NEW SYNTHETIC METHODOLOGIES FOR ACCESS TO 5-MEMBERED HETEROCYCLES

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ABSTRACT

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The majority of the work in this dissertation presents a new synthetic methodology to synthesize an imidazoline from either a chiral or a racemic aziridine. The purpose of synthesizing imidazolines is for their known biological activity. Previous research in the Tepe group has developed a method to diastereoselectively synthesize racemic imidazolines from the trimethyl silyl chloride mediated cycloaddition of imines with azlactones. This methodology allowed access to a variety of imidazolines that have been shown to inhibit NF-κB mediated gene transcription. NF-κB is a nuclear transcription factor of activated B cells found in almost all animal cell types. It is a protein complex, that binds to certain DNA sequences and controls the transcription of genes. An SAR study has been conducted in our research group on this class of compounds. The ability of the imidazolines to inhibit NF-κB mediated gene transcription was measured by an assay on human cervical epithelial (HeLa) cells and human whole blood. The results of these studies have determined which functional groups were essential for efficient inhibition of NF-κB. These studies have also determined that one imidazoline enantiomer was a much more potent inhibitor than the other. Although our research group had created a diastereoselective method to synthesize imidazolines, there was still not a method to synthesize chiral imidazolines. Due to the cost, time, and inefficiencies of separation of racemic imidazolines by chiral HPLC or by other resolution methods an enantioselective method was needed. This thesis represents the progress towards an enantioselective

synthesis of imidazolines. New synthetic methodologies to access an oxazolidin-2-one and an amino alcohol have been developed. In addition progress toward new synthetic methodologies to access guanidine heterocycles and diamines will also be discussed.

This dissertation is dedicated to my wife, Beth Kuszpit who has always stood by my side, as well as my brother, Greg Kuszpit, and my parents Sandra Kuszpit and Kenneth Kuszpit who have always supported me in everything I have pursued in my life.

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research style, he allowed me to pursue my own ideas and learn from my mistakes. I believe this research style was the best way for me to grow as a scientist. He has a great sense of humor and I always enjoyed cracking jokes with him. Sometimes they were jokes at the expense of others, but it was all in good fun. He is also a person that I respect and admire.

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KEY TO ABBREVIATIONS

BF_3•$O(Et)_2$:	Boron trifluoride diethyl etherate
Bh:	Benzhydryl
DABCO:	1,4-diazabicyclo[2.2.2]octane
DCE:	Dichloroethane
DCM:	Dichloromethane
DMAP:	4-dimethylamino pyridine
DME:	Dimethoxy ethane
DMF:	Dimethyl formamide
DMSO:	Dimethyl sulfoxide
DNA:	Deoxyribonucleic acid
EC50:	Half maximal effective concentration
EDCI:	Ethyldimethylaminopropyl carbodiimide
HeLa:	Human cervical epithelial
HRMS:	High resolution mass spectrometry
I-κB:	Inhibitory kappa B
LA:	Lewis Acid
MsOH:	Methanesulfonic acid
NBS:	N-Bromosuccinimide
NCS:	N-Chlorosuccinimide
NIS:	N-Iodosuccinimide
NF-κB:	Nuclear transcription factor kappa B

SAR:	Structure activity relationship
TfOH:	Triflic acid
THF:	Tetrahydrofuran
TNF-α:	Tumor necrosis factor alpha
Ts:	Tosyl
TMSCl:	Trimethylsilyl chloride
TEA:	Triethylamine
TCICA:	Trichloroisocyanuric acid
TBICA:	Tribromoisocyanuric acid

CHAPTER 1

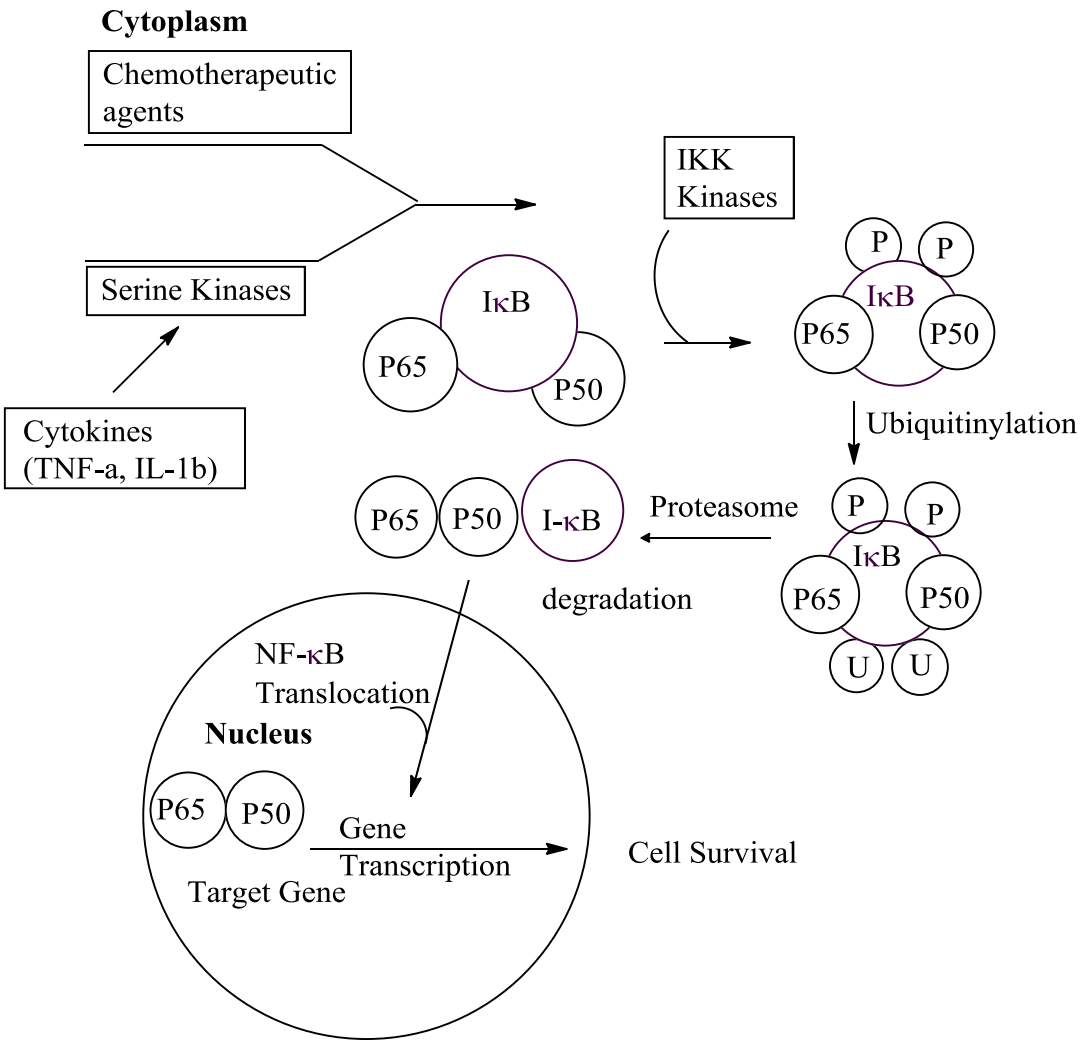
INHIBITION OF NF-κB GENE TRANSCRIPTION BY IMIDAZOLINES AND RELATED HETEROCYCLES

Apoptosis (programmed cell death) is a defense mechanism to remove infected, mutated, or damaged cells from the body.[1,2] Traditional cancer treatment uses ionizing radiation or chemotherapy to induce apoptosis in cancer cells.[1,2] One example of a chemotherapy drug is camptothecin which is a DNA topoisomerase I inhibitor and induces a stable ternary topoisomerase I-DNA cleavable complex.[1,2] This complex is recognized as damaged DNA and initiates a programmed cell death signaling pathway.[1,2] Another chemotherapy drug, cisplatin, covalently bonds to DNA base pairs, which induces a similar signaling pathway to that of camptothecin.[1,2] Unfortunately, camptothecin and cisplatin also initiate DNA repair signaling pathways. Cellular resistance is, in part, the result of activation of anti-apoptotic (cell survival) signaling pathways. One of the cell survival pathways activated by camptothecin and cisplatin is the NF-κB pathway and as a result the efficacy of chemotherapy is reduced.[1,2]

NF-κB is a mammalian transcription factor responsible for the regulation of many genes,[3,4] such as those associated with stress,[5] inflammatory stimuli,[6] anti-apoptosis,[7] and apoptosis.[8] Misregulation of NF-κB mediated gene transcription is associated with many

diseases, such as rheumatoid arthritis,[9] inflammatory bowel disease,[10-12] and cancer.[13,14] In most mammalian cells, NF-κB exists as either a p50/p50 homodimer or a p50/p65 heterodimer both of which are anti-apoptotic gene regulators. In non-stimulated normal cells, NF-κB is located in the cytoplasm and bound by I-κB.[15] The NF-κB pathway can be activated by the correct extracellular signal, such as cytokines TNF-α and IL-1ß, as seen in scheme 1-1.[4,6,16-18] IKK kinases phosphorylate I-κB on serine residues 32 and 36,[15,19] followed by ubiquitinylation and degradation of I-κB by the 26S proteasome.[20,21] The 26S proteasome degrades I-κB and releases NF-κB so NF-κB can go into the nucleus.[22] Inside the nucleus, NF-κB binds to various DNA control elements and initiates anti-apoptotic gene transcription and thus cell survival (Scheme 1-1).[2]

New chemotherapeutic methods have moved towards a combination of inducers of apoptosis and inhibitors of cancer cell survival pathways. There has been a search for small molecules that can either selectively induce apoptosis or inhibit cell survival pathways in cancer cells to prevent cellular chemoresistance.[1] One focus of the Tepe group has been the development of inhibitors of cancer cell survival pathways to improve traditional chemotherapy. The Tepe group has created small molecule imidazolines, which have been shown to inhibit the cancer cell survival signaling pathway mediated by NF-κB.[1] Therefore, imidazolines inhibit the NF-κB pathway, resulting in sensitization of cancer cells to chemotherapeutic agents like camptothecin, and subsequent reduction of chemoresistance.[1,2]



Scheme 1-1: Activation of NF-κB Pathway

The Tepe lab has prepared an imidazoline scaffold as a potent inhibitor of NF-κB mediated gene transcription. Inhibition of NF-κB has been shown to proceed by modulation of I-κB-α degradation by inhibition of the 20S proteasome, although the precise binding site within the 20S proteasome is still unknown at this time.[1,2] Racemic imidazolines were first developed in our laboratory by a 1,3-dipolar cycloaddition reaction

between azlactones and imines.[23] Compounds **1-1** and **1-1a** were shown to be inhibitors of NF-κB (**Figure 1-1**).[1]

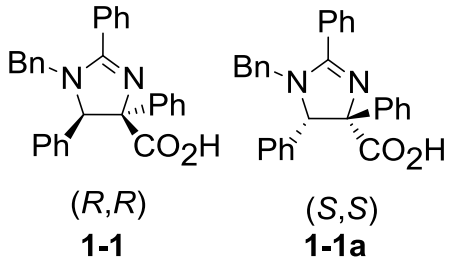
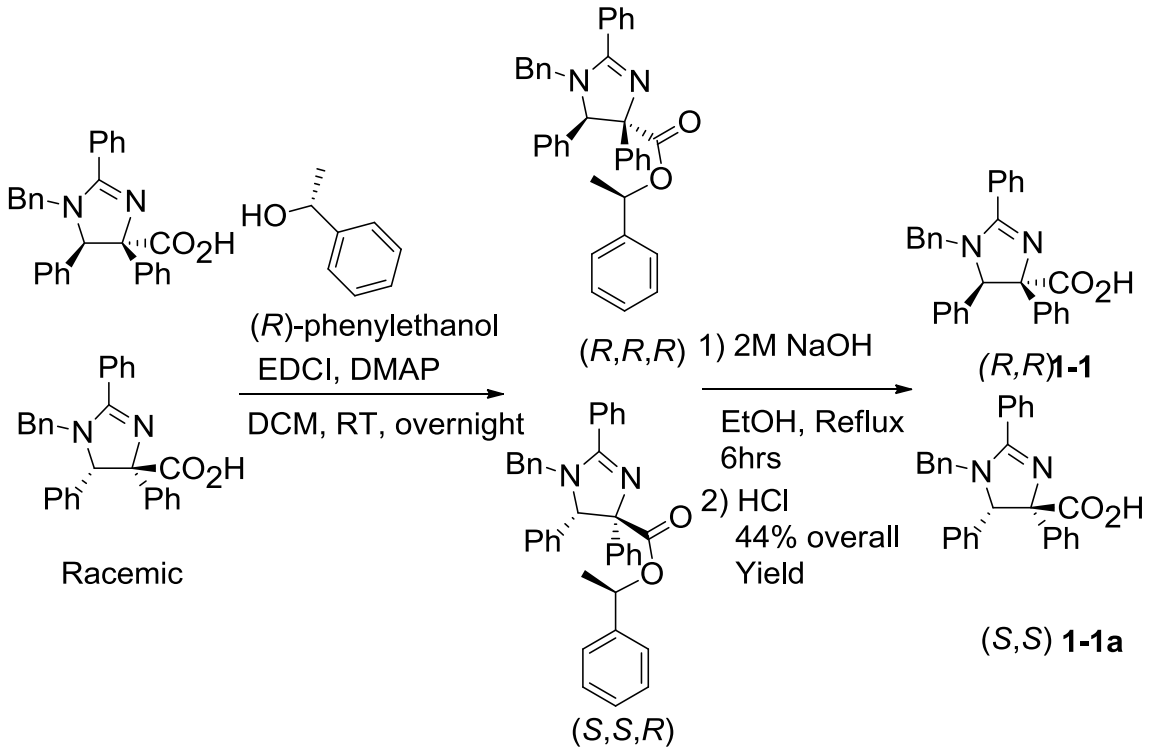


Figure 1-1: Compounds **1-1** and **1-1a**

Previously, the two enantiomers have been separated by reaction with *R*(+)-1-phenylethanol to yield two diastereomeric esters. The esters were then separated by column chromatography and the resolving agent was removed to yield each pure enantiomer (**Scheme 1-2**).[1]



Scheme 1-2: Resolution of Compounds **1-1** and **1-1a**.[1]

Resolution of the enantiomers of compound **1-1** was also accomplished by transformation of the carboxylic acid of compound **1-1** to the ethyl ester and separation on chiral HPLC. However, only small amounts of the compound could be separated at a time using this method. Since compounds **1-1** and **1-1a** are prone to spontaneous decarboxylation, they were transformed into the ethyl esters.[1,2] The resulting compounds **1-2** and **1-2a** were the lead compounds developed in our lab (**Figure 1-2**).[2]

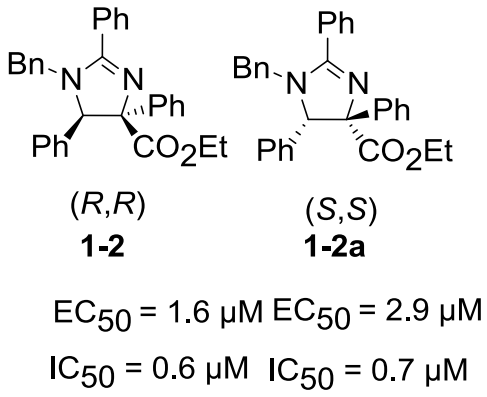


Figure 1-2: Compounds **1-2** and **1-2a**

Imidazolines **1-2** and **1-2a** were measured for their ability to inhibit NF-κB mediated gene transcription by using a luciferase based reporter assay in human cervical epithelial (HeLa) cells. Cells were pretreated for 30 minutes with compound **1-2** or **1-2a** (20 to 0.5 μM) followed by treatment with the cytokine TNF-α, which initiated the activation of the NF-κB pathway. This caused degradation of I-κB and translocation of NF-κB into the nucleus, where it initiated transcription of genes, including those needed for the production of the enzyme luciferase. Luciferase production was evaluated after 8 hours by a luminometer. From this data the EC_{50} values for compounds **1-2** and **1-2a** were determined to be 1.6 μM and 2.9 μM, respectively.

Since the discovery of the lead compounds, an SAR study has shown which functional groups on the imidazoline scaffold were essential for inhibition of NF-κB.[2,24] The Tepe group has also determined that the enantiomers of the lead compound were not equally potent inhibitors of NF-κB. The (*R*,*R*) enantiomer was a more potent inhibitor of NF-κB mediated gene transcription than the (*S,S*) enantiomer.[2,13] Separation of the enantiomers **1-1** and **1-1a** by resolution or chiral HPLC methods is very expensive and time

consuming. Clearly, an enantioselective synthesis of imidazolines would not require the enantiomers to be separated, assuming the enantioselectivity of the reaction was greater than 98% enantiomeric excess (ee). A new methodology may also be able to introduce new functional groups onto the imidazoline scaffold, while still maintaining the proper stereochemistry. The ultimate goal would be to not only synthesize chiral imidazolines, but to synthesize chiral imidazolines that are more potent inhibitors of NF-κB mediated gene transcription than the lead compound. This dissertation presents a new methodology to synthesize imidazolines enantioselectively.

The most recent work in the Tepe lab has synthesized nanomolar 20S proteasome inhibitors (Manuscript submitted to *J. Med. Chem.* 2013) (**Figure 1-3**).

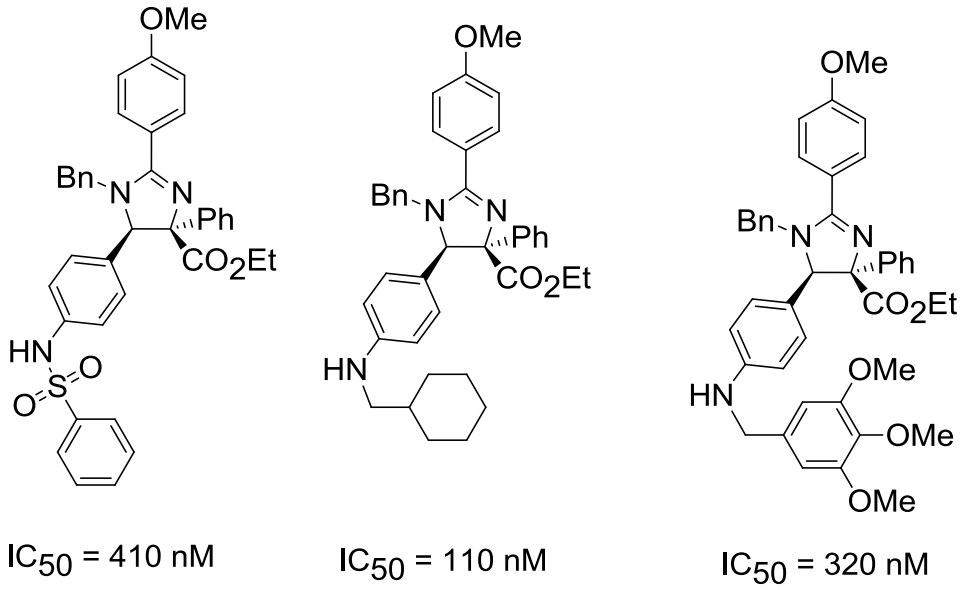
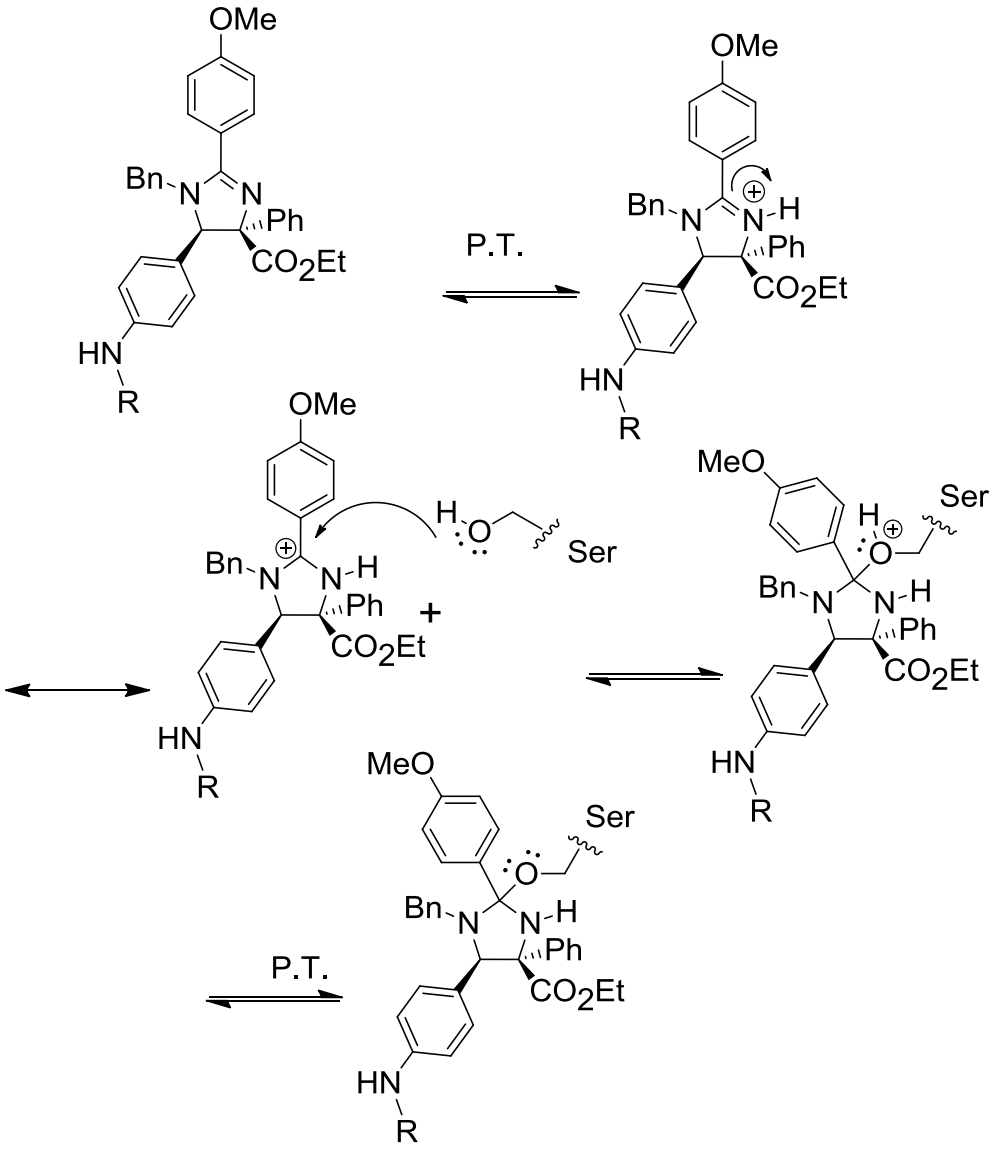


Figure 1-3: *Nano*-molar imidazoline proteasome inhibitors

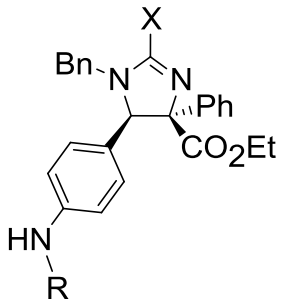
The mechanism for 20S proteasome inhibition by an imidazoline has been determined to be non-competitive.[25] We have also hypothesized that an imidazoline is a

covalent inhibitor of the 20S proteasome. An imidazoline may function as a covalent inhibitor through a covalent bond formed at the C-2 position of the imidazoline scaffold. Covalent bond formation at the C-2 position of the imidazoline may occur through a serine oxygen atom and this is aided by the fact that the N-1 nitrogen can be protonated in the 20S proteasome (**Scheme 1-3**).



Scheme 1-3: Possible mechanism for non-competitive covalent 20S proteasome inhibition

The substituent at the C-2 position of the imidazoline scaffold was almost always a substituted phenyl group. Placing an even stronger electron donating group than a *p*-MeO-Ph at the C-2 position would increase the carbocation stability at the C-2 position and may be the key to even more potent 20S proteasome inhibition (**Figure 1-4**).



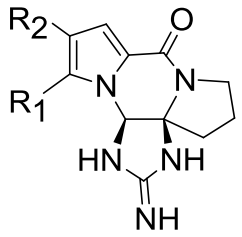
New Proteasome Scaffold

X = OMe, NH_2, NH-alkyl, NH-Aryl

R = Alkyl, SO_2-Ph, SO_2-Alkyl

Figure 1-4: Proposed new proteasome scaffold

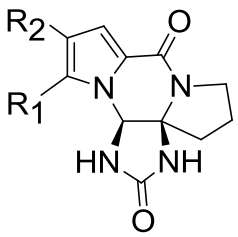
The Tepe lab is also interested in natural products and their derivatives as potential new 20S proteasome inhibitors. We are particularly interested in the Phakellins, Phakellstatins, Nagelamide M, and Palau'amine derivatives[26-28] (**Figure 1-5**).



$R_1 = R_2 = Br$, Dibromophakellin

$R_1 = H$, $R_2 = Br$, Bromophakellin

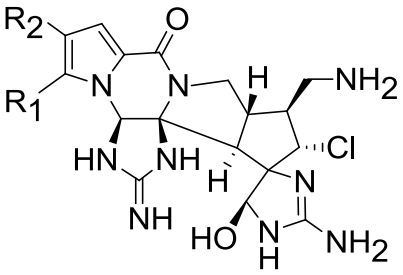
$R_1 = R_2 = H$ Phakellin



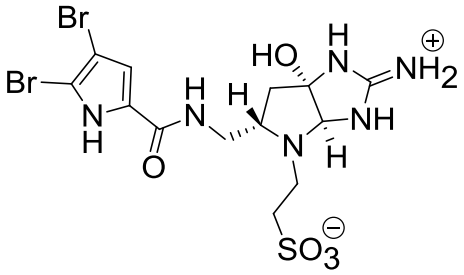
$R_1 = R_2 = Br$, Dibromophakellstatin

$R_1 = H$, $R_2 = Br$, Bromophakellstatin

$R_1 = R_2 = H$ Phakellstatin



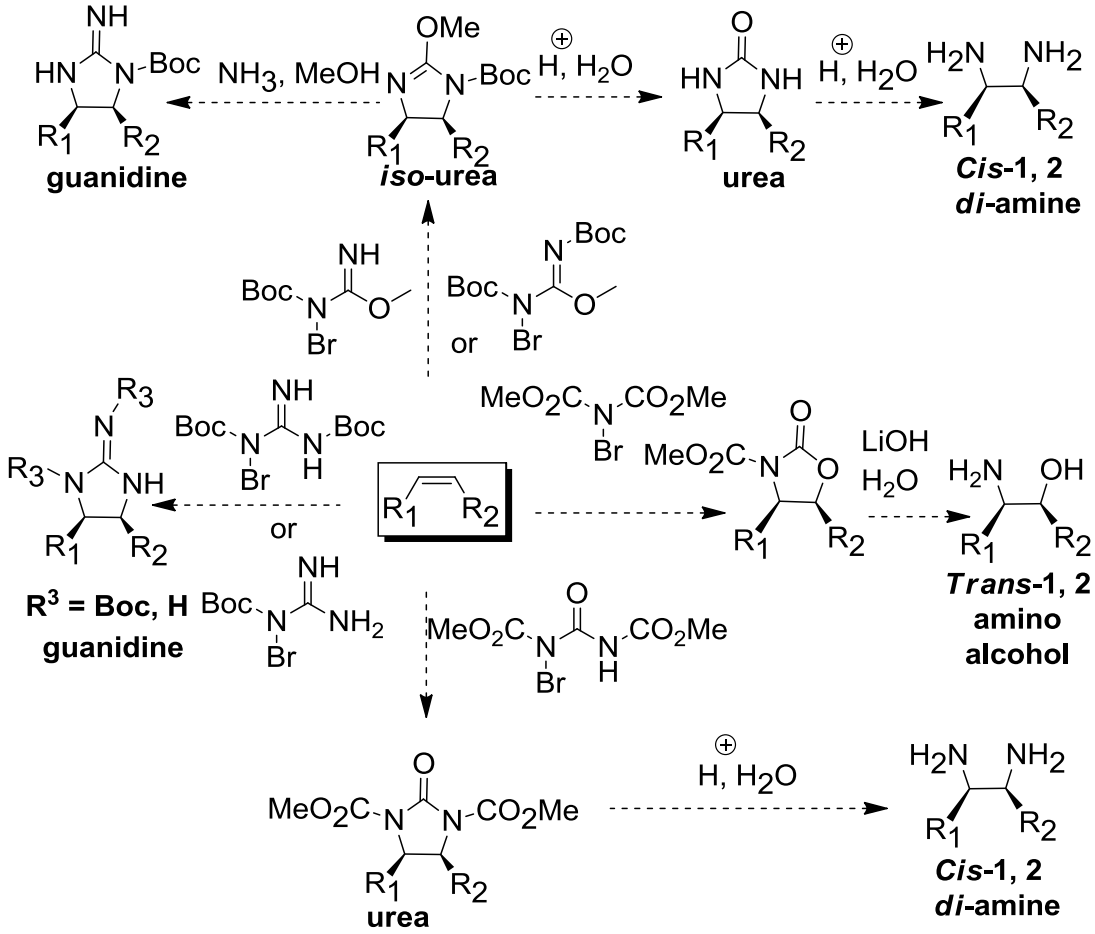
Palau'amine



Nagelamide M

Figure 1-5: Urea and guanidine ring-containing natural products

New synthetic methodologies to access these natural products are needed. New synthetic methodologies to synthesize imidazolines with the general scaffold in **Figure 1-5** are also needed. One way to create these scaffolds would be by guanidine addition, urea addition and an *iso*-urea addition to electron poor, electron rich, and electron neutral olefins. This dissertation represents the work towards the synthesis of new bromine reagents and their addition to olefins to create new 5-membered ring heterocycles. Initially studies have focused on racemic synthesis of these 5-membered heterocycles but future endeavors will focus on diastereoselective and/or enantioselective syntheses (**Scheme 1-4**).



Scheme 1-4: General synthesis of a guanidine, oxazolidin-2-one, a urea, a diamine and an amino alcohol via addition to an olefin with bromine reagents.

These synthetic methodologies will provide a method to make 1,2 amino alcohols and 1,2 diamines and hopefully lead to the next generation of proteasome inhibitors in our lab.

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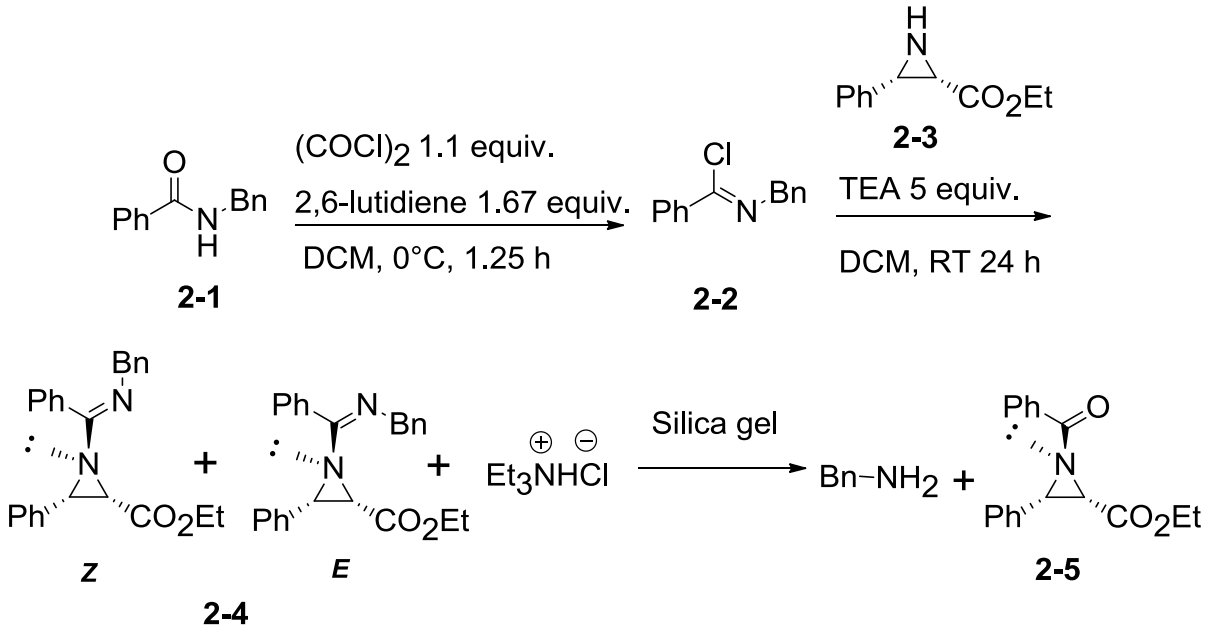
CHAPTER 2

RING EXPANSION OF AN AZIRIDINE AND AN AZETIDINE WITH VARIOUS ELECTROPHILES

In the Tepe lab we are interested in new synthetic methodologies to synthesize heterocycles. Among these heterocycles imidazolines have been shown to be 20S proteasome inhibitors.[1-6] The Tepe lab is interested in proteasome inhibition for the treatment of cancer. We desire to create new synthetic routes to synthesize new imidazolines as well as enantiopure imidazolines. I pursued a new methodology to synthesize an imidazoline enantioselectively. We hypothesized that we could synthesize an enantiopure imidazoline by developing a stereospecific reaction. We envisioned we could develop a ring expansion reaction of an enantiopure aziridine with an imidoyl electrophile to synthesize an enantiopure imidazoline. An imidoyl chloride proved to be the best imidoyl electrophile for a (3+2) aziridine ring expansion reaction. The details of this reaction have been described in detail in the master's thesis but will be summarized along with further progress made on this methodology.[7]

Methods to synthesize an imidoyl chloride have typically employed thionyl chloride, phosphorous pentachloride, or oxalyl chloride.[8-10] Oxalyl chloride was superior to both thionyl chloride and phosphorous pentachloride to synthesize (*Z*)-N-benzylbenzimidoyl chloride **2-2** with the greatest yield and shortest reaction time. Initial attempts to make the imidoyl aziridine **2-4** were by reaction of ethyl-3-phenylaziridine-2-carboxylate **2-3** with **2-2** in DCM with TEA present in excess. The ^{1}H NMR spectrum of

compound **2-4** was complicated because compound **2-4** existed as mixture of rotational isomers about the amidine bond. The phenyl and benzyl group can be *cis* (*Z*) or *trans* (*E*) to one another, but after purification of **2-4** by column chromatography caused hydrolysis of the imidoyl group to benzyl amine and aziridine **2-5**. Obviously, after hydrolysis of compound **2-4**, compound **2-5** did not contain any rotational isomers, but both **2-4** and **2-5** exist as the major invertomer with the nitrogen protecting group on the opposite side of the two *cis* aziridine substituents at the C-2 and C-3 positions (**Scheme 2-1**).



Scheme 2-1: Synthesis of aziridine invertomers

Since column chromatography was not sufficient to purify compound **2-4**, the solvent was removed and the triethyl ammonium hydrochloride salt (Et_3NHCl) was precipitated with ethyl acetate and removed by filtration. The product was concentrated *in vacuo* and then placed under high vacuum to remove the excess TEA. The product **2-4** was carried on to

the next reaction without further purification. The ring expansion reaction of the imidoyl aziridine to an imidazoline was attempted with various Lewis acids (**Table 2-1**). The proposed mechanism is discussed in my Master's Thesis.

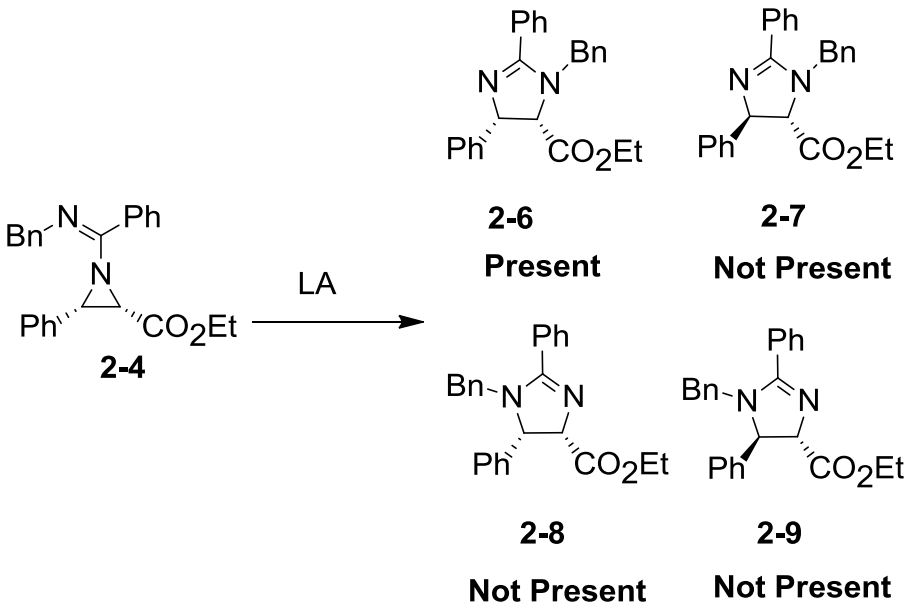


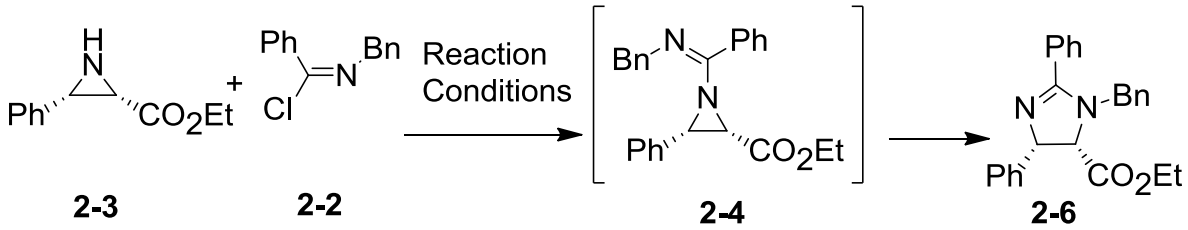
Table 2-1: Lewis acid isomerization of an imidoyl Aziridine to an imidazoline

Entry	Solvent	LA	LA equiv.	Temp. °C	Time h	% Yield **2-6**
1	DCM	BF_3•OEt_2	0.5	RT	24	No Rxn
2	DCM	BF_3•OEt_2	3.0	RT	36	No Rxn
3	$CHCl_3$	BF_3•OEt_2	5.0	Reflux	46	37[a]
4	$CHCl_3$	BF_3•OEt_2	2.0	Reflux	19	24[a]
5	THF	$AlCl_3$	0.5	RT	24	No Rxn
6	THF	$AlCl_3$	1.5	Reflux	48	No Rxn
7	THF	$MgBr_2$	0.5	Reflux	48	No Rxn
8	THF	$Zn(OTf)_2$	0.5	RT	24	Dec.
9	THF	$Sc(OTf)_3$	0.5	RT	24	Dec.
10	THF	$Yb(OTf)_3$	0.5	RT	24	Dec.
11	THF	$CuBr_2$	0.5	RT	24	Dec.
12	$CHCl_3$	BF_3•OEt_2, NaI	5.0, 1.0	Reflux	64	32

[a] These results were not reproducible which lead us to believe HCl was the true catalyst generated by residual water with chloroform or BF_3O•Et_2

The ring expansion of compound **2-4** was not observed in DCM or THF at room temperature. The only Lewis acid that successfully synthesized the imidazoline **2-6** in low yield was $BF_3O•Et_2$. The other imidazolines **2-7**, **2-8**, and **2-9** were not produced in this reaction. The ring expansion reaction was attempted with the metal triflates and $CuBr_2$ but did not yield imidazoline **2-6**. Instead workup with sat. aq. $NaHCO_3$ caused hydrolysis of compound **2-4** to compounds **2-5** and benzyl amine (**Table 2-1**, **entries 8-11**).
The imidoyl aziridine **2-4** was refluxed in chloroform with $BF_3O•Et_2$ with and without NaI to yield the *cis* imidazoline **2-6** (**Table 2-1, entries 3, 4, and 12**). Compound **2-8** was not formed in any of these reactions which could only occur by breaking the aziridine C-3 nitrogen bond. However, there was not any evidence for the formation of either *trans*-imidazoline stereoisomers compounds **2-7** or **2-9**.

Synthesis of an imidazoline in one step from an aziridine would be a more efficient procedure than trying to manipulate the water sensitive and acid sensitive intermediate imidoyl aziridine through a two step procedure. A methodology to synthesize an imidazoline in one step from an aziridine has been successful (**Table 2-2**). We discovered that the ring expansion of the imidoyl aziridine occurred by use of a Brønsted acid instead of a Lewis acid. The Brønstead acid was 2,6-lutidine•HCl which was generated in situ by reaction of an amide, $(COCl)_2$, and 2,6-lutidine to yield the imidoyl chloride.



2-3 **2-2** **2-4** **2-6**

Table 2-2: Optimization of one pot aziridine ring expansion to an imidazoline

Entry	Temp °C	Solvent	Time h	Base	**2-2** equiv.	Base equiv.	% Yield **2-6**
1	55	DCM	12	Hunig'sBase	1.5	6	0[a]
2	80	Toluene	12	TEA	1.5	2.4	0[a]
3	80	Toluene	9	DABCO	1.5	1.2	0[a]
4	80	Toluene	21	2,6-lutidine	1.5	1.5	20
5	80	Acetone	21	2,6-lutidine	1.5	1.5	37
6	80	MeCN	21	2,6-lutidine	1.5	1.5	20[b]
7	80	DMSO	21	2,6-lutidine	1.5	1.5	5[b]
8	80	DMF	9	2,6-lutidine	1.5	1.5	46
9	55	DMF	9	2,6-lutidine	1.5	1.5	32
10	RT	DMF	23	2,6-lutidine	1.5	1.5	10[b]
10	RT	DMF	117	2,6-lutidine	1.5	1.5	33[b]
11	RT	DMF	23	2,6-lutidine	1.5	7.5	38[b]
11	RT	DMF	44	2,6-lutidine	1.5	7.5	60[b]
11	RT	DMF	117	2,6-lutidine	1.5	7.5	67[b]
12	RT	DMF	65	Pyridine	1.5	7.5	62[b]
13	RT	DMF	65	DMAP	1.5	7.5	0[b]
14	55	DMF	21	2,6-lutidine	1.3	6.5	35
15	40	DCM	21	2,6-lutidine	1.1	5.5	46
16	55	DMF	21	2,6-lutidine	1.1	5.5	50
17	80	DMF	21	2,6-lutidine	1.1	5.5	47
18	80	DCM	21	2,6-lutidine	1.1	5.5	39
19	80	DCE	21	2,6-lutidine	1.1	5.5	37
20	55	DMF	21	2,6-lutidine	1.1	5.5	50[bc]
21	80	DMF	21	NaOAc	1.1	1.1	0
22	55	DMF	21	2,6-lutidine	1.1	5.5	50[bd]
23	130	DMF	3	2,6-lutidine	1.1	5.5	20[b]
24	55	DMF	6	2,6-lutidine	1.2	6	52
25	55	DMF	6	none	1.2	6	0

[a] The reaction stopped at the intermediate compound **2-4**. [b] Yield based on the crude ^{1}H NMR. [c] The imidoyl chloride was added over 4 hours with a syringe pump to compound **2-3**, DMF, and 2,6-lutidine. [d] Compound **2-3** was added over 4 hours with a syringe pump to the DMF, compound **2-2**, and 2,6-lutidine

A bulky base like 2,6-lutidine was the key in synthesizing the imidazoline **2-6**. Other bases stopped the reaction at the intermediate compound **2-4** (**Table 2-2, entries 1-3**). Excess of other bases like TEA would actually inhibit the formation of compound **2-6** and would stop the reaction at the intermediate compound **2-4**. This ring expansion reaction was optimized with respect to the solvent and DMF was found to be the best (**Table 2-2, entries 4-8, 17-19**). To minimize the formation of impurities the optimal temperature was determined to be 55°C (**Table 2-2, entry 16**). If the reaction was carried out at 80°C in DMF a new impurity, which was not present at 55°C formed and the new impurity was hard to remove by column chromatography (**Table 2-2, entry 8**). This ring expansion reaction of aziridine **2-3** with imidoyl chloride **2-2** to imidazoline **2-6** did occur very slowly at room temperature in $CDCl_3$ with 2,6-lutidine as the base. Two reactions were carried out in $CDCl_3$ and were monitored by ^{1}H NMR at room temperature. In one reaction 7.5 equivalents of 2,6-lutidine was used and in another reaction 1.5 equivalents of 2,6-lutidine was used (**Table 2-2, entries 10, 11**). It was observed by ^{1}H NMR that compound **2-6** was formed at a faster rate with 7.5 equivalents of 2,6 lutidine than with 1.5 equivalents of 2,6 lutidine. An excess amount of 2,6-lutidine did not stall the reaction at the intermediate imidoyl aziridine like other bases such as TEA, DABCO and Hünig's base. The reaction went to completion very fast at elevated temperatures in DMF, but a significant amount of decomposition occurred as well (**Table 2-2, entry 23**). The

formation of impurities formed when an excess of compound **2-2** was used. If less than one equivalent of compound **2-2** was used then residual aziridine **2-3** would be present at the end of the reaction. This was due to the fact that residual water in the reaction would hydrolyze some of the imidoyl chloride **2-2** to form benzyl benzamide. Changing the order of addition of either the imidoyl chloride to the aziridine in DMF with 2,6-lutidine or the addition of the aziridine to the imidoyl chloride in DMF with 2,6-lutidine had very little effect on the yield (**Table 2-2, entries 20, 22**). The best yield obtained was 52% of imidazoline **2-6** (**Table 2-2, entry 24**). These optimal reaction conditions were used to screen the scope of this methodology by the reaction of various imidoyl chlorides with *trans*-2,3 diphenyl aziridine. These results are summarized in the master's thesis.[7]

Upon completion of the master's thesis this methodology was further studied by the reaction of (*Z*)-benzylbenzimidoyl chloride with different aziridines substituted at the C-2 and C-3 positions. These aziridines were synthesized from the expoxide precusor. The epoxides were synthesized by the Darzen epoxidation reaction of an aldehyde with ethyl 2-chloroacetate. The expoxide was then opened at the C-3 position with NaN_3 and closed to the aziridine by the Staudinger reaction with PPh_3. The majority of the aziridines were synthesized from an epoxide and a few aziridines were synthesized by reaction of a nitrene with an alkene.

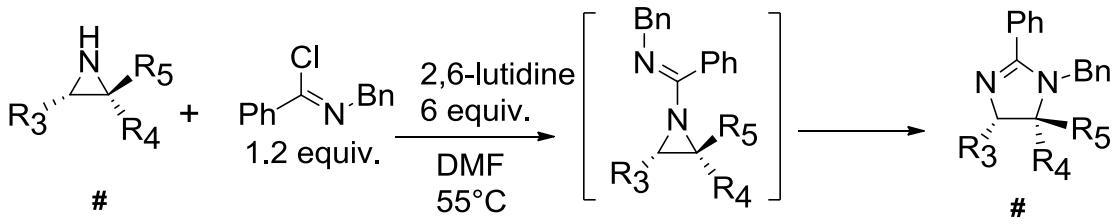


Table 2-3. Variation at R_3, R_4, and R_5 of the Aziridine Ring

Entry	Aziridine #	R_3	R_4	R_5	*T* (h)	Imidazoline #	yield (%)
1	**2-7**	*p*-MeO-C_6H_4	H	CO_2Et	10	**2-16**	45
2	**2-8**	Ph	H	CO_2Et	12	**2-17**	42
3	**2-9**	Ph	Me	CO_2Et	12	**2-18**	59
4	**2-10**	*p*-NO_2-C_6H_4	H	CO_2Et	6	**2-19**	40[a]
5	**2-11**	PhCH=CH	H	CO_2Et	20	**2-20**	41
6	**2-12**	*n*-C_6H_{13}	H	CO_2Et	12	**2-21**	40
7	**2-13**	Ph	H	COPh	12	**2-22**	41
8	**2-14**	Ph	Bn	H	12	**2-23**	40[a]
9	**2-15**	Ph	H	H	12	**NA**	0

[a] The compound was synthesized as a 2:1 mixture of regioisomers with a major regioisomer from breaking the aziridine C-3 nitrogen bond

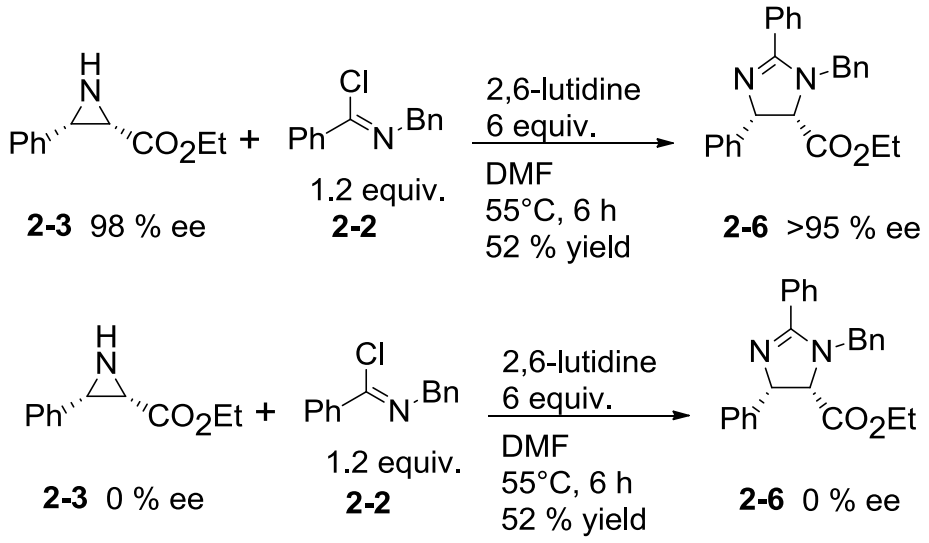
The scope of the reaction was subsequently investigated with respect to the R_3, R_4, and R_5 positions of the aziridine. Electron withdrawing and donating aryl groups, along with vinyl, ketone, ester, and alkyl functionalities were readily tolerated at these positions (**Table 2-3**).

It was important to note that it was not possible to have just a hydrogen atom for the R_4 and R_5 substituents at the C-2 position of the aziridine (**Table 2-3, entry 9**). With respect to the regiochemistry only one regioisomer was produced in all cases except when R_3 was a *p*-NO_2-C_6H_4- substituent or when R_4 was a benzyl substituent (**Table 2-3,**

entries 4, 8). A side product that formed in these reactions was a 2-imidazole due to oxidation of the imidazoline ring by loss of H_2. This oxidation may have occurred by residual oxygen in the reaction solution through a radical mechanism remove the two imidazoline methane CH protan atoms to form hydroxide radicals and the imidazole.

Of particular note is that this one pot reaction showed an overall retention of stereochemistry. In comparing the *cis* and *trans* stereoisomers of ethyl 3-phenylaziridine-2-carboxylate the stereochemistry was preserved to yield the *cis* and *trans* 2-imidazolines respectively (Compounds **2-6** and **2-17**). The coupling constants of the two methine imidazoline CH protons at the C-4 and C-5 positions of the imidazoline ring, were larger 12.0 Hz for the *cis* imidazoline **2-6**, and smaller 7.5 Hz for the *trans* imidazoline **2-17**.

The 2-imidazoline, compound **2-6**, was synthesized from both a racemic aziridine **2-3** and enantiopure aziridine **2-3** (98% ee). This would presumably yield the 2-imidazoline (**2-6**) as a racemate or enantiopure (98% ee) depending on the enantiopurity of the starting aziridine **2-3 (Scheme 2-2)**.



Scheme 2-2: Synthesis of enantiopure **2-6** and racemic imidazoline **2-6**

The racemate, compound **2-6**, was treated with (*S*)-Mosher's acid and analysis by ^{1}H NMR showed a 1:1 ratio of diasteromeric salts. However, the enantiopure compound **2-6** was also treated with (S)-Mosher's acid but only one diasteromeric salt was observed in the ^{1}H NMR spectrum. Thus the enantiopurity of compound **2-6** was preserved in the ring expansion reaction. A stereospecific ring expansion reaction of an enantiopure aziridine with an imidoyl chloride to yield an enantiopure imidazoline has been developed. Therefore, this methodology has provided a new way to synthesize enantiopure imidazolines of interest to our lab (**Figure 2-1**).

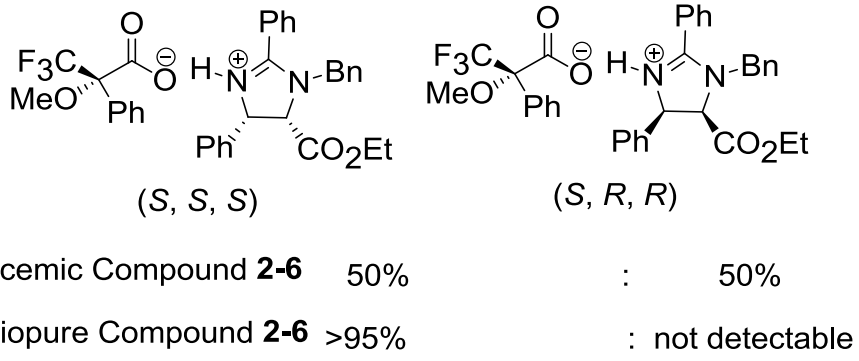


Figure 2-1: Determination of ee of compound **2-6** by Mosher's Acid

The synthesis of a 2-imidazoline with a quaternary carbon at the C-5 position (**2-18**) proceeded with complete retention of stereochemistry (**Table 2-1, entry 3**). The identity of compound **2-18** was supported by x-ray crystallography. The x-ray structure revealed that the phenyl at C-2 can be oriented above or below the plane of the imidazoline ring (**Figure 2-2**).

For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation

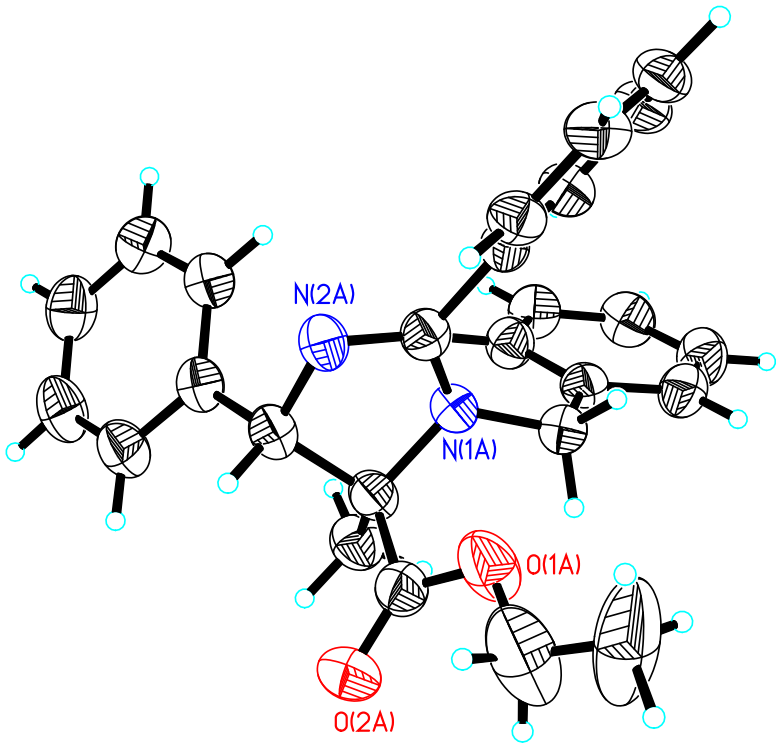
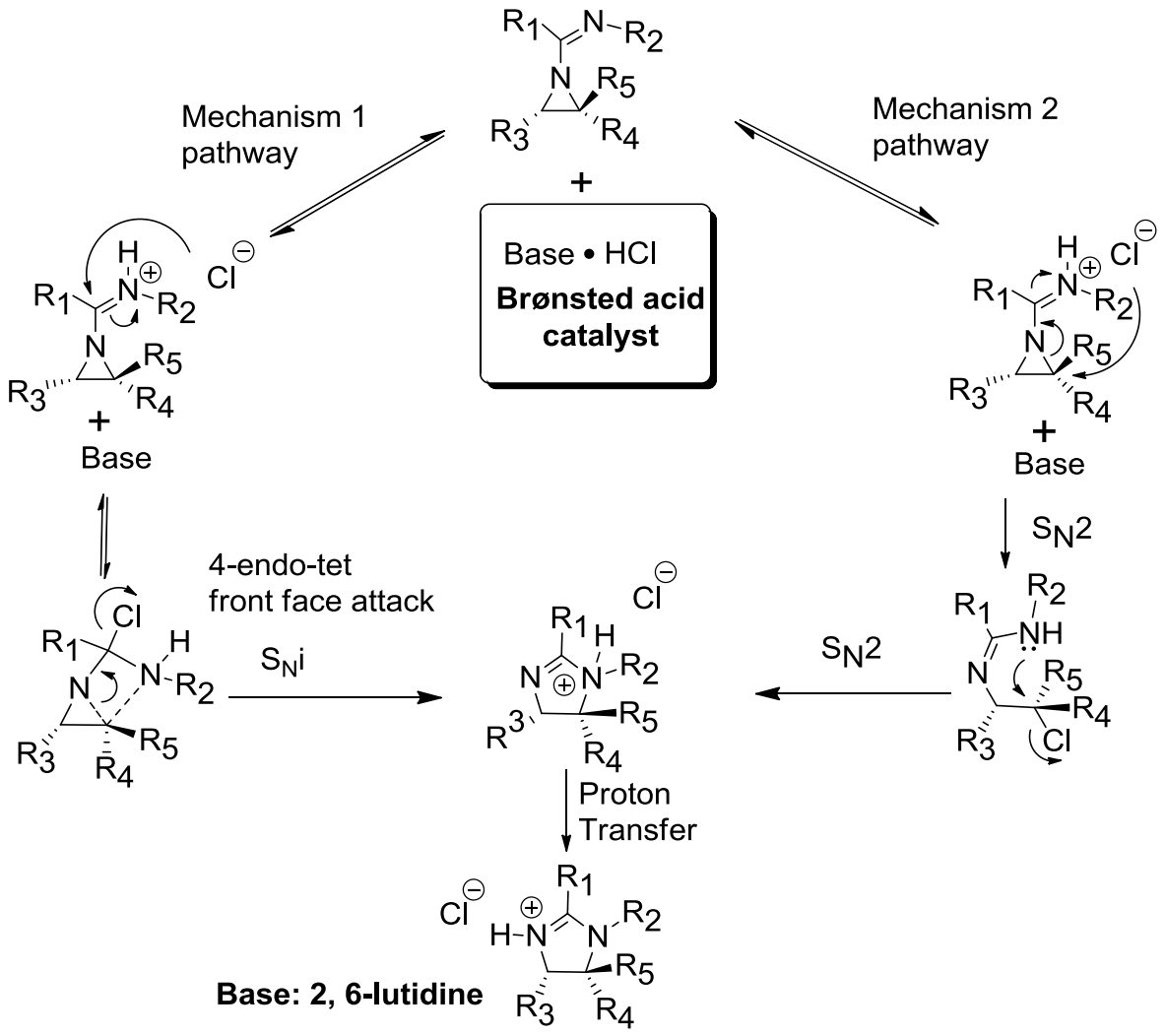


Figure 2-2: X-ray crystallography of compound **2-18**

This retention of stereochemistry could be accomplished by S_N2 attack of the chloride anion at the 2-position of the imidoyl aziridine ring carbon and then ring closure through a second S_N2 (**Mechanism 2**).[11-13] However, another possible mechanism could involve attack of the imidoyl carbon atom by the chloride anion followed by ring closure (**Mechanism 1**). This mechanism would be analogous to the earlier proposed mechanism of attack of the imidoyl carbon by the iodine anion from NaI and subsequent ring closure (**Scheme 2-3**).[11,14]



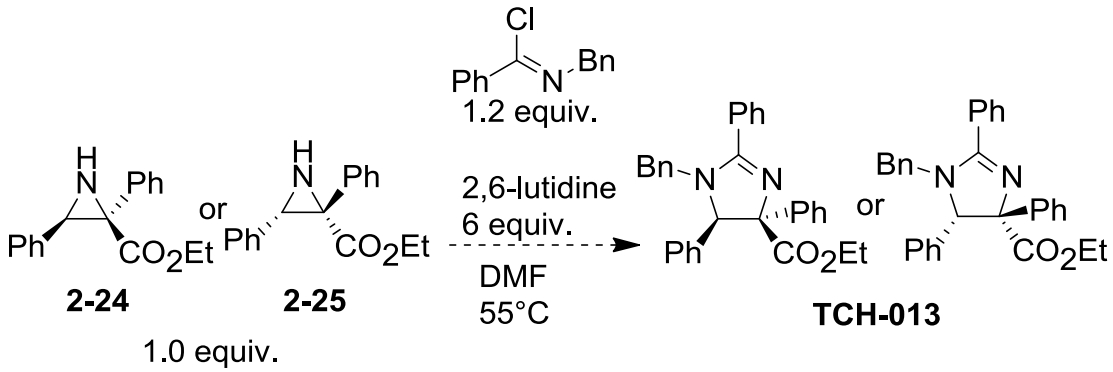
Scheme 2-3: Proposed reaction mechanism for imidazoline synthesis

The latter mechanism would suggest that an imidoyl aziridine would undergo ring expansion by a 4-endo-tet ring closure which is not favorable by Baldwin's rules for ring closure. Both a SN_i or a stepwise process are possible mechanisms; evidence for these mechanisms has been supported by Tomasini and coworkers[15] via the ring expansion of an *N-tert*-butoxycarbonyl aziridine to an oxazolidinone. These mechanisms for imidoyl aziridine isomerization to a 2-imidazoline would likely involve activation of the imidoyl

aziridine intermediate by the Brønsted acid, 2,6-lutidine•HCl. Nitrogen-carbon bond formation occurred at the most electropositive carbon atom in the imidoyl aziridine intermediate. The most electropositive carbon was the C-2 position of the aziridines in all of these reactions except when a *p*-NO_2-C_6H_4 substituent (aziridine **2-10**) was introduced at the C-3 position or a benzyl group (aziridine **2-14**) at the C-2 position. In this case the C-3 and C-2 positions of the aziridine ring carbons had similar electronics. Therefore, in both of these reactions of aziridine **2-10** or **2-14** with imidoyl chloride **2-2** yielded a mixture of 2-imidazoline regioisomers (**Table 2-3, entries 4, 8**).

We have developed a simple one pot stereospecific synthesis of 2-imidazolines from the ring expansion of an aziridine with an imidoyl chloride consistent with a Heine reaction. The scope of the reaction indicated that the reaction tolerated many diverse functional groups. The purification of imidoyl chlorides and imidoyl aziridines intermediates were not needed, therefore creating a simple one pot method to synthesize these biologically significant highly-substituted 2-imidazolines.

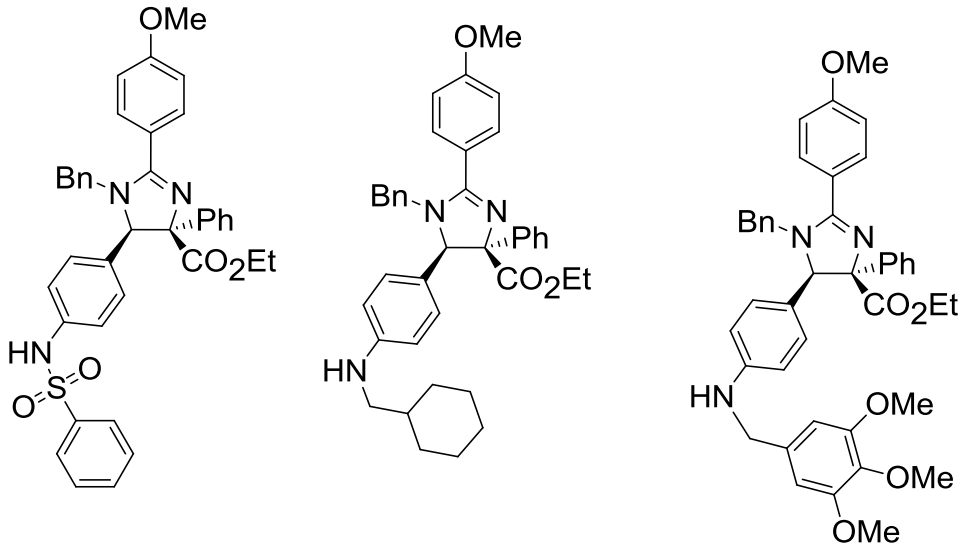
One limitation of the reaction scope was that it did not allow access to enantiopure *trans*-4,5-diphenyl imidazolines di-substituted at the C-5 position. Specifically the enantiomers of the lead compound **TCH-013** could not be synthesized through this methodology. This was due to the fact that there was not a known synthesis for either aziridine enantiomer **2-24** or **2-25** (**Scheme 2-4**).



Scheme 2-4: Proposed synthesis of **TCH-013**.

However, these imidazolines were tested for their ability to inhibit the 20S proteosome and were typically found to be EC_{50} 1-2 μM for the *trans*-4,5-diphenyl imidazolines (see master's thesis). The imidazolines **2-16** through **2-23** unfortunately were found to be poor inhibitors of the 20S proteosome. They were poor inhibitors because the imidazolines **2-16** through **2-23** contained the opposite regiochemistry than that of **TCH-013**. The regiochemistry and position of the benzyl substituent proved to be very important for 20S proteosome inhibition.[7]

Recently Teri Landsdell, Dillion Cogan, and Jake Ludwig have discovered that imidazolines **2-26, 2-27,** and **2-28** all inhibit the 20S proteosome in the nanomolar range (Manuscript submitted to *J. Med. Chem.* 2013) **(Figure 2-3**).



IC_{50} = 410 nM
2-26

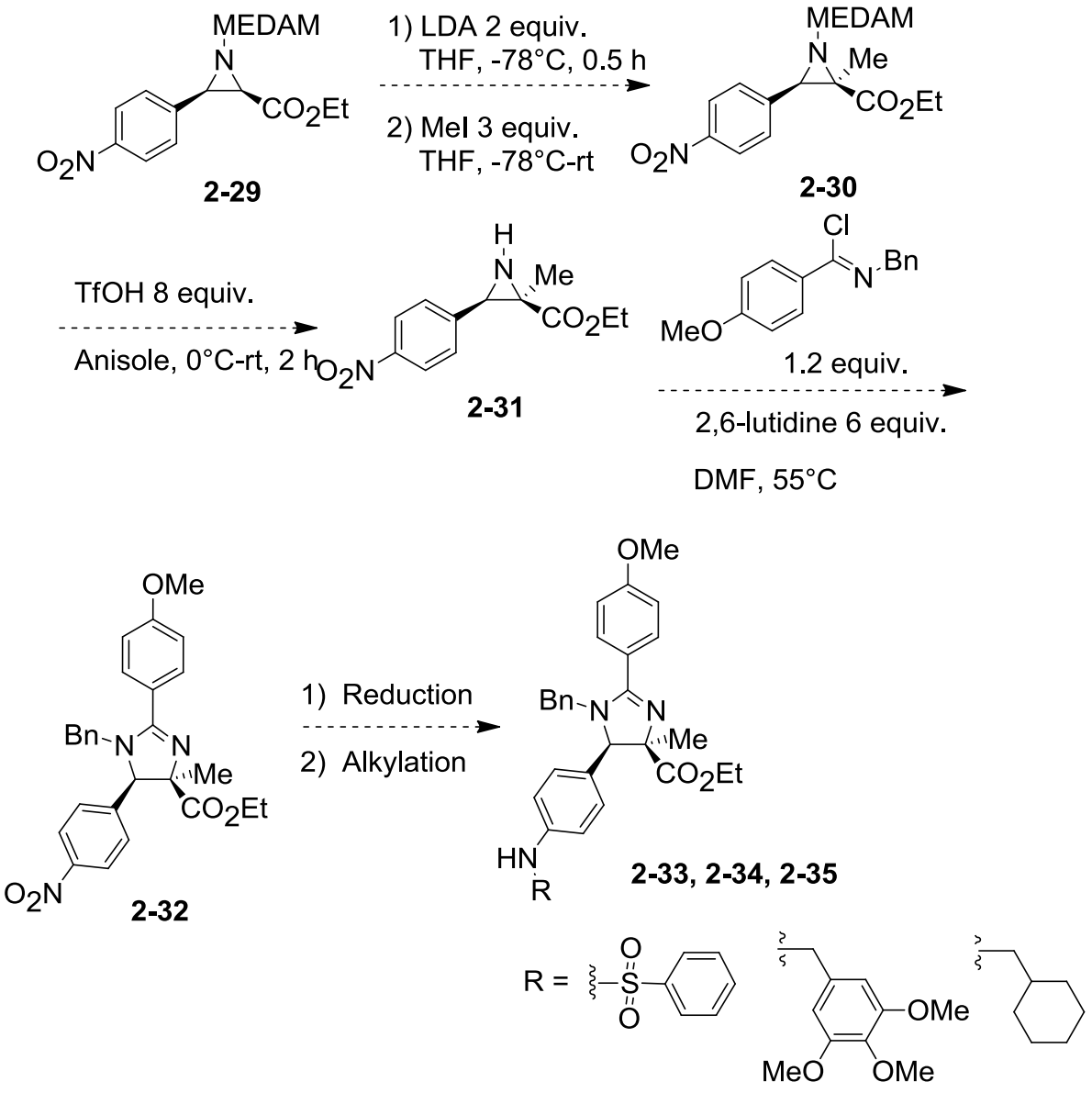
IC_{50} = 110 nM
2-27

IC_{50} = 320 nM
2-28

Figure 2-3: Nanomolar 20S Proteasome Inhibitors **2-26, 2-27, 2-28**

These nanomolar 20S proteasome inhibitors **2-26**, **2-27**, and **2-28** all contained substituted aniline substituent at the C-4 carbon of the imidazoline ring. As mentioned earlier the ring expansion of aziridine **2-10** with a *p*-NO_2 substituent gave imidazoline **2-19** in a 2:1 mixture of regioisomers because it this case the electronics of the aziridine C-3 and C-2 were similar. By making the C-3 carbon of the aziridine ring the most electropositive the desired imidazoline regioisomer would be synthesized by opening the aziridine at the C-3 position instead of the C-2 position. The imidazoline could be synthesized enantiopure by the reaction of an enantiopure aziridine **2-29** provided by the methodology by Wulff and coworkers.[16,17] Alkylation of aziridine **2-29** with methyl iodide followed by removal of the MDAM group would yield aziridine **2-31**. The ring expansion of **2-31** to **2-32** would be expected to yield the desired regiochemistry due to the increased sterics at C-2 position of aziridine **2-31.** The most electropositive carbon of aziridine **2-31** would be C-3 position

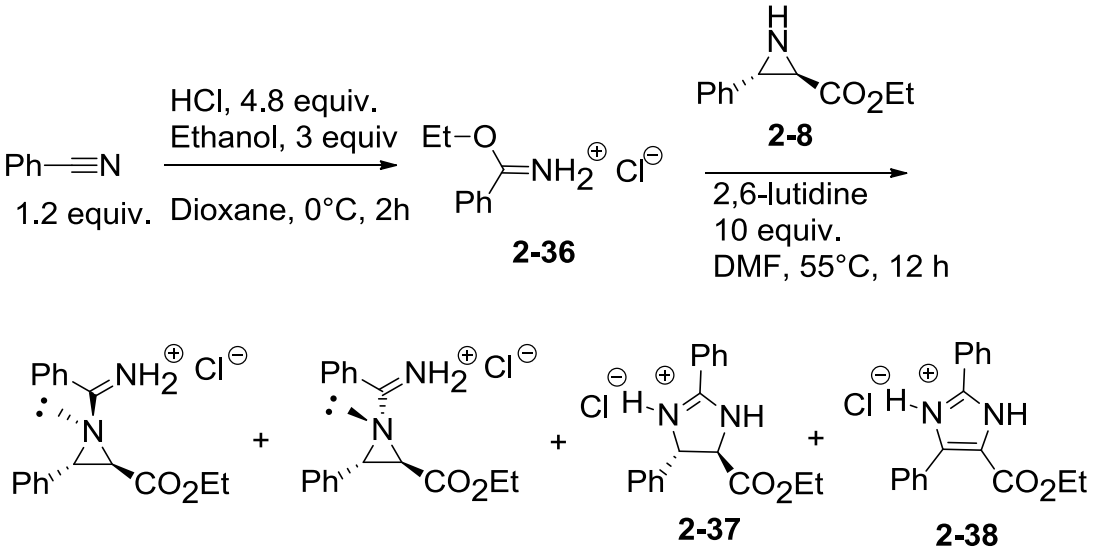
due to the donating methyl group at C-2 position and the electron withdrawing *p*-NO_2-Ph group at C-3 position. Reductive amination of **2-32** or reduction of **2-32** to an aniline followed by alkylation would yield the enantiopure imidazolines **2-33**, **2-34**, and **2-35** (**Scheme 2-5**).



Scheme 2-5: Proposed Synthesis of 26S Proteosome Inhibitors

The only difference between compounds **2-33, 2-34**, and **2-35** versus **2-26**, **2-27**, and **2-28** would be that a methyl group instead of a phenyl group would be at the imidazoline C-5 position. However, imidazolines substituted with a methyl group at the C-5 position have been shown to be potent 20S proteosome inhibitors based on SAR studies.[18,19] This would hopefully lead to a library of enantiopure 20S proteosome inhibitors.

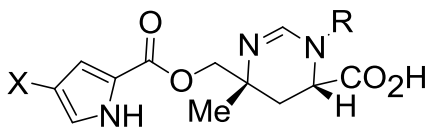
We next turned our attention to other applications of this ring expansion reaction. We first attempted the ring expansion reaction of an aziridine with ethyl benzimidate hydrogen chloride **2-36**. The best way to generate ethyl benzimidate hydrogen chloride was by reaction of benzonitrile with HCl (g) followed by addition of ethanol. Compound **2-36** was unstable and had to be used *in situ* with aziridine **2-8** under the usual reaction conditions. Unfortunately this reaction was not successful because the exocyclic nitrogen was less nucleophilic with a hydrogen atom substituent instead of an *N*-alkyl group substituent. The imidazoline **2-37** was also very prone to oxidation by residual oxygen in the reaction solution driven by "its strong desire" to become aromatic. The ring CH hydrogen atoms of **2-37** were oxidized to an imidazole **2-38** (**Scheme 2-6**).



Scheme 2-6: Attempted ring expansion of **2-8** with ethyl benzimidate•HCl

The ring expansion of aziridine **2-8** was also attempted with ethyl chloroformate and benzyl isocyanate under the standard reaction conditions. In both of these cases alkylation of aziridine **2-8** occurred but the ring expansion reaction to a heterocycle did not occur.

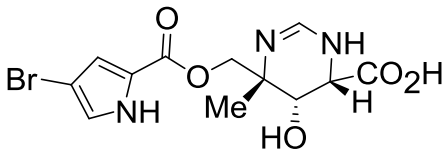
Instead of changing the nature of the electrophile we decided to keep the electrophile the same and change the nucleophile from an aziridine to an azetidine. Azetidines are four membered nitrogen heterocycles that have similar strain energy to that of an aziridine.[20] However, the bond angles of an azetidine are different than that of an aziridine.[21] Based on previous reports[20,22] we envisioned that an azetidine would undergo a (4+2) ring expansion with an imidoyl chloride to a six membered ring called a tetrahydropyrimidine. Tetrahydropyrimidines substituted at the C-4 and C-6 positions make up an important class of natural products known as the Manzacidins [23,24] (**Figure 2-4**).



