

The Synthesis of 2-Pyridones and Louisianin B

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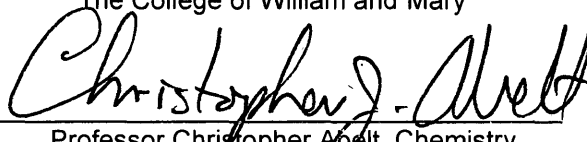
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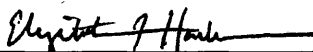


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ABSTRACT PAGE

We report formation of 2-pyridones from 2,5-diketopiperazines by first accessing a [2.2.2]-diazabicyclic structure formed from a domino sequence involving aldol condensation, alkene isomerization, and hetero-Diels-Alder cycloaddition. Conditions to produce the cycloreversion were optimized to reveal the desired pyridone functionality. The reaction pathway has been investigated with different diketopiperazines, aldehydes, and alkynal components, involving both inter and intramolecular cycloaddition templates. These efforts were directed toward the synthesis of louisianin B completed in 10 steps with 1.5% yield.

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Chapter 1

Synthetic Approaches Towards Constructing 2-Pyridones

Introduction

2-Pyridones are a common structural moiety found in several biologically active molecules. Recently, an increased interest in this class of compounds has emerged due to their wide array of properties, ranging from pharmacological to agrochemical activities.¹ 2-pyridones are 6-membered heterocyclic aromatic alkaloid motifs; however, other pyridone isomers exist, such as 4-pyridones. Below in **Figure 1.1** is a common numbering system for pyridone scaffolds, along with the pyridone and hydroxypyridine tautomers.

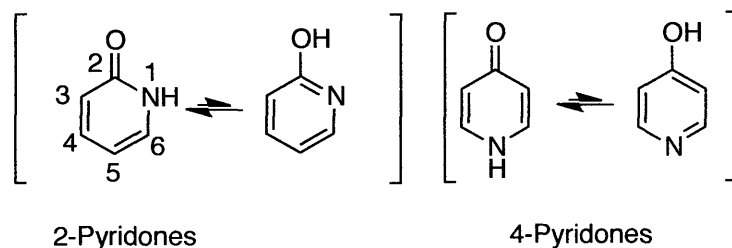


Figure 1.1 Structure and tautomeric forms of 2-pyridones and 4-pyridones

The stability of the 2-pyridone compared to the 2-hydroxypyridine has been debated for many years. It was found that only in very dilute nonpolar solvents or in the gas phase is the hydroxypyridine favored. In more concentrated solutions, the pyridone form is stabilized by forming a dimer through hydrogen bonding interactions. In aqueous solutions, 2-pyridone tautomers are found to be 1000:1 times more stable than

their hydroxypyridine counterparts.²

3-hydroxypyridines, a common scaffold of some bioactive molecules such as vitamin B6, can exhibit zwitterionic properties through a proton transfer from the hydroxyl group to the nitrogen in the ring system. They possess a dominant phenolic character that is caused by their inability to form the energetically favorable keto tautomers that are present in 2- and 4-pyridones.³

Possessing a wide variety of pharmacological and agrochemical properties, pyridones and their analogues have exhibited characteristics of DNA gyrase inhibitors, reverse transcriptase inhibitors for HIV-1, and mycotoxins. In 1864, the first pyridone alkaloid to be isolated was ricine, a poisonous crystalline substance found in castor beans. The structure was unknown at the time and not elucidated until 1904 by Maquenne and Philippe.⁴ Camptothecin, a 2-pyridone isolated in 1966 from the tree *Camptotheca acuminata* in China, was found to be a topoisomerase inhibitor, a characteristic of several anticancer drugs. Because of its biological activity, camptothecin has become a common synthetic target. However, in the 1980's, camptothecin failed clinical trials due to insolubility in the human body and toxicity. Derivatives of camptothecin have been approved by the FDA for the treatment of patients with ovarian, small-cell lung, and colorectal cancers.⁵ Huperzine A has recently been studied as a molecule of interest due to its potent reversible inhibition of acetylcholinesterase. For this reason, huperzine A has been viewed as a possible treatment of Alzheimer's disease to improve the cognitive function.¹ Aristopyridinone A was isolated in 2011 from *Aristolochia*, a traditional Chinese medicinal plant that possesses antibacterial, anti-inflammatory, and anti-

asthmatic properties.⁶ Most recently in 2013, four new 4-hydroxy-2-pyridones were isolated by Koyama from a fungus, *Stagonosporopsis cucurbitacearum*. One of the pyridones, didymellamide A, was shown to exhibit antifungal character against azole-resistant *C. albicans*.⁷ The structures of these natural products are shown in **Figure 1.2** below.

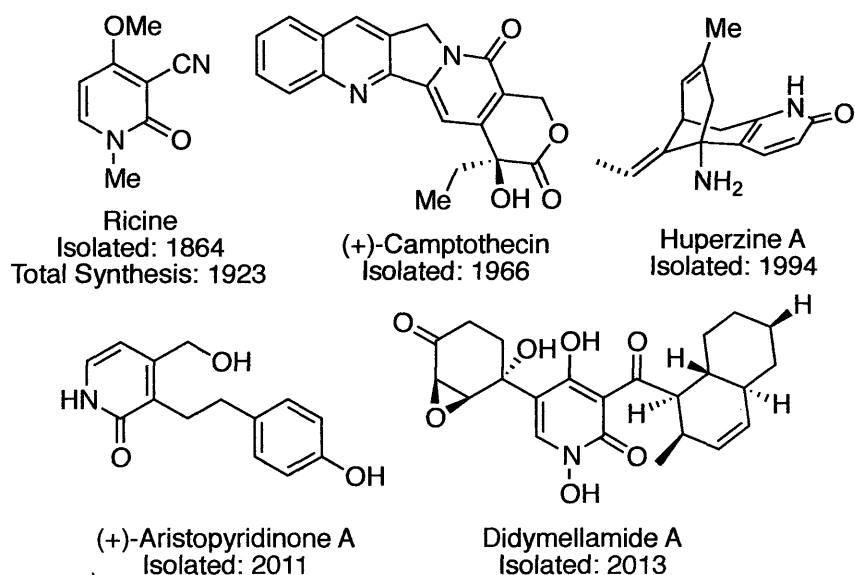
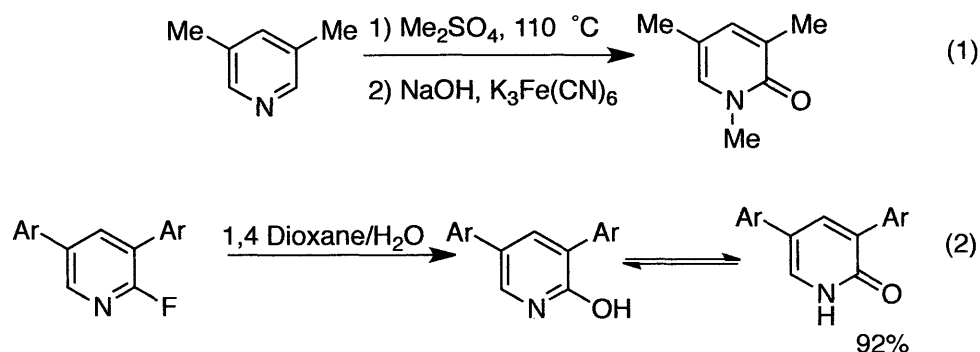


Figure 1.2 Isolated alkaloid natural products possessing a pyridone moiety

Synthetic Methods Toward Pyridones

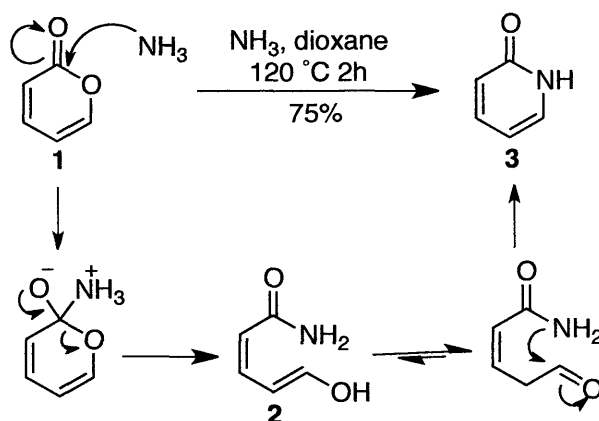
2-Pyridones have been accessed using two main strategies: functionalizing a pyridine core or constructing the heterocyclic ring through various types of reactions, including condensations, organometallics catalyzed [2+2+2] cyclizations, and cycloadditions. Oxidation of pyridines has been shown in several examples to be a facile route toward the formation of 2-pyridones (eq 1) (**Scheme 1.1**). Potassium ferricyanide can oxidize pyridines with high yields. Pyridones have also been constructed

through the hydrolysis of α -halopyridines, (eq 2) (**Scheme 1.1**).¹



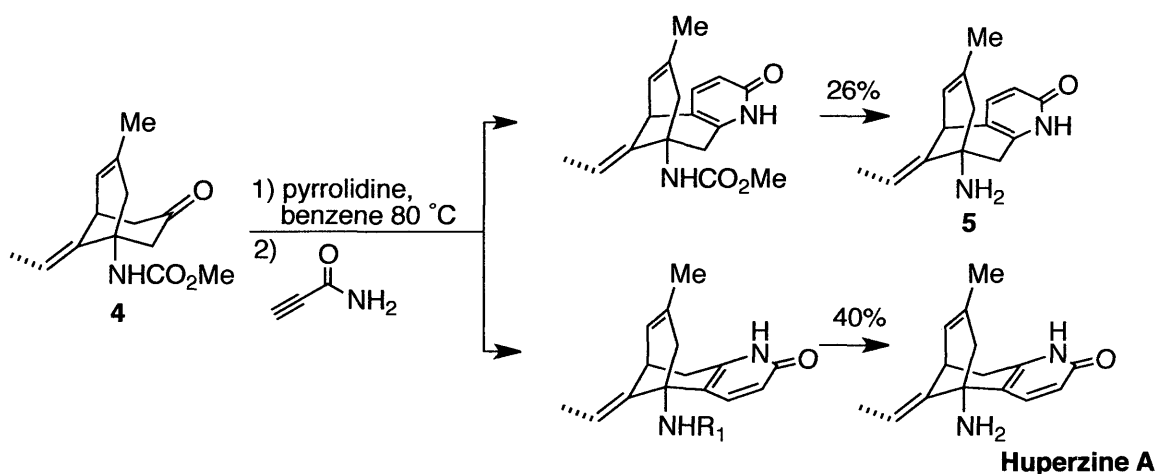
Scheme 1.1 Oxidative methods for the synthesis of 2-pyridones

Since condensations are believed to be the mechanism through which 2-pyridone derivatives, such as 4-hydroxy-2-pyridones, are constructed biologically, many groups have utilized this type of reaction to form the desired pyridone core structure. Pyrones have been converted into pyridones using a condensation reaction.⁸ Pyrone **1** was treated with ammonia, causing addition into the carbonyl, opening to intermediate **2** (**Scheme 1.2**). The nitrogen of the newly formed amide could then attack the aldehyde, closing the ring system to form the desired pyridone **3**.



Scheme 1.2 Conversion of pyrone to pyridone

In 2000, Camps synthesized the acetylcholinesterase inhibitor huperzine A through a condensation reaction (**Scheme 1.3**).⁹ The [3.3.1] bicyclic of the natural product was initially constructed, which required the pyridone moiety to be subsequently appended. The condensation of pyrrolidine with the ketone of bicyclic structure **4** afforded an enamine that could undergo a conjugate addition with propiolamide. Hydrolysis of the pyrrolidine reveals the ketone, allowing for condensation with the pendant amide, cyclizing and forming the desired 2-pyridone. While the conjugate addition was not appreciably regioselective, the 2-pyridone of huperzine A was synthesized by Camps with 40% yield, and the regioisomer, **5**, was produced with 26% yield.



Scheme 1.3 Pyridone formation in Camps synthesis of huperzine A

Organometallic reagents have been heavily used to synthesize 2-pyridones, a summary of, which is shown in **Table 1.1**. Yamazaki, in 1977, utilized methyl phenylpropiolate and methyl isocyanate along with a cobalt catalyst in their efforts to facilitate [2+2+2] cycloadditions, a general scheme of which is shown in **Figure 1.3**.¹⁰

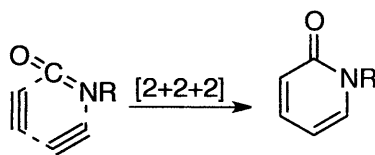


Figure 1.3 General [2+2+2] cycloaddition

In 1982, Hoberg used a nickel catalyst with both symmetric and asymmetric alkynes and isocyanates to form pyridones in a partially regioselective manner. Vollhardt, in 1984, utilized a cobalt catalyst to enable a pseudo intermolecular cycloaddition between a tethered alkyne and isocyanate pair and a second alkyne.¹¹ The purpose of tethering was to limit regioisomers that would be formed through the cyclization reactions that had been noted with previous organometallic reactions. Itoh, in 2005, looked to use the first ruthenium catalysts for pyridone synthesis, using a similar tethering approach with 1,6-diyne and isocyanates.¹² In 2009, Rovis was able to access both 2-pyridones and 4-pyridones using a rhodium catalyst in a regioselective intermolecular [2+2+2] cycloaddition.⁸ More recently, Takeuchi, in 2012, looked to use iridium as a catalyst when tethering two alkynes together and varying the substituents on the isocyanate.¹³ Kondo, in 2006, expanded on previous rhodium catalysis to achieve selectivity between the formation of pyridones and pyrimidines using isocyanates and symmetric alkynes.¹⁴ The proposed catalytic cycles for these transformations are shown in **Figure 1.4**.


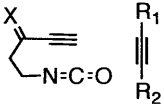
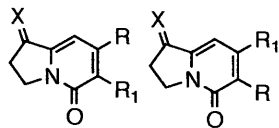

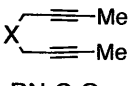
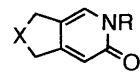
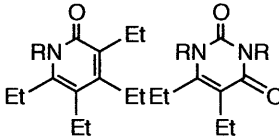
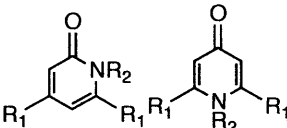
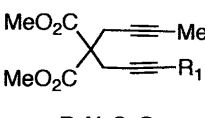
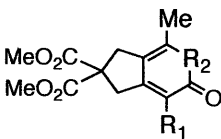
Author, Year	Metal Catalyst	Starting Material	Pyridone Scaffold
Hoberg, 1982	Ni(COD) ₂ PCy ₃	$2R_1\text{---}R_2$ $RN=C=O$	 $R_1 = \text{Ph, Et, Me, H}$ $R_2 = \text{Ph, Et, Me, H}$ $R_3 = \text{Ph,}$
Vollhardt, 1984	CpCo(CO) ₂	 $RN=C=O$	 $X = \text{H,}$  $R = \text{TMS, Me, } t\text{-Bu}$ $R_1 = \text{TMS, Et, CO}_2\text{Et}$
Itoh, 2005	CpRu(COD)Cl	 $RN=C=O$	 $X = -\text{C}(\text{CO}_2\text{Me})_2$ $-\text{O}$ $-\text{C}$ $-\text{NTs}$ $R = \text{Bn, Ph, Cyclohexane, Furan}$
Kondo, 2006	RhCl(PPh ₃) ₂	2Et---Et $RN=C=O$	 $R = \text{Bn, cyclohexane, furan, Ph}$ $R = \text{Ph, } p\text{-tolyl, } n\text{-hex, cyclohexyl, } p\text{-ClC}_6\text{H}_4$
Rovis, 2009	[Rh(C ₂ H ₄) ₂ Cl] ₂	$R_1\text{---}$ $R_2N=C=O$	 $R_1 = p\text{-MeO-C}_6\text{H}_4$ $R_2 = \text{Bn, PMB, Ph, } n\text{-hex, Cy}$
Takeuchi, 2012	[Ir(COD)Cl] ₂ , (R)-H ₈ -BINAP	 $R_2N=C=O$	 $R_1 = \text{Ph, TMS, CO}_2\text{Me}$ $R_2 = \text{Bu, } p\text{-MeO-C}_6\text{H}_4$

Table 1.1 Summary of organometallic catalysts for pyridone synthesis

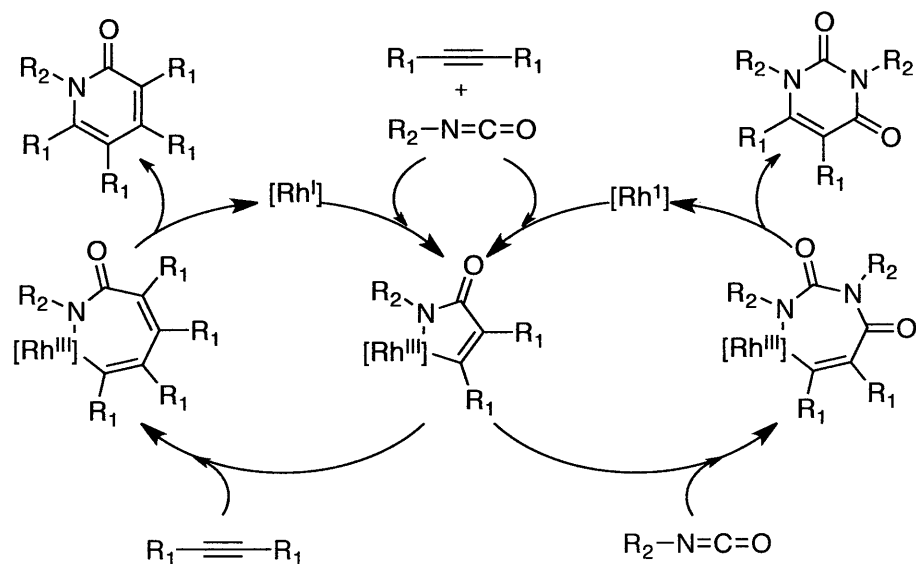
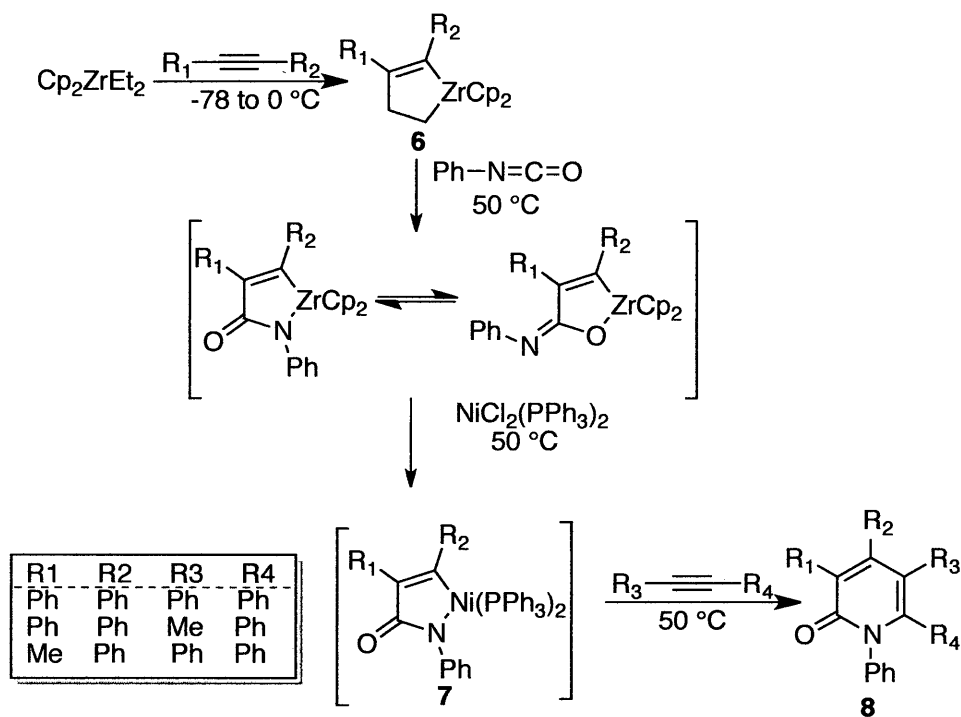


Figure 1.4 Proposed catalytic cycle for metal-catalyzed [2+2+2] cycloadditions

In 2002, Takahashi's work led to a highly regioselective 2-pyridone synthesis using stoichiometric amounts of both zirconium and nickel.¹⁵ Zirconium initially forms metallocycle **6** after reaction with an alkyne and isocyanate (**Scheme 1.4**). This is followed by transmetallation to form the nickel metallocycle **7**, after which regioselective insertion of a second alkyne occurs. Takahashi was able to produce a single regioisomer **8** with relatively high yields for each reaction by selective addition of the alkynes and isocyanates.



Scheme 1.4 Takahashi's proposed mechanism for cyclometallation and pyridone formation

Other organometallic reactions have been utilized to form 2-pyridones, including the palladium-catalyzed Stille reaction and the zinc-catalyzed Blaise tandem reaction.^{16,17} Choice of both metal and ligand can greatly impact the ability of transition metal mediated cyclization to form these alkaloid structures, and for this reason, many authors screen various metal and ligand combinations. Several of the abovementioned catalysts were incompatible with terminal alkynes; however, Tanaka, in 2005, reported the use of terminal alkynes to synthesize various pyridones with chiral rhodium catalysts.¹⁸ These are some of the examples of reactions that have been utilized to achieve the construction of 2-pyridone skeletons.

Cycloadditions and Cycloreversions to Produce 2-Pyridones

Cycloadditions and cycloreversions have been used to construct several types of aromatic systems, including pyrimidines,¹⁹ pyridines,²⁰ and pyridones.²¹ Cycloadditions are characterized by the interactions of two π systems from the diene and the dienophile. Thermal conditions allow the pericyclic donation of electrons from HOMO of the diene into the LUMO of the dienophile (Figure 1.5).

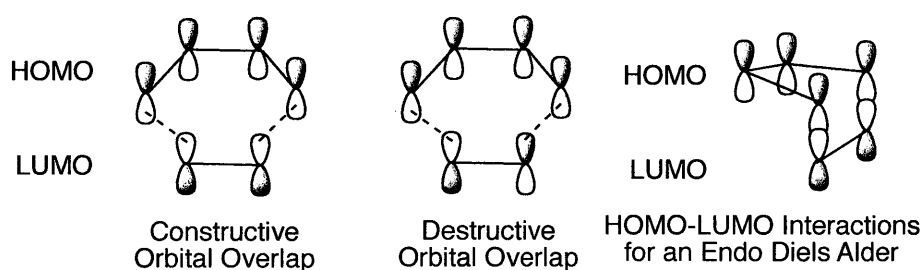
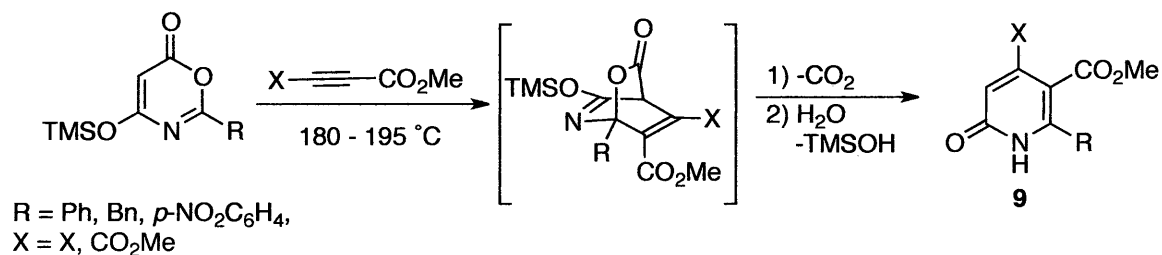


Figure 1.5 Orbital representation of a [4+2] cycloaddition

Diels-Alder cyclizations, $[4\pi + 2\pi]$ cycloadditions, conventionally occur with an electron rich diene and electron poor dienophile. Manipulations of the diene and dienophile by the addition of electron donating and electron withdrawing substituents, respectively, can help facilitate cycloadditions. Constructive overlap of the involved π orbitals is required for the cycloaddition to proceed. Cycloreversions, or retro-Diels-Alder reactions, are the reverse of cycloadditions, generating two separate π systems.

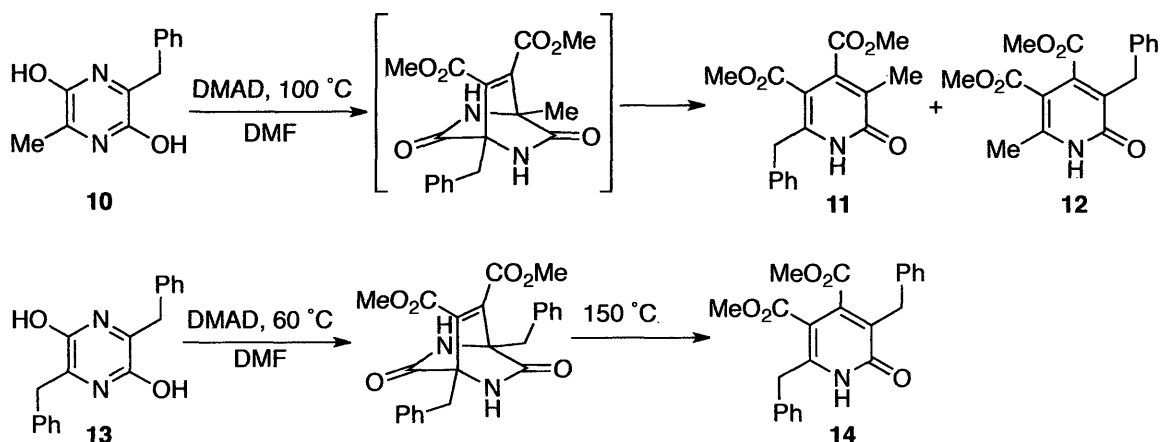
Cycloadditions of heterocyclic systems with a dienophile form bicyclic intermediates, which are often able to undergo a cycloreversion. In many of these cases, however, the bicyclic intermediate is not thermally stable and cannot be isolated due to the temperatures required to drive the cycloaddition. For a cycloreversion of a

bicyclic cycloadduct to occur, one bridge must be lost, although there are several possibilities for the specific byproduct formed.²² Diatomic nitrogen, carbon dioxide,¹ hydrogen cyanide,²⁰ and acetonitrile are some of the compounds that are commonly used as the cleaved bridge for the cycloreversion. Some examples of dienes and the corresponding leaving bridge include oxazoles, where water is subsequently lost as a byproduct of the cycloreversion, and monotriazines, in which diatomic nitrogen is expelled.²³ Oxazinones, for example, have been used because when the cycloreversion occurs, carbon dioxide is produced. Cycloadditions of oxazinones followed by cycloreversions have often been used to form pyridines; however Shioiri was able to form pyridones such as **9** using oxazinones (**Scheme 1.5**).²⁴



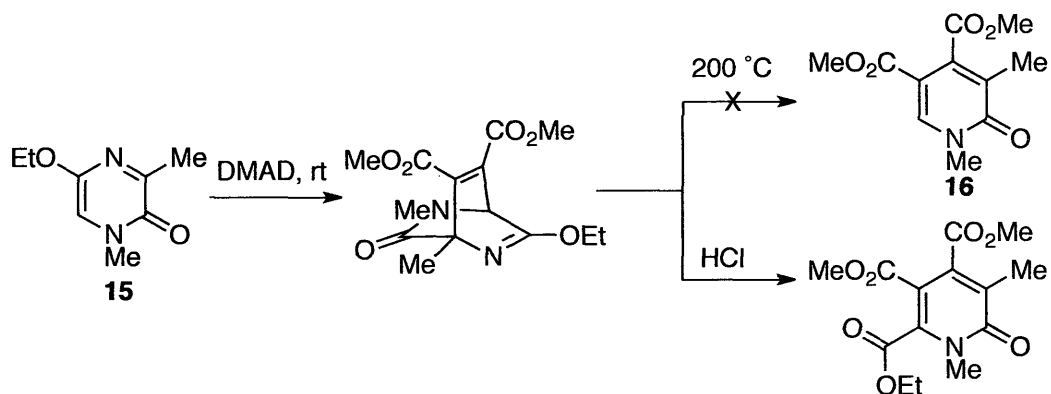
Scheme 1.5 Use of oxazinone to form 2-pyridones

In 1972, Sammes worked on using pyrazines to form pyridones through a Diels-Alder cycloaddition followed by cycloreversion (**Scheme 1.6**).²⁵ Using pyrazine **10**, heating to 100 °C for 30 minutes provided direct formation of two regioisomeric 2-pyridones, **11** and **12**, through loss of isocyanic acid. Symmetric pyrazine **13** was used to show that loss of isocyanic acid from cleavage of either bridge would produce the same pyridone, **14**, and not result in a mix of regioisomers.



Scheme 1.6 Utilization of pyrazines to form pyridones

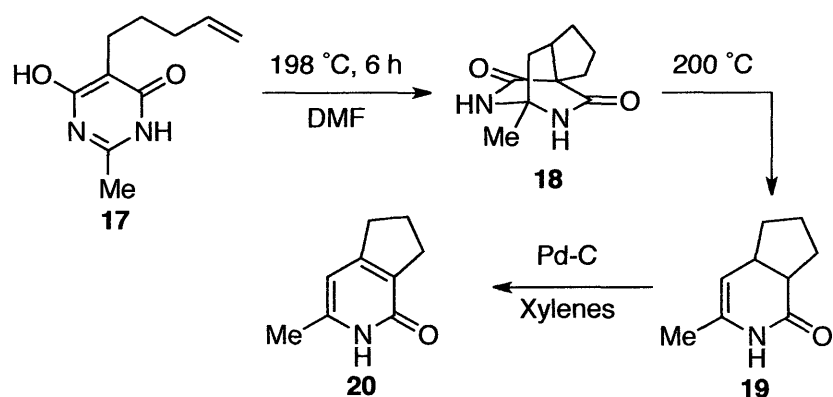
N-Alkyl pyrazinones were also investigated to exemplify the breadth of substrates that could be accessed (**Scheme 1.7**). However, with a protected nitrogen species, such as lactim *o*-ethyl ether **15**, the desired cycloreversion product **16** was not observed, even when the cycloadduct was heated to 200 °C. The authors instead used hydrochloric acid hydrolysis of the dimethyl acetylenedicarboxylate (DMAD) cycloadduct to access triester-substituted pyridones.



Scheme 1.7 Conversion of blocked pyrazinones to pyridones

Sammes, in 1978, furthered his previous work to construct

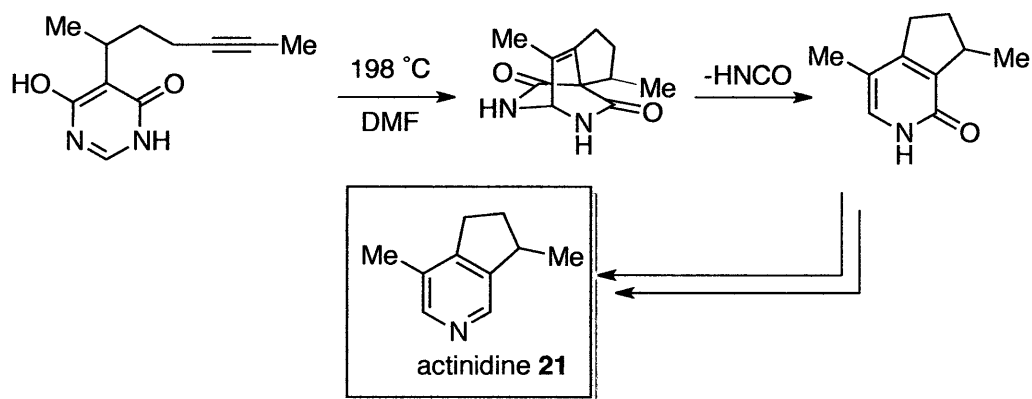
dihydropyridones, which could then be oxidized to the desired pyridone structures (**Scheme 1.8**).²⁶ The intramolecular cycloaddition between a dihydroxypyrimidine core and a pentene side chain of **17** required a temperature of 198 °C for 6 hours in DMF to produce the desired bicycle **18**. The cycloreversion then occurred through cleavage of either lactam bridge, resulting in the loss of isocyanic acid once heated to 200 °C for a prolonged number of hours, forming the desired dihydropyridone **19**. Direct access of the dihydropyridone was possible in one step if the starting pyrimidine was heated to 200 °C for an extended period of time.



Scheme 1.8 Formation of pyridones from dihydropyrimidines

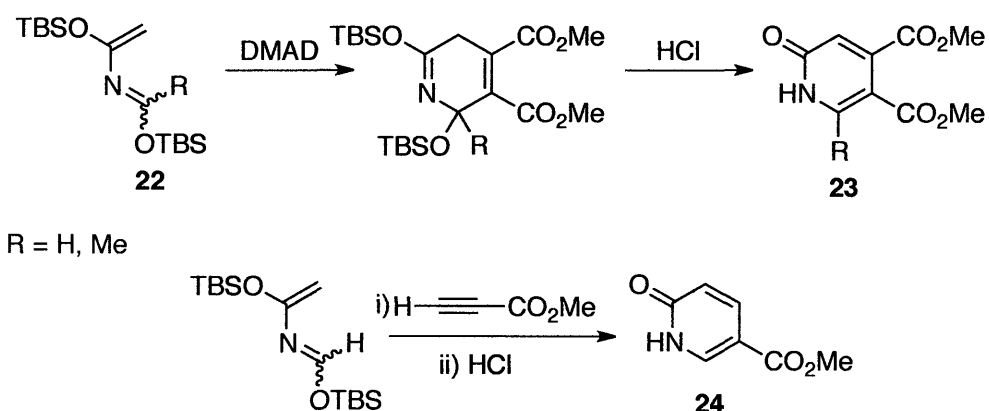
The use of the alkene side chains required a later oxidation by heating in xylenes over a palladium-carbon catalyst to access the desired pyridone core **20**. To assess the applicability of the reaction, Sammes looked at using a hexene side chain to act as the dienophile. Extended reaction times were required for the longer chain length substituent. Sammes extended his work by synthesizing actinidine, **21**, using an intramolecular cycloaddition,²¹ but this time using an alkyne side chain. This set up for subsequent

cycloreversion to form the aromatic system through loss of isocyanic acid (**Scheme 1.9**). Direct access of the 2-pyridone was achieved by using an alkyne; however, Sammes desired a pyridine in the final product.



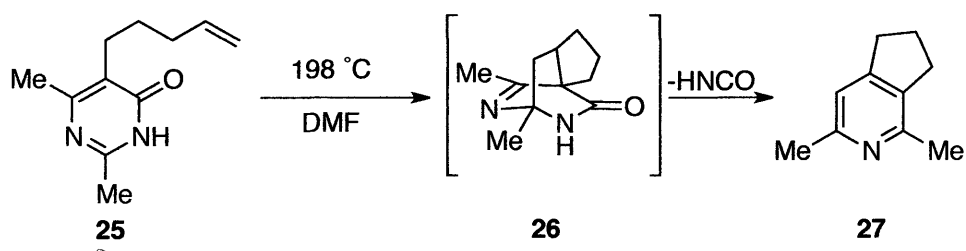
Scheme 1.9 Sammes synthesis of actinidine

Formation of pyridones through cycloadditions does not always require a cycloreversion as had been utilized in the above examples. In 1981, Ghosez utilized a Diels-Alder cycloaddition to form 2-pyridones.²⁷ Acetylacetamide and formylacetamide were converted into the necessary imides by using *tert*-butyldimethylsilyl triflate to form silylated ether azadiene, **22**. These could then be allowed to react with DMAD refluxing in chloroform to form the desired pyridone **23** after hydrolysis with HCl (**Scheme 1.10**). Formylacetamide was combined with methyl propiolate to form pyridone **24** regioselectively once refluxed in benzene for 14 hours followed by hydrolysis.



Scheme 1.10 Accessibility of pyridones using a Diels-Alder cycloaddition

Pyridines have also been synthesized using a cycloaddition followed by a cycloreversion. Sammes showed that this could be achieved using pyrimidine **25** and a pentene side chain that could undergo a cycloaddition. Heating the pyrimidine at 198 °C for 18 hours led to direct access of pyridine **27** (**Scheme 1.11**). The intermediate bicycle **26** was isolated when heated to 145 °C.

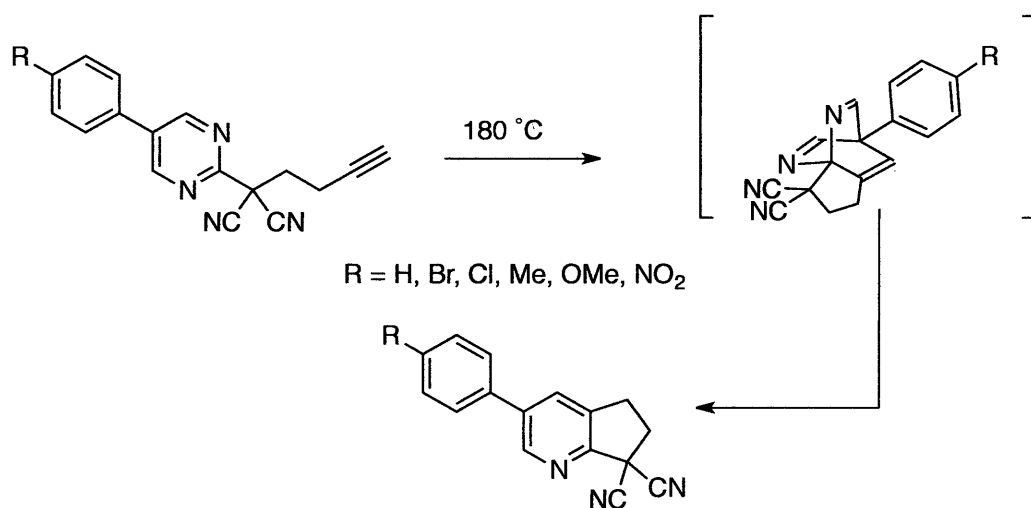


Scheme 1.11 Construction of pyridines from dimethylpyrimidines

Loss of either isocyanic acid or acetonitrile was possible with the bicyclic intermediate; however, Sammes observed only loss of isocyanic acid. Even with these two competitive cycloreversions, the cleavage of isocyanic acid was seen to be most favorable. Following the cycloreversion, aerial dehydrogenation produced the desired aromaticity, not

requiring the authors to perform a subsequent oxidation step.

In 1989, van der Plas looked at steric and electronic effects for inverse electron demand Diels-Alder reactions.²⁸ It was proposed that steric hindrance more greatly impacted the reaction rate than did electronic effects. Furthermore, the authors examined six different substrates and suggested that cycloadducts were formed as intermediates; however, they were not isolated. Instead, they were thought to undergo spontaneous cycloreversion to form pyridines when heated to 180 °C, a similar finding to Sammes' work from 1977. Several other cases reported that the intermediate cycloadduct could not be isolated, and instead, a cycloaddition followed by cycloreversion occurred in one process. In this work, van der Plas focused on substituent effects on the cycloaddition but also demonstrated that even though the substituents were varied, the cycloreversions in all six cases occurred spontaneously following the cycloaddition (**Scheme 1.12**).



Scheme 1.12 Cycloaddition and spontaneous cycloreversion to form pyridines

Constructing 2-pyridones through cycloadditions and cycloreversions has been studied for many years. Many of these reactions require high temperatures and several hours to form desired pyridones through a bicyclic intermediate. Heating some of the compounds proved to be futile, since even temperatures up to 200 °C could not produce decomposition of the bicycle into the desired pyridone. However, many authors noted that the intermediate bicycle could not be isolated and, instead, at high temperatures directly accessed the 2-pyridones.

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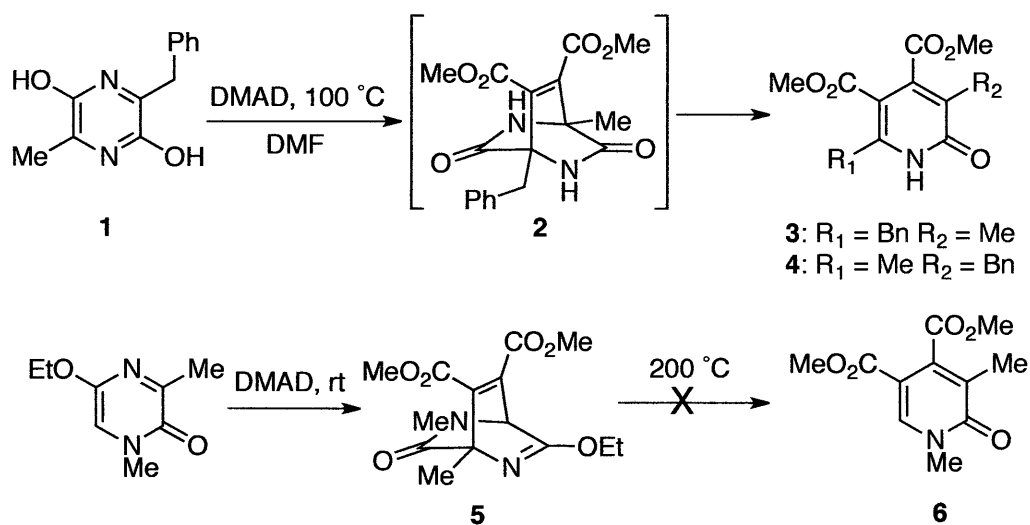
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Chapter 2

Methodological Approaches Toward 2-Pyridones

Previous Cycloreversions to Produce 2-Pyridones

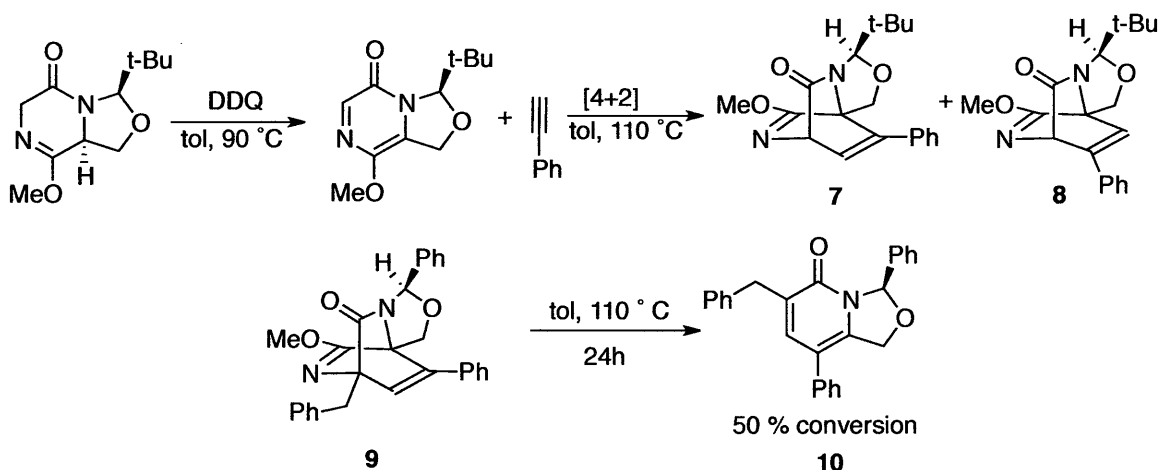
Sammes, in 1973, demonstrated how a 2,5-dihydroxypyrazine diene, such as **1**, could undergo a cycloaddition with a dienophile, dimethyl acetylenedicarboxylate (DMAD) (**Scheme 2.1**).¹ When heated to 100 °C for 30 minutes, both the cycloaddition and cycloreversion occurred, forming a 1:1 mixture of regioisomers, pyridones **3** and **4**. The bicyclic intermediate **2** was not isolated. Cycloadditions with *N*-alkyl pyrazinones were also explored with DMAD as the dienophile. Cycloadduct **5** formed at room temperature and was then heated to 200 °C to drive the cycloreversion; however, this was not a sufficient set of conditions to form the desired pyridone **6**.



Scheme 2.1 Sammes' work on cycloreversions to 2-pyridones

Development of Cycloaddition Conditions Towards [2.2.2]-Diazabicycles

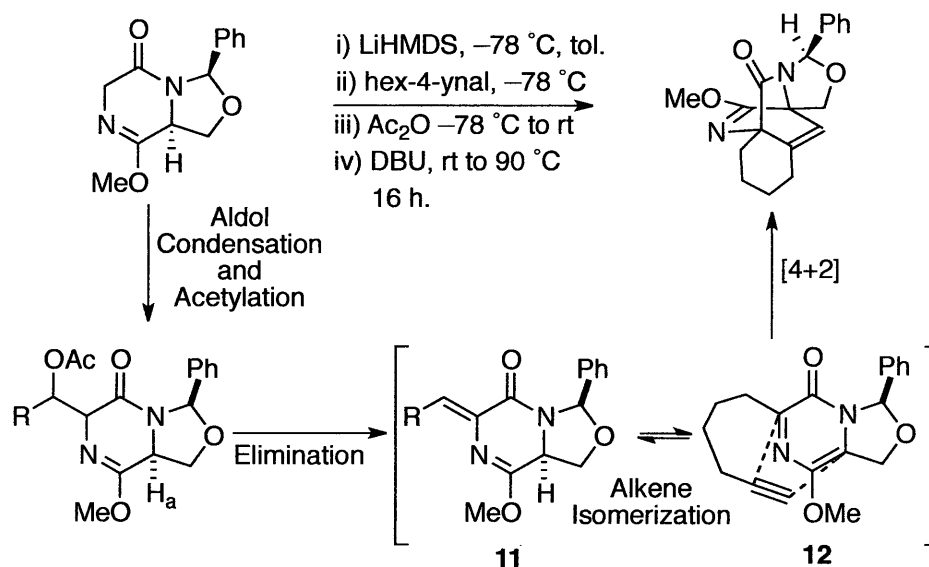
The class of molecules containing a [2.2.2]-diazabicyclic structure has members including malbrancheamides, brevianamides, and stephacidins and possesses a wide variety of biological activities.² Previous works in the Scheerer lab have demonstrated how [2.2.2]-diazabicycles can be constructed using a diketopiperazine (DKP) diene in an intermolecular Diels-Alder cycloaddition (**Scheme 2.2**).³ The intermolecular cycloadducts **7** and **8** with the lactim ether bridge proved to be stable in toluene to a temperature of 110 °C for 16 hours, similarly to Sammes' work with a lactim ethyl ether bridged cycloadduct. However, one intermolecular cycloadduct, **9**, underwent 50% conversion to 2-pyridone **10** once heated in toluene to 110 °C for 24 hours.



Scheme 2.2 Intermolecular cycloaddition examples from Scheerer lab

We wanted to investigate intramolecular examples to see if the bicyclic structures were stable to heating like regioisomers **7** and **8** or if they would undergo a cycloreversion, similarly to cycloadduct **9**. Beginning with a serine-derived DKP with

a chiral phenyl aminal substituent, a one-pot domino sequence, consisting of an aldol condensation, alkene isomerization, and intramolecular Diels-Alder cyclization, could be used to access the desired [2.2.2]-bicyclic core (**Scheme 2.3**).

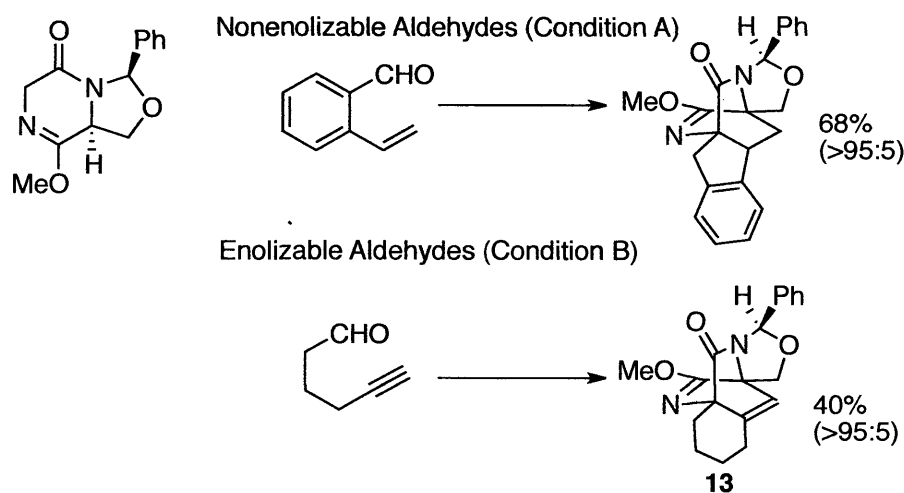


Scheme 2.3 Domino reaction sequence to access [2.2.2]-diazabicycles

Two sets of conditions were optimized so that we could study enolizable and non-enolizable aldehydes in the construction of eight different [2.2.2]-diazabicycles with good diastereoselectivity;⁴ a selection of examples is shown in **Scheme 2.4**. With nonenolizable aldehydes, it was possible to employ conditions of sodium methoxide in methanol followed by heating the reaction to $65\text{ }^{\circ}\text{C}$. However, this cannot be exploited with enolizable aldehydes due to potential undesired aldol products. To circumvent this, we envisioned a stepwise one-pot scheme accessing similar intermediates.

First, LiHMDS was used to form the DKP enolate, which is followed by subsequent aldol addition into the aldehyde. The derived metal alkoxide is

acetylated with acetic anhydride, facilitating elimination. Treatment with DBU both effects acetyl elimination to **11** and alkene isomerization to the azadiene **12**. Upon heating, the cycloaddition is observed with the pendant alkene or alkyne dienophile.



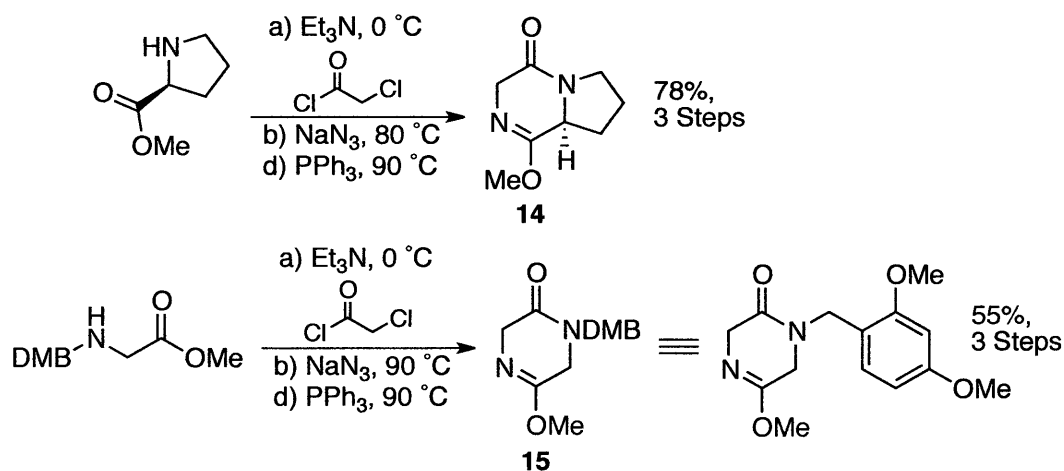
Condition A: a) DKP (1 equiv.), ArCHO (2 equiv.) at 0.15–0.2 M in MeOH, NaOMe (3 equiv.), 65 °C 16–24 h; Condition B: a) DKP (1 equiv.), LiHMDS (1.1 equiv.), –78 °C; b) RCHO (1.2 equiv.), –78 °C; c) Ac₂O (1.3 equiv.) –78 °C to rt; d) DBU (2 equiv.) rt to 90 °C, 16 h.

Scheme 2.4 Examples of [2.2.2]-diazabicyclic structures

One intramolecular example demonstrated use of an aliphatic alkyne as the reactive dienophile, as seen in cycloadduct **13** (Scheme 2.4). This cycloadduct was isolable and the cycloreversion product was not observed by NMR. Our lab had demonstrated that the [2.2.2]-diazabicycles we synthesized were generally stable to temperatures around 100 °C; however, one example had shown conversion to a 2-pyridone through a cycloreversion. For this reason, we looked to see if we could optimize conditions to undergo a cycloreversion to form 2-pyridones.

Diketopiperazine Syntheses

A chiral aminal substituent was necessary for our previous synthesis of the [2.2.2]-diazabicyclic structures; however, with our projected route, diastereoselectivity was not necessary due to the lack of stereochemistry present in the pyridone scaffold. Two DKPs were used in these efforts, one proline derived, **14**, and the other glycine derived, **15** (Scheme 2.5).



Scheme 2.5 Route towards the proline and glycine derived diketopiperazines

In both routes to the desired DKPs, the amino acid ester starting materials were acylated with chloroacetyl chloride. An azide displacement was then performed to set up for the Staudinger reduction of the azide, followed by an aza-Wittig cyclization to afford the proline and glycine derived DKPs in 78% and 55% yields, respectively.

