Abstract

SMITH, EMILIE DESPAGNET: Part I. Study of 1-Acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone as Synthetic Intermediates. Part II. Synthesis of Enantiopure Nicotine Derivatives from Nicotine. (Under the direction of Dr. Daniel L. Comins.)

Various methodologies were investigated to build synthetic intermediates from 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridones and to synthesize nicotine derivatives from nicotine.

In the first part of this document, the synthesis and reactivity of 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone were investigated. This dihydropyridone was synthesized from the addition of dimethylphenylsilyl Grignard to the 1-acyl-4-methoxypyridinium salt with a 90% yield and 98% de. A variety of reactions including 1,4-additions and the synthesis of the corresponding dihydropyridine was accomplished.

In the second part, various methodologies were discovered to synthesize enantiopure nicotine derivatives from nicotine. Regioselective substitution reactions for functionalization at C-4, C-5 and C-6 of the pyridine ring were achieved. The synthesis of novel C-4 substituted and unsubstituted dihydronicotines was also developed. The von Braun reaction was applied to give enantiopure pyrrolidine ring-opened products.

Part I. Study of 1-Acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone as Synthetic Intermediates.
Part II. Synthesis of Enantiopure Nicotine Derivatives from Nicotine.

By

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Dedication

This manuscript is dedicated to my husband, Jody and to my parents, Bernard and Janine, whose love, support and encouragement have helped me throughout this endeavor.

Ce manuscript est dedicacé à mon mari, Jody et à mes parents, Bernard et Janine: leur amour, leur soutien et leurs encouragements m'ont aidée tout au long de cet ouvrage.

Biography

The author, Emilie Despagnet Smith, was born in Mont-de-Marsan, France to Janine and Bernard Despagnet. She graduated from Charles Despiau High School in 1995 and continued her education in a scientific college at Paul Sabatier University in Toulouse, France, where she specialized in Chemistry. During her junior year, she went to the University of North Carolina at Chapel Hill for an exchange program where she met her future husband. She returned to Toulouse to complete her bachelor degree in the spring of 1999. She then came back to North Carolina to commence her graduate studies at North Carolina State University, where she joined the Comins group. The author completed her Ph.D. in Organic Chemistry in the summer of 2004.

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I would like to express my gratitude to my advisor, Dr. Daniel Comins, for his guidance and support. I really appreciate the wonderful opportunities you have given me! I would also like to thank my committee members for helping me review this manuscript and North Carolina State University for the education they have provided. I also would like to thank Dr. Roe for the biological testing of several samples on mosquitoes, as well as Targacept for the testing for CNS activity. This document would not have been possible without the continuing love and support of my husband - he always inspires me to achieve my fullest potential. My family and friends back home have helped me so much in getting through hard times. I thank them all from the bottom of my heart, especially my parents for always supporting my choices, my sister Sophie and my brother-in-law Philippe for always being there for me and my two best friends Sophie and Bérengère for not letting the distance destroy our friendship - we've come a long way since kindergarten and I treasure our friendship. My new family here has also helped me: I would like to thank them for their kindness and generosity and for making me feel so welcome in their home. I also want to thank the past and present members of the Comins group for creating a nice atmosphere in the lab. Thanks especially to those who gave me their friendship and emotional support. A special thank you goes to Debbie Sloan, for her patience, kindness, and ability to listen and give great advice. I would like to thank PLU for helping me to travel to conferences to present my work and also for providing some entertainment within the chemistry department.

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List of Symbols, Abbreviations and Terms

Abbreviation or Term	Explanation
$[\alpha]_D$	optical rotation
δ	chemical sift
Å	Angstroms
A $^{(1,3)}$	allylic strain
AChR	acetylcholine receptors
AIDS	acquired immuno deficiency syndrome
anal.	analysis
aq	aqueous
BF_3•OEt_2	boron trifluoride diethyl etherate
Bn	benzyl
bp	boiling point
brine	saturated aqueous sodium chloride
bs	broad singlet
Bu	butyl
n-Bu	normal butyl
s-Bu	secondary butyl
t-Bu	tertiary butyl
t-BuOK	potassium *tert*-butoxide
ºC	degree(s) Celsius

Calcd	calculated
CHP	cumene hydroxyperoxide
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
CNS	central nervous system
CuBr•DMS	copper bromide dimethyl sulfide complex
d	day
d	distance
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
de	diastereomeric excess
DEAD	diethylazodicarboxylate
DIBBHT	diisobutylaluminum 2,6-di-t-butyl-4-hydroxytoluene
DMF	dimethyl formamide
DMAP	4-(dimethylamino) pyridine
DME	dimethoxyethane
DMG	directed metallation group
dt	doublet of triplets
E	energy
ee	enantiomeric excess
elem.	elemental
eq	equivalent(s)
Et_2O	diethyl ether

EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
h	hour
H^+	proton or protic acid
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
iPr	isopropyl group
IR	infrared spectroscopy
J	coupling constant
kcal	kilo calories
L-selectride	lithium tri-*sec*-butylborohydride
LDA	lithium diisopropylamide
LiDMAE	lithium dimethylaminoethoxide
LiHMDS	lithium bis(trimethylsilyl) amide
LiTMP	lithium tetramethylpiperidine
LRMS	low resolution mass spectrometry
M	molar

m	multiplet
mAChR	muscarinic acetylcholine receptors
mCPBA	m-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
Men	menthyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
MOMCl	chloromethyl methyl ether
mp	melting point
Ms	methane sulfonate
MsCl	methane sulfonyl chloride
nAChR	neuronal acetylcholine receptors
NBS	*N*-bromosuccinimide
NCS	*N*-chorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NOE	nuclear overhauser effect

o.n.	overnight
PCC	pyridinium chlorochromate
Pd/C	Palladium on Carbon
$Pd(OH)_2/C$	Palladium hydroxide on Carbon
PG	protecting group
Ph	phenyl
PhMen	phenylmenthyl
ppm	parts per million
Pt/C	Platinum on Carbon
q	quartet
R	alkyl or aryl group
R*	chiral auliary
Radial PLC or RPLC	radial preparative layer chromatography
RBF	round bottom flask
R-M	alkyl or aryl metalated group
rt	room temperature
s	singlet
SAR	structure activity relationship
satd	saturated
SM	starting material
t	triplet
T	temperature
TBAF	tetrabutylaluminum fluoride

TBME	*tert*-butyl methyl ether
TCC	trans-2-(α-cumyl)cyclohexyl or trans-2-(α-cumyl)cyclohexanol
TEA	triethylamine
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMSCl	chloro trimethylsilane
TPAP	tetrapropylammonium perrethenate
x	times

Introduction

Because of their facile preparation, stability and ability to control the regio and stereochemistry of the introduction of ring substituents, 1-acyl-2,3-dihydropyridones are useful synthetic intermediates for the synthesis of various alkaloids and other natural products. These dihydropyridones can be used as precursors to 1-acyl-1,2-dihydropyridines which are also useful building blocks for alkaloid synthesis. Recently, our group investigated the reaction of (triphenylsilyl) magnesium bromide with chiral acylpyridinium salts. The synthesis of the corresponding dihydropyridone was obtained in high yield and high de, and several transformations were achieved with high stereocontrol. Encouraged by these results, we decided to expand the reactivity studies of that kind of dihydropyridone. The reactivity of 1-acyl-2-(dimethylphenylsilyl)-2,3-dihydro-4-pyridone was investigated. This dihydropyridone was synthesized from the addition of dimethylphenylsilyl Grignard to the 1-acyl-4-methoxypyridinium salt with a 90% yield and 98% de. A variety of reactions including 1,4-additions and the synthesis of the corresponding dihydropyridine were accomplished. The high sterocontrol involved in this methodology may open the door to the synthesis of useful intermediates.

Recent studies have shown the beneficial effects of nicotine for the treatment of various CNS disorders such as Parkinson's disease and Alzheimer's disease among others. Nicotine also possesses insecticidal activity, especially towards mosquitoes. However, detrimental effects including actions on both the cardiovascular and gastrointestinal systems, sleep disturbance and dependence limit the use of nicotine as a therapeutic reagent. One of the contemporary challenges is to synthesize nicotine derivatives that would display the same beneficial effects of nicotine at lower toxicity.

We have developed various methodologies to synthesize enantiopure nicotine derivatives using nicotine as starting material. These methods are more efficient than the ones currently existing since no resolution is required to obtain the desired enantiomer. Regioselective substitution reactions for functionalization at C-4, C-5 and C-6 of the pyridine ring were achieved. The synthesis of novel C-4 substituted and unsubstituted dihydronicotines was also developed. Several of these new nicotine derivatives exhibit selective biological properties. The von Braun reaction was also investigated and provided various pyrrolidine ring-opened nicotine derivatives.

Part I.

STUDY OF 1-ACYL-2-DIMETHYLPHENYLSILYL-2,3-DIHYDRO-4-PYRIDONE AS SYNTHETIC INTERMEDIATES.

I. Introduction

1-Acyl-2,3-dihydro-4-pyridones **1** are useful synthetic intermediates for the synthesis of various alkaloids and other natural products.[1] They are usually very stable and easy to prepare. They also allow the introduction of ring substituents with control of both regio and stereochemistry. They can be prepared from Grignard reagents and chiral 4-methoxypyridinium salts in high yield and enantioselectivity.[2] These dihydropyridones can be used as precursors to 1-acyl-1,2-dihydropyridines **2**[3] which are also useful building blocks for alkaloid synthesis.[4]

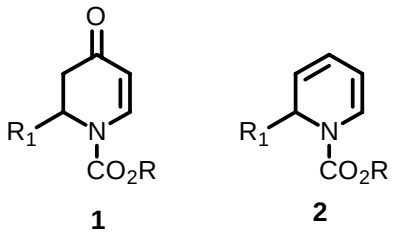


Figure 1. Structure of 1-acyl-2,3-dihydro-4-pyridones 1 and 1-acyl-1,2-dihydropyridines 2.

Recently, our group investigated the reaction of (triphenylsilyl)magnesium bromide with chiral 1-acylpyridinium salts.[5] The synthesis of the corresponding dihydropyridones **3** was obtained in high yield and high de and several subsequent transformations were achieved with high stereocontrol. Encouraged by these results, we decided to expand the reactivity studies on these useful heterocycles. The preparation and reactivity of 1-acyl-2-(dimethylphenylsilyl)-2, 3-dihydro-4-pyridones **4** were investigated.

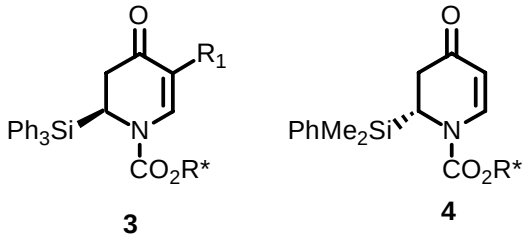
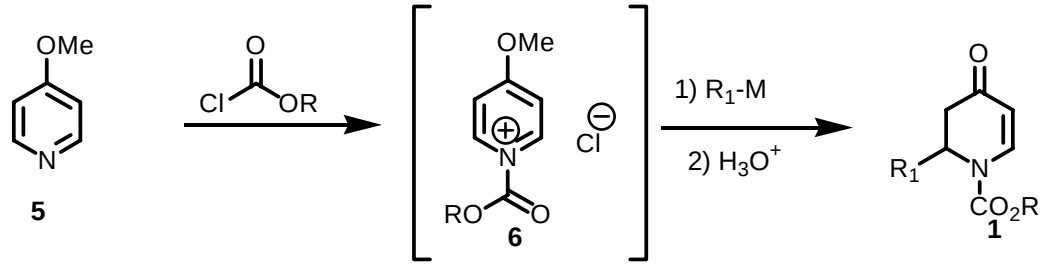


Figure 2. Structure of 1-acyl-2-(triphenylsilyl) 2,3-dihydro-4-pyridone 3 and 1-acyl-2-(dimethylphenylsilyl) 2,3-dihydro-4-pyridone 4.

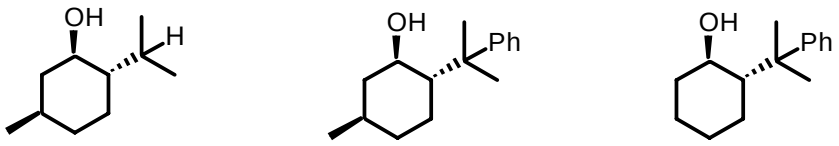
II. Review of the literature

1-Acyl-2,3-dihydro-4-pyridones **1** have been widely used in the synthesis of natural products. They are easily prepared from Grignard reagents or metallo enolates and a 4-methoxypyridinium salt[2] (Scheme 1).



Scheme 1. Preparation of racemic 1-acyl-2,3-dihydro-4-pyridones 1.

Due to A $^{(1,3)}$ strain, the C-2 substituent of a 1-acyl-2, 3-dihydropyridone is forced into a pseudo axial orientation, which provides a conformation bias in the molecule. Non racemic dihydropyridones are prepared according to the same method by using chiral 1-acylpyridinium salts. These salts are generated in situ from 4-methoxy-3-triisopropylsilyl pyridine and a chloroformate containing a chiral auxiliary. Three cyclohexyl based chiral auxiliaries are mainly used (Figure 3).



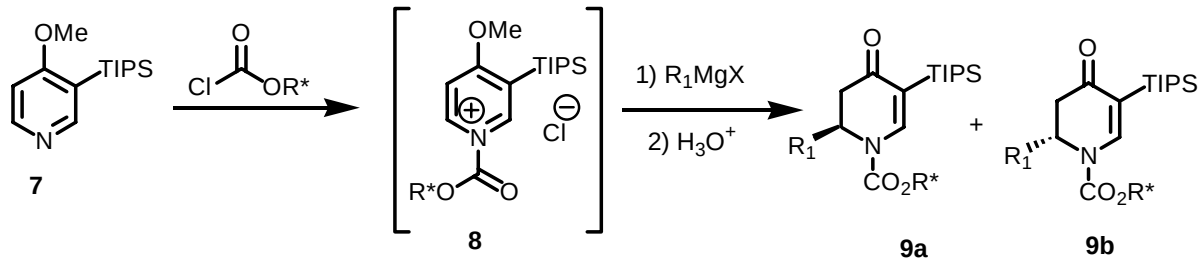
(-)-(8)-menthyl or (-)-Men

(-)-(8)-phenylmenthyl or (-)-8-PhMen

(-)-trans-2-(cumyl)cyclohexanol or (-)-TCC

Figure 3. Structure of the main chiral auxiliaries used.

Attack of a Grignard reagent, followed by hydrolysis with 10% HCl or a saturated solution of oxalic acid in water, affords chiral 1-acyl-2,3 dihydropyridones in high yield and diastereoselectivity (Scheme 2).



Scheme 2. Preparation of chiral 1-acyl-2,3-dihydro-4-pyridones 9.

The asymmetric induction comes from the phenyl ring of a chiral auxiliary that blocks one face of the pyridinium ring. The triisopropyl group at C-3 of the pyridinium ring is blocking the C-2 position, so the nucleophile attacks the C-6 position of the pyridinium ring from the opposite face of the phenyl ring (Figure 4). The absolute stereochemistry at C-2 of the major diastereomer has been shown to be the R configuration when (+)-TCC is used.

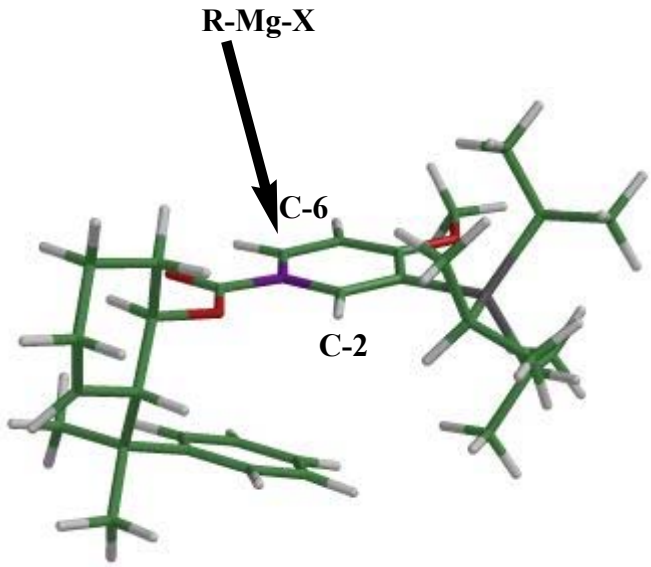
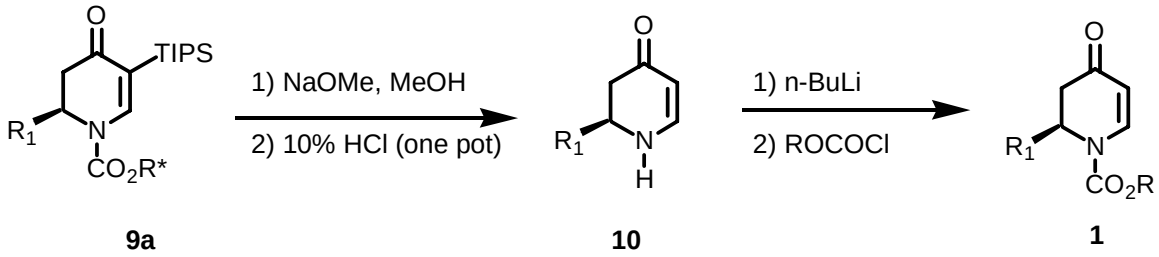


Figure 4. Attack of a Grignard reagent onto an acyl pyridinium salt. Molecular modeling performed using Mac Spartan Pro.

A one-pot procedure has been developed to remove both the chiral auxiliary and the triisopropylsilyl blocking group. Acylation of the nitrogen of dihydropyridone using *n*-butyllithium and a chloroformate yields the dihydropyridone **1**[2] (Scheme 3).

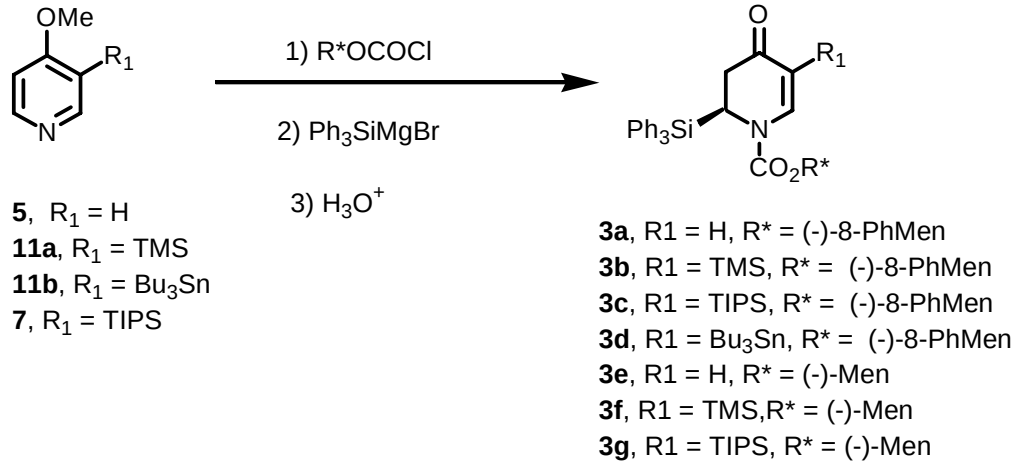


9a **10** **1**

Scheme 3. Removal of chiral auxiliary and TIPS group and acylation of dihydropyridone 10.

Recently, our group investigated the reaction of (triphenylsilyl)magnesium bromide with chiral 1-acylpyridinium salts.[5] The synthesis of the corresponding dihydropyridones **3** was

obtained in high yield and high de and several transformations were achieved with excellent stereocontrol (Scheme 4).



5, R_1 = H
11a, R_1 = TMS
11b, R_1 = Bu_3Sn
7, R_1 = TIPS

3a, R1 = H, R* = (-)-8-PhMen
3b, R1 = TMS, R* = (-)-8-PhMen
3c, R1 = TIPS, R* = (-)-8-PhMen
3d, R1 = Bu_3Sn, R* = (-)-8-PhMen
3e, R1 = H, R* = (-)-Men
3f, R1 = TMS,R* = (-)-Men
3g, R1 = TIPS, R* = (-)-Men

Scheme 4. Synthesis of various 1-Acyl-2 triphenylsilyl-2, 3 dihydro-4-pyridones 3.

It is worth noting that the configuration of the newly stereogenic center formed at C-2 is opposite that found in the major product of the reaction of alkyl or aryl Grignards with chiral 1-acylpyridinium salts. Also a large trialkylsilyl blocking group is not needed at C-3 of the pyridinium salt in order to effect excellent enantioselectivity. This may be explained by a chelation control mechanism (Figure 5).

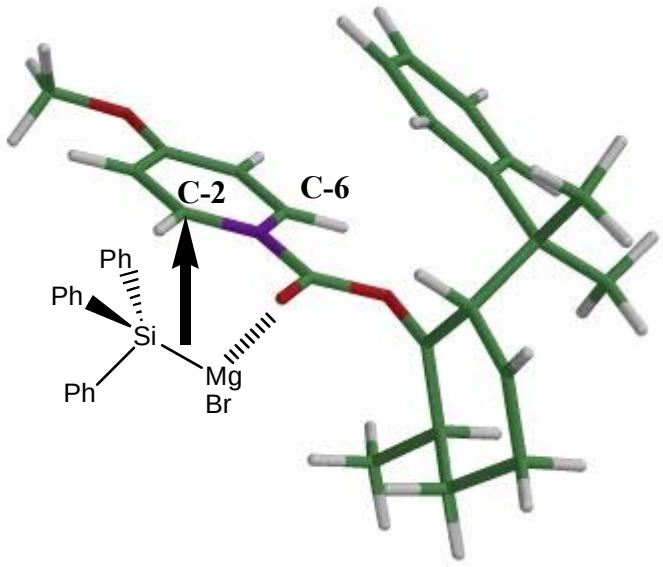


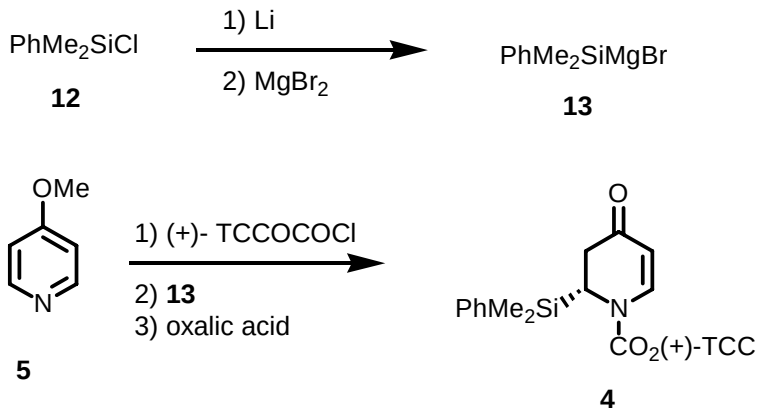
Figure 5. Attack of a silyl Grignard onto an acylpyridinium salt. Molecular modeling performed using Mac Spartan Pro.

We then turned our attention to the preparation and reactivity of 1-acyl-2-dimethylphenylsilyl-2, 3-dihydro-4-pyridone **4**.

III. Results and discussion

A. Synthesis of 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone **4.**

Dihydropyridone **4** was synthesized from 1,2 addition of dimethylphenylsilyl magnesium bromide to the 1-acyl-4-methoxypyridinium salt, followed by addition of a saturated solution of oxalic acid. The Grignard reagent was prepared from the chlorosilane by a lithium-halogen exchange followed by transmetallation with magnesium bromide (Scheme 5).



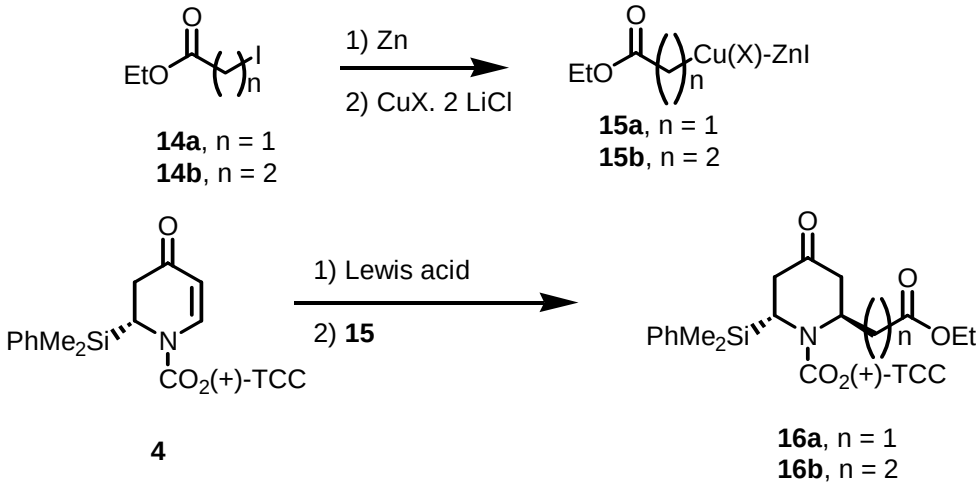
Scheme 5. Synthesis of 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone 4.

Remarkably, a 90% yield was obtained, and the diastereoselectivity of the reaction was determined to be 98% de by HPLC of the crude product. Synthetic transformations of dihydropyridone **4** were next investigated.

B. 1,4-Additions.

Organocopper-zinc reagents have been shown to undergo 1,4-addition on several unsaturated systems[6] but have never been tested on dihydropyridones. This reaction was investigated on dihydropyridone **4** (Scheme 6).

These organometallic reagents are made from an alkyl iodide via zinc insertion followed by transmetallation with a copper salt, either copper (II) acetate[6c] or copper (I) cyanide.[6a]



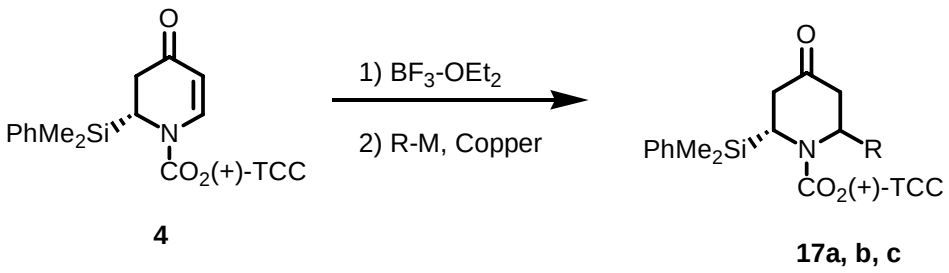
Scheme 6. 1,4-Additions on 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone 4 with organocopper-zinc reagents.

Several conditions were used (Table 1): copper (I) cyanide and TMSCl only afforded a low yield of product (entry 2) whereas copper (II) acetate and boron trifluoride diethyl etherate afforded 45% of product **16b** as a single diastereomer (entry 3). However this reaction proved to be very hard to reproduce.

Table 1. 1,4-Additions on 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone 4 with organocopper-zinc reagents.

Entry	RI	CuX	SM (eq)	Lewis Acid	Conditions	Results
1	**14b**	CuCN	1.4	TMSCl	-78 °C (3 h), RT (12 h)	SM only
2	**14b**	CuCN	1.4	TMSCl	-78 °C (3 h), RT (5 h)	14% **16b**, 20% SM
3	**14b**	$Cu(OAc)_2$	1.1	BF_3•OEt_2	-78 °C (8 h), -43 ºC (12 h)	45% **16b**
4	**14a**	$Cu(OAc)_2$	1.1	BF_3•OEt_2	-18 °C (5 h)	SM only

We decided to investigate the reactivity of other organocuprates (Scheme 7, Table 2).



4 **17a, b, c**

Scheme 7. 1,4-Additions on 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone 4 mediated by a copper reagent.

The cuprate of dimethylphenylsilylmagnesium bromide (entry 1) as well as the higher order cuprate (entry 3) did not give any reaction. However, the allyl cuprate (entry 2) afforded piperidone **17b** in 85% yield as a single diastereomer.

Table 2. 1,4-Additions on 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone 4 mediated by a copper reagent.

Entry	R-M	Copper reagent	Product	Yield
1	$PhMe_2SiMgCl$	$CuBr{\bullet}SMe_2$	**17a**	No reaction
2	AllylMgCl	$CuBr{\bullet}SMe_2$	**17b**	85% 1 diastereomer
3	$BnOCH_2SnBu_3$	Lipshultz's reagent	**17c**	No reaction

The product was found to be the trans piperidone by NOE analysis. A NOE signal was detected between H-6 and the methyl groups of the silyl group located at C-2 (Figure 6).

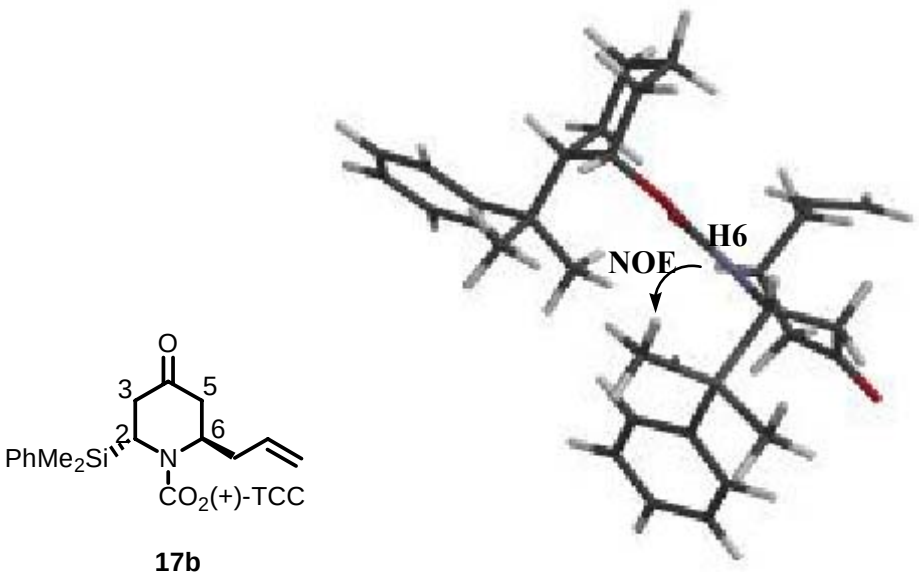
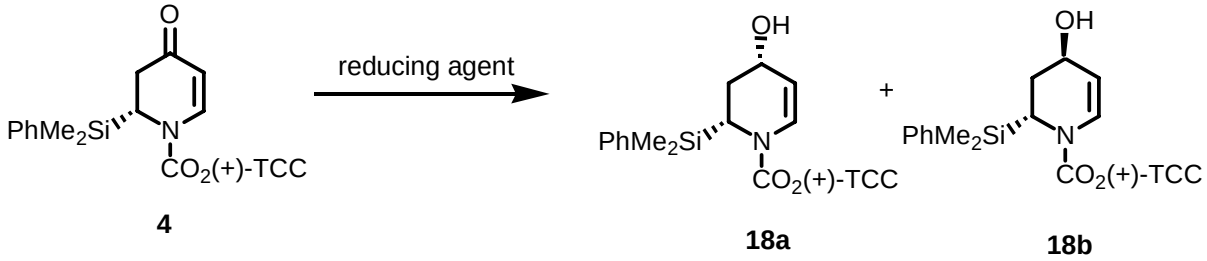


Figure 6. Low-energy conformation of piperidone 17b. Molecular modeling performed using Mac Spartan Pro.

C. Synthesis of the corresponding dihydropyridine **20**.

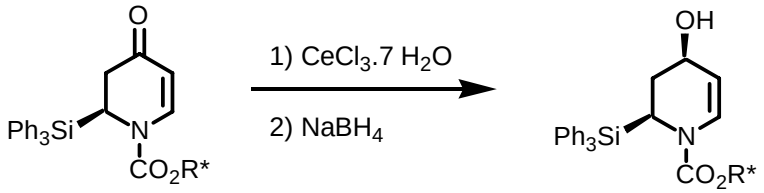
The synthesis of the corresponding dihydropyridine **20** was next envisioned. The first step is the reduction of the C-4 carbonyl (Scheme 8). Several reducing agents were tested (Table 3).



Scheme 8. Reduction of the keto function of 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone 4.

The Luche conditions[7] (entry 1) afforded a quantitative mixture of alcohol with a 20-40% de, cis alcohol **18a** being the major diastereomer. Reduction with L-Selectride (entry 2) also afforded a quantitative conversion with a 42% de.

In a previous study, Luche reduction of dihydropyridone afforded exclusively the axial alcohol **19** (cis product), demonstrating the effective top-face shielding of the carbonyl by the C-2 triphenylsilyl group[5] (Scheme 9). In this case, the smaller dimethylphenylsilyl group is less effective at blocking the C-4 carbonyl.



6a **19**

Scheme 9. Reduction of the keto function of 1-acyl-2 triphenylsilyl-2, 3 dihydro-4-pyridones 3a.

In order to improve the diastereoselectivity, diisobutylaluminum 2,6-di-t-butyl-4-hydroxytoluene or DIBBHT[8] reagent (Figure 7) was tested (entry 3). Previous unpublished results in our group revealed that this reagent afforded the trans alcohol exclusively. In this case, the reaction was very slow, probably due to the steric hindrance of the silyl group at C-2.

Table 3. Reduction of the keto function of 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone 4.

Entry	Reducing agent	Results
1	1) $CeCl_3$. 7 H_2O 2) $NaBH_4$	quantitative yield 20-40% de
2	L-selectride	100% yield 42% de
3	DIBBHT	95% SM, 5% product

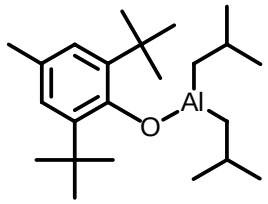
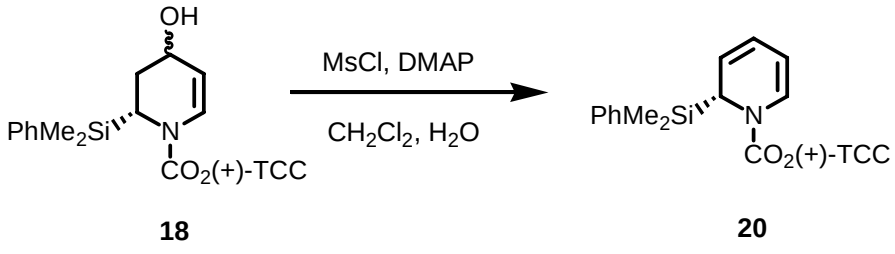


Figure 7. Diisobutylaluminum 2,6-di-*t*-butyl-4-hydroxytoluene or DIBBHT.

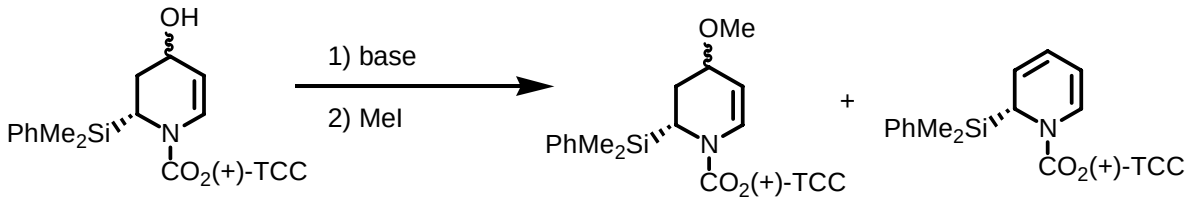
The second step of the dihydropyridine synthesis is the dehydration of the alcohol. The classical Furukawa conditions[9] gave only low yields, probably due to the acidity of the reagent (Scheme 10).



18 **20**

Scheme 10. Dehydration of alcohol 18 using the Furukawa conditions.

Other ways to dehydrate these alcohols had to be found. Interestingly, when the etherification of alcohol was performed (Scheme 11), the elimination product, i.e. the dihydropyridine **20** was obtained. However depending on the scale and the base used, a mixture of both products **21** and **20** was obtained (Table 4).



18 **21** **20**

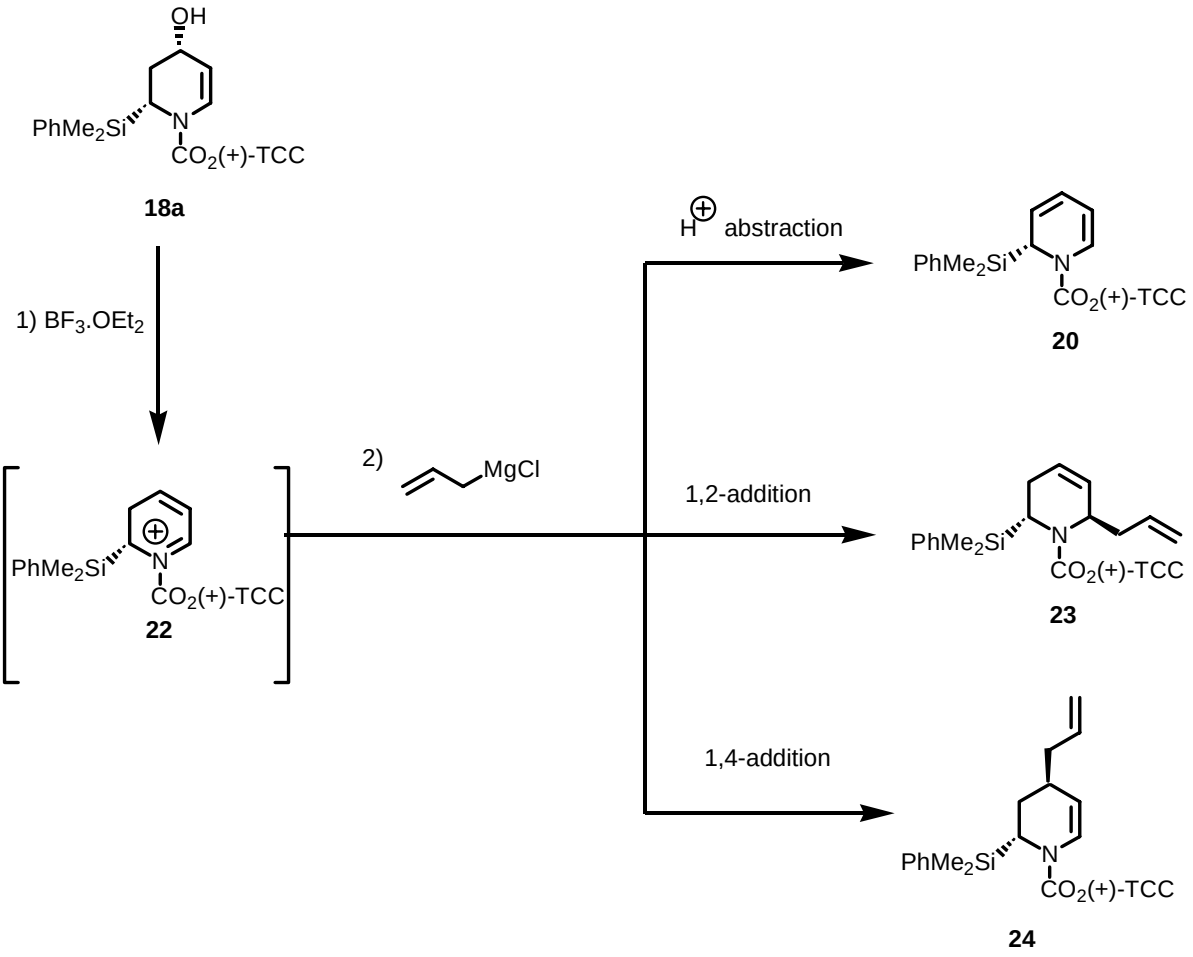
Scheme 11. Etherification of alcohol 18.

Table 4. Etherification conditions of alcohol 18.

Entry	**Scale (mg)**	**Alcohol**	**Base**	**Product**	**Yield**
1	50	**18b**	tBuOK	**21b**	65%
2	25	**18a**	NaH	SM	100%
3	25	**18a**	tBuOK	**21a**	18%
4	50	**18b**	NaH	**21b**	60%
5	700	**18a and b**	tBuOK	**20**	78%
6	200	**18a and b**	NaH	**20**	100%

Since this method was not reliable, the chemistry of the *N*-acyliminium ion was next investigated. Treatment of alcohol **18a** with BF_3•OEt_2 afforded the *N*-acyliminium ion **22** that could then undergo three possible reactions with Grignard reagents: 1,2-addition, 1,4-addition or proton abstraction to give the desired dihydropyridine **20** (Scheme 12).

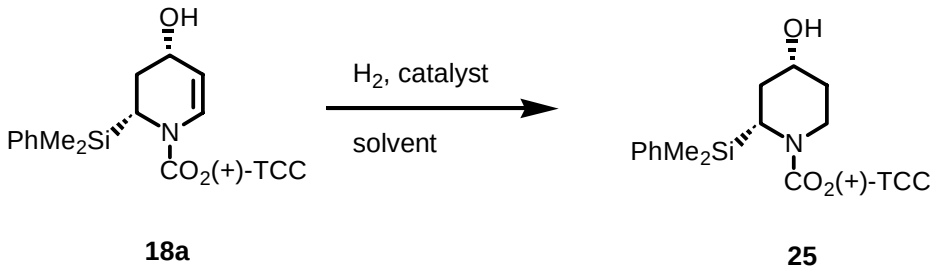
When the *N*-acyliminium ion **22**was treated with allylmagnesium chloride, only the desired product **20** was obtained in a quantitative yield. Dihydropyridine **20** was found to be very sensitive to acid and decomposed upon purification with silica gel.



Scheme 12. Formation and reactivity of *N*-acyliminium ion 22.

D. Miscellaneous reactions.

Other reactions were examined. First hydrogenation of alcohol **18a** was performed (Scheme 13) and **25** was obtained in 25% yield 98% yield with Pd/C and EtOAc (Table 5, entry 3).



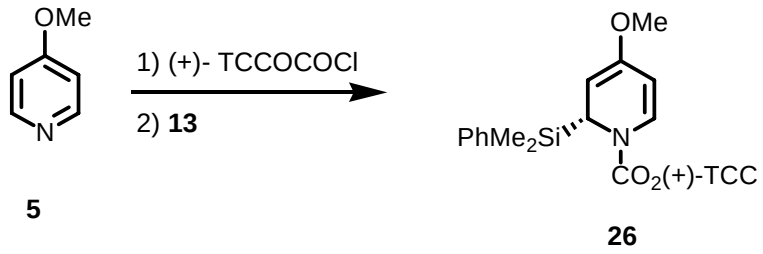
18a **25**

Scheme 13. Hydrogenation of alcohol 18.

Table 5. Hydrogenation of alcohol 18.

Entry	**Scale (mg)**	**Solvent**	**Reaction time**	**Catalyst**	**Results**
1	25	EtOH	4 h	$Pd(OH)_2/C$	Crude yield: 80%
2	20	EtOAc	2 h	$Pd(OH)_2/C$	66% yield
3	30	EtOAc	2 h	Pd/C	98% yield

Next, the synthesis of 4-methoxy-dihydropyridine **26** was envisioned. The sequence is the same as for the dihydropyridone except that the hydrolysis step is omitted and replaced by a regular work-up (Scheme 14). The 4-methoxydihydropyridine **26** was afforded in 60% yield, but this product was very sensitive to acidic conditions and purification.



Scheme 14. Synthesis of 4-methoxy-dihydropyridine 26.

The removal of the chiral auxiliary of **4** was next attempted. The usual conditions (NaOMe, MeOH, and reflux) decomposed the molecule. Various carbamate exchanges were attempted on compounds **4**, **18**, **21** and **25** but unfortunately all the conditions failed. Most of the reactions seemed to occur at the silane moiety located at the C-2 position. Since the chiral auxiliary could not be removed, the number of reactions that could be performed on the molecule was limited and no further chemistry was explored.

Part II.

SYNTHESIS OF

ENANTIOPURE NICOTINE DERIVATIVES

FROM NICOTINE

IV. Introduction

A. History of nicotine.

(*S*)-Nicotine **27** (Figure 8 and Figure 9) is the most abundant alkaloid isolated from genus *Nicotiana* plant. It is named after Jean Nicot, ambassador of France to Portugal, who introduced tobacco to France in the 16th century.[10, 11] Nicotine was first isolated in 1828 by Posselt and Reimann, and its chemical empirical formula was first proposed in 1843 by Melsens. Pinner[12] suggested the correct structure of nicotine in 1883. The first synthesis of nicotine was performed by Pictet and Rotshy[13] in 1904 but it wasn't until 1978 that Pitner identified the special orientation of natural (*S*)-nicotine.

Nicotiana tabacum is cultivated throughout the world for preparation of cigars, cigarettes, pipe and chewing tobacco. Nicotine constitutes 2-8% of the dry weigh of the cured leaf, although a much larger range exists in some *Nicotiana* plants. It occurs mainly as the (*S*)-(-) isomer although 11 % of (*R*)-(+)-nicotine has been found in smoke condensate from cigarettes due to pyrrolytic racemization of the (*S*)-isomer.[14] (*S*)-Nicotine will be referred as nicotine for further discussion.

B. Biological properties of nicotine.

Nicotine has a long history of being produced and used by humans for pharmacological purposes because of its numerous biological properties. Nicotine displays numerous effects on the central nervous system: in addition of being addictive, enhancement of the working memory and attention, increase of arousal and alertness and decrease of anxiety have been found.[15] Those many effects are due to the interaction of nicotine with the

nicotinic acetylcholine receptors (AChRs). Those receptors are located throughout the whole body and can be divided in three categories: muscarinic receptors (mAChRs), muscle-type nicotinic receptors and neuronal nicotinic receptors (nAChRs). Nicotine binds poorly with muscle-type nicotinic receptors and doesn't bind with mAChRs. Neuronal nicotinic receptors are the major target of nicotine in the body.[16] Of the minor alkaloids studied only nornicotine **28**, metanicotine **29** and anabasine **30** (Figure 8) have shown significant pharmacological activity: their actions are similar to those of nicotine but are less potent.[17]

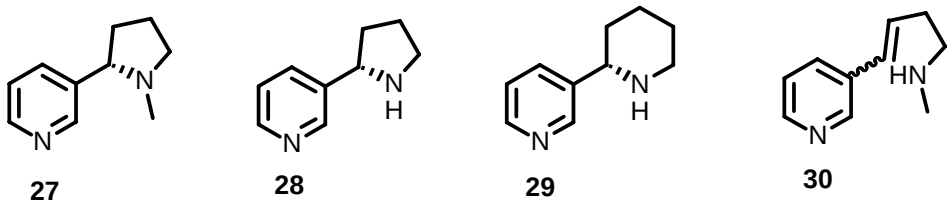


Figure 8. Structures of nicotine, nornicotine, metanicotine and anabasine.

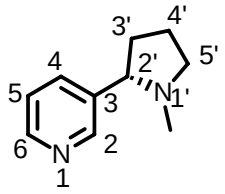
Nicotine also exhibits lethal effects: nicotine poisoning involves central and peripheral nervous systems. The symptoms of nicotine poisoning resemble those of tobacco poisoning and include nausea, vomiting and cardiac palpitations. Peripheral skeletal neuromuscular blockade causes death. A concentration of 0.5 mg/m^3 is the threshold limit for commercial use of nicotine.[10]

In addition to its CNS activity, nicotine has been widely used in the past as an insecticide. In fact aqueous solutions of nicotine were prepared before the conquest of the New World to kill soft bodied insects. Nowadays aqueous solutions of nicotine sulfate are still used throughout the world as insecticides.[10]

C. Chemical properties and reactivity of nicotine.

Nicotine exhibits both positive and negative effects on the human body that can be explained by its chemical properties.

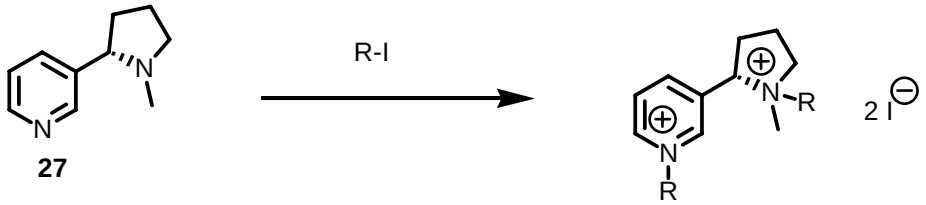
One of the interesting chemical features of nicotine is the fact that it is dibasic: nicotine contains both a pyridine and pyrrolidine ring that are perpendicular to each other.



27

Figure 9. Structure and numbering of (*S*)-nicotine.

The nitrogen atoms located on these rings have different pKa's resulting in competition reaction between the two. In 1853 and 1854, Planta and Von Stahschmidt reported the dialkylation of nicotine when treated with methyl or ethyl iodide.[18]

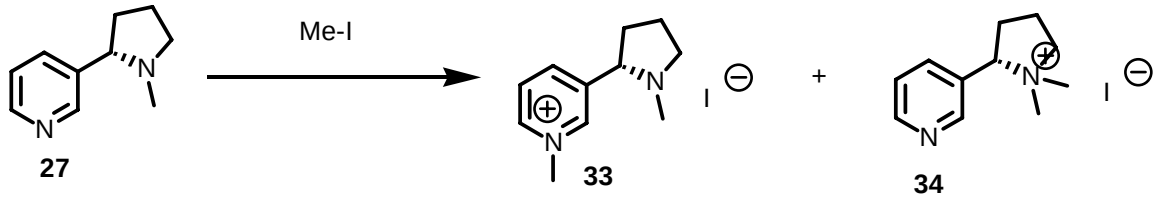


27

31, R = Me
32, R = Et

Scheme 15. Dialkylation of nicotine.

In 1984, Seeman[19] observed a 2.5:1 ratio of monoalkylated product **34** and **33**, indicating the greater reactivity of the pyrrolidine nitrogen: the pKa of N-1 is 3.04 and the pKa of N-1′ is 7.84.



Scheme 16. Monoalkylation of nicotine.

At a pH of 7.4, nicotine exists in two forms: the monoprotonated form **35** (Figure 10) and the uncharged form, with a 2:1 ratio.

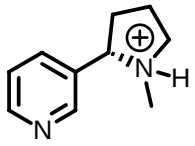


Figure 10. Monoprotonated form of nicotine.

The uncharged form can penetrate the lipoprotein membrane whereas the charged one cannot. This is an important feature as this allows nicotine to be absorbed through the skin and several organs such as liver, lungs and brain. The ionized form mimics acetylcholine (Figure 11), the neurotransmitter that activates nAChRs by opening the associated ion channel. Acetylcholine (**36**) (Figure 11) contains a positively charged quaternary nitrogen that is similar to the positively charged pyrrolidine nitrogen. The keto oxygen of the acetyl group of acetylcholine has Lewis base character like the pyridine nitrogen of nicotine.

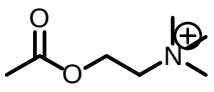
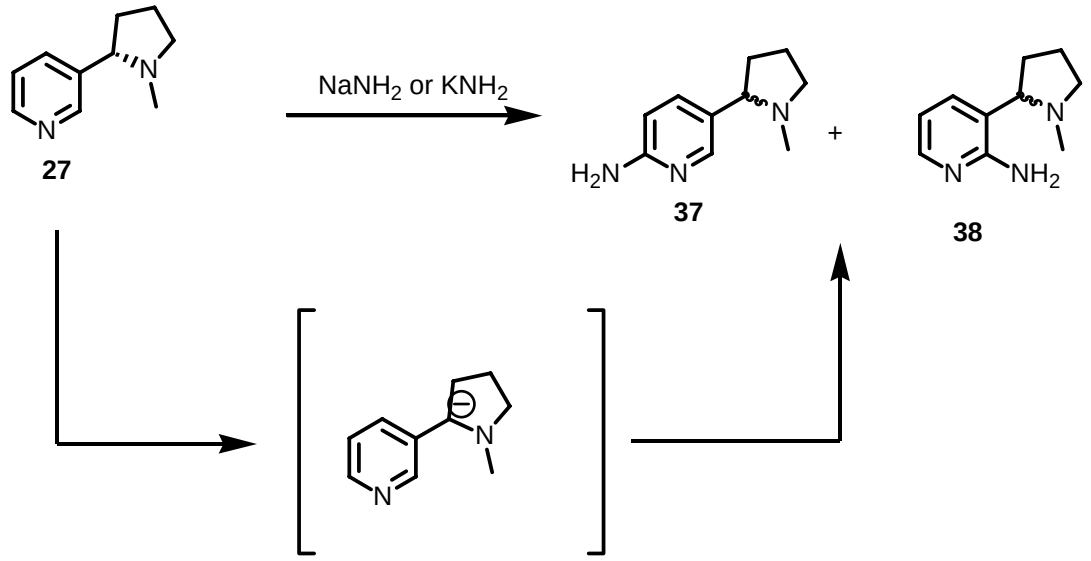


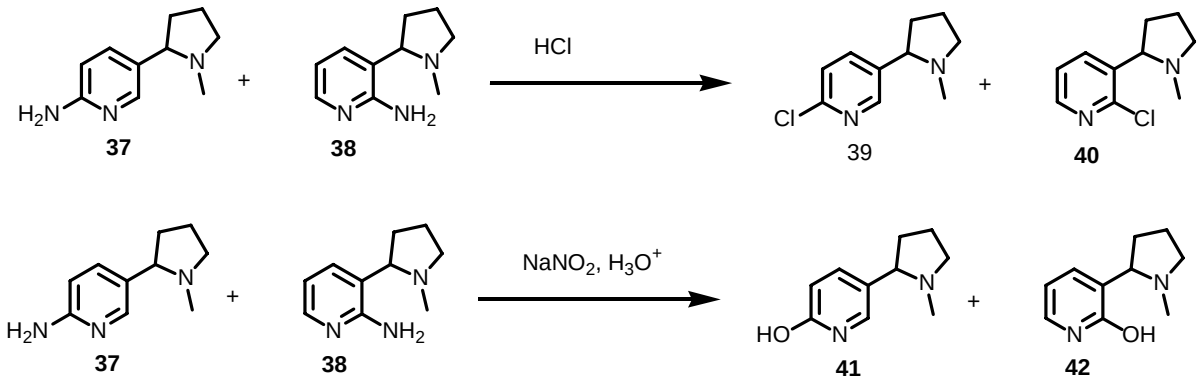
Figure 11. Structure of acetylcholine.

The reactivity of nicotine towards bases was tested by Tschitschibabin and Kirssanov in 1924. They prepared 2- and 6- amino nicotines by using sodium or potassium amide (Scheme 17).[20] However, this reaction resulted in racemization which they thought, occurred via the formation of a carbanion at C-2' of the pyrrolidine ring. This hypothesis was proved to be wrong by Seeman who found the correct intermediates responsible for the racemization (see page 27).



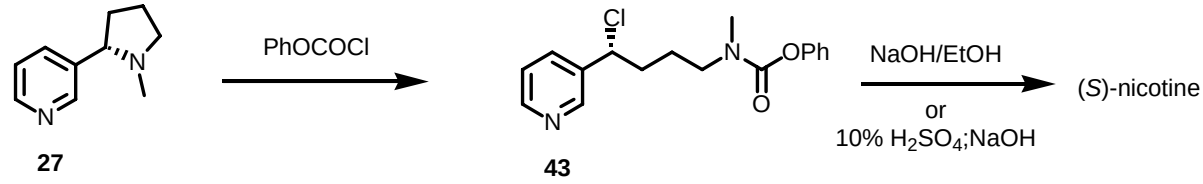
Scheme 17. Reactivity of nicotine with sodium amide.

They converted the aminonicotines to chloronicotines using HCl, and to the hydroxynicotines via formation of a diazonium salt with nitrous acid (Scheme 18).



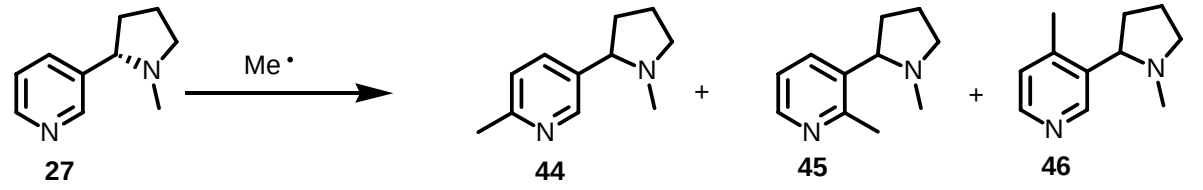
Scheme 18. Conversion of amino nicotines to chloro and hydroxyl nicotines.

Cosford and Bleicher demonstrated the pyrrolidine ring could be opened by chloroformates with inversion of configuration and subsequently reclosed with net retention of configuration (Scheme 19).[21]



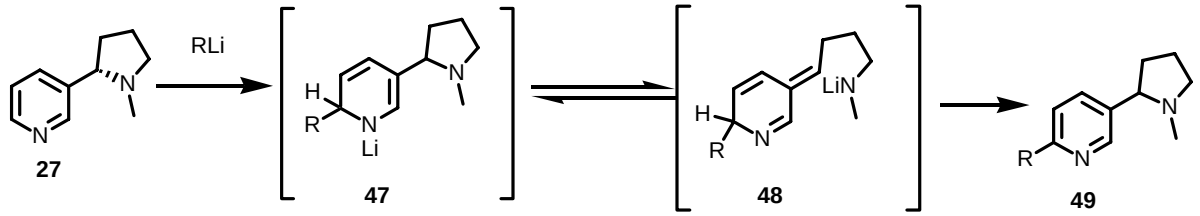
Scheme 19. Pyrrolidine ring opening with chloroformates.

In 1978, Itokawa investigated the methyl radical alkylation of nicotine and observed a mixture of products with racemization (Scheme 20).[22]



Scheme 20. Radical alkylation of nicotine.

In 1985, Seeman studied the addition of organolithium reagents to nicotine and observed the regiospecific formation of partially racemized 6-alkylnicotinoids. They disagreed with the carbanion intermediate proposed earlier and suggested the reversible cleavage of the pyrrolidine ring at the chiral center through intermediates **47** and **48** (Scheme 21).[23]



Scheme 21. Racemization of nicotine via pyrrolidine ring opening.

D. Problems that nicotine might solve.

Because of its numerous biological effects, nicotine has the potential to be used as a therapeutic agent as well as an insecticide.