X = Br, R = H, Manzacidin A

X = Br, R = Me, Manzacidin C

X = H, R = Me, Manzacidin D

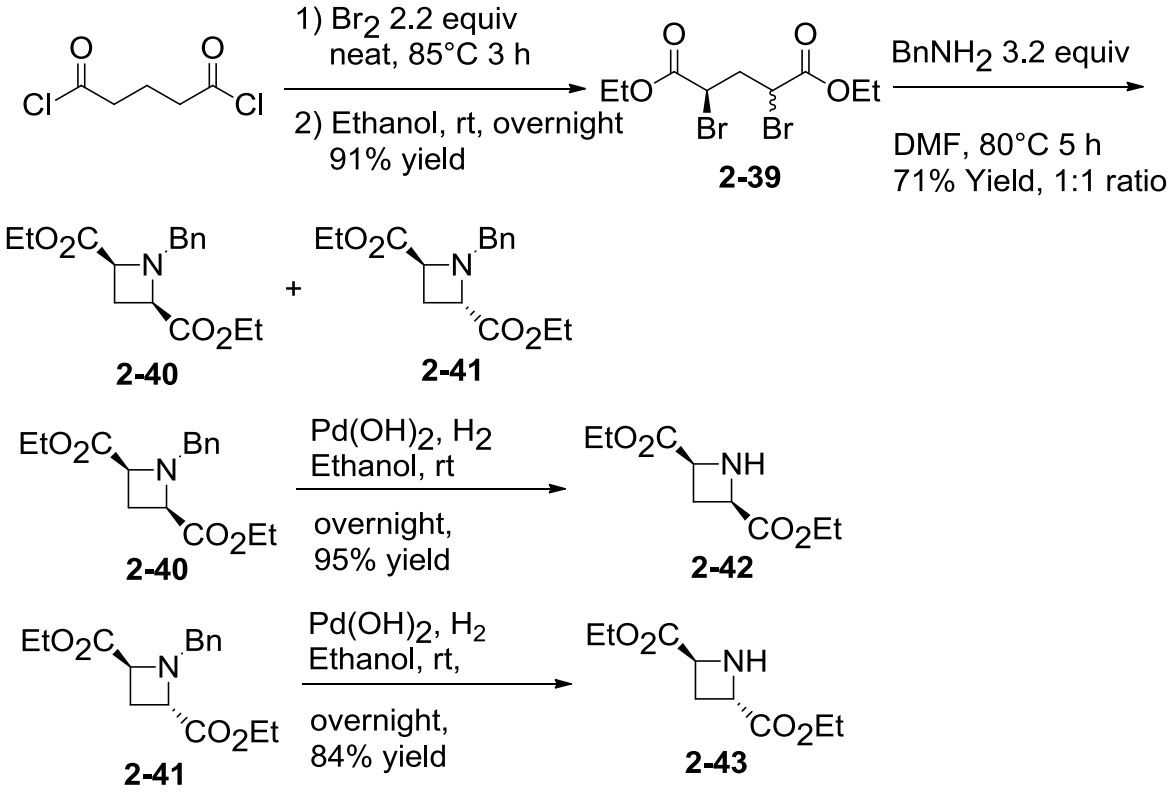


Manzacidin B

Figure 2-4: Manzacidin natural products

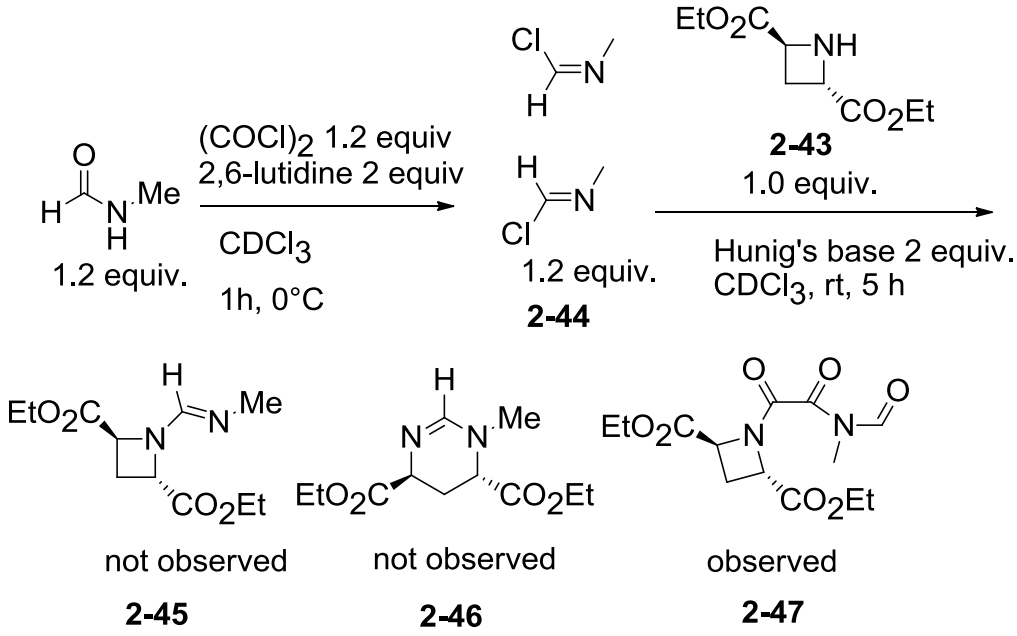
Analogous to a C-2 substituted ester aziridine which underwent a ring expansion to an imidazoline an azetidine substituted at the C-2 and C-4 positions with an ethyl ester group may also undergo a ring expansion to a tetrahydropyrimidine. The azetidines **2-42**

and **2-43** were thought of to be good substrates to try a ring expansion with an imidoyl chloride because they are activated by the ethyl ester groups at the azetidine C-2 and C-4 positions. Azetidines **2-42** and **2-43** were synthesized from commercially available glutaroyl dichloride. Glutaroyl dichloride was heated to 85°C with molecular bromine while being irradiated with a sunlamp followed by reaction with anhydrous ethanol to yield compound **2-39**.[25,26] Reaction of **2-39** with benzyl amine yielded **2-40** and **2-41**, which were separated by column chromatography. The benzyl protecting group was removed by hydrogenolysis with Pearlman's catalyst to yield **2-42** and **2-43**[25,26] (**Scheme 2-7**).



Scheme 2-7: Synthesis of *cis* and *trans*-diethyl azetidine-2,4-dicarboxylate

The Manzacidin natural products all contained a hydrogen atom substituent at the C-2 carbon and hydrogen or methyl substituent at the *N*-1 nitrogen. The synthon required would be an (*E*)-N-methylformimidoyl chloride **2-44**. Ring expansion of a formimidoyl chloride with an azetidine would yield a tetrahydropyrimidine with a methyl or benzyl substituent at the *N*-1 position. The benzyl protecting group could be removed to yield a hydrogen atom at the *N*-1 position. This would form the tetrahydropyrimidine ring in the Manzacidin natural products. However, transformation of a formamide into an imidoyl chloride is not well known. Very few examples exist in the literature and a formimidoyl chloride is considered an unstable molecule that will undergo decomposition.[27] The reaction of *N*-methyl formamide with oxalyl chloride with 2,6-lutidine did not yield an imidoyl chloride. When azetidine **2-43** was added to **2-44** the compound **2-47** was isolated and verified by x-ray crystallography. Unfortunately, the desired tetrahydropyrimidine **2-46** was not formed nor were the intermediates **2-44** and **2-45** (**Scheme 2-8**).



Scheme 2-8: Attempted Synthesis of tetrahydropyrimidine **2-46**

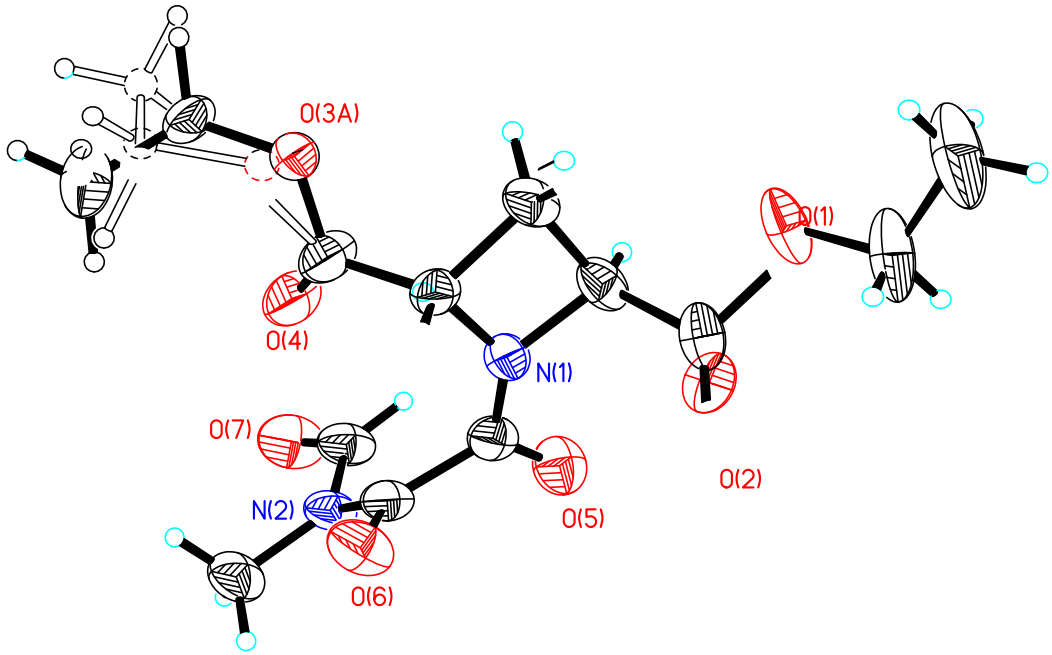
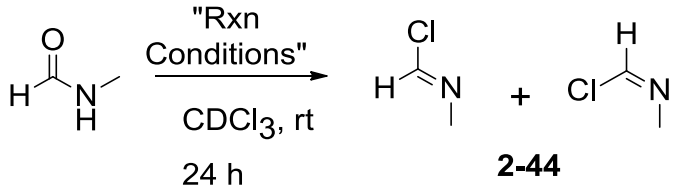


Figure 2-5: X-ray crystallography of compound **2-47**

N-methyl formamide underwent *N*-acylation with $(COCl)_2$ followed by nitrogen substitution of the azetidine **2-43** to yield compound **2-47**. A variety of reaction conditions were employed to synthesize (*E*)-*N*-methylformimidoyl chloride, but these reactions failed to yield any of the desired product. Instead reaction exclusively occurred at the nitrogen atom[28] of *N*-methyl formamide instead of the oxygen atom, a reaction did not occur, or a complicated mixture of products was obtained (**Table 2-2**).

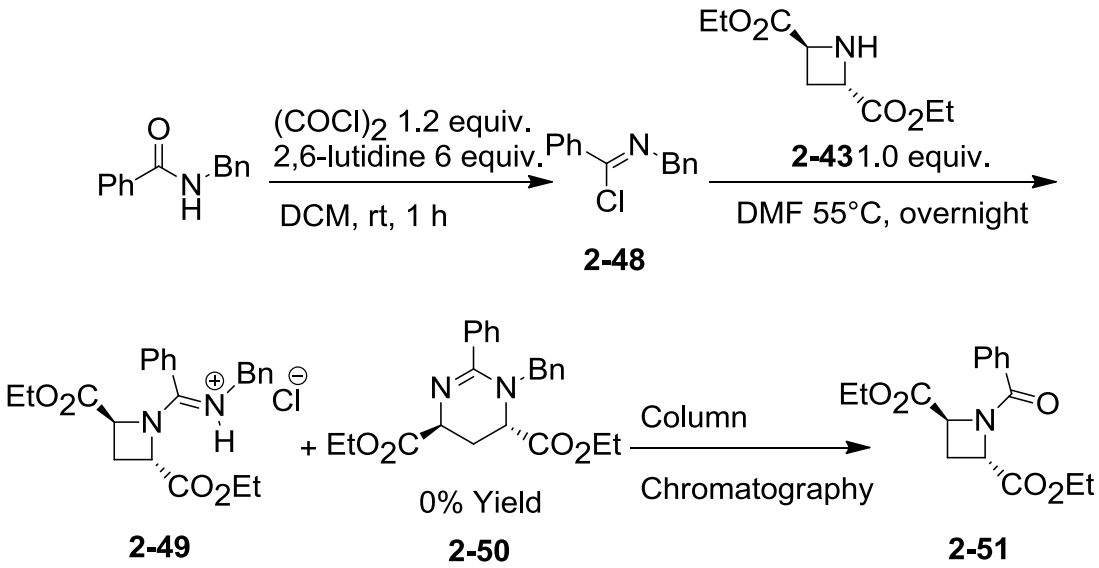
Table 2-4: Attempted Synthesis of (E)-N-methylformimidoyl chloride



entry	reagent	base	base equiv	yield (%) **2-44**
1	$SOCl_2$	2, 6-lutidine	2	0
2	$SOCl_2$	None	0	0[a]
3	PCl_5	None	0	0
4	PCl_5	2, 6-lutidine	6	0
5	$COCl_2$	2, 6-lutidine	6	0
6	$COCl_2$	None	0	0
7	CCl_4/PPh_3	None	0	0

[a] rxn was carried out at 75°C

Many of the reactions in **Table 2-4** gave evidence for decomposition products which could not be elucidated by NMR analysis. Frustrated by these results I went back to my standard reaction conditions with the *N*-benzyl benzamide with $(COCl)_2$ to yield the imidoyl chloride **2-48**. The reaction of imidoyl chloride **2-48** with azetidine **2-43** was attempted in DMF at 55°C with 6 equivalents of 2,6-lutidine. The tetrahydropyrimidine **2-50** was not synthesized but instead only the intermediate imidoyl azetidine **2-49**. Even upon heating to 140°C **2-49** did not undergo ring expansion to **2-50** (**Scheme 2-9**).



Scheme 2-9: Attempted synthesis of tetrahydropyrimidine **2-50**

The only compound that was isolated was **2-51** upon purification on silica gel due to hydrolysis of compound **2-49**. Similarly the reaction of the *cis*-azetidine also did not undergo ring expansion into a tetrahydropyrimidine. The reactions of an azetidine with an acid chloride, a chloroformate, or an isocyanate also did not lead to a ring expansion reaction to 6-membered heterocycle, but instead just alkylated the azetidine nitrogen atom. The bond angles of an azetidine were different than an aziridine bond angles and must have been the determining factor for prevention of the ring expansion to occur. Perhaps stronger reaction conditions are needed such as a stronger Brønstead acid or a different nucleophile besides chloride to cause the ring expansion to occur. This ring expansion of an azetidine with an imidoyl chloride should be possible analogous to an aziridine and should occur through one of the two possible proposed mechanisms for the aziridine ring expansion.

APPENDIX

EXPERIMENTAL

Acetonitrile, TEA, and DMF were distilled from calcium hydride under nitrogen. Toluene, and DCM were purified through a column packed with dry alumina and were dispensed by a nitrogen pressure delivery system. THF and ether were distilled from sodium under nitrogen. Acetone, DCE, and chloroform were distilled from calcium sulfate under nitrogen. Anisole was distilled from calcium hydride under nitrogen. All other reagents and solvents were purchased from Aldrich, Alfa Aesar, or TCI and used without further purification. All flasks were oven dried overnight and cooled under argon or nitrogen. All reactions were monitored by TLC with 0.25 μM precoated silica gel plates and UV light was used to visualize the compounds. It some cases phosphomolybdic acid (PMA) stain or I_2 was used to visualize the compounds. Column chromatography silica gel was provided by EM Science (230-400 mesh). All NMR spectra were recorded on a Varian Unity Plus-500 or 300 spectrometer. Chemical shifts are reported relative to the solvent peak of chloroform (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C). Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Melting points were determined on a Mel-Temp apparatus with a microscope attachment. HRMS were obtained at the Mass Spectrometry Facility of Michigan State University with a JEOL JMS HX-110 mass spectrometer.

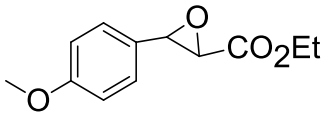
General procedure to neutralize silica gel

Silica gel was saturated with TEA, the slurry was mixed for 5 minutes and then concentrated *in vacuo* to remove the excess TEA to give a free flowing powder once again.

General Procedure for Darzen Epoxidation

The typical reaction scale was based on 3 g of the epoxide for a 100% yield reaction.[32] To a 250 mL round bottom flask under nitrogen was added THF (75 mL) and NaOEt (1 equiv.). This solution was cooled to 0°C in an ice water bath. The desired aldehyde (1 equiv.) was added to the reaction flask followed by addition of ethyl chloroacetate (1 equiv.). The solution was left in the ice water bath and was allowed to react and slowly warm to room temperature for approximately 18 hours. After 18 hours the solution was poured into a separatory funnel. Water (100 mL) was added to the separatory funnel and the solution was extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting epoxide was purified by silica gel chromatography.

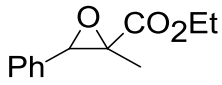
***Trans*-ethyl 3-(4-methoxyphenyl)oxirane-2-carboxylate**



The compound was synthesized by the general procedure. The silica gel was neutralized with TEA by the general procedure. The compound was purified by silica gel plug. 1: 2 DCM: hexane, $R_f = 0.7$ to give a mixture of the epoxide and residual *p*-methoxy benzaldehyde. The residual *p*-methoxy benzaldehyde was removed by vacuum distillation with heating to approximately 150°C *in vacuo* (approx. 10 mm Hg), the pure epoxide did not distill over at this temperature but removed the residual aldehyde to give the epoxide sufficiently pure for characterization. Oil; 48% yield; ^{1}H NMR (300 MHz) $CDCl_3$: 1.37 (3H, t, J = 7.2 Hz), 3.54 (1H, d, J = 1.8 Hz), 3.85 (3H, s), 4.08 (1H, d, J = 1.5 Hz), 4.23-

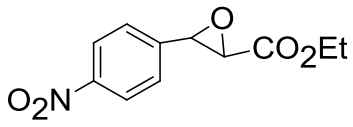
4.41 (2H, m), 6.92 (2H, d, J = 8.7 Hz), 7.25 (2H, d, J = 9 Hz); ^{13}C NMR (75 MHz) $CDCl_3$: 14.18, 55.38, 56.73, 57.93, 61.76, 114.15, 126.87, 127.27, 160.28, 168.43; IR (NaCl): 3154, 2984, 1740, 1516, 1466, 1251, 1205; HRMS: Calculated for $C_{12}H_{14}O_4$ (M^+): 223.0970; Found 223.0975.

Ethyl 2-methyl-3-phenyloxirane-2-carboxylate



The product was synthesized according to the general procedure except ethyl 2-bromopropanoate was used instead of ethyl chloroacetate. Residual benzaldehyde and ethyl 2-bromopropanote were removed *in vacuo* (approx. 10 mm Hg) at room temperature. Further purification was not needed; oil; 52% yield. The compound matched the reported literature data.[29] ^{1}H NMR (300 MHz) $CDCl_3$: 1.33 (1H, s), 1.35 (3H, t, J = 7.8 Hz), 4.29 (2H, m), 4.33 (1H, s), 7.29-7.40 (5H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 13.00, 14.51, 60.20, 62.10, 62.60, 126.80, 128.40, 134.00, 170.00.

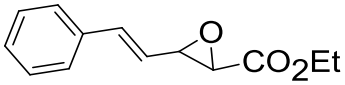
***Trans*-ethyl 3-(4-nitrophenyl)oxirane-2-carboxylate**



The compound was synthesized according to the general procedure. Residual *p*-nitro benzaldehyde was removed by sublimation at 150°C *in vacuo* (approx. 10 mm Hg). This left the residual epoxide which was purified by silica gel chromatography. The silica gel was neutralized with TEA by the general procedure. Silica gel chromatography, 1: 1 DCM: hexane, R_f = 0.1, 41% yield; solid; mp = 62-63°C; ^{1}H NMR (500 MHz) $CDCl_3$:

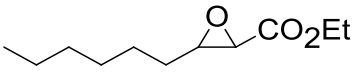
1.35 (3H, t, J = 7.0 Hz), 3.50 (1H, d, J = 2.0 Hz), 4.21 (1H, d, J = 2.0 Hz), 4.29-4.36 (2H, m), 7.49 (2H, d, J = 8.5 Hz), 8.25 (2H, d, J = 9.0 Hz); ^{13}C NMR (125 MHz) $CDCl_3$: 14.31, 56.89, 57.20, 57.23, 124.13, 126.93, 142.56, 148.49, 167.52; IR (NaCl): 3154, 2922, 1742, 1526, 1348, 1208. The compound has been previously reported.[30]

***Trans*-(E)-ethyl 3-styryloxirane-2-carboxylate**



The product was synthesized according to the standard procedure. The silica gel was neutralized according to the general procedure. Silica gel chromatography 25: 75 DCM: hexane R_f = 0.33; 46% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.34 (3H, t, J = 7.0 Hz), 3.52 (1H, d, J = 2.0 Hz), 3.77 (1H, d, J = 7.5 Hz), 5.88 (1H, dd, J_1 = 16.0 Hz, J_2 = 8.5 Hz), 6.88 (1H, d, J = 16.5 Hz), 7.21-7.46 (5H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 14.39, 55.34, 58.60, 62.02, 124.18, 126.87, 128.81, 128.97, 136.71, 165.82, 168.79; IR (NaCl): 2918, 1734, 1456, 1381, 1203; HRMS: Calculated for $C_{13}H_{14}O_3$ (M^+): 219.1021; Found 219.1024. The compound has been previously reported.[31]

***Trans*-ethyl 3-hexyloxirane-2-carboxylate**



The compound was synthesized according to the general procedure. Silica gel chromatography 25: 75 DCM: hexane R_f = 0.35 (visualize the product by using a I_2 stain), 38% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 0.89 (3H, t, J = 6.5 Hz), 1.31 (3H, t, J = 7.0 Hz),

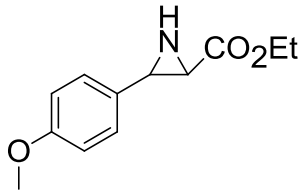
1.28-1.37 (6H, m), 1.42-1.51 (2H, m), 1.54-1.69 (2H, m), 3.15 (1H, dt, J_1 = 4.5 Hz, J_2 = 2.0 Hz), 3.21 (1H, d, J = 2.0 Hz), 4.18-4.29 (2H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 14.17, 14.28, 22.68, 25.86, 29.07, 31.62, 31.82, 53.22, 58.62, 61.61, 169.51; IR (NaCl): 2928, 1740, 1464, 1375, 1280, 1247, 1201; HRMS: Calculated for $C_{11}H_{21}O_3$ (M^+): 201.1491; Found 201.1497.

General Procedure for the Staudinger Reaction: Synthesis of ethyl aziridine-2-carboxylates

The typical reaction scale was based on 2 g of the aziridine for a 100% yield reaction.[32] To a 100 mL round bottom flask under nitrogen was added the epoxide (1 equiv.), NaN_3 (3 equiv.), NH_4Cl (3 equiv.), and 95% ethanol (50 mL). The reaction solution was brought to reflux for 12 hours. The reaction was then cooled to room temperature and poured into a separatory funnel along with water (100 mL). The solution was extracted with EtOAc (50 mL x 3), the combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude azide alcohol was used without further purification. The azide alcohol was added to a 100 mL round bottom flask along with MeCN (50 mL) and PPh_3 (0.9 equiv.). This solution was brought to reflux for 15 hours, cooled to room temperature, and the solvent was removed *in vacuo*. To the crude product was added ether (75 mL) followed by hexane (75 mL). This solution was put in the fridge for 30 minutes. The majority of the PPh_3O had precipitated out of the solution.

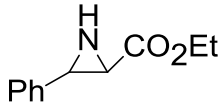
The PPh_3O was removed by vacuum filtration and the mother liquor was concentrated to dryness *in vacuo*. The resulting aziridine was purified by silica gel chromatography.

2-7: *Trans*-ethyl 3-(4-methoxyphenyl)aziridine-2-carboxylate



The product was synthesized according to the standard procedure. The crude product was purified by silica gel chromatography. The silica gel was neutralized with TEA by the general method and was purified by column chromatography. 1:3 DCM: hexane; R_f= 0.55; solid; mp = 46-48; 58% yield (2 steps); ^{1}H NMR (300 MHz) $CDCl_3$: 1.35 (3H, t, J = 6.9 Hz), 1.89 (1H, s, br), 2.56 (1H, d, J = 7.5 Hz), 3.24 (1H, d, J = 7.5 Hz), 3.84 (3H, s), 4.21-4.38 (2H, m), 6.89 (2H, d, J = 8.7 Hz), 7.27 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz) $CDCl_3$: 14.21, 39.38, 40.08, 53.32, 61.75, 113.92, 114.09, 127.27, 129.92, 159.32; IR (NaCl): 3155, 2984, 1721, 1515, 1250, 1219; HRMS Calculated for $C_{12}H_{16}NO_3$ (M^+): 222.1130; Found 222.1137.

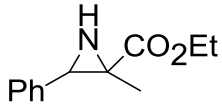
2-8: *Trans*-ethyl 3-phenylaziridine-2-carboxylate



The product was synthesized according to the standard procedure. The crude product was purified by silica gel chromatography; 20: 80 EtOAc: Hexane; R_f = 0.25; oil; 59% yield (2 steps). The compound matched the reported literature data.[32] ^{1}H NMR (300 mHz),

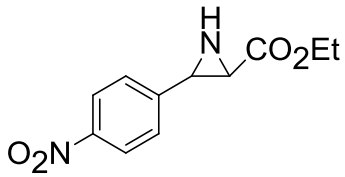
$CDCl_3$: 1.31 (3H, t, J = 7.0 Hz), 1.90 (1H, s, br), 2.58 (1H, s), 3.25 (1H, s), 4.25 (2H, m), 7.36-7.25 (5H, m); ^{13}C NMR (75 mHz), $CDCl_3$: 14.00, 39.30, 40.20, 61.60, 126.10, 127.60, 128.30, 137.80, 171.60.

2-9: *Trans*-ethyl 2-methyl-3-phenylaziridine-2-carboxylate



The product was synthesized according to the standard procedure. The crude product was purified by silica gel chromatography; 20: 80 EtOAc: hexane; R_f = 0.30; oil; 43% yield (2 steps). ^1H NMR (500 MHz) $CDCl_3$: 1.13 (3H, s), 2.14 (1H, s, br), 3.49 (1H, s), 4.24-4.29 (2H, m), 7.27-7.36 (5H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 14.54, 14.43, 41.03, 45.70, 62.23, 127.70, 128.23, 128.35, 136.04, 174.57; IR (NaCl): 2920, 1717, 1456, 1387, 1284, 1196; HRMS Calculated for $C_{12}H_{15}N_1O_2$ (M^+): 206.1181; Found 206.1189.

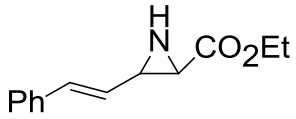
2-10: *Trans*-ethyl 3-(4-nitrophenyl)aziridine-2-carboxylate



The product was synthesized according to the standard procedure. Silica gel chromatography; the silica gel was neutralized with TEA by the general method; 1:3 DCM: hexane; R_f = 0.3; solid; mp 79-80°C; 56 % yield (2 steps), ^1H NMR (300 MHz) $CDCl_3$: 1.36 (3H, t, J = 7.2 Hz), 2.09 (1H, s, br), 2.61 (1H, s), 3.37 (1H, s), 4.26-4.37 (2H, m), 7.49 (2H, d, J = 9 Hz), 8.22 (2H, d, J = 9 Hz); ^{13}C NMR (75 MHz) $CDCl_3$: 14.10, 39.30, 40.02,

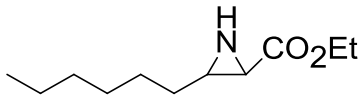
62.12, 123.60, 127.06, 145.57, 147.39, 170.88; IR (NaCl): 2927, 2856, 1724, 1464, 1376, 1213; HRMS Calculated for $C_{11}H_{12}N_2O_4$ (M^+): 237.0875; Found 237.0883.

2-11: *Trans*-(E)-ethyl 3-styrylaziridine-2-carboxylate



The product was synthesized according to the standard procedure. Silica gel chromatography; the silica gel was neutralized with TEA by the general method; 1:2 DCM: Hexane; R_f = 0.31; Oil; 27% yield (2 steps); ^{1}H NMR (300 MHz) $CDCl_3$: 1.36 (3H, t, J = 7.2 Hz), 1.74 (1H, s, br), 2.61 (1H, s, br), 2.95 (1H, d, J = 6.9 Hz), 4.21-4.37 (2H, m), 5.91 (1H, dd, J_1 = 15.9 Hz, J_2 = 7.8 Hz), 6.75 (1H, d, J = 15.9 Hz), 7.25-7.41 (5H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 14.23, 37.37, 40.31, 61.79, 126.31, 127.42, 127.88, 128.66, 133.21, 136.29, 171.87; IR (NaCl): 2984, 1722, 1452, 1373, 1213; HRMS: Calculated for $C_{13}H_{15}NO_2$ (M^+): 218.1174; Found 218.1181.

2-12: *Trans*-ethyl 3-hexylaziridine-2-carboxylate

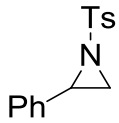


The product was synthesized according to the standard procedure with the exception that the reaction time for the Darzen reaction and Staudinger reaction was 24 hours. The crude product was purified by silica gel chromatography. 1: 2 DCM: Hexane, R_f = 0.36 (visualized spot by PMA stain); oil, 33% yield (two steps); ^{1}H NMR (500 MHz) $CDCl_3$: 0.89 (3H, t, J = 7.0 Hz), 1.2-1.35 (8H, m), 1.31 (3H, t, J = 7.0 Hz), 1.40-1.78 (3H, m), 2.22

(1H, dt, J_1 = 3.5 Hz, J_2 = 2.5 Hz), 2.28 (1H, d, J = 2.5 Hz), 4.16-4.27 (2H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 14.29, 14.43, 22.80, 27.30, 29.19, 31.98, 32.97, 35.55, 39.86, 61.69, 165.82. IR (NaCl): 2925, 1725, 1524, 1346, 1219; HRMS: Calculated for $C_{11}H_{22}N_1O_2$ (M^+): 200.1651; Found 200.1657.

Synthesis of Aziridines by other Methods

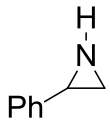
2-phenyl-1-tosylaziridine



Caution: Chloramine T can explode if heated; check MSDS. Chloramine T was sold as a hydrate but had to be dried in order for the reaction to work. Chloramine T was dried by placing it in a round bottom flask under *vacuo* at room temperature for 72 hours. The compound was prepared according to a literature method.[33] To a 100 mL round bottom flask under nitrogen was added chloramine T (2.97 g, 10.50 mmol), anhydrous acetonitrile (50 mL), and styrene (1.1 mL, 9.55 mmol). Pyridinium hydrogen tribromide (0.34 g, 0.95 mmol) was added to the round flask at room temperature. After 6 hours the reaction solution was poured into water (50 mL) and extracted with EtOAc (50 mL x 3), the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Silica gel chromatography 20: 80 EtOAc: hexane; R_f = 0.5; white solid; mp 94-96°C, 54% yield. The compound matched the reported literature data.[33] ^{1}H NMR (300 MHz), $CDCl_3$: 2.40 (1H, d, J = 4.6 Hz), 2.45 (3H, s), 3.0 (1H, d, J

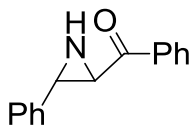
= 7.3 Hz), 3.80 (1H, dd, J_1 = 7.3 Hz, J_2 = 4.6 Hz), 7.15-7.45 (7H, m), 7.90 (2H, d, J = 8.2 Hz); ^{13}C NMR (75 MHz), $CDCl_3$: 23.5, 37.0, 42.5, 127.0, 128.0, 128.5, 129.0, 130.0, 135.5.

2-15: 2-phenylaziridine



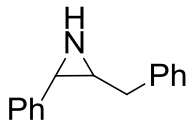
The compound was prepared according to the literature method.[34] 2-phenyl-1-tosylaziridine (0.30 g, 1.10 mmol), Mg^0 (0.13 g, 5.0 mmol), and anhydrous methanol (10 mL), was added to a 25 mL round bottom flask. The solution was sonicated at room temperature for 1 hour. NH_4Cl sat. aq was added to reaction flask until the excess Mg^0 was consumed and the solution was extracted with EtOAc (25 mL x 3). The combined organic extracts were washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography; 30: 70 EtOAc: hexane; R_f = 0.2; oil; 59% yield. The compound matched the reported literature data.[34] ^{1}H NMR (300 MHz), $CDCl_3$: 1.50 (1H, s, br), 1.81 (1H, d, J = 3.2 Hz), 2.21 (1H, d, J = 6.0 Hz), 3.02 (1H, m), 7.15-7.40 (5H, m); ^{13}C NMR (75 MHz), $CDCl_3$: 29.20, 32.10, 125.60, 126.70, 128.20, 140.70.

2-13: *Trans*-phenyl(3-phenylaziridin-2-yl)methanone



The compound was prepared according to the literature method.[35] To a 25 mL round bottom flask was added S,S-diphenylsulfilimine (0.58 g, 2.89 mmol), chalcone (0.30 g, 1.45 mmol), and benzene (4.5 mL). The solution was refluxed for 16 h and then concentrated *in vacuo*. The crude product was purified by silica gel chromatography; 100% DCM; R_f = 0.2; solid; mp 124-125°C; 63% yield. The compound matched the reported literature data.[36] ^{1}H NMR (300 MHz), $CDCl_3$: 2.67 (1H, s, br), 3.18 (1H, d, J = 7.1 Hz), 3.51 (1H, d, J = 5.6 Hz), 7.29-7.39 (5H, m), 7.47-7.51 (2H, m), 7.60 (1H, m), 8.0 (2H, m); ^{13}C NMR (75 MHz), $CDCl_3$: 43.51, 44.07, 126.18, 127.86, 128.30, 128.53, 128.79, 133.79, 135.89, 138.30, 195.68.

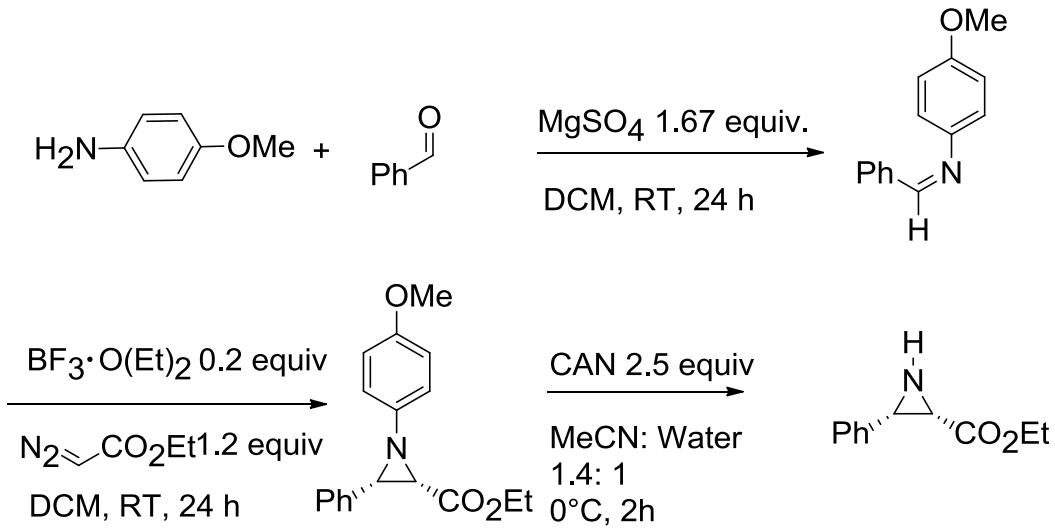
2-14: *Cis*-2-benzyl-3-phenylaziridine



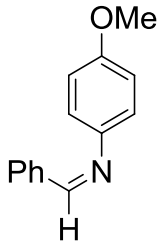
The compound was prepared by a literature method.[37] To a 250 mL round bottom flask cooled under nitrogen was added $LiAlH_4$ (0.34 g, 8.88 mmol) and THF (30 mL). To another 100 mL round bottom flask was added 1,3-diphenylpropan-2-one oxime (1g, 4.44 mmol), and THF (30 mL). The oxime/THF solution was added to the $LiAlH_4$ solution dropwise over 10 minutes with a syringe at room temperature. The solution was brought to reflux for 3 hours. The solution was then cooled to 0°C and water was slowly added followed by 2M NaOH until a white precipitate formed. The precipitated was removed by vacuum filtration and was washed with ether. The ether was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude compound was purified by silica gel

chromatography; 1: 1; ether: hexane; R_f = 0.3; 81% yield; solid mp 44-45°C. The compound matched the reported literature data.[37] ^{1}H NMR (500 MHz) $CDCl_3$ δ 1.21 (1H, s., br) 2.39 - 2.51 (1H, dd, J_1= 8.35 Hz, J_2 = 5.85 Hz), 2.52 - 2.71 (2H, m), 3.38 (1H, d, J =5.85 Hz), 7.09 (2H,d, *J*=7.34 Hz), 7.16 - 7.23 (1H, m) 7.23 - 7.29 (2H, m), 7.31 (1H, m), 7.37 (2H, t, J = 7.34 Hz) 7.44 (2H, d, J = 7.34 Hz); ^{13}C NMR (75 MHz), $CDCl_3$ δ 34.33, 37.19, 38.61, 126.07, 126.85, 127.84, 127.99, 128.29, 128.76, 137.52, 139.79

2-3: Synthesis of Racemic ethyl 3-phenylaziridine-2-carboxylate



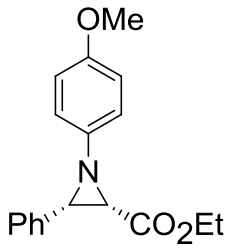
(Z)-N-benzylidene-4-methoxyaniline



The compound was synthesized by a literature method.[38] To a 250 mL round bottom flask was added 4-methoxyaniline (4.67 g, 38.00 mmol), $MgSO_4$ (7.64 g, 63.46 mmol), and

DCM (125 mL). The solution was mixed for 5 minutes under nitrogen at room temperature. Benzaldehyde (3.82 mL, 39.00 mmol) was added with a syringe. The solution was mixed for 24 hours and the $MgSO_4$ was removed by vacuum filtration. The mother liquor was concentrated to give a light brown solid. The compound was recrystallized from hexane, off-white solid, 91% yield, mp 72-73°C. The compound matched the reported literature data.[39] ^{1}H NMR (300 MHz), $CDCl_3$: 3.72 (3H, s), 6.43-7.49 (5H, m), 6.83 (2H, d, J = 9.0 Hz), 7.16 (2H, d, J = 9.0 Hz), 8.20 (1H, s); ^{13}C NMR (75 MHz), $CDCl_3$: 55.30, 158.40, 152.20, 145.60, 145.20, 144.20, 122.20, 115.50, 114.30, 112.00, 55.30.

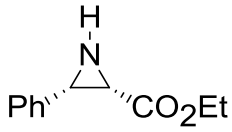
Racemic ethyl 1-(4-methoxyphenyl)-3-phenylaziridine-2-carboxylate



The compound was synthesized by a literature method.[40] To a 250 mL round bottom flask under nitrogen was added (Z)-N-benzylidene-4-methoxyaniline (2.5 g, 12.00 mmol), DCM (100 mL), and BF_3•$O(Et)_2$ (0.30 mL, 2.36 mmol). Ethyl diazoacetate (1.35 mL, 13.00 mmol) was added to the reaction solution with a syringe. The reaction starting releasing nitrogen gas and was mixed a room temperature for 24 hours. The reaction solution was washed with sat. aq. $NaHCO_3$ (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound was purified by silica gel chromatography 20: 80 EtOAc: hexane;

R_f = 0.4; oil; 51% yield. The compound matched the reported literature data.[40] ^{1}H NMR (300 MHz), $CDCl_3$: 0.87 (3H, t, J = 7.3 Hz), 3.03 (1H, d, J = 7.0 Hz), 3.40 (1H, d, J = 7.0 Hz), 3.62 (3H, s), 3.80-3.99 (2H, m), 6.69 (2H, d, J = 9.3 Hz), 6.87 (2H, d, J = 9.3 Hz), 7.36-7.44 (5H, m); ^{13}C NMR (75 MHz), $CDCl_3$: 13.70, 45.60, 47.20, 55.30, 60.71, 114.20, 120.60, 127.50, 127.60, 127.80, 128.30, 128.60, 134.60, 145.60, 155., 167.50.

2-3: Racemic ethyl 3-phenylaziridine-2-carboxylate

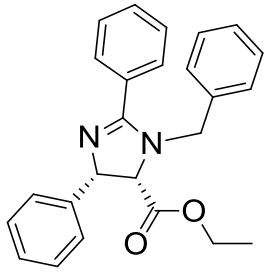


The compound was prepared by the literature method.[41] To a 250 mL round bottom flask was added 1-(4-methoxyphenyl)-3-phenylaziridine-2-carboxylate (1.80 g, 6.06 mmol), acetonitrile (120 mL) and water (80 mL). The round bottom flask was cooled in an ice bath and cerric ammonium nitrate (8.30 g, 15.15 mmol) was added. The reaction was maintained at 0°C for 2 hours and then sat. aq. $NaHCO_3$ was added until the pH was 7. Sodium bisulfate was added to consume the residual cerric ammonium nitrate. The pH was adjusted to 9 with sat. aq. $NaHCO_3$ and then the solution was extracted with EtOAc (50 mL x 3), the combined extracts were washed with brine (30 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography; 1: 1 hexane: ether; R_f = 0.13; white solid; mp 66-68°C. The compound matched the reported literature data and can be found in the my master's thesis.[7,16]

General procedure for synthesis of imidazolines

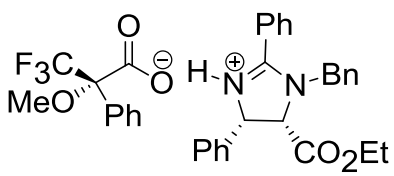
The reaction scale was based on 100 mg of the starting aziridine.[7] To a 10 mL round bottom flask under argon was added the desired amide (1.2 equiv.), 2,6-lutidine (6 equiv.), and DCM (4 mL). The solution was either cooled to 0°C or left at room temperature depending on the amide (located below). Oxalyl chloride (1.2 equiv.) was added to the round bottom flask over 3 minutes with a syringe. The reaction was mixed for the desired time (located below) and then the DCM was removed *in vacuo* at room temperature. This gave the crude product as a mixture of the desired imidoyl chloride, excess 2-6-lutidine (bp 144°C, 760 mm Hg), and 2,6-lutidine hydrogen chloride. This round bottom flask was then placed under argon again and the desired aziridine (100 mg, 1 equiv.) and DMF (4 mL) were added. The solution was heated to 55°C for the desired time (see Table 2 or 3). An aliquot of the reaction solution was taken, placed under vacuum (approx. 10 mm Hg) at room temperature and a ^{1}H NMR was taken to determine the imidazoline reaction times. The reactions could also be monitored by TLC 30:70 EtOAc: hexane and was the most polar spot on the bottom of the TLC as the imidazoline salt. The reaction solution was then cooled to room temperature and poured into a separatory funnel followed by an addition of sat. aq. $NaHCO_3$ (15 mL) and water (15 mL). The product was extracted with EtOAC (20 mL x 3), the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The imidazolines were purified by column chromatography on silica gel. In some cases the silica gel had to be neutralized with TEA to avoid product decomposition.

2-6: Racemic or enantiopure ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5- carboxylate

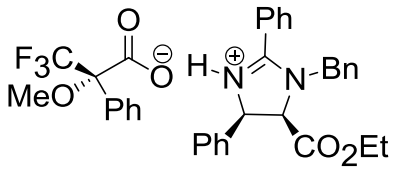


The compound was synthesized according to the general procedure. Either racemic or enantiopure ethyl 3-phenylaziridine-2-carboxylate was used. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 6 hours. Silica gel chromatography; 50: 50 EtOAc: hexane; $R_f = 0.35$; oil; 52% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 0.76 (3H, t, J = 7.0 Hz), 3.34-3.36 (2H, m), 4.15 (1H, d, J = 15.5 Hz), 4.42 (1H, d, J = 12.0 Hz), 4.68 (1H, d, J = 15.5 Hz), 5.55 (1H, d, J = 12.0 Hz), 7.08-7.27 (10H, m), 7.43-7.44 (3H, m), 7.71-7.72 (2H, m); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 13.36 (CH_3), 49.94 (CH_2), 60.39 (CH_2), 67.03 (CH) 71.32 (CH), 127.33 (CH), 127.51 (CH), 127.58 (CH), 127.65 (CH), 127.96 (CH), 128.42 (CH), 128.57 (CH), 129.99 (CH), 130.52 (CH), 130.70 (C), 136.25 (C), 139.00 (C), 146.33 (C), 169.79 (C); IR (NaCl) 3075, 2980, 1738, 1597, 1496, 1452, 1406, 1194, 1132, 1018; HRMS: Calculated for $C_{25}H_{25}N_2O_2$ (M^+): 385.1916; Found 385.1922.

Determination of enantiomeric excess of compound 2-19 by (*S*)-Mosher's Acid



(*S*, *S*, *S*)

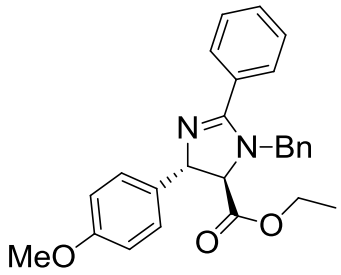


(*S*, *R*, *R*)

Racemic Compound **2-19**	50%	:	50%
Enantiopure Compound **2-19**	>95%	:	not detectable

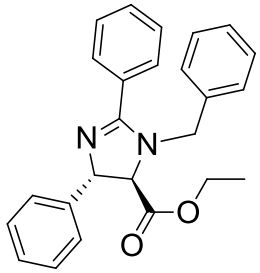
Racemic compound **2-6** and (*S*)-Mosher's acid were combined in equal molar quantities in an NMR tube along with $CDCl_3$. Analysis by ^{1}H NMR revealed that the (*S*, *R*, *R*) and the (*S*, *S*, *S*) diastereomeric salts were formed in a 50:50 mixture. Enantiopure compound **2-6** and (*S*)-Mosher's acid were combined in equal molar quantities in an NMR tube along with $CDCl_3$. Analysis by ^{1}HNMR revealed that only one the (*S*, *S*, *S*) diastereomeric salt was detected. (*S*, *R*, *R*) diastereomeric salt: ^{1}H NMR (500 MHz) $CDCl_3$: 0.78 (3H, t, J = 7.5 Hz), 3.34 (3H, s), 3.49-3.76 (2H, m), 4.33 (1H, d, J = 15.0 Hz), 4.62 (1H, d, J = 12.5 Hz), 4.94 (1H, d, J = 15.0 Hz), 5.86 (1H, d, J = 12.5 Hz), 7.15-7.90 (20H, m), 9.20 (1H, s, br). (*S*, *S*, *S*) diastereomeric salt: ^{1}H NMR (500 MHz) $CDCl_3$: 0.79 (3H, t, J = 7.5 Hz), 3.35 (3H, s), 3.49-3.76 (2H, m), 4.34 (1H, d, J = 15.0 Hz), 4.64 (1H, d, J = 12.5 Hz), 4.95 (1H, d, J = 15.0 Hz), 5.90 (1H, d, J = 12.5 Hz), 7.15-7.89 (20H, m), 9.51 (1H, s, br).

2-16: ethyl 1-benzyl-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydro-1H-imidazole-5-carboxylate



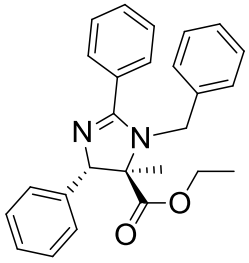
The compound was synthesized according to the general procedure. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 10 hours. Silica gel chromatography; 50: 50 EtoAc: hexane; R_f = 0.45; oil; 45 % yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.29 (3H, t, J = 7 Hz), 3.85 (3H, s), 3.97 (1H, d, J = 16.0 Hz), 4.20-4.26 (2H, m), 4.63 (1H, d, J = 8.0 Hz), 4.64 (1H, d, J = 16.0 Hz), 4.85 (1H, d, J = 8.0 Hz), 6.91-6.93 (2H, m), 7.05 (2H, d J = 7 Hz), 7.23-7.32 (5H, m), 7.43-7.49 (3H, m), 7.68-7.72 (2H, m); ^{13}C NMR (125 MHz) $CDCl_3$: (One CH carbon not found) 14.39 (CH_3), 40.01 (CH_2), 55.56 (CH_3), 61.53 (CH_2), 66.11 (CH), 76.00 (CH), 114.61 (CH), 127.67 (CH), 127.74 (CH), 128.68 (CH), 128.85 (CH), 128.86 (CH), 130.59 (CH), 130.71 (C), 132.83 (C), 136.64 (C), 159.79 (C), 167.22 (C), 172.19 (C); IR (NaCl): 3031, 2934, 1734, 1613, 1512, 1451, 1361, 1249, 1178; HRMS: Calculated for $C_{26}H_{27}N_2O_3$ (M^+): 415.1977; Found 415.2022.

2-17: **ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate**



The compound was synthesized according to the general procedure. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 12 hours. Silica gel column chromatography; 50: 50 EtOAc: hexane; $R_f = 0.4$; solid; 78-80°C; 42% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.27 (3H, t, J = 7.0 Hz), 3.97 (1H, d, J = 7.5 Hz), 4.12-4.28 (2H, m), 4.42 (1H, d, J = 15.5 Hz), 4.61 (1H, d, J = 15.5 Hz), 5.28 (1H, d, J = 7.5 Hz), 7.09 (2H, dd, $J_1 = 6.0$ Hz, $J_2 = 1.5$ Hz), 7.22-7.31 (10H, m), 7.46-7.49 (3H, m), 7.79-7.81 (2H, m); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 14.12 (CH_3), 51.32 (CH_2), 61.26 (CH_2), 69.92 (CH), 72.30 (CH), 126.58 (CH), 127.28 (CH), 127.67 (CH), 127.91 (CH), 128.43 (CH), 128.57 (CH), 128.58 (CH), 128.75 (CH), 130.29 (CH), 130.61 (C), 136.32 (C), 143.23 (C), 165.81 (C), 172.10 (C); IR (NaCl): 3030, 2980, 1734, 1593, 1496, 1448, 1221, 1184; HRMS: Calculated for $C_{25}H_{25}N_2O_2$ (M^+): 389.2023; Found 389.2027.

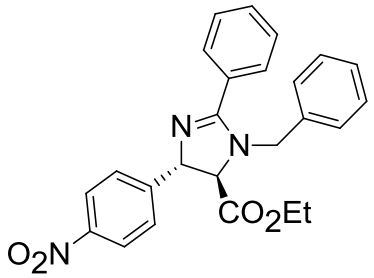
2-18: ethyl 1-benzyl-5-methyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate



The compound was synthesized according to the general procedure. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 12 hours. Silica gel column chromatography; 50: 50 EtOAc: hexane; $R_f = 0.3$; solid; mp 100-102°C; 59% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 0.97 (3H, s), 1.31 (3H, t, J = 7.0 Hz), 4.17 (2H, q, J = 7.0 Hz), 4.32 (1H, d, J = 17.5 Hz), 4.58 (1H, d, J = 17.5 Hz), 5.45 (1H, s), 7.18-7.42 (13H,

m), 7.62-7.64 (2H, m); ^{13}C NMR (125 MHz) $CDCl_3$: (One CH carbon not found); 14.42 (CH_3), 18.44 (CH_3), 48.36 (CH_2), 61.90 (CH_2), 73.67 (CH), 75.83 (C), 127.02 (CH), 127.27 (CH), 127.85 (CH), 128.29 (CH), 128.45 (CH), 128.63 (CH), 128.68 (CH), 130.14 (CH), 131.64 (C), 138.37 (C), 139.33 (C), 167.02 (C), 175.22 (C); IR (NaCl): 3029, 2988, 1732, 1616, 1595, 1497, 1454, 1421; HRMS: Calculated for $C_{29}H_{27}N_2$ (M^+): 403.2174; Found 403.2185.

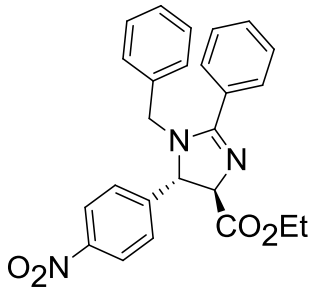
2-19: ethyl 1-benzyl-4-(4-nitrophenyl)-2-phenyl-4,5-dihydro-1H-imidazole-5-carboxylate



The compound was synthesized according to the general procedure. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 13 hours. Silica gel column chromatography; 40: 60 EtOAc: hexane; R_f = 0.29; oil; 13% yield; the regiochemistry was confirmed by NOESY. ^{1}H NMR (500 MHz) $CDCl_3$: 1.33 (3H, t, J = 7.5 Hz), 3.92 (1H, d, J = 7.5 Hz), 4.19-4.38 (2H, m), 4.35 (1H, d, J = 15.0 Hz), 4.71 (1H, d, J = 15.5 Hz), 5.38 (1H, d, J = 7.5 Hz), 7.02-7.04 (2H, m), 7.23-7.26 (3H, m), 7.38 (2H, d, J = 8.5 Hz), 7.50-7.54 (3H, m), 7.79-7.82 (2H, m), 8.15 (2H, d, J = 9.0 Hz); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 14.46 (CH_3), 51.48 (CH_2), 62.02 (CH_2), 69.30 (CH), 71.50 (CH), 124.03 (CH), 127.75 (CH), 128.23 (CH), 128.25 (CH), 128.99 (CH), 129.02 (CH), 129.09 (CH), 130.37 (C), 131.01 (CH), 136.09 (C), 147.46 (C), 150.76 (C), 167.10 (C),

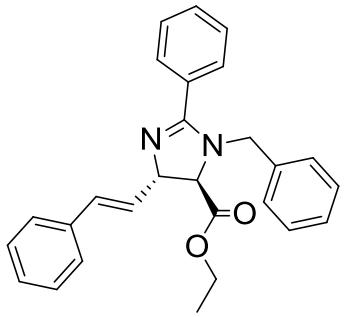
171.81 (C); IR (NaCl, $CDCl_3$): 3028, 2918, 1734, 1524, 1456, 1350; HRMS Calculated for $C_{25}H_{24}N_3O_4$ (M^+): 430.1767; Found 430.1780.

2-19: ethyl 1-benzyl-5-(4-nitrophenyl)-2-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate



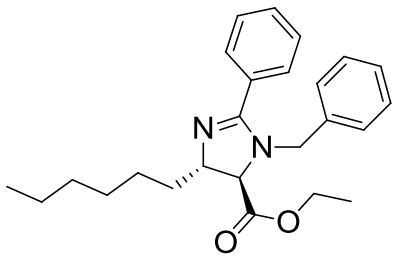
Silica gel column chromatography; 40: 60 EtOAc: hexane; R_f = 0.2; oil; 27% yield; the regiochemistry was confirmed by NOESY; ^{1}H NMR (500 MHz) $CDCl_3$: 1.30 (3H, t, 7.0 Hz), 4.04 (1H, d, J = 15.5 Hz), 4.18-4.31 (2H, m), 4.55 (1H, d, J = 8.0 Hz), 4.64 (1H, d, J = 15.5 Hz), 4.95 (1H, d, J = 15.5 Hz), 7.01 (2H, dd, J_1 = 5.5 Hz, J_2 = 2.0 Hz), 7.23-7.28 (4H, m), 7.47-7.28 (4H, m), 7.74-7.77 (2H, m), 8.23 (2H, d, J = 9.0 Hz); ^{13}C NMR (125 MHz) $CDCl_3$: 14.22 (CH_3), 51.25 (CH_2), 61.77 (CH_2), 66.35 (CH), 76.53 (CH), 124.46 (CH), 127.99 (CH), 128.14 (CH), 128.17 (CH), 128.94 (CH), 128.98 (CH), 129.03 (CH), 130.29 (C), 130.96 (CH), 135.84 (C), 147.89 (C), 148.74 (C), 167.82 (C), 171.56 (C); IR (NaCl): 3029, 2984, 1742, 1595, 1523, 1350; HRMS Calculated for $C_{25}H_{24}N_3O_4$ (M^+): 430.1767; Found 430.1780.

2-20: ethyl 1-benzyl-2-phenyl-4-styryl-4,5-dihydro-1H-imidazole-5-carboxylate



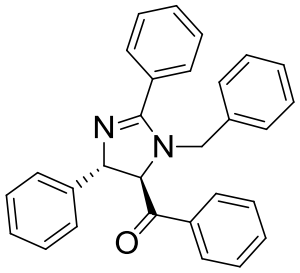
The compound was synthesized according to the general procedure. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 20 hours. The silica gel was neutralized by the general method. Silica gel column chromatography; 40: 60 EtOAc: hexane; R_f = 0.48; oil; 41% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.22 (3H, t, J = 7.0 Hz), 4.10-4.21 (2H, m), 4.20 (1H, d, J = 17 Hz), 4.46 (1H, d, J = 0.5 Hz), 4.47 (1H, d, J = 0.5 Hz), 4.49 (1H, d, J = 16.0 Hz), 6.08-6.14 (1H, m), 6.39 (1H, d, J = 16.0 Hz), 7.07 (2H, d, J = 5.0 Hz), 7.15-7.38 (11H, m), 7.55-7.59 (2H, m); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: (One CH carbon not found) 14.43 (CH_3), 49.50 (CH_2), 61.57 (CH_2), 66.39 (CH), 77.10 (CH), 126.86 (CH), 127.68 (CH), 127.72 (CH), 127.83 (CH), 128.33 (CH), 128.80 (CH), 128.86 (CH), 128.90 (CH), 130.54 (CH), 130.84 (C), 134.06 (CH), 136.40 (C), 137.10 (C), 167.39 (C), 172.09 (C); IR (NaCl): 3154, 2984, 1733, 1594, 1469, 1381, 1216, 1098; HRMS Calculated for $C_{27}H_{27}N_2O_2$ (M^+): 411.2073; Found 411.2086.

2-21: ethyl 1-benzyl-4-hexyl-2-phenyl-4,5-dihydro-1H-imidazole-5-carboxylate



The compound was synthesized according to the general procedure. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 12 hours. Silica gel chromatography; 50: 50 EtOAc: hexane; R_f = 0.4; oil; 40% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 0.86 (3H, t, J = 6.5 Hz), 1.26 (3H, t, J = 7.0 Hz), 1.27-1.39 (8H, m), 1.48-1.55 (1H, m), 1.62-1.71 (1H, m), 3.72 (1H, d, J = 7.0 Hz), 4.11-4.13 (1H, m), 4.11-4.33 (2H, m), 4.34 (1H, d, J = 15.5 Hz), 4.56 (1H, d, J = 15.5 Hz), 7.12 (2H, d, J = 7.0 Hz), 7.25-7.33 (3H, m), 7.42-7.44 (3H, m), 7.67-7.69 (2H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 14.09 (CH_3), 14.15 (CH_3), 22.57 (CH_2), 25.04 (CH_2), 29.14 (CH_2), 31.72 (CH_2), 36.77 (CH_2), 50.98 (CH_2), 61.07 (CH_2), 66.82 (CH), 69.82 (CH), 127.69 (CH), 127.94 (CH), 128.55 (CH), 128.62 (CH), 128.67 (CH), 130.11 (CH), 130.74 (C), 136.70 (C), 164.67 (C), 172.58 (C); IR (NaCl): 3029, 2928, 1734, 1595, 1452, 1409, 1244, 1199; HRMS Calculated for $C_{25}H_{33}N_2O_2$ (M^+): 393.2542; Found 393.2548.

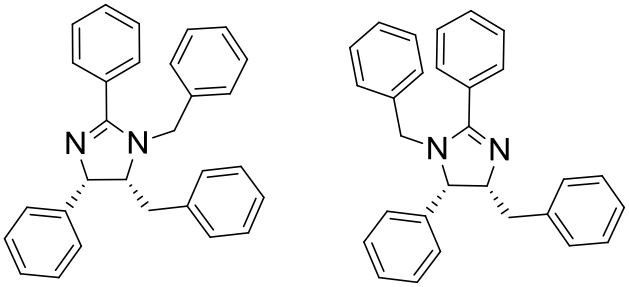
2-22: 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazol-5-yl)(phenyl)methanone



The compound was synthesized according to the general procedure. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 12 hours. Silica gel chromatorgraphy; 50: 50 EtOAc: hexane; R_f = 0.45; oil; 41% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 4.31 (1H, d, J = 15.5 Hz), 4.72 (1H, d, J = 15.5 Hz), 4.89 (1H, d, J = 6.5

Hz), 5.08 (1H, d, J = 6.5 Hz), 7.08-7.11 (2H, m), 7.14-7.17 (2H, m), 7.24-7.37 (6H, m), 7.37-7.41 (2H, m), 7.51-7.56 (3H, m), 7.57-7.61 (1H, m), 7.71 (2H, d, J = 8.0 Hz), 7.84-7.86 (2H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 51.10 (CH_2), 73.17 (CH), 73.25 (CH), 127.25 (CH) , 127.92 (CH), 128.04 (CH), 128.36 (CH), 128.89 (CH), 128.93 (CH), 128.94 (CH), 128.96 (CH), 129.03 (CH), 129.09 (CH), 130.60 (CH), 133.81 (CH), 134.96 (C), 136.70 (C), 142.96 (C), 165.82 (C), 166.27 (C), 197.66 (C); IR (NaCl): 3065, 2925, 1688, 1595, 1451, 1233; HRMS: Calculated for $C_{29}H_{25}N_2O$ (M^+): 417.1967; Found 417.1960.

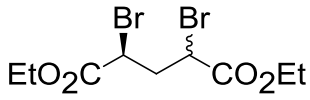
2-23: 1,5-dibenzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole and 1,4-dibenzyl-2,5-diphenyl-4,5-dihydro-1H-imidazole



The compound was synthesized according to the general procedure. The imidoyl chloride reaction time was 1.25 hours at 0°C. The imidazoline reaction time was 12 hours. Silica gel chromatorgraphy; 50: 50 EtOAc: hexane; R_f = 0.45; oil; 41% yield; the compounds were isolated as an inseparable mixture of regioisomers (2:1 ratio). **Regioisomer 1**: ^{1}H NMR (500 MHz) $CDCl_3$: 2.53 (1H, dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz), 3.01 (1H, dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz), 3.81 (1H, d, J = 16.0 Hz), 4.63 (1H, d, J = 11.0 Hz), 4.67 (1H, d, J = 16.0 Hz), 4.77-4.83 (1H, m), 6.80-7.90 (20H, m); **Regioisomer 2**: ^{1}H NMR (500 MHz) $CDCl_3$: 2.33 (1H, dd, J_1 = 7.5 Hz, J_2 = 6 Hz), 2.65 (1H, dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz), 3.61 (1H, d, J

= 16.0 Hz), 4.07-4.12 (1H, m), 4.49 (1H, d, J = 16.0 Hz), 5.30 (1H, d, J = 10.5 Hz), 6.80-7.90 (20H, m). **Both Regioisomers** ^{13}C NMR (125 MHz) $CDCl_3$: (3 carbon signals not found); 37.66, 38.96, 48.93, 51.30, 64.60, 66.88, 70.55, 72.75, 125.87, 126.37, 127.30, 127.67, 127.69, 127.75, 127.82, 128.10, 128.15, 128.20, 128.50, 128.58, 128.77, 128.79, 128.85, 128.92, 129.11, 129.20, 129.41, 130.25, 130.55, 131.60, 131.64, 137.40, 137.80, 138.42, 139.33, 139.80, 139.96, 165.75, 167.68; IR (NaCl, $CDCl_3$): 3028, 2918, 1616, 1595, 1452, 1412; HRMS Calculated for $C_{26}H_{27}N_2O_2$ (M^+): 399.2073; Found 399.2086.

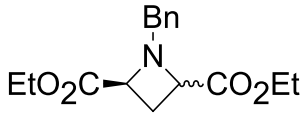
2-39: *Cis* and *trans*-diethyl 2,4-dibromopentanedioate



Cis and *trans*-diethyl 2,4-dibromopentanedioate was synthesized according to a known procedure.[25] To a 25 mL round bottom flask was added glutaryl dichloride (10 mL, 0.078 mol) and the flask was attached to a reflux condenser. The flask was placed in an oil bath preheated to 85°C. A sunlamp 300W was positioned as close as possible to the round bottom flask. Neat bromine (4.85 mL, 0.094 mol) was then added dropwise in small increments over a period of 1.25 h, while maintaining the temperature at 85°C. Attached to the reflux condenser was a tube connected to a beaker containing a solution of 1M NaOH (500 mL) and 10% aq. $Na_2S_2O_3$ (50 mL) to quench the HBr and excess Br_2. After the addition of Br_2 the reaction was maintained at 85°C for an additional 4 h. The reaction was then cooled to room temperature. To another 250 mL round bottom flask was added anhydrous ethanol (50 mL) under argon and the solution was cooled with an ice water bath. The reflux condenser was removed and replaced will a septum and put under argon. The

reaction solution was transferred to the ethanol solution over ¼ h with a canulla. The solution was stirred at room temperature overnight and then was poured into a sep. funnel containing $NaHCO_3$. The solution was slowly mixed until CO_2 stopped evolving and then was extracted 3x with ether. The ether extracts were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was pure enough to be used in the following reaction without further purification.

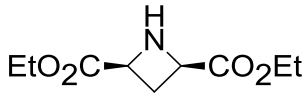
2-40 and 2-41: *Cis* and *trans*-diethyl 1-benzylazetidine-2,4-dicarboxylate



The compounds were synthesized by a modified procedure from the literature.[25,26] To a 500-mL round bottom flask was added *cis* and *trans*-diethyl 2,4-dibromopentanedioate (8 g, 24.48 mmol), DMF (200 mL), and benzyl amine (8.82 mL, 80.78 mmol). The reaction solution was heated to 85°C with an oil bath for 4 hours. The reaction solution was cooled to room temperature and poured into a sep. funnel containing 500 mL of 5% aq. LiBr solution. Water (1000 mL) was added to the sep. funnel and the product was extracted with EtOAc, died with $MgSO_4$, vacuum filtered, and concentrated in *vacuo*. The product was purified by silica gel chromatography, 1:9 ether: hexane until the *trans*-diethyl 1-benzylazetidine-2,4-dicarboxylate was isolated and then 1:2 ether: hexane to isolate the *cis*-diethyl 1-benzylazetidine-2,4-dicarboxylate. **2-40: *Cis* isomer:** $R_f = 0.30$; 1: 2 ether: hexane; yellow oil; 2.38 g, 35% yield; ^{1}H NMR (300 MHz), $CDCl_3$: 1.18 (6 H, t, J = 7.1 Hz), 2.41 (2H, m), 3.59 (2H, t, J = 8.3 Hz), 3.88 (2H, s), 4.08 (4 H, m), 7.29-7.33 (5H, m); ^{13}C NMR (75 MHz), $CDCl_3$: 14.00, 14.05, 24.69, 59.39, 59.44, 60.19, 60.71, 60.74,

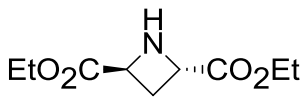
127.42, 128.16, 129.88, 135.59, 171.58, 171.63; **2-41: *Trans*-isomer:** R_f = 0.35; 1: 2 ether: hexane; yellow oil; 2.45 g, 36% yield; ^{1}H NMR (300 MHz), $CDCl_3$: 1.20 (6H, t, J = 7.1 Hz), 2.50 (2H, t, J = 6.8 Hz); 3.88 (2H, s), 4.12 (4 H, q, J = 7.1 Hz); 4.20 (2H, t, J = 6.7 Hz); 7.21-7.30 (5H, m); ^{13}C NMR (75 MHz), $CDCl_3$: 14.16, 14.19, 25.46, 55.74, 60.61, 60.64, 61.77, 61.80, 127.14, 128.15, 128.91, 137.12, 172.45, 172.48.

2-42: *Cis*-diethyl azetidine-2,4-dicarboxylate



To a 100-mL round bottom flask under nitrogen was added *cis*-diethyl 1-benzylazetidine-2,4-dicarboxylate (1.20 g, 4.11 mmol), anhydrous ethanol (40 mL), and $Pd(OH)_2$ on carbon (600 mg). A balloon filled with hydrogen was attached to the round bottom flask a needle was used to vent the nitrogen out of the flask and replace it with a hydrogen atmosphere. The reaction was mixed overnight at room temperature. The reaction solution was filtered through a glass frit containing celite and the celite was washed with DCM. The solvents were removed *in vacuo*. The product was consistent with the literature data.[25,26] Yellow oil; 0.79 g; 95% yield; ^{1}H NMR (500 MHz) (CDCl3) δ 1.26 (6H, t, J = 7.0 Hz), 2.27 (1H, m), 2.95 (1H, m), 3.0 (1H, s, br), 4.18 (4H, q, J = 6.85 Hz), 4.85 (2H, dd, J_1 = 10.30, J_2 = 5.90 Hz; ^{13}C NMR (75 MHz), $CDCl_3$ δ 14.05, 25.74, 58.65, 61.37, 171.02.

2-43: *Trans*-diethyl azetidine-2,4-dicarboxylate



To a 100-mL round bottom flask was added *trans*-diethyl 1-benzylazetidine-2,4-dicarboxylate (1.20 g, 4.11 mmol), anhydrous ethanol (40 mL), and $Pd(OH)_2$ on carbon (600 mg). A balloon filled with hydrogen was attached to the round bottom flask a needle was used to vent the nitrogen out of the flask and replace it with a hydrogen atmosphere. The reaction solution was filtered through a glass frit containing celite and the celite was washed with DCM. The solvents were removed *in vacuo*. The product was consistent with the literature data.[25,26] Silica gel chromatography; 50: 50 EtOAc: hexane; $R_f = 0.25$; yellow oil; 0.69 g; 84% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.18 - 1.31 (6, t, J = 6.85 Hz), 2.65 (2H, t, J = 7.80 Hz), 2.89 (1H, s, br), 4.18 (2H, m); 4.22 (2H, t, J = 7.80 Hz); ^{13}C NMR (75 MHz), $CDCl_3$ δ 14.12, 28.66, 55.74, 61.15, 76.83, 77.08, 77.33, 174.00.

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REFERENCES

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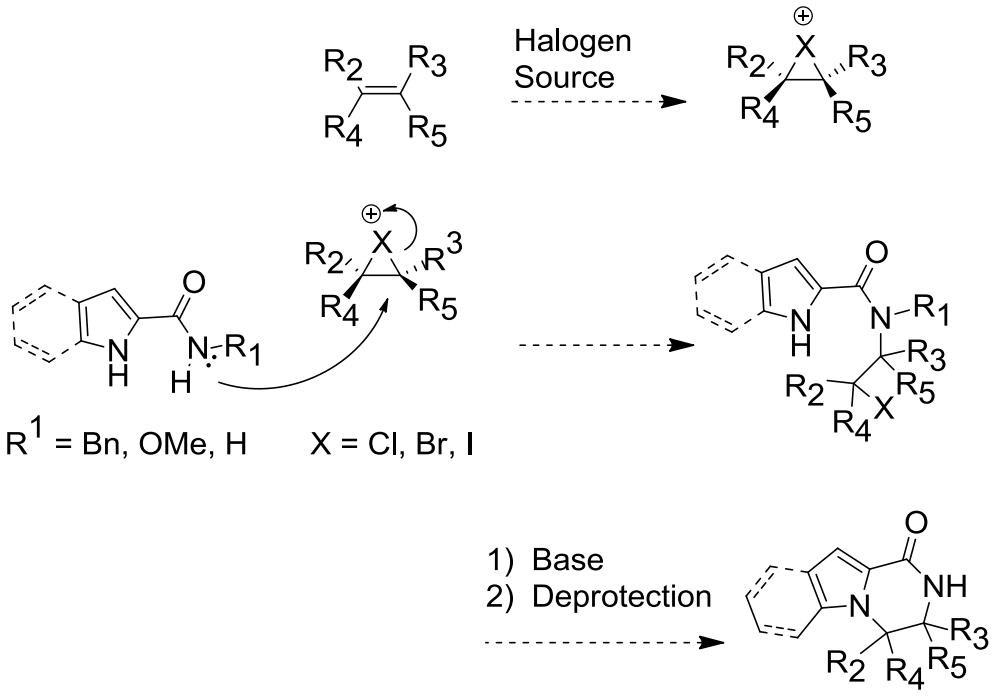
CHAPTER 3

REACTION OF BROMINE REAGENTS WITH OLEFINS AND SYNTHESIS OF HETEROCYCLES

Several syntheses of agesamide A and B, longamide, cyclooroidin, hanishin, and agelastatin A have already been developed.[1-3] Our lab is interested in the biological activity of these natural products and their analogs. Therefore, we would like to develop a new synthetic methodology to access these compounds. We envisioned one possible method may be by activation of an olefin with an electrophilic halogen source and subsequent nucleophilic attack by either the pyrrole nitrogen or the amide nitrogen of a 2-substituted indole or pyrrole. The indole / pyrrole nitrogen's lone pair of electrons is locked into the aromaticity of the indole / pyrrole ring and as a result the nitrogen atom is a poor nucleophile. The amide nitrogen would be predicted to be a better nucleophile than the indole / pyrrole nitrogen unless the amide was substituted with a strong electron withdrawing group. Reaction of the following compound with base would close the ring in a 6-exo-tet Baldwin favorable ring closure (**Scheme 3-1**).



Scheme 3-1: Proposed synthesis of biologically significant natural products

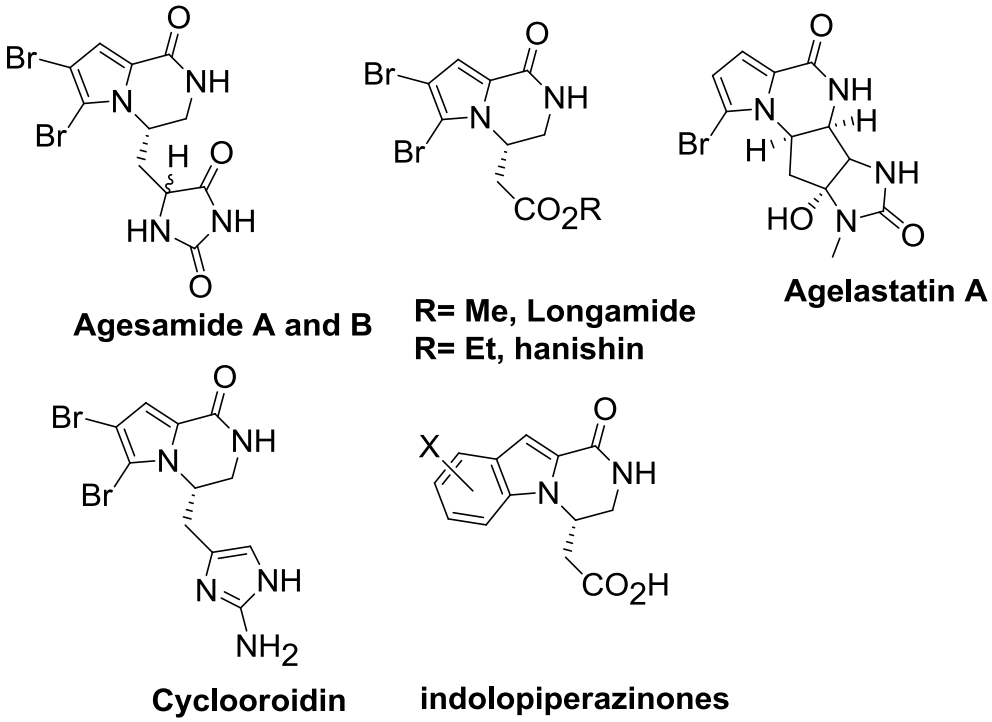
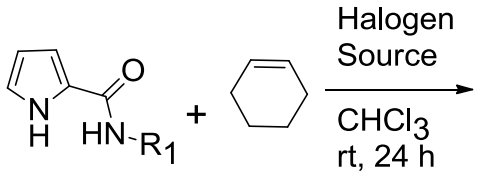


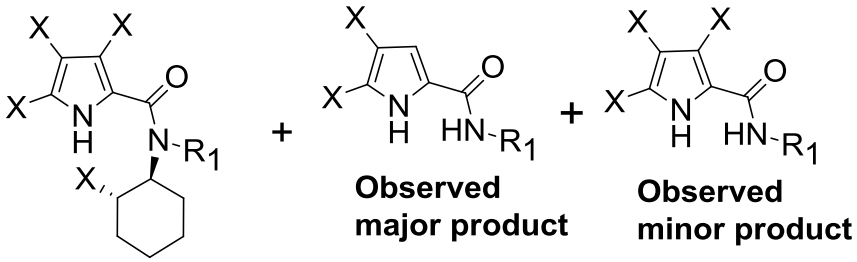
Figure 3-1: Biologically significant natural products

As expected initial trials of the reaction of cyclohexene with a pyrrole amide all resulted in halogenation of the C-2 position, C-3 position and very slowly the C-4 position of the pyrrole ring (**Table 3-1**). Reactions with benzyl (**3-1**), tosyl (**3-2**), and benzoyl (**3-3**) substituted pyrrole amides did not form any of the desired product **3-4** even with 3 or 4 equivalents of NBS for 24 hours. Theoretically it was also possible to halogenate the amide N-H of **3-1**, **3-2** or **3-3** with NBS but this was not observed by ^{1}H NMR. Analysis of these compounds by ^{1}H NMR showed that the amide and pyrrole NH peaks were exchangeable with D_2O (**Table 3-1**).

