)-C(161)	122.4(4)
C(163)-C(162)-C(167)	119.2(4)
C(161)-C(162)-C(167)	118.5(4)
C(164)-C(163)-C(162)	121.0(4)
C(163)-C(164)-C(165)	120.4(4)
C(166)-C(165)-C(164)	120.0(4)
C(165)-C(166)-C(167)	121.2(4)
C(166)-C(167)-C(168)	124.2(3)
C(166)-C(167)-C(162)	118.0(4)
C(168)-C(167)-C(162)	117.7(4)
C(159)-C(168)-C(167)	122.0(3)
C(159)-C(168)-C(169)	110.1(3)
C(167)-C(168)-C(169)	127.8(3)
N(11)-C(169)-C(168)	111.7(3)
N(11)-C(169)-C(157)	103.7(3)
C(168)-C(169)-C(157)	103.4(3)
C(173)-C(170)-C(156)	111.9(3)
C(173)-C(170)-C(171)	112.1(3)
C(156)-C(170)-C(171)	109.0(3)
C(173)-C(170)-C(172)	105.2(2)
C(156)-C(170)-C(172)	109.3(3)
C(171)-C(170)-C(172)	109.2(3)
N(12)-C(173)-O(12)	117.6(3)
N(12)-C(173)-C(170)	128.1(3)
O(12)-C(173)-C(170)	113.7(3)
O(12)-C(174)-C(175)	108.8(3)
O(12)-C(174)-C(186)	101.8(3)
C(175)-C(174)-C(186)	109.0(3)
C(176)-C(175)-C(174)	102.2(3)
C(185)-C(176)-C(177)	121.2(4)
C(185)-C(176)-C(175)	114.0(3)
C(177)-C(176)-C(175)	124.8(4)
...	

Table A28 continued...

C(178)-C(177)-C(176)	118.3(4)
C(177)-C(178)-C(179)	122.9(4)
C(178)-C(179)-C(180)	123.3(4)
C(178)-C(179)-C(184)	118.9(4)
C(180)-C(179)-C(184)	117.8(4)
C(181)-C(180)-C(179)	121.9(4)
C(180)-C(181)-C(182)	120.7(4)
C(183)-C(182)-C(181)	119.4(5)
C(182)-C(183)-C(184)	121.5(4)
C(183)-C(184)-C(185)	123.5(4)
C(183)-C(184)-C(179)	118.6(4)
C(185)-C(184)-C(179)	117.9(4)
C(176)-C(185)-C(184)	120.8(4)
C(176)-C(185)-C(186)	110.6(3)
C(184)-C(185)-C(186)	128.5(4)
N(12)-C(186)-C(185)	113.6(3)
N(12)-C(186)-C(174)	103.5(3)
C(185)-C(186)-C(174)	102.1(3)
N(13)-Cu(7)-N(14)	90.32(11)
N(13)-Cu(7)-Cl(13)	94.78(8)
N(14)-Cu(7)-Cl(13)	148.12(8)
N(13)-Cu(7)-Cl(14)	144.52(8)
N(14)-Cu(7)-Cl(14)	95.75(8)
Cl(13)-Cu(7)-Cl(14)	98.08(3)
C(187)-O(13)-C(188)	106.9(3)
C(204)-O(14)-C(205)	107.4(3)
C(187)-N(13)-C(200)	106.3(3)
C(187)-N(13)-Cu(7)	126.4(2)
C(200)-N(13)-Cu(7)	126.5(2)
C(204)-N(14)-C(217)	106.8(3)
C(204)-N(14)-Cu(7)	126.5(2)
C(217)-N(14)-Cu(7)	125.5(2)
N(13)-C(187)-O(13)	117.9(3)
N(13)-C(187)-C(201)	128.9(3)
O(13)-C(187)-C(201)	112.8(3)
O(13)-C(188)-C(189)	108.6(3)
O(13)-C(188)-C(200)	101.9(2)
C(189)-C(188)-C(200)	107.4(3)
C(190)-C(189)-C(188)	103.0(3)
C(199)-C(190)-C(191)	120.5(3)
C(199)-C(190)-C(189)	112.1(3)
C(191)-C(190)-C(189)	127.5(3)
C(192)-C(191)-C(190)	119.6(3)
C(191)-C(192)-C(193)	121.5(4)
C(198)-C(193)-C(194)	118.5(3)
C(198)-C(193)-C(192)	119.4(3)
...	

Table A28 continued...

C(194)-C(193)-C(192)	122.2(3)
C(195)-C(194)-C(193)	121.3(3)
C(194)-C(195)-C(196)	120.1(3)
C(197)-C(196)-C(195)	120.6(3)
C(196)-C(197)-C(198)	120.3(3)
C(193)-C(198)-C(197)	119.1(3)
C(193)-C(198)-C(199)	117.4(3)
C(197)-C(198)-C(199)	123.4(3)
C(190)-C(199)-C(198)	121.5(3)
C(190)-C(199)-C(200)	111.0(3)
C(198)-C(199)-C(200)	127.4(3)
N(13)-C(200)-C(199)	111.1(3)
N(13)-C(200)-C(188)	103.3(3)
C(199)-C(200)-C(188)	102.4(3)
C(187)-C(201)-C(204)	112.8(3)
C(187)-C(201)-C(203)	111.4(3)
C(204)-C(201)-C(203)	108.1(3)
C(187)-C(201)-C(202)	105.4(3)
C(204)-C(201)-C(202)	109.2(3)
C(203)-C(201)-C(202)	110.0(3)
N(14)-C(204)-O(14)	118.0(3)
N(14)-C(204)-C(201)	129.3(3)
O(14)-C(204)-C(201)	112.5(3)
O(14)-C(205)-C(206)	109.2(3)
O(14)-C(205)-C(217)	102.8(2)
C(206)-C(205)-C(217)	108.2(3)
C(207)-C(206)-C(205)	103.3(3)
C(216)-C(207)-C(208)	121.4(3)
C(216)-C(207)-C(206)	112.4(3)
C(208)-C(207)-C(206)	126.2(3)
C(209)-C(208)-C(207)	119.3(3)
C(208)-C(209)-C(210)	121.0(3)
C(209)-C(210)-C(211)	121.7(3)
C(209)-C(210)-C(215)	120.0(3)
C(211)-C(210)-C(215)	118.3(3)
C(212)-C(211)-C(210)	121.1(3)
C(211)-C(212)-C(213)	120.9(3)
C(214)-C(213)-C(212)	119.3(3)
C(213)-C(214)-C(215)	121.1(3)
C(214)-C(215)-C(216)	123.7(3)
C(214)-C(215)-C(210)	119.2(3)
C(216)-C(215)-C(210)	117.1(3)
C(207)-C(216)-C(215)	121.0(3)
C(207)-C(216)-C(217)	111.1(3)
C(215)-C(216)-C(217)	127.9(3)
N(14)-C(217)-C(216)	111.5(2)
...	

Table A28 continued...

N(14)-C(217)-C(205)	103.3(3)
C(216)-C(217)-C(205)	103.2(3)
N(16)-Cu(8)-N(15)	90.98(12)
N(16)-Cu(8)-Cl(15)	145.85(8)
N(15)-Cu(8)-Cl(15)	95.03(9)
N(16)-Cu(8)-Cl(16)	95.27(8)
N(15)-Cu(8)-Cl(16)	141.07(8)
Cl(15)-Cu(8)-Cl(16)	100.76(4)
C(218)-O(15)-C(219)	107.1(3)
C(235)-O(16)-C(236)	107.9(3)
C(218)-N(15)-C(231)	107.1(3)
C(218)-N(15)-Cu(8)	126.1(3)
C(231)-N(15)-Cu(8)	126.2(2)
C(235)-N(16)-C(248)	107.3(3)
C(235)-N(16)-Cu(8)	125.9(2)
C(248)-N(16)-Cu(8)	125.4(2)
N(15)-C(218)-O(15)	117.5(3)
N(15)-C(218)-C(232)	129.2(3)
O(15)-C(218)-C(232)	113.0(3)
O(15)-C(219)-C(220)	108.8(3)
O(15)-C(219)-C(231)	101.9(3)
C(220)-C(219)-C(231)	108.2(3)
C(221)-C(220)-C(219)	103.9(3)
C(230)-C(221)-C(222)	121.3(4)
C(230)-C(221)-C(220)	110.5(4)
C(222)-C(221)-C(220)	128.0(4)
C(223)-C(222)-C(221)	119.2(4)
C(222)-C(223)-C(224)	121.4(4)
C(225)-C(224)-C(223)	121.1(4)
C(225)-C(224)-C(229)	118.8(3)
C(223)-C(224)-C(229)	120.1(4)
C(226)-C(225)-C(224)	120.5(3)
C(225)-C(226)-C(227)	120.8(3)
C(228)-C(227)-C(226)	120.4(3)
C(227)-C(228)-C(229)	120.3(3)
C(228)-C(229)-C(230)	123.5(3)
C(228)-C(229)-C(224)	119.1(3)
C(230)-C(229)-C(224)	117.2(3)
C(221)-C(230)-C(229)	120.7(3)
C(221)-C(230)-C(231)	111.9(3)
C(229)-C(230)-C(231)	127.5(3)
N(15)-C(231)-C(230)	111.2(3)
N(15)-C(231)-C(219)	103.6(3)
C(230)-C(231)-C(219)	102.3(3)
C(235)-C(232)-C(218)	113.7(3)
C(235)-C(232)-C(234)	108.3(3)
...	

Table A28 continued...

C(218)-C(232)-C(234)	110.2(3)
C(235)-C(232)-C(233)	109.0(3)
C(218)-C(232)-C(233)	105.0(3)
C(234)-C(232)-C(233)	110.6(4)
N(16)-C(235)-O(16)	117.2(3)
N(16)-C(235)-C(232)	129.6(3)
O(16)-C(235)-C(232)	113.1(3)
O(16)-C(236)-C(237)	109.2(3)
O(16)-C(236)-C(248)	103.0(3)
C(237)-C(236)-C(248)	108.0(3)
C(238)-C(237)-C(236)	103.8(3)
C(247)-C(238)-C(239)	121.1(3)
C(247)-C(238)-C(237)	112.5(3)
C(239)-C(238)-C(237)	126.4(3)
C(240)-C(239)-C(238)	119.2(3)
C(239)-C(240)-C(241)	121.5(3)
C(240)-C(241)-C(242)	122.2(3)
C(240)-C(241)-C(246)	119.4(3)
C(242)-C(241)-C(246)	118.4(3)
C(243)-C(242)-C(241)	121.8(3)
C(242)-C(243)-C(244)	120.1(3)
C(245)-C(244)-C(243)	119.9(3)
C(244)-C(245)-C(246)	120.8(3)
C(247)-C(246)-C(245)	123.2(3)
C(247)-C(246)-C(241)	118.0(3)
C(245)-C(246)-C(241)	118.8(3)
C(238)-C(247)-C(246)	120.5(3)
C(238)-C(247)-C(248)	110.7(3)
C(246)-C(247)-C(248)	128.7(3)
N(16)-C(248)-C(247)	112.4(3)
N(16)-C(248)-C(236)	103.1(3)
C(247)-C(248)-C(236)	103.8(3)
Cl(20)-C(1S)-Cl(21)	112.5(4)
Cl(51)-C(1T)-Cl(50)	110.3(5)
Cl(22)-C(2S)-Cl(23)	110.1(4)
Cl(52)-C(2T)-Cl(53)	109.7(8)
Cl(24)-C(3S)-Cl(25)	110.7(4)
Cl(55)-C(3R)-Cl(54)	110.4(9)
Cl(85)-C(3T)-Cl(84)	108.0(9)
Cl(56)-C(4S)-Cl(87)	93.2(4)
Cl(56)-C(4S)-Cl(27)	109.2(4)
Cl(87)-C(4S)-Cl(27)	20.29(15)
Cl(56)-C(4S)-Cl(26)	17.55(19)
Cl(87)-C(4S)-Cl(26)	106.6(3)
Cl(27)-C(4S)-Cl(26)	119.2(3)
Cl(56)-C(4S)-Cl(86)	31.3(3)
...	

Table A28 continued...

Cl(87)-C(4S)-Cl(86)	107.2(3)
Cl(27)-C(4S)-Cl(86)	114.5(3)
Cl(26)-C(4S)-Cl(86)	16.27(17)
Cl(56)-C(4S)-Cl(57)	113.7(4)
Cl(87)-C(4S)-Cl(57)	37.6(2)
Cl(27)-C(4S)-Cl(57)	19.03(16)
Cl(26)-C(4S)-Cl(57)	117.8(3)
Cl(86)-C(4S)-Cl(57)	108.0(4)
Cl(28)-C(5S)-Cl(29)	110.9(4)
Cl(89)-C(5T)-Cl(88)	105.5(10)
Cl(61)-C(6S)-Cl(30)	114.0(3)
Cl(61)-C(6S)-Cl(31)	13.49(18)
Cl(30)-C(6S)-Cl(31)	104.8(4)
Cl(61)-C(6S)-Cl(60)	108.1(4)
Cl(30)-C(6S)-Cl(60)	17.2(2)
Cl(31)-C(6S)-Cl(60)	96.5(4)
Cl(33)-C(7S)-Cl(32)	108.0(2)
Cl(34)-C(8S)-Cl(35)	110.6(3)

Table A29: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for $CuCl_2 \cdot$**2.97**

	x	y	z	U(eq)
H(2)	7069	3314	2072	28
H(3A)	7297	4197	1473	31
H(3B)	6022	4473	1587	31
H(5)	6548	5843	1479	34
H(6)	6604	6795	2017	36
H(8)	6682	7270	2898	34
H(9)	6804	7071	3781	36
H(10)	7099	5869	4110	32
H(11)	7165	4877	3559	27
H(14)	7503	3839	2767	24
H(16A)	4512	2640	3110	36
H(16B)	4146	2988	2582	36
H(16C)	3282	3001	3123	36
H(17A)	3407	4902	3031	34
H(17B)	2604	4393	3077	34
H(17C)	3464	4379	2535	34
H(19)	2273	4381	4702	24
H(20A)	1728	3410	5090	26
H(20B)	1983	3051	4495	26
H(22)	2653	1793	5093	26
H(23)	4221	1020	5232	25
H(25)	6099	834	5308	27

...

Table A29 continued...

	x	y	z	U(eq)
H(26)	7550	1282	5271	30
H(27)	7477	2522	5058	30
H(28)	5942	3291	4867	26
H(31)	3953	4111	4874	21
H(33A)	6930	8362	2078	25
H(34A)	7130	9256	1484	27
H(34B)	5853	9504	1599	27
H(36A)	6271	10904	1492	29
H(37A)	6328	11868	2030	32
H(39A)	6496	12327	2899	32
H(40A)	6624	12132	3780	32
H(41A)	6904	10935	4114	27
H(42A)	7015	9938	3562	24
H(45A)	7408	8897	2756	21
H(47A)	4578	7628	3183	38
H(47B)	4165	7920	2653	38
H(47C)	3333	7918	3203	38
H(48A)	3234	9851	3054	35
H(48B)	2508	9286	3125	35
H(48C)	3340	9285	2575	35
H(50A)	2272	9375	4760	25
H(51A)	1739	8403	5154	27
H(51B)	1960	8051	4558	27
H(53A)	2650	6784	5152	25
H(54A)	4225	6008	5274	26
H(56A)	6120	5808	5321	28
H(57A)	7599	6237	5242	34
H(58A)	7527	7486	5034	30
H(59A)	5981	8252	4849	27
H(62A)	3984	9086	4910	22
H(64A)	4307	6544	6544	23
H(65A)	4903	5404	6160	25
H(65B)	4453	5105	6734	25
H(67A)	4020	4195	5970	23
H(68A)	2518	4053	5713	23
H(70A)	677	4578	5597	24
H(71A)	−792	5577	5645	26
H(72A)	−737	6754	5907	26
H(73A)	754	6919	6160	23
H(76A)	2789	6942	6219	18
H(78A)	2736	7567	8118	30
H(78B)	3487	6759	8157	30
H(78C)	2502	7095	8637	30
H(79A)	1609	5742	8011	32
H(79B)	1808	5976	8570	32
H(79C)	2793	5639	8091	32

...

Table A29 continued...

	x	y	z	U(eq)
H(81A)	−1130	7419	8785	22
H(82A)	−1575	8378	9382	28
H(82B)	−345	8140	9422	28
H(84A)	−854	9726	9499	32
H(85A)	−727	10717	8970	30
H(87A)	−526	11265	8080	30
H(88A)	−259	11140	7152	32
H(89A)	−157	9994	6758	28
H(90A)	−251	8981	7273	23
H(93A)	−1231	8146	8053	19
H(95A)	4336	1663	6476	26
H(96A)	4937	509	6107	26
H(96B)	4537	226	6694	26
H(98A)	4046	−745	6005	23
H(99A)	2543	−909	5764	24
H(10B)	728	−404	5617	26
H(10C)	−733	595	5623	28
H(10D)	−682	1788	5854	29
H(10E)	783	1978	6115	24
H(10F)	2771	2034	6182	20
H(10G)	1655	767	7895	30
H(10H)	1851	914	8475	30
H(10I)	2838	616	7988	30
H(11B)	2842	2520	8146	28
H(11C)	3570	1694	8143	28
H(11D)	2584	1994	8630	28
H(11E)	−1012	2353	8778	22
H(11F)	−1463	3282	9407	26
H(11G)	−227	3039	9436	26
H(11H)	−701	4605	9566	30
H(11I)	−630	5639	9065	30
H(11J)	−495	6253	8194	29
H(11K)	−270	6182	7272	32
H(12A)	−121	5060	6834	27
H(12B)	−225	4019	7321	22
H(12C)	−1174	3135	8078	19
H(12D)	7862	6719	7150	24
H(12E)	7253	7217	6409	36
H(12F)	6773	6510	6432	36
H(12G)	5103	7557	6102	40
H(13A)	3411	8218	6486	48
H(13B)	2134	8946	7252	48
H(13C)	1737	9381	8130	52
H(13D)	3057	9135	8638	44
H(13E)	4728	8376	8296	32
H(13F)	6713	7678	7703	23

...

Table A29 continued...

	x	y	z	U(eq)
H(14B)	7507	5105	8326	34
H(14C)	7503	4790	7751	34
H(14D)	6941	4463	8282	34
H(14E)	4724	5570	7783	36
H(14F)	5234	4750	7949	36
H(14G)	5794	5079	7418	36
H(14H)	3798	5440	9534	41
H(14I)	4496	4615	10129	51
H(14J)	5285	4180	9604	51
H(14K)	6708	3928	10334	72
H(14L)	7965	4423	10547	59
H(14M)	8797	5431	10572	61
H(15A)	8876	6605	10355	68
H(15B)	7656	7366	9878	59
H(15C)	6325	6912	9663	43
H(15D)	4526	6345	9780	30
H(15E)	7806	1768	7190	27
H(15F)	7109	2399	6514	37
H(15G)	6600	1712	6498	37
H(16D)	4872	2834	6282	41
H(16E)	3222	3488	6750	41
H(16F)	2037	4115	7594	49
H(16G)	1756	4361	8493	49
H(16H)	3173	4005	8946	41
H(16I)	4818	3304	8499	34
H(16J)	6746	2673	7819	25
H(17D)	4755	565	7729	34
H(17E)	5272	−261	7881	34
H(17F)	5866	104	7379	34
H(17G)	7435	96	8362	32
H(17H)	7505	−181	7765	32
H(17I)	6907	−548	8264	32
H(17J)	3566	503	9459	29
H(17K)	3987	−474	9997	37
H(17L)	4756	−890	9457	37
H(17M)	5980	−1447	10218	42
H(17N)	7360	−1231	10539	44
H(18A)	8434	−386	10703	47
H(18B)	8873	715	10568	42
H(18C)	7919	1649	10103	51
H(18D)	6501	1460	9776	40
H(18E)	4490	1202	9807	27
H(18F)	3075	3476	1491	31
H(18G)	2919	3172	648	37
H(18H)	1691	3288	936	37
H(19B)	1285	3886	−24	39

...

Table A29 continued...

	x	y	z	U(eq)
H(19C)	936	5008	−429	40
H(19D)	1053	6317	−504	37
H(19E)	1682	7256	−256	35
H(19F)	2644	7091	428	29
H(19G)	2873	6011	898	22
H(20C)	3472	4573	1176	23
H(20D)	−431	5502	1735	50
H(20E)	−1231	5333	2252	50
H(20F)	−531	4677	1837	50
H(20G)	750	4348	2963	54
H(20H)	200	3968	2591	54
H(20I)	−503	4622	3006	54
H(20J)	−1050	7107	3075	26
H(20K)	−1202	7092	3980	27
H(20L)	−1163	6232	3922	27
H(20M)	7	6164	4723	25
H(20N)	1762	5815	4798	25
H(21A)	3681	5615	4384	28
H(21B)	4993	5721	3672	32
H(21C)	4574	6218	2864	28
H(21D)	2811	6569	2779	23
H(21E)	706	7148	2861	21
H(21F)	2768	−1549	1317	33
H(22B)	2515	−1726	477	44
H(22C)	1288	−1569	776	44
H(22D)	968	−849	−186	46
H(22E)	764	309	−540	41
H(22F)	1091	1542	−570	39
H(22G)	1876	2370	−278	36
H(22H)	2789	2080	420	28
H(22I)	2810	990	870	22
H(23B)	3228	−449	1094	25
H(23C)	−733	472	1733	56
H(23D)	−1455	251	2261	56
H(23E)	−776	−368	1813	56
H(23F)	701	−743	2875	65
H(23G)	112	−1119	2521	65
H(23H)	−565	−500	2969	65
H(23I)	−1222	2023	3060	27
H(23J)	−1370	1974	3963	29
H(23K)	−1283	1108	3892	29
H(23L)	−118	1107	4702	24
H(24A)	1638	794	4769	26
H(24B)	3540	642	4356	29
H(24C)	4838	768	3647	35
H(24D)	4393	1236	2834	30

...

Table A29 continued...

	x	y	z	U(eq)
H(24E)	2638	1529	2743	24
H(24F)	531	2068	2831	23
H(1S1)	10480	7341	1348	34
H(1S2)	10162	6760	1009	34
H(1T1)	10219	6939	1142	35
H(1T2)	10492	7567	1458	35
H(2S1)	7831	9241	5104	49
H(2S2)	8288	8824	4529	49
H(2T1)	8633	8889	4249	81
H(2T2)	8108	9155	4859	81
H(3S1)	8372	8954	6217	20
H(3S2)	7811	9360	6788	20
H(3R1)	8424	8998	5849	72
H(3R2)	8200	8942	6488	72
H(3T1)	8638	9159	5715	74
H(3T2)	8532	8674	6240	74
H(4S1)	10104	1887	837	54
H(4S2)	10401	2266	1312	54
H(5S1)	8203	4148	4700	48
H(5S2)	8877	3922	4105	48
H(5T1)	8546	3864	4418	146
H(5T2)	7947	4243	4996	146
H(6S1)	8719	4101	5743	60
H(6S2)	8514	3683	6297	60
H(7S1)	5594	6777	1077	60
H(7S2)	4379	6935	1390	60
H(8S1)	6172	2259	684	65
H(8S2)	5204	2776	460	65

Table A30: Torsion angles (°) for $CuCl_2$·**2.97**

N(2)-Cu(1)-N(1)-C(1)	−9.9(3)
Cl(1)-Cu(1)-N(1)-C(1)	−114.8(3)
Cl(2)-Cu(1)-N(1)-C(1)	131.1(3)
N(2)-Cu(1)-N(1)-C(14)	−174.9(2)
Cl(1)-Cu(1)-N(1)-C(14)	80.2(3)
Cl(2)-Cu(1)-N(1)-C(14)	−33.9(2)
N(1)-Cu(1)-N(2)-C(18)	−8.2(3)
Cl(1)-Cu(1)-N(2)-C(18)	135.7(3)
Cl(2)-Cu(1)-N(2)-C(18)	−106.2(3)
N(1)-Cu(1)-N(2)-C(31)	−174.2(2)
Cl(1)-Cu(1)-N(2)-C(31)	−30.3(2)
Cl(2)-Cu(1)-N(2)-C(31)	87.9(3)
C(14)-N(1)-C(1)-O(1)	3.4(4)
Cu(1)-N(1)-C(1)-O(1)	−163.7(2)

...

Table A30 continued...

C(14)-N(1)-C(1)-C(15)	−173.2(3)
Cu(1)-N(1)-C(1)-C(15)	19.7(5)
C(2)-O(1)-C(1)-N(1)	6.2(4)
C(2)-O(1)-C(1)-C(15)	−176.6(3)
C(1)-O(1)-C(2)-C(3)	−126.8(3)
C(1)-O(1)-C(2)-C(14)	−12.3(3)
O(1)-C(2)-C(3)-C(4)	99.6(3)
C(14)-C(2)-C(3)-C(4)	−11.8(4)
C(2)-C(3)-C(4)-C(13)	8.8(4)
C(2)-C(3)-C(4)-C(5)	−171.9(4)
C(13)-C(4)-C(5)-C(6)	−0.8(6)
C(3)-C(4)-C(5)-C(6)	179.9(4)
C(4)-C(5)-C(6)-C(7)	0.4(6)
C(5)-C(6)-C(7)-C(8)	−177.5(4)
C(5)-C(6)-C(7)-C(12)	2.4(6)
C(6)-C(7)-C(8)-C(9)	179.5(4)
C(12)-C(7)-C(8)-C(9)	−0.4(5)
C(7)-C(8)-C(9)-C(10)	3.4(6)
C(8)-C(9)-C(10)-C(11)	−2.3(6)
C(9)-C(10)-C(11)-C(12)	−2.0(5)
C(10)-C(11)-C(12)-C(13)	−173.9(3)
C(10)-C(11)-C(12)-C(7)	5.0(5)
C(6)-C(7)-C(12)-C(11)	176.3(3)
C(8)-C(7)-C(12)-C(11)	−3.8(5)
C(6)-C(7)-C(12)-C(13)	−4.7(5)
C(8)-C(7)-C(12)-C(13)	175.2(3)
C(5)-C(4)-C(13)-C(12)	−1.7(5)
C(3)-C(4)-C(13)-C(12)	177.7(3)
C(5)-C(4)-C(13)-C(14)	178.6(3)
C(3)-C(4)-C(13)-C(14)	−2.0(4)
C(11)-C(12)-C(13)-C(4)	−176.7(3)
C(7)-C(12)-C(13)-C(4)	4.4(5)
C(11)-C(12)-C(13)-C(14)	2.9(6)
C(7)-C(12)-C(13)-C(14)	−176.0(3)
C(1)-N(1)-C(14)-C(13)	101.5(3)
Cu(1)-N(1)-C(14)-C(13)	−91.2(3)
C(1)-N(1)-C(14)-C(2)	−10.8(3)
Cu(1)-N(1)-C(14)-C(2)	156.5(2)
C(4)-C(13)-C(14)-N(1)	−117.0(3)
C(12)-C(13)-C(14)-N(1)	63.4(4)
C(4)-C(13)-C(14)-C(2)	−5.6(4)
C(12)-C(13)-C(14)-C(2)	174.7(3)
O(1)-C(2)-C(14)-N(1)	13.5(3)
C(3)-C(2)-C(14)-N(1)	129.8(3)
O(1)-C(2)-C(14)-C(13)	−105.4(3)
C(3)-C(2)-C(14)-C(13)	10.9(4)
...	

Table A30 continued...

N(1)-C(1)-C(15)-C(18)	−9.4(5)
O(1)-C(1)-C(15)-C(18)	173.9(3)
N(1)-C(1)-C(15)-C(17)	112.4(4)
O(1)-C(1)-C(15)-C(17)	−64.3(3)
N(1)-C(1)-C(15)-C(16)	−127.7(4)
O(1)-C(1)-C(15)-C(16)	55.6(4)
C(31)-N(2)-C(18)-O(2)	4.8(4)
Cu(1)-N(2)-C(18)-O(2)	−163.4(2)
C(31)-N(2)-C(18)-C(15)	−171.8(3)
Cu(1)-N(2)-C(18)-C(15)	20.1(5)
C(19)-O(2)-C(18)-N(2)	2.2(4)
C(19)-O(2)-C(18)-C(15)	179.4(3)
C(1)-C(15)-C(18)-N(2)	−12.3(5)
C(17)-C(15)-C(18)-N(2)	−132.6(4)
C(16)-C(15)-C(18)-N(2)	108.4(4)
C(1)-C(15)-C(18)-O(2)	171.0(3)
C(17)-C(15)-C(18)-O(2)	50.7(4)
C(16)-C(15)-C(18)-O(2)	−68.3(3)
C(18)-O(2)-C(19)-C(20)	−122.5(3)
C(18)-O(2)-C(19)-C(31)	−7.7(3)
O(2)-C(19)-C(20)-C(21)	102.2(3)
C(31)-C(19)-C(20)-C(21)	−8.7(3)
C(19)-C(20)-C(21)-C(30)	7.8(4)
C(19)-C(20)-C(21)-C(22)	−173.0(3)
C(30)-C(21)-C(22)-C(23)	−1.2(5)
C(20)-C(21)-C(22)-C(23)	179.6(3)
C(21)-C(22)-C(23)-C(24)	3.9(5)
C(22)-C(23)-C(24)-C(25)	178.5(3)
C(22)-C(23)-C(24)-C(29)	−2.1(5)
C(23)-C(24)-C(25)-C(26)	−178.5(3)
C(29)-C(24)-C(25)-C(26)	2.1(5)
C(24)-C(25)-C(26)-C(27)	0.1(6)
C(25)-C(26)-C(27)-C(28)	−1.0(6)
C(26)-C(27)-C(28)-C(29)	−0.5(6)
C(27)-C(28)-C(29)-C(24)	2.7(5)
C(27)-C(28)-C(29)-C(30)	−177.9(3)
C(25)-C(24)-C(29)-C(28)	−3.4(5)
C(23)-C(24)-C(29)-C(28)	177.1(3)
C(25)-C(24)-C(29)-C(30)	177.1(3)
C(23)-C(24)-C(29)-C(30)	−2.3(5)
C(22)-C(21)-C(30)-C(29)	−3.3(5)
C(20)-C(21)-C(30)-C(29)	175.9(3)
C(22)-C(21)-C(30)-C(31)	177.0(3)
C(20)-C(21)-C(30)-C(31)	−3.7(4)
C(28)-C(29)-C(30)-C(21)	−174.4(3)
C(24)-C(29)-C(30)-C(21)	5.0(5)
...	

Table A30 continued...

C(28)-C(29)-C(30)-C(31)	5.1(5)
C(24)-C(29)-C(30)-C(31)	−175.4(3)
C(18)-N(2)-C(31)-C(30)	102.4(3)
Cu(1)-N(2)-C(31)-C(30)	−89.4(3)
C(18)-N(2)-C(31)-C(19)	−9.1(3)
Cu(1)-N(2)-C(31)-C(19)	159.0(2)
C(21)-C(30)-C(31)-N(2)	−113.7(3)
C(29)-C(30)-C(31)-N(2)	66.7(4)
C(21)-C(30)-C(31)-C(19)	−2.0(3)
C(29)-C(30)-C(31)-C(19)	178.4(3)
O(2)-C(19)-C(31)-N(2)	9.9(3)
C(20)-C(19)-C(31)-N(2)	125.0(3)
O(2)-C(19)-C(31)-C(30)	−108.3(3)
C(20)-C(19)-C(31)-C(30)	6.7(3)
N(4)-Cu(2)-N(3)-C(32)	−9.4(3)
Cl(4)-Cu(2)-N(3)-C(32)	−113.4(3)
Cl(3)-Cu(2)-N(3)-C(32)	132.7(3)
N(4)-Cu(2)-N(3)-C(45)	−175.2(2)
Cl(4)-Cu(2)-N(3)-C(45)	80.8(3)
Cl(3)-Cu(2)-N(3)-C(45)	−33.1(2)
N(3)-Cu(2)-N(4)-C(49)	−9.0(3)
Cl(4)-Cu(2)-N(4)-C(49)	135.2(3)
Cl(3)-Cu(2)-N(4)-C(49)	−107.2(3)
N(3)-Cu(2)-N(4)-C(62)	−173.7(3)
Cl(4)-Cu(2)-N(4)-C(62)	−29.6(2)
Cl(3)-Cu(2)-N(4)-C(62)	88.0(3)
C(45)-N(3)-C(32)-O(3)	3.5(4)
Cu(2)-N(3)-C(32)-O(3)	−164.4(2)
C(45)-N(3)-C(32)-C(46)	−175.3(3)
Cu(2)-N(3)-C(32)-C(46)	16.8(5)
C(33)-O(3)-C(32)-N(3)	6.8(4)
C(33)-O(3)-C(32)-C(46)	−174.2(3)
C(32)-O(3)-C(33)-C(34)	−127.9(3)
C(32)-O(3)-C(33)-C(45)	−13.2(3)
O(3)-C(33)-C(34)-C(35)	97.5(3)
C(45)-C(33)-C(34)-C(35)	−13.9(4)
C(33)-C(34)-C(35)-C(44)	10.2(4)
C(33)-C(34)-C(35)-C(36)	−171.2(3)
C(44)-C(35)-C(36)-C(37)	0.0(5)
C(34)-C(35)-C(36)-C(37)	−178.5(3)
C(35)-C(36)-C(37)-C(38)	0.7(5)
C(36)-C(37)-C(38)-C(39)	−177.6(3)
C(36)-C(37)-C(38)-C(43)	0.3(5)
C(37)-C(38)-C(39)-C(40)	176.7(3)
C(43)-C(38)-C(39)-C(40)	−1.2(5)
C(38)-C(39)-C(40)-C(41)	3.5(6)
...	

Table A30 continued...