The dimethoxybenzyl (DMB) protecting group was selected because it could later be removed to reveal a free secondary amide. Initially, a pivaldehyde-glycine derived DKP, **16**, as well as a Boc protected DKP, **17**, had been synthesized for eventual cleavage

to reveal the unprotected pyridone (**Figure 2.1**). The Boc DKP was shown to be unstable when purified on silica gel, and the pivaldehyde-glycine DKP was not as efficient for the domino sequence compared with the DMB DKP. The cycloadducts from the pivaldehyde-glycine DKP were complicated by diastereomers. We envisioned that we could show the versatility of our methodology if we could utilize both the glycine DKP as well as the sterically congested proline DKP.

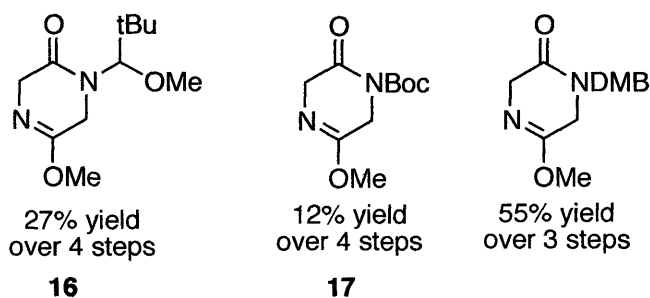
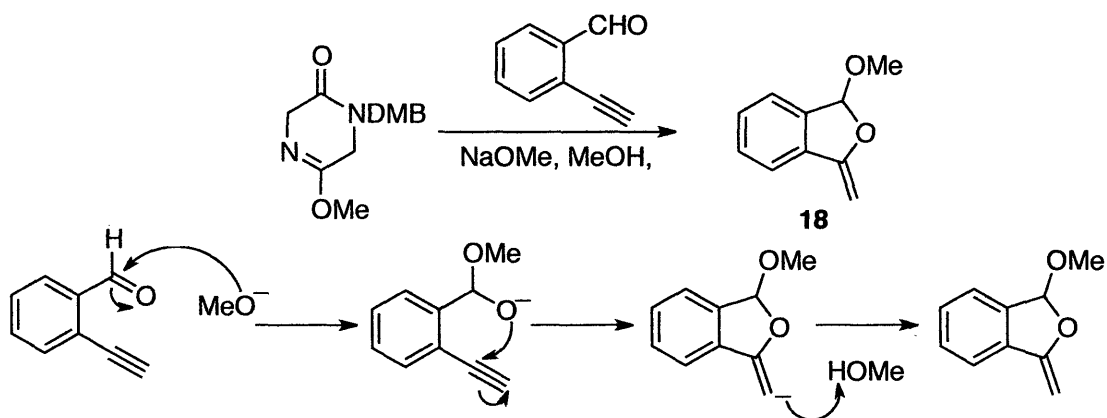


Figure 2.1 Pivaldehyde and Boc protected diketopiperazines

Cycloaddition Conditions and Initial Attempts Towards Cycloreversion

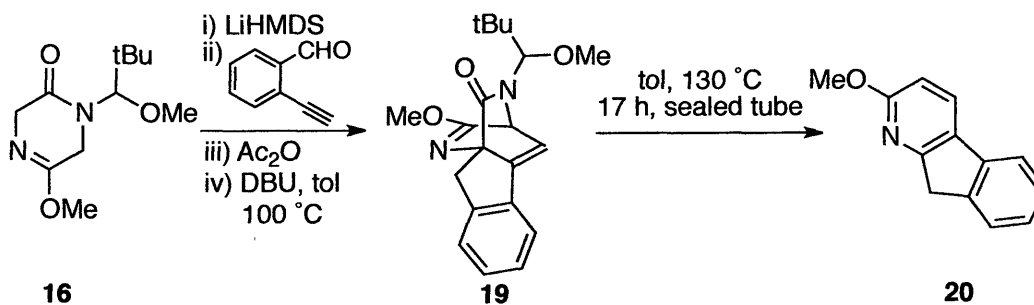
We wanted to build upon the one pot domino sequence to incorporate a cycloreversion. We began our studies with a commercially available non-enolizable aldehyde, 2-ethynylbenzaldehyde, and wanted to see if our previous conditions using sodium methoxide in methanol could produce the desired cycloadduct. Mostly starting material was present along with a significantly nonpolar compound. After isolation, the product was determined to be 1-methoxy-3-methylene-1,3-dihydroisobenzofuran, **18**, which is thought to form through addition of the alkoxide base into the carbonyl of the aldehyde, followed by addition into the unsaturated alkyne to cyclize (**Scheme 2.6**).



Scheme 2.6 Dihydroisobenzofuran formation from sodium methoxide conditions

We had to approach the reaction through the more stepwise pathway using the enolizable aldehyde conditions determined previously. We also wanted to look at a substituted alkyne; therefore 2-(phenylethynyl)benzaldehyde was synthesized and also used in the one-pot reactions. Using the stepwise conditions provided us with a way to form the desired cycloadducts. We were able to isolate the bicyclic intermediates and did not observe cycloreversion to occur in the one pot sequence when heated in toluene to 100 °C overnight. Since the bicycles were isolable, we wanted to see if accessing higher temperatures could drive the cycloreversion.

Our initial attempts involved the cycloaddition of the pivaldehyde-glycine derived DKP **16** and ethynylbenzaldehyde. Cycloadduct **19** was heated in toluene in a sealed tube at 130 °C for 17 hours, which was shown to be too mild, resulting in the isolation of the bicyclic starting material. The reaction was attempted again with DMF at 150 °C for 24 hours and showed signs of formation of a methoxypyridine **20**, an undesired cycloreversion that cleaved the bridge containing the amide (**Scheme 2.7**).



Scheme 2.7 Formation of methoxypyridine

Previous works required significantly higher temperatures than are possible with toluene, so we looked to utilize microwave technology to determine if we could pass the thermal threshold to cleave the desired bonds to form 2-pyridones selectively.

Previous Uses of Microwave Technology

Microwave Assisted Organic Synthesis (MAOS) was first reported to accelerate reaction rates when studied by Gedye and Giguere in 1986.⁶ The principle behind microwave-enhanced chemistry is that solvents or reagents can absorb the microwave irradiation and convert it to heat through dipolar interactions. As the electric field is changed, the dipoles of the reagent attempt to align with the field; consequentially, energy is lost in the form of heat. If there is not sufficient time for the dipoles to realign or if they align too quickly, no heat will be produced. Solvents are chosen based on physical properties, and those with small dielectric constants are preferred since they are microwave invisible (e.g. toluene, DCM, THF). The vessels that are used in microwaves are also generally microwave “invisible” and are made of borosilicate glass, quartz, or Teflon.

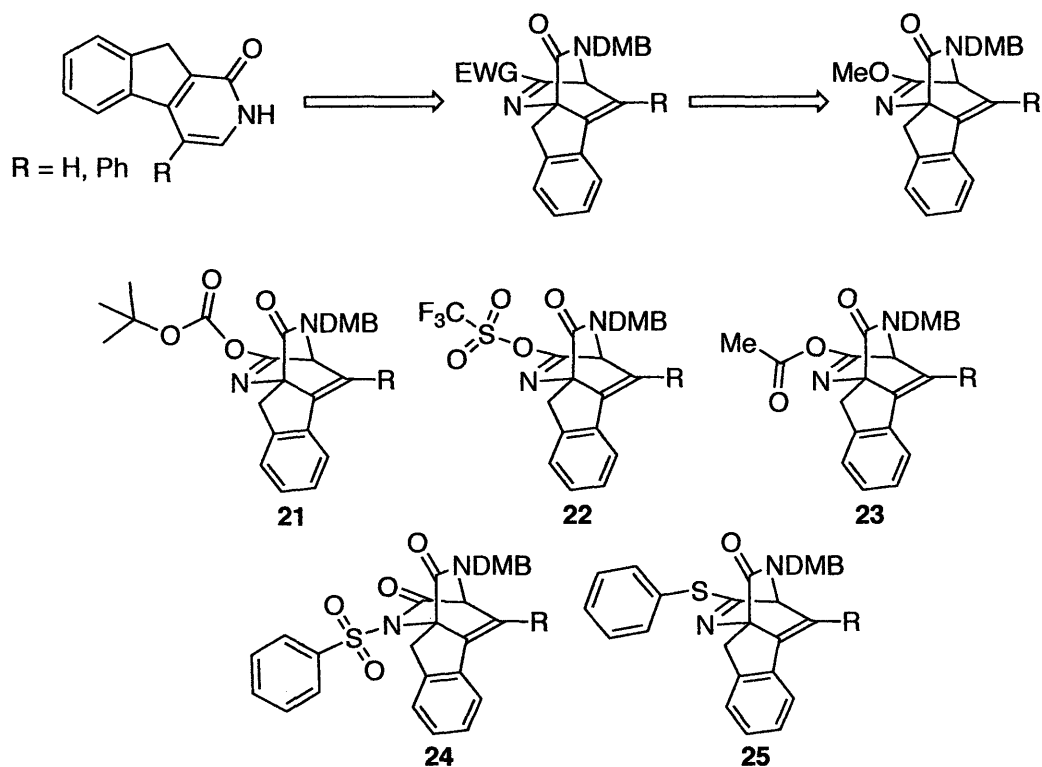
Organic reactions are frequently run in oil baths for conductive heating, where the vessel and the solution closest to the walls of the container are heated the most. Microwaves access the dipoles of the solvent and reagent to heat the system internally, known as in-core volumetric heating. Microwave reactions can occur in either open or sealed systems. High boiling microwave active solvents have been used in open systems; however, in the 1990s, Strauss began work with sealed systems. This advantage allows for accessibility of higher temperatures from the pressurized system without requiring changes in volume. The solvents used can be heated well above their boiling points at atmospheric pressures. For example, methanol can be heated more than 100 °C above its boiling point when submitted to microwave conditions in a sealed tube without risk of explosions.³

Various reactions including transition metal couplings, carbonylations, RCMs, radical reactions, and rearrangements have been shown to work well in microwaves.^{6,7} Cycloadditions were some of the first reaction types attempted in microwave systems. Dichlorobenzene and xylenes were solvents that had previously been used in some reactions to access temperatures to drive cycloadditions and cycloreversions. These high boiling solvents could prove to be problematic to separate from the product once the reaction was complete. Microwaves allow lower boiling solvents, such as toluene, to access temperatures much higher than their boiling points without the complication of solvent removal. With the controlled temperature and pressurized systems, we hoped to apply microwave technology to access our cycloreversion products.

Cycloreversions Using Microwave Technology

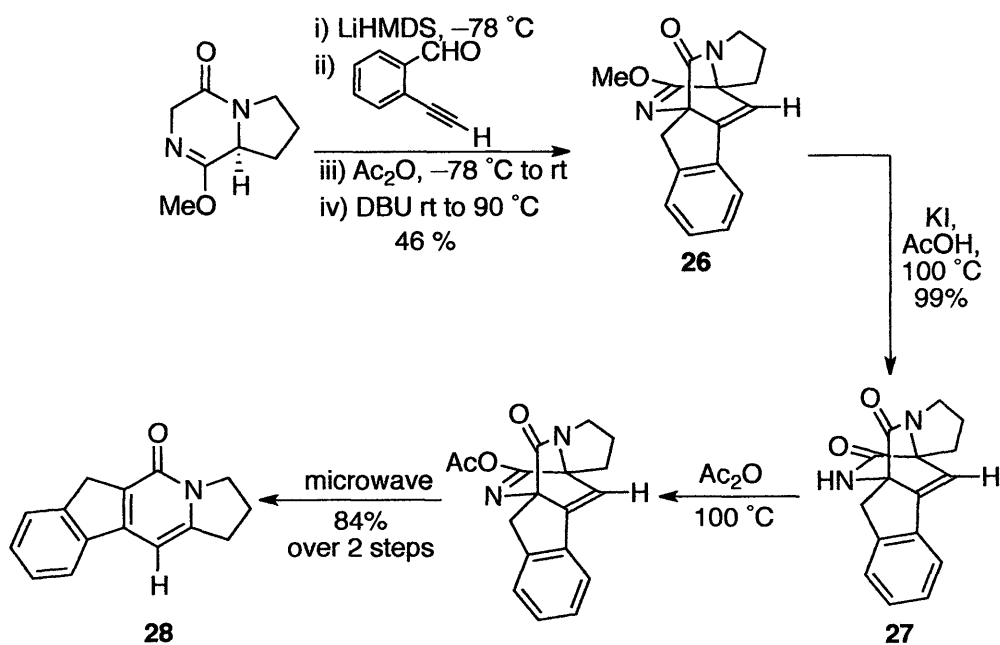
Submitting cycloadduct **19** to the microwave in toluene for 1 hour with a maximum temperature of 248 °C, we were able to cleave the bridge containing the pivaldehyde-protected lactam, producing methoxypyridine **20**, the undesired cycloreversion product (**Scheme 2.7**). Similar results were seen when heated in DMF to form the pyridine. This demonstrated that a cycloreversion could occur, but the electronics of the bridges had to be manipulated to form a 2-pyridone selectively.

We anticipated that substituting a more electron-withdrawing group in place of the methyl ether could produce the desired cleavage. Another group such as a more electron withdrawing substituent could pull electron density away from the bonds through induction, making the C-N bond weaker and more prone to breaking. Several groups with more electron-withdrawing character were explored including Boc (**21**), triflate (**22**), and acetate (**23**) protection on the oxygen as well as sulfonyl (**24**) protection on the nitrogen. An electron donating substituent, a thiophenol (**25**), was also used to determine whether it could facilitate the cycloreversion. This retrosynthetic scheme is shown in **Scheme 2.8**.



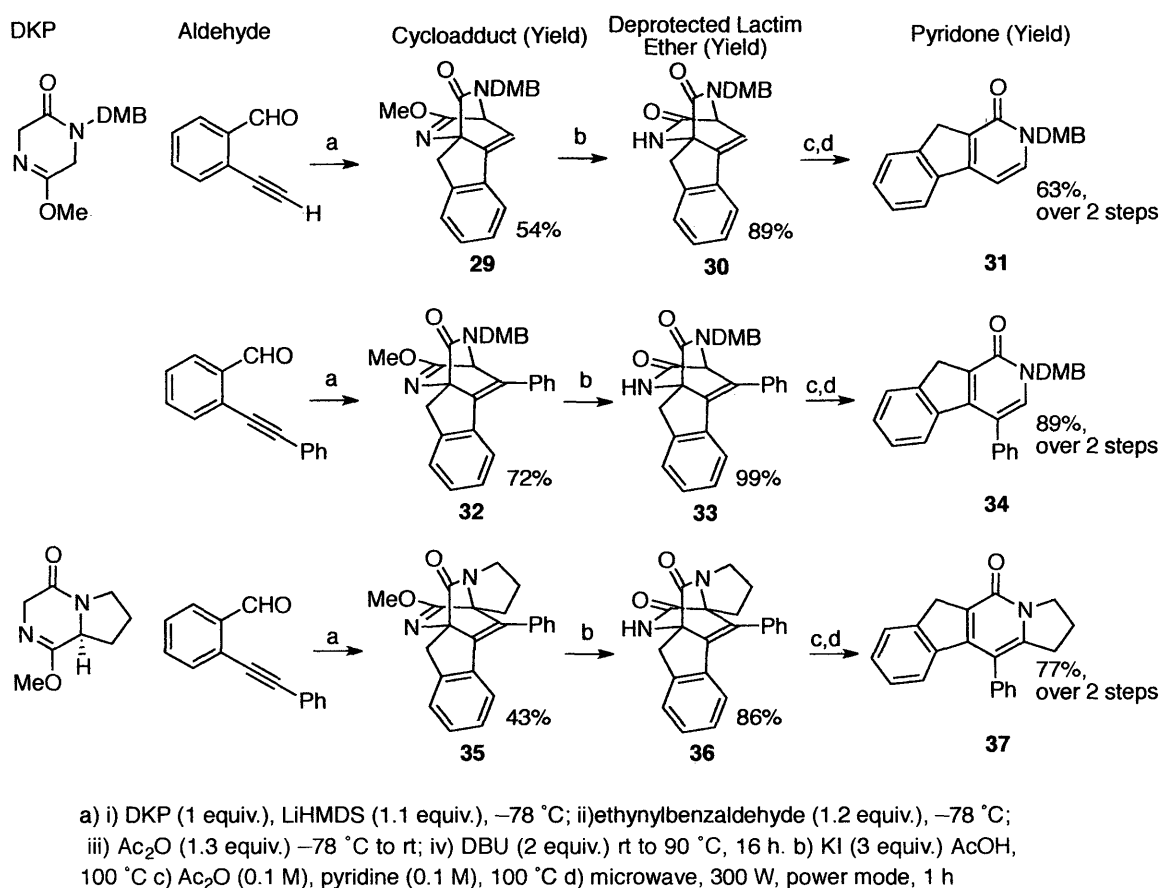
Scheme 2.8 Retrosynthesis using electron withdrawing substituents

The Boc protected cycloadduct **21** required temperatures no higher than 170 °C due to the thermal instability of the Boc group, leaving the lactam precursor from cleavage of the Boc group instead of the desired cycloreversion product. This protection did not seem practical because it requires at least two hours at the lower temperature so as not to cleave the protecting group preferentially. The acetate, triflate, sulfonyl, and thiophenol derivatives could withstand temperatures above 170 °C and worked well to facilitate the desired transformation. In practice, we selected acetate protection because it is a simple procedure, generally not requiring purification and instead allowing for direct submission to the microwave.



Scheme 2.9 Route toward 2-pyridones

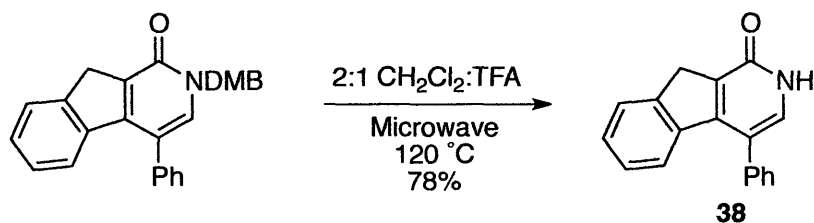
Using four examples of intramolecular cycloadducts that were subsequently acetylated, we have been able to demonstrate the microwave-assisted cycloreversions could be achieved (**Scheme 2.9**). Overall, we were able to show that our route can produce these 2-pyridones in a range from 31 to 60 percent yields over the course of four steps (**Scheme 2.10**).



Scheme 2.10 Synthesized [2.2.2]-diazabicycles and corresponding 2-pyridones

Deprotection of DMB Pyridones

After constructing the pyridones, we planned to deprotect the DMB containing products. TFA has been shown to cleave a DMB protecting group,⁸ and we utilized this in conjunction with microwave technology to reveal the final deprotected pyridone, **38**, for the phenyl-substituted example, **34**. This was completed in a 78% yield (**Scheme 2.11**). By establishing conditions for the deprotection, we were able to show the applicability of this route and the ability to reveal a secondary amide.



Scheme 2.11 Deprotection of DMB pyridone

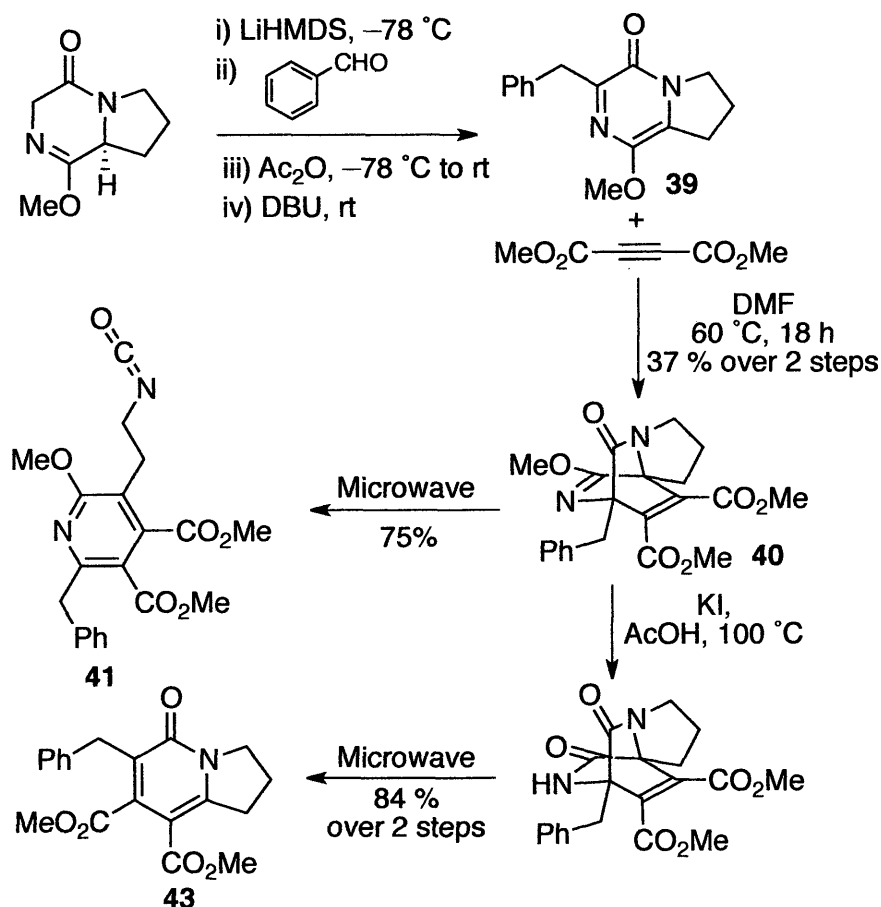
Intermolecular Examples

We have been able to demonstrate that aldol condensation, elimination, isomerization and intramolecular cycloaddition of diketopiperazines followed by cycloreversion can access 2-pyridones and wanted to extend our work to see if intermolecular examples could be produced. Dimethyl acetylenedicarboxylate (DMAD) was chosen as the dienophile and because of DMAD's ability to act as a Michael acceptor,⁹ azadiene **39** had to be isolated first, followed by the intermolecular cycloaddition with DMAD.

Using the proline DKP, we were able to isolate the cycloadduct **40**, in 37% yield. With this in hand, we wanted to see if the high temperature microwave conditions could reveal the desired cycloreversion with these intermolecular examples without requiring an electron-withdrawing substituent. Reaching a temperature of 253 °C provided methoxypyridine **41** with the isocyanate substituent that arose from cleavage of the undesired bridge (**Scheme 2.12**).

Attempting the same sequence of lactam formation (**42**) and acetylation followed by cycloreversion was shown to provide the desired 2-pyridone, **43**, in 75% yield from the cycloadduct, similarly to the intramolecular cases. For this specific example, the 2-

pyridone was accessed both in the microwave but also when the acetylation reaction was heated to 140 °C, showing how the thermal barrier was significantly lowered and could be achieved by heating with a traditional oil bath. This is the only example we have encountered where the barrier to the 2-pyridone was low enough to access using thermal heating with an oil bath. We have since directed our attention toward accessing intermolecular Diels-Alder examples using the DMB DKP and examples with other dienophiles such as phenylacetylene, but have yet to optimize conditions to produce a desired intermolecular cycloadduct.



Scheme 2.12 Intermolecular examples with formation of methoxypyridine and 2-pyridone

Enolizable Aldehyde Substrates

Intramolecular cases that were previously explored only looked at non-enolizable aldehydes, ethynyl benzaldehyde derivatives. Two examples of enolizable aldehydes were used, aldehyde **44** that we planned to use on our route toward louisianin B (Figure 2.2) and TMS protected pentynal **45** (Scheme 2.13). The former example will be discussed in more detail in Chapter 3 that focuses on the synthesis of louisianin B. The cycloaddition using the TMS protected aldehyde worked in high yield to form cycloadduct **46**. Similar conditions to form the 2-pyridone were employed and the final TMS pyridone, **48**, was constructed in three steps from the cycloadduct in 77% yield.

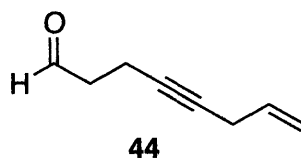
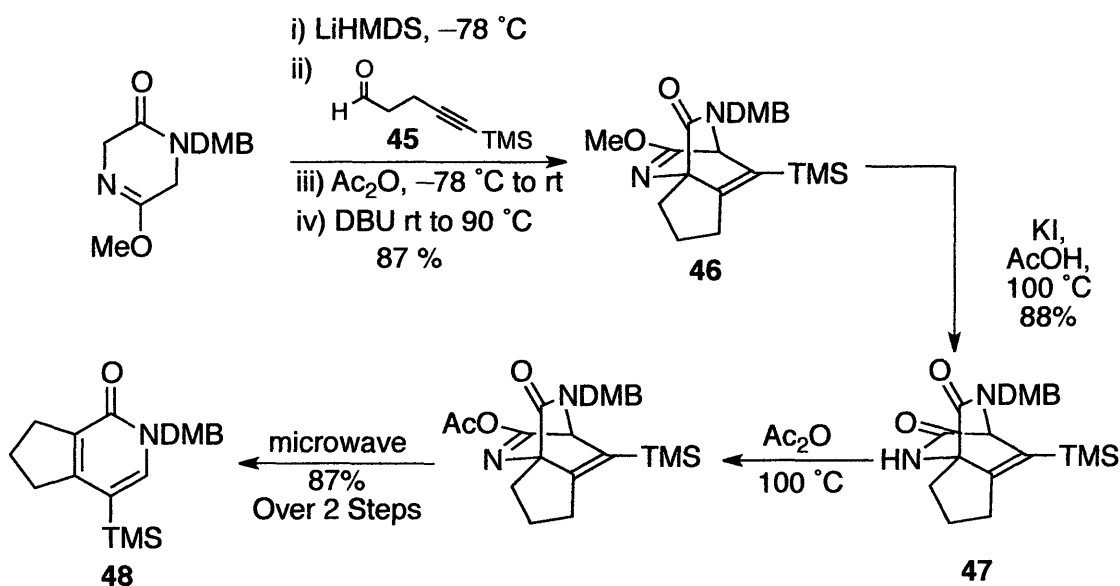


Figure 2.2 Enolizable aldehyde used toward louisianin B synthesis



Scheme 2.13 Enolizable aldehydes used in synthesis of 2-pyridones

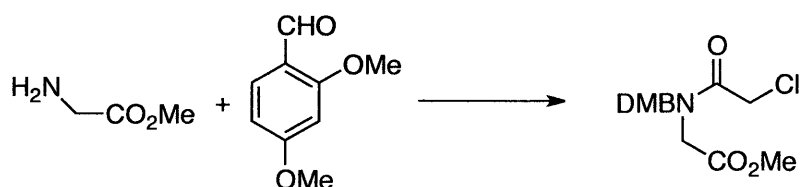
Conclusions

We were able to utilize our one-pot conditions to access several [2.2.2]-diazabicyclic cores using two DKPs and various alkynyl aldehydes. Thermal heating in an oil bath or in a sealed tube could not achieve the desired cycloreversion. Instead, we had to substitute an electron-withdrawing group, specifically an acetate, in place of a methyl ether. This allowed for more facile bond cleavage to access the desired 2-pyridones. Higher temperatures were also required, and for this reason we used microwave technology to heat the system well above the boiling point of the solvent, toluene. Once we accessed temperatures above 250 °C, we observed the desired cycloreversion to form 2-pyridones with yields ranging from 57 to 83% for the three steps after the formation of the bicyclic intermediate. Through this methodological work, we were able to use non-enolizable and enolizable aldehydes in intramolecular cycloadditions as well as begin to investigate intermolecular examples to form 2-pyridones.

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Experimental Section



Methyl 2-(2-chloro-N-(2,4-dimethoxybenzyl)acetamido)acetate. Following the procedure from Muhuhi, Joseck et al.¹ to a solution of 2,4-dimethoxybenzaldehyde (0.88 g, 5.34 mmol) dissolved in CH₂Cl₂ (40 mL) was added Et₃N (1.10 mL, 7.96 mmol), glycine methyl ester hydrochloride (1.00 g, 7.96 mmol) and NaB(OAc)₃H (2.20 g, 10.7 mmol). The slurry was vigorously stirred for 24 h at rt. The reaction mixture was quenched with the addition of saturated aqueous NaHCO₃ and the mixture was transferred to a separatory funnel. The organic layer was removed and the aqueous portion was extracted with CH₂Cl₂ (3 x 100 mL). The organic portions were combined, washed with brine, dried with sodium sulfate, filtered, and concentrated *in vacuo* to yield a clear oil (1.30 g, 5.44 mmol, 70% yield). The resulting product was used without purification. The oil was dissolved in CH₂Cl₂ (15 mL) and cooled to 0 °C. To the solution was added chloroacetyl chloride (0.45 ml, 5.71 mmol) and Et₃N (0.83 ml, 5.98 mmol) dropwise and the reaction mixture was warmed to rt and stirred for 18 h. The reaction mixture was filtered through celite and the filtrate was washed with NaHCO₃ (3 x 75 ml). The combined organic layers were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (elution: 25% to 85% EtOAc in hexanes) to afford the acetylated product (1.40

¹ Muhuhi, Joseck; Spaller, Mark R. *J. Org Chem.* **2006**, 71, 5515-5526.

g, 4.44 mmol, 82% yield) as a light orange oil: TLC (40% EtOAc in hexanes), R_f: 0.40 (UV, CAM); IR (film) 3002, 2953, 2839, 2361, 1749, 1662, 1614, 1509, 1457, 1440, 1294, 1267, 1210, 1130, 1033, 939, 835, 792, 709 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.25 (d, *J* = 8.2, 1H), 7.03 (d, *J* = 8.5, 1H), 6.46 (s, 1H), 6.44–6.41 (m, 1H), 4.58 (s, 1H), 4.52 (s, 2H), 4.35 (s, 2H), 4.11 (s, 2H), 4.03 (s, 1H), 4.02 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.76 (s, 1H), 3.70 (s, 1H), 3.69 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ 169.3, 167.1, 161.2, 158.7, 131.9, 130.1, 115.3, 104.2, 103.9, 98.8, 98.2, 55.4, 52.4, 52.1, 48.9, 48.2, 46.5, 45.0, 41.3. Exact mass calcd for C₁₄H₁₈ClNO₅Na [M+Na]⁺, 338.0768. Found 338.0765.



1-(2,4-dimethoxybenzyl)-5-methoxy-1,6-dihydropyrazin-2(3H)-one (15). To a solution of methyl 2-(2-chloro-*N*-(2,4-dimethoxybenzyl)acetamido)acetate (1.40 g, 4.44 mmol) dissolved in butanone (18 mL) was added NaN₃ (0.58 g, 8.89 mmol) and the mixture was brought to reflux with rapid stirring for 72 h. The mixture was cooled to rt, filtered through celite and concentrated *in vacuo* to yield a yellow oil (1.1 g, 3.5 mmol, 79% yield), which was used without purification. The intermediate product was dissolved in toluene (28 mL) at rt and PPh₃ (0.97 g, 3.68 mmol) was added. After gas evolution had steadied, the reaction vessel was heated to 90 °C for 19 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The resulting residue was purified by

flash column chromatography on silica gel (elution: 25% to 100% EtOAc in hexanes) to provide **15** (0.54 g, 1.94 mmol, 56% yield), a light yellow solid: TLC (60% EtOAc in hexanes), *R_f*: 0.12 (UV, CAM); IR (film) 2947, 2838, 2364, 1843, 1702, 1654, 1508, 1325, 1292, 1244, 1210, 1034, 938, 835, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.22 (d, $J = 8.6$ Hz, 1H), 6.47 (m, 1H), 6.45 (s, 1H), 4.58 (s, 2H), 4.17 (d, $J = 2.7$, 2H), 3.85 (d, $J = 2.7$, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3), δ 166.3, 161.0, 159.0, 158.4, 131.8, 116.4, 104.7, 98.6, 55.6, 53.1, 50.7, 45.9, 43.3; Exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$, 301.1159. Found 301.1156.

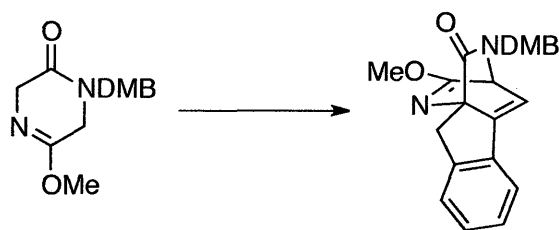
General Procedure A for aldol condensation / alkene isomerization / DKP Diels-Alder cycloaddition. To DMB protected diketopiperazine, **15**, (1 equiv, 0.50 – 1.8 mmol) in toluene (0.1 M) at -78 °C was added LiHMDS (1.0M in THF, 1.2 equiv) dropwise over 5 min by syringe. After stirring for 25 min at -78 °C the corresponding aldehyde (1.2 equiv) was added. The solution was stirred for 15 minutes, Ac_2O (1.3 equiv) was added at -78 °C. The reaction vessel was warmed to rt, stirred for 4.5 h and DBU (2 equiv) was added. The reaction vessel was heated to 100 °C for 19 h, and cooled to rt. The reaction was quenched with saturated NH_4Cl (10 mL) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography.

General procedure B for deprotection of lactim *O*-methyl ether. To a solution of the

cycloadduct (1 equiv, 0.09-0.45 mmol) in AcOH (0.1–0.2 M) was added KI (3 equiv) and the mixture was heated at 100 °C for 2 h. The reaction was diluted with water (50 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with sodium bicarbonate (3 x 100 mL). The organic phase was washed with brine, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to afford the deprotected lactim ether.

General procedure C for acetylation. The lactam intermediate product (1 equiv, 0.07–0.15 mmol) was dissolved in a 1:1 solution of Ac₂O (0.5 mL) and pyridine (0.5 mL) and heated at 100 °C for 16 h. The reaction was cooled to rt and concentrated. The resulting residue was used directly in the subsequent cycloreversion reaction without purification.

General procedure D for cycloreversion to pyridone. The acylated lactam intermediate (1 equiv, 0.03–0.15 mmol) was dissolved in toluene and heated for 1 h–1.5 h in the microwave (300 W, power mode). The reaction solution was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography in silica gel to afford the desired product.



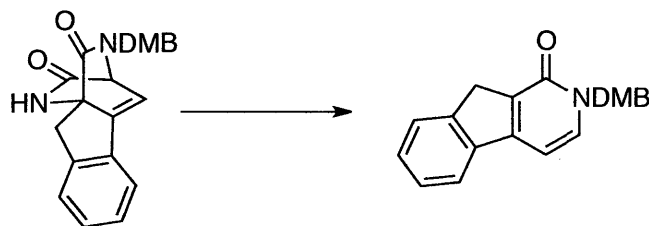
(3*S*,9*aS*)-11-(2,4-dimethoxybenzyl)-2-methoxy-3,9-dihydro-3,9*a*-

(epiminomethano)indeno[2,1-*b*]pyridin-10-one (29): Produced following general procedure A using **15** (50 mg, 1.8 mmol). The product was purified by flash chromatography on silica gel (elution: 25% to 100% EtOAc in hexanes) to yield the purified product **29** (38 mg, 0.97 mmol, 54% yield) as a rust colored solid: TLC (60% EtOAc in hexanes), *R_f*: 0.45 (UV, CAM); IR (film) 3002, 2945, 2837, 1684, 1615, 1589, 1507, 1466, 1334, 1306, 1266, 1210, 1160, 1036, 992, 934, 835, 756, 736 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.39 (d, *J* = 7.42 Hz, 1H), 7.30 (t, *J* = 8.20 Hz, 2H), 7.18 (t, *J* = 7.42 Hz, 2H), 7.04 (d, *J* = 8.60 Hz, 1H), 6.47 (d, *J* = 5.47 Hz, 1H), 6.44–6.39 (m, 2H), 4.81 (d, *J* = 5.47 Hz, 1H), 4.49 (d, *J* = 14.85 Hz, 1H), 4.43 (d, *J* = 14.45 Hz, 1H), 4.37 (d, *J* = 17.58 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.50 (d, *J* = 17.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 174.7, 171.1, 160.6, 158.6, 158.5, 147.6, 133.6, 131.1, 129.9, 126.8, 126.1, 122.0, 116.7, 115.4, 104.0, 98.3, 79.0, 59.2, 55.3, 55.2, 43.7, 35.5; Exact mass calcd for C₂₃H₂₂O₄N₂Na [M+Na]⁺, 413.1472. Found 413.1468.



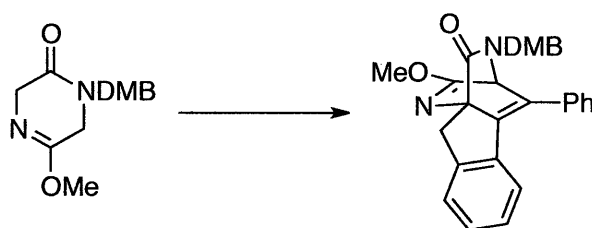
(3*S*,9*aS*)-11-(2,4-dimethoxybenzyl)-3,9-dihydro-3,9*a*-(epiminomethano)indeno[2,1-*b*]pyridine-2,10(1*H*)-dione (30): Produced according to general procedure B using **29** (35 mg, 0.09 mmol). The product was obtained without purification (30 mg, 0.08 mmol,

89% yield) as a brown solid: TLC (5% MeOH in Chloroform), R_f : 0.53 (UV, CAM); IR (film) 3203, 3072, 2942, 2841, 1707, 1683, 1629, 1589, 1505, 1466, 1303, 1210, 1158, 1039, 837, 754 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.56 (br s, 1H), 7.34–7.29 (m, 3H), 7.25 (m, 1H), 7.07 (d, $J = 7.82$ Hz, 1H), 6.55 (d, $J = 5.08$ Hz, 1H), 6.41 (s, 1H), 6.39 (d, $J = 2.34$ Hz, 1H), 4.61 (d, $J = 14.46$ Hz, 1H), 4.56 (dd, $J = 5.47/1.56$ Hz, 1H), 4.46 (d, $J = 14.46$ Hz, 1H) 4.21 (d, $J = 18.0$ Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.07 (d, $J = 18.0$, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 169.5, 160.8, 158.5, 156.1, 145.8, 133.0, 131.2, 130.4, 127.5, 126.0, 122.6, 117.5, 116.1, 104.0, 98.3, 69.5, 63.4, 55.3, 55.2, 44.2, 32.8; Exact mass calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$, 399.1315. Found 399.1311.



2-(2,4-dimethoxybenzyl)-2,9-dihydro-1*H*-indeno[2,1-*c*]pyridin-1-one (31): Following general procedure C, using **30** (25 mg, 0.066 mmol) the intermediate acylated product was produced (19 mg, 0.047 mmol, 71% yield). This intermediate product was used (12 mg, 0.03 mmol) to produce **31** following general procedure D. The product was purified by flash column chromatography on silica gel (elution: 30% to 70% EtOAc in hexanes) to afford the product (0.006 g, 0.018 mmol, 60% yield) as a yellow solid: TLC (60% EtOAc in hexanes), R_f : 0.40 (UV, KMnO_4); IR (film) 3067, 2962, 2839, 1700, 1507, 1464, 1277, 1267, 1210, 1038, 927, 828, 755 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.69–

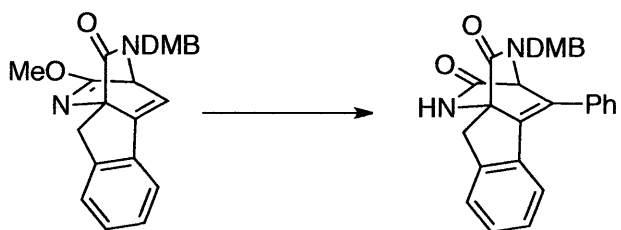
7.66 (m, 1H), 7.61–7.60 (m, 1H), 7.59 (d, $J = 1.56$ Hz, 1H), 7.42–7.37 (m, 2H), 6.64 (d, $J = 7.03$ Hz, 1H), 6.48–6.45 (m, 2H), 5.17 (s, 2H), 3.86 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.05 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.1, 160.8, 158.6, 150.4, 145.2, 140.1, 137.9, 132.2, 130.9, 128.3, 126.7, 125.2, 121.1, 117.1, 104.3, 99.6, 98.5, 77.3, 55.4, 46.9, 35.6; Exact mass calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$, 356.1257. Found 356.1253.



(3*S*,9*aS*)-11-(2,4-dimethoxybenzyl)-2-methoxy-4-phenyl-3,9-dihydro-3,9*a*-

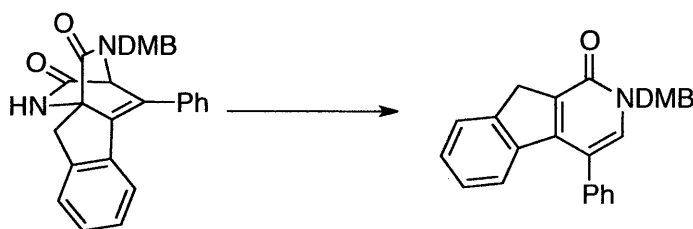
(epiminomethano)indeno[2,1-*b*]pyridin-10-one (32): Prepared according to general procedure A using **15** (100 mg, 0.36 mmol). The product was purified by flash chromatography on silica gel (elution: 20% to 65% EtOAc in hexanes) to afford a clear oil (120 mg, 0.25 mmol, 72% yield): TLC (40% EtOAc in hexanes), R_f : 0.40 (UV, CAM); IR (film) 3022, 3009, 2945, 2836, 1696, 1617, 1589, 1510, 1465, 1331, 1210, 1166, 1035, 991, 835 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.41 (d, $J = 7.82$ Hz, 1H), 7.38 (d, $J = 7.82$ Hz, 1H), 7.33–7.28 (m, 3H), 7.23 (d, $J = 0.78$ Hz, 1H), 7.21 (d, $J = 0.78$ Hz, 1H), 7.10 (d, $J = 8.21$ Hz, 1H), 7.08 (d, $J = 8.21$ Hz, 1H), 7.08 (d, $J = 7.42$ Hz, 1H), 7.01 (t, $J = 7.03$ Hz, 1H), 6.38 (dd, $J = 8.2/2.3$ Hz, 1H), 6.28 (d, $J = 2.3$ Hz, 1H), 5.00 (s, 1H), 4.67 (d, $J = 14.5$ Hz, 1H), 4.43 (d, $J = 14.5$ Hz, 1H), 4.41 (d, $J = 17.8$ Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 170.9, 160.8,

158.4, 149.9, 147.8, 135.4, 133.8, 132.5, 131.5, 129.7, 128.4, 127.8, 127.3, 126.4, 126.0, 122.2, 116.6, 104.3, 98.3, 79.5, 64.6, 55.28, 55.27, 54.9, 43.2, 35.5; Exact mass calcd for $C_{29}H_{26}N_2O_4Na$ $[M+Na]^+$, 489.1785. Found 489.1777.



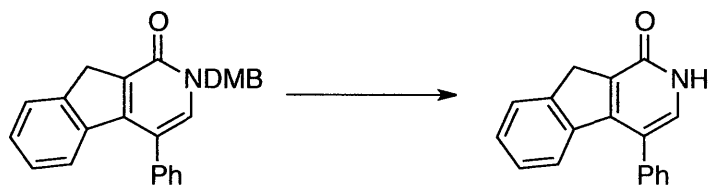
(3*S*,9*aS*)-11-(2,4-dimethoxybenzyl)-4-phenyl-3,9-dihydro-3,9*a*-

(epiminomethano)indeno[2,1-*b*]pyridine-2,10(1*H*)-dione (33): Following general procedure B, **32** (90 mg, 0.19 mmol) produced **33** without purification (88 mg, 0.188 mmol, 99% yield) as a yellow oil: TLC (40% EtOAc in hexanes), R_f : 0.18 (UV, CAM); IR (film) 3224, 3068, 2939, 2837, 1710, 1613, 1588, 1509, 1465, 1294, 1266, 1210, 1159, 1036, 936, 826, 761 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) 8.38 (br s, 1H), 7.40 (d, $J = 7.8$ Hz, 1H), 7.31–7.23 (m, 3H), 7.15 (d, $J = 8.2$ Hz, 2H), 7.07–7.01 (m, 4H), 6.38 (dd, $J = 8.4/2.1$ Hz, 2.3, 1H), 6.24 (d, $J = 2.3$ Hz, 1H), 4.59 (d, $J = 14.5$ Hz, 1H), 4.79 (s, 1H), 4.45 (d, $J = 14.1$ Hz, 1H), 4.25 (d, $J = 18.0$ Hz, 1H), 3.76 (s, 3H), 3.49 (s, 3H), 3.16 (d, $J = 17.6$, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 169.3, 161.0, 158.5, 147.3, 146.0, 134.9, 134.7, 133.4, 131.7, 130.2, 128.4, 128.3, 127.3, 127.1, 126.0, 122.8, 116.2, 104.4, 98.4, 69.9, 68.9, 55.3, 54.9, 43.7, 32.9; Exact mass calcd for $C_{28}H_{24}N_2O_4Na$ $[M+Na]^+$, 475.1628. Found 475.1625.



2-(2,4-dimethoxybenzyl)-4-phenyl-2,9-dihydro-1H-indeno[2,1-c]pyridin-1-one (34):

Following general procedure C, using **33** (70 mg, 0.15 mmol) the intermediate acylated product was produced (75 mg, 0.15 mmol, 100% yield). This intermediate product was used (70 mg, 0.15 mmol) to produce **34** following general procedure D. The product was purified by flash column chromatography on silica gel (elution: 20% to 80% EtOAc in hexanes) to afford the product (50 mg, 0.12 mmol, 90% yield) as a bright yellow solid: TLC (60% EtOAc in hexanes), R_f : 0.45 (UV, CAM); IR (film) 3053, 3001, 2835, 2361, 1648, 1612, 1590, 1505, 1457, 1430, 1377, 1287, 1266, 1207, 1158, 1125, 1034, 941, 834, 754, 704 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.57 (d, $J = 7.42$ Hz, 1H), 7.48–7.39 (m, 4H), 7.32 (t, $J = 1.17$ Hz, 2H), 7.26 (d, $J = 2.74$ Hz, 1H), 7.09 (t, $J = 7.82$ Hz, 2H), 6.97 (d, $J = 7.42$ Hz, 1H), 6.48 (s, 1H), 6.45 (s, 1H), 5.20 (s, 2H), 3.90 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.8, 158.5, 148.3, 145.6, 140.1, 137.2, 136.6, 132.2, 131.3, 129.7, 128.4, 127.8, 127.8, 126.2, 124.9, 123.7, 117.6, 117.0, 104.2, 98.5, 55.32, 55.27, 55.25, 47.0, 35.7; Exact mass calcd for $\text{C}_{27}\text{H}_{23}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$, 423.1570. Found 423.1564.



4-phenyl-2,9-dihydro-1*H*-indeno[2,1-*c*]pyridin-1-one (38): The DMB protected pyridone, **34**, (10 mg, 0.024 mmol) was dissolved in a 2:1 CH₂Cl₂:TFA (0.9 mL) and heated on temp mode in the microwave to 120 °C for 10 min. The product was purified by flash column chromatography on silica gel (elution: 0% to 15% MeOH in CHCl₃) to afford the product (4.9 mg, 0.024 mmol, 78% yield) as a white solid: TLC (60% EtOAc in hexanes), R_f: 0.35 (UV, CAM); IR (film) cm⁻¹ 2984, 1919, 1710, 1826, 1639, 1607, 1495, 1423, 1282, 1149, 1018, 945, 887; ¹H NMR (400 MHz, CDCl₃) 7.63 (d, *J* = 7.4 Hz, 1H), 7.52 (m, 4H), 7.45 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.29 (s, 1H), 7.13 (t, 7.6 Hz, 1H), 6.98 (d, *J* = 7.815, 1H), 3.90 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 161.2, 151.0, 145.0, 139.2, 135.5, 132.7, 130.4, 129.3, 128.24, 128.21, 127.8, 126.1, 124.6, 123.7, 119.6, 34.5; Exact mass calcd for C₁₈H₁₃NONa [M+Na]⁺, 282.0889. Found 282.0891.

General Procedure – Proline derived DKP

General Procedure E for aldol condensation / alkene isomerization / DKP Diels-Alder cycloaddition. To a solution of diketopiperazine **14** (1 equiv, 0.89–1.3 mmol) in toluene (0.1 M) at –78 °C was added LiHMDS (1 M in THF, 1.1 equiv) dropwise and the solution was stirred at –78 °C for 25 minutes. The corresponding aldehyde (1.2 equiv) was added and stirred for 15 minutes, followed by addition of Ac₂O (1.3 equiv). The

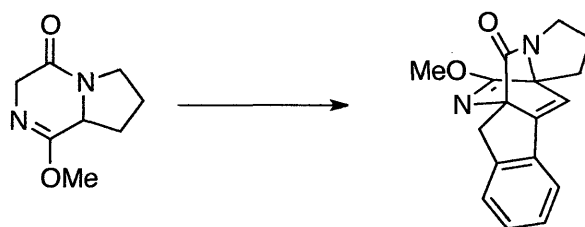
reaction mixture was warmed to rt and stirred for 4.5 h after which DBU (2 equiv) was added dropwise and the mixture was heated to 100 °C for 19 h. The reaction was quenched with saturated NH₄Cl and the aqueous phase was extracted with EtOAc (3 x 10 mL). The organic layer was washed with brine (10 mL), dried with sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (elution: 25% to 100% EtOAc in hexanes) to afford the desired product.

General Procedure F for deprotection of lactim *O*-methyl ether. The cycloadduct (1 equiv, 0.03–0.51 mmol) was dissolved in AcOH (0.05 M), KI (3 equiv) was added and the mixture was stirred at 100 °C for 2 h. The resulting mixture was quenched with water and the aqueous phase was extracted with EtOAc (3 x 150 ml) and then washed with sodium bicarbonate (3 x 100 ml). The organic phase was washed with brine, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The product was purified by flash column chromatography (elution: 25% to 100% EtOAc in hexanes) to afford the desired product.

General Procedure G for acetylation. The lactam bridge cycloadduct (1 equiv, 0.9–0.32 mmol) was dissolved in a 1:1 solution of Ac₂O (0.5 M) and pyridine (0.5 M) and stirred at 100 °C for 24 h. The solution was concentrated and submitted to the next step without purification.

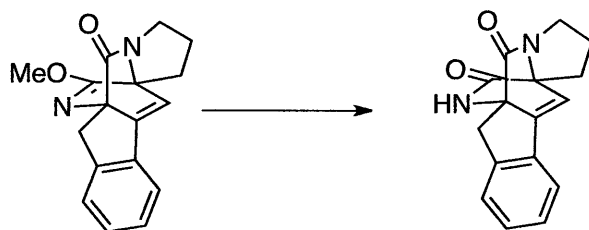
General Procedure H for cycloreversion to pyridone. The protected cycloadduct (1

equiv, 0.37–0.38 mmol), in toluene, was heated in the microwave (300 W, Power Mode) for 1 h. The solution was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography in silica gel (elution: 40% to 100% EtOAc in hexanes, 0% to 20% MeOH in chloroform) to afford the desired product.



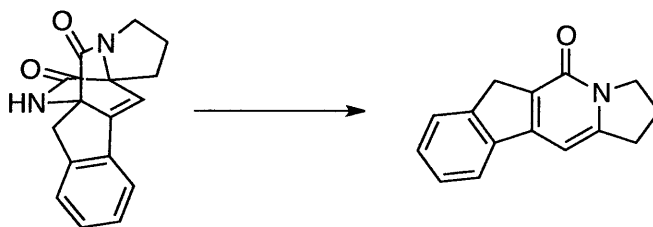
12-methoxy-2,3-dihydro-1*H*-5a,11a-(azenometheno)indeno[2,1-*f*]indolizin-5(6*H*)-one

(26): Produced following general procedure E using **14** (150 mg, 0.89 mmol). The product was purified by flash column chromatography on silica gel (elution: 30% to 100% EtOAc in hexanes) to afford the product (115 mg, 0.41 mmol, 46% yield) as a brown oil: TLC (40% EtOAc in hexanes), *R_f*: 0.20 (UV, KMnO₄); IR (film) 3269, 2984, 2951, 2879, 1735, 1617, 1454, 1437, 1339, 1221, 1175, 1107, 1041, 1006, 841, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.39 (d, *J* = 7.42 Hz, 1H), 7.34 (d, *J* = 7.82 Hz, 1H), 7.30 (d, *J* = 7.43 Hz, 1H), 7.20 (t, *J* = 7.42 Hz, 1H), 6.45 (s, 1H), 4.32 (d, *J* = 17.6 Hz, 1H), 3.77 (s, 3H), 3.51 (d, *J* = 18.0 Hz, 1H), 3.43–3.39 (m, 1H), 3.27–3.22 (m, 1H), 2.83–2.76 (m, 1H), 2.31–2.24 (m, 1H), 2.18–2.12 (m, 1H), 2.09–2.04 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 174.8, 169.5, 159.8, 147.5, 133.4, 129.8, 126.8, 126.0, 121.9, 119.7, 80.4, 70.4, 55.5, 42.1, 34.9, 27.0, 25.4; Exact mass calcd for C₁₇H₁₆N₂O₂Na [M+Na]⁺, 303.1104. Found 303.1102.