Table 3-1: Reaction of pyrrole amides with cyclohexene



SM#



R_1 = Bn, Ts, Bz

X = Br or H

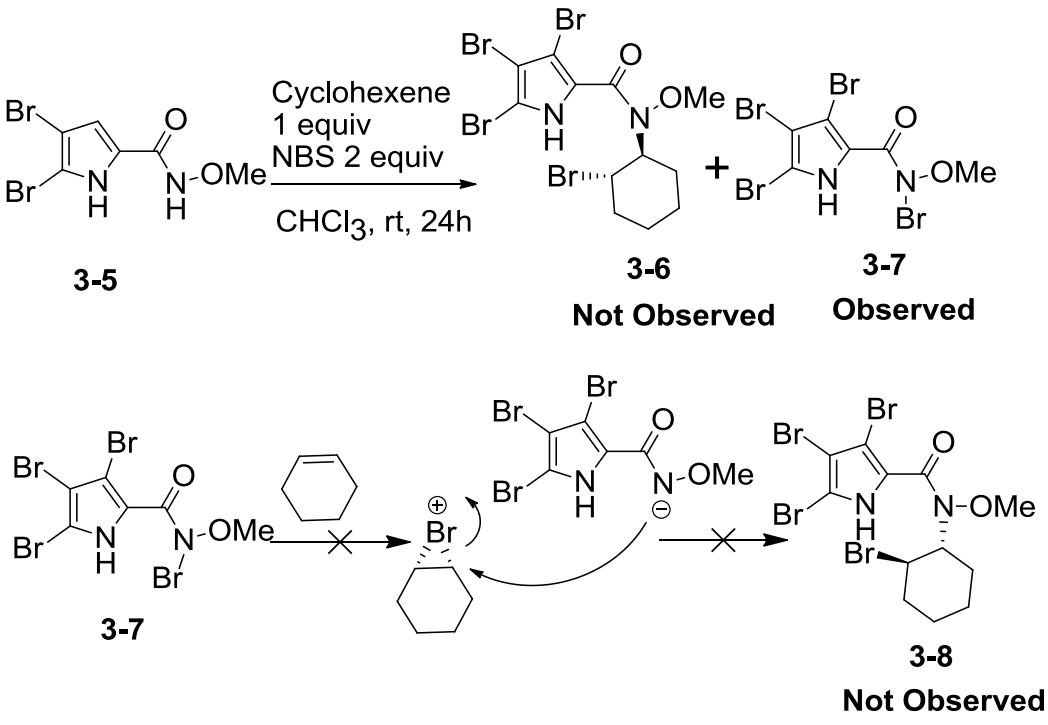
0% yield

3-4

entry	R_1	**SM#**	halogen Source	halogen source equiv.	Yield (%) **3-4**
1	Bn	**3-1**	NCS	3	0
2	Bn	**3-1**	NBS	3	0
3	Bn	**3-1**	NIS	3	0
4	Bn	**3-1**	NBS	4	0
5	Ts	**3-2**	NBS	4	0
6	Bz	**3-3**	NBS	4	0

One explanation for these results was that the pyrrole amide nitrogen was too poor of a nucleophile. The halonium ion intermediate formed with cyclohexene and an *N*-halosuccinimide was not attacked by the pyrrole amide nitrogen. Therefore 4,5-dibromo-*N*-methoxy-1H-pyrrole-2-carboxamide **3-5** was synthesized. This solved two problems now the pyrrole C-2 and C-3 positions of **3-5** were already brominated so only one

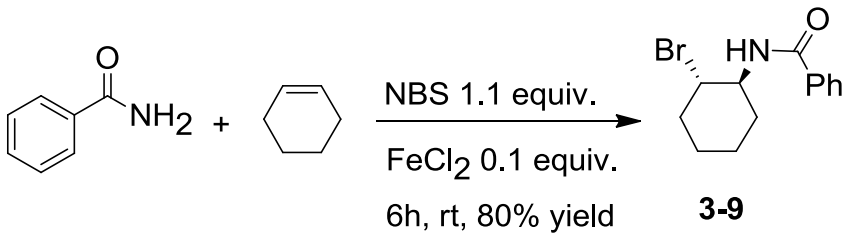
equivalent of NBS should be needed to synthesize compound **3-6**. Secondly, the pyrrole amide now had an electron donating *N*-OMe group and should increase the nitrogen amide nucleophilicity to attack the halonium ion formed with NBS and cyclohexene. Unfortunately, the reaction of compound **3-5** with cyclohexene and NBS only resulted in bromination of the amide N-H and some bromination at the C3-position of the pyrrole ring and compound **3-6** was not synthesized. As a result the reaction was repeated with 2 equivalents of NBS, but this only resulted in the formation of *N*,3,4,5-tetrabromo-*N*-methoxy-1*H*-pyrrole-2-carboxamide as the major product **3-7**. Once the bromo-amide was formed the bromine atom did not transfer to the cyclohexene to form a bromonium ion. As a result compound **3-8** was not formed and only the *N*-bromo pyrrole amide compound **3-7** was synthesized (**Scheme 3-2**).



Scheme 3-2: Reaction of **3-5** with cyclohexene and NBS

It seemed that the electronics of the amide nitrogen were very important. If the amide contained a nitrogen-electron withdrawing group (N-EWG) then bromination of the amide with NBS did not occur. If an amide contained an N-EWG then it was not nucleophilic enough to attack the bromonium ion intermediate formed with cyclohexene. If the amide contained a nitrogen-electron donating group (N-EDG) then the amide was more nucleophilic and may undergo substitution with the cyclohexene bromonium ion. However, the NBS just brominated the N-EDG instead of forming a bromonium ion with cyclohexene. Once compound **3-7** was formed it was too stable to react with cyclohexene through a bromonium ion intermediate to form the desired compound **3-8**.

These results led us to investigate the reaction of benzamide with cylohexene with various halogenating agents in the presence of different Lewis acids (**Table 3-2**). This model reaction was done to try to reproduce the results by Zhoa and coworkers (**Scheme 3-3**).[4]



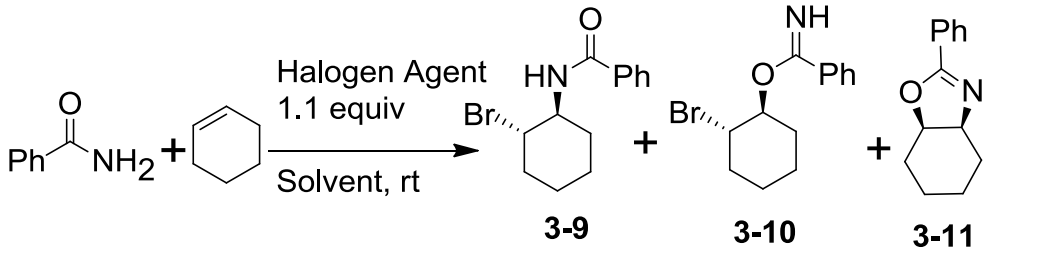
Scheme 3-3: Synthesis of compound **3-9** by Zhoa and coworkers[4]

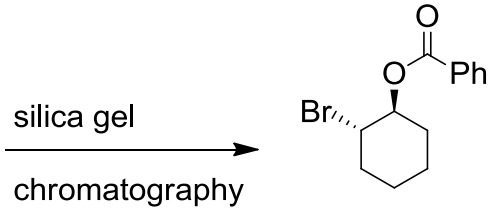
Initial results only gave low yields of a single product with NBS working the best. The presumed product was the result of attack of the amide nitrogen of benzamide on the cyclohexene-NBS halonium intermediate to yield *trans*-*N*-2-bromocyclohexyl benzamide **3-9**. However, purification of the crude product by silica gel chromatography revealed

compound **3-12** as the main product. *Trans*-2-bromocyclohexyl benzimidate **3-10** was evidently formed under these reaction conditions and then hydrolyzed into *trans*-2-bromocyclohexyl benzoate **3-12** during silica gel chromatography (**Table 3-2**). The product was isolated as a mixture of **3-10** and **3-12** as observed by ^{1}H NMR, ^{13}C NMR and LRMS. A review of the literature revealed another synthesis of **3-9** by Corey and coworkers.[5] The reaction of benzonitrile, water, NBS, BF_3•$O(Et)_2$, and cyclohexene yielded compound **3-9**. Undoubtedly, Corey and coworkers have made the right compound based on their mechanism and experimental data. The experimental data for **3-9** had the NH proton clearly identified by Corey and coworkers as well as the cyclized compound 4,5 dihydrooxazole **3-11**. In my hands compound **3-9** and **3-11** were not synthesized by the reaction of cyclohexene, NBS, benzamide and a Lewis acid but instead compound **3-10** was formed. Therefore, I could not reproduce the results by Zhoa and coworkers.

These reactions were very slow and gave low yields of **3-10**. The cyclohexene and halogenating reagent were consumed but approximately 70% of benzamide was recovered. There was also the formation of other impurities perhaps by elimination of the halonium/ cyclohexene ion intermediate. The last entry in the table resulted in decomposition and compound **3-9** was formed with TCICA. The results are summarized in the table below (**Table 3-2**).

Table 3-2: Reaction of NBS with benzamide and cyclohexene

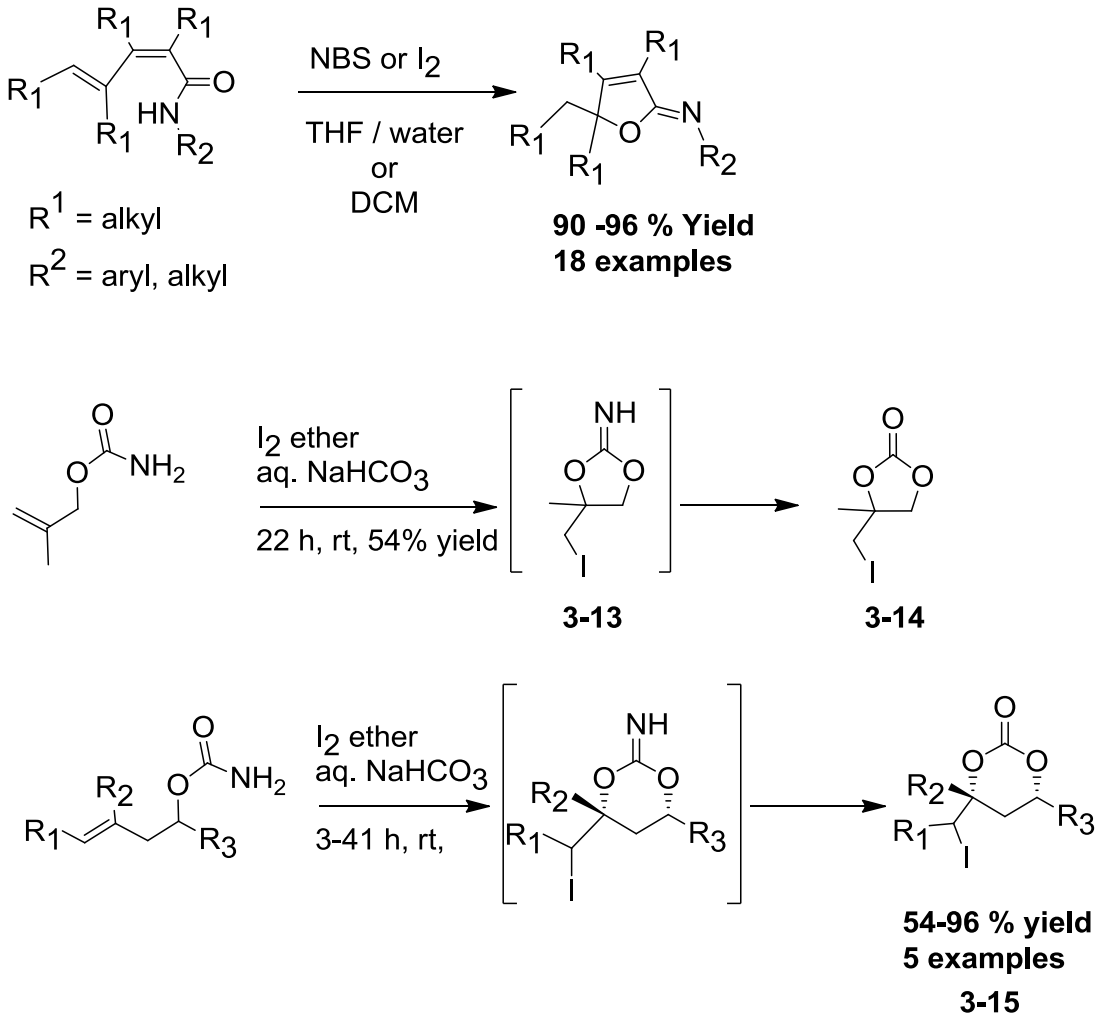




Entry	solvent	Halogen Agent	Lewis Acid	Lewis Acid equiv	Time (h)	X	yield (%) **3-12**
1	DCM	NCS	None	0	48	Cl	0
2	DCM	NBS	None	0	48	Br	27
3	EtOAc	NBS	$FeCl_2$	0.15	16	Br	26
4	EtOAc	NBS	CuI	0.15	16	Br	16
5	EtOAc	NBS	$CuBr_2$	0.15	16	Br	23
6	DCM	TCICA	None	0	1	Cl	dec

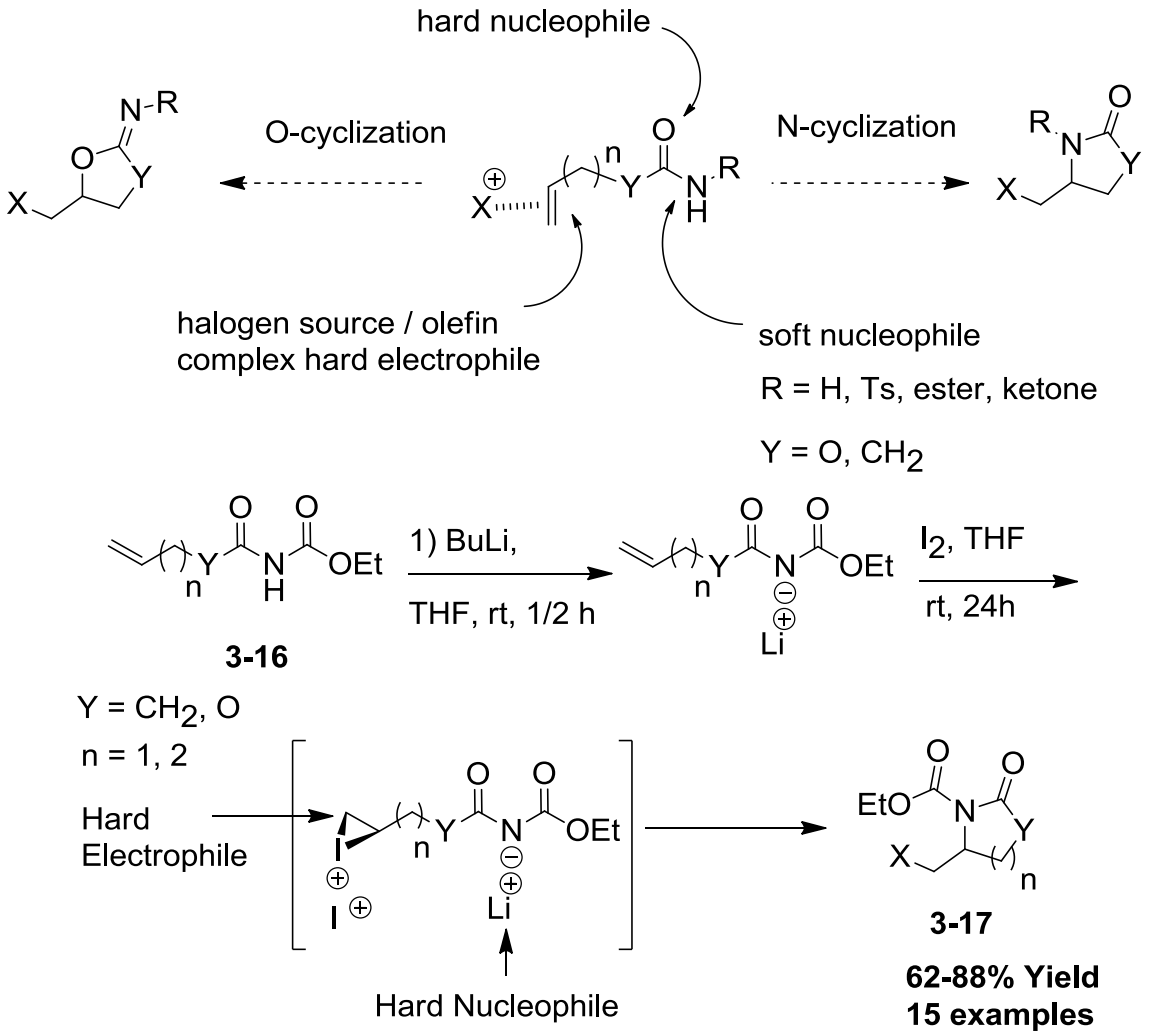
The benzamide oxygen atom was more nucleophilic than the nitrogen atom due to resonance of the amide electrons into the more electronegative carbonyl oxygen atom. The ability for oxygen versus nitrogen attack is illustrated by examples of intramolecular cyclization reactions shown below in the following schemes. An excellent paper by Zhenfeng Xi and coworkers[6] synthesized a variety of dioxolan-2-imines where the nitrogen

atom was substituted with an alkyl or aryl group. Another report by Uei and coworkers[7] studied the intramolecular cyclization to yield a 5 membered ring dioxolan-2-imine compound **3-13** which hydrolyzed to a dioxanone compound **3-14**. Uei and coworkers also reported this cyclization to 6 membered dioxanones **3-15**. The intramolecular amide cyclization to an dioxolan-2-imine and hydrolysis to an dioxolan-2-one has been reported by Corey,[8] Minobe,[9] and also currently being explored by the Borhan laboratory (**scheme 3-4**).



Scheme 3-4: Intramolecular oxygen cyclization

These reports were intramolecular examples instead of intermolecular examples. However, they help explain the synthesis of the imido ester compound **3-10** and hydrolysis to the ester compound **3-12**. The selectivity of oxygen versus nitrogen intramolecular selectivity was explained very well in a great paper by Taguchi.[10] Taguchi explained oxygen versus nitrogen attack by Hard Soft Acid Base (HSAB) theory. They reported that the amide or cabamate oxygen is a hard nucleophile and the halonium intermediate formed with a carbon-carbon pi bond is a hard electrophile. The amide or carbamate nitrogen atom is a soft nucleophile. Based on HSAB theory the hard electrophile should react with the hard nucleophile preferably over the soft nucleophile to give oxygen cyclization. However, Taguchi reported that if the amide nitrogen is substituted with an EWG then the pKa of the NH proton is significantly lowered. The reaction of compound **3-16** with BuLi to remove the NH proton converted the nitrogen into a strong hard nucleophile. Iodine was then added to this reaction to make the iodonium ion followed by *N*-cyclization to yield compound **3-17**. Taguchi and coworkers reported many examples to make 5 and 6 membered rings through this methodology (**Scheme 3-5**).

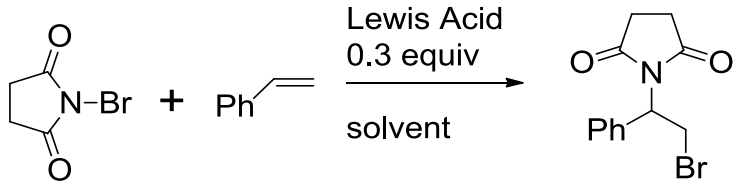


Scheme 3-5: Nitrogen cyclization versus oxygen cyclization via HSAB theory

Carbon amide nitrogen bond formation seemed more complicated than initially thought. One way to simplify the reaction would be to put the halogen atom on the amide or an imide nitrogen. This would make the nitrogen atom the nucleophile instead of the oxygen atom. So as a model reaction we decided to study the addition of NBS to styrene with various Lewis acid catalysts. $BF_3 \bullet OEt_2$ worked the best and yielded compound **3-18** in 81% yield and TMSOTf yielded compound **3-18** in 54% yield (**Table 2-3,entries 5 and**

11). All the other Lewis acids formed precipitates and the desired product was not formed (**Table 3-3**).

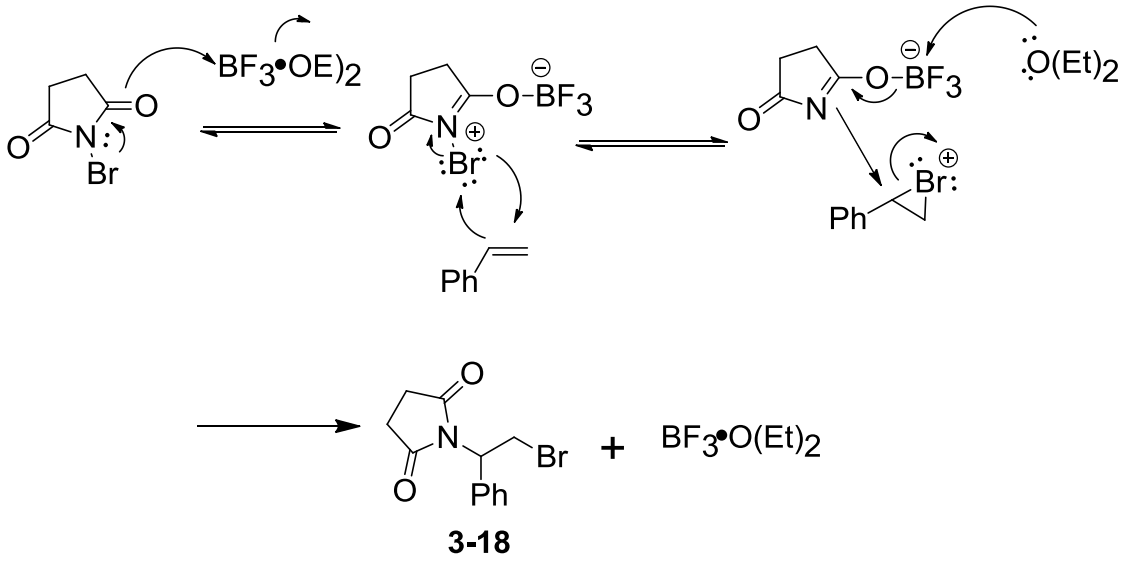
Table 3-3: Study on the Reaction of NBS with Styrene



3-18

Entry	solvent	Lewis acid	Time (h)	temp (°C)	**3-18** yield (%)
1	DCM	BF_3•OEt_2	18	rt	78
2	DCM	$TiCl_4$	18	rt	0
3	DCM	$SnCl_4$	18	rt	0
4	DCM	$ZnCl_2$	18	rt	0
5	DCM	TMSOTf	18	rt	54
6	THF	$TiCl_4$	18	rt	0
8	THF	$ZnCl_2$	18	rt	0
9	THF	$Zn(OTf)_2$	18	rt	0
10	THF	CuI	18	rt	0
11	DCM	BF_3•OEt_2	1	rt	81
12	DCM	none	18	rt	0

NBS was added to styrene to form 1-(2-bromo-1-phenylethyl)pyrrolidine-2,5-dione **3-18** in 81% yield. Presumably, BF_3•$O(Et)_2$ coordinated to the imide group and created an electrophilic bromine to initiate the addition to styrene (**Scheme 3-6**).



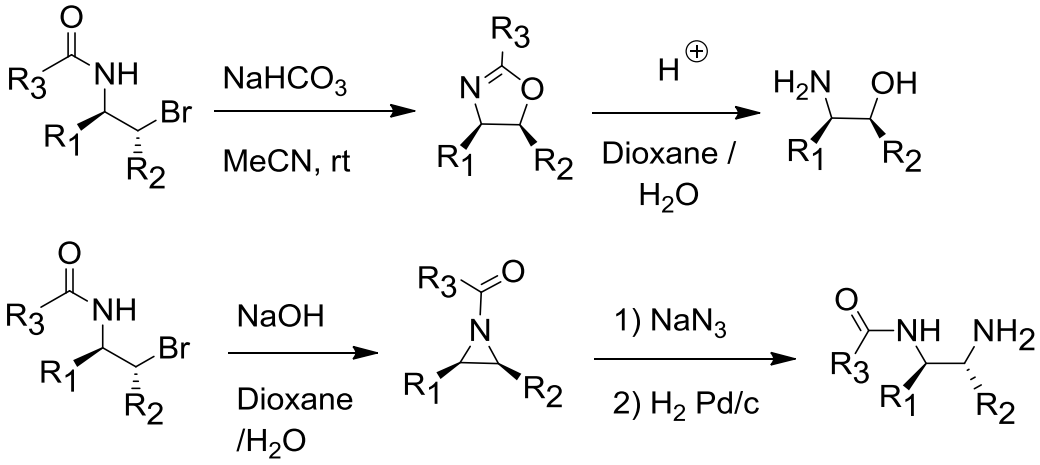
3-18

Scheme 3-6: Proposed mechanism for addition of NBS to styrene

Unfortunately, the reaction of cyclohexene, NBS, benzamide, and BF_3•$O(Et)_2$ did not yield the trans bromo amide adduct compound **3-9** but instead yielded compound **3-18**. This reaction was repeated with excess benzamide but still only compound **3-18** was formed and not compound **3-9**. The benzamide was a neutral and therefore a much poorer nucleophile than the negatively charged succinimide ion. By replacing the hydrogen atom on a nitrogen nucleophile with a bromine atom would increase its nucleophilicity based on the mechanism in **Scheme 3-6**. It was therefore determined that having the bromine atom on the intended nucleophile was the key for this reaction to work successfully. We were hoping to explore this reaction as a new amino-halogenation methodology of olefins.

Olefins are commercially available and easily synthetically accessible from commercially available aldehydes via the Wittig reaction. Aminohalogenation of an olefin creates both a nitrogen-carbon bond and carbon-halogen bond adjacent to one another. Thus it is a valuable tool to create a variety of different important organic building blocks.

Aminohalogenation of an olefin with Chloramine-T[11,12], $TsNH_2$[13,14], $TsNCl_2$[15-17] has already been extensively studied and is a great method to functionalize an olefin to a *cis*-*N*-Ts aziridine[18,19] via nitrogen substitution of the halogen atom. An *N*-Ts aziridine can undergo ring opening to yield important organic molecules such as a *trans*-1,2 diamine.[20,21] To this date addition of an amide to an olefin has been much less studied than $TsNH_2$, but has high synthetic utility. A 1-halo, 2-*N*-amide can undergo intramolecular nitrogen substitution to a *cis*-*N*-acyl aziridine[22] which can be opened with an azide and reduced to a *trans*-1,2-diamine.[23,24] A 1-halo, 2-N-amide can also undergo intramolecular oxygen attack to a 4,5-dihydrooxazole[22,25] and hydrolysis to a *cis* amino alcohol[26] (**Scheme 3-7**).



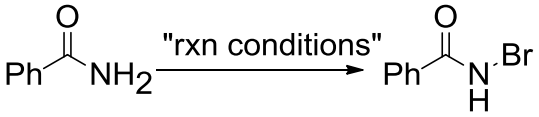
Scheme 3-7: Synthesis of important organic building blocks from an 1-bromo, 2-*N*-amide

Addition of an *N*-halo-amide / carbamate[27,28], or a *N*,*N*-dihaloamide / carbamate[29-32] to an olefin has been much less studied, but has been reported by Swern.[33] Swern reported the reaction occurred through a radical mechanism by initiation through heat or light to give *anti*-Markovnikov addition of the *N*-halo-amide / carbamate to an olefin. In addition, of the addition of *N*-halo-amide / carbamate, other reports have included radical *anti*-Markovnikov addition of a *N*-halo-imide to an olefin.[28,34] Markovnikov addition of a *N*-halo-imide has been reported to occur with activated olefins like an enol ether[35] or an enamine[36] without the use of radical initiator or a catalyst. A report by Heasley[37] and coworkers described the synthesis of a 1-bromo, 2-fluoride adduct by addition of an *N*-bromo-amine to an olefin in the presence of BF_3•OEt_2. In a side note they noticed that NBS underwent addition to cyclohexene to yield the *trans*-1-bromo, 2-*N*-imide stereoisomer adduct.[37] This report by Heasley and coworkers motivated us to explore this reaction. NBS has very little synthetic utility, but addition of other imides with easily removable nitrogen protecting groups would be much more synthetically useful. We wanted to synthesize an *N*-bromo imide that was not a sterically hindered nucleophile but also contained *N*-protecting groups that could be easily deprotected. Nitrogen methyl ester protecting groups accomplished both of these goals and improved the synthetic utility beyond simple NBS.

We needed a general procedure to synthesize *N*-bromo amides and *N*-Bromo imides. We first used benzamide as a model substrate to brominate the nitrogen amide. Of all the methods employed most of them resulted in no reaction and recovery of benzamide.

However, *N*-bromo-benzamide was synthesized by reaction with bromoacetate in CCl_4 (**Table 3-4, Entry 5**).

Table 3-4: Bromination of benzamide



3-19

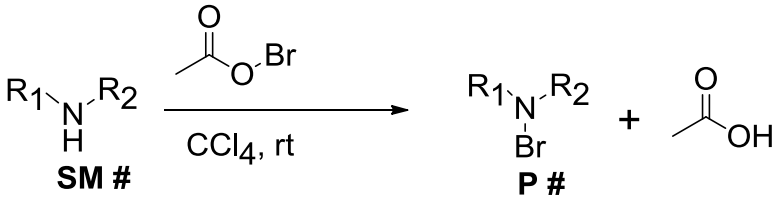
Entry	Reagents	Solvent	Temp	Time (h)	Yield (%) **3-19**
1	NaOH, Br_2	water	0	0.5	0[a]
2	NBS	DCM	reflux	18	0[a]
3	Br-hydantoin	DCM	refux	18	0[a]
4	BuLi, Br_2	THF	-78-rt	5	0[a]
5	$MeCO_2Br$	CCl_4	rt	1.5	100%

[a] No rxn occurred

Bromo-acetate was a general great method to brominate the *N*-H of an amide or the *N*-H of an imide.[38] In general the reaction worked well but did not successfully brominate the *N*-H of $(Boc)_2NH$ due to the sterically hindered boc groups which blocked the nitrogen proton from reacting. These reactions were carried out while taking care to protect the reaction solutions from light. An *N*-bromo amide or an *N*-bromo imide was isolated from the reaction solution by removal of the acetic acid by-product and CCl_4 by evaporation *in vacuo* at room temperature in the dark. Alternatively, the *N*-bromo products were also isolated by precipitation from the CCl_4 solution by adding hexene. If, the product was

heated *in vacuo* for too long a debromination reaction occurred to yield the *N*-H amide or *N*-H imide (**Table 3-5**).

Table 3-5: Bromination of amides and imides



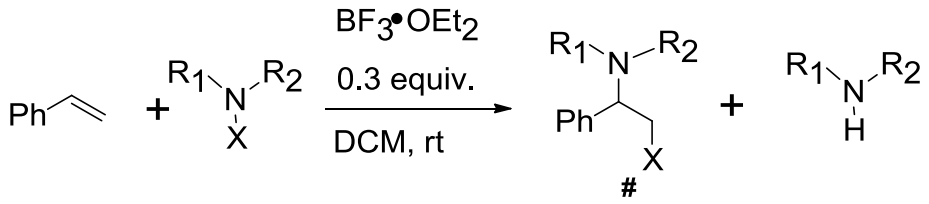
Entry	SM #	R_1	R_2	X	P #	Yield (%)
1	NA	PhCO	H	Br	**3-27**	100
2	NA	PhCO	Br	Br	**3-28**	100[a]
3	**3-20**	PhCO	Bn	Br	**3-29**	91:9[b]
4	NA	PhCO	Me	Br	**3-30**	100
5	**3-21**	PhCO	Ph	Br	**3-31**	0[c]
	3-22	PhCO	Cy	Br	**3-32**	100
6	**3-23**	PhCO	Boc	Br	**3-33**	100
7	**3-24**	CO_2Me	CO_2Me	Br	**3-34**	75
8	**3-25**	PhCO	Ts	Br	**3-35**	50[d]
9	**3-26**	Boc	Boc	Br	**3-36**	0

[a] $PhCON(Br)_2$ was synthesized, [b] ratio of *N*-bromo amide to *N*-H amide, [c] a mixture of products were formed, [d] the product was made by another method see experimental section

The *N*-bromo amides and *N*-bromo imides were reacted with styrene in the presence of BF_3**.**OEt_2 (**Table 3-6**). The reaction of NIS, styrene, and BF_3**.**OEt_2 was too vigorous and did not form the desired product **3-39**. NCS was not reactive enough under these conditions and did not form compound **3-37**. NBS was superior to the other *N*-halo-succinimides to form the desired product **3-38** in 81% yield (**Table 3-6**). Unfortunately, *N*-bromobenzamide debrominated back to benzamide in the presence of BF_3•OEt_2 and

styrene and did not form the desired product **3-40**. Similarly, debromination also occurred for *N*-benzyl, *N*-bromo benzamide, *N*-Methyl, *N*-bromo benzamide, *N*-cyclohexyl, *N*-bromo benzamide, *N*-cylohexyl, *N*-bromo benzamide and *N*-bromo-*N*-tosyl benzamide (**Table 3-6, entries 4, 6-9**). *N*,*N*-dibromobenzamide was reacted with styrene without catalyst to yield a mixture of regioisomers in 40% yield. *N*, *N*-dibromobenzamide was too reactive and did not seem to give a very useful reaction since it yielded a mixture of regioisomers. Compound **3-46** and **3-47** did undergo reaction with styrene in 41 and 81% yield (**Table 3-6, entries 10, 11**). As a result, as was seen with NBS, and with the earlier reported studies, two electron-withdrawing acyl groups on the nitrogen atom were needed to prevent the debromination reaction from occurring and formation of the desired addition product.

Table 3-6: Reaction of *N*-bromo amides and *N*-bromo imides with styrene



Entry	R_1	R_2	X	#	Yield (%)
1	NA[c]	NA[c]	Cl	**3-37**	Trace[a]
2	NA[c]	NA[c]	Br	**3-38**	81
3	NA[c]	NA[c]	I	**3-39**	0
4	PhCO	H	Br	**3-40**	0
5	PhCO	Br	Br	**3-41**	40[b]
6	PhCO	Bn	Br	**3-42**	0
7	PhCO	Me	Br	**3-43**	0
8	PhCO	Cy	Br	**3-44**	0
9	PhCO	Ts	Br	**3-45**	0
10	PhCO	Boc	Br	**3-46**	41
11	CO_2Me	CO_2Me	Br	**3-47**	81

[a] The rxn time was 24 h, [b] No cat was added, the yield was based on ^{1}H NMR and resulted in a mixture of regioisomers, [c] The N-halosuccinimides were used; entry 1 NCS, entry 2 NBS, entry 3 NIS

Other reagents such as $Ti(O^iPr)_4$, CuI, $TiCl_4$, $ZnCl_2$, $Zn(OTf)_2$ and $B(OPh)_3$ were screened as a potential catalyst for the reaction of compound **3-34** (Br-N-$(CO_2Me)_2$) with styrene and did not give any desired product **3-47** but instead yielded H-N-$(CO_2Me)_2$. However, stoichiometric TMSOTf, styrene, and Br-N$(CO_2Me)_2$ did yield compound **3-47** although the reaction was much slower than with BF_3•OEt_2. The reaction of **3-34** and styrene with a Brønsted acid such as TFA, CSA, or diphenyl phosphate all resulted in

debromination of compound **3-34** to yield H-N-$(CO_2Me)_2$. Only a trace amount of the desired product **3-47** was observed by ^{1}H NMR in these reactions with a Brønsted acid. The bromine added to styrene to yield (Z) and (E)-(2-bromovinyl)benzene as the only product that was able to be identified in these reactions.

Table 3-7: Br-N-$(CO_2Me)_2$ addition to olefins

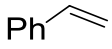
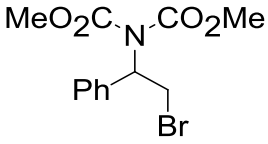
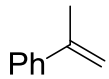
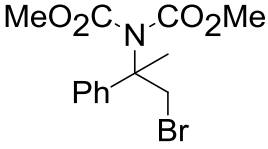
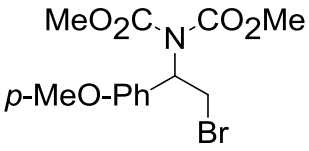
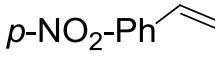
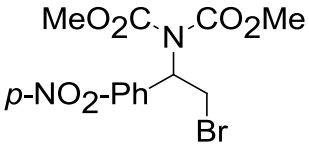
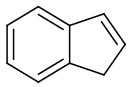
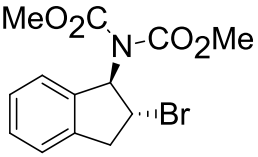
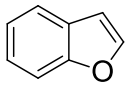
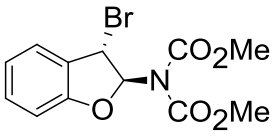
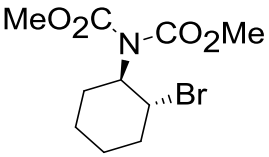
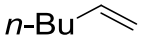
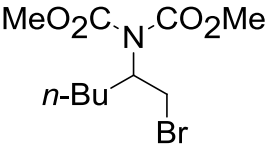
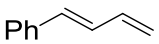
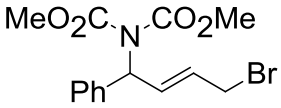
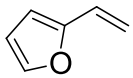
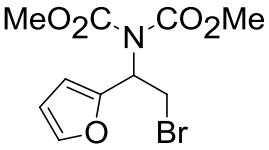
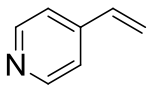
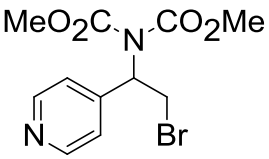
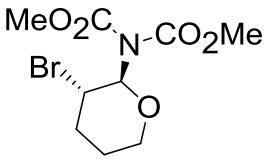
SM #	Substrate	Product	**P #**	Yield
NA			**3-47**	81
NA			**3-51**	0
NA			**3-52**	88
3-48			**3-53**	38
NA			**3-54**	52

Table7: Cont'd

SM #	Substrate	Product	#	Yield
NA			**3-55**	trace
NA			**3-56**	34[a]
NA			**3-57**	37[a, b]
3-49			**3-58**	50[c]
3-50			**3-59**	0
NA			**3-60**	0
NA			**3-61**	0[d]

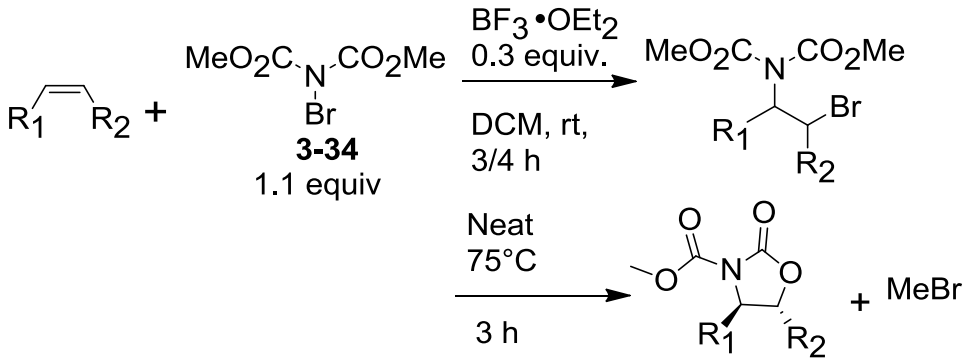
[a] 2.0 equiv. of **3-34** was used, [b] Rxn yielded a 52:48 mixture of regioismers, [c] 2:1 ratio of 1, 4 addition to 1, 2 addition to the terminal alkene, [d] The compound was synthesized but was thermally unstable and turned into a mess of anonymous products

Compound **3-34** underwent Markovnikov addition to an olefin in the presence of catalytic BF_3•OEt_2. The reaction worked the best in DCM or chloroform and occurred very quickly at room temperature (**Table 3-7**). The scope of the reaction was investigated and it was found to work well with styrene and indene, but lower yields were obtained with the aliphatic olefins. In contrast to indene an aromatic olefin, benzofuran, gave the desired product in very low yield (**Table 3-7, 3-55**). Once the bromonium ion was formed with benzofuran the driving force for the reaction was to regain aromaticity with the loss of a proton and formation of brominated benzofuran. Compound **3-34** did not undergo nucleophilic addition to benzofuran but instead resulted in formation of $NH(CO_2Me)_2$. Compound Br-$N(CO_2Me)_2$ did react with an enol ether but the resulting product **3-61** was thermally unstable. The identity of compound **3-61** was seen in the crude ^{1}H NMR spectrum.

After the synthesis of the 1-bromo, 2-*N*-imide we focused on deprotection of one of the two methyl carbamate groups of compound **3-47**. This would yield a *trans*-1-bromo, 2-*N*-methyl carbamate adduct which could be transformed into an aziridine or a 4,5-dihydrooxazole through intramolecular substitution of the bromine atom. However, it was observed via ^{1}H NMR that after **3-47** was purified by column chromatography that cyclization into a methyl-2-oxooxazolidine-3-carboxylate slowly occurred at room temperature to yield compound **3-63**, through loss of CH_3Br which was observed as a singlet in the ^{1}H NMR**.** Compounds **3-56** and **3-57** had to be purified on neutralized silica gel and were not very stable compounds. A two step reaction sequence seemed much more

efficient to yield a methyl 2-oxooxazolidine-3-carboxylate without purification of the 1-bromo, 2-*N*-imide adducts compounds **3-47**-**3-61**. A *trans*-1-bromo, 2-*N*-imide adduct was synthesized in only ¾ hours, was quenched with sat. aq. $NaHCO_3$, and then extracted with DCM. The *trans*-1-bromo, 2-*N*-imide adduct was concentrated *in vacuo* and underwent smooth transformation into a methyl 2-oxooxazolidine-3-carboxylate by heating neat at 75°C (**Table 3-8**).

Table 3-8: Synthesis of methyl 2-oxooxazolidine-3-carboxylate



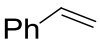
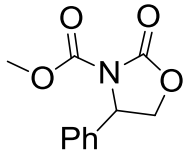
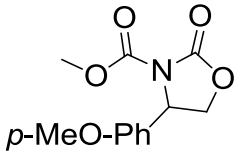
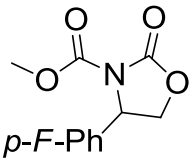
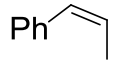
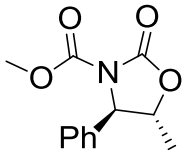
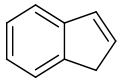
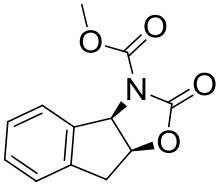
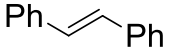
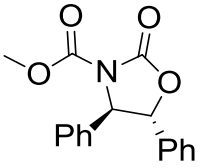
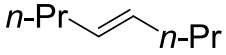
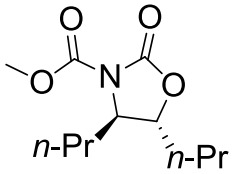
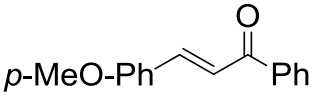
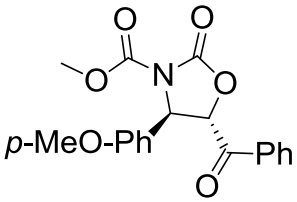
SM #	Substrate	Product	P #	Yield (2 Steps)
NA			**3-63**	78
NA	*p*-MeO-Ph 		**3-64**	83[a]
NA	*p*-*F*-Ph 		**3-65**	43[a]

Table 3-8: Cont'd

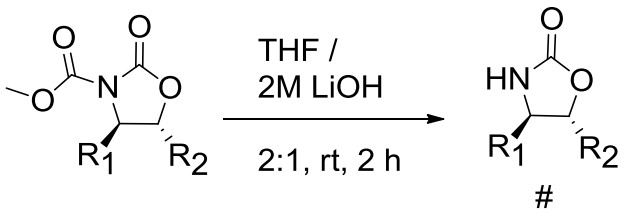
SM #	Substrate	Product	P #	Yield (2 Steps)
NA			**3-66**	52[b]
NA			**3-67**	48
NA			**3-68**	36
NA			**3-69**	NA[c]
3-62			**3-70**	50

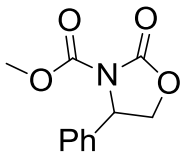
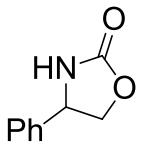
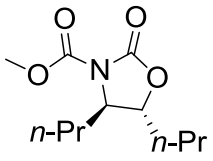
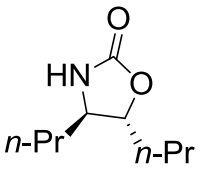
[a] The intermediate was purified before cyclization to **3-65** and **3-66**, [b] The compound was synthesized in a 2:1 mixture of regioisomers, [c] Compound **3-69** was synthesized with 2.0 equiv of **3-34** and could not be purified sufficiently without decomposition and was hydrolyzed to oxazolidin-2-one **3-72**

This two step reaction was investigated and worked better for electron donating styrenes than electron withdrawing styrenes to give the methyl-2-oxooxazolidine-3-carboxylates in good yields. The addition of **3-34** also worked well with an alpha beta unsaturated ketone to yield **3-70** in satisfactory yield. The reaction also occurred with

trans-4-octene but the methyl-2-oxooxazolidine-3-carboxylate **3-69** could not be isolated in high purity and was hydrolyzed in the following reaction to an oxazolidin-2-one **3-72** (**Table 3-9**). The methyl-2-oxooxazolidine-3-carboxylate could be easily deprotected to an *N*H-oxazolidin-2-one by reaction with LiOH and THF at room temperature to yield **3-71**[39] and **3-72**[40] and their spectral data were consistent with the reported literature data (**Table 3-9**). The second step in the reaction sequence occurred very efficiently through a 5-exo-tet ring closure via a S_N2 mechanism for the primary alkyl bromide substrates **3-63**, **3-64**, and **3-65**. The *trans* methyl-2-oxooxazolidine-3-carboxylates were formed in all other cases as supported by ^{1}H NMR and NOE. Carbon-carbon bond rotation occurred to give the thermodynamically more favorable *trans* methyl 2-oxooxazolidine-3-carboxylate stereoisomer presumably through a S_N1 mechanism. However, **3-67** was the *cis* stereoisomer due to the geometry of the indene starting material. The reason for mediocre yields in some cases was the result of the low yields obtained in the first step as the second step occurs in near quantitative yield.

Table 3-9: Hydrolysis of methyl 2-oxooxazolidine-3-carboxylate

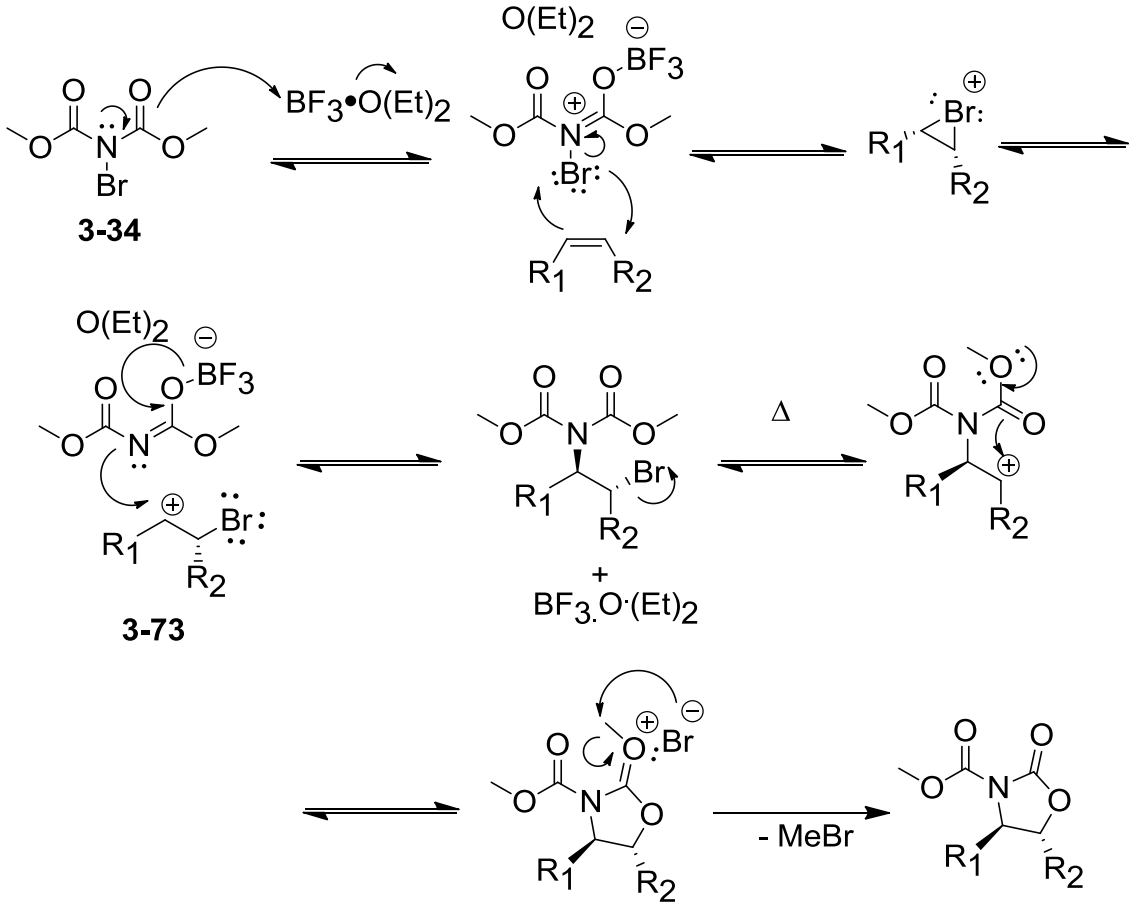


Entry	Substrate	Product	#	Yield
1			**3-71**	81
2			**3-72**	37[a]

[a] The compound was synthesized in three steps from *trans*-4-octene

The role of the BF_3•OEt_2 was to coordinate to the oxygen atom of compound **3-34** and release a positive bromonium cation (**Scheme 3-8**). This then formed a bromonium ion intermediate with the olefin followed by attack of the bromonium ion with the imide nitrogen atom. Evidence for a bromonium ion mediated mechanism over a radical mechanism was supported by several factors. First, the more stable the resulting bromonium ion intermediate the higher the yield for the 1-bromo, 2-*N*-imide adduct. This was seen by the yield from reaction of **3-34** with styrene, *p*-MeO styrene and *p*-NO_2 styrene (**Table 3-7**). Secondly, the reaction occurred through Markovnikov addition to the most stable carbon in the bromonium ion intermediate. In addition, the reaction of (E)-buta-1,3-dien-1-ylbenzene with **3-34** gave a 2:1 mixture of 1,4 addition and 1,2 addition to the terminal olefin (**Table 3-7, 3-58**). Thus the bromonium ion intermediate formed at the

terminal olefin and underwent rearrangement to the most stable benzylic/allylic carbocation before nucleophilic attack of the imide occurred. Lastly, the reaction gave only the *trans* 1-bromo, 2-*N*-imide stereoisomer in all cases and not a mixture of *anti* and *syn* stereoisomers.



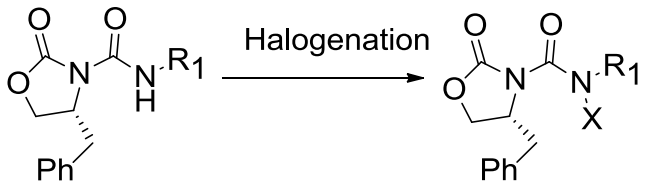
Scheme 3-8: Proposed reaction mechanism for formation of methyl 2-oxooxazolidine-3-carboxylate via a bromonium ion

The new aminobromination reagent **3-34** underwent Markovnikov addition regioselectivly and stereoselectivly to an olefin under catalytic Lewis acid conditions. This methodology provides a new synthetic route to an *N*-carbamate amino bromide with an easily removable carbamate protecting group. It also represents a new efficient synthesis of a methyl-2-oxooxazolidine-3-carboxylates in a two step sequence from an olefin. The

N-CO_2Me group can be easily removed by hydrolysis into an oxazolidin-2-one. The greatest attribute of this methodology is it may have the potential to provide a synthesis of an enantiomerically pure methyl-2-oxooxazolidine-3-carboxylate if a chiral Lewis acid is employed.

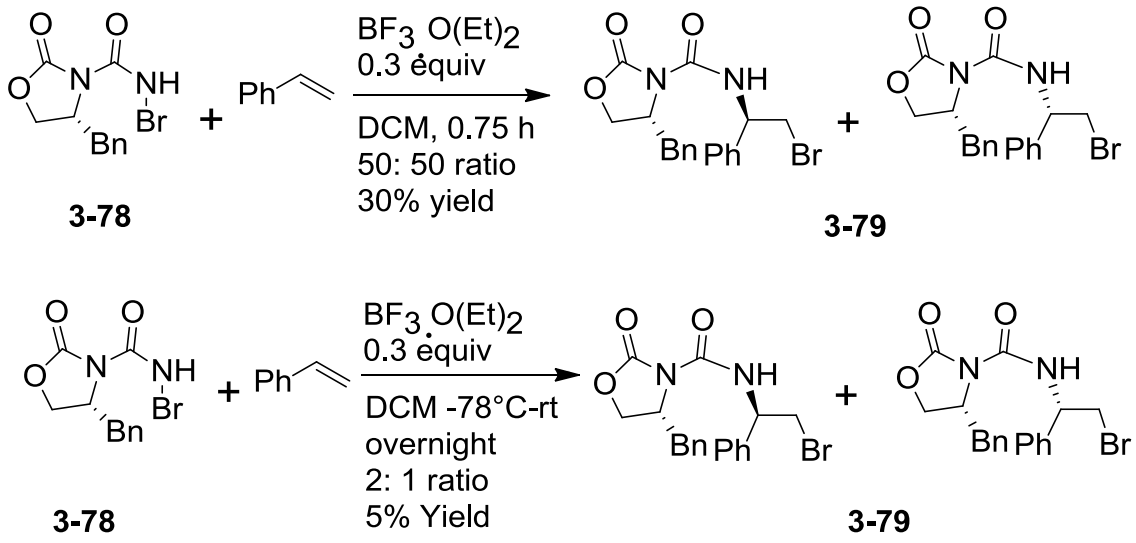
A chiral boron Lewis acid would be ideal to synthesize enantiopure methyl-2-oxooxazolidine-3-carboxylates. An enantiomerically pure methyl-2-oxooxazolidine-3-carboxylate could be hydrolyzed into an enantiomerically pure aminol alcohol. However, we first thought that an easier goal may be to synthesize an *N*-bromo imide with a chiral auxiliary and attempted a diastereoselective synthesis of a methyl-2-oxooxazolidine-3-carboxylate. We hoped to induce diastereoselectivity with an Evan's auxiliary. A couple of oxooxazolidine-3-carboxamides were synthesized by the reactions of (*S*)-4-benzyloxazolidin-2-one with an isocyanate. Halogenation of these substrates proved to be very difficult. Bromoacetate was not an effective method to brominate these substrates and resulted in no reaction and recovery of the starting materials. The only exception was that **3-77** was successfully brominated with bromo-acetate. Halogenation with dibromoisocyanuric acid (DBICA) or trichloroisocyanuric acid (TCICA) resulted in no reaction and recovery of the starting matericals. Bromination under basic conditions also failed (**Table 3-10**).

Table 3-10: Attempted halogenation of oxooxazolidine-3-carboxamides



SM #	R^1	X	Solvent	Method	Temp	P #	Yield (%)
3-74	Bz	Br	water	Br_2, $NaHCO_3$	rt	NA	0
3-74	Bz	Br	THF	NaH, Br_2	0°C-rt	NA	0
3-74	Bz	Br	DCM	DBICA	rt	NA	0
3-74	Bz	Br	$CHCl_3$	Br-acetate	rt	NA	0
3-74	Bz	Br	TFA	Br_2, Ag_2O	rt	NA	0
3-74	Bz	Cl	DCM	TCICA	rt	NA	0
3-75	Ph	Br	$CHCl_3$	Br-Acetate	rt	NA	0
3-75	Ph	Cl	$CHCl_3$	TCICA	reflux	NA	0
3-76	Ethyl	Br	$CHCl_3$	Br-Acetate	rt	NA	0
3-76	Ethyl	Br	$CHCl_3$	Br-Acetate	reflux	NA	0
3-77	H	Br	CCl_4	Br-Acetate	rt	**3-78**	74

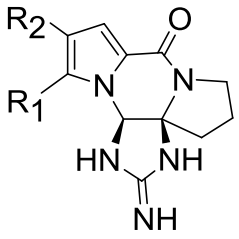
Compound **3-78** was reacted with styrene by the standard reaction conditions, but unfortunately an equal mixture of diastereomers was synthesized. This supported the mechanism above shown in **Scheme 3-8** that the reaction mechanism preceded through a bromonium ion. This 3-membered bromonium ion released its ring strain by opening to form a stable carbocation **3-73**, The sp^2 planar geometry of the carbocation would cause C-N bond formation to occur with approach of the chiral nucleophile to the *Re* or *Si* face with equal probability. Cooling the reaction may prevent the bromonium ion from opening up to a carbocation. A small amount of diasteroselectivity occurred by conducting the reaction at -78°C but unfortunately the yield dropped significantly. (**Scheme 3-9**).



Scheme 3-9: Attempted diastereoselective synthesis with Evan's auxillary

We decided to focus our attention on the synthesis of new bromine reagents for the construction of other interesting heterocycles. We decided to explore the reactions of an electron rich enol ether or an enamine with different bromine reagents. The reaction of Br-$N(CO_2Me)_2$ with an enol ether occurred without the need of a Lewis acid. In fact BF_3•OEt_2 was incompatible with an enol ether or an enamine and reacted with them to cause decomposition. The addition of urea and *N*-boc-guanidine to an electron rich olefin has been previously reported by Nicole Hewlett in our lab in the total synthesis of Dibromophakellin and some analogues[41] as well as by Al-Mourabit.[42,43] The addition of *N*-boc-guanidine and urea was accomplished in one pot with NBS as the bromine source.

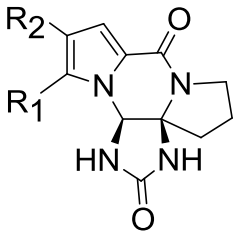
The synthesis of Dibromophakellin by Nicole Hewlett from the Tepe lab[41] led us to hypothesize that the addition of a urea or guanidine to an olefin and cyclization would be a great methodology to access important natural products (**Figure 3-2**).



$R_1 = R_2$ = Br, Dibromophakellin

R_1=H, R_2 = Br, Bromophakellin

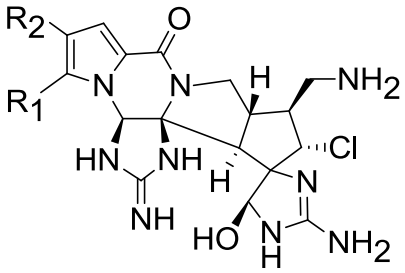
R_1=R_2= H Phakellin



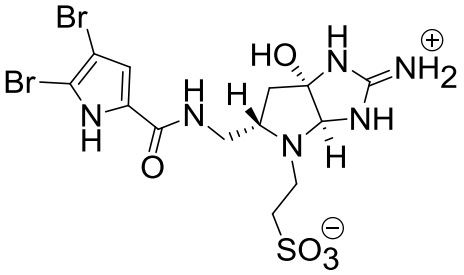
$R_1 = R_2$ = Br, Dibromophakellstatin

R_1=H, R_2 = Br, Bromophakellstatin

R_1=R_2= H Phakellstatin



Palau'amine

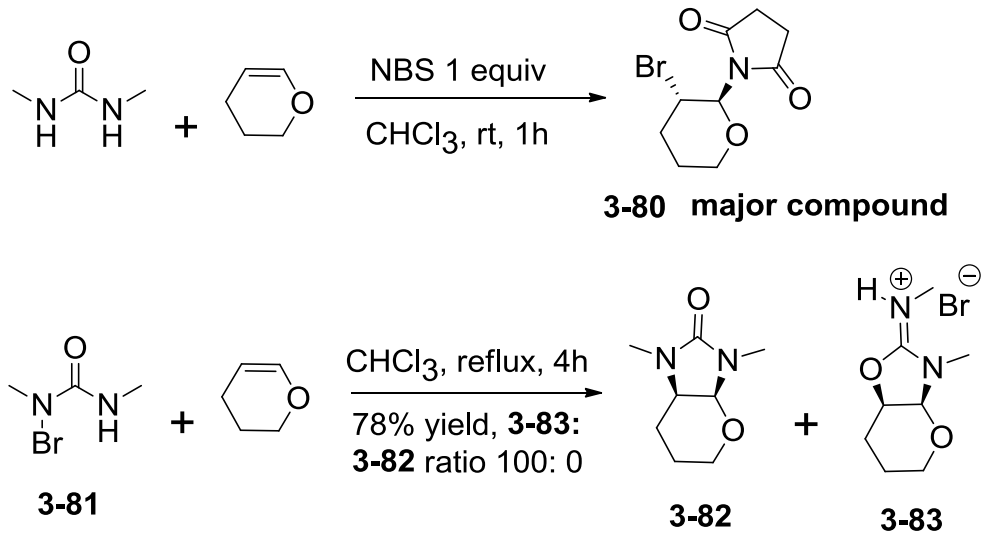


Nagelamide M

Figure 3-2: Urea and guanidine ring containing natural products[41]

In addition we wanted to better understand the reaction mechanism for the addition of an urea or guanidine to an electron rich olefin in the presence of NBS. We were interested in determining if the *N*-boc*, N*-bromoguanidine or *N*-bromourea were possible reaction intermediates before addition to an electron rich olefin or if the reaction occurred through a bromonium ion with the halogen source. The reaction was first investigated with 3,4-dihydro-2H-pyran, NBS, and 1,3-dimethyl urea. The major product isolated was the addition of NBS to 3,4-dihydro-2H-pyran to yield compound **3-80**. It was necessary to put the halogen atom on the nitrogen atom of the desired nucleophile to

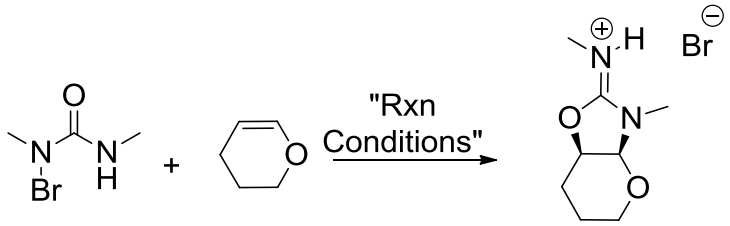
prevent the halogen source (NBS in this case) from undergoing reaction with the enol ether. 1-chloro-1,3-dimethylurea did not undergo reaction with 3,4-dihydro-2H-pyran even with reflux in $CHCl_3$. 1-bromo-1,3-dimethylurea did react with 3,4-dihydro-2H-pyran by refluxing in $CHCl_3$ to give 3-methylhexahydro-2H-pyrano[2,3-d]oxazol-2-ylidene)methanamine **3-83** and did not yield the urea **3-82**. Compound **3-83** was isolated as the HBr salt (**Scheme 3-10**).



Scheme 3-10: Addition of 1-bromo-1,3-dimethylurea to 3,4-dihydro-2H-pyran

This reaction was optimized with respect to the solvent and it was found that relatively non polar solvents were the key to obtain the desired product in high yield. $CHCl_3$ and DCM gave very similar yields (**Table 3-11**).

Table 3-11: Reaction optimization of addition of **3-83** to 3,4-dihydro-2H-pyran



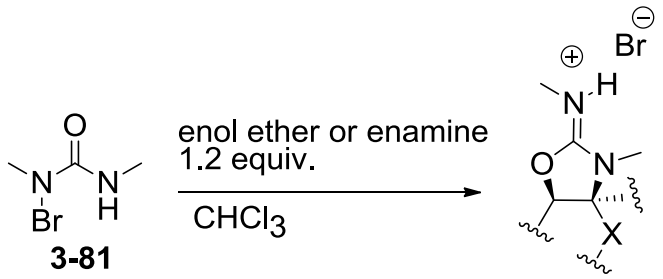
3-81 **3-83**

Entry	solvent	Time (h)	Temp °C	Yield **3-83**
1	$CDCl_3$	120	20	NA[a]
2	$CHCl_3$	4	61	78
3	THF	4	66	Trace
4	MeCN	4	55	0
5	DCM	4	40	76
6	CCl_4	4	77	33
7	Hexane	4	69	31
8	DCE	4	84	55
9	Toluene	4	75	50

[a] Monitored by ^{1}H NMR the reaction was very slow

The addition reaction was screened with a variety of alkenes, enol ethers and enamines. A reaction did not occur with simple alkenes like cyclohexene, styrene and *trans* stillbene. When BF_3•$O(Et)_2$ was added as a catalyst the 1-bromo-1,3-dimethylurea was transformed into 1,3-dimethylurea and the desired product was not formed. The scope of the reaction was unfortunately very limiting. The enol ether had to be disubstituted alpha to the oxygen atom if the enol ether was linear in order to yield the desired product. Compounds **3-87** and **3-88** were not synthesized under these reaction conditions (**Table 3-12, entries 1-2**).

Table 3-12: Cycloaddition reaction of *N*-bromourea with enol ethers and enamines



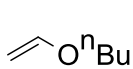
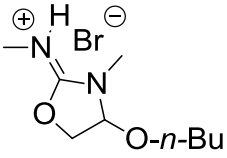
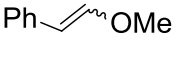
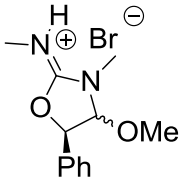
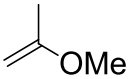
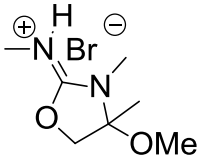
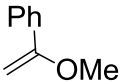
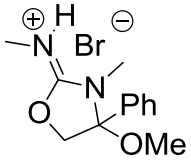
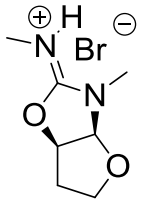
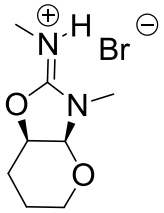
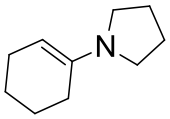
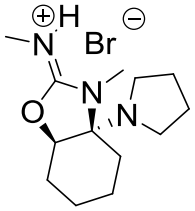
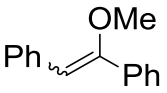
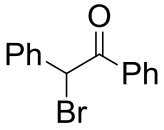
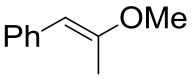
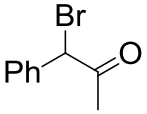
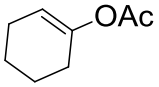
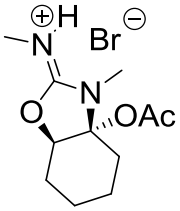
Entry	T (h)	Temp °C	SM #	Substrate	Product	P#	Yield (%)
1	24	rt	NA			**3-87**	0
2	2	reflux	NA			**3-88**	0
3	24	rt	NA			**3-89**	75
4	24	rt	**3-84**			**3-90**	80
5	24	rt	NA			**3-91**	0[a]

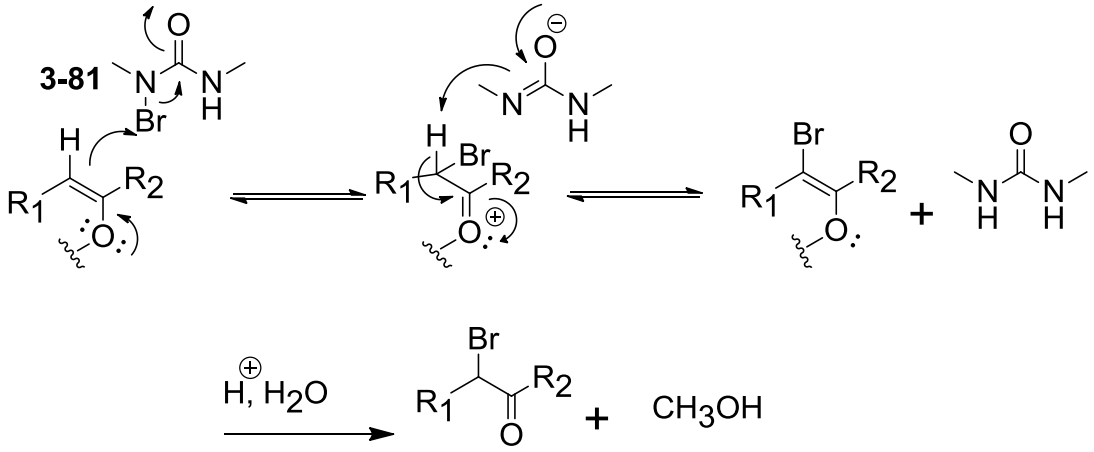
Table 3-12: Cont'd

Entry	T (h)	Temp °C	SM #	Substrate	Product	P#	Yield (%)
6	2	reflux	NA			**3-83**	78
7	24	rt	NA			**3-92**	0[a]
8	1	reflux	**3-85**			**3-93**	12
9	24	rt	**3-86**			**3-94**	23
10	24	rt	NA			**3-95**	0[a]

[a]Two regioisomers were observed by ^{1}H NMR but was not stable to purification

However, the enol ether did not have to be disubstituted alpha to the enol ether oxygen atom if the enol ether was a five or six membered ring (**Table 3-11, entries 5-6**). The product **3-91** was detected by ^{1}H NMR but was not stable enough to be isolated. The reactions of **3-81** with an enol acetate were successful. However, these products did not

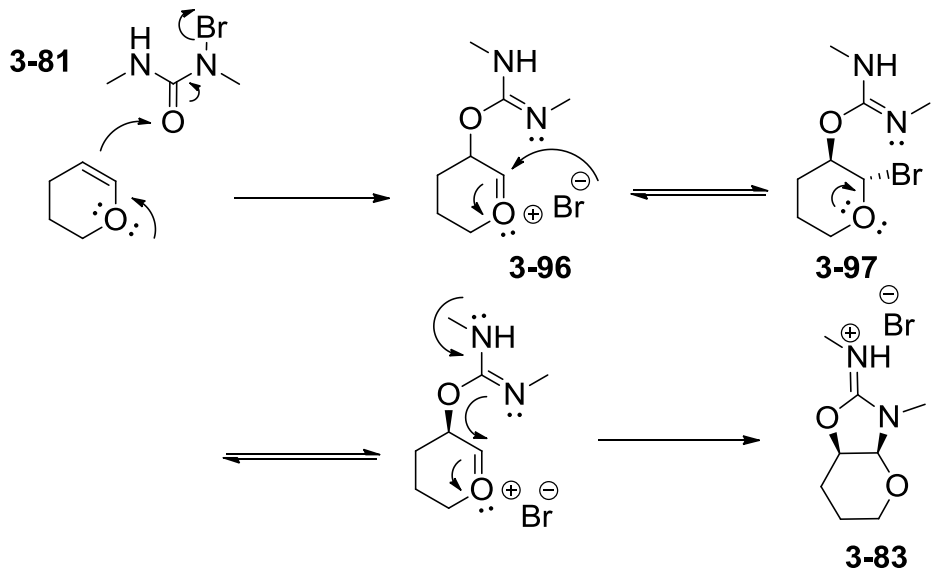
seem stable and unfortunately seemed to decompose even at room temperature after only a few hours. The reaction of an *N*-bromourea was much more exothermic with an enamine than an enol ether. In general the more electron rich the olefin was the faster the reaction occurred. The reactions of **3-81** with any of the linear enol ethers were not successful. Compound **3-81** did not act as a nucleophile but instead it simply acted as a base by abstracting a proton after the halonium ion was formed with any of the linear enol ethers (**Scheme 3-11**). As a result the alpha bromo ketones **3-93** and **3-94** were isolated after hydrolysis of the alpha bromo enol ethers during silica gel chromatography (**Table 3-11, entries 9, 10**).



Scheme 3-11: Enol ether alpha bromination mechanism

Reaction of 2,3-dihydrofuran or 1-(cyclohex-1-en-1-yl)pyrrolidine with **3-81** gave a mixture of two regioisomers **3-92**. Perhaps the reaction could go through multiple reaction mechanisms. One possible mechanism for the reaction of an enol ether with **3-81** was through a S_N2' mechanism. First attack of the enol ether pi bond on the oxygen atom of the bromourea **3-81** and loss of the bromine atom as a leaving group would yield the

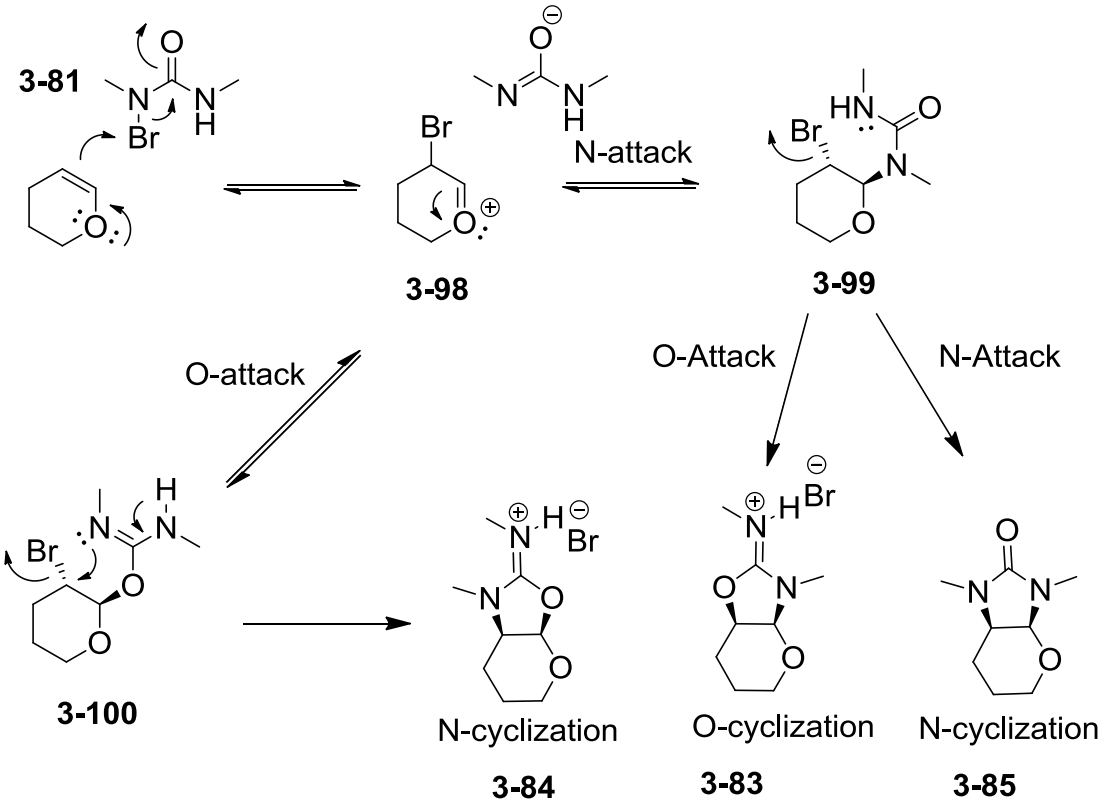
intermediates **3-96** and **3-97**. Secondly, ring closure to compound **3-83** would occur through an S_N1 mechanism through an oxonium carbocation. Typically a S_N2' mechanism was observed by addition of a nucleophile to an alkyl halide. There was not any literature precedent for a S_N2' mechanism between an enol ether and an *N*-bromourea. Nonetheless, this was one possible mechanism to explain the regiochemistry of the products (**Scheme 3-12**).



Scheme 3-12: S_N2' reaction mechanism for the addition of **3-81** with an enol or enamine with 3,4-dihydro-2H-pyran as an example

Yet another possible mechanism was formation of the bromonium ion intermediate followed by either attack of the oxygen atom or the nitrogen atom of the urea. The nucleophilicity of the nitrogen atom and oxygen atom are similar and as a result two different products may be formed. The attack of either the nitrogen atom or the oxygen atom would be expected to occur alpha to the enol ether oxygen atom or the enamine nitrogen atom due to the greater stability of a positive charge at the alpha position relative

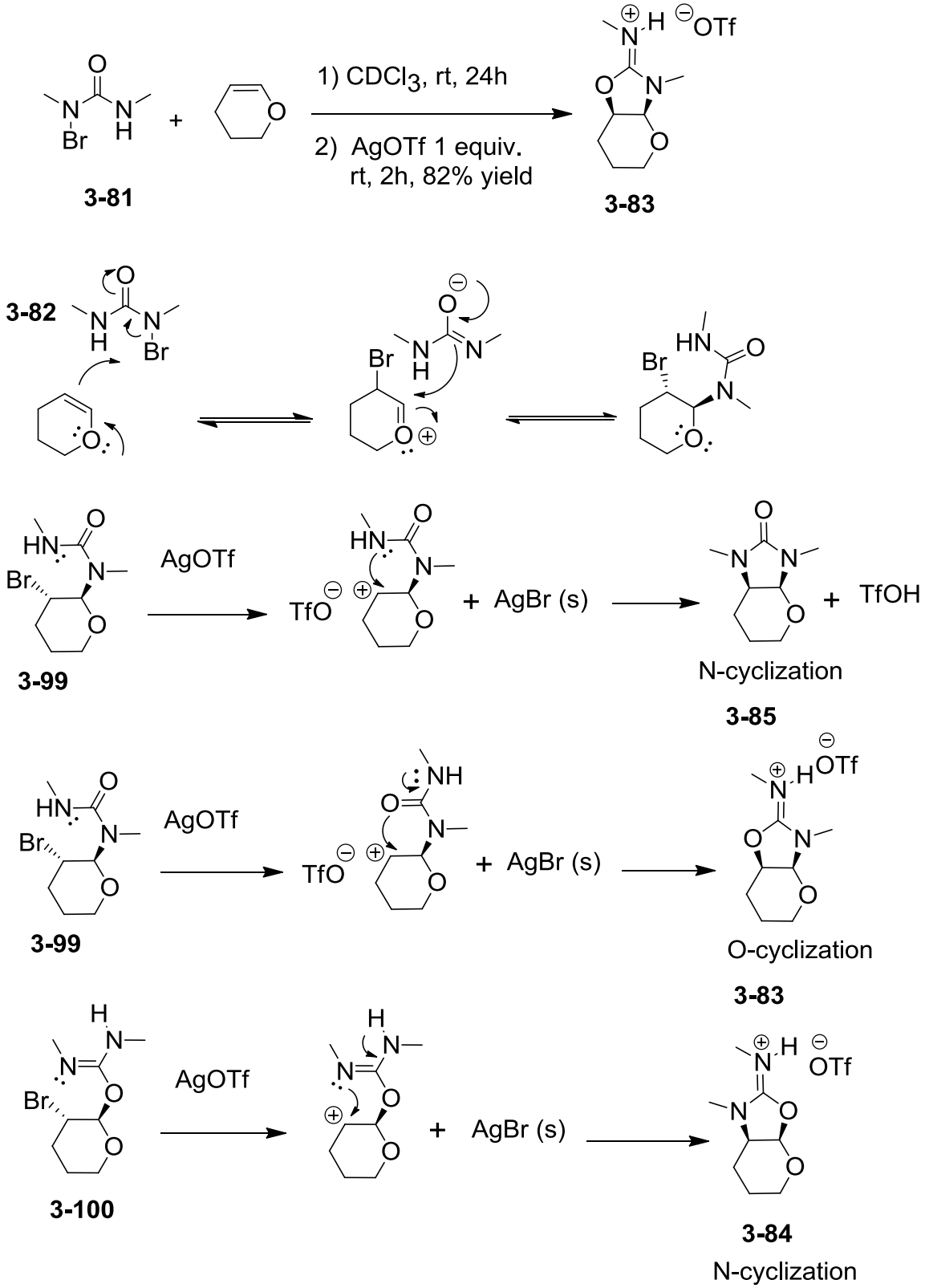
to the beta position. Nitrogen attack on the oxonium **3-98** would yield the intermediate **3-99** which could react further to make compound **3-83** through oxygen substitution or nitrogen substitution to yield **3-85** (**Scheme 3-13**).



