ARYNE REACTIONS IN THE SYNTHESIS OF HETEROCYCLIC MOLECULES

Thesis by

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To my parents.

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become one of my closest friends at Caltech. I can honestly say that one of the biggest things I will miss about the Stoltz Lab is being O'Cornered by Nick O'Connor. Our debates and our endless conversations about useless information on wikipedia (and sometimes chemistry) have been intregral to my experience during grad school. Kelvin Bates has been a great person to go line dancing with every Friday. Sam Shockley, Katerina Korch, Jeff Holder and Jared Moore have made the last five years memorable and so much fun both in and outside the lab.

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ABSTRACT

Reactive intermediates play an important the within the realm of chemical synthesis. Their high energy and transient nature make them difficult to observe and characterize, but it is these same properties that empower them to form bonds traditionally seen as difficult to prepare and unusual architectures quickly and efficiently. Herein, two reactive intermediates, arynes and transitient (2azaaryl)-cuprates, are exploited for their abilities to prepare important chemical motifs. Both serve as an avenue into the functionalization of arenes to provide products which hold value in a variety of fields including natural product total syntethis, pharmaseuticals and ligand design.

TABLE OF CONTENTS

CHAPTER 1   1

The Acyl-Amidation of Arynes

APPENDIX 1   17

Spectra Relevant to Chapter 1

CHAPTER 2   38

Progress Toward the Total Synthesis of Jorumyicn

APPENDIX 6   **130**

Prepartion of Benzotriazoles via an Aryne-Based Three-Component Cross-Coupling

LIST OF FIGURES

APPENDIX 1

CHAPTER 2

APPENDIX 2

APPENDIX 3

CHAPTER 3

APPENDIX 5

LIST OF SCHEMES

CHAPTER 1

CHAPTER 2

APPENDIX 3

APPENDIX 3

CHAPTER 3

APPENDIX 5

APPENDIX 6

LIST OF TABLES

LIST OF ABBREVIATIONS

A   adenine

$[\alpha]_D$ angle of optical rotation of plane-polarized light

Å   angstrom(s)

p-ABSA   *para*-acetamidobenzenesulfonyl azide

Ac   acetyl

AIBN   azobisisobutyronitrile

APCI   atmospheric pressure chemical ionization

app   apparent

aq   aqueous

Ar   aryl group

At   benztriazolyl

atm   atmosphere(s)

BHT   2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")

BINAP   (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)

Bn   benzyl

Boc   *tert*-butoxycarbonyl

bp   boiling point

br   broad

Bu   butyl

i-Bu   *iso*-butyl

n-Bu   butyl or *norm*-butyl

t-Bu   *tert*-butyl

Bz	benzoyl
C	cytosine
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
^{14}C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane

dba	dibenzylideneacetone
DBDMH	*N,N'*-dibromo-5,5-dimethylhydantoin
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutyl aluminum hydride
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)

E$^+$	electrophile
E	trans (entgegen) olefin geometry
EC$_{50}$	median effective concentration (50%)
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
HATU	2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
hv	light

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
iNOS	human-inducible nitric oxide synthase
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
KHMDS	potassium bis(trimethylsilyl)amide
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LICA	lithium isopropylcyclohexylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion

m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular seives
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu$^-$	nucleophile

o	ortho
[O]	oxidation
t-Oct	*tert*-octyl (1,1,3,3-tetramethylbutyl)
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
Piv	pivalate
pK_a	acid dissociation constant
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
RCM	ring-closing metathesis

REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
s	selectivity factor $= k_{\text{rel(fast/slow)}} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where $C =$ conversion
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase
Su	succinimide
t	triplet
T	thymine
TBAF	tetra-n-butylammonium fluoride
TBAT	tetra-n-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Tr	triphenylmethane (trityl)
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

CHAPTER 1

The Acyl-Amidation of Arynes

1.1 Introduction

Arynes have long been of interest to both physical organic and synthetic chemists. The structure of benzyne was first elucidated by J. D. Roberts in 1953 and since that time a number of methods to generate these reactive intermediates have been realized (Scheme 1.1).[1] Many of these procedures require high temperature or strong base such as *n*-butyllithium or sodium amide.[2] In 1983, Kobayashi and co-workers reported the in situ generation of arynes from corresponding *o*-silyl aryl triflates.[3] This has proven to be one of the mildest and most synthetically useful ways of generating arynes. Desilylation upon treatment of the *o*-silyl aryl triflate with fluoride ion induces an elimination of the triflate to furnish the highly strained triple bond characteristic of arynes. This method can be performed under ambient conditions and with a wide variety of fluoride sources. While these intermediates cannot be isolated and are difficult to observe

spectroscopically, they can be harnessed in a variety of reaction pathways to afford interesting and important architectures, often forming multiple carbon–carbon or carbon–heteroatom bonds in a single operation (Scheme 1.2).[4]

Scheme 1.1. *In situ generation of benzyne.*
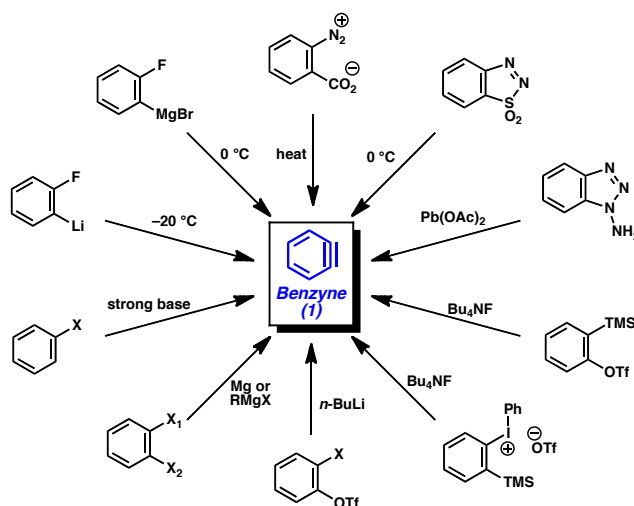
Scheme 1.2. *Representative reactions of benzyne (**1**).*
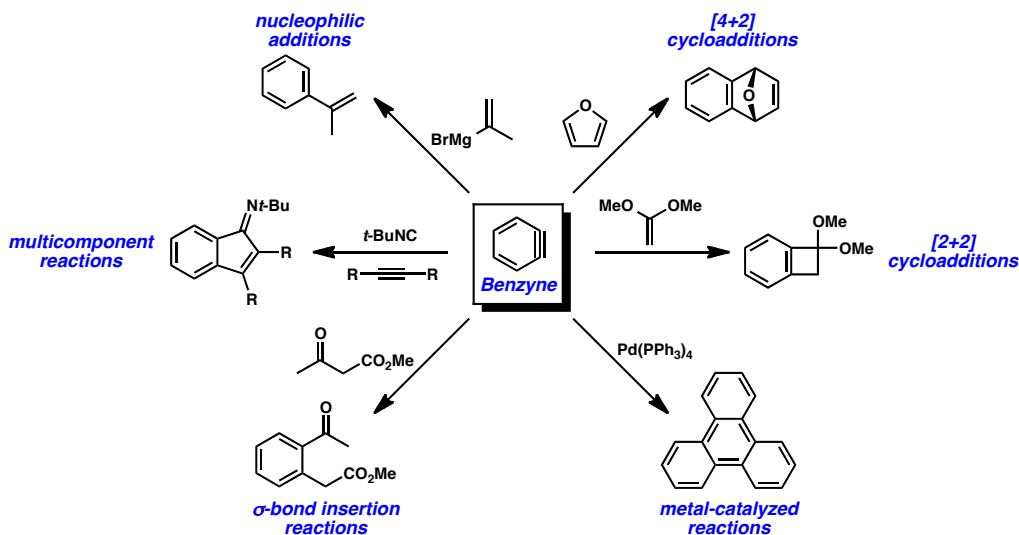
The Stoltz group has been interested in the synthetic utility of arynes for a number of years. In 2005, Tambar and Stoltz reported on the first acyl alkylation of arynes using β-ketoesters (Scheme 1.3).[5] Aryne insertion into the alpha, beta carbon–carbon bond of

β-ketoesters is thought to proceed through a formal [2+2] cycloaddition followed by fragmentation to afford acyl-alkylated products **5–10** in good yield. Since the Stoltz group's initial studies, aryne insertion into carbon–carbon bonds bearing electron withdrawing groups has been extended to a variety of substrate classes, including 1,3-diketones,[6] α-ketonitriles,[7] β-ketophosphonates,[8] and trifluoromethyl ketones,[9] among others (Scheme 1.3).[10] More recently, the Garg lab developed a procedure for embedding heteroarenes into cyclic ureas in order to probe the inherent regioselectivity of such reactions.[11]

Scheme 1.3. *The direct acyl alkylation of arynes.*

5	**6**	**7**	**8**	**9**	**10**
90% yield	84% yield	99% yield	85% yield	50% yield	65% yield
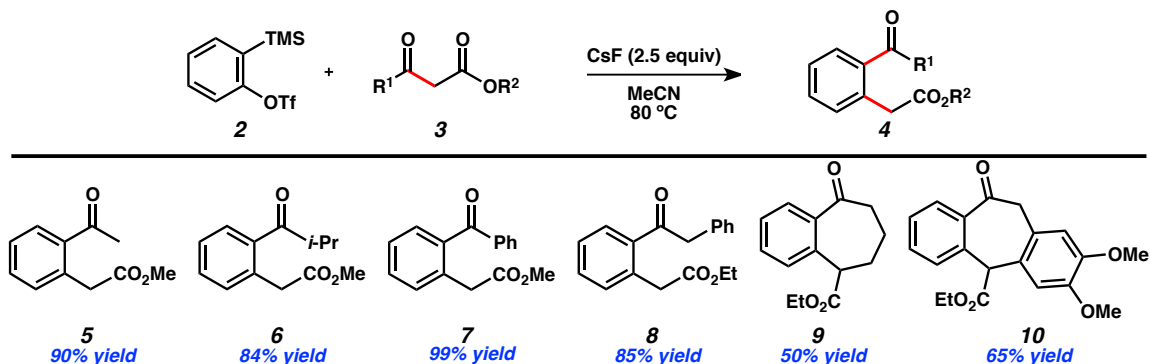
Scheme 1.4. *Insertion of arynes into C–C σ bonds.*
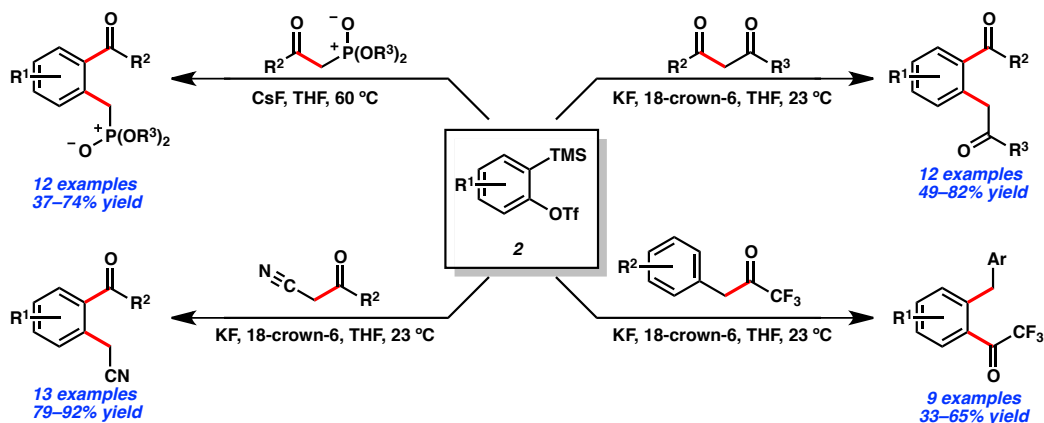
Previous work by the Greaney group demonstrated that the insertion of amides into arynes could afford similar acyl-aminated products (Scheme 1.5).[12] However, the scope of their method was focused on *N*-aryl benzamides substrates (**12**), which significantly limited further derivatization of the insertion products (**13**). These *N*-aryl *ortho*-acyl anilines (**13**) could be reacted further to prepare tricyclic polyaromatic systems, namely acridines (**14**) and acridones (**15**). We sought to address this limitation by developing a method of the insertion of arynes into the C–N bonds of imides (**16**) (Scheme 1.6). These *N*-acyl anilines (**17**) would be far more amenable to derivation therefore provide access to an array of important chemical motifs, such as indoles, quinolones and *ortho*-acyl anilines.

Scheme 1.5. *Greaney's Acyl-Amination and Derivatives.*
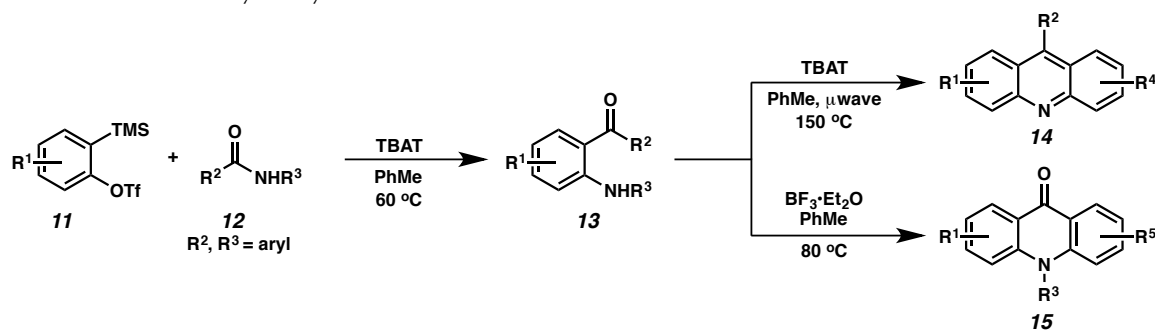
Scheme 1.6. *Acyl-Amidation of Arynes.*
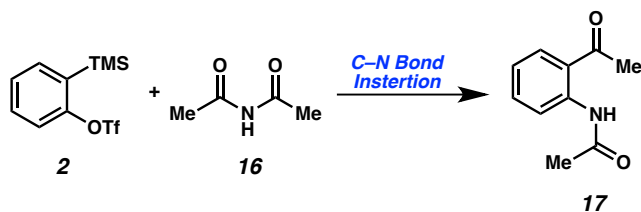
1.2 Acyl-Amidation of Arynes

We initiated our synthetic studies by optimizing conditions for the insertion reaction. Using acetylacetamide (**16**) as a model imide substrate and *ortho*-silylaryl triflate **2** as the aryne precursor, we observed the best yields for the insertion reaction in toluene at 60 °C and TBAT as a fluoride source (Table 1.1).

With optimized parameters in hand, we next set out to explore the substrate scope. Our method showed tolerance to imide substrates possessing both aliphatic and aromatic substituents, with yields ranging from modest to very good. Substrates bearing carbamate functionalities were also compatible, albeit with reduced yields (entries 7 and 8).

Table 1.1. *Scope of the Imide.*

Entry	R	R_1	X	Yield (%)
1	Me	Me	NH	89
2	Et	Et	NH	88
3	1-Ad	1-Ad	NH	84
4	Ph	Ph	NH	68
5	*i*-Pr	*i*-Pr	NH	78
6	*i*-Bu	*i*-Bu	NH	79
7	OMe	Bn	NH	24
8	OBn	Me	NH	31
9	CH_2CH_2Ph	CH_2CH_2Ph	NH	74
10	Me	Me	O	54

Having explored the substrate scope of this reaction with respect to the imide, we next investigated its tolerance with respect to the aryne precursor used (Table 1.2).

Although substituted phenyl ring systems provided fair to good yields, precursors bearing

nitrogen (i.e. indolyne and pyridyne) fared poorly.

Table 1.2. *Substituted Aryne Precursors.*

Entry	Aryne	Product	Yield (%)
1	**21**	**22**	31
2	**23**	**24**	44
3	**25**	**26**	65
4	**27**	**28**	47
5	**29**	**30**	47

Following previous research conducted by the Buchwald group,[13] we found that acylamide insertion products could be elaborated to substituted quinolone products by a base-initiated Camps cyclization in a two-step, one-pot sequence (see Table 1.3).

Additionally, these aryl ketoamides have previously been converted to indoles via McMurry couplings. *N*-deacylation of these ketoamides affords ketoanilines. Similarly, ketoester insertion products can be elaborated to chromones *via* base-initiated cyclization followed by condensation (Scheme 1.7). or to 1,3 diketones through Baker–Venkataraman rearrangements.[14] Our lab is making on-going efforts to explore the scope of this reaction and its potential in developing other valuable synthetic transformations.

Table 1.3. *Camps Cyclization of Ketoamide Insertion Products.*
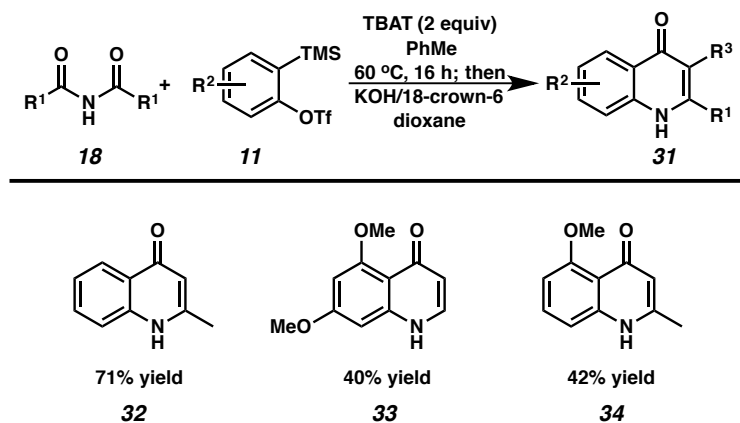
Scheme 1.7. *Derivatization of ortho-acyl anilides.*
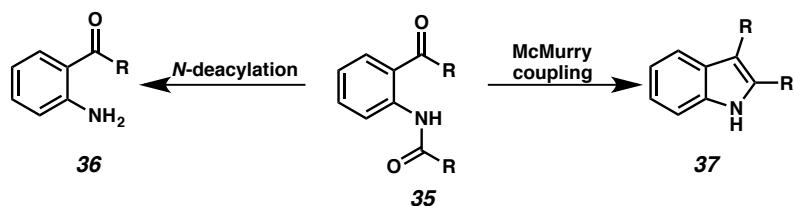
1.3 Conclusion

To summarize, we have discovered a method for inserting arenes into C–N and C–O σ bonds of imides and anhydrides, respectively to generate 1,2-ketoamide and ketoester products. These compounds are capable of further derivatization to provide a broad array of synthetically useful compounds. Our lab is making ongoing efforts to explore the scope of this reaction and its potential in developing other valuable synthetic transformations.

1.4 Experimental Procedures

1.4.1 Materials and Methods.

Unless otherwise stated, reactions were performed in flame-dried glassware under nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Reaction temperatures were controlled by an IKAmag temperature modulator. Thin layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. 1H and 13C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 125 MHz, respectively) and are reported relative to Me4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

1.4.2 Representative Procedure for Acyl-amidation

A 2-dram vial equipped with a magnetic stir bar was charged with TBAT and acetylacetamide. The vial was purged with nitrogen, and PhMe was added via syringe followed by silylaryltriflate. The vial was sealed and placed in an aluminum block preheated to 60 ^{o}C. The reaction mixture was stirred at this temperature for 16 h, then it was allowed to cool to 23 ^{o}C. The mixture was concentrated in vacuo and purified by column chromatography (10% EtOAc in hexanes) to afford a white solid. Characterization data match those previously reported.

1.4.3 Spectroscopic Data

The spectroscopic data for compounds **18-1**,[15] **18-4**,[15] **19-1**,[16] **19-2**,[17] **19-10**, **30**,[18] **32**,[19]

33[18] were identical to those previously reported.
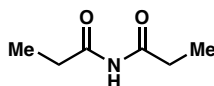
N-propionylpropionamide (18-2)

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73 (s, 1H), 2.62 (q, $J = 7.4$ Hz, 3H), 1.18 (t, $J = 7.4$ Hz,

4H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 175.17, 30.87, 8.52; IR (NaCl/Film) 3266.83,

3175.24,2978.35, 1736.17, 1503.45, 1421.79, 1181.11, 1072.97, 729.68 cm^{-1}; HRMS
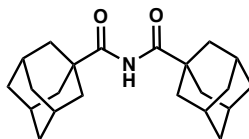
Di-1-adamantanecarboxamide (18-3)

^{1}H NMR (500 MHz, CDCl$_3$) δ 2.04 (dd, $J = 7.4, 2.6$ Hz, 6H), 1.93 (d, $J = 2.9$ Hz, 12H),

1.73 (m, 12H); IR (NaCl/Film) 2906.06, 2851.48, 1693.63, 1453.93, 1325.17, 1284.81,

1250.94, 1102.93, 952.74, 743.88.
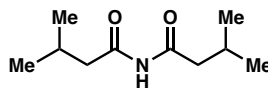
3-methyl-N-(3-methylbutanoyl)butanamide (18-6)

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.72 (br s, 1H), 2.47 (d, $J = $, 4H), 2.14 (heptet, $J = $, 2H);

^{13}C (125 MHz, CDCl$_3$) δ 173.9, 46.3, 25.2, 22.4; IR (NaCl/Film); HRMS (MM: ESI-

APCI) m/z calc'd for C$_{10}$H$_{19}$NO$_2$ [M+H]$^+$ = 186.1494, found 186.1500.
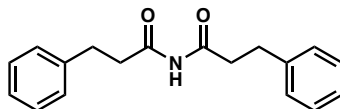
3-phenyl-N-(3-phenylpropanoyl)propanamide (18-9)

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.10 (s, 1H), 7.25 (m, 10H), 2.95 (m, 8H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.09, 140.33, 128.71, 128.54, 126.52, 39.20, 30.39; IR (NaCl/Film) 3147.72, 1675.04, 1494.86, 1453.56, 1380.88, 1311.33, 1199.44, 1146.83, 981.74, 725.51, 697.04 cm^{-1}; (MM: ESI-APCI) *m/z* calc'd for C$_{18}$H$_{19}$NO$_2$ [M+H]$^+$ = 282.1489, found 282.1489.
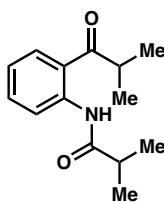
N-(2-isobutyrylphenyl)isobutyramide (19-5)**

^{1}H NMR (300 MHz, CDCl3) δ 11.80 (br s, 1H), 8.79 (d, *J* = 6 Hz, 1H), 7.93 (d, *J* = 6 Hz, 1H), 7.53 (t, *J* = 4.5 Hz, 1H), 7.10 (t, *J* = 6 Hz, 1H), 3.65 (sept, *J* = 6 Hz, 1H), 2.62 (sept, *J* = 6 Hz, 1H), 1.28 (d, *J* = 6 Hz, 6H), 1.22; ^{13}C (75 MHz, CDCl3) δ 209.2, 176.6, 141.7, 134.8, 130.6, 122.2, 121.1, 120.7, 37.6, 36.3, 19.6 (2 unresolved signals); IR (Neat Film, NaCl); HRMS (MM: ESI-APCI) *m/z* calc'd for C$_{14}$H$_{19}$NO$_2$ [M+H]$^+$ = 234.1489 , found 234.1490.
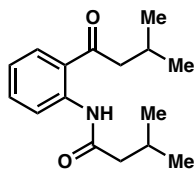
3-methyl-*N*-(2-(3-methylbutanoyl)phenyl)butanamide (19-6)

^{1}H NMR (300 MHz) δ 11.73 (br s, 1H), 8.77 (d, *J* = , 1H), 7.90 (d, *J* = , 1H), 7.53 (t, *J* = , 1H), 7.10 (t, *J* = , 1H), 2.88 (d, *J* = , 2H), 2.33–2.19 (m, 4H), 1.03–0.99 (m, 12H); ^{13}C (126 MHz) 205.0, 172.1, 141.0, 134.9, 130.4, 122.2, 121.92, 120.9, 49.0, 48.1, 26.3, 25.6, 22.7, 22.5. IR (Neat Film, NaCl); HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{23}NO_2$ [M+H]$^+$ = 262.1802 , found 262.1804.
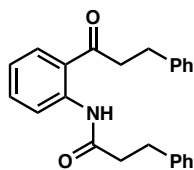
3-phenyl-*N*-(2-(3-phenylpropanoyl)phenyl)propanamide (19-9)

Observed as rotomers, major rotomer reported. ^{1}H NMR (500 MHz, CDCl$_3$) δ 11.71 (s, 1H), 8.76 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.89 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.55 (m, 1H), 7.40 (m, 1H), 7.26 (m, 10H), 3.35 (m, 2H), 3.09 (m, 2H), 3.03 (dd, *J* = 8.4, 7.1 Hz, 2H); IR (NaCl/Film) 3026.46, 2925.93, 1696.65, 1651.11, 1604.35, 1583.56, 1519.16, 1450.30, 1360.55, 1297.79, 1194.79, 1194.90, 976.10, 751.87, 698.56 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{23}NO_2$ [M+H]$^+$ = 358.1802, found 358.1812.
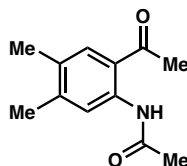
N-(2-acetyl-4,5-dimethylphenyl)acetamide (22)

^{1}H NMR (300 MHz, CDCl$_3$) δ 11.63 (br s, 1H), 8.53 (s, 1H), 7.61 (s, 1H), 2.63 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) δ 202.4 (C), 169.4 (C), 145.3, 139.1 (C), 132.4 (CH), 130.6 (C), 121.5 (CH), 119.8 (C), 28.6 (CH$_3$), 25.6 (CH$_3$), 20.6 (CH$_3$), 19.4 (CH$_3$); IR (Neat Film/NaCl); HRMS (MM: ESI-APCI) *m/z* calc'd for C$_{12}$H$_{15}$NO$_2$ [M+H]$^+$ = 206.1176, found 206.1171.
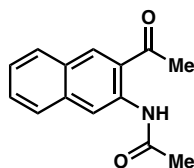
N-(3-acetylnaphthalen-2-yl)acetamide (24)

^{1}H NMR (300 MHz, CDCl$_3$) δ 11.5 (br s, 1H), 9.12, (s, 1H), 8.44 (s, 1H), 7.83 (d, *J* = 9.0 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 2.80 (s, 3H), 2.27 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) 203.0 (C), 169.3 (C), 136.7 (C), 136.1 (C), 134.3 (CH), 129.7 (CH), 128.9 (CH), 128.2 (C), 127.7 (CH), 125.6 (CH), 122.7 (C), 117.7 (CH), 28.7 (CH$_3$), 25.6 (CH$_3$). IR (Neat Film, NaCl); HRMS (MM: ESI-APCI) *m/z* calc'd for C$_{14}$H$_{13}$NO$_2$ [M+H]$^+$ = 228.1019, found 228.1022.
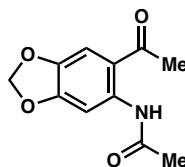
N-(6-acetylbenzo[d][1,3]dioxol-5-yl)acetamide (26)

^{1}H NMR (300 MHz, CDCl$_3$) δ 12.08 (br s, 1H), 8.37 (s, 1H), 7.25 (s, 1H), 6.02 (s, 2H), 2.57 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 200.6 (C), 169.5 (C), 152.9 (C), 142.4 (C), 139.3 (C), 115.1 (C), 109.6 (CH), 102.1 (CH), 101.5 (CH$_2$), 28.8 (CH$_3$), 25.6 (CH$_3$). IR (Neat Film, NaCl); HRMS (MM: ESI-APCI) *m/z* calc'd for C$_{11}$H$_{11}$NO$_4$ [M+H]$^+$ = 222.0761, found 222.0766.
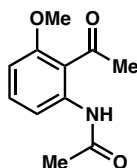
N-(2-acetyl-3-methoxyphenyl)acetamide (30)

^{1}H NMR (500 MHz, CDCl$_3$) δ 10.49 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.40 (td, *J* = 8.4, 0.5 Hz, 1H), 6.69 (dd, *J* = 8.4, 0.9 Hz, 1H), 3.90 (s, 3H), 2.61 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 204.58, 169.20, 160.00, 139.40, 133.90, 114.14, 106.31, 55.83, 33.73, 25.48; IR (NaCl/Film) 3086.81, 2947.73, 1698.62, 1639.62, 1634.03, 1528.84, 1470.57, 1470.57, 1403.54, 1273.11, 1243.38, 1195.89, 1093.22, 1017.32, 967.43, 802.27, 735.19, 610.77 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for C$_{11}$H$_{13}$NO$_3$ [M+H]$^+$ = 262.1802 , found 262.1804.

1.5 References

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Appendix 1

Spectra Relevant to Chapter 1

^{1}H NMR (500 MHz, CDCl$_3$) of compound **18-2**.
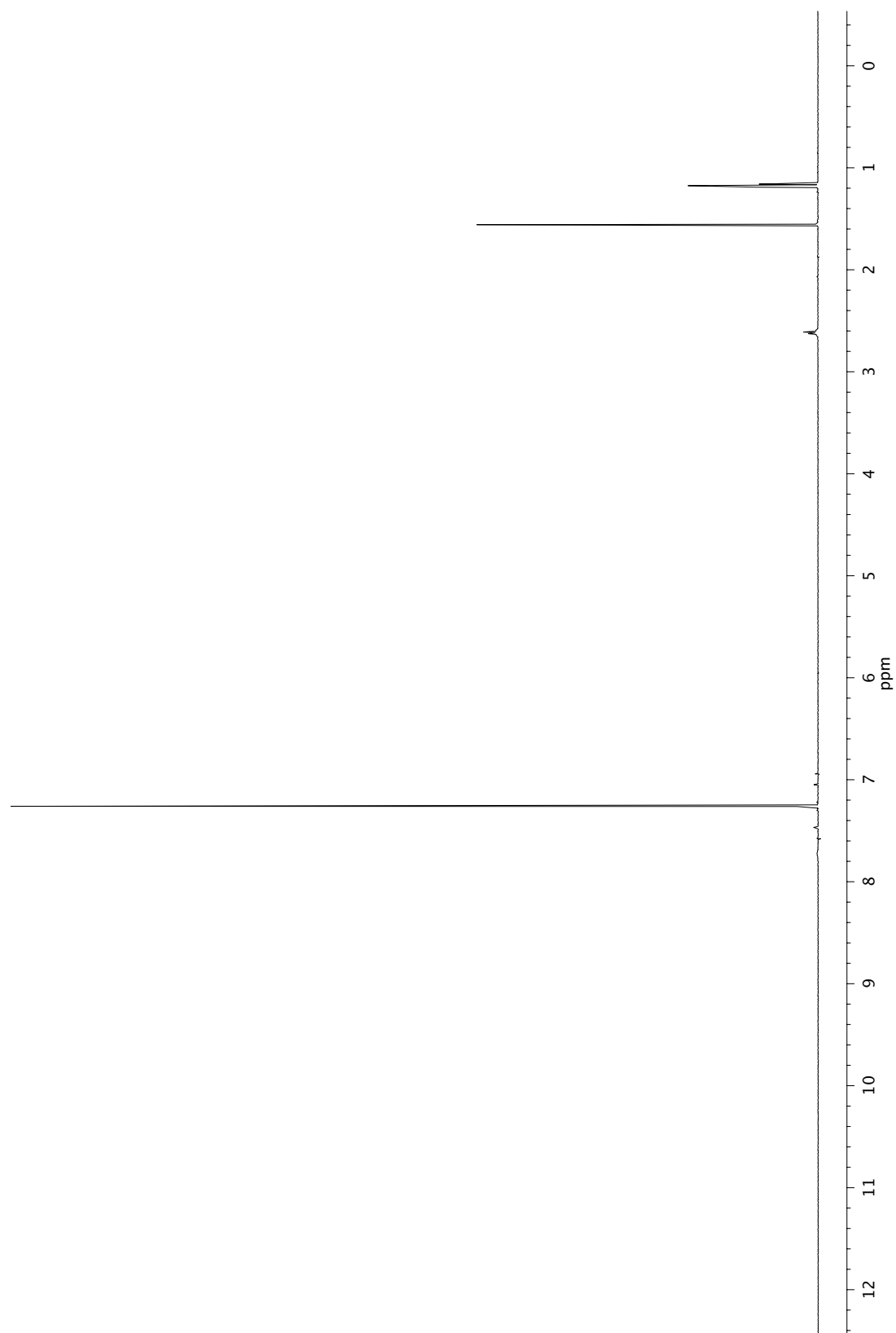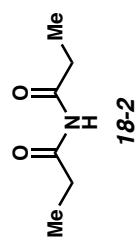
Infrared spectrum (Thin Film, NaCl) of compound **18-2**.
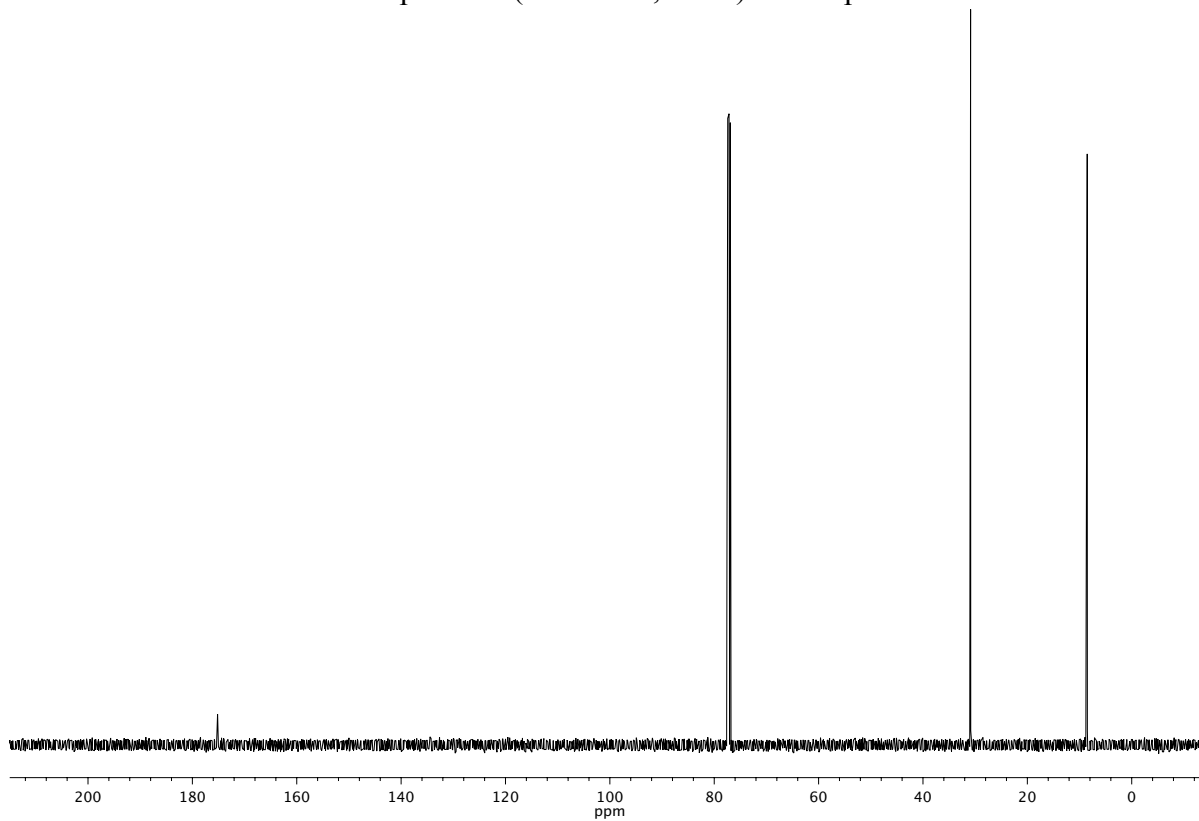
^{13}C NMR (126 MHz, CDCl$_3$) of compound **18-2**.
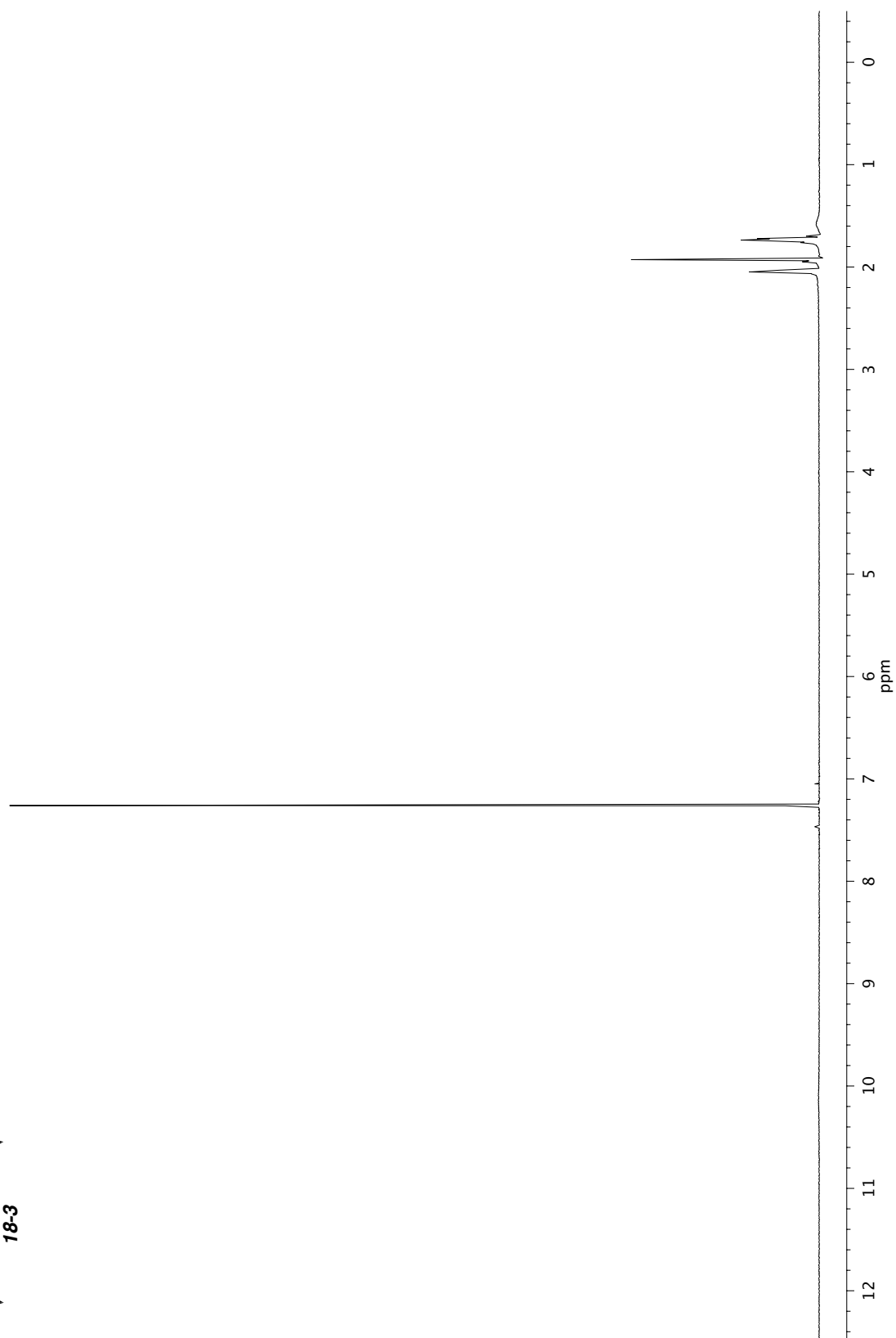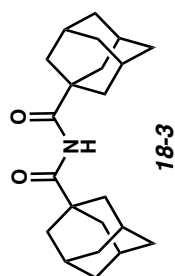
^{1}H NMR (500 MHz, CDCl$_3$) of compound **18-3**.

18-3

Infrared spectrum (Thin Film, NaCl) of compound **18-3**.

