THE DESIGN AND SYNTHESIS OF NOVEL PROTEASOME INHIBITORS: STUDIES ON THE SYNTHESIS OF NAGELAMIDE M AND ANALOGS, THE SYNTHESIS OF RAPAMYCIN BASED PROTEASOME INHIBITORS, AND THE SYNTHESIS OF TCH BASED MOLECULAR PROBES FOR BINDING SITE DETERMINATION

By

Matthew Basil Giletto

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ABSTRACT

THE DESIGN AND SYNTHESIS OF NOVEL PROTEASOME INHIBITORS: STUDIES ON THE SYNTHESIS OF NAGELAMIDE M AND ANALOGS, THE SYNTHESIS OF RAPAMYCIN BASED PROTEASOME INHIBITORS, AND THE SYNTHESIS OF TCH BASED MOLECULAR PROBES FOR BINDING SITE DETERMINATION

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The two primary physiologic mechanisms for the recycling of amino acids from no-longer needed or damaged proteins are autophagy and enzymatically via the proteasome. Inhibition of the proteasome has emerged as the preeminent means for treating cancers that constitutively overproduce proteins, particularly multiple myeloma.

Two drugs currently available for the treatment of multiple myeloma, Bortezomib™ and Kyprolis™, inhibit the proteasome by binding to the catalytically active sites through a competitive mechanism. While initially effective, over time the resistance that is typical of competitive binders emerges, and relapse rates are currently measured at 97 %, with the average survival time after being one year. Additionally the most common side effect is neuropathy, which typically does not abate after discontinuation of chemotherapy.

The current state of the art demonstrates the need not only for new proteasome inhibitors, but inhibitors that act through a different mechanism. The Tepe group was the first to develop such a molecule, imidazolines of the TCH-series, which bind to the proteasome via a noncompetitive mechanism. The details of the interaction of these molecules with the proteasome have been extensively studied, but the location of the binding site remains elusive. In this work, several molecular probes were designed and

synthesized (two diazirine photoaffinity-TCH hybrids and a biotin-TCH hybrid) to elucidate the location of the binding site. Currently biological testing is underway.

Additionally, a library of analogs based on the natural product rapamycin were designed and synthesized. An analog was discovered that was equipotent to the natural product itself, which could be synthesized on a gram scale in three steps from commercially available materials. To discover the binding site of these molecules, a diazirine photoaffinity probe was designed and synthesized. Enough biological data was generated to refine the library and design and synthesize a second generation of the analogs; currently biological testing of these analogs is underway.

Lastly, extensive studies on the total synthesis of the pyrrole-imidazole natural product nagelamide M were designed and performed. These studies relied mainly on the use of C-H activation to functionalize a methylene C-H bond adjacent to a heteroatom. None of the key reactions were successful, and the synthesis stalled at an early stage.

Overall this thesis describes several advances in the areas of drug discovery and proteasome inhibition, and perhaps most excitingly access to molecules that could elucidate the binding site of the TCH molecules.

Dedicated to my wife, Holeigh, and my daughter, Reagan.

ACKNOWLEDGMENTS

This has been an extraordinary adventure, and there are many people without whom it would have been impossible, or at least much less enjoyable. I would like to thank first and foremost my wife, Holeigh, for her belif in me and her unwavering support and devotion. And for her patience as we discovered together how true it is that behind every successful man is a woman rolling her eyes.

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Which brings me at last to Dr. Jetze Jans Tepe (I only recently learned what the second ‘J’ stood for). I would like to thank him for the opportunity to work in his laboratory and the creative freedom he allowed me. And for tolerating my sense of humor.

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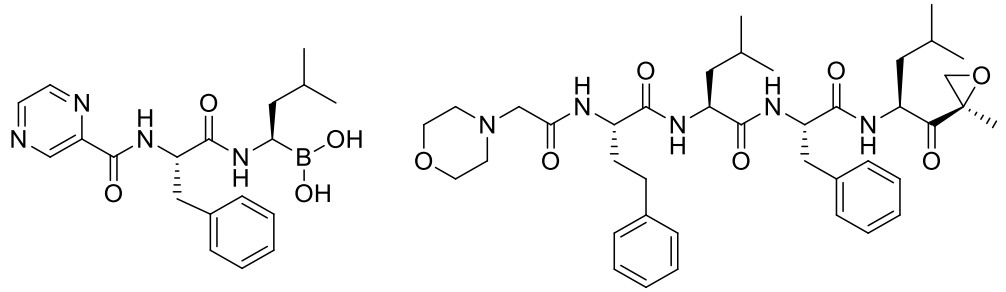
KEY TO ABBREVIATIONS

Asp	Aspartic acid
Boc	Tert-butoxycarbonyl
BHT	2,6-ditertbutyl hydroxytoluene
Bz	Benzyl
Cbz	Carbamoylbenzyloxy
DEAD	Diethylazodicarboxylate
$DfsNH_2$	2,6-difluorophenyl sulfamate
IC_{50}	Inhibition constant of 50 %
KIE	Kinetic isotope effect
Mbs	Methoxybenzenesulfonyl
NMR	Nuclear magnetic resonance
OAc	Acetate
Ph	Phenyl
PIA	Pyrrole-imidazole alkaloid
$Rh_2(esp)_2$	Bis[rhodium(α,α,α',α'-tetramethyl-1,3 benzenedipropionic acid]
SAR	Structure activity relationship
TBAF	Tetra-*N*-butyl ammonium fluoride
TBDMS	Tert-butyl dimethyl silyl
TBDPS	Tert-butyl diphenyl silyl
Tces	Trichloroethoxysulfonyl
TEA	Triethylamine
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
Ts	Tosyl

Chapter 1: Introduction

Multiple myeloma (MM) is a cancer of differentiated B-cells that is treated with competitive inhibitors of the proteasome.[1] Inhibiting the proteolytic activity of the proteasome in turn inhibits the action of signal transduction molecules necessary for tumorigenesis (NF-κB, TNF-α, IL-6 and others), effectively interrupting the cancer cycle and treating the disease.[2] All currently approved proteasome inhibitors, Bortezomib™ and Kyprolis™, and those in

Figure 1.1: Bortezomib and Kyprolis, Clinically Approved Proteasome Inhibitors

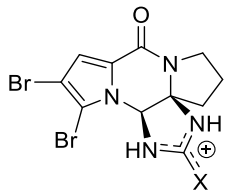


Bortezomib™ Kyprolis™

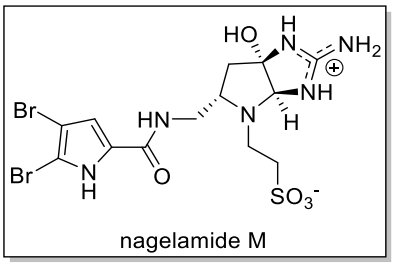
development act through a competitive mechanism.[3] They directly bind the three primary active sites in the proteasome, occluding any interaction between enzyme and substrate (a protein targeted for degradation).[4] While initially effective at treating MM, nearly all patients (~97 %) treated with approved proteasome inhibitors for MM relapse and develop resistance to treatment, after which the mean time of survival is less than 1 year.[5] This highlights the need not merely for new inhibitors of the proteasome to treat MM, but inhibitors that work through new mechanisms. Prior art developed in the Tepe research group led to the discovery of an imidazoline scaffold, TCH-013,[6] that has been shown to inhibit the activity of the proteasome through a noncompetitive pathway, providing the first example of a small molecule to act through such a mechanism. Additionally, the Tepe group synthesized several natural products containing similar structural motifs, among them dibromophakellin and dibromophakellstatin,[7] for evaluation as

proteasome inhibitors. This was a successful endeavor on multiple fronts. It led to the

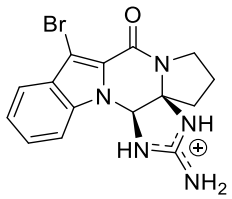
Figure 1.2: Dibromophakellin, Dibromophakellstatin, Nagelamide M and Indolophakellin



dibromophakellin (X = NH_2) IC_{50} = 11.9 μM
dibromophakellstatin (X = O) IC_{50} = 25.3 μM



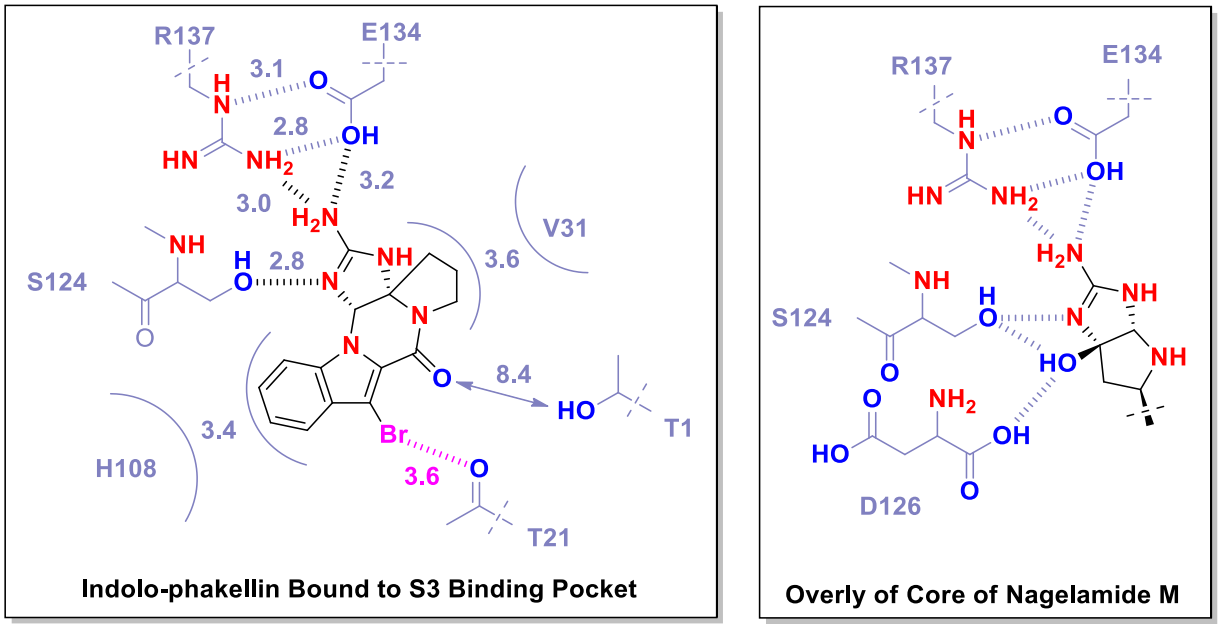
nagelamide M



indolo-phakellin analog IC_{50} = 25 μM

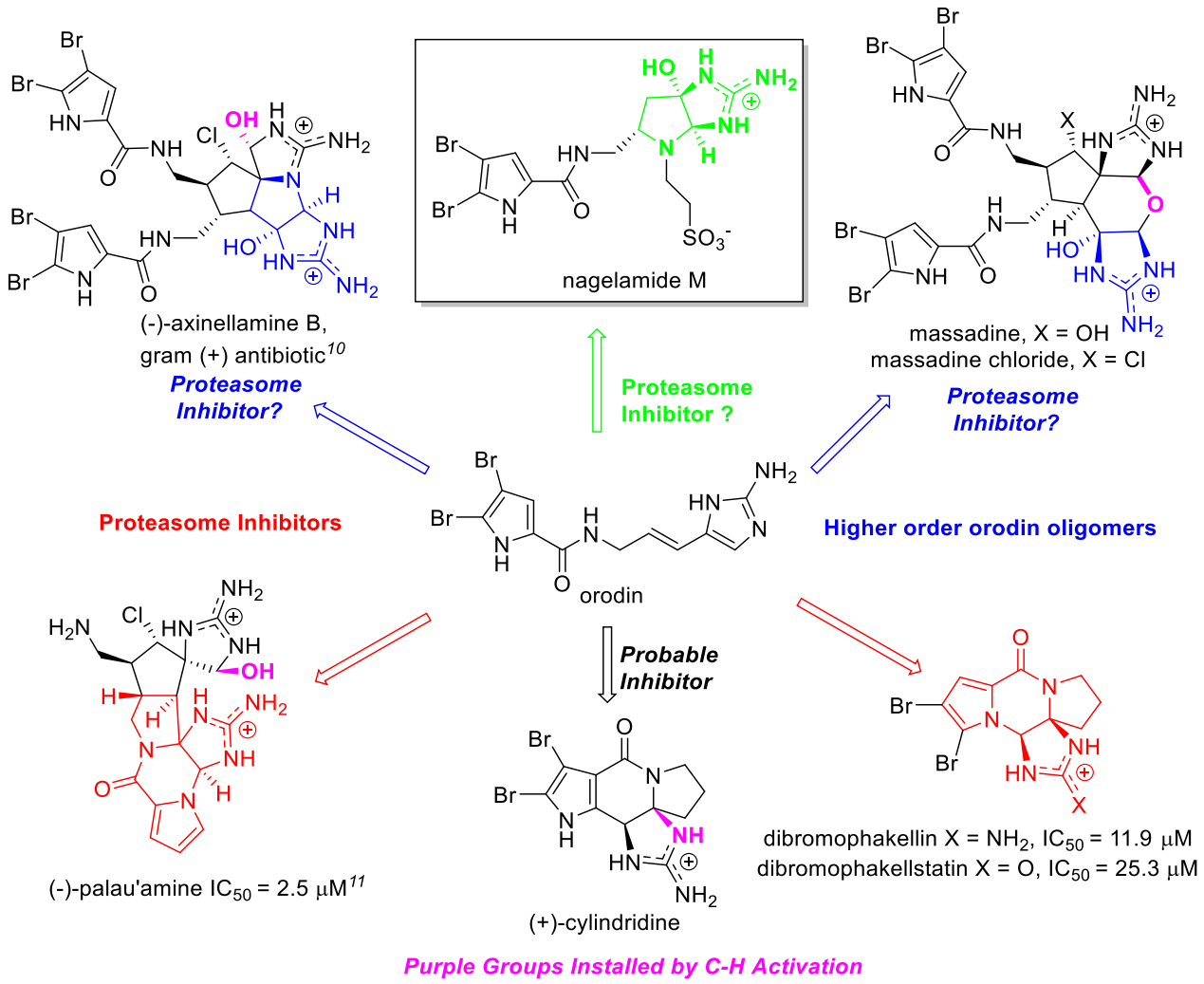
development of a new method for adding protected guanidines to double bonds in addition to providing the target molecules in sufficient quantity for biological evaluation. As expected, dibromophakellin and dibromophakellstatin were active against the proteasome (IC_{50} = 11.9 μM and 25.3 μM, respectively[8]), in comparable levels of activity to the imidazolines of the TCH series (IC_{50} = ~200 nM to ~2 μM[5,6]). A crystal structure of an indole analog of dibromophakellin was obtained in which it was bound to a different domain than Bortezomib™. The indolo-phakellin pictured in Figure 3 is the first example of a noncovalently binding inhibitor of the proteasome that binds to the S3 site exclusively. This discovery constitutes a new mechanism of proteasome inhibition, and opens the door to the development of an entirely new class of structures for drug design.[8]

Figure 1.3: Crystal Structure of Indolophakellin and Overlay of the Core of Nagelamide M



Overlaying the core of one such structure, the Pyrrole-Imidazole Alkaloid ("PIA") nagelamide M,[9] on to this crystal structure *in silico* reveals the potential to recapture all the established binding interactions and potentially add one with Asp 126. These features, in addition to the potential for methodology development and a first total synthesis, have attracted our interest and prompted our attempt at a total synthesis of this molecule.

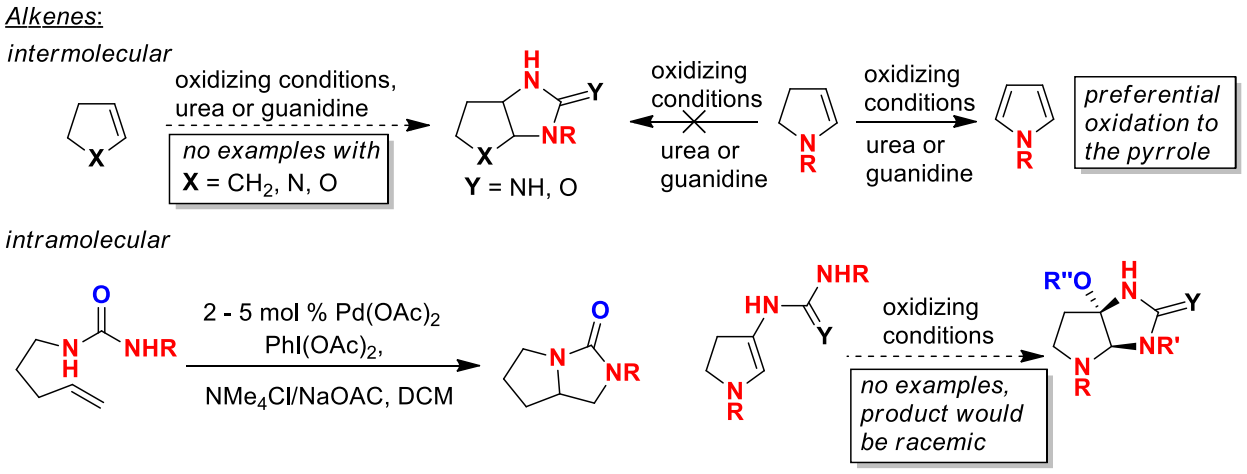
Figure 1.4: C-H Activation in the Synthesis of PIA's of the Orodin Family



Considering the high degree of heteroatom substitution in the target natural product and the success of the C-H activation chemistry in the synthesis of related molecules and natural products of the orodin family[12] (Figure 4), this method seemed an ideal place to start. At the onset of these studies (to the present), no examples of C-H amination with a methylene carbon adjacent to a heteroatom (nitrogen or oxygen) to form a [5.5] membered ring had been reported. While this is a very precise example to seek, it is a prevalent motif in this family of natural products and achieving this transformation could provide alternative routes to other complex members the family of orodin derived PIA's.[13]

From the perspective of methodology development, this problem is another manifestation of the elusive 1,2 vicinal diamination, which still poses significant challenges (Figure 5).[14-21] The current state of the art typically involves the oxidation of an alkene in the presence of a suitable

Figure 1.5: The 1,2 Vicinal Diamination of Alkenes and Current Limits

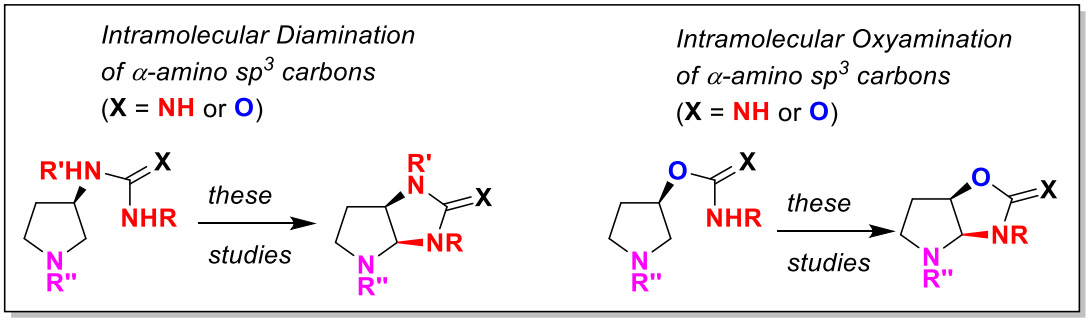


nitrogen source. Such an approach to nagelamide M would be less than ideal for several reasons. In addition to the lack of literature precedent, 2,3-dihydro-1*H*-pyrroles are known to aromatize to pyrroles under oxidative conditions.[22,23] The intramolecular diamination of alkenes is more developed than the intermolecular approach,[21] but again such an approach to nagelamide M would have several undesirable aspects. The issue of oxidative lability of 2,3-dihydro-1*H*-pyrroles could be exacerbated by adding a nitrogen at the 3-position, making synthesis and handling of such a precursor likely to be. If these obstacles were overcome the oxidation event, in the absence of asymmetric induction, would yield racemic products. While such a transformation may ultimately be possible, it is less desirable than substrate-induced asymmetry, which could be built in from the chiral pool.

These combined challenges reinforced the attractiveness of using a C-H bond as the oxidative substrate, as highlighted in Figure 6. In this case, the small size of the [5.5] ring system

being formed would require the *cis* fused product form exclusively,[46] and the stereochemistry could be established in the cyclization substrate. This particular problem has been an active area of research; in fact C-H activation is the only avenue currently available to access these structures. Solving this problem is significant because success would constitute an expansion of a prominent methodology, adding to the overall goal of synthesis by selective C-H oxidation, and

Figure 1.6: The Proposed Use of C-H Amination To Access the Core of Nagelamide M



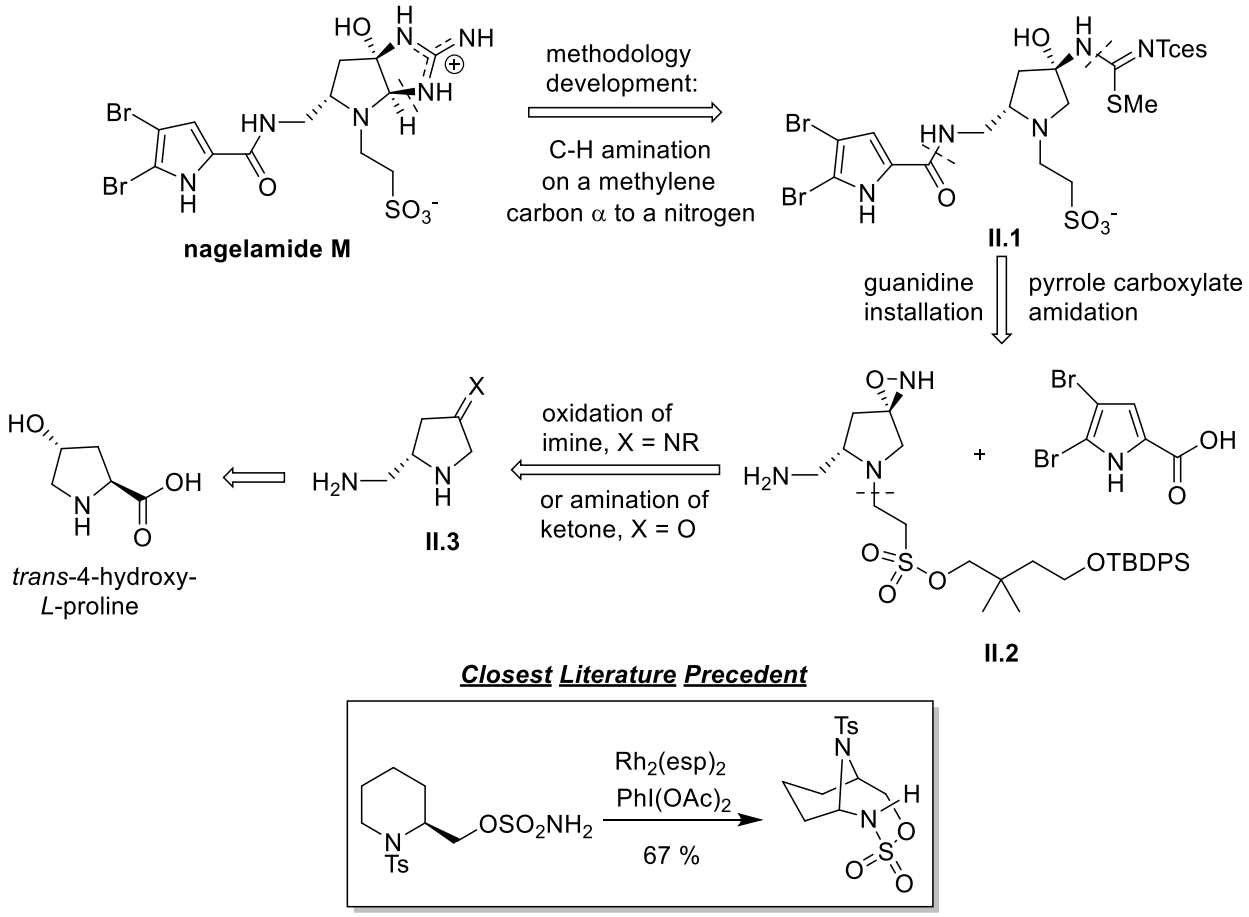
because it would provide rapid access to the core of nagelamide M and analogs that are expected to bind to a novel site in the proteasome.

Chapter 2: Studies on the Total Synthesis of Nagelamide M and Analogs

A retrosynthetic analysis of nagelamide M is presented in Figure 2.1, with the main challenges in this synthesis involving two oxidations, each highlighted in compounds **II.1** and **2.2**. More generally the problem could be formulated as the oxidative guanidinylation of a 3-hydroxyproline, but a one-step method for such a transformation on saturated compounds is not known.

The first key disconnection of the first step is the C-H amination of a methylene C-H bond α to a nitrogen atom. The only guiding example of such a transformation described in the literature involves an *N*-tosylated piperidine undergoing an intramolecular α-amination to form a [5.5] bicycle.[24] This example (Figure 2.1 and 2.17) is significant because it shows such a transformation is possible, and with the work presented herein will provide an account of the challenges encountered in attempting to expand this methodology.

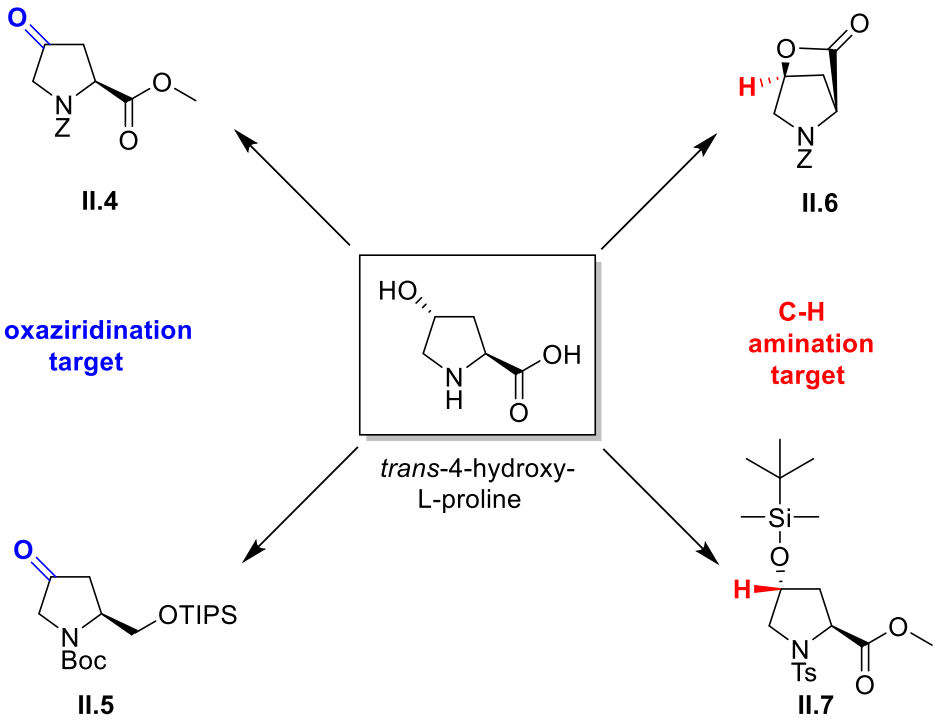
Figure 2.1: Retrosynthesis of the Pyrrole-Imidazole Alkaloid Nagelamide M



The oxaziridine moiety shown in compound **II.2** could be formed by the oxidation of an imine or the amination of a ketone, both of which are established transformations in the literature.[25,26]

The bromopyrrole amide could be synthesized by condensing the amine **II.2** and 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid.[27] Methodology has been developed by the Du Bois group for transforming an amine into an appropriately functionalized guanidine capable of undergoing C-H amination reactions.[28] As the stereochemistry established at this point will define the stereochemistry of the guanidine moiety, the ultimate choice of which path is used would depend on optimization studies that remain to be conducted. Conjugate addition of a vinyl sulfone at the

Figure 2.2: The Synthetic Versatility of *trans*-4-Hydroxy-*L*-Proline

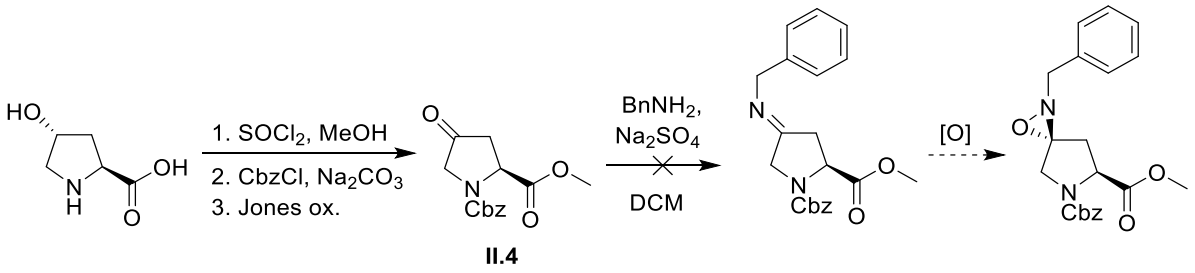


proline nitrogen would install the appropriate precursor alkyl chloride for the ethanesulfonate side chain. Aminoproline **II.3** (Figure 2.1) would be synthesized from the commercially available and inexpensive *trans*-4-hydroxy-*L*-proline. To explore all these possibilities, the substrates shown in the Figure 2.2 were each synthesized on a multi-gram scale to test their potential utility in the total synthesis of nagelamide M.

Synthesis of the Oxaziridine: Studies on the Oxidation of Imines and Amination of Ketones

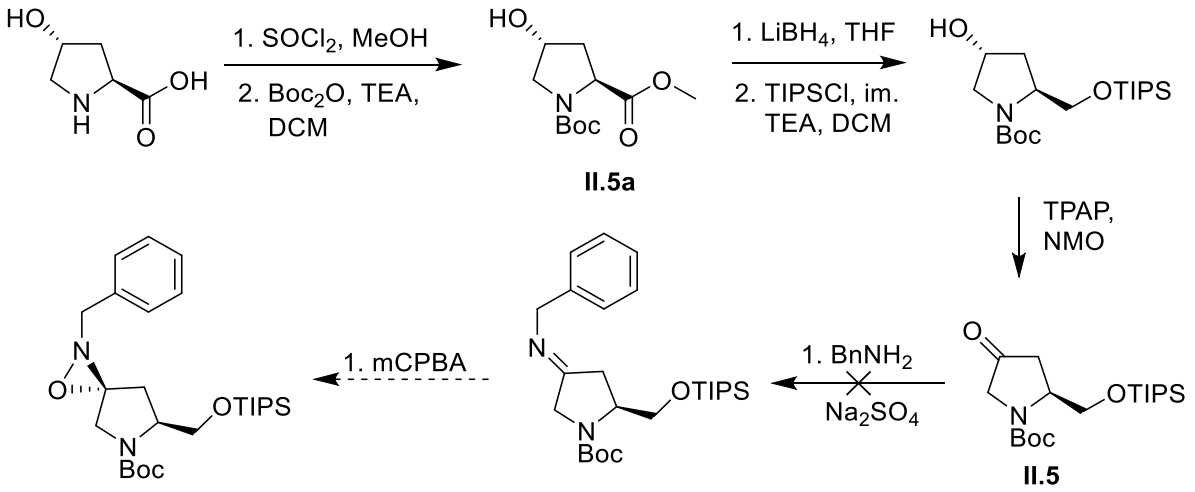
While it is possible to synthesize *N*,*O*-acetals (such as the one desired for nagelamide M) by C-H amination of an ether, other methods are available and were investigated. The oxidation of imines by peracids[29] (and other oxidants[30]) is well known and explored for its potential utility.

Figure 2.3: Attempted Oxaziridine Synthesis on Keto-Ester II.4



The keto-ester **II.4** was synthesized according to a known literature procedure, and first combined with benzylamine in DCM and sodium sulfate. Analysis of the crude reaction mixture revealed no imine formation, only decomposition of starting material (Figure 2.3). It was thought that having the carboxylate carbon in the correct oxidation state before synthesis of the

Figure 2.4: Synthesis and Attempted Oxidation of Prolinyl Ketone II.7

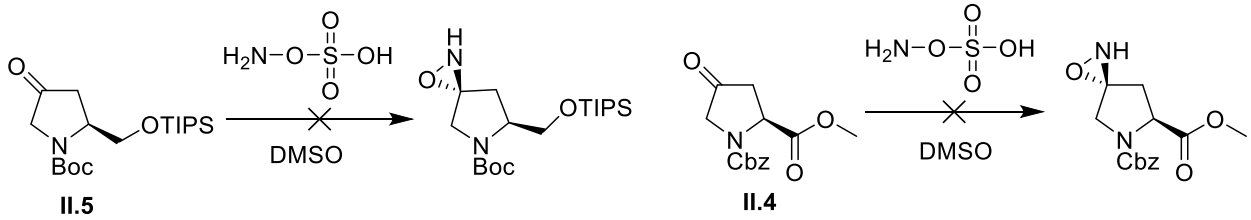


oxaziridine would be beneficial, as conditions capable of reducing the carboxylate would likely also reduce the oxaziridine (which may or may not be desirable). To this end, **II.5** was synthesized and subjected to the same conditions as **II.4**. Unfortunately, typical dehydrating conditions did not result in formation of the imine. The substrates themselves require mild conditions for imine formation, leaving little room for optimization. Acid catalysis could cause competitive enolate chemistry in both cases, and **II.5** could undergo *N*-deprotection.

Consequently, this approach was abandoned to investigate the amination of ketones.

The electrophilic amination of ketones is also a known though lesser used method to prepare oxaziridines and is postulated to operate through an addition-elimination mechanism.[26] This transformation is attractive because it would leave the oxaziridine nitrogen open for functionalization with the guanidine precursor (compound **II.2**, Figure 2.1). The reaction was attempted with both of the ketones above with hydroxylamine-*O*-sulfonic acid, unfortunately with no success.

Figure 2.5: Attempted Oxaziridination of Prolinyl Ketones II.4 and II.5



Again, the sensitivity of the substrates and the poor solubility of hydroxylamine-*O*-sulfonic acid limited the possibilities for optimization.

While these failures were a disappointment, they did effectively eliminate all other substrates for the oxidative synthesis of these targets apart from the C-H bond, the current state of the art of which is discussed below.

The C-H Amination Reaction in Total Synthesis

The selective oxidation of carbon-hydrogen bonds is one of the preeminent challenges of modern synthetic chemistry.[30,31] If realized in its ideal state, such a technology would add to the synthetic chemists repertoire of retrosynthetic motifs any desired C-H bond, constituting an advance with the potential to revolutionize organic chemistry.

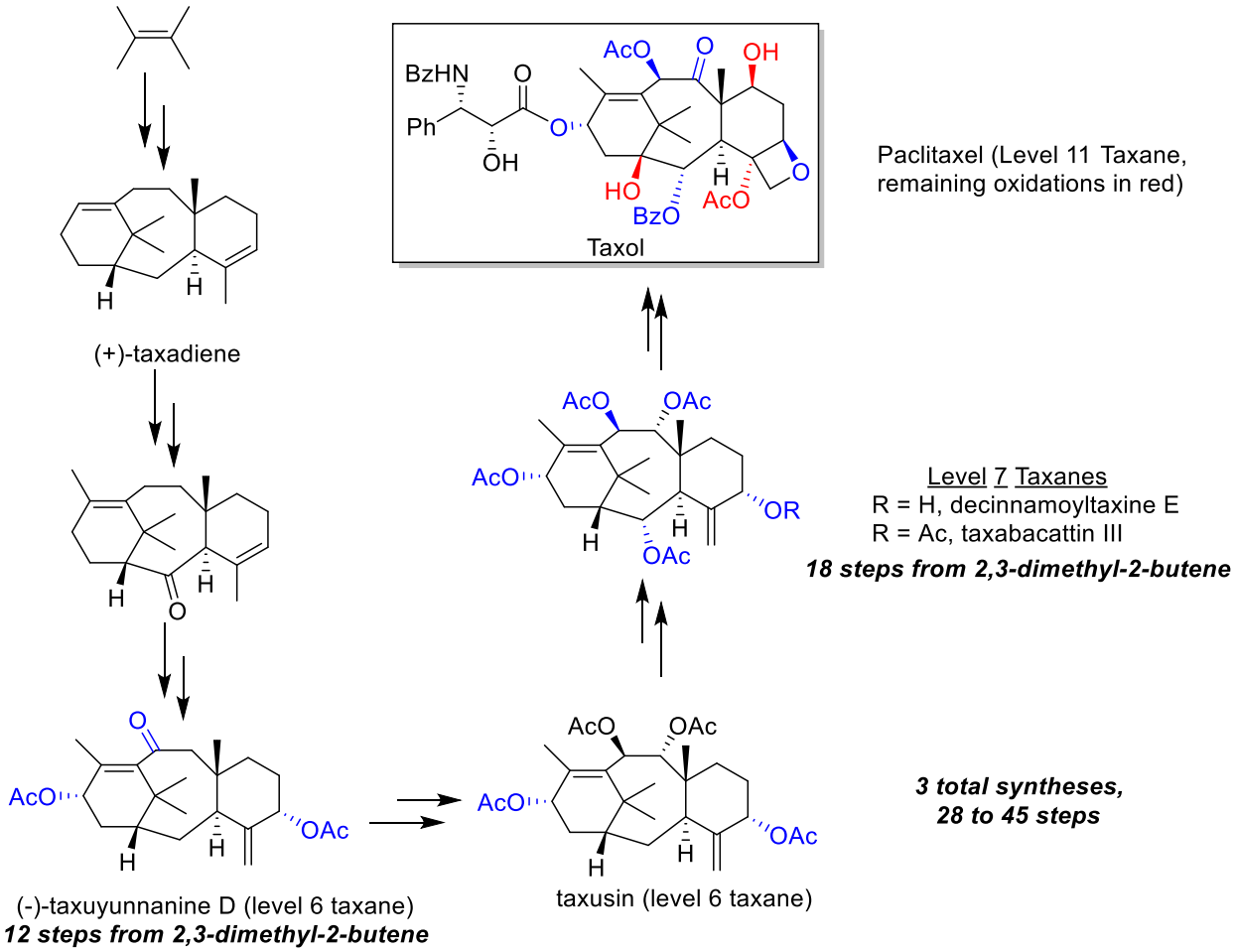
The most obvious embodiment of this revolution would be the simplification and/or shortening of the syntheses of heteroatom containing molecules of academic or commercial

interest. To create a picture of the current state of the art and how this work endeavors to add to it, some highlights from this growing body of work are discussed below.

While not an PIA, proof of this concept, the selective and sequential oxidation of C-H bonds to synthesize a complex natural product, is provided by the Baran group in their progress towards the natural product Taxol.[33,36] Originally discovered in 1971, and the target of multiple total syntheses,[34,35] this molecule of interest to the academic community as well as industry (currently sold as Paclitaxel for the treatment of breast cancer). Currently it is only available through semisynthesis, in which an advanced intermediate is synthesized in genetically engineered organisms and isolated for further chemical manipulation.[36] The Baran group is currently engaged in efforts to make the large scale chemical synthesis of Taxol a reality by employing a sequence of C-H activations to oxidize the starting material (+)-taxadiene to the intermediate (-)-taxuyunnanine D (shown in Figure 2.6).[33] The purpose of this endeavor is not to replace the semisynthesis as the source of Taxol for the pharmaceutical industry, but to discover a synthetic route that will produce enough material for medicinal chemistry to develop and optimize the SAR of Taxol.

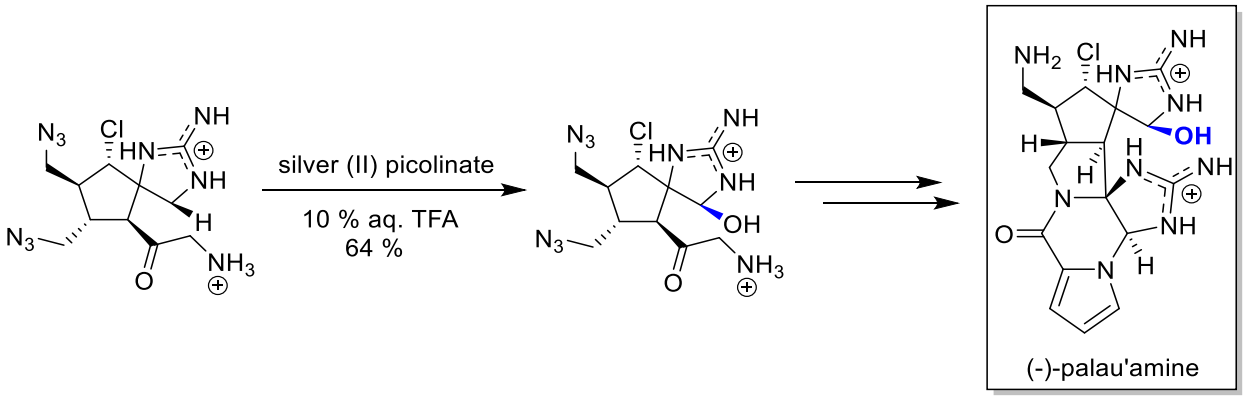
The natural products en route to the natural product are classified by number of oxidations relative to (+)-taxadiene, with Taxol itself being a level 11 taxane (9 C-H oxidations and 2 double bond installations). Over 100 level 11 taxanes have been discovered with unknown pharmacological potential.[36] Successfully completing this synthesis would in principle grant access to those compounds. Impressively, by pairing the relative order of C-H bond reactivity with an oxidizing agent of the appropriate strength, they achieve completely regio- and stereoselective transformations of the target.

Figure 2.6: The C-H Oxidation Route to Taxol



In an example closer to nagelamide M, several of the PIA's in Figure 4 feature the selective activation of a C-H bond on an advanced intermediate[37] which install heteroatoms that would be difficult or impossible to otherwise install. The utility of this transformation is highlighted in Figure 2.7 in the landmark total synthesis of palau'amine.[38]

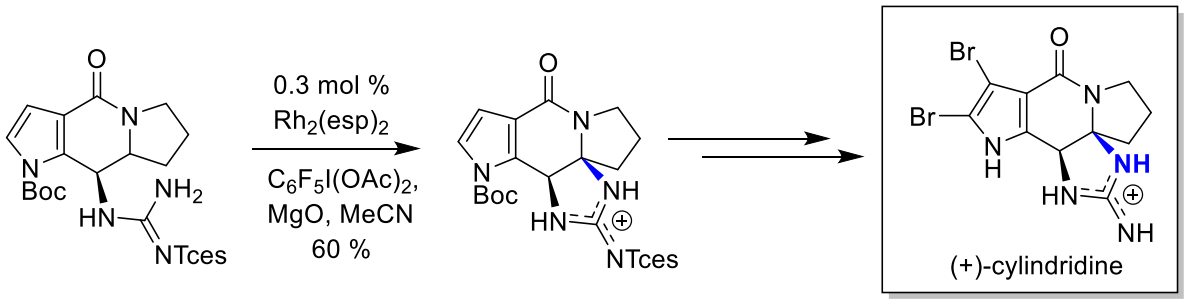
Figure 2.7: The C-H Oxidation to Install a Key Hydroxyl Group in Palau'amine



The Baran group employed the C-H oxidation highlighted in blue at a late stage on a highly functionalized intermediate; this approach was devised after previous routes involving earlier introduction of the indicated hydroxyl group stalled intractably.[38]

The key C-N bond formation in the total synthesis of cylindridine A[39] was accomplished via C-H amination of a tertiary C-H bond (Figure 2.8). This result is of particular interest as the total synthesis of this molecule was attempted in our laboratory as well.[40] The crucial C-N bond formation achieved with this methodology was resistant to a large variety of more conventional amination conditions.

Figure 2.8: C-H Amination to Install a Cyclic Guanidine in Cylindridine A

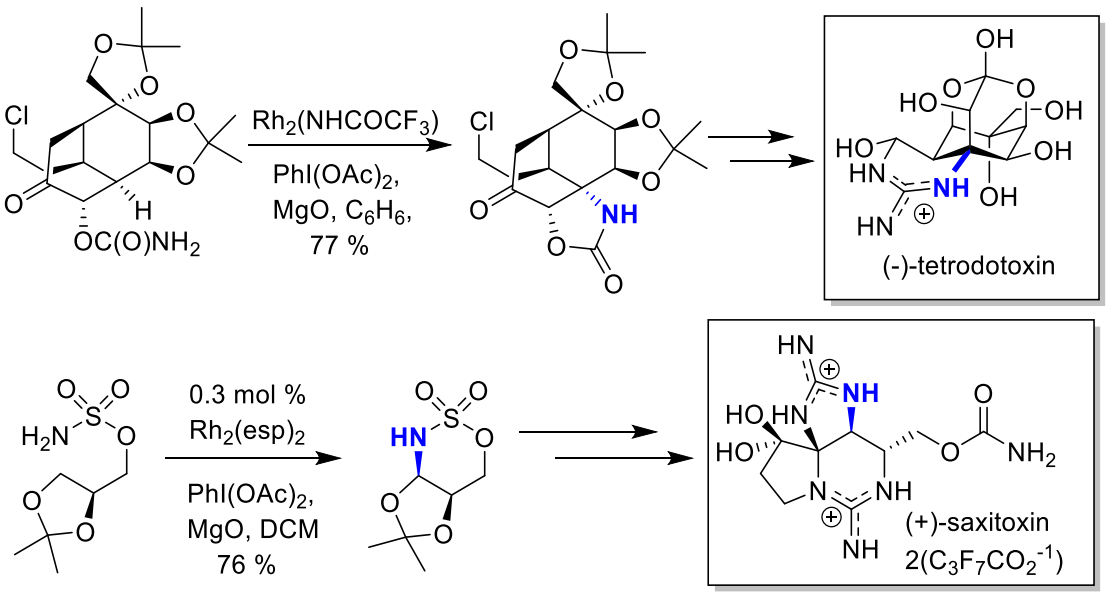


The Du Bois group developed C-H amination technology shown in Figure 2.9 that enabled the first enantioselective total synthesis of the natural product saxitoxin,[41,42] (which was recently reviewed)[43] approximately fifty years after it was first isolated in 1957[44] (and

structurally characterized in 1975[45,47]). Prior to this it had only been synthesized twice (both times as the racemate) by the Kishi group[48-50] and the Jacobi group.[51,52]

Tetrodotoxin, the famous Japanese *fugu* poison, had only been successfully synthesized twice before this route was discovered: originally racemic by Kishi[53] in 1972 and more recently an enantioselective route was disclosed by the the Isobe[54] group. In a comparison of the

Figure 2.9: Du Bois Total Syntheses of (-)-Tetrodotoxin and (+)-Saxitoxin



enantioselective versions the C-H amination route employed by Du Bois is much shorter (66 steps in Isobe versus 28 in Du Bois), highlighting the power of this technique to improve organic synthesis.

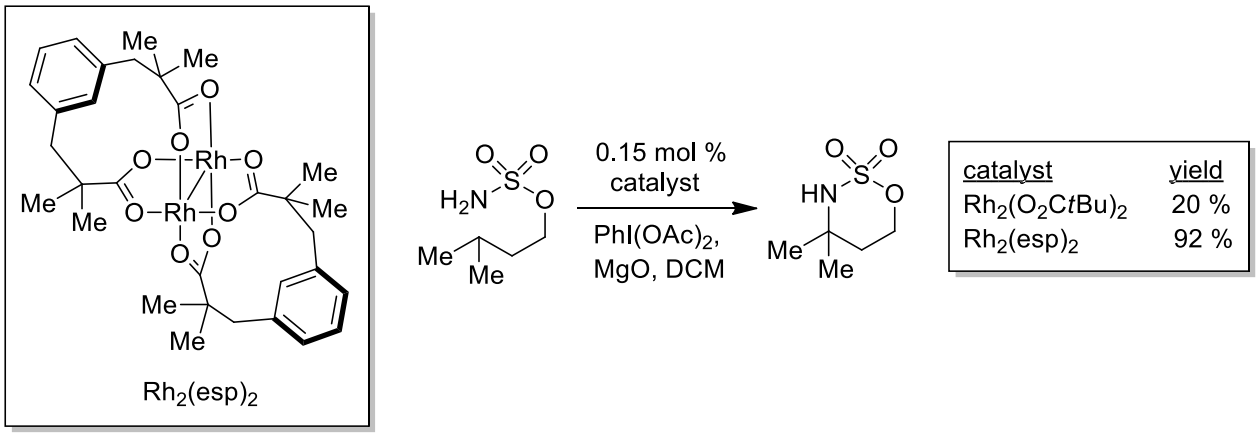
As these examples show, the utility of C-H activation in the synthetic manipulation of the guanidine and urea motifs, either directly[46] or with other precursors (carbamates[46] or sulfamates[41]) made this area of research an attractive means through which to synthesize many of the molecules of interest to the Tepe Research Group.

Expanding the Substrate Scope of Rhodium Catalyzed C-H Amination

At the outset of these studies, several examples of metal catalyzed C-H activations

(aminations and oxidations) had recently been reported. This subject has been recently reviewed.[56] For instance, urea's and guanidine's have been shown to undergo intramolecular *N*-cyclization[46] when in proximity to an oxidatively activated C-H bond.[19] Silver,[57] rhodium,[58] palladium,[59] and have all been shown to catalyze C-H amination[60] or oxidation[61] reactions. The most developed system for the necessary C-H aminations required to install the guanidine in nagelamide M (or a urea analog) was the rhodium dimer developed in the Du Bois group.

Figure 2.10: The Catalyst $Rh_2(esp)_2$ and Its Enhanced Activity[62]



catalyst	yield
$Rh_2(O_2CtBu)_2$	20 %
$Rh_2(esp)_2$	92 %

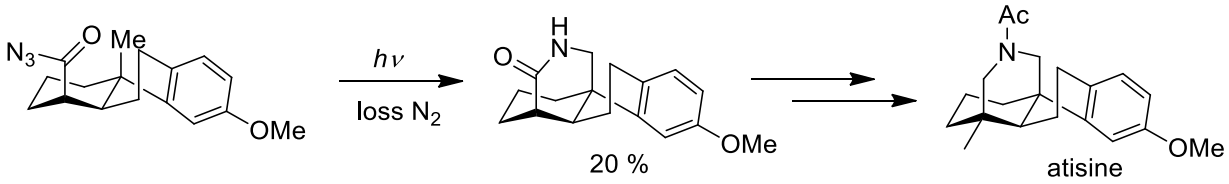
This catalyst, Bis[rhodium(α, α, α', α'-tetramethyl-1,3-benzenedipropionic acid], or "$Rh_2(esp)_2$", is pictured in Figure 1.10. While the simpler rhodium acetate dimer, $Rh_2(OAc)_4$, hadbeen shown to be effective at catalyzing C-H amination and carbene insertion,[62] drastic improvements in catalyst activity were achieved upon this ligand substitution. Many strapped dicarboxylate catalysts were synthesized in an SAR study, and none were comparable to $Rh_2(esp)_2$ in performance or substrate scope.[62] X-ray crystallographic analysis of these structures provides some insight as to the reason for this boost in performance. The four carboxylates would prefer to coordinate to the rhodium dimer at a ninety degree angle,[63] and this angle is best realized in the $Rh_2(esp)_2$ system. The other catalyst systems exhibit less than ideal bond angles in this respect, presumably inducing a degree of torsional strain that accelerates catalyst

degradation. While $Rh_2(OAc)_4$ exhibits almost ideal bond angles,[68,69] ligand substitution is observed under the standard reaction conditions, which presumably leads to catalyst decomposition through a different pathway.

Another advantage of a bidentate ligand system in a metal catalyzed process is the potential for stereoinduction, and there has been success on this front.[70] This feature made this route to nagelamide M even more appealing for the possibility that (if necessary) stereoinduction could be reagent, and not merely substrate, controlled.[71]

The mechanism of the rhodium catalyzed C-H amination has been an area of intense study. The uncatalyzed C-H amination reaction had been observed in the early 1960's, in the

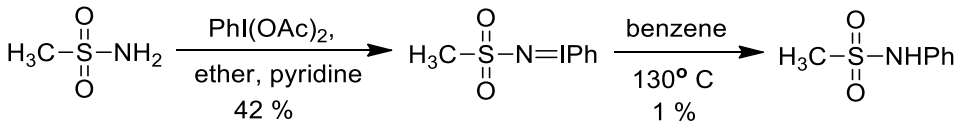
Figure 2.11: An Early Example of C-H Amination in Total Synthesis



total syntheses of the alkaloids garryine[72] and atisine[73] (pictured in Figure 2.11). In both cases, an azide was photolysed to the nitrene which underwent insertion with a C-H bond to form a ring. Neither reaction proceeded in high yield, nor were these examples particularly amenable to generalization (both exhibited a conformationally rigid system which positions the nitrene precursor in a position to form a six-membered ring), but they provide examples that the amination of a C-H bond is within the capability of a suitably disposed nitrene.

The next step in the evolution of this reaction came from a search for alternate sources (*i.e.* not originating from an alkyl or acyl azide) of nitrene precursors. Abramovitch[74] and coworkers discovered that sulfonyliminoiodinanes, of the general formula $RSO_2N{=}IPh$, can

Figure 2.12: The First Example of an Iminoindinane As A Nitrene Precursor

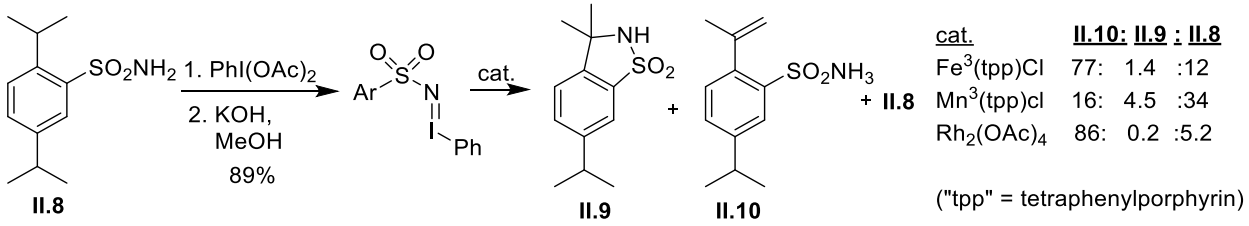


function as nitrene equivalents (Figure 1.12). Although in very low yield and under forcing conditions (1 % from 130 ºC benzene), the C-H amination product *N*- methanesufonyl aniline was synthesized.

The penultimate advance came when Breslow[75] and coworkers showed that preformed sulfonyliminoiodinanes could perform C-H amination reactions in the presence of a transition metal catalyst as shown in Figure 2.13. The focus of the study was the transition metals iron (III) and manganese (III) in porphyrin rings, but dirhodium tetraacetate was used included as an additional example, and prophetically gave the highest yields.

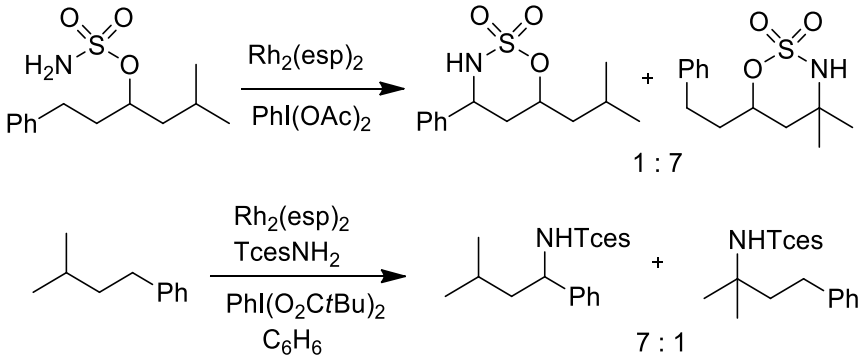
The most recent innovation was contributed by the Du Bois group[76,77] (and the Che group[78] in the context of rhodium porphyrins), when it was reported that the nitrene precursor could be generated *in situ* from multiple sources (carbamates,[76] sulfamates,[79] and sulfonamides[80]) and in the presence of a dirhodium or diruthenium transition metal catalyst effectively perform C-H aminations. This expanded the scope of the methodology beyond the previous limitation requiring the preformation of the iminoindinane precursor because many of the currently viable substrates do not form isolable iminoindinanes.

Figure 2.13: Transition Metal (III) Porphyrin Complexes Catalyze C-H Amination



Both the intermolecular and intramolecular rhodium catalyzed C-H aminations were employed in studies attempting the total synthesis of nagelamide M. Experimental and computational data support a concerted, asynchronous C-H insertion mechanism for the intramolecular pathway.[62] The intermolecular process is thought to proceed by a related but distinct mechanism, and many of the intermediates have been directly observed by mass spectrometry.[77] The primary difference between the two reactions is substrate preference. The

Figure 2.14: Substrate Preference in Inter- Versus Intramolecular C-H Amination



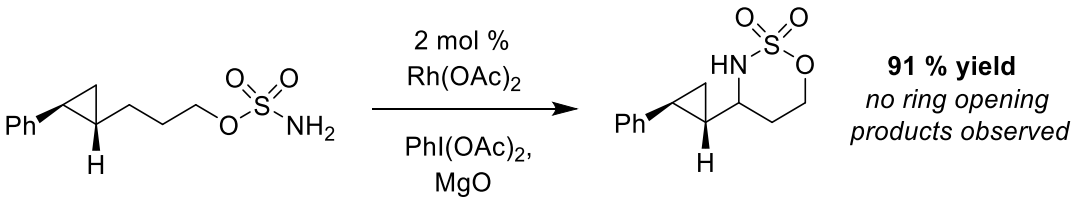
intramolecular reaction prefers tertiary over benzylic positions when given the option, while the reverse is true for the intermolecular process (Figure 2.14).[80] The Du Bois group proposed an explanation for this phenomenon by using linear free energy relationships and IR stretching parameters to develop a model for calculating the difference between the energy of activation of the benzylic and tertiary C-H amination reactions.[29] The mathematical model developed was used to accurately predict the most tertiary C-H-selective analog to date.

As these approaches require the preparation of different compounds, the data gleaned from these studies will be organized as approaching from the intermolecular and intramolecular pathways separately.

The Intramolecular $Rh_2(esp)_2$ C-H Amination Pathway

The mechanism of this reaction has been extensively studied, and the current opinion rests on a concerted asynchronous mechanism. One important clue comes from the stereospecificity of the reaction. To date, there have been no examples of an erosion of stereochemistry when enantiomerically or diastereomerically pure substrates are used.[76,81,82] While this itself does not exclude a radical mechanism, this result argues against it. The stereoretentive properties of this reaction suggest such a radical, if it exists, has a rate of internal return high enough to maintain the absolute configuration at the reacting center (~200 fs).[76] Additional support for this mechanism comes from the observed KIE of 2.6 and a Hammett ρ value of -0.55.[81,82] Finally, the intramolecular radical clock shown in Figure 2.15 was

Figure 2.15: Intramolecular Radical Clock Probe for Radical Intermediates

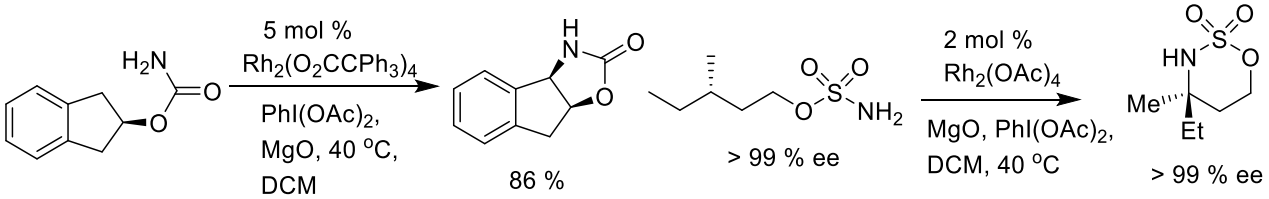


synthesized, and under reaction conditions no radical fragmentation products were observed. The rate constant for fragmentation of this particular clock is believed to be on the order of 7×10^{10} s^{-1}.[82] These results combined argue strongly for a concerted, asynchronous mechanism.

The earliest precursors for oxidative C-H amination investigated by the Du Bois group were α-ethereal C-H bonds with primary carbamates[72] and sulfamate esters (Figure 2.16).[73] The combination of either of these precursors with $PhI(OAc)_2$ and a commercial rhodium catalyst,

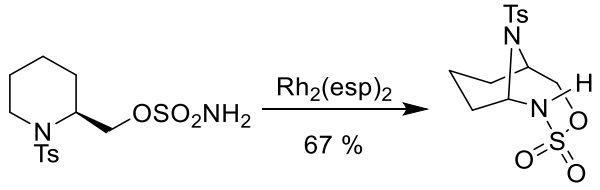
$Rh_2(OAc)_4$ or $Rh_2(oct)_4$, results in C-H amination to form the oxazolidin-2-one or [1,2,3]-oxathiazinane-2,2-dioxide, respectively.

Figure 2.16: Early Examples of Intramolecular Rhodium Catalyzed C-H Amination



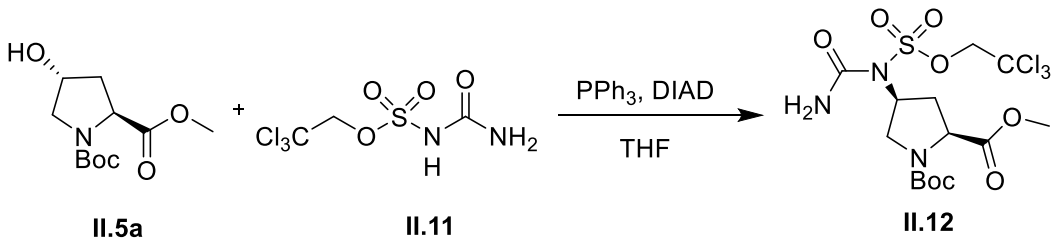
As was previously cited, one example exists for the intramolecular synthesis of a C-H amination α to an amine,[24] shown in Figure 2.17. Two challenges present themselves in the case of a total synthesis of nagelamide M; first the oxidative lability of to α-amino methylene hydrogens is sparsely precedented, and second is the limiting effect of bond angles on this reaction. The various nitrene precursors that could serve in this capacity are often indiscriminate of the electronics of the target but sensitive to the steric restrictions of the ring being formed.

Figure 2.17: Literature Precedent for an Intramolecular C-H α Amination



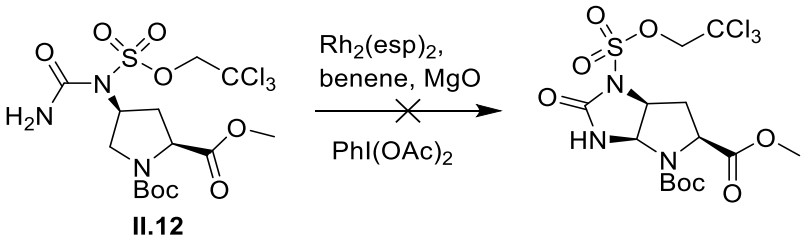
Sulfamates have been shown to form 5 and 6 membered rings,[62] and the regioselectivity of this ring closure will inform the development of this reaction manifold in this synthesis. As the C-H amination reaction had been extended to include appropriately functionalized guanidines and ureas[46] and the natural product (or analogs of interest) contains those motifs, the urideo-proline shown was synthesized. The cyclization precursor trichloroethoxysulfonyl urea, "Tces Urea", was synthesized according to a literature procedure.[46]

Figure 2.18: Synthesis of Urideo-Proline II.12 for C-H Amination



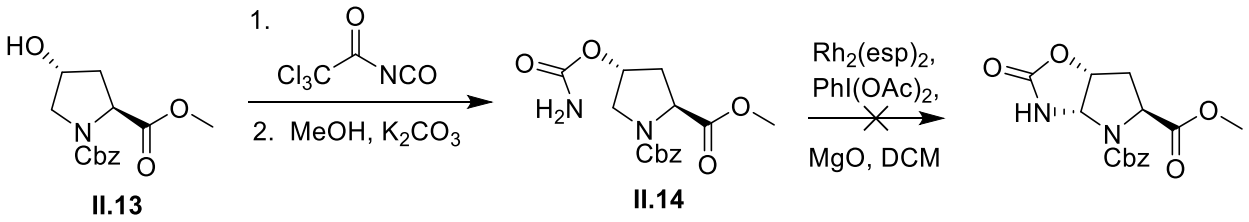
When subjected to C-H amination conditions to generate the [5.5] bicycle, no product was observed (Figure 2.19). On considering the reasons for its failure, it was thought the Boc group might be large enough to sterically occlude the nitrene-rhodium complex from

Figure 2.19: Attempted C-H Amination of II.9



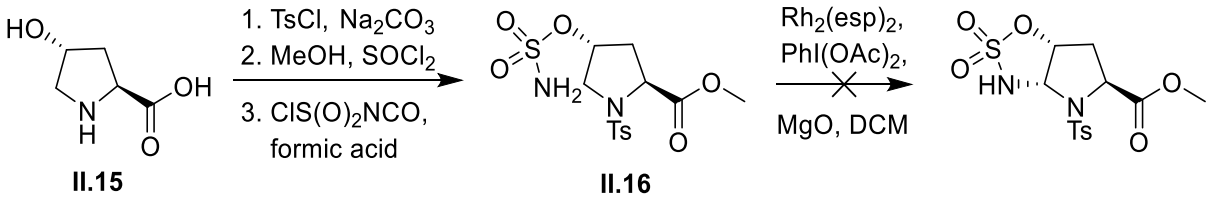
reaching the desired C-H bond. As this type of bond (Figures 2.1, 2.17) had been shown amenable to the desired oxidation, the failure was presumed to be due to steric constraints rather than electronics. To test this theory the Cbz-protected variant of **II.12** was synthesized, as it was though exchange of a *tert*-butyl group for a benzyl group would provide enough space for the oxidizing species to react at the desired bond. A carbamate was used in place of the Tces Urea because carbamates have also been viable substrates for C-H amination[73] and it was thought formation of the second ring might be facilitated by having it on the opposite face of the ester (again in an attempt to make the steric environment more favorable). This reaction failed under C-H amination conditions as well.

Figure 2.20: Attempted C-H Amination of Benzyl Carbamate II.14



At that point, a more intensive search of the literature[82] revealed that similar substrates had failed, perhaps due to the increased sp^2-character of the proline carbamate. In an effort to circumvent this, the carbamate protecting group was substituted for a tosylate, which is in accord with the literature example.[24] Still considering the problem to be one of sterics and not electronics, the carbamate ester was exchanged for sulfamate ester **II.16** shown in Figure 2.21. Bond angle has been shown to influence the ring formation in these reactions,[62] and it was

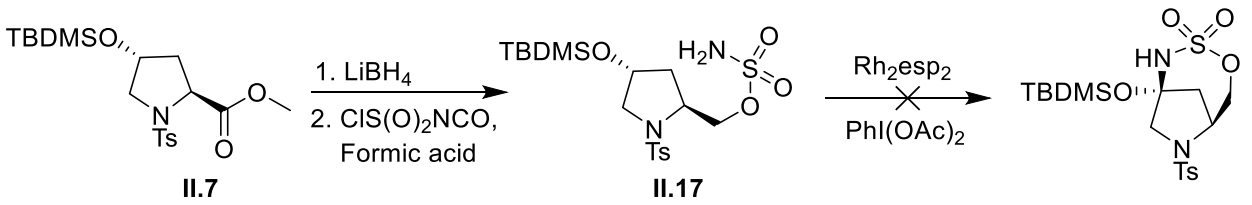
Figure 2.21: Attempted C-H Amination of Sulfamate Substrate



thought the larger O-S-N bond angle (compared to the O-C-N bond angle of the carbamate) might be more successful. This approach failed as well.

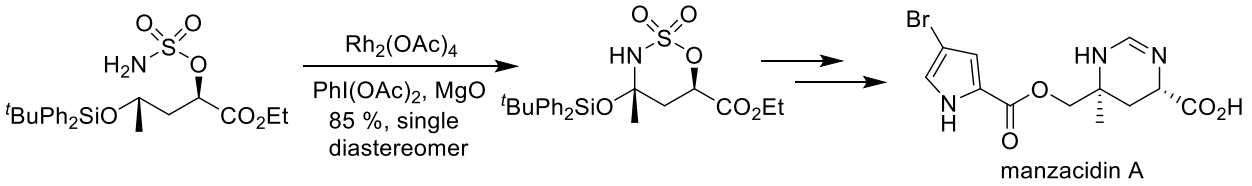
The following precursor **II.17** was synthesized. Silyl ester **II.7** was already in hand as a precursor for intermolecular C-H amination; this intermediate was readily reduced to its alcohol and sulfamoylated by known procedures.[75] At the time this study was conducted, the only intramolecular C-H amination forming a seven-membered ring was the one reported in Figure 2.17.[24] The only other relevant example provided in the total synthesis of manzacidin A, which used C-H amination as a key step to install an *N*,*O*-acetal like the one desired for nagelamide M.

Figure 2.22: Attempted Intramolecular C-H Amination of Precursor II.17



Of note is the success of the reaction in spite of the sterically bulky TBDPS-protected tertiary alcohol,[28] inferring the smaller TBDMS-protected tertiary alcohol would not be a steric impediment to the reaction. The formation of a seven-membered ring in is entropically less favorable than the six-membered ring, but the local electronic and steric environments in the two intermediates are almost identical, and as such the chance for success in this manifold could not be ignored. Intermediate **II.17** also provides for comparison of the electronics of activating a secondary α-amino C-H bond compared to a tertiary α-alkoxy C-H bond, as another possible product compared to that shown in Figure 2.23 is a seven-membered ring such as that shown in Figure 2.17.

Figure 2.23: C-H Amination in the Total Synthesis of the Natural Product Manzacidin A



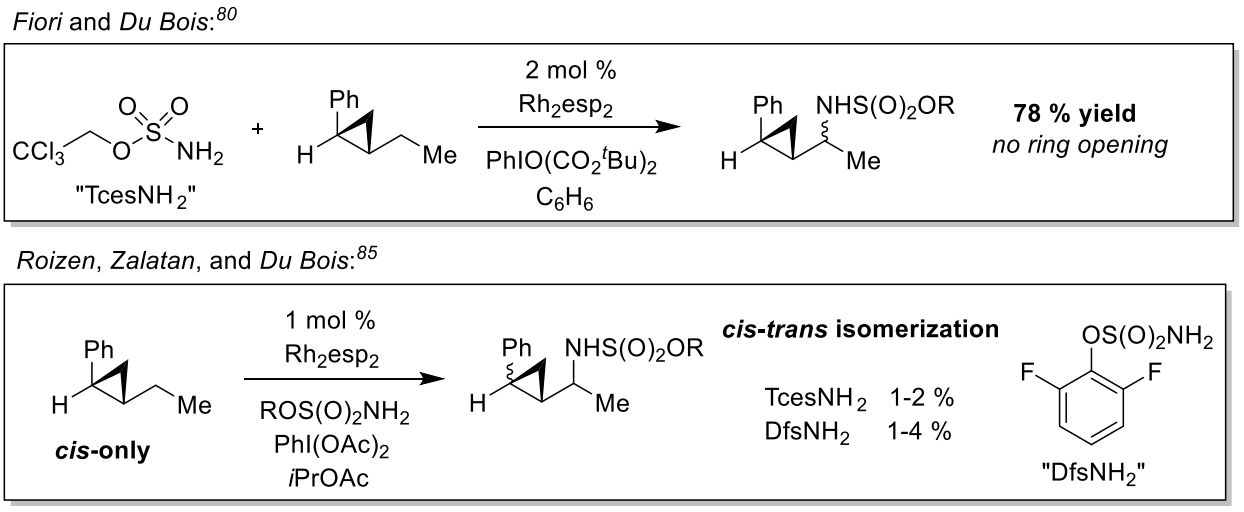
The Intermolecular Approach to Nagelamide M

The mechanism of this reaction has been studied as intensely as its intramolecular cousin, with the current opinion resting on a stepwise asynchronous oxidation event. The currently accepted catalytic cycle is depicted in Figure 2.26. Primary KIE's are high: 5.2 – 6.9 (depending on the amine source), suggesting C-H bond breaking is extensive in the transition state. Reactions with similarly high primary KIE's include ruthenium and copper-catalyzed nitrene

insertion reactions,[76] which are generally believed to proceed through a stepwise mechanism.

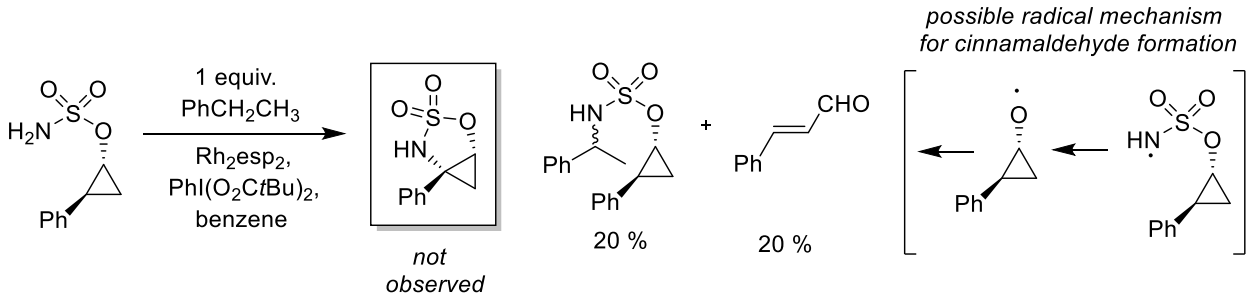
The data derived from cyclopropyl radical clock substrates varies. Fiori and Du Bois[76] disclose that no ring opening is observed, and in a different publication, Roizen, Zalatan, and Du Bois[85] disclose small amount of isomerization for a nearly identical system (Figure 2.24). Apart from the nitrogen source (which would not be expected to influence the stereochemical outcome of the reaction) the main difference in conditions is solvent; the di-*tert*-butyl iodoacetate is substituted for the diacetate merely to enhance the solubility of the oxidant. While solvent can be optimized to improve yield, it has not been known to alter the mechanism of the reaction.[84] The

Figure 2.24: An Apparent Discrepancy in Results



cyclopropyl sulfamate shown in Figure 2.25 was used to probe the intermolecular reaction, and the lack of intramolecular cyclization product is informative. A radical pathway could be used to explain the formation of cinnamaldehyde, but no direct evidence was observed for the possible radical intermediates. This is the only system reported to date that displays such fragmentation characteristics, perhaps due to the thermodynamically preferential formation of the extensively conjugated cinnamaldeyde system.

Figure 2.25: A Clock Experiment to Probe for the Presence of Radicals



While overwhelming evidence existed for the proposed mechanism, definitive evidence was not obtained until 2012. Several of the proposed intermediates were observed for the first time in a series of elegant mass spectrometry experiments.[77] The species proposed to be responsible for the oxidation event was directly detected, and the proposed catalytic cycle is shown in Figure 2.26.

Figure 2.26: The Mechanism of the Intermolecular $Rh_2(esp)_2$ C-H Amination

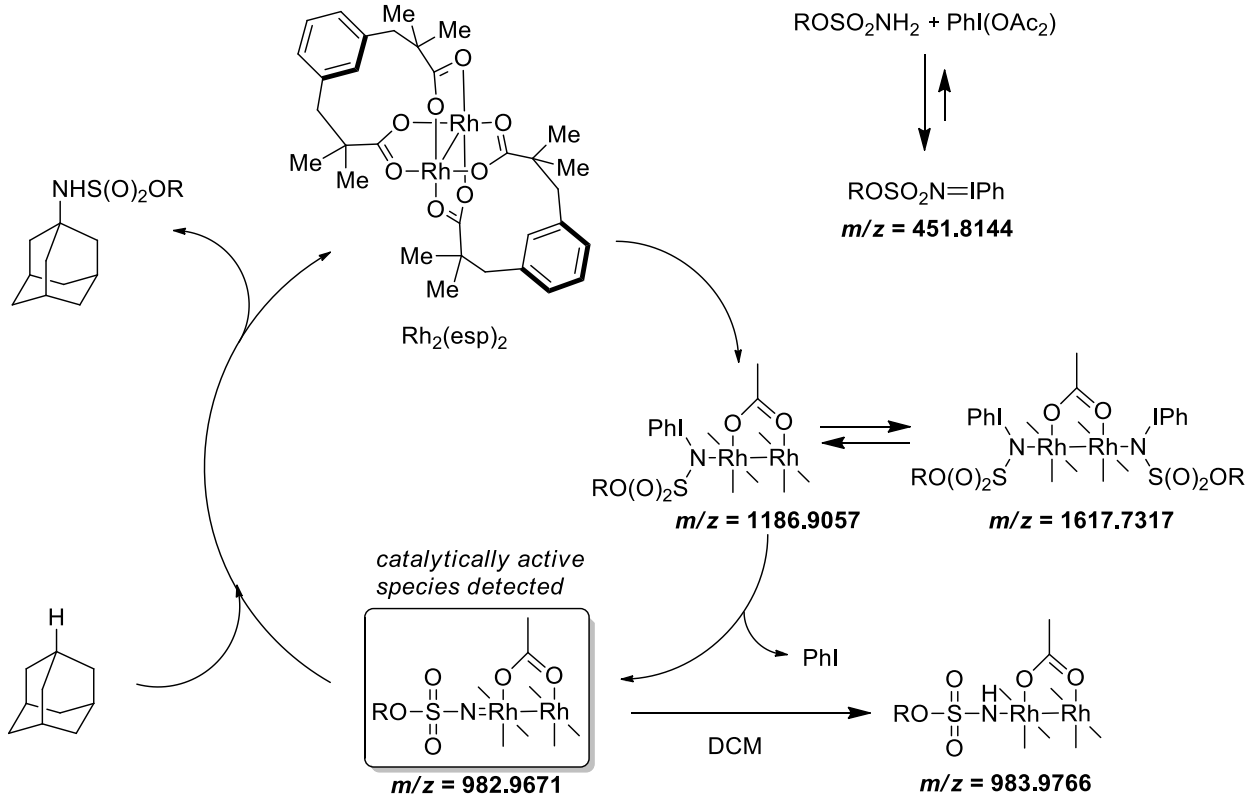
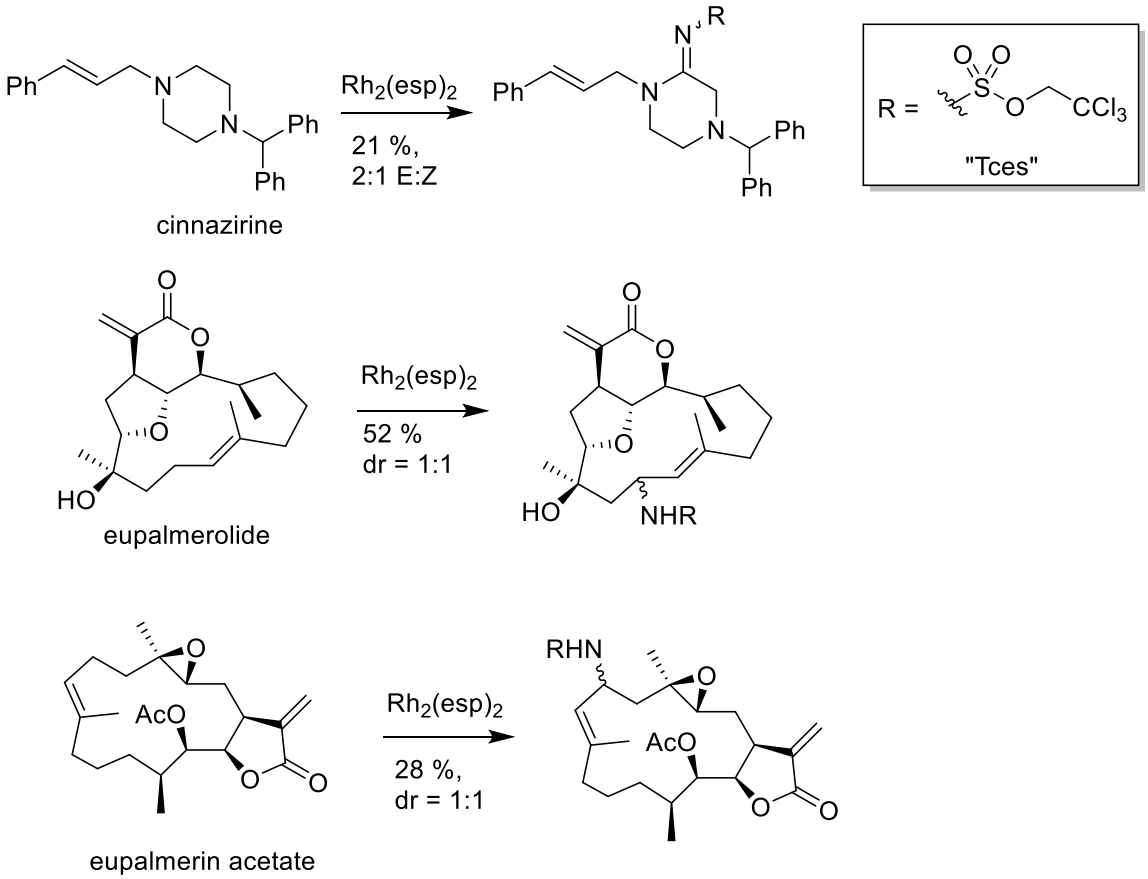


Figure 2.27 provides examples of the successful intermolecular C-H amination of natural products.[87] These examples established precedent that the same reaction might work on the desired substrate, and as these were the only related examples available at the time, the success of this approach would constitute an expansion of the methodology.

Notably, the reaction was shown to be successful on α-amino methylene C-H bonds (in cinnazirine), however the oxidation proceeded to the amidine product. It also selected the α-amino reaction site over the benzylic position, which is contrary to the established preference. The first breakthrough in intermolecular C-H amination in this manifold used 2,2,2-

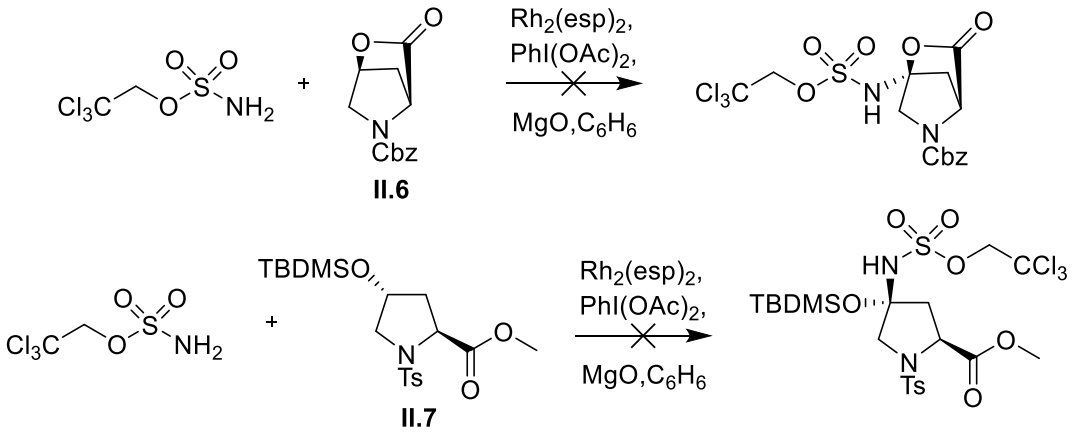
Figure 2.27: C-H Amination of Natural Products



trichoroethxysulfonamide, "$TcesNH_2$", as the nitrogen source.[80] Prior to this discovery, $TcesNH_2$ was used successfully in the rhodium catalyzed aziridination of alkenes.[88] As shown, it strongly

prefers benzylic hydrogens, though it will react with tertiary carbons. This was the first nitrogen source used in attempts to synthesize the *N*,*O*-acetal of nagelamide M from precursors **II.6** and **II.7** (Figure 2.28). The ethereal oxygen attached to this carbon would presumably be beneficial from an electronic perspective, as has been shown in the intramolecular case.[89] This approach was particularly attractive because the lactone substrate **II.6** was obtained on a multigram scale stereoselectively from an intramolecular Mitsonobu reaction of *N*-Cbz-*trans*-4-hydroxy-*L*-proline.[90,91] The established stereochemistry concomitantly set the stereochemical outcome of the C-H amination product as that reported for the natural product, and if successful this would have defined all the stereochemistry necessary for an enantioselective total synthesis of nagelamide M. The silyl protected proline **II.7** was prepared on a multigram scale has the opposite relative stereochemistry than that desired for the natural product, but the correct stereoisomeric alcohol could be obtained through several methods. Lactone **II.6** has been cleaved using methanol and sodium azide in quantitative yield,[90] additionally the Mitsonobu inversion of the alcohol of a functionalized *trans*-hydroxy-*L*-proline is known.[91] Either of these procedures could be used to

Figure 2.28: Attempted Intermolecular C-H Amination of II.6 and II.7

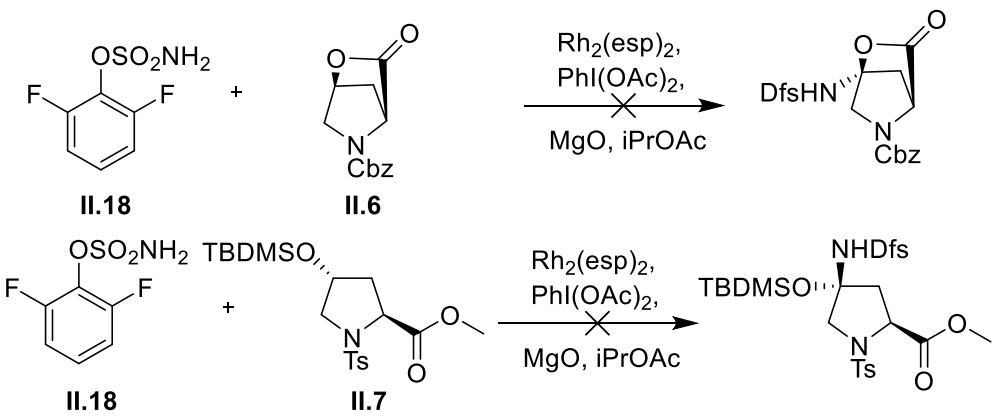


obtain the desired stereochemistry, but this step was postponed awaiting a successful C-H amination event. These substrates were inert when subjected to established conditions.

The Du Bois group has made progress is modulating the preferential intermolecular C-H amination of benzylic C-H bonds in the presence of tertiary C-H bonds, allowing for optimization based on the nitrogen source. One such reagent, shown in Figure 2.29, is 2,6-difluorophenyl sulfamate, "$DfsNH_2$".[85] The development of this reagent was guided by the observation that in intermolecular C-H amination reactions involving tertiary C-H bonds as the only target, much of the $TcesNH_2$ was consumed despite little product being formed.[85] The implication was that the methylene C-H bonds were being oxidized preferentially in comparison to the target tertiary C-H bond. To counteract this effect, aryl and phenolic sulfonamides were designed. The one that performed the best was the aforementioned 2,6-difluorophenol derivative, which was synthesized according to a literature procedure[84] for use in these studies.

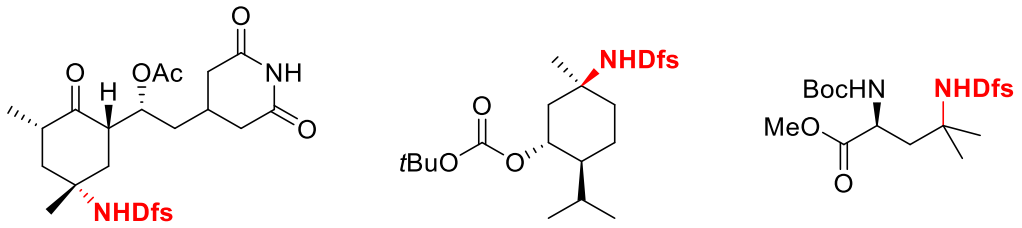
It should be noted that none of the examples provided in the publication show amination at a tertiary ether as desired in **II.6** and **II.7**; as the closest examples show selection for aliphatic

Figure 2.29: Attempted Intermolecular C-H Amination of II.6 and II.7 With $DfsNH_2$



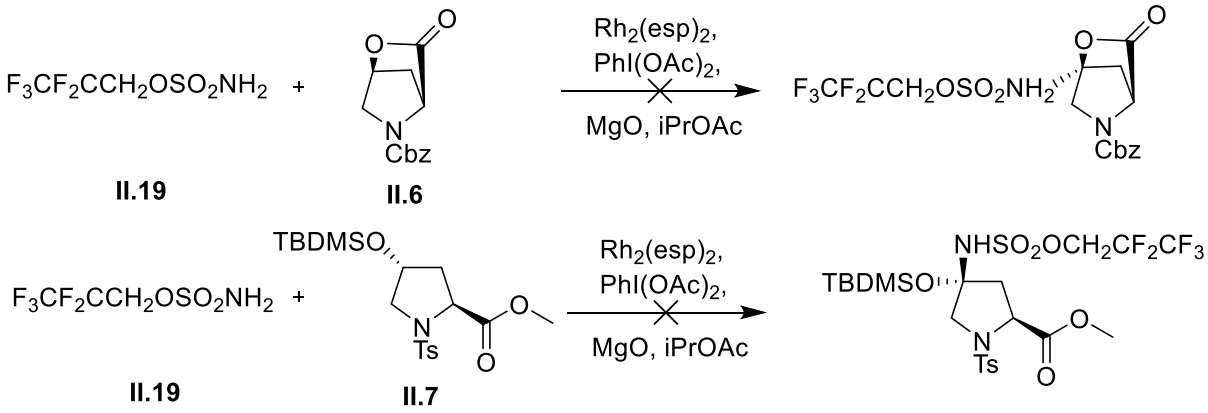
tertiary C-H bonds in the presence of α-keto tertiary C-H bonds and α-ester tertiary C-H bonds.[85] For each example shown in Figure 2.30 the regioisomer shown is the only one formed.

Figure 2.30: Examples Illustrating the Selectivity of $DfsNH_2$



The most recent improvement to this reaction employs 2,2,3,3,3-pentafluoropropanol-1-sulfamate as the nitrogen source (Figure 2.31). The efficacy of this reagent, which provides the highest tertiary-to-benzylic selectivity ratio yet observed (9.5:1), was predicted by a mathematical model of linear free energy relationships derived from the ground state IR stretching parameters of a library of sulfamate esters.[32]

Figure 2.31: Attempted C-H Animation of II.6 and II.7 with Sulfamate Ester II.19



None of these reagent combinations formed any desired product, and the methodology has not been developed further. This impasse prompted a change of tactic from C-H amination to C-H azidation.

C-H Azidation as a Method to Access These Substrates

During the course of these studies, several significant advances in the field of C-H azidation were disclosed. Azides were initially not considered as a route to access these molecules due to the reasons these publications address: typically harsh reaction conditions and

limited substrate scope of azidation reactions. However, the successful installation of an azide instead of a protected amine on the described substrates would be just as desirable as the initially sought after amines, as one the fundamental transformation is the same, and a reduction would be required to reveal the desired amine in either case.

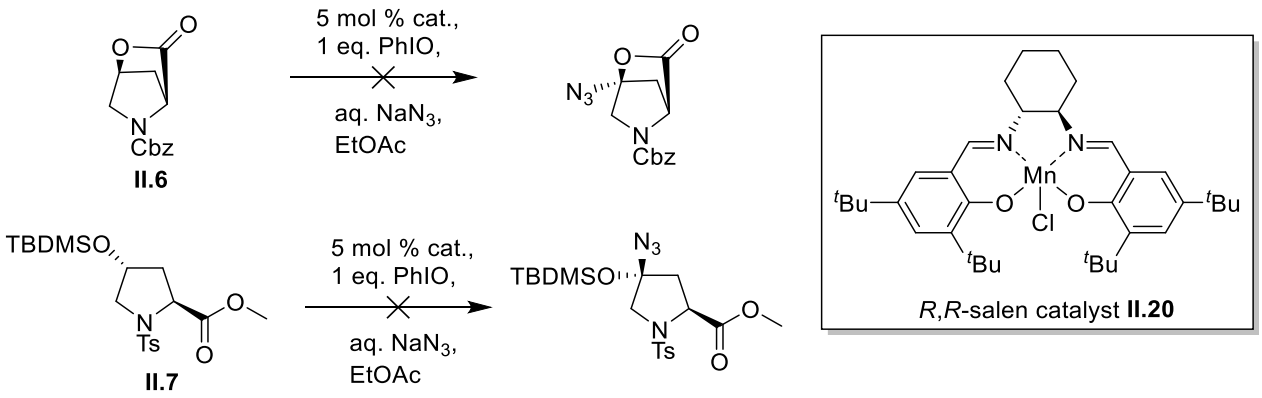
Hypervalent or electrophilic iodine species, for example IN_3, have been established as viable sources for aliphatic C-H azidation for some time,[92] but the use of this reagent is limited primarily to simple aliphatic molecules due to harsh conditions and the relative instability of the products. It does, however, provide the necessary proof-of-principle from which this manifold can be improved.

Transition metals have been successfully employed in this area. Palladium has been used to catalyze allylic azidations using NaN_3 as an azide source,[93] and an iron catalyst with the appropriate ligand has been reported to catalyze enantioselective C-H azidation of β-ketoesters with an azidiodinane.[94] The drawback to these methods is their dependence on local functionality to activate the C-H bond. This was the limit of the state of the art until the Hartwig[95] and Groves[96] groups each disclosed (respectively) iron and manganese catalyzed C-H azidation of unactivated, highly functionalized substrates.

The Groves system uses aqueous NaN_3 as the azide source, iodosobenzene as the stoichiometric oxidant, and either a manganese porphyrin or manganese salen complex as the catalyst. The manganese salen catalyst, initially described by Jacobsen,[97] was prepared according to the known procedure for use in these studies. This is, of course, out of step with the typical progression of methodology development, in which a racemic process is developed and subsequently rendered asymmetric. The reverse order was chosen here simply due to the comparative ease and inexpense of preparing the salen catalyst in comparison to purchasing or

synthesizing the porphyrin. Additionally there were no examples in which the porphyrin catalyst worked and the salen catalyst did not.

Figure 2.32: C-H Azidation Using the Groves Procedure

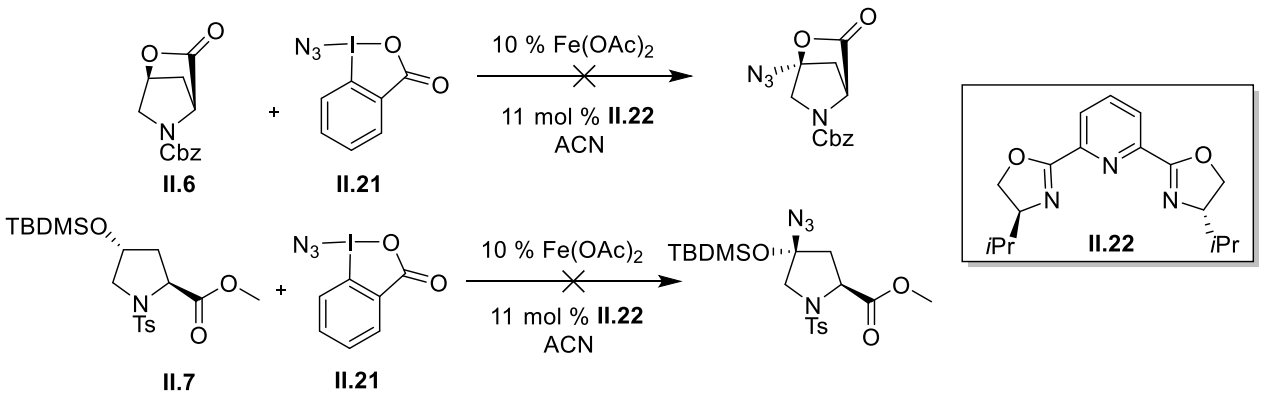


The intermediates **II.6** and **II.7** did not show any reactivity under the proscribed conditions (Figure 2.32). The reaction mechanism is thought to proceed through C-H abstraction by an Mn-centered radical, followed by recombination with an azide radical. The evidence for this comes from the dependence on regioselectivity on catalyst architecture (see published examples[96]) and KIE experiments. The azidation was conducted on a 1:1 mixture of toluene and d_8-toluene yielding a primary KIE of 9.3 (with the Manganese-salen catalyst),[96] which is substantially higher than the reported KIE of ~5 for hydrogen abstraction by azide radicals.[95,98] The reason for the lack of reactivity of the starting materials to these conditions is not apparent, as each has structural features that would favor radical abstraction; each would constitute a tertiary carbon centered radical that would benefit from stabilization by a local oxygen-centered lone pair. The lactone **II.6** might experience a barrier to radical C-H abstraction from the conformationally rigid structure inhibiting the required planarization of the intermediate, but conformationally stable radicals have been reported.[99]

The Hartwig group published a method using an iron catalyst with a box ligand and iodoazide **II.21** as an azide source as shown in Figure 2.33. The azide is easily prepared in two

steps from commercially available 2-iodobenzoic acid,[92] and the ligand is prepared in one step[100] by a known procedure.

Figure 2.33: C-H Azidation Using the Hartwig Procedure



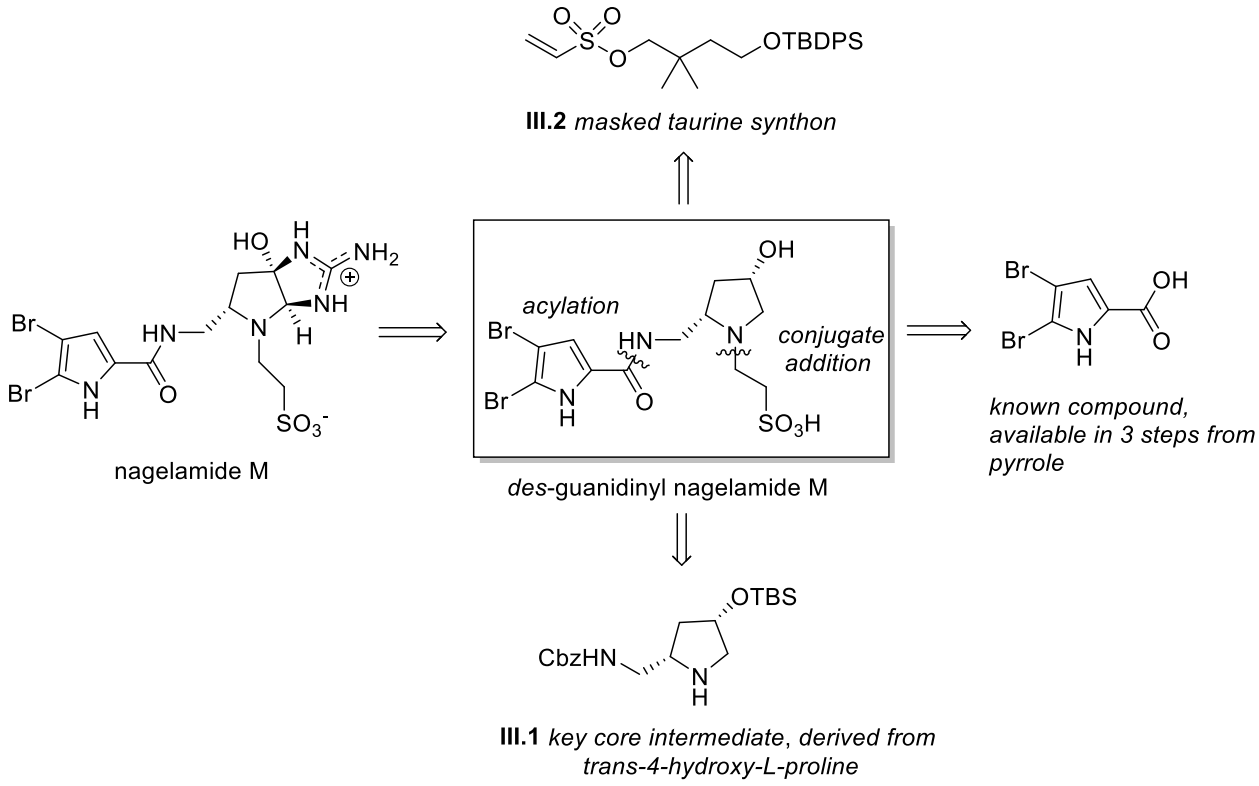
II.6 and **II.7** again proved inert to reaction conditions. The proposed mechanism is radical mediated, and the authors conducted several control experiments to detect radical intermediates. Additives that are known to quench radicals (TEMPO, BHT) completely inhibited the reaction, and replacing the catalyst with benzoyl peroxide and heat led to a decrease in yields and selectivity. The failure of the reaction is likely due to the same reasons as the Mn-salen system, but they remain obscure.

At present the substrates chosen for the total synthesis of nagelamide M have proven to be synthetic dead-ends and the synthesis is stalled as described.

Chapter 3: Synthesis of *Des*-Guanidinyl Nagelamide M

Given the synthetic inaccessibility of nagelamide M, but not wanting to abandon the project, the possibility of synthesizing a *des*-guanidinyl analog was proposed. Molecules of this series are of additional interest for potential biological activity. A retrosynthetic anaysis is shown in Figure 3.1 below. The key reaction in the forward direction is the conjugate addition between functionalized proline **III.1** and vinyl sulfone **III.2**, a reagent that was developed to synthesize protected taurine derivatives. This vinyl sulfone has been prepared on a multigram scale and

Figure 3.1: Retrosynthesis of *Des*-Guanidinyl Nagelamide M

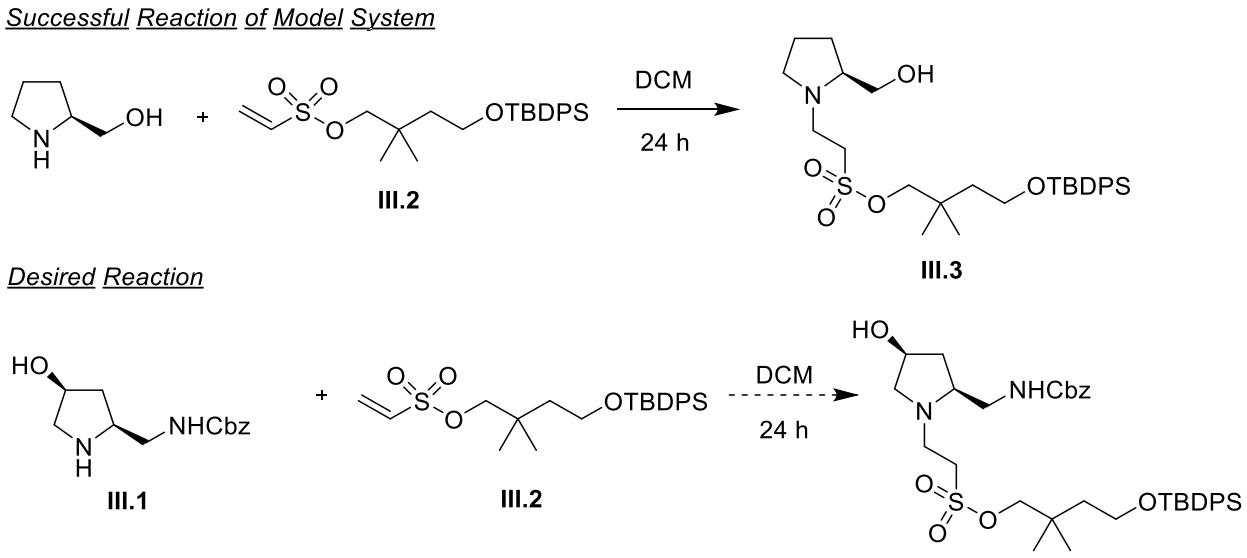


in a model system did react with (*S*)-pyrrolidin-2-ylmethanol to produce the desired product, establishing precedent for the desired reaction.

In the original report disclosing the preparation and reactivity [102] of the vinyl sulfone, primary and secondary amines were shown to be viable substrates and free hydroxyl groups were

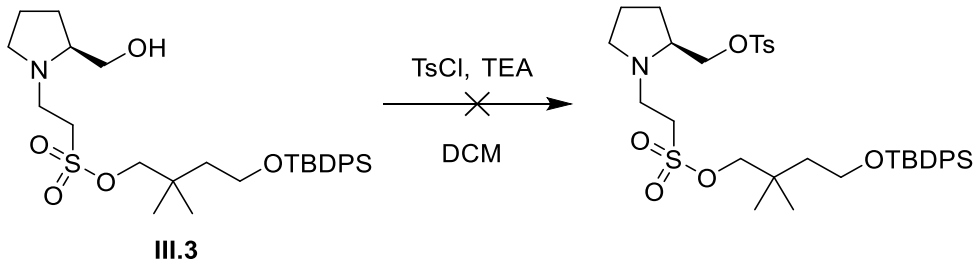
tolerated. Somewhat surprising was the lack of an example containing a proline derivative, which was the reason for testing the model system. Completing the synthesis with the model system would grant access to *des*-guanidinyl-*des*-hydroxyl nagelamide M. This compound would be desirable in establishing an SAR for these molecules, but also for establishing conditions to repeating the route with **III.1**, an intermediate that is more difficult to prepare.

Figure 3.2: Successful Reaction of a Model System and the Desired Reaction



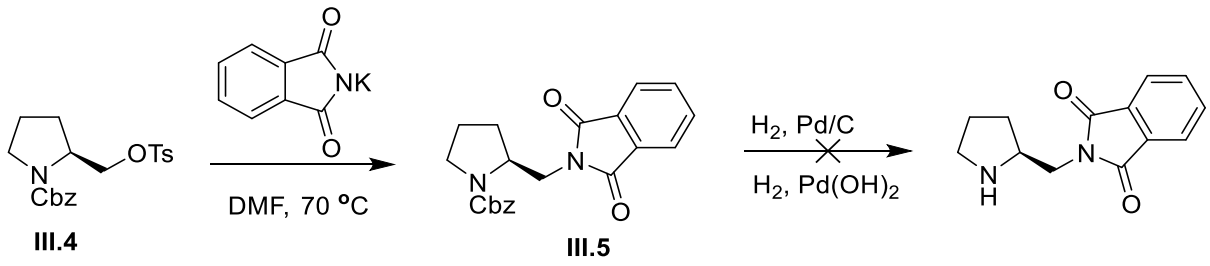
The attempted conversion of the prolinol to the *O*-tosylate (for subsequent nitrogenation) yielded only decomposition. The reason for this remain unclear as the conditions were mild, however the failure of this reaction established the need to convert the primary hydroxyl group to the protected amine before the conjugate addition step.

Figure 3.3: Failed Tosylation of the Primary Alcohol in Compound III.3



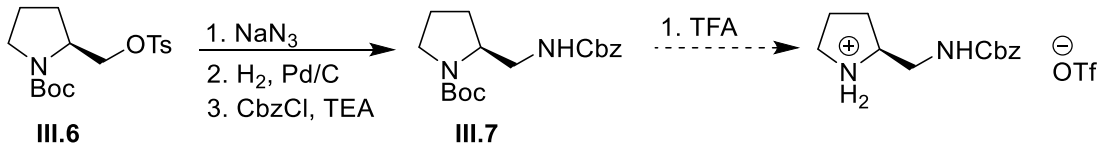
This result prompted the first attempt at the synthesis of a protected pyrrolidin-2-ylmethanamine. Commercially available benzyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate was tosylated and reacted with potassium phthalimide (Figure 3.4) to yield the bis-*N*-protected proline synthon. Reductive cleavage of the Cbz group failed under various hydrogenolytic conditions, necessitating a redesign in the route. The reason for the failure of this reaction is not immediately apparent; speculatively the conjugate acid generated in these conditions, TEA-HCl, could be acidic enough to catalyze the reverse reaction of the conjugate addition, but no direct evidence was obtained for this (the only observed products were decomposed unidentifiaby). The protecting group was changed from Cbz to Boc, as the rest of the molecule is expected to be stable to acidic conditions.

Figure 3.4: First Attempt at the Synthesis Prolinyl-Methanamine Core



Starting from commercially available (*S*)-pyrrolidin-2-ylmethanol the desired compound was obtained by Boc-protection and *O*-tosylation. The tosyl group was displaced with sodium azide, which was reduced to the amine with hydrogen and palladium. The Boc-group on the orthogonally protected proline core could be selectively deprotected with heat or acid, but this molecule was not completed due to the discovered negative impact of the methanamine on the SAR (such analogs are biologically inactive as shown in Figure 3.11).

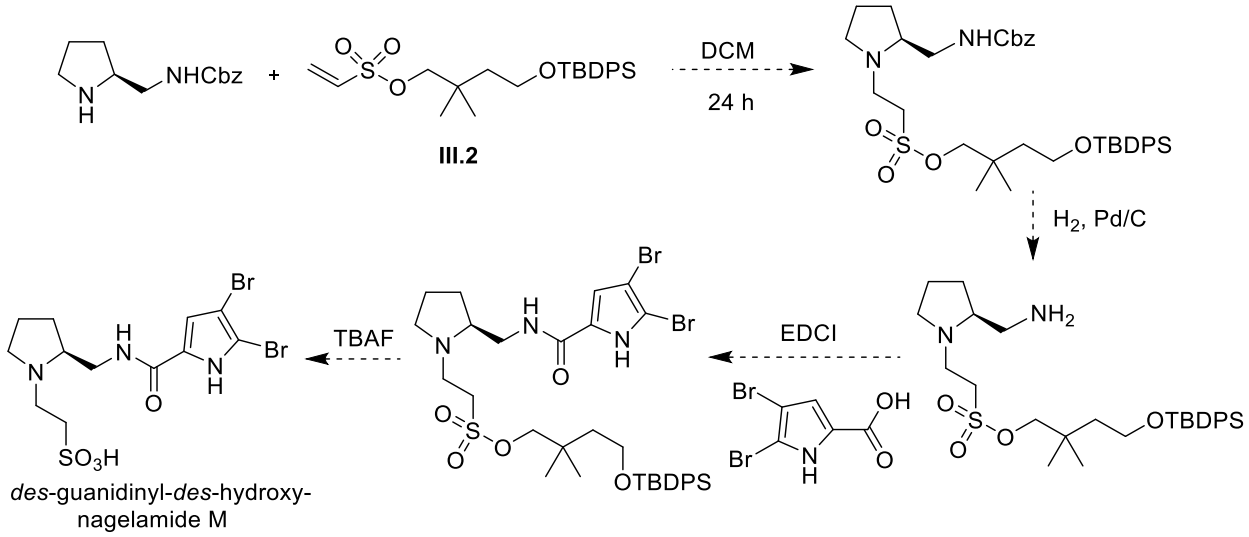
Figure 3.5: Second Synthesis of Prolinyl-methanamine Core



The proposed completion of the route is shown in Figure 3.6 below. After selective Boc-group removal the proline free base could be reacted with the vinyl sulfone to generate the protected taurine synthon. Hydrogenolysis of the Cbz-protecting group would likely reveal the primary amine. Coupling the amine to the carboxylic acid would likely require optimization, ideally beginning with neutral conditions. TBAF could be used to remove the silyl group revealing the sulfonic acid which could be purified by ion exchange chromatography.

While the biological effect of the ethanesulfonic acid moiety in this system has not been

Figure 3.6: Proposed Completion of the Synthesis Using the Model Compound

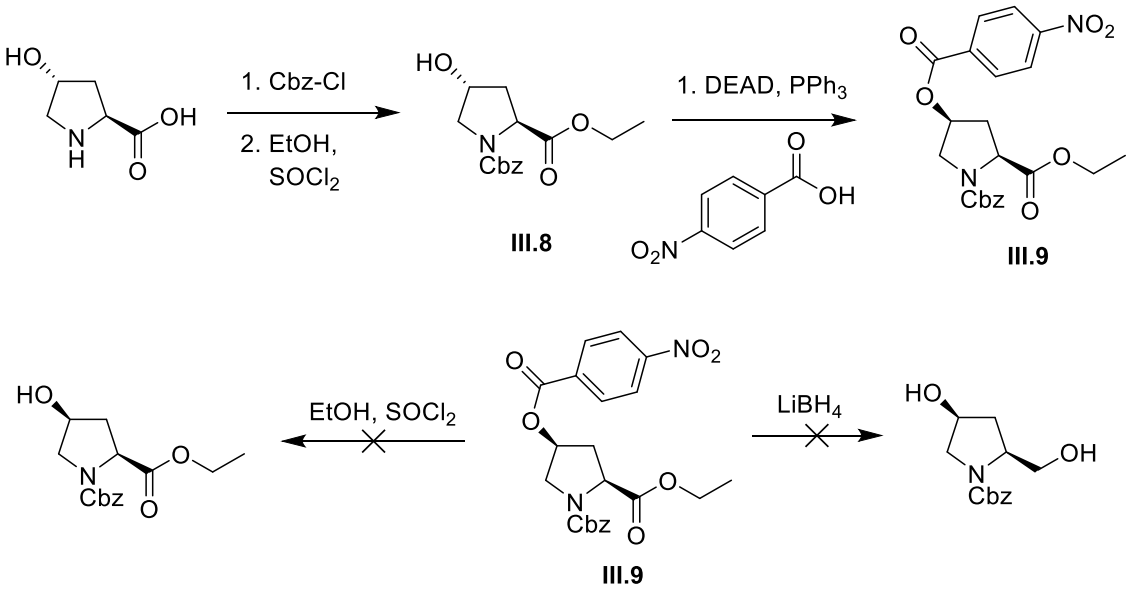


determined, experimental evidence suggests the bromopyrrole has a negative effect on biological activity. If the ethanesulfonic acid promotes biological activity, a different group could be attached as a side chain (Figure 3.11).

The preparation of the *cis*-hydroxy proline is detailed in the scheme below. Initially, the

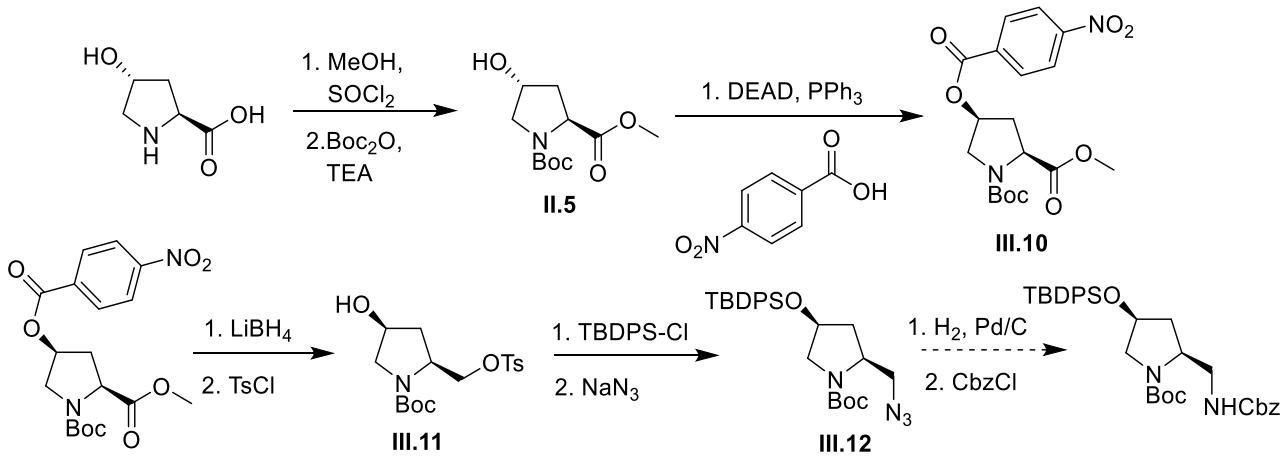
nitrogen was Cbz protected and the carboxylic acid esterified before the Mistunobu inversion of the C-4 stereocenter.[92] The Cbz-group was chosen because of its stability to acid, with the thought of subsequent selective hydrolysis of the nitro-benzoate ester. Such an approach would allow for orthogonal differentiation of the hydroxyl groups in **III.9**, rather than relying on differentiation from degree of substitution. Surprisingly, **III.9** was resistant to hydrolysis

Figure 3.7: First Synthesis of the Protected *cis*-hydroxy Proline III.9



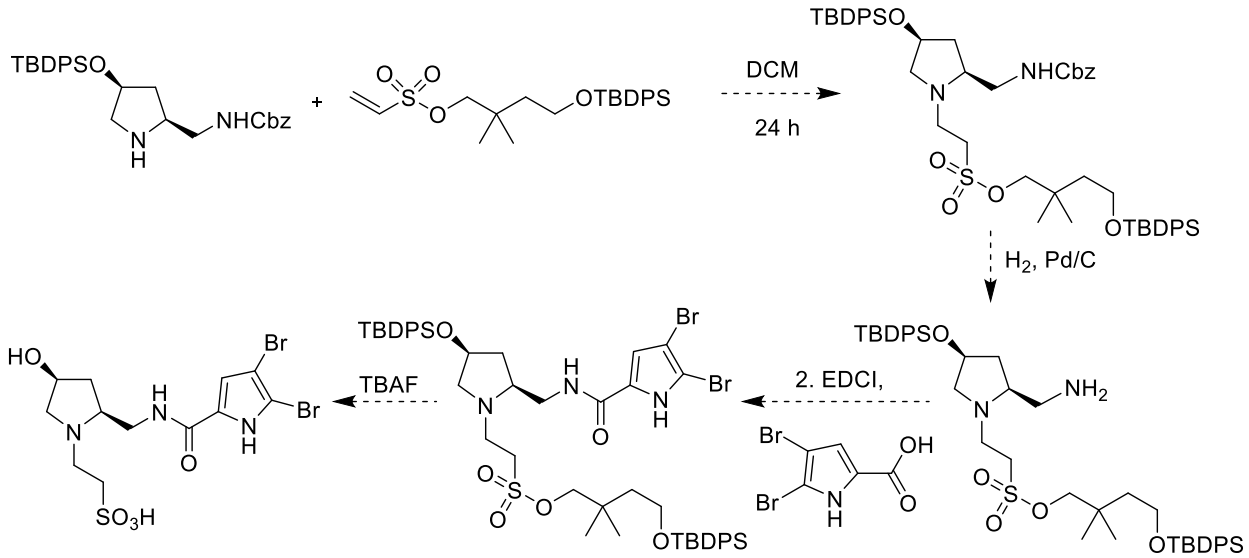
(starting material was recovered, in addition to a small amount of decomposed material) of the benzoate ester and reduction of the *bis*-ester with lithium borohydride (decomposition). The failure of these reactions may be rooted in the Cbz-protecting group, so this sequence was modified to incorporate the *N*-Boc protected variant[91] of *trans*-4-hydroxy-*L*-proline.

Figure 3.8: Proposed Completion of Synthesis of *O*-Protected III.1



The synthesis of the *des*-guanidinyl nagelamide M core was discontinued at the point of the azide (compound **III.12**) due to the discovered negative biological impact of having a nitrogen at that position. Some of the structures accessed on the way to this structure may find use as components of other molecules, guided by the newly obtained SAR data; these possibilities are explored in Figure 3.12. A proposed completion of the route to the original *des*-nagelamide M is shown in Figure 3.9.

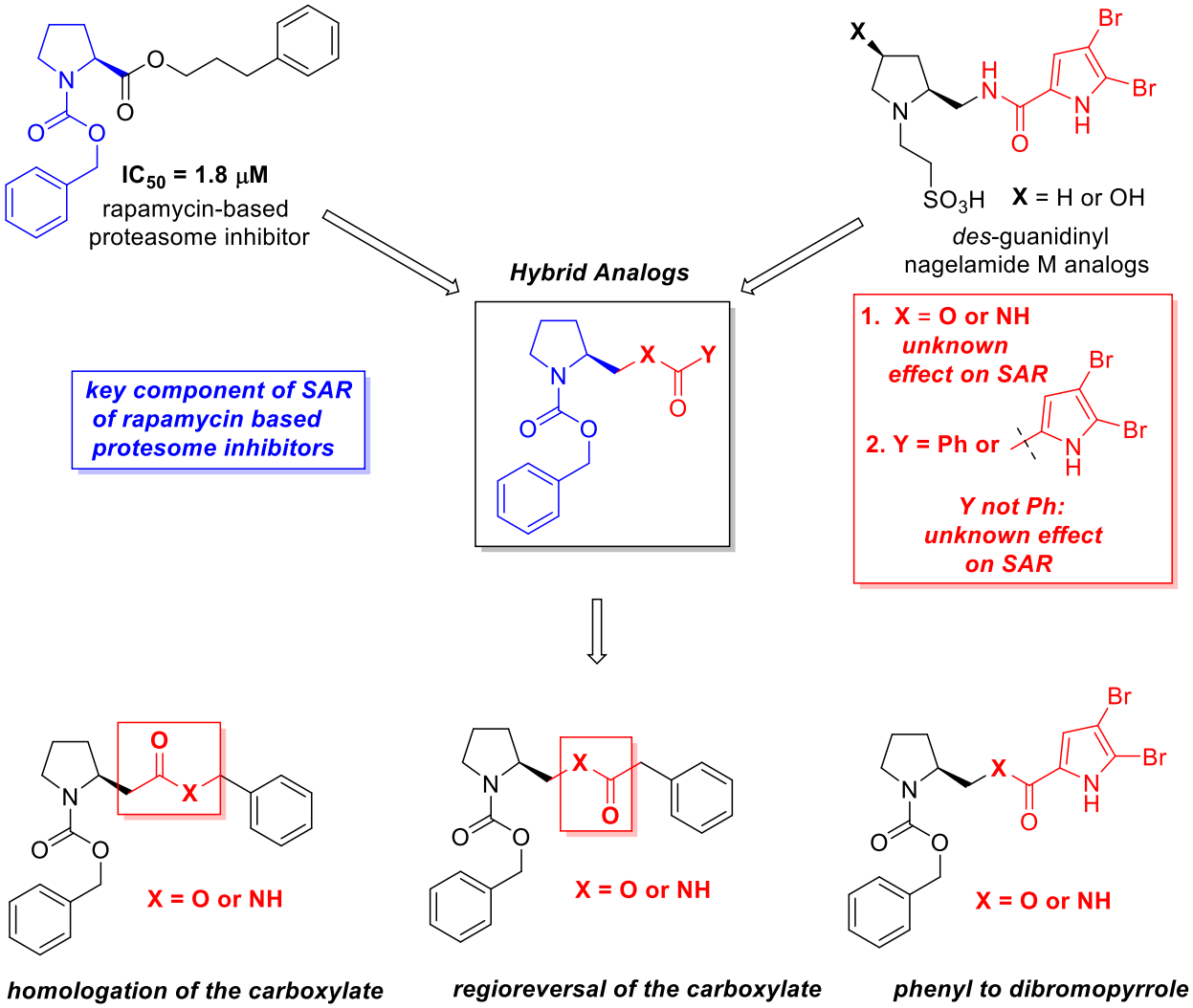
Figure 3.9: Proposed Completion of *Des*-Guanidinyl Nagelamide M



Whether or not molecules of the *des*-guanidinyl nagelamide M series will possess

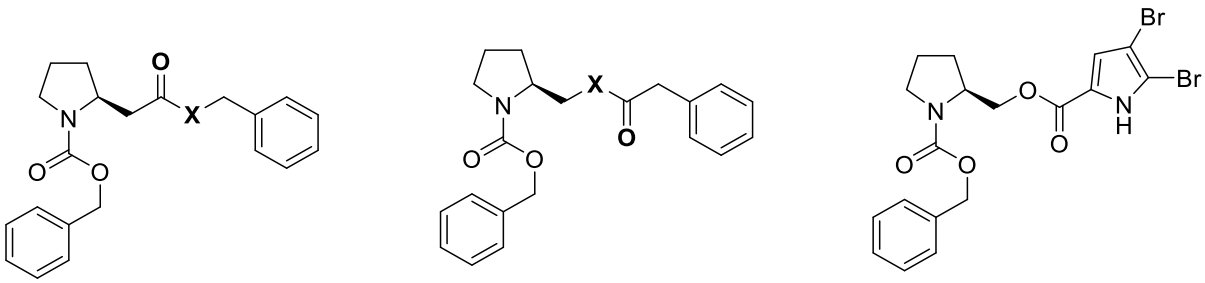
biological activity against the proteasome can only be determined by experiment, but other inquiries into the SAR of these compounds can be made. Comparing molecules of the *des*-guanidinyl nagelamide M series to known inhibitors of the proteasome based on the natural product rapamycin (discussed in Chapter 6), some similarities are observed that can be capitalized on. The key features of the *des*-guanidinyl nagelamide M analogs are the ethanesulfonate moiety and the dibromopyrrole moiety. It would be illuminating to isolate these features synthetically and test the biological activity of analogs containing only one variation, or analogs containing one variation from compounds of known activity. Such a study would reveal the importance of each structural change and most completely define the SAR.

Figure 3.10: Nagelamide/Rapamycin Hybrid Analogs



The proposed analogs were synthesized and tested for biological activity (results shown in Figure 3.11). The amide analogs **III.14** and **III.16** were inactive in proteasome inhibition assays, as was the dibromopyrrole **III.17**, shown in Figure 3.11. Consequently, the coupling reaction of benzyl (*S*)-2-(aminomethyl) pyrrolidine-1-carboxylate and 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid was not attempted, as the additive effect of two non-productive modifications was not expected to be productive. The ester analogs were active, and the most active, **III.15**, was chosen for further development.

Figure 3.11: Biological Activity of Nagelamide/Rapamycin Analog Hybrids



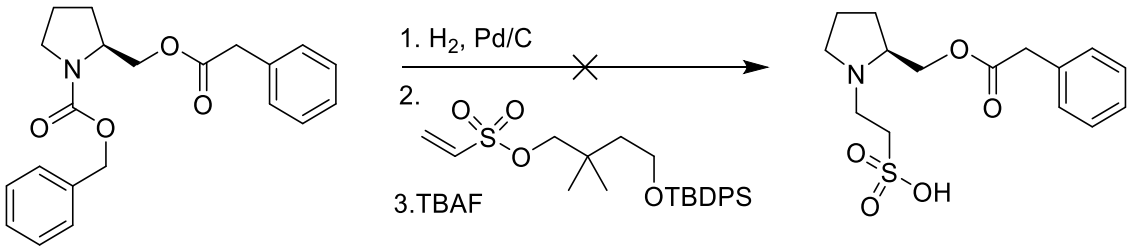
X = O, III.13 IC_{50} = 5 μM
X = NH, III.14 IC_{50} > 25 μM

X = **O, III.15** IC_{50} = 3 μM
X = **NH, III.16** IC_{50} > 25 μM

III.17 IC_{50} > 25 μM

The influence of the ethanesulfonate on the SAR could be explored in the same way, using the most active molecule from Figure 3.11. Potential routes to second-generation nagelamide/rapamycin sulfonate analogs are outlined in Figure 3.12 below.

Figure 3.12: Proposed Synthesis of Sulfonate Analogs of Nagelamide/Rapamycin Hybrids

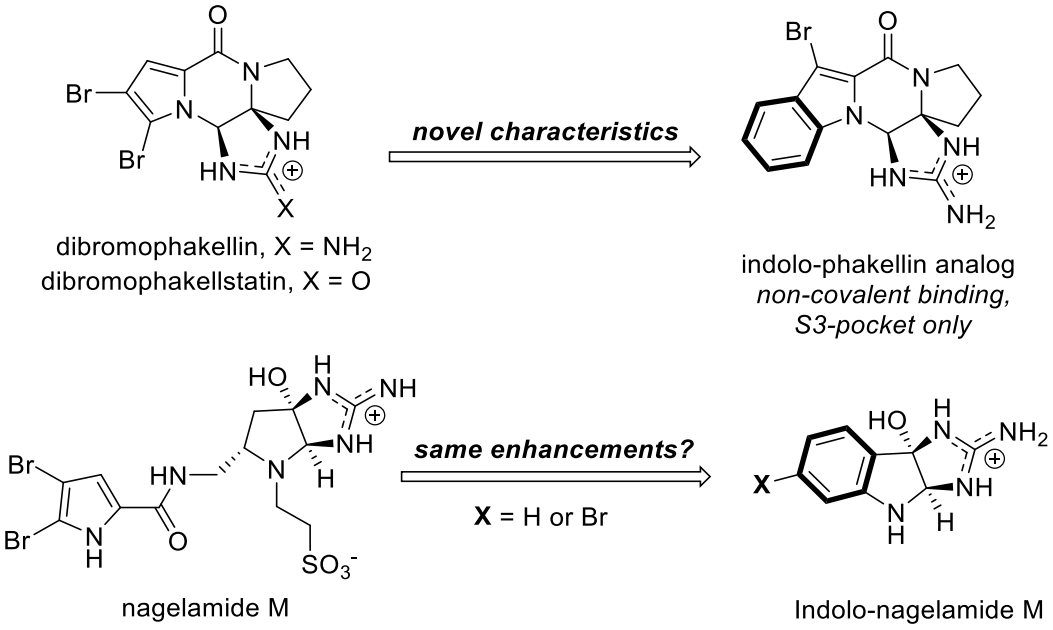


Removal of the Cbz-group was successful (and the product amine was fully characterized, **III.18**) but the conjugate addition step was not, yielding only starting materials. Standard variations to improve yield in conjugate addition reactions (adding excess nucleophile, using heat) did nothing to influence the yield.

Chapter 4: Studies on the Aminohydroxylaton of Indoles

A parallel line of research was initiated to study the oxidative functionalization of indoles, as the desired [5.5] ring appended to a benzene ring would also be of interest as a proteasome inhibitor, and the literature surrounding this transformation is more plentiful than the C-H amination of methylene C-H bonds previously attempted. Many of the shortcomings encountered using a 2,3-dihydropyrrole as a substrate would not apply to an indole, rendering the intramolecular approach shown in Chapter 1, Figure 5 potentially viable on a 3-amino indole substrate.

Figure 4.1: Desired Indole Analogs

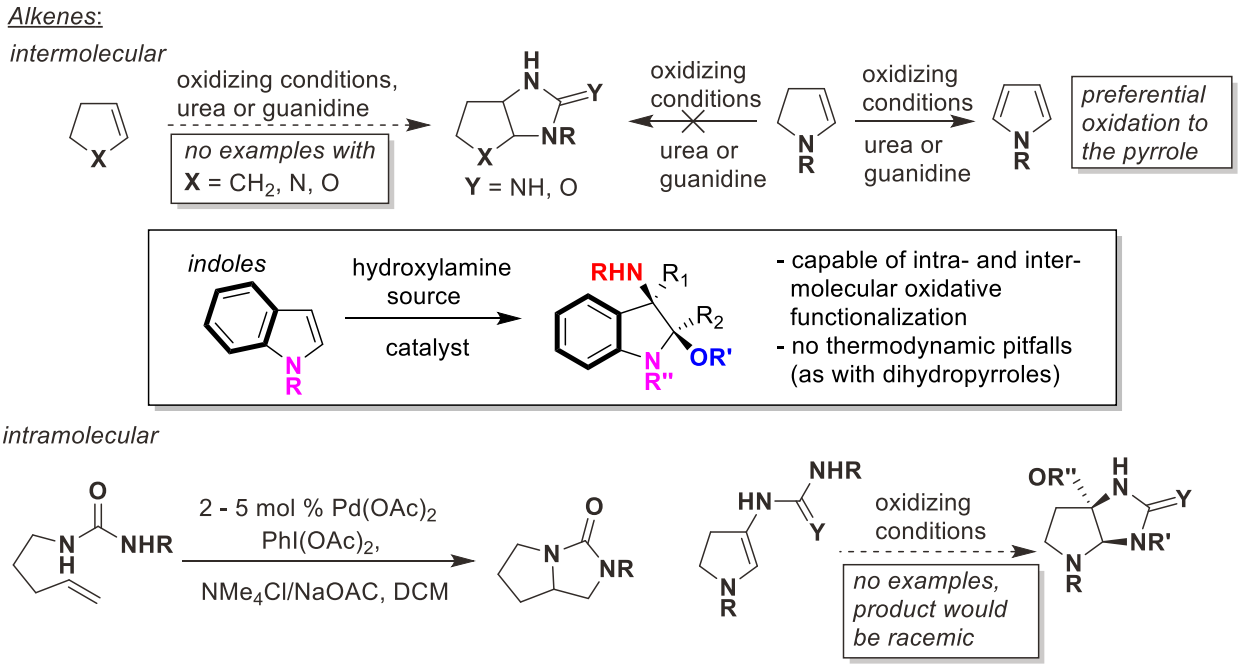


In terms of inhibitor design, a bromine in the 6-position on this indole would place it in a similar location to that of the bromine in indolo-phakellin,[8] and consequently would be expected to contribute to the binding interaction. If the route was successful, it could be readily altered to include a 6-bromo derivative.

The fundamental transformation desired in this system is the aminohydroxylation of an

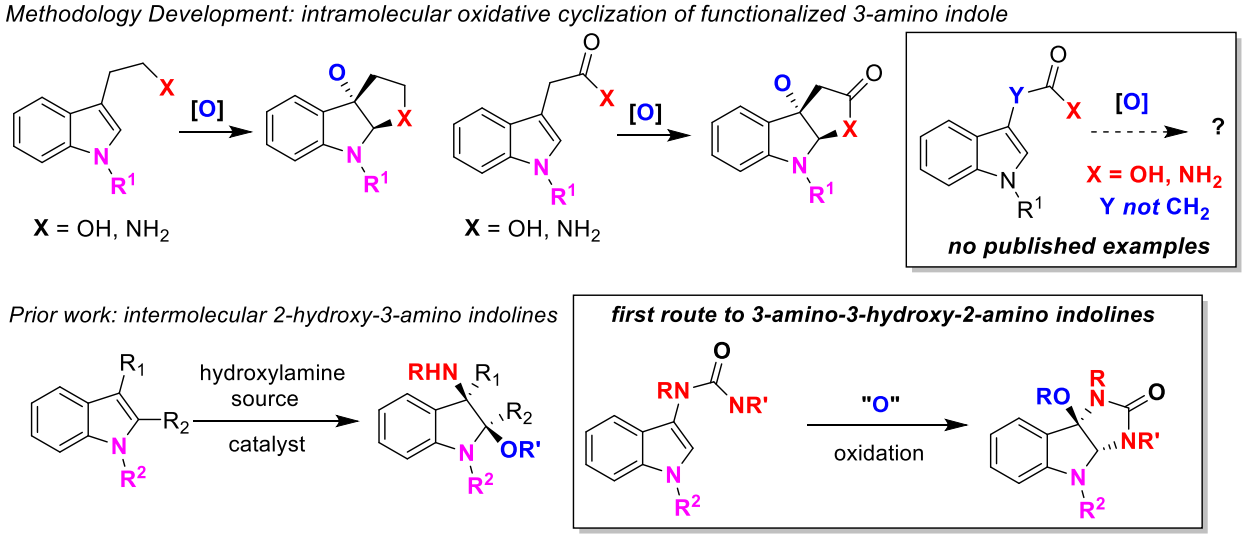
indole, with a urea nitrogen acting as the amine source. Using urea as an amine source is not thought to be an obstacle, since they have been used successfully in the intermolecular diamination of alkenes.[12] While the literature is replete with examples of the aminohydroxylation of alkenes[103] there are relatively few such examples on indoles.[104-110]

Figure 4.2: The Desirable Qualities of Indoles in Oxidative Functionalization



All of these examples give 2-hydroxy-3-amino indoles, which is the opposite of the required substitution pattern. The success of this transformation would constitute the development of a new methodology that offers the opposite regiochemical outcome compared to the previous examples. The indole **IV.2** (R, R^2 = H, R^1 = Bn, Figure 4.2 and 4.4) was synthesized as a substrate for oxidation followed by intramolecular cyclization (Figure 4.3).

Figure 4.3: Proposed Regio-Reversed Aminohydroxylation of Indoles via a Novel Substrate



From the commercially available methyl indole-3-carboxylate the product **IV.2** was synthesized and the structure was confirmed by X-ray crystallography. Extensive studies on the oxidative functionalization of this substrate were conducted, the results of which are shown in Table 4.1. The conditions screened mostly resulted in decomposition, but some unexpected reactivity was observed in certain instances.

Figure 4.4: Synthesis of the Indole Precursor

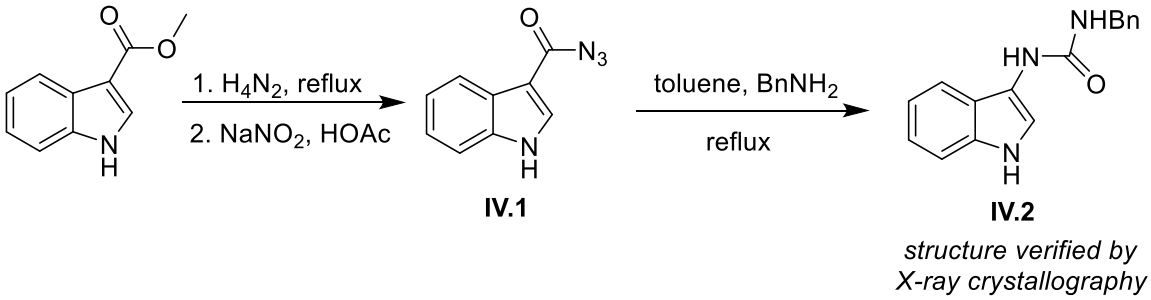
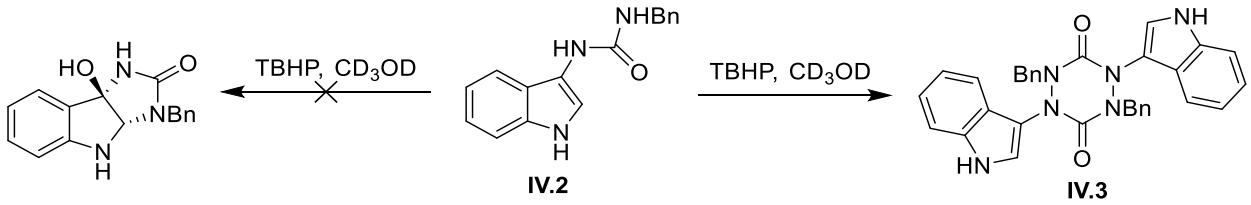


Table 4.1: Screen of Conditions for Oxidatizing IV.2

reactant	solvent	oxidant	result
0.6 mmol **IV.2**	CD_3OD	NBS	decomposition
0.6 mmol **IV.2**	CD_3OD	*m*CPBA	decomposition
0.6 mmol **IV.2**	CD_3OD	*Tert*-butyl hydroperoxide	precipitate
0.6 mmol **IV.2**	CD_3OD	NCS	inert
0.6 mmol **IV.2**	CD_3OD	Cat. H_2SO_4	inert
0.6 mmol **IV.2**	CD_3OD	Palau'chlor (**IV.3a)**	decomposition
0.6 mmol **IV.2**	CD_3OD	d_3 TFA	decomposition
0.6 mmol **IV.2**	CD_3OD	SAE	decomposition
0.6 mmol **IV.2**	CD_3OD	DMDO	inert
0.6 mmol **IV.2**	CD_3OD	oxaziridine	decomposition
0.6 mmol **IV.2**	CD_3OD	Bromine in CD_3OD	inert
0.6 mmol **IV.2**	CD_3OD	Bromine in HOAc	inert
0.6 mmol **IV.2**	CD_3OD	$TcesNH_2$, $Rh_2(esp)_2$, $PhI(OAc)_2$	inert
0.6 mmol **IV.2**	CD_3OD	OsO_4, NMO	inert

Of note was the product observed with the reaction of **IV.2** with TBHP in methanol. A precipitate was formed that was putatively identified as urazine **IV.3**.[79] This assignment was made based on the highly symmetric ^1H NMR spectrum and HRMS data effectively gave a mass of [M-2], which correlates with [M-H] for **IV.3** fragmented as *N*-benzyl-*N*-indolyl urea.

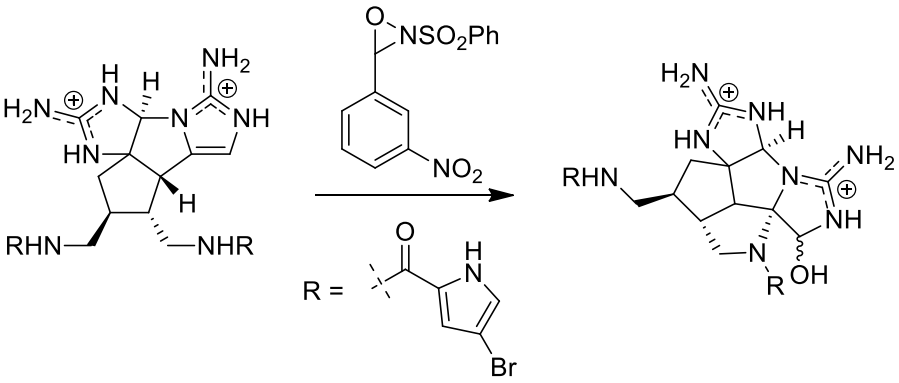
Figure 4.5: An Unexpected Urazine Synthesis



Attempts to repeat the experiment were unsuccessful, precluding complete characterization.

In a search of the literature for instructive examples as to how to proceed, the total synthesis of agliferin from the Harran group[111] indicated a similar transformation had been performed using a Davis oxaziridine on a 2-aminoimidazole ring, with the amide nitrogen acting

Figure 4.6: Sulfonyloxaziridine-Mediated Oxidative Cyclization of a Precursor to Agliferin

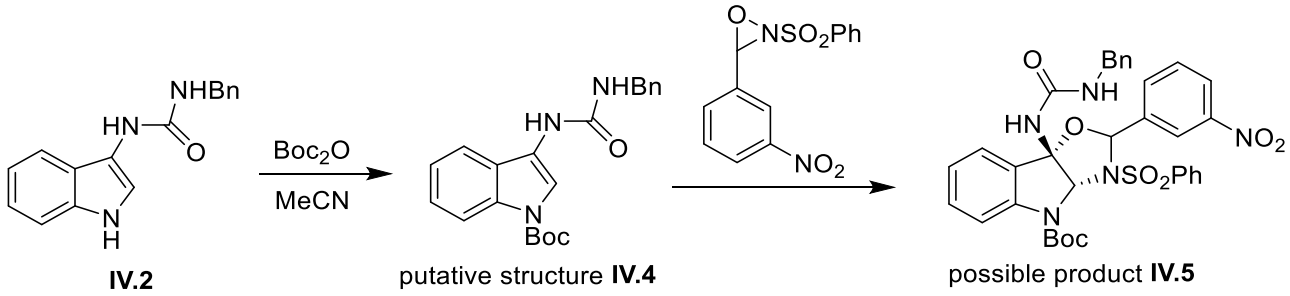


as a nucleophile. The indole **IV.2** did indeed react with the nitro-oxaziridine, however no products were isolable from the reaction mixture. Indications of product formation were obtained in the form of ^{1}H NMR (disappearance of C-H signals from C2 and C3 on the indole ring).

Taken this example in addition to the success the Dauben group[109] reported in the oxidative functionalization of indoles with electron withdrawing protecting groups on the indole nitrogen (Figure 4.8), it was thought installing such a group might tune the reactivity of the C2-C3 alkene to allow for the desired oxidation to occur. The Boc group was chosen for its electron withdrawing character in addition to its likely ability to increase the solubility of the substrate.

As the conditions for early *N*-Boc protection of the indole nitrogen were too harsh for its survival to the end urea, the Boc protection was attempted on the indole **IV.2**. A small amount of product was obtained, and assigned the structure **IV.4**. The assignment was tentative, as the location of *N*-Boc protection is most likely the indole nitrogen, this was not independently verifiable. When the *N*-Boc indole **IV.4** was reacted with the nitro-oxaziridine in d_4-CD_3OD, a solid precipitated out of the reaction mixture. This was isolated and redissolved in d_6-DMSO. It was pure enough

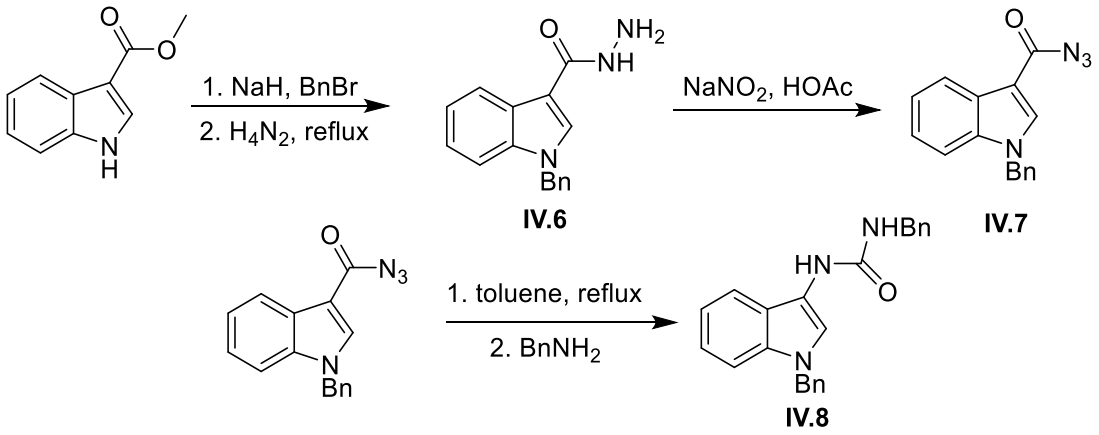
Figure 4.7: Attempted Oxidative Cyclization Indolyl-Urea IV.2



to be subjected to useful analysis, and a tentative structure **IV.5** was assigned (Figure 4.7). The Boc- protected urea was not stable to purification and the synthesis was not reproducible; consequently the reaction could not be repeated.

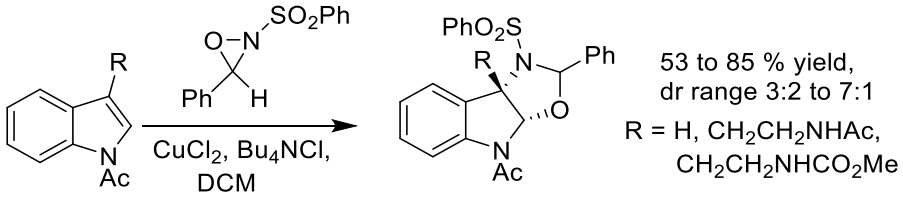
Similar difficulties were encountered when preparing *N*-benzoyl or *N*-tosyl derivatives (which underwent deprotection during hydrazine installation). While not an electron withdrawing group, an *N*-benzyl derivative **IV.8** shown in Figure 4.8 was successfully prepared on a gram scale in the hope that, once reacted with the nitro-oxaziridine, the reaction would again be successful and the presence of *N*-benzyl group would render the products isolable.

Figure 4.8: Synthesis of *N*-Benzyl Indole IV.8



During these studies another reference was discovered involving the copper (II) catalyzed oxyamidation of indoles with sulfonyloxaziridines.[108] There are marked differences between the examples and the system in question (no examples included a nitrogen at the 3-position on the indole, and the benzyl group is not electron withdrawing like the acetate), but copper catalysis might offer a solution to this problem. Under the same conditions the indolyl-urea **IV.2** yielded degradation products.

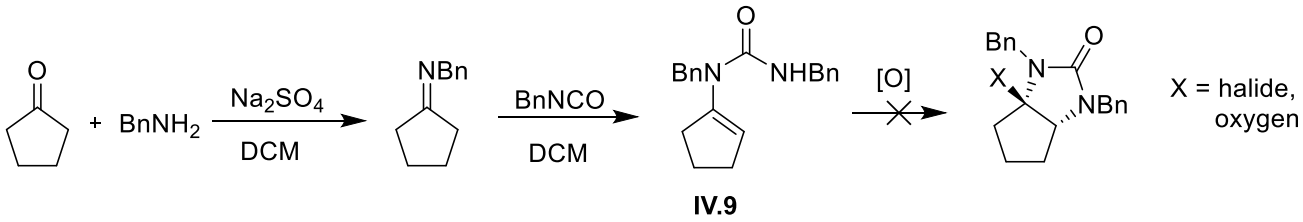
Figure 4.9: Copper(II) Catalyzed Oxyamidation of Indoles With a Sulfonyloxaziridine



The failure of the indole-urea reaction manifold to yield any information (or product) whatsoever was highly unsatisfying considering the extensive literature precedent for related systems.[104-110] To investigate the effect of the ring nitrogen atom α to the alkene, the alkenyl urea **IV.9** shown in Figure 4.10 was designed and synthesized. The alkenyl urea was subjected to the same battery of oxidative conditions as the indole urea **IV.2** above, all of which yielded only decomposition. In contrast to the indole urea, the alkenyl urea was not stable to storage or

purification through column chromatography.

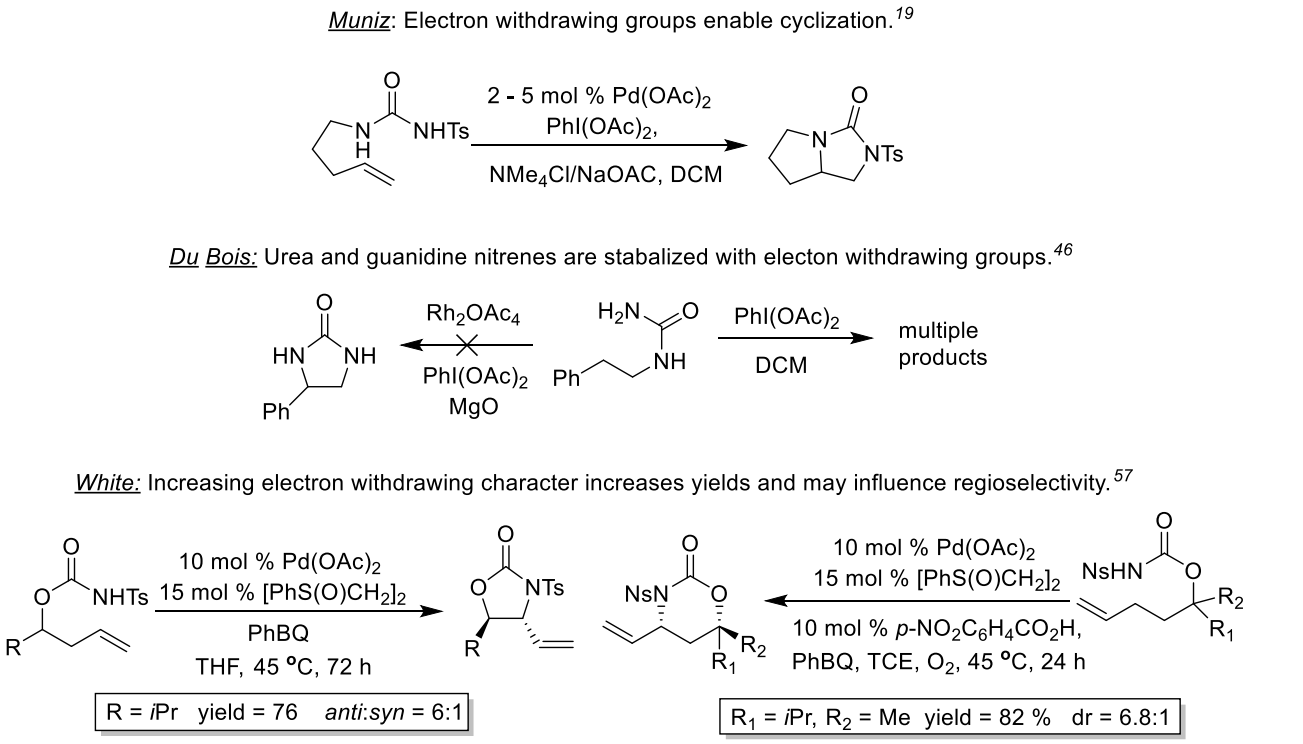
Figure 4.10: Cyclopentenyl Urea Model for Oxidative Cyclization



IV.9

This system was, however, more directly comparable to other systems and all successful examples had an electron withdrawing group at the nitrogen involved in the cyclization (Figure 4.10). When considered alongside the Du Bois work, the need for electronic deactivation of urea's and guanidine's emerges as the deciding factor in successfully manipulating these groups (Figure 4.11).[53]

Figure 4.11: Need for Electron Withdrawing Groups on Nitrene Precursors



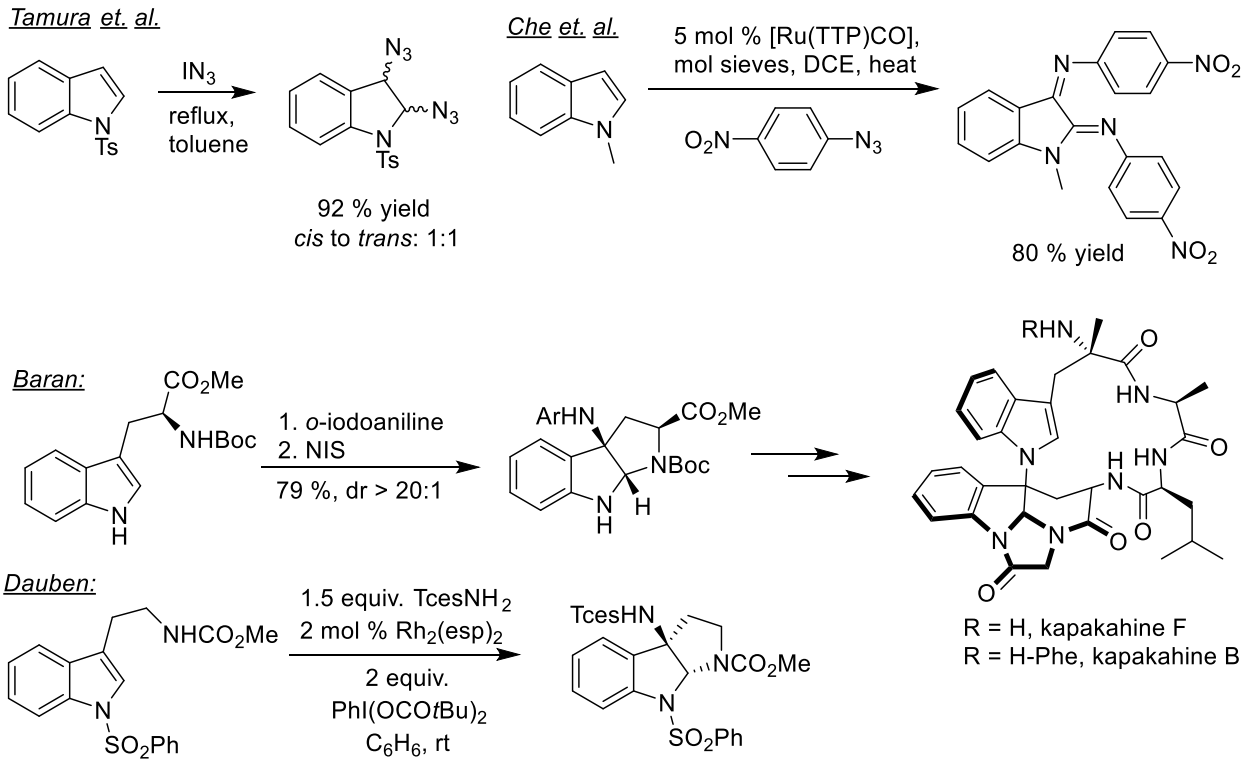
At this point the focus of the project was turned to the diamination of indoles.