1. Use of nicotine as a therapeutic drug for various CNS diseases.

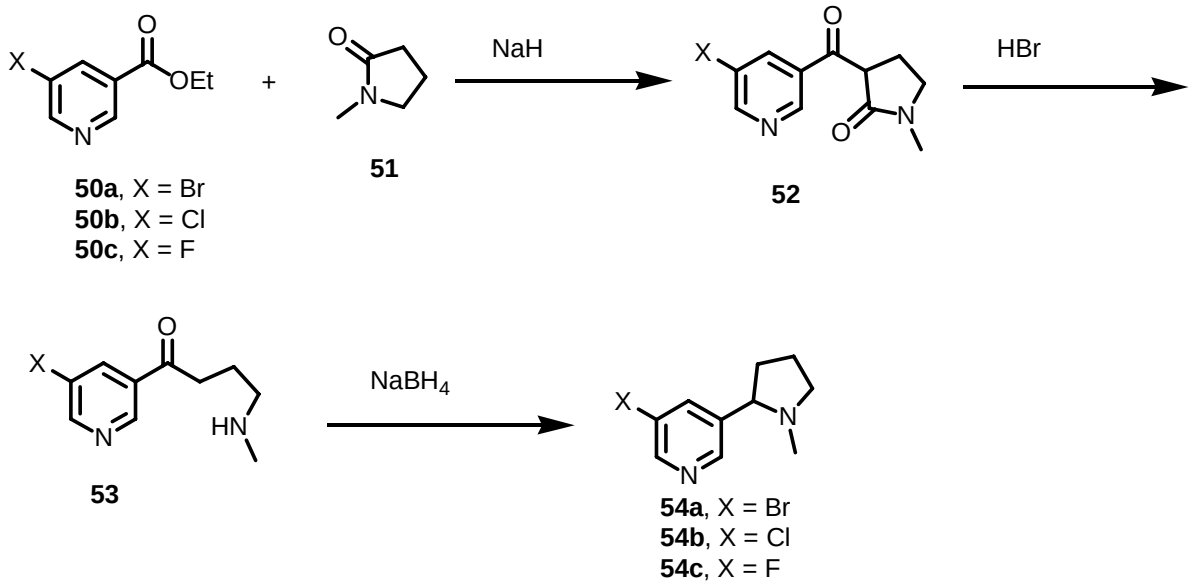
Recent studies have shown the beneficial effects following administration of nicotine on patients suffering from Parkinson's disease, anxiety, schizophrenia, Alzheimer's disease, uterative colitis and other CNS disorders.[24] However, detrimental effects including actions on both the cardiovascular and gastrointestinal systems, sleep disturbance and dependence limit the use of nicotine as a therapeutic reagent. One of the contemporary challenges is to synthesize nicotine derivatives that would display the same beneficial effects of nicotine at lower toxicity.

2. Use of nicotine as an insecticide.

The design of a new class of insecticides that would act against adult mosquitoes and have low human toxicity has become of high importance for several reasons. First, mosquitoes are the carrier of a variety of serious and deadly diseases, such as malaria, West Nile Virus, yellow fever and AIDS among others. Second, at the moment only two classes of chemical insecticides are used: the organophosphates and the pyrethroids. The organophosphates are on the verge of being removed from the market because of their high toxicity. In addition, mosquitoes have developed a common mechanism of resistance against both the organophosphates and the pyrethroids.[25] The development of a new class of insecticides is therefore imperative.

E. Previous work on the synthesis of nicotine derivatives.

The various uses of nicotine as a potential drug and as an insecticide make it a valuable subject of studies for chemists. Rondahl conducted an early study on the structure-activity relationship of nicotine analogues in 1977. He prepared racemic 5-bromo and 5-chloronicotines according to the same procedure used by Leete to prepare 5-fluoronicotine (Scheme 22).[26]



50a, X = Br
50b, X = Cl
50c, X = F

51

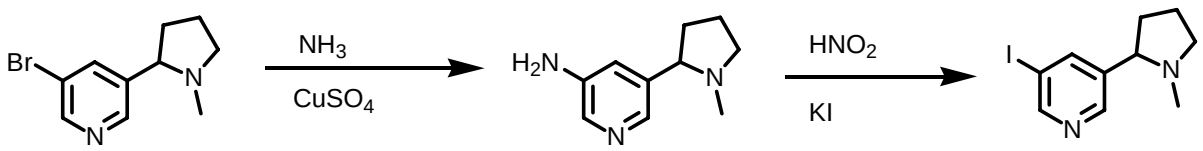
52

53

54a, X = Br
54b, X = Cl
54c, X = F

Scheme 22. Synthesis of 5-halonicotines.

Another method (Scheme 23) had to be employed for the synthesis of 5-iodonicotine, as the intermediate ketolactam **52** decomposed when reacting with HBr.



54a

55

54d, X = I

Scheme 23. Synthesis of 5-iodonicotine.

All the 5-halonicotines showed reduced activity on the guinea-pig *vas deferens*. Their order of potency was found to be F > Cl = I > Br with 5-fluoronicotine having 40% the activity of nicotine.[27]

More recently, Wang and al. demonstrated in 1998 the order of receptor affinity of the ring position of an additional methyl group to be: 6-methyl> 2'-methyl> 5-methyl> 2-methyl> 4-methyl.[28]

Modification of both the pyridine and pyrrolidine ring as well of conformation restriction of nicotine yielded several analogues that exhibit biological properties. Several nicotine derivatives are currently in different stages of clinical trials for various CNS disorders. The maleate salt of SIB-1508Y (**56**) is in Phase II clinical trials for the treatment of Parkinson's disease.[29]

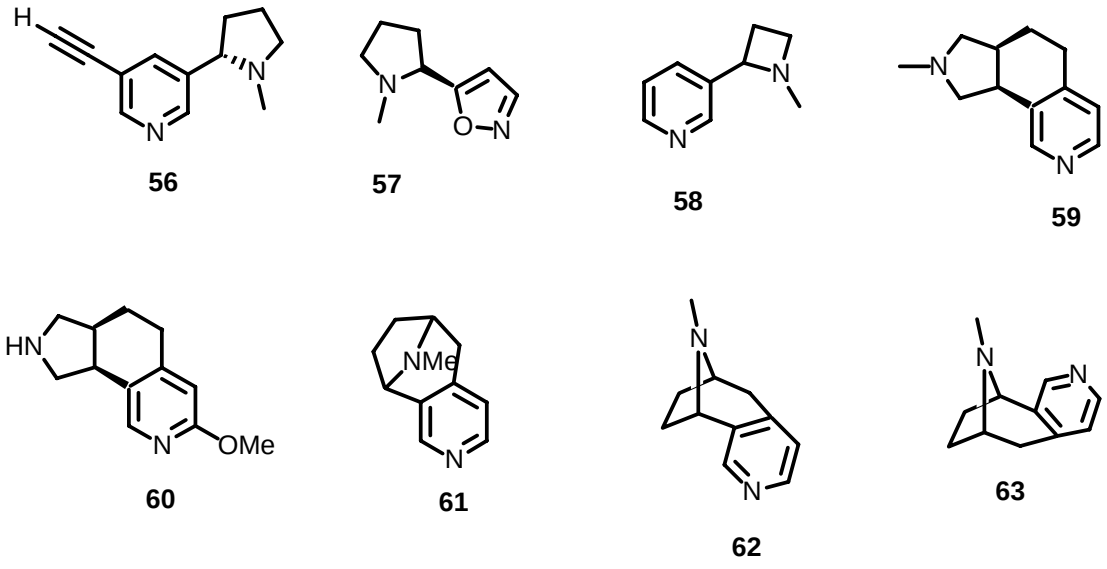
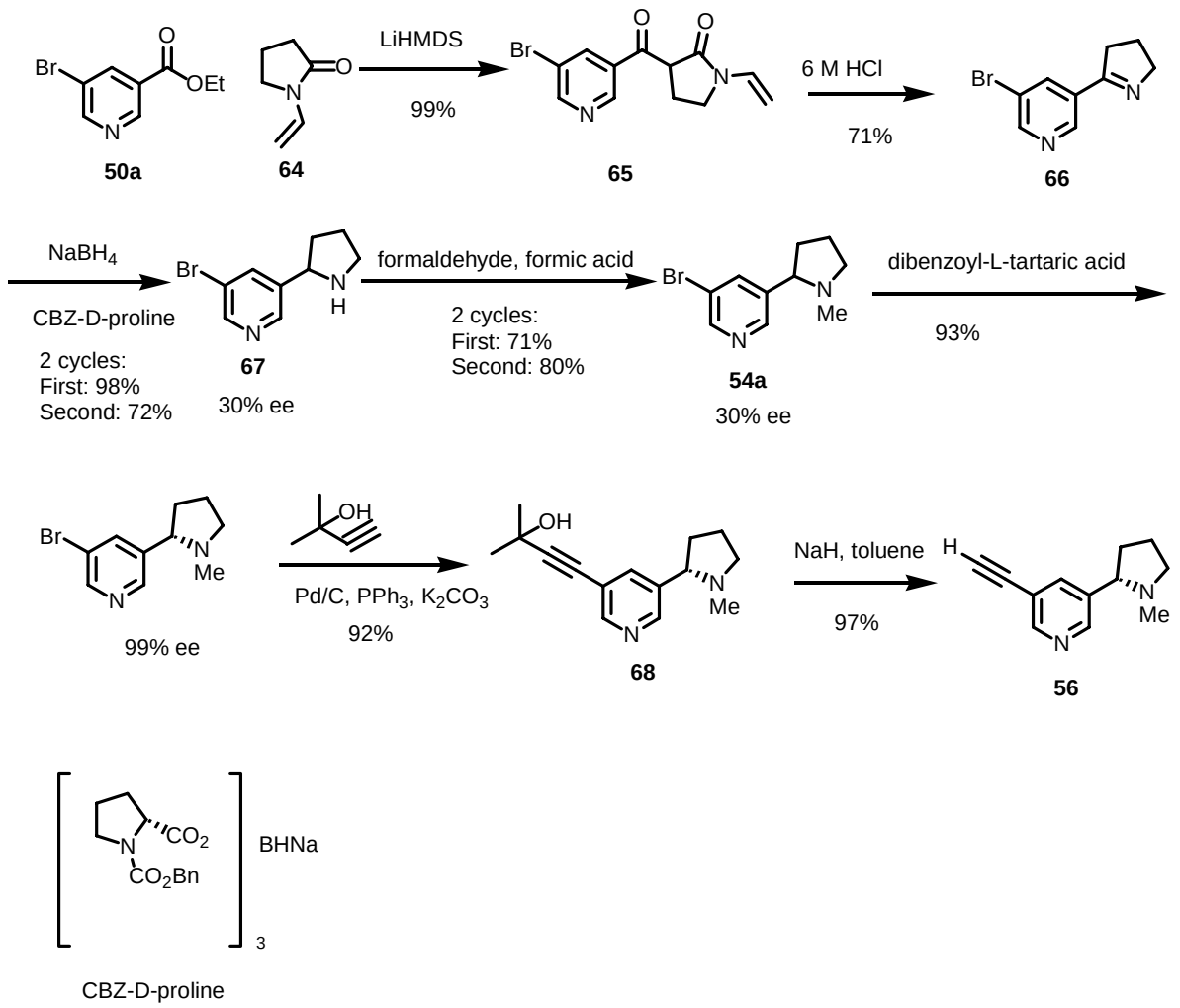


Figure 12. Structures of various potent nicotine derivatives.

Isosteric replacements of the pyridine ring as well as the pyrrolidine ring of nicotine have also been reported. The nAChR agonist ABT-418 **57** contains an isoxazole isostere of pyridine and was found some beneficial effects in the case of patients suffering from Alzheimer's disease.[30] Contraction of the pyrrolidine ring to a four-membered ring such as in compound **58** resulted in a 10-fold increase of the binding affinity compared to nicotine.[31]

Several torsionally constrained analogues were prepared in order to determine the active conformation of nicotine. In 1993, Glassco prepared a conformationally constrained isoquinoline **59** that exhibits modest affinity to the nAChRs.[32] A structurally related compound **60** was prepared by McDonald and was found to have in vivo activity for Parkinson's disease and pain.[a] Recently Rapoport reported the synthesis of bridged nicotine derivatives **61**, **62** and **63** that showed some potency in CNS binding.[33]

The main drawback of the synthesis of these nicotine derivatives is the use of racemic starting material, requiring a resolution to provide the desired enantiomer to the detriment of the overall yield. As shown in Scheme 24, even though each individual step is high yielding, only 23% of chiral product is isolated and several resolutions have to be performed in order to provide the desired enantiomer.[29c]



Scheme 24. Synthesis of SIB-1508Y.

F. Our approach to the synthesis of nicotine analogues.

A plethora of nicotine derivatives have been synthesized and display interesting biological properties. However, their synthesis is often low yielding because of the necessity to resolve the racemic material produced. We decided to investigate the regioselective synthesis of nicotine derivatives using natural (*S*)-nicotine as a starting material. Avoiding the use of a resolution to obtain enantiopure material will reduce both the length and the cost of the synthesis of these derivatives.

We applied 1-acylpyridinium salt chemistry to nicotine to make a variety of 1,4-dihydronicotines and C-4 substituted nicotine derivatives. We also studied the reductive disilylation of nicotine. The product resulting from that reaction was submitted to several transformations that yielded either 4-unsubstituted 1,4-dihydronicotines or C-5 substituted derivatives. Deprotonation of C-4 substituted derivatives was achieved and yielded C-6 and C-4 substituted nicotines. 4-Hydroxynicotines were synthesized form their corresponding 4-silylnicotines in high yield. Tetrahydronicotines were synthesized by hydrogenation of their corresponding dihydronicotines. Substitution at C-5 of dihydronicotines was also investigated. We also synthesized SIB-1508Y with an overall yield of 20% in 6 steps from nicotine. Finally, the von Braun reaction was also investigated and provided various pyrrolidine ring-opened nicotine derivatives. Several of these new nicotine derivatives were tested for both insecticidal and CNS activity and we explored their structure activity relationship or SAR.

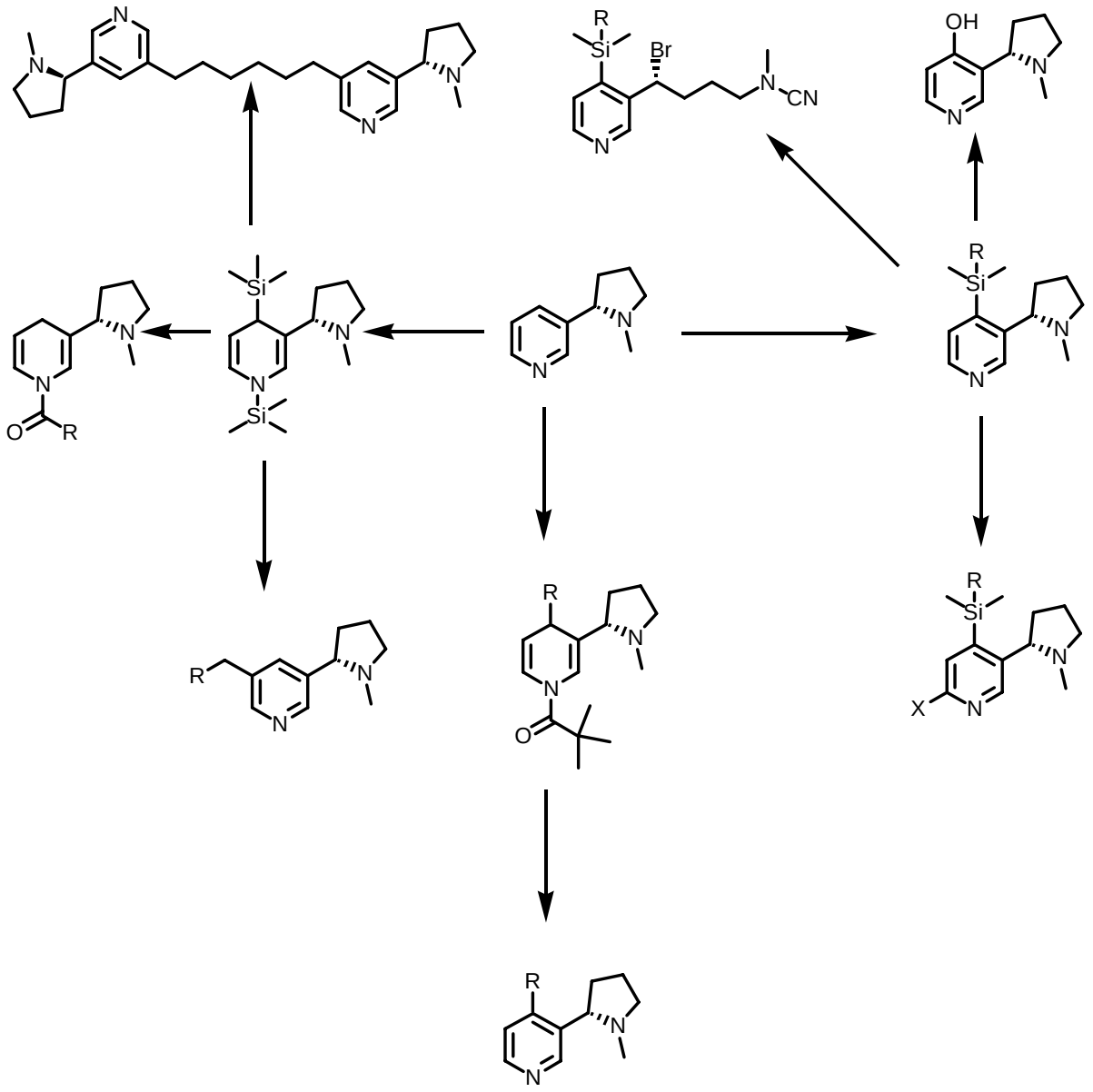


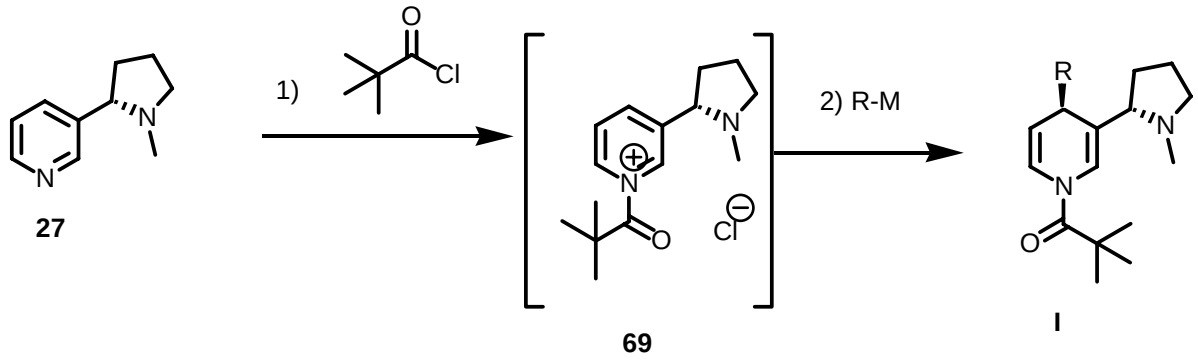
Figure 13. Summary of the methodologies investigated.

V. Synthesis of various derivatives via 1-acylpyridinium salt of nicotine

A. Two-step sequence to synthesize nicotine derivatives with a C-4 substituent.

We started our research on nicotine chemistry by studying the formation of 1-acylpyridinium salt of nicotine. In a previous study conducted in our laboratory, pivaloyl chloride was found to be the best reagent to form the pyridinium salt of nicotine, avoiding the

ring opening of the pyrrolidine.[34] Reaction of that salt with cuprate reagents would yield 1,4-dihydronicotines **I** (Scheme 25). We first tested the reactivity of 1-acylpyridinium salt of nicotine with alkyl and aryl cuprates. Such cuprates can be easily prepared from the transmetallation of their corresponding Grignard with CuBr•DMS. The results of these transformations are presented in Table 6. The yields range from 40% to 75.6% and all these dihydronicotines were isolated as a single distereomer. The stereochemistry was confirmed by X-ray analysis of product **71**.



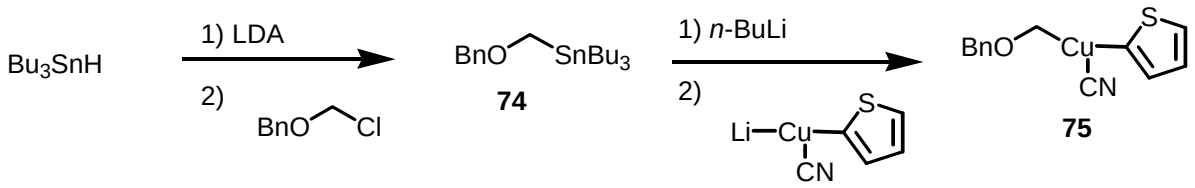
Scheme 25. 1,4-Addition of cuprate reagents onto the pyridinium salt of nicotine.

Table 6. Results of the addition of aryl and alkyl Grignard to 1-acylpyridinium salt of nicotine.

Entry	R-M	Product	Yield (%)
1	Me_2CuLi	**70**	70.5
2	PhCuLi	**71**	75.6
3	BuCuLi	**72**	40.0
4	BnCuLi	**73**	64

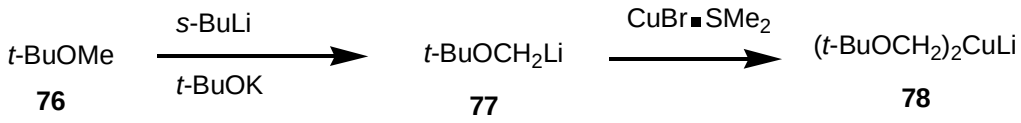
Encouraged by those results, we decided to expand the versatility of this transformation by introducing some functionalities on the cuprate reagents. Several cuprates were tested and their synthesis is listed below. The results of this transformation are presented in Table 7.

First the addition of the higher order cuprate **75** gave 80% yield of a mixture of diastereomers with a 40% de (entry 1). This cuprate was formed from the transmetallation of stannane **74** with the Lipshultz'reagent[35] (Scheme 26).



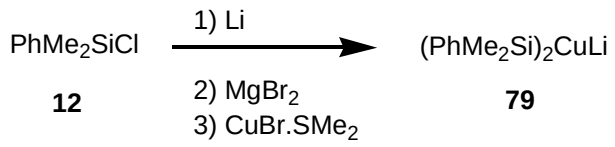
Scheme 26. Formation of benzyloxymethyl cuprate.

Next, the cuprate **78** made from *t*-butyl methyl ether yielded 60% of product as a single diastereomer (entry 2). Deprotonation of *tert*-butylmethyl ether **76** with *s*-butyllithium and potassium *tert*-butoxide followed by transmetallation with CuBr•SMe_2[36] (Scheme 27) led to *tert*-butylmethyl cuprate **78.**



Scheme 27. Formation of *tert*-butylmethyl cuprate 78.

The (dimethylphenylsilyl)cuprate **79** gave a surprisingly high yield of 84%. Two diastereomers were isolated to give 68% de (entry 3). This cuprate was made from transmetallation of (dimethylphenylsilyl) magnesium bromide with CuBr•DMS (Scheme 28).



12 **79**

Scheme 28. Formation of (dimethylphenylsilyl)cuprate 79.

Table 7. Results of 1,4-adddition of cuprate reagents onto 1-acylpyridinium salt of nicotine.

Entry	R-met	Conditions	Product	Results
1	**75**	1.5 eq of cuprate -78 °C (4 h)	**80**	80% yield 40% de
2	**78**	1.5 eq of cuprate -78 °C (3.5 h), -30 °C (o.n.)	**81**	60% product 40% SM 1 diastereomer
3	**79**	2 eq -78 °C (4 h), -30 °C (o.n.)	**82**	84% yield 68% de

The diastereoselectivity can be explained by coordination of the pyrrolidine nitrogen with the cuprate reagent. Molecular modeling of several pyridinium salts of nicotine-cuprate reagent complexes adding to both faces of the pyridine ring were performed. In the case of the phenylcuprate, attack from the top face, leading to the product with a (*S*, *S*) configuration was found more favorable than attack from the bottom by 0.5 kcal/mol. Also, the distance of approach between C-4 of the pyridine ring and the carbon of the phenyl group attached to the copper was significantly reduced by 1.89 Å in the case of attack from the top (Figure 14).

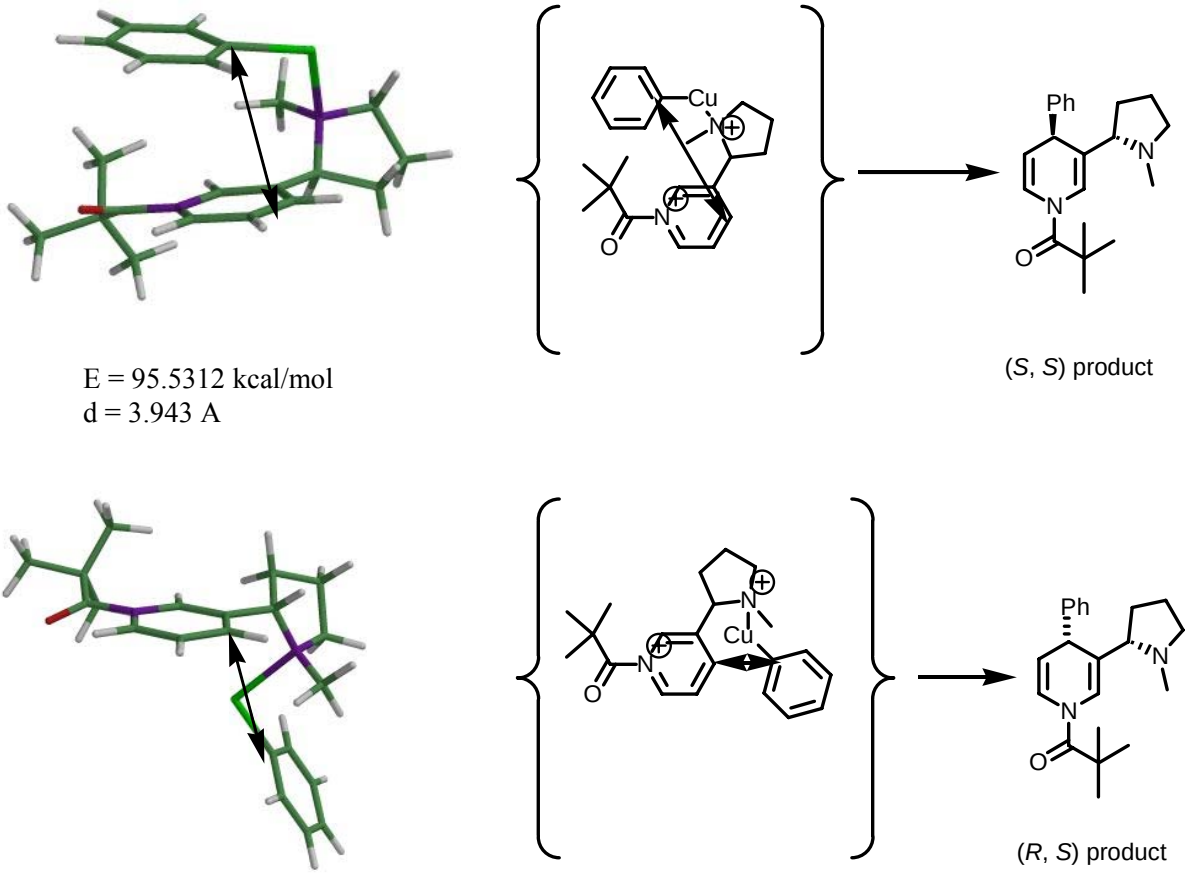


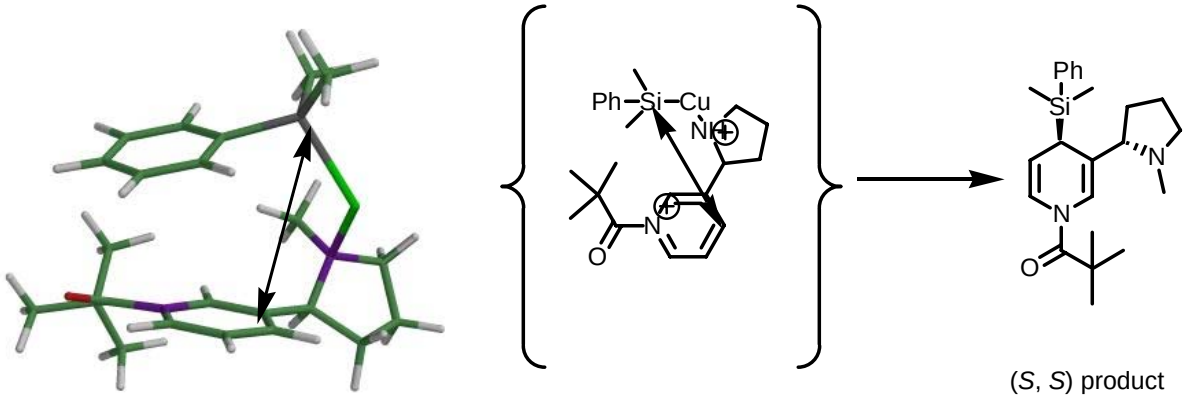
Figure 14. Lowest energy conformation of the nicotine salt-phenylcuprate complex. Molecular modeling performed using Mac Spartan pro. The pivaloyl salt complex was minimized by calculating the conformer distribution of all low-energy conformers using the Molecular Mechanics method. The copper complex was simplified to contain only the copper bonded to the phenyl group for modeling purposes.

The same calculations were performed for the other cuprate reagents.

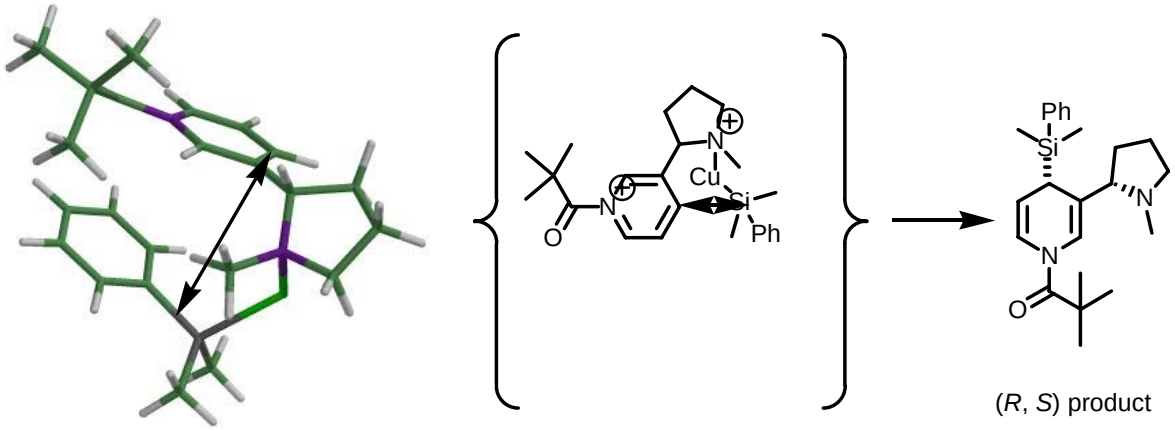
In the case of the silyl Grignard, both modes of attack were very close in energy and distance, justifying the low de obtained (Figure 15).

Similar results were obtained for the benzyloxymethyl cuprate where only 0.0023 kcal/mol and 0.007 Å separate the two modes of attack.

In the case of the *tert*-butoxymethyl cuprate the addition from the top face was found to be favored by 1.76 kcal/mol and by 1.416 Å.



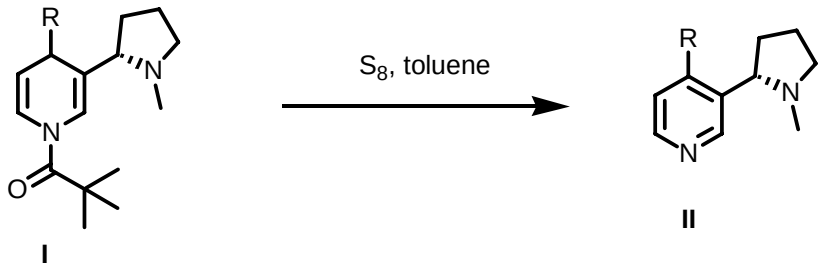
E = 115.7593 kcal/mol
d = 5.026 A



E = 115.7588 kcal/mol
d = 5.025 A

Figure 15. Lowest energy conformation of the nicotine salt- silyl cuprate complex.

In the second step oxidation with sulfur in refluxing toluene[37] provides good yield of 4-substituted nicotines **II** (Scheme 29, Table 8).



I II

Scheme 29. Aromatization of dihydropyridines with hot sulfur.

This reaction is usually slow (1 to 3 days) and requires reflux in toluene except in the case of substrate **82** (entry 8) where a temperature of only 90 °C was needed to get an 80% yield. In the case of substrate **81** addition of activated charcoal was required to provide 68% yield.

Table 8. Results of aromatization of dihydropyridines with hot sulfur.

Entry	Dihydronicotine	Conditions	Product	Yield
1	**70**	reflux (32 h)	**83**	78.5 %
2	**71**	reflux (32 h)	**84**	59 %[34]
3	**72**	reflux (32 h)	**85**	93 %
4	**73**	reflux (32 h)	**86**	64%
6	**80**	reflux (3 d)	**87**	60 %
7	**81**	Pd/C reflux (2 d)	**88**	68 %
8	**82**	90 °C (1.5 day)	**89**	80 %

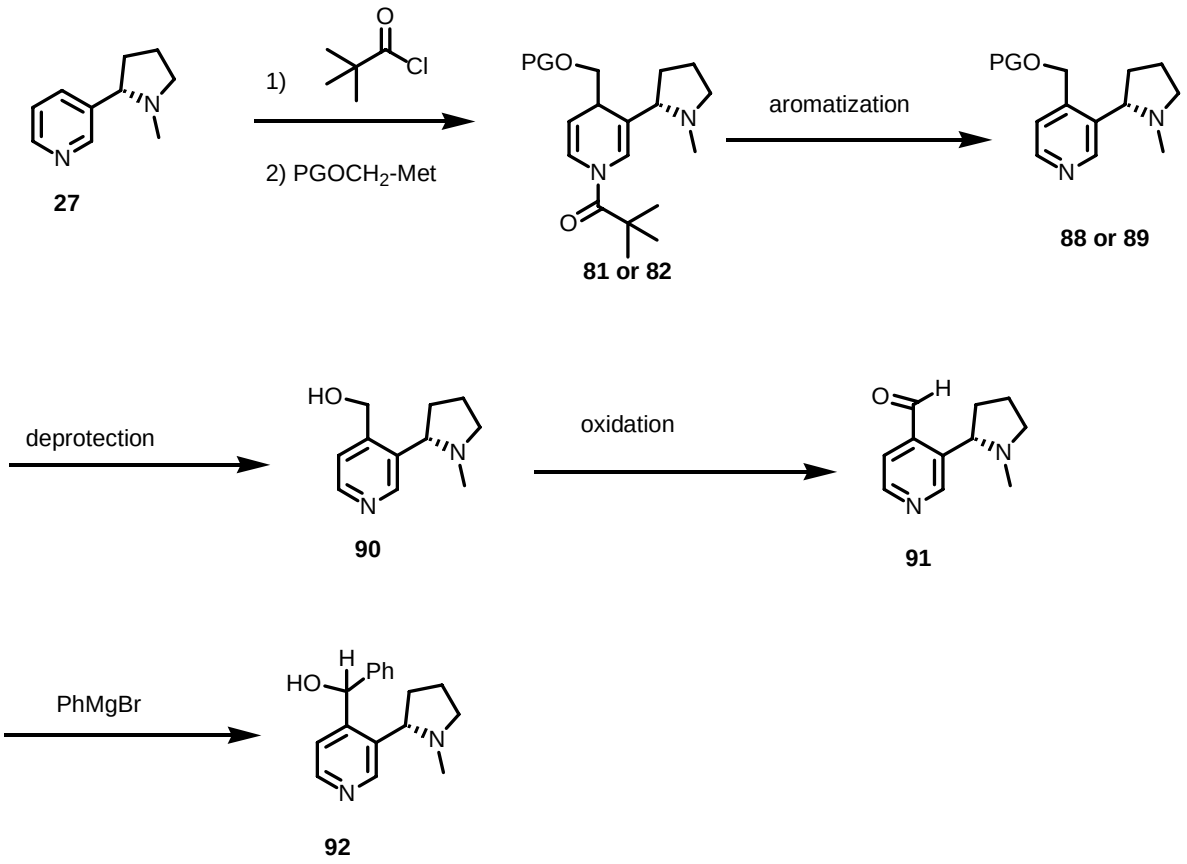
In summary, a two-step sequence was developed to synthesize numerous nicotine derivatives. In the first step, the addition of cuprate reagents onto 1-acyl pyridinium salt of nicotine leads to 1,4-dihydronicotines that can be aromatized using elemental sulfur and refluxing toluene.

B. Synthesis of catalyst.

1. Synthesis scheme

The synthesis of chiral catalyst **92** was next envisioned (Scheme 30). We believed that this molecule would exhibit some catalytic activities in the case of the addition of an alkyl group to benzaldehyde. Recently, nicotine itself has been used as a catalyst in the case of aqueous aldol condensation.[38]

The first step of the synthesis is the addition of a protected methyl alcohol to the pyridinium salt of nicotine to give dihydropyridine **81 or 82**. Aromatization followed by deprotection of the alcohol will lead to 4-(hydroxymethyl) nicotine **90**. Oxidation of this alcohol and addition of a phenyl Grignard will give the target molecule.

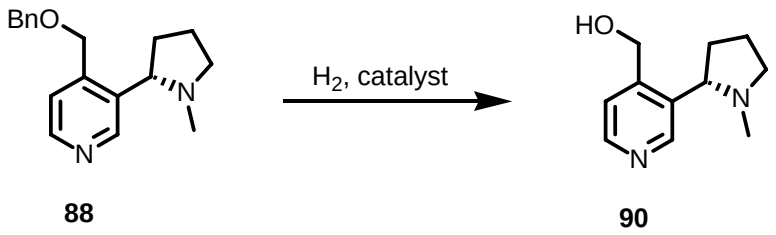


Scheme 30. Synthesis of chiral catalyst 92.

2. Synthesis of 4-hydroxymethylnicotine

4-Hydroxymethylnicotine was previously synthesized by Seeman[39] as a byproduct (5% yield) in the development of a ligand for radioimmunoassay for tobacco alkaloids. Deprotection of the hydroxymethyl group in compounds **81** and **82** would afford 4-hydroxymethylnicotine in a better yield than the previous synthesis.

Various hydrogenolysis conditions were tried to remove the benzyl protecting group in compound **81** (Scheme 31, Table 9). Since Pd/C only gave SM (entry1), Perlman's catalyst was tried but unfortunately the reaction seemed to open the pyrrolidine ring (entry 2). Phase transfer catalysis[40] (entry 3) was also attempted but yielded to the same results as entry 2.

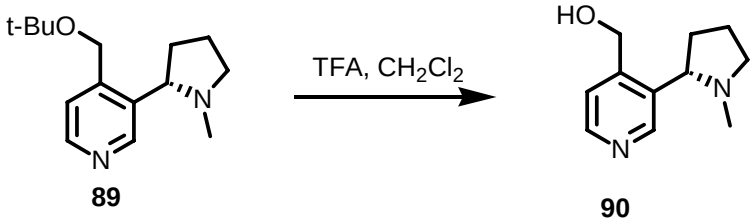


Scheme 31. Deprotection of 88 using hydrogenation.

Table 9. Hydrogenation conditions for deprotection of 88.

Entry	Conditions	Results
1	H_2, Pd/C, EtOH	SM
2	H_2, $Pd(OH)_2$/C, EtOH	Opening of the pyrrolidine ring
3	Cyclohexene, $Pd(OH)_2$/C, EtOH	Opening of the pyrrolidine ring

Removal of the *t*-butyl group (Scheme 32) was achieved by using a mixture of TFA and CH_2Cl_2[41] followed by anhydrous work-up to give 98% of alcohol **90**.



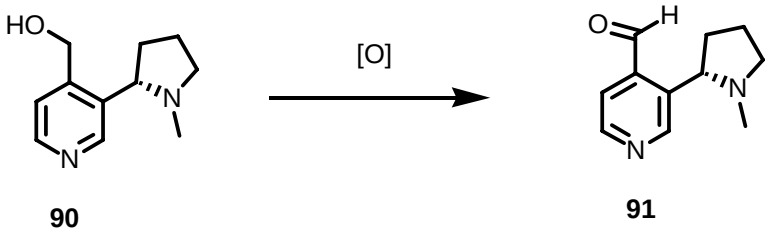
Scheme 32. Deprotection of *t*-butyl group on 89.

Table 10. Conditions for the deprotection of *t*-butyl group.

Entry	Scale (mmol)	TFA (mL)	CH_2Cl_2 (mL)	Conditions	Work up	Results
1	0.1	1	0	0 °C (2 h)	Aqueous	40% 40% SM
2	0.2	2	0	0 °C (o.n.)	Anhydrous	56%
3	1.4	10	15	0 °C (o.n.) 10°C (1 h)	Anhydrous	98%

3. Oxidation of methyl alcohol

The next step of the synthesis is the oxidation of methyl alcohol **90** (Scheme 33, Table 11).



90 **91**

Scheme 33. Oxidation of methyl alcohol 90.

The first oxidizing agent used was MnO_2, which is a classical choice for allylic and benzylic alcohol. After four days at rt the reaction seemed to have proceeded only half way and the mass recovery was low, suggesting some decomposition. Next, the Dess-Martin reagent was investigated but yielded decomposition. Swern oxidation and TPAP/NMO also yielded to decomposition. A paper by Guziek mentioned that ligand exchange seemed to occur at the

nitrogen atom when using DMAP-CrO_3.[42] A recent paper by Krhon described the use of a zirconium catalyst and cumene hydroperoxide for the oxidation of pyridine alcohols.[43] When this system was used at rt, only SM was detected. When the temperature was increased to 60 °C, the reaction proceeded fast (1 h) but the product was impossible to purify: RPLC, bulb to bulb distillation and Florisil column were attempted but all resulted in the decomposition of the aldehyde.

Table 11. Oxidation conditions for methyl alcohol 90.

Entry	Oxidant	Conditions	Results
1	MnO_2	rt (4 days)	1:1 mixture of SM and product (NMR)
2	Dess Martin	rt (2 h)	decomposition
3	TPAP/NMO	rt (4 h)	decomposition
4	Swern		decomposition
5	$Zr(OtBu)_4$, CHP	rt (2 h)	SM
6	$Zr(OtBu)_4$, CHP	60 °C (1 h) Purification: RPLC	crude NMR shows product decomposition after purification
7	$Zr(OtBu)_4$, CHP	60 °C (1 h) Purification: bulb to bulb distillation	crude NMR shows product decomposition after purification
8	$Zr(OtBu)_4$, CHP	60 °C (1 h) Purification: Florisil column	crude NMR shows product decomposition after purification

Since all the conditions tried for oxidizing 4-hydroxymethyl nicotine failed, the synthesis of the catalyst was abandoned.

C. Biological activities.

Preliminary tests were conducted by Dr. Roe's laboratory (NCSU) on the adult yellow fever mosquito. It was found that compounds **83, 87**, **88** and **89** exhibited more

activity than nicotine and a similar activity to malathion, an insecticide being currently used for the control of adult mosquitoes.

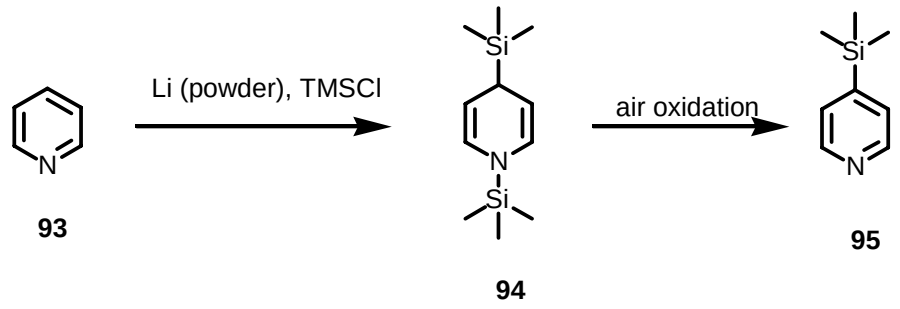
Apparently, a large lipophilic group at C-4 of the nicotinoid increases the insecticidal activity of nicotine, which is the opposite for CNS activity: substituted C-4 nicotine derivatives show less or no activity. These new nicotine derivatives could have a selective activity, meaning they could be developed as insecticides having reduced mammalian toxicity. More compounds need to be tested to determine a more detailed SAR.

Since compound **89** displayed the highest activity, we turned our attention to the synthesis of other 4-silylnicotines.

VI. Synthesis of Nicotine Derivatives via Reductive disilylation of nicotine

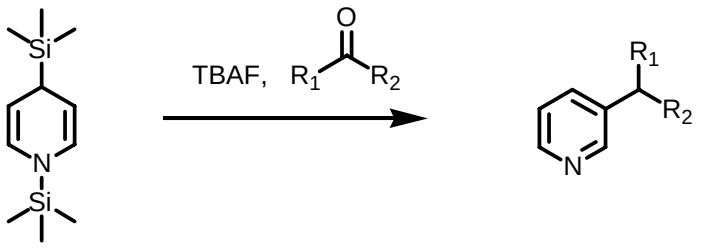
A. Review of the literature.

In 1970, Sulzbach discovered the reductive disilylation of pyridine with alkali metals and trimethylsilyl chloride[44] (Scheme 34). 1, 4- Bis(trimethylsilyl)-1, 4- dihydropyridine (**94**) was isolated with a 34% yield and was found to be extremely air sensitive; oxidation started once exposed to air and yielded to 4-(trimethylsilyl) pyridine (**95**).



Scheme 34. Reductive disilylation of pyridine with Li and TMSCl.

In 1984, Tsuge[45] reinvestigated this reaction and the reactivity of 1,4-dihydropyridine **94** with aldehydes and ketones in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF). A variety of 3-alkylpyridines **96** were prepared using that procedure (Scheme 35).

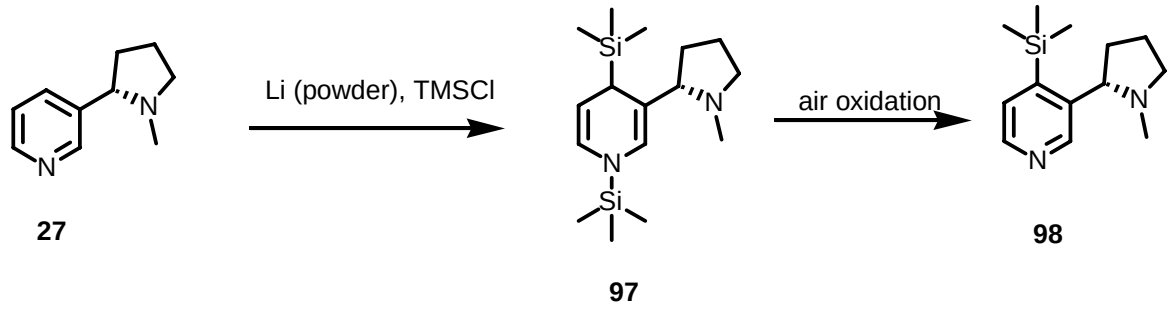


94 **96**

Scheme 35. Fluoride catalyzed reaction of 1,4-bis(trimethylsilyl)-1,4-dihydropyridine (94) with aldehydes and ketones.

B. Reductive disilylation of nicotine.

Interested by this reaction, we decided to study the reductive disilylation of nicotine (Scheme 36). The results are presented in Table 12. Initially, the reaction conditions described by Tsuge were used, only 4-trimethylsilylnicotine (**98**) was isolated (entry 1). With a careful distillation under argon, the desired product **97** was isolated with a 58% yield with a purity of 95% (determined by NMR) (entry 3). We discovered that the yield could be improved to 95% when the reaction was warmed to rt and a high vacuum (0.1 mm Hg) was used to distill the product (entry 4). No racemization seemed to occur as 4-trimethylsilyl nicotine (**98**) exhibited a high rotation $\{[\alpha]^{25}_{D}$ -124.1 (CH_2Cl_2, c 4.9)$\}$.



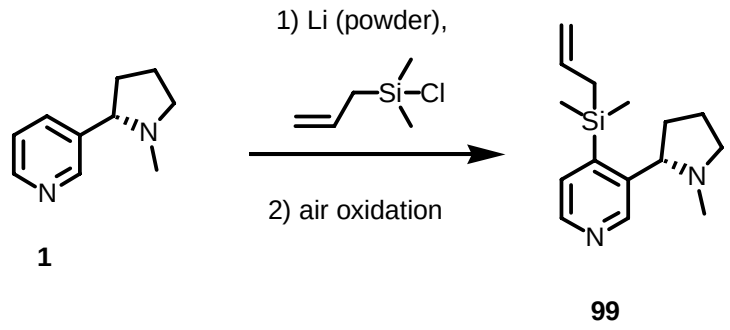
27 **97** **98**

Scheme 36. Reductive disilylation of nicotine.

Table 12. Results of reductive disilylation of nicotine.

Entry	**Scale (mmol)**	**Conditions**	**Results**
1	10	0 °C (1 h)	isolation of **98**
2	20	0 °C (3 h)	53% of **97**, **98** and SM
3	20	0 °C (1 h) distillation under Ar	58% of **97** (95% pure)
4	20	0 °C (1 h), rt (3 h) reaction and distillation under Ar (high vacuum)	95% of **97** (95% pure)

We then investigated the same reaction with allyldimethylchloro silane instead of TMSCl. After air oxidation, 4-(allyldimethylsilyl)nicotine (**99)** was obtained in 58% yield (Scheme 37).



1 **99**

Scheme 37. Synthesis of 4-allyldimethylsilylnicotine.

C. Reactivity of dihydronicotine **97** with various carbonyl compounds.

Several reactions were investigated on 1,4-bis(trimethylsilyl)-1,4-dihydronicotine **97** (Scheme 40)**.**

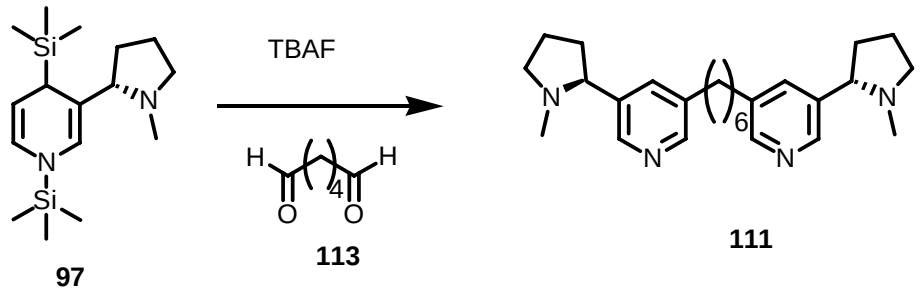
First, the fluoride catalyzed reaction of **97** with aldehydes was attempted (Scheme 40, reaction a). The reaction conditions described by Tsuge were applied to the 1,4-bis (trimethylsilyl)-1,4-dihydronicotine (**97**) with several aldehydes (Table 13). We found that a higher temperature was required to ensure reaction completion. Reaction with benzaldehyde yielded to 56% of 5–benzylnicotine (**100**) (entry 2). 2- Thiophenylcarboxaldehyde and 2-furaldehyde reacted in a similar manner, yielding 67% and 47% respectively of the corresponding 5-nicotine derivatives (entries 3 and 4).

Reflux temperature was needed in the case of dodecyl aldehyde to yield 70% of 5-dodecylnicotine **103** (entry 5).

Table 13. Conditions for the fluoride catalyzed reaction of 97 with various aldehydes.

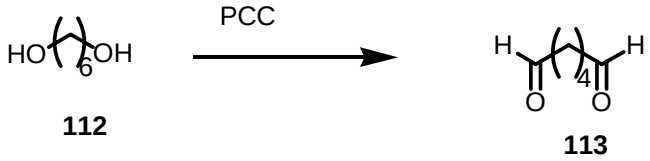
Entry	Aldehyde	Conditions	Results
1	benzaldehyde	rt (1 day)	31% **100**
2	benzaldehyde	50 °C (1 day)	56% **100**
3	2-thiophenecarboxaldehyde	50 °C (1 day)	67% **101**
4	2-furaldehyde	50 °C (1 day)	47% **102**
5	dodecyl aldehyde	reflux (1 day)	70% **103**

The success of this reaction allowed us to foresee the reactivity of dihydropyridine with a dialdehyde in order to synthesize a dimer (Scheme 38).



Scheme 38. Synthesis of dimer 111.

Oxidation of 1,6-hexanediol with PCC afforded 1,4 hexanedial in 61% yield (Scheme 39).[46]

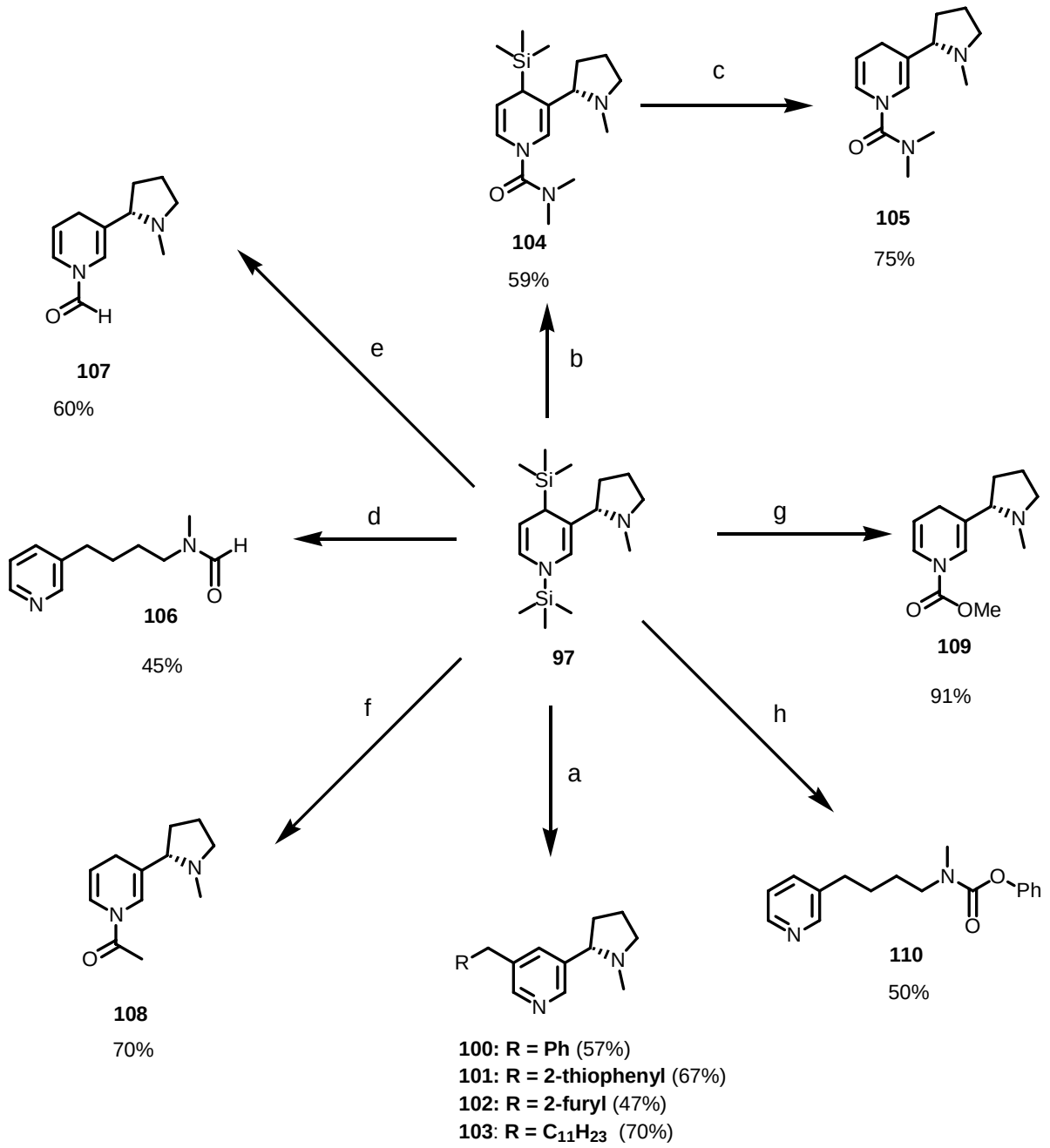


Scheme 39. Synthesis of hexanedial (113).

The reaction of dihydronicotine **97** and hexanedial required reflux for 15 h to give 51% of the desired dimer **111** (Table 14, entry 3).

Table 14. Fluoride catalyzed reaction of 97 with hexanedial.