2,3-dihydro-1*H*-5a,11a-(epiminomethano)indeno[2,1-*f*]indolizine-5,12(6*H*)-dione

(27): Produced following general procedure F using **26** (58 mg, 0.21 mmol). The product was obtained without purification (50 mg, 0.19 mmol, 98% yield) as a dark brown solid: TLC (60% EtOAc in hexanes), *R_f*: 0.30 (UV, KMnO₄); IR (film) 3229, 3070, 2976, 2942, 2879, 1691, 1465, 1393, 1326, 1260, 1195, 1156, 1086, 754, 668 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.66 (br. s, 1H), 7.38 (d, *J* = 7.82, 1H), 7.36–7.30 (m, 2H), 7.25 (m, 1H), 6.50 (s, 2H), 4.16 (d, *J* = 18.0, 1H), 3.51 (m, 1H), 3.30 (m, 1H), 3.12 (d, *J* = 17.6, 1H), 2.86 (m, 1H), 2.18–2.03 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 173.6, 168.1, 157.4, 146.2, 133.3, 130.7, 127.9, 126.4, 122.9, 122.0, 73.0, 70.7, 43.3, 32.8, 27.3, 25.5; Exact mass calcd for C₁₆H₁₄N₂O₂Na [M+Na]⁺, 289.0947. Found 289.0946.



2,3-dihydro-1*H*-indeno[2,1-*f*]indolizin-5(6*H*)-one (28): Following general procedure F, using **27** (26 mg, 0.09 mmol) the intermediate acylated product was produced (30 mg, 100% yield). This intermediate product was used (30 mg, 0.26 mmol) to produce

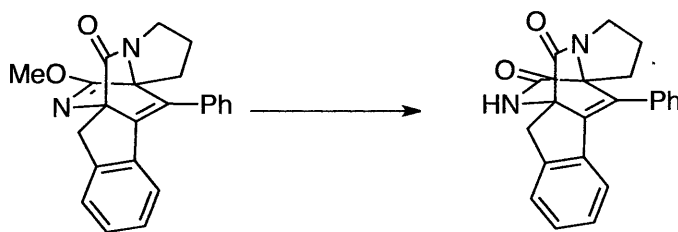
28 following general procedure H. The product was purified by flash column chromatography on silica gel (elution: 50% to 100% EtOAc in hexanes and 0% to 20% MeOH and EtOAc) to afford the product (18 mg, 0.08 mmol, 83% yield) as a dark brown solid: TLC (60% EtOAc in hexanes), R_f 0.10 (UV, KMnO_4); IR (film) 3420, 3053, 2964, 2896, 1657, 1570, 1457, 1295, 1296, 1241, 1152, 1096, 1019, 803, 772, 752 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.68 (m, 1H), 7.41–7.39 (m, 2H), 7.28 (d, $J = 2.74$, 1H), 6.62 (s, 1H), 4.24–4.20 (m, 2H), 3.83 (s, 2H), 3.18–3.14 (t, $J = 7.23$, 2H), 2.29–2.23 (m, 2H) ^{13}C NMR (100 MHz, CDCl_3) δ 160.5, 151.9, 150.7, 145.8, 140.4, 128.5, 128.1, 126.9, 125.5, 121.3, 95.5, 48.6, 35.2, 32.1, 22.2; Exact mass calcd for $\text{C}_{15}\text{H}_{13}\text{NONa}$ $[\text{M}+\text{Na}]^+$, 246.0889. Found 246.0887.



12-methoxy-11-phenyl-2,3-dihydro-1*H*-5a,11a-(azenometheno)indeno[2,1-

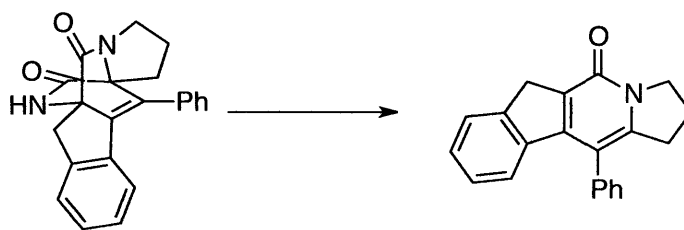
***f*]indolizin-5(6*H*)-one (35):** Produced following general procedure E using **14** (220 mg, 1.3 mmol). The product was purified by flash column chromatography on silica gel (elution: 20% to 80% EtOAc in hexanes) to afford the product (200 mg, 0.56 mmol, 43% yield) as a yellow oil: TLC (40% EtOAc in hexanes), R_f 0.20 (UV, KMnO_4); IR (film) 3052, 2883, 1691, 1622, 1399, 1324, 1287, 1174, 1129, 1007, 755, 743, 702 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.43–7.28 (m, 2H), 7.41–7.36 (m, 2H), 7.24–7.18 (m, 3H), 6.95

(s, 2H), 4.37 (d, $J = 18.0$ Hz, 1H), 3.87 (s, 3H), 3.53 (d, $J = 18.0$ Hz, 1H), 3.48–3.46 (m, 1H), 3.27–3.24 (m, 1H), 2.58–2.55 (m, 1H), 2.02–1.93 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 175.2, 169.9, 152.9, 147.6, 134.9, 134.0, 133.98, 132.0, 129.6, 128.7, 128.6, 128.0, 126.5, 125.9, 122.3, 79.9, 73.4, 55.9, 53.4, 42.6, 35.0, 25.5, 22.0; Exact mass calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$, 379.1417. Found 379.1414.

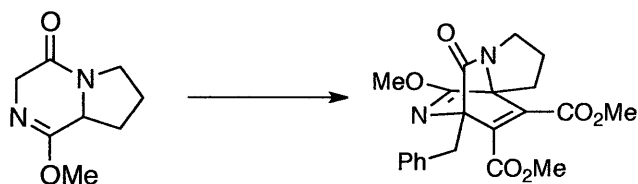


11-phenyl-2,3-dihydro-1*H*-5a,11a-(epiminomethano)indeno[2,1-*f*]indolizine-

5,12(6*H*)-dione (36): Produced following general procedure F using **35** (431 mg, 1.2 mmol). The product was purified by flash column chromatography on silica gel (elution: 25% to 100% EtOAc in hexanes) to afford the product (355 mg, 1.0 mmol, 87% yield) as a tan solid: TLC (60% EtOAc in hexanes), R_f : 0.30 (UV, KMnO_4); IR (film) 3229, 3057, 2979, 1959, 2882, 1669, 1467, 1394, 1331, 1313, 1266, 1199, 1154, 1074, 1031, 734, 704 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 8.32 (s, 1H), 7.26–7.37 (m, 3H), 7.32 (d, $J = 7.82$ Hz, 1H), 7.27–7.25 (m, 1H), 7.23–7.20 (m, 2H), 7.03–6.97 (m, 2H), 4.23 (d, $J = 18.0$ Hz, 1H), 3.57–3.53 (m, 1H), 3.36–3.30 (m, 1H), 3.20 (d, $J = 18.4$ Hz, 1H), 2.64–2.59 (m, 1H), 1.97–1.84 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 173.9, 168.1, 150.2, 145.9, 136.7, 133.7, 133.5, 130.0, 128.4, 128.3, 127.2, 125.9, 123.0, 75.8, 70.2, 43.3, 32.5, 25.5, 25.2; Exact mass calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$, 365.1260. Found 365.1260.

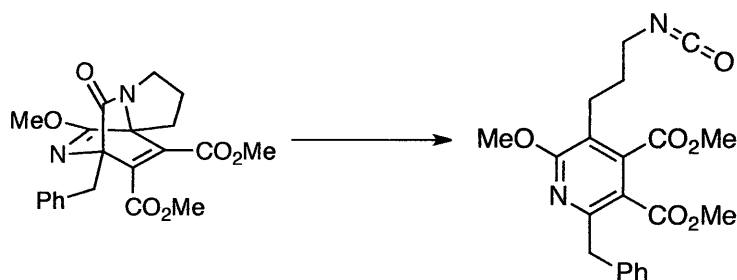


11-phenyl-2,3-dihydro-1H-indeno[2,1-f]indolizin-5(6H)-one (37): Following general procedure F, using **36** (110 mg, 0.32 mmol) the intermediate acylated product was produced (115 mg, 0.30 mmol, 94% yield). This intermediate product was used (115 mg, 0.30 mmol) to produce **37** following general procedure H. The product was purified by flash column chromatography on silica gel (elution: 40% to 100% EtOAc in hexanes and 0% to 20% MeOH and EtOAc) to afford the product (74 mg, 0.25 mmol, 83% yield) as a mustard yellow solid: TLC (60% EtOAc in hexanes), R_f : 0.45 (UV, KMnO_4); IR (film) 3411, 3051, 2980, 2896, 1642, 1623, 1564, 1531, 1495, 1442, 1387, 1285, 1208, 1165, 1029 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 7.57 (d, $J = 7.42$ Hz, 1H), 7.52–7.49 (m, 3H), 7.37–7.34 (m, 2H), 7.29 (m, 1H), 7.05 (t, $J = 7.82$ Hz, 1H), 6.63 (d, $J = 7.82$ Hz, 1H), 4.34–4.30 (m, 2H), 3.89 (s, 2H), 2.93 (t, $J = 7.03$ Hz, 2H), 2.25–2.17 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.5, 149.9, 148.0, 145.8, 140.3, 136.4, 130.1, 128.8, 128.0, 127.7, 126.2, 125.0, 123.7, 113.2, 77.3, 48.8, 34.9, 31.0, 21.8; Exact mass calcd for $\text{C}_{21}\text{H}_{17}\text{NONa}$ $[\text{M}+\text{Na}]^+$, 322.1202. Found 322.1200.



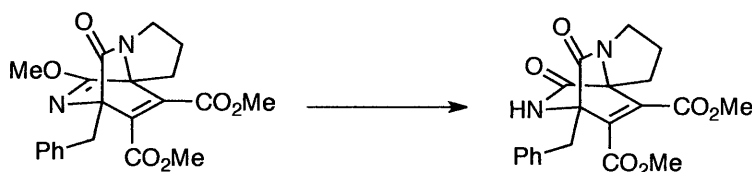
(6*S*,8*aS*)-dimethyl 6-benzyl-9-methoxy-5-oxo-2,3,5,6-tetrahydro-1*H*-6,8*a*-(*azenometheno*)indolizine-7,8-dicarboxylate (40): To proline DKP, **14**, (1.2 mmol) in toluene at $-78\text{ }^{\circ}\text{C}$ was added LiHMDS (1.0M in THF, 1.1 equiv.) dropwise over 5 minutes by syringe. After stirring for 25 minutes at $-78\text{ }^{\circ}\text{C}$, benzaldehyde (1.2 equiv.) was added to the solution. Ac_2O (1.3 equiv.) was added dropwise at $-78\text{ }^{\circ}\text{C}$, and the solution was allowed to warm to room temperature while stirring. DBU (2 equiv.) was added and the mixture stirred at rt for 16 hours. The reaction was washed with NH_4Cl (20 mL) and extracted with EtOAc (10 mL x 3). The organic layer was washed with brine (10 mL), dried with Na_2SO_4 , and then concentrated *in vacuo*. To the product (3.1 mmol) in DMF (20 mL) was added DMAD (1.2 equiv.). The reaction mixture was concentrated and purified by flash chromatography on silica gel (elution: 10%–50% EtOAc in hexanes) to afford a pale yellow solid (390 mg, 37% yield). TLC (60% EtOAc in hexanes), R_f : 0.60 (KMnO_4); IR (film) cm^{-1} 3036, 2990, 2959, 2890, 1740, 1694, 1636, 1496, 1434, 1388, 1206, 1144, 1097, 981, 1080, 894, 792, 698; ^1H NMR (400 MHz, CDCl_3) 7.57–7.55 (d, 2H, $J = 7.0$ Hz), 7.27–7.16 (m, 3H), 3.88 (s, 3H), 3.71 (s, 3H), 3.67 (d, 1H, $J = 15.4$ Hz), 3.45 (s, 3H), 3.18 (m, 1H), 2.80 (m, 1H), 2.49 (m, 1H), 2.04 (m, 1H), 1.91 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 168.2, 164.9, 162.4, 152.3, 138.0, 136.6, 130.8, 127.5, 126.3, 74.3, 68.3, 56.4, 52.3, 52.2, 43.0, 35.0, 25.9, 25.2; HRMS (ES⁺): Exact mass calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 421.1370 Found

421.1365.



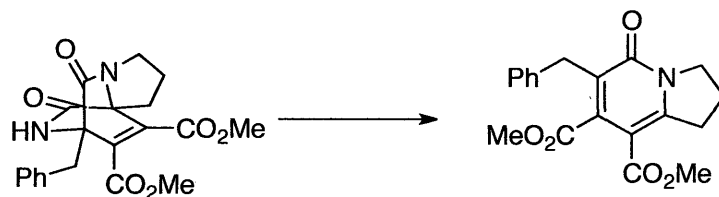
dimethyl 2-benzyl-5-(2-isocyanatoethyl)-6-methoxypyridine-3,4-dicarboxylate (41):

Cycloadduct **40** (20 mg, 0.05 mmol) in toluene (2 mL) was heated in the microwave at 300 W for 1 hr 15 min. The reaction was concentrated to afford a clear colorless oil (15 mg, 75% yield). TLC (60% EtOAc in hexane), R_f: 0.70 (KMnO₄); IR (film) cm⁻¹ 2952, 2277, 1735, 1653, 1576, 1440, 1297, 1262, 1194, 1089, 1075, 668; ¹H NMR (400MHz, CDCl₃) 7.31–7.26 (m, 3H), 7.22–7.16 (m, 2H), 4.29 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.32–3.30 (t, *J* = 6.4 Hz, 2H), 2.63–2.60 (t, *J* = 7.6 Hz, 2H), 1.88–1.83 (quintet, *J* = 7.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) 167.8, 167, 3, 162.7, 157.5, 143.7, 139.4, 129.4, 128.6, 128.4, 126.5, 122.2, 119.1, 117.7, 54.5, 53.0, 52.7, 42.9, 42.0, 30.9, 24.6; HRMS (ES⁺): Exact mass calcd for C₂₁H₂₂N₂O₆ 421.1370 Found 421.1366.



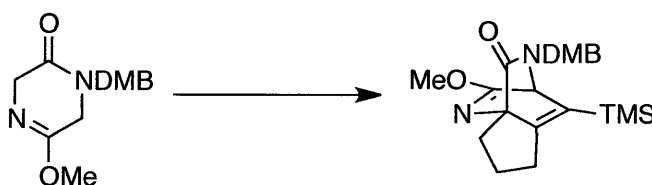
(6*S*,8*aS*)-dimethyl 6-benzyl-5,9-dioxo-2,3,5,6-tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-7,8-dicarboxylate (42): Cycloadduct **40** (250 mg, 0.63

mmol) in AcOH was added KI (3 equiv.) and stirred at 115 °C for 30 minutes. The reaction was diluted with water (50 mL) and Na₂CO₃ (10%, 20 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was washed with NaHCO₃ with thiosulfate (20 mL), brine (20 mL), dried with Na₂SO₄, and concentrated *in vacuo* to afford a pale yellow powder (240 mg, 100%). TLC (60% EtOAc in hexane), R_f: 0.30 (KMnO₄); IR (film) cm⁻¹ 3220, 2955, 1715, 1670, 1497, 1405, 1283, 1146, 1039, 970; ¹H NMR (400MHz, CDCl₃) 7.39–7.27 (m, 5H), 5.86 (s, 1H), 3.92 (d, 1H, *J* = 15 Hz), 3.82 (s, 3H), 3.80 (s, 3H), 3.52 (m, 1H), 3.34–3.27 (m, 2H), 2.83 (m, 1H), 2.30 (m, 1H), 2.09–2.00 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.6, 166.1, 163.7, 162.7, 147.7, 142.6, 133.4, 130.6, 129.2, 127.8, 70.9, 65.3, 52.8, 52.8, 43.8, 32.4, 25.7, 24.9; HRMS (ES⁺): Exact mass calcd for C₂₀H₂₀N₂O₆ 407.1214 Found 407.1209.



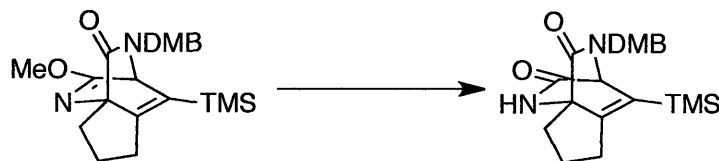
dimethyl 6-benzyl-5-oxo-1,2,3,5-tetrahydroindolizine-7,8-dicarboxylate (43): The DMAD lactam cycloadduct, **42**, (20 mg, 0.05 mmol) in Ac₂O (2 mL) was heated in a sealed tube to 140 °C for 17 hr and cooled to rt. The mixture was washed with NH₄Cl (20 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was washed with brine (10 mL), dried with Na₂SO₄, and then concentrated *in vacuo*. The product was purified by flash column chromatography (elution: 30-80% EtOAc in hexanes) to afford a white solid (15 mg, 84% yield). TLC (60% EtOAc in hexane), R_f: 0.20 (KMnO₄); IR (film) cm⁻¹

2952, 1740, 1713, 1652, 1600, 1540, 1416, 1382, 1295, 1240, 1168, 1093, 1002, 737; ¹H NMR (400MHz, CDCl₃) 7.35–7.34 (m, 2H), 7.26–7.24 (m, 2H) 7.15 (m, 1H), 4.16–4.13 (t, 2H, *J* = 7.6Hz), 3.88 (s, 2H), 3.82 (s, 6H), 3.50 (t, 2H, *J* = 7.8Hz), 2.19 (quintet, 2H, *J* = 7.8Hz); ¹³C NMR (100 MHz, CDCl₃) 167.9, 164.6, 161.1, 155.8, 142.2, 138.6, 129.0, 128.1, 126.6, 126.2, 102.7, 77.3, 52.5, 52.1, 49.7, 34.5, 33.6, 20.5; HRMS (ES⁺): Exact mass calcd for C₁₉H₁₉NO₅, 364.1155. Found 364.1151.



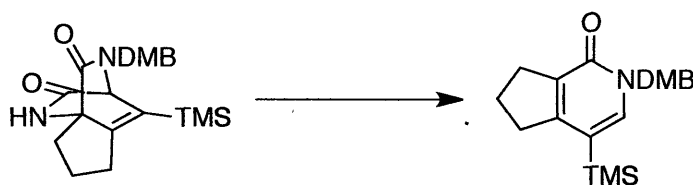
(3*R*,7*aS*)-9-(2,4-dimethoxybenzyl)-2-methoxy-4-(trimethylsilyl)-3,5,6,7-tetrahydro-3,7*a*-(epiminomethano)cyclopenta[*b*]pyridin-8-one (46): Prepared according to general procedure A using **15** (200 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (elution: 30% to 90% EtOAc in hexanes) to afford a yellow oil (260 mg, 87% yield): TLC (40% EtOAc in hexanes), *R*_f: 0.15 (UV, CAM); IR (film) 2959, 2839, 1679, 1615, 1576, 1506, 1459, 1405, 1333, 1250, 1140, 1035, 867, 843; (400 MHz, CDCl₃) 6.96 (dd, *J* = 8.42/1.6Hz, 1H), 6.40 (m, 2H), 4.66 (d, *J* = 2.0 Hz, 1H), 4.41 (dd, *J* = 14.7/1.4Hz, 1H), 4.19 (dd, *J* = 14.7/1.4 Hz, 1H) 3.784-3.782 (d, *J* = 2.0 Hz, 3H), 3.76–3.75 (d, *J* = 0.8 Hz, 3H), 3.624-3.622 (d, 0.8 Hz., 3H), 2.98 (m, 1H), 2.42 (m, 1H), 2.31 (m, 1H), 2.08-2.00 (m, 2H), 1.83 (m, 1H) 0.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 174.8, 170.5, 169.4, 160.4, 159.2, 130.8, 129.8, 116.7, 104.0, 98.1, 81.2, 79.0, 60.6, 55.1, 55.0, 54.7, 42.7, 29.5, 28.8, 26.3, -1.8. HRMS (ES⁺): Exact mass calcd for

C₁₄H₂₄O₂Si [M+Na]⁺, 275.1438. Found 275.1439.



(3*R*,7*aS*)-9-(2,4-dimethoxybenzyl)-4-(trimethylsilyl)-3,5,6,7-tetrahydro-3,7a-

(epiminomethano)cyclopenta[*b*]pyridine-2,8(1*H*)-dione (47): Following general procedure B, **46** (200 mg, 0.48 mmol) produced **47** without purification (170 mg, 88% yield) as a pale brown solid: TLC (60% EtOAc in hexanes), *R_f*: 0.4 (UV, KMnO₄); IR (film) cm⁻¹ 3516, 3209, 2945, 2834, 1680, 1614, 1507, 1447, 1292, 1251, 1209, 1036; ¹H NMR (400 MHz, CDCl₃) 8.04 (br. s, 1H), 7.03 (dd, *J* = 7.8/2.7Hz, 1H), 6.4-6.40 (m, 2H), 4.45 (d, *J* = 2.34, 2H), 4.08 (t, *J* = 1.8Hz, 1H), 3.79-3.77 (t, *J* = 3.7 Hz, 6H), 2.79 (m, 1H), 2.44-2.40 (m, 2H), 2.09-2.03 (m, 2H), 1.91 (m, 1H), 1.77 (m, 1H), 0.00 (d, *J* = 3.1 Hz, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 173.2, 169.4, 166.4, 160.8, 158.6, 134.1, 131.1, 116.4, 104.4, 98.5, 71.3, 65.5, 55.4, 55.3, 43.2, 29.0, 27.6, 26.6. HRMS (ES⁺): Exact mass calcd for C₂₁H₂₈N₂O₄Si [M+Na]⁺, 423.1711. Found 423.1714.



2-(2,4-dimethoxybenzyl)-4-(trimethylsilyl)-2,5,6,7-tetrahydro-1*H*-

cyclopenta[*c*]pyridin-1-one (48): Following general procedure C, using **47** (110 mg,

0.28 mmol) the intermediate acylated product was produced (118 mg, 97% yield). This intermediate product was used (118 mg, 0.27 mmol) to produce the pyridone, **48**, following general procedure D. The product was purified by flash column chromatography on silica gel (elution: 50% to 100% EtOAc in hexanes) to afford the product (85 mg, 0.24 mmol, 89% yield) as a brown oil: TLC (60% EtOAc in hexanes), R_f : 0.1 (UV, KMnO_4); IR (film) cm^{-1} 3168, 2963, 2834, 2475, 2064, 1699, 1636, 1496, 1456, 1374, 1319, 1253, 1041; ^1H NMR (400 MHz, CDCl_3) 7.43 (d, $J = 9.8$ Hz, 1H), 7.41 (s, 1H), 6.43 (d, $J = 2.0$, 2H), 5.05 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 2.82–2.76 (quartet, $J = 7.8$ Hz, 4H), 2.03–1.99 (quintet, 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.0, 160.6, 158.4, 157.9, 141.8, 132.5, 131.6, 117.4, 111.2, 105.0, 98.2, 55.3, 55.1, 46.4, 34.9, 29.5, 23.4, -0.9. HRMS (ES⁺): Exact mass calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_3\text{Si}$ $[\text{M}+\text{Na}]^+$, 380.1652. Found 380.1655.

Chapter 3

Synthesis of Louisianin B

Isolation of Louisianins

In 1995, Omura and co-workers isolated Louisianins A through D from a cultured broth of *Streptomyces* sp. WK-4028 from a soil sample collected in Louisiana.¹ Louisianins A (1) and B (2) are pyridones, while Louisianins C (3) and D (4) are pyridines (**Figure 3.1**). Members of this small family of molecules share a common feature that the pyridine or pyridone core is fused with a five-membered ring at the C-3 and C-4 positions. Louisianin B has a hydroxyl group instead of a carbonyl on the cyclopentane ring, giving it a stereocenter; however, Omura did not determine the stereochemistry of the natural product.

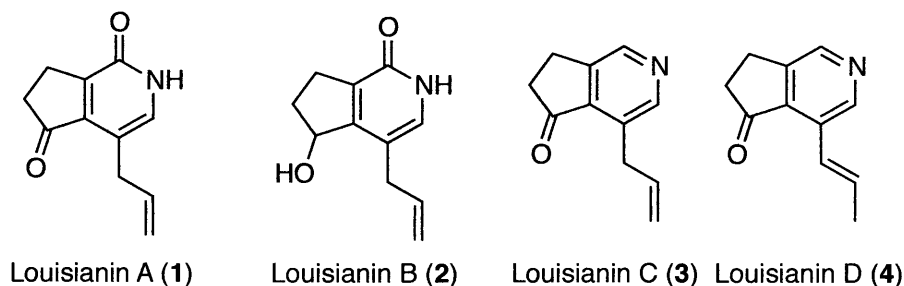


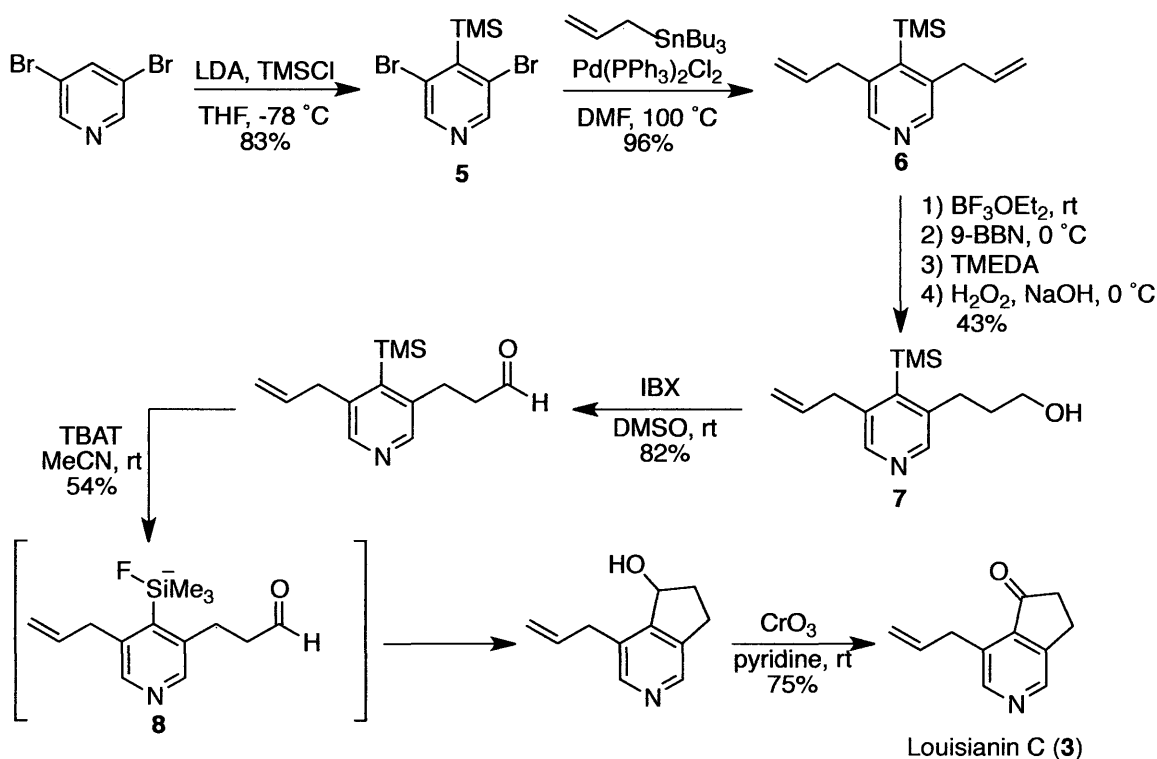
Figure 3.1 Louisianin family structures

Louisianin A has been shown to inhibit the growth of SC115 cancer cells, a class of androgen-dependent mouse mammary tumor cells. Louisianins C and D are isolated in very small amounts. To acquire sufficient material for the determination of biological activity, Omura demonstrated that the conversion of louisianin A to both

louisianin C and D was possible in 51% and 43% yields, respectively. After obtaining ample amounts of the pyridine natural products, it was determined that louisianin C and D are suppressors of vascular endothelial cells.²

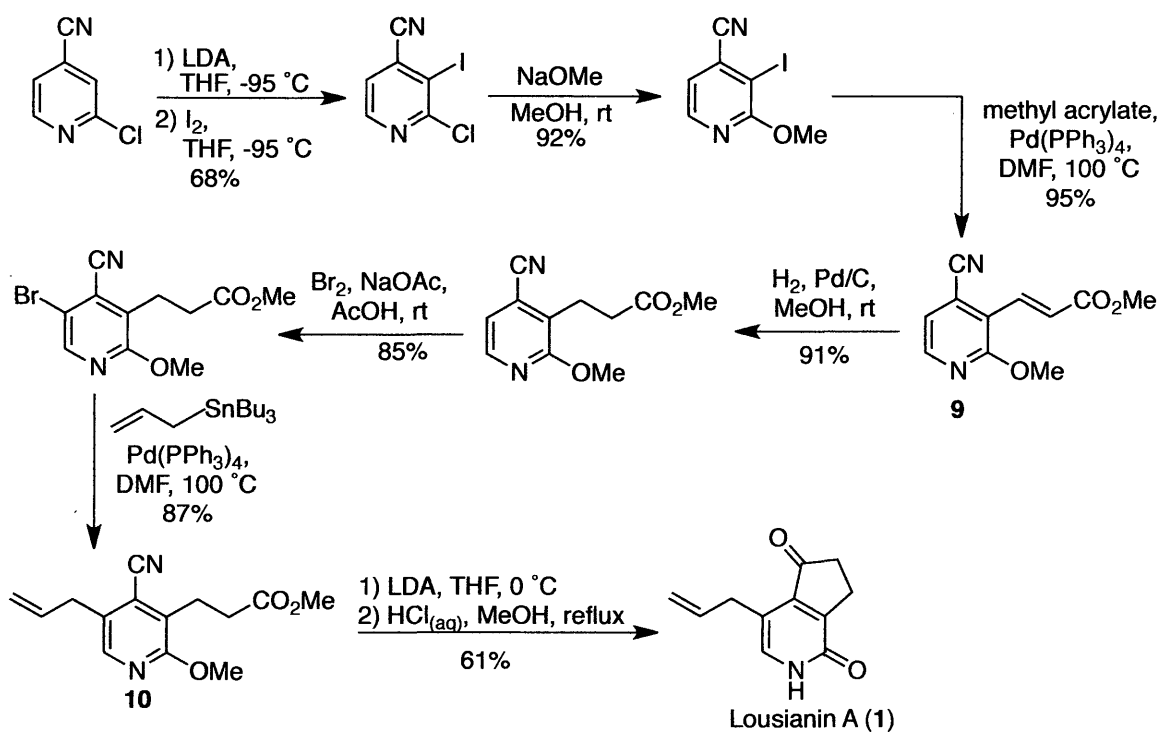
Previous Syntheses of Louisianin Family

Kelly, in 2003, completed the first synthesis of a member of the louisianin family, louisianin C (**Scheme 3.1**).³ Beginning with a symmetrical 3,5-dibromopyridine, Kelly treated the pyridine with LDA and trapped the lithiated intermediate with TMSCl to form **5**. A double Stille coupling produced allylated pyridine **6**. Hydroboration and oxidation of one allyl residue preceded formation of alcohol **7** followed by oxidation using iodoxybenzoic acid, IBX. TBAT was then used to fluorinate the TMS group, forming **8** which possesses more nucleophilic character at position 4 of the pyridine ring. This set up for subsequent desilylation and cyclization through nucleophilic addition into the aldehyde. An oxidation using CrO₃ provided the final product, louisianin C (**3**), in six steps with 11% overall yield. Kelly demonstrated how functionalization of a commercially available symmetric pyridine could construct the desired natural product.



Scheme 3.1 Kelly's synthesis of louisianin C

In 2006, Chang reported the first synthesis of louisianin A from a starting asymmetrical 2-chloro-4-cyanopyridine (**Scheme 3.2**).⁴ The C-3 position was deprotonated using LDA and subsequently iodinated. A Heck reaction was then utilized to couple the pyridine to methyl acrylate. This product **9** was then hydrogenated to afford the saturated chain, which would later be transformed into the fused cyclopentane ring system. A bromine was next attached at C-5, setting up for a Stille coupling to add the pendant allyl group onto the pyridine ring to form **10**. Finally, cyclization occurred through a Dieckmann condensation, in which nucleophilic attack on the nitrile closes the cyclopentanone ring and is followed by decarboxylation to form the final pyridone, louisianin A (**1**), in seven overall steps with 24% yield.

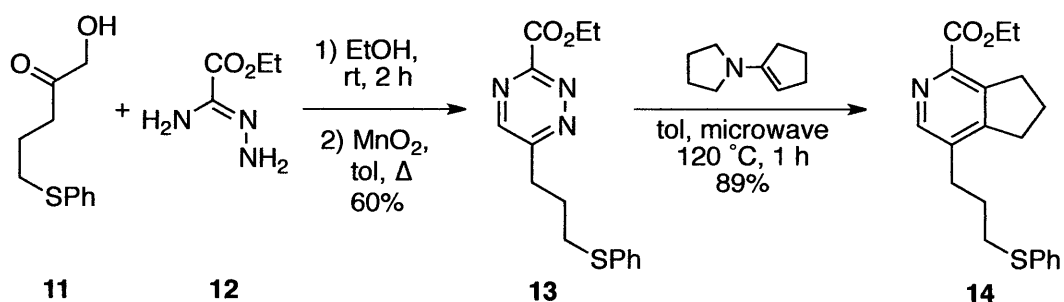


Scheme 3.2 Chang's synthesis of lousianin A

Previous syntheses of this family of molecules involved using a commercially available pyridine as the starting material. In 2006, Chang was able to synthesize lousianin D (4) in 10 steps with 20% yield overall. This was achieved by accessing a glutarimide through a [3+3] annulation of an α -sulfonyl acetamide with an α,β -unsaturated ester.⁵ Subsequent aromatization and allylation were required to achieve the desired natural product.

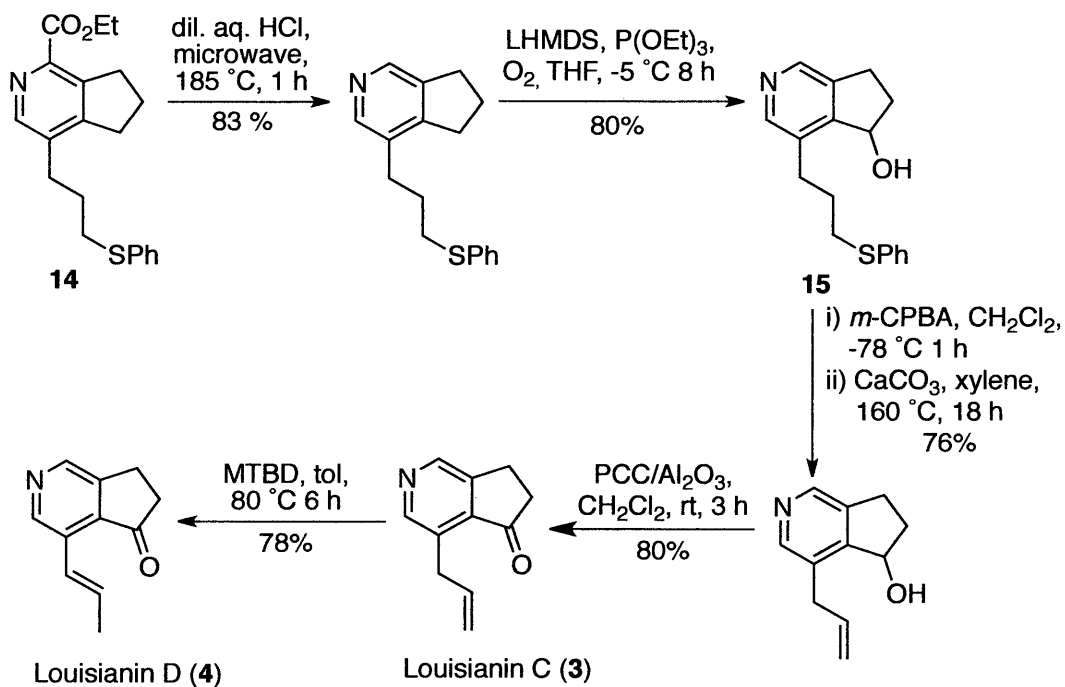
The previous syntheses were able to form lousianin A, C, and D. Lousianin B had not been synthesized until Taylor, in 2009, was able to access all four members of the lousianin family through an inverse electron demand Diels-Alder.⁶ A 1,2,4-triazine was used as the azadiene for the Diels-Alder. First, Taylor had to construct the triazine core

(**Scheme 3.3**). This required the condensation between **11** and **12** to form an amidrazone hydrazone, which underwent subsequent oxidative cyclocondensation to produce the needed triazine, **13**. This set up for the cycloaddition with an enamine, which is followed by cycloreversion in one pot with loss of diatomic nitrogen. This successfully constructed the pyridine core that was the common intermediate **14** on route to all four louisianin family members.



Scheme 3.3 Taylor's route to common intermediate

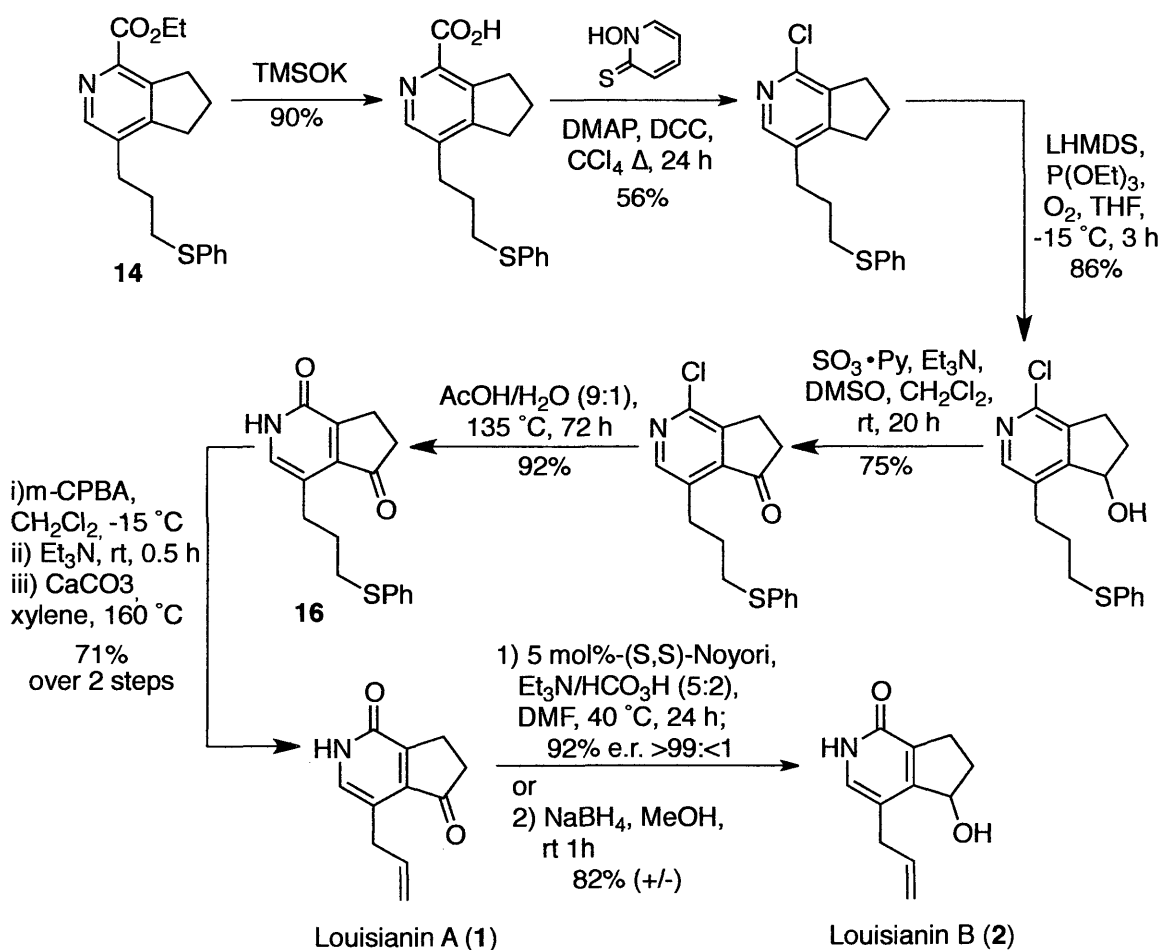
For the route to louisianin C and D, decarbonylation occurred after washing with dilute HCl, and oxidation of the cyclopentane ring was accomplished using LiHMDS and molecular oxygen to produce benzylic alcohol **15** (**Scheme 3.4**). The sulfide was then oxidized to the sulfoxide using *m*-CPBA, followed by heating to eliminate the benzenesulfonic acid. The secondary alcohol was then oxidized to reveal louisianin C (**3**) in 11 steps with 7.2% overall yield. Louisianin C was then converted into louisianin D (**4**) through an isomerization of the allyl group using 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) in toluene and heating to 80 °C. Louisianin D was synthesized in 12 steps with a 5.6% yield overall.



Scheme 3.4 Taylor's synthesis toward louisianin C and D

After producing the two pyridine natural products, Taylor aimed to synthesize the pyridones, louisianin A (1) and B (2). Using common intermediate 14, Taylor converted the ethyl ester into an acid using TMSOK (Scheme 3.5). The acid underwent radical decarboxylative halogenation through a Barton ester intermediate. An oxidation similar to that used toward louisianin C and D installed the benzylic alcohol functionality. A Parikh-Doering oxidation was then used to convert this benzylic alcohol into a ketone. Next, treatment with acetic acid and water hydrolyzed the chloropyridine to form the desired pyridone core 16. A similar approach for the allylation was subsequently employed to form louisianin A (1) in 11 steps with an overall yield of 3.8%. To access louisianin B required a reduction to form the benzylic alcohol. This was done in two

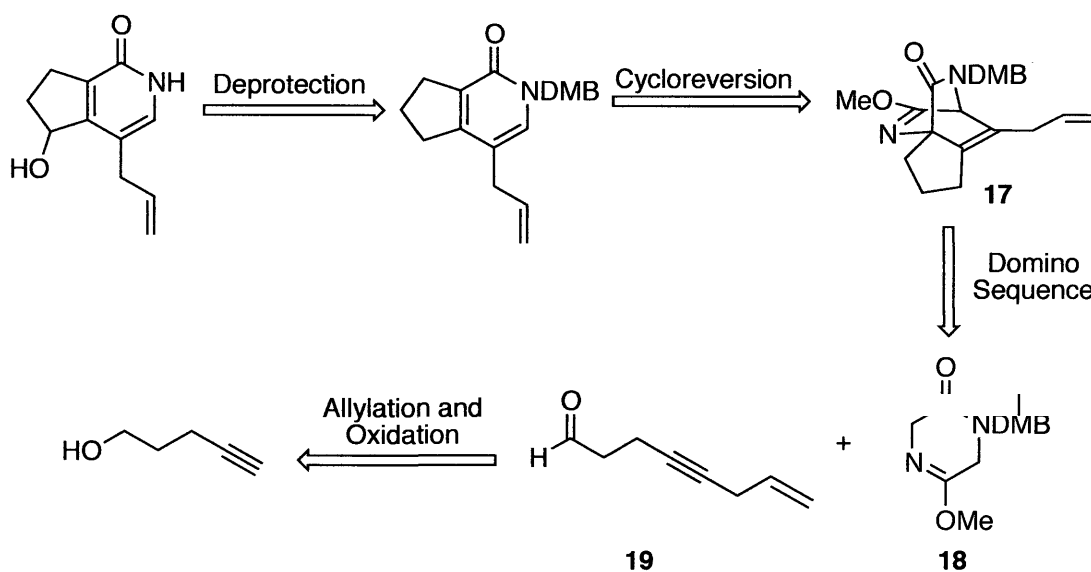
ways, either to form the racemic mixture or an enantiopure product. The racemic method required a sodium borohydride reduction; Taylor was able to synthesize racemic lousianin B (**2**) in 12 steps with an overall yield of 3.1%. The enantioselective synthesis of (-)-lousianin B was completed through a Noyori reduction using a ruthenium catalyst. The total synthesis of enantiopure (-)-lousianin B was completed in 12 steps in a 3.5% overall yield.



Scheme 3.5 Taylor's synthesis toward lousianin A and B

Route Towards Louisianin B

Having optimized cycloreversion conditions on model substrates, we anticipated an application toward the synthesis of louisianin B. We envisioned a late stage oxidation to install the hydroxyl functionality on the fused cyclopentane ring system, followed by a deprotection of the pyridone nitrogen to reveal the final natural product (**Scheme 3.6**). A similar sequence as described in Chapter 2 would be used to convert the cycloadduct **17** into the desired pyridone. This cycloadduct would be constructed from the DMB DKP **18** and aliphatic aldehyde **19**.

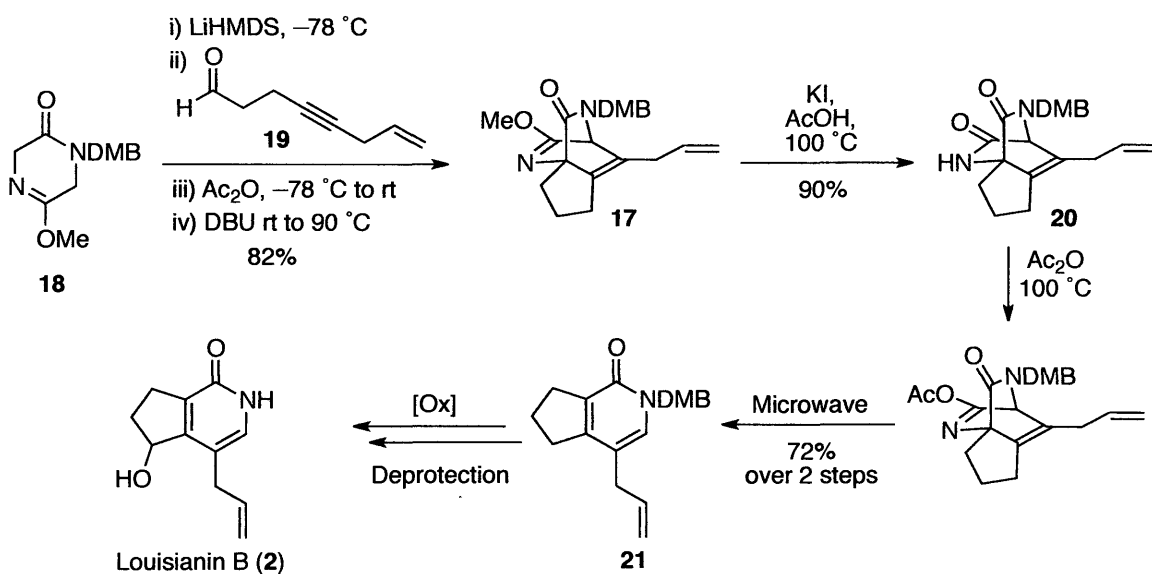


Scheme 3.6 Retrosynthesis of louisianin B route

Aldehyde **19** was simple in construction, first requiring an allylation of pent-4-yn-1-ol using allyl bromide, potassium carbonate, tetrabutylammonium chloride, and copper (I) chloride as a catalyst. Once the alkyne was allylated, it was oxidized using Parikh-Doering conditions to reveal the final aldehyde **19** with yield of 67% over two

steps. With the aliphatic aldehyde in hand, we attempted the one pot sequence with the DMB protected DKP **18** (Scheme 3.7). Enolization of **18** with LiHMDS was followed by addition of the aldehyde. Acetic anhydride was added to facilitate acetyl elimination upon addition of DBU. Subsequent isomerization converted the elimination product into the desired *endo* azadiene, setting up for an intramolecular Diels-Alder cycloaddition to produce cycloadduct **17**.

To access the desired louisianin pyridone, this cycloadduct was then submitted to the conditions that were optimized in the methodological section. Potassium iodide and acetic acid were used to deprotect the lactim ether bridge to form **20**, which could then be functionalized with the electron-withdrawing acetate group. Microwave irradiation was then able to afford the desired protected pyridone **21**. After this, the only remaining step besides deprotection was the oxidation of the benzylic position of the cyclopentane to yield louisianin B.



Scheme 3.7 Synthetic scheme towards louisianin B with aliphatic aldehyde

Since the desired oxidation position was benzylic with the most nucleophilic character, we anticipated that the pyridone would most likely enolize at that position. LiHMDS and LDA proved not to form the enolate, resulting in starting material. Knowing that enolization was the problematic step, we looked to use potassium *t*-butoxide as the base. Three equivalences of potassium *t*-butoxide caused oxidation at the desired benzylic position; however, we also observed isomerization of the allyl group resulting in **22** in 64% yield (**Figure 3.2**).

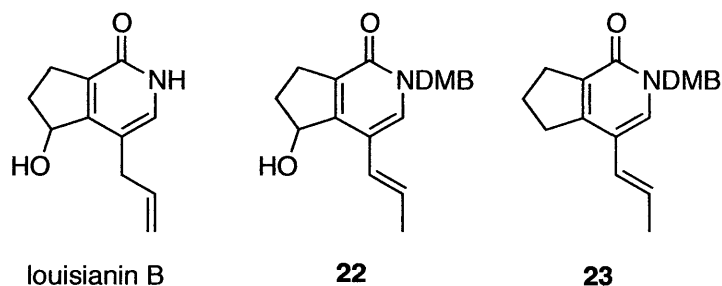


Figure 3.2 Louisianin B and products from K₂O_tBu oxidations

For this reason, we wanted to determine whether the isomerization or oxidation was occurring first; to accomplish this, we performed the reaction at 0 °C with only one equivalence of base. From this, we could determine that the isomerization was occurring first, forming **23**. Since the allyl group was inadvertently affected by the late stage oxidation, we concluded that oxidation could not be performed after installation of the allyl group without isomerization.

In 2006, Chang used potassium *t*-butoxide to isomerize an allyl group that had been installed on a pyridine ring in their synthesis of louisianin D, although their work

required the system to be heated to reflux in THF.⁵ Our experiment showed that even though the isomerization required heat for Chang, we were able to isomerize and oxidize our pyridone core at 0 °C.

Revised Route Towards Louisianin B

Because alkene isomerization during oxidation could not be prevented, we aimed to synthesize an oxygenated aldehyde. It was unclear whether a substrate with a β -alkoxy group would be compatible with the reaction conditions that had been optimized to form 2-pyridones. To form the desired azadiene **24** for the reaction sequence, DBU must deprotonate H_a ; however, deprotonation of H_b was possible, which could eliminate the β -alkoxy group to form elimination product **25** (Figure 3.3).