Chapter 5: Studies on the Diamination of Indoles

It was thought that simplifying the target from Indolo-nagelamide M to a dehydroxy analog might make for a more accessable target. The diamination of an indole would be required to synthesize this new target, *des*-hydroxyl-Indolo-nagelamide M.

The related intermolecular diamination of indoles is rare (either inter- or intramolecular). Two close examples are given[112,113] of the 2,3-diazidation of *N*-tosyl indole, however neither reported transformation to the 2,3-diamine. The diimidation of indole has been reported,[114] but otherwise these structures are synthesized by intramolecular oxidative cyclization.

Figure 5.1: The Oxidative 2,3-Diamination of Indoles

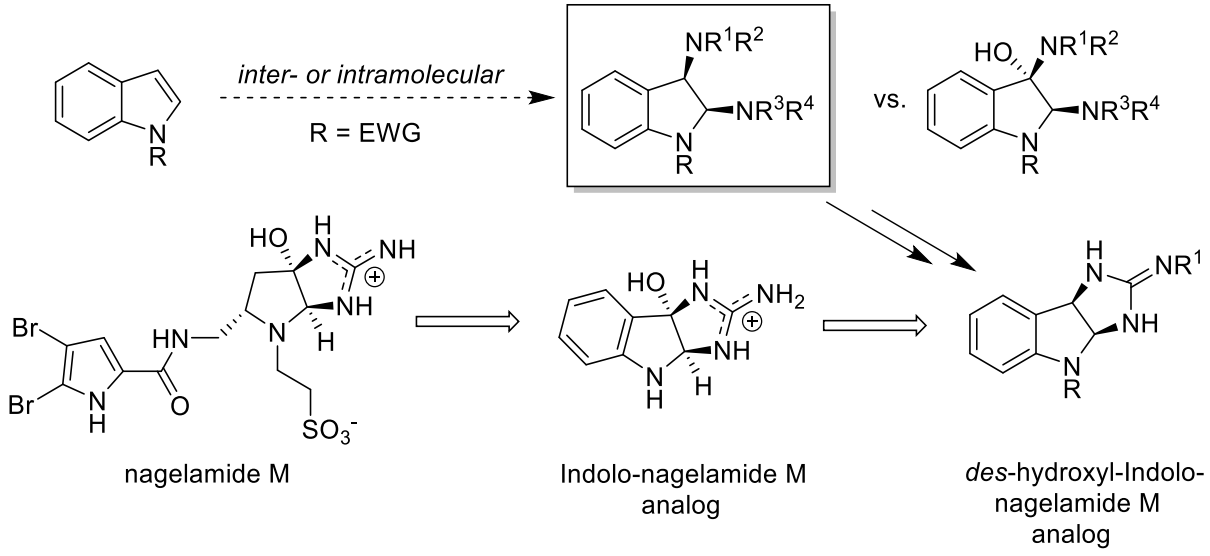


In addition to the precedent for aminohydroxylations, suitably functionalized indoles are known to undergo cyclizations to form cyclotryptamines (Figure 5.1).[115,116] As discussed previously the direct diamination of indoles is rare, which is perhaps not surprising considering

the persistent lack of a solution for the general problem of the diamination of alkenes. The closest procedures for alkenes involve using masked diamines (like *tert*-butyl sulfaomylcarbamate). [124]

The rarity of diamination of indoles is contrasted with the comparatively large number of methods for the amino-hydroxylation of alkenes[103] and indoles.[110] Several of these involve the activation of an *N,O*-bond, followed by subsequent reaction with an alkene. The simple substitution of the *N,O*-substrate for an *N,N*-substrate in an otherwise identical system as a point of departure for the extension of the successful aminoydroxylation procedures to the yet-undiscovered general diamination procedures seems to suggest itself. In addition to contributing a solution to the diamination of indoles, these compounds could be transformed into analogs of biological interest.

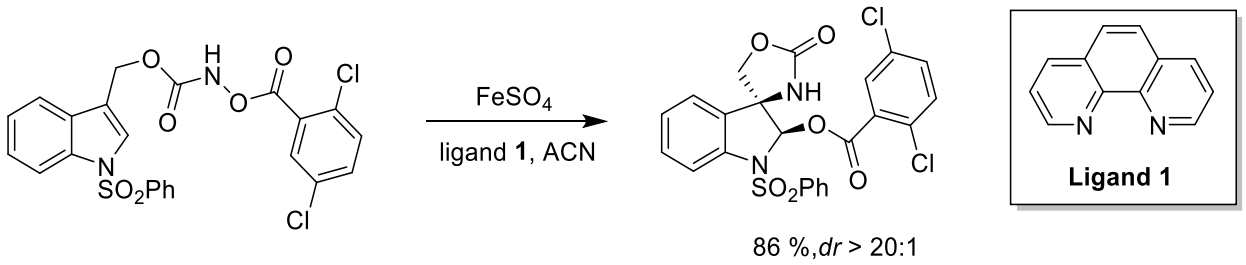
Figure 5.2: The Diamination of Indoles



The Xu group published methodology for the intramolecular aminohydroxylation of alkenes[103] and indoles[110] whose mechanistic rationale invokes an iron nitreneoid as a reactive intermediate. The tested substrate is shown in Figure 5.4. Having achieved synthetically useful

yields and *ee*'s, this system was chosen for modification in an attempt to achieve the diamination of indoles. The synthetic route to the aminohydroxylation substrates was easily modified to

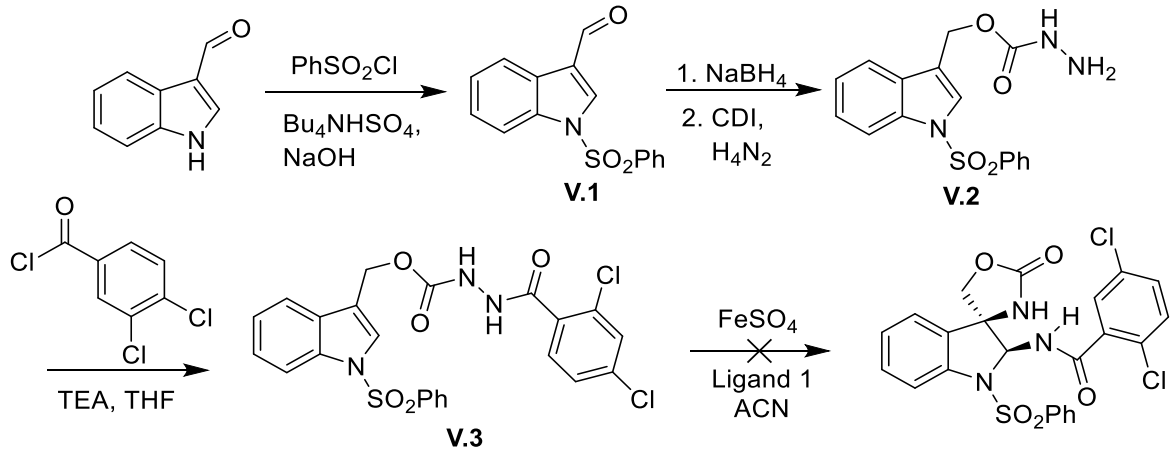
Figure 5.3: Xu's Methodology for the Aminohydroxylation of Alkenes/Indoles



synthesize the desired substrate, available on a gram-scale in four steps from commercially available indole-3-carboxaldehyde.[110]

When subjected to the same reaction conditions as the aminohydroxylation reaction (acetonitrile, 23°C, $Fe(OAc)_2$ and phenanthroline) no reaction was observed. This was a puzzling result, as the proposed mechanism (discussed below) defines the rate-determining step as reductive cleavage of the *N*,*O*-bond, which based on bond dissociation energies should be approximately as labile as the *N*,*N*-bond.[117]

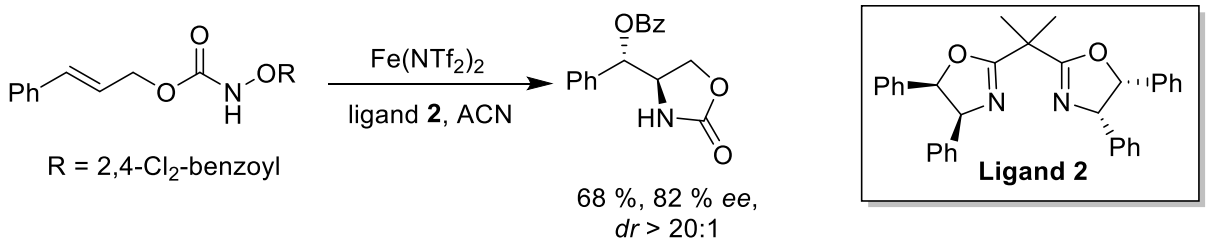
Figure 5.4: Synthesis of a Diamination Precursor



Mechanistic insight into this process are derived from the enantioselective reaction using

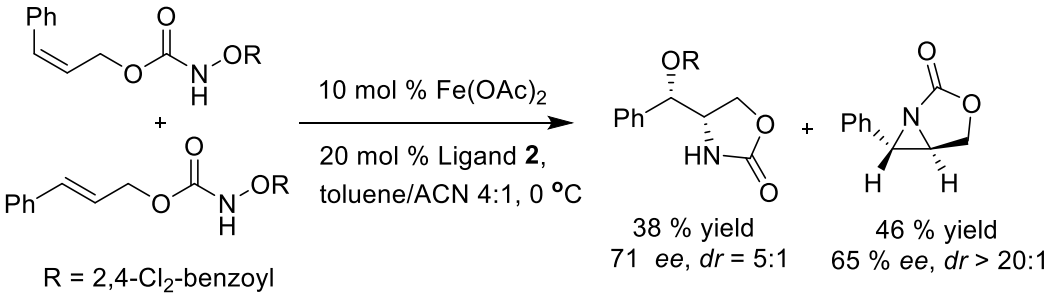
alkenes as a substrates, and is useful in pondering the failure of this reaction. While the above

Figure 5.5: Xu's Asymmetric Intramolecular Amiohydroxylation of Alkenes



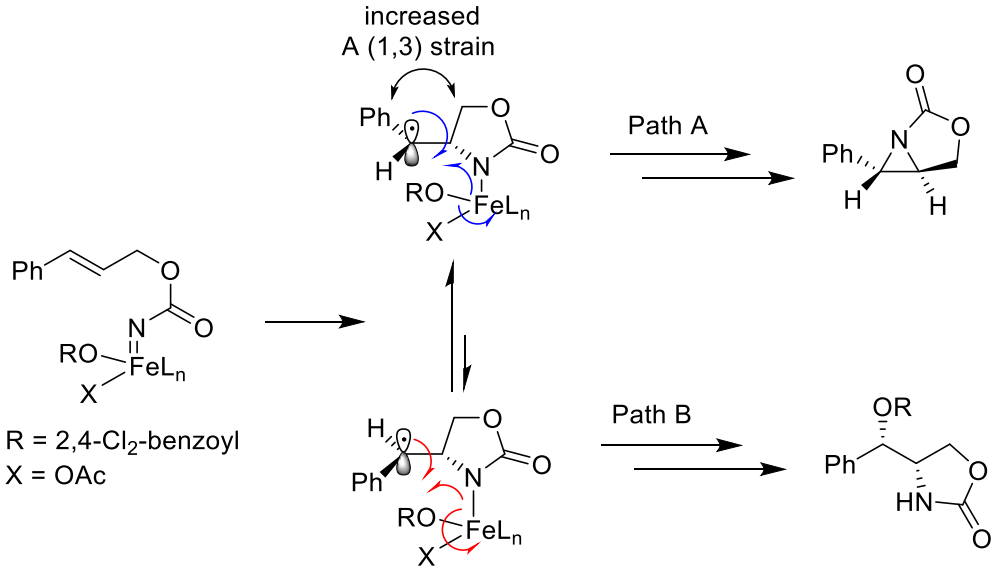
reaction is an enantioselective recitation of the same process with indoles, a new feature was elucidated in the study of this system. Using a mixture of the *cis* and *trans* olefins shown in Figure 5.5 (and the same chiral ligand **2**), two products were observed: one a stereoconvergent aminohydroxylation of the alkene and the other an aziridine (Figure 5.6). The sense of enantioinduction of the two products is the same, and they were not observed to interconvert under the reaction conditions. These results suggest two mechanistic possibilities, after reductive cleavage of the *N-O* bond a radical transfer process might operate (either through a Kharasch-

Figure 5.6: Stereoconvergent Aminohydroxylation of Olefins



type process or an iron nitrene), to form the oxazolidine ring and give the phenyl group time to isomerize. The distribution of final products are envisioned to originate from the favorability between radical recombination with the -OR group (presumably still appended to the iron ligand), or reductive elimination of the iron complex with recombination of the nascent nitrogen radical with the benzyl radical from the initial *N-O* cleavage. This is noteworthy to the discussion

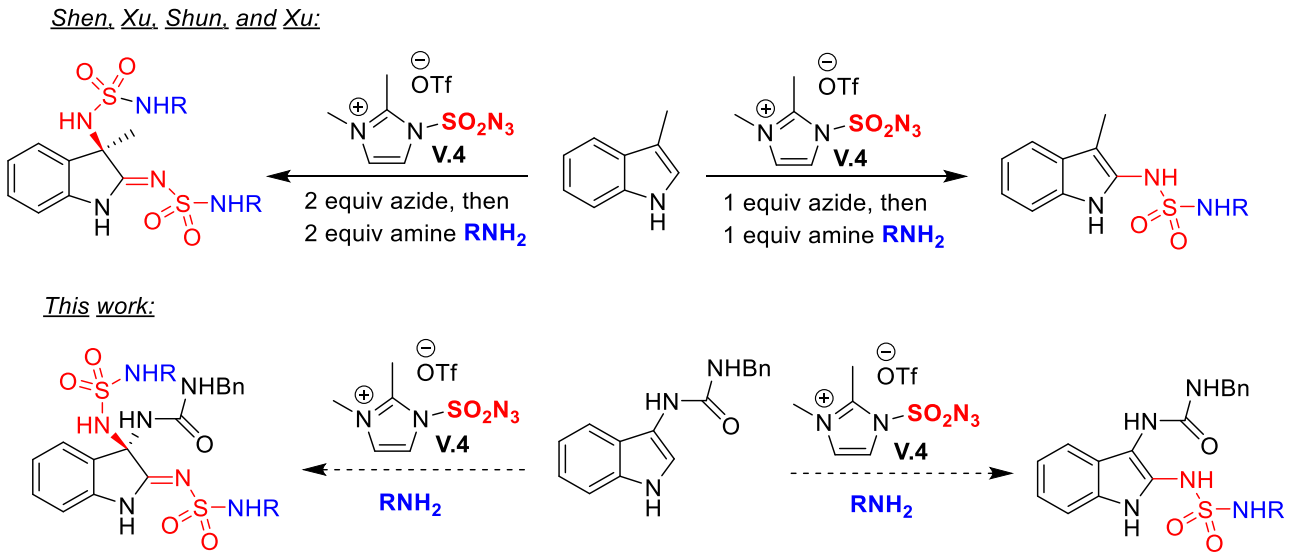
Figure 5.7: Proposed Mechanism for the Iron Nitrene Pathway



because the rhodium nitrenes studies previously do not exhibit these characteristics (i.e. Rh nitrenes react to give stereospecific products, iron nitrenes react to give stereoconvergent products). If the proposed mechanism is correct and the initial step is *N*,*O*-bond cleavage, the failure of this reaction is puzzling as the *N*,*N*-bond is considerably weaker than the *N*,*O*-bond (55 kcal/mol versus 38 kcal/mol respectively).[117]

It was thought changing the nature of the target from the starting indole might be a more effective approach, specifically exploring the oxidation of indoles to iminoindolines (which could be subsequently transformed into the desired intermediates en route to *des*-hydroxy-Indolo-nagelamide M). A method for achieving this transformation was recently disclosed using a sulfonyl azide (Figure 5.8). The reaction is believed to proceed through a cycloaddition of the azide with the alkene, followed by nitrogen extrusion to an aziridine which undergoes ring opening via a 1,2-hydride shift. Nearly all the examples were 3-alkyl substituted, however when indole and *N*-methylindole were reacted with an excess of the sulfonyl azide, the bis-imide was obtained (as the amidine-imide). The implication is the 3-alkyl group inhibits the reaction, and

Figure 5.8: 2,3-Dimethylimidazole-1-Sulfonyl Azide Triflate Functionalizing Indoles



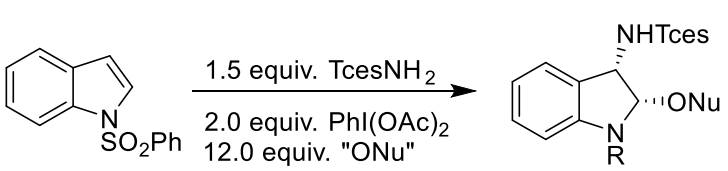
the sulfonyl azide might be reactive enough to overcome the inert nature of the indole urea.

If obtained, such a product could be manipulated to a desirable structure in several ways. Pyridine has been used to remove SO_2 from sulfonamides to reveal diamines,[14] which in this case would give the coveted 3-aminoindole motif. Alternatively the amidine could be reduced to the geminal diamine[122] and further functionalized (perhaps into a urea with an appropriately substituted isocyanate).[123] Under the published reaction conditions, the starting indolyl urea was inert.

Studies On the Intermolecular Diamination of Indoles

Initial studies in this area were inspired by work from the Dauben group in the amino-hydroxyation of *N*-protected indoles,[109] using a modified version of the Du Bois rhodium nitrene chemistry. The reaction was typically high yielding and tolerated functionality at the 3-position of the indole (not shown; unfortunately no examples including a heteroatom directly adjacent were disclosed). In the example with R = benzenesulfonyl and acetic acid as the nucleophile

Figure 5.9: Dauben's Intermolecular Oxyamidation of Indoles



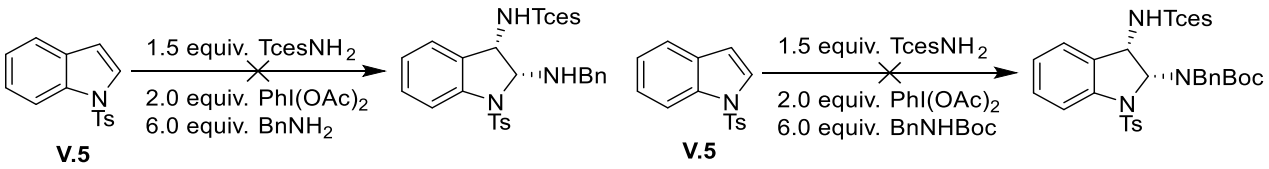
Nucleophile	yield
HOAc	76 %
*t*BuCO$_2$H	51 %
PhCO$_2$H	37 %

(which was successfully repeated by the author on the same scale and at the same yield to confirm the methodology), *syn* addition is the only product observed. This result was verified with X-ray crystallography, but no explanation for the stereochemistry was proposed.

As the starting materials were readily available, preliminary tests were conducted to extend this methodology to the diamination of indoles, simply by using an amine nucleophile instead of an oxygen based nucleophile. The first attempt, simply using benzyl amine in excess, did not lead to any product formation. Notably, the reaction mixture turned purple on the addition of benzyl amine.

In an attempt to modify the electronics of the nitrogen source and enable the reaction, *N*-Boc benzyl amine was synthesized and used as the excess nucleophile. While no purple color was observed, no reaction was observed either.

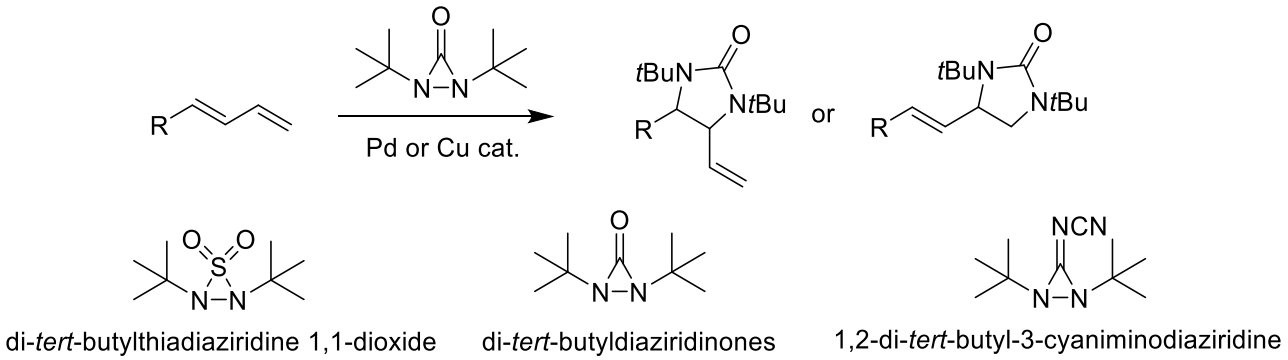
Figure 5.10: Attempted Extention to Diamination on Indoles



The Shi group at Colorado State University has developed a transition metal catalyzed methodology for the synthesis of diamines from alkenes using strained diaziridinones as a nitrogen source. The method favors dienes, which function to suppress β–hydride elimination, or if terminal aliphatic alkenes are used an internal alkene is generated through β–hydride elimination. This method provides access to the desired 1,2-diamine and to date has only been

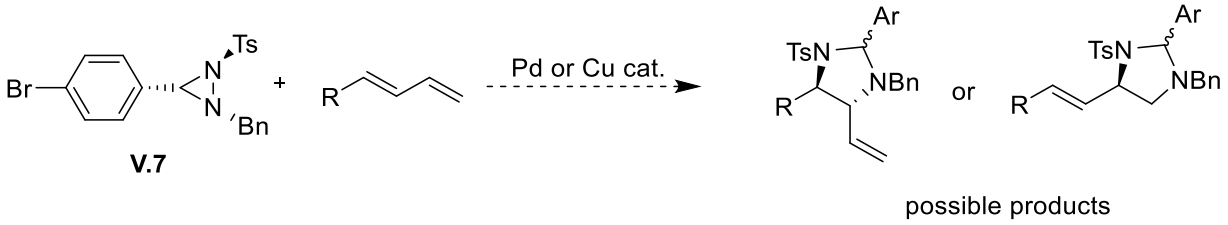
explored on the context of di-*tert*-butyldiaziridinones, di-*tert*-butylthiadiaziridine 1,1-dioxide, 1,2-di-*tert*-butyl-3-cyaniminodiaziridine derivative (as described in the Shi group's recent review).[124] If diaziridines were shown to possess similar reactivity in this manifold

Figure 5.11: The Shi Method for Diamination of Alkenes



such a discovery would constitute a significant advance in the methodology, as they inherently possess stereochemistry and the potential for transfer of this information to substrates would constitute a stereoselective diamination of alkenes. Their use in this methodology is conspicuously absent, in spite of their being strained heterocycles, presumably capable

Figure 5.12: Proposed Expansion of Shi Methodology to Include Diaziridines

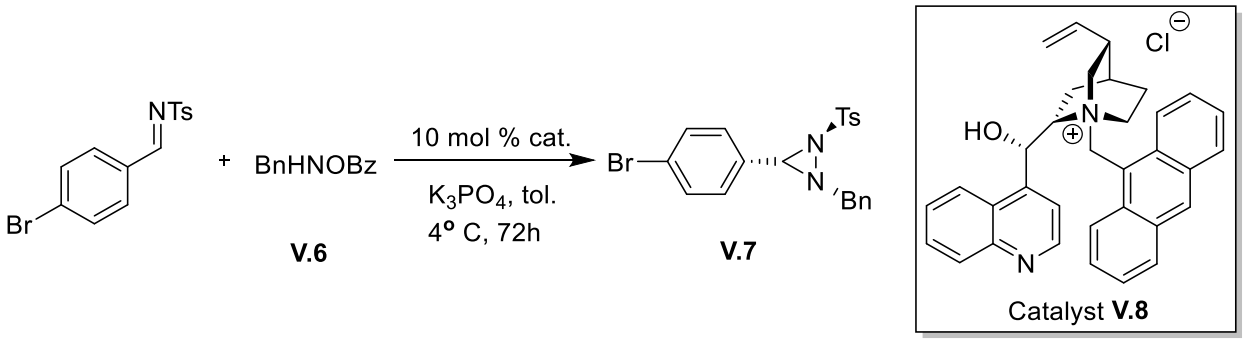


of the same reactivity as diaziridinones. This could be because the initial reports of alkene diamination by diaziridinones (and related compounds) with palladium[121] and copper[122] were both published in 2010, and the first enantio- and diastereo-selective synthesis of diaziridines was not reported until 2013.[128]

To test the viability of diaziridines as nitrogen sources under the Shi reaction conditions,

the following precursor was prepared, along with the alkene substrates. The bromo aldimine was prepared by acid catalyzed condensation of toluenesulfonamide and *p*-brombenzaldehyde, and *N*-benzyl-*O*-benzoyl hydroxylamine was prepared from a literature procedure.[128] This particular

Figure 5.13: Synthesis of the Diaziridine Substrate V.7

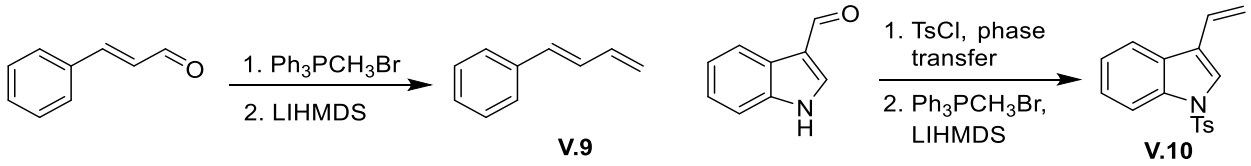


diaziridine was chosen for operational simplicity (in its pure form it is a solid) and because bromine is an excellent marker for detection in mass spectroscopy. It should also be noted that this catalyst was successfully used as a diastereoselective phase transfer catalyst in the synthesis of diaziridines, the *O*-benzhydryl derivative was used for the enantioselective variant of this reaction. The benzhydryl derivative was prepared once but was not used in these studies. Difficulty was encountered in reproducing the compound synthetically, and at this point in the investigation the enantioselective variant could be postponed pending the success of the racemic variant. The catalyst used was the one shown in Figure 5.13, which gave diastereomerically pure diaziridines[128] (as measured by ^{1}H NMR).

The substrate dienes were prepared from literature procedures (Figure 5.14): phenylbutadiene was prepared in one step from cinnamaldehyde,[130] and the 3-vinylindole in two steps from indole-3-carboxaldeyde.[131] The first substrate was prepared for direct comparison with Shi's work, being one of the test substrates used in their work. The vinylindole was prepared because of direct interest to this work; since the Shi group demonstrated the electronic

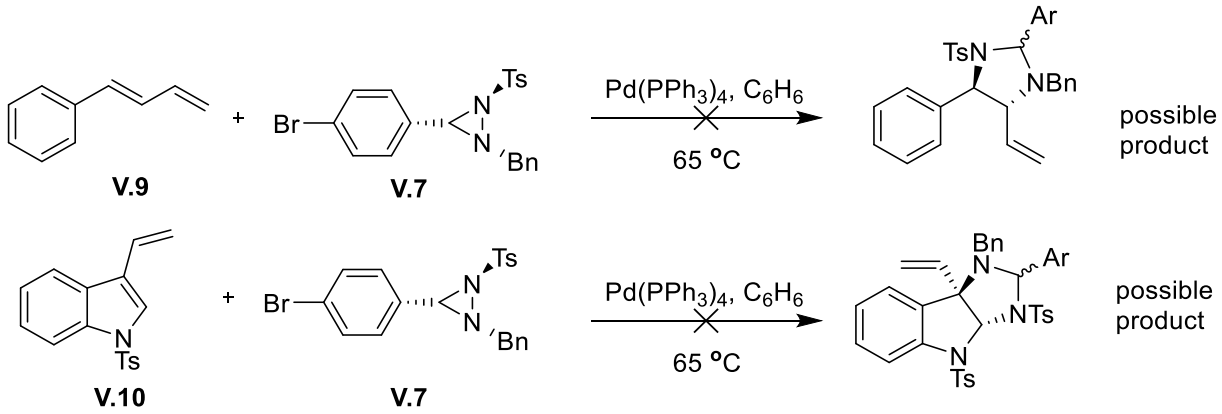
nature of the diene was not influential on the outcome of the reaction, indolyl diene **V.10** was expected to be a viable substrate for the methodology. In many examples electron rich substrates reacted with virtually the same efficacy as their electron poor analogs. Only one example was published using an aminodiene,[125] and while the effect of the diene substrate is a secondary

Figure 5.14: Substrate Alkenes for Diamination



mechanistic concern (the rate determining step being cleavage of the N-N bond), no examples included such an extensively conjugated system. Additionally, this would have been the desired substrate for the development of this method. Unfortunately, under the reaction conditions shown (duplicating the optimized conditions), no reaction occurred with either the vinylindole or the phenylbutadiene. To analyze these results, a discussion of the reaction mechanism is necessary.

Figure 5.15: Attempts at Palladium-Catalyzed Diamination of V.9 and V.10



Shown below is the proposed catalytic cycle for the palladium catalyzed diamination of dienes with diaziridinone and $Pd(PPh_3)_4$. Several features deserved comment. First is the NMR evidence for the oxidative addition of the palladium to the diazirirdinone. The four membered

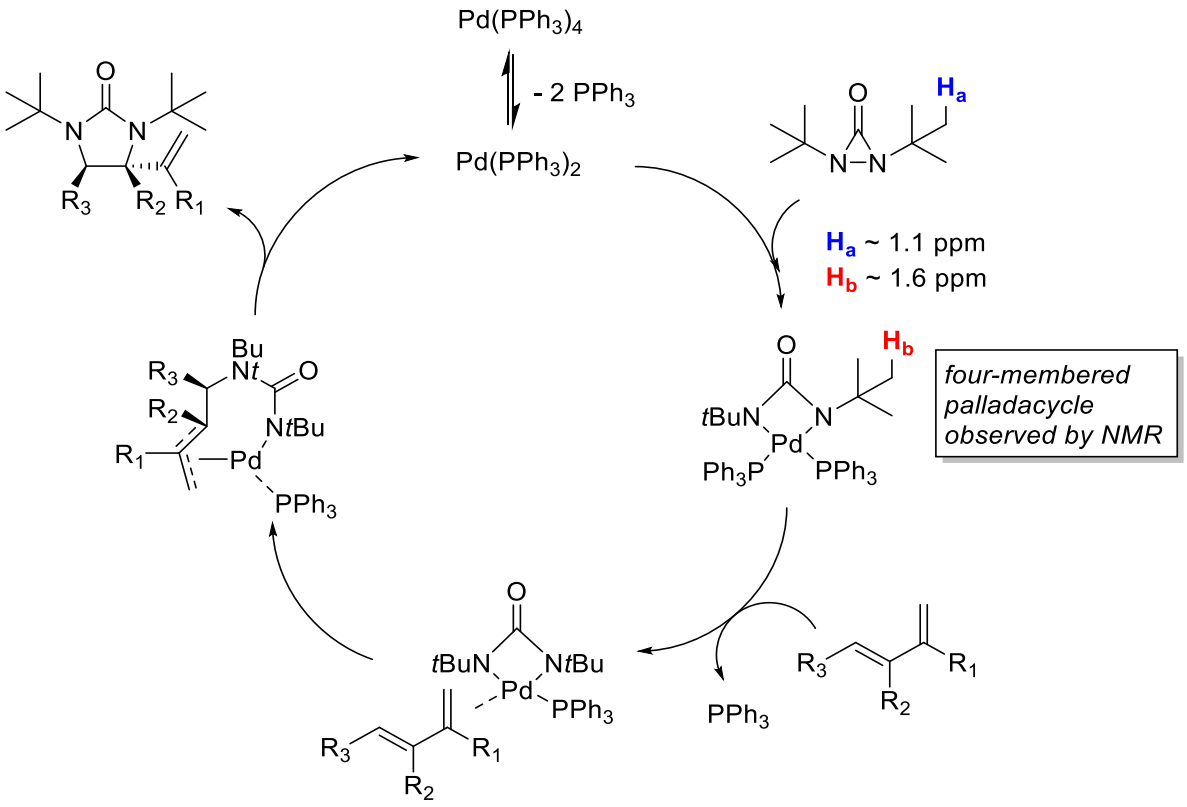
palladium (II) intermediate displays a downfield shift of ~0.5 ppm in the *tert*-butyl proton resonances.[125] After all the closed ring signal disappeared, a diene was added and the expected new diamine signals were observed. The remainder of the process follows the standard oxidative addition-reductive elimination catalytic cycle for palladium addition to alkenes.

Additionally, the palladium catalyzed variant prefers dienes to control the facile β-hydride elimination pathway. Terminal aliphatic alkenes have been used successfully with this method,[125] and either result in alkene transposition with the nascent diamine occupying the internal position[124] (with di-*tert*-butyldiaziridinone), effectively diaminating an alkane and regenerating the original alkene, or the terminal position with the generation of a new internal alkene[124] (with di-*tert*-butylthiadiaziridine 1,1-dioxide).

The demonstration that the rate-limiting step is oxidative addition of palladium to the N-N bond[126] implies that if the local environment around the new 4-membered palladacycle was chiral, the product diamine might be rendered chiral as well. After a series of ligand screens, the

Shi group discovered one ligand that performed admirably in the desired fashion, and this reaction manifold can be rendered asymmetric with high yield and high *ee*'s.[124] Alternatively, the product imidazolidinone can be deprotected and enantiomerically separated by crystallization.[124]

Figure 5.16: The Pd-Catalyzed Diamination of Dienes with Di-*tert*-butyldiaziridinone

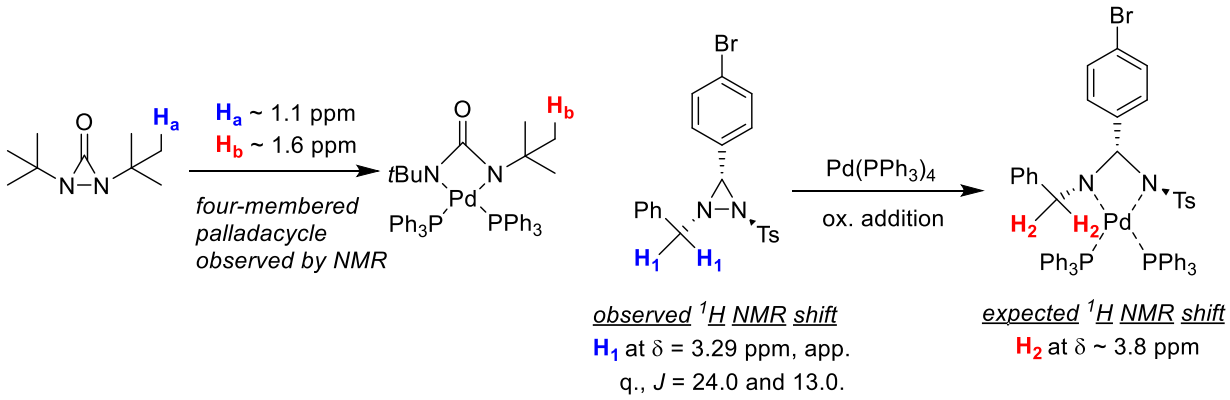


The only drawback to this method are the forcing conditions used in the deprotection; typically the *tert*-butyl groups are removed by refluxing in concentrated HCl, and removal of the carbonyl in the remaining urea often requires additional forcing conditions to reveal the desired diamine. This limits the substrate scope of the reaction and would require early use in the synthesis of complex molecules. Transfer of stereochemical information would be expected if an enantiomerically (or diastereomerically) pure diaziridine was reactive in this manifold, based on the demonstrated asymmetric induction observed from chiral palladium ligands.

Analysis of the crude reaction mixture by ^{1}H NMR showed no change in the reaction mixture during the proscribed course. Since the rate limiting step is oxidative addition to the *N*,*N*-bond, a change in ^{1}H NMR similar to that seen in di-*tert*-butyldiaziridinone would be expected if a four-membered diaziridine-palladacycle was formed. Luckily, the benzyl protons of

V.7 occupy an otherwise empty region of the spectrum and are very distinct: a quartet centered around 3.29 ppm with coupling constants of J = 24.0 and 13.0 Hz. Presumably, if oxidative addition has occurred, this peak would have experienced a downfield shift to approximately 3.8 ppm. The crude reaction mixture reveals this not to have been the case, as the signals remained unchanged throught the course of the reaction.

Figure 5.17: Expected ^{1}H-NMR Shifts On Successful Oxidative Addition



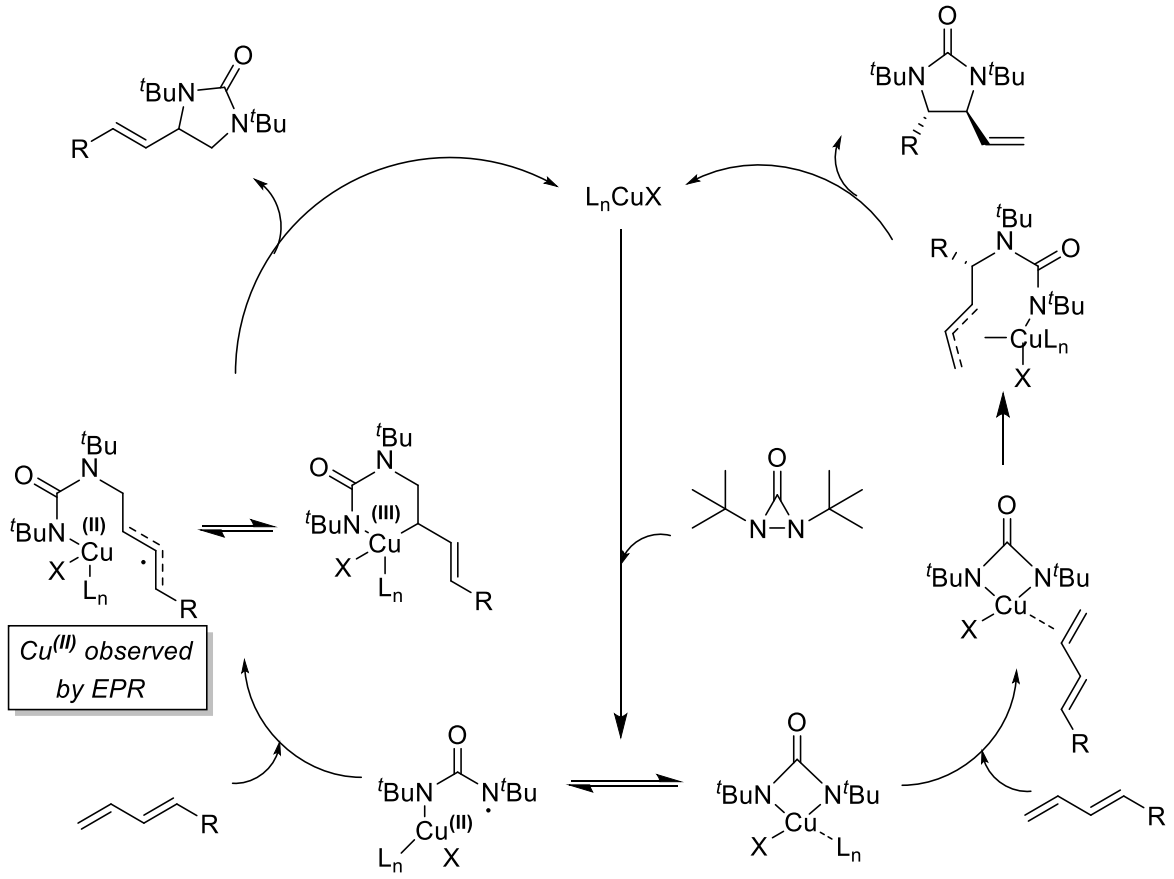
At this point it was decided to repeat the reaction using the copper catalyzed variant. This reaction is thought to proceed through a radical process (discussed below) and it was hypothesized that the *N*,*N*-bond, while inert to oxidative addition by palladium, might be it was susceptible to radical reduction with copper.

The Shi group additionally discovered a copper (I) catalyzed variant of the same reaction with several distinct features, the most prominent of which is reagent-based control of regioselectivity.[126] Depending on the particular copper salt used, either internal or terminal diamination could be effected, though a terminal double bond is required in the diene substrate in all cases. Mechanistically the reaction is thought to proceed through two different pathways, and the regioselectivity is thought to originate from the relative position of the equilibrium between two copper species (shown in the Figure 5.18). The first step is likely reduction of the N-N bond to form a nitrogen centered radical that is likely in equilibrium with the four-membered copper

(III) species shown in the figure.

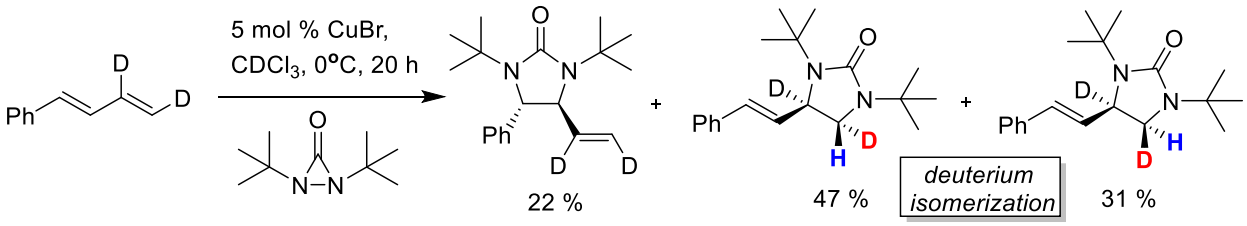
The addition to terminal double bonds is thought to proceed through a radical process.

Figure 5.18: Copper Catalyzed Diamination of Olefins



The direct observation of the copper (II) radical species by EPR provides support for this. The nitrogen centered radical could add to the terminal end of the double bond, producing the resonance stabilized radical shown in the figure, which may exist in equilibrium with the six-membered copper (III) containing ring shown adjacent. The last step would involve reductive elimination of the copper (III) species or radical combination in the copper (II) species to form the diamination product. Additional evidence for the radial mechanism in the diamination of terminal double bond comes in the observed isomerization of the deuterated substrate shown above.[125]

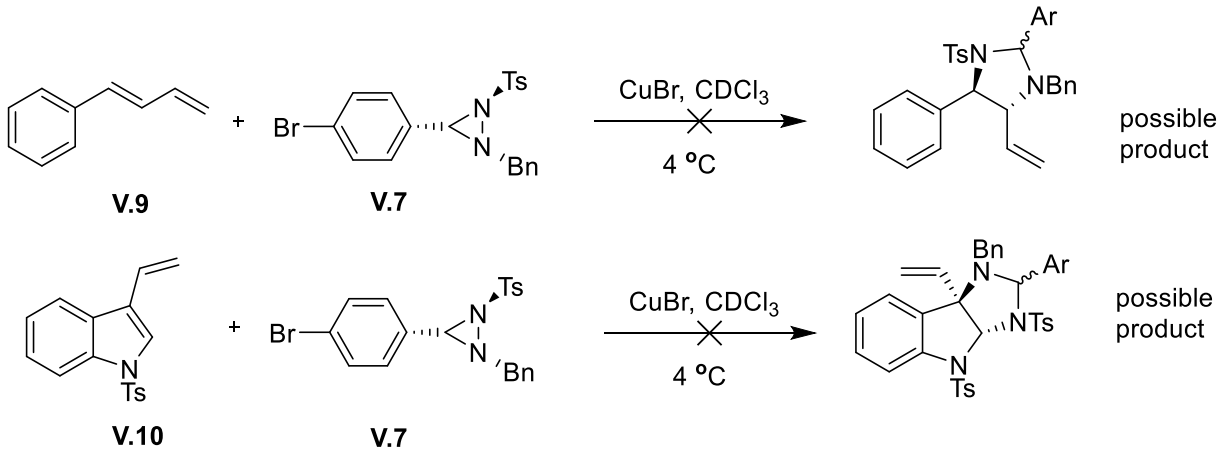
Figure 5.19: Deuterium Isomerization in the Copper Catalyzed Diamination of Dienes



The first clue that the internal diamination mechanism proceeded through a different mechanism comes from the fact that the internal diamination product observed shows no deuterium isomerization.[125] To further probe the mechanistic possibilities, careful study of the reaction using 1,4-diphenylbutadiene as a substrate was performed. Little to no product was formed under these circumstances, suggesting radical addition to an internal double bond is unfavorable, even in the presence of such an extensively conjugated system.[124] This information, coupled with the fact that manipulating the reaction conditions can strongly favor terminal versus internal addition, suggested that copper acts similarly to palladium in the palladum catalyzed version of this reaction.

The reactions shown below in Figure 5.20 were preformed according to the proscribed procedures. Again, analysis of the crude reaction mixtures with ^{1}H NMR revealed no reaction occurred, merely the persistence of starting materials. The evidence that diazridines are not viable substrates for this reaction manifold could be related to the structural differences between these two classes of molecules. The carbonyl in di-*tert*-butyl diaziridinone has an IR stretching frequency[132] of 1880 cm^{-1}, which is above the typical range for carbonyl compounds, indicating a high degree of mechanical strain. This likely weakens the *N*,*N*-bond in way that is absent in the diaziridine. Additionally, the *tert*-butyl groups are known to add kinetic stability to small, reactive heterocycles[134] and were presumably chosen (at least in part) for this reason. It is

Figure 5.20: Copper Catalyzed Diamination With Diaziridines

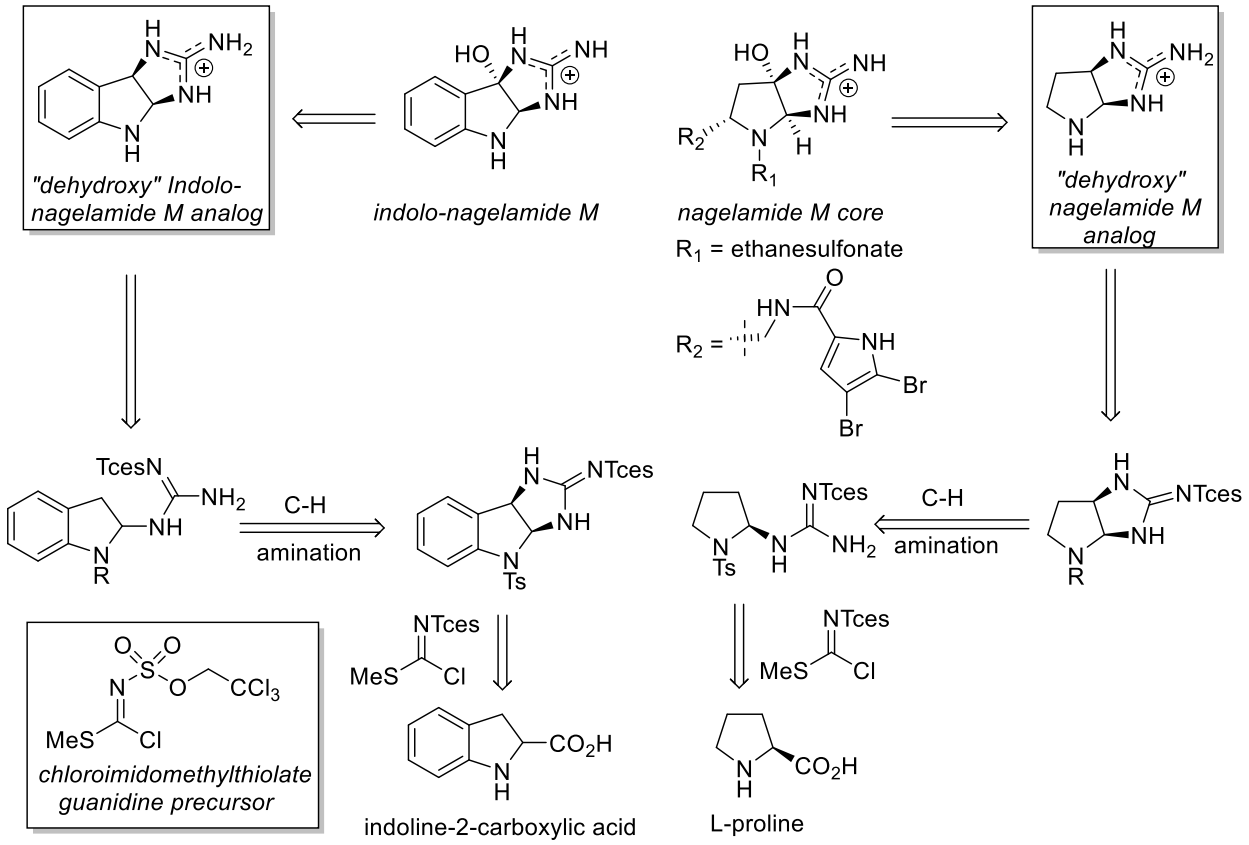


possible they assist in activation of the *N*,*N*-bond to relieve steric congestion. If this in correct, they could also sterically prevent reductive elimination to reform the *N*,*N*-bond. These features obviously play a crucial role in *N*,*N*-bond activation, and these results confirm their presence is required for reactivity.

Chapter 6: Studies on the Functionalization of Indolines and Indanes

Another route to *des*-hydroxyl-Indolo-nagelamide M was envisioned using the amination of a C-H bond as a substrate, as opposed to the oxidation of an alkene. The new route to these compounds is shown in Figure 6.1.

Figure 6.1: Retrosynthesis of Dehydroxy-Analogs of Nagelamide M

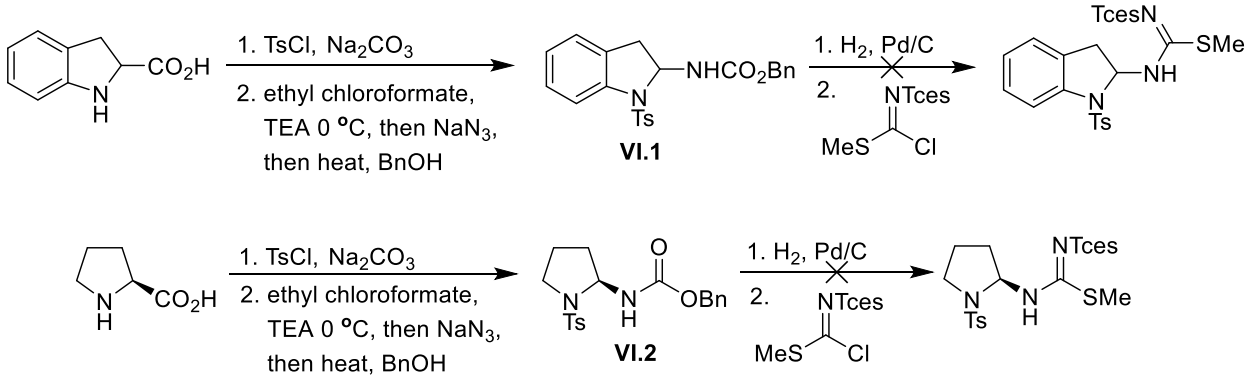


The proline derivative, if successfully synthesized, would yield the closest analog to nagelamide M. To synthesize this analog would require the C-H activation at a secondary carbon, which is not amply precedented. The likelihood of synthesizing this molecule is thus rendered somewhat speculative. In contrast the indole derivative, if successfully synthesized, is anticipated to proceed more smoothly, as the final step requires the well-precedented C-H amination of a benzylic C-H bond. Surprisingly, neither 2-aminoproline and 2-aminoindoline nor

their carbamates were known compounds at the time these studies were initiated. The closest literature precedent for this transformation involves the transformation shown below on Z-pyroglutamic acid.[135] Using the method for the synthesis of acyl azides developed by Sheehan,[136] the carboxylic acid was transformed into a benzyl carbamate via a Curtius rearrangement. In parallel, the known guanidine precursor was prepared in four steps from commercially available *p*-methoxybenzenesulfonyl chloride.[41]

Hydrogenolysis of the Cbz group was achieved in both cases (Figure 6.2), but the free amines were not amenable to purification. Attempts at coupling the crude amine with the guanidine precursor were not successful, and this route was abandoned.

Figure 6.2: Synthesis of Dehydroxy-Analog Cyclization Precursors

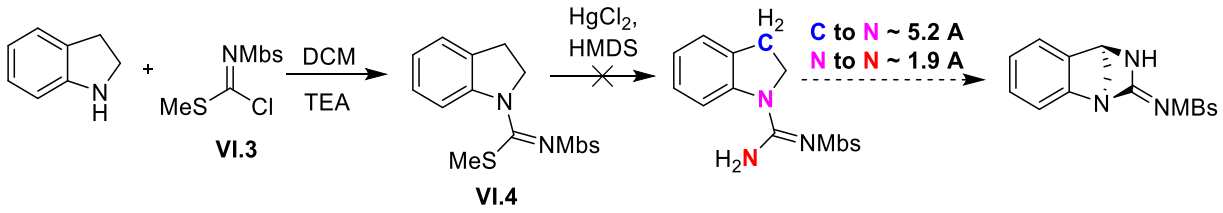


Data collected from several sources (Figure 4.10) implies the need for electronic deactivation of guanidines and ureas to render them viable for synthetic manipulation. Methodology pioneered by the Du Bois group in the manipulation of these moieties has focused on substituents that have electron-withdrawing character for the steps that require synthesis (i.e., the C-H amination step) and are removable through mild reductive cleavage. To this end, the "Tces", 2,2,2-trichloroethoxysulfamate, and the "Mbs", *p*-methoxybenzenesulfonyl, groups have emerged as the most useful. In addition to tuning the reactivity of the guanidine or urea, they exhibit the added benefit of simplying purification. In many cases the Tces or Mbs protected

cyclization product can be purified by standard silica gel chromatography, which is often not the case with guanidines or ureas protected with more conventional groups (Boc or Cbz).[136] The Mbs moiety has been used primarily in the context of intramolecular C-H aminations (total synthesis of saxitoxin[41]), while Tces has been used in both inter- and intramolecular C-H aminations.[46]

The guanidine precursor was designed for installation into primary and secondary amines, but there are no examples of CH animation on benzylic carbons on indolines with the Mbs moiety. To test the viability of this reaction and potentially design a biologically active analog, the guanidine precursor was installed in the indoline core and the synthesis was continued to the fully protected guanidine. The synthesis of this analog provides an opportunity to test the transformation of the methylthio-moiety to the guanidine with mercury (II) chloride and hexamethyldisilylazide.

Figure 6.3: Synthesis of a Guanidine Precursor from a Secondary Amine

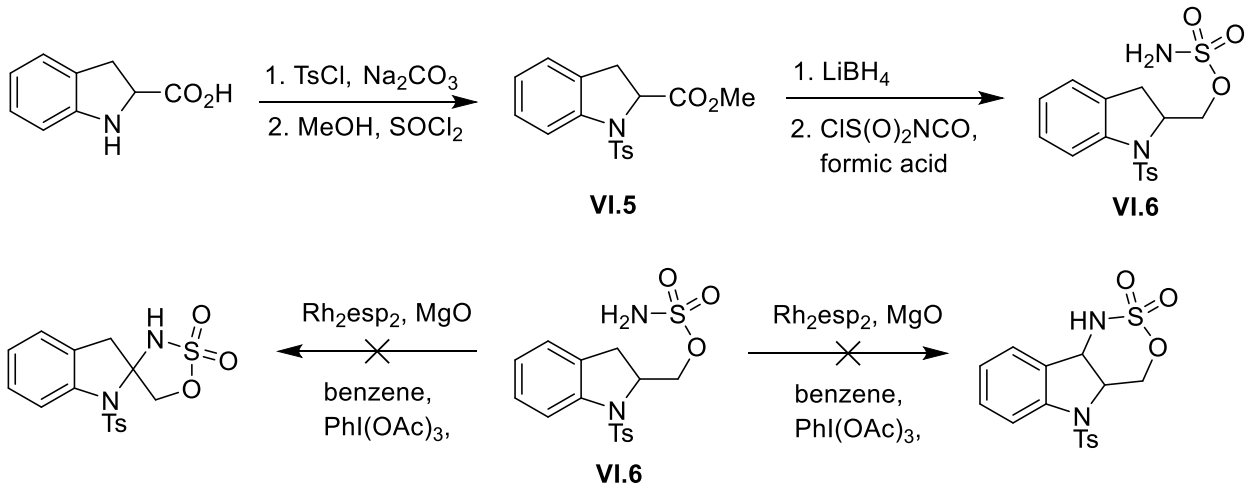


During the course of this synthesis, the question was posed as to whether the steric constraints of this molecule would prohibit the ring closure: mainly, could the guanidine nitrogen in **IV.4** could reach the benzylic carbon and form the structure shown in Figure 5.3. Additionally there are no examples of the guanidine or urea amination precursors forming six-membered rings. To answer this question, a crystal structure of **VI.4** was obtained, disclosing the exact bond angles and bond lengths. Substituting the $-NH_2$ bond length from the crystal structure of the free base of guanidine[137] allows for a reasonable approximation of the new structure and for an

approximation of the distance to benzylic carbon C3 (Figure 6.3). The law of cosines was used to determine the some of the necessary bond lengths and angles that would be required to form the product **IV.4**. The results of this analysis (detailed in the Supporting Information) revealed the benzylic carbon to be too far away for the (hypothetical) guanidine nitrogen to form a bond with it, and synthesis of this molecule was discontinued.

The intramolecular C-H amination of indoline-2-carboxylate derivative **VI.6** allows for a comparison of the oxidative susceptibility of a tertiary α-amino C-H bond and a secondary benzylic C-H bond. Sulfamates have been shown to form five and six membered rings. The possibility of ring size (forming a [5.5] ring) may have been the factor leading to the failure of these routes, as the published examples only involve [5.6] rings. In either case the product would be useful, as the direct guanidinylation of sulfamates followed by cleavage of the sulfamate and

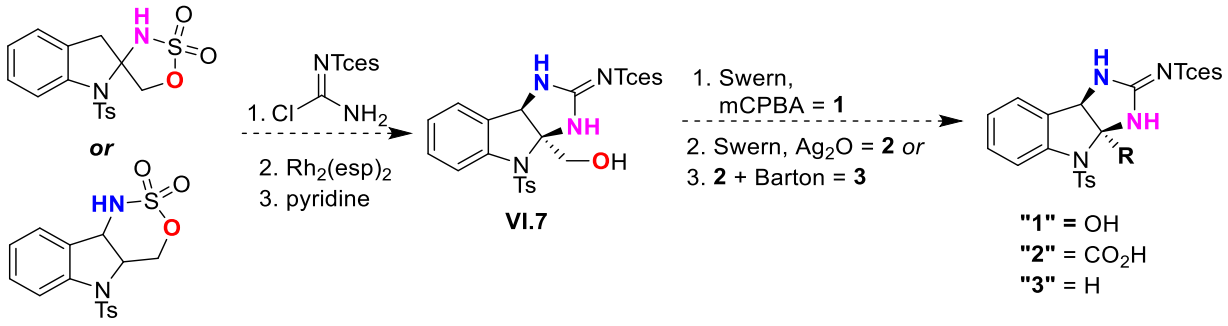
Figure 6.4: Attempted Intramolecular C-H Amination of Indoline Derivative IV.6



extrusion of SO_2 was reported in several intermediates in the total synthesis of saxitoxin.[41] Such an intermediate could be oxidatively cyclized and the hydroxymethyl group could be left as is, shortened by a methylene unit through an oxidation followed by a Bayer-Villager rearrangement,

or oxidized to a carboxylic acid (which could be decarboxylated through a Barton decarboxylation).

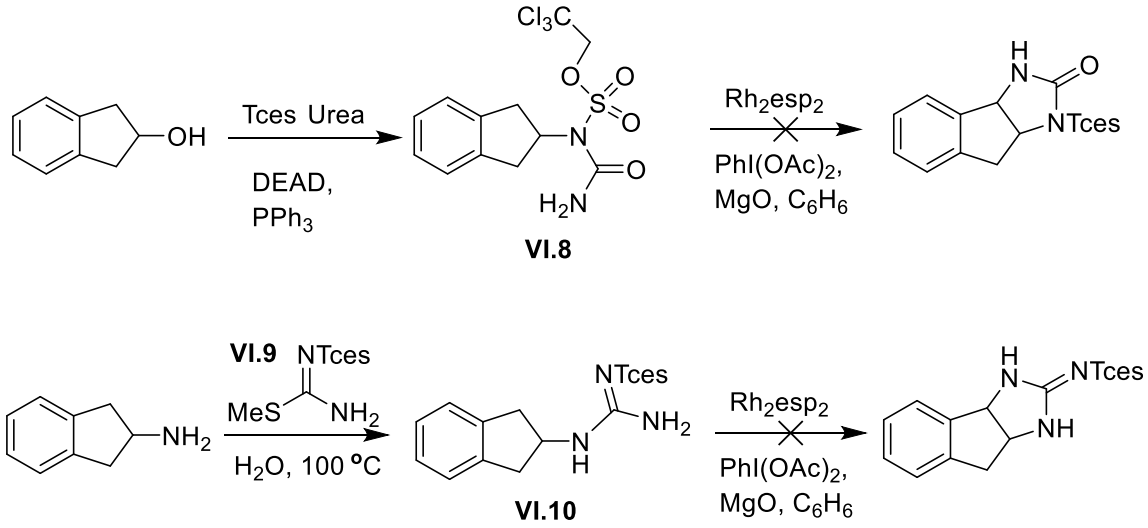
Figure 6.5: A Proposed Convergent Approach to Compound VI.7



Substrate **VI.6** was inert to reaction conditions as well.

One final simplification was conceived and carried out in a final attempt to make these molecules, shown in Figure 5.6. These analogs were designed from commercially available 2-indanol and 2-aminoindan, following the. The substitution of the indole nitrogen for a methylene (as compared to the analogs described in Figure 6.2) was expected to make the product easier to synthesize, as as several similar examples have been published.[46] The Tces-guanidine precursor

Figure 6.6: Synthesis of Indanyl C-H Amination Analogs

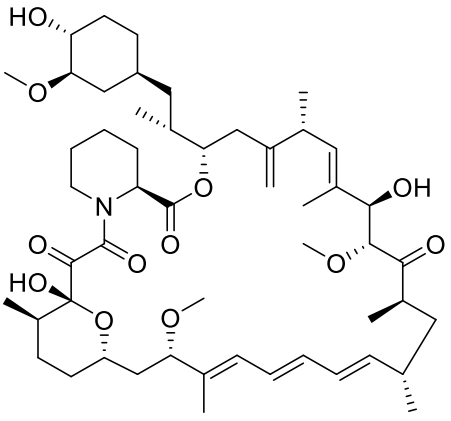


VI.10 was reactive under these conditions but it produced an intractable mixture of (presumably) multiple products, none of which were isolable. The Tces urea compound **VI.8** was inert to reaction conditions.

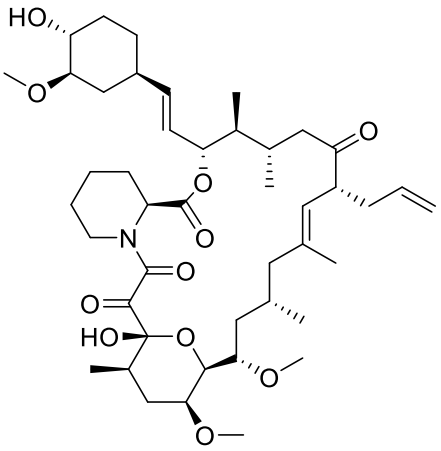
Chapter 7: Rapamycin Analogs as Inhibitors of the Proteasome and a Rapamycin-Based Diazirine Photoaffinity Probe

Not wanting to limit the discovery of new protesome inhibitors to the pyrrole-imidazole alkaloid family alone, other natural products were considered for work in this area. To that end, the natural product rapamycin was selected as a candidate, owing to its discovery to allosterically inhibit the proteasome with an IC_{50} = 1.9 μm.[136] The synthesis of a series of analogs designed based on rapamycin and its congener FK-506 was published[137] in an SAR study attempting to probe their effect on peptidyl-proline isomerase inhibitors (before the Schrieber group disclosed the mechanism on action involved the inhibition of mTor).[138] This work would serve as a guide for our work with these compounds.

Figure 7.1: The Natural Products Rapamycin and FK-506



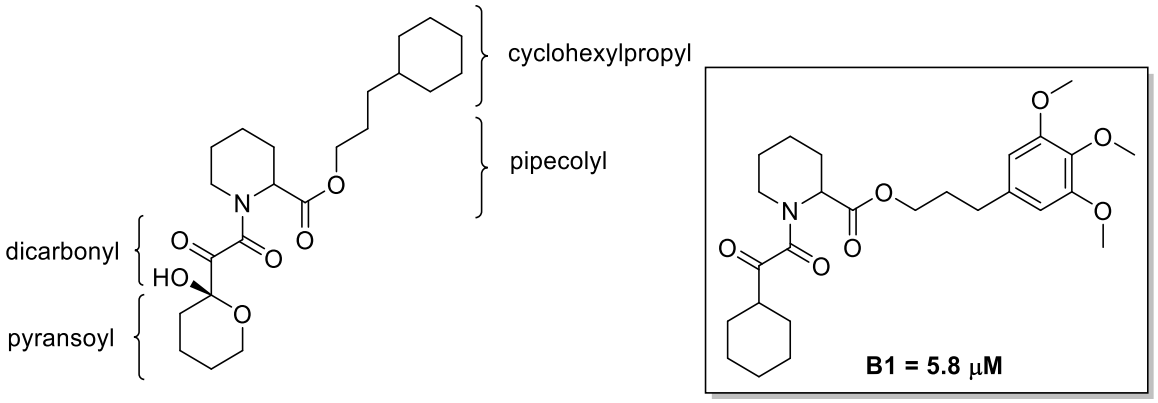
Rapamycin



FK-506

In collaboration with the Gaczynska group, [136] which studies proteasome inhibition, a series of analogs based on the SAR optimized motifs was planned to further their studies. The original SAR, published by the Holt group[137] disclosed four key features for optimum potency in their molecules, which are shown in Figure 7.2. Additionally, the Gacyznska group had

Figure 7.2: SAR-Optimized Analogs of Rapamycin



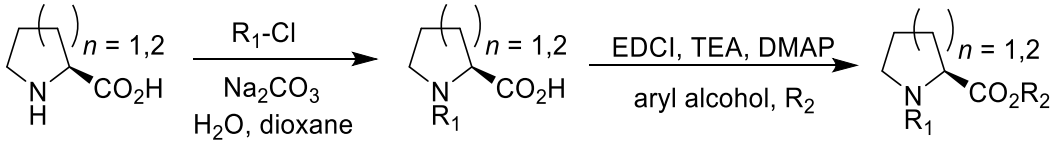
Key features for activity in the Holt SAR

prepared by Gaczynska group

synthesized a lead compound based on these structures with potency close to the natural product.

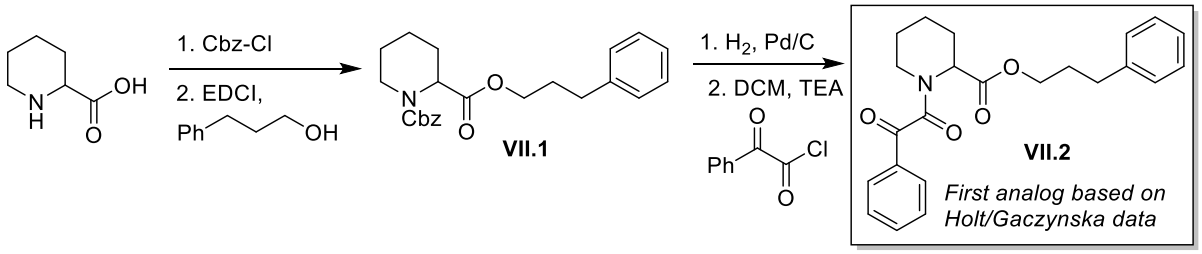
Using this combined data as a starting point, the synthesis of these molecules was planned around *L*-pipecolic acid and *L*-proline, which can be functionalized at the carboxylic acid and the amine with known chemistry to synthesize the desired molecules. The general scheme for the synthesis of these compounds is shown in Figure 7.3.

Figure 7.3: The Synthesis of Rapamycin Analogs



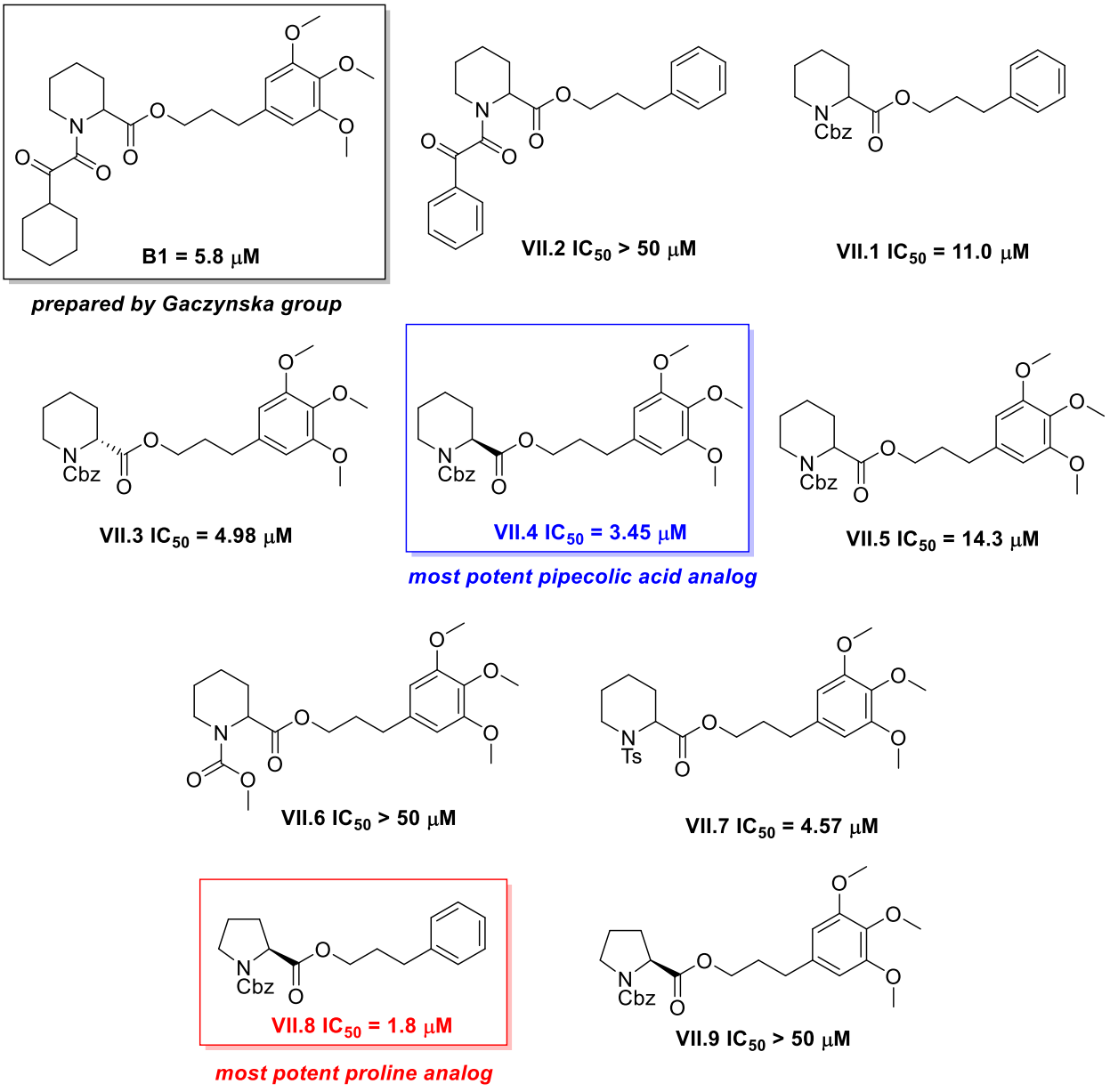
The initial target was modeled closely on the SAR proposed by Holt and the synthesis is shown in the figure below. Racemic pipecolic acid was Cbz-protected at the ring nitrogen and the acid was esterified with 3-phenyl propanol. The Cbz group was removed by hydrogenolysis and after column chromatography was acylated with the acid chloride shown.

Figure 7.4: Synthesis of an Initial Analog of Rapamycin Based on Previous SAR Data



Having developed a viable route, a first-generation series of analogs were planned, varying ring size and the nature of the aryl moiety. In addition to the target molecule shown above, the protected intermediates were tested for biological activity. Two of these molecules were unexpectedly more potent than the strongest known thus far, and this discovery prompted a change in the direction of the project. All of the molecules tested in the initial series are shown in the figure below (all biological testing and reported activities were performed by the Gaczynska group).

Figure 7.5: First Generation Analogs and Activities

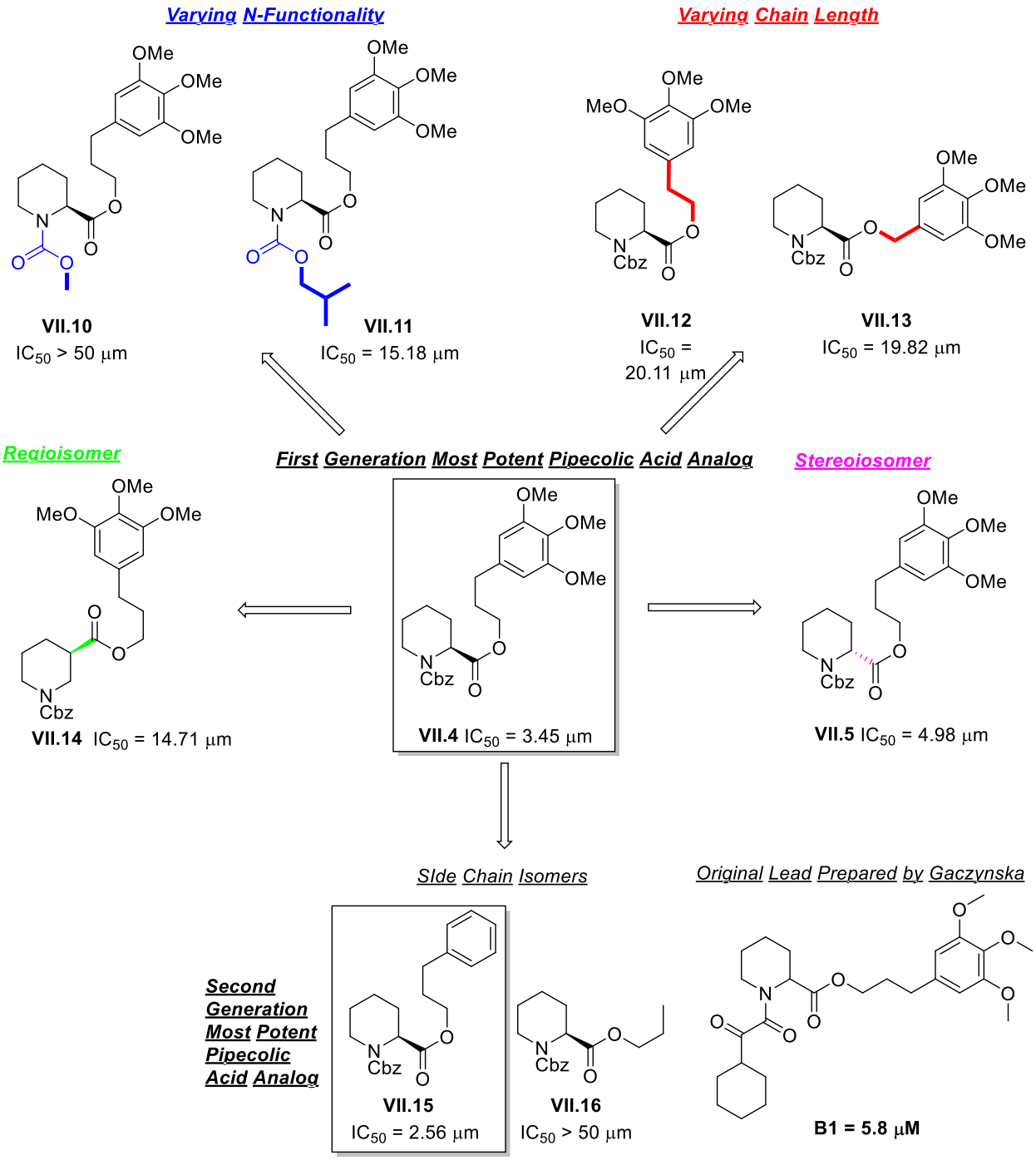


The activity of each of the enantiomers of pipecolic acid compared to the racemate is worth discussing. Typically there is either an order (or more) of magnitude difference in activity between enantiomers or their individual activities add up to that of the racemate.[139] As these characteristics were not observed in this system, molecular modeling was used in an attempt to explain this result (modeling conducted by C. Jones, Tepe Group). The modeling results indicate

the enantiomers bind to two different subunits of the α-ring, which in the absence of other empirical data is a reasonable explanation for the observed results.

The analogs based on *L*-pipecolic acid are shown in Figure 7.6, with the most potent being **VII.4**, with R_1 as carbamoylbenzyloxy and R_2 as the 3,4,5-trimethoxyphenyl alcohol. Surprisingly, the most potent analog synthesized did not include either a 6-membered ring or a functionalized aryl moiety; rather it was analog **VII.8**, an *L*-proline derivative with R_1 as carbamoyloxybenzyl and R_2 as 3-phenyl-1-propanol.

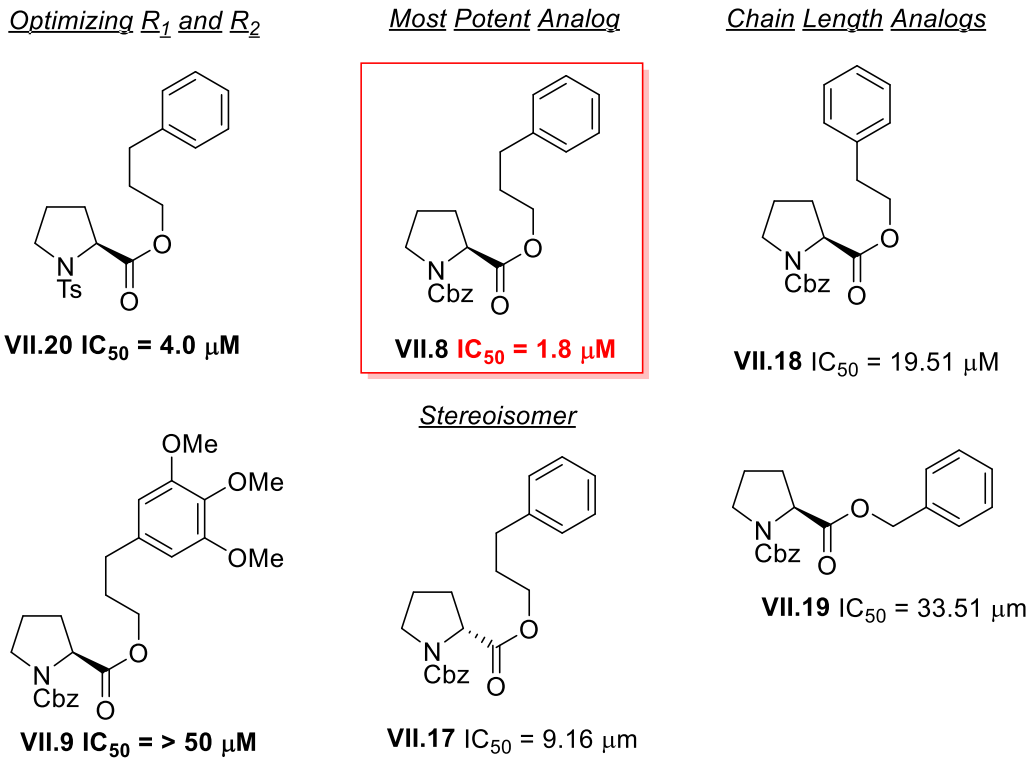
Figure 7.6: *L*-Pipecolic Acid-Based Rapamycin Analogs Synthesized to Probe the SAR



A comparison of the most potent analog from each series leads to several illuminating conclusions. The aryl functionality of R_2 in the pipecolic acid series is substantially larger with its three methoxy groups as opposed to the simple benzene ring in the proline series. The IC_{50}'s

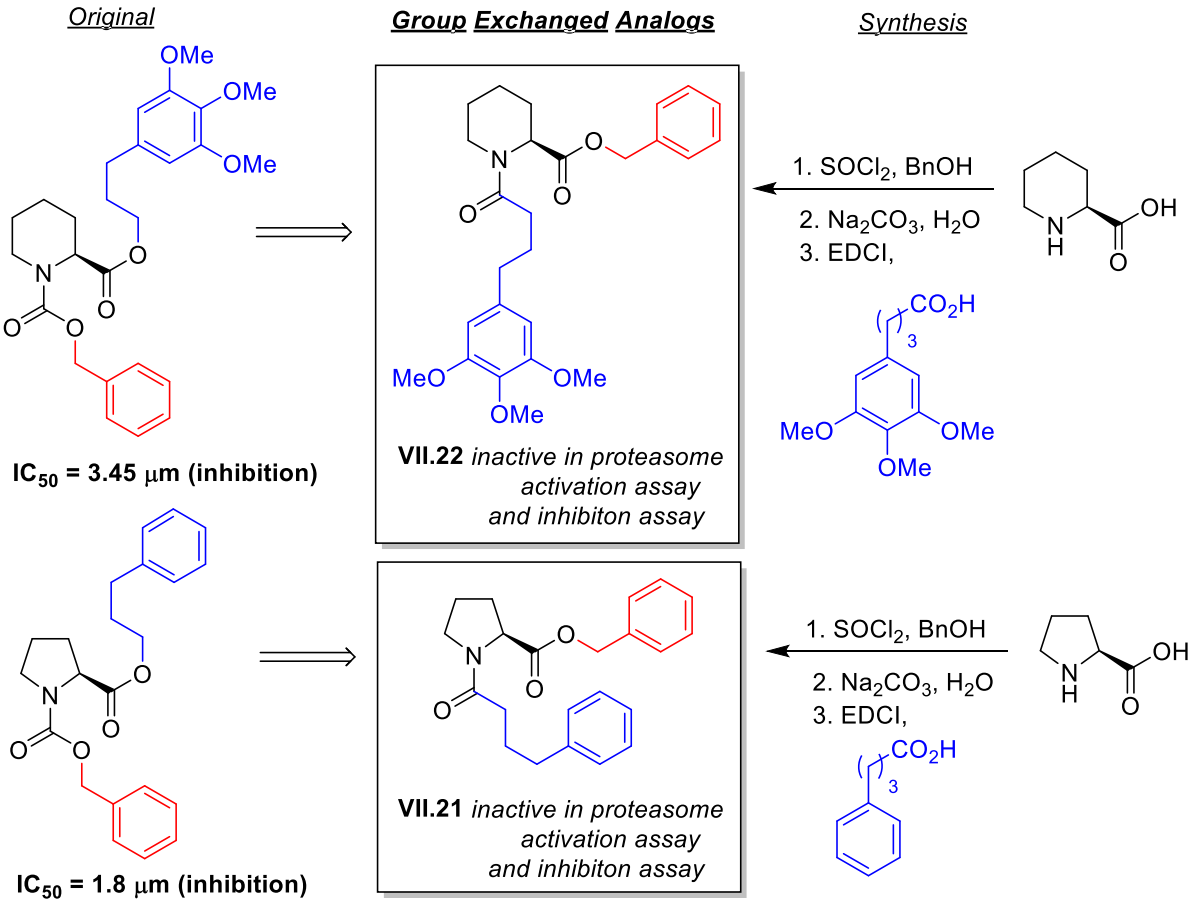
of **VII.4** and **VII.5** demonstrate the size of the trimethoxy-aryl group is not a hindrance to binding, however binding is almost completely inhibited upon contracting the ring size from 6 to 5. The conformational dynamics of 5-membered rings is known to be substantially different[135] from that of 6-membered rings, and analogs synthesized to exploit this feature are shown in Figure 7.7.

Figure 7.7: Proline-Based Analogs



These observations along with molecular modeling drew us to the following compounds, in which the R_1 and R_2 groups had been exchanged on the heterocyclic core. Another compound of interest in the Tepe group is a proteasome activator based on the 2-phenothiazine core. This compound was modeled *in silico* and the binding conformation looks similar to **VII.4** with R groups interchanged, as shown in Figure 7.8. These molecules were synthesized to explore the possibility of creating molecular switches, with tunable proteasome activating or inhibiting characteristics, based on the location of the side chains.

Figure 7.8: Group-Exchanged Analogs

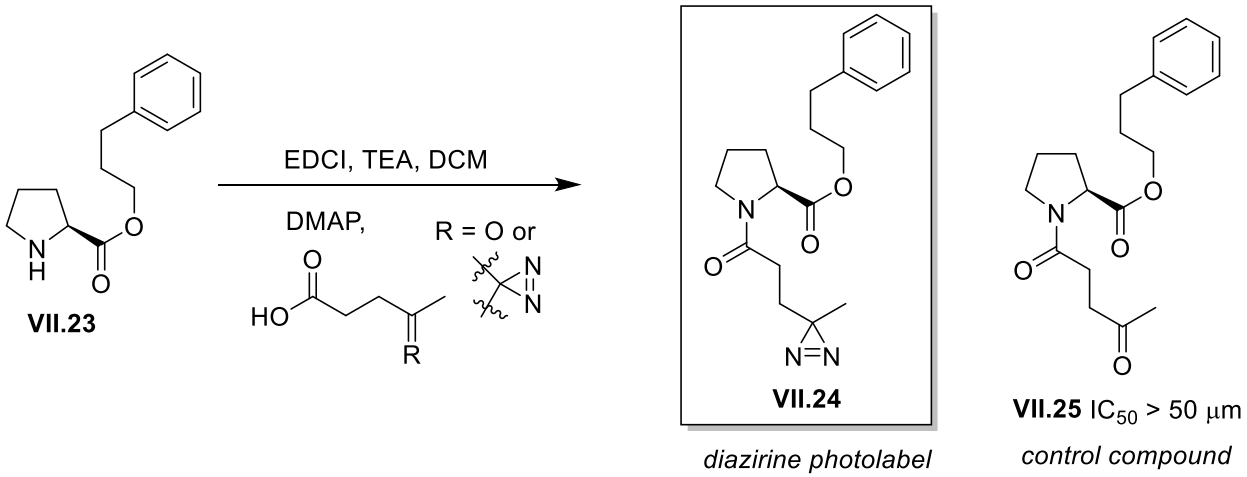


These analogs were inert when tested for proteasome activation and inhibition (E. Njomen, Tepe group).

While *in silico* studies of small molecules bound to proteins can be very instructive, they are much more so if used in collaboration with biological data; if the binding site of these inhibitors was known the modeling data could be much more effective in designing analogs. To that end, an analog incorporating a diazirine photolabel was synthesized (Figure 7.9) by coupling amine **VII.23** and 3-(3-methyl-3*H*-diazirin-3-yl)propanoic acid (synthesized from levulanic acid).[140] This compound was synthesized in the hope that upon binding and irradiation, the diazirine would extrude dinitrogen to reveal a carbene, which would insert into a local covalent bond. The covalently bound inhibitor-protein complex would then be enzymatically digested and

analyzed by mass spectrometry, the results of which would reveal the binding site. This method

Figure 7.9: Rapamycin Analog-Diazirine Photolabel and Control Compound

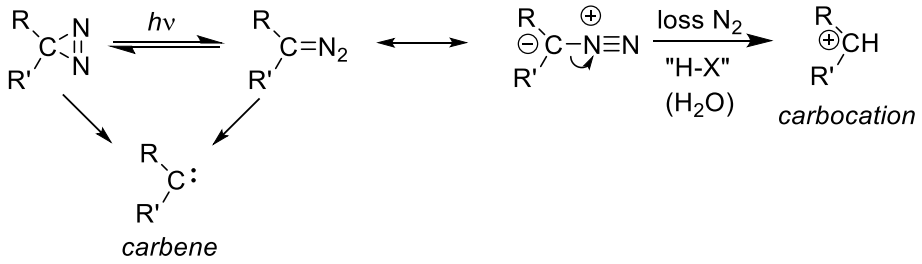


of elucidating the binding site of small molecules to proteins has been in existence for some time[141] and has a long history of success.

It should be noted that in both the precursor 3-(3-methyl-3*H*-diazirin-3-yl)propanoic acid and **VII.24**, the diazirine carbon[140] (chemical shift $\delta = 72$ in $CDCl_3$) was absent in ^{13}C NMR. Support for the proposed structures is given in the ^{1}H NMR, high-resolution mass spectrometry, and IR analysis. Additionally, the compounds are stable to storage and in solution (arguing against the presence of a carbene), however the proposed structures remain unconfirmed. Additional ^{13}C NMR experiments (HMBC) were unable to find the missing carbon.

Although diazirines were first synthesized in 1960,[142] their use as photoprobes was not discovered until the 1970's by the Knowles group.[143] Scheme 7.10 below shows the pathways for diazirine photolysis. Studies of these systems by ultrafast spectroscopy indicates the photochemistry of diazirines is complex, and many exotic intermediates have been characterized chemically and spectroscopically.[141]

Scheme 7.10: Photochemical Pathways From Diazirines to Carbenes and Carbocations



The principal modification to diazirine photolables has been the incorporation of an α-trifluoromethyl group, which was discovered ten years later.[144] This modification has been shown to preferentially influence the formation of a carbene over other less reactive intermediates.[141]As a general trend, aromatic diazirines generate more carbenes in comparison to aliphatic diazirines.[141] Generally the α-trifluoromethyl group will favor the formation of the carbene and render any diazo-intermediate so stable as to be unreactive to normal photolysis conditions (the chemistry of aryl α-trifluoromethyl diazirines is explored in Chapter 8).

The diazirine photolabel was tested for biological activity (Gaczynska group) and found to be of sufficiently active to conduct the photolabeling experiment. We are currently awaiting the results of this data from our collaborators (Bohmann Group, Southwest Research Institute).

Chapter 8: Synthesis of Two TCH-Diazirine Photoaffinity Labels and a TCH-Biotin Conjugate

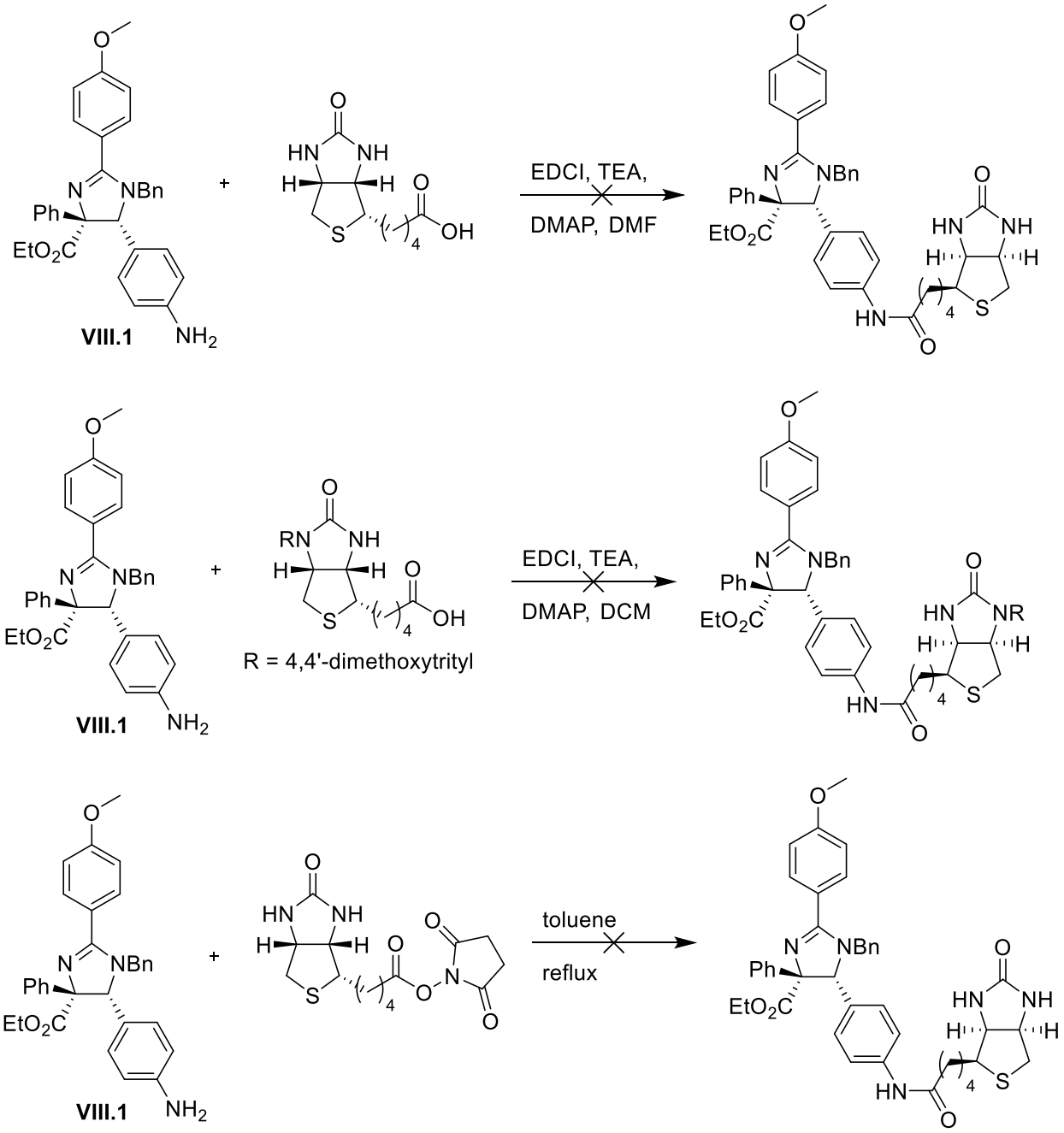
A great deal of work has been done to elucidate the nature of the binding interaction between compounds of the TCH series and the proteasome, and most of the details of that interaction are now known.[5,6] The final piece of the puzzle yet to be solved is the location of the binding site (or sites) of the TCH molecules to the proteasome. Attempts at using X-ray crystallography, as in the case of Indolophakellin (Figure 3), have not been successful, leaving the matter to molecular probes. Two of the most commonly used probes are active molecule-biotin hybrids and diazirine photoaffinity probes, and both were employed in attempts to modify the TCH pharmacophore to create hybrid probes for binding studies.

Biotin has been used successfully in this area when chemically incorporated into a biologically active molecule.[146] The difficulty with this method is ascertaining to what extent, if any, the biotin conjugate alters the activity profile of the molecule in question. Since this cannot be determined beforehand, several known TCH molecules were synthesized for ligation to biotin at various locations in the hopes of synthesizing a probe that would have comparable activity to its parent TCH compound.

The structural diversity in the library of known TCH compounds is extensive and offers many opportunities for the incorporation of a biotin label. Another known TCH compound, TCH-157 (compound **VIII.1**, Figure 8.1), possessing an aniline was prepared for coupling with biotin. Attempts to functionalize TCH-157 with biotin are shown in Figure 8.1 (TCH-157 was prepared[6] on a gram scale). EDCI coupling with the unaltered biotin to TCH-157 in DMF was attempted, but unsuccessful. Attention was then turned to the commercially available 4,4'-dimethoxytrityl ("DMT") protected biotin and the hydroxylsuccinimide biotin. The large DMT

group addresses the poor solubility of biotin, and the hydroxylsuccinimide serves both to increase solubility in organic solvents as well as activate the carbonyl group for coupling. The aniline functionality in TCH-157 has been successfully coupled to carboxylic acid derivatives

Figure 8.1: Initial Attempts at Synthesizing a TCH/Biotin Conjugate

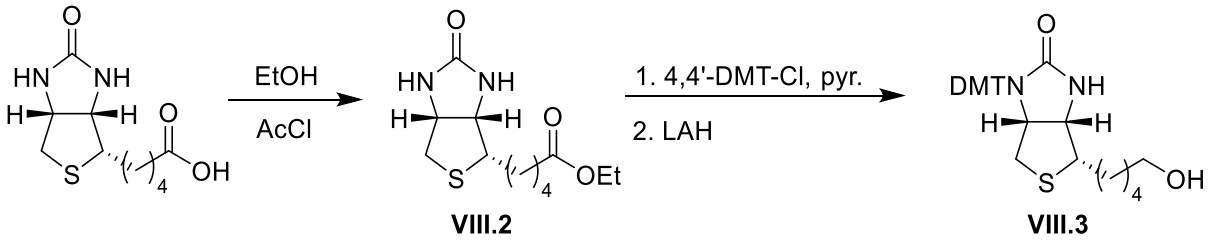


in the synthesis of other molecules (Figure 7.5), which makes the failure of these two reactions

puzzling, however no coupled product was observed.

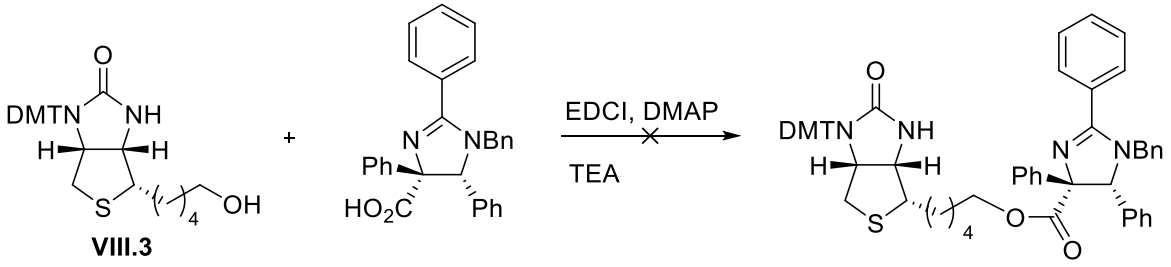
As discussed, biotin and its reduced congener biotinol are exhibit poor solubility in organic most solvents,[147] making them difficult to work with in a synthetic context. Several solutions have been reported to circumvent this problem, but the most popular is the one shown below in Figure 8.2, which employs the use of the 4,4'-dimethoxytrityl ('DMT') protecting

Figure 8.2: Synthesis of DMT-Protected Biotinol



group to enhance solubility. The DMT group adds regioselectively to the position shown, regardless of the amount added. All of the intermediates are purified by column chromatography and the final protected biotinol can be prepared on a multigram scale as a white solid. This reaction failed to provide any coupled product as well (Figure 8.3).

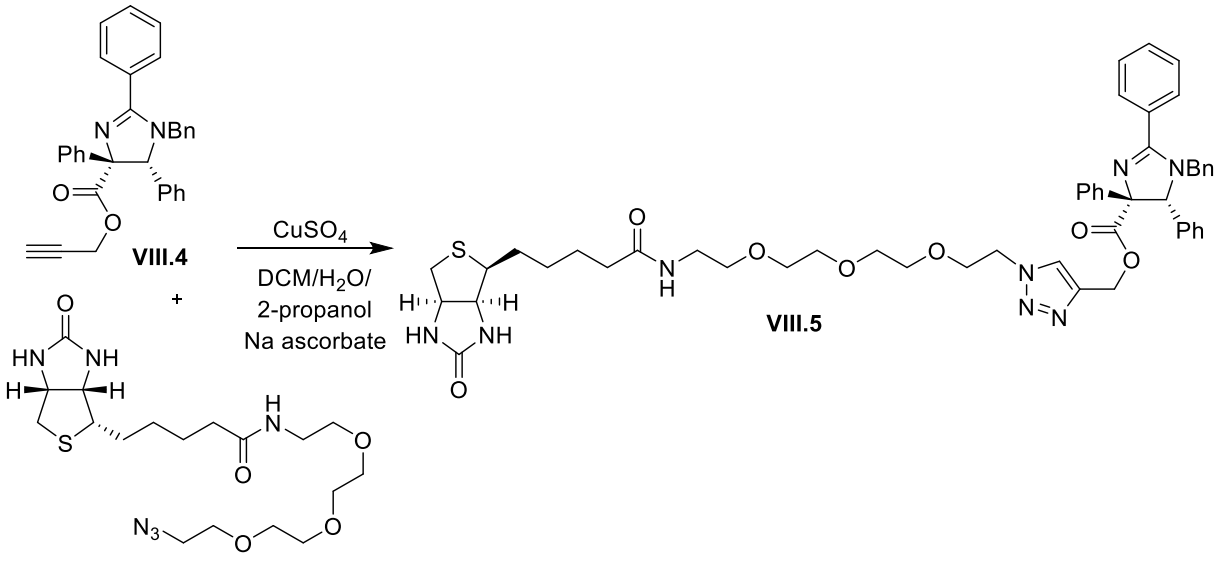
Figure 8.3: Attempted Coupling of DMT-Protected Biotinol to TCH-001



Biotin and several modified forms are commercially available, one of which being a PEG-ylated azide. The azide moiety of this molecule could react with an alkyne to form a triazole via "Click" chemistry, effectively creating a TCH-biotin probe. This method has been successfully used before,[147] and an alkynyl ester of TCH-001 was synthesized as shown in

Figure 8.4 for this reaction. This reaction was successful, and the probe is currently under investigation for biological activity.

Figure 8.4: Synthesis of a TCH/Biotin Conjugate

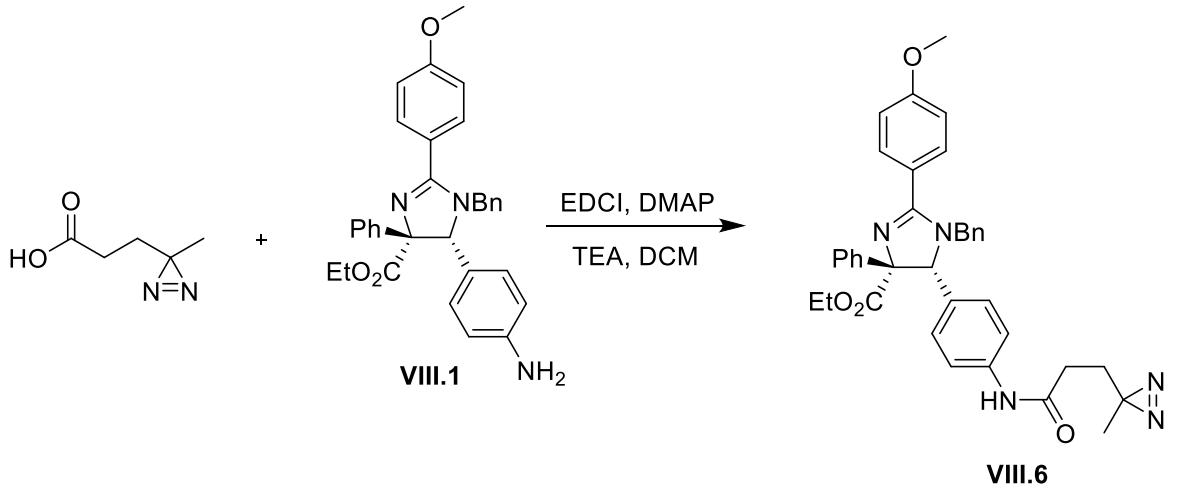


Another important tool for elucidating the binding site of TCH compounds is photoaffinity probes. These probes are typically employed in determining binding site locations in small molecule-protein interactions by synthesizing a hybrid molecule consisting of a known biologically active component and a diazirine, which functions as a protected carbene. The hybrid molecule is exposed to the target of interest (typically a protein or enzyme) under conditions that allow for binding (at least for binding of the original active compound; the main drawback in the use of photoaffinity probes is the possible influence of the probe on biological activity of the parent compound). The free carbene is generated by irradiating diazirines with a specific wavelength of light to generate a carbene and cause dinitrogen expulsion as a leaving group. The hope is the controlled generation of such a reactive intermediate in close proximity to the binding site of the parent compound to form a covalent bond. In this case, the protein/TCH conjugate would be enzymatically digested and the binding site would be identified using mass

spectrometry.

Many photoaffinity probes have been prepared and incorporated into complex molecules, providing many alternatives should a given route fail. An initial foray into this area involved the preparation of known diazirine 3-(3-methyl-3*H*-diazirin-3-yl)propanoic acid and EDCI coupling to TCH-157.

Figure 8.5: Synthesis of a First Generation Photoaffinity Probe



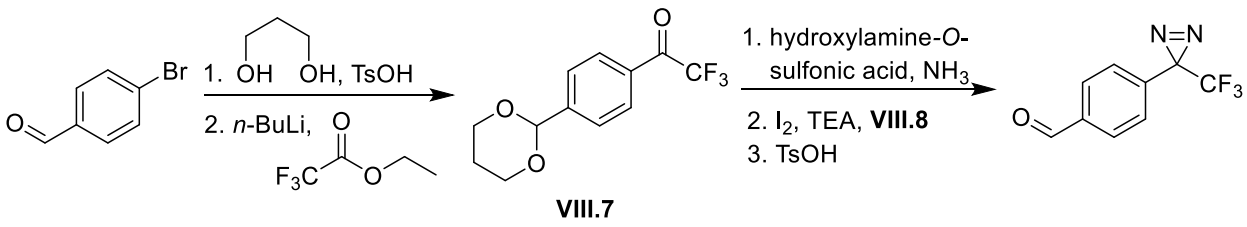
It should be noted that in both the precursor 3-(3-methyl-3*H*-diazirin-3-yl)propanoic acid and **VIII.6**, the diazirine carbon[140] (chemical shift δ = 72 in $CDCl_3$) was absent in ^{13}C NMR. Support for the proposed structures is given in the ^{1}H NMR, high-resolution mass spectrometry, and IR analysis. Additionally, the compounds are stable to storage and in solution (arguing against the presence of a carbene), however the proposed structures remain unconfirmed. Additional ^{13}C NMR experiments (HMBC) were unable to find the missing carbon.

This molecule was successfully synthesized and preliminary testing (by E. Njomen, Tepe group) indicated the molecule is biologically active. A sample was sent to our collaborators for the photolabelling and mass spectrometry experiments.

The chemistry of diazirines and their use as biological probes has been discussed in

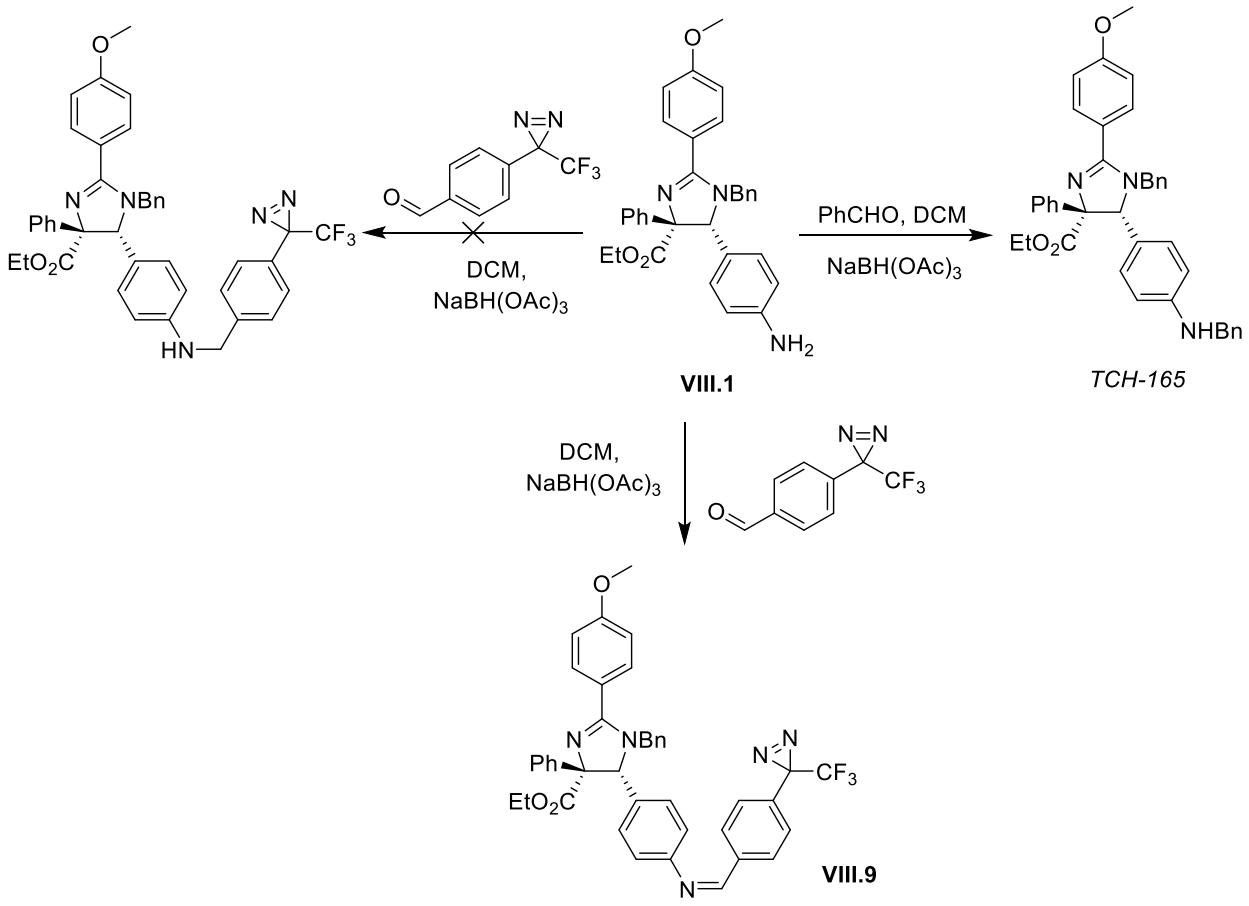
Chapter 7. Considering the possibility that an α-trifluoromethyl probe might succeed where an alkyl probe failed, the aryl α-trifluoromethyl diazirine shown in Figure 8.6 was synthesized on a 1 g scale (the precursor diaziridine has been synthesized on a 20 g scale). Somewhat surprisingly, the product was discovered to be volatile, something that is not mentioned in

Figure 8.6: Synthesis of 4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzaldehyde



literature descriptions of this compound.[145] As an alternative strategy to isolating the aldehyde, the crude deprotection reaction was extracted into DCM, dried over sodium sulfate, and carried on to the reductive amination step.

Figure 8.7: Synthesis of a Second-Generation TCH-Diazirine Photolabel



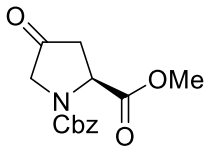
Somewhat surprisingly (after purification by silica gel chromatography and purification on an Autocolumn) the product isolated was the imine, which was obtained on a ~ 200 mg scale. The relative stability of this compound (as compared to typical imines, most of which are subject to hydrolysis on silica gel) may make it suitable for photolabeling studies, though the best course of action would be to reduce the imine (to prevent hydrolysis on the timescale of the labelling experiment).

This result is expected to be particularly significant because of the great success of the aryl α-trifluoromethyl diazirine group in photolabeling experiments, and because of its structural

similarity to TCH-165, the benchmark of the TCH-series of molecules. Labeling experiments and other biological experiments are currently under way.

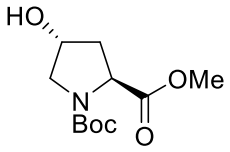
Chapter 9: Experimental

Figure 9.1: Compound II.4



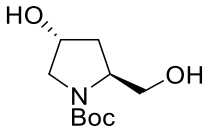
(*S*)-1-benzyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (II.4). To a 250 mL roundbottom flask containing a stir bar was added (2*S*,4*R*)-1-benzyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (8.2 g, 29.3 mmol). To the open flask was added reagent grade acetone (300 mL), and stirring commenced. To this mixture was added the Jones reagent[3] (8.79 g CrO_3, 88 mmol) dropwise over a period of 5 minutes. After addition was complete an exotherm was observed and bubbles formed. After approximately 10 minutes a green precipitate was observed (presumably Cr^{III} salts) and a purple color persisted in solution. The reaction was allowed to proceed at room temperature for an additional 30 minutes, at which time 2-propanol was added (5 mL). On addition of the alcohol the green color previously noted turned blue. The reaction mixture was filtered to remove solids and concentrated to a 2-layered mixture. To this material was added diethyl ether (50 mL) and this was filtered through Florisil. The Florisil was washed twice with diethyl ether and the filtrate was concentrated *in vacuo* to yield a clear oil. The product was purified by column chromatography (35:65 ethyl acetate: hexanes) to yield the product as a clear oil (3.7 g, 46 %). Spectroscopic data matches that reported for this compound.[146] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.37 – 7.32 (5H, m), 5.23 (1H, app d), 5.16 – 5.13 (1H, m), 4.89 – 4.82 (1H, m), 4.02 – 3.91 (2H, m), 3.77 – 3.63, (3H, m), 2.99 – 2.90 (1H, m), 2.62 – 2.58 (1H, app dd). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 207.7, 207.1, 171.8, 171.8, 154.9, 154.1, 135.9, 128.6, 128.5, 128.4, 128.3, 128.0, 67.7, 67.6, 56.0, 55.9, 52.8, 52.6, 52.4, 41.1, 40.5, 25.6.

Figure 9.2: Compound II.5a



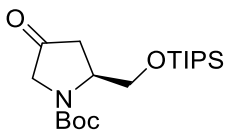
(2*S*,4*R*)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (II.5a). To a 250 mL roundbottom flask was added a stir bar, (4.0 g, 22.0 mmol) and DCM (50 mL). Stirring commenced and the reaction vessel was sealed and flushed with N_2 for 10 minutes. To this solution was added TEA (9.2 mL, 6.67 g, 66.0 mol) dropwise via syringe. The reaction was cooled to 0^o C by placing the vessel in an ice water bath. The seal was removed and di-*tert*-butyl dicarbonate (25 mmol, 5.4 g) was added in one portion, after which the reaction vessel was resealed and flushed with N_2. The solution was allowed to warm to room temperature and stir overnight. The reaction mixture was transferred to a separatory funnel, HCl (50 mL of 6.6 M) was added, and the organic layer extracted. The layers were separated and the organic layer was washed with saturated sodium carbonate (2 x 100 mL) and water (100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the product as a clear oil (4.7 g, 91 %). Spectroscopic data matches that reported for this compound.[147] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 4.49 to 4.37 (2H, m), 3.72 (3H, s), 3.65 - 3.48 (3H, m), 2.77 – 2.66 (1H, br m), 2.62 - 2.43 (1H, m), 2.07 - 1.98 (1H, m), 1.43 (9H, 2 s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 173.7, 173.4, 154.5, 154.0, 80.4, 80.3, 70.0, 69.3, 57.9, 57.4, 54.7, 54.6, 52.2, 52.0, 39.0, 38.4, 28.3, 28.2.

Figure 9.3: Compound II.5b



(2*S*,4*R*)-*tert*-butyl 4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate. (II.5b) To a 250 mL roundbottom flask was added a stir bar, (2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (11.5 g, 45.0 mmol) and THF (40 mL). Stirring commenced and the reaction vessel was cooled to 0^{o} C in an ice water bath. Lithium borohydride (45 mL of a 2.0 M solution in THF, 90.0 mmol) was added dropwise and the reaction was allowed to warm to room temperature and stir overnight, during which time the reaction mixture solidified. It was quenched with saturated ammonium chloride (added dropwise until no more gas evolved). Water was added (50 mL) followed by ethyl acetate (100 mL). The biphasic mixture was transferred to a separatory funnel and partitioned. The aqueous layer was washed with ethyl acetate (50 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield a clear oil. The crude was purified by silica gel chromatography (1:1 ethyl acetate: DCM). The product was obtained as a clear oil (4.0 g, 41 %). Spectroscopic data matches that reported for this compound.[148] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 5.19 – 5.18 (1H, m), 4.34 (1H, s), 4.12 (1H, m), 3.66 (1H, m), 3.57 – 3.49 (2H, m), 3.43 – 3.40 (1H, s), 2.62 (1H, br s), 2.05 – 2.01 (1H, m), 1.68 – 1.58 (1H, m) 1.46 (9H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 157.0, 80.6, 69.2, 67.0, 58.8, 55.7, 37.4, 28.4.

Figure 9.4: Compound II.5

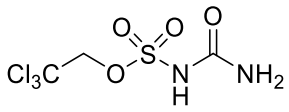


(*S*)-*tert*-Butyl 4-Oxo-2-(((triisopropylsilyl)oxy)methyl)-pyrrolidine-1-carboxylate (II.5). To a 250 mL roundbottom flask was added a stir bar, (2*S*,4*R*)-*tert*-butyl 4-hydroxy-2-(hydroxymethyl) pyrrolidine-1-carboxylate (4.0 g, 18.4 mmol), DMAP (0.150 g, 1.8 mmol) and DCM (100 mL). The reaction vessel was sealed, stirring commenced, and the sealed vessel was flushed with nitrogen. TEA (3.0 mL, 2.2 g, 22 mmol) was added dropwise via syringe, followed by TIPS-Cl (4.5 mL, 3.6 g, 19 mmol). The reaction mixture was allowed to stir overnight. The following day, water (100 mL) was added to quench the reaction. The biphasic mixture was transferred to a separatory funnel and partitioned. The organic layer was dried over sodium sulfate and the crude material was concentrated *in vacuo.* The crude protected alcohol was purified by silica gel chromatography (1:1 ethyl acetate: hexanes) to yield 4.5 g (65 %) of the mono-TIPS alcohol, which was carried on to the next step.

To a 250 mL roundbottom flask was added a stir bar, the mono-TIPS alcohol from above (8.8 mmol, 3.3 g), and 50 mL dichloromethane. Activated 4 Å molecular sieves (13.0 g) were added, followed by tetra-N-propylammonium perruthenate (0.44 mmol, 0.154 g), followed by 4-methylmorpholine N-oxide (1.54 g, 13.2 mmol). The vessel was sealed and the reaction mixture was stirred overnight and then filtered through silica plug with ethyl acetate, and the filtrate was concentrated by *in vacuo*. The residue was purified by silica gel column chromatography (2:3 ethyl acetate: hexanes) to yield 2.2 g (95%) of the product as a colorless liquid. Spectroscopic data matches that reported for this compound.[149] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 4.46 − 3.61 (5H, m), 2.83−2.63 (1H, m), 2.60−2.46 (1H, m), 1.48 (9H, s), 1.16−0.95 (21H, m); ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 210.8, 210.3, 153.7, 80.2, 80.2, 65.9, 65.4, 60.3, 55.8, 55.3, 54.1, 53.5, 40.7, 40.1, 28.4, 28.3, 21.0, 17.8, 17.6, 14.1, 12.2, 12.0, 11.8, 11.7,

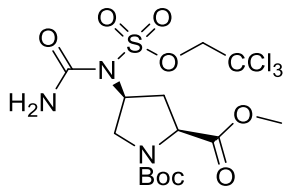
11.5.

Figure 9.5: Compound II.11



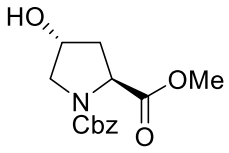
2,2,2-trichloroethyl carbamoylsulfamate (II.11). To a 100 mL roundbottom flask was added a stir bar, chlorosulfonyl isocyanate (3.3 mL, 5.30 g, 37.5 mmol), and chlorobenzene (17 mL). Sitrring commenced and a solution of 2,2,2-trichloroethanol (3.6 mL, 5.60 g, 37.5 mmol) in chlorobenzene (25 mL) was added dropwise via syringe. The reaction was heated at reflux for 12 h. Following this period, the reaction was cooled to room temperature and the condenser was replaced by a short path distillation head equipped with a 100 mL receiving flask. The chlorobenzene was removed by distillation to give a light brown viscous residue. This material was dissolved in DCM (40 mL) and the solution was cooled to 0 °C in an ice-water bath. Hexamethyldisilazane (7.9 mL, 6.04 g, 37.5 mmol) was then added dropwise via syringe. The reaction mixture was stirred at room temperature for 4 hours. The solution was concentrated *in vacuo* to give an off-white solid, which was subsequently dissolved in methanol (40 mL) and acetic acid (300 μL). The resulting slurry was stirred vigorously for 5 hours after which time all volatile materials were removed *in vacuo* and the oily product was dried azetropically with toluene (50 mL). The remaining solid was recrystallized from ethyl acetate: hexanes (300 mL of a 3:1 mixture) to give the desired product as an amorphous white powder (2.21 g, 22%). Spectroscopic data matches that reported for this compound.[150] ^{1}H NMR (d_6-DMSO) (500 MHz) δ: 7.09 (br s, 2H), 5.42 (br s, 2H), 4.49 (2H, s). ^{13}C NMR (d_6-DMSO) (125 MHz) δ: 161.1, 96.5, 77.9. M.P. = 165 ºC.

Figure 9.6: Compound II.12



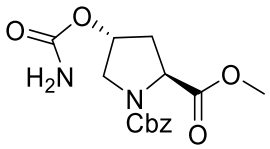
(2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-(1-((2,2,2-trichloroethoxy)sulfonyl)ureido)pyrrolidine-1,2-dicarboxylate (II.12). To a 250 mL roundbottom flask containing a stir bar was added (2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (1.8 g, 7.3 mmol), 2,2,2-trichloroethyl carbamoylsulfamate (2.52 g, 9.4 mmol), and triphenylphosphine (2.46 g, 9.4 mmol). The reaction vessel was sealed with a septum and freshly distilled THF (15 mL) was added via syringe. Stirring commenced and all solids dissolved. Diisopropylazodicarboxylate (DIAD) was added dropwise (1.86 mL, 1.89 g, 9.4 mmol). A yellow color was observed during DIAD addition, but this color disappeared shortly after addition was complete. The reaction was allowed to stir at room temperature overnight. The next day the reaction mixture was concentrated *in vacuo* to an oil. The crude product was purified by flash column chromatography (gradient 1:9 to 3:7 ethyl acetate: hexanes, R_f = 0.15). The desired fractions were combined and concentrated to give the product as a white solid (2.8 g, 78 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.03 (1H, br s), 6.11 - 5.95 (1H, br d), 5.41 (1H, br s), 4.66 (2H, s), 4.52 - 4.38 (1H, dd, *J* = 11 Hz), 3.75 (3H, s), 2.55 – 2.45 (1H, m), 2.39 (1H, app d, *J* = 14 Hz), 1.80 (1H, s), 1.45 (9H, app d). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 172.4, 172.3, 159.4, 153.9, 153.6, 93.5, 80.9, 80.8, 78.4, 77.6, 76.4, 57.4, 57.2, 52.5, 52.4, 52.2, 51.6, 36.1, 35.1, 28.3, 28.2. HRMS calc'd for [M+Na] = 520.0091, observed [M+Na] = 520.0094. IR (NaCl, DCM): 1744, 1693, 1639, 1444, 1407, 1344, 1177, 1017, 853. M.P. = 120 – 121º C.

Figure 9.7: Compound II.13



1-benzyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (II.13). To a 100 mL roundbottom flask containing a stir bar was added *trans*-4-hydroxy-*L*-proline methyl ester HCl salt (5.4 g, 30.0 mmol), followed by water/dioxane mixture (60 mL of a 1:1 solution). Stirring commenced, and sodium bicarbonate was added (5.6 g, 40.0 mmol). To the stirring mixture was added Cbz-Cl dropwise (5.0 mL, 5.9 g, 35.0 mmol). The reaction mixture was allowed to stir overnight. The following day the reaction mixture was concentrated to approximately half the original volume *in vacuo*. The crude reaction mixture was transferred to a separatory funnel and extracted with DCM (4 x 50 mL). The organic layers were combined and washed with dilute HCl (20 mL of a 1.0 M solution). The organic layer was dried over sodium sulfate and concentrated to dryness *in vacuo* to yield the product as a clear oil (8.2 g, 99 %). Spectroscopic data matches that reported for this compound.[151] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.27 (5H, m), 5.21 – 5.00 (2H, m), 4.52 – 4.48 (2H, m), 3.76 – 3.63 (3H, m), 2.35 – 2.26 (1H, m), 2.12 – 2.06 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 173.2, 172.0, 155.0, 154.5, 136.3, 136.2, 128.4, 128.4, 128.0, 128.0, 127.9, 127.8, 70.1, 69.4, 67.2, 57.8, 57.6, 55.2, 54.6, 52.4, 52.1, 39.1, 38.4.

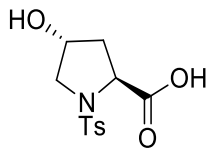
Figure 9.8: Compound II.14



(2*S*,4*R*)-1-benzyl 2-methyl 4-(carbamoyloxy)pyrrolidine-1,2-dicarboxylate (II.14). To a 100

mL roundbottom flask containing a stir bar was added (2*S*,4*R*)-1-benzyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (2.0 g, 7.1 mmol). The vessel was sealed with a septa and flushed with nitrogen. DCM (30 mL) was added and stirring commenced. To this mixture, trichloroacetyl ioscyanate was added dropwise (1.0 mL, 1.59 g, 8.5 mmol). The reaction progress was monitored by TLC (1:1 ethyl acetate: hexanes), which indicated starting material was consumed (after 10 minutes). The crude reaction mixture was concentrated *in vacuo* to a foam. The reaction mixure was dissolved in methanol (30 mL) and 25 mg potassium carbonate was added (as a catalyst to generate methoxide). The reaction progress is monitored by TLC (1:1 ethyl acetate: hexanes), and on completion (10 minutes) the reaction was stopped by concentrating *in vacuo* to give the crude product as an oil. The pure product is obtained by column chromatography (1:1 ethyl acetate: hexanes, R_f = 0.60) as a clear oil (2.1 g, 92 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.28 (5H, m), 5.23 – 5.01 (3H, m), 4.70 (2H, br s), 4.48 – 4.40 (1H, m), 3.81 – 3.69 (3H, m), 3.54 (1H, s), 2.48 – 2.40 (1H, m), 2.23 – 2.15 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 172.6, 172.5, 155.6, 154.7, 154.1, 128.4, 128.4, 128.1, 128.1, 127.9, 127.9, 73.3, 72.6, 67.3, 57.8, 57.6, 52.6, 52.5, 52.3, 52.2, 36.7, 35.7. HRMS calc'd for [M+H] = 323.1243, observed [M+H] = 323.1248. IR (NaCl, DCM): 1732, 1716, 1701, 1596, 1420, 1354, 1212, 1074, 1032.

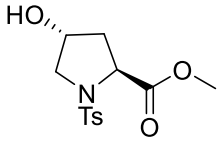
Figure 9.9: Compound II.15a



(2*S*,4*R*)-methyl 4-hydroxy-1-tosylpyrrolidine-2-carboxylate (II.15a). To a 250 mL roundbottom flask containing a stir bar was added *trans*-4-hydroxy-L-proline (5.0 g, 38.1 mmol) and sodium carbonate (8.29 g, 79.8 mmol), followed by 100 mL water. To this mixture was

added tosyl chloride (8.55 g, 45.6 mmol). The mixture was allowed to stir at room temperature for 48 hours, during which time nearly all the tosyl chloride dissolved. After this time, the reaction mixture was acidified with 2N HCl until bubbles stopped evolving. During acidification, a solid precipitated. This was filtered and washed with water (50 mL) and hexanes (50 mL). The solid was dried *in vacuo* to constant weight to yield the product as a white solid (6.68 g, 55 %). Spectroscopic data matches that reported for this compound.[152] ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 12.74 (1H, br s), 7.67 (2H, app quartet, *J* = 6.5, 2.0 Hz), 7.39 (2H, d, *J* = 8.0 Hz), 4.84 (1H, d, *J* = 3.5 Hz), 4.19 (1H, br d, *J* = 3.5 Hz), 4.01 (1H, t, *J* = 8.0 Hz), 3.44 (1H, quartet, *J* = 10.0, 4.0 Hz), 3.07 (1H, app quartet, *J* = 11.5, 2.0 Hz), 2.38 (3H, s), 1.94 – 1.91 (2H, m). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 173.7, 143.6, 134.8, 130.0, 127.9, 68.8, 60.0, 56.7, 21.4. M.P. = 151 ºC.

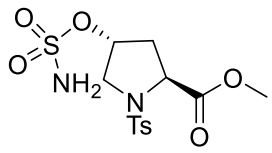
Figure 9.10: Compound II.15b



(2*S*,4*R*)-methyl 4-hydroxy-1-tosylpyrrolidine-2-carboxylate (II.15b). To a 250 mL roundbottom flask containing a stir bar was added (6.61 g, 23 mmol) and methanol (100 mL). Stirring commenced and the vessel was cooled to 0 ºC in an ice-water bath. To this mixture was slowly added thionyl chloride (1.5 mL, 2.44 g, 21 mmol) dropwise over 10 minutes. The ice-water bath was removed and the reaction vessel was placed in a heating mantle. A reflux condenser was attached to the roundbottom flask and the reaction mixture was heated to reflux overnight. The next day, the reaction was cooled to room temperature and transferred to a separatory funnel. To this was added ethyl acetate (100 mL) and water (50 mL). The water layer was separated and discarded. The mixture was then washed with saturated sodium bicarbonate

(50 mL) and water again (50 mL). The organic layer was dried on sodium sulfate and concentrated to dryness *in vacuo* to yield the product as a white solid (7.42 g, 99 %). Spectroscopic data matches that previously reported for this compound.[153] ^{1}H NMR (500 MHz) ($CDCl_3$) δ TMS: 7.76 (2H, d, *J* = 9.5 Hz), 7.31 (2H, d, *J* = 8.5), 4.44 (1H, quintet, *J* = 6.5, 4.0, 2.5 Hz), 4.38 (1H, t, *J* = 7.5 Hz), 3.73 (3H, s), 3.59 (1H, dd, *J* = 11.0, 4.0 Hz), 3.37 (1H, dt, *J* = 11.0, 2.0 Hz), 2.41 (3H, s), 2.26 – 2.17 (1H, m), 2.11 – 2.06 (1H, m), 1.18 (1H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ TMS: 172.5, 143.8, 134.6, 129.6, 127.7, 70.1, 59.3, 56.3, 52.5, 39.4, 22.5. Melting point = 94 – 96º C.

Figure 9.11: Compound II.16



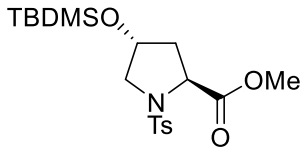
(2*S*,4*R*)-methyl 4-(sulfamoyloxy)-1-tosylpyrrolidine-2-carboxylate (II.16). A 50 mL roundbottom flask containing a stir bar was sealed and flushed with nitrogen. To this vessel was added chlorosulfonyl isocyanate (1.15 mL, 1.88 g, 21,75 mmol) and stirring commenced. The vessel was cooled in an ice-water bath and 95 % formic acid was added dropwise (0.67 mL, 0.825 g, 21.75 mmol). Vigorous bubbling and solidification of the mixture was observed. To this was added acetonitrile (5 mL), upon which the solid dissolved. The reaction was allowed to proceed for 8 hours, during which time it warmed to room temperature.

In a separate roundbottom flask (50 mL) containing a stir bar was added (2*S*,4*R*)-methyl 4-hydroxy-1-tosylpyrrolidine-2-carboxylate (2.94 g, 9.8 mmol). The vessel was sealed with a septa and flushed with nitrogen. To this was added dimethylacetamide (20 mL) by syringe. The mixture was stirred until the solid dissolved, upon which time this solution was withdrawn into a syringe and added dropwise to the chlorosulfonyl isocyanate/formic acid mixture from the first

reaction vessel, and was allowed to proceed overnight.

To the reaction mixture was added ethyl acetate (100 mL). This was transferred to a separatory funnel and the crude mixture was washed four times with water (100 mL) and four times with saturated sodium chloride (100 mL). This was dried over sodium sulfate and concentrated *in vacuo*. The crude was recrystallized by dissolving in ethyl acetate and adding hexanes to yield the pure product as a brown solid (1.97 g, 51 %). ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 7.68 (2H, d, *J* = 7.5 Hz), 7.56 (2H, br s), 7.32 (2H, d, *J* = 8.0 Hz), 4.95 (1H, br t, *J* = 2.0 Hz), 4.18 (1H, t, *J* = 7.5 Hz), 3.72 (1H, dd, *J* = 12.0, 4.0 Hz), 3.65 (3H, s), 3.50 (1H, br d, *J* = 12.0 Hz), 2.49 (1H, br t, *J* = 1.5 Hz), 2.38 – 2.34 (4H, m), 2.29 – 2.23 (1H, m). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 171.8, 144.3, 134.4, 130.3, 127.7, 77.6, 59.3, 54.1, 52.8, 36.8, 21.5. HRMS [M+H] calc'd = 379.0634, observed [M+H] = 379.0634. IR (NaCl, DCM): 1752, 1598, 1437, 1372, 1310, 1180, 1160, 1055, 955, 898, 819. M.P. = 138 – 139º C.

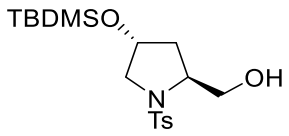
Figure 9.12: Compound II.7



methyl (2*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-tosylpyrrolidine-2-carboxylate (II.7). To an oven dried 100 mL roundbottom flask containing a stir bar was added (2*S*,4*R*)-methyl 4-hydroxy-1-tosylpyrrolidine-2-carboxylate (3.0 g, 10.0 mmol), followed by acetonitrile (30 mL). To this mixture was added (in the order described) imidazole (1.02 g, 15.0 mmol), TBS-Cl (1.65 g, 11.0 mmol), and DMAP (0.043 g, 0.35 mmol). The vessel was sealed with a septa and flushed with nitrogen. Within 15 minutes crystals precipitated (presumably imidazole HCl salt). The reaction was allowed to proceed overnight.

The following day the reaction was quenched by adding methanol (2 mL), which dissolved the precipitate. The crude reaction was transferred to a separatory funnel and partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (2 x 30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a clear oil. The crude product was purified by silica gel chromatography (1:4 ethyl acetate: hexanes, R_f = 0.48) to yield the pure product as a white solid (3.6 g, 87 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.74 (2H, d, *J* = 7.0 Hz), 7.30 (2H, d, *J* = 8.5 Hz), 4.37 - 4.25 (1H, m), 4.23 (1H, t, *J* = 7.5 Hz), 3.79 (3H, s), 3.64 (1H, dd, *J* = 20.0 Hz, 4.0 Hz), 3.19 – 3.17 (1H, m), 2.45 (3H, s), 2.08 – 2.04 (2H, m), 0.70 (9H, s), - 0.81 (6H, app t, *J* = 3.0 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 172.6, 143.6, 134.2, 129.6, 127.7, 70.3, 59.7, 56.7, 52.5, 40.1, 25.5, 21.5, 17.7, - 4.9, - 5.1. HRMS = [M+H] calc'd = 414.1770, observed = 414.1769. IR (NaCl, DCM): 2952, 2856, 1740, 1471, 1350, 1020, 838. M.P. = 74 ºC.

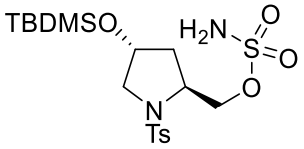
Figure 9.13: Compound II.7a



((2*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-tosylpyrrolidin-2-yl)methanol (II.7a). To a 100 mL roundbottom flask containing a stir bar and methyl (2*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-tosylpyrrolidine-2-carboxylate (2.2 g, 5.8 mmol) was added THF (50 mL). The reaction vessel was sealed and flushed with nitrogen while stirring commenced. To this mixture was added dropwise lithium borohydride (3.5 mL of a 2.0 M solution in THF, 7.0 mmol). The reaction mixture was allowed to stir overnight. The following day, the reaction mixture was quenched with saturated ammonium chloride (1.5 mL) and the crude reaction mixture was concentrated to dryness as a white solid. This material was dissolved in ethyl acetate (50 mL) and washed with

water (50 mL). The aqueous phase was extracted with an additional portion of ethyl acetate (50 mL) and the organic phases were combined, dried over sodium sulfate, and concentrated to dryness *in vacuo* to yield a white solid. The crude product was purified by silica gel chromatography (1:4 ethyl acetate: hexanes, R_f = 0.15) to yield the product as a white solid (2.0 g, 89 % yield). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.74 (2H, d, *J* = 8.5 Hz), 7.30 (2H, d, *J* = 7.0 Hz), 4.25 (1H, br s), 3.89 (1H, t, *J* = 7.0 Hz), 3.67 – 3.62 (3H, m), 3.22 (1H, br d, *J* = 11.0 Hz), 3.06 (1H, br s), 2.42 (3H, m), 1.92 – 1.87 (1H, br m), 1.76 – 1.72 (1H br m), 0.70 (9H, s), - 0.082 (3H, s), - 0.102 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 143.7, 133.5, 129.7, 127.8, 69.4, 65.2, 60.9, 58.6, 38.7, 25.5, 21.5, 17.8, - 4.9, - 5.0. HRMS calc'd for [M+H] = 386.1821, observed = 386.1829. IR: (NaCl, DCM): 3434, 2858, 1644, 1471, 1372, 1183.

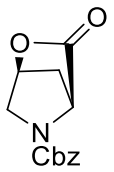
Figure 9.14: Compound II.17



((2*S*,4*R*)-4-((tert-butyldimethylsilyl)oxy)-1-tosylpyrrolidin-2-yl)methyl sulfamate (II.17). An oven dried 100 mL roundbottom flask containing a stir bar was sealed with a septa and flushed with nitrogen. To this vessel was added chlorosulfonyl isocyanate (1.0 mL, 1.70 g, 12.0 mmol) via syringe. Stirring commenced and the reaction vessel was cooled to 0 ºC in an ice water bath. To the reaction mixture was added 95 % formic acid (0.450 mL, 12.0 mmol) dropwise via syringe. Vigorous evolution of gas was observed, and the reaction mixture turned into a white solid before addition of the formic acid was complete. To the white solid was added acetonitrile (10 mL) via syringe, after which the precipitate dissolved. The reaction mixture was allowed to warm to room temperature over 8 hours. In a separate reaction vessel, ((2*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-tosylpyrrolidin-2-yl)methanol (2.0 g, 5.20 mmol) was dissolved in

dimethylacetamide (20 mL) and transferred to the reaction vessel containing the chlorosulfonyl isocyanate/formic acid/acetonitrile mixture via cannula. The combined reaction mixture was allowed to stir at room temperature overnight. The following day, the reaction mixture was quenched by the addition of ethyl acetate (200 mL). The crude reaction mixture was transferred to a separatory funnel and washed with water (3 x 300 mL) and brine (3 x 300 mL). The crude reaction mixture was purified by silica gel chromatograpy (1:3 ethyl acetate: hexanes, R_f = 0.15) to yield the product as a clear oil (0.900 g, 37 % yield). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.72 (2H, d, *J* = 7.5 Hz), 7.31 (2H, d, *J* = 7.5 Hz), 5.19 (2H, br s), 4.55 (1H, dd, *J* = 10.0, 5.5 Hz), 4.41 (1H, dd, *J* = 10.0, 2.5 Hz), 4.29 (1H, quintet, *J* = 5.5, 4.5 Hz), 3.90 – 3.79 (1H, m), 3.62 (1H, dd, *J* = 11.0, 4.0 Hz), 3.18 – 3.15 (1H, m), 2,42 (3H, s), 2.11 – 2.06 (1H, m), 1.85 – 1.80 (1H, m), 0.07 (9H, s), - 0.09 (3H, s), - 0.10 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 144.0, 133.2, 129.8, 127.8, 71.6, 69.4, 57.7, 57.0, 38.4, 25.6, 21.5, 17.9, - 4.9, - 5.1. HRMS calc'd for [M+Na] = 487.1369, observed = 487.1387. IR (NaCl, DCM): 3482, 2952, 2856, 1458, 1340, 1157, 1094, 951, 835. M.P. = 72 ºC.

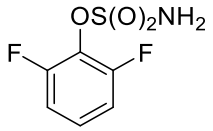
Figure 9.15: Compound II.6



(1*S*,4*S*)-benzyl 3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (II.6). To a 250 mL roundbottom flask was added a stir bar and (2*S*,4*R*)-1-((benzyloxy)carbonyl)-4-hydroxypyrrolidine-2-carboxylic acid, 10.07 g, 38.0 mmol), followed by triphenylphosphine (11.0 g, 42.0 mmol). The reaction vessel was sealed and flushed with nitrogen. Freshly distilled THF (130 mL) was added by syringe. Stirring commenced and the reaction vessel was cooled to 0 ºC in an ice-water bath. Diisopropylazodicarboxylate (DIAD) was added dropwise (8.26 mL,

8.48 g, 42.0 mmol). During DIAD addition a white solid formed. Ten minutes after DIAD addition the reaction vessel was removed from the ice-water bath, and allowed to stir at room temperature overnight (shortly after removing the ice-water bath the solid formed on DIAD addition dissolved). The following day the reaction mixture was concentrated *in vacuo*. The crude reaction mixture was redissolved in a minimum amount of ethyl acetate and purified by silica gel chromatography (gradient 1:9 to 1:1 ethyl acetate: hexanes) to afford the purified compound as a solid (4.2 g, 48 % yield). Spectroscopic data matches that previously reported for this compound.[154] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.38 – 7.31 (5H, m), 5.19 – 5.10 (3H, br s), 4.75 – 4.61 (1H, br s), 3.60 (1H, d, *J* = 10 Hz), 3.54 (1H, br s), 2.23 (1H, td, *J* = 11, 2.5, 1), 2.03 (1H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 170.7, 154.4, 135.8, 128.5, 128.3, 128.1, 78.2, 67.9, 67.7, 57.6, 50.0, 39.2. M.P. = 94 – 95º C.

Figure 9.16: Compound II.18

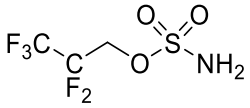


2,6-difluorophenyl sulfamate (II.18). A 100 mL roundbottom flask containing a stir was sealed with a septa and flushed with nitrogen for 5 minutes. To the reaction vessel was added chlorosulfonyl isocyanate (3.75 mL, 6.06 g, 43 mmol), followed by acetonitrile (6 mL). The reaction vessel was cooled to 0 °C in an ice water bath. To the cooled reaction mixture was added 95 % formic acid dropwise (1.65 mL, 2.02 g, 43.7 mmol). During the addition vigorous bubbling was observed and the reaction mixture solidified to a white solid. After the addition of formic acid was complete, acetonitrile was added for a second time (12 mL). The white solid dissolved to produce a clear solution, which was removed from the ice bath and allowed to stir at room temperature for 2 hours. This reaction mixture was again cooled to 0 °C before addition of

the alcohol. A separate 50 mL reaction vessel was charged with 2,6-difluorophenol (2.53 g, 19.5 mmol), sealed with a septa and flushed with nitrogen for 5 minutes. To this was added dimethyl acetamide (10 mL). The alcohol/dimethylacetamide solution was transferred to the chlorosulfonyl isocyanate/acid solution via cannula, and the mixture was allowed to stir at room temperature overnight.

The following day, water was added to the reaction mixture (80 mL). This was transferred to a separatory funnel and washed twice with ether (80 mL). The organic layers were combined and washed four times with water (150 mL per wash). The organic layer was dried over sodium sulfate and concentrated to dryness *in vacuo*. The crude product was recrystallized by dissolving in hot acetone and adding chloroform, to yield the title compound as a pink solid (2.91 g, 72 %). Spectroscopic data matches that reported for this compound.[155] ^{1}H NMR (500 MHz) (d_6-acetone) δ: 7.52 (2H, br s), 7.43 – 7.37 (1H, m), 7.21 – 7.15 (1H, m). ^{13}C NMR (125 MHz) (d_6-acetone) δ: 156.2, 127.9, 126.9, 112.6. M.P. = 103 ºC.

Figure 9.17: Compound II.19

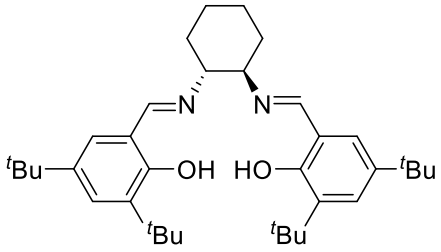


2,2,3,3,3-pentafluoropropanol sulfamate (II.19). A 100 mL roundbottom flask containing a stir was sealed with a rubber septa and flushed with nitrogen for 5 minutes. To the reaction vessel was added chlorosulfonyl isocyanate (6.0 mL, 9.9 g, 70.0 mmol). The reaction vessel was cooled to 0 °C in an ice water bath. To the cooled reaction mixture was added 95 % formic acid dropwise (2.62 mL, 3.12 g, 69.0 mmol). During the addition vigorous bubbling was observed and the reaction mixture solidified to a white solid. After the addition of formic acid was complete, anhydrous acetonitrile was added (18 mL). The white solid dissolved to produce a

clear solution, which was removed from the ice bath and allowed to stir at room temperature for 6 hours. This reaction mixture was again cooled to 0 °C before addition of the alcohol. A separate 50 mL reaction vessel was charged with 2,2,3,3,3-pentafluoropropanol (5.0 g, 33.0 mmol), sealed with a septa and flushed with nitrogen for 5 minutes. To this was added anhydrous dimethylacetamide (18 mL). The alcohol/dimethylacetamide solution was transferred to the chlorosulfonyl isocyanate/acid solution via cannula, and the mixture was allowed to stir at room temperature overnight.

The next day water (20 mL) was added to the reaction mixture and the reaction mixture was transferred to a separatory funnel. This was washed twice with ethyl acetate (50 mL). The organic layers were combined and washed with water (4 x 50 mL). The organic layer was dried on sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (3:7 ethyl acetate hexanes) to yield the purified product as a clear oil (4.83 g, 64 %). Spectroscopic data matches that reported for this compound.[156] ^{1}H NMR (500 MHz) (d_6-acetone) δ: 7.20 (2H, br s), 4.71 (2H, dt, J = 12.5 Hz, 1.0 Hz). ^{13}C NMR (125 MHz) (d_6-acetone) δ: 120.2 (qt, J_{CF} = 283.6, 34.2 Hz), 113.7 (tq, J_{CF} = 253.4, 38.0 Hz), 65.2 (t, J_{CF} = 27.9 Hz).

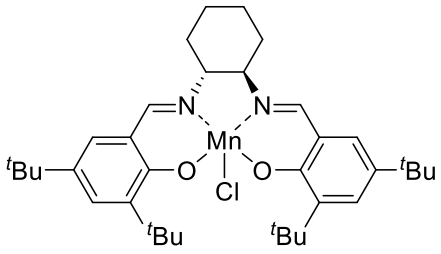
Figure 9.18: Compound II.20a



6,6'-((1E,1'E)-(((1*R*,2*R*)-cyclohexane-1,2 diyl)bis(azanylylidene)) bis(methanylylidene)) bis(2,4-di-tert-butylphenol) (II.20a). To a 100 mL flask with a stir bar was added anhydrous ethanol (25 mL), followed by (1*R*, 2*R*)-1,2-diamino-cyclohexane (1.0 g, 8.7 mmol). To this mixture was added 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (4.1 g, 17.5 mmol). The vessel was

attached to a reflux condenser which was sealed with a septa and flushed with nitrogen. The sealed reaction vessel was heated to reflux for 1.5 hours. Solid persisted throughout the reflux period. After the prescribed time, the reaction mixture was cooled to room temperature and the product was filtered through a fritted funnel and washed with cold ethanol (3 x 50 mL). The precipitate was dried *in vacuo* to yield the product as a yellow solid (4.07 g, 85 %). Spectroscopic data matches that known for this compound.[157] ^{1}H NMR (500 MHz) ($CDCl_3$): 13.7 (1H, br s), 8.31 (1H, s), 7.31 (1H, d, *J* = 2.5 Hz), 6.99 (1H, d, *J* = 3.5 Hz), 3.30 (1H, m), 1.96 – 1.87 (2H, m), 1.74 (1H, m), 1.54 – 1.42 (10H, m), 1.24 (9H, s). ^{13}C NMR (125 MHz) ($CDCl_3$): 165.8, 157.9, 139.8, 136.3, 126.7, 126.0, 117.8, 72.4, 34.9, 34.0, 33.2, 31.4, 29.4, 24.3. HRMS calc'd for [M+H] = 547.4264, observed = 547.4276. M. P. = 224 ºC.

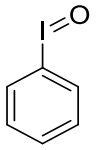
Figure 9.19: Compound II.20



6,6'-((1E,1'E)-(((1*R*,2*R*)-cyclohexane-1,2 diyl)bis(azanylylidene)) bis(methanylylidene)) bis(2,4-di-tert-butylphenol) manganese chloride (II.20). To a 100 mL roundbottom flask containing a stir bar was added 6,6'-((1E,1'E)-(((1*R*,2*R*)-cyclohexane-1,2 diyl)bis(azanylylidene)) bis(methanylylidene)) bis(2,4-di-tert-butylphenol) (0.546 g, 1.0 mmol), followed by manganese(II) tetrahydrate (1.22 g, 5.0 mmol), followed by ethanol (25 mL). Stirring commenced, a reflux condenser was attached to the reaction vessel, and the reaction mixture was heated to reflux for 8 hours. After 7 hours had elapsed, LiCl (0.212 g, 5.0 mmol) was added in one portion, and refluxing continued for the final hour. After this, the reaction mixture was

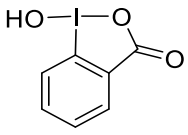
allowed to cool to room temperature and 25 mL water was added. The reaction vessel was sealed and placed in a – 20 ºC freezer overnight. The following day, the reaction mixture was filtered on a fritted funnel and the dark brown solid that was collected was washed with water (50 mL). Remaining solvent was removed *in vacuo* and to yield the pure product as a brown solid (0.858 g, 130 %; the product is known to crystallize with one or more molecules of ethanol, which account for the excess yield[158]). HRMS calc'd for [M-Cl] = 599.3409, observed = 599.3414. M. P. = no melting observed below 250 ºC (consistent with the literature report).

Figure 9.20: Iodosylbenzene



Iodosylbenzene. This compound was prepared according to a literature procedure.[13] To a 1000 mL roundbottom flask containing a stir bar was added diacetoxyiodobenzene (16.0 g, 50.0 mmol). To this vessel was added aqueous NaOH (1.88 M, 532 mL), and this mixture was stirred at room temperature for 3 hours. After this period, the reaction mixture was filtered (fritted funnel) and washed three times with water (250 mL per wash). The solid product was air dried and transferred to a 250 mL roundbottom flask in which it was dried *in vacuo* overnight to yield the product as a free flowing yellow powder (9.36 g, 90 %). M.P. = 220 ºC.

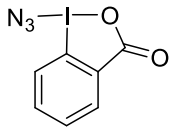
Figure 9.21: Compound II.21a



1-hydroxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1H)-one (II.21a). In a 250 mL roundbottom flask was added a stir bar, 2-iodo-benzoic acid (8.95 g, 36 mmol), and aqueous acetic acid (100 mL of a 30

% acetic acid/water solution). To this mixture was added sodium metaperiodate (7.72 g, 36 mmol). The reaction mixture was placed in a heating mantle on a magnetic stir plate and stirring commenced. The reaction vessel was wrapped in aluminum foil (to protect it from ambient light), the vessel and apparatus were placed behind a blast shield. The reaction mixture was heated to reflux for four hours then cooled to room temperature. Once cool water was added (50 mL). The reaction mixture was stirred for an additional 40 minutes. At this point, the reaction mixture was filtered, and the solid was washed twice with water (50 mL) and three times with acetone (50 mL). The solid was dried *in vacuo* to yield the product as a white, crystalline powder (8.8 g, 92 %). Spectroscopic data match that reported for this compound.[159] ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 8.03 – 7.93 (3H, m), 7.83 (1H, d, J = 8.0 Hz), 7.69 (1H, t, J = 7.5 Hz). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 168.1, 134.9, 131.9, 131.9, 131.5, 130.8, 126.7, 120.8. M.P. = 251 ºC.