C(39)-C(40)-C(41)-C(42)	−1.0(5)
C(40)-C(41)-C(42)-C(43)	−3.6(5)
C(41)-C(42)-C(43)-C(44)	−173.5(3)
C(41)-C(42)-C(43)-C(38)	5.7(5)
C(39)-C(38)-C(43)-C(42)	−3.3(5)
C(37)-C(38)-C(43)-C(42)	178.7(3)
C(39)-C(38)-C(43)-C(44)	176.0(3)
C(37)-C(38)-C(43)-C(44)	−2.0(5)
C(36)-C(35)-C(44)-C(43)	−1.8(5)
C(34)-C(35)-C(44)-C(43)	176.9(3)
C(36)-C(35)-C(44)-C(45)	179.1(3)
C(34)-C(35)-C(44)-C(45)	−2.2(4)
C(42)-C(43)-C(44)-C(35)	−178.0(3)
C(38)-C(43)-C(44)-C(35)	2.7(5)
C(42)-C(43)-C(44)-C(45)	0.9(5)
C(38)-C(43)-C(44)-C(45)	−178.4(3)
C(32)-N(3)-C(45)-C(44)	99.7(3)
Cu(2)-N(3)-C(45)-C(44)	−92.3(3)
C(32)-N(3)-C(45)-C(33)	−11.5(3)
Cu(2)-N(3)-C(45)-C(33)	156.5(2)
C(35)-C(44)-C(45)-N(3)	−117.7(3)
C(43)-C(44)-C(45)-N(3)	63.3(4)
C(35)-C(44)-C(45)-C(33)	−6.7(4)
C(43)-C(44)-C(45)-C(33)	174.3(3)
O(3)-C(33)-C(45)-N(3)	14.6(3)
C(34)-C(33)-C(45)-N(3)	131.0(3)
O(3)-C(33)-C(45)-C(44)	−103.7(3)
C(34)-C(33)-C(45)-C(44)	12.8(3)
N(3)-C(32)-C(46)-C(49)	−4.6(5)
O(3)-C(32)-C(46)-C(49)	176.6(3)
N(3)-C(32)-C(46)-C(48)	118.8(4)
O(3)-C(32)-C(46)-C(48)	−60.1(3)
N(3)-C(32)-C(46)-C(47)	−121.4(4)
O(3)-C(32)-C(46)-C(47)	59.8(3)
C(62)-N(4)-C(49)-O(4)	4.8(4)
Cu(2)-N(4)-C(49)-O(4)	−162.3(2)
C(62)-N(4)-C(49)-C(46)	−169.6(3)
Cu(2)-N(4)-C(49)-C(46)	23.3(5)
C(50)-O(4)-C(49)-N(4)	2.9(4)
C(50)-O(4)-C(49)-C(46)	178.1(3)
C(32)-C(46)-C(49)-N(4)	−17.2(5)
C(48)-C(46)-C(49)-N(4)	−139.2(3)
C(47)-C(46)-C(49)-N(4)	102.1(4)
C(32)-C(46)-C(49)-O(4)	168.2(3)
C(48)-C(46)-C(49)-O(4)	46.2(4)
C(47)-C(46)-C(49)-O(4)	−72.5(3)
...	

Table A30 continued...

C(49)-O(4)-C(50)-C(51)	−122.9(3)
C(49)-O(4)-C(50)-C(62)	−8.7(3)
O(4)-C(50)-C(51)-C(52)	101.7(3)
C(62)-C(50)-C(51)-C(52)	−8.6(3)
C(50)-C(51)-C(52)-C(61)	7.2(4)
C(50)-C(51)-C(52)-C(53)	−173.8(3)
C(61)-C(52)-C(53)-C(54)	−1.1(5)
C(51)-C(52)-C(53)-C(54)	180.0(3)
C(52)-C(53)-C(54)-C(55)	3.2(5)
C(53)-C(54)-C(55)-C(56)	178.1(3)
C(53)-C(54)-C(55)-C(60)	−1.5(5)
C(60)-C(55)-C(56)-C(57)	1.2(5)
C(54)-C(55)-C(56)-C(57)	−178.4(3)
C(55)-C(56)-C(57)-C(58)	1.5(6)
C(56)-C(57)-C(58)-C(59)	−2.5(6)
C(57)-C(58)-C(59)-C(60)	0.7(5)
C(58)-C(59)-C(60)-C(55)	1.9(5)
C(58)-C(59)-C(60)-C(61)	−179.1(3)
C(56)-C(55)-C(60)-C(59)	−2.8(5)
C(54)-C(55)-C(60)-C(59)	176.8(3)
C(56)-C(55)-C(60)-C(61)	178.1(3)
C(54)-C(55)-C(60)-C(61)	−2.2(4)
C(53)-C(52)-C(61)-C(60)	−2.8(5)
C(51)-C(52)-C(61)-C(60)	176.2(3)
C(53)-C(52)-C(61)-C(62)	178.1(3)
C(51)-C(52)-C(61)-C(62)	−2.8(4)
C(59)-C(60)-C(61)-C(52)	−174.6(3)
C(55)-C(60)-C(61)-C(52)	4.4(5)
C(59)-C(60)-C(61)-C(62)	4.3(5)
C(55)-C(60)-C(61)-C(62)	−176.7(3)
C(49)-N(4)-C(62)-C(61)	101.7(3)
Cu(2)-N(4)-C(62)-C(61)	−91.2(3)
C(49)-N(4)-C(62)-C(50)	−9.8(3)
Cu(2)-N(4)-C(62)-C(50)	157.4(2)
C(52)-C(61)-C(62)-N(4)	−114.3(3)
C(60)-C(61)-C(62)-N(4)	66.7(4)
C(52)-C(61)-C(62)-C(50)	−2.7(3)
C(60)-C(61)-C(62)-C(50)	178.3(3)
O(4)-C(50)-C(62)-N(4)	10.8(3)
C(51)-C(50)-C(62)-N(4)	125.4(3)
O(4)-C(50)-C(62)-C(61)	−107.5(3)
C(51)-C(50)-C(62)-C(61)	7.1(3)
N(6)-Cu(3)-N(5)-C(63)	−9.7(3)
Cl(5)-Cu(3)-N(5)-C(63)	133.6(3)
Cl(6)-Cu(3)-N(5)-C(63)	−109.8(3)
N(6)-Cu(3)-N(5)-C(76)	−175.2(2)
...	

Table A30 continued...

Cl(5)-Cu(3)-N(5)-C(76)	−31.9(2)
Cl(6)-Cu(3)-N(5)-C(76)	84.8(3)
N(5)-Cu(3)-N(6)-C(80)	−9.0(3)
Cl(5)-Cu(3)-N(6)-C(80)	−111.8(3)
Cl(6)-Cu(3)-N(6)-C(80)	134.4(3)
N(5)-Cu(3)-N(6)-C(93)	−174.7(2)
Cl(5)-Cu(3)-N(6)-C(93)	82.5(3)
Cl(6)-Cu(3)-N(6)-C(93)	−31.2(2)
C(76)-N(5)-C(63)-O(5)	2.4(4)
Cu(3)-N(5)-C(63)-O(5)	−165.1(2)
C(76)-N(5)-C(63)-C(77)	−172.0(3)
Cu(3)-N(5)-C(63)-C(77)	20.5(5)
C(64)-O(5)-C(63)-N(5)	5.9(4)
C(64)-O(5)-C(63)-C(77)	−178.7(2)
C(63)-O(5)-C(64)-C(65)	−126.7(3)
C(63)-O(5)-C(64)-C(76)	−10.8(3)
O(5)-C(64)-C(65)-C(66)	103.0(3)
C(76)-C(64)-C(65)-C(66)	−9.3(3)
C(64)-C(65)-C(66)-C(75)	5.1(4)
C(64)-C(65)-C(66)-C(67)	−176.5(3)
C(75)-C(66)-C(67)-C(68)	−4.5(5)
C(65)-C(66)-C(67)-C(68)	177.3(3)
C(66)-C(67)-C(68)-C(69)	2.9(5)
C(67)-C(68)-C(69)-C(70)	−179.5(3)
C(67)-C(68)-C(69)-C(74)	1.8(5)
C(74)-C(69)-C(70)-C(71)	0.4(5)
C(68)-C(69)-C(70)-C(71)	−178.3(3)
C(69)-C(70)-C(71)-C(72)	2.4(5)
C(70)-C(71)-C(72)-C(73)	−1.8(5)
C(71)-C(72)-C(73)-C(74)	−1.5(5)
C(72)-C(73)-C(74)-C(75)	−175.7(3)
C(72)-C(73)-C(74)-C(69)	4.2(5)
C(70)-C(69)-C(74)-C(73)	−3.6(4)
C(68)-C(69)-C(74)-C(73)	175.1(3)
C(70)-C(69)-C(74)-C(75)	176.4(3)
C(68)-C(69)-C(74)-C(75)	−5.0(4)
C(67)-C(66)-C(75)-C(74)	1.3(5)
C(65)-C(66)-C(75)-C(74)	179.7(3)
C(67)-C(66)-C(75)-C(76)	−177.2(3)
C(65)-C(66)-C(75)-C(76)	1.2(4)
C(73)-C(74)-C(75)-C(66)	−176.6(3)
C(69)-C(74)-C(75)-C(66)	3.5(4)
C(73)-C(74)-C(75)-C(76)	1.6(5)
C(69)-C(74)-C(75)-C(76)	−178.4(3)
C(63)-N(5)-C(76)-C(75)	102.5(3)
Cu(3)-N(5)-C(76)-C(75)	−89.8(3)
...	

Table A30 continued...

C(63)-N(5)-C(76)-C(64)	−9.0(3)
Cu(3)-N(5)-C(76)-C(64)	158.7(2)
C(66)-C(75)-C(76)-N(5)	−118.4(3)
C(74)-C(75)-C(76)-N(5)	63.3(4)
C(66)-C(75)-C(76)-C(64)	−6.9(3)
C(74)-C(75)-C(76)-C(64)	174.8(3)
O(5)-C(64)-C(76)-N(5)	11.7(3)
C(65)-C(64)-C(76)-N(5)	129.4(3)
O(5)-C(64)-C(76)-C(75)	−107.7(3)
C(65)-C(64)-C(76)-C(75)	9.9(3)
N(5)-C(63)-C(77)-C(80)	−10.9(5)
O(5)-C(63)-C(77)-C(80)	174.5(3)
N(5)-C(63)-C(77)-C(79)	111.4(4)
O(5)-C(63)-C(77)-C(79)	−63.2(3)
N(5)-C(63)-C(77)-C(78)	−129.7(3)
O(5)-C(63)-C(77)-C(78)	55.6(3)
C(93)-N(6)-C(80)-O(6)	4.0(4)
Cu(3)-N(6)-C(80)-O(6)	−163.7(2)
C(93)-N(6)-C(80)-C(77)	−172.2(3)
Cu(3)-N(6)-C(80)-C(77)	20.1(5)
C(81)-O(6)-C(80)-N(6)	7.3(4)
C(81)-O(6)-C(80)-C(77)	−175.9(2)
C(63)-C(77)-C(80)-N(6)	−11.1(5)
C(79)-C(77)-C(80)-N(6)	−130.9(3)
C(78)-C(77)-C(80)-N(6)	109.4(4)
C(63)-C(77)-C(80)-O(6)	172.5(3)
C(79)-C(77)-C(80)-O(6)	52.8(3)
C(78)-C(77)-C(80)-O(6)	−67.0(3)
C(80)-O(6)-C(81)-C(82)	−129.6(3)
C(80)-O(6)-C(81)-C(93)	−14.5(3)
O(6)-C(81)-C(82)-C(83)	97.6(3)
C(93)-C(81)-C(82)-C(83)	−13.9(4)
C(81)-C(82)-C(83)-C(92)	8.1(4)
C(81)-C(82)-C(83)-C(84)	−177.3(3)
C(92)-C(83)-C(84)-C(85)	0.1(5)
C(82)-C(83)-C(84)-C(85)	−174.1(4)
C(83)-C(84)-C(85)-C(86)	−0.5(6)
C(84)-C(85)-C(86)-C(87)	177.8(4)
C(84)-C(85)-C(86)-C(91)	0.5(5)
C(85)-C(86)-C(87)-C(88)	−178.9(3)
C(91)-C(86)-C(87)-C(88)	−1.6(5)
C(86)-C(87)-C(88)-C(89)	2.0(5)
C(87)-C(88)-C(89)-C(90)	−1.2(5)
C(88)-C(89)-C(90)-C(91)	−0.1(5)
C(89)-C(90)-C(91)-C(92)	178.2(3)
C(89)-C(90)-C(91)-C(86)	0.6(5)

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Table A30 continued...

C(87)-C(86)-C(91)-C(90)	0.3(5)
C(85)-C(86)-C(91)-C(90)	177.6(3)
C(87)-C(86)-C(91)-C(92)	−177.4(3)
C(85)-C(86)-C(91)-C(92)	−0.1(5)
C(84)-C(83)-C(92)-C(91)	0.3(5)
C(82)-C(83)-C(92)-C(91)	175.3(3)
C(84)-C(83)-C(92)-C(93)	−173.8(3)
C(82)-C(83)-C(92)-C(93)	1.2(4)
C(90)-C(91)-C(92)-C(83)	−177.9(3)
C(86)-C(91)-C(92)-C(83)	−0.3(5)
C(90)-C(91)-C(92)-C(93)	−4.9(5)
C(86)-C(91)-C(92)-C(93)	172.7(3)
C(80)-N(6)-C(93)-C(92)	98.6(3)
Cu(3)-N(6)-C(93)-C(92)	−93.3(3)
C(80)-N(6)-C(93)-C(81)	−12.9(3)
Cu(3)-N(6)-C(93)-C(81)	155.1(2)
C(83)-C(92)-C(93)-N(6)	−121.3(3)
C(91)-C(92)-C(93)-N(6)	65.2(4)
C(83)-C(92)-C(93)-C(81)	−9.8(3)
C(91)-C(92)-C(93)-C(81)	176.6(3)
O(6)-C(81)-C(93)-N(6)	16.1(3)
C(82)-C(81)-C(93)-N(6)	133.6(3)
O(6)-C(81)-C(93)-C(92)	−102.8(3)
C(82)-C(81)-C(93)-C(92)	14.6(3)
N(8)-Cu(4)-N(7)-C(94)	−9.5(3)
Cl(7)-Cu(4)-N(7)-C(94)	133.3(3)
Cl(8)-Cu(4)-N(7)-C(94)	−109.4(3)
N(8)-Cu(4)-N(7)-C(107)	−174.9(2)
Cl(7)-Cu(4)-N(7)-C(107)	−32.1(2)
Cl(8)-Cu(4)-N(7)-C(107)	85.3(3)
N(7)-Cu(4)-N(8)-C(111)	−11.3(3)
Cl(7)-Cu(4)-N(8)-C(111)	−113.1(3)
Cl(8)-Cu(4)-N(8)-C(111)	133.5(3)
N(7)-Cu(4)-N(8)-C(124)	−175.4(2)
Cl(7)-Cu(4)-N(8)-C(124)	82.8(3)
Cl(8)-Cu(4)-N(8)-C(124)	−30.6(2)
C(107)-N(7)-C(94)-O(7)	3.6(4)
Cu(4)-N(7)-C(94)-O(7)	−163.8(2)
C(107)-N(7)-C(94)-C(108)	−167.4(3)
Cu(4)-N(7)-C(94)-C(108)	25.2(5)
C(95)-O(7)-C(94)-N(7)	3.8(4)
C(95)-O(7)-C(94)-C(108)	176.2(3)
C(94)-O(7)-C(95)-C(96)	−124.2(3)
C(94)-O(7)-C(95)-C(107)	−8.9(3)
O(7)-C(95)-C(96)-C(97)	102.3(3)
C(107)-C(95)-C(96)-C(97)	−9.6(4)

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Table A30 continued...

C(95)-C(96)-C(97)-C(106)	7.2(4)
C(95)-C(96)-C(97)-C(98)	−174.9(3)
C(106)-C(97)-C(98)-C(99)	−3.0(5)
C(96)-C(97)-C(98)-C(99)	179.3(3)
C(97)-C(98)-C(99)-C(100)	2.9(5)
C(98)-C(99)-C(100)-C(101)	179.5(3)
C(98)-C(99)-C(100)-C(105)	0.3(5)
C(99)-C(100)-C(101)-C(102)	−178.5(3)
C(105)-C(100)-C(101)-C(102)	0.7(5)
C(100)-C(101)-C(102)-C(103)	1.8(5)
C(101)-C(102)-C(103)-C(104)	−1.7(5)
C(102)-C(103)-C(104)-C(105)	−0.9(5)
C(103)-C(104)-C(105)-C(100)	3.3(5)
C(103)-C(104)-C(105)-C(106)	−177.3(3)
C(101)-C(100)-C(105)-C(104)	−3.2(5)
C(99)-C(100)-C(105)-C(104)	176.0(3)
C(101)-C(100)-C(105)-C(106)	177.4(3)
C(99)-C(100)-C(105)-C(106)	−3.5(4)
C(98)-C(97)-C(106)-C(105)	−0.2(5)
C(96)-C(97)-C(106)-C(105)	177.8(3)
C(98)-C(97)-C(106)-C(107)	−179.8(3)
C(96)-C(97)-C(106)-C(107)	−1.8(4)
C(104)-C(105)-C(106)-C(97)	−176.0(3)
C(100)-C(105)-C(106)-C(97)	3.4(4)
C(104)-C(105)-C(106)-C(107)	3.5(5)
C(100)-C(105)-C(106)-C(107)	−177.1(3)
C(94)-N(7)-C(107)-C(106)	102.1(3)
Cu(4)-N(7)-C(107)-C(106)	−90.3(3)
C(94)-N(7)-C(107)-C(95)	−8.8(3)
Cu(4)-N(7)-C(107)-C(95)	158.9(2)
C(97)-C(106)-C(107)-N(7)	−115.0(3)
C(105)-C(106)-C(107)-N(7)	65.4(4)
C(97)-C(106)-C(107)-C(95)	−4.3(3)
C(105)-C(106)-C(107)-C(95)	176.2(3)
O(7)-C(95)-C(107)-N(7)	10.4(3)
C(96)-C(95)-C(107)-N(7)	126.3(3)
O(7)-C(95)-C(107)-C(106)	−107.3(3)
C(96)-C(95)-C(107)-C(106)	8.6(3)
N(7)-C(94)-C(108)-C(111)	−17.9(5)
O(7)-C(94)-C(108)-C(111)	170.7(3)
N(7)-C(94)-C(108)-C(109)	102.5(4)
O(7)-C(94)-C(108)-C(109)	−68.9(3)
N(7)-C(94)-C(108)-C(110)	−137.9(3)
O(7)-C(94)-C(108)-C(110)	50.8(3)
C(124)-N(8)-C(111)-O(8)	4.0(4)
Cu(4)-N(8)-C(111)-O(8)	−162.4(2)

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Table A30 continued...

C(124)-N(8)-C(111)-C(108)	−173.5(3)
Cu(4)-N(8)-C(111)-C(108)	20.1(5)
C(112)-O(8)-C(111)-N(8)	8.5(4)
C(112)-O(8)-C(111)-C(108)	−173.6(3)
C(94)-C(108)-C(111)-N(8)	−6.6(5)
C(109)-C(108)-C(111)-N(8)	−124.8(4)
C(110)-C(108)-C(111)-N(8)	115.2(4)
C(94)-C(108)-C(111)-O(8)	175.9(3)
C(109)-C(108)-C(111)-O(8)	57.7(3)
C(110)-C(108)-C(111)-O(8)	−62.3(3)
C(111)-O(8)-C(112)-C(113)	−131.0(3)
C(111)-O(8)-C(112)-C(124)	−16.3(3)
O(8)-C(112)-C(113)-C(114)	96.1(3)
C(124)-C(112)-C(113)-C(114)	−14.5(3)
C(112)-C(113)-C(114)-C(123)	8.8(4)
C(112)-C(113)-C(114)-C(115)	−175.7(3)
C(123)-C(114)-C(115)-C(116)	1.5(5)
C(113)-C(114)-C(115)-C(116)	−173.7(3)
C(114)-C(115)-C(116)-C(117)	−1.5(5)
C(115)-C(116)-C(117)-C(118)	178.2(3)
C(115)-C(116)-C(117)-C(122)	0.1(5)
C(116)-C(117)-C(118)-C(119)	−179.9(3)
C(122)-C(117)-C(118)-C(119)	−1.7(5)
C(117)-C(118)-C(119)-C(120)	1.2(5)
C(118)-C(119)-C(120)-C(121)	0.5(5)
C(119)-C(120)-C(121)-C(122)	−1.7(5)
C(120)-C(121)-C(122)-C(123)	178.4(3)
C(120)-C(121)-C(122)-C(117)	1.2(5)
C(116)-C(117)-C(122)-C(121)	178.8(3)
C(118)-C(117)-C(122)-C(121)	0.6(5)
C(116)-C(117)-C(122)-C(123)	1.4(5)
C(118)-C(117)-C(122)-C(123)	−176.8(3)
C(115)-C(114)-C(123)-C(122)	0.0(5)
C(113)-C(114)-C(123)-C(122)	175.8(3)
C(115)-C(114)-C(123)-C(124)	−175.3(3)
C(113)-C(114)-C(123)-C(124)	0.5(4)
C(121)-C(122)-C(123)-C(114)	−178.7(3)
C(117)-C(122)-C(123)-C(114)	−1.4(5)
C(121)-C(122)-C(123)-C(124)	−4.3(5)
C(117)-C(122)-C(123)-C(124)	173.0(3)
C(111)-N(8)-C(124)-C(123)	97.7(3)
Cu(4)-N(8)-C(124)-C(123)	−95.6(3)
C(111)-N(8)-C(124)-C(112)	−14.1(3)
Cu(4)-N(8)-C(124)-C(112)	152.5(2)
C(114)-C(123)-C(124)-N(8)	−121.4(3)
C(122)-C(123)-C(124)-N(8)	63.7(4)

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Table A30 continued...

C(114)-C(123)-C(124)-C(112)	−9.5(3)
C(122)-C(123)-C(124)-C(112)	175.6(3)
O(8)-C(112)-C(124)-N(8)	18.0(3)
C(113)-C(112)-C(124)-N(8)	133.9(3)
O(8)-C(112)-C(124)-C(123)	−101.1(3)
C(113)-C(112)-C(124)-C(123)	14.9(3)
N(10)-Cu(5)-N(9)-C(125)	−7.5(3)
Cl(10)-Cu(5)-N(9)-C(125)	−107.0(3)
Cl(9)-Cu(5)-N(9)-C(125)	135.6(3)
N(10)-Cu(5)-N(9)-C(138)	−175.8(2)
Cl(10)-Cu(5)-N(9)-C(138)	84.8(3)
Cl(9)-Cu(5)-N(9)-C(138)	−32.7(2)
N(9)-Cu(5)-N(10)-C(142)	−15.0(3)
Cl(10)-Cu(5)-N(10)-C(142)	125.9(3)
Cl(9)-Cu(5)-N(10)-C(142)	−116.5(3)
N(9)-Cu(5)-N(10)-C(155)	−175.5(3)
Cl(10)-Cu(5)-N(10)-C(155)	−34.6(3)
Cl(9)-Cu(5)-N(10)-C(155)	83.0(3)
C(138)-N(9)-C(125)-O(9)	5.0(4)
Cu(5)-N(9)-C(125)-O(9)	−165.0(2)
C(138)-N(9)-C(125)-C(139)	−173.0(3)
Cu(5)-N(9)-C(125)-C(139)	17.0(5)
C(126)-O(9)-C(125)-N(9)	7.6(4)
C(126)-O(9)-C(125)-C(139)	−174.0(2)
C(125)-O(9)-C(126)-C(127)	−130.0(3)
C(125)-O(9)-C(126)-C(138)	−16.1(3)
O(9)-C(126)-C(127)-C(128)	92.1(3)
C(138)-C(126)-C(127)-C(128)	−18.2(4)
C(126)-C(127)-C(128)-C(137)	13.9(4)
C(126)-C(127)-C(128)-C(129)	−167.2(3)
C(137)-C(128)-C(129)-C(130)	−4.9(5)
C(127)-C(128)-C(129)-C(130)	176.3(4)
C(128)-C(129)-C(130)-C(131)	6.7(6)
C(129)-C(130)-C(131)-C(132)	177.9(4)
C(129)-C(130)-C(131)-C(136)	−2.2(5)
C(130)-C(131)-C(132)-C(133)	−178.8(4)
C(136)-C(131)-C(132)-C(133)	1.4(6)
C(131)-C(132)-C(133)-C(134)	1.9(6)
C(132)-C(133)-C(134)-C(135)	−2.9(6)
C(133)-C(134)-C(135)-C(136)	0.5(6)
C(134)-C(135)-C(136)-C(137)	−176.6(3)
C(134)-C(135)-C(136)-C(131)	2.7(5)
C(132)-C(131)-C(136)-C(137)	175.7(3)
C(130)-C(131)-C(136)-C(137)	−4.1(5)
C(132)-C(131)-C(136)-C(135)	−3.6(5)
C(130)-C(131)-C(136)-C(135)	176.5(3)

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Table A30 continued...

C(129)-C(128)-C(137)-C(136)	−1.6(5)
C(127)-C(128)-C(137)-C(136)	177.4(3)
C(129)-C(128)-C(137)-C(138)	177.0(3)
C(127)-C(128)-C(137)-C(138)	−4.0(4)
C(135)-C(136)-C(137)-C(128)	−174.6(3)
C(131)-C(136)-C(137)-C(128)	6.0(5)
C(135)-C(136)-C(137)-C(138)	7.0(5)
C(131)-C(136)-C(137)-C(138)	−172.3(3)
C(125)-N(9)-C(138)-C(137)	95.4(3)
Cu(5)-N(9)-C(138)-C(137)	−94.2(3)
C(125)-N(9)-C(138)-C(126)	−14.8(3)
Cu(5)-N(9)-C(138)-C(126)	155.5(2)
C(128)-C(137)-C(138)-N(9)	−118.1(3)
C(136)-C(137)-C(138)-N(9)	60.4(4)
C(128)-C(137)-C(138)-C(126)	−7.7(3)
C(136)-C(137)-C(138)-C(126)	170.8(3)
O(9)-C(126)-C(138)-N(9)	18.2(3)
C(127)-C(126)-C(138)-N(9)	133.0(3)
O(9)-C(126)-C(138)-C(137)	−98.7(3)
C(127)-C(126)-C(138)-C(137)	16.1(3)
N(9)-C(125)-C(139)-C(142)	−4.4(5)
O(9)-C(125)-C(139)-C(142)	177.5(3)
N(9)-C(125)-C(139)-C(141)	119.4(4)
O(9)-C(125)-C(139)-C(141)	−58.8(3)
N(9)-C(125)-C(139)-C(140)	−120.4(4)
O(9)-C(125)-C(139)-C(140)	61.5(3)
C(155)-N(10)-C(142)-O(10)	6.1(4)
Cu(5)-N(10)-C(142)-O(10)	−157.5(2)
C(155)-N(10)-C(142)-C(139)	−164.8(3)
Cu(5)-N(10)-C(142)-C(139)	31.6(5)
C(143)-O(10)-C(142)-N(10)	5.7(4)
C(143)-O(10)-C(142)-C(139)	178.0(3)
C(125)-C(139)-C(142)-N(10)	−21.6(5)
C(141)-C(139)-C(142)-N(10)	−144.2(3)
C(140)-C(139)-C(142)-N(10)	96.9(4)
C(125)-C(139)-C(142)-O(10)	167.1(3)
C(141)-C(139)-C(142)-O(10)	44.6(4)
C(140)-C(139)-C(142)-O(10)	−74.3(3)
C(142)-O(10)-C(143)-C(144)	−126.2(4)
C(142)-O(10)-C(143)-C(155)	−14.1(4)
O(10)-C(143)-C(144)-C(145)	94.2(4)
C(155)-C(143)-C(144)-C(145)	−15.1(4)
C(143)-C(144)-C(145)-C(154)	10.9(5)
C(143)-C(144)-C(145)-C(146)	−172.4(4)
C(154)-C(145)-C(146)-C(147)	−0.5(7)
C(144)-C(145)-C(146)-C(147)	−177.0(5)

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Table A30 continued...

C(145)-C(146)-C(147)-C(148)	0.9(7)
C(146)-C(147)-C(148)-C(149)	−179.3(4)
C(146)-C(147)-C(148)-C(153)	−1.6(7)
C(147)-C(148)-C(149)-C(150)	178.1(4)
C(153)-C(148)-C(149)-C(150)	0.4(7)
C(148)-C(149)-C(150)-C(151)	−0.7(7)
C(149)-C(150)-C(151)-C(152)	1.1(7)
C(150)-C(151)-C(152)-C(153)	−1.3(6)
C(151)-C(152)-C(153)-C(148)	1.0(6)
C(151)-C(152)-C(153)-C(154)	−179.2(4)
C(147)-C(148)-C(153)-C(152)	−178.2(4)
C(149)-C(148)-C(153)-C(152)	−0.5(6)
C(147)-C(148)-C(153)-C(154)	2.0(6)
C(149)-C(148)-C(153)-C(154)	179.7(4)
C(146)-C(145)-C(154)-C(153)	1.0(6)
C(144)-C(145)-C(154)-C(153)	178.0(4)
C(146)-C(145)-C(154)-C(155)	−179.1(4)
C(144)-C(145)-C(154)-C(155)	−2.0(5)
C(152)-C(153)-C(154)-C(145)	178.5(4)
C(148)-C(153)-C(154)-C(145)	−1.7(6)
C(152)-C(153)-C(154)-C(155)	−1.5(6)
C(148)-C(153)-C(154)-C(155)	178.4(4)
C(142)-N(10)-C(155)-C(154)	96.9(4)
Cu(5)-N(10)-C(155)-C(154)	−99.5(3)
C(142)-N(10)-C(155)-C(143)	−14.4(4)
Cu(5)-N(10)-C(155)-C(143)	149.2(2)
C(145)-C(154)-C(155)-N(10)	−118.8(4)
C(153)-C(154)-C(155)-N(10)	61.2(5)
C(145)-C(154)-C(155)-C(143)	−7.8(4)
C(153)-C(154)-C(155)-C(143)	172.2(4)
O(10)-C(143)-C(155)-N(10)	16.8(4)
C(144)-C(143)-C(155)-N(10)	131.2(3)
O(10)-C(143)-C(155)-C(154)	−100.5(3)
C(144)-C(143)-C(155)-C(154)	13.9(4)
N(12)-Cu(6)-N(11)-C(156)	−14.3(3)
Cl(12)-Cu(6)-N(11)-C(156)	−115.9(3)
Cl(11)-Cu(6)-N(11)-C(156)	131.3(3)
N(12)-Cu(6)-N(11)-C(169)	−180.0(3)
Cl(12)-Cu(6)-N(11)-C(169)	78.4(3)
Cl(11)-Cu(6)-N(11)-C(169)	−34.4(3)
N(11)-Cu(6)-N(12)-C(173)	−9.9(3)
Cl(12)-Cu(6)-N(12)-C(173)	135.4(3)
Cl(11)-Cu(6)-N(12)-C(173)	−111.8(3)
N(11)-Cu(6)-N(12)-C(186)	−168.8(3)
Cl(12)-Cu(6)-N(12)-C(186)	−23.5(3)
Cl(11)-Cu(6)-N(12)-C(186)	89.3(3)

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Table A30 continued...

C(169)-N(11)-C(156)-O(11)	5.1(4)
Cu(6)-N(11)-C(156)-O(11)	−162.8(2)
C(169)-N(11)-C(156)-C(170)	−174.1(3)
Cu(6)-N(11)-C(156)-C(170)	17.9(5)
C(157)-O(11)-C(156)-N(11)	7.6(4)
C(157)-O(11)-C(156)-C(170)	−173.0(3)
C(156)-O(11)-C(157)-C(158)	−129.5(3)
C(156)-O(11)-C(157)-C(169)	−16.1(3)
O(11)-C(157)-C(158)-C(159)	90.9(3)
C(169)-C(157)-C(158)-C(159)	−18.8(4)
C(157)-C(158)-C(159)-C(168)	14.9(4)
C(157)-C(158)-C(159)-C(160)	−166.1(3)
C(168)-C(159)-C(160)-C(161)	−4.7(5)
C(158)-C(159)-C(160)-C(161)	176.3(4)
C(159)-C(160)-C(161)-C(162)	5.6(6)
C(160)-C(161)-C(162)-C(163)	179.7(4)
C(160)-C(161)-C(162)-C(167)	−1.4(5)
C(161)-C(162)-C(163)-C(164)	178.8(4)
C(167)-C(162)-C(163)-C(164)	−0.1(6)
C(162)-C(163)-C(164)-C(165)	3.2(6)
C(163)-C(164)-C(165)-C(166)	−3.3(6)
C(164)-C(165)-C(166)-C(167)	0.1(6)
C(165)-C(166)-C(167)-C(168)	−175.2(3)
C(165)-C(166)-C(167)-C(162)	3.0(5)
C(163)-C(162)-C(167)-C(166)	−3.0(5)
C(161)-C(162)-C(167)-C(166)	178.1(3)
C(163)-C(162)-C(167)-C(168)	175.3(3)
C(161)-C(162)-C(167)-C(168)	−3.6(5)
C(160)-C(159)-C(168)-C(167)	−0.4(5)
C(158)-C(159)-C(168)-C(167)	178.7(3)
C(160)-C(159)-C(168)-C(169)	176.1(3)
C(158)-C(159)-C(168)-C(169)	−4.8(4)
C(166)-C(167)-C(168)-C(159)	−177.3(3)
C(162)-C(167)-C(168)-C(159)	4.5(5)
C(166)-C(167)-C(168)-C(169)	6.9(5)
C(162)-C(167)-C(168)-C(169)	−171.3(3)
C(156)-N(11)-C(169)-C(168)	95.7(3)
Cu(6)-N(11)-C(169)-C(168)	−96.2(3)
C(156)-N(11)-C(169)-C(157)	−15.0(3)
Cu(6)-N(11)-C(169)-C(157)	153.1(2)
C(159)-C(168)-C(169)-N(11)	−118.2(3)
C(167)-C(168)-C(169)-N(11)	58.0(4)
C(159)-C(168)-C(169)-C(157)	−7.3(4)
C(167)-C(168)-C(169)-C(157)	168.9(3)
O(11)-C(157)-C(169)-N(11)	18.4(3)
C(158)-C(157)-C(169)-N(11)	133.0(3)

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Table A30 continued...