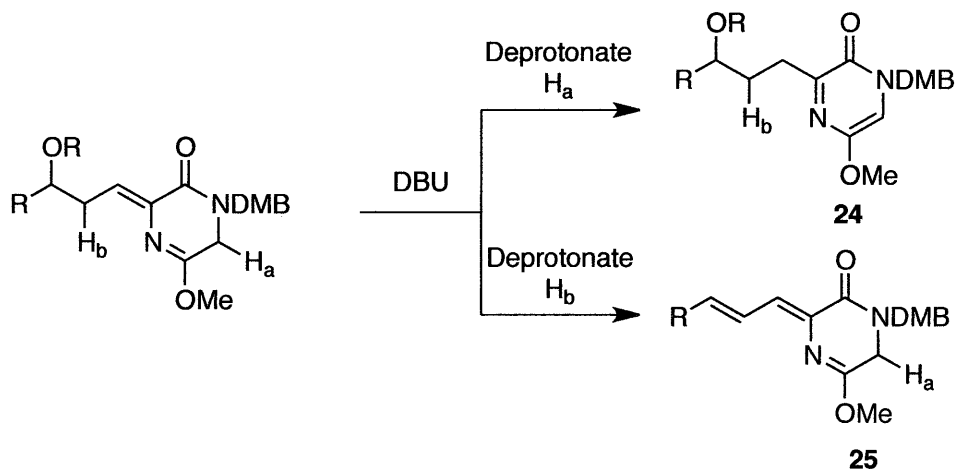
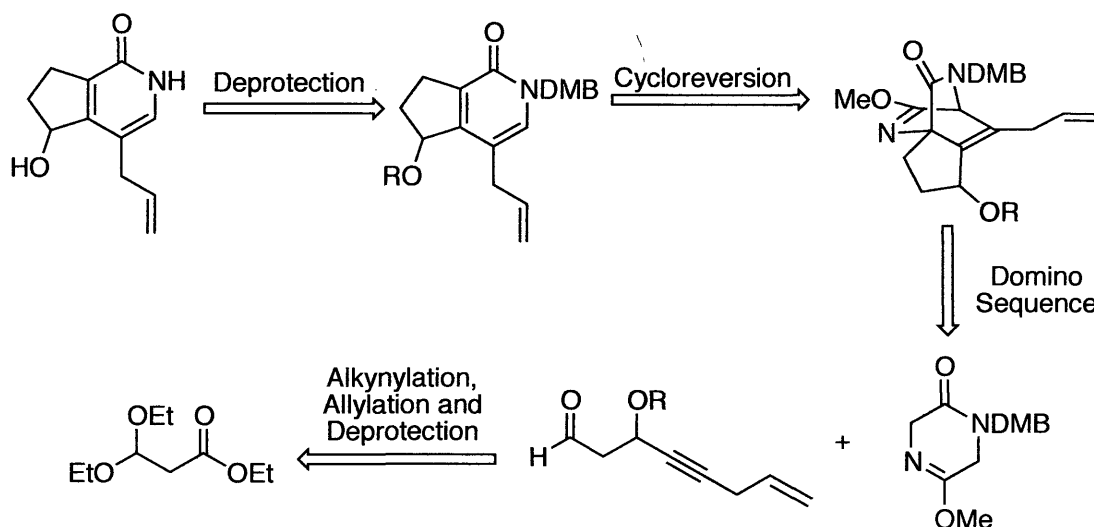


Figure 3.3 Possible sites of deprotonation to form azadiene or elimination product

Even though it could not be predicted which position would deprotonate first, we proposed a scheme in which the aldehyde would be constructed with a β functionality and

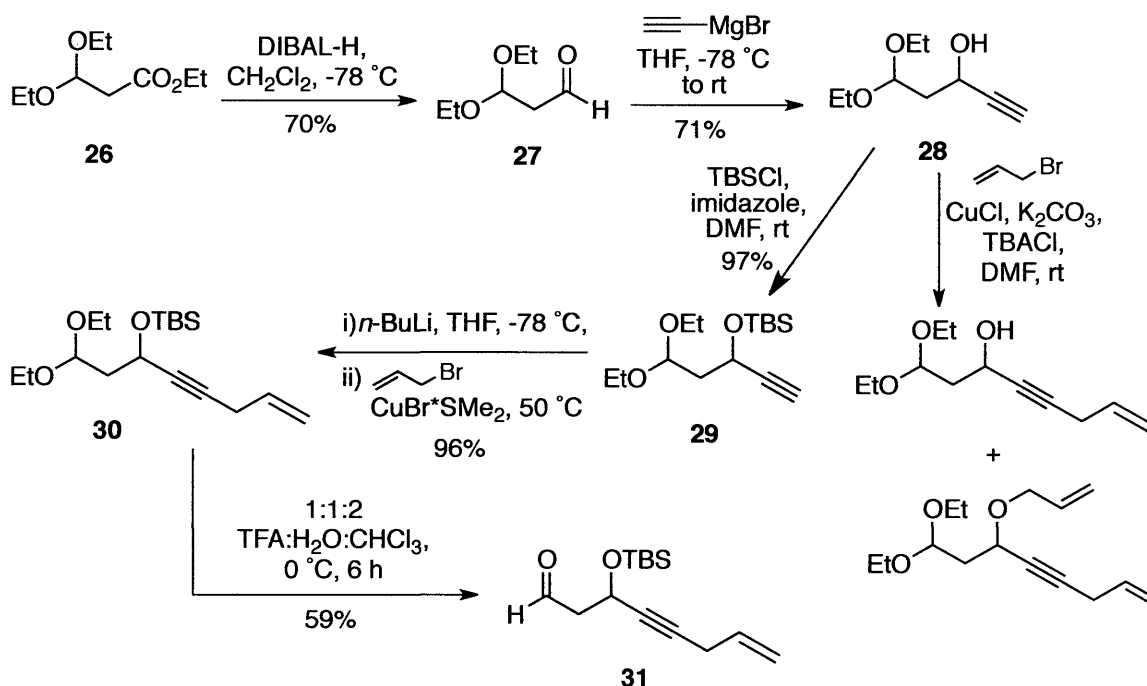
carried through the domino sequence. This would set up for use of the optimized cycloreversion conditions from Chapter Two and finally a deprotection of the pyridone and benzylic alcohol to reveal louisianin B (**Scheme 3.8**).



Scheme 3.8 Retrosynthesis of revised route using oxidized aldehyde

We decided to form the alkyne functionality through addition into the carbonyl. This step would install the alkyne as well as form the alcohol that is present in louisianin B. Beginning with diethoxy propanoate, **26**, we reduced the ethyl ester to aldehyde **27** (**Scheme 3.9**). This reduction set up for the Grignard addition of ethynylmagnesium bromide into the aldehyde to form secondary alcohol **28**. Because of the non-stereospecific manner of the Grignard reaction, two enantiomers were produced and carried through the route. Initial attempts to attach an allyl group to the alkyne used the same conditions as the initial route with allyl bromide, potassium carbonate, tetrabutylammonium chloride, and the copper (I) chloride catalyst. It was noted that in

one instance, the alcohol was allylated. For this reason, we first protected the alcohol with TBSCl to prevent undesired allylation. Once the alcohol **29** was protected, we could use a stronger base, specifically *n*-BuLi, to deprotonate the alkyne, which could then act as the nucleophile and undergo an S_N2 displacement with allyl bromide to form the allylated product **30**. The last step required deprotection of the acetal to reveal the final oxygenated aldehyde **31**.



Scheme 3.9 Synthesis of oxidized aldehyde

The aldehyde is sensitive and must be used directly. Both stable aldehyde hydrate **32** and the product **33** arising from elimination of the β -siloxy residue are observed (**Figure 3.4**). Overall, the oxidized aldehyde could be synthesized in 5 steps with 30% yield.

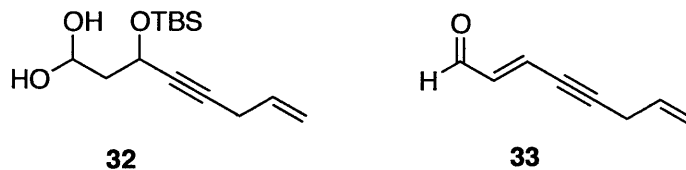


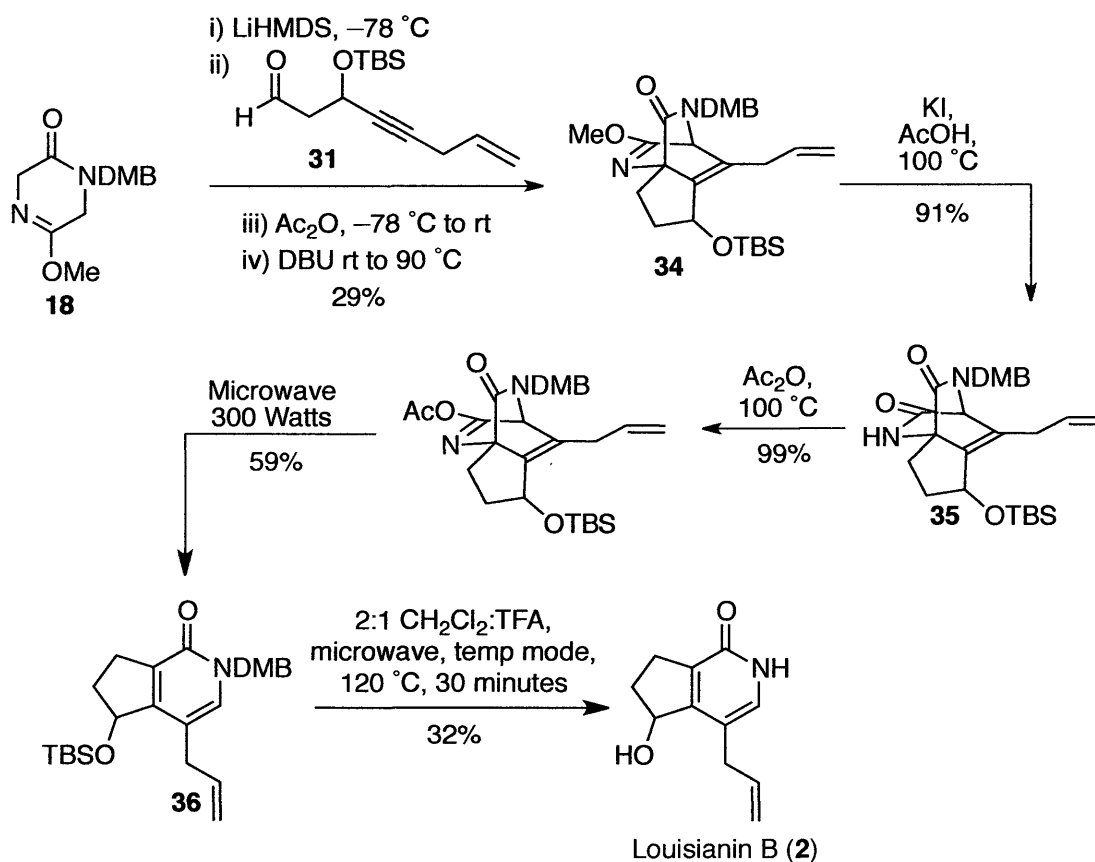
Figure 3.4 Structure of hydrate and elimination products

With the oxygenated aldehyde, we were able to attempt a one-pot domino sequence using the DMB DKP (**Scheme 3.10**). However, initial efforts with the one-pot reaction resulted in a majority of DKP starting material. We proposed that the problematic step in the reaction sequence was the aldol addition and have been currently adjusting conditions to optimize the sequence. Two diastereomeric cycloadducts **34a** and **34b** were synthesized from the domino sequence, differing at the stereocenter containing the TBS protected alcohol with a diastereomeric ratio of 3:2. This demonstrated that the β -siloxy group did not have a significant impact on the diastereoselectivity of the cycloaddition.

The lactim ether deprotection in acetic acid risked loss of the TBS group; however, we did not observe this with our product. Once lactam **35** was formed, we acetylated it and submitted the product to microwave irradiation without purification. Use of the microwave for one hour and fifteen minutes resulted in the desired protected pyridone **36**.

The only remaining step required to access louisianin B was the removal of both the DMB and TBS groups. We anticipated that we could cleave both protecting groups simultaneously with the TFA conditions that we had previously utilized to cleave

the DMB group. After submission to the microwave for 10 minutes in 2:1 CH₂Cl₂:TFA, using temperature mode that would hold at 120 °C, we observed that complete conversion was not achieved. We resubmitted the reaction mixture and held it at 120 °C for 30 minutes. It was observed that both the DMB group as well as the TBS group had been cleaved. Comparing our ¹H NMR spectrum to Taylor's supported that we had successfully constructed louisianin B. Overall, there were 10 steps in our synthesis with an overall yield of 1.5% to access the desired pyridone.



Scheme 3.10 Revised synthesis toward louisianin B with oxidized aldehyde

By forming an oxygenated aldehyde, we were able to construct the

louisianin pyridone core efficiently, which revealed the final natural product after removal of two protecting groups. Previously, only non-oxygenated aldehydes had been utilized in our one-pot domino sequence, and it is interesting that the protected alcohol was able to persist through the cycloreversion conditions. This example suggests that a wider group of aldehydes could potentially be used to access pyridones with these types of oxygenated substituents.

Conclusion

Overall, we were able to demonstrate the applicability of our methodological work by applying it to the synthesis of louisianin B. We initially had attempted to use an aliphatic aldehyde to achieve this goal, but a late stage oxidation proved to be incompatible with the allyl substituent on the pyridone core. Eventually, we were able to synthesize an aldehyde with a protected alcohol in the β position and use it in the domino sequence to construct the desired [2.2.2]-diazabicyclic core. Furthermore, the protected alcohol was able to withstand the conditions to form the 2-pyridone, showing a potentially useful set of new aldehydes that could be explored with these conditions. While conditions for this route have not yet been fully optimized, we have been able to show that the final natural product can be formed through this sequence of conditions. Overall, we have demonstrated the synthesis of louisianin B in 10 steps with a 1.5% yield.

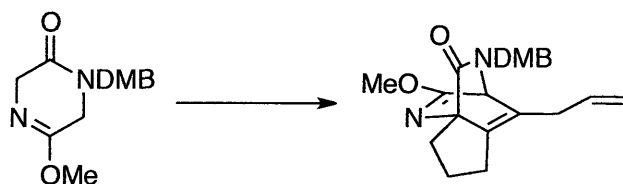
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5. Chen, H.; Hsu, R.; Chang, M. Efficient Synthesis of Fused Bicyclic Glutarimides. Its Application to (\pm)-Alloyohimbane and Louisianin D. *Org. Lett.* **2006**, *8*, 3033-3035.
6. Catozzi, N.; Edwards, M.; Raw, S.; Wasnaire, P.; Taylor, R. Synthesis of the Louisianin Alkaloid Family via a 1,2,4-Triazine Inverse-Electron Demand Diels-Alder Approach. *J. Org. Chem.*, **2009**, *74*, 8343-8354.

Experimental Section



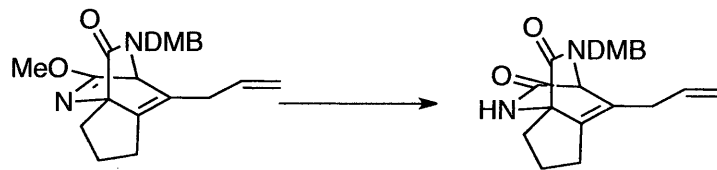
oct-7-en-4-ynal (19). To oct-7-en-4-yn-1-ol (400 mg, 3.2 mmol) dissolved in dichloromethane (10 mL) was added *i*-Pr₂NEt (1.7 mL, 9.7 mmol) at 0 °C. A stock solution of SO₃·pyr (790 mg, 4.8), DMSO (7.5 mL) in dichloromethane (4.5 mL) was prepared at 0 °C. Small increments of the stock solution were added to the reaction flask until the reaction appeared to be complete as tracked by TLC. The reaction appeared to be complete after about 1 hr. After cooling, the reaction was diluted with HCl (10 mL) and the organic layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were diluted with NaHCO₃ (10 mL), washed with brine (10 mL), dried with NaSO₄, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (elution: 5% to 25% Et₂O in pentane) to afford product oct-7-en-4-ynal (265 mg, 67% yield) as colorless liquid; TLC (40% EtOAc in hexane) *R*_f = 0.60 (KMnO₄); IR (film) cm⁻¹ 3086, 3014, 2982, 2904, 2830, 2731, 1718, 1642, 1412, 1358, 1286, 1193, 1058, 993, 918, 850; ¹H NMR (400MHz, CDCl₃) 9.80 (s, 1H, CHO), 5.79 (m, 1H, C₇H), 5.28 (ddd, *J* = 16.8/3.1/1.6 Hz, 1H), 5.10 (dt, *J* = 9.8/1.6 Hz, 1H), 2.93–2.91 (m, 2H), 2.68–2.66 (m, 2H), 2.54–2.50 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 200.6, 132.7, 115.6, 80.3, 77.6, 42.7, 22.8, 11.9; Exact mass calcd for C₈H₁₀ONa [M+Na]⁺, 267.1356, Found 267.1354.



(3*S*,7*aS*)-4-allyl-9-(2,4-dimethoxybenzyl)-2-methoxy-3,5,6,7-tetrahydro-3,7a-

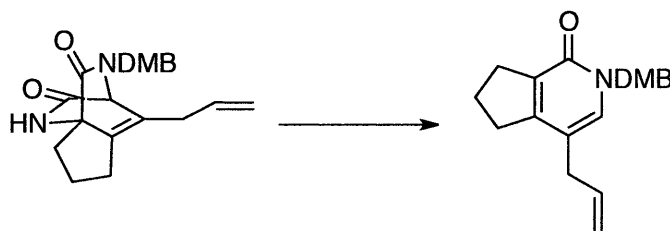
(epiminomethano)cyclopenta[*b*]pyridin-8-one (17): To diketopiperazine **18** (195 mg, 0.68 mmol) in toluene (7 mL) at $-78\text{ }^{\circ}\text{C}$ was added LiHMDS (1.0M in THF, 1.1 equiv.) dropwise over 5 minutes by syringe. After stirring for 25 minutes at $-78\text{ }^{\circ}\text{C}$, aldehyde **18** (125 mg, 1.2 equiv.) was added to the solution. Ac_2O (0.093 ml, 1.3 equiv.) was added dropwise at $-78\text{ }^{\circ}\text{C}$, and the solution was allowed to warm to room temperature while stirring. DBU (0.203 ml, 2 equiv.) was added and the mixture stirred at rt for 16 hours. The reaction was washed with NH_4Cl (20 mL) and extracted with EtOAc (10 mL x 3). The organic layer was washed with brine (10 mL), dried with Na_2SO_4 , and then concentrated *in vacuo*. The reaction mixture was concentrated and purified by flash chromatography on silica gel (elution: 10% - 50% EtOAc in hexanes) to afford a pale yellow oil (220 mg, 82% yield). TLC (40% EtOAc in hexanes), R_f : 0.25 (CAM); IR (film) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3); 6.94 (d, 1H, $J = 7.8$ Hz), 6.37 (s, 1H), 6.35 (d, 1H, $J = 7.0$ Hz), 5.52 (m, 1H), 4.94 (s, 2H, $J = 10.2$), 4.75 (d, 1H $J = 1.6$), 4.37 (s, 1H), 4.30 (m, 2H), 3.73(s, 3H), 3.72 (s, 3H), 3.60 (s, 3H), 2.88 (m, 1H), 2.68 (dd, 1H, $J = 15.6/6.3$), 2.52 (dd, 1H, $J = 15.6/6.6$ Hz), 2.25 (m, 1H). 2.14 (m, 1H), 2.06–1.96 (m, 2H), 1.70 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.3, 171.8, 160.6, 158.4, 151.8, 133.9, 131.0, 130.6, 116.9, 116.6, 104.0, 98.1, 79.7, 61.1, 55.2, 55.0, 54.9, 42.8, 34.2, 30.0, 26.2, 26.1; HRMS (ES⁺): Exact mass calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 405.1784

Found 405.1784.



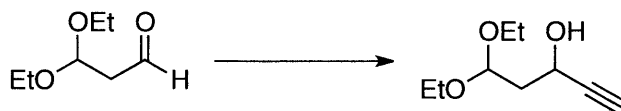
(3*S*,7*aS*)-4-allyl-9-(2,4-dimethoxybenzyl)-3,5,6,7-tetrahydro-3,7*a*-

(epiminomethano)cyclopenta[*b*]pyridine-2,8(1*H*)-dione (20): To product 17 (150 mg, 0.39 mmol) in AcOH was added KI (3 equiv.) and stirred at 100 °C for 2.45 hr. The reaction was diluted with water (20 mL) and Na₂CO₃ (10%, 10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was washed with NaHCO₃ with thiosulfate (10 mL), brine (10 mL), dried with Na₂SO₄, and concentrated *in vacuo* to afford a tan powder (130 mg, 90% yield). TLC (60% EtOAc in hexane), R_f: 0.35 (KMnO₄); IR (film) cm⁻¹ 2960, 2838, 1696, 1663, 1456, 1418, 1294, 1210, 1158, 1039, 922, 826; ¹H NMR (400MHz, CDCl₃) 7.75 (br. s, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.43-6.38 (m, 2H), 5.53 (m, 1H), 4.99 (d, *J* = 10.2 Hz, 1H), 4.93 (dd, *J* = 16.8/1.6 Hz, 1H), 4.54 (d, *J* = 14.5 Hz, 1H), 4.38 (d, 14.5 Hz, 1H), 4.20 (d, *J* = 1.6 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.74 (m, 2H), 2.59 (dd, *J* = 15.2/5.9 Hz, 1H), 2.33-2.30 (m, 2H), 2.06-1.88 (m, 1H), 1.86-1.78 (m, 1H), 1.77-1.67 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) 173.9, 170.3, 160.8, 158.6, 149.4, 133.7, 133.3, 131.3, 117.3, 116.6, 104.1, 98.3, 70.2, 65.8, 55.3, 55.1, 43.3, 34.7, 27.7, 26.4, 26.3; HRMS (ES⁺): Exact mass calcd for C₂₁H₂₄N₂O₄ [M+Na]⁺, 391.1628. Found 391.1624.



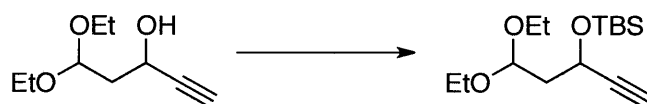
4-allyl-2-(2,4-dimethoxybenzyl)-2,5,6,7-tetrahydro-1H-cyclopenta[c]pyridin-1-one

(21): The lactam cycloadduct **20** (32 mg, 0.087) in Ac₂O (0.2 mL) and pyridine (0.2 mL) was heated in a sealed tube to 100 °C for 19.5 hr and cooled to rt. The mixture was concentrated *in vacuo*. The intermediate product was dissolved in toluene (2 mL) and heated in a microwave system on power mode (300 W maximum) for 1.5 hr. The reaction was concentrated *in vacuo* to afford a tan solid (25.8 mg, 91% yield). TLC (60% EtOAc in hexane), R_f: 0.25 (CAM); IR (film) cm⁻¹ 2956, 2849, 1696, 1646, 1561, 1457, 1290, 1267, 1210, 1158, 1032, 920, 836; ¹H NMR (400MHz, CDCl₃) 7.35 (d, *J* = 9.0 Hz, 1H), 7.12 (s, 1H), 6.45-6.42 (m, 2H), 5.83 (m, 1H), 5.15 (m, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.08–3.06 (d, *J* = 6.3 Hz, 2H), 2.87–2.82 (t, *J* = 7.42 Hz, 2H), 2.77–2.74 (t, *J* = 7.4 Hz, 2H), 1.87 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) 160.6, 158.4, 154.6, 135.8, 134.6, 131.9, 117.5, 116.3, 114.8, 104.1, 98.3, 55.3, 55.2, 46.6, 34.2, 32.4, 30.3, 23.2; HRMS (ES⁺): Exact mass calcd for C₂₀H₂₃NO₃ [M+Na]⁺, 348.1570 Found 348.1566.



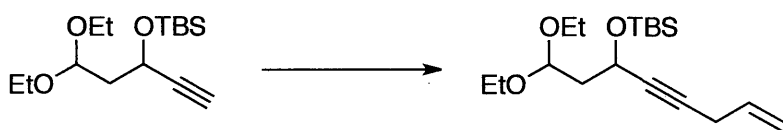
5,5-diethoxypent-1-yn-3-ol (28): To 3,3-diethoxypropanal (1.1 g, 8.22 mmol) in THF (70 mL) at -78 °C was added ethynyl magnesium bromide (22.5 mL, 0.5 M, 12.4 mmol)

dropwise. The reaction vessel was slowly warmed to room temperature and then stirred overnight. The reaction was washed with NH₄Cl (50 mL) and extracted with EtOAc (3 x 25 mL). The organic layer was washed with brine (30 mL), dried with Na₂SO₄, and then concentrated *in vacuo*. The reaction mixture was purified by flash chromatography on silica gel (elution: 5%–50% EtOAc in hexanes) to afford a yellow oil (925 mg, 71% yield). TLC (40% EtOAc in hexanes), R_f: 0.40 (KMnO₄); IR (film) cm⁻¹ 3419, 3294, 2973, 2892, 2118, 1445, 1375, 1349, 1215, 1130, 1057, 848, 806; H NMR (400 MHz, CDCl₃) 4.77 (t, *J* = 5.67 Hz, 1H), 4.46 (m, 1H), 3.68–3.53 (m, 2H), 3.52–3.41 (m, 2H), 2.41 (d, *J* = 1.95 Hz, 1H), 1.96 (t, *J* = 5.67 Hz, 2H), 1.18–1.05 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 101.0, 84.1, 72.7, 62.3, 61.8, 58.9, 40.2, 15.2, 15.2; HRMS (ES⁺): Exact mass calcd for [M+Na]⁺, 195.0992. Found 195.0993.



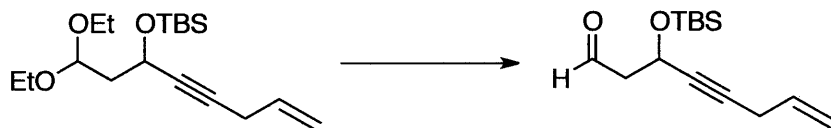
***tert*-butyl((5,5-diethoxypent-1-yn-3-yl)oxy)dimethylsilane (29):** To **28** (200 mg, 1.16 mmol) in DMF (0.6 mL) was added imidazole (166 mg, 2.44 mmol) stirred at rt for 30 min. *Tert*-butyl chlorodimethylsilane (192.9 mg, 1.28 mmol) was added at rt and the reaction was allowed to stir overnight. The reaction was diluted with water (mL), extracted with EtOAc (3 x mL). The organic layer was washed with brine (mL), dried with Na₂SO₄, and concentrated *in vacuo* to afford a yellow oil (322 mg, 97% yield). TLC (40% EtOAc in hexane), R_f: 0.70 (KMnO₄); IR (film) cm⁻¹ 3312, 2978, 2934, 2858, 2110, 1718, 1636, 1617, 1374, 1275, 1123, 1093, 1062, 935, 840; ¹H NMR (400MHz,

CDCl₃) 4.58 (dd, $J = 4.86/1.95$ Hz, 1H), 4.21 (m, 1H), 3.64–3.33 (m, 2H), 2.32 (d, $J = 2.35$ Hz, 1H), 1.98–1.85 (m, 2H), 1.14–1.10 (td, $J = 7.03/2.34$ Hz, 6H), 0.82 (s, 9H), 0.06–0.03 (d, $J = 14.8$ Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) 99.9, 85.1, 72.4, 61.7, 61.2, 59.5, 42.6, 25.7, 18.1, 15.3, 15.25, –4.6, –5.3; HRMS (ES⁺): Exact mass calcd for [M+Na]⁺, 309.1856. Found 309.1858.

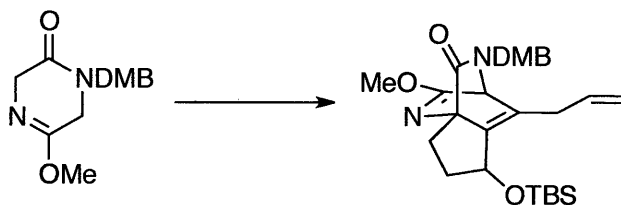


***tert*-butyl((1,1-diethoxyoct-7-en-4-yn-3-yl)oxy)dimethylsilane (30):** To **29** (250 mg, 0.87 mmol) in THF (0.6 mL) at –78 °C was added *n*-BuLi (2.84M, mmol) dropwise. The reaction was stirred for 30 min at –78 °C. To the solution was added allyl bromide (92 μL, 1.07 mmol) and copper (I) bromide dimethyl sulfide (9.2 mg, 0.045 mmol) and the reaction was heated to 50 °C overnight. The mixture was washed with NH₄Cl (10 mL), extracted with EtOAc (3 x 10 mL). The organic layer was washed with brine (10 mL), dried with Na₂SO₄ and concentrated *in vacuo* to afford a yellow oil (268 mg, 94% yield). TLC (40% EtOAc in hexane), *R*_f: 0.80 (KMnO₄); IR (film) cm^{–1} 2978, 2935, 2860, 1643, 1373, 1351, 1253, 1123, 19087, 1074, 985, 915, 834, 778; ¹H NMR (400MHz, CDCl₃) 5.77 (m, 1H), 5.28 (d, $J = 17.2$ Hz, 1H), 5.08 (dd, $J = 9.96$ Hz, 1H), 4.65 (t, $J = 5.28$ Hz, 1H), 4.48 (m, 1H), 3.56 (m, 4H), 2.96–2.94 (m, 2H), 1.97 (m, 2H), 0.884–0.881 (d, $J = 1.77$ Hz, 9H), 0.79–0.09 (d, $J = 11.9/0.78$ Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) 132.3, 115.9, 100.0, 83.8, 81.0, 61.5, 60.928, 59.9, 42.9, 25.7, 25.6, 22.9, 18.0, 15.3, 15.2, –4.5,

-5.2; HRMS (ES+): Exact mass calcd for $C_{20}H_{23}NO_3$ $[M+Na]^+$, 349.2169. Found 349.2169.

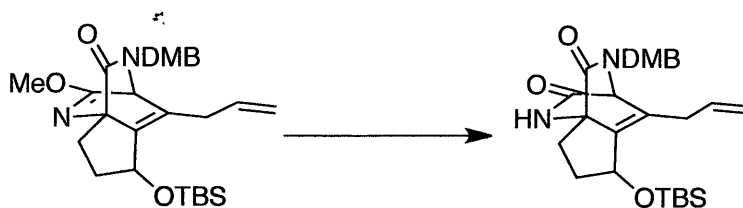


3-((*tert*-butyldimethylsilyl)oxy)oct-7-en-4-ynal (31): To **30** (225 mg, 0.69 mmol) dimethylsilane dissolved in $CHCl_3$ (6 mL) was chilled to 0 °C. A 1:1 mixture of TFA in H_2O (6 mL) was added dropwise. The reaction was allowed to stir at 0 °C for 2.5 h and warmed to room temp and allowed to stir for 3 h. The reaction was quenched with $NaHCO_3$ (10 mL), extracted with $CHCl_3$ (3 x 10 mL). The organic layer was washed with brine (10 mL), dried with Na_2SO_4 and concentrate *in vacuo* to afford a pale yellow oil (102 mg, 59% yield). TLC (40% EtOAc in hexane), R_f : 0.85 ($KMnO_4$); IR (film) cm^{-1} 2959, 2934, 2887, 2856, 2740, 2711, 2234, 1732, 1696, 1636, 1561, 1458, 1339, 1282, 1143, 988, 914, 835, 781; 1H NMR (400MHz, $CDCl_3$) 9.71 (s, 1H), 5.66 (m, 1H), 5.16 (dq, 1H, $J = 17.2/1.7$ Hz), 5.00 (dq, 1H, $J = 10.2/1.6$ Hz), 4.76 (m, 1H) 2.87–2.84 (m, 2H) 2.66–2.51 (qdd, $J = 17.3/6.2/2.8$ Hz, 2H), 0.88 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.8, 132.0, 116.2, 82.8, 82.4, 58.5, 51.6, 25.6, 22.0, 18.0, -4.5, -5.2; HRMS (ES+): Exact mass calcd for $C_{14}H_{24}O_2Si$ $[M+Na]^+$, 275.1438. Found 275.1440.



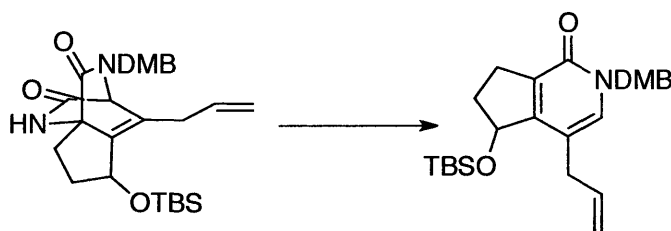
(3*S*,7*aS*)-4-allyl-5-((*tert*-butyldimethylsilyl)oxy)-9-(2,4-dimethoxybenzyl)-2-methoxy-3,5,6,7-tetrahydro-3,7*a*-(epiminomethano)cyclopenta[*b*]pyridin-8-one (34*a* and 34*b*):

Prepared according to general procedure A using DKP 17 (50 mg, 0.18 mmol) and aldehyde 31. The product was purified by flash chromatography on silica gel (elution:) to afford two diastereomers as clear oils (**34a**: 15 mg, 0.029 mmol, 16% yield) (**34b**: 12 mg, 0.023 mmol, 13% yield): **33a**: TLC (40% EtOAc in hexane), *R_f*: 0.55 (UV, CAM); ¹H NMR (400 MHz, CDCl₃) 7.00 (d, *J* = 7.4 Hz, 1H), 6.44–6.40 (m, 2H), 5.56 (m, 1H), 5.04 (d, *J* = 9.8 Hz, 1H), 4.93 (dd, *J* = 17.2/1.6 Hz, 1H), 4.73 (t, *J* = 5.67 Hz, 1H), 4.45 (s, 1H), 4.36 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 2.94 (dd, *J* = 15.6/5.9, 1H), 2.80–2.66 (m, 2H), 2.37 (m, 1H), 2.10–1.93 (m, 2H), 1.67 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.0, 172.2, 160.8, 158.5, 152.0, 134.7, 134.1, 131.3, 117.3, 117.1, 104.8, 104.1, 98.4, 78.0, 70.6, 61.8, 55.4, 55.3, 55.2, 43.0, 36.3, 33.0, 26.4, 25.8, 25.7, 18.0, -4.4 -4.9; **33b**: TLC (40% EtOAc in hexane), *R_f*: 0.65 (UV, CAM).



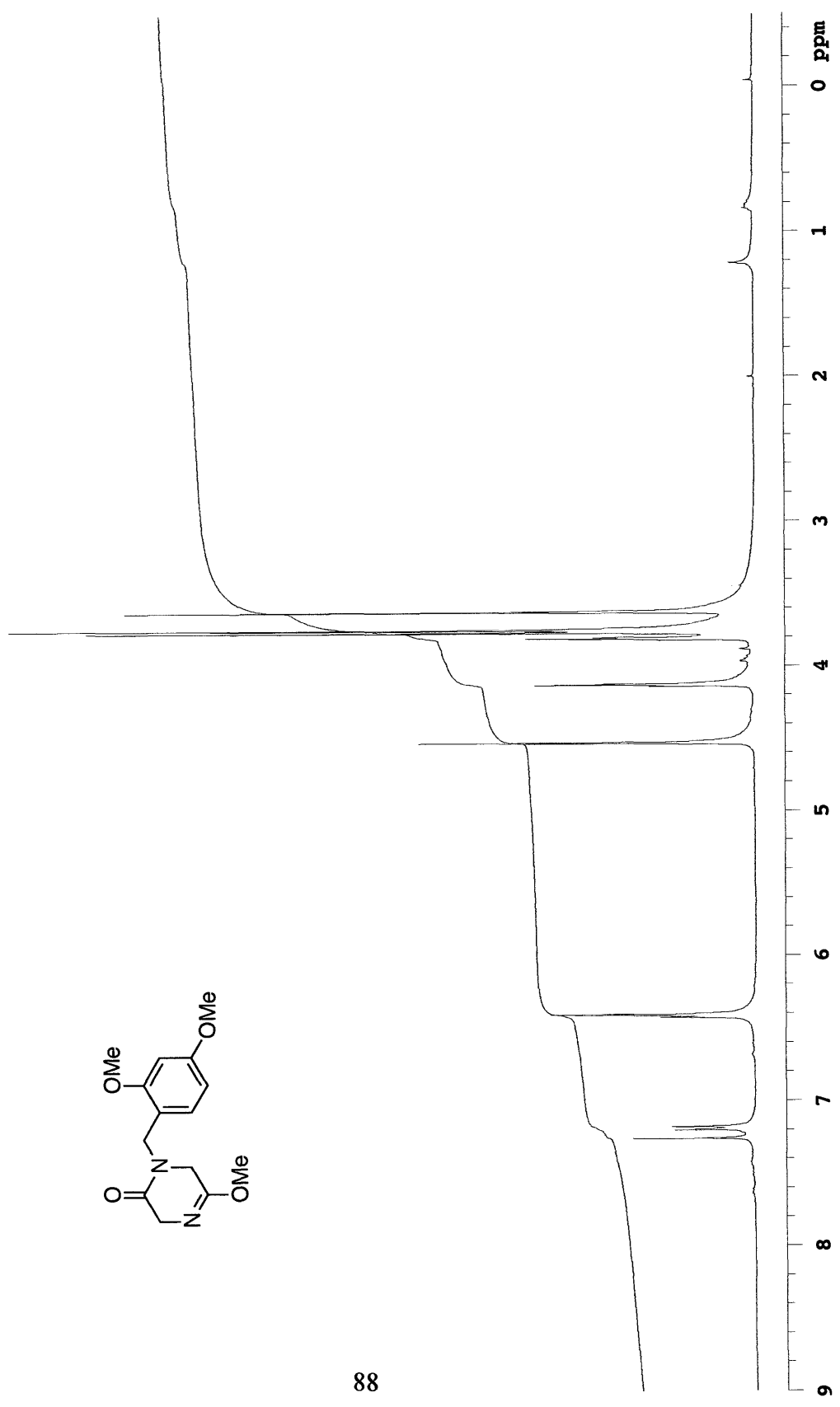
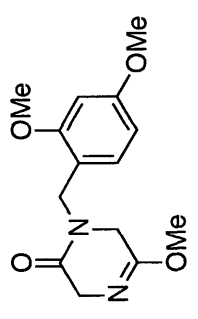
To product a mixture of **34a** and **34b** (36 mg, 0.071 mmol) in AcOH was added KI (3 equiv.) and stirred at 100 °C for 1.5 hr. The reaction was diluted with water (15 mL)

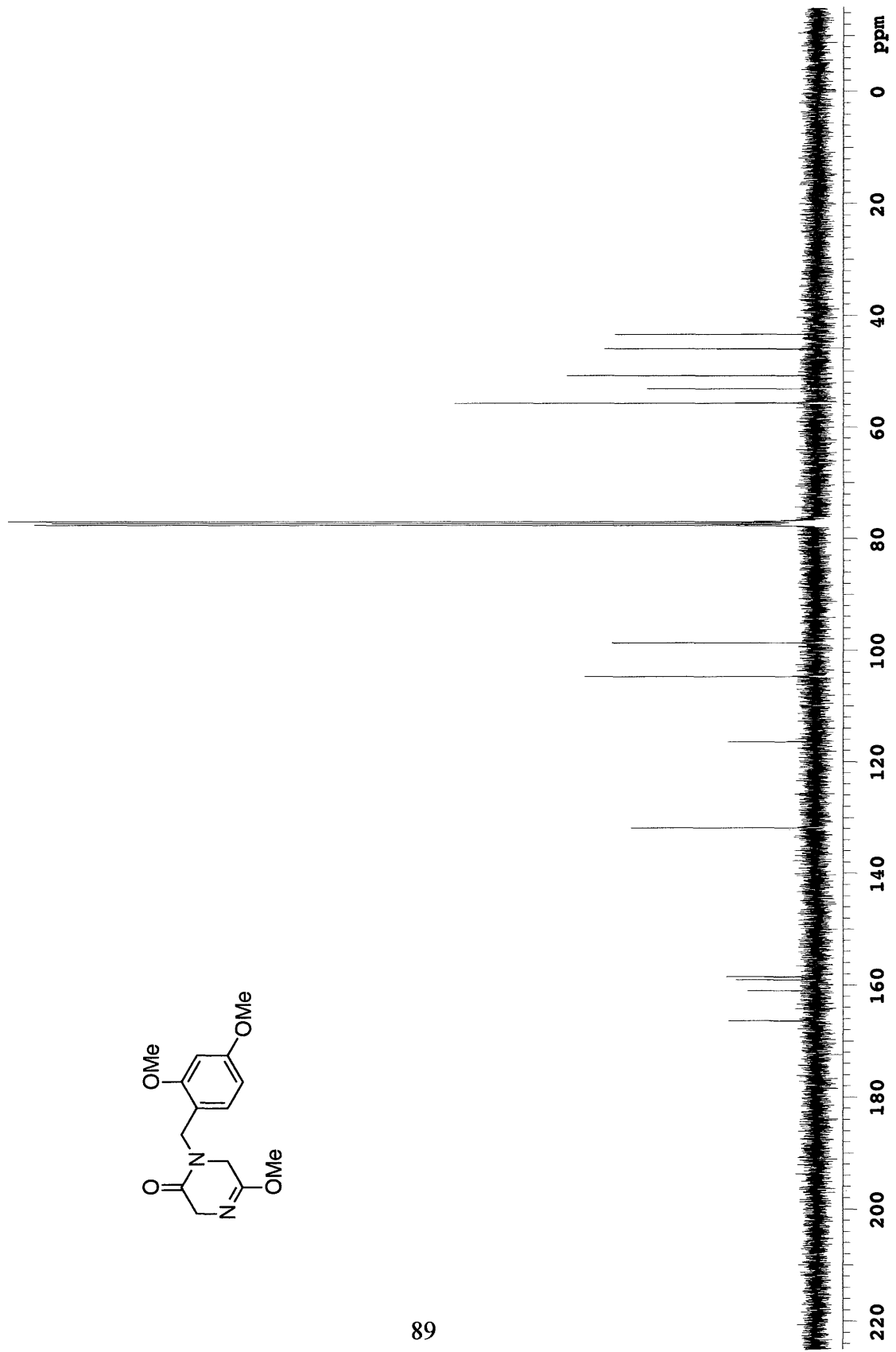
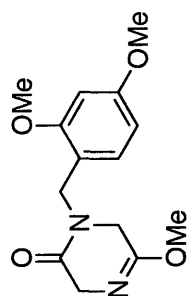
and Na₂CO₃ (10%, 10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was washed with NaHCO₃ with thiosulfate (10 mL), brine (10 mL), dried with Na₂SO₄, and concentrated *in vacuo* to afford a tan powder (32 mg, 91% yield).

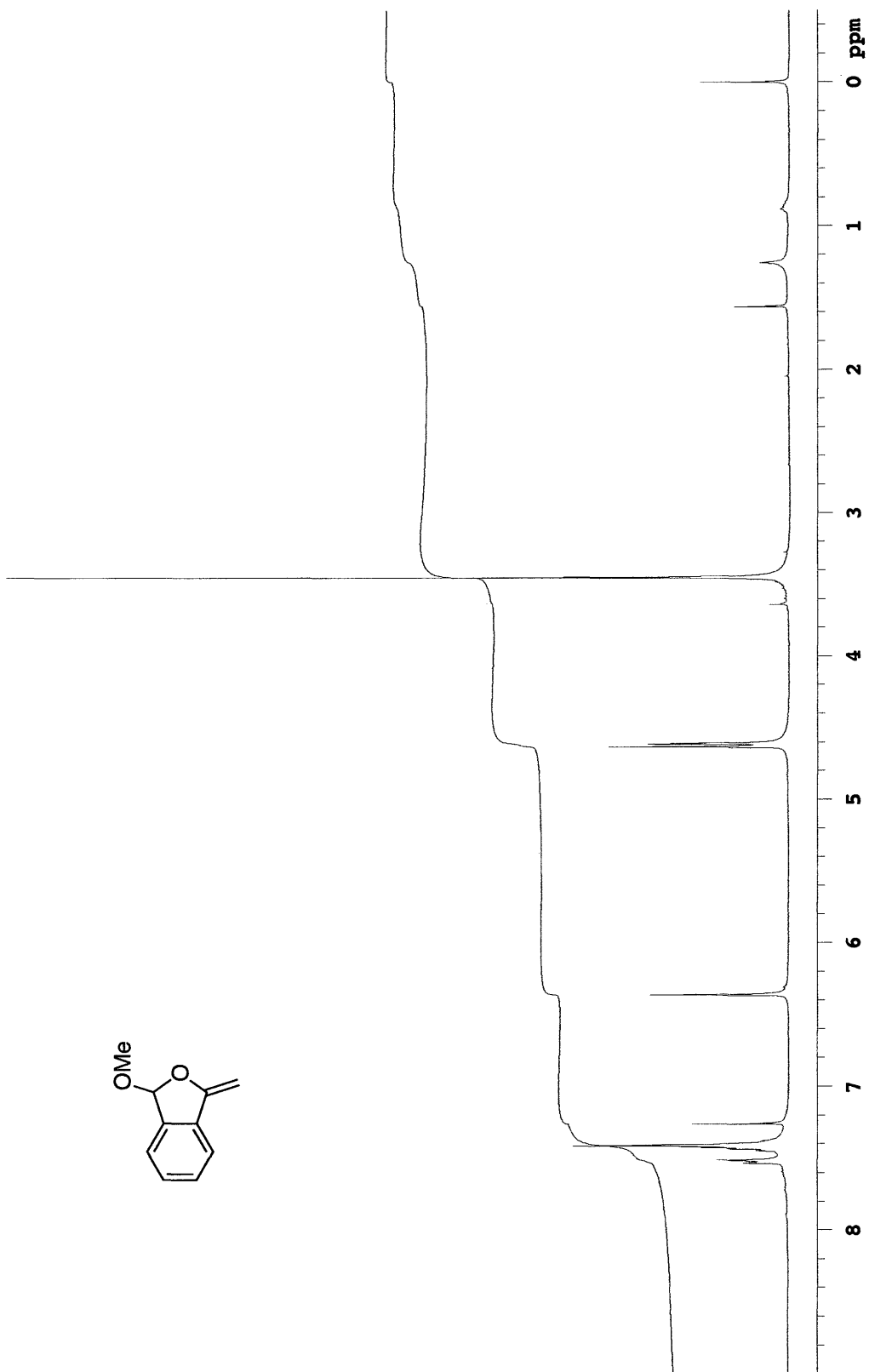
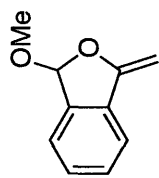


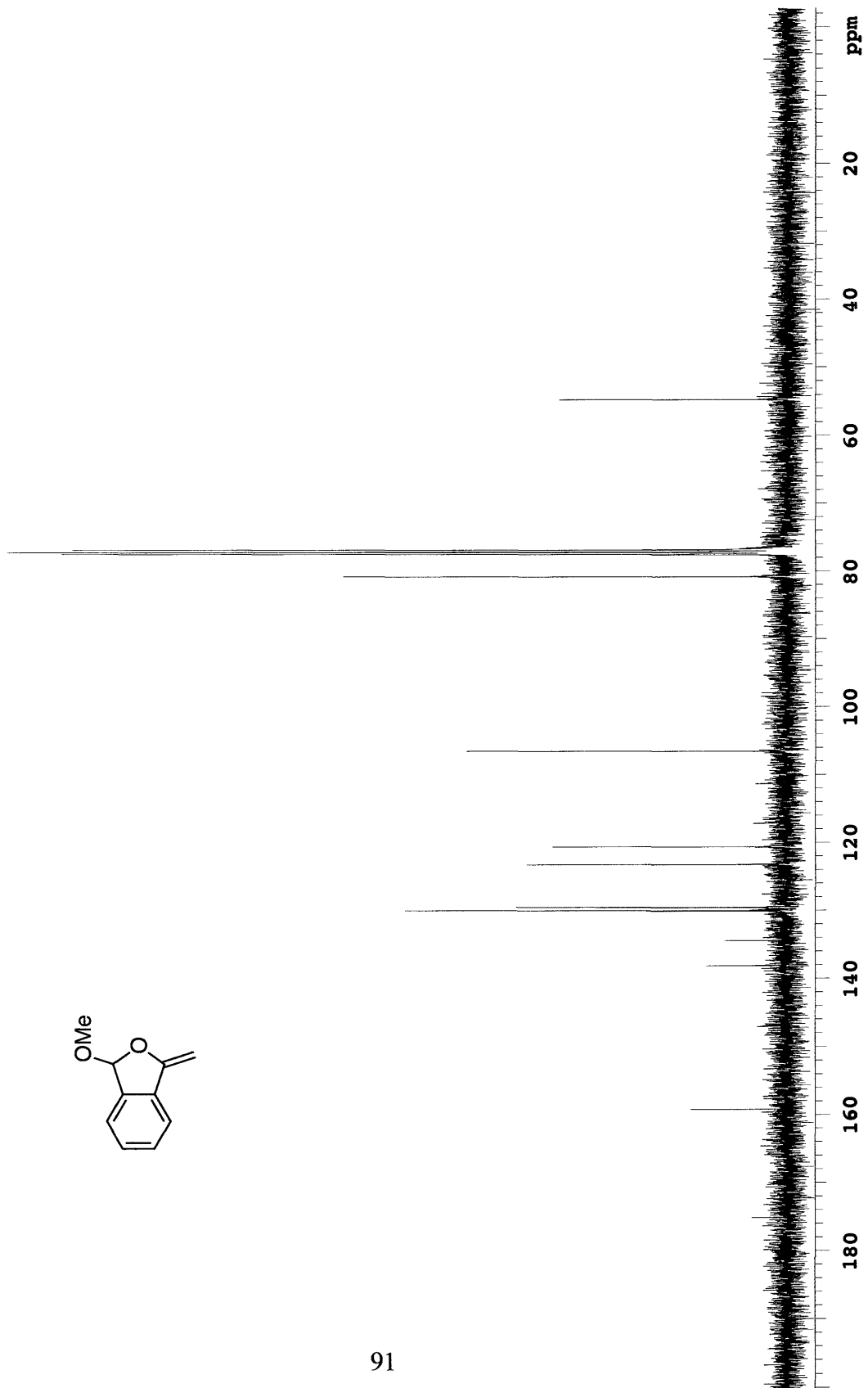
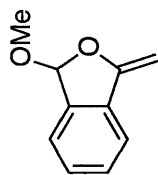
4-allyl-5-((*tert*-butyldimethylsilyl)oxy)-2-(2,4-dimethoxybenzyl)-2,5,6,7-tetrahydro-1*H*-cyclopenta[*c*]pyridin-1-one (35): Following general procedure C, using lactam **34** (32 mg, 0.064 mmol) the intermediate acylated product was produced (34 mg, 0.063 mmol, 98% yield). This intermediate product was used to produce the desired acetylated product following general procedure D. The product was purified by flash column chromatography on silica gel (elution:) to afford the product **36** (17 mg, 0.037 mmol, 59% yield) as a yellow oil : TLC (5% MeOH in chloroform), R_f: 0.6 (UV, CAM).