Figure 9.22: Compound II.21

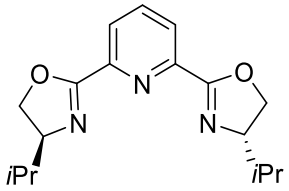


1-azido-1λ3-benzo[*d*][1,2]iodaoxol-3(1H)-one (II.21). To an oven dried 100 mL roundbottom flask was added a stir bar and 1-hydroxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1H)-one (2.12 g, 8 mmol). The flask was sealed with a septa and flushed with nitrogen for 5 minutes. To the sealed vessel was added acetonitrile (20 mL). Stirring commenced, and the solid dispersed to form a suspension. To the stirring suspension was added $TMSN_3$ dropwise via syringe (2.12 mL, 2.12 g, 16 mmol). The reaction was allowed to proceed overnight. Within one hour of adding the $TMSN_3$ the solid had dissolved, and over time a solid began to precipitate.

The following day, the reaction was quenched by the addition of ether (50 mL) and the suspension was filtered (fritted funnel) and washed with ether. The yellow solid was dried *in*

vacuo to yield the product (1.00 g, 44 %). Spectroscopic data matches that reported for this compound.[159] ^{1}H NMR (500 MHz) (20:1 $CDCl_3$:TFA) δ: 8.36 – 8.34 (1H, m), 8.32 – 7.98 (2H, m), 7.85 (1H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 170.6, 169.8, 138.0, 137.0, 134.1, 133.8, 132.3, 132.2, 128.9, 128.7, 127.0, 126.4, 118.6, 117.7, 115.6, 113.3, 111.0. IR (NaCl, DCM): 3002, 2597, 2453, 2131, 2061, 1990, 1653, 1437, 1314. M.P. = 135 ºC (detonation).

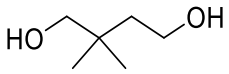
Figure 9.23: Compound II.22



2,6-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)pyridine (II.22). To an oven dried 100 mL roundbottom flask was added a stir bar, pyridine-2,6-dicarbonitrile (0.387 g, 3 mmol), and $Zn(OTf)_2$ (0.054 g, 0.015 mmol). The reaction vessel was sealed with a septa and purged with argon for 5 minutes. To this mixture was added anhydrous toluene (20 mL). This mixture was stirred for 5 minutes, at which time (*S*)-(+)-2-amino-3-methyl-1-butanol (0.618 g, 6 mmol) was added via syringe dissolved in anhydrous toluene (10 mL). The reaction mixture was heated to reflux for 48 hours. After this period, the reaction mixture was cooled to room temperature and transferred to a separatory funnel. The crude reaction mixture was partitioned between ethyl acetate (20 mL) and saturated sodium bicarbonate (30 mL). The organic later was washed with brine (30 mL), dried over sodium sulfate and concentrated *in vacuo* to yield the product as a white solid (0.730 g, 80 %). Spectroscopic data matches that reported for this compound.[160,161] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.22 (2H, d, *J* = 8.0 Hz), 7.86 (1H, t, *J* = 7.5 Hz), 4.54 (2H, quart., *J* = 8.0 Hz, 2.0 Hz), 4.23 (2H, t, *J* = 8.0 Hz), 4.17 – 4.14 (2H, m), 1.87 (2H, septet, *J* = 7.0

Hz), 1.05 (6H, d, *J* = 6.0 Hz), 0.94 (6H, d, *J* = 6.0 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 162.2, 146.9, 137.1, 125.7, 72.9, 70.9, 32.8, 19.0, 18.3. M.P. = 148 ºC.

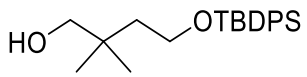
Figure 9.24: Compound III.2a



2,2-dimethylbutane-1,4-diol (III.2a). An oven dried 1000 mL roundbottom containing a stir bar was charge with 500 mL THF and cooled to 0 ºC in an ice bath. Stirring commenced and lithium aluminum hydride (7.4 g, 200.0 mmol) was added slowly. The reaction vessel was sealed with a septa and flushed with nitrogen. In a separate oven dried reaction vessel (250 mL) 2,2-dimethyl succinic acid (10.0 g, 68.0 mmol) was dissolved in THF (100 mL). An endotherm was observed on dissolution. The succinic acid/THF solution was cannulated into the LAH/THF solution, during which hydrogen gas evolved. After the gas evolution stopped, the reaction vessel was removed from the ice water bath and placed in a heating mantle. A reflux condenser was affixed to the roundbottom flask and the septa was transferred to the top of the condenser (to keep the reaction apparatus under positive pressure of nitrogen). The reaction mixture was heated to reflux and allowed to reflux overnight. The following day the reaction mixture was cooled to 0 ºC in an ice bath and quenched with methanol (20 mL), water (20 mL), and 15 % w/v potassium hydroxide (20 mL). The reaction mixture was concentrated *in vacuo* to ~ 20 % original volume and the inorganic salts were separated by filtration on a fritted funnel. The inorganic salts were washed twice with boiling ethyl acetate (2 x 100 mL). The organic layers were combined and dried over magnesium sulfate and filtered. The organic layers were dried again over sodium sulfate (twice) and concentrated *in vacuo* to yield the product as a clear oil (6.5 g, 81 %). Spectroscopic data matches that reported for this compound.[162] ^{1}H NMR (500 MHz) ($CDCl_3$) δ:

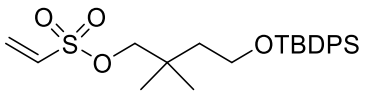
3.71 (2H, t, *J* = 5.5 Hz), 3.34 (2H, s), 1.55 (2H, t, *J* = 5.5 Hz), 0.922 (6H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 71.5, 59.1, 42.7, 34.9, 24.9.

Figure 9.25: Compound III.2b



4-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethylbutan-1-ol (III.2b). To a 250 mL roundbottom containing 2,2-dimethylbutane-1,4-diol (6.50 g, 55.0 mmol) was added DMF (100 mL) and imidazole (8.5 g, 125.0 mmol) and TBDPS-Cl (13.0 mL, 13.7 g, 50.0 mmol) The reaction vessel was sealed with a septa and flushed with nitrogen, and allowed to stir at room temperature for 60 hours. The reaction mixture was quenched with saturated sodium bicarbonate (100 mL) and extracted with ether (4 x 50 mL). The crude product was purified by silica gel chromatography (1:9 acetone: hexanes) to yield the title compound (14.6 g, 75%) as a colourless oil. Spectroscopic data matches that reported for this compound.[162] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.59–7.63 (4H, m), 7.46 – 7.38 (6H, m), 3.71 (2H, t, *J* = 5.5 Hz), 3.37 (2H, d, *J* = 6.5 Hz), 3.25 (1H, t, *J* = 6.5 Hz), 1.56 – 1.53 (2H, m), 1.05 (9H, s), 0.897 (6H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 135.5, 134.7, 132.9, 129.8, 127.7, 71.5, 61.0, 41.9, 35.0, 26.7, 26.5, 25.0, 19.0.

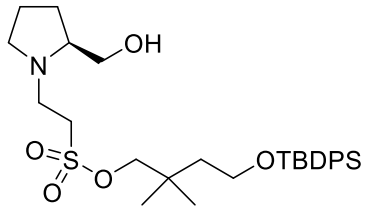
Figure 9.26: Compound III.2



4-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethylbutyl ethenesulfonate (III.2). To a 250 mL roundbottom flask was containing 4-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethylbutan-1-ol (3.4 g, 9.5 mmol) was added a stir bar and DCM (100 mL). The reaction vessel was sealed with a septa and flushed with nitrogen. Stirring commenced and the reaction vessel was cooled to 0 ºC in an ice-water bath. To the stirring mixture was added dropwise 2-chloroethane-1-sulfonyl

chloride (2.18 mL, 3.4 g, 20.9 mmol). Once addition of the sulfonyl chloride was complete, TEA (7.25 mL, 5.25 g, 52.0 mmol) was added dropwise. After the TEA addition was complete, the reaction had turned rust-colored and a solid had precipitated. The reaction mixture was allowed to stir overnight while warming to room temperature. The following day the reaction mixture was quenched with the addition of 10 % w/v sodium carbonate (100 mL). The biphasic mixture was transferred to a separatory funnel and partitioned. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product was dissolved in a minimum amount of DCM and purified by silica gel chromatography (10 % acetone in hexanes) to yield the pure product as a brown oil (2.5 g, 59 %). Spectroscopic data matches that reported for this compound.[162] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.66 – 7.64 (4H, m), 7.45 – 7.38 (6H, m), 6.44 – 6.31 (2H, m), 6.04 (1H, d, *J* = 9.5 Hz), 3.85 (2H, s), 3.70 (2H, t, *J* = 6.5, 6.5 Hz), 1.58 (2H, t, *J* = 7.0, 7.0 Hz), 1.03 (9H, s), 0.961 (6H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 135.5, 133.5, 132.2, 130.0, 129.6, 127.7, 78.8, 60.3, 40.9, 33.8, 26.8, 24.2, 19.0.

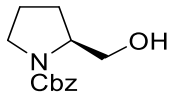
Figure 9.27: Compound III.3



4-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethylbutyl (*S*)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)ethane-1-sulfonate (III.3). To a 100 mL roundottom flask containing a stir bar and 4-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethylbutyl ethenesulfonate (2.5 g, 5.6 mmol) was added DCM (20 mL). Stirring commenced and to the reaction mixture was added (*S*)-pyrrolidin-2-ylmethanol (5.0 g, 4.95 mmol). The reaction mixture was allowed to stir overnight and the following day concentrated *in vacuo*. The crude material was purified by silica gel chromatography (dissolved

in DCM and applied to the column, eluted in 3:7 acetone: hexanes) to yield the product as a clear oil (2.6 g, 95 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.68 – 7.66 (4H, m), 7.45 – 7.38 (6H, m), 3.96 (2H, app quartet, *J* = 9.5, 2.5 Hz), 3.73 (2H, t, *J* = 6.5, 6.5 Hz), 3.63 (1H, dd, *J* = 11.0, 3.0 Hz), 3.39 (1H, br d, *J* = 11.0 Hz), 3.32 – 3.21 (3H, m), 3.18 – 3.14 (1H, m), 2.80 – 2.76 (1H, m), 2.66 – 2.63 (1H, m), 2.55 (1H, br s), 2.31 – 2.26 (1H, m), 1.90 – 1.73 (4H, m), 1.60 (2H, t, *J* = 6.5, 6.5 Hz), 1.05 (9H, s), 0.972 (6H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 135.5, 133.5, 129.6, 127.7, 77.6, 64.7, 62.1, 60.3, 54.2, 49.4, 48.3, 40.9, 33.8, 27.3, 26.8, 24.2, 23.7, 19.0. HRMS calc'd for [M+H] = 548.2866, observed = 548.2879. IR (NaCl, DCM): 3420, 3073, 2958, 1644, 1352, 1165, 1108, 956, 822, 739.

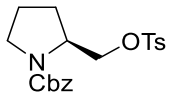
Figure 9.28: Compound III.4a



benzyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (III.4a). To a 500 mL roundbottom flask containing a stir bar was added (*S*)-pyrrolidin-2-ylmethanol (2.90 mL, 3.0 g, 29.7 mmol) followed by DCM (100 mL). Stirring commenced and the reaction vessel was cooled to 0 ºC in an ice-water bath. To the stirring mixture was added TEA (5.6 mL, 4.04 g, 40.0 mmol) followed by Cbz-Cl (3.7 mL, 4.42 g, 26.0 mmol). The reaction vessel was sealed with a septa and allowed to warm to room temperature while stirring overnight. The following day, the reaction mixture was transferred to a separatory funnel and extracted with dilute HCl (50 mL of a 10 % v/v solution). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a pink oil. The crude material was purified by silica gel chromatography (1:1 ethyl acetate: hexanes) to yield the pure product as a clear, colorless oil (6.0 g, 86 %). Spectroscopic data matches that reported for this compound.[163] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.37 – 7.30 (5H, m), 5.15 (2H, dd, *J* = 13.5, 1.0 Hz), 4.38 (1H, br s), 4.04 –

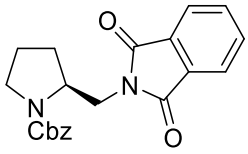
3.95 (1H, m), 3.68 – 3.61 (2H, m), 3.58 – 3.53 (1H, m), 3.41 – 3.36 (1H, m), 2.07 – 2.00 (1H, m), 1.91 – 1.75 (2H, m), 1.62 – 1.55 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 157.2, 136.4, 128.5, 128.1, 127.9, 67.2, 60.8, 47.3, 28.6, 24.0.

Figure 9.29: Compound III.4



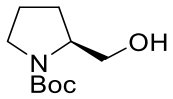
benzyl (*S*)-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (III.4).To a 250 mL roundbottom flask containing a stir bar and benzyl (*S*)-2-((tosyloxy)methyl)- pyrrolidine-1-carboxylate (6.0 g, 25.5 mmol) was added DCM (50 mL) followed by TEA (4.8 mL, 3.53 g, 35.0 mmol) and tosyl chloride (4.85 g) in one portion. The reaction mixture was allowed to stir overnight. The following day the the reaction mixture was transferred to a separatory funnel and extracted with dilute HCl (35 mL of a 10 % v/v solution). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an orange oil. The crude material was purified by silica gel chromatography (1:1 ethyl acetate: hexanes) to yield the pure product as a clear oil (6.3 g, 65 %). Spectroscopic data matches that reported for this compound.[*164*] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.73 (2H, ddd, *J* = 11.5, 27.0, 8.5 Hz), 7.38 – 7.26 (7H, m), 5.09 – 4.96 (2H, m), 4.19 – 3.90 (3H, m), 3.42 – 3.32 (2H, m), 2.42 (3H, d, *J* = 7.5 Hz), 2.00 – 1.79 (5H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 154.7, 154.2, 144.8, 144.7, 136.6, 136.3, 135.5, 132.8, 130.0, 129.8, 129.8, 128.5, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.5, 69.8, 69.6, 67.0, 66.7, 57.6, 56.1, 55.4, 49.3, 47.0, 46.7, 28.5, 27.6, 26.8, 24.2, 23.8, 23.7, 22.8, 21.6.

Figure 9.30: Compound III.5



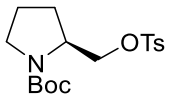
benzyl (*S*)-2-((1,3-dioxoisoindolin-2-yl)methyl)pyrrolidine-1-carboxylate (III.5). To a 100 mL oven-dried roundbottom flask containing a stir bar and benzyl (*S*)-2-((tosyloxy)methyl)-pyrrolidine-1-carboxylate (6.3 g, 16.2 mmol) was added potassium phthalimide (5.0 g, 27.0 mmol). The reaction vessel was sealed with a septa, flushed with argon, and DMF (40 mL) was added via syringe. The reaction vessel was heated to 70 ºC in an oil bath and stirred overnight. The following day the reaction was diluted with ethyl acetate (100 mL), transferred to a separatory funnel and washed with aqueous sodium bicarbonate (150 mL) and brine (3 x 70 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an oil. The crude material was purified by silica gel chromatography (1:2 ethyl acetate: hexanes, R_f = 0.28) to yield the pure product as an oil (3.4 g, 58 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.82 – 7.80 (1H, m), 7.76 – 7.75 (1H, m), 7.69 – 7.66 (2H, m), 7.33 – 7.26 (5H, m), 5.12 – 4.77 (2H, m), 4.40 – 4.31 (1H, m), 3.91 – 3.81 (1H, m), 3.69 (1H, ddd, *J* = 33.5, 13.5, 6.0 Hz), 3.50 – 3.39 (2H, m), 2.03 – 1.89 (3H, m), 1.83 – 1.79 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 168.5, 168.3, 155.2, 154.8, 136.9, 136.4, 133.9, 133.7, 132.1, 131.8, 129.8, 128.3, 127.8, 127.8, 127.7, 127.6, 123.2, 123.2, 66.9, 66.5, 55.9, 55.6, 46.5, 46.1, 40.5, 29.1, 28.3, 23.6, 22.6. HRMS calc'd for [M+H] = 365.1501, observed = 365.1508. IR (NaCl, DCM): 3065, 2955, 1771, 1716, 1699, 1653, 1558, 1506, 1418, 1361, 1109.

Figure 9.31: Compound III.6a



***tert*-butyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (III.6a).** To a 100 mL roundbottom flask containing a stir bar was added (*S*)-2-(hydroxymethyl)pyrrolidine (1.0 mL, 1.0 g, 9.9 mmol) and DCM (30 mL). Stirring commenced and to the reaction mixture was added Boc anhydride (1.96 g, 9.0 mmol) as a solid in one portion. The reaction vessel was sealed with a septa and flushed with nitrogen, and allowed to proceed overnight. The following day the reaction mixture was concentrated *in vacuo* to yield the crude product as a yellow oil. The crude material was purified by silica gel chromatography (1:3 ethyl acetate: hexanes) to yield the pure product as a clear oil (1.68 g, 93 %). Spectroscopic data matches that reported for this compound.[165] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 4.78 -4.76 (1H, m), 3.97 – 3.95 (1H, m), 3.65 – 3.55 (3H, m), 3.46 – 3.41 (1H, m), 3.32 – 3.27 (1H, m), 2.03 – 1.96 (1H, m), 1.84 – 1.71 (3H, m), 1.54 – 1.46 (13H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 157.2, 80.2, 67.8, 60.2, 47.5, 28.9, 28.4, 24.0.

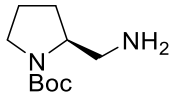
Figure 9.32: Compound III.6



***tert*-butyl (*S*)-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (III.6).** To a 500 mL roundbottom flask containing a stir bar was added *tert*-butyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (12.4 g, 62.0 mmol) followed by DCM (200 mL). The reaction vessel was sealed with a septa, flushed with nitrogen, and cooled to 0 ºC in an ice-water bath. To the stirring mixture was added TEA (11.2 mL, 8.08 g, 80.0 mmol) followed by tosyl chloride (12.3 g, 65.0 mmol, dissolved in 50.0 mL DCM). The reaction was allowed to stir overnight while warming to

room temperature. The following day the reaction mixture was transferred to a separatory funnel and washed with 10 % HCl (50 mL) and brine (150 mL). The crude product was concentrated *in vacuo* to yield a brown oil which was purified by silica gel chromatography (1:4 ethyl acetate: hexanes, R_f = 0.46) to yield the pure product as a clear oil (4.1 g, 19 %). Spectroscopic data matches that reported for this compound.[165] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.76 (2H, d, *J* = 7.5 Hz), 7.34 (2H, br s), 4.12 – 3.86 (3H, m), 3.34 – 3.26 (2H, m), 2.44 (3H, s), 1.96 – 1.78 (5H, m), 1.38 (9H, d, *J* = 25.0 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 154.4, 154.0, 144.9, 144.7, 132.8, 130.0, 129.8, 129.0, 128.1, 127.8, 126.0, 79.9, 79.5, 69.9, 67.7, 55.5, 46.9, 46.4, 30.7, 28.3, 27.6, 23.8, 23.7, 22.8, 21.6, 21.4. HRMS calc'd for [M+Na] = 378.1351, observed = 378.1375. IR (NaCl, DCM): 2975, 1694, 1395, 1364, 1175, 969, 665, 552.

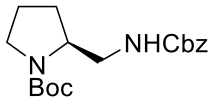
Figure 9.33: Compound III.7a



***tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate (III.7a).** To a 250 mL roundbottom flask was containing a stir bar was added *tert*-butyl (*S*)-2-(tosyloxymethyl)pyrrolidine-1-carboxylate (37.0 g, 104 mmol) followed by DMF (60 mL). Stirring commenced, and to the reaction mixture was added sodium azide (8.12 g, 125.0 mmol). The reaction vessel was sealed with a septa, flushed with nitrogen, and heated to 70 ºC overnight. The following day, the reaction mixture was cooled to room temperature and transferred to a separatory funnel. The reaction mixture was partitioned between ethyl acetate (200 mL) and 10 % HCl (100 mL). The organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to a yellow oil. The crude material was purified by passing it through a silica plug (eluting in 1:4 ethyl acetate: hexanes) to yield the product, *tert*-butyl (*S*)-2-(azidomethyl)pyrrolidine-1-

carboxylate, as a clear oil (9.5 g, 40 %). The product was dissolved in methanol (150 mL) to which 10 % palladium on carbon was added (1.5 g). A stir bar was added to the reaction vessel and stirring commenced. A hydrogen balloon was affixed to the reaction vessel and hydrogen gas was applied to the stirring mixture overnight. The following day the hydrogen balloon was removed and the reaction mixture was concentrated *in vacuo*. The black oil was dissolved in ethyl acetate and filtered through celite. The filtrate was concentrated *in vacuo* to yield an oil. The crude material was extracted into aqueous HCl and partitioned. The aqueous layer was made basic and back-extracted into ethyl acetate (3 x 100 mL). The organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield the pure product as a clear oil (5.0 g, 21 %) Spectroscopic data matches that reported for this compound.[166] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 3.78 – 3.70 (1H, m), 3.44 – 3.30 (2H, m), 2.83 – 2.76 (1H, m), 2.65 (1H, dd, *J* = 13.0, 6.5 Hz), 1.93 – 1.85 (1H, m), 1.84 – 1.80 (3H, m), 1.45 (9H, br s), 1.15 (2H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 155.1, 79.3, 79.1, 59.7, 46.9, 46.6, 45.4, 29.0, 28.5, 28.4, 23.8, 23.1.

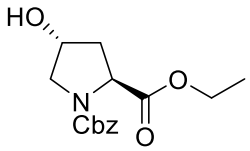
Figure 9.34: Compound III.7



***tert*-butyl (*S*)-2-((((benzyloxy)carbonyl)amino)methyl)pyrrolidine-1-carboxylate (III.7).** To a 250 mL roundbottom flask containing a stir bar was added *tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate (4.1 g, 20.0 mmol) followed by DCM (100 ml). The reaction vessel was stirred, sealed with a septa, and flushed with nitrogen. To the stirring mixture was added TEA (4.17 mL, 3.03 g, 30.0 mmol), followed by Cbz-Cl (3.50 mL, 4.25 g, 25.0 mmol). A precipitate formed on Cbz-Cl addition and the reaction mixture was allowed to stir

overnight. The following day, the mixture was transferred to a separatory funnel and washed with 10 % HCl (1 x 50 mL), followed by saturated aqueous sodium bicarbonate (1 x 100 mL). The organic layer was partitioned, dried over sodium sulfate, and concentrated *in vacuo* to yield a clear oil. The crude material was purified by silica ge chromatography (1:3 ethyl acetate:hexanes, R_f = 0.35) to yield the product as a clear oil (4.00 g, 60 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.35 – 7.31 (5H, m), 6.02 (1H, br s), 5.13 – 5.09 (2H, m), 3.94 – 3.88 (1H, m), 3.44 – 3.24 (4H, m), 2.00 – 1.80 (4H, m), 1.45 (9H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 128.4, 127.9, 79.7, 66.7, 66.4, 56.8, 47.0, 46.0, 29.2, 28.5, 28.4, 23.8. HRMS calc'd for [M+H] = 355.1971, observed = 355.1968.

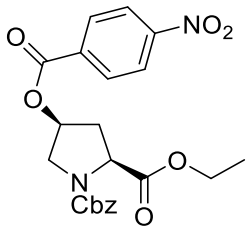
Figure 9.35: Compound III.8



1-benzyl 2-ethyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (III.8). To a 250 mL roundbottom flask containing a stir bar was added *trans*-4-hydroxy-*L*-proline (2.62 g, 20.0 mmol) followed by sodium carbonate (3.15 g, 30.0 mmol) and water (50 mL). Stirring commenced and the solids dissolved. To the stirring mixture was added toluene (50 mL) followed by Cbz-Cl (2.71 mL, 3.23 g, 19.0 mmol) via syringe. The reaction mixture was stirred vigorously overnight. The following day, the reaction mixture was transferred to a separatory funnel and partitioned. The aqueous layer was made acidic (pH ~ 2 by pH paper) and extracted with ethyl acetate (2 x 100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the product, (2*S*,4*R*)-1-((benzyloxy)carbonyl)-4-hydroxypyrrolidine-2-carboxylic acid as a clear oil (5.06 g, 96 %). This material was carried on to the next step with no further purification. The oil previously obtained was dissolved in ethanol

(200 mL) and cooled to 0 ºC in an ice-water bath. Stirring commenced and to the reaction mixture was added thionyl chloride (2.5 mL, 4.1 g, 35.0 mmol). The reaction vessel was transferred to a heating mantle and heated to reflux overnight. The following day, the reaction mixture was cooled to room temperature and concentrated *in vacuo* to yield a clear oil. The crude oil was dissolved in ethyl acetate (150 mL), transferred to a separatory funnel and washed with sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the product as a clear oil (5.56 g, 98 %). Spectroscopic data matches that reported for this compound.[167] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.35 – 7.30 (5H, m), 5.18 – 5.02 (2H, m), 4.51 – 4.45 (2H, m), 4.23 – 4.18 (1H, m), 4.03 – 3.98 (1H, m), 3.72 – 3.54 (2H, m), 2.35 – 2.26 (1H, m), 2.12 – 2.06 (1H, m), 1.99 – 1.26 (1H, m), 1.28 – 1.09 (3H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 172.7, 172.5, 154.9, 154.5, 136.4, 136.2, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 70.2, 69.4, 67.2, 67.2, 61.3, 61.1, 57.9, 57.7, 55.2, 54.6, 39.2, 38.4, 14.1, 13.9.

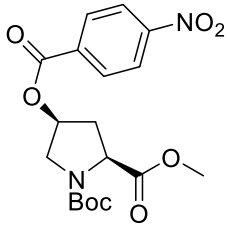
Figure 9.36: Compound III.9



1-benzyl 2-ethyl (2*S*,4*S*)-4-((4-nitrobenzoyl)oxy)pyrrolidine-1,2-dicarboxylate (III.9). To a 500 L roundbottom flask containing 1-benzyl 2-ethyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (17.8 g, 60.0 mmol) and a stir bar was added THF (250 mL). Stirring commenced and to the reaction mixture was added triphenylphosphine (22.2 g, 85.0 mmol) and *para*-nitrobenzoic acid (13.7 g, 85.0 mmol). The reaction vessel was sealed and flushed with nitrogen. The reaction vessel was cooled to 0 ºC in an ice bath and diethyl azodicarboxylate (13.3 mL,

14.7 g, 85.0 mmol) was added dropwise. The reaction mixture was allowed to stir overnight. The following day the crude reaction mixture was concentrated *in vacuo* to a yellow solid. The crude product was dissolved in ethyl acetate (100 mL) and extracted with saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield an orange solid. The crude product was dissolved in dichloromethane (100 mL) and filtered through a plug of silica gel. The product was concentrated again *in vacuo* and the purified product was obtained by recrystallization from ethyl acetate as a white solid (14.35 g, 54 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 8.30 (2H, d, *J* = 8.5 Hz), 8.15 (2H, d, *J* = 8.5 Hz), 7.39 – 7.31 (5H, m), 5.60 (1H, br s), 5.24 – 5.13 (2H, m), 2.65 (1H, dd, *J* = 9.5, 2.0 Hz), 4.20 – 4.14 (1H, m), 4.07 (1H, q, *J* = 7.5, 7.5 Hz), 3.91 – 3.83 (2H, m), 2.64 – 2.48 (2H, m), 1.21 – 1.06 (3H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.4, 171.2, 163.9, 163.8, 154.5, 150.7, 136.2, 134.9, 134.9, 130.9, 130.8, 128.5, 128.4, 128.1, 128.1, 128.0, 127.9, 123.5, 74.3, 73.3, 67.4, 67.3, 61.4, 61.4, 58.0, 57.6, 52.8, 52.4, 36.6, 35.6, 14.1, 14.1. HRMS calc'd for [M+H] = 443.1454, observed = 443.1454. IR (NaCl, DCM): 1722, 1715, 1705, 1525, 1416, 1348, 1272, 1196, 1103, 1061, 1013. M.P. = 136 ºC.

Figure 9.37: Compound III.10



1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-((4-nitrobenzoyl)oxy)pyrrolidine-1,2-dicarboxylate (III.10). To an oven-dried 500 mL roundbottom flask containing a stir bar was added 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (18.2 g, 74.0 mmol) followed

by freshly distilled THF (250 mL). To the reaction vessel was added triphenylphosphine (25.1 g, 96.0 mmol) and *para*-nitrobenzoic acid (15.8 g, 95.0 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. Stirring commenced and the reaction vessel was cooled to 0 ºC in an ice-water bath. To the stirring mixture was added dropwise diethylazodicarboxylate (15.1 mL, 16.8 g, 97.0 mmol). The reaction mixture was allowed to stir overnight while warming to room temperature. The following day, the reaction mixture was concentrated *in vacuo* to approx. 20 % original volume and diluted with ethyl acetate (200 mL). The crude material was transferred to a separatory funnel and washed with sodium bicarbonate (100 mL) and brine (3 x 100 mL). The crude material was concentrated again *in vacuo* to yield an oil. The oil was dissolved in a minimum amount of DCM (~ 50 mL) and purified by silica gel chromatography (gradient ethyl acetate: hexanes 1:9 to 1:4 to 1:3) to yield the product as an oil (24.2 g, 83 %). Spectroscopic data matches that reported for this compound.[168] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 8.26 (2H, d, *J* = 9.5 Hz), 8.13 (2H, d, *J* = 9.5 Hz), 5.56 (1H, br s), 4.60 – 4.46 (1H, m), 3.83 – 3.67 (5H, m), 2.62 – 2.50 (1H, m), 2.44 (1H, br d, *J* = 14.0 Hz), 1.45 (9H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 172.3, 172.1, 163.9, 163.8, 153.9, 153.6, 150.6, 135.0, 130.8, 130.8, 128.8, 128.6, 123.5, 123.4, 80.5, 80.5, 74.5, 73.4, 64.4, 62.9, 57.7, 57.4, 52.5, 52.3, 52.2, 52.1, 36.4, 35.5, 28.3, 28.2. Crystal Structure:

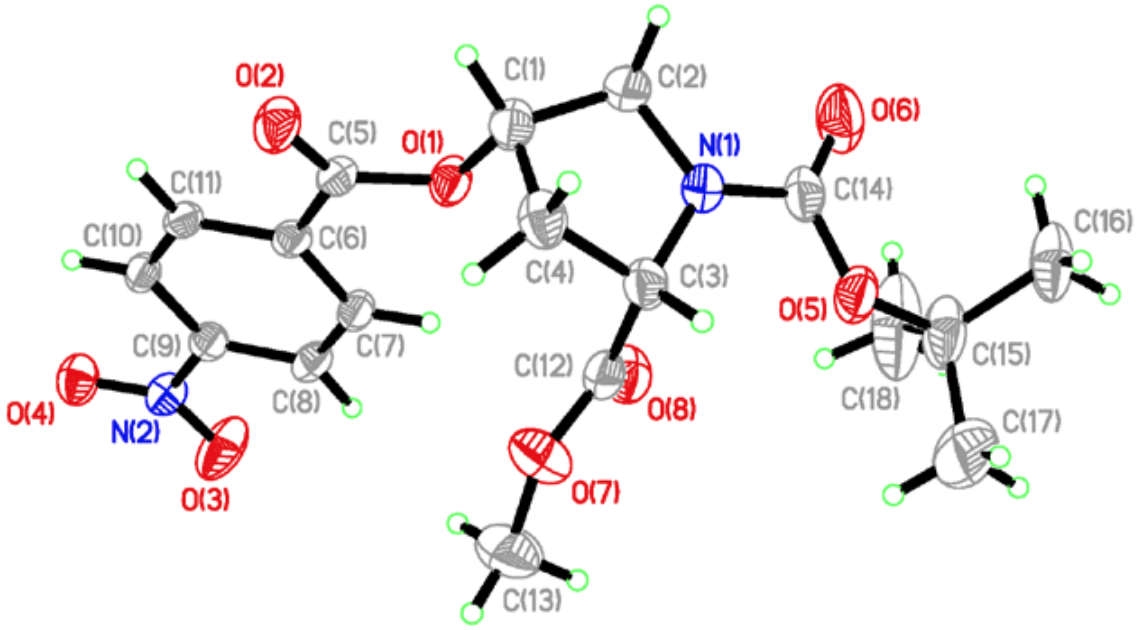


Table 9.1: Bond Lengths and Bond Angles for Compound III.10

Bond Angles

O1	C1	1.466(2)
O1	C5	1.333(2)
O2	C5	1.204(2)
O3	N2	1.219(2)
O4	N2	1.220(2)
O5	C14	1.341(3)
O5	C15	1.475(3)
O6	C14	1.208(3)
O7	C12	1.329(3)
O7	C13	1.447(3)
O8	C12	1.202(3)
N1	C2	1.468(3)
N1	C3	1.452(3)
N1	C14	1.354(3)
N2	C9	1.472(2)
C1	C2	1.513(3)
C1	C4	1.516(3)

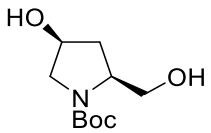
Bond Lengths

C5	O1	C1	117.03(13)
C14	O5	C15	120.1(2)
C12	O7	C13	116.1(2)
C3	N1	C2	112.80(16)
C14	N1	C2	120.48(18)
C14	N1	C3	125.87(17)
O3	N2	O4	123.76(16)
O3	N2	C9	117.71(14)
O4	N2	C9	118.53(13)
O1	C1	C2	106.22(15)
O1	C1	C4	107.92(16)
C2	C1	C4	104.71(15)
N1	C2	C1	103.50(17)
N1	C3	C4	101.66(17)
N1	C3	C12	112.05(17)
C12	C3	C4	113.47(15)
C1	C4	C3	102.91(16)

Table 9.1 (cont'd)

C3	C4	1.536(3)	O1	C5	C6	111.88(14)
C3	C12	1.530(3)	O2	C5	O1	124.55(16)
C5	C6	1.497(2)	O2	C5	C6	123.57(15)
C6	C7	1.401(2)	C7	C6	C5	121.66(14)
C6	C11	1.390(2)	C11	C6	C5	117.65(14)
C7	C8	1.384(2)	C11	C6	C7	120.69(15)
C8	C9	1.387(2)	C8	C7	C6	119.87(15)
C9	C10	1.390(2)	C7	C8	C9	118.13(14)
C10	C11	1.383(2)	C8	C9	N2	118.62(14)
C15	C16	1.521(3)	C8	C9	C10	123.06(16)
C15	C17	1.515(6)	C10	C9	N2	118.31(14)
C15	C18	1.516(4)	C11	C10	C9	118.14(14)
			C10	C11	C6	120.10(14)
			O7	C12	C3	109.75(17)
			O8	C12	O7	124.67(19)
			O8	C12	C3	125.58(19)
			O5	C14	N1	110.08(19)
			O6	C14	O5	126.64(19)
			O6	C14	N1	123.2(2)
			O5	C15	C16	110.39(18)
			O5	C15	C17	101.6(3)
			O5	C15	C18	108.82(19)
			C17	C15	C16	110.6(2)
			C17	C15	C18	112.4(3)
			C18	C15	C16	112.5(3)

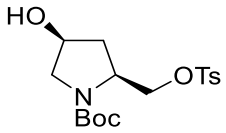
Figure 9.38: Compound III.11a



***tert*-butyl (2*S*,4*S*)-4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (III.11a).** To a 250 mL roundbottom flask containing a stir bar was added 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-((4-nitrobenzoyl)oxy)pyrrolidine-1,2-dicarboxylate (7.2 g, 18.2 mmol). THF was added (100 mL),

the reaction vessel was sealed with a septa, flushed with nitrogen, and cooled to 0 ºC in an ice-water bath. Stirring commenced and lithium borohydride solution was added dropwise (45 mL of a 2.0 M solution in THF, 90.0 mmol). As per the procedure, the reaction was allowed to warm to room temperature and stir for 40 hours. The reaction mixture was quenched by cooling to 0 ºC in an ice-water bath and adding saturated aqueous ammonium chloride. The quenched reaction mixture was concentrated *in vacuo* to yield the crude material, which was dissolved in ethyl acetate (150 mL) and partitioned with water (100 mL). The organic layer was washed with brine (2 x 100 mL) and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (1:3 ethyl acetate: hexanes) to yield the pure product as a white solid (2.6 g, 66 %). Spectroscopic data matches that reported for this compound.[169] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 4.30 (1H, t, *J* = 5.0, 5.0 Hz), 4.08 (1H, dd, *J* = 10.0, 2.0 Hz), 4.03 (1H, br s), 3.60 – 3.44 (5H, m), 2.35 (1H, br s), 1.86 (1H, br s), 1.46 (9H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 155.7, 80.8, 69.8, 69.0, 64.7, 63.9, 58.4, 58.2, 56.8, 38.2, 37.5.

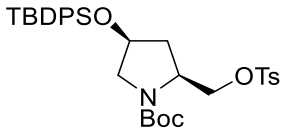
Figure 9.39: Compound III.11



***tert*-butyl (2*S*,4*S*)-4-hydroxy-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (III.11).** To a 250 mL roundbottom flask containing *tert*-butyl (2*S*,4*S*)-4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (2.6 g, 11.9 mmol) and a stir bar was added DCM (150 mL) followed by pyridine (1.85 mL, 1.81 g, 23.0 mmol). The reaction vessel was sealed with a septa, flushed with nitrogen, and cooled to 0 ºC in an ice-water bath. In a separate reaction vessel, tosyl chloride (2.66 g, 14.0 mmol) was dissolved in DCM (30 mL) and added dropwise to

the stirring solution of DCM and the *cis*-diol. The reaction mixture was allowed to warm to room temperature and stirred overnight. The following day, the reaction mixture was transferred to a separatory funnel and washed with dilute HCl (50 mL of a 10 % v/v solution of HCl in water). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a white solid. The crude product was purified by silica gel chromatography (1:1 ethyl acetate: hexanes, R_f = 0.55) to yield the product as a white solid (1.4 g, 32 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.78 (2H, br d), 7.34 (2H, br d), 4.40 – 4.18 (3H, m), 4.04 (2H, br d), 3.55 – 3.47 (1H, m), 3.31 (1H, br d), 2.45 – 2.43 (3H, m), 2.39 – 2.26 (1H, m), 2.03 – 2.01 (1H, m), 1.43 – 1.38 (9H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 154.5, 154.1, 145.2, 144.9, 132.7, 130.0, 129.9, 127.9, 127.7, 80.3, 80.0, 70.6, 70.4, 70.0, 69.8, 55.5, 55.2, 55.1, 36.5, 35.9, 34.6, 28.3, 21.6, 21.6. HRMS calc'd for [M+Na] = 394.1301, observed = 394.1301. IR (NaCl, DCM): 3428, 2976, 1690, 1676, 1598, 1401, 1365, 1257, 1115, 1002, 835, 736, 665, 554. M.P. = 108 ºC.

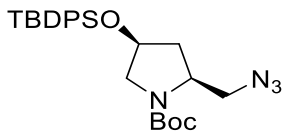
Figure 9.40: Compound III.12a



***tert*-butyl (2*S*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (III.12a).** To a 250 mL roundbottom flask containing a stir bar was added *tert*-butyl (2*S*,4*S*)-4-hydroxy-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (1.4 g, 3.7 mmol) and DCM (50 mL). Stirring commenced and imidazole was added (0.204 g, 3.0 mmol), followed by DMAP (0.120 g, 1.0 mmol) and TBDPSCl (0.808 mL, 0.849 g. 3.1 mmol). On addition of the silyl chloride, a white precipitate formed. The rreation mixture was allowed to stir overnight. The

following day the reaction mixture was transferred to a separatory funnel and extracted with 10 % HCl (30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an oil. The crude material was purified by silica gel chromatography (1:4 ethyl acetate:hexanes, Rf = 0.7) to yield the pure product as a clear oil that solidified on standing (2.1 g, 92 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.29 (2H, d, *J* = 8.5 Hz), 7.65 – 7.62 (3H, m), 7.45 – 7.38 (8H, m), 4.35 – 4.21 (1H, m), 3.96 – 3.74 (3H, m), 3.54 – 3.27 (2H, m), 2.49 (4H, s), 2.24 – 2.07 (2H, m), 1.44 – 140 (9H, m), 1.06 – 1.02 (9H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 146.9, 141.6, 135.7, 135.6, 135.6, 133.1, 130.2, 129.9, 127.8, 127.7, 127.0, 71.0, 28.4, 28.2, 26.8, 26.6, 21.8, 18.9. HRMS calc'd for [M+Na] = 632.2478, observed = 632.2482. IR (NaCl, DCM): 3121, 2922, 1684, 1458, 1364, 1097, 922, 820, 765, 655.

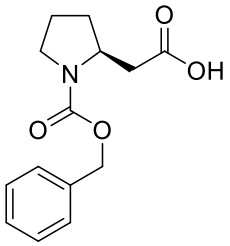
Figure 9.41: Compound III.12



***tert*-butyl (2*S*,4*S*)-2-(azidomethyl)-4-hydroxypyrrolidine-1-carboxylate (III.12).** To a 100 mL roundbottom flask containing a stir bar was added *tert*-butyl (2*S*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (2.1 g, 3.4 mmol) followed by DMF (30 mL). Stirring commenced and to the reaction mixture was added sodium azide (5.0 g, 77.0 mmol). The reaction vessel was sealed with a septa and flushed with argon. The reaction mixture was heated to 70 **º** C overnight. The following day, the reaction mixture was quenched with the addition of ethyl acetate (150 mL). The reaction mixture was transferred to a separatory funnel and washed with water (4 x 100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an

oil. This material was purified by silica gel chromatography (1:3 ethyl acetate:hexanes) to yield the pure product as a clear oil (1.3 g, 79 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.65 – 7.62 (4H, m), 746 – 7.38 (6H, m), 4.76 (1H, d, *J* = 8.5 Hz), 4.33 – 4.24 (1H, m), 3.97 – 3.69 (3H, m), 3.46 – 3.24 (2H, m), 2.09 – 1.63 (2H, m), 1.43 (9H, s), 1.06 (9H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 156.9, 135.7, 135.6, 133.4, 133.1, 129.9, 129.9, 127.8, 127.7, 80.3, 71.0, 68.2, 59.6, 55.2, 37.5, 28.4, 26.8, 18.9. HRMS calc'd for [M+H] = 481.2635, observed = 481.2607. IR (NaCl, DCM): 3074, 2933, 2099, 1668, 1540, 1405, 1341, 1255, 1165, 1109, 1036, 909.

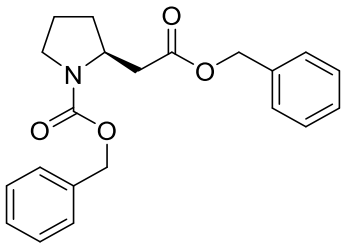
Figure 9.42: Compound III.13a



(*S*)-2-(1-((benzyloxy)carbonyl)pyrrolidin-2-yl)acetic acid (III.13a). To a 500 mL roundbottom flask containing a stir bar was added benzyl (*S*)-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (17.3 g, 44.4 mmol), DMF (50 mL), and KCN (5.12 g, 80.0 mmol). The reaction vessel was sealed and flushed with argon. Stirring commenced and the reaction vessel was heated to 70 ºC overnight. The following day, the crude material was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic layer was washed with water (100 mL) and brine (200 mL). The aqueous layers were combined and treated with $KMnO_4$ (until the solution maintained a purple color) to destroy any unreacted cyanide. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a brown oil. The crude material was purified by silica gel chromatography (1:1 ethyl acetate: hexanes) to yield the

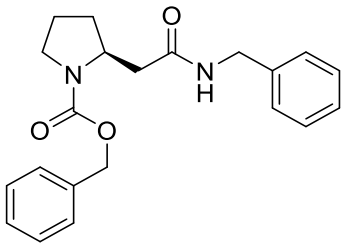
purified product as a clear oil (10.2 g, 94 %). The product, benzyl (*S*)-2-(cyanomethyl)pyrrolidine-1-carboxylate, was added to a 500 mL roundbottom flask with a stir bar, acetic acid (50 mL) and concentrated HCl (50 mL). Stirring commenced, and the reaction vessel was heated to reflux overnight. The following day, the reaction vessel was cooled to room temperature, transferred to a separatory funnel and extracted with ether (200 mL). The organic layer was discarded and the aqueous layer was diluted to 400 mL with water. Dioxane was added to the reaction mixture with a stir bar. Stirring commenced and sodium carbonated was added until the reaction mixture was basic (by pH paper). To the stirring mixture was added Cbz-Cl (6.0 mL, 7.14 g, 42.0 mmol) and the reaction mixture was stirred overnight. The following day, the reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (200 mL). The crude reaction mixture was made acidic by addition of concentrated HCl and extracted with ethyl acetate (4 x 150 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield the pure product as a clear oil (7.2 g, 62 %). Spectroscopic data matches that reported for this compound.[170] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 10.55 (1H, br s), 7.37 – 7.31 (5H, m), 5.15 – 5.11 (2H, m), 4.26 – 4.21 (1H, m), 3.44 – 3.41 (2H, m), 3.06 – 2.82 (1H, m), 2.2 – 2.37 (1H, m), 2.13 – 2.07 (1H, m), 1.90 – 1.80 (3H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 176.7, 176.5, 154.9, 154.7, 136.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 66.8, 54.3, 53.8, 46.8, 46.5, 39.0, 38.4, 31.4, 30.8, 23.5, 22.7.

Figure 9.43: Compound III.13



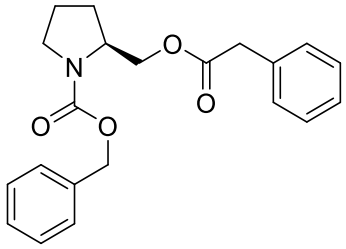
benzyl (*S*)-2-(2-(benzyloxy)-2-oxoethyl)pyrrolidine-1-carboxylate (III.13). To a 100 mL roundbottom flask containing a stir bar was added (*S*)-2-(1-((benzyloxy)carbonyl)pyrrolidin-2-yl)acetic acid (0.865 g, 3.2 mmol) followed by DCM (20 mL). Stirrinng commenced and to the reaction mixture was added TEA (0.835 mL, 0.606 g, 6.0 mmol) followed by EDCI (0.684 g, 3.6 mmol), benzyl alcohol (0.311 mL, 0.324 g, 3.0 mmol), and DMAP (0.120 g, 1.0 mmol). The reaction mixture was allowed to stir overnight. The following day the reaction mixture was transferred to a separatory funnel and washed with 10 % HCl (20 mL) and sodium bicarbonate (30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a yellow oil. The crude product was purified by silica gel chromatography (1:3 ethyl acetate: hexanes, R_f = 0.65) to yield the pure product as a clear oil (0.746 g, 66 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.30 (10H, m), 5.14 – 5.07 (2H, m), 4.28 – 4.23 (1H, m), 3.46 – 3.39 (2H, m), 3.06 – 2.83 (1H, m), 2.44 – 2.36 (1H, m), 2.11 – 2.04 (2H, m), 1.89 – 1.75 (3H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.2, 171.0, 154.6, 136.9, 136.7, 135.9, 135.7, 128.5, 128.5, 128.4, 128.2, 128.2, 128.1, 127.9, 127.8, 6.8, 66.6, 66.2, 54.5, 54.0, 46.7, 46.4, 39.3, 38.3, 31.3, 30.5, 23.5, 22.7. HRMS calc'd for [M+H] = 354.1705, observed = 354.1716. IR (NaCl, DCM): 3030, 2961, 1732, 1697, 1410, 1210, 742, 697.

Figure 9.44: Compound III.14



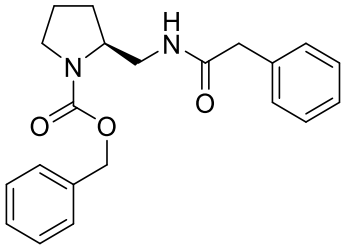
benzyl (*S*)-2-(2-(benzylamino)-2-oxoethyl)pyrrolidine-1-carboxylate (III.14). To a 100 mL roundbottom flask containing a stir bar was added (*S*)-2-(1-((benzyloxy)carbonyl)pyrrolidin-2-yl)acetic acid (0.984 g, 3.7 mmol) followed by DCM (20 mL). Stirrinng commenced and to the reaction mixture was added TEA (1.10 mL, 0.808 g, 8.0 mmol) followed by EDCI (0.798 g, 4.2 mmol), benzylamine (0.436 mL, 0.428 g, 4.0 mmol), and DMAP (0.120 g, 1.0 mmol). The reaction mixture was allowed to stir overnight. The following day the reaction mixture was transferred to a separatory funnel and washed with 10 % HCl (20 mL) and sodium bicarbonate (30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a yellow oil. The crude product was purified by silica gel chromatography (1:1 ethyl acetate: hexanes, R_f = 0.25) to yield the product as an oil the solidifies on standing (0.524 g, 40 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.33 – 7.19 (10H, m), 6.46 – 5.67 (1H, m), 5.19 – 5.01 (2H, m), 4.44 – 4.29 (2H, m), 4.19 – 4.12 (1H, m), 3.44 – 3.35 (2H, m), 2.75 – 2.60 (1H, m), 2.43 – 1.79 (5H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 170.6, 170.3, 155.1, 154.6, 138.3, 136.7, 128.6, 128.5, 128.0, 127.7, 127.4, 127.3, 66.8, 66.7, 55.7, 54.9, 46.8, 46.5, 43.4, 41.4, 40.8, 31.1, 30.7, 23.6, 22.8. HRMS calc'd for [M+H] = 353.1865, observed = 353.1873. IR (NaCl, DCM): 3307, 3062, 2953, 1699, 1646, 1547, 1453, 1312, 1211, 1003, 917, 749, 698.

Figure 9.45: Compound III.15



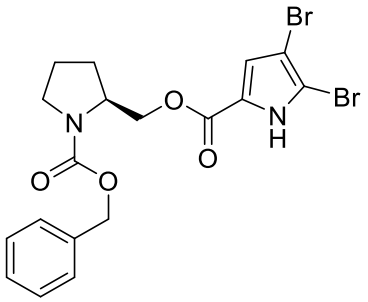
benzyl (*S*)-2-((2-phenylacetoxy)methyl)pyrrolidine-1-carboxylate (III.15). To a 100 mL roundbottom flask containing a stir bar was added benzyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (0.789 g, 3.35 mmol), followed by DCM (20 mL). The reaction vessel was sealed, flushed with nitrogen, and stirring commenced. To the stirring mixture was TEA (0.835 mL, 0.606 g, 6.0 mmol) via syringe followed by EDCI (0.646 g, 3.4 mmol), phenylacetic acid (0.476 g, 3.5 mmol) and DMAP (0.120 g, 1.0 mmol). The reaction mixture was stirred overnight. The following day the reaction mixture was transferred to a separatory funnel and washed with 10 % HCl (20 mL) and sodium bicarbonate (30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a yellow oil. The crude material was purified by silica gel chromatography (1:3 ethyl acetate: hexanes, R_f = 0.45) to yield the pure product as a clear oil (0.454 g, 38 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.26 (10H, m), 5.13 (2H, s), 4.25 – 4.07 (3H, m), 3.61 (2H, d, *J* = 19.5 Hz), 3.48 – 3.28 (2H, m), 1.95 – 1.87 (1H, m), 1.79 – 1.74 (3H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.3, 154.9, 154.8, 136.8, 136.6, 133.9, 133.8, 129.2, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.1, 127.0, 67.0, 66.7, 65.2, 64.6, 56.0, 55.4, 47.0, 46.5, 41.4, 41.3, 28.6, 27.7, 23.7, 22.9. HRMS calc'd for [M+H] = 354.1705, observed = 354.1717. IR. (NaCl, DCM): 2955, 1736, 1699, 1412, 1356, 1254, 1179, 957, 725, 699.

Figure 9.46: Compound III.16



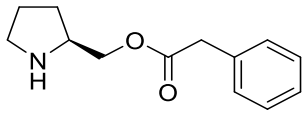
benzyl (*S*)-2-((2-phenylacetamido)methyl)pyrrolidine-1-carboxylate (III.16). To a 100 mL roundbottom flask containing a stir was added benzyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate (0.90 mL, 1.01 g, 4.35 mmol), followed by DCM (20 mL). Stirring commenced and to the reaction mixture was added TEA (0.975 mL, 0.707 g, 7.0 mmol) followed by EDCI (0.950 g, 5.0 mmol), phenylacetic acid (0.584 g, 4.3 mmol), and DMAP (0.120 g, 1.0 mmol). The reaction vessel was sealed with a septa, flushed with nitrogen, and allowed to stir overnight. The following day, the reaction mixture was transferred to a separatory funnel and washed with 10 % HCl (20 mL) followed by sodium bicarbonate (50 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a yellow oil. The crude material was purified by silica gel chromatography (1:1:0.05 ethyl acetate: hexanes: methanol, R_f = 0.15) to yield the pure product as a clear oil (1.12 g, 73 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.38 – 7.15 (10H, m), 7.22 – 6.95 (1H, m), 5.07 (2H, s), 3.99 – 3.96 (1H, m), 3.64 – 3.32 (5H, m), 3.23 – 3.18 (1H, m), 1.98 – 1.76 (3H, m), 1.69 – 1.65 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.4, 156.5, 136.5, 135.1, 129.4, 129.2, 128.8, 128.7, 128.7, 128.5, 128.4, 128.0, 127.8, 127.0, 126.8, 67.0, 66.4, 57.0, 46.8, 45.6, 45.1, 43.9, 42.3, 29.3, 24.1, 23.8. HRMS calc'd for [M+H] = 353.1865, observed = 353.1884. IR (NaCl, DCM): 3335, 2983, 1700, 1650, 1560, 1409, 1335, 1248, 1099, 988, 919, 855, 800.

Figure 9.47: Compound III.17



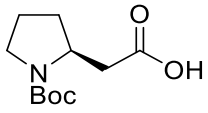
(*S*)-(1-((benzyloxy)carbonyl)pyrrolidin-2-yl)methyl 4,5-dibromo-1*H*-pyrrole-2-carboxylate (III.17). To a 50 mL roundbotto flask containing a stir bar was added benzyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (0.235 g, 1.0 mmol) followed by DCM (5 mL). Stirring commenced and to the reaction mixture was added 4,5-dibromo-2-carboxylic acid (0.266 g, 1.0 mmol), EDCI (0.290 g, 1.1 mmol), TEA (0.420 mL, 0.303 g, 3.0 mmol), and DMAP (0.012 g, 0.1 mmol). The reaction vessel was sealed, flushed with nitrogen, and allowed to stir overnight. The following day the reaction mixture was transferred to a separatory funnel and extracted with 10 % HCl (5 mL) and saturated sodium bicarbonate solution (10 mL). The organic layer was dried over sodium sulfate and concentarated *in vacuo* to yield the crude product as a red oil. This material was dissolved in a minimum amount of DCM and purified by silica gel chromatography (3:7 ethyl acetate: hexanes, R_f = 0.25) to yield the pure product as a yellow oil (0.112 g, 20 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 10.30 – 9.52 (1H, m), 7.35 – 7.30 (5H, m), 6.88 – 6.81 (1H, m), 5.21 – 5.04 (2H, m), 4.31 – 4.13 (3H, m), 3.51 – 3.48 (2H, m), 2.07 – 1.77 (4H, m), 1.29 – 1.22 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 159.3, 158.7, 155.9, 154.9, 136.5, 128.5, 128.0, 127.8, 123.8, 117.8, 117.7, 106.6, 100.5, 67.0, 65.9, 65.2, 56.1, 55.5, 46.9, 46.6, 29.7, 28.6, 27.3, 23.8, 23.0. HRMS calc'd for [M+H] = 484.9712, observed = 484.9715. IR (NaCl, DCM): 3418, 2961, 1701, 1671, 1450, 1287, 1180, 976, 857, 767, 733, 684.

Figure 9.48: Compound III.18



(*S*)-pyrrolidin-2-ylmethyl 2-phenylacetate (III.18). To a 500 mL roundbottom flask containing benzyl (*S*)-2-((2-phenylacetoxy)methyl)pyrrolidine-1-carboxylate (2.43 g, 6.9 mmol) was added ethyl acetate (200 mL) and 10 % palladium on carbon (2.3 g). Stirring commenced and a hydrogen was applied to the reaction mixture with a balloon affixed to the roundbottom flask. The reaction stirred for 18 hours at which time the balloon was removed, the reaction mixture was filtered through celite and concentrated *in vacuo* to yield the product as a clear oil which required no further purification (1.43 g, 94 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.36 – 7.26 (5H, m), 5.07 (1H, br s), 4.25 (1H, dq, *J* = 12.5, 5.0, 2.0 Hz), 3.71 – 3.66 (3H, m), 3.60 – 3.55 (2H, m), 3.47 – 3.42 (1H, m), 2.08 – 2.01 (1H, m), 1.95 – 1.79 (2H, m), 1.60 – 1.54 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 172.4, 134.2, 128.9, 128.7, 127.0, 67.5, 61.6, 48.4, 42.4, 28.3, 24.4. HRMS calc'd for [M+H] = 220.1337, observed = 220.1334. IR (NaCl, DCM): 3413, 2884, 1636, 1436, 1301, 1181, 1048, 1003.

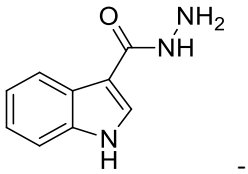
Figure 9.49: (*S*)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)acetic acid



(*S*)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)acetic acid. To a 250 mL flask containing a stir bar and (S)-2-(pyrrolidin-2-yl)acetic acid (1.05 g, 8.1 mmol) was added a 1:1 mixture of dioxane/aqueous sodium carbonate (50 mL total, containing 2.62 g/25.0 mmol sodium carbonate). The solid dissolved and stirring commenced. To the stirring mixture was added solid

Boc anhydride (2.18 g, 10.0 mmol), and the reaction mixture was allowed to stir overnight. The following day, the crude mixture was transferred to a separatory funnel and washed with ethyl acetate (100 mL). The organic layer was discarded and the aqueous layer was made acidic by the addition of conc. HCl (until pH ~ 2 by pH paper). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield the product as a yellow solid (1.9 g, 93 %) which needed no further purification. ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 11.36 (1H, br s), 4.14 – 4.10 (1H, br s), 3.33 (2H, br s), 2.98 – 2.79 (1H, m), 2.31 (1H, dd, *J* = 15.5, 9.5 Hz), 2.09 – 2.02 (1H, m), 1.86 – 1.75 (3H, m), 1.43 (9H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 176.7, 176.5, 154.6, 154.4, 79.9, 79.8, 53.8, 46.6, 46.1, 39.1, 38.8, 31.3, 30.9, 28.5, 28.4, 28.2, 23.4, 22.7. HRMS calc'd for [M+H] = 230.1392, observed = 230.1344.

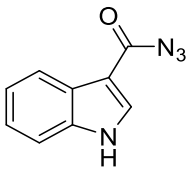
Figure 9.50: Compound IV.1a



1*H*-indole-3-carbohydrazide (IV.1a). To a 25 mL roundbottom flask containing a stir bar was added methyl-3-indole carboxylate (3.22 g, 18 mmol) and 15 mL hydrazine hydrate (~15 % water). Stirring commenced and a reflux condenser was attached to the flask. The reaction mixture was heated to reflux overnight. Shortly after reaching reflux, all solid dissolved. The next day the reaction mixture was cooled to room temperature and a solid precipitates. The solid was filtered and washed with water and dried *in vacuo* to yield the product (1.93 g, 61 %). Spectroscopic data matches that reported for this compound.[171] ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 11.57 (1H, br s), 9.15 (1H, s), 8.13 (1H, d, *J* = 8 Hz), 7.96 (1H, s), 7.41 (1H, d, *J* = 8 Hz), 7.15

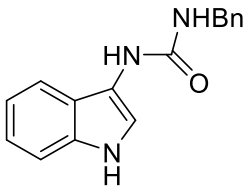
– 7.07 (2H, m), 4.33 (2H, br s). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 165.6, 136.4, 127.5, 126.5, 122.2, 121.3, 120.7, 112.2, 109.4. Melting point = 228 – 230º C.

Figure 9.51: Compound IV.1



1*H*-indole-3-carbonyl azide (IV.1). To a 50 mL roundbottom containing a stir bar was added 1*H*-indole-3-carbohydrazide (1.69 g, 9.6 mmol). To this was added 15 mL glacial acetic acid. Stirring commenced and the solid dissolved in the roundbottom. In a 50 mL Erlenmeyer flask was placed sodium nitrite (1.92 g, 28.9 mmol) and 5 mL water. After the sodium nitrite dissolved it was added dropwise to the 1*H*-indole-3-carbohydrazide/acetic acid solution. During the addition an exotherm was observed, followed by the precipitation of a solid and towards the end of the addition an orange vapor evolved. The reaction mixture was allowed to stir at room temperature for 20 minutes, at which time it was poured into HCl (1000 mL of a 5 % v/v solution) and stirred for an additional 20 minutes. The solid was collected by filtration, transferred to a roundbottom flask and dried under vaccum to yield the product (1.17 g, 65 %). Spectroscopic data matches that reported for this compound.[171] ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 12.15 (1H, s), 8.19 (1H, d, J = 3 Hz), 8.05 (1H, m), 7.52 – 7.50 (1H, m), 7.26 – 7.22 (2H, m). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 167.7, 137.3, 135.1, 125.8, 123.6, 122.6, 120.8, 113.2, 108.3. Melting point = 132º C (violent decomposition).

Figure 9.52: Compound IV.2



1-benzyl-3-(1*H*-indol-3-yl)urea (IV.2). To a 25 mL roundbottom flask containing a stir bar was added 1*H*-indole-3-carbonyl azide (1.10 g, 5.9 mmol), followed by toluene (30 mL), and anhydrous benzyl amine (2.0 mL, 1.96 g, 18 mmol). A reflux condenser was attached to the roundbottom and the reaction mixture was heated to reflux for 3 hours. During approximately the first 30 minutes of this period, the azide dissolved and the reaction mixture turned dark red. At approximately 90 minutes, a solid began to precipitate. When the 3 hour period was up, the reaction mixture was cooled to room temperature and the product was filtered and washed with toluene (twice with 10 mL). This product was dried under vacuum to a constant weight, yielding the product (1.49 g, 95 %). The product can be recrystallized by dissolving in acetone and adding ethyl acetate until a precipitate is observed, but this does not affect the resultant NMR spectra. ^{1}H NMR (500 MHz) (d_6-DMSO) (amide rotamers) δ: 10.63 (1H, s), 8.24 (1H, s), 7.48 (1H, d, J = 8 Hz), 7.41 – 7.34 (1H, m), 7.33 – 7.29 (5H, m), 7.24 – 7.22 (1H, m), 7.04 – 6.95 (1H, m), 6.49 (1H, t, J = 6.0, 5.5 Hz), 4.31 (2H, d, J = 6 Hz). ^{13}C NMR (125 MHz) (d_6-DMSO) (amide rotamers) δ: 156.2, 141.1, 140.9, 134.2, 128.7, 128.6, 128.2, 127.6, 127.5, 127.0, 127.0, 126.6, 122.2, 121.6, 121.4, 120.7, 118.3, 117.5, 116.2, 112.2, 111.8, 43.4, 42.2. HRMS [M+H] calc'd = 266.1293, observed = 266.1295. IR (NaCl, DCM): 3424, 2999, 2914, 2021, 1669, 1652, 1436, 1314, 1217. M.P. = 124 – 128º C. Crystal structure:

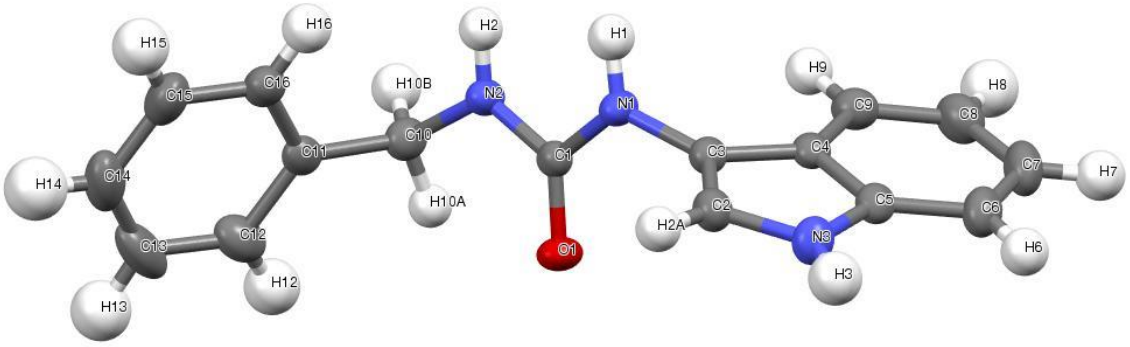


Table 9.2: Bond Angles and Bond Lengths for IV.2

Bond Lengths

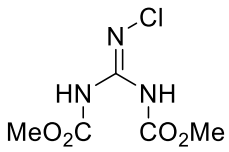
Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.2362(17)	C5	C6	1.395(2)
N1	C1	1.3652(18)	C6	C7	1.372(3)
N1	C3	1.4200(18)	C7	C8	1.398(3)
N2	C1	1.3481(18)	C8	C9	1.376(2)
N2	C10	1.4523(19)	C10	C11	1.510(2)
N3	C2	1.375(2)	C11	C12	1.386(2)
N3	C5	1.375(2)	C11	C16	1.387(2)
C2	C3	1.355(2)	C12	C13	1.400(3)
C3	C4	1.438(2)	C13	C14	1.367(3)
C4	C5	1.408(2)	C14	C15	1.374(3)
C4	C9	1.397(2)	C15	C16	1.383(2)

Table 9.2 (cont'd)

Bond Angles

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1	N1	C3	122.68(13)	C6	C5	C4	121.81(15)
C1	N2	C10	122.13(14)	C7	C6	C5	117.40(17)
C5	N3	C2	109.05(14)	C6	C7	C8	121.53(16)
O1	C1	N1	122.46(13)	C9	C8	C7	121.28(17)
O1	C1	N2	123.10(13)	C8	C9	C4	118.55(16)
N2	C1	N1	114.44(13)	N2	C10	C11	114.09(14)
C3	C2	N3	109.52(14)	C12	C11	C10	120.11(16)
N1	C3	C4	125.79(14)	C12	C11	C16	118.57(16)
C2	C3	N1	126.70(14)	C16	C11	C10	121.27(14)
C2	C3	C4	107.48(13)	C11	C12	C13	120.1(2)
C5	C4	C3	106.22(13)	C14	C13	C12	120.50(19)
C9	C4	C3	134.39(14)	C13	C14	C15	119.68(19)
C9	C4	C5	119.38(14)	C14	C15	C16	120.4(2)
N3	C5	C4	107.69(13)	C15	C16	C11	120.76(18)
N3	C5	C6	130.50(15)				

Figure 9.53: Compound IV.3a



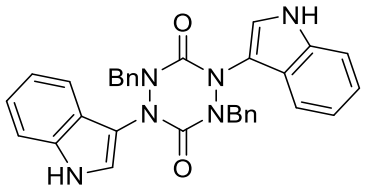
Palau'chlor (IV.3a). To a 500 mL roundbottom flask containing a stir bar was added (in the order listed) *S*-methyl isothiourea hemisulfate (20.0 g, 72.0 mmol), sodium carbonate (15.2 g, 144.0 mmol), TBAB (0.92 g, 2.85 mmol), DCM (100 mL), and water (80 mL). Stirring commenced and the reaction vessel was cooled in an ice water bath. To this mixture was added aqueous sodium hydroxide (25 %, 8.6 g in 40 mL water), followed by methyl chloroformate dropwise (25 mL, 30.7 g, 325.0 mmol). The reaction mixture was stirred for one hour at 0 ºC and two hours at room temperature. The remaining white solid that persisted was dissolved by adding excess DCM (100 mL) and stirring vigorously. The reaction mixture was stirred for an additional

two hours at room temperature, at which point it was transferred to a separatory funnel and partitioned. The organic layer was washed with water and dried over sodium sulfate. The organic layer was concentrated *in vacuo* to yield *bis*-carboxymethyl-*S*-methylisothiourea hemisulfate as a white solid (16.5 g, 56 %). M.P. = 86 ºC.

To a 500 mL roundbottom flask containing a stir bar was added *bis*-carboxymethyl-S-methylisothiourea hemisulfate (14.0 g, 80.0 mmol) and methanol (370 mL). Stirring commenced and ammonia was added (30 mL of a 7.0 N solution of ammonia in methanol). The reaction was allowed to stir overnight. The following day the reaction mixture was concentrated *in vacuo* to a white solid. M.P. = over 300 ºC. The crude material was carried on to the next step.

To a 250 mL roundbottom flask containing a stir bar was added *bis*-carboxymethyl guanidine (12.7 g, 72.0 mmol) followed by 150 mL DCM. The suspension was stirred at room temperature for 10 minutes, at which time *t*-butyl hypochlorite was added (8.0 mL). After 10 minutes, an additional portion of *t*-butyl hypochlorite (1 mL). The suspension cleared shortly after. The reaction was allowed to proceed for one hour at room temperature, at which time it was concentrated *in vacuo* to yield the product as a free-flowing white solid (14.2 g, 95 % yield). Spectroscopic data matches that reported for this compound.[172] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 9.82 (1H, br s), 8.09 (1H, br s), 3.86 (3H, s), 3.78 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 152.9, 150.6, 149.1, 54.0, 53.2. M.P. = 103 ºC.

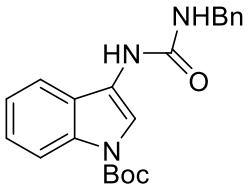
Figure 9.54: Compound IV.3



1,4-dibenzyl-2,5-di(1H-indol-3-yl)-1,2,4,5-tetrazinane-3,6-dione (IV.3). To a vial containing

1-benzyl-3-(1*H*-indol-3-yl)urea (0.026 g, 0.10 mmol) was added d_4-methanol (1.0 mL), followed by TBHP (0.020 mL of a 5.0 M solution). The reaction mixture was transferred to an NMR tube for monitoring. Crystals began to form during the course of the reaction. The reaction mixture was left in the NMR tube overnight. The following day, it was observed that more crystals had grown. The d_4-methanol was decanted from the NMR tube, and the crystals were dried by heating the NMR tube with a heat gun. The crystals were redissolved in d_6-DMSO (0.8 mL) and analyzed by NMR. The irreproducibility of this reaction precluded complete characterization; the structure reported is based on available data. ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 7.47 (1H, d, *J* = 8.0 Hz), 7.40 (1H, s), 7.34 – 7.28 (5H, m), 7.24 (1H, m), 7.06 (1H, t, *J* = 7.5 Hz), 6.96 (1H, t, *J* = 7.5 Hz), 4.30 (2H, s). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 156.1, 141.1, 143.0, 128.7, 127.5, 127.0, 121.6, 118.3, 117.4, 116.0, 111.7, 43.2. HRMS = calc'd for [$C_{16}H_{15}N_3O$, negative ion mode] = 264.1137, observed = 264.1133.

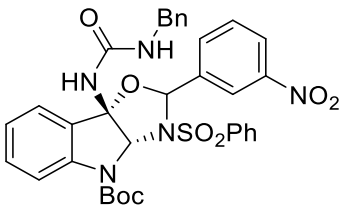
Figure 9.55: Compound IV.4



***tert*-butyl 3-(3-benzylureido)-1*H*-indole-1-carboxylate (IV.4)**. To a 50 mL roundbottom flask containing a stir bar was added 1-benzyl-3-(1*H*-indol-3-yl)urea (0.250 g, 1.0 mmol) and acetonitrile (3 mL). Stirring commenced and Boc anhydride was added (0.261 g, 1.2 mmol), followed by DMAP (0.012 g, 01 mmol). The reaction mixture was allowed to stir overnight. The following day the reaction was concentrated *in vacuo* and purified by silica gel chromatograpy (3:7 ethyl acetate: hexanes) to yield the product as a clear oil (0.102 g, 27 %). The irreproducibility of this reaction precluded complete characterization; the structure reported is

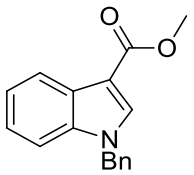
based on available data. ^{1}H NMR (500 MHz) (CD_3OD) δ: 8.13 (1H, br d, *J* = 7.0 Hz), 7.82 (1H, br s), 7.54 (1H, d, *J* = 8.0 Hz), 7.34 – 7.22 (6H, m), 4.43 (2H, s), 1.66 (9H, s). ^{13}C NMR (125 MHz) (CD_3OD) δ: 156.6, 149.8, 139.4, 128.1, 126.9, 126.7, 124.4, 122.0, 119.9, 116.7, 114.7, 112.1, 83.2, 43.3, 27.0.

Figure 9.56: Compound IV.5



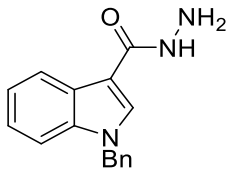
***tert*-butyl (3a*S*,8b*S*)-8b-(3-benzylureido)-2-(3-nitrophenyl)-3-(phenylsulfonyl)-2,3,3a,8b-tetrahydro-4H-oxazolo[4,5-b]indole-4-carboxylate (IV.5).** To a test tube was added *tert*-butyl 3-(3-benzylureido)-1*H*-indole-1-carboxylate (0.102 g, 0.27 mmol) and CD_3OD (0.5 mL). To a separate test tube was added 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (0.097 g, 0.32 mmol). These solutions were combined and placed in an NMR tube. The reaction was monitored by NMR and allowed to proceed overnight. The following day, crystals had precipitated in the NMR tube. The CD_3OD was decanted and the NMR tube was briefly heated with a heat gun (to evaporate excess solvent). d_6-DMSO (0.8 mL) was added to the NMR tube and the spectra reported was obtained. The irreproducibility of this reaction precluded complete characterization; the structure reported is based on available data. ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 8.16 (1H, t, *J* = 2.0 Hz), 8.06 (1H, d, *J* = 7.5 Hz), 7.96 (1H, ddd, *J* = 10.0, 2.5, 1.0 Hz), 7.81 (1H, d, *J* = 7.5), 7.49 – 7.45 (2H, m), 7.39 – 7.31 (5H, m), 7.29 – 7.21 (3H, m), 7.08 – 6.99 (5H, m), 6.68 (1H, s), 5.86 (1H, s), 4.47 (1H, dd, *J* = 15.0 Hz, 5.5 Hz), 4.32 (1H, dd, *J* = 15.0 Hz, 5.5 Hz), 1.48 (9H, s).

Figure 9.57: Compound IV.6



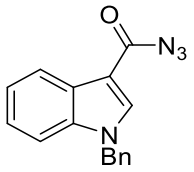
methyl 1-benzyl-1*H*-indole-3-carboxylate (IV.6). To a 50 mL roundbottom flask containing a stir bar was added methyl-indole-3-carboxylate (3.5 g, 20 mmol). The reaction vessel was sealed and flushed with nitrogen, and anhydrous DMF was added by syringe (20 mL). Stirring commenced until the solid had dissolved. The septum was removed and sodium hydride (60 % dispersion in oil, 1.12 g, 28 mmol) was added in one portion. The septum was replaced and the reaction vessel was flushed again with nitrogen. As the sodium hydride dissolved, gas evolved and the reaction mixture turned dark brown. After 30 minutes, benzyl bromide (3 mL, 4.44 g, 26 mmol) was added dropwise. The reaction was allowed to continue for 2 hours, at which time it was opened to the air and water was added (5 mL, dropwise). The reaction mixture was transferred to a separatory funnel and partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (3 x 50 mL), dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (1:4 ethyl acetate:hexanes) to yield the product (3.9 g, 74 %). Spectroscopic data matches that known for this compound.[173] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.15 (1H, d, *J* = 7 Hz), 7.86 (1H, s), 7.35 – 7.23 (6H, m), 7.16 (2H, d, *J* = 2H), 5.17 (2H, s), 3.92 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 165.4, 136.7, 135.8, 134.5, 129.0, 128.1, 127.0, 126.7, 122.9, 122.0, 121.7, 110.3, 107.5, 51.0, 50.7. M.P. = 104º C.

Figure 9.58: Compound IV.7



1-benzyl-1*H*-indole-3-carbohydrazide (IV.7). To a 100 mL roundbottom flask containing a stir bar was added methyl 1-benzyl-1*H*-indole-3-carboxylate, followed by DMF (4 mL anhydrous) and hydrazine (98 %, 15 mL). This mixture was heated to reflux overnight. On cooling to room temperature the next day the reaction mixture solidified. The solid was transferred to a filter, washed with water (4 x 50 mL), and dried *in vacuo* to yield the product (3.49 g, 89 %). ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 9.19 (1H, br s), 8.13 (1H, d, J = 7.5 Hz), 8.08 (1H, s), 7.50 (1H, d, J = 7.5 Hz), 7.42 – 7.10 (6H, m), 5.43 (2H, s), 4.35 (2H, br s). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 165.1, 144.5, 137.8, 136.4, 131.0, 129.1, 128.0, 127.6, 127.0, 122.5, 121.6, 121.1, 111.0, 109.1, 49.4. HRMS [M+H] calc'd = 266.1293, observed = 266.1293. Melting point = 141 – 143º C.

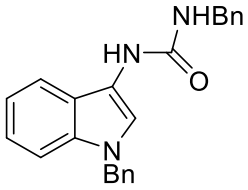
Figure 9.59: Compound IV.7a



1-benzyl-1*H*-indole-3-carbonyl azide (IV.7a). To a 100 mL roundbottom flask containing a stir bar was added 1-benzyl-1*H*-indole-3-carbohydrazide (3.49 g, 13 mmol) followed by glacial acetic acid (20 mL). Stirring commenced and the solid dissolved. In a separate flask, sodium nitrite (1.5 g, 26 mmol) was dissolved in water (10 mL). The aqueous sodium nitrite was added dropwise to the vigorously stirring mixture of in acetic acid over a period of 15 minutes. Early in the addition an exotherm was observed, followed by the formation of a precipitate and the

thickening of the reaction mixture. At the end of the addition an orange gas evolved. The reaction mixture was stirred at room temperature for 20 minutes, at which time it was poured into dilute HCl (250 mL of a 5 % v/v solution) and stirred for an additional 20 minutes. At the end of this period, the product was filtered and the solid was dried under vacuum to yield the product (3.15 g, 90 %). ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 8.44 (1H, s), 8.06 (1H, m) 7.58 (1H, m) 7.34 – 7.24 (7H, m), 5.53 (2H, s). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 167.4, 137.9, 137.2, 137.1, 129.1, 128.2, 127.8, 126.5, 123.7, 123.0, 121.1, 112.2, 107.7, 50.2. IR (NaCl, DCM): 3002, 2916, 2148, 1655, 1522, 1438, 1315, 1230, 1171. M.P. = 110 – 111º C (decomposition, gas evolution).

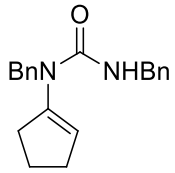
Figure 9.60: Compound IV.8



1-benzyl-3-(1-benzyl-1*H*-indol-3-yl)urea (IV.8). To a 250 mL roundbottom flask containing a stir bar was added 1-benzyl-1*H*-indole-3-carbonyl azide (2.24 g, 8.1 mmol) and toluene (100 mL, dried over molecular sieves). Stirring commences and the reaction mixture was heated to reflux for 30 minutes, at which point all the solid had dissolved. To this mixture benzyl amine (anhydrous) was added by syringe (1.65 mL, 1.60 g, 15 mmol). The reaction mixture was removed from the heat source and allowed to cool to room temperature. During this period a sand-like precipitate formed. Once cool the reaction mixture was filtered with a fritted funnel and washed with toluene (2 x 20 mL). The product thus obtained was dried *in vacuo* (1.33 g, 45 %). ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 8.42 (1H, s), 7.56 (1H, s), 7.52 (1H, d, J = 8.0 Hz), 7.40 (1H, d, J = 9.5 Hz), 7.34 – 7.16 (10H, m), 7.09 (1H, app t, J = 8.0 Hz), 6.99 (1H, app t, J = 8.0

Hz), 6.54 (1H, t, *J* = 6.5 Hz), 5.32 (2H, s), 4.30 (2H, d, *J* = 6.0 Hz). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 155.9, 141.0, 138.9, 134.0, 128.9, 128.7, 127.7, 127.5, 127.5, 127.1, 122.0, 121.5, 118.5, 117.8, 116.4, 110.3, 49.3, 43.4. HRMS [M+H] calc'd = 356.1763, observed = 356.1756. IR (NaCl, DCM): 3428, 2998, 2913, 1682, 1556, 1313, 1223, 1044, 953. M.P. = 185 ºC.

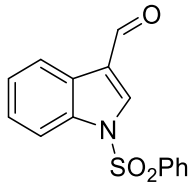
Figure 9.61: Compound IV.9



1,3-dibenzyl-1-(cyclopent-1-en-1-yl)urea (IV.9). To a 100 mL roundbottom flask containing a stir bar was added sodium sulfate (5.0 g, 35 mmol) and anhydrous DCM (50 mL). The reaction vessel was sealed with a septa and flushed with nitrogen. To the mixture was added cyclopentanone (5.0 mL, 4.07 g, 56.5 mmol) via syringe, followed by anhydrous benzyl amine (1.53 mL, 1.51 g, 14.2 mmol) via syringe. The reaction mixture was allowed to stir overnight. The following day the reaction mixture was filtered (fritted funnel) and concentrated to a yellow oil on a rotary evaporator. The crude product was concentrated *in vacuo* for 24 hours to remove excess cyclopentanone, yielding the product as a yellow oil (2.4 g, 100%). To a 100 mL roundbottom flask containing N-cyclopentylidene-1-phenylmethanamine (2.54 g, 14.6 mmol) was added anhydrous DCM (50 mL) and a stir bar. The reaction vessel was sealed with a septa and flushed with nitrogen. To the reaction mixture was added benzyl isocyanate (1.8 mL, 1.94 g, 14.6 mmol) via syringe. The reaction was allowed to continue overnight. The next day the reaction was concentrated to dryness *in vacuo* to yield the product as a red oil (4.1g, 100 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.37 – 7.23 (10H, m), 5.46 (1H, app t, *J* = 2.0 Hz), 5.42 (1H, br t, *J* = 5.0 Hz), 4.72 (2H, s), 4.49 (2H, d, *J* = 5.5 Hz), 2.38 – 2.35 (2H, m), 2.32 – 2.28 (2H, m), 1.87

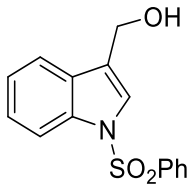
(2H, quintet, J = 7.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ TMS: 156.5, 143.1, 139.6, 138.9, 128.6, 128.4, 128.3, 127.6, 127.4, 127.4, 127.1, 127.1, 126.9, 124.1, 49.8, 44.7, 44.1, 32.3, 30.2, 22.0. HRMS calc'd for [M+H] = 307.1810, observed = 307.1814. IR (NaCl, DCM): 3350, 3061, 2949, 1650, 1585, 1038.

Figure 9.62: Compound V.1



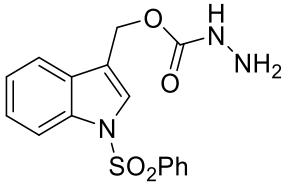
1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (V.1). To a 250 mL roundbottom flask containing a stir bar was added (in the sequence described) indole-3-carboxaldehyde (1.45 g, 10.0 mmol), DCM (75 mL), tetrabutylammonium hydrogen sulfate (0.170 g, 0.50 mmol), freshly ground NaOH (0.440 g, 11.0 mmol), and water (50 mL). The reaction vessel was cooled to 0 ºC in an ice-water bath and stirred at this temperature for 30 minutes. At this time, phenylsulfonyl chloride (1.4 mL, 1.94 g, 11.0 mmol) was added dropwise. The reaction was allowed to proceed for 3 hours, at which time it was transferred to a separatory funnel and partitioned. The organic layer was washed with water (100 mL) and subsequently dried over sodium sulfate and concentrated *in vacuo* to a solid. The crude product was dissolved in a minimum amount of DCM and purified by silica gel chromatography (1:4 ethyl acetate: hexanes). The purified product was obtained as a white solid (1.4 g, 58 %). Spectroscopic data matches that reported for this compound.[173] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 10.10 (1H, s), 8.26 (2H, m), 7.99 – 7.96 (3H, m), 7.63 – 7.60 (1H, m), 7.53 – 7.50 (2H, m), 7.44 – 7.36 (2H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 185.3, 137.3, 136.1, 135.2, 134.7, 129.7, 127.1, 126.4, 126.2, 125.1, 122.6, 122.5, 113.2. M.P. = 154 ºC.

Figure 9.63: Compound V.1a



(1-(phenylsulfonyl)-1*H*-indol-3-yl)methanol (V.1a). To a 250 mL roundbottom containing a stir bar was added 1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (1.4 g, 4.9 mmol) and methanol (100 mL). The reaction vessel was heated until the starting material dissolved. To the reaction mixture was added sodium borohydride (0.226 g, 6.0 mmol). The reaction was allowed to proceed at room temperature for 2 hours. At this time the crude reaction mixture was concentrated to a white solid on a rotary evaporator and purified by silica gel chromatography (2:3 ethyl acetate: hexanes). The purified product was obtained as a white solid (1.4g, 100 %). Spectroscopic data matches that reported for this compound.[174] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.01 (1H, dt, *J* = 8.0 Hz, 1.0 Hz), 7.91 – 7.89 (2H, m), 7.63 – 7.61 (1H, m), 7.56 – 7.52 (2H, m), 7.46 – 7.43 (2H, m), 7.37 – 7.33 (1H, m), 7.28 – 7.25 (2H, m), 4.83 (2H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 138.1, 135.4, 133.8, 129.3, 126.8, 125.1, 123.7, 123.4, 122.4, 119.9, 113.7, 57.1. M.P. = 81 ºC.

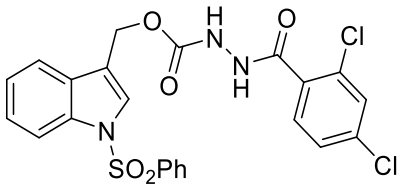
Figure 9.64: Compound V.2



(1-(phenylsulfonyl)-1*H*-indol-3-yl)methyl hydrazinecarboxylate (V.2). To a 100 mL flask containing a stir bar was added (1-(phenylsulfonyl)-1*H*-indol-3-yl)methanol (1.4 g, 4.8 mmol), followed by acetonitrile (50 mL). Stirring commenced, and CDI was added (2.43 g, 15 mmol),

and the reaction vessel was sealed and flushed with nitrogen. To the reaction mixture was added hydrazine (98 %, 0.630 mL, 0.640 g, 20 mmol). The reaction mixture was allowed to stir at room temperature overnight. The following day, the reaction mixture was concentrated *in vacuo* to yield the crude product which was purified by silica gel chromatography (1:1 ethyl acetate: hexanes, R_f = 0.13) to yield the pure product as a white solid (0.900 g, 54 %) ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.99 (1H, d, *J* = 8.5 Hz), 7.91 (2H, m), 7.64 (1H, s), 7.60 – 7.54 (2H, m), 7.48 – 7.45 (2H, m), 7.37 – 7.34 (1H, m), 7.29 – 7.26 (3H, m), 5.97 (1H, br s), 5.28 (2H, s), 3.76 (2H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 158.4, 138.0, 135.1, 133.9, 129.4, 129.3, 126.8, 125.6, 125.1, 123.5, 119.7, 117.5, 113.6, 58.8. HRMS calc'd for $[C_{15}H_{12}NO_2S]^+$ = 270.0583, observed = 270.0623. IR (NaCl, DCM): 3415, 3355, 1698, 1636, 1506, 1447, 1367, 1121, 1058. M.P. = 110 ºC.

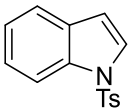
Figure 9.65: Compound V.3



(1-(phenylsulfonyl)-1*H*-indol-3-yl)methyl 2-(2,4-dichlorobenzoyl)hydrazine-1-carboxylate (V.3). To a 50 mL roundbottom flask containing a stir bar was added (1-(phenylsulfonyl)-1*H*-indol-3-yl)methyl hydrazinecarboxylate (0.700 g, 2.0 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. To this was added (in the sequence listed) THF (20 mL) via syringe, TEA (0.417 mL, 0.303 g, 3.0 mmol), and 2,4-dichlorobenzoyl chloride (0.308 mL, 0.459 g, 2.20 mmol, dissolved in 2 mL THF). The reaction mixture turned cloudy on addition of 2,4-dichlorobenzoyl chloride. The reaction was allowed to stir for 30 minutes at room temperature, at which time TLC analysis revealed the starting material to be consumed (1:1 ethyl

acetate: hexanes). The reaction was quenched with the addition of water (5 mL), and transferred to a separatory funnel where it was partitioned with DCM (40 mL). The organic layer was dried over sodium sulfate and concentrated on a rotary evaporator to a white solid. The crude product was purified by silica gel chromatography (1:1 ethyl acetate: hexanes, R_f = 0.75) to yield the product as a white solid (1.1 g, 95 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.16 (1H, br s), 7.96 (1H, d, *J* = 8.0 Hz), 7.88 (2H, d, *J* = 8.0 Hz), 7.65 (1h, s), 7.56 (1H, d, *J* = 7.0 Hz), 7.51 (1H, t, *J* = 7.0 Hz), 7.42 (3H, app t, *J* = 7.0 Hz), 7.33 (1H, t, *J* = 7.5 Hz), 7.25 (2H, br s), 7.11 (1H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 165.0, 155.9, 137.9, 137.8, 135.0, 134.0, 132.1, 131.5, 130.3, 130.2 129.3, 129.2, 127.5, 126.8, 125.9, 125.2, 123.6, 119.7, 117.0, 113.6, 59.6. HRMS calc'd for [M+Na] = 540.0164, observed = 540.0176. IR (NaCl, DCM): 3447, 3350, 1652, 1590, 1373, 1175, 1122. M.P. = 139 ºC.

Figure 9.66: Compound V.4

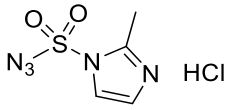


1-tosyl-1*H*-indole (V.4). To a 250 mL roundbottom flask containing a stir bar was added indole (5.9 g, 50.0 mmol) and aqueous NaOH (24 g, 60.0 mmol, NaOH in 50 mL water). Stirring commenced and toluene was added (75 mL), followed by TBAB (1.6 g, 4.9 mmol). To this mixture was added tosyl chloride (9.65 g, 50.0 mmol). After stirring for 2 hours at room temperature, TLC analysis (1:5 ethyl acetate: hexanes) revealed starting material was still present. To push the reaction to completion, an additional portion of NaOH (1.4 g, 35.0 mmol) and tosyl chloride (0.646g, 3.4 mmol). The reaction was allowed to stir overnight.

The following day, the reaction mixture was transferred to a separatory funnel and partitioned. The organic layer was washed with water (50 mL), dried over sodium sulfate, and

concentrated to dryness on a rotary evaporator. The crude product was dissolved in a minimal amount of DCM and purified by column chromatography (1:9 ethyl acetate: hexanes) to yield the product as a white solid (6.9 g, 51 %). Spectroscopic data matches that reported for this compound.[175] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.02 (1H, d, *J* = 8.5 Hz), 7.78 (2H, d, *J* = 8.5 Hz), 7.59 (1H, d, *J* = 4.0 Hz), 7.47 (1H, d, *J* = 7.0 Hz), 7.33 (1H, t, *J* = 8.0 Hz), 7.27 – 7.20 (3H, m), 6.67(1H, d, *J* = 3.5 Hz), 2.33 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 144.9, 135.2, 134.7, 130.7, 129.8, 126.8, 126.3, 124.5, 123.2, 121.3, 113.5, 109.0, 21.5. M.P. = 82 ºC.

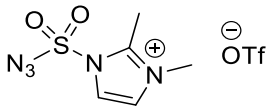
Figure 9.67: Compound V.5a



2-methyl-1*H*-imidazole-1-sulfonyl azide hydrochloride (V.5a). To a 1000 mL roundbottom flask containing a stir bar was added acetonitrile (450 mL) and sodium azide (32.5 g, 500.0 mmol). The reaction vessel was cooled to 0 ºC in an ice water bath and stirring commenced. Ad addition funnel with a pressure equalizing vent was added to the roundbottom flask, and was charged with a mixture of freshly distilled sulfuryl chloride (40.0 mL, 67.0 g, 500.0 mmol) and acetonitrile (50 mL). The sulfuryl chloride/acetonitrile solution was added dropwise to the acetonitrile/sodium azide solution over a period of 40 minutes. The addition funnel was removed and the reaction vessel was sealed with a septa and flushed with nitrogen. The reaction was allowed to continue overnight. The following day, the reaction mixture was cooled to 0 ºC in an ice water bath and 2-methylimidazole (82.1 g, 500.0 mmol) was added in portions. The reaction was allowed to warm to room temperature and stirred for 6 hours. At this time water was added (250 mL), followed by ethyl acetate (250 mL). The mixture was allowed to stir at room temperature for 15 minutes. The mixture was transferred to a separatory funnel and the layers

were partitioned. The aqueous layer was extracted with ethyl acetate (250 mL per extraction for 3 extractions). The organic layers were combined and washed twice with saturated sodium bicarbonate (300 mL per extraction). The organic layer was dried over sodium sulfate and placed in a 2000 mL beaker with a stir bar. The beaker was cooled to 0 ºC in an ice water bath and a solution of acetyl chloride in ethanol (54.0 mL, 750.0 mmol in 170 mL ethanol) was added dropwise over 30 minutes. Towards the end of addition a solid formed. The reaction mixture was allowed to stir for an additional 30 minutes at which time the solid was collected by filtration (over a fritted funnel) and washed twice with dry diethyl ether. The solid was transferred to a 500 mL roundbottom flask and dried *in vacuo* to yield the product as a white crystalline solid (35.8 g, 32 % yield. Spectroscopic data matches that known for this compound.[176] ^{1}H NMR (500 MHz) (CD_3OD) δ: 8.07 (1H, d, *J* = 2.0 Hz), 7.67 (1H, d, *J* = 2.5 Hz), 2.88 (3H, s). ^{13}C NMR (125 MHz) (CD_3OD) δ: 148.8, 121.4, 119.1, 11.8. M.P. = 103 ºC.

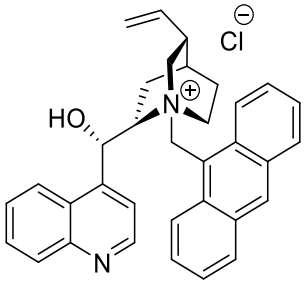
Figure 9.68: Compound V.5



1-(azidosulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (V.5). The free-base of 2-methyl-1*H*-imidazole-1-sulfonyl azide hydrochloride was generated by dissolving 11.4 g (51.3 mmol) of the HCl salt in 100 mL saturated sodium bicarbonate and extracting twice with ethyl acetate (100 mL per extraction). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield the free base as a clear oil (8.8 g, 47.0 mmol, 92 % yield). To the free base was added anhydrous diethyl ether (200 mL), followed by a stir bar. The reaction vessel was sealed with a septa and flushed with nitrogen. The reaction vessel was cooled to 0 ºC in an ice water bath and methyl triflate (6.9 mL, 10.0 g, 61.0 mmol) was added dropwise.

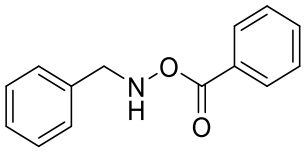
After 4 hours the product was collected by filtration (fritted funnel) and washed with diethyl ether to yield the pure product (15.9 g, 88 % yield). Spectroscopic data matches that known for this compound.[176] ^{1}H NMR (500 MHz) (CD_3OD) δ: 8.09 (1H, d, *J* = 2.0 Hz), 7.73 (1H, d, *J* = 2.5 Hz), 3.94 (3H, s), 2.88 (3H, s). ^{13}C NMR (125 MHz) (CD_3OD) δ: 148.5, 123.1, 121.6, 120.3, 119.0, 35.1, 10.4. M.P. = 72 ºC.

Figure 9.69: Compound V.8



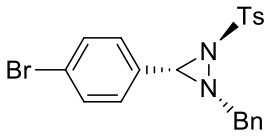
(1*S*,2*R*,4*S*,5*R*)-1-(anthracen-9-ylmethyl)-2-((*S*)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium chloride (V.8). To a 100 mL roundbottom containing a stir bar was added conchonine (1.0 g, 3.4 mmol) and 9-chloromethylanthracene (0.780 g, 3.44 mmol). To this reaction mixture was added toluene (40 mL). The reaction mixture was heated to reflux for 4 hours, during which time a solid precipitates. The solid is filtered on a fritted funnel and dissolved in chloroform (80 mL). Any remaining solid is filtered away, and petroleum ether was added to the filtrate, which caused the pure product to precipitate. This product was collected by filtration and remaining solvent was removed *in vacuo*. The pure product is isolated as an off-white solid (0.537 g, 32 %).[177] HRMS calc'd for [M-Cl] = 485.2593, observed = 485.2601. M.P. = 220 ºC.

Figure 9.70: Compound V.6



***O*-benzoyl-*N*-benzylhydroxylamine (V.6).** To a 250 mL roundbottom containing a stir bar was added DCM (80 mL) and benzyl amine (1.75 mL, 1.71 g, 16.0 mmol). Stirring commenced and the reaction vessel was cooled to 0 ºC in an ice water bath. Saturated aqueous sodium bicarbonate solution was added (40 mL). To the reaction mixture was added benzoyl peroxide (3.87 g, 16.0 mmol, 70 % benzoyl peroxide 30 % water, corrected for actual amount of benzoyl peroxide). The reaction was stirred for 1.5 hours at 0 ºC, at which time it was transferred to a separatory funnel. The layers were partitioned and the aqueous layer was washed with DCM (50 mL). The organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an oil. The crude product was purified by silica gel chromatography (1:9 ethyl acetate: hexanes) to yield the product as a clear oil (1.9 g, 53 %). Spectroscopic data matches that reported for this compound.[178] 8.06 – 7.99 (2H, m), 7.57 (1H, m), 7.57 – 7.30 (8H, m), 4.27 (2H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 166.8, 150.4, 135.7, 133.3, 132.0, 129.9, 129.3, 128.9, 128.7, 128.6, 128.5, 128.2, 127.9, 127.0, 56.7.

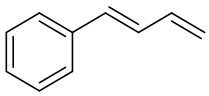
Figure 9.71: Compound V.7



(*S*)-1-benzyl-3-(4-bromophenyl)-2-tosyldiaziridine (V.7).To a 50 mL roundbottom containing a stir bar was added *O*-benzoyl-*N*-benzylhydroxylamine (1.0 g, 4.4 mmol) and toluene (40 mL). To this mixture was added (in the order described) potassium phosphate tribasic (1.80 g, 8.8

mmol), followed by (1*S*,2*R*,4*S*,5*R*)-1-(anthracen-9-ylmethyl)-2-((*S*)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium chloride (0.020 g, 0.04 mmol), and N-(4-bromobenzylidene)-4-methylbenzenesulfonamide (1.2 g, 3.3 mmol). The reaction vessel was sealed and flushed with argon for 5 minutes. The reaction was transferred to the cold room, and was stirred at 4 ºC for 3 days. At the end of this period a precipitate had formed. The crude reaction was filtered and concentrated *in vacuo* to a yellow oil. The crude material was purified by silica gel chromatography (gradient 1:1 to 1:0 DCM: hexanes) to yield the product as a white solid (0.644 g, 45 %). Spectroscopic data matches that reported for this compound.[178] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.70 (2H, d, *J* = 8.5 Hz), 7.56 (2H, dd, *J* = 7.0, 2.0 Hz), 7.39 (2H, d, *J* = 2.0 Hz), 7.16 – 7.14 (3H, m), 7.09 – 7.06 (2H, m), 6.91 (2H, d, *J* = 7.0 Hz), 4.85 (1H, s), 3.29 (2H, app quartet, *J* = 24.0, 13.0 Hz), 2.41 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 145.0, 135.5, 132.4, 131.7, 130.7, 129.7, 129.4, 129.1, 128.1, 128.8, 128.4, 128.1, 127.1, 124.1, 62.7, 56.1, 21.7. HRMS calc'd for [M+Na] = 465.0248, observed = 465.0238. M.P. = 114 – 116 ºC.

Figure 9.72: Compound V.9

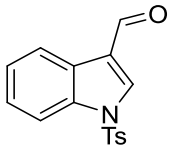


(*E*)-buta-1,3-dien-1-ylbenzene (V.9). To an oven dried 100 mL roundbottom flask containing a stir bar was added methyl triphenylphosphonium bromide (2.9 g, 7.2 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. To this vessel was added THF (25 mL); stirring commenced and the reaction vessel was cooled to 0 ºC in an ice water bath. To this mixture was added LiHMDS dropwise via syringe (8.5 mL, 8.5 mmol, 1.0 M in hexanes). The reaction mixture turned yellow on addition of LiHMDS and was removed from the ice water bath. The reaction was allowed to continue at room temperature until all remaining methyl

triphenylphosphonium bromide dissolved (~ 45 minutes). At the point *trans*-cinnamaldehyde (1.1 mL, 1.15 g, 8.4 mmol) was added dropwise. The reaction mixture was allowed to stir overnight.

The following day, the reaction was quenched with methanol (5 mL) and concentrated to an oily solid on a rotary evaporator. Hexanes was added (30 mL) to the crude product, which caused a white precipitate to form. The solid was separated by filtration (fritted funnel) and the filtrate was concentrated again to an oil on a rotary evaporator. Hexanes was added again, and charcoal was added. The charcoal solution was filtered through a pad of silica gel, which was washed with hexanes. The filtrate and washings were combined and concentrated *in vacuo* to yield the product as an oil (0.822 g, 75 %). Spectroscopic data matches that reported for this compound.[179] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.42 (2H, d, *J* = 7.0 Hz), 7.34 – 7.31 (2H, m), 7.25 – 7.23 (1H, m), 6.80 (1H, dd, *J* = 16.0, 10.0 Hz), 6.59 – 6.48 (2H, m), 5.35 (1H, d, *J* = 16.5 Hz), 5.19 (1H, d, *J* = 10.0 Hz). ^{13}C NMR (500 MHz) ($CDCl_3$) δ: 137.1, 137.1, 132.8, 129.6, 128.6, 127.6, 126.4, 117.6.

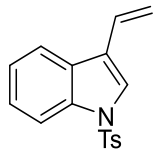
Figure 9.73: Compound V.10a



1-tosyl-1*H*-indole-3-carboxaldehyde (V.10a). To a 500 mL roundbottom flask containing a stir bar was added (in the order specified) indole-3-carboxaldehyde (2.0 g, 13.8 mmol), benzene (50 mL), aqueous NaOH (30 % w/v, 50 mL), and tosyl chloride (2.8 g, 14.4 mmol). Vigorous stirring commenced, followed by the addition of tetrabutylammonium bromide (0.44 g, 0.138 mmol). The reaction was stirred for 30 minutes at room temperature, at which time it was transferred to a separatory funnel and partitioned. The organic layer was washed with water (50

mL) and dried over sodium sulfate. The crude reaction mixture was concentrated to an oil on a rotary evaporator. The crude product was purified by recrystallization by dissolving the oil in a minimum amount of DCM and adding hexanes until a white precipitate formed. The solid was filtered and washed with hexanes. Remaining solvent was removed by drying *in vacuo* to yield the product as a white solid (2.6 g, 63 %). Spectroscopic data matches that reported for this compound.[180] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 10.09 (1H, s), 8.25 – 8.23 (2H, m), 7.94 (1H, d, *J* = 8.5 Hz), 7.85 (2H, d, *J* = 8.5 Hz), 7.40 (1H, t, *J* = 7.5 Hz), 7.36 (1H, t, *J* = 7.5 Hz) 7.29 (2H, d, *J* = 8.0 Hz) 2.37 (3H, s). ^{13}C NMR (500 MHz) ($CDCl_3$) δ: 185.3, 146.1, 136.2, 135.1, 134.3, 130.3, 127.2, 126.3, 126.2, 125.0, 122.6, 122.3, 113.2, 21.6. M.P. = 138 ºC.

Figure 9.74: Compound V.10

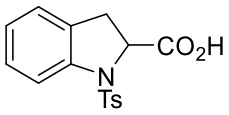


1-tosyl-3-vinyl-1*H*-indole (V.10). To a 100 mL roundbottom flask containing a stir bar was added methyl triphenylphosphonium bromide (1.7 g, 4.8 mmol). The reaction vessel was sealed and flushed with nitrogen. To the vessel was added THF (40 mL) via syringe. Stirring commenced, and LiHMDS was added dropwise via syringe (5.5 mL, 5.5 mmol, 1.0 M in hexanes). The reaction mixture was stirred at room temperature until the solid dissolved (~ 2 hours). At this time, 1-tosyl-1*H*-indole-carboxaldehyde was added dropwise (1.2 g, 3.9 mmol, dissolved in 5 mL THF). On addition of the aldehyde, the reaction mixture turned red. The reaction was allowed to proceed overnight.

The following day, the reaction mixture was quenched with water (5 mL) and transferred to a separatory funnel. To the mixture was added brine (50 mL) and ether (100 mL), followed by extraction. The layers were separated and the aqueous layer was washed with ether a second time

(50 mL). The organic layers were combined and washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to yield the crude product as an oil. The crude product was purified by silica gel chromatography (1:19 ethyl acetate: hexanes) to yield the crude product as a tan solid (0.500 g, 44 %). Spectroscopic data matches that reported for this compound.[180] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.00 (1H, d, *J* = 4.0 Hz), 7.78 – 7.74 (3H, m), 7.61 (1H, s), 7.36 – 7.32 (1H, m), 7.29 – 7.26 (1H, m), 7.26 – 7.21 (2H, m), 6.77 (1H, dd, *J* = 18.0 Hz, 11.5 Hz), 5.80 (1H, d, *J* = 18.0 Hz), 5.36 (1H, d, *J* = 12.0 Hz), 2.34 (3H, s). ^{13}C NMR (500 MHz) ($CDCl_3$) δ: 145.0, 135.4, 135.1, 129.9, 128.9, 127.5, 126.8, 124.9, 124.0, 123.5, 120.9, 120.4, 115.3, 113.7, 21.5. M.P. = 101 ºC.

Figure 9.75: Compound VI.1

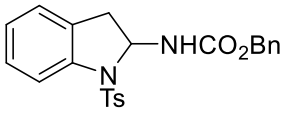


1-tosylindoline-2-carboxylic acid (VI.1). To a 250 mL roundbottom flask containing a stir bar was added indoline-2-carboxylic acid (5.0 g, 30.0 mmol), followed by water (150 mL). Stirring commenced, and potassium carbonate was added (9.10 g, 66 mmol). The potassium carbonate was allowed to dissolve (~ 5 minutes), and tosyl chloride was added (6.08 g, 32.0 mol). The reaction mixture was allowed to stir overnight.

The following day all solids had dissolved, leaving a brown solution. The reaction mixture was cooled to 0 ºC in an ice water bath and 100 mL DCM was added. While stirring, concentrated HCl was added until the aqueous layer was acidic (pH ~ 2 by pH paper). The reaction mixture was warmed to room temperature and stirred for 5 minutes. The reaction mixture was transferred to a separatory funnel and partitioned. The aqueous layer was extracted with an additional portion of DCM (100 mL). The organic layers were combined and dried over

sodium sulfate and concentrated to dryness on a rotary evaporator to yield a brown solid. Residual solvent was removed *in vacuo* to yield the product as a brown solid (8.2 g, 83 %). Spectroscopic data matches that reported for this compound.[181] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.81 (1H, br s), 7.66 – 7.60 (3H, m), 7.24 – 7.22 (3H, m), 7.08 7.02 (2H, m), 4.79 (1H, app quartet, J = 9.5, 5.0 Hz), 3.19 (2H, t, J = 4.5 Hz), 2.37 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 175.32, 144.7, 140.9, 133.9, 129.8, 129.6, 128.2, 127.3, 125.0, 124.8, 116.0, 62.0, 32.6, 21.5. M.P. = 186 ºC.

Figure 9.76: Compound VI.2

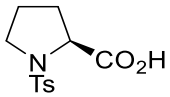


benzyl (1-tosylindolin-2-yl)carbamate (VI.2). To a 250 mL roundbottom flask containing a stir bar was added 1-tosylindoline-2-carboxylic acid (7.9 g, 25 mmol). To this vessel was added THF (100 mL) and stirring commenced while cooling the vessel to 0 ºC in an ice water bath. To this mixture was added TEA (3.7 mL, 2.52 g, 26 mmol), followed by ethyl chloroformate (2.5 mL, 2.81 g, 26 mmol). A solid precipitated, and after 10 minutes of stirring an solution of aqueous sodium azide was added (19.5 g, 300 mmol in 50 mL water) in one portion. This mixture was was allowed to stir for 30 minutes at to 0 ºC. The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate three times (100 mL per extraction). The organic layers were combined, dried over sodium sulfate, and concentrated to a red oil on a rotary evaporator (behind a blast shield). The oil was dried *in vacuo* for 10 minutes to remove residual solvent. The oil was dissolved in anhydrous toluene (100 mL) and heated on an oil bath. Bubbles evolved after 2 minutes and stopped after 10 minutes (presumably nitrogen gas). To the reaction mixture was added benzyl alcohol (4.2 mL, 4.36 g, 40.0 mmol), and the reaction

mixture was heated to an internal temperature of 60 ºC (direct measurement of solution by thermometer) overnight.

The following day the reaction was cooled to room temperature and a small amount of solid was filtered from the crude reaction mixture on a fritted funnel. The reaction mixture was concentrated to dryness as a black solid. The crude product was purified by silica gel chromatography (3:7 ethyl acetate: hexanes) to yield the product as a white solid (5.5 g, 52 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.70 – 7.64 (2H, m), 7.36 – 7.34 (6H, m), 7.24 – 7.18 (3H, m), 7.08 – 7.01 (2H, m), 5.92 – 5.89 (1H, br m), 5.50 (1H, br s), 5.14 (2H, q, *J* = 17.0, 12.5 Hz), 4.71 (1H, s), 3.20 (1H, dd, *J* = 17.0, 8.5 Hz), 2.89 (1H, br d, *J* = 17.0 Hz), 2.36 (3H, s). ^{13}C NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 154.9, 144.3, 140.8. 140.5, 136.0, 134.8, 129.7, 129.6, 128.8, 128.5, 128.5, 128.2, 128.1, 128.0, 127.6, 127.3, 127.2, 126.9, 125.0, 124.4, 115.5, 69.6, 67.0, 65.3, 36.9, 21.5. HRMS calc'd for [M – H] = 421.1222, observed = 421.1222. IR (NaCl, DCM): 1749, 1716, 1635, 1521, 1436, 1260. M.P. = 66 – 70º C.

Figure 9.77: Compound VI.3a

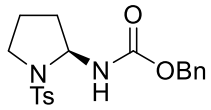


tosyl-*L*-proline (VI.3a). To a 250 mL roundbottom flask containing a stir bar was added *L*-proline (10.26 g, 89 mmol) and water (100 mL). Stirring commenced, and sodium carbonate was added (20.21 g, 196 mmol). After bubbles ceased to evolve, tosyl chloride was added (19.06 g, 100 mmol) and the reaction was allowed to stir overnight.

The following day, DCM was added (100 mL) and the reaction was cooled to 0 ºC in an ice water bath. Concentrated HCl was added until the aqueous layer was acidic (pH ~ 2 by pH paper). The reaction mixture was transferred to a separatory funnel and washed with water. The

aqueous layer was extracted with DCM (100 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield the pure compound as an oil (21.1 g, 88 %). Spectroscopic data matches that reported for this compound.[182] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.75 (2H, 2, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.0 Hz), 7.09 (1H, br s), 4.20 (1H, q, *J* = 8.0, 4.5 Hz), 3.54 – 3.50 (1H, m), 3.18 (1H, q, *J* = 15.5, 4.0 Hz), 2.39 (3H, s), 2.10 – 2.06 (1H, m), 1.94 – 1.88 (2H, m), 1.63 – 1.60 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 176.9, 143.7, 134.3, 129.7, 127.6, 127.5, 61.2, 48.9, 30.8, 24.6, 21.5.

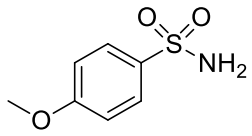
Figure 9.78: Compound VI.3



benzyl (*S*)-(1-tosylpyrrolidin-2-yl)carbamate (VI.3). To a 500 mL roundbottom flask containing a stir bar was added tosyl-*L*-proline (18.9 g, 70.0 mmol). To this vessel was added THF (150 mL) and stirring commenced while cooling the vessel to 0 ºC in an ice-water bath. To this mixture was added TEA (9.75 mL, 7.07 g, 70 mmol), followed by isobutyl chloroformate (9.15 mL, 9.51 g, 70 mmol). A solid precipitated, and after 10 minutes of stirring an solution of aqueous sodium azide was added (65.0 g, 1.0 mol in 200 mL water) in one portion. This mixture was stirred for 30 minutes at to 0 ºC. The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to a red oil. The oil was dissolved in toluene (100 mL) and heated on an oil bath. Gas evolved after 2 minutes and stopped after 10 minutes (presumably nitrogen gas). To the reaction mixture was added benzyl alcohol (12.0 mL, 12.5 g, 70.0 mmol), and the reaction mixture was heated to an internal temperature of 60 ºC (direct measurement of solution by thermometer) overnight.

The following day, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator. The oil was triturated by adding a minimal amount of ethyl acetate and hexanes and concentrated *in vacuo*. The solid was washed with ethyl acetate (2 x 50 mL) and dried *in vacuo* to yield the pure product (5.27 g, 18 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.78 – 7.71 (2H, m), 7.37 – 7.26 (7H, m), 5.31 (2H, s), 5.15 – 5.11 (2H, m), 3.57 (1H, br s), 3.08 (1H, m), 2.42 (3H, app s), 1.91 – 1.66 (4H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 155.0, 143.8, 143.7, 136.2, 134.3, 129.8, 129.7, 129.7, 128.7, 128.7, 128.5, 128.3, 128.1, 128.1, 127.6, 126.9, 67.9, 67.7, 66.7, 66.3, 65.3, 48.6, 33.9, 22.9, 22.8, 21.5. HRMS calc'd for [M+Na] = 397.1198, observed = 397.1197. IR (NaCl, DCM): 3467, 1648, 1539, 1455, 1238. M.P. = 134 – 136 ºC.

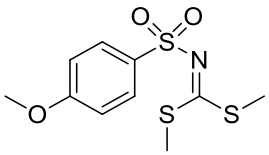
Figure 9.79: Compound VI.4a



4-methoxybenzenesulfonamide (VI.4a). To a 250 mL roundbottom flask containing a stir bar was added 100 mL saturated NH_4OH and *p*-methoxybenzene sulfonyl chloride (7.28 g, 37.8 mmol). Stirring commenced. Within 1 hour most of the starting material had dissolved, and a solid began to form, creating a cloudy solution. The reaction was allowed to proceed overnight. The following day, the reaction mixture was filtered (fritted funnel) and washed with water three times (50 mL per wash). The product was obtained as a white crystalline powder and dried *in vacuo* to remove residual solvent (5.6 g, 79 %). Spectroscopic data matches that reported for this compound.[183] ^{1}H NMR (500 MHz) (d_6-DMSO) δ: 7.74 (2H, d, *J* = 8.5 Hz), 7.20 (2H, br s), 7.07

(2H, d, J = 9.5), 3.81 (3H, s). ^{13}C NMR (125 MHz) (d_6-DMSO) δ: 162.0, 136.6, 128.1, 114.4, 56.0. M.P. = 108 ºC.

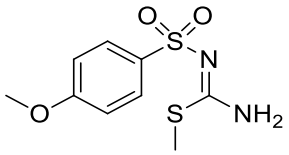
Figure 9.80: Compound VI.4b



dimethyl (4-methoxyphenyl)sulfonylcarbonimidodithioate (VI.4b). To a 100 mL roundbottom flask containing a stir bar was added 4-methoxybenzenesulfonamide (5.3 g, 28.8 mmol) and DMF (23 mL). The reaction vessel was cooled to 0 ºC in an ice-water bath. Stirring commenced, and to this mixture was added (in the sequence indicated) sodium hydroxide (2.1 mL of a 20.0 M solution, 42.0 mmol) and carbon disulfide (1.07 mL, 17.8 mmol). The mixture was stirred for 15 minutes, at which time sodium hydroxide (1.0 mL of a 20.0 M solution, 20.0 mmol) was added, followed by carbon disulfide (0.54 mL, 9.0 mmol). The reaction mixture was stirred for an additional 15 minutes, at which time sodium hydroxide (1.0 mL of a 20.0 M solution, 20.0 mmol) and carbon disulfide (0.54 mL) addition was repeated. This mixture was stirred for 20 minutes at 0 ºC and 2 hours at room temperature. At this time, the reaction vessel was cooled to 0 ºC in an ice-water bath and dimethyl sulfate was added dropwise (6.1 mL, 8.11 g, 65 mmol). On addition of dimethyl sulfate the reaction turns yellow. The reaction vessel was warmed to room temperature and stirred for 3 hours. After this time period, the reaction vessel was again cooled to 0 ºC and water was added (40 mL). The reaction mixture was stirred vigorously for 1 hour. During this time an orange solid forms. After the 1 hour period has elapsed, the solid is filtered (fritted funnel) and washed with water twice (50 mL per wash). The crude solid is transferred to a 100 mL roundbottom flask and methanol is added (60 mL). The

reaction vessel is heated until the solid dissolves, at which time the vessel is allowed to cool to room temperature. Crystals precipitate and are collected with a fritted funnel and washed twice with methanol (20 mL per wash). To obtain a second crop, the filtrates are combined and placed in a 250 mL roundbottom, sealed with a septa and placed in - 20 ºC overnight. The combined crops are dried *in vacuo* to obtain the pure compound (3.24 g, 39 %). Spectroscopic data matches that reported for this compound.[184] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.92 (2H, d, *J* = 8.5 Hz), 6.97 (2H, d, *J* = 8.5 Hz), 3.86 (3H, s), 2.52 (6H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 184.0, 163.0, 132.3, 129.4, 113.9, 55.6, 16.4. M.P. = 77 ºC.

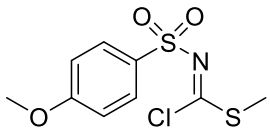
Figure 9.81: Compound VI.4c



methyl N'-(4-methoxyphenyl)sulfonylcarbamimidothioate (VI.4c). To a 50 mL roundbottom flask containing a stir bar was added dimethyl (4-methoxyphenyl) sulfonylcarbonimidodithioate (2.71 g, 9.3 mmol). To the vessel was added methanol (10 mL) and ammonia (2.5 M in methanol, 2.5 mL, 10 mmol). The reaction vessel was sealed with a septa and stirring commenced while the reaction vessel was heated to 50 ºC in an oil bath for 1 hour. At this time an aliquot was removed and concentrated *in vacuo* to a white solid. ^{1}H NMR revealed ~ 95 % conversion to product. To drive the reaction to completion, ammonia in methanol (2.5 M, 1.0 mL, 2.5 mmol) was added. The vessel was sealed and heated to 50 ºC for another hour. The solvent was removed on a rotary evaporator and the product was dried *in vacuo* to yield the product as a white solid (2.41 g, 99 %). Spectroscopic data matches that reported for this compound.[185] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.87 (2H, d, *J* = 8.5 Hz), 6.96 (2H, d, *J* = 8.5 Hz),

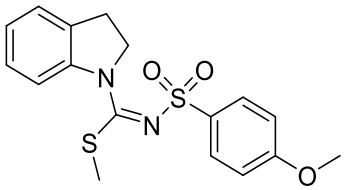
3.87 (3H, s), 2.37 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 168.6, 162.6, 133.8, 128.4, 113.9, 55.5, 14.0. M.P. = 148 ºC.

Figure 9.82: Compound VI.4



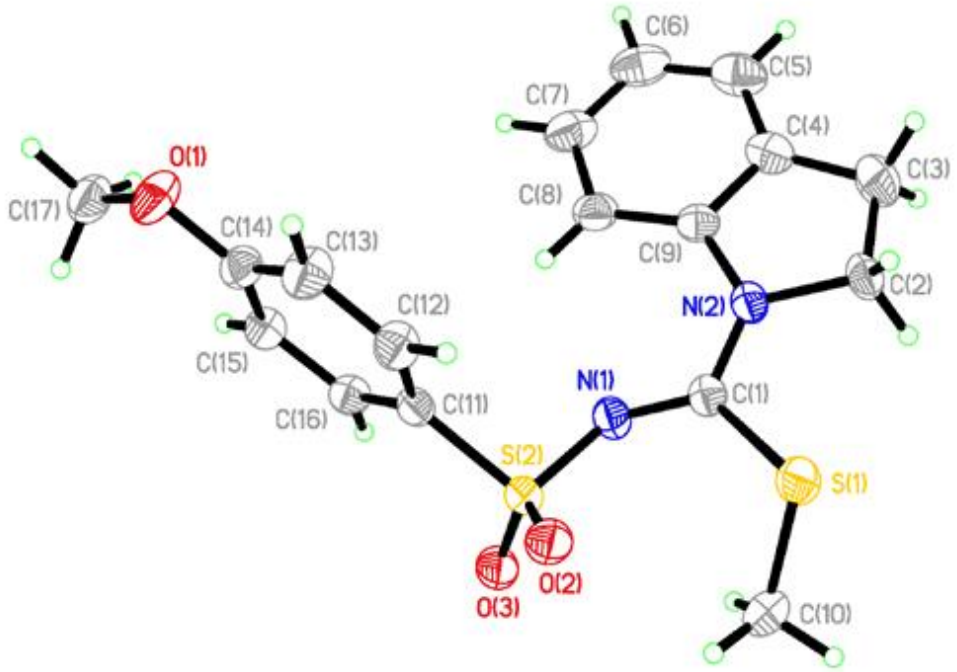
methyl (4-methoxyphenyl)sulfonyl)carbonochloridoimidothioate (VI.4). To a 100 mL roundbottom flask containing a stir bar was added dimethyl (4-methoxyphenyl)-sulfonylcarbonimidodithioate (2.0 g, 6.9 mmol). DCM was added to the reaction vessel (50 mL). The reaction vessel was sealed, flushed with nitrogen, and stirring commenced. To the reaction mixture was added sulfuryl chloride (1.10 mL, 1.84 g, 13.7 mmol) dropwise via syringe. After the addition of sulfuryl chloride the reaction was heated to 40 ºC in an oil bath for 3 hours. At 3 hours, the vessel was opened and the reaction mixture was analyzed by TLC (3:7 ethyl acetate: hexanes), which revealed the consumption of all starting material. The crude reaction mixture was concentrated *in vacuo* to yield a solid which was purified by silica gel chromatography (3:7 ethyl acetate: hexanes) to yield the pure product was a solid (1.9 g, 99 %). Spectroscopic data matches that reported for this compound.[18] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.87 (2H, d, J = 8.5 Hz), 6.96 (2H, d, J = 9.0 Hz), 3.87 (3H, s), 2.37 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 168.6, 162.6, 133.8, 128.4, 113.9, 55.5, 14.0. M.P. = 74 ºC.

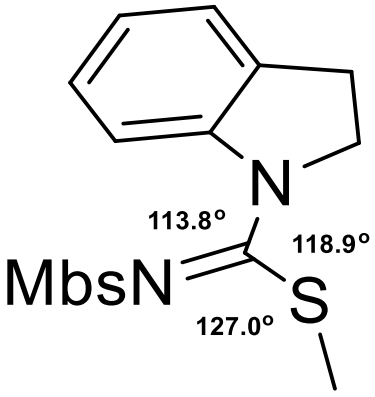
Figure 9.83: Compound VI.5



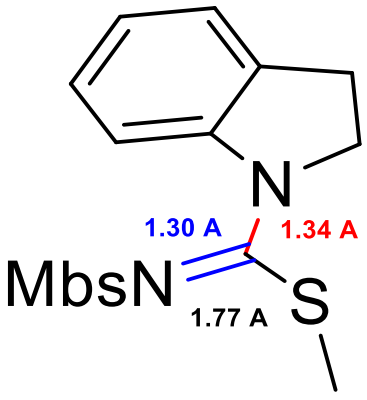
methyl N-((4-methoxyphenyl)sulfonyl)indoline-1-carbimidothioate (VI.5). To a 50 mL roundbottom flask containing a stir bar was added methyl (4-methoxyphenyl)sulfonyl)-carbon chloridothiolate (1.28 g, 4.6 mmol), followed by DCM (15 mL). Stirring commenced, and indoline was added dropwise (0.471 mL, 0.500 g, 4.2 mmol). Before TEA could be added, the reaction solidified (~ 10 seconds after indoline addition). The reaction vessel was sealed with a septa and flushed with nitrogen. To the solid mixture was added TEA (0.702 mL, 0.509 g, 5.0 mmol) via syringe. The reaction mixture was allowed to stir overnight.

The following day the reaction was concentrated *in vacuo* to yield the crude product as a yellow solid. The crude product was dissolved in a minimal amount of DCM and purified by silica gel chromatograpy (3:7 ethyl acetate: hexanes, R_f = 0.20). to yield the purified product as a tan crystalline solid (1.05 g, 67 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.95 – 7.92 (2H, m), 7.58 (1H, d, *J* = 7.5 Hz), 7.18 (1H, d, *J* = 7.0 Hz), 7.02 – 6.94 (4H, m), 4.31 (2H, t, *J* = 8.0 Hz), 3.88 (3H, s), 3.13 (2H, t, *J* = 8.0 Hz), 2.75 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 162.1, 161.9, 141.7, 135.7, 133.7, 128.5, 127.1, 125.2, 125.1, 117.7, 113.7, 55.5, 53.2, 27.5, 18.3. HRMS calc'd for [M+H] = 363.0837, observed = 363.0838. IR: (NaCl, DCM): 2930, 2840, 1506, 1390. M.P. = 139 ºC. Crystal Structure:

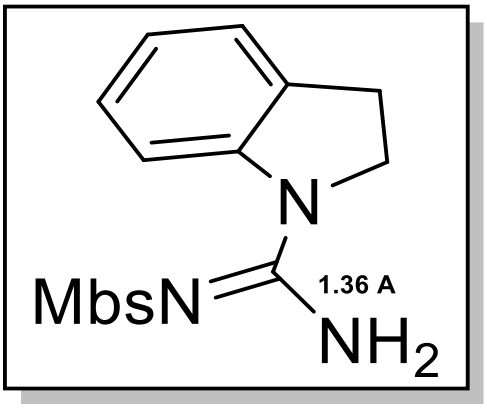




44 bond angles



44 bond lengths



cyclization precursor with approximated C-N bond angle

Table 9.3: Bond Lengths and Bond Angles for Compound VI.5

Bond Lengths

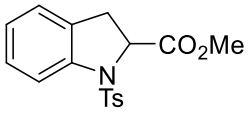
Atom	Atom	Length/Å
S1	C1	1.7710(17)
S1	C10	1.805(2)
S2	O2	1.4412(13)
S2	O3	1.4375(13)
S2	N1	1.6019(15)
S2	C11	1.7613(18)
O1	C14	1.363(2)
O1	C17	1.428(2)
N1	C1	1.309(2)
N2	C1	1.344(2)
N2	C2	1.487(2)
N2	C9	1.425(2)
C2	C3	1.526(3)

Bond Angles

Atom	Atom	Atom	Angle/°
C1	S1	C10	102.95(8)
O2	S2	N1	113.88(8)
O2	S2	C11	107.08(8)
O3	S2	O2	117.28(8)
O3	S2	N1	108.49(8)
O3	S2	C11	107.60(8)
N1	S2	C11	101.06(8)
C14	O1	C17	116.43(14)
C1	N1	S2	128.56(12)
C1	N2	C2	123.06(14)
C1	N2	C9	126.94(14)
C9	N2	C2	109.71(14)
N1	C1	S1	127.24(13)
N1	C1	N2	118.91(15)
N2	C1	S1	113.83(12)
N2	C2	C3	105.23(15)
C4	C3	C2	104.55(15)
C5	C4	C3	129.26(18)
C5	C4	C9	119.90(19)

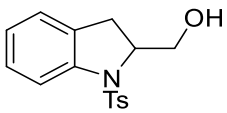
The law of cosines, $c^2 = a^2 + b^2 - 2ab[cos(C)]$, was used to determine the length between N1 and C3 as 5.266 angstroms. The same law of cosines was used to determine the length of the hypothetical guanidine nitrogen from N2 as 1.984 angstroms. Considering the nitrogen that would be forming the ring is at most 2 angstroms away from N2 and the carbon bonding partner is 5 angstroms away, the likelihood of forming the desired bond was too low to pursue.

Figure 9.84: Compound VI.6



methyl 1-tosylindoline-2-carboxylate (VI.6). To a 500 mL roundbottom flask containing a stir bar was added 1-tosylindoline-2-carboxylic acid (7.70 g, 28.5 mmol) and methanol (200 mL). Stirring commenced and the reaction mixture was cooled to 0 ºC in an ice water bath. Thionyl chloride was added dropwise (11.4 g, 96.0 mmol, 7.0 mL). Once addition was complete, the reaction vessel was attached to a reflux condenser and placed in a heating mantle. The reaction mixture was heated to reflux overnight. The following day the reaction mixture was concentrated to approximately half the original volume *in vacuo*. Ethyl acetate (100 mL) and water (100 mL) was added to the reaction vessel and the crude reaction mixture was transferred to a separatory funnel. The aqueous layer was separated and the organic layer was washed with saturated sodium bicarbonate (100 mL) followed by brine (100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the pure product as a brown solid (7.70 g, 82 % yield). Spectroscopic data matches that reported for this compound.[41] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.69 – 7.66 (2H, m), 7.58 (1H, d, *J* = 8.0 Hz), 7.23 – 7.19 (3H, m), 7.06 – 6.99 (2H, m), 4.79 (1H, quartet, *J* = 8.5, 5.5 Hz), 3.80 (3H s), 3.21 – 3.16 (1H, m), 3.11 – 3.07 (1H, m), 2.37 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 171.6, 144.4, 141.3, 134.5, 129.7, 129.5, 128.1, 127.3, 124.8, 124.3, 115.6, 62.2, 52.9, 33.0, 21.5. M.P. = 67 ºC.

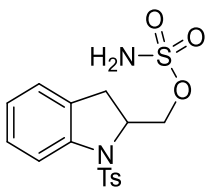
Figure 9.85: Compound VI.7a



(1-tosylindolin-2-yl)methanol (VI.7a). To a 500 mL roundbottom flask containing a stir bar

was added methyl 1-tosylindoline-2-carboxylate (7.70 g, 23.0 mmol), followed by THF (100 mL). The reaction vessel was sealed, flushed with nitrogen, and cooled to 0 ºC in an ice-water bath. Stirring commenced and lithium borohydride was added dropwise (26.0 mmol, 13.0 mL of a 2.0 M solution in THF). The reaction was allowed to warm to room temperature and continued overnight. The following day, the reaction was quenched by the addition of saturated ammonium chloride (10.0 mL) and concentrated to approximately half the original volume *in vacuo*. The crude reaction mixture was transferred to a separatory funnel and partitioned between ethyl acetate and water (by adding 100 mL of each to the separatory funnel). The aqueous layer was extracted with an additional portion of ethyl acetate (50 mL). The organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an oil. The crude material was purified by silica gel chromatography (1:4 ethyl acetate: hexanes, R_f = 0.42) to yield the final product as a yellow solid (5.50 g, 78 % yield). Spectroscopic data matches that reported for this compound.[187] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.69 (1H, d, *J* = 8.0 Hz), 7.52 (2H, app quartet, *J* = 6.5, 1.5 Hz), 7.25 – 7.15 (3H, m), 7.04 – 7.03 (2H, m), 4.31 – 4.26 (1H, m), 3.72 (2H, br s), 2.79 (1H, dd, *J* = 16.0, 9.5 Hz), 2.63 (16.0, 3.5 Hz), 2.45 (1H, br s), 2.35 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 144.2, 141.2, 134.3, 132.0, 129.6, 127.8, 127.1, 125.1, 117.6, 65.5, 63.5, 31.2, 21.5. IR (NaCl, DCM): 3483, 1636, 1349, 1091, 1041. M.P = 111 ºC.

Figure 9.86: Compound VI.7



(1-tosylindolin-2-yl)methyl sulfamate (VI.7). To an oven dried 100 mL roundbottom flask containing a stir bar was added chlorosulfonyl isocyanate (5.08 g, 36.3 mmol, 3.10 mL) via

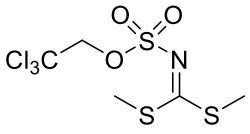
syringe. The reaction vessel was sealed with a septa and flushed with nitrogen. The reaction vessel was cooled to 0 ºC in an ice-water bath and 95 % formic acid was added dropwise (1.65 g, 1.35 mL, 36.3 mmol). Vigorous bubbling was observed and the reaction mixture became a white solid during the acid addition. After the addition of formic acid was complete, anhydrous acetonitrile was added (10 mL) via syringe, and the white solid dissolved. The reaction vessel was allowed to warm to room temperature and stirred for 8 hours.

In a separate 50 mL oven dried roundbottom flask was added (1-tosylindolin-2-yl) methanol (5.0 g, 16.5 mmol). The reaction vessel was sealed and dimethylacetamide was added (25 mL). The vessel containing the chlorosulfonyl isocyanate/formic acid mixture was again cooled to 0 ºC in an ice water bath and the (1-tosylindolin-2-yl) methanol/dimethyl formamide solution was added via cannula. The reaction mixture was stirred overnight.

The following day the reaction mixture was quenched by the addition of water (30 mL). The crude product was transferred to a separatory funnel and diluted with ethyl acetate (300 mL). The organic layer was washed 5 times with water (400 mL per wash) and three times with brine (200 mL per wash). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to a white foam. The crude product was purified by silica gel chromatography (3:7 ethyl acetate: hexanes, R_f = 0.21) to yield the pure product as a tan powder (3.7 g, 59 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.63 (1H, d, *J* = 8.5 Hz), 7.53 (2H, d, *J* = 8.5 Hz), 7.25 – 7.16 (3H, m), 7.05 – 7.04 (2H, m), 5.18 (2H, br s), 4.55 (1H, app quartet, *J* = 9.5, 2.5 Hz), 4.36 (1H, dd, *J* = 6.0, 5.25 Hz), 4.25 (1H, dd, *J* = 7.0, 5.5 Hz), 2.87 – 2.74 (2H, m), 2.35 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 144.5, 140.8, 133.9, 131.0, 129.8, 128.1, 127.1, 125.4, 125.3, 117.3, 71.5, 59.9, 31.2, 21.5. HRMS calc'd for [M+H] = 383.0735, observed = 383.0738. IR (NaCl, DCM): 3391, 3298, 1636,

1352, 1166, 1091, 814. M.P. = 127 ºC.

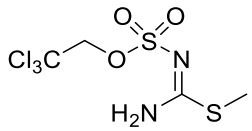
Figure 9.87: Compound VI.10a



2,2,2-trichloroethyl (bis(methylthio)methylene)sulfamate (VI.10a). To a 100 mL roundbottom flask containing a stir bar was added 2,2,2-trichloroethoxysulfamate (6.85 g, 30.0 mmol) and DMF (23 mL). The reaction vessel was cooled to 0 ºC in an ice-water bath. Stirring commenced, and to this mixture was added (in the sequence indicated) sodium hydroxide (2.1 mL of a 20.0 M solution, 42.0 mmol) and carbon disulfide (1.07 mL, 17.8 mmol). The mixture was stirred for 15 minutes, at which time sodium hydroxide (1.0 mL of a 20.0 M solution, 20.0 mmol) was added, followed by carbon disulfide (0.7 mL, 0.882 g, 11.5 mmol). The reaction mixture was stirred for an additional 15 minutes, at which time the sodium hydroxide and carbon disulfide addition was repeated (1.0 mL 20.0M NaOH and 0.7 mL carbon disulfide). This mixture was stirred for 20 minutes at 0 ºC and 2 hours at room temperature. At this time, the reaction vessel was cooled to 0 ºC in an ice-water bath and dimethyl sulfate was added dropwise (6.1 mL, 8.11 g, 65 mmol). On addition of dimethyl sulfate the reaction turns yellow. The reaction vessel was warmed to room temperature and stirred for 3 hours. After this time period, the reaction vessel was again cooled to 0 ºC and water was added (40 mL). The reaction mixture was stirred vigorously for 1 hour. During this time an orange solid forms. After the 1 hour period has elapsed, the solid was filtered and washed with water (2 x 50 mL). The crude solid is transferred to a 100 mL roundbottom flask and methanol is added (60 mL). The reaction vessel was heated until the solid dissolves, at which time the vessel is allowed to cool to room temperature. Crystals precipitate and are collected through filtration (fritted funnel) and washed

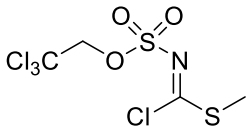
twice with methanol (20 mL per wash). To obtain a second crop of crystals, the filtrates are combined and placed in a 250 mL roundbottom, sealed with a septa and placed in - 20 ºC overnight. The combined crops are dried *in vacuo* to obtain the pure compound (3.93 g, 40 %). Spectroscopic data matches that reported for this compound.[150] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 4.75 (2H, s), 2.63 (6H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 189.8, 93.2, 79.2, 16.6. M.P. = 62 ºC.

Figure 9.88: Compound VI.10



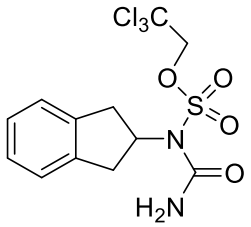
2,2,2-trichloroethyl-(amino(methylthio)methylene)sulfamate (VI.10). To a 25 mL roundbottom flask containing a stir bar was added 2,2,2-trichloroethyl (bis(methylthio)methylene)sulfamate (2.2 g, 6.6 mmol) and methanol (10 mL). The reaction vessel was sealed with a septa and wrapped with parafilm. The sealed vessel was immersed in an oil bath heated to 50 ºC. After immersion in the oil bath, ammonia was added by syringe (2 ml of 4.0 M solution in methanol, 8.0 mmol). The reaction was heated to 50 ºC for 90 minutes, at which time it was removed from the oil and allowed to cool to room temperature. The reaction mixture was concentrated to a solid on a rotary evaporator and residual solvent was removed *in vacuo* to yield the pure product as a solid (2.01 g, 100 %). Spectroscopic data matches that reported for this compound.[150] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 4.69 (2H, s), 2.47 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 171.7, 93.5, 78.7, 14.2. M.P. = 90 ºC.

Figure 9.89: 2,2,2-trichloroethyl-(chloro(methylthio)methylene)sulfamate



2,2,2-trichloroethyl-(chloro(methylthio)methylene)sulfamate. To a 25 mL roundbottom flask containing a stir bar was added 2,2,2-trichloroethyl(bis(methylthio)methylene)sulfamate (1.51 g, 4.51 mmol) followed by DCM (5 mL). The reaction vessel was sealed, flushed with nitrogen and stirring commenced, after which sulfuryl chloride was added via syringe (0.903 mL, 1.50 g, 11.2 mmol). The reaction was stirred for 6 hours at room temperature, at which time the reaction mixture was concentrated *in vacuo* to yield the crude product as a yellow solid. The crude product was purified by silica gel chromatography (gradient 1:9 to 1:5 ethyl acetate: hexanes) to yield the product as a white solid (1.39 g, 98 % yield). Spectroscopic data matches that reported for this compound.[150] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 4.78 (2H, s), 2.56 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 166.4, 92.7, 79.5, 18.3. M.P. = 62 ºC.

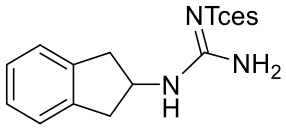
Figure 9.90: Compound VI.9



2,2,2-trichloroethyl carbamoyl(2,3-dihydro-1H-inden-2-yl)sulfamate (VI.9). To a 100 mL roundbottom flask containing a stir bar was added 2-indanol (0.900 g, 6.7 mmol) followed by 2,2,2-trichloroethyl carbamoylsulfamate (2.0 g, 7.4 mmol), followed by triphenylphosphine (1.93 g, 7.4 mmol). The vessel was sealed with a septa and flushed with nitrogen. To the sealed vessel was added THF via syringe (20 mL), followed by dropwise addition of diethylazidicarboxylate

(1.05 mL, 1.28 g, 7.4 mmol). The reaction mixture was allowed to stir overnight. The following day, the crude reaction mixture was concentrated *in vacuo*. The crude product was purified by multiple rounds of silica gel chromatography (gradient ethyl acetate: hexanes gradient 1:9 – 1:5 – 1:3) to yield the pure product as a white solid (1.1 g, 43 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.26 – 7.20 (4H, m), 6.99 (1H, br s), 5.68 (1H, quintet, *J* = 3.5 Hz), 5.46 (1H, br s), 4.70 (2H, s), 3.34 (2H, dd, *J* = 17.0, 5.5 Hz), 3.20 (2H, dd, *J* = 17.0, 2.0 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 159.9, 139.6, 127.1, 124.7, 93.7, 80.6, 78.5, 39.5. HRMS calc'd for [M – H] = 384.9589, observed = 384.9583. IR (NaCl, DCM): 3459, 3353, 1626, 1541, 1455, 1339, 1179, 1089, 1018, 853, 746. M.P. = 58 ºC.

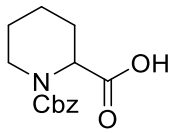
Figure 9.91: Compound VI.11



2,2,2-trichloroethyl-(amino((2,3-dihydro-1*H*-inden-2-yl)amino)methylene)sulfamate (VI.11). To a 25 mL roundbottom flask containing a stir bar was added 2-aminoindan (0.860 mL, 0.897 g, 6.6 mmol), followed by 2,2,2-trichloroethyl-(amino(methylthio)methylene)sulfamate (1.97 g, 6.6 mmol). To the reaction mixture was added water (7 mL). The reaction vessel was sealed with a septa and wrapped with parafilm. The reaction vessel was immersed in an oil bath heated to 105 ºC for 4 hours. After 1.5 hours, all the organic material had formed a brown layer on the underneath the aqueous layer. At 4 hours, the reaction vessel was removed from the oil bath and cooled to room temperature. DCM was added (20 mL), and the reaction mixture was heated with a heat gun to dissolve the crude reaction in the DCM. The crude mixture was transferred to a separatory funnel and partitioned. The aqueous layer was extracted once with DCM (20 mL). The organic layers were combined, dried over

sodium sulfate, and concentrated *in vacuo* to a purple oil. The crude material was dissolved in a minimum amount of DCM and purified by silica gel chromatograpy (gradient 1:4 to 3:7 ethyl acetate: hexanes, R_f = 0.12) to obtain the product as tan needles (1.4 g, 55 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.26 – 7.18 (4H, m), 6.06 (3H, br s), 4.57 (3H, s), 3.33 (2H, d, *J* = 10.0 Hz), 2.89 (2H, d, *J* = 15.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 156.4, 127.2, 124.8, 94.0, 78.1, 52.8, 39.7. HRMS = calc'd for [M – H] = 383.9749, observed = 383.9738. IR (NaCl, DCM): 3460, 3352, 2945, 1717, 1635, 1540, 1310, 1018. M.P. = 119 ºC.

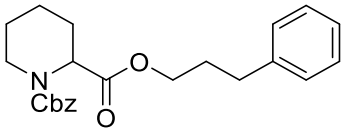
Figure 9.92: Compound VII.1a



1-((benzyloxy)carbonyl)piperidine-2-carboxylic acid (VII.1a). To a 100 mL roundbottom containing a stir bar was added piperidine-2-carboxylic acid (1.29 g, 10.0 mmol) followed by a water: dioxane mixture (40 mL of a 1:1 mixture). Stirring commenced and sodium carbonate was added (2.41 g, 23.0 mmol). Gas evolved; once the evolution had ceased most of the solid had dissolved. To this stirring mixture was added Cbz-Cl (1.7 mL, 2.04 g, 12.0 mmol) dropwise. The reaction mixture was allowed to stir overnight. The following day, the reaction mixture was concentrated to approximately half-volume *in vacuo*. This mixture was transferred to a separatory funnel and extracted with DCM (50 mL). This extract was discarded. In the separatory funnel, the aqueous layer was acidified by addition of concentrated HCl until the aqueous layer was acidic (pH ~ 2 by pH paper). The acidified aqueous layer was extracted 3 times with DCM (50 mL per extraction). The organic layers were combined and dried over sodium sulfate and concentrated *in vacuo* to yield the pure product as a clear oil (2.3 g, 88 %).

Spectroscopic data matches that reported for this compound.[192] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 10.08 (1H, br s), 7.37 -7.31 (5H, m), 5.16 (2H, m), 5.01 – 4.90 (1H, app d), 4.10 (1H, app d), 3.10 – 2.97 (1H, m), 2.25 (1H, dd, *J* = 27.5, 12.5 Hz), 1.73 – 1.63 (3H, m), 1.47 – 1.23 (2H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 177.6, 177.5, 156.7, 155.9, 136.4, 128.4, 128.0, 127.8, 67.5, 67.4, 54.3, 54.1, 41.9, 41.7, 26.6, 26.5, 24.6, 24.4, 20.7, 20.6.

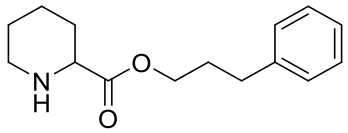
Figure 9.93: Compound VII.1



1-benzyl 2-(3-phenylpropyl) piperidine-1,2-dicarboxylate (VII.1). To a 250 mL roundbottom flask containing a stir bar was added 1-((benzyloxy)carbonyl)piperidine-2-carboxylic acid (2.3 g, 8.8 mmol), followed by DCM (40 mL). To the reaction vessel was added (in the order listed) EDCI (1.72 g, 9.0 mmol), TEA (1.4 mL, 1.01 g, 10.0 mmol), and DMAP (0.245 g, 2 .0 mmol). The reaction vessel was sealed and flushed with nitrogen. Stirring commenced and 3-phenyl-1-propanol was added via syringe (1.22 mL, 1.22 g, 9.0 mmol). The reaction was allowed to proceed overnight. The following day, the reaction was transferred to a separatory funnel in which it was washed with water (50 mL), dilute HCl (50 mL 0.5 M HCl), saturated aqueous sodium bicarbonate (50 mL) and brine. The crude product was dried over sodium sulfate and concentrated to dryness *in vacuo*. The crude product was purified by silica gel chromatography (1:4 ethyl acetate: hexanes, R_f = 0.30) to yield the pure product as a clear oil (1.5 g, 44 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ : 7.35 – 7.13 (10H, m), 5.16 – 5.13 (2H, m), 4.97 – 4.85 (1H, m), 4.15 – 4.05 (3H, m), 3.10 – 2.94 (1H, m), 2.68 – 2.61 (2H, m), 2.27 – 2.19 (1H, m), 1.98 – 1.89 (2H, m), 1.71 – 1.62 (3H, m), 1.47 – 1.41 (1H, m), 1.29 – 1.21 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.6, 156.5, 155.4, 141.0, 136.6, 128.4, 128.4,

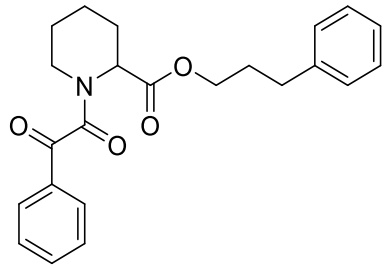
127.9, 127.8, 126.0, 67.3, 67.2, 64.3, 54.6, 54.4, 41.9, 41.8, 32.0, 26.8, 26.7, 24.7, 24.5, 20.7, 20.6. HRMS calc'd for [M+H] = 382.2018, observed = 382.2044. IR (NaCl, DCM): 3028, 2943, 2860, 1737, 1710, 1454, 1417, 1336, 1255, 1255, 1203, 1163, 1090, 1044.

Figure 9.94: Compound VII.2a



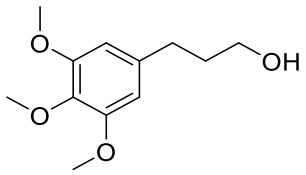
3-phenylpropyl piperidine-2-carboxylate (VII.2a). To a 250 mL roundbottom flask containing a stir bar was added 1-benzyl 2-(3-phenylpropyl) piperidine-1,2-dicarboxylate (1.5 g, 3.9 mmol) followed by ethanol (100 mL) and 10 % palladium on carbon (100 mg). Stirring commenced, and a balloon containing hydrogen was affixed to the reaction vessel. Hydrogen gas was applied to the ethanol/palladium mixture in this manner and the reaction was allowed to stir overnight. The following day, the balloon was removed and the crude reaction mixture was concentrated *in vacuo* to a dark oil. The crude was redissolved in ethyl acetate and filtered through celite. The filtrate was concentrated *in vacuo* to yield an oil. The crude material was purified through silica gel chromatography (1:4:0.01 ethyl acetate: hexanes: methanol, R_f = 0.57) to yield the product as a clear oil (0.533 g, 54 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.28 – 7.25 (2H, m), 7.19 – 7.15 (3H, m), 4.17 – 4.08 (2H, m), 3.32 (1H, dd, *J* = 9.5, 3.5 Hz), 3.06 (1H, dt, *J* = 12.0, 4.0 Hz), 2.69 – 2.61 (3H, m), 1.99 – 1.93 (4H, m), 1.79 – 1.76 (1H, m), 1.57 – 1.40 (4H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 173.5, 141.1, 128.4, 128.3, 126.0, 64.0, 58.6, 45.7, 32.1, 30.1, 29.2, 25.8, 24.1. HRMS calc'd for [M+H] = 248.1651, observed = 248.1658. IR (NaCl, DCM): 3501, 1735, 1454, 1184, 1055, 744.

Figure 9.95: Compound VII.2



3-phenylpropyl 1-(2-oxo-2-phenylacetyl)piperidine-2-carboxylate (VII.2). To a 250 mL roundbottom flask containing 3-phenylpropyl piperidine-2-carboxylate (1.0 g, 4.0 mmol) was added DCM (20 mL). The reaction vessel was sealed with a septa, flushed with nitrogen, and cooled to 0 ºC. To the stirring mixture was added 2-oxo-2-phenacetyl chloride (1.00 g, 6.0 mmol) dropwise via syringe. Immediately after the acid chloride addition, TEA (1.01 g, 10.0 mmol) was added dropwise. The reaction mixture was allowed to stir overnight. The next day, the reaction mixture was concentrated to approximately 20 % original volume and a white solid precipitated. The crude reaction mixture was purified by silica gel chromatography (1:3 ethyl acetate: hexanes, R_f = 0.50) to yield the product as an opaque oil (1.3 g, 85 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.05 – 7.96 (2H, m), 7.65 – 7.57 (1H, m), 7.52 – 7.45 (2H, m), 7.31 – 7.10 (5H, m), 5.42 (1H, d, *J* = 5.5 Hz), 4.65 – 4.08 (3H, m), 3.50 (1H, br d, *J* = 13.0 Hz), 3.24 (1H, td, *J* = 15.0, 15.0, 3.5 Hz), 3.01 (0.1 H, td, *J* = 10.0, 10.0, 2.5 Hz), 2.73 (2H, t, *J* = 7.5 Hz), 2.59 (0.3 H, t, *J* = 7.0 Hz), 2.39 – 2.36 (1H, m), 2.21 – 2.01 (2H, m), 1.91 – 1.70 (3H. m), 1.61 – 1.34 (4H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 191.7, 191.3, 170.4, 170.1, 167.4, 166.7, 140.8, 140.7, 134.8, 133.1, 133.0, 129.9, 129.7, 129.0, 128.8, 128.5, 128.5, 128.4, 128.3, 126.1, 126.1, 64.9, 56.6, 51.6, 44.2, 39.2, 32.1, 32.0, 30.2, 30.0, 27.3, 26.3, 24.8, 24.4, 21.2, 21.0. HRMS calc'd for [M+H] = 380.1862, observed = 380.1862. IR (NaCl, DCM): 3029, 2947, 1734, 1683, 1647, 1446, 1224, 1162.

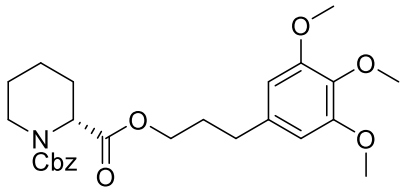
Figure 9.96: Compound VII.3a



3-(3,4,5-trimethoxyphenyl)propan-1-ol (VII.3a). To an oven dried roundbottom flask containing a stir bar was added freshly distilled THF (150 mL). The reaction vessel was immersed in an ice water bath, sealed with a septa, and flushed with nitrogen for 15 minutes while stirring. The septa was removed and LAH was added slowly (1.70 g, 45.0 mmol). The vessel was sealed and flushed with nitrogen for 10 minutes. To the reaction mixture was added dropwise via syringe 3,4,5-trimethoxycinnamic acid (9.94 g, 42.0 mmol, dissolved in 80 mL THF). Vigorous bubbling was observed. The reaction was allowed to warm to room temperature and continued overnight. The next day, the reaction mixture was cooled to 0 ºC in an ice water bath and methanol was added dropwise until no gas evolution was observed. After this, concentrated HCl was added dropwise until no gas evolution was observed. The reaction mixture was removed from the ice bath and stirred at room temperature for 20 minutes. The crude reaction mixture was concentrated *in vacuo* to approximately one-third the original volume and transferred to a separatory funnel. To the crude was added water (100 mL) and DCM (100 mL). The reaction mixture was partitioned and extracted with DCM (4 x 50 mL per extraction). The organic layers were combined and concentrated *in vacuo* to yield an orange oil that was purified through silica gel chromatography (1:1 ethyl acetate: hexanes, R_f = 0.24) to yield the product as an oil (4.4 g, 46 %). Occasionally the reduction of the allylic alcohol was incomplete, yielding approximately 10 % (by ^{1}H NMR integration) of the allylic alcohol. This impurity can easily be converted to the alkane through catalytic hydrogenation (hydrogen balloon over 10 % palladium on carbon in ethyl acetate). This step was performed as needed. Spectroscopic data matches that

reported for this compound.[188] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 6.42 (2H, s), 3.85 (3H, s), 3.82 (6H, s), 3.69 (2H, t, *J* = 6.5 Hz), 2.66 (2H, t, *J* = 7.0 Hz), 1.92 – 1.88 (2H, m), 1.51 (1H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 153.1, 137.6, 136.0, 105.2, 62.2, 60.8, 56.0, 34.3, 32.5.