O(11)-C(157)-C(169)-C(168)	−98.3(3)
C(158)-C(157)-C(169)-C(168)	16.3(4)
N(11)-C(156)-C(170)-C(173)	3.7(5)
O(11)-C(156)-C(170)-C(173)	−175.5(3)
N(11)-C(156)-C(170)-C(171)	128.3(3)
O(11)-C(156)-C(170)-C(171)	−51.0(4)
N(11)-C(156)-C(170)-C(172)	−112.5(4)
O(11)-C(156)-C(170)-C(172)	68.3(3)
C(186)-N(12)-C(173)-O(12)	7.6(4)
Cu(6)-N(12)-C(173)-O(12)	−154.7(2)
C(186)-N(12)-C(173)-C(170)	−162.8(3)
Cu(6)-N(12)-C(173)-C(170)	34.8(5)
C(174)-O(12)-C(173)-N(12)	4.8(4)
C(174)-O(12)-C(173)-C(170)	176.7(3)
C(156)-C(170)-C(173)-N(12)	−32.4(4)
C(171)-C(170)-C(173)-N(12)	−155.2(3)
C(172)-C(170)-C(173)-N(12)	86.2(4)
C(156)-C(170)-C(173)-O(12)	156.8(3)
C(171)-C(170)-C(173)-O(12)	34.0(4)
C(172)-C(170)-C(173)-O(12)	−84.6(3)
C(173)-O(12)-C(174)-C(175)	−129.2(3)
C(173)-O(12)-C(174)-C(186)	−14.2(3)
O(12)-C(174)-C(175)-C(176)	96.0(3)
C(186)-C(174)-C(175)-C(176)	−14.3(4)
C(174)-C(175)-C(176)-C(185)	8.8(4)
C(174)-C(175)-C(176)-C(177)	−173.3(3)
C(185)-C(176)-C(177)-C(178)	0.5(6)
C(175)-C(176)-C(177)-C(178)	−177.2(4)
C(176)-C(177)-C(178)-C(179)	−0.1(6)
C(177)-C(178)-C(179)-C(180)	178.5(4)
C(177)-C(178)-C(179)-C(184)	−0.8(6)
C(178)-C(179)-C(180)-C(181)	178.0(4)
C(184)-C(179)-C(180)-C(181)	−2.7(6)
C(179)-C(180)-C(181)-C(182)	1.4(6)
C(180)-C(181)-C(182)-C(183)	0.3(7)
C(181)-C(182)-C(183)-C(184)	−0.6(6)
C(182)-C(183)-C(184)-C(185)	179.9(4)
C(182)-C(183)-C(184)-C(179)	−0.7(6)
C(178)-C(179)-C(184)-C(183)	−178.4(4)
C(180)-C(179)-C(184)-C(183)	2.3(5)
C(178)-C(179)-C(184)-C(185)	1.1(5)
C(180)-C(179)-C(184)-C(185)	−178.2(3)
C(177)-C(176)-C(185)-C(184)	−0.2(5)
C(175)-C(176)-C(185)-C(184)	177.8(3)
C(177)-C(176)-C(185)-C(186)	−177.7(3)
C(175)-C(176)-C(185)-C(186)	0.2(4)

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Table A30 continued...

C(183)-C(184)-C(185)-C(176)	178.8(4)
C(179)-C(184)-C(185)-C(176)	−0.6(5)
C(183)-C(184)-C(185)-C(186)	−4.2(6)
C(179)-C(184)-C(185)-C(186)	176.4(3)
C(173)-N(12)-C(186)-C(185)	93.9(3)
Cu(6)-N(12)-C(186)-C(185)	−104.1(3)
C(173)-N(12)-C(186)-C(174)	−15.9(3)
Cu(6)-N(12)-C(186)-C(174)	146.0(2)
C(176)-C(185)-C(186)-N(12)	−119.8(3)
C(184)-C(185)-C(186)-N(12)	62.9(5)
C(176)-C(185)-C(186)-C(174)	−9.1(4)
C(184)-C(185)-C(186)-C(174)	173.6(3)
O(12)-C(174)-C(186)-N(12)	17.8(3)
C(175)-C(174)-C(186)-N(12)	132.6(3)
O(12)-C(174)-C(186)-C(185)	−100.4(3)
C(175)-C(174)-C(186)-C(185)	14.4(4)
N(14)-Cu(7)-N(13)-C(187)	−8.8(3)
Cl(13)-Cu(7)-N(13)-C(187)	139.7(3)
Cl(14)-Cu(7)-N(13)-C(187)	−109.2(3)
N(14)-Cu(7)-N(13)-C(200)	−176.8(3)
Cl(13)-Cu(7)-N(13)-C(200)	−28.3(2)
Cl(14)-Cu(7)-N(13)-C(200)	82.8(3)
N(13)-Cu(7)-N(14)-C(204)	−12.9(3)
Cl(13)-Cu(7)-N(14)-C(204)	−112.5(3)
Cl(14)-Cu(7)-N(14)-C(204)	132.1(3)
N(13)-Cu(7)-N(14)-C(217)	−178.8(2)
Cl(13)-Cu(7)-N(14)-C(217)	81.6(3)
Cl(14)-Cu(7)-N(14)-C(217)	−33.8(2)
C(200)-N(13)-C(187)-O(13)	7.8(4)
Cu(7)-N(13)-C(187)-O(13)	−162.1(2)
C(200)-N(13)-C(187)-C(201)	−164.1(3)
Cu(7)-N(13)-C(187)-C(201)	26.0(5)
C(188)-O(13)-C(187)-N(13)	5.2(4)
C(188)-O(13)-C(187)-C(201)	178.3(3)
C(187)-O(13)-C(188)-C(189)	−128.2(3)
C(187)-O(13)-C(188)-C(200)	−14.9(4)
O(13)-C(188)-C(189)-C(190)	89.4(3)
C(200)-C(188)-C(189)-C(190)	−20.1(4)
C(188)-C(189)-C(190)-C(199)	16.0(4)
C(188)-C(189)-C(190)-C(191)	−164.5(4)
C(199)-C(190)-C(191)-C(192)	0.6(6)
C(189)-C(190)-C(191)-C(192)	−178.9(4)
C(190)-C(191)-C(192)-C(193)	1.8(6)
C(191)-C(192)-C(193)-C(198)	−0.6(6)
C(191)-C(192)-C(193)-C(194)	178.5(4)
C(198)-C(193)-C(194)-C(195)	3.3(6)

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Table A30 continued...

C(192)-C(193)-C(194)-C(195)	−175.8(4)
C(193)-C(194)-C(195)-C(196)	−0.4(6)
C(194)-C(195)-C(196)-C(197)	−2.4(6)
C(195)-C(196)-C(197)-C(198)	2.1(5)
C(194)-C(193)-C(198)-C(197)	−3.6(5)
C(192)-C(193)-C(198)-C(197)	175.6(3)
C(194)-C(193)-C(198)-C(199)	178.1(3)
C(192)-C(193)-C(198)-C(199)	−2.8(5)
C(196)-C(197)-C(198)-C(193)	0.9(5)
C(196)-C(197)-C(198)-C(199)	179.2(3)
C(191)-C(190)-C(199)-C(198)	−4.1(5)
C(189)-C(190)-C(199)-C(198)	175.4(3)
C(191)-C(190)-C(199)-C(200)	175.1(3)
C(189)-C(190)-C(199)-C(200)	−5.3(4)
C(193)-C(198)-C(199)-C(190)	5.2(5)
C(197)-C(198)-C(199)-C(190)	−173.1(3)
C(193)-C(198)-C(199)-C(200)	−174.0(3)
C(197)-C(198)-C(199)-C(200)	7.7(5)
C(187)-N(13)-C(200)-C(199)	92.6(3)
Cu(7)-N(13)-C(200)-C(199)	−97.5(3)
C(187)-N(13)-C(200)-C(188)	−16.5(3)
Cu(7)-N(13)-C(200)-C(188)	153.4(2)
C(190)-C(199)-C(200)-N(13)	−117.4(3)
C(198)-C(199)-C(200)-N(13)	61.8(4)
C(190)-C(199)-C(200)-C(188)	−7.6(4)
C(198)-C(199)-C(200)-C(188)	171.6(3)
O(13)-C(188)-C(200)-N(13)	18.6(3)
C(189)-C(188)-C(200)-N(13)	132.7(3)
O(13)-C(188)-C(200)-C(199)	−96.9(3)
C(189)-C(188)-C(200)-C(199)	17.2(4)
N(13)-C(187)-C(201)-C(204)	−19.7(5)
O(13)-C(187)-C(201)-C(204)	168.0(3)
N(13)-C(187)-C(201)-C(203)	−141.5(4)
O(13)-C(187)-C(201)-C(203)	46.3(4)
N(13)-C(187)-C(201)-C(202)	99.3(4)
O(13)-C(187)-C(201)-C(202)	−72.9(4)
C(217)-N(14)-C(204)-O(14)	5.1(4)
Cu(7)-N(14)-C(204)-O(14)	−162.9(2)
C(217)-N(14)-C(204)-C(201)	−170.9(3)
Cu(7)-N(14)-C(204)-C(201)	21.1(5)
C(205)-O(14)-C(204)-N(14)	3.7(4)
C(205)-O(14)-C(204)-C(201)	−179.7(3)
C(187)-C(201)-C(204)-N(14)	−5.6(5)
C(203)-C(201)-C(204)-N(14)	117.9(4)
C(202)-C(201)-C(204)-N(14)	−122.5(4)
C(187)-C(201)-C(204)-O(14)	178.2(3)

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Table A30 continued...

C(203)-C(201)-C(204)-O(14)	−58.2(4)
C(202)-C(201)-C(204)-O(14)	61.3(4)
C(204)-O(14)-C(205)-C(206)	−124.9(3)
C(204)-O(14)-C(205)-C(217)	−10.2(3)
O(14)-C(205)-C(206)-C(207)	98.1(3)
C(217)-C(205)-C(206)-C(207)	−13.1(4)
C(205)-C(206)-C(207)-C(216)	9.9(4)
C(205)-C(206)-C(207)-C(208)	−170.1(3)
C(216)-C(207)-C(208)-C(209)	−1.9(5)
C(206)-C(207)-C(208)-C(209)	178.1(3)
C(207)-C(208)-C(209)-C(210)	1.9(5)
C(208)-C(209)-C(210)-C(211)	−179.1(3)
C(208)-C(209)-C(210)-C(215)	2.0(5)
C(209)-C(210)-C(211)-C(212)	−177.4(3)
C(215)-C(210)-C(211)-C(212)	1.4(5)
C(210)-C(211)-C(212)-C(213)	0.8(5)
C(211)-C(212)-C(213)-C(214)	−1.3(5)
C(212)-C(213)-C(214)-C(215)	−0.5(5)
C(213)-C(214)-C(215)-C(216)	−175.8(3)
C(213)-C(214)-C(215)-C(210)	2.7(5)
C(209)-C(210)-C(215)-C(214)	175.7(3)
C(211)-C(210)-C(215)-C(214)	−3.1(4)
C(209)-C(210)-C(215)-C(216)	−5.7(4)
C(211)-C(210)-C(215)-C(216)	175.4(3)
C(208)-C(207)-C(216)-C(215)	−2.0(5)
C(206)-C(207)-C(216)-C(215)	177.9(3)
C(208)-C(207)-C(216)-C(217)	177.3(3)
C(206)-C(207)-C(216)-C(217)	−2.8(4)
C(214)-C(215)-C(216)-C(207)	−175.8(3)
C(210)-C(215)-C(216)-C(207)	5.8(4)
C(214)-C(215)-C(216)-C(217)	5.1(5)
C(210)-C(215)-C(216)-C(217)	−173.4(3)
C(204)-N(14)-C(217)-C(216)	99.2(3)
Cu(7)-N(14)-C(217)-C(216)	−92.6(3)
C(204)-N(14)-C(217)-C(205)	−11.0(3)
Cu(7)-N(14)-C(217)-C(205)	157.2(2)
C(207)-C(216)-C(217)-N(14)	−115.8(3)
C(215)-C(216)-C(217)-N(14)	63.4(4)
C(207)-C(216)-C(217)-C(205)	−5.6(3)
C(215)-C(216)-C(217)-C(205)	173.7(3)
O(14)-C(205)-C(217)-N(14)	12.5(3)
C(206)-C(205)-C(217)-N(14)	127.9(3)
O(14)-C(205)-C(217)-C(216)	−103.8(3)
C(206)-C(205)-C(217)-C(216)	11.6(3)
N(16)-Cu(8)-N(15)-C(218)	−8.7(3)
Cl(15)-Cu(8)-N(15)-C(218)	137.7(3)

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Table A30 continued...

Cl(16)-Cu(8)-N(15)-C(218)	−108.3(3)
N(16)-Cu(8)-N(15)-C(231)	−178.3(3)
Cl(15)-Cu(8)-N(15)-C(231)	−31.9(3)
Cl(16)-Cu(8)-N(15)-C(231)	82.1(3)
N(15)-Cu(8)-N(16)-C(235)	−11.3(3)
Cl(15)-Cu(8)-N(16)-C(235)	−111.8(3)
Cl(16)-Cu(8)-N(16)-C(235)	130.2(3)
N(15)-Cu(8)-N(16)-C(248)	−175.9(2)
Cl(15)-Cu(8)-N(16)-C(248)	83.6(3)
Cl(16)-Cu(8)-N(16)-C(248)	−34.4(2)
C(231)-N(15)-C(218)-O(15)	6.2(4)
Cu(8)-N(15)-C(218)-O(15)	−165.1(2)
C(231)-N(15)-C(218)-C(232)	−167.0(3)
Cu(8)-N(15)-C(218)-C(232)	21.8(5)
C(219)-O(15)-C(218)-N(15)	5.2(4)
C(219)-O(15)-C(218)-C(232)	179.4(3)
C(218)-O(15)-C(219)-C(220)	−127.4(3)
C(218)-O(15)-C(219)-C(231)	−13.3(4)
O(15)-C(219)-C(220)-C(221)	91.6(3)
C(231)-C(219)-C(220)-C(221)	−18.4(4)
C(219)-C(220)-C(221)-C(230)	15.0(4)
C(219)-C(220)-C(221)-C(222)	−169.2(4)
C(230)-C(221)-C(222)-C(223)	−0.6(6)
C(220)-C(221)-C(222)-C(223)	−176.0(4)
C(221)-C(222)-C(223)-C(224)	3.1(6)
C(222)-C(223)-C(224)-C(225)	176.3(4)
C(222)-C(223)-C(224)-C(229)	−1.6(6)
C(223)-C(224)-C(225)-C(226)	−174.4(4)
C(229)-C(224)-C(225)-C(226)	3.5(6)
C(224)-C(225)-C(226)-C(227)	−0.2(6)
C(225)-C(226)-C(227)-C(228)	−2.7(6)
C(226)-C(227)-C(228)-C(229)	2.1(5)
C(227)-C(228)-C(229)-C(230)	177.2(3)
C(227)-C(228)-C(229)-C(224)	1.2(5)
C(225)-C(224)-C(229)-C(228)	−4.0(5)
C(223)-C(224)-C(229)-C(228)	173.9(3)
C(225)-C(224)-C(229)-C(230)	179.7(3)
C(223)-C(224)-C(229)-C(230)	−2.3(5)
C(222)-C(221)-C(230)-C(229)	−3.4(6)
C(220)-C(221)-C(230)-C(229)	172.7(3)
C(222)-C(221)-C(230)-C(231)	178.1(3)
C(220)-C(221)-C(230)-C(231)	−5.8(4)
C(228)-C(229)-C(230)-C(221)	−171.3(3)
C(224)-C(229)-C(230)-C(221)	4.8(5)
C(228)-C(229)-C(230)-C(231)	6.9(5)
C(224)-C(229)-C(230)-C(231)	−177.0(3)

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Table A30 continued...

C(218)-N(15)-C(231)-C(230)	95.1(3)
Cu(8)-N(15)-C(231)-C(230)	−93.6(3)
C(218)-N(15)-C(231)-C(219)	−14.1(4)
Cu(8)-N(15)-C(231)-C(219)	157.1(2)
C(221)-C(230)-C(231)-N(15)	−115.9(3)
C(229)-C(230)-C(231)-N(15)	65.7(4)
C(221)-C(230)-C(231)-C(219)	−5.8(4)
C(229)-C(230)-C(231)-C(219)	175.8(3)
O(15)-C(219)-C(231)-N(15)	16.2(4)
C(220)-C(219)-C(231)-N(15)	130.7(3)
O(15)-C(219)-C(231)-C(230)	−99.6(3)
C(220)-C(219)-C(231)-C(230)	15.0(4)
N(15)-C(218)-C(232)-C(235)	−13.6(5)
O(15)-C(218)-C(232)-C(235)	173.0(3)
N(15)-C(218)-C(232)-C(234)	−135.4(4)
O(15)-C(218)-C(232)-C(234)	51.2(4)
N(15)-C(218)-C(232)-C(233)	105.5(4)
O(15)-C(218)-C(232)-C(233)	−67.9(4)
C(248)-N(16)-C(235)-O(16)	3.9(4)
Cu(8)-N(16)-C(235)-O(16)	−163.0(2)
C(248)-N(16)-C(235)-C(232)	−171.3(3)
Cu(8)-N(16)-C(235)-C(232)	21.8(5)
C(236)-O(16)-C(235)-N(16)	4.4(4)
C(236)-O(16)-C(235)-C(232)	−179.6(3)
C(218)-C(232)-C(235)-N(16)	−10.2(5)
C(234)-C(232)-C(235)-N(16)	112.6(4)
C(233)-C(232)-C(235)-N(16)	−126.9(4)
C(218)-C(232)-C(235)-O(16)	174.4(3)
C(234)-C(232)-C(235)-O(16)	−62.7(4)
C(233)-C(232)-C(235)-O(16)	57.7(4)
C(235)-O(16)-C(236)-C(237)	−124.6(3)
C(235)-O(16)-C(236)-C(248)	−10.1(3)
O(16)-C(236)-C(237)-C(238)	100.3(3)
C(248)-C(236)-C(237)-C(238)	−11.0(4)
C(236)-C(237)-C(238)-C(247)	8.5(4)
C(236)-C(237)-C(238)-C(239)	−173.2(3)
C(247)-C(238)-C(239)-C(240)	−3.1(5)
C(237)-C(238)-C(239)-C(240)	178.7(3)
C(238)-C(239)-C(240)-C(241)	3.1(5)
C(239)-C(240)-C(241)-C(242)	−179.7(3)
C(239)-C(240)-C(241)-C(246)	1.3(5)
C(240)-C(241)-C(242)-C(243)	−177.3(3)
C(246)-C(241)-C(242)-C(243)	1.7(5)
C(241)-C(242)-C(243)-C(244)	0.7(6)
C(242)-C(243)-C(244)-C(245)	−1.5(6)
C(243)-C(244)-C(245)-C(246)	−0.2(5)

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Table A30 continued...

C(244)-C(245)-C(246)-C(247)	−176.0(3)
C(244)-C(245)-C(246)-C(241)	2.7(5)
C(240)-C(241)-C(246)-C(247)	−5.6(4)
C(242)-C(241)-C(246)-C(247)	175.4(3)
C(240)-C(241)-C(246)-C(245)	175.7(3)
C(242)-C(241)-C(246)-C(245)	−3.4(4)
C(239)-C(238)-C(247)-C(246)	−1.3(5)
C(237)-C(238)-C(247)-C(246)	177.1(3)
C(239)-C(238)-C(247)-C(248)	179.2(3)
C(237)-C(238)-C(247)-C(248)	−2.5(4)
C(245)-C(246)-C(247)-C(238)	−175.7(3)
C(241)-C(246)-C(247)-C(238)	5.6(5)
C(245)-C(246)-C(247)-C(248)	3.7(5)
C(241)-C(246)-C(247)-C(248)	−175.0(3)
C(235)-N(16)-C(248)-C(247)	101.4(3)
Cu(8)-N(16)-C(248)-C(247)	−91.7(3)
C(235)-N(16)-C(248)-C(236)	−9.8(3)
Cu(8)-N(16)-C(248)-C(236)	157.2(2)
C(238)-C(247)-C(248)-N(16)	−115.4(3)
C(246)-C(247)-C(248)-N(16)	65.1(4)
C(238)-C(247)-C(248)-C(236)	−4.6(4)
C(246)-C(247)-C(248)-C(236)	175.9(3)
O(16)-C(236)-C(248)-N(16)	11.7(3)
C(237)-C(236)-C(248)-N(16)	127.1(3)
O(16)-C(236)-C(248)-C(247)	−105.7(3)
C(237)-C(236)-C(248)-C(247)	9.7(4)

Table A31: Anisotropic displacement parameters ($Å^2 \times 10^3$) for $CuCl_2 \cdot$**2.97**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cu(1)	14(1)	17(1)	18(1)	2(1)	−3(1)	−5(1)
Cl(1)	25(1)	19(1)	21(1)	1(1)	−8(1)	−9(1)
Cl(2)	17(1)	23(1)	34(1)	4(1)	−8(1)	−2(1)
O(1)	24(1)	29(1)	17(1)	−2(1)	1(1)	−12(1)
O(2)	16(1)	30(1)	19(1)	3(1)	−4(1)	−6(1)
N(1)	16(1)	15(1)	18(1)	0(1)	0(1)	−5(1)
N(2)	14(1)	16(1)	17(1)	2(1)	−1(1)	−4(1)
C(1)	19(2)	17(1)	14(1)	−1(1)	−1(1)	−2(1)
C(2)	25(2)	24(2)	19(2)	−1(1)	1(1)	−9(1)
C(3)	25(2)	33(2)	20(2)	1(1)	1(1)	−14(2)
C(4)	19(2)	25(2)	22(2)	2(1)	0(1)	−6(1)
C(5)	25(2)	34(2)	25(2)	11(1)	−1(1)	−12(2)
C(6)	23(2)	28(2)	40(2)	14(2)	−5(2)	−11(2)
C(7)	13(2)	22(2)	38(2)	4(1)	−2(1)	−6(1)
C(8)	16(2)	20(2)	49(2)	−2(2)	−1(2)	−6(1)
C(9)	17(2)	26(2)	46(2)	−6(2)	1(2)	−11(1)
C(10)	20(2)	31(2)	30(2)	−5(2)	−1(1)	−12(1)
C(11)	13(2)	27(2)	26(2)	−1(1)	2(1)	−9(1)
C(12)	14(2)	22(2)	24(2)	−1(1)	3(1)	−7(1)
C(13)	14(2)	21(2)	23(2)	2(1)	2(1)	−5(1)
C(14)	18(2)	22(2)	16(1)	1(1)	0(1)	−3(1)
C(15)	13(1)	14(1)	19(1)	1(1)	−1(1)	−4(1)
C(16)	25(2)	20(2)	28(2)	−2(1)	−2(1)	−11(1)
C(17)	23(2)	22(2)	20(2)	4(1)	−5(1)	−2(1)
C(18)	19(2)	18(1)	16(1)	2(1)	−2(1)	−7(1)
C(19)	16(2)	24(2)	17(2)	−1(1)	1(1)	−5(1)
C(20)	21(2)	24(2)	20(2)	0(1)	−2(1)	−8(1)
C(21)	19(2)	19(1)	14(1)	2(1)	−2(1)	−7(1)
C(22)	25(2)	22(2)	18(2)	−4(1)	1(1)	−11(1)
C(23)	28(2)	20(2)	16(1)	3(1)	−2(1)	−11(1)
C(24)	21(2)	21(2)	12(1)	1(1)	−1(1)	−6(1)
C(25)	26(2)	20(2)	19(2)	2(1)	−4(1)	−5(1)
C(26)	27(2)	23(2)	25(2)	7(1)	−8(1)	−4(1)
C(27)	23(2)	28(2)	28(2)	5(1)	−7(1)	−12(1)
C(28)	23(2)	24(2)	21(2)	6(1)	−8(1)	−10(1)
C(29)	18(2)	22(2)	16(1)	2(1)	−3(1)	−7(1)
C(30)	19(2)	18(1)	14(1)	2(1)	−2(1)	−7(1)
C(31)	14(1)	18(1)	19(1)	0(1)	−1(1)	−5(1)
Cu(2)	15(1)	16(1)	15(1)	2(1)	−2(1)	−6(1)
Cl(3)	18(1)	21(1)	28(1)	4(1)	−6(1)	−2(1)
Cl(4)	26(1)	20(1)	19(1)	0(1)	−4(1)	−10(1)
O(3)	26(1)	29(1)	15(1)	−2(1)	0(1)	−14(1)
O(4)	16(1)	31(1)	19(1)	3(1)	−2(1)	−7(1)

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Table A31 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(3)	17(1)	14(1)	16(1)	1(1)	0(1)	−4(1)
N(4)	15(1)	19(1)	16(1)	2(1)	−1(1)	−6(1)
C(32)	17(2)	15(1)	13(1)	0(1)	0(1)	−2(1)
C(33)	23(2)	21(2)	17(1)	−3(1)	2(1)	−9(1)
C(34)	22(2)	31(2)	17(2)	1(1)	−2(1)	−12(1)
C(35)	17(2)	25(2)	18(2)	3(1)	0(1)	−6(1)
C(36)	18(2)	32(2)	21(2)	11(1)	−1(1)	−7(1)
C(37)	18(2)	27(2)	32(2)	11(1)	−4(1)	−5(1)
C(38)	15(2)	17(1)	30(2)	4(1)	−2(1)	−4(1)
C(39)	19(2)	15(1)	44(2)	0(1)	−4(2)	−5(1)
C(40)	19(2)	23(2)	39(2)	−5(1)	−3(2)	−7(1)
C(41)	16(2)	25(2)	28(2)	−2(1)	−1(1)	−10(1)
C(42)	15(2)	20(2)	23(2)	0(1)	0(1)	−6(1)
C(43)	11(1)	19(1)	20(2)	1(1)	2(1)	−5(1)
C(44)	11(1)	21(1)	17(1)	1(1)	0(1)	−6(1)
C(45)	13(1)	20(1)	16(1)	2(1)	2(1)	−3(1)
C(46)	15(1)	16(1)	18(1)	0(1)	−3(1)	−5(1)
C(47)	27(2)	22(2)	29(2)	−4(1)	2(1)	−14(1)
C(48)	21(2)	27(2)	23(2)	4(1)	−6(1)	−4(1)
C(49)	20(2)	17(1)	20(2)	1(1)	−4(1)	−8(1)
C(50)	16(2)	22(2)	20(2)	1(1)	2(1)	−5(1)
C(51)	19(2)	29(2)	20(2)	2(1)	0(1)	−11(1)
C(52)	22(2)	20(2)	17(1)	2(1)	−3(1)	−5(1)
C(53)	23(2)	25(2)	16(1)	−2(1)	2(1)	−14(1)
C(54)	30(2)	19(1)	17(1)	0(1)	−2(1)	−12(1)
C(55)	24(2)	19(1)	13(1)	0(1)	−2(1)	−7(1)
C(56)	30(2)	20(2)	19(2)	3(1)	−7(1)	−6(1)
C(57)	28(2)	30(2)	25(2)	6(1)	−6(2)	−4(2)
C(58)	24(2)	33(2)	22(2)	5(1)	−5(1)	−13(2)
C(59)	26(2)	28(2)	18(2)	8(1)	−7(1)	−12(1)
C(60)	21(2)	21(1)	13(1)	1(1)	−1(1)	−8(1)
C(61)	19(2)	20(1)	12(1)	1(1)	0(1)	−8(1)
C(62)	17(2)	21(1)	16(1)	0(1)	1(1)	−6(1)
Cu(3)	12(1)	13(1)	11(1)	2(1)	−2(1)	−2(1)
Cl(5)	24(1)	16(1)	15(1)	4(1)	−1(1)	−5(1)
Cl(6)	14(1)	20(1)	21(1)	1(1)	−6(1)	−4(1)
O(5)	15(1)	27(1)	17(1)	−3(1)	−5(1)	3(1)
O(6)	20(1)	23(1)	12(1)	4(1)	−2(1)	−1(1)
N(5)	14(1)	14(1)	12(1)	1(1)	−1(1)	−3(1)
N(6)	10(1)	16(1)	12(1)	0(1)	0(1)	−2(1)
C(63)	12(1)	14(1)	16(1)	0(1)	−3(1)	−2(1)
C(64)	16(2)	22(2)	18(1)	−1(1)	−2(1)	−4(1)
C(65)	15(2)	24(2)	20(2)	−3(1)	−3(1)	0(1)
C(66)	16(2)	17(1)	15(1)	1(1)	−1(1)	−1(1)
C(67)	17(2)	17(1)	19(2)	3(1)	1(1)	−2(1)
C(68)	24(2)	15(1)	17(1)	1(1)	−3(1)	−5(1)

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Table A31 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(69)	22(2)	17(1)	11(1)	1(1)	−2(1)	−7(1)
C(70)	26(2)	21(2)	16(1)	1(1)	−3(1)	−10(1)
C(71)	23(2)	30(2)	16(1)	0(1)	−7(1)	−11(1)
C(72)	21(2)	22(2)	21(2)	0(1)	−6(1)	−3(1)
C(73)	19(2)	18(1)	17(1)	−3(1)	−3(1)	−1(1)
C(74)	15(1)	17(1)	12(1)	1(1)	−1(1)	−3(1)
C(75)	15(1)	17(1)	13(1)	0(1)	1(1)	−4(1)
C(76)	11(1)	17(1)	14(1)	−2(1)	3(1)	−1(1)
C(77)	14(1)	16(1)	16(1)	0(1)	−4(1)	−2(1)
C(78)	22(2)	25(2)	17(1)	−2(1)	−9(1)	−10(1)
C(79)	21(2)	14(1)	30(2)	8(1)	−7(1)	−3(1)
C(80)	19(2)	15(1)	12(1)	1(1)	0(1)	−6(1)
C(81)	19(2)	20(1)	14(1)	3(1)	−1(1)	−4(1)
C(82)	27(2)	26(2)	15(1)	−2(1)	1(1)	−8(1)
C(83)	17(2)	22(2)	16(1)	−2(1)	−3(1)	−5(1)
C(84)	29(2)	31(2)	20(2)	−8(1)	−5(1)	−9(2)
C(85)	24(2)	24(2)	30(2)	−9(1)	−7(1)	−9(1)
C(86)	17(2)	16(1)	30(2)	−1(1)	−6(1)	−3(1)
C(87)	19(2)	15(1)	39(2)	0(1)	−2(1)	−6(1)
C(88)	20(2)	19(2)	38(2)	8(1)	−2(2)	−5(1)
C(89)	18(2)	21(2)	25(2)	5(1)	2(1)	−1(1)
C(90)	17(2)	16(1)	21(2)	1(1)	1(1)	0(1)
C(91)	10(1)	14(1)	19(1)	0(1)	−1(1)	0(1)
C(92)	13(1)	15(1)	16(1)	−2(1)	−1(1)	−3(1)
C(93)	15(1)	16(1)	15(1)	0(1)	1(1)	−4(1)
Cu(4)	13(1)	13(1)	13(1)	2(1)	−3(1)	−3(1)
Cl(7)	27(1)	17(1)	18(1)	6(1)	−1(1)	−6(1)
Cl(8)	15(1)	20(1)	23(1)	2(1)	−7(1)	−5(1)
O(7)	12(1)	29(1)	16(1)	−3(1)	−3(1)	2(1)
O(8)	18(1)	24(1)	14(1)	3(1)	−1(1)	0(1)
N(7)	14(1)	17(1)	13(1)	1(1)	−3(1)	−2(1)
N(8)	12(1)	15(1)	15(1)	0(1)	−2(1)	−2(1)
C(94)	11(1)	16(1)	18(1)	1(1)	−2(1)	−3(1)
C(95)	16(2)	27(2)	18(2)	−3(1)	−2(1)	−4(1)
C(96)	15(2)	25(2)	22(2)	−5(1)	−3(1)	0(1)
C(97)	15(1)	22(2)	13(1)	2(1)	−1(1)	−4(1)
C(98)	21(2)	16(1)	18(2)	2(1)	−1(1)	−2(1)
C(99)	26(2)	16(1)	17(1)	2(1)	−2(1)	−8(1)
C(100)	24(2)	21(1)	11(1)	2(1)	−2(1)	−9(1)
C(101)	25(2)	27(2)	14(1)	3(1)	−2(1)	−12(1)
C(102)	22(2)	33(2)	20(2)	2(1)	−8(1)	−11(1)
C(103)	22(2)	29(2)	21(2)	−2(1)	−7(1)	−3(1)
C(104)	18(2)	22(2)	18(1)	−2(1)	−3(1)	−1(1)
C(105)	14(1)	22(1)	11(1)	1(1)	−1(1)	−3(1)
C(106)	17(2)	16(1)	11(1)	−1(1)	1(1)	−5(1)
C(107)	13(1)	19(1)	15(1)	−1(1)	1(1)	−3(1)