Scheme 3-13: Bromonium mechanism for the cycloaddition of **3-81** with an enol ether or an enamine with 3,4-dihydro-2H-pyran as an example

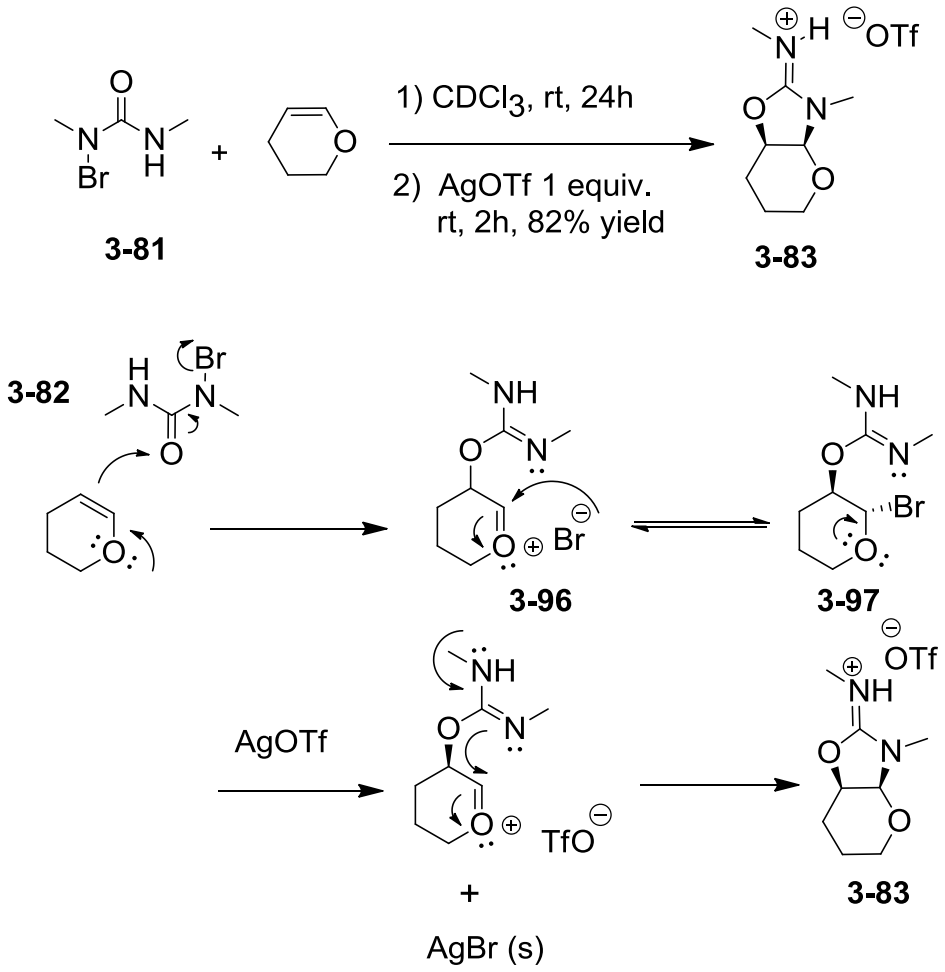
The compounds **3-83**, **3-84**, and **3-85** can be can be distinguished from one another by NMR and other experimental observations. The reaction of *N*-bromourea **3-81** with 3,4-dihydro-2H-pyran at room temperature slowly formed the desired product over several days. This reaction seemed to show the accumulation of **3-97** or **3-99** as an intermediate. The *N*-H proton of compound **3-97** or **3-99** was a broad singlet around 5.0 ppm in the ^{1}H

NMR. After the intermediate **3-97** or **3-99** was formed AgOTf was added and a yellow solid AgBr(S) precipitated out of the solution. If compounds **3-99** and **3-100** were formed as intermediates the silver would have to abstract the bromine to make a secondary carbocation in the case of the bromonium mechanism (**Scheme 3-14**).



Scheme 3-14: Bromonium mechanism and ring closure through AgOTf abstraction

In the S_N2' mechanism AgOTf would abstract the bromine atom of intermediate **3-97** and would result in an oxonium carbocation. Analysis of ^1H NMR showed formation of the product **3-83** as a TfOH salt and the formation of this product occurred without refluxing in chloroform as shown in above in **Table 3-11** (**Scheme 3-15**).



Scheme 3-15: S_N2' mechanism for addition of an enol ether with a *N*-bromourea and ring closure with AgOTf

If the reaction mechanism of the reaction of an *N*-bromourea with an enol ether is an S_N2' mechanism in the first step of the reaction then how is an alpha bromo ketone formed in

some cases (**Table 3-12, entries 8, 9**)? An enol ether that contained a conjugated Π system of electrons like enol ether **3-85** or **3-86** did not form the desired heterocycle with the *N*-bromo urea, but instead an α-bromoketone which can only be explained by a bromonium mechanism. However, the isolated yield of the alpha bromoketones were low so perhaps the reaction occurred through a combination of a bromonium mechanism and a S_N2' mechanism. The reaction also gave a mixture of regioisomers (**Table 3-12, Entries 5, 7**) which supports the idea that the reaction of an enol ether with a *N*-bromourea must then go through both mechanisms.

Compounds **3-83**, **3-84**, and **3-85** have would have different chemical shifts in their ^{13}C NMR and ^{1}H NMR. The reaction to yield compound **3-83** by refluxing in chloroform **Table 3-12** or by forming compound **3-83** by bromine abstraction with AgOTf showed an acid proton at around 10 ppm in the ^{1}H NMR. Compound **3-85** was not supported by the NMR data because an acid proton was not observed in the ^{1}H NMR. There was also a doublet in the ^{1}H NMR with an integration of 3 consistent with the methyl group on the imide nitrogen coupling with the acid *N*-H proton. After washing the unknown product with aqeous $NaHCO_3$; analysis by ^{1}H NMR showed that the acid proton at 10 ppm was absent. The methyl doublet transformed from a doublet into a singlet when the unknown product was washed with $NaHCO_3$. This acid proton at 10 ppm was consistent with a protonated imine of structures **3-83** or **3-84**. The ^{13}C NMR spectra of structure **3-83** or **3-84** showed carbon peaks at C1 = 85.27 ppm and C2 = 72.92 ppm. The ^{13}C NMR shifts of

the carbon peak at C2 of compound **3-85** should be less than 72.92 ppm because the carbon peak of a C-N bond would be more up field than a C-O bond (**Figure 3-3**).

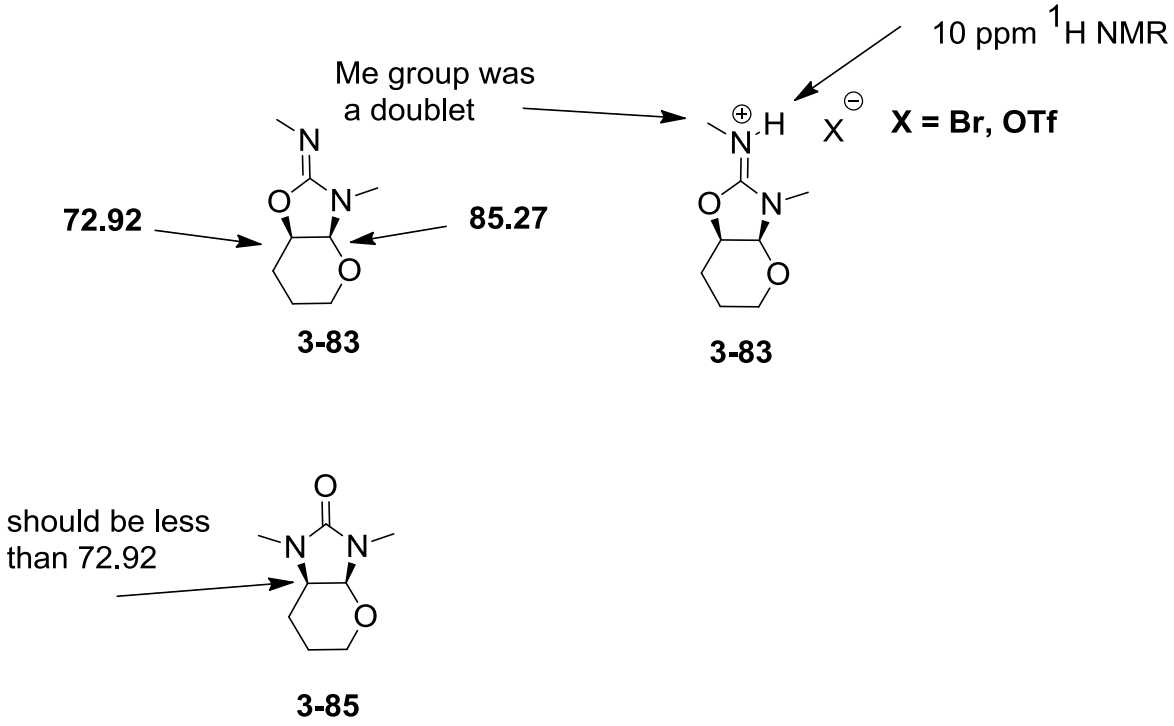
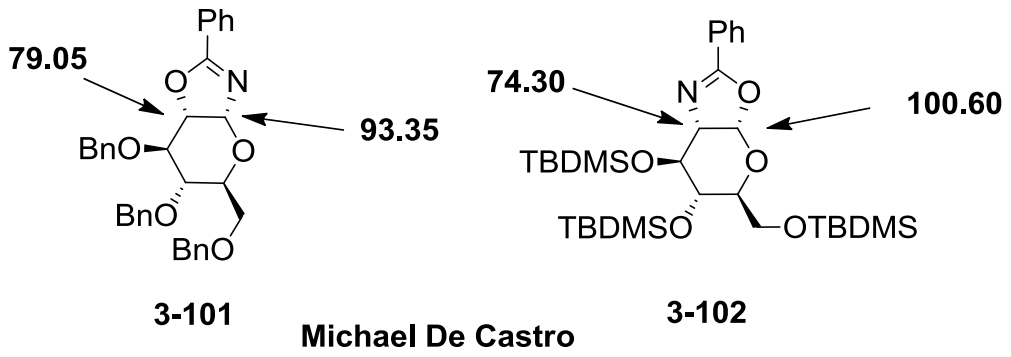


Figure 3-3: NMR data for compound **3-83**

Compound **3-83** and **3-84** were distinquished from one another by comparing the ^{13}C NMR shifts of the peaks at the C1 and C2 positions. A report by Castro[44] and coworkers provided experimental data for the chemical shifts of the peaks at the C1 and C2 position of some similar compounds. As shown below in **Figure 3-3** compound **3-101** had ^{13}C NMR chemical shifts of 79.05 ppm for the C-O bond and 93.35 ppm for the C-N bond at the C2 and C1 positions. Compound **3-102** had ^{13}C NMR chemical shifts of 74.30 ppm for the C-N bond and 100.60 ppm for the C-O bond at the C2 and C1 positions (**Figure 3-4**).



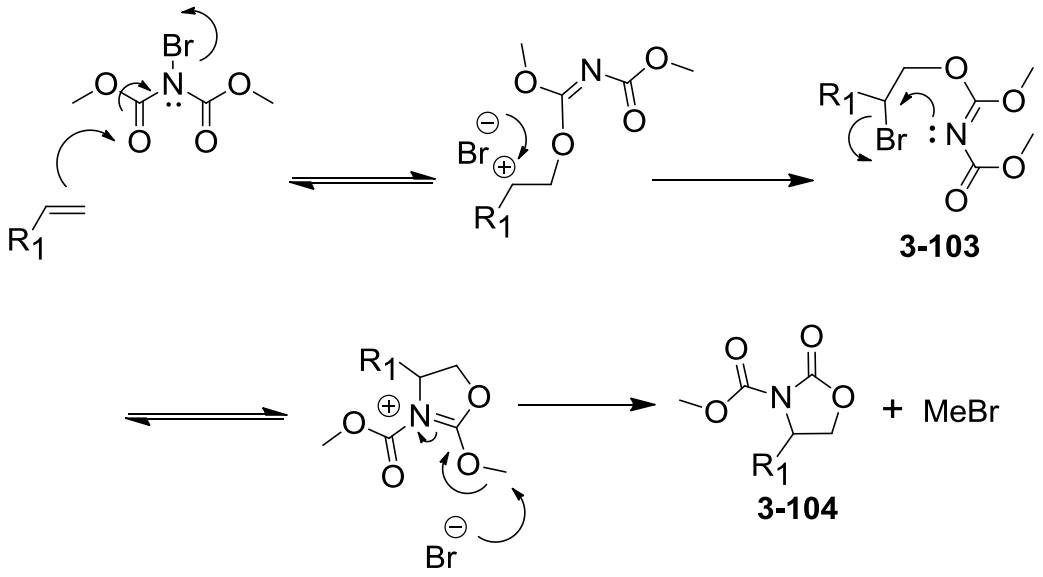
3-101 3-102

Figure 3-4: Experimental data for compounds **3-101** and **3-102** by Castro[44]

The ^{13}C NMR chemical shifts of the unknown product at the C2 and C1 positions were closer to the data of compound **3-101** than **3-102**. Two oxygen atoms attached to the same carbon would have a chemical shift of around 100 ppm in the ^{13}C NMR and the data for the unknown compound showed a carbon peak at 85.27 ppm for a carbon attached to a nitrogen atom and oxygen atom. Therefore, the regiochemistry was decided to be **3-83** and not **3-84** which could have formed through either a bromonium or S_N2' mechanism.

An S_N2' mechanism was the only rationale to explain the regiochemistry of the boc group after the addition of *N*-bocguanidine to an enamine reported by Nicole Hewlett in our lab.[41] This reaction was presumed to occur by first forming *N*-boc, *N*-bromoguanidine with N-bocguanidine and NBS. In contrast to the reactions of an enol ether with *N*-bromourea the reactions of Br-N$(CO_2Me)_2$ **3-34** with an olefin was proposed to occurr only through a bromonium ion mechanism and not a S_N2' mechanism (**scheme 3-8**). Reaction of compound **3-34** with cyclohexene yielded the *trans* 1-bromo, 2-*N*-imide adduct

and not the *cis* 1-bromo, 2-*N*-imide adduct. The coupling constants between the two methine protons were around 5 Hz. The coupling constants were consistent with the data by Corey for a *trans* 1-bromo, 2-*N*-amide adduct.[22] If the reaction of **3-34** did occur through an S_N2' reaction (**scheme 3-16**) then compound **3-103** would be the isolated intermediate and not the *trans* 1-bromo, 2-*N*-imide adducts in **Table 3-7**.



Scheme 3-16: Formation of a methyl 2-oxooxazolidine-3-carboxylate through a S_N2' mechanism

Compound **3-103** was not supported by ^{1}H NMR data because a singlet with an integration of 6 was observed instead of two singlets both of which would have an integration of 3. Compound **3-103** was also not supported by the ^{13}C NMR data because two different peaks downfield would be observed one for the C=O group and one for the C=N group. However only one peak downfield was present in the ^{13}C NMR due to two symmetrical C=O groups in the intermediate *trans* 1-bromo, 2-*N*-imide adduct (**Table 3-7**). Compound

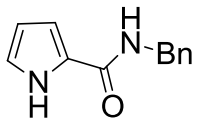
3-103 was not supported by the IR data because a C=N stretch was not present but just one C=O stretch. The identity of the *trans* 1-bromo, 2-*N*-imide adducts in **Table 3-7** are supported by ^{1}H NMR, ^{13}C NMR, and IR.

A bromonium ion mechanism versus an S_N2' mechanism must depend on the substrate, *N*-bromo compound, and the reaction conditions. The Lewis acid BF_3•OEt_2 coordinated to one of the oxygen atoms of Br-N$(CO_2Me)_2$. This would prevent the olefin from nucleophilically attacking the C=O oxygen atom via a S_N2' mechanism. A Lewis acid also made the bromine atom "fall off" the N-bromo compound to make a bromine cation and therefore favored a bromonium ion mechanism. An electron neutral olefin does not have a very nucleophilic carbon-carbon pi bond. However an enol ether or an enamine has a much more nucleophilic carbon-carbon pi bond. Therefore, a neutral olefin occurred through a bromonium ion mechanism and an electron rich olefin occurred through a S_N2' mechanism. The reaction of Br-N$(CO_2Me)_2$ with an electron rich 3,4-dihydro-2H-pyran occurred through a bromonium ion mechanism and not a S_N2' mechanism without BF_3•OEt_2 (**Table 3-7, 3-61**). This result meant that the structure of the *N*-bromo compound must also be important for a S_N2' over a bromonium ion mechanism. The electronics of a *N*-bromoguanidine or a *N*-bromourea favored an S_N2' mechanism whereas the electronics of a *N*-bromo imide **3-34** favored a bromonium ion mechanism.

APPENDIX

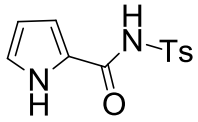
EXPERIMENTAL

3-1: N-benzyl-1H-pyrrole-2-carboxamide



To a 25-mL round bottom flask under nitrogen was added 1,4-dioxane (5 mL) and pyrrole (0.52 mL, 7.46 mmol). Benzyl isocyanate (0.92 mL, 7.46 mmol) was added followed by BF_3•$(OEt)_2$ (0.94 mL, 7.46 mmol). The reaction was mixed for 24 hours and then the reaction was partitioned between EtOAc and $NaHCO_3$ aq., the EtOAC was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography. The compound matched the reported literature data.[45] Solid; mp = 118-120°C; 52% Yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 4.65 (2H, d, J = 8.9 Hz (m, 1H), 6.23 (1H, m), 6.35 (1H, br), 6.60 (1H, m), 6.91 (1H, m). 7.25-7.40 (5H, m), 10.06 (1H, s, br). ^{13}C NMR (300 MHz) ($CDCl_3$) δ 43.5, 109.8, 109.8, 122.4, 125.9, 127.7, 127.9, 129.0, 138.8, 161.8.

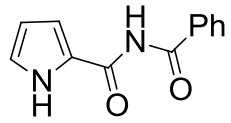
3-2: *N*-(1*H*-Pyrrol-2-ylcarbonyl)-4-methylbenzenesulfonamide



To a 50-mL round bottom flask under nitrogen was added 1,4-dioxane (10 mL) and pyrrole (1.03 mL, 14.93 mmol). The round bottom flask was cooled to 0°C with an ice bath and tosyl isocyanate (2.28 mL, 14.93 mmol) was added dropwise with a syringe over 3 minutes. The reaction was mixed for 1 hour during that time the product began to

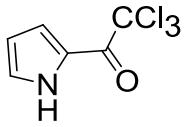
precipitate out of the reaction solution. The solvent was removed *in vacuo*. The compound matched the reported literature data.[46] White solid; mp 224-225°C; quantitative yield; ^{1}H NMR (300 MHz) (DMSO-*d6*) δ 2.37 (3H, s), 6.12 (1H, m), 7.00 (1H, m), 7.11 (1H, m), 7.39 (2H, d, J = 8.4 Hz), 7.84 (2H, d, J = 8.4 Hz). ^{13}C NMR (300 MHz) (DMSO-*d6*) δ 21.1, 109.6, 114.9, 123.3, 125.1, 127.7, 129.4, 137.1, 144.0, 157.9.

3-3: N-benzoyl-1H-pyrrole-2-carboxamide



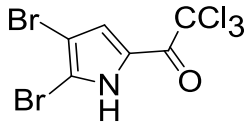
Benzoyl isocyante (water sensitive) was made and used immediately for reaction with pyrrole. To a 250-mL round bottom flask was added benzamide (5.42 g, 44.80 mmol) and DCE (100 mL). $(COCl)_2$ (4.60 mL, 53.75 mmol) was added with a syringe over 5 minutes. The solution was mixed at room temperature for 10 minutes and then was heated to reflux for 4 hours. The reaction solution was cooled to room temperature and the solvent was removed in *vacuo* at room temperature (dimerization of the benzoyl isocyante can occur at elevated temperatures while concentrating). To the crude benzoyl isocyante under an argon atmosphere was added 1,4-dioxane (60 mL), and pyrrole (3.09 mL, 44.80 mmol). The reaction was mixed overnight and then the solvent was removed in *vacuo* to give a solid. The solid was triturated with EtOAc, the solvent was removed and the compound was dried *in vacuo*. The compound matched the reported literature data.[46] Solid, mp = 180-181°C; 80% Yield; ^{1}H NMR (500 MHz) (DMSO-*d6*) δ 3.44 (3H, s), 6.21 (1H, m),

7.10 (1H, m), 7.24 (1H, m), 7.51-7.86 (5H, m). ^{13}C NMR (75 MHz) (DMSO-*d6*) δ 110.2, 115.8, 125.6, 125.8, 126.0, 129.2, 132.9, 135.2, 159.8, 168.3.



2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone

To a 100-mL round bottom flask was added pyyrole (3.09 mL, 44.78 mmol) and anhydrous ether (50 mL). The solution was mixed at room temperature under nitrogen and 2,2,2-trichloroacetyl chloride (6.50 mL, 58.21 mmol) was added all at once with a syringe. The solution was mixed for 24 hours and turned a purple color. The reaction was washed with $NaHCO_3$ aq., the ether was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The compound matched the reported literature data.[2] Solid 72-74°C, 88% Yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 6.76 (1H, m), 7.10 (1H, m), 7.33 (1H, m), 9.46 (1H, s, br). ^{13}C NMR (75 MHz) ($CDCl_3$) δ 111.9, 121.2, 123.01, 127.10, 173.2.

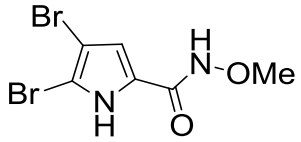


2,2,2-trichloro-1-(4,5-dibromo-1H-pyrrol-2-yl)ethanone

To a 250-mL round bottom flask was added 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone (8.36 g, 39.34 mmol) and reagent grade chloroform (100 mL). The solution was mixed under nitrogen with an adaptor and vent line to an Erlenmeyer flask containing 1M NaOH aq. to trap HBr. The solution was cooled to -10°C with a ice/ NaCl bath and Br_2 (4.06 mL, 78.67 mmol) slowly added with a syringe over 5 minutes. The solution was allowed to

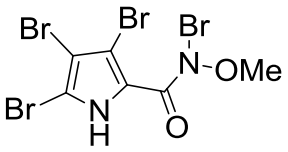
slowly warm to room temperature over the course of 2.5 hours. The reaction solution was washed with $NaHCO_3$ aq., dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The compound matched the reported literature data.[47] Oil; 92% Yield; ^{1}H NMR (500 MHz) (DMSO-*d6*) δ 7.36 (1H, s), 9.52 (1H, s, br). ^{13}C NMR (75 MHz) (DMSO-*d6*) δ 94.1, 100.9, 114.6, 122.5, 123.3, 170.9.

3-5: 4,5-dibromo-N-methoxy-1H-pyrrole-2-carboxamide



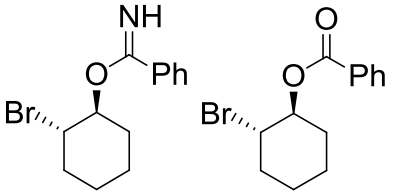
To a sealed tube was added 2,2,2-trichloro-1-(4,5-dibromo-1H-pyrrol-2-yl)ethanone (4.4 g, 11.88 mmol), methoxyamine hydrogen chloride (1.5 g, 17.83 mmol), TEA (8 mL), and DCM (2 mL). The tube was sealed and heated to 80°C for 12 hours. The solution was cooled to room temperature and poured into EtOAc (50 mL). The solution was extracted with 1M HCl aq., then with $NaHCO_3$ aq., washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was triturated with ether (40 mL) and hexane (20 mL). The liquid was decanted off and the solid was dried *in vacuo*. Compound was consistent with the literature data.[48] Solid; mp = 199-200°C; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.94 (3H, s), 7.26 (1H, s, br), 9.39 (1H, s), 10.18 (1H, s, br); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 65.22, 100.41, 104.01, 106.43, 122.81, 157.35.

3-7: N,3,4,5-tetrabromo-N-methoxy-1H-pyrrole-2-carboxamide



To a 10-mL round bottom flask was added 4,5-dibromo-*N*-methoxy-1H-pyrrole-2-carboxamide (0.1 g, 0.34 mmol), $CHCl_3$ (4 mL), cyclohexene (34.25 uL, 0.34 mmol), and NBS (0.12 g, 0.68 mmol). The solution was mixed for 24 h at room temperature. The solvent was removed *in vacuo*. The crude product was added ether and was washed with water to remove the succinimide, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Solid; mp 178-180°C ; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.78 (3H, s), 9.21 (1H, s, br, exchanges with D_2O). ^{13}CNMR (125 MHz) ($CDCl_3$) δ 65.23, 100.47, 104.02, 106.52, 122.74, 157.4; IR (NaCl) 2910, 2849, 1653, 1558; HRMS: Compound was not stable HRMS could not be obtained.

3-10: *Trans*-2-bromocyclohexyl benzimidate and 3-12: *Trans*-2-bromocyclohexyl benzoate

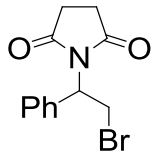


To a round bottom flask was added benzamide (100 mg, 0.83 mmol), $CHCl_3$ (3 mL), cyclohexene (83.56 uL, 0.83 mmol), and NBS (162 mg, 0.91 mmol). The reaction was mixed for 48 h and then the solvent was removed *in vacuo*. The reaction was purified by silica gel chromatography and some of the product hydrolyzed upon purification into *Trans*-2-bromocyclohexyl benzoate. Oil; 27 % overall Yield; ^{1}H NMR (500 MHz)

($CDCl_3$) δ 1.40–2.50 (6 H, m), 4.21-4.26 (2H, m), 4.47 (1H, s, br), 7.40-7.64 (5H, m); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 169.6, 131.2, 130.1, 128.0, 127.9, 82.4, 53.1, 35.2, 30.7, 24.9, 23.0; IR (NaCl): 2939, 1533, 1074; LRMS for $C_{13}H_{16}BrNO$ (M^+) 282.1 (52%) 284.1 (48%).

3-12: *Trans*-2-bromocyclohexyl benzoate; ^{1}HNMR (500 MHz) ($CDCl_3$) δ 1.40–2.50 (6 H, m), 4.12 (1H, m), 5.18 (1H, m), 7.46-7.64 (5H, m); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 23.3, 25.6, 31.5, 35.8, 55.1, 79.0, 128.5, 128.9, 130.5, 133.5, 170.7; IR (NaCl): 2939, 1637, 1074; LRMS for $C_{13}H_{15}BrO_2$ (M^+): 283.1 (52 %), 285.1 (48%).

3-13: 1-(2-bromo-1-phenylethyl)pyrrolidine-2,5-dione

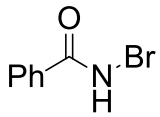


To a 10-mL round bottom flask under nitrogen was added NBS (0.1 g, 0.56 mmol), DCM (4 mL), styrene (0.07 mL, 0.56 mmol), and BF_3•OEt_2 (20 uL, 0.17 mmol). The solution was mixed for 1h at room temperature and then was quenched with $NaHCO_3$ sat. aq. solution. The product was extracted with DCM, dried over $MgSO_4$, filtered, and concentration *in vacuo*. The product was purified by silica gel chromatography; 50:50 DCM: hexane; R_f = 0.5; solid; mp = 90-92°C ; ^{1}H NMR (500 MHz) δ 2.71 (4H, s), 3.83 (1H, dd, J_1 = 10.5 Hz, J_2 = 5.5 Hz), 4.66 (1H, t, J = 10.5 Hz), 5.44 (1H, dd, J_1 = 10.5 Hz, J_2 = 5.5 Hz), 7.33 (3H, m), 7.48 (2H, d, J = 6.5 Hz); ($CDCl_3$) ^{13}CNMR (125 MHz)

($CDCl_3$) δ 28.2, 30.6, 57.7, 128.4, 129.2, 129.2, 136.9, 177.2. IR (NaCl): 1705, 1390, 1363, 1140.

General procedure for bromination of amides and imides through bromo-acetate with bromo-benzamide as a representative example

3-14: *N*-bromo benzamide

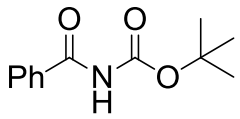


Bromoacetate was made *in situ* for the bromination of benzamide.[38] The hood lights were turned off. To a 250-mL round bottom flask under nitrogen was added silver acetate (2g, 11.98 mmol) and CCl_4 (60mL). The flask was cooled in an ice bath for 15 minutes and then Br_2 (0.62 mL, 11.98 mmol) was added neat with a syringe over 1 minute (addition time seemed to be very important slow addition times gave much lower yield). $AgBr_{(S)}$ formed instantly and the ice bath and round bottom flask were wrapped with aluminium foil. The reaction was mixed for 20 minutes at 0°C, vacuum filtered and washed once with CCl_4 (10mL) into an oven dried round bottom flask. The concentration of bromoacetate was determined by titration. PPh_3 (10 mg, 0.04 mmol) and $CHCl_3$ (1 mL) were added to a 20-mL vial. The bromoacetate solution was added dropwise until the PPh_3 $CHCl_3$ solution changed from colorless to yellow. From this volume the molarity of the bromoacetate solution was then determined. Typically, the concentration was ½ of the theoretical concentration. To a 25-mL round bottom flask under nitrogen was added benzamide (0.1g,

0.83 mmol), and bromoacetate solution in CCl_4 (1.2 equiv., 1.00 mmol). The round bottom flask was wrapped with aluminium foil and mixed at room temperature for 1.5 h. The solvent was removed *in vacuo* at room temperature while keeping the flask wrapped in aluminium foil (Prolonged exposure to high vacuum or heating on the rotovap caused debromination to occur). The orange solid was briefly dried under high vacuum for ten minutes. The compound was stored in the freezer (seemed stable for a few days in the freezer). The compound was consistent with the literature data.[49] Solid; mp=127-129°C; quantitative Yield; ^{1}HNMR (500 MHz) ($CDCl_3$) δ 6.79 (s, 1H), 7.39-7.56 (3H, m), 7.77-7.81 (2H, m); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 127.89, 128.66, 132.06, 133.17, 169.74.

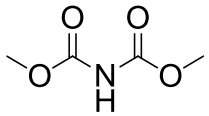
Compounds 3-20, 3-21, and 3-22 have been reported in the master's thesis[50]

3-23: *N*-Boc benzamide



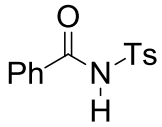
To a round bottom flask under nitrogen was added freshly prepared benzoyl isocyanate (2 g, 13.51 mmol), toluene (100 mL) and *tert*-butanol (2 g, 27.02 mmol). The solution was mixed at room temperature overnight and then filtered. The solid was dried *in vacuo*. The compound matched the reported literature data.[51] Solid; mp = 149-151°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (9H, s), 7.41–7.83 (5H, m), 8.10 (1H, s, br); ^{13}CNMR (125 MHz, $CDCl_3$) δ 28.2, 82.9, 127.7, 128.9, 132.9, 133.5, 149.9, 165.5.

3-24: N-methyl ester methyl carbamate



To a dry 500 mL round bottom flask under nitrogen was added methyl carbamate (10 g, 0.133 mol), DCE (200 mL), and $(COCl)_2$ (11.43 mL, 0.133 mol) was added all at once. The solution was heated to reflux for 19 h and then was cooled to room temperature under nitrogen. MeOH (26.80 mL, 0.66 mol) was added all at once and the solution was mixed for 5 h and concentrated *in vacuo* to give a white solid. The solid was triturated with ether (100 mL), filtered and dried *in vacuo*. The product was isolated in 90% yield. The product contained a small amount of impurity (<10%) and could be removed by a tedious column chromatography $R_f = 0.2$ PMA stain, 100% $CHCl_3$ but found it much more efficient to just to use the reagent with the small impurity in the following step. Compound has been previously synthesized.[52] Solid; mp = 128-130°C; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.78 (6H, s), 7.20 (1H, s, br); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 53.0 (CH_3). 151.9 (C).

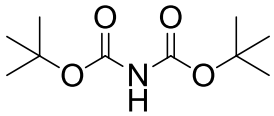
3-25: N-Tosyl benzamide



To a 25 mL round bottom flask was added tosylamide (3 g, 17.54 mmol) and benzoyl chloride (3.06 mL, 26.32 mmol). The solution was heated to 140°C with an oil bath for 1h and then was cooled to room temperature to form a solid. The solid was triturated with ethanol (10 mL) and was filtered. The product was dried *in vacuo* and matched the reported literature data.[53] Solid; mp = 147-149; 39% Yield; ^{1}HNMR (500 MHz)

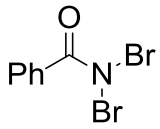
(Acetone-*D6*) δ 2.46 (3H, s), 7.46 (2H, d, J = 8.0 Hz), 7.52 (2H, t, J = 8.0 Hz), 7.64 (1H, t, J = 7.0 Hz), 7.95 (2H, d, J = 8.5 Hz), 8.02 (2H, d, J =8.5 Hz), 10.90 (1H, s, br); ^{13}C NMR (Acetone-*D6*) δ 21.88, 129.22, 129.50, 129.79, 130.54, 133.02, 134.31, 137.94, 145.84, 166.14.

3-26: N-Boc *tert*-butyl carbamate



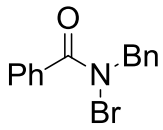
The compound was made by the following literature procedure.[54] A solution of DMAP (0.61g, 5.0mmol) in MeCN (15ml) was slowly added to a solution of formamide (2.5g, 56mmol) and Boc_2O (24 g, 110 mol) in MeCN (15ml). After stirring for 4h at room temperature the yellow solution was cooled down to 0 °C and *N*,*N*-diethylethylenediamine (6.97g, 60mmol) was slowly added. The resulting mixture was stirred while cooled in the ice bath and allowed to slowly warm to room temperature for 12h. The crude reaction was then filtered through a thin pad of silica and the solvent was removed *in vacuo*. Silica gel chromatography; EtOAc: hexane 1:5; R_f = 0.3; 92 % yield; white solid; mp = 118-119 °C; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 6.79 (1H, br), 1.46 (18H, s). ^{13}C NMR (125 MHz, CDCl3) δ 28.0, 81.9, 149.7.

3-28: *N*, *N*-dibromobenzamide



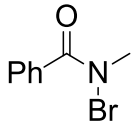
Bromoacetate was made by the general procedure above. To a round bottom flask was added benzamide (0.1 g, 0.83 mmol) and bromo-acetate in CCl_4 (2.5 equiv., 2.06 mmol). The reaction solution was mixed for 2h at room temperature and the compound was isolated as described above. The compound was unstable and was used immediately in the next reaction with styrene.

3-29: *N*-bromo, *N*-benzyl benzamide



Bromoacetate was made by the general procedure above. To a round bottom flask was added *N*-benzylbenzamide (0.1 g, 0.47 mmol) and bromoacetate in CCl_4 (1.5 equiv., 0.71 mmol). The reaction solution was mixed for 7h at room temperature and the compound was isolated by removing the solvent *in vacuo* as described in the general procedure above. The compound seemed to be unstable and contained some impurities, but was used immediately in the next reaction with styrene and BF_3•$O(Et)_2$.

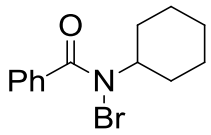
3-30: *N*-bromo, *N*-methyl benzamide



Bromo-acetate was made by the general procedure above. To a round bottom flask was added N-methylbenzamide (0.3 g, 1.41 mmol) and bromoacetate in CCl_4 (1.5 equiv., 2.11 mmol). The reaction solution was mixed for 2h at room temperature and the compound was isolated by removing the solvent *in vacuo* as described in the general procedure above.

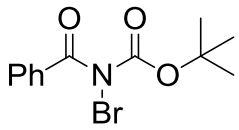
The compound seemed to be unstable and contained some impurities, but was used immediately in the next reaction with styrene and BF_3•$O(Et)_2$.

3-32: *N*-bromo, *N*-cyclohexyl benzamide



Bromo-acetate was made by the general procedure above. To a round bottom flask was added N-cyclohexylbenzamide (0.3 g, 1.07 mmol) and bromoacetate in CCl_4 (1.5 equiv., 1.60 mmol). The reaction solution was mixed for 2h at room temperature and the compound was isolated by removing the solvent *in vacuo* as described in the general procedure above. The compound seemed to be unstable and contained some impurities, but was used immediately in the next reaction with styrene and BF_3•$O(Et)_2$.

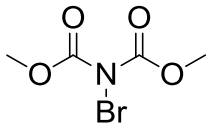
3-33: *N*-bromo, *N*-boc benzamide



Bromoacetate was made by the general procedure. To a 250 mL round bottom flask under nitrogen was added *tert*-butyl benzoylcarbamate (1.9 g, 8.59 mmol) and bromoacetate in CCl_4 (12.89 mmol). The reaction flask was wrapped in aluminium foil and the solution was mixed at room temperature for 3h. The compound was isolated by adding excess hexanes to precipitate out the product by the general procedure described above. The product was not very stable and was storred in the freezer. Yellow solid, mp = 100-102°C; ^{1}HNMR (500 MHz) ($CDCl_3$) 1.25 (9H, s), 7.42-7.63 (5H, m); ^{13}CNMR (125 MHz)

($CDCl_3$) δ 21.96, 80.61, 122.90, 123.00, 126.64, 129.62, 146.32, 164.97; IR (NaCl) 1741, 1653, 1228, 1143; HRMS: Not stable molecule could not obtain HRMS.

3-34: N-methyl ester methyl, N-bromocarbamate:

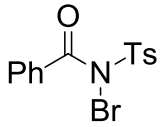


Bromo-acetate was made in situ and was used immediately. To a 250 mL round bottom flask under argon was added AgOAc (4g, 0.024 mol) and CCl_4 (120 mL). The reaction flask was cooled in an ice bath for ¼ h and then Br_2 (1.23 mL, 0.024 mol) was added neat dropwise over 2 minutes. After the addition of Br_2 the flask was stirred for another 1/3 h at 0°C and the formation of a yellow solid formed (AgBr). The reaction solution was vacuum filtered to remove the AgBr and the mother liquor (Bromoacetate solution) was poured into a dry 500 mL round bottom flask under argon at room temperature. Compound **3-24** (1.6 g, 0.012 mol) was added neat all at once to the bromo-acetate in CCl_4 at room temperature. The reaction exothermed and was stirred for 2.5 h and then the reaction solution was poured into a 1L Erlenmeyer and hexanes (500 mL) was added and the flask was parafilmed and placed in the freezer for 3h. A precipitate formed and was isolated by vacuum filtration and was washed with hexanes. The white solid was briefly dried at room temperature *in vacuo* for 5 minutes to remove residual solvent and acetic acid. The compound was placed in an amber bottle and was stored in the freezer and was found to be stable for several weeks. (Compound **3-34** would undergo debromination when isolated by removing the CCl_4 *in vacuo* with heating and was found that crystallization worked better. Also compound **3-28** would undergo debromination under prolonged time *in vacuo* or with

heating *in vacuo*. White solid; mp = 76-78°C; 75% Yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.89 (6H, s); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 55.57 (CH_3), 152.03 (C); IR (NaCl): 1782, 1190.

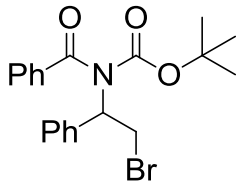
HRMS: Compound is not very stable, HRMS could not be obtained.

3-35: *N*-bromo, *N*-tosyl benzamide



To a beaker was added *N*-tosylbenzamide (1.8 g, 6.55 mmol), and NaOH (2M, 40 mL) at room temperature. To a 20 mL vial was added CCl_4 (1 mL) and Br_2 (0.36 mL, 7.20 mmol). The Br_2/CCl_4 solution was added to the *N*-tosylbenzamide/ NaOH solution dropewise. The reaction was mixed for 2h add then was poured into a sep. funnel. The solution was extracted with $CHCl_3$ (1x), EtOAc (2x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Compound matched the reported literature data.[53] White solid; mp = 204-206°C; 52% Yield; ^{1}H NMR (Acetone-*D6*) δ 2.28 (3H, s), 7.13–8.00 (9H, m); ^{13}C NMR (Acetone-*D6*) δ 21.81, 127.44, 128.45, 129.09, 130.00, 130.64, 132.49, 138.22, 143.21, 165.28.

3-46: *tert*-butyl benzoyl(2-bromo-1-phenylethyl)carbamate



Compound **3-46** was synthesized by the general procedure below (**Table 3-7**), *N*-boc, *N*-Bromo benzamide and styrene were used. ^{1}HNMR (500 MHz) ($CDCl_3$) δ 1.05 (9H, s), 4.06 (1H, dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz), 4.58 (1H, dd, J_1 = 10 Hz, J_2 = 2 Hz), 5.92 (1H, dd, J_1 = 5.5 Hz, J_2 = 1.5 Hz), 7.37-7.68 (10H, m); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 27.43, 33.25, 60.85, 83.72, 128.01, 128.20, 128.38, 128.40, 128.77, 131.65, 137.88, 133.05, 153.33, 173.45.

General synthesis of styrenes compounds 3-48, 3-49, 3-50

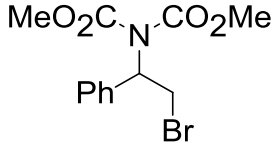
To 100 mL round bottom flask was added PPh_3MeI, THF (100 mg of PPh_3MeI per mL of THF) and the solution was cooled to 0°C for 20 minutes. BuLi (2.5 M in hexanes, 1.05 equiv.) was added dropwise the solution turned a dark red color. The solution was mixed for 20 minutes and the appropriate aldehyde was added (1 equiv) dropwise and the solution was mixed for 3 hours. The solution turned from red to yellow and the reaction solution was quenched with water and extracted with EtOAc (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude styrene was purified by silica gel chromatography 50:50 DCM: hexane. The styrenes were commercially available and matched the literature data.

General Procedure for Addition of Compound 3-34 to an Olefin (Table 3-7)

To a 10 mL round bottom flask under argon were added DCM (4 mL) and the olefin (50 mg if a solid or 50 µL in a liquid). BF_3•$O(Et)_2$ (0.3 equiv.) was measured with a 50 µL syringe and set aside. The *N*-bromo imide **3-34** (1.1 equiv.) was added all at once neat followed by immediate addition of the BF_3•$O(Et)_2$. The reaction was exothermic and

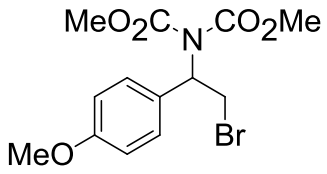
would often form a color for about a minute from dark yellow, orange and purple. The solution was mixed at room temperature for 3/4 hour and was then poured into a sep. funnel containing sat. aq. $NaHCO_3$. The solution was extracted with DCM (3x), dried with $MgSO_4$, vacuum filtered, and concentration in *vacuo* at room temperature. Prolonged heating of the crude product at a higher temperature when concentrating *in vacuo* caused a reaction to occur to yield a methyl-2-oxooxazolidine-3-carboxylate. The crude product was purified by silica gel chromatography.

3-47: Table 3-7



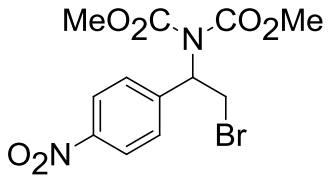
The compound was synthesized according to the general procedure. Column chromatography 97:3 DCM : TEA; R_f = 0.3; oil; 111 mg; 81% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.78 (6H, s), 4.01 (1H, dd, J_1 = 10.5 Hz, J_2 = 6.1 Hz) 4.31 (1H, t, J = 10.3 Hz) 5.78 (1H, dd, J_1 = 9.8, J_2 = 5.9 Hz), 7.25-7.40 (5H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 32.2 (CH_2), 54.0 (CH_3), 60.9 (CH), 127.4 (CH), 128.1 (CH), 128.4 (CH), 137.1 (CH), 154.2 (C); IR (NaCl): 2957, 1753, 1709, 1344, 1296, 1253; LRMS Calculated for $C_{12}H_{14}BrNO_4$ (M +Na): 339.9978; Found 340.1334

3-52: Table 3-7



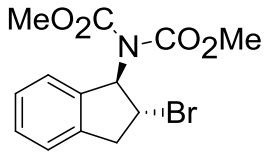
The compound was synthesized according to the general procedure. Column chromatography 97 : 3 DCM : TEA; R_f = 0.5; oil; 113 mg; 88% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.75 (3H, s) 3.77 (6H, s) 3.94 (1H, dd, J_1 = 10.3 Hz, J_2 = 5.9 Hz) 4.28 (1H, t, J = 10.3 Hz) 5.69 (1H, dd, J_1 = 10.3, J_2 = 5.4 Hz), 6.85 (2H, d, J = 8.1 Hz), 7.29 (1H, d, J = 8.1 Hz); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 32.4 (CH_2), 54.0 (CH_3), 55.2 (CH_3), 60.7 (CH), 113.8 (CH), 129.0 (CH), 129.1 (C), 154.3 (C), 159.4 (C); IR (NaCl): 2975, 1751, 1707, 1253; HRMS Calculated for $C_{13}H_{16}BrNO_5$ (M +Na): 368.0106; Found 368.0110.

3-53: Table 3-7



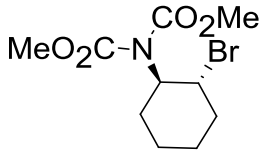
The compound was synthesized according to the general procedure. Column chromatography 100 % DCM, R_f = 0.45; oil; 45 mg; 38% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.79 (6 H, s), 4.05 (1H, dd, J_1 = 10.5, J_2 = 6.6 Hz), 4.23 (1H, t, J = 10.5 Hz), 5.83 (1H, dd, J_1 = 8.8, J_2 = 6.9 Hz), 7.57 (2H, d, J = 8.3 Hz) 8.20 (2H, d, J =8.8 Hz); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 30.8 (CH_2), 54.4 (CH_3), 60.3 (CH), 123.7 (CH), 128.6 (CH), 144.2 (C), 147.6 (C), 153.9 (C).

3-54: Table 3-7



The compound was synthesized according to the general procedure. Column chromatography 97 : 3 DCM : TEA; R_f = 0.5; oil; 78 mg; 52% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.32 (1H, dd, J_1 = 8.4 Hz, J_2 = 7.8 Hz), 3.71 (1H, dd, J_1 = 8.4 Hz, J_2 = 7.8 Hz), 3.76 (6H, s), 4.95 (1H, q, J = 7.8 Hz) 6.16 (1H, d, J =7.3 Hz) 7.08 (1H, d, J = 7.3 Hz), 7.17-7.27 (3H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 41.9 (CH_2), 49.7 (CH), 54.0 (CH_3), 70.9 (CH), 121.8 (CH), 124.4 (CH), 127.3 (CH), 128.3 (CH), 138.9 (C), 139.4 (C), 154.1 (C); IR (NaCl): 2955, 1757, 1713, 1342; HRMS Calculated for $C_{13}H_{14}BrNO_4$ (M +Na): 349.9996; Found 350.0004.

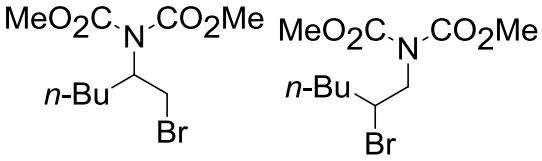
3-56: Table 3-7



The compound was synthesized according to the general procedure but 2.0 equivalents of **3-34** was used instead of 1.1 equivalents. The crude product was dissolved in ether and was washed once with sat. aq. $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography on TEA neutralized silica gel; the crude product was loaded on the column with $CHCl_3$ and eluted with 100 % hexane, R_f = 0.8 visualized with PMA stain; oil; 49 mg; 34% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.30–1.46 (2H, m), 1.68-1.75 (1H, m), 1.79-1.86 (2H, m), 1.87-1.94 (1H, m), 1.96-2.05 (1H, m), 2.42-2.48

(1H, m), 3.84 (6H, s), 4.30 (1H, m), 4.72 (1H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 25.4 (CH_2), 26.7 (CH_2), 30.4 (CH_2), 38.3 (CH_2), 53.2 (CH), 53.9 (CH_3), 63.8 (CH), 154.5 (C); IR (NaCl): 2955, 1753, 1437, 1228; HRMS Calculated for $C_{10}H_{17}BrNO_4$ (M +H): 294.0339; Found 294.00341.

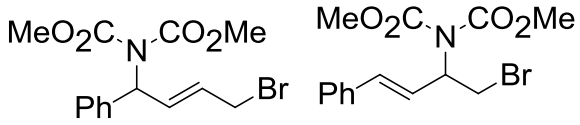
3-57: Table 3-7



The compound was synthesized according to the general procedure but 2.0 equivalents of **3-34** were used instead of 1.1 equivalents. The crude product was dissolved in ether and was washed once with sat. aq. $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography on TEA neutralized silica gel; the crude product was loaded on the column with $CHCl_3$ and was eluted with 100 % hexane, R_f = 0.8 visualized with PMA stain; oil; 44 mg; 37% yield; 52: 48 ratio **Regioisomer 1:** ^{1}H NMR (500 MHz) ($CDCl_3$) δ 0.80-0.91 (3H, m), 1.24-1.35 (4H, m), 1.65 - 1.92 (2H, m), 3.51 (1H, dd, J_1 = 10.3, J_2 = 5.9 Hz, 1 H), 3.83 (6H, s), 3.86 (1H, dd, J_1 = 10.3, J_2 = 4.9 Hz), 4.56 (1H, m). **Regioisomer 2:** ^{1}H NMR (500 MHz) δ 0.80 - 0.91 (3H, m), 1.24-1.35 (4H, m), 1.65-1.92 (2H, m), 3.84 (6H, s), 3.95 (1H, dd, J_1 = 14.2, J_2 = 5.9 Hz), 4.13 (1H, dd, J_1 = 14.2, J_2 = 8.3), 4.25 (1H, m); **Both Regioisomers** ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 13.81 (CH_3), 13.83 (CH_3), 22.0 (CH_2), 22.3 (CH_2), 28.7 (CH_2), 29.5 (CH_2), 30.8 (CH_2), 33.9

(CH_2), 35.5 (CH_2), 52.5 (CH_2), 53.7 (CH), 53.9 (CH_3), 54.0 (CH_3), 59.5 (CH), 154.0 (C), 154.5 (C); IR (NaCl): 2959, 1755, 1705, 1437, 1346; HRMS Calculated for $C_{10}H_{18}BrNO_4$ (M +Na): 318.0315; Found 318.0317.

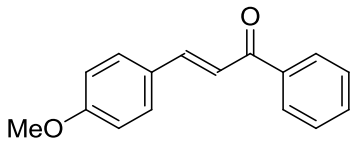
3-58: Table 3-7



Ratio = 2 : 1

The compound was synthesized according to the general procedure. Column chromatography 100 % DCM, R_f = 0.45; oil; 63 mg; 50% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ **Regioisomer 1** (1,4 addition product) ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.75 (6H, s), 4.04 (2H, d, J = 7.34 Hz), 5.98-6.08 (1H, m), 6.11 (1H, d, J = 8.30 Hz), 6.36 (1H, dd, J_1 = 16.0 Hz, J_2 = 8.30 Hz), 7.29-7.40 (5H, m); **Regioisomer 2** (1,2 addition product) ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.67 (1H, dd, J_1 = 10.3 Hz, J_2 = 6.4 Hz), 3.87 (6H, s), 3.99 (1H, t, J = 9.8 Hz), 5.30 (1H, m), 6.40 (1H, m), 6.67 (1H, d, J = 16 Hz), 7.25-7.40 (5H, m); ^{13}C NMR and DEPT (**Both Regioisomers**) (125 MHz) ($CDCl_3$) δ 31.42 (CH_2), 32.82 (CH_2), 53.88 (CH_3), 54.12 (CH_3), 60.74 (CH), 60.8 (CH), 124.34 (CH), 126.41(CH), 126.7 (CH), 127.42 (CH), 128.32 (CH), 128.41 (CH), 128.62 (CH), 131.36 (CH), 131.8 (CH), 135.15 (CH), 135.91 (C), 139.05 (C), 154.02 (C), 154.06 (C); IR (NaCl): 2953, 1753, 1707, 1282, 1259; HRMS Calculated for $C_{14}H_{16}BrNO_4$ (M +Na): 364.0161; Found 364.0160.

3-55: (E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one



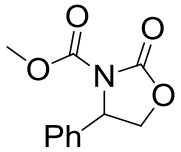
To a 100 ml round bottom flask was added NaOH (2.5 M, 5 mL, 12.5 mmol) and ethanol (3 mL). The solution was cooled with an ice water bath. Acetophenone (10 mmol) and *p*-methoxy benzaldehyde (10 mmol) were added neat all at once to the solution. The solution was allowed to slowly warm to room temperature over 3h. Solids formed and the product was extracted with EtoAc (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The solid was triturated with ether to give a yellow solid, 80% yield. The product is commercially available and the product matched the literature data.

General Procedure for Synthesis of methyl-2-oxooxazolidine-3-carbylates (Table 3-8)

To a 10 mL round bottom flask under argon were added DCM (4 mL) and the olefin (50 mg if a solid or 50 µL in a liquid). BF_3•$O(Et)_2$ (0.3 equiv.) was measured with a 50 µL syringe and set aside. The N-bromo imide **3-34** was added all at once neat followed by immediate addition of the BF3•O(Et)2 . The solution exothermed and would often form a color for about a minute from dark yellow, orange and purple. The solution was mixed at room temperature for 3/4 hour and was then poured into a sep. funnel containing sat. aq. $NaHCO_3$. The solution was extracted with DCM (3x), dried with $MgSO_4$, vacuum filtered, and concentration *in vacuo*. The crude compound was transferred into a 20 mL glass vial and the solvent was removed *in vacuo* to yield a residue. The crude product was heated in the glass vial neat under nitrogen atmosphere with an oil bath to 75°C for 3 h unless

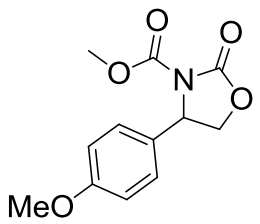
otherwise indicated. The crude product could be dissolved in ether and washed with water to remove residual H-N($CO_2Me)_2$ if needed. The crude methyl-2-oxooxazolidine-3-carboxylate was purified by silica gel chromatography.

3-63: methyl 2-oxo-4-phenyloxazolidine-3-carboxylate



The compound was made by the general procedure above. The crude product was purified by column chromatography; 98:2 DCM: TEA; $R_f = 0.32$; solid mp = 79-82°C; 75 mg; 78% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.76 (3H, s), 4.23 (1H, dd, $J_1 = J_2$ 8.80 Hz), 4.68 (1H, t, J = 8.80 Hz), 5.29 (1H, dd, J_1 = 8.80, J_2 = 4.40 Hz), 7.31 (2H, d, J = 6.85), 7.33-7.40 (3H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 53.9 (CH_3), 58.4 (CH), 69.5 (CH_2), 125.8 (CH), 128.8 (CH), 129.1 (CH), 138.8 (C), 151.1 (C), 151.9 (C); IR (NaCl): 2959, 1882, 1734, 1342, 1080; HRMS Calculated for $C_{11}H_{11}NO_4$ (M+Na): 244.0586; Found 244.0586.

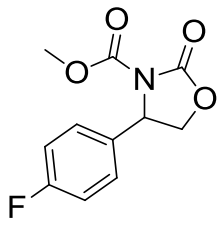
3-64: methyl 4-(4-methoxyphenyl)-2-oxooxazolidine-3-carboxylate



3-52 was synthesized and purified by the general procedure above. **3-52** was heated neat at 75°C for 3h and was transformed into **3-64** and did not require further purification. Oil, 77mg; 83% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.80 (3H, s), 3.81 (3H, s), 4.24 (1H, dd,

J_1 = 8.80 Hz, J_2 = 3.91 Hz) 4.67 (1H, t, J = 8.56 Hz), 5.26 (1H, dd, J_1 = 8.56 Hz, J_2 = 4.16 Hz), 6.92 (2H, d, J = 8.80 Hz) 7.27 (2H, d, J = 8.80 Hz); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 53.97 (CH_3), 55.29 (CH_3), 58.09 (CH), 69.72 (CH_2), 114.51(CH), 127.41 (CH), 130.73 (C), 151.28 (C), 151.93 (C), 159.94 (C); IR NaCl: 1819, 1720, 1253, 1080; HRMS Calculated for $C_{12}H_{13}NO_5$ (M +Na): 274.0696; Found 244.06091.

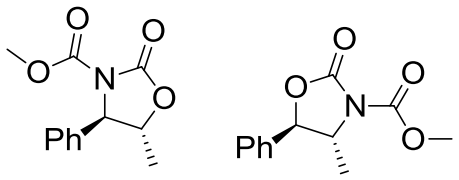
3-65: methyl 4-(4-fluorophenyl)-2-oxooxazolidine-3-carboxylate



The compound was made by the general procedure for the intermediate 1-bromo, 2-*N* imide and was purified by column chromatography. Oil; R_f = 0.5; 100% DCM; the intermediate was heated neat at 75°C for 3h to yield compound **3-65** and did not require any further purification. Solid mp = 67-68°C; 42 mg; 43% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.79 (3H, s), 4.23 (1H, dd, J_1 = 9.05 Hz, J_2 = 4.16 Hz), 4.69 (1H, t, J = 8.80 Hz), 5.30 (1H, dd, J = 8.56, J_2 = 4.16 Hz), 7.09 (2H, t, J = 8.56 Hz,), 7.30-7.45 (2H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ54.08 (CH_3), 57.87 (CH), 69.48 (CH_2), 116.13 (d, $^2J_{c/f}$ = 22.50 Hz), (CH), 127.86 (d, $^3J_{c/f}$ = 8.75 Hz), (CH), 134.60 (d, $^4J_{c/f}$ = 3.80 Hz), (C), 151.17 (C), 151.69 (C), 161.84 (d, $^1J_{c/f}$ = 246.30 Hz), (C); IR NaCl: 1819, 1734, 1336, 1080;

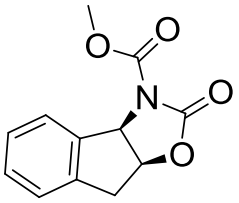
HRMS Calculated for $C_{11}H_{10}NO_4F$ (M +Na): 262.0497; Found 262.0492.

3-66: *trans*-methyl 5-methyl-2-oxo-4-phenyloxazolidine-3-carboxylate and *trans*-methyl 4-methyl-2-oxo-5-phenyloxazolidine-3-carboxylate



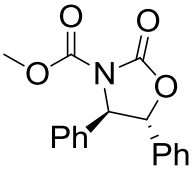
The compound was made by the general procedure above. The crude product was dissolved in ether and was washed with sat. aq. $NaHCO_3$, the ether layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography 98:2 DCM: TEA; R_f = 0.35; Oil ; 48 mg; 52% yield; **Regioisomer 1:** ^{1}H NMR (500 MHz) ($CDCl_3$) δ 0.98 (3H, d, J = 6.35 Hz), 3.77 (3H, s), 4.94 (1H, m), 5.24 (1H, d, J = 7.8 Hz), 7.15-7.40 (5H, m) **Regioisomer 2:** 1.51 (3H, d, J = 6.35 Hz), 3.76 (3H, s), 4.45 (1H, m), 4.80 (1H, d, J = 4.4 Hz), 7.15-7.40 (5H, m); **Both Regioisomers:** ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 15.9 (CH_3), 20.2 (CH_3), 54.0 (CH_3), 54.0 (CH_3), 62.7 (CH), 65.6 (CH), 74.8 (CH), 78.4 (CH), 125.9 (CH), 126.7 (CH), 128.9 (CH), 128.9 (CH), 129.2 (CH), 129.2 (CH), 134.9 (C), 138.3 (C), 151.2 (C), 151.5 (C), 151.6 (C),152.02 (C); IR NaCl: 1819, 1734, 1327, 1074; HRMS Calculated for $C_{12}H_{13}NO_4$ (M +Na): 258.0744; Found 258.0742.

3-67: *cis*-methyl 2-oxo-8,8a-dihydro-2H-indeno[1,2-d]oxazole-3(3aH)-carboxylate



The compound was made by the general procedure above. The crude product was dissolved in ether and was washed with sat. aq. $NaHCO_3$, the ether layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography 1: 1 ether: hexane; $R_f = 0.5$; solid mp = 98-100°C; 48 mg; 48% yield; ^1H NMR (500 MHz) ($CDCl_3$) δ 3.38 (2H, m), 4.00 (3H, s), 5.31 (1H, m), 5.79 (1H, d, J = 6.85 Hz), 7.29 (2H, d, J = 5.4 Hz), 7.37 (1H, t, J = 7.3 Hz), 7.66 (2H, d, J = 7.83 Hz); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 38.0 (CH_2), 54.2 (CH_3), 63.7 (CH), 77.7 (CH), 125.3 (CH), 126.7 (CH), 128.1 (CH), 130.1 (CH), 138.4 (C), 139.6 (C), 151.2 (C), 152.2 (C); IR (NaCl): 1824, 1734, 1334, 1253, 1068; HRMS Calculated for $C_{12}H_{11}NO_4$ (M +Na): 256.0586; Found 256.0586.

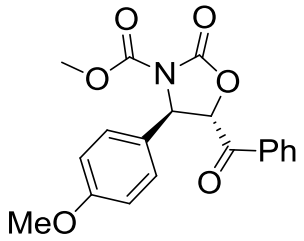
3-68: *trans*-methyl 2-oxo-4,5-diphenyloxazolidine-3-carboxylate



The compound was made by the general procedure above except that the residue only had to be heated at 75°C for 1 h to yield **3-68**. The crude product was purified by column chromatography 1: 1 ether:hexane; Rf = 0.28; solid; mp = 120-122°C ; 30 mg; 36% yield; ^1H NMR (500 MHz) ($CDCl_3$) δ 3.78 (3H, s), 5.13 (1H, d, J = 4.89 Hz), 5.34 (1H, d, J = 4.89 Hz), 7.33 (4H, m), 7.43 (6H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 54.1

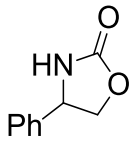
(CH3), 66.6 (CH), 82.4 (CH), 125.2 (CH), 126.0 (CH), 129.1 (CH), 129.2 (CH), 129.4 (CH), 129.4 (CH), 137.2 (C), 138.4 (C), 151.2 (C), 151.6 (C); IR (NaCl): 1824, 1797, 1327, 1074; HRMS Calculated for $C_{17}H_{15}NO_4$ (M +Na): 320.0901; Found 320.0899.

3-70: *trans*-methyl 5-benzoyl-4-(4-methoxyphenyl)-2-oxooxazolidine-3-carboxylate



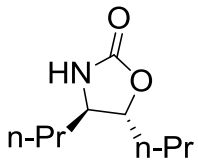
The compound was made by the general procedure above except that the residue only had to be heated at 75°C for 1 h to yield **3-70**. The crude product was dissolved in ether and was washed with sat. aq. $NaHCO_3$, the ether layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography 40:57:3 EtOAc: hexane: TEA; R_f = 0.45; oil; 34 mg; 50% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.77 (3H, s), 3.83 (3H, s) 5.48 (1H, d, J = 2.93), 5.55 (1H, d, J = 2.93 Hz) 6.96 (2H, d, J = 8.80 Hz), 7.32 (2H, d, J = 8.31 Hz), 7.51 (1H, t, J = 7.58 Hz), 7.66 (1H, t, J = 7.34 Hz), 7.91 (2H, d, J = 7.85 Hz); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 54.1 (CH_3), 55.4 (CH_3), 59.5 (CH), 79.9 (CH), 114.8 (CH), 127.7 (CH), 129.1 (CH), 129.1 (CH), 129.8 (C), 132.8 (CH), 134.8(C), 150.5 (C), 150.8 (C), 160.3 (C), 191.3 (C); IR (NaCl): 1821, 1792, 1728, 1369, 1082; HRMS Calculated for $C_{19}H_{17}NO_6$ (M +Na): 378.0959; Found 378.0954.

3-71: 4-phenyloxazolidin-2-one



Compound **3-56** (50 mg) was dissolved in THF (2 mL) and 2M LiOH (1 mL) was added. The solution was mixed fast to cause and emulsion for 2h at room temperature. The crude reaction was poured into a sep. funnel containing water. The product was extracted EtOAc (3x), dried with $MgSO_4$, filtered and concentrated *in vacuo* to give a solid. The solid was triturated with 50: 50 ether: hexane (3 mL) was placed in the fridge for 1h. The solvent was removed from the crystals with a pipette and the crystals were dried *in vacuo*. solid mp = 132-133; 30 mg; 81% yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 4.19 (1H, dd, J_1 = 8.56, J_2 = 7.09 Hz), 4.74 (1H, t, J = 8.80 Hz), 4.96 (1H, t, J = 7.83 Hz), 5.76 (1H, s, br), 7.31-7.43 (5H, m); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 56.36 (CH), 72.52 (CH_2), 126.03 (CH), 128.87 (CH), 129.21 (CH), 139.40 (C), 159.49 (C).

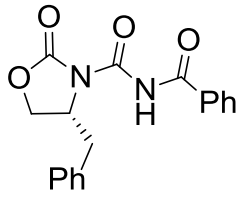
3-72: *trans*-4,5-dipropyloxazolidin-2-one



The compound was made by the general procedure above. The crude product was hydrolyzed to **3-72** by dissolving in THF (2 mL) and cooling the crude reaction to 0°C. 2M LiOH (1 mL) was added and the solution was mixed fast to cause an emulsion for 2h while warming slowly to room temperature. The crude product was extracted with EtOAc, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by

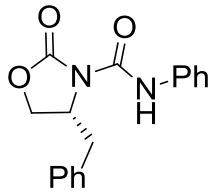
column chromatography; 100% DCM; R_f = 0.2 (PMA stain); oil; 20 mg; 37% yield (over 3 steps). The compound matched the reported literature data.[40] ^{1}H NMR (500 MHz) ($CDCl_3$) δ 0.94 (6H, m), 1.28-1.73 (8H, m), 3.42 (1H, q, J = 6.03 Hz), 4.15 (1H, dt, J = 7.95, 5.07 Hz) 6.21 (1H, s, br.); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 13.75 (CH_3), 13.83 (CH_3), 18.15 (CH_2), 18.74 (CH_2), 36.88 (CH_2), 37.51 (CH_2), 57.85 (CH), 82.50 (CH), 159.56 (C).

3-74: (*R*)-N-benzoyl-4-benzyl-2-oxooxazolidine-3-carboxamide



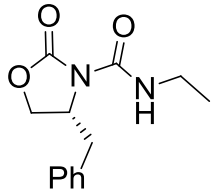
To a 100 mL round bottom flask was added (*S*)-4-benzyloxazolidin-2-one (0.5 g, 3.38 mmol), toluene (50 mL), benzyl isocyanate (0.67 g, 5.41 mmol), and TEA (0.04 mL, 0.34 mmol). The solution was heated to 80°C with an oil bath for 3 h. The reaction solution was cooled to room temperature and concentrated *in vacuo*. The solid was triturated with EtOAc, the EtOAc was decanted, and the solid was dried *in vacuo*. ^{1}HNMR (500 MHz) ($CDCl_3$) δ 2.94(1H, dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz), 3.48 (1H, dd, J_1 = 10.5 Hz, J_2 = 2.5 Hz), 4.32-4.40 (2H, m), 4.83 (1H, m), 7.29 (2H, d, J = 7.0 Hz), 7.31 (1H, t, J = 7.5 Hz), 7.35 (2H, t, J = 7.5 Hz), 7.51 (2H, t, J = 8.0 Hz), 7.62 (1H, t, J = 7.5 Hz), 7.97 (2H, d, J = 8.5 Hz), 11.64 (1H, s, br); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 28.00, 55.05, 67.12, 127.55, 127.78, 129.05, 129.10, 129.45, 132.53, 133.36, 134.62, 146.64, 155.65, 164.07.

3-75: (*R*)-4-benzyl-2-oxo-N-phenyloxazolidine-3-carboxamide



To a sealed tube was added (S)-4-benzyloxazolidin-2-one (0.5 g, 3.38 mmol), toluene (20 mL), phenyl isocyanate (0.37 mL, 3.38 mmol), and TEA (0.09 mL, 0.04 mmol). The solution was heated to 100°C with an oil bath for 24 h. The reaction solution was cooled to room temperature and concentrated *in vacuo*. The solid was triturated with EtOAc, the EtOAc was decanted, the solid was dried *in vacuo*. mp = 97-98°C; ^{1}HNMR (500 MHz) ($CDCl_3$) δ 1.29 (3H, t, J = 7.5 Hz), 2.90 (1H, dd, J_1 = 9 Hz, J_2 = 4.5 Hz), 3.44 (1H, dd, J_1 = 10.5 Hz, J_2 = 3 Hz), 4.30 (2H, m), 4.79 (1H, m), 7.16 (1H, t, J = 7.5 Hz), 7.25-7.40 (8H, m), 7.56 (2H, d, J = 7.5 Hz), 9.93 (1H, s, br); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 38.43, 55.14, 66.59, 120.08, 124.43, 127.38, 128.99, 129.11, 129.5, 135.09, 137.04, 148.78, 155.61; IR (NaCl): 3275, 1755, 1601, 1554, 1400, 1223; HRMS Calculated for $C_{17}H_{16}N_2O_3$ (M +Na): 319.1060; Found 319.1059.

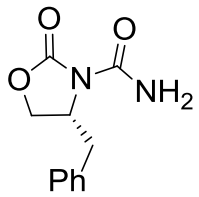
3-76: (*R*)-4-benzyl-N-ethyl-2-oxooxazolidine-3-carboxamide



To a sealed tube was added (*S*)-4-benzyloxazolidin-2-one (0.3 g, 2.02 mmol), toluene (20 mL), ethyl isocyanate (0.16 mL, 5.41 mmol), and TEA (0.23 mL, 0.04 mmol). The solution was heated to 60°C with an oil bath for 16 h. The reaction solution was cooled to

room temperature and concentrated *in vacuo*. The product was purified by silica gel chromatography. Oil, 95% Yield 70%; R_f = 0.5; 10:90 EtOAc: DCM; ^{1}HNMR (500 MHz) ($CDCl_3$) δ 1.31(3H, t, J =5 Hz), 2.87 (1,H, dd, J_1 = 10.0 Hz, J_2 = 5.0 Hz), 3.37(1H, dd, J_1 =10.0 Hz, J_2 =5.0 Hz), 4.27 (4H, m), 4.71 (1H, m), 7.20-7.35 (5H, m), 10.19 (1H, s, br); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 14.19, 37.97, 54.98, 62.50, 66.83, 127.50, 129.06, 129.47, 146.82, 150.32, 154.96; IR (NaCl): 3254, 1794, 1759, 1529, 1400, 1186.

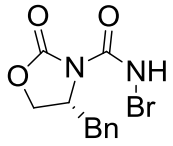
3-77: (*R*)-4-benzyl-2-oxooxazolidine-3-carboxamide



To a 100 ml round bottom flask under argon was added (*S*)-4-benzyloxazolidin-2-one (1.0 g, 5.64 mmol) and THF (30 mL). The solution was cooled with a dry ice/acetone bath for 20 minutes. BuLi (2.48 mL, 6.21 mmol, 2.5 M in hexanes) was added dropwise the solution was mixed for 5 minutes and then taken out of the dry ice bath and placed in an ice bath. After 20 minutes the flask was placed in the dry ice / acetone bath once again for 20 minutes. To another dry round bottom flask was added *p*-NO_2-phenyl chloroformate (1.14 g, 5.64 mmol) and THF (10 mL). This solution was added to the reaction solution with a canulla over 2 minutes. The reaction was left in the dry ice bath to slowly warm up to room temperature overnight. Dioxane (20 mL) was added to the reaction solution and excess ammonia was bubbled into the reaction solution for about 20 minutes. The ammonia gas was generated by adding concentrated NH_4OH in an addition funnel to solid

NaOH in a round bottom flask attached to an outlet valve with a rubber tube and a pipette to bubble the ammonia gas. The reaction instantly turned bright yellow and exothermed. The rxn was mixed for another 3h. The crude reaction was portioned between EtOAc and water, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography; 20: 80 EtoAc: DCM, $R_f = 0.3$; 50% yield; ^{1}HNMR (500 MHz) ($CDCl_3$) δ 2.89 (1H, dd, $J_1 = 13.69$, $J_2 = 9.29$ Hz), 3.36 (1H, dd, $J_1 = 13.69$, $J_2 = 2.93$ Hz), 4.09 - 4.29 (2H, m), 4.68 (1H, m) 5.17 (1H, s, br), 7.19 - 7.36 (5H), 7.77 (1H, s, br); ^{13}C NMR and DEPT (125 MHz) ($CDCl_3$) δ 38.33 (CH_2), 54.81 (CH), 66.4 (CH_2), 127.33 (CH), 128.93 (CH), 129.49 (CH), 135.05 (C), 151.85 (C), 155.34 (C); IR (NaCl): 3427, 3262, 1747, 1718, 1680, 1595, 1375.

3-78: (*R*)-4-benzyl-N-bromo-2-oxooxazolidine-3-carboxamide

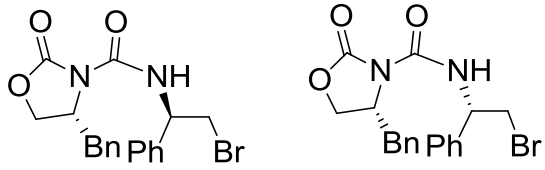


Bromoacetate was made by the general procedure in CCl_4. To a dry round bottom flask under argon was added (*R*)-4-benzyl-2-oxooxazolidine-3-carboxamide (0.6 g, 2.73 mmol) and bromoacete in CCl_4 (0.2 M, 15 mL). The solution turned from dark orange to yellow over 2.5 h. An aliquot was taken in $CDCl_3$ (CCl_4 not present in ^{1}H NMR) to determine acetic acid by-product had formed and the desired product. Hexane (100 mL) was added to the reaction solution and a precipitate formed placed in the freezer for 1h. The solids were filtered and washed them with hexane. The solids were briefly dried under high vacuum

for about 10 minutes and stored the solid in the freezer. The compound looked like a mixture of product and some starting material could be seen the ^{13}C NMR. Due to the instability of the product purification was not attempted. The major ^{13}C NMR product peaks could be elucidated. mp = 82-84°C; 74% yield; $^{1}HNMR$ (500 MHz) ($CDCl_3$) δ 2.78 - 2.92 (1H, m), 3.27 - 3.40 (1H, m), 4.08 - 4.21 (1H, m), 4.21 - 4.38 (2H, m), 4.60 - 4.76 (1H, m), 7.05 - 7.24 (2H, m,), 7.25 - 7.39 (3H, m), 8.05 (1H, s);$^{13}CNMR$ and DEPT (125 MHz) ($CDCl_3$) δ 38.22, 55.96, 67.27, 127.48, 127.93, 129.03, 129.43, 151.0, 155.68; IR (NaCl): 3267, 1753, 1701, 1400, 1226

HRMS: Molecule was not stable

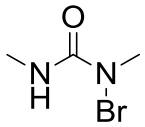
3-79: (R)-4-benzyl-N-((R)-2-bromo-1-phenylethyl)-2-oxooxazolidine-3-carboxamide and (R)-4-benzyl-N-((S)-2-bromo-1-phenylethyl)-2-oxooxazolidine-3-carboxamide



To a 10 mL round bottom flask under argon were added DCM (4 mL) and styrene (0.05 mL, 0.44 mmol). BF3•O(Et)2 (16 uL, 0.13 mmol) was measured with a 50 µL syringe and set aside. (*R*)-4-benzyl-N-bromo-2-oxooxazolidine-3-carboxamide (130 mg, 0.44 mmol) was added all at once neat followed by immediate addition of the $BF_3•O(Et)_2$. The reaction was exothermic and mixed at room temperature for 3/4 hour and was then poured into a sep. funnel containing sat. aq. $NaHCO_3$. The solution was extracted with DCM (3x), dried with $MgSO_4$, vacuum filtered, and concentration *in vacuo* at room temperature.