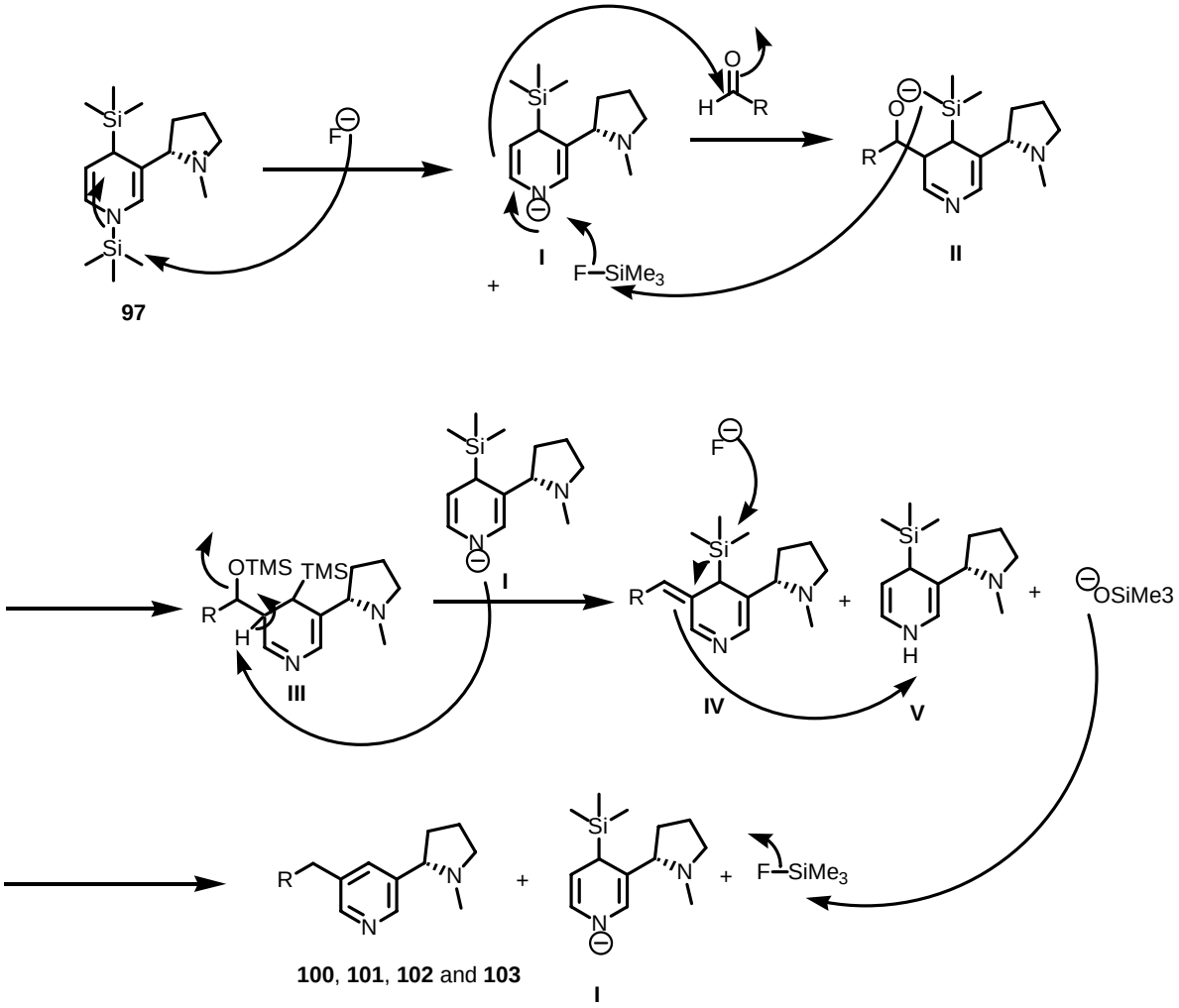
Entry	**Scale (mmol)**	**Conditions**	**Results**
1	5.6	70 ºC (18 h)	12% **111**
2	1.13	Reflux (1 d)	48% **111**
3	8	Reflux (15 h)	51% **111**



Scheme 40. Reactivity of 1, 4-bis(trimethylsilyl)-1, 4-dihydronicotine (97) with various carbonyl reagents.

Reaction conditions: a) RCOH, TBAF (10 mmol %), THF; b) dimethylcarmabyl chloride, CH_2Cl_2; c) TBAF, THF; d) trifluoroethyl formate, TBAF (10 mmol %), THF; e) ethyl formate, TBAF (10 mmol %), THF; f) trifluoroethyl acetate, TBAF (10 mmol %), THF; g) methyl carbonate, TBAF (10 mmol %), THF; h) phenyl carbonate, TBAF (10 mmol %), THF.

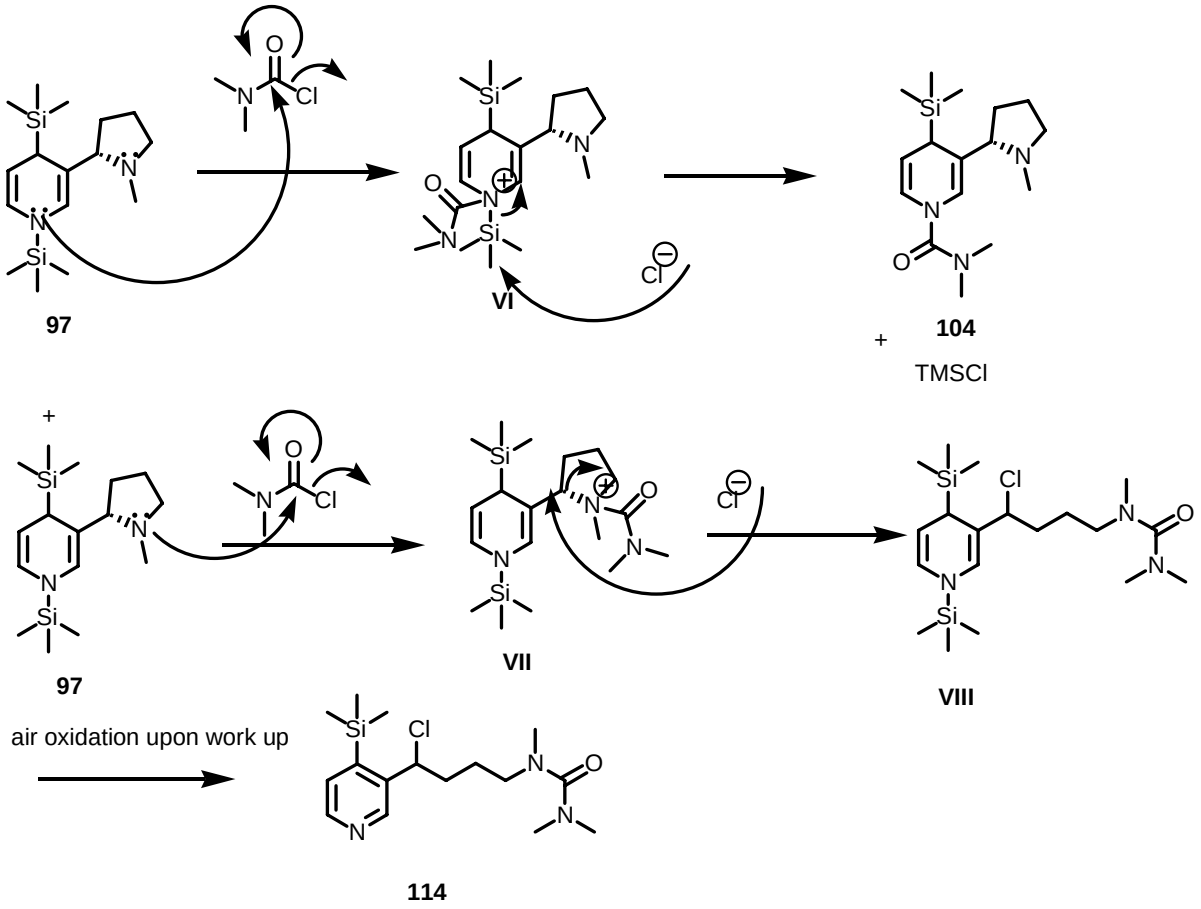
One possible mechanism for the formation of C-5 substituted nicotines is proposed in Scheme 41. Due to the lability of the N-Si bond, the TMS group located at N-1 is removed by fluoride to give amide ion **I**. Attack of the aldehyde at C-5 leads to intermediate **II**. The intermediated alkoxide reacts with fluorotrimethylsilane to regenerate fluoride and to give intermediate **III**. Amide ion **I** acts as a base to remove the proton located at C-5, leading to the elimination of trimethylsilyl alkoxide. Removal of the TMS group located at C-4, followed by aromatization and protonation of the external double bond affords the expected product and regenerates both the fluorine and amide ion **I**.



Scheme 41. Proposed mechanism for the addition of aldehydes to 97.

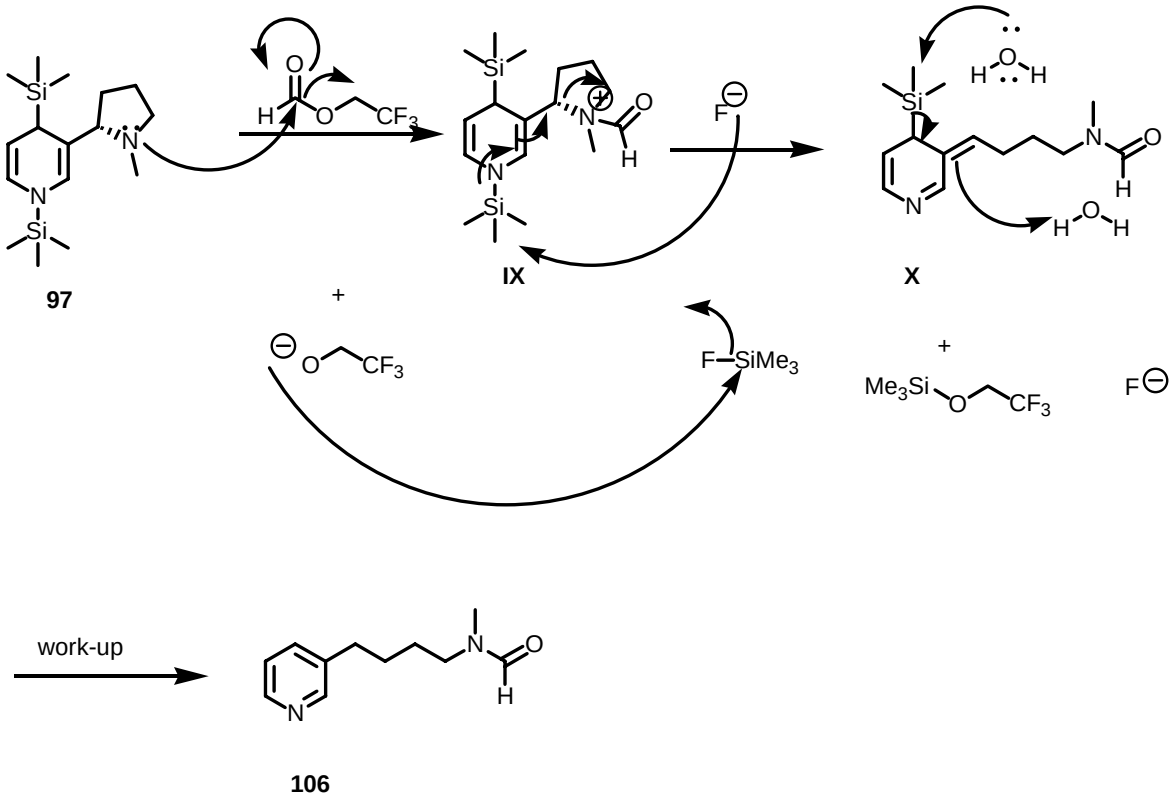
We next attempted the carbamylation at the nitrogen of the pyridine ring (Scheme 40, reaction b). Reaction of 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (**97**) with dimethyl carbamyl chloride in methylene chloride yielded 59% of the desired dihydronicotine. The reaction proceeded very slowly (1 day at rt is required), increasing the temperature resulted in decomposition. The byproduct of the reaction was found to be the pyrrolidine ring-opened product **114**. The formation of the byproduct can be explained by a competing reaction at N-1′ (Scheme 42): attack of the carbamyl chloride occurs at both N-1 and N-1′ giving ammonium salts **VI** and **VII** respectively with **VI** being the major product. Chloride can attack the TMS group located at N-1 yielding the expected product **104**. It can also attacks at C-2′ to give pyrrolidine opened product **VIII** that can be oxidized upon work up to product **114**. Although detected in the crude NMR spectrum this product was never isolated.

Removal of the TMS group located on C-4 was achieved with a stoichiometric amount of TBAF with a 75% yield to give 1, 4-dihydronicotine **105** (Scheme 40, reaction c).



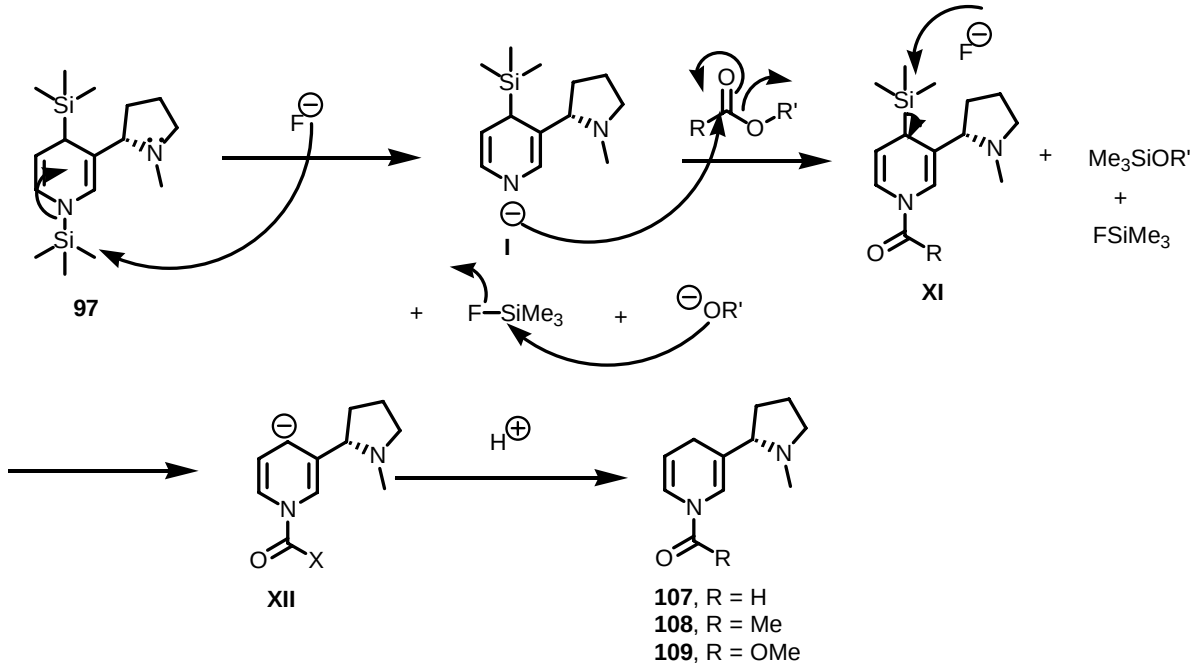
Scheme 42. Proposed mechanism for the carbamylation of 97.

Encouraged by these results, we decided to expand the versatility of the fluoride catalyzed reaction of 1,4-dihydronicotine **97** by diversifying the carbonyl reagents used. Trifluoroethyl formate gave the pyrrolidine opened product **106** with a 45% yield (Scheme 40, reaction d). A possible mechanism for this reaction is proposed in the scheme below (Scheme 43). First formylation at the nitrogen of the pyrrolidine occurs. Then removal of the TMS group located on N-1 by fluoride followed by opening of the pyrrolidine ring give intermediate **X**. Removal of the second TMS group located at C-4 during the work-up followed by aromatization affords product.



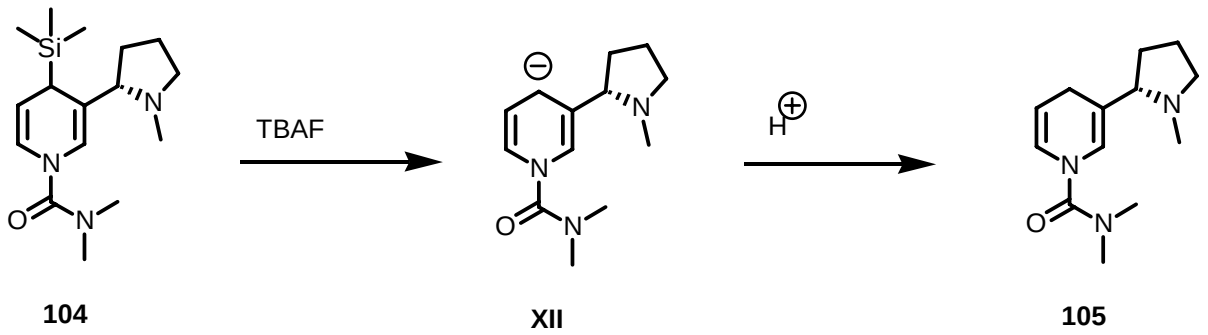
Scheme 43. Possible mechanism for the formation of pyrrolidine ring opened product.

When less reactive reagents were used such as ethyl formate (Scheme 40, reaction e), trifluoroethyl acetate (Scheme 40, reaction f) and methyl carbonate (Scheme 40, reaction g), exclusive substitution at N-1 occurred to give 1,4-dihydronicotines **107, 108** and **109** in 60, 70 and 91% yield respectively. To the best of our knowledge, this is the first example of a synthesis of 4-unsubstitued 1,4-dihydronicotines. No ring-opened product was detected. A possible mechanism is proposed below (Scheme 44). First, removal of the TMS group at N-1 affords anion **I** that attacks the acylating agent. We believe that first step is repeated until the acylating agent has completely reacted, producing a stoichiometric amount of fluoride. Then removal of the second TMS group followed by protonation during the work-up of the formed anion **XIII** yields the product.



Scheme 44. Possible mechanism for the formation of 1,4-dihydronicotines.

Reaction of dihydronicotine **104** with TBAF indicates the existence of intermediate **XII** (Scheme 45). A dark color is observed when TBAF is added to the SM. Also, that step failed when a catalytic amount of TBAF was used, proving that the removal of the TMS group located at C-4 requires a stoichiometric amount of TBAF.

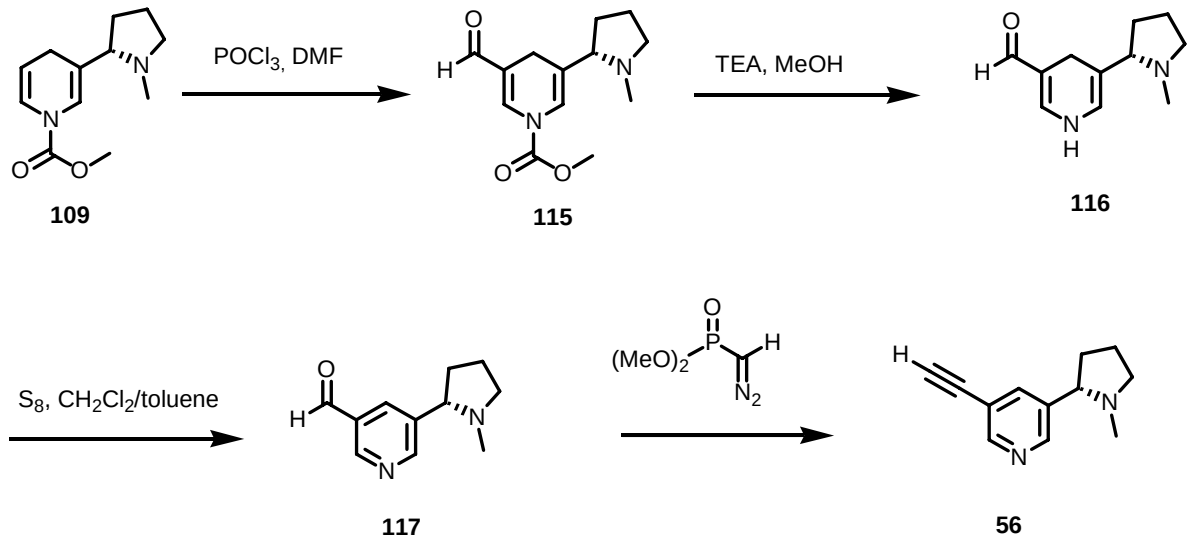


Scheme 45. Mechanism for the removal of TMS group of 104.

We were surprised to discover that phenyl carbonate yielded the pyrrolidine opened product. The difference in nucleophilicity between N-1 and N-1′ accounts for these results. In the absence of TBAF, only more reactive reagents such as trifluoroethyl formate and phenyl carbonate react at N-1′, leading to the ring-opened product. Once TBAF is added, the formation of amide ion **I** (pKa = 36) causes N-1 to be more basic than N-1′ (pKa = 8.05) therefore more nucleophile than N-1′.

D. Synthesis of SIB-1508Y.

With dihydronicotine **109** in hand, we next attempted the synthesis of SIB-1508Y (Scheme 46). Formylation of **109** using the Vilsmeir-Hack reagent was achieved in 55% yield. Removal of the methyl carbamate with triethylamine in methanol resulted in a quantitative yield of the vinylogous amide **116** that was then aromatized with a stoichiometric amount of elemental sulfur in refluxing CH_2Cl_2/toluene mixture (1:1) in a 83% yield. In the last step, conversion of pyridine carboxaldehyde **117** to acetylene was achieved using the Gilbert-Seyferth reagent[47] to yield 51% of SIB-1508Y. The overall yield of the synthesis was found to be 20%, which is comparable to the previous synthesis but no resolution was required in this case.



Scheme 46. Synthesis of SIB -1508Y.

In summary, the reductive disilylation of nicotine proved to be very fruitful: 1,4-bis(trimethylsilyl)-1,4-dihydronicotine **97** was found to be a valuable intermediate for the synthesis of novel nicotine derivatives. Both C-5 substituted nicotine analogues and 4-unsubstituted 1,4-dihydronicotines as well as 4-silyl nicotines were obtained. That novel chemistry allowed us to synthesize SIB-1508Y in a comparable yield as the one described earlier with the omission of the resolution steps.

E. Biological activity.

These new nicotinoids were tested for both insecticidal and CNS activity (by Targacept). Interestingly, substitution at C-5 proved to be less efficient than the substitution at C-4 for insecticidal activity as compounds **100**-**102** were less potent than **88** and **89**.

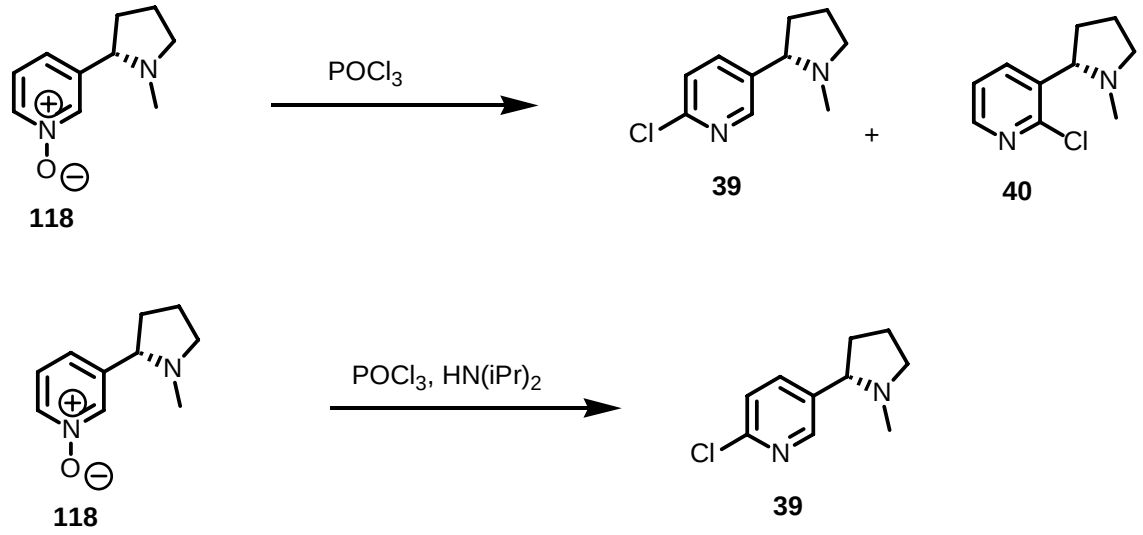
Also, the 4-unsubstituted-1,4-dihydronicotines displayed some CNS activity, especially compounds **107** and **109**. It is worth noting that these dihydronicotines did not show any insecticidal activity. Once again, those new compounds seem to have selective activity.

We then turned our attention to the effect of the substitution at C-6.

VII. Substitution at C-6

A. Via the *N*-oxide.

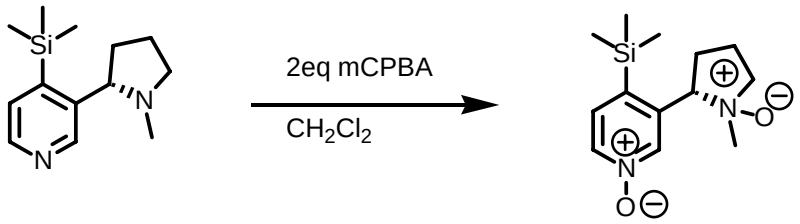
Nicotine *N*-oxide was recently treated with 10 equivalents of phosphorus oxychloride to give a mixture of 2-chloro and 6-chloro nicotines in low yield.[48] Addition of 3.4 equivalents of diisopropylamine eliminated the formation of the 2-chloronicotine, yielding 38% of 6-chloronicotine (Scheme 47).



Scheme 47. Chlorination of nicotine *N*-oxide with $POCl_3$ and with a mixture of $POCl_3$ and diisopropylamine.

We decided to investigate the introduction of chlorine at C-6 via mono *N*-oxide of C-4 substituted nicotine.

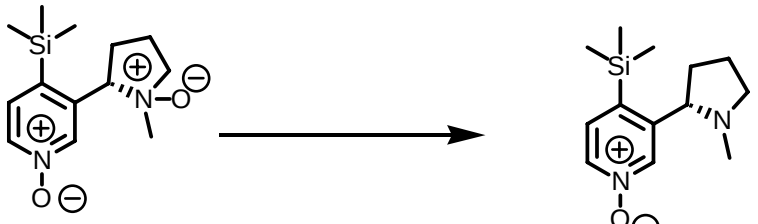
Bis-*N*-oxidation of 4-(trimethylsilyl)nicotine **34** was achieved in a quantitative yield by using 2 equivalents of mCPBA (Scheme 48).



98 **119**

Scheme 48. *N*-Oxidation of 4-(trimethylsilyl)nicotine 98.

Cleavage of the *N*′-oxide located on the pyrrolidine ring was surprisingly challenging (Scheme 49, Table 15). Carbon disulfide[49] was unsuccessful as it yielded a mixture of SM and 4-TMS nicotine resulting from the cleavage of both *N*- and *N*′- oxides (entry 1). Sodium bisulfite in acetic acid and water only gave cleavage of both *N*-oxides, yielding to 4-TMS-nicotine (entry 2). Replacing water by methanol allowed some product formation (entry 3 and 4). Finally when only one equivalent of the reagent was employed in methanol a quantitative yield of mono *N*-oxide was obtained after stirring for 1 h at 0 ºC (entry 6).



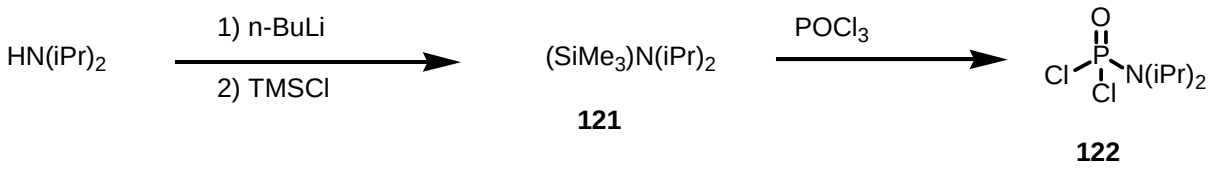
119 **120**

Scheme 49. Cleavage of *N*-1′-oxide of 119.

Table 15. Cleavage of *N*-1′-oxide of 119.

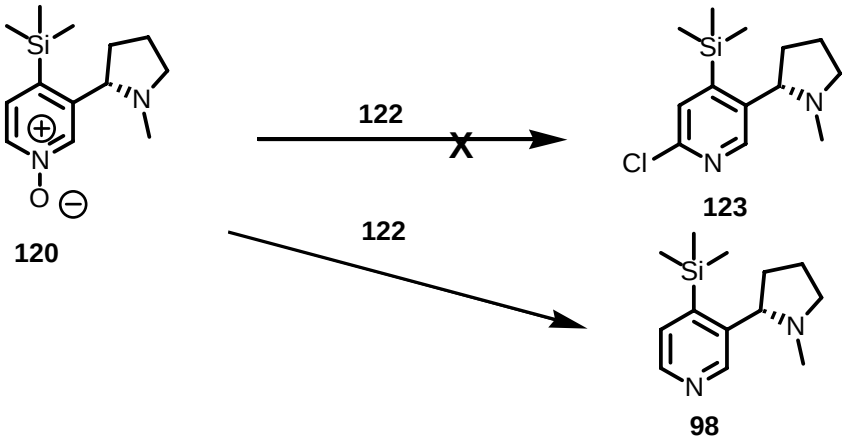
Entry	Scale (mmol)	Reagents	Conditions	Results
1	1	CS_2	rt (o.n.)	48% SM 20% **98**
2	0.053	$NaHSO_3$ (2 eq), HOAc (2.5 eq), H_2O	0 °C (0.5 h)	Mostly **98**
3	0.75	$NaHSO_3$ (2 eq), HOAc (2.5 eq), MeOH	0 °C (1 h)	34% **120**
4	0.86	$NaHSO_3$(1.6 eq), HOAc (2.5 eq), MeOH	0 °C (0.5 h)	72% **120**
5	1.71	$NaHSO_3$ (1 eq), MeOH	0 °C (0.5 h)	34% **120** 42% SM
6	0.57	$NaHSO_3$ (1 eq), MeOH	0 °C (1 h)	99% **120**

Following the procedure described by Schmidt and Neitmeir, we attempted the chlorination of the mono *N*-oxide. However, those conditions proved to be unsuccessful as either nicotine or 4-TMS nicotine was recovered. We decided to synthesize a different chlorinating agent from TMS-diisopropylamine and phosphorus oxychloride (Scheme 50).



Scheme 50. Synthesis of chlorinating agent 122.

Unfortunately, this reagent only resulted in the cleavage of the N-oxide, affording 4-TMS nicotine (Scheme 51).



Scheme 51. Reaction of *N*-oxide with chlorinating agent 122.

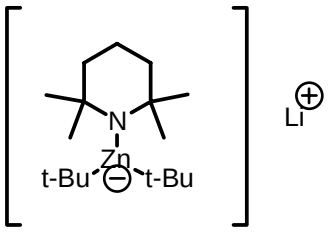
Finally, tetramethylphosphoamidic chloride was also tested but gave the same results.

We then turned our attention to the selective deprotonation of nicotine at C-6.

B. Via deprotonation.

1. Use of TMP-Zincate.

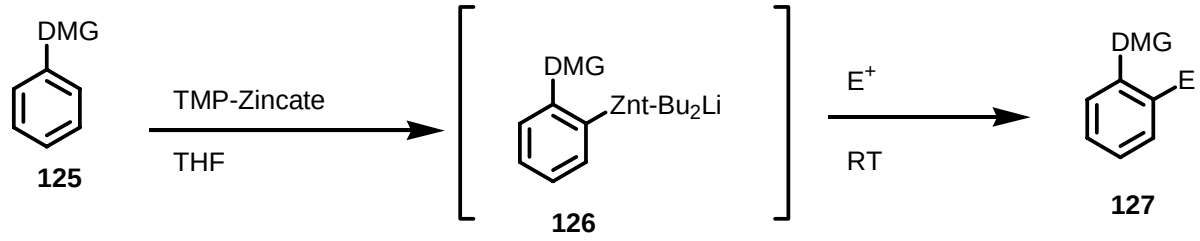
Recently, Kondo et al. reported the use of trialkylzincates as chemoselective metalating reagents for the halogen-metal exchange reaction of aryl halides with electrophilic functional groups.[50] They also developed a new chemoselective metalating reagent prepared from di-*tert*-butylzinc and LiTMP or TMP-Zincate (Figure 16).[51]



124

Figure 16. Structure of TMP-Zincate.

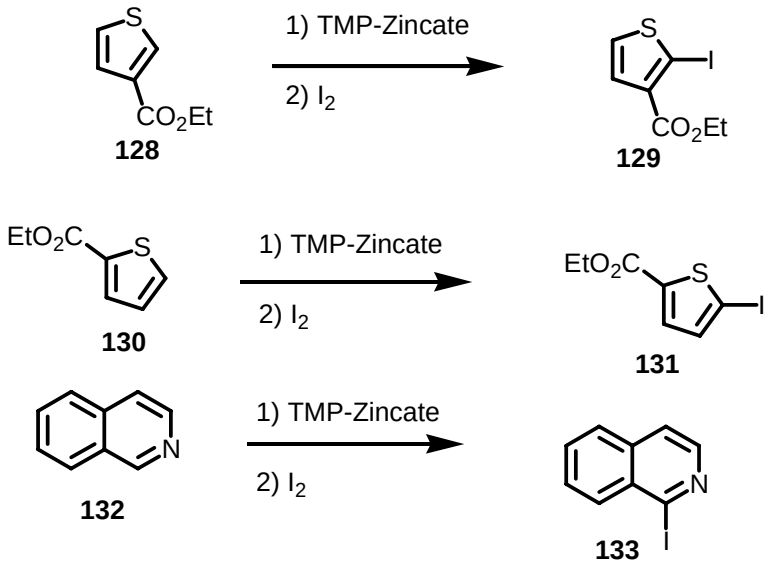
They observed highly selective deprotonation of functionalized aromatic and heteroaromatic compounds (Scheme 52).



125 **126** **127**

Scheme 52. Deprotonation of aromatic compounds with TMP-Zincate.

When treated with TMP-Zincate and I_2, ethyl-3-thiophenecarboxylate yielded exclusively the 2-iodo derivative. Attack at the carbon α to the heteroatom was also observed in the case of ethyl 2-thiophene carboxylate and quinoline (Scheme 53).



Scheme 53. Deprotonation of various heterocycles with TMP-Zincate.

We decided to investigate the reactivity of TMP-Zincate on nicotine. We anticipated the zincation to occur mainly at C-2 due to the possible complexation of Li to both the pyrrolidine and the pyridine nitrogen. Zincation at C-6 would yield only 1 intermediate with complexation at pyridine nitrogen (Figure 17).

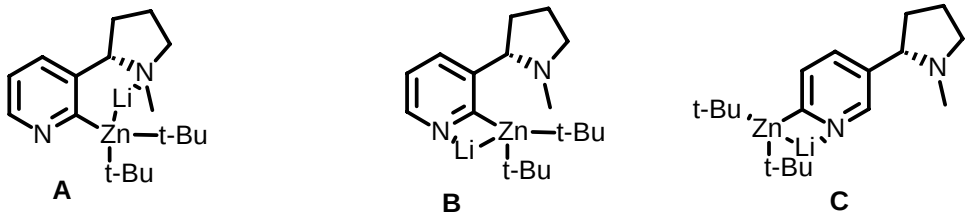
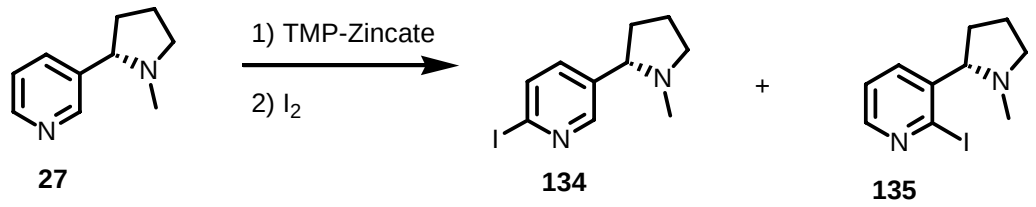


Figure 17. Two possible intermediates for zincation at C-6 of nicotine (A and B) and one intermediate for zincation at C-2 (C).

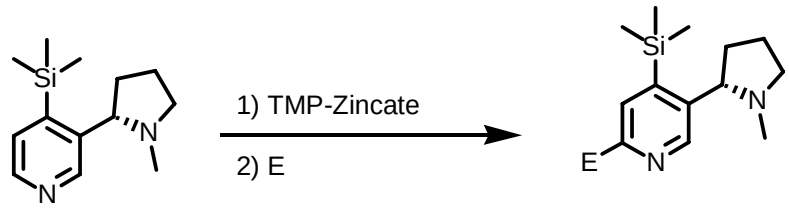
Earlier results[52] showed that when treated with nicotine, TMP-Zincate gave low yield of a product mixture with 6-iodo nicotine being the major product (Scheme 54).



27 **134** **135**

Scheme 54. Deprotonation of nicotine with TMP-Zincate.

The bulkiness of the base probably renders the zincation at C-2 more difficult. In the case of 4-substituted nicotines, only one product was isolated resulting from deprotonation at C-6 (Scheme 55, Table 16). Of the several electrophiles tested, only iodine gave a low yield of product (entry 6). Bromine caused pyrrolidine ring opening (entry 1 and 3) and NCS gave traces of product (entry 2).



120

136, E=Br
123, E=Cl
137, E=I

Scheme 55. Deprotonation of 4-silylnicotine with TMP-Zincate.

Table 16. Conditions for the fonctionalization at C-6 using TMP-Zincate.

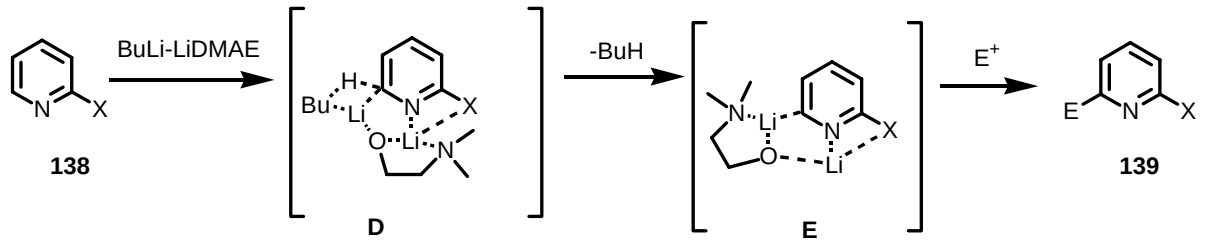
Entry	E^+	Scale (mmol)	TMP-Zincate (eq)	$[ZnCl_2]$	Reaction time	Results
1	Br_2	1.43	1.1	0.5 M	exothermic reaction: cool to 0°C (1 h) then rt (1 h)	Crude NMR shows new aromatic region and ring-opened product
2	NCS	1.7	1.1	0.5 M	add at 0°C then rt (o.n.)	Mostly SM, traces of **123**
3	Br_2	1.01	1.1	2 M	0°C (3 h)	Mostly ring-opened product
4	I_2	0.5	1.1	2.4 M	add at 0°C then rt (15 h)	SM
5	I_2	0.88	1.1	1 M	0°C (3 h) rt (12 h)	SM
6	I_2	1.75	2.2	0.5 M	0°C (1 h)	15% **137** 50% SM

Because of the low yield, we decided to turn our attention to the use of a new base.

2. Use of BuLi-LiDMAE.

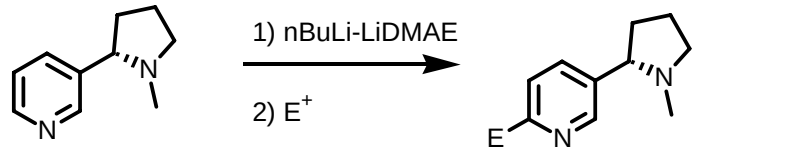
a) Deprotonation at C-6

Recently Fort and Gros developed a new unimetal superbase composed of *n*-BuLi and lithium dimethylaminoethoxide or BuLi-LiDMAE[53] for the selective α-lithiation of pyridine derivatives in apolar solvents (hexanes or toluene). The regioselectivity is due to the formation of aggregates between BuLi-LiDMAE and substrates via lithium chelation of pyridine nitrogen and heteroatom at C-2 (Scheme 56).



Scheme 56. Mechanism for the deprotonation of pyridines with BuLi-LiDMAE.

When nicotine was treated with that superbase, exclusive deprotonation at C-6 occurred in moderate to high yields (Scheme 57).[52]



134, E = I, 55%
39, E = Cl, 77%
140, E = Br, 27%
141, E = $SiPh(Me)_2$, 92%

Scheme 57. Deprotonation of nicotine with BuLi-LiDMAE.

This regioselectivity can be explained by steric hindrance that would be created by attack at the base at C-2 (Figure 18).

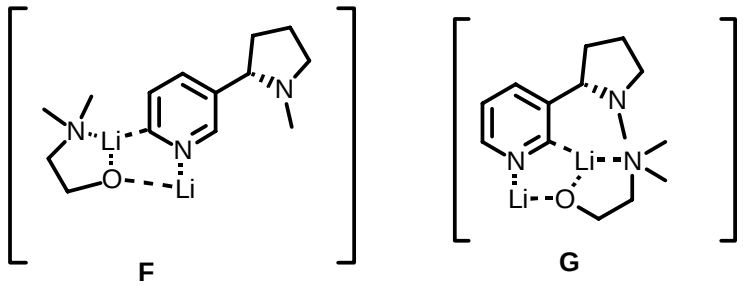
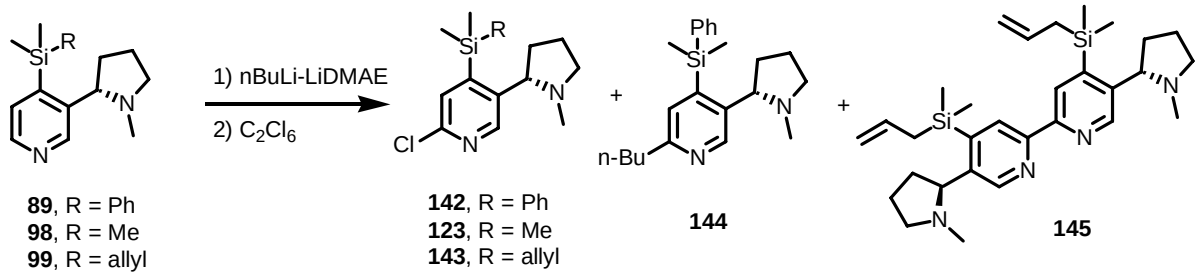


Figure 18. Intermediates resulting from deprotonation at C-2 (F) and C-6 (G) with BuLi-LiDMAE.

Encouraged by those results, we then tried the deprotonation of C-4 substituted nicotine derivatives.



89, R = Ph
98, R = Me
99, R = allyl

142, R = Ph
123, R = Me
143, R = allyl

144

145

Scheme 58. Deprotonation of various 4-silylnicotines with BuLi-LiDMAE.

Table 17. Deprotonation of silyl nicotines with BuLi-LiDMAE.

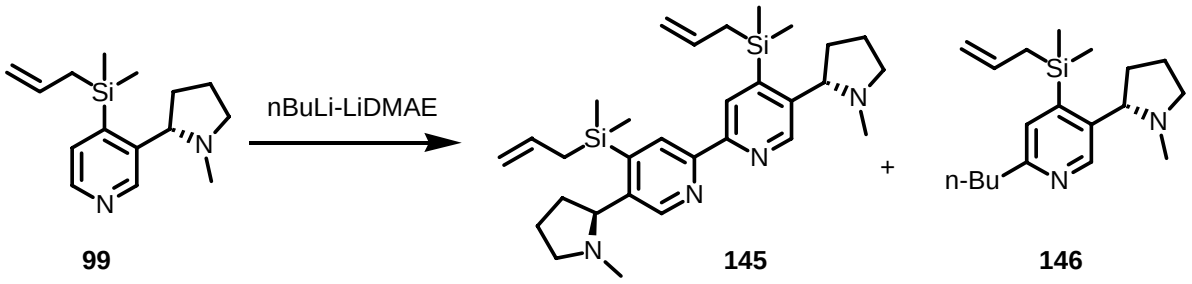
Entry	Substrate	Conditions	Results
1	**98**	First step: 0 ºC (1.5 h) Second step: -78 ºC (1 h)	53% **123**
2	**89**	First step: 0 ºC (1.5 h) Second step: -78 ºC (1.5 h)	21% **142** 26% **144**
3	**89**	First step:-20 ºC (1.5 h) Second step: -78 ºC (2 h)	43% **142** 11% **144**
4	**99**	First step:-20 ºC (45 min) Second step: -78 ºC (1 h)	6% **143** ,20% **145** and 20% SM
5	**99**	First step:-30 ºC (2.5 h) Second step: -78 ºC (3 h)	56% **143**

In the case of 4-TMS nicotine **98**, only the desired product was observed in 53% yield. When the same conditions were employed, 4-dimethylphenylsilyl nicotine **89** yielded 21% of

desired product **142** and 26% of byproduct **144**, resulting from the nucleophilic attack of butyl at C-6. When the temperature of the deprotonation step was lowered to -20 ºC, 43% of desired product was observed with 11% of byproduct **144**. Those conditions were applied to 4-allyldimethylsilyl nicotine **99** and to our surprise only 6% of desired product **143** was obtained, along with 20% of dimer **145**. Dimerization occurs from nucleophilic attack of C-6 lithiated nicotine on SM. Lowering the temperature of deprotonation to -30 ºC avoided dimerization and resulted in 56% of desired product **143**.

b) Dimer formation

We then tried to capitalize on dimer formation which could provide valuable potent targets (Scheme 59, Table 18).



99 **145** **146**

Scheme 59. Synthesis of dimer 145.

Deprotonation of SM with 3 equivalents of base, followed by addition of only one equivalent of hexachloroethane afforded 26% of the 6-chloro product **143** and 12% of the 6-butyl byproduct **146** (entry 1). Lowering the amount of base and suppressing dichloroethane to avoid competition between electrophiles only recovered SM (entry 2). Finally, deprotonation of half the SM using the usual conditions followed by addition of the other half afforded the desired dimer in 41% yield (entry 3).

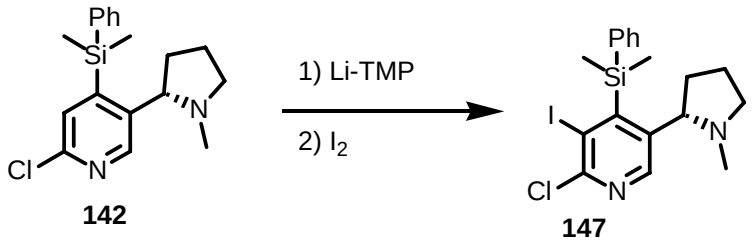
Table 18. Formation of dimer 145.

Entry	Scale (mmol)	Conditions	Results
1	0.88	3 eq base, -20 ºC (1 h) 1 eq C_2Cl_6, -20 ºC (2 h)	26% **143**, 12% **146**, 11% SM
2	0.55	1.5 eq base, -20 ºC (overnight)	SM
3	0.56	Deprotonate half the material: -30 ºC (2.5 h) then add other half of SM: -78 ºC → -20 ºC (overnight)	41% **146**, 55% SM

c) Deprotonation at C-5

We next investigated the ortho directing effect of the chlorine located at C-6 to introduce substituents at C-5. In a previous study, LiTMP was found to be the best base to deprotonate at C-5.

When **142** was submitted to those conditions, 32% of 5-iodo product **147** was isolated (Scheme 60). HMQC and HMBC experiments confirmed the location of the iodine on the pyridine ring.



142 **147**

Scheme 60. Deprotonation at C-5 with Li-TPM.

Bigger electrophiles, such as ethyl formate or trifluoroethyl formate resulted in no reaction, probably due to the steric hindrance caused by the silyl group at C-4.

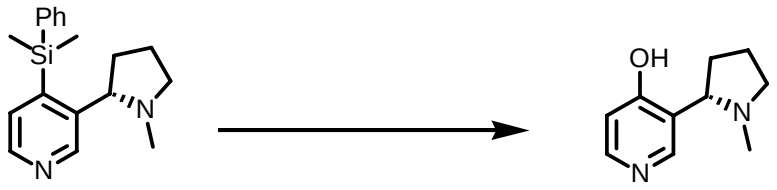
3. Biological activity**.**

Adding a substituent at C-6 did not change the potency of the compounds, since compounds **142** and **144** showed the same insecticidal activity as **89**. Dimer **146** has yet not been tested.

VIII. Formation and reactivity of 4-hydroxynicotines.

A. Formation of 4-hydroxynicotines.

Dimethylphenylsilyl groups have been used as a masked hydroxyl group.[54] They can easily be oxidized and converted to an hydroxyl group by using the Tamao's procedure (mCPBA or H_2O_2).[55] However, only one example of hydroxylation of an aromatic silane has been published.[56] No example of hydroxylation of heterocyclic silane has yet been reported. We tried to convert 4-(dimethylphenylsilyl)nicotine (**89**) to the 4-hydroxynicotine (**148**) **(**Scheme 61**,** Table 19**)**. First we tried a modification of the Tamao's conditions and were able to isolate 30% of product (entry 1). Then we were pleased to find that the conditions used for the aromatic silanes gave a high yield of **148**. The temperature had to be increased to 55 °C (entry 3 and 4) and the work up had to be modified: this compound was found to be highly water soluble so an anhydrous work up was necessary to obtain good yields (entry 4).



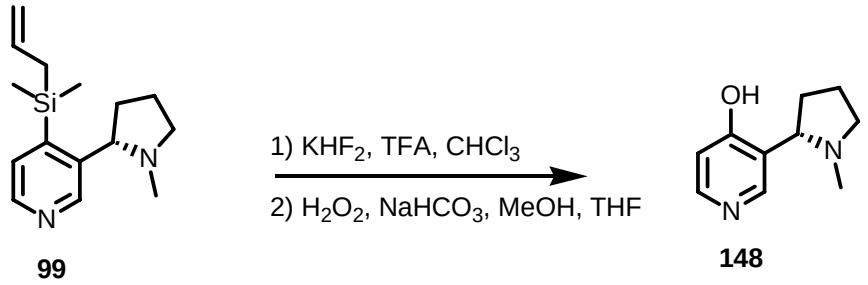
89 **148**

Scheme 61. Oxidation of 89.

Table 19. Oxidation conditions for 89.

Entry	Reagents	Conditions	Work-up	Results
1	TFA, KHF_2, MeOH, H_2O_2, $NaHCO_3$	rt (15 h)	aqueous	30% SM, 30% **148**
2	KHF_2, H_2O_2, MeOH	rt (3 days)	aqueous	crude NMR shows 1:1 mixture of **SM** and **148**
3	KHF_2, H_2O_2, MeOH	55 °C (5 h)	aqueous: product in aqueous phase. Filter crude through Celite to remove inorganic impurities	91% crude yield 10% SM crystallization in toluene: 46%
4	KHF_2, H_2O_2, MeOH	55 °C (8 h)	anhydrous	82% **148**

We also studied allyldimethylsilyl group as a precursor to the hydroxyl group. In this case, the silyl has to be transformed into the fluoro silane with potassium hydrogen fluoride and trifluoroacetic acid before the oxidation step can be performed (Scheme 62).



99 **148**

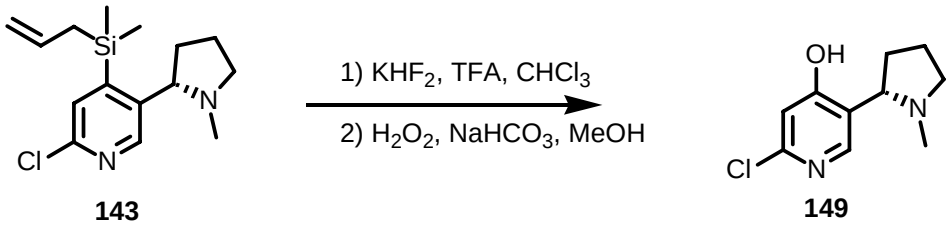
Scheme 62. Oxidation of 99.

Reflux temperature in the oxidation step followed by an anhydrous work up afforded 87% of 4-hydroxynicotine (Table 20, entry 3).

Table 20. Conditions for the oxidation of 99.

Entry	Scale (mmol)	Conditions	Work-up	Results
1	0.5	First step: rt (1 h) Second step: rt (3 h)	1) Remove solvent 2) Add EtOAc 3) Add $NaHSO_3$ (10% in H_2O) 4) Add $NaHCO_3$ (Satd. in H_2O) until pH basic 5) Extract with EtOAc 6) Dry over K_2CO_3	no product detected
2	0.35	First step: rt (0.5 h) Second step: reflux (3 h)	1) Add solid K_2CO_3 until pH basic 2) Filter through Celite 3) Wash with EtOAc	product mostly in aqueous phase
3	0.26	First step: rt (30 min) Second step: reflux (2 h)	same as entry 2	87 % **148**

Using the same conditions, 4-hydroxy-6-chloronicotine (**149**) was synthesized from 4-allyldimethylsilyl-6-chloro nicotine in 69% yield (Scheme 63).

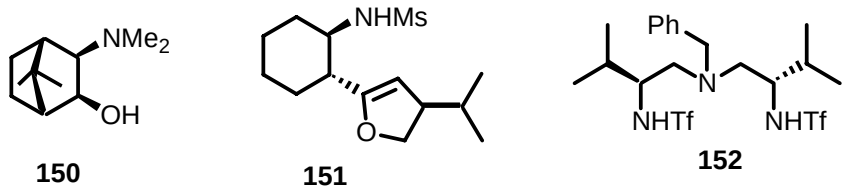


Scheme 63. Oxidation of 6-chloro-4-allyldimethylsilyl nicotine.

B. Reactivity of 4-hydroxynicotine

1. Catalytic activity

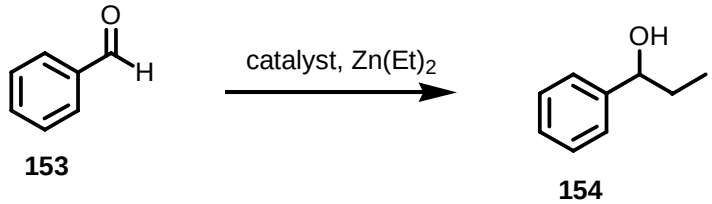
Since Oguni and Omi demonstrated (S)-leucinol could catalyze the addition of diethylzinc to benzaldehyde with a 49% ee[57], research on asymmetric organozinc additions to carbonyls has expanded. Noyori et al.[58] discovered that the amino alcohol [(-)-DAIB] **150** (Figure 19) was a highly enantioselective ligand for the dialkylzinc addition to aldehydes as they obtained 95% ee with only 2 mol% of **150**. Oxazolines also exhibit enantioselective catalytic properties and more recently, aminooxazoline **151** (Figure 19) gave a 98% ee for the ddition of diethylzinc to cyclohexanecarboxaldehyde.[59] The addition of diethylzinc to aldehydes can also be improved by the use of Ti(*i*-PrO)$_4$ as Lake and Moberg demonstrated in their recent study of the effects of adding monodente and bidente coordinating compounds under various conditions using catalyst **152**.[60]



150 **151** **152**

Figure 19. Structures of catalysts for the addition of dialkylzinc to aldehydes.

4-Hydroxynicotine (**148)** was tested as a catalyst to perform this transformation. The reaction proceeded in high yield (90%) but only afforded low ee: 14% when Ti(*i*-PrO)$_4$ was used and 8% without it.



153 **154**

Scheme 64. Catalytic asymmetric alkylzinc additions to benzaldehyde.

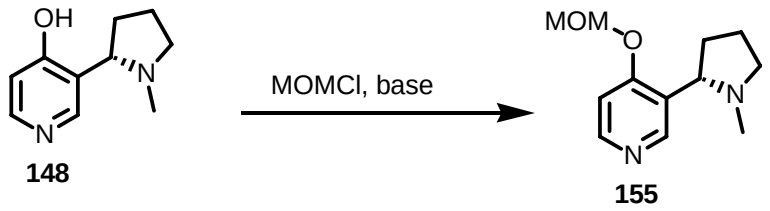
Table 21. Conditions for the catalytic asymmetric alkylzinc additions to benzaldehyde.

Entry	**Scale (mmol)**	**$ZnEt_2$ (eq)**	**Ti(*i*PrO)$_4$**	**Conditions**	**Results**
1	1	1.2	1.2	0 °C (o.n.), rt (4 h)	90% **154**, 14% ee
2	1	2.2	0	0 °C (2 d)	8% ee

2. Etherification

We turned our attention to the introduction of an ortho directed metallation group or DMG that will allow the functionalization at the C-5 position of nicotine ring.

First introduction of MOM group (Scheme 65, Table 22) was attempted on 4-hydroxynicotine.



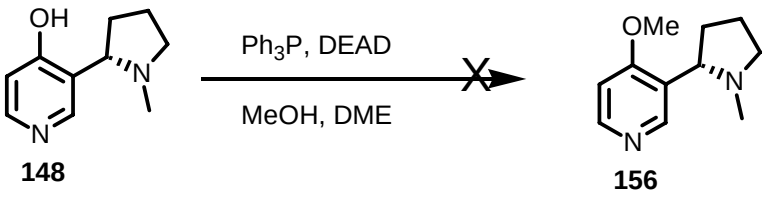
Scheme 65. Protection of 4-hydroxynicotine with a MOM group.

Sodium hydride proved to be unsuccessful as no product was isolated (entry 1 and 2). Potassium *tert*-butoxide however afforded 81% of product. However, this product was not very stable and decomposed rapidly on silica gel and after a few days stored in a refrigerator.

Table 22. Conditions for the protection of 4-hydroxynicotine with a MOM group.

Entry	Scale (mmol)	Base	Solvent	Conditions	Work-up	Results
1	0.6	NaH	DMF	rt (3 h)	aqueous	69% crude yield
2	0.79	NaH	DMF	rt (2 h)	anhydrous	Salt formation
3	0.75	tBuOK	DME	rt (2 h)	anhydrous	81% **155**

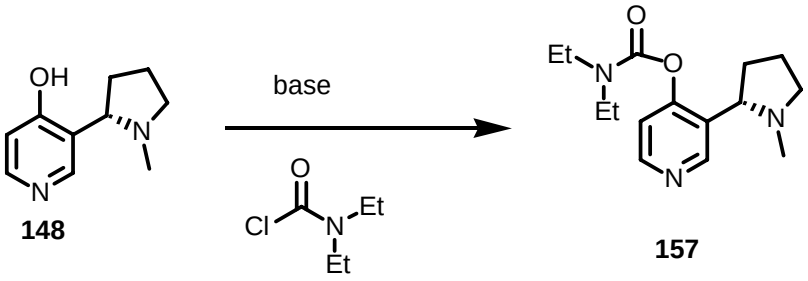
We also tried the Mitsonobu conditions to introduce a methyl group (Scheme 66). Unfortunately, only SM was recovered.



Scheme 66. Mitsonobu reaction to introduce a methyl group.

3. Carbamylation

We then tried to introduce a carbamyl group, since these groups have been found to be good DMG (Scheme 67, Table 23).



Scheme 67. Carbamylation of 4-hydroxynicotine.