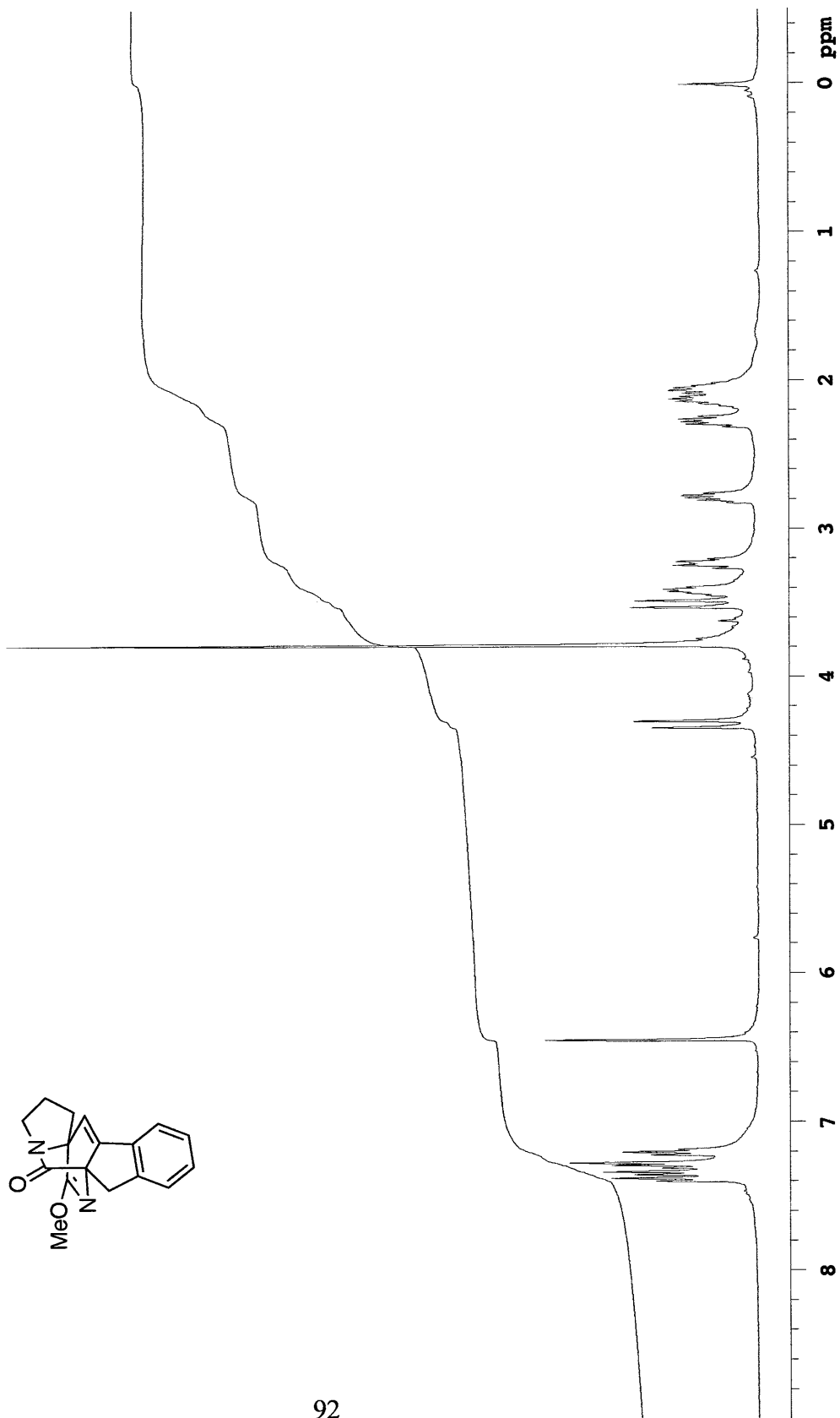
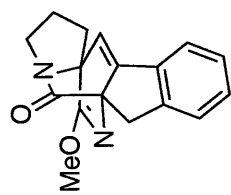
**Supporting Information for
Chapter 2**

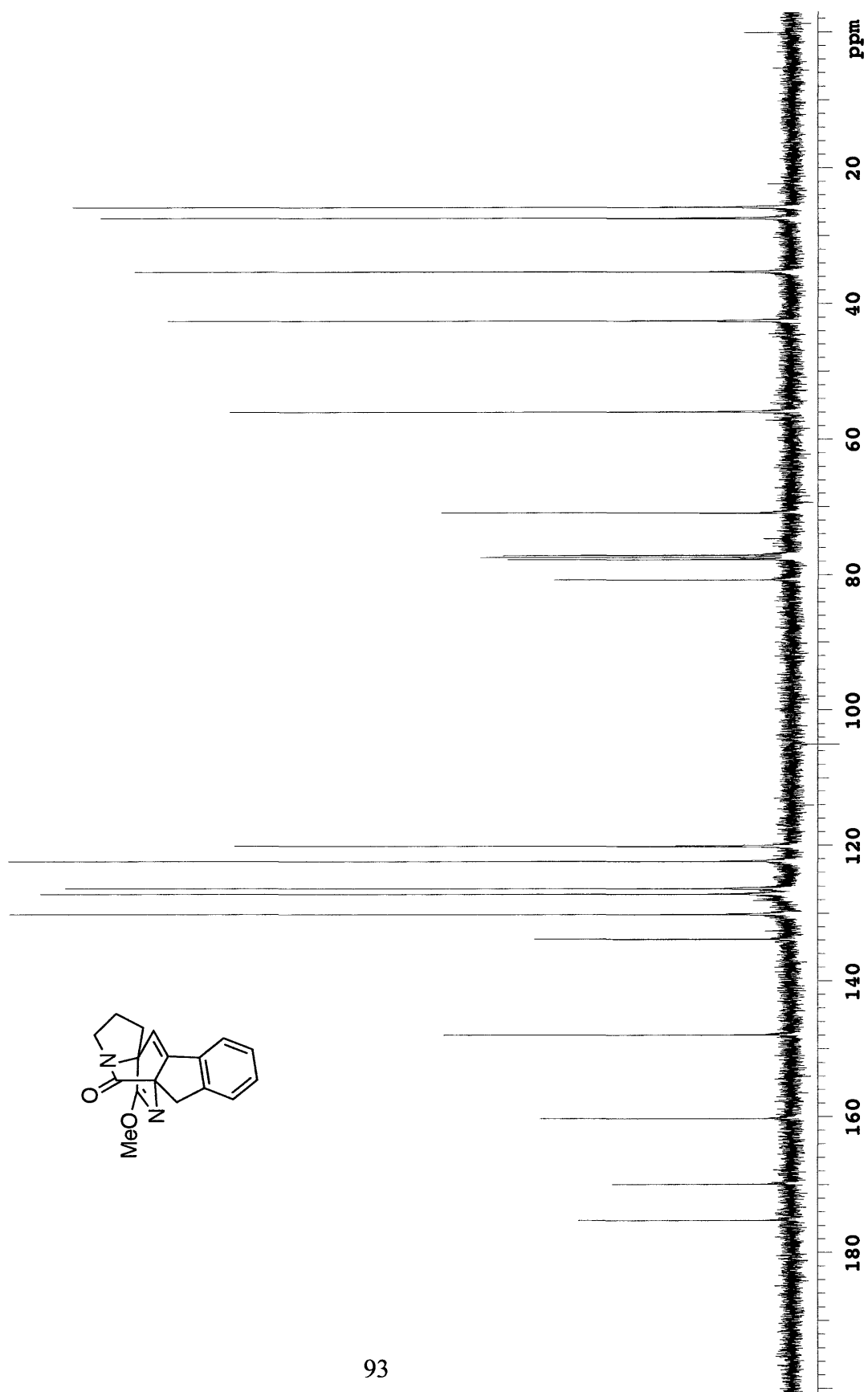


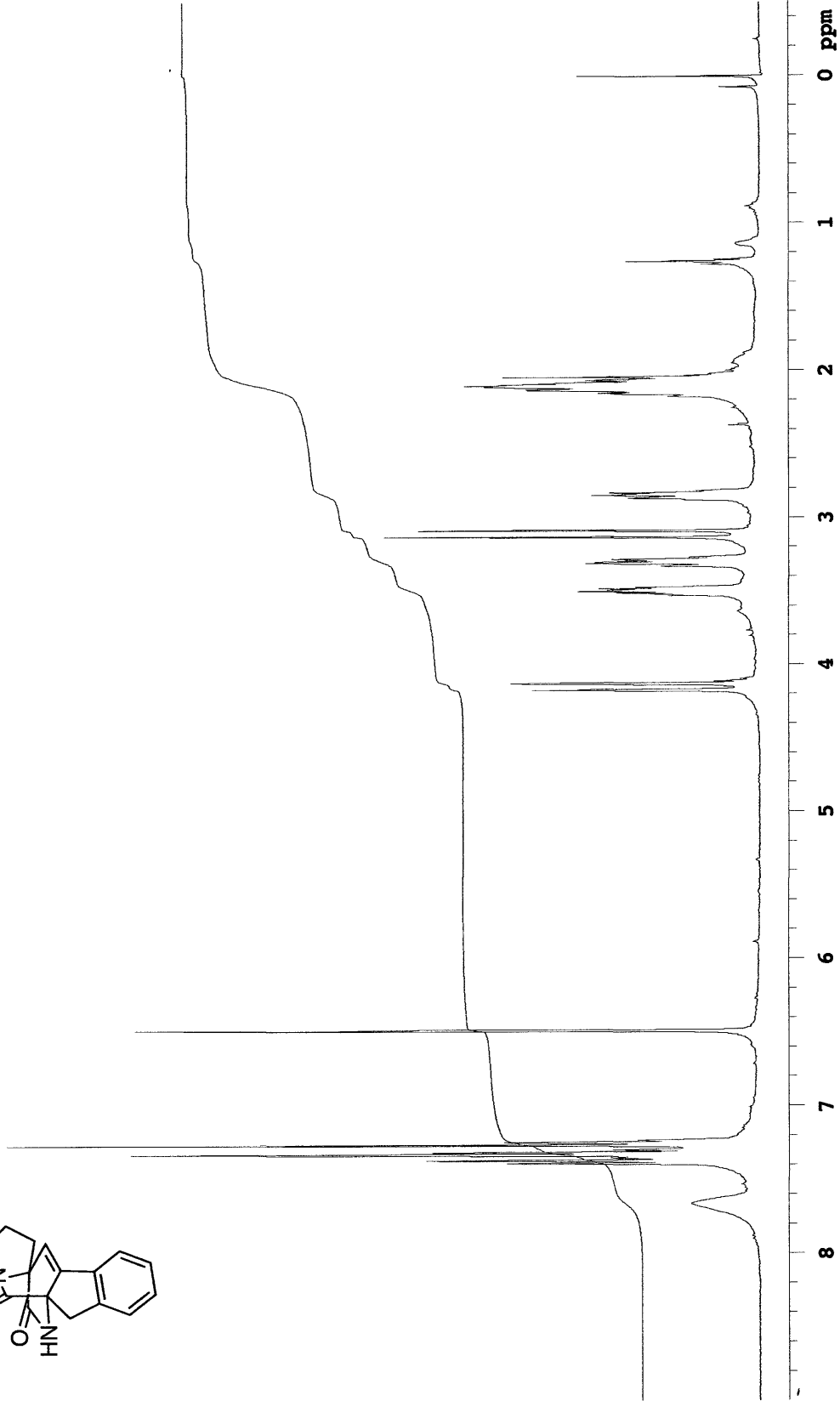
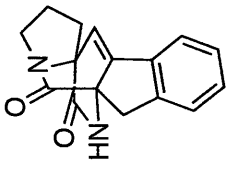


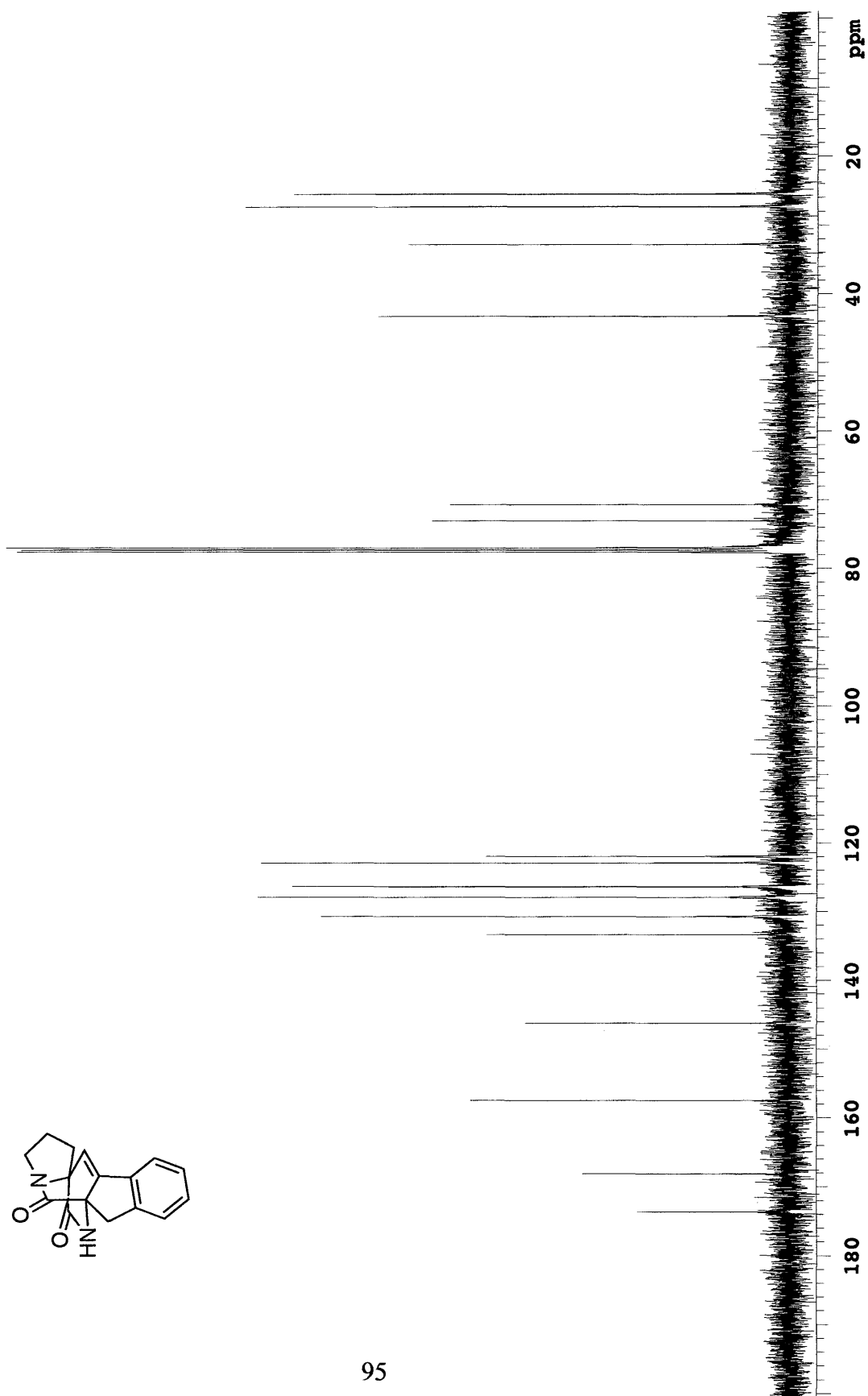
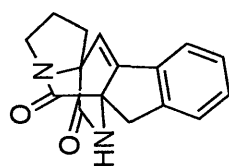


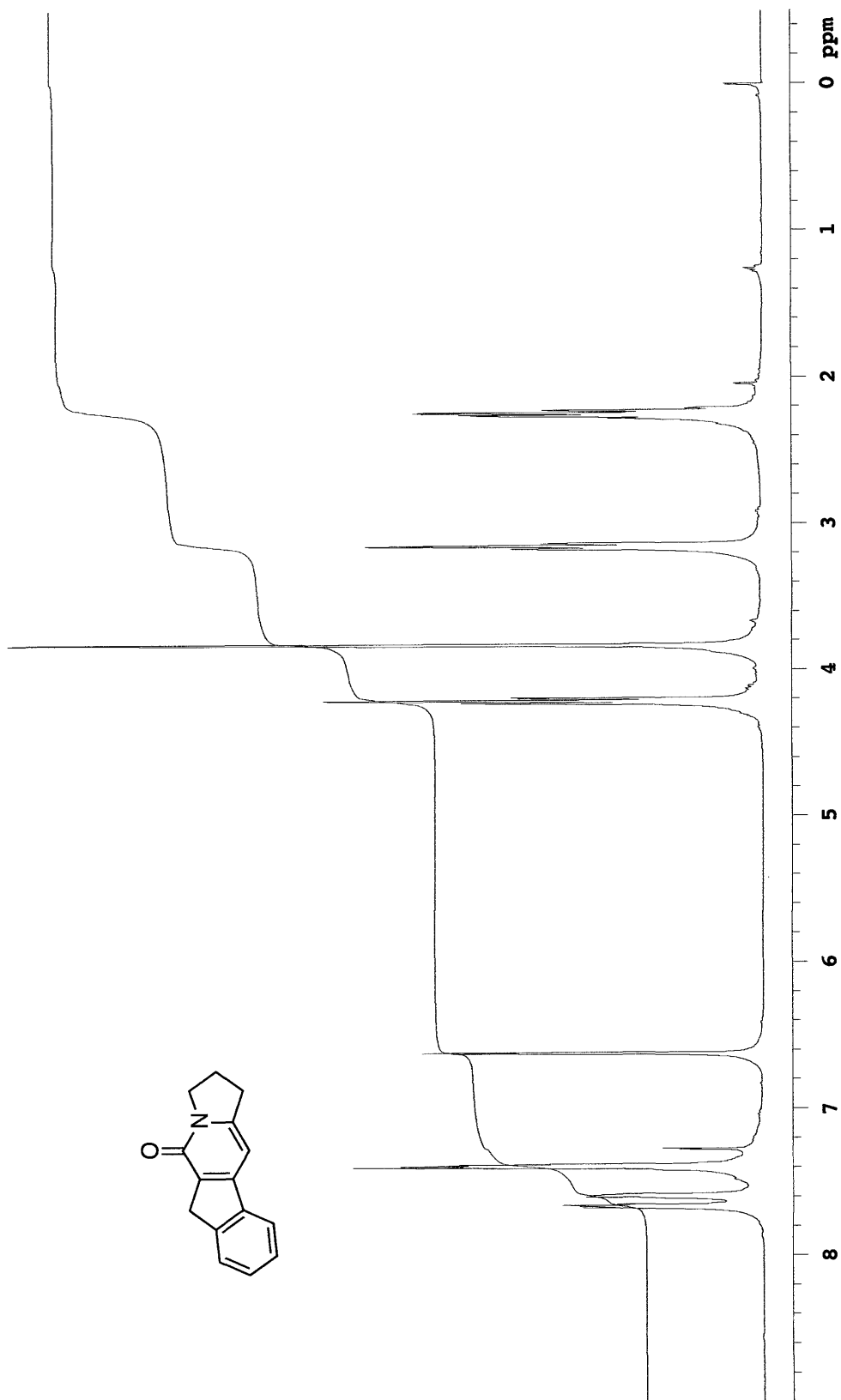
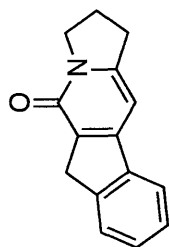


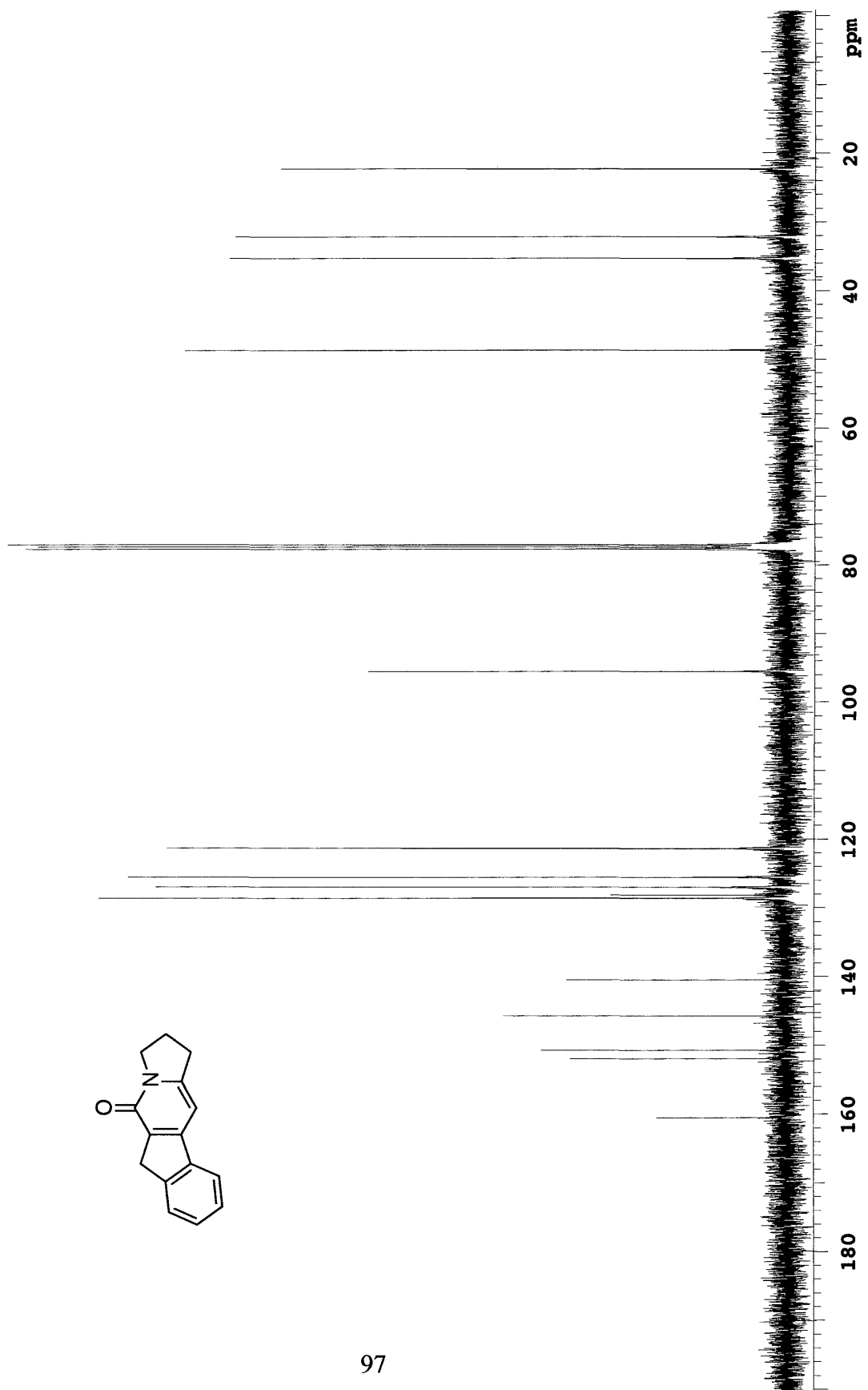
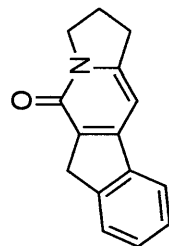


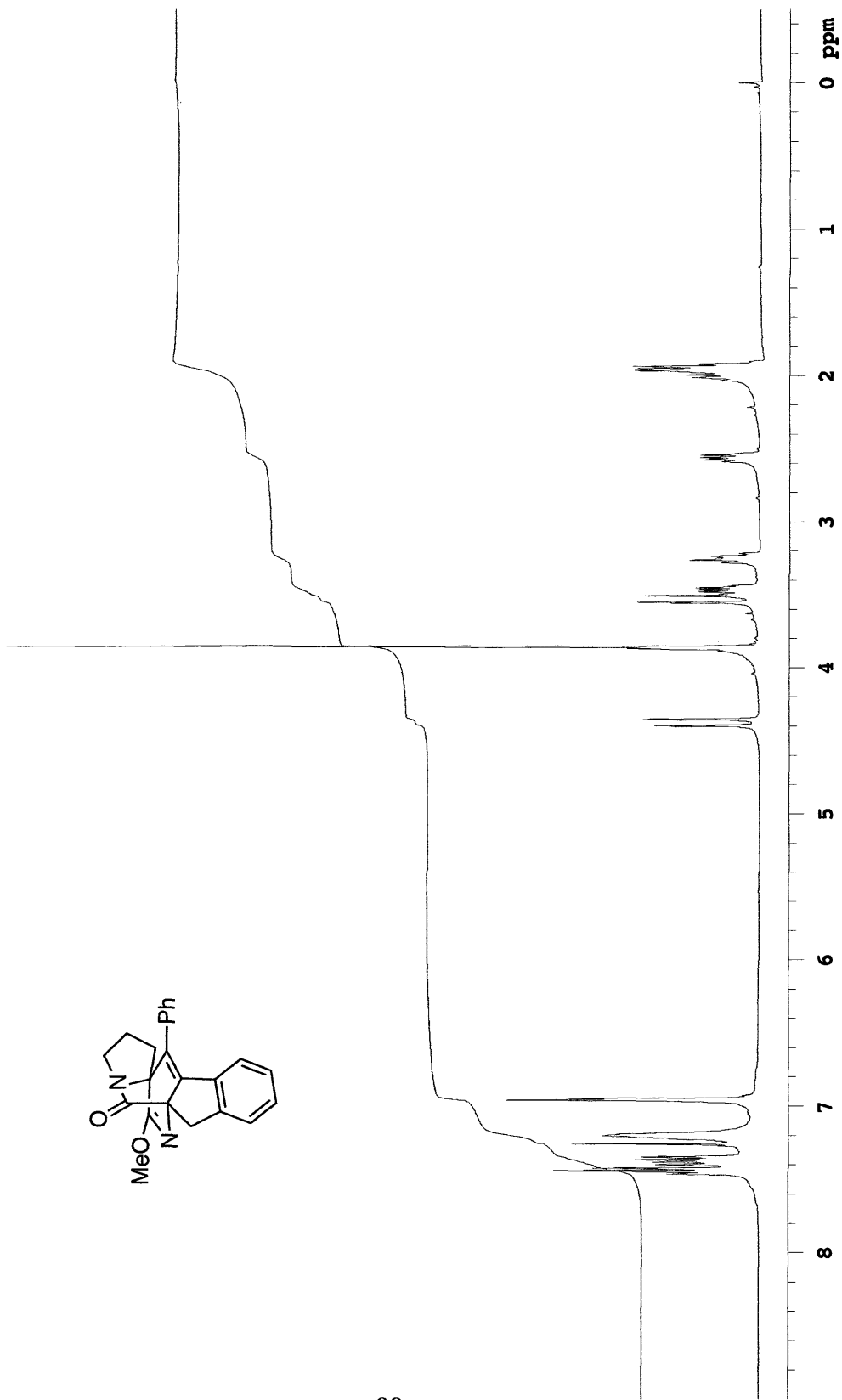
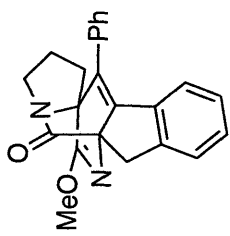


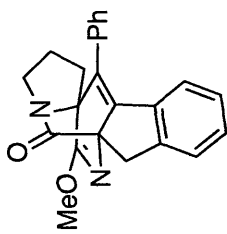
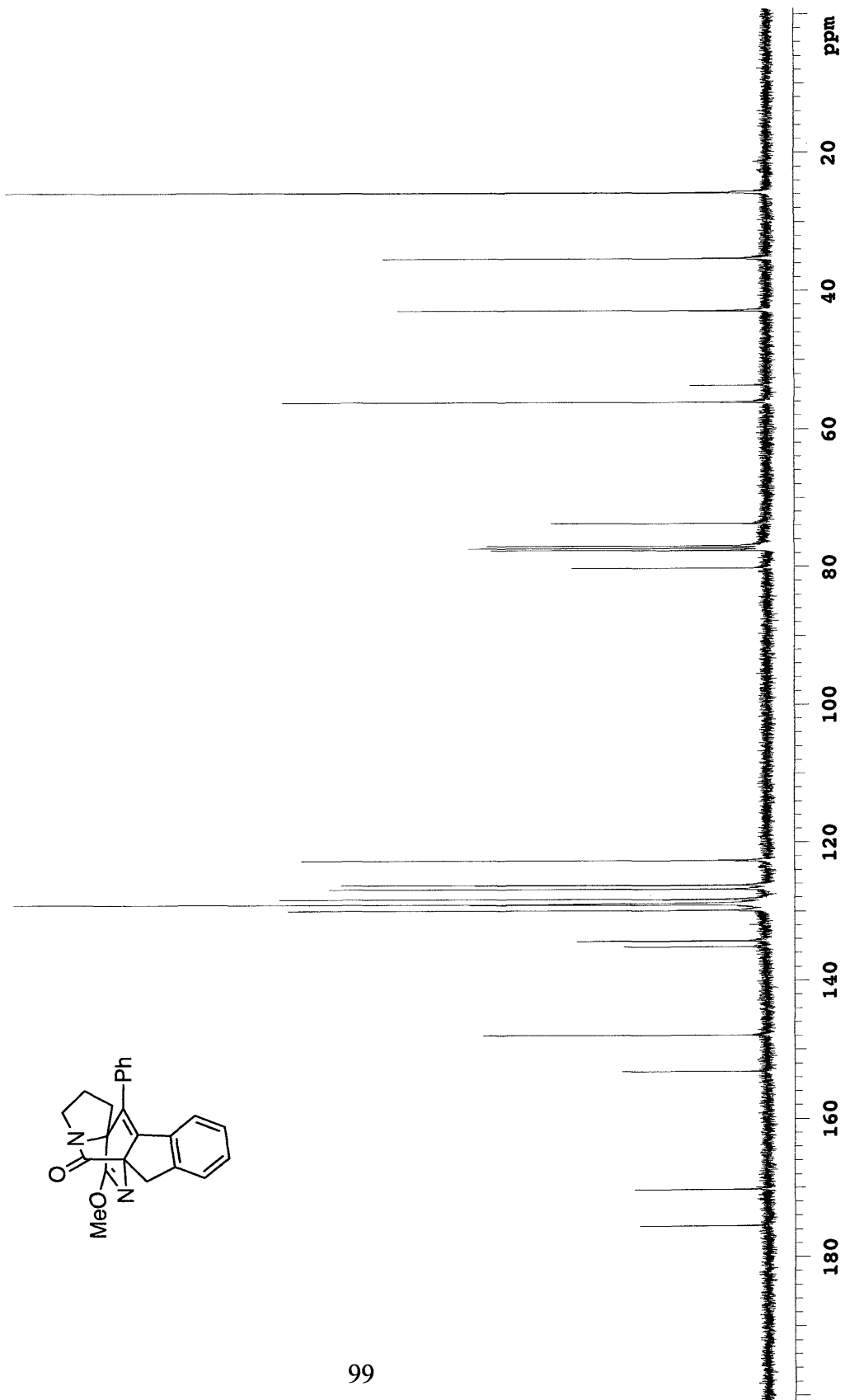


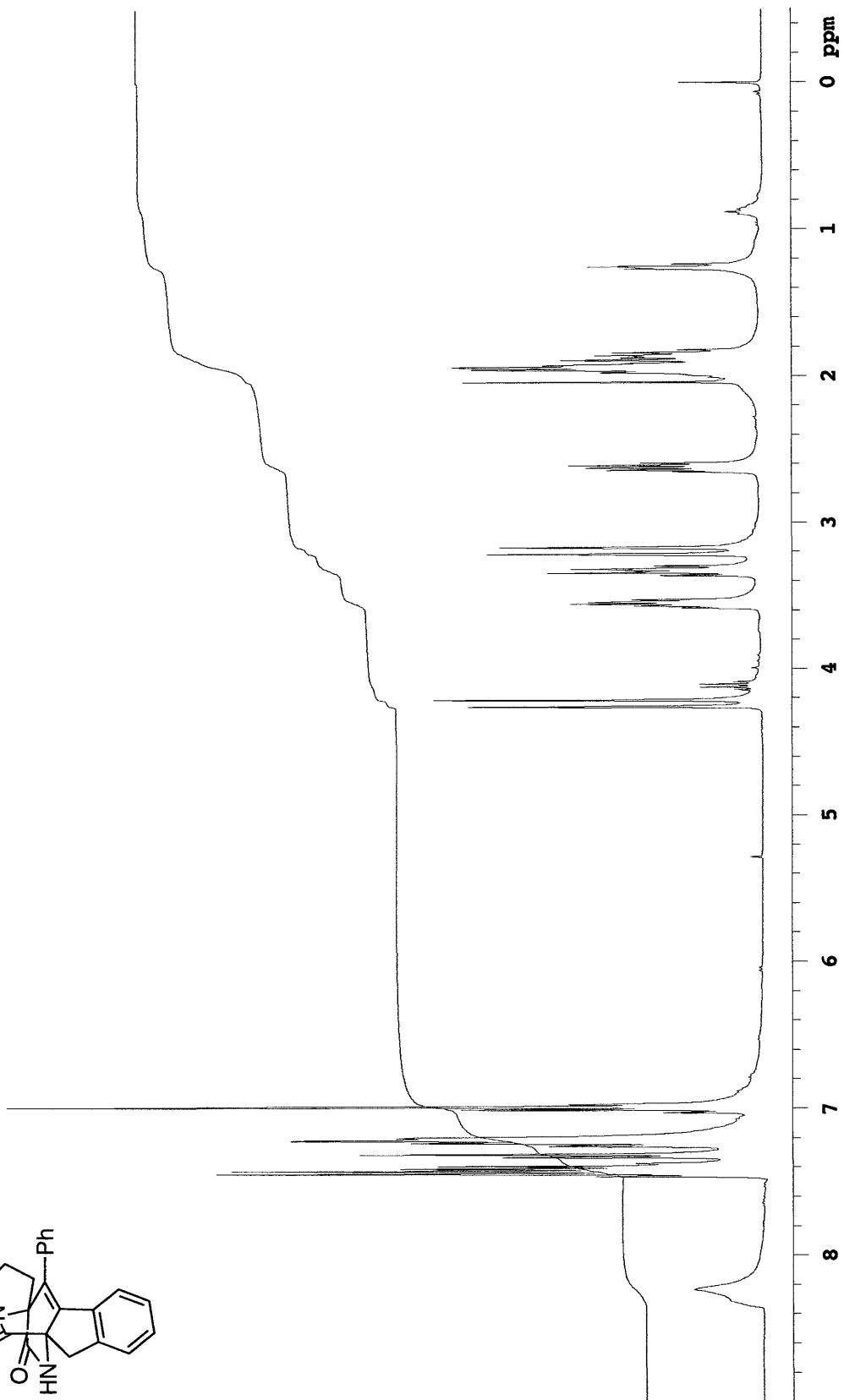
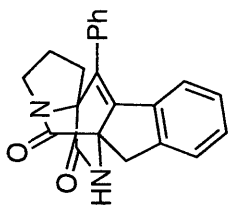


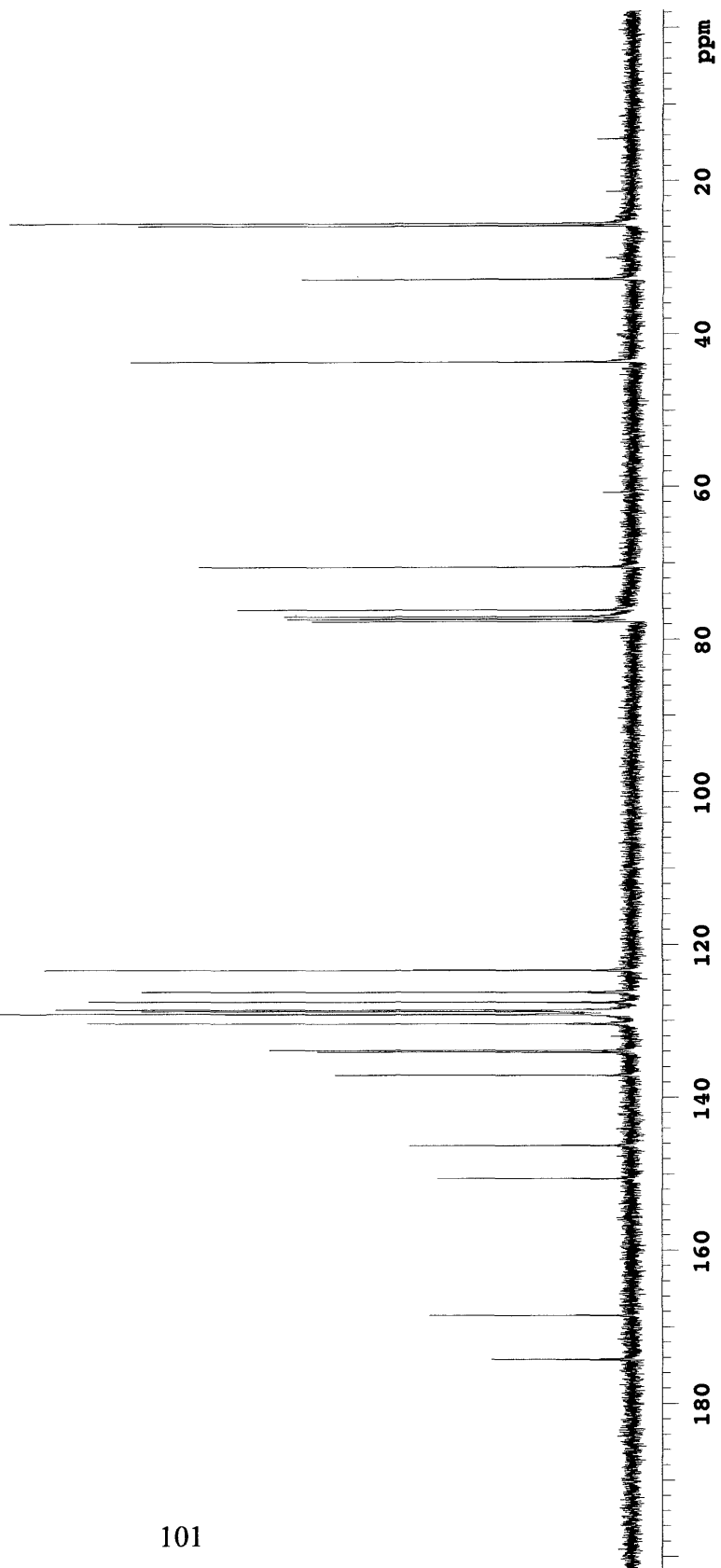
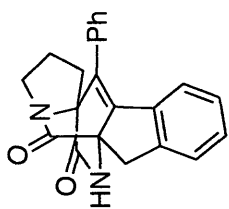


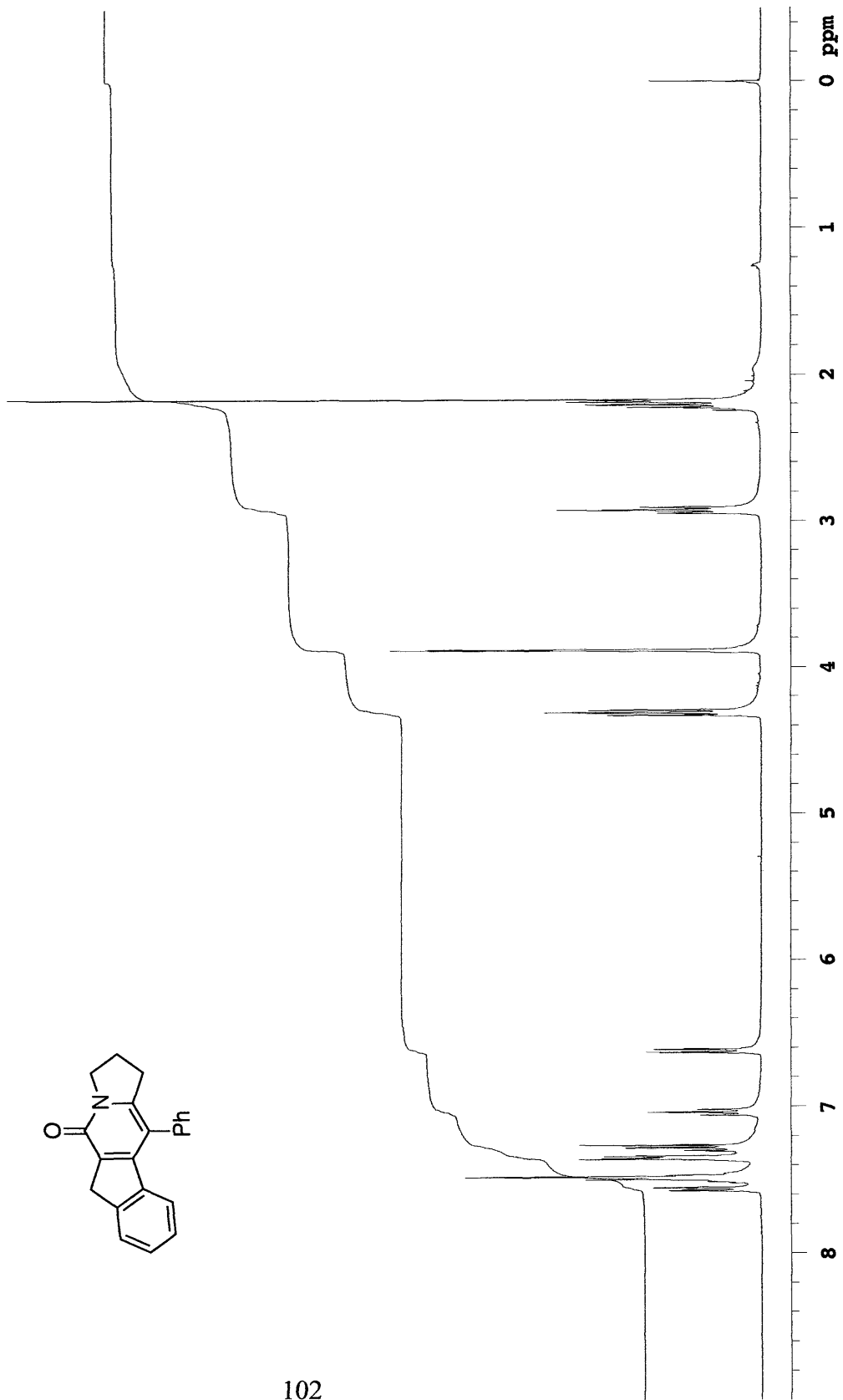
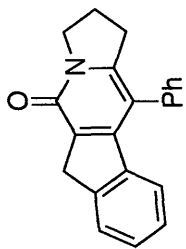


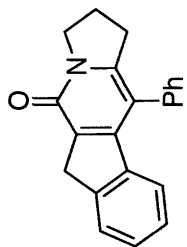
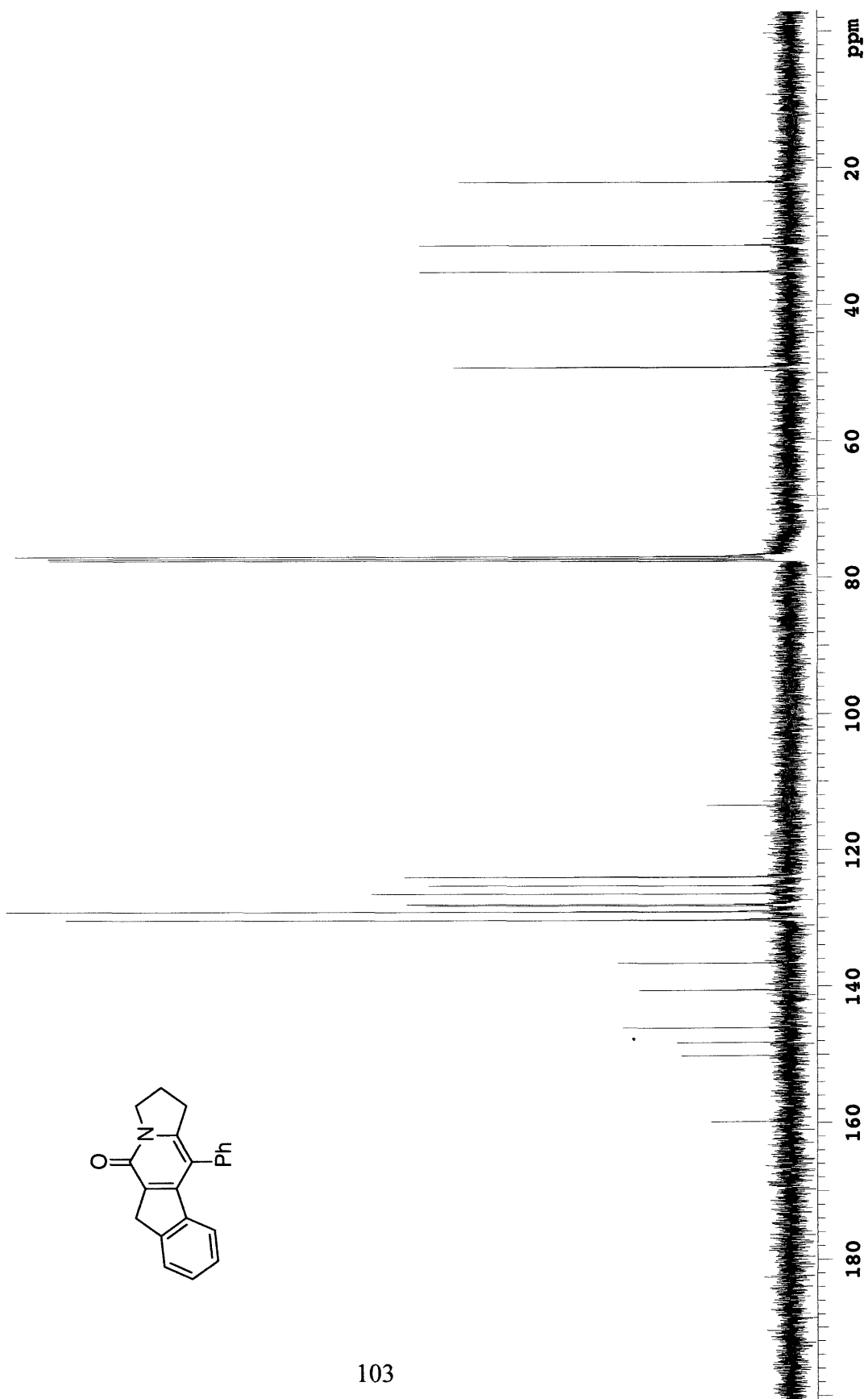


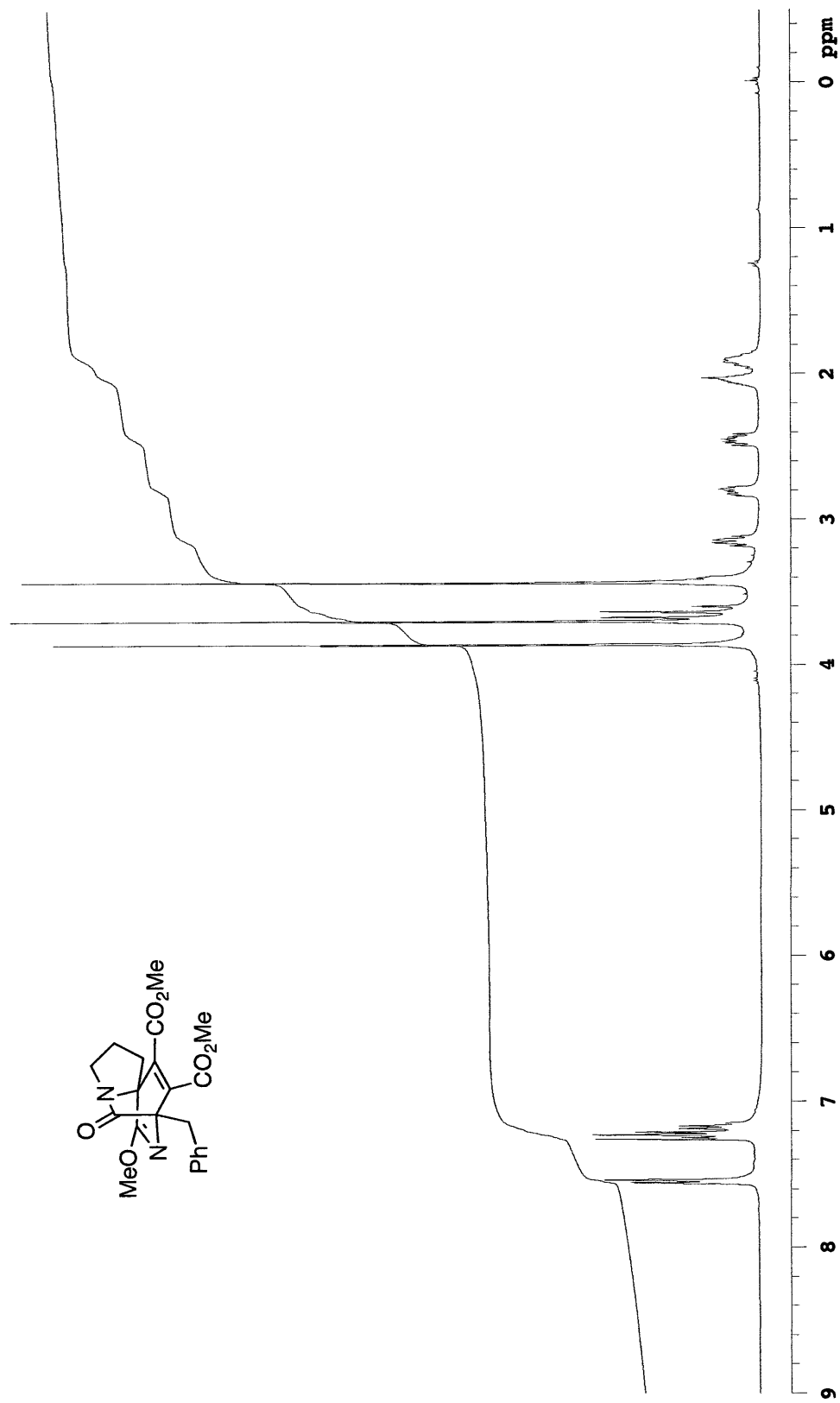


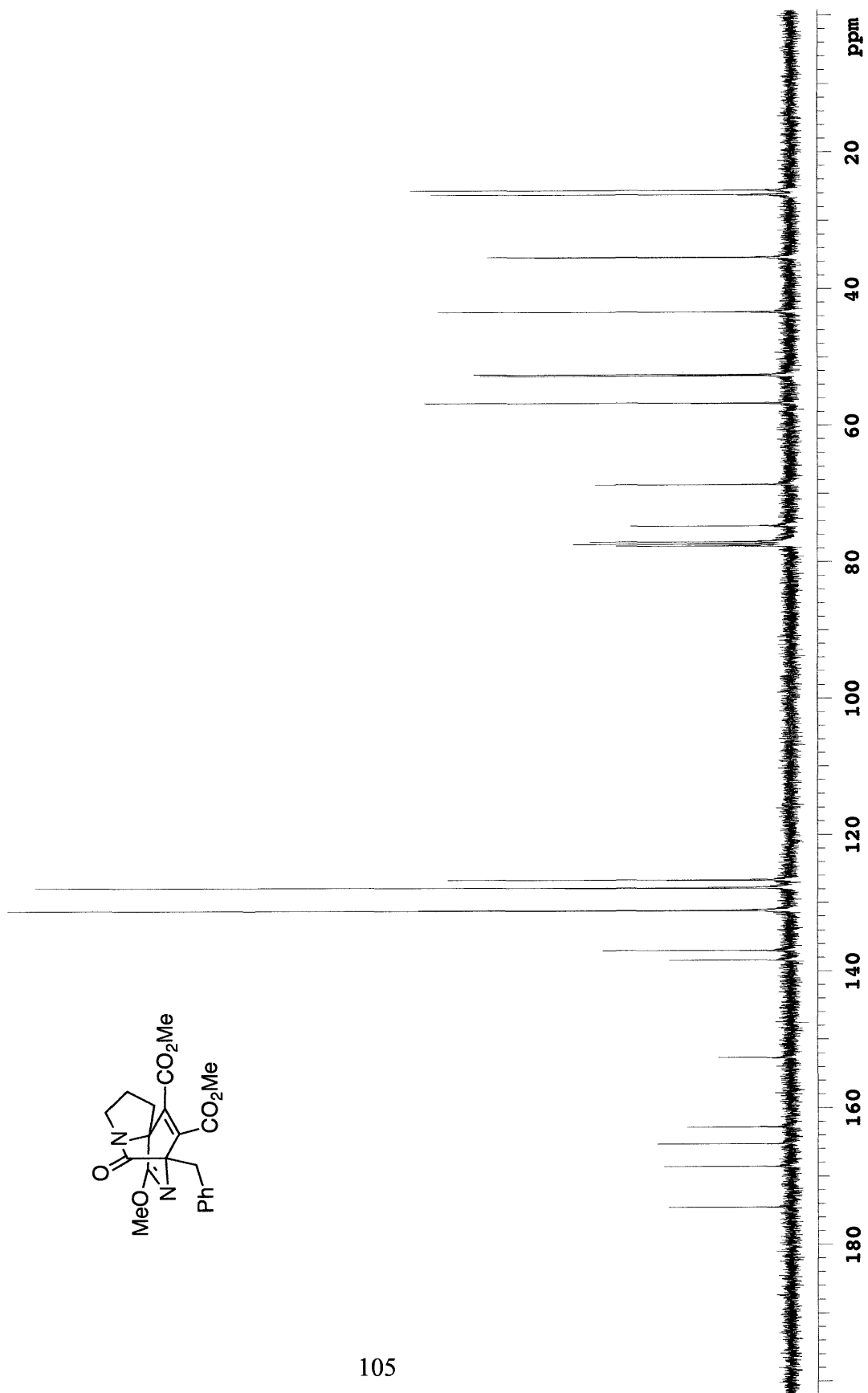
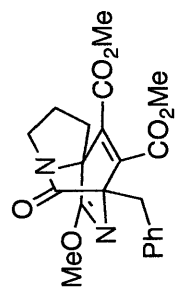