Column Chromatography 100 % DCM, $R_f = 0.5$; The product were a 1:1 mixture of diastereomers. Three ^{1}H NMR peaks were clearly resolved from one another and are assigned different chemical shifts but the rest of the peaks overlap one another so they were assigned identical chemical shifts. **Diastereomer 1:** ^{1}H NMR (500 MHz) ($CDCl_3$) δ 2.87 (1H, dd, $J_1 = 13.45$, $J_2 = 9.05$ Hz), 3.25 (1H, dd, $J_1 = 13.69$, $J_2 = 2.93$ Hz), 3.62 - 3.73 (1H, m) 3.73 - 3.84 (1H, m), 4.17 - 4.34 (2H, m), 4.61 - 4.74 (1H, m), 5.29 - 5.37 (1H, m), 7.09 - 7.56 (10H, m), 8.62 (1H, s, br). **Diastereomer 2:** ^{1}H NMR (500 MHz) ($CDCl_3$) δ 2.91 - 3.00 (1H, dd, $J_1 = 13.45$, $J_2 = 9.05$ Hz), 3.29 - 3.36 (1H, dd, $J_1 = 13.69$, $J_2 = 2.93$ Hz), 4.17 - 4.34 (2H, m), 4.61 - 4.74 (1H, m), 5.29 - 5.37 (1H, m), 7.09 - 7.56 (10H, m), 8.63 (1H, s, br); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 36.34, 36.41, 38.35, 38.39, 54.92, 54.95, 55.04, 55.04 66.63, 66.67, 125.97, 126.48, 126.51, 127.32, 127.35, 128.32, 128.68, 128.90, 128.90, 128.96, 129.48, 129.54, 134.97, 134.99, 138.84, 138.86, 150.87, 150.87, 155.60, 155.60; IR (NaCl): 1753, 1701, 1539, 1230.

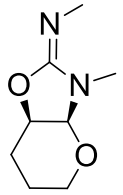
3-81: 1-bromo-1,3-dimethylurea



To a 25 mL round bottom flask under nitrogen was added 1,3-dimethyl urea (1 g, 11.36 mmol), $CDCl_3$ (10 mL), and TBICA (1.67 g, 4.54 mmol). The solution was mixed at room temperature wrapped in aluminium foil. The hood lights were turned off and the solution was mixed for 15h and the solution was filtered via a glass frit. The solution was diluted to

a volume of 18.9 mL with $CDCl_3$ to give a concentration of 100 mg / mL of 1-bromo-1,3-dimethylurea. The solution was storred in the freezer wrapped in aluminum foil (concentrating the solution under vacuum caused irreproducible results with debromination sometimes occurred). ^{1}H NMR (500 MHz) ($CDCl_3$) δ 2.78 (3H, d, J = 7.50 Hz), 3.35 (3H, s), 5.35 (1H, s, br); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 28.51, 44.84, 160.40, 162.30; LRMS $C_3H_7BrN_2O$ (M+H) 167.

3-83: 3-methylhexahydro-2H-pyrano[2,3-d]oxazol-2-ylidene)methanamine

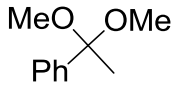


To a 10 mL round bottom flask under nitrogen was added 1-bromo-1,3-dimethylurea (1.0 mL, 0.60 mmol, 100 mg / mL soln in $CHCl_3$), $CHCl_3$ (2 mL) and 3,4-Dihydropyran (66.60 uL, 0.72 mmol). The solution was heated to reflux for 2h and then was cooled to room temperature. To the residue was added $NaHCO_3$ sat. aq. and was extracted with DCM, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by silica gel chromatography on TEA neutralized silica gel. Flash chromatography 100% DCM via a short silica plug. Oil, 78 % Yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.58 (1H, m), 1.70 (1H, m), 1.79 (1H, m), 2.12 (1H, m), 2.79 (3H, s), 2.89 (3H, s), 3.46 (1H, m), 3.66 (1H, m), 4.31 (1H, m), 4.83 (1H, d, J = 4.5 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 10.30 (CH_2), 22.99 , 29.29, 33.08, 60.30, 72.92, 85.27, 154.92; HRMS calculated for $C_8H_{15}N_2O_2$ (M + H) 171.1134; found 171.1127.

Synthesis of enol ethers

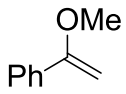
Some precursor reagents had to be synthesized to synthesize some of the enol ethers.

1,1-dimethoxyethyl)benzene



To a 25 mL round bottom flask was added benzaldehyde (3 mL, 27.21 mmol), trimethoxymethane (3.4 mL, 32.66 mmol), and PTSA (0.22 g, 1.36 mmol). The solution was mixed overnight and poured into ether and was extracted with $NaHCO_3$ sat. aq., dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The product matched the commercially available starting material.

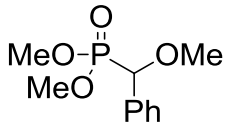
3-84: (1-methoxyvinyl)benzene



To a round bottom flask under argon was added (1,1-dimethoxyethyl)benzene (1 g, 6.58 mmol), DCM (50 mL), and Hünig's base (1.49 mL, 8.55 mmol). The solution was cooled to -20°C with a NaCl / ice bath and TMSOTf (1.25 mL, 7.23 mmol) was added over 2 minutes with a syringe. The solution turned bright red and was left in the ice bath to slowly warm to room temperature for 4h. The solution was concentrated *in vacuo* and triturated with ether (50 mL), and filtered via a plug of $MgSO_4$. The mother liquor was concentrated *in vacuo* and was synthesized in high yield. Unfortunately, polymerization occurred during vacuum distillation but some product was isolated (bp = 50°C) to give a colorless oil. The compound matched the reported literature data.[55] 10% Yield; Oil; ^1H

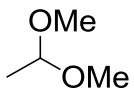
NMR (500 MHz) ($CDCl_3$) δ 3.72 (3H, s), 4.20 (1H, d, J = 2.2 Hz), 4.68 (1H, d, J = 2.6 Hz), 7.31 (5H, m); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 55.2, 81.7, 82.1, 125.3, 125.4, 128.1, 128.4.

dimethyl (methoxy(phenyl)methyl)phosphonate



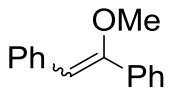
To a 25 mL round bottom flask under nitrogen was added $P(OMe)_3$ (3.25 mL, 27.57 mmol), (dimethoxymethyl)benzene (4.0 g, 27.57 mmol), and TMSCl (5.58 mL, 46.32 mmol). The reaction was mixed for 48 h at room temperature. The reaction solution was slowly poured into a solution of $NaHCO_3$ sat. aq. and was extracted with DCM, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by vacuum distillation. The starting materials distilled over first at 30°C and then the product at 118°C 1 mmHg (oil bath was 142°C; compound decomposed at >150°C). Compound matched the reported literature data.[56] Colorless Oil; 40% Yield; ^1H NMR (500 MHz) ($CDCl_3$) δ 3.37 (3H, s), 3.63 (3H, d, J = 10.5 Hz), 3.67 (3H, d, J = 10.5 Hz, 4.51 (1H, d, J = 15.7 Hz), 7.32-7.43 (5H, m); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 58.48 (d, J = 1.9 Hz), 58.59 (d, J = 2.85), 80.82 (d, J = 168.75), 127.83, 127.87 (d, J = 5.0 Hz), 128.41, 128.43 (d, J = 2.5 Hz), 128.47, 128.49 (d, J = 2.5 Hz), 134.03, 134.05 (d, J = 2.5 Hz).

1,1-dimethoxyethane



To a 25 mL sealed tube was added acetaldehyde (6.35 mL, 0.11 mol), trimethoxymethane (12.4 mL, 0.11 mol). The solution was cooled to -20°C with a dry ice / NaCl bath and one crystal of PTSA was added and the tube was not sealed (**Caution: the reaction is exothermic and acetaldehyde has a bp = 20°C and can boil away and build up pressure in sealed tube**). After reaction for 0.33 h the reaction stopped exotherming so much and the rest of the PTSA (1 g, 5.68 mmol) was added. The cap was sealed and the tube was left in the ice bath overnight. The product was purified by atmospheric distillation (bp = 61°C); colorless liquid; 62% Yield; the data was consistent with the commercially available starting material.

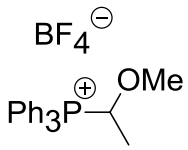
3-85: (1-methoxyethene-1,2-diyl)dibenzene



To a 10 mL round bottom flask was added dimethyl (methoxy(phenyl)methyl)phosphonate (0.2 g, 0.88 mmol) and THF (5 mL). The solution was cooled to -78°C and n-BuLi (0.35 mL, 2.5 M solution in hexanes, 0.88 mmol) was added dropwise. The solution turned from colorless to a bright yellow colored solution. Benzaldehyde (88.0 uL, 0.88 mmol) was added to THF (2 mL) and the solution was cooled to -78°C. The aldehyde solution was added to the enolate over 2 minutes. The reaction was left in the dry ice bath and allowed to slowly warm to room temperature and react overnight. The reaction solution had formed a semisolid solution due to inorganic salts and was dissolved in water and extracted with ether, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by silica gel chromatography; 9 : 1 hexane : DCM; $R_f = 0.28$; Oil; 67% Yield. The compound matched the reported lit data.[57] 3: 2 ratio; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.65 (3H, s),

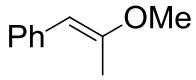
3.82 (3H, s), 5.84 (1H, s), 6.12 (1H, s), 6.97 (2H, d, J = 8.0 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.11 (2H, t, J = 8.0 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.29 (3H, m), 7.36 (5H, m), 7.41 (2H, t, J = 7.5 Hz), 7.57 (2H, d, J =8.0 Hz), 7.73 (2H, d, J = 8.0 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 55.51, 57.91, 101.50, 112.76, 125.21, 126.55, 126.6, 127.94, 128.18, 128.32, 128.37, 128.46, 128.54, 128.59, 128.85, 129.29, 135.91, 136.23, 136.38, 136.88, 156.25, 157.25

(1-methoxyethyl)triphenylphosphonium tetrafluoroboride



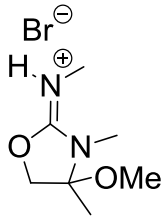
The compound was made to the literature procedure.[58] To a 250 mL round bottom flask was added 1,1-dimethoxyethane (3.26 g, 36.22 mmol), toluene (100 mL) and Ph_3P (9.5 g, 36.22 mmol). The solution was cooled to 0°C and BF_3•OEt_2 (6.8 mL, 54.33 mmol) was added slowly over 5 minutes. After 0.5 h at 0°C the reaction formed an oil layer so the flask was removed from the ice bath and formed solids after 0.25 h. The reaction solution was mixed for 24 h. The crystals were isolated by vacuum filtration. The crystals were washed with ether and dried in *vacuo*. The compound matched the reported literature data. White solid; mp = ; 80% Yield; ^{1}H NMR (300 MHz, $CHCl_3$ = 7.26) δ 1.65 (3H, dd, J_1 = 6.4 Hz, J_2 = 17.8 Hz), 3.55 (3H, s,), 5.69 (1H, dq, J_1 = 4.4, J_2 = 6.4 Hz), 7.64−7.84 (15H, m); ^{13}C NMR (75 MHz) δ 14.92, 59.47 (d, J = 10.5 Hz), 72.88 (d, J = 66.0 Hz), 116.60 (d, J = 82.5 Hz), 130.37 (d, J = 12.8 Hz), 134.23 (d, J = 9.8 Hz), 135.17 (d, J = 2.3 Hz).

3-86: (E)-(2-methoxyprop-1-en-1-yl)benzene



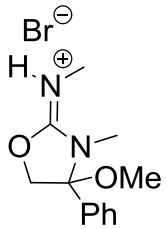
To a 25 mL round bottom flask was added (1-methoxyethyl)triphenylphosphonium tetrafluoroborate (0.8 g, 1.96 mmol) and THF (8 mL). The solution was cooled to -40°C with a dry ice / acetonitrile bath and NaHMDS (2.54 mL, 2.54 mmol, 1.0 M in THF) was added dropwise. The solution turned a blood red color. To a 10 mL round bottom flask was added benzaldehyde (0.20 mL, 1.96 mmol) and THF (2 mL). This solution was cooled to -40°C and was added to the red solution over 2 minutes with a canulla. The solution turned yellow and was mixed at -40 for ten minutes. It was then taken out of the dry ice/ acetonitrile bath to warm to room temperature and react for 2.5 h. Water was added to the reaction solution and it was extracted with ether, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography; 97: 3 DCM: TEA; $R_f = 0.95$; the product still contained some impurities but was pure enough for the next reaction. Product was consistent with the reported literature data.[59] The compound could not be isolated in high purity due to hydrolysis on silica gel. Approximately 33% yield, 96 mgs but contained a little bit of impurities and was used in the next reaction immediately. Mixture of E and Z isomers; Oil; ^{1}HNMR (500 MHz) ($CDCl_3$) δ 3 2.02 (3H, s), 2.07 (3H, s), 3.68 (3H, s), 3.75 (3H, s), 5.33 (1H, s), 5.61 (1H, s), 7.10-7.60 (10H, m); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 18.1, 18.9, 25.5, 34.9, 54.7, 55.3, 99.6, 100.1, 106.6, 125.2, 125.3, 127.9, 128.2, 128.8, 136.8, 153.5.

3-89: N-(4-methoxy-3,4-dimethyloxazolidin-2-ylidene)methanaminium bromide



To a 10 mL round bottom flask under nitrogen was added 1-bromo-1,3-dimethylurea (1.0 mL, 0.60 mmol, 100 mg / mL soln in $CDCl_3$), $CHCl_3$ (2 mL) and 2-methoxyprop-1-ene (69 uL, 0.72 mmol). The solution was mixed for 24 h and the solution was concentrated *in vacuo* at room temperature (heating caused decomposition). The residue was triturated with EtOAc / hexane to give crystals and the solvent was removed with a pipette. The crystals were dried *in vacuo* at room temperature. Solid; mp = 118-120°C; 75% Yield; ^{1}HNMR (500 MHz) ($CDCl_3$) δ 1.62 (3H, s), 2.99 (3H, d, J = 4.5 Hz), 3.13 (3H, s), 4.57 (1H, d, J = 6.60 Hz), 4.78 (1H, d, J = 6.60 Hz), 10.42 (1H, s, br); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 22.72, 27.83, 28.63, 50.54, 75.33, 94.28, 160.14; IR NaCl: 1705, 1543, 1248, 1006; HRMS calculated for $C_7H_{15}N_2O_2$ (M+H) 159.1134; found 159.1127

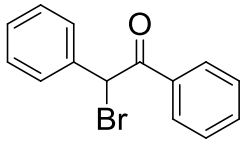
3-90: N-(4-methoxy-3-methyl-4-phenyloxazolidin-2-ylidene)methanaminium bromide



To a 10 mL round bottom flask under nitrogen was added 1-bromo-1,3-dimethylurea (1.0 mL, 0.60 mmol, 100 mg / mL soln in $CDCl_3$), $CHCl_3$ (2 mL) and (1-methoxyvinyl)benzene (96.50 mg, 0.72 mmol). The solution was mixed for 24 h and the

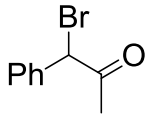
solution was concentrated *in vacuo* at room temperature. The residue was triturated with EtOAc / hexane to give crystals and the solvent was removed with a pipette. The crystals were dried *in vacuo* at room temperature. Solid; mp = 258-260°C; 80% Yield; ^{1}H NMR (500 MHz) ($CDCl_3$) δ 3.14 (3H, s), 3.14 (3H, s), 3.40 (3H, s), 4.67 (1H, d, J = 11.0 Hz), 4.98 (1H, d, J = 11.0 Hz), 7.44 (5H, m), 10.90 (1H, s, br); ^{13}CNMR (125 MHz) ($CDCl_3$) δ 28.63, 28.74, 50.46, 77.44, 96.88, 126.04, 129.10, 130.08, 134.76, 160.36; IR (NaCl): 1699, 1539, 1130, 981; HRMS calculated for $C_{12}H_{17}N_2O_2$ (M+H) 221.1290; found 221.1288

3-93: 2-bromo-1,2-diphenylethanone



To a 10 mL round bottom flask was added (*E*) and (*Z*)-(1-methoxyethene-1,2-diyl)dibenzene (50 mg, 0.18 mmol), $CHCl_3$(3 mL), and 1-bromo-1,3-dimethylurea (0.37 mL, 0.22 mmol, 100 mg / mL soln in $CDCl_3$). The solution was heated to reflux for 1h and then was cooled to room temperature and concentrated *in vacuo*. The product matched the literature data.[60] The product was purified by silica gel chromatography; 2: 1 hexane: DCM; R_f = 0.35; Solid; mp = 44-46; 12% Yield; ^{1}H NMR ($CDCl_3$) δ 6.40 (1H, s), 7.35-7.61 (8H, m), 7.91-8.01 (2H, m); ^{13}C NMR ($CDCl_3$) δ 51.1, 128.3, 128.5, 128.6, 128.7, 133.3, 135.4, 190.6.

3-94: 1-bromo-1-phenylpropan-2-one



To a 10 mL round bottom flask was added (*Z*) and (*E*)-(2-methoxyprop-1-en-1-yl)benzene (50 mg, 0.24 mmol), $CHCl_3$(3 mL), and 1-bromo-1,3-dimethylurea (0.5 mL, 0.27 mmol, 100 mg / mL soln in $CDCl_3$). The solution was heated to reflux for 1h and then was cooled to room temperature and concentrated *in vacuo*. The product has been previously synthesized.[60] The product was purified by silica gel chromatography; 15% Yield; Oil; ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.90 (3H, d, J = 7.0 Hz); 5.30 (1H, q, J = 7 .0 Hz), 7.40-7.60 (3H, m), 8.00 (2H, d, J = 9.0 Hz); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 20.2, 62.8, 129.1, 129.5, 133.1, 136.2, 198.5.

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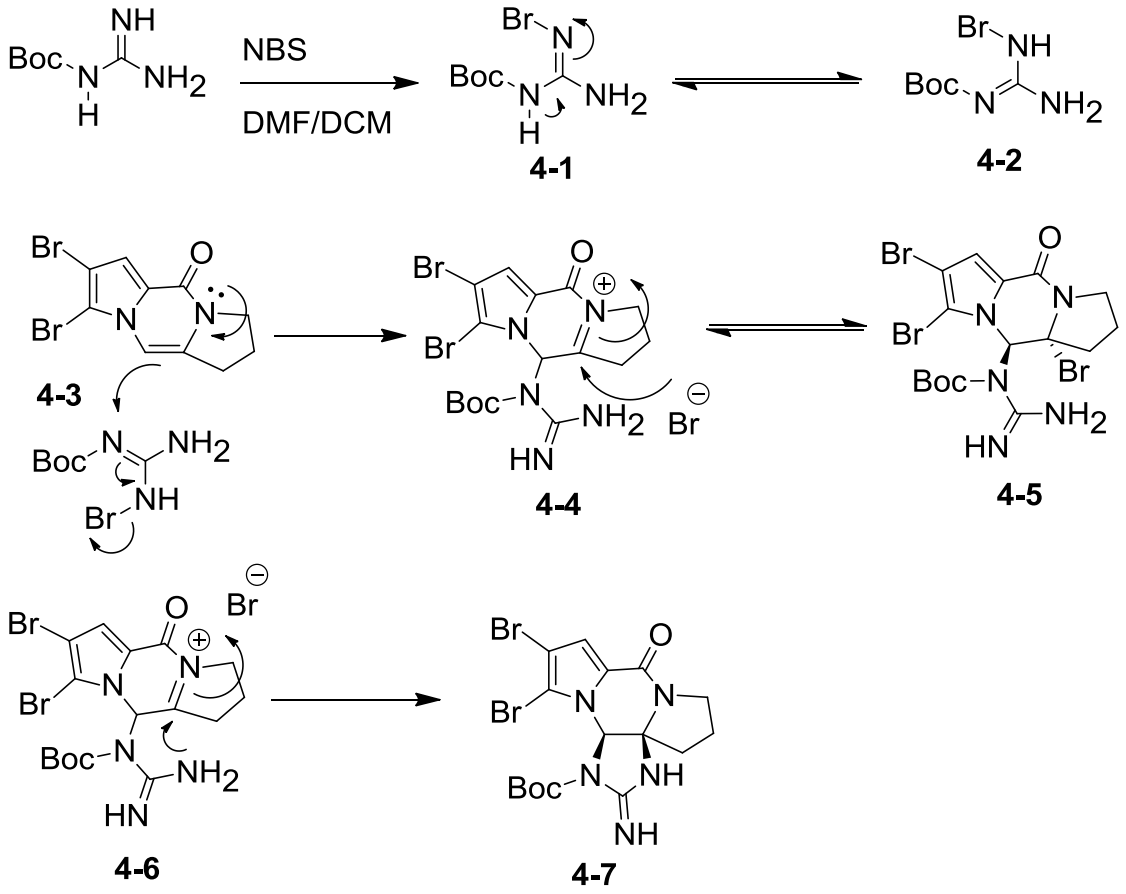
CHAPTER 4

FUTURE DIRECTIONS FOR SYNTHESIS OF NEW HETEROCYCLES WITH BROMINE REAGENTS

The Tepe lab is interested in the total synthesis of natural products and their derivatives as potential new 20S proteasome inhibitors. We are particularly interested in the Phakellins, Phakellstatins, Nagelamide M, and Palau'amine derivatives[1-3] The total synthesis of Dibromophakellin has been accomplished by Nicole Hewlett.[1] The 5 membered guanidine heterocycle in Dibromophakellin was a key step in the synthesis. This 5-membered guanidine ring was synthesized by the reaction of NBS, *N*-boc guanidine, and enamine **4-3**. The reaction presumably occurred first by synthesis of *N*-bromo, *N*-boc guanidine by reaction of *N*-boc guanidine with NBS. NBS should not brominate the carbamate nitrogen NH because this is the most electron deficient nitrogen in *N*-bocguanidine and is the hardest to brominate. Instead one of the other two nitrogens of *N*-bocguanidine should be brominated to yield compound **4-1** or **4-2**. The reaction of **4-1** or **4-2** with an enamine occurred through an S_N2' mechanism based on conversation with our lab (**Scheme 4-1)**. The reaction of compound **4-2** with enamine **4-3** would yield the intermediate **4-4** which is equilibrium with compound **4-5**. The intermediate **4-4** will react further to close the guanidine ring through an iminium cation (**Scheme 4-1**).



Scheme 4-1: Possible mechanism for the synthesis of Dibromophakellin

It may be possible to synthesize the Phakellstatin natural products from the reaction of enamine **4-3** with *N*-bromoisourea **4-8** through a S_N2' reaction and ring closure to a 5 membered isourea ring. Hydrolysis of the isourea or deprotection of the benzyl group with hydogenation would yield the 5-membered urea ring. Similarly, enamine **4-9** and *N*-bromoguanidine **4-2** could theoretically be used to synthesize Palau'amine type derivatives. Lastly, enamine **4-10** and *N*-bromoguanidine **4-2** could be used to synthesize Nagelamide M (**Figure 4-1**).

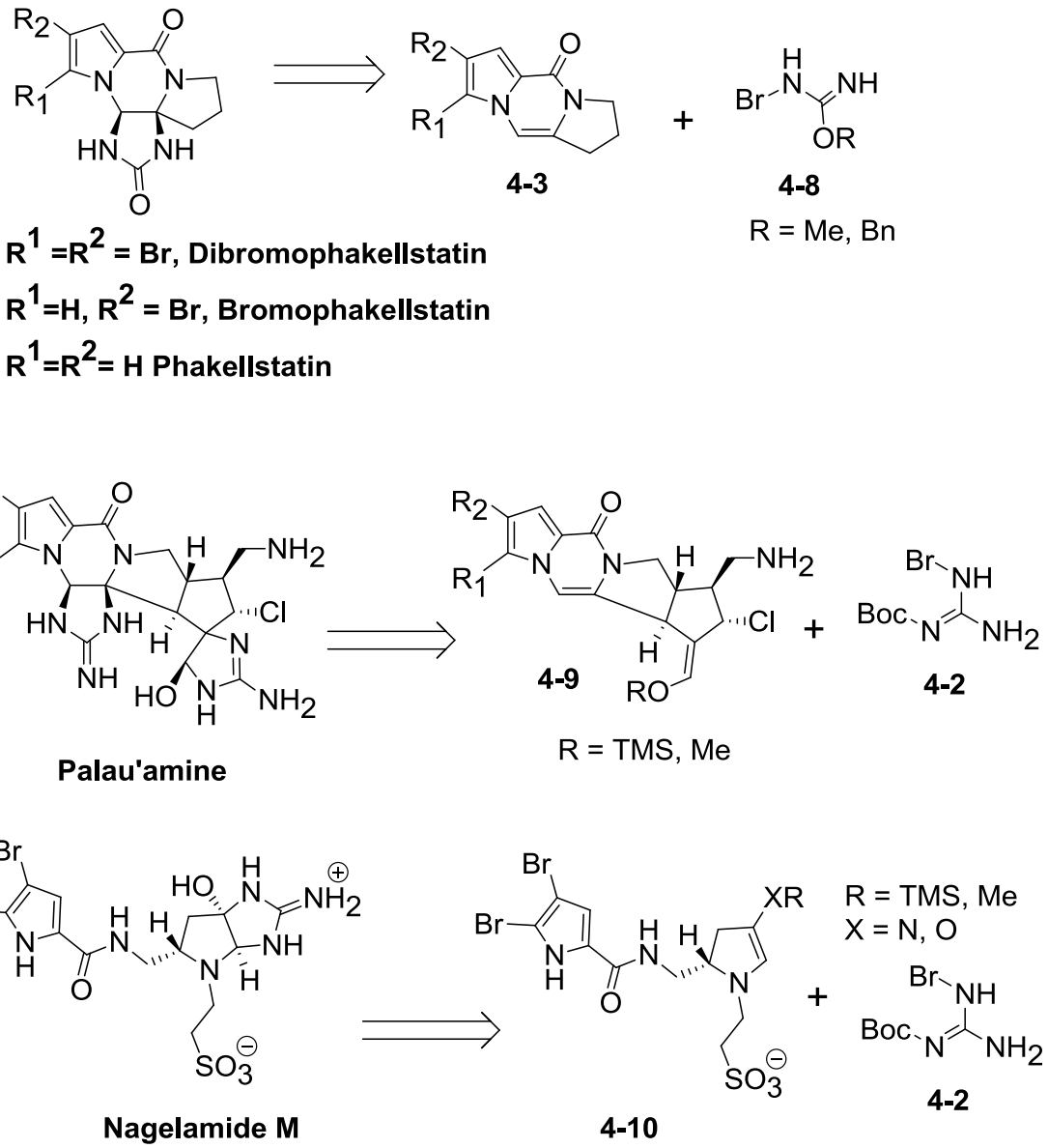


Figure 4-1: Synthetic strategy to access important natural products through the S_N2' reaction

Based on the *N*-bromo imide **3-34** we can design new brominating reagents to access these biologically significant natural products and proteasome inhibitors. By analyzing **3-34** previous studies have shown that the two acyl groups can be a benzoyl group, a methyl ester group or a boc group. If we replace one of the carbonyl oxygen

atoms with a NH we will have an *N*-boc, *N*-bromomethyl carbamimidate **4-11**. *N*-boc, *N*-bromomethyl carbamimidate is not a C-2 symmetrical bromine reagent, but if we place another boc group on that reagent than the new bromine reagent *N*, *N*-di-boc, *N*-bromomethyl carbamimidate **4-14** would be C-2 symmetrical. *N*-boc, *N*-bromomethyl carbamimidate can be transformed into *N*-boc, *N*-bromoguanidine **4-12** by replacing the OMe group with an NH_2 group. If, another boc group is placed on *N*-boc, *N*-bromoguanidine then we will synthesize *N*,*N*-diboc, *N*-bromoguanidine **4-15**, which would be another C-2 symmetrical bromine reagent. **(Figure 4-2)**.

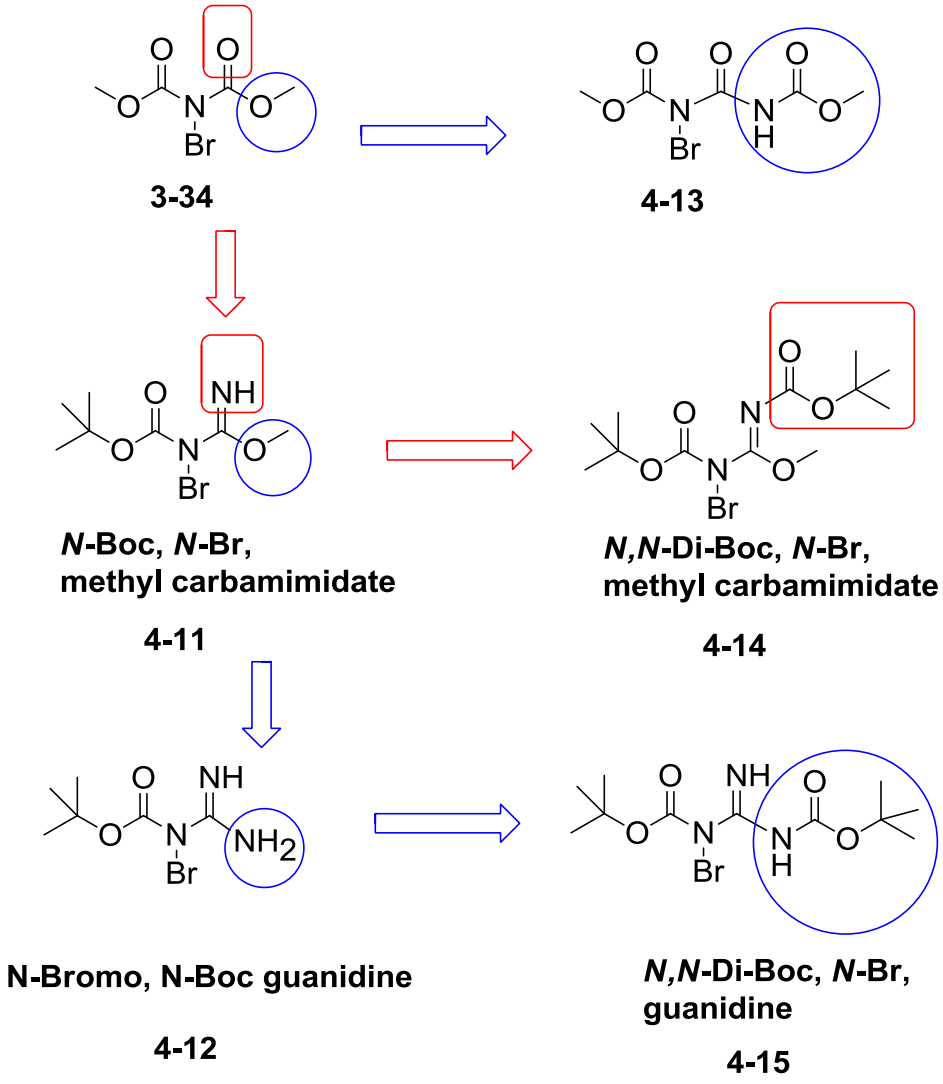
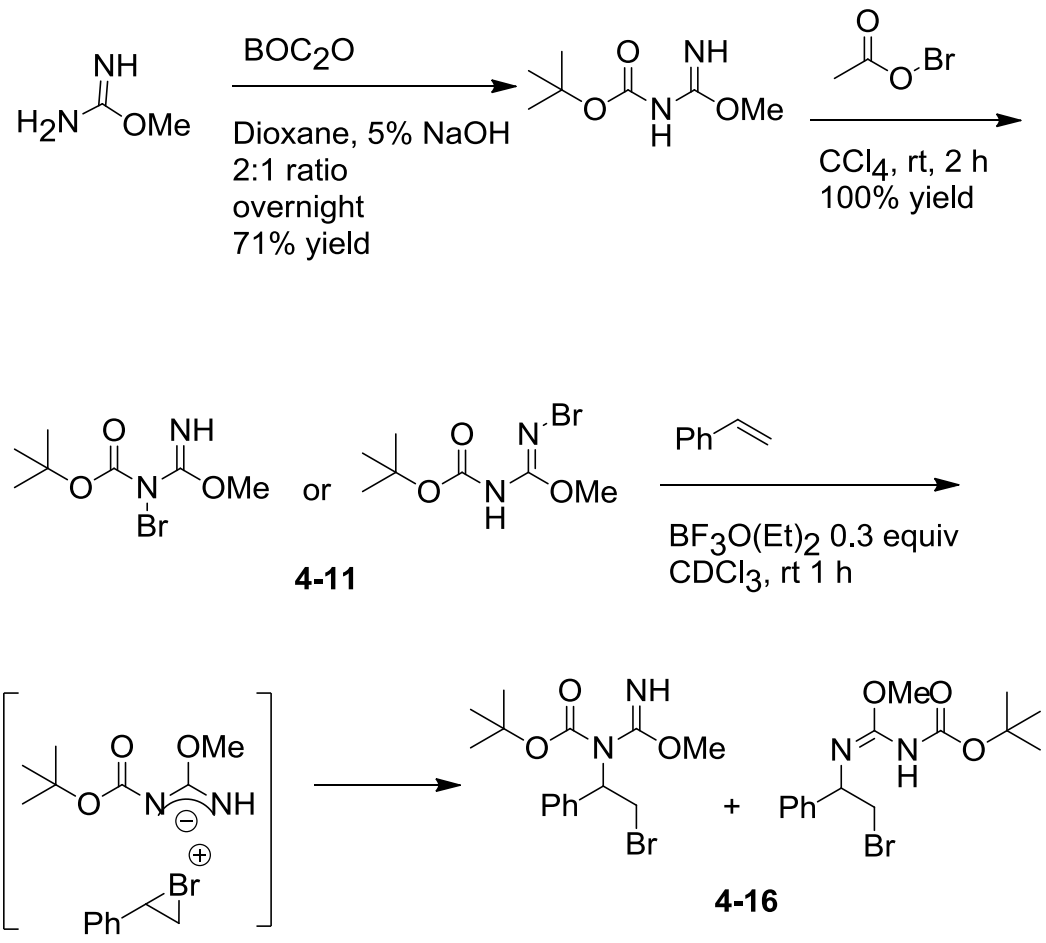


Figure 4-2: Proposed new bromine reagents for the synthesis of new heterocycles

These new bromine reagents may create new synthetic methods to synthesize urea and guanidine heterocycles. Methyl carbamimidate hydrogen chloride was protected with a boc group and was successfully brominated with bromoacetate to yield compound **4-11**. The compound **4-11** did not precipitate from a solution of hexane/CCl_4, but instead was isolated by carefully removing the solvent at room temperature *in vacuo* while the flask was wrapped in aluminum foil. Compound **4-11** can exist as two different forms because

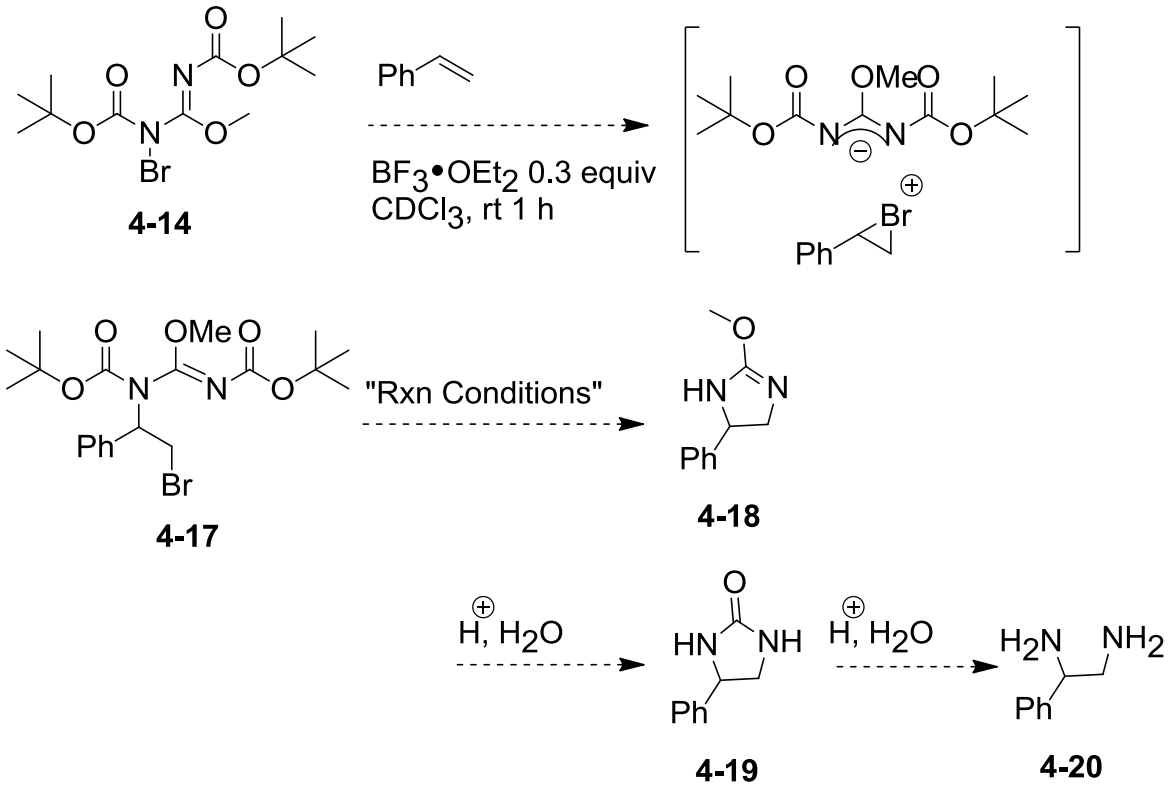
either nitrogen atom could be brominated. When **4-11** was reacted with styrene with BF_3•OEt_2 once the bromine forms the bromonium ion with styrene two different products can be formed. In fact a mixture of regioisomers was formed **4-16**. Cyclization of **4-16** to a 5-membered heterocycle was attempted by heating the crude product neat but did not form the desired product (**Scheme 4-2**).



Scheme 4-2: Synthesis of compound **4-16**

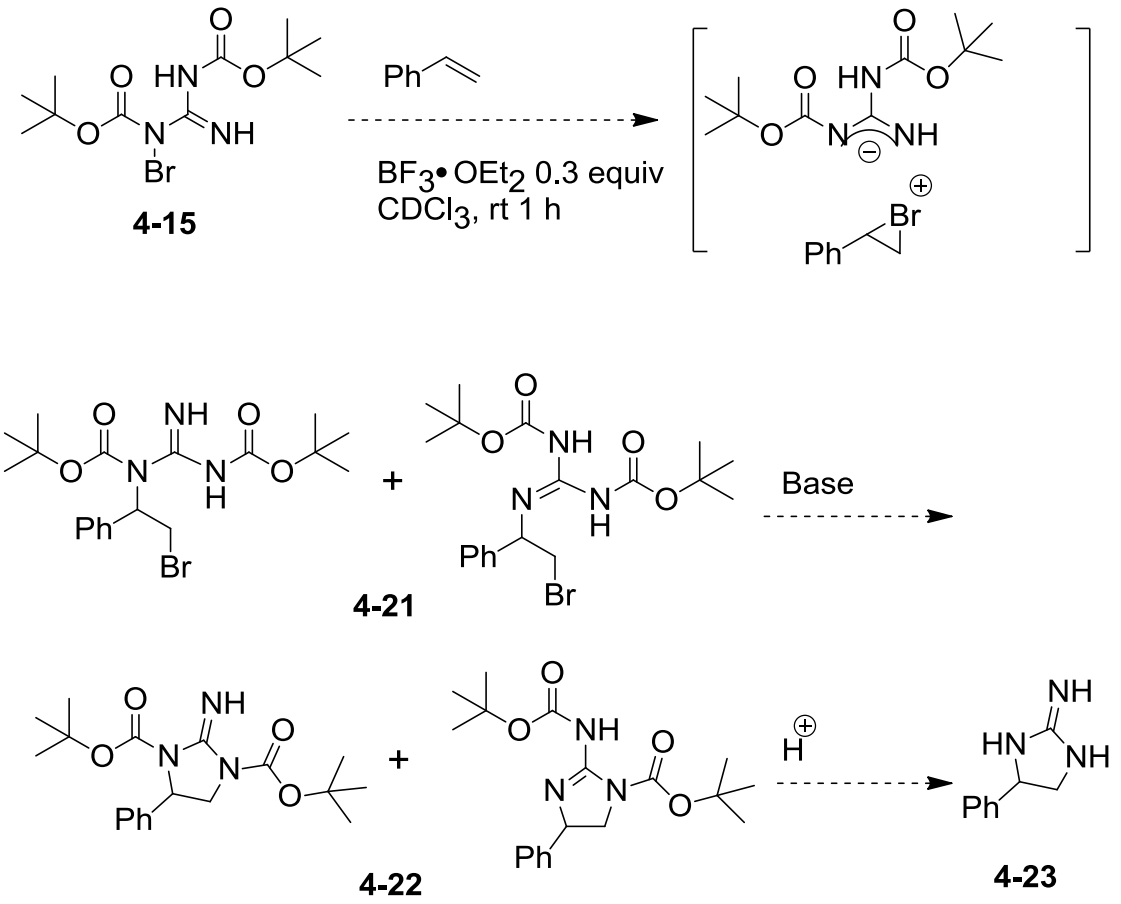
However, one way to get around a mixture of regioisomers would be to use a C-2 symmetrical bromine agent **4-14** or **4-15**. Upon reaction of compound **4-14** with styrene

and BF_3•OEt_2 would yield the intermediate **4-17** which has the potential to synthesize the isourea compound **4-18**. The isourea can undergo reaction with acid and water to yield the urea **4-19** and further hydrolysis to the diamine **4-20** (**Scheme 4-3**).



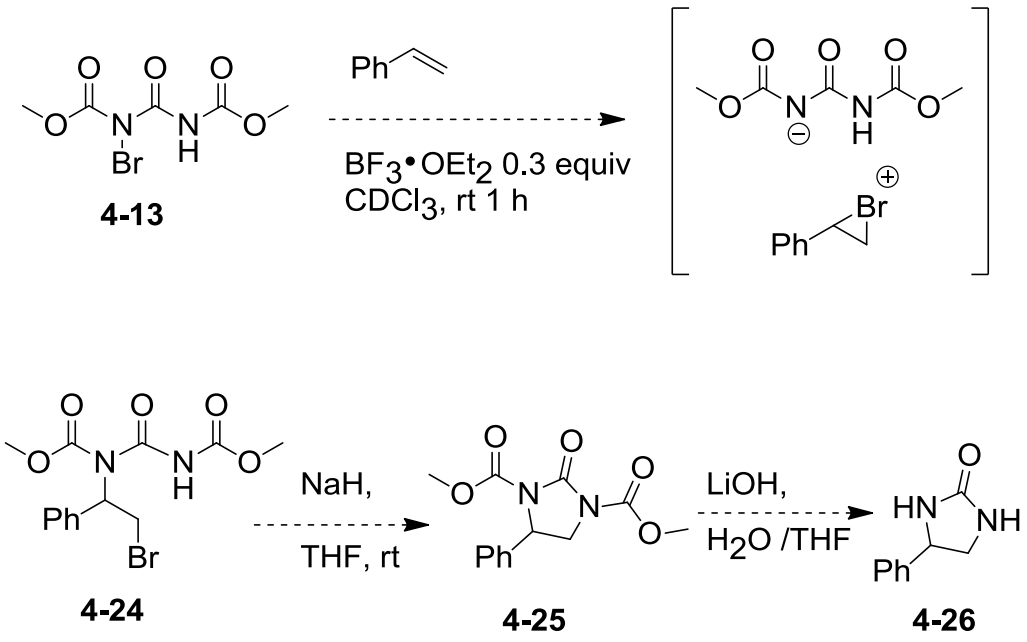
Scheme 4-3: Proposed synthesis of isourea and urea heterocycles.

N,*N*-di-boc, N-bromoguanidine **4-15** could be a new methodology to form guanidine heterocycles. Two possible boc guanidine heterocycles **4-22** could be synthesized from the intermediates **4-21**. The boc group could then be removed to synthesize the cyclic guanidine **4-23** (**Scheme 4-4**).



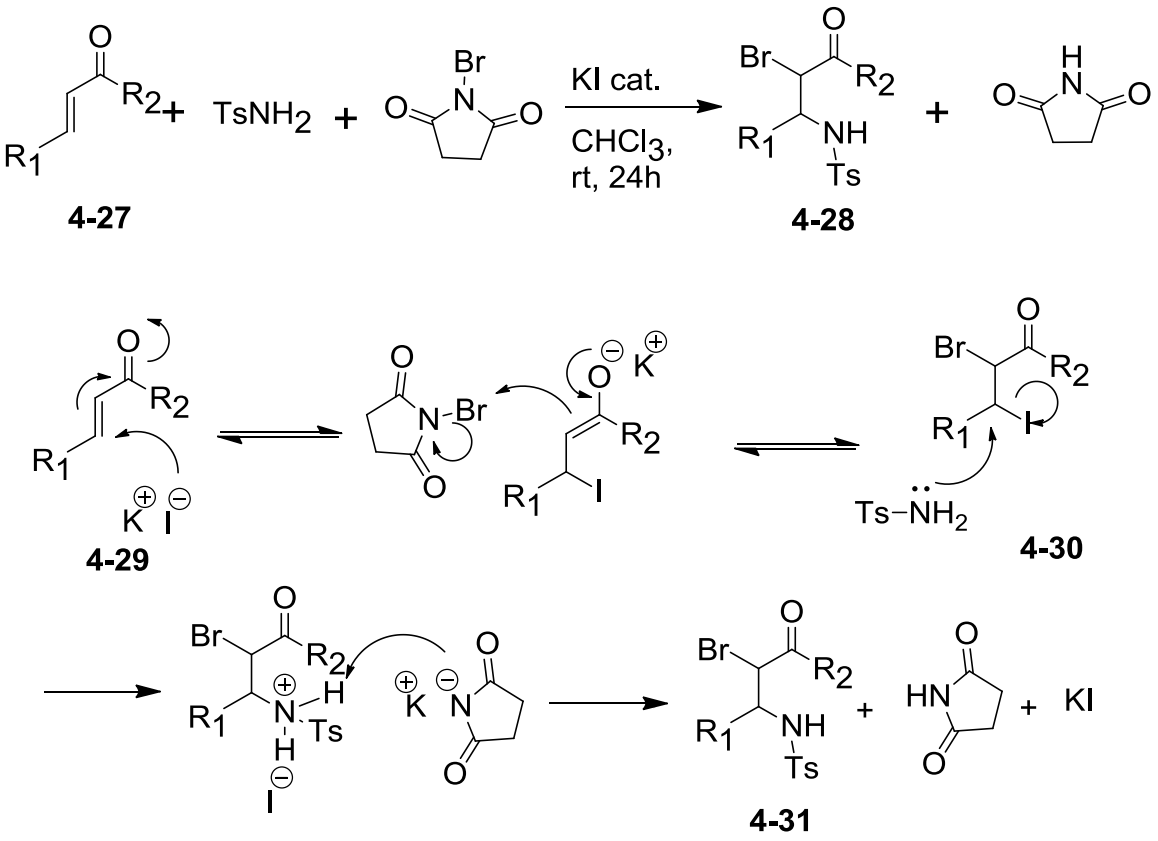
Scheme 4-4: Proposed synthesis of guanidine heterocyle **4-23**.

Perhaps a better way to make an urea heterocycle would be with bromine reagent **4-13**. After addition of **4-13** to styrene compound **4-24** would contain a very acid proton. Deprotonation with a strong base like NaH should close the ring through a 5-exo-tet ring closure to yield compound **4-25**. The CO_2Me groups could be easily hydrolyzed to yield the urea **4-26** which could be further hydrolyzed to a diamine if desired (**Scheme 4-5**).



Scheme 4-5: Proposed synthesis of urea heterocyle **4-26**.

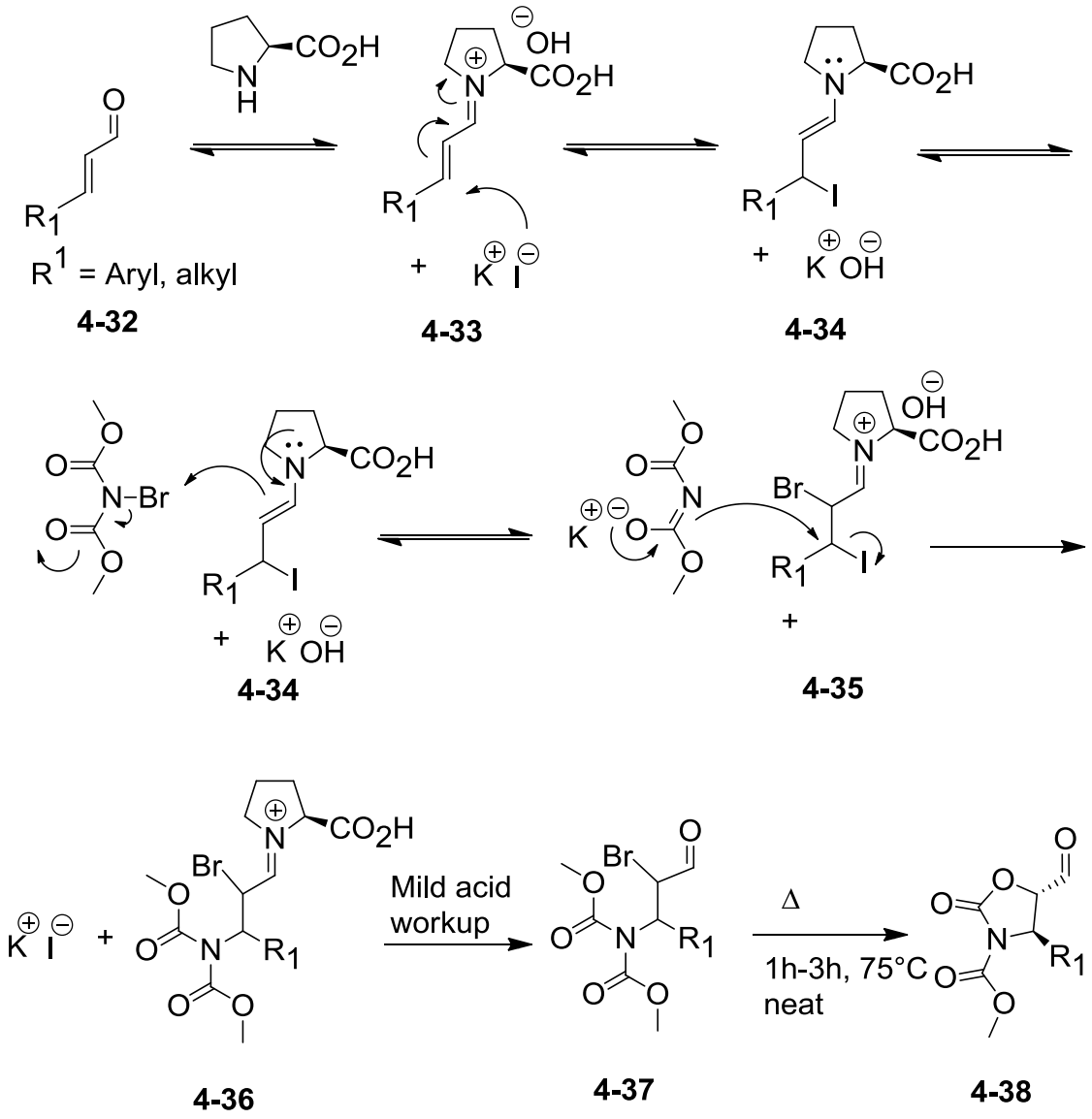
The combination of these bromine reagents with BF_3•OEt_2 and neutral olefins may allow for new synthetic methodologies to access urea and guanidine heterocycles. However, Br-N(CO_2Me)$_2$ **3-34** failed to add to an electron poor alpha beta unsaturated olefin. A paper by Wei and coworkers presented a new methodology to make alpha bromo, beta tosyl ketones.[4] We may be able to use compound **3-34** with their reaction conditions to synthesis an amino alcohol. The key to the methodology by Wei was the catalyst KI. KI reacted with an alpha beta unsaturated olefin **4-27** by 1,4-addition followed by abstraction of the bromine from NBS to yield **4-30**. This intermediate can then undergo substitution of the iodide atom with $TsNH_2$ to yield compound **4-31** and succinimide (**Scheme 4-6**).



Scheme 4-6: Addition of $TsNH_2$ to an alpha beta unsaturated olefin

Based on this mechanism it may be possible to add various bromine reagents to an alpha-beta unsaturated aldehyde by use of catalytic Iodine source and an organo catalyst. However, this can only be accomplished if I-Br is not being formed in the reaction of NBS and KI, which Wei did not mention the possibility of I-Br being formed. The organocatalyst is based on the work by MacMillan.[5] This work has been pursued by Travis Bethel and use of compound Br-$N(CO_2Me)_2$. Formation of the iminium **4-33** by condensation of the organocatalyst with the aldehyde **4-32** would undergo attack by the iodide anion to yield an enamine **4-34**. The enamine would undergo reaction with Br-$N(CO_2Me)_2$ to yield compound **4-35**. Compound **4-35** has several electrophilic sites but

hopefully nucleophilic attack would occur at the alpha or beta position and not at the iminium carbon to yield compound **4-36**. After removing the organocatalyst by workup and heating compound **4-37** the compound **4-38** should be synthesized. Heating compound **4-47** should result in formation of a carbocation and formation of the *trans*-diastereomer **4-38** (**Scheme 4-7**).



Scheme 4-7: Proposed synthesis of Oxazolidin-2-ones from alpha-beta unsaturated aldehydes

Hopefully this methodology will provide a new methodology to access an amino alcohol from hydrolysis of compound **4-38**. This would not yield the amino alcohol enantiomerically pure because the oxazoldin-2-one ring formation occurred through a carbocation as mentioned earlier. However, an organocatalyst methodology with KI may allow for an enantioselective synthesis of urea and guanidine rings from reaction of an *N*-bromourea or *N*-bromoguanidine with alpha beta unsaturated aldehyde or ketone. These methodologies will hopefully allow the Tepe lab to synthesize new 20S proteasome inhibitors and new guanidine and urea containing natural products.