We first tried the conditions used in the case of 4-hydroxypyridine[32] but decomposition resulted (entry 1). We then used NaH as a base. DMF was used as solvent but decomposition resulted after removal of the solvent at high temperature (entry 2). A no work up procedure was attempted by loading the crude material with the DMF on a column. Both silica gel (entry 3) and Florisil (entry 4) were tried but they both led to decomposition. We then switched to DME, which is easier to remove than DMF. After a few hours at rt, the desired product was detected (entries 5-8). Increase in the amount of NaH and temperature allowed the completion of the reaction (entries 7-10). However, the product was found

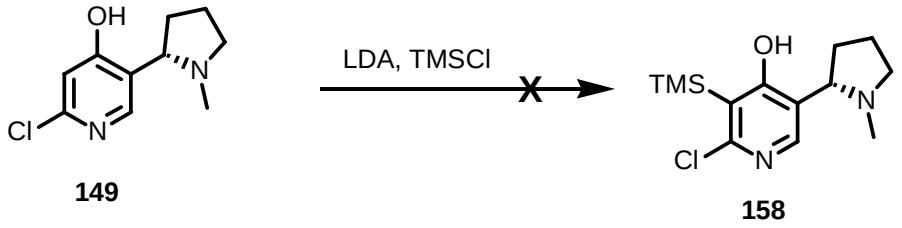
sensitive to purification: neutral alumina (entries 9 and 10) yielded at the best 26% of product (entry 10). Finally the same conditions used for the introduction of the MOM group yielded 34% of product (entry 11). The product was found very unstable.

Table 23. Conditions for the carbamylation for 4-hydroxynicotine.

Entry	Scale (mmol)	Base	Solvent	Conditions	Results
1	0.1	3 eq TEA	toluene	reflux (2 h)	decomposition
2	0.05	1 eq NaH	DMF	rt (3 h) no work up	new spot: decomposition after evaporation of DMF
3	0.056	1 eq NaH	DMF	rt (2 h) no work up: RPLC with DMF	decomposition on silica gel
4	0.43	1 eq NaH	DMF	rt (2 h) Florisil column with DMF	decomposition
5	0.063	1.2 eq NaH	DME	rt (4 h)	crude looks promising
6	0.15	2 eq NaH	DME	rt (5 h)	mixture of SM and product
7	0.15	3 eq NaH	DME	40 °C (2 h)	still SM
8	0.15	3 eq NaH	DME	50 °C (o.n) Purification: basic Al_2O_3	no more SM decomposition after purification
9	0.34	3 eq NaH	DME	55 °C (5 h) Purification: neutral Al_2O_3	some product isolated: confirmed by HRMS
10	2.5	3 eq NaH	DME	55 °C (6 h) Purification: neutral Al_2O_3	26% **157** a lot of decomposition
11	0.67	2 eq tBuOK	DME	55 °C (6 h) Purification: neutral Al_2O_3	34% **157**

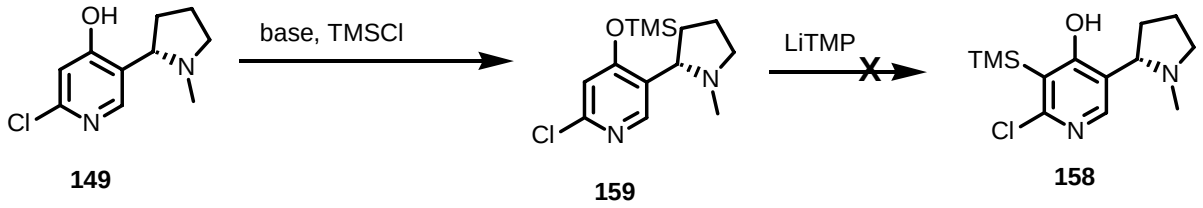
4. Introduction of a TMS group at C-5.

Since the introduction of a DMG group was problematic, we tried to functionalize 6-chloro-4-hydroxy nicotine (**149**) at C-5 by a one-pot procedure. However this procedure resulted in decomposition.



Scheme 68. Introduction of a TMS group in a one pot-procedure.

We then tried to form trimethylsilyloxy ether **159** and to deprotonate using LiTMP. Deprotonation of **149** with potassium *tert*-butoxide did not form the desired product. Sodium hydride seemed to work better but the second step did not yield the expected product: an unknown product was obtained.



Scheme 69. Introduction of a TMS group from deprotonation of trimethylsilyloxy ether 159.

In summary, both (dimethylphenyl)silyl nicotine and (allyldimethyl)silyl nicotine were converted to 4-hydroxynicotine in high yield. The 6-chloro-4-(allyldimethyl)silylnicotine was also converted to 6-chloro-4-hydroxynicotine in 69% yield.

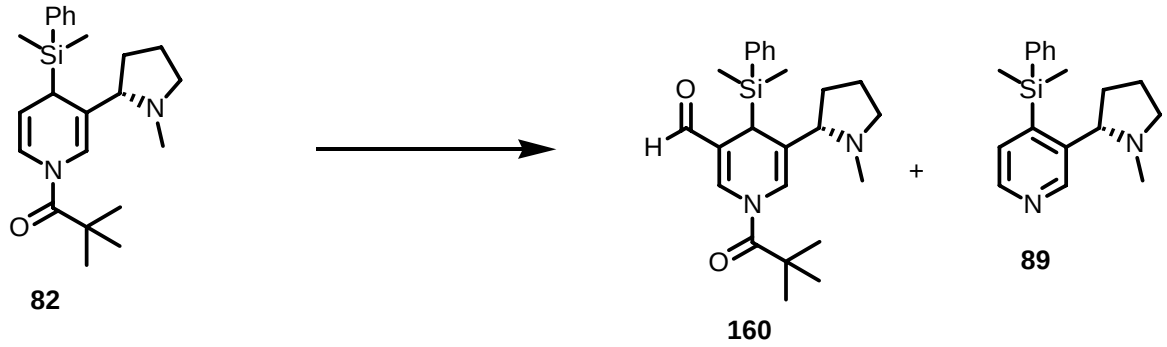
4-Hydroxynicotine is a catalyst of the addition of ethylzinc to benzaldehyde but gave a low ee. Finally, various ways to introduce a DMG group were attempted but were not very successful.

IX. Reactivity of some dihydropyridines of nicotine

A. Formylation reaction.

Formylation reactions using the Vilsmeier-Hack reagent were attempted on dihydropyridine **82** (Scheme 70, Table 24). This reaction is interesting because it allows functionalization at the C-5 position of the nicotine.

Two reagents were tried: the classic DMF and $POCl_3$ and the modified DMF and oxalyl chloride. The latter did not yield any product. When the reaction was quenched with NaOAc 25% yield of the desired product **160** was isolated (entry 1). Surprisingly, when the reaction was quenched with K_2CO_3, only the aromatized product **89** was isolated (entry 2).

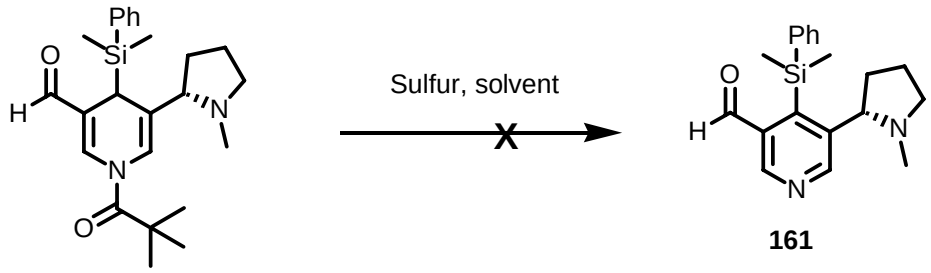


Scheme 70. Formylation reaction of dihydropyridine 82.

Table 24. Conditions for formylation of dihydropyridine 82.

Entry	Reagents	Conditions	Results
1	$POCl_3$, DMF	rt (2 days) quench: NaOAc	25% **160**
2	$POCl_3$, DMF	rt (2.5 days) quench: K_2CO_3	23% **89**
3	DMF, $(COCl)_2$	rt (2 days)	SM
4	DMF, $(COCl)_2$	rt (4.5 h)	SM
5	DMF, $(COCl)_2$	reflux	SM only

Aromatization of aldehyde **160** was attempted in hot sulfur (Scheme 71). Several solvents were tried with high bp but only SM was recovered (Table 25).



160 **161**

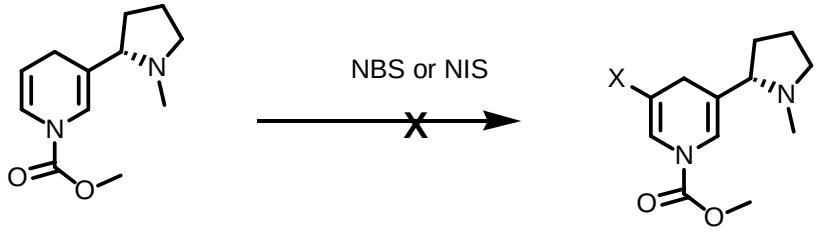
Scheme 71. Aromatization of aldedyde 160.

Table 25. Conditions for aromatization of aldedyde 160.

Entry	Scale (mmol)	Solvent	Conditions	Results
1	0.36	toluene	reflux (2 days)	66% SM
2	0.36	xylenes	reflux (1 day)	58% SM
3	0.27	1,2,3 trimethylbenzene	reflux (1 day)	SM

B. Halogenation reaction

Halogenation at C-5 was next attempted on dihydronicotine **109.** However, none of the reagents tested afforded the desired product: pyrrolidine ring-opening or decomposition was observed.



109

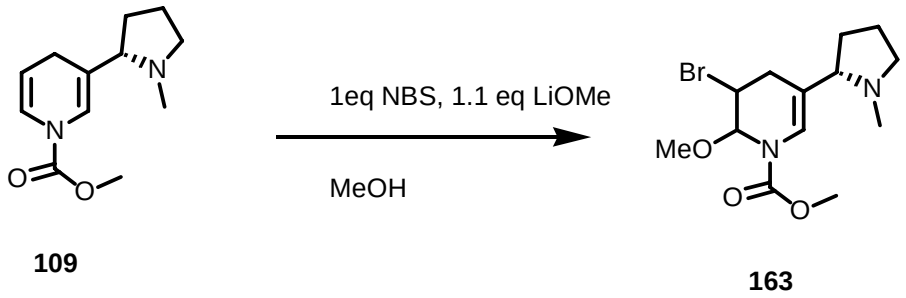
162a, X = Br
162b, X = I

Scheme 72. Halogenation at C-5 of dihydropyridine 109.

Table 26. Conditions for the halogenation at C-5 of dihydropyridine 109.

Entry	Scale (mmol)	NBS or NIS	NBS or NIS eq	Solvent	Conditions	Results
1	0.92	NBS	1	CH_2Cl_2 (5 mL)	rt (20 h)	11% ring-opened product, 32% SM
2	0.71	NBS	1.5	THF (10 mL)	rt (16 h)	13% mixture of ring-opened product and SM
3	0.69	NBS	1.5	CH_2Cl_2 (5 mL)	50 °C (3 h)	2.5% ring-opened product
4	0.61	NBS	1	HOAc (5 mL)	rt (4 h)	19% ring-opened product 15% SM
5	0.44	NBS	1	HOAc (0.5 mL) NaOAc (1 eq)	rt (3 h)	49% crude, very messy
6	0.48	NBS	1	HOAc (1 mL) NaOAc (2 eq)	rt (1 h)	71% crude, mostly product After RPLC only 8 mg of SM
7	0.1	NIS	1	CH_2Cl_2 (5 mL)	rt (16 h)	8% SM

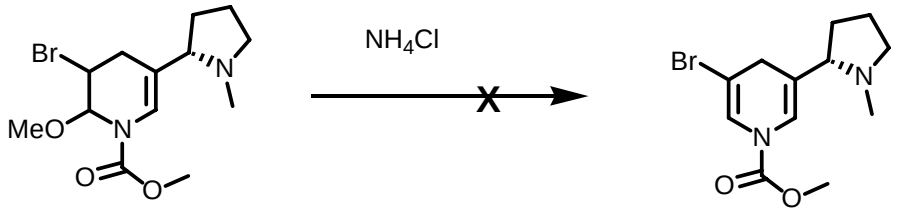
When dihydronicotine **109** was treated with NBS and LiOMe in MeOH a quantitative yield of tetrahydronicotine **163** was obtained (Scheme 73).



109 **163**

Scheme 73. Formation of tetrahydronicotine 163.

However, the methoxy group at C-6 could not be elilminated (Scheme 74). The conditions described that worked on a similar system[61] did not yield the desired product (Table 27).



163 **162a**

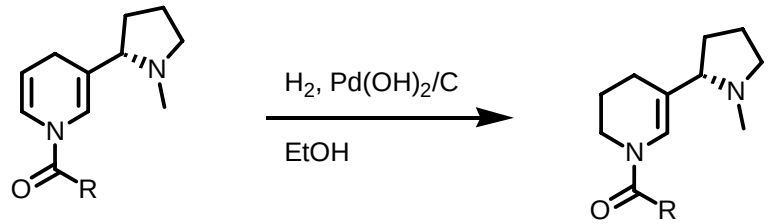
Scheme 74. Removal of methoxy group at C-6.

Table 27. Attempts at removing methoxy group at C-6.

Entry	Scale (mmol)	Conditions	Results
1	0.19	0.1 eq NH_4Cl 100 ºC (1 d)	SM
2	0.19	1 eq NH_4Cl reflux in toluene (1 d)	SM
3	0.38	1 eq NH_4Cl reflux in acetonitrile (4 h)	SM and new aromatic peaks
4	0.38	1 eq NH_4Cl reflux in acetonitrile (1 d)	10% SM 30% nicotine

C. Synthesis of tetrahydronicotines.

A variety of tetrahydronicotines were prepared from hydrogenation of their corresponding dihydronicotines (Scheme 75).



109, R = OMe
107, R = H
105, R = NMe_2

164, R = OMe
165, R = H
166, R = NMe_2

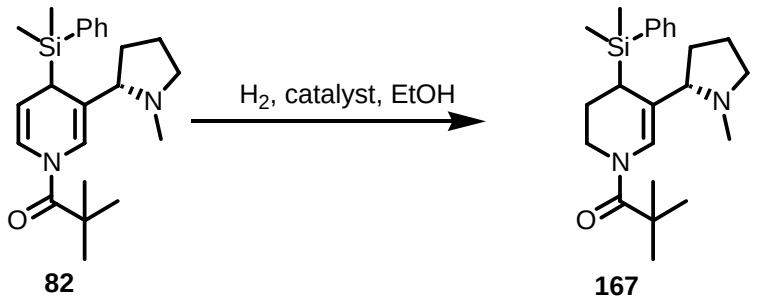
Scheme 75. Hydrogenation of dihydronicotines.

For dihydronicotines **109**, **107** and **105**, $Pd(OH)_2/C$ afforded tetrahydronicotines in moderate to high yield (Table 28).

Table 28. Results of the hydrogenation of dihydronicotines.

Entry	Substrate	Conditions	Product	Results
1	R = Me	rt (30 min)	**164**	80%
2	R = H	rt (1 h)	**165**	43%
3	R = NMe_2	rt (1 h)	**166**	14%
4	R = NMe_2	rt (2 h)	**166**	35%

In the case of 4-dimethylphenylsilyl dihydronicotine **82**, a different catalyst had to be used (Scheme 76). We found that Pt/C worked the best to afford only a 33% yield of product (Table 29, entry 3).



82 **167**

Scheme 76. Hydrogenation of 4-dimethylphenylsilyl dihydronicotine 82.

Table 29. Conditions for the hydrogenation of 4-dimethylphenylsilyl dihydronicotine 82.

Entry	Catalyst	Conditions	Results
1	$Pd(OH)_2/C$	rt (4 days)	SM only
2	Pd/C	rt (2 days)	SM only
3	Pt/C	rt (o.n.)	33% **167**

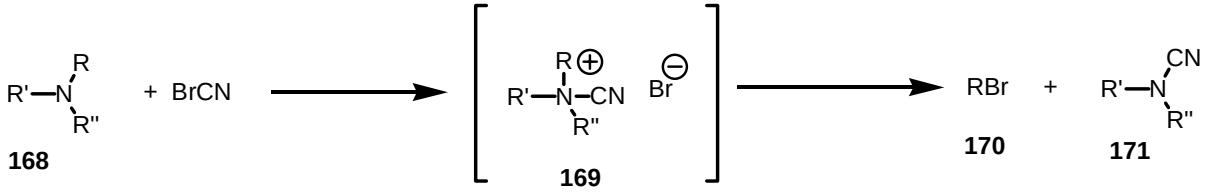
In conclusion, formylation of dihydronicotine **82** was only achieved in low yield. The synthesis of tetrahydronicotines was achieved in reasonable to high yield. Those tetrahydronicotines were found to have similar CNS activity as their corresponding dihydronicotines.

X. Pyrrolidine ring opening reactions.

A. The von Braun reaction.

In 1900, Julius von Braun described the reaction of a tertiary amine with cyanogen bromide.[62] Scholl and Norr[63] apparently reported the same reaction five weeks after the submission of von Braun paper.

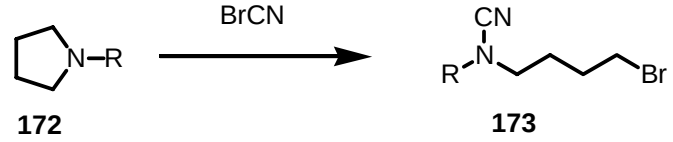
Generally, the addition of cyanogen bromide to a tertiary amine **168** yields an alkyl bromide **170** and a disubstituted cyanamide **171** via a quaternary nitrogen salt complex **169** (Scheme 77).



168 **169** **170** **171**

Scheme 77. Reaction of cyanogen bromide and a tertiary amine.

In the case of a monocyclic amine such as a *N*-substituted pyrrole **172**, ring opening product **173** is usually obtained (Scheme 78).

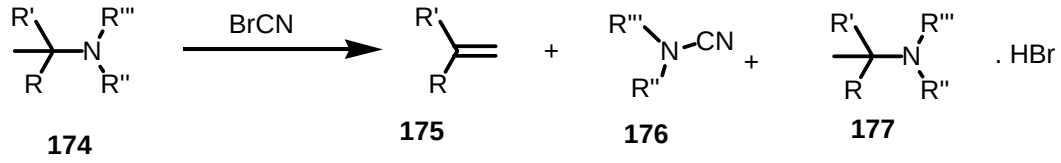


172 **173**

R ≠ Me

Scheme 78. Reaction of cyanogen bromide with a *N*-substituted pyrrole.

When an amine contains a secondary or a tertiary alkyl group such as **174**, formation of an olefin **175** from an elimination reaction is a typical competitive reaction (Scheme 79).



174 **175** **176** **177**

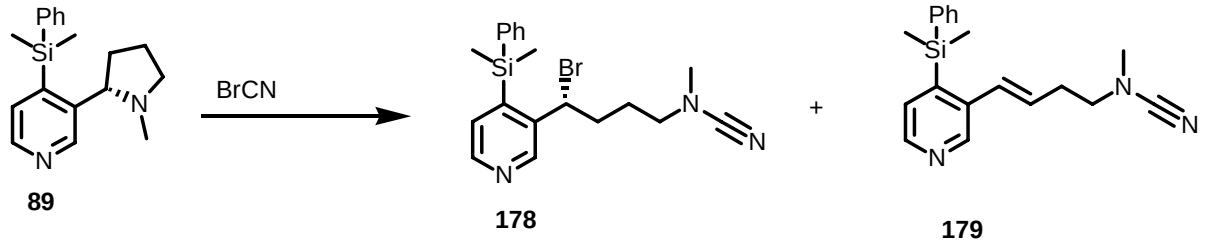
Scheme 79. Reaction of cyanogen bromide with an amine containing a tertiary alkyl group.

A considerable amount of amine is converted to the hydrobromide **177** and therefore does not react with cyanogen bromide.

Because this reaction proceeds via a S_N2 mechanism, a chiral cyclic material should give a chiral product with opposite configuration. This feature prompted us to investigate the von Braun reaction involving some nicotine derivatives.

B. Application of the von Braun reaction to some nicotine derivatives.

We selected 4-silylnicotines as staring material since they exhibit the most biological activity. First, 4-(dimethylphenylsilyl)nicotine (**89**) only gave low yield of the expected product (Scheme 80, Table 30). Elimination reaction occurred sometimes in higher yield than the desired product (entry 1 and 3). Methylene chloride seemed to prevent that elimination reaction but only yielded 15% of product **178**. Surprisingly chloroform gave the best yield, along with 24% of elimination product.



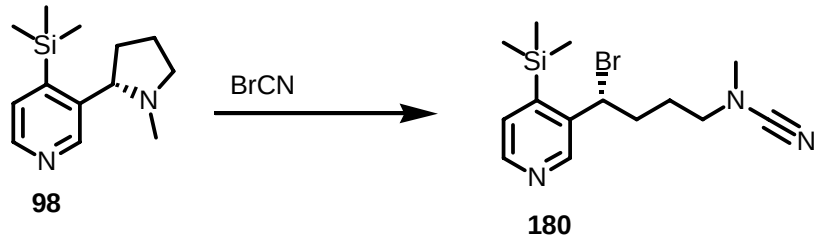
89 **178** **179**

Scheme 80. The von Braun reaction with 4-(dimethylphenylsilyl)nicotine (89).

Table 30. Conditions for the addition of cyanogen bromide to 4-(dimethylphenylsilyl) nicotine (89).

Entry	Scale (mmol)	BrCN (eq)	Solvent	Conditions	Results
1	0.3	1	CH_2Cl_2	rt (1 d)	10% **178**, 16% SM
2	0.4	5	CH_2Cl_2	reflux (20 h)	15% **178**, 5% **179**
3	0.7	10	$CHCl_3$	reflux (1 d)	17% **178**, 24% **179**, 30% SM

When 4-TMS nicotine was used, a better yield of desired product was obtained and no elimination product as observed (Scheme 81, Table 31).



98 **180**

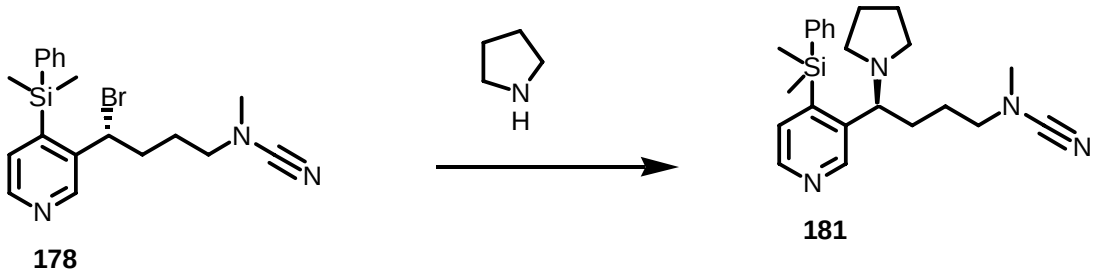
Scheme 81. The von Braun reaction with 4-TMS-nicotine (98).

Table 31. Conditions for the addition of cyanogen bromide to 4-TMS-nicotine (98).

Entry	Scale (mmol)	BrCN (eq)	Solvent	Conditions	Results
1	0.85	10	CH_2Cl_2	reflux (1 d)	15% **180**
2	0.55	5	CH_2Cl_2	reflux (3 h)	36% **180**

Intermolecular S_N2 substitution with pyrrolidine should lead to enantiopure nicotine derivatives of (*S*)-configuration (Scheme 82).

Stirring compounds **178** in 1 mL of pyrrolidine at RT afforded 34% of product **181** and 47% of elimination product **179.**



178 **181**

Scheme 82. Substitution reaction with pyrrolidine.

In summary, the von Braun reaction allowed the synthesis of novel enantiopure ring-opened nicotine derivatives. Yields were rather low due to competitive elimination reaction. Those new compounds have yet not been tested for insecticidal activity.

Conclusion

In the first part, the synthesis of 1-acyl-2-dimethylphenylsilyl-2,3-dihydro-4-pyridone **4** was achieved in high yield and enantioselectivity. Several transformations were performed in reasonable to good yield and usually high stereoselectivity. 1,4-Additions mediated by a copper reagent afforded a 85% yield of trans piperidone **17b** as a single diastereomer, and reduction of the keto function under the Luche conditions or with L-Selectride afforded a quantitative mixture of alcohols **18** with 40% de. The synthesis of dihydropyridine **20** was achieved by using the *N*-acyliminium ion chemistry in a high yield. Other reactions including hydrogenation of alcohol **18a** and synthesis of 4-methoxydihydropyridine **26** gave good results. Unfortunately, no conditions could be found to remove the chiral auxiliary.

In conclusion, several new potential intermediates for the synthesis of alkaloid rings have been synthesized. The high stereocontrol involved in this methodology paves the road to the asymmetric synthesis of numerous synthetic intermediates.

In the second part, new methods to synthesize enantiopure nicotine derivatives from nicotine have been developed. A two-step procedure was designed where 1,4-adddition to 1-acylpyridinium salt of nicotine, followed by aromatization in hot sulfur, usually affords substituted nicotine at C-4 in moderate to high yield. In the first step, the pyrrolidine ring seems to control the attack of the cuprate.

Reductive disilylation of nicotine was successful and gave to 95% of the bis (trimethylsilyl) dihydropyridine. When 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (**97**) was treated with aldehydes in the presence of a catalytic amount of TBAF, C-5 substituted nicotines were obtained in moderate to good yield (47-70%). When **97** was treaded with methyl carbonate, ethyl formate and trifuoroethyl acetate *N*-1 substitution occurred leading to 1,4-

dihydronicotines in high yield (60-91%). With phenyl carbonate and trifluoroethyl formate, opening of the pyrrolidine ring was observed. When a dialdehyde was used with 2 equivalents of dihydronicotine, formation of a dimer occurred in 51% yield. SIB-1508Y was synthesized with a 20% overall yield from natural (*S*)-nicotine.

Substitution at C-6 of 4-trialkylsilylnicotine was achieved by using BuLi-LiDMAE. Formation of a dimer was observed in the case of 4-(allyldimethylsilyl)nicotine in 40% yield. Subsequent deprotonation at C-5 with Li-TMP afforded trisubstituted nicotine derivative.

Oxidation of 4-(dimethylphenylsilyl) nicotine and 4-(allyldimethylsilyl)nicotine yielded 4-hydroxynicotine in high yield (82 and 89%, respectively). 6-Chloro-4-(allyldimethyl)silyl nicotine was also converted to 6-chloro-4-hydroxynicotine in 69% yield. 4-Hydroxynicotine is a catalyst of the addition of ethylzinc to benzaldehyde but low ee's resulted. Various ways to introduce a DMG group at C-4 were attempted but were not very successful.

Formylation reactions were performed by using Vilsmeir Hack reagents but only low yields were obtained. Tetrahydronicotines were obtained from hydrogenation of their corresponding dihydronicotines in moderate to high yield.

The von Braun reaction was investigated and yielded novel enantiopure ring-opened nicotine derivatives; however, a competitive elimination reaction caused this reaction to be low yielding.

The success in uncovering new methods for synthesizing enantiopure nicotine derivatives provides rich opportunities for exploring new routes to interesting and potentially useful compounds based on nicotine.

Experimental Section

General

All reactions were conducted under an argon atmosphere using oven-dried glassware. THF and toluene were distilled from sodium/benzophenone ketyl prior to use. Pyridines and amines were distilled from calcium hydride and stored with molecular sieves. Nicotine was distilled under vacuum and kept under argon in a brown bottle. All other solvents and reagents were purchased commercially, kept under argon atmosphere, and used directly. Melting points were obtained from a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial PLC was performed on a Chromatotron manufactured by Harrison and Associates in Palo Alto, California using glass plates coated with 1, 2 or 4 mm layers of Kieselgel 60 PF254 containing gypsum. Elemental analyses were performed by Atlantic Microlab Inc. IR spectra were recorded using a Perkin-Elmer 1430, MIDAC M2000 or JASCO FT/IR-410 spectrometer in a nitrogen atmosphere. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz), Varian Mercury 300 (300 MHz) or Varian Mercury 400 (400 MHz) spectrometers. Chemical shifts are in ppm units with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption of 77.23 ppm for ^{13}C NMR. Optical rotations were determined with a Randolf Research Autopol III automatic polarimeter manufactured in Flanders, New Jersey. All HPLC determinations used two Waters and Associates equipment systems of Miliford, Massachusetts. The 600 E multi solvent system delivery system uses a 486 λ tunable ultraviolet detector with a PORASIL analytical column, and the 501 pump model uses a 440 detector with either a Chiralcel OJ or OD column. These HPLC systems were used to determine all diastereomeric

and enantiomeric ratios. High resolution mass spectra were determined by a JEOL HX1110HF mass spectrometer.

Preparation of Dimethylphenylsilylmagnesium Chloride (13). Freshly cut lithium wire (0.05g, 8 mmol) was washed in hexanes and then in THF and was placed in a flask containing 10 mL of THF under Argon. Chlorodimethylphenylsilane **2** (0.25 mL, 1.5 mmol) was added and the solution was stirred at room temperature for 4-12 h (the solution first formed a white precipitate then turned light yellow within 30 min and gradually brown as a homogeneous, dark solution of dimethylphenylsilyl lithium). When preparing a 5-mmol scale, it might take as long as 2 days for the reaction to go to completion. In a separate flask containing 10 mL of THF and 0.1 g (4 mmol) of magnesium turnings under argon was added 0.16 mL (1.8 mmol) of dibromoethane, and the mixture was refluxed for 3 h and then cooled to room temperature. The solution of dimethylphenylsilylithium was transferred via a syringe to the solution of magnesium bromide forming a purple solution. The mixture was stirred at room temperature for 30 minutes and added directly to the 1-acylpyridinium salt via a syringe.

Preparation of 2-(Dimethylphenylsilanyl)-4-oxo-3,4-dihydro-2*H*-pyridine-1-carboxylic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (4). Toluene (5.5 mL), TCC chloroformate (1 mmol) and 4-methoxypyridine (0.11 mL, 1.1 mmol) were stirred under argon at -23 °C for 15 minutes. The solution of the pyridinium salt was then cooled to -85 °C (Et_2O/CO_2) and dimethylphenylsilylmagnesium chloride (**13**) was added dropwise over 15 min. The mixture was stirred for 30 min at – 85 °C and allowed to come to room temperature for another 30 min. A saturated solution of oxalic acid (5.5 mL) was added, and the mixture was stirred for 5 min at room temperature and then extracted with ether. The combined organic layers were washed with water (2 x) and brine, dried over $MgSO_4$ and

concentrated. Purification of the crude product by radial PLC (5% EtOAc/hexanes) yielded 400 mg (88%) of **4** as a white foam. The product was crystallized in 5% EtOAc/hexanes to give white crystals. IR (thin film, neat, NaCl) 2928, 1711, 1669, 1593, 1256, 1190 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.01 (m, 10 H), 6.41 (d, 1 H, *J* = 8.2 Hz), 4.80 (d, 1 H, *J* = 8.2 Hz), 4.73 (dd, 1 H, *J* = 4 and 10.5 Hz), 4.32 (d, 1 H, *J* = 9 Hz), 2.76 (dd, 1 H, *J* = 9 and 16.8 Hz), 2.31 (d, 1 H, *J* = 16.8 Hz), 2.18-1.70 (m, 5 H), 1.30 (s, 5 H), 1.17 (s, 5 H), 0.32 (s, 3 H), 0.22 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.39; 151.88; 151.001; 142.61; 135.27; 134.02; 129.60; 128.02; 127.84; 125.30; 124.78; 106.47; 77.89; 51.17; 44.30; 39.35; 36.73; 33.28; 30.08; 26.74; 25.86; 24.59; 22.15; -3.55; mp: 115-116°C. Anal. Calcd for $C_{29}H_{37}NO_3Si$: C, 73.22; H, 7.84; N, 2.94. Found: C, 73.41; H, 7.95; N, 2.93. HRMS Calcd for $C_{29}H_{37}NO_3Si$: 476.2621 $[M+H]^+$. Found: 476.2639 $[M+H]^+$. $[\alpha]^{23}_D$ -18.9 (c 19.1, CH_2Cl_2).

Preparation of 2- (Dimethylphenylsilanyl)-6- (3-ethoxycarbonylpropyl)-4- oxocyclo hexanecarboxylic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (16b). A solution of zinc powder (0.0745 g, 1.14 mmol) and dibromoethane (3.4 μL, 0.04 mmol) in THF (0.08 mL) was heated to 65 ºC for 2 min and then cooled to rt. TMSCl (4.4 μL, 0.035 mmol) was added and the mixture was stirred at rt for 15 min. A solution of 4-iodo-butyric acid ethyl ester (0.16 mL, 1.09 mmol) in THF (0.44 mL) was added to the activated zinc, and the solution was heated at 35 ºC for 12 h. In a separate flask, a solution of anhydrous copper (II) acetate (0.1035 g, 0.57 mmol) and lithium chloride (0.0483 g, 1.14 mmol) in THF (0.066 mL) was stirred at rt for 30 min. It was then cooled to -18 ºC. The organozinc solution prepared above was added dropwise, and the reaction mixture was stirred at -18 ºC for 10

min. In a separate flask, a solution of **4** (0.254 g, 0.53 mmol) in THF (1 mL) was cooled to -78 ºC. It was then treated with BF_3•OEt_2 (0.2 mL, 1.6 mmol), and the solution was stirred at -78 ºC for 5 min. The solution was canulated into the organocopper zinc reagent. The reaction mixture was stirred at -18 ºC for 5 h. The reaction was quenched with a satd solution of ammonium chloride (1 mL). The aqueous phase was extracted with ether (2 x). The combined organic layers were washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (10% EtOAc/hexanes) to afford 0.1376 g (44%) of product **16b**. IR (thin film, neat, NaCl) 2926, 1694, 1386, 1249, 1259.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.02 (m, 10 H), 6.82 (s, 1 H), 4.83 – 4.75 (m, 1 H), 4.35 (d, 1 H, *J* = 7.47 Hz), 4.15 (q, 2 H, *J* = 7.1 Hz), 3.25 (t, 2 H, *J* = 6.8 Hz), 2.88 – 2.80 (m, 1 H), 2.68 – 2.63 (m, 1 H), 2.44 (t, 2 H, *J* = 7.14 Hz), 2.18 – 1.58 (m, 16 H), 0.39 (s, 3 H), 0.34 (s, 3 H).

Preparation of 2-Allyl-6-(dimethylphenylsilanyl)-4-oxo-piperidine-1-carboxylic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (17b).

To a solution of **4** (50 mg, 0.1 mmol) in THF (1 ml) was added CuBr•SMe_2 (62 mg, 0.3 mmol). The heterogeneous mixture was cooled to -78 ˚C and BF_3•OEt_2 (0.05 ml, 0.3 mmol) was added. After stirring for 30 min at -78 ˚C, allylmagnesium chloride (0.15 ml, 0.3 mmol) was slowly added, and the mixture was stirred at -78˚C for 3 h and was then allowed to warm to room temperature for 1 h. A solution of 20% NH_4OH/NH_4Cl (50:50) was added (1 ml) and the aqueous phase was extracted with ether. The combine organic layers were washed with water and brine and dried over K_2CO_3. Purification by radial PLC (5% EtOAc/hexanes) afforded 45 mg (85%) of **17b** as a clear oil. IR (thin film, neat, NaCl) 2929, 2858, 1722,

1688, 1402, 1308, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.515-7.00 (m, 10H), 5.41-5.27 (m, 1 H), 4.97 (d, 1 H, *J* = 9.9 Hz), 4.88-4.73 (m, 2 H), 4.25 (dd, 1 H, *J* = 5 and 8 Hz), 2.50-1.59 (m, 7 H), 1.32-1.14 (m, 11 H), 0.37 (s, 3 H), 0.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.04, 154.91, 153.19, 137.13, 134.02, 133.99, 129.47, 127.96, 124.99, 124.77, 117.70, 76.14, 51.07, 49.88, 42.44, 42.24, 41.00, 40.35, 39.39, 33.72, 30.72, 30.58, 26.74, 26.05, 24.71, 21.79, -2.58, -3.94. LRMS Calcd for $C_{32}H_{43}NO_3Si$: $[M+H]^+$ 518.30. Found: 518.35 $[M+H]^+$. $[\alpha]^{23}_D$ -48.2 (c 1 , CH_2Cl_2).

Preparation of 2- (Dimethylphenylsilanyl)-4- hydroxy-3, 4- dihydro-2*H*-pyridine-1-carboxylic acid 2- (1-methyl-1-phenylethyl) cyclohexyl ester (18).

Preparation A: To a solution of **4** (188 mg, 0.396 mmol) in methanol (6 mL) was added $CeCl_3 \bullet 7H_2O$ (177 mg, 0.475 mmol) and the mixture was stirred at room temperature until the starting material was dissolved (0.5 – 1 h). The mixture was cooled to 0 °C and $NaBH_4$ (23 mg, 0.6 mmol) was slowly added. After stirring for 30 min, the ice bath was removed, and the solution was stirred for 1 h at room temperature. The solvent was then removed under reduced pressure and to the residue was added CH_2Cl_2 (20 mL), water (24 mL) and 10% HCl (6 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification by radial PLC (10% EtOAc/hexanes) yielded 200 mg (100%) of a mixture of cis (**18a**) and trans (**18b**) as a white foam.

Preparation B: To a solution of **4** (90 mg, 0.19 mmol) in 5 ml of THF cooled at -78 °C was slowly added L-Selectride (0.19 ml, 0.19 mmol). The reaction mixture was stirred for 1 h at -78 °C and then poured into a saturated solution of $NaHCO_3$ at 0 °C. The aqueous layer was

extracted with ether, and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification by radial PLC (10% EtOAc/hexanes) afforded 71 mg (68%) of **18a** and **18b**.

18a: IR (thin film, neat, NaCl) 3437, 2962, 1671, 1408, 1260, 1106, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.03 (m, 10 H), 6.06 (d, 1 H, *J* = 8.4 Hz), 4.82-4.77 (m, 1 H), 4.51 (dd, 1 H, *J* = 4.8 and 8.4 Hz), 4.08 (t, 1 H, *J* = 4.8 Hz), 3.95 (s, 1 H), 2.06 (dt, 1 H, *J* = 2.4 and 12.8 Hz), 1.96-1.59 (m, 6 H), 1.31 (s, 5 H), 1.22 (s, 5 H), 0.39 (s, 3 H), 0.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.01, 138.06, 134.16, 133.99, 129.06, 128.00, 127.84, 127.72, 127.26, 125.05, 125.04, 106.89, 76.48, 51.24, 46.10, 40.93, 39.77, 33.76, 32.34, 27.52, 27.11, 25.91. 25.37, 24.67, 11.42, -2.08, -2.33. HRMS: Calcd for $C_{29}H_{39}NO_3Si$: 478.2777 $[M+H]^+$. Found: 478.2789 $[M+H]^+$. $[\alpha]^{23}_D$ -81.79 (c 1.57, CH_2Cl_2).

18b: IR (thin film, neat, NaCl) 3444, 2930, 1644, 1383, 1337, 1257, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.07 (m, 10 H), 5.96 (d, 1 H, *J* = 8.4 Hz), 4.73 (td, 1 H, *J* = 4.5 and 12 Hz), 4.40 (d, 1 H, *J* = 8.4 Hz), 4.07 (m, 1 H), 4.02 (dd, 1 H, *J* = 2.7 and 6 Hz), 1.31 (s, 5 H), 1.21 (s, 5 H), 0.32 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.00, 151.58, 136.91, 133.89, 129.31, 127.98, 127.78, 126.28, 125.16, 125.13, 108.45, 62.83, 51.29, 43.15, 39.81, 33.69, 33.28, 27.55. 27.15, 25.95, 25.43, 24.68, -0.01, -2.83, -3.29. HRMS: Calcd for $C_{29}H_{39}NO_3Si$: 478.2777 $[M+H]^+$. Found: 478.2789 $[M+H]^+$. $[\alpha]^{23}_D$ -2.14 (c 2.52, CH_2Cl_2).

Preparation of 2- (Dimethylphenylsilanyl)-4- methoxy-3, 4- dihydro-2*H*-pyridine-1-carboxylic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (21). To a stirred solution of

18b (680 mg, 1.42 mmol) in THF (10 mL) under argon and at -78 °C was added first iodomethane (0.53 mL, 8.52 mmol) and then tBuOK (210 mg, 1.7 mmol). The mixture was stirred at -78 °C for 30 min and was allowed to warm to room temperature for another 30 min. The mixture was then with a saturated solution of $NaHCO_3$, and the aqueous layer was extracted with ether. The combined organic layers were dried over K_2CO_3. After evaporation of the solvent under reduced pressure, the crude product was purified by radial PLC (5% EtOAc/hexanes) to give 580 mg (83%) of **21** as a clear oil. IR (thin film, neat, NaCl) 2927, 2857, 1695, 1649, 1382, 1339, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.04 (m, 10 H); 6.12 (d, 1 H, *J* = 8.4 Hz); 4.76-4.66 (m, 2 H); 4.07 (dd, 1 H, *J* = 2.4 and 6.4 Hz); 3.47 (s, 1 H), 3.047 (s, 3 H); 2.07-1.56 (m, 7 H); 1.30 (s, 5 H); 1.21 (s, 5 H); 0.31 (s, 3 H); 0.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.09, 151.34, 137.15, 133.94, 129.25, 127.99, 127.74, 126.36, 125.27, 125.17, 105.97, 70.97, 55.37, 42.91, 39.88, 33.72, 28.80, 27.24, 25.98, 25.92, 24.71, -2.54, -3.51. HRMS Calcd for $C_{30}H_{41}NO_3Si$: 492.29 $[M+H]^+$ Found: 492.42 $[M+H]^+$. $[\alpha]^{23}_D$ +2.77° (c 1.22, CH_2Cl_2).

Preparation of 2- (Dimethylphenylsilanyl)-2*H*- pyridine-1-carboxylic acid 2- (1-methyl-1-phenylethyl)cyclohexyl ester (20). To a stirred solution of **18a** (25 mg, 0.05 mmol) in THF (2 mL) cooled at -78 ˚C was added BF_3•OEt_2 (0.01mL, 0.1 mmol), and the resulting mixture was stirred for 30 min at -78 ˚C. A solution of allylmagnesium chloride in THF (0.075 mL, 0.15 mmol) was added, and the reaction mixture was stirred at -78 ˚C for 3 h and then was allowed to warm to room temperature for 1 h. The reaction mixture was treated with 5 mL of water, and the aqueous phase was extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent in

vacuo, the crude product was purified by radial PLC (hexanes + 1% TEA) to yield 23 mg (100%) of **20** as a clear oil. IR (thin film, neat, NaCl) 2926, 2863, 1694, 1386, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.08 (m, 10 H), 5.94 (d, 1H, *J* = 7.6Hz), 5.61 (dd, 1 H, *J* = 5Hz and 9.6 Hz), 5.37 (dd, 1 H, *J* = 6.2 Hz and 9.6 Hz), 4.82 (ddd, 1 H, *J* = 7.6 Hz, 5 Hz and 0.8 Hz), 4.76 (d, 1 H, *J* = 6.2Hz), 4.70 (dt, 1 H, *J* = 8Hz and 4.4 Hz), 1.99-0.3 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.63, 151.26, 134.1, 129.19, 128.46, 127.91, 127.77, 127.64, 126.01, 125.76, 125.24, 125.15, 122.08, 119.78, 107.76, 51.42, 47.75, 39.99, 33.67, 27.37, 27.22, 26.85, 26.35, 26.28, 25.98, 24.69m -0.01, -3.55, -4.54. $[\alpha]^{23}_{D}$ -207.8 (c 0.56, CH_2Cl_2)

Preparation of 2-(Dimethylphenylsilanyl)-4-methoxy-2*H*-pyridine-1-carboxylic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (26). Toluene (5.5 mL), TCC chloroformate (1 mmol) and 4-methoxypyridine (0.11 mL, 1.1 mmol) were stirred under argon and at -23 °C for 15 minutes. The solution of the pyridinium salt was then cooled to -85 °C (Et_2O/CO_2) and dimethylphenylsilylmagnesium chloride (**13**) (1.5 mmol) was added dropwise over 15 min. The mixture was stirred for 30 min at – 85 °C and then allowed to come to room temperature for another 30 min. A saturated solution of sodium bicarbonate (5.5 mL) was added, and the mixture was stirred for 5 min at room temperature and then extracted with ether. The combined organic layers were washed with water (2 x) and brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by radial PLC (5% EtOAc/hexanes) yielded 294 mg (66%) of **26** as a clear oil. IR (thin film, neat, NaCl) 2930, 2357, 1695, 1426, 1253 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.56-7.1 (m, 10 H), 5.92 (d, 1 H, J=7.8 Hz), 4.74-4.67 (m, 2 H), 4.24-4.22 (m, 1 H), 3.46 (s, 3 H), 1.98-1.22 (m, 15 H), 0.37-0.29 (m, 7 H); ^{13}C NMR (75 MHz) δ 154.62, 151.87, 127.83, 125.41, 125.31, 124.86, 75.44, 51.50,

49.16, 44.97, 40.05, 34.07, 29.70, 27.33, 27.13, 26.54, 26.28, 26.20, 26.10, 24.76, 24.57, 0.86, 0.45, -0.01; $[\alpha]^{23}_{D}$ -40.9 (c 0.66, CH_2Cl_2).

Preparation of 2-(Dimethylphenylsilanyl)-4-hydroxy-piperidine-1-carboxylic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (25). To 30 mg (0.06 mmol) of **18a** was added 3 mg of $Pd(OH)_2/C$. EtOAc (2 mL) was added and the mixture was stirred under H_2 for 2 h. The solution was filtered through a pad of Celite and concentrated. Purification by radial PLC (10% EtOAc/hexanes) yielded 29 mg (98%) of **25** as a clear oil. IR (thin film, neat, NaCl) 2926, 2863, 1694, 1386, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.13 (m, 10 H), 4.68 (m, 2 H), 2.96-2.84 (m, 2 H), 2.02-1.23 (m, 21 H), 0.18-0.17 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.36, 154.54, 133.89, 127.83, 127.69, 127.52, 125.31, 125.25, 70.30, 69.77, 51.67, 51.47, 48.77, 48.00, 45.19, 44.39, 35.27, 35.07, 34.92, 33.94, 33.89, 26.08, 26.02, 24.71, 24.41, 1.14, -0.01, -0.44, -1.09. $[\alpha]^{23}_{D}$ +27 (c 0.63, CH_2Cl_2).

Preparation of (*S*, *S*)-1-[4-*tert*-Butoxymethyl-3-(1-methylpyrrolidin-2-yl)-4*H*-pyridin-1-yl]-2,2-dimethylpropan-1-one (81). Potassium *tert*-butoxide (0.5 g, 4 mmol) was suspended in 16 mL of *tert*-butylmethyl ether (TBME). After cooling at -78 °C, the well-stirred mixture was treated with *s*-butyllithium (3 mL, 4 mmol) over 2 min. A bright orange color was observed and stirring at -78 °C was continued for 2 h. A solution of $CuBr•SMe_2$ (0.4 g, 2 mmol) in isopropyl sulfide (3 mL) and TBME (5 mL) was slowly added. The resulting cuprate solution was stirred at -78 °C for 40 min.

In a separate flask, a solution of nicotine (0.16 mL, 1 mmol) in THF (1 mL) was cooled to 0 °C and treated with pivaloyl chloride (0.12 mL, 1 mmol). The mixture was stirred at 0 °C for

1.5 h. It was cooled to -78 °C, and treated with the cuprate solution prepared above. The reaction mixture was stirred for 3 h at -78 °C. After addition of a saturated aqueous solution of NH_4Cl (20 mL), the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with 20% NH_4Cl/NH_4OH, water and brine, and were dried over K_2CO_3. After evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (hexanes) to afford 0.217 g (58%) of **81** as a yellow oil. IR (thin film, neat, NaCl) 2968, 1661, 1311 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21 (s, 1 H), 7.07 (d, I H, *J* = 8 Hz), 5.24 (dd, 1 H, *J* = 4.8 and 8 Hz), 3.58 (dd, 1 H, *J* = 4 and 8 Hz), 3.12 (t, 1 H, *J* = 8.8 Hz), 3.07 - 3.00 (m, 2 H), 2.57 (t, 1 H, *J* = 6.8 Hz), 2.28-2.08 (m, 5 H), 1.94-1.70 (m, 4 H), 1.35-1.12 (m, 19 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 173.3, 123.7, 122.9, 119.9, 110.3, 72.3, 72.2, 70.3, 66.0, 56.6, 40.2, 39.2, 39.1, 36.2, 31.0, 28.0, 27.9, 27.3, 27.2, 22.6; HRMS Calcd for $C_{20}H_{34}N_2O_2$: 335.2699 $[M+H]^+$. Found: 335.2715 $[M+H]^+$. $[\alpha]^{29}_D$ -9.6 (c 4.3, CH_2Cl_2).

Preparation of (*S*)-4-*tert*-Butoxymethyl-3-(1-methylpyrrolidin-2-yl)-pyridine (88). A solution of **81** (0.194 g, 0.5 mmol), sulfur (0.02 g, 0.5 mmol) and toluene (5 mL) was refluxed for 1 d. After filtration of the mixture through a pad of Celite and evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (hexanes) to afford 0.091 g (54%) of **88** as a yellow oil. IR (thin film, neat, NaCl) 2970, 2778, 1594, 1362, 1193, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.72 (s, 1 H), 8.45 (d, 1 H, *J* = 6.4 Hz), 7.40 (d, 1 H, *J* = 6.4 Hz), 4.52 (s, 2 H), 3.32-3.20 (m, 3 H), 2.32-2.22 (m, 2 H), 2.18 (s, 3 H), 1.96-1.66 (m, 4 H), 1.29 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.3, 147.7, 146.2,

135.3, 121.4, 73.4, 65.2, 59.6, 56.5, 40.2, 33.7, 27.20, 22.4; HRMS Calcd for $C_{15}H_{24}N_2O$: 249.1967 $[M+H]^+$. Found: 249.1964 $[M+H]^+$. $[\alpha]^{28}_D$ -108.2 (c 3.4, CH_2Cl_2).

Preparation of (*S*, *S*)-1-[4-Benzyloxymethyl-3-(1-methylpyrrolidin-2-yl)-4H-pyridin-1-yl]-2,2-dimethylpropan-1-one (80). To a stirred solution of (benzyloxymethyl)tributyl stannane (prepared according to reference 35) (0.308 g, 0.75 mmol) in THF (0.75 mL) cooled at -78 °C was added *n*- butyllithium (0.35 mL, 0.75 mmol). After stirring at -78 °C for 30 min, the Lipshultz reagent (3 mL, 0.75 mmol) was introduced dropwise, and the mixture was allowed to stir for 30 min at -78 °C.

In a separate flask, a stirred solution of nicotine (0.08 mL, 0.5 mmol) in THF (1 mL) was cooled at 0 °C and treated with pivaloyl chloride (0.06 mL, 0.5 mmol). This solution was stirred at 0 °C for 1.5 h. The cuprate solution prepared above was transferred via a double tipped needle surrounded by a layer of dry ice to the pyridinium salt of nicotine previously cooled to -78 °C. After addition of a saturated aqueous solution of NH_4Cl (10 mL), the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with 20% NH_4Cl/NH_4OH, water and brine, and were dried over K_2CO_3. After evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (hexanes) to afford 0.107 g (70%) of **80**. IR (thin film, neat, NaCl) 2928, 1772, 1724, 1656, 1599, 1454, 1364, 1267, 1153, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.01 – 6.94 (m, 5 H), 6.80 (d, 1 H, *J* = 8 Hz), 4.93 (dd, 1 H, *J* = 4.8 Hz and 8 Hz), 4.18 (d, 2 H, *J* = 6.8 Hz), 3.37 (dd, 1 H, *J* = 4 Hz and 8.4 Hz), 3.05 (t, 1 H, *J* = 8 Hz), 2.87 – 2.83 (m, 1 H), 2.74 (t, 1 H, *J* = 7.6 Hz), 2.25 (t, 1 H, *J* = 7.6 Hz), 1.85 (s, 3 H), 1.81 – 1.77 (m, 1 H), 1.58 – 1.37 (m, 4 H), 1.01 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.65, 138.51, 128.09, 127.28, 127.22, 124.40,

123.45, 119.32, 109.80, 74.32, 72.78, 70.55, 56.69, 40.32, 39.31, 35.62, 30.74, 28.06, 22.74; HRMS Calcd for $C_{23}H_{32}N_2O_2$: 369.2542 $[M+H]^+$. Found: 369.2543 $[M+H]^+$. $[\alpha]^{28}_D$ +26.6 (c 5.6, CH_2Cl_2).

Preparation of (*S*)-4-Benzyloxymethyl-3-(1-methylpyrrolidin-2-yl)pyridine (87). A solution of **80** (0.176 g, 0.48 mmol), sulfur (0.015 g, 0.48 mmol) and toluene (5 mL) was refluxed for 3 d. After filtration of the mixture through a pad of Celite and evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (hexanes) to afford 0.08 g (60%) of **87** as a yellow oil. IR (thin film, neat, NaCl) 3436, 1637, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1 H), 8.47 (d, 1 H, *J* = 4.8 Hz), 7.40 – 7.27 (m, 6 H), 4.62 (d, 2 H, *J* = 13.2 Hz), 3.34 – 3.18 (m, 2 H), 2.28 – 2.18 (m, 2 H), 2.15 (s, 3 H), 2.11 – 1.09 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.31, 148.37, 145.16, 137.86, 128.67, 128.06, 127.98, 122.14, 72.92, 68.19, 65.88, 57.07, 40.75, 34.28, 27.83, 22.91; HRMS Calcd for $C_{18}H_{22}N_2O$: 283.1810 $[M+H]^+$. Found: 283.1800 $[M+H]^+$. $[\alpha]^{24}_D$ -75.9 (c 2.5, CH_2Cl_2).

Preparation of 1-[4-(Dimethylphenylsilanyl)-3-(1-methyl-pyrrolidin-2-yl)-4*H*-pyridin-1-yl]-2,2-dimethylpropan-1-one (82). First a solution of (dimethylphenylsilyl)magnesium bromide (4 mmol) in THF was prepared according to our previous procedure and cooled to -78 °C. A solution of CuBr• SMe_2 (0.4 g, 2 mmol) in 4 mL of diisopropyl sulfide was added dropwise to the solution of the Grignard reagent prepared above. The resulting solution was then stirred at -78° C for 30 min during which time it turned brown-orange. In the meantime, a solution of nicotine (0.16 mL, 1 mmol) in 1 mL of THF was cooled to 0 °C and was treated with pivaloyl chloride (0.12 mL, 1 mmol). The salt was stirred at 0 °C for 1.5 h. It was then

cooled to -78 °C and the solution of the cuprate prepared above was injected via a double tipped needle surrounded by dry ice. The reaction mixture was then stirred at –78 °C for 4 h and then at -30 °C overnight. After warming to room temperature, the mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with ether (3 x). The combined organic layers were washed with 20% NH_4Cl/NH_4OH (50:50) (3 x), water, and brine, and were dried over K_2CO_3. The solvent was removed under reduced pressure to afford 0.6 g of crude material. Purification by radial PLC (5% EtOAc/hexanes) yielded 0.312 g (81%) of product **82** as a mixture of diastereomers and 0.04 g (25 %) of nicotine. The diastereomers were separated by radial PLC (hexanes) and the de was determined to be 68%.

Diastereomer (*S, S*): IR (thin film, neat, NaCl) 2960, 1649, 1321, 1115, 814 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ 7.49-7.29 (m, 6 H), 6.97 (s, 1 H), 4.99 (dd, 1 H, *J* = 5.6 and 7.2 Hz), 2.99 (t, 1 H, *J* = 7.2 Hz), 2.36 (d, 1 H, *J* = 5.6 Hz), 2.31 (t, 1 H, *J* = 8 Hz), 2.15 (s, 3 H), 2.06-1.00 (m, 14 H), 0.35-0.29 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 148.7, 146.4, 133.1, 133.5, 129.1, 128.9, 127.6, 127.4, 123.7, 118.6, 110.2, 68.1, 66.8, 56.6, 40.8, 38.7, 35.4, 32.1, 30.1, 27.6, -1.5, -1.6. HRMS Calcd for $C_{23}H_{34}N_2OSi$: 383.2519 $[M+H]^+$. Found: 383.2520 $[M+H]^+$. $[\alpha]^{25}_D$ -67.3 (c 4, CH_2Cl_2).

Diastereomer (*R, S*): IR (thin film, neat, NaCl) 2960, 1849, 1321 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.29 (m, 6 H), 6.86 (s, 1 H), 4.97 (t, 1 H, *J* = 6.6 Hz), 3.75-3.1 (m, 2 H), 2.88 (t, 1 H, *J* = 6.4 Hz), 2.45-1.57 (m, 8 H), 1.27 (s, 9 H), 0.35 (s, 3 H), 0.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 149.0, 146.7, 137.7, 133.9, 133.8, 128.8, 127.8, 127.6, 127.4, 111.5, 69.5, 56.5, 56.1, 40.3, 39.8, 39.0, 27.7, 27.5, 22.9, 22.4, -1.3, -1.4; HRMS Calcd for $C_{23}H_{34}N_2OSi$: 383.2519 $[M+H]^+$. Found: 383.2520 $[M+H]^+$. $[\alpha]^{25}_D$ +23.8 (c 7, CH_2Cl_2).

Preparation of (*S*)-4-(Dimethylphenylsilanyl)-3-(1-methylpyrrolidin-2-yl)pyridine (89). To a solution of **82** (1 g, 2.6 mmol) in 80 mL of toluene was added sublimed sulfur (0.09 g, 2.6 mmol). The reaction mixture was stirred and heated at 90 °C for 2 days. Evaporation of the solvent under reduced pressure afforded 1.11 g of crude product. Purification by radial PLC (5% EtOAc/hexanes) yielded 0.6 g (76 %) of product **89** as a yellow oil. IR (thin film, neat, NaCl) 2950, 2774, 1579, 1427, 1251 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1 H), 8.27 (d, 1 H, *J* = 6.8 Hz), 7.31-7.13 (m, 6 H), 3.03 (t, 1 H, *J* = 10.8 Hz), 2.95-2.90 (m, 1 H), 1.97-1.86 (m, 2 H), 1.69 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 146.2, 145.4, 144.3, 137.0, 133.5, 132.6, 128.9, 128.0, 127.5, 127.1, 68.0, 56.0, 39.4, 35.3, 22.1, -1.69, -1.74. HRMS Calcd for $C_{18}H_{24}N_2Si$: 297.1787 $[M+H]^+$. Found: 297.1801 $[M+H]^+$. $[\alpha]^{25}_D$ -82.1 (c 4, CH_2Cl_2).