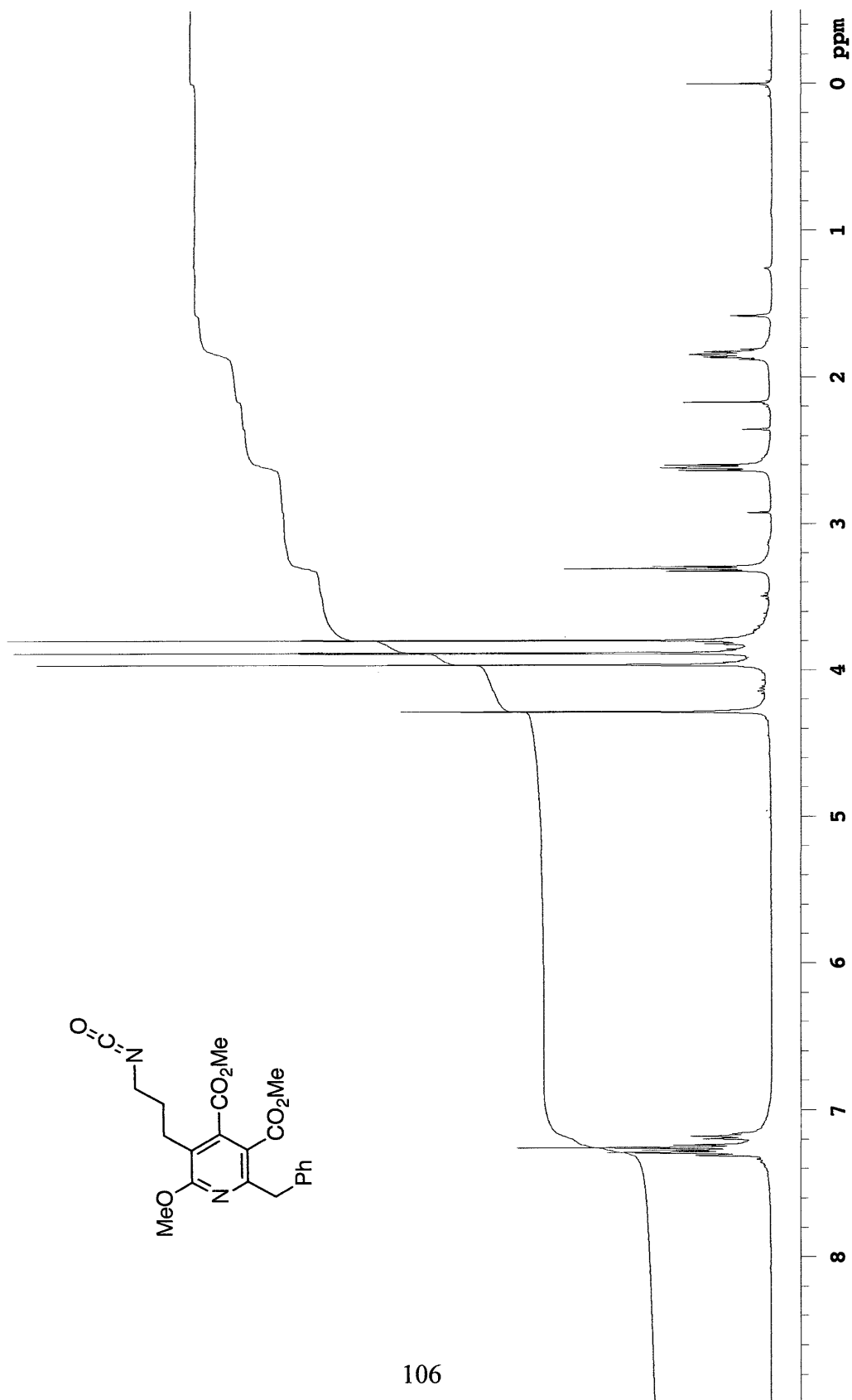
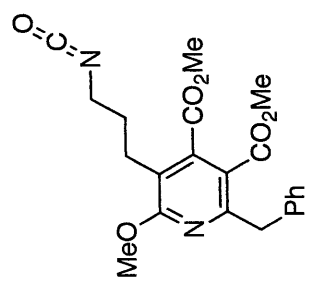


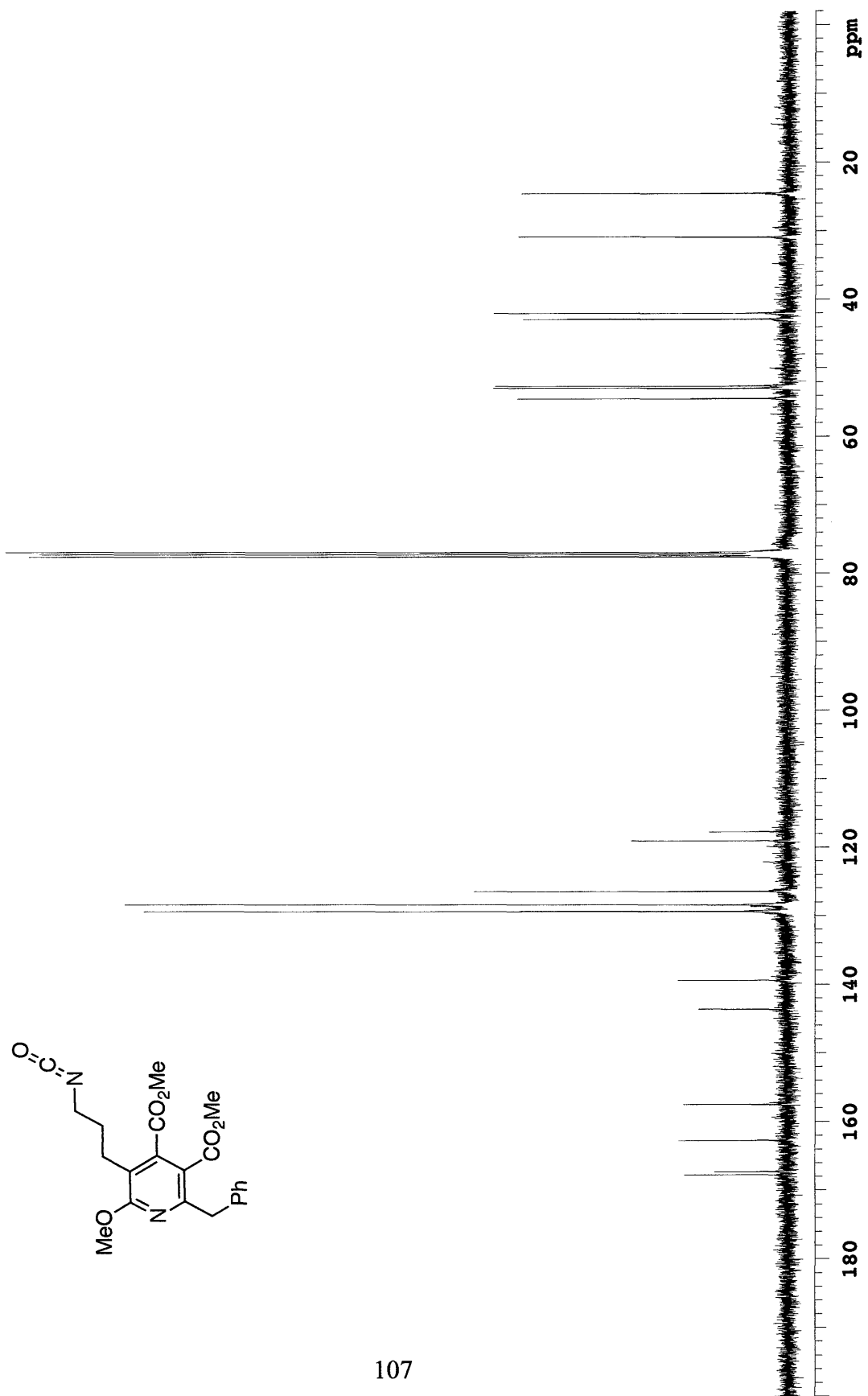
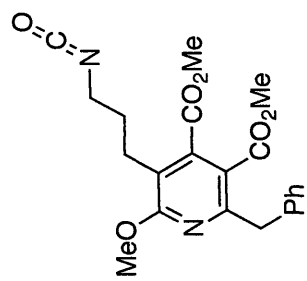


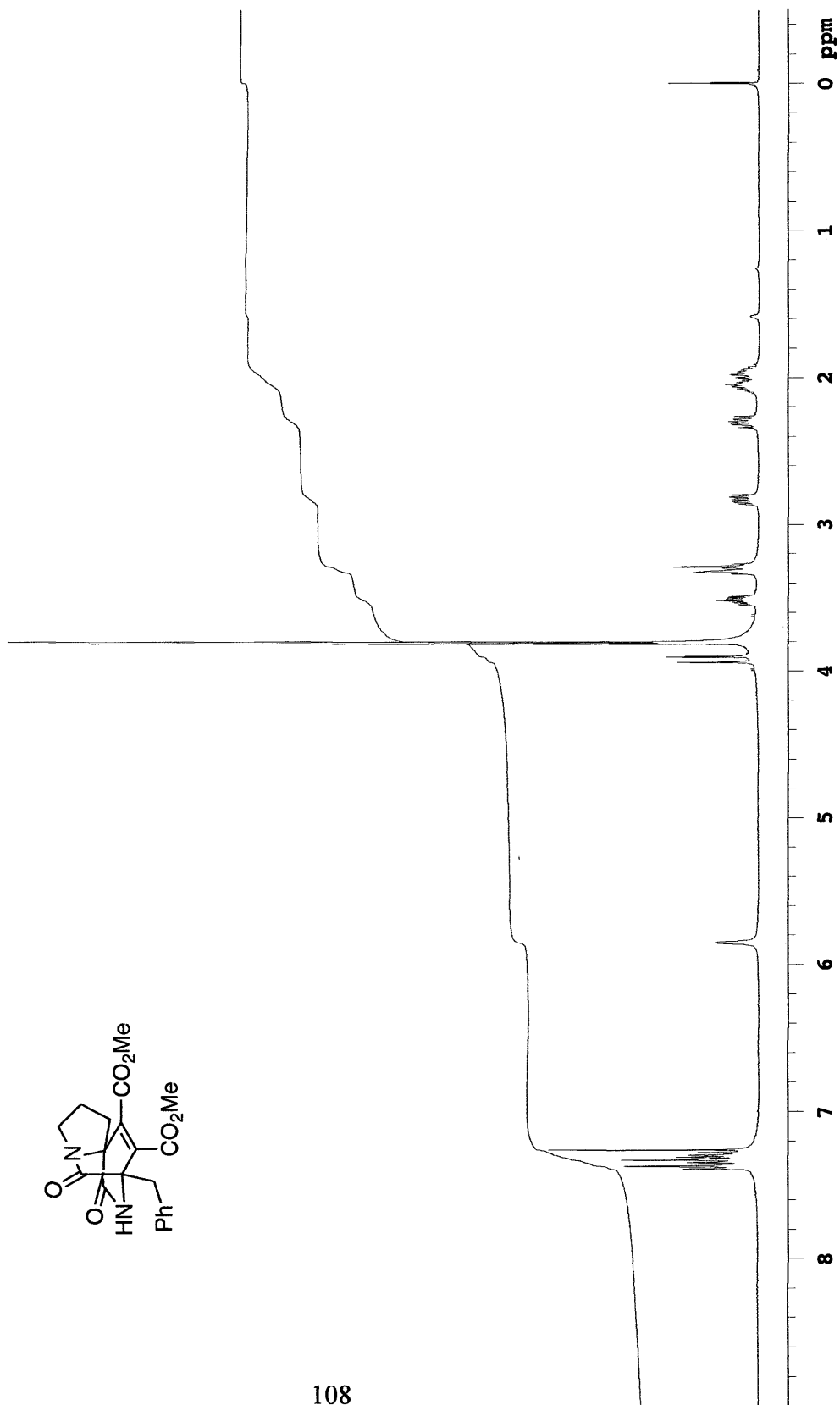
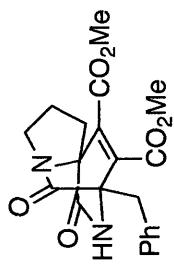


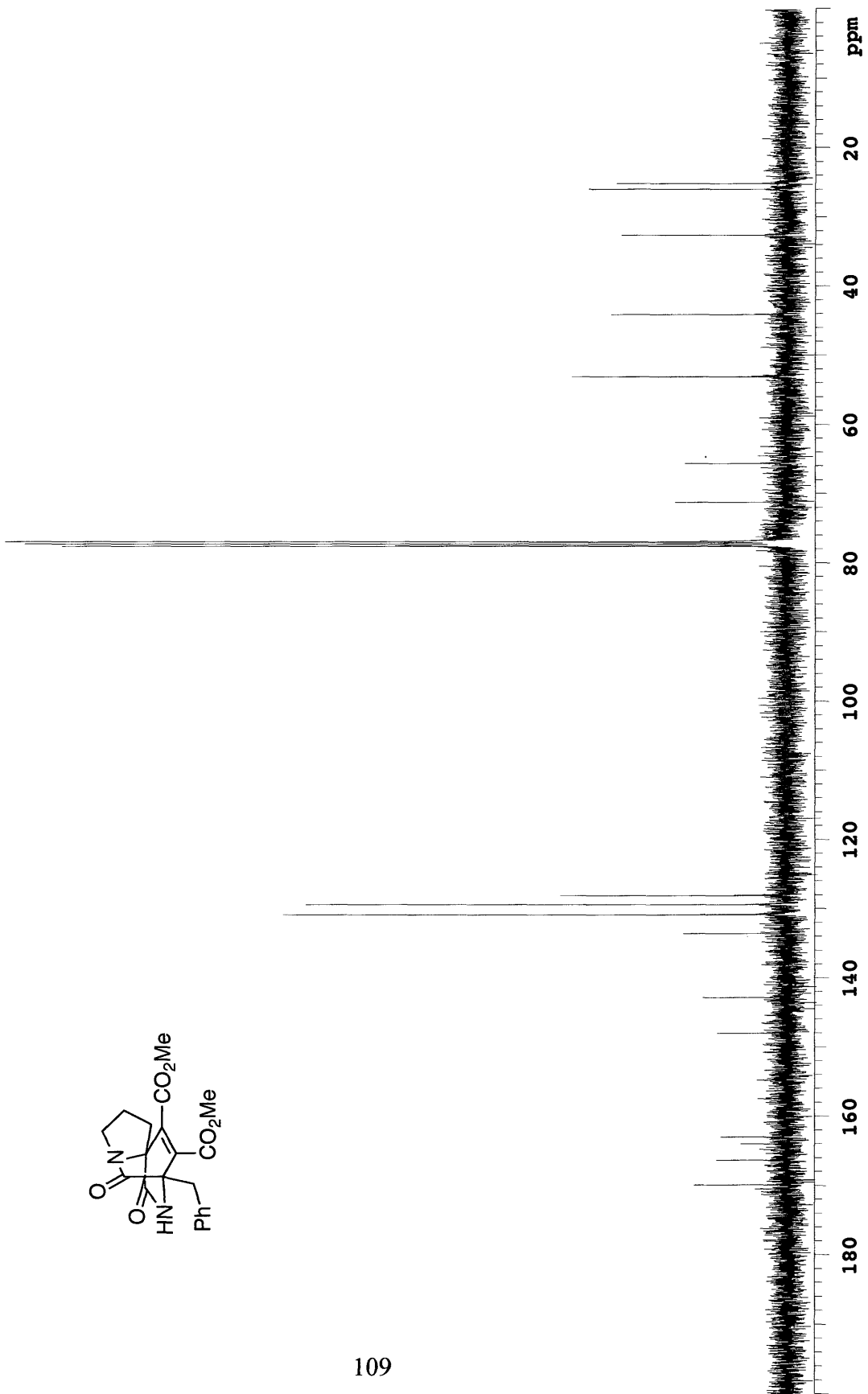
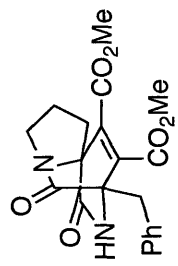


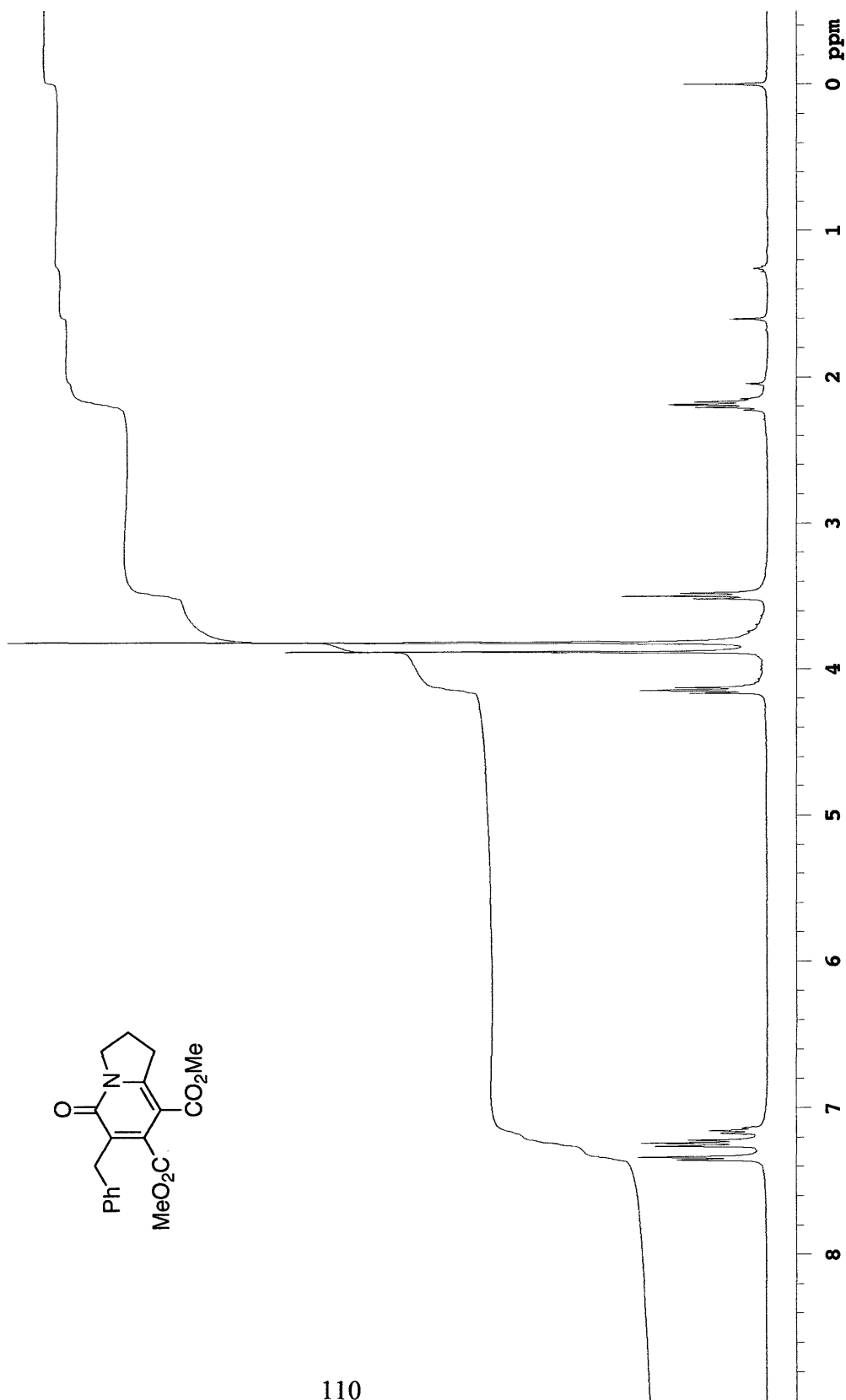
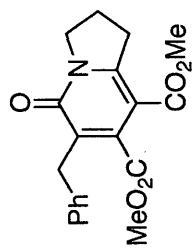


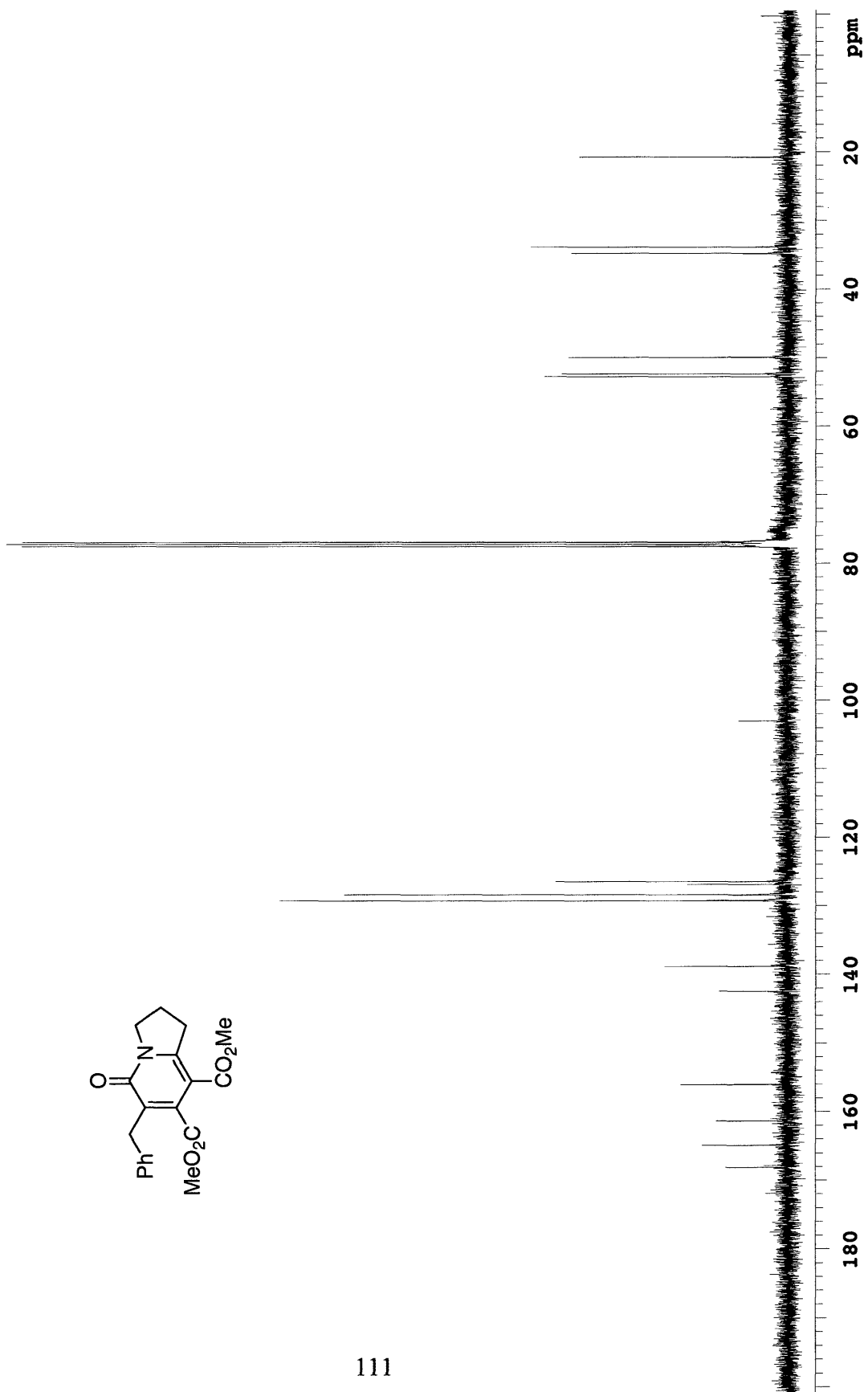
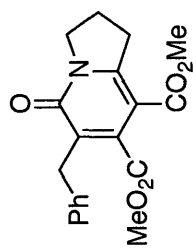


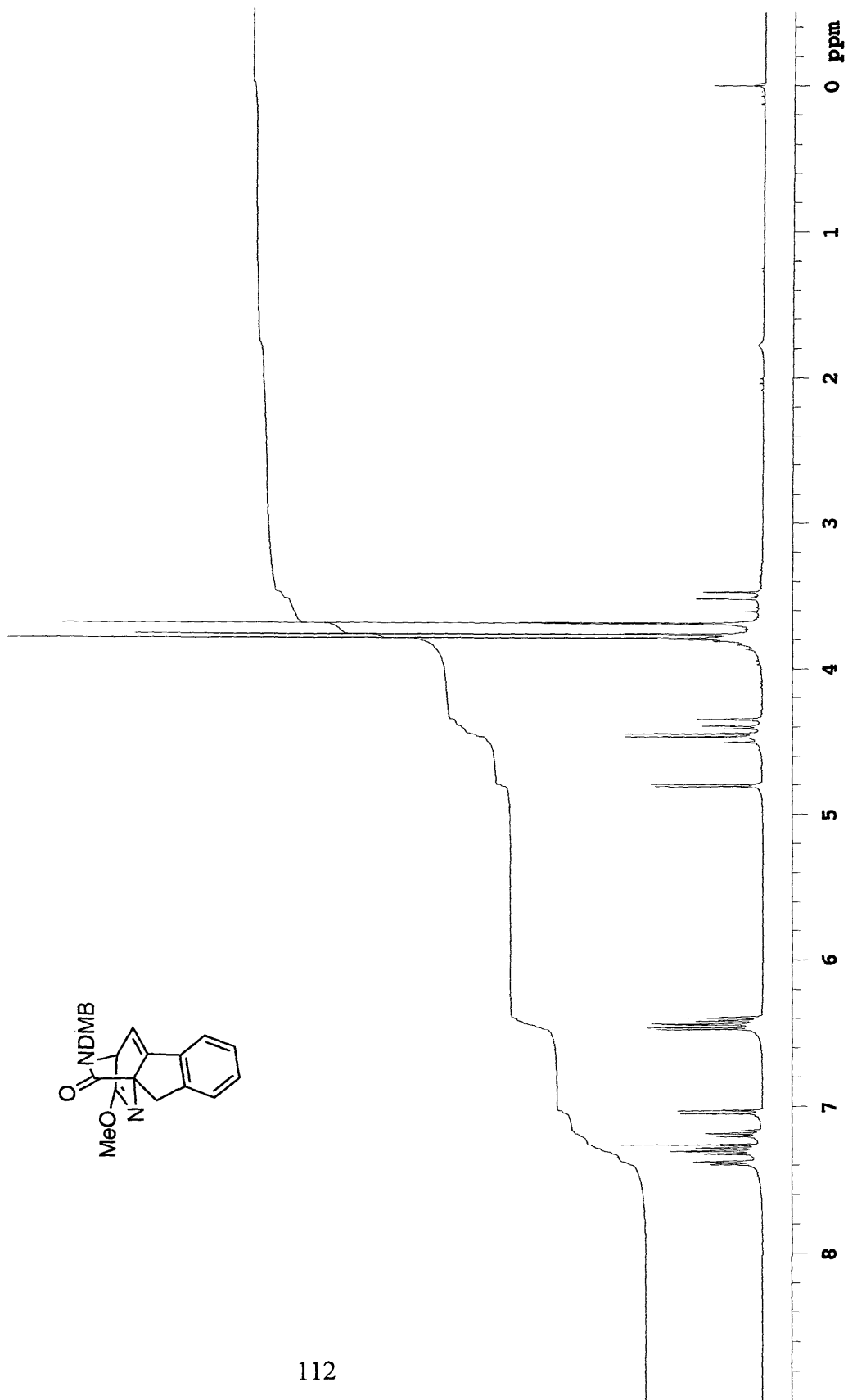
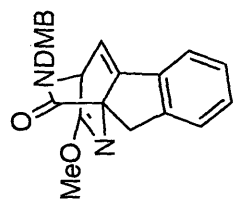


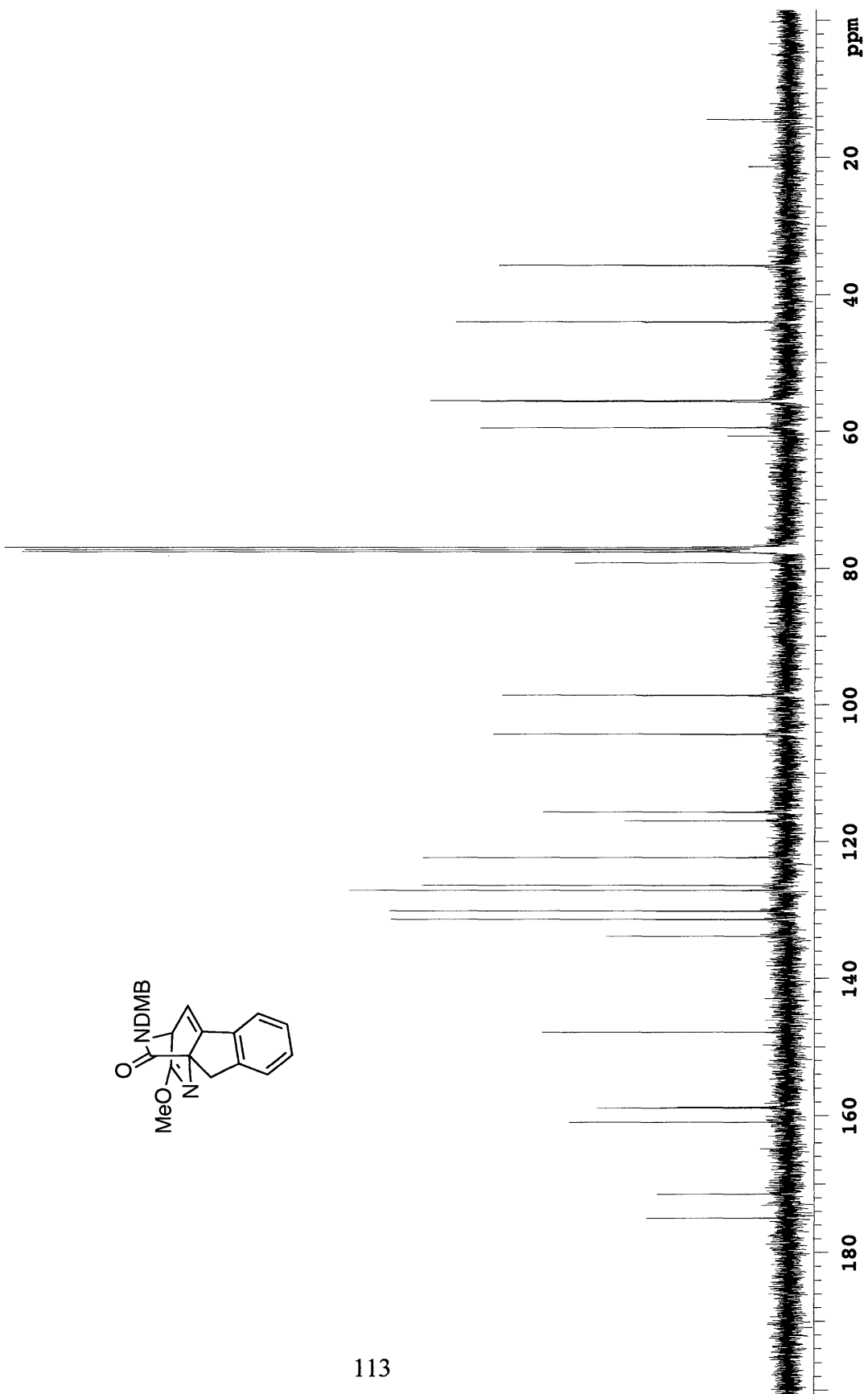
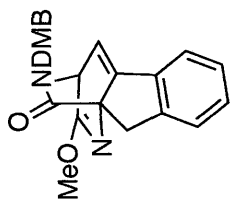


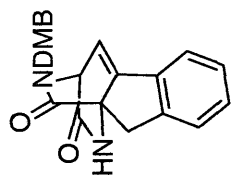
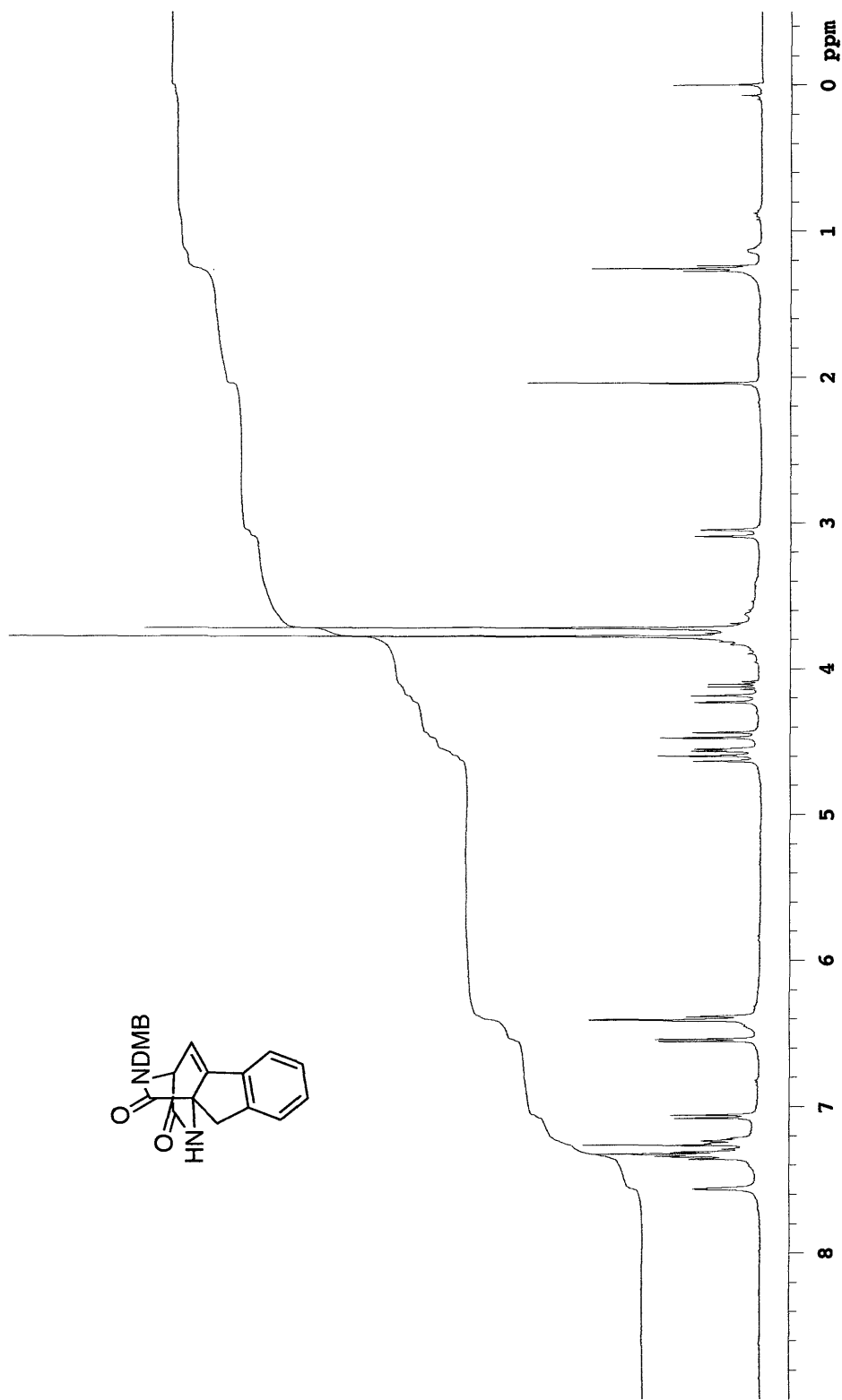


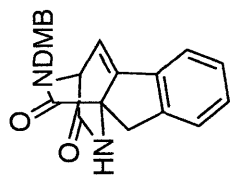


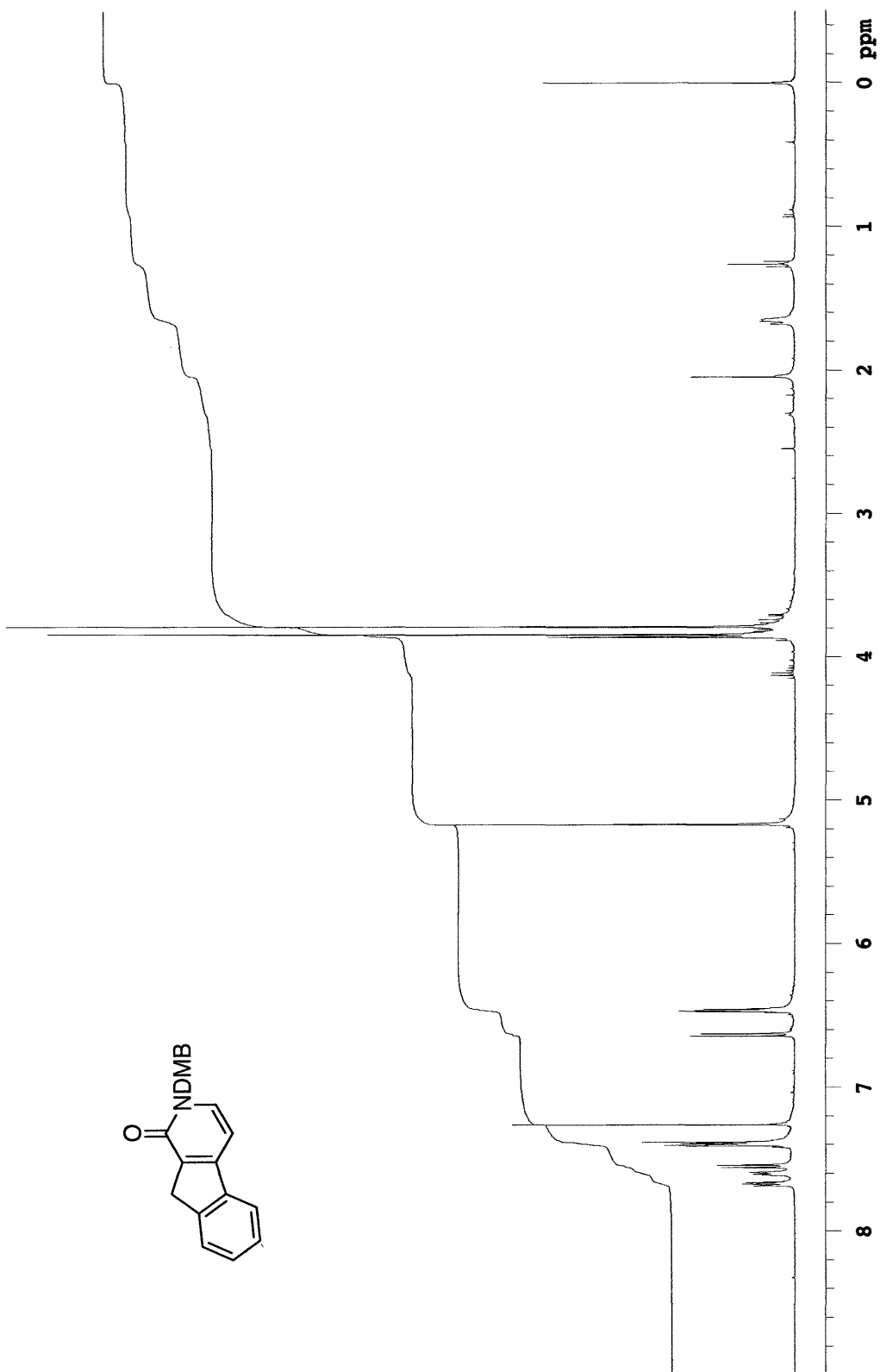
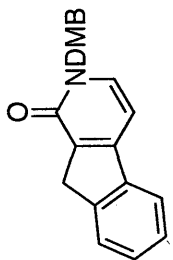


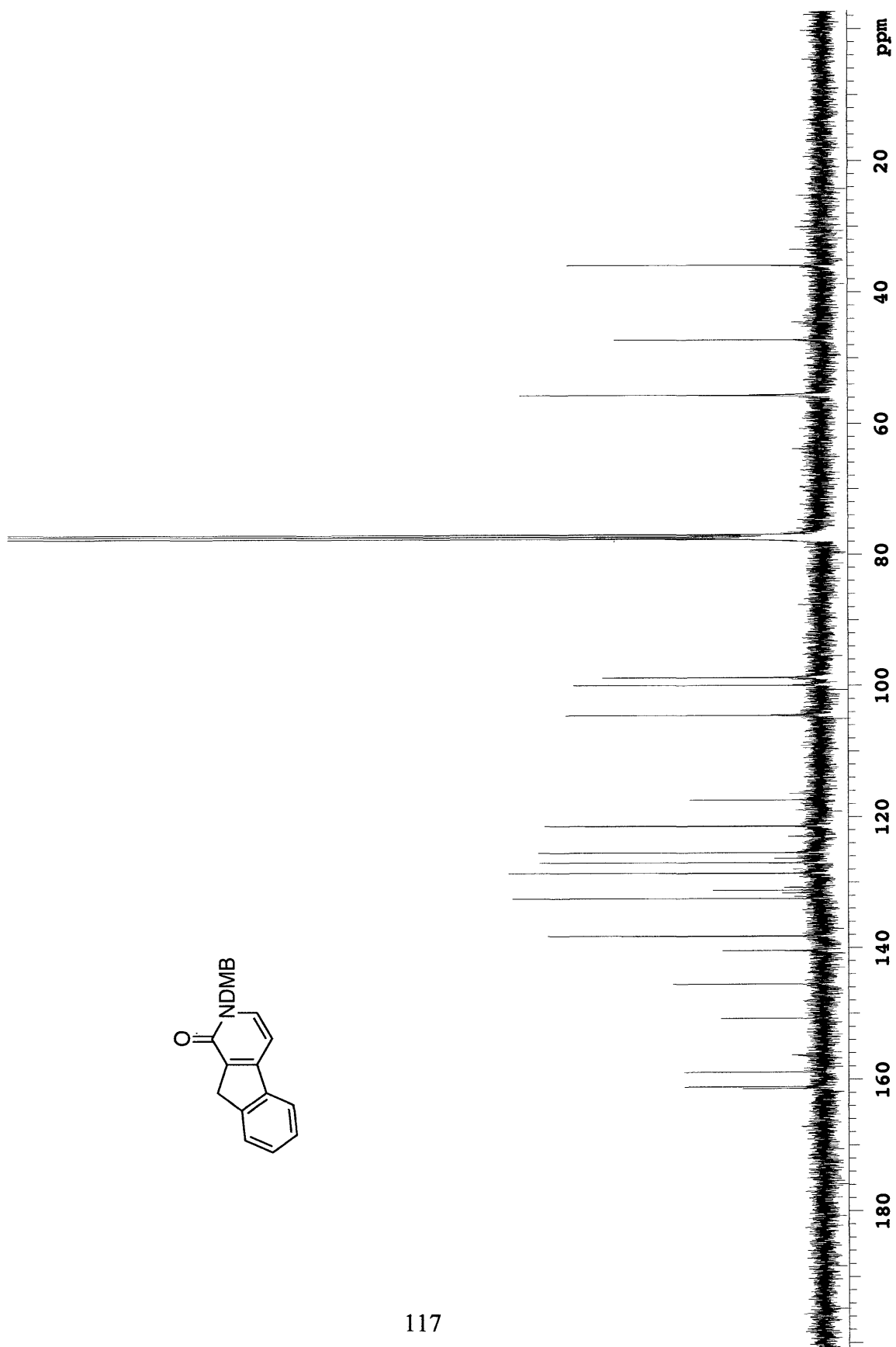
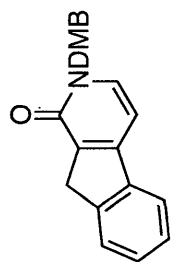


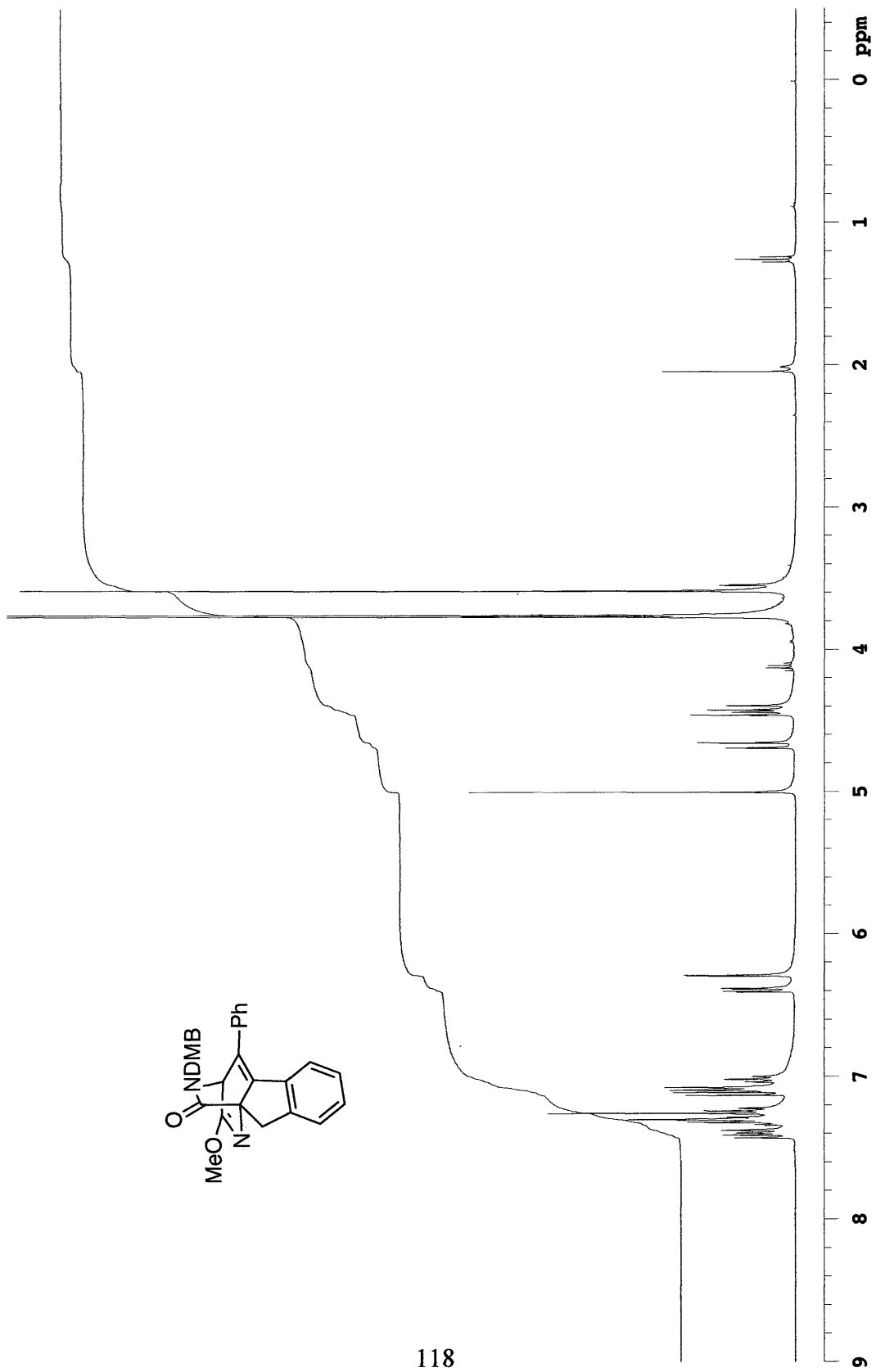
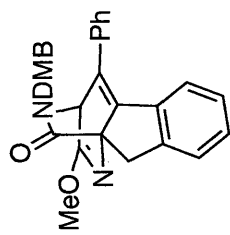


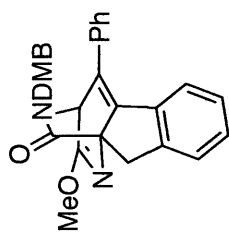




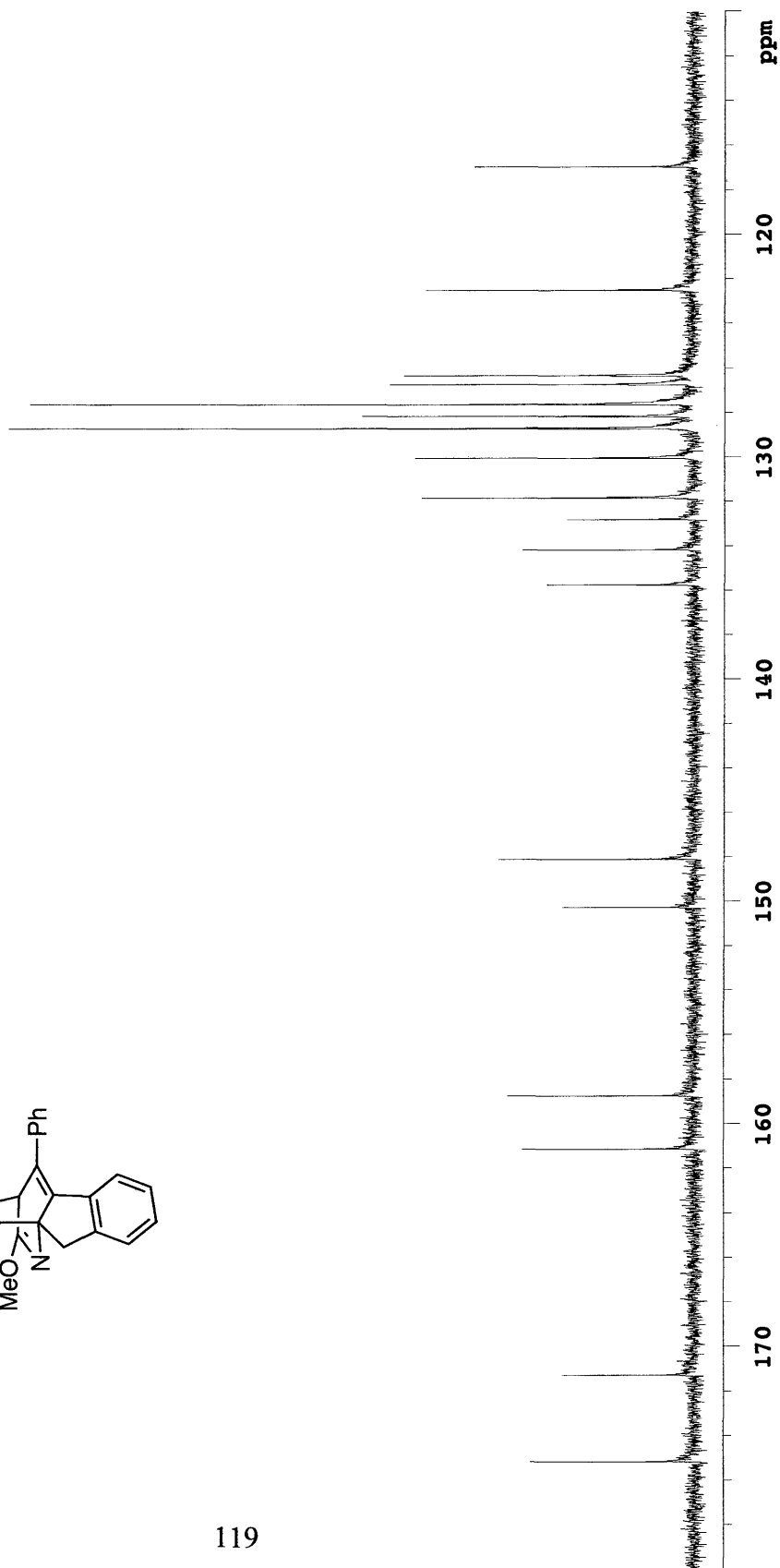


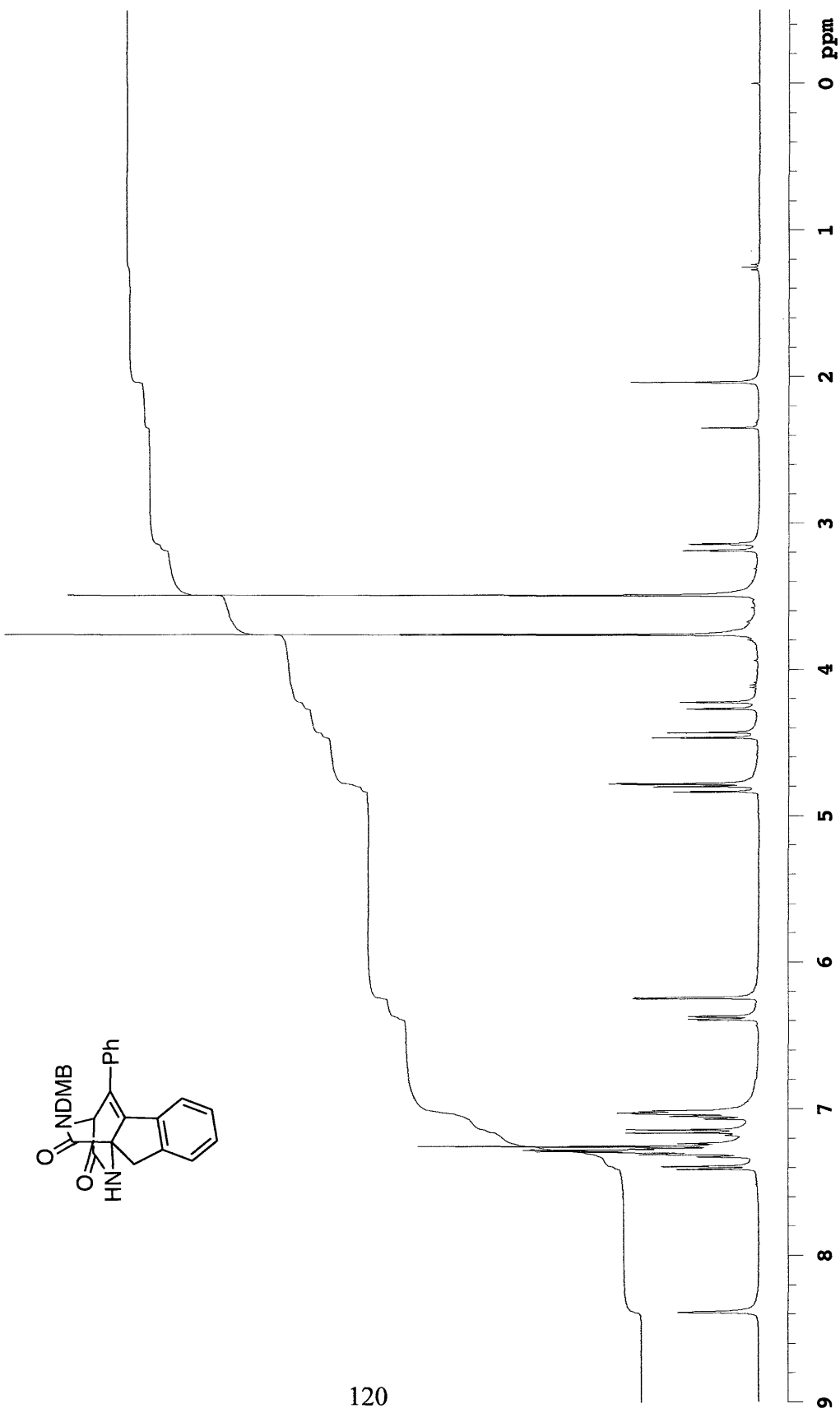
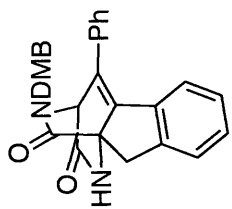