Figure 9.97: Compound VII.3

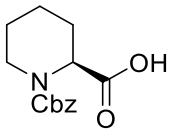


1-benzyl 2-(3-(3,4,5-trimethoxyphenyl)propyl) (*R*)-piperidine-1,2-dicarboxylate (VII.3).

To a 50 mL roundbottom flask containing a stir bar was added (*R*)-1-((benzyloxy)-carbonyl)piperidine-2-carboxylic acid (purchased from Sigma, 0.258 g, 1.0 mmol) was added DCM (10 mL) followed by TEA (0.306 mL, 0.222 g, 2.2 mmol), EDCI (0.209 g, 1.1 mmol), 3-(3,4,5-trimethoxyphenyl)propan-1-ol (0.226 g, 1.0 mmol), and DMAP (0.012 g, 0.10 mmol). The reaction vessel was sealed, flushed with nitrogen, and stirred overnight. The following day, the reaction mixture was transferred to a separatory funnel and washed with water (50 mL). The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to yield the product as an oil. The crude material was purified by silica gel chromatograpy (1:3 ethyl acetate: hexanes, R_f = 0.22) to obtain the pure product as a clear oil (0.189 g, 40 % yield). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.30 (5H, m), 6.43 – 6.37 (2H, m), 5.16 – 5.14 (2H, m), 4.98 – 4.87 (1H, m), 4.18 – 4.05 (3H, m), 3.88 – 3.83 (9H, m), 3.12 – 2.89 (1H, m), 2.65 – 2.56 (2H, m), 2.27 – 2.21 (1H, m), 1.99 – 1.89 (2H, m), 1.72 – 1.63 (3H, m), 1.48 – 1.40 (1H, m), 1.31 – 1.23 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 172.8, 171.6, 156.5, 153.1, 153.1, 136.7, 136.5, 136.3, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 105.2, 105.2, 105.1, 67.3, 67.2, 66.8, 64.3, 64.2, 63.8, 60.8, 60.4, 56.0, 56.0, 54.7, 54.4, 41.9, 41.8, 36.1, 32.6,

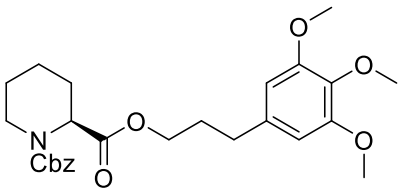
32.4, 31.3, 30.3, 30.2, 26.7, 24.7, 24.5, 20.7, 20.7, 20.5, 14.2. HRMS calc'd for [M+H] = 472.2335, observed = 472.2337. IR (NaCl, DCM): 2943, 1727, 1704, 1591, 1504, 1452, 1421, 1335, 1245, 1128, 1016.

Figure 9.98: Compound VII.4a



1-((benzyloxy)carbonyl) (*S*)-piperidine-2-carboxylic acid (VII.4a). To a 100 mL roundbottom containing a stir bar was added (*S*)-piperidine-2-carboxylic acid (0.500 g, 3.8 mmol) followed by a 1:1 mixture of water: dioxane (20 mL). Stirring commenced and sodium carbonate was added (0.525 g, 5.0 mmol). Gas evolved; once the evolution had ceased most of the solid had dissolved. To this stirring mixture was added Cbz-Cl (0.325 mL, 0.391 g, 2.3 mmol) dropwise. The reaction mixture was allowed to stir overnight. The following day, the reaction mixture was concentrated to approximately half-volume on a rotary evaporator. This mixture was transferred to a separatory funnel and extracted with DCM (50 mL). This extract was discarded. In the separatory funnel, the aqueous layer was acidified by addition of concentrated HCl until the aqueous layer was acidic (pH ~ 2 by pH paper). The acidified aqueous layer was extracted with DCM (3 x 50 mL). The organic layers were combined and dried over sodium sulfate and concentrated *in vacuo* to yield the pure product as a clear oil (0.904 g, 89 %). Spectroscopic data matches that reported for this compound.[192] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 10.08 (1H, br s), 7.37 -7.31 (5H, m), 5.16 (2H, m), 5.01 – 4.90 (1H, app d), 4.10 (1H, app d), 3.10 – 2.97 (1H, m), 2.25 (1H, dd, *J* = 27.5, 12.5 Hz), 1.73 – 1.63 (3H, m), 1.47 – 1.23 (2H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 177.6, 177.5, 156.7, 155.9, 136.4, 128.4, 128.0, 127.8, 67.5, 67.4, 54.3, 54.1, 41.9, 41.7, 26.6, 26.5, 24.6, 24.4, 20.7, 20.6.

Figure 9.99: Compound VII.4

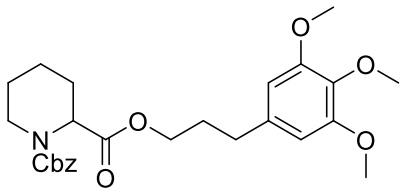


1-benzyl 2-(3-(3,4,5-trimethoxyphenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (VII.4). To a 100 mL roundbottom flask containing a stir bar was added (*S*)-2-piperidine carboxylic acid (0.250 g, 1.9 mmol), followed by a water: dioxane mixture (10 mL of a 1:1 mixture). Stirring commenced and sodium carbonate was added (0.630 g, 6.0 mmol), followed by Cbz-Cl (0.328 mL, 0.391 g, 2.3 mmol). The reaction mixture was stirred at room temperature for 48 hours. After this time, the reaction mixture was transferred to a separatory funnel and made acidic by the dropwise addition of concentrated HCl (pH ~ 2 measured by pH paper). The acidified reaction mixture was extracted with DCM (3 x 20 mL). The organic layers were combined, dried over sodium sulfate, and concentrated to dryness *in vacuo* to yield the crude product as a clear oil (0.432 g, 91 %). The crude mixture was carried on to the following step.

To a 50 mL roundbottom flask containing a stir bar was added 1-benzyl 2-(3-(3,4,5-trimethoxyphenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (0.432 g, 1.7 mmol) was added DCM (10 mL) followed by TEA (0.696 mL, 0.505 g, 5.0 mmol), EDCI (0.380 g, 2.0 mmol), 3-(3,4,5-trimethoxyphenyl)propan-1-ol (0.384 g, 1.7 mmol), and DMAP (0.024 g, 0.20 mmol). The reaction vessel was sealed, flushed with nitrogen, and stirred overnight. The following day, the reaction mixture was transferred to a separatory funnel and washed with water (50 mL). The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to yield the product as an oil. The crude material was purified by silica gel chromatograpy (1:3 ethyl acetate: hexanes, R_f = 0.22) to obtain the pure product as a clear oil (0.527 g, 66 % yield). ^{1}H NMR (500

MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.30 (5H, m), 6.43 – 6.37 (2H, m), 5.16 – 5.11 (2H, m), 4.98 – 4.86 (1H, m), 4.18 – 4.05 (3H, m), 3.86 – 3.83 (9H, m), 3.12 – 2.89 (1H, m), 2.65 – 2.56 (2H, m), 2.27 – 2.12 (1H, m), 2.07 – 1.89 (2H, m), 1.72 – 1.63 (2H, m), 1.48 – 1.40 (1H, m), 1.31 – 1.22 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.6, 153.1, 136.7, 136.5, 136.2, 128.4, 128.0, 127.7, 105.2, 67.3, 67.2, 64.3, 64.2, 60.8, 56.0, 54.7, 54.4, 41.9, 32.4, 30.3, 30.2, 26.7, 24.7, 24.5, 20.7, 20.6. HRMS calc'd for [M+H] = 472.2335, observed = 472.2333. IR (NaCl, DCM): 2942, 1735, 1703, 1590, 1504, 1420, 1334, 1128, 1014.

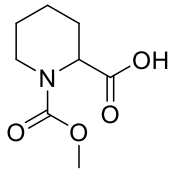
Figure 9.100: Compound VII.5



1-benzyl 2-(3-(3,4,5-trimethoxyphenyl)propyl)piperidine-1,2-dicarboxylate (VII.5). To a 250 mL roundbottom flask containing a stir bar and 1-((benzyloxy)carbonyl)piperidine-2-carboxylic acid (5.6 g, 20.0 mmol) was added DCM (100 mL). Stirring commenced and the following reagents were added in the order listed: TEA (4.2 mL, 3.0 g, 30.0 mmol), EDCI (4.20 g, 22.0 mmol), DMAP (0.248 g, 2.0 mmol), and 3-(3,4,5-trimethoxyphenyl)propan-1-ol (4.47 g, 19.8 mmol, dissolved in 10 mL DCM). The reaction mixture was sealed with a septa, flushed with nitrogen, and allowed to proceed overnight. The following day, the reaction mixture was transferred to a separatory funnel and extracted with water. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product. This material was purified by silica gel chromatography (1:3 ethyl acetate: hexanes, R_f = 0.22) to yield the pure product as a clear oil (4.7 g, 50 %). ^1H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.35 – 7.25 (5H, m), 6.39 – 6.36 (2H, m), 5.15 – 5.10 (2H, m), 4.97 – 4.85 (1H, m), 4.17 – 4.04 (3H, m), 3.83 – 3.82

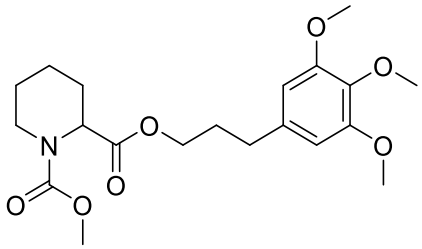
(9H, m), 3.10 – 2.94 (1H, app dt), 2.40 – 2.55 (2H, m), 1.98 – 1.88 (2H, m), 1.71 – 1.62 (3H, m), 1.47 – 1.39 (1H, m), 1.29 – 1.21 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.6, 153.1, 136.7, 136.5, 136.1, 128.4, 127.9, 127.7, 105.2, 67.3, 67.2, 64.2, 60.8, 56.0, 54.6, 54.4, 41.9, 32.4, 30.3, 26.7, 24.7, 24.5, 20.7, 20.6. HRMS calc'd for [M+Na] = 494.2155, observed = 494.2157. IR (NaCl, DCM): 2941, 1736, 1701, 1589, 1508, 1336, 1164, 1011, 981.

Figure 9.101: Compound VII.6a



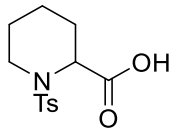
1-(methoxycarbonyl)piperidine-2-carboxylic acid (VII.6a). To a 50 mL roundbottom flask containing a stir bar was added racemic pipecolic acid (1.29 g, 10.0 mmol) and water (10 mL) followed by 2N aqueous sodium hydroxide (0.933 g, 20.0 mmol in 10 mL water). Stirring commenced and methyl chloroformate was added (0.847 mL, 1.03 g, 11.0 mmol). The reaction mixture was allowed to stir overnight. The following day the reaction was quenched with the addition of concentrated HCl (until pH ~ 2 by pH paper) and extracted twice with ethyl acetate (30 mL per extraction). The organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to yield the crude product as a clear oil. The crude material was purified by silica gel chromatography (1:1 ethyl acetate: hexanes) to yield the pure produce as a clear oil (1.09 g, 58 %). Spectroscopic data matches that reported for this compound.[193] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 9.65 (1H, br s), 4.90 (1H, app d), 4.04 (1H, app dd), 3.72 (3H, app d), 3.06 – 2.94 (1H, m), 2.25 (1H, br t, *J* = 15.0 Hz), 1.73 – 1.64 (3H, m), 1.44 – 1.27 (2H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 177.5, 177.4, 157.3, 156.6, 54.3, 54.0, 53.0, 41.8, 41.6, 26.7, 26.5, 24.6, 24.4, 20.6.

Figure 9.102: Compound VII.6



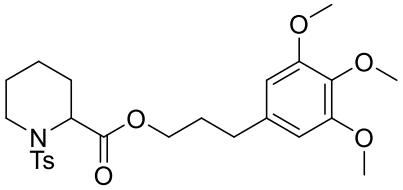
1-methyl 2-(3-(3,4,5-trimethoxyphenyl)propyl) piperidine-1,2-dicarboxylate (VII.6). To a 50 mL roundbottom flask was added 1-(methoxycarbonyl)piperidine-2-carboxylic acid (1.09 g, 5.8 mmol) followed by DCM (20 mL). Stirring commenced and to the reaction mixture was added the following (in the order listed): EDCI (1.14 g, 6.0 mmol) and DMAP (0.122 g, 1.0 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. To the stirring reaction mixture was added via syringe (in the order listed): TEA (1.4 mL, 1.01 g, 10.0 mmol) followed by 3-(3,4,5-trimethoxyphenyl)propan-1-ol (1.17 g, 5.1 mmol dissolved in 5.0 mL DCM). The reaction mixture was allowed to stir overnight. The following day, the reaction was quenched by the addition of water (20 mL) and partitioned in a separatory funnel. The organic layer was dried over sodium sulfate and concentrated to dryness *in vacuo* to yield the crude product as an oil. The crude material was purified by silica gel chromatograpy (1:2 ethyl acetate: hexanes, R_f = 0.42) to yield the pure product as a clear oil. ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 6.39 (2H, s), 4.95 – 4.80 (1H, m), 4.17 – 4.11 (2H, m), 3.87 – 3.82 (9H, m), 3.72 – 3.70 (3H, m), 3.08 – 2.92 (1H, m), 2.62 (2H, br t, *J* = 7.0 Hz), 2.25 – 2.23 (1H, m), 1.96 (2H, quintet, *J* = 7.0 Hz), 1.72 – 1.63 (4H, m), 1.44 – 1.42 (1H, br m), 1.29 – 1.21 (1H, m).). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.7, 15.1, 136.7, 136.2, 105.2, 64.2, 60.8, 56.0, 54.3, 52.8, 41.8, 32.4, 30.3, 26.7, 24.7, 24.5, 20.7. HRMS calc'd for [M+H] = 396.2022, observed = 396.2019. IR (NaCl, DCM): 2944, 1735, 1699, 1652, 1448, 1242.

Figure 9.103: Compound VII.7a



1-tosylpiperidine-2-carboxylic acid (VII.7a). To a 50 mL roundbottom flask containing a stir bar was added racemic pipecolic acid (1.29 g, 10.0 mmol) followed by water (30 mL). Stirring commenced and sodium carbonate was added (2.62 g, 25.0 mmol), followed by tosyl chloride (2.09 g, 11.0 mmol). The reaction mixture was allowed to stir overnight. The following day the reaction mixture was made acidic by the addition of conc. HCl (until pH ~ 2 by pH paper) and extracted twice with DCM (30 mL per extraction). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the product as a white solid. The crude material was purified by silica gel chromatography (1:1 ethyl acetate: hexanes) to yield the product as a white solid (1.1 g, 38 %). Spectroscopic data matches that reported for this compound.[194] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.67 (2H, d, *J* = 2.0 Hz), 7.26 (2H, d, *J* = 2.0 Hz), 4.76 (1H, br d, *J* = 5.0 Hz), 3.72 (1H, br d, *J* = 11.5 Hz), 3.19 (1H, td, *J* = 13.0 Hz, 2.5 Hz), 2.40 (3H, s), 2.13 (1H, br d, *J* = 13.5 Hz), 1.74 – 1.60 (3H, m), 1.44 – 1.25 (2H, br m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 177.0, 143.4, 136.9, 129.5, 127.1, 54.7, 42.5, 27.4, 24.4, 21.5, 20.0. M.P. = 108 ^{o}C.

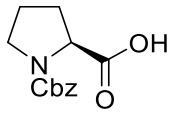
Figure 9.104: Compound VII.7



3-(3,4,5-trimethoxyphenyl)propyl 1-tosylpiperidine-2-carboxylate (VII.7). To a 50 mL roundbottom flask was added 1-(methoxycarbonyl)piperidine-2-carboxylic acid (1.13 g, 3.9 mmol) followed by DCM (20 mL). Stirring commenced and to the reaction mixture was added

the following (in the order listed): EDCI (0.764 g, 4.0 mmol) and DMAP (0.122 g, 1.0 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. To the stirring reaction mixture was added via syringe (in the order listed): TEA (0.835 mL, 0.606 g, 6.0 mmol) followed by 3-(3,4,5-trimethoxyphenyl)propan-1-ol (0.829 g, 3.6 mmol dissolved in 5.0 mL DCM). The reaction mixture was allowed to stir overnight. The following day, the reaction was quenched by the addition of water (20 mL) and partitioned in a separatory funnel. The organic layer was dried over sodium sulfate and concentrated to dryness *in vacuo* to yield the crude product as an oil. The crude material was purified by silica gel chromatograpy (1:2 ethyl acetate: hexanes, R_f = 0.19) to yield the pure product as a clear oil. ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.67 (2H, d, *J* = 8.5 Hz), 7.22 (2H, d, *J* = 7.5 Hz), 6.38 (2H, s), 4.75 (1H, br d, *J* = 4.0 Hz), 4.07 – 3.96 (2H, m), 3.88 (6H, s), 3.82 (3H, s), 3.73 – 3.70 (1H, m), 3.23 (1H, dt, *J* = 13.0, 13.0, 3.0 Hz), 2.59 (2H, t, *J* = 7.0, 7.0 Hz), 2.38 (3H, s), 2.14 – 2.10 (1H, m), 1.90 – 1.84 (2H, m), 1.76 – 1.61 (3H, m), 1.46 – 1.42 (1H, m), 1.32 – 1.26 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 170.8, 153.3, 153.1, 143.1, 138.1, 137.1, 136.6, 136.2, 129.4, 127.2, 127.1, 105.2, 64.3, 60.8, 65.1, 56.0, 55.0, 48.3, 42.5, 32.4, 30.1, 27.7, 24.6, 21.5, 20.0. HRMS calc'd for [M+H] = 492.2056, observed = 492.2055. IR (NaCl, DCM): 3062, 2942, 1735, 1652, 1590, 1507, 1421, 1337, 1240, 1157, 1128.

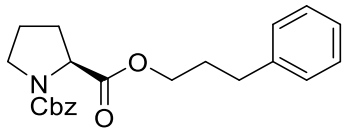
Figure 9.105: Compound VII.8a



((benzyloxy)carbonyl)-*L*-proline (VII.8a). To a 100 mL roundbottom flask containing a stir bar was added *L*-proline (1.15 g, 10.0 mmol), followed by a 1:1 water: dioxane mixture (20 mL). Stirring commenced and sodium carbonate (2.41 g, 23.0 mmol) was added in one portion. After

gas ceased to evolve, Cbz-Cl was added dropwise (1.7 mL, 1.2 g, 12.0 mmol). The reaction was allowed to stir overnight. The following day, the reaction mixture was transferred to a separatory funnel and extracted with ether twice (50 mL per extraction). The aqueous layer was acidified with concentrated HCl (pH ~ 2 by pH paper) and extracted three times with ethyl acetate (50 mL per extraction). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the product as a clear oil (2.5 g, 100 %). The crude material is suitable for use, but an analytical sample was prepared by purification through silica gel chromatography (elute in 1:4 ethyl acetate: hexanes). Spectroscopic data matches that reported for this compound.[195] ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 8.76 (1H, br s), 7.38 – 7. 26 (5H, m), 5.22 – 5.14 (2H, m), 4.41 (1H, doublet of quartets, J = 24.5, 8.0, 4.5 Hz), 3.65 – 3.45 (2H, m), 2.32 – 1.88 (4H, m) ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 178.2, 176.2, 155.9, 154.4, 136.4, 136.2, 128.5, 128.4, 128.1, 127.9, 127.6, 67.5, 67.1, 59.3, 58.6, 46.9, 46.6, 30.9, 29.2, 24.3, 23.4.

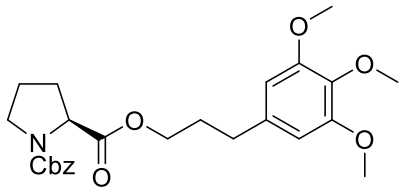
Figure 9.106: Compound VII.8



1-benzyl 2-(3-phenylpropyl) (*S*)-pyrrolidine-1,2-dicarboxylate (VII.8). To a 250 mL oven dried roundbottom flask containing a stir bar was added ((benzyloxy)carbonyl)-*L*-proline (2.50 g, 10.0 mmol), followed by DCM (100 mL). Stirring commenced, and to the reaction mixture was added (in the order listed) TEA (1.7 mL, 1.21 g, 12.0 mmol), EDCI (2.0 g, 11.0 mmol), DMAP (0.244 g, 0.2 mmol), and 3-phenyl-1-propanol (1.49 g, 1.49 mL, 11.0 mmol). The reaction vessel was sealed and flushed with nitrogen and allowed to react overnight. The following day, the reaction mixture was transferred to a separatory funnel and extracted with water (once, 100 mL). The crude reaction mixture was concentrated on a rotary evaporator and purified through silica

gel chromatography (1:4 ethyl acetate: hexanes, R_f = 0.33) to yield the pure product as a clear oil (2.1 g, 57 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.39 – 7.12 (10H, m), 5.20 – 5.07 (2H, m), 4.43 – 4.34 (1H, m), 4.19 – 4.14 (1H, m), 4.07 – 3.97 (1H, m), 3.70 – 3.45 (2H, m), 2.74 – 2.67 (1H, m), 2.58 (1H, t, *J* = 7.5 Hz), 2.30 – 2.18 (1H, m), 2.03 – 1.81 (5H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 181.3, 172.8, 172.6, 154.3, 141.1, 140.9, 136.7, 136.5, 128.5, 128.4, 128.4, 128.3, 128.3, 127.9, 127.9, 127.8, 127.8, 126.0, 126.0, 125.8, 109.2, 67.0, 66.9, 64.3, 64.3, 62.3, 59.3, 58.9, 46.9, 46.4, 34.2, 32.0, 32.0, 31.9, 30.9, 30.2, 30.0, 29.9, 29.8, 26.8, 24.3, 23.5. HRMS calc'd for [M+H] = 368.1826, observed = 368.1862. IR (NaCl, DCM): 2955, 1743, 1705, 1652, 1416, 1119, 1088, 746.

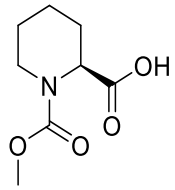
Figure 9.107: Compound VII.9



1-benzyl 2-(3-(3,4,5-trimethoxyphenyl)propyl) (*S*)-pyrrolidine-1,2-dicarboxylate (VII.9). To a 100 mL roundbottom flask containing ((benzyloxy)carbonyl)-*L*-proline (1.59 g, 6.4 mmol) was added a stir bar and DCM (50 mL). The reaction mixture was stirred and the following reagents were added in the order listed: EDCI (1.33 g, 7.0 mmol), DMAP (0.122 g, 1.0 mmol), and TEA (1.01 g, 10.0 mmol). The reaction vessel was sealed and flushed with nitrogen. To the stirring mixture was added 3-(3,4,5-trimethoxyphenyl)propan-1-ol (1.44 g, 6.4 mmol) via syringe dissolved in DCM (10 mL). The reaction was allowed to stir overnight. The following day, the reaction was quenched with water (50 mL), transferred to a separatory funnel and partitioned. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (1:3 ethyl acetate: hexanes, R_f = 0.51) to yield the

pure product as a clear oil (1.3 g, 42 % yield). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.24 (5H, m), 6.39 – 6.34 (2H, app d), 5.19 – 5.06 (2H, m), 4.38 (1H, ddd, *J* = 19.5, 15.5, 3.5 Hz), 4.19 – 4.00 (2H, m), 3.84 – 3.80 (9H, m), 3.66 – 3.47 (2H, m), 2.62 (1H, t, *J* = 7.5 Hz), 2.51 (1H, t, *J* = 8.0 Hz), 2.28 – 2.20 (1H, m), 2.02 – 1.80 (5H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 172.8, 172.7, 154.8, 154.2, 153.1, 153.1, 136.9, 136.7, 136.6, 136.5, 136.1, 136.1, 128.4, 128.3, 127.9, 127.8, 127.7, 105.2, 105.1, 66.9, 66.9, 64.3, 64.2, 60.8, 59.3, 58.9, 56.0, 46.9, 46.4, 32.3, 32.3, 31.0, 30.3, 30.1, 29.9, 24.3, 23.5. HRMS calc'd for [M+H] = 368.1862, observed = 368.1869. IR (NaCl, DCM): 2961, 2839, 1734, 1647, 1593, 1507, 1419, 1126, 911.

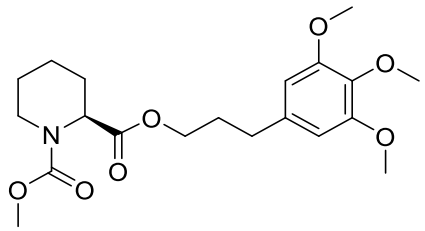
Figure 9.108: Compound VII.10a



1-(methoxycarbonyl) (*S*)-piperidine-2-carboxylic acid (VII.10a). To a 50 mL roundbottom flask containing a stir bar was added (*S*)-pipecolic acid (0.250 g, 1.9 mmol) and water (5 mL) followed by 2N aqueous sodium hydroxide (0.200 g, 5.0 mmol in 5 mL water). Stirring commenced and methyl chloroformate was added (0.160 mL, 0.198 g, 2.1 mmol). The reaction mixture was allowed to stir overnight. The following day the reaction was quenched with the addition of concentrated HCl (until pH ~ 2 by pH paper) and extracted twice with ethyl acetate (30 mL per extraction). The organic layers were dried over sodium sulfate and concentrated to dryness *in vacuo* to yield the crude product as a clear oil. The crude material was purified by silica gel chromatography (1:1 ethyl acetate: hexanes) to yield the pure produce as a clear oil (0.238 g, 66 %). Spectroscopic data matches that reported for this compound.[193] ^{1}H NMR (500

MHz) ($CDCl_3$) (amide rotamers) δ: 9.65 (1H, br s), 4.90 (1H, app d), 4.04 (1H, app dd), 3.72 (3H, app d), 3.06 – 2.94 (1H, m), 2.25 (1H, br t, *J* = 15.0 Hz), 1.73 – 1.64 (3H, m), 1.44 – 1.27 (2H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers): 177.5, 177.4, 157.3, 156.6, 54.3, 54.0, 53.0, 41.8, 41.6, 26.7, 26.5, 24.6, 24.4, 20.6.

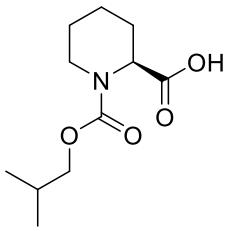
Figure 9.109: Compound VII.10



1-methyl 2-(3-(3,4,5-trimethoxyphenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (VII.10). To a 50 mL roundbottom flask was added 1-(methoxycarbonyl) (*S*)-piperidine-2-carboxylic acid (0.238 g, 1.32 mmol) followed by DCM (10 mL). Stirring commenced and to the reaction mixture was added the following (in the order listed): EDCI (0.304 g, 1.6 mmol) and DMAP (0.060 g, 0.5 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. To the stirring reaction mixture was added via syringe (in the order listed): TEA (0.350 mL, 0.252 g, 2.5 mmol) followed by 3-(3,4,5-trimethoxyphenyl)propan-1-ol (0.293 g, 1.3 mmol dissolved in 3.0 mL DCM). The reaction mixture was allowed to stir overnight. The following day, the reaction was quenched by the addition of water (10 mL) and partitioned in a separatory funnel. The organic layer was dried over sodium sulfate and concentrated to dryness *in vacuo* to yield the crude product as an oil. The crude material was purified by silica gel chromatograpy (1:2 ethyl acetate: hexanes, R_f = 0.42) to yield the pure product as a clear oil (0.222 g, 44 %). ^1H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 6.39 (2H, s), 4.95 – 4.80 (1H, m), 4.17 – 4.11 (2H, m), 3.87 – 3.82 (9H, m), 3.72 – 3.70 (3H, m), 3.08 – 2.92 (1H, m), 2.62 (2H, br t, *J* = 7.0 Hz), 2.25 – 2.23 (1H, m), 1.96 (2H, quintet, *J* = 7.0 Hz), 1.72 – 1.63 (4H, m), 1.44 – 1.42 (1H, br

m), 1.29 – 1.21 (1H, m).). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.7, 15.1, 136.7, 136.2, 105.2, 64.2, 60.8, 56.0, 54.3, 52.8, 41.8, 32.4, 30.3, 26.7, 24.7, 24.5, 20.7. HRMS calc'd for [M+H] = 396.2022, observed = 396.2019. IR (NaCl, DCM): 2944, 1735, 1699, 1652, 1448, 1242.

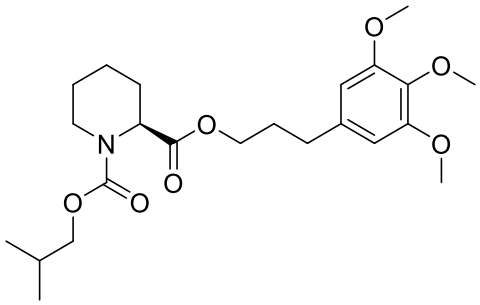
Figure 9.110: Compound VII.11a



1-(isobutoxycarbonyl) (*S*)-piperidine-2-carboxylic acid (VII.11a). To a 50 mL roundbottom flask containing a stir bar was added (*S*)-pipecolic acid (0.250 g, 1.9 mmol) and water (5 mL) followed by 2N aqueous sodium hydroxide (0.200 g, 5.0 mmol in 5 mL water). Stirring commenced and isobutyl chloroformate was added (0.275 mL, 0.285 g, 2.1 mmol).The reaction mixture was allowed to stir overnight. The following day, the reaction was quenched by the addition of concentrated HCl (until the mixture was pH ~ 2 by pH paper) and extracted with ethyl acetate (2 x 25 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield the crude product as an oil. The crude material was purified by filtering through a plug of silica gel (1:2 ethyl acetate: hexanes) to yield the pure product as a clear oil which solidifies on standing (0.302 g, 69 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 10.31 (1H, br s), 4.91 (1H, br d), 4.05 (1H, br d), 3.92 – 3.82 (2H, m), 3.07 – 2.95 (1H, m), 2.25 (1H, br t, *J* = 14.0 Hz), 1.98 – 1.90 (1H, m), 1.74 – 1.65 (3H, m), 1.46 – 1.40 (1H, m), 1.36 – 1.28 (1H, m), 0.92 (6H, dd, *J* = 21.0, 7.0 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 177.7, 177.5, 156.9, 156.2, 71.9, 71.8, 54.2, 54.0, 41.7, 41.5, 27.9, 26.7, 26.5, 24.6, 24.4, 20.7, 20.6, 19.0. HRMS calc'd for [M – H] = 228.1241, observed = 228.1233. IR (NaCl,

DCM): 3095, 2960, 2874, 1744, 1704, 1667, 1470, 1434, 1386, 1259, 1167, 1044, 973. M.P. = 67 ºC.

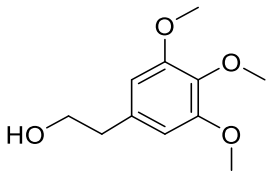
Figure 9.111: Compound VII.11



1-isobutyl 2-(3-(3,4,5-trimethoxyphenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (VII.11). To a 100 mL roundbottom flask containing a stir bar was added 1-(isobutoxycarbonyl)piperidine-2-carboxylic acid (0.302 g, 1.32 mmol) followed by DCM (10 mL). To this solution was added 3-(3,4,5-trimethoxyphenyl)propan-1-ol (0.316 g, 1.4 mmol dissolved in 2 mL DCM). Stirring commenced and the following reagents were added in the order listed: EDCI (0.304 g, 1.6 mmol), TEA (0.350 mL, 0.252 g, 2.5 mmol) and DMAP (0.06 g, 0.50 mmol). The reaction vessel was sealed, flushed with nitrogen, and allowed to stir overnight. The following day, the reaction mixture was transferred to a separatory funnel and washed with water (50 mL). The organic layer was dried with sodium sulfate and concentrated *in vacuo* to yield the crude product as an oil. This material was purified by silica gel chromatography (1:3 ethyl acetate: hexanes, R_f = 0.32) to yield the pure product as a clear oil (0.301 g, 52 % yield). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 6.39 (2H, s), 4.95 – 4.83 (1H, br d), 4.17 – 3.91 (4H, m), 3.90 – 3.82 (9 H, m), 3.09 – 2.93 (1H, br dt), 2.62 (2H, br t, *J* = 7.0 Hz), 2.25 – 2.22 (1H, m), 1.99 – 1.89 (3H, m), 1.74 – 1.64 (3H, m), 1.45 – 1.43 (1H, m), 1.30 – 1.22 (1H, m), 0.94 – 0.88 (6H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.8, 171.8, 156.8, 156.2, 153.1, 136.7, 136.2, 105.2, 71.7, 71.6, 64.3, 64.2, 60.8, 56.0, 54.5, 54.3, 41.7, 32.4, 30.3,

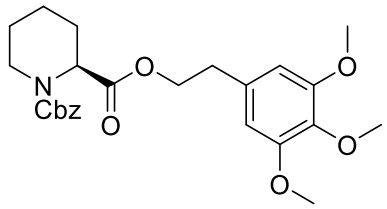
30.3, 27.9, 26.8, 26.7, 24.7, 24.5, 20.8, 20.6, 19.0. HRMS calc'd for [M+H] = 438.2492, observed = 438.2494. IR (NaCl, DCM): 2948, 1735, 1701, 1591, 1457, 1421, 1292, 1016.

Figure 9.112: Compound VII.12a



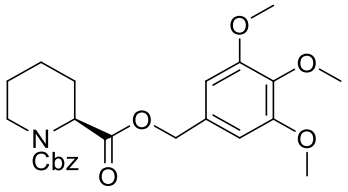
2-(3,4,5-trimethoxyphenyl)ethan-1-ol (VII.12a). To a 250 mL roundbottom flask was added a stir bar and freshly distilled THF (100 mL). The reaction vessel was cooled in an ice-water bath and stirring commenced. LAH (1.11 g, 30.0 mmol) was added in portions. The reaction vessel was sealed with a septa and flushed with nitrogen. In a separate vessel 3,4,5-trimethoxyphenylacetic acid (4.52 g, 20.0 mmol) was dissolved in THF (30 mL), and was added dropwise to the LAH/THF solution. The reaction was allowed to warm to room temperature and proceed overnight. The following day, the reaction vessel was cooled in an ice-water bath and the reaction was quenched with water (until gas no longer evolved) and concentrated HCl (~ 1 mL). The reaction mixture was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a clear, yellow oil. The crude material was purified with silica gel chromatography (1:1 ethyl acetate: hexanes) to yield the final product as a yellow oil that solidified on standing (2.9 g, 68 %). Spectroscopic data matches that reported for this compound.[197] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 6.45 (2H, s), 3.87 – 3.83 (11H, m), 2.81 (2H, t, *J* = 7.0, 7.0 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 153.2, 136.5, 134.2, 105.8, 63.5, 60.8, 56.0, 39.5. M.P. = 40 ºC.

Figure 9.113: Compound VII.12



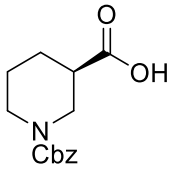
1-benzyl 2-(3,4,5-trimethoxyphenethyl) (*S*)-piperidine-1,2-dicarboxylate (VII.12). To a 500 mL roundbottom flask containing a stir bar and (*S*)-1-((benzyloxy)carbonyl)piperidine-2-carboxylic acid (0.386 g, 1.5 mmol) was added DCM (10 mL). Stirring commenced, and in the order listed was added TEA (0.417 mL, 0.303 g, 3.0 mmol), EDCI (0.323 g, 1.7 mmol), DMAP (0.060 g, 0.50 mmol), and 2-(3,4,5-trimethoxyphenyl)ethan-1-ol (0.318 g, 1.5 mmol). The reaction vessel was sealed, flushed with nitrogen, and allowed to stir overnight. The following day, the reaction mixture was quenched with water (10 mL) and partitioned in a separatory funnel. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to a yellow oil. The crude product was purified by silica gel chromatography (1:3 ethyl acetate: hexanes) to yield the product as a clear oil (0.145 g, 21 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.37 – 7.29 (5H, m), 6.41 (2H, d, *J* = 14.0 Hz), 5.16 – 5.10 (2H, m), 4.95 – 4.82 (1H, m), 4.38 – 4.29 (2H, m), 4.09 – 3.99 (1H, m), 3.84 (6H, app d, *J* = 3.5 Hz), 3.81 (3H, app d, *J* = 5.0 Hz), 3.00 – 2.80 (3H, m), 2.17 (1H, t, *J* = 16.0 Hz), 1.67 – 1.56 (3H, m), 1.43 – 1.38 (1H, m), 1.55 – 1.10 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.6, 171.6, 156.5, 155.9, 153.2, 136.6, 136.6, 133.2, 133.1, 128.4, 128.0, 127.8, 105.7, 67.3, 67.1, 65.5, 65.4, 60.8, 56.0, 54.6, 54.4, 41.8, 41.7, 35.4, 35.3, 26.7, 24.6, 24.4, 20.6, 20.5. HRMS calc'd for [M+Na] = 480.1998, observed = 480.2011. IR (DCM, NaCl): 1746, 1697, 1597, 1421, 1362, 1190, 1022.

Figure 9.114: Compound VII.13



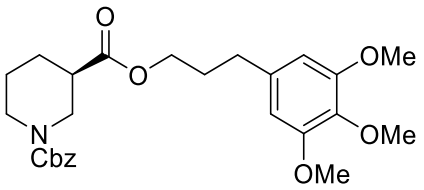
1-benzyl 2-(3,4,5-trimethoxybenzyl) piperidine-1,2-dicarboxylate (VII.13). To a 100 mL roundbottom flask containing a stir bar was added 1-((benzyloxy)carbonyl)piperidine-2-carboxylic acid (0.435 g, 1.6 mmol), followed by DCM 1 mL). The reaction mixture was stirred and the following reagents were added (in the order listed): TEA (0.417 mL, 0.303 g, 3.0 mmol), EDCI (0.342 g, 1.8 mmol), and DMAP (0.060 g, 0.50 mmol). Stirring commenced and the reaction vessel was sealed with a septa and flushed with nitrogen. To this mixture was added 3,4,5-trimethoxybenzyl alcohol (0.273 mL, 0.336 g, 1.7 mmol, dissolved in 2.0 mL DCM) via syringe. The reaction mixture was allowed to stir overnight. The following day, the reaction mixture was transferred to a separatory funnel and extracted with water (50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a clear oil. The crude material was purified by silica gel chromatograpy (1:3 ethyl acetate: hexanes, R_f = 0.28) to yield the final product as a clear oil (0.371 g, 50 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.35 – 7.25 (5H, m), 6.55 – 6.52 (2H, m), 5.15 – 4.89 (5H, m), 4.14 – 4.03 (1H, m), 3.83 – 3.82 (9H, m), 3.11 – 2.96 (1H, m), 2.28 – 2.21 (1H, m), 1.70 – 1.41 (4H, m), 1.28 – 1.22 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.5, 156.4, 155.9, 153.3, 137.7, 136.5, 131.4, 131.2, 128.4, 128.4, 128.0, 127.7, 127.6, 104.9, 104.8, 67.3, 67.2, 66.8, 60.8, 56.1, 54.7, 54.4, 41.9, 41.8, 26.7, 24.7, 24.5, 20.7, 20.6. HRMS calc'd for [M+Na] = 466.1842, observed = 466.1845. IR (NaCl, DCM): 2941, 1734, 1699, 1592, 1457, 1420, 1242, 1192, 1127.

Figure 9.115: Compound VII.14a



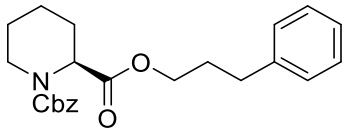
(*R*)-1-((benzyloxy)carbonyl)piperidine-3-carboxylic acid (VII.14a). To a 100 mL roundbottom flask containing a stir bar was added (*R*)-3-pipecolic acid (1.0 g, 7.7 mmol) followed by 1,4-dioxane (10 mL) and water (10 mL). Stirring commenced and sodium carbonate was added (2.1 g, 20.0 mmol) followed by Cbz-Cl (1.20 mL, 1.44 g, 8.5 mmol). The reaction mixture was stirred overnight. The following day the reaction was quenched by the addition of HCl (36 mmol HCl 10 mL of a 3.6 M solution). The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 20 mL per extraction). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield the crude product as an oil. This material was dissolved in a 1:1 mixture of ethyl acetate: hexanes and passed through a plug of silica gel to yield the crude product as a an oil that on standing turns into a waxy, white solid (1.74 g, 84 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.38 – 7.29 (5H, m), 5.17 – 5.10 (2H, m), 4.27 – 4.15 (1H, m), 3.97 (1H, dt, *J* = 9.5, 3.5, 3.5 Hz), 3.17 – 3.06 (1H, m), 2.96 – 2.90 (1H, m), 2.51 (1H, br s), 2.10 – 2.07 (1H, m), 1.74 – 1.65 (2H, m) 1.50 (1H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers): 178.8, 155.2, 136.6, 128.5, 128.0, 127.9, 67.2, 45.4, 44.1, 40.9, 27.0, 24.0. HRMS calc'd for [M+H] = 264. 1236, observed = 264.1259; calc'd for [M+Na] = 286. 1055, observed = 286. 1058. IR (NaCl, DCM): 3435, 2953, 1732, 1697, 1473, 1291, 1150, 1078. M.P. = 97 ºC.

Figure 9.116: Compound VII.14



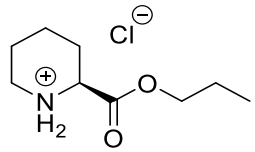
1-benzyl 3-(3-(3,4,5-trimethoxyphenyl)propyl) (*R*)-piperidine-1,3-dicarboxylate (VII.14). To a 100 mL roundbottom flask containing (*R*)-1-((benzyloxy)carbonyl)piperidine-3-carboxylic acid (0.542 g, 2.0 mmol) was added a stir bar followed by DCM (15 mL), EDCI (0.414 g, 2.2 mmol), TEA (0.696 mL, 0.505 g, 5.0 mmol), DMAP (0.060 g, 0.5 mmol), and 3-(3,4,5-trimethoxyphenyl)propan-1-ol (0.461 g, 2.0 mmol). The reaction mixture was stirred overnight. The reaction mixture was transferred to a separatory funnel and washed with dilute HCl (10 mL 5 % HCl v/v) followed by saturated aqueous sodium bicarbonate (20 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (1:2 ethyl acetate: hexanes) to yield the product as a clear oil (0.453 g, 48 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.30 (5H, m), 6.39 (2H, s), 5.16 – 5.11 (2H, m), 4.28 – 3.90 (4H, m), 3.84 – 3.82 (9H, m), 3.15 – 3.04 (1H, m), 2.95 – 2.90 (1H, m), 2.62 (2H, br t, J = 7.0 Hz), 2.08 – 2.05 (1H, m), 1.97 – 1.92 (2H, m), 1.72 – 1.62 (2H, m), 1.50 (1H, br s). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers): 173.2, 155.1, 153.1, 136.8, 136.7, 136.2, 128.5, 128.0, 127.8, 105.2, 67.1, 63.9, 60.8, 56.0, 45.7, 44.2, 41.3, 32.5, 30.2, 27.2, 24.3. HRMS calc'd for [M+H] = 472.2335, observed = 472.2331. IR (NaCl, DCM): 2491, 1733, 1698, 1589, 1420, 1237, 1127.

Figure 9.117: Compound VII.15



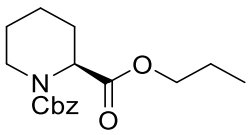
1-benzyl 2-(3-phenylpropyl) (*S*)-piperidine-1,2-dicarboxylate (VII.15). To a 50 mL roundbottom flask containing a stir bar was added 1-((benzyloxy)carbonyl) (*S*)-piperidine-2-carboxylic acid (0.523 g, 1.98 mmol), followed by DCM (20 mL). To the reaction vessel was added (in the order listed) EDCI (0.45 g, 2.5 mmol), TEA (0.696 mL, 0.505 g, 5.0 mmol), and DMAP (0.060 g, 0.50 mmol). The reaction vessel was sealed and flushed with nitrogen. Stirring commenced and 3-phenyl-1-propanol was added via syringe (0.258 mL, 0.258 g, 1.9 mmol). The reaction was allowed to proceed overnight. The following day, the reaction was transferred to a separatory funnel in which it was washed with water (10 mL), dilute HCl (10 mL 0.5 M HCl), saturated aqueous sodium bicarbonate (20 mL) and brine. The crude product was dried over sodium sulfate and concentrated to dryness *in vacuo*. The crude product was purified by silica gel chromatography (1:4 ethyl acetate: hexanes, R_f = 0.30) to yield the pure product as a clear oil (0.276 g, 38 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.35 – 7.13 (10H, m), 5.16 – 5.13 (2H, m), 4.97 – 4.85 (1H, m), 4.15 – 4.05 (3H, m), 3.10 – 2.94 (1H, m), 2.68 – 2.61 (2H, m), 2.27 – 2.19 (1H, m), 1.98 – 1.89 (2H, m), 1.71 – 1.62 (3H, m), 1.47 – 1.41 (1H, m), 1.29 – 1.21 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 171.6, 156.5, 155.4, 141.0, 136.6, 128.4, 128.4, 127.9, 127.8, 126.0, 67.3, 67.2, 64.3, 54.6, 54.4, 41.9, 41.8, 32.0, 26.8, 26.7, 24.7, 24.5, 20.7, 20.6. HRMS calc'd for [M+H] = 382.2018, observed = 382.2044. IR (NaCl, DCM): 3028, 2943, 2860, 1737, 1710, 1454, 1417, 1336, 1255, 1255, 1203, 1163, 1090, 1044.

Figure 9.118: Compound VII.16a



(*S*)-2-(propoxycarbonyl)piperidin-1-ium chloride (VII.16a). To a 100 mL roundbottom flask containing a stir bar was added (*S*)-pipecolic acid (0.250 g, 1.9 mmol) and 1-propanol (40 mL). Stirring commenced and thionyl chloride was added to the mixture dropwise (0.5 mL). A reflux condenser was attached to the flask and the reaction mixture was heated to reflux overnight. The following day the reaction mixture was cooled to room temperature and concentrated *in vacuo* to approximately 20 % original volume. To this mixture was added diethyl ether (40 mL). The reaction mixture turned white and solid began to form. The crude mixture was placed placed in a – 20 ºC freezer overnight. The following day the solid was filtered and washed with ether. The solid material was dried under vaccum to yield the pure product as a white solid (0.269 g, 68 %). ^{1}H NMR (500 MHz) (d_6-DMSO): 9.69 (1H, br s), 9.37 (1H, br s), 4.16 – 4.07 (2H, m), 4.04 (1H, dd, *J* = 11.0, 3.5 Hz), 3.20 (1H, br d, *J* = 12.5 Hz), 2.87 (1H, td, *J* = 11.5, 3.0 Hz), 2.07 – 2.04 (1H, m), 1.72 – 1.52 (7H, m), 0.89 (3H, t, *J* = 8.0 Hz). ^{13}C NMR (125 MHz) (d_6-DMSO): 169.2, 67.4, 55.9, 43.7, 26.0, 21.8, 21.6, 21.4, 10.6. HRMS calc'd for [M-Cl] = 172.1338, observed = 172.1333. IR (NaCl, DCM): 1653, 1558, 1456, 1373, 1226.M.P. = 162 ºC.

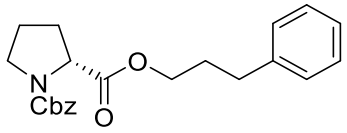
Figure 9.119: Compound VII.16



1-benzyl 2-propyl (*S*)-piperidine-1,2-dicarboxylate (VII.16). To a 50 mL roundbottom flask containing a stir bar was added (*S*)-2-(propoxycarbonyl)piperidin-1-ium chloride (0.220 g, 1.06

mmol) followed by dioxane (2 mL) and water (2 mL). Stirring commenced and sodium carbonate was added as a solid (0.315 g, 3.0 mmol), followed by Cbz-Cl (0.170 mL, 0.204 g, 1.2 mmol). The reaction mixture was stirred at rom temperature overnight. The following day the reaction was quenched by the addition of HCl (24.0 mmol, 2 mL conc. HCl and 8 mL distilled water). The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 15 mL per extraction). The crude material was concentrated *in vacuo* to yield an oil, which was purified by silica gel chromatography (1:2 ethyl acetate: hexanes) to yield the pure product as a clear oil (0.266 g, 75 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.36 – 7.30 (5H, m), 5.17 – 5.09 (2H, m), 4.95 – 4.83 (1H, m), 4.13 – 4.03 (3H, m), 3.10 – 2.94 (1H, m), 2.27 – 2.19 (1H, m), 1.70 – 1.58 (5H, m), 1.46 – 1.40 (1H, m), 1.29 – 1.21 (1H, m), 0.94 – 0.88 (3H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers): 171.7, 171.6, 156.5, 155.9, 136.6, 128.5, 128.4, 127.9, 127.7, 67.2, 67.1, 66.6, 54.6, 54.4, 41.8, 41.8, 26.8, 26.7, 24.7, 24.5, 21.9, 20.7, 20.6, 10.4. HRMS calc'd for [M+H] = 306.1705, observed = 306.1708. IR (NaCl, DCM): 2979, 1698, 1669, 1540, 1419.

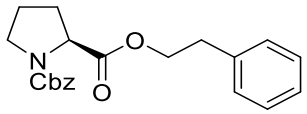
Figure 9.120: Compound VII.17



1-benzyl 2-(3-phenylpropyl) (*R*)-pyrrolidine-1,2-dicarboxylate (VII.17). To a 100 mL roundbottom flask containing a stir bar and ((benzyloxy)carbonyl)-*D*-proline (purchased from Sigma; 2.1 g, 8.4 mmol) was added DCM (50 mL). Stirring commenced and the following reagents were added (in the order listed) EDCI (1.71 g, 9.0 mmol), TEA (2.52 mL, 2.02 g, 20.0 mmol), DMAP (0.120 g, 0.1 mmol) and 3-phenyl-1-propanol (0.952 mL, 0.952 g, 7.0 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. Stirring commenced and

the reaction was allowed to proceed overnight. The following day, the reaction mixture was transferred to a separatory funnel and washed with water (50 mL) and brine (50 mL). The crude material was concentrated *in vacuo* to yield an oil which was dissolved in a minimum amount of DCM and purified by silica gel chromatography (1:4 ethyl acetate:hexanes) to yield the product as a clear oil (1.8 g, 59 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.39 – 7.12 (10H, m), 5.20 – 5.07 (2H, m), 4.39 (1H, ddd, *J* = 29.0, 7.0, 3.5 Hz), 4.18 – 4.15 (1H, m), 4.06 – 3.98 (1H, m), 3.69 – 3.0 (1H, m), 3.58 – 3.49 (1H, m), 2.69 (1H, t, *J* = 8.0, 8.0 Hz), 2.58 (1H, t, *J* = 7.5, 7.5 Hz), 2.28 – 2.09 (1H, m), 2.04 – 1.81 (5H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers) δ: 172.8, 172.6, 154.8, 154.3, 141.1, 140.9, 136.7, 136.5, 128.4, 128.4, 128.3, 128.3, 127.9, 127.9, 127.8, 127.8, 126.0, 126.0, 67.0, 66.9, 64.3, 64.0, 59.3, 58.9, 46.9, 46.4, 32.0, 31.9, 30.9, 30.2, 30.0, 29.9, 24.3, 23.5. HRMS calc'd for [M+Na] = 390.1681, observed = 390.1696. IR (NaCl, DCM): 2955, 1743, 1706, 1452, 1414, 1352, 1194, 1118, 1028, 748.

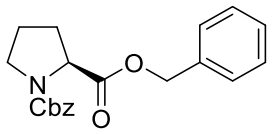
Figure 9.121: Compound VII.18



1-benzyl 2-phenethyl (*S*)-pyrrolidine-1,2-dicarboxylate (VII.18). To a 100 mL roundbottom flask containing a stir bar and ((benzyloxy)carbonyl)-*L*-proline (2.3 g, 9.2 mmol) was added DCM (50 mL). Stirring commenced and the following reagents were added (in the order listed) EDCI (2.18, 11.5 mmol), TEA (2.52 mL, 2.02 g, 20.0 mmol), DMAP (0.120 g, 0.1 mmol) and 2-phenylethanol (0.976 mL, 0.976 g, 8.0 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. Stirring commenced and the reaction was allowed to proceed overnight. The following day, the reaction mixture was transferred to a separatory funnel and washed with water (50 mL) and brine (50 mL). The crude material was concentrated *in vacuo* to yield an oil

which was dissolved in a minimum amount of DCM and purified by silica gel chromatography (gradient 1:9 to 1:4 ethyl acetate: hexanes) to yield the product as a clear oil (0.985 g, 33 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.40 – 7.14 (11H, m), 5.24 – 5.01 (3H, m), 4.48 – 4.31 (2H, m), 4.27 – 4.17 (1H, m), 3.66 – 3.43 (2H, m), 2.96 (1H, t, *J* = 7.0, 7.0 Hz), 2.81 (1H, t, *J* = 7.0, 7.0 H), 2.25 – 1.81 (5H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers): 172.7, 172.5, 154.8, 154.2, 137.6, 137.4, 136.7, 136.6, 128.9, 128.8, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 126.6, 126.5, 67.0, 66.9, 66.9, 66.9, 66.8, 66.7, 65.4, 65.3, 59.2, 58.9, 46.9, 46.9, 46.4, 46.3, 35.0, 34.8, 30.9, 29.8, 24.3, 24.2, 23.5, 23.4. HRMS calc'd for [M+Na] = 376.1525, observed = 376.1525. IR (NaCl, DCM): 3063, 2956, 1744, 1708, 1586, 1453, 1415, 1352, 1277, 1172, 1088, 999, 749, 699.

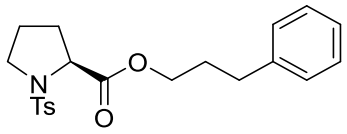
Figure 9.122: Compound VII.19



dibenzyl (*S*)-pyrrolidine-1,2-dicarboxylate (VII.19). To a 100 mL roundbottom flask containing a stir bar was added benzyl-*L*-prolinate (purchased from Alfa Aesar, 0.858 g, 4.4 mmol) followed by DCM (20 mL). The vessel was sealed with a septa and flushed with nitrogen. To the stirring reaction mixture was added TEA (0.835 mL, 0.606 g, 6.0 mmol) and Cbz-Cl (0.580 mL, 0.697 g, 4.1 mmol). The reaction mixture was allowed to stir overnight. The following day the reaction mixture was transferred to a separatory funnel and extracted with dilute HCl (20 mL of 5 % HCl v/v) and saturated sodium bicarbonate solution (20 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product. The crude material was purified by silica gel chromatography (1:2 ethyl acetate: hexanes, R_f = 0.4) to yield the product as a clear oil (0.724 g, 51 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide

rotamers) δ: 7.38 – 7.23 (10H, m), 5.24 – 5.12 (2H, m), 5.09 – 5.00 (2H, m), 4.48 – 4.38 (1H, m), 3.67 – 6.57 (1H, m), 3.55 – 3.46 (1H, m), 2.29 – 2.19 (1H, m), 2.05 – 1.86 (3H, m). ^{13}C NMR (125 MHz) (500 MHz) ($CDCl_3$) (amide rotamers) δ: 172.6, 172.4, 154.9, 154.2, 136.7, 136.5, 135.7, 135.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 67.0, 66.9, 66.8, 66.7, 59.2, 58.9, 46.9, 46.4, 30.9, 29.9, 24.3, 23.5. HRMS for [M+H] = 340.1549, observed = 340.1549. IR (NaCl, DCM): 2957, 1744, 1704, 1652, 1416, 1275, 1168, 1087, 986, 697.

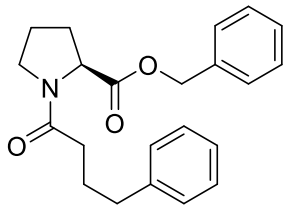
Figure 9.123: Compound VII.20



3-phenylpropyl tosyl-*L*-prolinate (VII.20). To a 50 mL roundbottom flask containing a stir bar was added 3-phenylpropyl *L*-prolinate (0.471 g, 2.0 mmol) followed by DCM (10 mL), and TEA (0.417 mL, 0.303 g, 3.0 mmol). To this mixture was added tosyl chloride dissolved in DCM (0.399 g, 2.1 mmol dissolved in 3.0 mL DCM). On addition a white precipitate was formed, and the reaction was allowed to stir overnight. The following day, the reaction mixture was transferred to a separatory funnel and extracted wth dilute HCl (20 mL of 5 % HCl v/v) followed by saturated aqueous sodium bicarbonate (30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (1:3 ethyl acetate: hexanes, R_f = 0.40) to yield the purified product as a clear oil (0.742 g, 96 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.77 (2H, d, *J* = 8.0 Hz), 7.31 – 7.28 (4H, m), 7.21 – 7.19 (3H, m), 4.31 (1H, dd, *J* = 8.5, 3.0 Hz), 4.18 – 4.10 (2H, m), 3.52 – 3.48 (1H, m), 3.35 – 3.30 (1H, m), 2.70 (2H, t, *J* = 7.5 Hz), 2.42 (3H, s), 2.06 – 1.94 (5H, m), 1.80 – 1.75 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 172.1, 143.5, 141.0, 135.3, 129.6, 128.4, 127.5, 126.0, 64.6, 60.5, 48.4, 32.0,

30.9, 30.1, 24.6, 21.5. HRMS calc'd for [M+H] = 388.1583, observed = 388.1593. IR (NaCl, DCM): 1652, 1540, 1277, 1094.

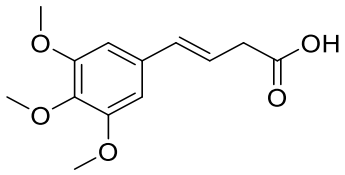
Figure 9.124: Compound VII.21



2-benzyl 1-(3-phenylpropyl) (*S*)-pyrrolidine-1,2-dicarboxylate (VII.21). (*S*)-2-((benzyloxy) carbonyl)pyrrolidin-1-ium chloride was purchased and the free base was generated by dissolving the acid salt in water (3.0 g, 12.4 mmol dissolved in 10 mL distilled water) and adding sodium carbonate (2.1 g, 20.0 mmol). The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield the product, benzyl-*L*-prolinate (2.41 g, 95 %), as a clear oil. To a 10 mL roundbottom flask containing a stir bar was added benzyl-*L*-prolinate (1.10 g, 5.4 mmol) followed by DCM (25 mL). Stirring commenced and 4-phenylbutanoyl chloride was added dropwise (1.0 g, 5.4 mmol) and TEA (1.67 mL, 1.21 g, 12.0 mmol). An exotherm was observed and a white precipitate was formed. The reaction was allowed to stir overnight. The following day the reaction mixture was transferred to a separatory funnel and washed with dilute HCl (10 mL 5 % HCl v/v) followed by saturated aqueous sodium bicarbonate (20 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (1:2 ethyl acetate: hexanes, R_f = 0.25) to yield the pure product as a clear oil (1.12 g, 59 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.38 – 7.30 (7H, m), 7.29 – 7.13 (3H, m), 5.22 – 5.12 (2H, m), 4.57 – 4.31 (1H, m), 3.66 – 3.53 (1H, m), 3.44 – 3.39 (1H, m), 2.68 (1H, t, *J* = 7.5 Hz), 2.62 – 2.37 (1H, m), 2.37 – 2.11 (3H, m), 2.06 – 1.86 (5H, m). ^{13}C NMR (125 MHz) ($CDCl_3$)

(amide rotamers) δ: 172.2, 171.6, 141.7, 135.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 125.8, 67.1, 66.7, 59.4, 58.7, 46.9, 46.3, 35.1, 35.1, 33.4, 33.4, 31.4, 29.1, 26.1, 26.0, 24.7, 22.5. HRMS calc'd for [M+H] = 352.1913, observed = 352.1947. IR (NaCl, DCM): 2859, 1733, 1698, 1506, 1455, 1420, 1396, 1127.

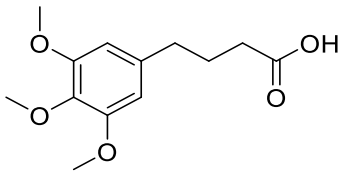
Figure 9.125: Compound VII.22a



(*E*)-4-(3,4,5-trimethoxyphenyl)but-3-enoic acid (VII.22a). To a 250 mL roundbottom flask containing a stir bar was added (2-carboxyethyl)triphenylphosphonium bromide (11.3 g, 27.2 mmol) followed by DMF (20 mL). The reaction vessel was sealed with a septa and flushed with nitrogen. The reaction mixture was heated to aid in the dissolution of the phosphonium salt. After the salt was dissolved, the reaction vessel was cooled to 0 ºC in an ice-water bath, opened to the atmosphere, and sodium hydride (2.18 g, 28 mmol, of a 60 % dispersion in oil) was added in portions. Gas evolved and the reaction vessel was re-sealed under nitrogen. In a separate vessel 3,4,5-trimethoxybenzaldehyde (5.4 g, 27.5 mmol) was dissolved in DMF (20 mL). The aldehyde/DMF solution was added dropwise to the sodium hydride/phosphonium salt solution. Once addition was complete, the reaction vessel was heated to 50 ºC in an oil bath overnight. The following day the reaction mixture was poured into ice-water (200 mL). This solution was extracted with hexanes (1 x 200 mL) and ethyl acetate (1 x 200 mL). The solution was made acidic by the addition of HCl (50 mL of 5 % HCl v/v) and extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield a yellow oil. This material was dissolved in a minimum amount of ethyl acetate and filtered

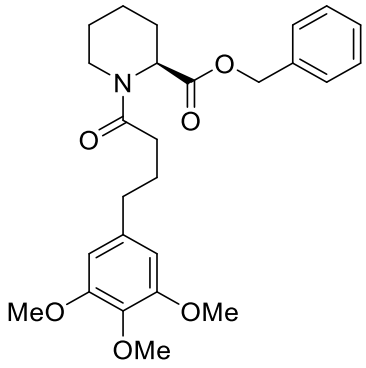
through a plug of silica gel. This material was concentrated *in vacuo* to yield a yellow oil which was ultimately purified by silica gel chromatography (1:3 ethyl acetate: hexanes, R_f = 0.2) to yield the product as a yellow solid (2.10 g, 31 %). Spectroscopic data matches that reported for this compound.[198] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 6.60 (2H, s), 6.45 (1H, d, *J* = 16.0 Hz), 6.23 – 6.17 (1H, m), 3.87 (6H, s), 3.84 (3H, s), 3.30 (2H, dd, *J* = 7.0, 1.0 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 177.4, 153.3, 137.8, 133.9, 132.3, 120.2, 103.3, 60.9, 56.1, 56.0, 37.8. M.P. = 72 ºC.

Figure 9.126: Compound VII.22b



4-(3,4,5-trimethoxyphenyl)butanoic acid (VII.22b). To a 250 mL roundbottom flask containing a stir bar was added (*E*)-4-(3,4,5-trimethoxyphenyl)but-3-enoic acid (2.05 g, 8.1 mmol). Ethyl acetate (100 mL) was added, followed by 10 % palladium on carbon (1.2 g). Stirring commenced and a balloon containing hydrogen was affixed to the roundbottom flask and a hydrogen atmosphere was applied to the reaction mixture. The reaction stirred overnight and the following day was filtered through celite and concentrated *in vacuo* to yield the pure product (2.07 g, 99 %) as a gray solid. ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 6.39 (2H, s), 3.91 (1H, d, *J* = 8.0 Hz), 3.84 (6H, s), 3.81 (3H, s), 2.61 (2H, t, *J* = 8.0 Hz), 2.39 (2H, t, *J* = 7.5 Hz), 1.96 (2H, quintet, *J* = 7.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 179.7, 153.1, 136.9, 136.1, 107.2, 105.3, 60.8, 56.2, 56.0, 35.4, 33.3, 26.2. HRMS calc'd for [M+H] = 255.1232, observed = 255.1237. IR (NaCl, DCM): 3390, 2938, 1734, 1705, 1590, 1507, 1457, 1333, 1283, 1126. M.P. = 70 ºC.

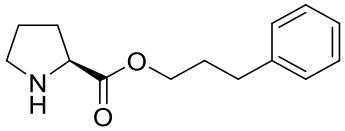
Figure 9.127: Compound VII.22



benzyl (*S*)-1-(4-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (VII.22). To a 100 mL roundbottom flask containing a stir bar was added benzyl (*S*)-piperidine-2-carboxylate (0.475 g, 2.1 mmol) and DCM (15 mL). Stirring commenced and 4-(3,4,5-trimethoxyphenyl) butanoic acid was added (0.533 g, 2.1 mmol) as a solid, followed by EDCI (0.437 g, 2.3 mmol), TEA (0.560 mL, 0.404 g, 4.0 mmol), and DMAP (0.060 g, 0.5 mmol). The reaction vessel was sealed with a septa, flushed with nitrogen, and stirred overnight. The following day the reaction mixture was transferred to a separatory funnel and washed with water (20 mL) and saturated sodium bicarbonate solution (20 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material was isolated as an oil and purified by silica gel chromatography (1:2 ethyl acetate: hexanes, R_f = 0.2) to yield the pure product as a clear oil (0.463 g, 48 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: 7.37 – 7.29 (5H, m), 6.42 – 6.39 (2H, m), 5.45 (0.8 H, d, *J* = 5.0 H), 5.22 – 5.13 (2H, m), 4.58 – 4.54 (0.35 H, m), 3.85 – 3.82 (9H, m), 3.69 (1H, br d, *J* = 13.0 Hz), 2.66 – 2.54 (2H, m), 2.43 – 2.21 (3H, m), 2.01 – 1.91 (2H, m), 1.71 – 1.59 (4H, m), 1.45 – 1.23 (2H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers): 172.9, 171.3, 153.0, 137.6, 136.0, 135.7, 128.6, 128.5, 128.2, 128.2, 128.0, 105.3, 105.2, 66.8, 60.8, 56.0, 51.9, 43.3, 35.7, 32.5, 26.6, 25.3, 20.9. HRMS calc'd for [M+H] =

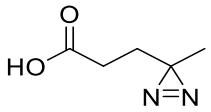
456.2386, observed = 456.2387. IR (NaCl, DCM): 1736, 1645, 1588, 1455, 1353, 1319, 1238, 1126.

Figure 9.128: Compound VII.23



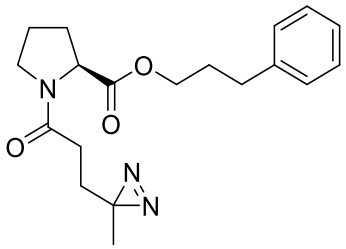
3-phenylpropyl *L*-prolinate (VII.23). To a 500 mL roundbottom containing 1-benzyl 2-(3-phenylpropyl) (*S*)-pyrrolidine-1,2-dicarboxylate (2.51 g, 6.80 mmol) was added a stir bar and ethyl acetate (200 mL). Stirring commenced and 10 % palladium on carbon was added (1.0 g). The reaction vessel was affixed with a hydrogen balloon and hydrogen was applied to the stirring reaction mixture. The reaction was allowed to proceed overnight, and on the following day the balloon was removed and the crude material was filtered through celite. The organic layer was transferred to a separatory funnel and washed with aqueous acid (50 mL of 5 % HCl v/v). The aqueous layer was washed with ethyl acetate (100 mL). The aqueous layer was made basic by addition of sodium carbonate (pH ~ 10 by pH paper) and was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield the product as a clear oil. (1.21 g, 76 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.31 – 7.18 (5H, m), 4.15 (2H, t, *J* = 7.0, 7.0 Hz), 3.76 (1H, dd, *J* = 5.5, 2.5 Hz), 3.11 – 3.06 (1H, m), 2.94 – 2.89 (1H, m), 2.70 (2H, t, *J* = 7.5, 7.5 Hz), 2.18 – 2.10 (2H, m), 2.01 – 1.96 (2H, m), 1.88 – 1.72 (3H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 175.5, 141.0, 128.4, 128.3, 126.0, 64.2, 59.8, 47.0, 32.1, 30.3, 30.2, 25.5. HRMS calc'd for [M+H] = 234.1494, observed = 234.1493. IR (NaCl, DCM): 3425, 1734, 1698, 1684, 1653, 1540, 1455, 1418, 1349, 1167.

Figure 9.129: Compound VII.24a



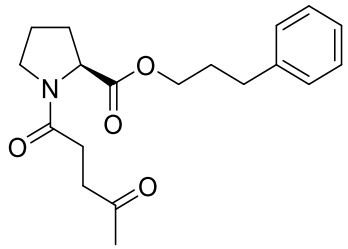
3-(3-methyl-3H-diazirin-3-yl)propanoic acid (VII.24a). To a 50 mL roundbottom flask containing a stir bar was added an ammonia/methanol solution (7.0 M in ammonia, 15 mL). Stirring commenced and the reaction vessel was sealed with a septa and flushed with argon. The reaction vessel was cooled to 0 ºC in an ice-water bath. To this solution was added dropwise levulanic acid (1.32 mL, 1.50 g, 12.9 mmol, dissolved in 1.0 mL methanol). The reaction mixture was stirred for 3 hours at 0 ºC, at which time the ice-water bath was removed and hydroxylamine-*O*-sulfonic acid (1.53 g, 15.0 mmol) was added as a solid. The reaction vessel was resealed, flushed with argon, and allowed to stir overnight. The following day the reaction mixture was filtered (a solid has precipitated) and concentrated *in vacuo* to yield 3-(3-methyldiaziridin-3-yl)propanoic acid (100%) as a clear oil. This material was carried on to the next step without additional purification. The 3-(3-methyldiaziridin-3-yl)propanoic acid was dissolved in methanol (10.0 mL) and TEA was added (2.70 mL, 3.37 g, 33.0 mmol). Stirring commenced and the reaction vessel was cooled to 0 ºC in an ice-water bath. Iodine was added until a purple color persisted. At that time, the reaction mixture was diluted with ethyl acetate (20 mL) and transferred to a separatory funnel. The organic layer was washed with 10 % HCl (10 mL) followed by sodium bisulfite (10 mL of a 10 % w/v solution) and finally with brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the product as a yellow oil (1.31 g, 85 %). Spectroscopic data matches that reported for this compound.[199] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 2.23 (2H, t, *J* = 7.5 Hz), 1.72 (2H, t, *J* = 7.5 Hz), 1.04 (3H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 177.5, 29.3, 28.3, 25.0, 19.6.

Figure 9.130: Compound VII.24



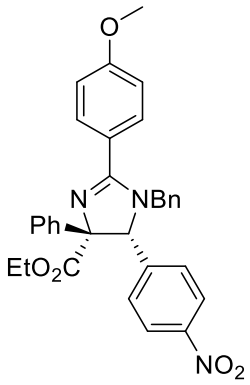
3-phenylpropyl (3-(3-methyl-3*H*-diazirin-3-yl)propanoyl)-*L*-prolinate (VII.24). To a 50 mL roundbottom flask containing a stir bar was added 3-(3-methyl-3*H*-diazirin-3-yl)propanoic acid (0.322 g, 2.6 mmol) followed by DCM (10 mL), EDCI (0.608 g, 3.0 mmol), DMAP (0.060 g, 0.50 mmol) and TEA (0.835 mL, 0.606 g, 6.0 mmol). Stirring commenced, and 3-phenylpropyl *L*-prolinate was added (0.629 g, 2.7 mmol). The reaction vessel was sealed with a septa, flushed with nitrogen, and stirred overnight. The crude reaction mixture was transferred to a separatory funnel and extracted with dilute HCl (50 mL of 5 % HCl v/v) and saturated aqueous sodium bicarbonate (100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (1:1 ethyl acetate: hexanes, R_f = 0.30) to yield the pure product as a clear oil (0.544 g, 58 %). ^{1}H NMR (500 MHz) ($CDCl_3$) (amide rotamers) δ: ^{13}C NMR (125 MHz) ($CDCl_3$) (amide rotamers): 172.2, 170.0, 141.1, 128.5, 128.4, 128.3, 126.1, 125.9, 64.9, 64.3, 59.4, 58.7, 46.9, 46.4, 32.0, 31.4, 30.2, 30.1, 29.3, 29.2, 29.0, 28.5, 25.5, 24.7, 22.5, 20.0. *Missing carbon at 72 ppm, see text for discussion.* HRMS calc'd for [M+H] = 344.1974, observed = 344.1971. IR (NaCl, DCM): 2055, 1733, 1651, 1558, 1396, 1174.

Figure 9.131: Compound VII.25



3-phenylpropyl (4-oxopentanoyl)-*L*-prolinate (VII.25). To a 100 mL roundbottom flask containing a stir bar was added levulinic acid (0.307 mL, 0.348 g, 3.0 mmol) followed by DCM (20 mL), EDCI (0.608 g, 3.2 mmol), TEA (1.39 mL, 1.01 g, 10.0 mmol), DMAP (0.120 g, 1.0 mmol) and 3-phenylpropyl *L*-prolinate (0.700 g, 3.0 mmol). The reaction mixture was stirred overnight. The following day the reaction mixture was transferred to a separatory funnel and washed with dilute HCl (10 mL 5 % HCl v/v) followed by sodium bicarbonate (30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (1:1 ethyl acetate: hexanes R_f = 0.70) to yield the pure product as a clear oil (0.988 g, 96 %). ^{1}H NMR (500 MHz) ($CDCl_3$, amide rotamers) δ: 7.30 – 7.26 (2H, m), 7.20 – 7.16 (3H, m), 4.54 – 4.47 (1H, m), 4.19 – 4.11 (2H, m), 3.69 – 3.64 (1H, m), 3.62 – 3.55 (1H, m), 2.97 – 2.91 (1H, m), 2.72 – 2.62 (4H, m), 2.61 – 2.48 (1H, m), 2.31 – 1.90 (10H, m). ^{13}C NMR (125 MHz) ($CDCl_3$, amide rotamers): 207.7, 172.3, 170.4, 141.1, 128.5, 128.4, 128.4, 128.3, 126.1, 125.9, 64.9, 64.3, 59.4, 58.8, 46.9, 46.4, 38.1, 37.7, 32.0, 31.4, 30.2, 30.0, 29.3, 28.5, 24.7, 22.6. HRMS calc'd for [M+H] = 332.1862, observed = 332.1873. IR (NaCl, DCM): 2955, 1699, 1652, 1558, 1456, 1419.

Figure 9.132: Compound VIII.1a



ethyl (4*R*,5*R*)-1-benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (VIII.1a). To a 250 mL roundbottom flask containing a stir bar was added toluene (100 mL), followed by anhydrous benzylamine (3.26 mL, 3.19 g, 60.0 mmol), followed by *para*-nitrobenzaldehyde (9.0 g, 60.0 mmol). The reaction mixture was heated to reflux overnight using a Dean-Stark apparatus for the azeotropic removal of water. The following day, the reaction mixture was cooled to room temperature and concentrated *in vacuo* to yield the imine (14.4 g, 100 % yield) as an oil which was used in the next step without purification.

In a separate 250 mL roundbottom flask containing a stir bar was added phenylglycine (10.0 g, 66.0 mmol), followed by water (400 mL) and sodium carbonate (19.5 g, 186.0 mmol). Stirring commenced and *p*-methoxybenzoyl chloride was added dropwise (11.8 g, 69.2 mmol, dissolved in 200 mL 1,4-dioxane) and the reaction mixture was allowed to stir overnight. The following day, the reaction mixture was made acidic by the addition of dilute HCl (dropwise addition of 50 mL of 20 % v/v HCl), at which time a white solid precipitated. The crude product was filtered and washed with ethyl ether, dissolved in ethyl acetate, washed with water (3 x 100 mL per extraction), dried over sodium sulfate and concentrated *in vacuo* to yield a white solid.

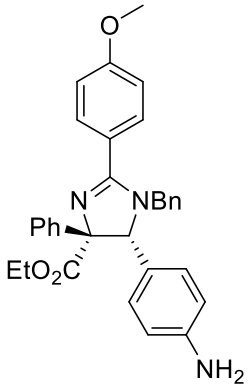
The crude product was purified by recrystallization (dissolve in a minimum amount of ethyl acetate and heat, precipitate by adding hexanes) to yield the pure product as a white solid, which was dried *in vacuo* to a constant weight (8.3 g, 44 %). The protected 2-phenylglycine (8.3 g, 32.1 mmol) was transformed to the corresponding azlactone by dissolving in DCM (200 mL) and adding TFAA (4.8 mL, 7.2 g, 33.3 mmol). The reaction was stirred under nitrogen for 2 hours, during which time a yellow color developed (diagnostic of the formation of the azlactone). After this time, the reaction mixture was transferred to a separatory funnel and extracted twice with saturated sodium bicarbonate (2 x, 50 mL per extraction). The crude azlactone was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a yellow solid.

In a 500 mL roundbottom flask with a stir bar the imine previously described (8.3 g, 31.0 mmol) was dissolved in anhydrous DCM (300 mL). To this mixture was added the protected phenylglycine azlactone previously described (7.4 g, 31.0 mmol). Stirring commenced, and to the reaction mixture was added freshly distilled TMSCl (5.04 mL, 4.32 g, 40.0 mmol) was added. The reaction vessel was connected to a reflux condenser which was sealed with a septa and flushed with nitrogen. The reaction mixture was heated to reflux overnight. The following day, the reaction mixture was concentrated to dryness and 300 mL ethyl acetate was added. The reaction vessel was cooled at 0 ºC for 3 hours, at which time the precipitate was filtered and washed with ethyl acetate and hexanes. The sand-like solid was dried *in vacuo* to yield the imidazoline as the HCl salt (4.3 g, 27 % yield).

The imidazoline HCl salt (4.3 g, 8.4 mmol) was suspended in DCM (20 mL) in a 50 mL roundbottom flask, followed by EDCI (1.80, 9.5 mmol), TEA (2.08 mL, 1.51 g, 15.0 mmol), DMAP (0.120 g, 1.0 mmol), and ethyl alcohol (0.870 mL, 0.690 g, 15.0 mmol). The reaction vessel was sealed with a septa, flushed with nitrogen, and allowed to stir overnight. The

following day, the reaction mixture was transferred to a separatory funnel and extracted with water (25 mL). The organic layer was dried over sodium sulfate, concentrated *in vacuo,* and purified by silica gel chromatography (2:3 ethyl acetate hexanes to 2:3:0.2 ethyl acetate: hexanes: TEA) to yield the product as an orange solid (2.0 g, 44 %). Spectroscopic data matches that reported for this compound.[197] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.22 (2H, dd, *J* = 10.0, 1.5 Hz), 7.77 (2H, dd, *J* = 10.0, 2.0 Hz), 7.69 – 7.67 (2H, m), 7.55 (2H, d, *J* = 8.5 Hz), 7.35 – 7.25 (3H, m), 7.11 – 7.06 (1H, m), 7.06 – 7.00 (4H, m), 6.72 (2H, d, *J* = 7.5 Hz), 4.91 (1H, s), 4.64 (1H, d, *J* = 16.0 Hz), 3.86 – 3.83 (4H, m), 3.74 – 3.70 (1H, m), 3.67 – 3.62 (1H, m), 0.828 (3H, t, *J* = 6.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 170.5, 165.6, 161.5, 147.6, 146.3, 143.6, 135.9, 130.5, 128.9, 128.5, 128.2, 127.7, 127.6, 127.2, 126.5, 123.6, 122.0, 114.1, 83.1, 73.1, 61.3, 55.4, 49.7, 13.6.

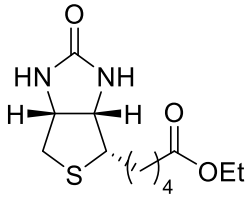
Figure 9.133: Compound VIII.1



ethyl (4*R*,5*R*)-5-(4-aminophenyl)-1-benzyl-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (VIII.1) To a 250 mL roundbottom flask with a stir bar was added ethyl (4*R*,5*R*)-1-benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (2.0 g, 3.7 mmol), followed by glacial acetic acid (50 mL). Stirring commenced, and to the reaction mixture was added zinc dust (3.0 g, 46.0 mmol). An exotherm

was observed, and the reaction was allowed to continue for two hours. At this time, the reaction mixture was filtered and the filter was washed with water. Water was added to the crude mixture (100 mL) and solid sodium carbonate was added until no bubbles were observed (the product collects as a solid on top of the aqueous layer once the mixture is sufficiently basic). The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield the product as an orange solid which needed no further purification (2.1 g, quantitative yield). Spectroscopic data match that reported for this compound.[197] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.73 – 7.68 (4H, m), 7.32 – 7.26 (2H, m), 7.25 – 7.24 (1H, m), 7.15 – 7.04 (5H, m), 6.97 – 6.95 (2H, m), 6.75 (2H, d, *J* = 7.0 Hz), 6.66 (2H, d, *J* = 8.5 Hz), 4.79 (1H, s), 4.61 (1H, d, *J* = 15.5 Hz), 3.85 – 3.82 (4H, m), 3.78 – 3.63 (4H, m), 0.88 (3H, t, *J* = 6.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 171.1, 165.0, 161.0, 146.4, 144.4, 137.1, 130.3, 129.2, 128.3, 127.8, 127.5, 127.2, 127.1, 127.1, 126.9, 123.0, 114.9, 113.8, 82.4, 73.5, 60.9, 55.3, 48.4, 13.6.

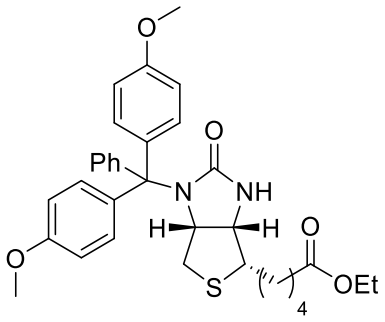
Figure 9.134: Compound VIII.2



Biotin ethyl ester (VIII.2). To a 500 mL roundbottom flask containing a stir bar was added biotin (5.0 g, 20.4 mmol) followed by ethanol (250 mL). The starting material did not dissolve, but stirring commenced and the reaction mixture was cooled to 0 ºC in an ice bath. Acetyl chloride was added dropwise (2.0 mL, 2.2 g, 28.2 mmol). The ice bath was removed and the reaction mixture was allowed to stir overnight. By the following day the biotin had dissolved, indicating completion of the reaction. The reaction mixture was concentrated *in vacuo* to yield

the crude product as a white solid. The product was purified by dissolving the crude solid in a minimum of acetone and precipitating with hexanes. The solid was filtered and dried *in vacuo* to yield the pure product as a white solid (3.4 g, 59 % yield). Spectroscopic data matches that reported for this compound.[198] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 5.90 (1H, br s), 5.48 (1H, br s), 4.50 (1H, dd, *J* = 10.0, 5.0 Hz), 4.30 (1H, dd, *J* = 7.5, 5.5 Hz), 4.11 (2H, quartet, *J* = 7.5 Hz), 3.17 – 3.13 (1H, m), 2.90 (1H, dd, *J* = 12.5, 4.5 Hz), 2.73 (1H, d, *J* = 12.5 Hz), 2.31 (2H, t, *J* = 7.5 Hz), 1.74 – 1.63 (4H, m), 1.49 – 1.40 (2H, m), 1.24 (3H, t, *J* = 8.0 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 173.7, 163.6, 61.9, 60.3, 60.1, 55.4, 40.5, 33.9, 28.3, 28.2, 24.7, 14.2.

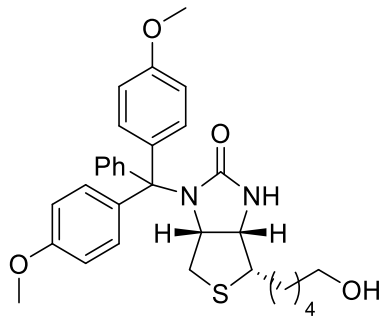
Figure 9.135: Compound VIII.3a



(4,4')-DMT-Biotin ethyl ester (VIII.3a). To a 100 mL roundbottom flask was added a stir bar and biotin ethyl ester (3.4 g, 11.7 mmol). The reaction vessel was sealed with a septa and flushed with nitrogen. To the vessel was added anhydrous pyridine (50 mL). Stirring commenced, and on complete dissolution of the solid (~ 5 minutes) the septa was removed and 4,4'-dimethoxytrityl chloride was added (4.39 g, 13.0 mmol). The reaction mixture was stirred for 3 hours at which time methanol was added (5.0 mL). The reaction mixture was concentrated *in vacuo* and redissolved in DCM. The organic layer was washed with dilute HCl (80 mL of 5 % v/v HCl) and saturated bicarbonate. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an oil. The crude material was purified by silica gel

chromatography (100 % DCM to 5 % methanol in DCM) to yield the pure product was a yellow foam (3.4 g, 49 % yield). Spectroscopic data matches that reported for this compound.[198] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.30 – 7.21 (5H, m), 7.17 – 7.11 (4H, m), 6.82 – 6.79 (4H, m), 5.81 (1H, br s), 4.36 – 4.33 (1H, m), 4.29 – 4.26 (1H, m), 4.18 – 4.08 (3H, m), 3.77 (6H, s), 3.10 – 3.06 (1H, m), 2.42 – 2.39 (1H, m), 2.28 – 2.22 (3H, m), 2.03 (1H, s), 1.64 – 1.55 (4H, m), 1.44 – 1.31 (2H, m), 1.25 (4H, td, *J* = 5.0, 5.0, 2.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 173.5, 171.1, 163.7, 161.6, 158.5, 158.3, 147.4, 143.7, 139.5, 135.8, 135.8, 131.3, 129.7, 129.1, 127.8, 127.7, 127.5, 127.0, 126.8, 113.1, 113.0, 112.8, 112.7, 81.3, 72.6, 65.3, 61.7, 60.3, 60.2, 60.2, 60.1, 59.8, 55.3, 55.2, 55.2, 54.2, 40.4, 39.0, 33.9, 33.9, 33.7, 28.6, 28.3, 28.2, 28.1, 24.7, 24.6, 24.5, 21.0, 14.2, 14.2.

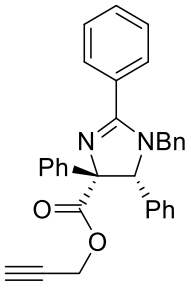
Figure 9.136: Compound VIII.3



(4,4')-DMT-Biotinol (VIII.3). To a 500 mL roundbottom flask containing (4,4')-DMT-Biotin ethyl ester (3.4 g, 5.8 mmol) was added a stir bar and THF (200 mL). Stirring commenced, and the reaction vessel was cooled to 0 ºC in an ice bath. Powdered LAH was added in portions (0.985, 26.0 mmol). After addition was complete, the reaction vessel was sealed with a septa and flushed with nitrogen. The reaction was allowed to warm to room temperature and proceed overnight. The following day, the reaction was quenched with ethanol, water, and water saturated with sodium sulfate. The crude reaction mixture was concentrated *in vacuo* to remove

ethanol and THF. The crude was transferred to a separatory funnel and extracted with ethyl acetate (3 x 100 mL per extraction). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an oil. The crude was purified by silica gel chromatography (100 % DCM to 5 % methanol in DCM) to yield the pure product as a white solid (2.7 g, 89 %). Spectroscopic data matches that reported for this compound.[198] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.30 – 7.14 (9H, m), 6.84 – 6.80 (4H, m), 6.16 – 5.47 (1H, br m), 4.37 – 4.17 (2H, m), 3.79 (6H. s), 3.66 – 3.55 (2H, m), 3.13 – 3.01 (1H, m), 2.45 (1H, d, *J* = 12.5 Hz), 2.28 (1H, dd, *J* = 13.0, 4.5 Hz), 2.17 (1H, br s), 1.68 – 1.56 (3H, m), 1.55 – 1.45 (1H, m), 1.41 -1.38 (4H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 158.3, 158.2, 143.7, 135.8, 135.7, 131.3, 129.9, 129.7, 129.1, 128.1, 127.8, 127.7, 127.7, 127.5, 126.9, 113.1, 112.9, 112.8, 72.7, 65.5, 61.6, 59.6, 55.4, 55.2, 55.2, 54.3, 40.4, 39.1, 32.0, 31.5, 29.0, 28.1, 25.6. HRMS calc'd for [M+Na] = 555.2293, observed = 555.2294.

Figure 9.137: Compound VIII.4



prop-2-yn-1-yl (4*R*,5*R*)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (VIII.4). To a 250 mL roundbottom flask containing a stir bar was added toluene (100 mL), followed by anhydrous benzylamine (3.26 mL, 3.2 g, 29.5 mmol), followed by benzaldehyde (2.98 mL, 3.1 g, 29.5 mmol). The reaction mixture was heated to reflux overnight using a Dean-Stark apparatus for the azeotropic removal of water. The following day, the reaction mixture was cooled to room temperature and concentrated *in vacuo* to yield the imine (6.3 g, 100 % yield) as

an oil which was used in the next step without purification. In a separate 250 mL roundbottom flask containing a stir bar was added phenylglycine (10.0 g, 66.1 mmol), followed by aqueous sodium hydroxide (1.0 N, 132 mL). Stirring commenced and benzoyl chloride was added dropwise (8.4 mL, 10.2 g, 72.8 mmol, dissolved in 40 mL 1,4-dioxane) and the reaction mixture was allowed to stir overnight. The following day, the reaction mixture was made acidic by the addition of dilute HCl (dropwise addition of 50 mL of 20 % v/v HCl), at which time a white solid precipitated. The crude product was dissolved in ethyl acetate, partitioned in a separatory funnel, dried over sodium sulfate and concentrated *in vacuo* to yield a white solid. The crude product was purified by recrystallization (dissolve in a minimum amount of 1:9 methanol:ethyl acetate and heat, precipitate by adding hexanes) to yield the pure product as a white solid, which was dried *in vacuo* to a constant weight (8.3 g, 49 %).

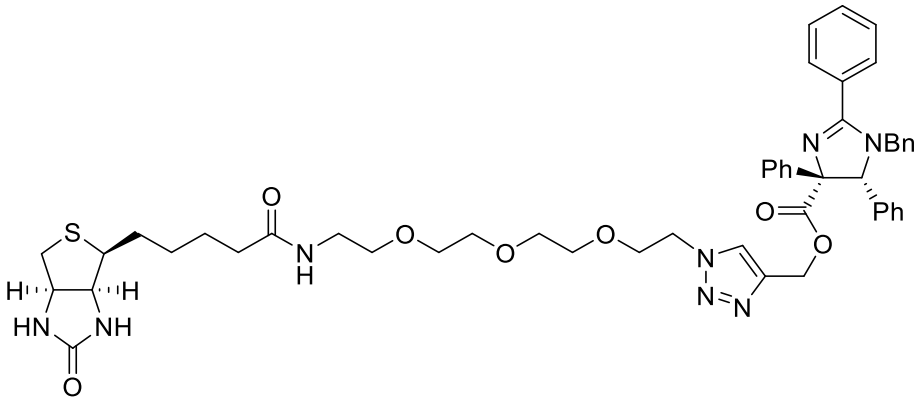
The *N*-benzoyl 2-phenylglycine (8.3 g, 32.1 mmol) was transformed to the corresponding azlactone by dissolving in DCM (200 mL) and adding TFAA (4.8 mL, 7.2 g, 33.3 mmol). The reaction was stirred under nitrogen for 2 hours, during which time a yellow color developed (diagnostic of the formation of the azlactone). After this time, the reaction mixture was transferred to a separatory funnel and extracted twice with saturated sodium bicarbonate (2 x, 50 mL per extraction). The crude azlactone was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as a yellow solid.

In a 500 mL roundbottom flask with a stir bar the imine previously (6.3 g, 29.5 mmol) described was dissolved in anhydrous DCM (300 mL). To this mixture was added the *N*-benzoyl -phenylglycine azlactone previously described (7.0 g, 32.1 mmol). Stirring commenced, and to the reaction mixture was added freshly distilled TMSCl (4.1 mL, 3.50 g, 32.4 mmol) was added. The reaction vessel was connected to a reflux condenser which was sealed with a septa and

flushed with nitrogen. The reaction mixture was heated to reflux overnight. The following day, the reaction mixture was concentrated to dryness and 300 mL ethyl acetate was added. The reaction vessel was cooled at 0 ºC for 3 hours, at which time the precipitate was filtered and washed with ethyl acetate and hexanes. The sand-like solid was dried *in vacuo* to yield the imidazoline as the HCl salt (7.7 g, 51 % yield).

The imidazoline HCl salt (1.40 g, 3.0 mmol) was suspended in DCM (20 mL) in a 50 mL roundbottom flask, followed by EDCI (0.665 g, 3.5 mmol), TEA (1.25 mL, 0.909 g, 9.0 mmol), DMAP (0.120 g, 1.0 mmol), and propargyl alcohol (0.290 mL, 0.280 g, 5.0 mmol). The reaction vessel was sealed with a septa, flushed with nitrogen, and allowed to stir overnight. The following day, the reaction mixture was transferred to a separatory funnel and extracted with water (25 mL). The organic layer was dried over sodium sulfate, concentrated *in vacuo*, and purified by silica gel chromatography (3:7 ethyl acetate hexanes to 1:1:0.1 ethyl acetate: hexanes: TEA) to yield the product as an oil (0.646 g, 46 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.82 – 7.77 (4H, m), 7.52 – 7.50 (3H, m), 7.43 – 7.30 (8H, m), 7.15 – 7.07 (3H, m), 6.77 (2H, d, *J* = 7.0 Hz), 4.95 (1H, s), 4.66 (1H, d, *J* = 16.0 Hz), 4.27 (1H, dd, *J* = 15.5, 2.5 Hz), 4.05 (1H, dd, *J* = 15.5, 2.5 Hz), 3.86 (1H, d, *J* = 16.0 Hz), 2.24 (1H, t, *J* = 2.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 170.1, 165.8, 143.5, 137.5, 136.5, 130.4, 128.8, 128.7, 128.6, 128.1, 127.6, 127.4, 127.2, 126.8, 83.0, 76.8, 74.6, 73.9, 52.4, 48.6. HRMS calc'd for [M+H] = 471.2073, observed = 471.2106. IR (NaCl, DCM): 3293, 3062, 2935, 2128, 1739, 1615, 1571, 1448, 1360, 1217, 1066, 731, 699.

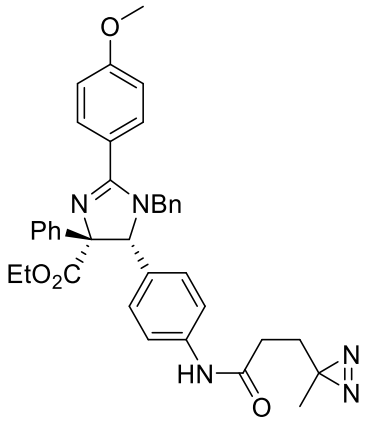
Figure 9.138: Compound VIII.5



(1-(13-oxo-17-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)-3,6,9-trioxa-12-azaheptadecyl)-1*H*-1,2,3-triazol-4-yl)methyl (4*R*,5*R*)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (VIII.5). To a 25 mL roundbottom flask containing a stir bar was added N-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanamide ("Azide-PEG3-Biotin conjugate" purchased from Aldrich, 100 mg, 0.22 mmol) followed by DCM/2-propanol (3.0 mL of a 1:1 mixture) and prop-2-yn-1-yl (4*R*,5*R*)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (0.137 g, 0.29 mmol). Stirring commenced and water was added (3.0 ml) followed by copper(II) sulfate pentahydrate (0.50 g, 0.20 mmol) and sodium ascorbate (0.099 g, 0.5 mmol). The organic layer turned brown and the reaction mixture was allowed to stir for 48 hours at room temperature. The crude reation mixture was transferred to a separatory funnel and partitioned. The aqueous layer was washed with DCM (1 x 5 mL), and the organic layers were combined, dried over sodium sulfate filtered through celite (washed with DCM) and concentrated *in vacuo* to yield the crude product as a tan foam (0.271 g). The crude material was purified by silica gel chromatography (crude was dissolved in DCM and applied to a column packed in 1:1:0.1 ethyl acetate:hexanes:TEA. The unreacted alkyne was eluted in this solvent system. The product is eluted in 1:4 methanol:ethyl acetate, R_f = 0.1) to yield the pure product as

a clear oil (0.047 g, 23 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.75 – 7.70 (4H, m), 7.49 – 7.48 (3H, m), 7.32 – 7.26 (10H, m), 7.13 – 7.10 (1H, m), 7.07 – 7.04 (2H, m), 6.78 (1H, br s), 6.70 (2H, d, *J* = 7.0 Hz), 6.12 (1H, br s), 5.29 (1H, br s), 4.89 (1H, s), 4.79 – 4.58 (3H, m), 4.44 – 4.39 (3H, m), 4.26 – 4.24 (1H, m), 3.80 – 3.77 (3H, m), 3.52 – 3.47 (10H, m), 3.37 – 3.35 (2H, m), 3.12 – 3.07 (4H, m), 2.84 (1H, dd, *J* = 13.0, 4.0 Hz), 2.68 (1H, br d, *J* = 12.5 Hz), 2.12 (2H, t, *J* = 8.0 Hz), 1.71 – 1.56 (4H, m), 1.41 – 1.36 (7H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 173.2, 165.8, 163.5, 142.0, 128.8, 128.7, 128.4, 128.1, 127.6, 127.5, 127.1, 126.7, 125.9, 125.3, 76.7, 73.8, 70.5, 70.3, 70.3, 70.0, 69.8, 69.2, 61.7, 60.0, 58.4, 55.4, 50.0, 48.6, 45.7, 40.5, 39.0, 35.7, 35.7, 28.0, 28.0, 25.4, 8.6. HRMS calc'd for [M+H] = 915.4227, observed = 915.4205. IR (NaCl, DCM): 3478, 3405, 3391, 2098, 1645, 1450, 1353, 1240, 1179, 1096, 1029, 980, 699.

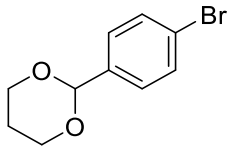
Figure 9.139: Compound VIII.6



Ethyl (4*R*,5*R*)-1-benzyl-2-(4-methoxyphenyl)-5-(4-(3-(3-methyl-3H-diazirin-3-yl)propanamido)phenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (VIII.6). To a roundbottom flask containing a stir bar and ethyl (4*R*,5*R*)-5-(4-aminophenyl)-1-benzyl-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (1.2 g, 2.3 mmol) was added DCM (10 mL), EDCI (0.451 g, 2.3 mmol), TEA (0.696 mL, 0.505 g, 5.0 mmol), and DMAP (0.060 g, 0.50 mmol). Stirring commenced, the reaction vessel was sealed with a septa and

flushed with nitrogen. To the stirring mixture was added 3-(3-methyl-3*H*-diazirin-3-yl)propanoic acid (0.268 g, 2.2 mmol) dropwise. The reaction mixture was allowed to stir overnight. The following day the reaction mixture was transferred to a separatory funnel and extracted with dilute HCl (10 mL of a 5 % HCl v/v solution) followed by aqueous sodium bicarbonate (20 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an oil. The crude material was purified by silica gel chromatography (1:1:0.04 ethyl acetate: hexanes: TEA) to yield the pure product as an orange oil (0.542 g, 40 %). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.03 (1H, br s), 7.72 – 7.70 (2H, m), 7.67 (2H, d, *J* = 8.0 Hz), 7.55 (2H, d, *J* = 8.5 Hz), 7.35 – 7.26 (6H, m), 7.14 – 7.11 (1H, m), 7.08 – 7.05 (2H, m), 6.99 – 6.96 (2H, m), 6.73 (2H, d, *J* = 7.5 Hz), 4.86 (1H, s), 4.62 (1H, d, *J* = 16.5 Hz), 3.85 (3H, s), 3.80 (1H, d, *J* = 15.5 Hz), 3.74 – 3.69 (1H, m), 3.68 – 3.63 (1H, m), 2.18 (2H, t, *J* = 7.5 Hz), 1.81 (2H, dt, *J* = 8.0, 8.0, 3.0 Hz), 1.05 (3H, s), 0.838 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 170.9, 169.8, 165.3, 161.3, 143.9, 138.2, 136.6, 133.3, 130.3, 128.7, 128.4, 128.1, 127.5, 127.4, 127.1, 126.7, 119.8, 114.0, 82.3, 73.0, 61.0, 55.4, 48.6, 31.4, 297, 25.4, 19.9, 13.6. *Missing carbon at 72 ppm, see text for discussion.* HRMS calc'd for [M+H] = 616.2924, observed = 616.2923. IR (NaCl, DCM): 2089, 1696, 1632, 1507, 1473, 1396.

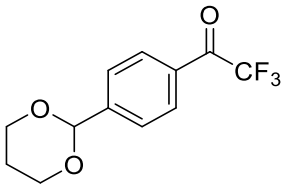
Figure 9.140: Compound VIII.7a



2-(4-bromophenyl)-1,3-dioxane (VIII.7a). To a 500 mL roundbottom flask containing a stir bar was added *p*-bromobenzaldehyde (20.0 g, 108.0 mmol) followed by toluene (200 mL). Stirring commenced, and to the reaction mixture was added 1,3-propane diol (10.2 mL, 10.6 g, 140.0

mmol) and tosyl acid (0.200 g, 1.0 mmol). The reaction mixture was heated to reflux overnight in a Dean-Stark apparatus. The following day the reaction mixture was allowed to cool to room temperature and extracted with sodium bicarbonate (100 mL) and brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the product as a white solid (25.4 g, 98 %). Spectroscopic data matches that reported for this compound.[199] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.50 – 7.49 (2H, m), 7.37 – 7.36 (2H, m), 5.46 (1H, s), 4.01 – 3.95 (2H, m), 2.26 – 2.17 (1H, m), 1.47 – 1.43 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$): 137.7, 131.3, 127.8, 122.8, 100.8, 67.3, 25.6. M.P. = 72 ºC.

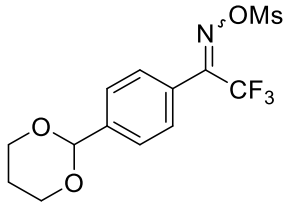
Figure 9.141: Compound VIII.7



1-(4-(1,3-dioxan-2-yl)phenyl)-2,2,2-trifluoroethan-1-one (VIII.7). To a 500 mL oven dried roundbottom flask containing 2-(4-bromophenyl)-1,3-dioxane (25.4 g, 105.0 mmol) was added THF (300 mL) and a stir bar. The reaction vessel was sealed, flushed with nitrogen, and stirring commenced and once all the solid had dissolved the reaction mixture was cooled to – 78 ºC in a dry ice-acetone bath. To the stirring mixture was added *n*-butyllithium dropwise (46.0 mL of a 2.5 M solution in hexanes). The reaction mixture was allowed to stir at – 78 ºC for 30 minutes, at which time ethyl trifluoroacetate was added dropwise (15.0 mL, 17.8 g, 126.5 mmol dissolved in 150 mL THF). The reaction mixture was allowed to stir at – 78 ºC for 2 hours, at which time it was allowed to warm to room temperature. The reaction was quenched with saturated ammonium chloride (20.0 mL) and concentrated to ~ 20 % original volume *in vacuo*. The remaining biphasic liquid was partitioned between ethyl acetate (200 mL) and water (100 mL).

The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to yield the product as a waxy, white solid (15.5 g, 75 %). Spectroscopic data matches that reported for this compound.[199] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.06 (2H, d, *J* = 8.5 Hz), 7.66 (2H, d, *J* = 8.5 Hz), 5.56 (1H, s), 4.17 (2H, dd, *J* = 11.5, 5.5 Hz), 4.02 (2H, dt, *J* = 13.0, 13.0, 2.5 Hz), 2.22 (1H, m), 1.49 (1H, dd, *J* = 13.0, 2.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 180.2 (q, $^{2}J_{CF}$ = 34.5), 145.8, 130.1, 130.1, 129.9, 126.8, 117.7 (q, $^{1}J_{CF}$ = 291.4), 100.1, 67.4, 25.6.

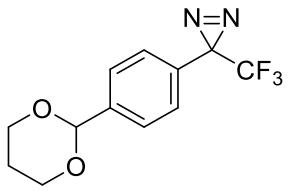
Figure 9.142: Compound VIII.8a



1-(4-(1,3-dioxan-2-yl)phenyl)-2,2,2-trifluoroethan-1-one O-methylsulfonyl oxime (VIII.8a). To a 500 mL roundbottom containing a stir bar and 1-(4-(1,3-dioxan-2-yl)phenyl)-2,2,2-trifluoroethan-1-one (15.5 g, 59.6 mmol) was added 300 mL of ethanol. Stirring commenced and powdered sodium hydroxide (12.8 g, 321.0 mmol) was added, followed by hydroxylamine HCl (22.3 g, 321.0 mmol). The reaction mixture was heated to reflux overnight. The following day, the reaction mixture was cooled to room temperature, filtered, and concentrated *in vacuo* to yield the product as a white solid (16.4 g, 100 %). The product was carried on to the next step with no further purification. The oxime was dissolved in DCM (100 mL) and cooled to 0 ºC in an ice-water bath. Stirring commenced, and to the reaction mixture was added TEA (20.0 mL, 15.1 g, 150.0 mmol), DMAP (1.2 g, 10.0 mmol), and mesyl chloride (10.0 mL, 15.1 g, 133.8 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The following day the reaction mixture was transferred to a separatory funnel and washed with 10 % HCl (200 mL), sodium bicarbonate (200 mL) and brine. The organic layer was dried over

sodium sulfate and concentrated *in vacuo* to yield the product mesylated oxime. The crude material was purified by silica gel chromatography (1:4 ethyl acetate: petroleum ether) to yield the product as a mixture of *cis* and *trans* isomers (20.1 g, 85 %). Spectroscopic data matches that reported for this compound.[199] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.64 (2H, d, *J* = 8.5 Hz), 5.55 (1H, s), 4.28 (2H, dd, *J* = 10.5, 4.0 Hz), 4.01 (2H, dt, *J* = 10.5, 10.5, 1.5 Hz), 3.24 (3H, s), 2.22 (1H, m), 1.47 (1H, m). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 154.7, 142.4, 128.4, 126.6, 126.6, 126.5, 124.6, 119.5 (q, $^{1}J_{CF}$ = 274.1), 100.3, 100.2, 67.4, 37.3, 36.7, 36.6, 31.5, 25.6 5 (q, $^{2}J_{CF}$ = 34.7),

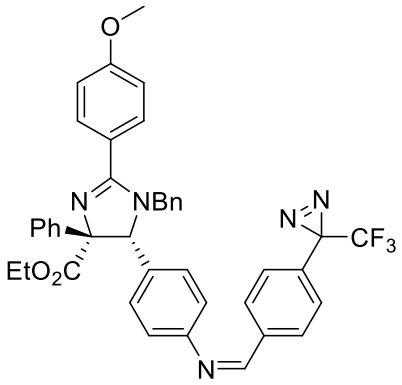
Figure 9.143: Compound VIII.8



3-(4-(1,3-dioxan-2-yl)phenyl)-3-(trifluoromethyl)-3*H*-diazirine (VIII.8). To a 250 mL roundbottom flask containing 1-(4-(1,3-dioxan-2-yl)phenyl)-2,2,2-trifluoroethan-1-one O-methylsulfonyl oxime (20.1 g, 56.6 mmol) was added methanol (50 mL) and a stir bar. The reaction vessel was sealed with a septa and flushed with nitrogen. Stirring commenced and the reaction vessel was cooled to – 78 ºC in a dry ice-acetone bath. To the stirring mixture was added ammonia (7.0 M in methanol, 30.0 mL, 210.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. The following day the reaction mixture was concentrated *in vacuo* to yield 3-(4-(1,3-dioxan-2-yl)phenyl)-3-(trifluoromethyl)diaziridine (15.5 g, 100 %) as a yellow oil. Spectroscopic data matches that reported for this compound.[199] ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.53 (2H, d, *J* = 8.5 Hz), 7.21 (2H, d, *J* = 8.5 Hz), 5.51 (1H, s), 4.27 (2H, ddd, *J* = 11.0, 3.0, 1.0 Hz), 3.99 (2H, dt, 13.5, 13.5, 2.5 Hz), 2.27 – 2.17 (1H, m), 1.48 – 1.44 (1H, m). ^{13}C

NMR (125 MHz) ($CDCl_3$): 140.2, 129.4, 126.5, 126.4, 122.0 (q, $^1J_{CF}$ = 277.9), 100.5, 67.3, 28.3 (q, $^2J_{CF}$ = 38.8). ^{19}F NMR δ: - 65.2.

Figure 9.144: Compound VIII.9



Ethyl (4*R*,5*R*)-1-benzyl-2-(4-methoxyphenyl)-4-phenyl-5-(4-(((Z)-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzylidene)amino)phenyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (VIII.9). To a 250 mL roundbottom flask containing a stir bar and 3-(4-(1,3-dioxan-2-yl)phenyl)-3-(trifluoromethyl)-3*H*-diazirine (0.900 g, 3.3 mmol) was added a 1:2 water:acetone mixture (40 mL) and Amberlyst-15 pellets (0.150 g). The reaction vessel was sealed, flushed with nitrogen, and stirred at room temperature for 72 hours. At this time, the reaction mixture was transferred to a separatory funnel and washed with DCM (20 mL x 1). The organic layer was dried over sodium sulfate and transferred to a 100 mL roundbottom flask with a stir bar. The conversion of the starting material to the product aldehyde, 4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzaldehyde, was assumed to be 100 %, and quantity of material used in the next step was based on this assumption.

Molecular sieves were added (4 angstrom pellets), followed by ethyl (4*R*,5*R*)-5-(4-aminophenyl)-1-benzyl-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (1.5 g, 3.4 mmol). Stirring commenced and once the imidazoline had dissolved, sodium

triacetoxyborohydride (0.840 g, 4.0 mmol) was added in one portion. The reaction vessel was sealed with a septa, flushed with nitrogen, and stirred overnight. The following day, the reaction mixture was transferred to a separatory funnel and quenched with saturated sodium bicarbonate (50 mL x 1). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the crude product as an orange foam. The crude material was purified by silica gel chromatography (3:7:0.01 ethyl acetate:hexanes:TEA, R_f = 0.3). Analytically pure material can be obtained in this manner, but a small portion (50 mg) was purified by Autocolumn (product eluted in 100 % ethyl acetate in a method that ramped from 5 % to 100 % ethyl acetate:hexanes, method MG-9-67). The combined yield obtained was 200 mg (8 % from starting aldehyde) of material as a yellow oil. ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.49 (1H, s), 7.96 (2H, d, *J* = 8.0 Hz), 7.75 (4H, d, *J* = 8.5 Hz), 7.43 (2H, d, *J* = 8.0 Hz), 7.36 – 7.29 (5H, m), 7.24 (2H, d, *J* = 8.5 Hz), 7.15 – 7.06 (3H, m), 7.09 (2H, 9.0 Hz), 6.77 (2H, d, *J* = 7.5 H), 4.91 (1H, s), 4.67 (1H, d, *J* = 16.0 Hz), 3.87 (3H, s), 3.86 (1H, d, *J* = 16.0 Hz). 3.79 – 3.74 (1H, m), 3.72 – 3.65 (1H, m), 0.86 (3H, t, *J* = 6.5 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$): 170.9, 165.2, 161.2, 158.7, 151.3, 144.2, 137.1, 136.7, 136.4, 132.0, 130.4, 129.1, 129.0, 128.4, 128.0, 127.4, 127.3, 127.2, 126.8, 126.7, 126.7, 123.0, 122.7, 120.9, 120.8 (q, $^{1}J_{CF}$ = 276.1), 113.9, 82.7, 73.4, 61.0, 55.3, 48.9, 13.6 (q, $^{2}J_{CF}$ = 39.8). ^{19}F NMR δ: – 64.8. HRMS calc'd for [M + H] = 702.2692, observed = 702.2680. IR (NaCl, DCM): 3033, 2935, 2099, 1728, 1613, 1514, 1447, 1419, 1343, 1252, 1231, 1187, 1157, 1092, 1069, 1031, 938, 830, 737, 697.