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Table A31 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(108)	12(1)	16(1)	16(1)	−1(1)	−5(1)	−2(1)
C(109)	17(2)	13(1)	28(2)	3(1)	−3(1)	−3(1)
C(110)	20(2)	22(2)	17(1)	−2(1)	−7(1)	−7(1)
C(111)	15(1)	14(1)	15(1)	0(1)	−1(1)	−2(1)
C(112)	18(2)	20(1)	15(1)	2(1)	−1(1)	−2(1)
C(113)	24(2)	22(2)	15(1)	0(1)	1(1)	−5(1)
C(114)	13(1)	21(2)	20(2)	−2(1)	0(1)	−2(1)
C(115)	22(2)	32(2)	22(2)	−10(1)	−1(1)	−9(1)
C(116)	18(2)	23(2)	34(2)	−9(1)	−6(1)	−4(1)
C(117)	14(2)	15(1)	32(2)	−5(1)	−4(1)	−1(1)
C(118)	20(2)	15(1)	40(2)	−1(1)	−6(1)	−6(1)
C(119)	23(2)	19(2)	40(2)	8(1)	−8(2)	−7(1)
C(120)	18(2)	22(2)	25(2)	5(1)	−4(1)	−2(1)
C(121)	14(1)	18(1)	20(2)	−1(1)	−3(1)	0(1)
C(122)	10(1)	12(1)	24(2)	−1(1)	−3(1)	−1(1)
C(123)	11(1)	16(1)	18(1)	−2(1)	−2(1)	−2(1)
C(124)	14(1)	16(1)	14(1)	0(1)	0(1)	−3(1)
Cu(5)	19(1)	18(1)	21(1)	−2(1)	1(1)	−7(1)
Cl(9)	26(1)	27(1)	25(1)	−3(1)	−3(1)	−14(1)
Cl(10)	31(1)	23(1)	30(1)	−2(1)	7(1)	−4(1)
O(9)	24(1)	21(1)	19(1)	0(1)	0(1)	−9(1)
O(10)	32(2)	20(1)	29(1)	0(1)	8(1)	−10(1)
N(9)	11(1)	20(1)	23(1)	4(1)	−4(1)	−4(1)
N(10)	14(1)	23(1)	19(1)	3(1)	−2(1)	−3(1)
C(125)	13(1)	16(1)	21(2)	3(1)	−5(1)	−4(1)
C(126)	21(2)	21(2)	21(2)	5(1)	−5(1)	−10(1)
C(127)	40(2)	34(2)	19(2)	6(1)	−6(2)	−16(2)
C(128)	27(2)	28(2)	34(2)	15(1)	−12(2)	−18(2)
C(129)	44(2)	37(2)	32(2)	21(2)	−20(2)	−24(2)
C(130)	48(3)	33(2)	58(3)	31(2)	−39(2)	−25(2)
C(131)	26(2)	22(2)	63(3)	23(2)	−23(2)	−13(2)
C(132)	30(2)	22(2)	76(3)	20(2)	−29(2)	−9(2)
C(133)	19(2)	16(2)	97(4)	9(2)	−20(2)	−2(1)
C(134)	25(2)	21(2)	62(3)	−1(2)	−4(2)	−6(2)
C(135)	18(2)	16(1)	47(2)	5(1)	−7(2)	−6(1)
C(136)	18(2)	17(1)	42(2)	10(1)	−11(2)	−9(1)
C(137)	20(2)	20(1)	30(2)	12(1)	−8(1)	−12(1)
C(138)	16(2)	18(1)	24(2)	3(1)	−5(1)	−8(1)
C(139)	14(1)	14(1)	18(1)	0(1)	−3(1)	−4(1)
C(140)	13(2)	22(2)	29(2)	0(1)	−3(1)	0(1)
C(141)	21(2)	25(2)	30(2)	1(1)	−11(1)	−6(1)
C(142)	10(1)	18(1)	22(2)	3(1)	−1(1)	−2(1)
C(143)	33(2)	23(2)	35(2)	4(2)	14(2)	−4(2)
C(144)	47(3)	27(2)	37(2)	9(2)	18(2)	−6(2)
C(145)	44(3)	40(2)	27(2)	14(2)	11(2)	7(2)
C(146)	54(3)	56(3)	37(2)	29(2)	23(2)	15(3)

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Table A31 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(147)	37(3)	60(3)	31(2)	16(2)	7(2)	11(2)
C(148)	36(2)	68(3)	18(2)	3(2)	0(2)	17(2)
C(149)	38(3)	76(4)	23(2)	−9(2)	−11(2)	16(2)
C(150)	34(3)	93(4)	38(2)	−19(3)	−13(2)	1(3)
C(151)	37(2)	72(3)	33(2)	−13(2)	−5(2)	−3(2)
C(152)	26(2)	52(2)	24(2)	−3(2)	−6(2)	0(2)
C(153)	26(2)	51(2)	13(2)	1(2)	1(1)	9(2)
C(154)	26(2)	39(2)	21(2)	7(2)	6(1)	8(2)
C(155)	23(2)	25(2)	20(2)	4(1)	3(1)	−1(1)
Cu(6)	19(1)	22(1)	22(1)	−4(1)	0(1)	−8(1)
Cl(11)	28(1)	44(1)	35(1)	−7(1)	−3(1)	−22(1)
Cl(12)	36(1)	24(1)	28(1)	−4(1)	6(1)	−8(1)
O(11)	23(1)	23(1)	19(1)	2(1)	1(1)	−8(1)
O(12)	22(1)	19(1)	26(1)	2(1)	2(1)	−6(1)
N(11)	13(1)	21(1)	22(1)	4(1)	−5(1)	−6(1)
N(12)	15(1)	23(1)	16(1)	3(1)	−1(1)	−2(1)
C(156)	11(1)	21(1)	20(2)	2(1)	−4(1)	−4(1)
C(157)	20(2)	25(2)	24(2)	8(1)	0(1)	−10(1)
C(158)	32(2)	35(2)	25(2)	12(2)	−6(2)	−12(2)
C(159)	29(2)	27(2)	33(2)	11(1)	−9(2)	−16(2)
C(160)	42(2)	34(2)	34(2)	20(2)	−16(2)	−21(2)
C(161)	31(2)	33(2)	45(2)	26(2)	−18(2)	−15(2)
C(162)	23(2)	22(2)	51(2)	20(2)	−10(2)	−9(1)
C(163)	25(2)	26(2)	71(3)	25(2)	−11(2)	−7(2)
C(164)	26(2)	21(2)	67(3)	6(2)	−2(2)	0(2)
C(165)	30(2)	20(2)	48(2)	−1(2)	−1(2)	−4(2)
C(166)	24(2)	18(2)	44(2)	4(1)	−5(2)	−8(1)
C(167)	22(2)	19(2)	44(2)	15(2)	−8(2)	−11(1)
C(168)	18(2)	22(2)	30(2)	13(1)	−6(1)	−11(1)
C(169)	16(2)	21(2)	27(2)	3(1)	−5(1)	−7(1)
C(170)	12(1)	16(1)	16(1)	0(1)	−3(1)	−3(1)
C(171)	21(2)	23(2)	26(2)	3(1)	−9(1)	−7(1)
C(172)	13(2)	24(2)	23(2)	1(1)	−2(1)	0(1)
C(173)	11(1)	17(1)	22(2)	4(1)	−2(1)	−2(1)
C(174)	19(2)	23(2)	27(2)	1(1)	3(1)	−5(1)
C(175)	26(2)	23(2)	35(2)	3(1)	4(2)	−2(1)
C(176)	33(2)	24(2)	18(2)	1(1)	7(1)	3(2)
C(177)	42(2)	27(2)	27(2)	4(1)	1(2)	−2(2)
C(178)	39(2)	39(2)	23(2)	2(2)	−1(2)	1(2)
C(179)	30(2)	42(2)	15(2)	−5(1)	1(1)	−3(2)
C(180)	36(2)	52(3)	23(2)	−8(2)	−5(2)	−2(2)
C(181)	31(2)	45(2)	25(2)	−9(2)	−8(2)	−2(2)
C(182)	49(3)	47(2)	31(2)	−7(2)	−10(2)	−12(2)
C(183)	34(2)	40(2)	22(2)	−6(2)	−4(2)	−6(2)
C(184)	32(2)	31(2)	19(2)	−5(1)	1(1)	−3(2)
C(185)	24(2)	31(2)	17(2)	1(1)	4(1)	0(1)

...

Table A31 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(186)	19(2)	21(2)	23(2)	1(1)	3(1)	−2(1)
Cu(7)	15(1)	16(1)	17(1)	4(1)	−1(1)	−3(1)
Cl(13)	15(1)	27(1)	24(1)	4(1)	−4(1)	−6(1)
Cl(14)	28(1)	16(1)	24(1)	8(1)	−4(1)	−6(1)
O(13)	23(1)	15(1)	33(1)	1(1)	7(1)	−4(1)
O(14)	14(1)	29(1)	21(1)	−4(1)	2(1)	−3(1)
N(13)	13(1)	17(1)	18(1)	1(1)	0(1)	0(1)
N(14)	16(1)	16(1)	14(1)	2(1)	0(1)	−1(1)
C(187)	18(2)	15(1)	21(2)	5(1)	−1(1)	−3(1)
C(188)	22(2)	15(1)	35(2)	1(1)	7(1)	−4(1)
C(189)	32(2)	14(2)	41(2)	−8(1)	7(2)	−7(1)
C(190)	24(2)	20(2)	33(2)	−3(1)	4(1)	−9(1)
C(191)	38(2)	34(2)	31(2)	−9(2)	0(2)	−23(2)
C(192)	32(2)	46(2)	24(2)	−5(2)	−7(2)	−13(2)
C(193)	20(2)	32(2)	19(2)	−1(1)	−1(1)	−6(1)
C(194)	26(2)	41(2)	23(2)	4(2)	−6(2)	−3(2)
C(195)	37(2)	22(2)	20(2)	6(1)	−2(2)	1(2)
C(196)	28(2)	17(2)	26(2)	1(1)	−2(1)	−4(1)
C(197)	17(2)	15(1)	19(2)	−1(1)	1(1)	−3(1)
C(198)	14(1)	22(2)	17(1)	−2(1)	2(1)	−4(1)
C(199)	16(2)	20(1)	19(2)	0(1)	2(1)	−6(1)
C(200)	18(2)	14(1)	23(2)	0(1)	3(1)	−4(1)
C(201)	16(2)	24(2)	22(2)	2(1)	1(1)	−8(1)
C(202)	19(2)	48(2)	33(2)	−10(2)	−5(2)	−7(2)
C(203)	44(2)	33(2)	28(2)	6(2)	9(2)	−18(2)
C(204)	14(2)	22(2)	19(1)	6(1)	−2(1)	−2(1)
C(205)	16(2)	25(2)	20(2)	4(1)	−2(1)	−1(1)
C(206)	18(2)	30(2)	16(1)	4(1)	−1(1)	−3(1)
C(207)	24(2)	17(1)	15(1)	−1(1)	−2(1)	−2(1)
C(208)	23(2)	20(1)	19(2)	1(1)	−2(1)	−7(1)
C(209)	27(2)	19(1)	16(1)	−1(1)	−6(1)	−3(1)
C(210)	19(2)	16(1)	21(2)	−3(1)	−6(1)	−2(1)
C(211)	21(2)	26(2)	24(2)	−4(1)	−11(1)	−2(1)
C(212)	22(2)	27(2)	33(2)	−9(1)	−10(2)	−3(1)
C(213)	18(2)	24(2)	27(2)	−6(1)	−1(1)	−6(1)
C(214)	22(2)	17(1)	20(2)	−2(1)	−4(1)	−5(1)
C(215)	19(2)	12(1)	22(2)	−2(1)	−5(1)	−4(1)
C(216)	18(2)	15(1)	16(1)	2(1)	−5(1)	−2(1)
C(217)	17(2)	14(1)	17(1)	1(1)	−3(1)	0(1)
Cu(8)	16(1)	20(1)	17(1)	5(1)	0(1)	−4(1)
Cl(15)	16(1)	40(1)	24(1)	4(1)	−2(1)	−6(1)
Cl(16)	39(1)	21(1)	22(1)	7(1)	0(1)	−10(1)
O(15)	29(2)	16(1)	42(2)	2(1)	15(1)	−7(1)
O(16)	14(1)	33(1)	25(1)	−4(1)	5(1)	−3(1)
N(15)	17(1)	17(1)	20(1)	5(1)	1(1)	0(1)
N(16)	15(1)	20(1)	17(1)	3(1)	−2(1)	0(1)

...

Table A31 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(218)	20(2)	17(1)	27(2)	11(1)	1(1)	−3(1)
C(219)	24(2)	13(1)	38(2)	3(1)	8(2)	−4(1)
C(220)	38(2)	16(2)	50(2)	−5(2)	12(2)	−13(2)
C(221)	25(2)	22(2)	37(2)	−8(1)	4(2)	−10(1)
C(222)	36(2)	43(2)	40(2)	−16(2)	1(2)	−22(2)
C(223)	29(2)	49(2)	25(2)	−7(2)	−5(2)	−14(2)
C(224)	18(2)	34(2)	20(2)	−2(1)	1(1)	−7(1)
C(225)	26(2)	42(2)	22(2)	2(2)	−4(2)	2(2)
C(226)	37(2)	22(2)	21(2)	6(1)	2(2)	3(2)
C(227)	32(2)	15(1)	20(2)	0(1)	5(1)	−7(1)
C(228)	19(2)	15(1)	17(1)	1(1)	4(1)	−4(1)
C(229)	15(2)	24(2)	15(1)	−2(1)	2(1)	−3(1)
C(230)	19(2)	18(1)	25(2)	−3(1)	4(1)	−6(1)
C(231)	19(2)	15(1)	24(2)	3(1)	5(1)	−3(1)
C(232)	19(2)	28(2)	26(2)	5(1)	3(1)	−8(1)
C(233)	19(2)	48(2)	42(2)	−16(2)	−2(2)	−6(2)
C(234)	58(3)	33(2)	36(2)	7(2)	11(2)	−24(2)
C(235)	15(2)	25(2)	18(2)	7(1)	1(1)	0(1)
C(236)	16(2)	27(2)	22(2)	3(1)	−2(1)	−1(1)
C(237)	14(2)	36(2)	18(2)	3(1)	−2(1)	−1(1)
C(238)	15(2)	22(2)	19(2)	3(1)	−2(1)	−2(1)
C(239)	22(2)	21(2)	15(1)	2(1)	−1(1)	−5(1)
C(240)	24(2)	21(2)	19(2)	2(1)	−5(1)	−3(1)
C(241)	17(2)	16(1)	22(2)	−4(1)	−3(1)	−2(1)
C(242)	19(2)	29(2)	25(2)	−4(1)	−8(1)	−3(1)
C(243)	19(2)	34(2)	35(2)	−9(2)	−9(2)	−5(2)
C(244)	17(2)	32(2)	27(2)	−6(1)	0(1)	−10(1)
C(245)	20(2)	20(1)	20(2)	0(1)	−1(1)	−8(1)
C(246)	16(2)	15(1)	20(2)	0(1)	−3(1)	−3(1)
C(247)	17(2)	18(1)	16(1)	2(1)	−2(1)	−1(1)
C(248)	13(1)	25(2)	16(1)	2(1)	−1(1)	1(1)
C(7S)	72(4)	33(2)	36(2)	13(2)	−10(2)	−1(2)
Cl(32)	76(1)	51(1)	51(1)	−6(1)	−32(1)	−24(1)
Cl(33)	32(1)	55(1)	34(1)	−8(1)	−9(1)	−3(1)
C(8S)	54(3)	61(3)	51(3)	−12(2)	0(2)	−28(3)
Cl(34)	51(1)	61(1)	83(1)	−30(1)	−13(1)	−15(1)
Cl(35)	43(1)	46(1)	63(1)	17(1)	−19(1)	−12(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2\left[h^2a*^2U^{11}+...+2hka*b*U^{12}\right]$

A.2.6 *Structural Data for β-methyl Ketone* **3.57**

Suitable crystals for X-ray analysis were obtained by crystallization from hot Et_2O and hexanes (approx. 5:1 v/v).

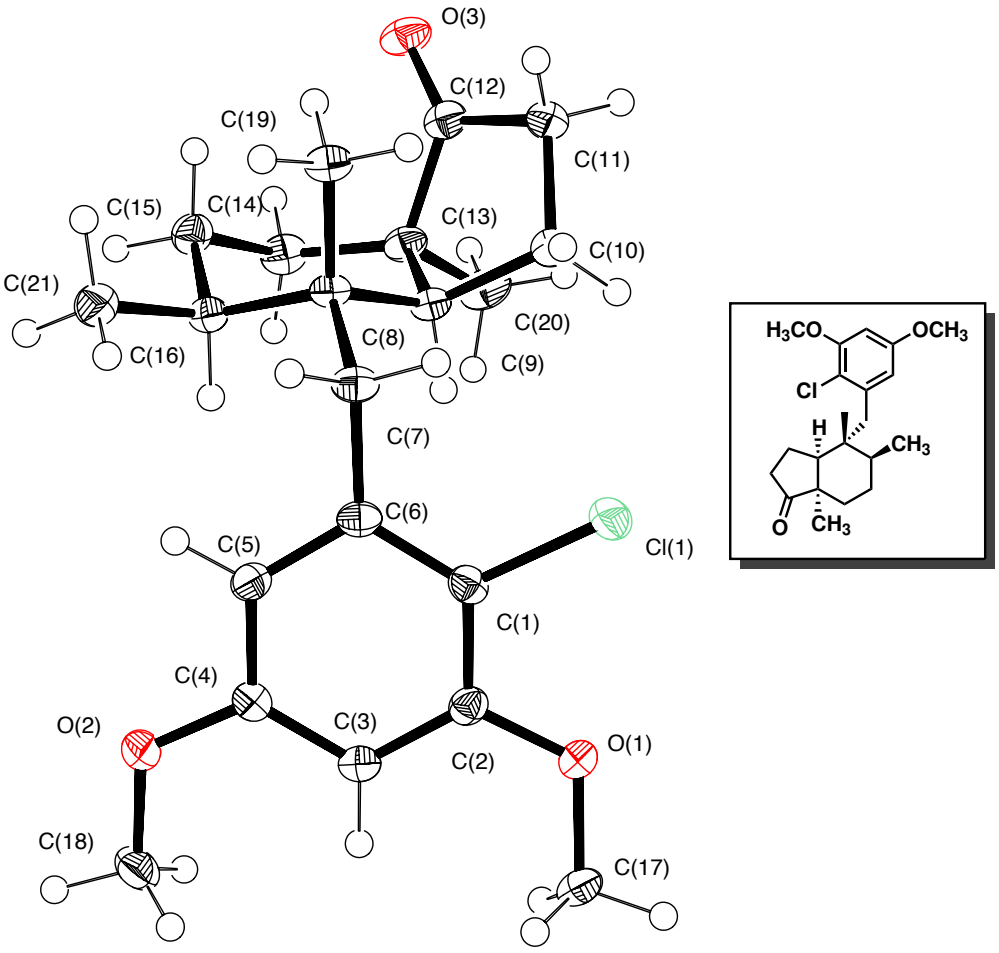

Figure A6: ORTEP drawing of β-methyl ketone **3.57** shown at 50% probability

Table A32: Crystal data and structure refinement for **3.57**

Empirical formula	$C_{21}H_{29}ClO_3$
Formula weight	364.89
Temperature	143(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 7.6944(4) Å $\alpha = 90°$.
	b = 19.9366(11) Å $\beta = 98.290(2)°$.
	c = 12.1637(7) Å $\gamma = 90°$.
Volume	1846.42(18) $Å^3$
Z	4
Density (calculated)	1.313 Mg/m^3
Absorption coefficient	0.224 mm^{-1}
F(000)	784
Crystal size	0.13 x 0.05 x 0.03 mm^3
Theta range for data collection	1.98 to 28.28°.
Index ranges	−10<=h<=10, −26<=k<=26, −16<=l<=16
Reflections collected	29305
Independent reflections	4583 [R(int) = 0.0305]
Completeness to theta = 28.28°	100.0%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9933 and 0.9714
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4583 / 0 / 231
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0366, wR2 = 0.0840
R indices (all data)	R1 = 0.0521, wR2 = 0.0918
Extinction coefficient	na
Largest diff. peak and hole	0.331 and −0.217 e.$Å^{-3}$

Table A33: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **3.57**

	x	y	z	U(eq)
Cl(1)	11743(1)	3756(1)	−1137(1)	26(1)
O(1)	13371(1)	4529(1)	678(1)	25(1)
O(2)	8389(1)	4536(1)	2701(1)	30(1)
O(3)	8573(1)	503(1)	−679(1)	28(1)
C(1)	10764(2)	3949(1)	30(1)	19(1)
C(2)	11719(2)	4356(1)	840(1)	19(1)
C(3)	10970(2)	4557(1)	1762(1)	20(1)
C(4)	9264(2)	4359(1)	1841(1)	21(1)
C(5)	8326(2)	3957(1)	1034(1)	21(1)
C(6)	9066(2)	3730(1)	123(1)	19(1)
C(7)	8003(2)	3284(1)	−733(1)	20(1)
C(8)	7812(2)	2525(1)	−443(1)	18(1)
C(9)	9683(2)	2206(1)	−231(1)	19(1)
C(10)	10482(2)	2082(1)	−1316(1)	24(1)
C(11)	9954(2)	1361(1)	−1681(1)	26(1)
C(12)	9314(2)	1040(1)	−686(1)	22(1)
C(13)	9783(2)	1501(1)	315(1)	21(1)
C(14)	8657(2)	1404(1)	1233(1)	25(1)
C(15)	6832(2)	1699(1)	940(1)	23(1)
C(16)	6900(2)	2437(1)	608(1)	20(1)
C(17)	14249(2)	5036(1)	1386(1)	25(1)
C(18)	9300(2)	4927(1)	3577(1)	29(1)
C(19)	6636(2)	2226(1)	−1463(1)	22(1)
C(20)	11701(2)	1318(1)	777(1)	30(1)
C(21)	5046(2)	2735(1)	506(1)	26(1)

Table A34: Bond lengths (Å) and angles (°) for **3.57**

Cl(1)-C(1)	1.7432(13)
O(1)-C(2)	1.3586(16)
O(1)-C(17)	1.4330(16)
O(2)-C(4)	1.3694(16)
O(2)-C(18)	1.4209(17)
O(3)-C(12)	1.2127(16)
C(1)-C(6)	1.3974(19)
C(1)-C(2)	1.3998(18)
C(2)-C(3)	1.3918(18)
C(3)-C(4)	1.3870(19)
C(3)-H(3)	0.95
C(4)-C(5)	1.3868(18)
...	

Table A34 continued...

C(5)-C(6)	1.3922(18)
C(5)-H(5)	0.95
C(6)-C(7)	1.5151(18)
C(7)-C(8)	1.5666(18)
C(7)-H(7A)	0.99
C(7)-H(7B)	0.99
C(8)-C(19)	1.5452(17)
C(8)-C(16)	1.5541(18)
C(8)-C(9)	1.5607(18)
C(9)-C(13)	1.5533(18)
C(9)-C(10)	1.5534(19)
C(9)-H(9)	1
C(10)-C(11)	1.5420(19)
C(10)-H(10A)	0.99
C(10)-H(10B)	0.99
C(11)-C(12)	1.513(2)
C(11)-H(11A)	0.99
C(11)-H(11B)	0.99
C(12)-C(13)	1.5264(19)
C(13)-C(14)	1.5203(19)
C(13)-C(20)	1.5454(19)
C(14)-C(15)	1.516(2)
C(14)-H(14A)	0.99
C(14)-H(14B)	0.99
C(15)-C(16)	1.5295(19)
C(15)-H(15A)	0.99
C(15)-H(15B)	0.99
C(16)-C(21)	1.5340(19)
C(16)-H(16)	1
C(17)-H(17A)	0.98
C(17)-H(17B)	0.98
C(17)-H(17C)	0.98
C(18)-H(18A)	0.98
C(18)-H(18B)	0.98
C(18)-H(18C)	0.98
C(19)-H(19A)	0.98
C(19)-H(19B)	0.98
C(19)-H(19C)	0.98
C(20)-H(20A)	0.98
C(20)-H(20B)	0.98
C(20)-H(20C)	0.98
C(21)-H(21A)	0.98
C(21)-H(21B)	0.98
C(21)-H(21C)	0.98
C(2)-O(1)-C(17)	117.52(10)
C(4)-O(2)-C(18)	118.05(11)
...	

Table A34 continued...

C(6)-C(1)-C(2)	121.76(12)
C(6)-C(1)-Cl(1)	121.05(10)
C(2)-C(1)-Cl(1)	117.14(10)
O(1)-C(2)-C(3)	123.29(12)
O(1)-C(2)-C(1)	116.90(12)
C(3)-C(2)-C(1)	119.81(12)
C(4)-C(3)-C(2)	118.71(12)
C(4)-C(3)-H(3)	120.6
C(2)-C(3)-H(3)	120.6
O(2)-C(4)-C(5)	115.26(12)
O(2)-C(4)-C(3)	123.67(12)
C(5)-C(4)-C(3)	121.07(12)
C(4)-C(5)-C(6)	121.37(12)
C(4)-C(5)-H(5)	119.3
C(6)-C(5)-H(5)	119.3
C(5)-C(6)-C(1)	117.19(12)
C(5)-C(6)-C(7)	119.69(12)
C(1)-C(6)-C(7)	123.07(12)
C(6)-C(7)-C(8)	118.05(11)
C(6)-C(7)-H(7A)	107.8
C(8)-C(7)-H(7A)	107.8
C(6)-C(7)-H(7B)	107.8
C(8)-C(7)-H(7B)	107.8
H(7A)-C(7)-H(7B)	107.1
C(19)-C(8)-C(16)	109.57(11)
C(19)-C(8)-C(9)	113.28(11)
C(16)-C(8)-C(9)	109.46(10)
C(19)-C(8)-C(7)	104.78(10)
C(16)-C(8)-C(7)	111.27(10)
C(9)-C(8)-C(7)	108.43(10)
C(13)-C(9)-C(10)	102.57(10)
C(13)-C(9)-C(8)	115.25(11)
C(10)-C(9)-C(8)	113.14(11)
C(13)-C(9)-H(9)	108.5
C(10)-C(9)-H(9)	108.5
C(8)-C(9)-H(9)	108.5
C(11)-C(10)-C(9)	105.89(11)
C(11)-C(10)-H(10A)	110.6
C(9)-C(10)-H(10A)	110.6
C(11)-C(10)-H(10B)	110.6
C(9)-C(10)-H(10B)	110.6
H(10A)-C(10)-H(10B)	108.7
C(12)-C(11)-C(10)	105.44(11)
C(12)-C(11)-H(11A)	110.7
C(10)-C(11)-H(11A)	110.7
C(12)-C(11)-H(11B)	110.7
C(10)-C(11)-H(11B)	110.7
H(11A)-C(11)-H(11B)	108.8
O(3)-C(12)-C(11)	125.86(13)
O(3)-C(12)-C(13)	125.67(13)
C(11)-C(12)-C(13)	108.47(11)
C(14)-C(13)-C(12)	114.53(11)
C(14)-C(13)-C(20)	108.59(11)
C(12)-C(13)-C(20)	104.57(11)
C(14)-C(13)-C(9)	115.49(11)
C(12)-C(13)-C(9)	102.27(10)
C(20)-C(13)-C(9)	110.78(11)
C(15)-C(14)-C(13)	112.67(11)
C(15)-C(14)-H(14A)	109.1
C(13)-C(14)-H(14A)	109.1
C(15)-C(14)-H(14B)	109.1
C(13)-C(14)-H(14B)	109.1
H(14A)-C(14)-H(14B)	107.8
C(14)-C(15)-C(16)	111.64(11)
C(14)-C(15)-H(15A)	109.3
C(16)-C(15)-H(15A)	109.3
C(14)-C(15)-H(15B)	109.3
C(16)-C(15)-H(15B)	109.3
H(15A)-C(15)-H(15B)	108
C(15)-C(16)-C(21)	109.15(11)
C(15)-C(16)-C(8)	111.29(11)
C(21)-C(16)-C(8)	114.48(11)
C(15)-C(16)-H(16)	107.2
C(21)-C(16)-H(16)	107.2
C(8)-C(16)-H(16)	107.2
O(1)-C(17)-H(17A)	109.5
O(1)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
O(1)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
O(2)-C(18)-H(18A)	109.5
O(2)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(2)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(8)-C(19)-H(19A)	109.5
C(8)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(8)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5

Table A34 continued...

H(19B)-C(19)-H(19C)	109.5
C(13)-C(20)-H(20A)	109.5
C(13)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(13)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(16)-C(21)-H(21A)	109.5
C(16)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(16)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5

Table A35: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **3.57**

	x	y	z	U(eq)
H(3)	11614	4824	2326	25
H(5)	7154	3834	1103	26
H(7A)	8537	3310	−1426	25
H(7B)	6808	3477	−898	25
H(9)	10478	2516	255	23
H(10A)	10007	2408	−1897	28
H(10B)	11776	2127	−1176	28
H(11A)	9011	1365	−2327	31
H(11B)	10975	1113	−1886	31
H(14A)	8555	919	1382	29
H(14B)	9246	1619	1921	29
H(15A)	6194	1657	1588	28
H(15B)	6178	1441	319	28
H(16)	7637	2676	1231	24
H(17A)	14490	4866	2149	37
H(17B)	13501	5435	1368	37
H(17C)	15358	5154	1127	37
H(18A)	9630	5359	3282	43
H(18B)	10360	4688	3909	43
H(18C)	8538	5004	4144	43
H(19A)	5496	2454	−1566	34
H(19B)	6463	1746	−1343	34
H(19C)	7205	2288	−2127	34
H(20A)	11739	866	1097	44
H(20B)	12162	1641	1354	44
H(20C)	12419	1331	174	44

...

Table A35 continued...

	x	y	z	U(eq)
H(21A)	4636	2722	1232	40
H(21B)	4248	2473	−31	40
H(21C)	5071	3201	251	40

Table A36: Torsion angles (°) for **3.57**

C(17)-O(1)-C(2)-C(3)	−11.31(19)
C(17)-O(1)-C(2)-C(1)	169.30(12)
C(6)-C(1)-C(2)-O(1)	178.72(12)
Cl(1)-C(1)-C(2)-O(1)	−3.98(16)
C(6)-C(1)-C(2)-C(3)	−0.7(2)
Cl(1)-C(1)-C(2)-C(3)	176.61(10)
O(1)-C(2)-C(3)-C(4)	179.20(12)
C(1)-C(2)-C(3)-C(4)	−1.42(19)
C(18)-O(2)-C(4)-C(5)	177.71(12)
C(18)-O(2)-C(4)-C(3)	−2.0(2)
C(2)-C(3)-C(4)-O(2)	−178.95(12)
C(2)-C(3)-C(4)-C(5)	1.3(2)
O(2)-C(4)-C(5)-C(6)	−178.84(12)
C(3)-C(4)-C(5)-C(6)	0.9(2)
C(4)-C(5)-C(6)-C(1)	−2.9(2)
C(4)-C(5)-C(6)-C(7)	179.28(12)
C(2)-C(1)-C(6)-C(5)	2.83(19)
Cl(1)-C(1)-C(6)-C(5)	−174.37(10)
C(2)-C(1)-C(6)-C(7)	−179.45(12)
Cl(1)-C(1)-C(6)-C(7)	3.35(18)
C(5)-C(6)-C(7)-C(8)	−77.95(16)
C(1)-C(6)-C(7)-C(8)	104.38(15)
C(6)-C(7)-C(8)-C(19)	178.68(12)
C(6)-C(7)-C(8)-C(16)	60.35(15)
C(6)-C(7)-C(8)-C(9)	−60.08(15)
C(19)-C(8)-C(9)-C(13)	−76.96(14)
C(16)-C(8)-C(9)-C(13)	45.64(14)
C(7)-C(8)-C(9)-C(13)	167.19(10)
C(19)-C(8)-C(9)-C(10)	40.63(15)
C(16)-C(8)-C(9)-C(10)	163.24(10)
C(7)-C(8)-C(9)-C(10)	−75.21(13)
C(13)-C(9)-C(10)-C(11)	33.10(13)
C(8)-C(9)-C(10)-C(11)	−91.69(13)
C(9)-C(10)-C(11)-C(12)	−14.10(14)
C(10)-C(11)-C(12)-O(3)	169.94(13)
C(10)-C(11)-C(12)-C(13)	−10.96(14)
O(3)-C(12)-C(13)-C(14)	−23.79(19)

...

Table A36 continued...

C(11)-C(12)-C(13)-C(14)	157.11(11)
O(3)-C(12)-C(13)-C(20)	94.94(16)
C(11)-C(12)-C(13)-C(20)	−84.15(13)
O(3)-C(12)-C(13)-C(9)	−149.49(13)
C(11)-C(12)-C(13)-C(9)	31.42(13)
C(10)-C(9)-C(13)-C(14)	−163.91(11)
C(8)-C(9)-C(13)-C(14)	−40.52(16)
C(10)-C(9)-C(13)-C(12)	−38.85(12)
C(8)-C(9)-C(13)-C(12)	84.55(13)
C(10)-C(9)-C(13)-C(20)	72.12(13)
C(8)-C(9)-C(13)-C(20)	−164.48(12)
C(12)-C(13)-C(14)-C(15)	−74.90(15)
C(20)-C(13)-C(14)-C(15)	168.66(11)
C(9)-C(13)-C(14)-C(15)	43.55(16)
C(13)-C(14)-C(15)-C(16)	−54.11(16)
C(14)-C(15)-C(16)-C(21)	−170.94(11)
C(14)-C(15)-C(16)-C(8)	61.74(15)
C(19)-C(8)-C(16)-C(15)	68.73(14)
C(9)-C(8)-C(16)-C(15)	−56.06(13)
C(7)-C(8)-C(16)-C(15)	−175.88(11)
C(19)-C(8)-C(16)-C(21)	−55.63(14)
C(9)-C(8)-C(16)-C(21)	179.59(11)
C(7)-C(8)-C(16)-C(21)	59.76(14)

Table A37: Anisotropic displacement parameters ($Å^2$x 10^3) for **3.57**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	33(1)	25(1)	22(1)	−4(1)	10(1)	−5(1)
O(1)	22(1)	27(1)	29(1)	−7(1)	8(1)	−8(1)
O(2)	26(1)	38(1)	28(1)	−15(1)	10(1)	−8(1)
O(3)	27(1)	17(1)	38(1)	−1(1)	−2(1)	−3(1)
C(1)	25(1)	17(1)	17(1)	1(1)	5(1)	0(1)
C(2)	19(1)	16(1)	23(1)	2(1)	4(1)	−1(1)
C(3)	22(1)	18(1)	21(1)	−2(1)	1(1)	−2(1)
C(4)	22(1)	20(1)	21(1)	−2(1)	4(1)	0(1)
C(5)	19(1)	19(1)	26(1)	−2(1)	3(1)	−2(1)
C(6)	23(1)	14(1)	19(1)	1(1)	0(1)	0(1)
C(7)	25(1)	16(1)	19(1)	0(1)	−2(1)	−1(1)
C(8)	20(1)	16(1)	17(1)	0(1)	−1(1)	−2(1)
C(9)	19(1)	16(1)	21(1)	−1(1)	0(1)	−3(1)
C(10)	25(1)	22(1)	26(1)	−3(1)	6(1)	−4(1)
C(11)	26(1)	22(1)	29(1)	−7(1)	6(1)	−2(1)
C(12)	17(1)	18(1)	31(1)	−1(1)	−1(1)	3(1)
C(13)	21(1)	16(1)	25(1)	1(1)	−1(1)	−1(1)
C(14)	29(1)	21(1)	23(1)	5(1)	0(1)	−2(1)
C(15)	26(1)	23(1)	22(1)	2(1)	5(1)	−4(1)
C(16)	20(1)	19(1)	20(1)	−2(1)	1(1)	−2(1)
C(17)	23(1)	21(1)	30(1)	−1(1)	3(1)	−7(1)
C(18)	27(1)	34(1)	25(1)	−12(1)	3(1)	3(1)
C(19)	24(1)	20(1)	22(1)	−1(1)	−3(1)	−2(1)
C(20)	23(1)	24(1)	39(1)	2(1)	−6(1)	1(1)
C(21)	22(1)	26(1)	31(1)	−3(1)	3(1)	−1(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2 \left[h^2 a *^2 U^{11} + ... + 2hka * b * U^{12}\right]$

A.2.7 *Structural Data for α-methyl Ketone* **3.58**

Suitable crystals for X-ray analysis were obtained by crystallization from hot Et_2O and hexanes (approx. 5:1 v/v).