^{13}C NMR (126 MHz, CDCl$_3$) of compound **18-3.**

^{1}H NMR (300 MHz, CDCl$_3$) of compound **18-6**.
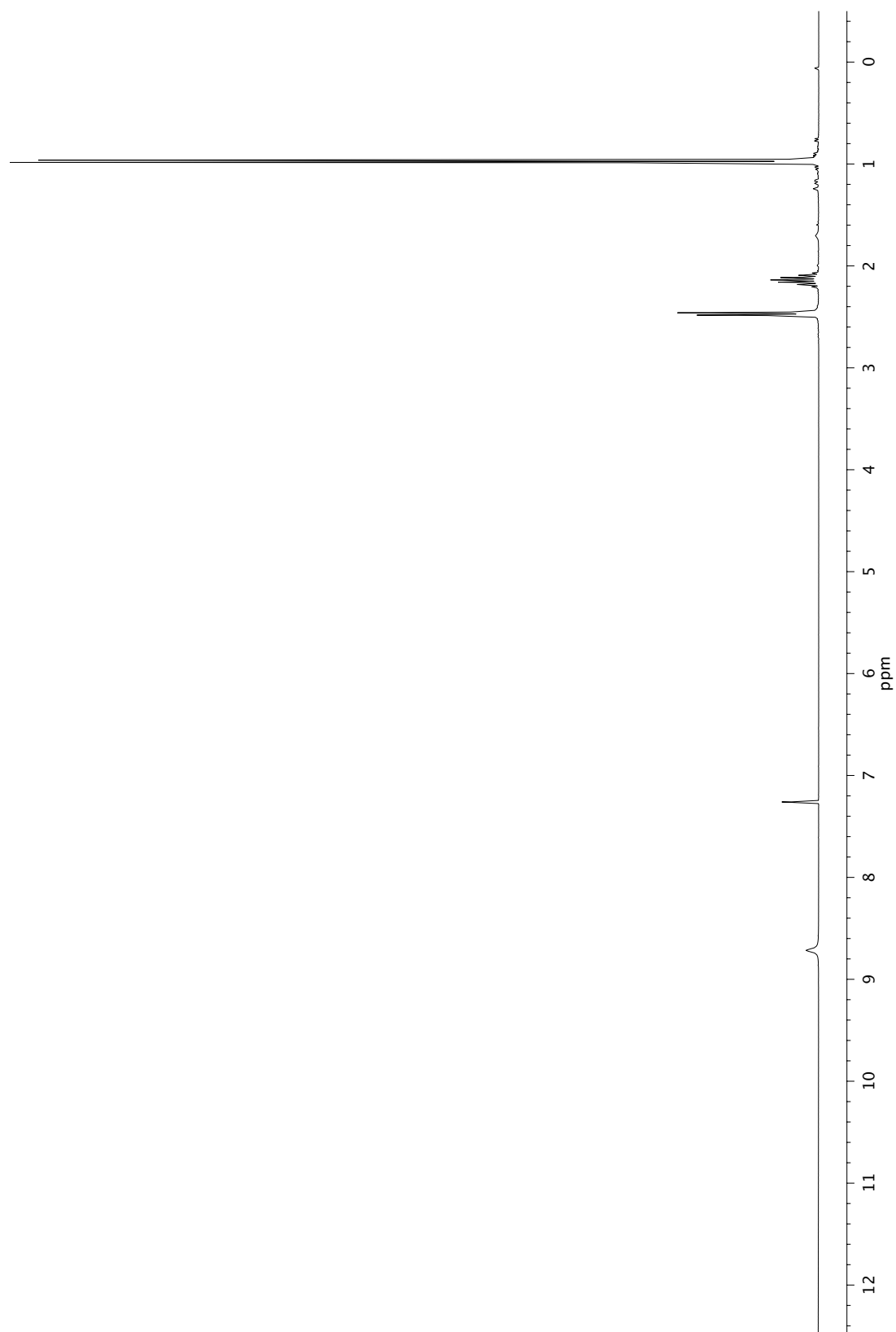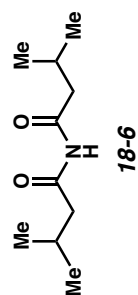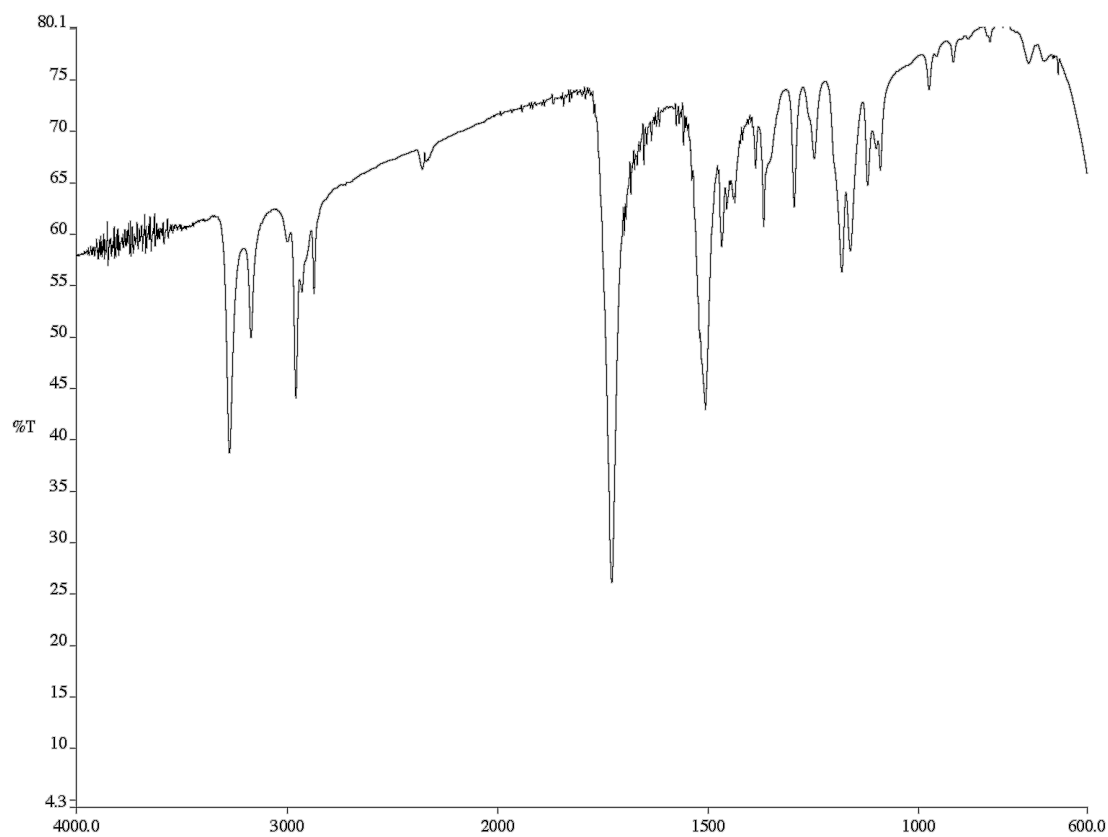
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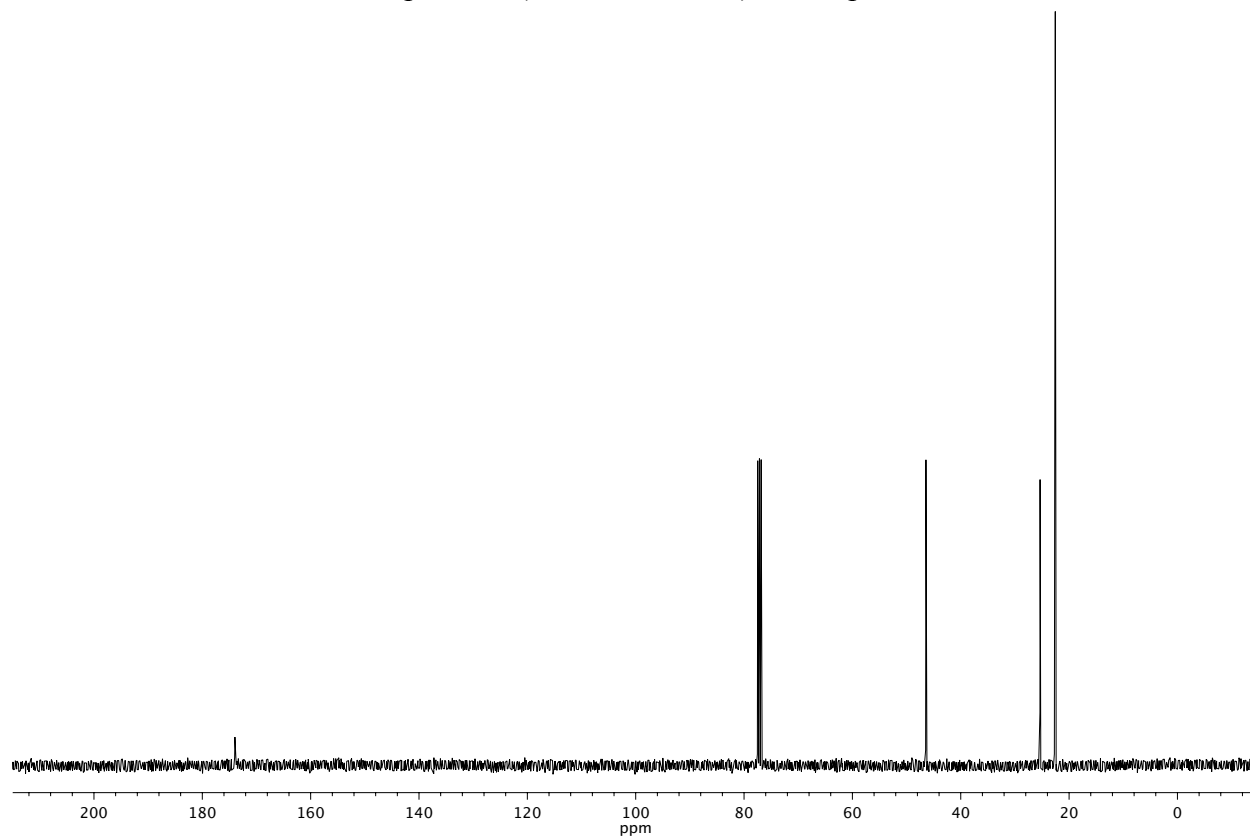
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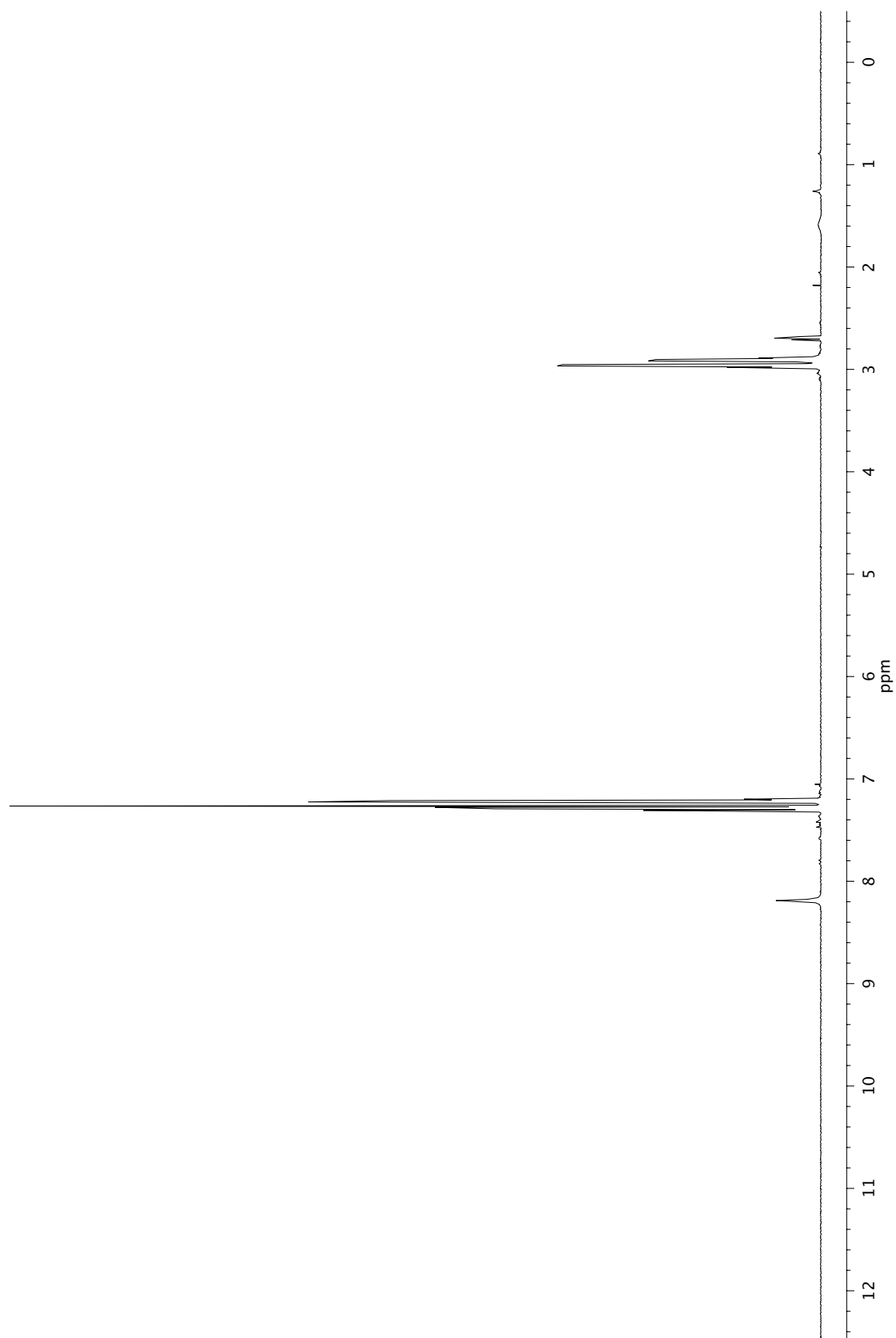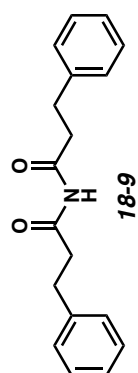
^{1}H NMR (500 MHz, CDCl$_3$) of compound **18-6**.

Infrared spectrum (Thin Film, NaCl) of compound **18-9**.
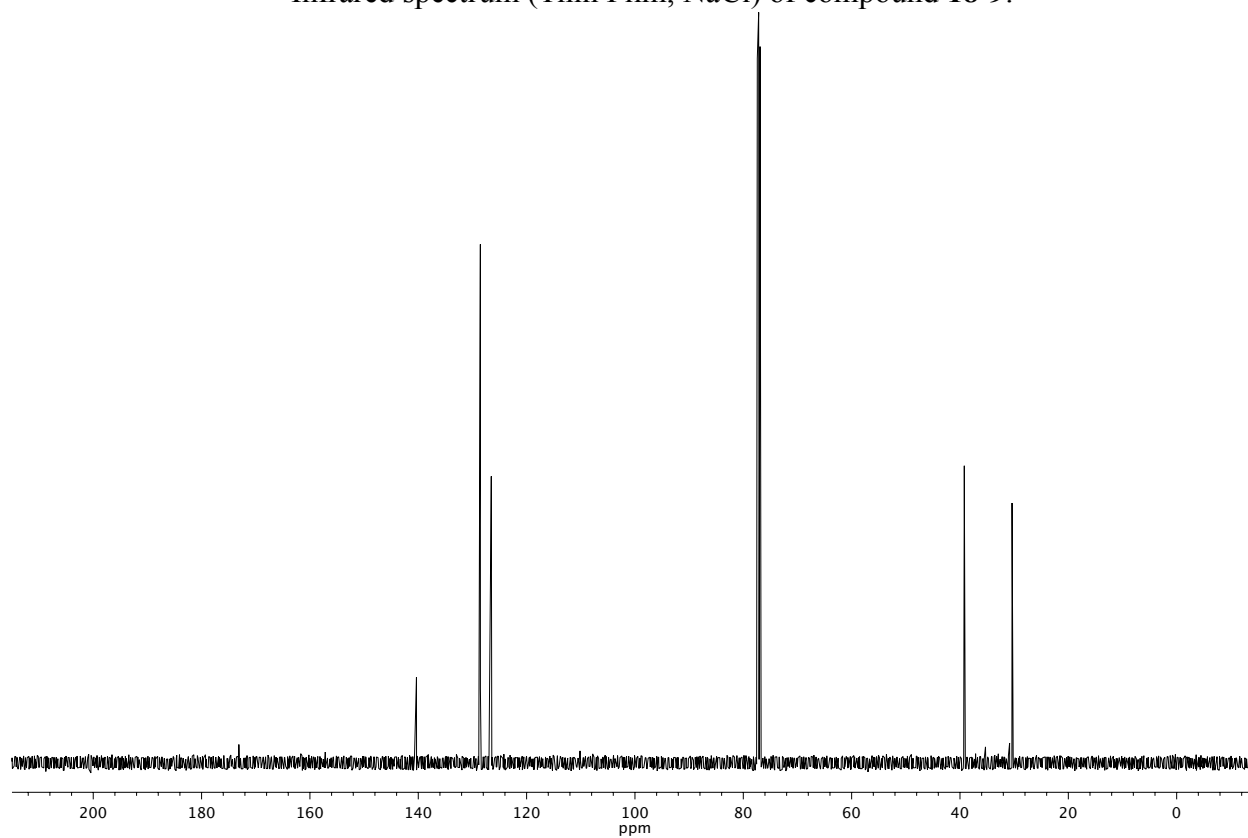
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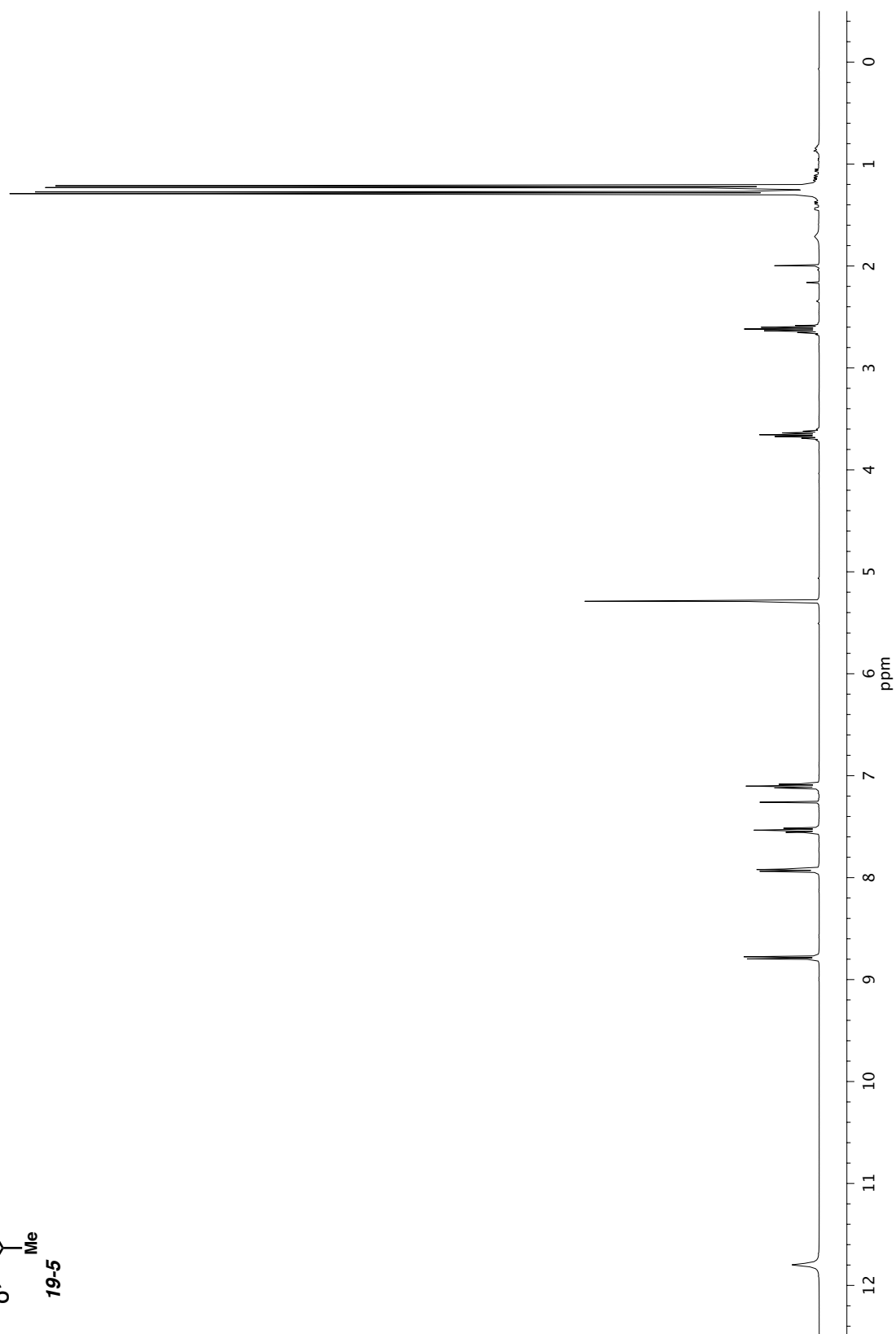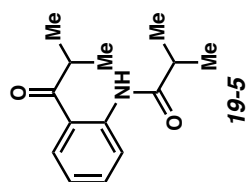
^{1}H NMR (300 MHz, CDCl$_3$) of compound **19-5**.

Infrared spectrum (Thin Film, NaCl) of compound **19-6**.
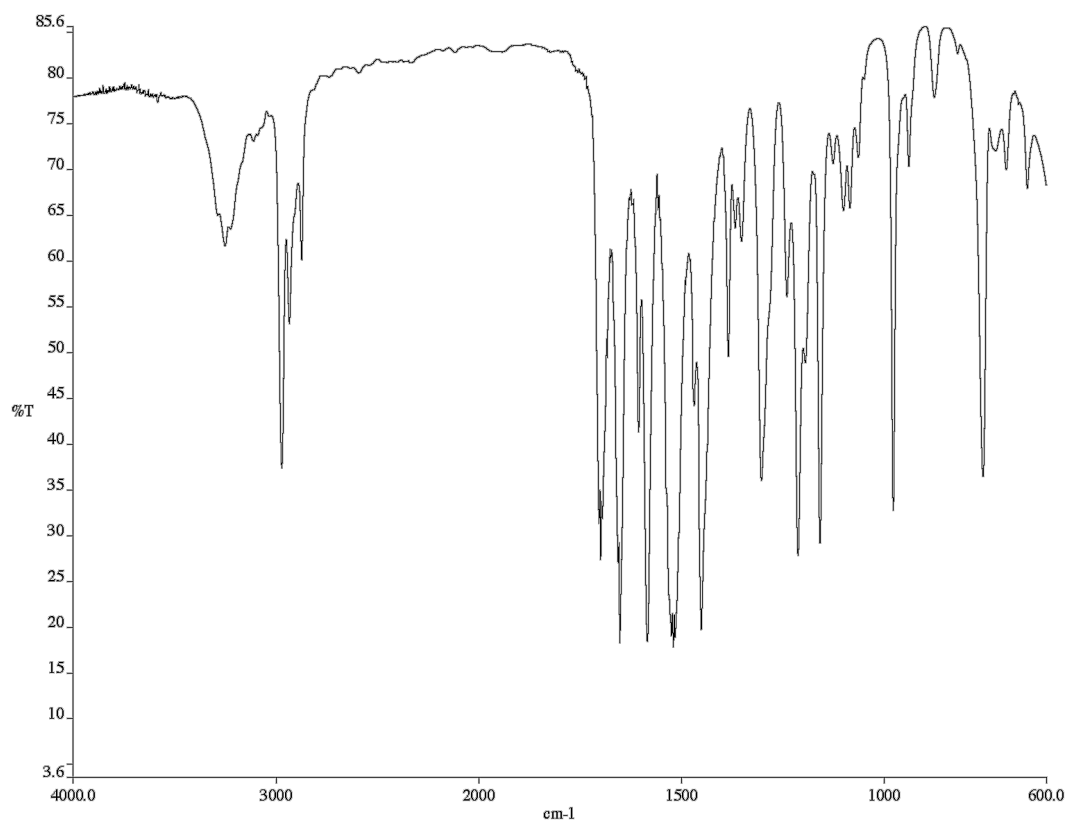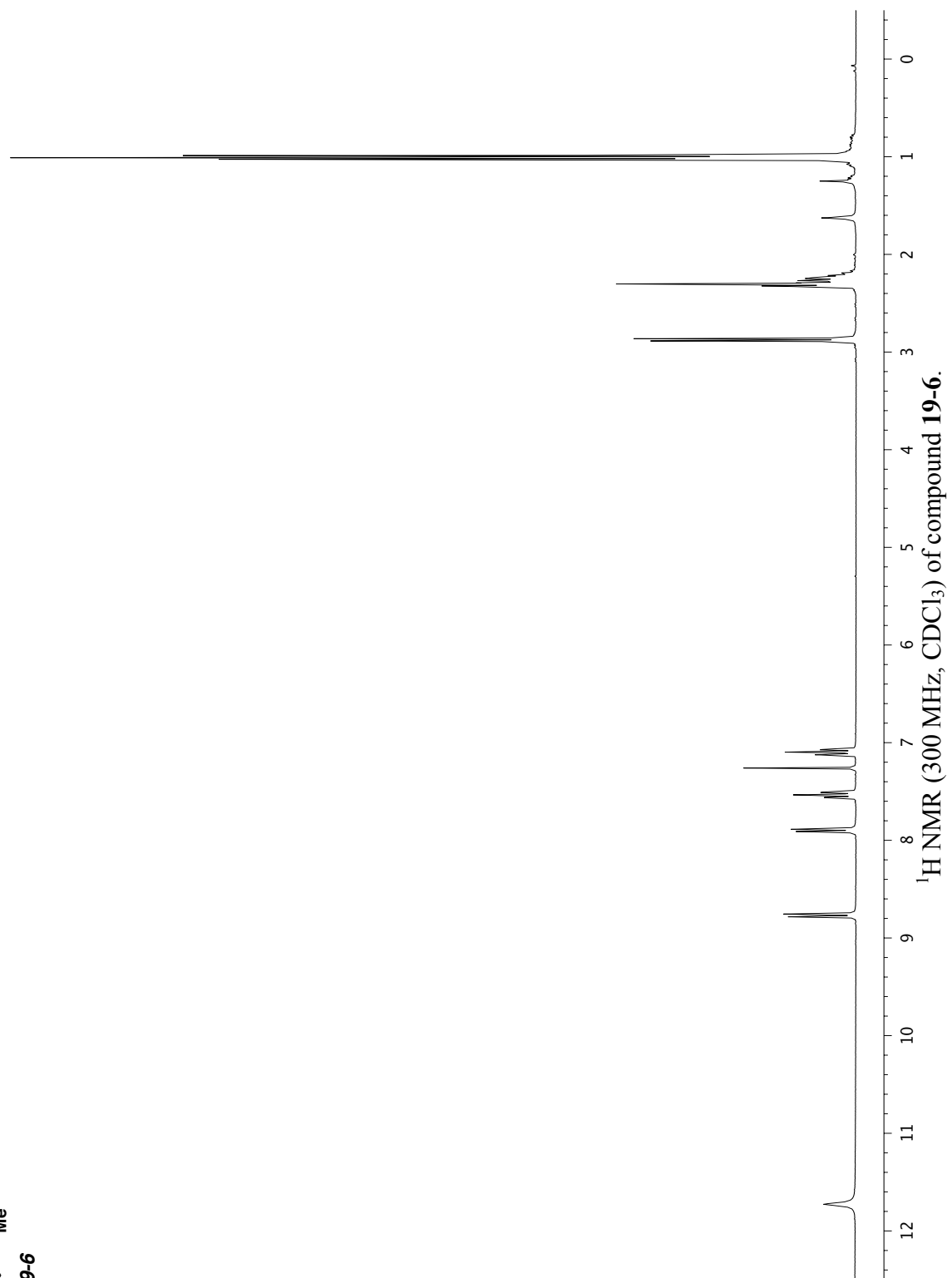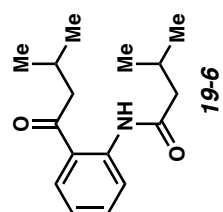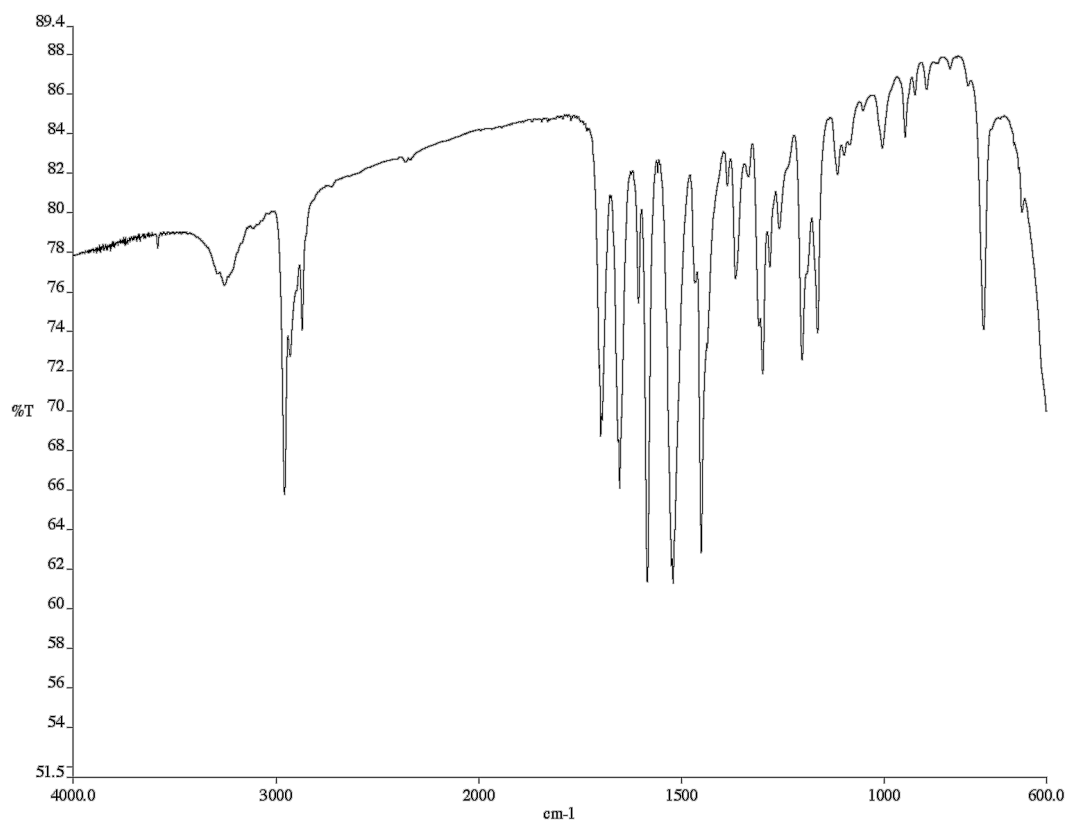
^{13}C NMR (126 MHz, CDCl$_3$) of compound **19-6**.

^{1}H NMR (300 MHz, CDCl$_3$) of compound **19-6**.

Infrared spectrum (Thin Film, NaCl) of compound **19-6**.
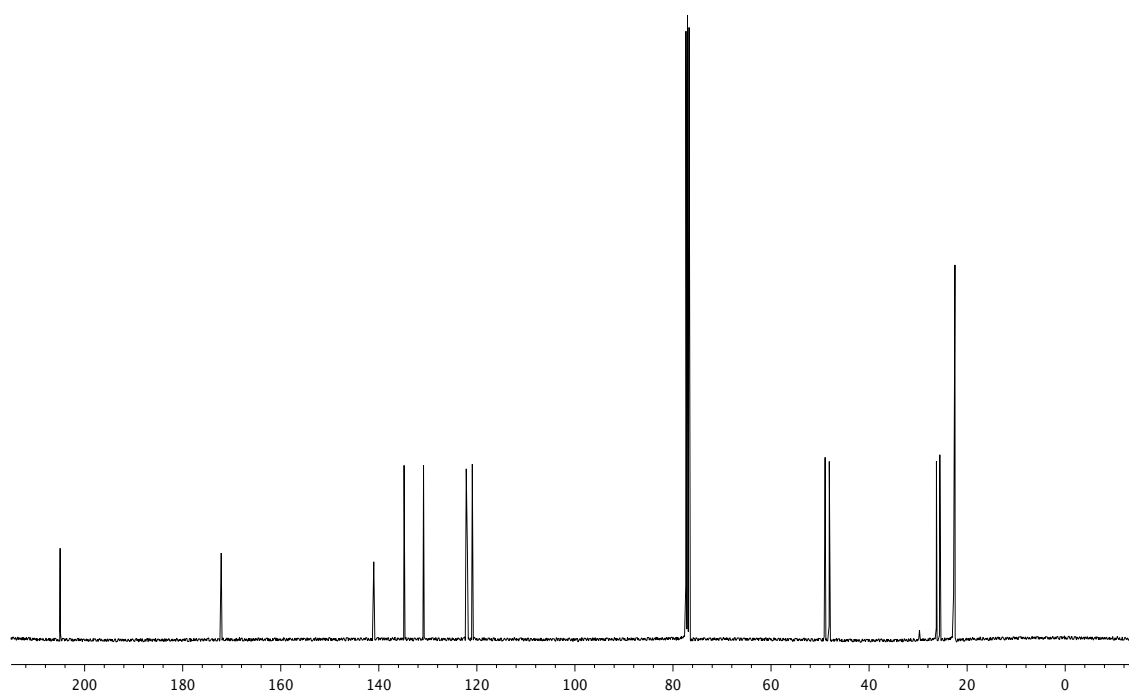
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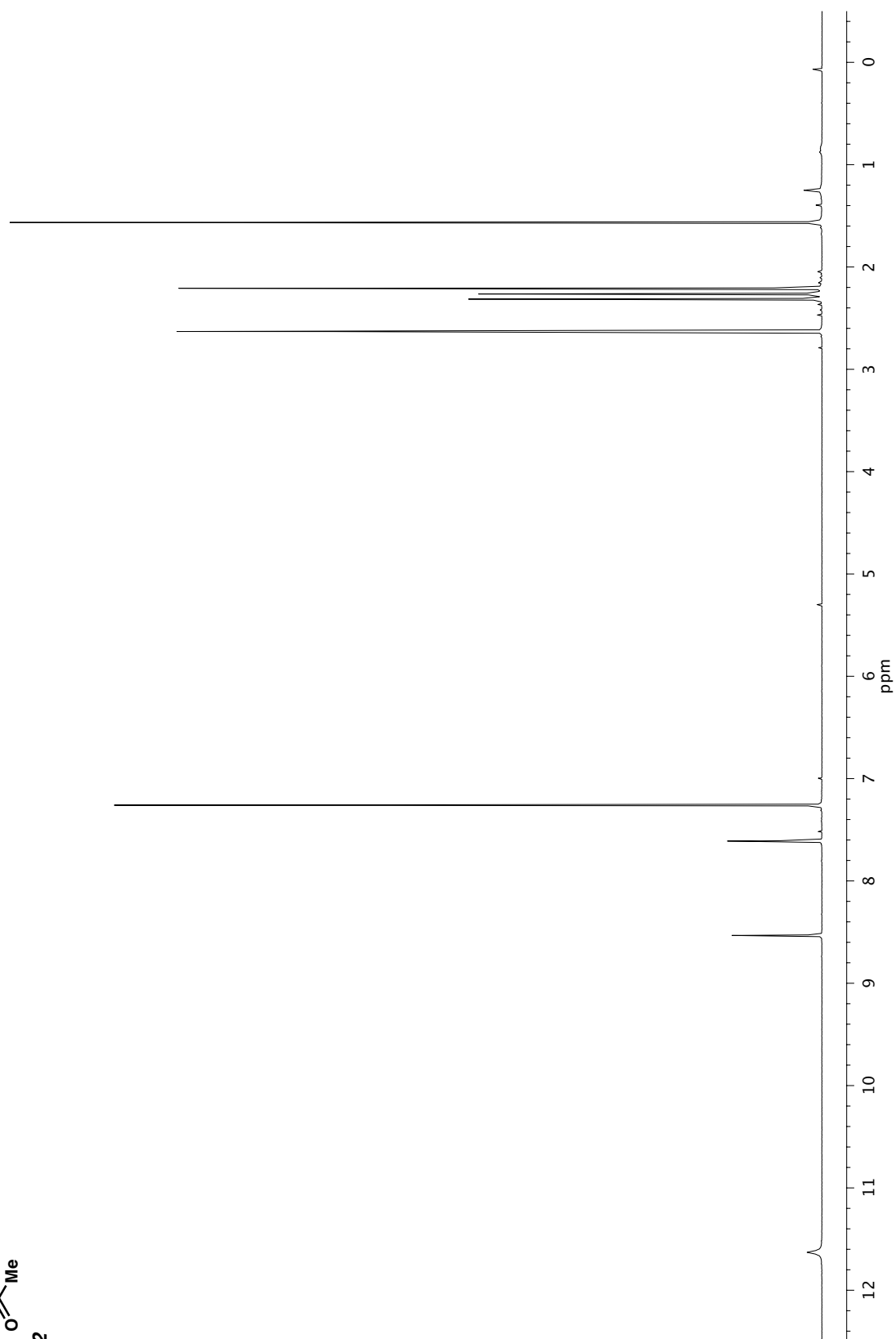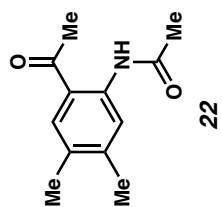
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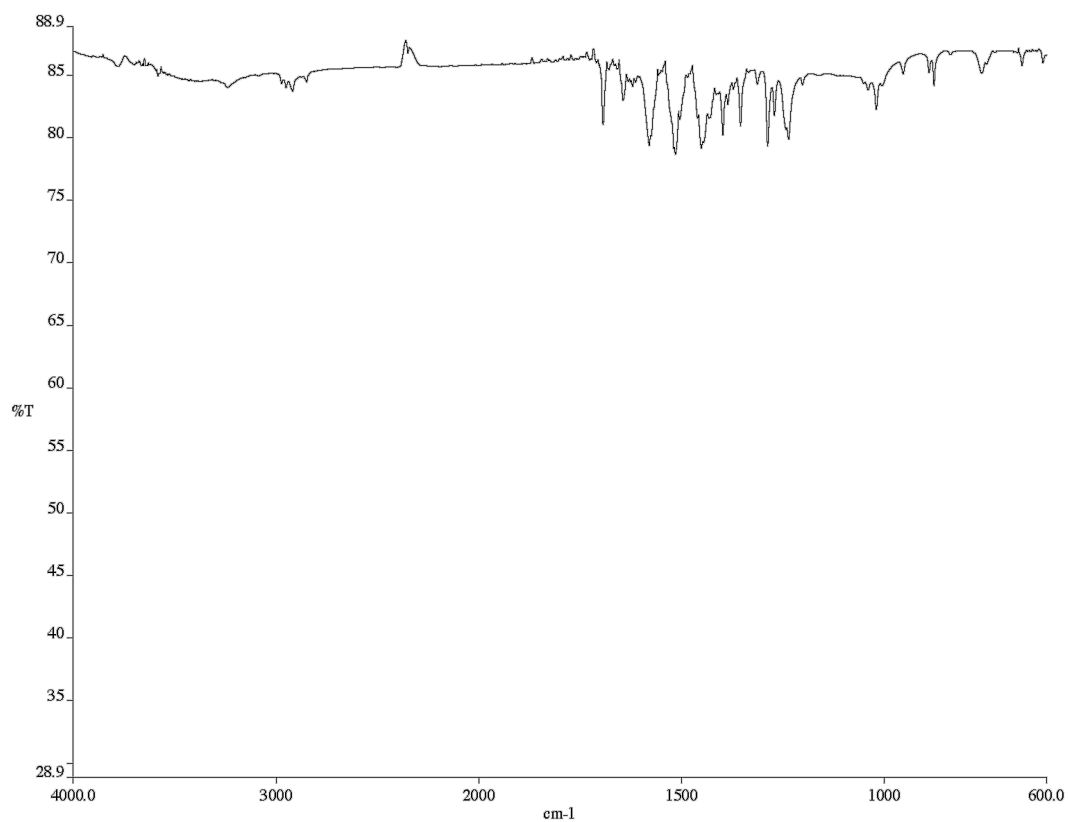
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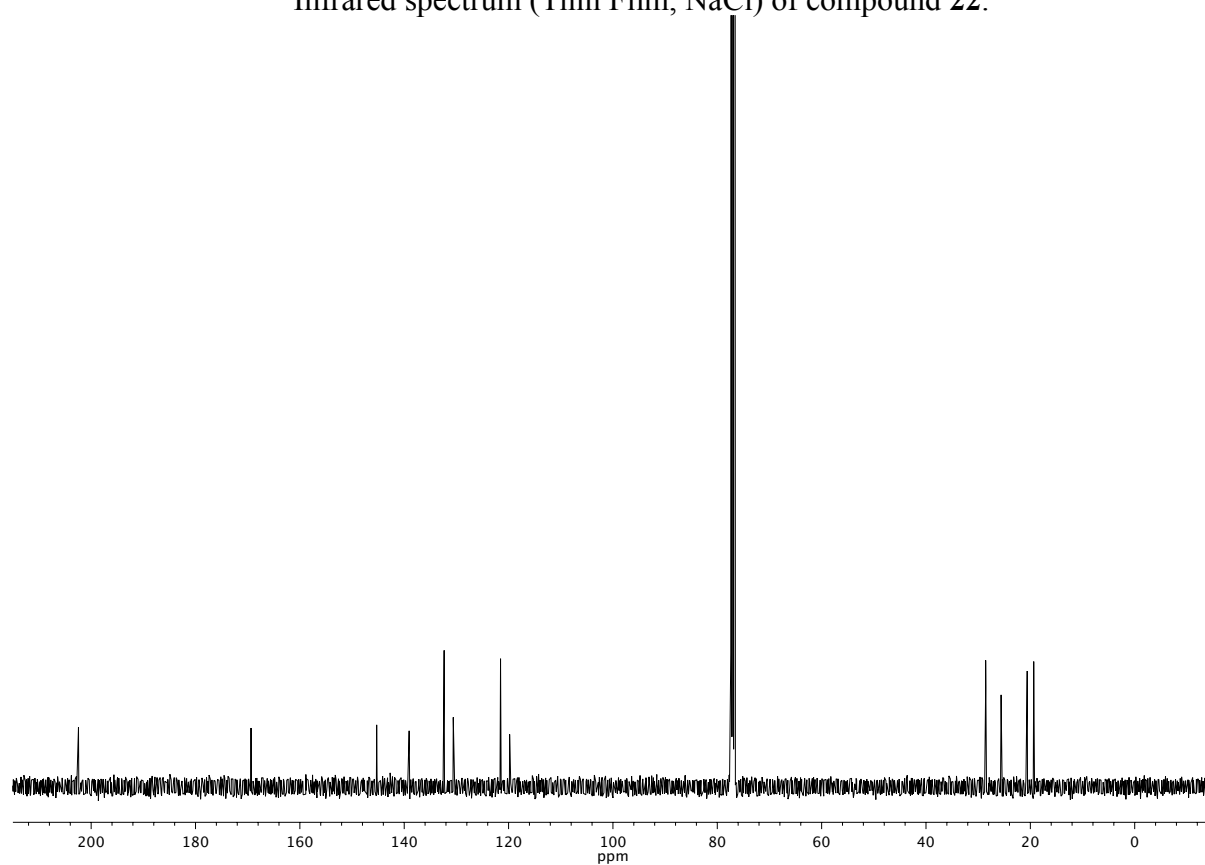
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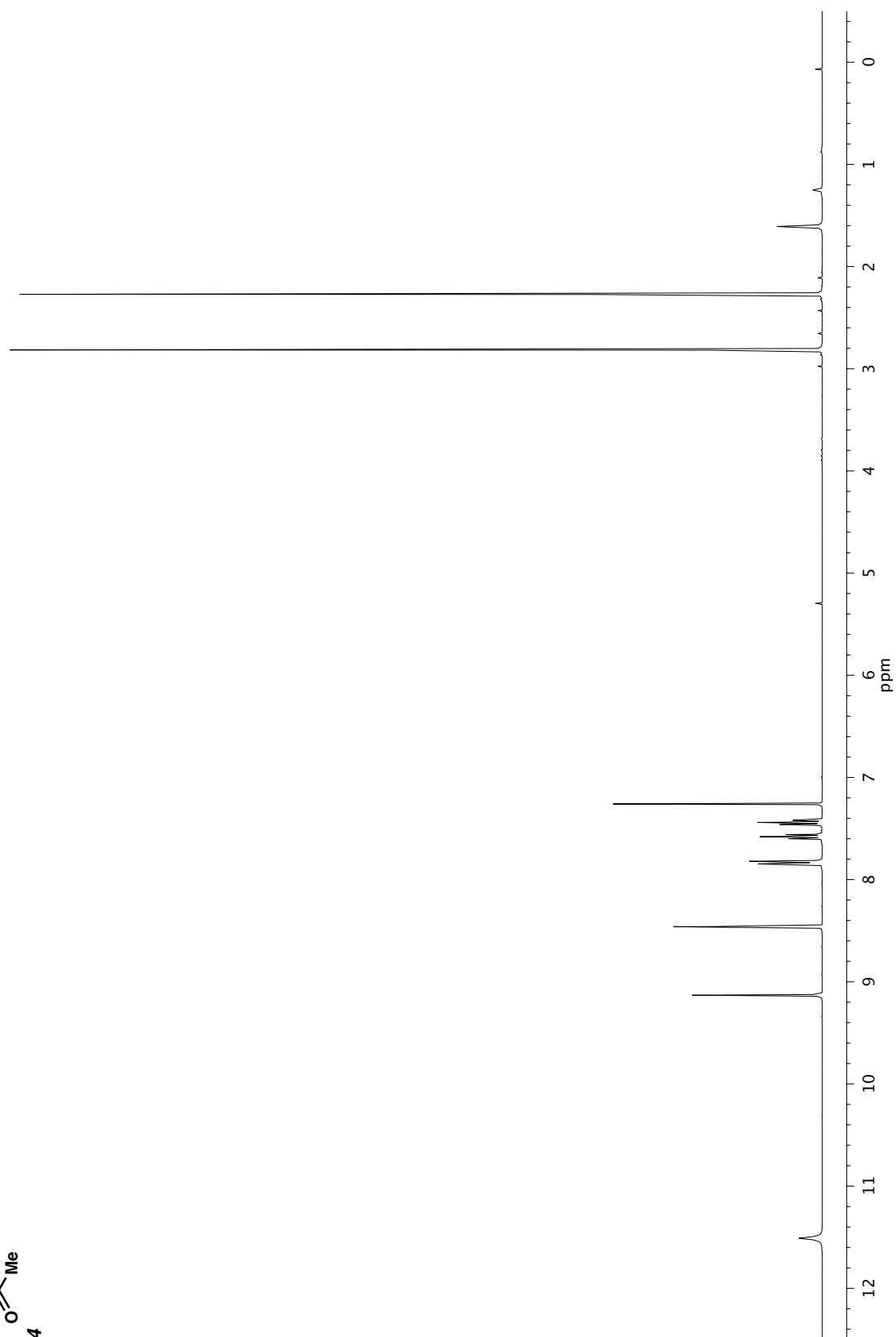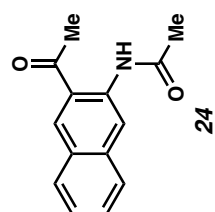
^{1}H NMR (300 MHz, CDCl$_3$) of compound **24**.
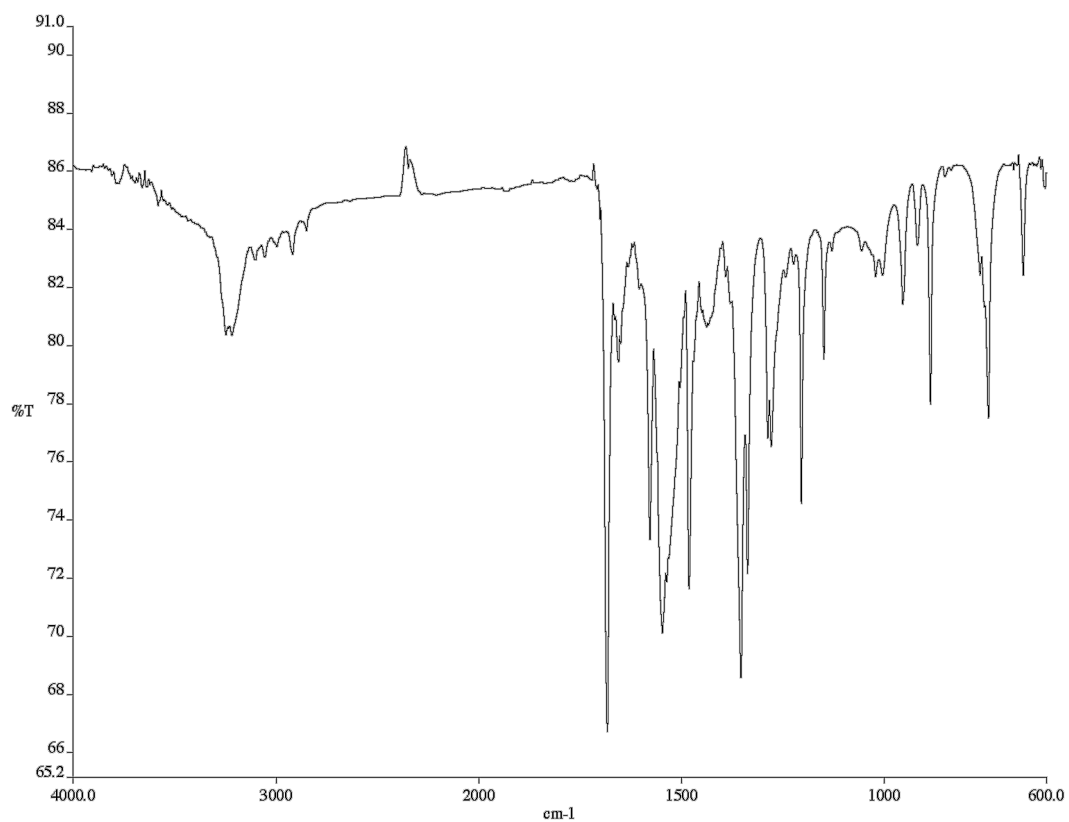
Infrared spectrum (Thin Film, NaCl) of compound **24**.