APPENDIX

Figure 10.1: ^{1}H and ^{13}C Spectra of Compound II.4

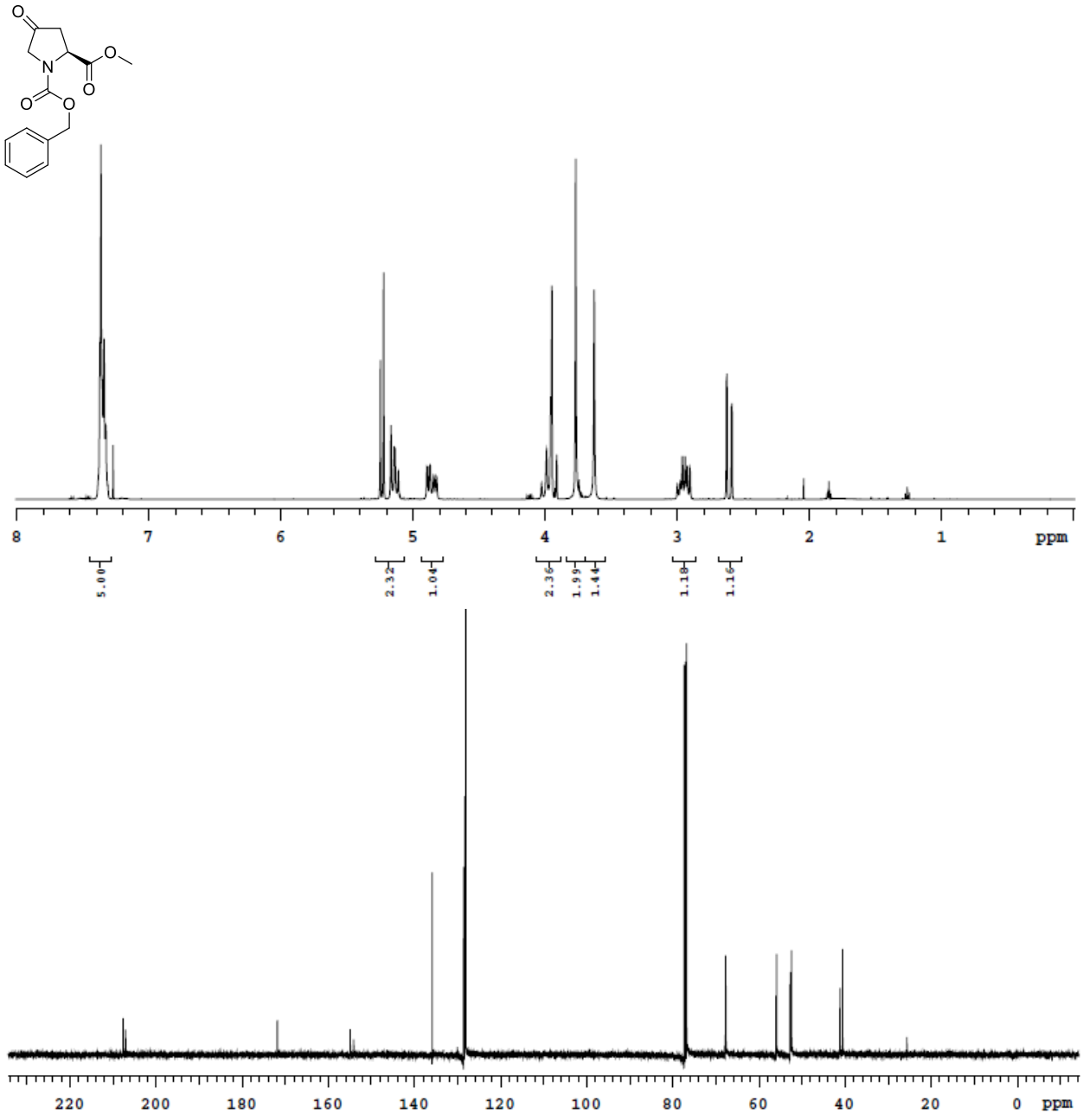


Figure 10.2: ^{1}H and ^{13}C Spectra of Compound II.5a

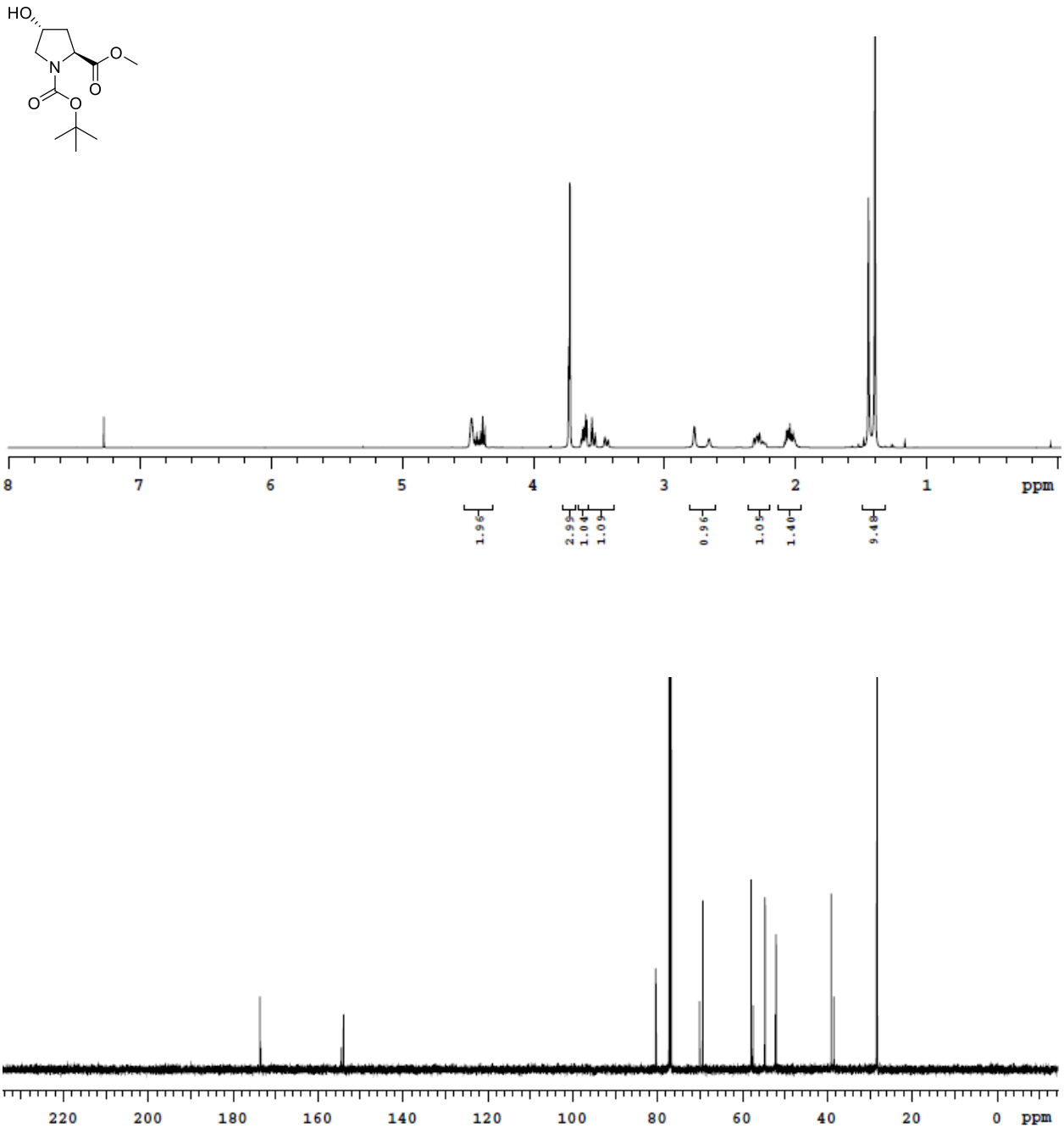


Figure 10.3: ^{1}H and ^{13}C Spectra of Compound II.5b

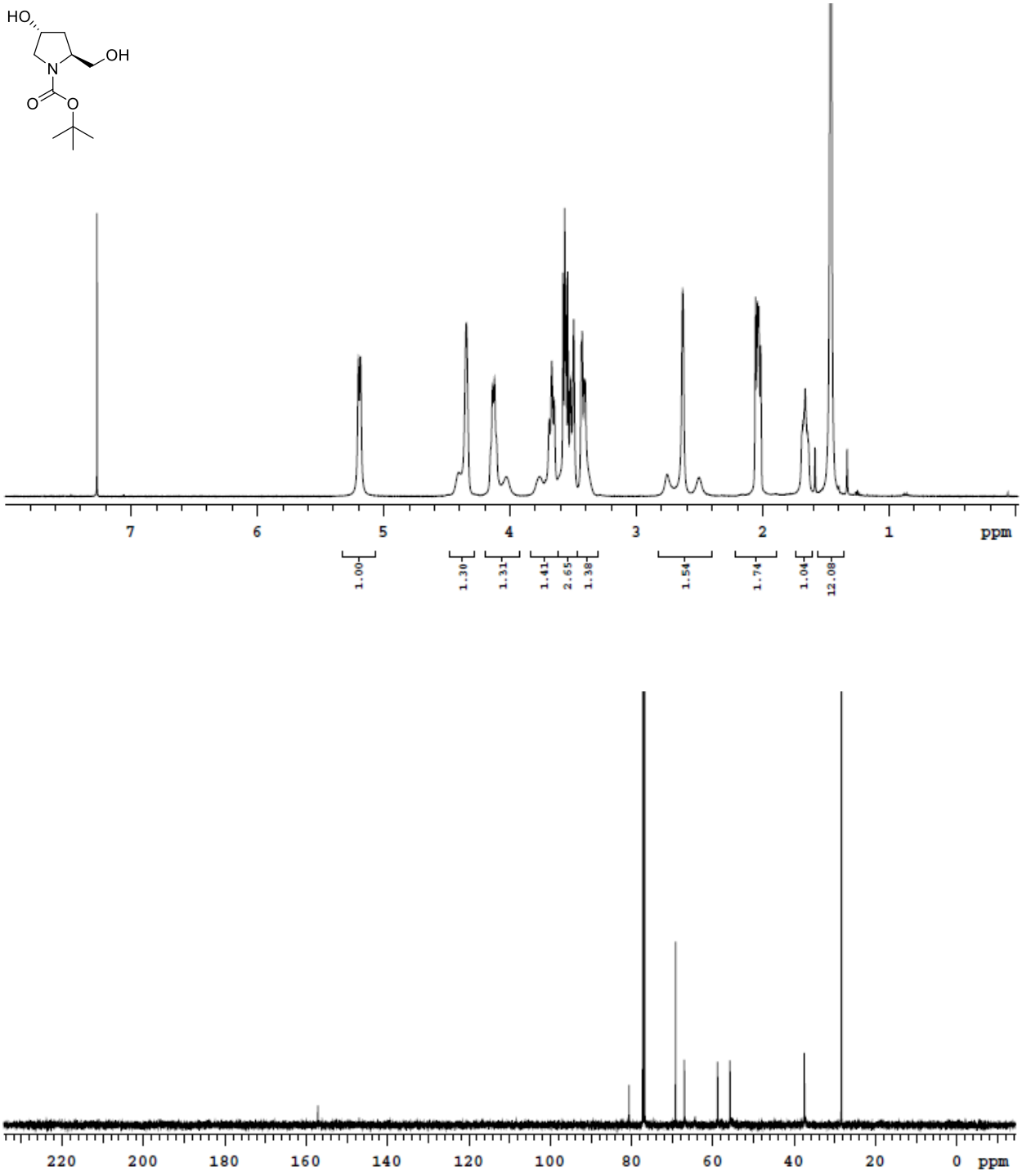


Figure 10.4: gCOSY Spectra of Compound II.5b

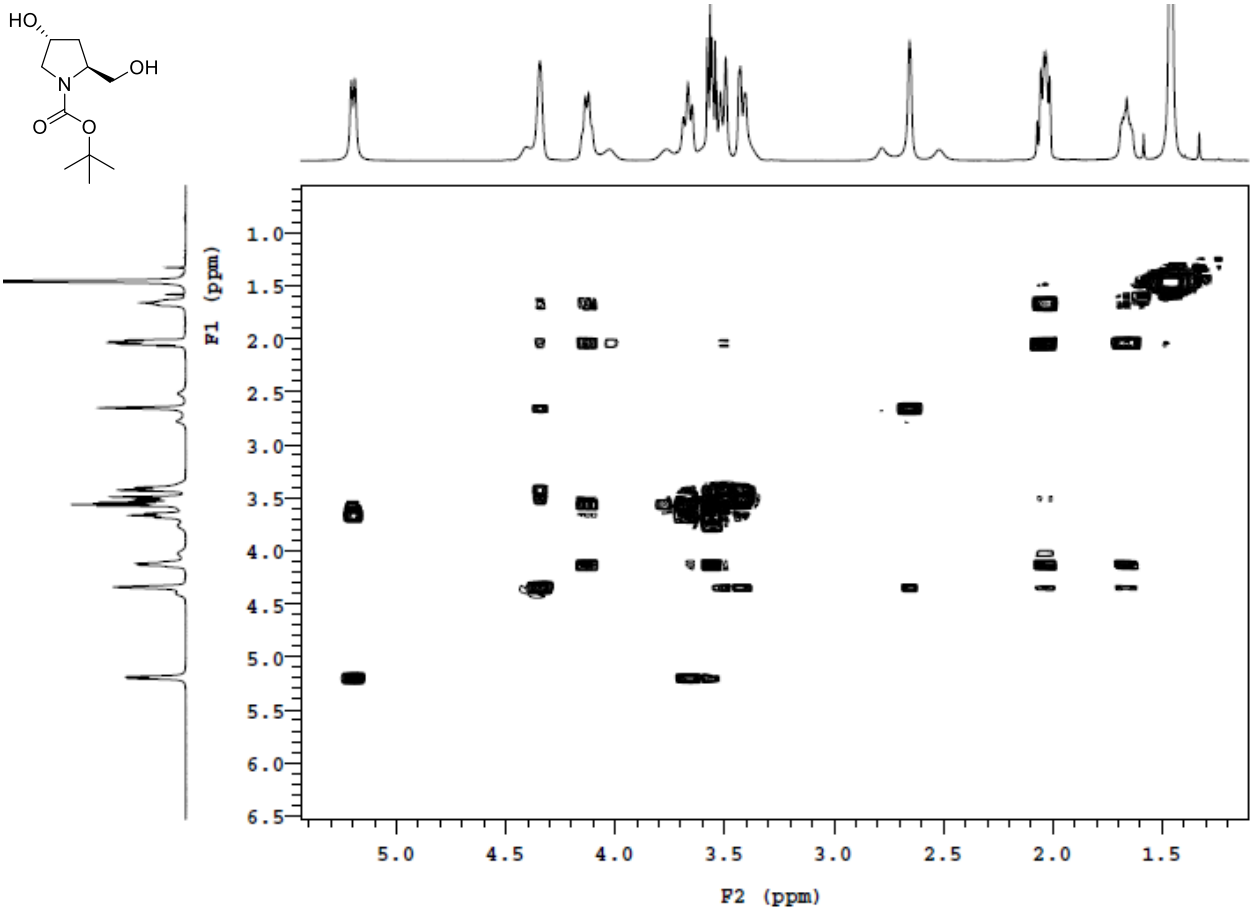


Figure 10.5: gHMQC Spectra of Compound II.5b

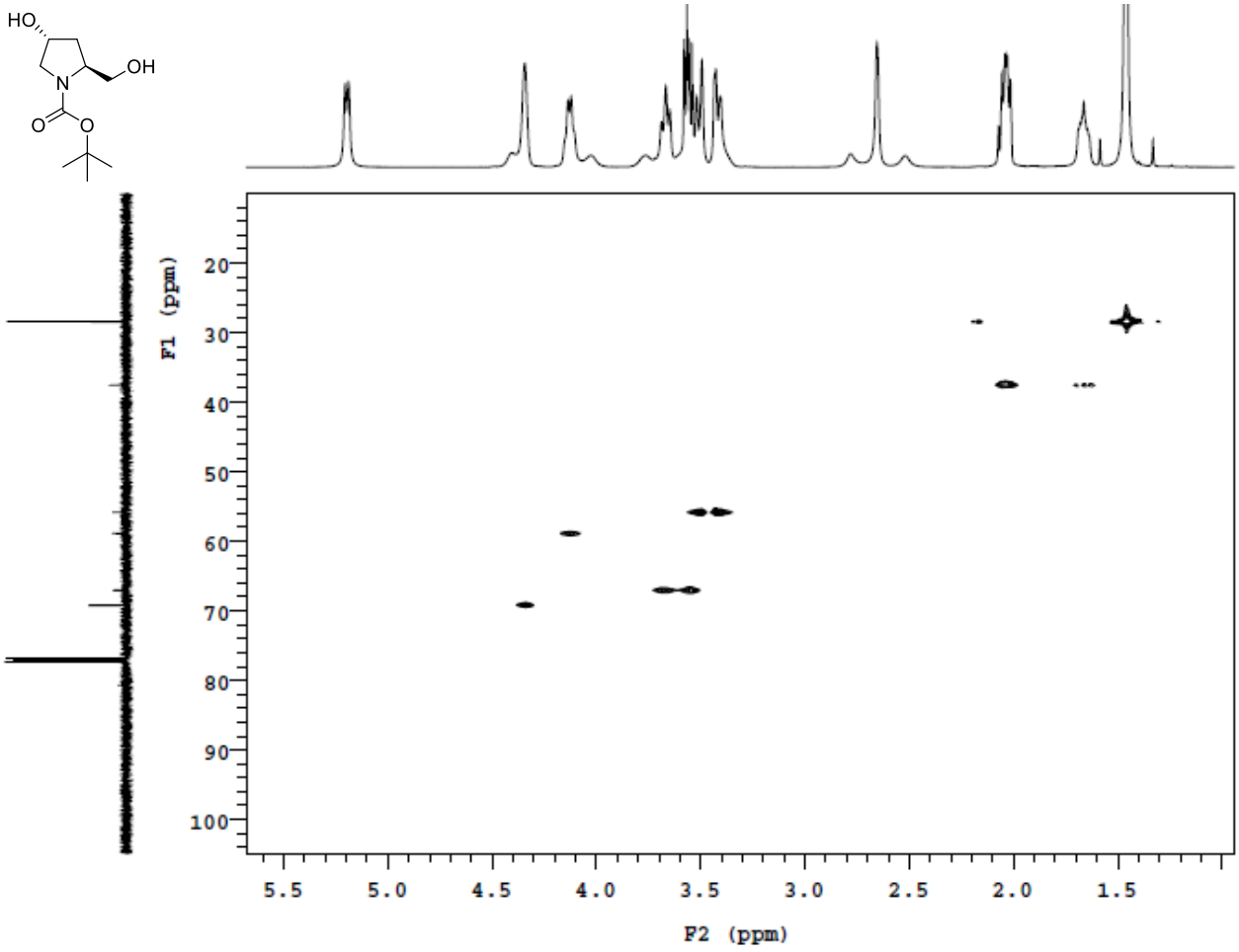


Figure 10.6: ^{1}H and ^{13}C Spectra of Compound II.5

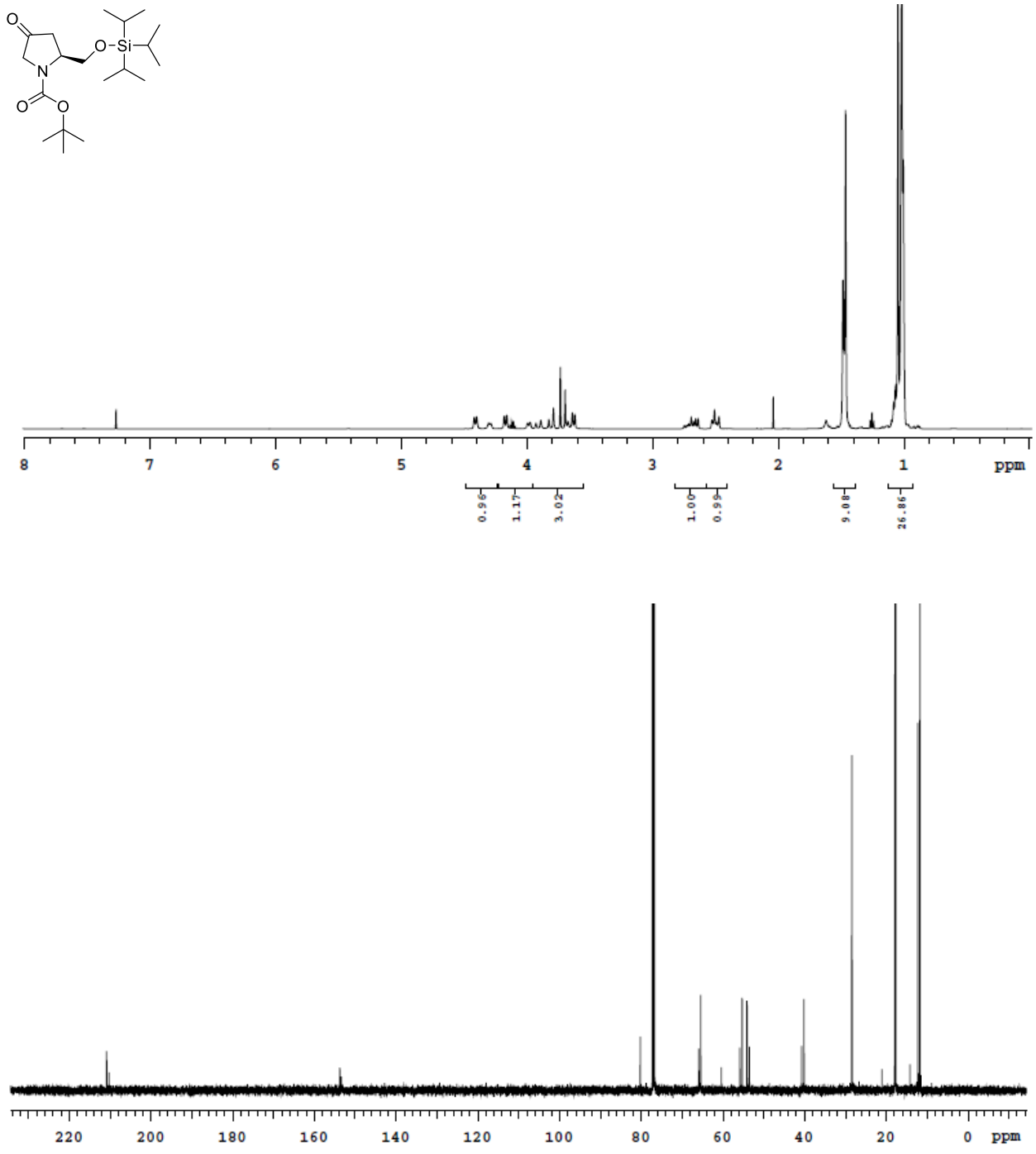


Figure 10.7: ^{1}H and ^{13}C Spectra of Compound II.11

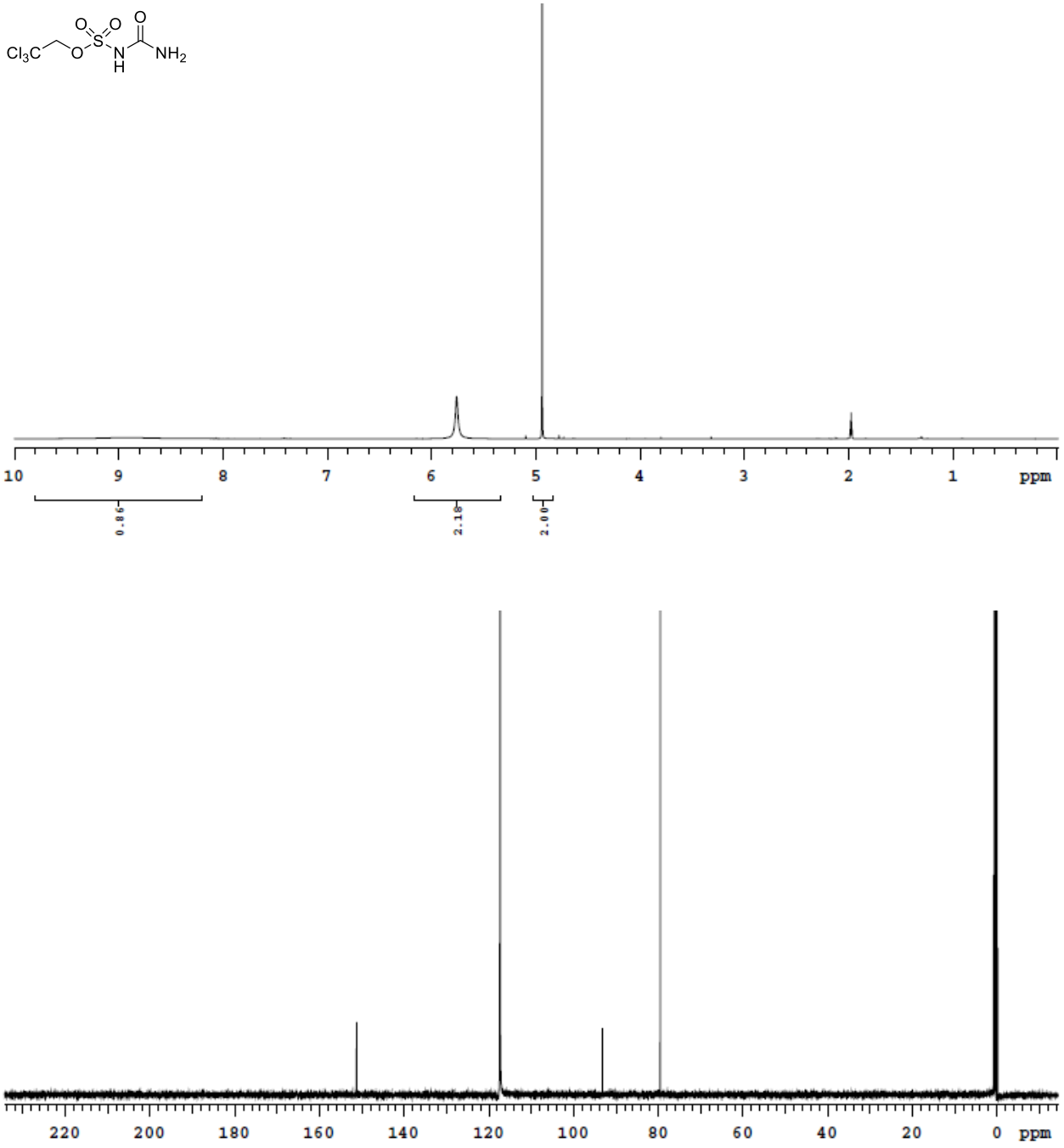


Figure 10.8: ^{1}H and ^{13}C Spectra of Compound II.12

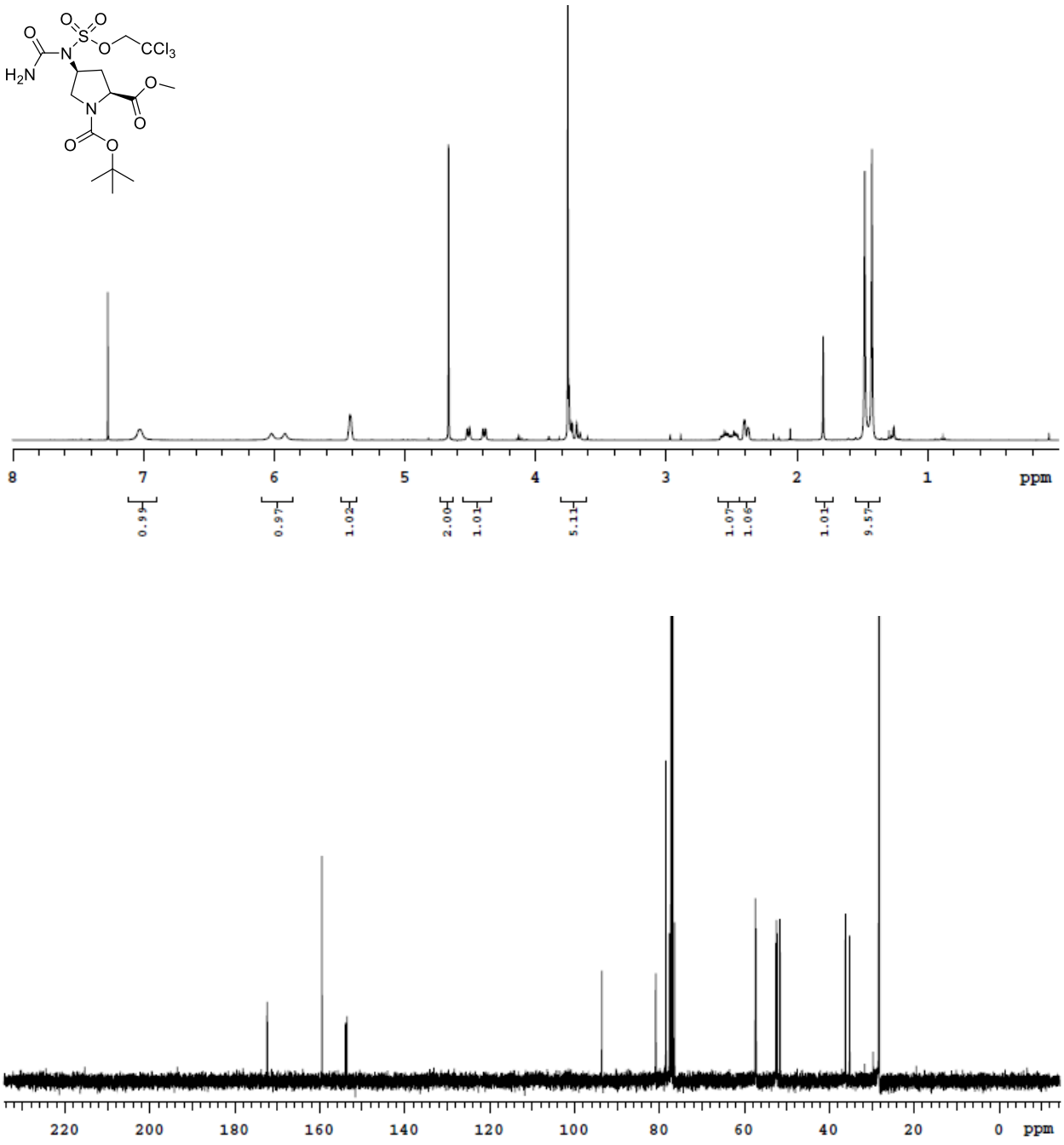


Figure 10.9: ^{1}H and ^{13}C Spectra of Compound II.13

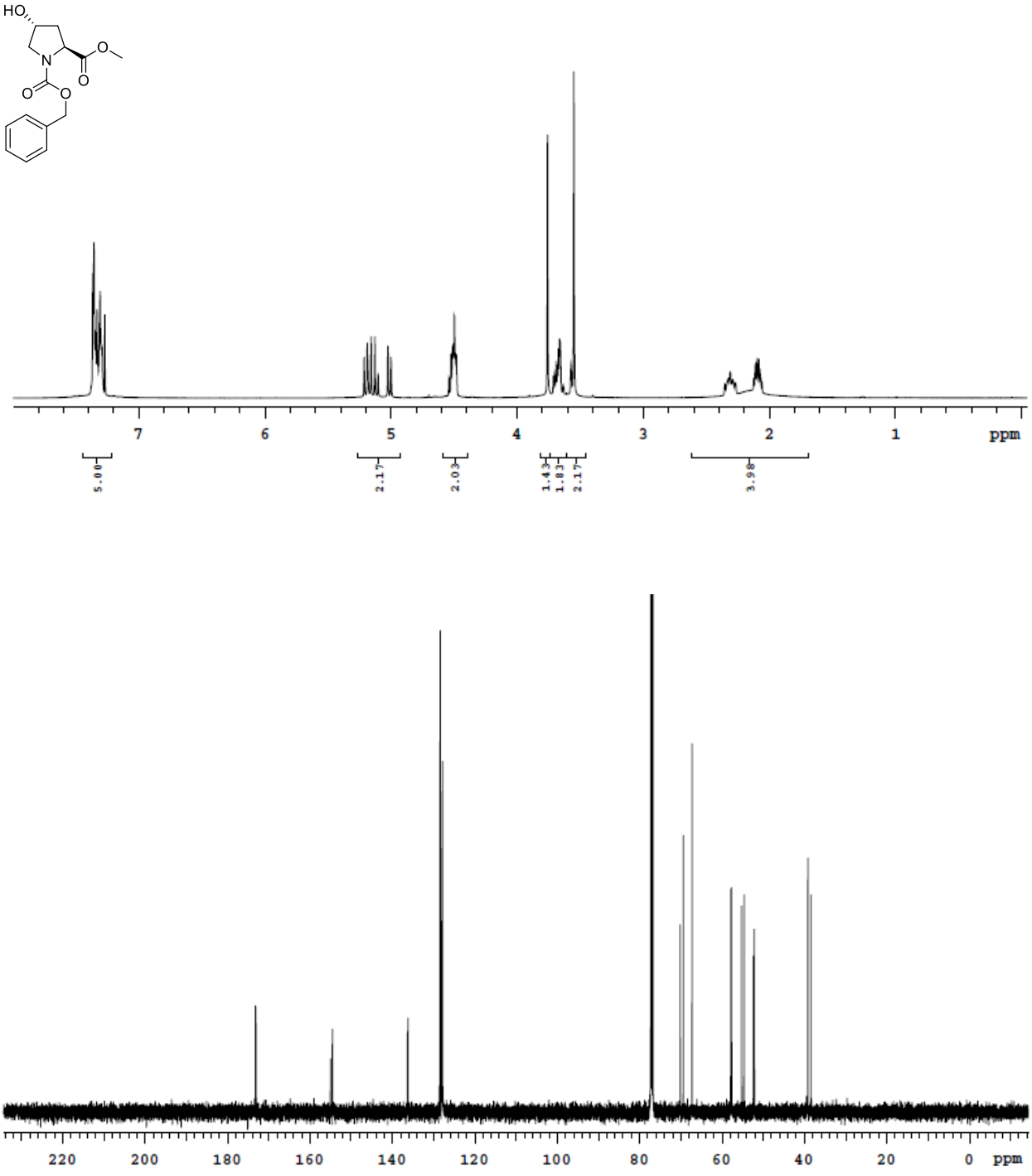


Figure 10.10: ^{1}H and ^{13}C Spectra of Compound II.14

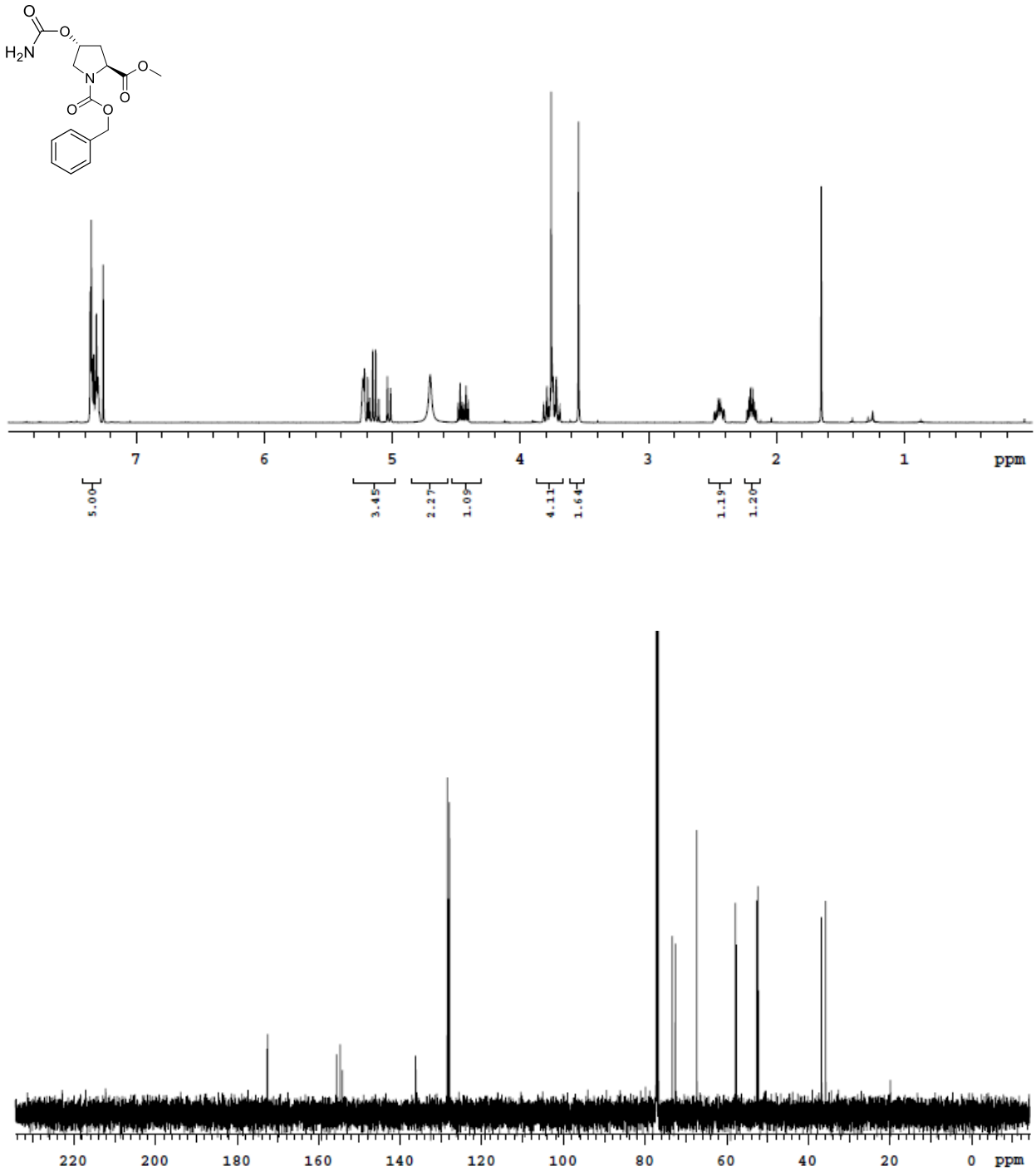


Figure 10.11: ^{1}H and ^{13}C Spectra of Compound II.15a

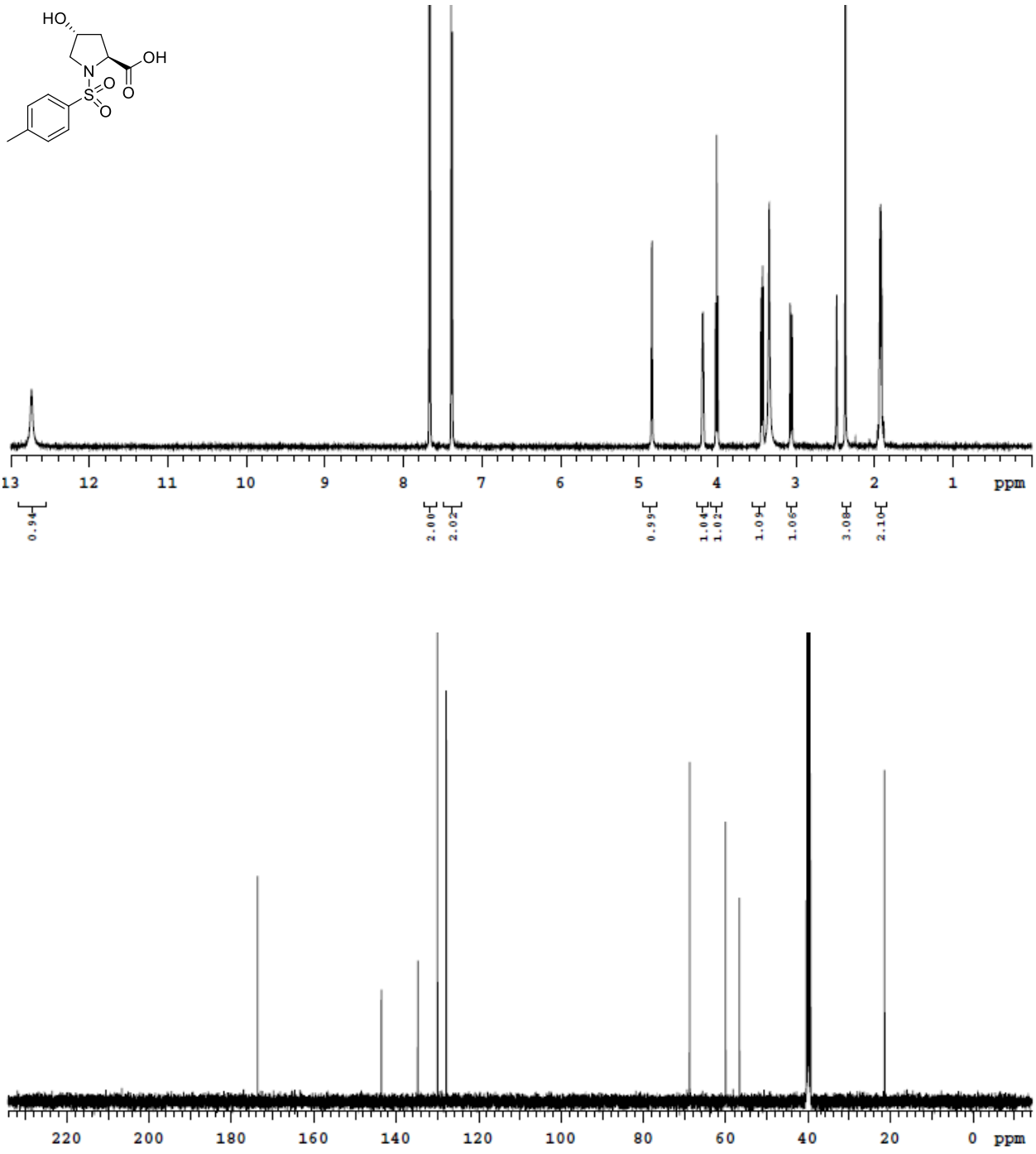


Figure 10.12: ^{1}H and ^{13}C Spectra of Compound II.15b

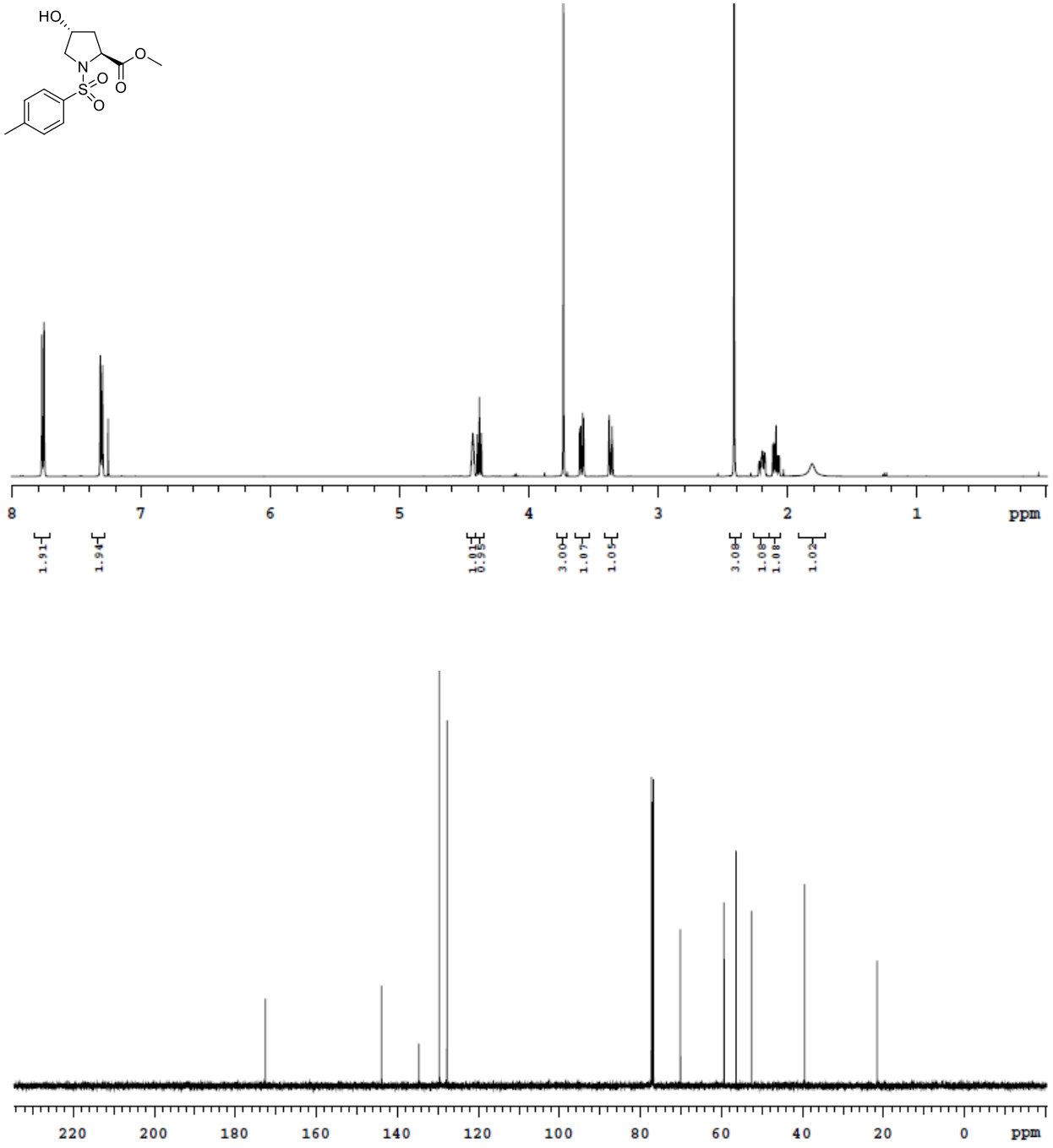


Figure 10.13: ^{1}H and ^{13}C Spectra of Compound II.16

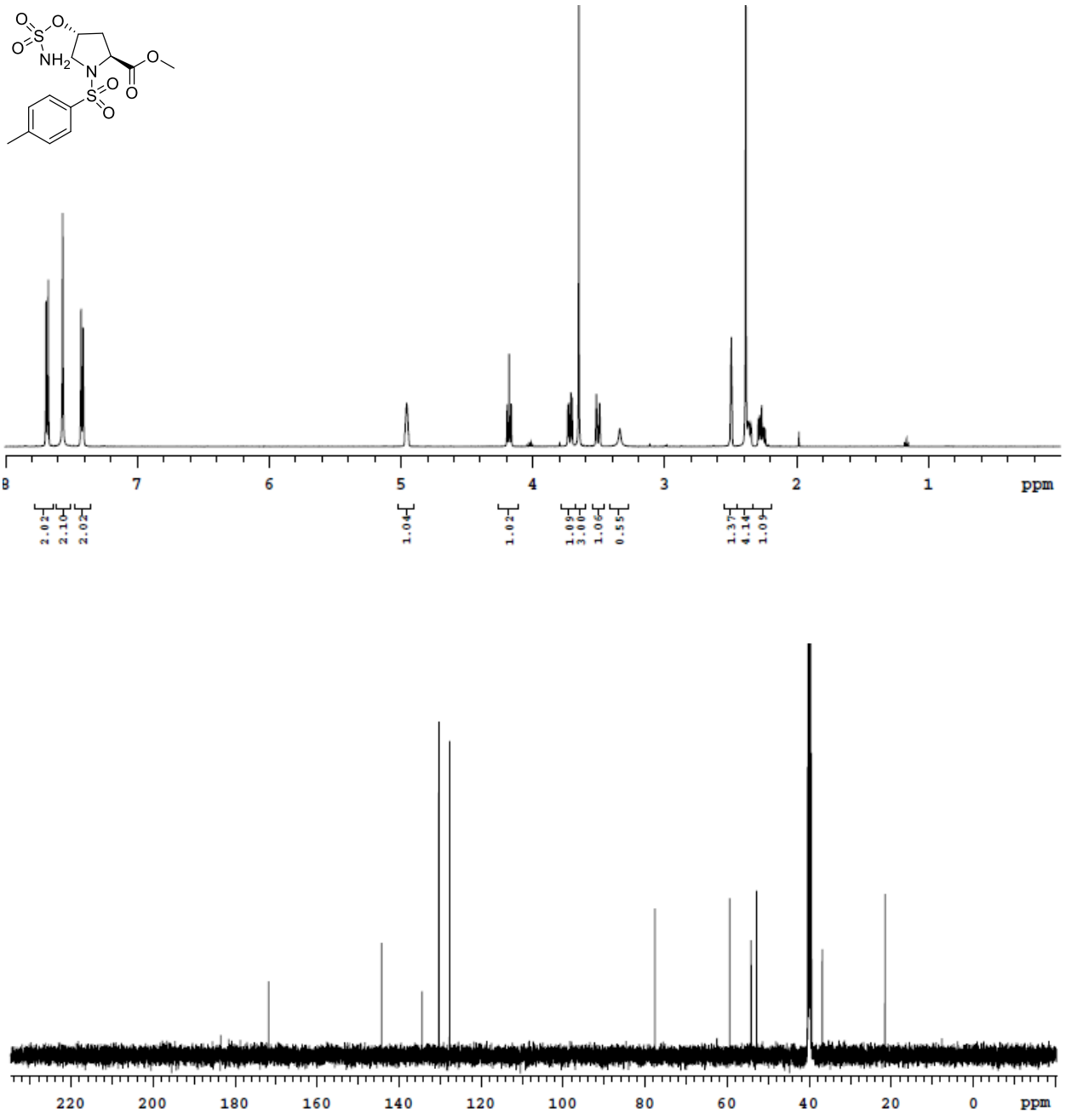


Figure 10.14: ^{1}H and ^{13}C Spectra of Compound II.7

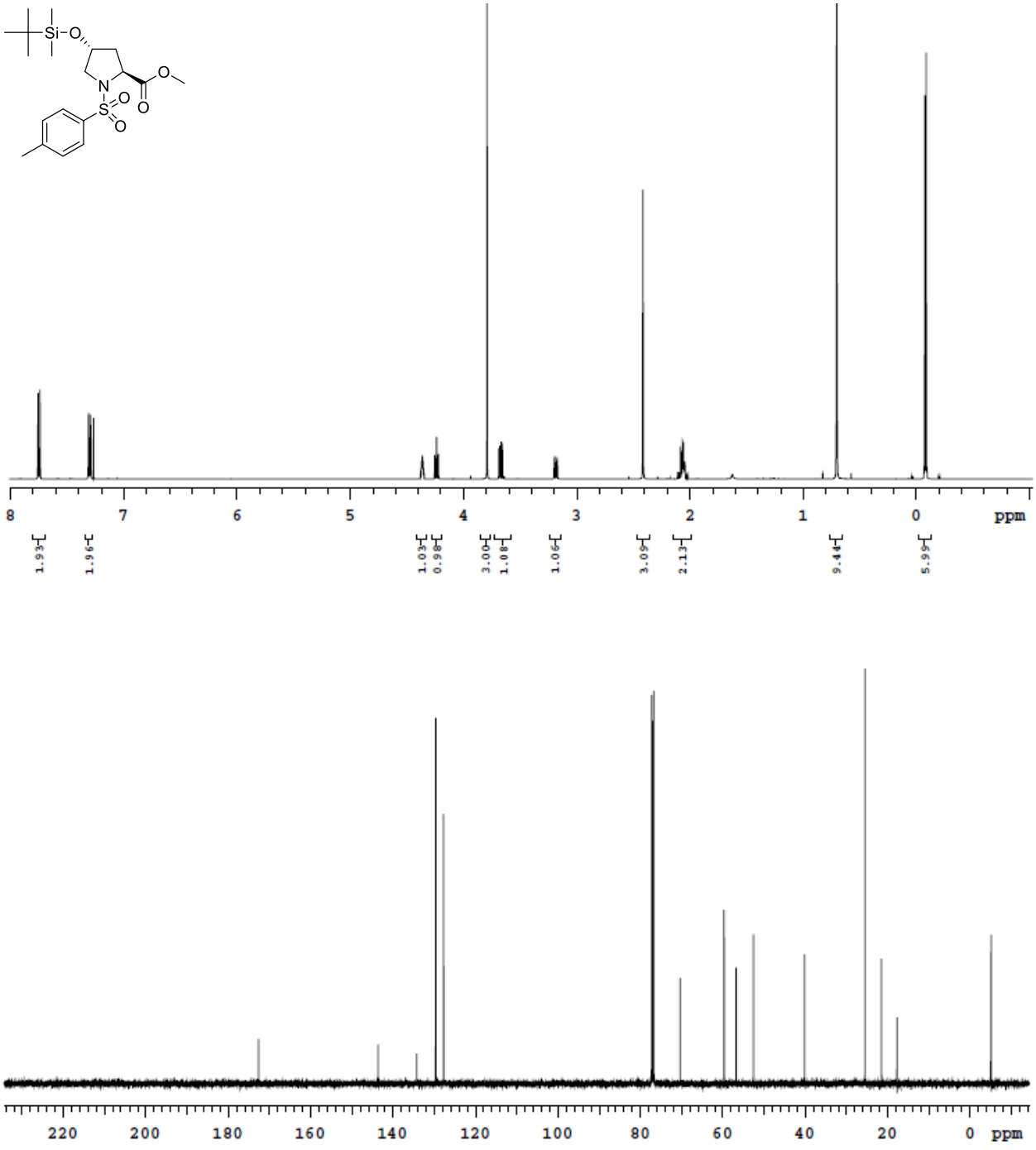


Figure 10.15: ^{1}H and ^{13}C Spectra of Compound II.7a

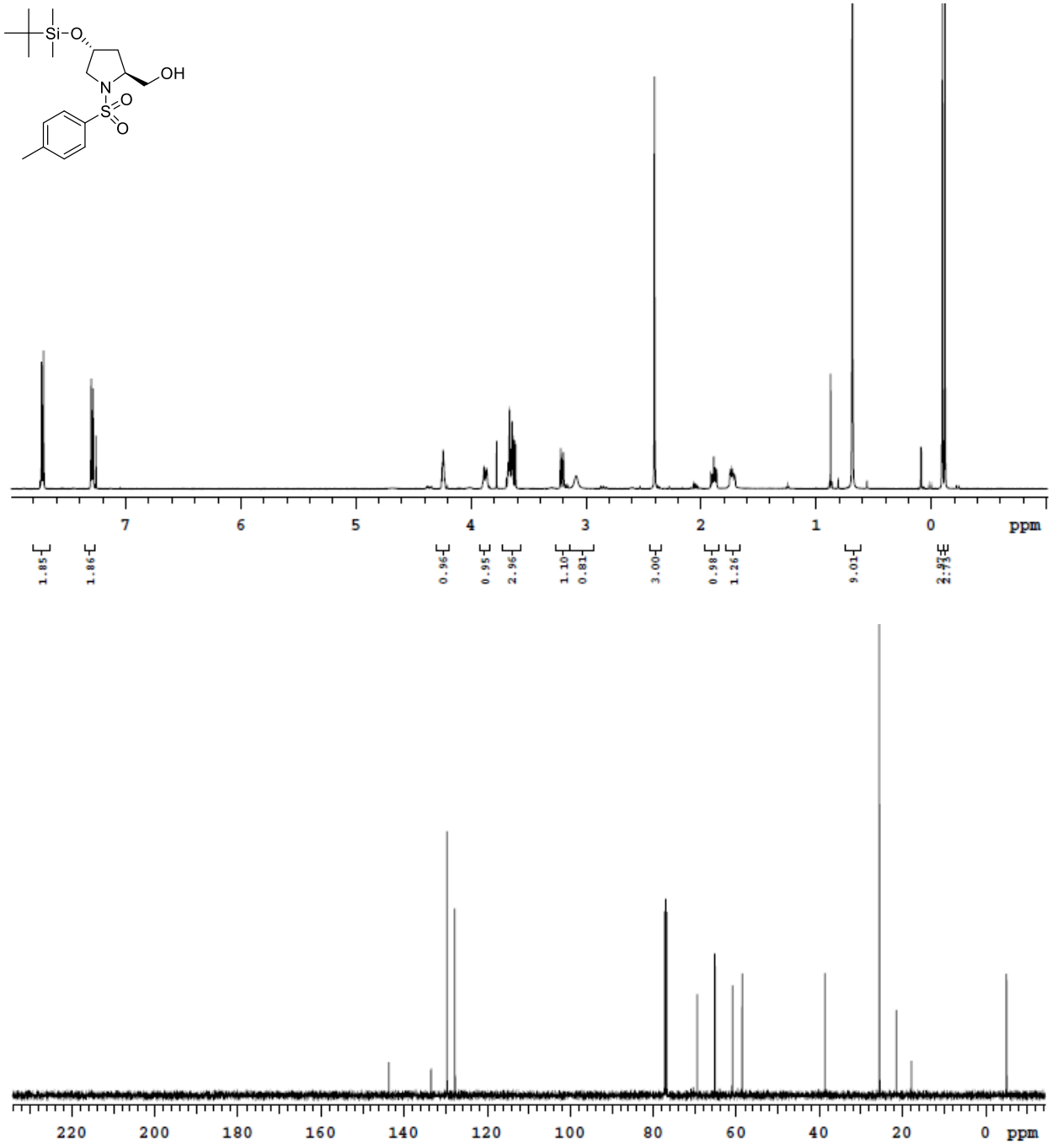


Figure 10.16: ^{1}H and ^{13}C Spectra of Compound II.17a

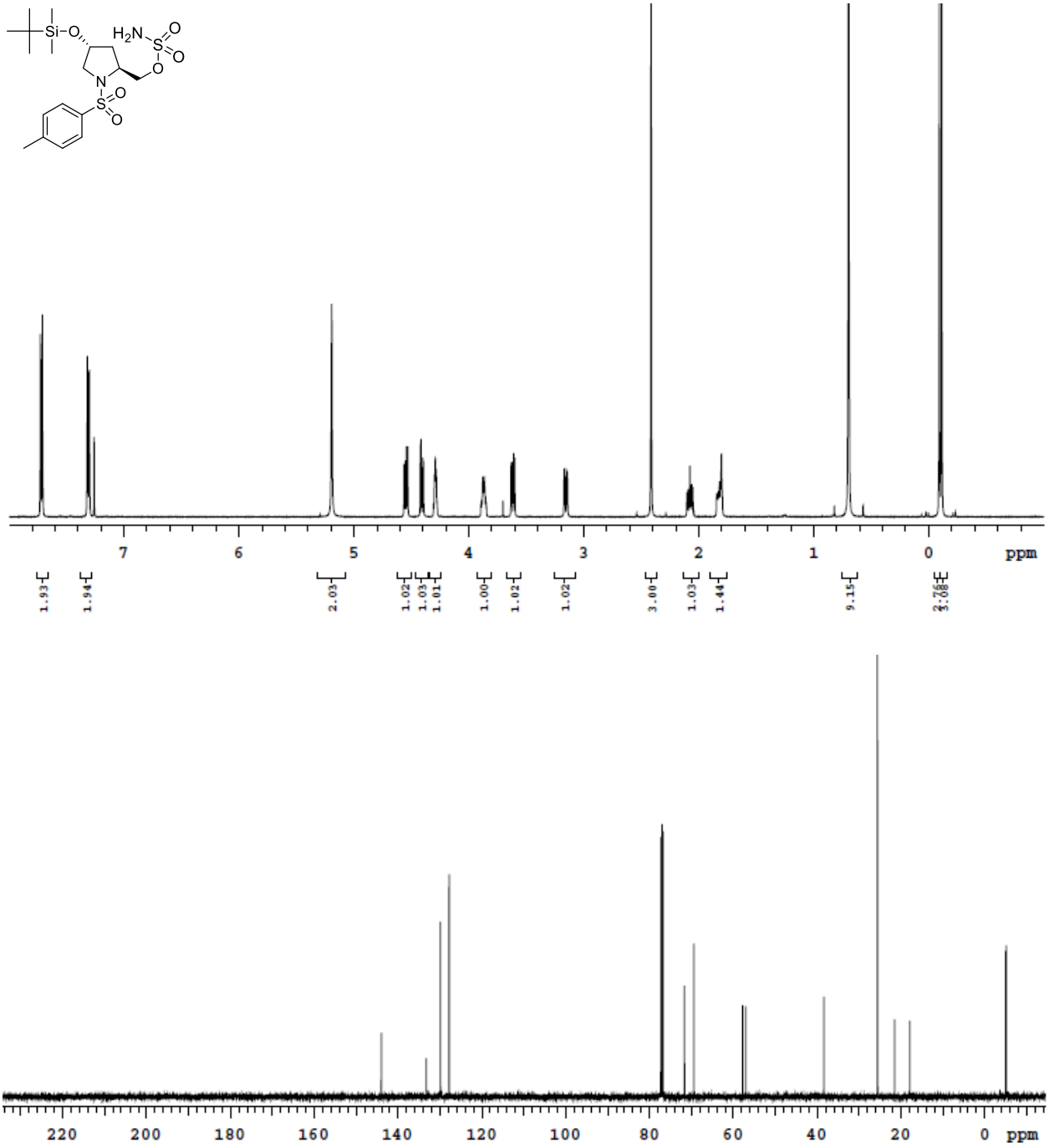


Figure 10.17: ^{1}H and ^{13}C Spectra of Compound II.6

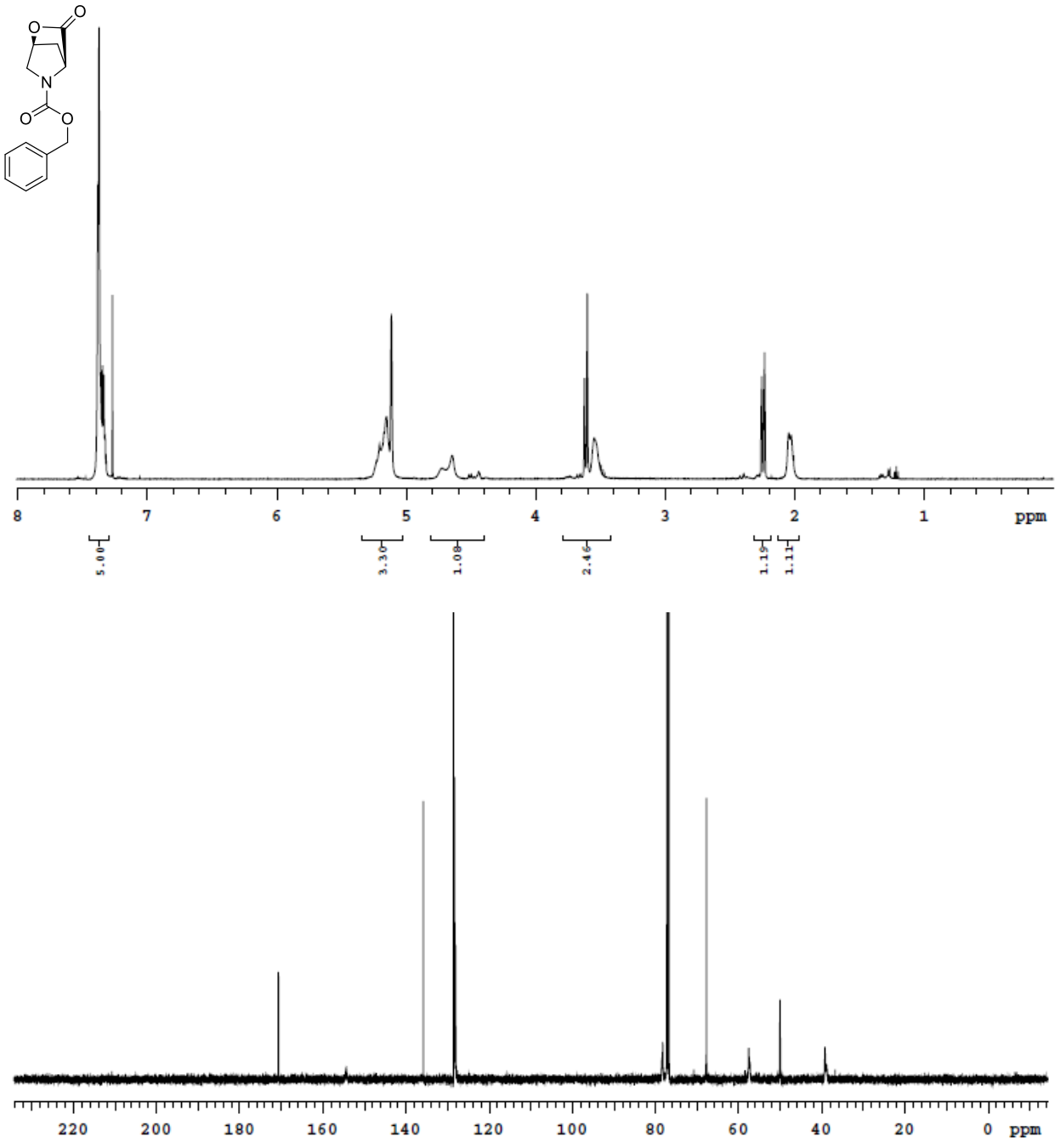


Figure 10.18: ^{1}H and ^{13}C Spectra of Compound II.18

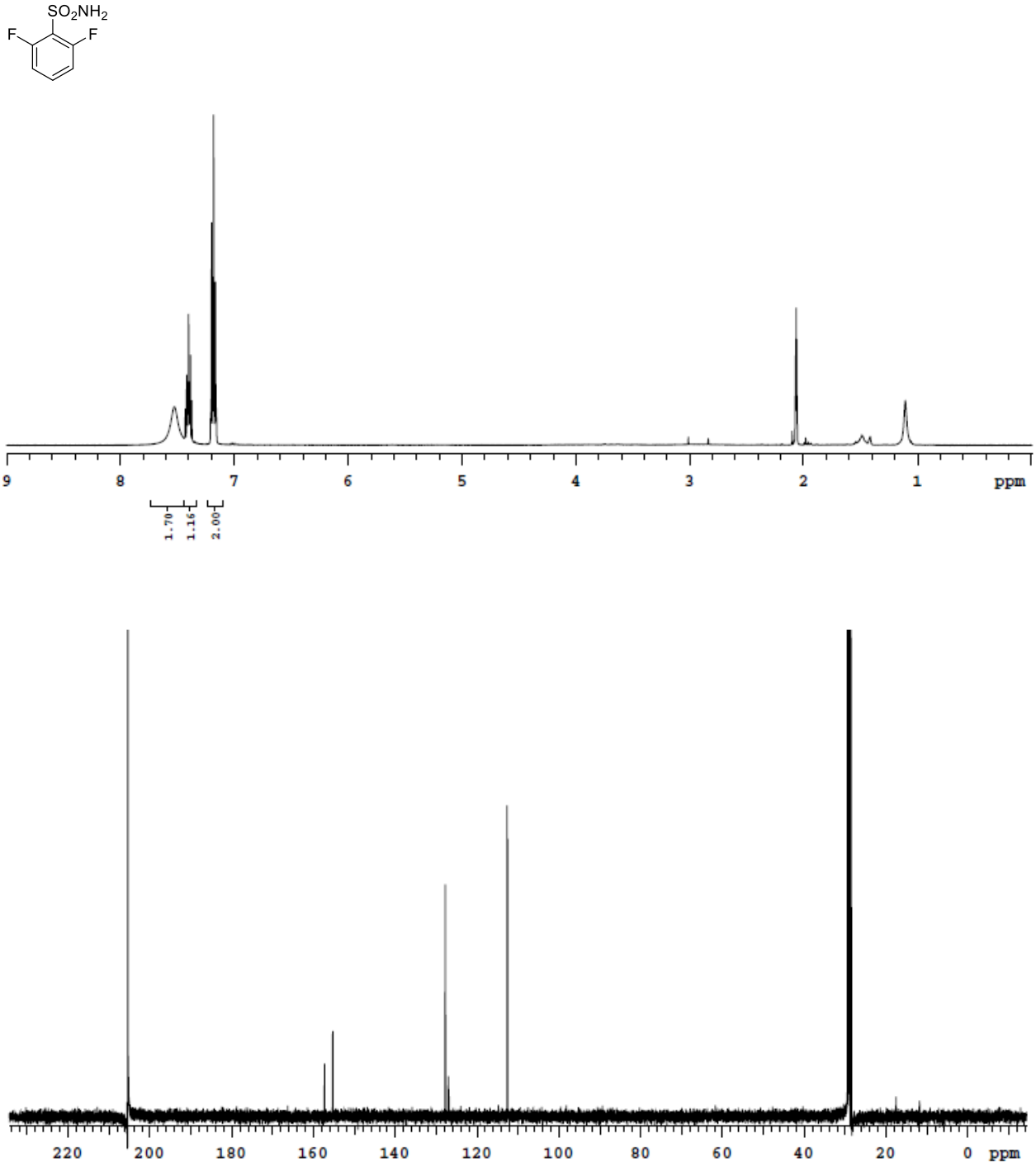


Figure 10.19: ^{1}H and ^{13}C Spectra of Compound II.19

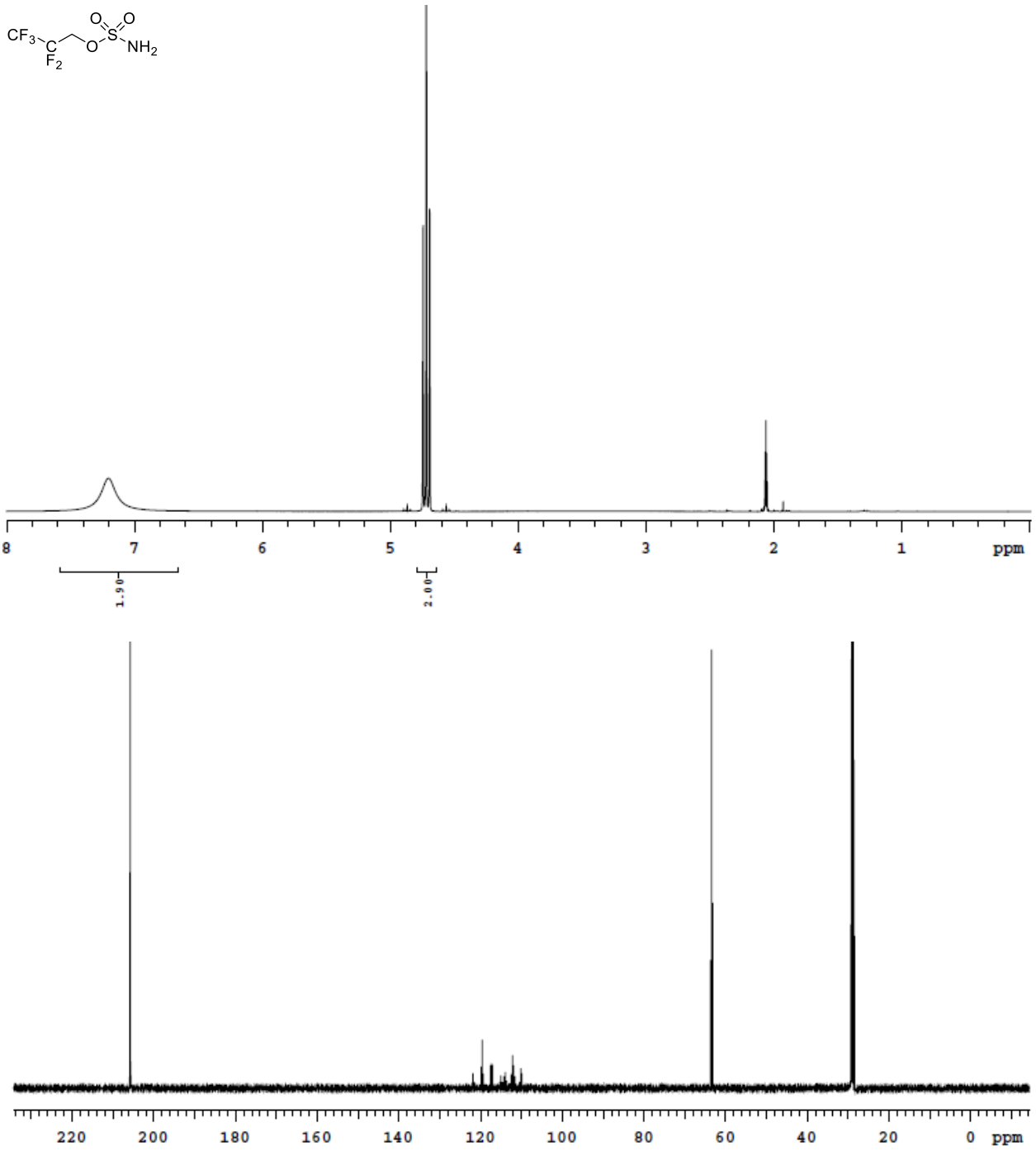


Figure 10.20: ^{1}H and ^{13}C Spectra of Compound II.20a

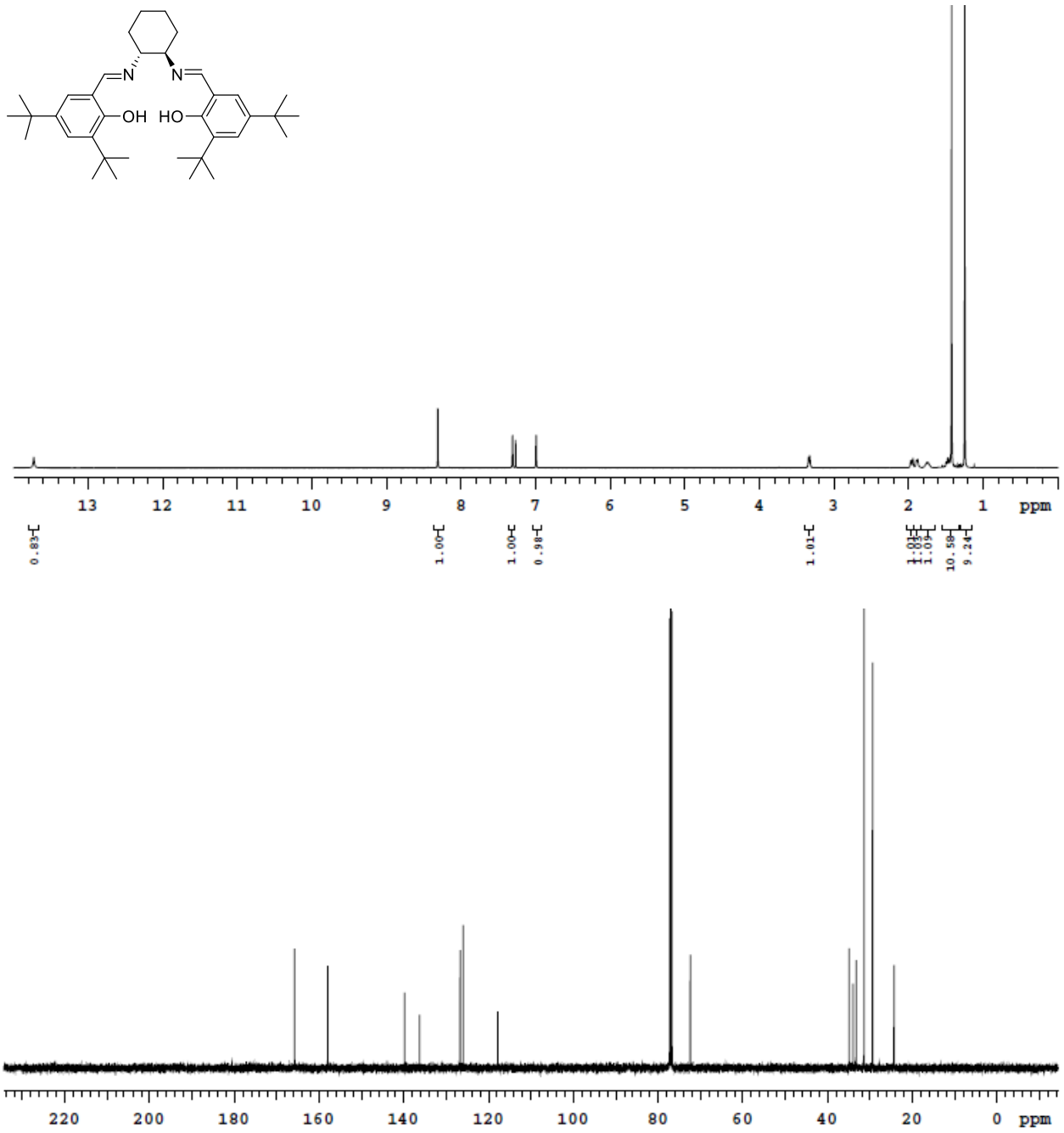


Figure 10.21: ^{1}H and ^{13}C Spectra of Compound II.21a

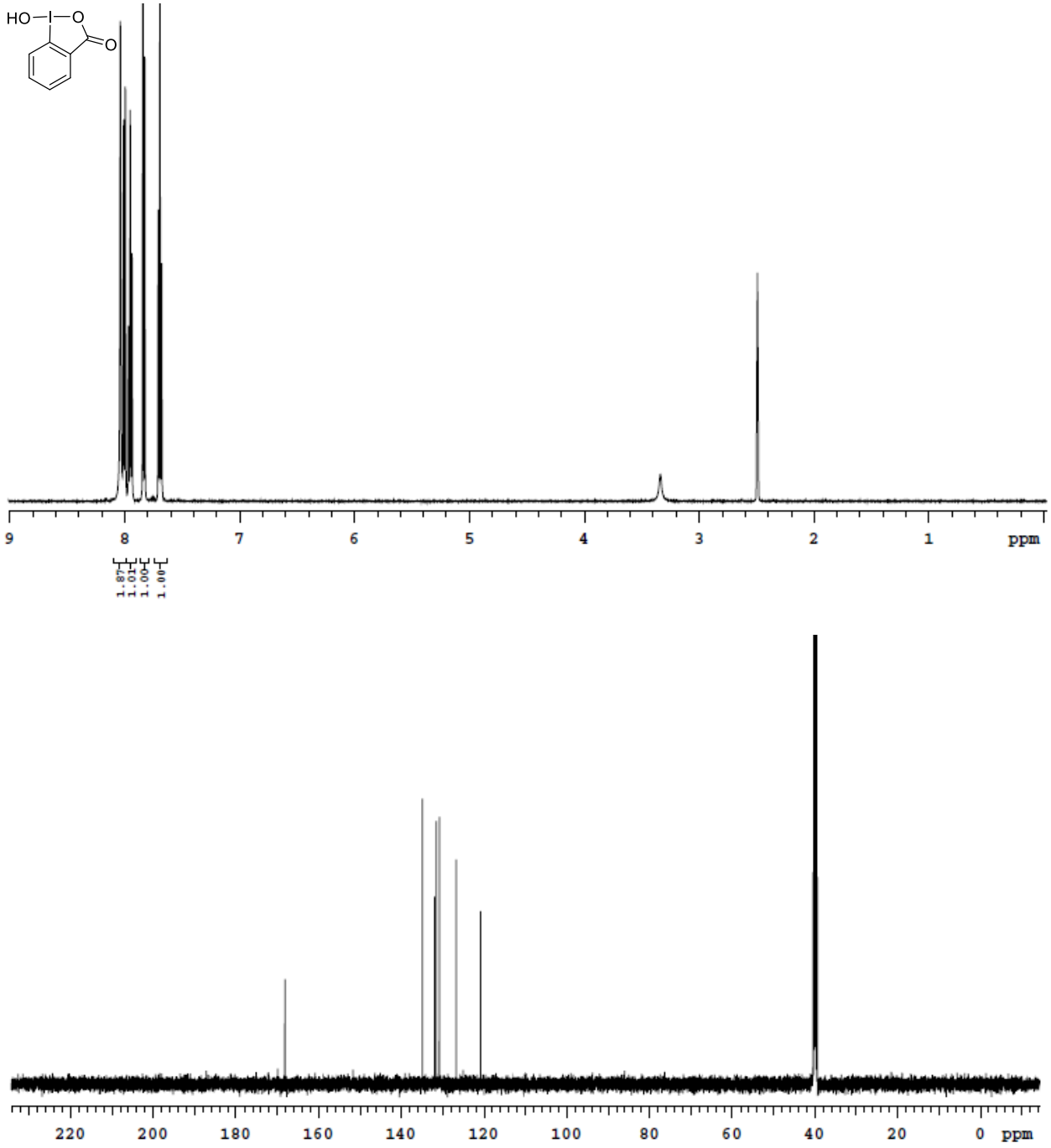


Figure 10.22: ^{1}H and ^{13}C Spectra of Compound II.21

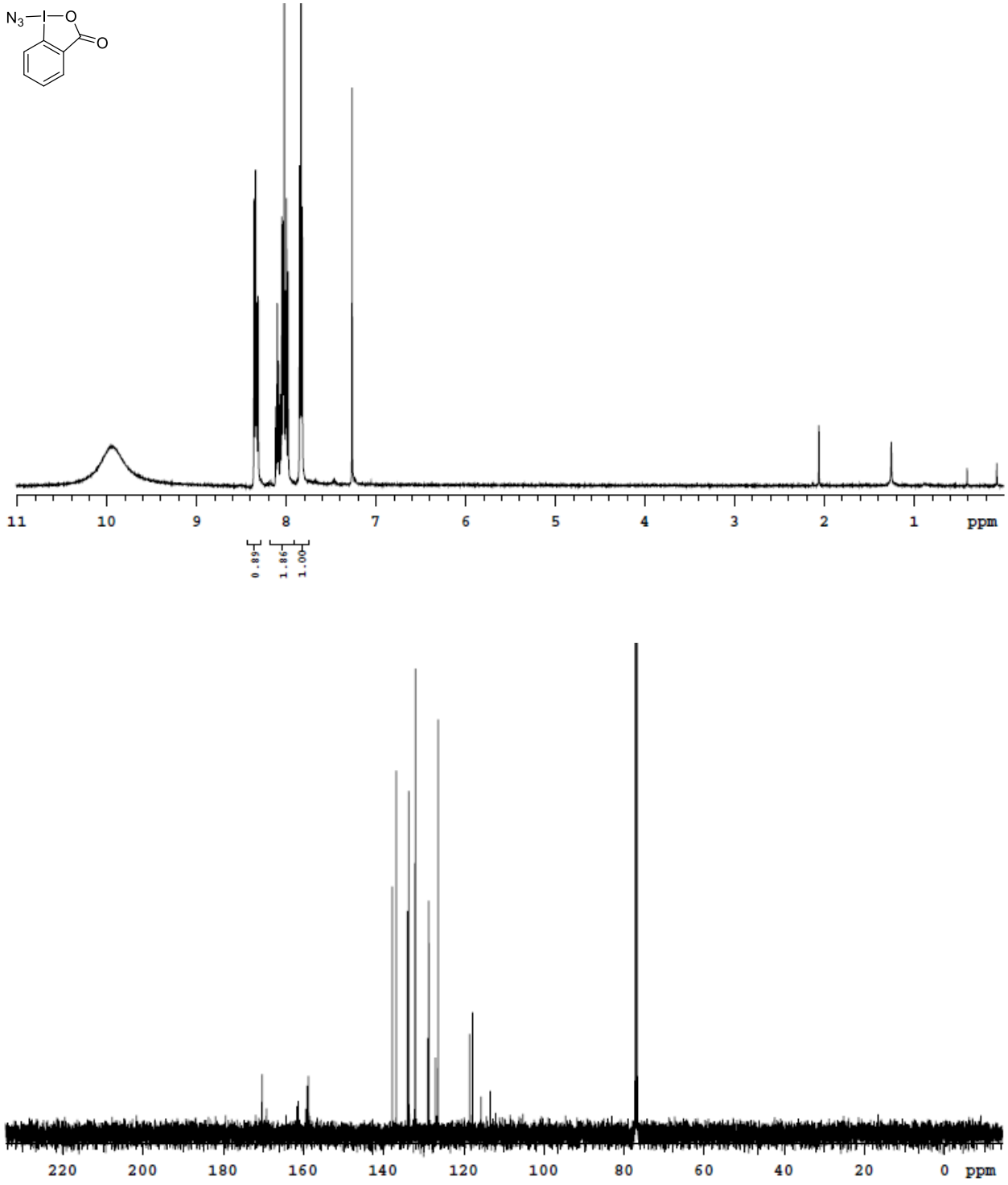


Figure 10.23: ^{1}H and ^{13}C Spectra of Compound II.22

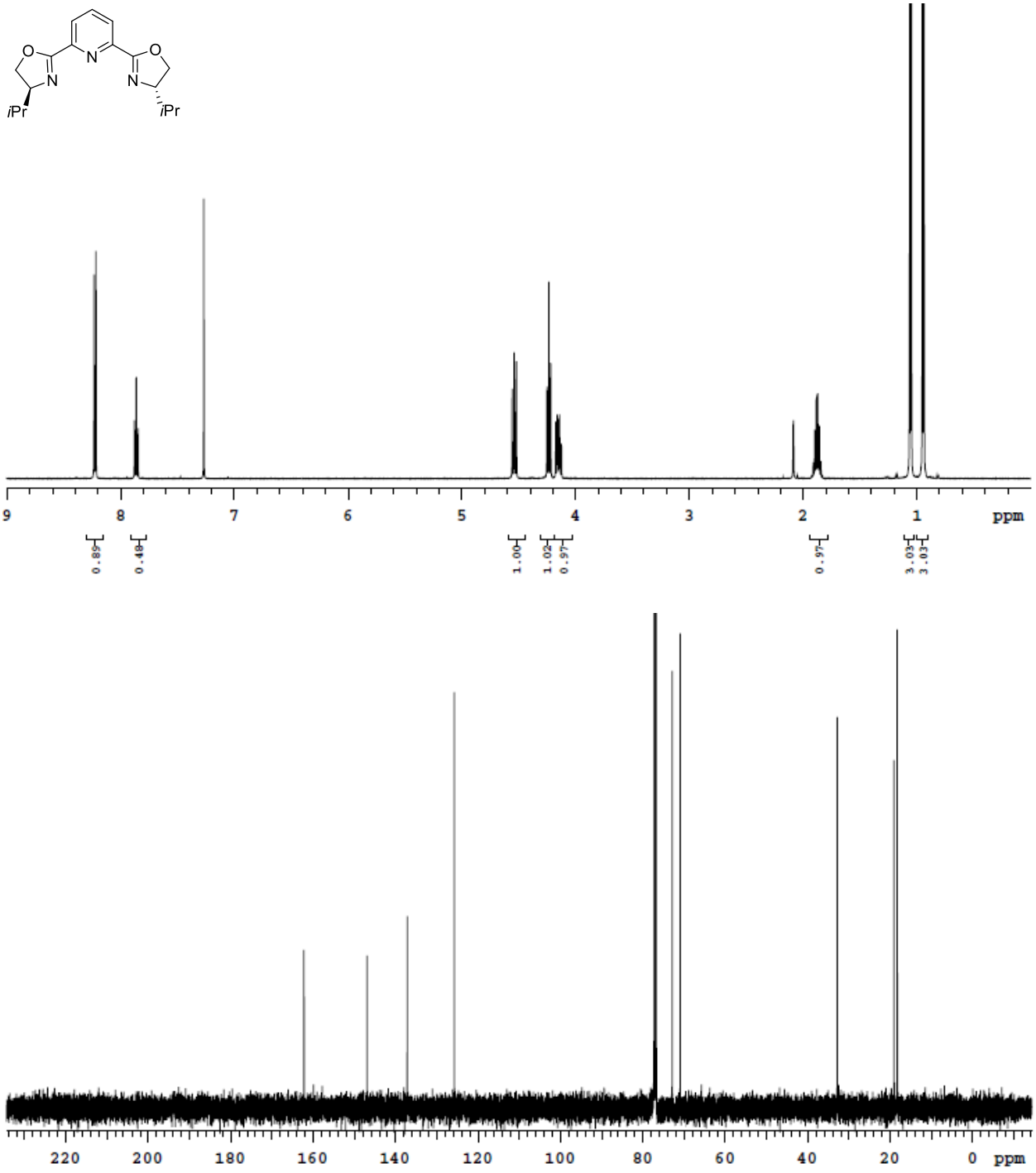


Figure 10.24: ^{1}H and ^{13}C Spectra of Compound III.2a

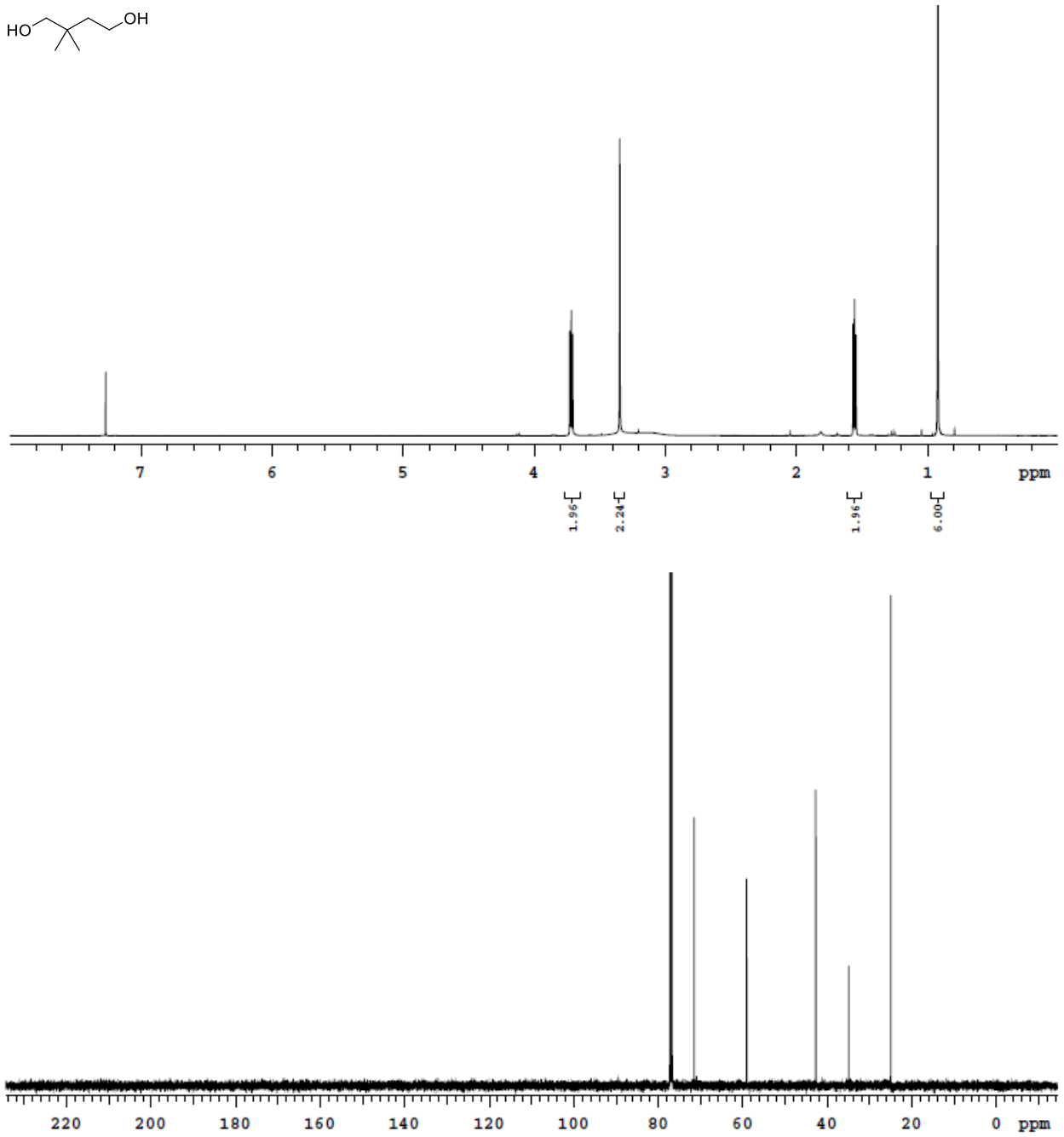


Figure 10.25: ^{1}H and ^{13}C Spectra of Compound III.2b

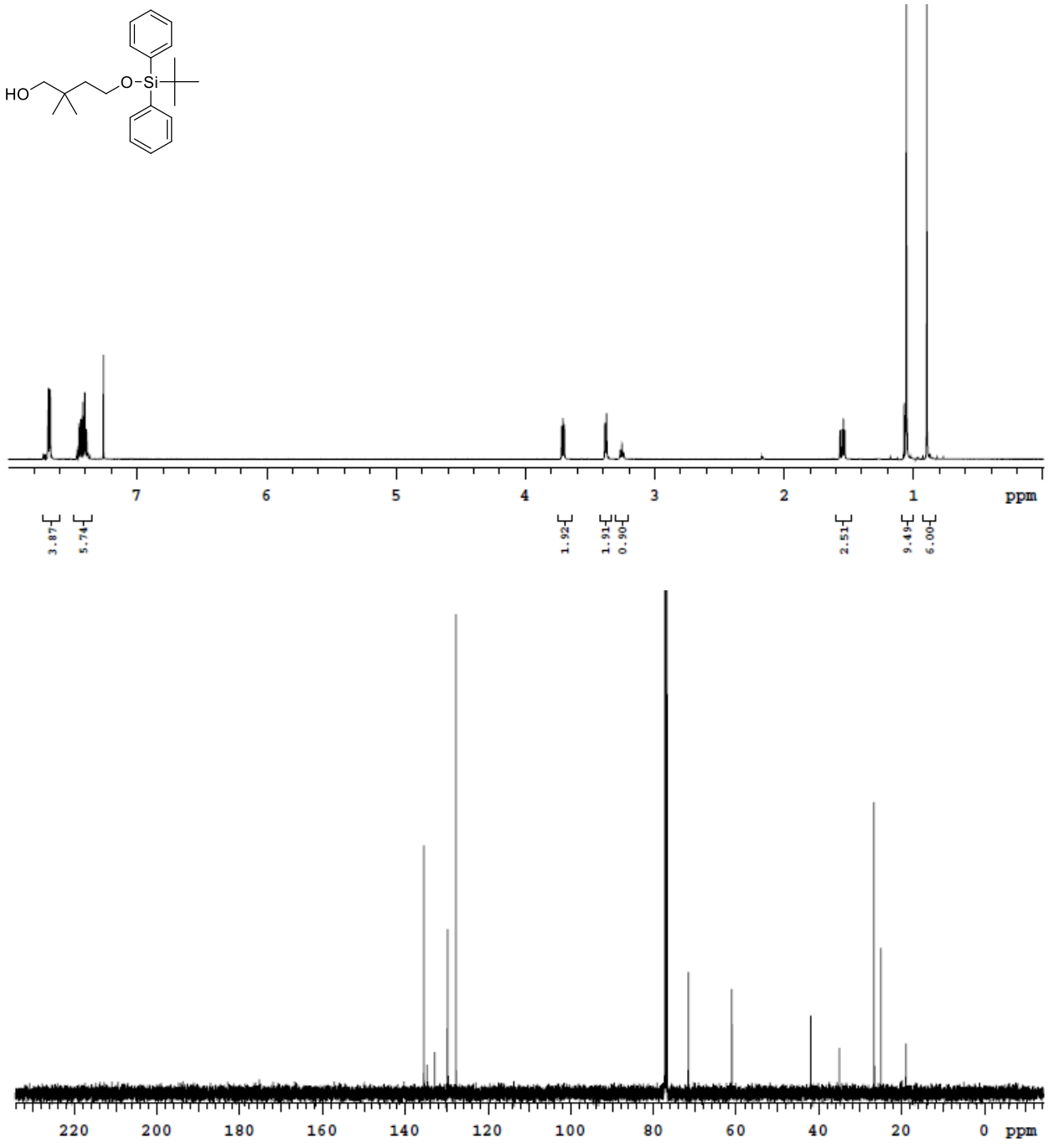


Figure 10.26: ^{1}H and ^{13}C Spectra of Compound III.2

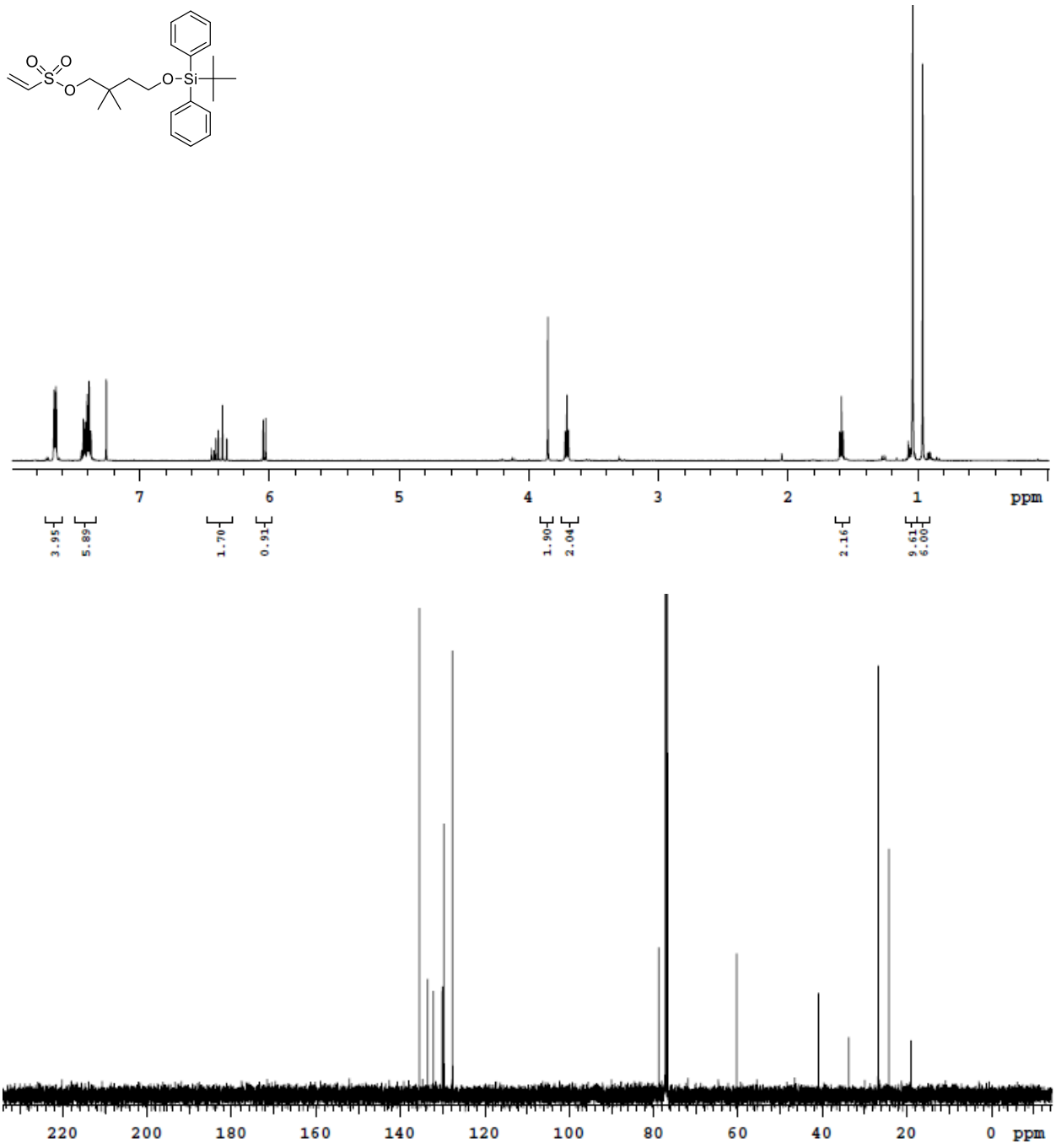


Figure 10.27: ^{1}H and ^{13}C Spectra of Compound III.3

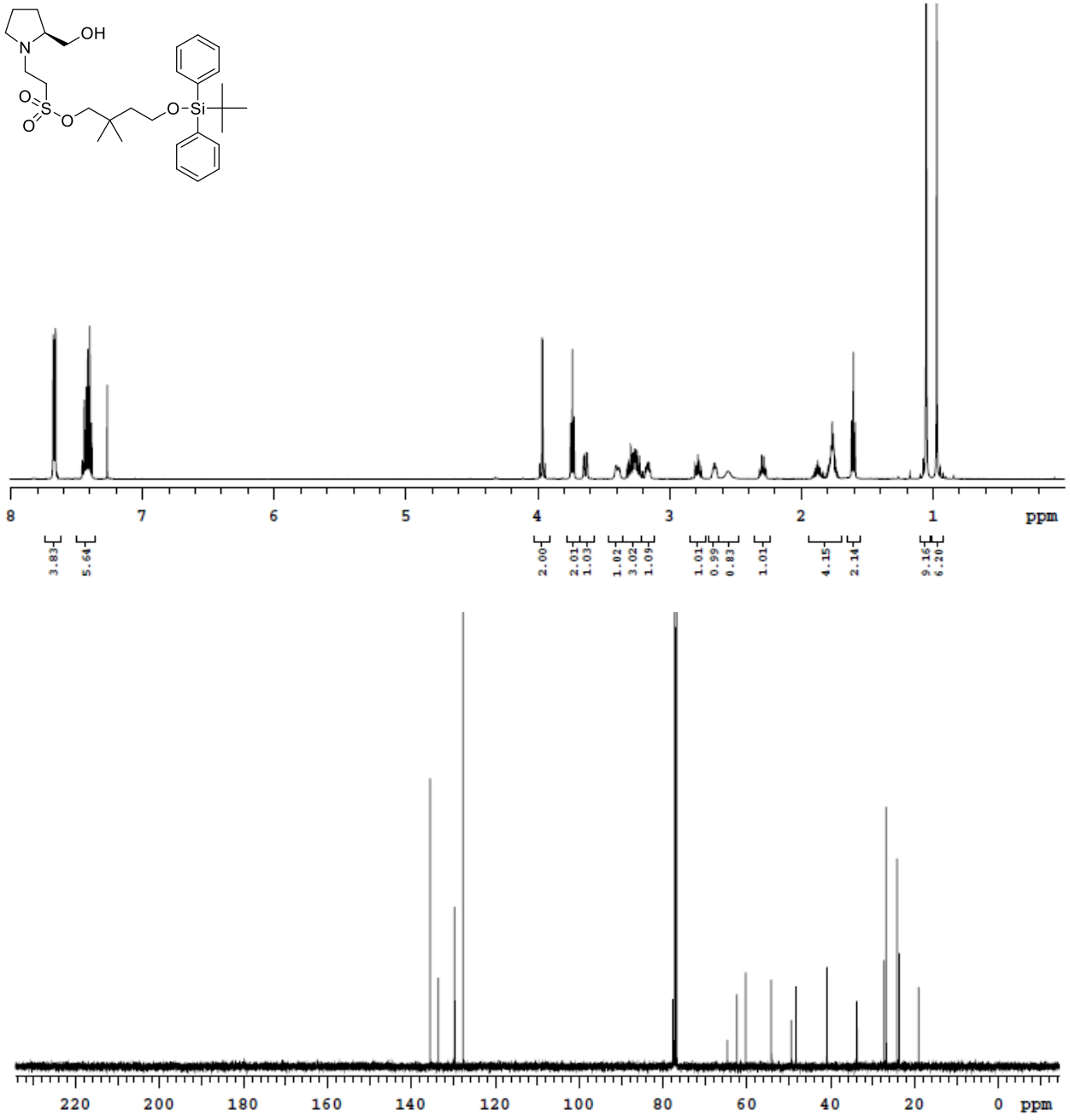


Figure 10.28: gCOSY Spectra of Compound III.3

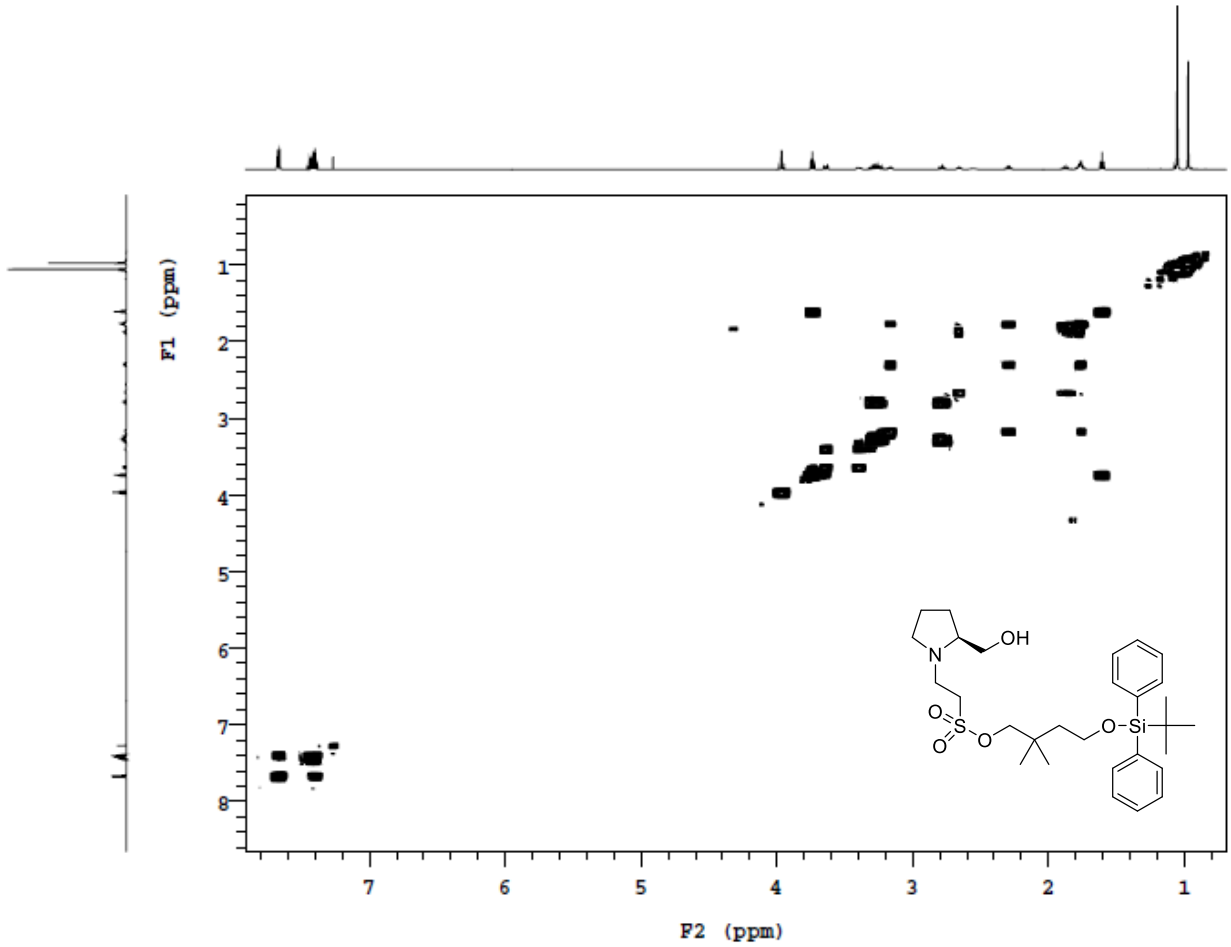


Figure 10.29: gHMQC Spectra of Compound III.3

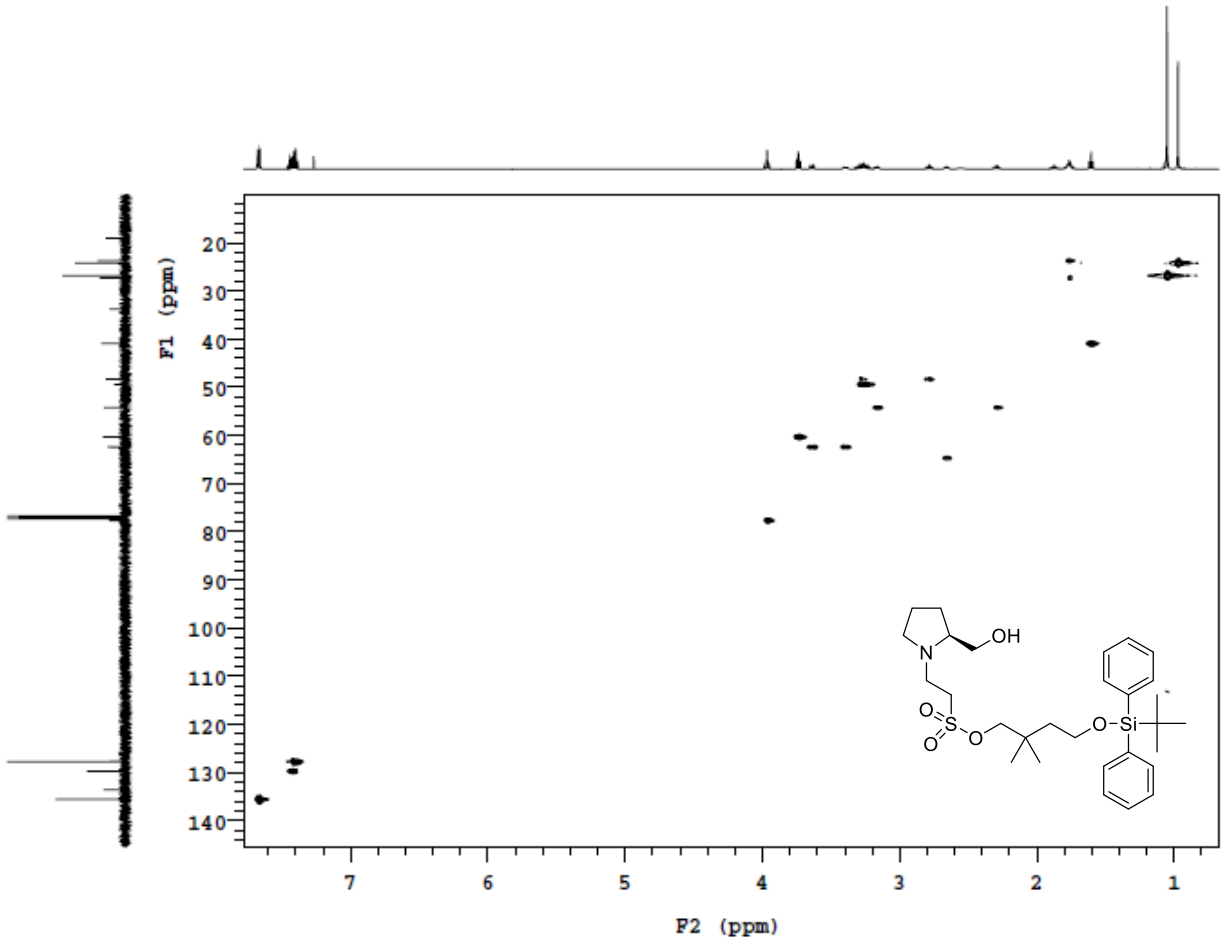


Figure 10.30: ^{1}H and ^{13}C Spectra of Compound III.4a

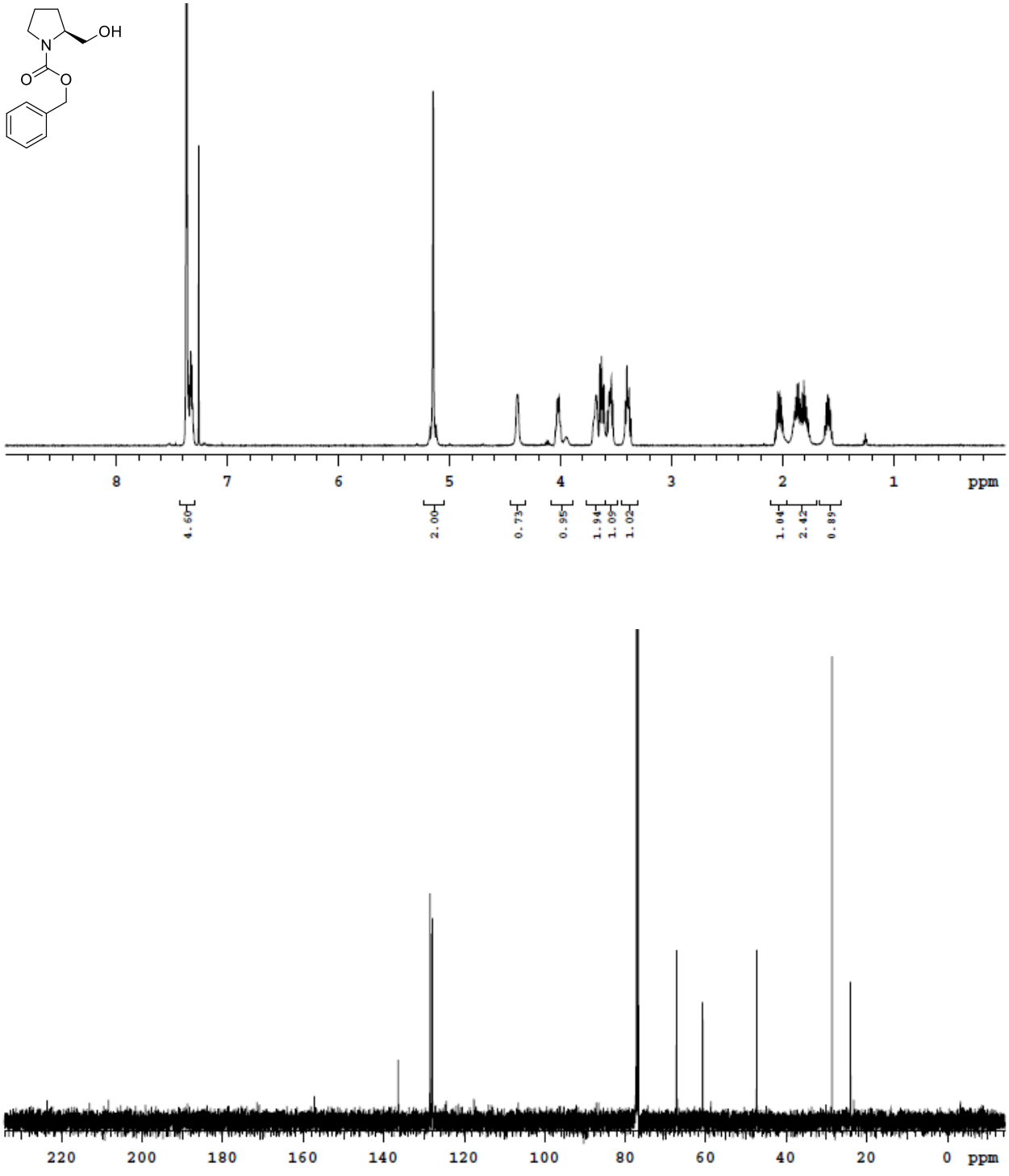


Figure 10.31: ^{1}H and ^{13}C Spectra of Compound III.4

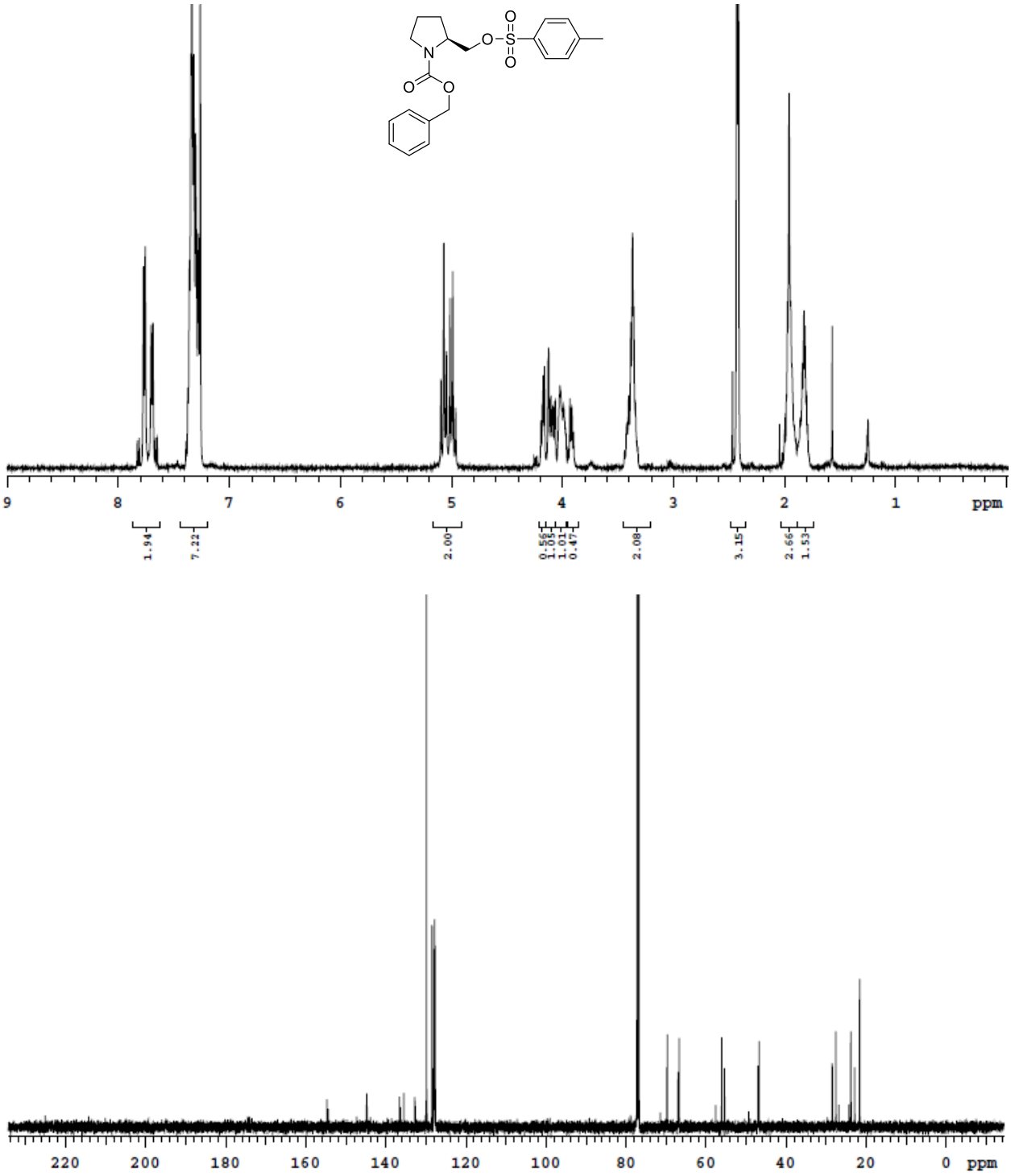


Figure 10.32: gCOSY Spectra of Compound III.4

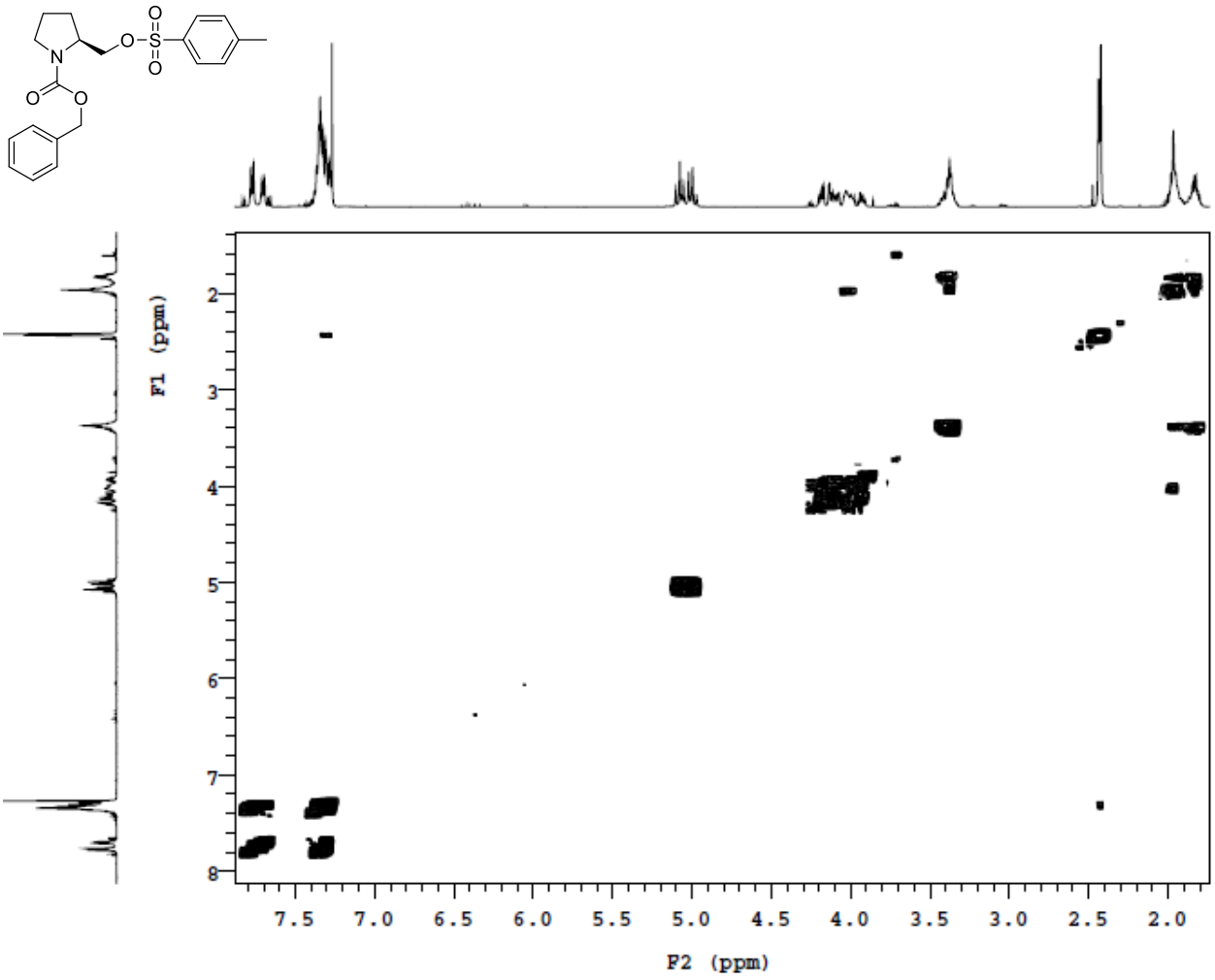


Figure 10.33: gHMQC Spectra of Compound III.4

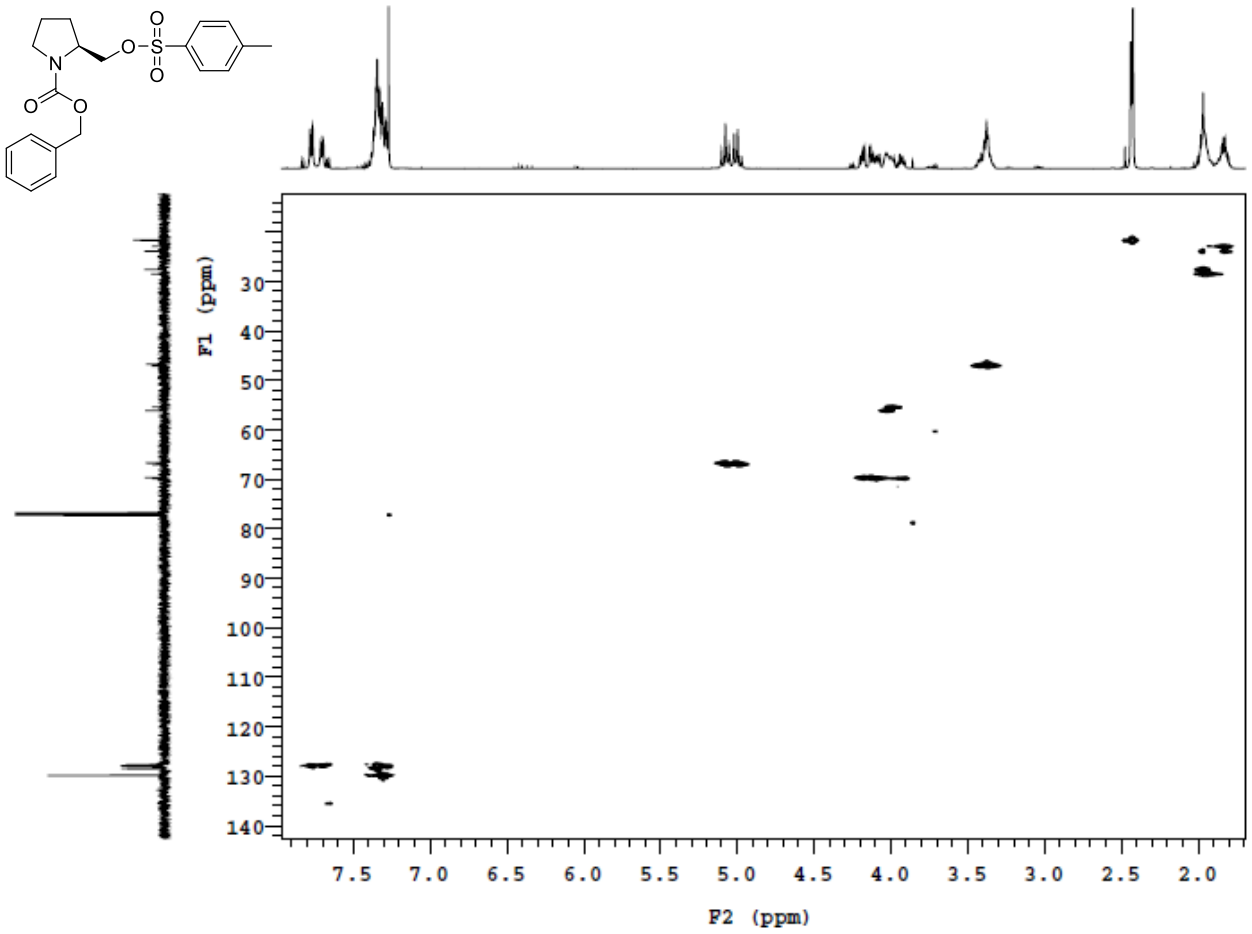


Figure 10.34: ^{1}H and ^{13}C Spectra of Compound III.5

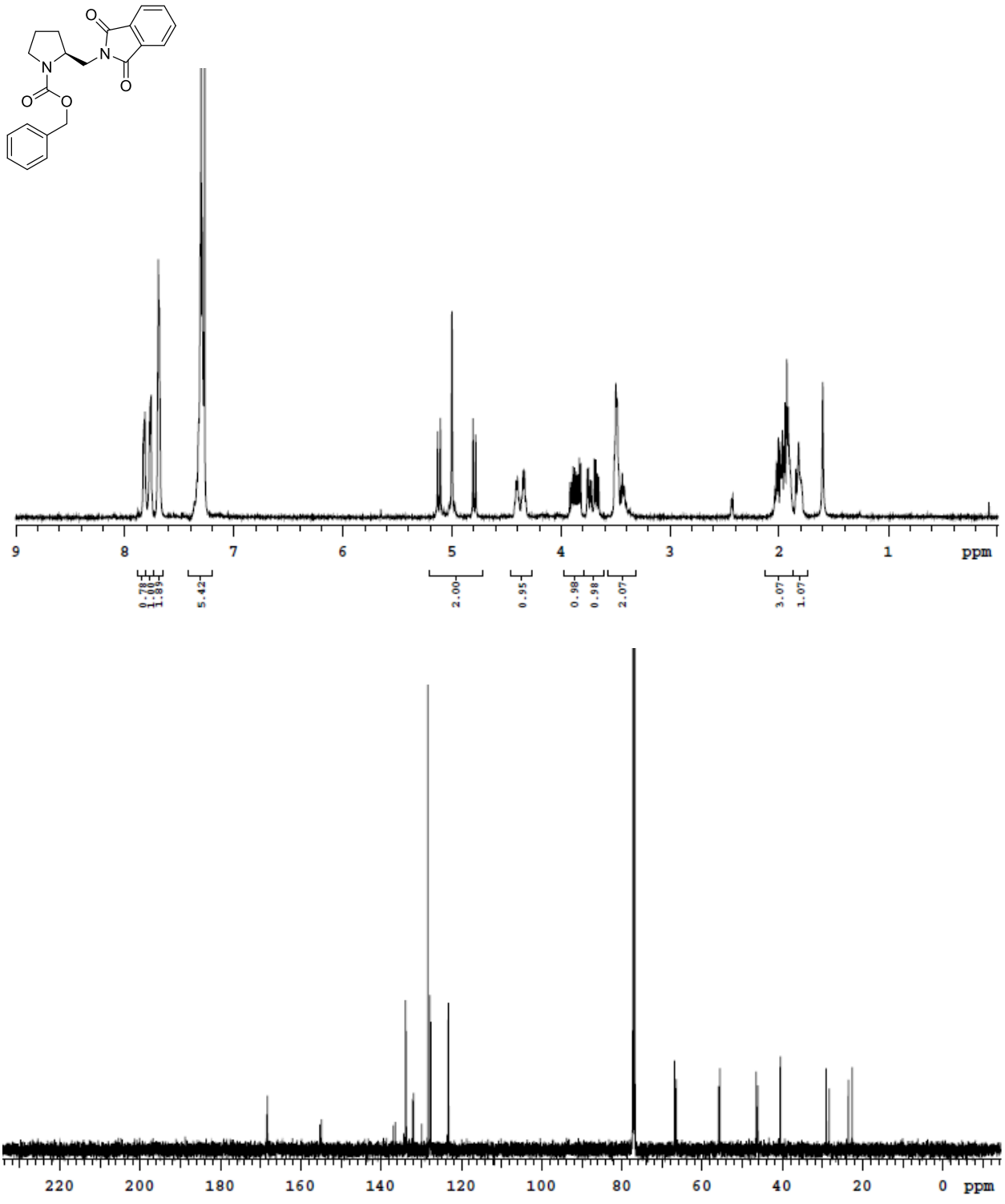


Figure 10.35: ^{1}H and ^{13}C Spectra of Compound III.6a

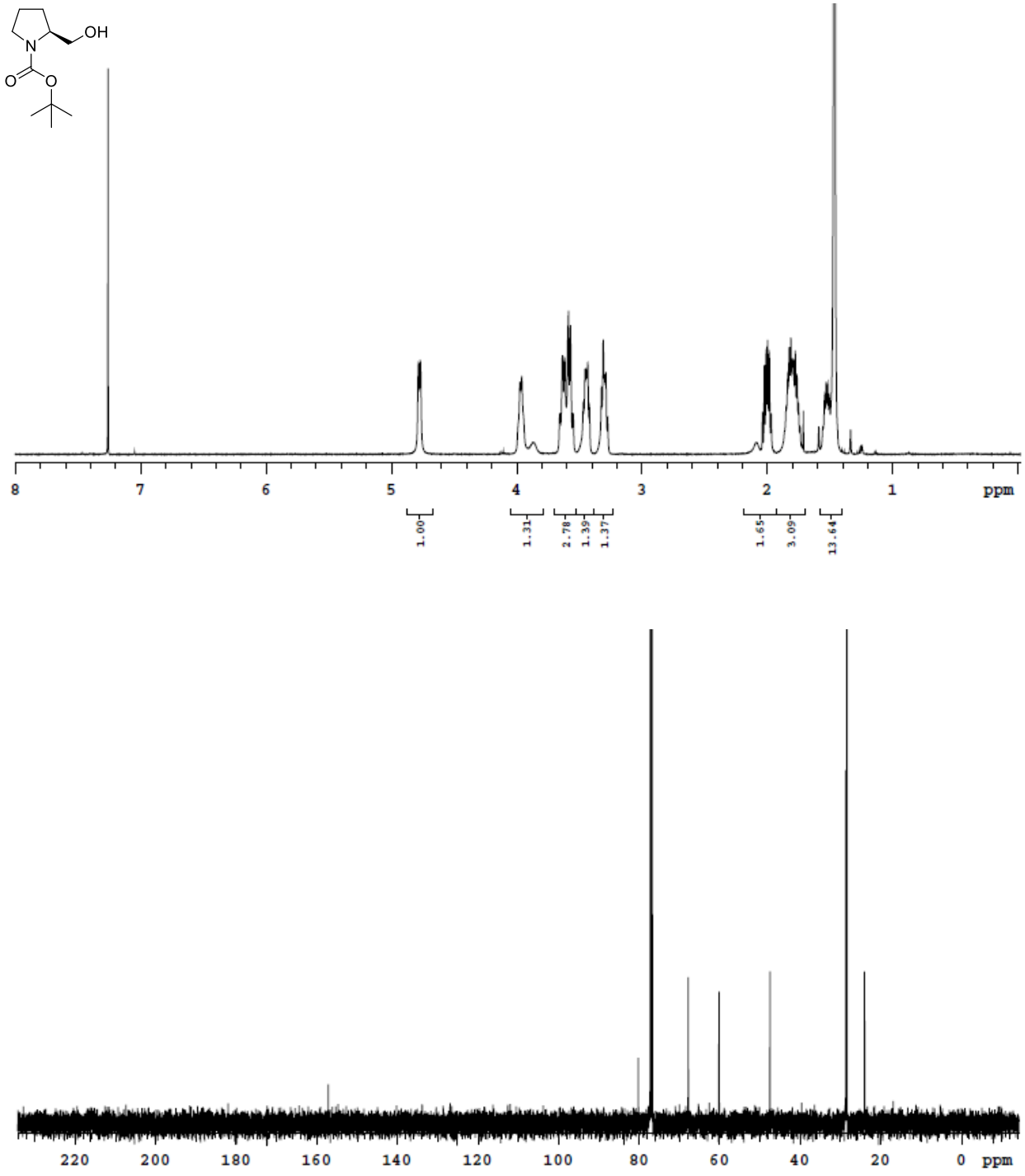


Figure 10.36: ^{1}H and ^{13}C Spectra of Compound III.6

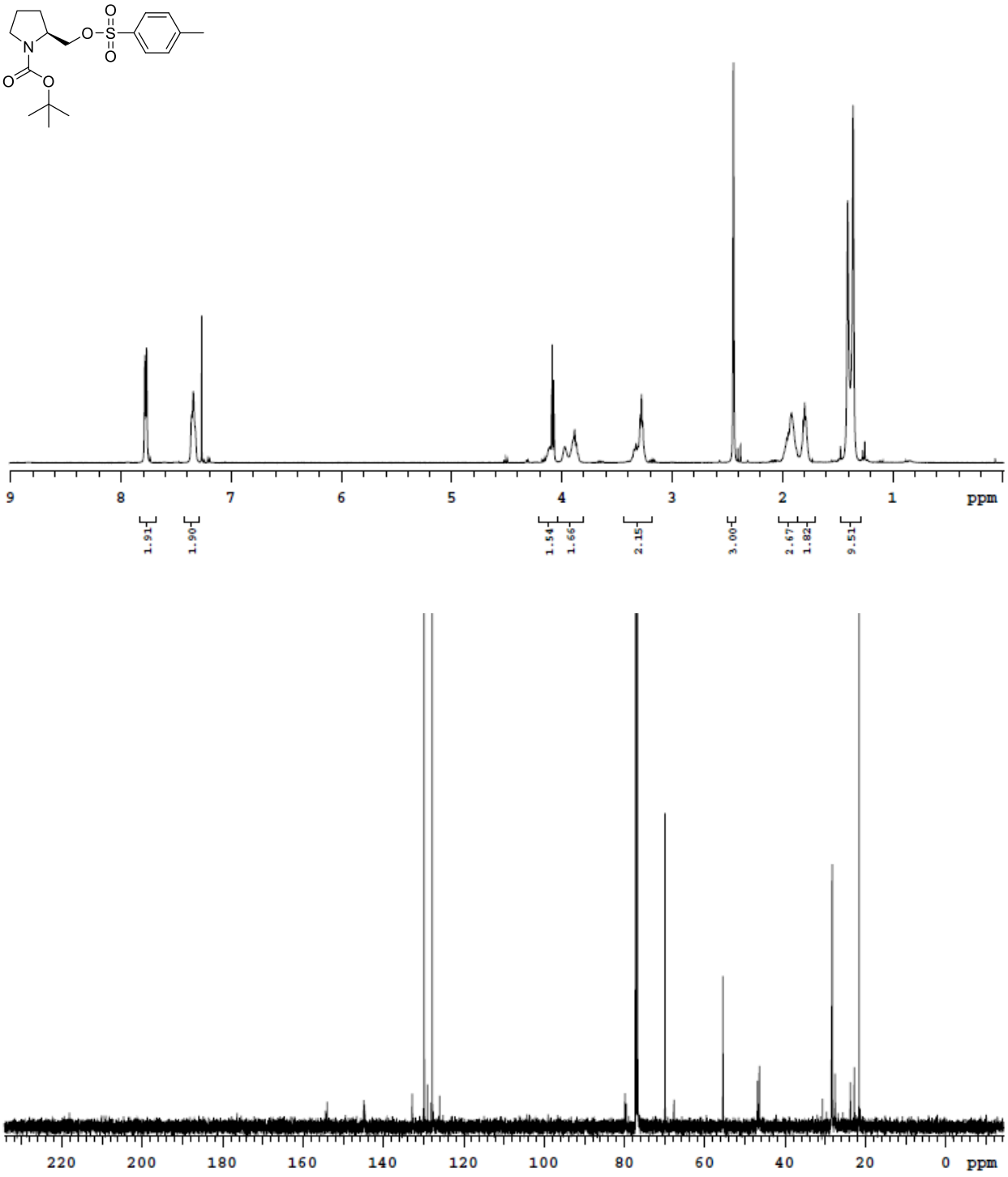


Figure 10.37: gCOSY Spectra of Compound III.6

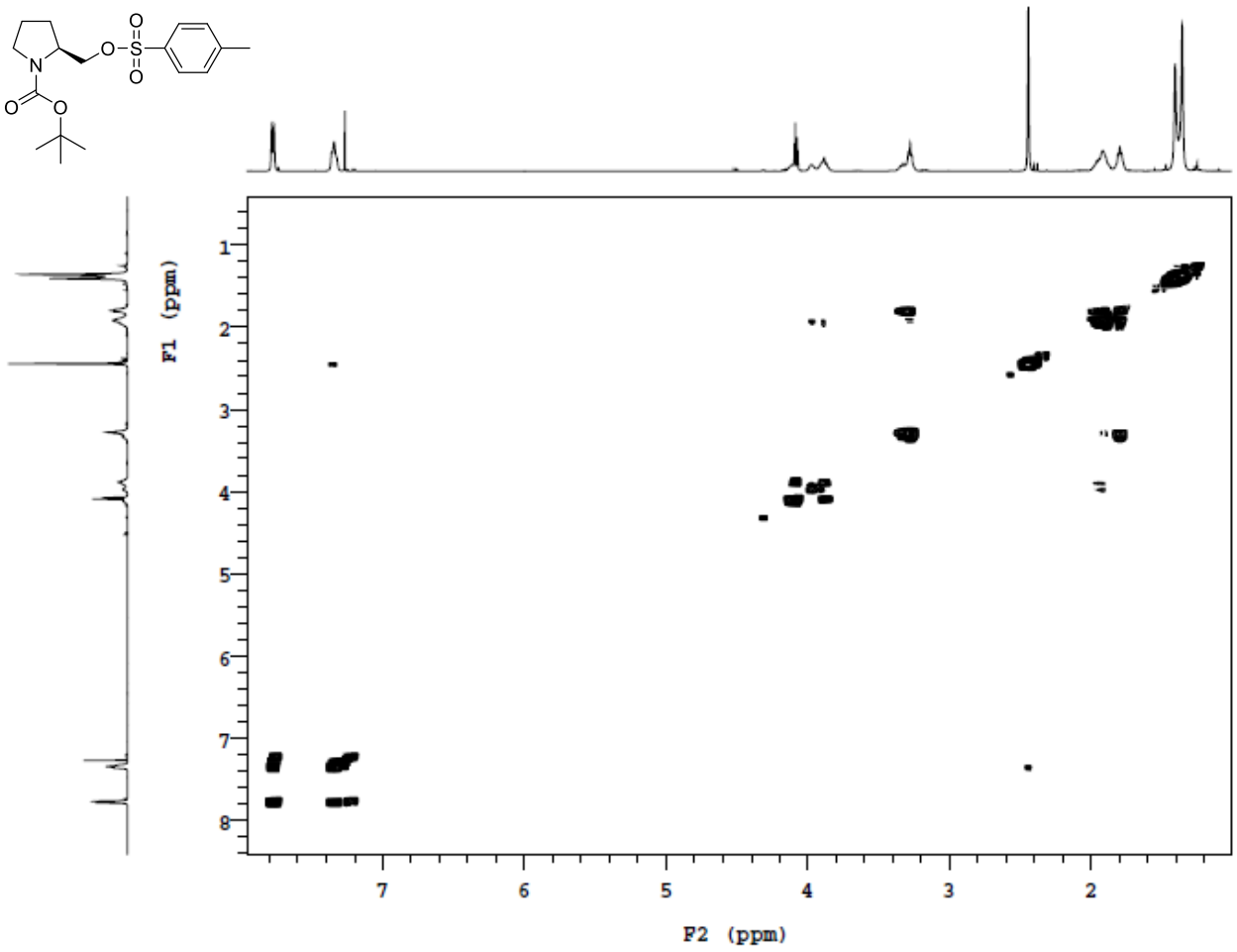


Figure 10.38: gHMQC Spectra of Compound III.6

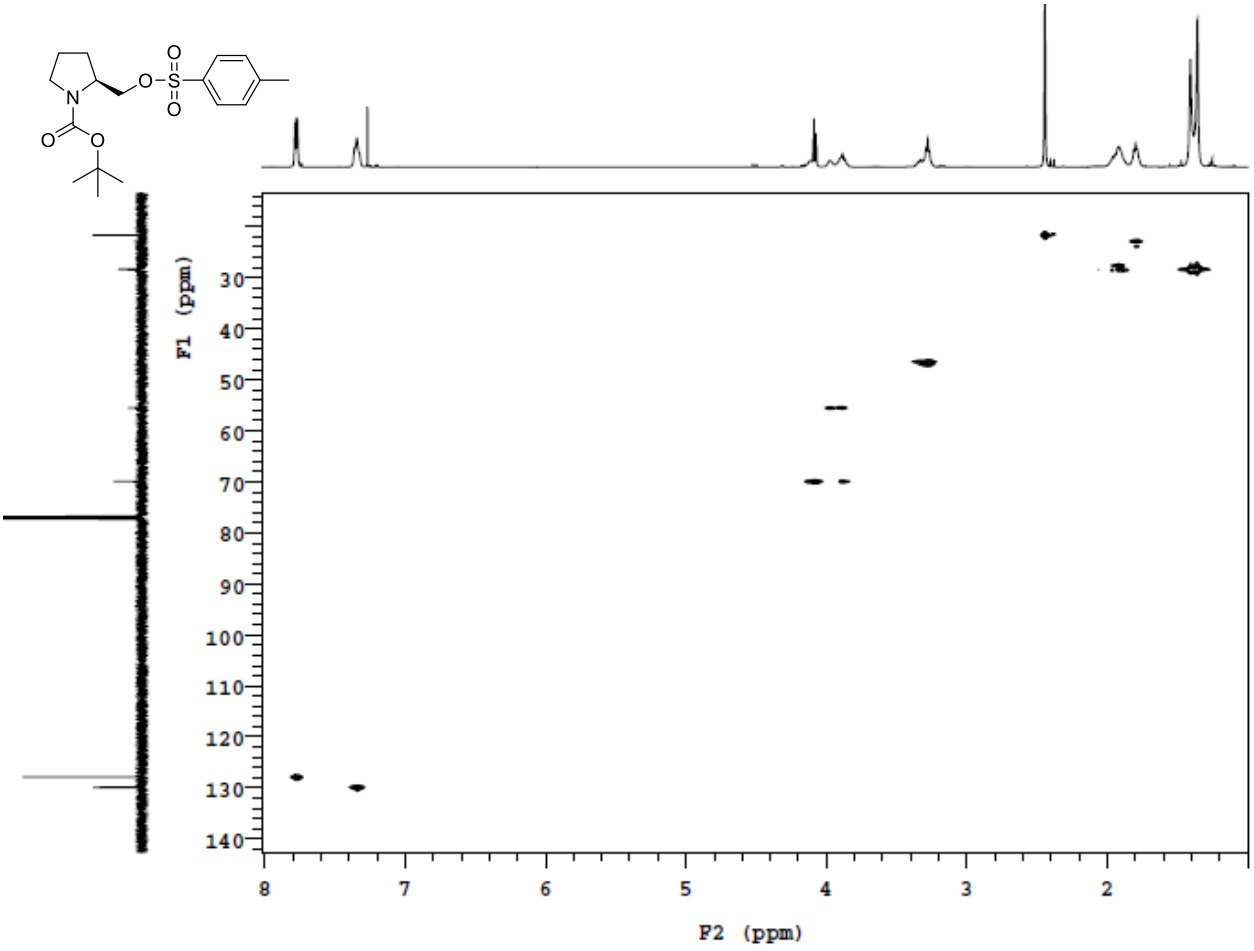


Figure 10.39: ^{1}H and ^{13}C Spectra of Compound III.7a

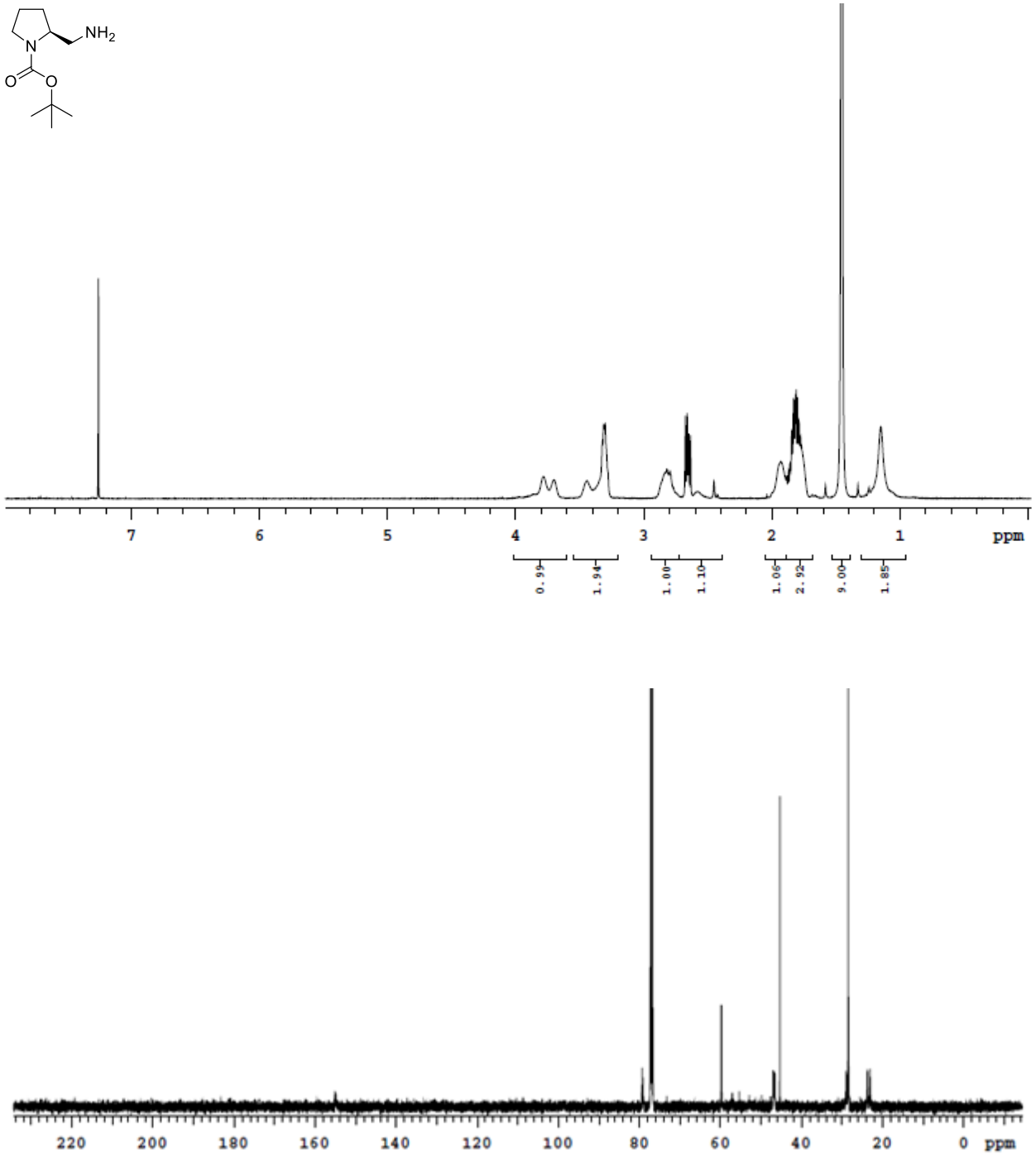


Figure 10.40: ^{1}H and ^{13}C Spectra of Compound III.7

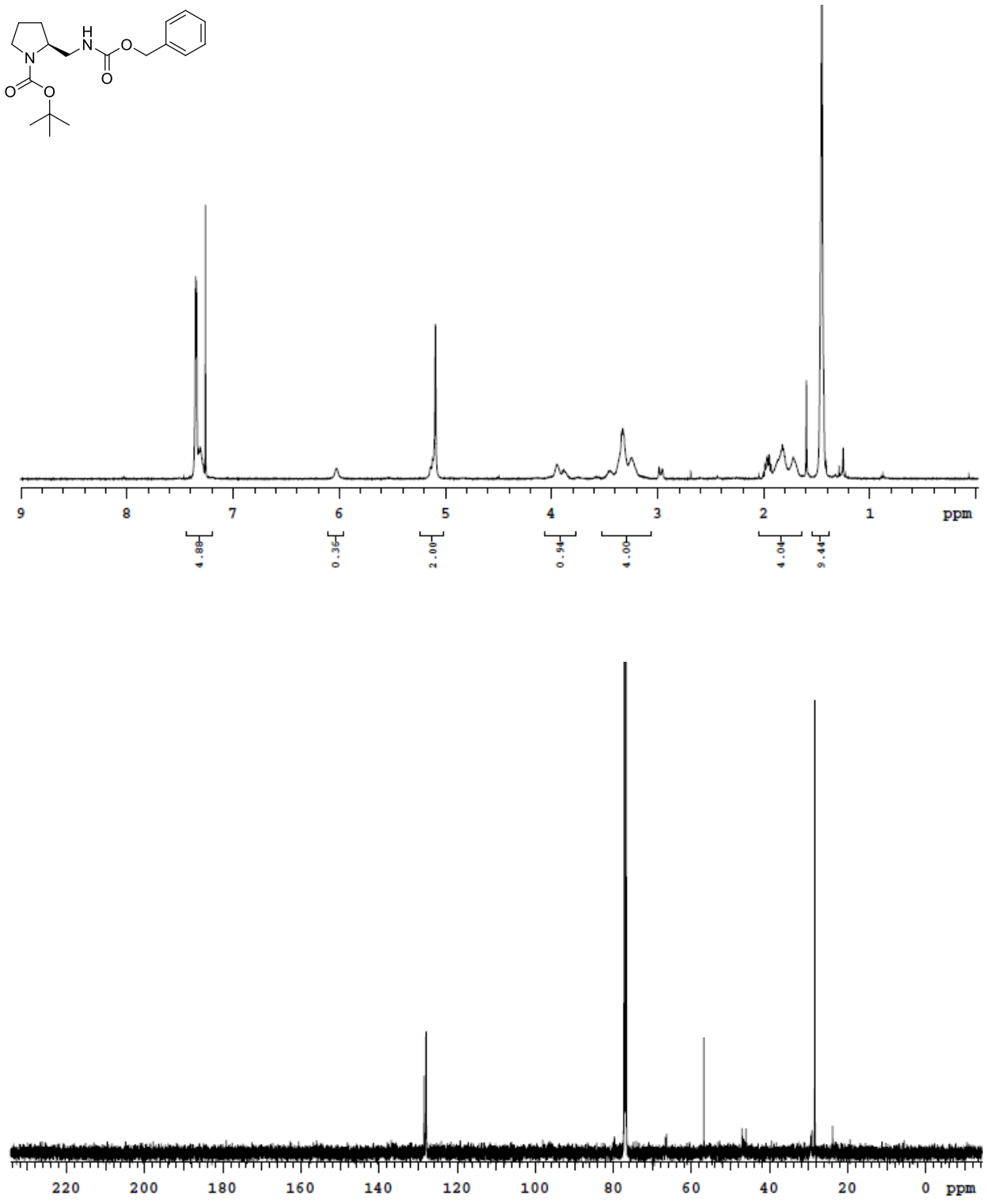


Figure 10.41: ^{1}H and ^{13}C Spectra of Compound III.8

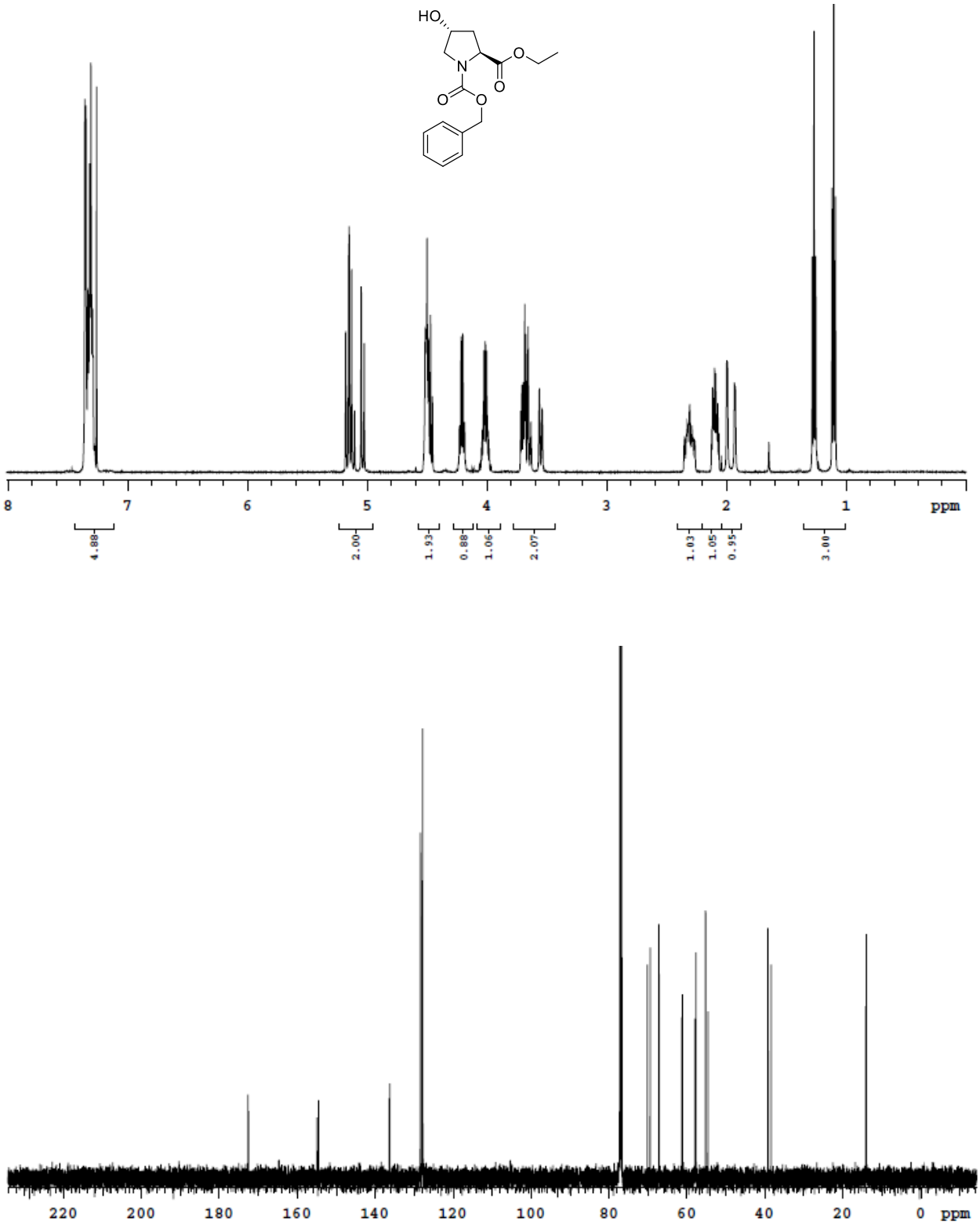


Figure 10.42: ^{1}H and ^{13}C Spectra of Compound III.9

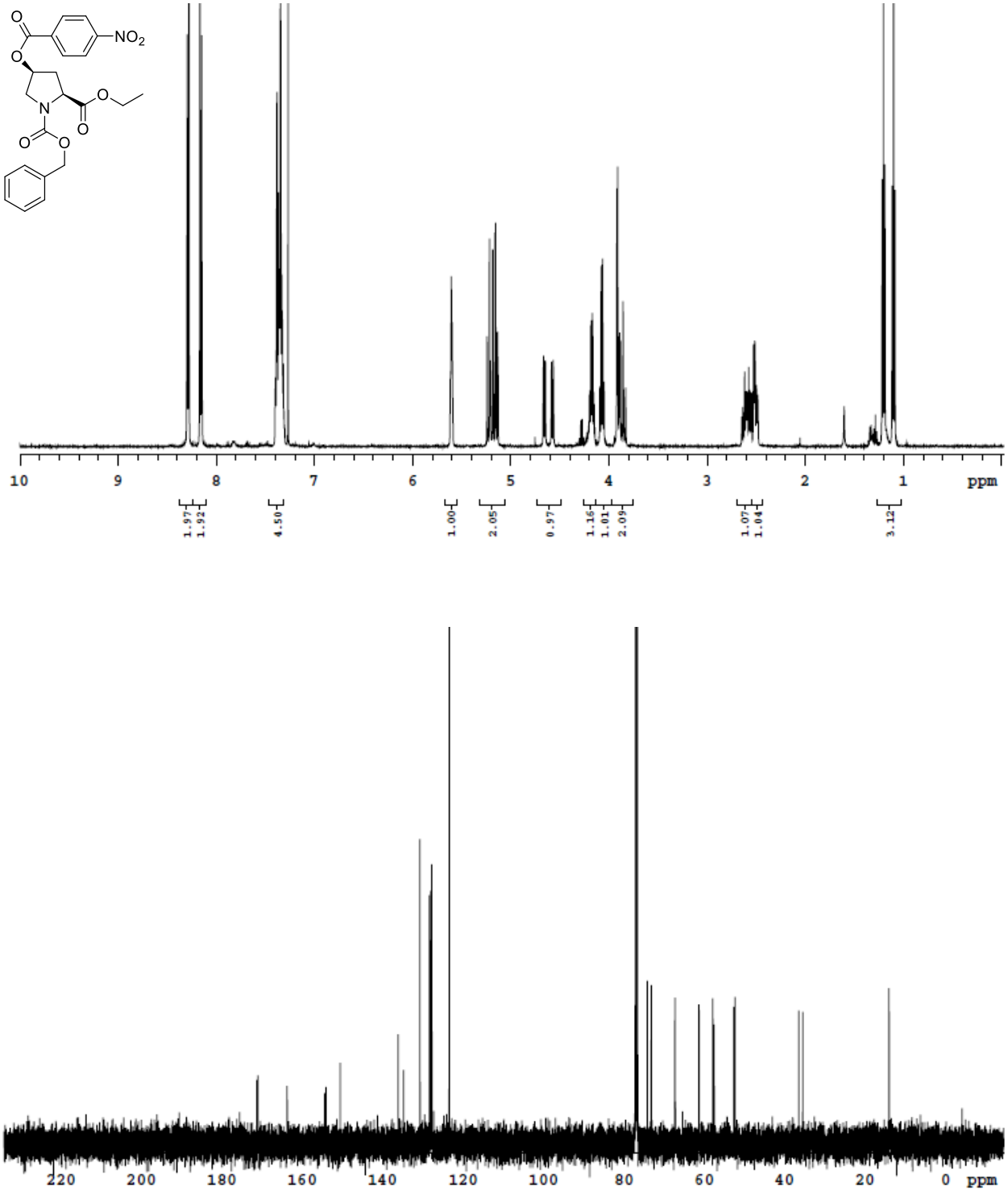


Figure 10.43: ^{1}H and ^{13}C Spectra of Compound III.10