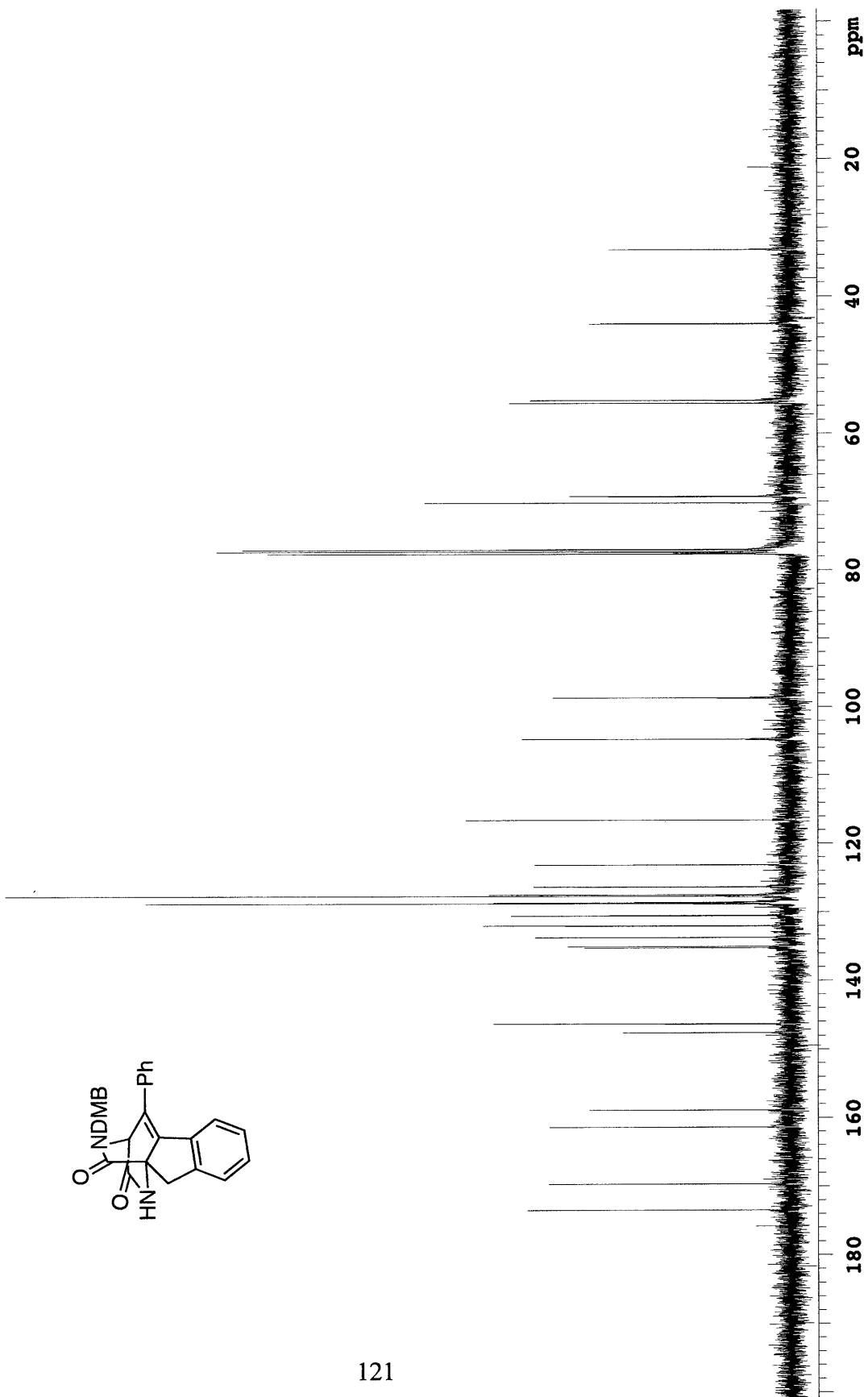


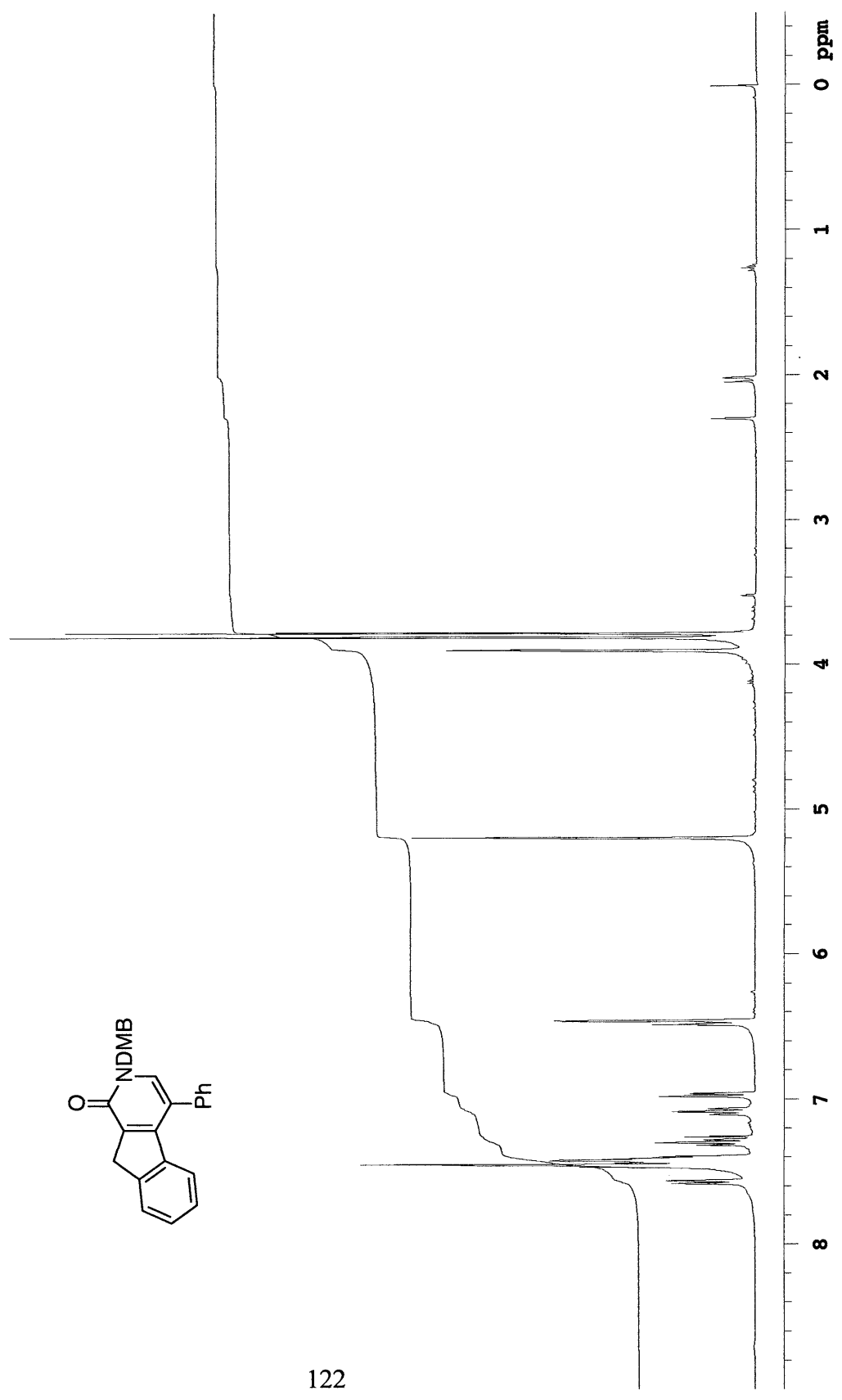
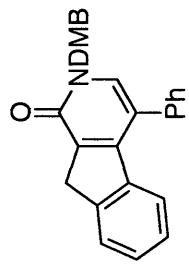


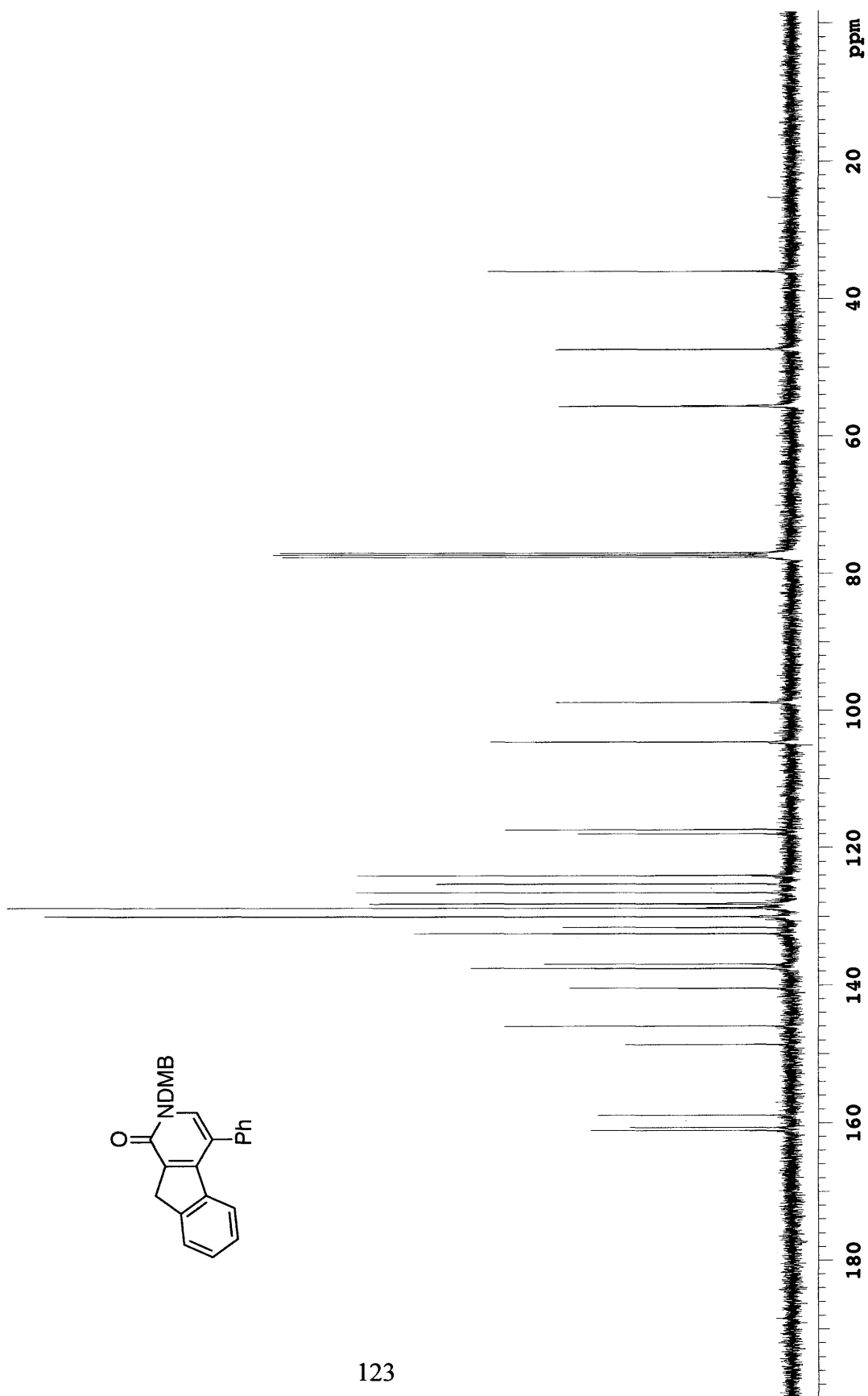
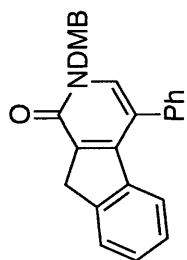
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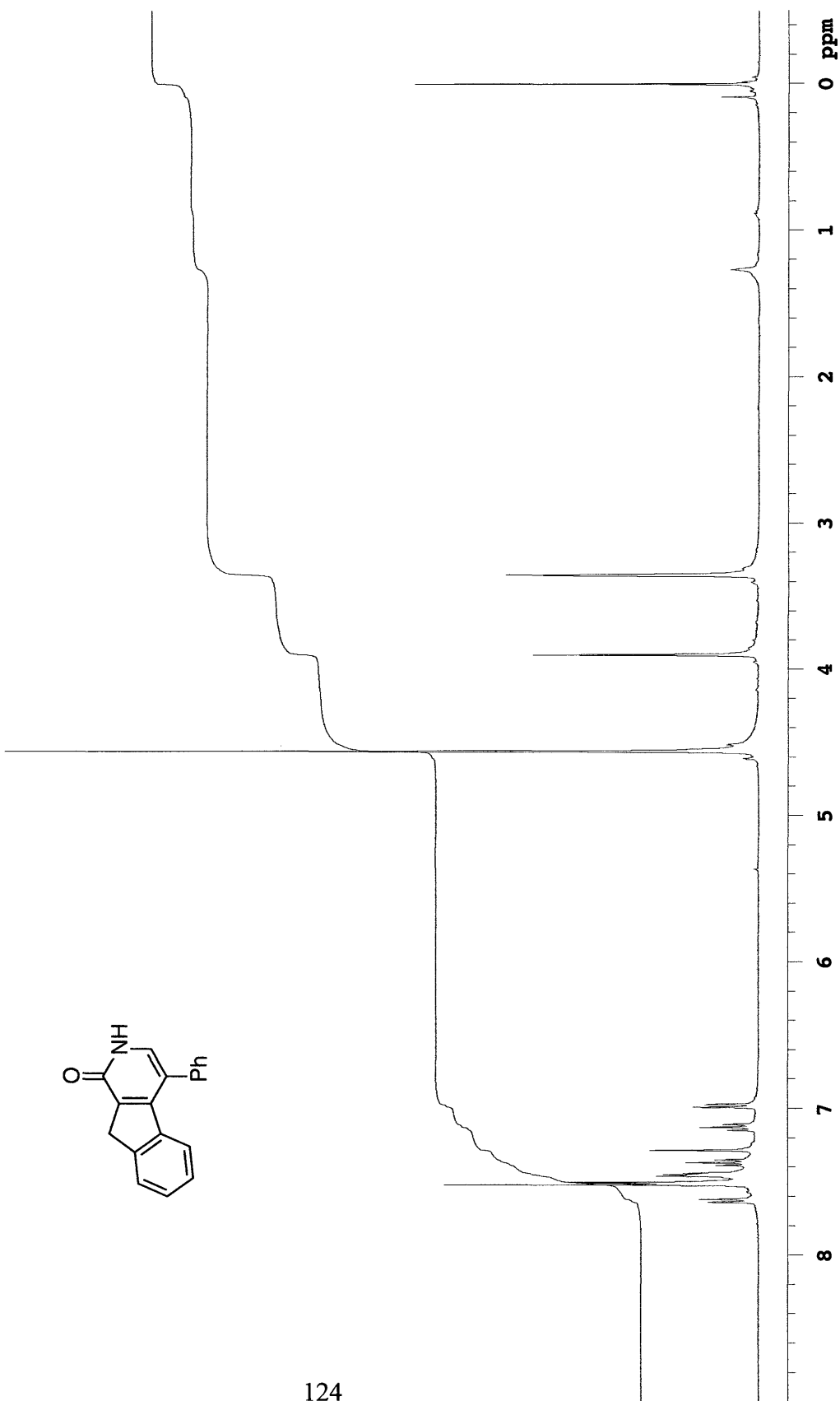
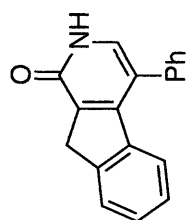


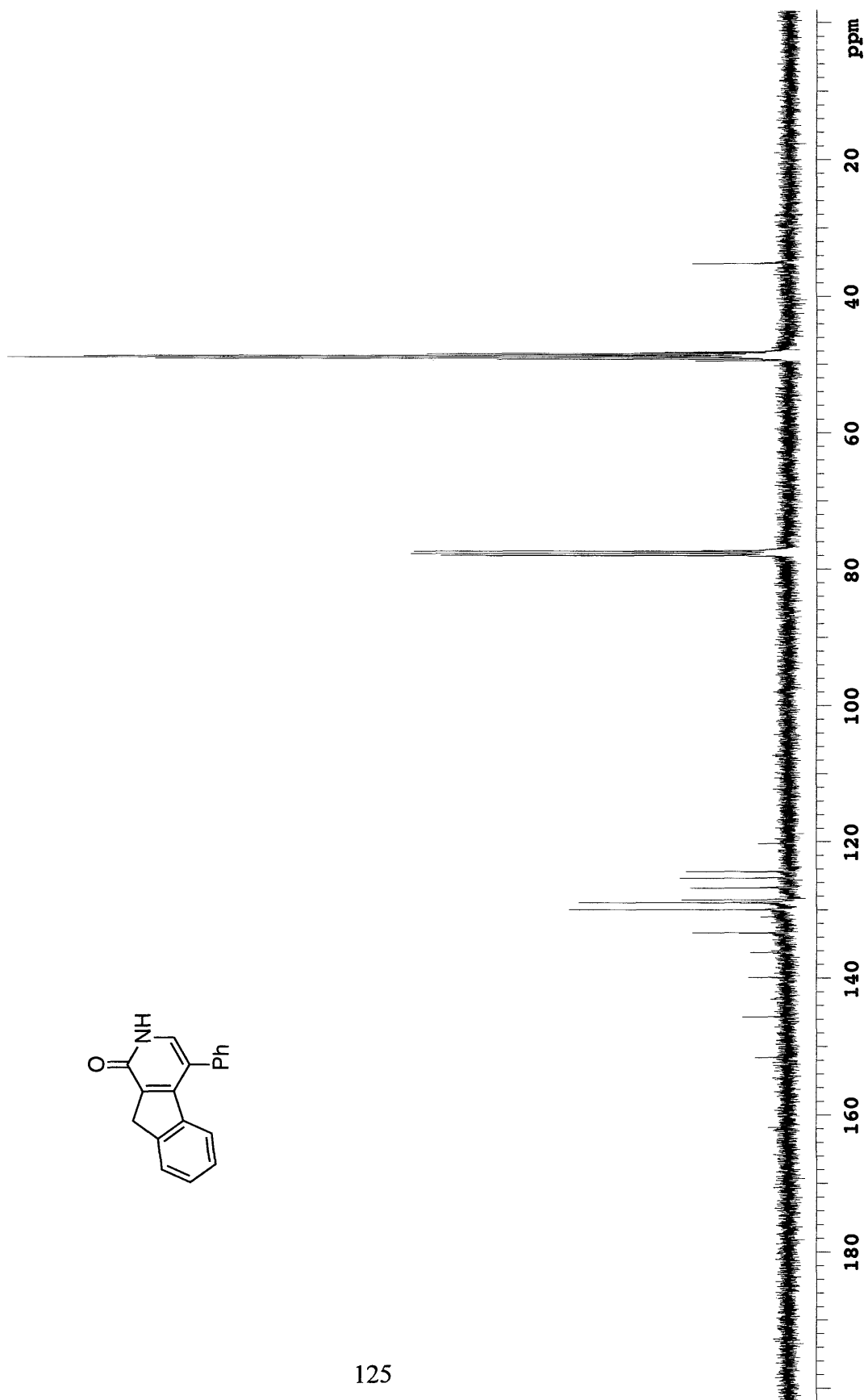
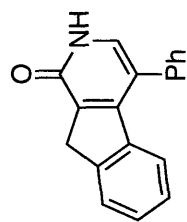


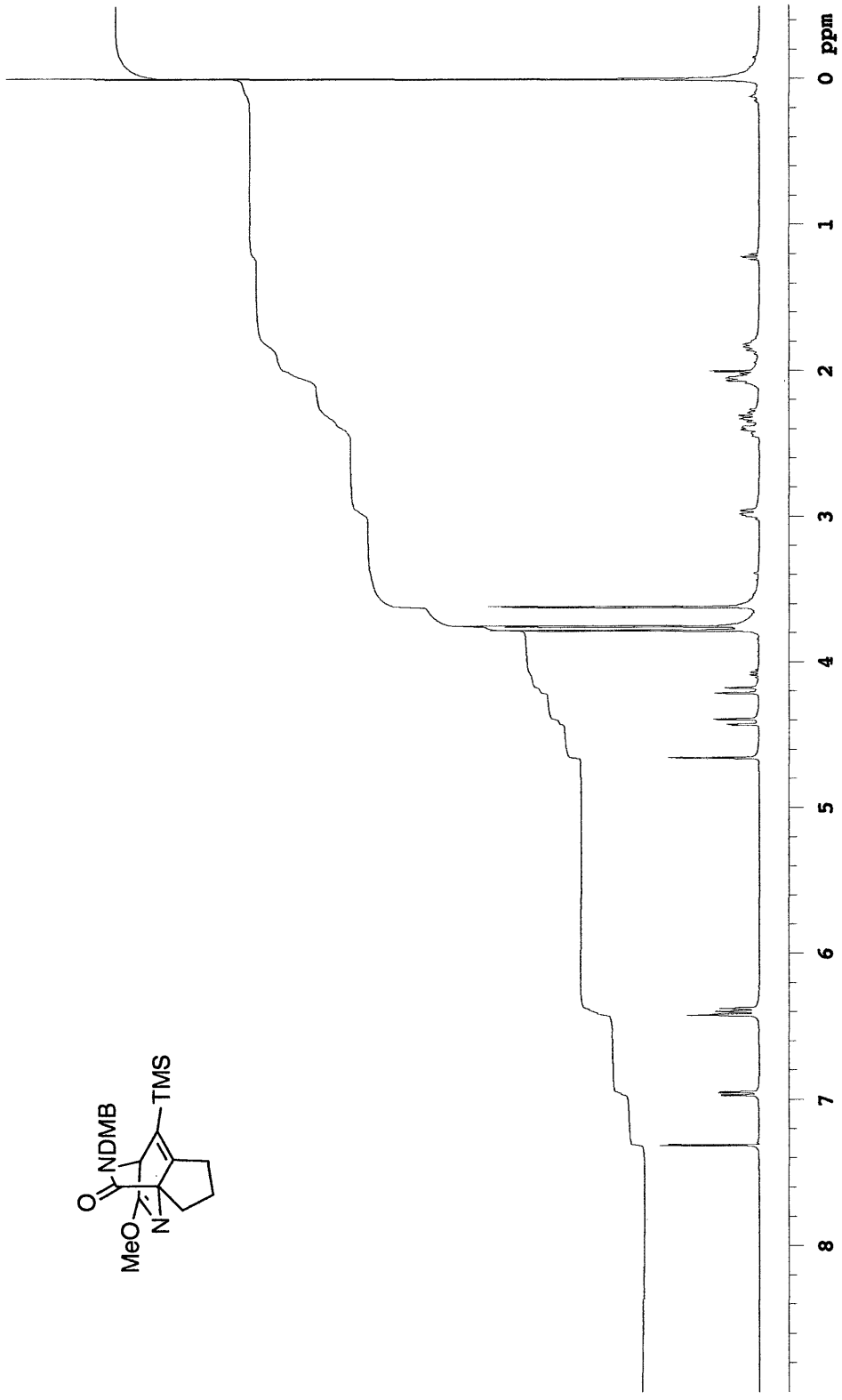
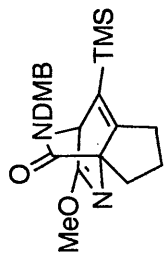


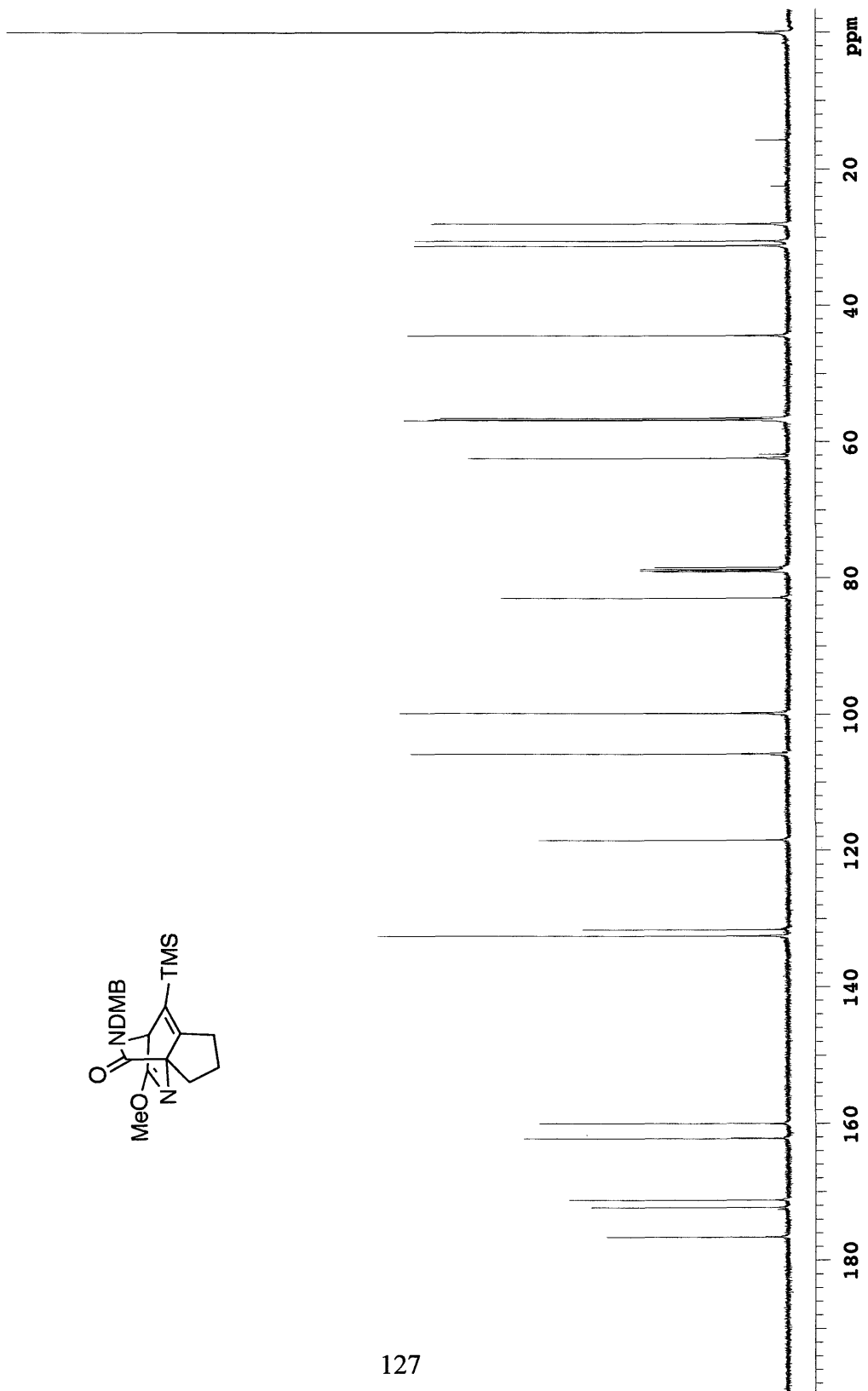
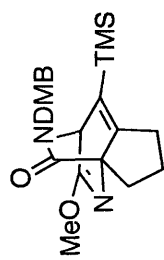


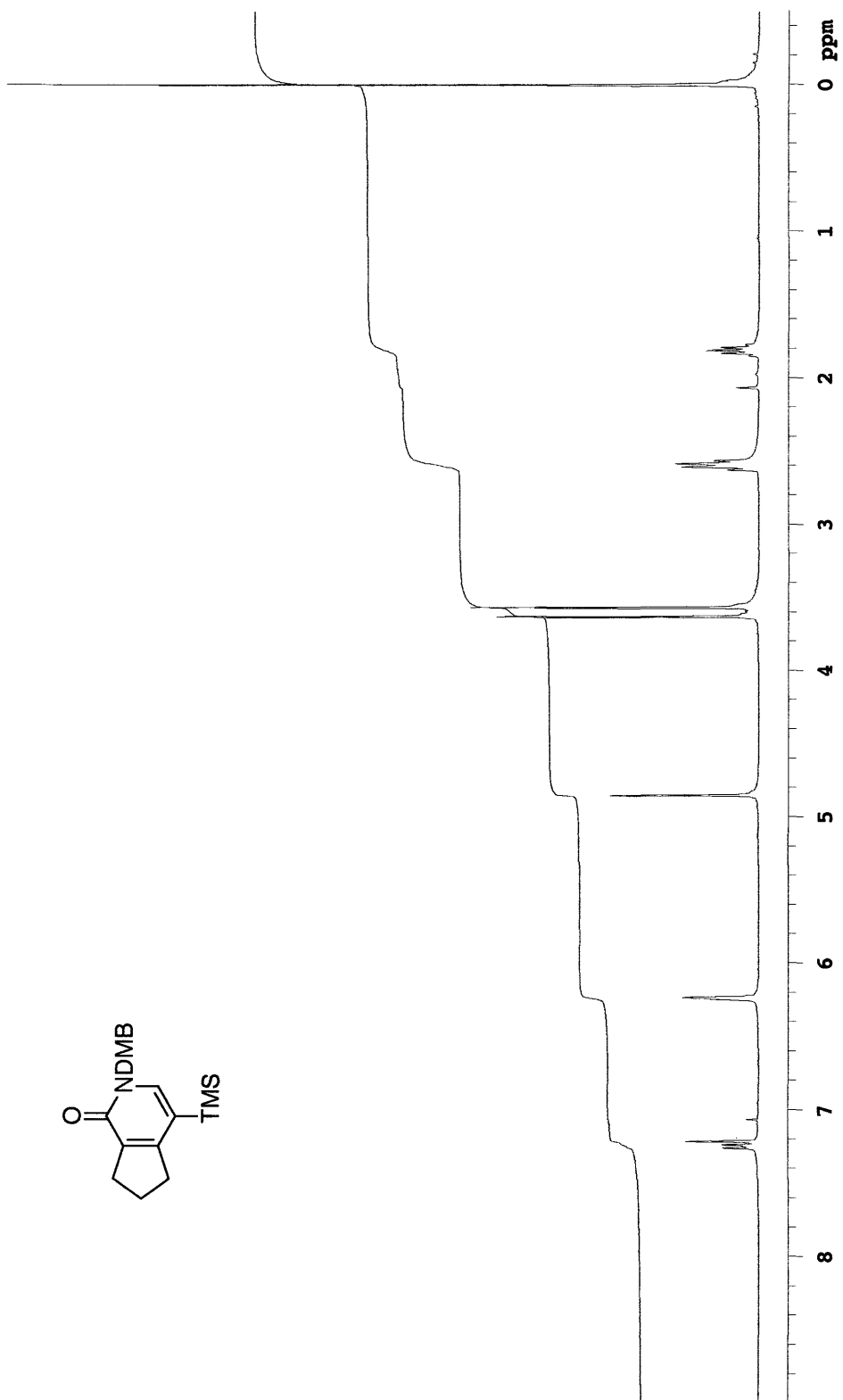
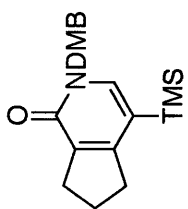


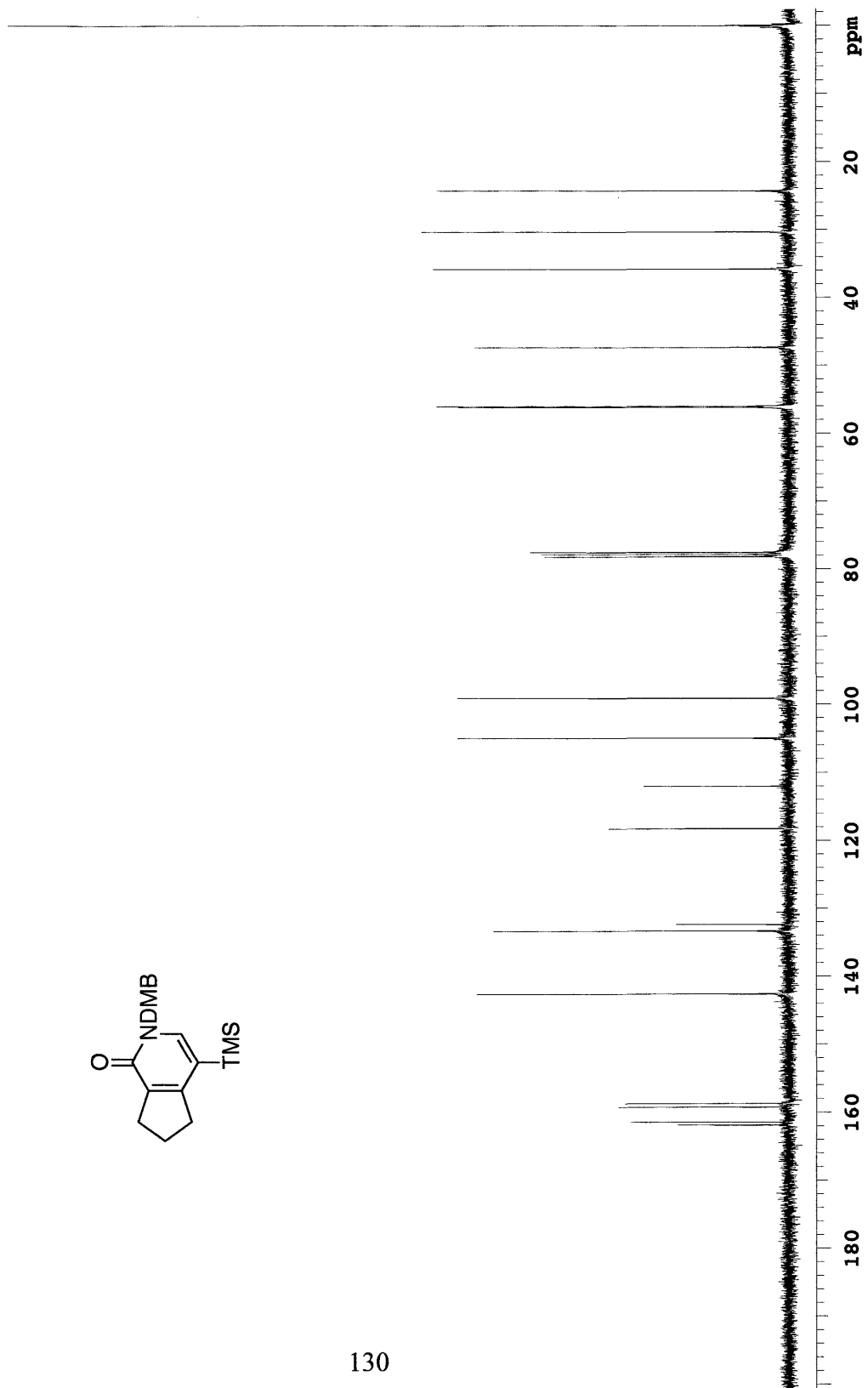
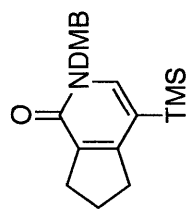




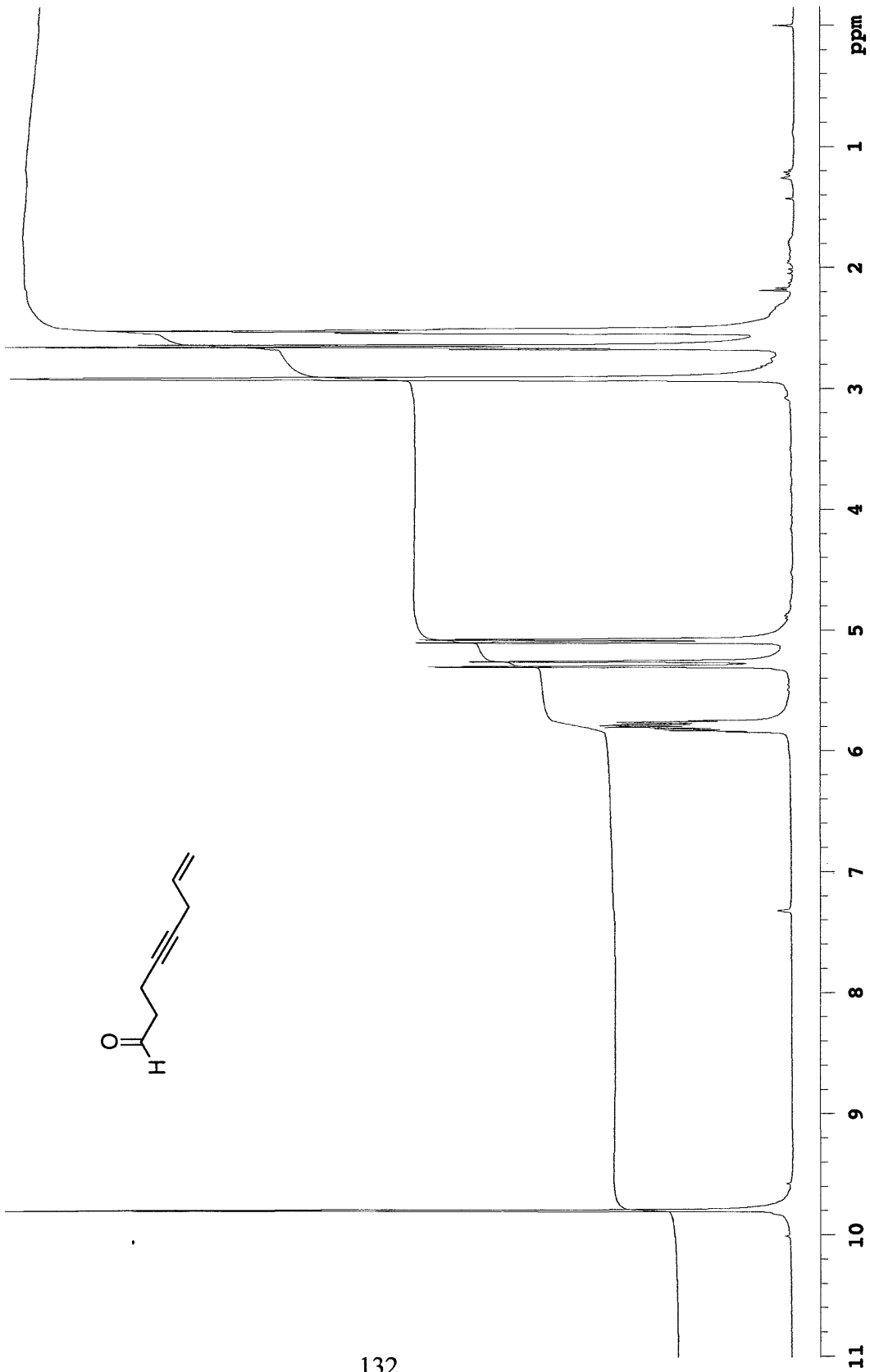


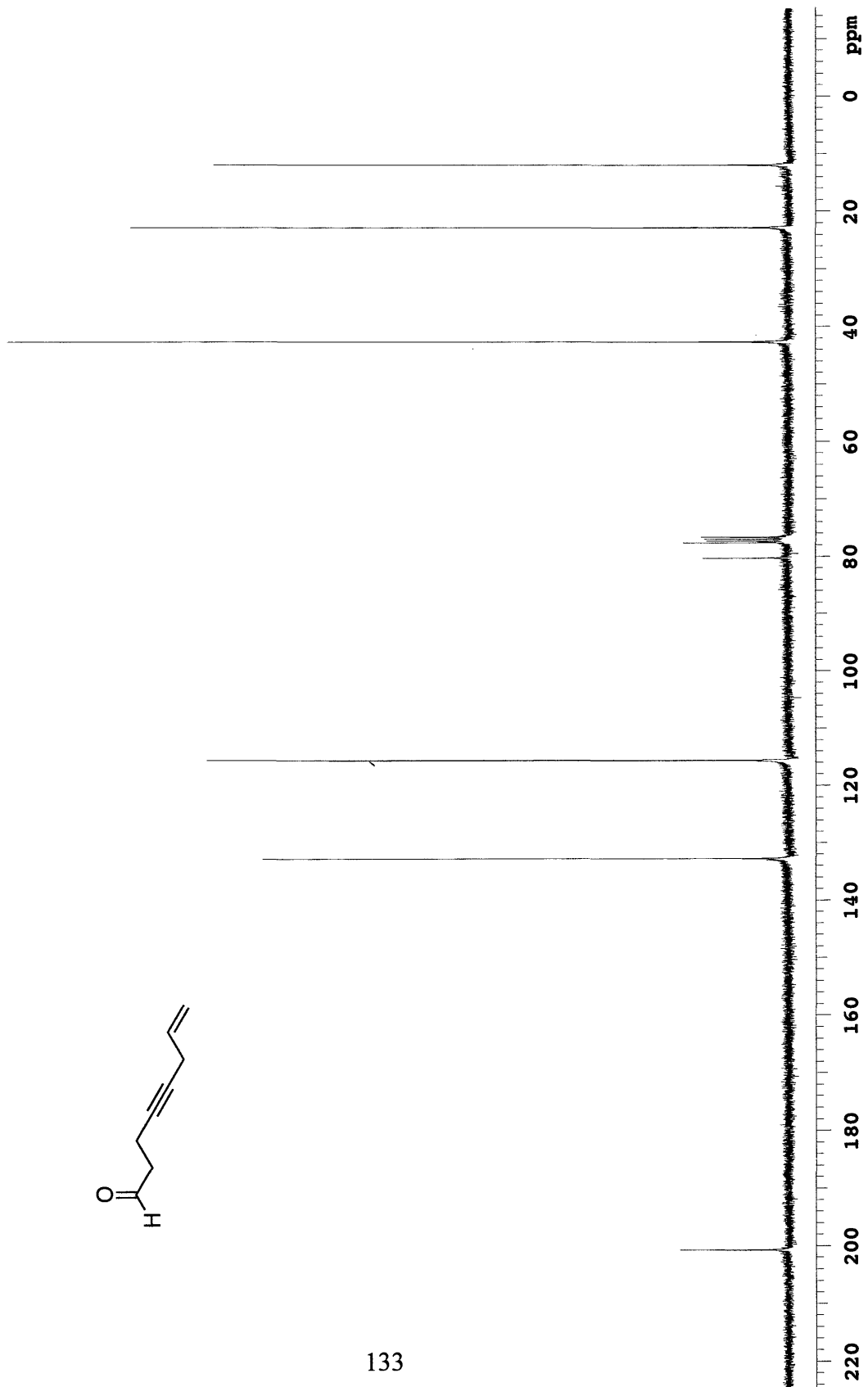


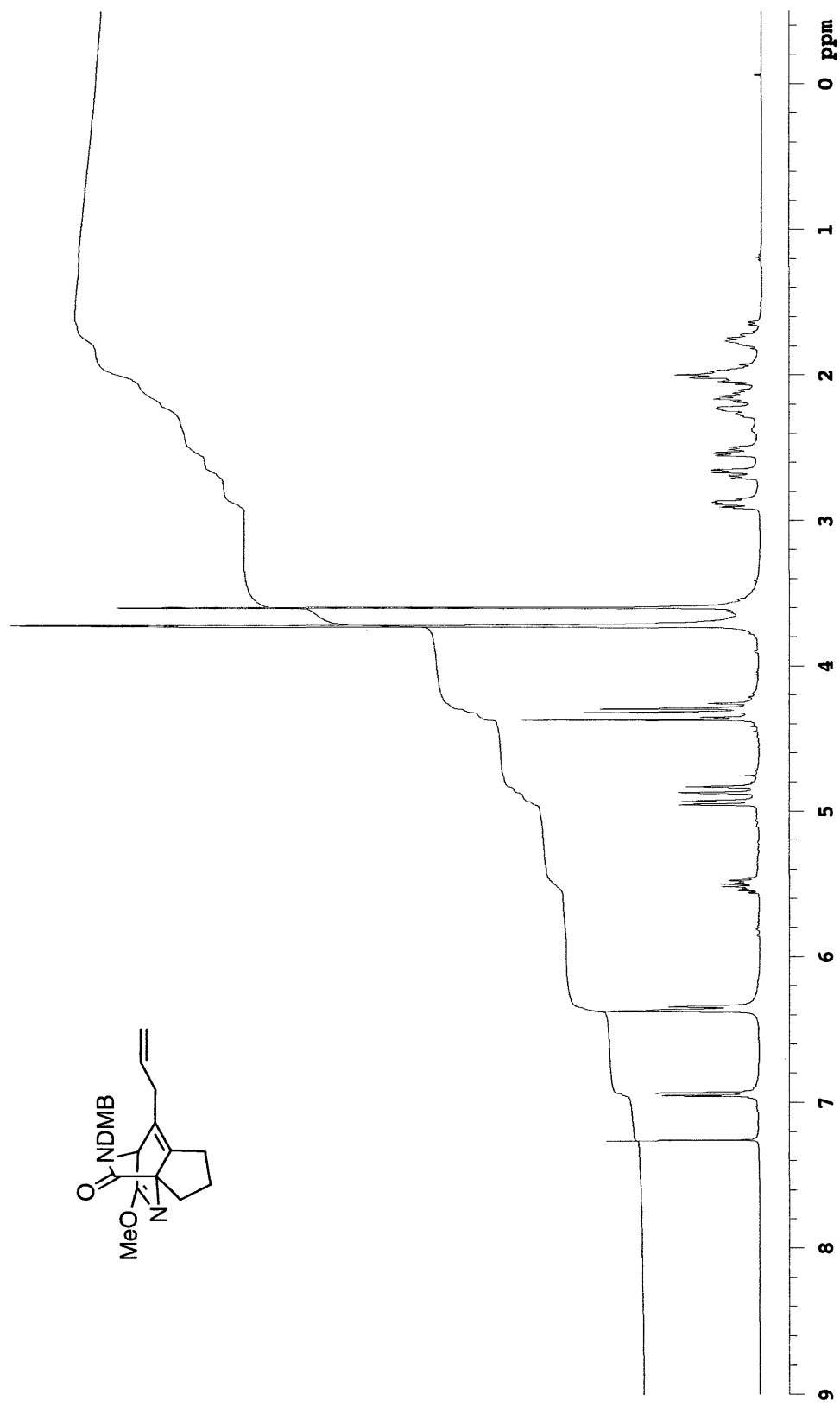


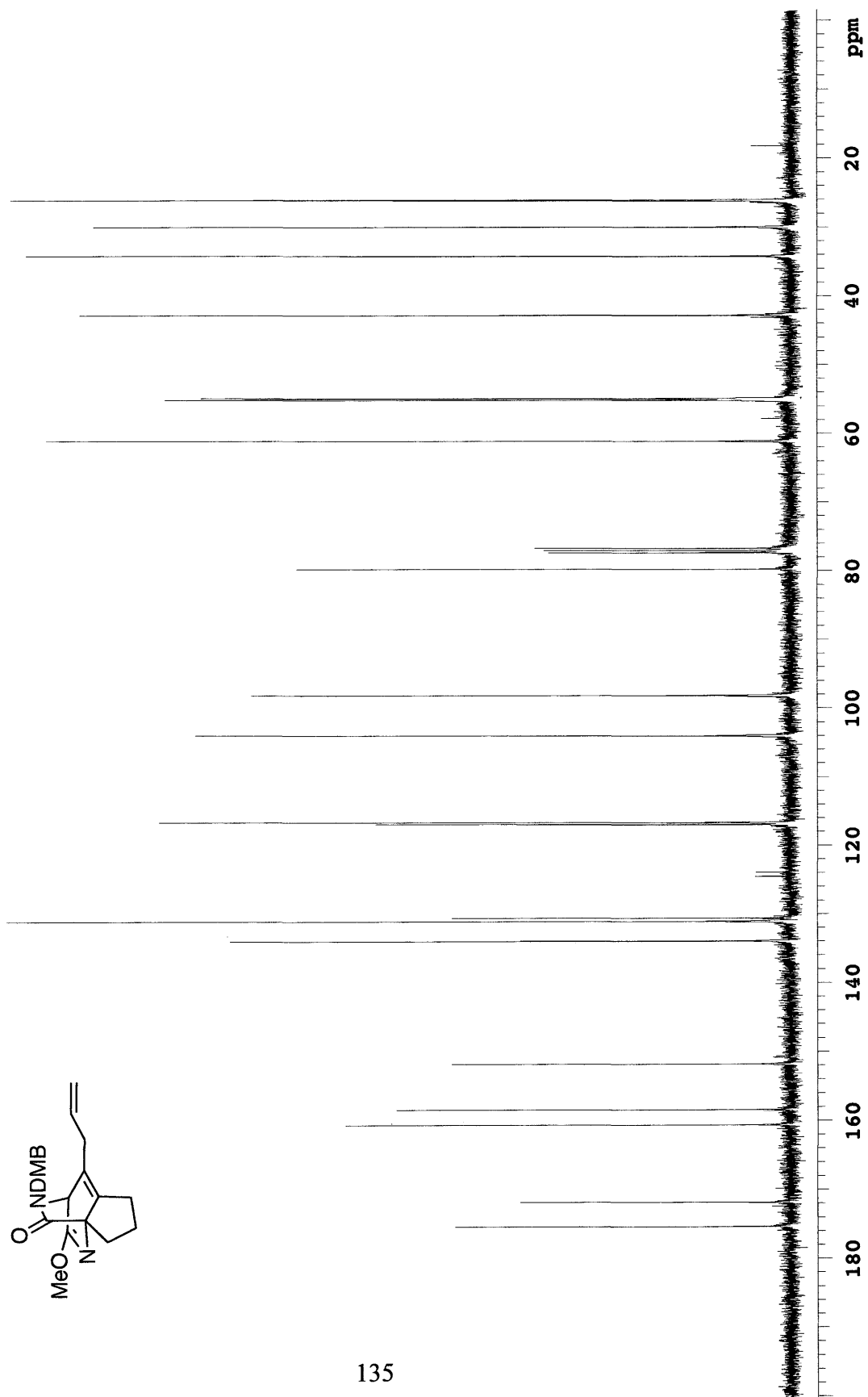
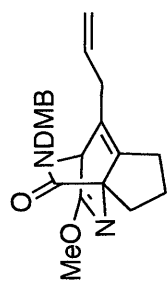