APPENDIX

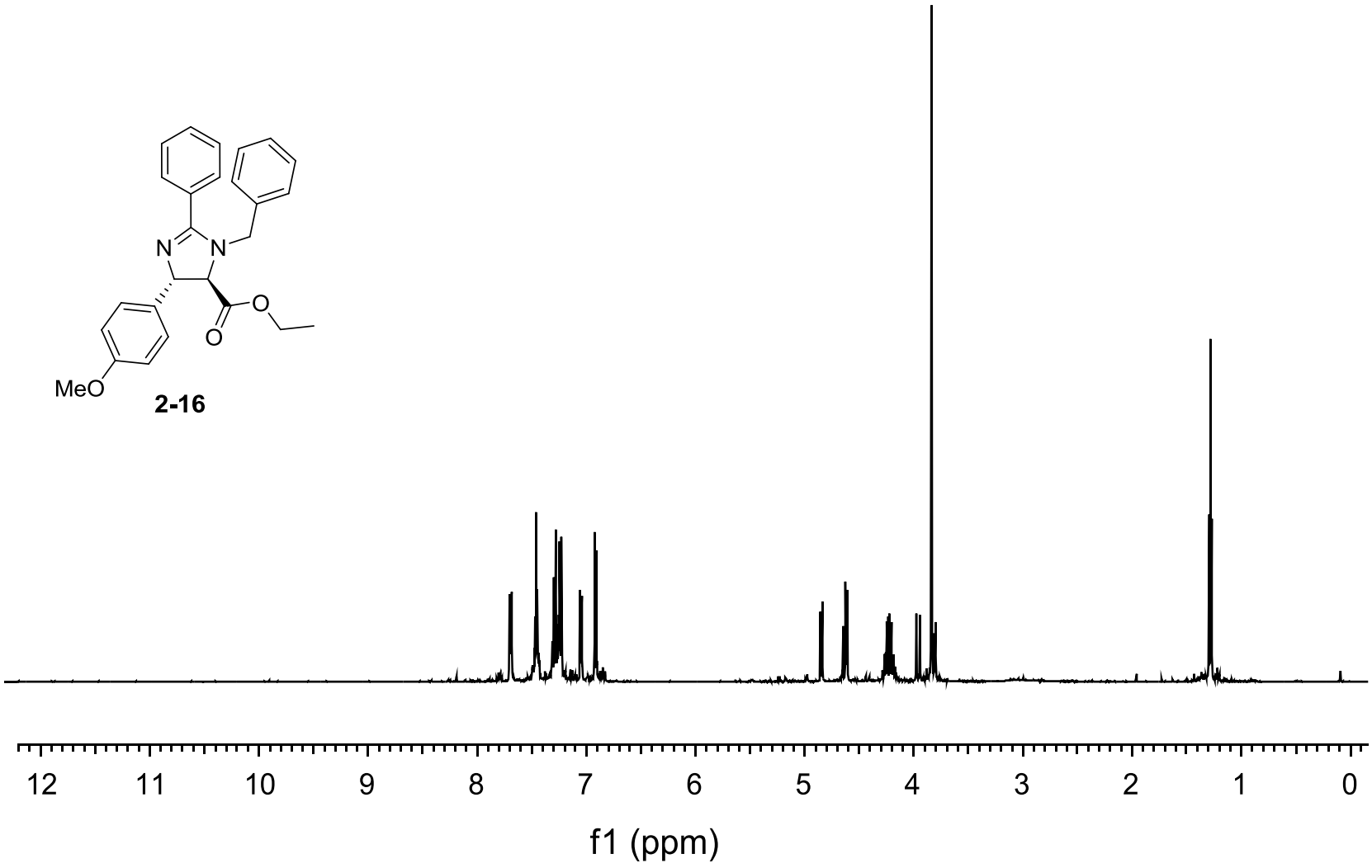


Figure 4-3: ^{1}H NMR spectrum for compound **2-16**

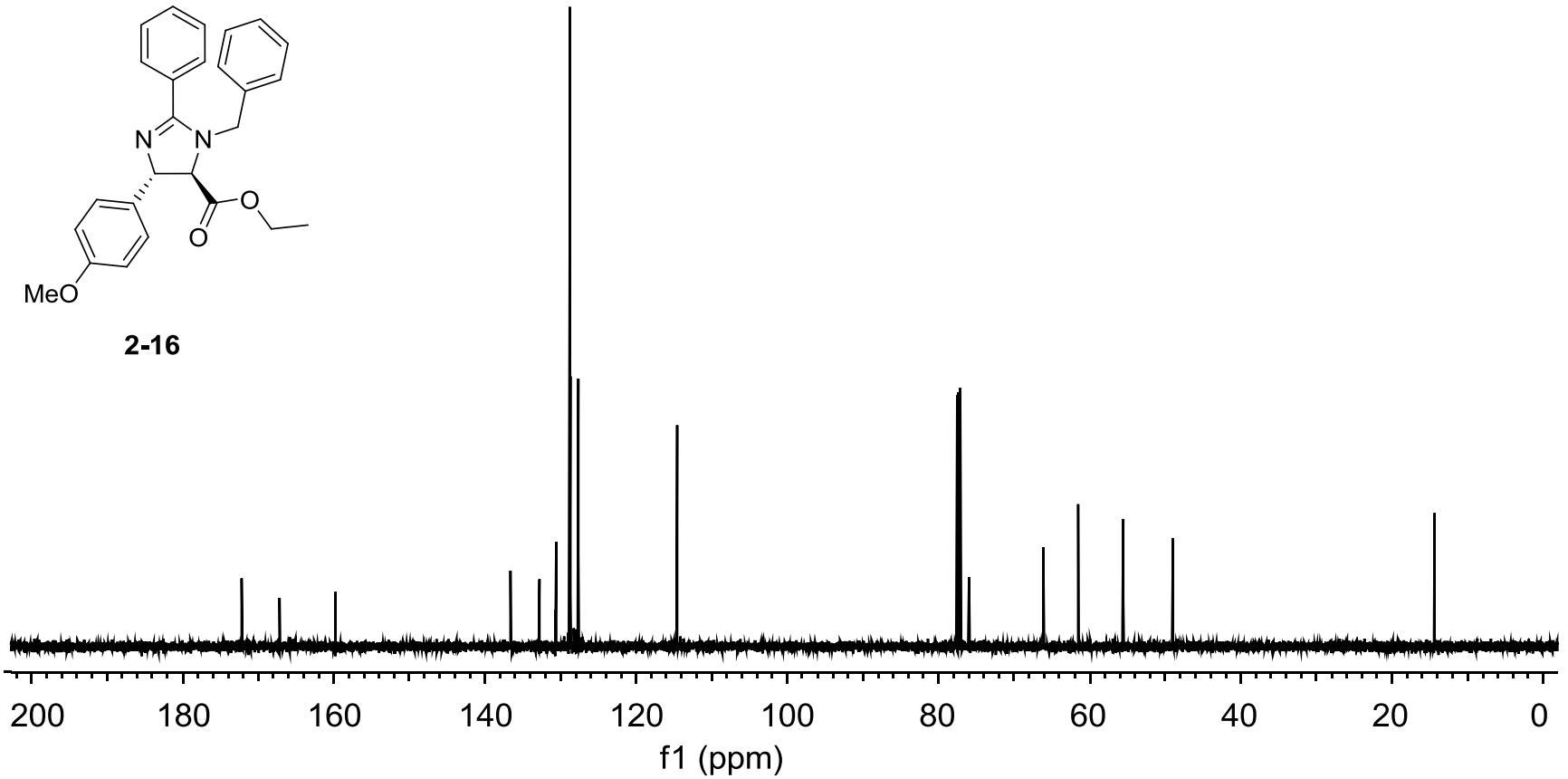


Figure 4-4: ^{13}C NMR spectrum for compound **2-16**

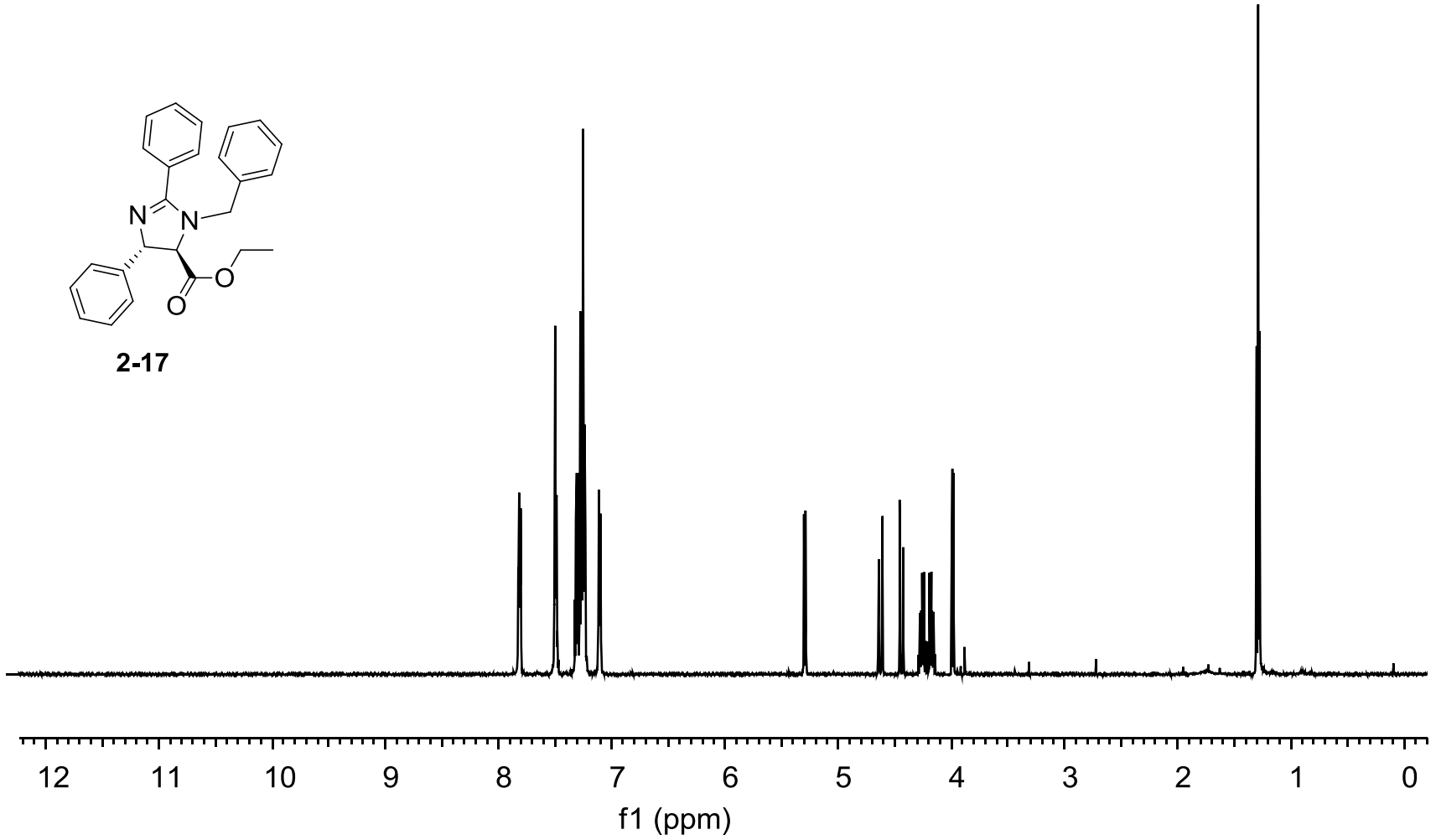


Figure 4-5: ^{1}H NMR spectrum for compound **2-17**

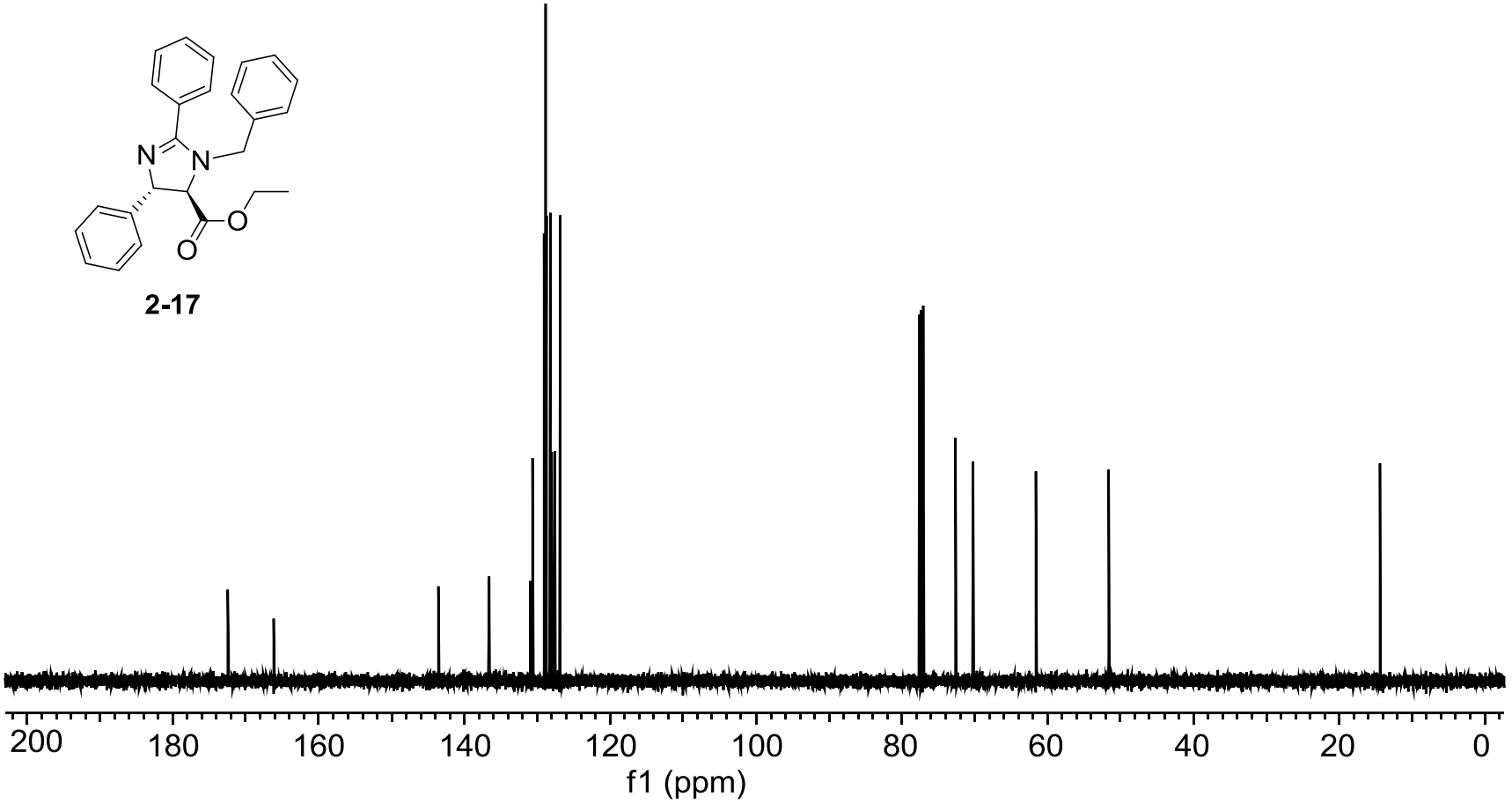


Figure 4-6: ^{13}C NMR spectrum for compound **2-17**

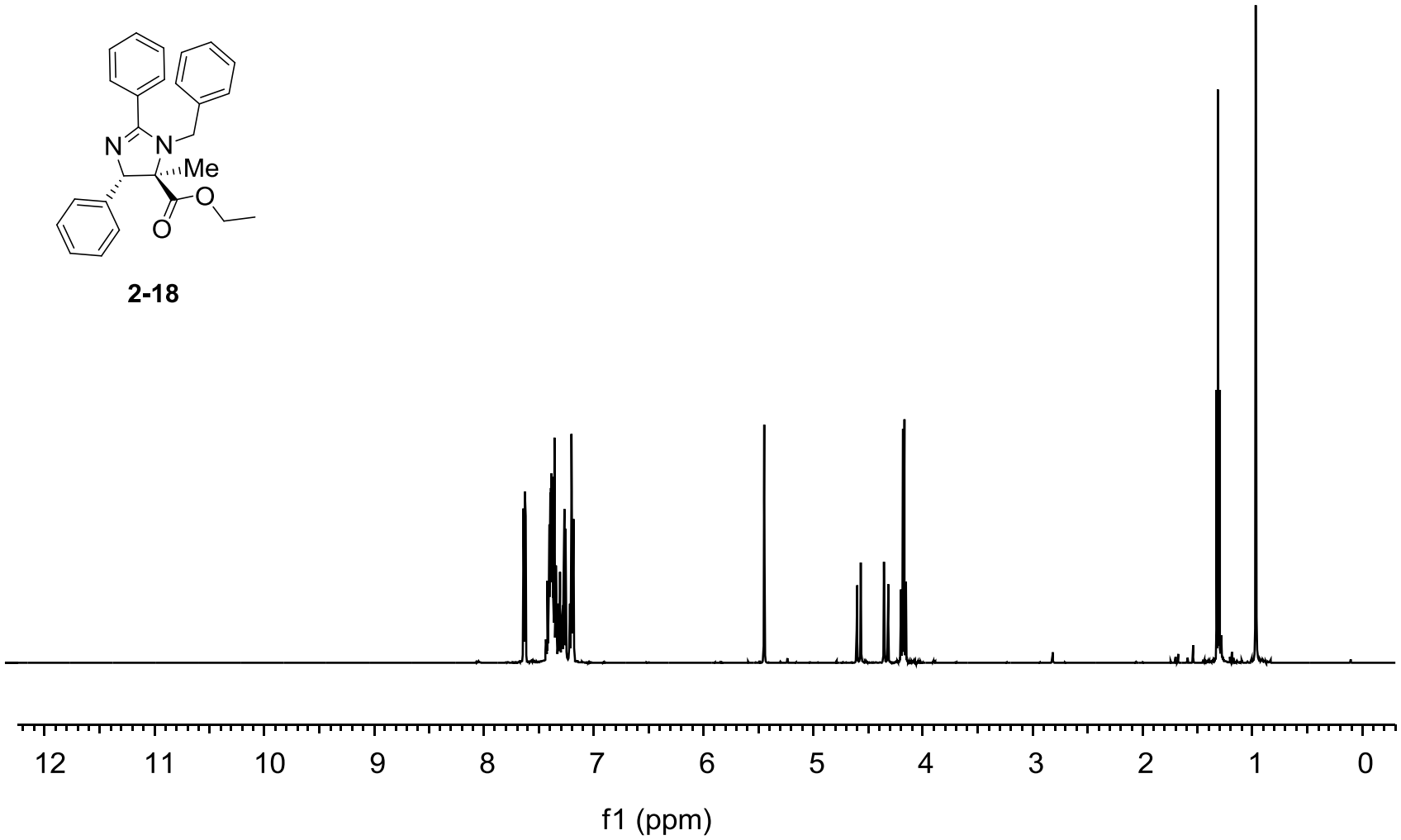


Figure 4-7: ^{1}H NMR spectrum for compound **2-18**

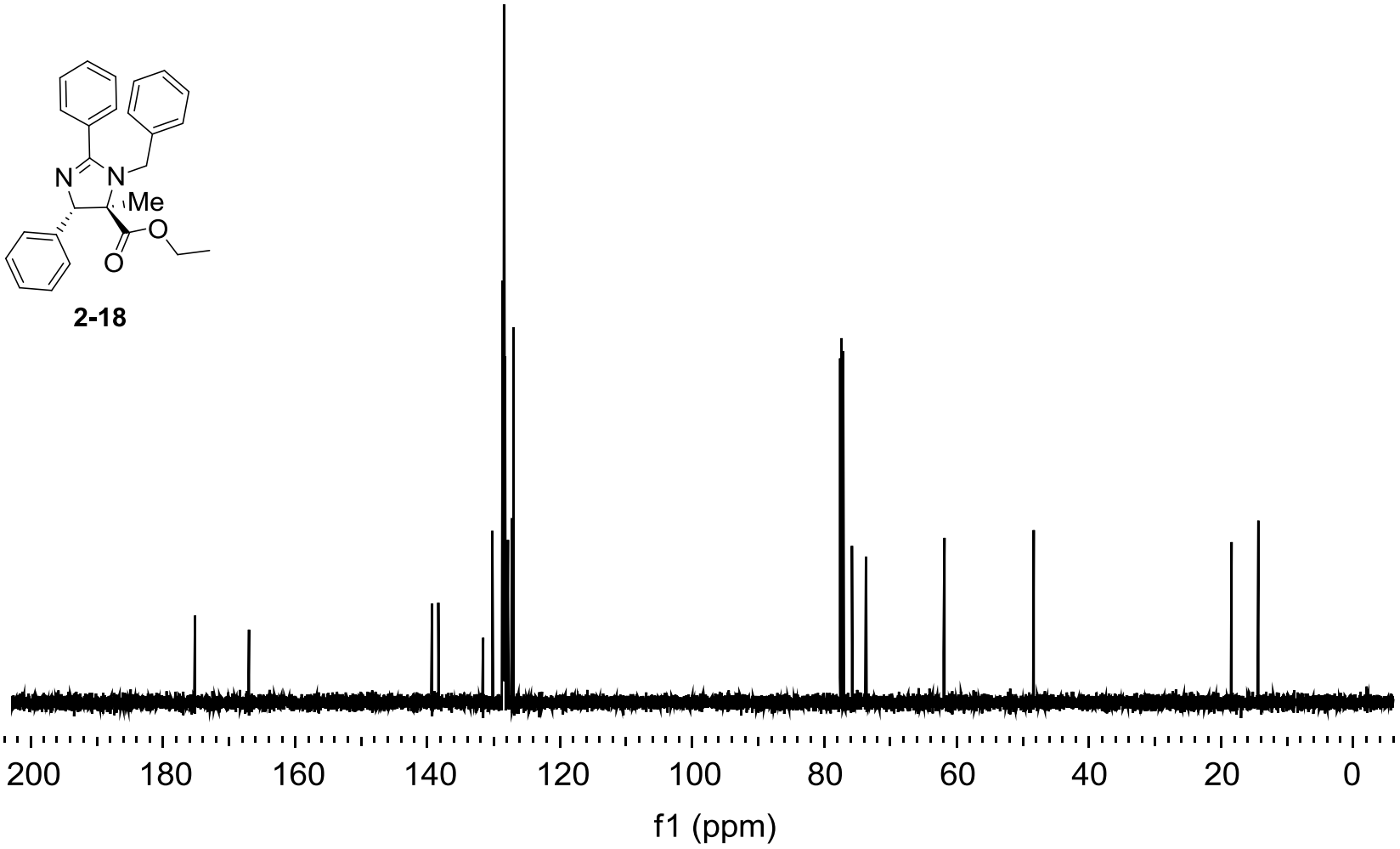


Figure 4-8: ^{13}C NMR spectrum for compound **2-18**

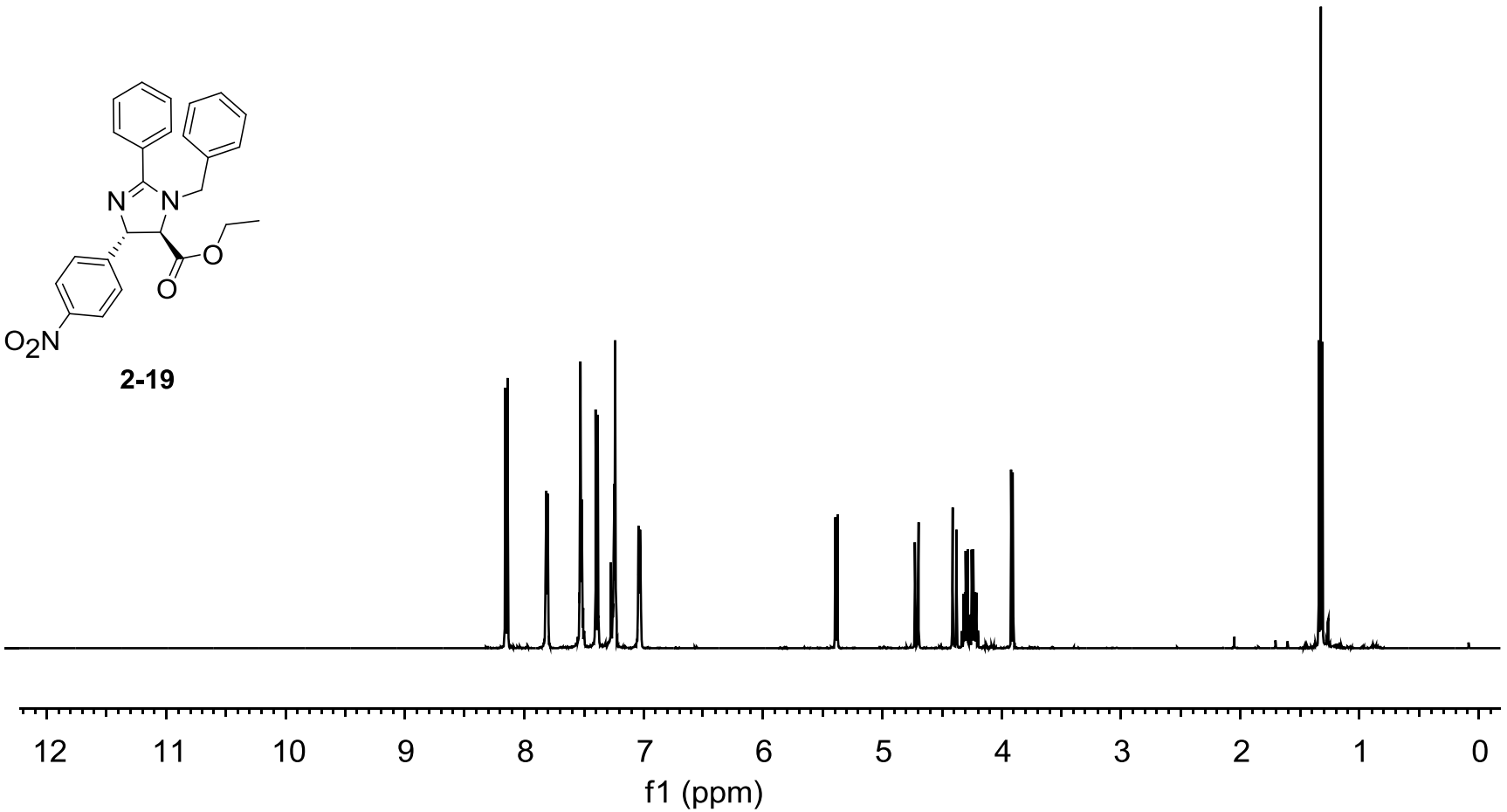


Figure 4-9: ^{1}H NMR spectrum for compound **2-19** regioisomer 1

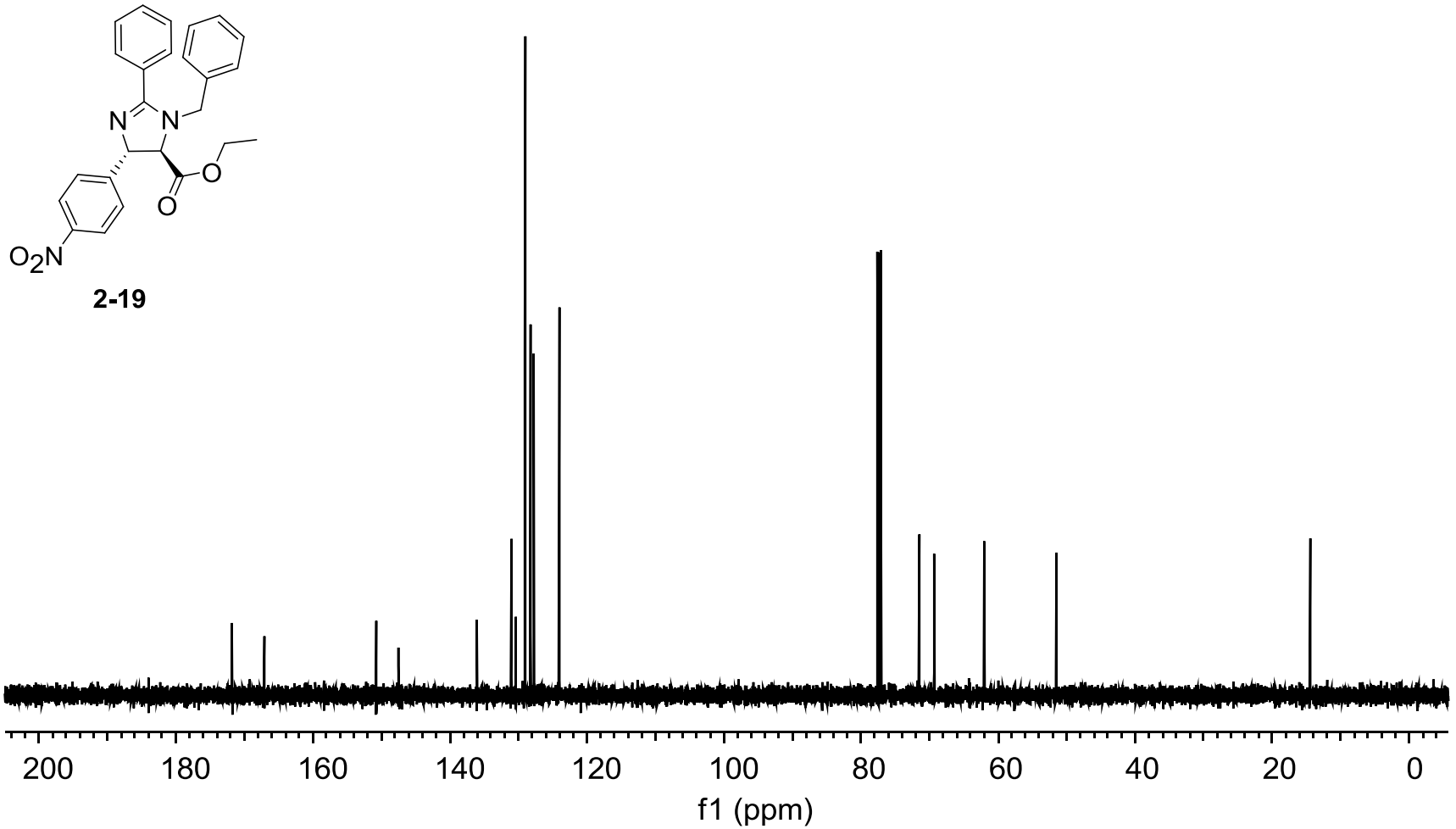


Figure 4-10: ^{13}C NMR spectrum for compound **2-19** regioisomer 1

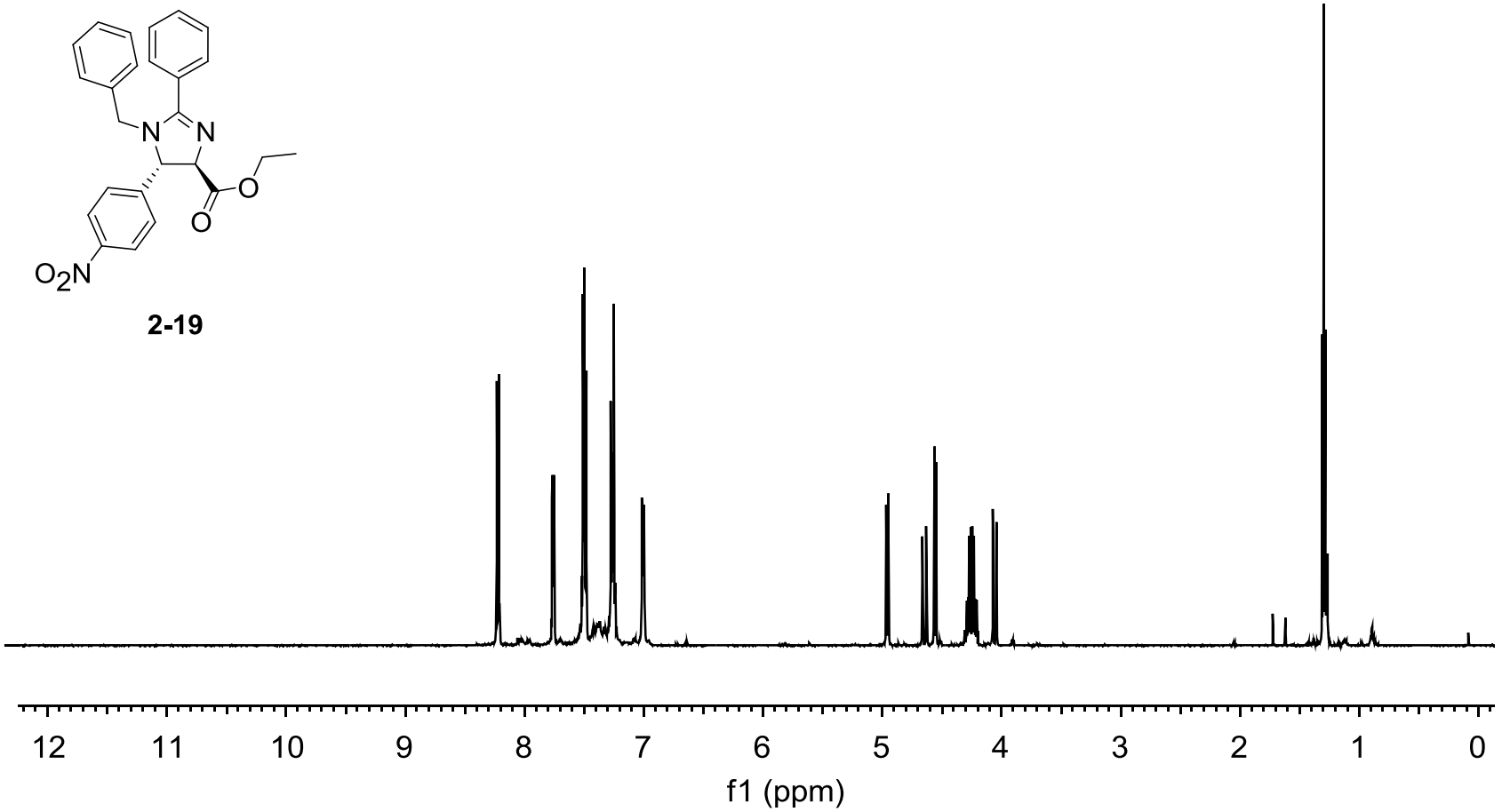


Figure 4-11: ^{1}H NMR spectrum for compound **2-19** regioisomer 2

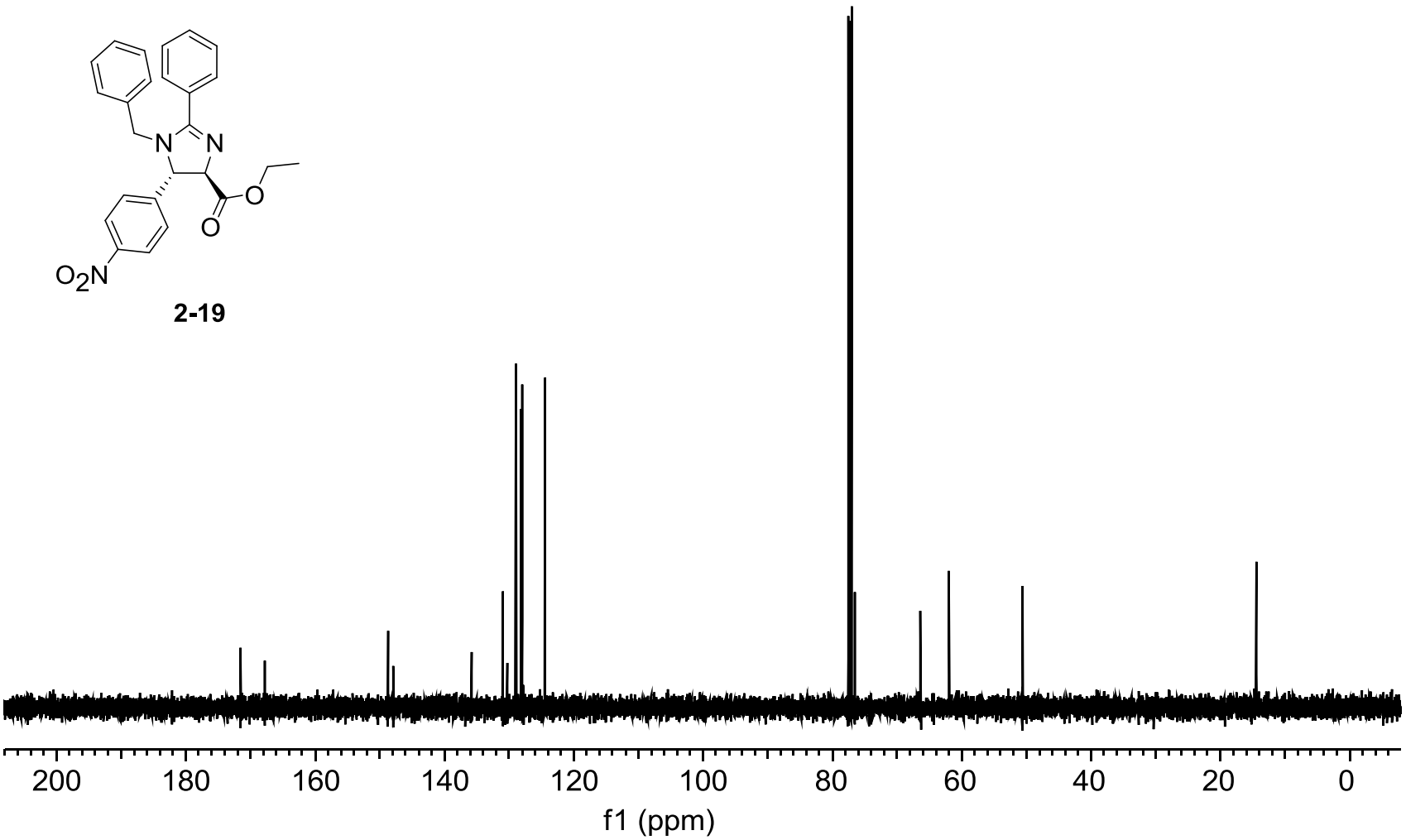


Figure 4-12: ^{13}C NMR spectrum for compound **2-19** regioisomer 2

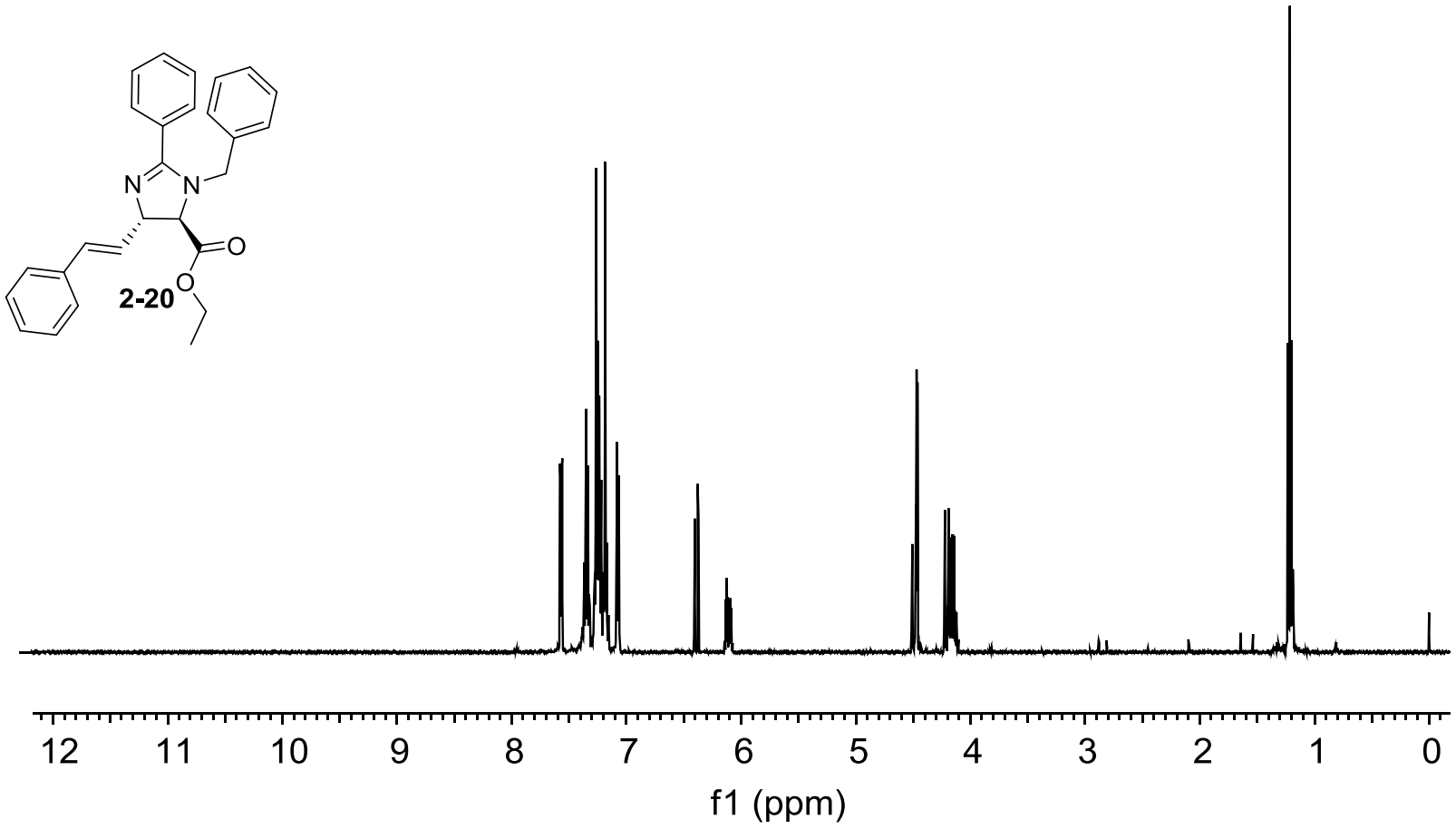


Figure 4-13: ^{1}H NMR spectrum for compound **2-20**

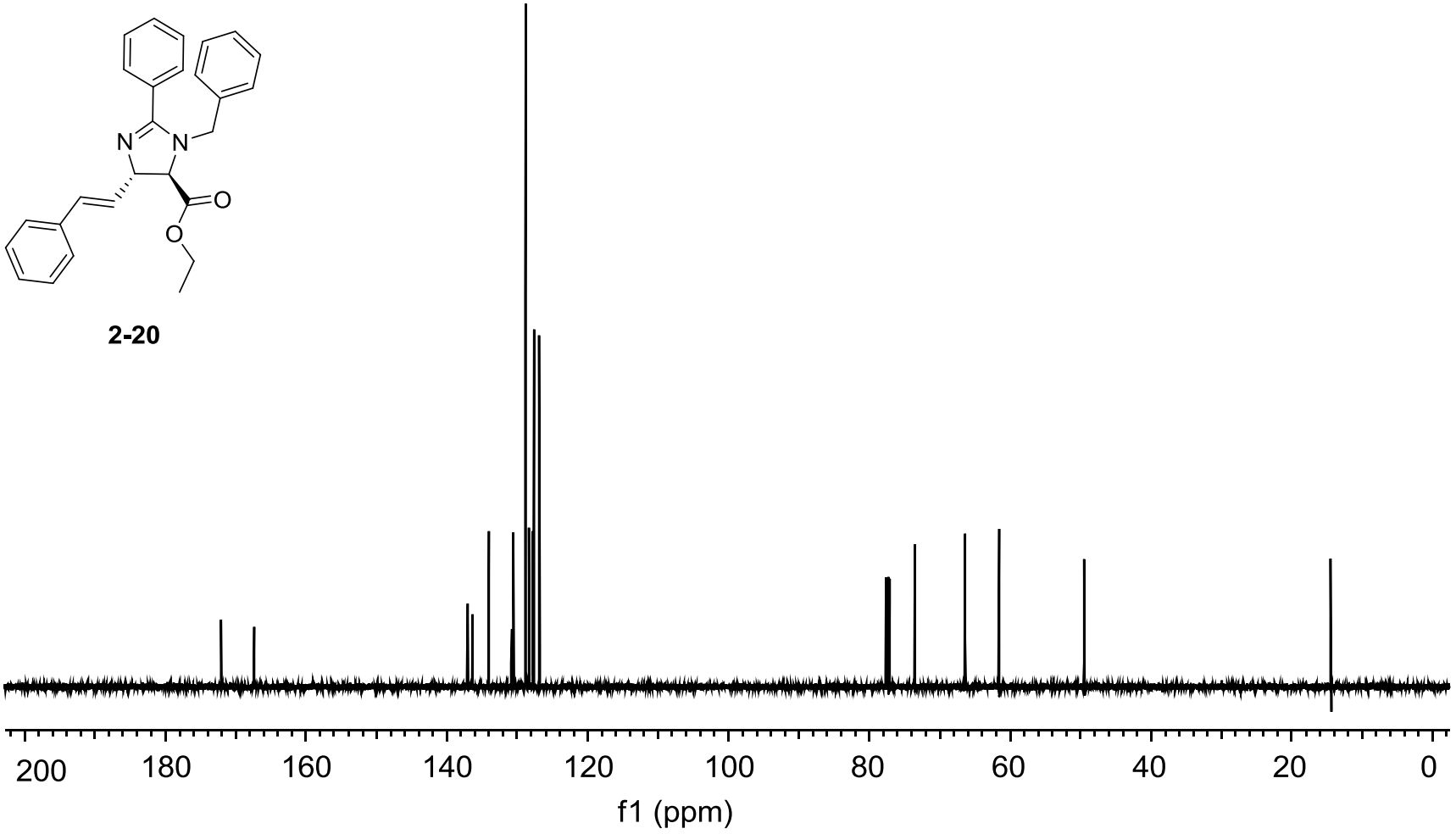


Figure 4-14: ^{13}C NMR spectrum for compound **2-20**

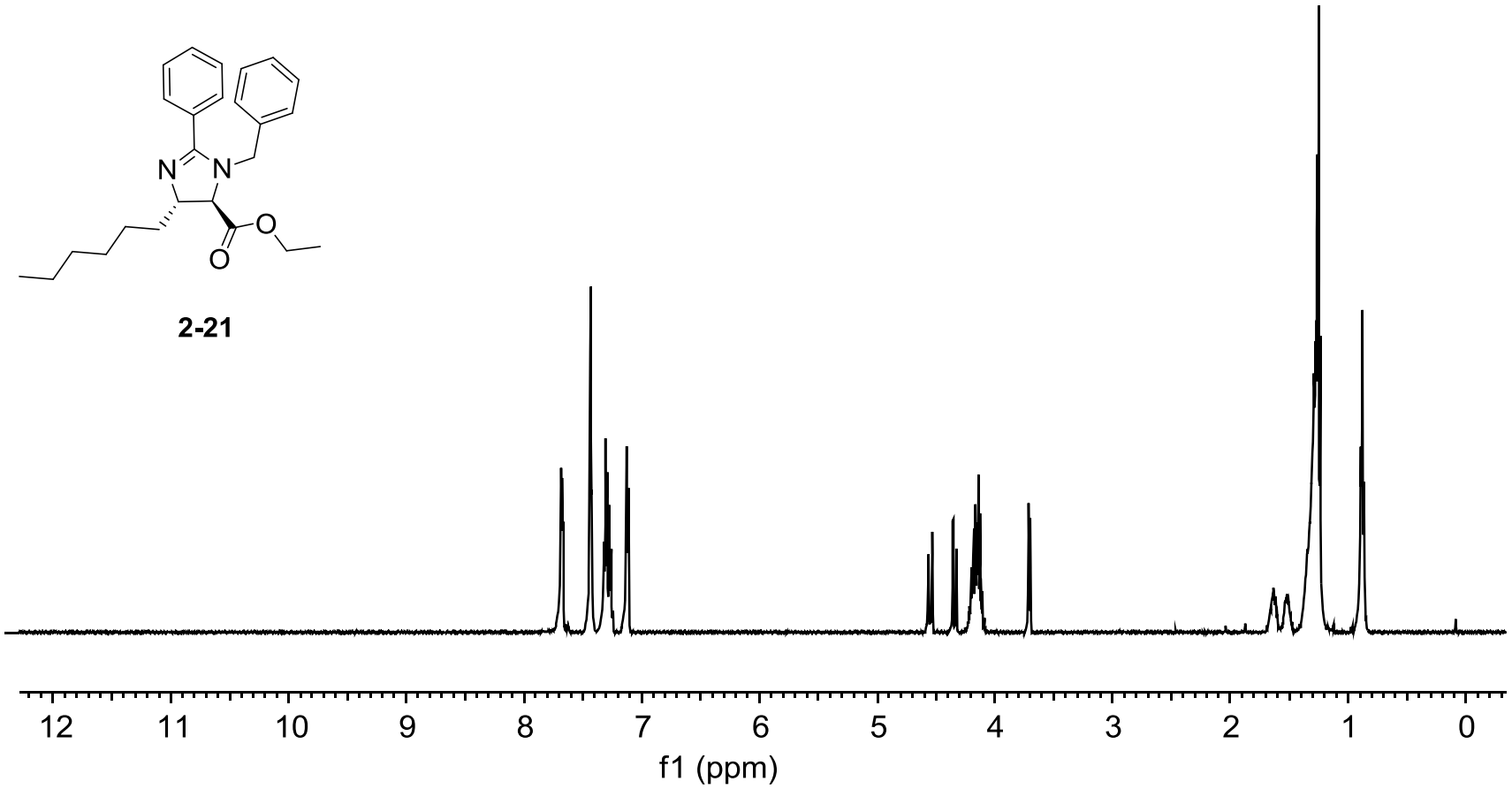


Figure 4-15: ^{1}H NMR spectrum for compound **2-21**

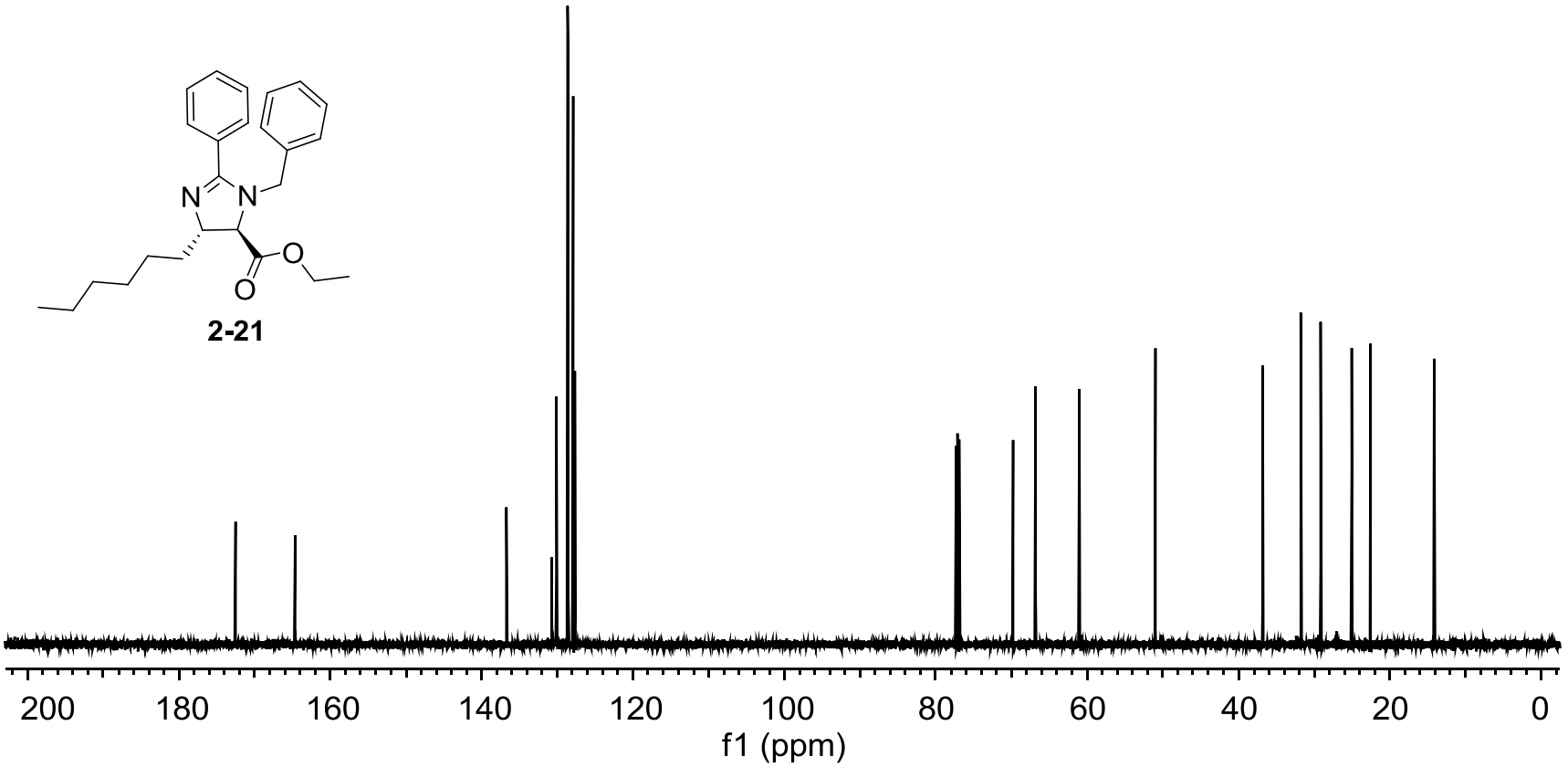


Figure 4-16: ^{13}C NMR spectrum for compound **2-21**

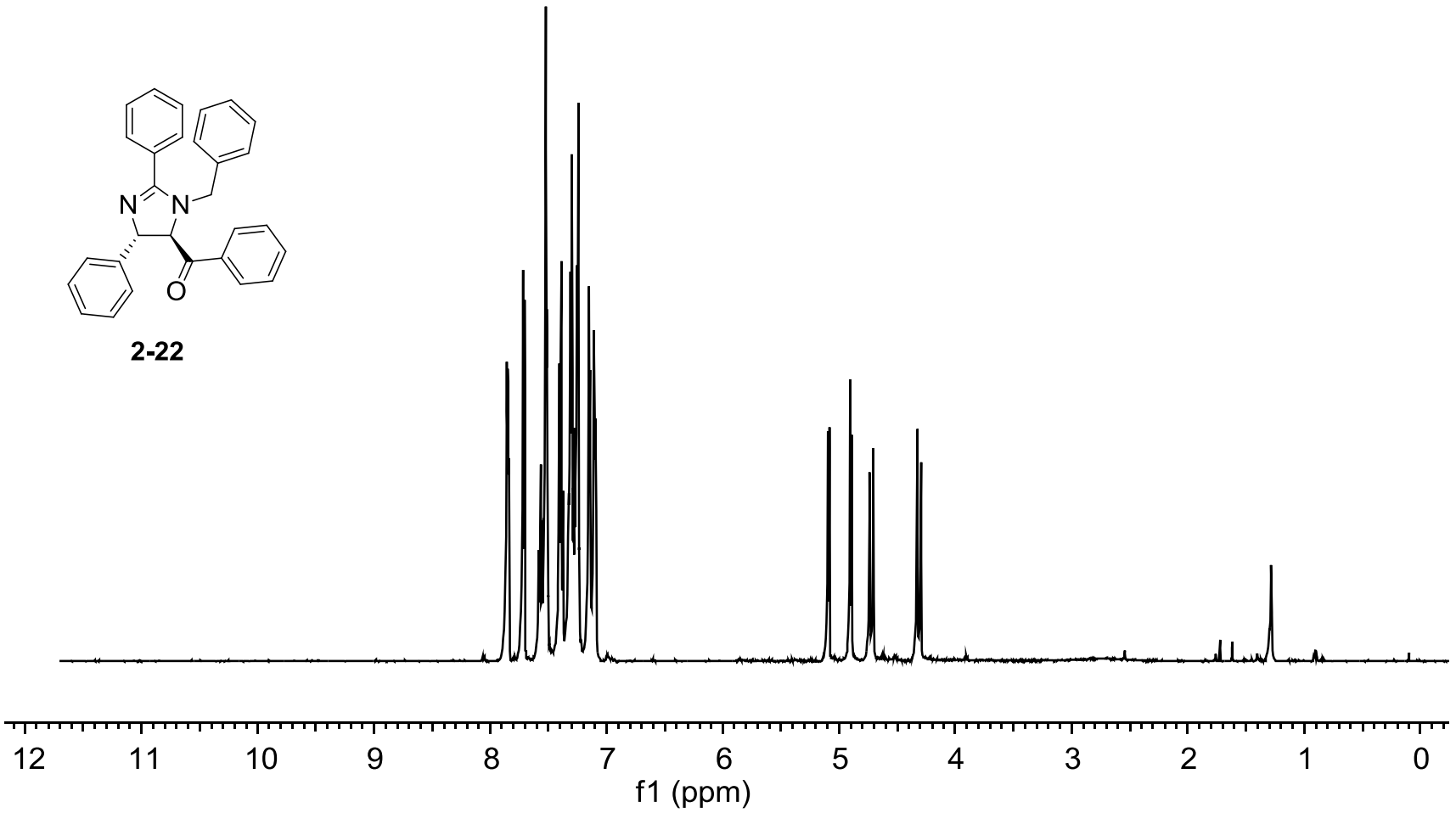


Figure 4-17: ^{1}H NMR spectrum for compound **2-22**

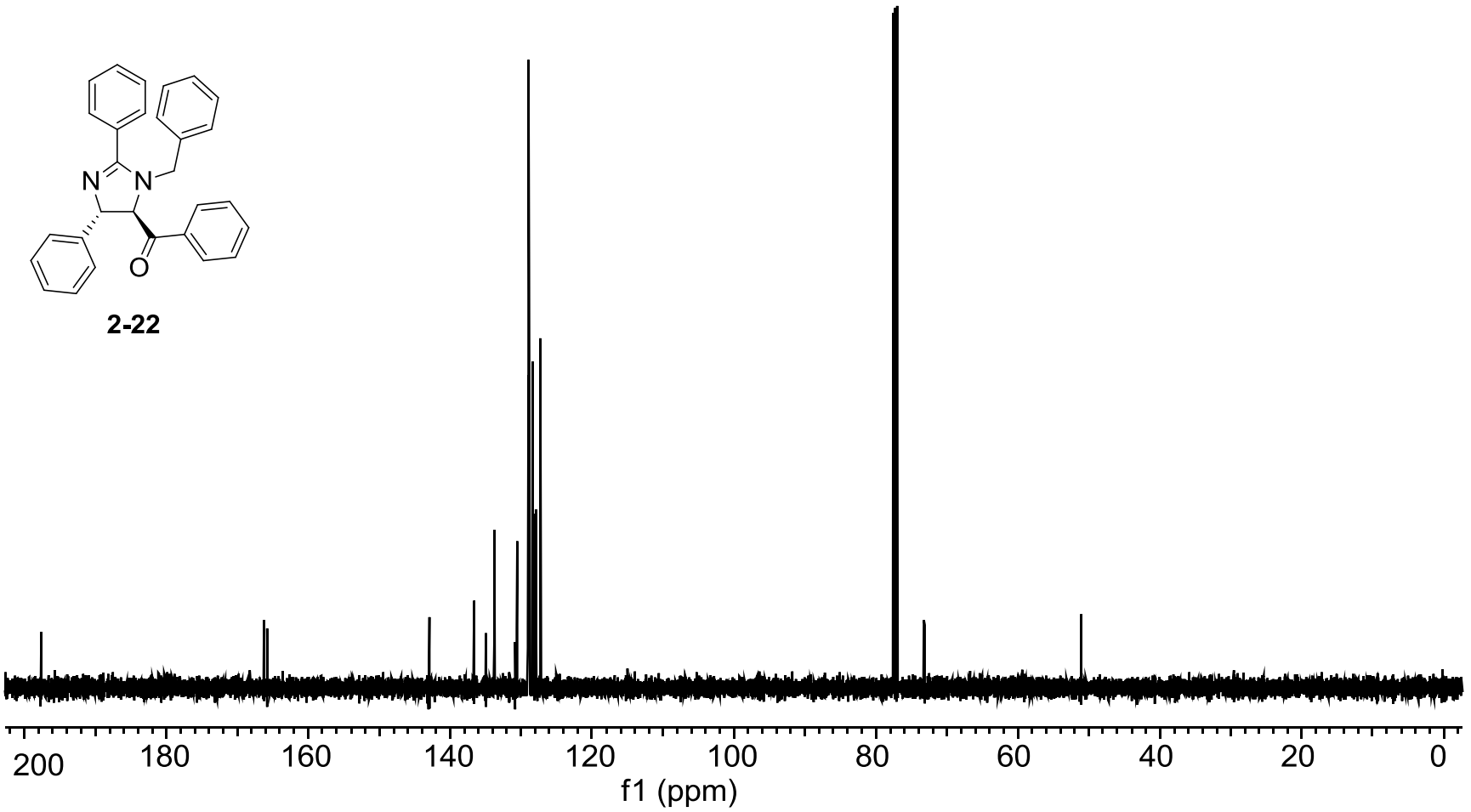


Figure 4-18: ^{13}C NMR spectrum for compound **2-22**

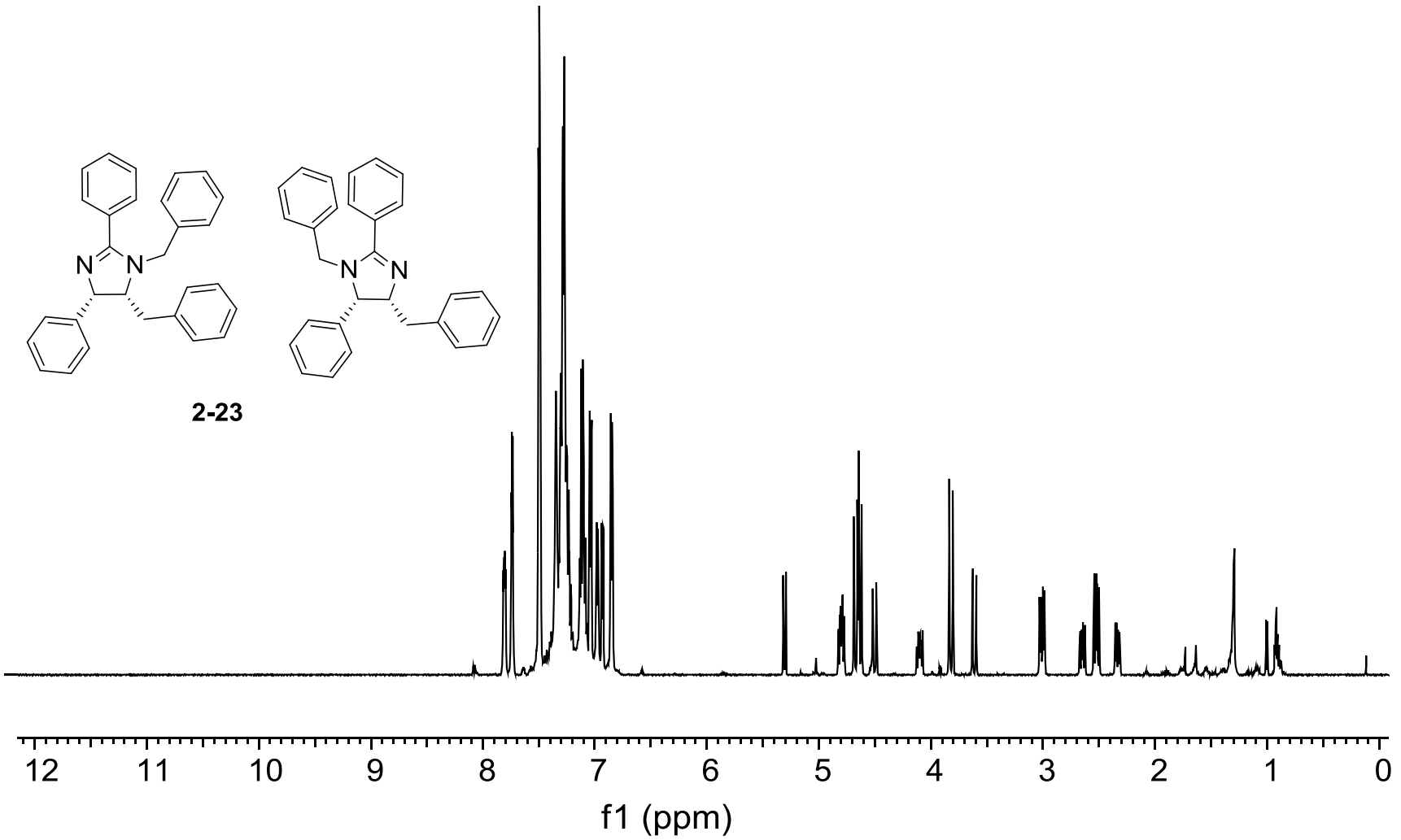


Figure 4-19: ^{1}H NMR spectrum for compound **2-23**

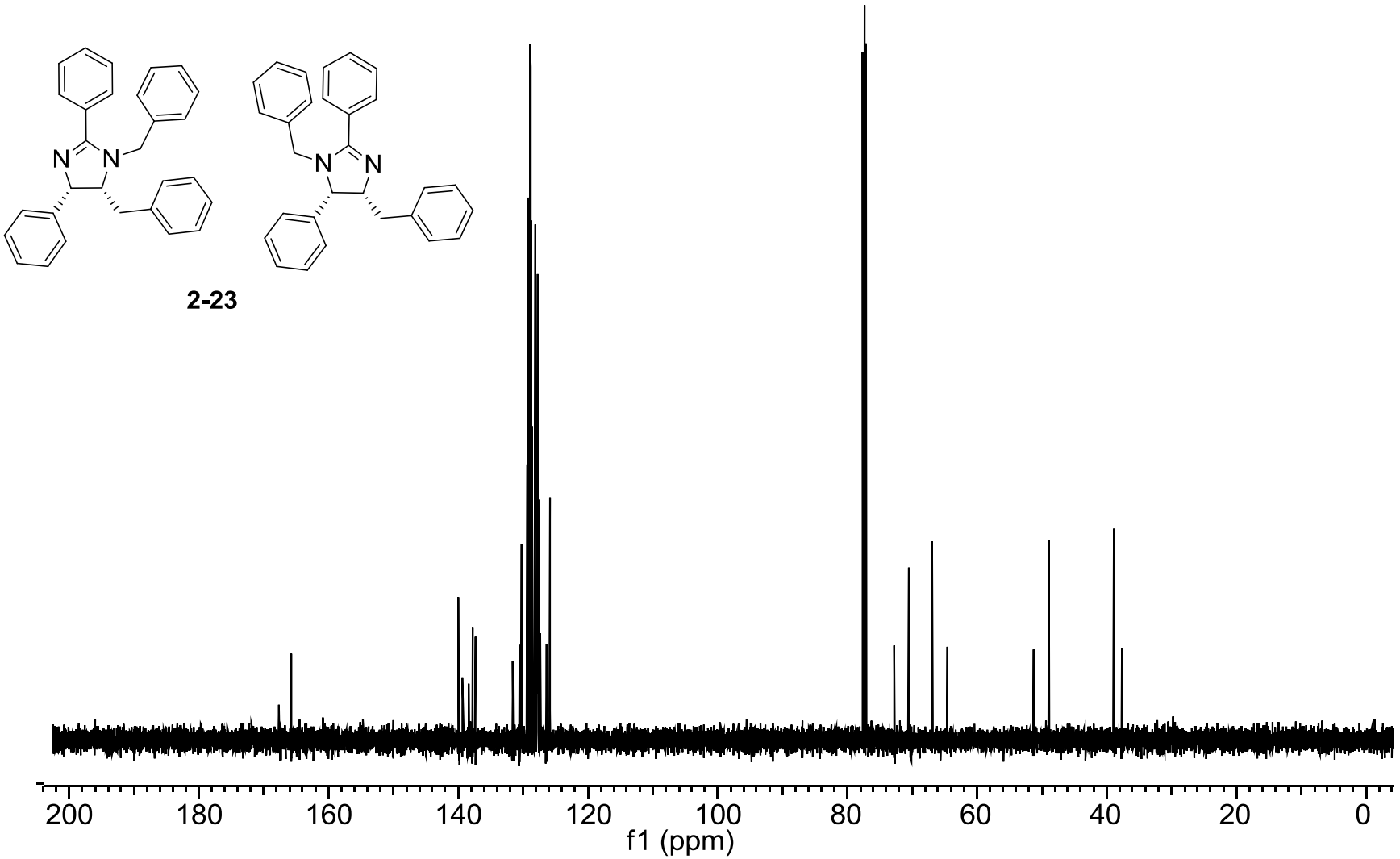


Figure 4-20: ^{13}C NMR spectrum for compound **2-23**

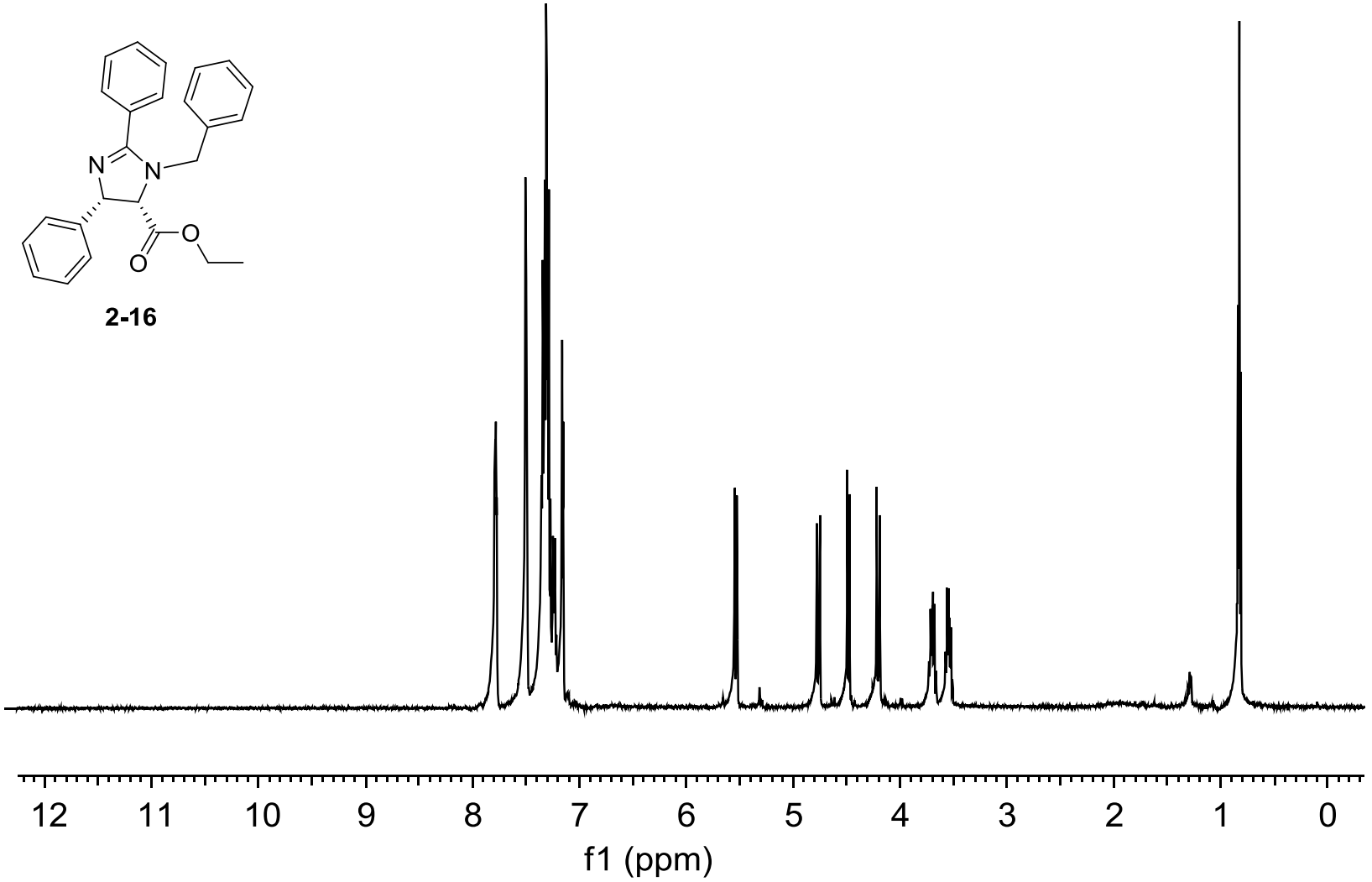


Figure 4-21: ^{1}H NMR spectrum for compound **2-16**

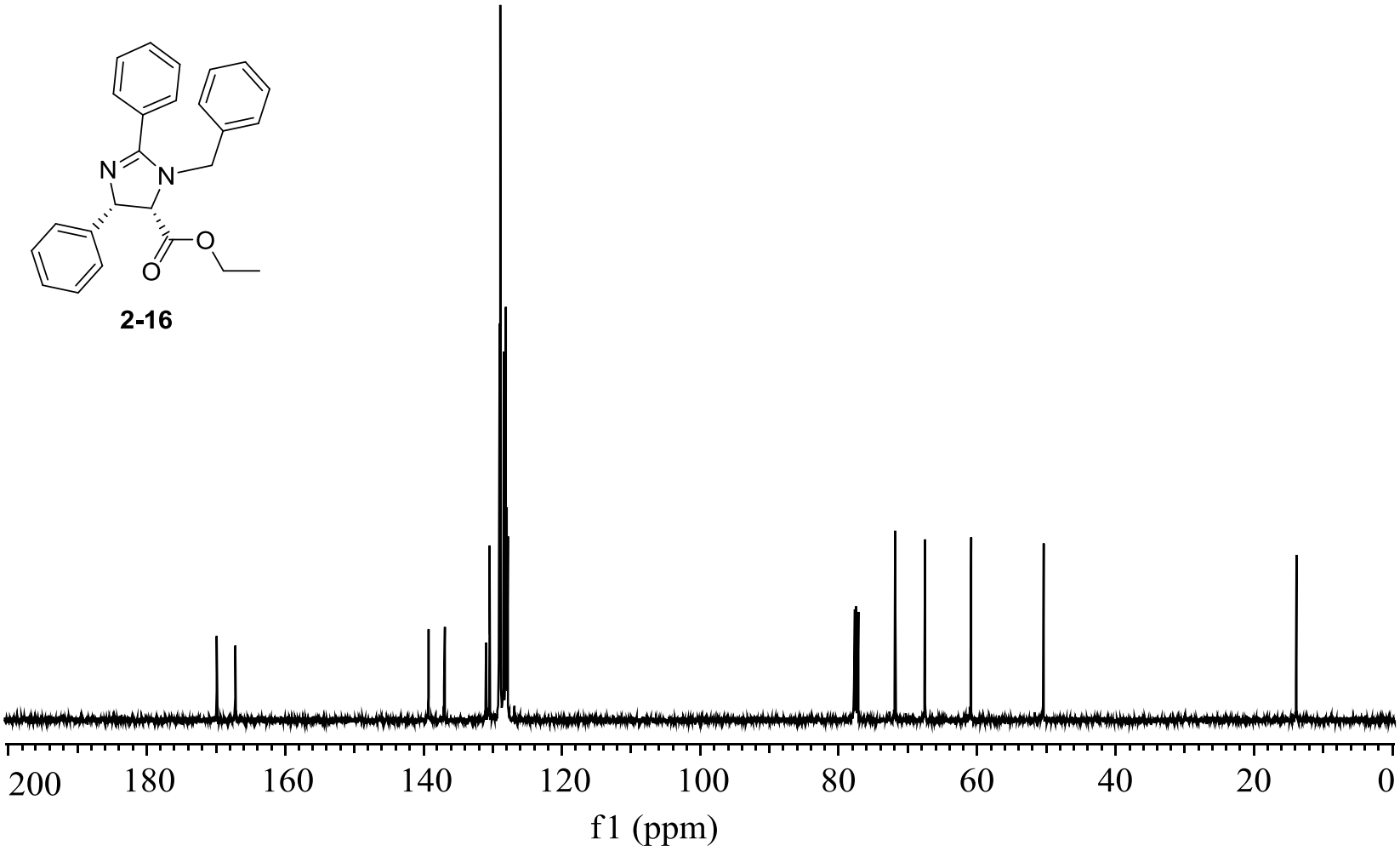


Figure 4-22: ^{13}C NMR spectrum for compound **2-16**

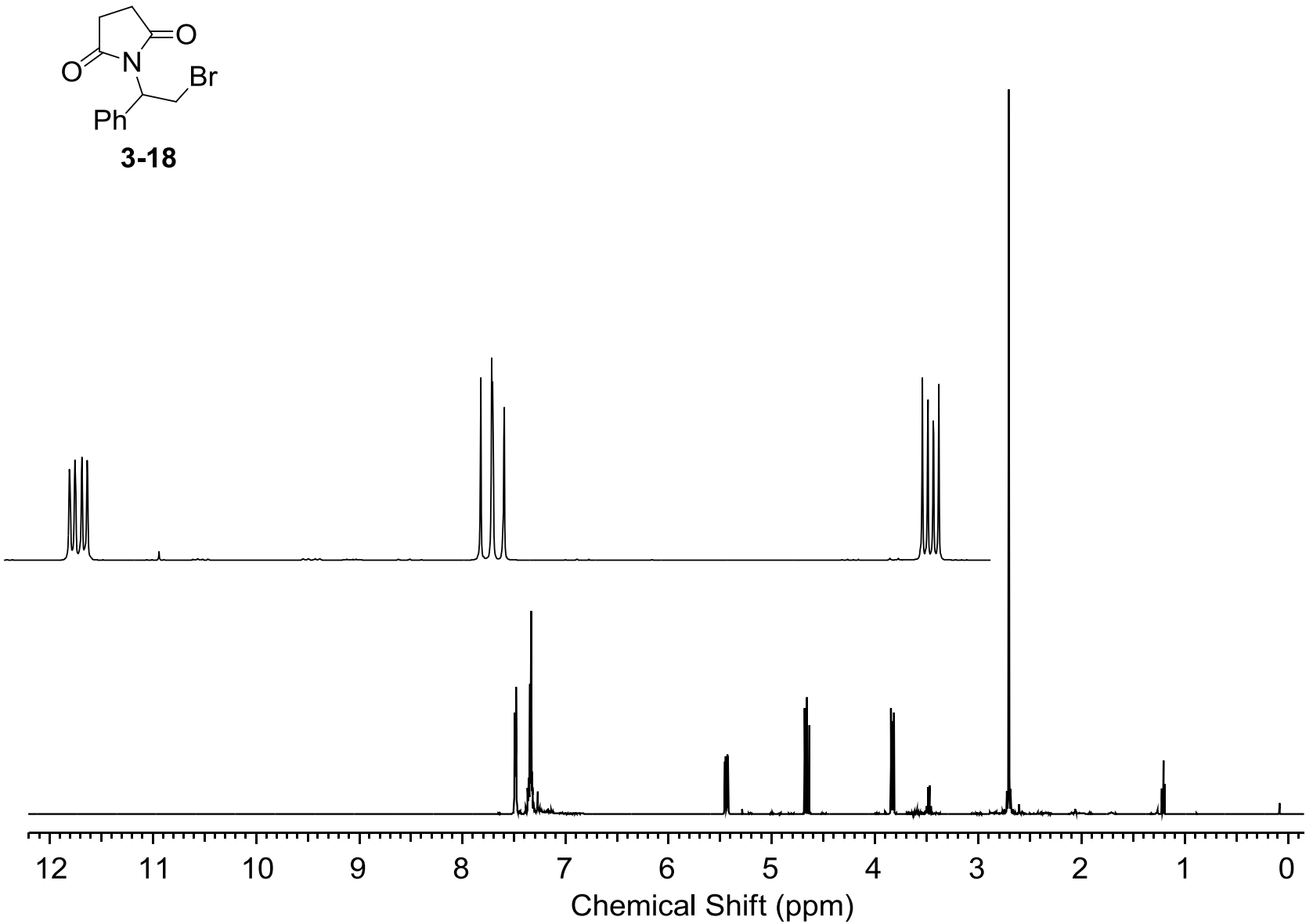
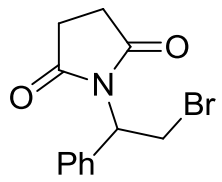