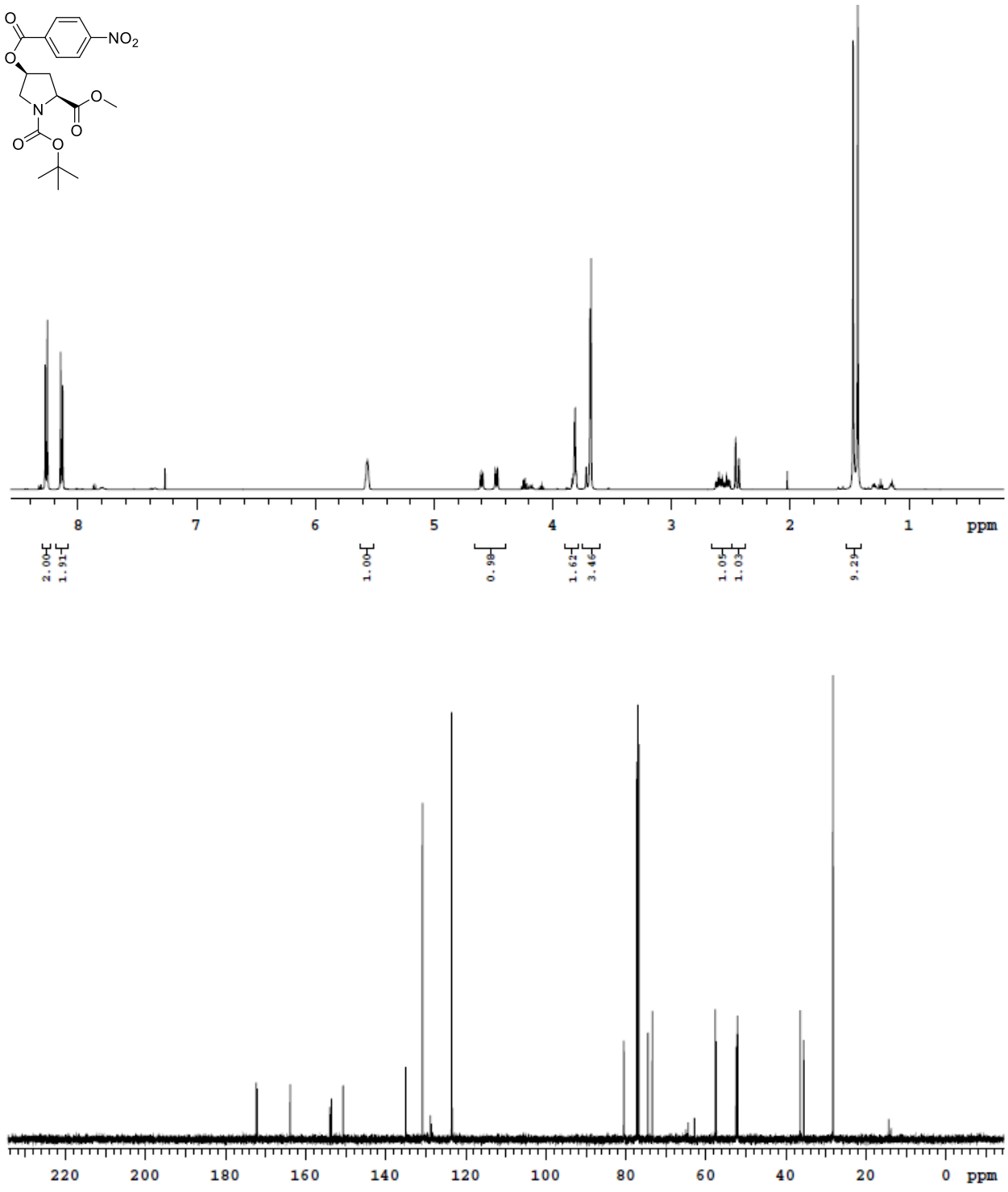


Figure 10.44: ^{1}H and ^{13}C Spectra of Compound III.11a

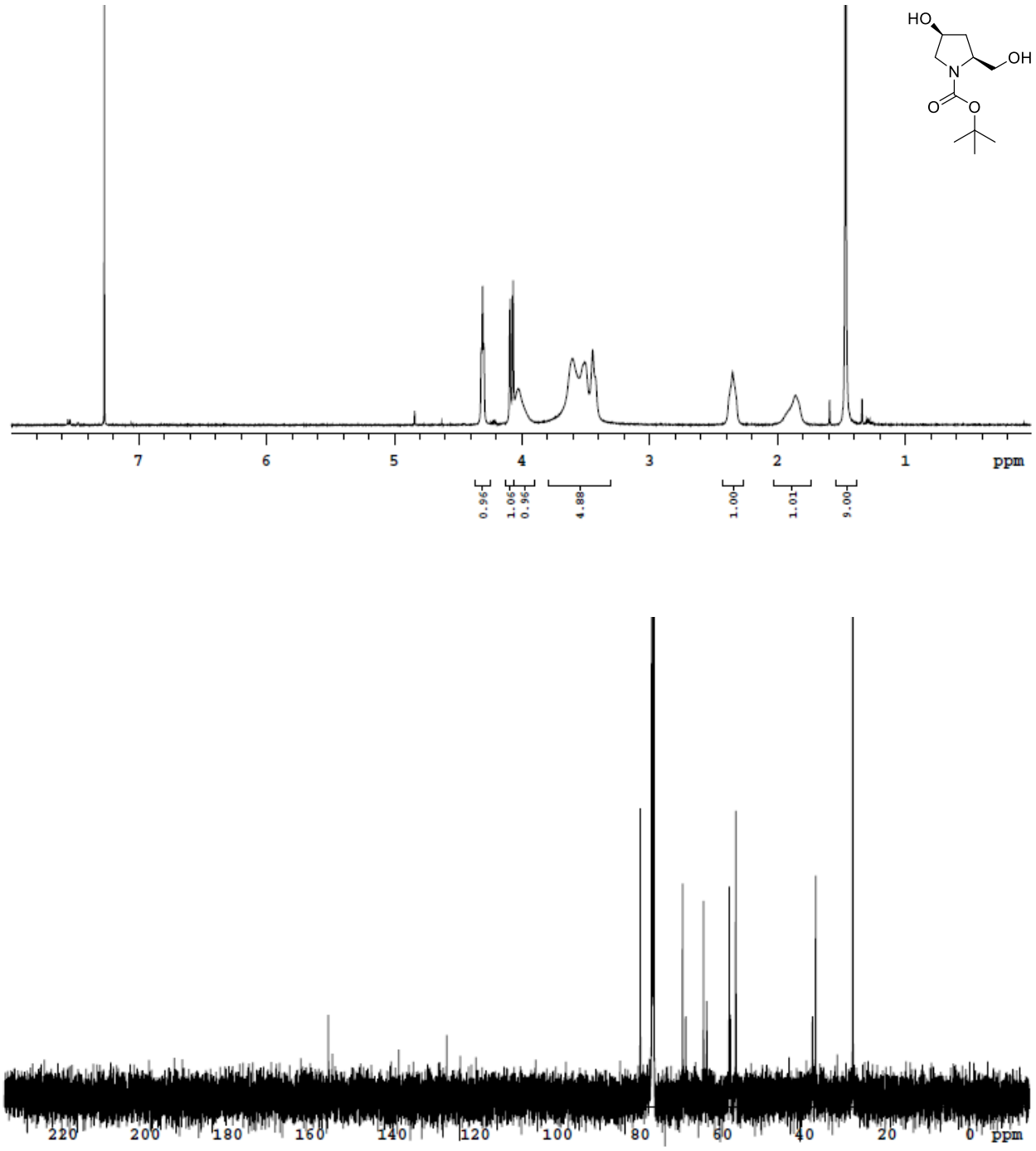


Figure 10.45: ^{1}H and ^{13}C Spectra of Compound III.11

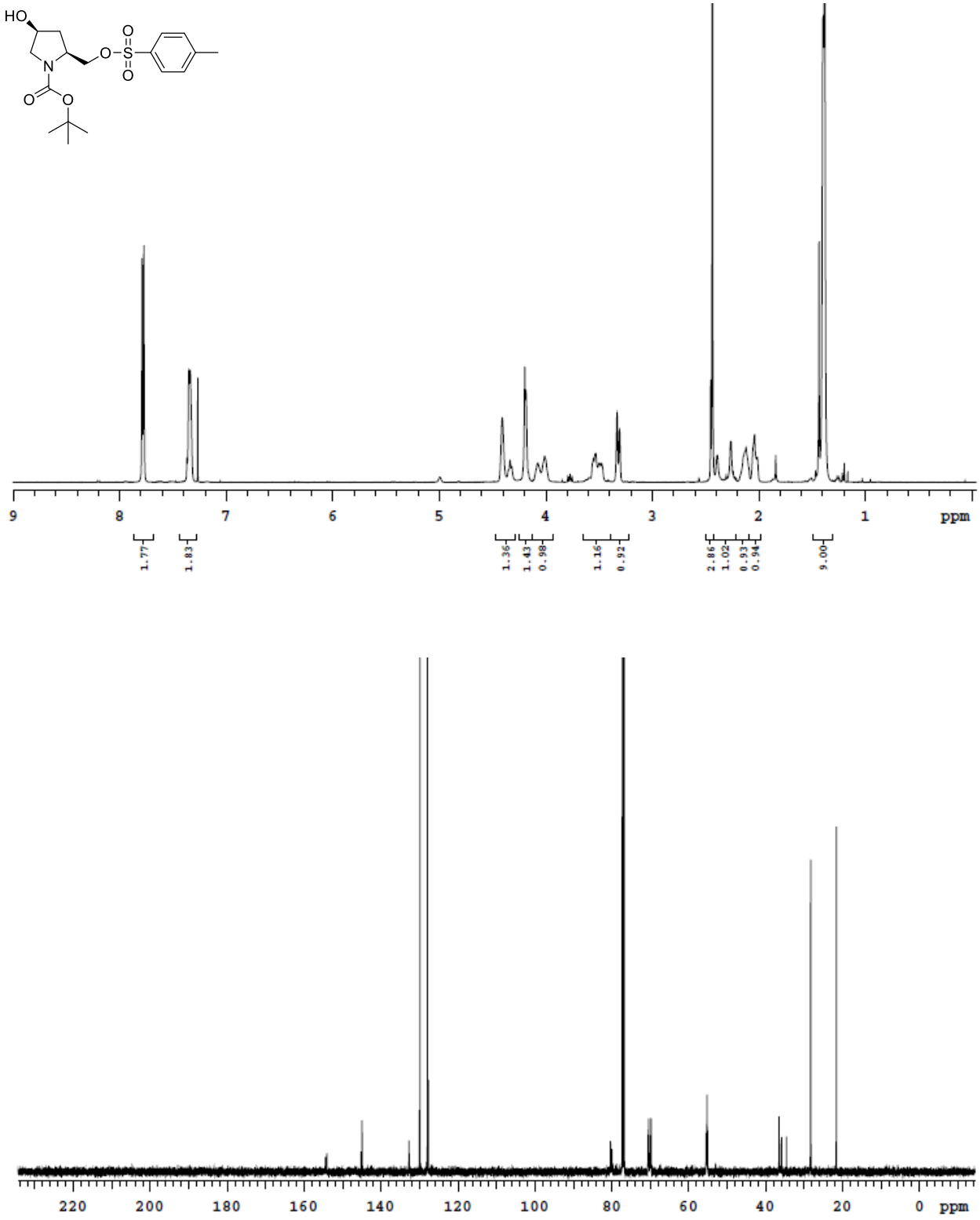


Figure 10.46: gCOSY Spectra of Compound III.11

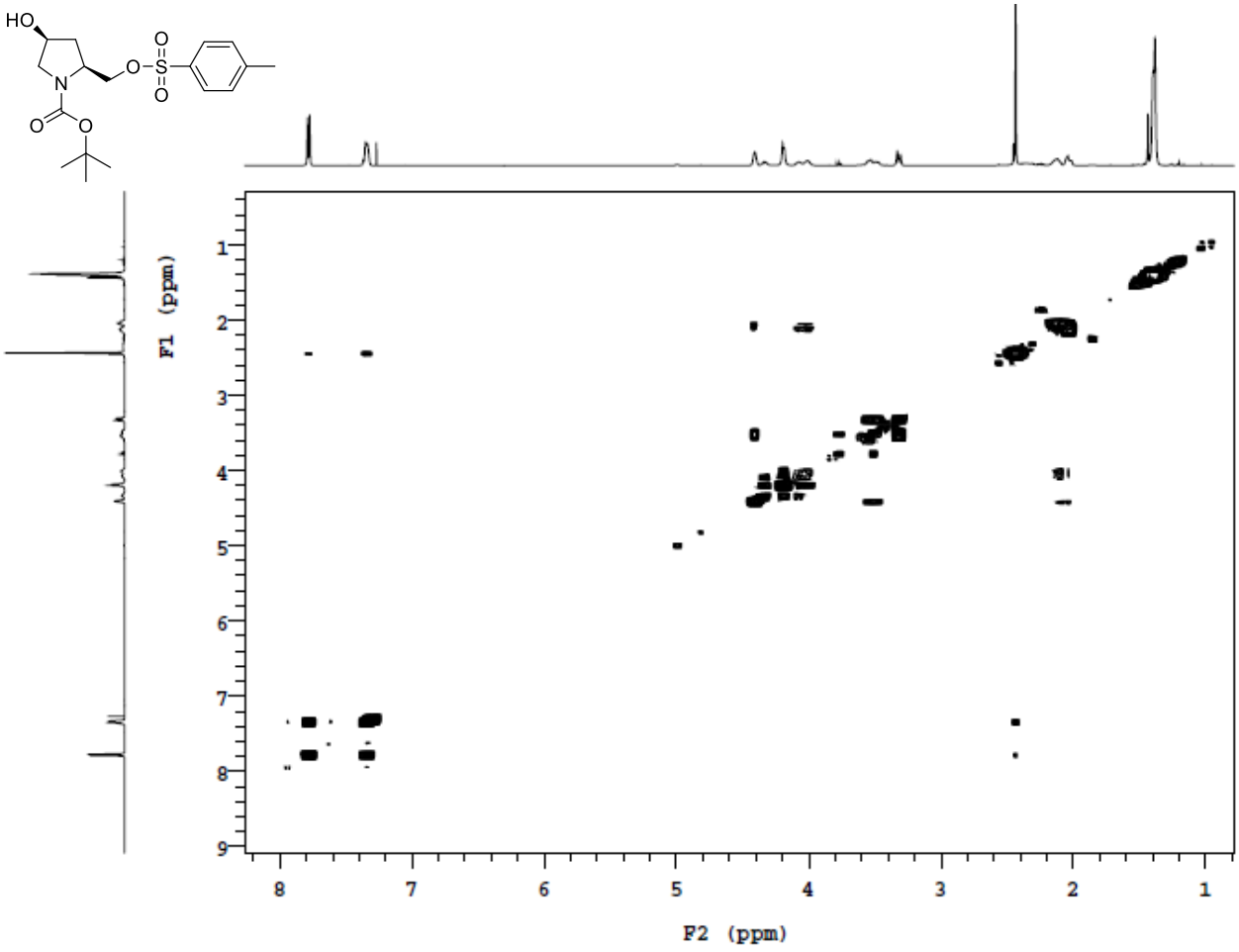


Figure 10.47: gHMQC Spectra of Compound III.11

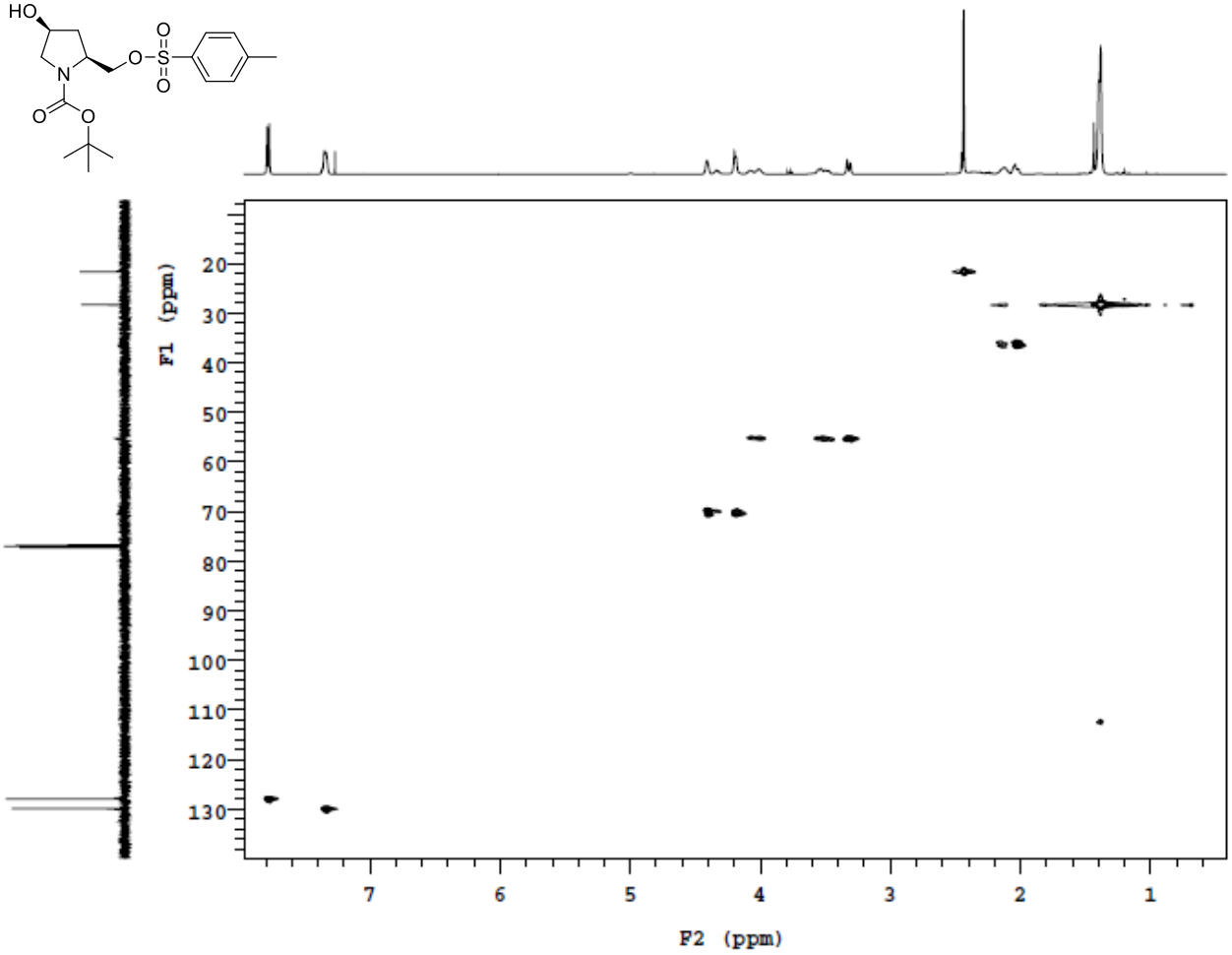


Figure 10.48: ^{1}H and ^{13}C Spectra of Compound III.12a

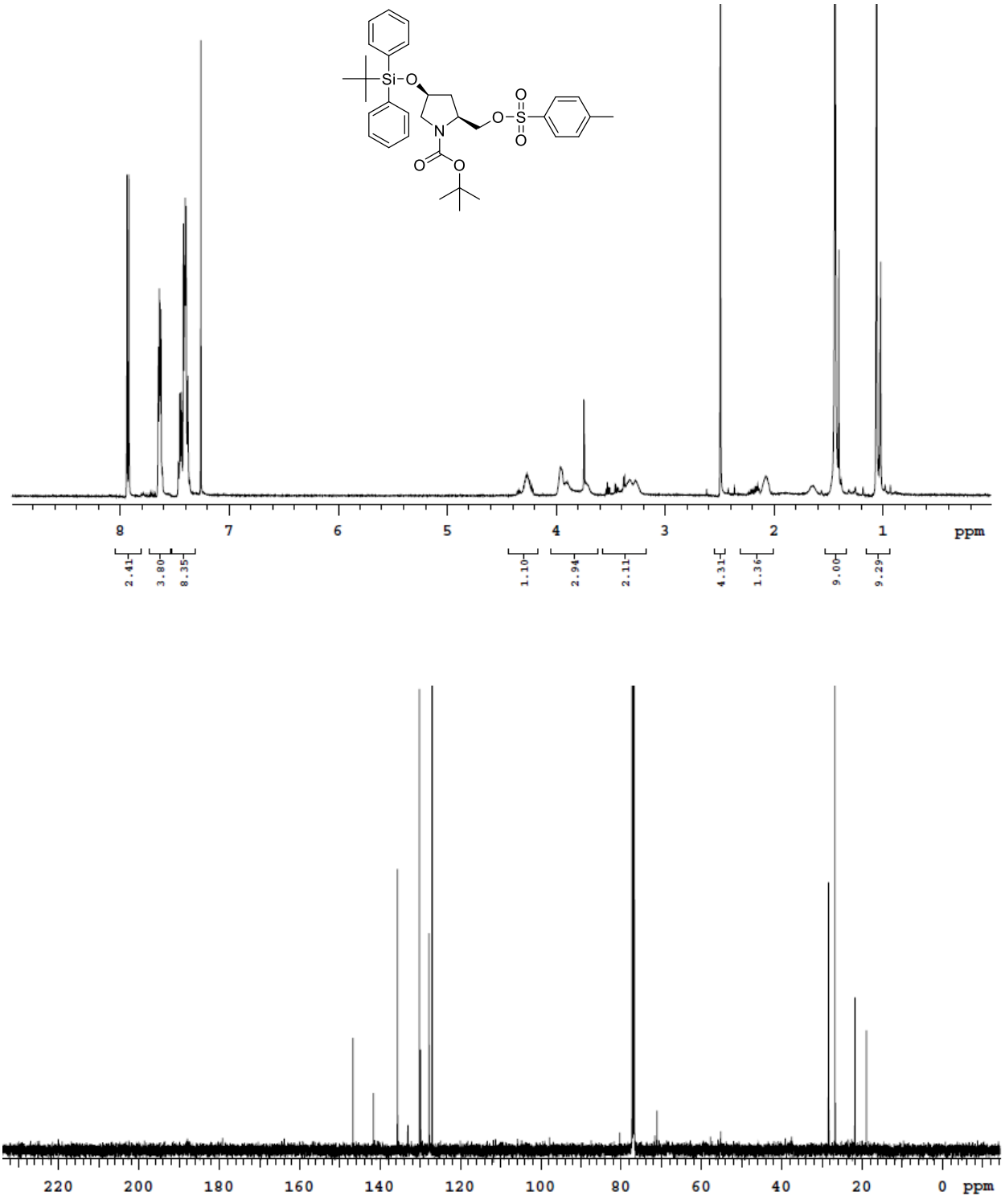


Figure 10.49: ^{1}H and ^{13}C Spectra of Compound III.12

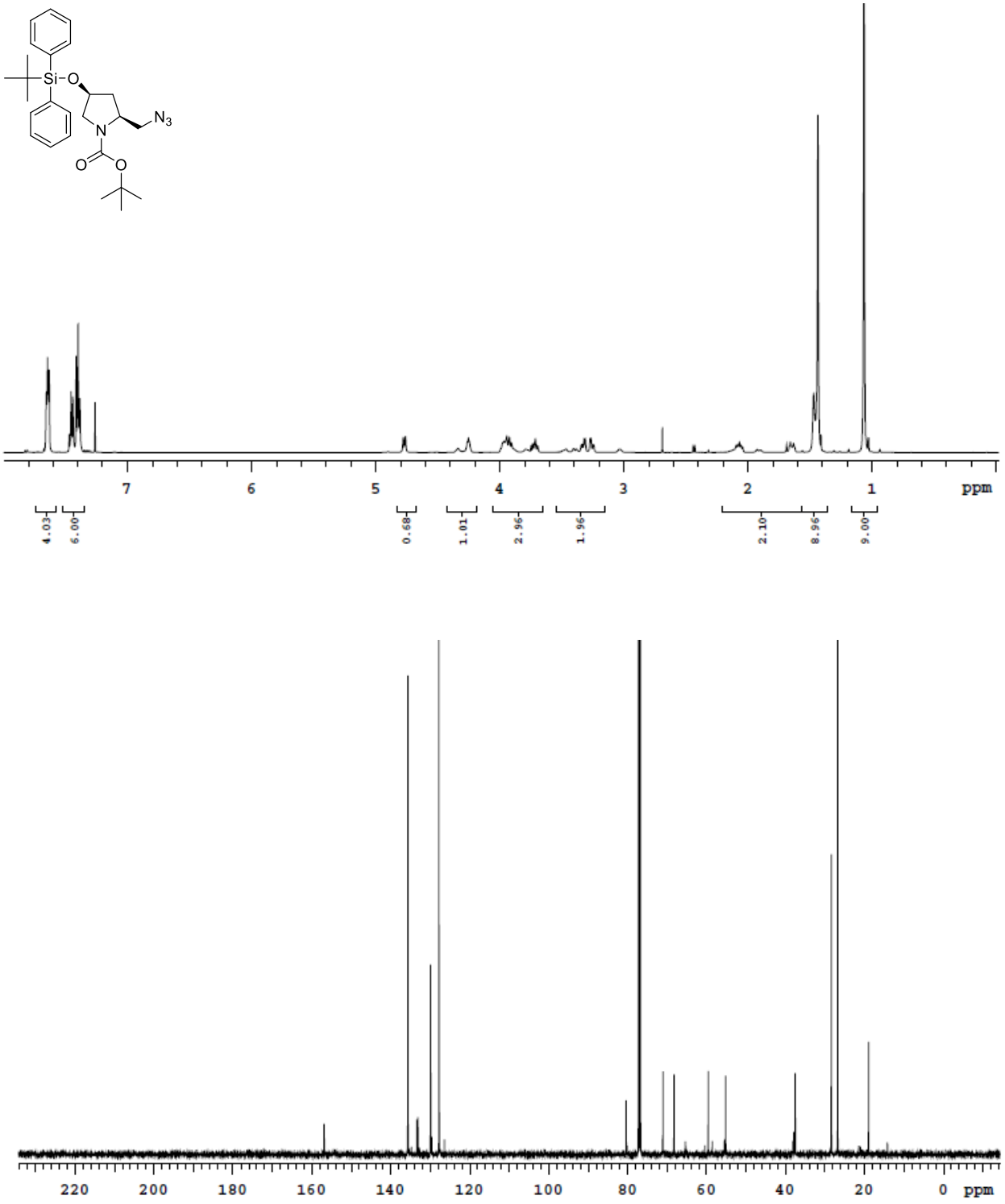


Figure 10.50: ^{1}H and ^{13}C Spectra of Compound III.13a

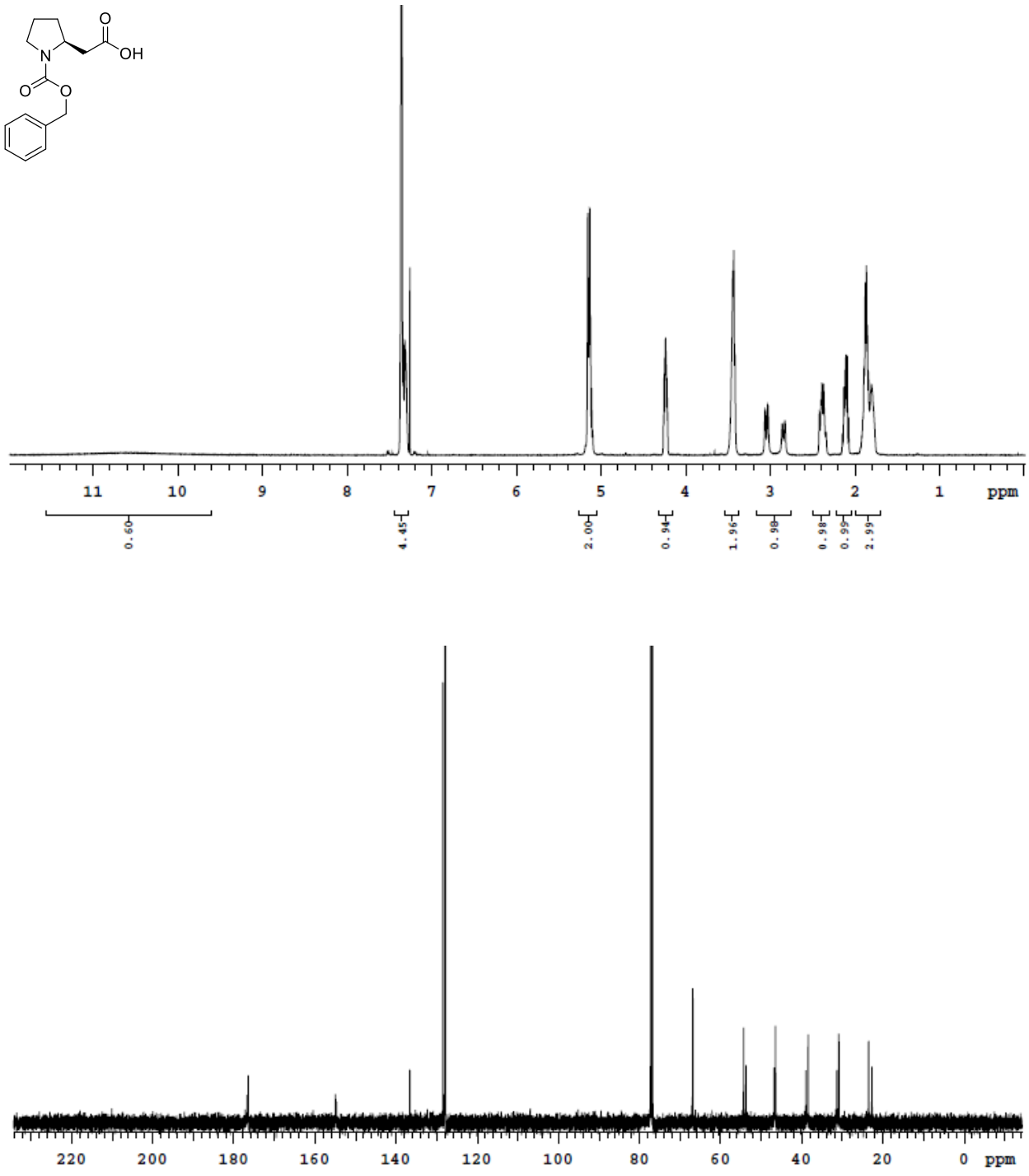


Figure 10.51: ^{1}H and ^{13}C Spectra of Compound III.13

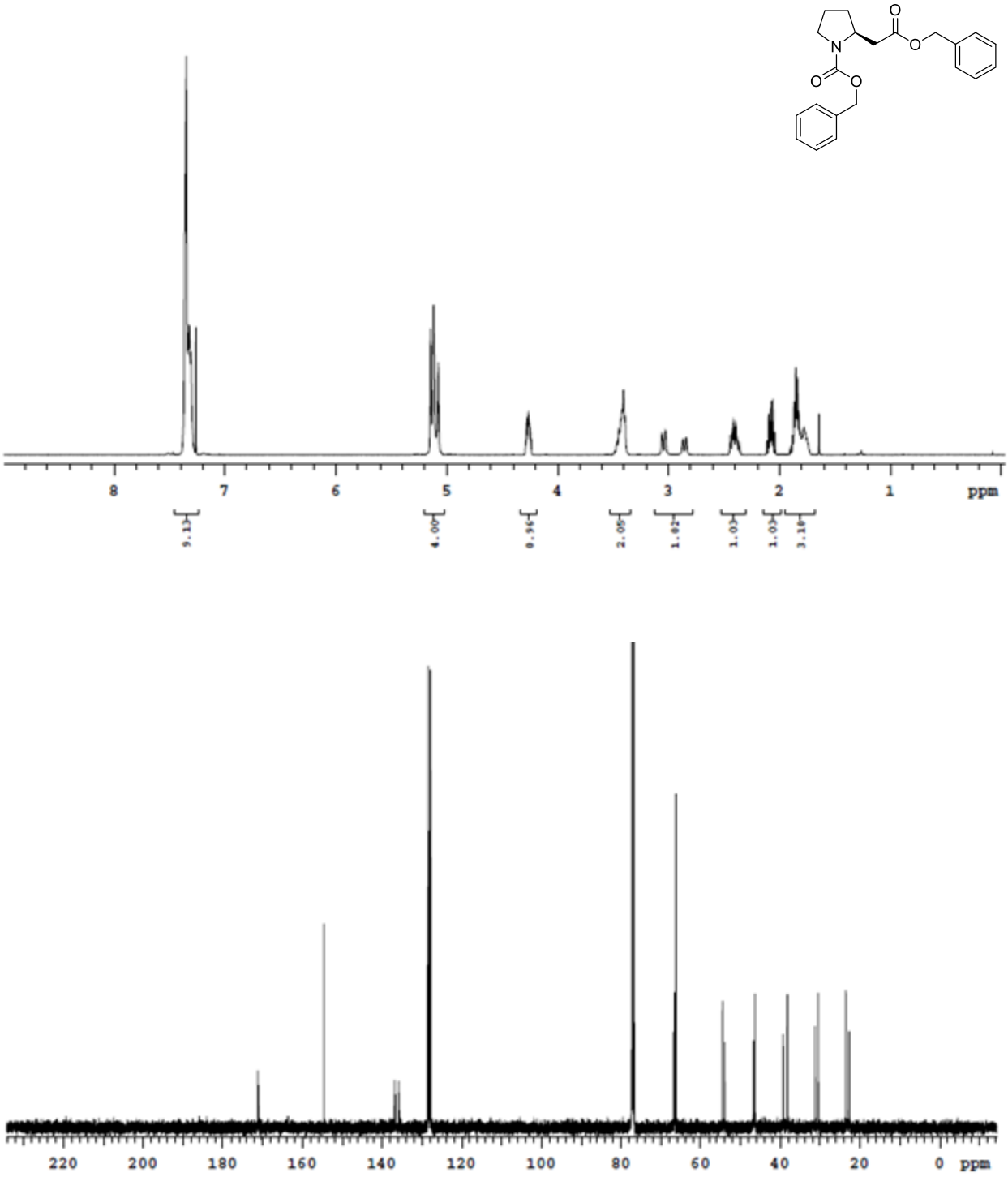


Figure 10.52: ^{1}H and ^{13}C Spectra of Compound III.14

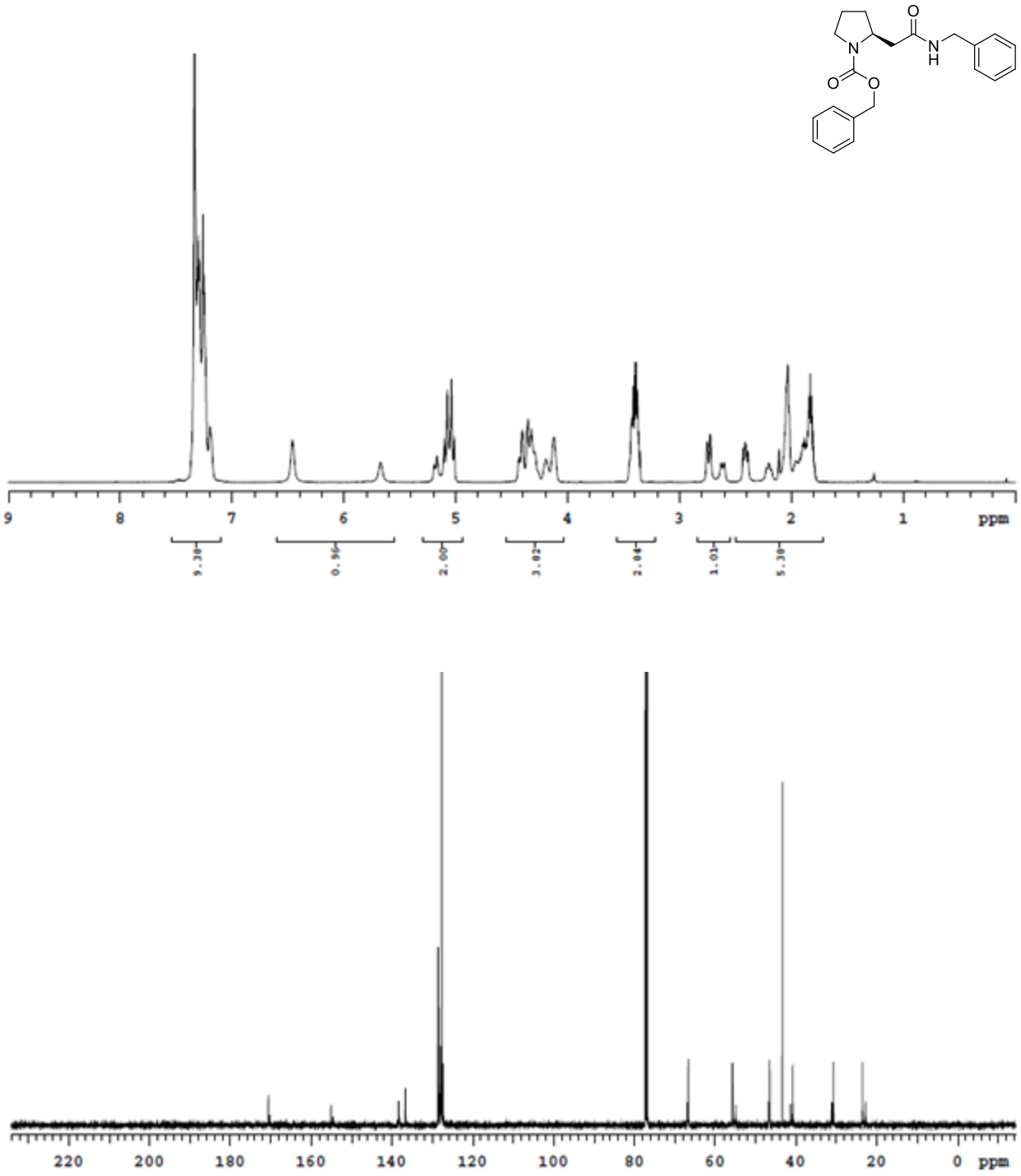


Figure 10.53: ^{1}H and ^{13}C Spectra of Compound III.15

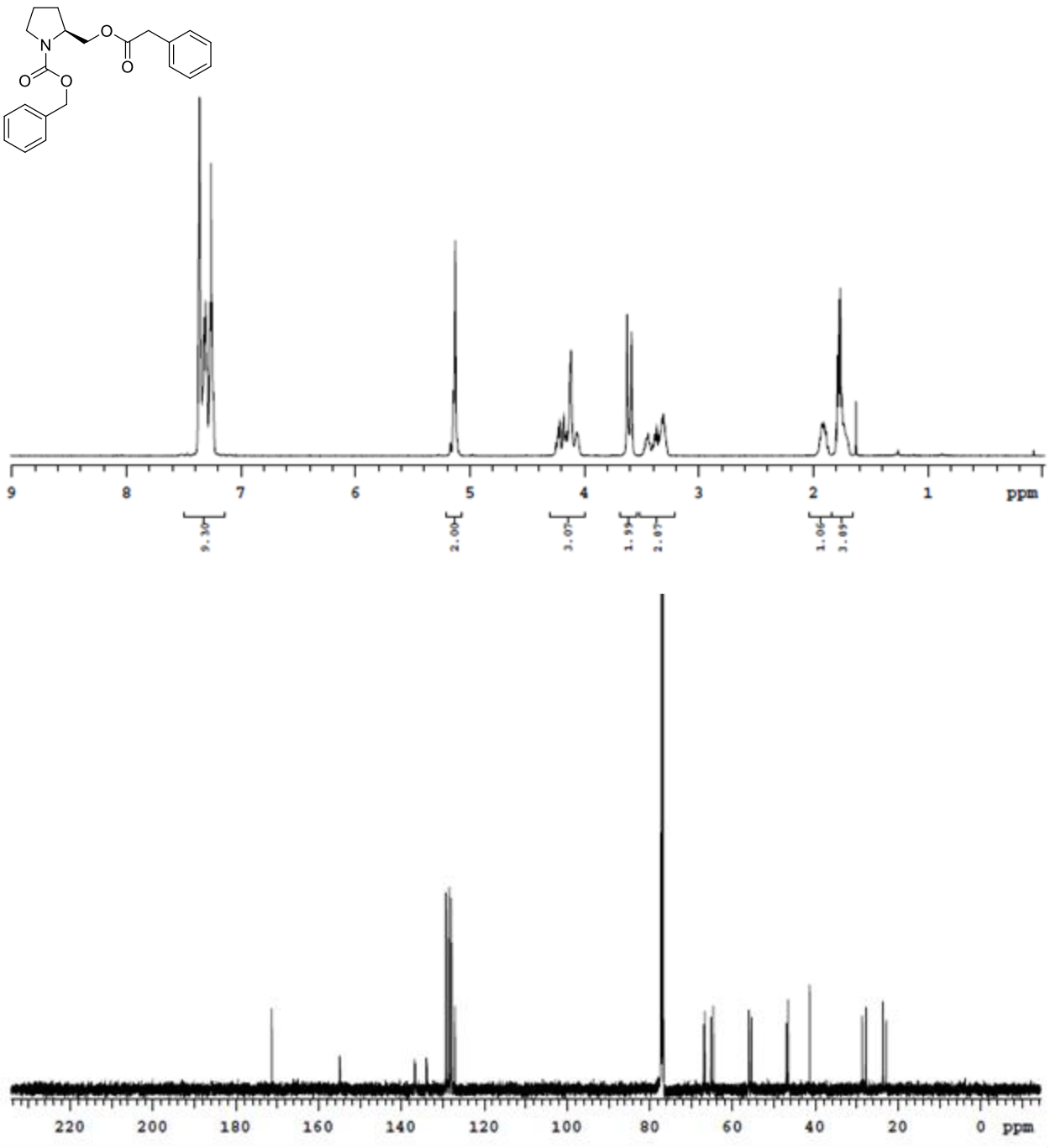


Figure 10.54: ^{1}H and ^{13}C Spectra of Compound III.16

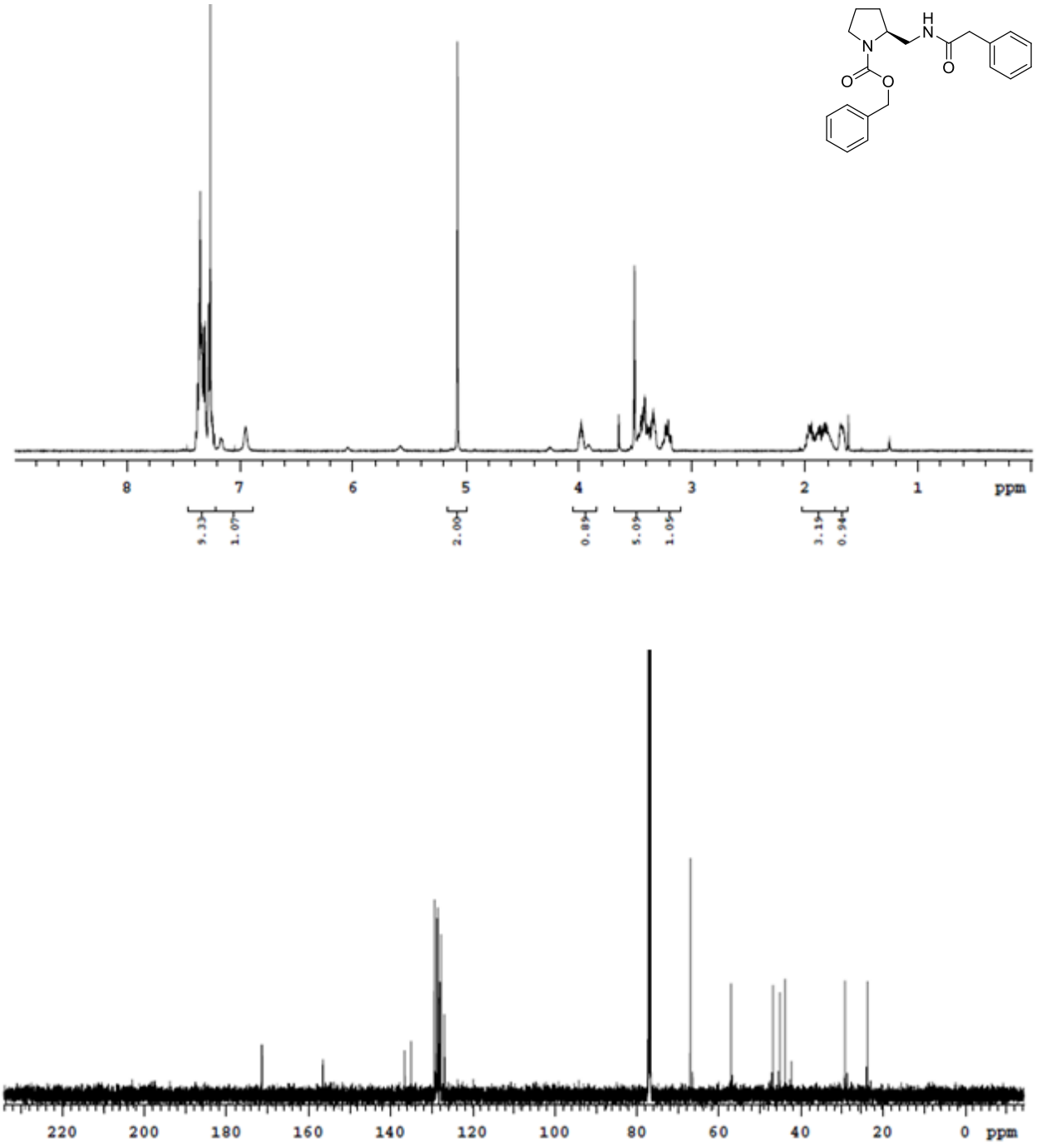


Figure 10.55: ^{1}H and ^{13}C Spectra of Compound III.17

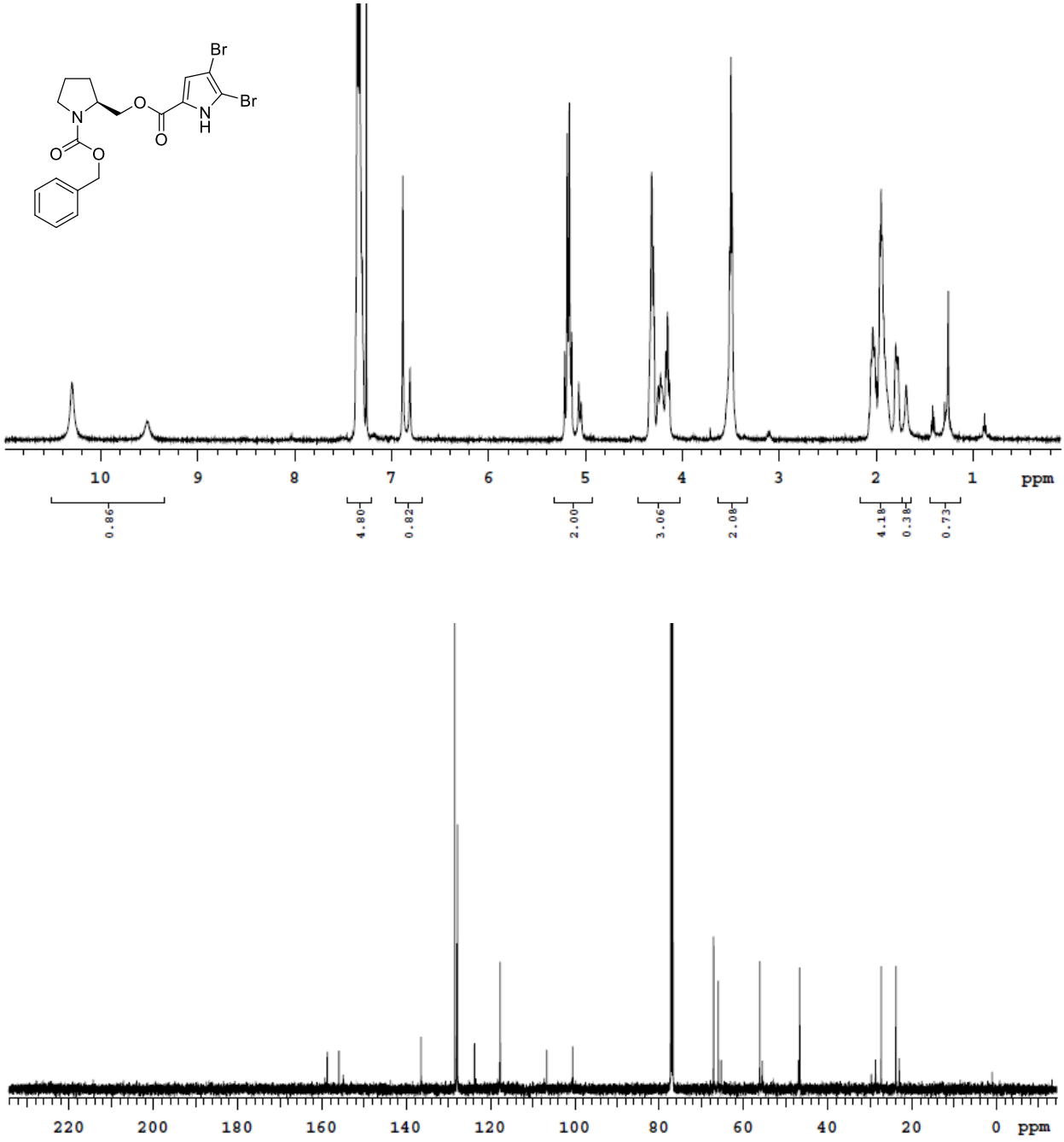


Figure 10.56: ^{1}H and ^{13}C Spectra of Compound III.18

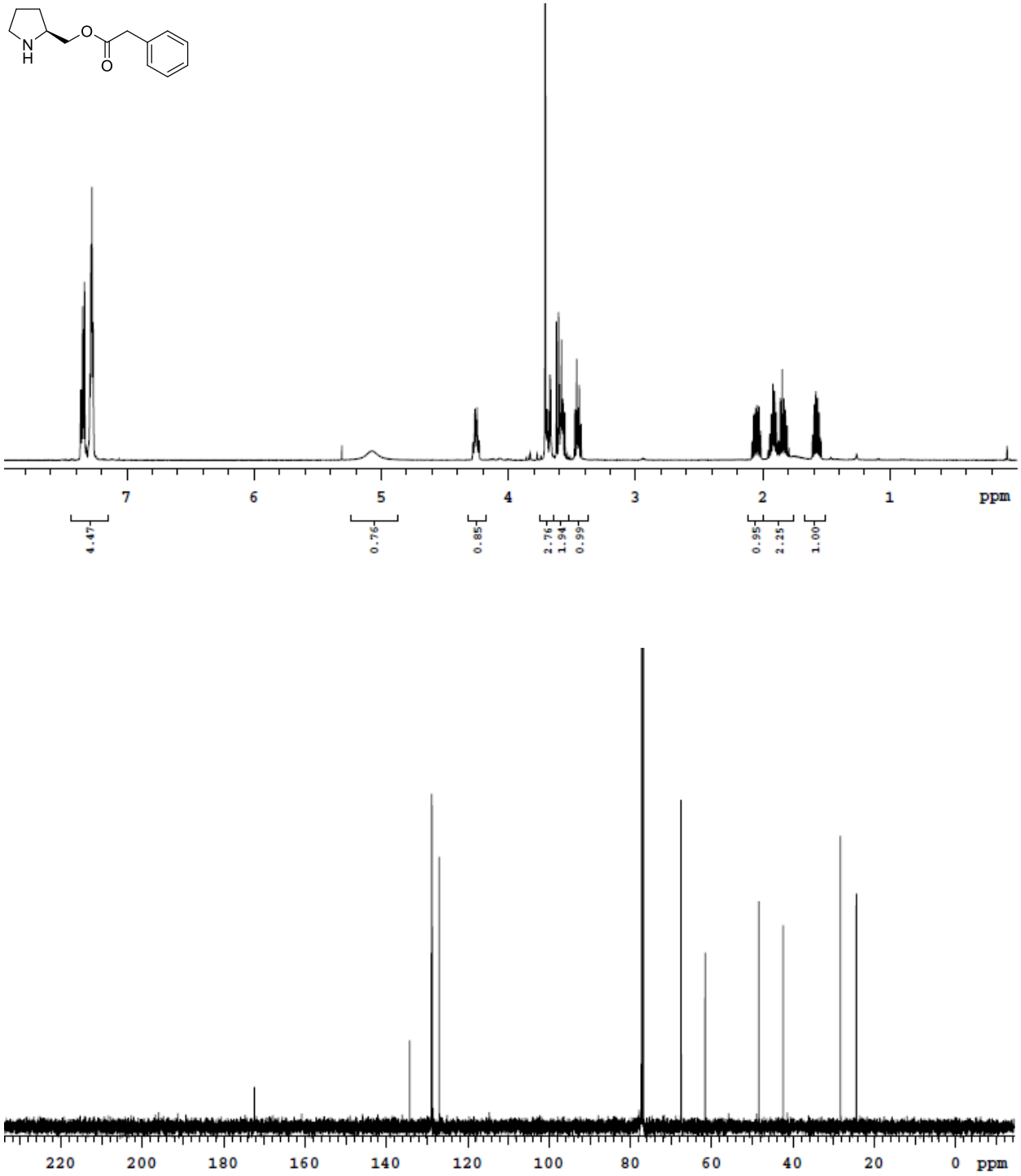


Figure 10.57: ^{1}H and ^{13}C Spectra of *N*-Boc-Homo-*L*-proline

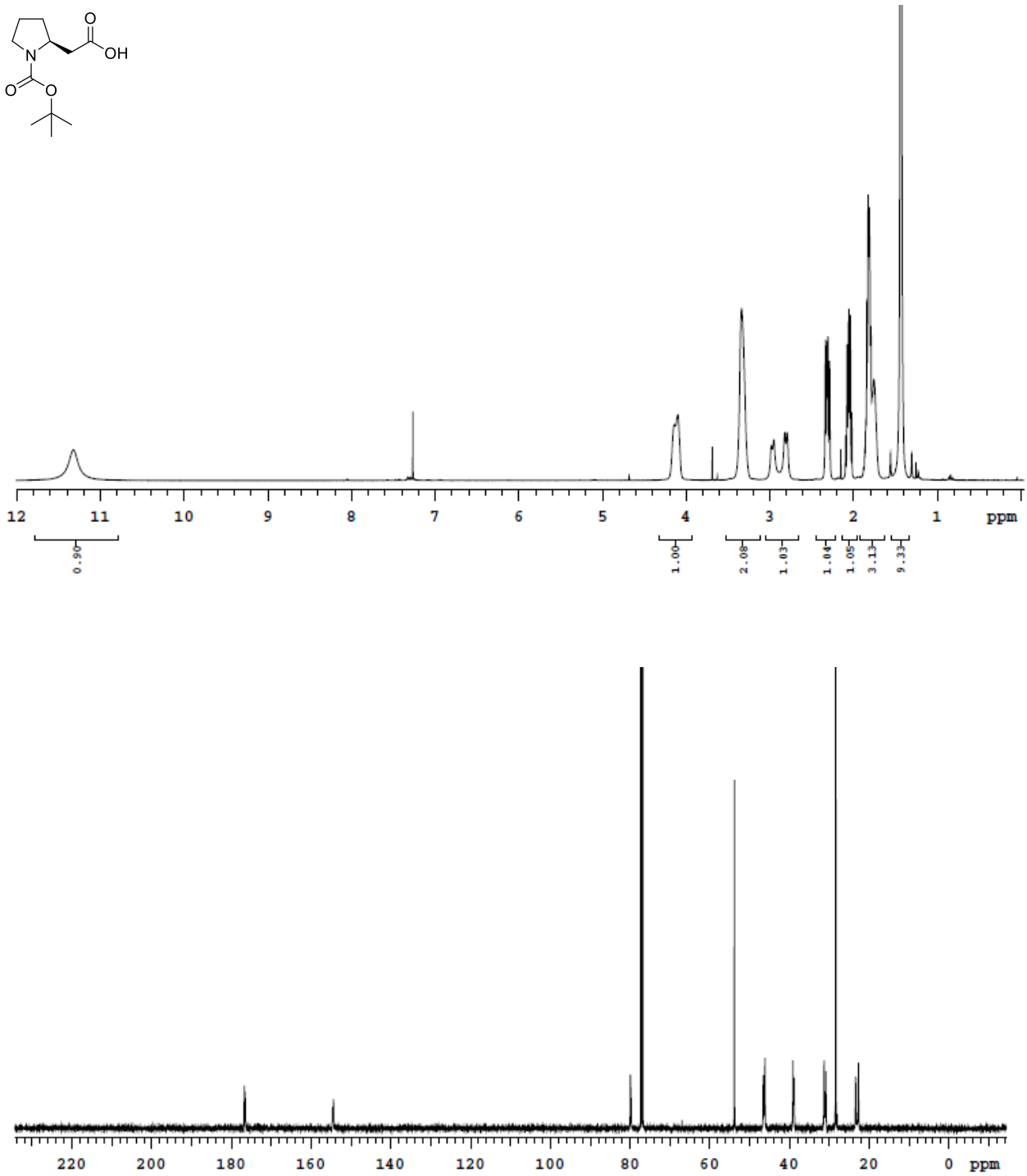


Figure 10.58: ^{1}H and ^{13}C Spectra of Compound IV.1a

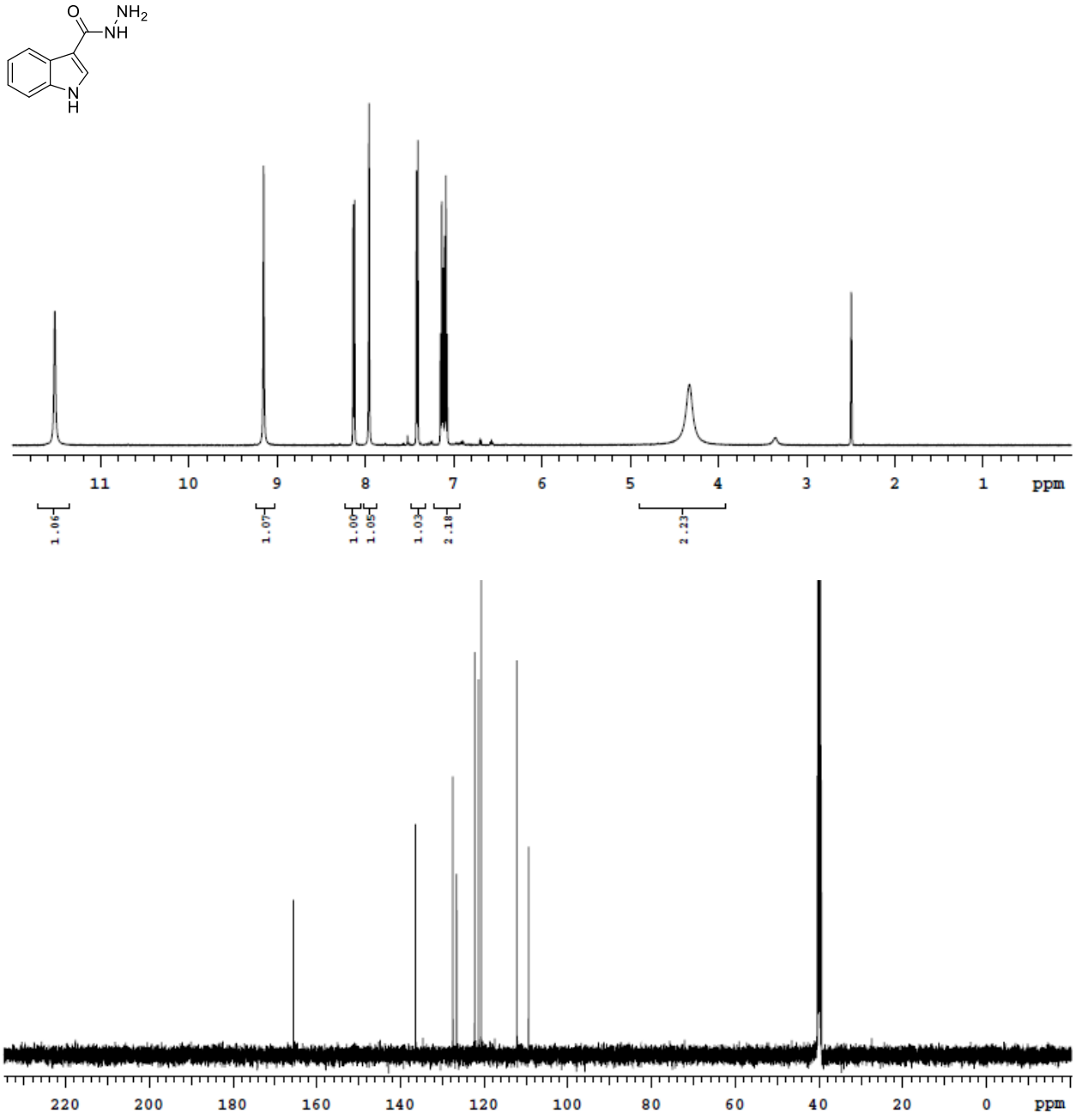


Figure 10.59: ^{1}H and ^{13}C Spectra of Compound IV.1

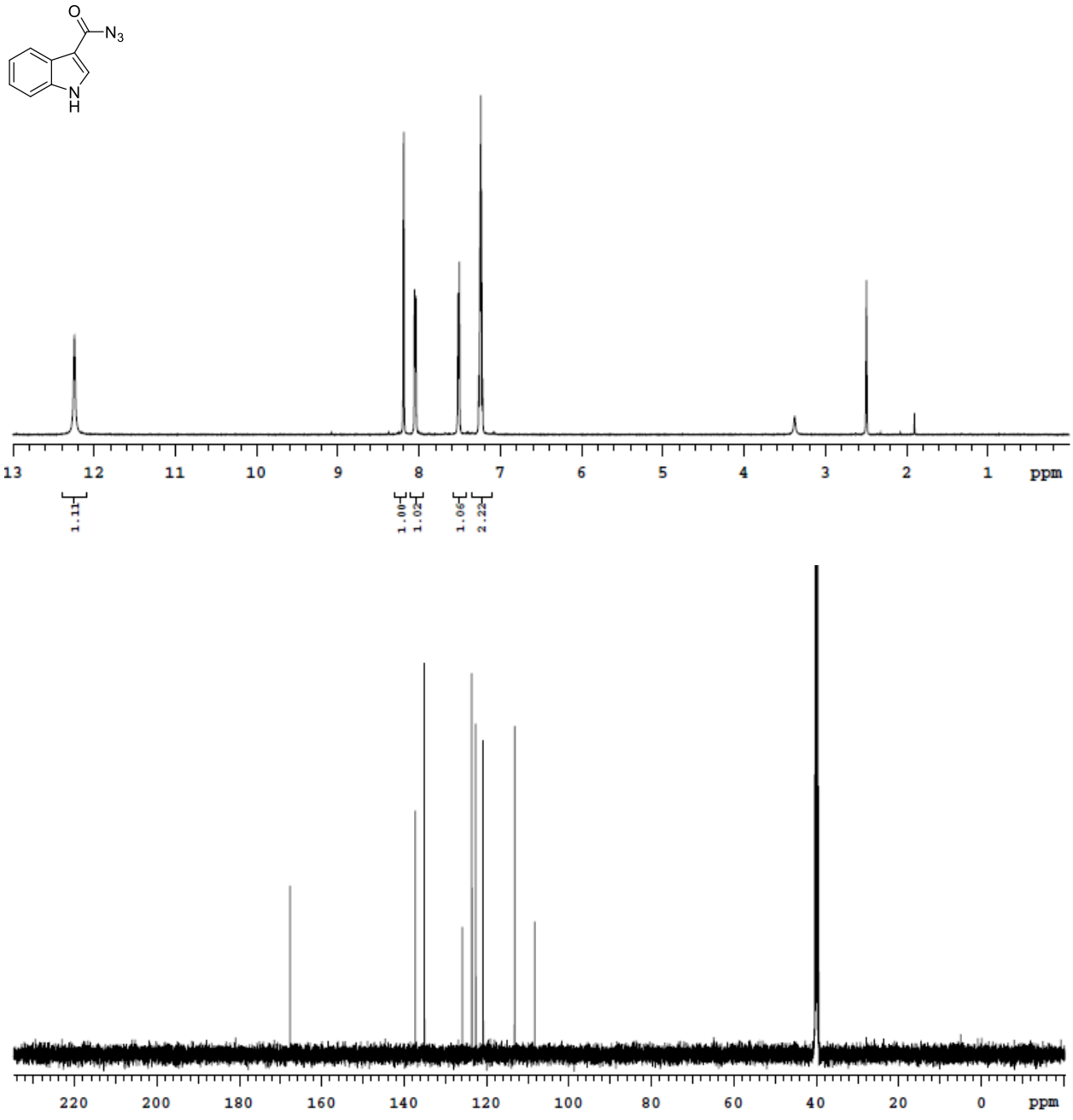


Figure 10.60: ^{1}H and ^{13}C Spectra of Compound IV.2.

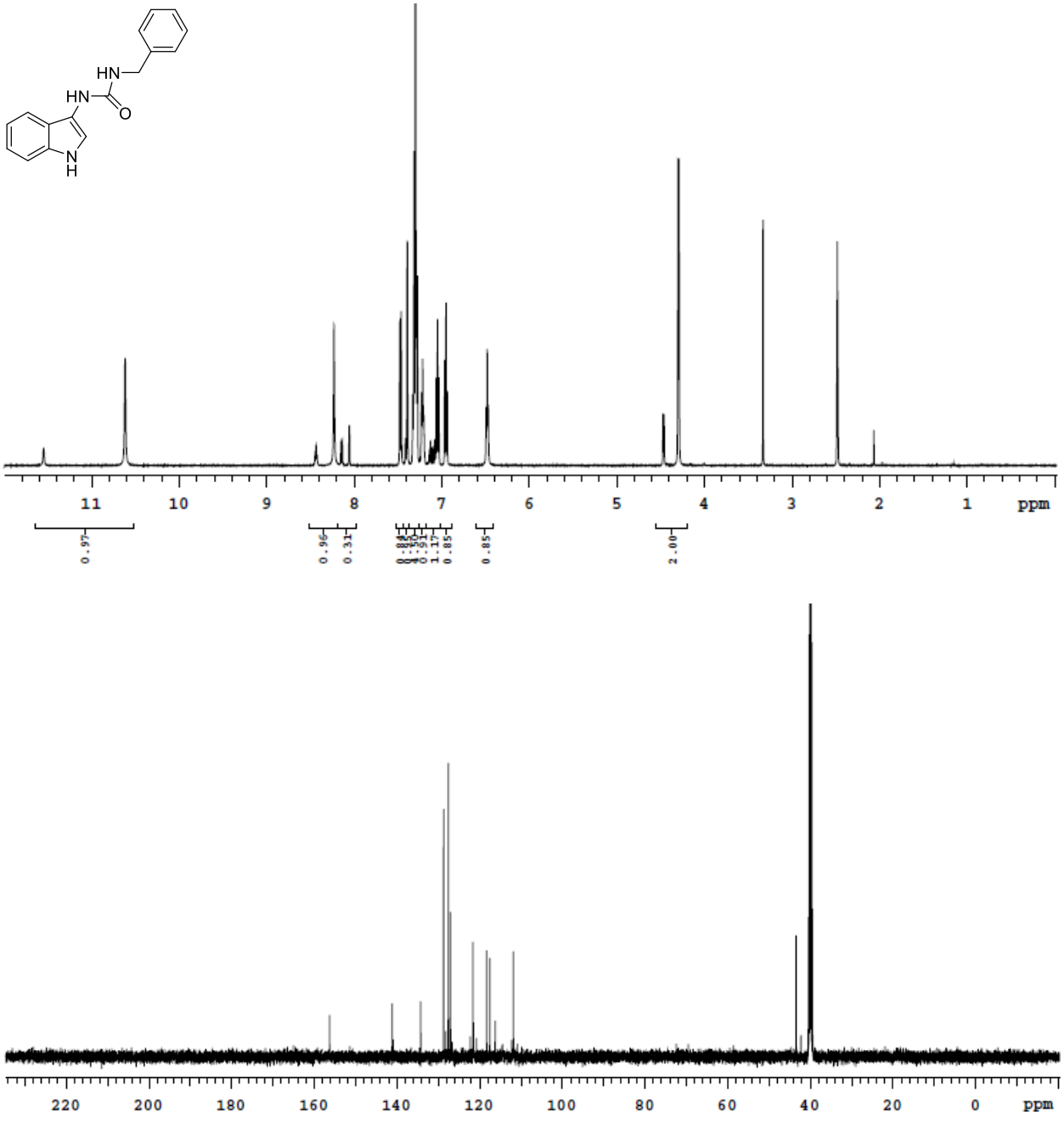


Figure 10.61: gCOSY Spectra of Compound IV.2

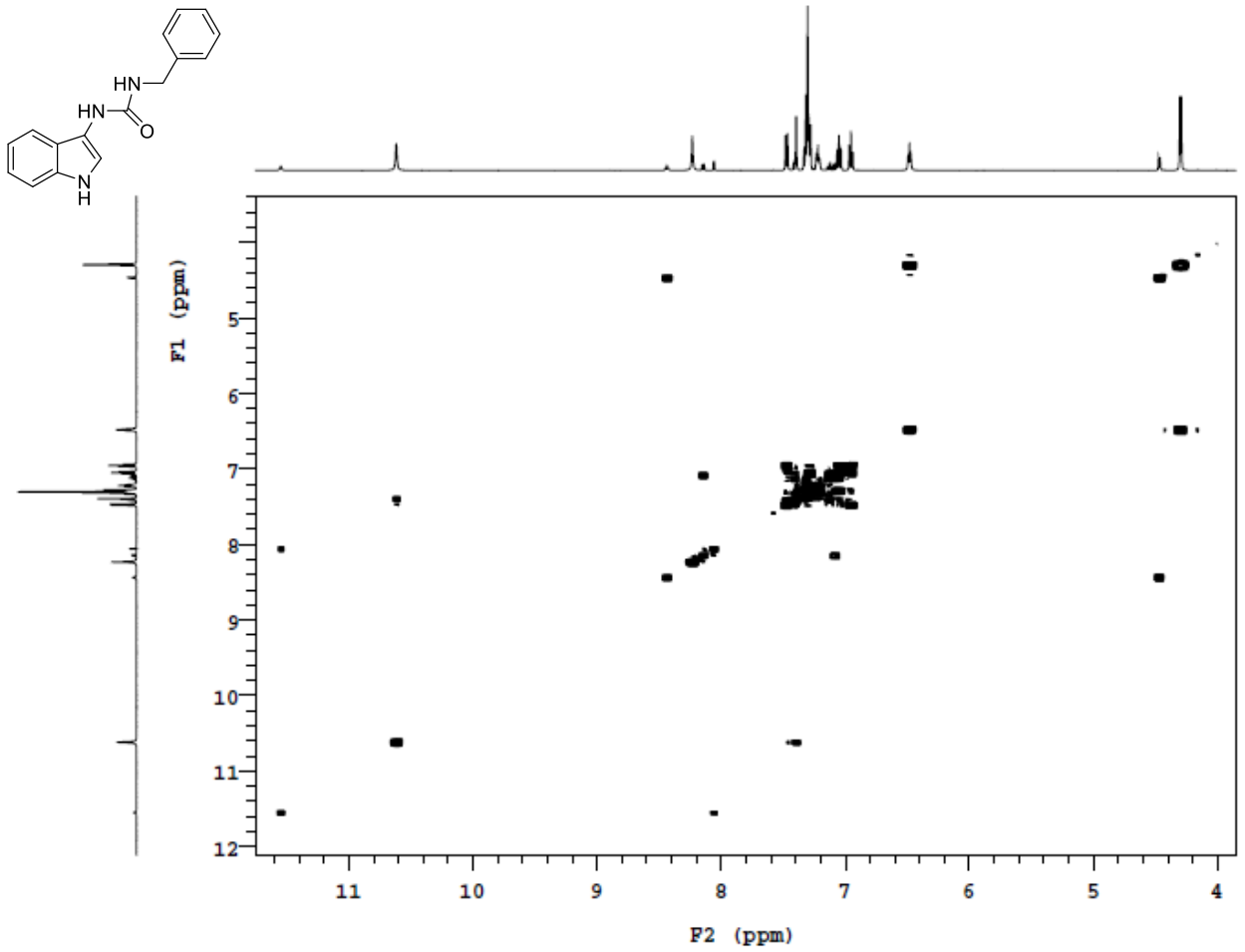


Figure 10.62: gHMQC Spectra of Compound IV.2

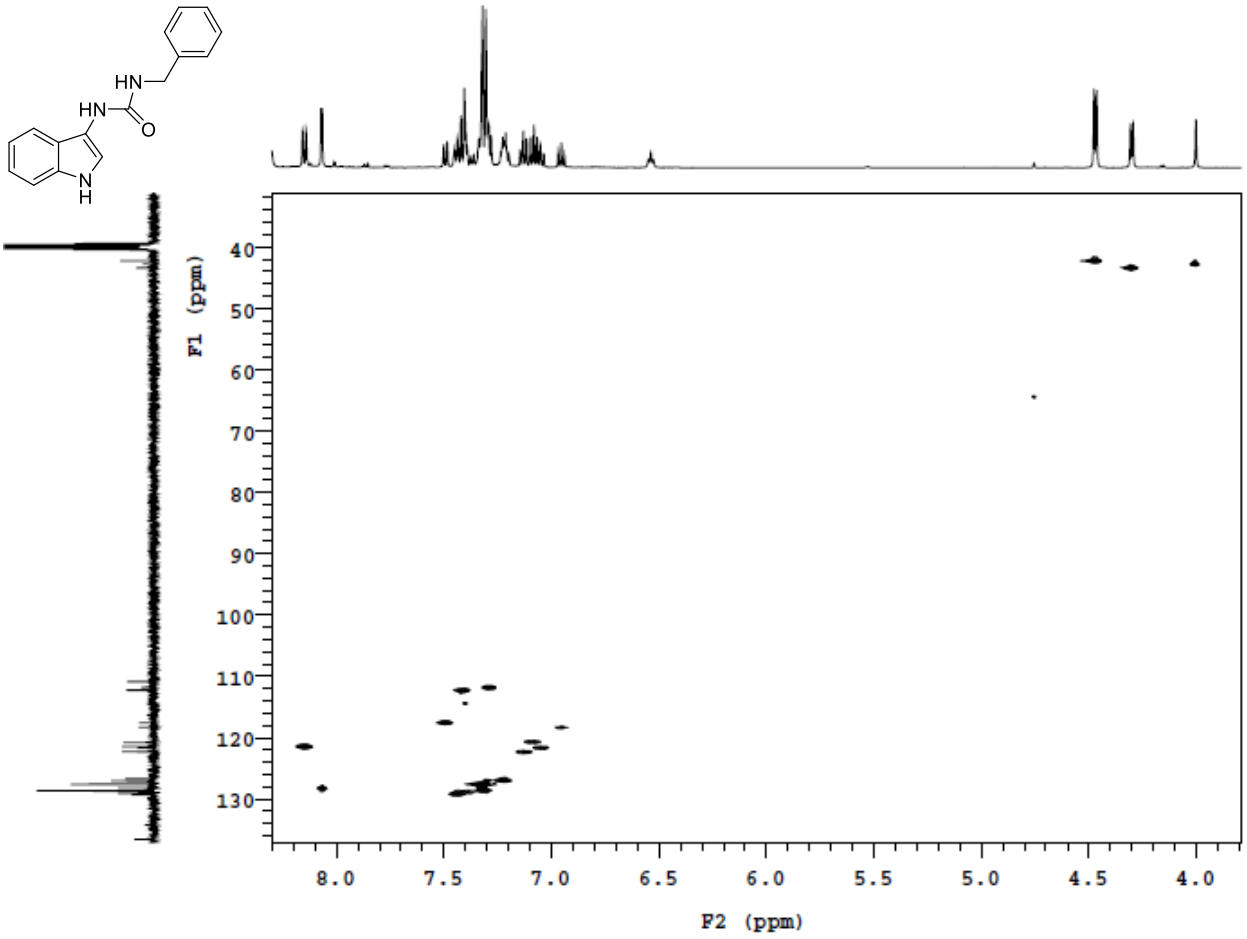


Figure 10.63: ^{1}H and ^{13}C Spectra of Compound IV.3a

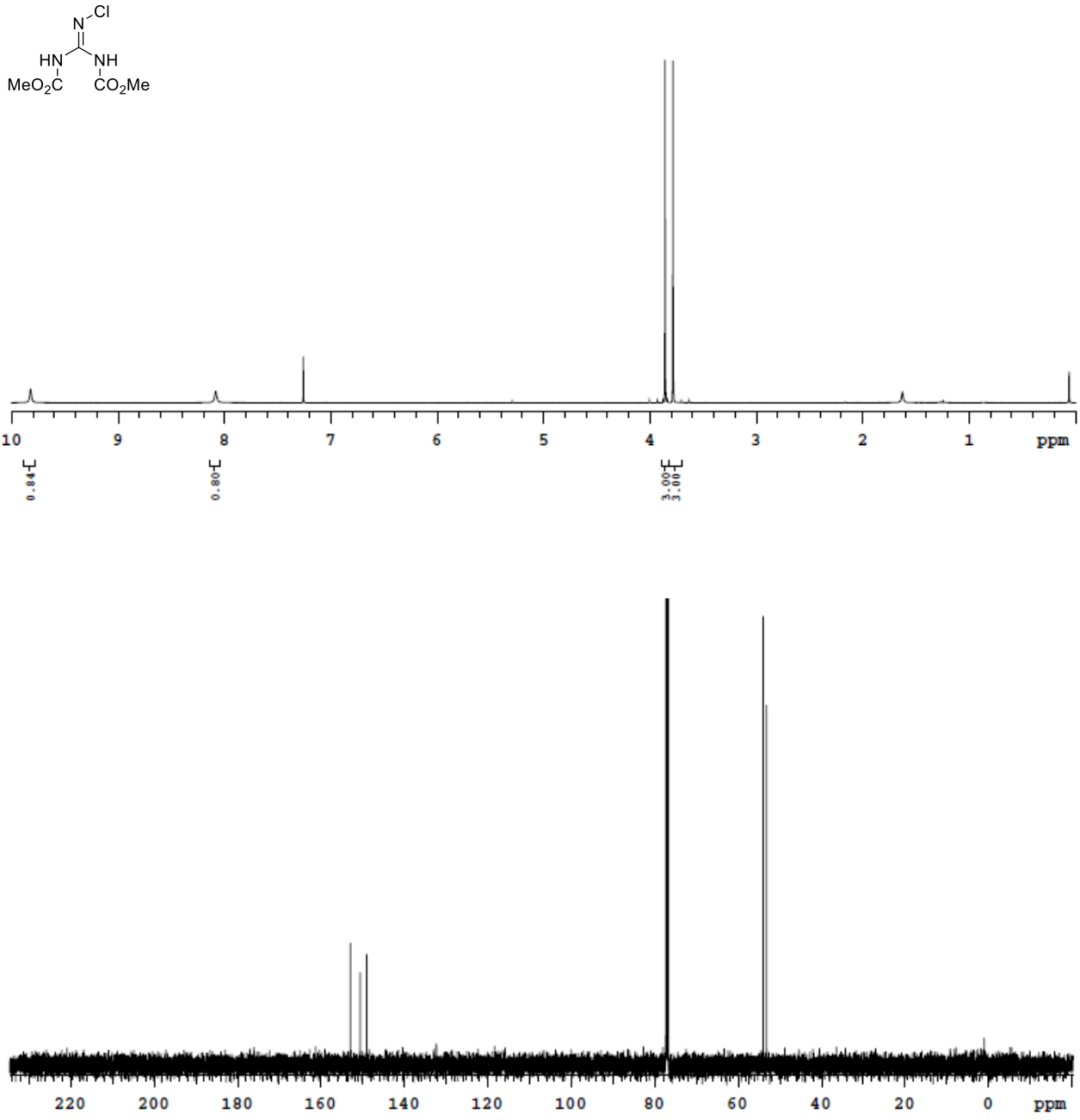


Figure 10.64: ^{1}H and ^{13}C Spectra of Compound IV.3

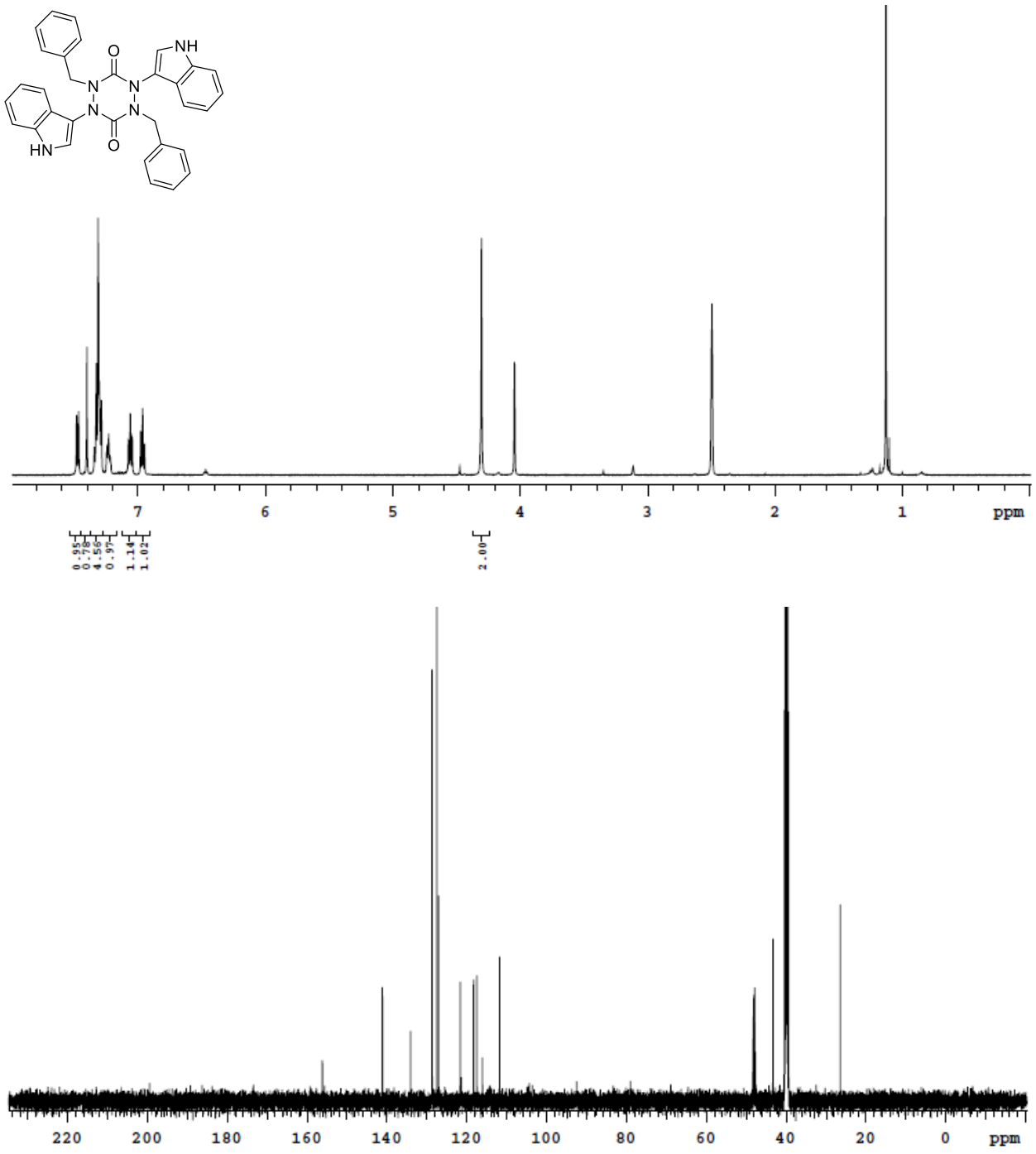


Figure 10.65: gHMQC Spectra of Compound IV.3

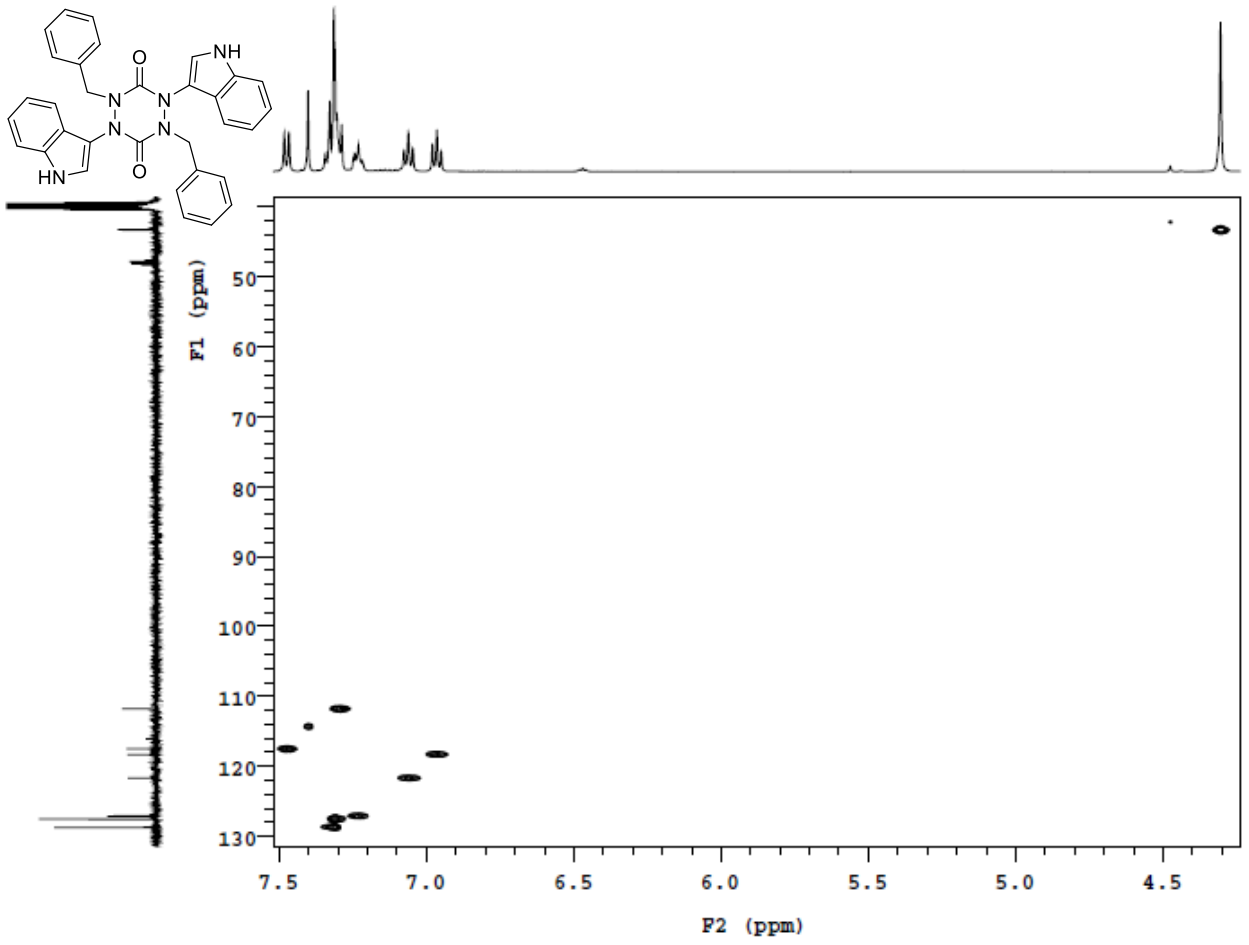


Figure 10.66: ^{1}H and ^{13}C Spectra of Compound IV.4

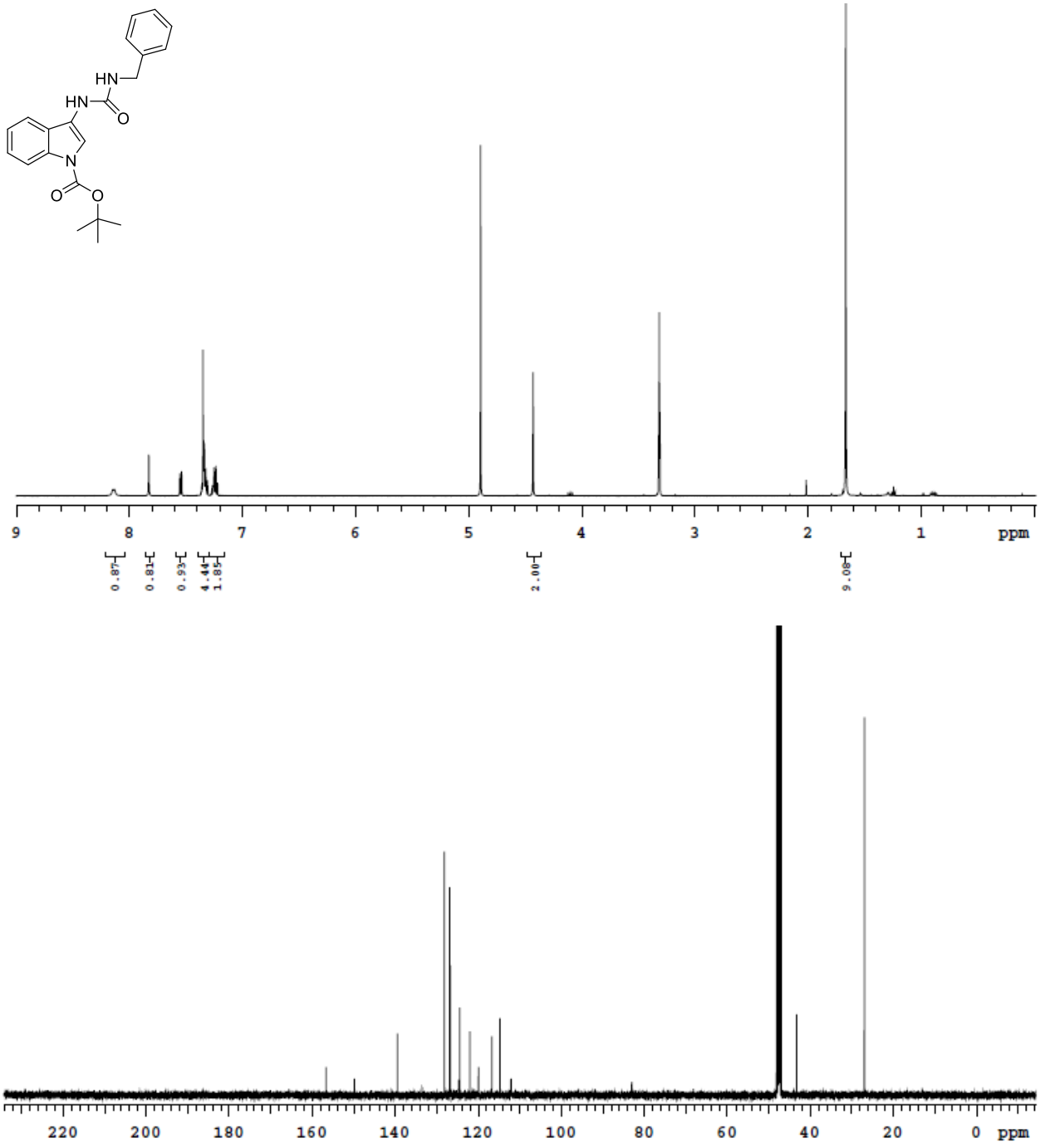


Figure 10.67: ^{1}H Spectra of Compound IV.5

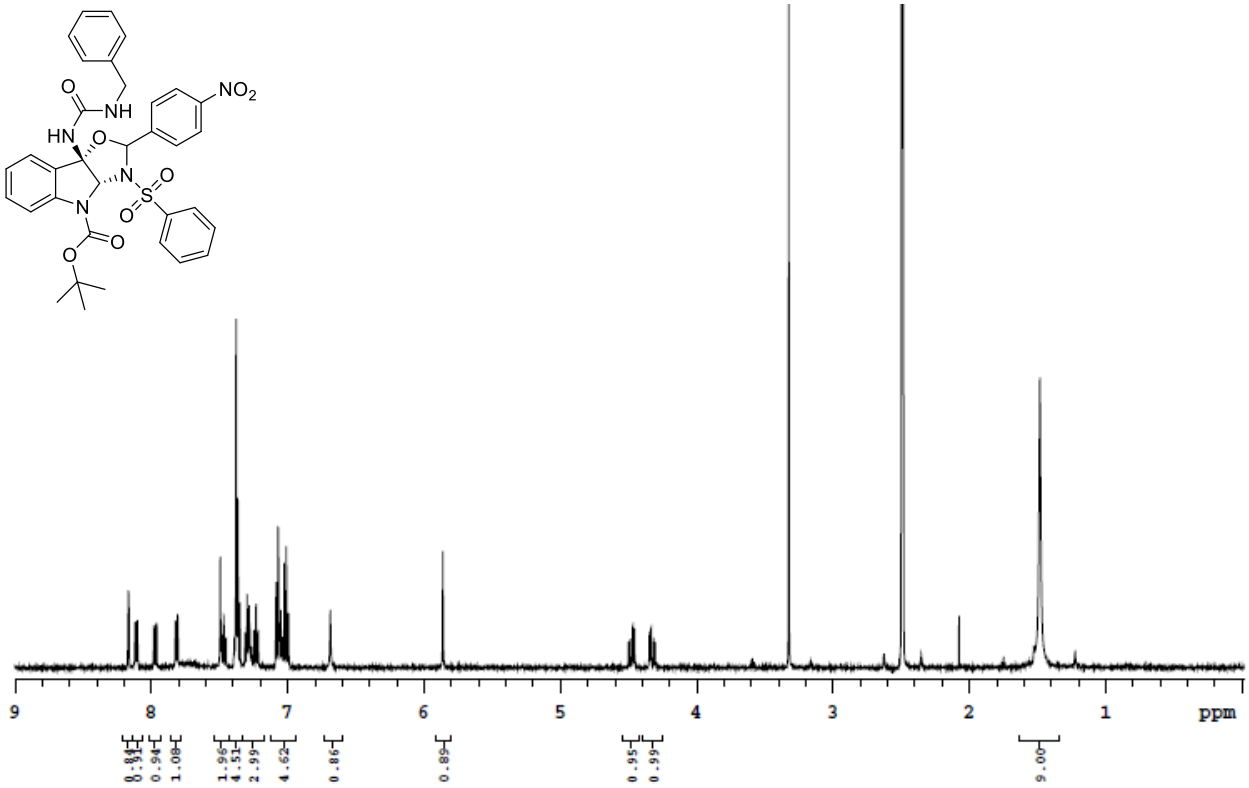


Figure 10.68: ^{1}H and ^{13}C Spectra of Compound IV.6

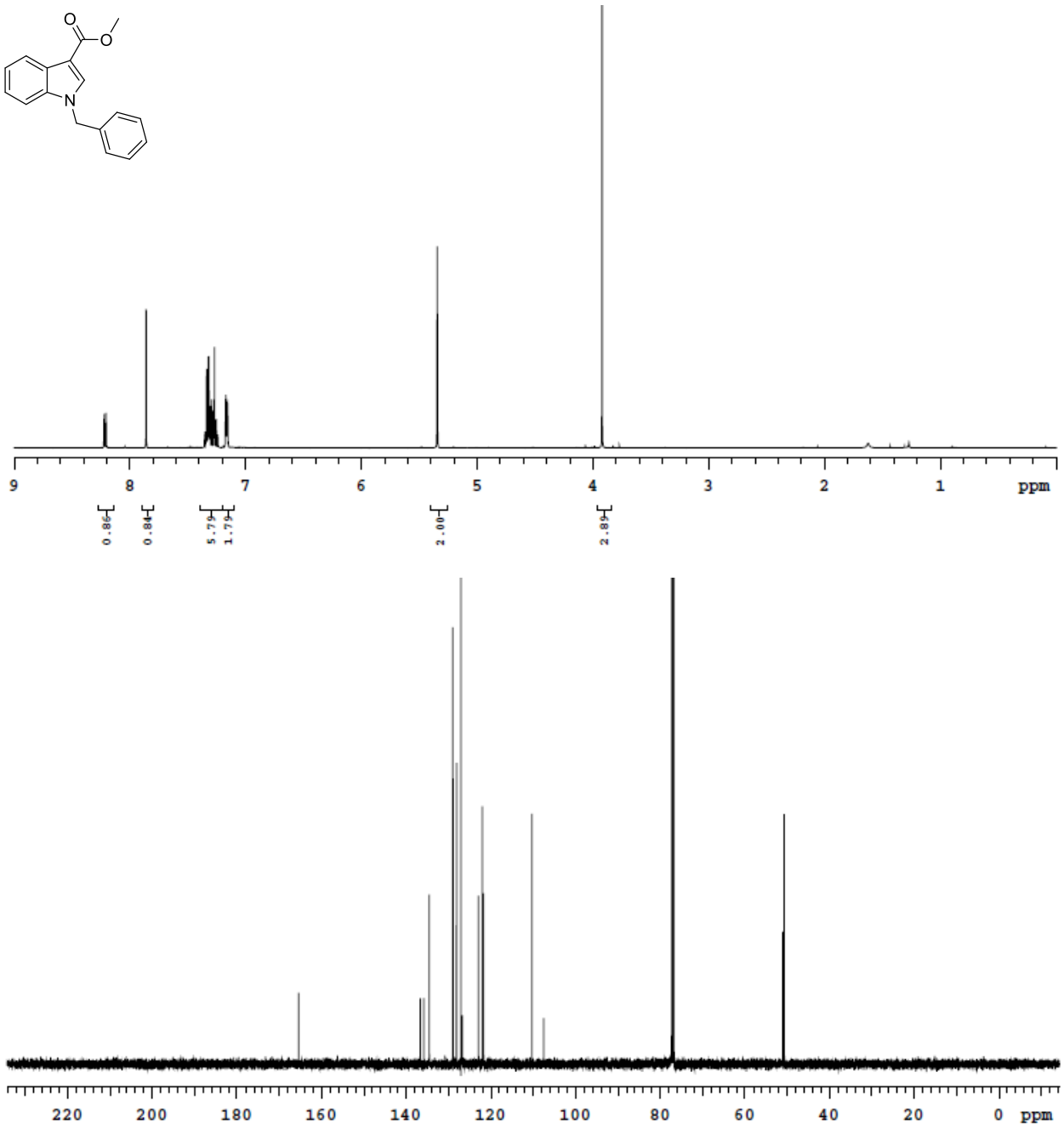


Figure 10.69: ^{1}H and ^{13}C Spectra of Compound IV.7

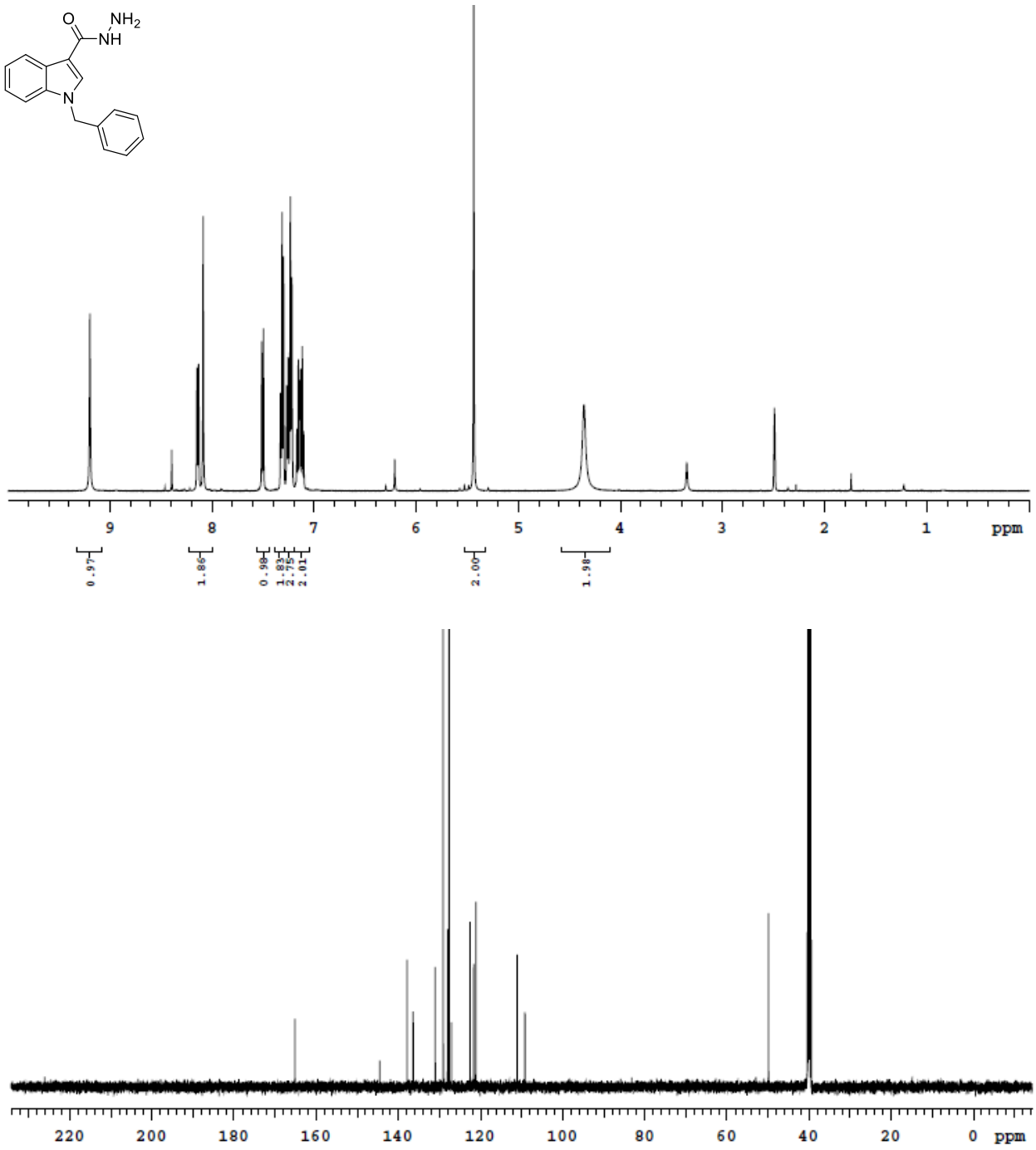


Figure 10.70: ^{1}H and ^{13}C Spectra of Compound IV.7a

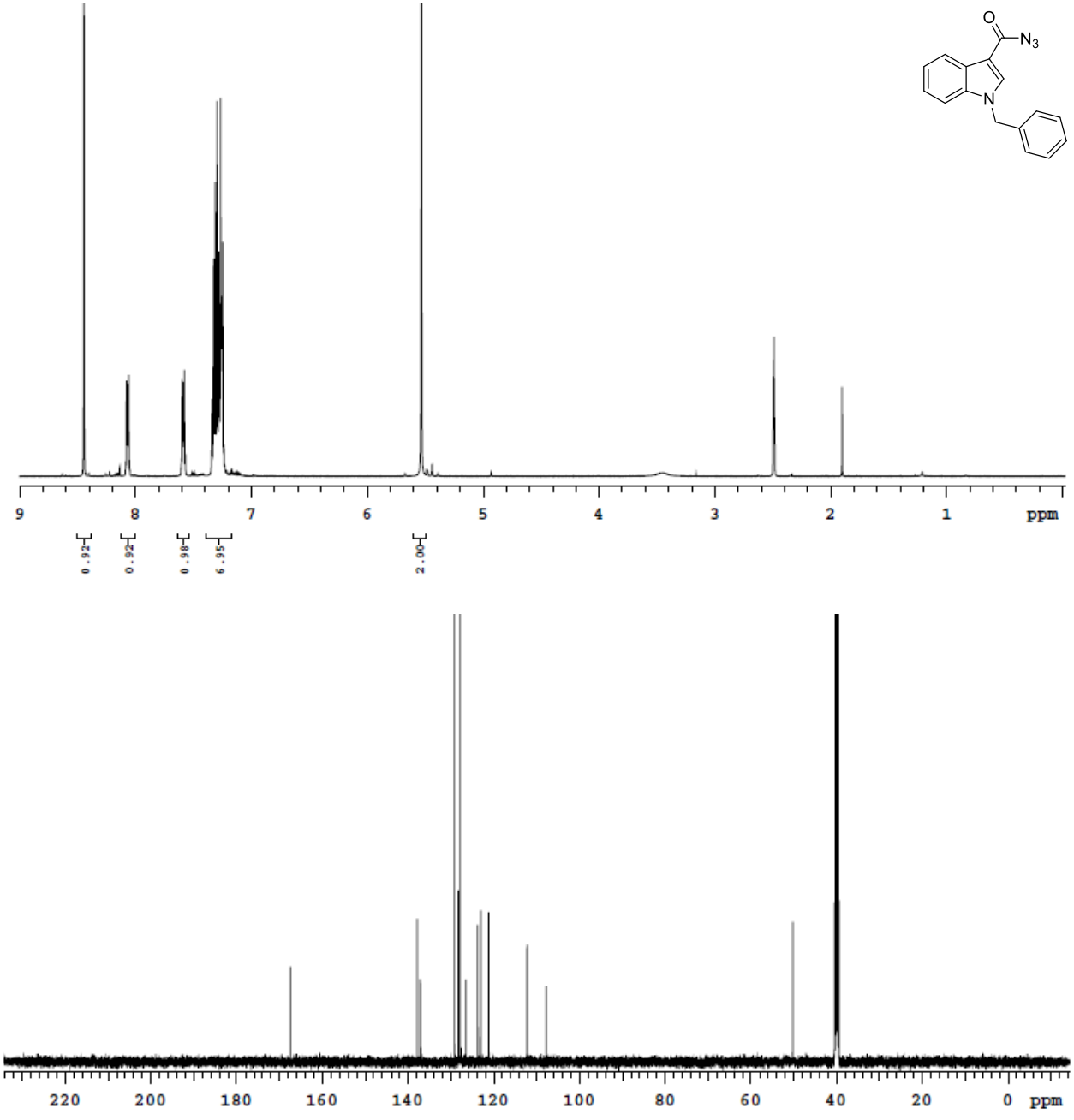


Figure 10.71: ^{1}H and ^{13}C Spectra of Compound IV.8

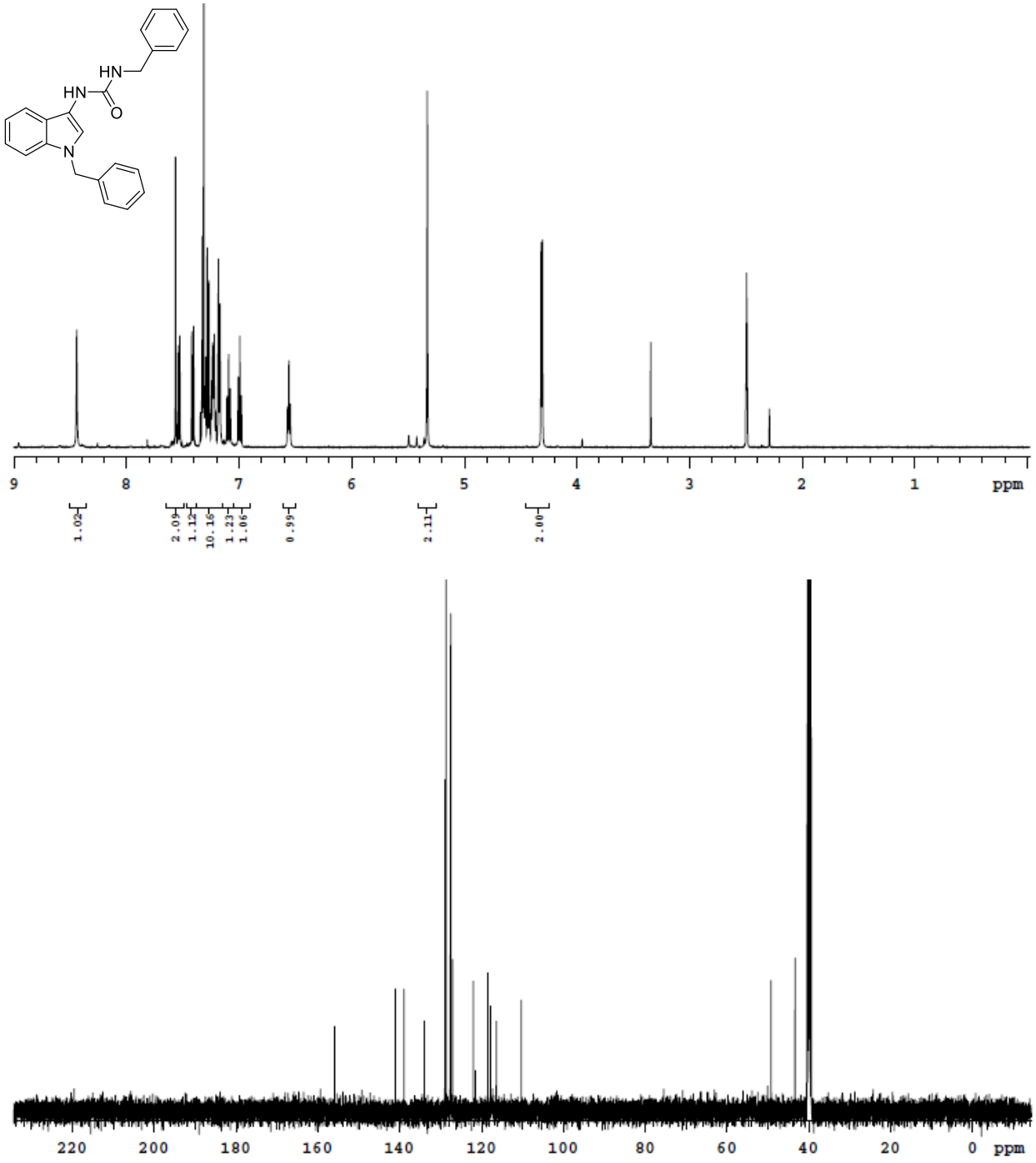


Figure 10.72: ^{1}H and ^{13}C Spectra of Compound IV.9

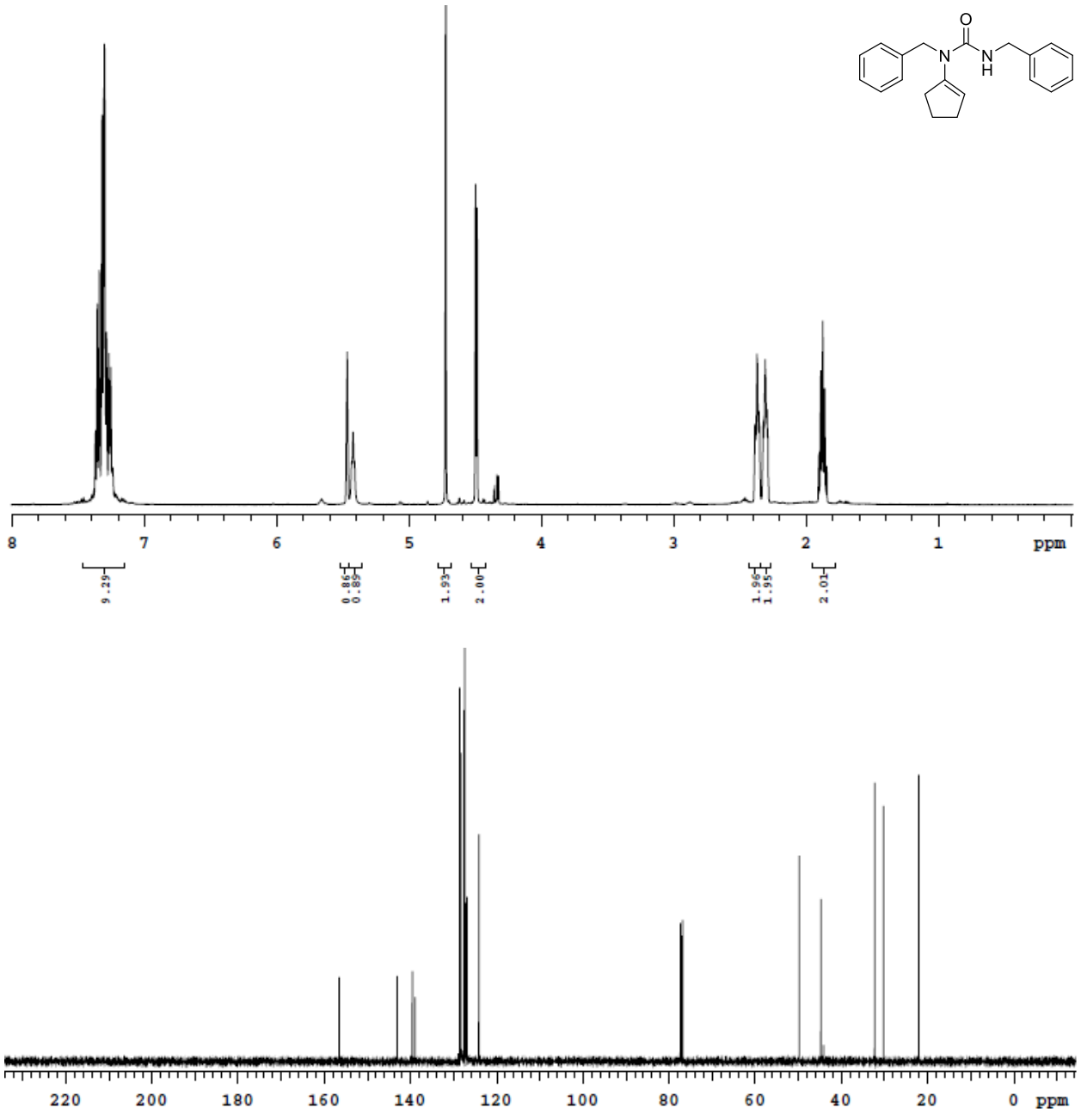


Figure 10.73: gCOSY Spectra of Compound IV.9

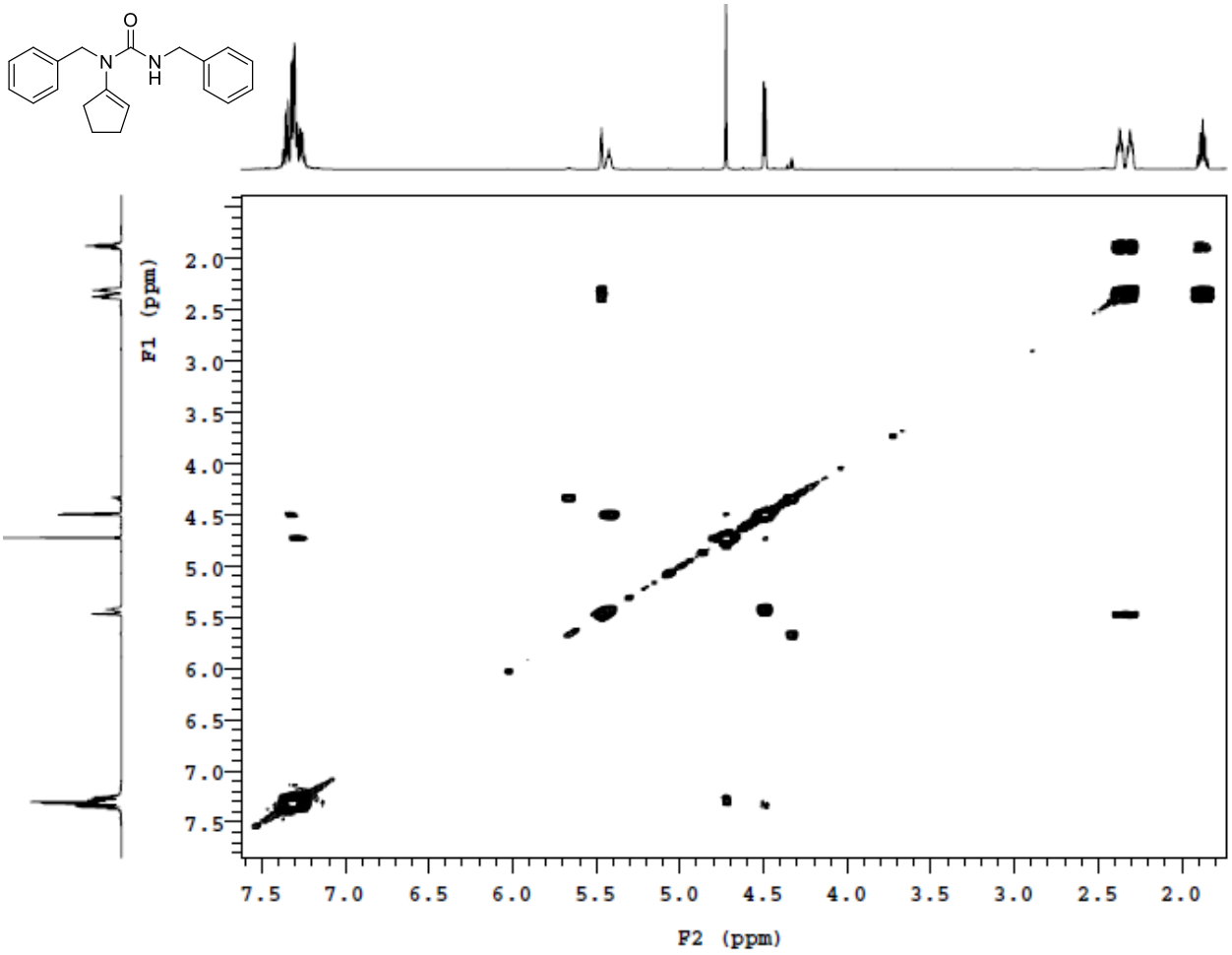


Figure 10.74: gHMQC Spectra of Compound IV.9

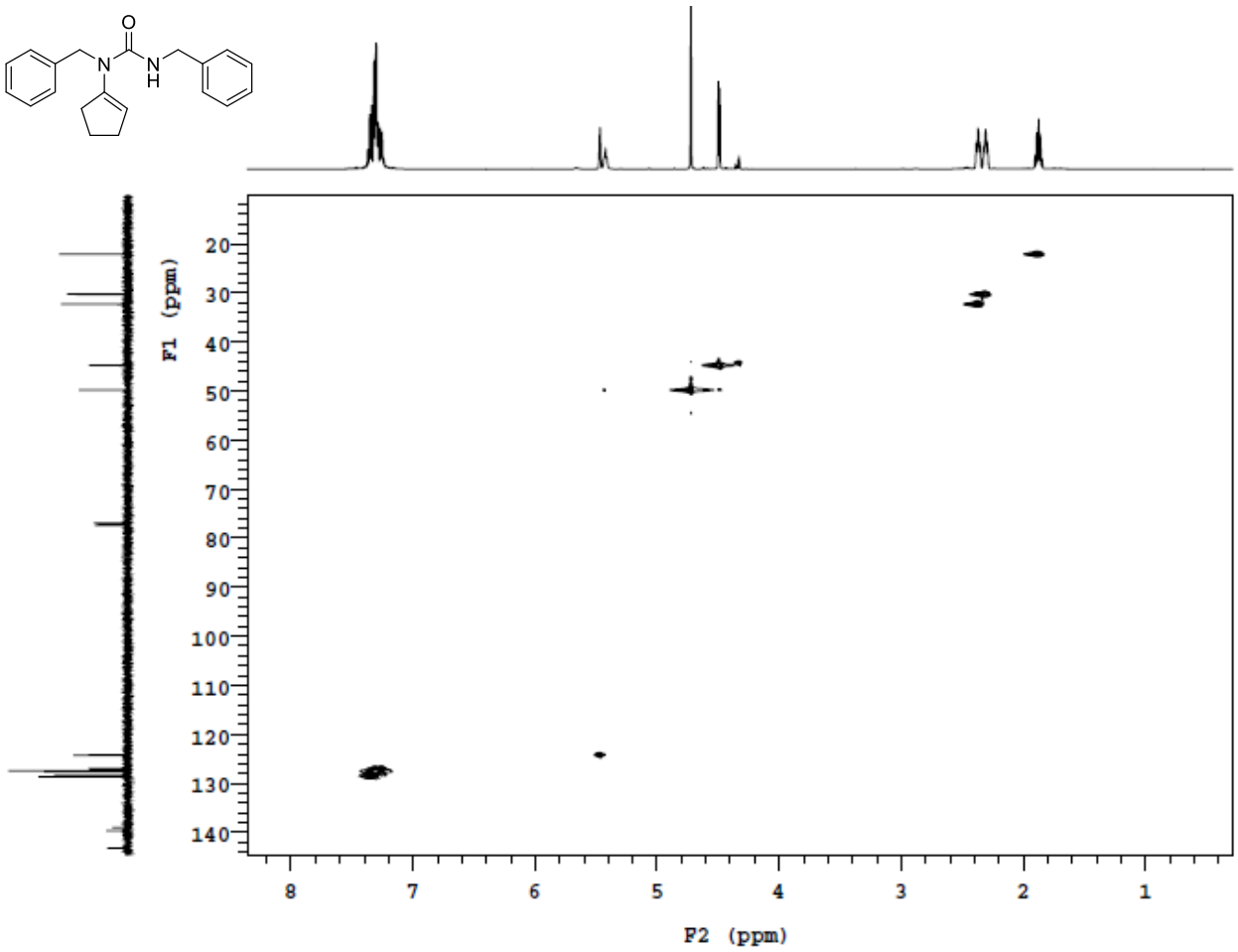


Figure 10.75: ^{1}H and ^{13}C Spectra of Compound V.1

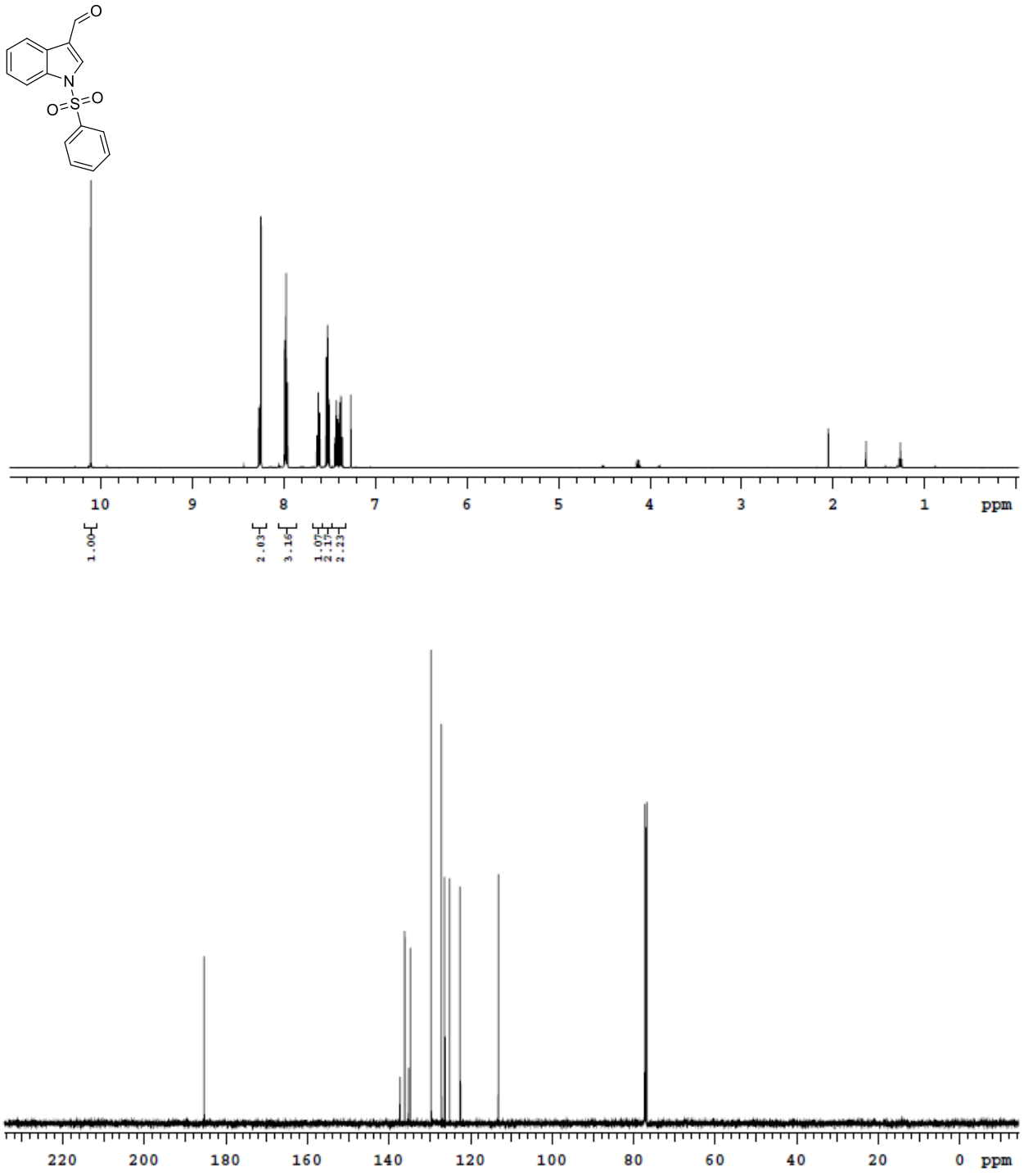


Figure 10.76: ^{1}H and ^{13}C Spectra of Compound V.1a

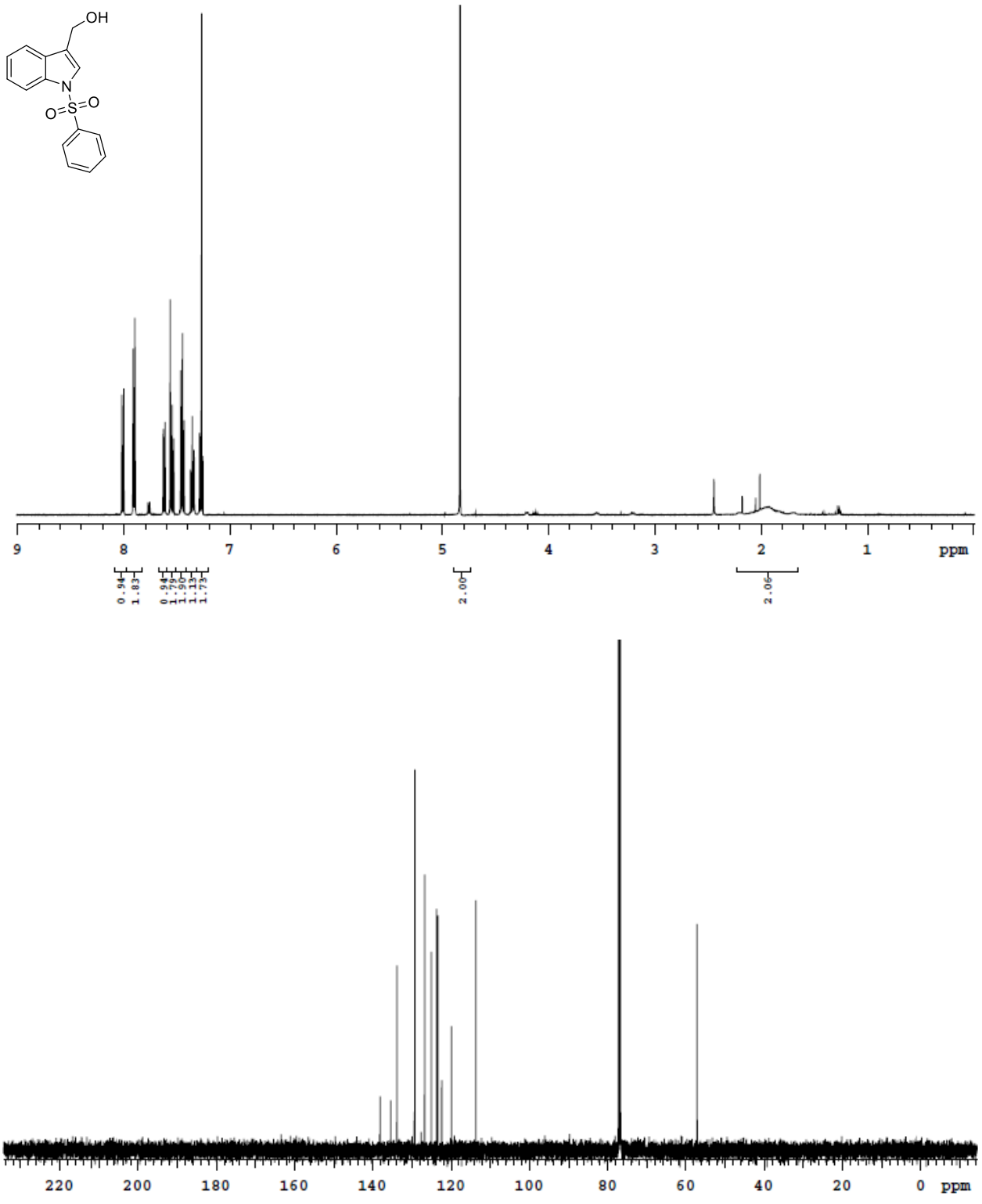


Figure 10.77: ^{1}H and ^{13}C Spectra of Compound V.2

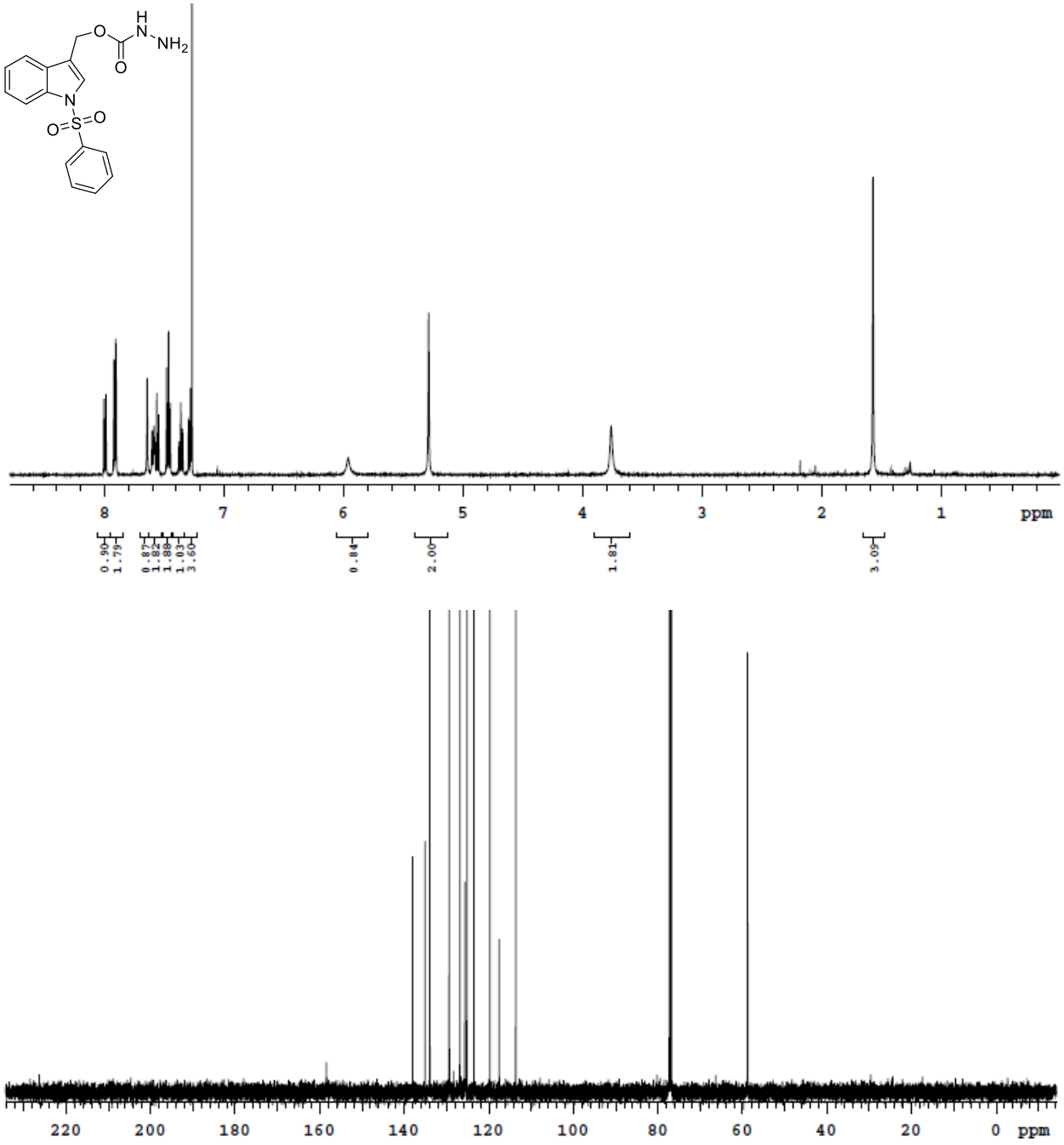


Figure 10.78: ^{1}H and ^{13}C Spectra of Compound V.3

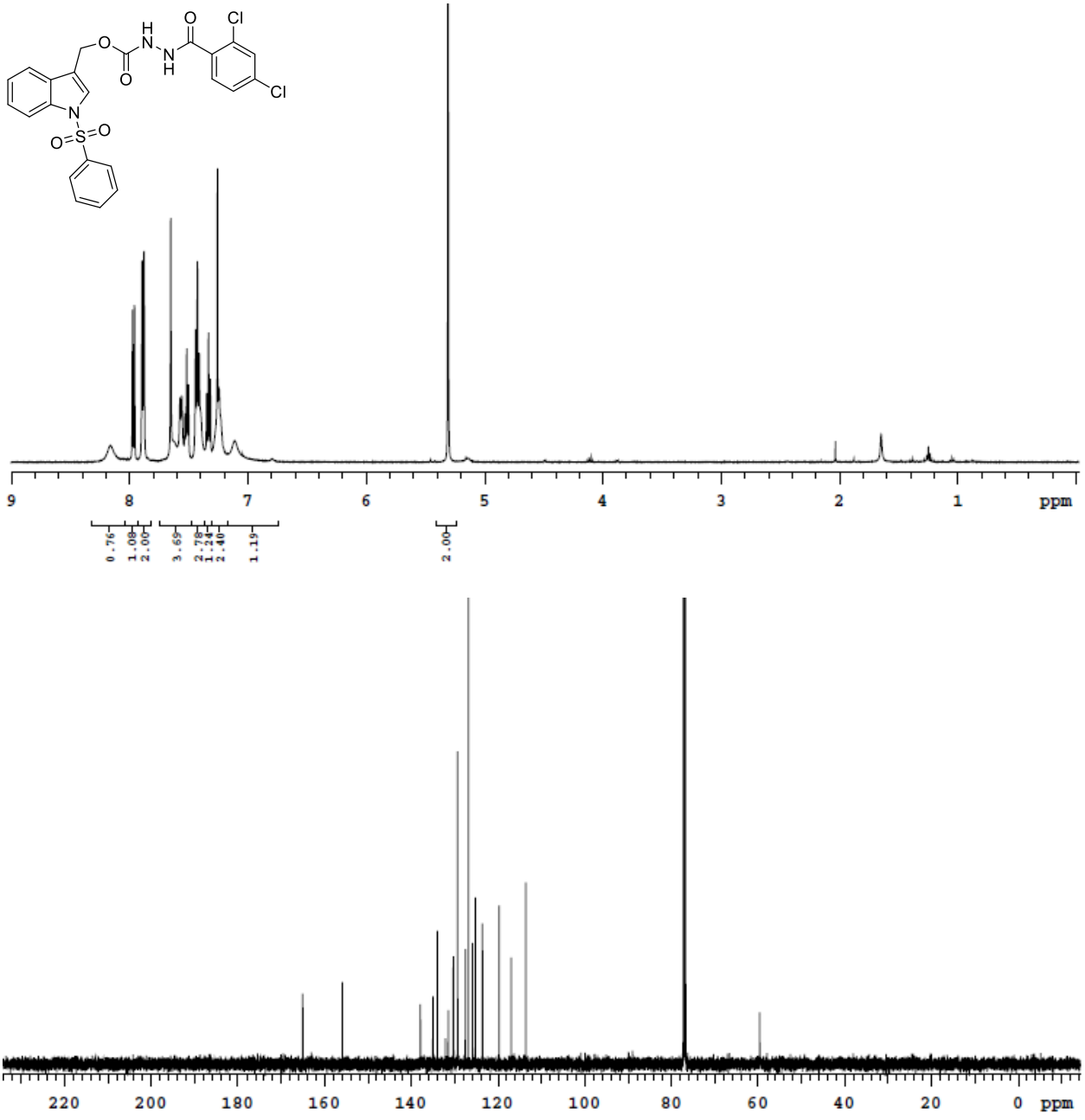


Figure 10.79: gHMQC Spectra of Compound V.3

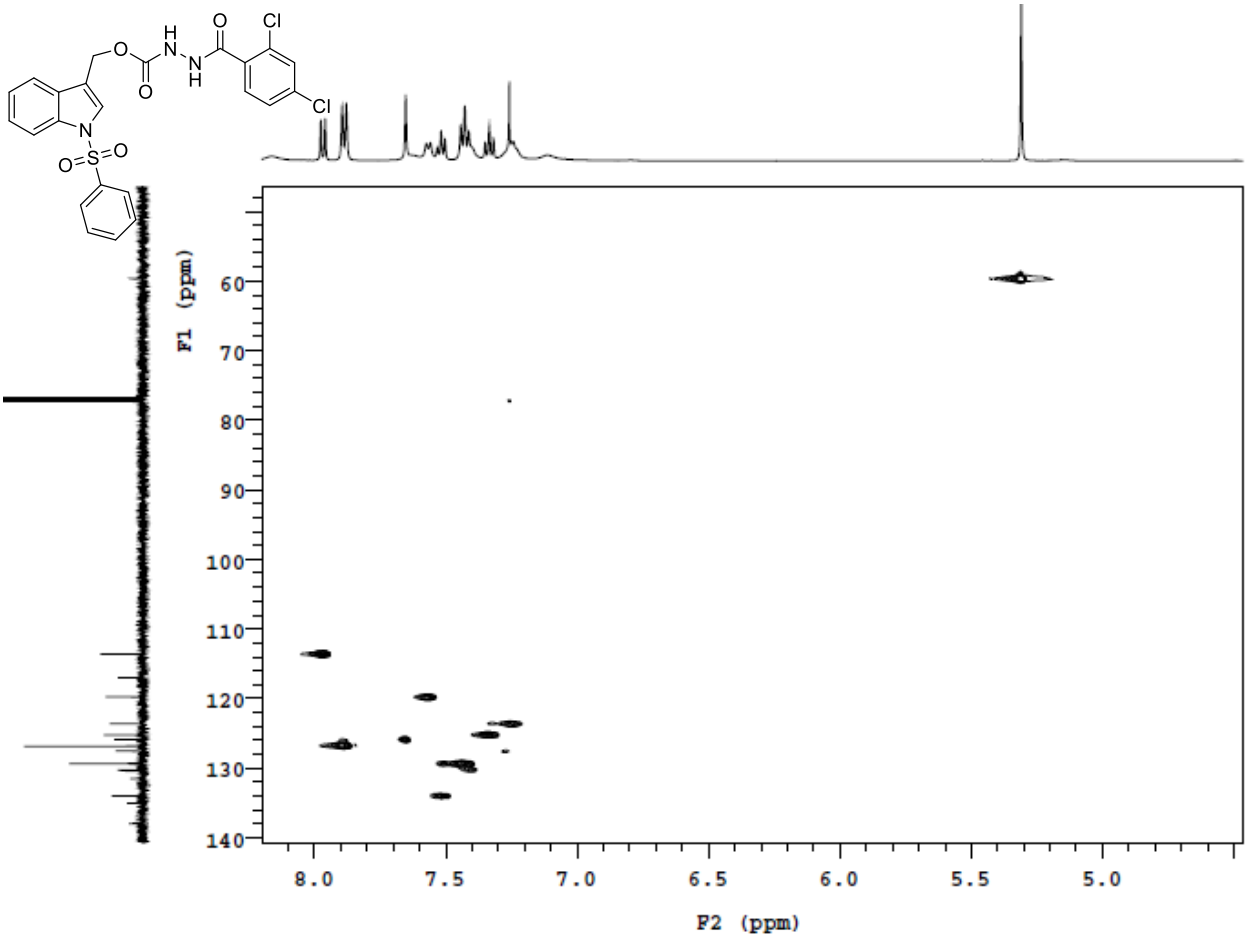


Figure 10.80: ^{1}H and ^{13}C Spectra of Compound V.4

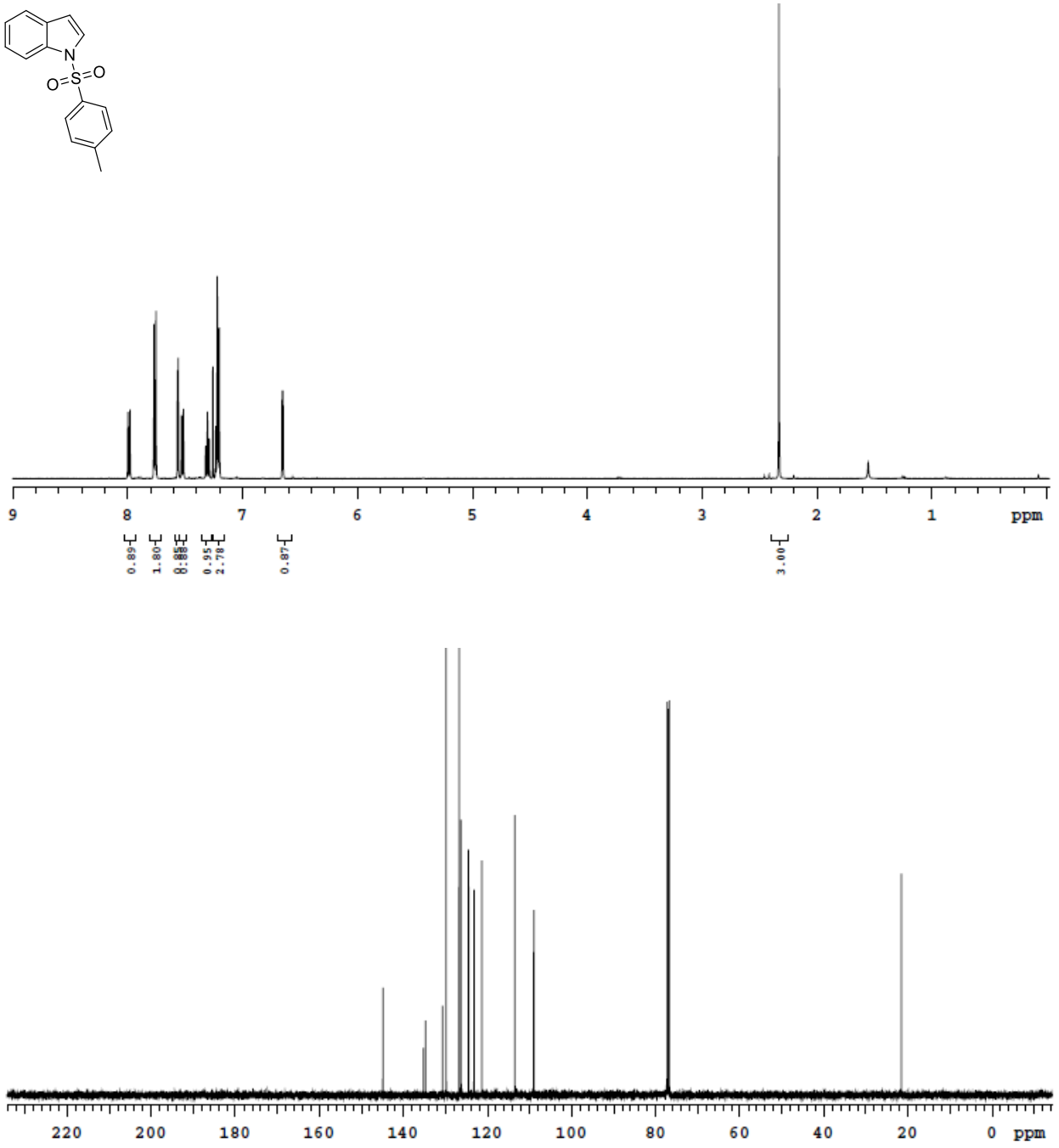


Figure 10.81: ^{1}H and ^{13}C Spectra of Compound V.5a

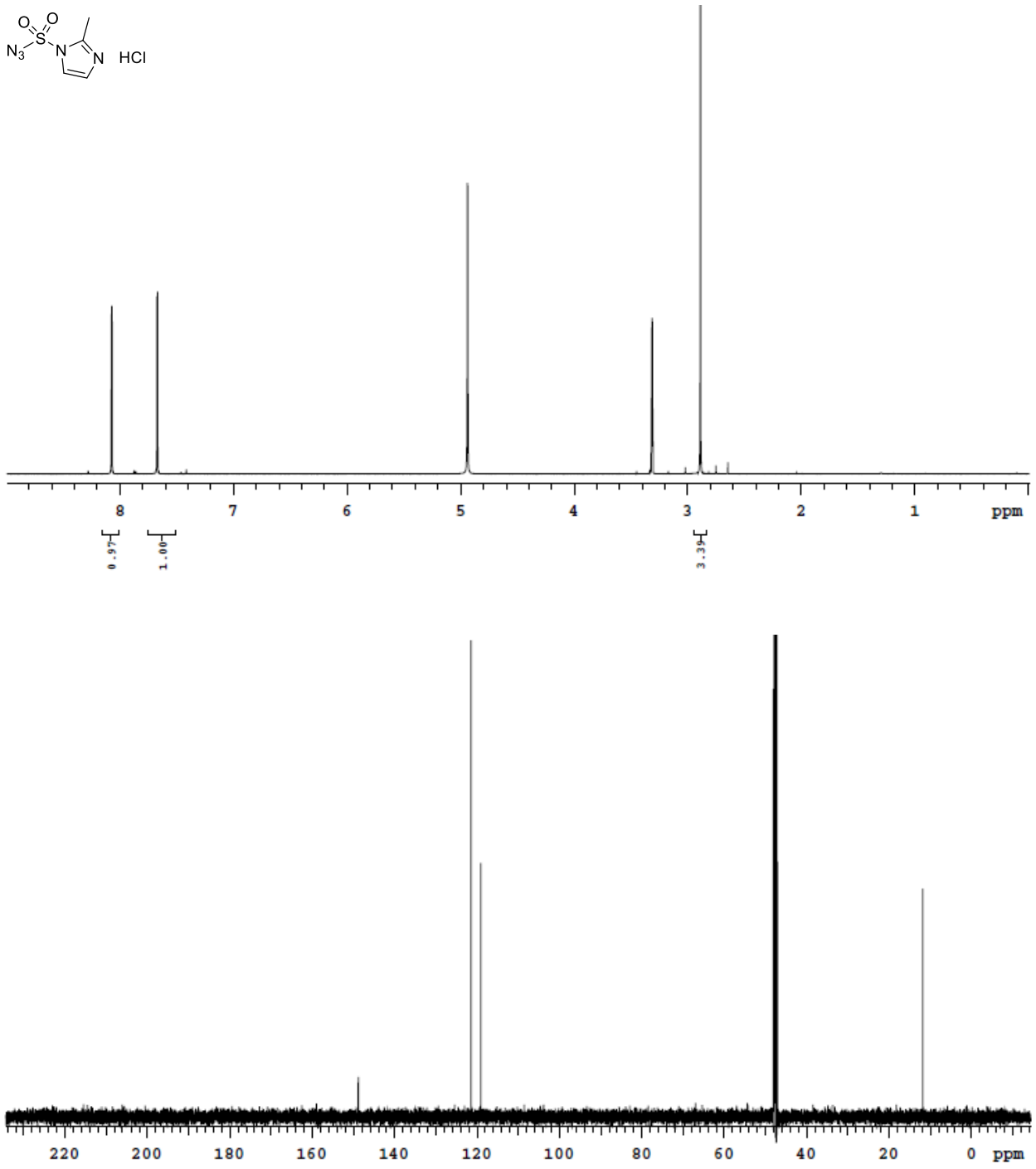


Figure 10.82: ^{1}H and ^{13}C Spectra of Compound V.5

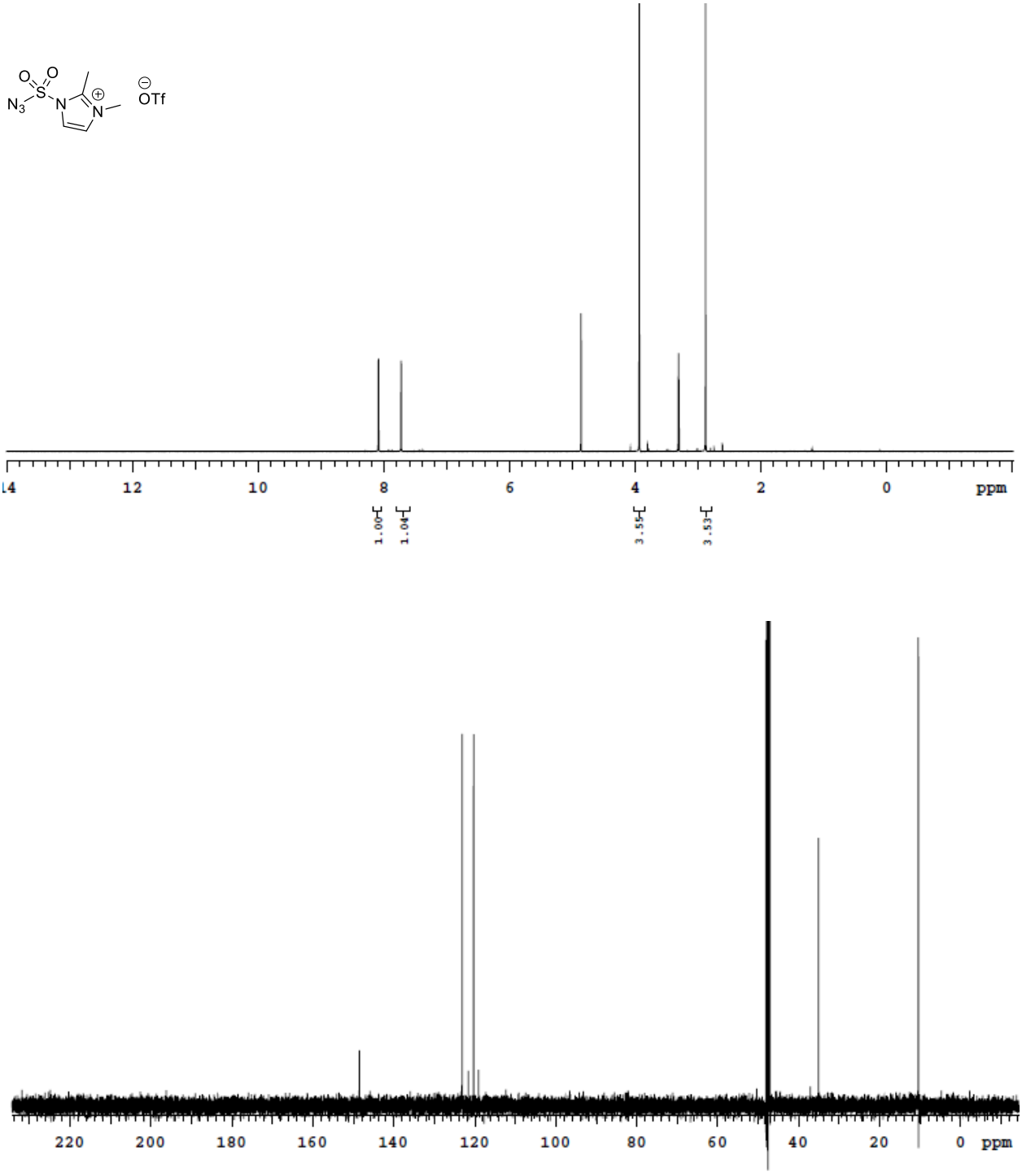


Figure 10.83: ^{1}H and ^{13}C Spectra of Compound V.6

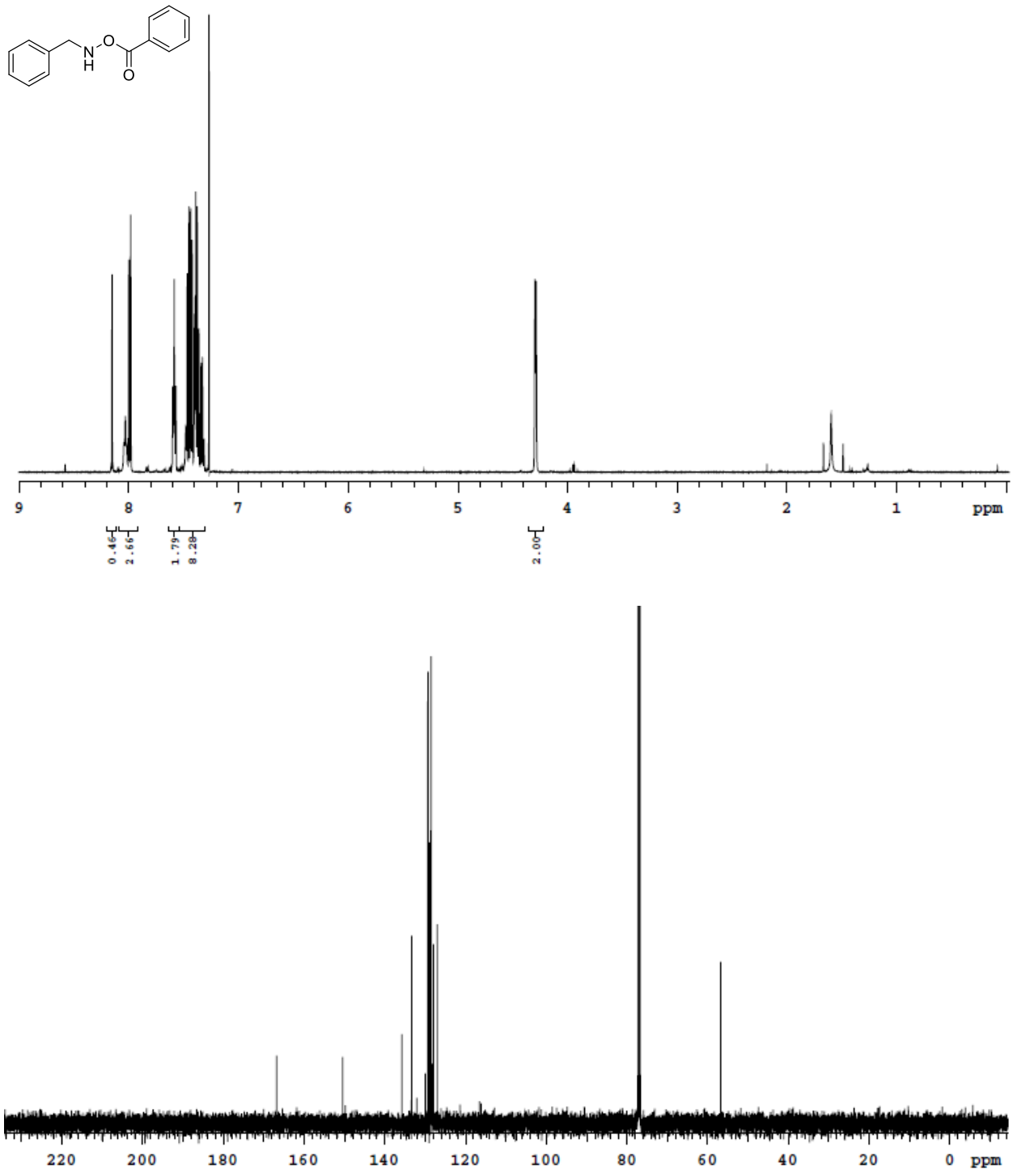


Figure 10.84: ^{1}H and ^{13}C Spectra of Compound V.7

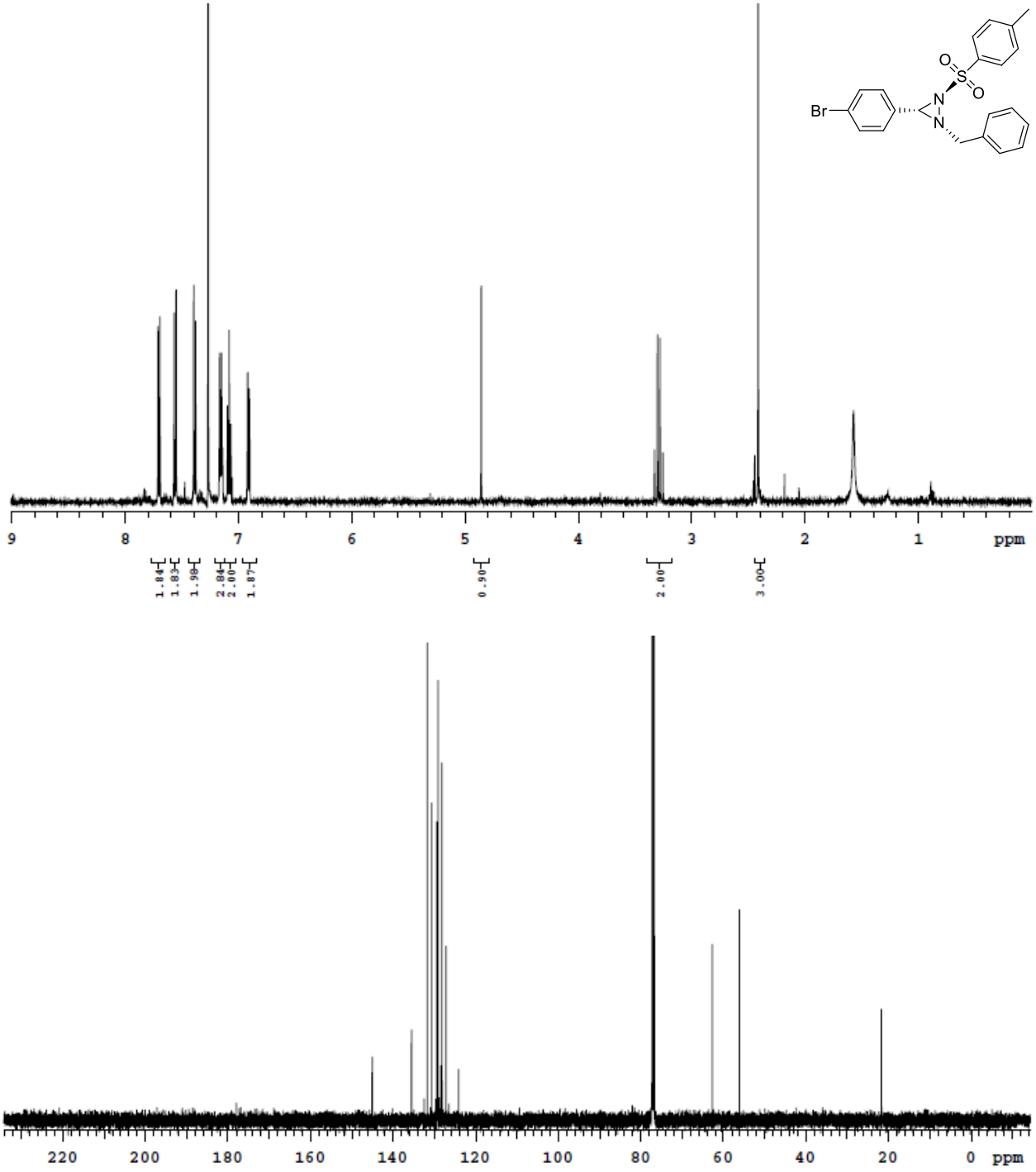
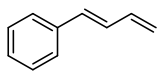
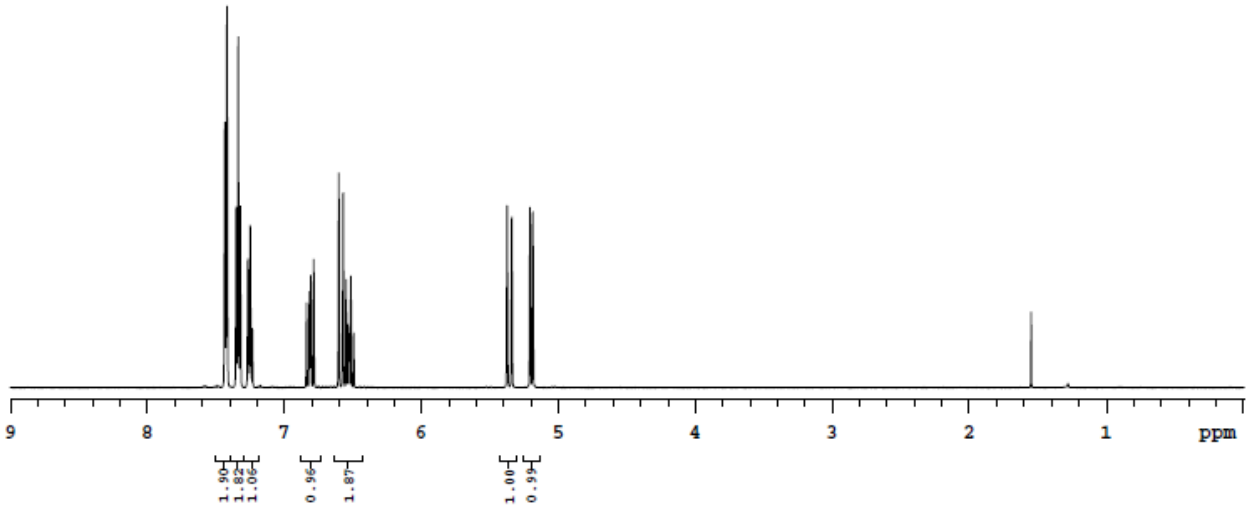