^{13}C NMR (126 MHz, CDCl$_3$) of compound **24**.

^{1}H NMR (300 MHz, CDCl$_3$) of compound **26**.
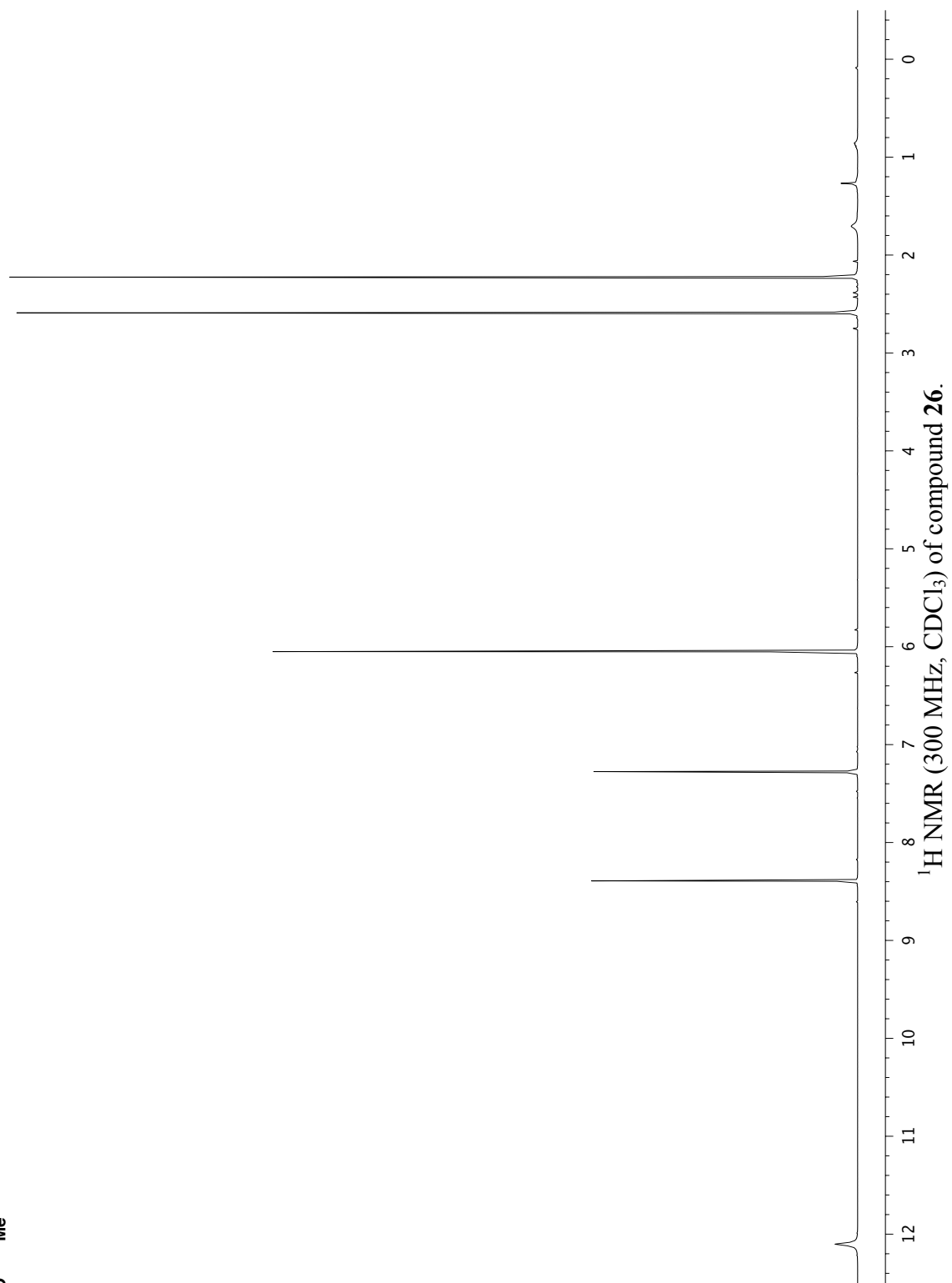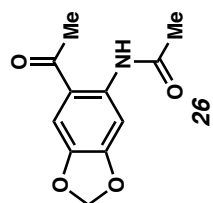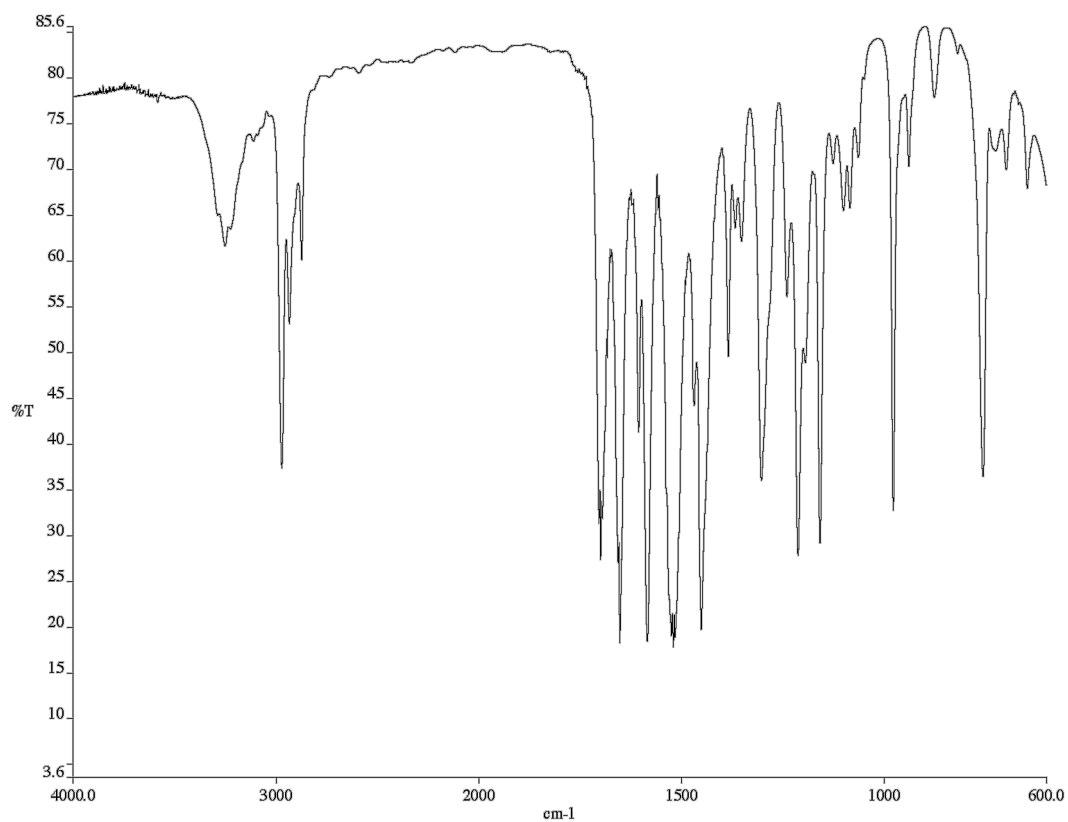
Infrared spectrum (Thin Film, NaCl) of compound **26**.
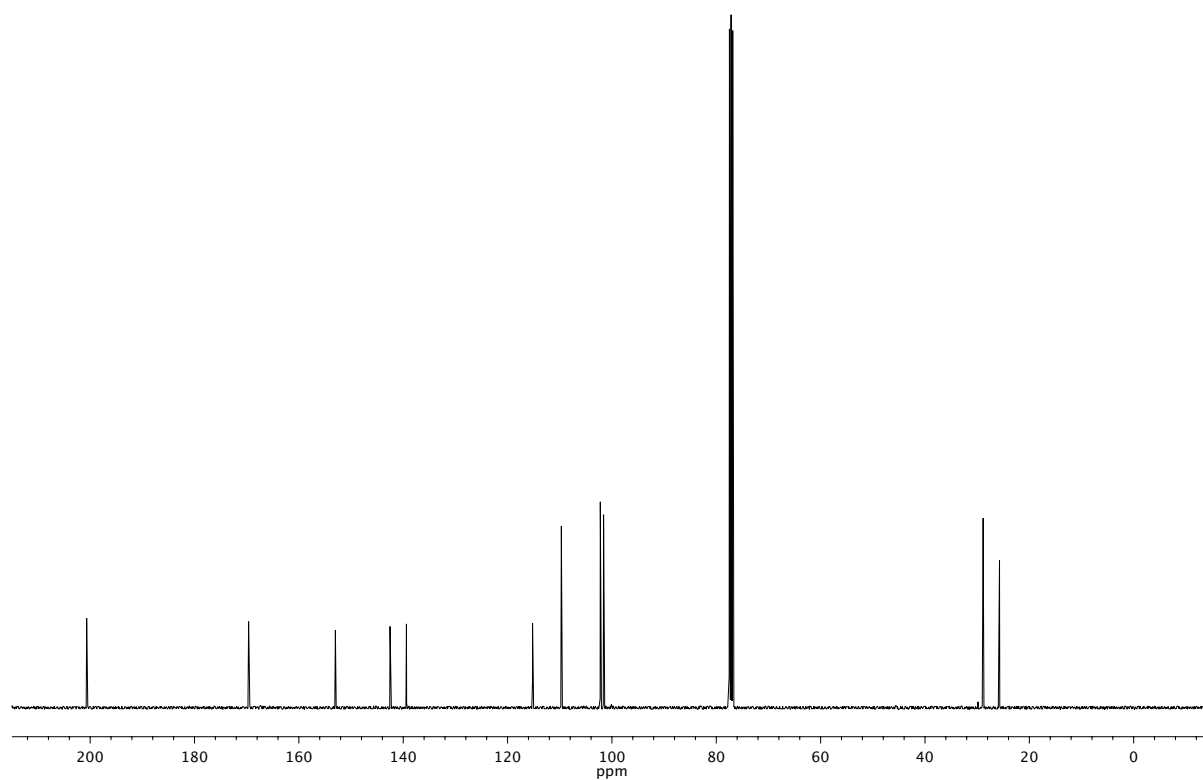
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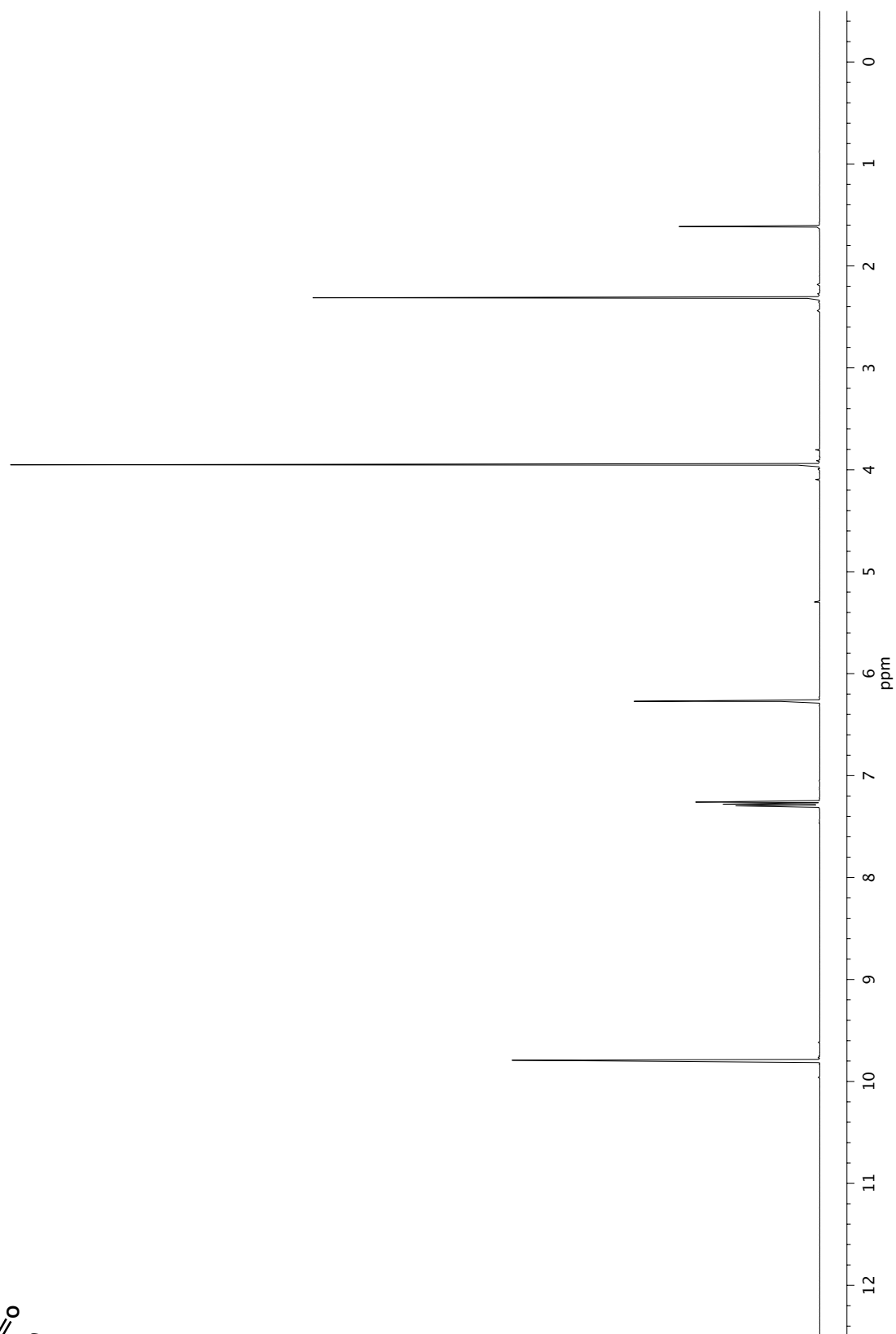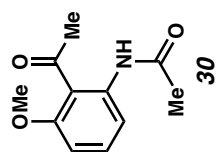
^{1}H NMR (500 MHz, CDCl$_3$) of compound **3g**.

Infrared spectrum (Thin Film, NaCl) of compound **3g**.
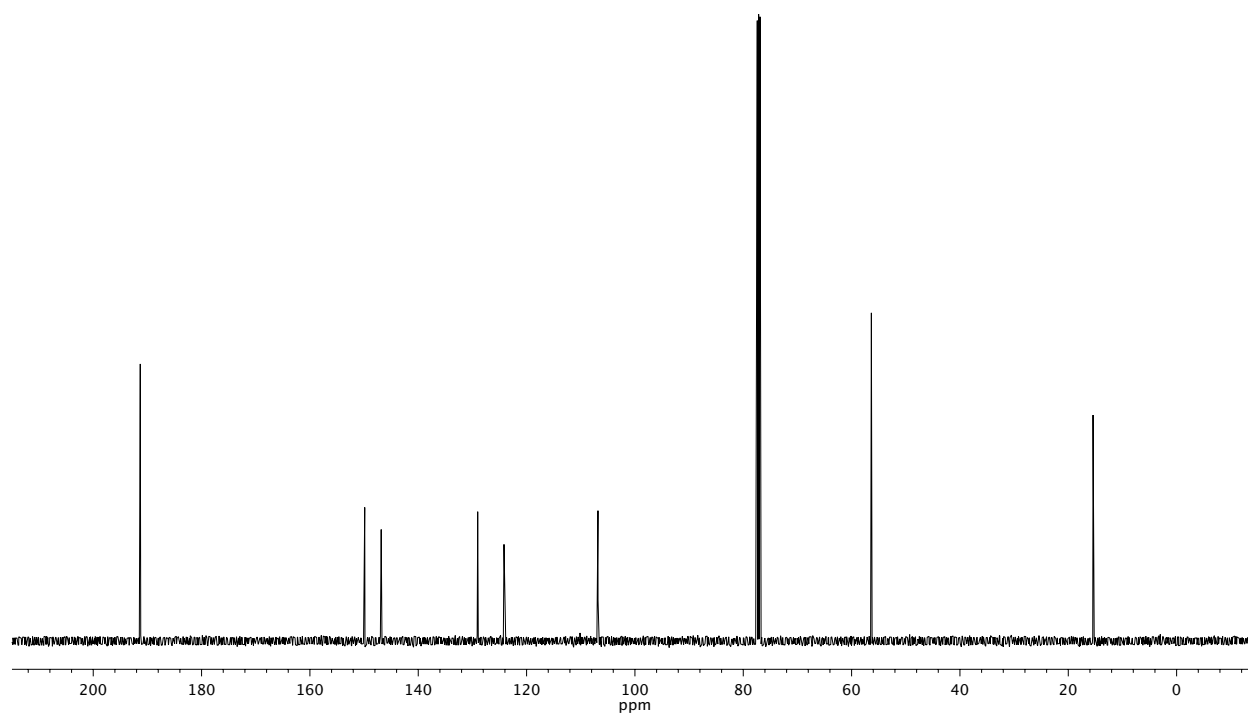
^{13}C NMR (126 MHz, CDCl$_3$) of compound **3g**.

CHAPTER 2

Progress Toward the Total Synthesis of Jorumycin

2.1 Introduction

Over the past decades, the tetrahydroisoquinoline (THIQ) alkaloids have piqued the attention of medicinal, biological, and chemical communities due to their novel biochemical modes of action, the potent biological properties they exhibit, and the complex molecular architectures characteristic of these molecules (Figure 1).[1] With more than 60 naturally occurring representatives, this family of compounds boasts a remarkable degree of structural diversity that translates into a wide array of antineoplastic/antiproliferative properties. For example, jorumycin (**50**) inhibits the growth of A549 human lung carcinoma and HT29 human colon carcinoma cell lines at extremely low concentrations ($IC_{50} = 0.24$ nM).[2] Saframycins A (**51**) and S (**52**) display nanomolar cytotoxicity toward L1210 leukemia cell lines ($IC_{50} = 5.6$, 5.3 nM, respectively). The therapeutic potential of these molecules is perhaps best conveyed by those members that have advanced through human clinical trials. Ecteinascidin 743

(Trabectedin, Yondelis, **53**) is approved in Europe, Russia, and South Korea for the treatment of soft tissue sarcomas and has been granted priority review by the FDA within the U.S. as a treatment for patients with advanced soft tissue sarcoma (STS), including liposarcoma and leiomyosarcoma subtypes, and phase III trials were recently completed.[3, 4a] In addition to their various antineoplastic properties, the THIQ alkaloids also possess broad-spectrum antibiotic activity against the Gram-positive and Gram-negative bacterial strains responsible for infectious diseases such as meningitis, pneumonia, strep throat, and diphtheria.[5]

Figure 2.1. *Tetrahydroisoquinoline natural products.*

Jorumycin (50)

R = CN, Saframycin A (51)
R = OH Saframycin S (52)

Ecteinascidin 743
(Trabectedin, Yondelis®, 53)

Quinocarcin (54)
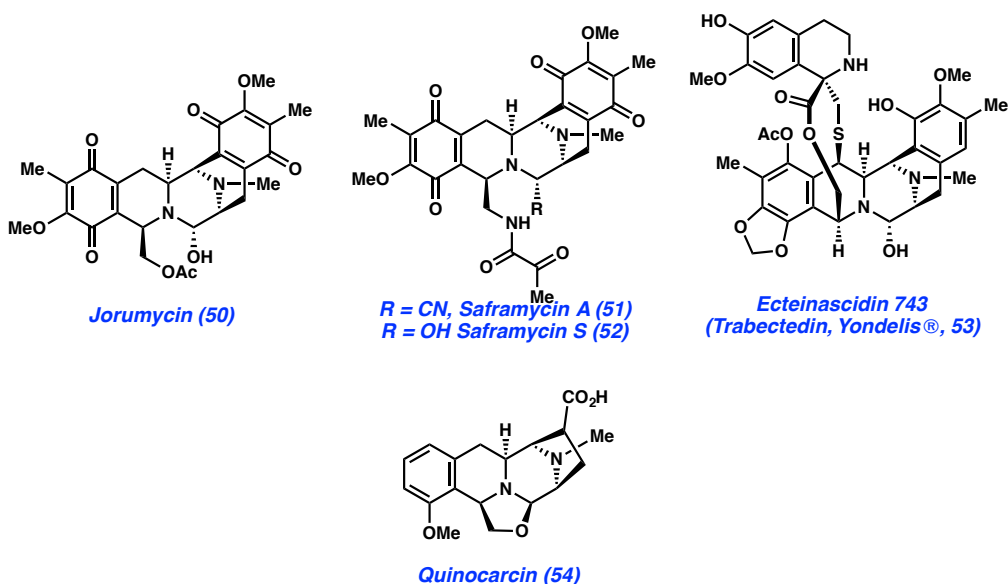
While the numerous biological properties of the THIQ alkaloids make them ideal targets for pharmaceutical development, the isolation of material from natural sources is often expensive and low yielding.[1] Fortunately, in such cases, chemical synthesis can provide an alternative means to produce the quantities necessary for advanced biological testing. It is therefore of critical to develop synthetic methods that assemble these

important molecules in a concise and efficient manner. In 2010, we published on the total synthesis of quinocarcin (**54**), a mono-THIQ, and have recently turned our attention to the preparation of the related bis-THIQ alkaloids. In pursuit of this goal, we devised a general technique to rapidly construct the core of the THIQ alkaloids while providing avenues to introduce the varying peripheral functionality that make up this large and diverse class of natural products.

As the first such molecule to investigate, we selected jorumycin (**50**), a bioactive isolate from the sea slug *Jorunna funebris*.[6,7] Taking into account the fundamental structural features that jorumycin (**50**) shares with other members of the class of bis-THIQ natural products containing the potent saframycins, safracins, renieramycins and cribrostatins, we believe that jorumycin will serve as the cornerstone for a general, convergent, and concise strategy to its relatives.[2,8,9]

Herein, we have devised a synthetic route, which obviates such a need. Instead, our route to jorumycin hinges on a diastereoselective reduction of a bis-tetrahydroisoquinoline, which itself can be prepared from a highly convergent cross-coupling of two isoquinoline subunits.

2.2 Retrosynthetic Analysis of Jorumycin

Retrosynthetically, we envisioned that the pentacyclic bis-THIQ core of jorumycin (**50**) could be accessed by late-stage assembly of the central C-ring piperazine. Consequently, we are targeted bis-THIQ **55**, which could undergo cyclization to form the pentacyclic core of jorumycin. To construct this intermediate, we planned to reduce bis-isoquinoline **56** by a diastereoselective tetra-hydrogenative pathway. We believed that

this bis-isoquinoline could furnished by an Csp^2–H/Csp^2–OTf cross-coupling of two component isoquinolines (**57** and **58**), each of which could be prepared by methods previously developed in our laboratories from a single aryne precursor **59**.[10] This highly modular approach distinguishes itself from previous syntheses by convergently generating the carbon framework of the bis-THIQ alkaloids in a regio- and stereoselective manner without the use of one or more Pictet-Spengler reactions in a linear sequence.[1] Strategies utilizing the Pictet-Spengler reaction necessitate the use of electron-rich arenes. Our approach eliminates this need and allows one to envision access to an array of THIQ analogs, simply by varying the aryne precursor.

Scheme 2.1. *Retrosynthetic Analysis of Jorumycin.*
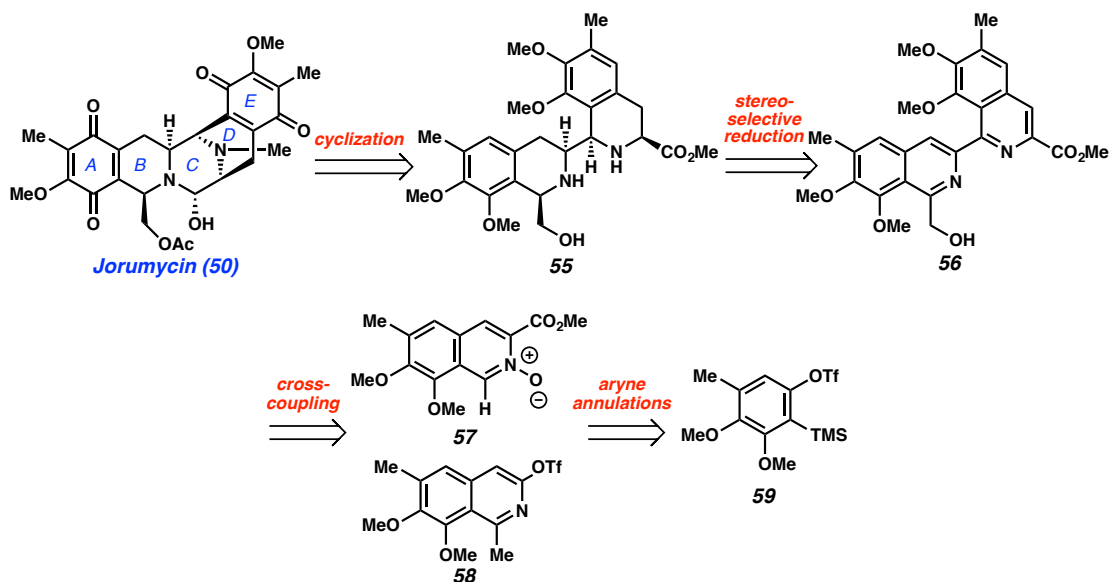
2.3 Synthesis of Jorumycin

We began our synthesis of jorumycin by looking to prepare isoquinolines **57** and **58** (Scheme 2.2). Our lab has developed two methods for the regioselective synthesis of

highly substituted isoquinolines.[10] The *N*-oxide coupling partner **57** was attained through the annulation of silyl aryl triflate **58** with methyl 2-formamidoacrylate (**60**). Subsequent oxidation using *m*CPBA affords the Csp^2–H coupling partner **57**. We next turned our attention to 3-isoquinoline triflate **58**. Acyl-alkylation of the same silyl aryl triflate **58** was accomplished upon exposure to KF and methyl acetoacetate (**62**). Subsequent condensation with ammonium hydroxide furnished 3-hydroxy isoquinoline **63**, which was quantitatively triflated using triflic anhydride to afford our desired isoquinoline Csp^2–OTf coupling partner (**58**).

Scheme 2.2. *Preparation of isoquinolines **57** and **58**.*
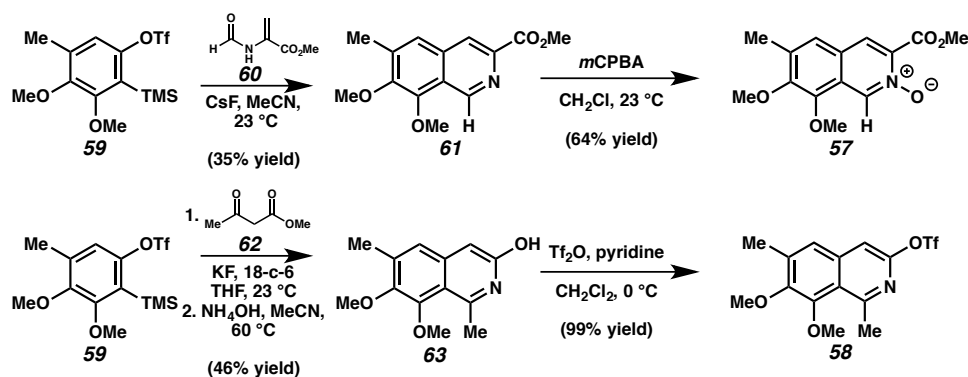
We next examined the convergent coupling of the two isoquinoline fragments. To this end, we investigated Pd-catalyzed oxidative coupling reactions, originally reported by Fagnou, that enable the coupling of aryl halides and heterocyclic *N*-oxides by C–H functionalization.[11] In the event, isoquinoline *N*-oxide **57** and triflate **58** were successfully coupled to furnish bis-isoquinoline **64** using modified Fagnou conditions (Scheme 2.3).

Scheme 2.3. *Cross-coupling of isoquinolines 57 and 58.*
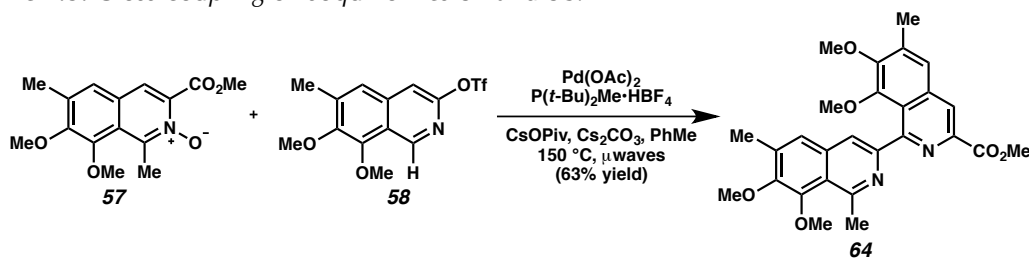
While the cross-coupling of our two isoquinoline quinolone fragments represents a highly convergent route to the bis-THIQ, the scalablity of our aryne annulation reaction to prepare isoquinoline ester **61** was not ideal (22% yield from **59** to **57**) and led us to devise an alternative route to bis-isoquinoline **64**. While methyl 2-formamidoacrylate (**65**) proved to be a difficult substrate for our aryne annulation methodology, methyl 2-acetamidoacrylate (**65**) has been a robust annulation partner. We therefore pursued a sequence in which aryne annulation, saponification and amide formation furnishes serine derivative **67** (Scheme 2.4). Dehydration affords amidoacrylate **68**, which we can use in a second regio-selective aryne annulation reaction thus providing bis-isoquinoline **64**. While this route provides a similar overall yield to the cross-coupling strategy, it has proven to be more scalable, providing greater quantities of bis-isoquinoline **64**.

With a robust method for the preparation of bis-isoquinoline **64** available, we turned our attention to the latter steps of the synthesis, namely oxidation of C(22), tetrahydrogenation of the bis-isoquinoline core and C-ring formation. Initially, we found that bis-isoquinoline **11** undergoes smooth benzylic oxidation upon treatment with SeO_2 at C(22) and subsequent reduction of the resultant aldehyde to afford the hydroxymethyl bis-isoquinoline **7** in 86% yield (Scheme 2.4).

Scheme 2.4. *Alternative approach to bis-isoquinoline* **64**.
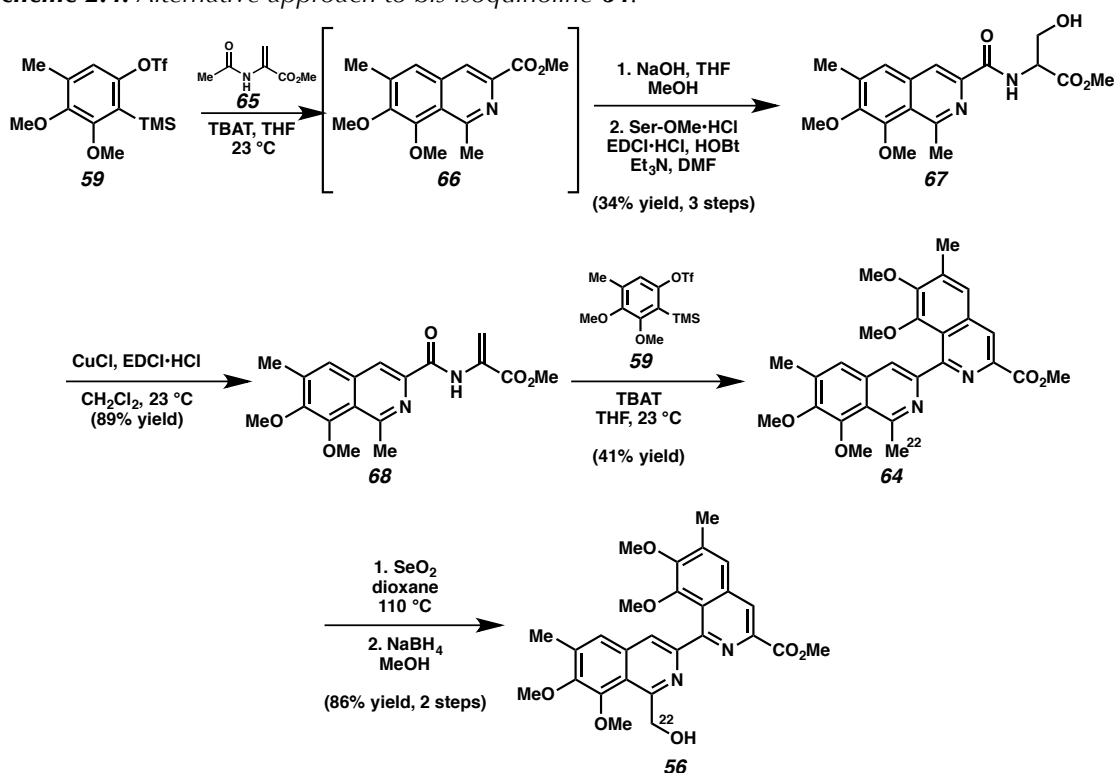
With bis-isoquinoline **56** in hand, we turned our attention to the key reduction of this intermediate.[12] After extensive experimentation we discovered that exposure of bis-isoquinoline **56** to Adams' catalyst, hydrogen gas, and acetic acid, followed by LiOH-induced cyclization provides a pentacyclic lactam. This compound was treated with formaldehyde and NaBH₃CN to install a CH₃ at N(12) with the desired all *cis* stereochemistry (Scheme 2.5). This allowed for the isolation of THIQ **73** in 21% yield overall yield. Although the isolated yield of THIQ **73** is moderate, it is the only characterizable bis-THIQ structure that we have been able to isolate to date. Given the complexity of the tetrahydrogenation reaction, it is remarkable that the process procedes with good diastereoselectivity. We believe this diastereoselectivity is a function of a self-reinforcing situation, wherein each hydrogenation enhances the stereoselectivity of the subsequent event (Scheme 2.5).