Figure 4-23: ^{1}H NMR spectrum for compound **3-18**



3-18

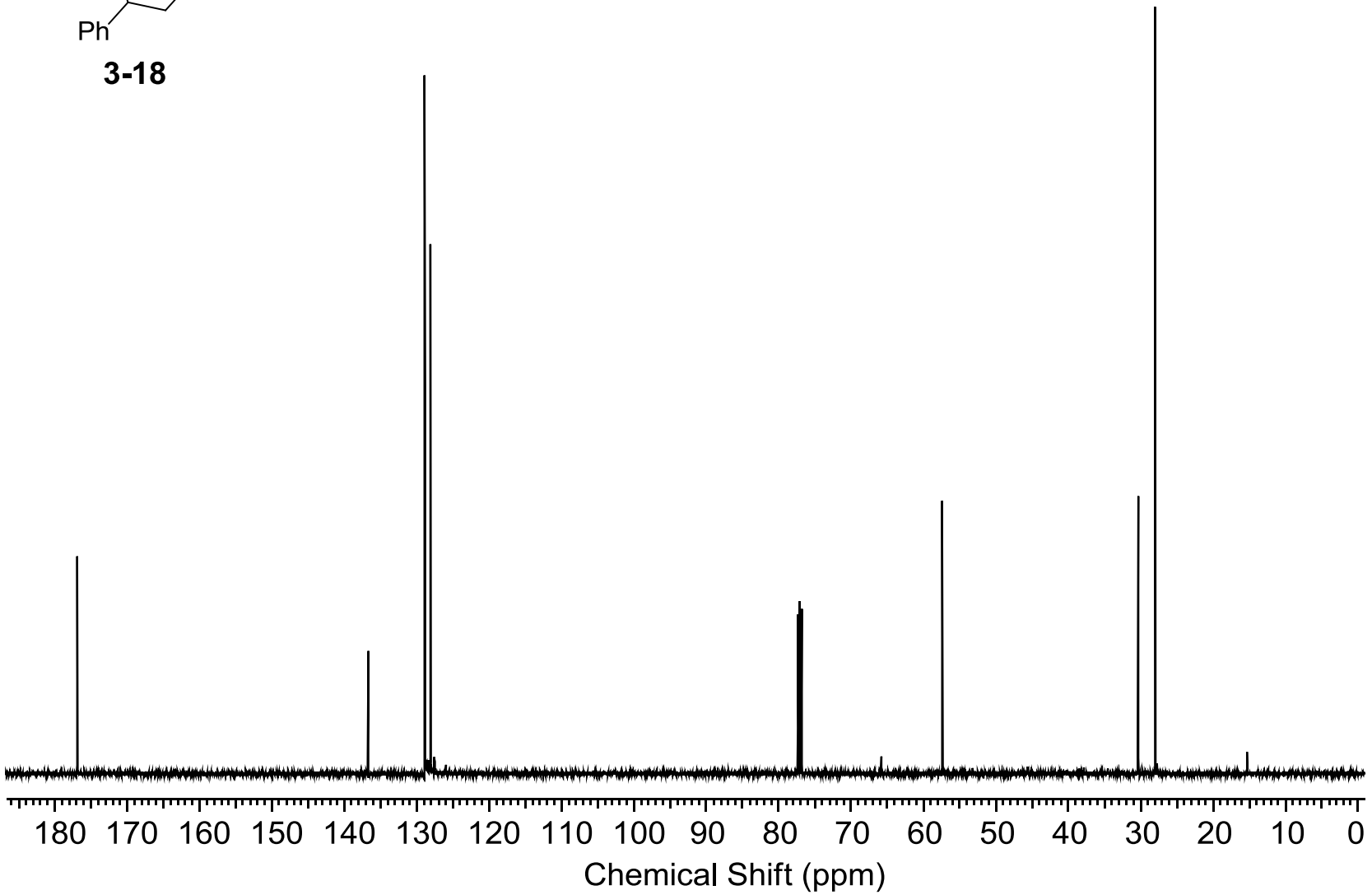


Figure 4-24: ^{13}C NMR spectrum for compound **3-18**

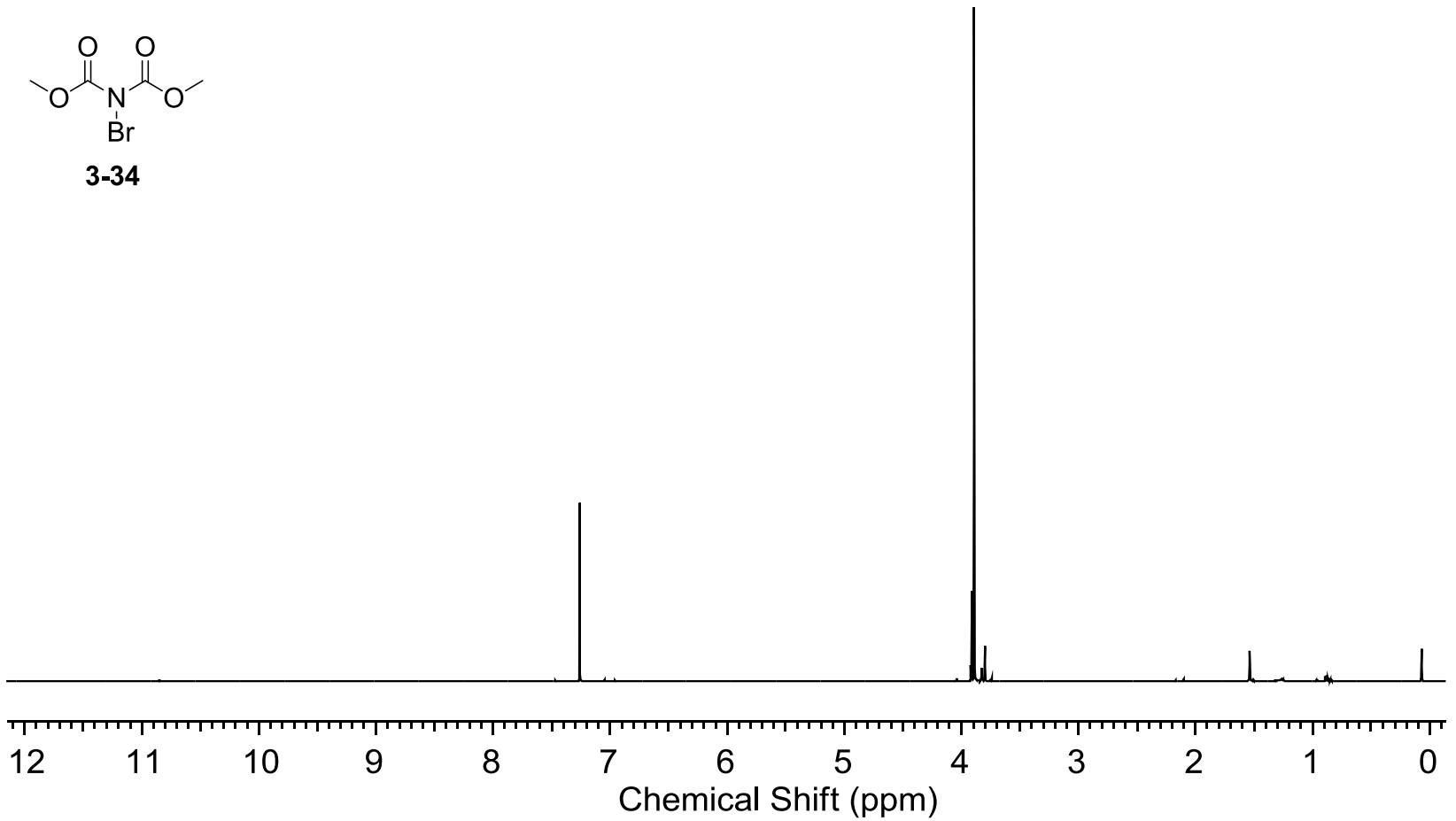


Figure 4-25: ^{1}H NMR spectrum for compound **3-34**

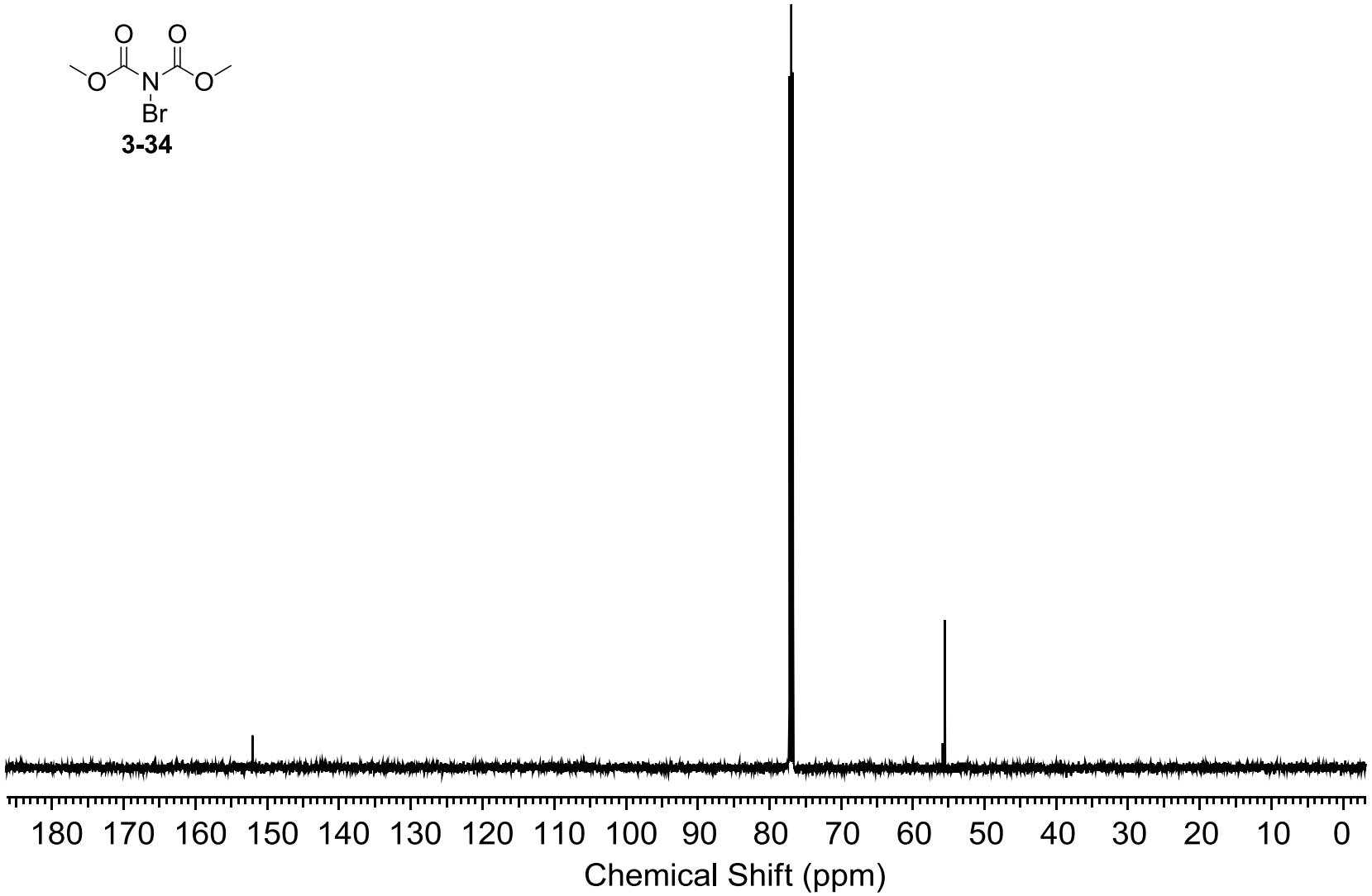


Figure 4-26: ^{13}C NMR spectrum for compound **3-34**

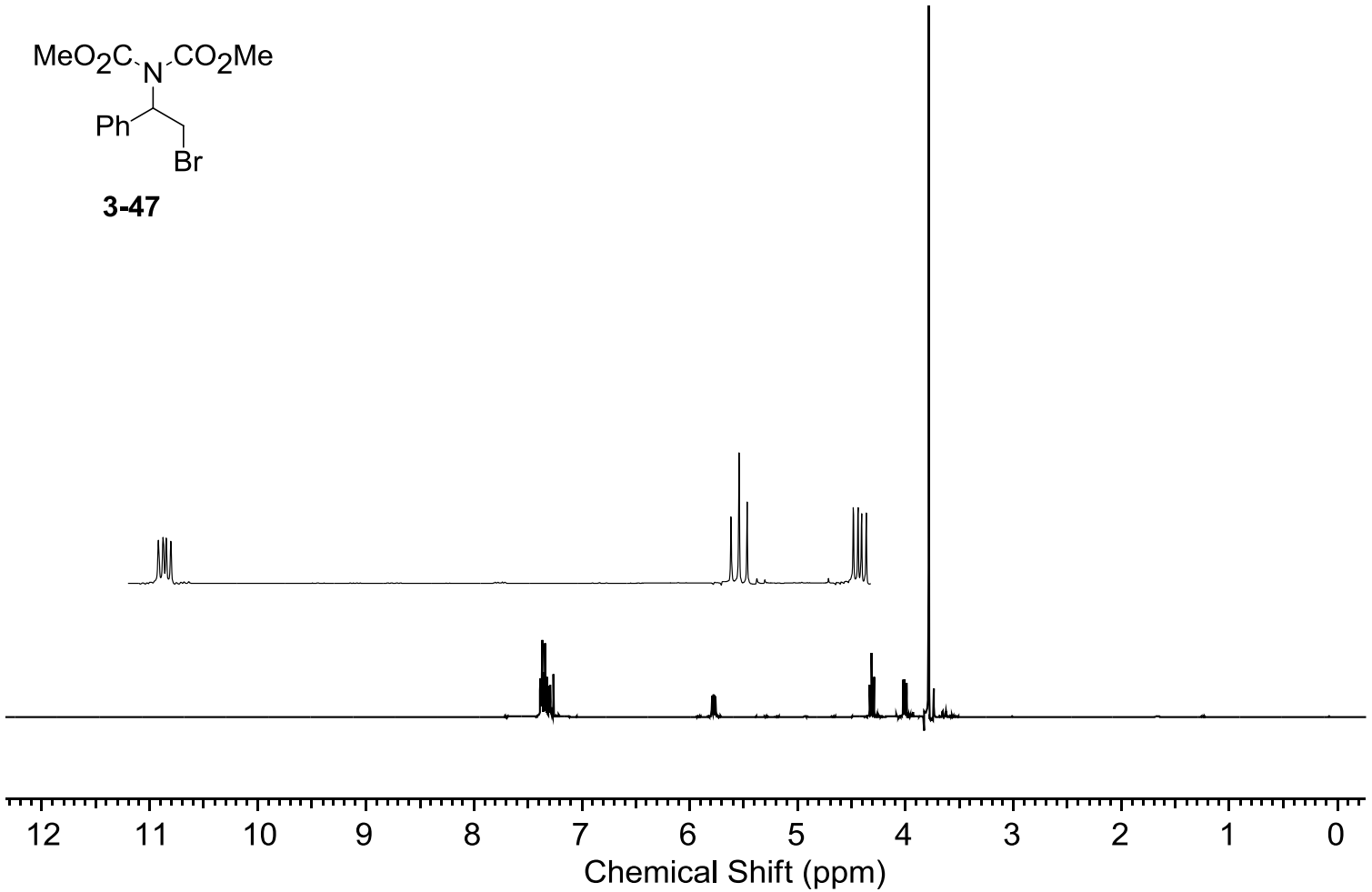


Figure 4-27: ^{1}H NMR spectrum for compound **3-47**

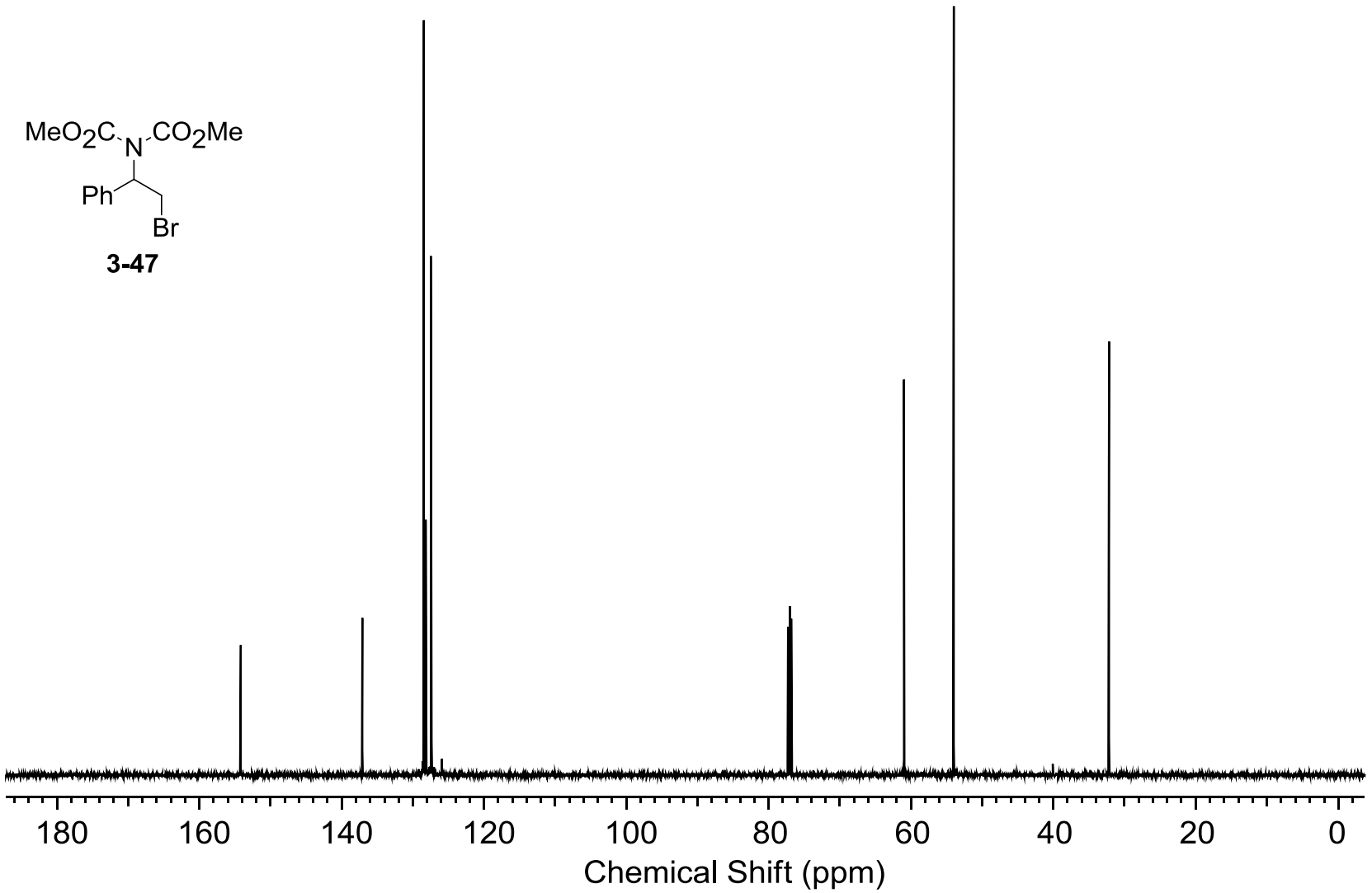


Figure 4-28: ^{13}C NMR spectrum for compound **3-47**

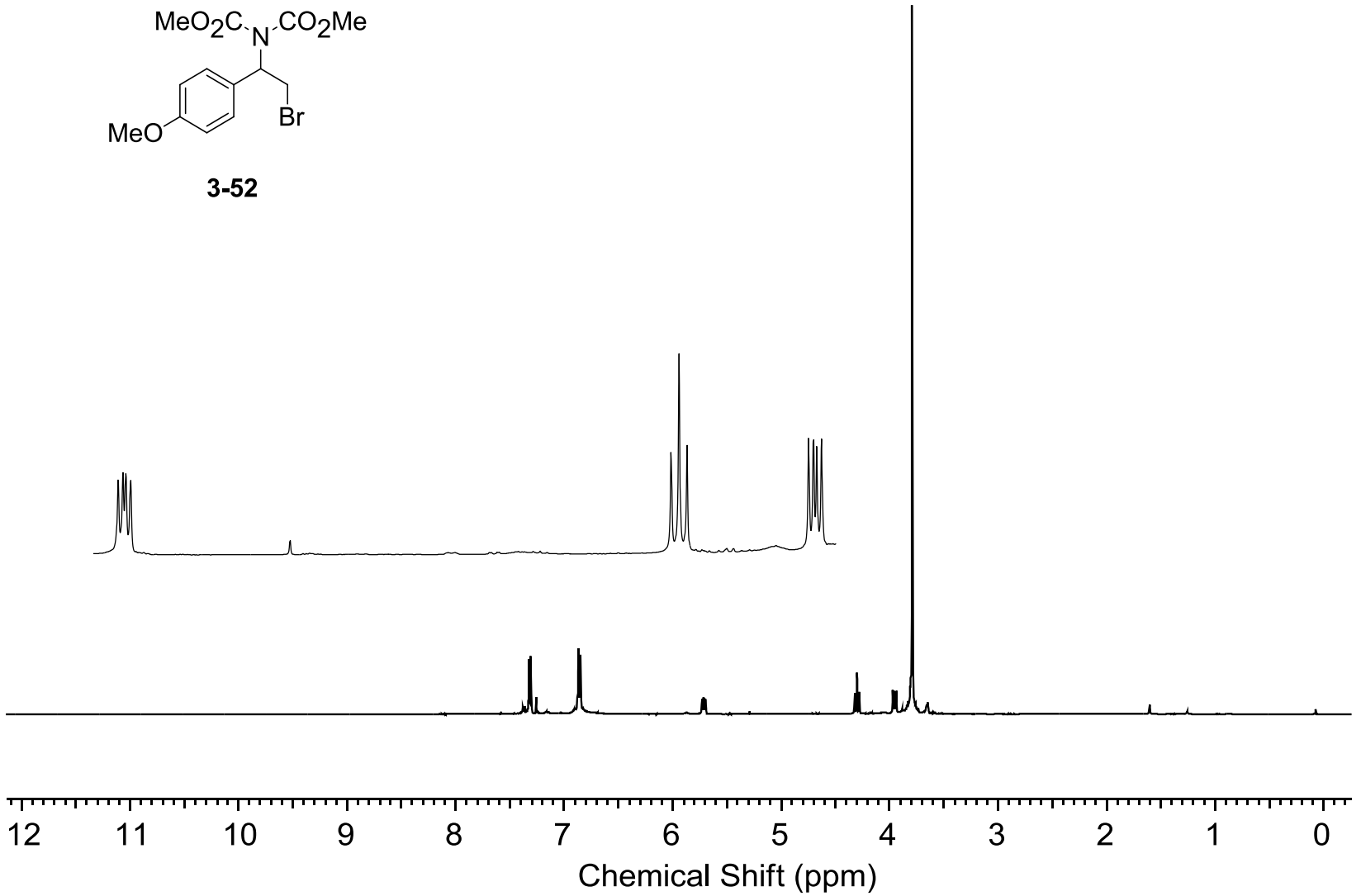


Figure 4-29: ^{1}H NMR spectrum for compound **3-52**

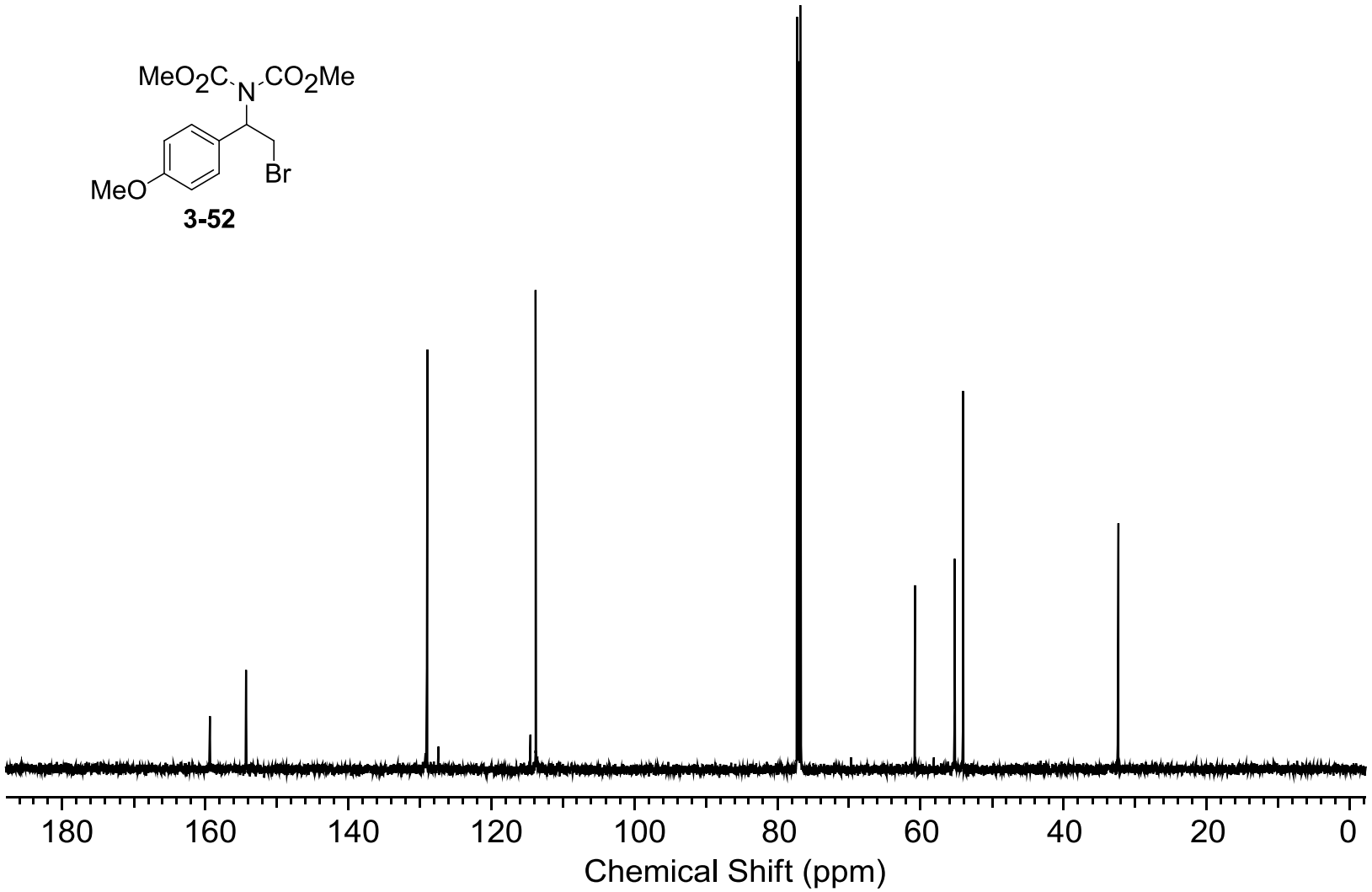


Figure 4-30: ^{13}C NMR spectrum for compound **3-52**

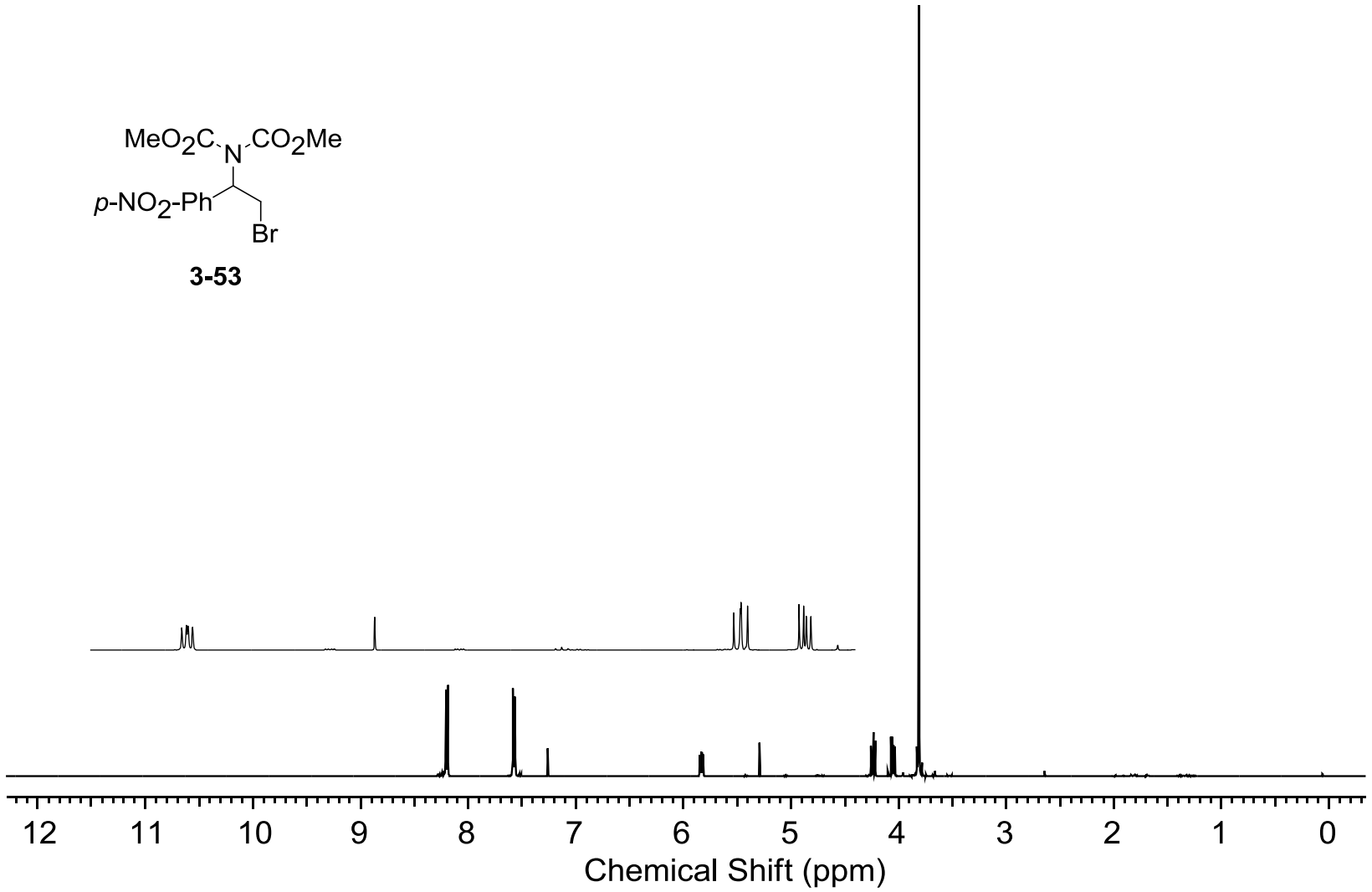


Figure 4-31: ^{1}H NMR spectrum for compound **3-53**

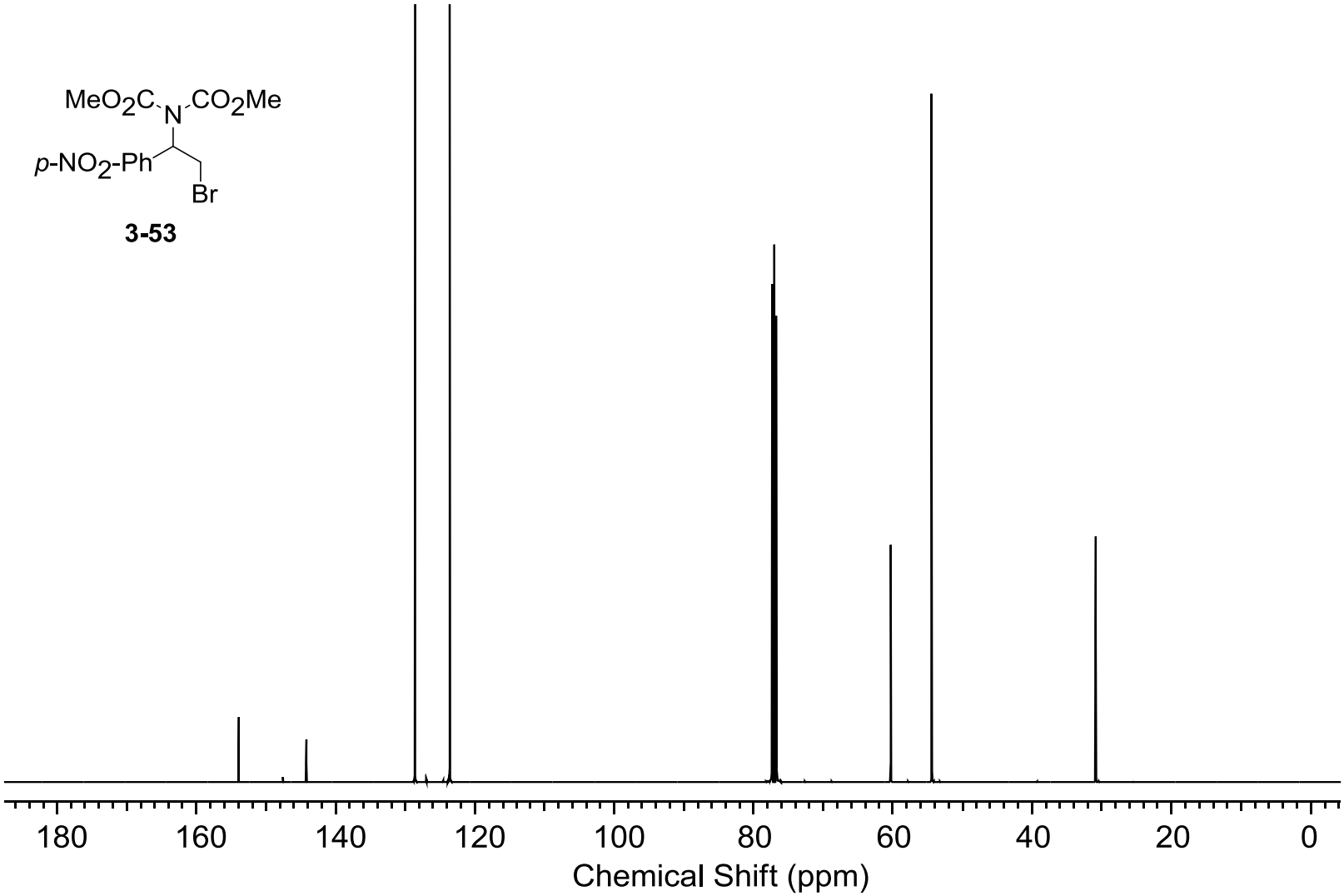


Figure 4-32: ^{13}C NMR spectrum for compound **3-53**

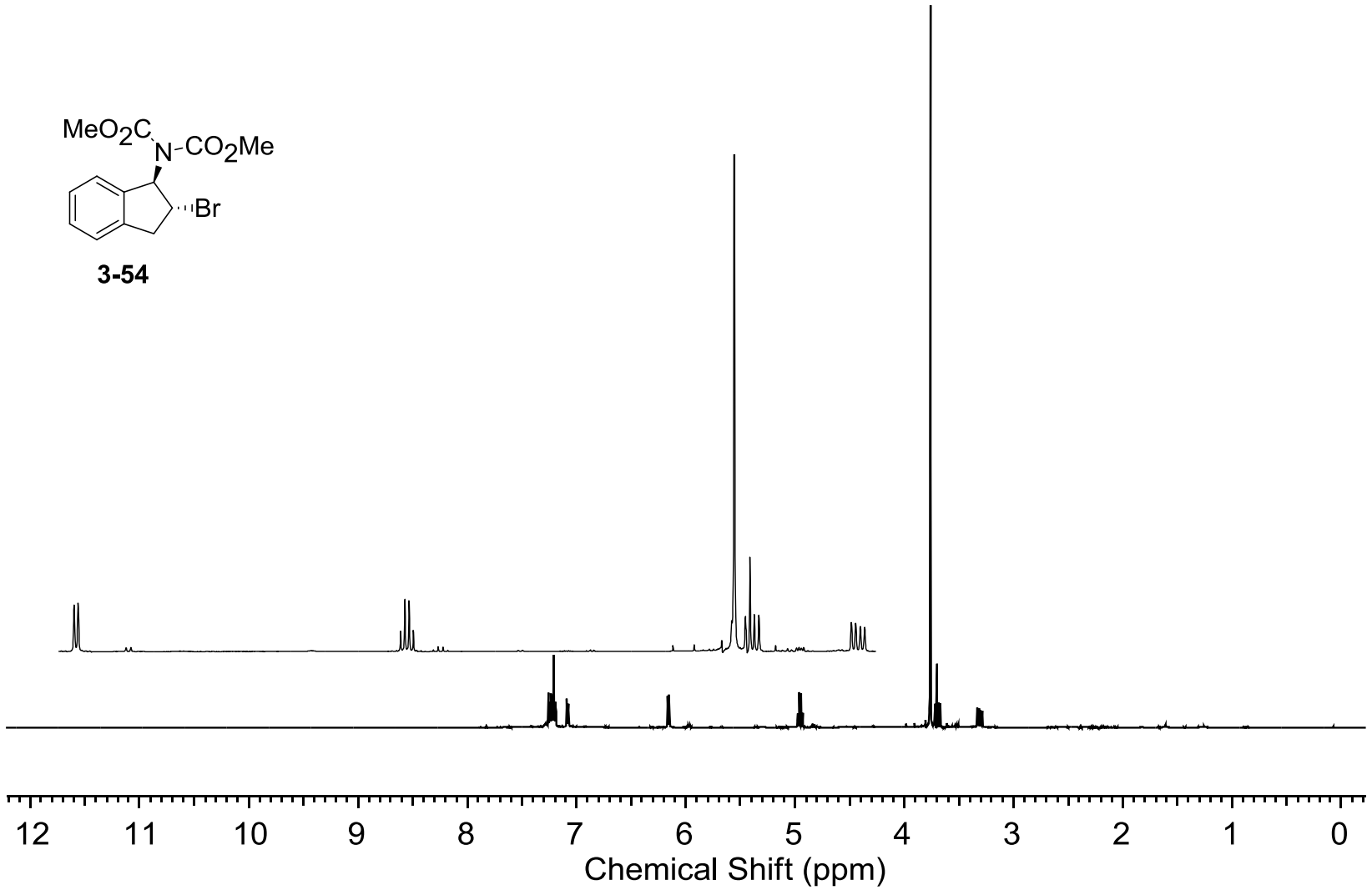


Figure 4-33: ^{1}H NMR spectrum for compound **3-54**

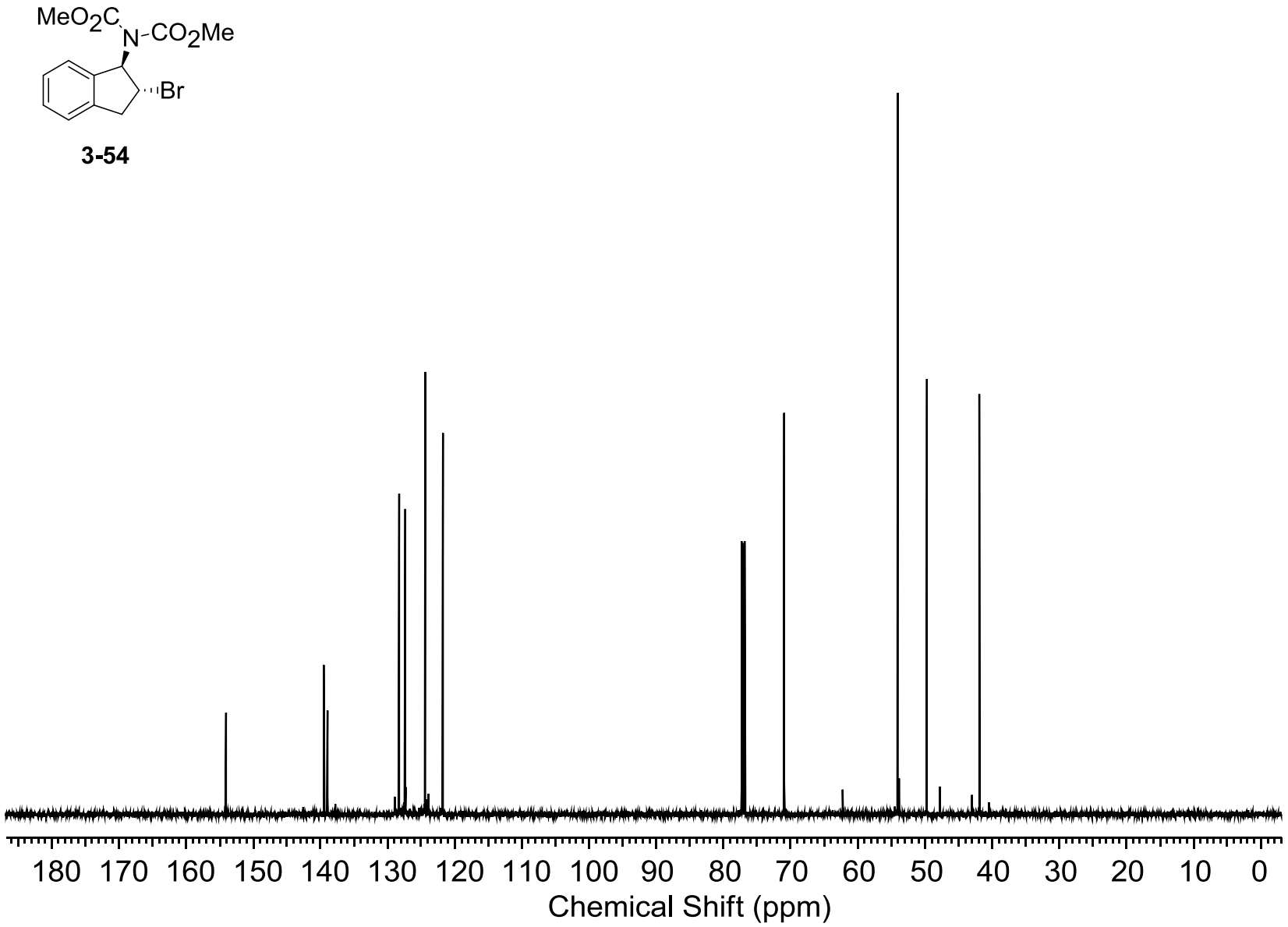


Figure 4-34: ^{13}C NMR spectrum for compound **3-54**

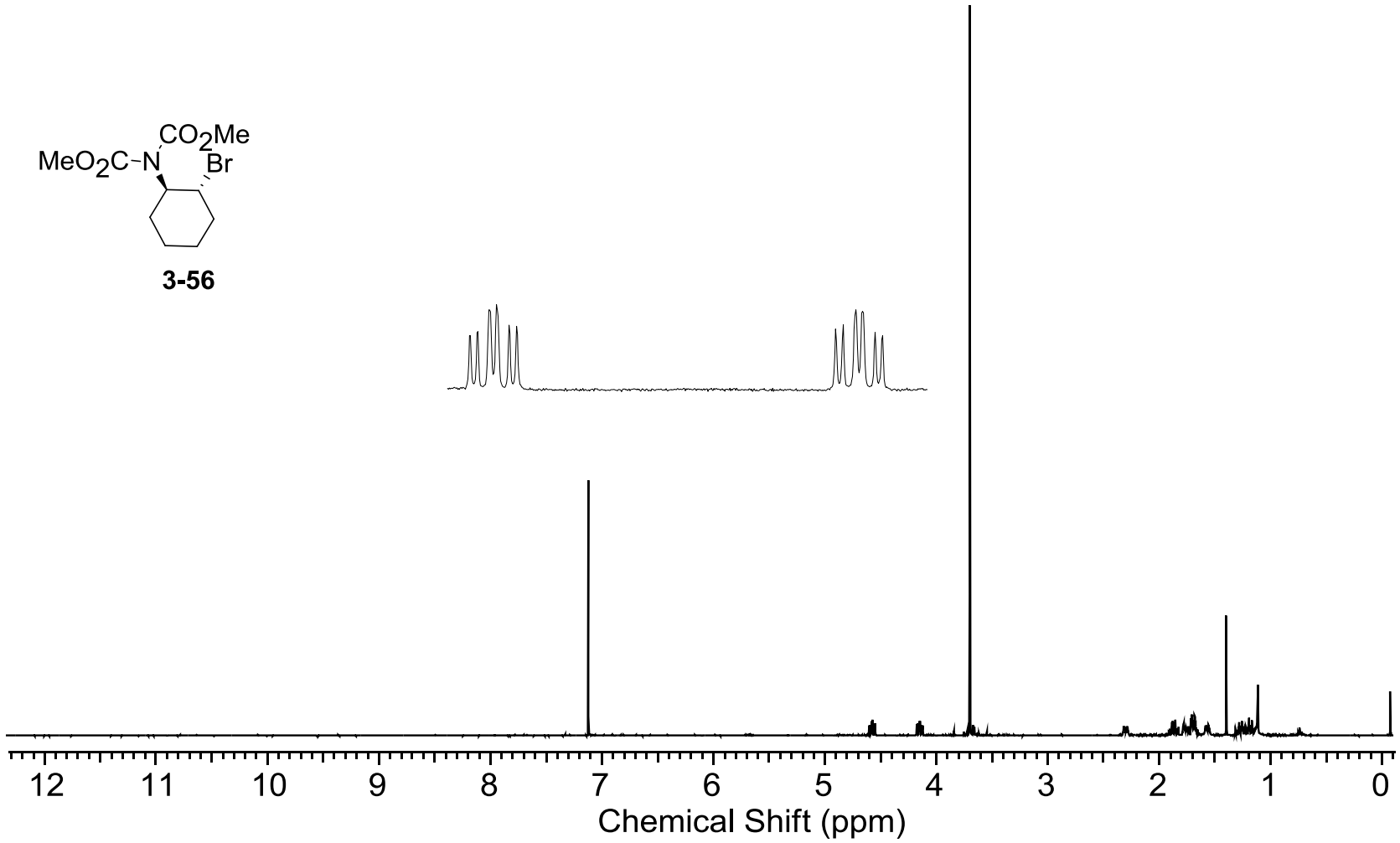


Figure 4-35: ^{1}H NMR spectrum for compound **3-56**

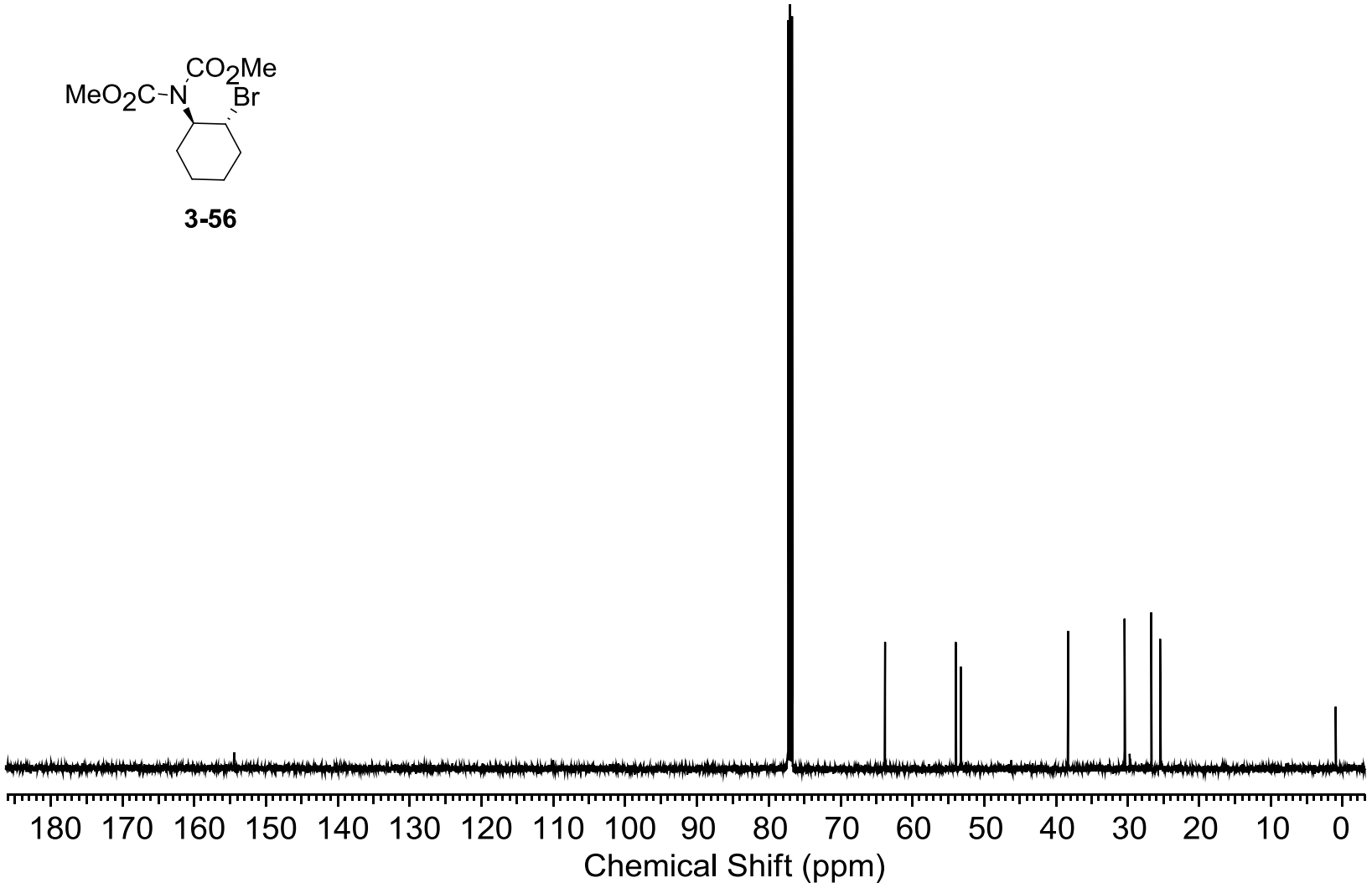


Figure 4-36: ^{13}C NMR spectrum for compound **3-56**

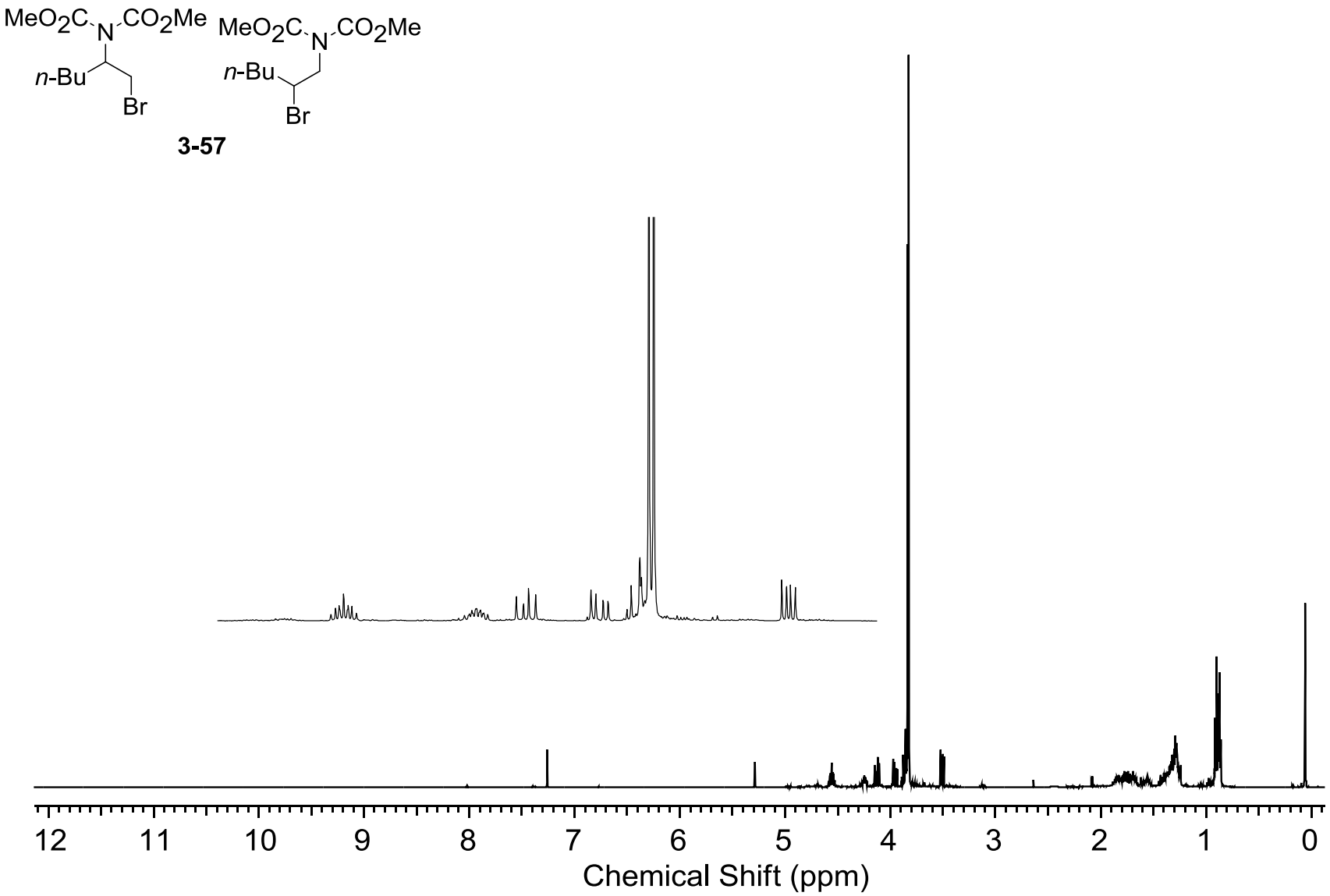


Figure 4-37: ^{1}H NMR spectrum for compound **3-57**

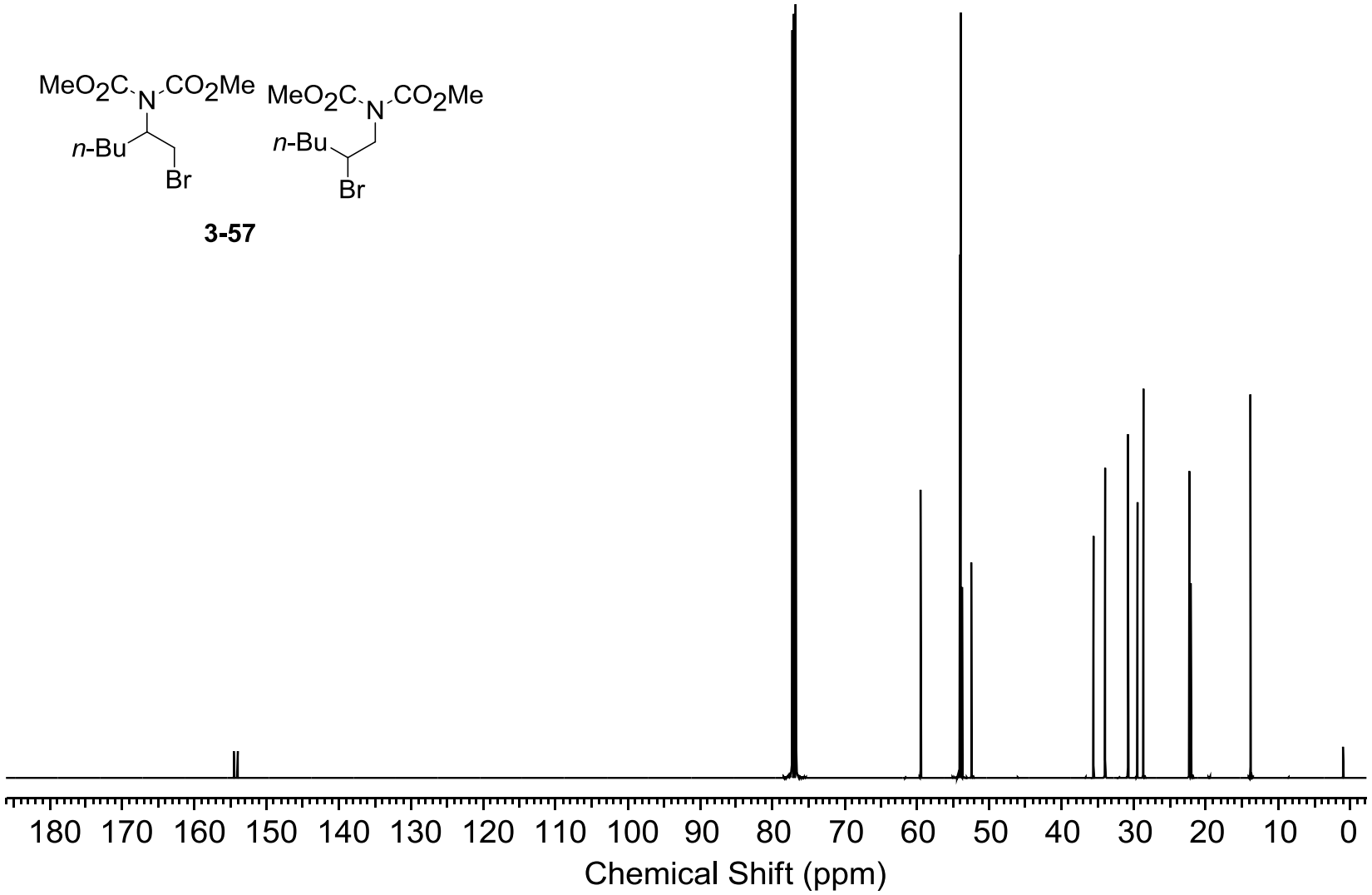


Figure 4-38: ^{13}C NMR spectrum for compound **3-57**

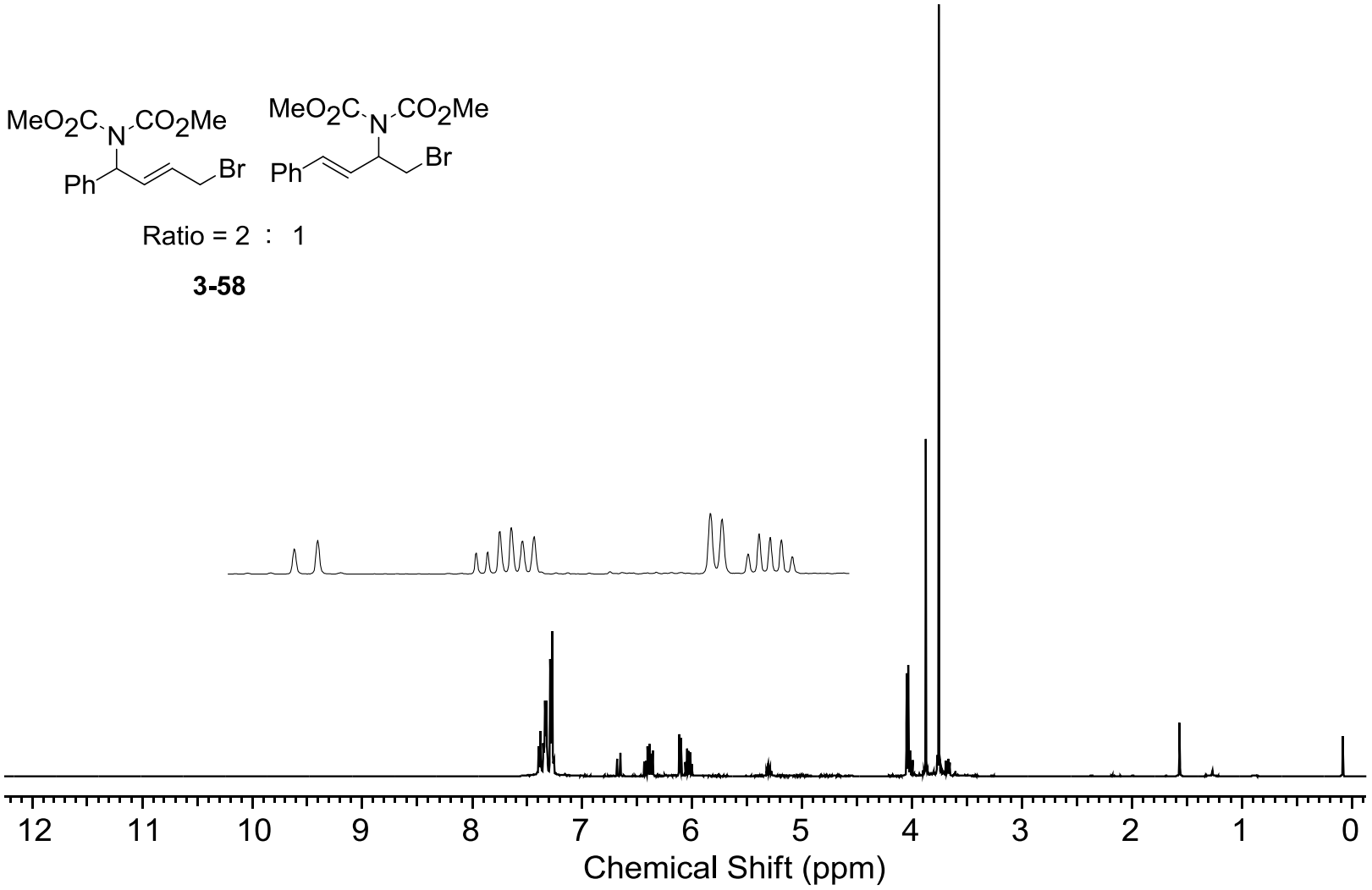


Figure 4-39: ^{1}H NMR spectrum for compound **3-58**

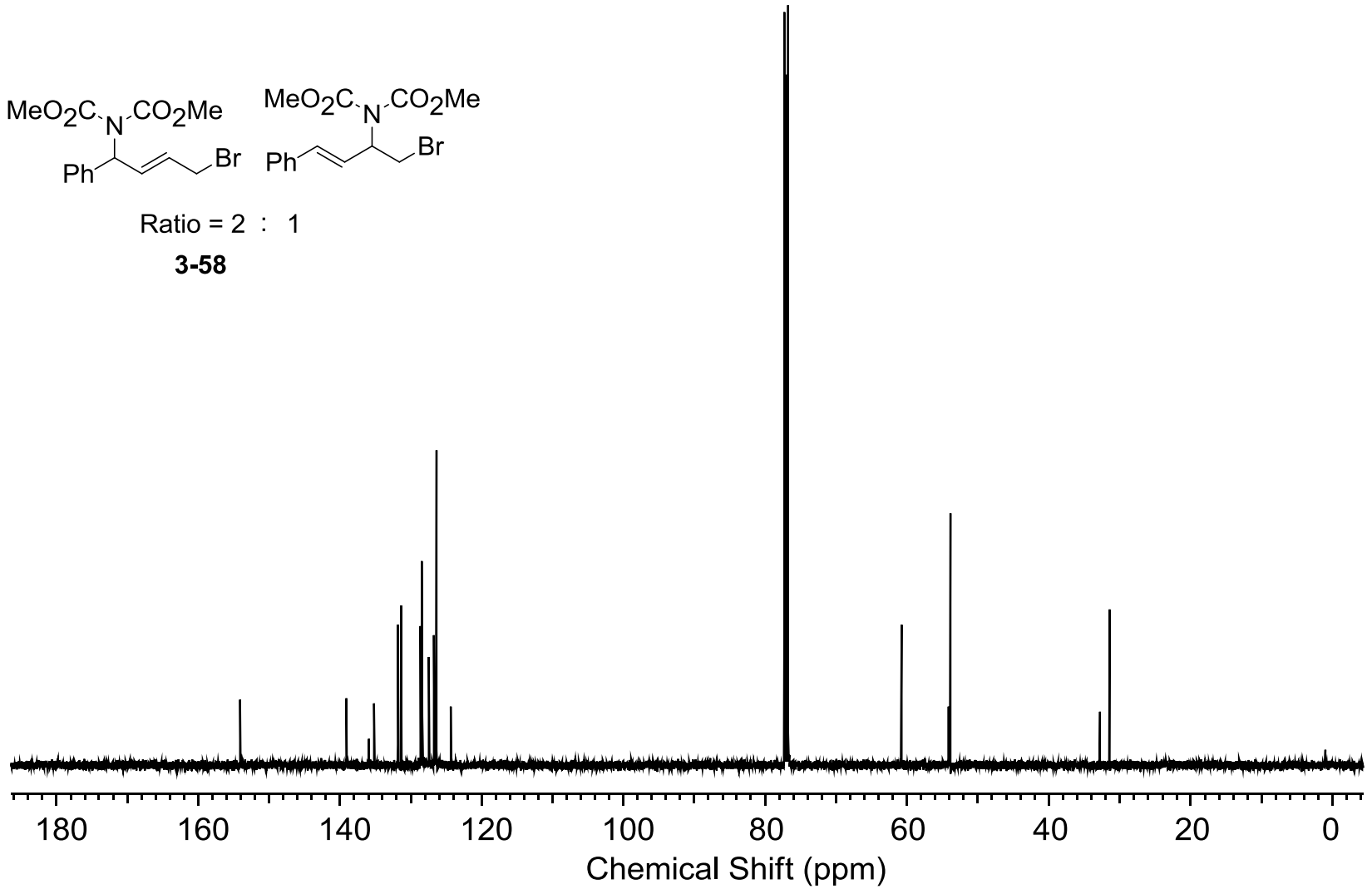


Figure 4-40: ^{13}C NMR spectrum for compound **3-58**

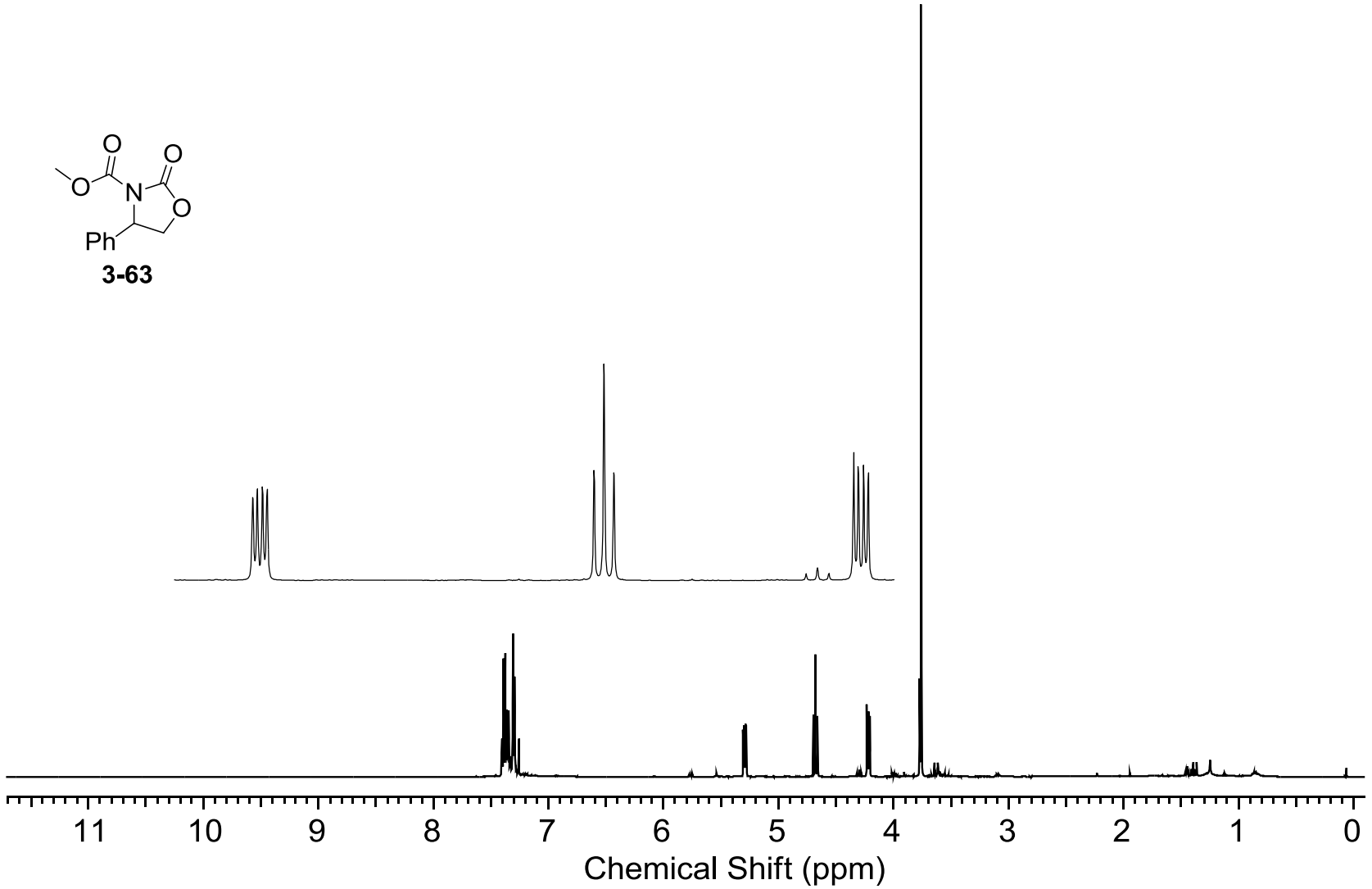


Figure 4-41: ^{1}H NMR spectrum for compound **3-63**

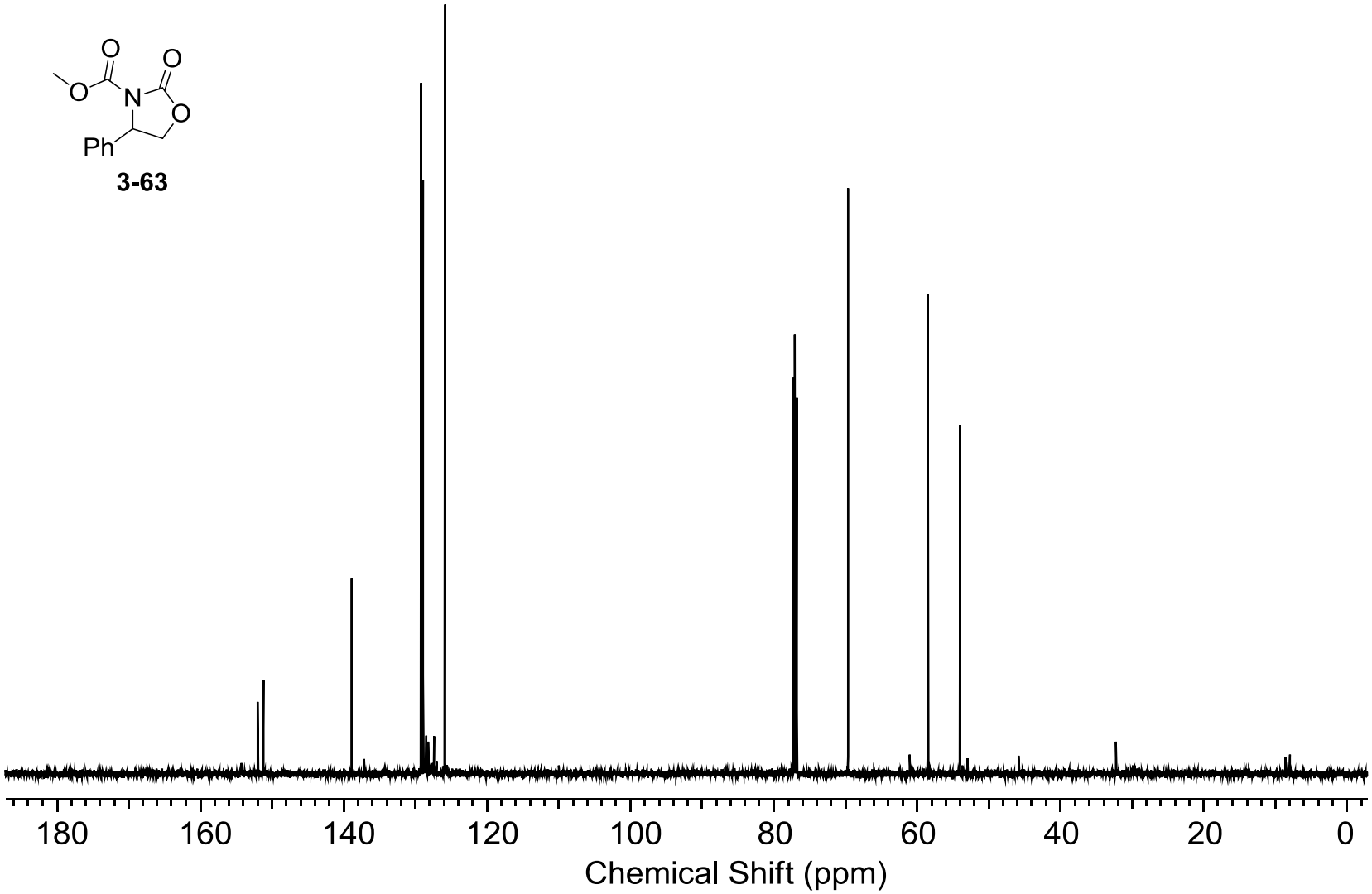


Figure 4-42: ^{13}C NMR spectrum for compound **3-63**

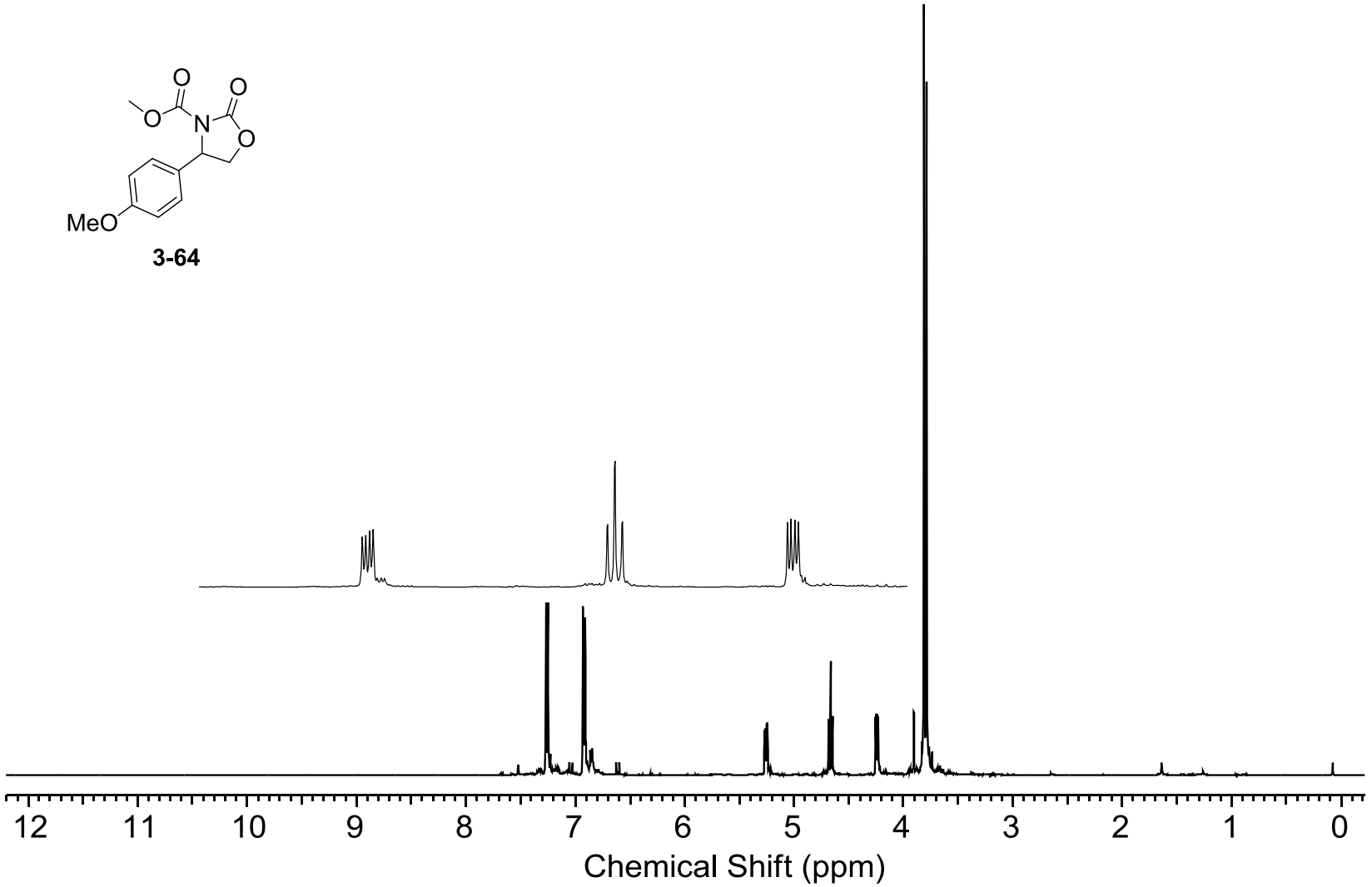


Figure 4-43: ^{1}H NMR spectrum for compound **3-64**

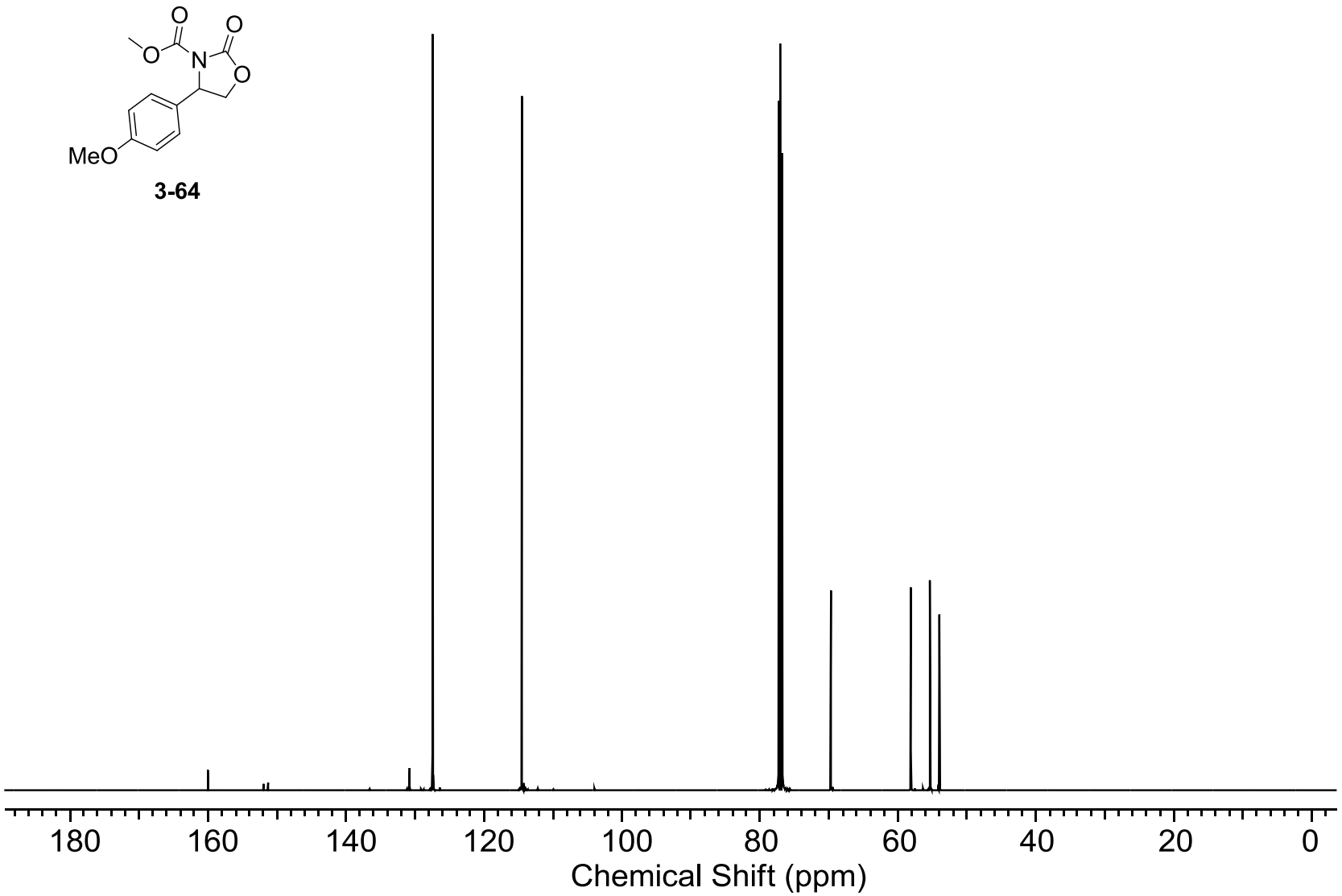


Figure 4-44: ^{13}C NMR spectrum for compound **3-64**

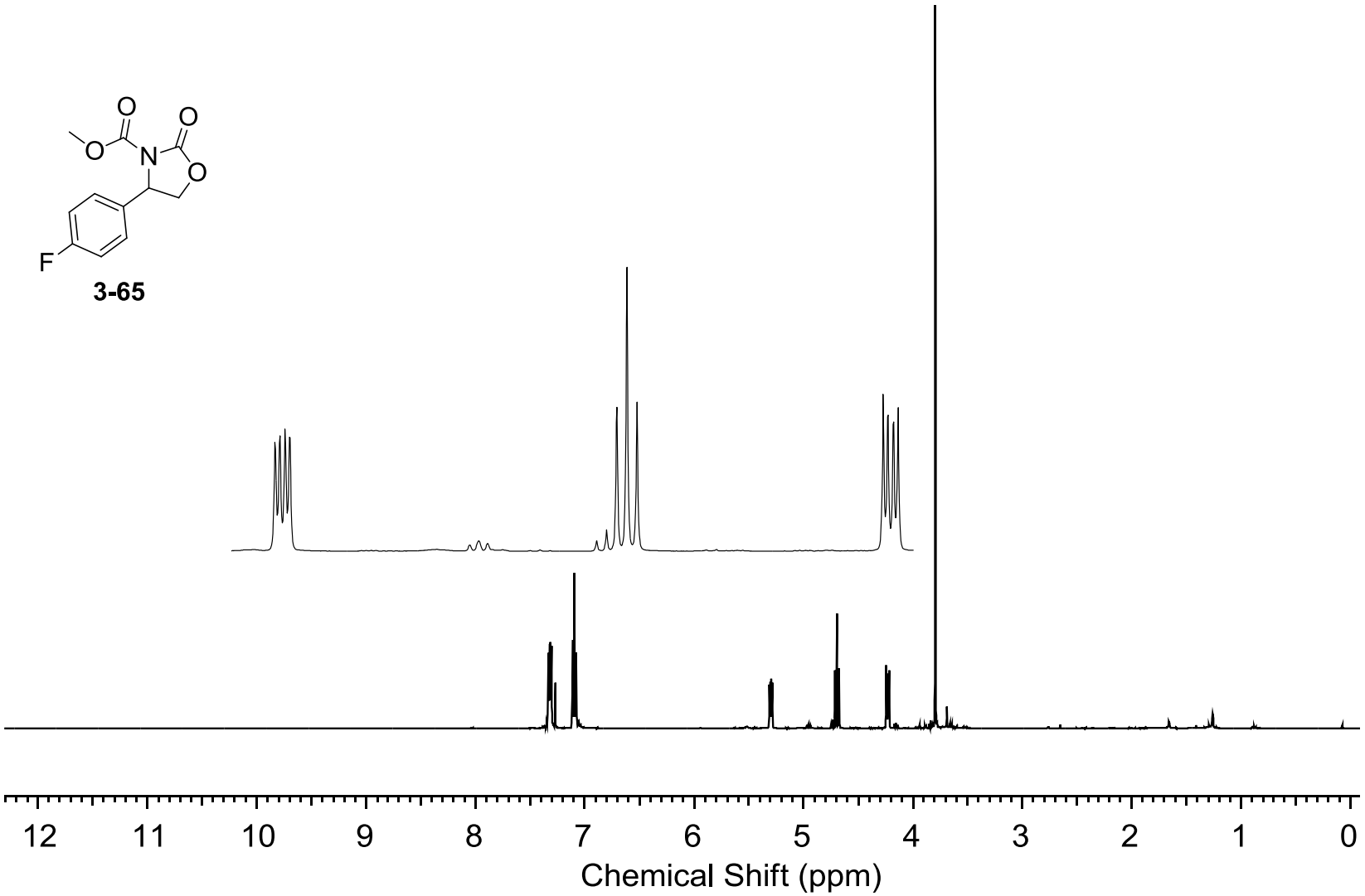


Figure 4-45: ^{1}H NMR spectrum for compound **3-65**

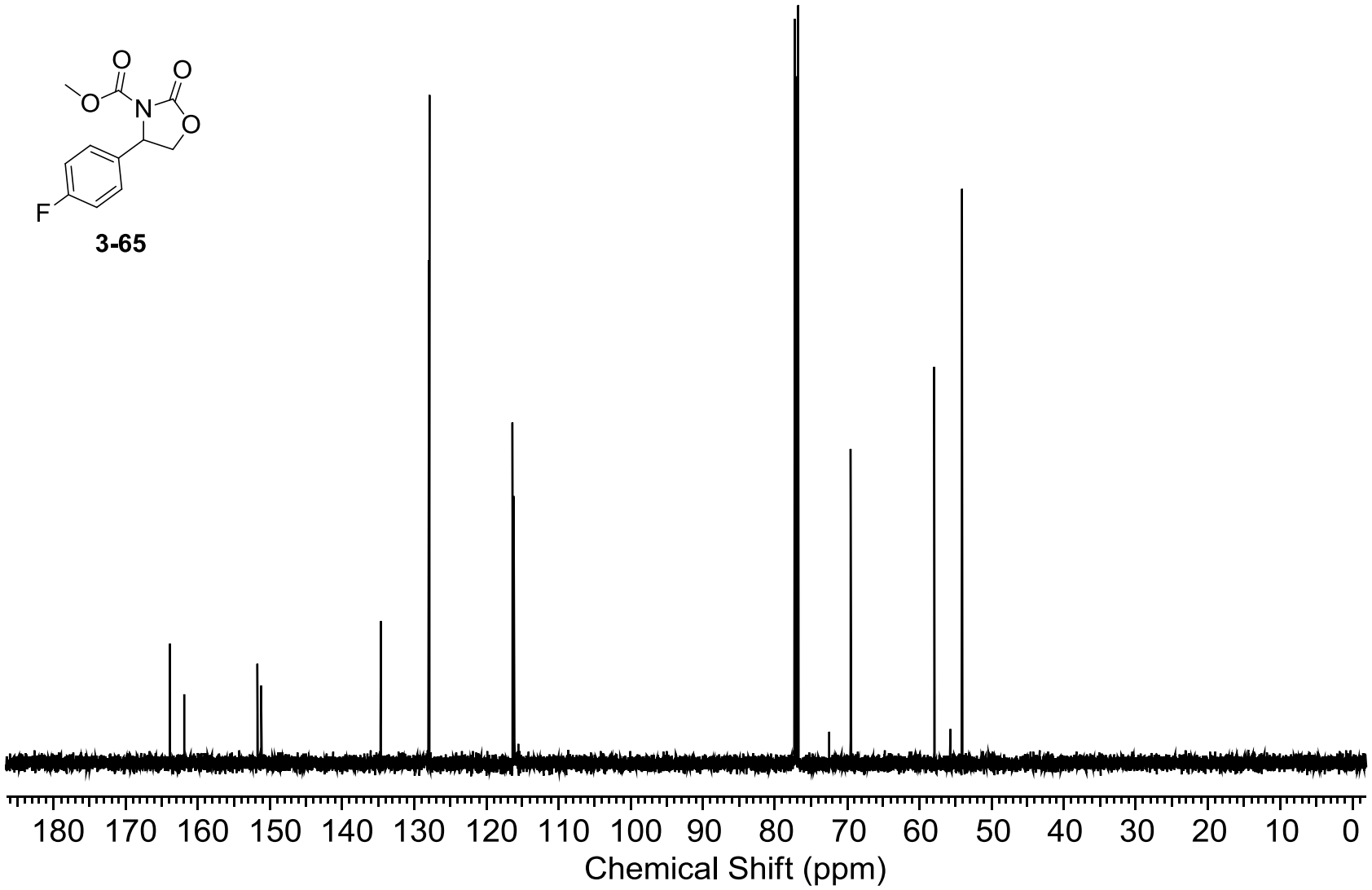
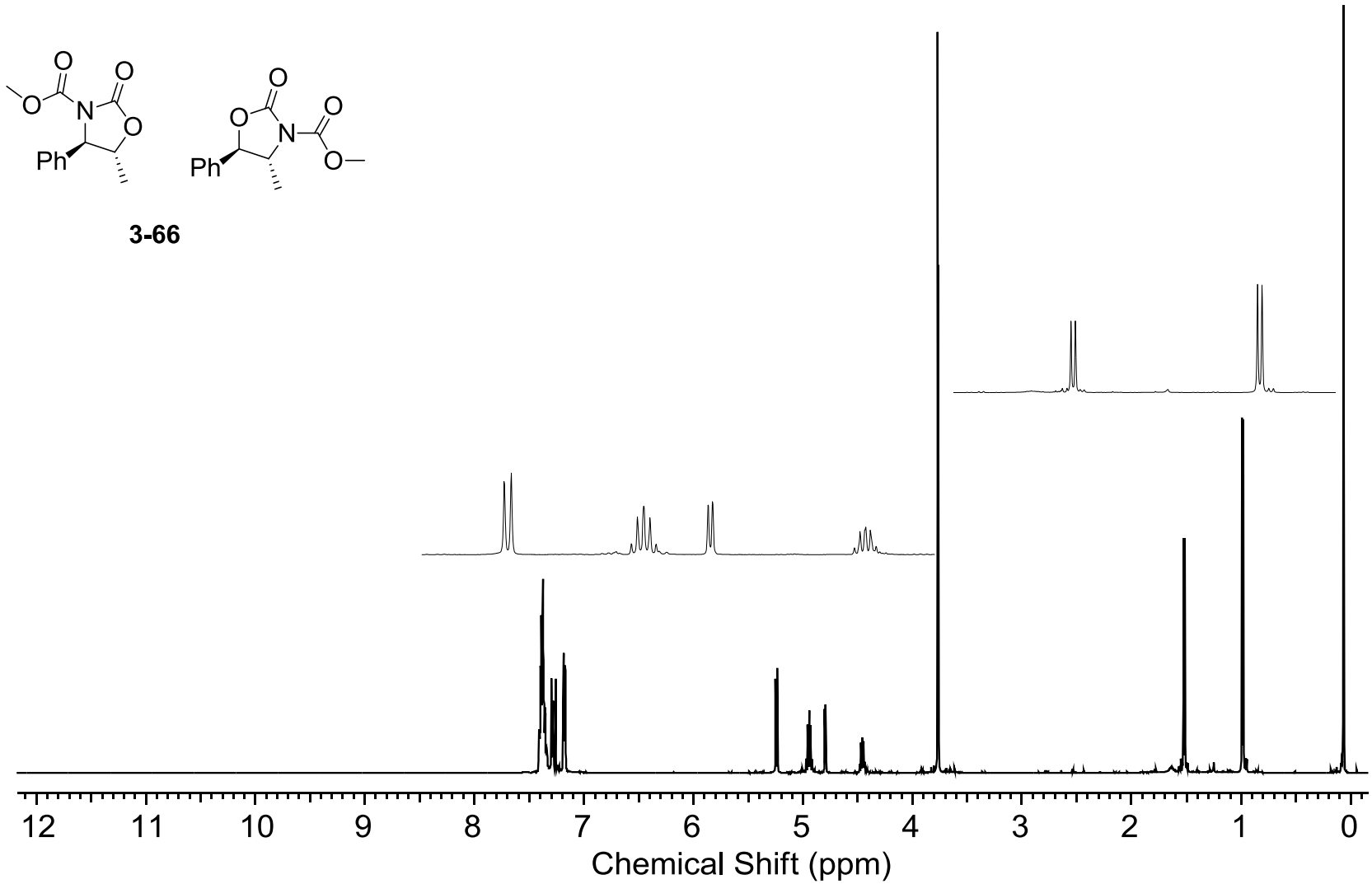