Figure 10.85: ^{1}H and ^{13}C Spectra of Compound V.9





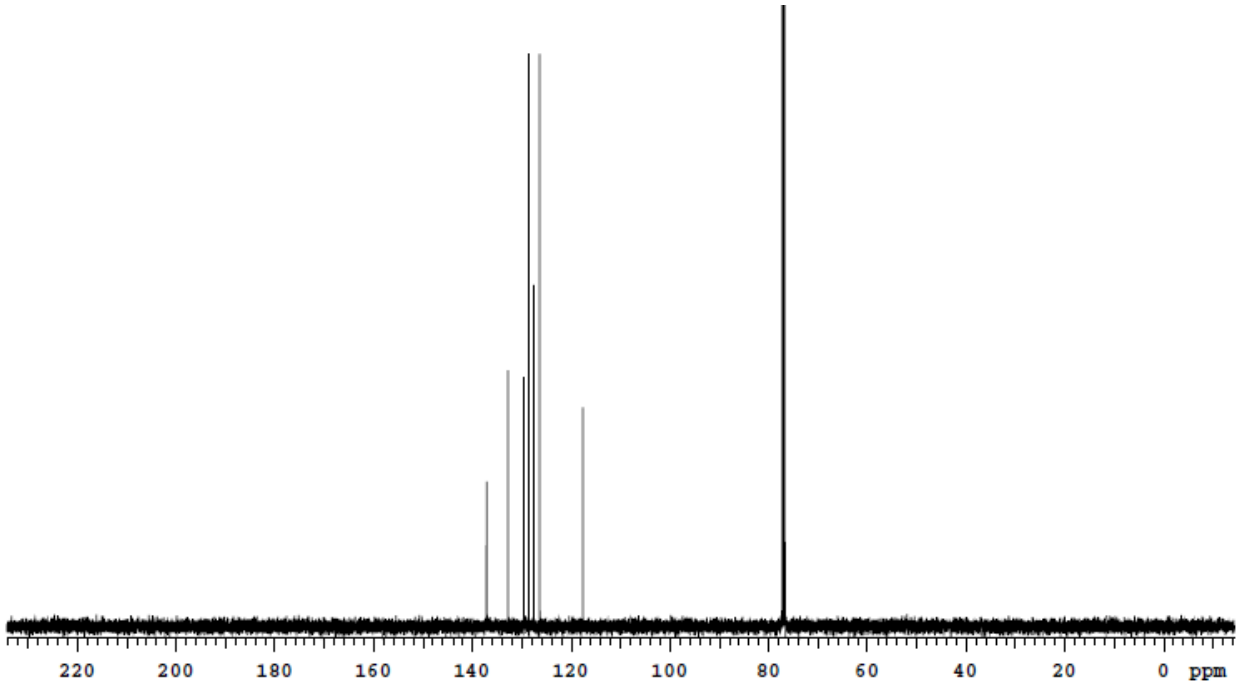


Figure 10.86: ^{1}H and ^{13}C Spectra of Compound V.10a

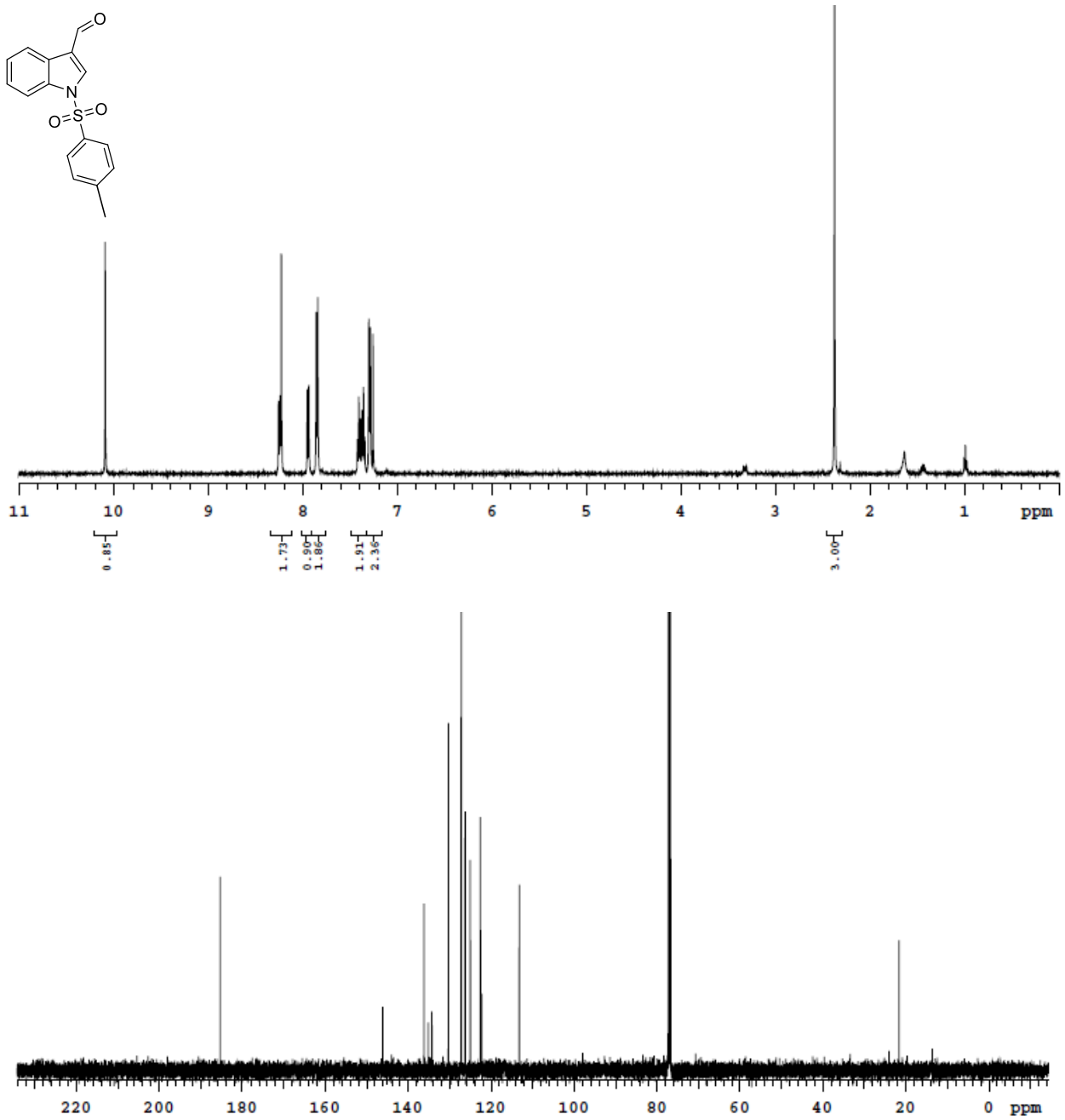


Figure 10.87: ^{1}H and ^{13}C Spectra of Compound V.10

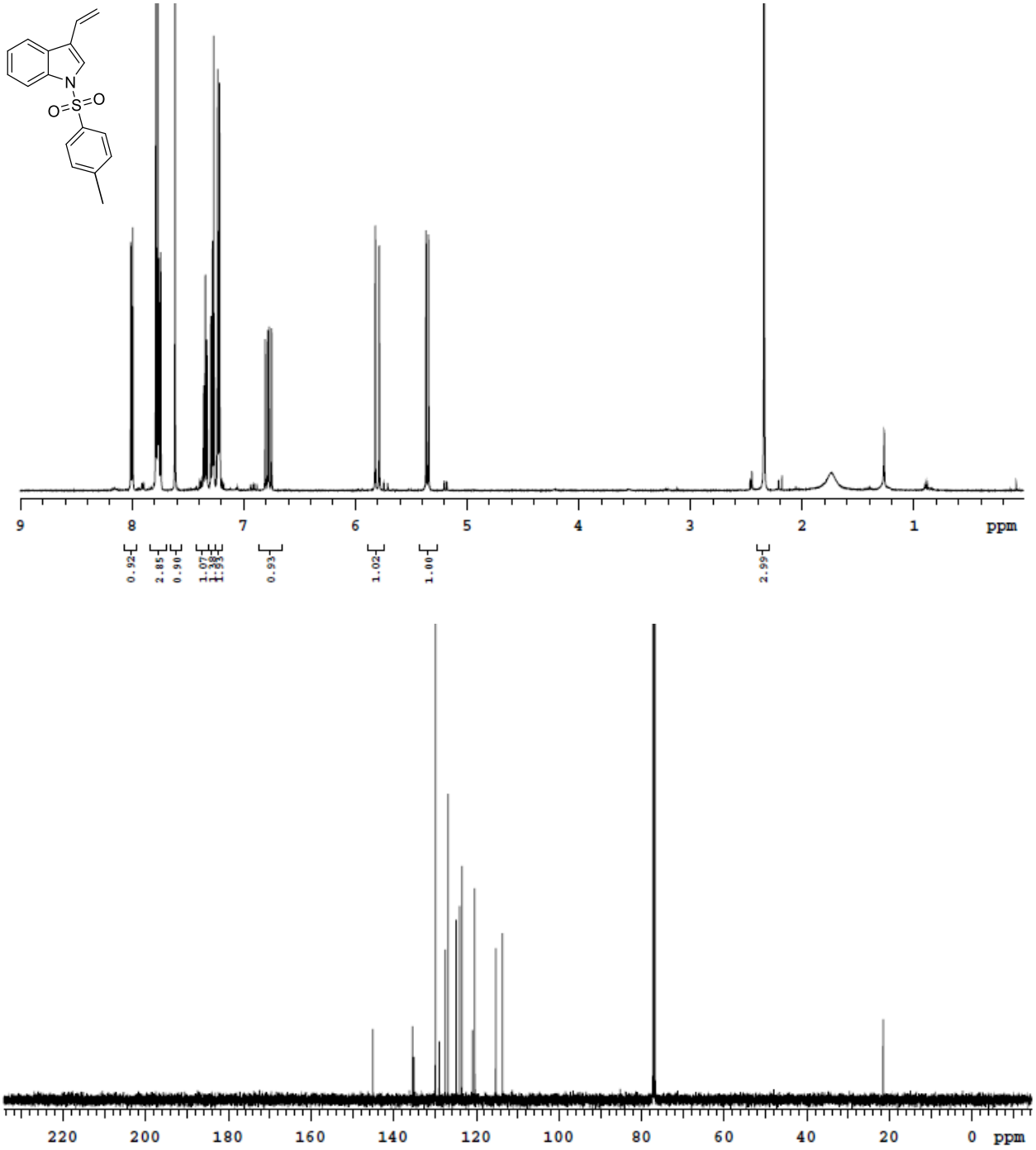


Figure 10.88: ^{1}H and ^{13}C Spectra of Compound VI.1

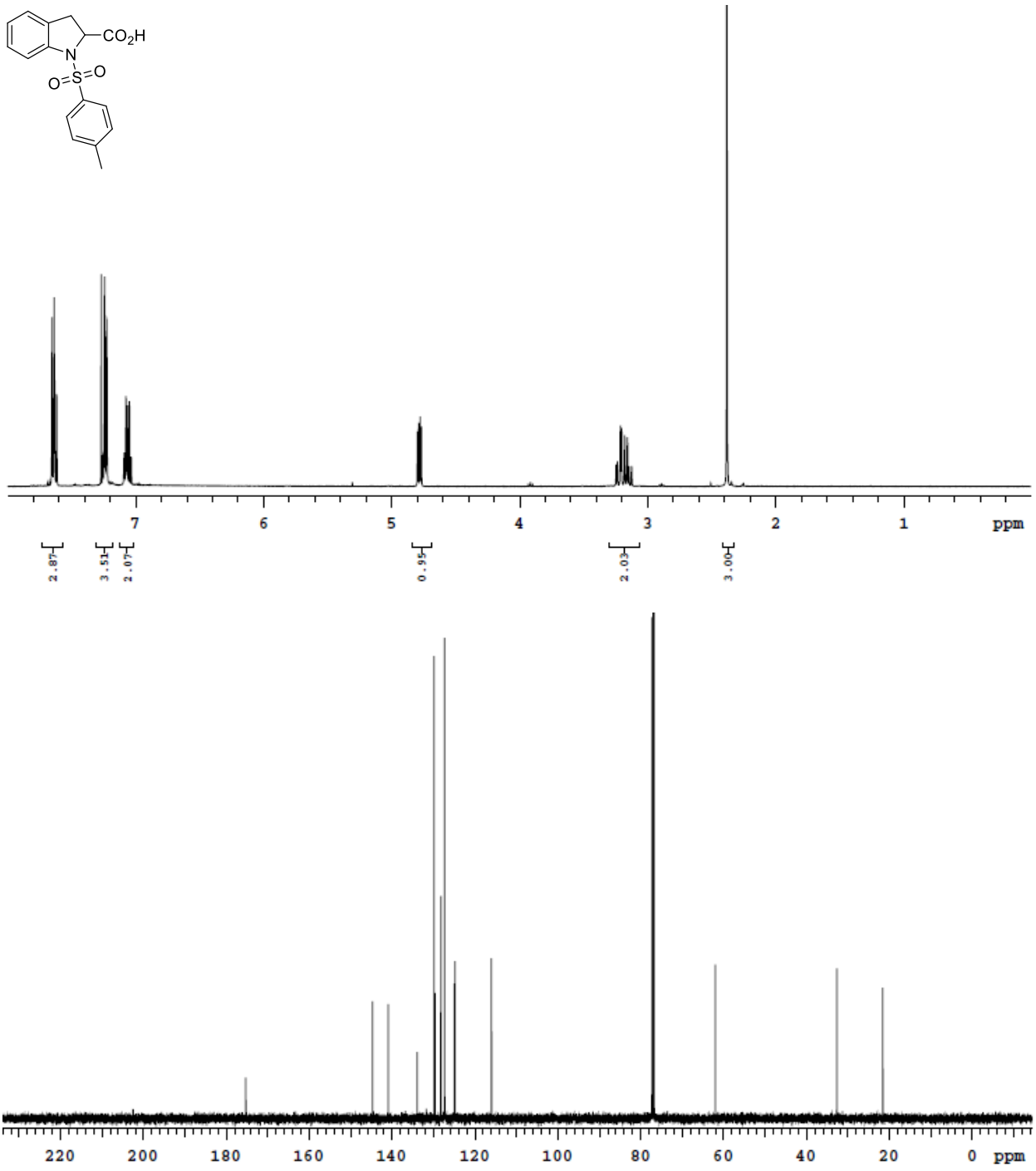


Figure 10.89: ^{1}H and ^{13}C Spectra of Compound VI.2

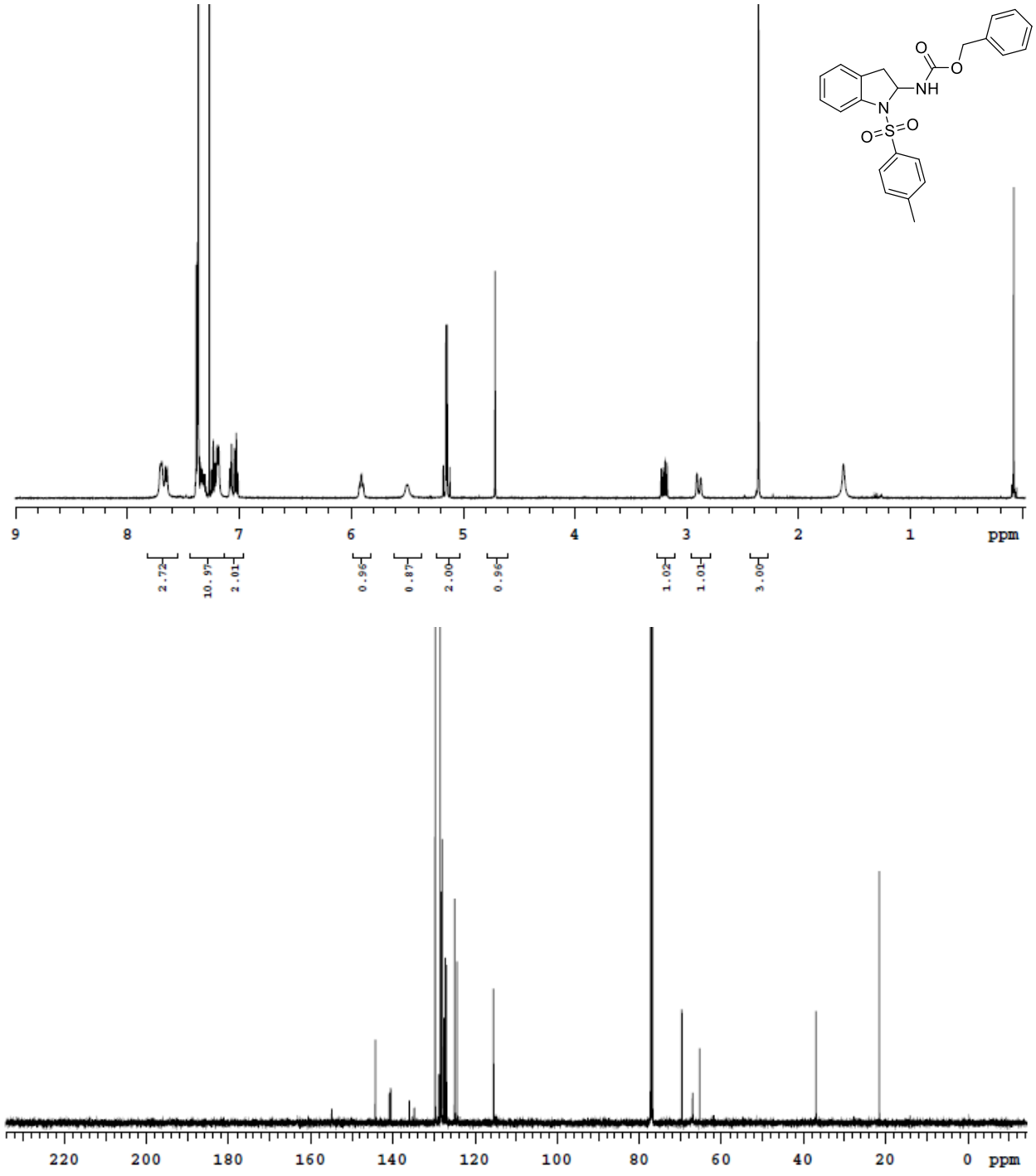


Figure 10.90: gHMQC Spectra of Compound VI.2

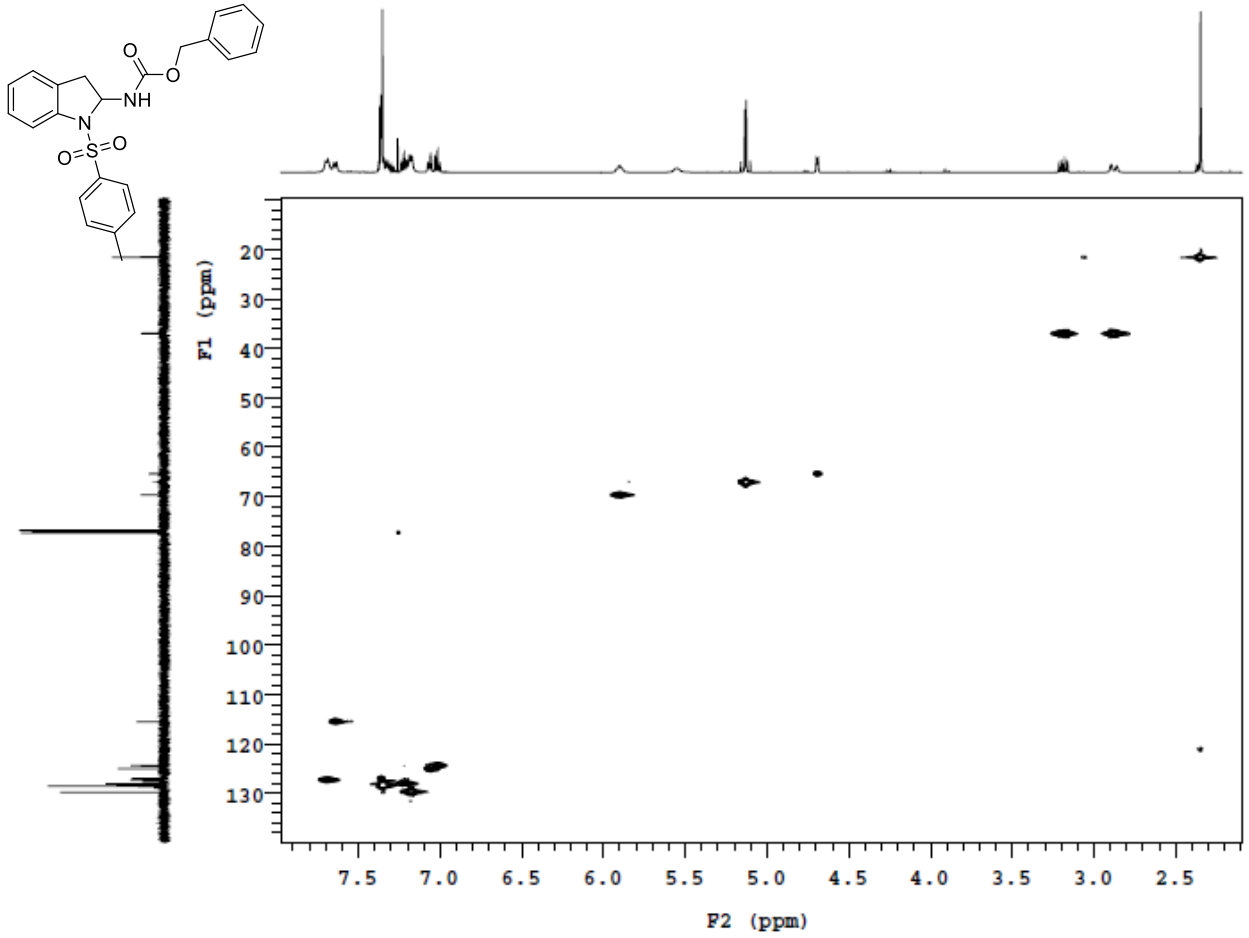


Figure 10.91: ^{1}H and ^{13}C Spectra of Compound VI.3a

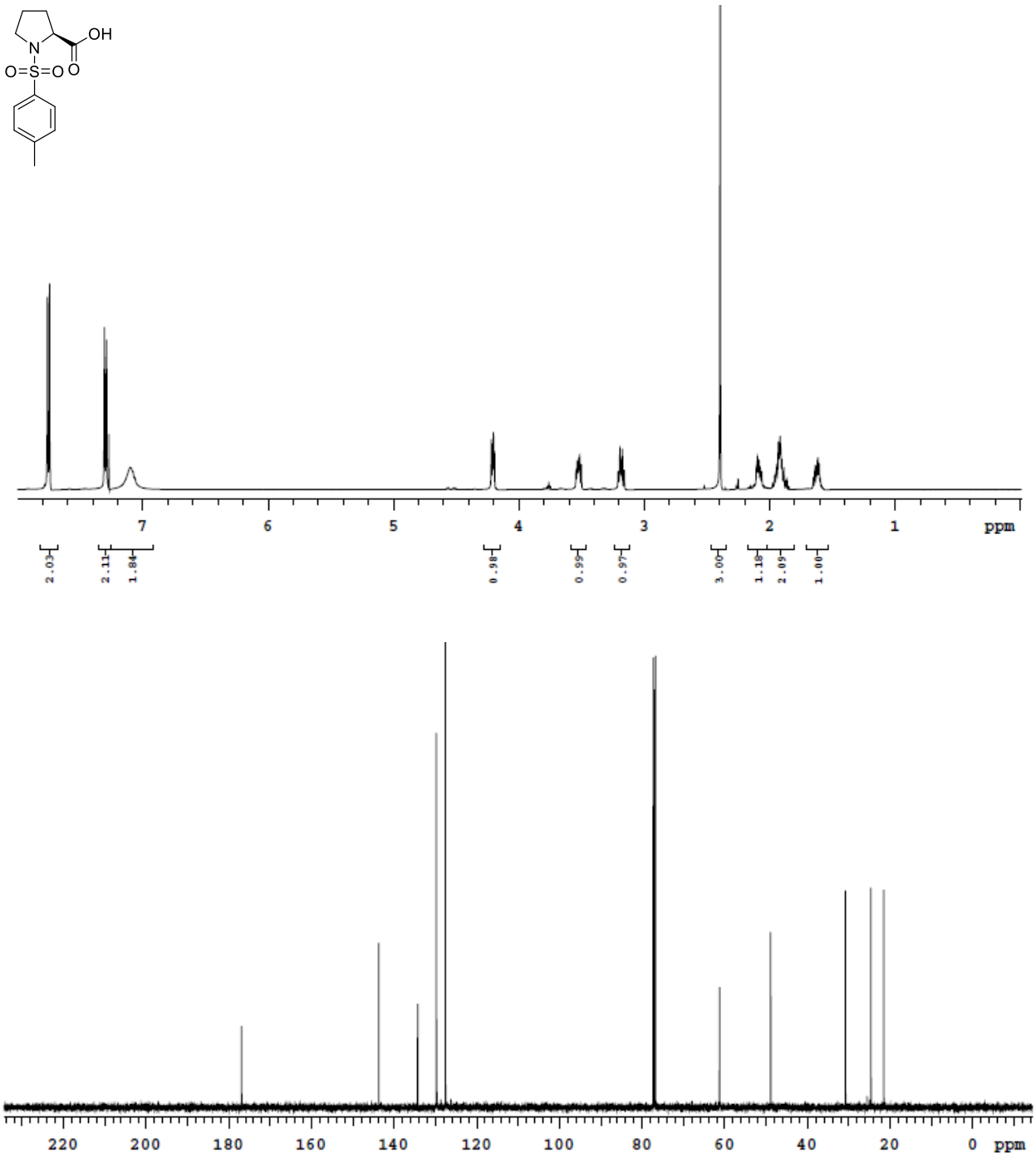


Figure 10.92: ^{1}H and ^{13}C Spectra of Compound VI.3

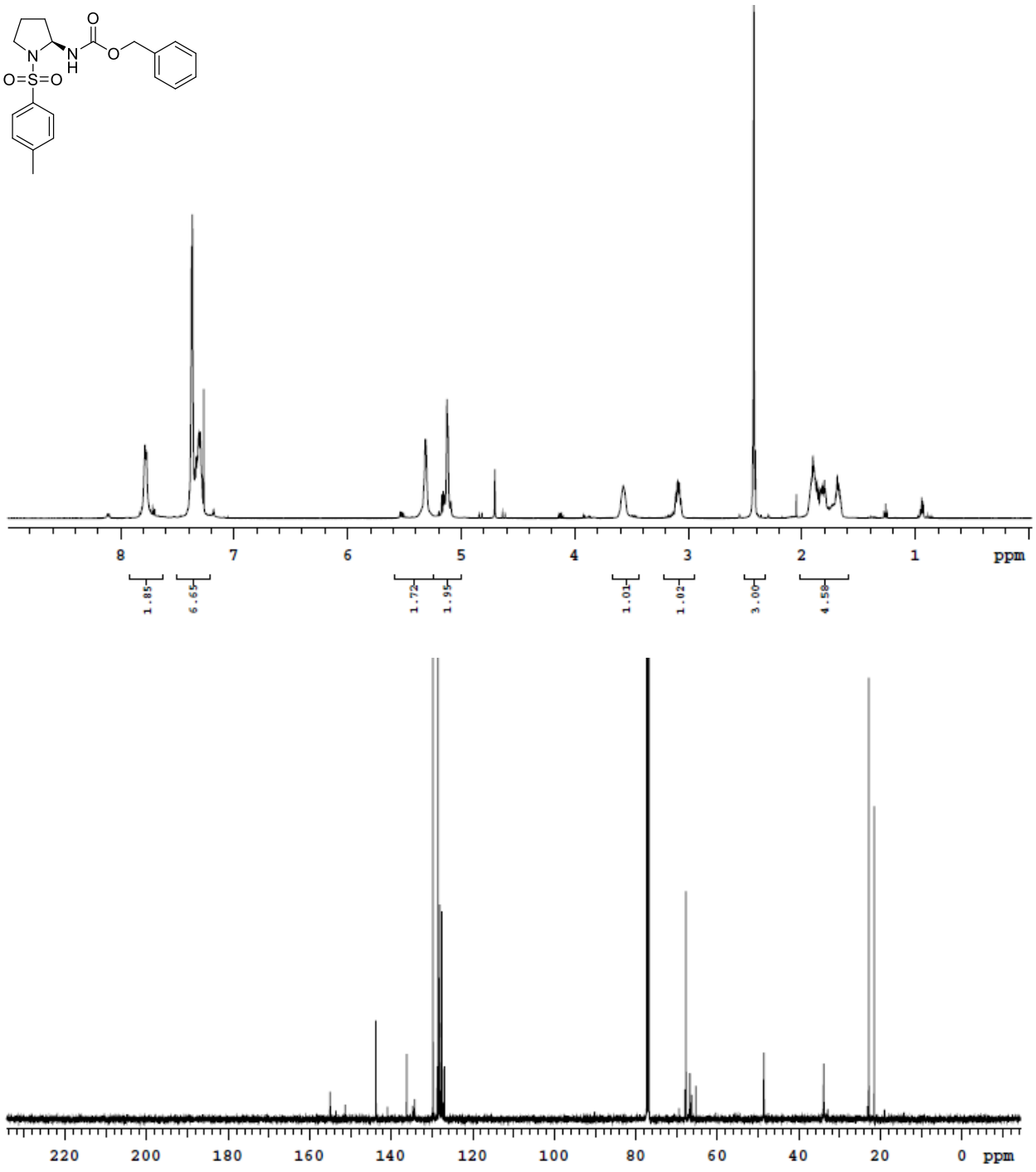


Figure 10.93: gHMQC Spectra of Compound VI.3

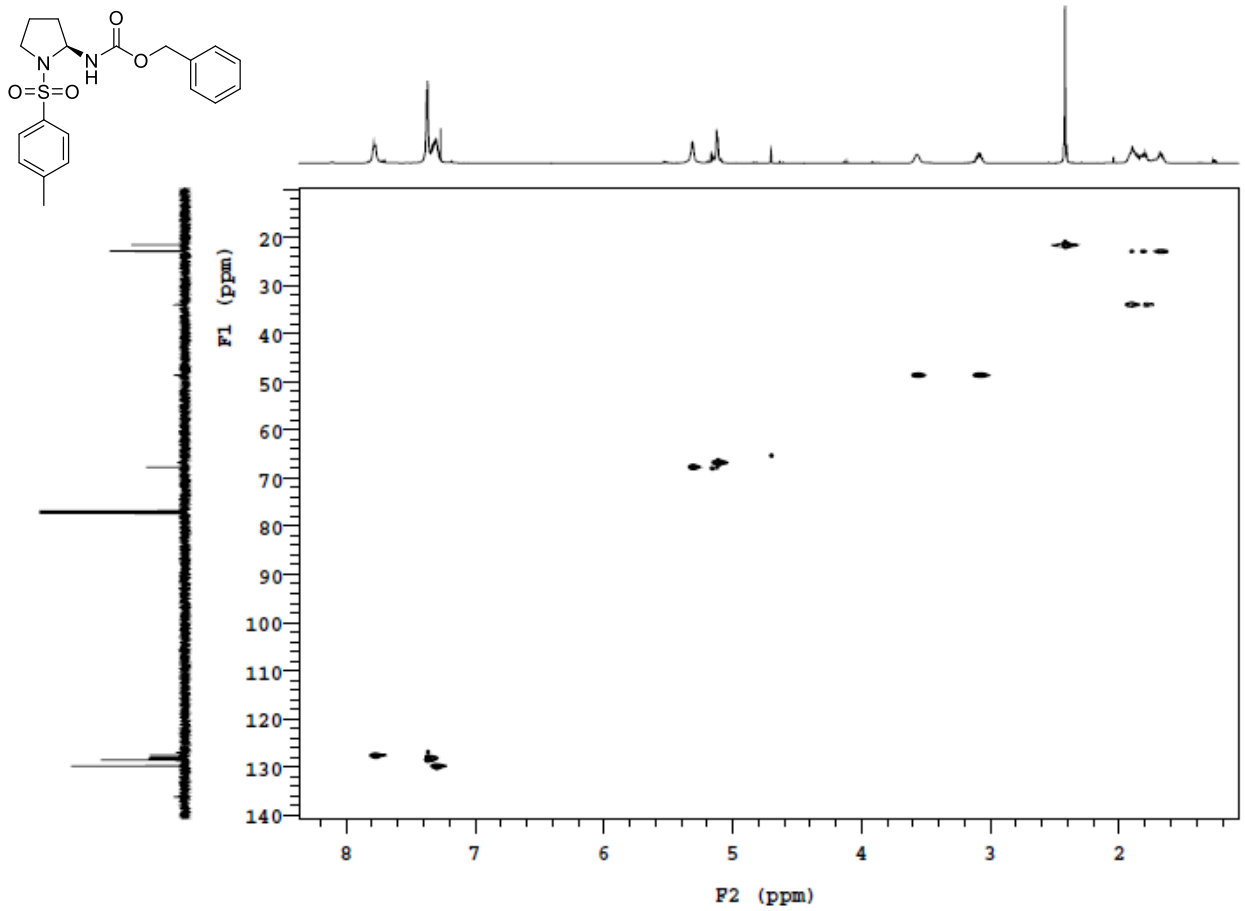


Figure 10.94: ^{1}H and ^{13}C Spectra of Compound VI.4a

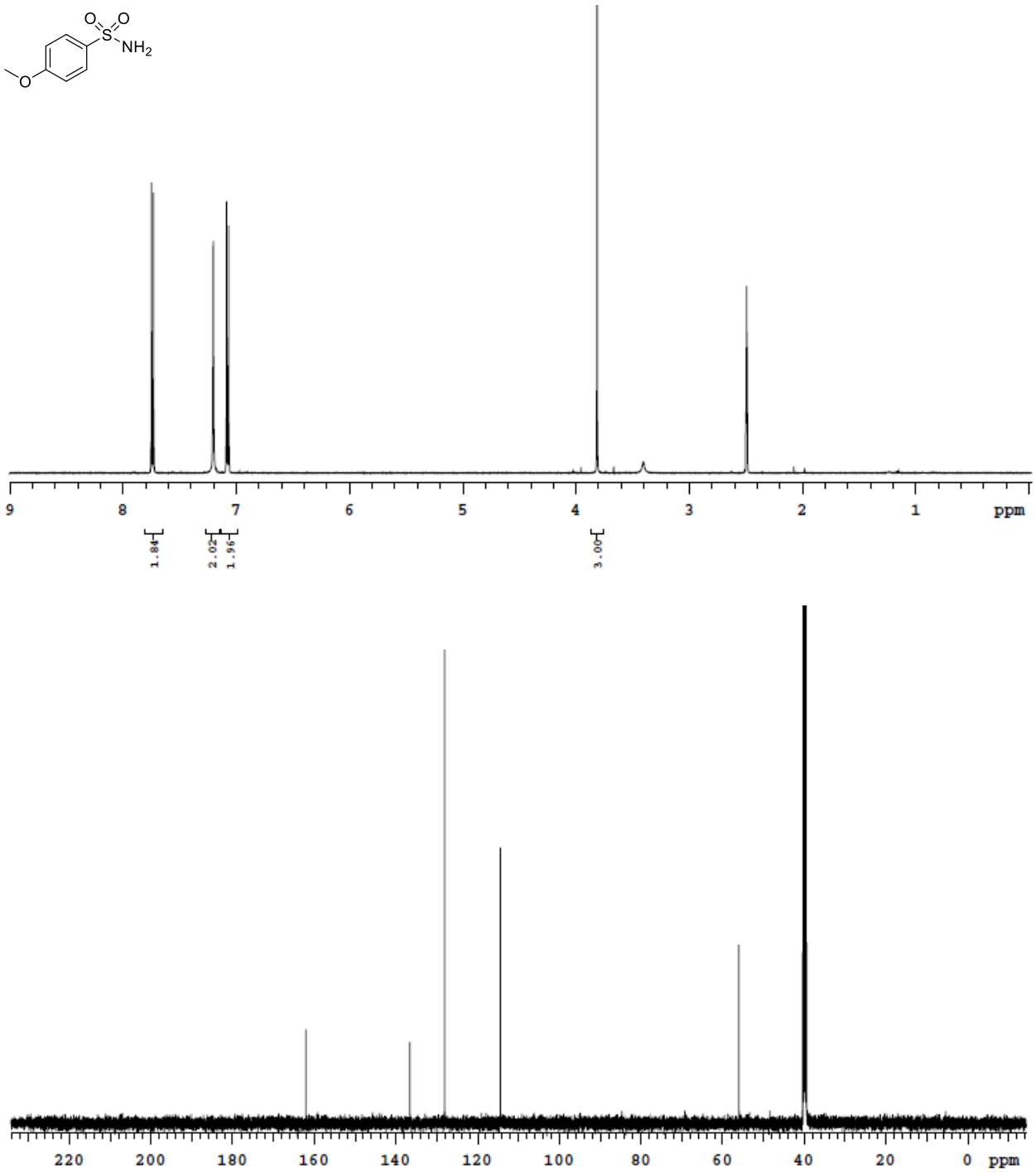


Figure 10.95: ^{1}H and ^{13}C Spectra of Compound VI.4b

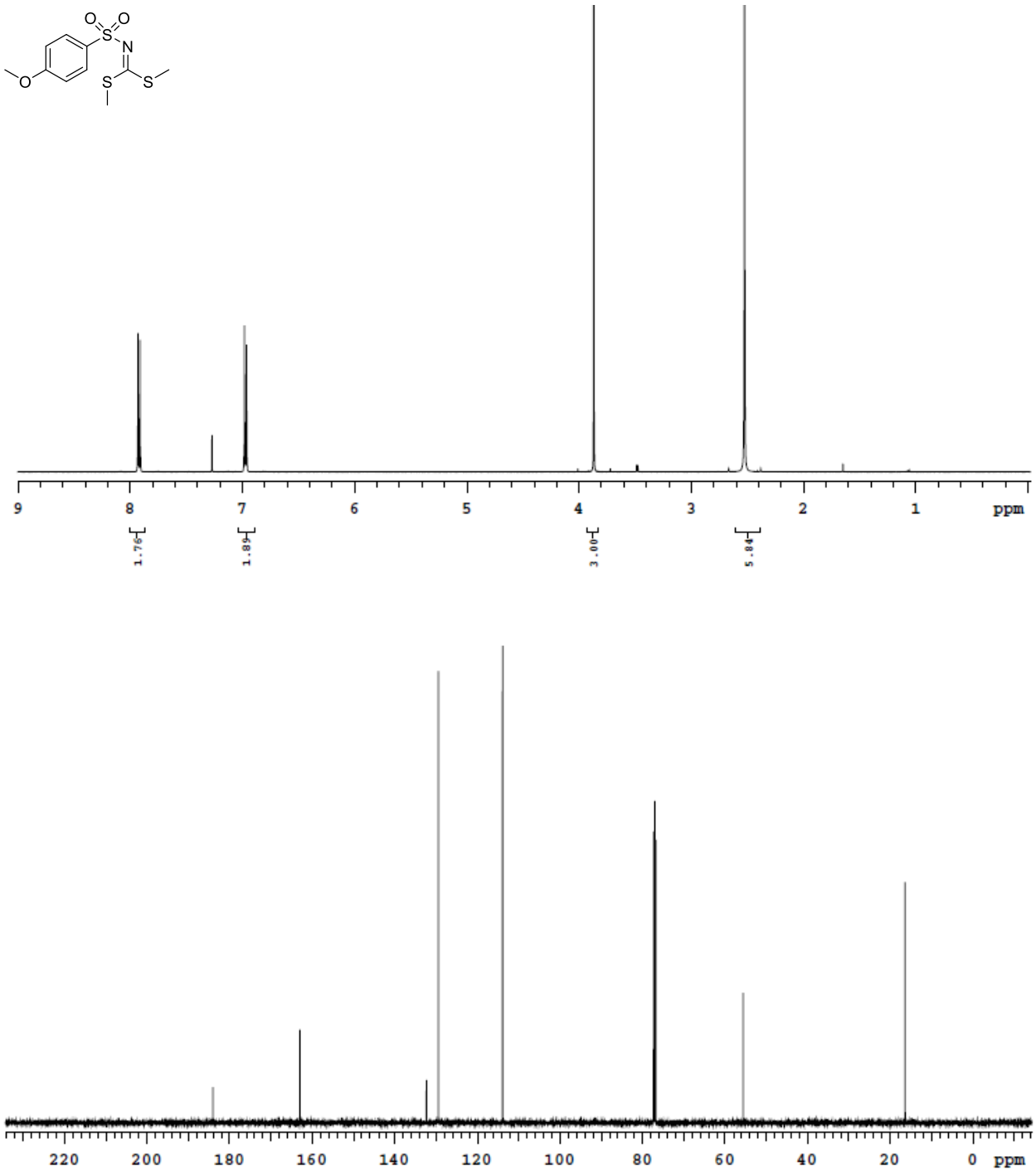


Figure 10.96: ^{1}H and ^{13}C Spectra of Compound VI.4c

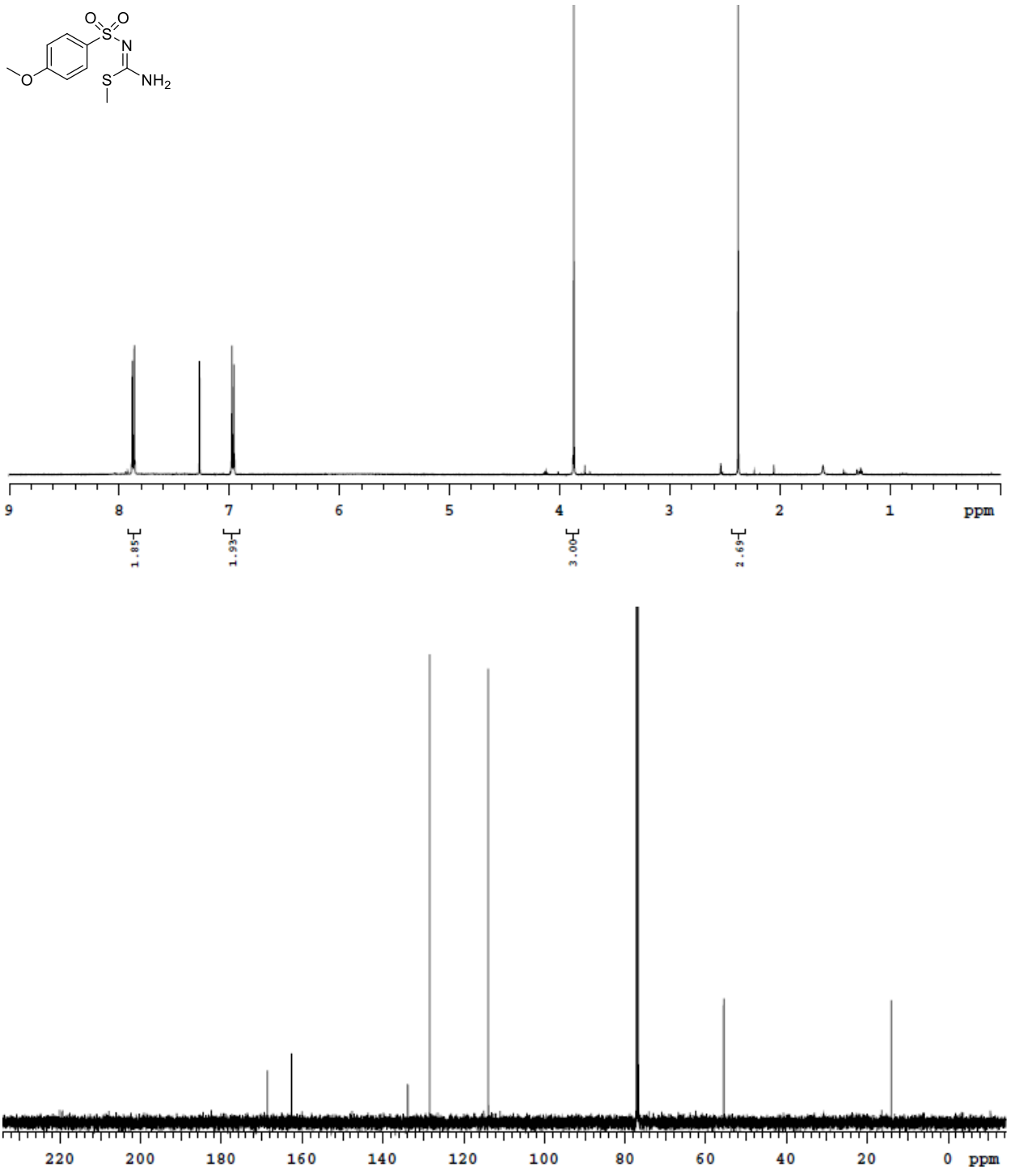


Figure 10.97: ^{1}H and ^{13}C Spectra of Compound VI.4

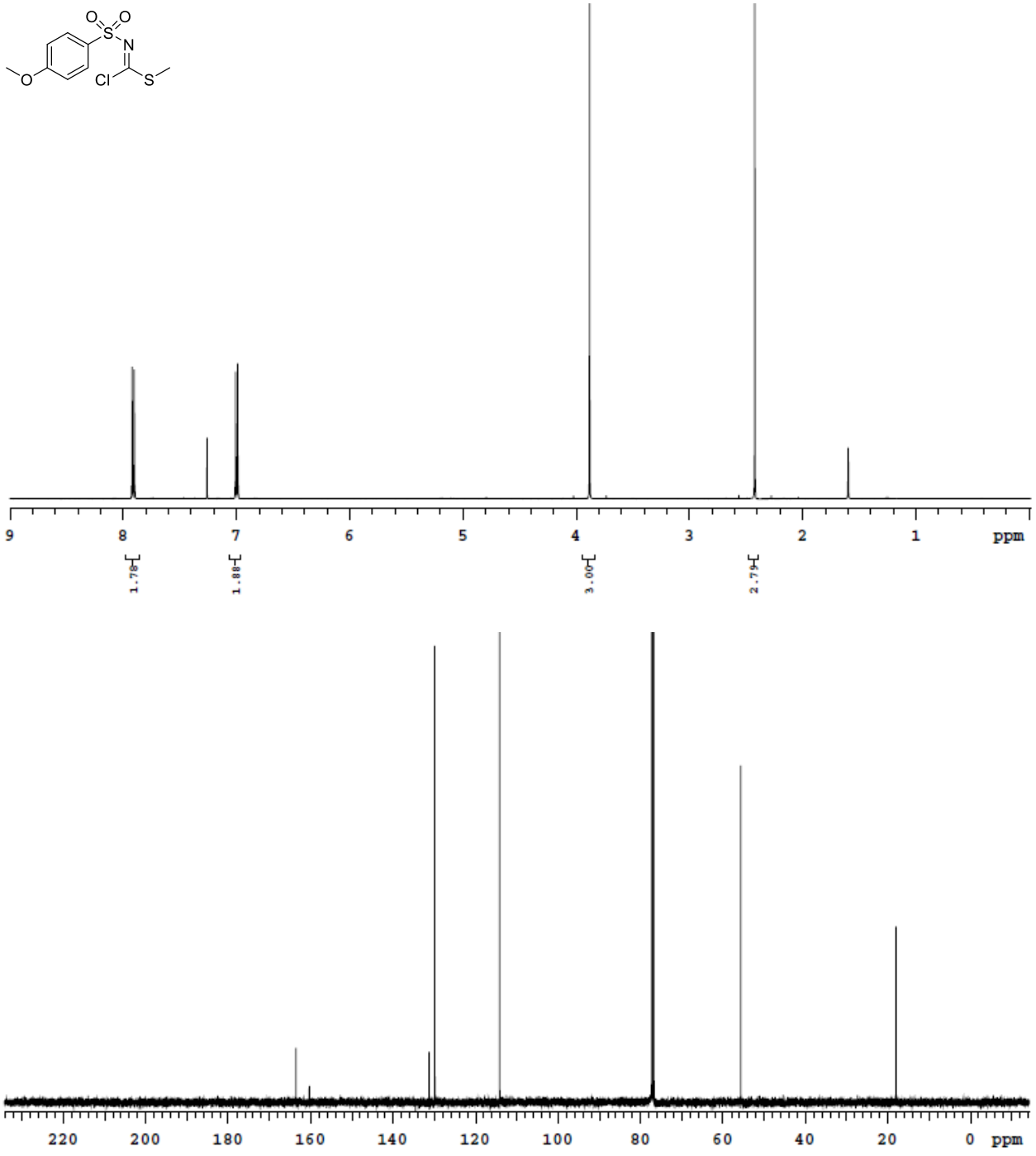


Figure 10.98: ^{1}H and ^{13}C Spectra of Compound VI.5

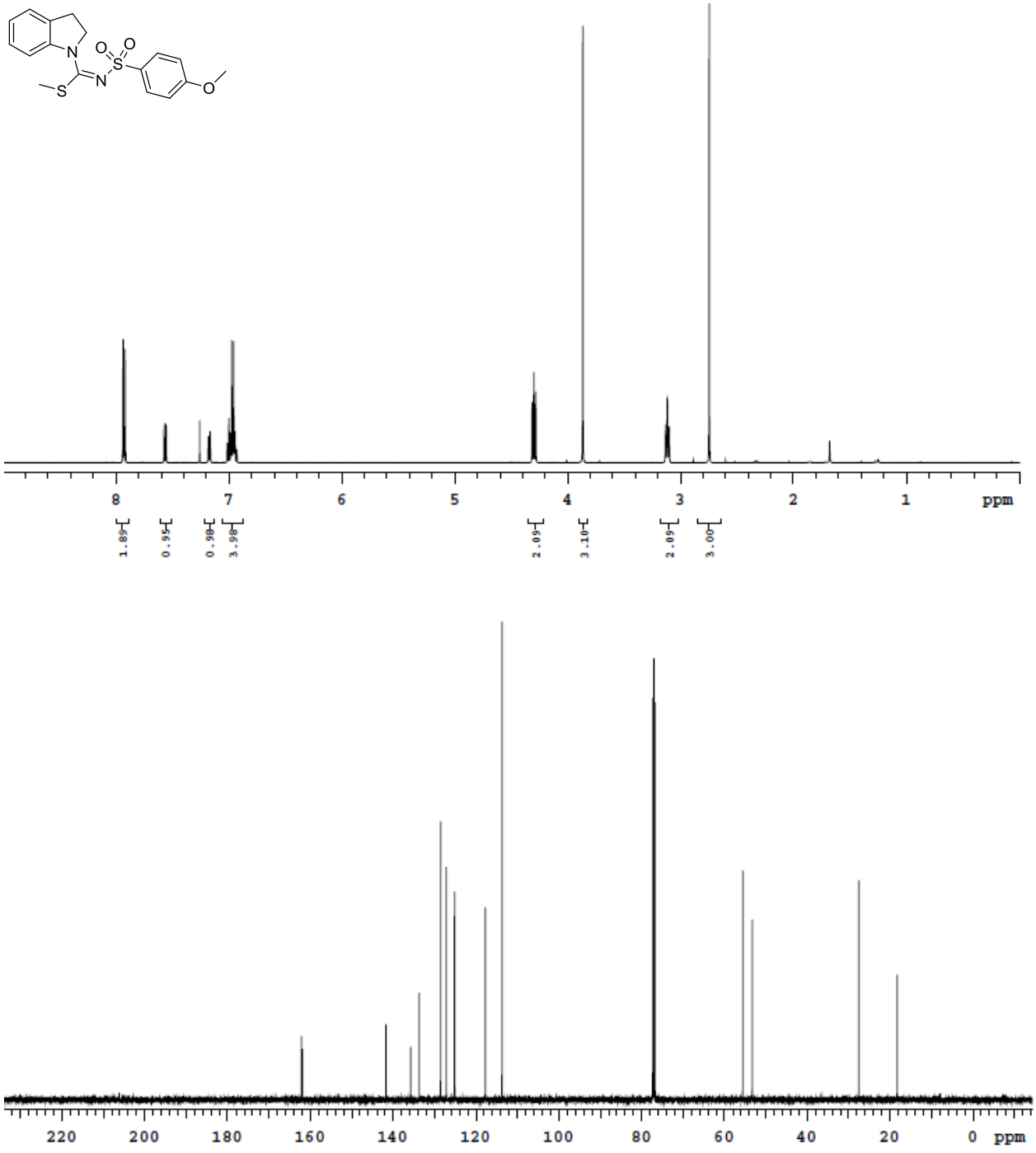


Figure 10.99: ^{1}H and ^{13}C Spectra of Compound VI.6

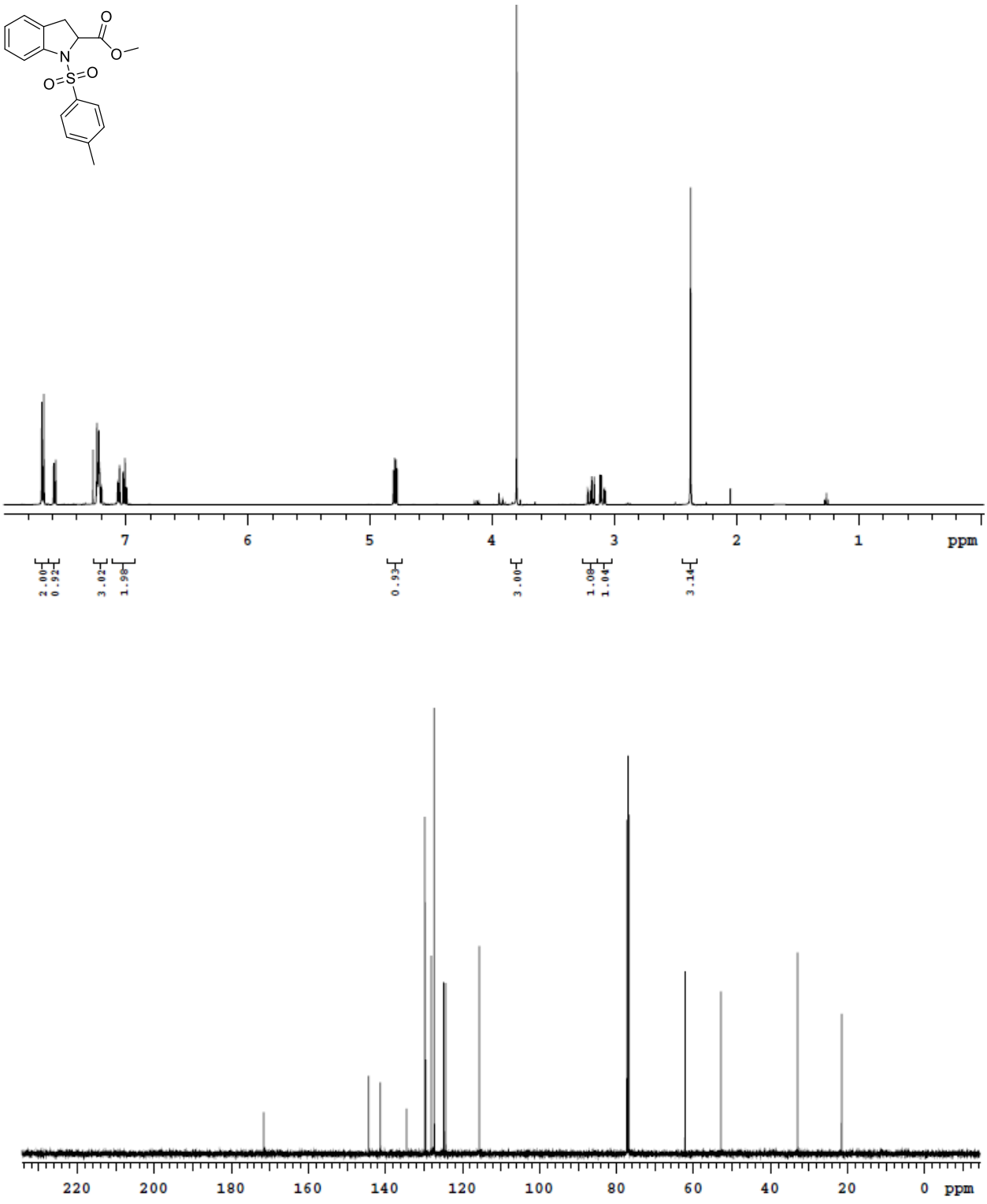


Figure 10.100: ^{1}H and ^{13}C Spectra of Compound VI.7a

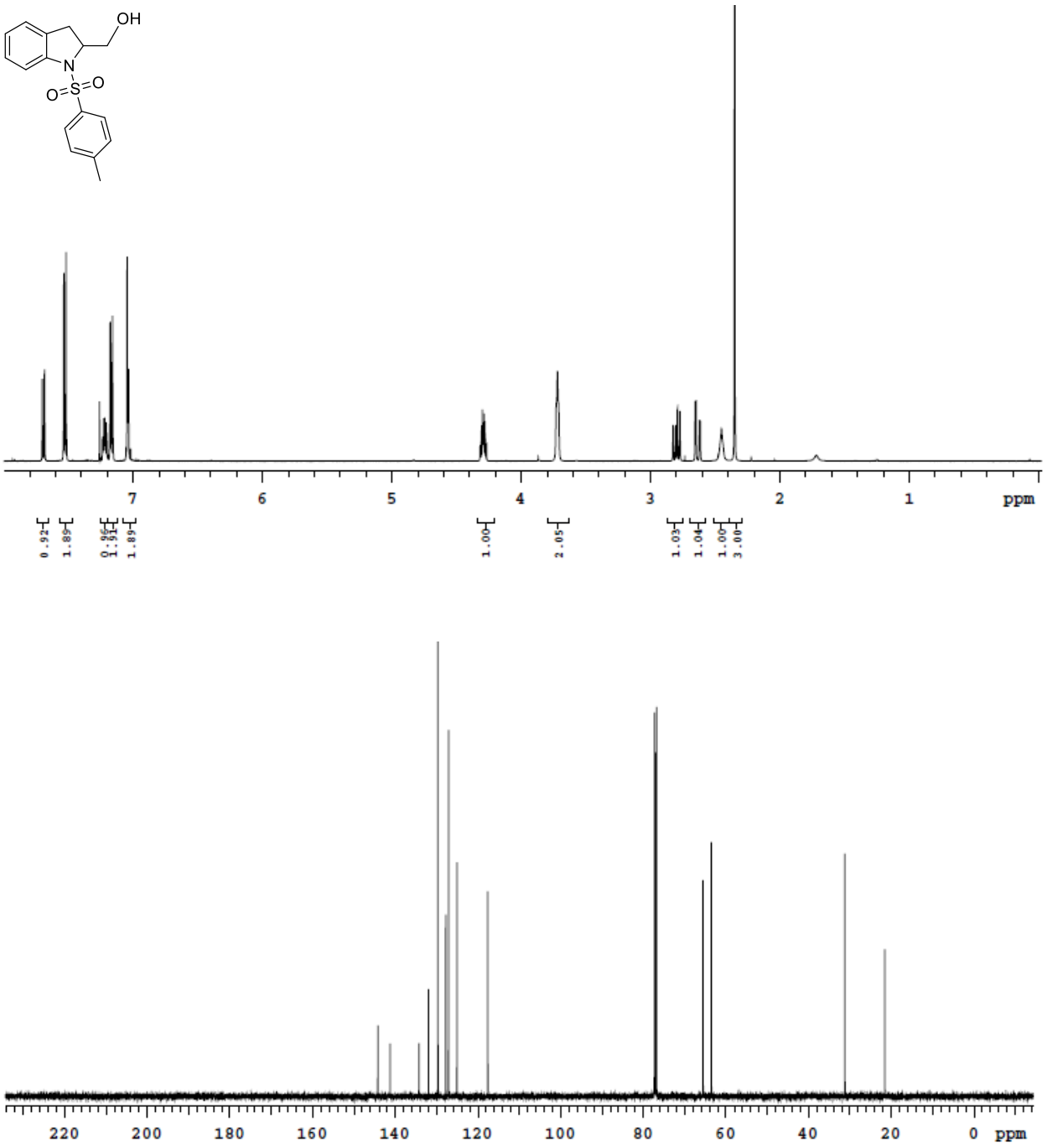


Figure 10.101: ^{1}H and ^{13}C Spectra of Compound VI.7

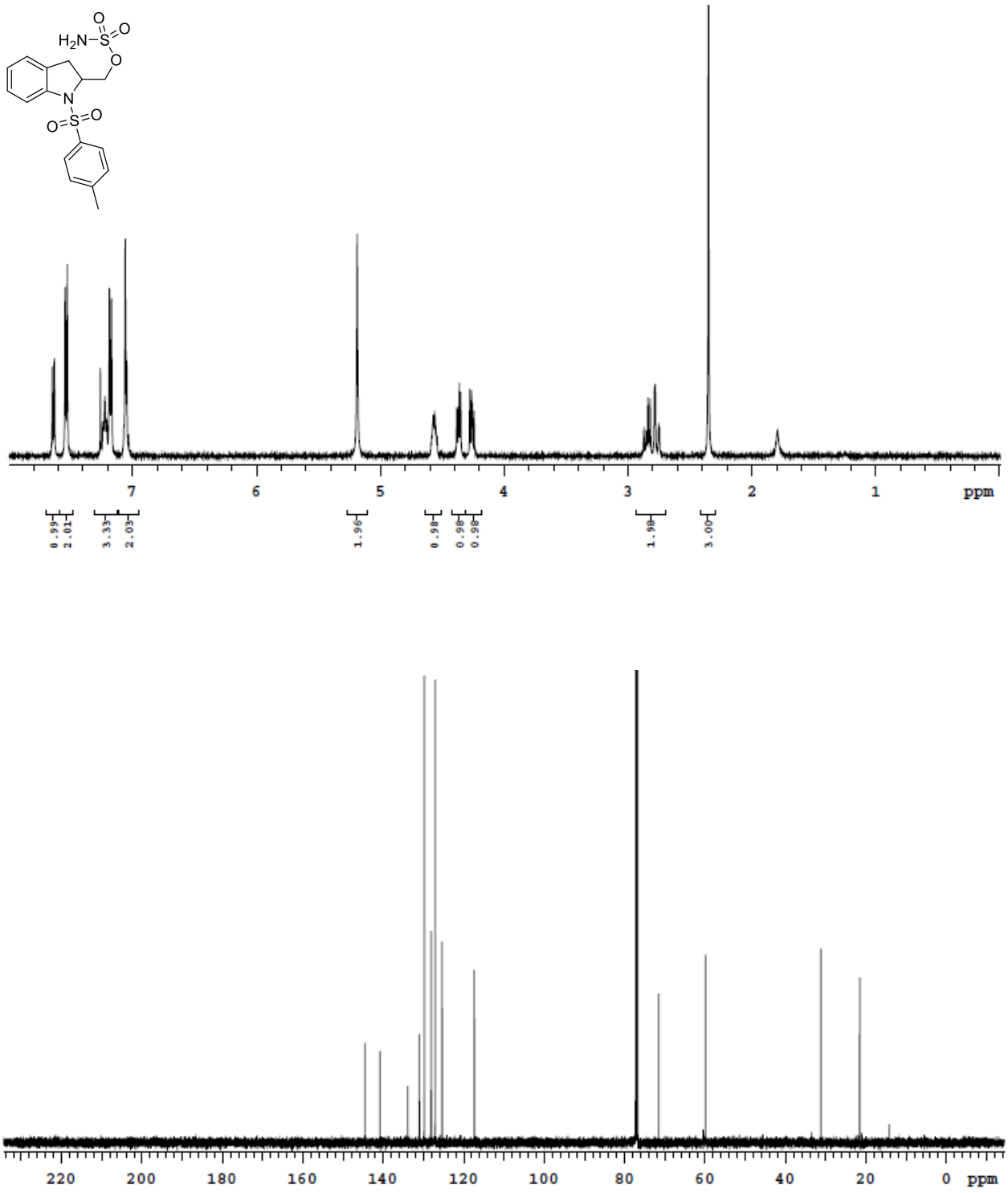


Figure 10.102: ^{1}H and ^{13}C Spectra of Compound VI.10a

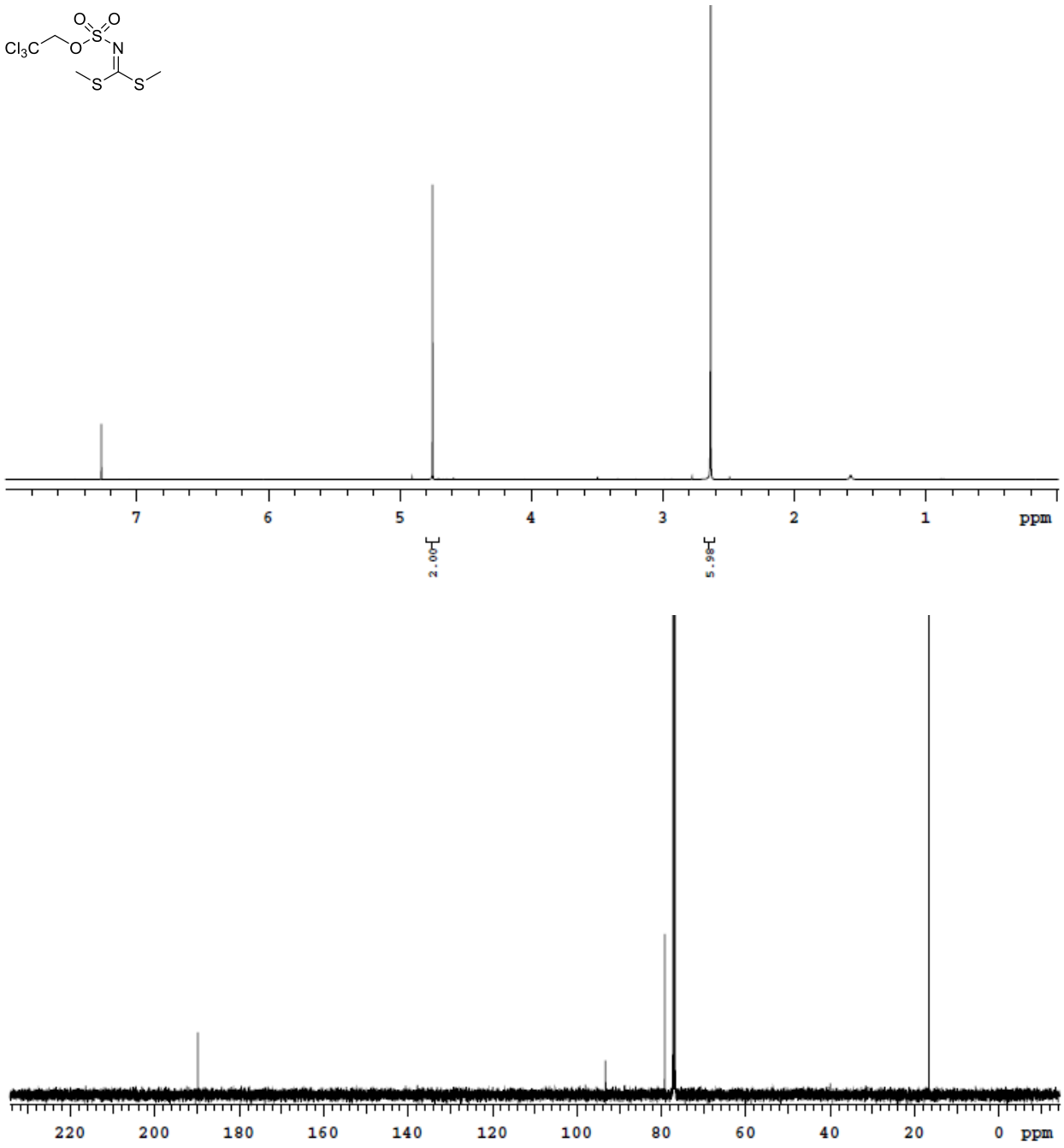


Figure 10.103: ^{1}H and ^{13}C Spectra of Compound VI.10

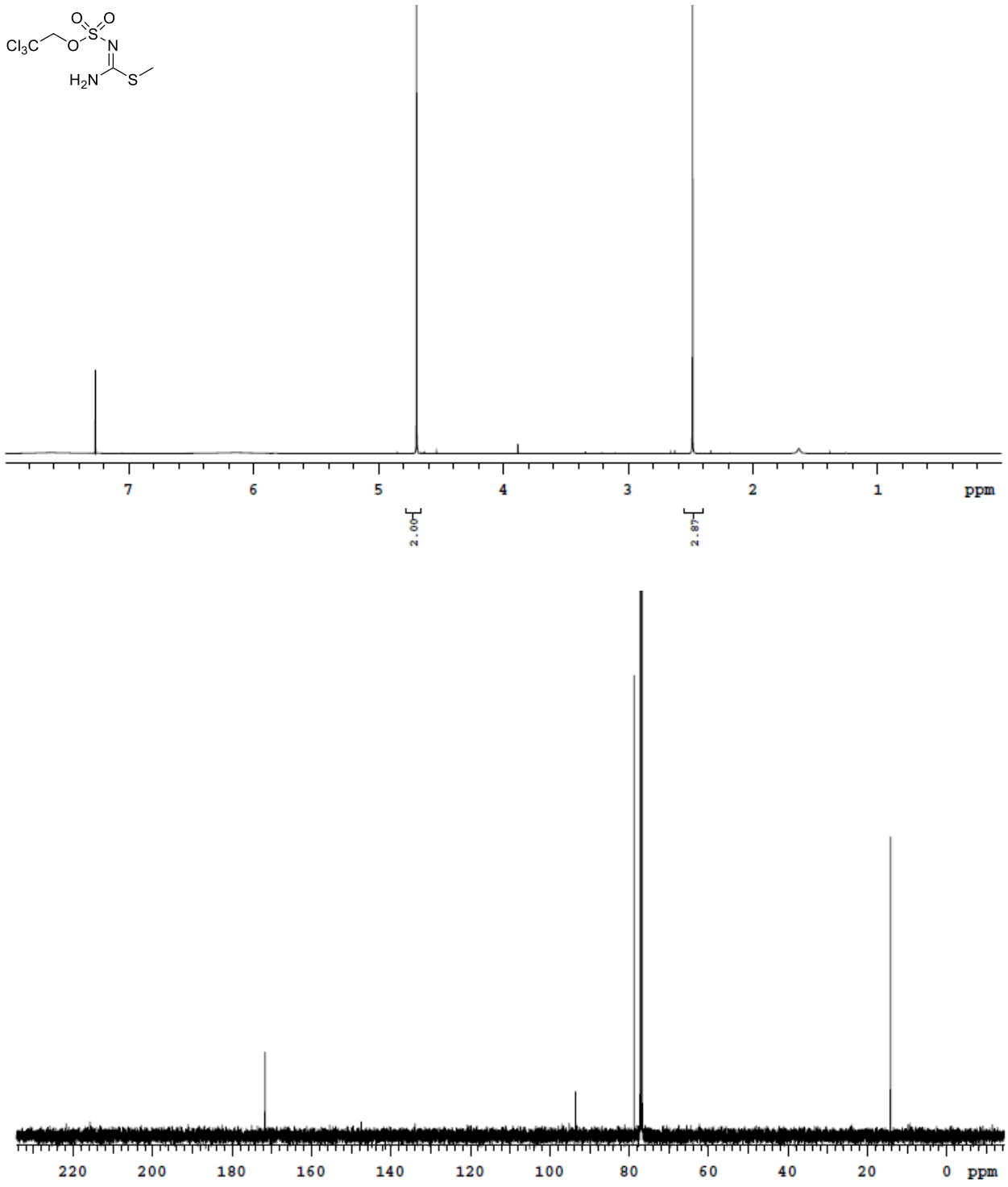


Figure 10.104: ^{1}H and ^{13}C Spectra of 2,2,2-trichloroethyl-(chloro(methylthio)methylene)sulfamate