Scheme 2.5. *The Diastereoselective Reduction of Bis-Isoquinoline **56***.
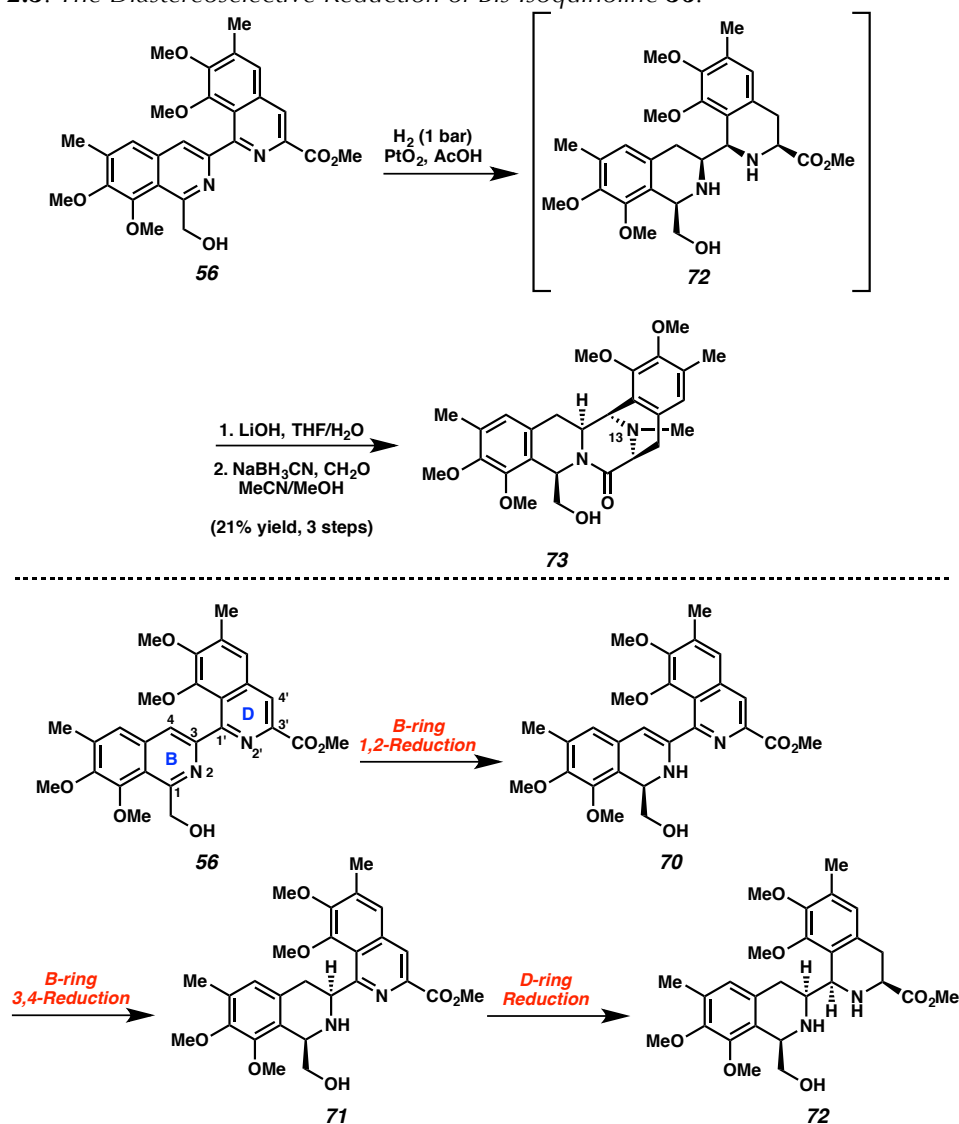
With this highly diastereoselective reduction/cyclization sequence, we have accessed the core of the bis-THIQ alkaloid natural products in a highly convergent and rapid manner in 9 steps from aryne precursor **59**. Selective bis-demethylation of pentacycle **73** provides bis-phenol **74**, which can be advanced to several bis-THIQ alkaloids by known sequences of minimal steps. In the case of jorumycin (**1**), 4 steps are needed for intermediate **74**.[13]

Scheme 2.6. *Completion of the Synthesis of Jorumycin.*
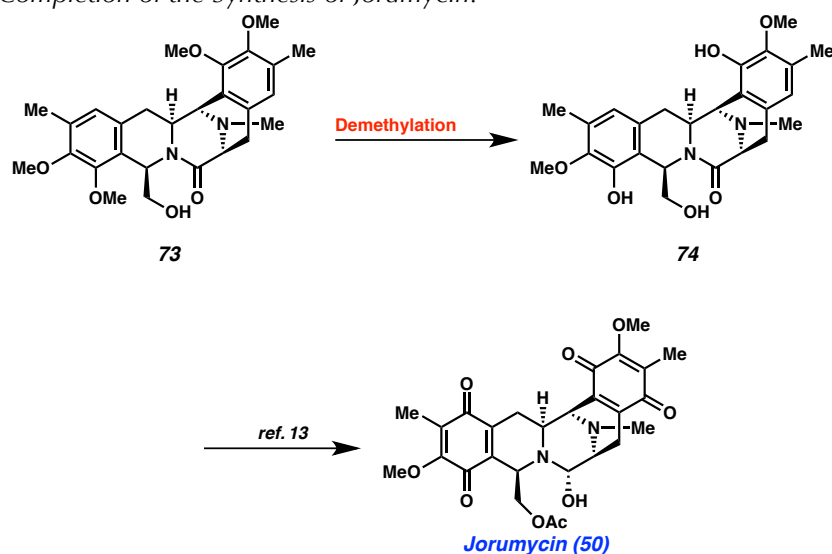
A highly convergent synthesis of (±)-jorumycin has been achieved. Unlike previous syntheses, our approach relies on the convergent cross-coupling of two isoquinoline subunits followed by a highly diastereoselective reduction and cyclization sequence to access the pentacyclic core, eliminating the need for electron-rich arenes to perform electrophilic aromatic substitution reactions. Our laboratory is currently using this strategy to prepare other members of this important class of natural products along with non-natural derivatives thereof.

2.4 EXPERIMENTAL SECTION

2.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to CHCl$_3$ (δ 7.24). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to CHCl$_3$ (δ 77.23). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

2.4.2 Preparative Procedures Spectroscopic Data
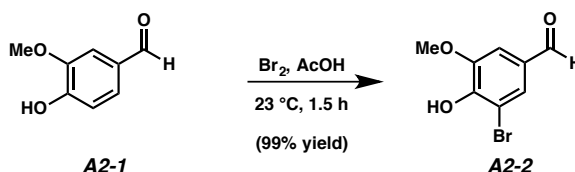
3-Bromovanillin (A2-2)

The following procedure was adopted from a literature report by Rao and Stuber.[14] A single-neck, 2 L round-bottom flask was charged with vanillin (**A2-1**, 50 g, 328.6 mmol). Glacial acetic acid was added (1.1 L, 3.0 M). Following this, a mechanical stirrer was affixed to the flask through the neck and, with vigorous but even stirring, the vanillin dissolved to form a pale yellow solution. At this point, neat bromine (16.84 mL, 361.5 mmol) was added in a rapid dropwise fashion to the stirring solution through the flask neck to produce a deep red-orange solution. Following addition, the reaction was maintained with vigorous stirring for 90 minutes, after which time TLC analysis indicated formation of the product (R_f = 0.32, 15% ethyl acetate in hexanes). The reaction also results in the formation of a bright orange-yellow precipitate when nearing completion. Upon completion of the reaction, the mechanical stirrer was disengaged and the contents of the reaction flask were poured onto chilled deionized water (0 °C, 600 mL), resulting in further precipitation of a pale yellow solid from the bright orange aqueous layer. The reaction flask was washed into this flask with more chilled water. While still cooled, the contents of the 1 L Erlenmeyer flask were filtered over a glass frit to separate the desired solid product. The isolated solid product (**A2-2**, 75.25 g, 99% yield) was transferred to a flask and dried under vacuum for a period of 8 hours
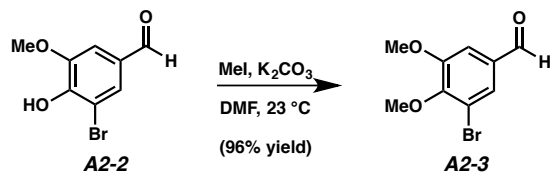
3-bromo-4,5-dimethoxy benzaldehyde (A2-3)

To a 1 L round-bottom flask was added anhydrous K_2CO_3 (113.56 g, 821.6 mmol), followed by a solution of bromobenzaldehyde **A2-2** (75.25 g, 325.66 mmol) in reagent grade acetone (700 mL). A mechanical stirrer was affixed to the reaction flask, and vigorous stirring was required to generate an evenly distributed, maroon suspension. To this stirring mixture was added Me_2SO_4 (77.74 mL, 821.69 mmol) over 1 minute via funnel. The reaction was left to stir vigorously at 25 °C for 8 hours, at which point TLC analysis confirmed the conversion of phenol **A2-2** to a less polar product. The reaction contents were then vacuum filtered over a glass frit to separate residual solid K_2CO_3. The filtered solid was washed with acetone (2 x 100 mL) and methanol (100 mL). The organic filtrate was concentrated to an orange oil and purified by flash chromatography (5% → 50% ethyl acetate in hexanes eluent) to yield bromobenzaldehyde **A2-3** (76.6 g, 96% yield), which was isolated as a white powder: R_f = 0.56 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.86 (s, 1H), 7.67 (d, J = 1.80 Hz, 1H), 7.40 (d, J = 1.85 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 189.83, 154.17, 151.81, 133.03, 128.77, 117.92, 110.09, 60.83, 56.25; IR (NaCl/film) 2945, 2860, 1692, 1588, 1566, 1486, 1469, 1452, 1420, 1393, 1380, 1312, 1281, 1240, 1212, 1144, 1133, 1048, 993, 855, 840 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_9H_9BrO_3$ [M]$^+$: 243.9735, found 243.9731.
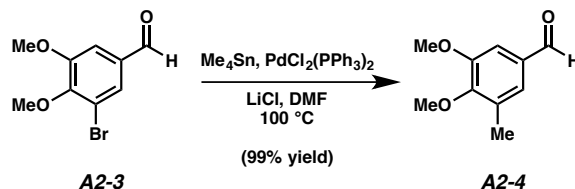
3,4-dimethoxy-5-methylbenzaldehyde (A2-4)

A 250 mL round-bottom flask was charged with lithium chloride (4.32 g, 102.00 mmol) and then flame dried. To this flask was added a solution of benzaldehyde **A2-3** (5.0 g, 20.40 mmol) in *N,N*-dimethylformamide (200 mL) that had been rigorously sparged with argon. Next, $PdCl_2(PPh_3)_2$ (0.358 g, 0.51 mmol) was added to the stirring mixture, producing a bright yellow-orange solution that was stirred vigorously. A reflux condenser was affixed to the top of the reaction flask before adding, dropwise, neat tetramethyltin (7.06 mL, 51.0 mmol). The reaction vessel was sealed under an argon atmosphere and heated to reflux in 100 °C oil bath. The reaction was maintained at reflux for 3 hours; during this period the color of the solution changed to dark red-orange.[15] TLC analysis of the reaction after this period showed full consumption of the starting material. The reaction was cooled to room temperature and then quenched by the addition of H_2O (200 mL). The aqueous layer was thoroughly extracted with ethyl acetate (5 x 200 mL), and the combined organic layers were washed with brine (150 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to furnish benzaldehyde **A2-4** as a colorless oil (3.63 g, 99% yield): R_f = 0.42 (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.17 (d, *J* = 1.71 Hz, 1H), 7.16 (d, *J* = 0.60 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.14, 153.02,

152.70, 126.95, 108.79, 60.05, 55.65, 15.75; IR (NaCl/film) 2939, 2833, 1693, 1586,

1491, 1465, 1422, 1387, 1329, 1299, 1233, 1140, 1096, 1003, 856 cm^{-1}; HRMS (MM:

ESI-APCI) *m/z* calc'd for $C_{10}H_{12}O_3$ [M]$^+$: 180.0786, found 180.0779.
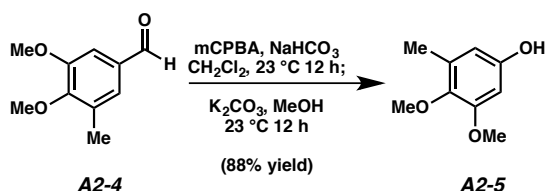
3,4-dimethoxy-5-methylphenol (A2-5)

A 250 mL round-bottom flask was charged with anhydrous NaHCO$_3$ (0.467 g,

0.56 mmol). To this, was added a solution of benzaldehyde **A2-4** (1.00 g, 5.55 mmol) in

CH$_2$Cl$_2$ (11 mL). This mixture was vigorously stirred until the NaHCO$_3$ fully dissolved.

At this point, *m*-CPBA (1.92 g, 11.10 mmol) was added as a solid in a single portion to

the pale yellow solution. Immediately, the solution turned bright yellow, and was

maintained with stirring at 25 °C under an atmosphere of N$_2$. Notable accumulation of

precipitate resulted in increasing turbidity of the solution, and after 6 hours, TLC analysis

indicated formation of a new product (R_f = 0.22, hexanes) and consumption of

benzaldehyde **A2-4**. At this time, methanol (110 mL) and anhydrous K$_2$CO$_3$ (2.30 g,

16.65 mmol) were added, and the solution turned maroon in color. The reaction was

maintained at 25 °C for 12 hours, resulting in formation of a new polar product. The

reaction was stopped by concentration under vacuum to yield a dark maroon solid. This

solid was dissolved in H$_2$O (100 mL), and then neutralized with concentrated aqueous

HCl (6 mL). **Warning:** vigorous gas evolution. The resulting suspension was extracted

with CH$_2$Cl$_2$ (5 x 100 mL), and the combined organic extracts were washed with

saturated aqueous NaHCO$_3$ (2 x 200 mL) to remove benzoate byproducts. The organic

layers were dried with Na$_2$SO$_4$, concentrated under vacuum, and purified by flash

chromatography (30% ethyl acetate in hexanes eluent) to provide phenol **A2-5** (0.822 g,

4.89 mmol, 88% yield) as a white solid: R_f = 0.30 (30% ethyl acetate in hexanes); ^{1}H

NMR (500 MHz, CDCl$_3$) δ 6.29 (d, J = 2.80 Hz, 1H), 6.20 (d, J = 2.80 Hz, 1H), 4.53 (s,

1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.36,

151.78, 141.12, 132.41, 108.36, 98.17, 60.35, 55.69, 15.85; IR (NaCl/film) 3272, 2957,

1614, 1483, 1463, 1440, 1430, 1348, 1268, 1226, 1219, 1196, 1181, 1154, 1096, 1001,

854, 772, 737 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for C$_9$H$_{12}$O$_3$ [M]$^+$: 168.0786,

found 168.0753.
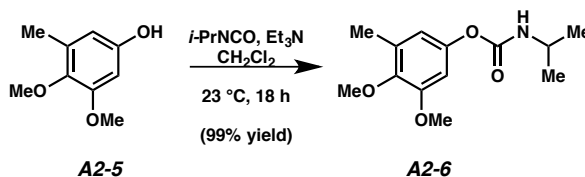
Isopropyl carbamate A2-6

This procedure was adopted from the literature procedure reported by Bronner, et

al.[16] A 100 mL round-bottom flask was charged with a solution of phenol **A2-5** (1.696 g,

10.08 mmol) in CH$_2$Cl$_2$ (35 mL). The solution was stirred at 25 °C under an atmosphere

of N$_2$ before neat isopropyl isocyanate (1.483 mL, 15.12 mmol) was added via syringe.

The solution turned orange, and after 5 minutes of stirring, freshly distilled Et$_3$N (0.281

mL, 2.02 mmol) was added via syringe to effect the formation of a dark purple solution.

The reaction was maintained with stirring for 18 hours at 25 °C. Following this period,

TLC analysis showed conversion of phenol **A2-5** to a single product. The reaction was

concentrated to an orange-brown residue and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to provide isopropyl carbamate **A2-6** as a clear, pale yellow oil (2.553 g, 10.08 mmol, 99% yield): R_f = 0.48 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.55 (d, J = 2.65 Hz, 1H), 6.54 (d, J = 2.65 Hz, 1H), 2.79 (s, 1H), 3.87 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.24 (s, 3H), 1.23 (d, J = 7.25 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.92, 152.87, 146.66, 144.62, 115.29, 104.21, 60.15, 55.78, 43.44, 22.93, 15.91; IR (NaCl/film) 3326, 2972, 2936, 1715, 1604, 1529, 1490, 1466, 1422, 1332, 1220, 1190, 1175, 1142, 1095, 1050, 1009, 936, 854, 773 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for C$_{13}$H$_{19}$NO$_4$ [M]$^+$: 253.1314, found 253.1319.
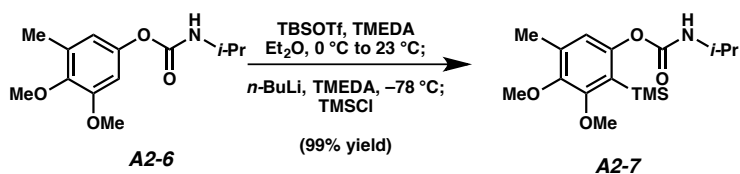
TMS carbamate A2-7

    This procedure was adopted from the literature procedure reported by Bronner, et al.[3] To a solution of isopropyl carbamate **A2-6** (9.10 g, 35.9 mmol) in diethyl ether (180 mL) was added freshly distilled TMEDA (5.90 mL, 39.5 mmol). The solution was cooled to 0 °C. Distilled TBSOTf (9.00 mL, 39.5 mmol) was then added. The resulting solution was maintained for 10 minutes at 0 °C and then the flask was allowed to warm to 23 °C over 30 minutes. Additional TMEDA was then added to the mixture (21.5 mL, 144 mmol). The reaction was then cooled to −78 °C with vigorous stirring to avoid aggregation of triflate salts. Next, *n*-BuLi (2.5 M in hexanes, 58.0 mL, 144 mmol) was added dropwise. The solution was maintained with stirring at −78 °C for 4 hours, after which time freshly distilled TMSCl (32.0 mL, 251 mmol) was added dropwise. The

reaction vessel was allowed to warm to 23 °C over the course of two hours. At this point,

TLC analysis indicated the presence of a single, new product. Saturated aqueous

$NaHSO_4$ solution (150 mL) was added and stirred with the reaction mixture for 0.5 hour.

The layers were separated and the organic layer was washed with an additional 150 mL

of the $NaHSO_4$ solution. The combined aqueous layers were then extracted with diethyl

ether (3 x 250mL). The combined organic extracts were washed with brine (250 mL),

dried with Na_2SO_4, and then concentrated under vacuum to a colorless crystalline solid.

Purification via flash chromatography (5% → 15% ethyl acetate in hexanes eluent)

provided pure TMS carbamate **A2-7** (11.6 g, 99% yield): R_f = 0.63 (15% ethyl acetate in

hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.69 (d, J = 7.08 Hz, 1H), 3.89 (m,

1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.23 (s, 3H), 1.23 (d, J = 6.75, 6H), 0.29 (s, 9H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 156.69, 153.00, 149.33, 147.28, 133.33, 121.79, 118.88,

59.19, 58.54, 42.27, 21.88, 14.83, 0.13; IR (NaCl/film) 3326, 2971, 2937, 1710, 1601,

1530, 1464, 1384, 1370, 1324, 1247, 1220, 1193, 1179, 1080, 1026, 987, 844, 810, 759

cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{16}H_{27}NO_4Si$ $[M+H]^+$: 326.1734, found

326.1725.

A2-7 → (99% yield) → **A2-8**

Et$_2$NH, *n*-BuLi

THF, −78 °C to 23 °C
then PhNTf$_2$;
Et$_2$NH
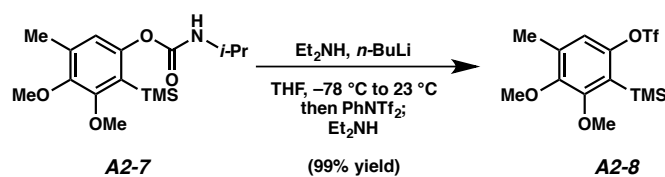
Silyl aryl triflate A2-8

To a solution of TMS carbamate **A2-7** (13.2 g, 40.5 mmol) in THF (160 mL) at − 78 °C

was added diethylamine (6.30 mL, 60.8 mmol), followed by *n*-BuLi (2.5 M in hexanes,

24.3 mL, 60.8 mmol). After 20 minutes, the reaction was allowed to warm to 23 °C for

30 minutes. PhNTf$_2$ (21.7 g, 60.8 mmol) was then added in one portion. The reaction was maintained with stirring for 4 hours at 23 °C, after which point more diethylamine was added (7.50 mL, 72.9 mmol). The reaction was stirred at 23 °C for 12 hours. The reaction was then filtered on a silica pad, and washed with 25% EtOAc in hexanes. Evaporation of the solvent, followed by purification via flash chromatography (2% ethyl acetate in hexanes eluent) yielded silyl aryl triflate **A2-8** (14.9 g, 99% yield) as a pale yellow oil that crystallize upon cooling: R_f = 0.68 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.87 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.27 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.72, 150.74, 149.21, 135.84, 117.49 (q, J = 320 Hz), 124.53, 117.96, 60.79, 60.03, 16.43, 1.41; ^{19}F NMR (282 MHz, CDCl$_3$) δ –73.10; IR (NaCl/film) 2956, 2858, 1600, 1464, 1420, 1383, 1368, 1292, 1248, 1213, 1179, 1142, 1068, 1023, 982, 930, 873, 846, 764 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for C$_{13}$H$_{19}$F$_3$O$_5$SSi [M]$^+$: 372.0675, found 372.0674.
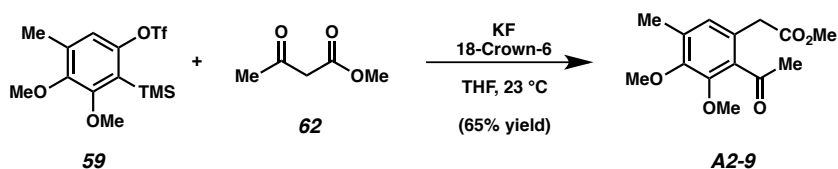
Ketoester A2-9

To a solution of silyl aryl triflate **59** (1.86 g, 5.00 mmol) in THF (50 mL) was added methyl acetoacetate (**62**, 0.54 mL, 5.00 mmol), KF (872 mg, 15.0 mmol) and 18-crown-6 (4.00 g, 15.0 mmol) at 23 °C. The reaction was maintained at this temperature for 16 hours, at which time TLC analysis indicated complete consumption of silyl aryl triflate **59**. The solution was diluted with diethyl ether (150 mL) and water (150 mL). The

aqueous layer was extracted with diethyl ether (3 x 150 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification of this residue by flash chromatography (10% EtOAc in hexanes eluent) furnished ketoester **A2-9** (860 mg, 65% yield) as a colorless solid: R_f = 0.49 (4:1 hexanes:ethyl acetate) along with the corresponding α-arylation bi-product (170 mg, 13% yield, not characterized); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 3.60 (s, 2H), 2.53 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.67, 172.20, 150.95, 150.51, 134.57, 134.26, 128.77, 126.84, 61.37, 60.28, 52.20, 37.96, 32.46, 16.09; IR (NaCl/film) 2951, 2849, 1740, 1692, 1604, 1568, 1484, 1451, 1437, 1400, 1351, 1306, 1269, 1200, 1167, 1147, 1078, 1040, 1012 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{11}H_{10}O_2N$ [M+H]$^+$: 267.1227, found 267.1233.

A2-9   *63*
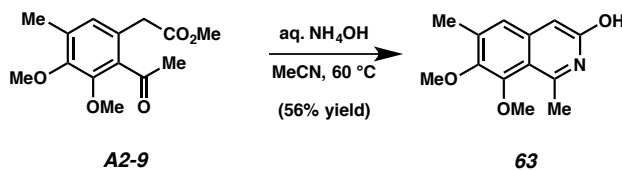
3-Hydroxyisoquinoline 63

Ketoester **A2-9** (735 mg, 2.76 mmol) was dissolved in MeCN (2 mL) in a pressure flask with a sealable top. To this was added 28–30% aqueous ammonium hydroxide (4 mL), and the flask was sealed. The reaction was maintained at 60 °C with vigorous stirring for 18 hours. At this point, a yellow solid was generated and TLC analysis indicated the complete consumption of the starting material. The reaction mixture was then cooled to 23 °C, and the solid was filtered and washed with water. The resulting yellow residue was analytically pure 3-hydroxyisoquinoline **63** (324 mg, 1.32 mmol). The filtrate was diluted with dichloromethane (5 mL), NH$_4$Cl saturated solution

was added (10 mL) and the phase were separated. The aquous layer was further extracted with CH_2Cl_2 (5x 15 mL). The organic layers were dried on Na_2SO_4, filtered and concentrated. Purification of this residue by flash chromatography (5% MeOH in CH_2Cl_2 eluent) furnished 3-hydroxyisoquinoline **63** (51 mg, 0.22 mmol). Overall, 3-hydroxyisoquinoline **63** (375 mg, 1.54 mmol, 56% yield) was obtained as a yellow solid: R_f = 0.10 (95:5 CH_2Cl_2:MeOH) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.94 (s, 1H), 6.52 (s, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.01 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.99, 149.63, 149.62, 146.04, 142.71, 140.48, 121.54, 113.27, 104.86, 60.63, 60.35, 21.23, 17.43; IR (NaCl/film) 2938, 1690, 1458, 1324 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{16}O_3N$ [M+H]$^+$: 234.1125, found 234.1125.
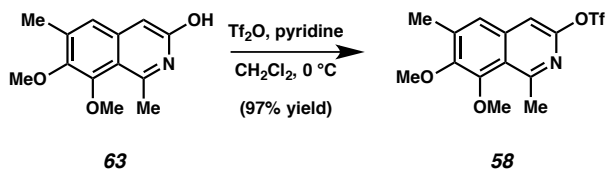
Isoquinoline triflate 58

3-Hydroxyisoquinoline **163** was dissolved in dry CH_2Cl_2 (6 mL). To this solution, was added pyridine (1.00 mL, 12.2 mmol), and the reaction was cooled to 0 °C. Triflic anhydride (0.31 mL, 1.83 mmol) was added dropwise to the cold solution, which was maintained at 0 °C for 40 minutes. At this time, TLC analysis indicated complete consumption of the starting material. The reaction was quenched at 0 °C by the addition of saturated aqueous $NaHCO_3$ (10 mL) followed by warming to 23 °C. The mixture was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated under vaccuum. The resulting residue was purified by flash chromatography (5% ethyl acetate in hexanes eluent) to furnish isoquinoline triflate **58**

(433 mg, 97% yield): $R_f = 0.83$ (hexanes:ethyl acetate 1:1); ^{1}H NMR (500 MHz, CDCl$_3$)

δ 7.37 (s, 1H), 7.19 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.05 (s, 3H), 2.42 (s, 3H); [13]C

NMR (125 MHz, CDCl$_3$) δ158.84, 151.22, 150.68, 150.09, 139.41, 137.00, 123.79,

123.11, 118.97 (q, $J = 320$ Hz), 107.83, 60.99, 60.38, 26.91, 17.20; IR (NaCl/film) 2961,

2924, 2853, 1604, 1552, 1452, 1413, 1377, 1352, 1332, 1260, 1208, 1094, 1059, 1016,

966, 940, 799, 699 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for C$_{11}$H$_{10}$O$_2$N [M+H]$^+$:

366.0618, found 366.0637.
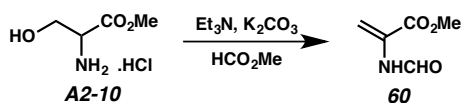
2-(Formamido)acrylic acid methyl ester 60[17]

A mixture of serine methyl ester hydrochloric salt **A2-10** (15.6 g, 100 mmol),

K$_2$CO$_3$ (55.3 g, 400 mmol), and a catalytic amount of Et$_3$N (160 μL) in methyl formate

(320 mL) was stirred for 16 h at 23 °C. The salts were filtered, and the solvent was

removed under reduced pressure. Quick purification by column chromatography

(hexanes-ethyl acetate 40:60) afforded the desired product **60** (7.15 g, 55%). White solid,

R_f0.56 (hexanes:ethyl acetate 1:1), trans:cis 88:12. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.55

(d, $J = 11.2$ Hz, 1H, cis), 8.39 (s, 1H, trans), 7.79 (br, 1H, trans), 7.52 (br, 1H, cis), 6.62

(s, 1H, trans), 5.95 (s, 1H, trans), 5.67 (s, 1H, cis), 5.42 (s, 1H, cis), 3.84 (s, 3H). [13]C

NMR (125 MHz, CDCl$_3$) δ 164.34, 161.14 (*cis*), 159.65 (*trans*), 130.35, 110.58 (*trans*),

104.80 (*cis*), 53.25.
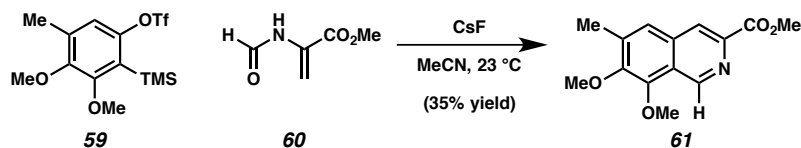
Isoquinoline 57[,18]

To silyl aryl triflate **59** (37 mg, 0.10 mmol) and methyl-2-formamidoacrylate (**60**, 39 mg, 0.30 mmol) stirring in MeCN (10 mL) at 23 °C was added CsF (92 mg, 0.60 mmol). The flask was maintained at 23 °C for 6 hours. Afterward, HCl 1N (1 mL) was added and the reaction was further stirred for 15 min. The mixture was then basified with $NaHCO_3$ saturated solution and EtOAc was added. The phases were separated, and the aqueous layer was extracted with EtOAc (3x 20 mL). The organic layers were dried on Na_2SO_4, filtered and concentrated. The resulting red residue was purified by flash chromatography (25% ethyl acetate in hexanes eluent) to furnish isoquinoline **61** (10 mg, 36% yield) as a red solid: $R_f = 0.35$ (1:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.42 (s, 1H), 7.49 (s, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.72, 151.15, 147.65, 147.35, 141.05, 139.42, 132.91, 125.02, 124.29, 123.24, 61.80, 60.69, 53.01, 17.56; IR (NaCl/Film) 2949, 2855, 1738, 1717, 1620, 1570, 1483, 1456, 1418, 1386, 1321, 1285, 1257, 1196, 1141, 1105, 1085, 1006, 984, 906, 818, 802, 777 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ [M+H]$^+$: 262.1074, found 262.1070.
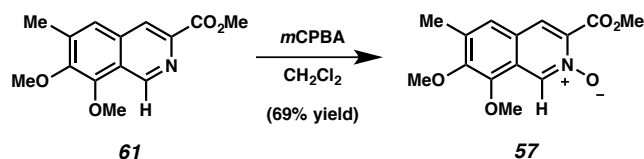
Isoquinoline *N*-oxide 57

To a solution of isoquinoline **61** (575 mg, 2.20 mmol) in dichloromethane (22 mL) at 0 °C was added *m*CPBA (1.10 g, 4.40 mmol, 70% w/w). The reaction was allowed to reach 23 °C and was further stirred for 24 hours. After this time, TLC analysis indicated complete consumption of the isoquinoline. The reaction mixture was directly purified by flash chromatography (10% acetone in dichloromethane to 10% acetone/ 2% MeOH in dichloromethane eluent) providing isoquinoline *N*-oxide **57** (421 mg, 69% yield): R_f = 0.12 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.95 (s, 1H), 7.86 (s, 1H), 7.33 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 162.65, 152.03, 144.45, 137.97, 137.41, 133.29, 125.77, 125.17, 125.13, 123.72, 61.53, 60.66, 53.52, 17.14. IR (NaCl/film) 2951, 2850, 1742, 1623, 1607, 1558, 1475, 1447, 1418, 1374, 1277, 1258, 1209, 1144, 1100, 1073, 1002, 958, 936, 828 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for C$_{11}$H$_{10}$O$_2$N [M+H]$^+$: 278.1028, found 278.1034.
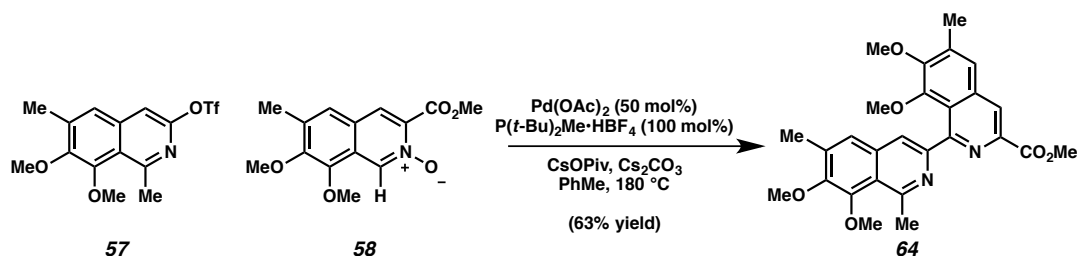
Bis-isoquinoline 64

Palladium acetate (34 mg, 0.15 mmol) was added to a flame-dried high pressure glassware containing cesium carbonate (280 mg, 0.86 mmol), cesium pivalate (136 mg, 0.58 mmol) and di-*tert*-butylmethylphosphonium tetrafluoroborate (72 mg, 0.29 mmol). The vessel was sealed. The vessel evacuated and backfilled with nitrogen atmosphere three times. Next, toluene (5 mL) was added to the reaction vial, which was subsequently heated to 60 °C in an oil bath. The suspension was maintained at this temperature for 1 hour with vigorous stirring. Concomitant to this step, isoquinoline triflate **95** (106 mg, 0.29 mmol) was added to a flask containing isoquinoline *N*-oxide **94** (240 mg, 0.86 mmol). Toluene (10 mL) was added to the flask under an argon atmosphere. Upon cooling the palladium solution to room temperature, the isoquinolines solution was added. Next, the sealed tube was heated at 180 °C for 4 hours. At the completion of this step, the content was filtered over a short plug of celite, the plug was washed with CH_2Cl_2 and acetone. Removal of the solvent and purification of the crude residue by flash chromatography (25% ethyl acetate in hexanes to 50% ethyl acetate in hexanes to 10% acetone/ 2% MeOH in dichloromethane) yielded bis-isoquinoline **64** (87 mg, 63% yield) as a white solid, along with isoquinoline **61** (56 mg, 25% yield recovered) and isoquinoline *N*-oxide **57** (70 mg, 30% yield recovered). Bis-isoquinoline : $R_f = 0.16$ (1:1 EtOAc:Hexanes) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.59 (s, 1H), 7.57 (s, 1H),

7.38 (s, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H), 3.79 (s, 3H), 3.37 (s, 3H), 3.11 (s,

3H), 2.45 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.82, 157.67, 155.46,

152.70, 152.52, 150.55, 149.71, 149.08, 139.81, 138.99, 137.18, 135.16, 134.85, 124.78,

124.21, 123.84, 123.52, 122.02, 117.04, 61.03, 60.72, 60.44, 60.24, 53.00, 27.04, 17.30,

17.20; IR (NaCl/film) 2930, 1719, 1555, 1395, 1318, 1262, 1121, 1096 cm^{-1}; HRMS

(MM: ESI-APCI) *m/z* calc'd for C$_{27}$H$_{29}$O$_6$N$_2$ [M+H]$^+$: 477.2020, found 477.2030.
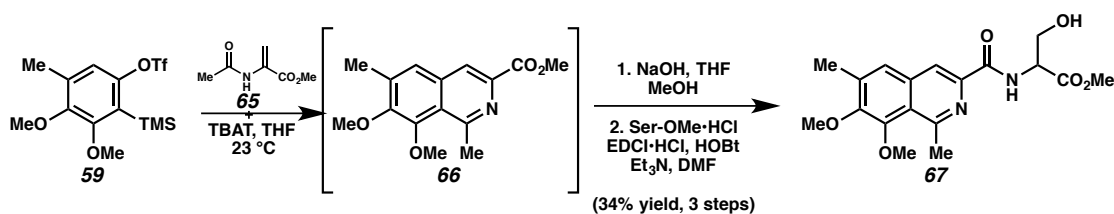
Isoquinoline 67

TBAT (1.450 g, 2.686 mmol) was added to a flame-dried round bottom flask

equipped with a magnetic stir bar. The flask was sealed with a septum, evacuated and

back-filled with N$_2$. THF (6.0 mL) and methyl 2-acetamidoacrylate **65** (576.6 mg, 4.027

mmol) were sequentially added via syringe. To the solution was then added a solution of

aryne precursor **59** (500.0 g, 1.343 mmol) in THF (7.0 mL), and the reaction mixture was

stirred at room temperature for 20 hours. The mixture was evaporated in vaccuo and the

resulting residue was purified by silica gel flash column chromatography (0% ethyl

acetate in hexanes to 50% ethyl acetate in hexanes) to give a mixture of isoquinoline **66**

and methyl 2-acetamidoacrylate (**65**) as a brown solid.

The mixture was dissolved with THF (9.0 mL) and methanol (9.0 mL). To the

solution was added 2 M aqueous sodium hydroxide solution (9.06 mL, 18.12 mmol), and

the reaction mixture was warmed up to 50 °C and stirred at 50 °C for one hour. The

reaction mixture was allowed to cool to room temperature and acidified with 10% citric acid in water. The mixture was extracted with dichloromethane/2-propanol (10:1, v/v). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude isoquinoline the carboxylic acid as a brown solid.