Preparation of (*S*)-[3-(1-Methylpyrrolidin-2-yl)pyridin-4-yl]methanol (90). To a solution of **81** (0.3g, 1.3 mmol) in CH_2Cl_2 (10 mL) cooled at 0 ºC was slowly added TFA (15 mL). The reaction mixture was stirred at 0 ºC overnight. The solvent was removed under reduced pressure and anhydrous MeOH (10 mL) was added. Solid K_2CO_3 was added until pH was basic. The mixture was filtered through a pad of Celite, and the crude material was purified by radial PLC (5% EtOAc/hexanes) to afford 0.2368 g (90%) of **90** as a yellow oil. The data were identical as those described in the literature.

Preparation of (*S*) -3- (1-Methylpyrrolidin-2-yl)-1, 4- bis-trimethylsilanyl-1, 4-dihydropyridine (97) and (*S*) -3- (1-Methylpyrrolidin-2-yl)-4-trimethylsilanylpyridine

(98). To a suspension of lithium powder (0.42 g, 60 mmol) in freshly distilled THF (20 mmol) cooled at 0 °C was added freshly distilled trimethylchlorosilane (7.6 mL, 60 mmol). A solution of (*S*)-nicotine (3.2 mL, 20 mmol) in THF (20 mL) was added dropwise over 20 min. The reaction mixture was stirred at 0 °C for 1 h then warmed to rt for 3 h. The solution was decanted over 1 h and the liquid portion was canulated into a two- neck flask mounted with a distillation apparatus under Ar. After removal of THF by distillation at atmospheric pressure, the product was distilled under vacuum (0.5 mm Hg, bp 110 – 115 °C) to give 5.88 g (95%) of **97** as a yellow oil (95% pure by NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1 H), 5.78 – 5.72 (m, 1 H), 4.37 – 4.29 (m, 1 H), 3.06 – 2.93 (m, 1 H), 2.4-1.4 (m, 10 H), 0.08 (s, 9 H), -0.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.49, 126.41, 121.14, 102.08, 101.00, 66.67, 57.21, 41.05, 32.52, 26.41, 21.84, -0.83, -0.90, -2.43, -2.64. HRMS Calcd for $C_{16}H_{32}N_2Si_2$: 309.2182 $[M+H]^+$. Found: 309.2166 $[M+H]^+$.

Preparation of (*S*) -3- (1-Methylpyrrolidin-2-yl) -4- trimethylsilanylpyridine (98). Following the same conditions and quantities as above, after decantation of excess powder Li, the liquid portion was transferred into a 100 mL RBF and stirred under air overnight. After removal of the solvent under reduced pressure, the crude material was purified by radial PLC (5% EtOAc/hexanes) to afford 2.7 g (58%) of product **98** as a clear oil. IR (thin film, neat, NaCl): 2955, 2768, 1338, 1243, 1844 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1 H), 8.42 (d, 1 H, *J* = 6.4 Hz), 7.28 (dd, 1 H, *J* = 1.2 and 6.8 Hz), 3.36 – 3.24(m, 2 H), 2.35 – 1.60 (m, 8 H), 0.37 (s, 9 H); ^{13}C NMR (100 MHz, CDCl3) δ 149.16, 147.64, 147.01, 127.88, 68.89, 56.94, 40.45, 36.50, 22.82, 0.51. HRMS Calcd for $C_{13}H_{22}N_2Si$: 235.1631 $[M+H]^+$. Found: 235.1639 $[M+H]^+$. $[\alpha]^{25}_D$ -124 (CH_2Cl_2, c 4.9).

Preparation of (*S*)-4-(Allyldimethylsilanyl)-3-(1-methylpyrrolidin-2-yl)pyridine (99). To a suspension of lithium powder (0.21 g, 30 mmol) in freshly distilled THF (10 mmol) cooled at 0 °C was added freshly distilled allyldimethylchlorosilane (4.4 mL, 30 mmol). A solution of (*S*)-nicotine (1.6 mL, 10 mmol) in THF (10 mL) was added dropwise over 20 min. The reaction mixture was stirred at 0 °C for 1 h then warmed to rt for 3 h. The solution was decanted, and the liquid portion was canulated to a 100 mL RBF and stirred under air overnight. After removal of the solvent under reduced pressure, the crude material was purified by radial PLC (20% EtOAc/hexanes) to afford 1.02 g (55%) of product **99** as a clear oil. IR (thin film, neat, NaCl): 2966, 2836, 2776, 1630, 1579, 1399, 1251, 1163, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ8.49 (s, 1 H), 8.44 (dd, 1 H, *J* = 0.9 Hz and 5 Hz), 7.28 (dd, 1 H, *J* = 0.6 Hz and 4.8 Hz), 5.81 – 5.66 (m, 1 H), 4.94 – 4.87 (m, 2 H), 3.37 – 3.26 (m, 2 H), 2.37 – 1.67 (m, 10 H), 0.39 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.28, 147.01, 146.06, 144.63, 133.78, 128.23, 114.47, 68.94, 56.93, 40.49, 36.57, 24.11, 22.84, -1.55, -1.66. HRMS Calcd for $C_{15}H_{24}N_2Si$: 216.1787 $[M+H]^+$. Found: 216.1792 $[M+H]^+$. $[\alpha]^{28}_D$ -122 (c 11.2, CH_2Cl_2)

General Procedure for the Addition of Aldehydes to 97: Preparation of (*S*)-3-benzyl-5-(1-methylpyrrolidin-2-yl)-pyridine (100). To a stirred solution of benzaldehyde (0.05 mL, 0.51 mmol) in freshly distilled THF (1 mL) was added dropwise **97** (0.10 g, 0.34 mmol). A degassed solution of TBAF in THF (0.04 mL, 0.04 mmol) stored over molecular sieves was slowly added to the mixture. The reaction mixture was warmed to 60 ºC, stirred under Ar for 1 d and poured into a saturated aqueous solution of $NaHCO_3$. The product was extracted with diethyl ether (2 x). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by

radial PLC (10% MeOH/EtOAc) to give 0.048 g (56%) of **100** as a clear oil. IR (thin film, neat, NaCl): 3236, 2954, 2778, 1666, 1613, 1449, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.34 (m, 2 H), 7.88 (dd, 1 H, *J* = 1.6 and 13.2 Hz), 7.37 – 7.24 (m, 4 H), 5.84 (s, 1 H), 3.13 – 3.02 (m, 2 H), 2.25 – 1.69 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.43, 147.42, 143.90, 140.11, 138.19, 133.30, 133.25, 128.82, 127.95, 126.81, 74.24, 74.03, 69.15, 57.04, 40.47, 35.10, 22.51. HRMS Calcd for $C_{17}H_{20}N_2$: 252.1626 $[M+H]^+$. Found: 252.1635 $[M+H]^+$. $[\alpha]^{25}_D$ -126 (c 1.51, CH_2Cl_2).

(*S*)-3-(1-Methylpyrrolidin-2-yl)-5-thiophen-2-ylmethylpyridine (101). Following the general procedure, 2-thiophenecarboxaldehyde (0.07 mL, 0.75 mmol), **97** (0.2 mL, 0.68 mmol) and TBAF (0.07 mL, 0.07 mmol) in THF (1 mL) were stirred at 50 ºC for 1 d to give 0.118 g (67%) of **101** as a yellow oil. IR (thin film, neat, NaCl): 2967, 2943, 2911, 2836, 2778, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 2 H), 7.58 (s, 1 H), 7.14 (dd, 1 H, *J* = 1.6 Hz and 6.4 Hz), 6.93 – 6.90 (m, 1 H), 6.79 – 6.78 (m, 1 H), 4.14 (s, 2 H), 3.25 – 3.03 (m, 2 H), 2.33 – 1.68 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.76, 147.79, 142.73, 138.60, 135.79, 135.02, 126.97, 125.44, 124.31, 68.74, 57.01, 40.42, 35.17, 33.22, 22.57. HRMS Calcd for $C_{15}H_{18}N_2S$: 259.1269 $[M+H]^+$. Found: 259.1262 $[M+H]^+$. $[\alpha]^{25}_D$ -91.2 (c 0.45, CH_2Cl_2).

(*S*)-3-Furan-2-ylmethyl-5-(1-methylpyrrolidin-2-yl)pyridine (102). Following the general procedure, 2-furaldehyde (0.06 mL, 0.75 mmol), **97** (0.2 mL, 0.68 mmol) and TBAF (0.07 mL, 0.07 mmol) in THF (1 mL) were stirred at 50 ºC for 1 d to yield 0.077 g (47%) of **102** as a yellow oil. IR (thin film, neat, NaCl): 2967, 2942, 2777, 1455, 1432, 1416 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 2 H, *J* = 6.6 Hz), 7.56 (s, 1 H), 7.33 (s, 1 H), 6.29 (dd, 1 H, *J* = 1.8 Hz and 3 Hz), 6.01 – 6.00 (m, 1 H), 3.97 (s, 2 H), 3.27 – 3.05 (m, 2 H), 2.32 – 1.71 (m, 8

H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.47, 149.11, 148.01, 141.90, 138.67, 135.21, 133.65, 110.47, 106.70, 68.89, 57.17, 40.57, 35.32, 31.86, 22.73. HRMS Calcd for $C_{15}H_{18}N_2O$: 243.1497 $[M+H]^+$. Found: 243.1502 $[M+H]^+$. $[\alpha]^{25}_D$ -84.8 (c 1.3, CH_2Cl_2).

(*S*)-3-Dodecyl-5-(1-methylpyrrolidin-2-yl)pyridine (103). Following the general procedure, dodecyl aldehyde (1.2 mL, 5.44 mmol), **97** (0.8 mL, 2.72 mmol) and TBAF (0.27 mL, 0.27 mmol) in THF (1 mL) were refluxed for 2 d to yield 0.625 g (70%) of **103** as a yellow oil. IR (thin film, neat, NaCl): 2925, 2854, 1457 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (t, 2 H, *J* = 2.55 Hz), 7.51 (t, 1 H, *J* = 1.95 Hz), 3.28 – 3.03 (m, 2 H), 2.59 (t, 1 H, *J* = 7.8 Hz), 2.32 – 2.15 (m, 4 H), 2.00 – 1.61 (m, 5 H), 1.25 (s, 19 H), 0.90 – 0.86 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ149.06, 147.17, 134.70, 69.06, 57.25, 40.61, 35.31, 33.18, 32.11, 31.42, 29.85, 29.83, 29.75, 29.59, 29.56, 29.44, 22.89, 22.70, 14.34. HRMS Calcd for $C_{22}H_{38}N_2$: 331.3113 $[M+H]^+$. Found: 331.3109 $[M+H]^+$. $[\alpha]^{25}_D$ -56.5 (c 0.92, CH_2Cl_2).

Preparation of (*S*, *S*)-5,5'-hexyl-1,6- Bis-(1-methylpyrrolidin-2-yl)-[3,3']bipyridinyl (111). Following the general procedure, 1,6 hexanedial (0.55 g, 4.8 mmol), **97** (2.485 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol) in THF (10 mL) were refluxed for 15 h to afford 0.616 g (51%) of product **111** as an orange oil. IR (thin film, neat, NaCl): 2936, 2863, 1737, 1731, 1681, 1195, 1072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1 H), 8.42 (s, 2 H), 7.51 (s, 1 H), 7.23 (s, 1 H), 6.47 (s, 1 H), 4.41 – 1.00 (m, 32 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.15, 123.89, 120.68, 120.43, 110.25, 49.92, 35.76, 34.77, 31.75, 26.29. LRMS Calcd for $C_{26}H_{38}N_4$: 407.12 $[M+H]^+$. Found: 407.15 $[M+H]^+$. $[\alpha]^{28}_D$ -88 (c 2.6, CH_2Cl_2).

(*S*)- 3- (1-Methylpyrrolidin-2-yl) -4- trimethylsilanyl-4H-pyridine-1-carboxylic acid dimethylamide (104). To a stirred solution of **97** (0.2 mL, 1.36 mmol) in CH_2Cl_2 (6 mL) under Ar was added dropwise dimethylcarbamyl chloride (0.19 mL, 2.04 mmol). The reaction mixture was stirred at rt for 1 d. It was then poured into a saturated aqueous solution of $NaHCO_3$ (3 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x). The combined organic layers were washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded 0.49 g of crude material that was purified by radial PLC (5% EtOAc/hexanes) to yield 0.251 g (59%) of **104** as a clear oil. IR (thin film, neat, NaCl): 3363, 2924, 2348, 1657, 1449, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.65 (d, 1 H, *J* = 6.9 Hz), 6.35 (s 1 H), 4.83 – 4.78 (m, 1 H), 3.14-3.09 (m, 1 H), 2.88 (s, 6 H), 2.80-1.25 (m, 13 H), 0.085 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.29, 147.15, 128.04, 124.49, 120.09, 106.29, 68.23, 57.35, 41.47, 38.53, 33.04, 30.34, 29.91, 22.37, 0.63, - 2.00. HRMS Calcd for $C_{16}H_{29}N_3OSi$: 308.2157 $[M+H]^+$. Found: 308.2157 $[M+H]^+$. $[\alpha]^{25}_D$ -15.2 (c 0.15, CH_2Cl_2).

(*S*)-3-(1-Methylpyrrolidin-2-yl)-4H-pyridine-1-carboxylic acid dimethylamide (105). A solution of **104** (0.023 g, 0.075 mmol) and TBAF (0.075 mL, 0.075 mmol) in THF (5 mL) was stirred at rt for 1 h. The reaction mixture was quenched with 5 mL of a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ether (2 x). The combined organic layers were washed with brine and dried over K_2CO_3. Evaporation of the solvent under reduced pressure and purification of the crude material by radial PLC (5% EtOAc/hexanes) afforded 0.033 g (75%) of **105** as a clear oil. IR (thin film, neat, NaCl): 2953, 2910, 1659, 1627, 1440, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 6.45

– 6.41 (m, 1 H), 4.87 – 4.82 (m, 1 H), 3.10 – 3.05 (m, 1 H), 2.9 (s, 6 H), 2.80 – 2.78 (m, 2 H), 2.22 – 1.73 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.97, 125.89, 122.98, 114.93, 130.46, 70.72, 56.75, 40.34, 38.65, 28.57, 22.43, 21.72. HRMS Calcd for $C_{13}H_{21}N_3O$: 236.1763 $[M+H]^+$. Found: 236.1761 $[M+H]^+$. $[\alpha]^{24}_D$ -27.6 (c 0.29, CH_2Cl_2).

***N*-Methyl-*N*-(4-pyridin-3-yl-butyl)formamide (106).** To a solution of trifluoroethyl formate (0.08 mL, 0.82 mmol) in THF (2 mL) was slowly added **97** (0.2 mL, 0.68 mmol). A degassed solution of TBAF in THF (0.07 mL, 0.07 mmol) was slowly added and the reaction mixture was stirred at 50 ºC for 1 d. After addition of a saturated aqueous solution of $NaHCO_3$ (2 mL), the aqueous phase was extracted with diethyl ether (3 x). The combined organic layers were washed with brine and dried over K_2CO_3. Evaporation of the solvent under reduced pressure and purification of the crude material by radial PLC (20%EtOAc/hexanes) afforded 0.059 g (45%) of **106** as a yellow oil. IR (thin film, neat, NaCl) 2930, 2861, 1671, 1422, 1397 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 8.03 (s, 1 H), 7.51 – 7.48 (m, 1 H), 7.25 – 7.21 (m, 1 H), 3.39 – 3.25 (m, 2 H), 2.91 – 2.83 (m, 4 H), 2.67 – 2.63 (m, 2 H), 1.63 – 1.58 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.59, 149.88, 147.66, 147.46, 135.76, 123.44, 49.31, 32.54, 28.17, 27.84, 27.45, 26.06. HRMS Calcd for $C_{11}H_{16}N_2O$: 193.1335 $[M+H]^+$. Found: 193.1341 $[M+H]^+$.

(*S*)-3-(1-Methypyrrolidin-2-yl)-4H-pyridine-1-carbaldehyde (107). To a solution of ethyl formate (0.12 mL, 1.5 mmol) in THF (5 mL) was slowly added **97** (0.4 mL, 1.06 mmol). A degassed solution of TBAF in THF (0.14 mL, 0.14 mmol) was slowly added, and the reaction mixture was stirred at rt for 1 h. After addition of a saturated aqueous solution of

$NaHCO_3$ (2 mL), the aqueous phase was extracted with diethyl ether (3 x). The combined organic layers were washed with brine and dried over K_2CO_3. Evaporation of the solvent under reduced pressure and purification of the crude material by radial PLC (pentane) afforded 0.112 g (55 %) of **107** as a yellow oil. IR (thin film, neat, NaCl) 2964, 2831, 1673, 1598, 1430 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.09 (m, 1 H), 6.98 – 6.93 (m, 1 H), 6.43 – 6.37 (m, 1 H), 5.23 – 5.07 (m, 1 H), 3.11 – 1.70 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.61, 158.38, 123.45, 120.10, 119.87, 117.15, 109.82, 107.91, 70.22, 69.87, 56.76, 56.73, 40.44, 40.31, 29.20, 28.74, 28.85, 22.97, 22.59, 22.50. HRMS Calcd for $C_{11}H_{16}N_2O$: 193.1341 $[M+H]^+$. Found: 193.1354 $[M+H]^+$. $[\alpha]^{24}_D$ -77.6 (c 2.48, CH_2Cl_2).

(*S*)-1-[3-(1-Methylpyrrolidin-2-yl)-4H-pyridin-1-yl]ethanone (108). To a solution of trifluoroethyl acetate (0.053 g, 0.37 mmol) in THF (1 mL) was added **97** (0.1 mL, 0.34 mmol). A degassed solution of TBAF in THF (0.04 mL, 0.04 mmol) was added dropwise, and the reaction mixture was stirred at rt for 1 d. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL). The aqueous layer was extracted with ether (2 x), and the combined organic layers were washed with brine and dried over K_2CO_3. The solvent was removed under reduced pressure and the crude material was purified by radial PLC (5% EtOAc/hexanes) to afford 0.057 g (70%) of **108** as a yellow oil. IR (thin film, neat, NaCl): 2957, 2924, 2853, 1673, 1377, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 – 7.13 (m, 1 H), 6.53 – 6.49 (m, 1 H), 5.14 – 5.02 (m, 1 H), 3.69 – 3.06 (m, 3 H), 2.8 (s, 2 H), 2.60 – 2.50 (m, 1 H), 2.22 – 1.17 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.69, 148.77, 135.07, 123.97, 122.17, 120.72, 119.51, 108.10, 107.90, 70.75, 57.18, 56.92, 56.85, 40.54, 40.52,

40.38, 29.40, 26.68, 22.66, 22.63, 22.59, 21.69, 21.66, 21.64. HRMS Calcd for $C_{12}H_{18}N_2O$: 207.1497 $[M+H]^+$. Found: 207.1484 $[M+H]^+$. $[\alpha]^{25}_D$ -55.48 (c 0.18, CH_2Cl_2)

General procedure for the addition of carbonates to (*S*)-3-(1-methylpyrrolidin-2-yl)-1, 4-bis-trimethylsilanyl-1,4-dihydropyridine (97). Preparation of (*S*) -3- (1-methyl pyrrolidin-2-yl)-4H-pyridine-1-carboxylic acid methyl ester (109). To a solution of dimethyl carbonate (0.05 mL, 0.6 mmol) in 2 mL of dry THF was slowly added **97** (0.2 mL, 0.68 mmol). A solution of TBAF in THF (0.06 mL, 0.06 mmol) was added dropwise and the reaction mixture was stirred at rt for 1 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ether (2 x), and the combined organic layers were washed with brine and dried over K_2CO_3. The solvent was removed under reduced pressure, and the crude material was purified by radial PLC (hexanes) to afford 0.137 g (91%) of **109** as a clear oil. IR (thin film, neat, NaCl): 2949, 2826, 2764, 1721, 1695, 1437, 1334, 1313, 1194, 983 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 – 6.51 (m, 2 H), 4.88 – 4.77 (m, 1 H), 3.65 (s, 3 H), 2.95 – 2.91 (m, 1 H), 2.64 – 2.62 (m, 2 H), 2.41 – 2.33 (m, 1 H), 2.05 – 1.93 (m, 5 H), 1.68 – 1.53 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.81, 123.15, 122.74, 120.28, 119.63, 118.08, 117.71, 106.22, 105.94, 70.37, 56.60, 53.05, 40.16, 40.08, 28.76, 28.38, 22.37, 21.56, 21.05. HRMS Calcd for $C_{12}H_{18}N_2O_2$: 223.1447 $[M+H]^+$. Found: 223.1434 $[M+H]^+$. $[\alpha]^{24}_D$ -65.5 (c 0.08, CH_2Cl_2).

Methyl-(4-pyridin-3-yl-butyl)carbamic acid phenyl ester (110). Following the general procedure above, diphenyl carbonate (0.218 g, 1.02 mmol), **97** (0.2 mL, 0.68 mmol) and TBAF (0.07 mL, 0.07 mmol) in THF (2 mL) were stirred at rt for 18 h to yield 0.167 g (50%) of **110** as a yellow oil. . IR (thin film, neat, NaCl): 2934, 2861, 1719, 1206 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 8.45 (s, 2 H), 7.51 – 7.05 (m, 6 H), 3.89 – 3.45 (m, 2 H), 3.06 (s, 2 H), 2.98 (s, 2 H), 2.68 (m, 2 H), 1.89 – 1.66 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.00, 147.59, 136.03, 135.95, 129.35, 125.37, 125.28, 123.49, 121.85, 49.01, 34.94, 34.56, 32.70, 28.21, 58.26, 26.92. HRMS Calcd for $C_{17}H_{20}N_2O_2$: 285.1603 $[M+H]^+$. Found: 285.1599 $[M+H]^+$.

(*S*)-3-Formyl-5-(1-methylpyrrolidin-2-yl)-4H-pyridine-1-carboxylic acid methyl ester (115). To a solution of DMF (0.04 mL, 0.54 mmol) in 4 mL of CH_2Cl_2 cooled at 0 °C was slowly added $POCl_3$ (0.025 mL, 0.27 mmol). The ice bath was removed and the reaction mixture was stirred at rt for 30 min. The mixture was then transferred via a double tipped needle to a solution of **109** (0.040 g, 0.18 mmol) in 4 mL of CH_2Cl_2 cooled at 0 °C. The reaction mixture was stirred at rt for 1 d. A solution of NaOAc (0.024g, 0.29 mmol) in 0.5 mL of water was added, and the reaction mixture was stirred at rt for 20 min. A saturated aqueous solution of $NaHCO_3$ was slowly added until pH was basic (about 10 mL). The aqueous layer was then extracted with CH_2Cl_2 (4 x), and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (15% EtOAc/hexanes) to afford 0.024 g (54%) of **115** as white crystals. Mp 78 - 79 °C. IR (thin film, neat, NaCl): 2955, 2767, 1731, 1667, 1620, 1437, 1394, 1203, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.45 (s, 1 H), 7.65 (m, 1 H), 6.81 (s, 1 H), 3.91 (s, 3 H), 3.12 – 3.07 (m, 1 H), 2.93(s, 2 H), 2.59 (m, 1 H), 2.20 – 2.12 (m, 3 H), 1.81 – 1.62 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.13, 141.44, 122.61, 120.52, 118.42, 69.75, 56.98, 54.47, 40.61, 29.45, 22.91, 19.86. HRMS Calcd for $C_{13}H_{18}N_2O_3$: 251.1396 $[M+H]^+$. Found: 251.1390 $[M+H]^+$. $[\alpha]^{25}_D$ -51.7 (c 0.8, CH_2Cl_2).

(*S*)-5-(1-Methylpyrrolidin-2-yl)-1,4-dihydropyridine-3-carbaldehyde (116). To a solution of **115** (0.012g, 0.05 mmol) in 2 mL of anhydrous MeOH was slowly added triethylamine (0.02 mL, 0.15 mmol), and the reaction mixture was stirred at rt for 1 d. Evaporation of the solvent afforded a quantitative yield (0.010 g) of **116** as a yellow oil. The product was used without further purification. IR (thin film, neat, NaCl) 3416 – 3244, 2957, 1595, 1509, 1377, 1228 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.14 (s, 1 H), 6.85 (d, 1 H, J = 6 Hz), 6.48 (s, 1 H), 6.00 – 5.99 (m, 1 H), 3.05 –3.00 (m, 3 H), 2.45 (m, 1 H), 2.19 – 2.11 (m, 4 H), 1.83 – 1.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.59, 146.95, 119.91, 119.01, 112.67, 70.03, 57.03, 40.69, 28.96, 22.80, 20.37. HRMS Calcd for $C_{11}H_{16}N_2O$: 193.1341 $[M+H]^+$. Found: 193.1334 $[M+H]^+$. $[\alpha]^{28}_D$ -80.7 (c 0.55, CH_2Cl_2).

(*S*)-5-(1-Methylpyrrolidin-2-yl)pyridine-3-carbaldehyde (117). A solution of **116** (0.011 g, 0.044 mmol) and elemental sulfur (1.5 mg, 0.044 mmol) in 2 mL of toluene was refluxed for 1 d. After filtration through a pad of Celite, and evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (5% EtOAc/hexanes then EtOAc) to afford 7 mg (83%) of **117** as a clear oil. IR (thin film, neat, NaCl): 2991, 2955, 2724, 2510, 1693, 1683, 1202, 1183, 1135, 1049, 834 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.13 – 10.12 (m, 1 H), 8.97 – 8.96 (m, 1 H), 8.79 (s, 1 H), 8.18 (s, 1 H), 3.30 – 3.20 (m, 2 H), 2.38 – 1.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.26, 154.81, 150.91, 135.13, 131.69, 68.53, 57.19, 40.64, 40.64, 35.66, 23.02. HRMS Calcd for $C_{11}H_{14}N_2O$: 191.1184 $[M+H]^+$. Found: 191.1182 $[M+H]^+$.

(*S*)-3-Ethynyl-5-(1-methylpyrrolidin-2-yl)pyridine or SIB-1508Y (56). To a solution of tBuOK in THF (0.08 mL, 0.08 mmol) cooled at –78 °C was added dropwise a solution of methyl diazomethyl phosphonate (prepared according to the procedure described in the literature) in THF (0.1 mL, 0.08 mmol). The solution was stirred at –78 °C for 5 min, then a solution of **117** (0.0126g, 0.066 mmol) in THF (1 mL) was added via a double tipped needle. The reaction mixture was stirred at –78 °C for 16 h, then allowed to warm to rt over 2 h. After evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (10% EtOAc/hexanes) to afford 6.1 mg (51%) of **56** as a clear oil. The data were identical to those described in the literature.[29c]

Preparation of 3-(1-Methyl-1-oxy-pyrrolidin-2-yl)-4-trimethylsilanyl-pyridine 1-oxide (119). To a solution of **98** (0.45 g, 1.94 mmol) in CH_2Cl_2 (6 mL) cooled at 0 ºC was slowly added a solution of mCPBA (0.7 g, 4.08 mmol) in CH_2Cl_2 (6 mL). The ice bath was removed and the reaction mixture was stirred at rt for 16 h. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (basic Al_2O_3, 10% MeOH/EtOAc) to afford 0.417 g (98%) of **119** as a yellow oil. IR (thin film, neat, NaCl) 2956, 2870, 2669, 2498, 1661, 1459, 1402, 1253, 1153, 1039, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1 H), 9.20 (s, 1 H), 8.31 (d, 1 H, J = 2.6 Hz), 7.94 – 7.90 (m, 1 H), 7.16 – 7.13 (m, 2 H), 3.56 – 1.84 (m, 29 H), 0.15 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.48, 152.84, 151.73, 151.37, 141.34, 124.97, 78.28, 71.40, 54.17, 49.71, 49.43, 49.15, 48.87, 48.58, 29.52, 21.05. HRMS Calcd for $C_{13}H_{22}N_2O_2Si$: 267.1529 $[M+H]^+$. Found: 267.1524 $[M+H]^+$.

Preparation of (*S*)-3-(1-Methylpyrrolidin-2-yl)-4-trimethylsilanylpyridine 1-oxide (120). To a solution of **119** (0.2282 g, 0.86 mmol) in MeOH (5 mL) cooled at 0 ºC was slowly added a solution of sodium bisulfite (40% in water, 0.6 mL). Acetic acid (0.9 mL) was then introduced and the reaction mixture was stirred at 0 ºC for 30 min. Solid K_2CO_3 was added until pH was basic. The mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (neutral Al_2O_3, 10% MeOH/EtOAc) to afford 0.155 g (72%) of **120** as a yellow oil. IR (thin film, neat, NaCl) 2929, 2865, 1724, 1664, 1636, 1604, 1453, 1246, 1071, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, 1 H, *J* = 1.5 Hz), 8.05 – 8.02 (m, 1 H), 7.28 – 7.26 (m, 1 H), 3.36 (t, 1 H, *J* = 7.8 Hz), 3.22 (t, 1 H, *J* = 7.5 Hz), 2.36 – 1.57 (m, 8 H), 0.36 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.16, 138.38, 137.89, 136.32, 130.85, 67071, 56.76, 40.41, 36.42, 23.19, 0.47. HRMS Calcd for $C_{13}H_{22}N_2OSi$: 251.1580 $[M+H]^+$. Found: 251.1579 $[M+H]^+$. $[\alpha]^{24}_D$ -139.7 (c 1.14, CH_2Cl_2).

Preparation of (*S*)-2-Iodo-5-(1-methyl-pyrrolidin-2-yl)-4-trimethylsilanylpyridine (137). Under Ar atmosphere, 2,2,6,6-tetramethyl piperidine (0.51 mL, 3.04 mmol) was added to dry THF (6 mL) and the mixture was cooled to –78 °C. *n*- Butyllithium was slowly added at –78 °C and then the mixture was stirred at 0 °C for 30 min. In a separate flask, a solution of zinc chloride in THF (6.62 mL, 3.31 mmol) was cooled to –78 °C and *tert*- butyllithium (3.9 mL, 6.62 mmol) was slowly added. The mixture was stirred at –78 °C for 1 h. The solution of di (*tert*-butyl)zinc prepared was then introduced via a double tipped needle into the solution of TMP-lithium cooled at –78 °C. The mixture was allowed to warm to rt for 1 h. To the mixture was added a solution of 4-(trimethylsilanyl)nicotine **(98)** (0.323 g, 1.38 mmol) in

THF (4 mL). The mixture was stirred at rt overnight and the solution turned brown orange. A solution of iodine (1.65 g, 5.52 mmol) was slowly added at 0 °C and the reaction mixture was allowed to warm to rt for 7 h. A saturated aqueous solution of $NaHCO_3$ (2 mL) was added. The aqueous layer was extracted with ether (3 x). The combined organic layers were washed with water and dried over K_2CO_3. The solvent was removed under reduced pressure and the crude material was purified by radial PLC (hexanes) to afford 0.053 g (15%) of **137** as a yellow oil and 0.2 g (62%) of **98**. IR (thin film, neat, NaCl): 2954, 1446, 1251, 1092, 840 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1 H), 7.62 (s, 1 H), 3.28 – 3.23 (m, 2 H), 2.30 – 1.62 (m, 8 H), 0.34 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.56, 150.87, 144.29, 138.80, 117.14, 68.34, 56.95, 40.49, 36.71, 22.89, 0.44. HRMS Calcd for $C_{13}H_{21}N_2ISi$: 361.0597 $[M+H]^+$. Found: 361.0611 $[M+H]^+$. $[\alpha]^{24}_D$ -88.68 (c 2.5, CH_2Cl_2)

Preparation of (*S*)-2-Chloro-5-(1-methyl-pyrrolidin-2-yl)-4-trimethylsilanyl-pyridine (123). A solution of 2-dimethylaminoethanol (0.57 mL, 5.7 mmol) in hexanes (7 mL) was cooled to 0 °C and treated with *n*-butyllithium (5.2 mL, 11.4 mmol). After 30 min at 0 °C, a solution of 4-(trimethylsilanyl)nicotine **(98)** (0.4461 g, 1.9 mmol) in hexanes (3.5 mL) was added dropwise, and the mixture was stirred at 0 °C for 1.5 h. The mixture was cooled to – 78 °C and a solution of hexachloroethane (1.8 g, 7.6 mmol) in hexane (5 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to rt over 20 min. The hydrolysis was performed at 0 °C with water (10 mL). The aqueous layer was extracted with ether (2 x). The combined organic layers were dried over K_2CO_3. The solvent was removed under reduced pressure and the crude material was purified by radial PLC (hexanes) to afford 0.271 g (53%) of **123** as a yellow oil. IR (thin film, neat, NaCl):

2956, 2779, 1252, 1119, 1074, 840 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (s, 1 H), 7.27 (s, 1 H), 3.33 – 3.22 (m, 2 H), 2.33 – 1.61 (m, 8 H), 0.35 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.29, 152.05, 149.41, 148.47, 128.10, 126.76, 68.06, 56.80, 40.32, 36.61, 22.74, 0.56, 0.28. HRMS Calcd for $C_{13}H_{21}N_2ClSi$: 268.1163 $[M]^+$. Found: 268.1139$[M]^+$. $[\alpha]^{24}_D$ -101.7 (c 14, CH_2Cl_2).

Preparation of (*S*) -2- Chloro -4- (dimethylphenylsilanyl) -5- (1-methylpyrrolidin-2-yl) pyridine (142). Same as for the preparation of **123**: 0.437 g (1.47 mmol) of **89**, 4.41 mL (8.82 mmol) of *n*-BuLi, 0.44 mL (4.41 mmol) of dimethylamino ethanol and 1.39 g (5.88 mmol) of C_2Cl_6 gave 0.209 g (43%) of **142** as a yellow oil and 11% of **144** as a yellow oil. **142**: IR (thin film, neat, NaCl): 2956, 2782, 1567, 1451, 1428, 1361, 1252, 1119, 816 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1 H), 7.62 (s, 1 H), 7.45 – 7.32 (m, 6 H), 3.15 – 3.09 (m, 2 H), 1.89 – 1.25 (m, 8 H), 0.63 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.47, 148.75, 134.20, 129.51, 128.08, 127.65, 68.56, 56.78, 40.11, 38.08, 35.94, 32.94, 32.47, 22.86, 22.67, 14.19, -0.92, -0.97. HRMS Cacd for $C_{18}H_{23}N_2ClSi$: 331.1397 $[M+H]^+$. Found: 331.1397 $[M+H]^+$. $[\alpha]^{25}_D$ -84 (c 6.7, CH_2Cl_2).

144: IR (thin film, neat, NaCl): 3068, 2956, 2871, 2779, 1581, 1457, 1370, 1251, 1112, 815 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1 H), 7.46 – 7.19 (m, 5 H), 3.11 (q, 2 H, *J* = 7.8 Hz), 2.77 (t, 2 H, J = 8 Hz), 2.08 – 1.38 (m, 13 H), 0.95 (t, 3 H, *J* = 7.2 Hz), 0.62 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.36, 148.61, 146.31, 141.27, 138.05, 134.15, 133.27, 129.49, 128.05, 127.78, 127.65, 68.50, 56.72, 40.05, 37.95, 35.87, 32.44, 22.81, 22.61, 14.16, -0.98, -1.03. HRMS Cacd for $C_{22}H_{32}N_2Si$: 353.2413 $[M+H]^+$. Found: 353.2422 $[M+H]^+$. $[\alpha]^{25}_D$ -65.2 (c 9.37, CH_2Cl_2).

Preparation of (*S*) -4- (Allyldimethylsilanyl) -2- chloro -5- (1-methylpyrrolidin-2-yl)-pyridine (143). Following the same procedure as above, **99** (0.8166 g, 3.13 mmol) in hexanes (5 mL) was cooled to -30 ºC and treated with *n*-BuLi (7.35 mL, 16.9 mmol) and dimethylamino ethanol (0.89 mL, 9.39 mmol) in hexanes (15 mL) for 2.5 h. The solution was cooled to -78 ºC and treated with C_2Cl_6 (6.58 g, 12.52 mmol) in toluene (10 mL), and the mixture was stirred for 3 h to afford 0.515g (56%) of product **143** as a yellow oil. IR (thin film, neat, NaCl): 2959, 1631, 1453, 1252, 1119, 1074, 1049, 837 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.65 (s, 1 H), 7.27 (s, 1 H), 5.77 – 5.65 (m, 1 H), 4.94 – 4.87 (m, 2 H), 3.37 – 3.26 (m, 2 H), 2.37 – 1.25 (m, 10 H), 0.37 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.73, 143.71, 133.43, 128.63, 115.05, 68.31, 56.98, 40.54, 36. 84, 23.98, 22.93, -1.59, -1.71. HRMS Cacd for $C_{15}H_{23}N_2ClSi$: 295.1397 $[M+H]^+$. Found: 295.1392 $[M+H]^+$. $[\alpha]^{28}_D$ -72.8 (c 0.46, CH_2Cl_2).

Preparation of (*S*)-4-(Allyldimethylsilanyl)-2-butyl-5-(1-methylpyrrolidin-2-yl)-pyridine (146). Following the same procedure as above, **99** (0.2304 g, 0.88 mmol) in hexanes (8 mL) was cooled to -20 ºC and treated with *n*-BuLi (2.6 mL, 4.75 mmol) and dimethylamino ethanol (0.26 mL, 2.64 mmol) in hexanes (2 mL), and the mixture was stirred for 1 h. The solution was then treated with C_2Cl_6 (0.21 g, 0.88 mmol) in THF (5 mL) for 2 h at -20 ºC to afford 0.2596 g (26%) of **143** product and 0.2786 g (12%) of product **146** as a yellow oil. IR (thin film, neat, NaCl): 2957, 2777, 1630, 1456, 1251 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 1 H), 7.11 (s, 1 H), 5.77 – 5.73 (m, 1 H), 4.93 – 4.87 (m, 2 H), 3.31 – 3.24 (m, 2 H), 2.78 – 2.74 (m, 2 H), 2.30 – 2.16 (m, 5 H), 1.86 – 1.67 (m, 6 H), 1.43 – 1.38 (m, 3 H), 0.96 –

0.93 (m, 3 H), 0.37 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ159.47, 148.67, 134.11, 127.29, 114.44, 68.89, 57.02, 40.58. 38.04, 36.64, 32.47, 24.30, 22.84, 22.80, 14.19, -1.38, -1.48. HRMS Cacd for $C_{19}H_{32}N_2Si$: 317.2413 $[M+H]^+$. Found: 317.2408 $[M+H]^+$. $[\alpha]^{28}_D$ -99 (c 1.39, CH_2Cl_2).

Preparation of (*S*, *S*)-4,4'-Bis-(allyldimethylsilanyl)-5,5'-bis-(1-methylpyrrolidin-2-yl)-[2,2']bipyridinyl (145). A solution of BuLi-LiDMAE was prepared according to the above procedure with *n*-BuLi (1.3 mL, 3.02 mmol), dimethylamino ethanol (0.16 mL, 1.68 mmol) in hexanes (4 mL) and added to a solution of **99** (0.1436 g, 0.56 mmol) in hexanes (2 mL) cooled at -30 ºC. The solution was stirred at -30 ºC for 2.5 h and then cooled to -78 ºC. It was then treated with **99** (0.219 g, 0.84 mmol), warmed to -20 ºC and stirred overnight at that temperature. The hydrolysis was then performed at 0 °C with water (10 mL). The aqueous layer was extracted with ether (2 x). The combined organic layers were dried over K_2CO_3. The solvent was removed under reduced pressure and the crude material was purified by radial PLC (hexanes) to afford 0.12 g (41%) of product **145** as a yellow oil. IR (thin film, neat, NaCl): 2960, 1630, 1571, 1453, 1253, 1153, 817 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 2 H), 8.38 (s, 2 H), 5.82 – 5.71 (m, 2 H), 4.96 – 4.87 (m, 4 H), 3.42 – 3.28 (m, 4 H), 2.38 – 1.62 (m, 20 H), 0.45-0.40 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.91, 148.96, 147.15, 134.16, 125.74, 114.52, 68.90, 57.07, 40.55, 36.63, 24.35, 22.99, -1.42. HRMS Calcd for $C_{30}H_{46}N_4Si_2$: 519.3339 $[M+H]^+$. Found: 519.3351 $[M+H]^+$. $[\alpha]^{28}_D$ -174 (c 1.12, CH_2Cl_2).

Preparation of (*S*)-2-Chloro-4-(dimethylphenylsilanyl)-3-iodo-5-(1-methylpyrrolidin-2-yl)pyridine (147). To a solution of 2,2,6,6-tetramethyl piperidine (0.13 mL, 0.78 mmol) in THF (2 mL) at –78 °C was slowly added *n*-butyllithium (0.39 mL, 0.78 mmol). After stirring at –78 °C for 30 min, a solution of **142** (0.0696 g, 0.26 mmol) in THF (2 mL) was added dropwise, and the solution was stirred at –78 °C for 1 h. A solution of I_2 (0.24 g, 1.04 mmol) in THF (5 mL) was then slowly injected and the reaction mixture was stirred at –78 °C for 4 h. After addition of a saturated aqueous solution of $NaHCO_3$ (5 mL), the aqueous phase was extracted with ether (3 x). The combined organic layers were washed with water and brine, dried over $NaHSO_3$ and filtered through a pad of $NaHSO_3$. Evaporation of the solvent under reduced pressure and purification of the crude material by radial PLC (5% EtOAc/hexanes) afforded 0.0264 g (32 %) of **147** as a yellow oil. IR (thin film, neat, NaCl): 2935, 1695, 1570, 1454, 1428, 1360, 1254, 1114, 821cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1 H), 7.50 - 7.36 (m, 5 H), 4.56 – 4.51 (m, 1 H), 2.53 – 1.50 (m, 9 H), 0.66 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.36, 151.06, 150.88, 147.74, 140.90, 136.05, 134.00, 130.47, 129.87, 128.70, 61.34, 29.82, 28.36, 28.01, -1.67, -1.71. HRMS Calcd for $C_{18}H_{22}IClN_2Si$: 457.0364 $[M+H]^+$. Found: 457.0342 $[M+H]^+$. $[\alpha]^{24}_D$ -19.8 (c 0.02, CH_2Cl_2)

Preparation of (*S*)-3-(1-Methylpyrrolidin-2-yl)pyridin-4-ol (148) from 89. To a solution of **89** (0.9 g, 3.2 mmol) in 10 mL of methanol was added potassium hydrogen fluoride (0.25 g, 3.2 mmol). A solution of 30% hydrogen peroxide in water (0.88 mL, 7.7 mmol) was slowly added, and the reaction mixture was stirred and heated at 55 °C for 8 h. To the crude mixture was added K_2CO_3 until the pH of the solution became slightly basic (8-9). After filtration of the solid and evaporation of the solvent, the crude product was purified by radial

PLC (EtOAc) to yield 82% of **148** as a white solid. IR (neat) 2598, 23448, 1643 cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$) δ 8.68 (s, 1 H), 8.58-8.56 (m, 1 H), 8.12 (dd, 1 H, *J* =1.5 and 8 Hz), 7.47 (dd, 1 H, *J* =5.1 and 8 Hz), 4.61 (dd, 1 H, *J* = 7.2 and 12 Hz), 3.79-3.59 (m, 2 H), 2.94 (s, 3 H), 2.72-2.1 (m, 4 H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 152.8, 151.4, 141.3, 124.9, 78.3, 71.4, 54.1, 29.5, 21.1. HRMS Calcd for $C_{10}H_{14}N_2O$: 179.1184 $[M+H]^+$. Found: 179.1190 $[M+H]^+$. $[\alpha]^{25}_D$ +23.8 (c 0.8, MeOH).

Preparation of (*S*)-3-(1-Methylpyrrolidin-2-yl)pyridin-4-ol (148) from 99. A solution of **99** (0.0682 g, 0.26 mmol) in chloroform (0.5 mL) was treated with TFA (0.04 mL, 0.52 mmol) and potassium hydrogen fluoride (0.04 g, 0.52 mol). The mixture was stirred at rt for 30 min. The solvent was then removed under reduced pressure and replaced by MeOH (1 mL) and THF (1 mL). The mixture was then treated with $NaHCO_3$ (0.13 g, 1.3 mmol) and hydrogen peroxide (0.47 mL, 4.68 mmol) and heated to reflux for 2 h. After cooling the solution to rt, solid K_2CO_3 was added until the pH of the solution became slightly basic. It was then filtered through Celite with an EtOAc wash. Removal of the solvent under reduced pressure and purification by radial PLC (50% EtOAc/MeOH) afforded 0.0398 g (87%) of product **148**.

Preparation of (*S*)-2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-4-ol (152). Following the same procedure as above, **143** (0.1814 g, 0.64 mmol), TFA (0.1 mL, 1.28 mmol), KHF_2 (0.11 g, 1.28 mmol), $CHCl_3$ (2 mL), MeOH (2 mL), THF (2 mL), $NaHCO_3$ (0.32 g, 3.2 mmol) and H_2O_2 (1.2 mL, 11.52 mmol) afforded after radial PLC (15% MeOH/CH_2Cl_2) 0.094 g (69%) of product.**149** as a yellow oil. IR (thin film, neat, NaCl): 3500, 2961, 1646, 1557, 1526 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 8.48 (d, 1 H, *J* = 3.2 Hz), 8.04 (d, 1 H, *J* =

3.2 Hz), 8.01 (s, 1 H), 7.50 – 7.47 (m, 1 H), 6.45 (s, 1 H), 3.81 – 1.60 (m, 23 H); ^{13}C NMR (100 MHz, CD_3OD) δ 153.26, 143.75, 143.66, 125.49, 117.02, 77.97, 77.32, 71.23, 70.18, 53.74, 52.99, 33.85, 32.05, 29.53, 27.36, 23.29, 21.02, 14.14, 9.32. HRMS Calcd for $C_{10}H_{13}ClN_2O$: 213.0795 $[M+H]^+$. Found: 213.0786 $[M+H]^+$. $[\alpha]^{29}_D$ +18 (c 1.5, CH_2Cl_2).

Preparation of (*S*)-4-Methoxymethoxy-3-(1-methylpyrrolidin-2-yl)pyridine (155). To a solution of **148** (0.1331 g, 0.75 mmol) in DME (5 mL) cooled at 0 ºC was added a solution of tBuOK (0.18 g, 1.5 mmol) in DME (4 mL). The mixture was warmed to rt over 2 h and MOMCl (0.07 mL, 0.9 mmol) was added dropwise. The reaction mixture was stirred for 4 h at rt. After removal of the solvent under reduced pressure, the crude material was purified by radial PLC (5% EtOAc/hexanes) to afford 0.1347 g (81%) of product **155**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, 1 H, *J* = 7.6 Hz), 9.28 (s, 1 H), 8.52 (1 H, *J* = 10.8 Hz), 8.07 (dd, 1 H, J = 8 and 10.8 Hz), 6.23 (s, 1 H), 3.60 – 3.46 (m, 2 H), 2.42 – 1.84 (m, 5 H).

Preparation of (*S*)-Diethyl-carbamic acid 3-(1-methyl-pyrrolidin-2-yl)-pyridin-4-yl ester (157). To a solution of **148** (0.1203 g, 0.67 mmol) in DME (5 mL) cooled at 0 ºC was slowly added a solution of *t*-BuOK (0.16 g, 1.34 mmol) in DME (3 mL). The mixture was warmed to rt over 2 h, then diethylcarbamyl chloride (0.1 mL, 0.8 mmol) was injected. The reaction mixture was stirred at 55 ºC for 4 h. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (neutral Alumina, 50% EtOAc/MeOH) to afford 0.0794 g (43%) of product **157** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1 H), 8.77 (d, 1 H, *J* = 4.4 Hz), 8.21 (d, 1 H, *J* = 10.8 Hz), 7.41 (q, 1 H, *J* =

6 Hz), 3.27 – 2.87 (m, 6 H), 2.83 (s, 3 H), 2.02 (q, 4 H, J = 10.5 Hz), 1.14 – 1.06 (m, 6 H). HRMS Calcd for $C_{15}H_{23}N_3O_2$: 278.1869 $[M+H]^+$. Found: 278.1873 $[M+H]^+$.

General Procedure for the Preparation of Tetrahydronicotines: Preparation of (*S*)-5-(1-Methylpyrrolidin-2-yl)-3,4-dihydro-2H-pyridine 1-carboxylic acid methyl ester (164). $Pd(OH)_2/C$ (0.03 g) was added to 3-(1-methylpyrrolidin-2-yl)-4H-pyridine-1-carboxylic acid methyl ester (**109**) (0.2758 g, 1.2 mmol). Ethanol (5 mL) was added to the flask and the solution was submitted to reduced pressure for a few seconds. The mixture was then placed under a balloon of H_2 and the reaction mixture was stirred at rt for 0.5 h. After filtration of the mixture through a pad of Celite and evaporation of the solvent under reduced pressure, purification of the crude material by radial PLC (50% EtOAc/MeOH) afforded 0.204 g (76%) of **164** as a yellow oil. IR (thin film, neat, NaCl) 2934, 1863, 2772, 1704, 1447, 1365, 1260, 1188 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 – 6.54 (m, 1 H), 3.75 – 3.68 (m, 2 H), 3.57 – 3.48 (m, 1 H), 2.57(m, 2 H), 2.43 (s, 3 H), 1.97 (m, 3 H), 1.84 (m, 2 H), 1.63 (m, 2 H), 1.46 – 1.44 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.41, 119.92, 52.97, 52.66, 52.20, 50.05, 44.81, 42.12, 42.01, 36.72, 35.41, 35.29, 33.84, 31.12, 30.28, 29.67, 25.12, 24.94, 24.65, 21.89. HRMS Calcd for $C_{12}H_{20}N_2O_2$: 225.1603 $[M+H]^+$. Found: 225.1613 $[M+H]^+$. $[\alpha]^{24}_D$ +5.5 (c 1.15, CH_2Cl_2).

Preparation of (*S*) -5- (1-Methylpyrrolidin-2-yl) -3, 4- dihydro -2H- pyridine-1-carbaldehyde (165). Following the above procedure, 0.0489 g of 3-(1-methylpyrrolidin-2-yl)-4H-pyridine-1-carbaldehyde (**107**), 0.005 g of $Pd(OH)_2/C$ and 5 mL of ethanol were stirred for 1 h to yield 0.0209 g (45%) of **165** as a yellow oil. IR (thin film, neat, NaCl) 2935, 2865, 1657, 1409 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 – 7.96 (m, 1 H), 6.85 –

6.26 (s, 1 H), 3.59 – 3.44 (m, 2 H), 2.58 – 2.57 (m, 2 H), 2.43 – 2.42 (m, 3 H), 2.10 – 1.46 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.05, 159.39, 121.25, 120.17, 117.43, 52.15, 44.12, 39.00, 36.75, 35.09, 29.67, 29.64, 26.51, 26.13, 25.53, 22.17, 20.95. HRMS Calcd for $C_{11}H_{18}N_2O$: 195.1497 $[M+H]^+$. Found: 195.1494 $[M+H]^+$. $[\alpha]^{24}_D$+2.5 (c 0.78, CH_2Cl_2).

Preparation of (*S*)-5-(1-Methylpyrrolidin-2-yl)-3,4-dihydro-2H-pyridine-1-carboxylic acid dimethylamide (166). Following the above procedure, 0.0495 g of 3-(1-methyl-pyrrolidin-2-yl)-4H-pyridine-1-carboxylic acid dimethylamide (**105**), 0.005 g of $Pd(OH)_2$/C and 5 mL of ethanol were stirred for 2 h to yield 0.017 g (34%) of **166** as a yellow oil. IR (thin film, neat, NaCl) 2931, 2859, 1642, 1489, 1452, 1378, 1251, 1155, 839 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 1 H), 3.84 (s, 1 H), 3.15 (t,1 H, J = 5.7 Hz), 2.84 – 2.76 (m, 9 H), 2.65 – 2.33 (m, 1 H), 1.97 – 1.85 (m, 2 H), 1.65 – 1.20 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.45, 124.03, 116.14, 50.35, 43.97, 39.61, 38.92, 36.72, 35.63, 27.64, 25.80, 25.29, 21.52. HRMS Calcd for $C_{13}H_{23}N_3O$: 238.1841 $[M+H]^+$. Found: 238.1844 $[M+H]^+$. $[\alpha]^{24}_D$+2.5 (c 0.78, CH_2Cl_2).

Preparation of (*S*) -1- [4-(Dimethylphenylsilanyl) -5- (1-methylpyrrolidin-2-yl) -3, 4-dihydro-2H-pyridin-1-yl]-2,2-dimethyl-propan-1-one (167). Pt/C (0.03 g), **82** (0.0319 g, 0.082 mmol) and ethanol (2 mL) were added to a flask, and the mixture was submitted to reduced pressure for a few seconds. The mixture was placed under a balloon of H_2 and the reaction mixture was stirred at rt for 16 h. After filtration through a pad of Celite, and evaporation of the solvent under reduced pressure, purification of the crude material by radial PLC (10% EtOAc/hexanes) afforded 0.041 g (33%) of product **167** as a yellow oil. IR (thin film, neat, NaCl) 2954, 1663, 1402, 1198 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.16

(m, 6 H), 3.70 – 3.00 (m, 3 H), 2.48 (t, 1 H, J = 11.4 Hz), 2.20 (s, 3 H), 2.10– 1.25 (m, 17 H), 0.33 (s, 3 H), 0.30 (s, 3 H);^{13}C NMR (75 MHz, $CDCl_3$) δ 133.98, 129.32, 128.05, 120.19, 68.72, 57.24, 51.75, 44.85, 42.89, 41.54, 39.39, 33.16, 32.93, 28.51, 22.56, 25.28, 22.76, -2.25, -2.57. HRMS Calcd for $C_{23}H_{36}N_2OSi$: 385.2675 $[M+H]^+$. Found: 385.2688 $[M+H]^+$. $[\alpha]^{28}_D$ -36.8 (c 0.63, CH_2Cl_2).

Preparation of 3- Bromo -2- methoxy -5- (1-methylpyrrolidin-2-yl)-3,4-dihydro- 2H-pyridine-1-carboxylic acid methyl ester (163). A solution of **109** (0.0852 g, 0.38 mmol), NBS (0.068 g, 0.38 mmol) and lithium methoxide (0.016 g, 0.42 mmol) in MeOH (2 mL) was stirred at rt for 4 h. The solvent was removed under reduced pressure and replaced by CH_2Cl_2 (2 mL). The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x), and the combined organic layers were washed with brine and dried over K_2CO_3. The solvent was removed under reduced pressure to afford 0.1267 g (100%) of **163** as a yellow oil. IR (thin film, neat, NaCl) 2954, 2932, 1662, 1603, 1461, 1330, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 – 6.71 (m, 1 H), 5.52 – 5.37 (m, 1 H), 4.37 (bs, 1 H), 3.84 – 3.68 (m, 3 H), 3.44 – 3.39 (m, 3 H), 3.11 – 1.67 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 118.52, 114.52, 84.065, 93.74, 70.94, 56.89, 56.78, 53.63, 43.36, 40.44, 30.09, 25.85, 22.17. HRMS Calcd for $C_{13}H_{21}BrN_2O_3$: 333.0814 $[M+H]^+$. Found: 333.0813 $[M+H]^+$.

Preparation of 4- (Dimethylphenylsilanyl) -1- (2,2-dimethyl-propionyl) -5- (1-methyl-pyrrolidin-2-yl)-1,4-dihydro-pyridine-3-carbaldehyde (160). Phosphorus oxychloride (0.05 mL, 0.55 mmol) was slowly added to a solution of DMF (0.08 mL, 1.1 mmol) in

CH_2Cl_2 (1 mL) was cooled to 0 ºC. The solution was warmed to rt over 25 min, then transferred via a double tipped needle into a solution of **82** (0.095 g, 0.25 mmol) in CH_2Cl_2 (3 mL) cooled at 0 ºC. The ice bath was removed and the reaction mixture was stirred at rt for 2 d. Water (2 mL) and sodium acetate (0.15 g) were added and the mixture was stirred overnight. The aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with $NaHCO_3$, water and brine, and dried over K_2CO_3. Removal of solvent under reduced pressure and purification of the crude material by radial PLC (10% EtOAc/hexanes) afforded 0.0234 g (23%) of product **160** as a yellow oil. IR (thin film, neat, NaCl) 2926, 2855, 1642, 1461, 1400, 1351, 1309, 1249, 1151, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.42 (s, 1 H), 7.82 (s, 1 H), 7.51 – 7.31 (m, 5 H), 6.92 (s, 1 H), 5.30 (s, 1 H), 2.96 – 2.76 (m, 2 H), 2.18 – 1.19 (m, 18 H), 0.35 – 0.28 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.13, 149.35, 143.32, 134.29, 129.67, 128.20, 127.95, 118.05, 66.91, 57.36, 56.85, 41.42, 40.15, 35.96, 32.51, 29.91, 28.43, 28.08, 27.98, 22.81, -2.68, -4.42. HRMS Calcd for $C_{24}H_{34}N_2O_2Si$: 411.2468 $[M+H]^+$. Found: 411.2472 $[M+H]^+$. $[\alpha]^{22}_D$ +12 (c 0.45, CH_2Cl_2).

General procedure for the preparation of pyrrolidine opened product. Preparation of (*R*)-{4-Bromo-4-[4-(dimethylphenylsilanyl)pyridin-3-yl]-butyl}-methyl-cyanamide (178). A solution of **89** (0.1108 g, 0.37 mmol) and cyanogen bromide (1.2 mL, 3.7 mmol) in $CHCl_3$ was refluxed for 1 d. The reaction mixture was filtered through a pad of Celite. After evaporation of the solvent under reduced pressure, the crude material was purified by radial PLC (30% EtOAc/hexanes) to afford 0.0244 g (17%) of product **178** as an orange oil, 0.0282 g (24%) of **179** as a yellow oil and 0.033 g (30%) of **89**.