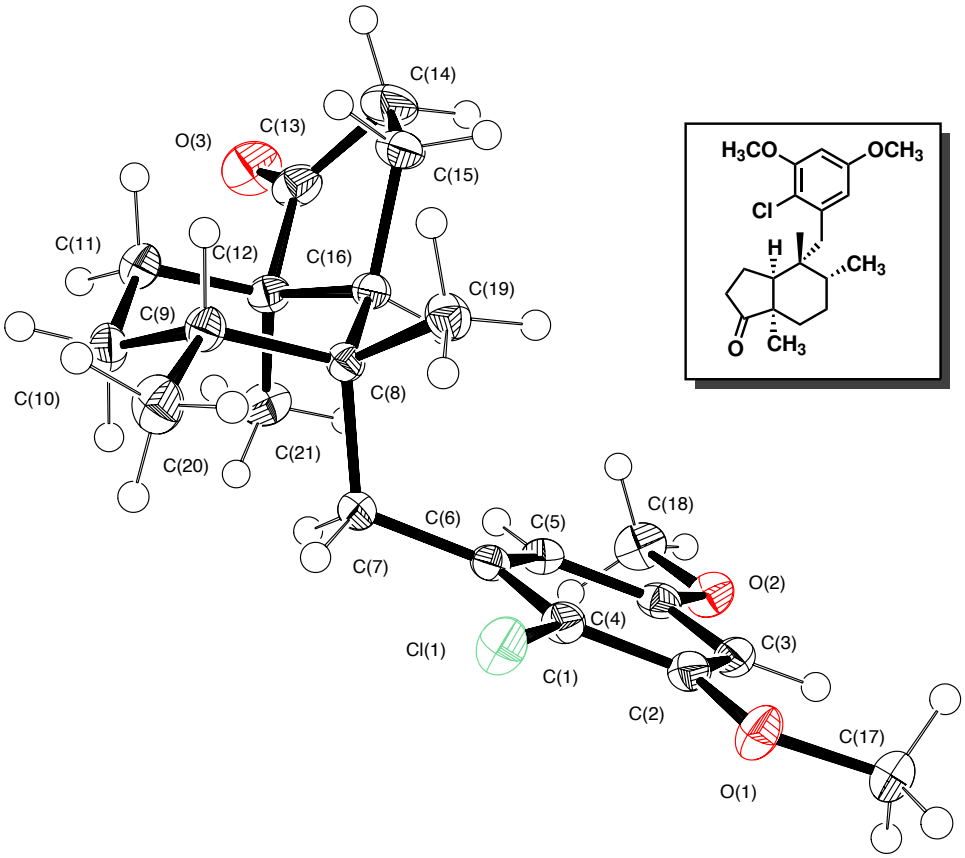

Figure A7: ORTEP drawing of α-methyl ketone **3.58** shown at 50% probability

Table A38: Crystal data and structure refinement for **3.58**

Empirical formula	$C_{21}H_{29}ClO_3$
Formula weight	364.89
Temperature	143(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 17.3130(12) Å $\alpha = 90°$.
	b = 7.2226(5) Å $\beta = 101.394(3)°$.
	c = 15.0735(11) Å $\gamma = 90°$.
Volume	1847.7(2) $Å^3$
Z	4
Density (calculated)	1.312 Mg/m^3
Absorption coefficient	0.224 mm^{-1}
F(000)	784
Crystal size	0.15 x 0.12 x 0.08 mm^3
Theta range for data collection	2.40 to 28.00°.
Index ranges	−22<=h<=22, −8<=k<=9, −17<=l<=19
Reflections collected	26894
Independent reflections	4435 [R(int) = 0.0200]
Completeness to theta = 28.00°	99.5%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9823 and 0.9672
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4435 / 0 / 231
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0330, wR2 = 0.0908
R indices (all data)	R1 = 0.0355, wR2 = 0.0930
Extinction coefficient	na
Largest diff. peak and hole	0.344 and −0.266 e.$Å^{-3}$

Table A39: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **3.58**

	x	y	z	U(eq)
Cl(1)	4508(1)	6621(1)	10743(1)	27(1)
O(1)	4403(1)	3107(1)	11520(1)	26(1)
O(2)	1637(1)	2254(1)	10639(1)	25(1)
O(3)	85(1)	8494(1)	6962(1)	39(1)
C(1)	3631(1)	5405(1)	10664(1)	20(1)
C(2)	3675(1)	3667(1)	11094(1)	20(1)
C(3)	2994(1)	2645(1)	11066(1)	21(1)
C(4)	2274(1)	3369(1)	10624(1)	20(1)
C(5)	2231(1)	5085(1)	10207(1)	19(1)
C(6)	2917(1)	6124(1)	10207(1)	18(1)
C(7)	2858(1)	7988(1)	9742(1)	18(1)
C(8)	2839(1)	7974(1)	8700(1)	17(1)
C(9)	3007(1)	9966(1)	8390(1)	21(1)
C(10)	2317(1)	11278(1)	8402(1)	24(1)
C(11)	1567(1)	10611(2)	7781(1)	24(1)
C(12)	1325(1)	8661(2)	8049(1)	20(1)
C(13)	756(1)	7952(2)	7208(1)	27(1)
C(14)	1163(1)	6530(2)	6732(1)	33(1)
C(15)	2034(1)	6688(2)	7172(1)	25(1)
C(16)	2029(1)	7290(1)	8157(1)	18(1)
C(17)	4470(1)	1305(2)	11916(1)	28(1)
C(18)	882(1)	2956(2)	10224(1)	30(1)
C(19)	3484(1)	6661(2)	8502(1)	23(1)
C(20)	3771(1)	10832(2)	8913(1)	29(1)
C(21)	891(1)	8761(2)	8837(1)	27(1)

Table A40: Bond lengths (Å) and angles (°) for **3.58**

Cl(1)-C(1)	1.7381(10)
O(1)-C(2)	1.3585(13)
O(1)-C(17)	1.4269(13)
O(2)-C(4)	1.3696(12)
O(2)-C(18)	1.4256(14)
O(3)-C(13)	1.2120(15)
C(1)-C(6)	1.3905(14)
C(1)-C(2)	1.4078(14)
C(2)-C(3)	1.3836(14)
C(3)-C(4)	1.3943(15)
C(3)-H(3)	0.95
C(4)-C(5)	1.3848(14)
...	

Table A40 continued...

C(5)-C(6)	1.4051(14)
C(5)-H(5)	0.95
C(6)-C(7)	1.5119(14)
C(7)-C(8)	1.5652(13)
C(7)-H(7A)	0.99
C(7)-H(7B)	0.99
C(8)-C(19)	1.5377(13)
C(8)-C(9)	1.5571(13)
C(8)-C(16)	1.5579(13)
C(9)-C(10)	1.5271(15)
C(9)-C(20)	1.5343(15)
C(9)-H(9)	1
C(10)-C(11)	1.5199(15)
C(10)-H(10A)	0.99
C(10)-H(10B)	0.99
C(11)-C(12)	1.5453(15)
C(11)-H(11A)	0.99
C(11)-H(11B)	0.99
C(12)-C(21)	1.5271(14)
C(12)-C(13)	1.5323(15)
C(12)-C(16)	1.5539(14)
C(13)-C(14)	1.5053(18)
C(14)-C(15)	1.5266(17)
C(14)-H(14A)	0.99
C(14)-H(14B)	0.99
C(15)-C(16)	1.5481(14)
C(15)-H(15A)	0.99
C(15)-H(15B)	0.99
C(16)-H(16)	1
C(17)-H(17A)	0.98
C(17)-H(17B)	0.98
C(17)-H(17C)	0.98
C(18)-H(18A)	0.98
C(18)-H(18B)	0.98
C(18)-H(18C)	0.98
C(19)-H(19A)	0.98
C(19)-H(19B)	0.98
C(19)-H(19C)	0.98
C(20)-H(20A)	0.98
C(20)-H(20B)	0.98
C(20)-H(20C)	0.98
C(21)-H(21A)	0.98
C(21)-H(21B)	0.98
C(21)-H(21C)	0.98
C(2)-O(1)-C(17)	117.45(9)
C(4)-O(2)-C(18)	117.05(9)
...	

Table A40 continued...

C(6)-C(1)-C(2)	121.55(9)
C(6)-C(1)-Cl(1)	121.59(8)
C(2)-C(1)-Cl(1)	116.85(8)
O(1)-C(2)-C(3)	124.07(9)
O(1)-C(2)-C(1)	116.38(9)
C(3)-C(2)-C(1)	119.54(10)
C(2)-C(3)-C(4)	119.35(9)
C(2)-C(3)-H(3)	120.3
C(4)-C(3)-H(3)	120.3
O(2)-C(4)-C(5)	124.23(9)
O(2)-C(4)-C(3)	114.75(9)
C(5)-C(4)-C(3)	121.02(9)
C(4)-C(5)-C(6)	120.55(9)
C(4)-C(5)-H(5)	119.7
C(6)-C(5)-H(5)	119.7
C(1)-C(6)-C(5)	117.94(9)
C(1)-C(6)-C(7)	122.33(9)
C(5)-C(6)-C(7)	119.70(9)
C(6)-C(7)-C(8)	116.50(8)
C(6)-C(7)-H(7A)	108.2
C(8)-C(7)-H(7A)	108.2
C(6)-C(7)-H(7B)	108.2
C(8)-C(7)-H(7B)	108.2
H(7A)-C(7)-H(7B)	107.3
C(19)-C(8)-C(9)	109.06(8)
C(19)-C(8)-C(16)	108.36(8)
C(9)-C(8)-C(16)	109.72(8)
C(19)-C(8)-C(7)	109.06(8)
C(9)-C(8)-C(7)	109.08(8)
C(16)-C(8)-C(7)	111.53(7)
C(10)-C(9)-C(20)	109.78(9)
C(10)-C(9)-C(8)	112.16(8)
C(20)-C(9)-C(8)	114.56(9)
C(10)-C(9)-H(9)	106.6
C(20)-C(9)-H(9)	106.6
C(8)-C(9)-H(9)	106.6
C(11)-C(10)-C(9)	111.77(9)
C(11)-C(10)-H(10A)	109.3
C(9)-C(10)-H(10A)	109.3
C(11)-C(10)-H(10B)	109.3
C(9)-C(10)-H(10B)	109.3
H(10A)-C(10)-H(10B)	107.9
C(10)-C(11)-C(12)	111.79(9)
C(10)-C(11)-H(11A)	109.3
C(12)-C(11)-H(11A)	109.3
C(10)-C(11)-H(11B)	109.3
...	

Table A40 continued...

C(12)-C(11)-H(11B)	109.3
H(11A)-C(11)-H(11B)	107.9
C(21)-C(12)-C(13)	108.92(9)
C(21)-C(12)-C(11)	111.15(9)
C(13)-C(12)-C(11)	104.61(9)
C(21)-C(12)-C(16)	116.41(9)
C(13)-C(12)-C(16)	103.68(9)
C(11)-C(12)-C(16)	111.11(8)
O(3)-C(13)-C(14)	125.81(11)
O(3)-C(13)-C(12)	124.49(11)
C(14)-C(13)-C(12)	109.68(9)
C(13)-C(14)-C(15)	104.93(9)
C(13)-C(14)-H(14A)	110.8
C(15)-C(14)-H(14A)	110.8
C(13)-C(14)-H(14B)	110.8
C(15)-C(14)-H(14B)	110.8
H(14A)-C(14)-H(14B)	108.8
C(14)-C(15)-C(16)	104.21(9)
C(14)-C(15)-H(15A)	110.9
C(16)-C(15)-H(15A)	110.9
C(14)-C(15)-H(15B)	110.9
C(16)-C(15)-H(15B)	110.9
H(15A)-C(15)-H(15B)	108.9
C(15)-C(16)-C(12)	103.39(8)
C(15)-C(16)-C(8)	114.70(8)
C(12)-C(16)-C(8)	117.31(8)
C(15)-C(16)-H(16)	106.9
C(12)-C(16)-H(16)	106.9
C(8)-C(16)-H(16)	106.9
O(1)-C(17)-H(17A)	109.5
O(1)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
O(1)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
O(2)-C(18)-H(18A)	109.5
O(2)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(2)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(8)-C(19)-H(19A)	109.5
C(8)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(8)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
...	

Table A40 continued...

H(19B)-C(19)-H(19C)	109.5
C(9)-C(20)-H(20A)	109.5
C(9)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(9)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(12)-C(21)-H(21A)	109.5
C(12)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(12)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5

Table A41: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **3.58**

	x	y	z	U(eq)
H(3)	3018	1462	11345	25
H(5)	1734	5564	9919	23
H(7A)	3311	8751	10037	22
H(7B)	2374	8609	9846	22
H(9)	3066	9867	7745	25
H(10A)	2224	11377	9027	28
H(10B)	2452	12525	8207	28
H(11A)	1650	10581	7150	29
H(11B)	1136	11494	7809	29
H(14A)	1081	6797	6076	40
H(14B)	962	5272	6817	40
H(15A)	2300	7624	6859	30
H(15B)	2305	5483	7160	30
H(16)	1880	6176	8480	21
H(17A)	4138	1229	12372	41
H(17B)	5020	1072	12204	41
H(17C)	4298	376	11445	41
H(18A)	775	4095	10532	44
H(18B)	478	2032	10270	44
H(18C)	876	3224	9586	44
H(19A)	3338	5379	8605	35
H(19B)	3985	6958	8904	35
H(19C)	3538	6809	7871	35
H(20A)	3921	11879	8569	43
H(20B)	4192	9903	9002	43
H(20C)	3690	11269	9504	43

...

Table A41 continued...

	x	y	z	U(eq)
H(21A)	401	9460	8651	41
H(21B)	1225	9381	9352	41
H(21C)	769	7505	9013	41

Table A42: Torsion angles (°) for **3.58**

C(17)-O(1)-C(2)-C(3)	3.82(15)
C(17)-O(1)-C(2)-C(1)	−176.46(9)
C(6)-C(1)-C(2)-O(1)	−179.90(9)
Cl(1)-C(1)-C(2)-O(1)	−0.66(12)
C(6)-C(1)-C(2)-C(3)	−0.17(15)
Cl(1)-C(1)-C(2)-C(3)	179.07(8)
O(1)-C(2)-C(3)-C(4)	178.71(9)
C(1)-C(2)-C(3)-C(4)	−1.01(15)
C(18)-O(2)-C(4)-C(5)	−2.26(14)
C(18)-O(2)-C(4)-C(3)	177.88(9)
C(2)-C(3)-C(4)-O(2)	−179.63(9)
C(2)-C(3)-C(4)-C(5)	0.51(15)
O(2)-C(4)-C(5)-C(6)	−178.68(9)
C(3)-C(4)-C(5)-C(6)	1.16(15)
C(2)-C(1)-C(6)-C(5)	1.79(15)
Cl(1)-C(1)-C(6)-C(5)	−177.41(7)
C(2)-C(1)-C(6)-C(7)	179.99(9)
Cl(1)-C(1)-C(6)-C(7)	0.79(14)
C(4)-C(5)-C(6)-C(1)	−2.28(14)
C(4)-C(5)-C(6)-C(7)	179.48(9)
C(1)-C(6)-C(7)-C(8)	97.30(11)
C(5)-C(6)-C(7)-C(8)	−84.53(11)
C(6)-C(7)-C(8)-C(19)	−45.73(11)
C(6)-C(7)-C(8)-C(9)	−164.75(8)
C(6)-C(7)-C(8)-C(16)	73.90(10)
C(19)-C(8)-C(9)-C(10)	169.47(9)
C(16)-C(8)-C(9)-C(10)	50.93(11)
C(7)-C(8)-C(9)-C(10)	−71.52(10)
C(19)-C(8)-C(9)-C(20)	−64.51(11)
C(16)-C(8)-C(9)-C(20)	176.95(8)
C(7)-C(8)-C(9)-C(20)	54.50(11)
C(20)-C(9)-C(10)-C(11)	171.84(9)
C(8)-C(9)-C(10)-C(11)	−59.58(11)
C(9)-C(10)-C(11)-C(12)	58.82(11)
C(10)-C(11)-C(12)-C(21)	80.97(11)
C(10)-C(11)-C(12)-C(13)	−161.63(9)
C(10)-C(11)-C(12)-C(16)	−50.37(11)

...

Table A42 continued...

C(21)-C(12)-C(13)-O(3)	45.20(15)
C(11)-C(12)-C(13)-O(3)	−73.71(13)
C(16)-C(12)-C(13)-O(3)	169.77(11)
C(21)-C(12)-C(13)-C(14)	−136.13(10)
C(11)-C(12)-C(13)-C(14)	104.96(10)
C(16)-C(12)-C(13)-C(14)	−11.56(11)
O(3)-C(13)-C(14)-C(15)	166.64(12)
C(12)-C(13)-C(14)-C(15)	−12.01(13)
C(13)-C(14)-C(15)-C(16)	30.94(12)
C(14)-C(15)-C(16)-C(12)	−38.15(11)
C(14)-C(15)-C(16)-C(8)	−167.09(9)
C(21)-C(12)-C(16)-C(15)	149.71(9)
C(13)-C(12)-C(16)-C(15)	30.14(10)
C(11)-C(12)-C(16)-C(15)	−81.72(10)
C(21)-C(12)-C(16)-C(8)	−82.98(11)
C(13)-C(12)-C(16)-C(8)	157.46(8)
C(11)-C(12)-C(16)-C(8)	45.60(11)
C(19)-C(8)-C(16)-C(15)	−42.86(11)
C(9)-C(8)-C(16)-C(15)	76.12(10)
C(7)-C(8)-C(16)-C(15)	−162.90(8)
C(19)-C(8)-C(16)-C(12)	−164.47(8)
C(9)-C(8)-C(16)-C(12)	−45.49(11)
C(7)-C(8)-C(16)-C(12)	75.48(10)

Table A43: Anisotropic displacement parameters ($Å^2$x 10^3) for **3.58**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	20(1)	26(1)	33(1)	5(1)	−3(1)	−7(1)
O(1)	22(1)	25(1)	30(1)	8(1)	−1(1)	1(1)
O(2)	21(1)	28(1)	26(1)	4(1)	5(1)	−6(1)
O(3)	25(1)	51(1)	37(1)	2(1)	−7(1)	−2(1)
C(1)	19(1)	20(1)	19(1)	−1(1)	2(1)	−4(1)
C(2)	21(1)	21(1)	18(1)	0(1)	2(1)	1(1)
C(3)	25(1)	20(1)	18(1)	2(1)	6(1)	−1(1)
C(4)	21(1)	23(1)	16(1)	−2(1)	6(1)	−5(1)
C(5)	18(1)	23(1)	16(1)	−1(1)	4(1)	0(1)
C(6)	21(1)	18(1)	15(1)	−2(1)	4(1)	−1(1)
C(7)	20(1)	17(1)	18(1)	−1(1)	2(1)	0(1)
C(8)	17(1)	16(1)	18(1)	−1(1)	5(1)	−1(1)
C(9)	21(1)	18(1)	23(1)	1(1)	6(1)	−4(1)
C(10)	27(1)	16(1)	28(1)	1(1)	5(1)	−1(1)
C(11)	25(1)	22(1)	25(1)	4(1)	3(1)	2(1)
C(12)	18(1)	24(1)	18(1)	1(1)	2(1)	−1(1)
C(13)	25(1)	33(1)	22(1)	3(1)	0(1)	−7(1)
C(14)	34(1)	40(1)	23(1)	−8(1)	0(1)	−7(1)
C(15)	29(1)	28(1)	19(1)	−5(1)	6(1)	−3(1)
C(16)	20(1)	18(1)	16(1)	−1(1)	4(1)	−2(1)
C(17)	32(1)	24(1)	26(1)	5(1)	2(1)	5(1)
C(18)	20(1)	37(1)	31(1)	2(1)	4(1)	−6(1)
C(19)	22(1)	23(1)	25(1)	−2(1)	8(1)	2(1)
C(20)	24(1)	26(1)	35(1)	1(1)	6(1)	−9(1)
C(21)	21(1)	37(1)	25(1)	4(1)	8(1)	5(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2 \left[h^2 a*^2 U^{11} + ... + 2hka*b*U^{12}\right]$

A.2.8 *Structural Data for Imidazolium Salt* **4.28**

Suitable crystals for X-ray analysis were obtained by slow diffusion of Et_2O into a CH_2Cl_2 solution.

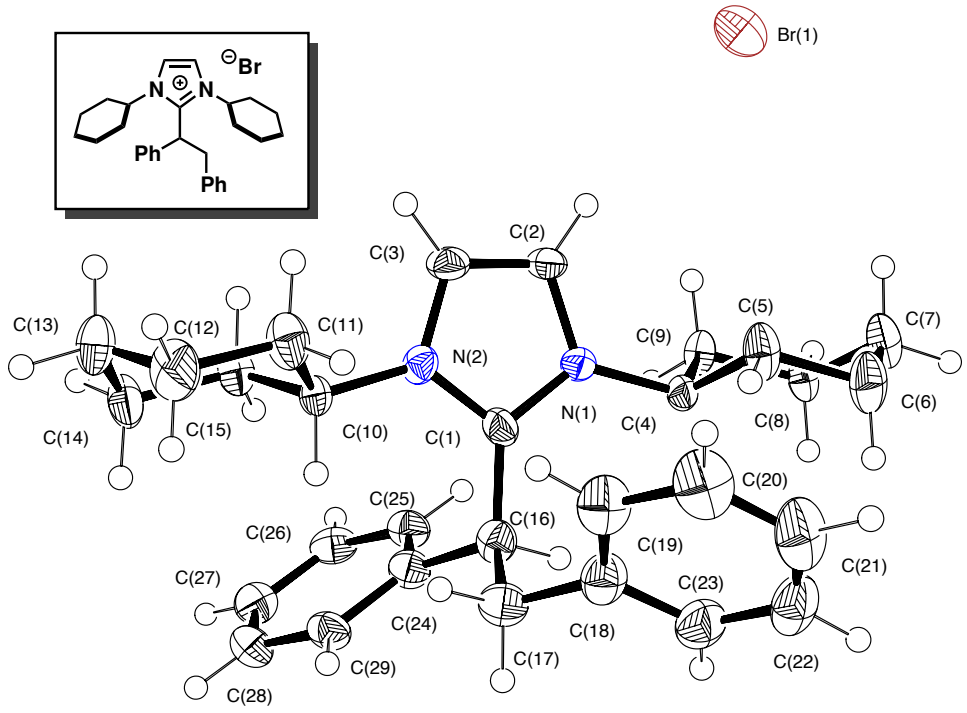

Figure A8: ORTEP drawing of imidazolium salt **4.28** shown at 50% probability

Table A44: Crystal data and structure refinement for **4.28**

Empirical formula	$C_{29}H_{37}BrN_2$
Formula weight	493.52
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Fdd2
Unit cell dimensions	a = 28.7310(17) Å $\alpha = 90°$.
	b = 54.389(3) Å $\beta = 90°$.
	c = 15.6412(7) Å $\gamma = 90°$.
Volume	24442(2) $Å^3$
Z	32
Density (calculated)	1.073 Mg/m^3
Absorption coefficient	1.361 mm^{-1}
F(000)	8320
Crystal size	0.25 x 0.18 x 0.10 mm^3
Theta range for data collection	1.50 to 30.82°.
Index ranges	0<=h<=41, 0<=k<=78, −19<=l<=22
Reflections collected	18347
Independent reflections	18347 [R(int) = 0.0000]
Completeness to theta = 30.82°	99.7%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8759 and 0.7272
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	18347 / 1 / 577
Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R1 = 0.0556, wR2 = 0.1435
R indices (all data)	R1 = 0.0786, wR2 = 0.1512
Absolute structure parameter	0.065(6)
Extinction coefficient	na
Largest diff. peak and hole	1.036 and −0.694 e.$Å^{-3}$

Table A45: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **4.28**

	x	y	z	U(eq)
Br(1)	6440(1)	2320(1)	3979(1)	43(1)
N(1)	7007(1)	2888(1)	1795(2)	24(1)
N(2)	7662(1)	3071(1)	2080(2)	24(1)
C(1)	7307(1)	3060(1)	1501(2)	27(1)
C(2)	7186(1)	2785(1)	2534(2)	25(1)
C(3)	7594(1)	2897(1)	2700(2)	29(1)
C(4)	6549(1)	2816(1)	1430(2)	25(1)
C(5)	6168(1)	2882(1)	2079(3)	36(1)
C(6)	5698(1)	2808(1)	1696(3)	44(1)
C(7)	5682(1)	2534(1)	1491(3)	42(1)
C(8)	6072(1)	2474(1)	869(2)	31(1)
C(9)	6549(1)	2546(1)	1216(2)	28(1)
C(10)	8065(1)	3238(1)	2078(2)	28(1)
C(11)	8094(1)	3376(1)	2922(2)	38(1)
C(12)	8505(1)	3546(1)	2959(3)	49(1)
C(13)	8951(1)	3405(1)	2776(3)	49(1)
C(14)	8936(1)	3271(1)	1914(3)	42(1)
C(15)	8512(1)	3099(1)	1895(2)	33(1)
C(16)	7287(1)	3188(1)	646(2)	30(1)
C(17)	7145(1)	3463(1)	748(2)	37(1)
C(18)	6681(1)	3492(1)	1199(2)	39(1)
C(19)	6656(1)	3548(1)	2076(3)	44(1)
C(20)	6221(2)	3581(1)	2459(3)	54(1)
C(21)	5817(1)	3552(1)	2002(4)	56(1)
C(22)	5847(1)	3494(1)	1148(3)	52(1)
C(23)	6265(1)	3460(1)	757(3)	45(1)
C(24)	7725(1)	3144(1)	133(2)	30(1)
C(25)	7840(1)	2903(1)	−89(2)	31(1)
C(26)	8248(1)	2849(1)	−506(2)	33(1)
C(27)	8550(1)	3037(1)	−728(2)	35(1)
C(28)	8439(1)	3278(1)	−524(2)	37(1)
C(29)	8028(1)	3332(1)	−104(2)	31(1)
Br(2)	3459(1)	2138(1)	3952(1)	37(1)
N(3)	1830(1)	2200(1)	1818(2)	24(1)
N(4)	2358(1)	1925(1)	2097(2)	24(1)
C(30)	2023(1)	1989(1)	1540(3)	38(1)
C(31)	2070(1)	2277(1)	2521(2)	23(1)
C(32)	2398(1)	2106(1)	2696(2)	24(1)
C(33)	1415(1)	2332(1)	1494(2)	28(1)
C(34)	1031(1)	2323(1)	2160(3)	35(1)
C(35)	600(1)	2455(1)	1836(3)	44(1)
C(36)	716(1)	2720(1)	1605(2)	37(1)
		...		

Table A45 continued...

	x	y	z	U(eq)
C(37)	1106(1)	2730(1)	944(2)	38(1)
C(38)	1545(1)	2596(1)	1261(2)	32(1)
C(39)	2650(1)	1702(1)	2089(2)	27(1)
C(40)	2613(1)	1572(1)	2960(2)	33(1)
C(41)	2922(1)	1341(1)	2958(3)	43(1)
C(42)	3426(1)	1411(1)	2739(3)	50(1)
C(43)	3455(1)	1539(1)	1878(3)	47(1)
C(44)	3149(1)	1769(1)	1868(2)	33(1)
C(45)	1936(1)	1871(1)	659(2)	37(1)
C(46)	1655(1)	1632(1)	771(3)	45(1)
C(47)	1194(1)	1680(1)	1259(3)	43(1)
C(48)	1122(1)	1600(1)	2099(3)	50(1)
C(49)	692(1)	1626(1)	2510(3)	47(1)
C(50)	334(1)	1735(1)	2060(3)	49(1)
C(51)	390(1)	1812(1)	1229(3)	46(1)
C(52)	810(1)	1787(1)	850(3)	39(1)
C(53)	2368(1)	1834(1)	144(2)	42(1)
C(54)	2618(1)	2044(1)	−76(2)	39(1)
C(55)	3046(1)	2027(1)	−481(2)	40(1)
C(56)	3223(1)	1800(1)	−692(2)	42(1)
C(57)	2971(1)	1591(1)	−497(3)	43(1)
C(58)	2544(2)	1604(1)	−98(2)	41(1)

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

Table A46: Bond lengths (Å) and angles (°) for **4.28**

N(1)-C(1)	1.353(3)
N(1)-C(2)	1.383(4)
N(1)-C(4)	1.488(3)
N(2)-C(1)	1.366(4)
N(2)-C(3)	1.371(4)
N(2)-C(10)	1.473(3)
C(1)-C(16)	1.509(5)
C(2)-C(3)	1.345(4)
C(2)-H(2A)	0.95
C(3)-H(3A)	0.95
C(4)-C(9)	1.510(4)
C(4)-C(5)	1.534(4)
C(4)-H(4A)	1
C(5)-C(6)	1.531(5)
C(5)-H(5A)	0.99
C(5)-H(5B)	0.99
	...

Table A46 continued...

C(6)-C(7)	1.524(5)
C(6)-H(6A)	0.99
C(6)-H(6B)	0.99
C(7)-C(8)	1.520(5)
C(7)-H(7A)	0.99
C(7)-H(7B)	0.99
C(8)-C(9)	1.526(4)
C(8)-H(8A)	0.99
C(8)-H(8B)	0.99
C(9)-H(9A)	0.99
C(9)-H(9B)	0.99
C(10)-C(15)	1.519(4)
C(10)-C(11)	1.522(5)
C(10)-H(10A)	1
C(11)-C(12)	1.501(5)
C(11)-H(11A)	0.99
C(11)-H(11B)	0.99
C(12)-C(13)	1.520(6)
C(12)-H(12A)	0.99
C(12)-H(12B)	0.99
C(13)-C(14)	1.534(6)
C(13)-H(13A)	0.99
C(13)-H(13B)	0.99
C(14)-C(15)	1.534(4)
C(14)-H(14A)	0.99
C(14)-H(14B)	0.99
C(15)-H(15A)	0.99
C(15)-H(15B)	0.99
C(16)-C(24)	1.511(4)
C(16)-C(17)	1.556(4)
C(16)-H(16A)	1
C(17)-C(18)	1.517(5)
C(17)-H(17A)	0.99
C(17)-H(17B)	0.99
C(18)-C(23)	1.392(5)
C(18)-C(19)	1.407(6)
C(19)-C(20)	1.396(6)
C(19)-H(19A)	0.95
C(20)-C(21)	1.372(7)
C(20)-H(20A)	0.95
C(21)-C(22)	1.374(7)
C(21)-H(21A)	0.95
C(22)-C(23)	1.359(6)
C(22)-H(22A)	0.95
C(23)-H(23A)	0.95
C(24)-C(29)	1.391(4)

...

Table A46 continued...

C(24)-C(25)	1.399(4)
C(25)-C(26)	1.371(5)
C(25)-H(25A)	0.95
C(26)-C(27)	1.388(5)
C(26)-H(26A)	0.95
C(27)-C(28)	1.386(5)
C(27)-H(27A)	0.95
C(28)-C(29)	1.384(5)
C(28)-H(28A)	0.95
C(29)-H(29A)	0.95
N(3)-C(30)	1.345(4)
N(3)-C(31)	1.363(4)
N(3)-C(33)	1.485(3)
N(4)-C(30)	1.343(4)
N(4)-C(32)	1.361(4)
N(4)-C(39)	1.477(3)
C(30)-C(45)	1.539(5)
C(31)-C(32)	1.354(4)
C(31)-H(31A)	0.95
C(32)-H(32A)	0.95
C(33)-C(34)	1.518(5)
C(33)-C(38)	1.524(4)
C(33)-H(33A)	1
C(34)-C(35)	1.518(4)
C(34)-H(34A)	0.99
C(34)-H(34B)	0.99
C(35)-C(36)	1.528(5)
C(35)-H(35A)	0.99
C(35)-H(35B)	0.99
C(36)-C(37)	1.524(5)
C(36)-H(36A)	0.99
C(36)-H(36B)	0.99
C(37)-C(38)	1.542(4)
C(37)-H(37A)	0.99
C(37)-H(37B)	0.99
C(38)-H(38A)	0.99
C(38)-H(38B)	0.99
C(39)-C(44)	1.518(5)
C(39)-C(40)	1.541(5)
C(39)-H(39A)	1
C(40)-C(41)	1.536(4)
C(40)-H(40A)	0.99
C(40)-H(40B)	0.99
C(41)-C(42)	1.537(6)
C(41)-H(41A)	0.99
C(41)-H(41B)	0.99

...