The crude carboxylic acid, DL-serine methyl ester hydrochloride (355.2 mg, 2.283 mmol), 1-hydroxybenzotriazole (HOBt) hydrate (235.9 mg, 1.746 mmol), triethylamine (0.49 mL, 3.49 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) hydrochloride (437.7 mg, 2.283 mmol) and *N,N*-dimethylformamide (DMF, 4.0 mL) were stirred at room temperature for 13 hours. Saturated aqueous sodium bicarbonate solution (20 mL) and water (10 mL) were added to the reaction mixture. The mixture was then extracted with ethyl acetate (2 x 30 mL, 1 x 20 mL). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The resulting residue was purified by silica gel flash column chromatography (50% ethyl acetate in hexanes) to give **67** (174.3 mg, 0.4810 mmol, 36% yield from **59**) as a tan foam: R_f = 0.23 (50% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.12 (d, *J* = 7.5 Hz, 1H), 8.24 (s, 1H), 7.49 (d, *J* = 1.2 Hz, 1H), 4.94 (dt, *J* = 7.7, 4.0 Hz, 1H), 4.16 (t, *J* = 3.9 Hz, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.87 (s, 3H), 3.29 (s, 1H), 3.12 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.02, 165.30, 156.09, 151.70, 149.48, 140.25, 137.64, 134.02, 125.05, 123.51, 118.36, 77.46, 77.21, 76.95, 63.10, 60.61, 60.01, 55.03, 52.59, 26.95, 16.77 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for C$_{18}$H$_{22}$N$_2$O$_6$ [M+H]$^+$: 363.1551, found 363.1551.
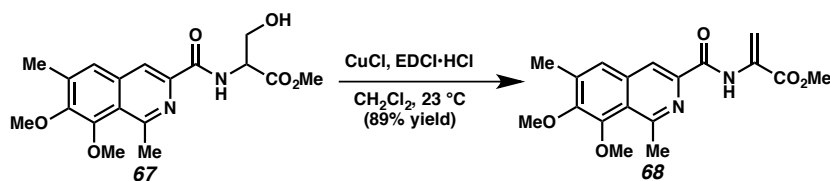
Acrylate 68

To a solution of methyl isoquinoline **67** (542.5 mg, 1.497 mmol) in dichloromethane (18.7 mL) were added EDCI hydrochloride (717.4 mg, 3.743 mmol) and copper (I) chloride (44.5 mg, 0.449 mmol). The reaction mixture was stirred at room temperature for 5 hours. To the reaction mixture were then added saturated aqueous sodium bicarbonate (25 mL) and water (40 mL), and the mixture was extracted with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and evaporated in vaccuo. The resulting residue was purified by silica gel flash column chromatography (dichloromethane as eluent) to give **68** (457.1 mg, 1.327 mmol 89% yield) as a white solid: R_f = 0.82 (50% ethyl acetate in hexanes); mp 155.0 − 156.0 °C (from dichloromethane and hexanes); ^{1}H NMR (500 MHz, cdcl$_3$) δ 10.79 (s, 1H), 8.32 (m, 1H), 7.56 (dd, J = 0.9, 0.5 Hz, 1H), 6.89 (s, 1H), 6.06 (d, J = 1.6 Hz, 1H), 4.03 (s, 3H), 4.00 (s, 3H), 3.97 (s, 3H), 3.20 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 164.60, 163.87, 156.31, 152.03, 149.81, 140.83, 138.03, 134.43, 131.37, 125.23, 123.89, 118.47, 108.73, 77.28, 77.02, 76.77, 60.77, 60.15, 52.89, 27.32, 16.89 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for C$_{18}$H$_{20}$N$_2$O$_5$ [M+H]$^+$: 345.1445, found 345.1430.
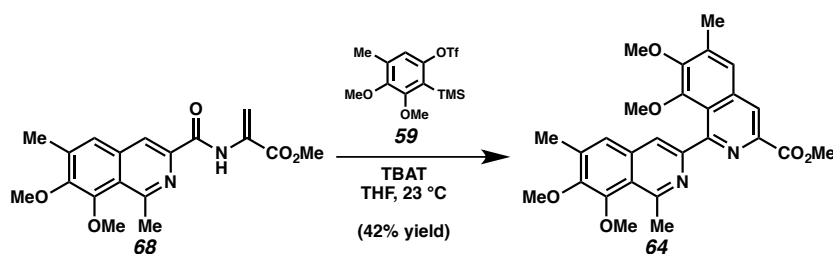
Bis-isoquinoline 64

TBAT (8.114 g, 15.03 mmol) was added to a flame-dried round bottom flask equipped with a magnetic stir bar. The flask was sealed with a septum, evacuated and back-filled with N_2. THF (8.0 mL) and a solution of acrylate **26** (862.8 mg, 2.505 mmol) in THF (8.0 mL) were sequentially added via syringe. A solution of aryne precursor **7b** (2.799 g, 7.515 mmol) in THF (8.0 mL) was then added to the reaction mixture, which was stirred at room temperature for 20 hours. The volatiles of the reaction mixture were removed in vaccuo, and the resulting residue was purified by silica gel flash column chromatography (0% ethyl acetate in hexanes to 70% ethyl acetate in hexanes) to give **22** (494.9 mg, 1.038 mmol 42% yield) spectroscopic data can be found above.
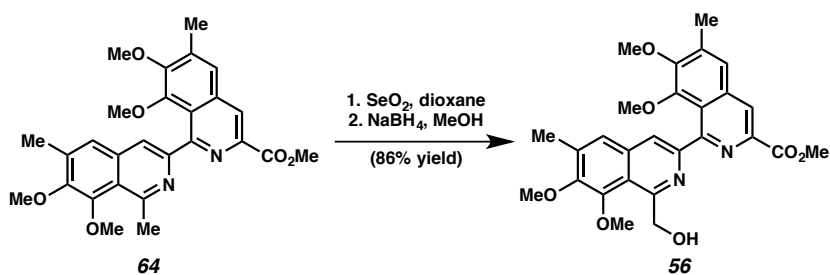
Bis-isoquinoline alcohol 56

Selenium dioxide (17 mg, 0.150 mmol) was added to a solution of **93** (35 mg, 0.075 mmol) in dioxane (1.5 mL). The reaction mixture was subsequently heated to 110 °C for 4 hours. After this time, the solution was filtered on celite and washed with

EtOAc. The solvent was removed, and MeOH (4 mL) was added. NaBH$_4$ (17 mg, 0.45 mmol) was subsequently added and the reaction was stirred for 12 h. At which time another portion of NaBH$_4$ (17 mg, 0.45 mmol) was added, and the reaction was kept at 23 °C for another 4 h. After this period of time, water and EtOAc were added and the organic phases were separated. Extraction of the aqueous layer with EtOAc, followed by drying the organic layers with Na$_2$SO$_4$, filtration and concentration gave the crude residue which was purified by flash chromatography (50% ethyl acetate in hexanes) yielded bis-isoquinoline **56** (32 mg, 86% yield) as a off-white solid: R_f = 0.46 (60:40 EtOAc:Hexanes) ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.49 (s, 1H), 7.77 (s, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 5.28 (d, J = 2.6 Hz, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 3.81 (s, 3H), 3.32 (s, 3H), 2.47 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.65, 156.97, 155.30, 152.62, 151.17, 150.44, 149.21, 148.86, 139.67, 139.23, 138.05, 135.08, 134.64, 124.76, 124.22, 123.75, 123.62, 119.92, 117.86, 64.30, 60.98, 60.78, 60.42, 60.33, 53.03, 17.31, 17.19; IR (NaCl/film) 3350, 2947, 2853, 1722, 1557, 1454, 1394, 1323, 1263, 1121, 1098, 1009 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for C$_{27}$H$_{29}$O$_7$N$_2$ [M+H]$^+$: 493.1969, found 493.1994.
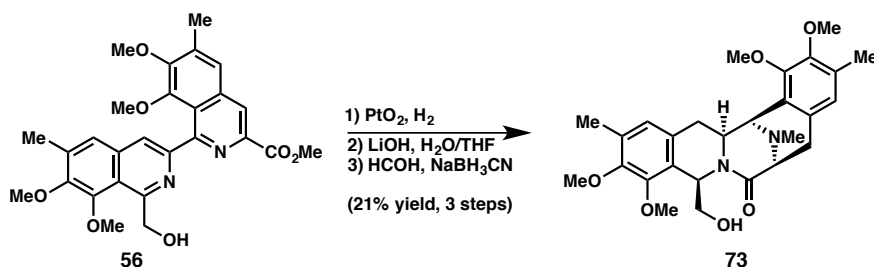
Bis-terahydroisoqinoline 73

To bis-isoquinoline **56** (18 mg, 0.036 mmol) in acetic acid (1.5 mL) was added

PtO$_2$ (4 mg, 0.016 mmol). The reaction mixture was putted under a hydrogen atmosphere

and stirred at 23 °C for 24 h. Upon complete conversion of the bis-isoquinoline by LC-

MS, the mixture was treated with NaOH 1N and dilute with dichloromethane. The

aqueous layer was further extracted with dichloromethane (4x), the organic phase dried

on Na$_2$SO$_4$, filtered, concentrated. The crude residue was then diluted in THF (1.5 mL)

and H$_2$O (1.5 mL), and lithium hydroxide was added (15 mg, 0.640 mmol). The reaction

mixture was stirred at 23 °C for 20 h and was followed by LC-MS. Upon completion, the

reaction mixture was diluted with water and dichloromethane. The phases were

separated, and the aqueous layer was further extracted with dichloromethane (4x), the

organic phases dried on Na$_2$SO$_4$, filtered, concentrated. The residue was then diluted in

MeCN (2 mL) and formaldehyde (0.15 mL, 37% w/w) was added. The mixture was

stirred for 15 minute at 23 °C. Afterward, NaBH$_3$CN (20 mg, 0.320 mmol) was added

and the reaction kept at 23°C for 30 min. HCl 2N (2 mL) was added and the solution

stirred for 24 h. The mixture was then poured in NaHCO$_3$ saturated solution,

dichloromethane was added and the phases separated. The aqueous phase was washed 4x

with dichloromethane, and the organic phases were dried on Na$_2$SO$_4$, filtered and

concentrated. The residue was purified by prep TLC (4% MeOH/1% Et$_3$N/ 95%

CH$_2$Cl$_2$), affording the bis-tetrahydroisoquinoline intermediate **73** (4 mg, 21% yield); ^{1}H

NMR (500 MHz, CDCl$_3$) δ 6.73 (s, 1H), 6.70 (s, 1H), 5.74 (dd, *J* = 6.2, 3.8 Hz, 1H), 4.14

(dd, *J* = 3.8, 1.3 Hz, 1H), 3.99 (dt, *J* = 12.7, 2.9 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.74

(s, 6H), 3.68 (dt, *J* = 6.8, 1.2 Hz, 1H), 3.43 (dt, *J* = 9.9, 4.5 Hz, 1H), 3.26-3.17 (m, 2H),

3.05 (s, 1H), 2.93 (dd, *J* = 15.2, 2.5 Hz, 1H), 2.87 (d, *J* = 17.2 Hz, 1H), 2.45 (s, 3H), 2.26

(dd, *J* = 15.2, 12.7 Hz, 1H), 2.21 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.43, 150.89,

149.90, 149.64, 149.41, 132.22, 132.12, 131.66, 128.87, 126.20, 125.04, 124.73, 122.28,

69.22, 60.73, 60.51, 60.26, 60.17, 60.09, 59.10, 55.82, 53.00, 40.36, 31.88, 28.99, 16.03,

15.93.

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Appendix 2

Spectra Relevant to Chapter 2
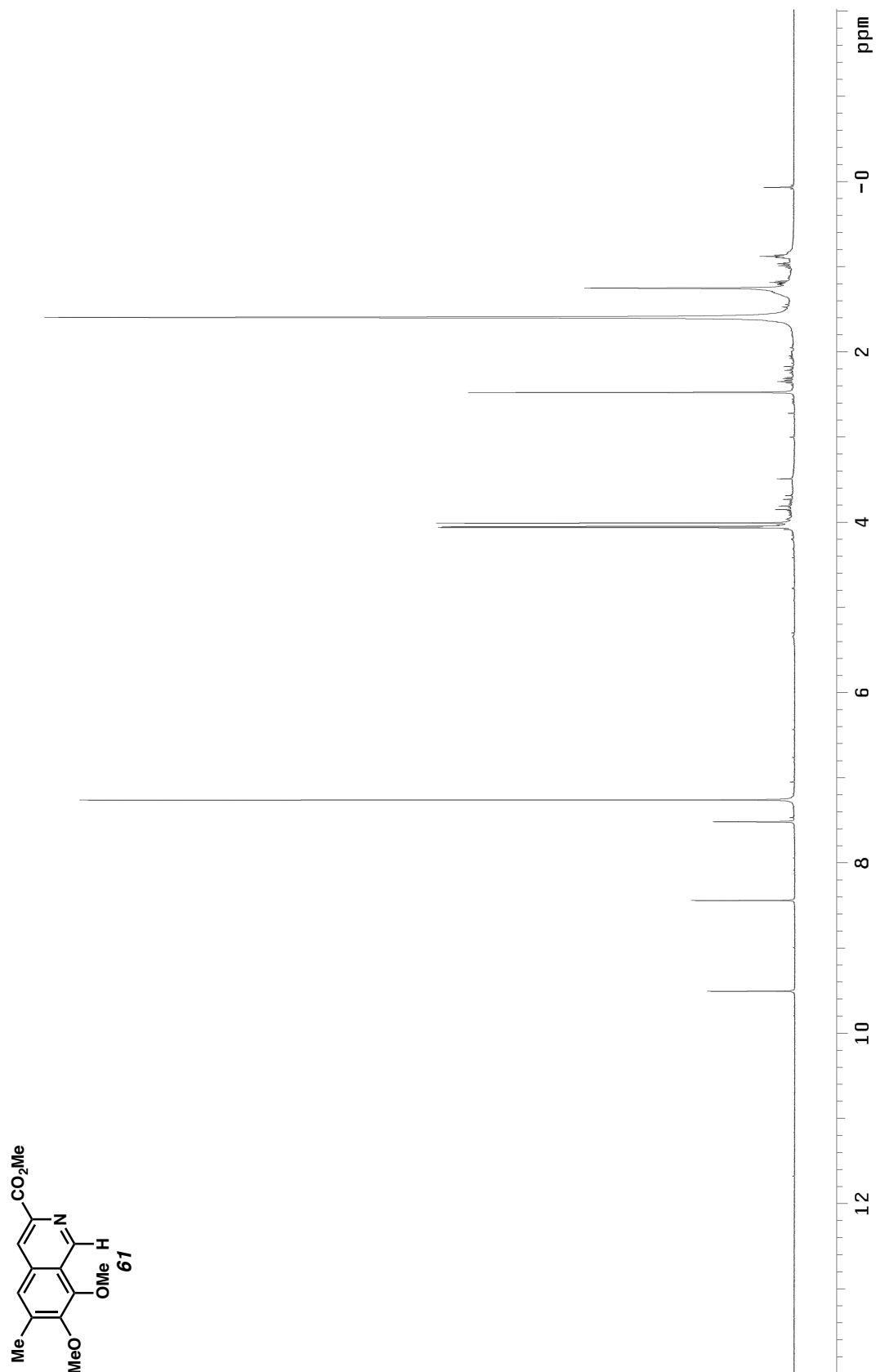
Figure A2.1.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **61**
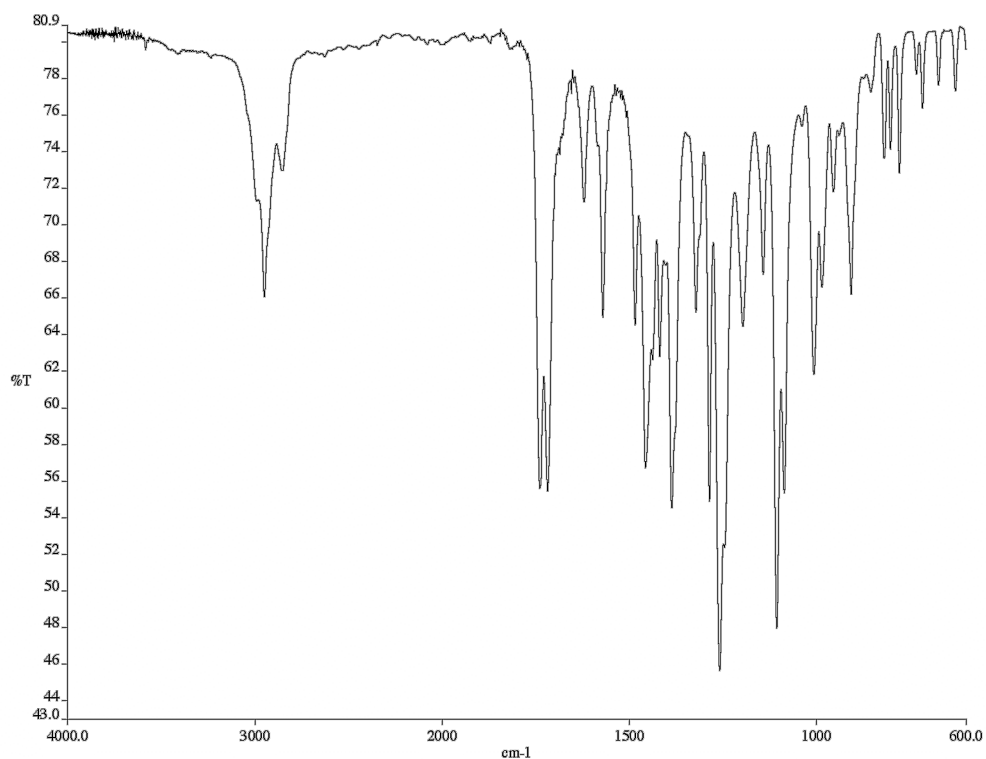
Figure A2.1.2 Infrared spectrum (thin film/NaCl) of compound **61**
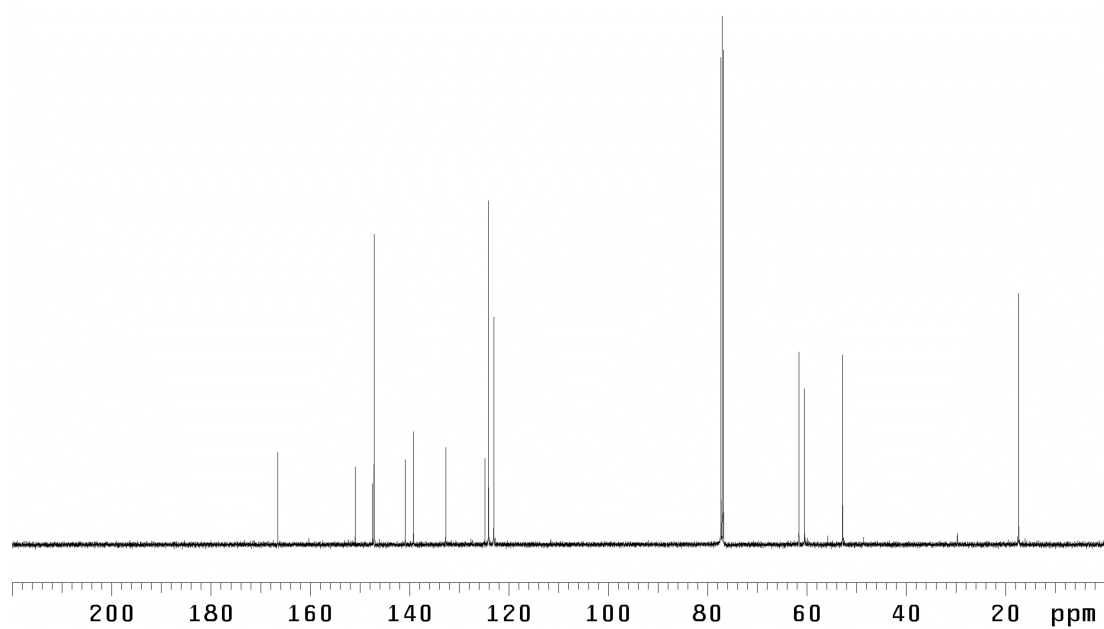
Figure A2.1.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **61**
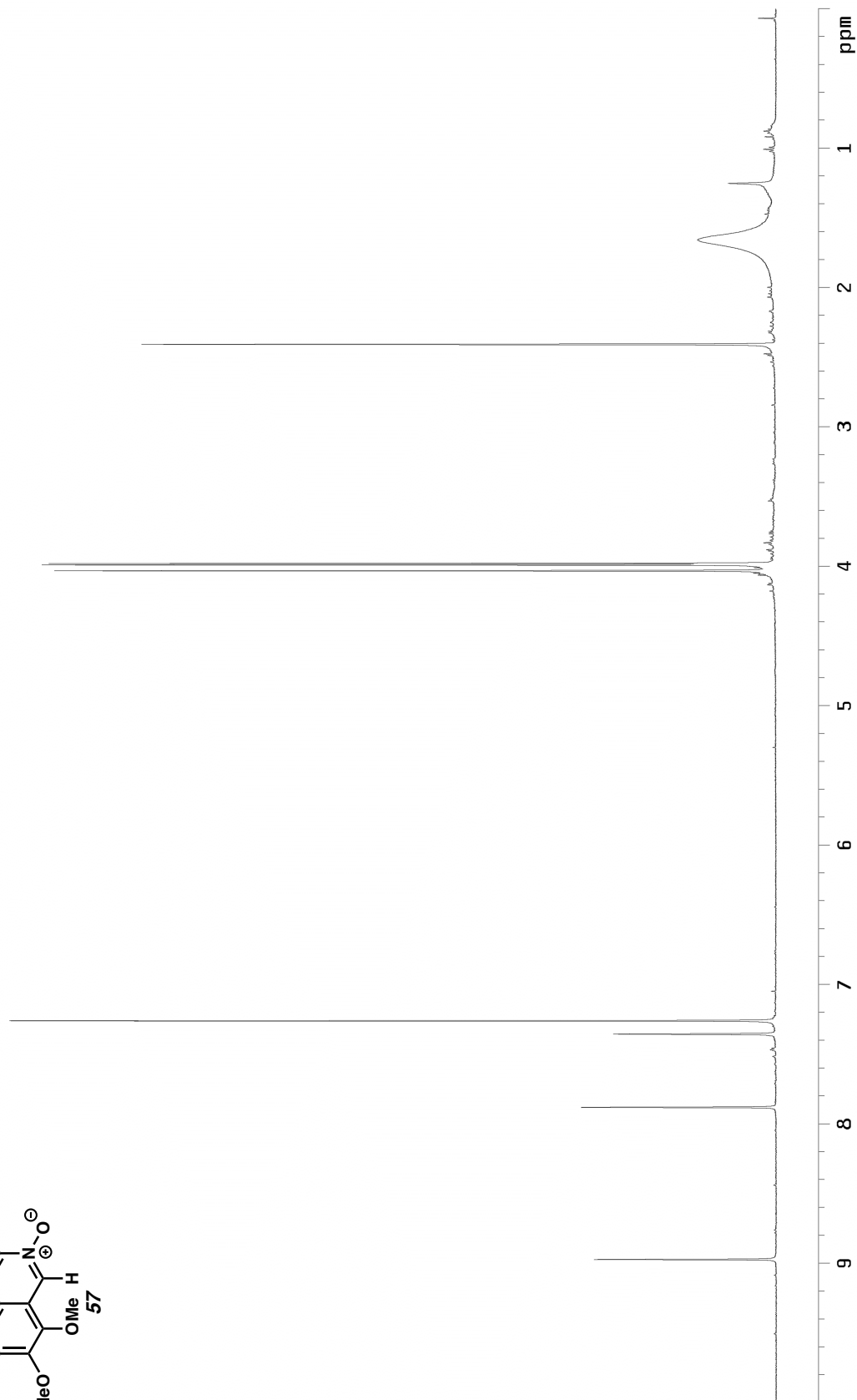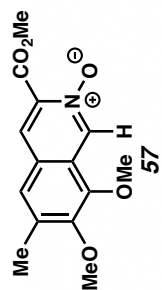
Figure A2.2.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **75**
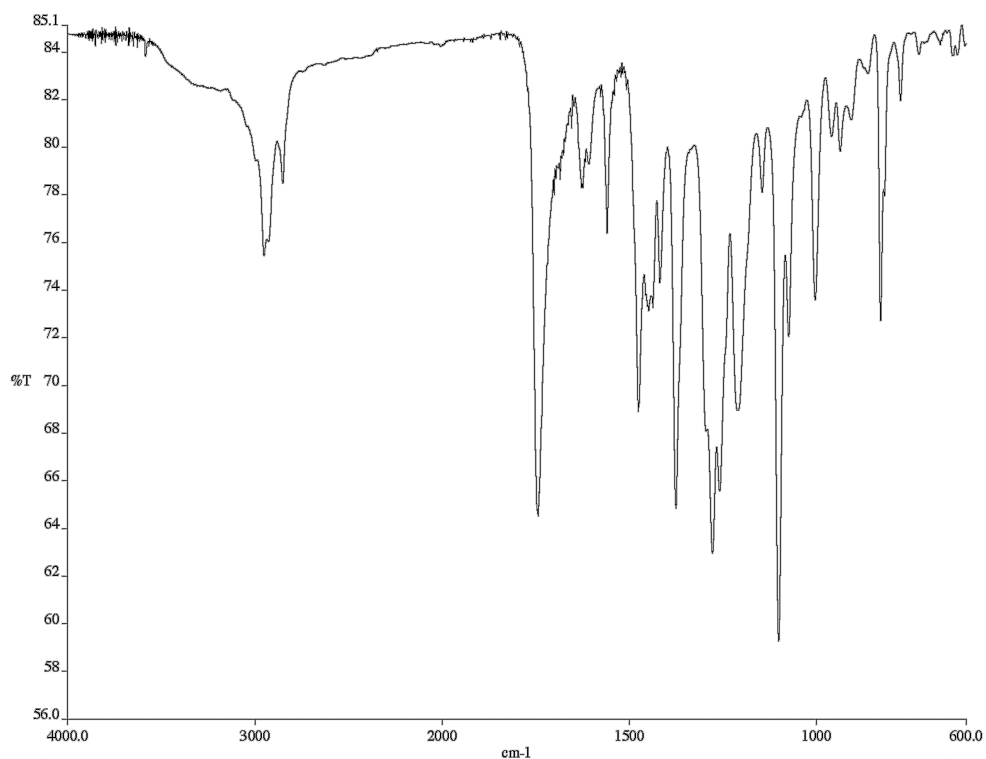
Figure A2.2.2 Infrared spectrum (thin film/NaCl) of compound **75**
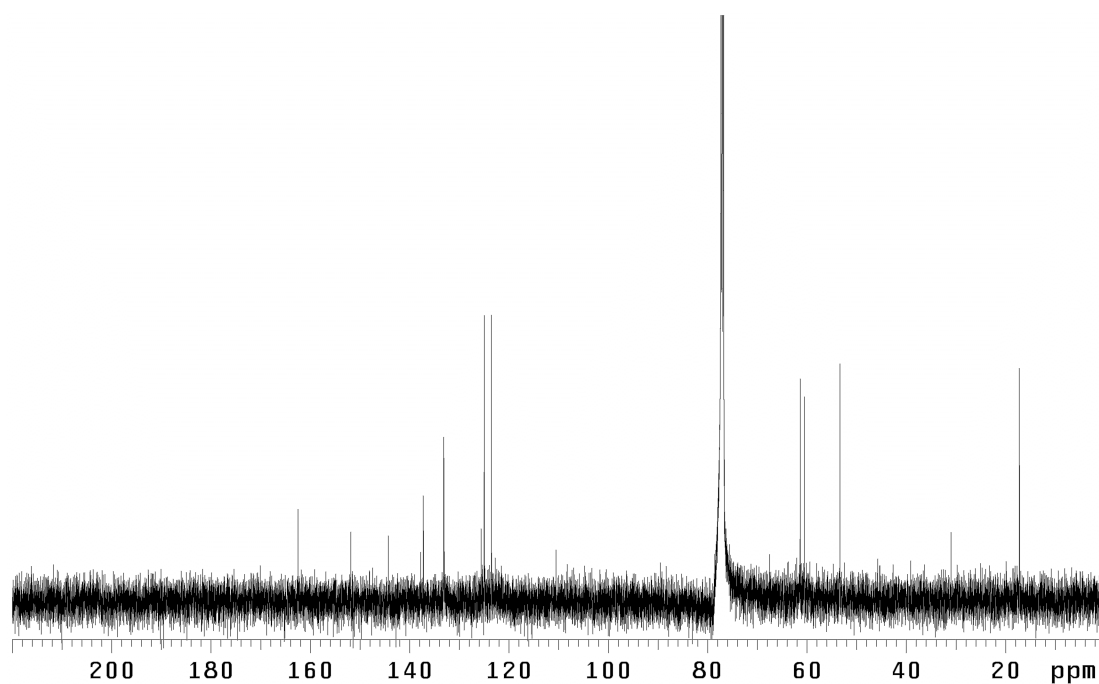
Figure A2.2.3 ^{13}C NMR (125 MHz, CDCl$_3$) of compound **75**
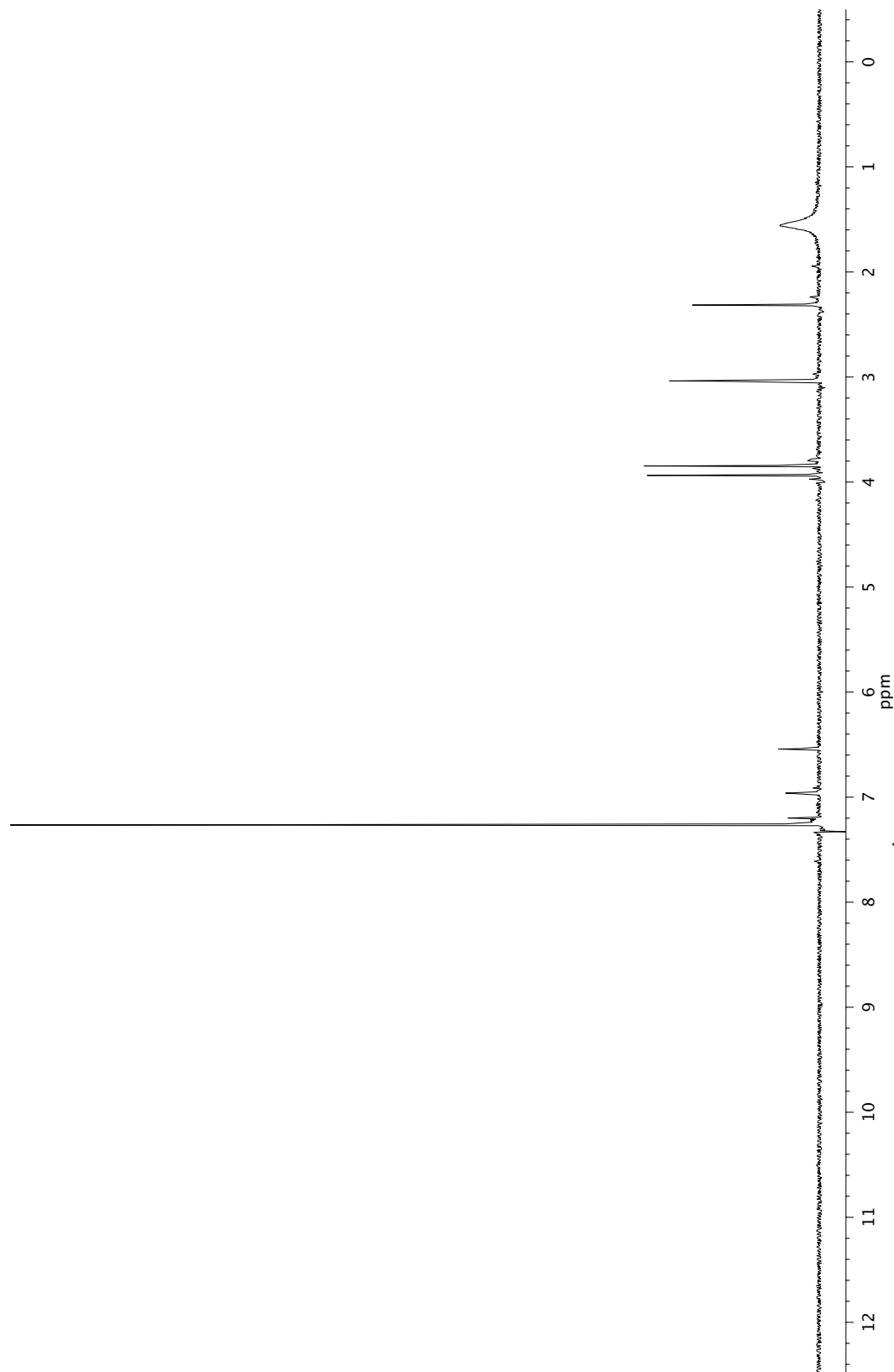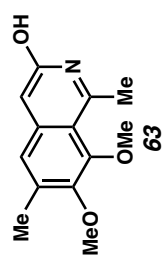
Figure A2.3.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **63**.

Figure A2.3.2 Infrared spectrum (Thin Film, NaCl) of compound **63**.
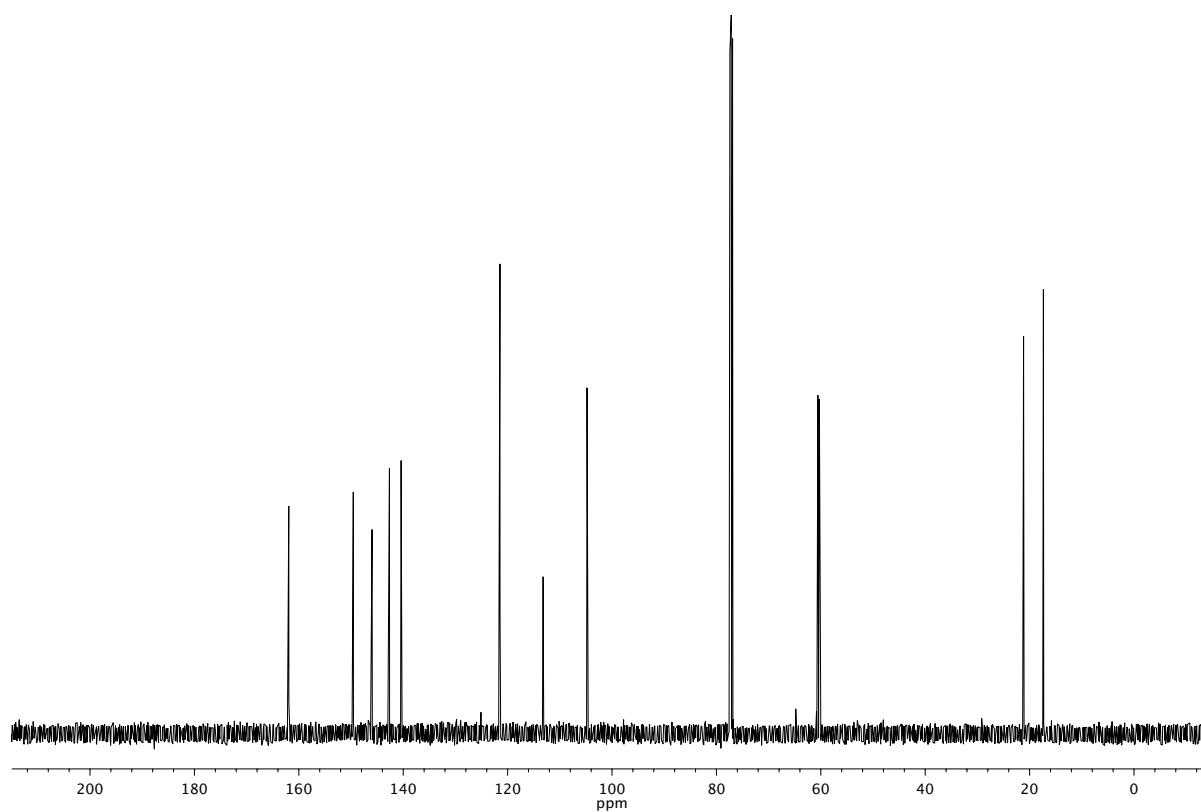
Figure A2.3.2 ^{13}C NMR (126 MHz, CDCl$_3$) of compound **63**.
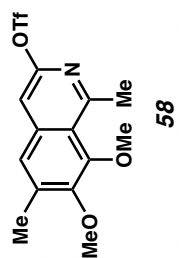
Figure A2.4.1. ^{1}H NMR (500 MHz, CDCl$_3$) of compound **58**.
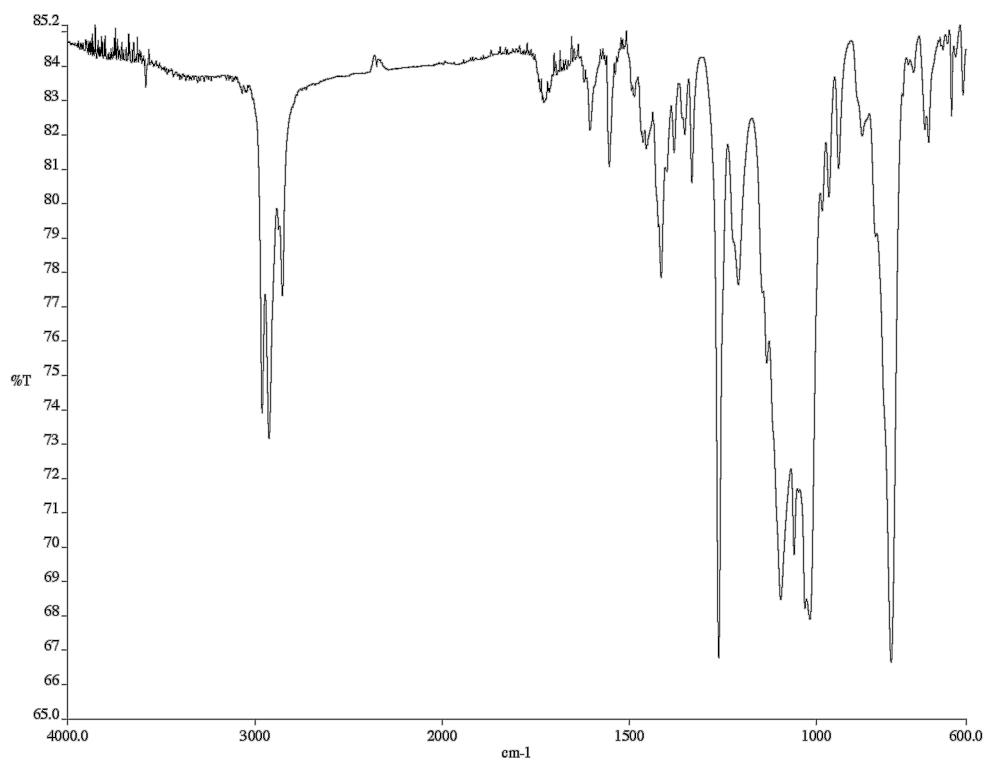
Figure A2.4.2. Infrared spectrum (thin film/NaCl) of compound **58**.
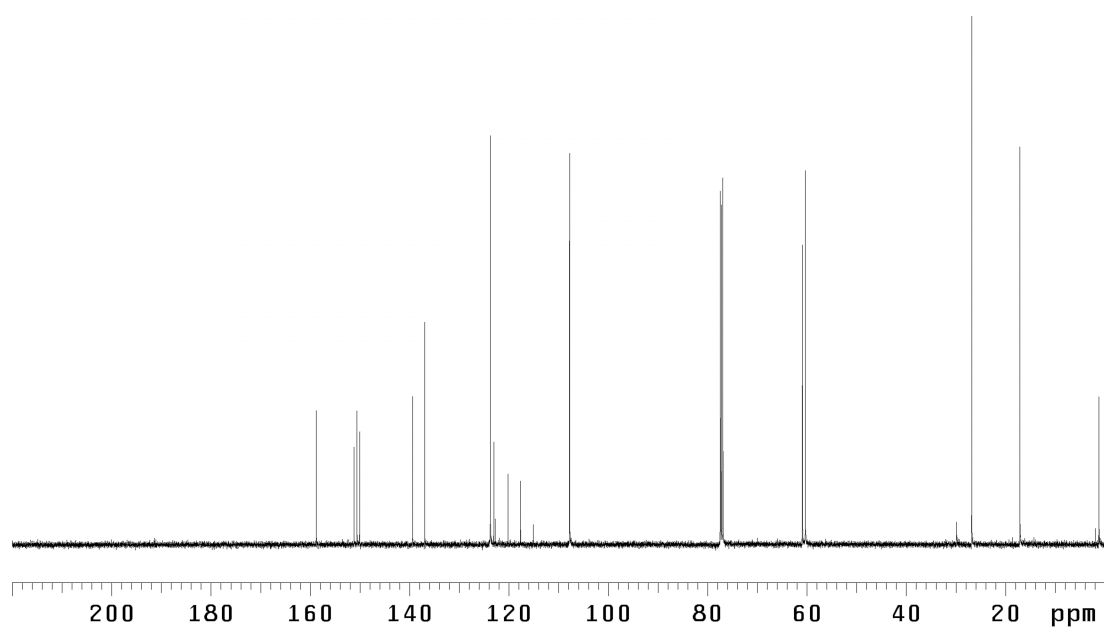
Figure A2.4.3. ^{13}C NMR (125 MHz, CDCl$_3$) of compound **58**.
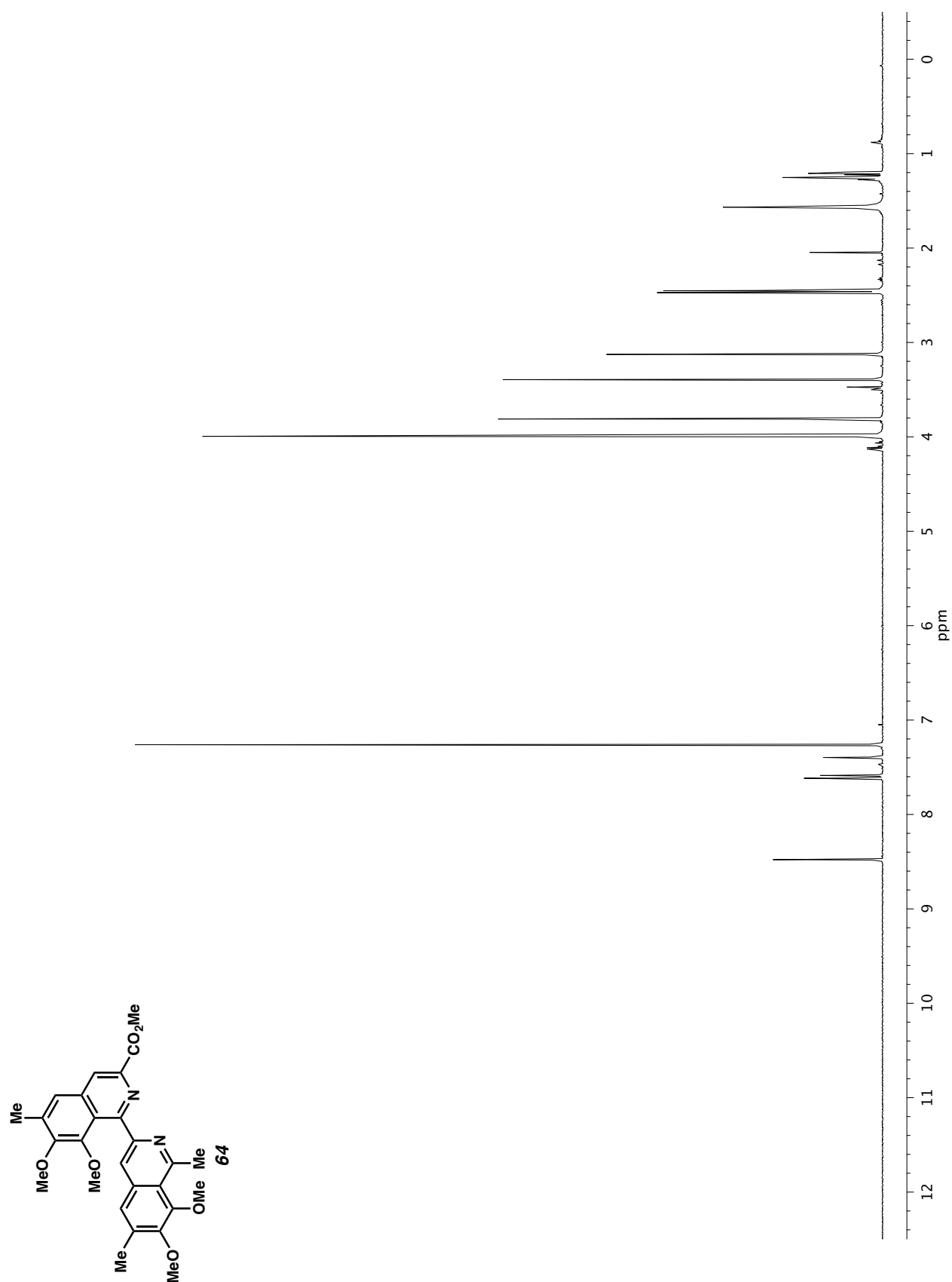
Figure A2.5.1. ^{1}H NMR (500 MHz, CDCl$_3$) of compound **64**.