178: IR (thin film, neat, NaCl) 2956, 2212, 1658, 1580, 1428, 1407, 1254, 1163, 1109, 1088, 837, 818 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79 (s, 1 H), 8.50 (d, 1 H, *J* = 6 Hz), 7.47 – 7.36 (m, 6 H), 4.79 (dd, 1 H, J = 4 and 13.2 Hz), 2.84 – 2.11 (m, 9 H), 0.69 (s, 3 H), 0.61 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.11, 148.23, 134.07, 130.22, 128.88, 128.65, 52.11, 51.61, 38.77, 36.85, 26.06, -1.33, -2.47. HRMS Calcd for $C_{19}H_{24}N_3BrSi$: 402.1001 $[M+H]^+$. Found: 402.1011 $[M+H]^+$. $[\alpha]^{29}_D$ -3.1 (c 1.65, CH_2Cl_2).

179: IR (thin film, neat, NaCl) 2952, 2211, 1574, 1428, 1404, 1251, 1171, 1111, 967, 816 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1 H), 8.45 (d, 1 H, *J* = 6.1 Hz), 7.48 – 7.25 (m, 6 H), 6.47 (s, 1 H), 5.98 – 5.88 (m, 1 H), 2.90 (t, 2 H, *J* = 9.6 Hz), 2.79 (s, 3 H), 2.39 – 2.36 (m, 2 H), 0.59 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.52, 146.82, 134.72, 131.43, 129.75, 129.21, 128.49, 128.35, 60.61, 52.37, 39.15, 31.17, 21.27, 14.39, -1.76. HRMS Calcd for $C_{19}H_{23}N_3Si$: 322.1740 $[M+H]^+$. Found: 322.1757 $[M+H]^+$.

Preparation of (*R*)- [4- Bromo-4- (4-trimethylsilanylpyridin-3-yl) butyl] – methyl - cyanamide (180). Following the same procedure as above, **98** (0.2812 g, 1.2 mmol) and cyanogen bromide (4 mL, 12 mmol) in CH_2Cl_2 (2 mL) afforded 0.0613 g (30%) of product **180** as an orange oil. IR (thin film, neat, NaCl) 2953, 2212, 1254, 1091, 843, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.81 (s, 1 H), 8.43 (d, 1 H, *J* = 6.8 Hz), 7.28 – 7.26 (m, 1 H), 5.03 (dd, 1 H, *J* = 7.2 and 12.4 Hz), 3.18 – 1.62 (m, 9 H), 0.37 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.65, 148.20, 146.95, 146.65, 142.75, 131.51, 128.71, 128.38, 52.33, 51.69, 39.14, 37.13, 26.63, -0.03, -0.36. HRMS Calcd for $C_{14}H_{22}N_3BrSi$: 340.0845 $[M+H]^+$. Found: 340.0861 $[M+H]^+$. $[\alpha]^{24}_D$ -0.5 (c 2.8, CH_2Cl_2).

Preparation of (*S*)-{4-[4-(Dimethylphenylsilanyl)pyridin-3-yl]-4-pyrrolidin-1-yl-butyl}-methyl-cyanamide (181). A solution of **178** (0.0224 g, 0.056 mmol) in pyrrolidine (1 mL) was stirred at rt for 2 h. After evaporation of the pyrrolidine under reduced pressure, the crude material was purified by radial PLC to afford 0.018 g (17%) of **179** and 0.067 g (34%) of **171**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (s, 1 H), 8.46 (d, 1 H, J = 4.8 Hz), 7.49 – 7.33 (m, 6 H), 3.46 (bs, 1 H), 2.73 – 2.67 (m, 4 H), 2.28 – 2.21 (m, 4 H), 1.75 – 1.25 (m, 10 H), 0.67 (s, 3 H), 0.67 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.71, 147.31, 134.36, 129.81, 128.32, 53.50, 52.40, 38.63, 32.49, 23.55, 22.08, -0.37, -0.49. HRMS Calcd for $C_{23}H_{32}N_4Si$: 393.2475 $[M+H]^+$. Found: 393.2456 $[M+H]^+$.