Table A46 continued...

C(42)-C(43)	1.518(6)
C(42)-H(42A)	0.99
C(42)-H(42B)	0.99
C(43)-C(44)	1.532(4)
C(43)-H(43A)	0.99
C(43)-H(43B)	0.99
C(44)-H(44A)	0.99
C(44)-H(44B)	0.99
C(45)-C(53)	1.493(5)
C(45)-C(46)	1.542(5)
C(45)-H(45A)	1
C(46)-C(47)	1.551(6)
C(46)-H(46A)	0.99
C(46)-H(46B)	0.99
C(47)-C(48)	1.398(6)
C(47)-C(52)	1.403(5)
C(48)-C(49)	1.401(6)
C(48)-H(48A)	0.95
C(49)-C(50)	1.379(6)
C(49)-H(49A)	0.95
C(50)-C(51)	1.374(7)
C(50)-H(50A)	0.95
C(51)-C(52)	1.351(6)
C(51)-H(51A)	0.95
C(52)-H(52A)	0.95
C(53)-C(54)	1.393(5)
C(53)-C(58)	1.403(5)
C(54)-C(55)	1.386(5)
C(54)-H(54A)	0.95
C(55)-C(56)	1.373(5)
C(55)-H(55A)	0.95
C(56)-C(57)	1.383(6)
C(56)-H(56A)	0.95
C(57)-C(58)	1.377(5)
C(57)-H(57A)	0.95
C(58)-H(58A)	0.95
C(1)-N(1)-C(2)	109.2(2)
C(1)-N(1)-C(4)	128.0(2)
C(2)-N(1)-C(4)	122.9(2)
C(1)-N(2)-C(3)	109.4(2)
C(1)-N(2)-C(10)	127.8(2)
C(3)-N(2)-C(10)	122.8(2)
N(1)-C(1)-N(2)	106.3(3)
N(1)-C(1)-C(16)	126.6(3)
N(2)-C(1)-C(16)	126.6(2)
C(3)-C(2)-N(1)	107.6(2)

...

Table A46 continued...

C(3)-C(2)-H(2A)	126.2
N(1)-C(2)-H(2A)	126.2
C(2)-C(3)-N(2)	107.5(3)
C(2)-C(3)-H(3A)	126.2
N(2)-C(3)-H(3A)	126.2
N(1)-C(4)-C(9)	109.9(2)
N(1)-C(4)-C(5)	108.5(3)
C(9)-C(4)-C(5)	111.9(2)
N(1)-C(4)-H(4A)	108.8
C(9)-C(4)-H(4A)	108.8
C(5)-C(4)-H(4A)	108.8
C(6)-C(5)-C(4)	108.1(3)
C(6)-C(5)-H(5A)	110.1
C(4)-C(5)-H(5A)	110.1
C(6)-C(5)-H(5B)	110.1
C(4)-C(5)-H(5B)	110.1
H(5A)-C(5)-H(5B)	108.4
C(7)-C(6)-C(5)	111.4(3)
C(7)-C(6)-H(6A)	109.3
C(5)-C(6)-H(6A)	109.3
C(7)-C(6)-H(6B)	109.3
C(5)-C(6)-H(6B)	109.3
H(6A)-C(6)-H(6B)	108
C(8)-C(7)-C(6)	108.9(3)
C(8)-C(7)-H(7A)	109.9
C(6)-C(7)-H(7A)	109.9
C(8)-C(7)-H(7B)	109.9
C(6)-C(7)-H(7B)	109.9
H(7A)-C(7)-H(7B)	108.3
C(7)-C(8)-C(9)	112.3(3)
C(7)-C(8)-H(8A)	109.2
C(9)-C(8)-H(8A)	109.2
C(7)-C(8)-H(8B)	109.2
C(9)-C(8)-H(8B)	109.2
H(8A)-C(8)-H(8B)	107.9
C(4)-C(9)-C(8)	109.2(2)
C(4)-C(9)-H(9A)	109.8
C(8)-C(9)-H(9A)	109.8
C(4)-C(9)-H(9B)	109.8
C(8)-C(9)-H(9B)	109.8
H(9A)-C(9)-H(9B)	108.3
N(2)-C(10)-C(15)	111.0(2)
N(2)-C(10)-C(11)	110.2(3)
C(15)-C(10)-C(11)	111.3(3)
N(2)-C(10)-H(10A)	108.1
C(15)-C(10)-H(10A)	108.1

...

Table A46 continued...

C(11)-C(10)-H(10A)	108.1
C(12)-C(11)-C(10)	112.4(3)
C(12)-C(11)-H(11A)	109.1
C(10)-C(11)-H(11A)	109.1
C(12)-C(11)-H(11B)	109.1
C(10)-C(11)-H(11B)	109.1
H(11A)-C(11)-H(11B)	107.9
C(11)-C(12)-C(13)	110.0(3)
C(11)-C(12)-H(12A)	109.7
C(13)-C(12)-H(12A)	109.7
C(11)-C(12)-H(12B)	109.7
C(13)-C(12)-H(12B)	109.7
H(12A)-C(12)-H(12B)	108.2
C(12)-C(13)-C(14)	112.5(3)
C(12)-C(13)-H(13A)	109.1
C(14)-C(13)-H(13A)	109.1
C(12)-C(13)-H(13B)	109.1
C(14)-C(13)-H(13B)	109.1
H(13A)-C(13)-H(13B)	107.8
C(13)-C(14)-C(15)	109.2(3)
C(13)-C(14)-H(14A)	109.8
C(15)-C(14)-H(14A)	109.8
C(13)-C(14)-H(14B)	109.8
C(15)-C(14)-H(14B)	109.8
H(14A)-C(14)-H(14B)	108.3
C(10)-C(15)-C(14)	111.3(3)
C(10)-C(15)-H(15A)	109.4
C(14)-C(15)-H(15A)	109.4
C(10)-C(15)-H(15B)	109.4
C(14)-C(15)-H(15B)	109.4
H(15A)-C(15)-H(15B)	108
C(1)-C(16)-C(24)	111.5(2)
C(1)-C(16)-C(17)	111.2(3)
C(24)-C(16)-C(17)	115.1(3)
C(1)-C(16)-H(16A)	106.1
C(24)-C(16)-H(16A)	106.1
C(17)-C(16)-H(16A)	106.1
C(18)-C(17)-C(16)	112.1(3)
C(18)-C(17)-H(17A)	109.2
C(16)-C(17)-H(17A)	109.2
C(18)-C(17)-H(17B)	109.2
C(16)-C(17)-H(17B)	109.2
H(17A)-C(17)-H(17B)	107.9
C(23)-C(18)-C(19)	117.8(4)
C(23)-C(18)-C(17)	120.8(3)
C(19)-C(18)-C(17)	121.4(3)
...	

Table A46 continued...

C(20)-C(19)-C(18)	119.5(4)
C(20)-C(19)-H(19A)	120.2
C(18)-C(19)-H(19A)	120.2
C(21)-C(20)-C(19)	121.2(4)
C(21)-C(20)-H(20A)	119.4
C(19)-C(20)-H(20A)	119.4
C(20)-C(21)-C(22)	118.6(4)
C(20)-C(21)-H(21A)	120.7
C(22)-C(21)-H(21A)	120.7
C(23)-C(22)-C(21)	121.7(4)
C(23)-C(22)-H(22A)	119.2
C(21)-C(22)-H(22A)	119.2
C(22)-C(23)-C(18)	121.1(4)
C(22)-C(23)-H(23A)	119.4
C(18)-C(23)-H(23A)	119.4
C(29)-C(24)-C(25)	118.2(3)
C(29)-C(24)-C(16)	123.1(3)
C(25)-C(24)-C(16)	118.6(3)
C(26)-C(25)-C(24)	121.5(3)
C(26)-C(25)-H(25A)	119.3
C(24)-C(25)-H(25A)	119.3
C(25)-C(26)-C(27)	119.7(3)
C(25)-C(26)-H(26A)	120.2
C(27)-C(26)-H(26A)	120.2
C(28)-C(27)-C(26)	119.8(3)
C(28)-C(27)-H(27A)	120.1
C(26)-C(27)-H(27A)	120.1
C(29)-C(28)-C(27)	120.3(3)
C(29)-C(28)-H(28A)	119.9
C(27)-C(28)-H(28A)	119.9
C(28)-C(29)-C(24)	120.5(3)
C(28)-C(29)-H(29A)	119.8
C(24)-C(29)-H(29A)	119.8
C(30)-N(3)-C(31)	108.3(2)
C(30)-N(3)-C(33)	129.4(2)
C(31)-N(3)-C(33)	122.2(2)
C(30)-N(4)-C(32)	108.9(2)
C(30)-N(4)-C(39)	127.8(2)
C(32)-N(4)-C(39)	123.3(2)
N(4)-C(30)-N(3)	107.7(3)
N(4)-C(30)-C(45)	126.1(3)
N(3)-C(30)-C(45)	125.3(3)
C(32)-C(31)-N(3)	107.7(2)
C(32)-C(31)-H(31A)	126.1
N(3)-C(31)-H(31A)	126.1
C(31)-C(32)-N(4)	107.2(2)
...	

Table A46 continued...

C(31)-C(32)-H(32A)	126.4
N(4)-C(32)-H(32A)	126.4
N(3)-C(33)-C(34)	109.4(3)
N(3)-C(33)-C(38)	109.9(2)
C(34)-C(33)-C(38)	112.1(2)
N(3)-C(33)-H(33A)	108.5
C(34)-C(33)-H(33A)	108.5
C(38)-C(33)-H(33A)	108.5
C(33)-C(34)-C(35)	110.3(3)
C(33)-C(34)-H(34A)	109.6
C(35)-C(34)-H(34A)	109.6
C(33)-C(34)-H(34B)	109.6
C(35)-C(34)-H(34B)	109.6
H(34A)-C(34)-H(34B)	108.1
C(34)-C(35)-C(36)	110.4(3)
C(34)-C(35)-H(35A)	109.6
C(36)-C(35)-H(35A)	109.6
C(34)-C(35)-H(35B)	109.6
C(36)-C(35)-H(35B)	109.6
H(35A)-C(35)-H(35B)	108.1
C(37)-C(36)-C(35)	110.8(3)
C(37)-C(36)-H(36A)	109.5
C(35)-C(36)-H(36A)	109.5
C(37)-C(36)-H(36B)	109.5
C(35)-C(36)-H(36B)	109.5
H(36A)-C(36)-H(36B)	108.1
C(36)-C(37)-C(38)	111.5(3)
C(36)-C(37)-H(37A)	109.3
C(38)-C(37)-H(37A)	109.3
C(36)-C(37)-H(37B)	109.3
C(38)-C(37)-H(37B)	109.3
H(37A)-C(37)-H(37B)	108
C(33)-C(38)-C(37)	108.8(3)
C(33)-C(38)-H(38A)	109.9
C(37)-C(38)-H(38A)	109.9
C(33)-C(38)-H(38B)	109.9
C(37)-C(38)-H(38B)	109.9
H(38A)-C(38)-H(38B)	108.3
N(4)-C(39)-C(44)	109.9(2)
N(4)-C(39)-C(40)	109.3(2)
C(44)-C(39)-C(40)	112.2(3)
N(4)-C(39)-H(39A)	108.4
C(44)-C(39)-H(39A)	108.4
C(40)-C(39)-H(39A)	108.4
C(41)-C(40)-C(39)	109.5(3)
C(41)-C(40)-H(40A)	109.8
...	

Table A46 continued...

C(39)-C(40)-H(40A)	109.8
C(41)-C(40)-H(40B)	109.8
C(39)-C(40)-H(40B)	109.8
H(40A)-C(40)-H(40B)	108.2
C(40)-C(41)-C(42)	110.1(3)
C(40)-C(41)-H(41A)	109.6
C(42)-C(41)-H(41A)	109.6
C(40)-C(41)-H(41B)	109.6
C(42)-C(41)-H(41B)	109.6
H(41A)-C(41)-H(41B)	108.2
C(43)-C(42)-C(41)	111.2(3)
C(43)-C(42)-H(42A)	109.4
C(41)-C(42)-H(42A)	109.4
C(43)-C(42)-H(42B)	109.4
C(41)-C(42)-H(42B)	109.4
H(42A)-C(42)-H(42B)	108
C(42)-C(43)-C(44)	110.8(3)
C(42)-C(43)-H(43A)	109.5
C(44)-C(43)-H(43A)	109.5
C(42)-C(43)-H(43B)	109.5
C(44)-C(43)-H(43B)	109.5
H(43A)-C(43)-H(43B)	108.1
C(39)-C(44)-C(43)	109.9(3)
C(39)-C(44)-H(44A)	109.7
C(43)-C(44)-H(44A)	109.7
C(39)-C(44)-H(44B)	109.7
C(43)-C(44)-H(44B)	109.7
H(44A)-C(44)-H(44B)	108.2
C(53)-C(45)-C(30)	113.8(3)
C(53)-C(45)-C(46)	112.5(3)
C(30)-C(45)-C(46)	109.6(3)
C(53)-C(45)-H(45A)	106.8
C(30)-C(45)-H(45A)	106.8
C(46)-C(45)-H(45A)	106.8
C(45)-C(46)-C(47)	111.0(3)
C(45)-C(46)-H(46A)	109.4
C(47)-C(46)-H(46A)	109.4
C(45)-C(46)-H(46B)	109.4
C(47)-C(46)-H(46B)	109.4
H(46A)-C(46)-H(46B)	108
C(48)-C(47)-C(52)	116.1(4)
C(48)-C(47)-C(46)	122.5(3)
C(52)-C(47)-C(46)	121.2(4)
C(47)-C(48)-C(49)	122.0(4)
C(47)-C(48)-H(48A)	119
C(49)-C(48)-H(48A)	119
...	

Table A46 continued...

C(50)-C(49)-C(48)	117.9(4)
C(50)-C(49)-H(49A)	121.1
C(48)-C(49)-H(49A)	121.1
C(51)-C(50)-C(49)	121.6(4)
C(51)-C(50)-H(50A)	119.2
C(49)-C(50)-H(50A)	119.2
C(52)-C(51)-C(50)	119.4(4)
C(52)-C(51)-H(51A)	120.3
C(50)-C(51)-H(51A)	120.3
C(51)-C(52)-C(47)	123.0(4)
C(51)-C(52)-H(52A)	118.5
C(47)-C(52)-H(52A)	118.5
C(54)-C(53)-C(58)	118.6(3)
C(54)-C(53)-C(45)	116.9(3)
C(58)-C(53)-C(45)	124.4(3)
C(55)-C(54)-C(53)	120.9(3)
C(55)-C(54)-H(54A)	119.6
C(53)-C(54)-H(54A)	119.6
C(56)-C(55)-C(54)	120.0(4)
C(56)-C(55)-H(55A)	120
C(54)-C(55)-H(55A)	120
C(55)-C(56)-C(57)	119.5(3)
C(55)-C(56)-H(56A)	120.3
C(57)-C(56)-H(56A)	120.3
C(58)-C(57)-C(56)	121.5(3)
C(58)-C(57)-H(57A)	119.3
C(56)-C(57)-H(57A)	119.3
C(57)-C(58)-C(53)	119.4(4)
C(57)-C(58)-H(58A)	120.3
C(53)-C(58)-H(58A)	120.3

Table A47: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **4.28**

	x	y	z	U(eq)
H(2A)	7046	2658	2863	30
H(3A)	7797	2861	3162	35
H(4A)	6494	2912	894	30
H(5A)	6221	2793	2622	43
H(5B)	6172	3060	2198	43
H(6A)	5446	2848	2106	53
H(6B)	5642	2903	1166	53
H(7A)	5720	2437	2022	50
H(7B)	5377	2491	1234	50
H(8A)	6016	2561	323	37
H(8B)	6069	2295	748	37
	...			

Table A47 continued...

	x	y	z	U(eq)
H(9A)	6620	2448	1734	34
H(9B)	6792	2511	783	34
H(10A)	8019	3362	1611	33
H(11A)	7806	3473	3004	45
H(11B)	8116	3256	3396	45
H(12A)	8524	3623	3533	59
H(12B)	8467	3679	2532	59
H(13A)	9002	3283	3237	59
H(13B)	9217	3521	2779	59
H(14A)	9225	3175	1834	51
H(14B)	8913	3392	1443	51
H(15A)	8491	3020	1325	40
H(15B)	8554	2968	2327	40
H(16A)	7029	3108	321	36
H(17A)	7388	3550	1077	44
H(17B)	7126	3540	175	44
H(19A)	6932	3563	2405	53
H(20A)	6205	3625	3046	65
H(21A)	5523	3571	2270	67
H(22A)	5570	3478	824	62
H(23A)	6272	3413	172	54
H(25A)	7632	2773	52	37
H(26A)	8322	2683	−642	39
H(27A)	8832	3001	−1018	42
H(28A)	8647	3407	−673	44
H(29A)	7952	3498	23	37
H(31A)	2016	2424	2831	28
H(32A)	2617	2110	3153	29
H(33A)	1302	2247	966	34
H(34A)	1140	2401	2695	42
H(34B)	954	2149	2288	42
H(35A)	356	2452	2284	53
H(35B)	477	2368	1327	53
H(36A)	435	2802	1372	44
H(36B)	813	2810	2125	44
H(37A)	1183	2904	822	46
H(37B)	997	2654	405	46
H(38A)	1785	2595	806	39
H(38B)	1674	2681	1767	39
H(39A)	2530	1589	1637	32
H(40A)	2714	1684	3421	40
H(40B)	2286	1525	3069	40
H(41A)	2803	1222	2532	52
H(41B)	2912	1262	3528	52
H(42A)	3551	1521	3188	60
H(42B)	3620	1260	2727	60
		...		

Table A47 continued...

	x	y	z	U(eq)
H(43A)	3351	1425	1423	56
H(43B)	3781	1585	1759	56
H(44A)	3269	1890	2288	40
H(44B)	3160	1846	1294	40
H(45A)	1734	1987	332	45
H(46A)	1845	1510	1091	55
H(46B)	1585	1561	202	55
H(48A)	1373	1526	2400	59
H(49A)	648	1571	3080	56
H(50A)	41	1757	2331	59
H(51A)	136	1881	924	55
H(52A)	846	1844	280	47
H(54A)	2494	2202	52	47
H(55A)	3217	2171	−613	48
H(56A)	3516	1787	−970	51
H(57A)	3095	1434	−640	51
H(58A)	2371	1459	11	49

Table A48: Torsion angles (°) for **4.28**

C(2)-N(1)-C(1)-N(2)	−2.6(3)
C(4)-N(1)-C(1)-N(2)	176.0(3)
C(2)-N(1)-C(1)-C(16)	169.6(3)
C(4)-N(1)-C(1)-C(16)	−11.8(5)
C(3)-N(2)-C(1)-N(1)	3.4(3)
C(10)-N(2)-C(1)-N(1)	−176.7(3)
C(3)-N(2)-C(1)-C(16)	−168.8(3)
C(10)-N(2)-C(1)-C(16)	11.1(5)
C(1)-N(1)-C(2)-C(3)	0.9(3)
C(4)-N(1)-C(2)-C(3)	−177.8(3)
N(1)-C(2)-C(3)-N(2)	1.3(3)
C(1)-N(2)-C(3)-C(2)	−3.0(3)
C(10)-N(2)-C(3)-C(2)	177.2(3)
C(1)-N(1)-C(4)-C(9)	121.7(3)
C(2)-N(1)-C(4)-C(9)	−59.9(4)
C(1)-N(1)-C(4)-C(5)	−115.6(3)
C(2)-N(1)-C(4)-C(5)	62.8(3)
N(1)-C(4)-C(5)-C(6)	179.8(2)
C(9)-C(4)-C(5)-C(6)	−58.7(3)
C(4)-C(5)-C(6)-C(7)	58.9(4)
C(5)-C(6)-C(7)-C(8)	−58.4(4)
C(6)-C(7)-C(8)-C(9)	57.1(4)
N(1)-C(4)-C(9)-C(8)	178.3(3)
C(5)-C(4)-C(9)-C(8)	57.6(4)
C(7)-C(8)-C(9)-C(4)	−56.8(4)
C(1)-N(2)-C(10)-C(15)	−111.2(3)
C(3)-N(2)-C(10)-C(15)	68.7(4)
C(1)-N(2)-C(10)-C(11)	125.1(3)
C(3)-N(2)-C(10)-C(11)	−55.1(4)
N(2)-C(10)-C(11)-C(12)	179.0(3)
C(15)-C(10)-C(11)-C(12)	55.4(4)
C(10)-C(11)-C(12)-C(13)	−55.1(4)
C(11)-C(12)-C(13)-C(14)	56.5(5)
C(12)-C(13)-C(14)-C(15)	−56.6(4)
N(2)-C(10)-C(15)-C(14)	−178.5(3)
C(11)-C(10)-C(15)-C(14)	−55.4(4)
C(13)-C(14)-C(15)-C(10)	55.5(4)
N(1)-C(1)-C(16)-C(24)	−120.8(3)
N(2)-C(1)-C(16)-C(24)	49.9(4)
N(1)-C(1)-C(16)-C(17)	109.2(3)
N(2)-C(1)-C(16)-C(17)	−80.1(4)
C(1)-C(16)-C(17)-C(18)	−57.1(4)
C(24)-C(16)-C(17)-C(18)	174.8(3)
C(16)-C(17)-C(18)-C(23)	−80.1(4)
C(16)-C(17)-C(18)-C(19)	99.2(4)
C(23)-C(18)-C(19)-C(20)	−3.0(5)
C(17)-C(18)-C(19)-C(20)	177.7(3)
C(18)-C(19)-C(20)-C(21)	2.2(6)
C(19)-C(20)-C(21)-C(22)	−1.6(6)
C(20)-C(21)-C(22)-C(23)	1.8(6)
C(21)-C(22)-C(23)-C(18)	−2.7(6)
C(19)-C(18)-C(23)-C(22)	3.3(5)
C(17)-C(18)-C(23)-C(22)	−177.4(3)
C(1)-C(16)-C(24)-C(29)	−116.7(3)
C(17)-C(16)-C(24)-C(29)	11.2(4)
C(1)-C(16)-C(24)-C(25)	60.9(4)
C(17)-C(16)-C(24)-C(25)	−171.2(3)
C(29)-C(24)-C(25)-C(26)	2.0(5)
C(16)-C(24)-C(25)-C(26)	−175.7(3)
C(24)-C(25)-C(26)-C(27)	−1.1(5)
C(25)-C(26)-C(27)-C(28)	0.2(5)
C(26)-C(27)-C(28)-C(29)	−0.3(5)
C(27)-C(28)-C(29)-C(24)	1.2(5)
C(25)-C(24)-C(29)-C(28)	−2.1(5)
C(16)-C(24)-C(29)-C(28)	175.6(3)
C(32)-N(4)-C(30)-N(3)	−4.3(4)
C(39)-N(4)-C(30)-N(3)	176.7(3)
C(32)-N(4)-C(30)-C(45)	165.3(3)
C(39)-N(4)-C(30)-C(45)	−13.7(6)
C(31)-N(3)-C(30)-N(4)	4.4(4)

Table A48 continued...

C(33)-N(3)-C(30)-N(4)	−172.5(3)
C(31)-N(3)-C(30)-C(45)	−165.3(3)
C(33)-N(3)-C(30)-C(45)	17.8(6)
C(30)-N(3)-C(31)-C(32)	−2.9(4)
C(33)-N(3)-C(31)-C(32)	174.3(3)
N(3)-C(31)-C(32)-N(4)	0.2(3)
C(30)-N(4)-C(32)-C(31)	2.5(4)
C(39)-N(4)-C(32)-C(31)	−178.4(3)
C(30)-N(3)-C(33)-C(34)	112.7(4)
C(31)-N(3)-C(33)-C(34)	−63.8(3)
C(30)-N(3)-C(33)-C(38)	−123.9(4)
C(31)-N(3)-C(33)-C(38)	59.7(4)
N(3)-C(33)-C(34)-C(35)	−179.3(3)
C(38)-C(33)-C(34)-C(35)	58.5(4)
C(33)-C(34)-C(35)-C(36)	−57.2(4)
C(34)-C(35)-C(36)-C(37)	56.8(4)
C(35)-C(36)-C(37)-C(38)	−56.7(4)
N(3)-C(33)-C(38)-C(37)	−178.8(3)
C(34)-C(33)-C(38)-C(37)	−56.9(4)
C(36)-C(37)-C(38)-C(33)	55.9(4)
C(30)-N(4)-C(39)-C(44)	110.2(4)
C(32)-N(4)-C(39)-C(44)	−68.7(4)
C(30)-N(4)-C(39)-C(40)	−126.2(3)
C(32)-N(4)-C(39)-C(40)	54.9(4)
N(4)-C(39)-C(40)-C(41)	−179.3(3)
C(44)-C(39)-C(40)-C(41)	−57.0(3)
C(39)-C(40)-C(41)-C(42)	56.2(4)
C(40)-C(41)-C(42)-C(43)	−57.8(4)
C(41)-C(42)-C(43)-C(44)	57.8(5)
N(4)-C(39)-C(44)-C(43)	178.8(3)
C(40)-C(39)-C(44)-C(43)	56.9(4)
C(42)-C(43)-C(44)-C(39)	−56.6(4)
N(4)-C(30)-C(45)-C(53)	−45.7(5)
N(3)-C(30)-C(45)-C(53)	122.2(4)
N(4)-C(30)-C(45)-C(46)	81.3(4)
N(3)-C(30)-C(45)-C(46)	−110.8(4)
C(53)-C(45)-C(46)-C(47)	−176.4(3)
C(30)-C(45)-C(46)-C(47)	55.9(4)
C(45)-C(46)-C(47)-C(48)	−108.7(4)
C(45)-C(46)-C(47)-C(52)	77.3(4)
C(52)-C(47)-C(48)-C(49)	−0.3(5)
C(46)-C(47)-C(48)-C(49)	−174.5(3)
C(47)-C(48)-C(49)-C(50)	−0.1(5)
C(48)-C(49)-C(50)-C(51)	1.2(5)
C(49)-C(50)-C(51)-C(52)	−1.9(5)
C(50)-C(51)-C(52)-C(47)	1.6(5)
...	

Table A48 continued...

C(48)-C(47)-C(52)-C(51)	−0.5(5)
C(46)-C(47)-C(52)-C(51)	173.9(3)
C(30)-C(45)-C(53)-C(54)	−61.7(4)
C(46)-C(45)-C(53)-C(54)	172.9(4)
C(30)-C(45)-C(53)-C(58)	115.6(4)
C(46)-C(45)-C(53)-C(58)	−9.8(5)
C(58)-C(53)-C(54)-C(55)	−3.8(6)
C(45)-C(53)-C(54)-C(55)	173.7(3)
C(53)-C(54)-C(55)-C(56)	1.8(6)
C(54)-C(55)-C(56)-C(57)	−0.1(5)
C(55)-C(56)-C(57)-C(58)	0.4(6)
C(56)-C(57)-C(58)-C(53)	−2.4(6)
C(54)-C(53)-C(58)-C(57)	4.1(6)
C(45)-C(53)-C(58)-C(57)	−173.2(4)

Table A49: Anisotropic displacement parameters ($Å^2$x 10^3) for **4.28**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	50(1)	40(1)	39(1)	−7(1)	13(1)	0(1)
N(1)	24(1)	22(1)	27(1)	5(1)	−3(1)	−2(1)
N(2)	24(1)	23(1)	26(1)	−2(1)	−5(1)	−3(1)
C(1)	24(1)	22(1)	36(2)	6(1)	2(1)	−4(1)
C(2)	31(1)	24(1)	21(2)	5(1)	−1(1)	−2(1)
C(3)	36(2)	32(1)	18(1)	3(1)	−4(1)	−4(1)
C(4)	19(1)	23(1)	34(2)	8(1)	−3(1)	−3(1)
C(5)	24(1)	25(1)	59(2)	−11(1)	8(1)	2(1)
C(6)	24(2)	40(2)	68(3)	−10(2)	9(2)	6(1)
C(7)	25(1)	42(2)	58(2)	−2(2)	10(2)	−6(1)
C(8)	21(1)	31(1)	40(2)	−2(1)	3(1)	−8(1)
C(9)	19(1)	31(1)	34(2)	−6(1)	0(1)	1(1)
C(10)	24(1)	27(1)	32(2)	3(1)	−6(1)	−10(1)
C(11)	35(2)	38(2)	40(2)	−13(1)	1(1)	−11(1)
C(12)	53(2)	49(2)	45(2)	−15(2)	−10(2)	−21(2)
C(13)	39(2)	52(2)	56(3)	−5(2)	−15(2)	−22(2)
C(14)	27(2)	45(2)	55(2)	2(2)	0(2)	−13(1)
C(15)	27(2)	34(2)	38(2)	−3(1)	1(1)	−6(1)
C(16)	30(2)	26(1)	34(2)	−3(1)	−2(1)	−2(1)
C(17)	42(2)	23(1)	45(2)	4(1)	−1(2)	2(1)
C(18)	33(2)	37(2)	46(2)	−3(1)	1(1)	7(1)
C(19)	43(2)	34(2)	55(2)	−10(2)	3(2)	6(1)
C(20)	55(2)	34(2)	74(3)	−14(2)	11(2)	7(2)
C(21)	38(2)	32(2)	97(4)	−9(2)	14(2)	11(2)
C(22)	35(2)	30(2)	90(3)	5(2)	−11(2)	4(1)
C(23)	41(2)	37(2)	56(2)	7(2)	−5(2)	6(2)
C(24)	33(2)	25(1)	30(2)	0(1)	1(1)	0(1)
C(25)	39(2)	26(1)	28(2)	0(1)	−2(1)	−4(1)
C(26)	46(2)	33(1)	19(2)	−4(1)	−3(1)	3(1)
C(27)	35(2)	38(2)	32(2)	−1(1)	2(1)	4(1)
C(28)	35(2)	42(2)	34(2)	6(1)	7(1)	−4(1)
C(29)	39(2)	23(1)	31(2)	2(1)	−2(1)	−6(1)
Br(2)	35(1)	42(1)	33(1)	−5(1)	−8(1)	−1(1)
N(3)	25(1)	22(1)	24(1)	−8(1)	−10(1)	6(1)
N(4)	25(1)	23(1)	25(1)	−4(1)	−4(1)	8(1)
C(30)	39(2)	29(1)	45(2)	−15(1)	−22(2)	13(1)
C(31)	23(1)	20(1)	27(2)	−6(1)	−4(1)	0(1)
C(32)	23(1)	22(1)	28(2)	−3(1)	−6(1)	2(1)
C(33)	28(1)	23(1)	35(2)	−7(1)	−16(1)	10(1)
C(34)	25(2)	29(1)	51(2)	1(1)	−10(1)	2(1)
C(35)	22(2)	39(2)	73(3)	5(2)	−2(2)	7(1)
C(36)	30(2)	31(1)	50(2)	−6(1)	−3(1)	12(1)
C(37)	35(2)	37(2)	43(2)	8(1)	−8(1)	12(1)

...

Table A49 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(38)	30(2)	34(2)	34(2)	8(1)	−1(1)	11(1)
C(39)	30(1)	20(1)	30(2)	−3(1)	−6(1)	11(1)
C(40)	30(2)	30(1)	40(2)	6(1)	1(1)	4(1)
C(41)	52(2)	25(1)	51(2)	8(1)	−6(2)	11(1)
C(42)	40(2)	43(2)	66(3)	14(2)	−8(2)	21(2)
C(43)	40(2)	41(2)	59(3)	3(2)	8(2)	22(2)
C(44)	37(2)	34(2)	29(2)	2(1)	2(1)	16(1)
C(45)	37(2)	34(2)	40(2)	1(1)	2(1)	2(1)
C(46)	44(2)	40(2)	53(2)	−10(2)	0(2)	−3(2)
C(47)	30(2)	32(2)	67(3)	14(2)	−7(2)	−12(1)
C(48)	35(2)	36(2)	77(3)	11(2)	−15(2)	−14(1)
C(49)	50(2)	32(2)	59(3)	−5(2)	6(2)	−13(2)
C(50)	34(2)	35(2)	77(3)	−19(2)	1(2)	0(1)
C(51)	37(2)	33(2)	68(3)	−14(2)	−11(2)	4(1)
C(52)	34(2)	24(1)	59(2)	−1(1)	−14(2)	−8(1)
C(53)	51(2)	36(2)	38(2)	10(1)	18(2)	16(2)
C(54)	56(2)	35(2)	28(2)	7(1)	9(2)	11(2)
C(55)	49(2)	50(2)	22(2)	−3(1)	−4(1)	−2(2)
C(56)	35(2)	57(2)	34(2)	−4(2)	1(1)	10(2)
C(57)	47(2)	40(2)	42(2)	−10(2)	2(2)	14(2)
C(58)	63(2)	32(2)	28(2)	−2(1)	7(2)	13(2)

The anisotropic displacement factor exponent takes the form: $-2\pi^2\left[h^2a*^2U^{11}+...+2hka*b*U^{12}\right]$

A.2.9 *Structural Data for Imidazolium Salt* **4.37**

Suitable crystals for X-ray analysis were obtained by slow diffusion of hexane into a $CHCl_3$ solution at -20 °C in a dry box.