Figure 4-46: ^{13}C NMR spectrum for compound **3-65**



3-66

Figure 4-47: ^{1}H NMR spectrum for compound **3-66**

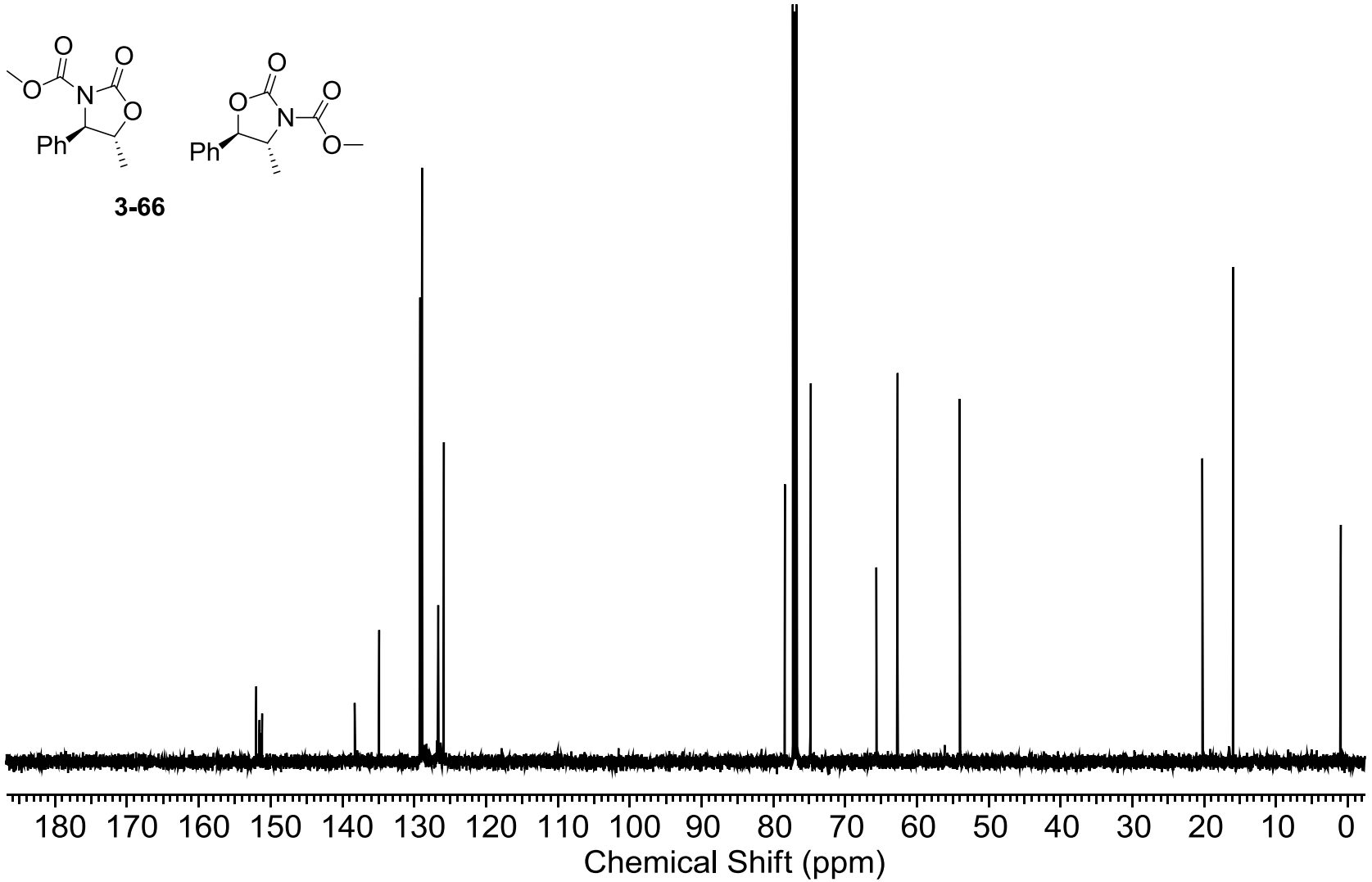
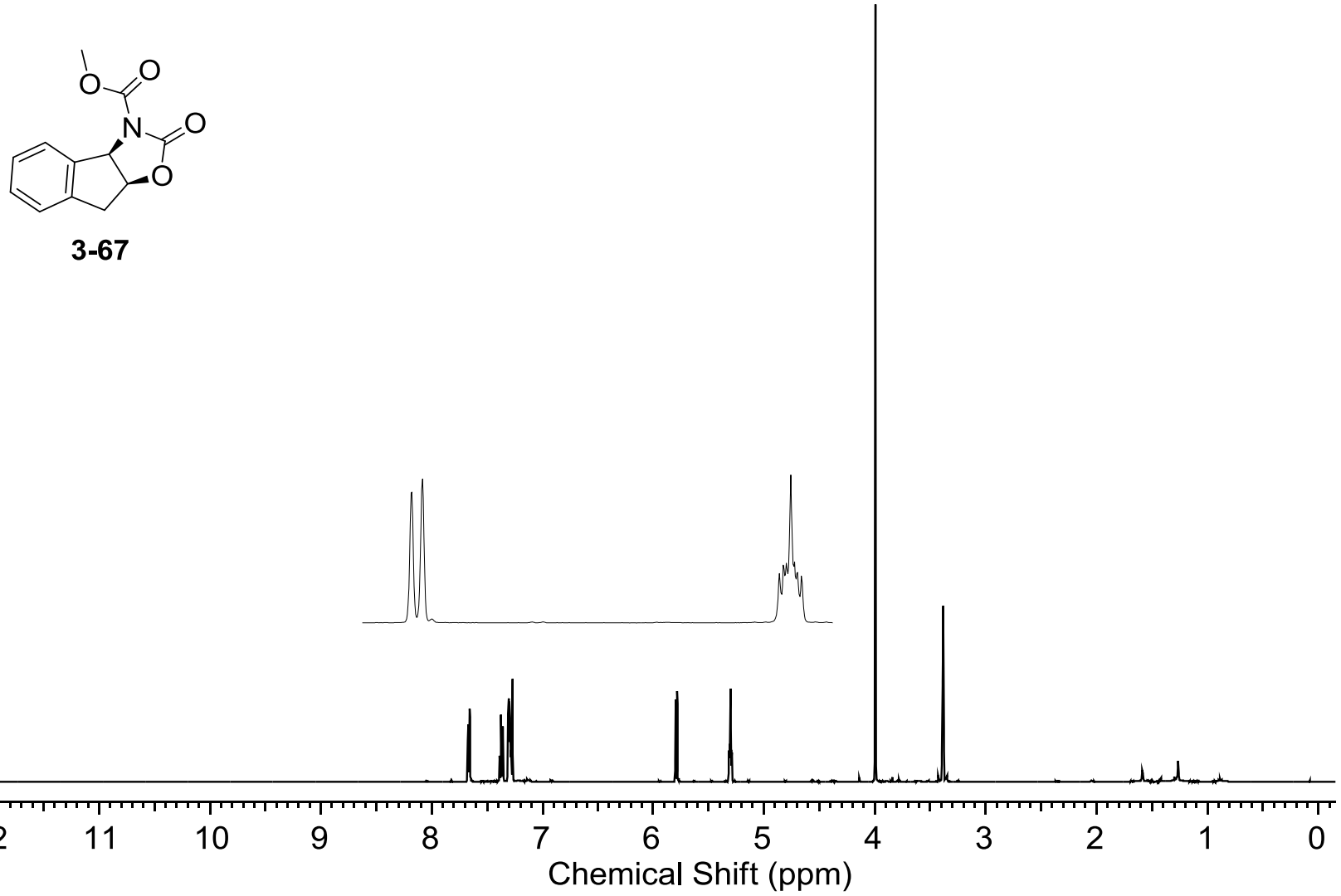
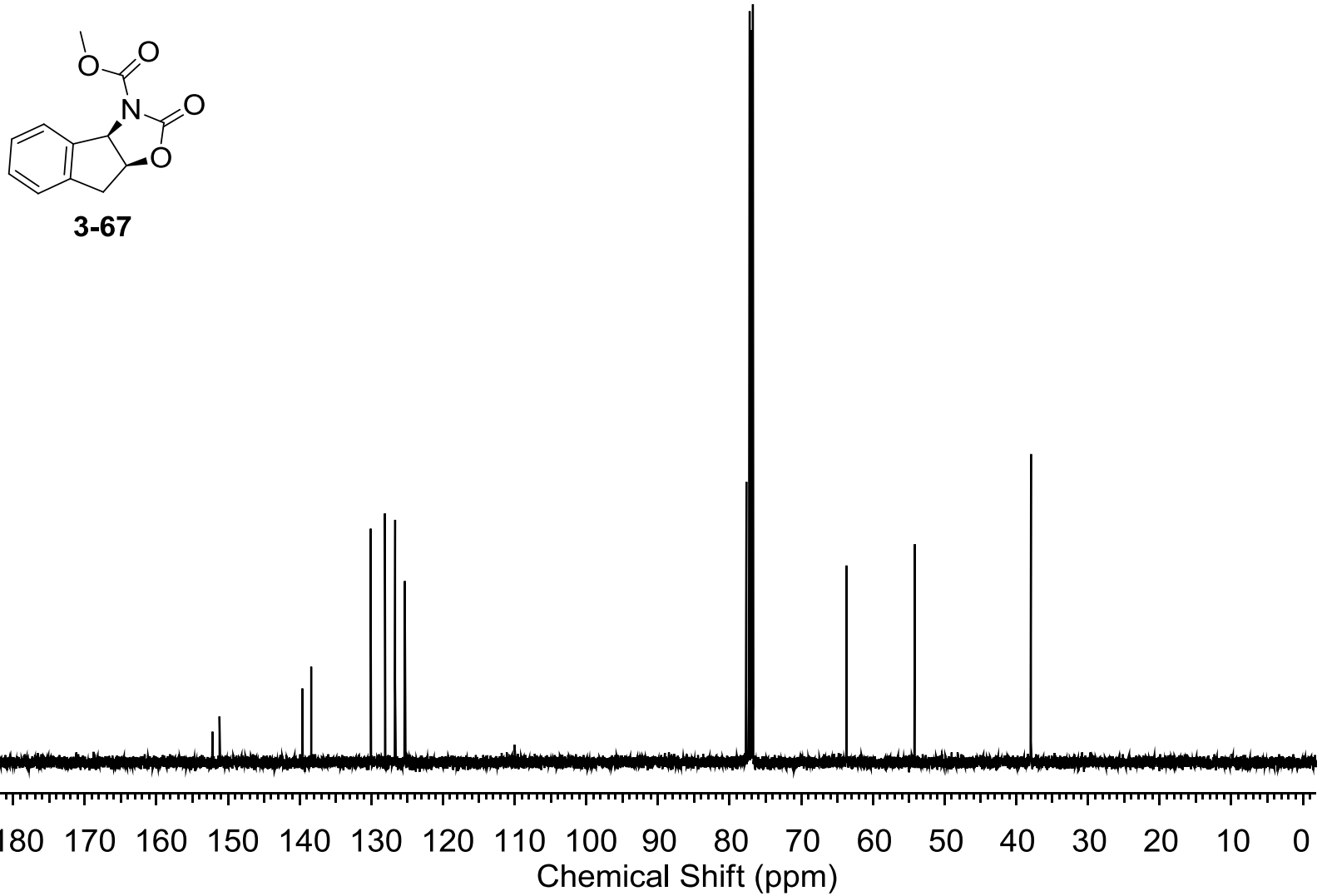


Figure 4-48: ^{13}C NMR spectrum for compound **3-66**



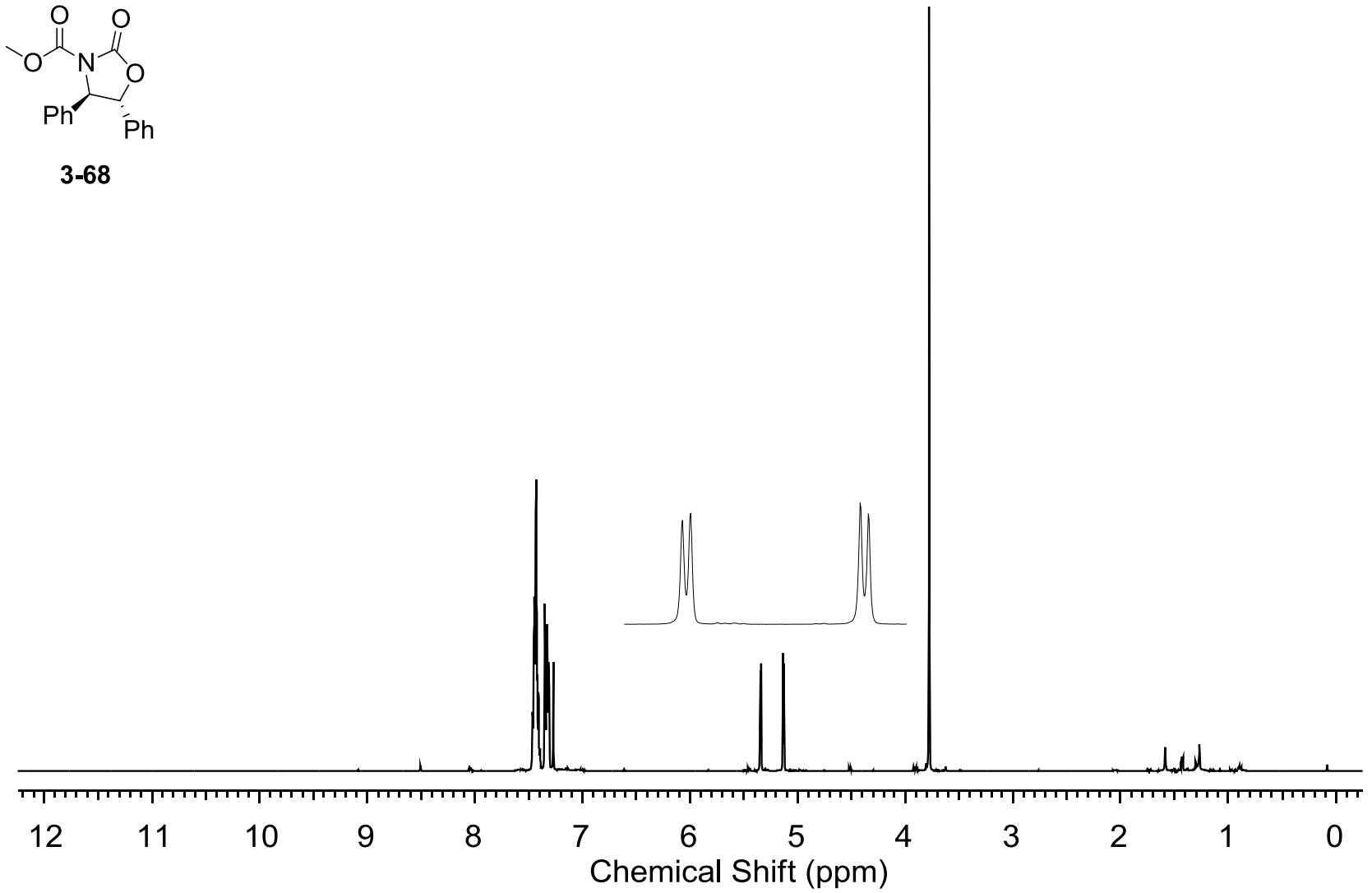
3-67

Figure 4-49: ^{1}H NMR spectrum for compound **3-67**



3-67

Figure 4-50: ^{13}C NMR spectrum for compound **3-67**



3-68

Figure 4-51: ^{1}H NMR spectrum for compound **3-68**

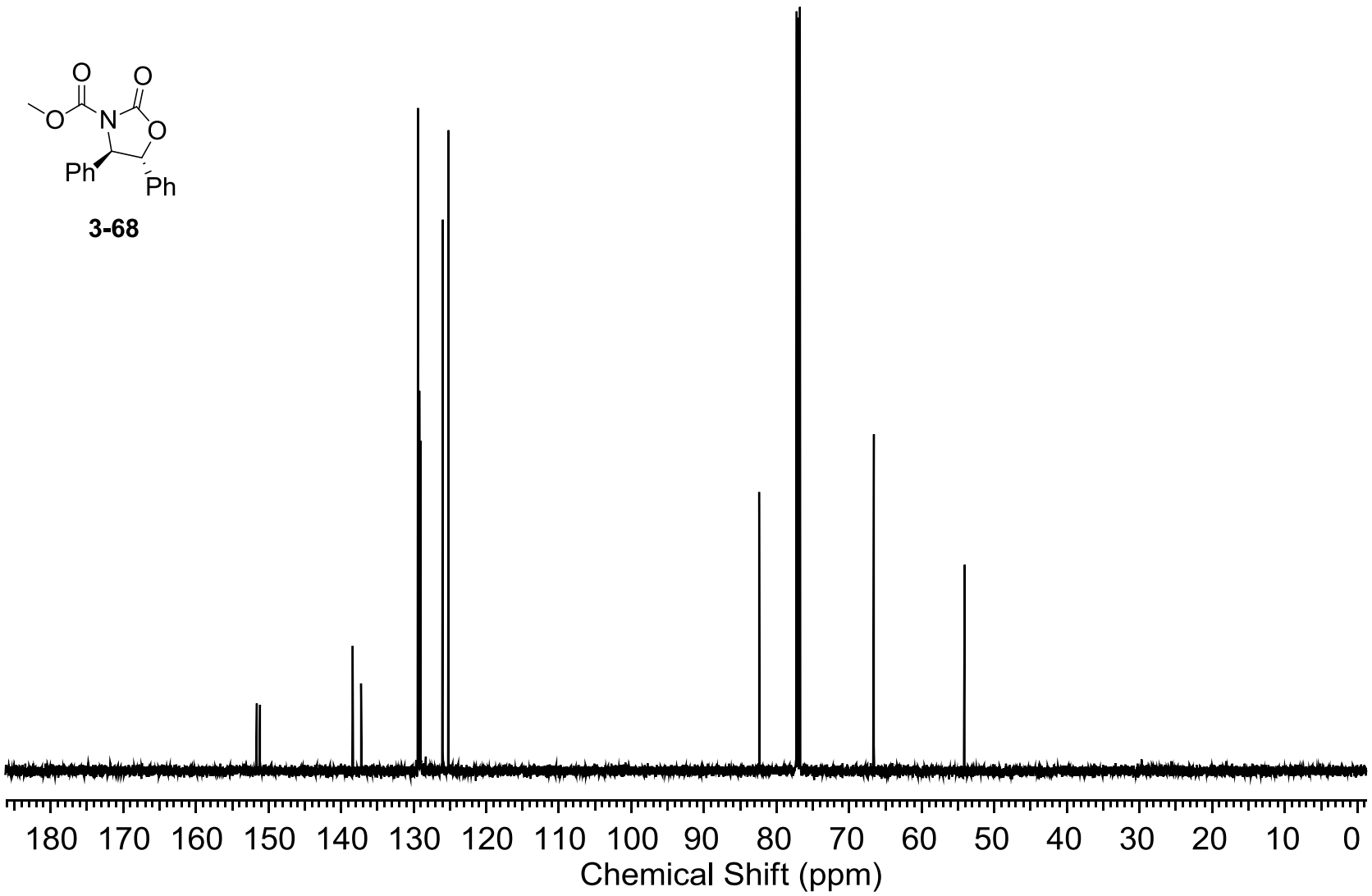
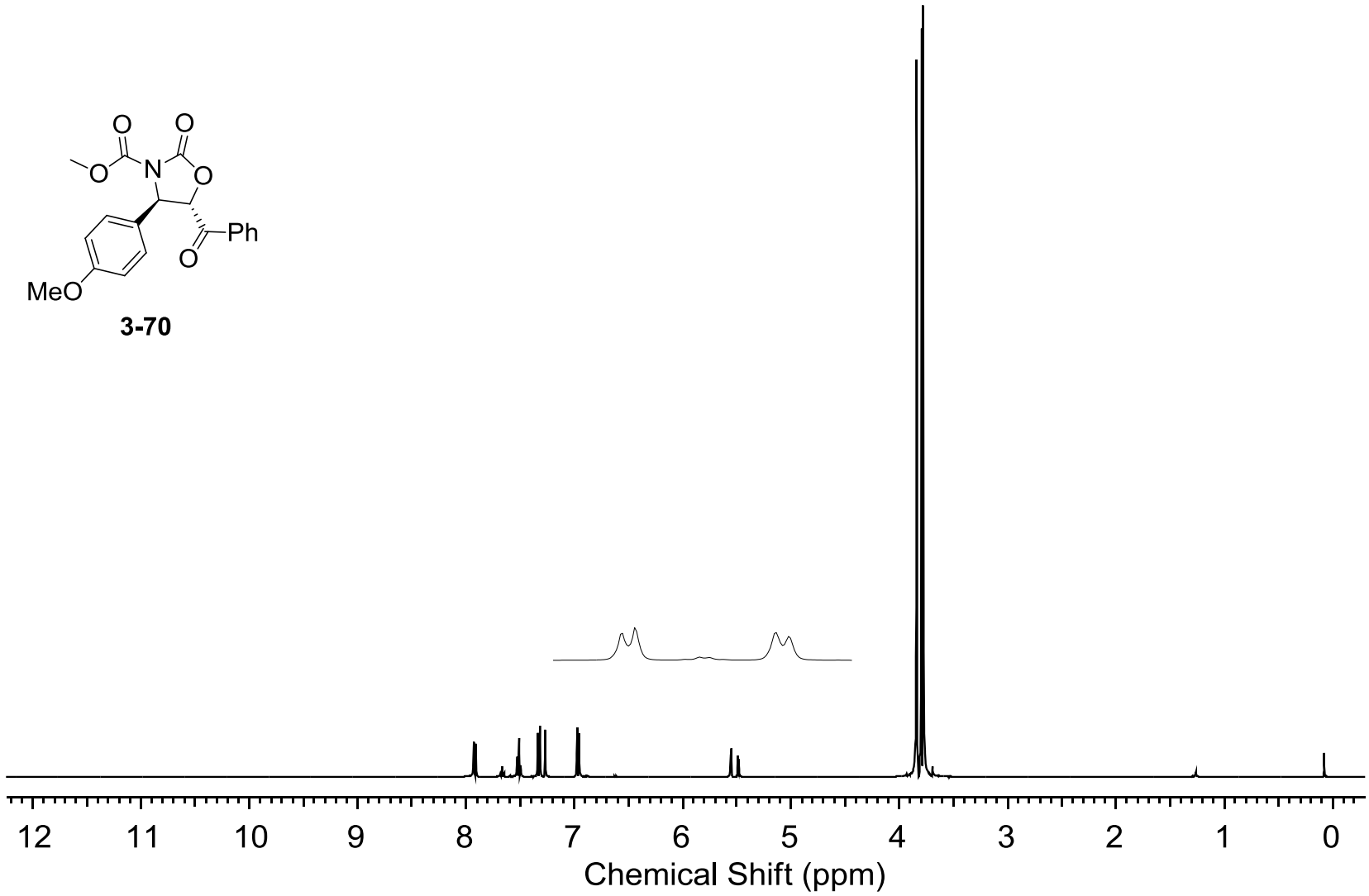


Figure 4-52: ^{13}C NMR spectrum for compound **3-68**



3-70

Figure 4-53: ^{1}H NMR spectrum for compound **3-70**

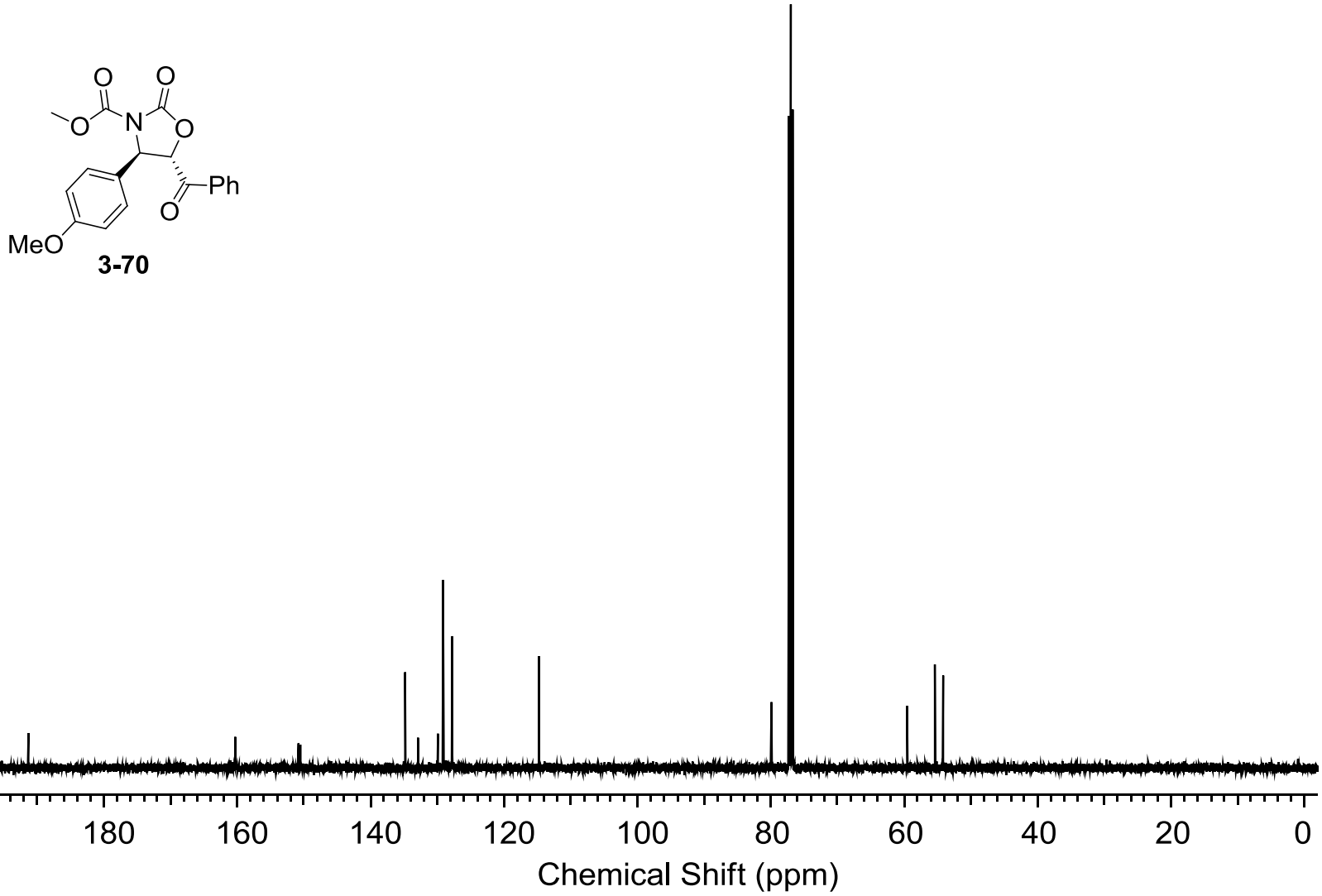


Figure 4-54: ^{13}C NMR spectrum for compound **3-70**

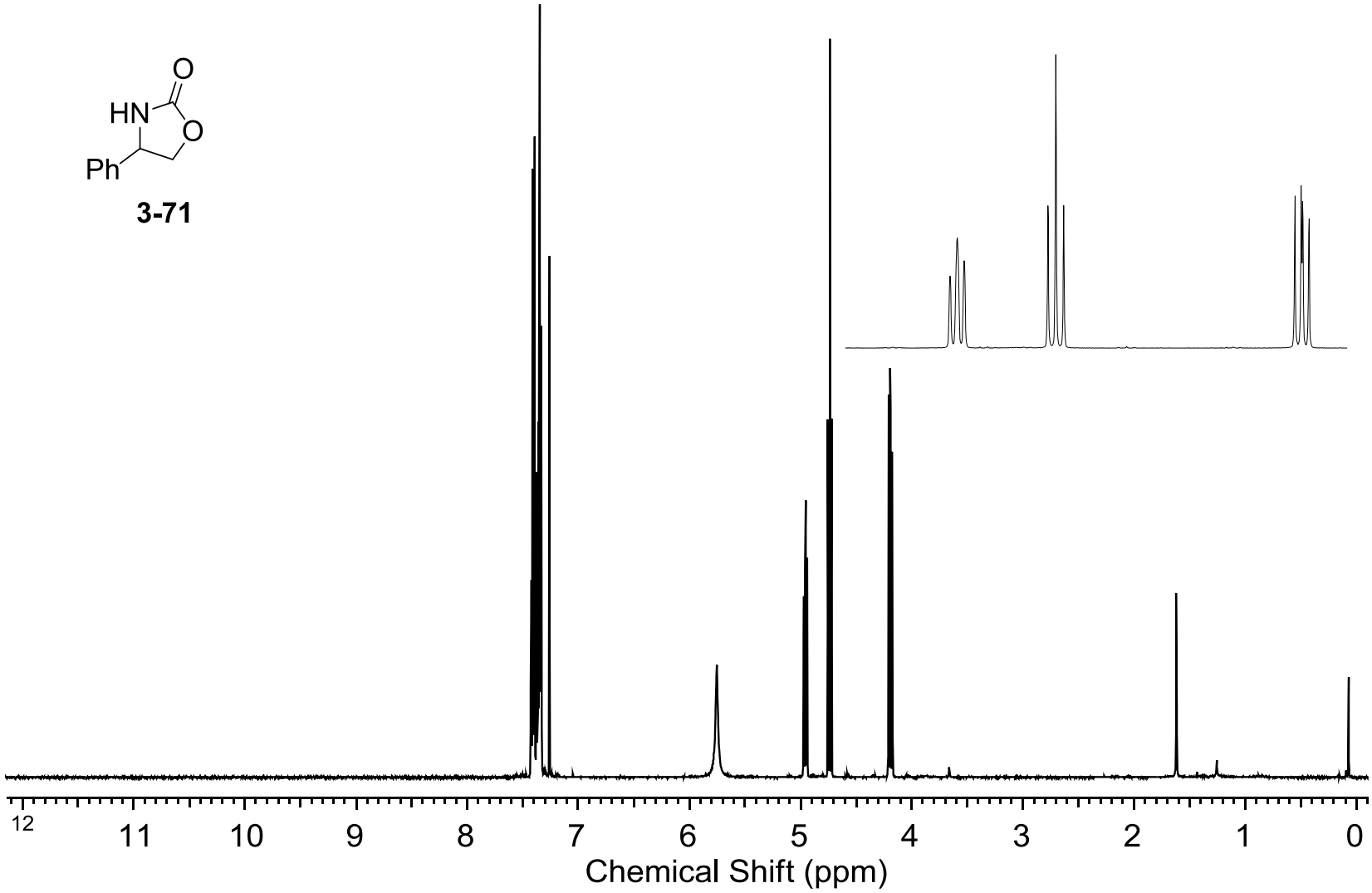


Figure 4-55: ^{1}H NMR spectrum for compound **3-71**

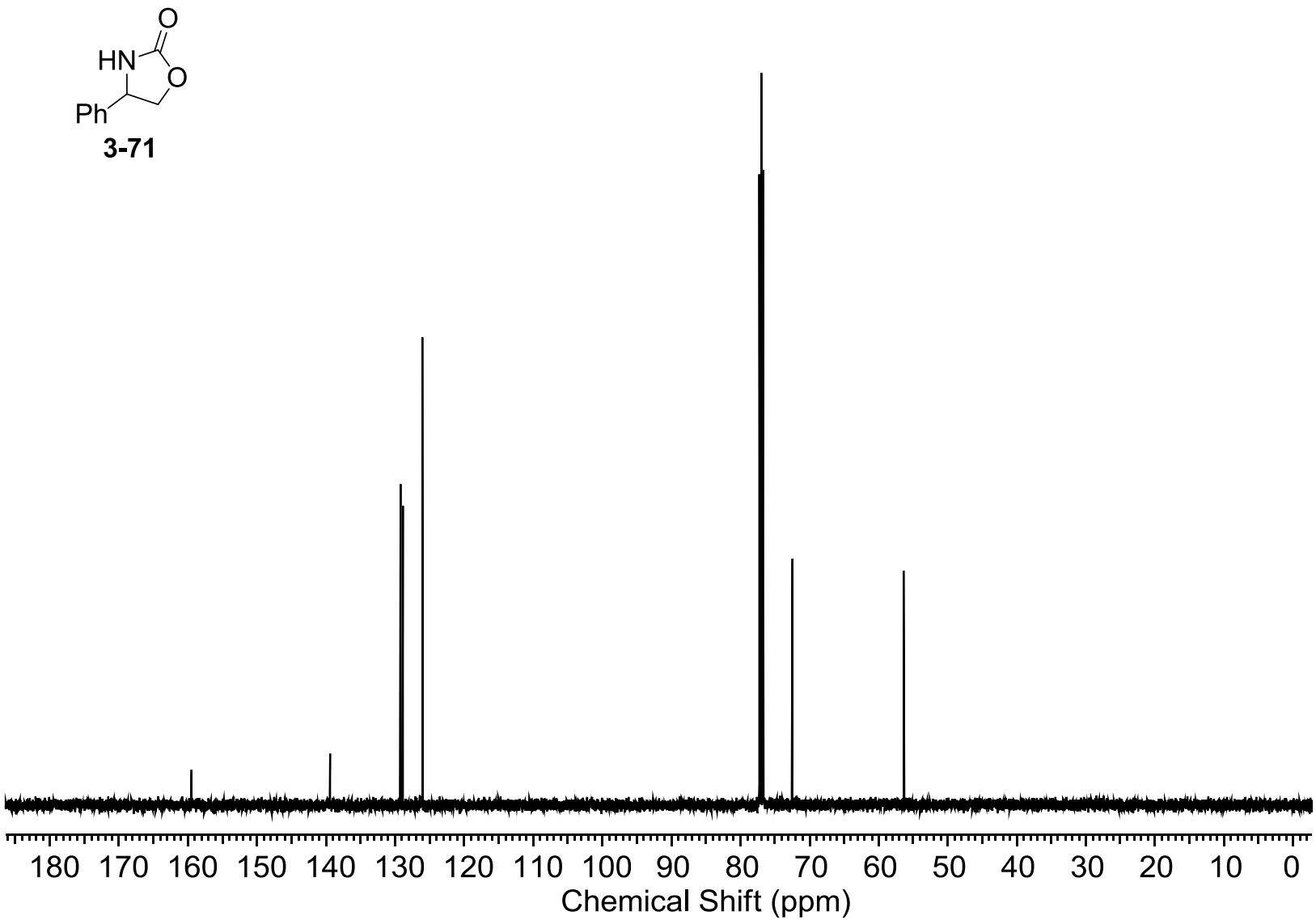
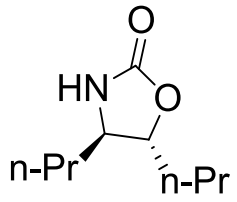


Figure 4-56: ^{13}C NMR spectrum for compound **3-71**



3-72

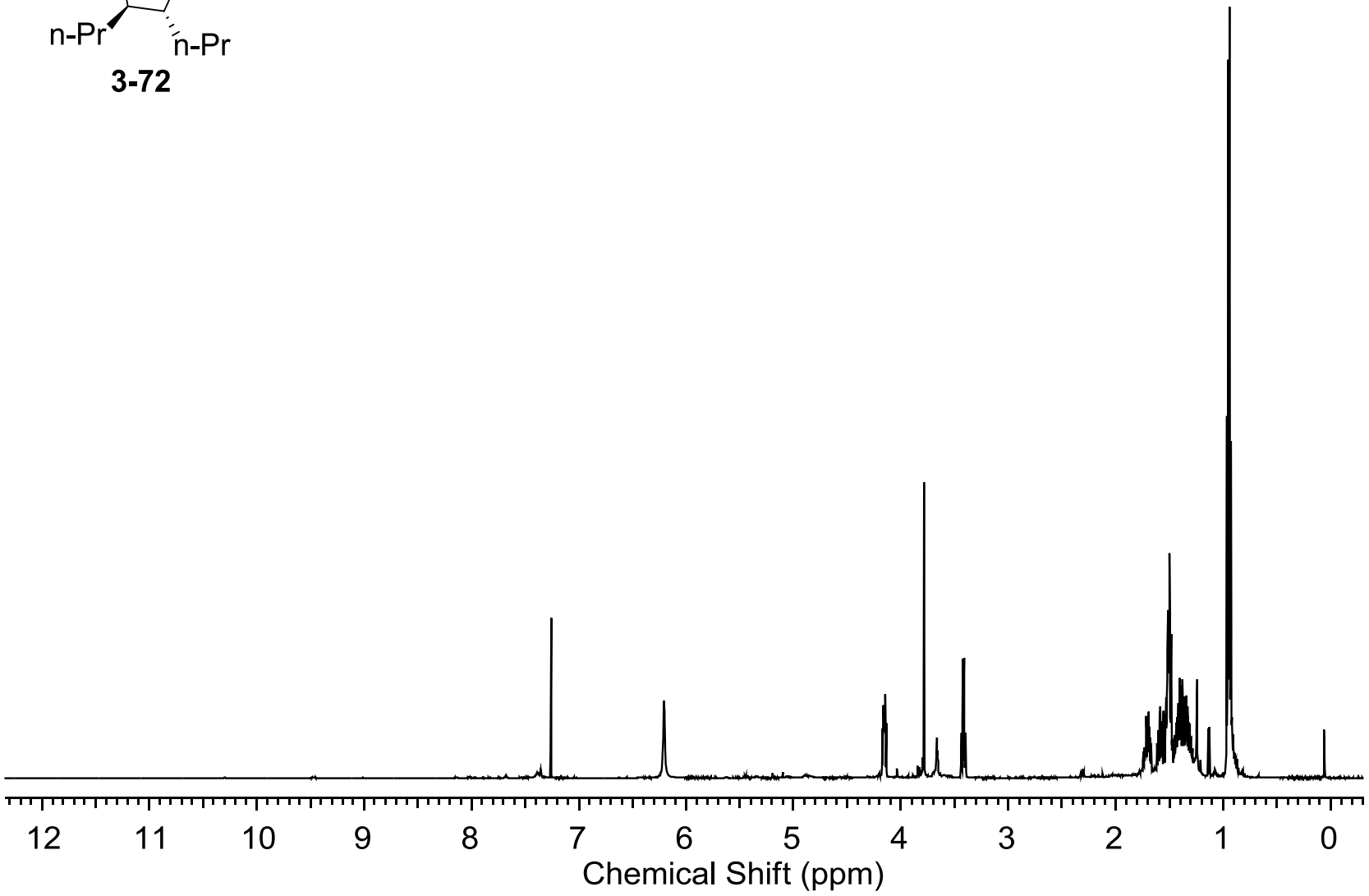


Figure 4-57: ^{1}H NMR spectrum for compound **3-72**

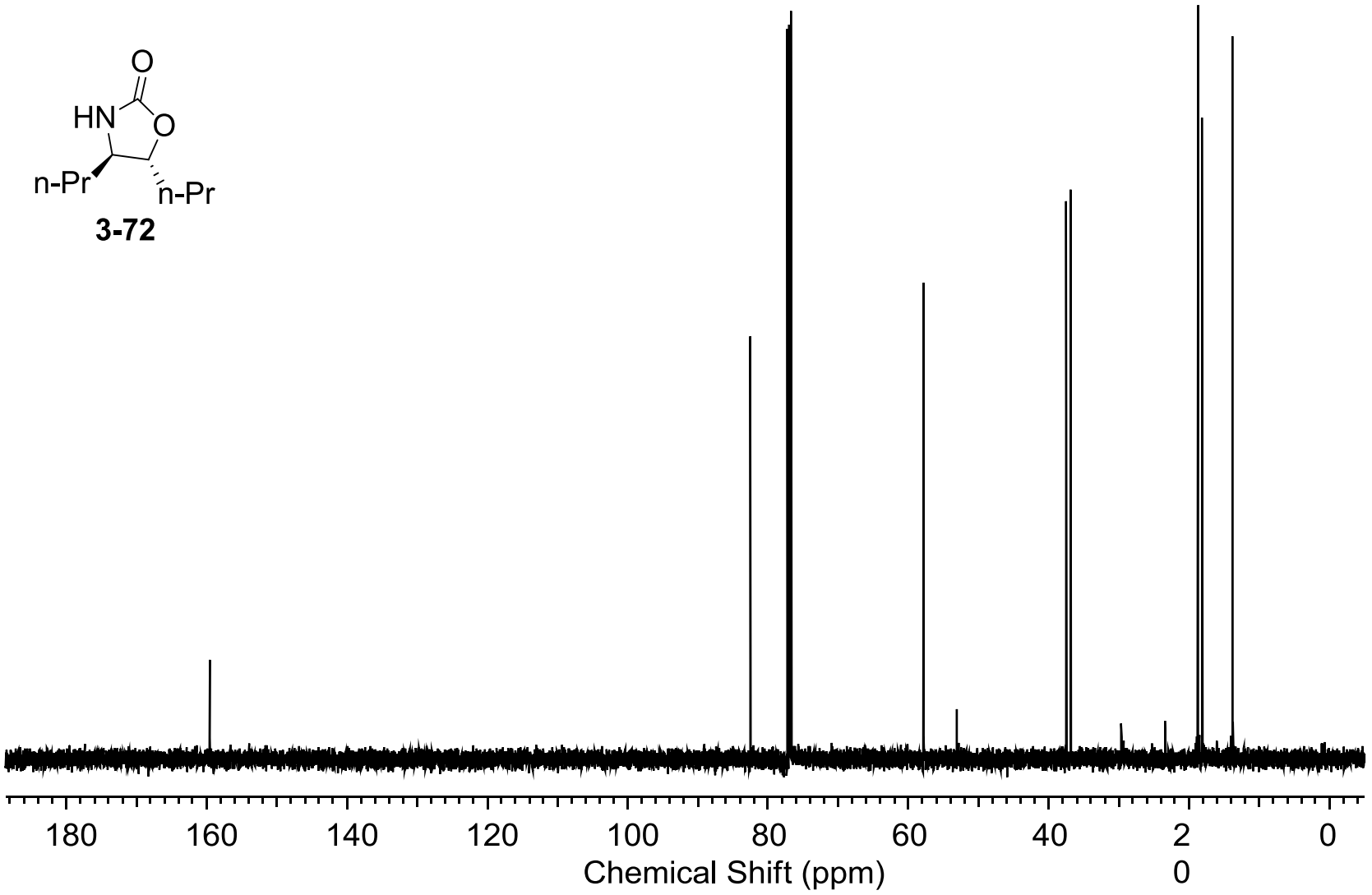


Figure 4-58: ^{13}C NMR spectrum for compound **3-72**

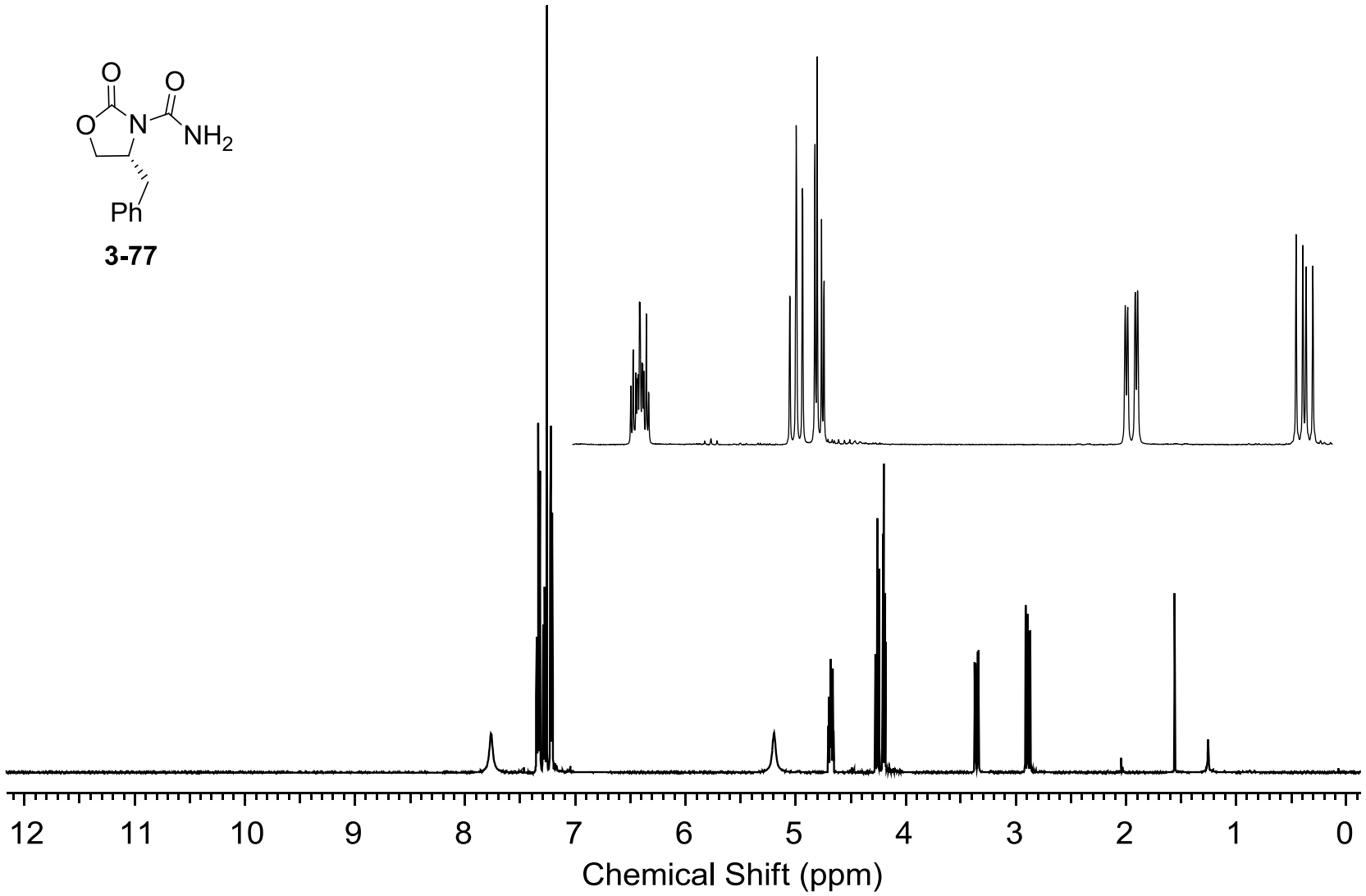


Figure 4-59: ^{1}H NMR spectrum for compound **3-77**

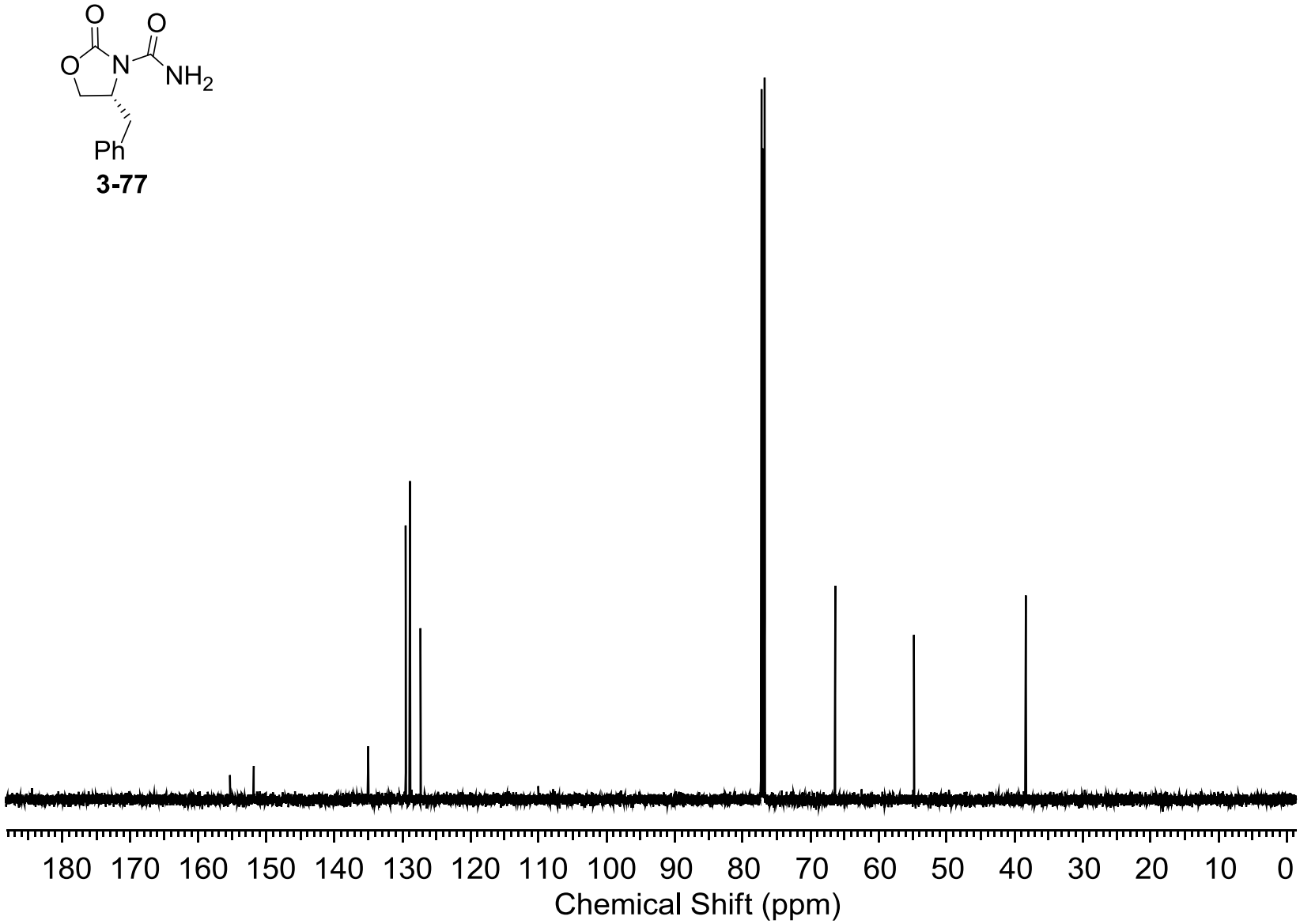


Figure 4-60: ^{13}C NMR spectrum for compound **3-77**

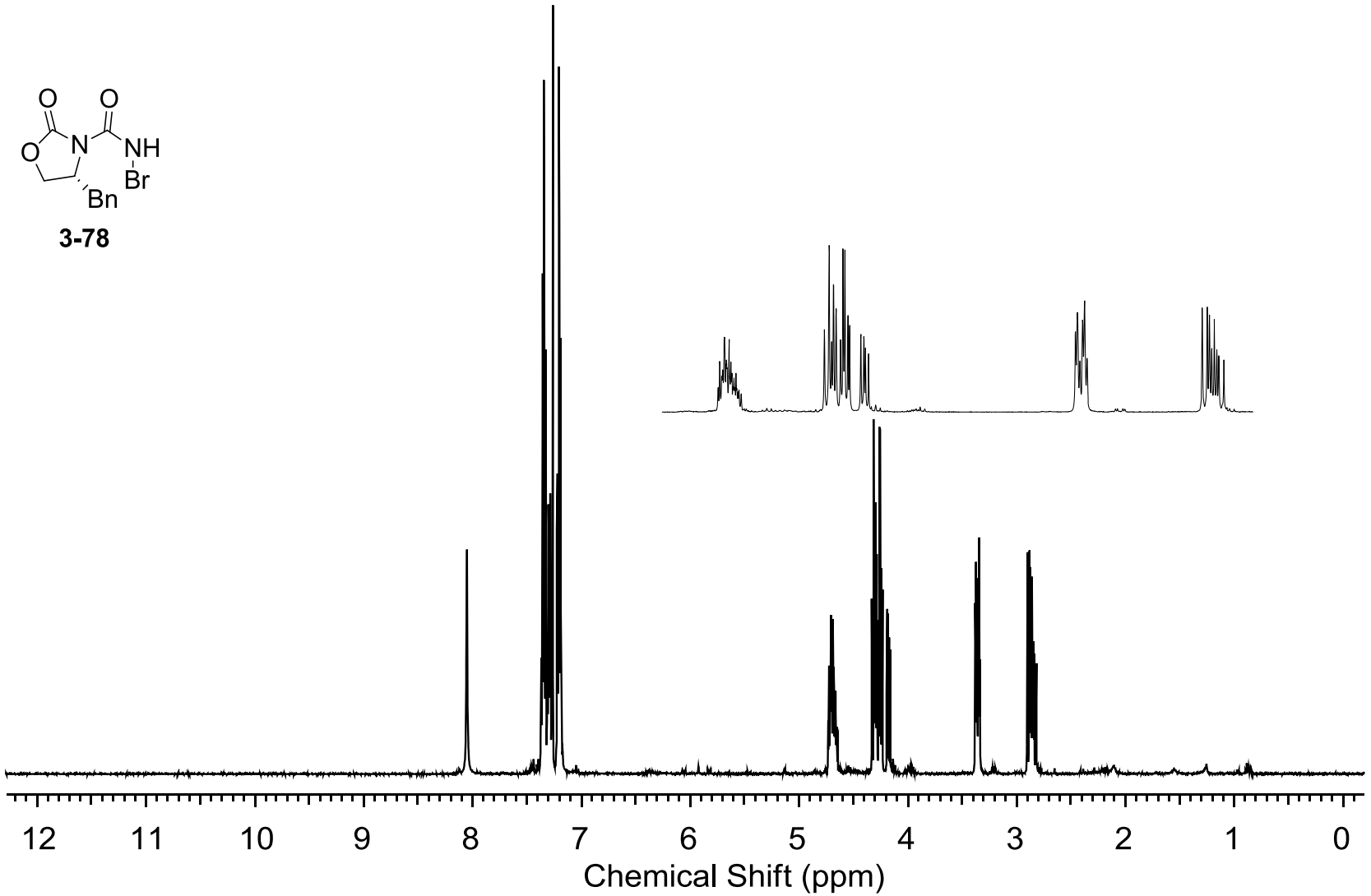


Figure 4-61: ^{1}H NMR spectrum for compound **3-78**

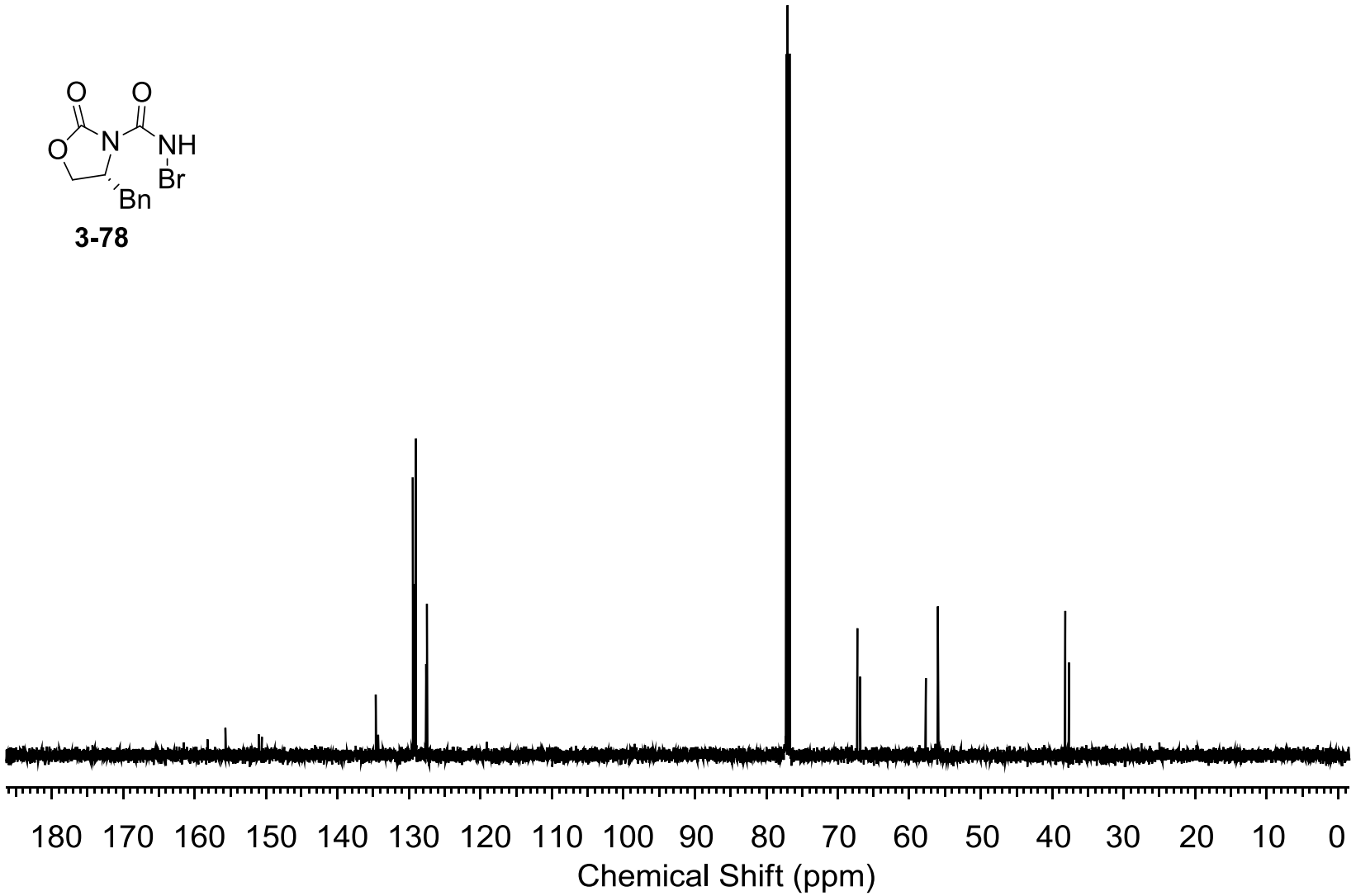


Figure 4-62: ^{13}C NMR spectrum for compound **3-78**

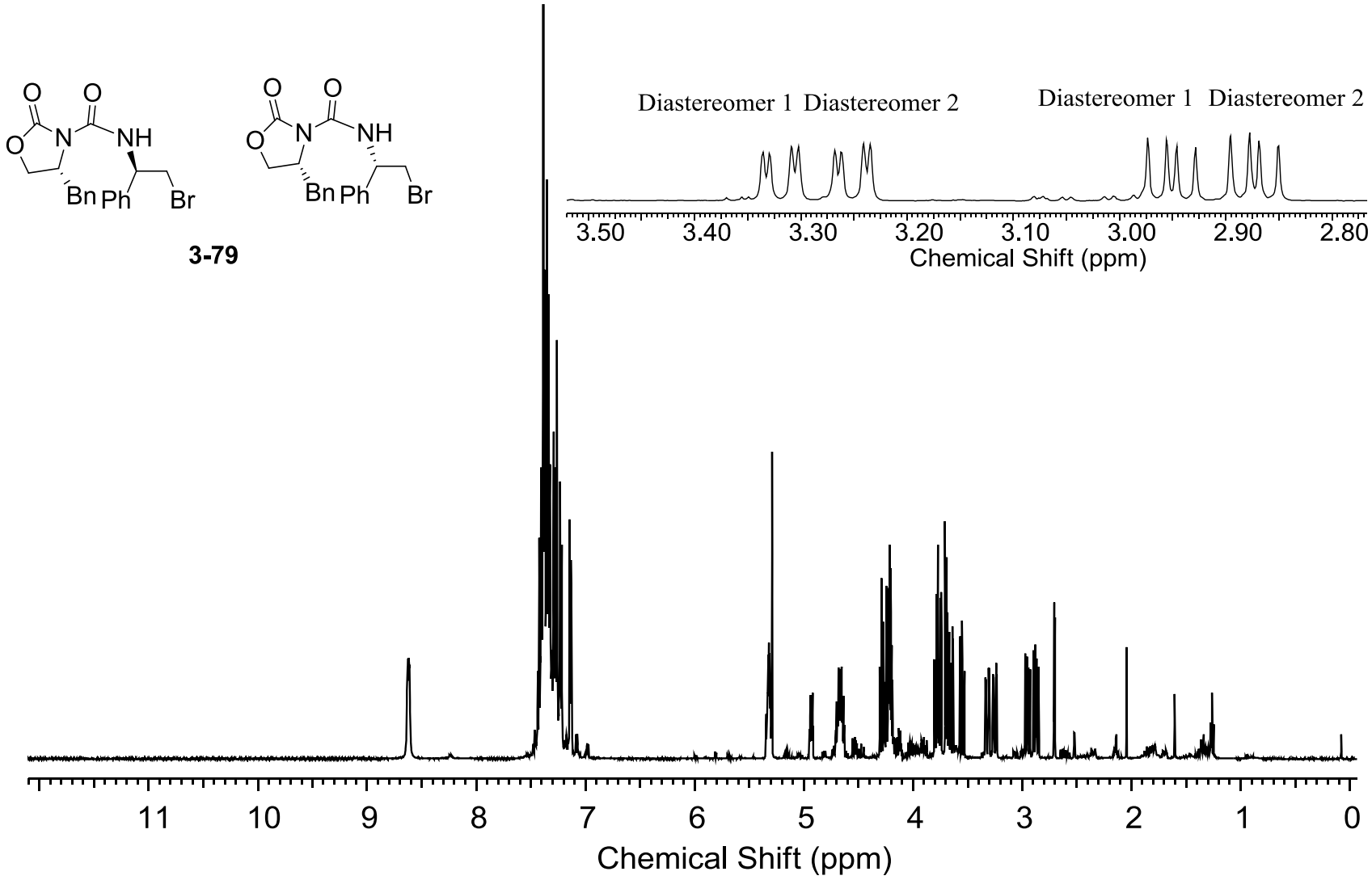


Figure 4-63: ^{1}H NMR spectrum for compound **3-79**

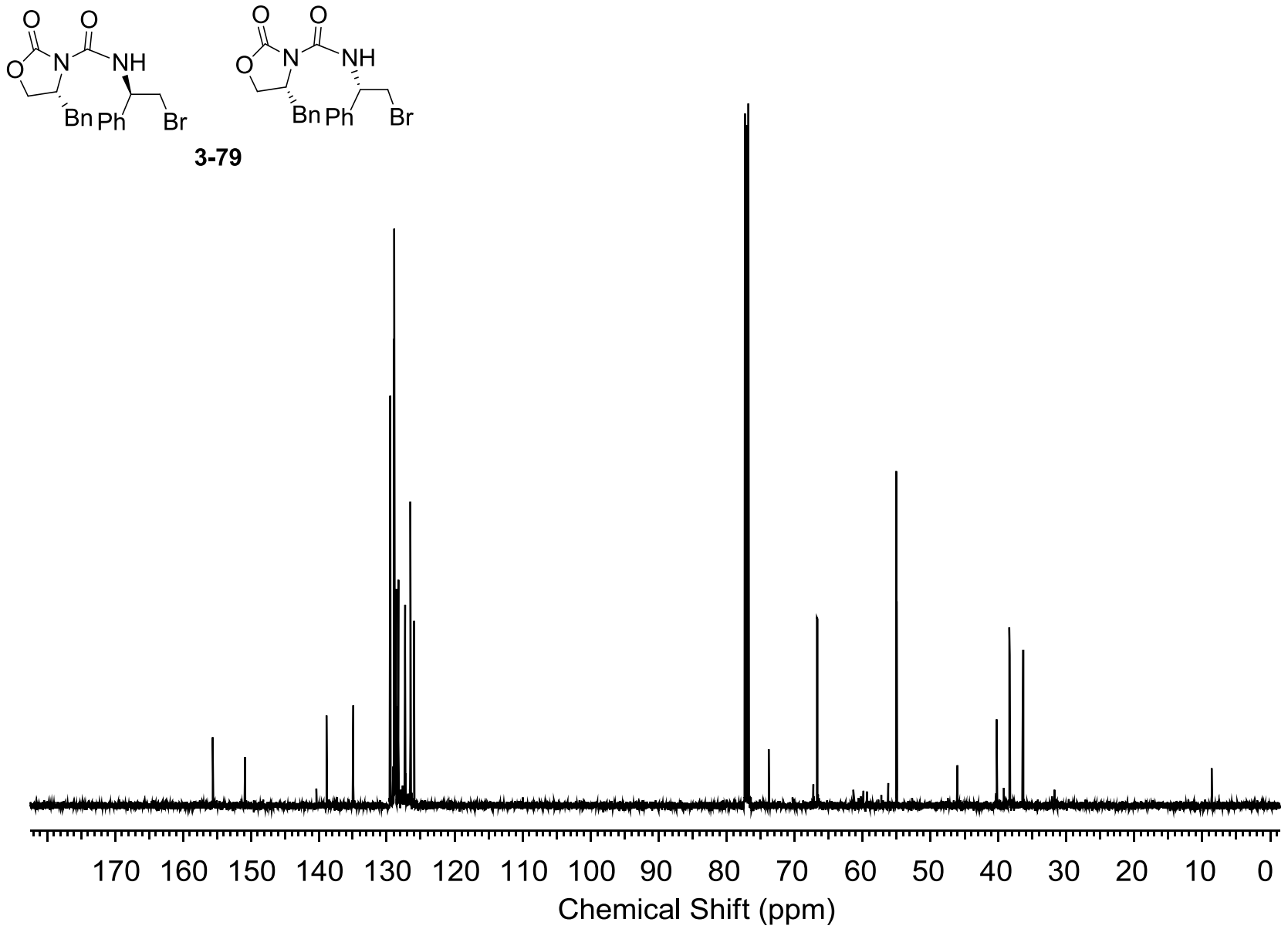


Figure 4-64: ^{13}C NMR spectrum for compound **3-79**

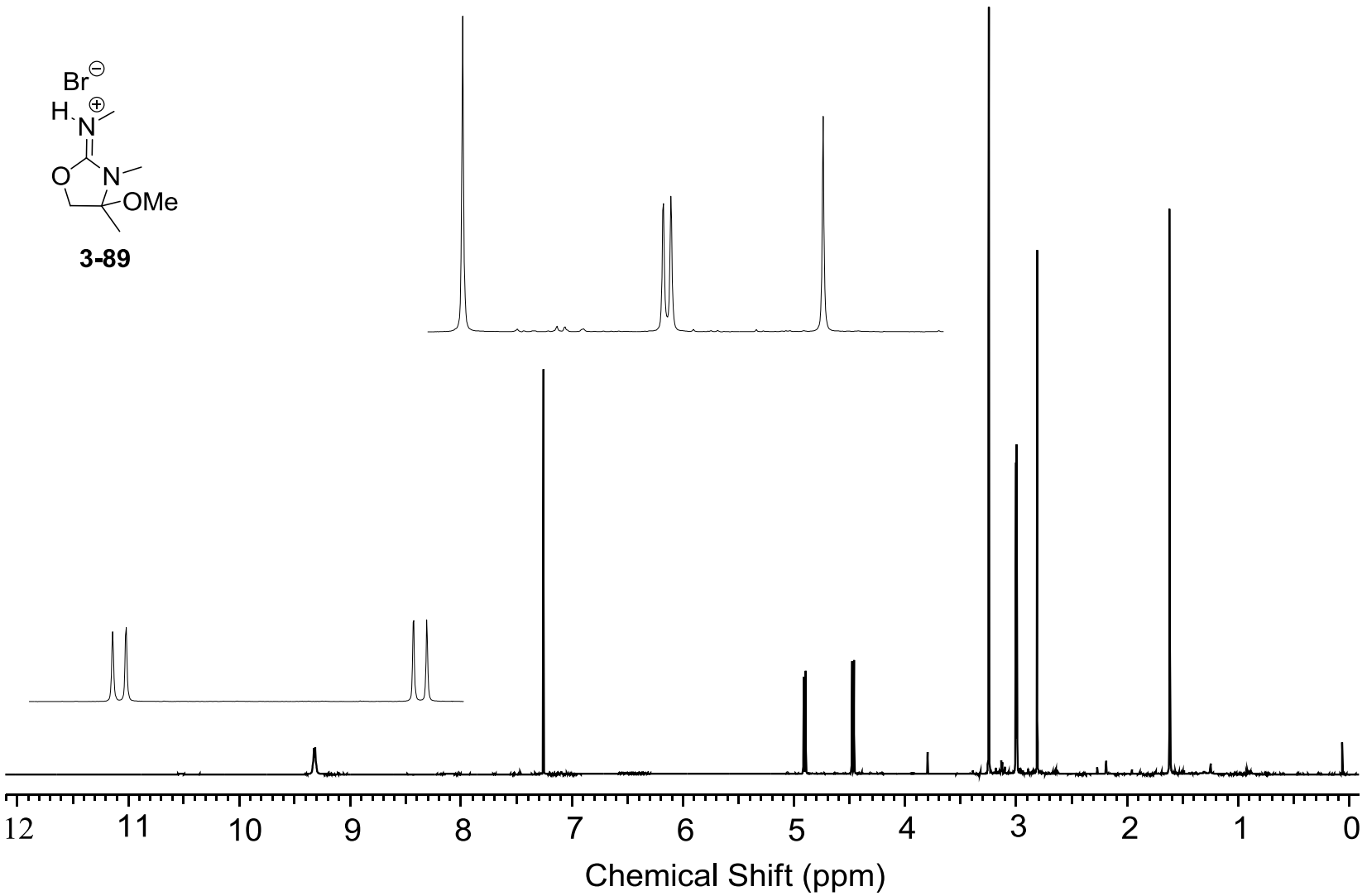


Figure 4-65: ^{1}H NMR spectrum for compound **3-89**

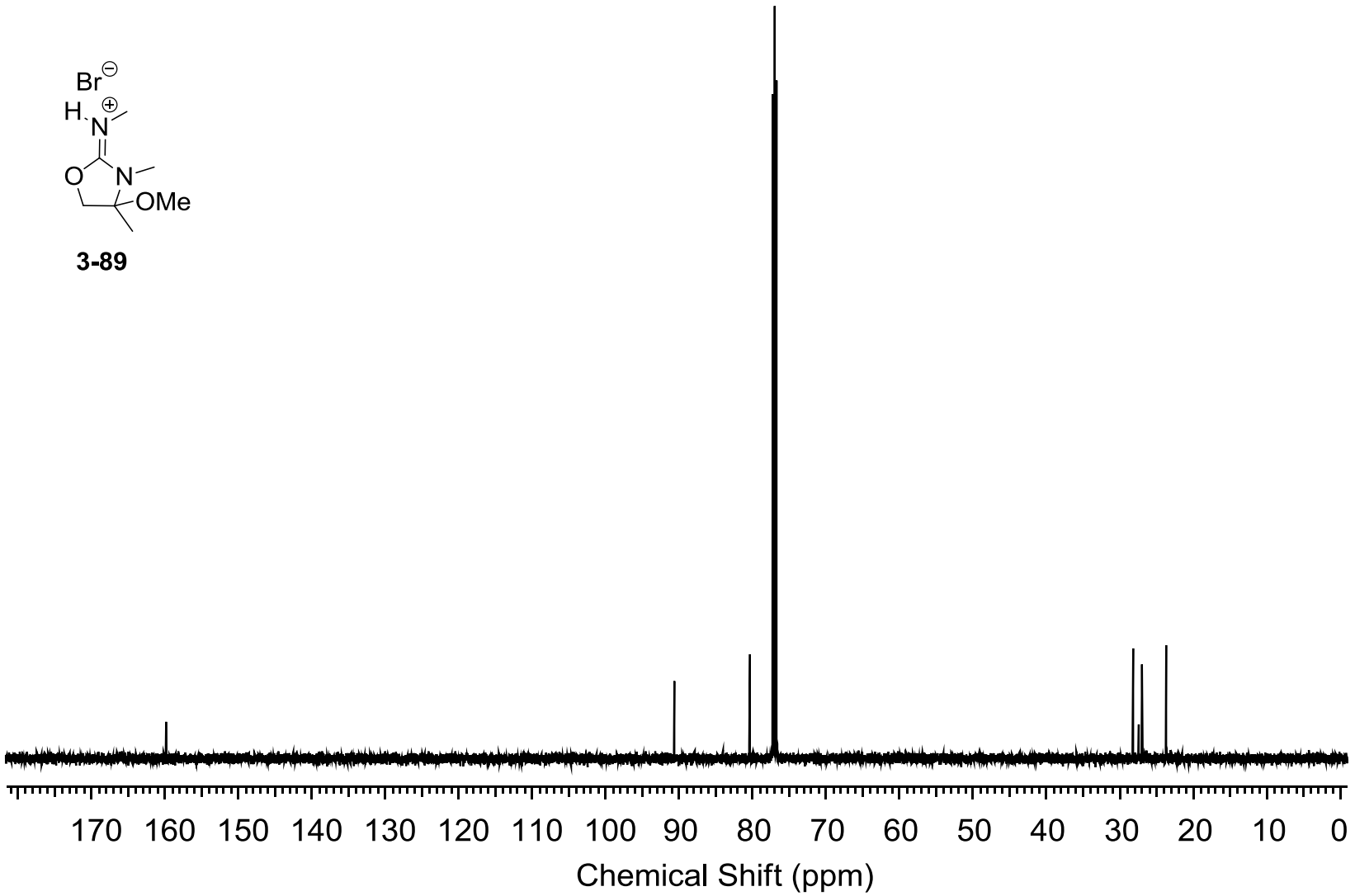


Figure 4-66: ^{13}C NMR spectrum for compound **3-89**

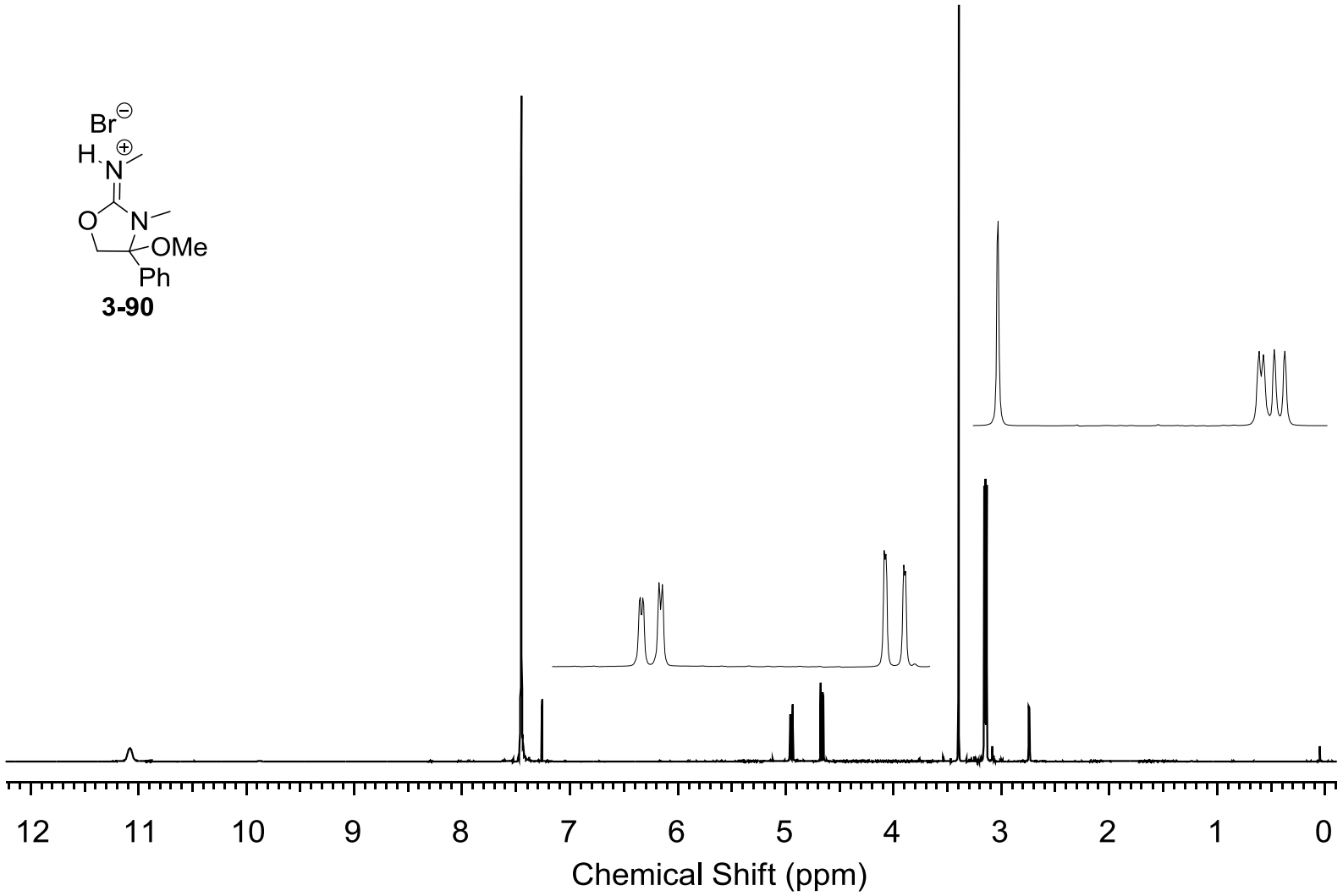
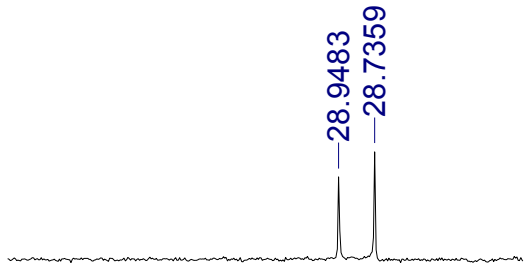

Br
H
N
O
N
OMe
Ph
3-90
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

Figure 4-67: ^{1}H NMR spectrum for compound **3-90**



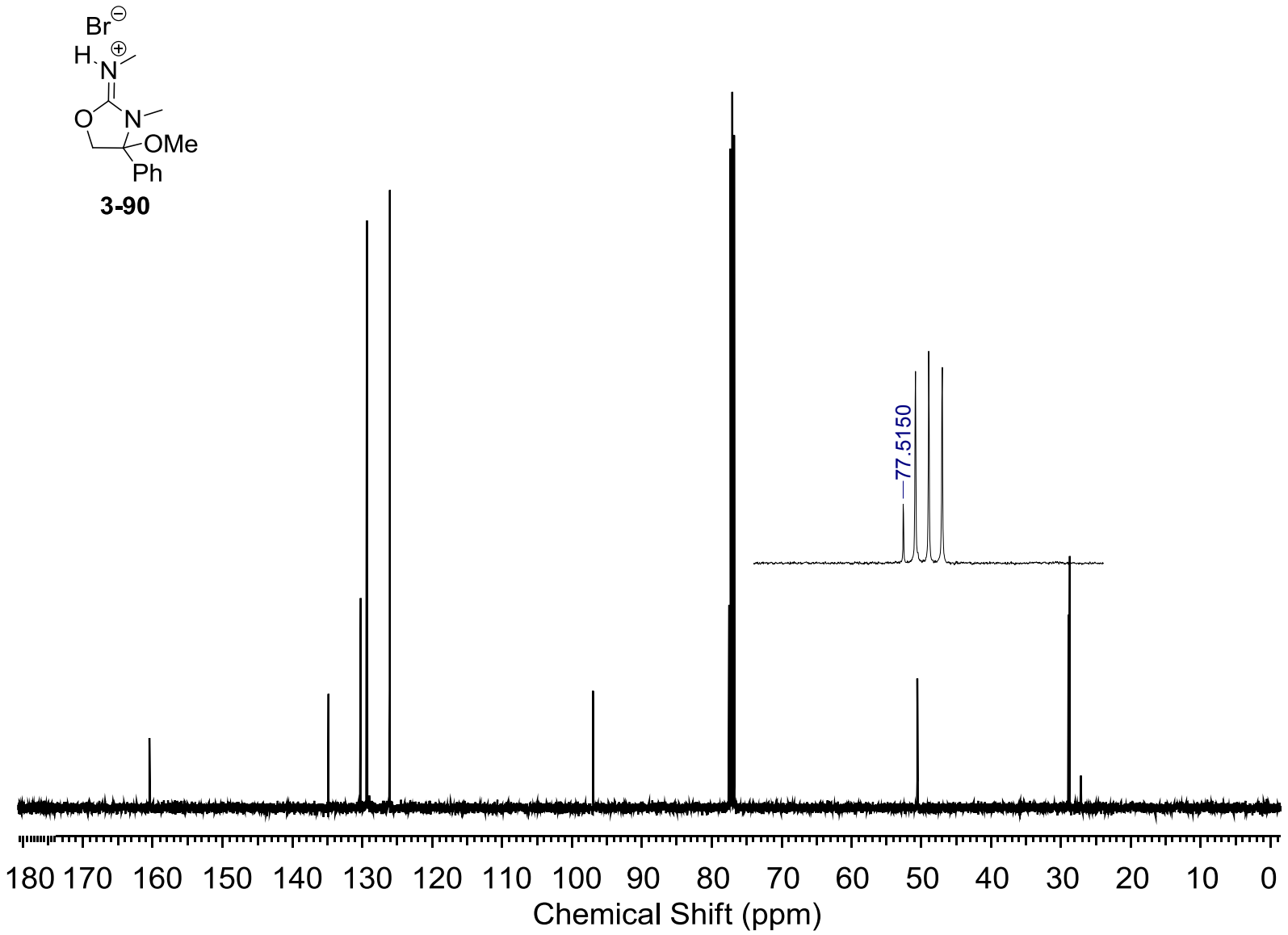


Figure 4-68: ^{13}C NMR spectrum for compound **3-90**

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REFERENCES

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(4) Wei, J.; Zhang, L.; Chen, Z.; Shi, X.; Cao, J. *Org. Biomol. Chem.* **2009**, *7*, 3280.

(5) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.