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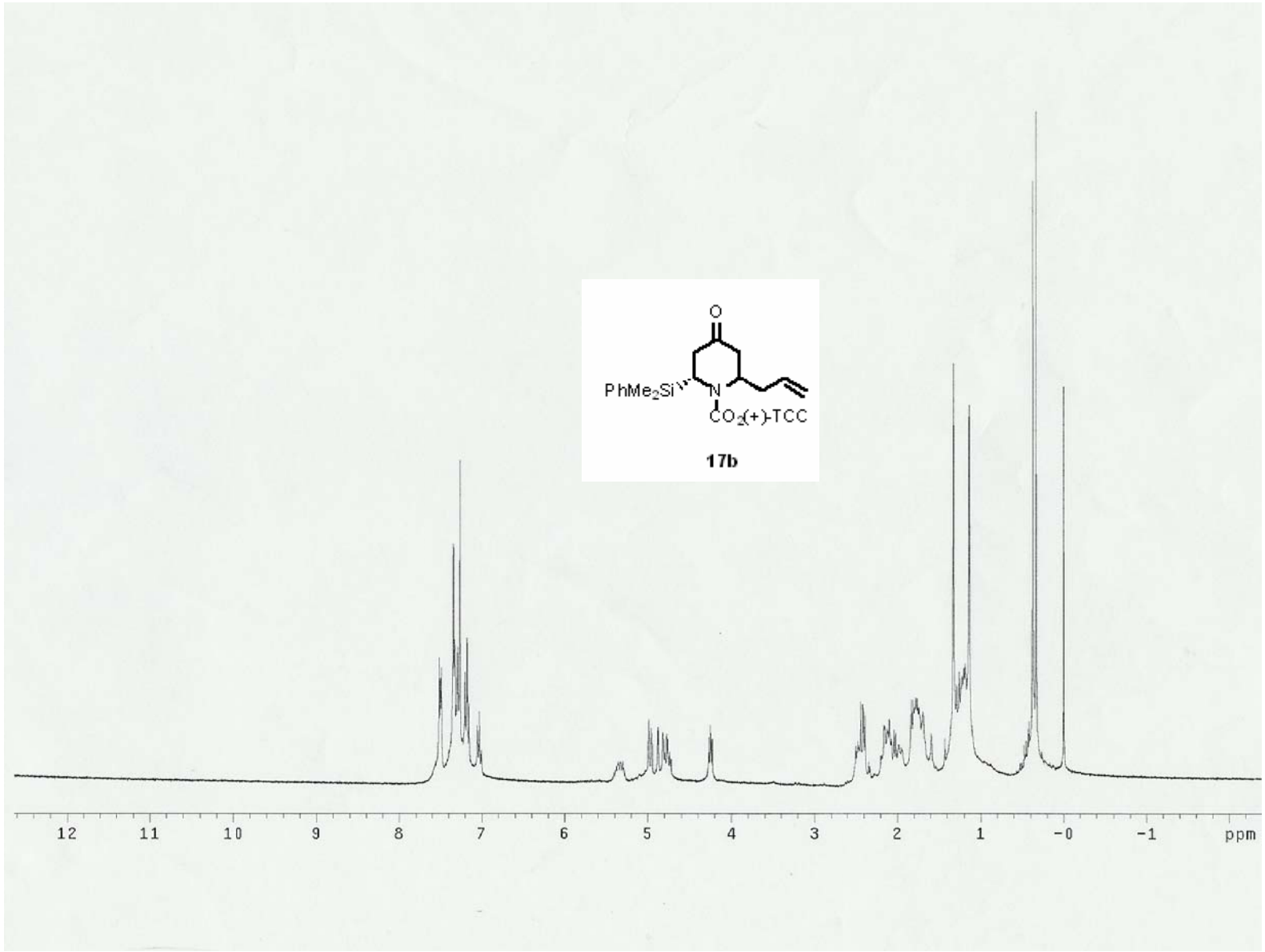
Appendices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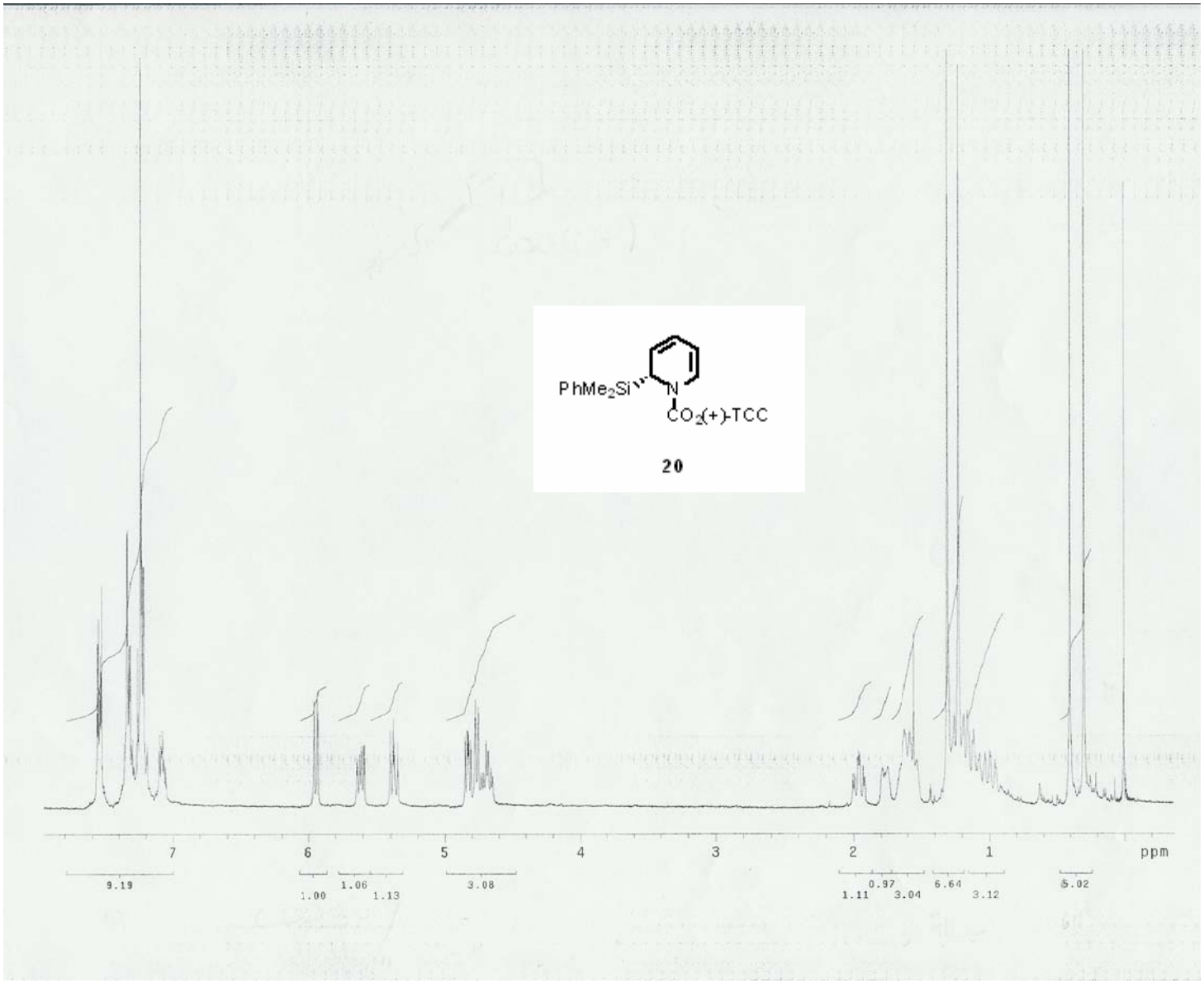
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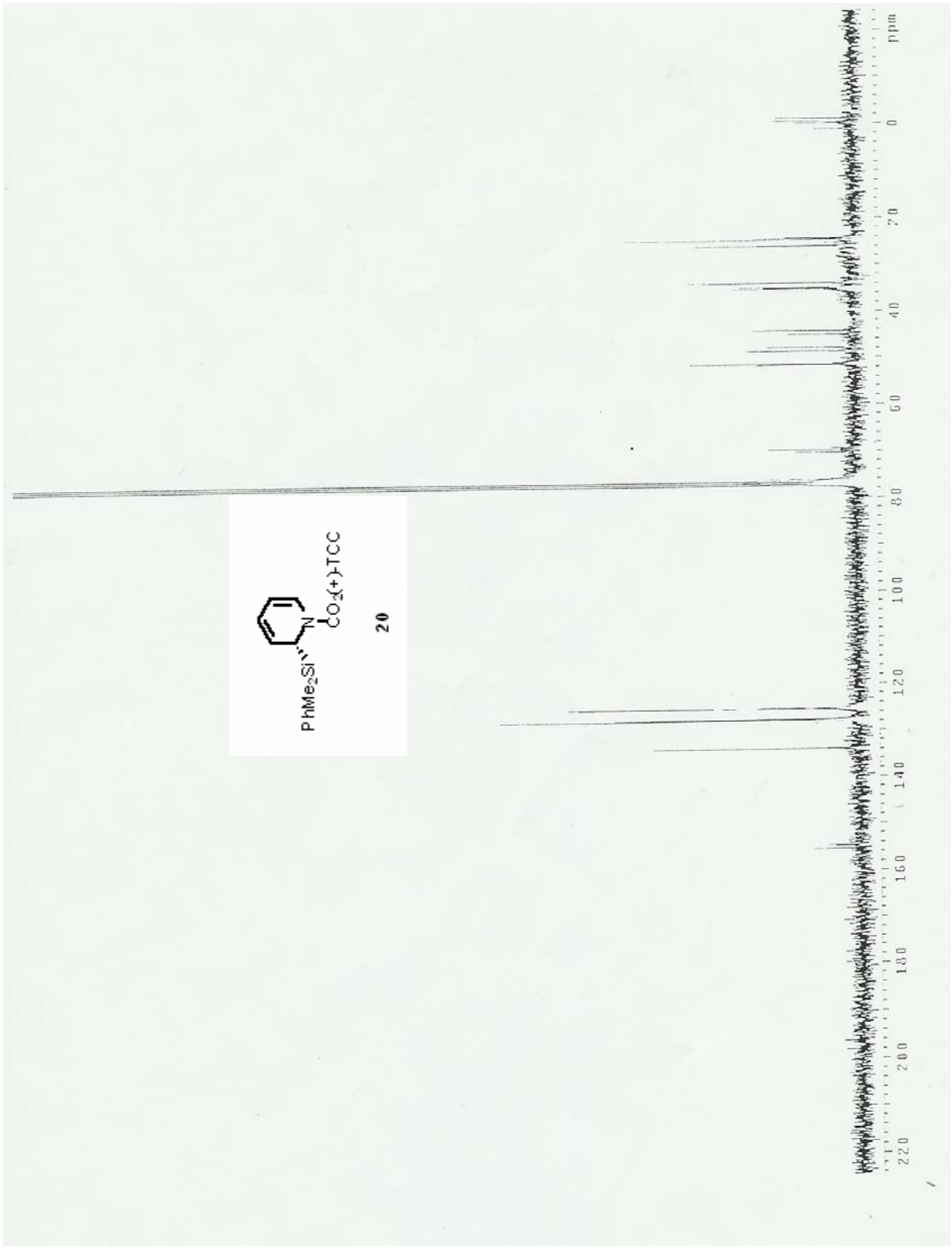
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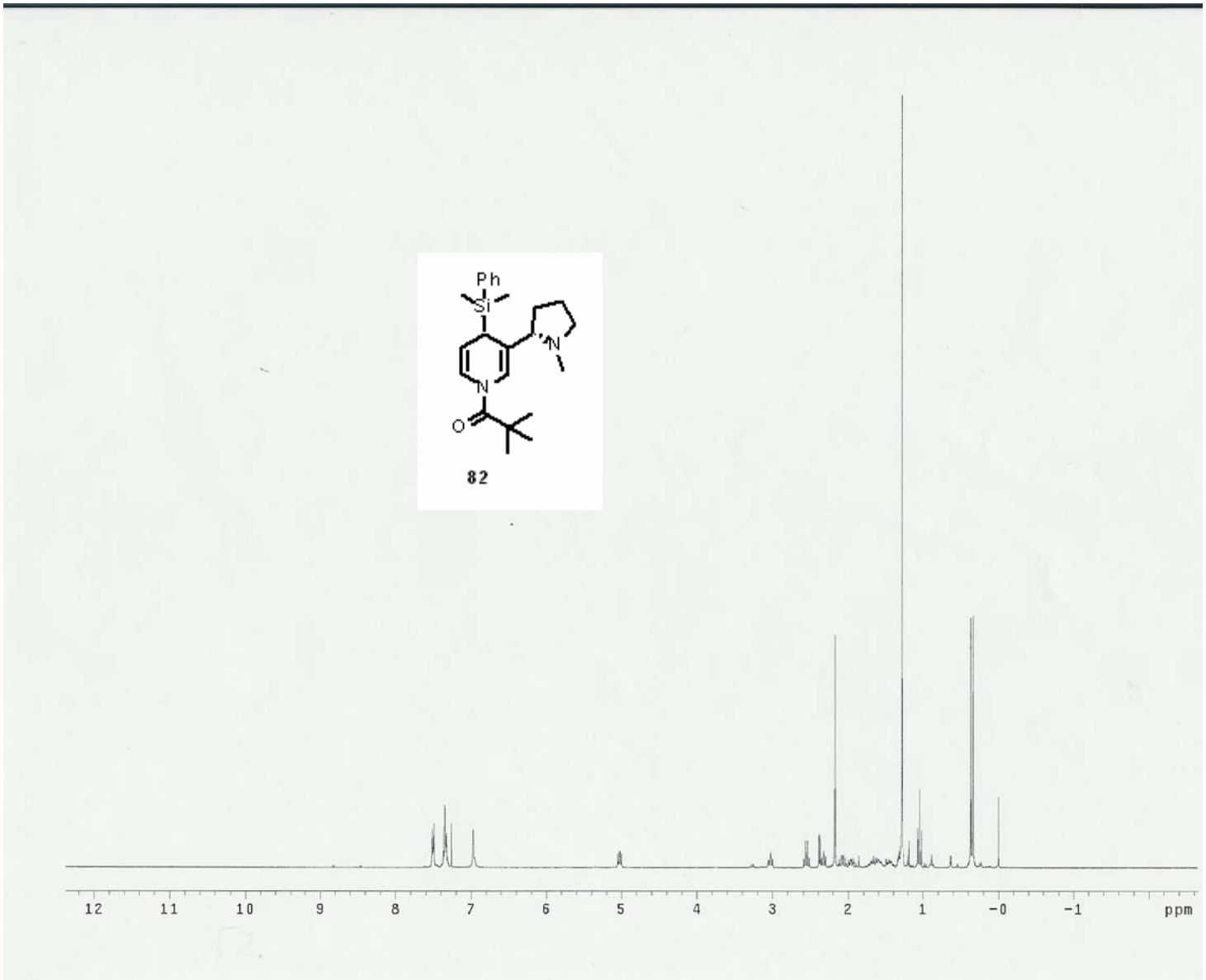
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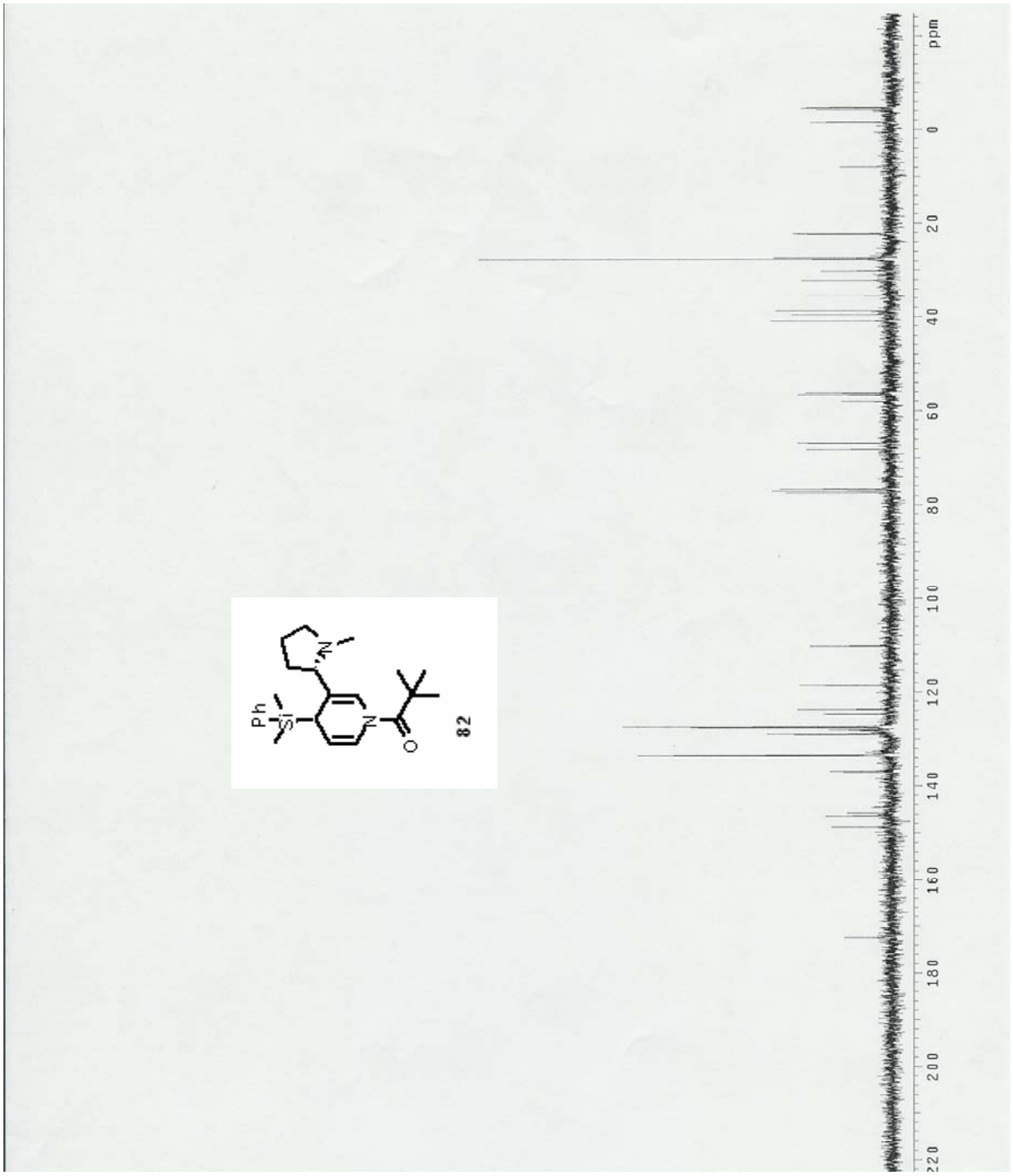
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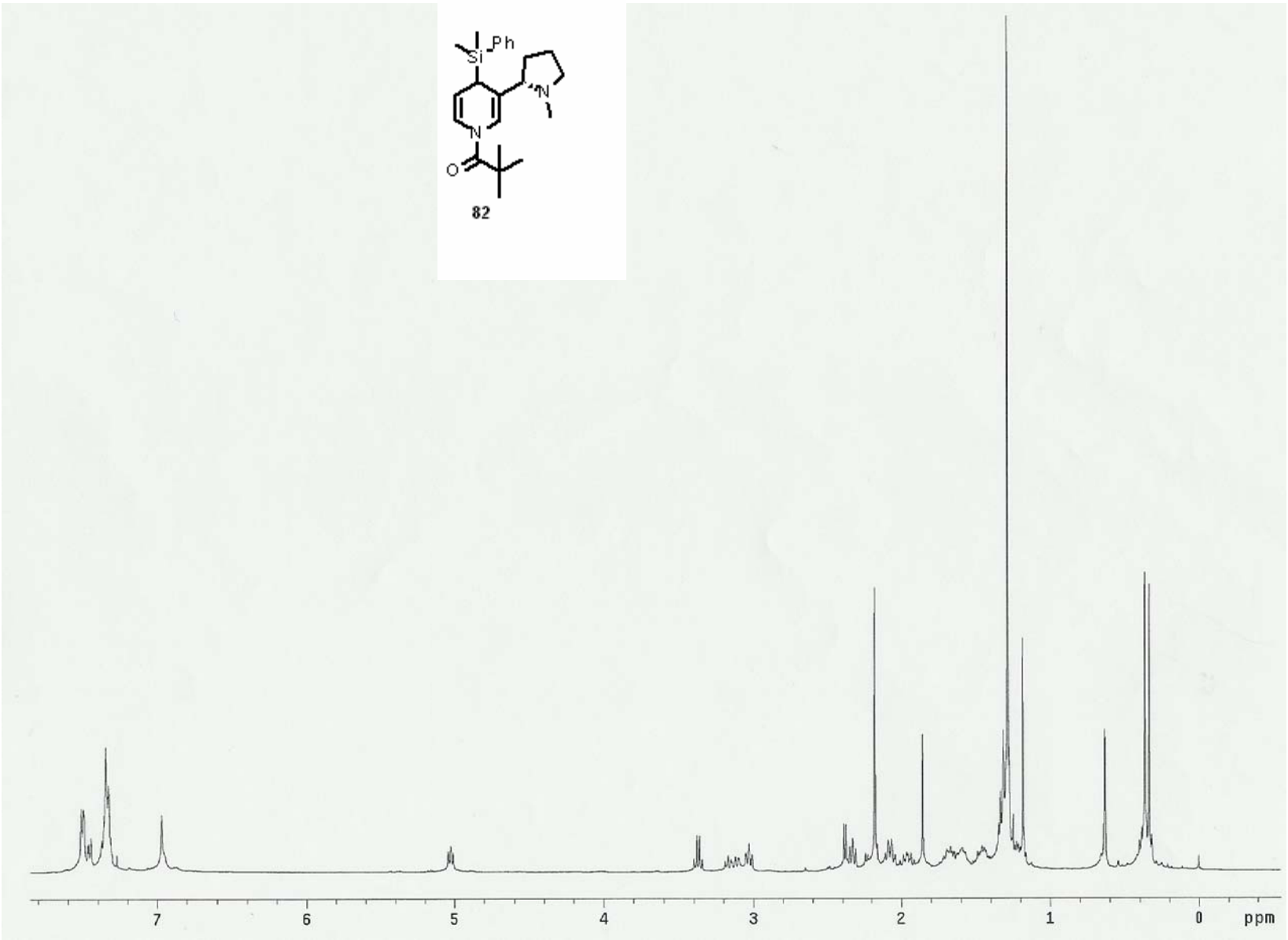
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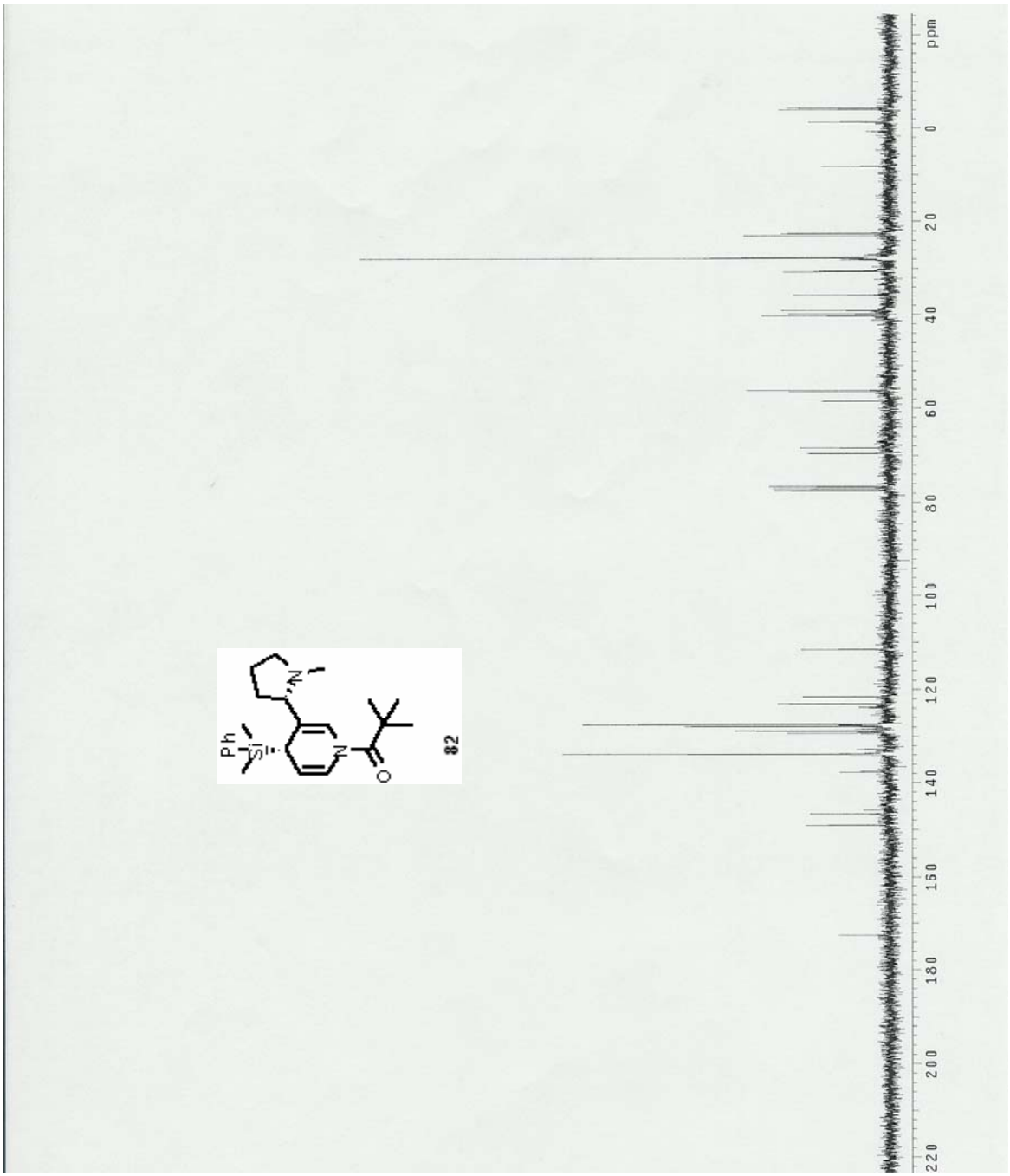
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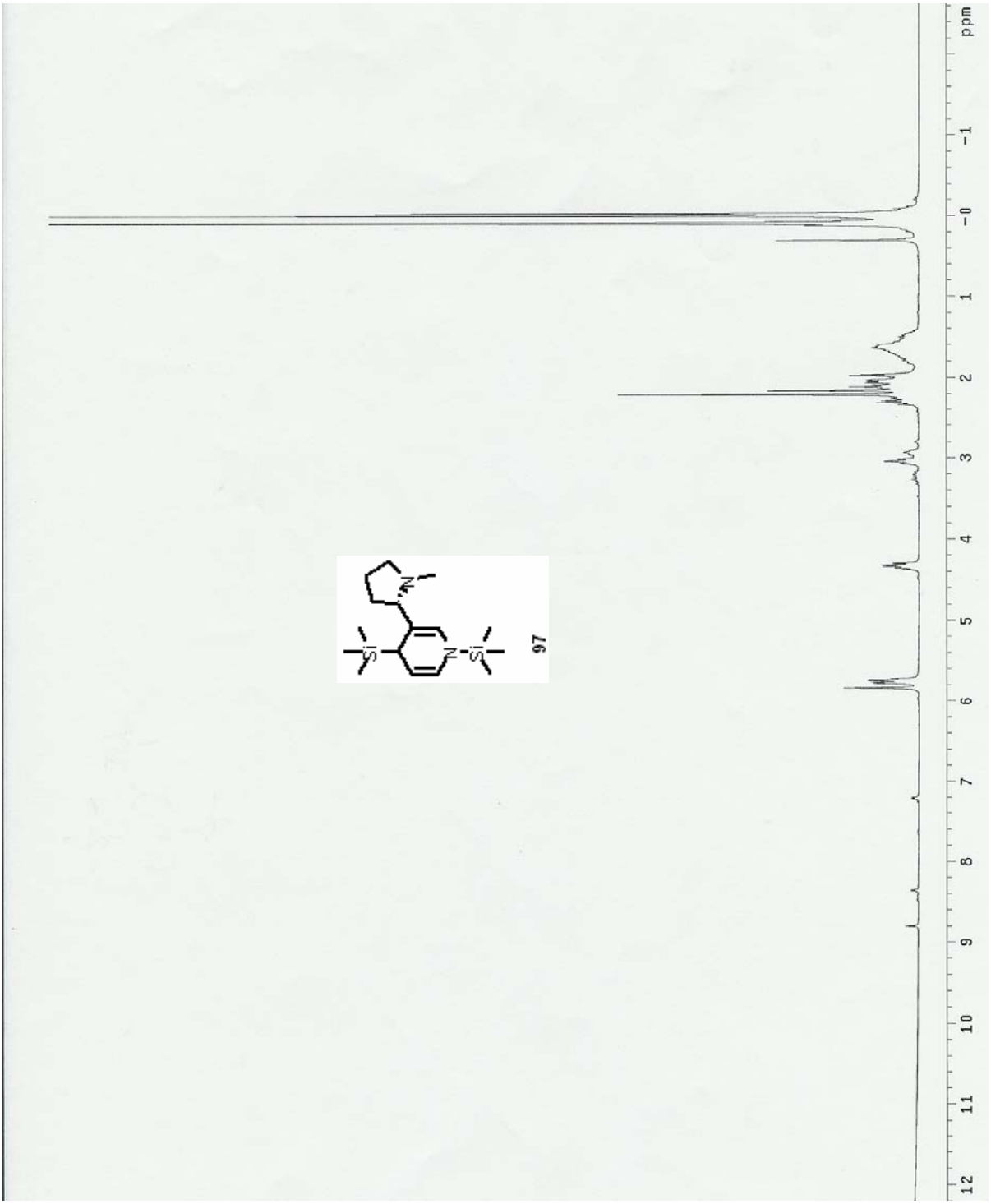
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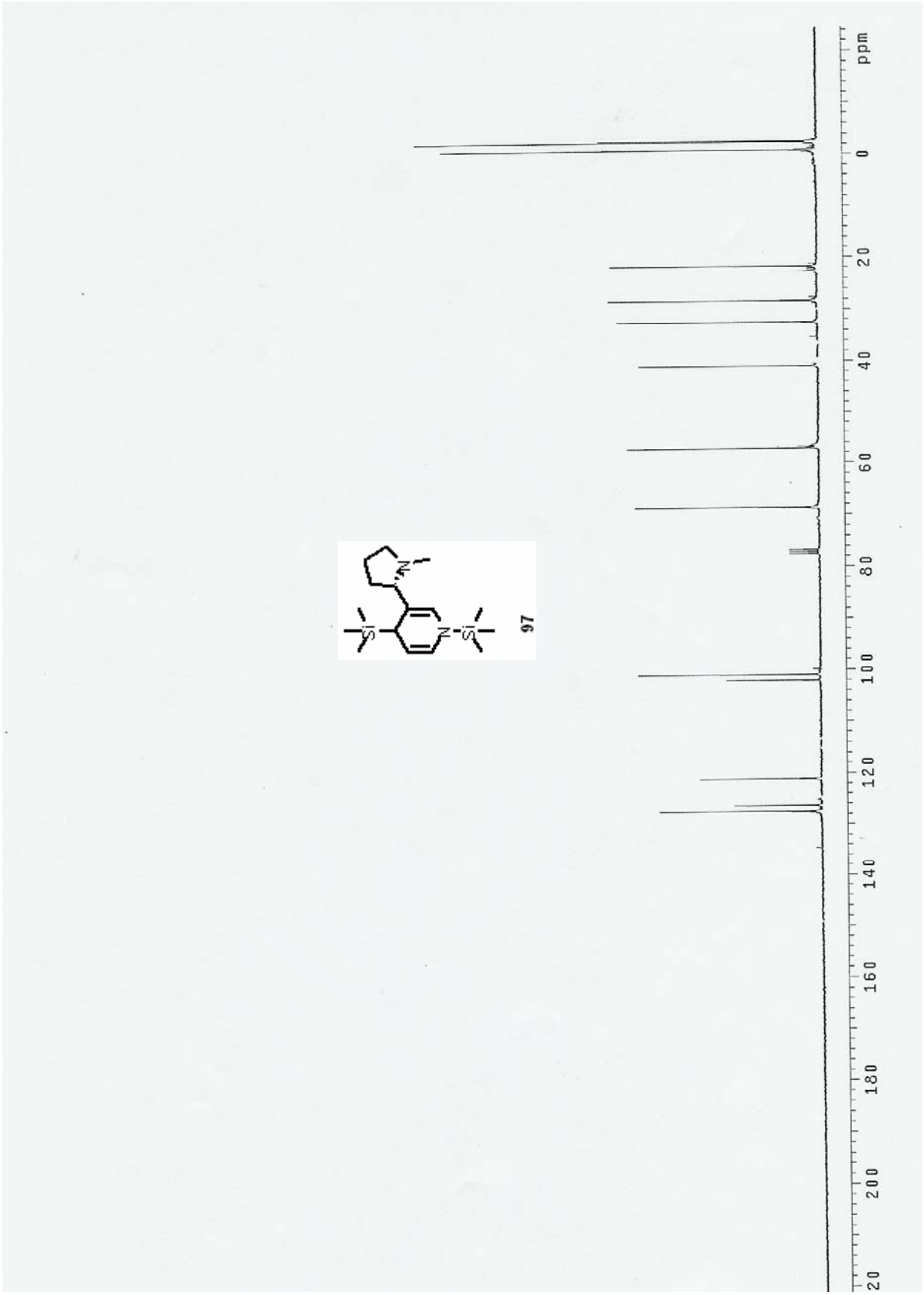
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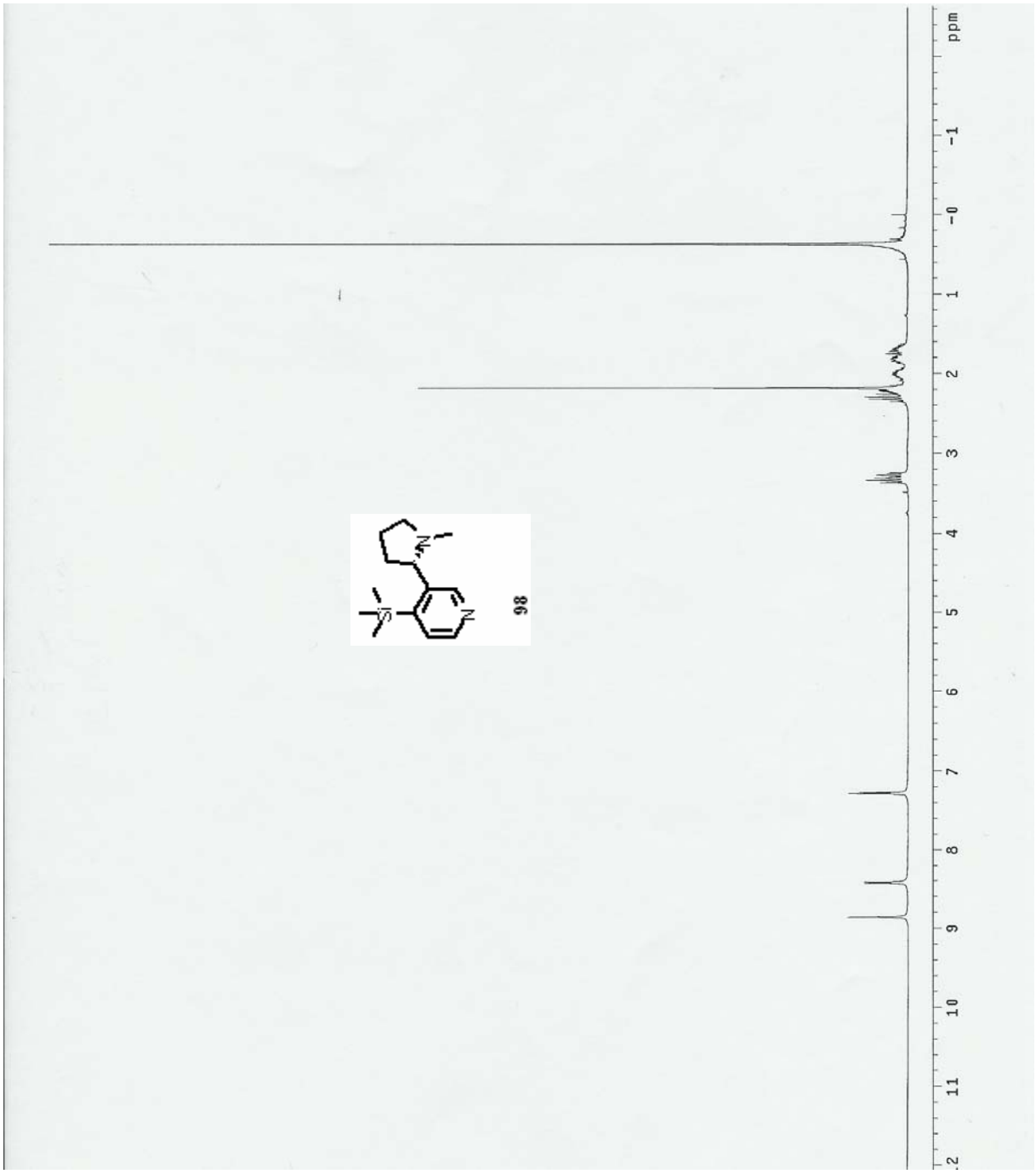
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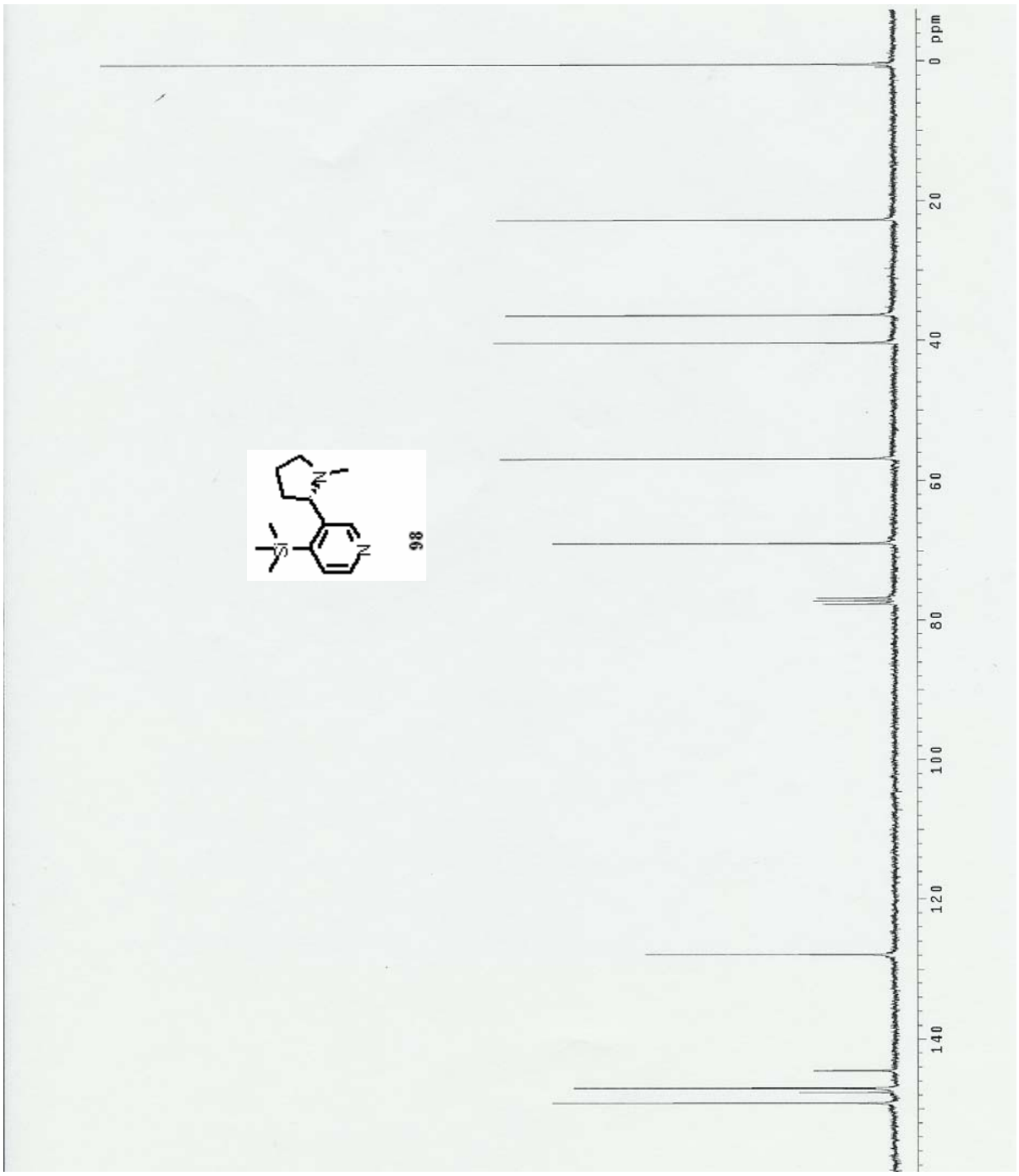
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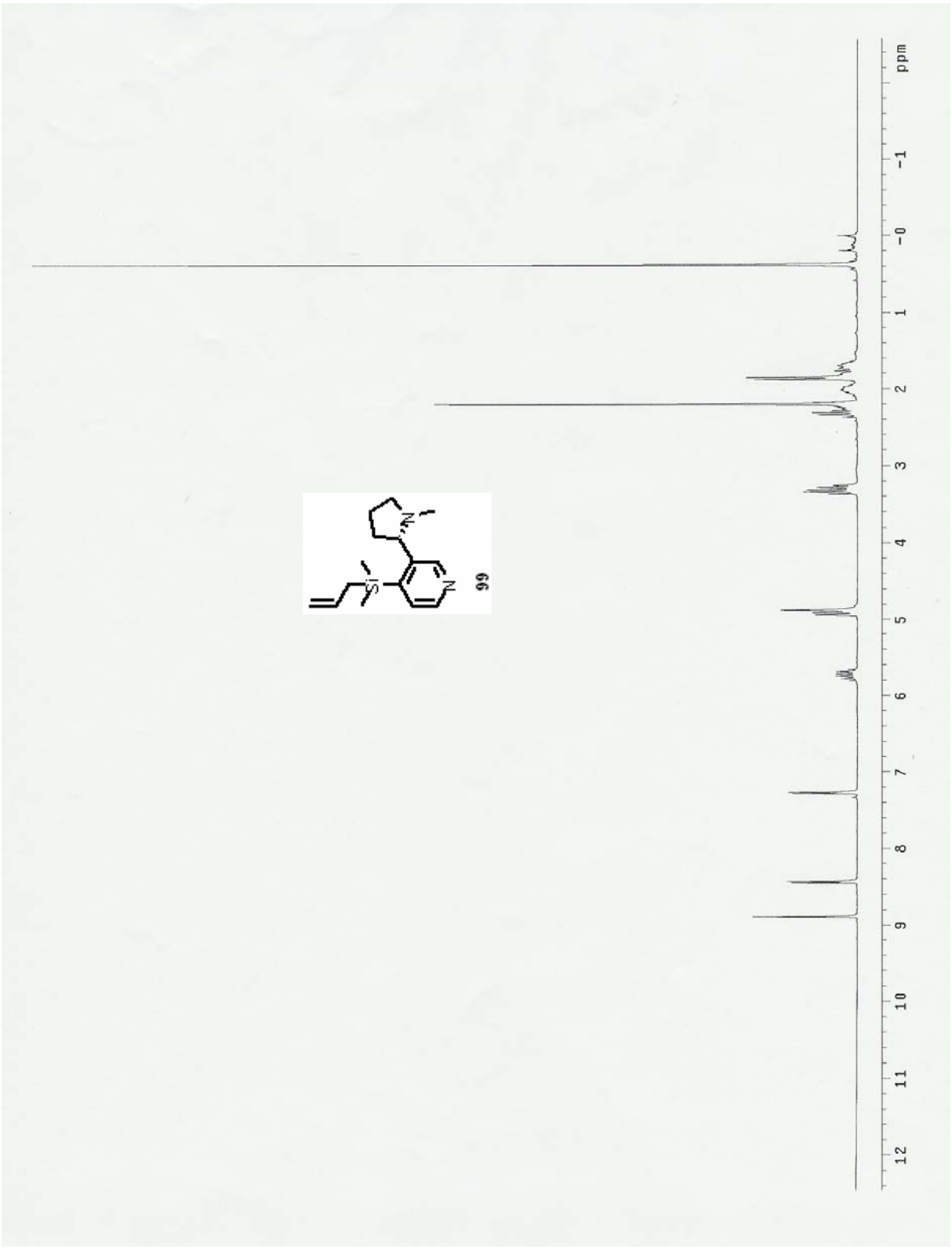
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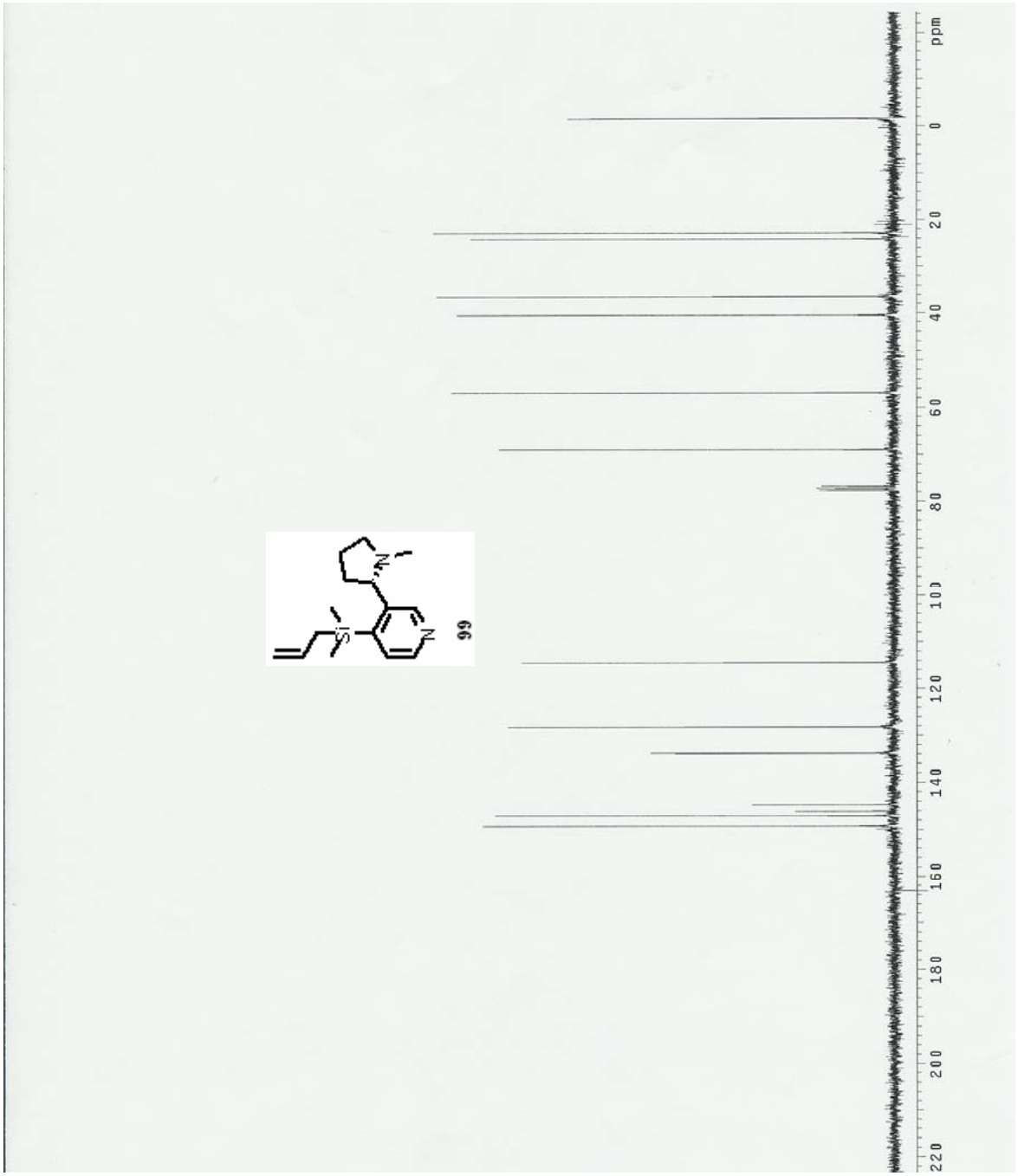
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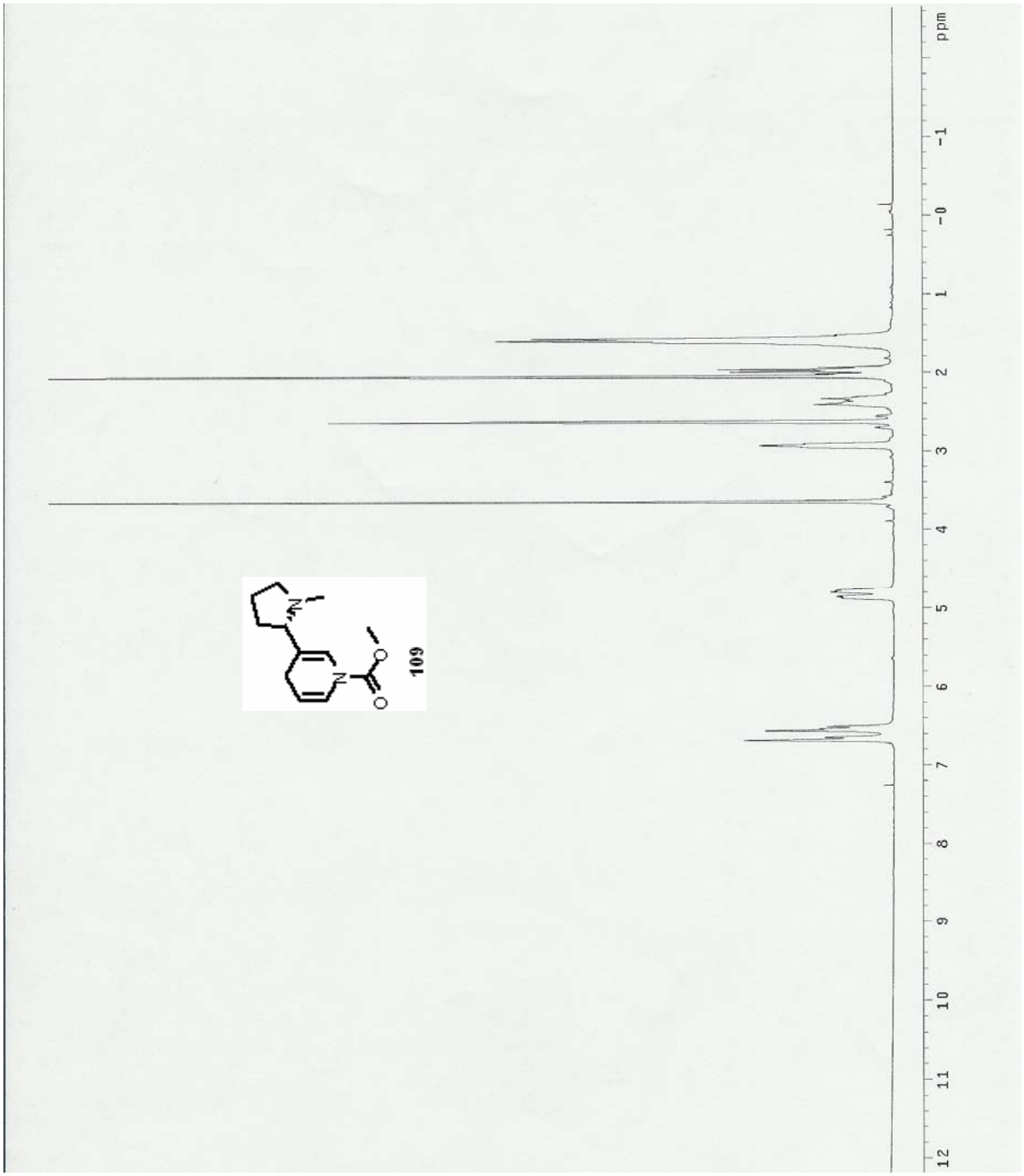
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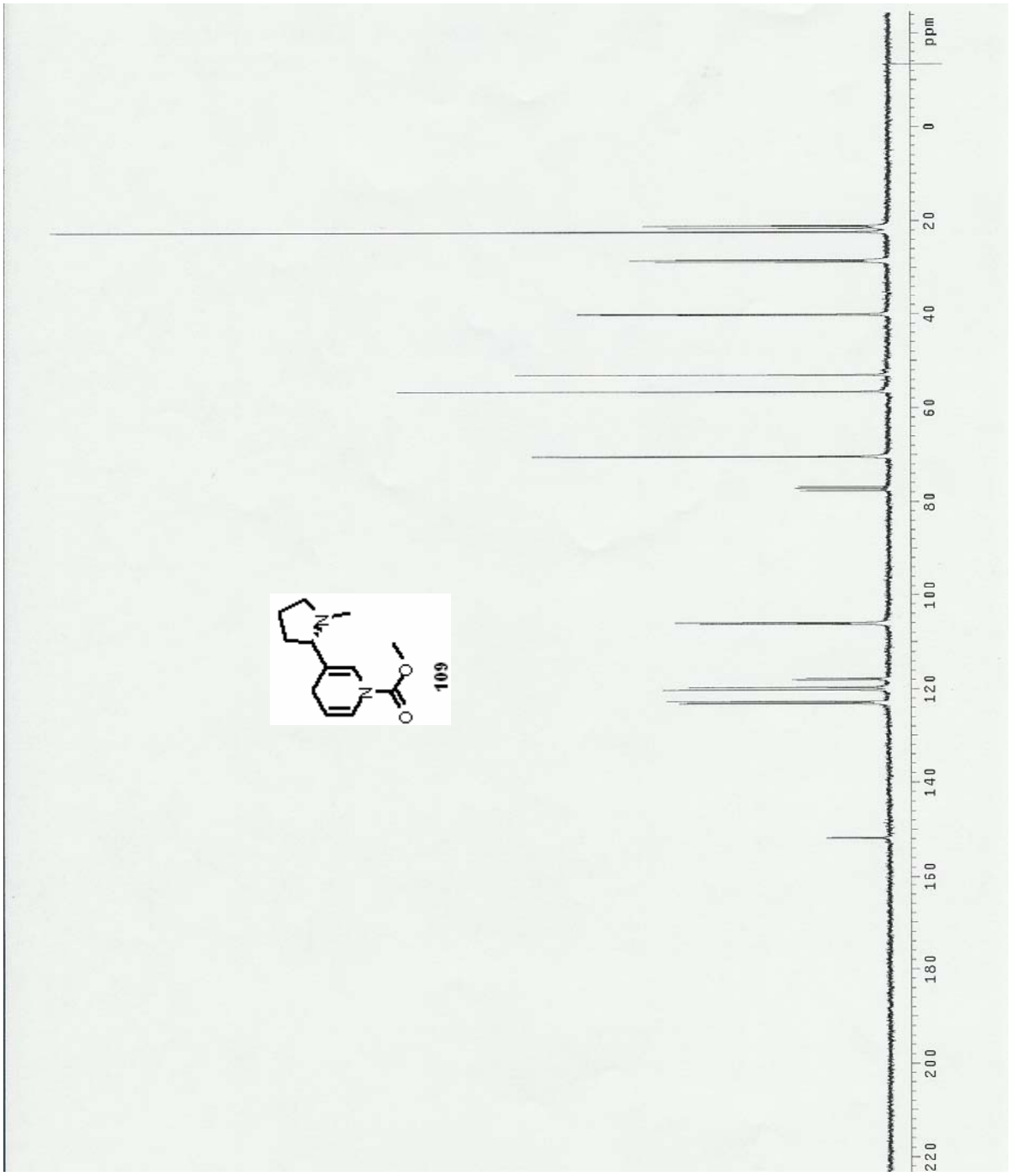
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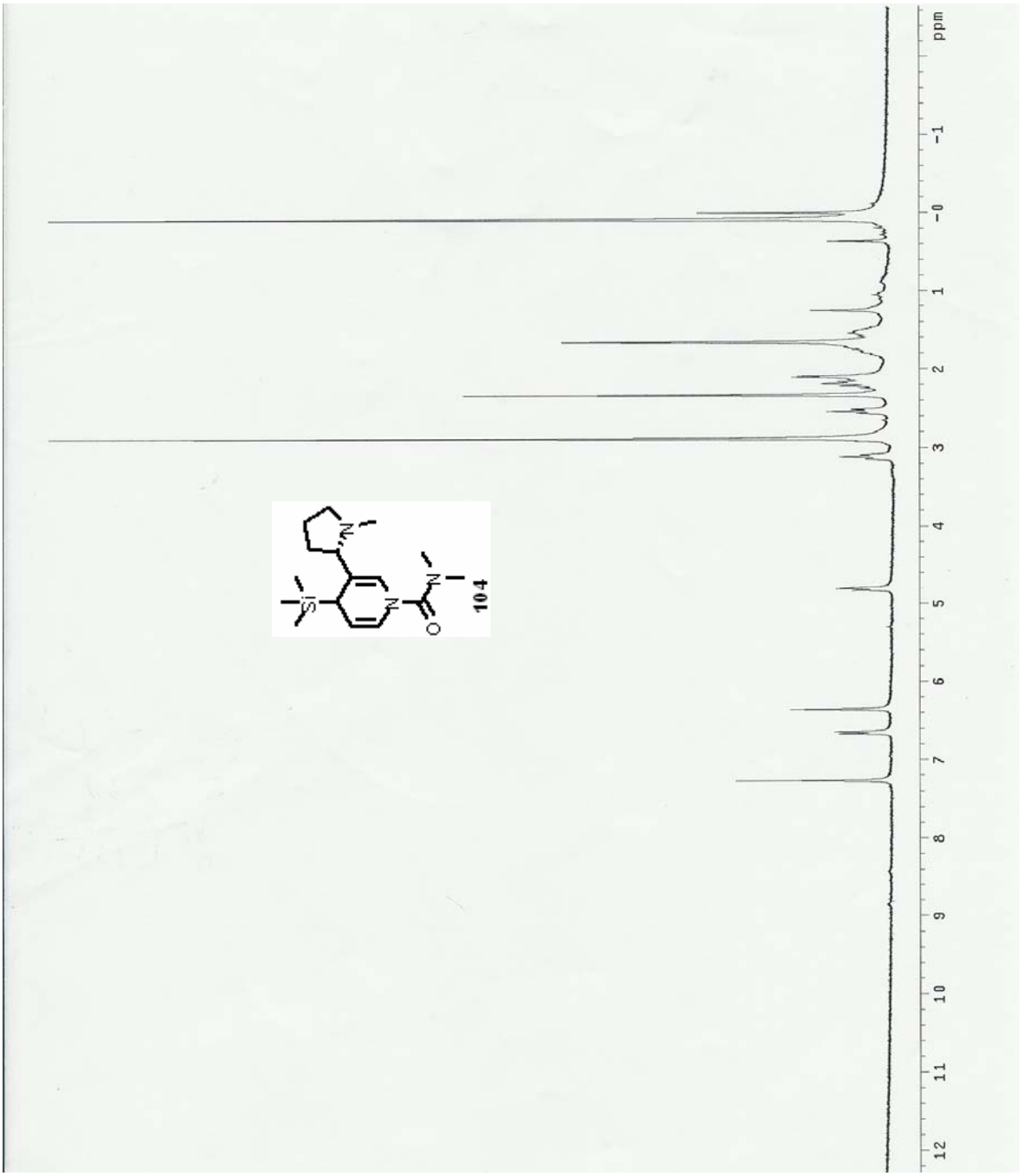
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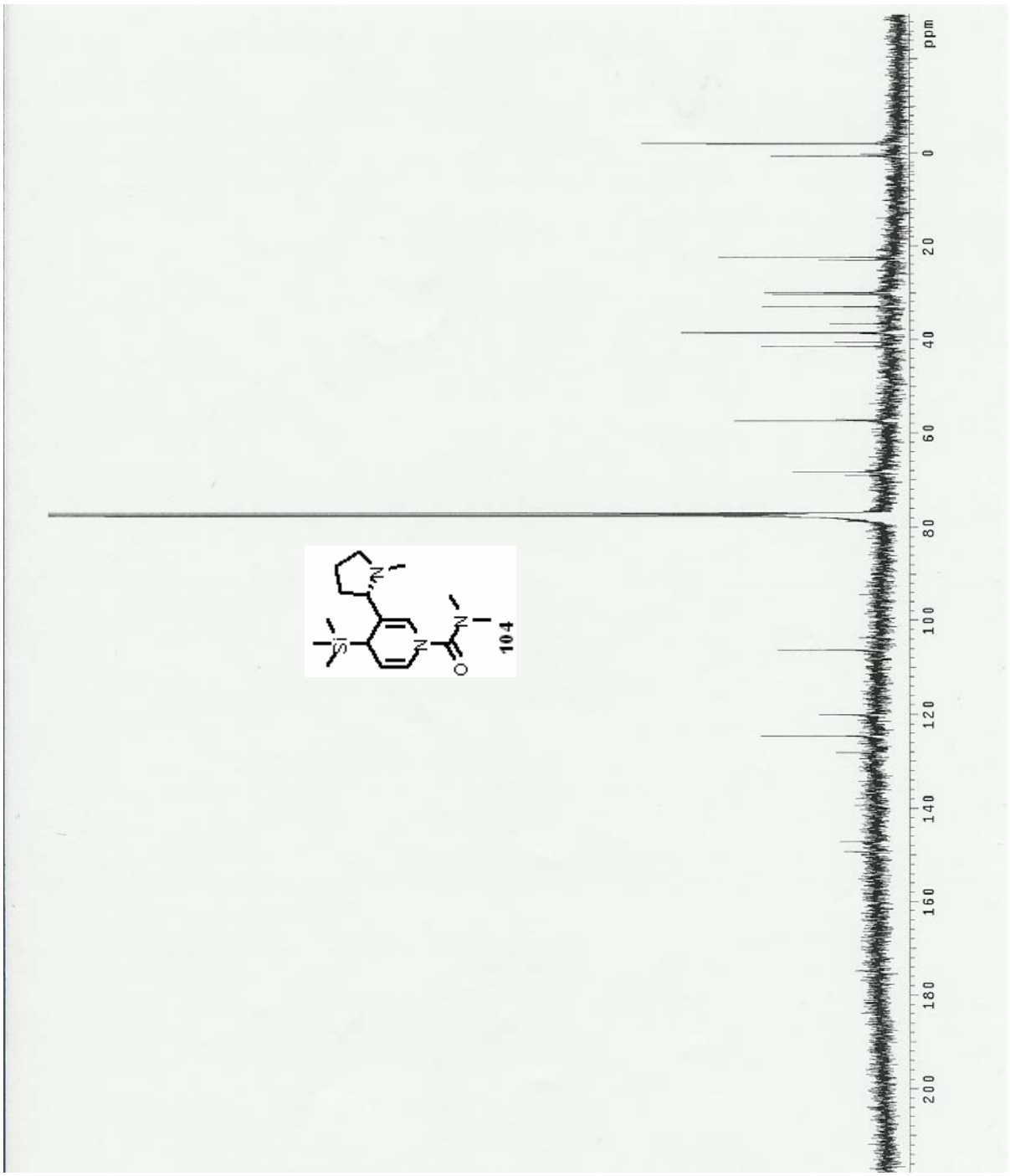
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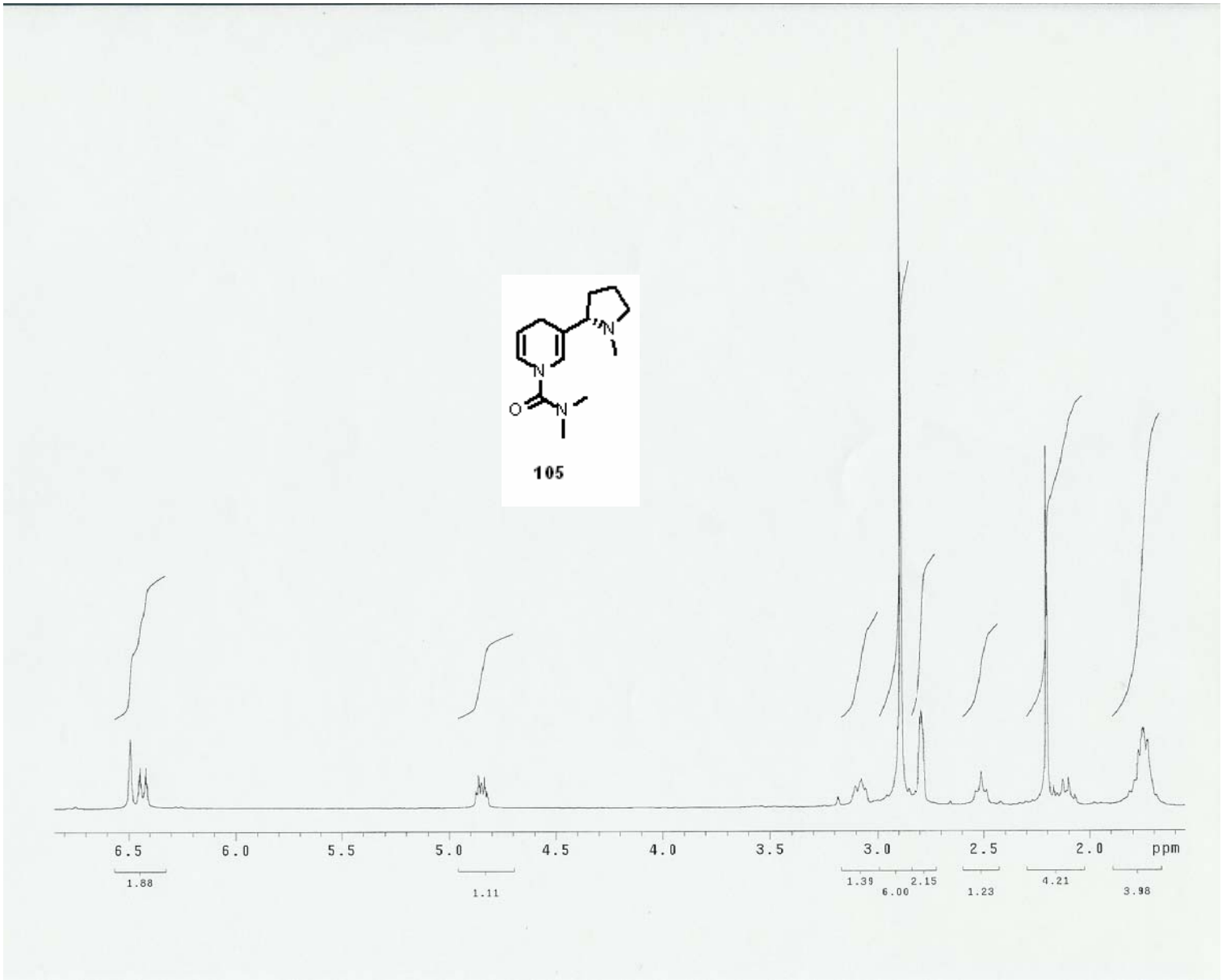
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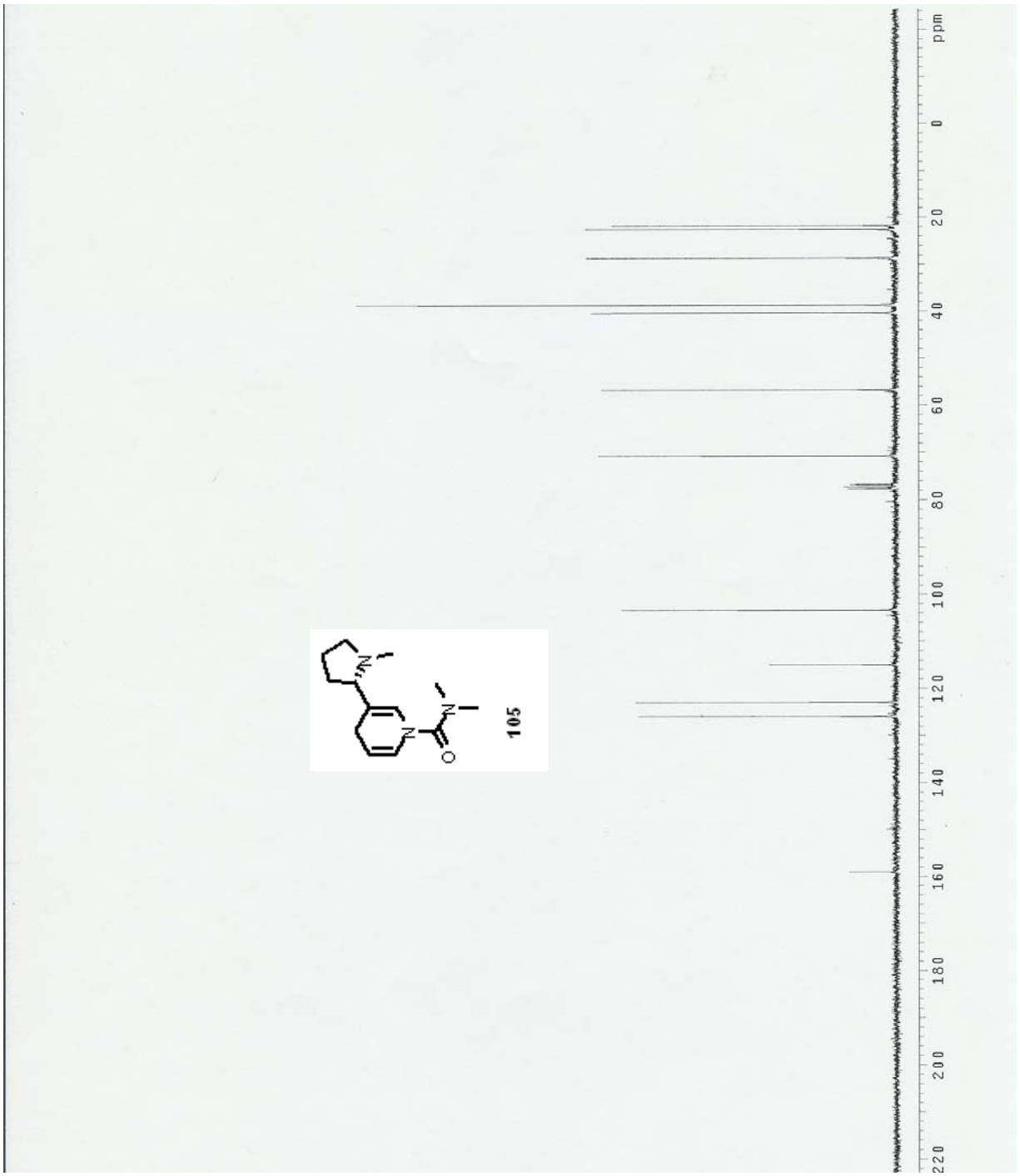
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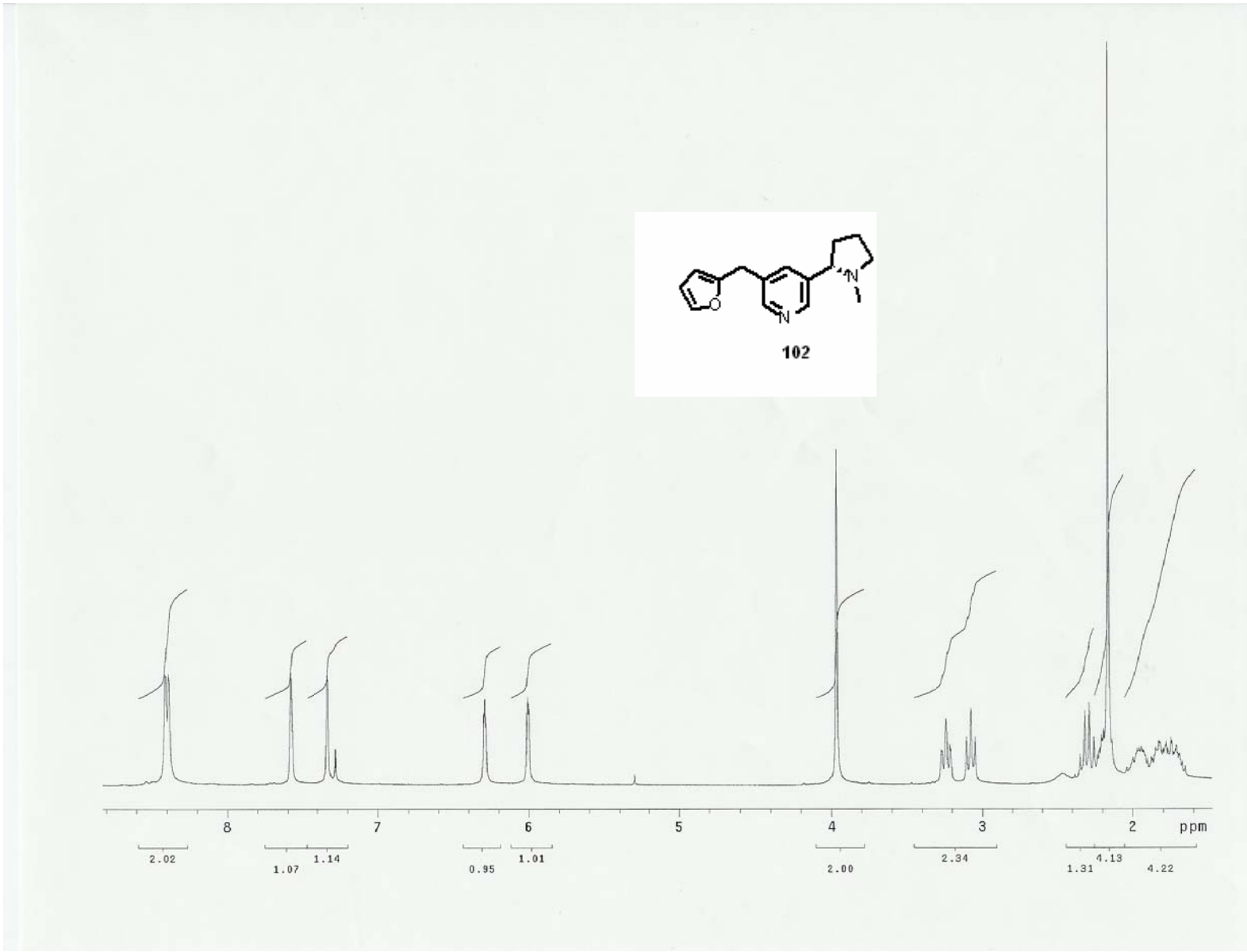
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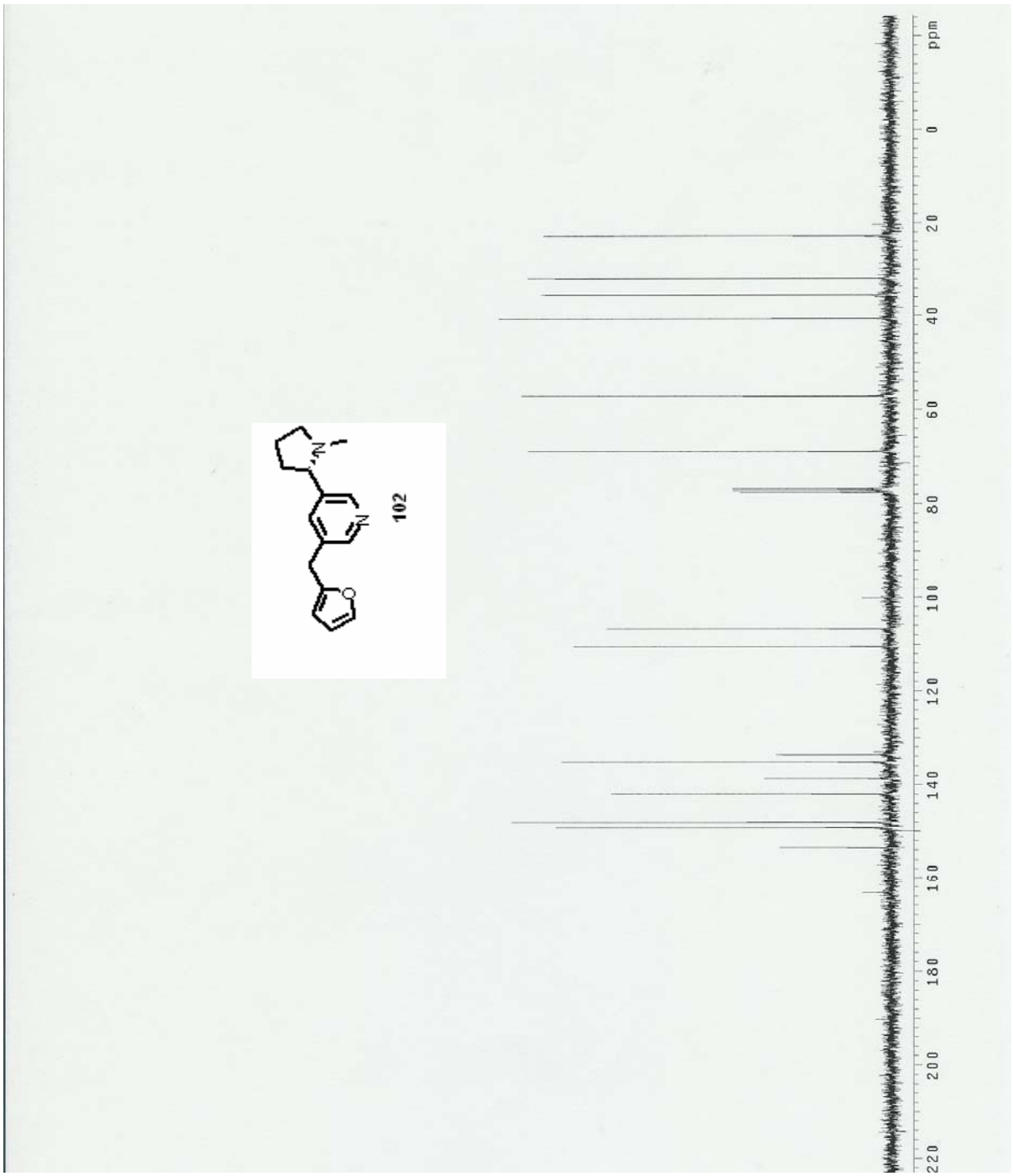
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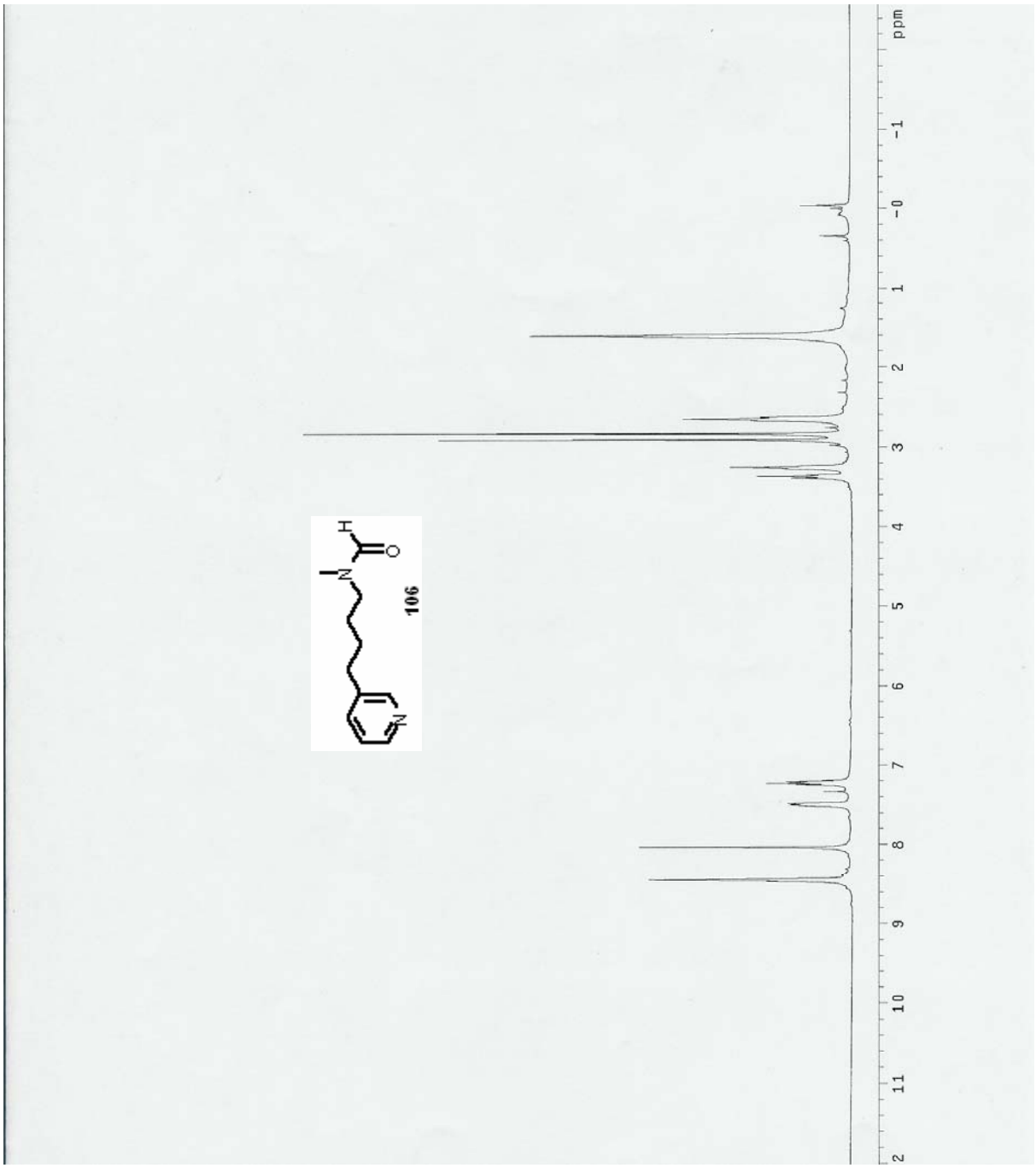
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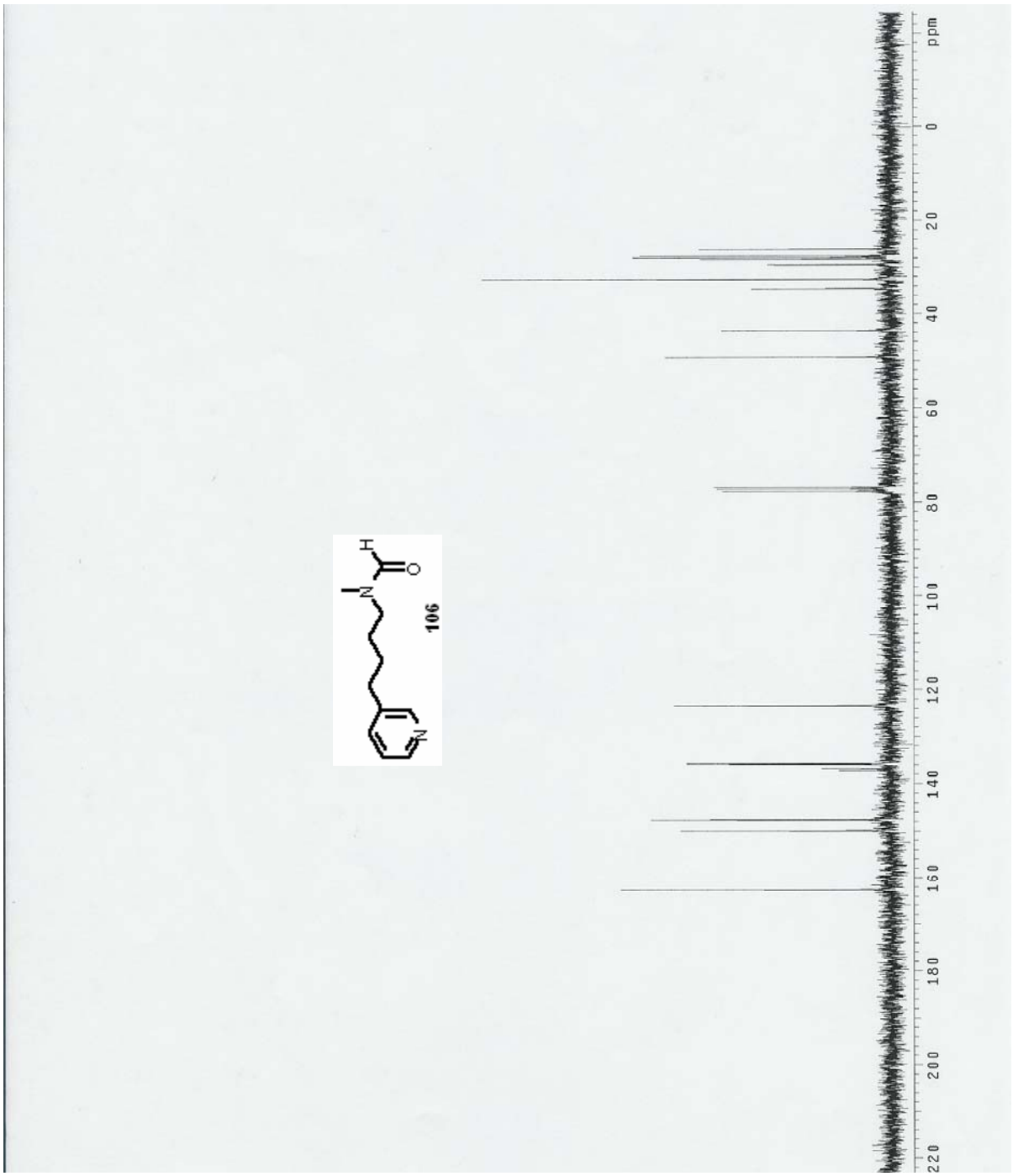
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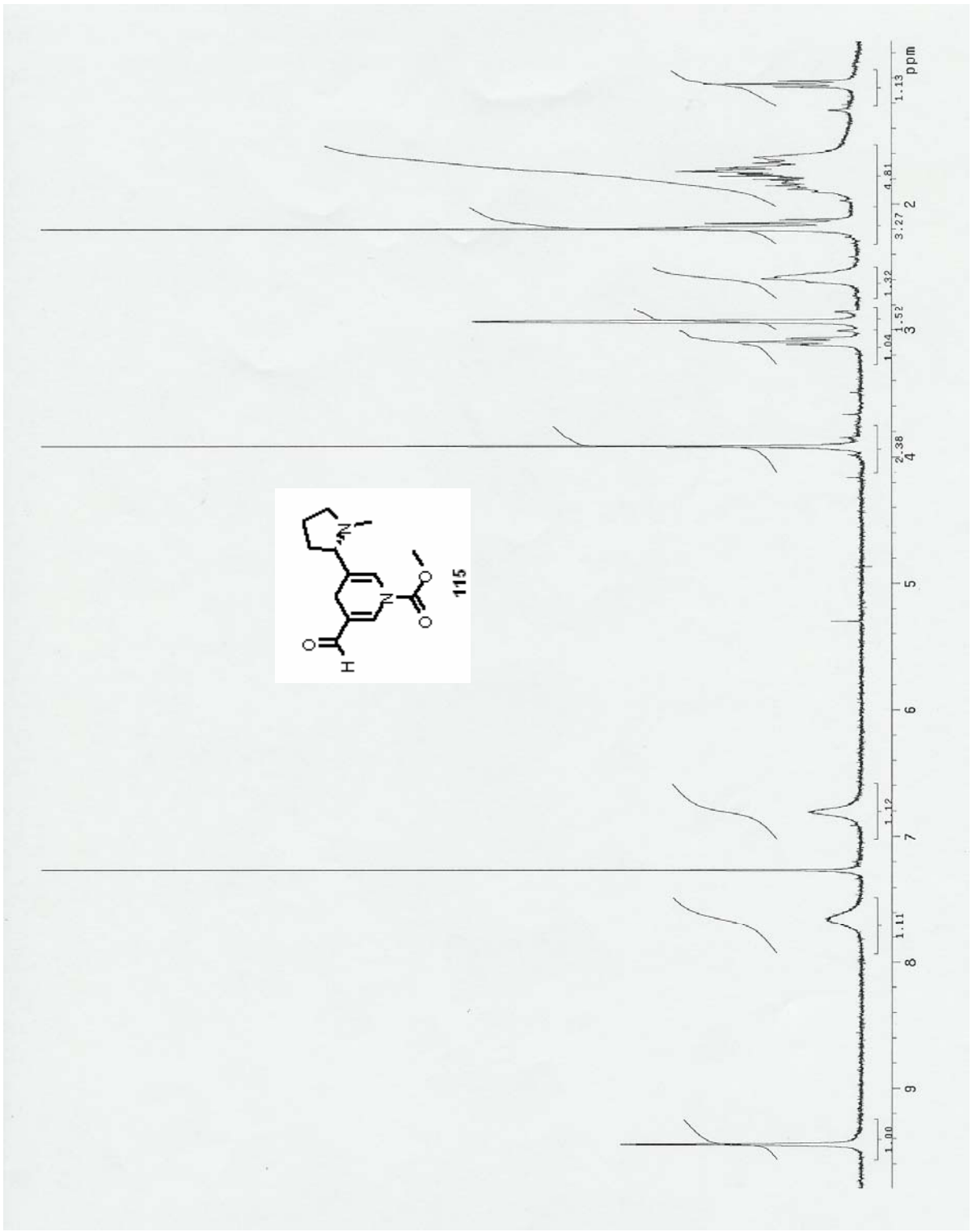
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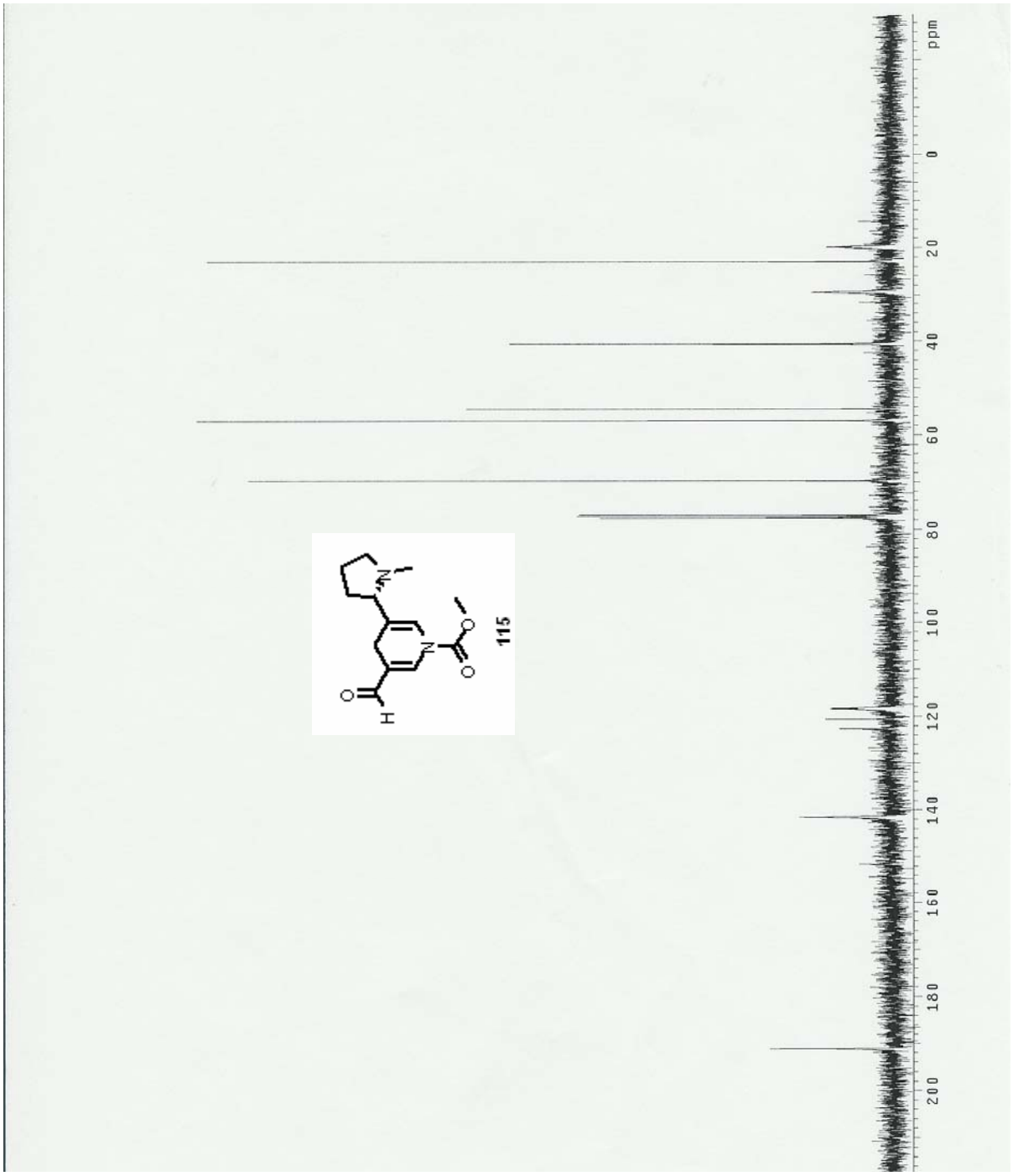
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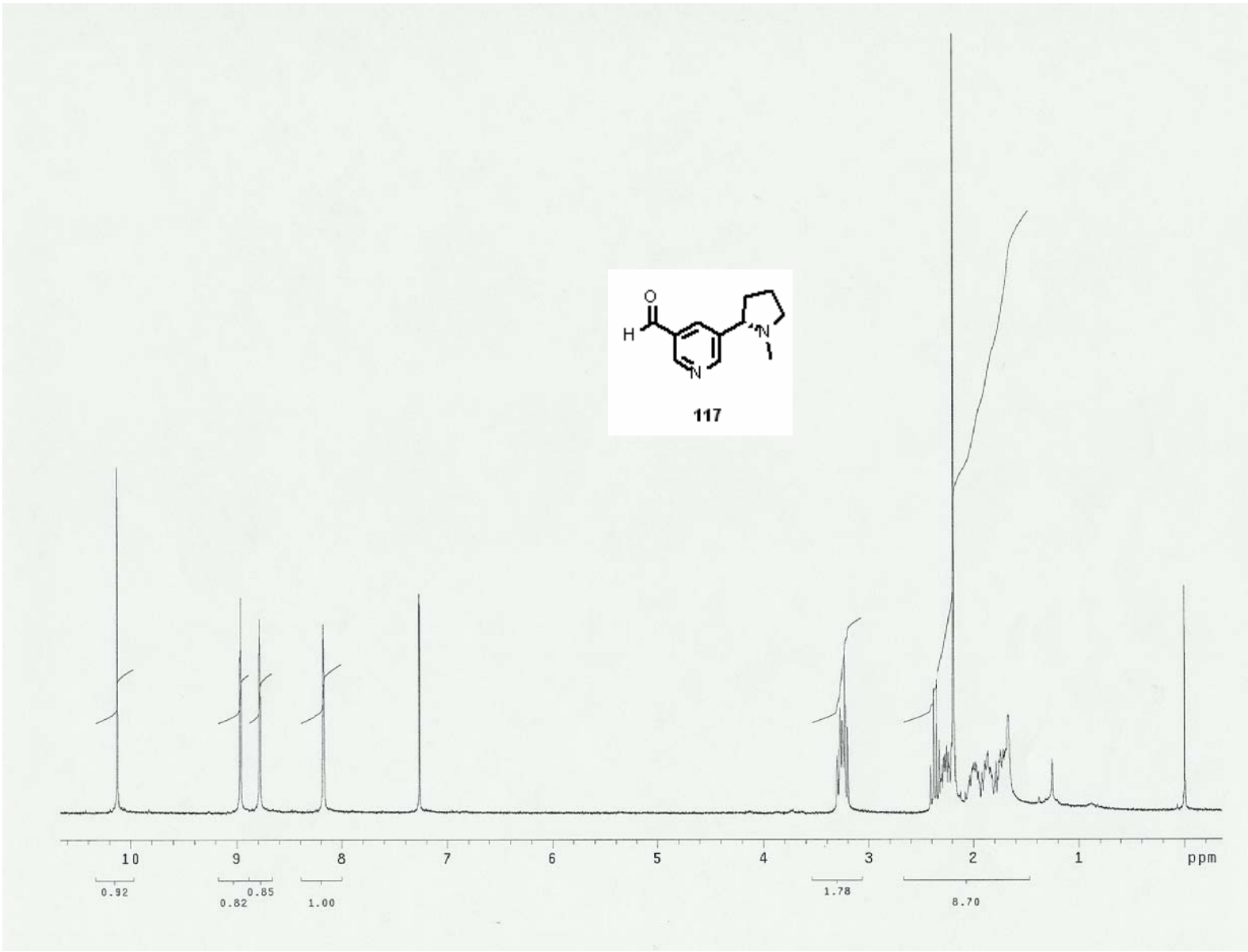
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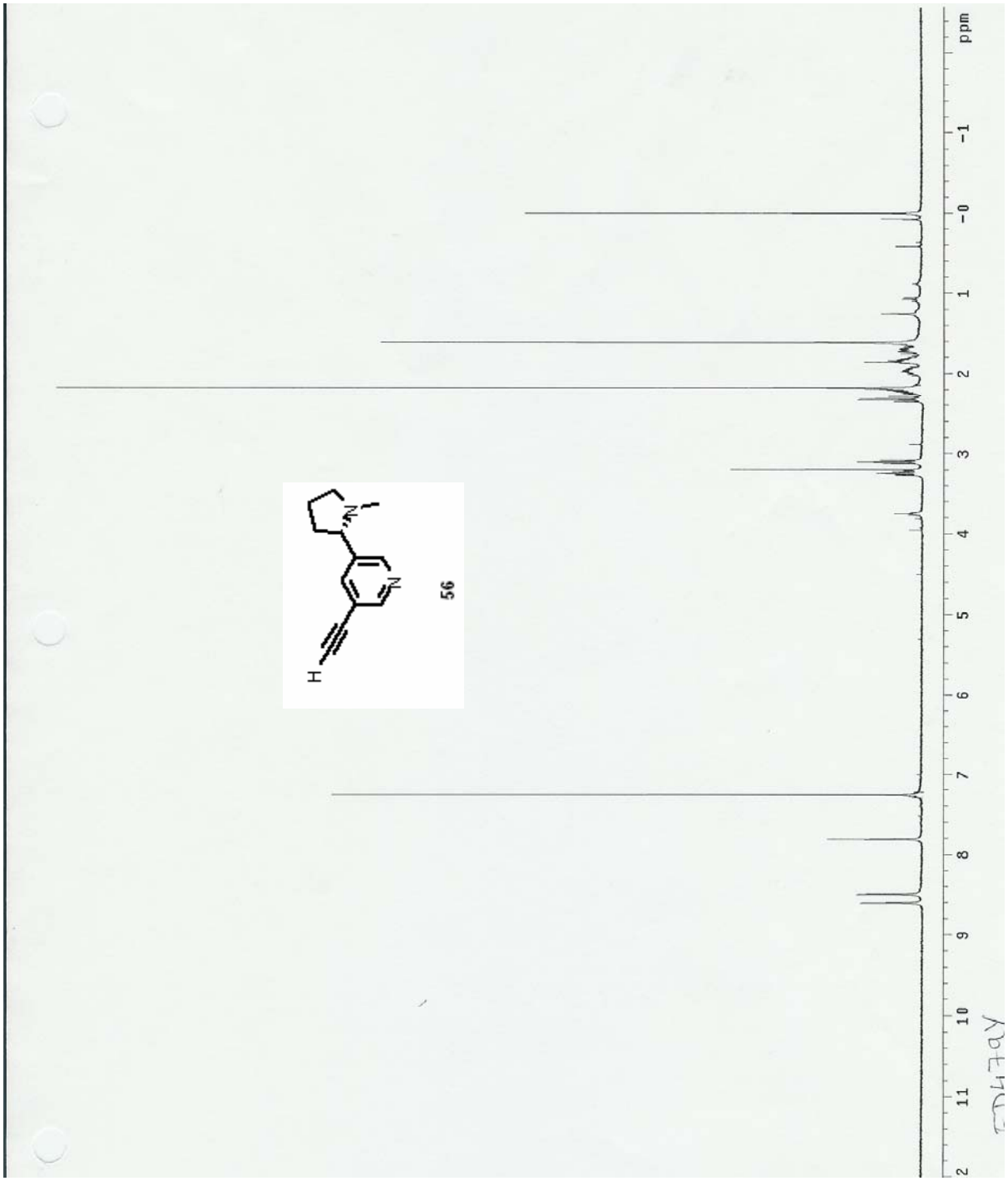
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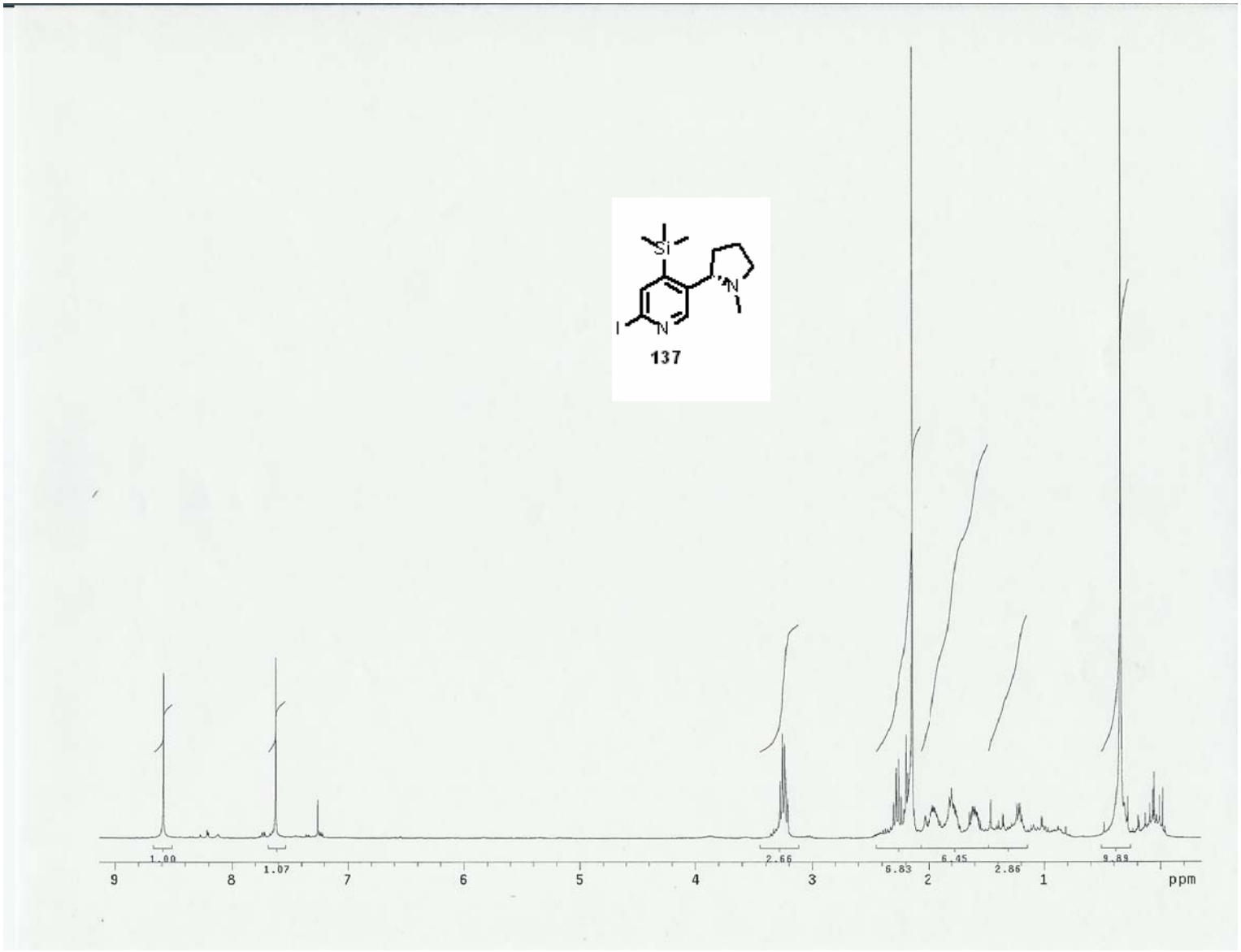
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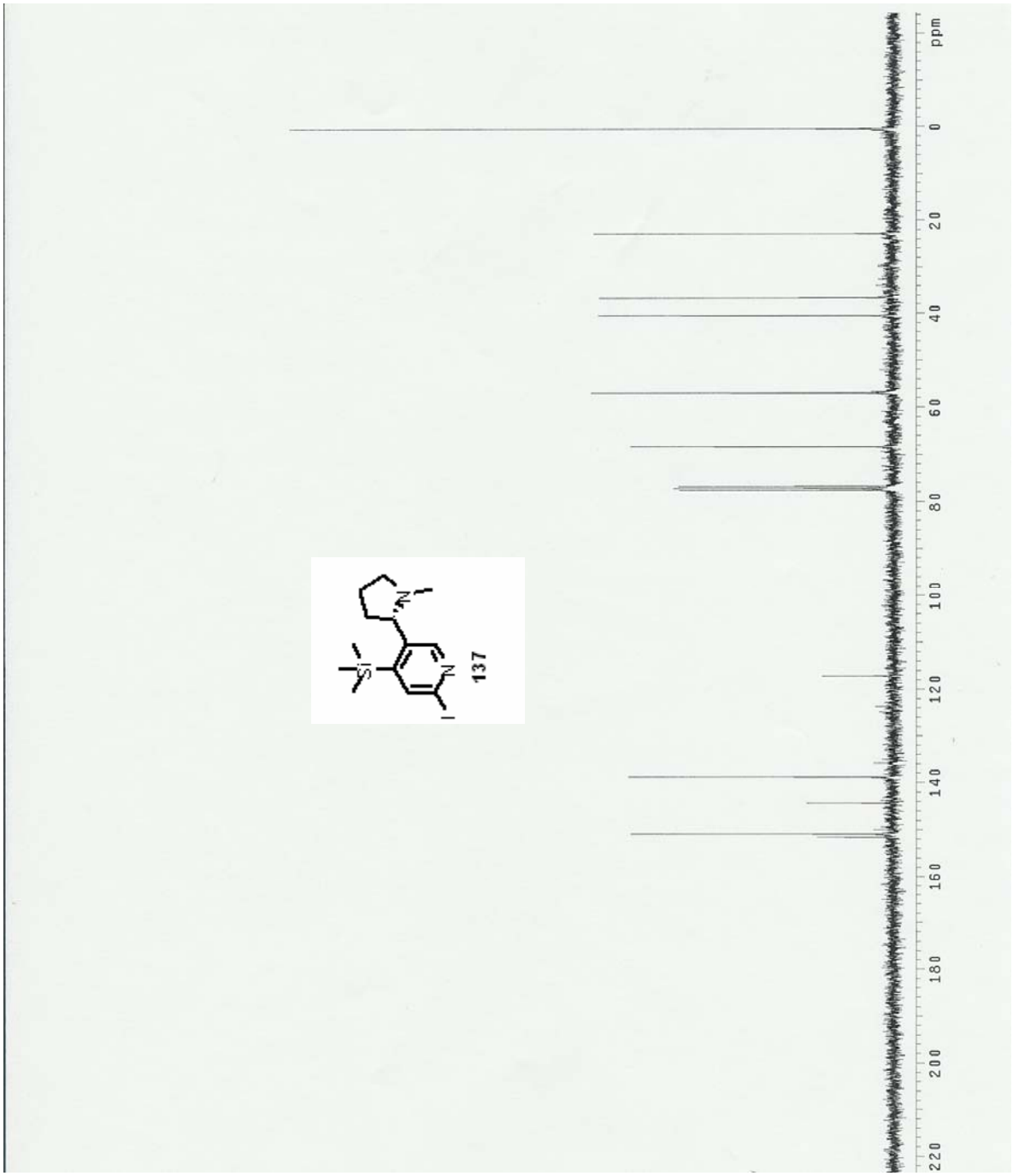
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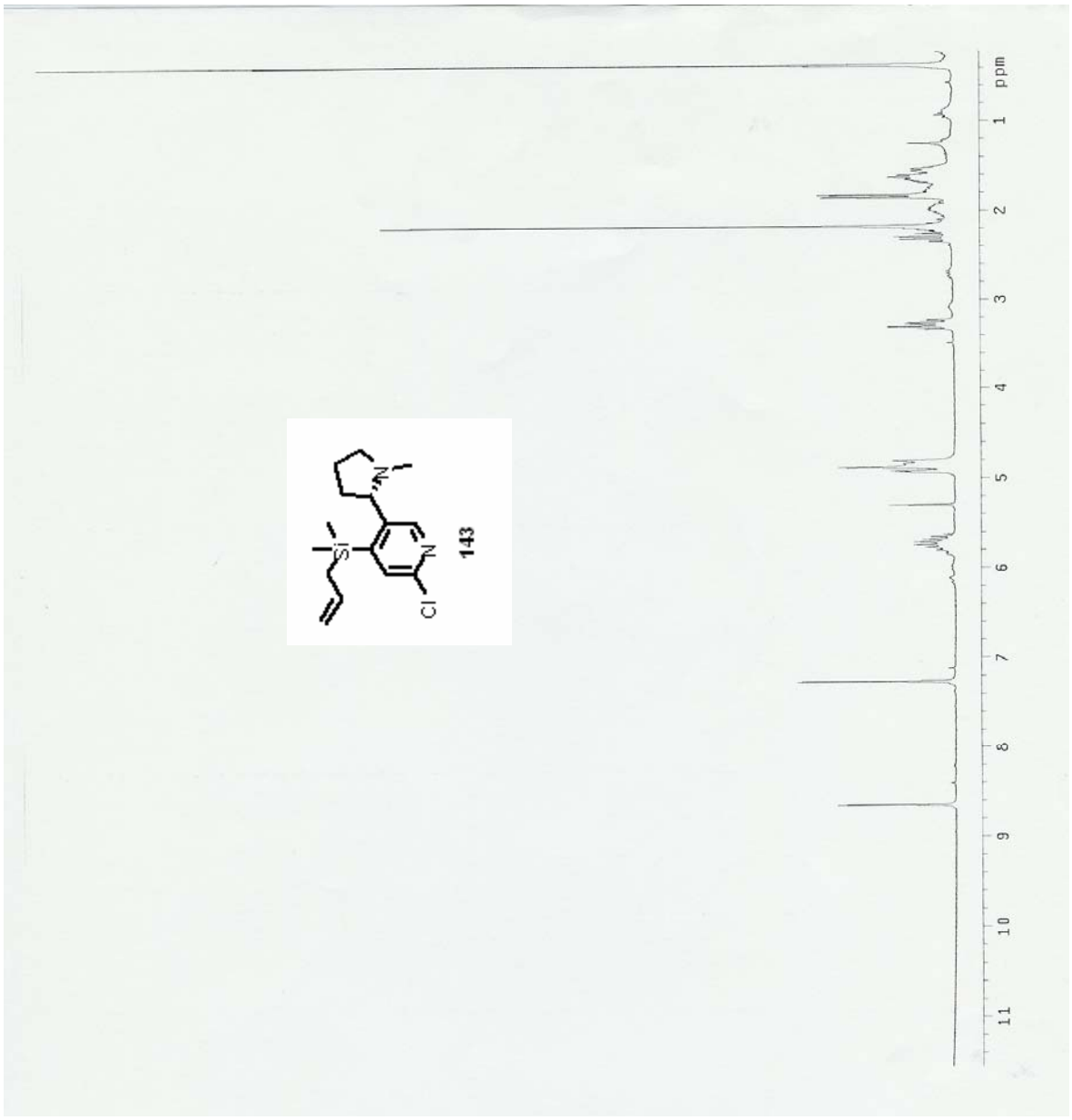
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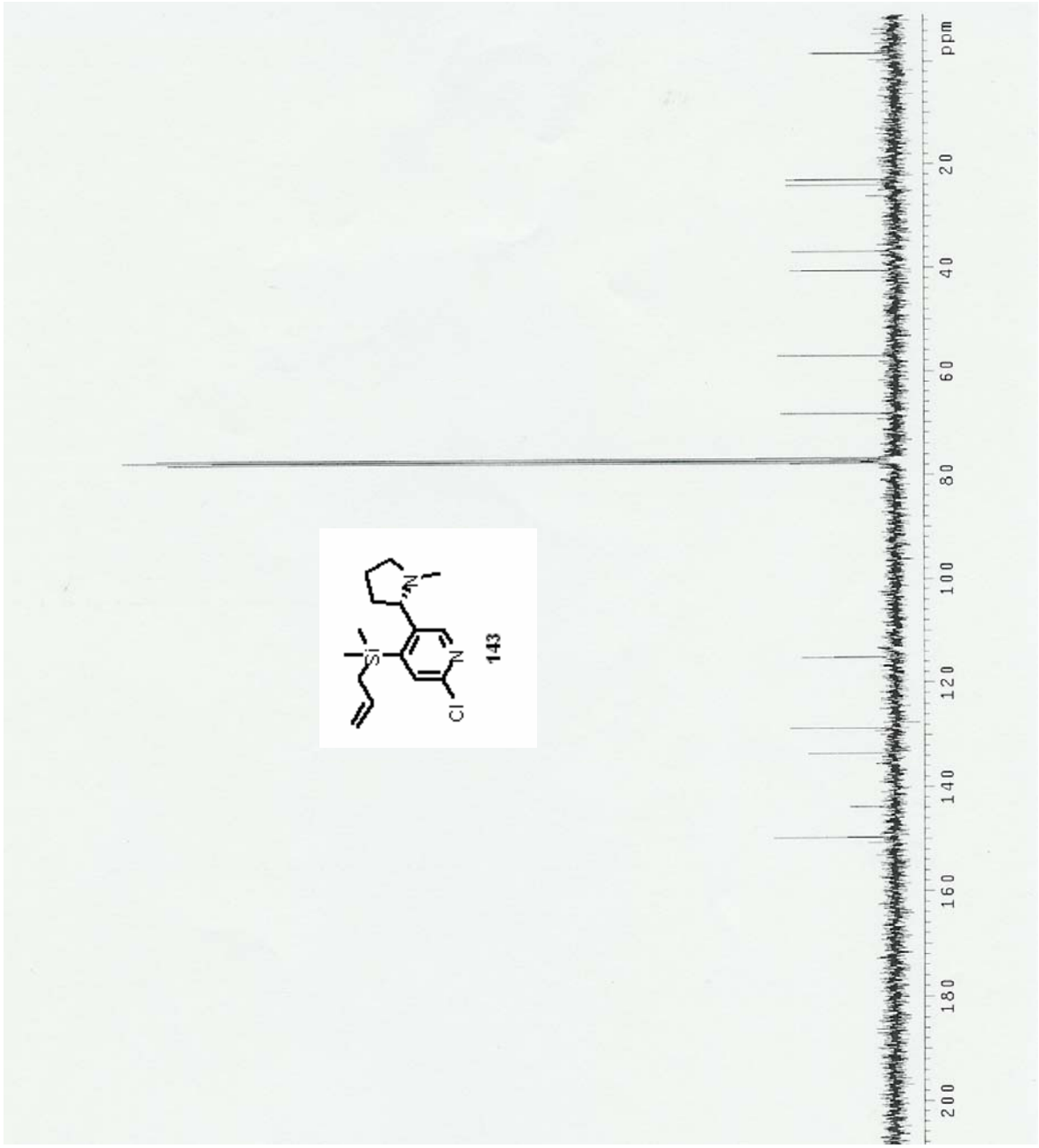
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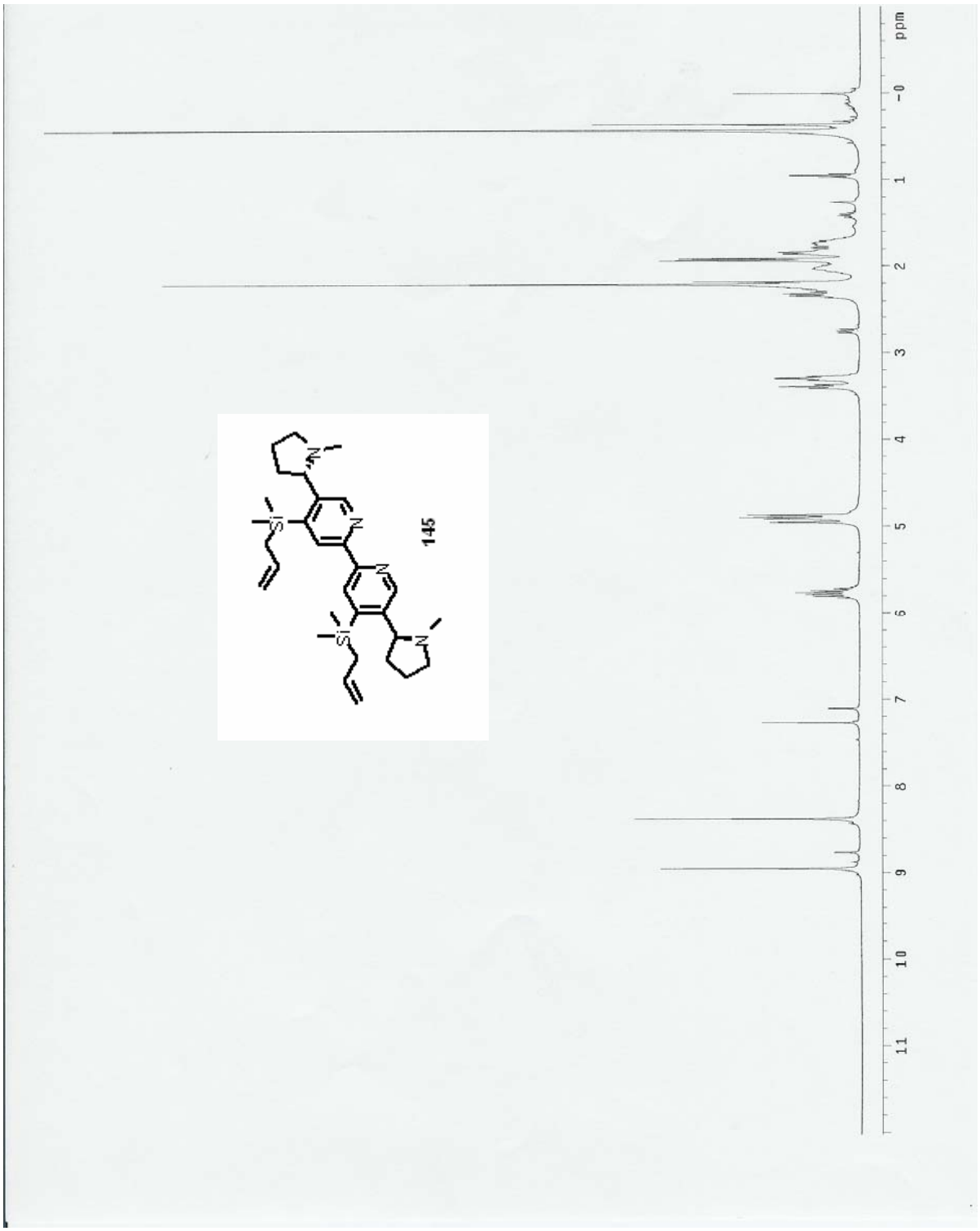
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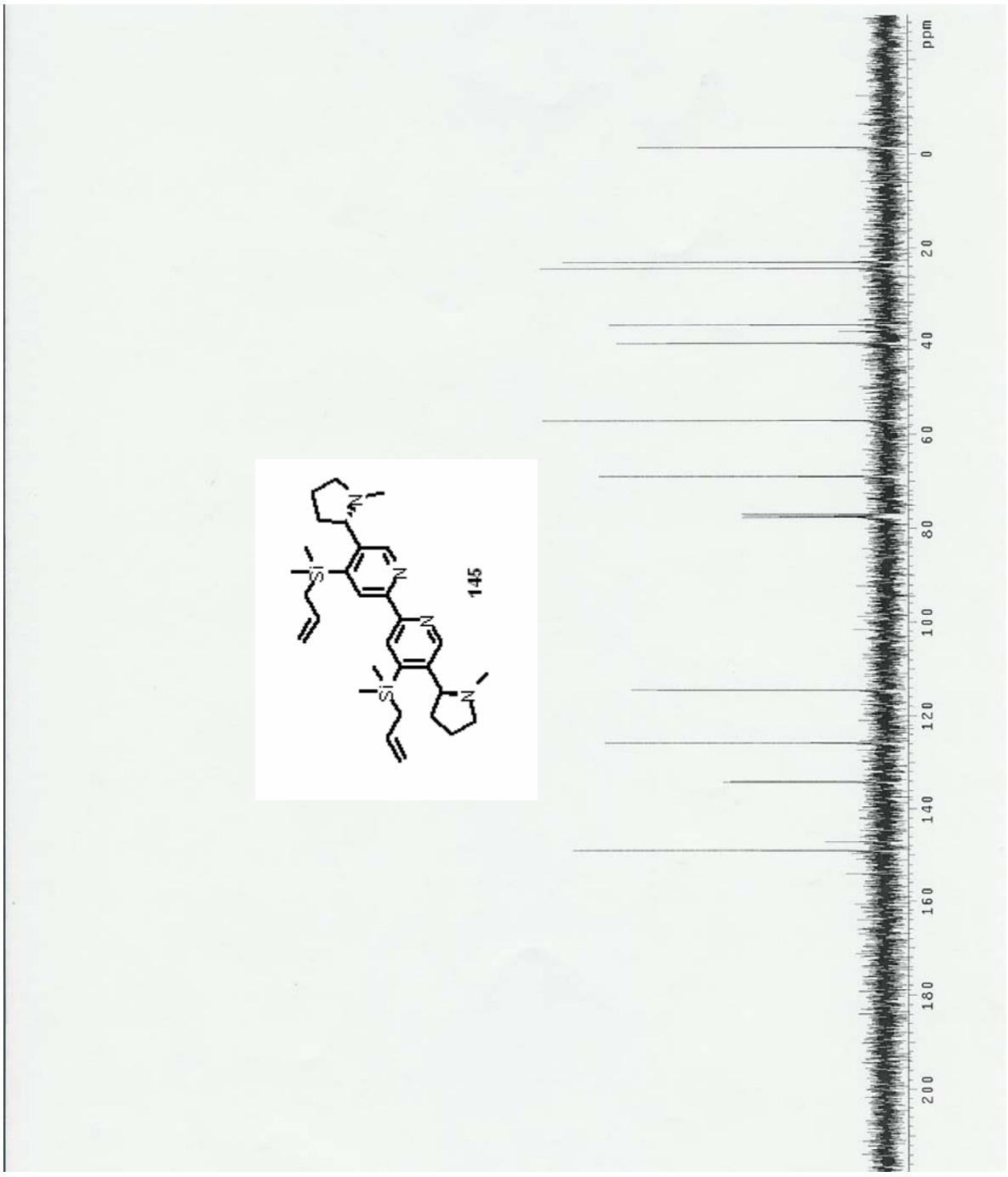
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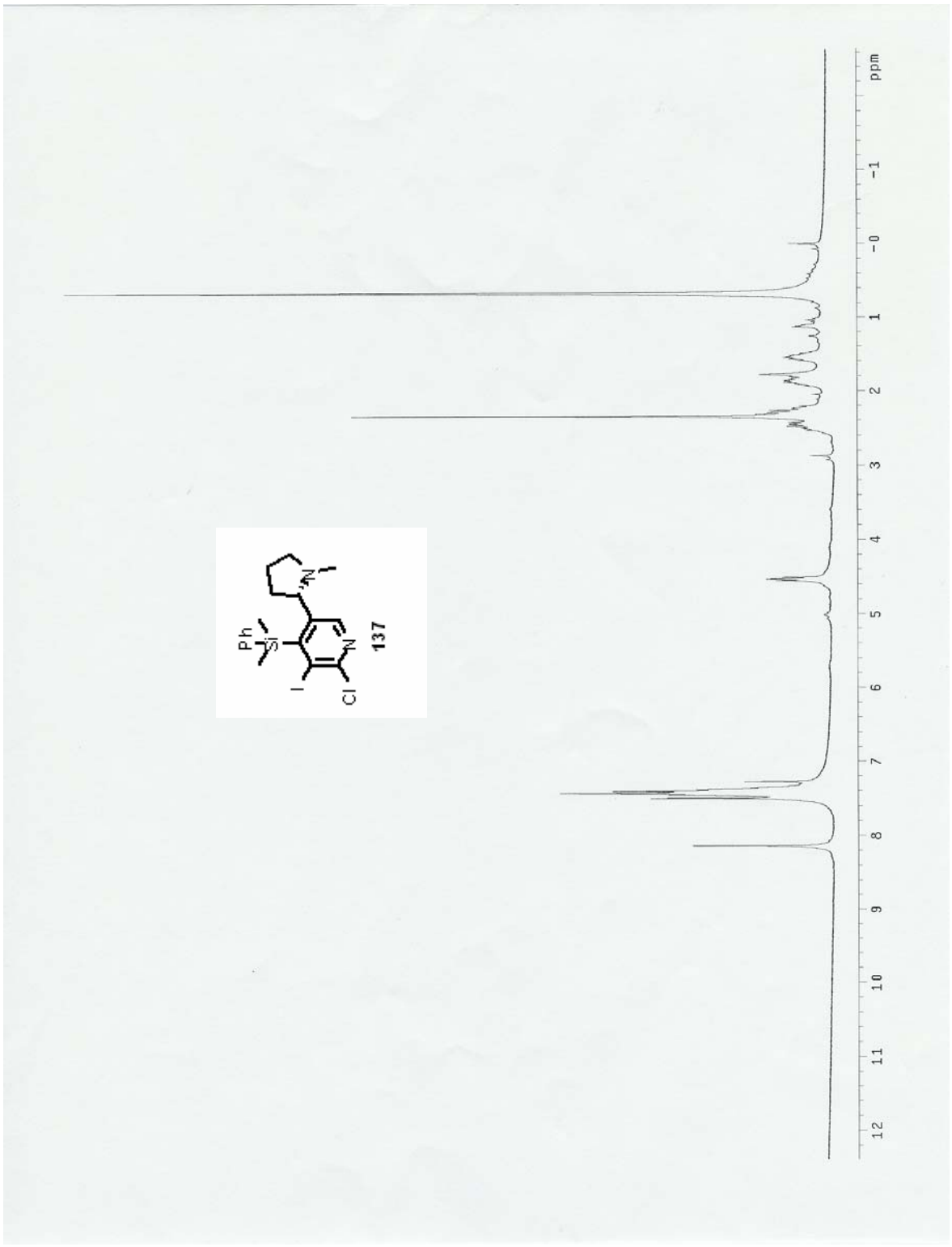
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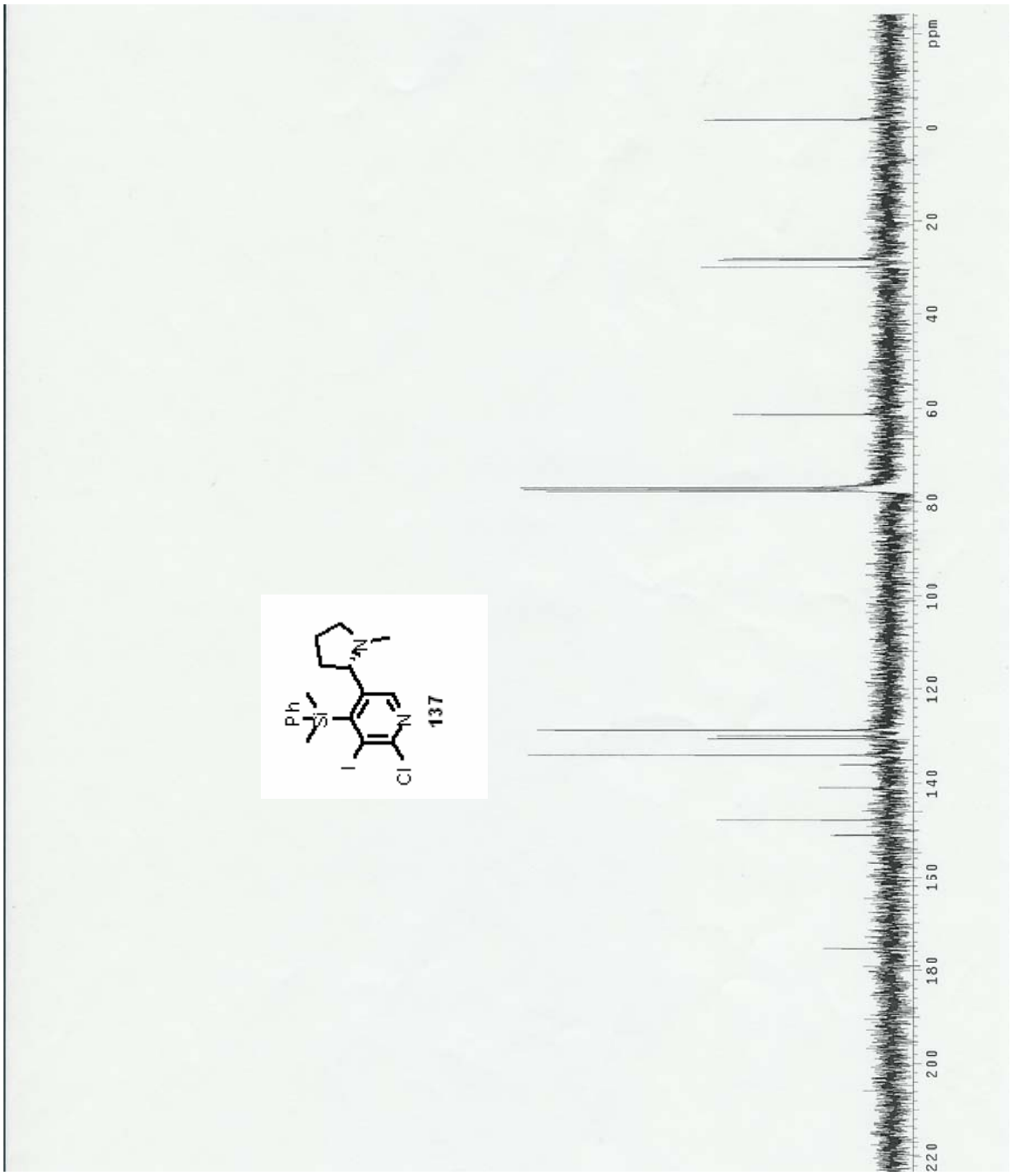
10
9
8
7
6
5
4
3
2
1
-0
-1