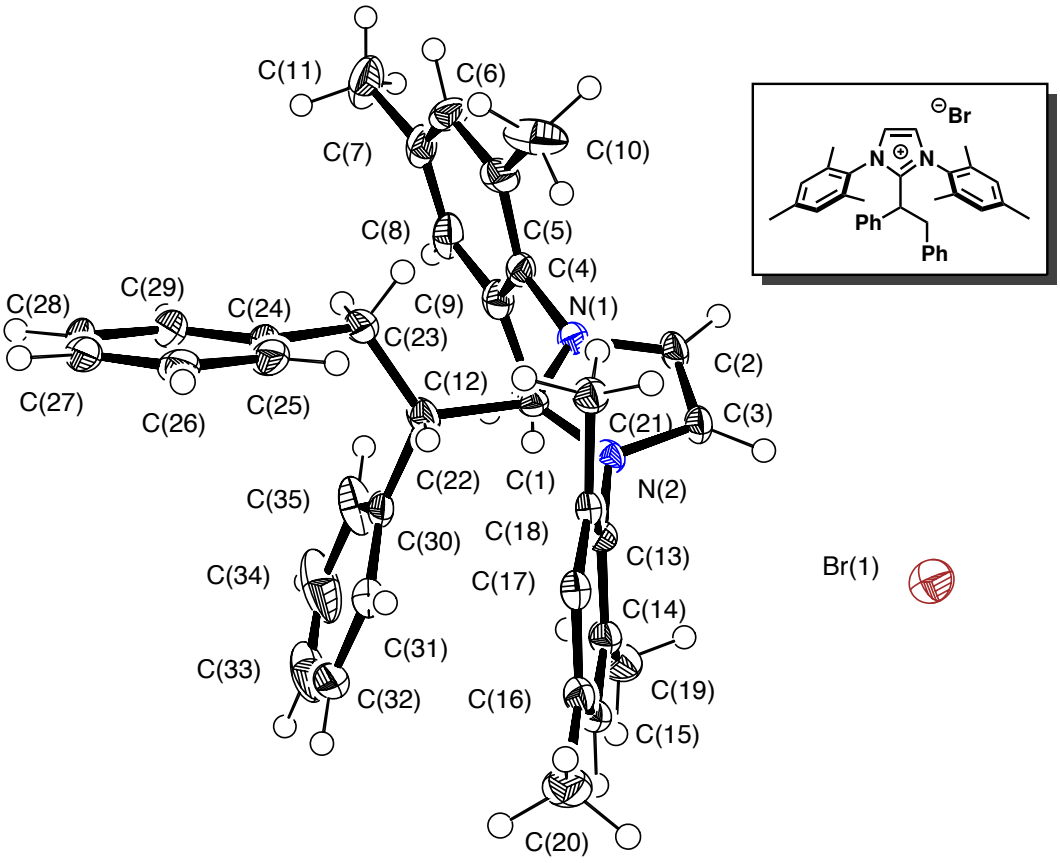

Figure A9: ORTEP drawing of imidazolium salt **4.37** shown at 50% probability

Table A50: Crystal data and structure refinement for **4.37**

Empirical formula	$C_{37}H_{43}BrCl_4N_2O$
Formula weight	753.44
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P −1
Unit cell dimensions	a = 11.8192(9) Å α = 112.692(5)°. b = 11.9317(10) Å β = 93.816(5)°. c = 14.5923(12) Å γ = 96.976(5)°.
Volume	1870.0(3) $Å^3$
Z	2
Density (calculated)	1.336 Mg/m^3
Absorption coefficient	1.416 mm^{-1}
F(000)	780
Crystal size	0.17 x 0.08 x 0.05 mm^3
Theta range for data collection	1.52 to 28.71°.
Index ranges	−15<=h<=15, −15<=k<=16, −19<=l<=19
Reflections collected	31263
Independent reflections	9546 [R(int) = 0.0462]
Completeness to theta = 28.71°	98.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9377 and 0.7938
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9546 / 345 / 489
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0610, wR2 = 0.1381
R indices (all data)	R1 = 0.1000, wR2 = 0.1534
Extinction coefficient	na
Largest diff. peak and hole	0.735 and −0.677 e.$Å^{-3}$

Table A51: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **4.37**

	x	y	z	U(eq)
Br(1)	1403(1)	4925(1)	3543(1)	35(1)
N(1)	2069(2)	3995(2)	7185(2)	19(1)
N(2)	2968(2)	3639(2)	5887(2)	19(1)
C(1)	2863(2)	3370(3)	6696(2)	19(1)
C(2)	1668(3)	4669(3)	6679(2)	24(1)
C(3)	2228(3)	4445(3)	5867(2)	22(1)
C(4)	1643(3)	3968(3)	8084(2)	22(1)
C(5)	2215(3)	4780(3)	9013(2)	29(1)
C(6)	1799(3)	4708(3)	9862(2)	34(1)
C(7)	853(3)	3861(4)	9785(3)	35(1)
C(8)	275(3)	3120(3)	8848(3)	31(1)
C(9)	648(3)	3156(3)	7976(3)	26(1)
C(10)	3220(3)	5749(4)	9120(3)	46(1)
C(11)	431(4)	3765(4)	10714(3)	51(1)
C(12)	−35(3)	2407(3)	6968(3)	34(1)
C(13)	3757(3)	3191(3)	5159(2)	19(1)
C(14)	3329(3)	2233(3)	4234(2)	23(1)
C(15)	4106(3)	1801(3)	3567(2)	26(1)
C(16)	5277(3)	2294(3)	3792(2)	25(1)
C(17)	5652(3)	3244(3)	4718(2)	21(1)
C(18)	4906(3)	3726(3)	5410(2)	19(1)
C(19)	2069(3)	1678(3)	3976(3)	33(1)
C(20)	6101(3)	1805(4)	3040(3)	35(1)
C(21)	5341(3)	4804(3)	6383(2)	22(1)
C(22)	3517(3)	2506(3)	6959(3)	33(1)
C(23)	3960(4)	2866(5)	8007(4)	25(1)
C(24)	4981(7)	2274(10)	8171(8)	23(1)
C(25)	6041(4)	2601(5)	7901(4)	29(1)
C(26)	6998(5)	2123(5)	8085(4)	32(1)
C(27)	6917(7)	1349(11)	8579(9)	36(2)
C(28)	5889(7)	1021(8)	8858(6)	36(2)
C(29)	4915(5)	1493(5)	8670(5)	30(1)
C(23X)	4639(7)	2872(7)	7474(6)	19(2)
C(24X)	5119(11)	2170(20)	8049(15)	25(2)
C(25X)	6235(9)	1938(9)	7981(7)	28(2)
C(26X)	6692(13)	1290(20)	8496(17)	37(2)
C(27X)	6039(11)	921(15)	9099(10)	35(2)
C(28X)	4911(9)	1108(8)	9156(7)	34(2)
C(29X)	4467(9)	1731(10)	8624(8)	29(2)
C(30)	3076(3)	1169(3)	6293(2)	22(1)
C(31)	3629(3)	539(3)	5492(3)	32(1)
C(32)	3192(4)	−683(4)	4884(3)	51(1)

...

Table A51 continued...

	x	y	z	U(eq)
C(33)	2211(4)	−1249(4)	5086(4)	64(1)
C(34)	1677(4)	−624(4)	5876(5)	62(1)
C(35)	2102(3)	575(4)	6478(3)	41(1)
C(1S)	6967(4)	7179(4)	8291(3)	45(1)
Cl(1S)	6236(2)	6470(2)	9003(1)	64(1)
Cl(2S)	7783(3)	8619(2)	9004(2)	71(1)
Cl(1T)	5987(11)	7059(16)	8942(8)	64(1)
Cl(2T)	7830(30)	8500(20)	9244(18)	71(1)
C(2S)	688(5)	8523(4)	8044(3)	59(1)
Cl(3S)	1818(1)	8408(1)	8821(1)	61(1)
Cl(4S)	450(1)	10069(1)	8408(1)	61(1)
O(1)	9368(3)	3347(2)	4223(2)	42(1)

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

Table A52: Bond lengths (Å) and angles (°) for **4.37**

N(1)-C(1)	1.340(4)
N(1)-C(2)	1.386(4)
N(1)-C(4)	1.447(4)
N(2)-C(1)	1.347(4)
N(2)-C(3)	1.383(4)
N(2)-C(13)	1.448(4)
C(1)-C(22)	1.505(4)
C(2)-C(3)	1.348(5)
C(2)-H(2A)	0.95
C(3)-H(3A)	0.95
C(4)-C(9)	1.388(4)
C(4)-C(5)	1.392(4)
C(5)-C(6)	1.392(5)
C(5)-C(10)	1.509(5)
C(6)-C(7)	1.381(6)
C(6)-H(6A)	0.95
C(7)-C(8)	1.382(5)
C(7)-C(11)	1.514(5)
C(8)-C(9)	1.389(5)
C(8)-H(8A)	0.95
C(9)-C(12)	1.505(5)
C(10)-H(10A)	0.98
C(10)-H(10B)	0.98
C(10)-H(10C)	0.98
C(11)-H(11A)	0.98

...

Table A52 continued...

C(11)-H(11B)	0.98
C(11)-H(11C)	0.98
C(12)-H(12A)	0.98
C(12)-H(12B)	0.98
C(12)-H(12C)	0.98
C(13)-C(18)	1.389(4)
C(13)-C(14)	1.401(4)
C(14)-C(15)	1.380(5)
C(14)-C(19)	1.514(4)
C(15)-C(16)	1.400(5)
C(15)-H(15A)	0.95
C(16)-C(17)	1.387(4)
C(16)-C(20)	1.510(5)
C(17)-C(18)	1.386(4)
C(17)-H(17A)	0.95
C(18)-C(21)	1.506(4)
C(19)-H(19A)	0.98
C(19)-H(19B)	0.98
C(19)-H(19C)	0.98
C(20)-H(20A)	0.98
C(20)-H(20B)	0.98
C(20)-H(20C)	0.98
C(21)-H(21A)	0.98
C(21)-H(21B)	0.98
C(21)-H(21C)	0.98
C(22)-C(23X)	1.410(8)
C(22)-C(23)	1.460(6)
C(22)-C(30)	1.515(4)
C(22)-H(22)	1
C(23)-C(24)	1.520(7)
C(23)-H(23A)	0.99
C(23)-H(23B)	0.99
C(24)-C(29)	1.385(8)
C(24)-C(25)	1.394(8)
C(25)-C(26)	1.382(7)
C(25)-H(25A)	0.95
C(26)-C(27)	1.373(10)
C(26)-H(26A)	0.95
C(27)-C(28)	1.367(9)
C(27)-H(27A)	0.95
C(28)-C(29)	1.397(9)
C(28)-H(28A)	0.95
C(29)-H(29A)	0.95
C(23X)-C(24X)	1.521(12)
C(23X)-H(23C)	0.99
C(23X)-H(23D)	0.99

...

Table A52 continued...

C(24X)-C(29X)	1.379(12)
C(24X)-C(25X)	1.383(11)
C(25X)-C(26X)	1.393(14)
C(25X)-H(25B)	0.95
C(26X)-C(27X)	1.371(13)
C(26X)-H(26B)	0.95
C(27X)-C(28X)	1.381(13)
C(27X)-H(27B)	0.95
C(28X)-C(29X)	1.384(11)
C(28X)-H(28B)	0.95
C(29X)-H(29B)	0.95
C(30)-C(35)	1.376(5)
C(30)-C(31)	1.379(5)
C(31)-C(32)	1.392(5)
C(31)-H(31A)	0.95
C(32)-C(33)	1.377(7)
C(32)-H(32A)	0.95
C(33)-C(34)	1.353(8)
C(33)-H(33A)	0.95
C(34)-C(35)	1.367(6)
C(34)-H(34A)	0.95
C(35)-H(35A)	0.95
C(1S)-Cl(1T)	1.573(13)
C(1S)-Cl(2S)	1.747(5)
C(1S)-Cl(1S)	1.778(5)
C(1S)-Cl(2T)	1.79(2)
C(1S)-H(1S1)	0.99
C(1S)-H(1S2)	0.99
C(2S)-Cl(3S)	1.747(5)
C(2S)-Cl(4S)	1.776(5)
C(2S)-H(2S1)	0.99
C(2S)-H(2S2)	0.99
O(1)-H(1O)	0.808(19)
O(1)-H(2O)	0.816(19)
C(1)-N(1)-C(2)	109.5(3)
C(1)-N(1)-C(4)	126.9(3)
C(2)-N(1)-C(4)	123.5(3)
C(1)-N(2)-C(3)	109.7(3)
C(1)-N(2)-C(13)	125.7(2)
C(3)-N(2)-C(13)	124.5(3)
N(1)-C(1)-N(2)	106.8(3)
N(1)-C(1)-C(22)	128.2(3)
N(2)-C(1)-C(22)	125.0(3)
C(3)-C(2)-N(1)	107.2(3)
C(3)-C(2)-H(2A)	126.4
N(1)-C(2)-H(2A)	126.4

...

Table A52 continued...

C(2)-C(3)-N(2)	106.8(3)
C(2)-C(3)-H(3A)	126.6
N(2)-C(3)-H(3A)	126.6
C(9)-C(4)-C(5)	123.0(3)
C(9)-C(4)-N(1)	117.9(3)
C(5)-C(4)-N(1)	119.1(3)
C(6)-C(5)-C(4)	117.6(3)
C(6)-C(5)-C(10)	120.0(3)
C(4)-C(5)-C(10)	122.3(3)
C(7)-C(6)-C(5)	121.1(3)
C(7)-C(6)-H(6A)	119.4
C(5)-C(6)-H(6A)	119.4
C(6)-C(7)-C(8)	119.1(3)
C(6)-C(7)-C(11)	120.6(4)
C(8)-C(7)-C(11)	120.3(4)
C(7)-C(8)-C(9)	122.2(3)
C(7)-C(8)-H(8A)	118.9
C(9)-C(8)-H(8A)	118.9
C(4)-C(9)-C(8)	116.8(3)
C(4)-C(9)-C(12)	121.7(3)
C(8)-C(9)-C(12)	121.5(3)
C(5)-C(10)-H(10A)	109.5
C(5)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(5)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(7)-C(11)-H(11A)	109.5
C(7)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(7)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(9)-C(12)-H(12A)	109.5
C(9)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(9)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(18)-C(13)-C(14)	122.8(3)
C(18)-C(13)-N(2)	118.6(2)
C(14)-C(13)-N(2)	118.6(3)
C(15)-C(14)-C(13)	117.3(3)
C(15)-C(14)-C(19)	121.0(3)
C(13)-C(14)-C(19)	121.6(3)
C(14)-C(15)-C(16)	122.0(3)

...

Table A52 continued...

C(14)-C(15)-H(15A)	119
C(16)-C(15)-H(15A)	119
C(17)-C(16)-C(15)	118.2(3)
C(17)-C(16)-C(20)	121.2(3)
C(15)-C(16)-C(20)	120.6(3)
C(18)-C(17)-C(16)	122.2(3)
C(18)-C(17)-H(17A)	118.9
C(16)-C(17)-H(17A)	118.9
C(17)-C(18)-C(13)	117.5(3)
C(17)-C(18)-C(21)	120.3(3)
C(13)-C(18)-C(21)	122.2(3)
C(14)-C(19)-H(19A)	109.5
C(14)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(14)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(16)-C(20)-H(20A)	109.5
C(16)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(16)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(18)-C(21)-H(21A)	109.5
C(18)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(18)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(23X)-C(22)-C(23)	47.4(4)
C(23X)-C(22)-C(1)	122.9(4)
C(23)-C(22)-C(1)	117.9(3)
C(23X)-C(22)-C(30)	120.8(4)
C(23)-C(22)-C(30)	120.6(3)
C(1)-C(22)-C(30)	112.4(2)
C(23X)-C(22)-H(22)	52.8
C(23)-C(22)-H(22)	100.2
C(1)-C(22)-H(22)	100.2
C(30)-C(22)-H(22)	100.2
C(22)-C(23)-C(24)	114.5(5)
C(22)-C(23)-H(23A)	108.6
C(24)-C(23)-H(23A)	108.6
C(22)-C(23)-H(23B)	108.6
C(24)-C(23)-H(23B)	108.6
H(23A)-C(23)-H(23B)	107.6
C(29)-C(24)-C(25)	118.3(6)

...

Table A52 continued...

C(29)-C(24)-C(23)	121.4(6)
C(25)-C(24)-C(23)	120.1(6)
C(26)-C(25)-C(24)	121.4(6)
C(26)-C(25)-H(25A)	119.3
C(24)-C(25)-H(25A)	119.3
C(27)-C(26)-C(25)	119.5(6)
C(27)-C(26)-H(26A)	120.3
C(25)-C(26)-H(26A)	120.3
C(28)-C(27)-C(26)	120.2(8)
C(28)-C(27)-H(27A)	119.9
C(26)-C(27)-H(27A)	119.9
C(27)-C(28)-C(29)	120.7(7)
C(27)-C(28)-H(28A)	119.7
C(29)-C(28)-H(28A)	119.7
C(24)-C(29)-C(28)	119.9(6)
C(24)-C(29)-H(29A)	120.1
C(28)-C(29)-H(29A)	120.1
C(22)-C(23X)-C(24X)	121.6(9)
C(22)-C(23X)-H(23C)	106.9
C(24X)-C(23X)-H(23C)	106.9
C(22)-C(23X)-H(23D)	106.9
C(24X)-C(23X)-H(23D)	106.9
H(23C)-C(23X)-H(23D)	106.7
C(29X)-C(24X)-C(25X)	118.2(10)
C(29X)-C(24X)-C(23X)	122.1(9)
C(25X)-C(24X)-C(23X)	119.6(10)
C(24X)-C(25X)-C(26X)	120.7(11)
C(24X)-C(25X)-H(25B)	119.6
C(26X)-C(25X)-H(25B)	119.6
C(27X)-C(26X)-C(25X)	119.5(13)
C(27X)-C(26X)-H(26B)	120.2
C(25X)-C(26X)-H(26B)	120.2
C(26X)-C(27X)-C(28X)	120.9(12)
C(26X)-C(27X)-H(27B)	119.6
C(28X)-C(27X)-H(27B)	119.6
C(27X)-C(28X)-C(29X)	118.5(10)
C(27X)-C(28X)-H(28B)	120.7
C(29X)-C(28X)-H(28B)	120.7
C(24X)-C(29X)-C(28X)	122.0(10)
C(24X)-C(29X)-H(29B)	119
C(28X)-C(29X)-H(29B)	119
C(35)-C(30)-C(31)	119.2(3)
C(35)-C(30)-C(22)	119.8(3)
C(31)-C(30)-C(22)	121.0(3)
C(30)-C(31)-C(32)	119.6(4)
C(30)-C(31)-H(31A)	120.2
...	

Table A52 continued...

C(32)-C(31)-H(31A)	120.2
C(33)-C(32)-C(31)	119.7(4)
C(33)-C(32)-H(32A)	120.2
C(31)-C(32)-H(32A)	120.2
C(34)-C(33)-C(32)	120.2(4)
C(34)-C(33)-H(33A)	119.9
C(32)-C(33)-H(33A)	119.9
C(33)-C(34)-C(35)	120.4(4)
C(33)-C(34)-H(34A)	119.8
C(35)-C(34)-H(34A)	119.8
C(34)-C(35)-C(30)	120.8(4)
C(34)-C(35)-H(35A)	119.6
C(30)-C(35)-H(35A)	119.6
Cl(1T)-C(1S)-Cl(2S)	104.1(6)
Cl(1T)-C(1S)-Cl(1S)	27.7(7)
Cl(2S)-C(1S)-Cl(1S)	114.4(3)
Cl(1T)-C(1S)-Cl(2T)	96.2(12)
Cl(2S)-C(1S)-Cl(2T)	13.8(8)
Cl(1S)-C(1S)-Cl(2T)	102.2(10)
Cl(1T)-C(1S)-H(1S1)	135.2
Cl(2S)-C(1S)-H(1S1)	108.6
Cl(1S)-C(1S)-H(1S1)	108.6
Cl(2T)-C(1S)-H(1S1)	108.7
Cl(1T)-C(1S)-H(1S2)	89.4
Cl(2S)-C(1S)-H(1S2)	108.6
Cl(1S)-C(1S)-H(1S2)	108.6
Cl(2T)-C(1S)-H(1S2)	120.5
H(1S1)-C(1S)-H(1S2)	107.6
Cl(3S)-C(2S)-Cl(4S)	111.5(2)
Cl(3S)-C(2S)-H(2S1)	109.3
Cl(4S)-C(2S)-H(2S1)	109.3
Cl(3S)-C(2S)-H(2S2)	109.3
Cl(4S)-C(2S)-H(2S2)	109.3
H(2S1)-C(2S)-H(2S2)	108
H(1O)-O(1)-H(2O)	100(5)

Table A53: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **4.37**

	x	y	z	U(eq)
H(2A)	1103	5191	6868	28
H(3A)	2134	4778	5376	26
H(6A)	2173	5251	10505	40
H(8A)	−399	2568	8800	37
H(10A)	3483	5588	8464	69
H(10B)	3847	5726	9583	69
...				

Table A53 continued...

	x	y	z	U(eq)
H(10C)	2983	6562	9381	69
H(11A)	605	3003	10756	77
H(11B)	−401	3759	10678	77
H(11C)	816	4472	11308	77
H(12A)	−474	1664	6982	50
H(12B)	489	2174	6457	50
H(12C)	−564	2897	6809	50
H(15A)	3838	1151	2935	31
H(17A)	6447	3576	4883	26
H(19A)	1948	991	3318	50
H(19B)	1614	2306	3961	50
H(19C)	1830	1378	4483	50
H(20A)	6859	2317	3288	53
H(20B)	5818	1826	2401	53
H(20C)	6161	956	2943	53
H(21A)	5951	4594	6747	33
H(21B)	4709	5003	6790	33
H(21C)	5646	5517	6246	33
H(22)	4248	2631	6678	40
H(23A)	3333	2649	8356	30
H(23B)	4188	3772	8319	30
H(25A)	6108	3164	7585	35
H(26A)	7706	2329	7872	38
H(27A)	7578	1039	8728	43
H(28A)	5836	467	9184	43
H(29A)	4209	1278	8883	36
H(23C)	4690	3735	7956	23
H(23D)	5169	2878	6978	23
H(25B)	6694	2220	7579	34
H(26B)	7451	1116	8430	44
H(27B)	6367	528	9484	42
H(28B)	4450	816	9552	40
H(29B)	3690	1858	8655	34
H(31A)	4305	935	5357	38
H(32A)	3569	−1125	4331	61
H(33A)	1907	−2081	4669	76
H(34A)	1002	−1022	6012	74
H(35A)	1720	1003	7031	50
H(1S1)	7479	6627	7900	54
H(1S2)	6393	7272	7810	54
H(2S1)	−21	8008	8073	71
H(2S2)	866	8205	7344	71
H(1O)	9940(30)	3750(40)	4160(40)	62
H(2O)	9320(40)	3730(40)	4814(17)	62

Table A54: Torsion angles (°) for **4.37**

C(2)-N(1)-C(1)-N(2)	0.0(3)
C(4)-N(1)-C(1)-N(2)	178.0(3)
C(2)-N(1)-C(1)-C(22)	−179.0(3)
C(4)-N(1)-C(1)-C(22)	−1.0(5)
C(3)-N(2)-C(1)-N(1)	−0.1(3)
C(13)-N(2)-C(1)-N(1)	178.2(2)
C(3)-N(2)-C(1)-C(22)	179.0(3)
C(13)-N(2)-C(1)-C(22)	−2.8(4)
C(1)-N(1)-C(2)-C(3)	0.1(3)
C(4)-N(1)-C(2)-C(3)	−178.0(3)
N(1)-C(2)-C(3)-N(2)	−0.1(3)
C(1)-N(2)-C(3)-C(2)	0.1(3)
C(13)-N(2)-C(3)-C(2)	−178.1(3)
C(1)-N(1)-C(4)-C(9)	−94.3(4)
C(2)-N(1)-C(4)-C(9)	83.5(4)
C(1)-N(1)-C(4)-C(5)	88.0(4)
C(2)-N(1)-C(4)-C(5)	−94.2(4)
C(9)-C(4)-C(5)-C(6)	4.0(5)
N(1)-C(4)-C(5)-C(6)	−178.4(3)
C(9)-C(4)-C(5)-C(10)	−173.3(3)
N(1)-C(4)-C(5)-C(10)	4.3(5)
C(4)-C(5)-C(6)-C(7)	0.0(5)
C(10)-C(5)-C(6)-C(7)	177.4(3)
C(5)-C(6)-C(7)-C(8)	−3.5(5)
C(5)-C(6)-C(7)-C(11)	178.1(3)
C(6)-C(7)-C(8)-C(9)	3.2(5)
C(11)-C(7)-C(8)-C(9)	−178.4(3)
C(5)-C(4)-C(9)-C(8)	−4.3(5)
N(1)-C(4)-C(9)-C(8)	178.1(3)
C(5)-C(4)-C(9)-C(12)	172.0(3)
N(1)-C(4)-C(9)-C(12)	−5.6(4)
C(7)-C(8)-C(9)-C(4)	0.6(5)
C(7)-C(8)-C(9)-C(12)	−175.7(3)
C(1)-N(2)-C(13)-C(18)	−77.2(4)
C(3)-N(2)-C(13)-C(18)	100.7(3)
C(1)-N(2)-C(13)-C(14)	102.4(3)
C(3)-N(2)-C(13)-C(14)	−79.6(4)
C(18)-C(13)-C(14)-C(15)	1.4(5)
N(2)-C(13)-C(14)-C(15)	−178.2(3)
C(18)-C(13)-C(14)-C(19)	−179.2(3)
N(2)-C(13)-C(14)-C(19)	1.1(5)
C(13)-C(14)-C(15)-C(16)	−0.1(5)
C(19)-C(14)-C(15)-C(16)	−179.5(3)
C(14)-C(15)-C(16)-C(17)	0.0(5)

...

Table A54 continued...

C(14)-C(15)-C(16)-C(20)	−179.5(3)
C(15)-C(16)-C(17)-C(18)	−1.1(5)
C(20)-C(16)-C(17)-C(18)	178.4(3)
C(16)-C(17)-C(18)-C(13)	2.2(4)
C(16)-C(17)-C(18)-C(21)	−176.6(3)
C(14)-C(13)-C(18)-C(17)	−2.4(5)
N(2)-C(13)-C(18)-C(17)	177.2(3)
C(14)-C(13)-C(18)-C(21)	176.4(3)
N(2)-C(13)-C(18)-C(21)	−4.0(4)
N(1)-C(1)-C(22)-C(23X)	−97.9(6)
N(2)-C(1)-C(22)-C(23X)	83.3(6)
N(1)-C(1)-C(22)-C(23)	−42.6(5)
N(2)-C(1)-C(22)-C(23)	138.6(4)
N(1)-C(1)-C(22)-C(30)	104.5(4)
N(2)-C(1)-C(22)-C(30)	−74.3(4)
C(23X)-C(22)-C(23)-C(24)	−45.7(6)
C(1)-C(22)-C(23)-C(24)	−156.1(5)
C(30)-C(22)-C(23)-C(24)	59.6(6)
C(22)-C(23)-C(24)-C(29)	−116.9(9)
C(22)-C(23)-C(24)-C(25)	69.1(10)
C(29)-C(24)-C(25)-C(26)	2.7(13)
C(23)-C(24)-C(25)-C(26)	176.8(6)
C(24)-C(25)-C(26)-C(27)	−2.6(11)
C(25)-C(26)-C(27)-C(28)	2.1(15)
C(26)-C(27)-C(28)-C(29)	−1.7(17)
C(25)-C(24)-C(29)-C(28)	−2.2(13)
C(23)-C(24)-C(29)-C(28)	−176.3(7)
C(27)-C(28)-C(29)-C(24)	1.8(14)
C(23)-C(22)-C(23X)-C(24X)	58.6(10)
C(1)-C(22)-C(23X)-C(24X)	157.9(10)
C(30)-C(22)-C(23X)-C(24X)	−46.3(12)
C(22)-C(23X)-C(24X)-C(29X)	−41(2)
C(22)-C(23X)-C(24X)-C(25X)	137.4(14)
C(29X)-C(24X)-C(25X)-C(26X)	−1(3)
C(23X)-C(24X)-C(25X)-C(26X)	−179.7(17)
C(24X)-C(25X)-C(26X)-C(27X)	−2(3)
C(25X)-C(26X)-C(27X)-C(28X)	4(3)
C(26X)-C(27X)-C(28X)-C(29X)	−3(2)
C(25X)-C(24X)-C(29X)-C(28X)	2(3)
C(23X)-C(24X)-C(29X)-C(28X)	−179.2(13)
C(27X)-C(28X)-C(29X)-C(24X)	0(2)
C(23X)-C(22)-C(30)-C(35)	122.2(5)
C(23)-C(22)-C(30)-C(35)	66.4(5)
C(1)-C(22)-C(30)-C(35)	−79.7(4)
C(23X)-C(22)-C(30)-C(31)	−58.7(6)
C(23)-C(22)-C(30)-C(31)	−114.5(4)
C(1)-C(22)-C(30)-C(31)	99.4(4)
C(35)-C(30)-C(31)-C(32)	0.3(5)
C(22)-C(30)-C(31)-C(32)	−178.8(3)
C(30)-C(31)-C(32)-C(33)	0.1(5)
C(31)-C(32)-C(33)-C(34)	−0.4(6)
C(32)-C(33)-C(34)-C(35)	0.3(7)
C(33)-C(34)-C(35)-C(30)	0.1(6)
C(31)-C(30)-C(35)-C(34)	−0.4(5)
C(22)-C(30)-C(35)-C(34)	178.7(3)

...

Table A55: Hydrogen bonds (Å and °) for **4.37**

D−H...A	d(D−H)	d(H...A)	d(D...A)	∠(DHA)
O(1)−H(1O)...Br(1)#1	0.808(19)	2.53(2)	3.313(3)	165(5)
O(1)−H(2O)...Br(1)#2	0.816(19)	2.58(2)	3.372(3)	163(5)

Symmetry transformations used to generate equivalent atoms:
#1 $x+1, y, z$
#2 $-x+1, -y+1, -z+1$

Table A56: Anisotropic displacement parameters (Å^{2}x 10^3) for **4.37**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	28(1)	44(1)	34(1)	15(1)	3(1)	11(1)
N(1)	18(1)	22(1)	19(1)	8(1)	2(1)	7(1)
N(2)	16(1)	18(1)	23(1)	6(1)	0(1)	5(1)
C(1)	19(1)	18(1)	16(1)	3(1)	−1(1)	5(1)
C(2)	23(2)	23(2)	30(2)	14(1)	5(1)	12(1)
C(3)	22(2)	22(2)	25(2)	13(1)	3(1)	9(1)
C(4)	23(2)	26(2)	21(2)	11(1)	6(1)	13(1)
C(5)	28(2)	31(2)	26(2)	4(1)	4(1)	17(1)
C(6)	39(2)	46(2)	16(2)	6(2)	5(1)	26(2)
C(7)	43(2)	47(2)	30(2)	23(2)	17(2)	33(2)
C(8)	30(2)	39(2)	38(2)	26(2)	14(2)	17(2)
C(9)	22(2)	29(2)	32(2)	15(1)	5(1)	11(1)
C(10)	36(2)	40(2)	39(2)	−9(2)	2(2)	−1(2)
C(11)	69(3)	74(3)	39(2)	39(2)	27(2)	46(2)
C(12)	26(2)	39(2)	37(2)	18(2)	−1(2)	0(2)
C(13)	21(1)	20(1)	18(2)	7(1)	4(1)	7(1)
C(14)	24(2)	21(2)	23(2)	8(1)	0(1)	6(1)
C(15)	32(2)	21(2)	21(2)	4(1)	−3(1)	8(1)
C(16)	32(2)	25(2)	24(2)	12(1)	7(1)	15(1)
C(17)	22(2)	21(2)	25(2)	12(1)	2(1)	7(1)
C(18)	24(2)	17(1)	20(2)	10(1)	1(1)	7(1)
C(19)	26(2)	29(2)	34(2)	4(2)	−5(1)	3(1)
C(20)	35(2)	42(2)	28(2)	9(2)	10(2)	17(2)
C(21)	22(2)	20(2)	23(2)	8(1)	1(1)	3(1)
C(22)	38(2)	22(2)	33(2)	4(1)	−13(2)	14(1)
C(23)	28(2)	25(2)	22(2)	6(2)	2(2)	12(2)
C(24)	26(2)	21(3)	19(3)	5(2)	−3(2)	9(2)
C(25)	29(2)	34(3)	21(2)	6(2)	−2(2)	14(2)
C(26)	30(3)	36(3)	22(2)	1(2)	−5(2)	16(2)
C(27)	39(3)	33(3)	25(3)	−1(2)	−15(3)	20(3)

...

Table A56 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(28)	52(3)	27(3)	25(3)	7(2)	−14(3)	16(2)
C(29)	34(3)	29(3)	25(3)	8(2)	−7(2)	10(2)
C(23X)	21(3)	20(3)	17(3)	8(3)	−3(3)	4(3)
C(24X)	31(3)	25(3)	19(3)	8(3)	−7(3)	7(3)
C(25X)	36(3)	26(3)	18(3)	3(3)	−8(3)	14(3)
C(26X)	41(4)	32(4)	27(4)	0(3)	−16(4)	18(4)
C(27X)	49(4)	25(4)	24(5)	4(3)	−21(4)	15(3)
C(28X)	49(4)	25(4)	25(4)	11(3)	−14(3)	8(3)
C(29X)	38(4)	27(4)	23(4)	13(3)	−8(3)	8(3)
C(30)	25(2)	20(1)	23(2)	11(1)	−3(1)	6(1)
C(31)	45(2)	29(2)	27(2)	14(1)	4(2)	15(2)
C(32)	85(3)	35(2)	27(2)	2(2)	−12(2)	33(2)
C(33)	73(3)	22(2)	78(3)	13(2)	−50(2)	−1(2)
C(34)	39(2)	35(2)	118(4)	44(2)	−14(2)	−4(2)
C(35)	33(2)	37(2)	70(3)	34(2)	11(2)	13(2)
C(1S)	50(2)	38(2)	39(2)	5(2)	−6(2)	14(2)
Cl(1S)	54(1)	92(2)	40(1)	22(1)	−4(1)	5(1)
Cl(2S)	83(1)	30(1)	76(2)	1(1)	−37(1)	16(1)
Cl(1T)	54(1)	92(2)	40(1)	22(1)	−4(1)	5(1)
Cl(2T)	83(1)	30(1)	76(2)	1(1)	−37(1)	16(1)
C(2S)	80(3)	42(2)	46(3)	12(2)	−8(2)	9(2)
Cl(3S)	58(1)	67(1)	55(1)	20(1)	7(1)	16(1)
Cl(4S)	87(1)	45(1)	48(1)	15(1)	9(1)	15(1)
O(1)	50(2)	26(1)	40(2)	6(1)	8(1)	−2(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2\left[h^2a*^2U^{11}+...+2hka*b*U^{12}\right]$

A.2.10 *Structural Data for Imidazolium Salt* **4.30**

Suitable crystals for X-ray analysis were obtained by slow diffusion of Et_2O into a $CHCl_3$ solution at room temperature in a dry box.