Figure A2.5.2. Infrared spectrum (Thin Film, NaCl) of compound **64**.
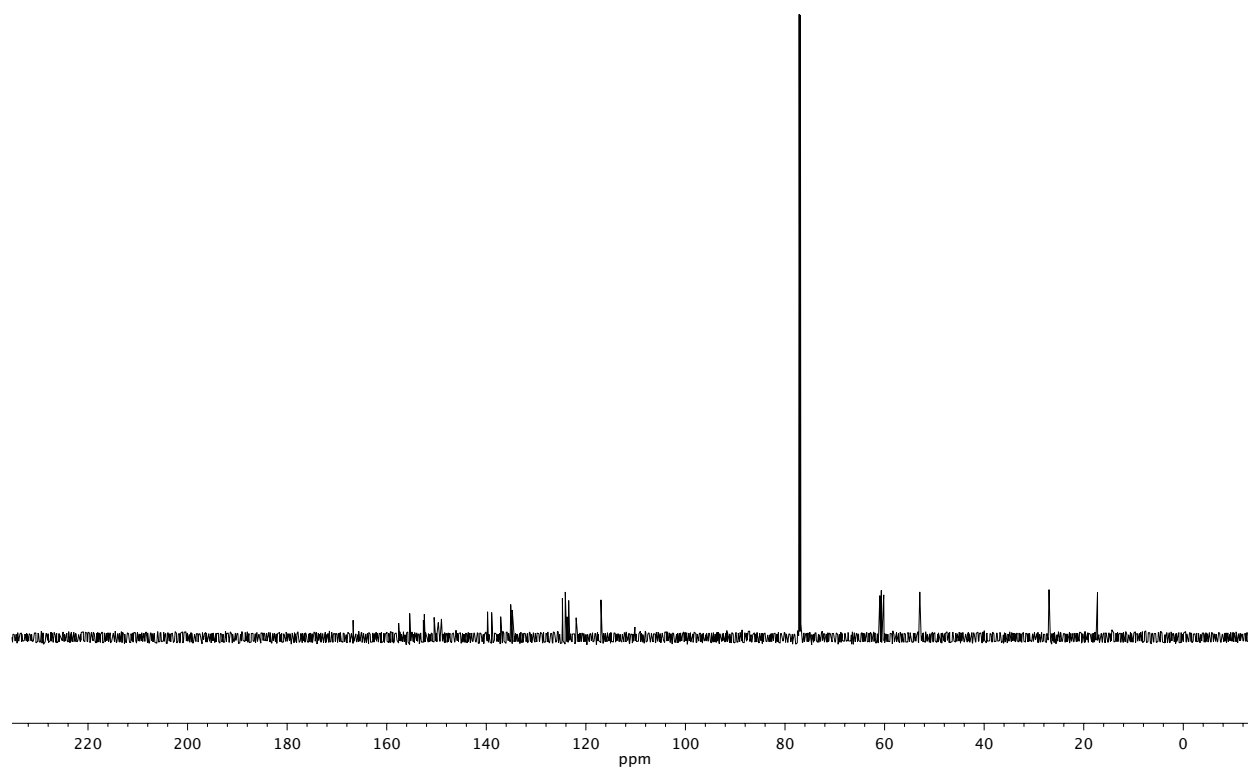
Figure A2.5.3. ^{13}C NMR (126 MHz, CDCl$_3$) of compound **64**.
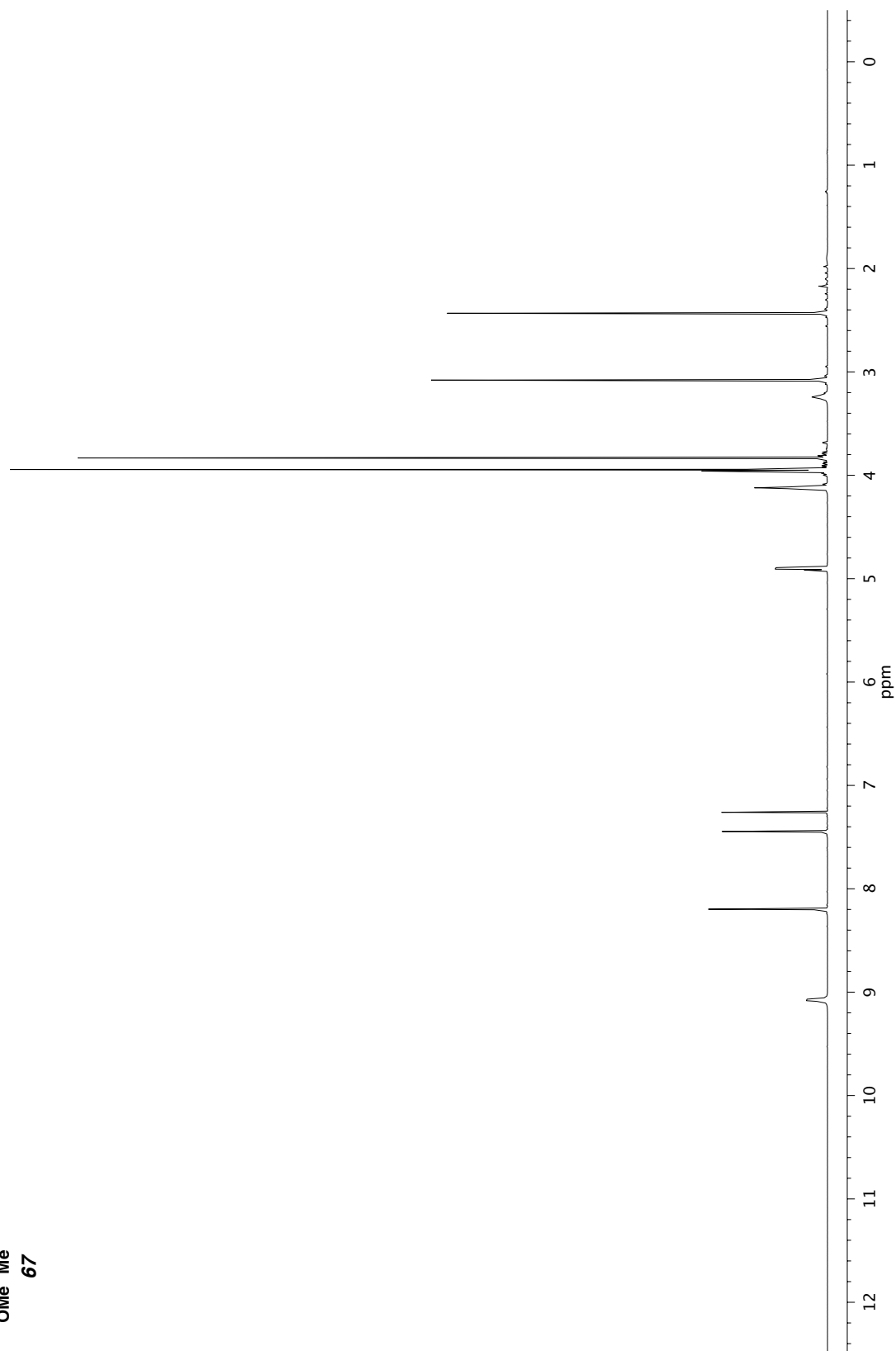
Figure 2.6.1. ^{1}H NMR (500 MHz, CDCl$_3$) of compound **67**.

Figure 2.6.2. Infrared spectrum (Thin Film, NaCl) of compound **67**.
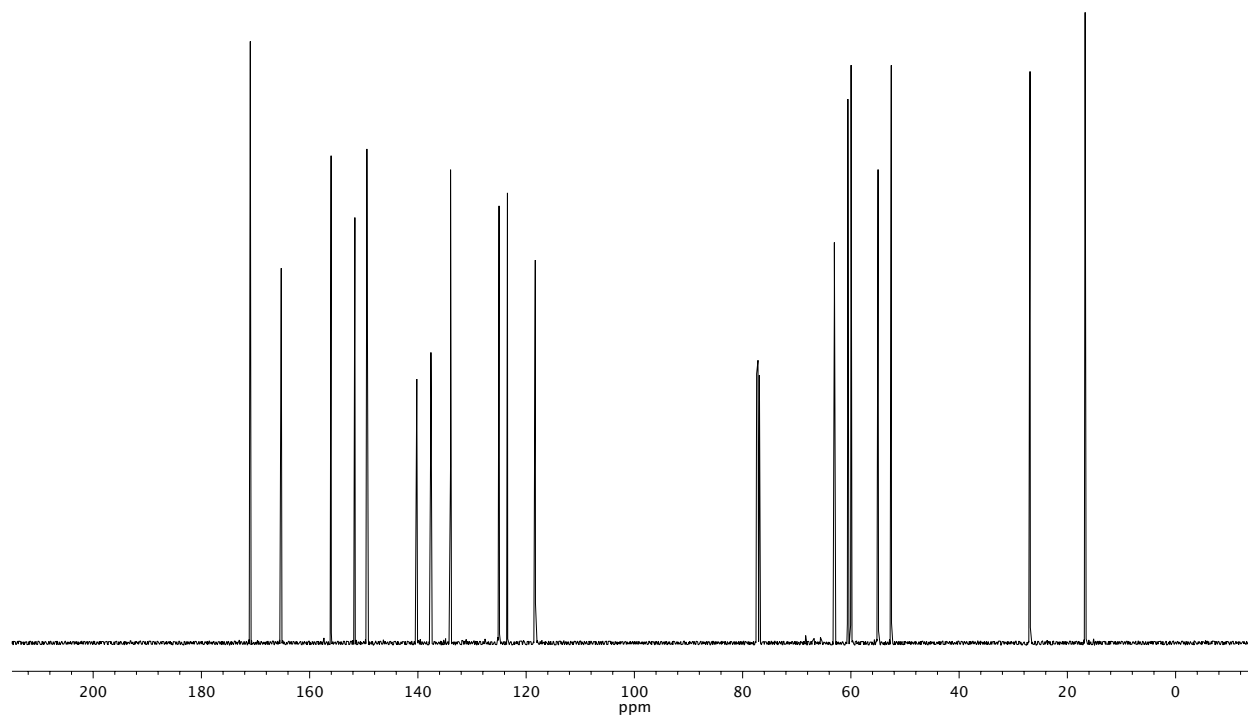
Figure 2.6.3. ^{13}C NMR (126 MHz, CDCl$_3$) of compound **67**.
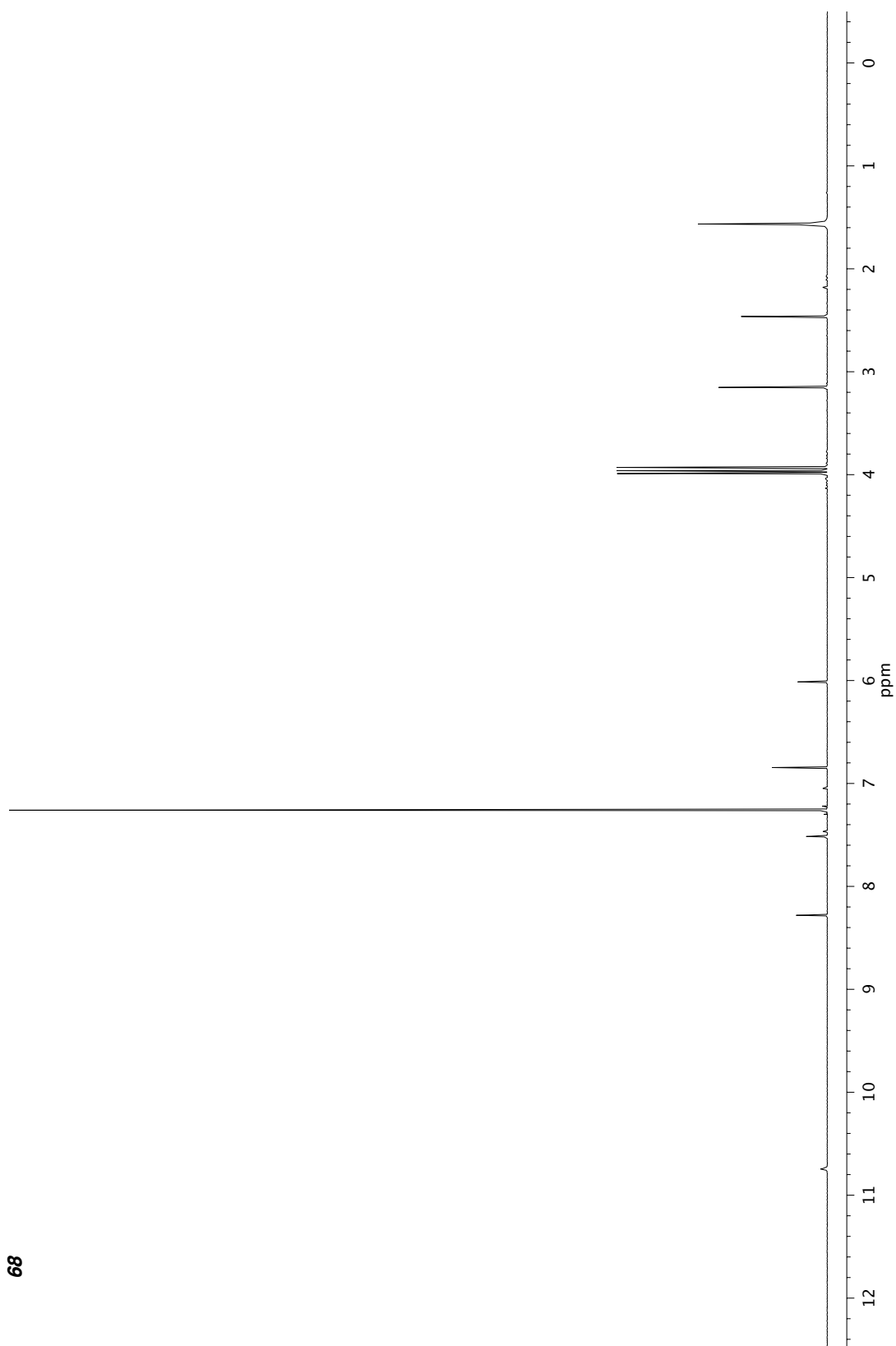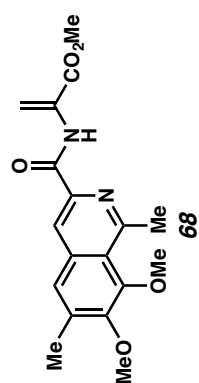
Figure A2.7.1. ^{1}H NMR (500 MHz, CDCl$_3$) of compound **68**.

Figure A2.7.2. Infrared spectrum (Thin Film, NaCl) of compound **68**.
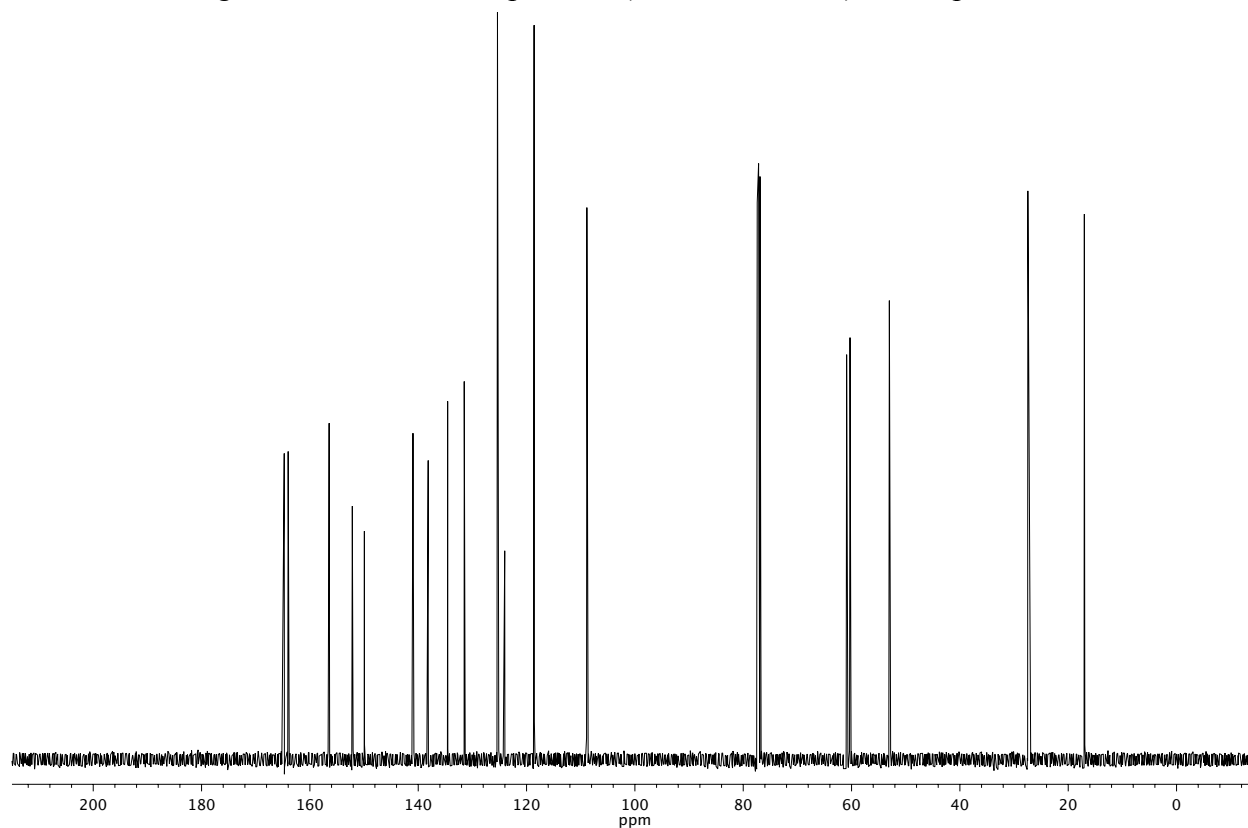
Figure A2.7.3. ^{13}C NMR (126 MHz, CDCl$_3$) of compound **68**.
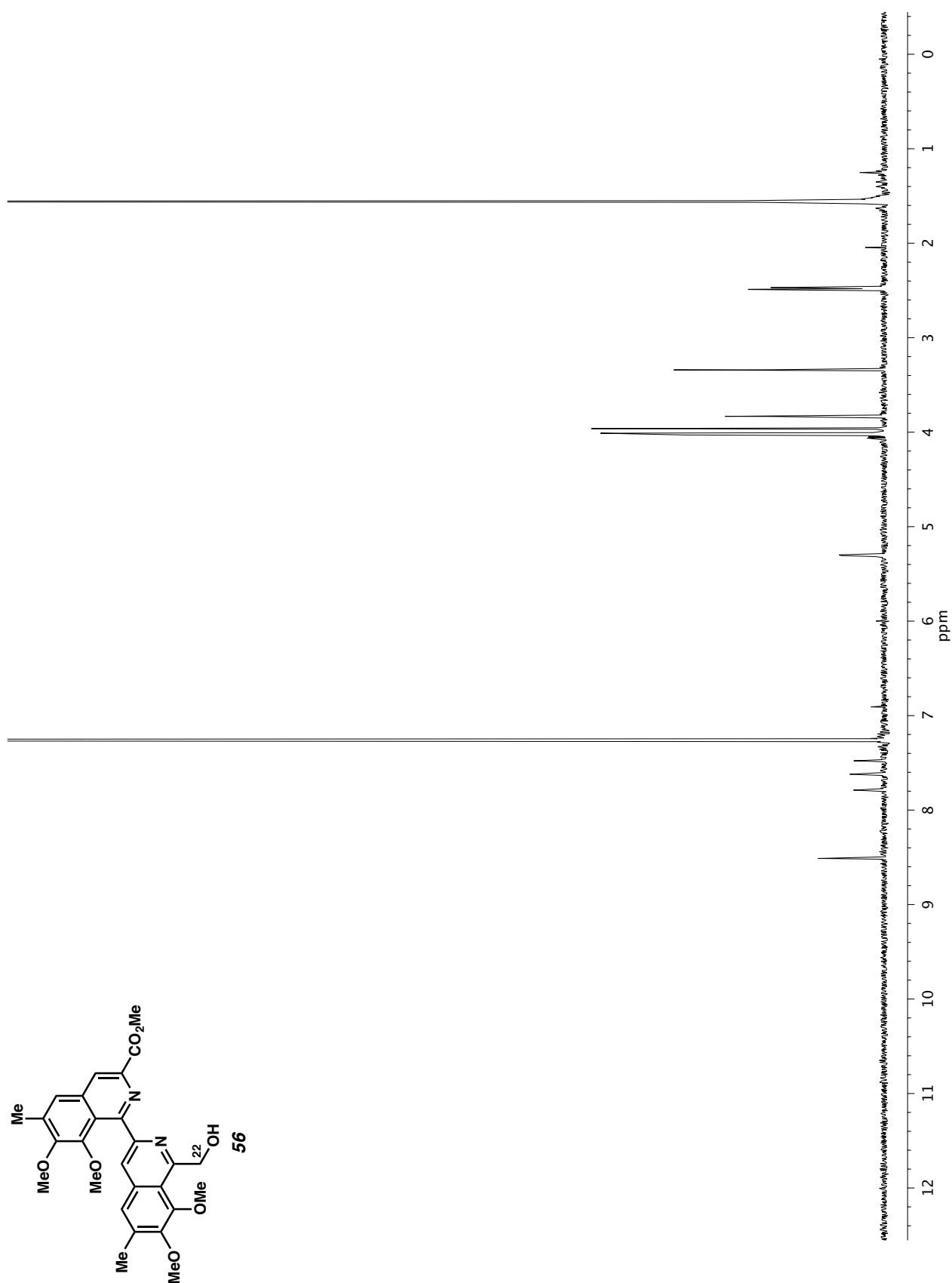
Figure A2.8.1. ^{1}H NMR (500 MHz, CDCl$_3$) of compound **87**.

Figure A2.8.2. Infrared spectrum (Thin Film, NaCl) of compound **56**.

Figure A2.8.3. ^{13}C NMR (126 MHz, CDCl$_3$) of compound **56**.

Figure A2.9.1. ^{1}H NMR (500 MHz, CDCl$_3$) of compound **73**.

Figure A2.9.2. Infrared spectrum (Thin Film, NaCl) of compound **73**.

Figure A2.9.3. ^{13}C NMR (126 MHz, CDCl$_3$) of compound **73**.

Appendix 3

A Tin-Free Route to a Complex Aryne Precursor

A3.1 Introduction and Synthesis

The synthetic sequence originally devised for the preparation of aryne precursor **59** proved to be reliable and high yielding.[1] However the third step of the route relied on the cross-coupling of 3-bromovanillin (**A2-1**) with tetramethyl tin (Scheme A3-1). While this reaction proceeded in quantitative yield, its sensitivity to oxygen and its use of a highly toxic stannane (i.e. tetramethyl tin) limited its scalability. To overcome this challenge, we developed a tin-free route to benzaldehyde **A2-4**.

Scheme A3-1. *First generation synthesis of benzaldehyde* **A2-4**.
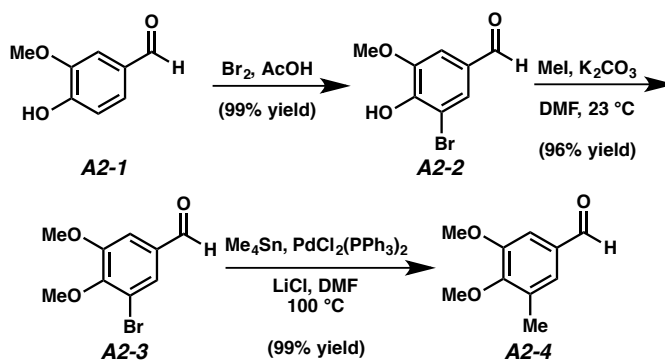
We began with the Wolff–Kishner reduction of *ortho*-vanillin (**A3-1**), which upon treatment with hydrazine monohydrate and potassium hydroxide afforded 6-methyl guaiacol (**A3-2**) in quantitative yield (Scheme A3-2). This synthetic step could be performed on 100 g (657.2 mol) scale. With 6-methyl guaiacol (**A3-2**) in hand, we sought to prepare aldehyde **A3-4** using a Duff reaction. Exposure of 6-methyl guaiacol (**A3-2**) to hexamethylenetetramine (HMTA) (**3-3**) in acetic acid furnished benzaldehyde **A3-4** in 62% yield in a regioselective manner. The Duff reaction to prepare this aldehyde could be carried out on as large as 180 g scale with without loss of yield. Methylation of phenol **A3-4** using MeI could be accomplished in 85% yield give aldehyde **A2-4**. This synthetic sequence allows us to access the identical benzaldehyde intermediate (**A2-4**) used in our first generation synthesis, however in a more scalable fashion, providing 125 g of the desired arene (**A2-4**). This material was taken forward as previously disclosed to afford aryne precursor **59** in just 4 steps and 76% yield from aldehyde **A2-4**.

Scheme A3-2. *Preparation of Benzaldehyde* **A2-4**.
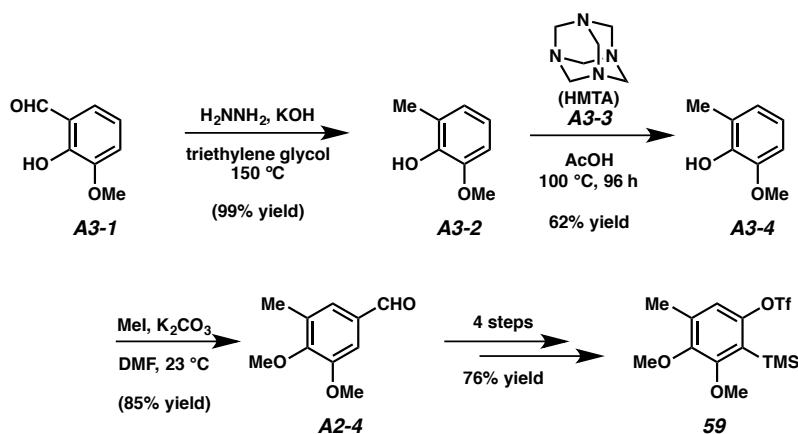
A3.2 Experimental Section

A3.2.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to CHCl$_3$ (δ 7.24). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to CHCl$_3$ (δ 77.23). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

A3.2.2 Experimental Procedures
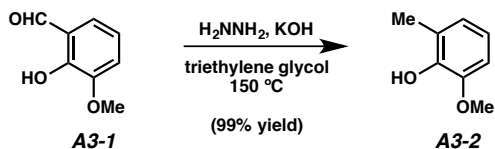
6-methyl guaiacol (A3-1)

O-vanillin (**A3-1**) (100.0 g, 0.6572 mol) was dissolved in triethylene glycol (500.0 mL) in a 3-neck round-bottom flask equipped with a reflux condenser, overhead stirrer and an internal thermometer. Hydrazine monohydrate was added (63.5 ml, 1.31 mol) dropwise through the condenser. The reaction mixture was heated to 110 °C for 10 min. After which time, the reaction was cooled to ~90 °C and KOH (228.0 g, 4.063 mol) was added portion-wise. (WARNING: Addition of KOH was exothermic and gas evolved). The orange solution was heated to 150 °C for 12 h. The reaction was then cooled to room temperature and the base neutralized (pH = 7) using NH_4Cl (aq.). This was extracted 4 times with $CHCl_3$. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and volatiles were removed in vacuo to afford 6-methyl guaiacol (**A3-2**, 90.81g, 0.6572 mol, 99% yield). Spectroscopic data were identical to literature reported values.[2]
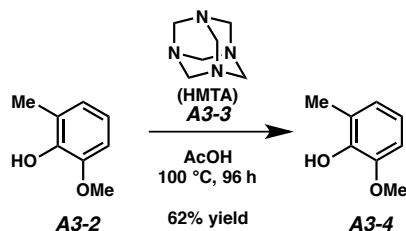
Benzaldehyde A3-4[3]

6-methyl guaiacol (**A3-2**) (181.6 g, 1.314 mol) was placed in a 12 L 3-neck round-bottom flask equipped with an overhead stirrer, temperature probe and reflux condenser to this flask was added acetic acid (6.0 L). Hexamethylenetetramine (460.5 g. 3.285 mol) was added portion-wise. A small increase in temperature was observed during addition (~8 °C). The reaction mixture was stirred and heated to an internal temperature of 100 °C using a heating mantle. It was kept at 100 °C for 96 h. The yellow/orange solution darkened to brown over the course of the reaction. At this time the heating mantle was removed and volatiles were removed in vacuo. The brown residue was split into two parts for ease of handling. Water was added to each part and extracted with CH_2Cl_2 (4 x 200 mL). The organic layers were combined and washed with brine. The organic layers were then dried over Na_2SO_4, filtered and the volatiles were removed in vacuo. The residue was filtered through a silica pad using 50% EtOAc in Hexanes. The solvent was removed in vacuo. The desired aldehyde (**A3-4**) could be recrystallized from CH_2Cl_2 (136.0 g, 0.8180 mol, 61% yield) as a tan solid. R_f = 0.36 (20% EtOAc in Hexanes); ^{1}H NMR; (500 MHz, CDCl$_3$) δ 9.80 (s, 1H), 7.31 (m, 1H), 7.29 (m, 1H), 6.28 (s, 1H), 3.96 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 191.17, 149.74, 146.70, 128.88, 128.80, 124.03, 106.68, 77.27, 77.02, 76.76, 56.21, 15.28; IR (NaCl/film) 3322, 3007, 2841, 1665, 1651, 1593, 1501, 1463, 1428, 1404, 1366, 1311, 1195, 1146, 1094, 1011, 985,

931, cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_{10}O_3$ [M+H]: 167.0703, found

167.0709.
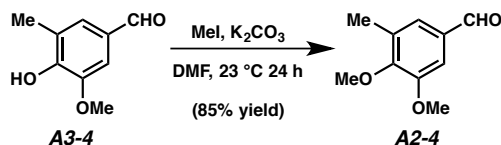
Benzaldehyde A2-4

Phenol **A3-4** (1.00 g, 6.02 mmol) and K_2CO_3 (1.22 g, 9.02 mmol) were dissolved in dry

DMF (9.0 mL)^4 in a flame-dried round bottom flask equipped with a magnetic stir bar

and a rubber septum under nitrogen atmosphere. Methyl iodide (0.450 mL, 7.22 mmol)

was added drop-wise via syringe and the reaction was stirred at ambient temperature for

24 h. At which time, 20 mL of saturated aqueous $NaHCO_3$ was added. This was then

extracted with Et_2O (3 x 25 mL). The organic layers were combined, washed with water

(2 x 25 mL), dried over Na_2SO_4, filtered and the volatiles were removed in vacuo to

cleanly afford desired benzaldehyde **A2-4** (0.918 g, 5.09 mmol, 85% yield) without need

for further purification. Spectroscopic data were identical to that reported in chapter 1 of

this thesis.

A3.3 References

1. Tadross, P. M.; Gilmore, C. D.; Bugg, P.; Virgil, S. C. Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224–1227.

2. Stevens, R. V.; Angle, S. R.; Kloc, K.; Mak, K. F.; Liu, Y. X.; Trueblood, K. N. *J.*

2. Stevens, R. V.; Angle, S. R.; Kloc, K.; Mak, K. F.; Liu, Y. X.; Trueblood, K. N. *J. Org. Chem.* **1986**, *51*, 4347–4353.

3. Razafindrabe, C. R.; Aubry, S.; Bourdon, B.; Andriantsiferana, M.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron*, **2010**, *66*, 9061–9066.

4. On large scale (>100 g), dry MeCN was used and heated to 50 °C for 24 h. Aqueous work up was not performed. Volatiles were removed in vacuo and the desired aldehyde could be recrystallized from CH_2Cl_2/hexanes.
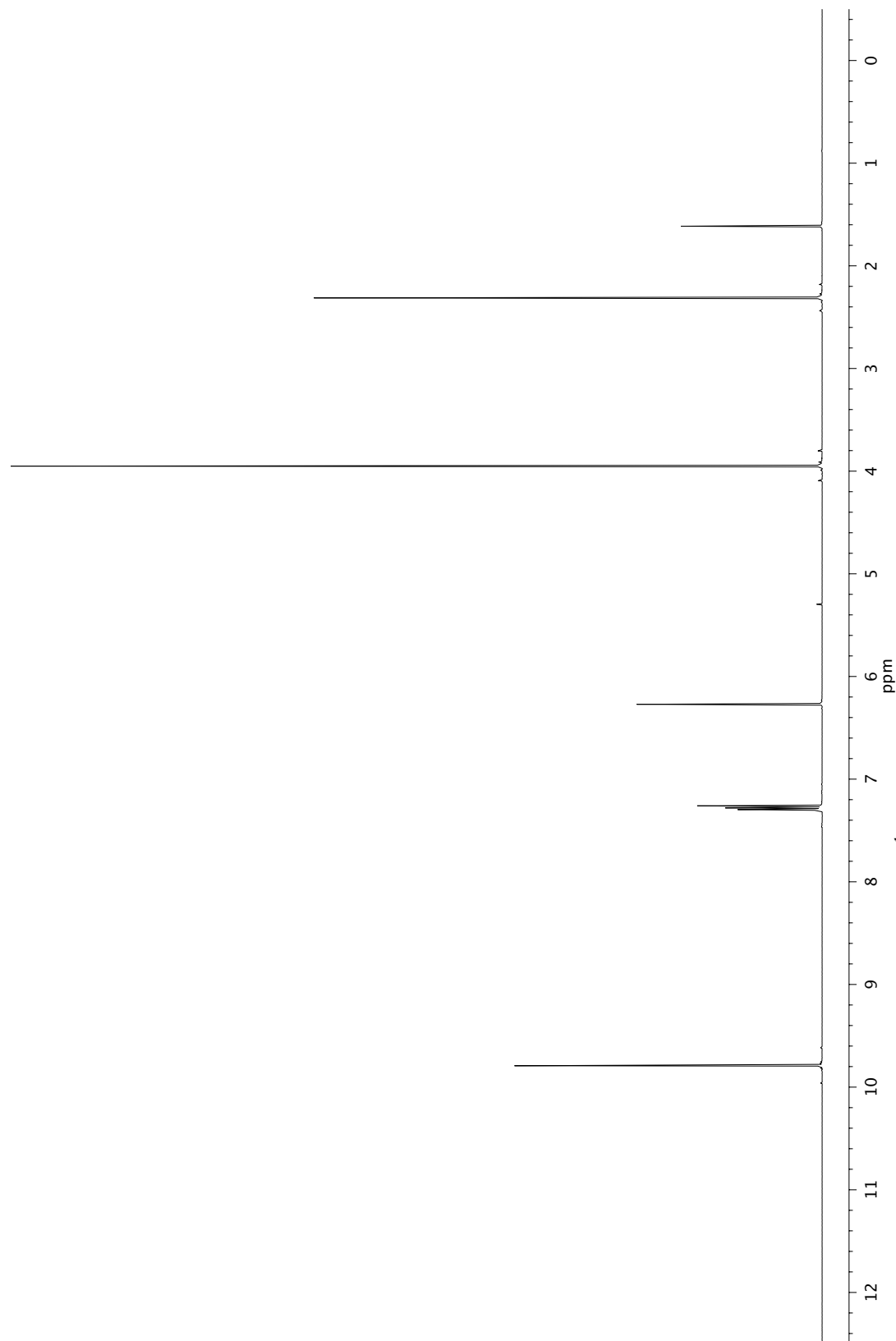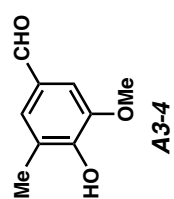
Figure A3.1.1 ^{1}H NMR (500 MHz, CDCl$_3$) of compound **A3-4**.