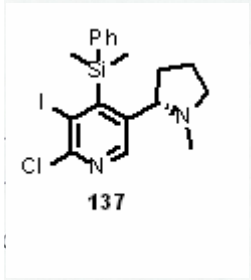

Ph
Si
I
Cl
N
137
ppm
0
20
40
60
80
100
120
140
150
180
200
220

Archive directory: /export/home/comins/vnmrsys/data
Sample directory: comins_17Jun2003-16:38:24
File: gHMBC

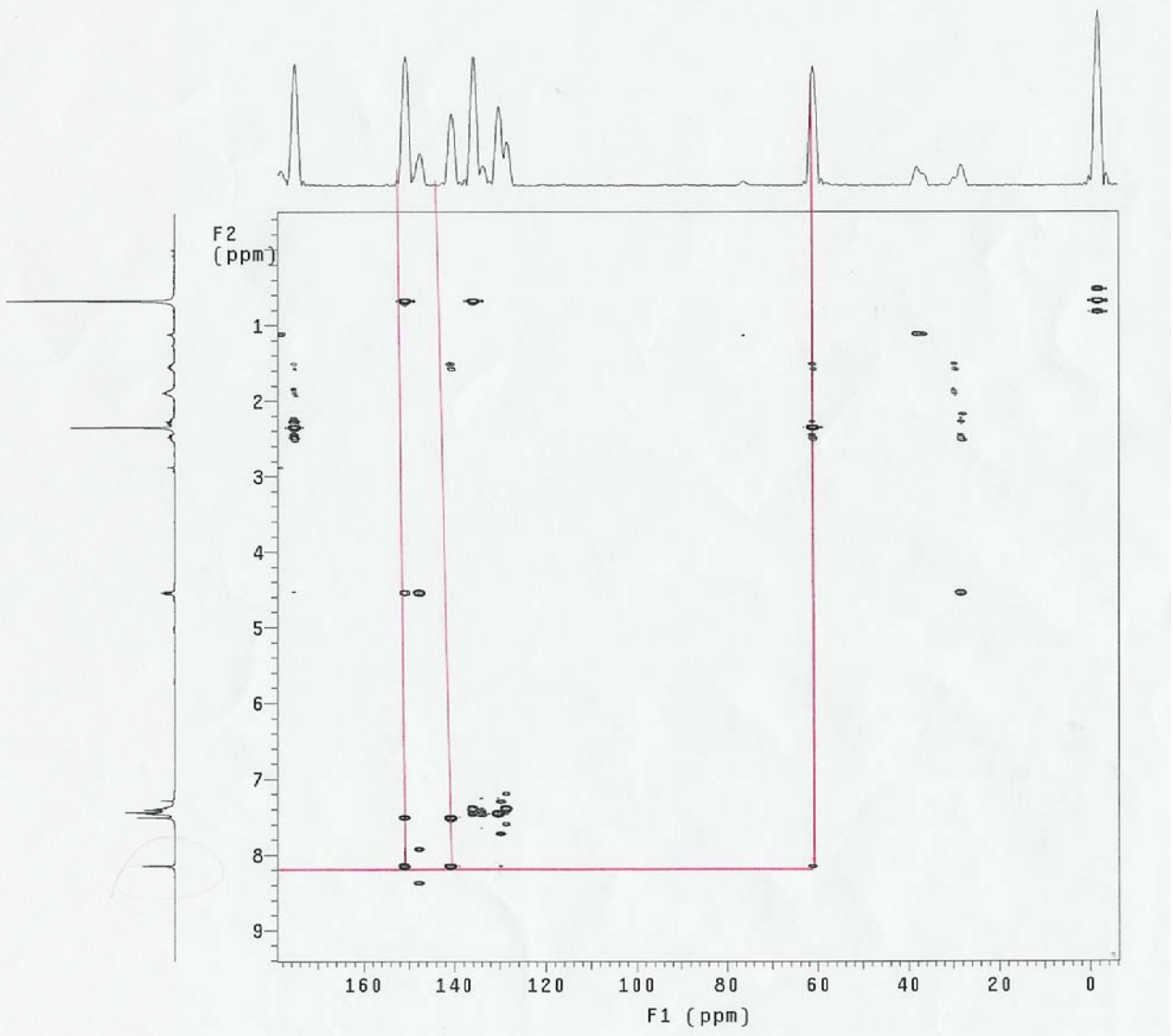
ulse Sequence: gHMBC

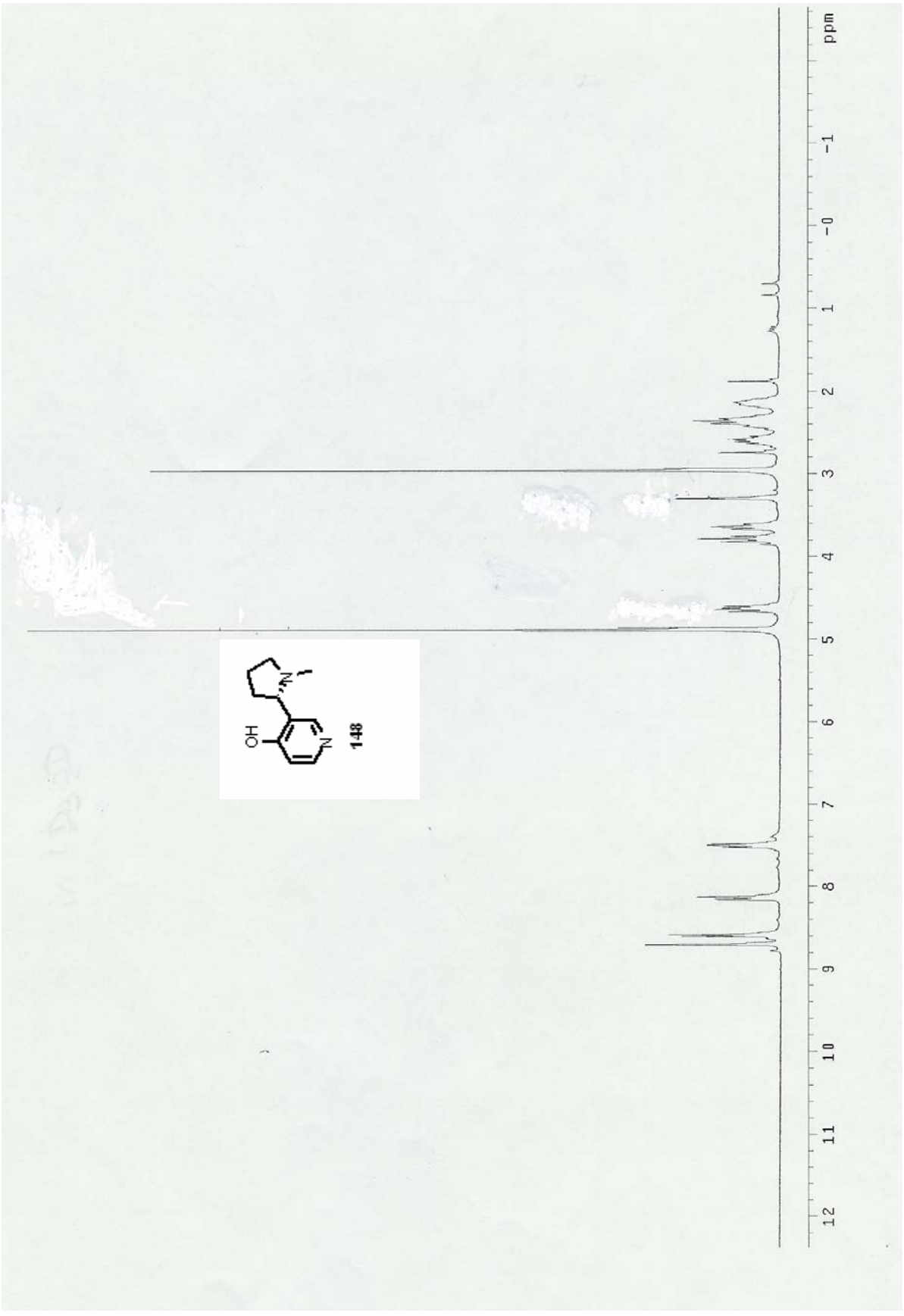
Solvent: CDCl3
Ambient temperature
ercury-400BB "ncsumerc400"

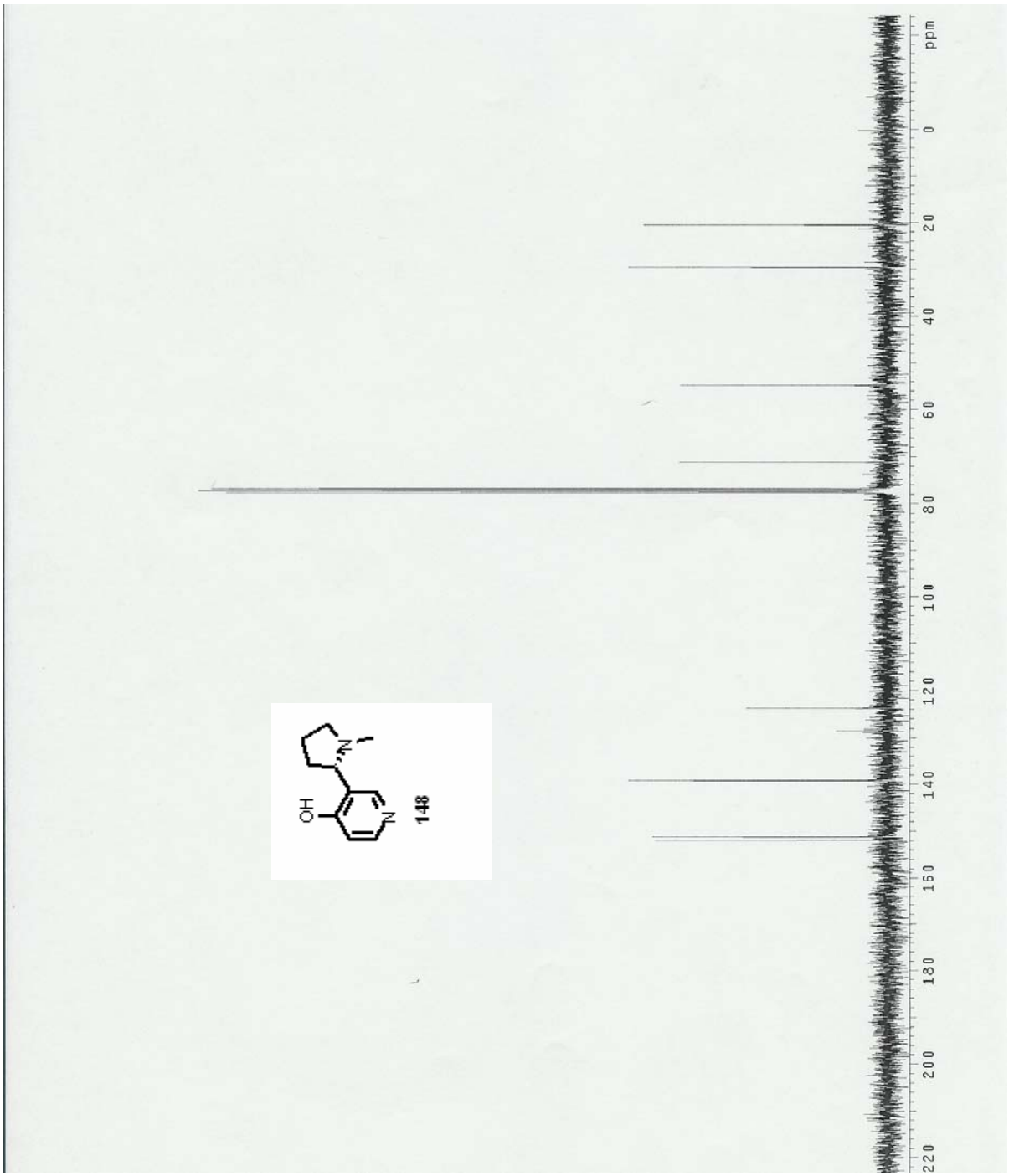
Relax. delay 1.000 sec
Acq. time 0.160 sec
Width 6410.3 Hz
2D Width 24154.6 Hz
8 repetitions
256 increments
BSERVE H1, 400.1351868 MHz
ATA PROCESSING
Sine bell 0.080 sec
1 DATA PROCESSING
Sine bell 0.005 sec
T size 2048 x 2048
otal time 45 min, 42 sec

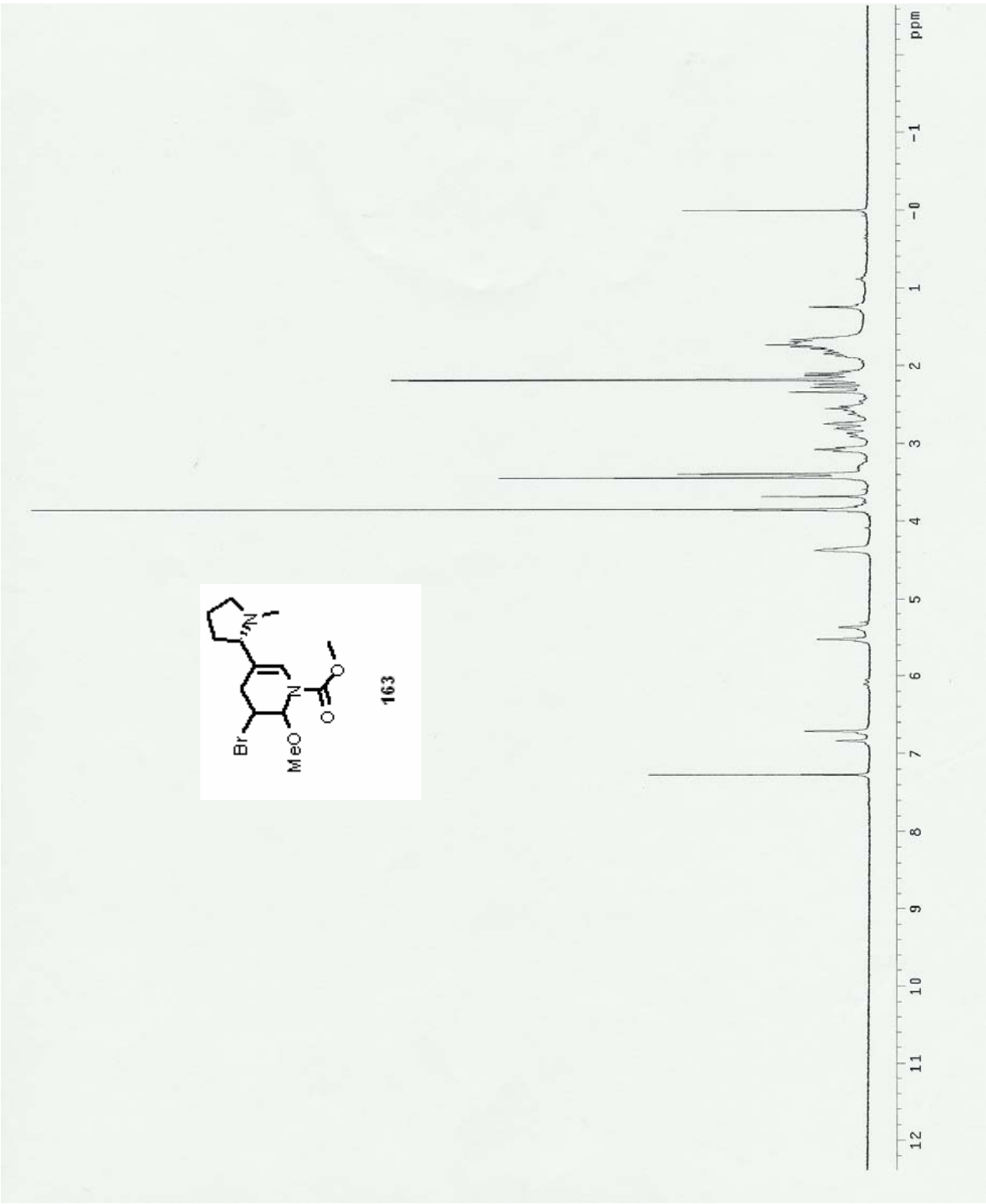


137

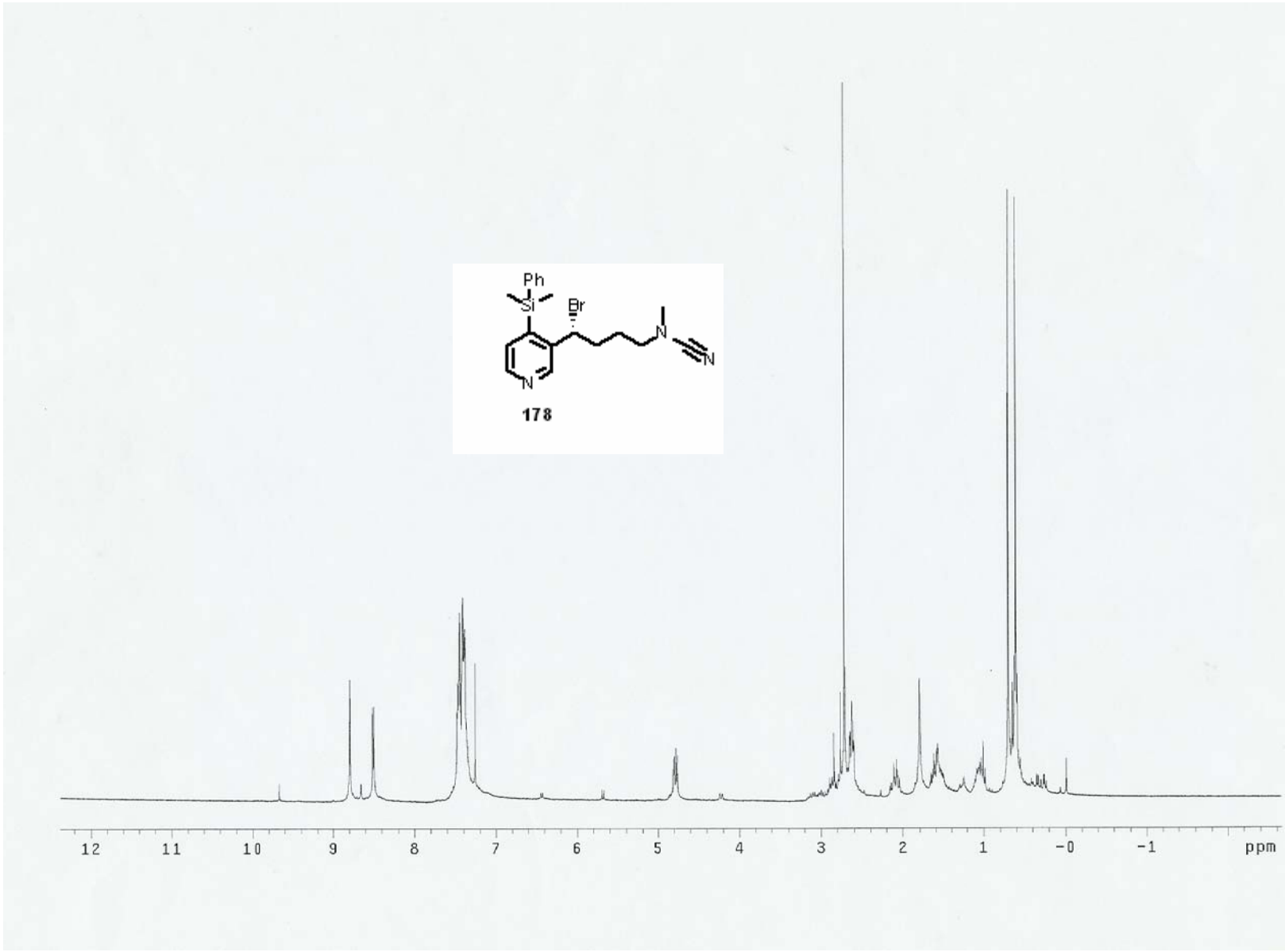


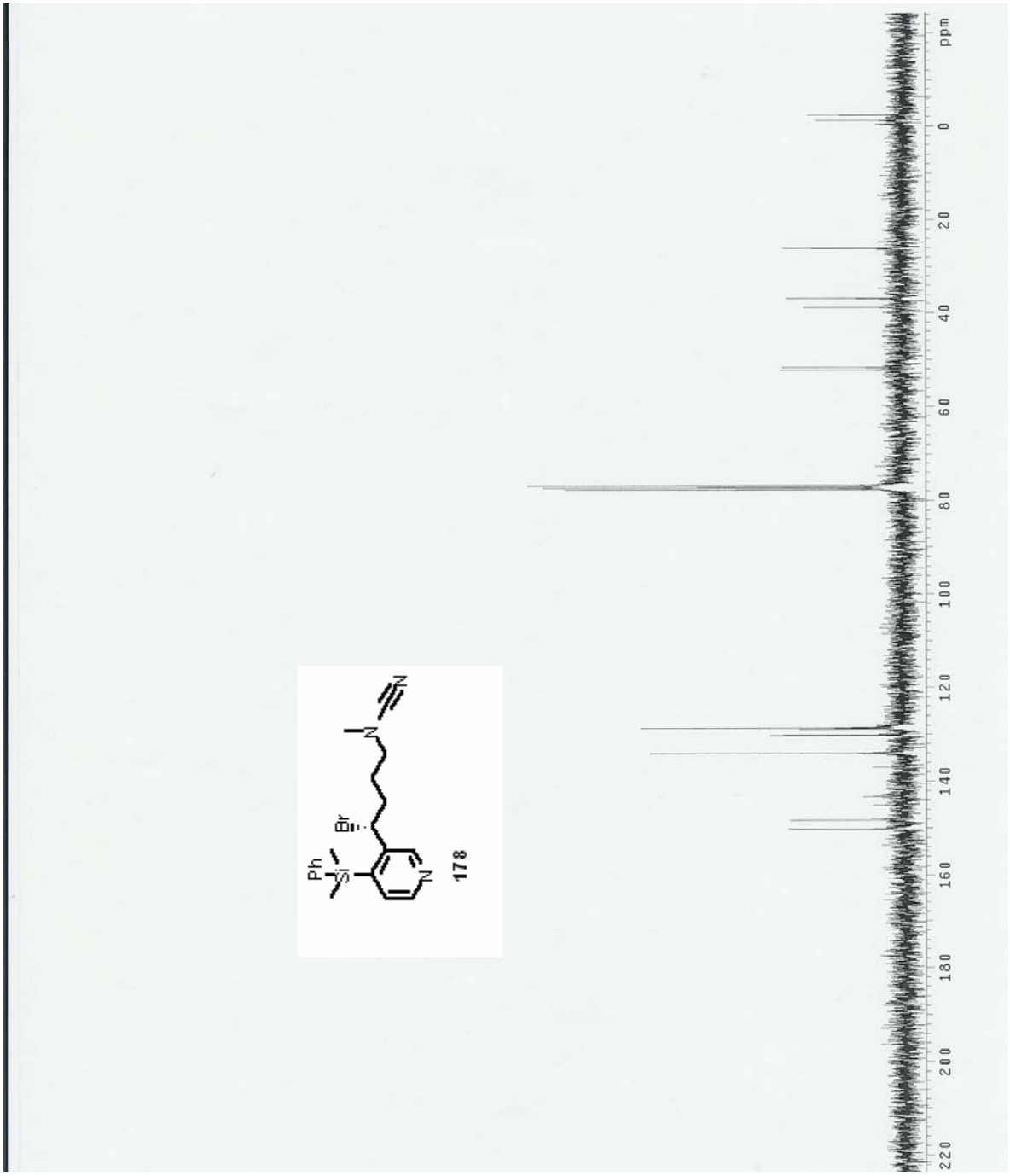

OH
N
148
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

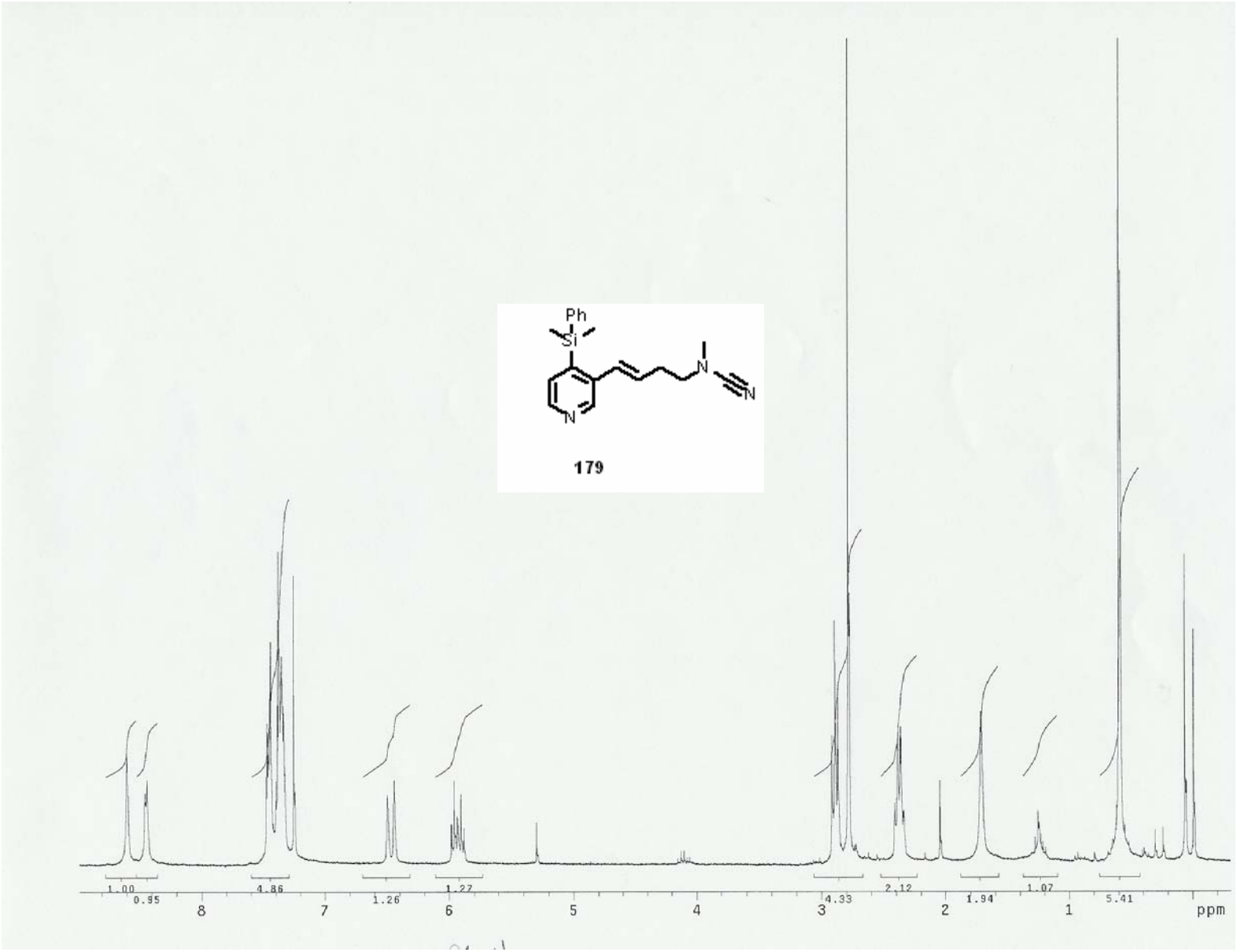

OH
N
148
ppm
0
20
40
60
80
100
120
140
150
180
200
220

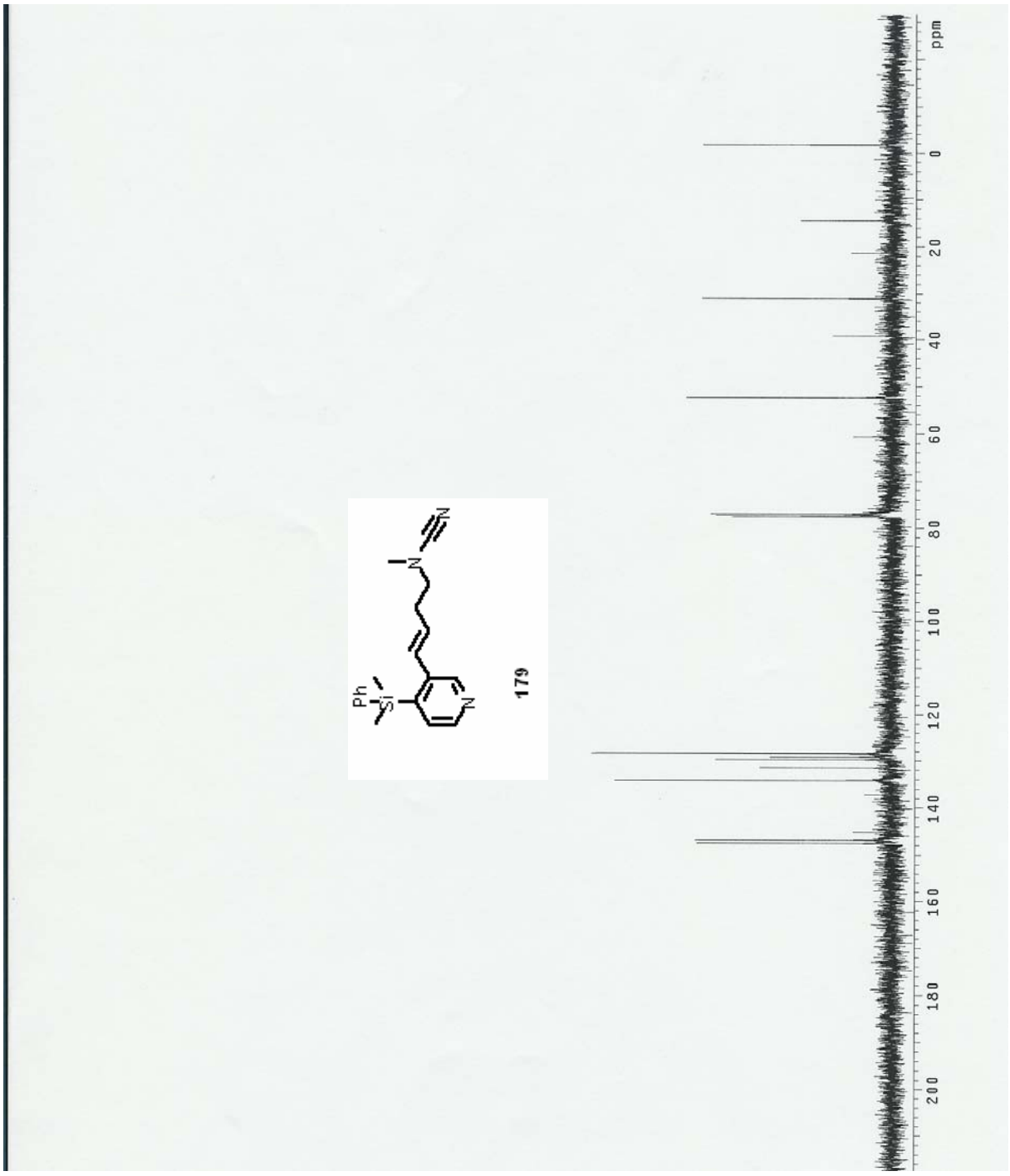

Br
MeO
O
O
163
12
11
10
9
8
7
6
5
4
3
2
1
−0
−1
ppm

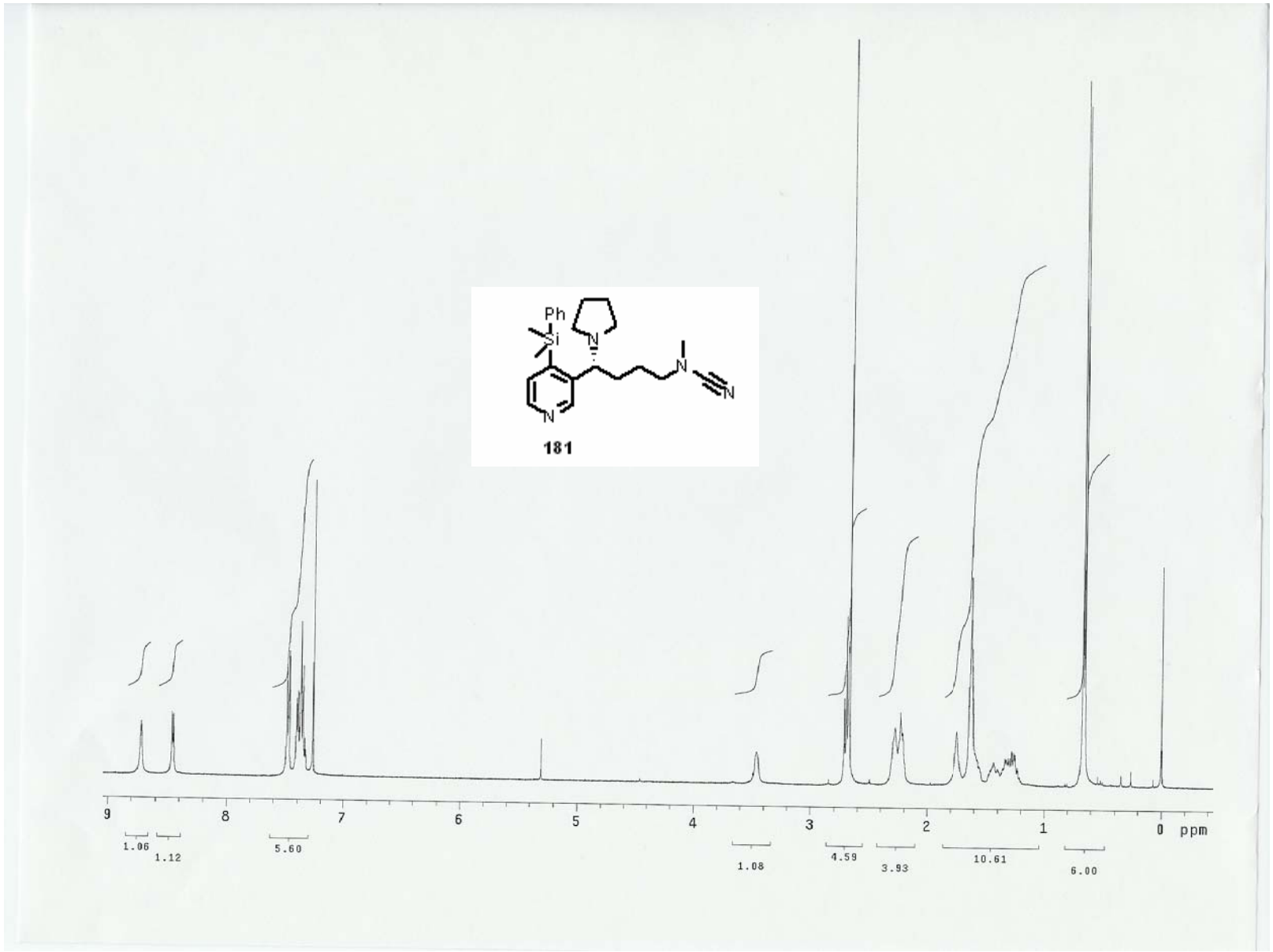
Br
MeO
N
O
O
163
118.520
114.516
84.065
83.738
77.657
77.230
76.809
70.942
56.885
56.738
53.628
43.355
40.438
30.086
25.854
22.717
120
110
100
90
80
70
60
50
40
30
20
ppm

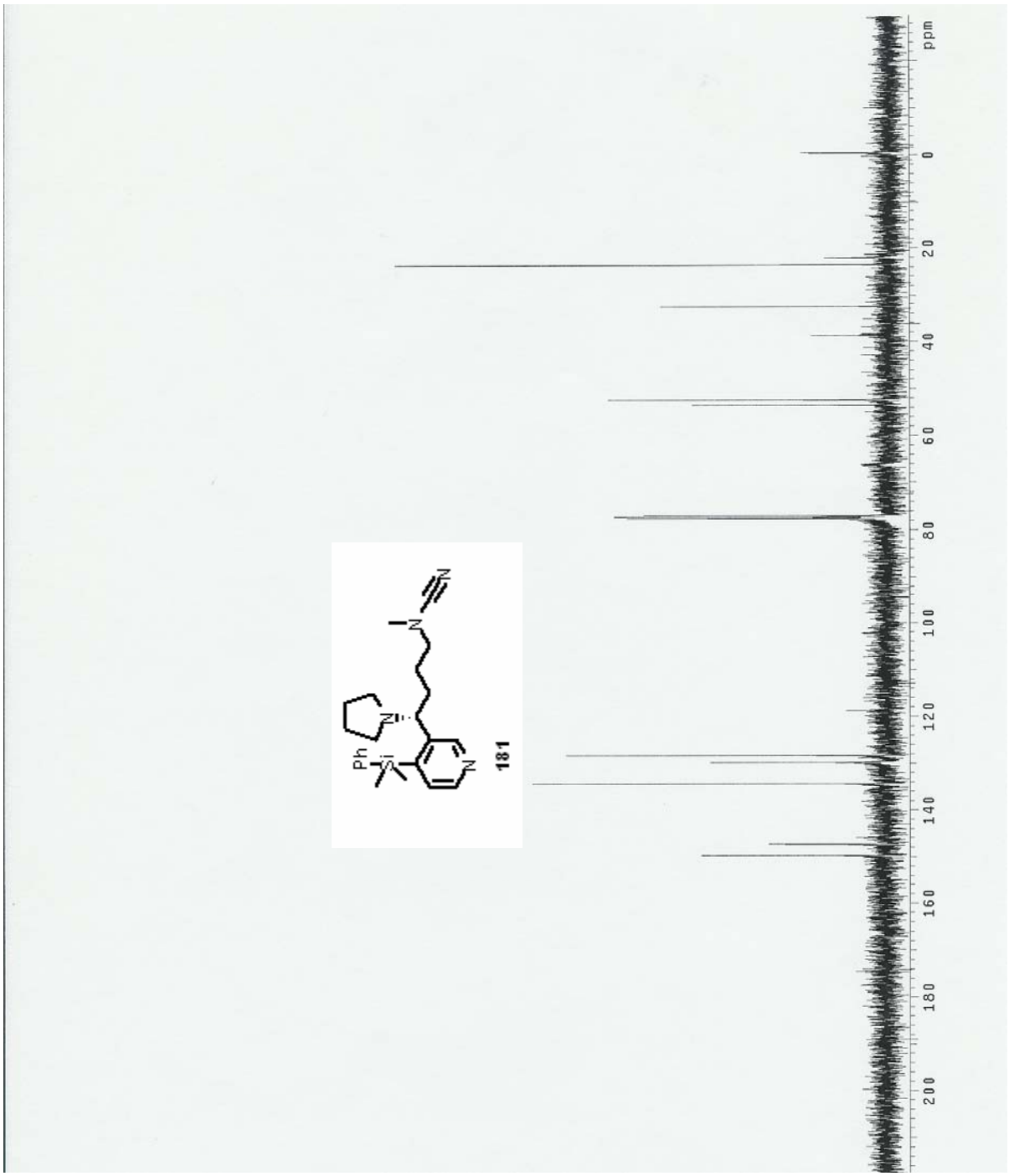

Ph
Si
Br
N
N
178
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm


Ph
Si
Br
N
N
178
ppm
0
20
40
60
80
100
120
140
160
180
200
220


Ph
Si
N
N
N
179
1.00
0.95
4.86
1.26
1.27
4.33
2.12
1.94
1.07
5.41
8
7
6
5
4
3
2
1
ppm


Ph
Si
N
N
179
ppm
0
20
40
60
80
100
120
140
160
180
200


Ph
Si
N
N
N
N
181
9
8
7
6
5
4
3
2
1
0
ppm
1.06
1.12
5.60
1.08
4.59
3.93
10.61
6.00


ppm
0
20
40
60
80
100
120
140
160
180
200
Ph
181