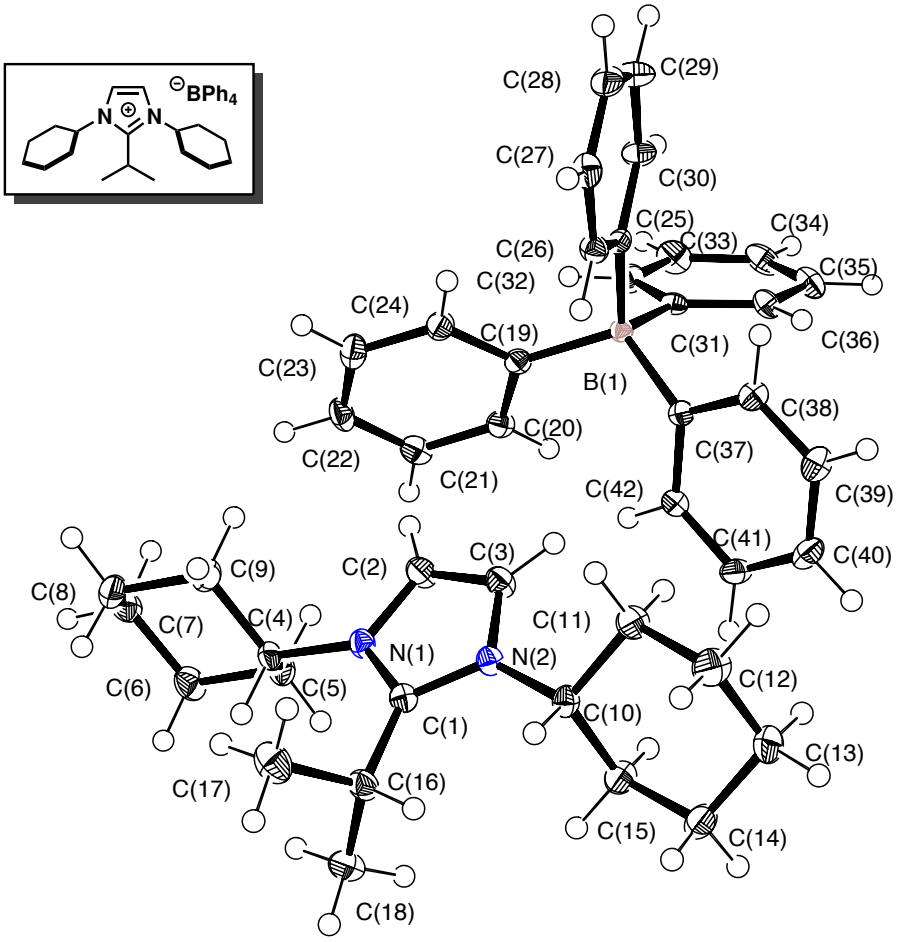

Figure A10: ORTEP drawing of imidazolium salt **4.30** shown at 50% probability

Table A57: Crystal data and structure refinement for **4.30**

Empirical formula	$C_{43}H_{53}BCl_2N_2$
Formula weight	679.58
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 12.8426(8) Å $\alpha = 90°$.
	b = 14.7152(9) Å $\beta = 90°$.
	c = 19.9415(13) Å $\gamma = 90°$.
Volume	3768.6(4) $Å^3$
Z	4
Density (calculated)	1.198 Mg/m^3
Absorption coefficient	0.205 mm^{-1}
F(000)	1456
Crystal size	0.35 x 0.15 x 0.10 mm^3
Theta range for data collection	1.72 to 28.62°.
Index ranges	−17<=h<=17, −19<=k<=19, −26<=l<=26
Reflections collected	73941
Independent reflections	9632 [R(int) = 0.0452]
Completeness to theta = 28.62°	99.7%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9798 and 0.9318
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9632 / 0 / 433
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0363, wR2 = 0.0899
R indices (all data)	R1 = 0.0422, wR2 = 0.0941
Absolute structure parameter	0.00(4)
Extinction coefficient	na
Largest diff. peak and hole	0.656 and −0.523 e.$Å^{-3}$

Table A58: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **4.30**

	x	y	z	U(eq)
N(1)	2437(1)	8450(1)	8609(1)	16(1)
N(2)	2153(1)	7643(1)	7720(1)	16(1)
B(1)	6677(1)	8011(1)	7151(1)	13(1)
C(1)	1694(1)	8017(1)	8262(1)	16(1)
C(2)	3378(1)	8354(1)	8282(1)	21(1)
C(3)	3202(1)	7852(1)	7730(1)	20(1)
C(4)	2317(1)	8978(1)	9236(1)	17(1)
C(5)	2638(1)	9964(1)	9125(1)	21(1)
C(6)	2482(1)	10501(1)	9770(1)	24(1)
C(7)	3081(1)	10074(1)	10350(1)	29(1)
C(8)	2763(2)	9082(1)	10453(1)	30(1)
C(9)	2924(1)	8535(1)	9807(1)	25(1)
C(10)	1624(1)	7140(1)	7172(1)	17(1)
C(11)	2358(1)	6460(1)	6845(1)	23(1)
C(12)	1773(1)	5937(1)	6302(1)	29(1)
C(13)	1330(1)	6581(1)	5775(1)	28(1)
C(14)	620(1)	7282(1)	6099(1)	27(1)
C(15)	1173(1)	7801(1)	6660(1)	22(1)
C(16)	562(1)	7924(1)	8436(1)	20(1)
C(17)	394(1)	7405(1)	9094(1)	29(1)
C(18)	−21(1)	8832(1)	8421(1)	29(1)
C(19)	6304(1)	8519(1)	7848(1)	15(1)
C(20)	5970(1)	9437(1)	7854(1)	18(1)
C(21)	5660(1)	9883(1)	8435(1)	21(1)
C(22)	5686(1)	9437(1)	9047(1)	22(1)
C(23)	6022(1)	8541(1)	9065(1)	23(1)
C(24)	6319(1)	8100(1)	8479(1)	19(1)
C(25)	7207(1)	7032(1)	7333(1)	14(1)
C(26)	6602(1)	6288(1)	7549(1)	17(1)
C(27)	7031(1)	5460(1)	7736(1)	20(1)
C(28)	8096(1)	5329(1)	7706(1)	22(1)
C(29)	8718(1)	6037(1)	7487(1)	25(1)
C(30)	8279(1)	6874(1)	7308(1)	19(1)
C(31)	7524(1)	8651(1)	6750(1)	14(1)
C(32)	8132(1)	9317(1)	7064(1)	20(1)
C(33)	8852(1)	9849(1)	6720(1)	26(1)
C(34)	8995(1)	9734(1)	6035(1)	25(1)
C(35)	8414(1)	9077(1)	5705(1)	22(1)
C(36)	7704(1)	8550(1)	6059(1)	18(1)
C(37)	5702(1)	7864(1)	6626(1)	14(1)
C(38)	5677(1)	7119(1)	6187(1)	18(1)
C(39)	4959(1)	7043(1)	5667(1)	21(1)
C(40)	4215(1)	7713(1)	5570(1)	22(1)
C(41)	4198(1)	8449(1)	6004(1)	22(1)
C(42)	4926(1)	8518(1)	6519(1)	18(1)
C(43)	6263(1)	10440(1)	5783(1)	30(1)
Cl(1)	5307(1)	11152(1)	6129(1)	54(1)
Cl(2)	6743(1)	10870(1)	5019(1)	45(1)

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

Table A59: Bond lengths (Å) and angles (°) for **4.30**

N(1)-C(1)	1.3404(18)
N(1)-C(2)	1.3807(19)
N(1)-C(4)	1.4801(17)
N(2)-C(1)	1.3492(18)
N(2)-C(3)	1.3822(19)
N(2)-C(10)	1.4836(18)
B(1)-C(25)	1.634(2)
B(1)-C(31)	1.646(2)
B(1)-C(37)	1.646(2)
B(1)-C(19)	1.648(2)
C(1)-C(16)	1.501(2)
C(2)-C(3)	1.345(2)
C(2)-H(2A)	0.95
C(3)-H(3A)	0.95
C(4)-C(9)	1.525(2)
C(4)-C(5)	1.526(2)
C(4)-H(4A)	1
C(5)-C(6)	1.523(2)
C(5)-H(5A)	0.99
C(5)-H(5B)	0.99
C(6)-C(7)	1.523(2)
C(6)-H(6A)	0.99
C(6)-H(6B)	0.99
C(7)-C(8)	1.529(3)
C(7)-H(7A)	0.99
C(7)-H(7B)	0.99
C(8)-C(9)	1.532(2)
C(8)-H(8A)	0.99
C(8)-H(8B)	0.99
C(9)-H(9A)	0.99
C(9)-H(9B)	0.99

Table A59 continued...

C(10)-C(11)	1.522(2)
C(10)-C(15)	1.524(2)
C(10)-H(10A)	1
C(11)-C(12)	1.526(2)
C(11)-H(11A)	0.99
C(11)-H(11B)	0.99
C(12)-C(13)	1.524(2)
C(12)-H(12A)	0.99
C(12)-H(12B)	0.99
C(13)-C(14)	1.520(2)
C(13)-H(13A)	0.99
C(13)-H(13B)	0.99
C(14)-C(15)	1.530(2)
C(14)-H(14A)	0.99
C(14)-H(14B)	0.99
C(15)-H(15A)	0.99
C(15)-H(15B)	0.99
C(16)-C(18)	1.532(2)
C(16)-C(17)	1.533(2)
C(16)-H(16A)	1
C(17)-H(17A)	0.98
C(17)-H(17B)	0.98
C(17)-H(17C)	0.98
C(18)-H(18A)	0.98
C(18)-H(18B)	0.98
C(18)-H(18C)	0.98
C(19)-C(24)	1.402(2)
C(19)-C(20)	1.417(2)
C(20)-C(21)	1.390(2)
C(20)-H(20A)	0.95
C(21)-C(22)	1.386(2)
C(21)-H(21A)	0.95
C(22)-C(23)	1.387(2)
C(22)-H(22A)	0.95
C(23)-C(24)	1.391(2)
C(23)-H(23A)	0.95
C(24)-H(24A)	0.95
C(25)-C(30)	1.398(2)
C(25)-C(26)	1.4091(19)
C(26)-C(27)	1.389(2)
C(26)-H(26A)	0.95
C(27)-C(28)	1.383(2)
C(27)-H(27A)	0.95
C(28)-C(29)	1.384(2)
C(28)-H(28A)	0.95
C(29)-C(30)	1.400(2)

...

Table A59 continued...

C(29)-H(29A)	0.95
C(30)-H(30A)	0.95
C(31)-C(32)	1.4009(19)
C(31)-C(36)	1.4047(19)
C(32)-C(33)	1.393(2)
C(32)-H(32A)	0.95
C(33)-C(34)	1.389(2)
C(33)-H(33A)	0.95
C(34)-C(35)	1.388(2)
C(34)-H(34A)	0.95
C(35)-C(36)	1.389(2)
C(35)-H(35A)	0.95
C(36)-H(36A)	0.95
C(37)-C(42)	1.4014(19)
C(37)-C(38)	1.405(2)
C(38)-C(39)	1.391(2)
C(38)-H(38A)	0.95
C(39)-C(40)	1.386(2)
C(39)-H(39A)	0.95
C(40)-C(41)	1.387(2)
C(40)-H(40A)	0.95
C(41)-C(42)	1.393(2)
C(41)-H(41A)	0.95
C(42)-H(42A)	0.95
C(43)-Cl(1)	1.7555(17)
C(43)-Cl(2)	1.7606(18)
C(43)-H(43A)	0.99
C(43)-H(43B)	0.99
C(1)-N(1)-C(2)	109.33(12)
C(1)-N(1)-C(4)	127.70(12)
C(2)-N(1)-C(4)	122.96(12)
C(1)-N(2)-C(3)	108.87(12)
C(1)-N(2)-C(10)	126.39(12)
C(3)-N(2)-C(10)	124.62(12)
C(25)-B(1)-C(31)	109.71(11)
C(25)-B(1)-C(37)	109.99(11)
C(31)-B(1)-C(37)	105.54(10)
C(25)-B(1)-C(19)	109.54(11)
C(31)-B(1)-C(19)	110.05(11)
C(37)-B(1)-C(19)	111.94(11)
N(1)-C(1)-N(2)	107.25(12)
N(1)-C(1)-C(16)	127.87(13)
N(2)-C(1)-C(16)	124.86(13)
C(3)-C(2)-N(1)	107.19(13)
C(3)-C(2)-H(2A)	126.4
N(1)-C(2)-H(2A)	126.4

...

Table A59 continued...

C(2)-C(3)-N(2)	107.36(13)
C(2)-C(3)-H(3A)	126.3
N(2)-C(3)-H(3A)	126.3
N(1)-C(4)-C(9)	110.68(12)
N(1)-C(4)-C(5)	110.41(11)
C(9)-C(4)-C(5)	112.07(13)
N(1)-C(4)-H(4A)	107.8
C(9)-C(4)-H(4A)	107.8
C(5)-C(4)-H(4A)	107.8
C(6)-C(5)-C(4)	109.61(12)
C(6)-C(5)-H(5A)	109.7
C(4)-C(5)-H(5A)	109.7
C(6)-C(5)-H(5B)	109.7
C(4)-C(5)-H(5B)	109.7
H(5A)-C(5)-H(5B)	108.2
C(5)-C(6)-C(7)	111.07(13)
C(5)-C(6)-H(6A)	109.4
C(7)-C(6)-H(6A)	109.4
C(5)-C(6)-H(6B)	109.4
C(7)-C(6)-H(6B)	109.4
H(6A)-C(6)-H(6B)	108
C(6)-C(7)-C(8)	111.16(14)
C(6)-C(7)-H(7A)	109.4
C(8)-C(7)-H(7A)	109.4
C(6)-C(7)-H(7B)	109.4
C(8)-C(7)-H(7B)	109.4
H(7A)-C(7)-H(7B)	108
C(7)-C(8)-C(9)	110.63(14)
C(7)-C(8)-H(8A)	109.5
C(9)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
C(9)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	108.1
C(4)-C(9)-C(8)	109.53(12)
C(4)-C(9)-H(9A)	109.8
C(8)-C(9)-H(9A)	109.8
C(4)-C(9)-H(9B)	109.8
C(8)-C(9)-H(9B)	109.8
H(9A)-C(9)-H(9B)	108.2
N(2)-C(10)-C(11)	111.12(12)
N(2)-C(10)-C(15)	110.45(11)
C(11)-C(10)-C(15)	111.59(12)
N(2)-C(10)-H(10A)	107.8
C(11)-C(10)-H(10A)	107.8
C(15)-C(10)-H(10A)	107.8
C(10)-C(11)-C(12)	109.37(13)
...	

Table A59 continued...

C(10)-C(11)-H(11A)	109.8
C(12)-C(11)-H(11A)	109.8
C(10)-C(11)-H(11B)	109.8
C(12)-C(11)-H(11B)	109.8
H(11A)-C(11)-H(11B)	108.2
C(13)-C(12)-C(11)	111.04(14)
C(13)-C(12)-H(12A)	109.4
C(11)-C(12)-H(12A)	109.4
C(13)-C(12)-H(12B)	109.4
C(11)-C(12)-H(12B)	109.4
H(12A)-C(12)-H(12B)	108
C(14)-C(13)-C(12)	110.68(14)
C(14)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13A)	109.5
C(14)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	108.1
C(13)-C(14)-C(15)	111.84(13)
C(13)-C(14)-H(14A)	109.2
C(15)-C(14)-H(14A)	109.2
C(13)-C(14)-H(14B)	109.2
C(15)-C(14)-H(14B)	109.2
H(14A)-C(14)-H(14B)	107.9
C(10)-C(15)-C(14)	110.32(12)
C(10)-C(15)-H(15A)	109.6
C(14)-C(15)-H(15A)	109.6
C(10)-C(15)-H(15B)	109.6
C(14)-C(15)-H(15B)	109.6
H(15A)-C(15)-H(15B)	108.1
C(1)-C(16)-C(18)	112.92(13)
C(1)-C(16)-C(17)	112.26(13)
C(18)-C(16)-C(17)	112.50(13)
C(1)-C(16)-H(16A)	106.2
C(18)-C(16)-H(16A)	106.2
C(17)-C(16)-H(16A)	106.2
C(16)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(16)-C(18)-H(18A)	109.5
C(16)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(16)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
...	

Table A59 continued...

H(18B)-C(18)-H(18C)	109.5
C(24)-C(19)-C(20)	114.57(13)
C(24)-C(19)-B(1)	123.51(12)
C(20)-C(19)-B(1)	121.89(12)
C(21)-C(20)-C(19)	123.04(14)
C(21)-C(20)-H(20A)	118.5
C(19)-C(20)-H(20A)	118.5
C(22)-C(21)-C(20)	120.13(14)
C(22)-C(21)-H(21A)	119.9
C(20)-C(21)-H(21A)	119.9
C(21)-C(22)-C(23)	118.76(14)
C(21)-C(22)-H(22A)	120.6
C(23)-C(22)-H(22A)	120.6
C(22)-C(23)-C(24)	120.51(14)
C(22)-C(23)-H(23A)	119.7
C(24)-C(23)-H(23A)	119.7
C(23)-C(24)-C(19)	122.99(14)
C(23)-C(24)-H(24A)	118.5
C(19)-C(24)-H(24A)	118.5
C(30)-C(25)-C(26)	115.14(13)
C(30)-C(25)-B(1)	123.28(12)
C(26)-C(25)-B(1)	121.56(12)
C(27)-C(26)-C(25)	123.06(14)
C(27)-C(26)-H(26A)	118.5
C(25)-C(26)-H(26A)	118.5
C(28)-C(27)-C(26)	120.18(14)
C(28)-C(27)-H(27A)	119.9
C(26)-C(27)-H(27A)	119.9
C(27)-C(28)-C(29)	118.65(14)
C(27)-C(28)-H(28A)	120.7
C(29)-C(28)-H(28A)	120.7
C(28)-C(29)-C(30)	120.71(14)
C(28)-C(29)-H(29A)	119.6
C(30)-C(29)-H(29A)	119.6
C(25)-C(30)-C(29)	122.25(14)
C(25)-C(30)-H(30A)	118.9
C(29)-C(30)-H(30A)	118.9
C(32)-C(31)-C(36)	114.85(13)
C(32)-C(31)-B(1)	123.40(12)
C(36)-C(31)-B(1)	121.73(12)
C(33)-C(32)-C(31)	122.95(14)
C(33)-C(32)-H(32A)	118.5
C(31)-C(32)-H(32A)	118.5
C(34)-C(33)-C(32)	120.20(14)
C(34)-C(33)-H(33A)	119.9
C(32)-C(33)-H(33A)	119.9

...

Table A59 continued...

C(35)-C(34)-C(33)	118.74(14)
C(35)-C(34)-H(34A)	120.6
C(33)-C(34)-H(34A)	120.6
C(34)-C(35)-C(36)	119.99(14)
C(34)-C(35)-H(35A)	120
C(36)-C(35)-H(35A)	120
C(35)-C(36)-C(31)	123.26(14)
C(35)-C(36)-H(36A)	118.4
C(31)-C(36)-H(36A)	118.4
C(42)-C(37)-C(38)	115.05(13)
C(42)-C(37)-B(1)	123.25(12)
C(38)-C(37)-B(1)	121.15(12)
C(39)-C(38)-C(37)	122.93(14)
C(39)-C(38)-H(38A)	118.5
C(37)-C(38)-H(38A)	118.5
C(40)-C(39)-C(38)	120.22(14)
C(40)-C(39)-H(39A)	119.9
C(38)-C(39)-H(39A)	119.9
C(39)-C(40)-C(41)	118.64(14)
C(39)-C(40)-H(40A)	120.7
C(41)-C(40)-H(40A)	120.7
C(40)-C(41)-C(42)	120.42(14)
C(40)-C(41)-H(41A)	119.8
C(42)-C(41)-H(41A)	119.8
C(41)-C(42)-C(37)	122.71(14)
C(41)-C(42)-H(42A)	118.6
C(37)-C(42)-H(42A)	118.6
Cl(1)-C(43)-Cl(2)	111.73(10)
Cl(1)-C(43)-H(43A)	109.3
Cl(2)-C(43)-H(43A)	109.3
Cl(1)-C(43)-H(43B)	109.3
Cl(2)-C(43)-H(43B)	109.3
H(43A)-C(43)-H(43B)	107.9

Table A60: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **4.30**

	x	y	z	U(eq)
H(2A)	4029	8597	8421	26
H(3A)	3706	7674	7407	24
H(4A)	1563	8972	9361	20
H(5A)	3379	9991	8989	25
H(5B)	2214	10234	8762	25
H(6A)	1731	10519	9882	29
H(6B)	2723	11134	9703	29
H(7A)	2943	10421	10765	35

...

Table A60 continued...

	x	y	z	U(eq)
H(7B)	3837	10106	10255	35
H(8A)	2022	9053	10587	36
H(8B)	3186	8813	10818	36
H(9A)	3674	8517	9693	29
H(9B)	2679	7904	9873	29
H(10A)	1033	6793	7374	20
H(11A)	2626	6032	7186	27
H(11B)	2957	6784	6644	27
H(12A)	2252	5501	6083	35
H(12B)	1199	5587	6509	35
H(13A)	1907	6893	5541	33
H(13B)	932	6228	5439	33
H(14A)	−1	6973	6285	32
H(14B)	381	7717	5753	32
H(15A)	1739	8176	6468	26
H(15B)	672	8213	6884	26
H(16A)	245	7542	8075	24
H(17A)	778	6830	9079	44
H(17B)	−350	7280	9153	44
H(17C)	646	7773	9470	44
H(18A)	110	9138	7993	43
H(18B)	223	9218	8790	43
H(18C)	−770	8723	8471	43
H(20A)	5957	9762	7443	21
H(21A)	5429	10496	8413	25
H(22A)	5479	9738	9446	26
H(23A)	6048	8227	9481	28
H(24A)	6544	7485	8507	23
H(26A)	5867	6357	7567	21
H(27A)	6591	4982	7885	24
H(28A)	8395	4763	7832	26
H(29A)	9450	5955	7458	30
H(30A)	8726	7351	7165	23
H(32A)	8048	9410	7532	24
H(33A)	9248	10292	6955	31
H(34A)	9482	10098	5797	30
H(35A)	8501	8987	5236	27
H(36A)	7323	8100	5822	21
H(38A)	6172	6646	6246	21
H(39A)	4979	6530	5378	25
H(40A)	3727	7668	5213	26
H(41A)	3686	8909	5949	26
H(42A)	4895	9028	6810	22
H(43A)	5963	9829	5707	36
H(43B)	6846	10377	6105	36

Table A61: Torsion angles (°) for **4.30**

C(2)-N(1)-C(1)-N(2)	0.31(16)
C(4)-N(1)-C(1)-N(2)	178.86(13)
C(2)-N(1)-C(1)-C(16)	178.61(14)
C(4)-N(1)-C(1)-C(16)	−2.8(2)
C(3)-N(2)-C(1)-N(1)	−0.25(16)
C(10)-N(2)-C(1)-N(1)	−176.42(12)
C(3)-N(2)-C(1)-C(16)	−178.62(14)
C(10)-N(2)-C(1)-C(16)	5.2(2)
C(1)-N(1)-C(2)-C(3)	−0.26(17)
C(4)-N(1)-C(2)-C(3)	−178.89(13)
N(1)-C(2)-C(3)-N(2)	0.10(17)
C(1)-N(2)-C(3)-C(2)	0.09(17)
C(10)-N(2)-C(3)-C(2)	176.35(13)
C(1)-N(1)-C(4)-C(9)	116.53(16)
C(2)-N(1)-C(4)-C(9)	−65.10(18)
C(1)-N(1)-C(4)-C(5)	−118.78(15)
C(2)-N(1)-C(4)-C(5)	59.59(18)
N(1)-C(4)-C(5)-C(6)	178.50(12)
C(9)-C(4)-C(5)-C(6)	−57.62(17)
C(4)-C(5)-C(6)-C(7)	56.40(18)
C(5)-C(6)-C(7)-C(8)	−56.83(18)
C(6)-C(7)-C(8)-C(9)	56.67(18)
N(1)-C(4)-C(9)-C(8)	−178.61(13)
C(5)-C(4)-C(9)-C(8)	57.66(17)
C(7)-C(8)-C(9)-C(4)	−56.34(18)
C(1)-N(2)-C(10)-C(11)	−152.99(13)
C(3)-N(2)-C(10)-C(11)	31.41(19)
C(1)-N(2)-C(10)-C(15)	82.61(17)
C(3)-N(2)-C(10)-C(15)	−92.98(16)
N(2)-C(10)-C(11)-C(12)	178.07(13)
C(15)-C(10)-C(11)-C(12)	−58.18(17)
C(10)-C(11)-C(12)-C(13)	58.22(18)
C(11)-C(12)-C(13)-C(14)	−57.01(19)
C(12)-C(13)-C(14)-C(15)	55.03(19)
N(2)-C(10)-C(15)-C(14)	−179.54(12)
C(11)-C(10)-C(15)-C(14)	56.33(17)
C(13)-C(14)-C(15)-C(10)	−54.48(18)
N(1)-C(1)-C(16)-C(18)	66.0(2)
N(2)-C(1)-C(16)-C(18)	−115.99(16)
N(1)-C(1)-C(16)-C(17)	−62.5(2)
N(2)-C(1)-C(16)-C(17)	115.55(16)
C(25)-B(1)-C(19)-C(24)	−8.02(18)
C(31)-B(1)-C(19)-C(24)	−128.72(13)
C(37)-B(1)-C(19)-C(24)	114.26(14)
...	

Table A61 continued...

C(25)-B(1)-C(19)-C(20)	169.87(12)
C(31)-B(1)-C(19)-C(20)	49.18(17)
C(37)-B(1)-C(19)-C(20)	−67.85(16)
C(24)-C(19)-C(20)-C(21)	−1.3(2)
B(1)-C(19)-C(20)-C(21)	−179.41(13)
C(19)-C(20)-C(21)-C(22)	1.2(2)
C(20)-C(21)-C(22)-C(23)	−0.3(2)
C(21)-C(22)-C(23)-C(24)	−0.4(2)
C(22)-C(23)-C(24)-C(19)	0.2(2)
C(20)-C(19)-C(24)-C(23)	0.6(2)
B(1)-C(19)-C(24)-C(23)	178.68(13)
C(31)-B(1)-C(25)-C(30)	15.53(18)
C(37)-B(1)-C(25)-C(30)	131.20(14)
C(19)-B(1)-C(25)-C(30)	−105.37(15)
C(31)-B(1)-C(25)-C(26)	−166.50(12)
C(37)-B(1)-C(25)-C(26)	−50.83(16)
C(19)-B(1)-C(25)-C(26)	72.61(16)
C(30)-C(25)-C(26)-C(27)	1.1(2)
B(1)-C(25)-C(26)-C(27)	−177.03(13)
C(25)-C(26)-C(27)-C(28)	−1.1(2)
C(26)-C(27)-C(28)-C(29)	0.1(2)
C(27)-C(28)-C(29)-C(30)	0.8(2)
C(26)-C(25)-C(30)-C(29)	−0.2(2)
B(1)-C(25)-C(30)-C(29)	177.91(14)
C(28)-C(29)-C(30)-C(25)	−0.8(2)
C(25)-B(1)-C(31)-C(32)	−97.35(15)
C(37)-B(1)-C(31)-C(32)	144.19(13)
C(19)-B(1)-C(31)-C(32)	23.24(17)
C(25)-B(1)-C(31)-C(36)	81.28(15)
C(37)-B(1)-C(31)-C(36)	−37.18(16)
C(19)-B(1)-C(31)-C(36)	−158.13(12)
C(36)-C(31)-C(32)-C(33)	0.7(2)
B(1)-C(31)-C(32)-C(33)	179.43(14)
C(31)-C(32)-C(33)-C(34)	0.1(2)
C(32)-C(33)-C(34)-C(35)	−0.5(2)
C(33)-C(34)-C(35)-C(36)	0.0(2)
C(34)-C(35)-C(36)-C(31)	0.8(2)
C(32)-C(31)-C(36)-C(35)	−1.2(2)
B(1)-C(31)-C(36)-C(35)	−179.91(13)
C(25)-B(1)-C(37)-C(42)	161.97(12)
C(31)-B(1)-C(37)-C(42)	−79.76(15)
C(19)-B(1)-C(37)-C(42)	39.95(17)
C(25)-B(1)-C(37)-C(38)	−26.92(17)
C(31)-B(1)-C(37)-C(38)	91.35(14)
C(19)-B(1)-C(37)-C(38)	−148.94(13)
C(42)-C(37)-C(38)-C(39)	2.1(2)
...	

Table A61 continued...

B(1)-C(37)-C(38)-C(39)	−169.74(13)
C(37)-C(38)-C(39)-C(40)	−1.0(2)
C(38)-C(39)-C(40)-C(41)	−0.7(2)
C(39)-C(40)-C(41)-C(42)	1.0(2)
C(40)-C(41)-C(42)-C(37)	0.2(2)
C(38)-C(37)-C(42)-C(41)	−1.7(2)
B(1)-C(37)-C(42)-C(41)	169.94(13)

Table A62: Anisotropic displacement parameters (Å^{2}x 10^3) for **4.30**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	18(1)	17(1)	15(1)	−3(1)	1(1)	−1(1)
N(2)	17(1)	15(1)	16(1)	−1(1)	1(1)	−2(1)
B(1)	14(1)	12(1)	13(1)	0(1)	−1(1)	1(1)
C(1)	18(1)	12(1)	17(1)	0(1)	1(1)	0(1)
C(2)	17(1)	24(1)	23(1)	−7(1)	2(1)	−1(1)
C(3)	17(1)	21(1)	21(1)	−4(1)	3(1)	−2(1)
C(4)	18(1)	18(1)	14(1)	−4(1)	2(1)	1(1)
C(5)	27(1)	18(1)	18(1)	−4(1)	2(1)	2(1)
C(6)	27(1)	21(1)	25(1)	−8(1)	2(1)	2(1)
C(7)	24(1)	40(1)	24(1)	−17(1)	−3(1)	6(1)
C(8)	35(1)	40(1)	16(1)	−2(1)	−2(1)	15(1)
C(9)	31(1)	24(1)	18(1)	0(1)	−2(1)	8(1)
C(10)	19(1)	16(1)	15(1)	−2(1)	0(1)	−3(1)
C(11)	27(1)	18(1)	24(1)	−6(1)	−3(1)	4(1)
C(12)	33(1)	23(1)	32(1)	−12(1)	−8(1)	4(1)
C(13)	28(1)	35(1)	20(1)	−9(1)	−2(1)	1(1)
C(14)	30(1)	30(1)	20(1)	−3(1)	−8(1)	6(1)
C(15)	26(1)	18(1)	21(1)	−1(1)	−3(1)	2(1)
C(16)	15(1)	26(1)	20(1)	−2(1)	3(1)	−3(1)
C(17)	30(1)	27(1)	32(1)	4(1)	10(1)	−3(1)
C(18)	21(1)	37(1)	29(1)	3(1)	3(1)	7(1)
C(19)	13(1)	16(1)	17(1)	−2(1)	−1(1)	−2(1)
C(20)	17(1)	17(1)	19(1)	−1(1)	−1(1)	0(1)
C(21)	17(1)	18(1)	27(1)	−6(1)	0(1)	−1(1)
C(22)	19(1)	28(1)	18(1)	−10(1)	3(1)	−4(1)
C(23)	25(1)	28(1)	16(1)	−2(1)	0(1)	−4(1)
C(24)	20(1)	20(1)	17(1)	0(1)	−1(1)	0(1)
C(25)	16(1)	14(1)	12(1)	0(1)	−2(1)	1(1)
C(26)	17(1)	17(1)	18(1)	1(1)	2(1)	0(1)
C(27)	27(1)	15(1)	18(1)	2(1)	3(1)	−2(1)
C(28)	29(1)	16(1)	22(1)	3(1)	−2(1)	6(1)
C(29)	17(1)	22(1)	37(1)	4(1)	−4(1)	4(1)
C(30)	16(1)	17(1)	25(1)	2(1)	−2(1)	−1(1)
C(31)	13(1)	11(1)	19(1)	1(1)	0(1)	2(1)
C(32)	17(1)	22(1)	20(1)	−2(1)	−1(1)	−2(1)
C(33)	19(1)	24(1)	33(1)	−5(1)	0(1)	−8(1)
C(34)	19(1)	20(1)	34(1)	1(1)	11(1)	−2(1)
C(35)	23(1)	20(1)	24(1)	0(1)	9(1)	2(1)
C(36)	19(1)	14(1)	20(1)	−2(1)	4(1)	0(1)
C(37)	13(1)	14(1)	14(1)	3(1)	1(1)	−1(1)
C(38)	20(1)	14(1)	19(1)	1(1)	−2(1)	−1(1)
C(39)	26(1)	18(1)	20(1)	0(1)	−3(1)	−5(1)
C(40)	19(1)	28(1)	19(1)	4(1)	−5(1)	−5(1)

...

Table A62 continued...

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(41)	17(1)	27(1)	22(1)	4(1)	−1(1)	5(1)
C(42)	16(1)	21(1)	17(1)	0(1)	2(1)	3(1)
C(43)	32(1)	27(1)	32(1)	4(1)	11(1)	7(1)
Cl(1)	50(1)	50(1)	62(1)	−6(1)	23(1)	20(1)
Cl(2)	72(1)	31(1)	31(1)	4(1)	16(1)	6(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2 \left[h^2 a*^2 U^{11} + ... + 2hka*b*U^{12}\right]$