Figure A3.1.2 Infrared spectrum (Thin Film, NaCl) of compound **A3-4**.
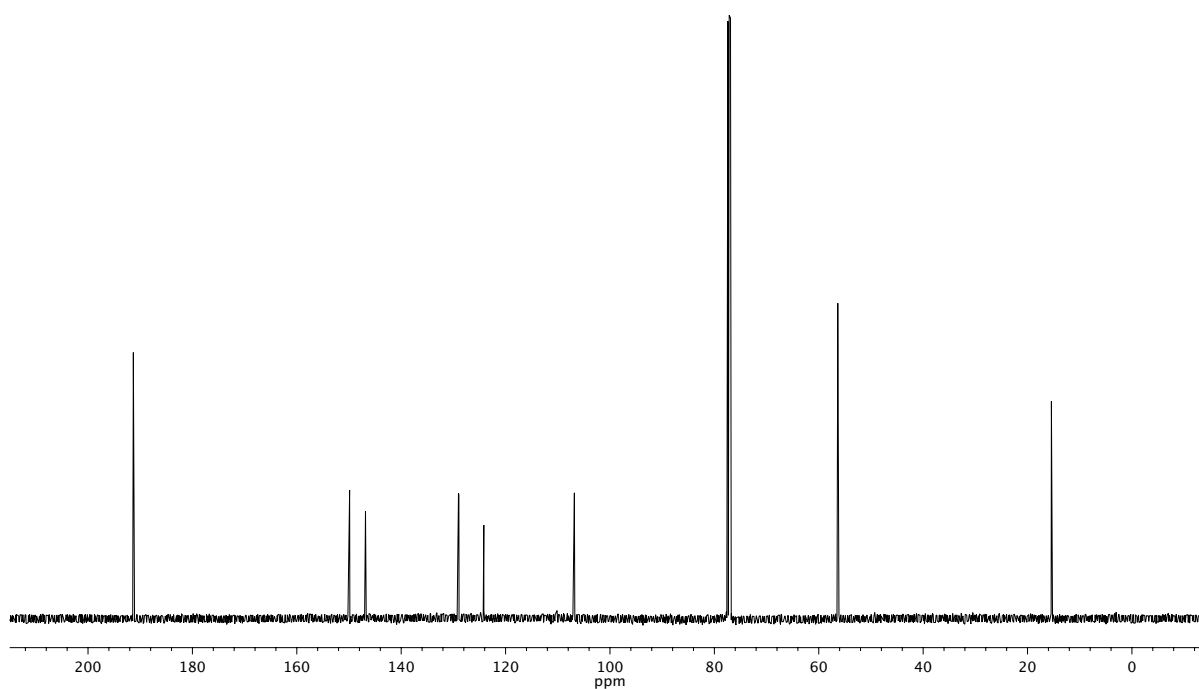
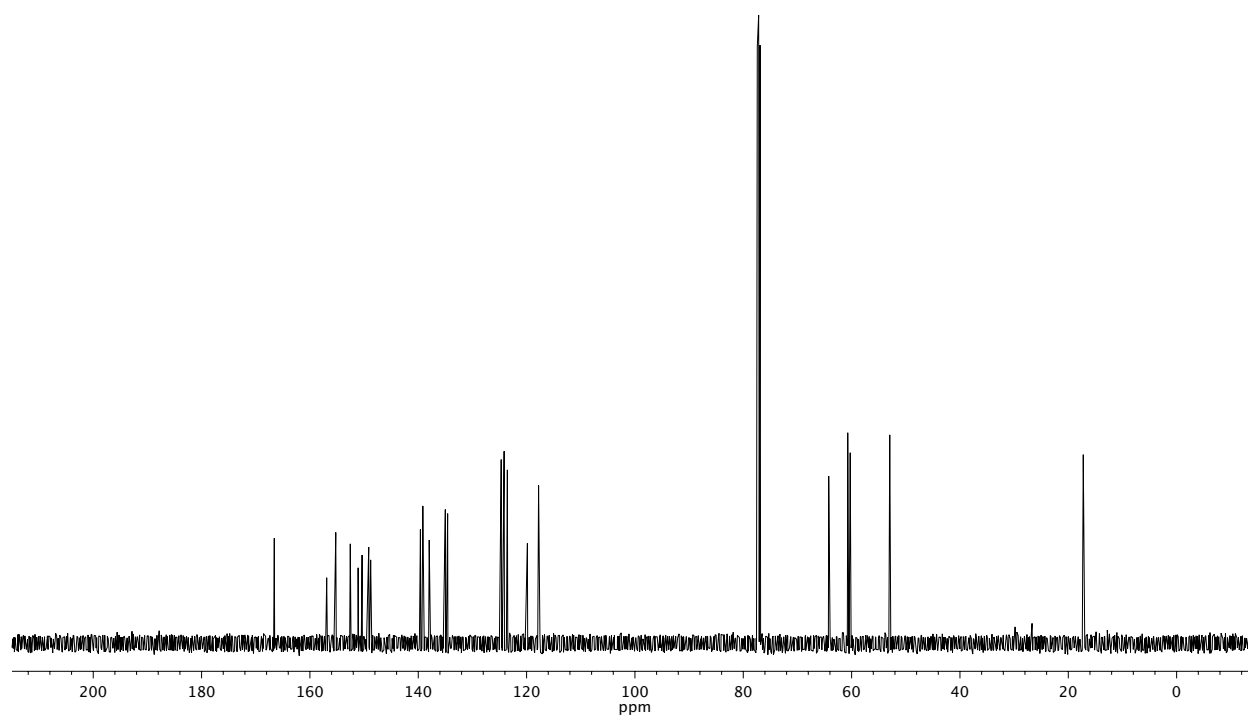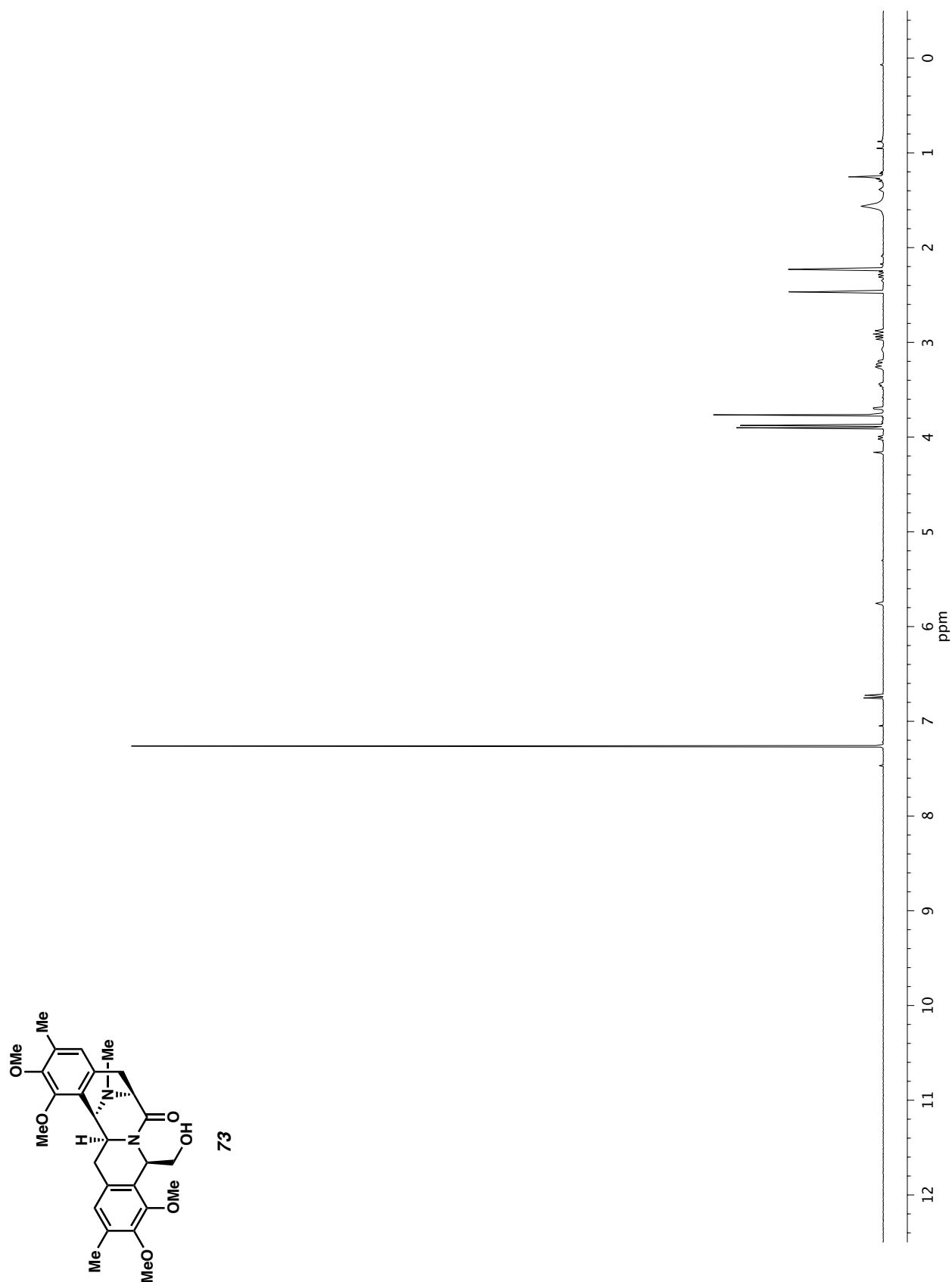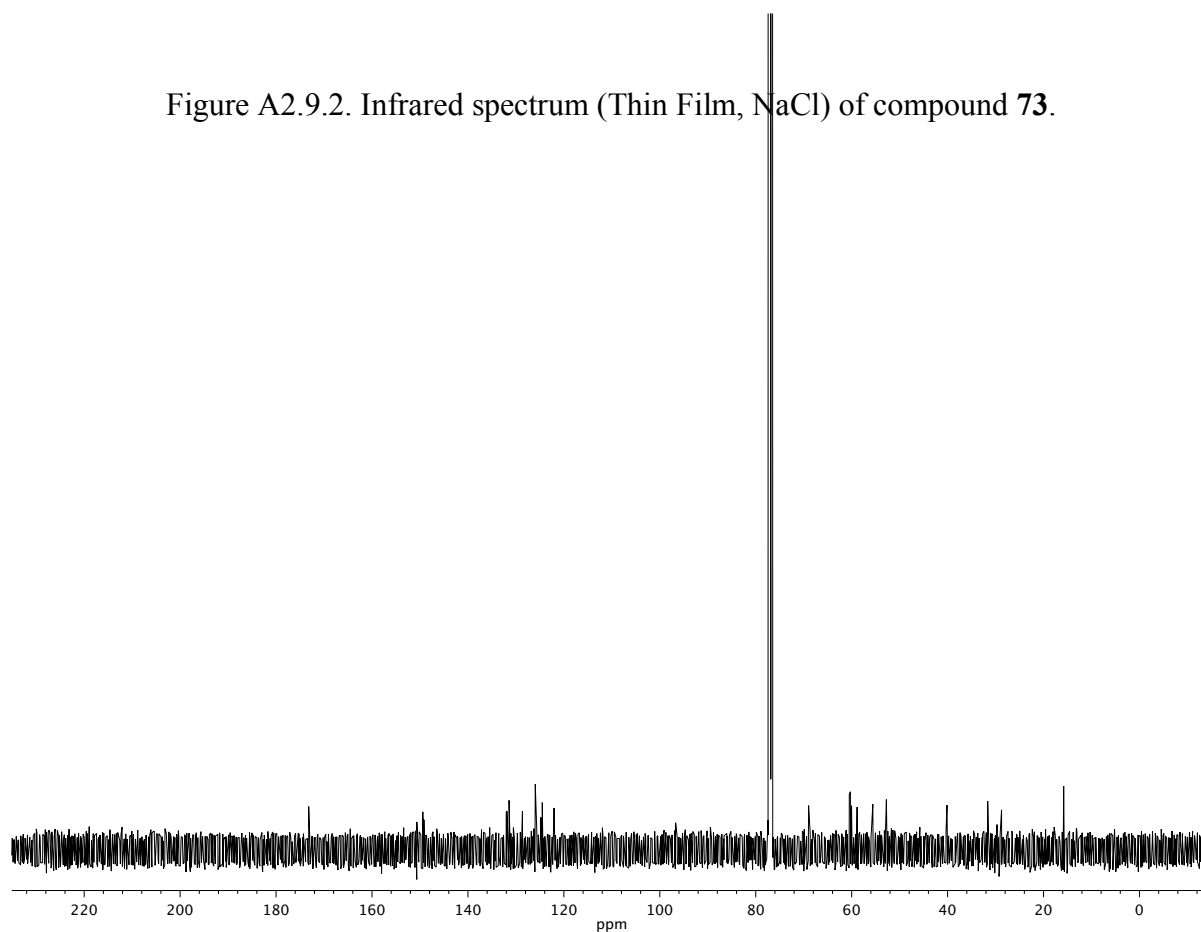Figure A3.1.3 ^{13}C NMR (126 MHz, CDCl$_3$) of compound **A3-4**.

Appendix 4

Synthetic Summary of The Total Synthesis of Jorumycin

Scheme A4-1. *Preparation of aryne precursor* **59**.
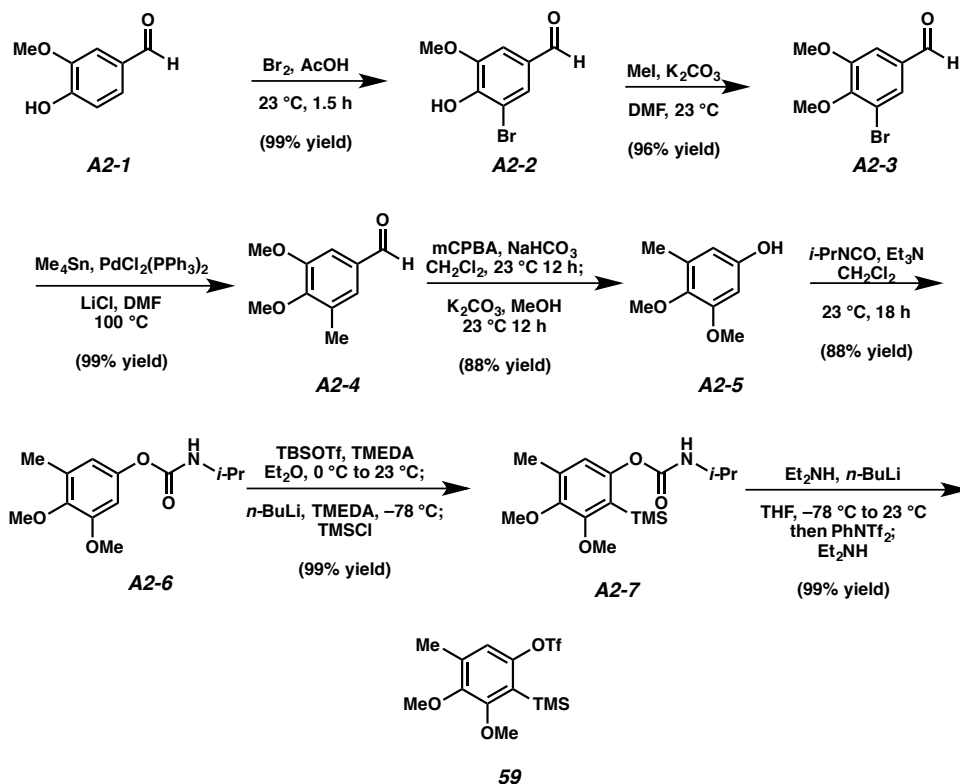
Scheme A4-2. *Aryne annulations*
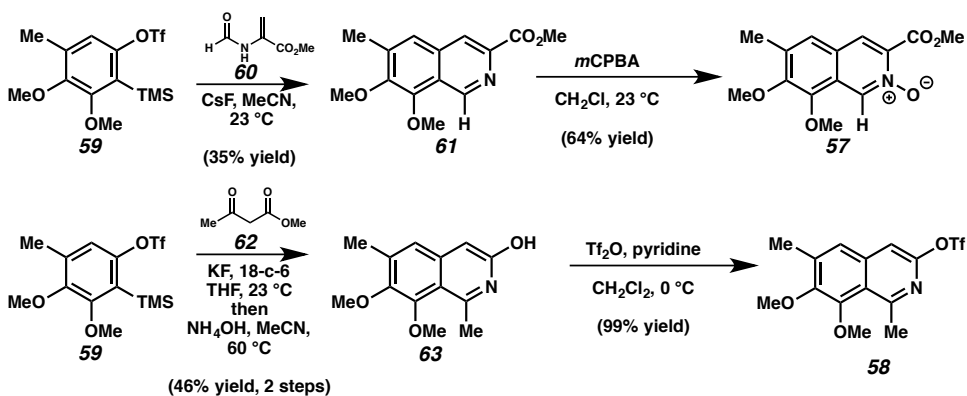
Scheme A4-3. *Cross-coupling of isoquinolines* **57** *and* **58**.
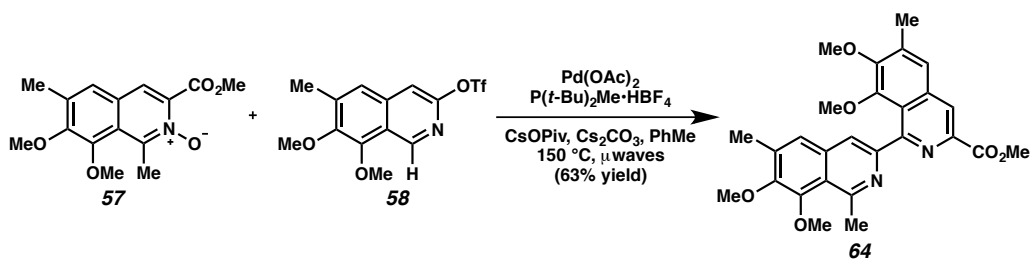
Scheme A4-4. *Alternative approach to bis-isoquinoline* **XX**.
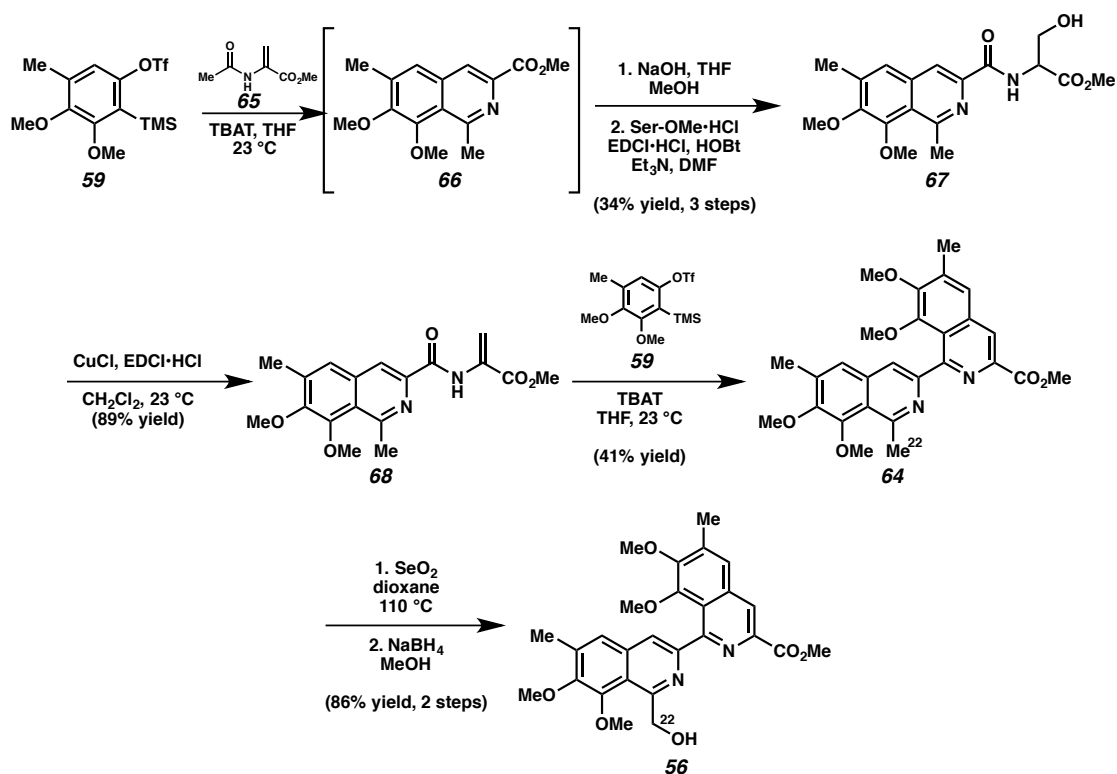
Scheme A4-5. *Origins of Diastereoselectivity for the Reduction of Bis-Isoquinoline XX.*
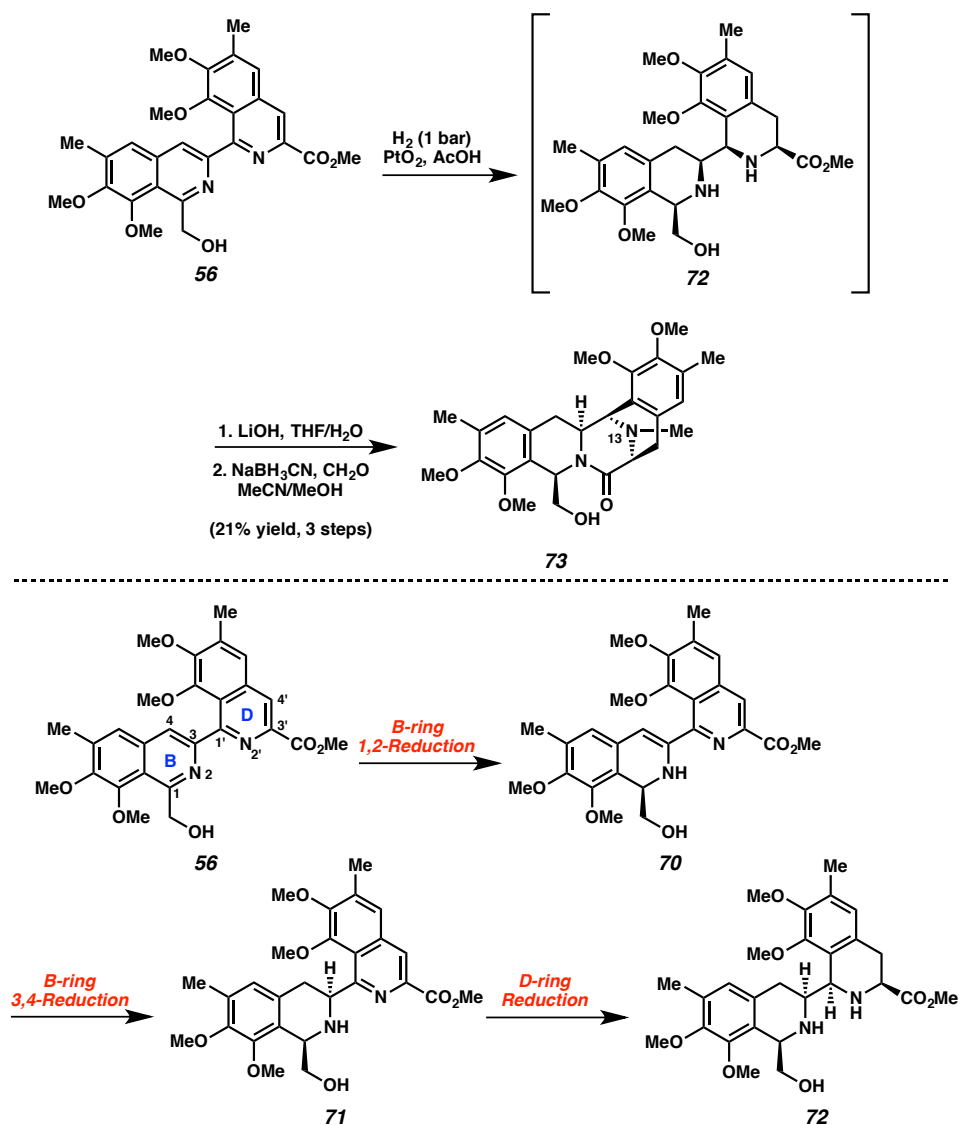
Scheme A4-6. *Completion of the Synthesis of Jorumycin.*
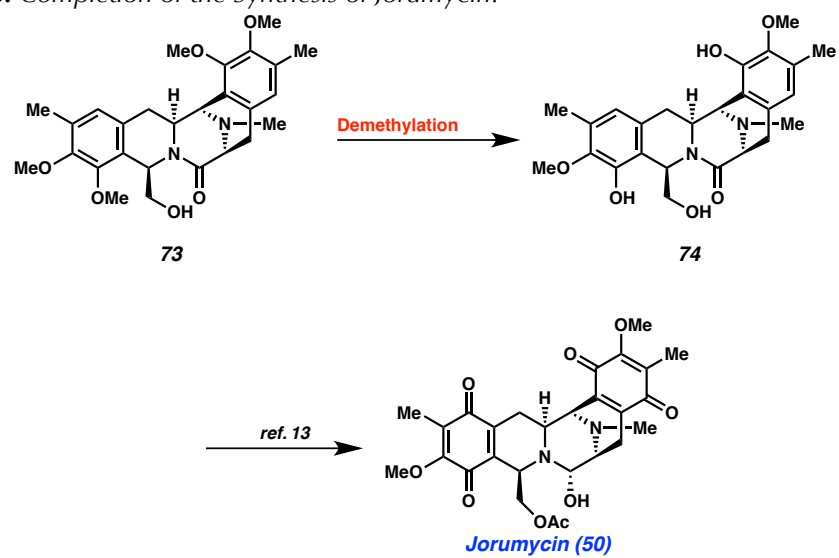
CHAPTER 3

Decarboxylative Cross-Coupling of (2-azaaryl)carboxylates with Aryl

Halides

3.1 Introduction

The 2-substituted pyridine motif (Figure 3.1), is present in a number of important small molecules,[1] however 2-azaaryl nucleophiles typically used in cross-coupling reactions, such as organozincs, Grignards, organolithiums, organostannanes, and boronic acids, are notoriously unstable and difficult to prepare.[2] While some modifications have been made to improve their synthetic viability, especially within the realm of boronic acid derivatives, these approaches are often inconvenient or produce toxic waste.[3] The development of a decarboxylative method of generating these organometallic species (e.g., **86**) in situ from (2-azaaryl)carboxylates (**85**) represents a desirable alternative to traditional aryl nucleophiles for the synthesis of 2-aryl pyridine structures (**87**) (Scheme

3.1). 2-(azaaryl)carboxylates are generally inexpensive, are stable to both air and water,

and represent a more ecologically friendly alternative to their organometallic

counterparts.

Figure 1.1. *The importance of 2-substituted pyridine.*

HIV protease inhibitor
88

MMP-13 inhibitor
89

2-pyridiyl-epothilone B
natrual product derivative
90

metal complexing ligand
91

alkaloid
from Anabasis aphylia
92
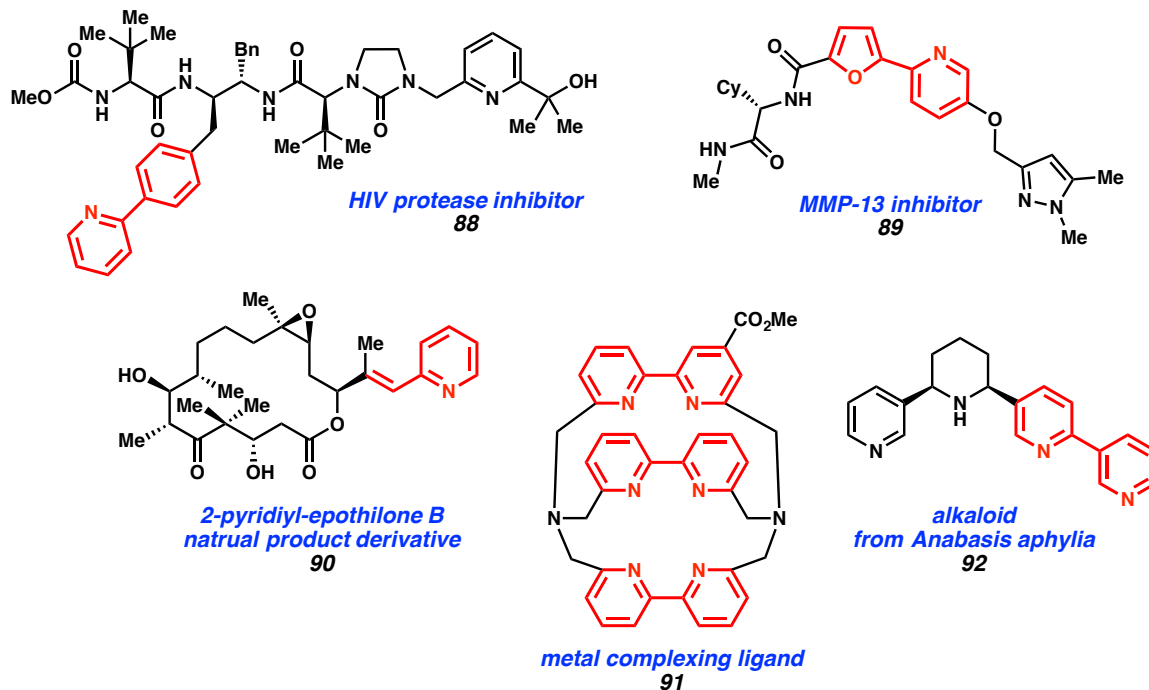
Scheme 3.1. *Decarboxylative cross-coupling of aryl carboxylic acids with aryl halides.*
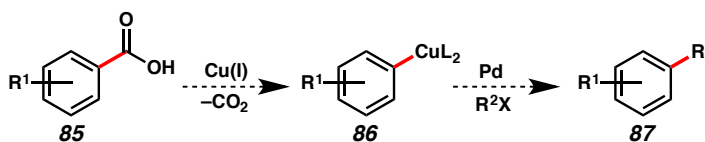
Myers and co-workers reported the first practical decarboxylative cross-coupling

in 2002,[4] a palladium-catalyzed decarboxylative Heck-type olefination (Scheme 3.2).

This work demonstrated that olefinated arenes are accessible from benzoic acids and

olefins in the presence of catalytic palladium(II) triflate and silver carbonate. This represented an important advance as it provided an alternative to aryl halides and aryl pseudo-halides usually used in Heck reactions. A critical development within the field of decarboxylative cross-coupling was reported in 2006; Goossen and co-workers disclosed a catalytic decarboxylative cross-coupling reaction, utilizing a dual-catalyst system of copper and palladium. Mechanistically, this dual catalyst approach likely proceeds through a decarboxylative cupration of the arylcarboxylate partner. The resulting aryl copper species subsequently undergoes transmetallation onto the palladium, which furnishes the coupled product through reductive elimination (Figure 3.2).[5] Unlike typical cross-couplings, which require stoichiometric aryl organometallic nucleophiles, decarboxylative couplings proceed through an in situ generation of the nucleophilic coupling partner.

A variety of non-aryl carboxylates have proven to act as efficient coupling partners in decarboxylative cross-coupling reactions,[6] including alkynes,[7] α-keto acids,[8] and 2-(2-azaaryl)acetates.[9] While these represent great advances within the field, the robust coupling of a key class of molecules, namely 2-(azaaryl)carboxylates, has been elusive. Recently, during the course of our own work on this topic, Wu and co-workers reported on the palladium-catalyzed decarboxylative cross-coupling reactions of 2-picolinic acid.[10] In light this work, we sought to supplement their studies with our own findings.

Our laboratory became interested in the cross-coupling to (2-azaaryl)nucleophiles within the context of jorumycin. We sought to prepare the bisisoquinoline **100** via a

convergent cross-coupling between two aryl fragments. Because both of our coupling partners were isoquinolines, we initiated exploration of the decarboxylative cross-coupling between 3-triflyl isoquinoline **98** and 1-carboxy isoquinoline **99** (Scheme 3.3). Owing to the importance of these motifs, we also looked to develop a general method of performing the decarboxylative cross-coupling of (2-azaaryl)carboxylates with aryl electrophiles.

Scheme 3.2. *Myers's decarboxylative olefination and Goossen's decarboxylative coupling of benzoic acids and aryl bromides.*
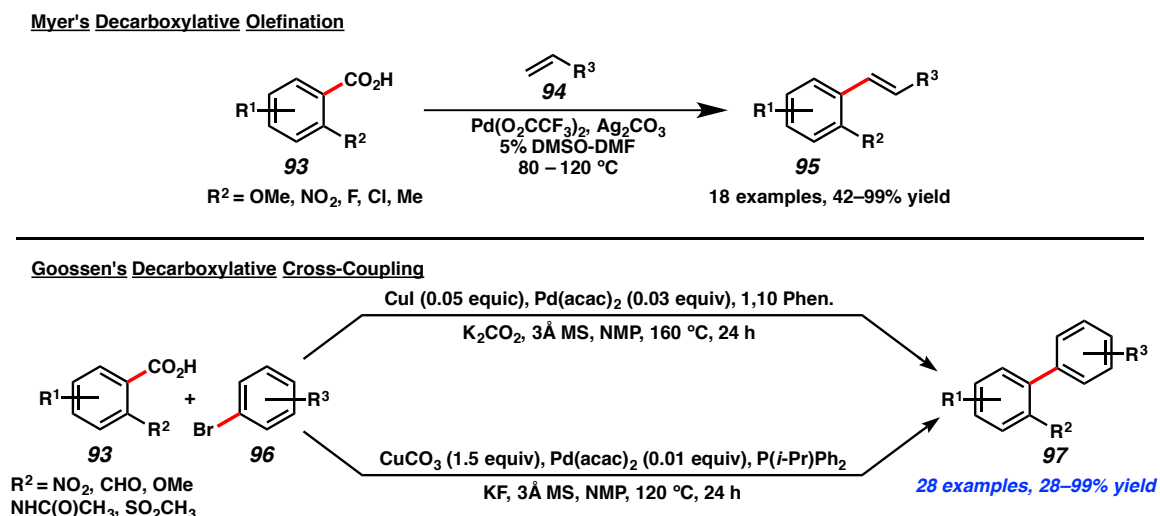
Both of the isoquinoline fragments necessary for the decarboxylative cross-coupling could be prepared utilizing methodologies developed within our laboratory which exploit the unique reactivity of arynes. Isoquinoline triflate **99** could be accessed through the acyl-alkylation of aryne-precursor **59** followed by condensation with ammonium hydroxide to afford 3-hydroxy isoquinoline **63**, which could be quantitatively triflated using triflic anhydride to furnish our electrophilic coupling partner (**98**).

Scheme 3.3. *The decarboxylative cross-coupling of two isoquinolines for the total synthesis of jorumycin.*
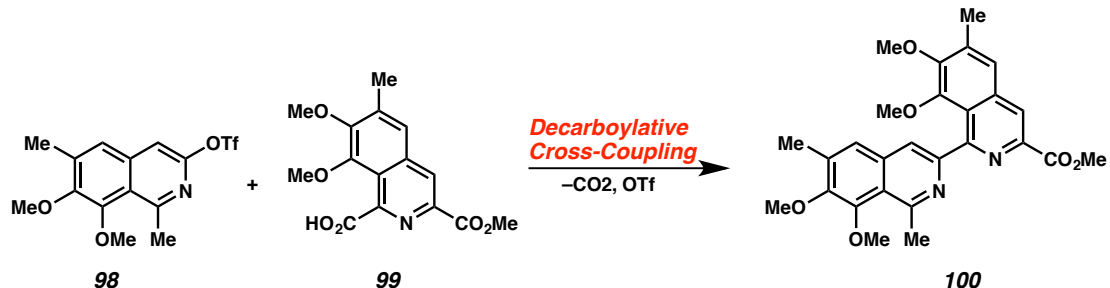
1-carboxy isoquinoline **99** was prepared using our aryne annulation methodology, in which aryne precursor **59** is treated with a fluoride source and methyl acetamido acrylate **65**. The methyl group could be selectively oxidized in a two-step protocol to the carboxylic acid (**99**). Because each of these coupling partners requires many steps to prepare, we focused our efforts on developing a more general approach to this problem.

Scheme 3.4. *Preparation of isoquinoline triflate 98 and carboxylic acid 99.*
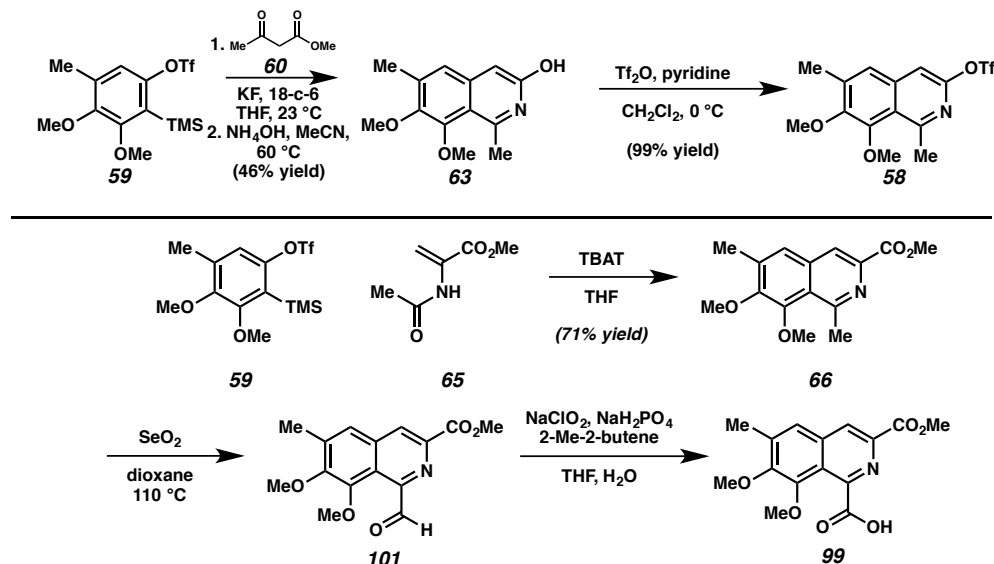
3.2 Optimization of a Decarboxylative Cross-coupling of Picolinic Acid with

Bromobenzene

To develop a general cross-coupling methodology, we selected simple substrates for optimization studies, namely picolinic acid (**102**) and bromobenzene (**103**, Table 3.1). We began our investigations by applying conditions similar to those reported by Goossen with disappointing results. (Table 3.1, entry 1). Using the same catalyst system we examined microwave irradiation and observed an increase in yield over heating in an oil bath (Table 3.1, entry 2). Similar results were disclosed by Goossen and Crabtree who independently reported enhanced yields using microwave irradiation.[11]

With these initial results in hand we set about screening palladium and copper sources. Both palladium(II) and palladium(0) sources were examined, with palladium(II) iodide providing 2-phenyl pyridine (**104**) in 36% yield (Table 3.1, entry 2). Ultimately, cuprous oxide (Cu_2O), the copper source reported by Goossen and co-workers, gave consistently higher yields than copper (I) halides (Table 3.1, entries 12–16). Importantly, for both copper and palladium sources, weakly coordinating counterions were favored. While these results were encouraging, we sought to further improve the system. Concurrent with these studies, we examined several other solvents, however were limited to high boiling solvents as a consequence of the temperatures required for the copper-catalyzed decarboxylation of picolinic acid (Table 3.1, entries 17–20).

Table 3.1. *Decarboxylative cross-coupling of picolinic acid with aryl halides.*

Entry	Cu Source	Pd Source	Solvent	Temperature (°C)	Heat Source	% Yield*
1	Cu_2O	PdI_2	NMP	170	Oil bath	6
2	Cu_2O	PdI_2	NMP	170	μwave	36
3	Cu_2O	PdI_2	NMP	120	μwave	-
4	Cu_2O	$PdCl_2$	NMP	170	μwave	9
5	Cu_2O	$PdBr_2$	NMP	170	μwave	12
6	Cu_2O	PdI_2	NMP	170	μwave	36
7	Cu_2O	$Pd(OAc)_2$	NMP	170	μwave	6
8	Cu_2O	$Pd(acac)_2$	NMP	170	μwave	8
9	Cu_2O	$Pd(TFA)_2$	NMP	170	μwave	14
10	Cu_2O	$Pd(F_6\text{-}acac)_2$	NMP	170	μwave	6
11	Cu_2O	$Pd(PPh_3)_4$	NMP	170	μwave	13
12	Cu_2O	$Pd_2(dba)_2$	NMP	170	μwave	14
13	CuCl	PdI_2	NMP	170	μwave	7
14	CuBr	PdI_2	NMP	170	μwave	16
15	CuI	PdI_2	NMP	170	μwave	31
16	CuOTf	PdI_2	NMP	170	μwave	20
17	Cu_2O(1.0eq)	PdI_2	NMP	170	μwave	7
18	Cu_2O	PdI_2	DMSO	170	μwave	12
19	Cu_2O	PdI_2	DMF	170	μwave	4
20	Cu_2O	PdI_2	NMP:Quin(1:1)	170	μwave	18
21	Cu_2O	PdI_2	Toluene	170	μwave	2

Conditions: 0.4645 mmol **102**, 1.3935 mmol **103**, 10% mol Cu, 5% mol Pd, 15% mol PPh_3, 30% mol 1,10 phen., 0.5 mL Solvent *Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard

With these copper and palladium sources, we next examined several phosphine ligands. None showed improvement over the triphenylphosphine used in our initial studies. During the course of our studies we discovered that preheating the mixture at 50 ºC for 10 minutes prior to heating to 190 ºC was advantageous. Gratifyingly, we discovered that changing from the bidentate ligand 1,10 phenanthroline to the monodentate ligand pyridine caused a substantial increase in yield (Table 3.2, entry 6).

Table 3.2. *Investigation of P- and N- ligands for the decarboxylative cross-coupling of picolinic acid*

with aryl halides.