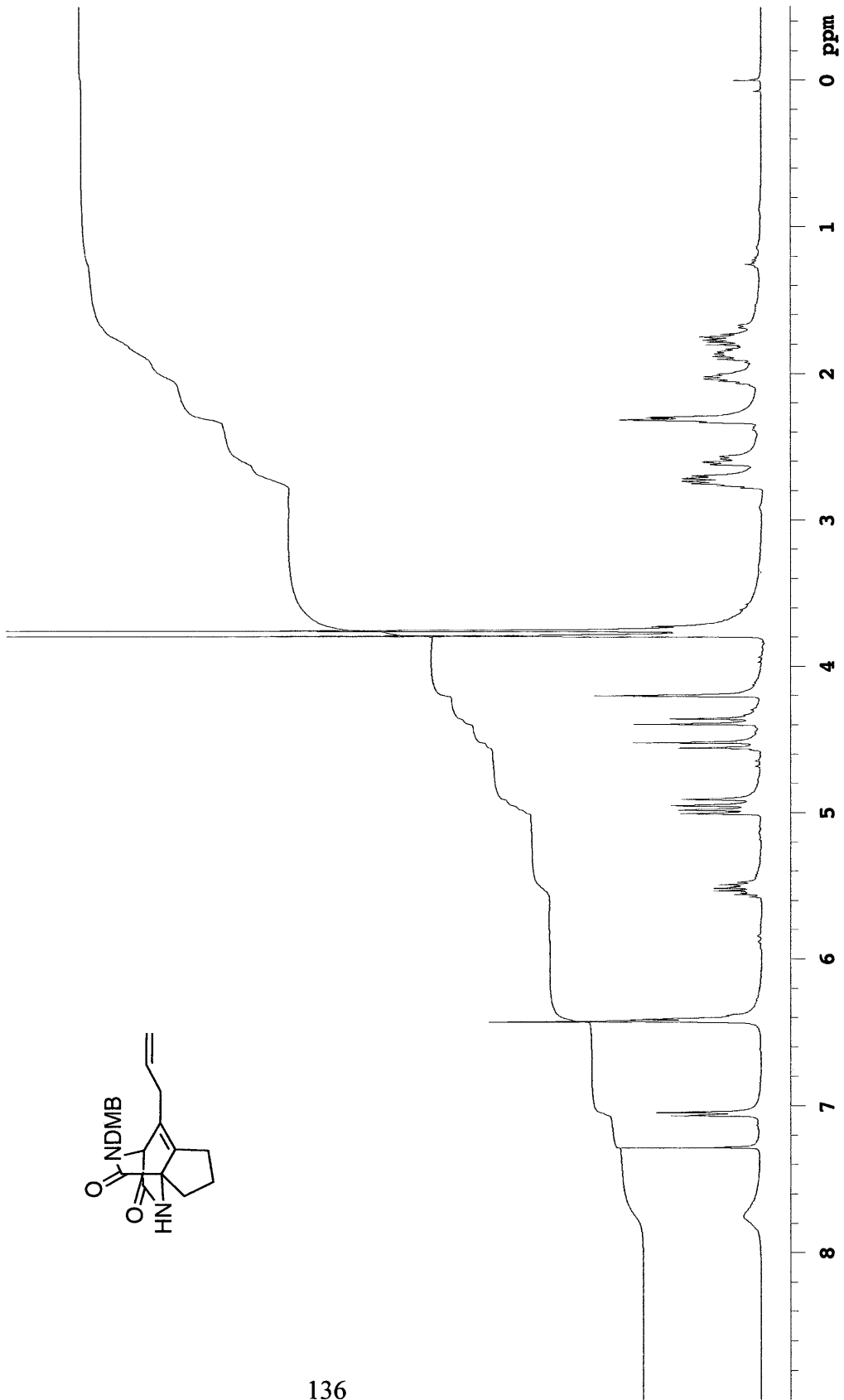
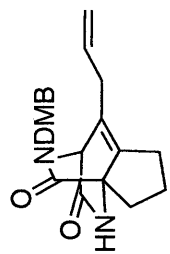
**Supporting Information for
Chapter 3**

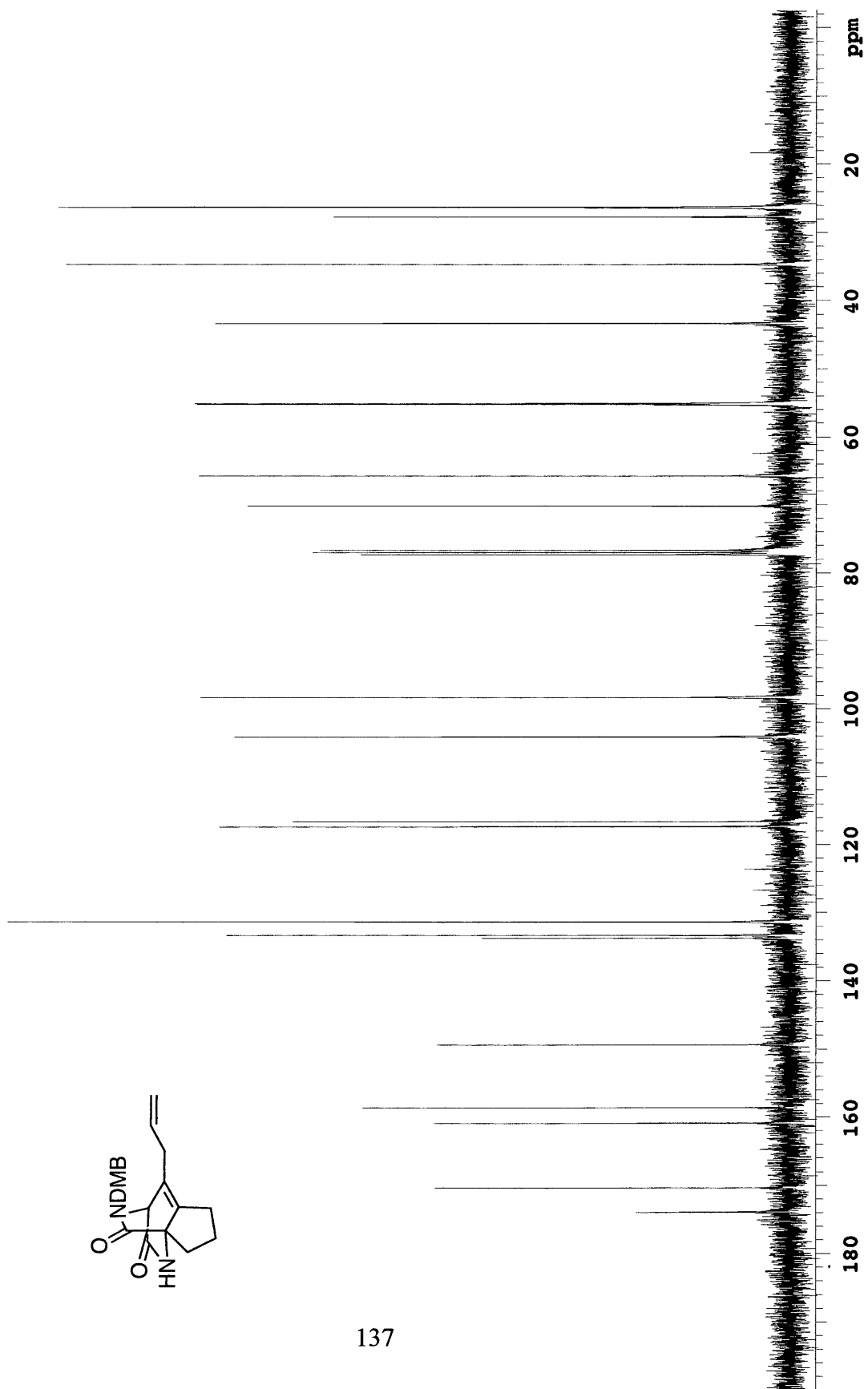


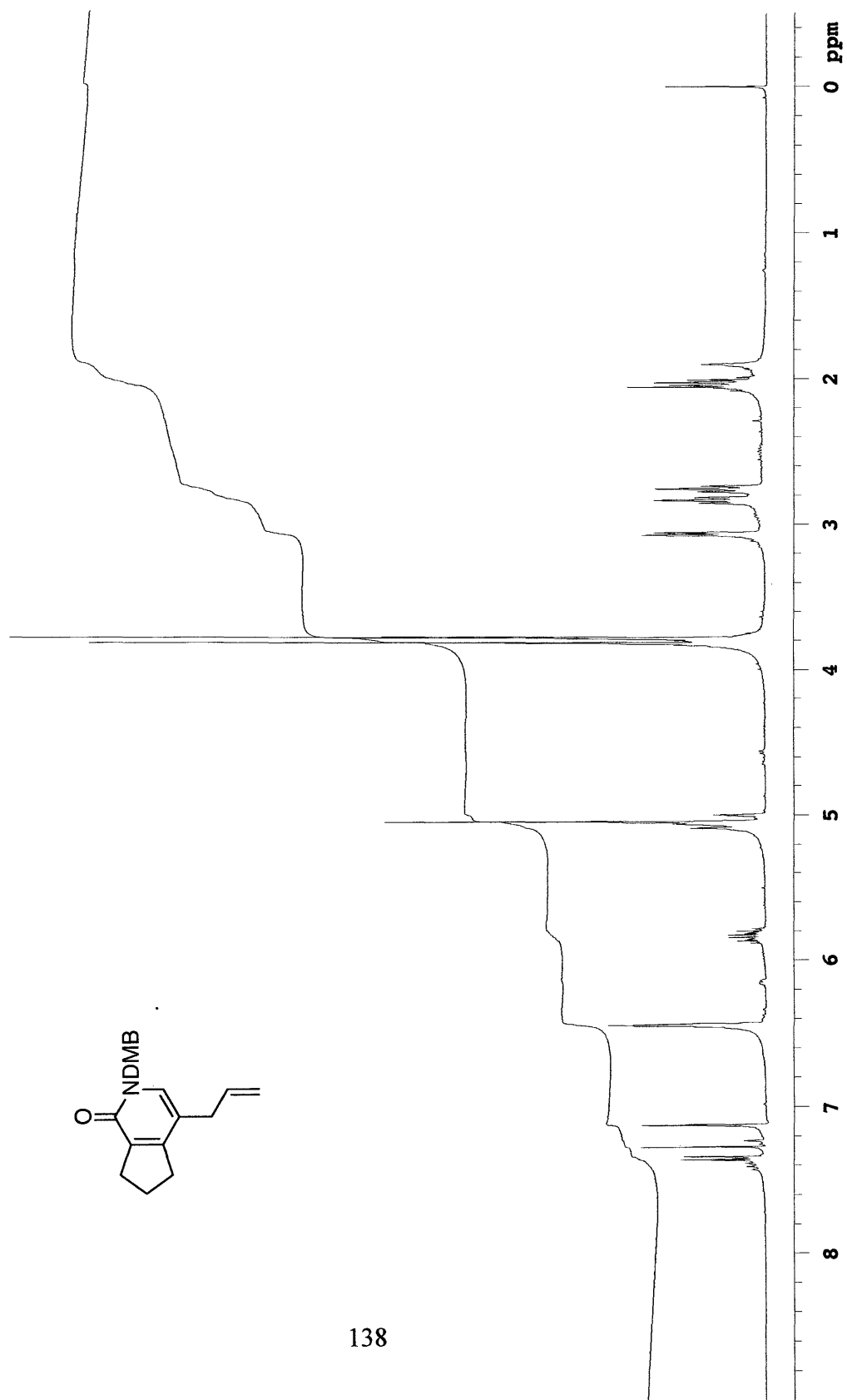
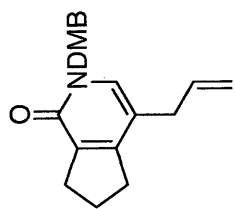


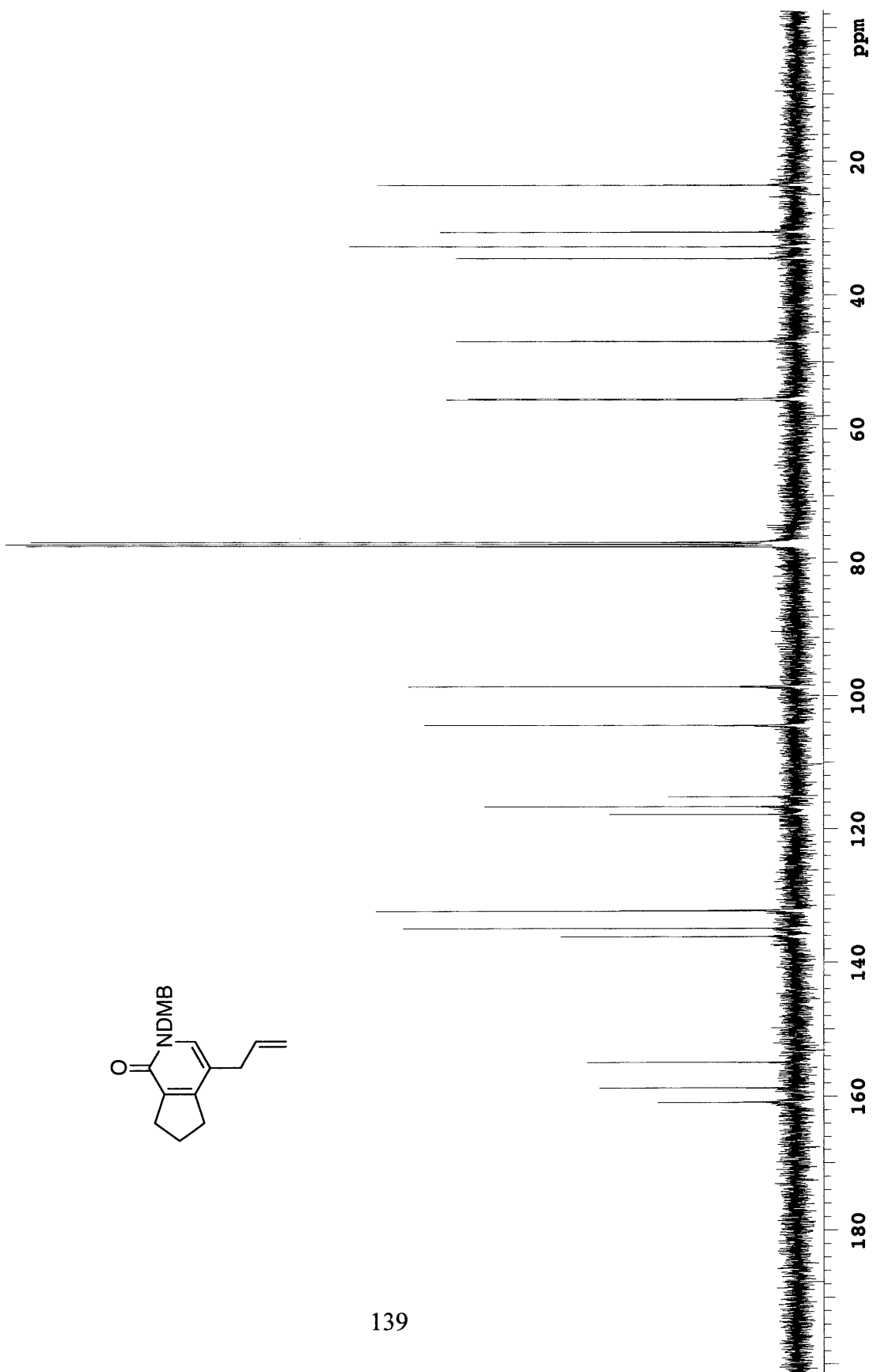
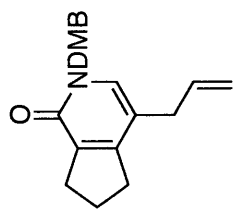


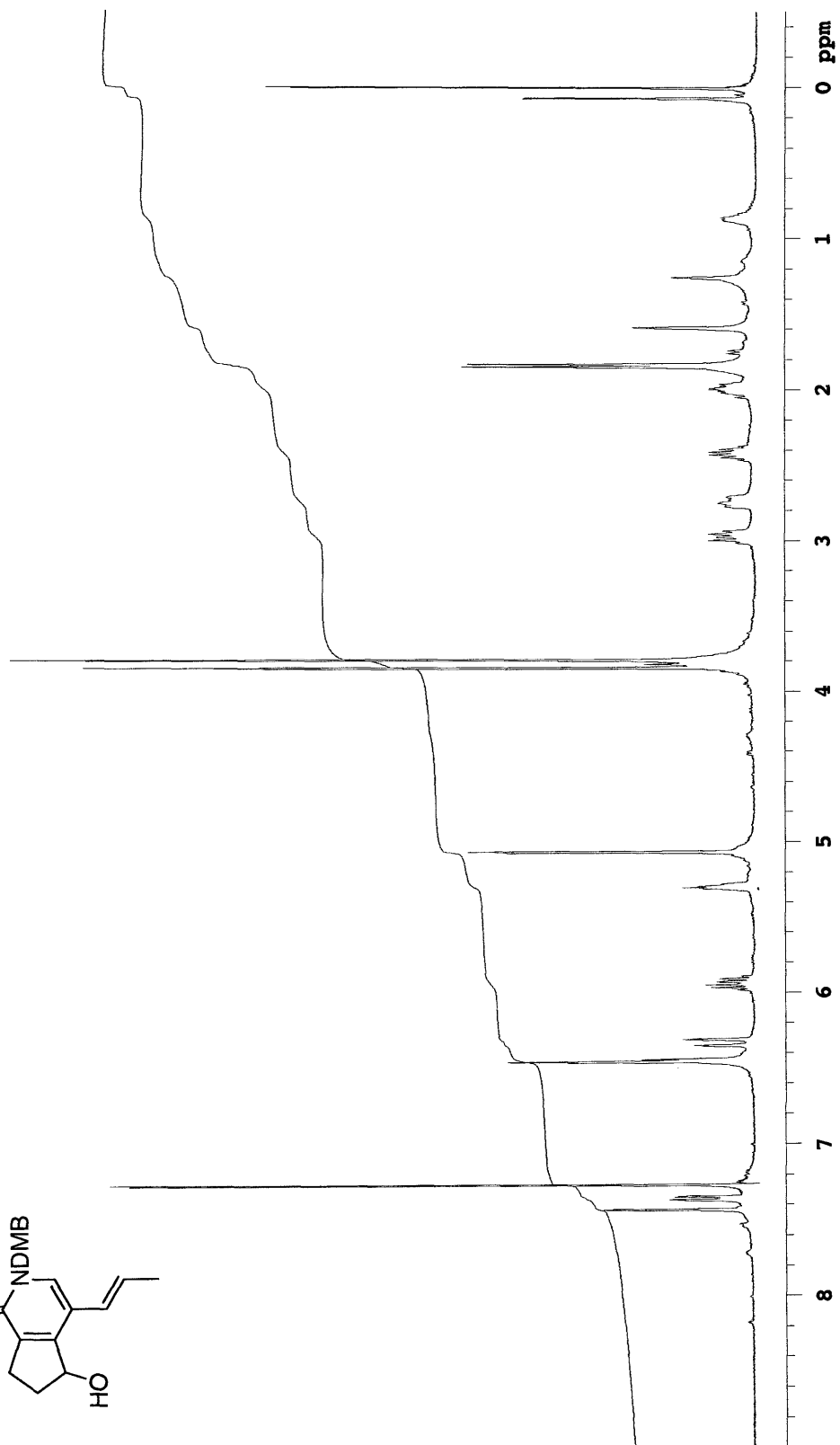
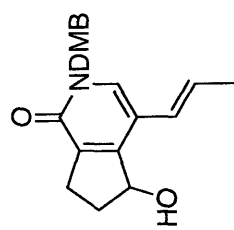


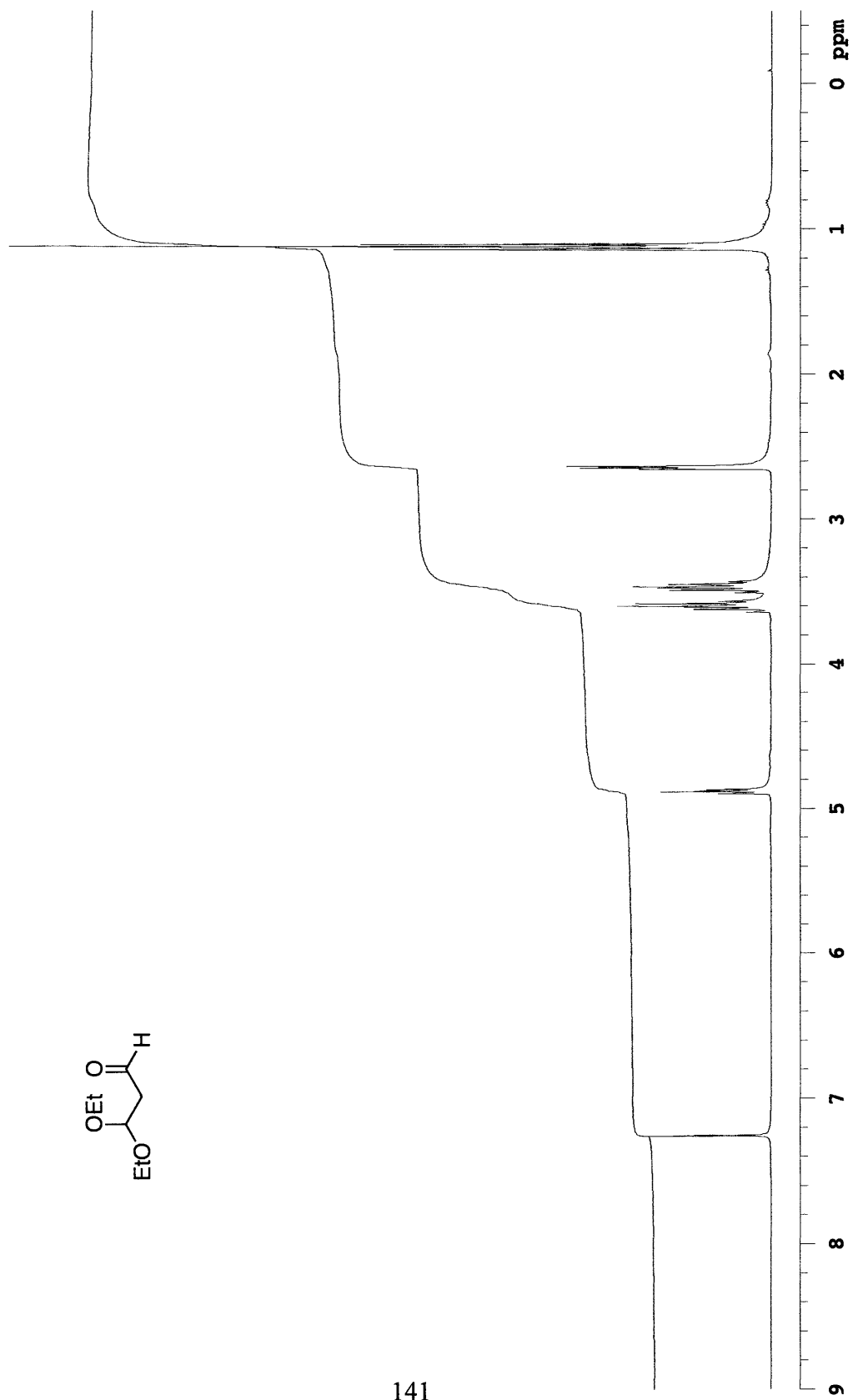
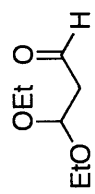


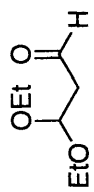




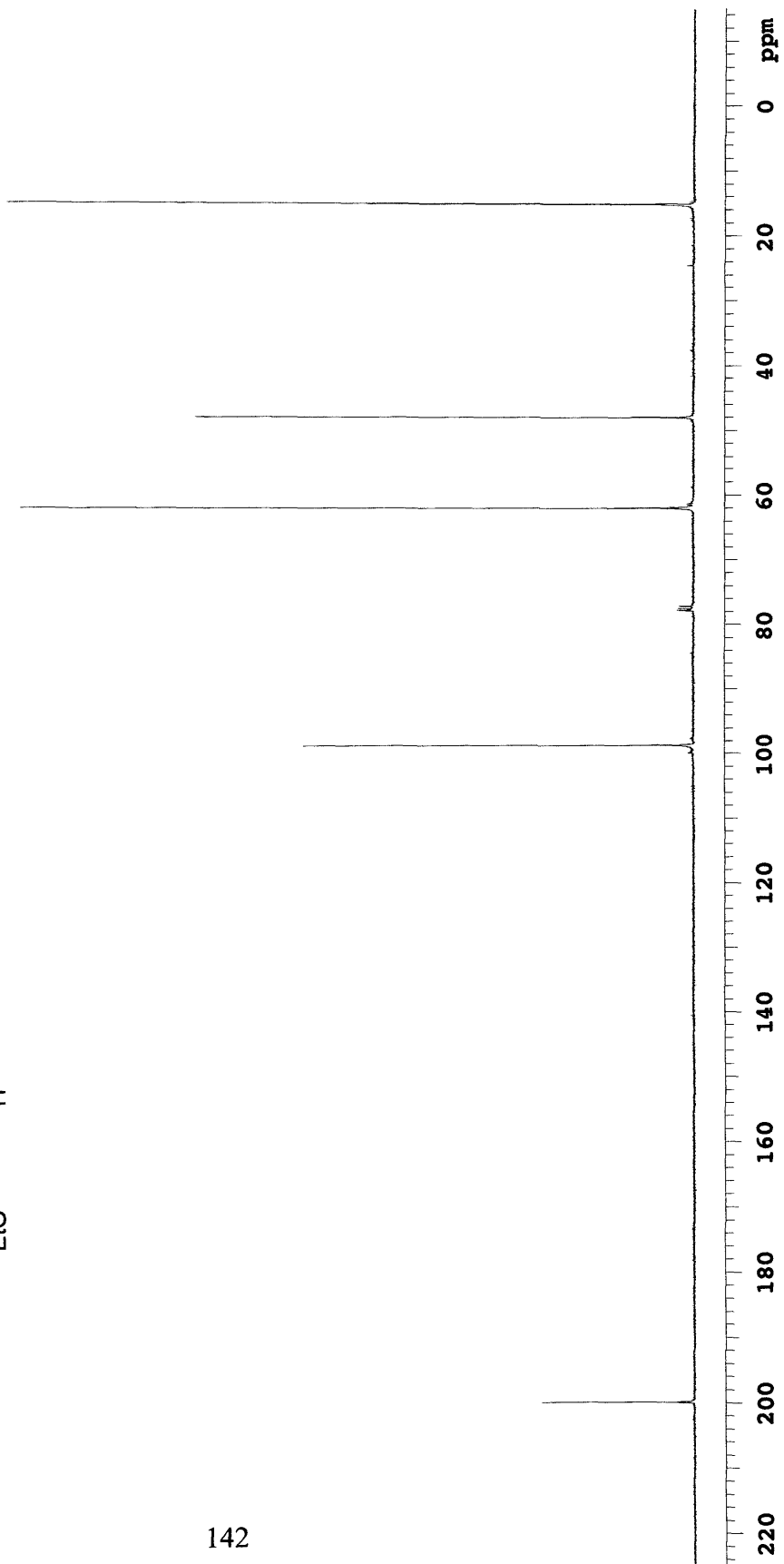


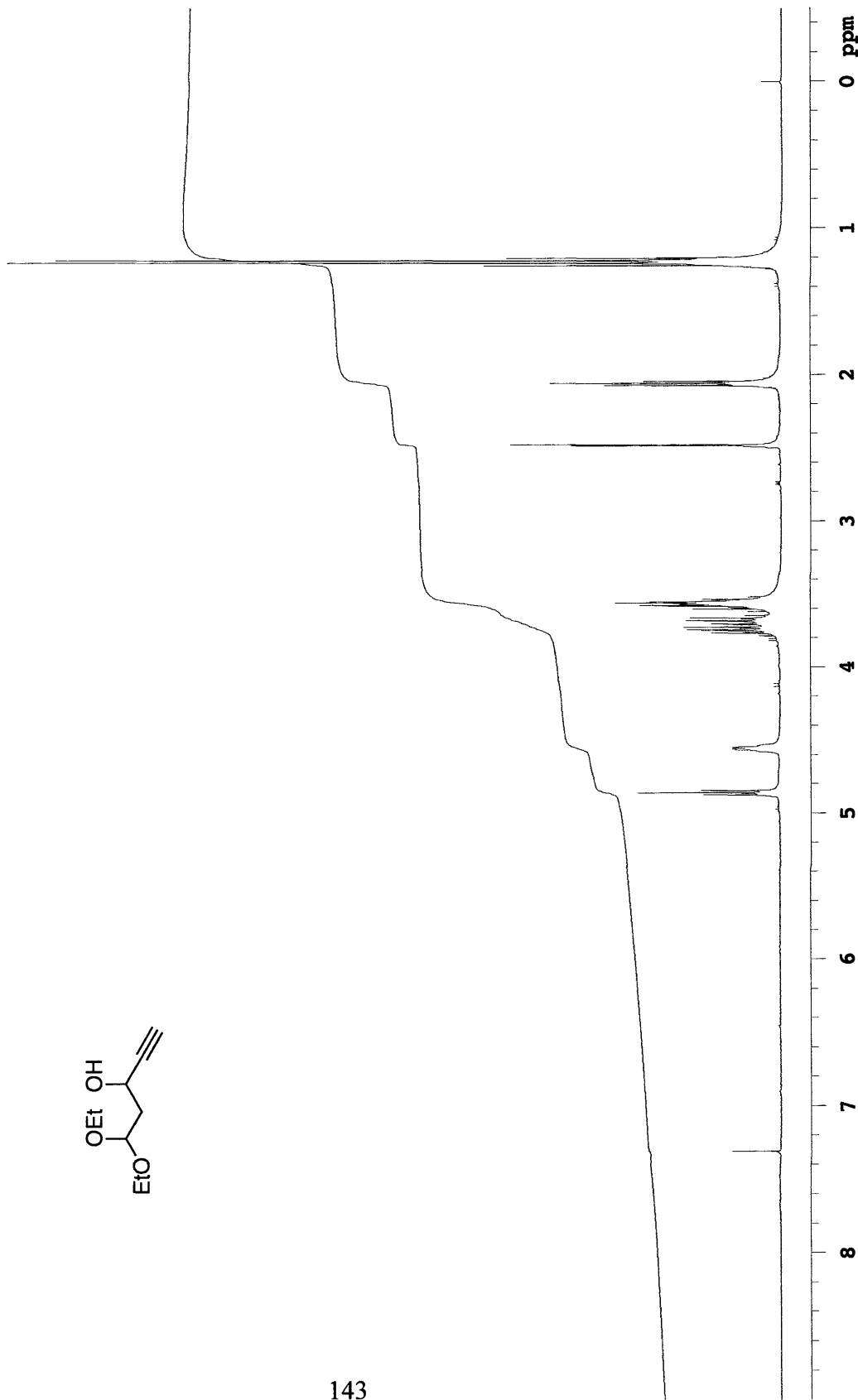
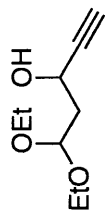


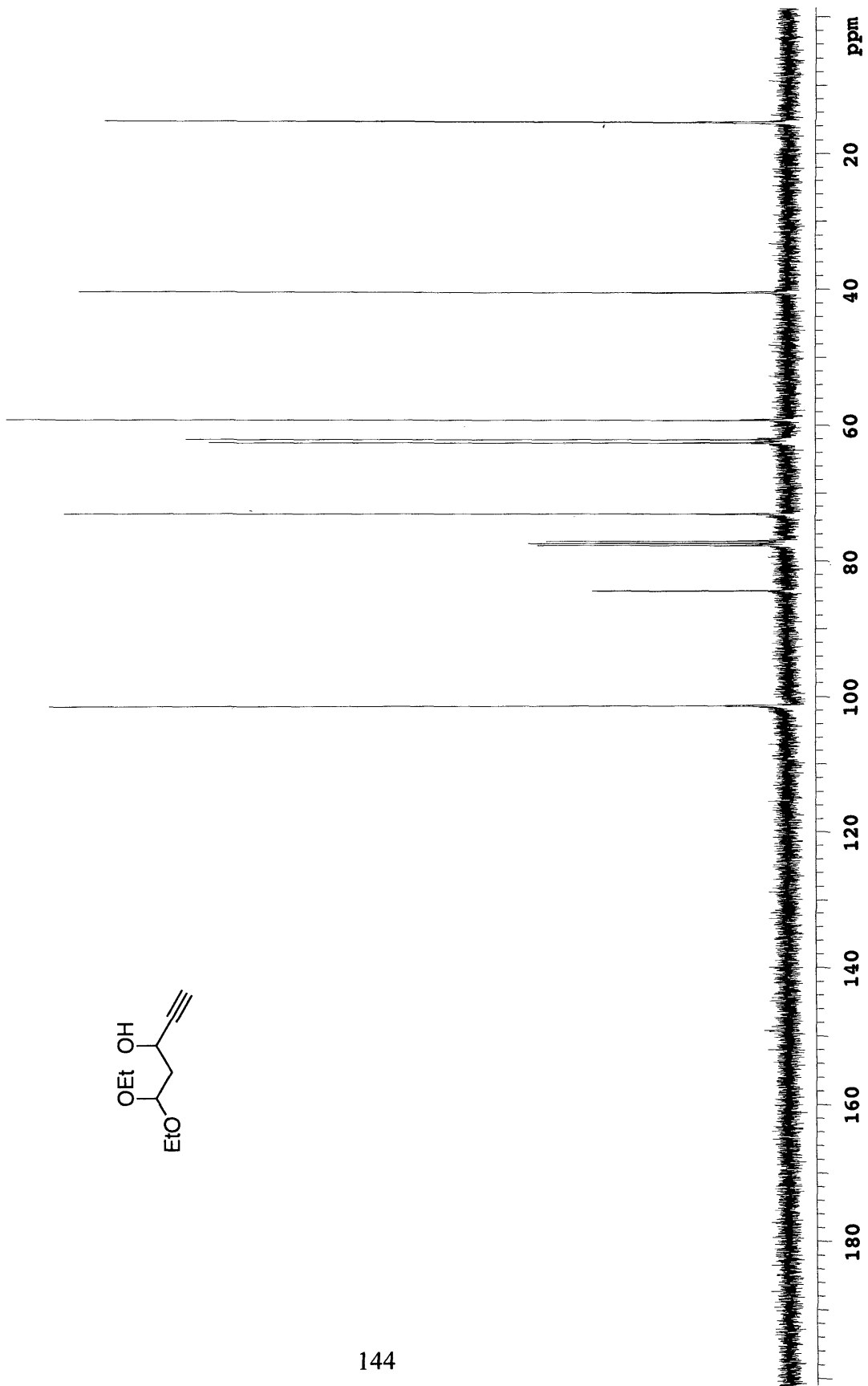
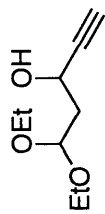


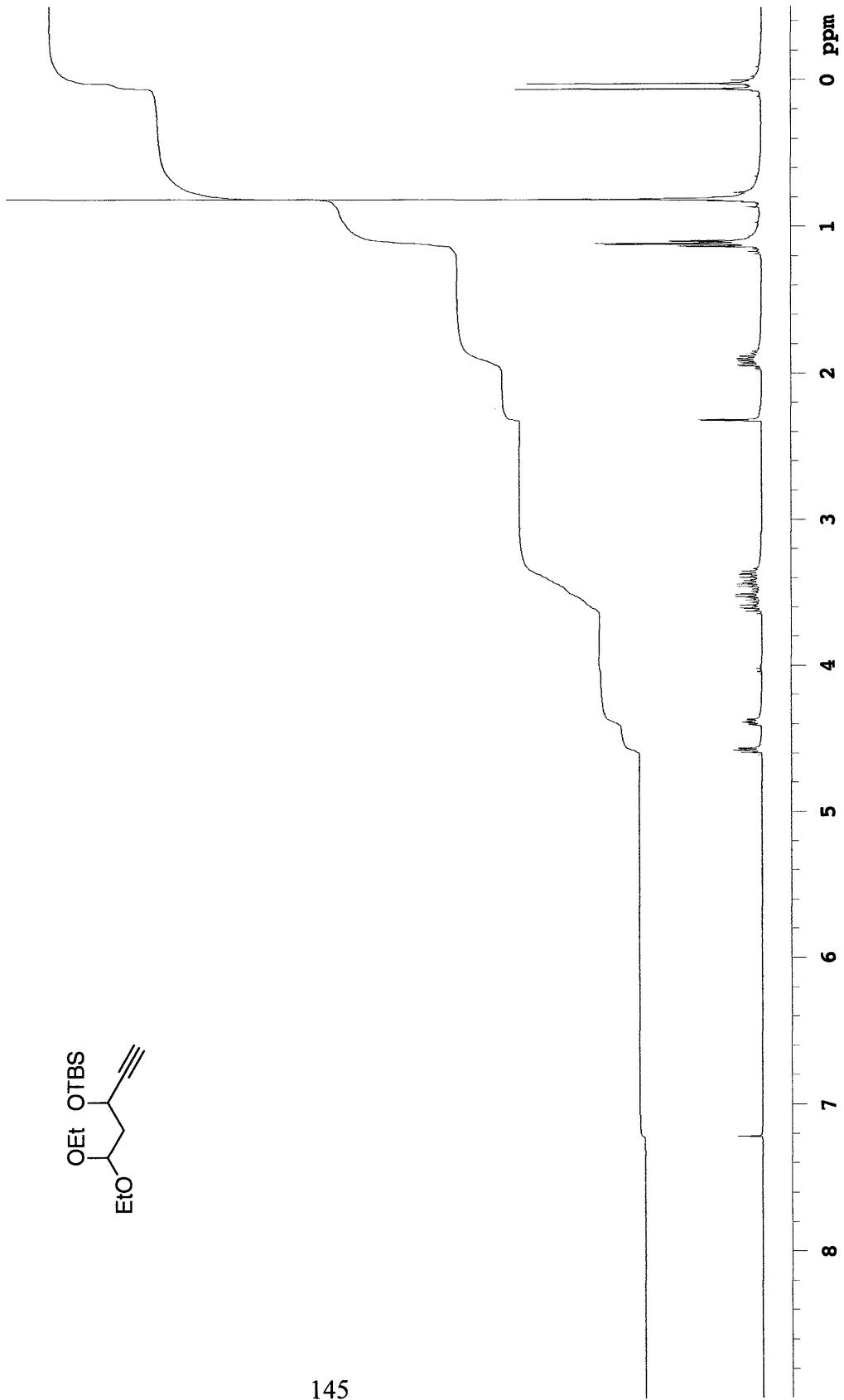
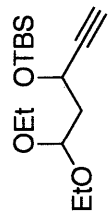


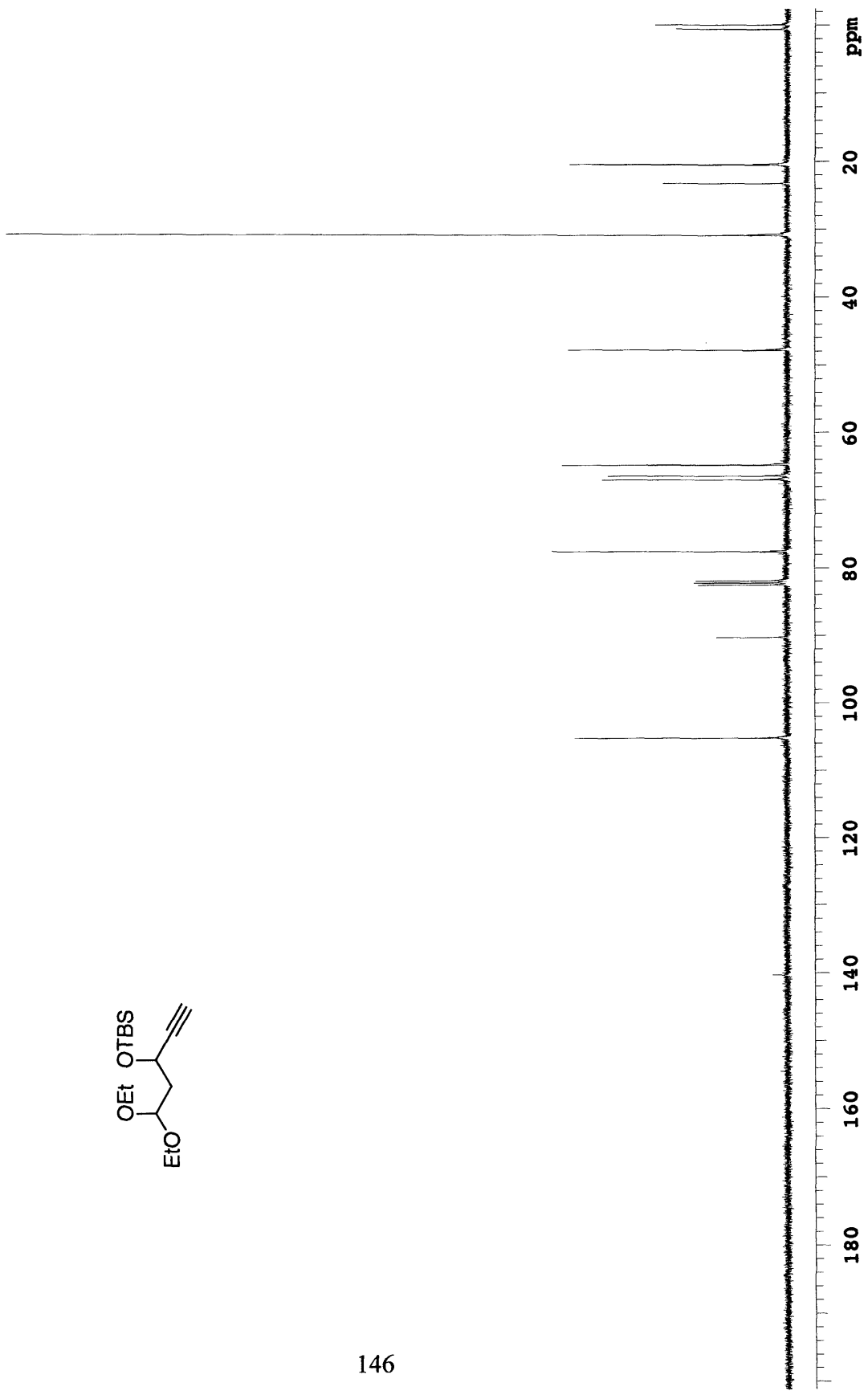
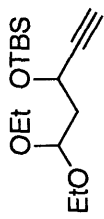
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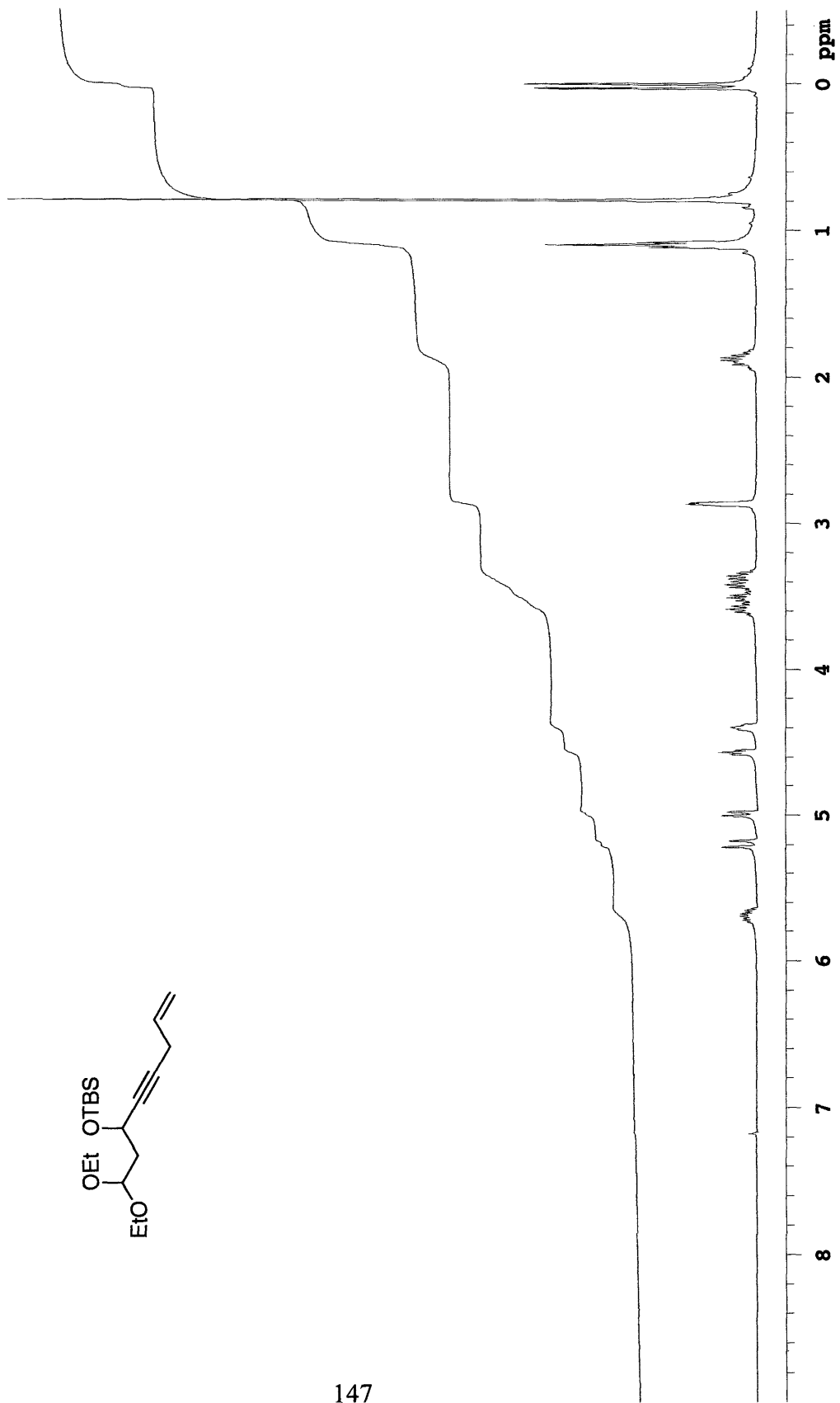
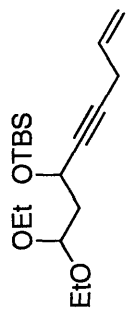


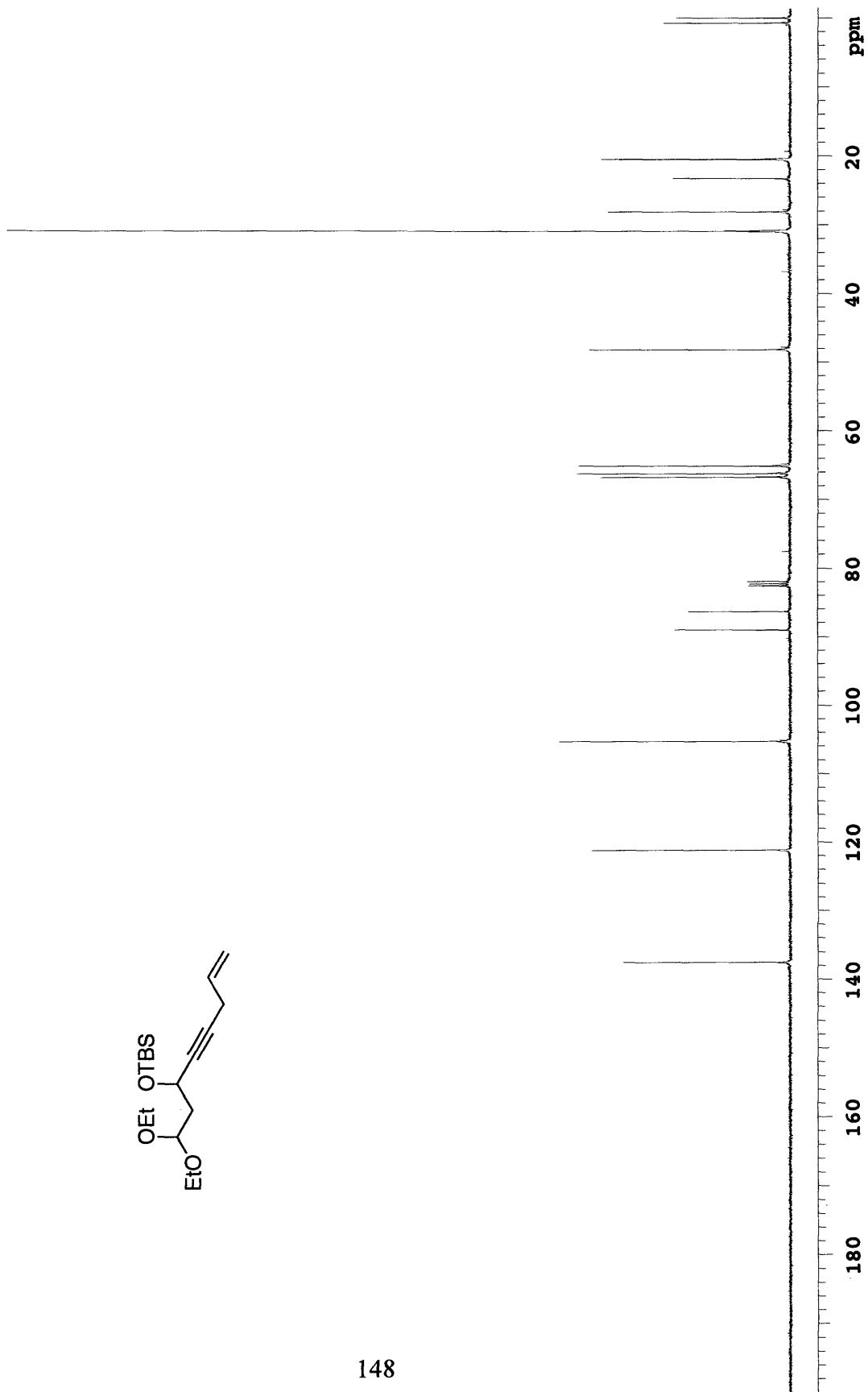
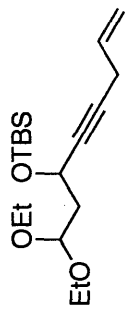


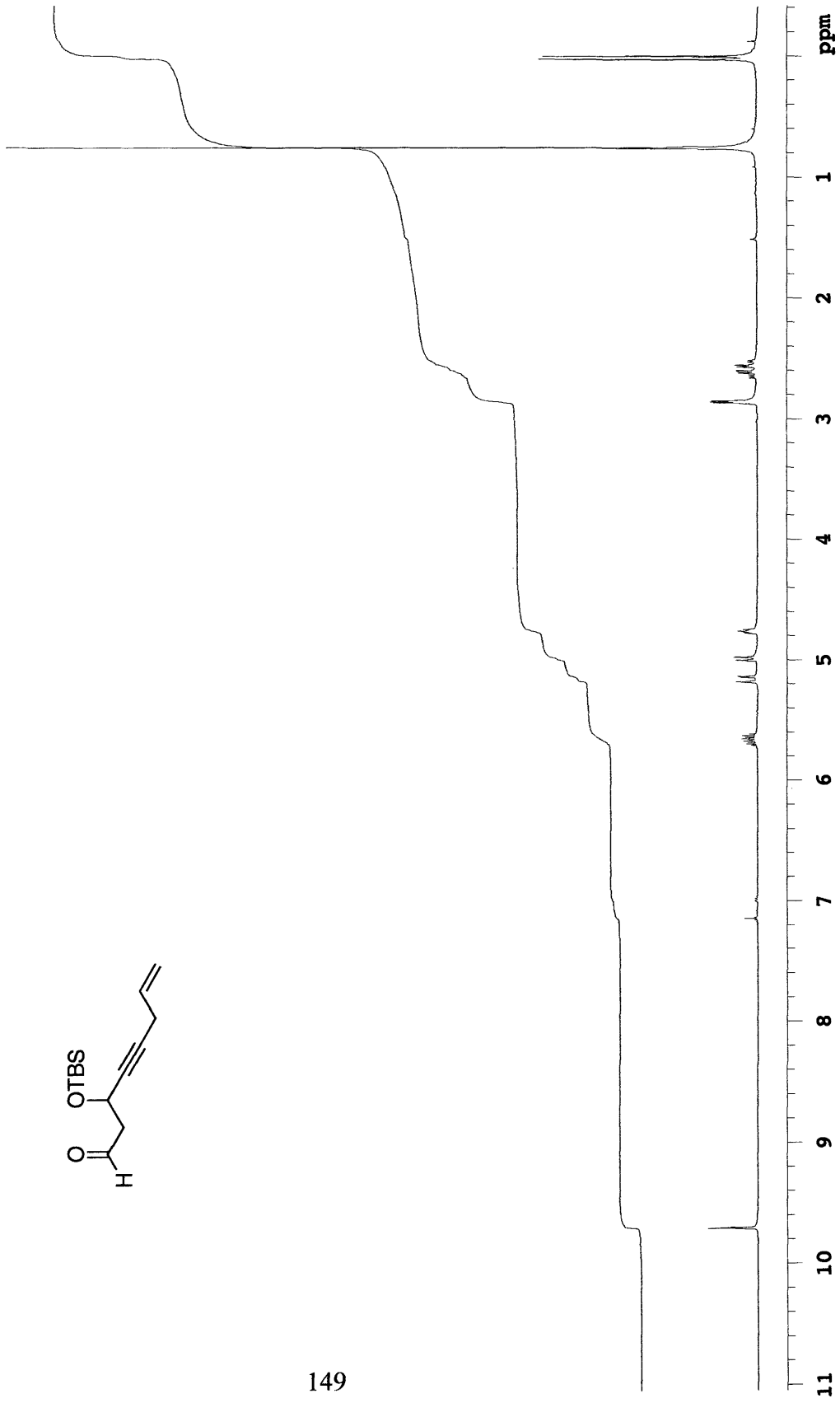
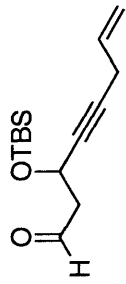


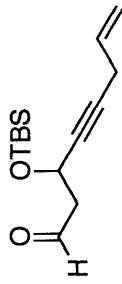












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