Entry	R	Cu Source	Pd Source	Solvent	Phosphine Ligand	Nitrogen Ligand	Temperature (°C)	Heat Source	Base	% Yield*
1	H	Cu_2O	PdI_2	NMP	dppm	1,10 Phen	170	μwave	K_2CO_3	7
2	H	Cu_2O	PdI_2	NMP	dppb	1,10 Phen	170	μwave	K_2CO_3	16
3	H	Cu_2O	PdI_2	NMP	dppe	1,10 Phen	170	μwave	K_2CO_3	31
4	H	Cu_2O	PdI_2	NMP	BINAP	1,10 Phen	170	μwave	K_2CO_3	6
5	H	Cu_2O	PdI_2	NMP	PPh_3/KF	1,10 Phen	170	μwave	K_2CO_3	2
6	H	Cu_2O	PdI_2	NMP	PPh_3	Pyridine	50→190	μwave	K_2CO_3	52
7	K	Cu_2O	PdI_2	NMP	PPh_3	Pyridine	50→190	μwave	-	62
8	K	Cu_2O	PdI_2	NMP	PPh_3	2,6 Lutidene	50→190	μwave	-	46
9	K	Cu_2O	PdI_2	NMP	PPh_3	Ethyl Isonicotinate	50→190	μwave	-	49
10	K	Cu_2O	PdI_2	NMP	PPh_3	DMAP	50→190	μwave	-	56
11	K	Cu_2O	PdI_2	NMP	PPh_3	4-MeO Pyridine	50→190	μwave	-	43
12	K	Cu_2O	PdI_2	NMP	PPh_3	DABCO	50→190	μwave	-	43
13	K	Cu_2O	PdI_2	NMP	PPh_3	Et_3N	50→190	μwave	-	38
14	K	Cu_2O	PdI_2	NMP	PPh_3	Hunig's Base	50→190	μwave	-	60
15	K	Cu_2O	PdI_2	NMP	PPh_3	TMEDA	50→190	μwave	-	27
16	K	Cu_2O	PdI_2	NMP	PPh_3	$(iPr)_2NH$	50→190	μwave	-	51
17	K	Cu_2O	PdI_2	NMP	PPh_3	Quinuclidine	50→190	μwave	-	62

Conditions: 0.4645 mmol **105**, 1.3935 mmol **103**, 10% mol Cu, 5% mol Pd, 15% mol *P*-ligand, 30% mol *N*-ligand, 0.5 mL Solvent *Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard

The implementation of a pre-formed potassium picolinate salt lead to a 10% increase in yield over its in situ generated counterpart (Table 3.2, entry 7). In examining the stereoelectronics of the *N*-ligand we discovered sterically encumbered nitrogen-contain ligands proved detrimental to the yield (Table 3.2, entries 8 and 13), while both electron-rich and deficient ligands also did not improve yields. Interestingly, as observed with 1,10 phenanthroline, other bidentate ligands such as TMEDA lead to lower yields (Table 3.2, entry 15). We hypothesize the formation of a stable 18 electron copper complex (**12**) is detrimental to decarboxylation (Figure 3.3).

Scheme 3.5. *Proposed mechanism of the decarboxylative cross-coupling of picolinic acid with aryl*

halides.
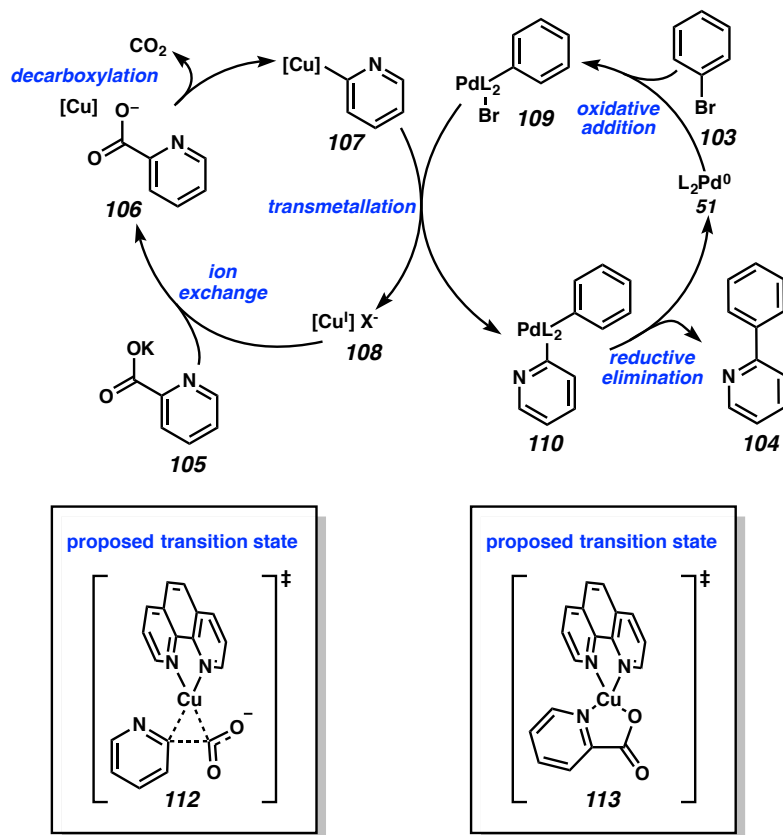
With a suitable *N*-ligand in hand we hoped to gain better insight into the influence of the

P-ligands on our catalytic system; like their nitrogen counter parts, bidentate phosphorous

ligands performed poorly under the reaction conditions (Table 3.3, entries 8 and 13). We

also reexamined copper sources, this time including copper(II) salts (Table 3.3, entries

16–20). All of these were inferior to copper(I) oxide. We investigated other counter ions

of the picolinate salts such as cesium and sodium (Table 3.3, entries 14 and 15). None of

these fared as well as potassium; confirming a trend was also observed in Goossen's

studies.

Table 3.3. *Investigation of P-ligands and copper sources for the decarboxylative cross-coupling of picolinic acid with aryl halides.*
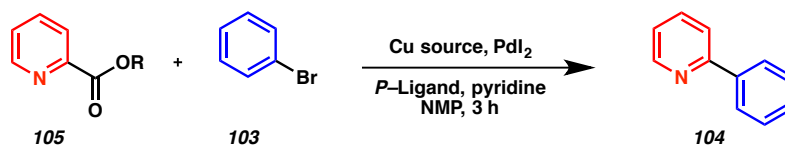
Entry	R	Cu Source	P-Ligand	% Yield*
1	K	Cu_2O	$P(o\text{-Tolyl})_3$	26
2	K	Cu_2O	$P(Cy)_3$	42
3	K	Cu_2O	$P(t\text{-Bu})_3$	21
4	K	Cu_2O	$P(2\text{-Furyl})_3$	42
5	K	Cu_2O	$P((CF_3)_2Ph)_3$	36
6	K	Cu_2O	$P(4\text{-MeO-Ph})_3$	45
7	K	Cu_2O	$P(EtO)_3$	31
8	K	Cu_2O	dppe	46
9	K	Cu_2O	Ph_2PO	49
10	K	Cu_2O	$(PhO)_2POH$	20
11	K	Cu_2O	JohnPhos	44
12	K	Cu_2O	$AsPh_3$	48
13	K	Cu_2O	BINAP	38
14	Na	Cu_2O	PPh_3	4
15	Cs	Cu_2O	PPh_3	1
16	K	Cu(OAc)	PPh_3	34
17	K	$Cu_2(CO_3)(OH)_2$	PPh_3	29
18	K	$Cu(SO_4)$	PPh_3	47
19	K	CuO	PPh_3	27
20	K	$Cu(OTf)_2$	PPh_3	31

Conditions: 0.4645 mmol **105**, 1.3935 mmol **103**, 10% mol Cu, 5% mol Pd, 15% mol *P*-ligand, 30% mol *N*-ligand, 0.5 mL NMP *Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard

One of the unproductive side-reactions of our decarboxylative cross-coupling is the formation of biphenyl through an Ullmann-type dimerization of bromobenzene. By modulating the stoichiometry of bromobenzene (**103**) we attempted to suppress the unproductive dimerization and increase cross-coupling (Table 3.4). Ultimately, reducing the equivalents of bromobenzene from 3.0 to 2.0 was slightly beneficial to our yield (Table 3.4, entry 5).

Table 3.4. *Examination of the equivalents of bromobenzene in the decarboxylative cross-coupling of picolinic acid with aryl halides.*

Entry	Bromobenzene (equiv)	% Yield*
1	3.0	62
2	2.0	65
3	1.0	55
4	0.75	57

Conditions: 0.4645 mmol **105**, X mmol **103**, 10% mol Cu_2O, 5% mol PdI_2, 15% mol PPh_3, 30% mol pyridine, 0.5 mL NMP **Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard
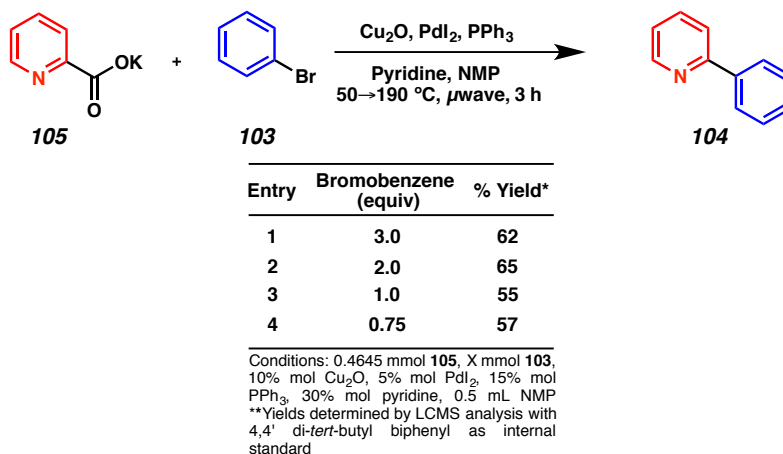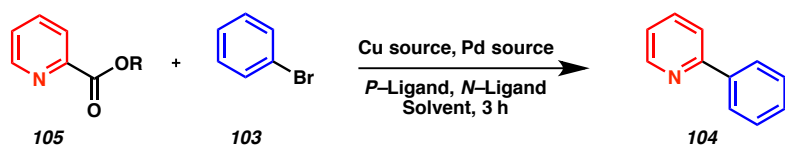
Concurrent to these studies, we examined the impact of reaction times on the yield of our cross-coupling. Though a reaction time of 8 hours provided the highest yield of 2-phenylpyridine at 72%, it represented only a marginal improvement over shorter times (Table 3.5).

Table 3.5. *Examination of reaction time in the decarboxylative cross-coupling of picolinic acid with aryl halides.*

Entry	Time (h)	% Yield*
1	0.5	15
2	1.0	38
3	2.5	64
4	4	62
5	5	69
6	8	72

Conditions: 0.4645 mmol **105**, 0.929 mmol **103**, 10% mol Cu_2O, 5% mol PdI_2, 15% mol PPh_3, 30% mol pyridine, 0.5 mL NMP **Yields determined by LCMS analysis with 4,4' di-*tert*-butyl biphenyl as internal standard
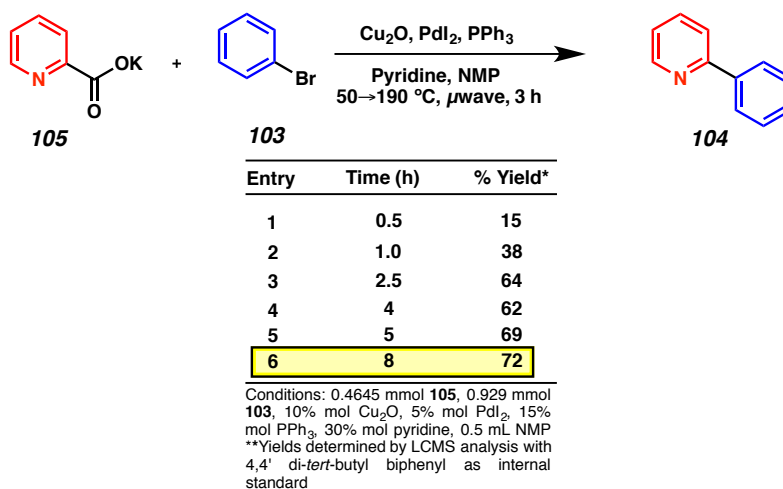
In order to better understand the reaction mechanism, we performed a series of control experiments in which we omitted each of the reagents. We discovered pyridine was not able to facilitate the necessary deprotonation of picolinic acid in situ (Table 3.6, entry 1). Omission of triphenylphosphine substantially decreased the yield of 2-phenyl pyridine (**10**) (Table 3.6, entry 2). Both copper and palladium proved crucial for our reaction; removal of either metal lead to little or no reactivity (Table 3.6, entries 3 and 4). Ultimately, pyridine was not necessary to facilitate the reaction (Table 3.6, entry 5). However this is most likely due to an unproductive protodecarboxylative side reaction that produces pyridine from picolinic acid. 2-Phenylpyridine is a common substrate for functional group directed C–H activation and can serve as a ligand for copper or palladium.[12] Consequently, we explored the possibility of product inhibition. However, yields were not effected by addition of 2-phenylpyridine to the reaction (Table 3.6, entry 6), ruling out this inhibitory interaction.

Table 3.6. *Control experiments for the decarboxylative cross-coupling of picolinic acid with aryl halides.*

Entry	R	Cu Source	Pd Source	Solvent	Phosphine Ligand	Nitrogen Ligand	Temperature (°C)	Heat Source	Addative	% Yield*
1	H	Cu$_2$O	PdI$_2$	NMP	PPh$_3$	pyridine	50→190	µwave	Pyridine	5
2	K	Cu$_2$O	PdI$_2$	NMP	-	pyridine	50→190	µwave	-	22
3	K	-	PdI$_2$	NMP	PPh$_3$	pyridine	50→190	µwave	-	9
4	K	Cu$_2$O	-	NMP	PPh$_3$	pyridine	50→190	µwave	-	0
5	K	Cu$_2$O	PdI$_2$	NMP	PPh$_3$	-	50→190	µwave	-	62
6	K	Cu$_2$O	PdI$_2$	NMP	PPh$_3$	pyridine	50→190	µwave	2-phenyl pyridine	65

Conditions: 0.4645 mmol **105**, 0.929 mmol **103**, 10% mol Cu$_2$O, 5% mol PdI$_2$, 15% mol PPh$_3$, 30% mol pyridine, 0.5 mL NMP **Yields determined by LCMS analysis with 4,4' di-tert-butyl biphenyl as internal standard

3.3 The cross-coupling of (2-azaaryl)carboxylates with aryl halides

With our best conditions to date identified, we turned our attention to examination of the substrate scope of the decarboxylative cross-coupling (Figure 4). Electronically neutral aryl halides (**104** and **117**) performed well under the reaction conditions. Both electron rich and electron deficient aryl halides fared modestly (**118** and **119**). One of the major byproducts of reactions using electron deficient aryl bromides was an Ullmann-type coupled product. Heteroaromatic halides produced coupled products in disappointingly low yields (**123** and **124**). Most interestingly, other (2-azaaryl)carboxylates performed well under the reaction conditions (**125** and **126**).

Table 3.7. *The decarboxylative cross-coupling of picolinic acid with aryl halides.*

Conditions: 0.4645 mmol **114**, 0.929 mmol **115**, 10% mol Cu$_2$O, 5% mol PdI$_2$, 15% mol PPh$_3$, 30% mol pyridine, 0.5 mL NMP, *isolated yields

Lastly, attempts to perform the decarboxylative cross-coupling within the context of our synthesis of jorumycin proved unfruitful, resulting mainly in the proto-decarboxylation of carboxy isoquinoline **99**.

3.4 Conclusion

Decarboxylative coupling is an attractive alternative to traditional cross-coupling reactions. The starting materials are stable and inexpensive, and the byproducts of these reactions are less toxic and easier to dispose of than traditional organometallic reagents and boronic acids. 2-metallated heteroarenes are particularly unstable, difficult to prepare and expensive. Herein we have reported an approach to circumvent the need to use these undesirable reagents. We have shown that 2-(azaaryl)carboxylates can be effectively used in decarboxylative cross-coupling reactions with aryl halides to furnish 2-(azaaryl)arenes, a motif present in a wide variety of important small molecules.

3.5 EXPERIMENTAL SECTION

Spectral data for compounds **104**, **117**, **118**, **119**, **120**, **121**, **122**, **123**, **124**, **125** and **126** were consistent with previously reported data.[10,13, 14]

A representative procedure for the decarboxylative cross-coupling of (2-azaaryl)carboxylates with aryl halides:

2-phenylpyridine (104) The potassium salt of picolinic acid (**105**) (74.9 mg, 0.464 mmol), PPh$_3$ 18.3 mg (0.0697 mmol) PPh$_3$, 8.4 mg (0.046 mmol) PdI$_2$, and 6.6 mg (0.046 mmol) Cu$_2$O were added to a flame-dried 2.0 mL microwave vial equipped with a spin vane. The vial was sealed, evacuated and back-filled with argon (3 times). 0.50 mL NMP (degassed with Ar, >10 min.) and 97.6 µL (0.929 mmol) bromobenzene (**103**) were added sequentially via syringe. The mixture was stirred at room temperature for 10 min. The mixture was then irradiated in the microwave, with a 90 s prestirring period followed by 10 min at 50 °C and increase in temperature to 190 °C. The reaction was heated at this temperature for 6 h. The crude mixture was purified on a silica column.

3.6 References

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Appendix 5

The Ring-Expansive Acyl-Alkylation of Arynes

A5.1 Introduction

The ring-expansive direct acyl alkylation of arynes has been successfully showcased in the total synthesis of a number of natural products to date by the Stoltz group, including (+)-amurensinine (**A5-5**) and (–)-curularin (**A5-10**).[1,2] The 2006 synthesis of (+)-amurensinine began with the acyl-alkylation of an aryne generated in situ from sesamol-derived silyl aryl triflate **A5-1**, with benzannulated β-ketoester **A5-2**, resulting in direct access of the tetracyclic core **A5-3** (Scheme A5.1). The synthesis was completed in 11 additional steps. Subsequent to this work, the benzannulated macrolactone (–)-curularin was completed in 6 steps from known compounds (Scheme A5.2). Lactone **A5-9** was prepared via ring-expansive acyl-alkylation from unsymmetrical aryne precursor **A5-5** and chiral 10-membered lactone **A5-7**. Debenzylation revealed the resorcinol core, completing the total synthesis. These two

syntheses highlight the utility of acyl-alkylation and its ability to rapidly prepare complex

benzannulated motifs within the context of natural product total synthesis.

Scheme A5.1. *Total synthesis of (+)-amurensinine (**A5-5**).*
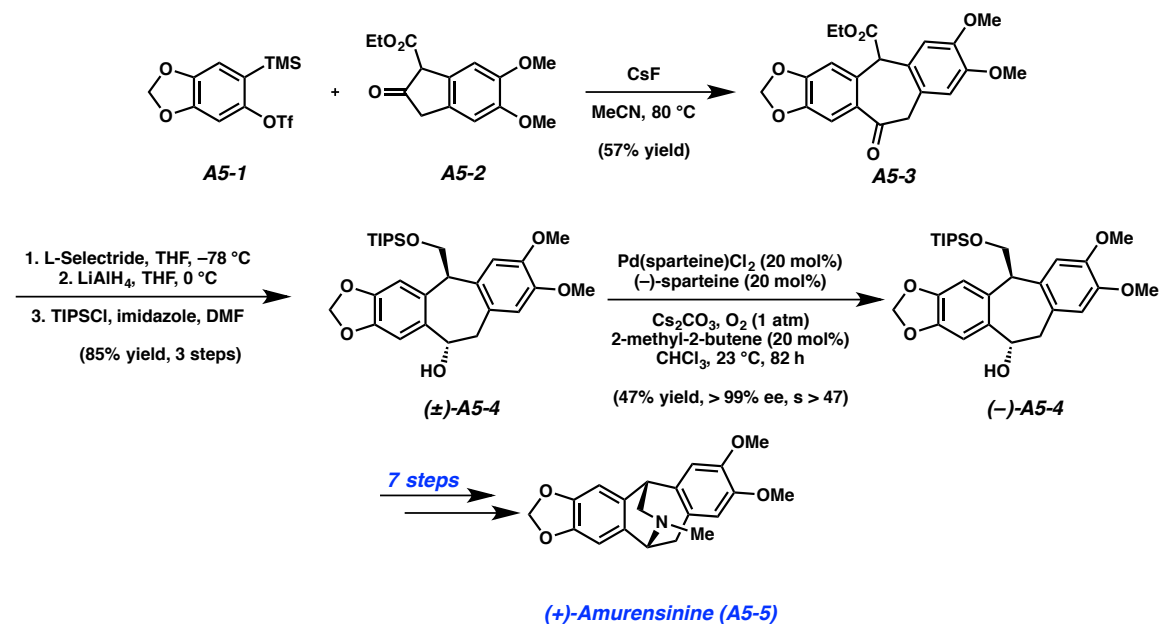
Scheme 2. *Total synthesis of (−)-curvularin (**A5-10**).*
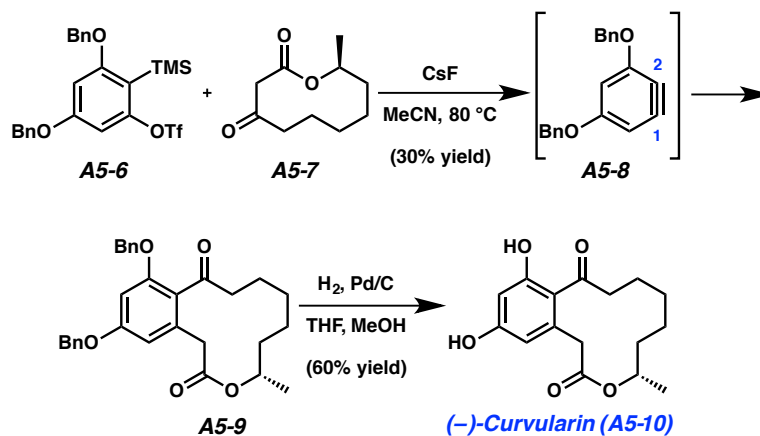
A5.2 The Development of the Ring Expansive Acyl-Alkyation of Arynes with Heterocyclic β-ketoesters

Thus far only fused carbocycles and lactones have been reported as products of this ring expansive acyl-alkylation methodology. An investigation utilizing this methodology to form benzannulated heterocyclic frameworks had not been pursued.

We hoped to expand the methodology to heterocyclic β-ketoesters to prepare benzannulated heterocycles, providing a convergent, single-step strategy to synthesize a variety of important structural motifs including benzazepine derivatives (**A5-16**, **A5-17** and **A5-20**), benzoxypines derivatives (**A5-18** and **A5-19**), as well as more challenging larger rings (**A5-21** and **A5-22**) (Scheme A5.3). These heterocycles are found in the cores of many biologically active natural products. In particular, benzazepine derivatives are a scaffold within many important pharmaceuticals such as galantamine (**A5-11**), a treatment for Alzheimer's disease, and fenoldopam (**A5-12**), an antihypertensive agent (Figure A5.1).[3,4] By developing reaction conditions to prepare the cores of these important molecules, we would be able to rapidly access complex intermediates, providing a more convergent approach to these compounds.

Figure A5.1. *Benzannulated heterocycles in biologically active compounds.*

A5-11
Fendolopam

A5-12
Galantamine
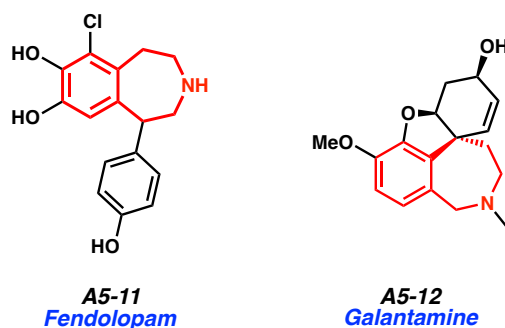
Scheme A5.3. *Proposed products of ring expansive acyl-alkylation of arynes.*
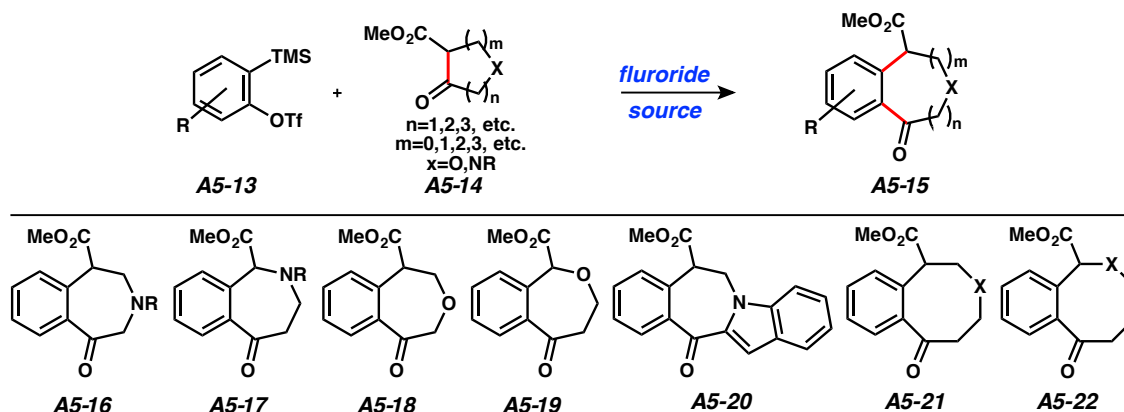
We choose β-ketoester **A5-23** on which to optimize our ring-expansive acyl-alkylation. While less prevalent in natural products and pharmaceuticals it does not require a protecting group, thereby simplifying optimization. We began our development by replicating the previously reported conditions of Tambar and co-workers (Scheme A5.4). This lead to a 2 to 1 mixture of acyl alkylated product **A5-24** and α-arylated product **A5-25** in 48% combined yield.

Scheme A5.4. *The acyl-alkylation of benzyne with β-ketoester **A5-23**.*
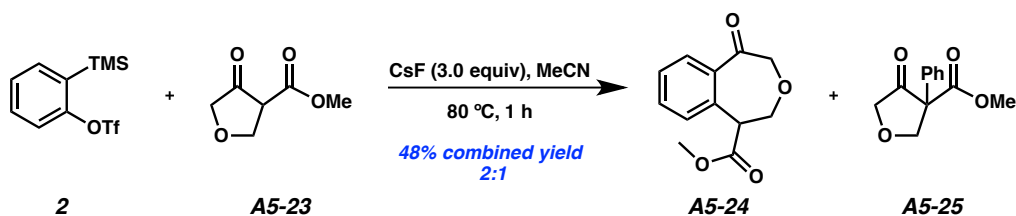
We next examined the effect of varying the fluoride source on the reaction (Table A5.1, entries 1–3). Both TBAT and KF/18-Crown-6 gave higher yields of our desired acyl-alkylated product. Interestingly, we saw no undesired α-arylated β-ketoester. Increasing the temperature to 40 ºC had a positive effect on the yield (Table A5.1, entry

4–5). However at higher temperature, we observed a decrease in yield. Extended reaction times also led to lower yields (Table A5.1, entries 6–7). This is most likely due to over arylation at either of the two α-carbons of our acyl-alkylated product. However, decreasing equivalents of fluoride source or aryne precursor had a deleterious effect on the yield.

Table A5.1. *Optimization of the ring-expansive acyl-alkylation of arynes.*
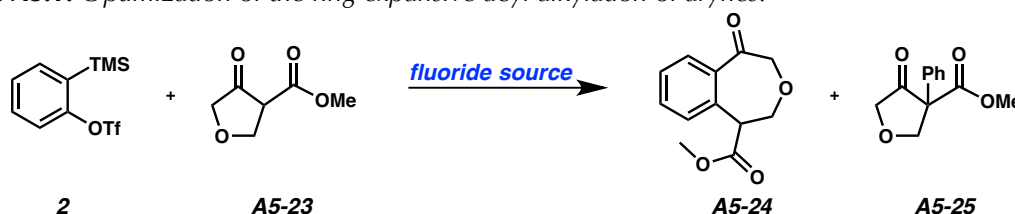
Entry	Fluoride Source	Solvent	Time (h)	Temperature (°C)	% yield*	26 : 32
1	KF/18-crown-6	THF	1.0	20	46	1 : 0
2	CsF	MeCN	0.5	80	48	2 : 1
3	TBAT	THF	3.0	20	46	1 : 0
4	KF/18-crown-6	THF	0.5	40	54	2 : 1
5	TBAT	THF	3.0	40	46	3 : 1
6	TBAT	THF	16	20	63	5 : 1
7	KF/18-crown-6	THF	3.0	20	22	1 : 0
8	KF/18-Crown-6 (1.5 equiv)	THF	2.0	20	28	1 : 0

*isolated yield. Conditions: 0.33 mmol **2**, 0.26 mmol **A5-23**, 0.67 mmol fluoride source, 2.5 mL solvent

During our investigation of any potential side reactions, we hoped to rule out any elimination pathways. To probe this possibility, we separately subjected β-ketoester **A5-23** and benzoxapene **A5-24** to the reaction conditions. Gratifyingly, both compounds were stable to these conditions and were recovered in near quantitative yields (Scheme A5.5).

Scheme A5.5. *Potential unproductive side reactions of ring-expansive acyl alkylation*
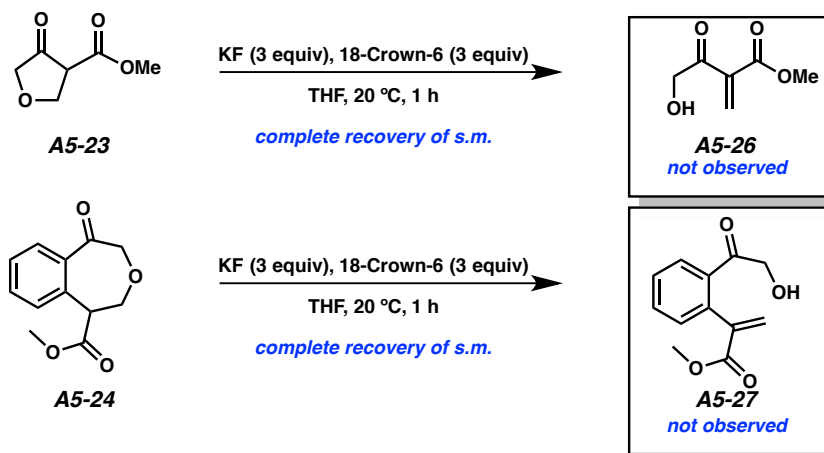
Similarly, changes in solvent did not improve yields (Table A5.2). We were limited to ethereal solvents due to the solubility restrictions of our fluoride source, KF/18-Crown-6. In reactions that used any non-ethereal solvents, we were only able to isolate starting material. The use of a pregenerated enolate of our β-ketoester using sodium hydride or potassium *tert*-butoxide resulted in recovery of starting material.

Table A5.2. *Solvent effects on ring-expansive acyl-alkylation.*

Entry	Solvent	Time (h)	% Yield*
1	dioxane	1	16
2	diethyl Ether	24	25
3	dimethyloxyethane	0.33	30
4	TBME	24	9
5	2-methyl THF	2	46

Conditions: **2** (1.25 equiv), **A5-23** (1.00 equiv), KF/18-Crown-6 (3.0 equiv)
*isolated yield

A5.3 Future Directions

We will expand this methodology to other heterocyclic β-keto esters, includes 6-, 7- and 8-membered rings. Nitrogen-bearing heterocycles provide the opportunity to attenuate the nucleophilicity of the heteroatom through the introduction of a protection groups. We hope this will bring about synthetically useful yields which could eventually be applied to one of a number of natural products contain these benzanulated heterocycles.

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Appendix 6

Prepartion of Benzotriazoles via an Aryne-Based Three-Component

Cross-Coupling

1H-benzo[d][1,2,3]triazoles (hereafter referred to as benzotriazoles) have been used in a variety of applications within the context of organic synthesis.[1] The implementation of arynes has allowed for facile preparation of this important class of molecules. Huisgen 1,3 dipolar cycloadditions, commonly referred to as "click" reactions, have found broad application in the synthesis of 1,2,3 triazoles.[2] Specifically, organoazides have been shown to readily undergo [3+2] cycloaddition with the characteristic strained triple bond of aryne without the need of transition metal catalysts.

While this reactivity has been known since the early 1960s, in 2008 Larock and co-workers reported a simple procedure using alkyl azides and arynes generated in situ from the fluoride-induced *ortho*-elimination of *o*-(trimethylsilyl)aryl triflates (Scheme A6.1, eq 1). The use of microwave irradiation development has lead to decreased

reaction times and improved yields. The need to pre-generate the organoazides was alleviated by a method developed by Beihl and Ankati. This methodology utilized alkyl halides in the presence of sodium azide to followed by [3+2] cycloaddition (Scheme A6.1, eq. 2).

Scheme A6-1. *Previous preparations of benzotriazoles from benzyne.*
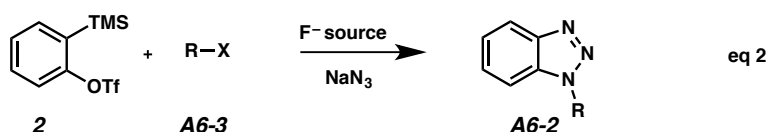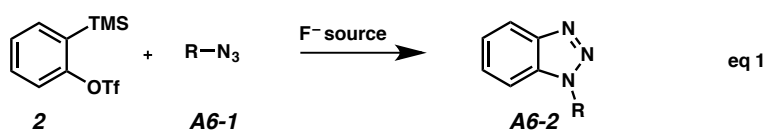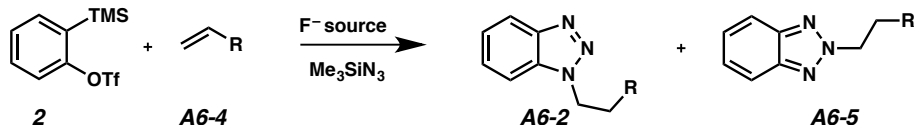
Continuing our sustained interest in 3-component couplings, we sought to examine the use of electrophiles in the preparation of benzotriazoles. We initiated our studies by attempting to react sodium azide with methyl acrylate and an in situ generated aryne. However, this lead to no detectable 3-componant coupling products. Switching our azide source to trimethylsilyl azide lead to a mixture of three benzotriazole products. Both 1-phenyl benzotriazole (**A6-9**) and 3-benzotrizaole-1-yl propionic acid methyl ester (**A6-9**) were prepared in 43% and 41% yield, respectively (Scheme A6.2). Interestingly, 3-benzotriazole-2-yl propionic acid methyl ester (**A6-8**) was also isolated in 10% yield,

suggesting initial formation of a benzotriazole anion, followed by subsequent nucleophilic attack. However no 2-phenyl benzotriazole (**A6-10**) was observed.

A similar mixture of products was observed when the reaction is performed with methyl vinyl ketone. Intriguingly, both 1- and 2-phenyl benzotriazole (**A6-9, A6-10**) were formed (Scheme A6.2). Finally, when the aryne was used as the electrophile, a mixture of 1-phenyl benzoltrizale (**A6-9**) and 2-phenyl benzotriazole (**A6-10**) are produced in 74% and 18% yield, respectively.

Scheme A6.2. *Preparation of benzotriazoles from aryne.*
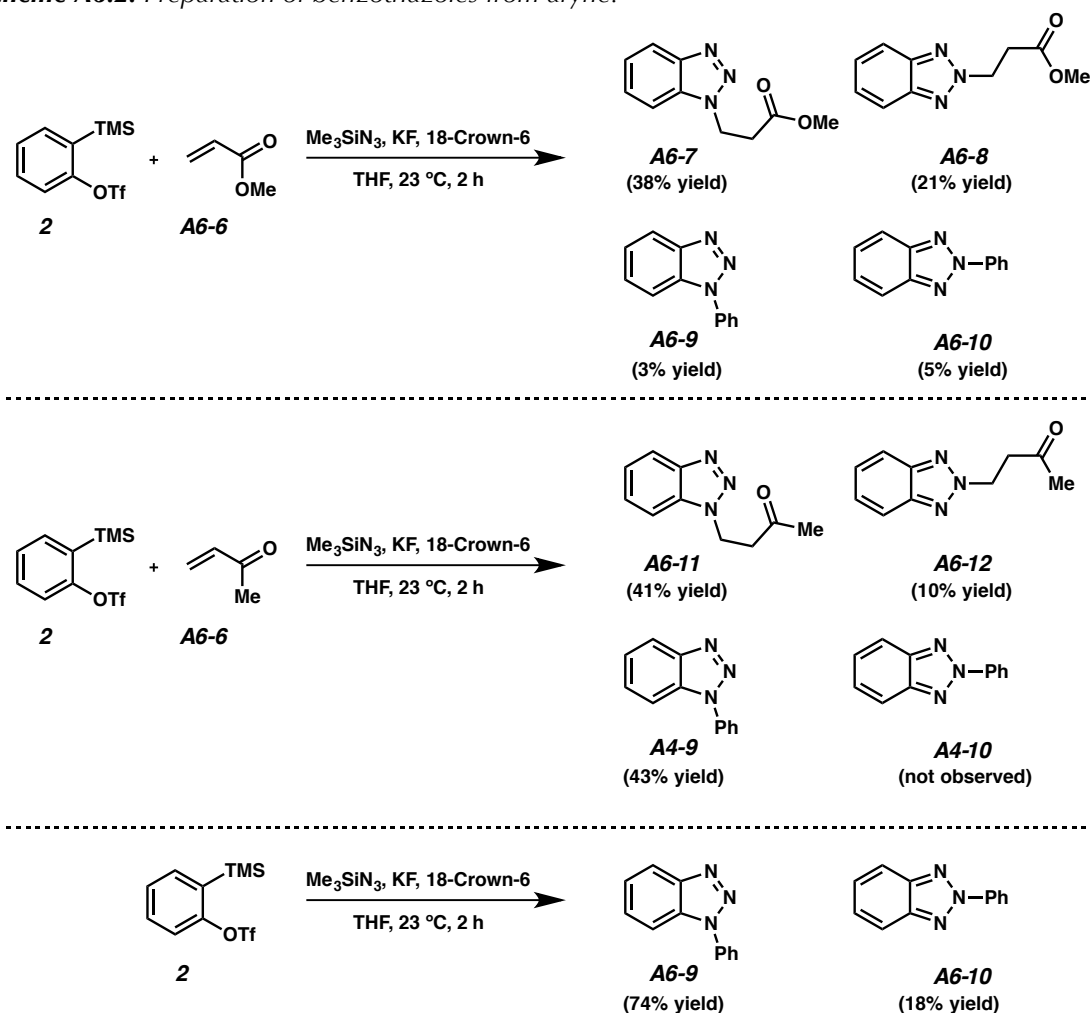
Herein we have report a novel 3-component coupling for the synthesis of *N*-substituted benzotriazoles, exploiting the reactivity of benzyne and its propensity to undergo dipolar cycloadditions.

Representative Procedure

Representative procedure: A flame-dried 2 dram vial equipped with a stir bar was sequentially charged with 18-crown-6 (194.8 mg, 0.75 mmol, 2.2 equiv.) and potassium fluoride (42.8 mg, 0.75 mmol, 2.2 equiv.). The vial was sealed with a septum and parafilm. The vial was evacuated and back-filled with N2 3 times. THF (3.3 mL), aryne precursor (**2**) (0.081 mL, 0.34 mmol, 1.0 equiv.), trimethylsilyl azide (0.044 mL, 0.34 mmol, 1.0 equiv), and methyl vinyl ketone (0.054 mL, 0.68 mmol, 2.0 equiv) were sequentially added via syringe. This was stirred at room temperature (23 °C) for 2 hours, at which time aryne precursor had been fully consumed, as indicated by TLC (silica, 10% hexanes in EtOAc). After 2 hours, the reaction mixture was diluted with 10 mL Et$_2$O. This was washed 3 times with 10 mL brine. The aqueous layers were combined and extracted with 20 mL Et$_2$O. The organic layers were combined and dried over sodium sulfate. This was filtered and the solvent was removed in vacuo to afford a yellow-brown oil. The resultant oil was purified on a silica column (1 cm x 20 cm) using a gradient of 15% to 60% EtOAc in hexanes as an eluent.

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ABOUT THE AUTHOR

Christopher Haley was born on November 18, 1987 in Boston, MA to John and Amy Haley. He spent the first 18 years of his life living in the town of Wellesley, MA, a suburban town west of Boston. When Christopher was five, the Haleys welcomed the addition of Christopher's younger brother, James, to the family, and they've been brothers ever since. While this meant that Christopher was forced to share his toys, it also meant Christopher had a great companion for family trips, playing video games with and someone to blame whenever anything broke.

His time in Wellesley was spent pursuing a variety of interests. For a number of years he attempted to hone his skills at various sports: soccer, baseball, tennis and even figure skating. While attending Wellesley High School, he settled on track and field, running the 300m hurdles and the 4x400m relay. He also took classical piano lessons for 9 years and received his Eagle Scout award in 2004. It was through the Boy Scouts that Christopher developed a love of the outdoors, which has only grown deeper with time. His hiking, backpacking and camping trips are some of his most cherished memories.

Upon graduating from high school in 2006, Christopher left suburban life behind and began his undergraduate studies in the big city at New York University in New York City. While there, he was fortunate enough to learn organic chemistry from Prof. Maitland Jones, Jr., whom he subsequently worked for as a teaching assistant. While an undergraduate student, Christopher carried out research in the laboratory of Prof. David I. Schuster. Prof. Jones and Prof. Schuster, instilled in Christopher a love of organic chemistry. During his time at NYU, Christopher thoroughly explored the city. He particularly loved attending Broadway shows, operas and concerts.

After receiving his B.S. in chemistry, he set his sights on receiving a Ph.D. from the California Institute of Technology. While at Caltech, Christopher worked in the laboratory of Prof. Brian M. Stoltz, an advisor who further enriched his knowledge and interest in organic chemistry. He worked on a variety of projects within the field of synthetic organic chemistry.

Upon graduation, Christopher will be a staff scientist at the law firm of Choate, Hall & Stewart in Boston, MA.