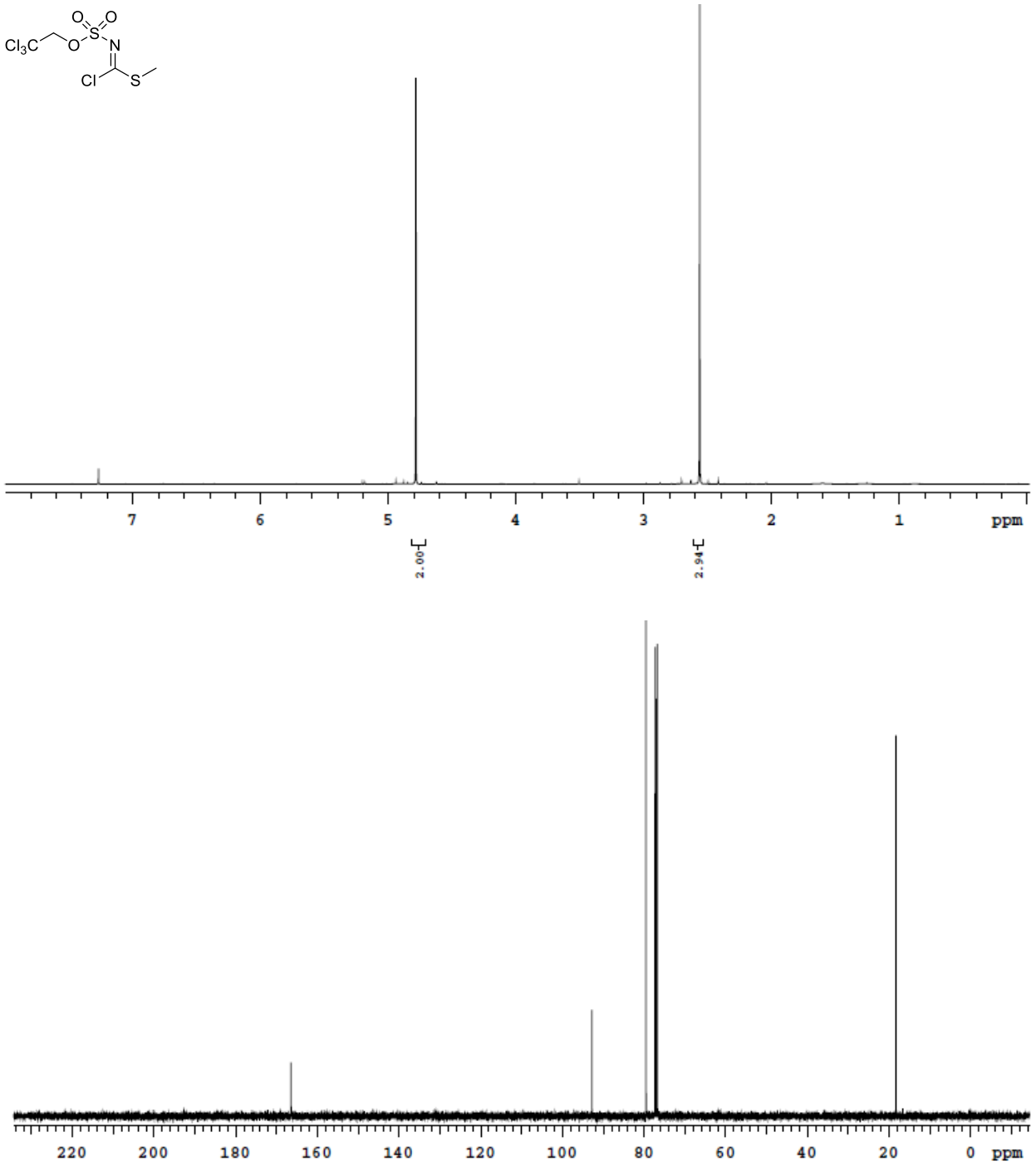


Figure 10.105: ^{1}H and ^{13}C Spectra of Compound VI.9

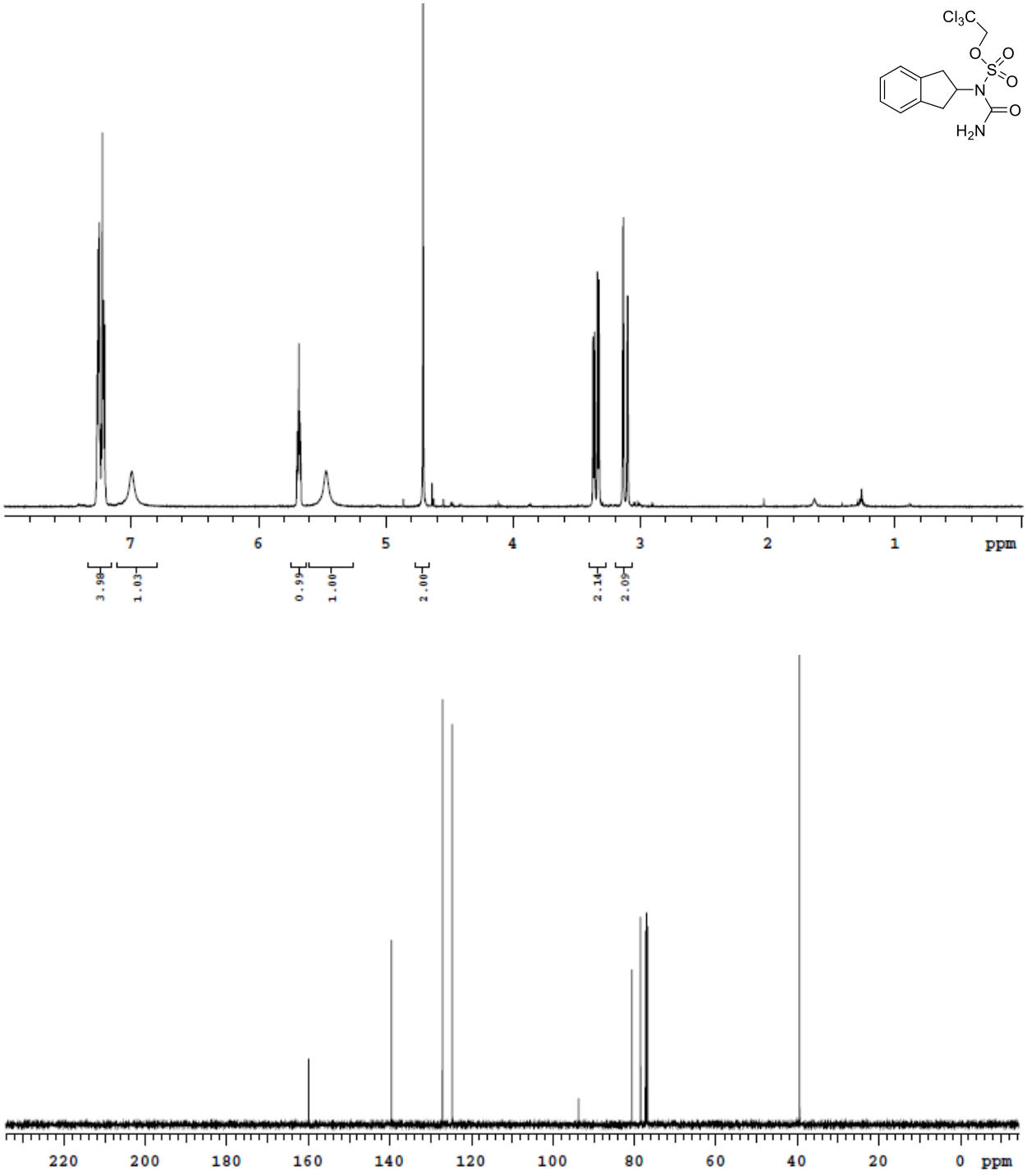


Figure 10.106: ^{1}H and ^{13}C Spectra of Compound VI.11

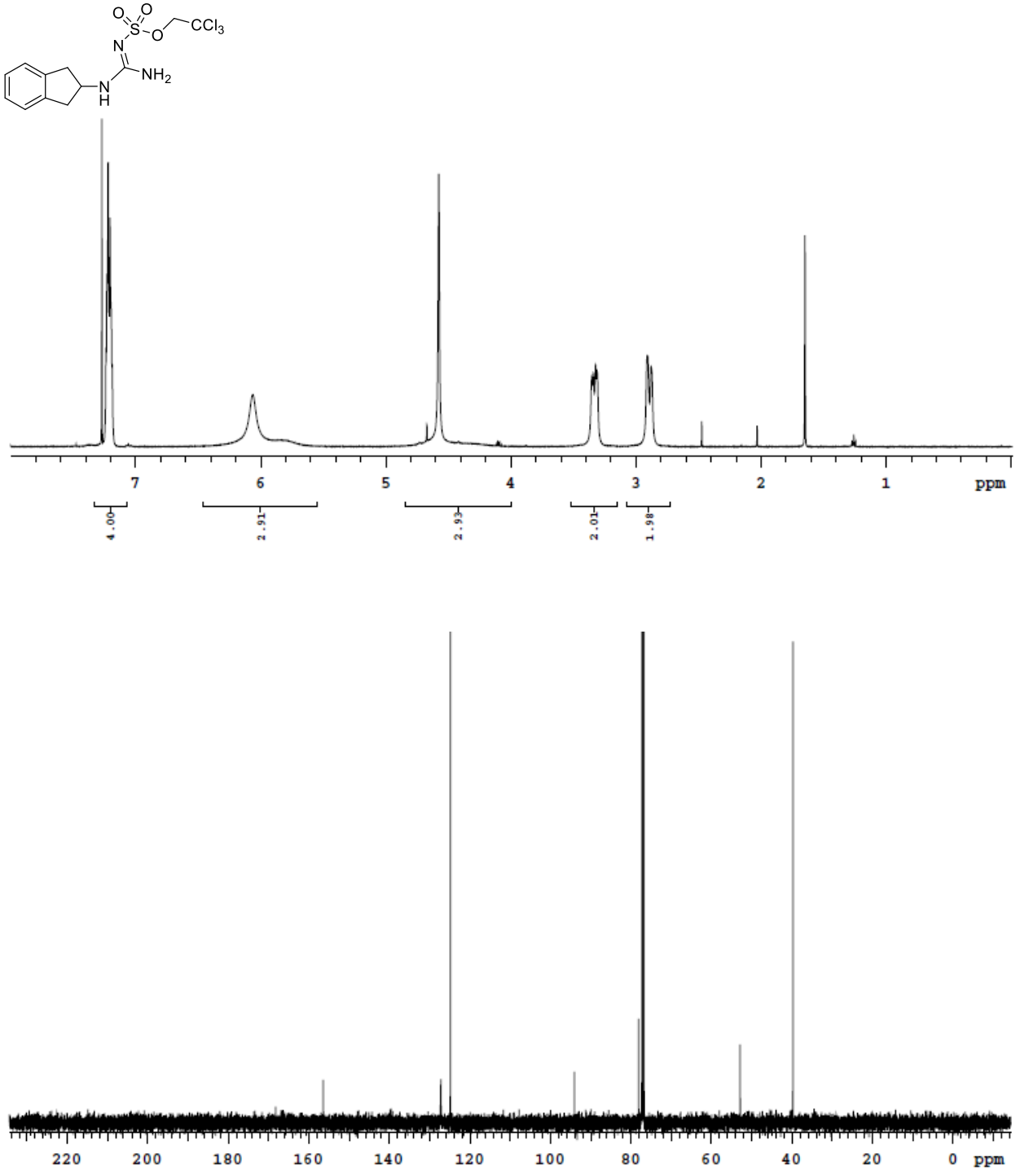


Figure 10.107: gHMQC Spectra of Compound VI.11

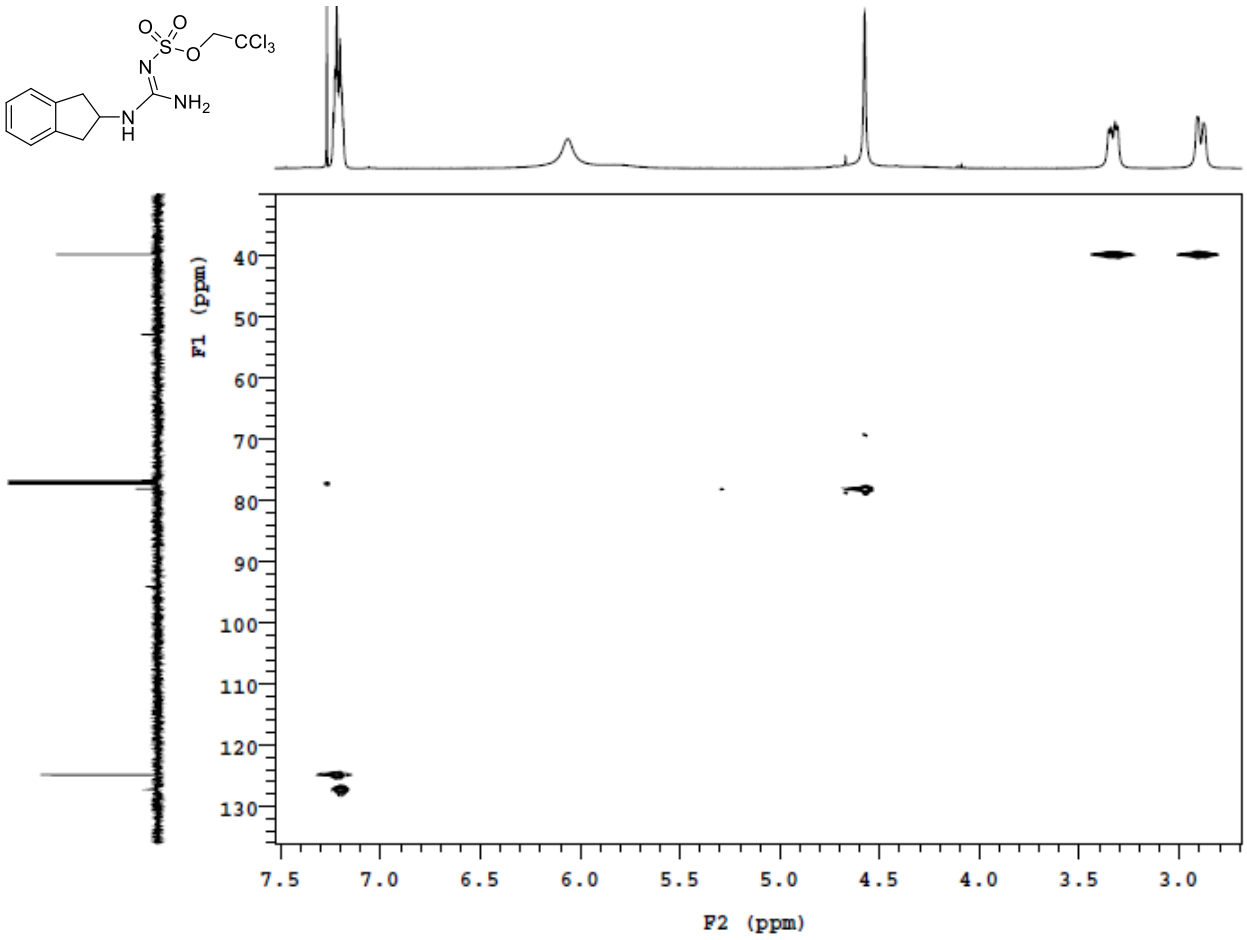


Figure 10.108: ^{1}H and ^{13}C Spectra of Compound VII.1a

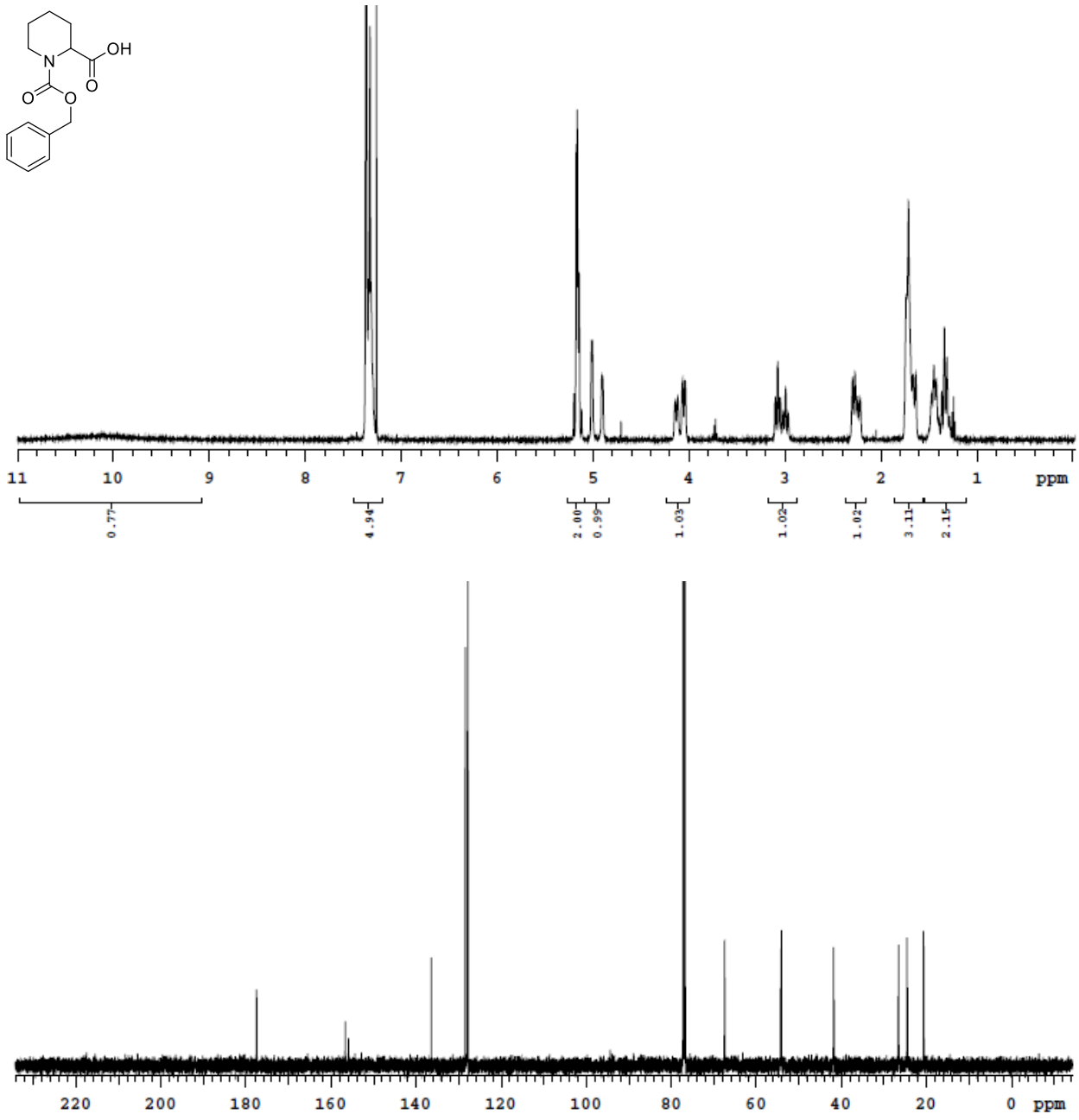


Figure 10.109: ^{1}H and ^{13}C Spectra of Compound VII.1

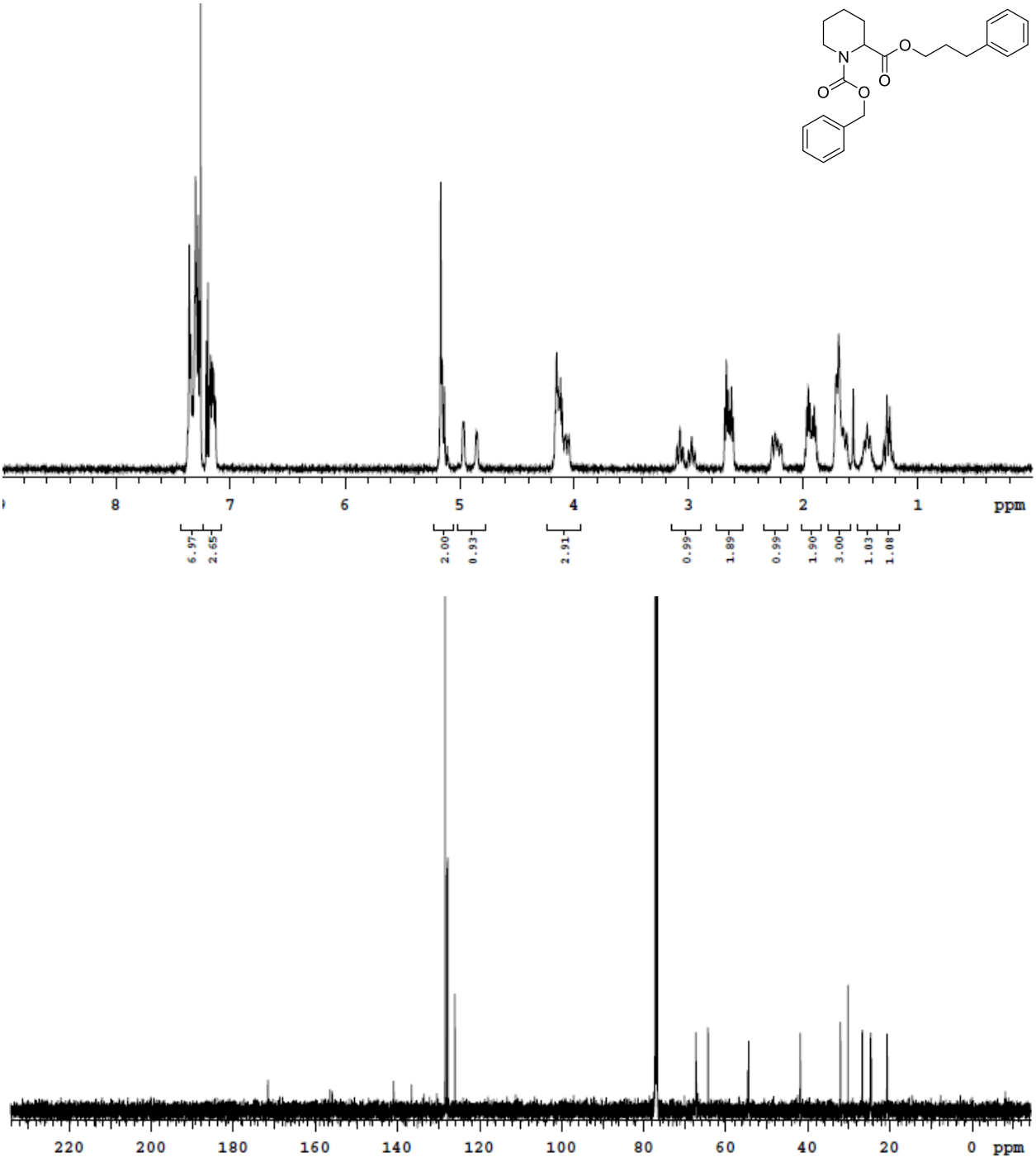


Figure 10.110: ^{1}H and ^{13}C Spectra of Compound VII.2a

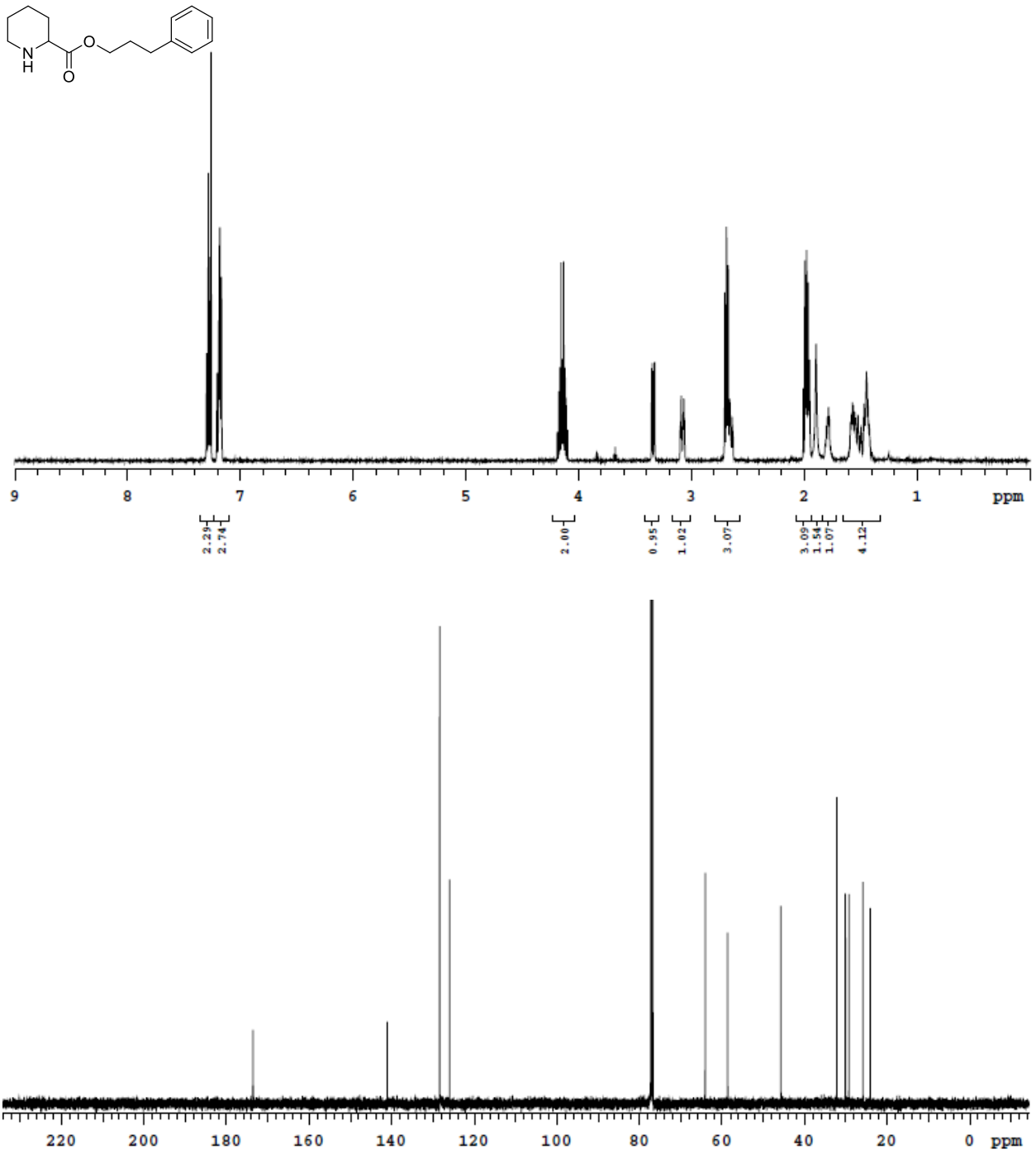


Figure 10.111: ^{1}H and ^{13}C Spectra of Compound VII.2

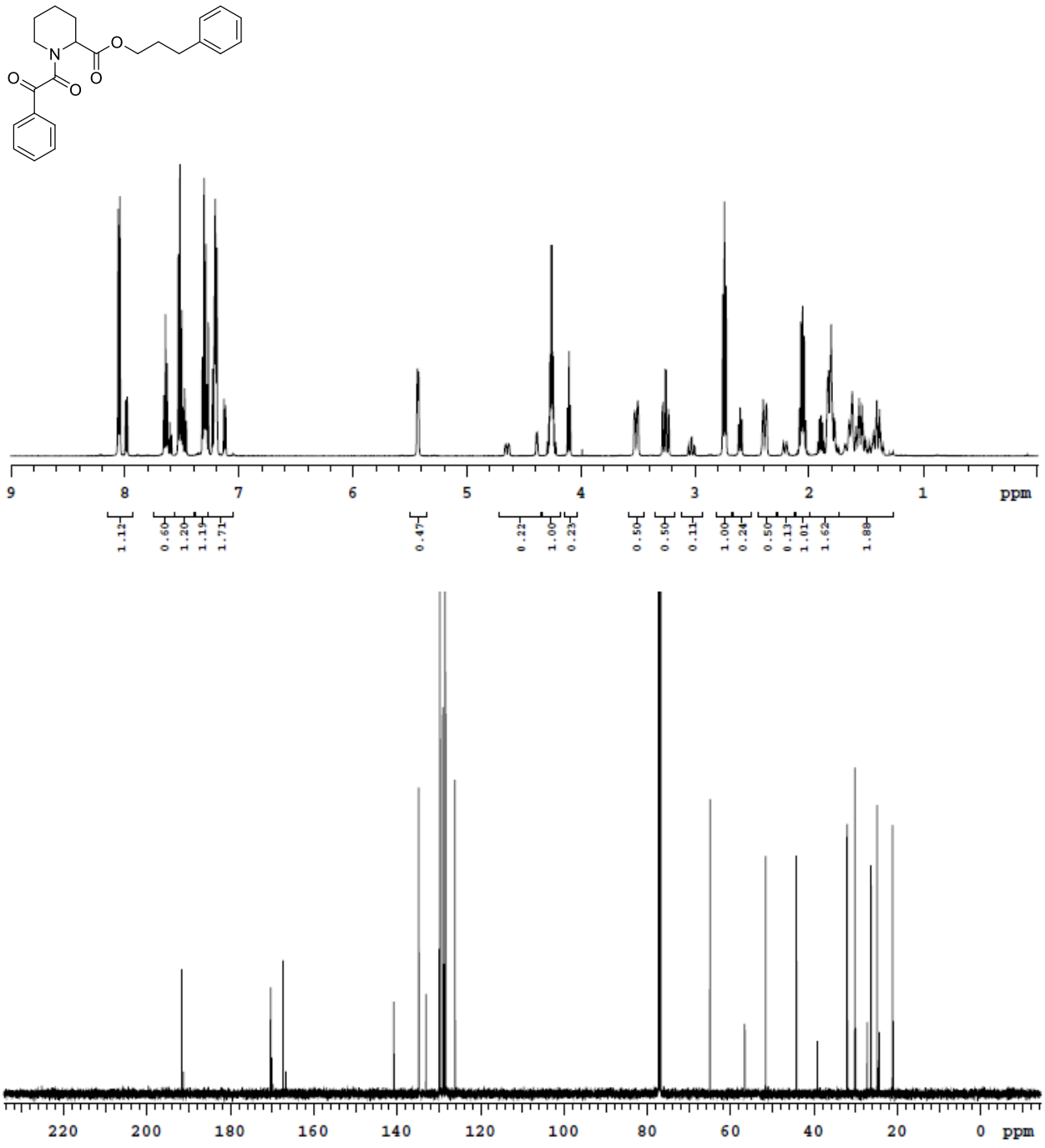


Figure 10.112: gCOSY Spectra of Compound VII.2

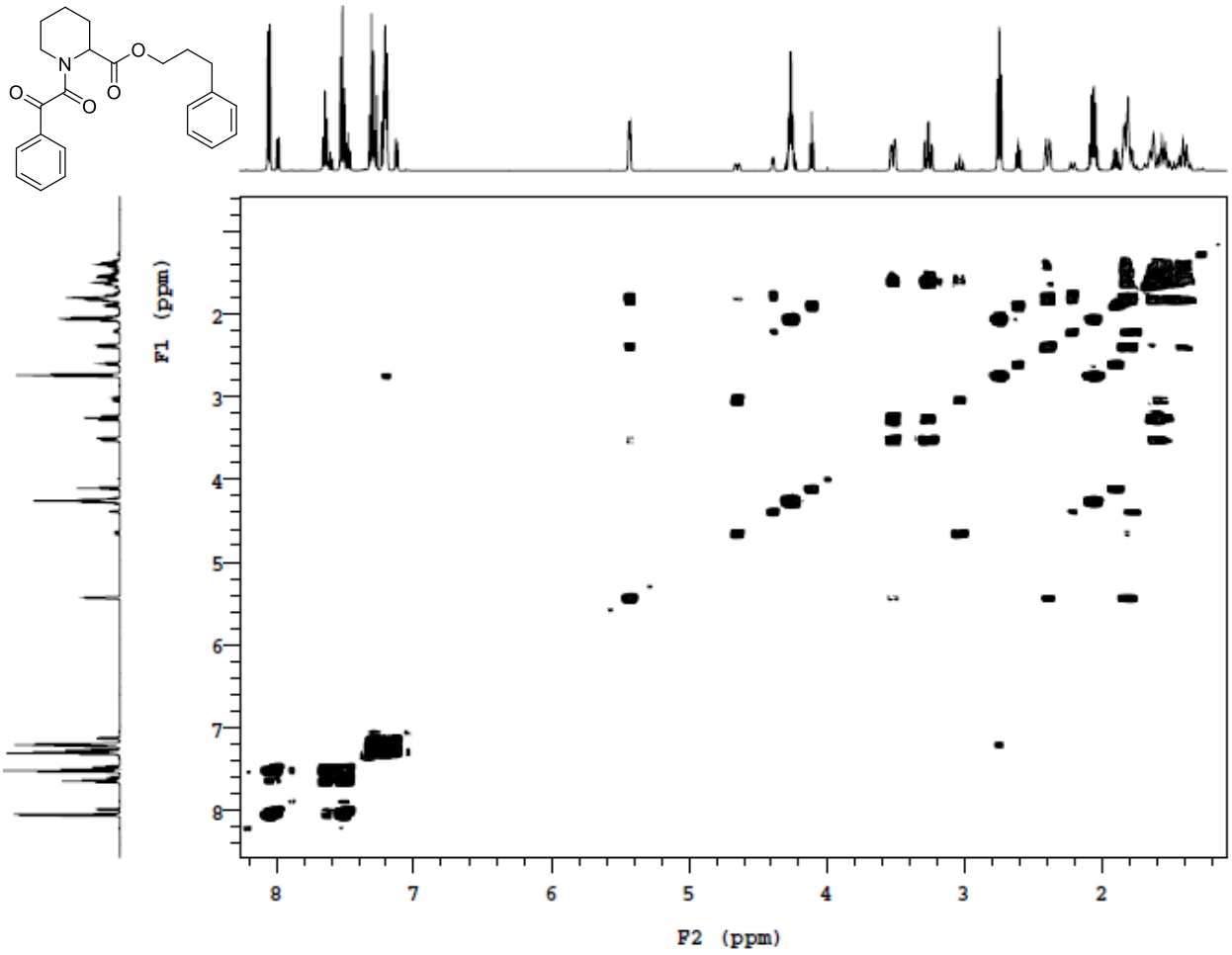


Figure 10.113: gHMQC Spectra of Compound VII.2

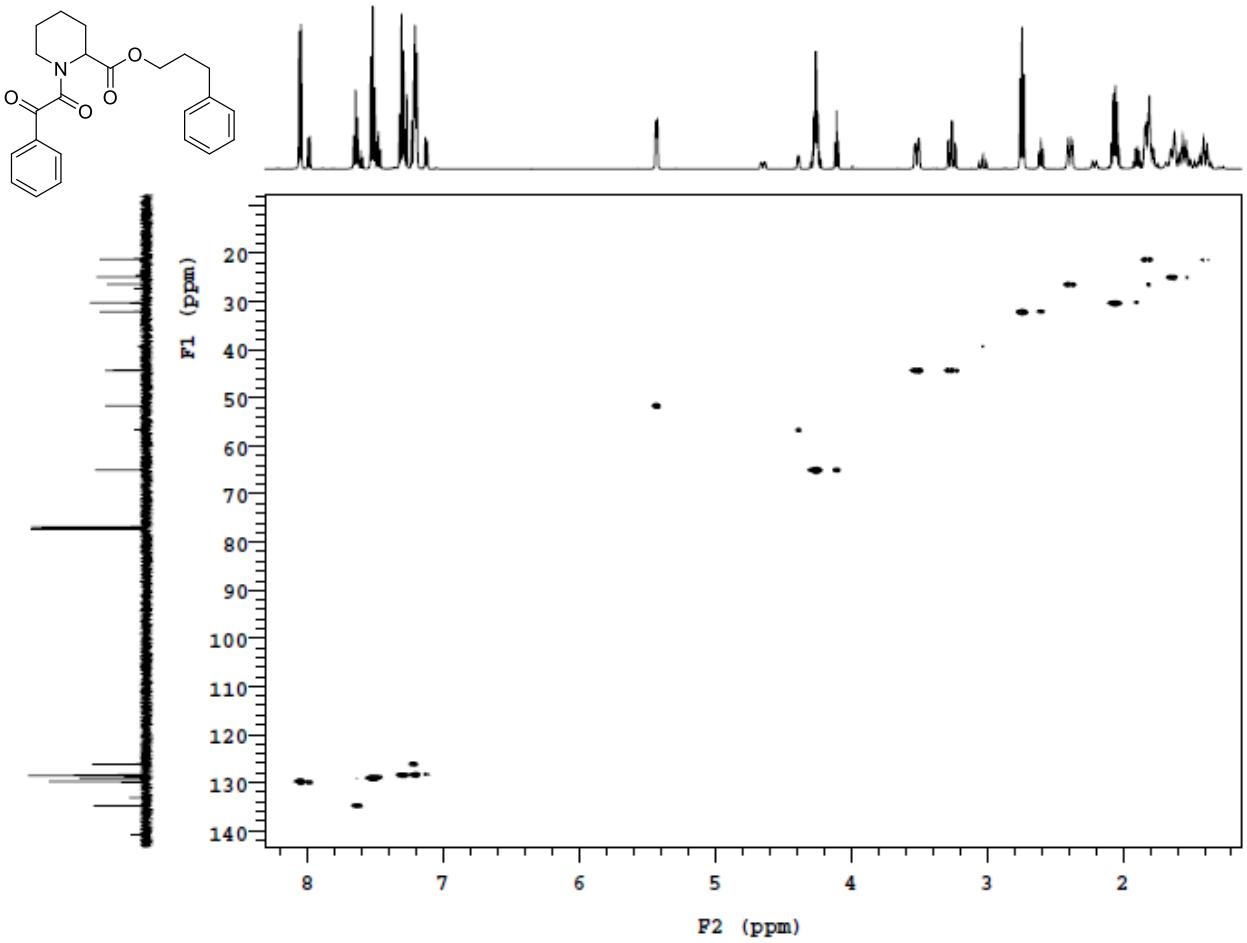


Figure 10.114: ^{1}H and ^{13}C Spectra of Compound VII.3a

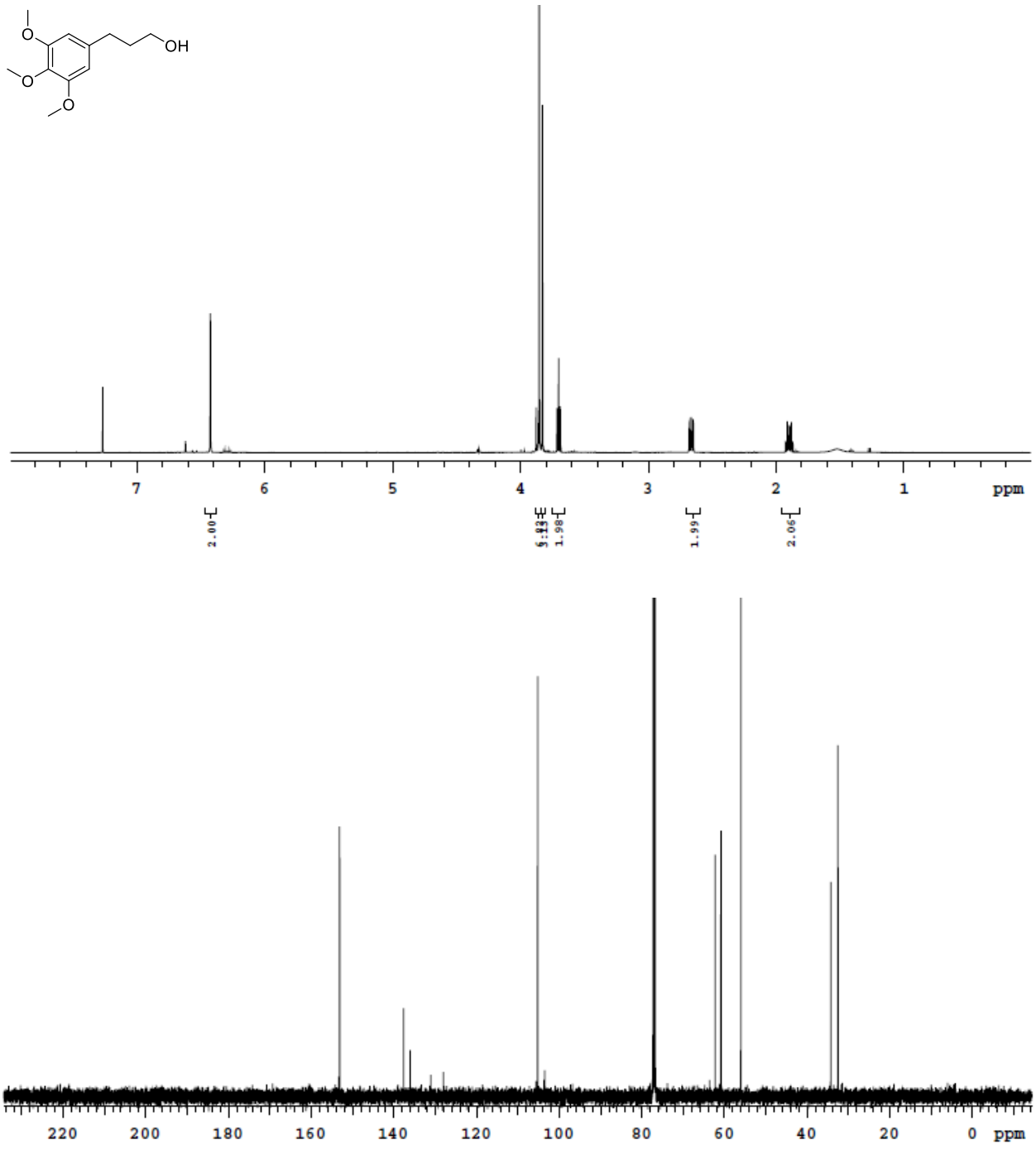


Figure 10.115: ^{1}H and ^{13}C Spectra of Compound VII.3

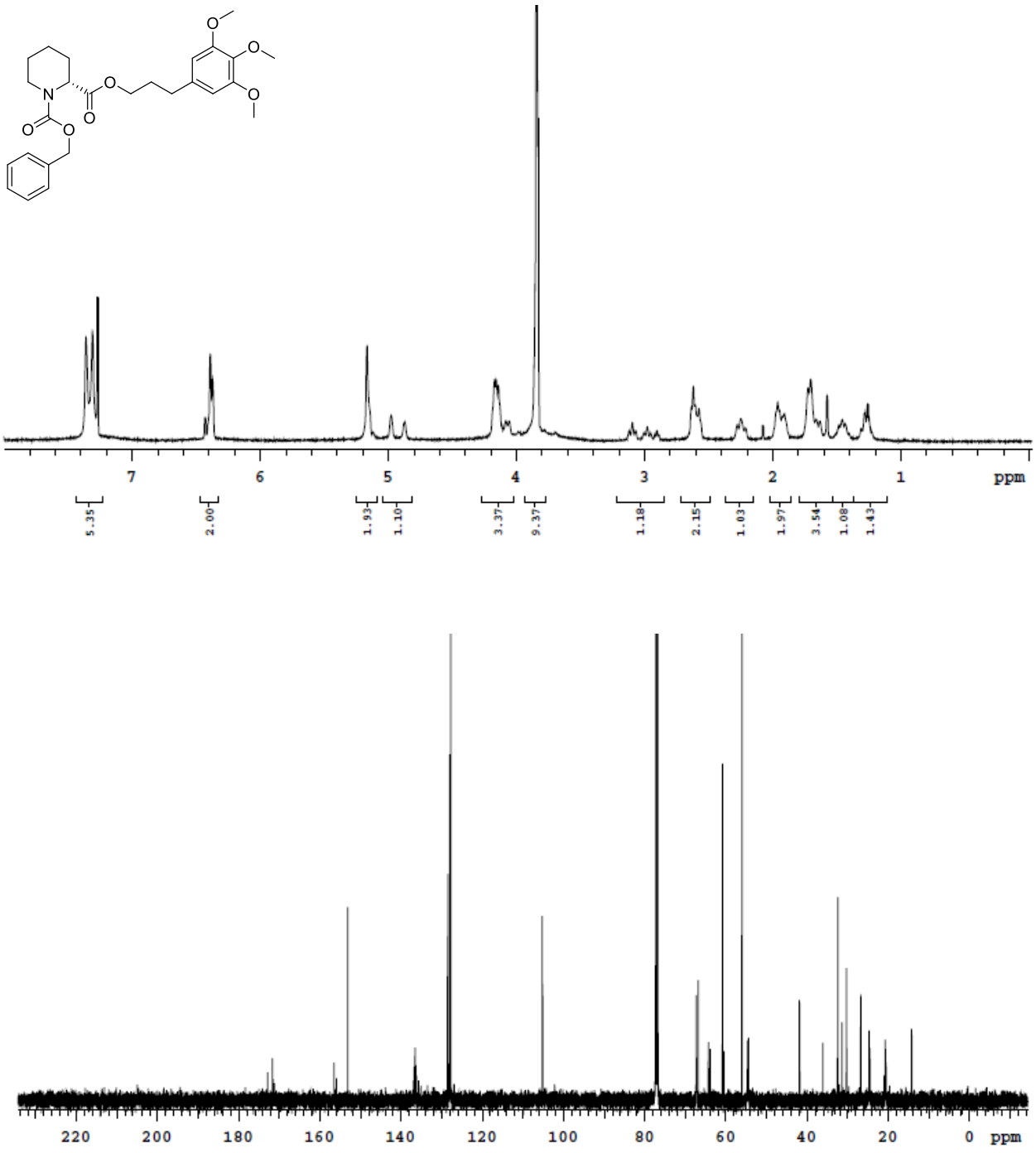


Figure 10.116: ^{1}H and ^{13}C Spectra of Compound VII.4a

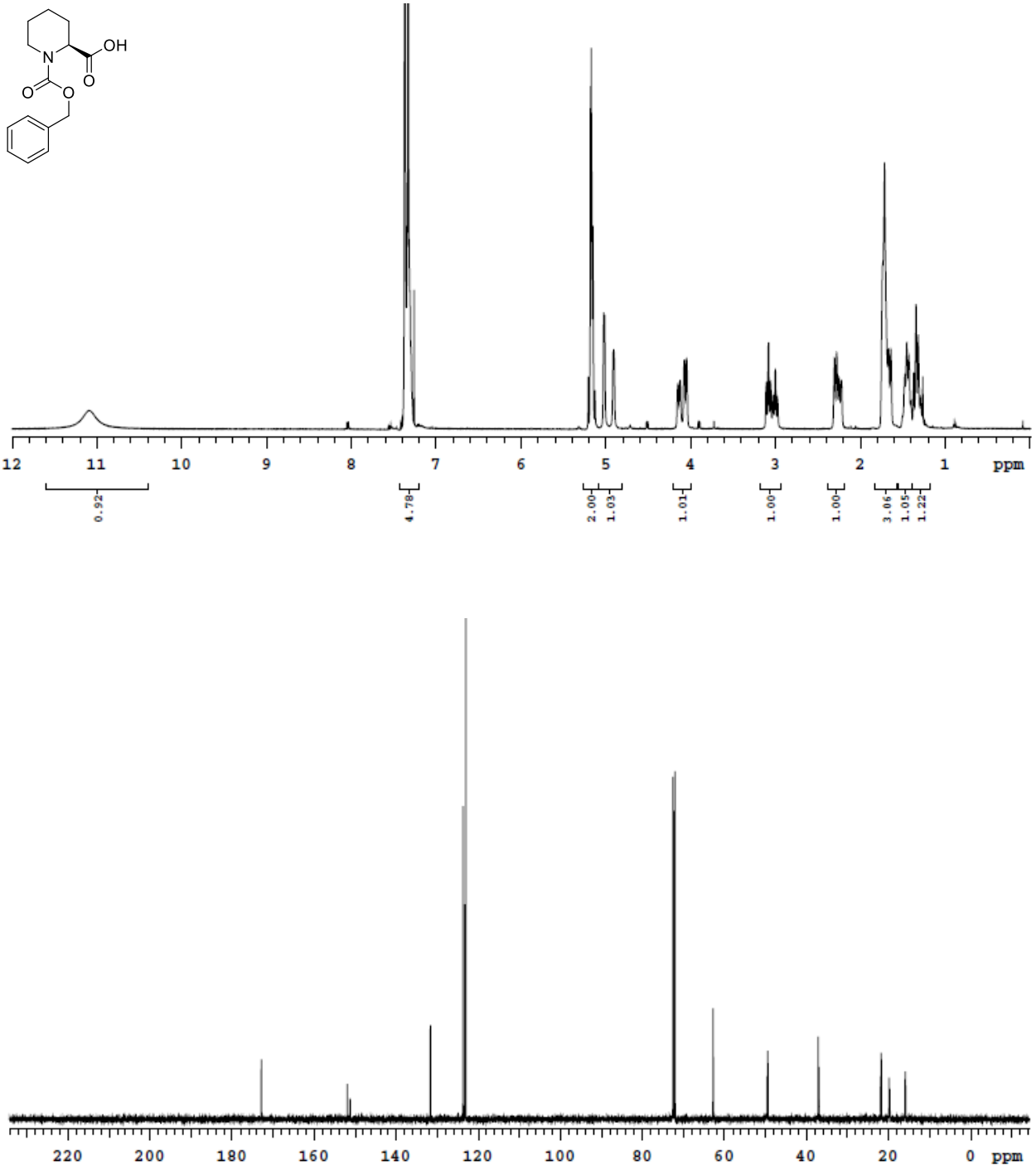


Figure 10.117: ^{1}H and ^{13}C Spectra of Compound VII.4

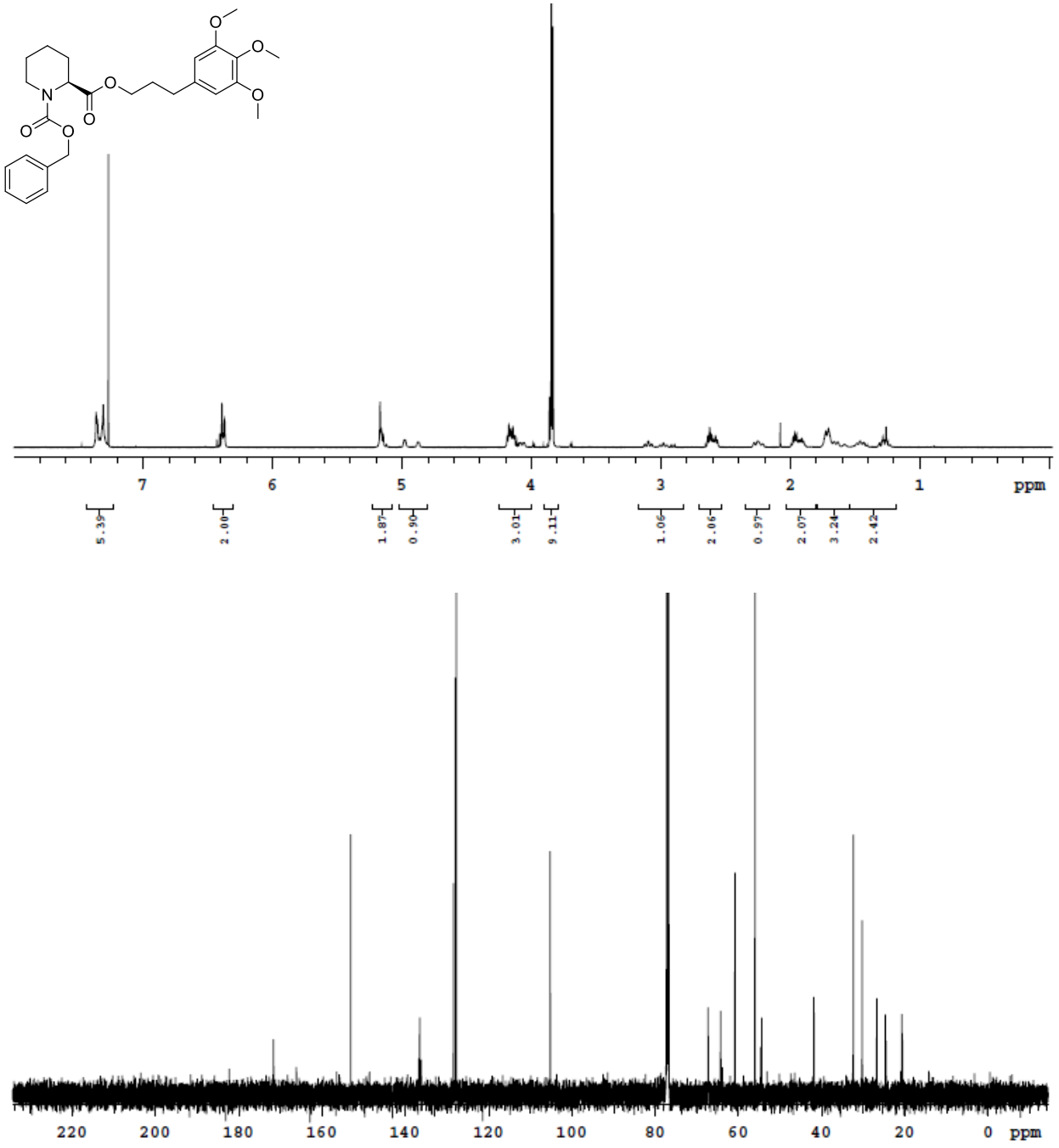


Figure 10.118: ^{1}H and ^{13}C Spectra of Compound VII.5

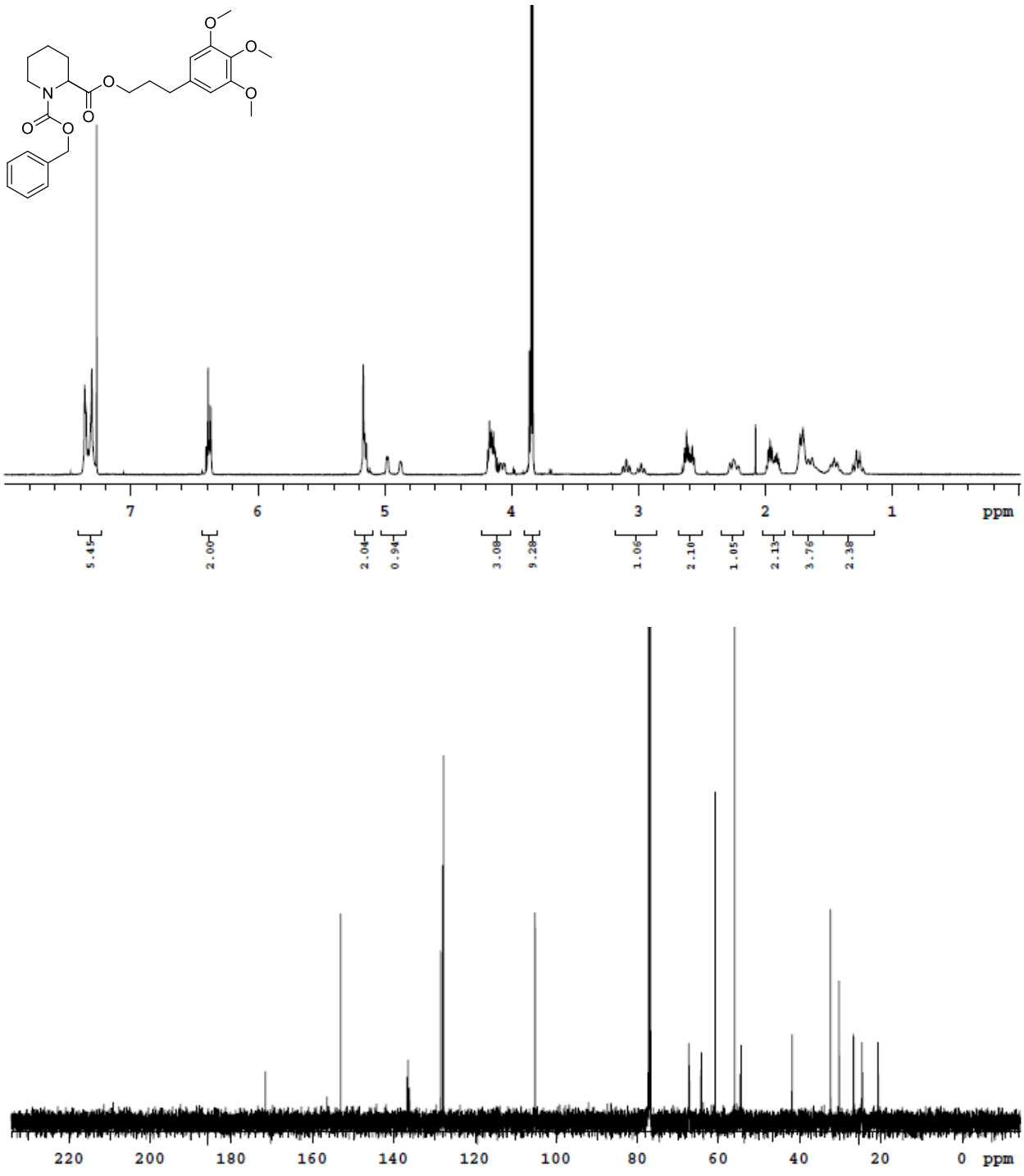


Figure 10.119: gCOSY Spectra of Compound VII.5

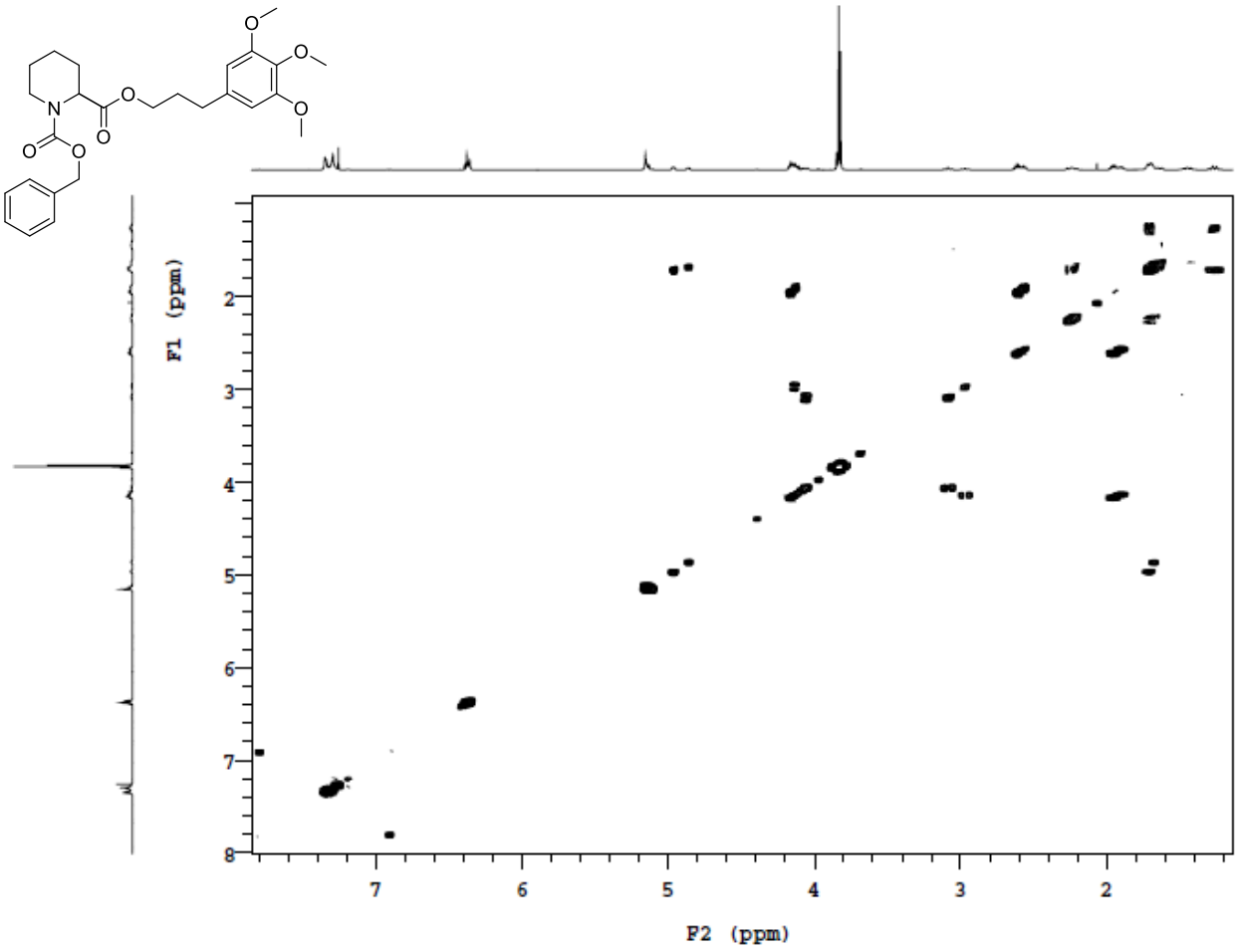


Figure 10.120: gHMQC Spectra of Compound VII.5

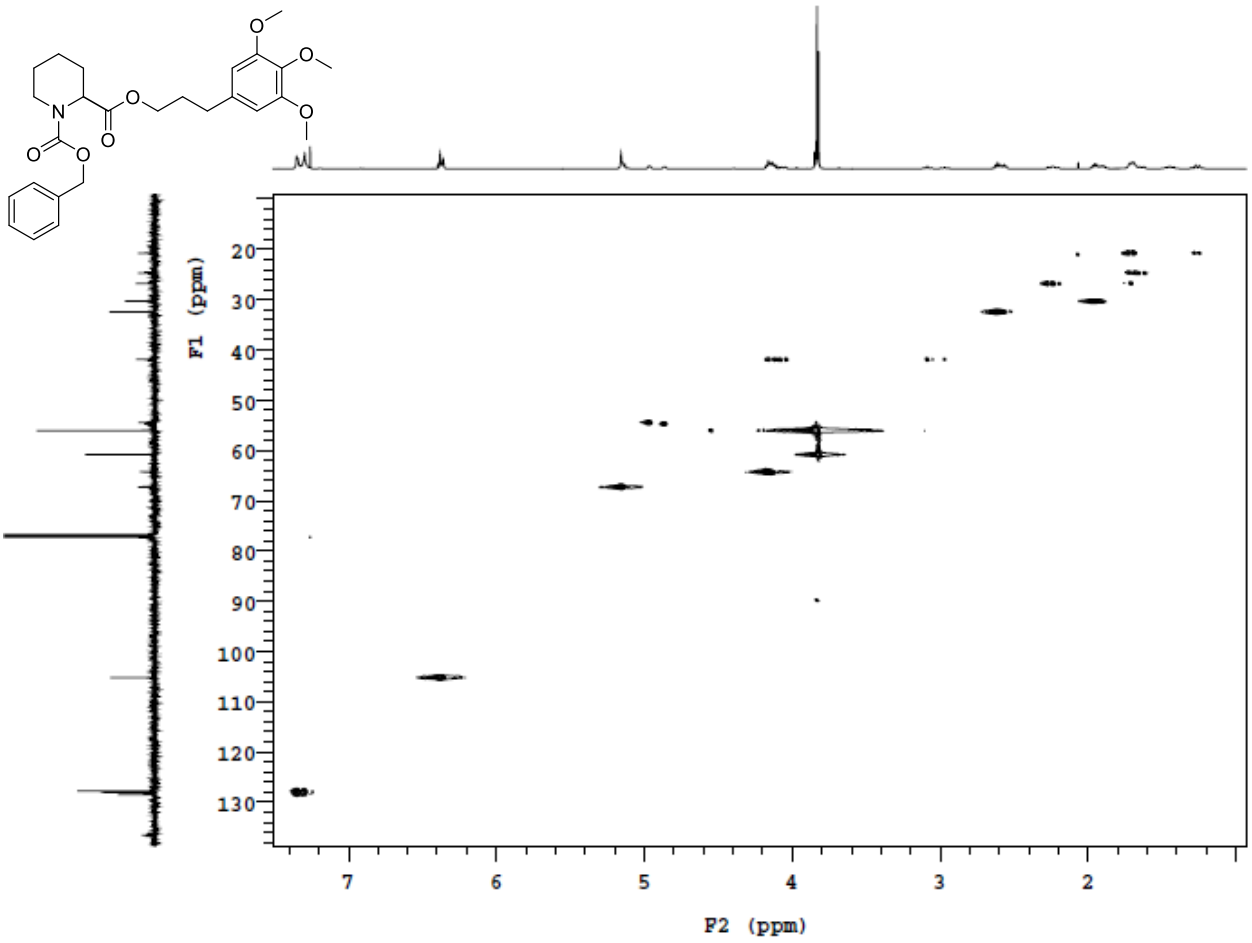


Figure 10.121: ^{1}H and ^{13}C Spectra of Compound VII.6a

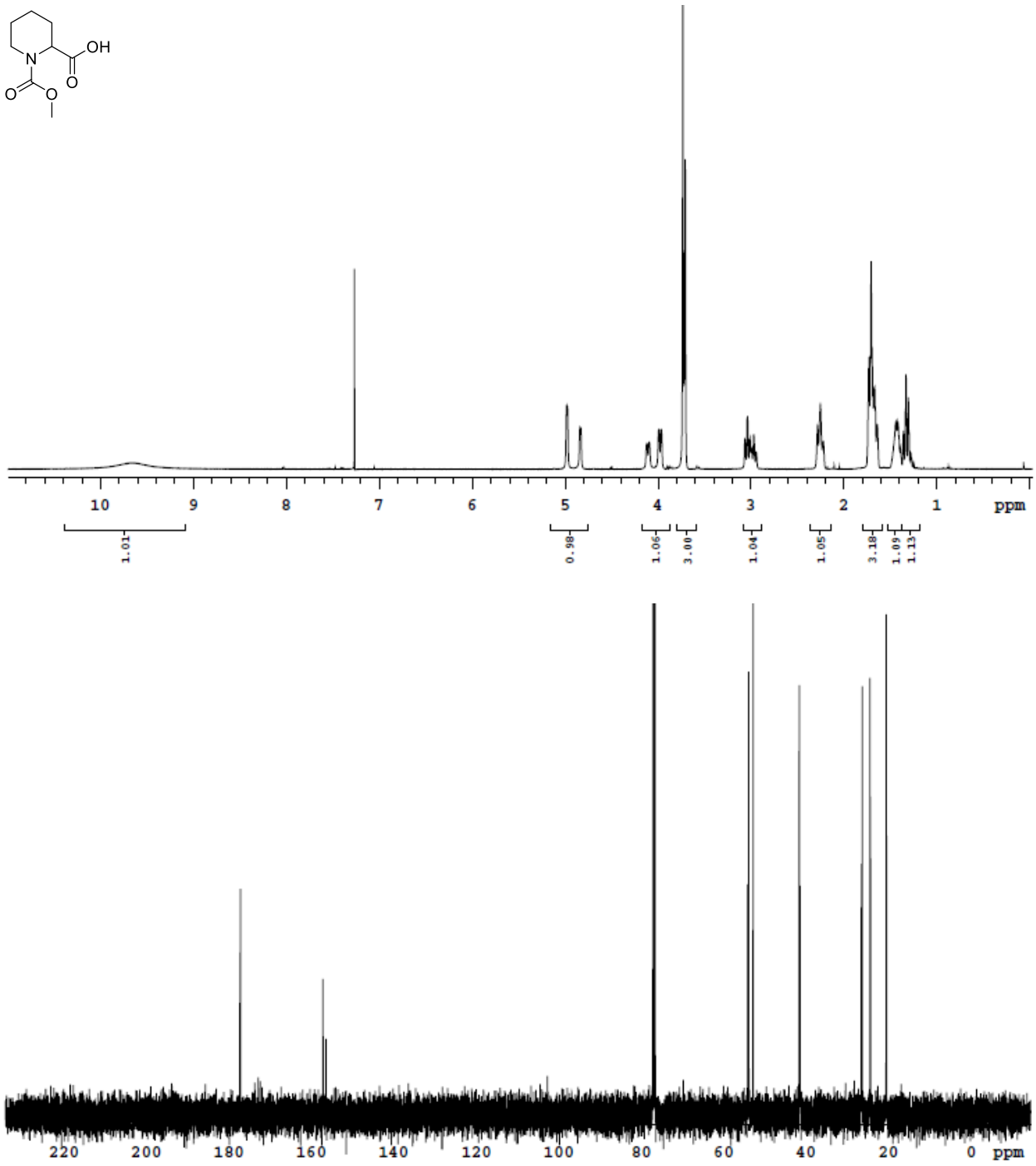


Figure 10.122: ^{1}H and ^{13}C Spectra of Compound VII.6

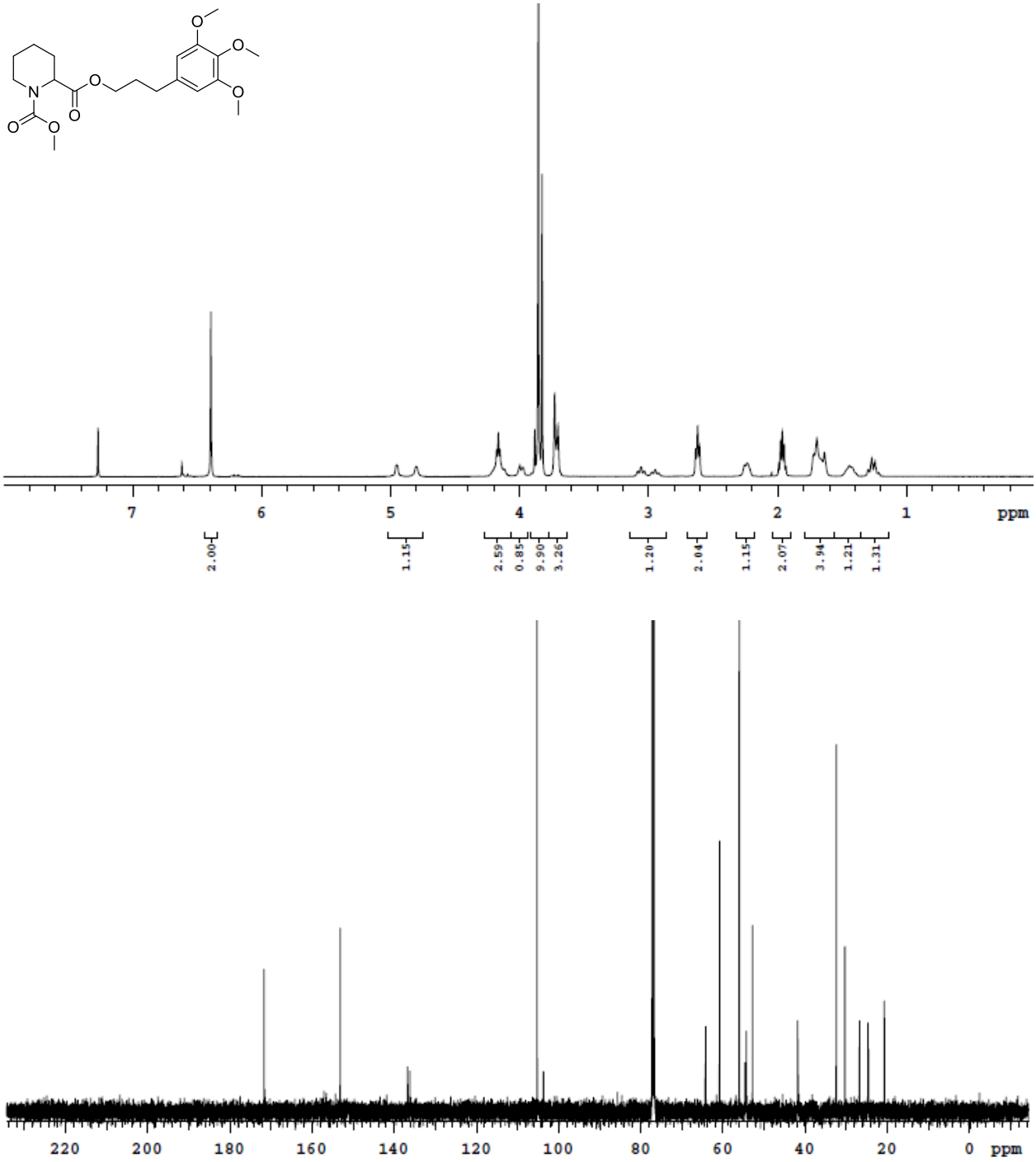


Figure 10.123: gHMQC Spectra of Compound VII.6

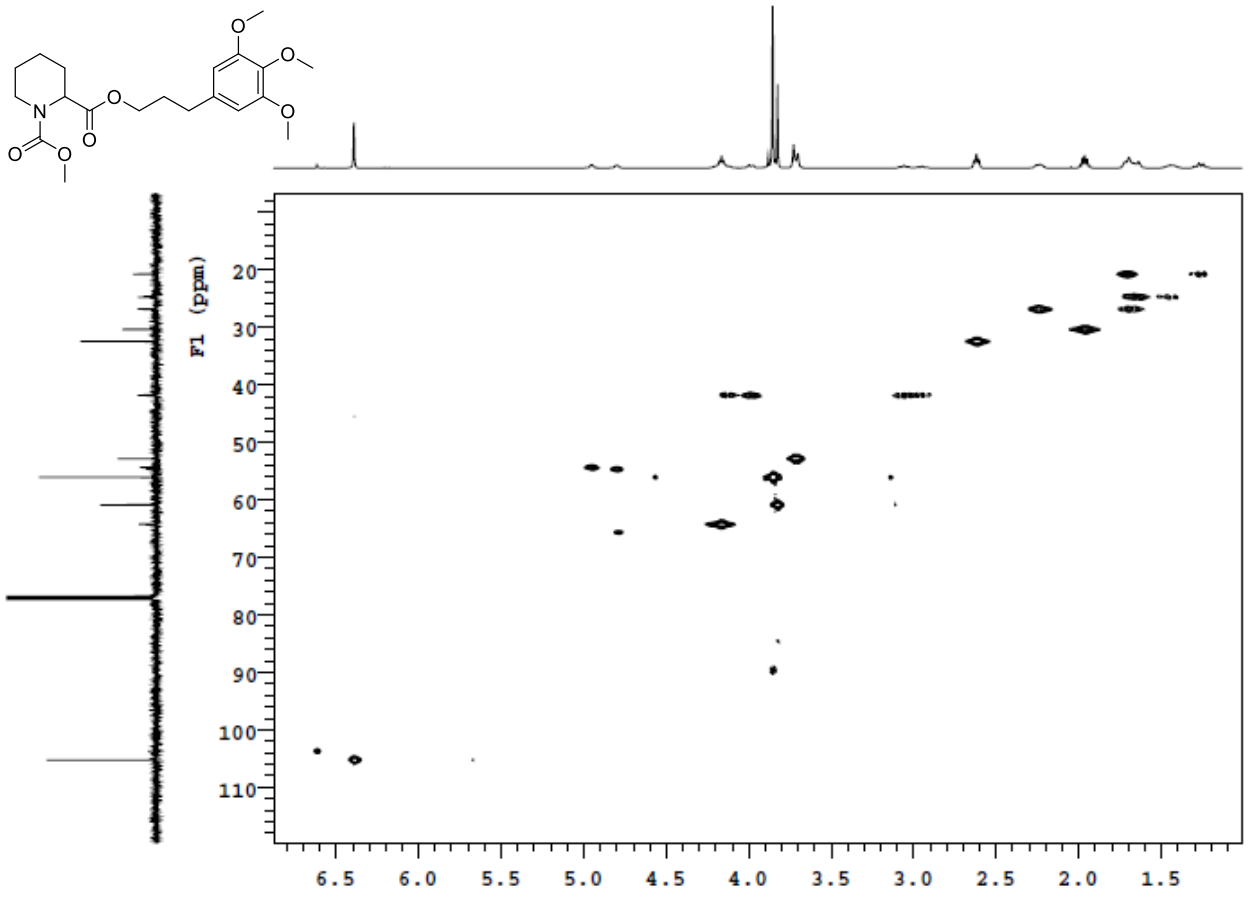


Figure 10.124: ^{1}H and ^{13}C Spectra of Compound VII.7a

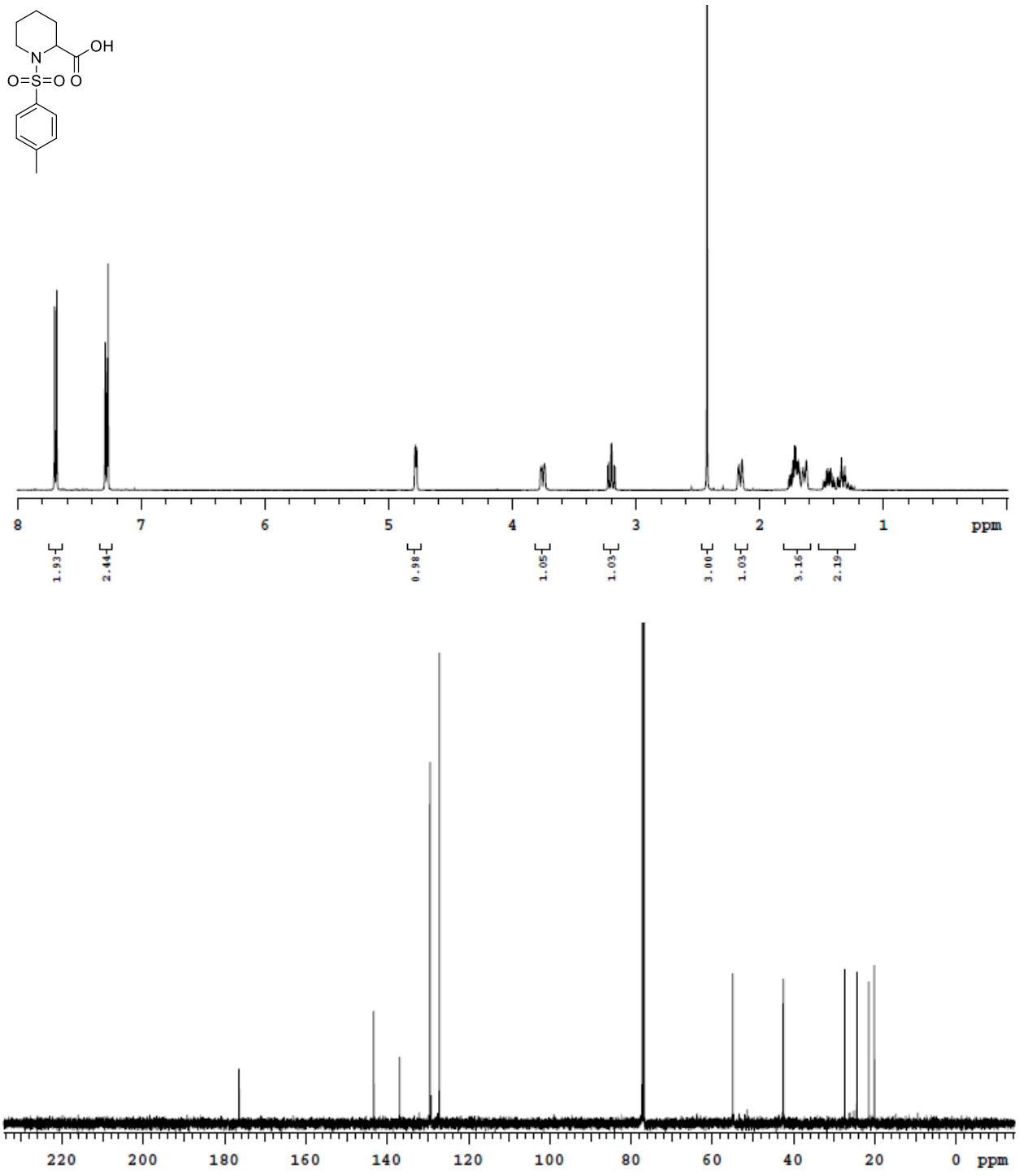


Figure 10.125: ^{1}H and ^{13}C Spectra of Compound VII.7

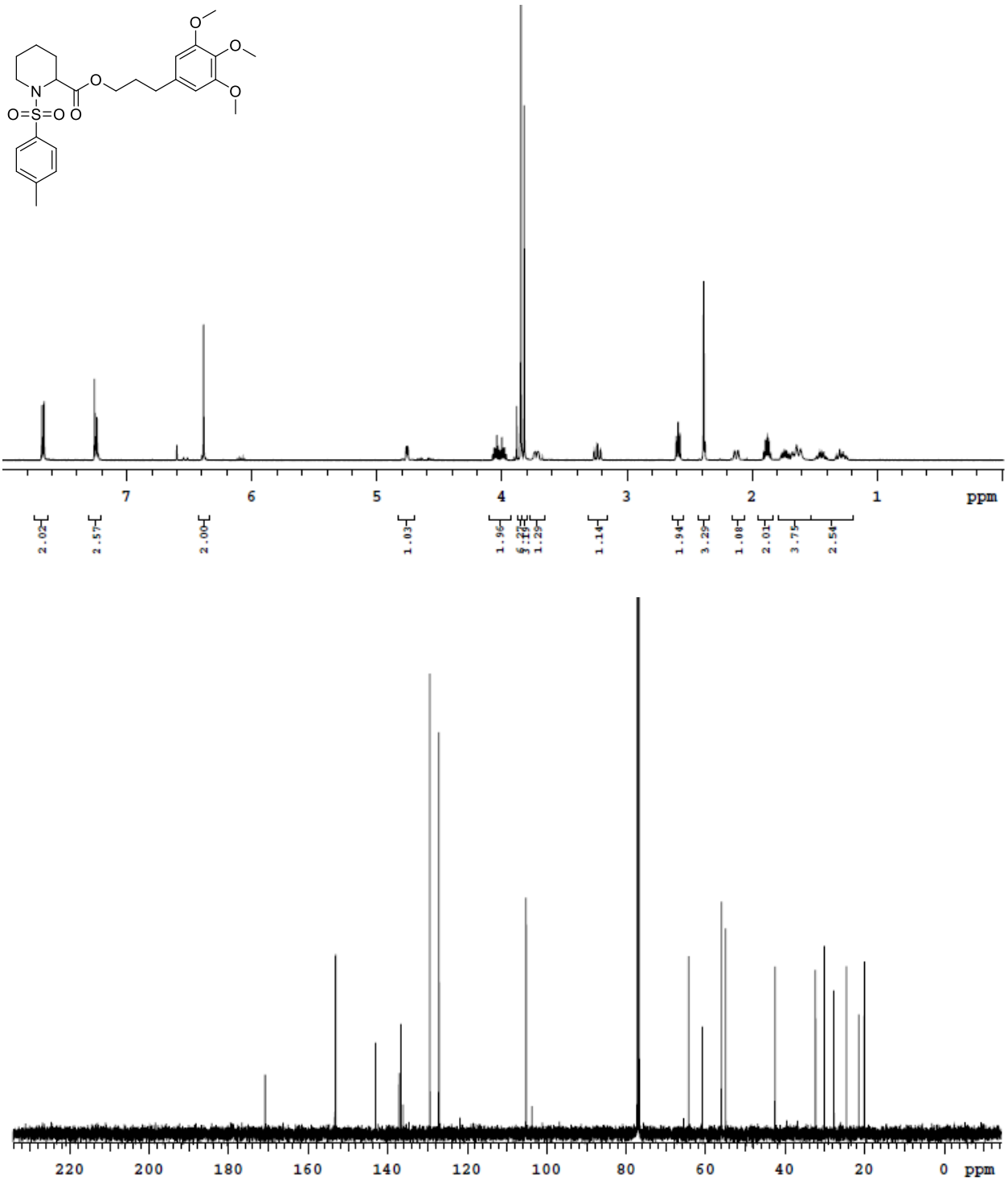


Figure 10.126: gCOSY Spectra of Compound VII.7

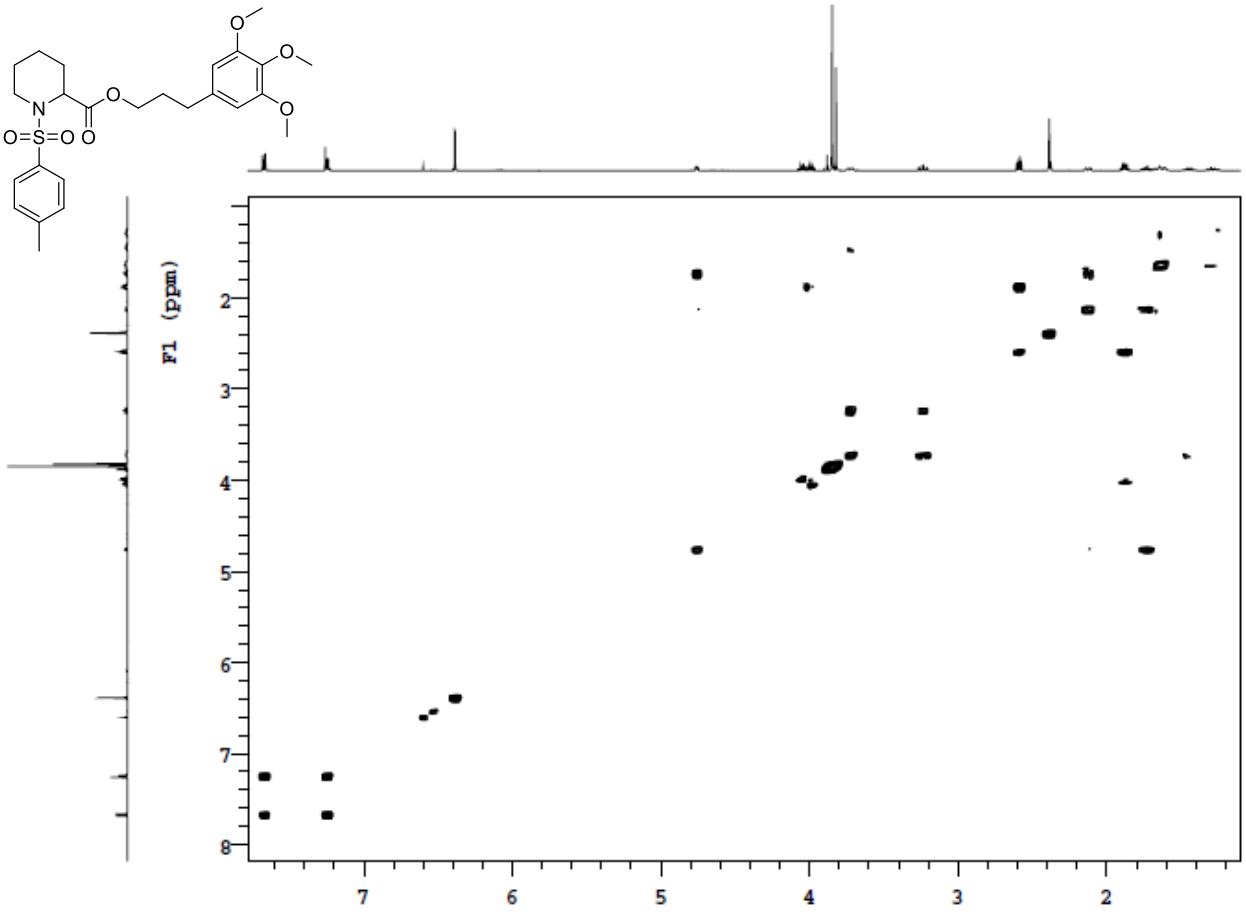


Figure 10.127: ^{1}H and ^{13}C Spectra of Compound VII.8a

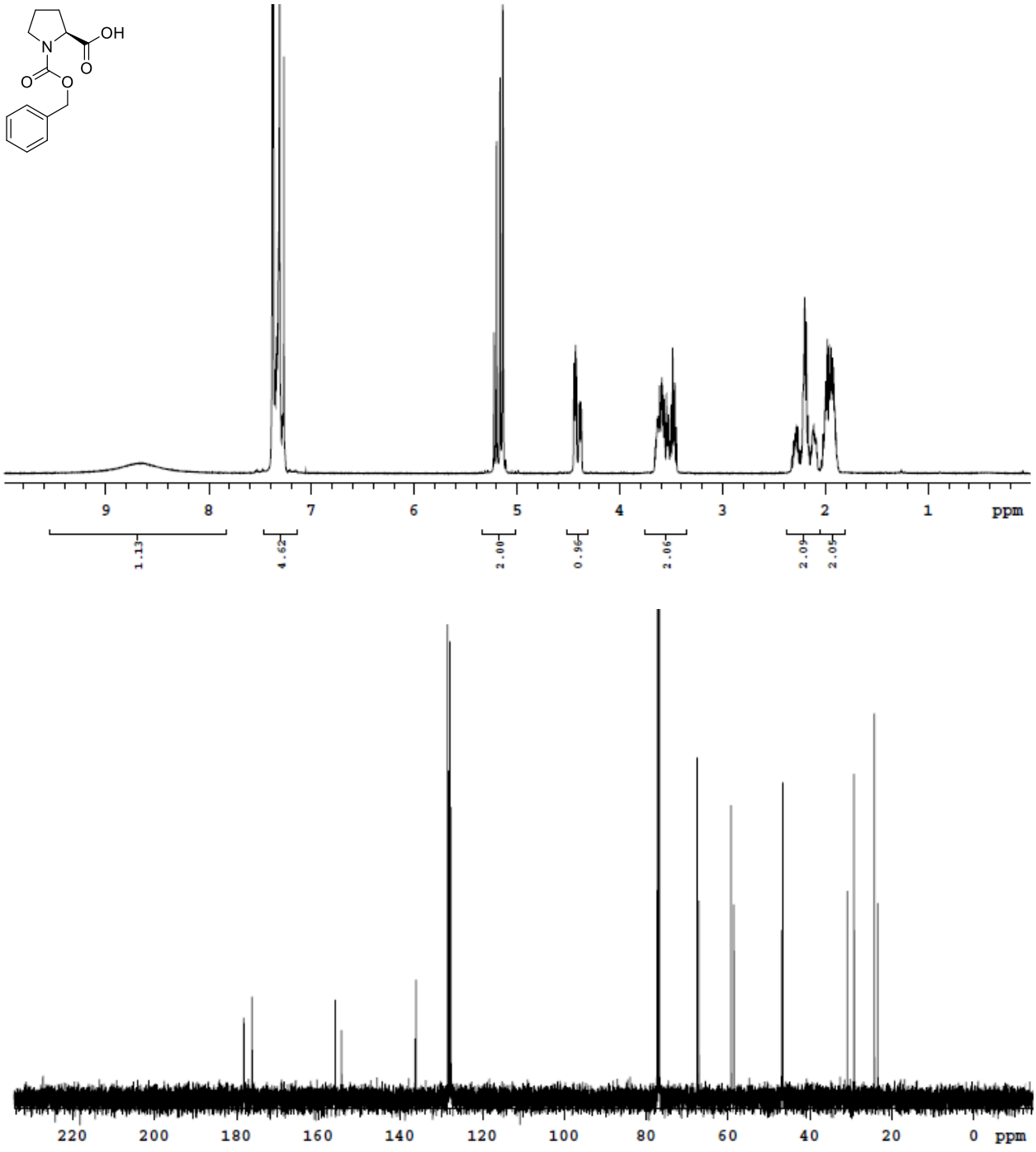


Figure 10.128: ^{1}H and ^{13}C Spectra of Compound VII.8

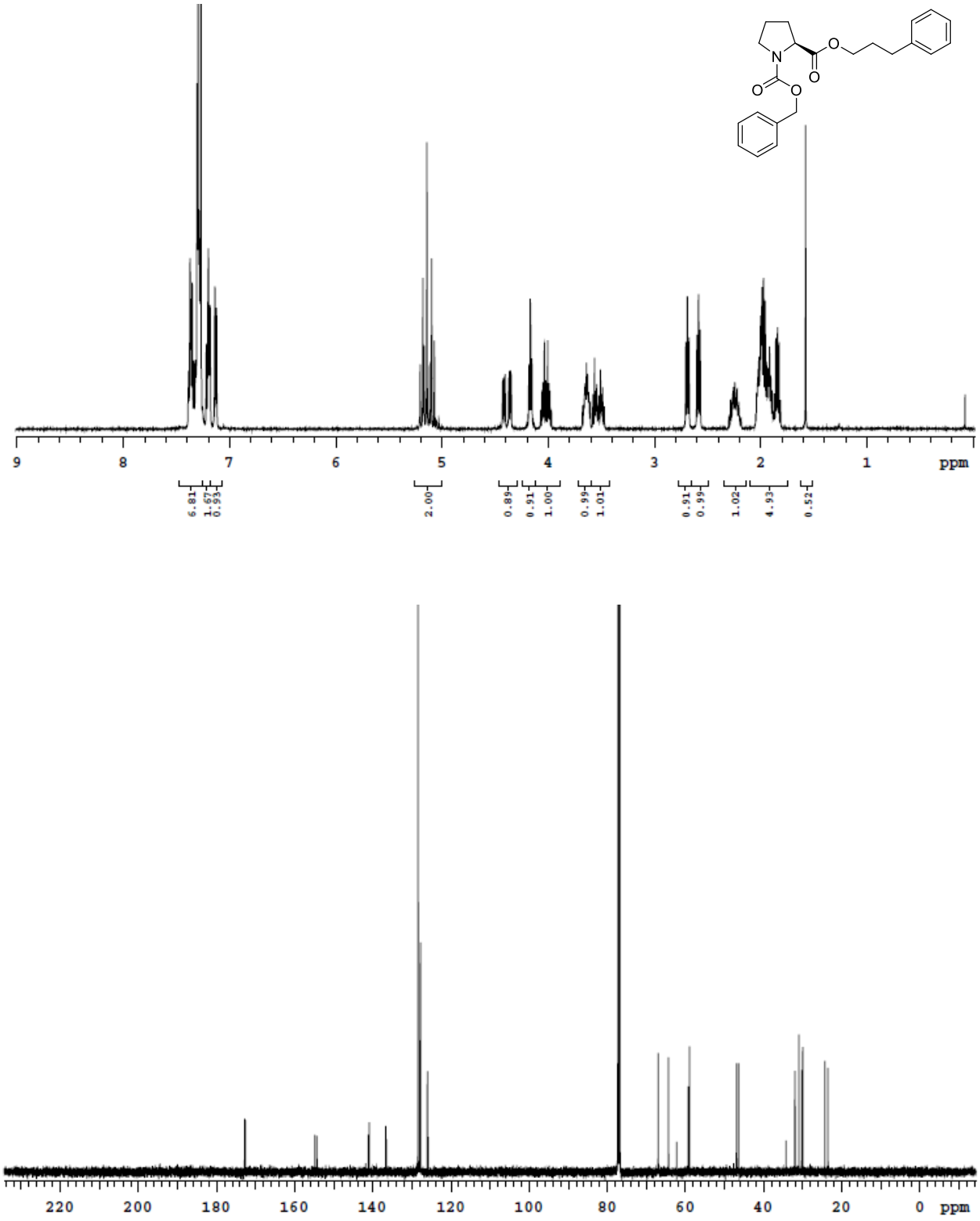


Figure 10.129: gCOSY Spectra of Compound VII.8

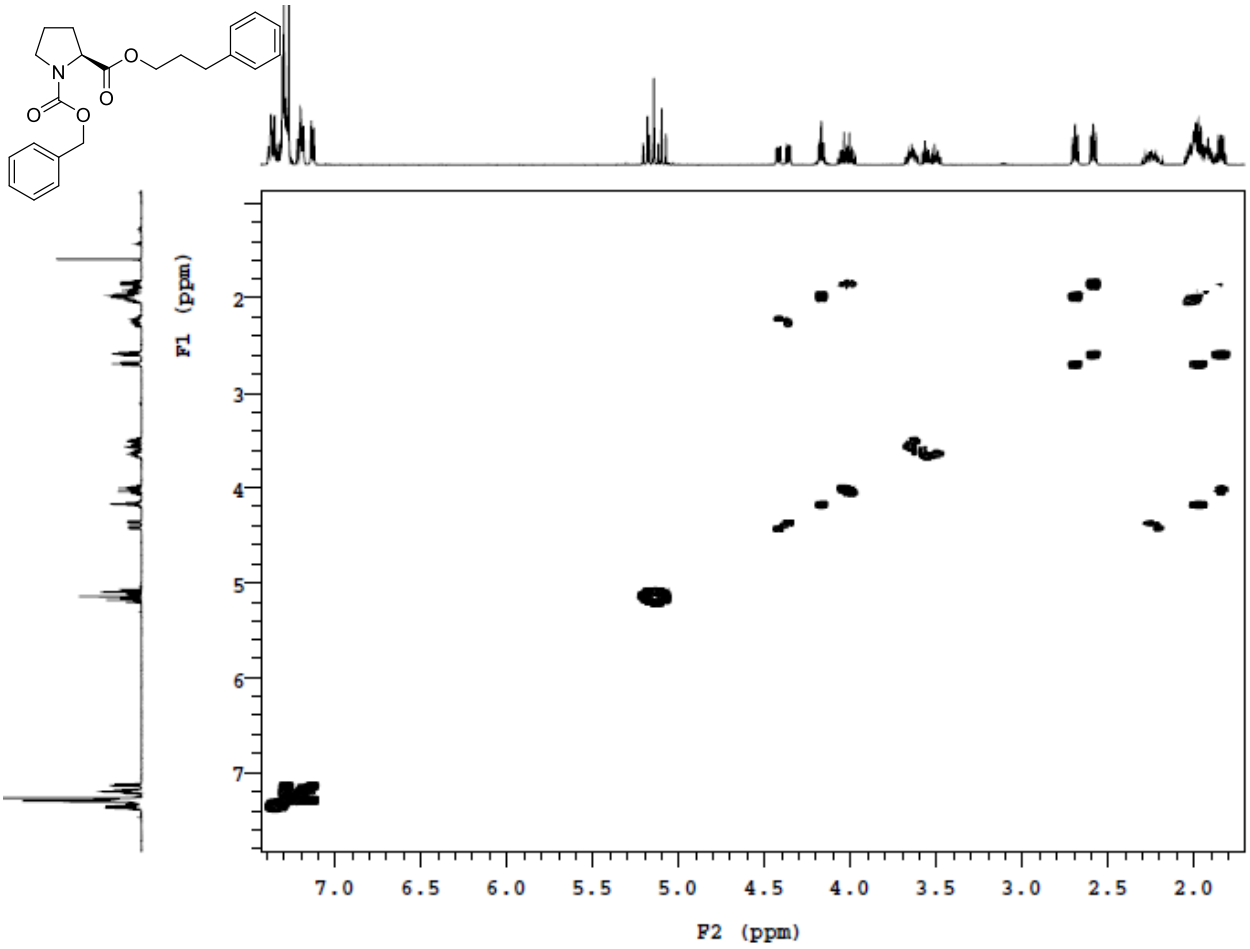


Figure 10.130: gHMQC Spectra of Compound VII.8

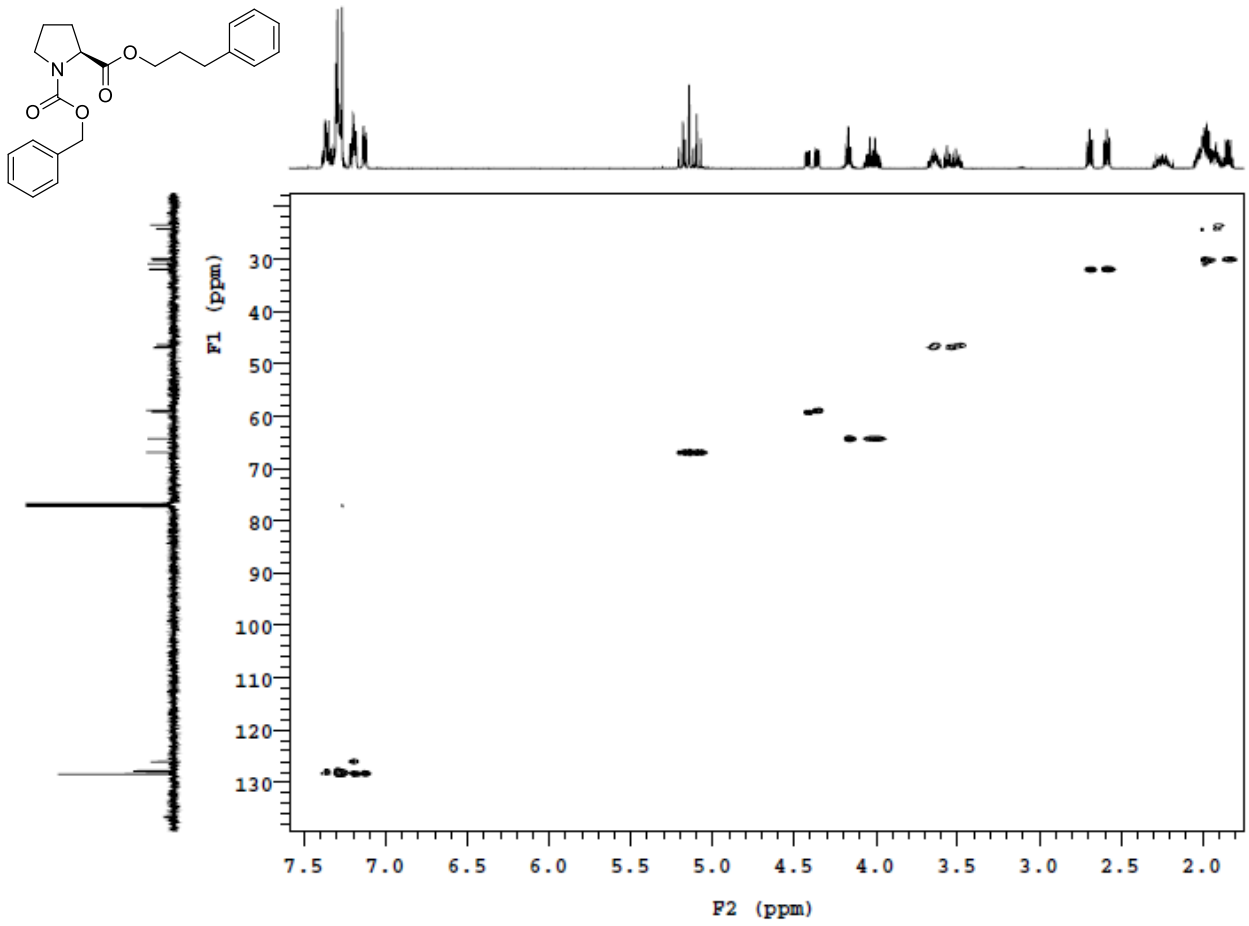


Figure 10.131: ^{1}H and ^{13}C Spectra of Compound VII.9

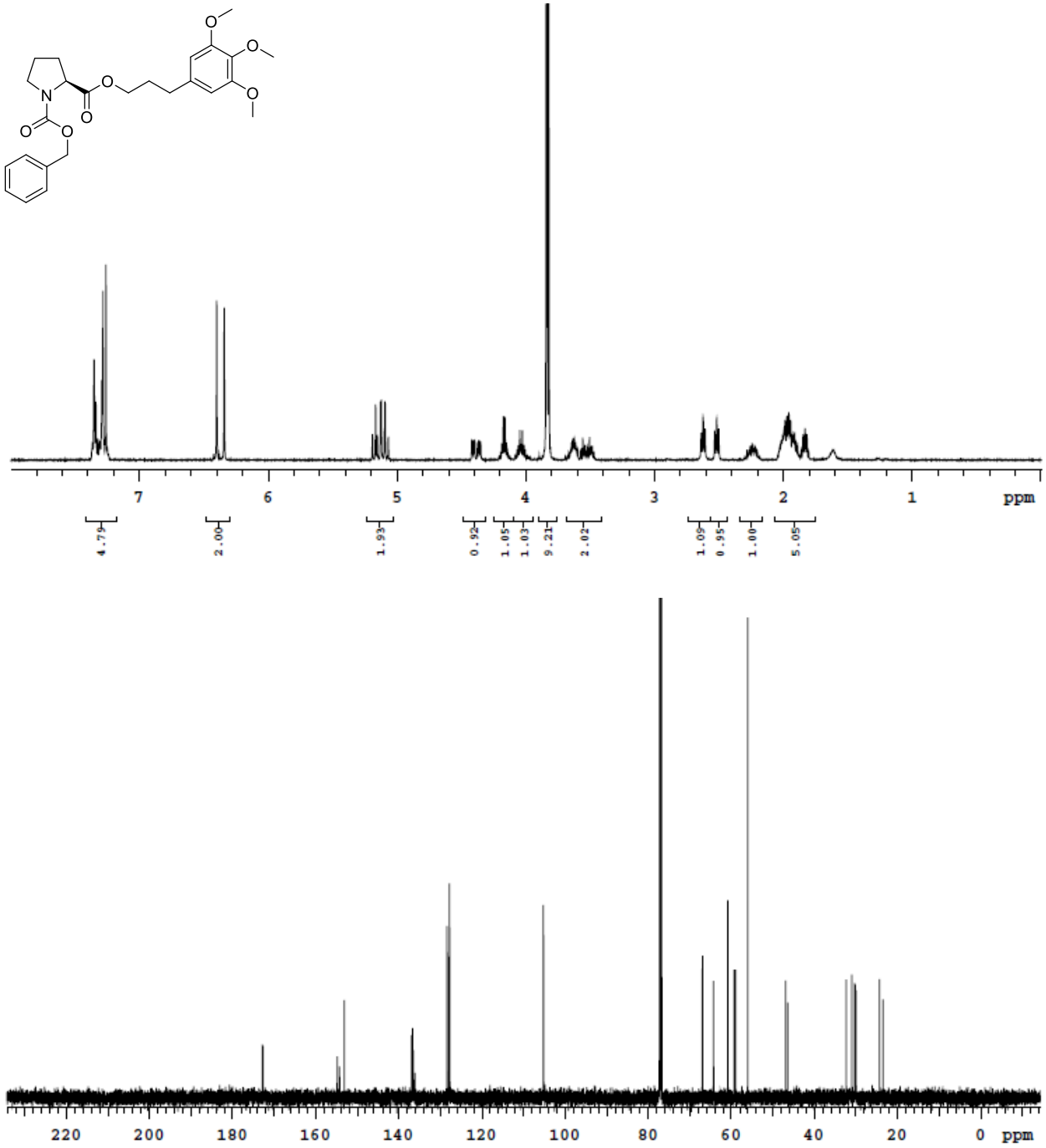


Figure 10.132: gCOSY Spectra of Compound VII.9

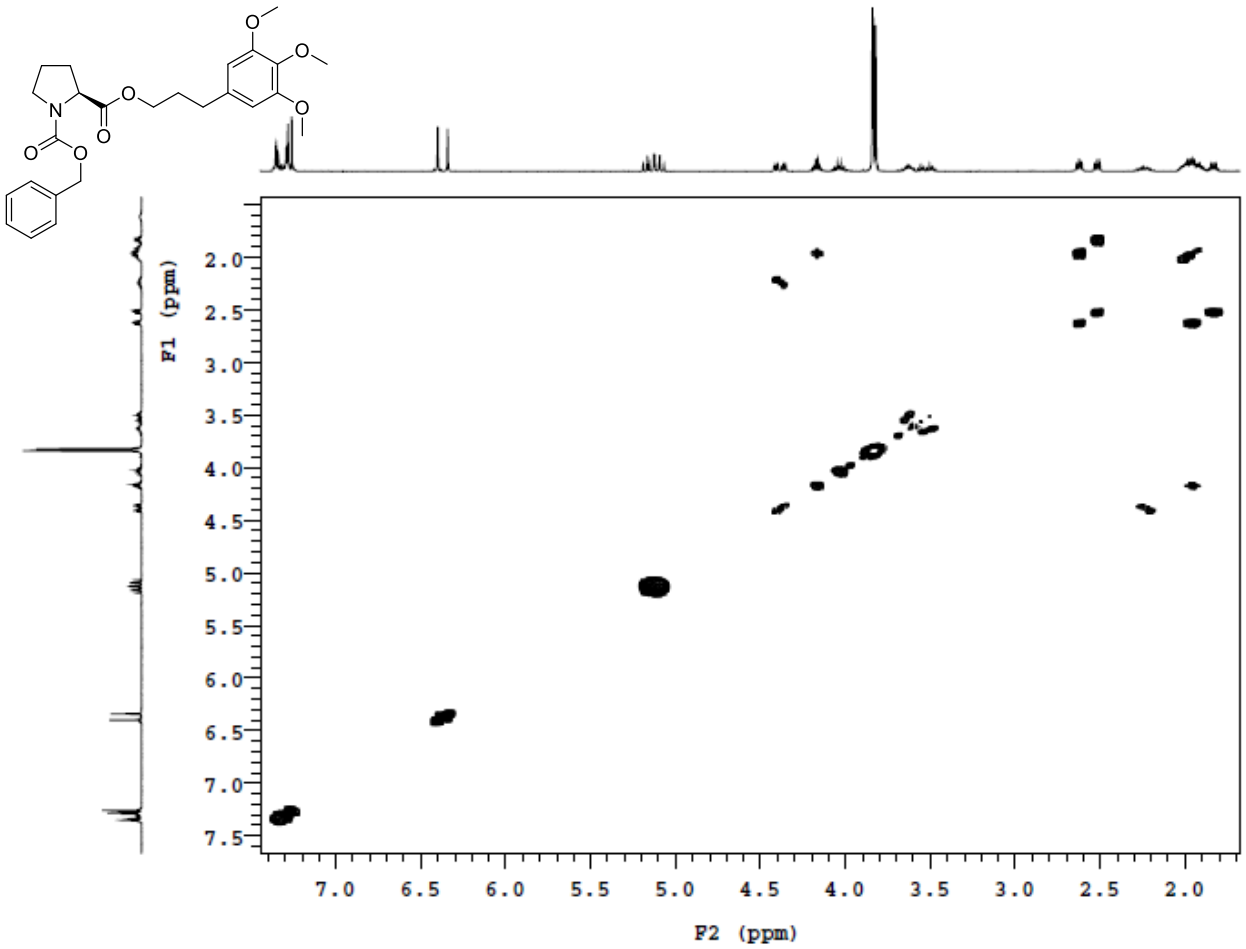


Figure 10.133: gHMQC Spectra of Compound VII.9

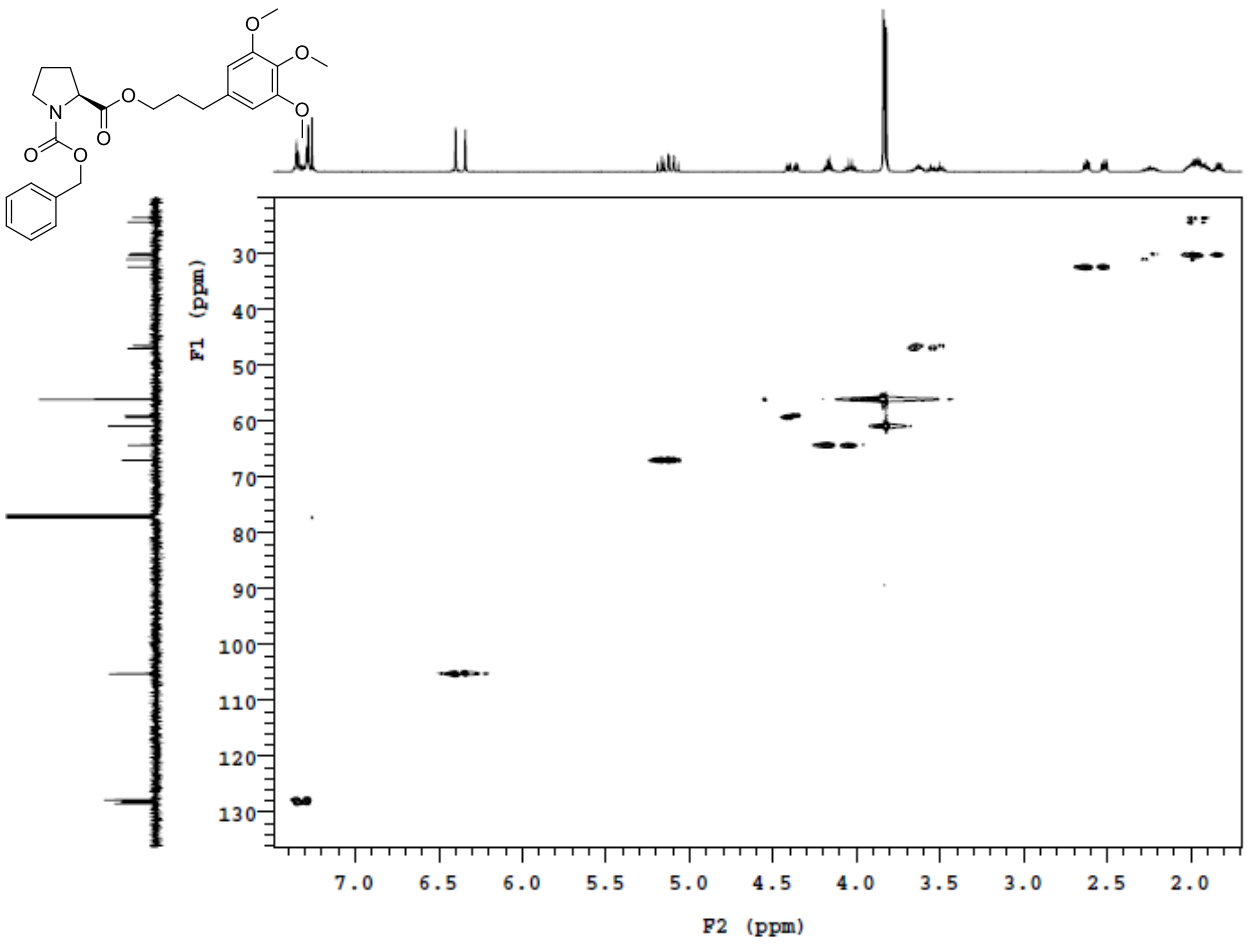


Figure 10.134: ^{1}H and ^{13}C Spectra of Compound VII.10a

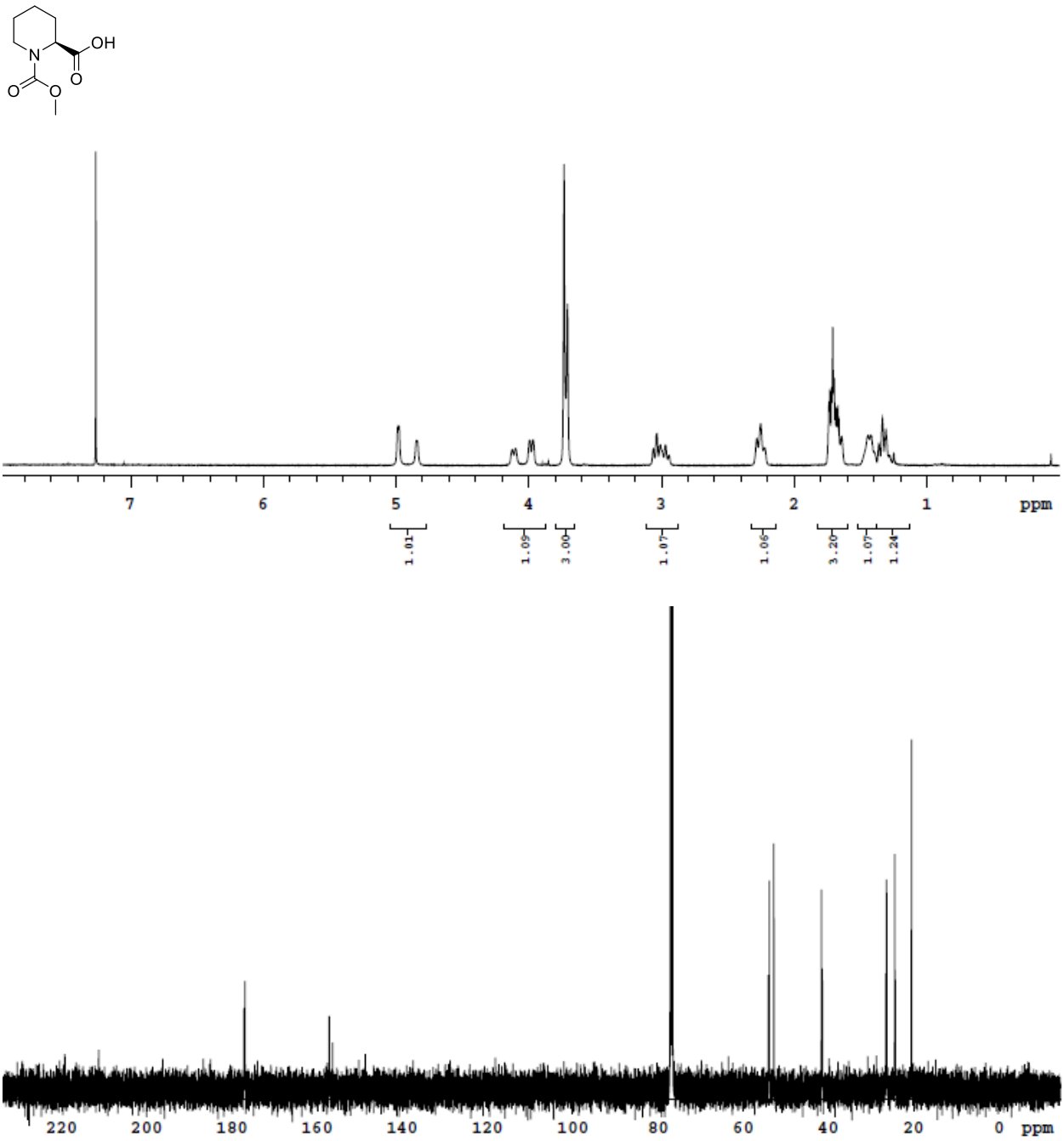


Figure 10.135: ^{1}H and ^{13}C Spectra of Compound VII.10

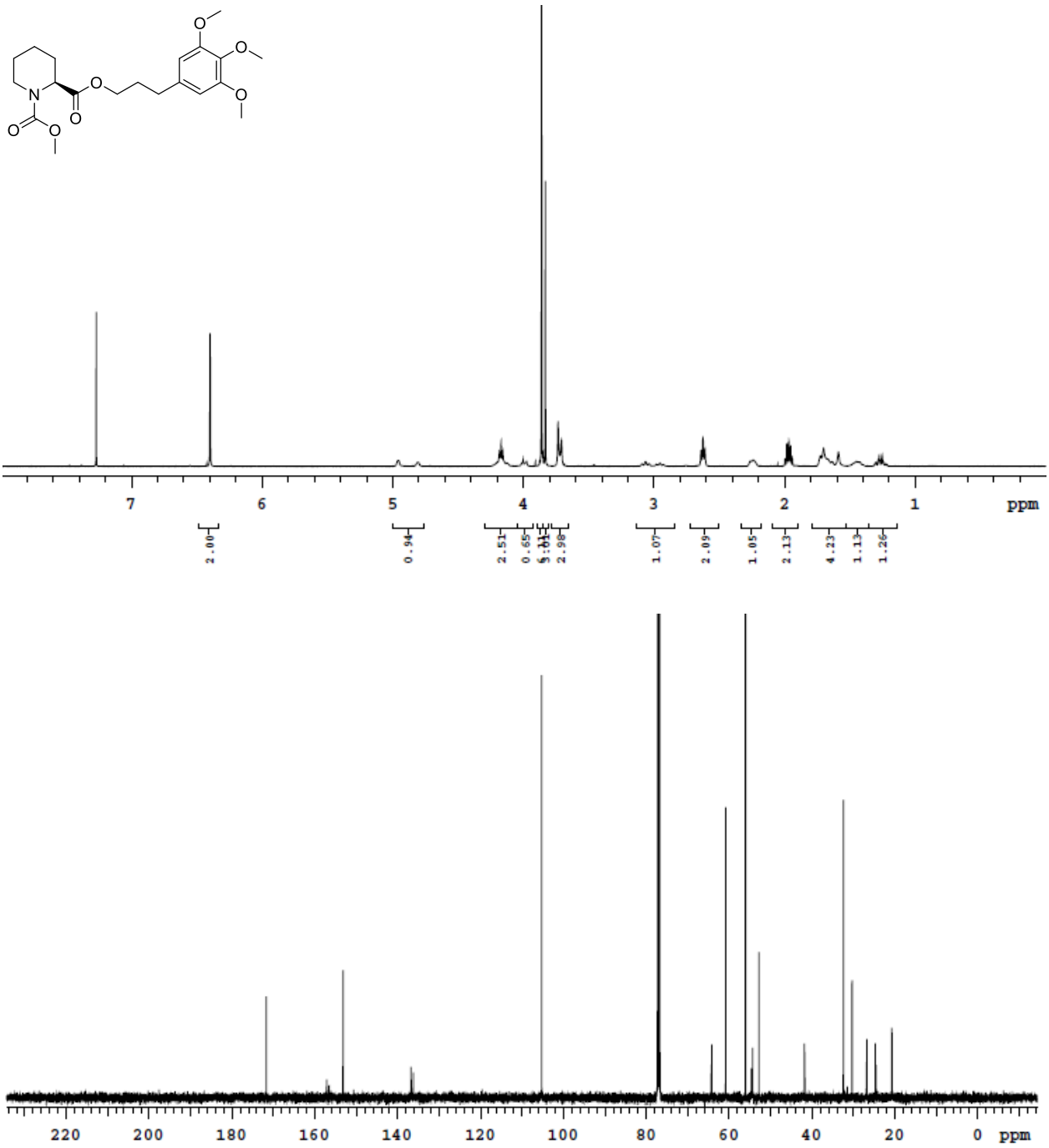


Figure 10.136: ^{1}H and ^{13}C Spectra of Compound VII.11a

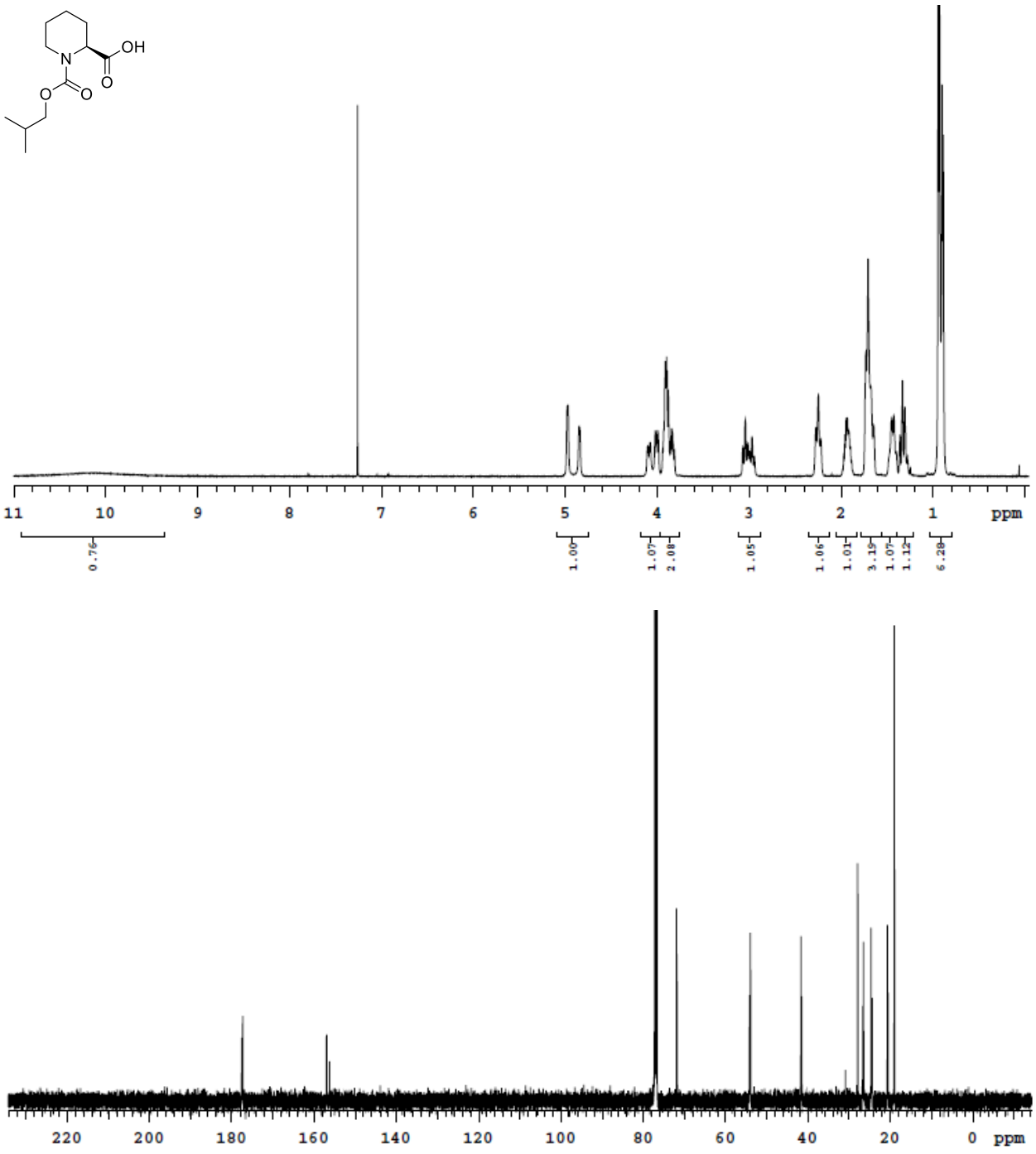


Figure 10.137: ^{1}H and ^{13}C Spectra of Compound VII.11

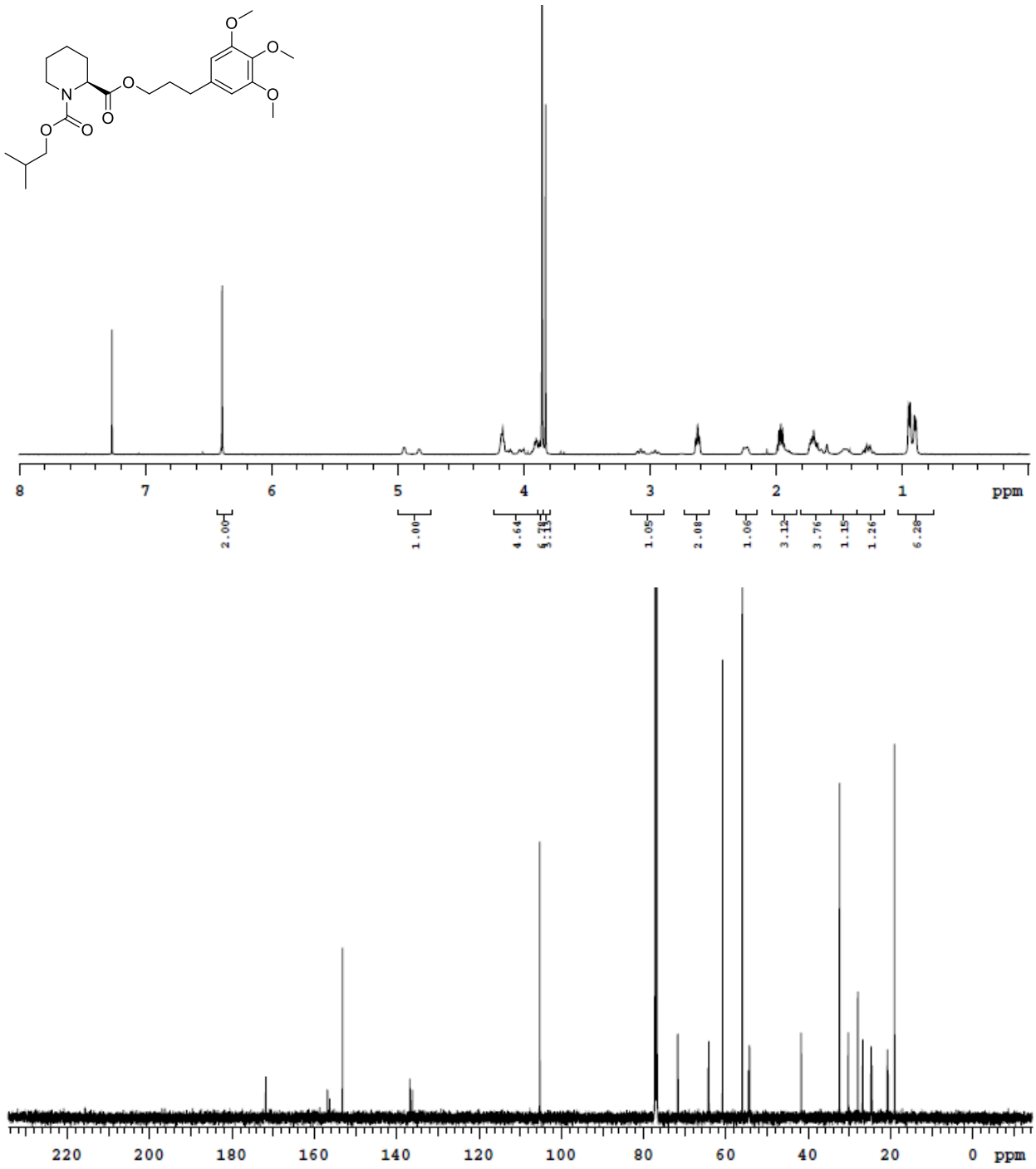


Figure 10.138: ^{1}H and ^{13}C Spectra of Compound VII.12a

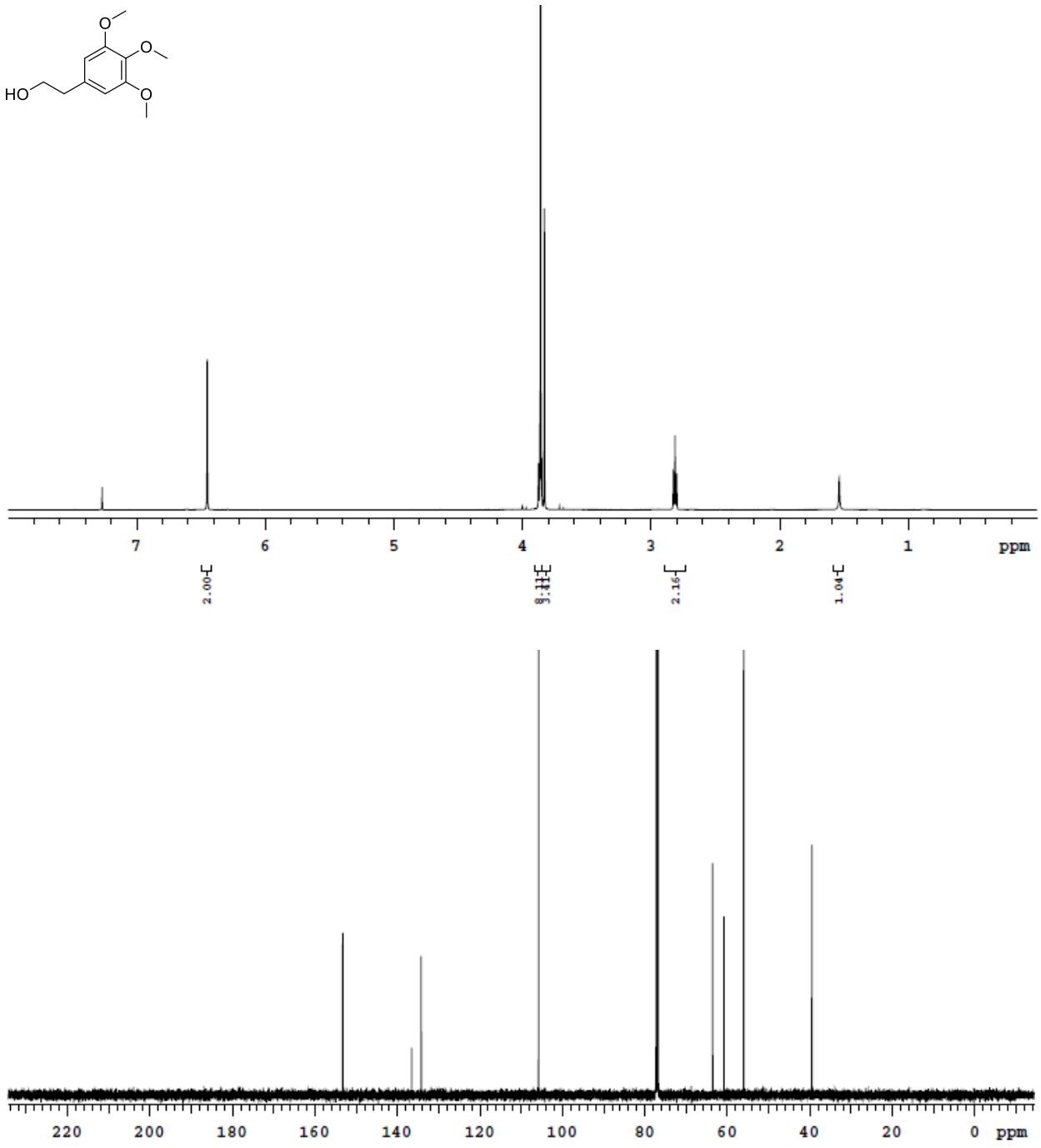


Figure 10.139: ^{1}H and ^{13}C Spectra of Compound VII.12

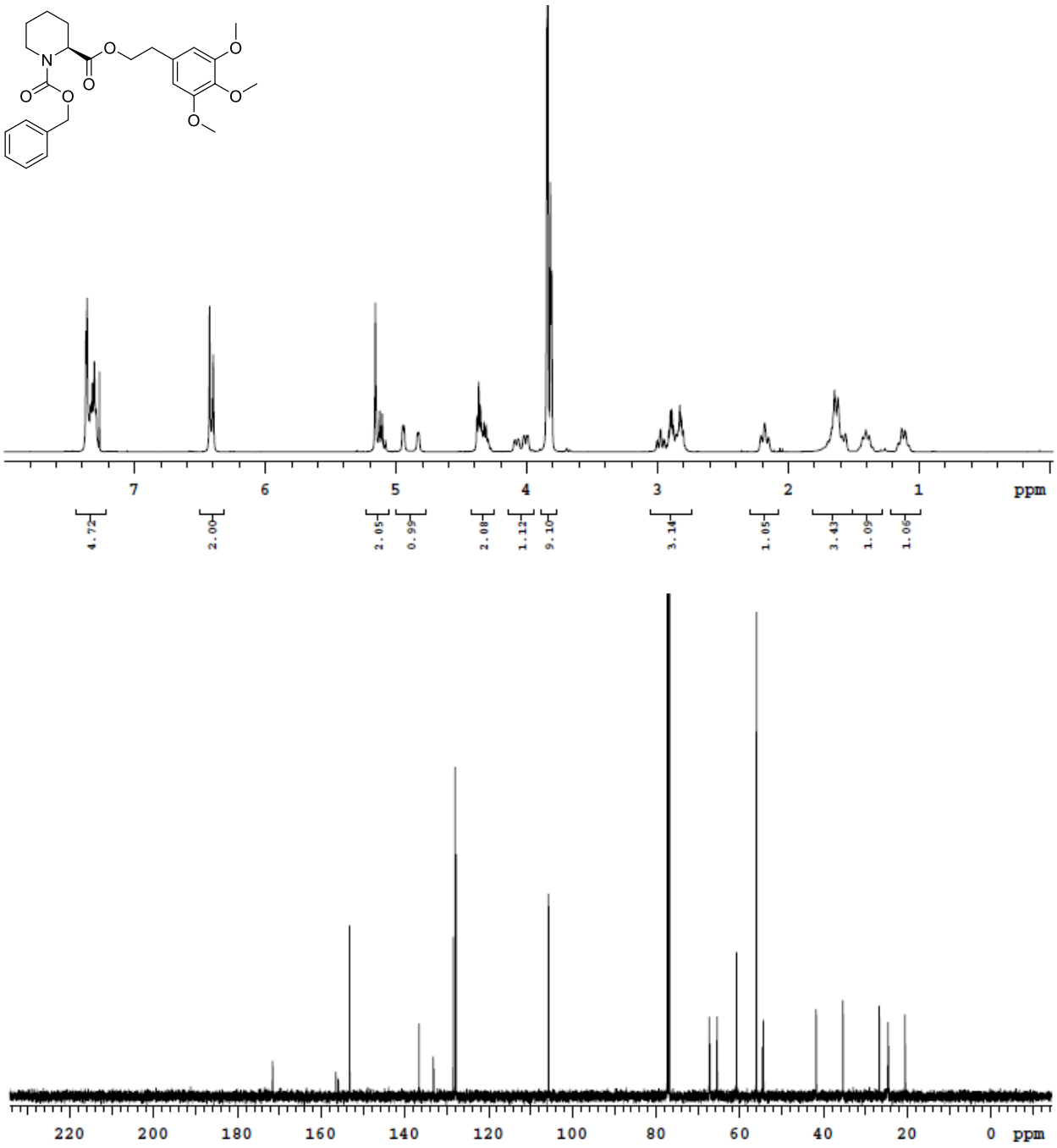


Figure 10.140: ^{1}H and ^{13}C Spectra of Compound VII.13

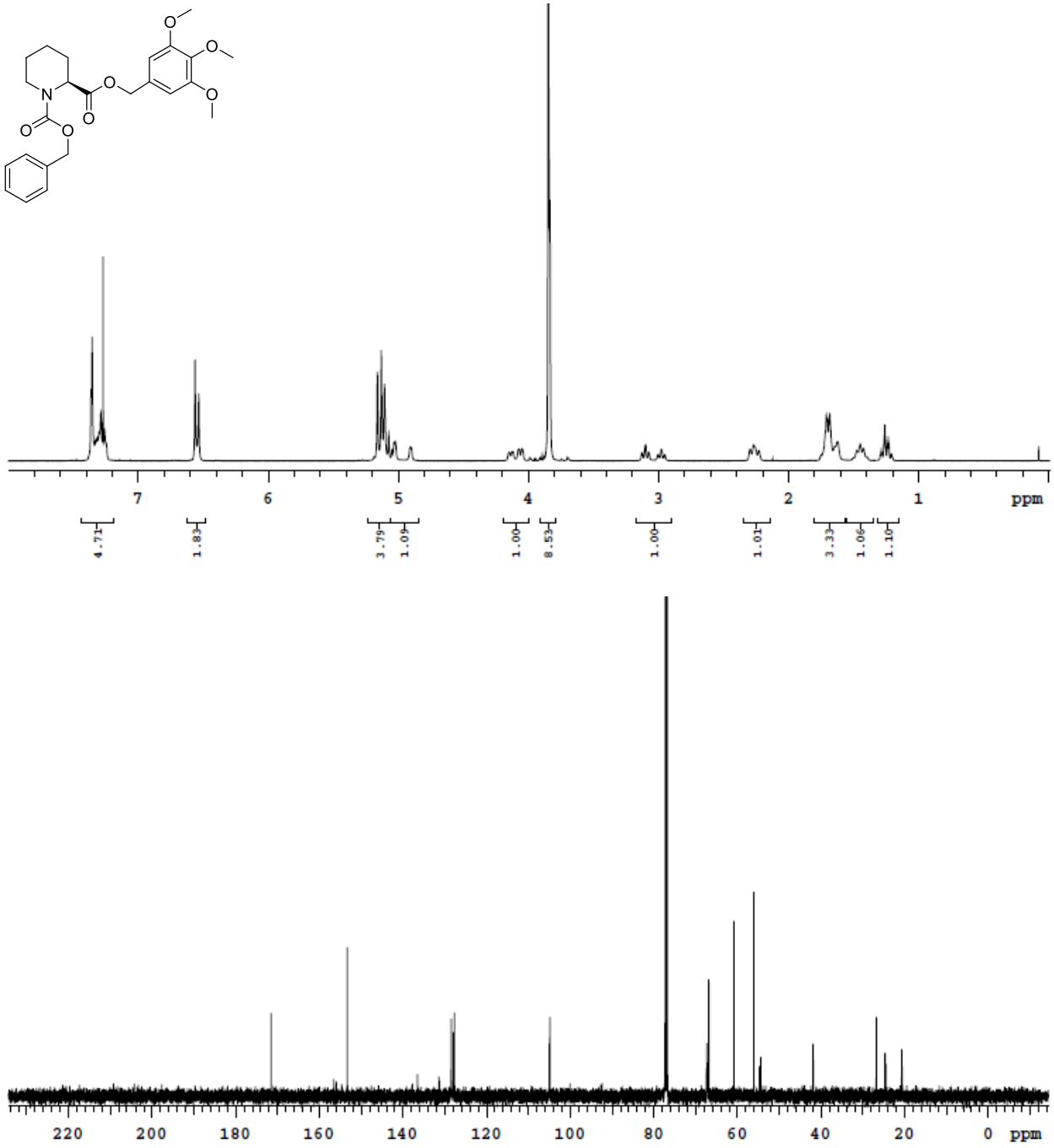


Figure 10.141: ^{1}H and ^{13}C Spectra of Compound VI.14a

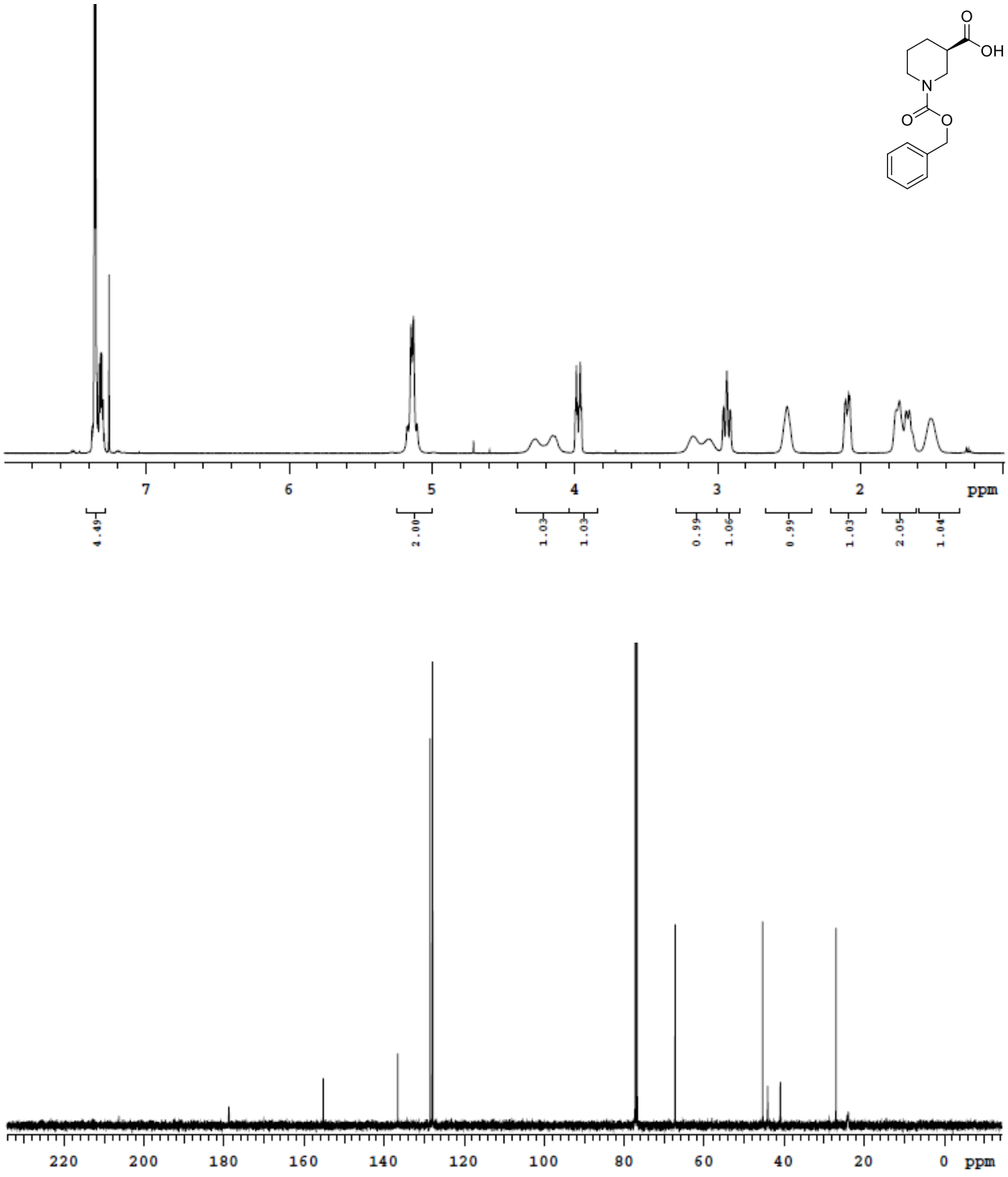


Figure 10.142: ^{1}H and ^{13}C Spectra of Compound VII.14

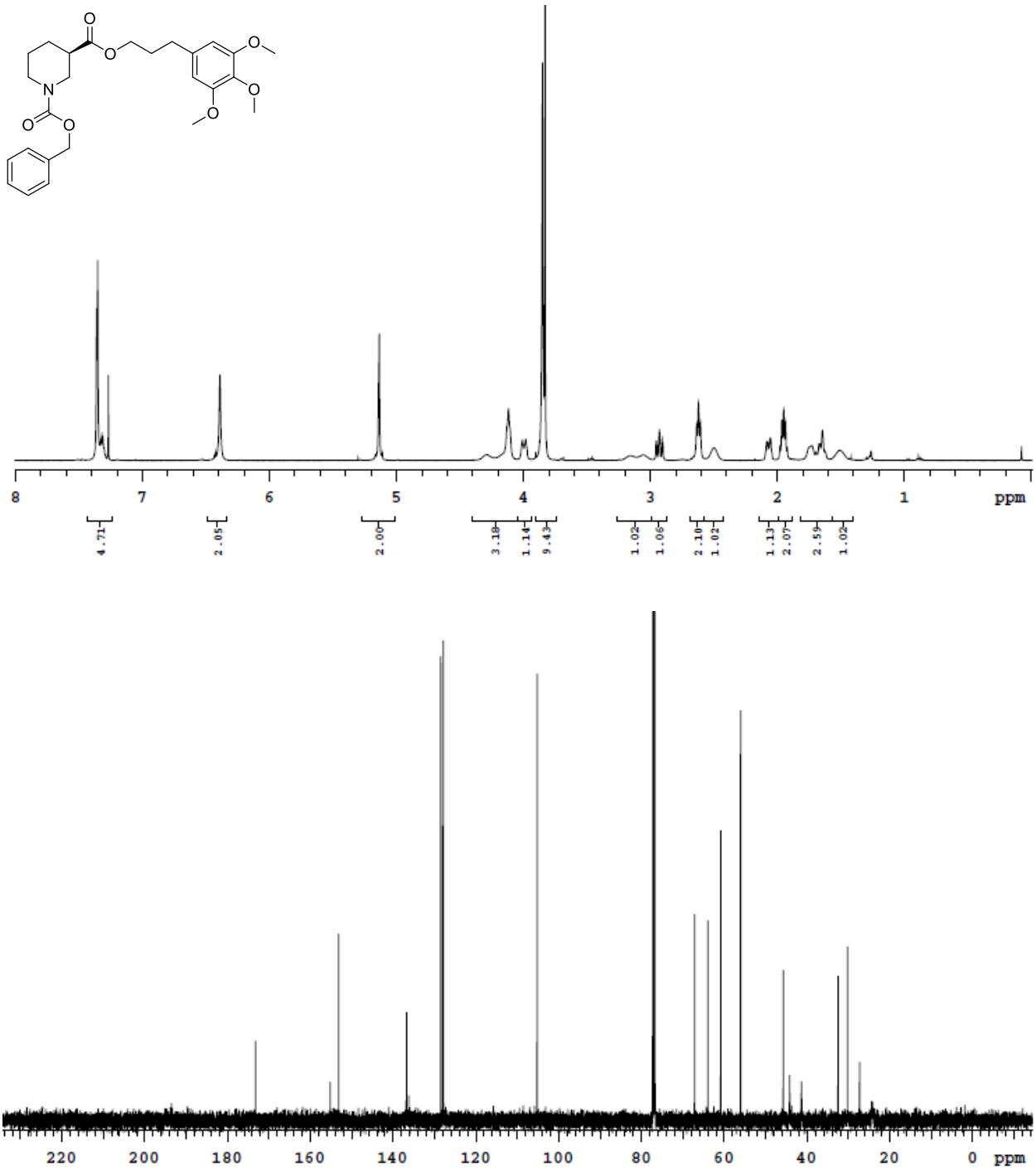


Figure 10.143: ^{1}H and ^{13}C Spectra of Compound VII.15

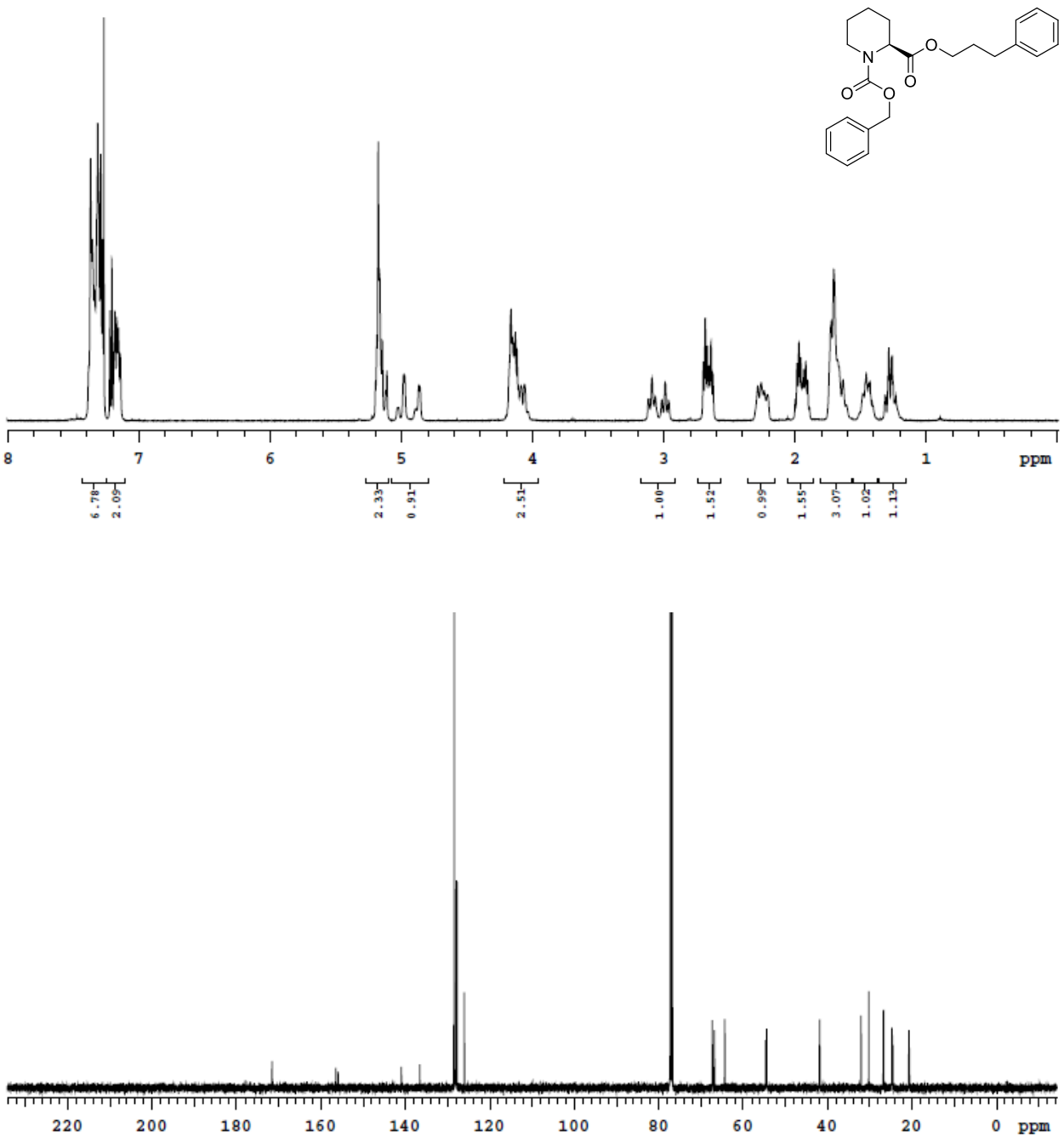


Figure 10.144: ^{1}H and ^{13}C Spectra of Compound VII.16a

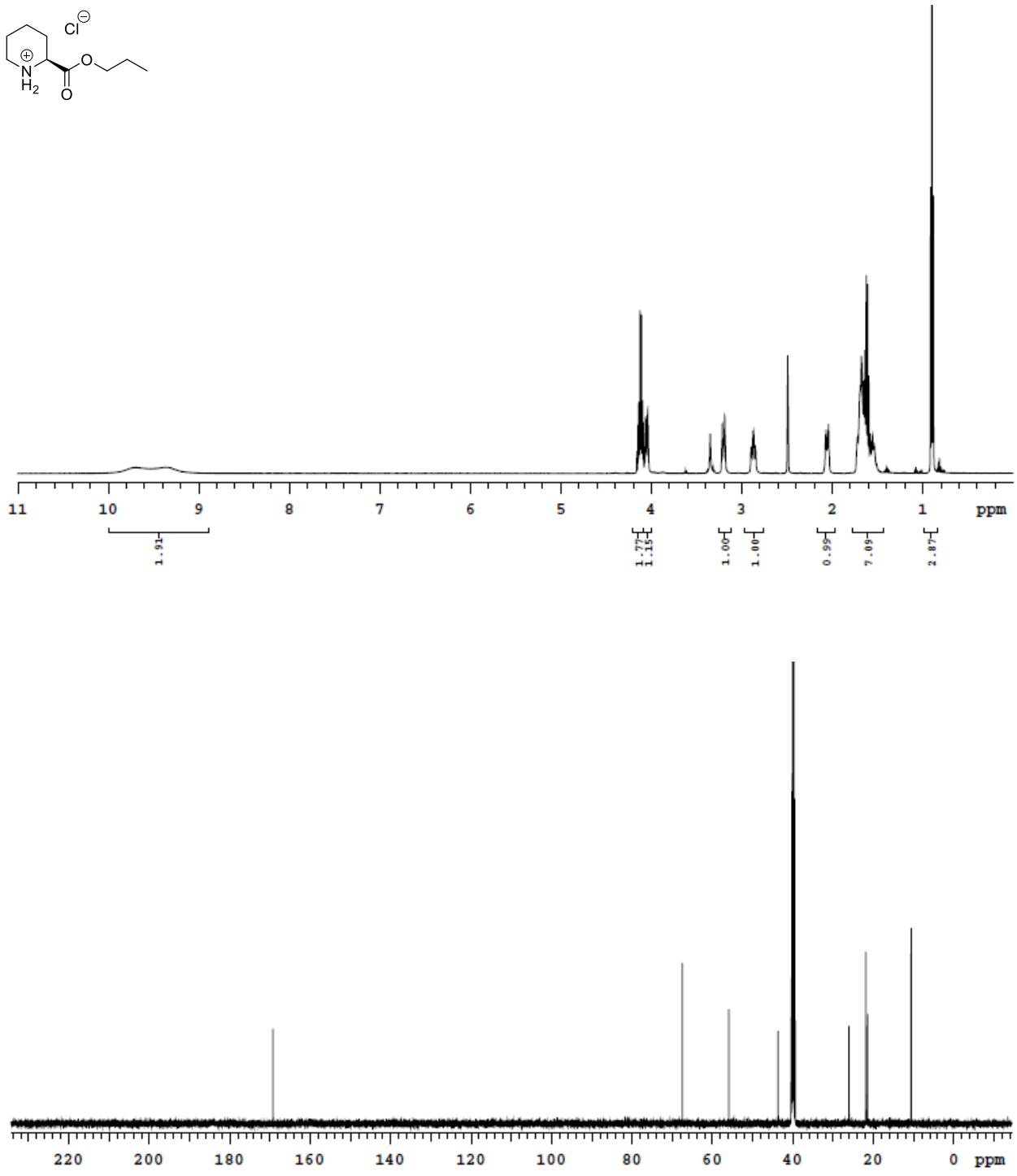


Figure 10.145: ^{1}H and ^{13}C Spectra of Compound VII.16

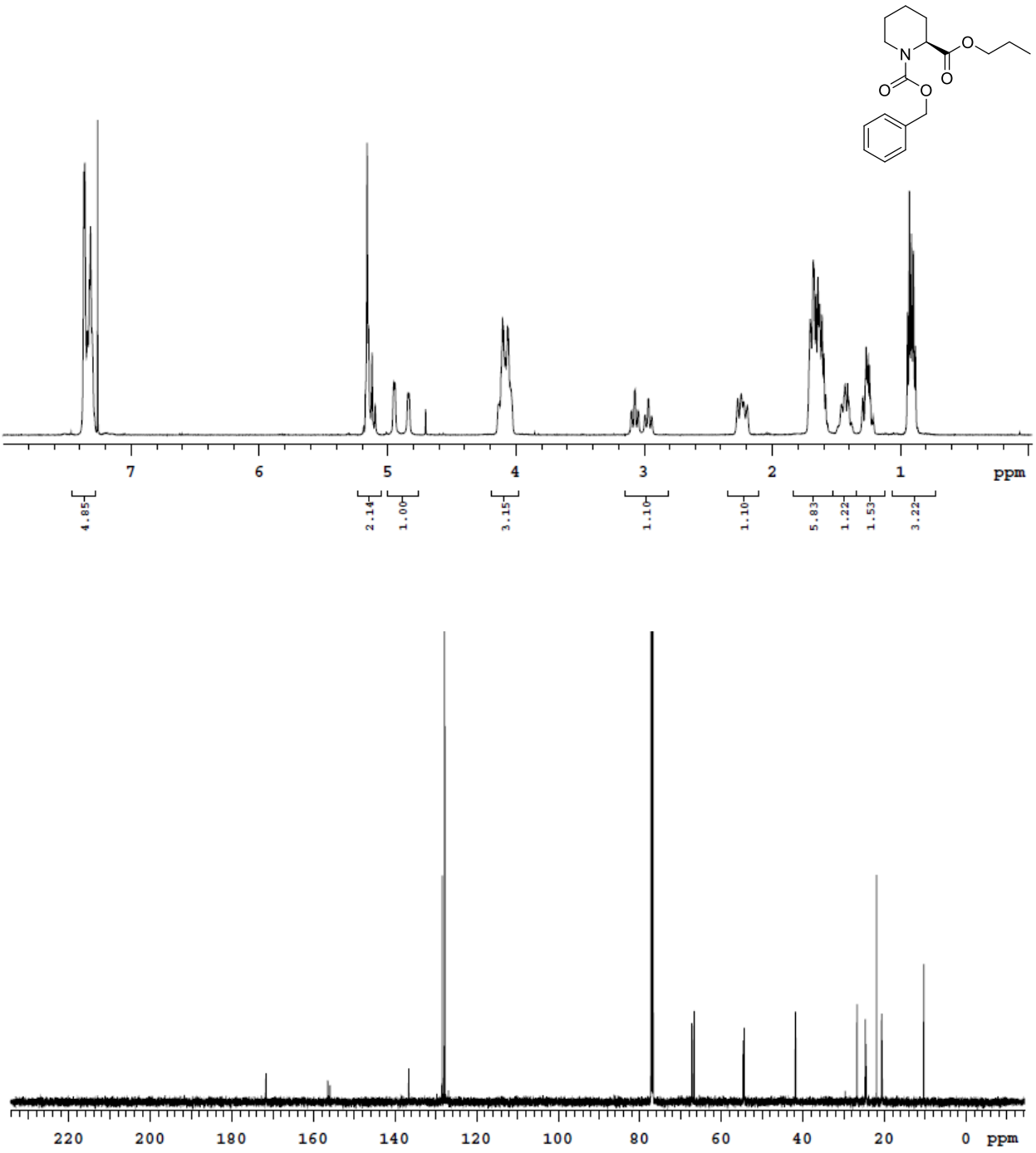


Figure 10.146: ^{1}H and ^{13}C Spectra of Compound VII.17

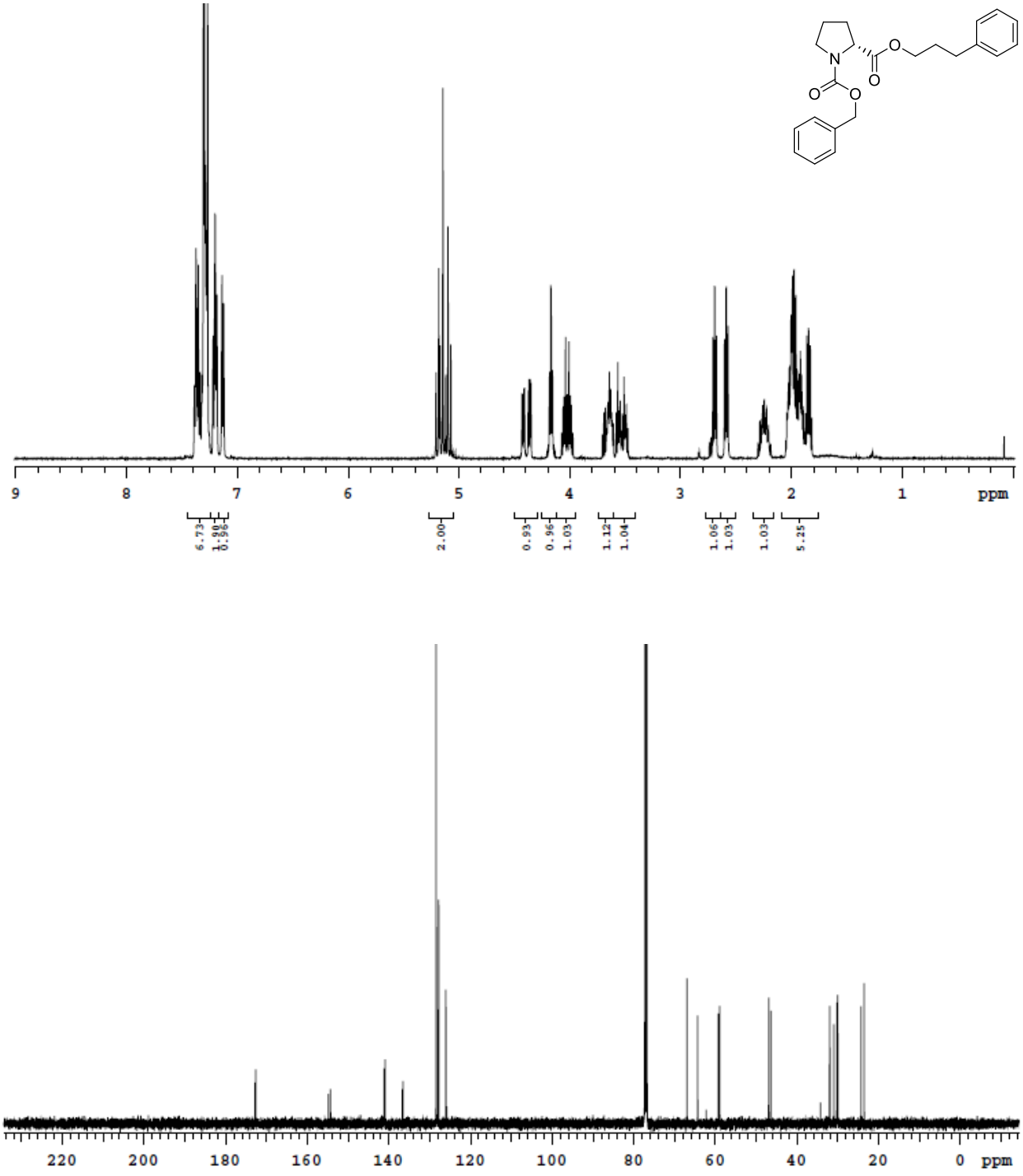


Figure 10.147: ^{1}H and ^{13}C Spectra of Compound VII.18

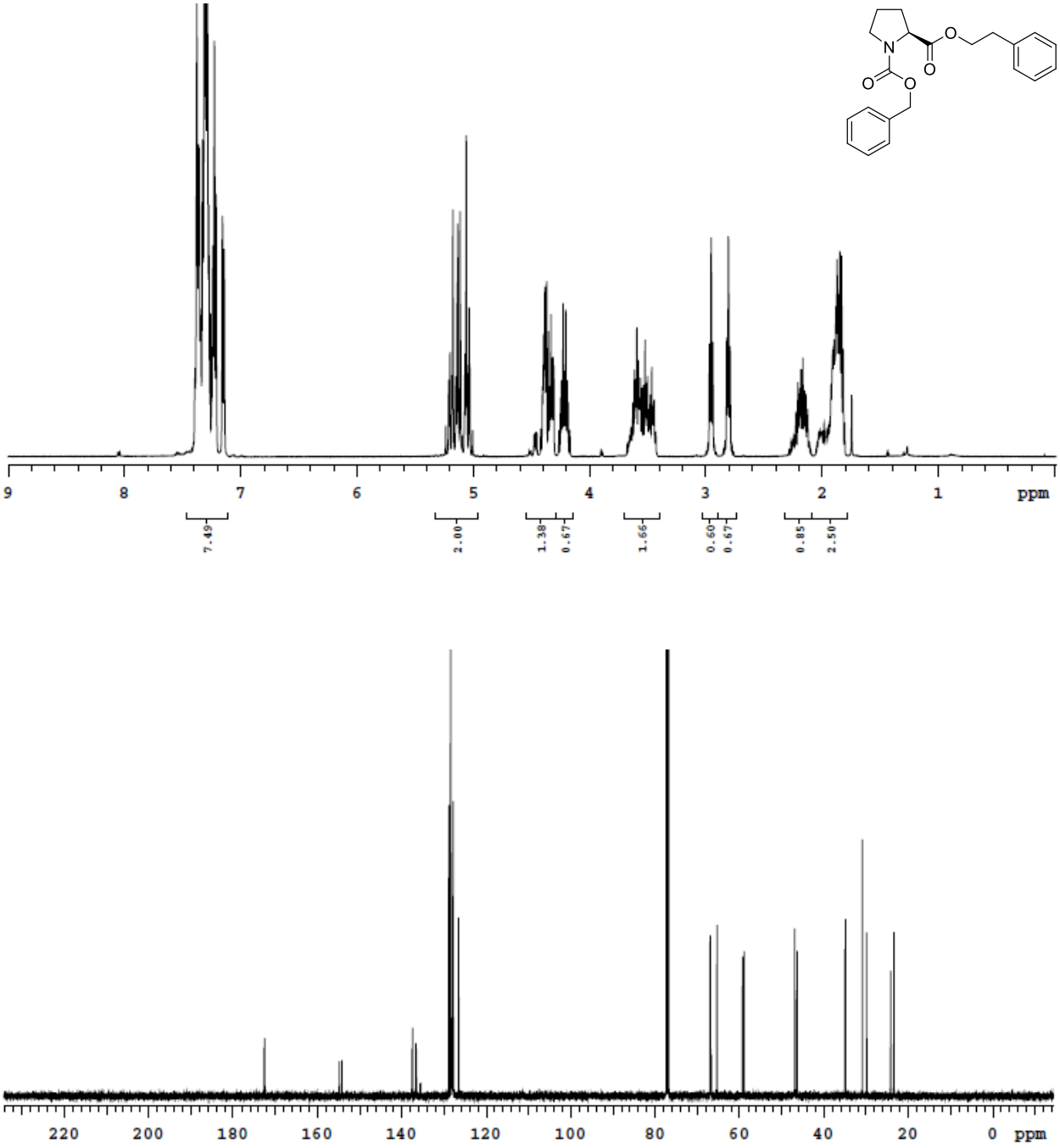


Figure 10.148: gCOSY Spectra of Compound VII.18

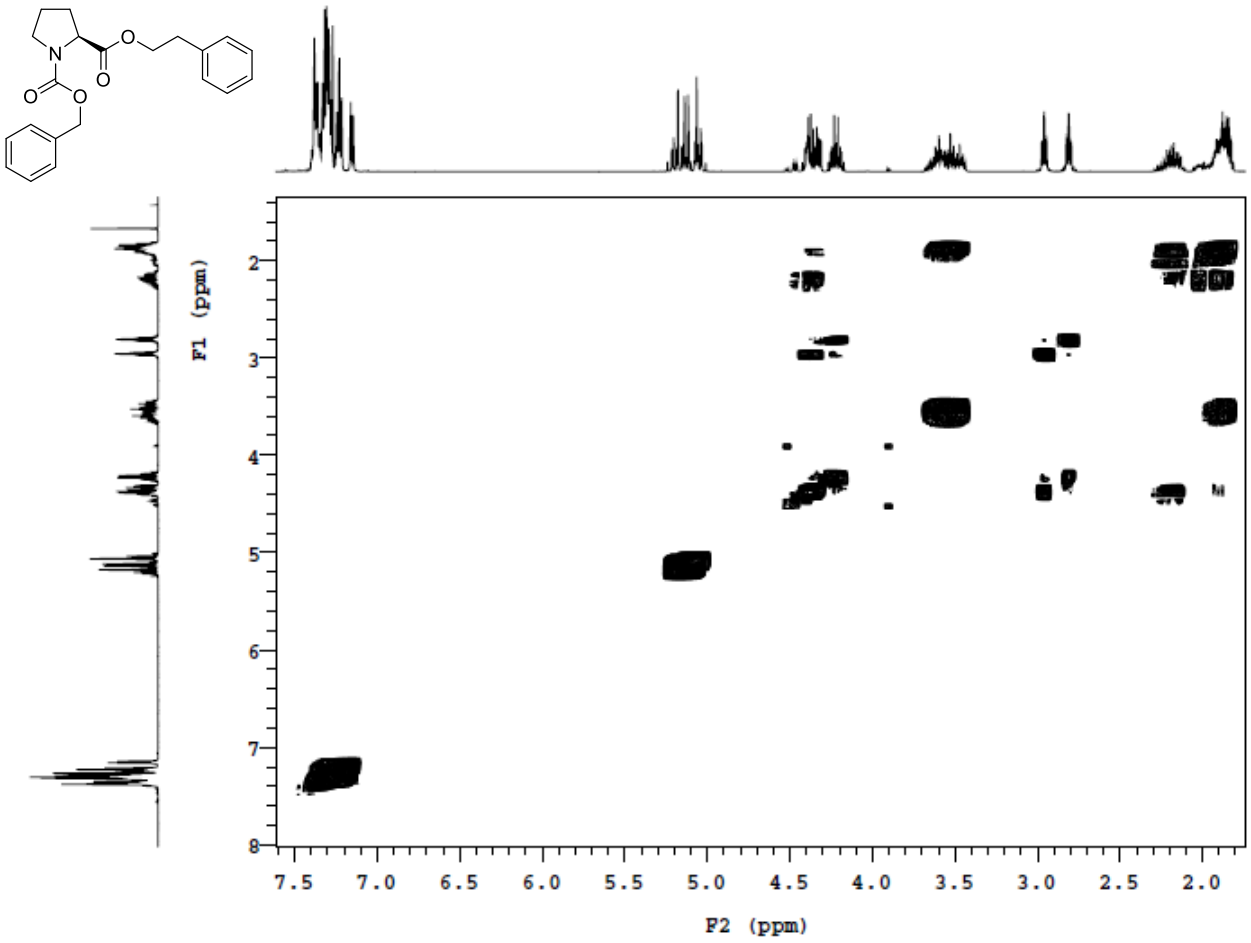


Figure 10.149: gHMQC Spectra of Compound VII.18

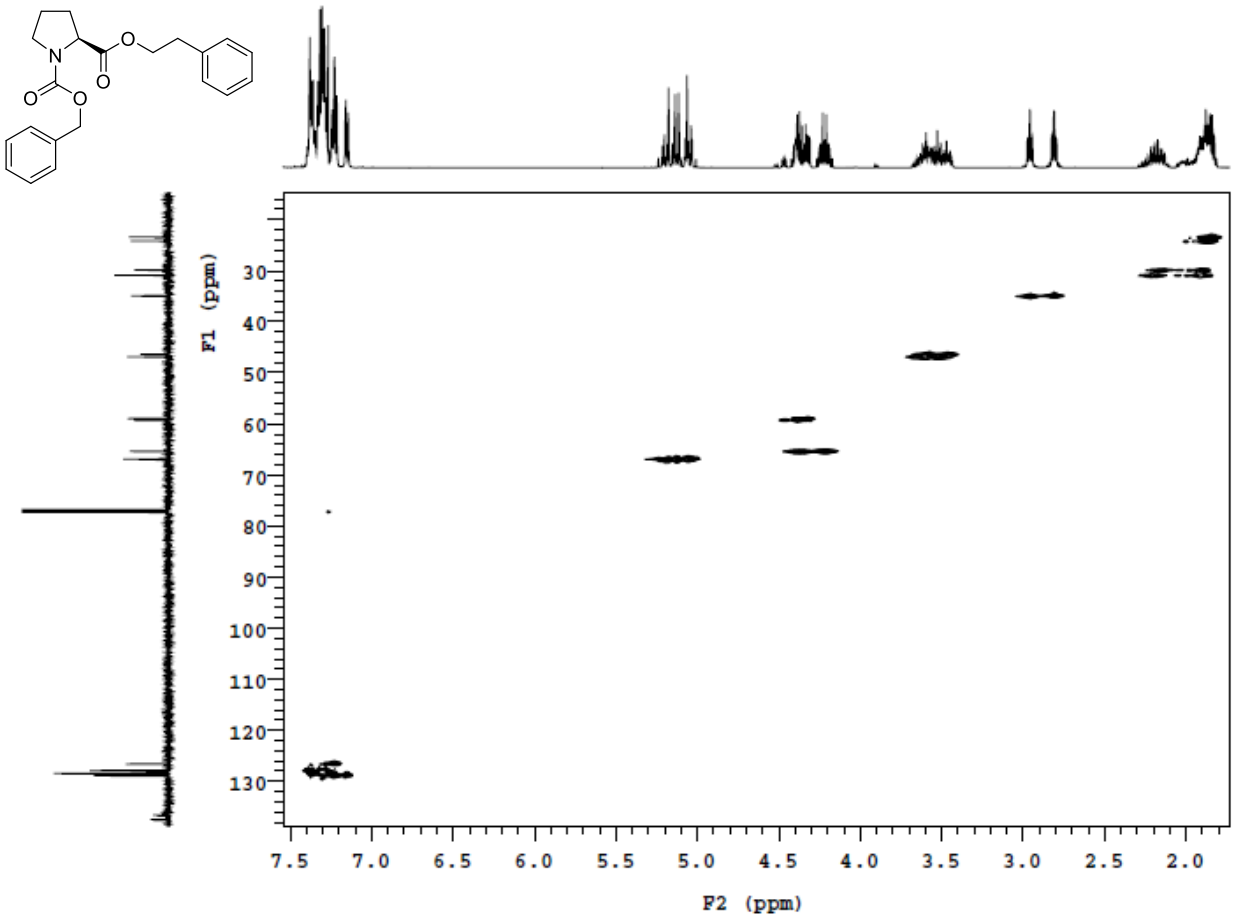


Figure 10.150: ^{1}H and ^{13}C Spectra of Compound VII.19

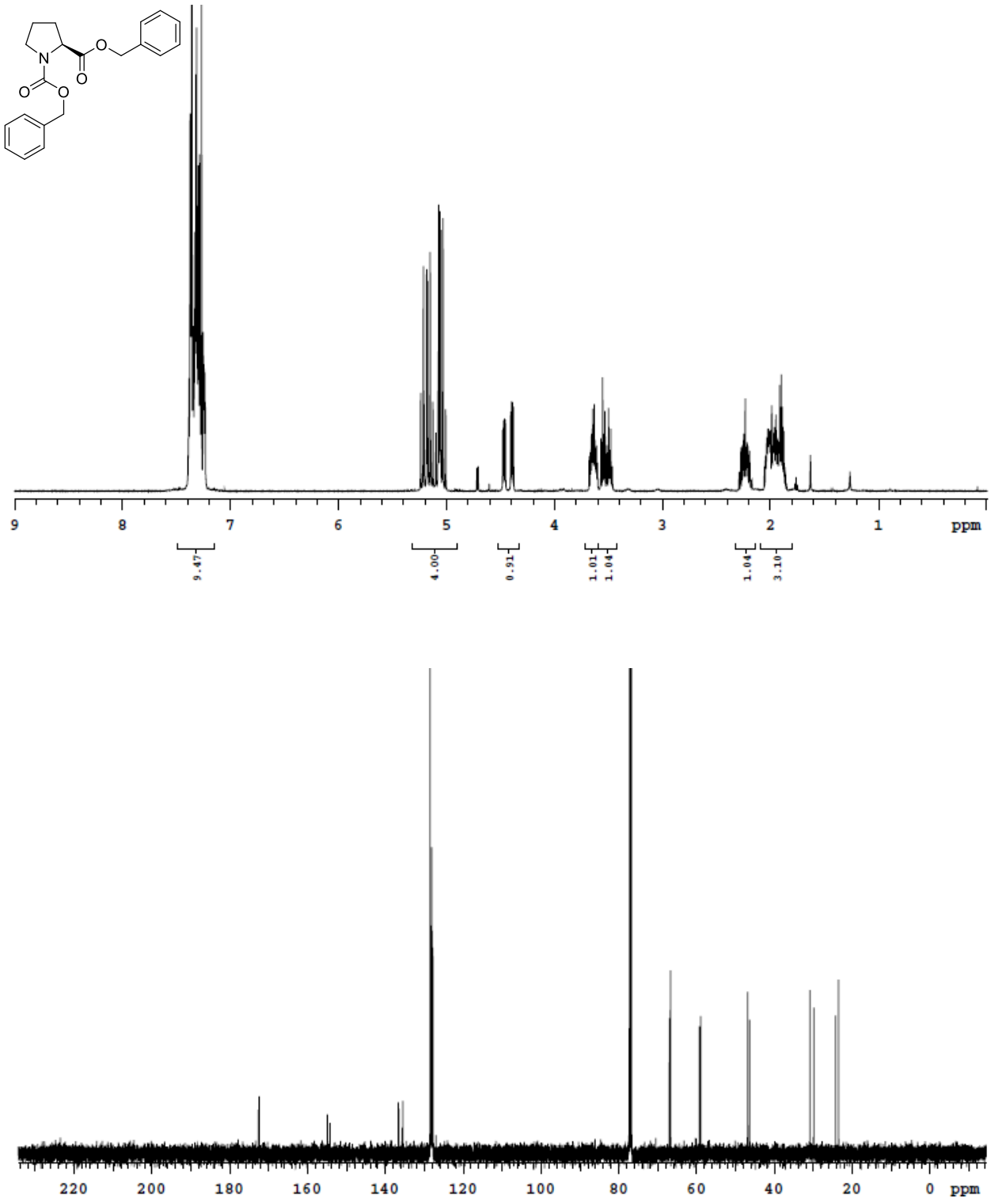


Figure 10.151: ^{1}H and ^{13}C Spectra of Compound VII.20

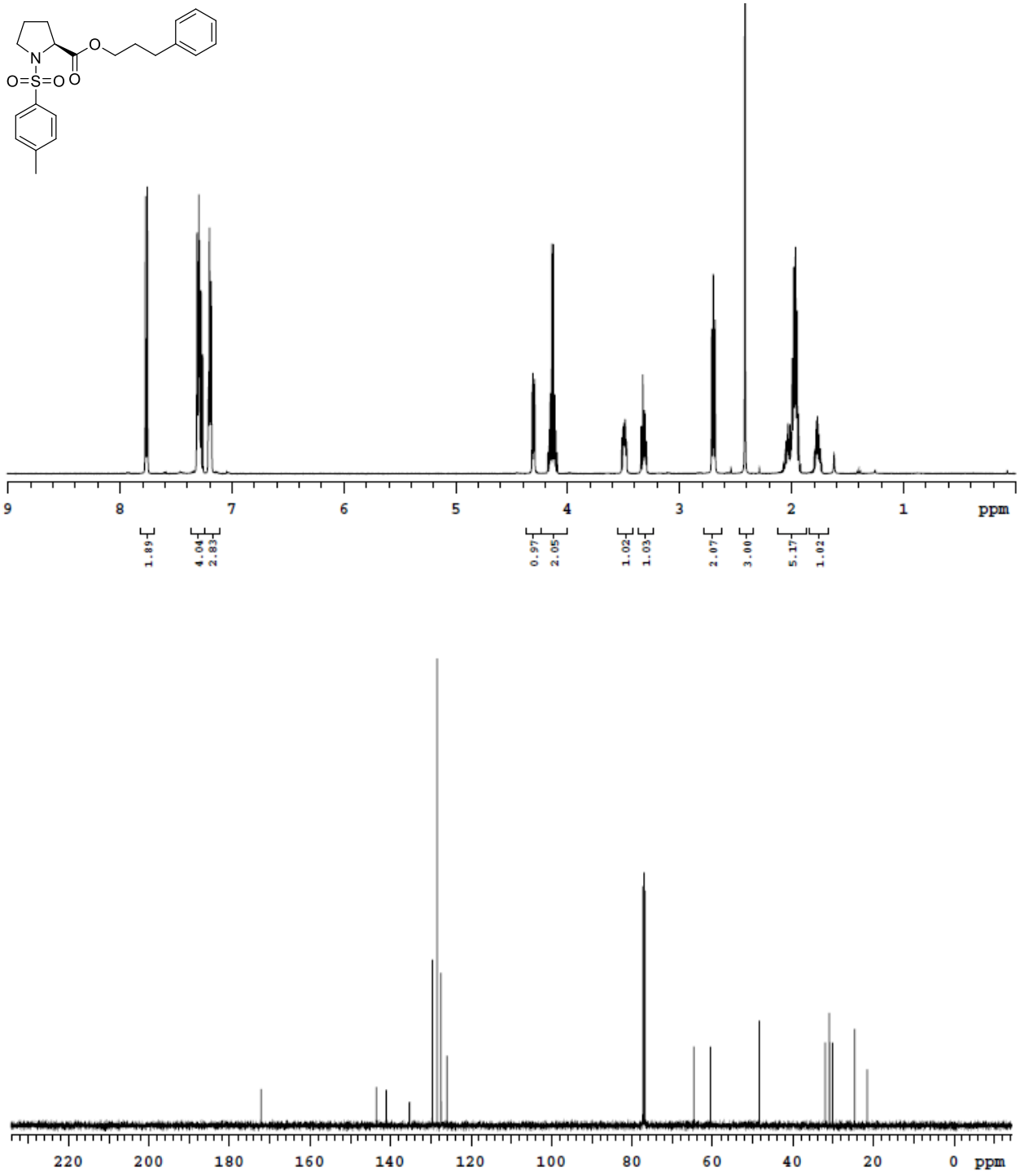


Figure 10.152: ^{1}H and ^{13}C Spectra of Compound VII.21

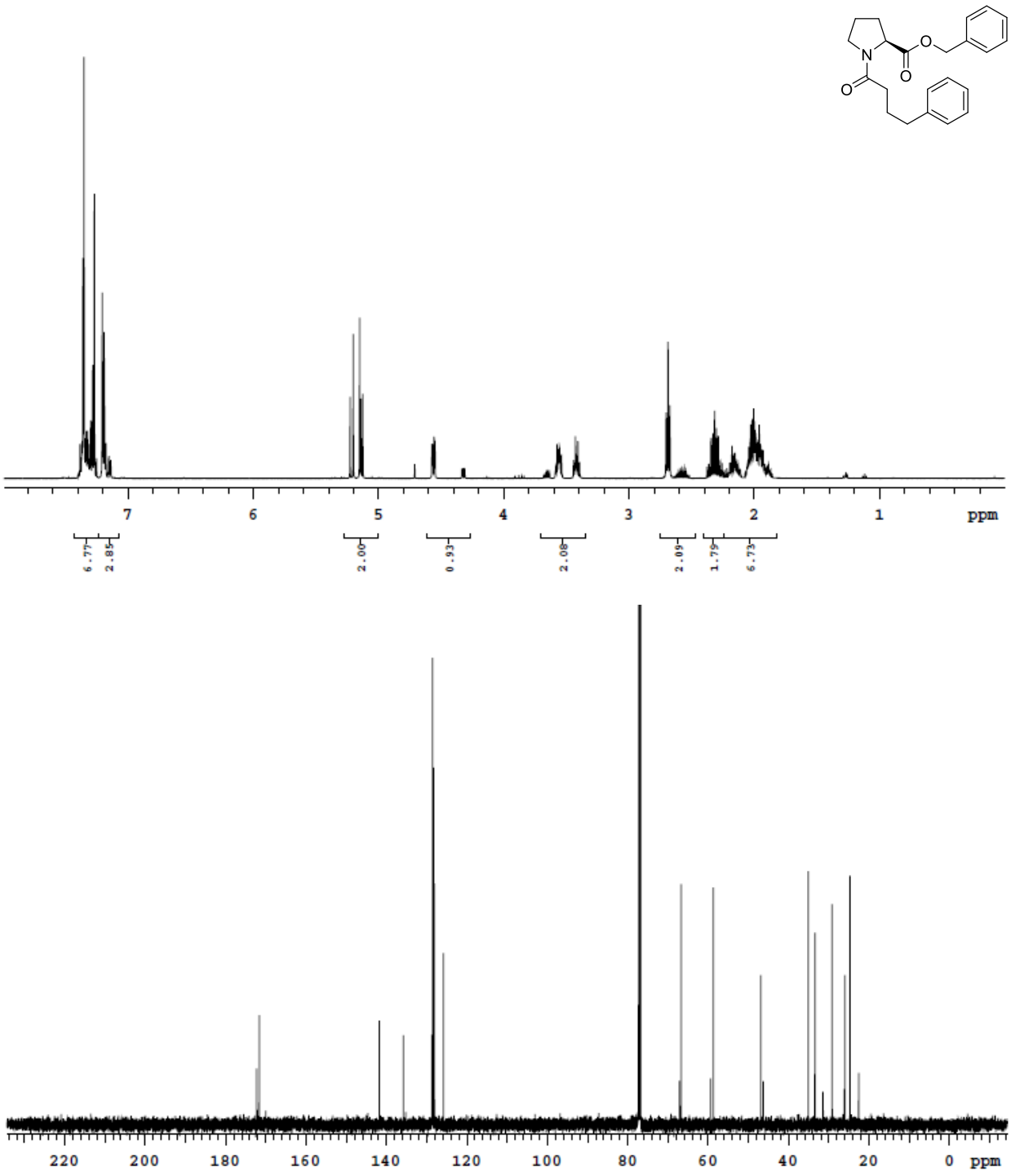


Figure 10.153: ^{1}H and ^{13}C Spectra of Compound VII.22a

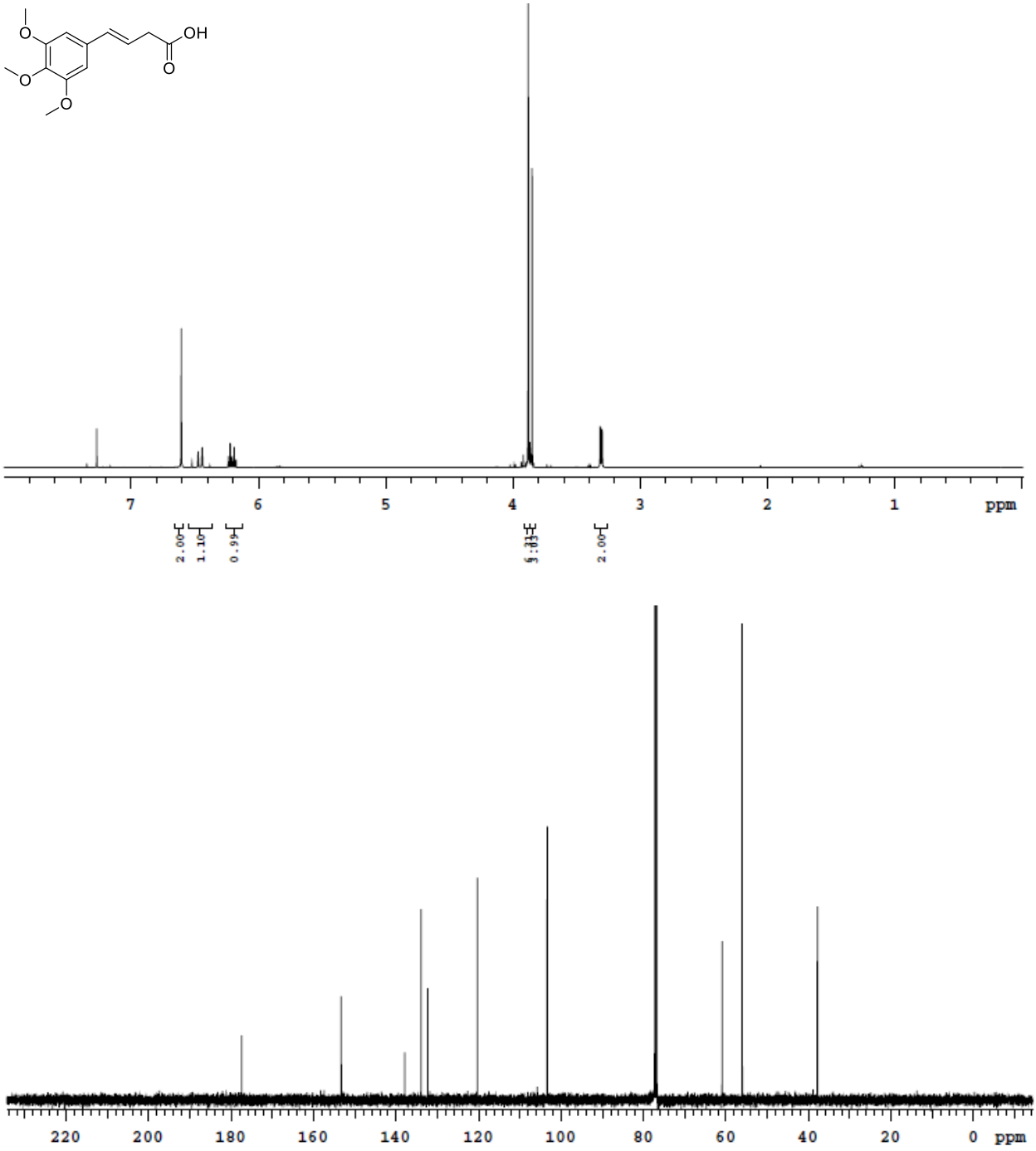


Figure 10.154: ^{1}H and ^{13}C Spectra of Compound VII.22b

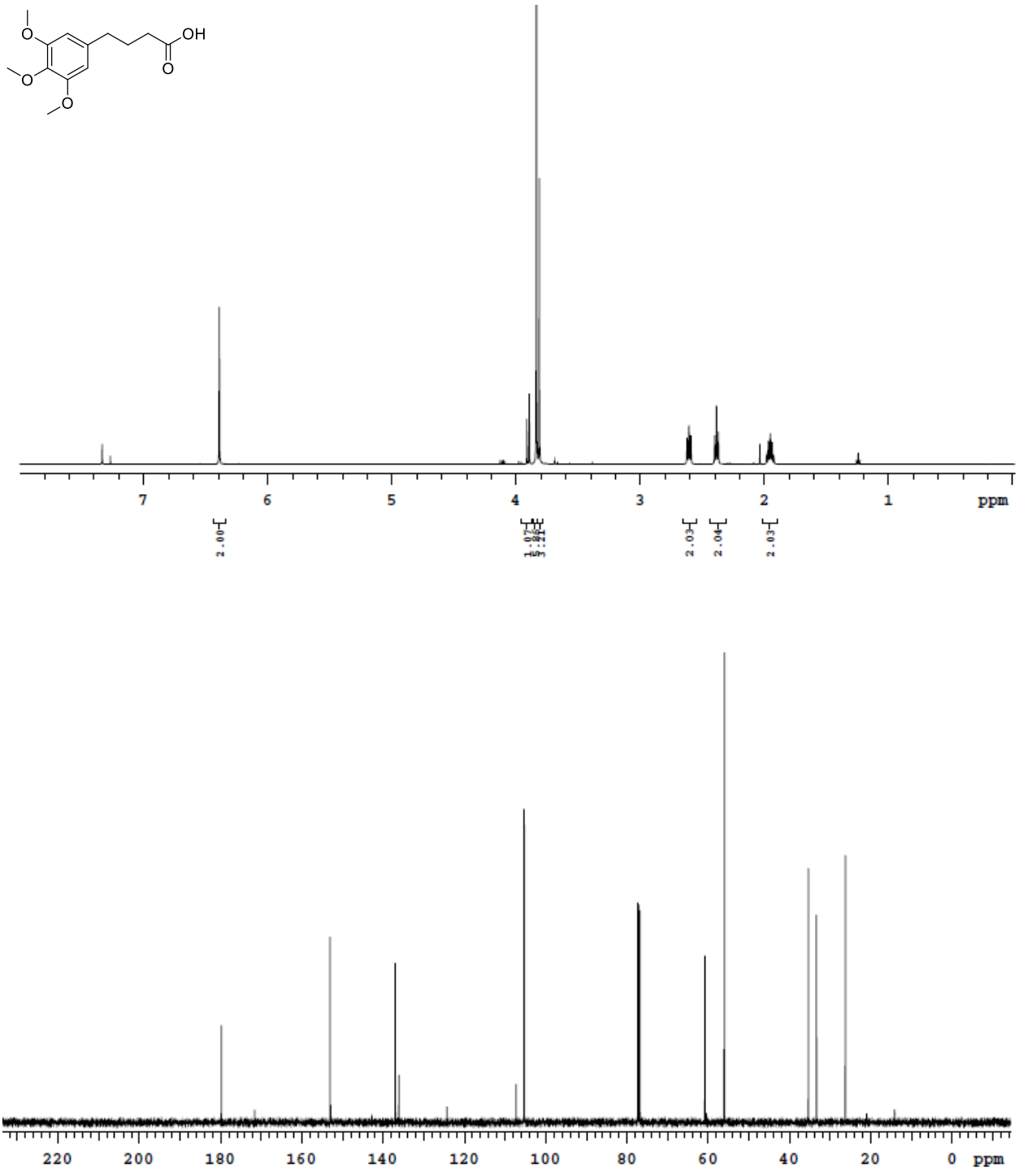


Figure 10.155: ^{1}H and ^{13}C Spectra of Compound VII.22

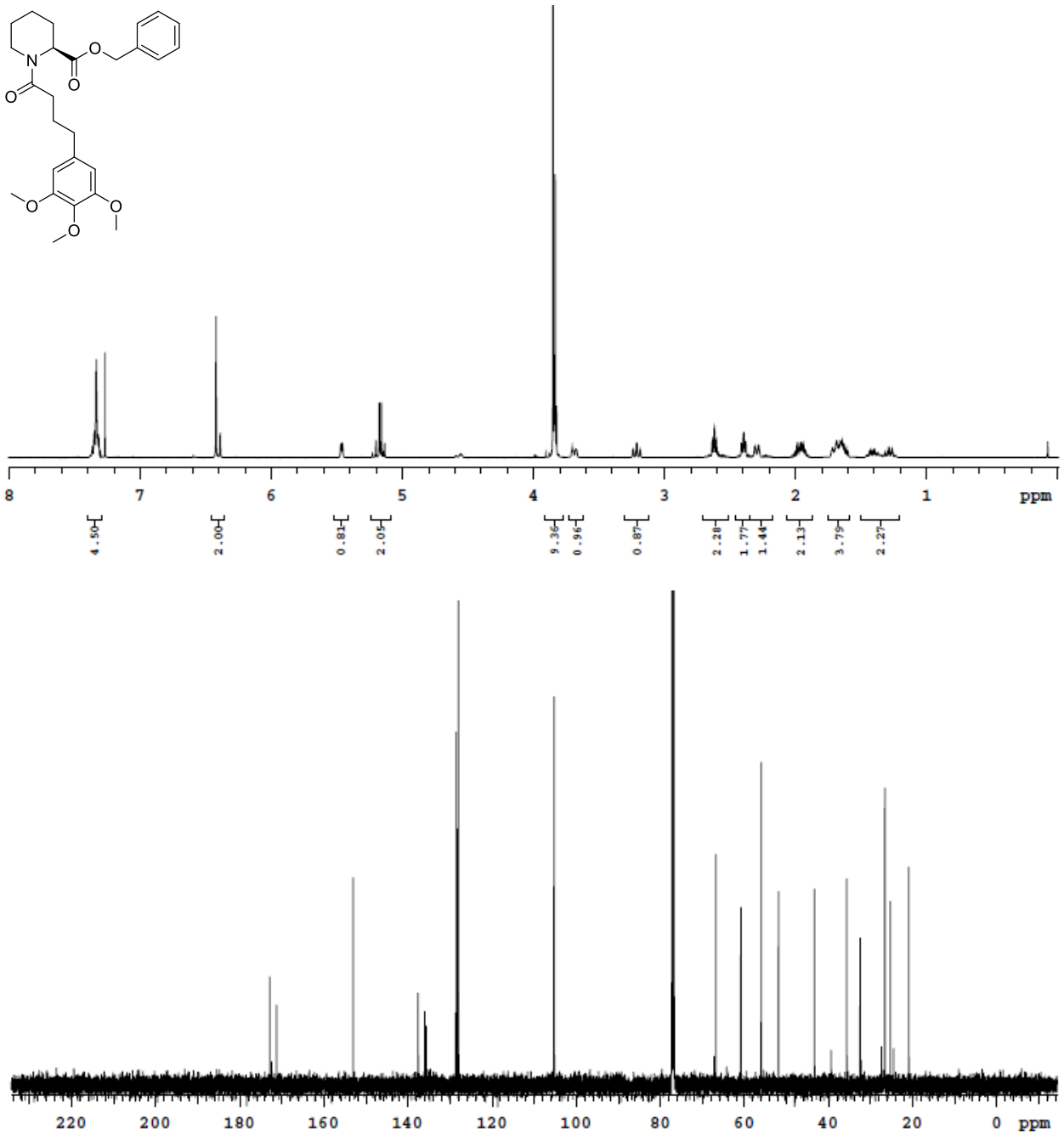


Figure 10.156: gCOSY Spectra of Compound VII.22

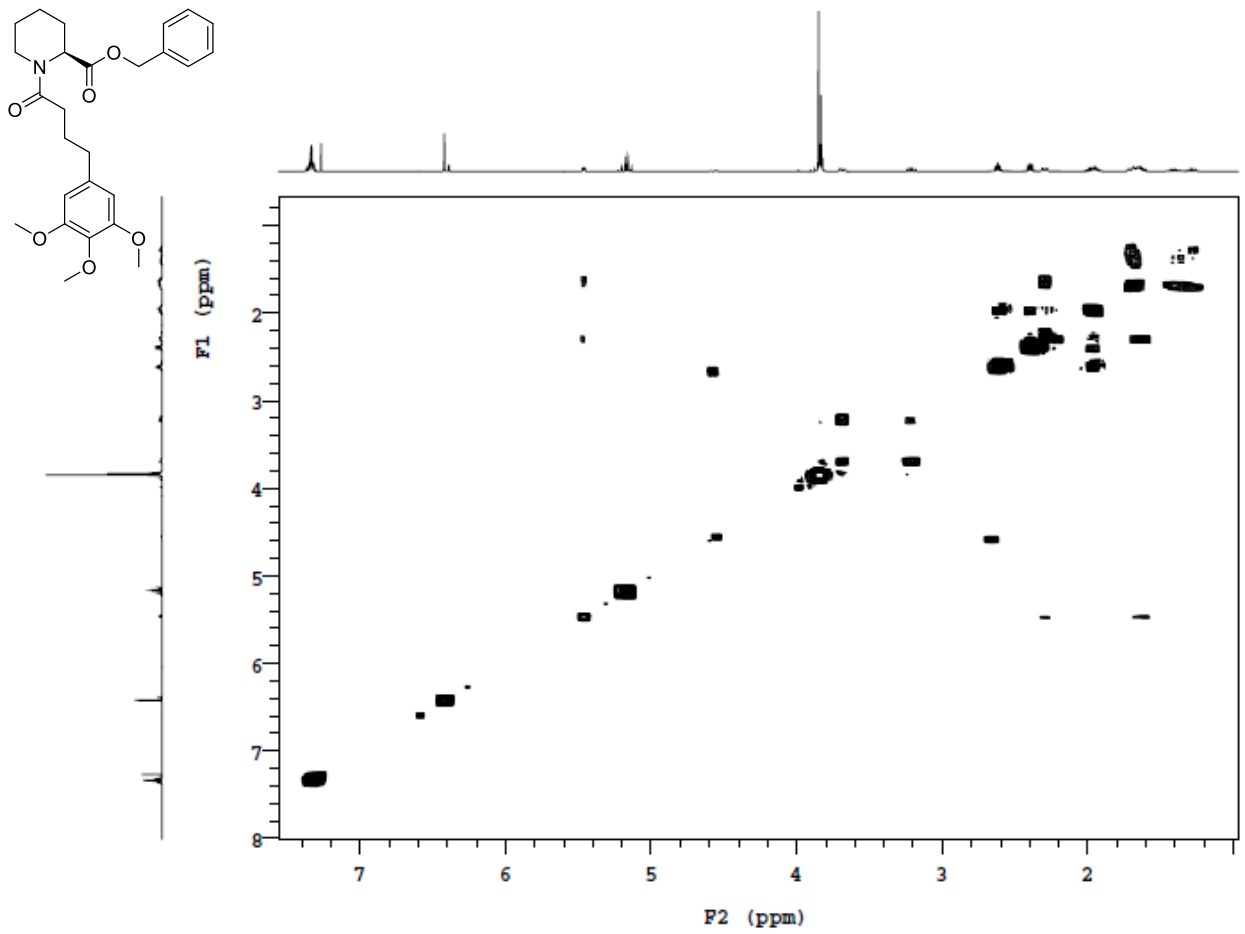


Figure 10.157: gHMQC Spectra of Compound VII.22

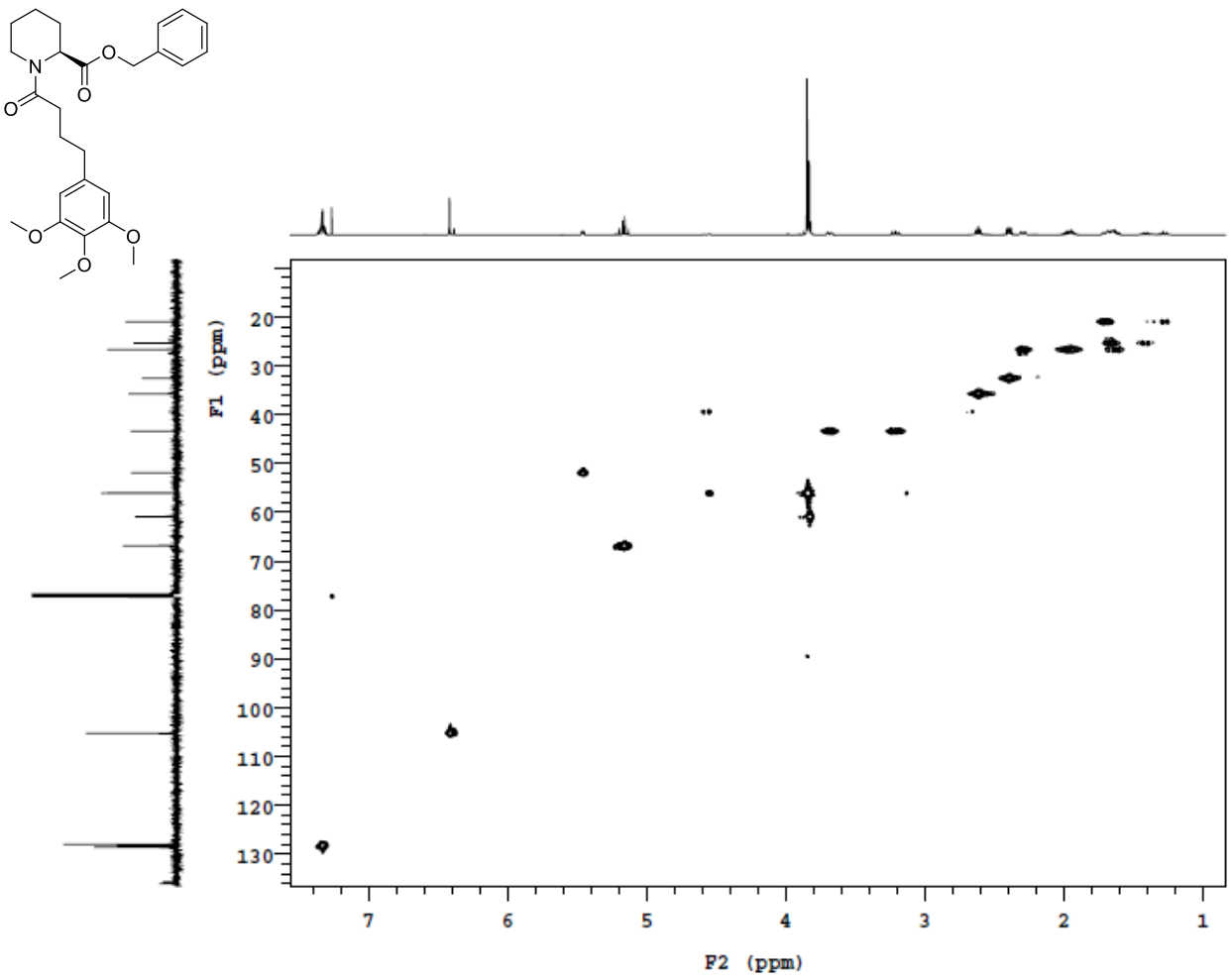


Figure 10.158: ^{1}H and ^{13}C Spectra of Compound VII.23

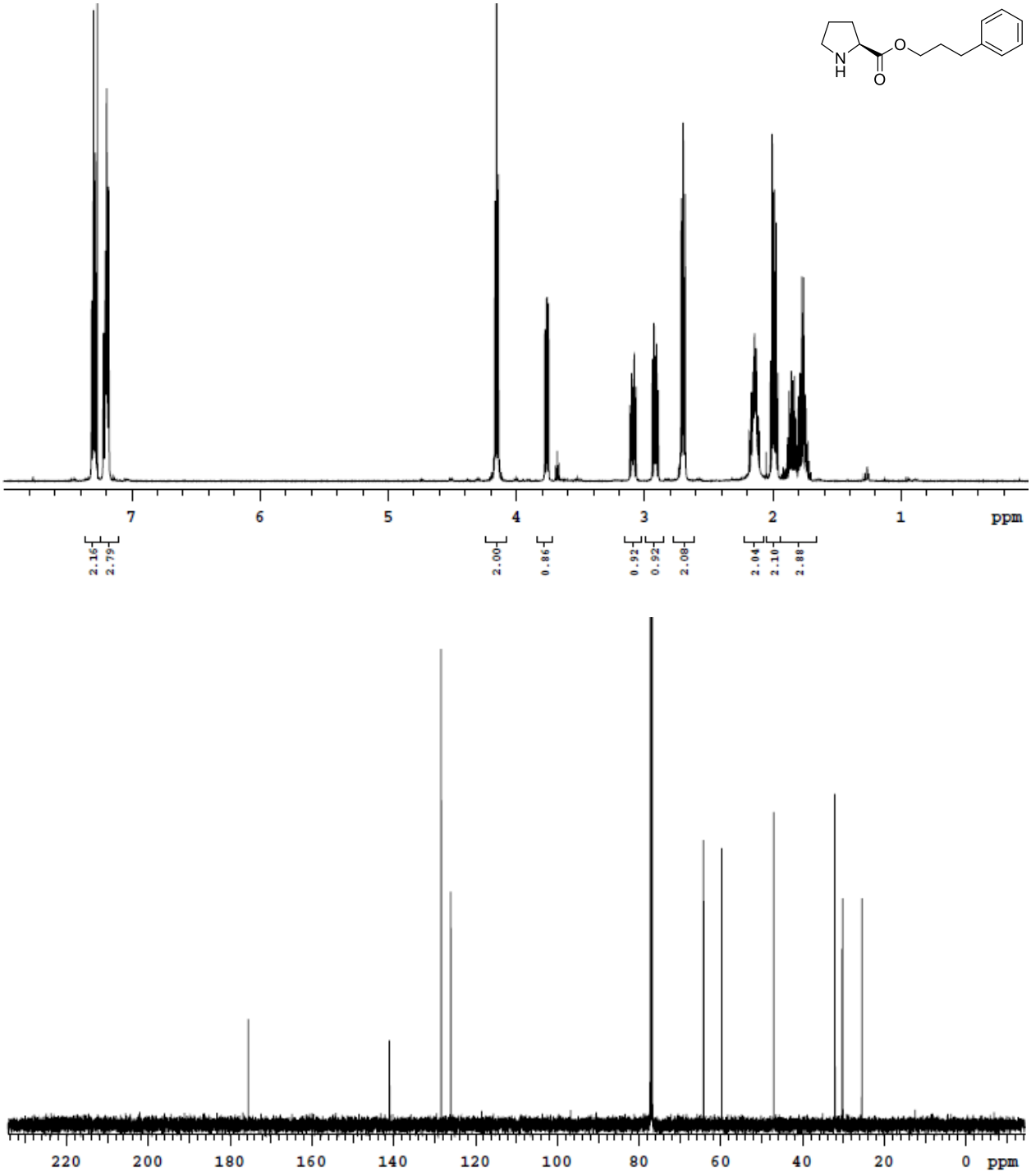
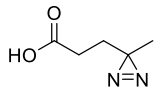
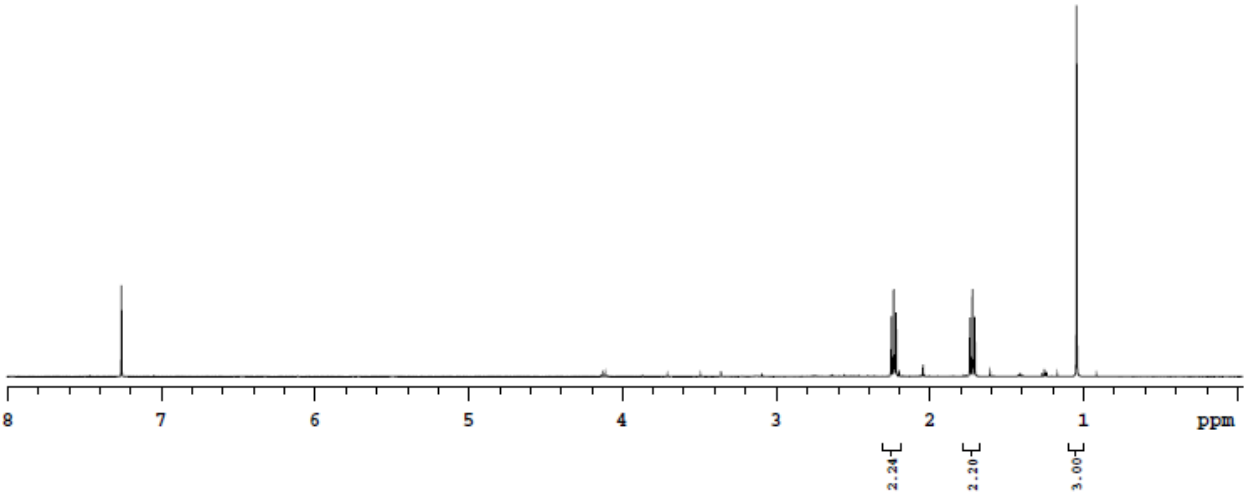


Figure 10.159: ^{1}H and ^{13}C Spectra of Compound VII.24a





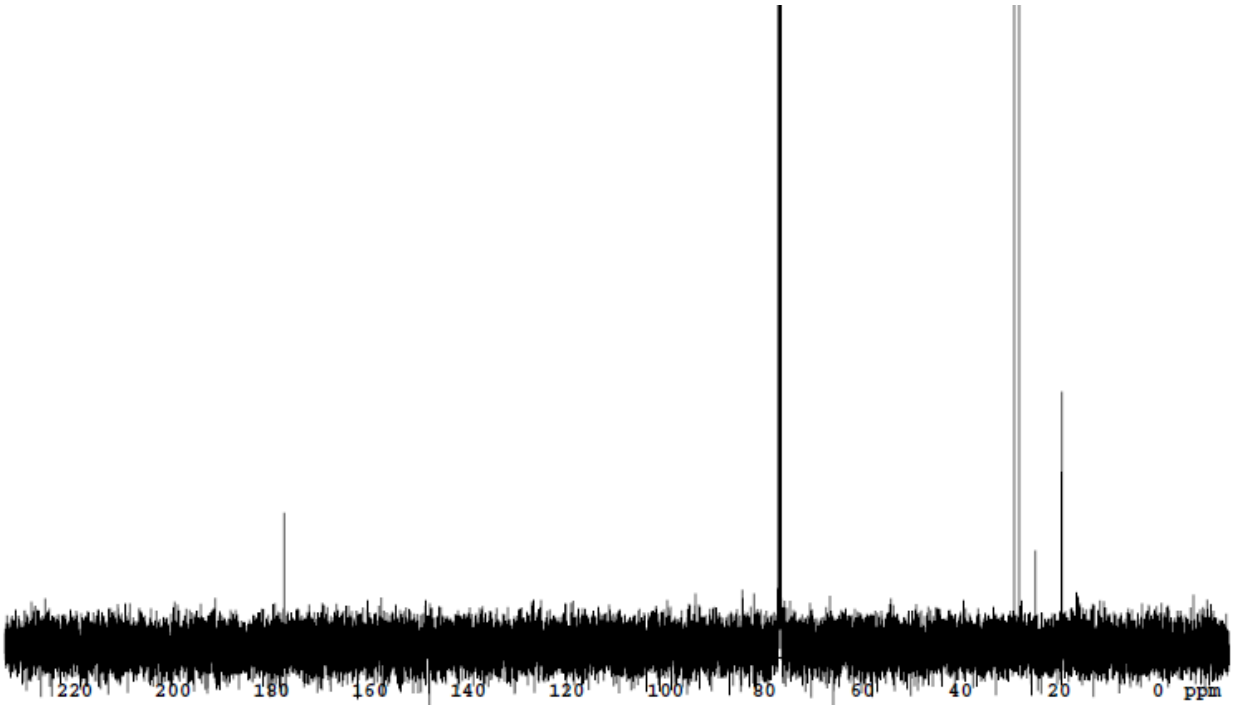


Figure 10.160: ^{1}H and ^{13}C Spectra of Compound VII.24

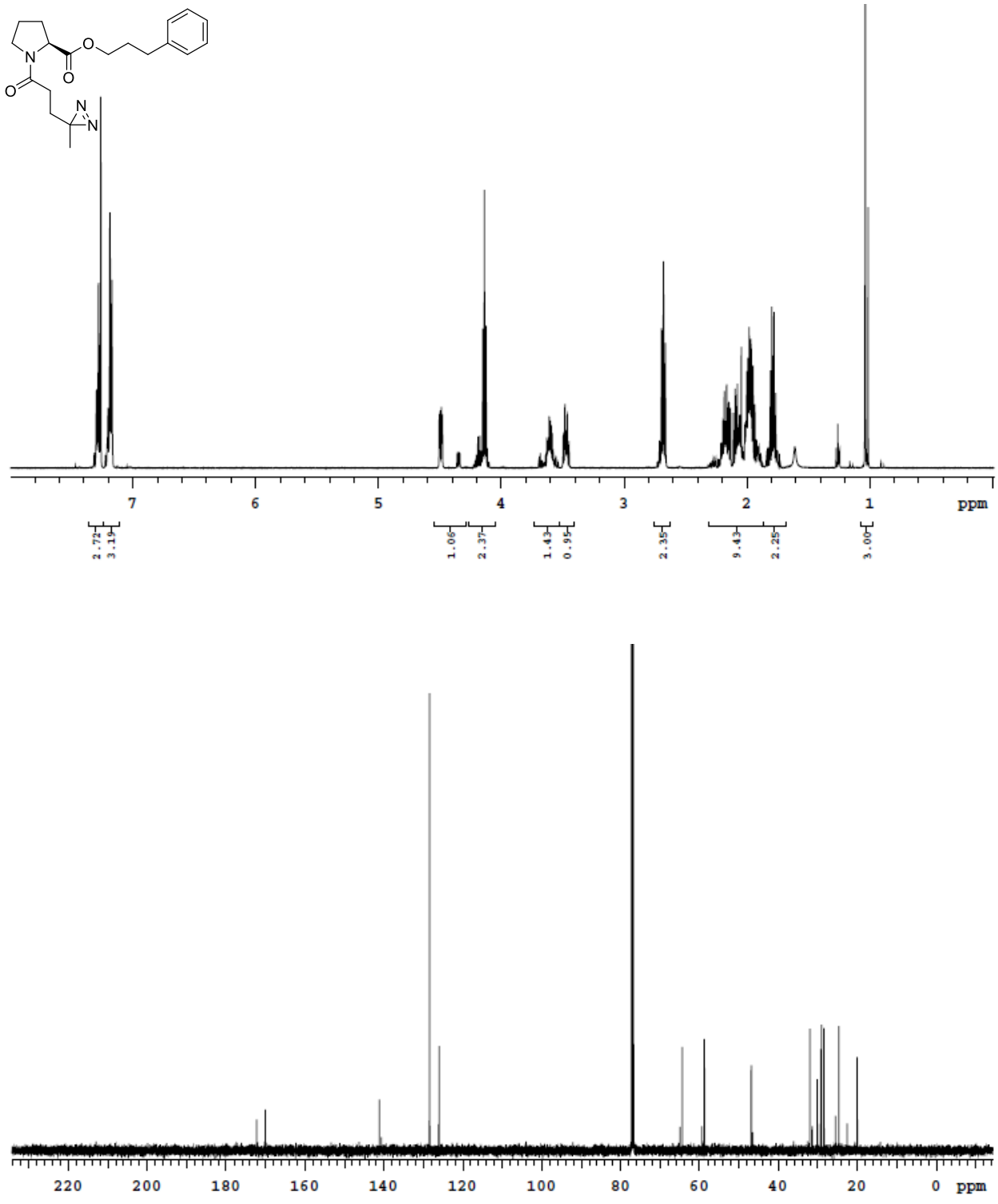


Figure 10.161: ^{1}H and ^{13}C Spectra of Compound VII.25

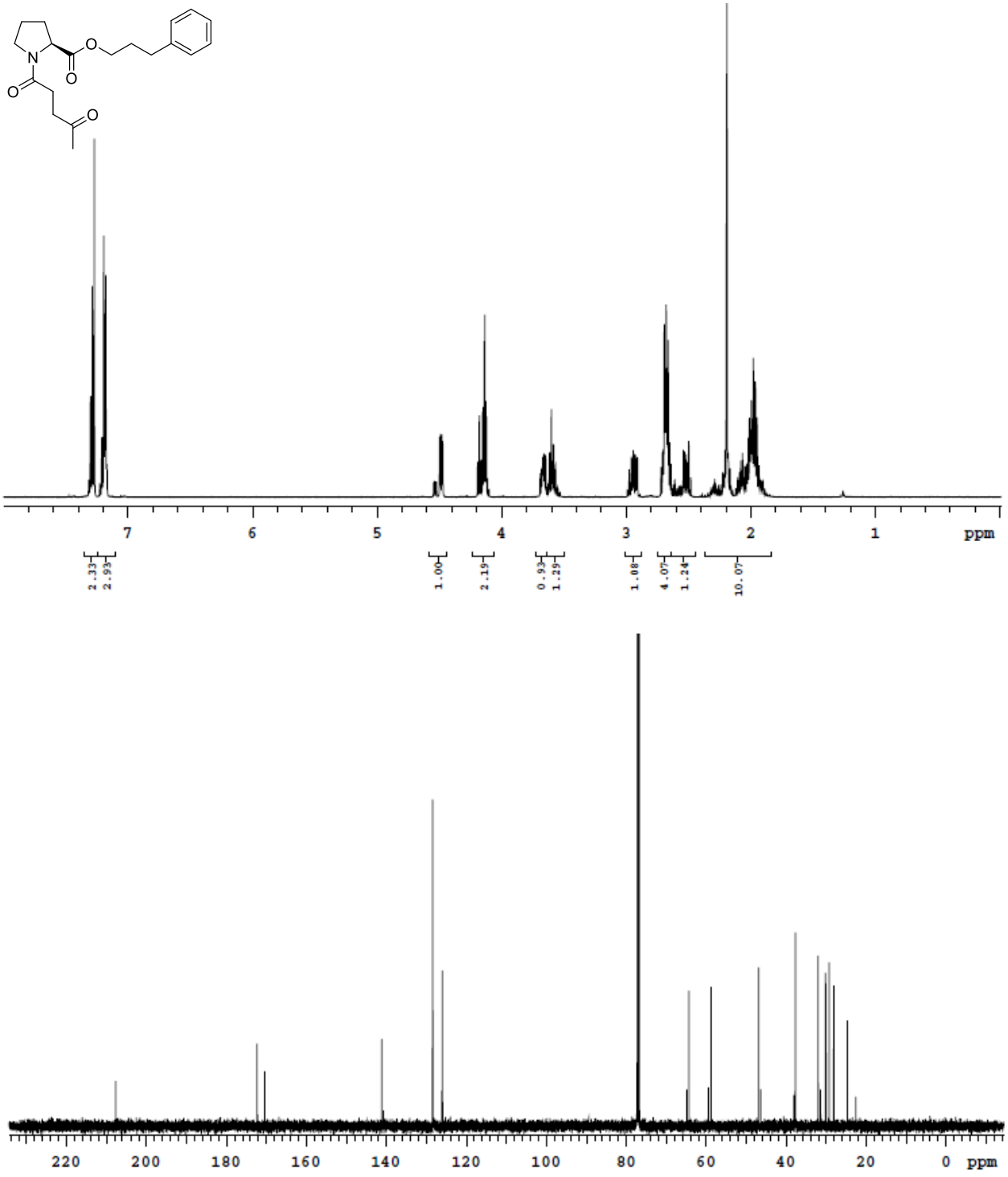


Figure 10.162: ^{1}H and ^{13}C Spectra of Compound VIII.1a

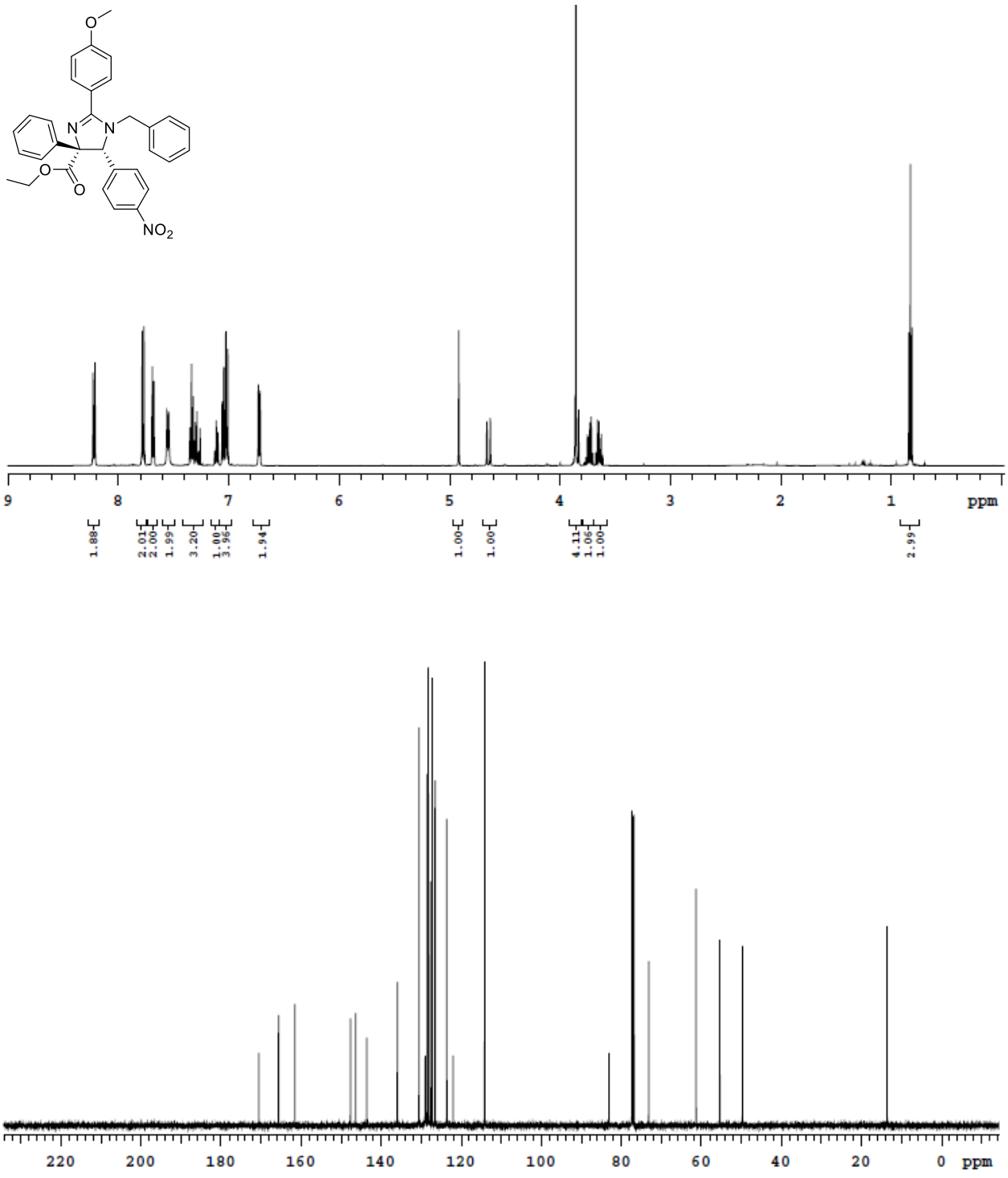


Figure 10.163: ^{1}H and ^{13}C Spectra of Compound VIII.1

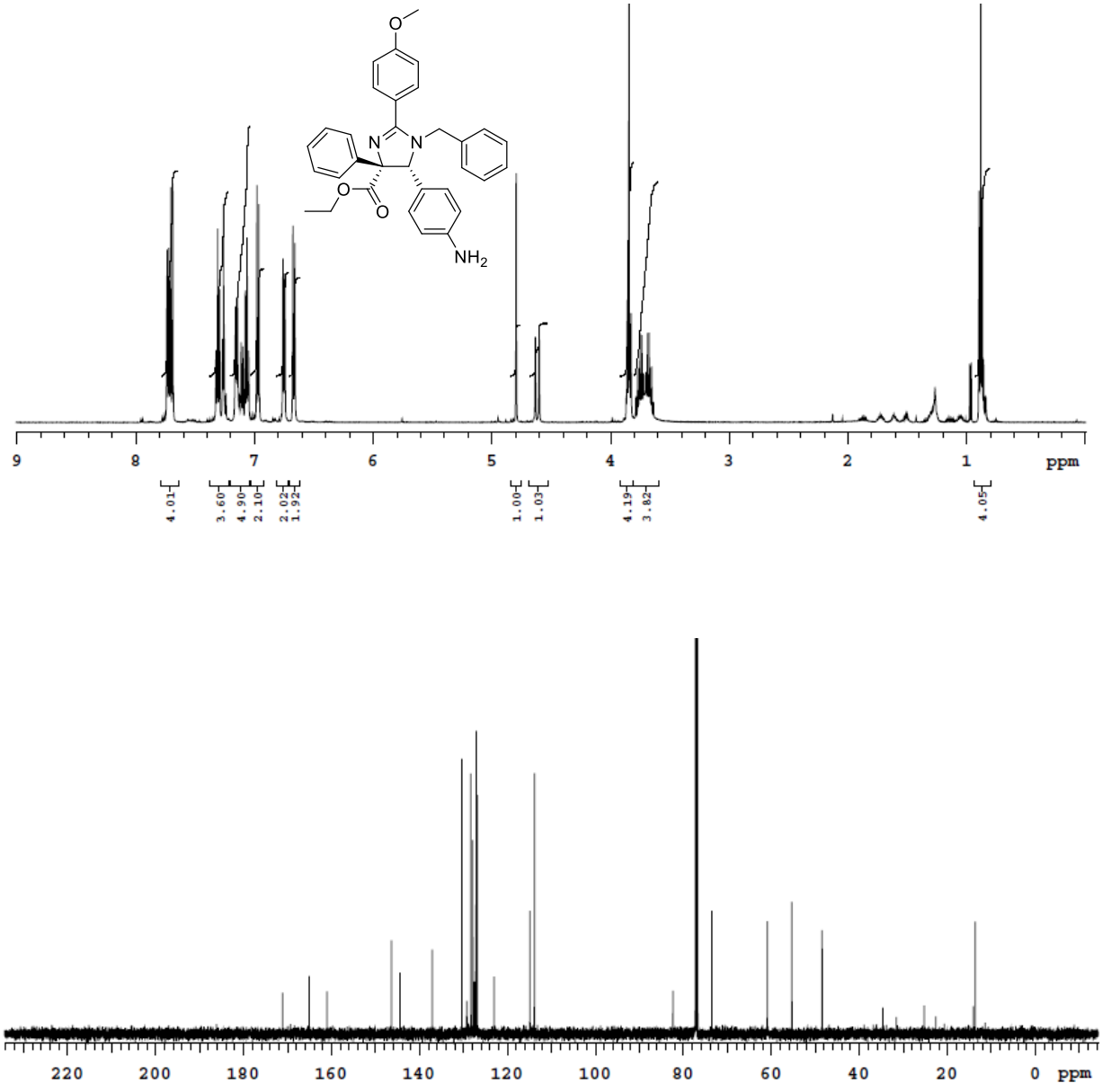


Figure 10.164: ^{1}H and ^{13}C Spectra of Compound VIII.2

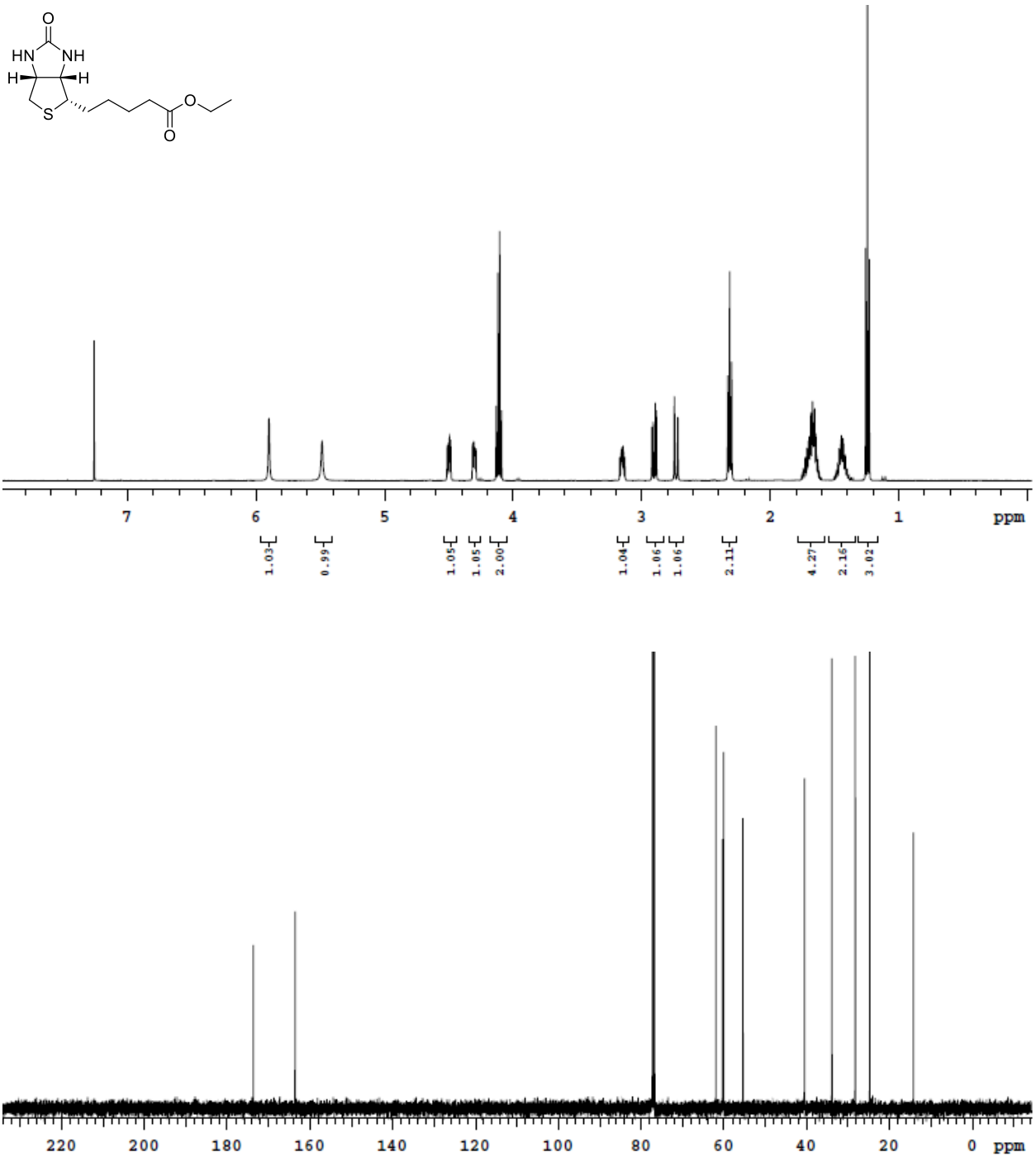


Figure 10.165: ^{1}H and ^{13}C Spectra of Compound VIII.3a

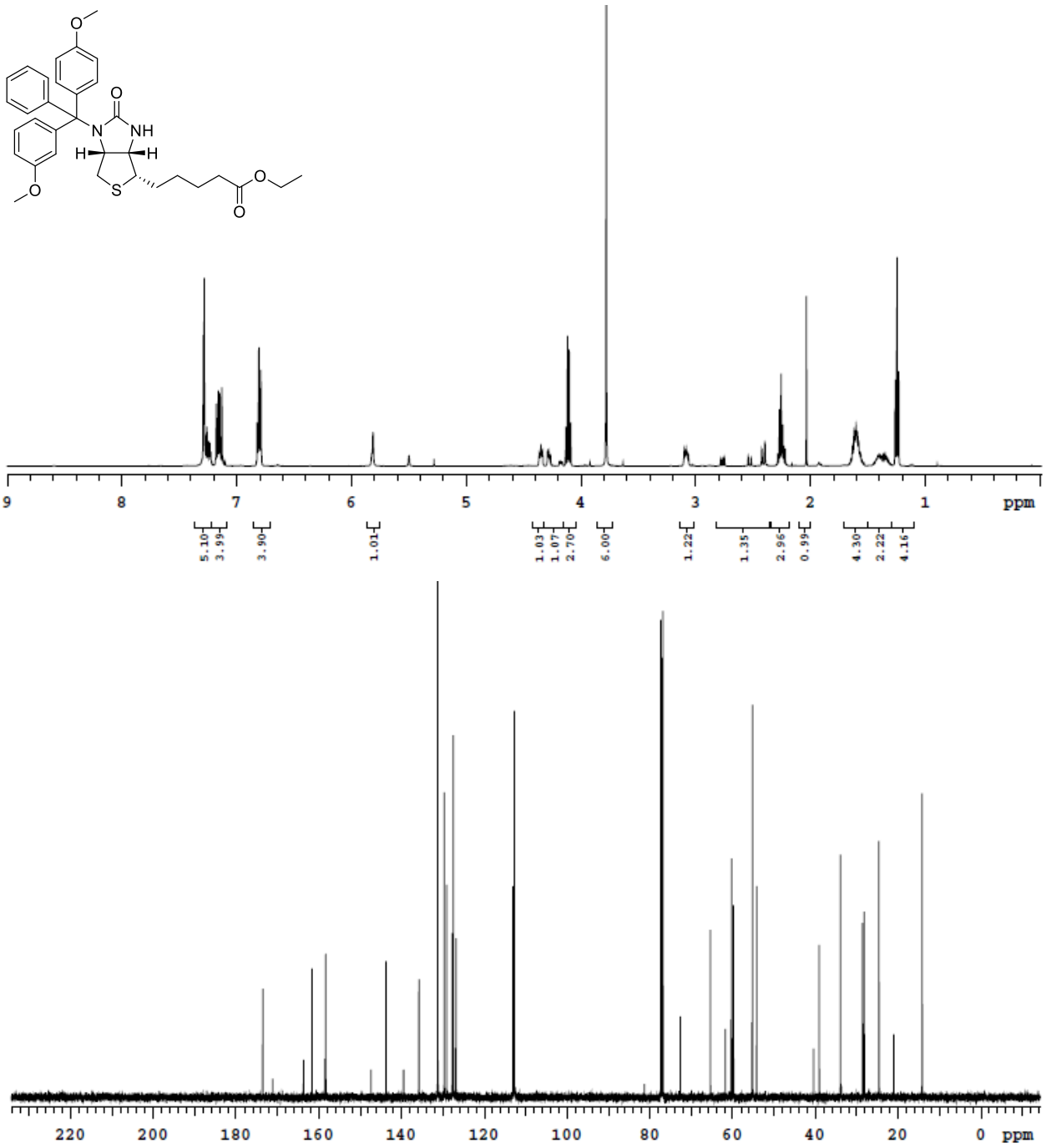


Figure 10.166: ^{1}H and ^{13}C Spectra of Compound VIII.3

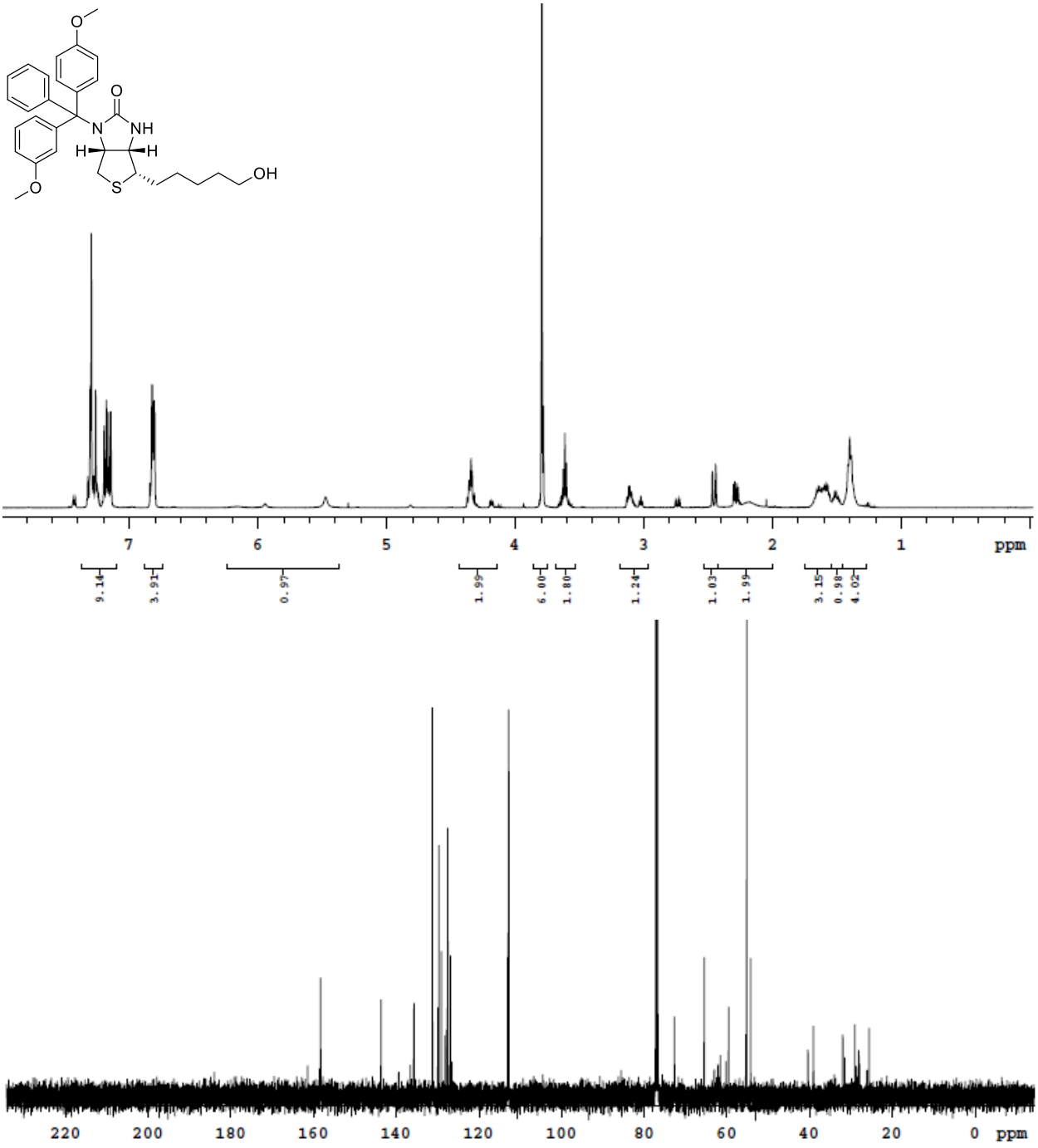


Figure 10.167: ^{1}H and ^{13}C Spectra of Compound VIII.4

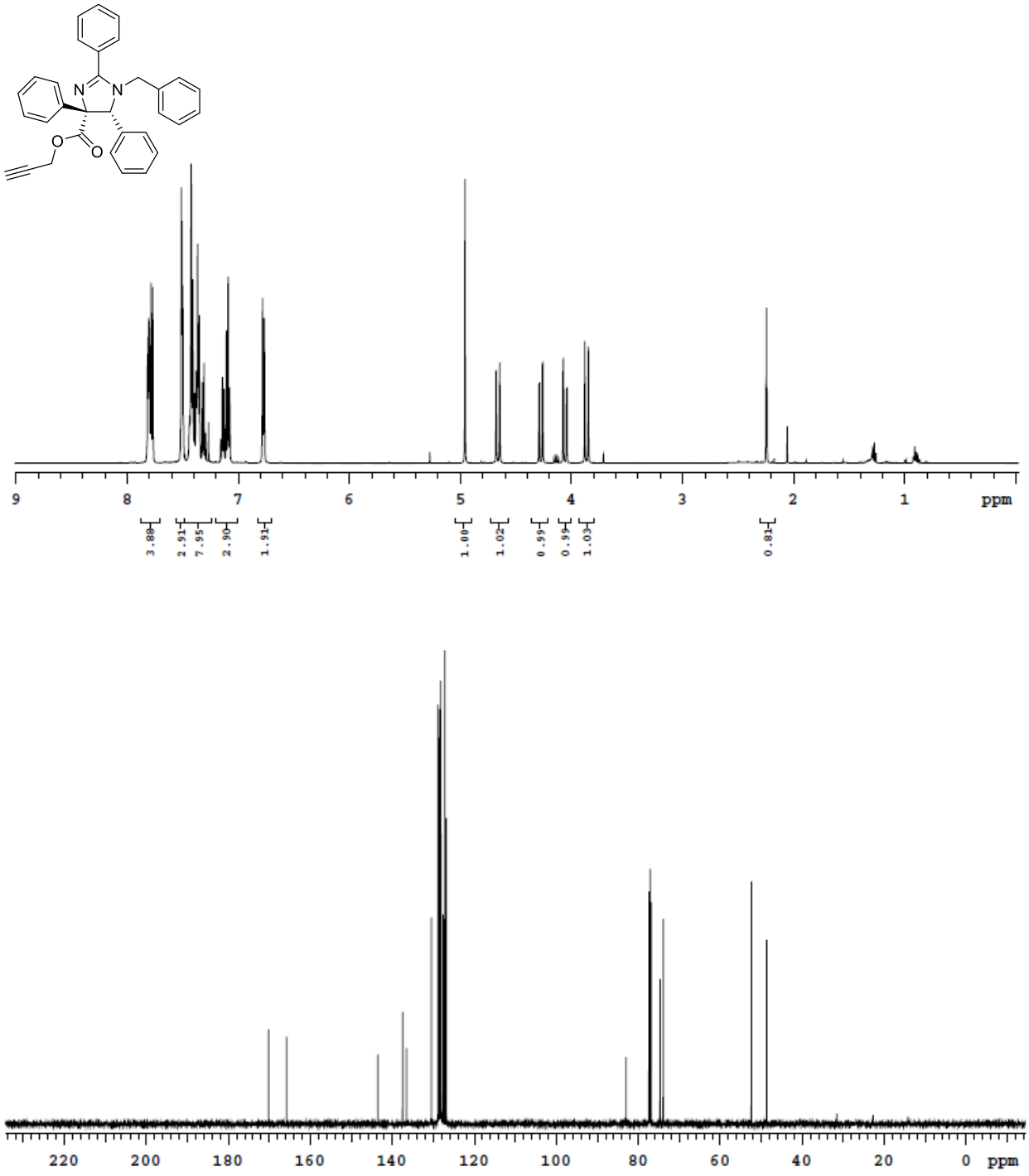


Figure 10.168: ^{1}H and ^{13}C Spectra of Compound VIII.5

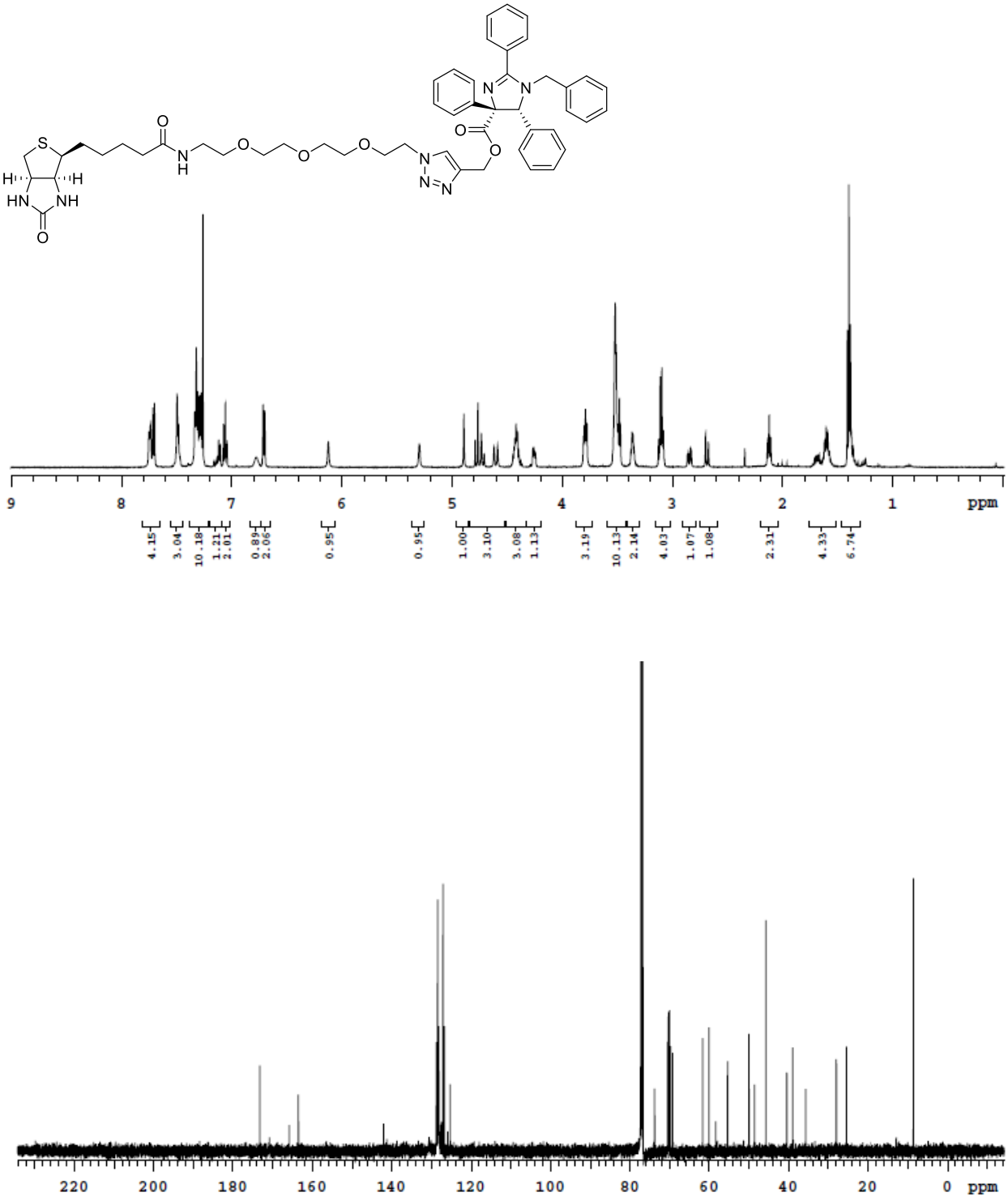


Figure 10.169: gHMQC Spectra of Compound VIII.5

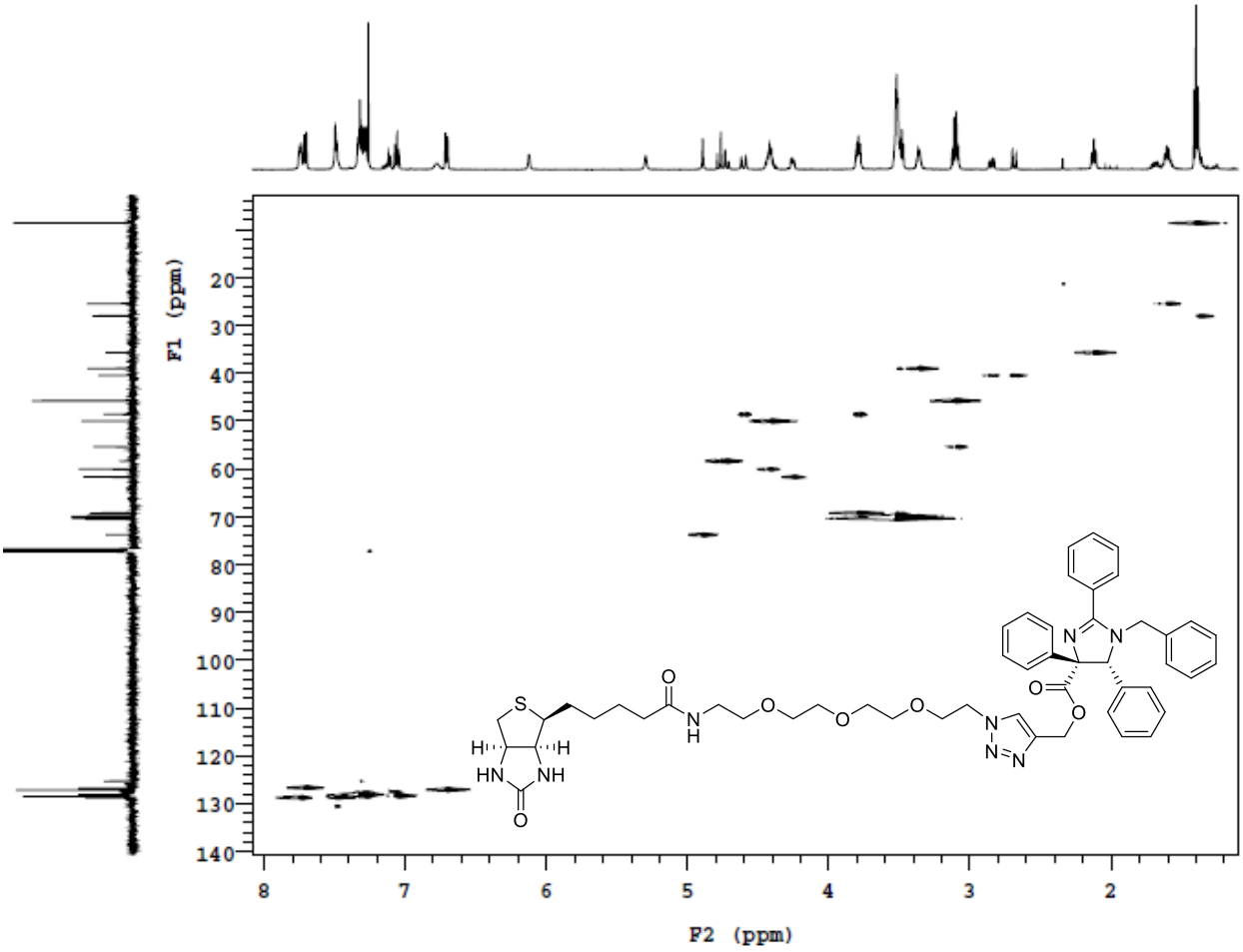


Figure 10.170: ^{1}H and ^{13}C Spectra of Compound VIII.6

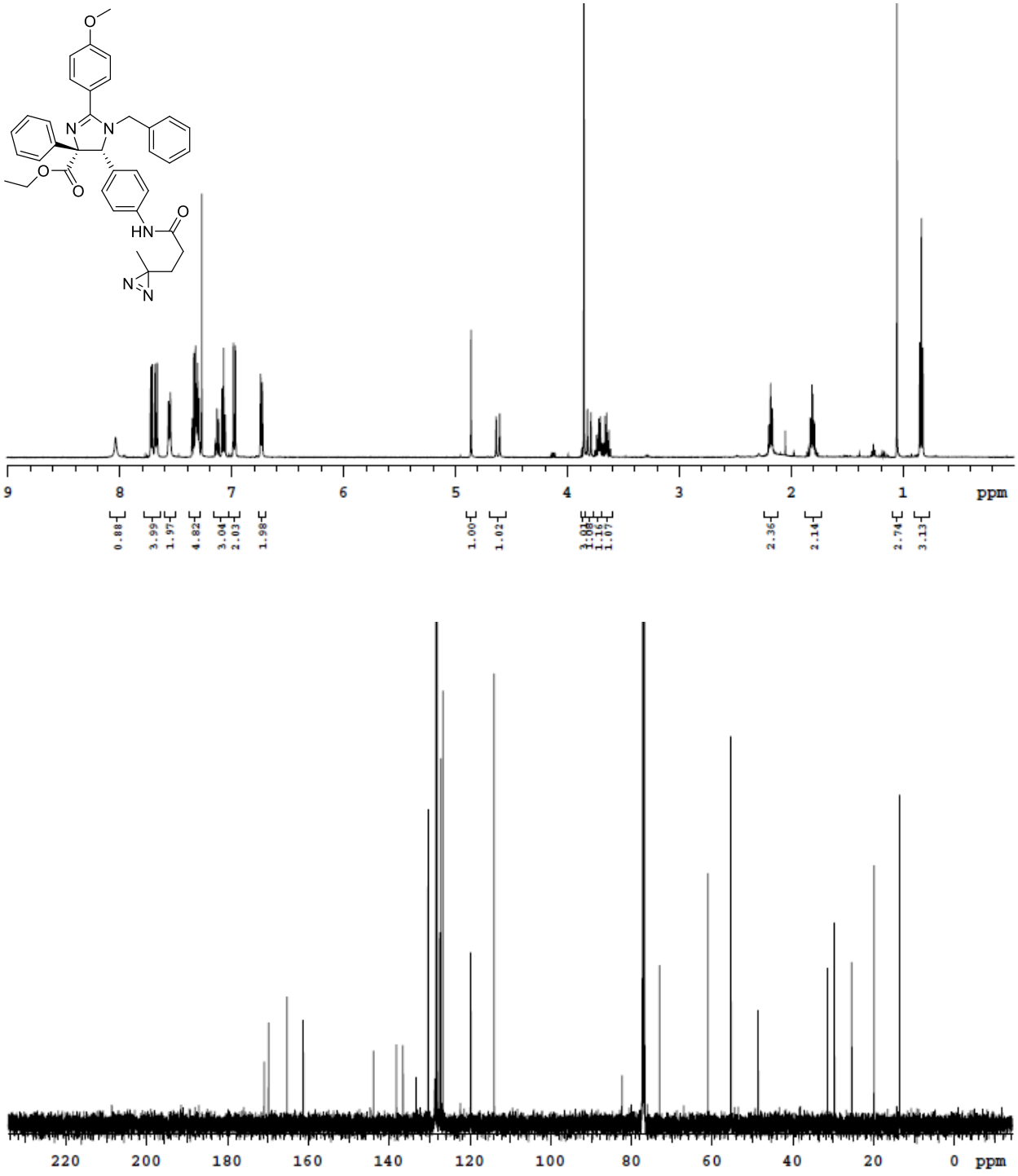


Figure 10.171: ^{1}H and ^{13}C Spectra of Compound VIII.7a

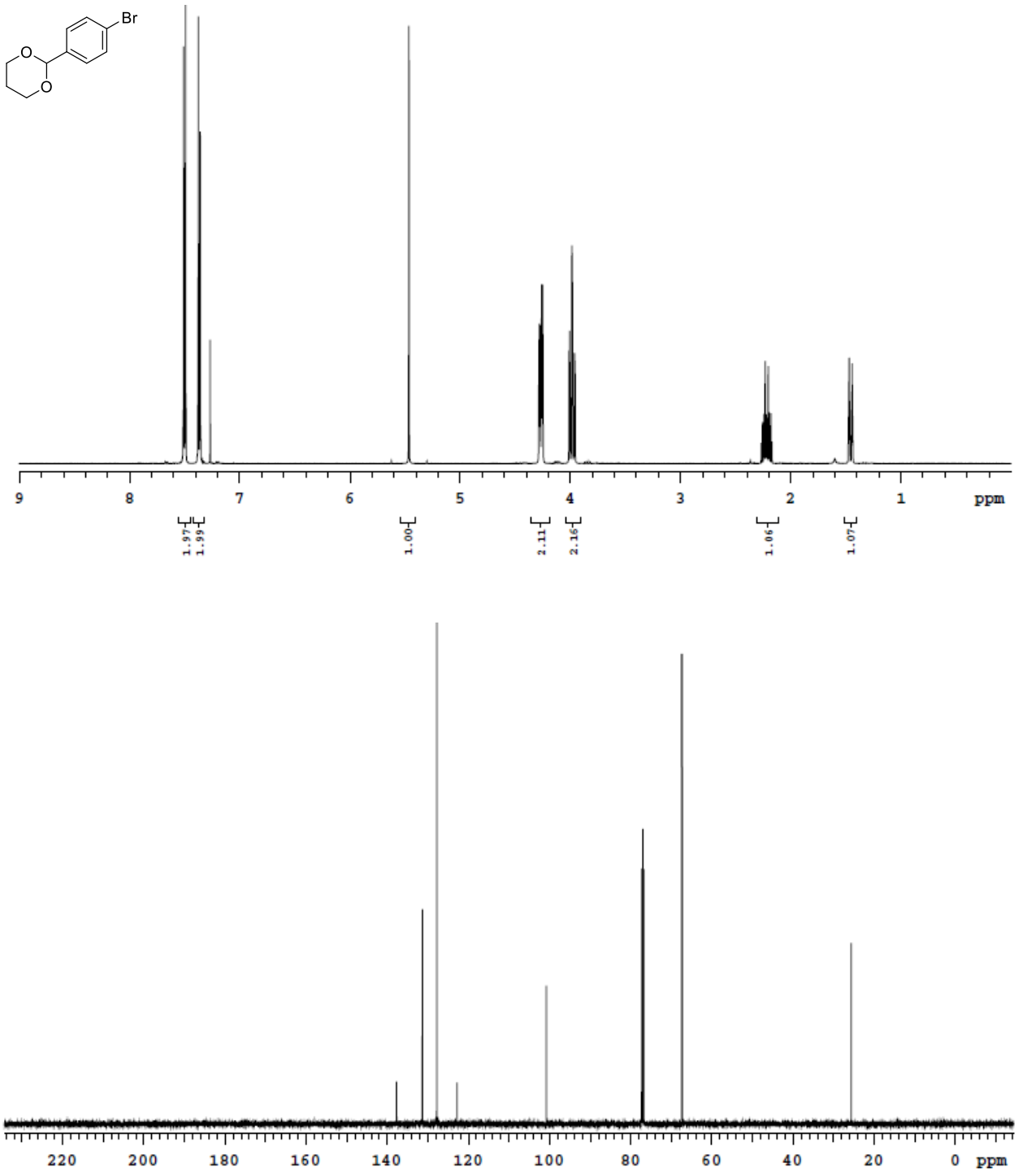


Figure 10.172: ^{1}H and ^{13}C Spectra of Compound VIII.7

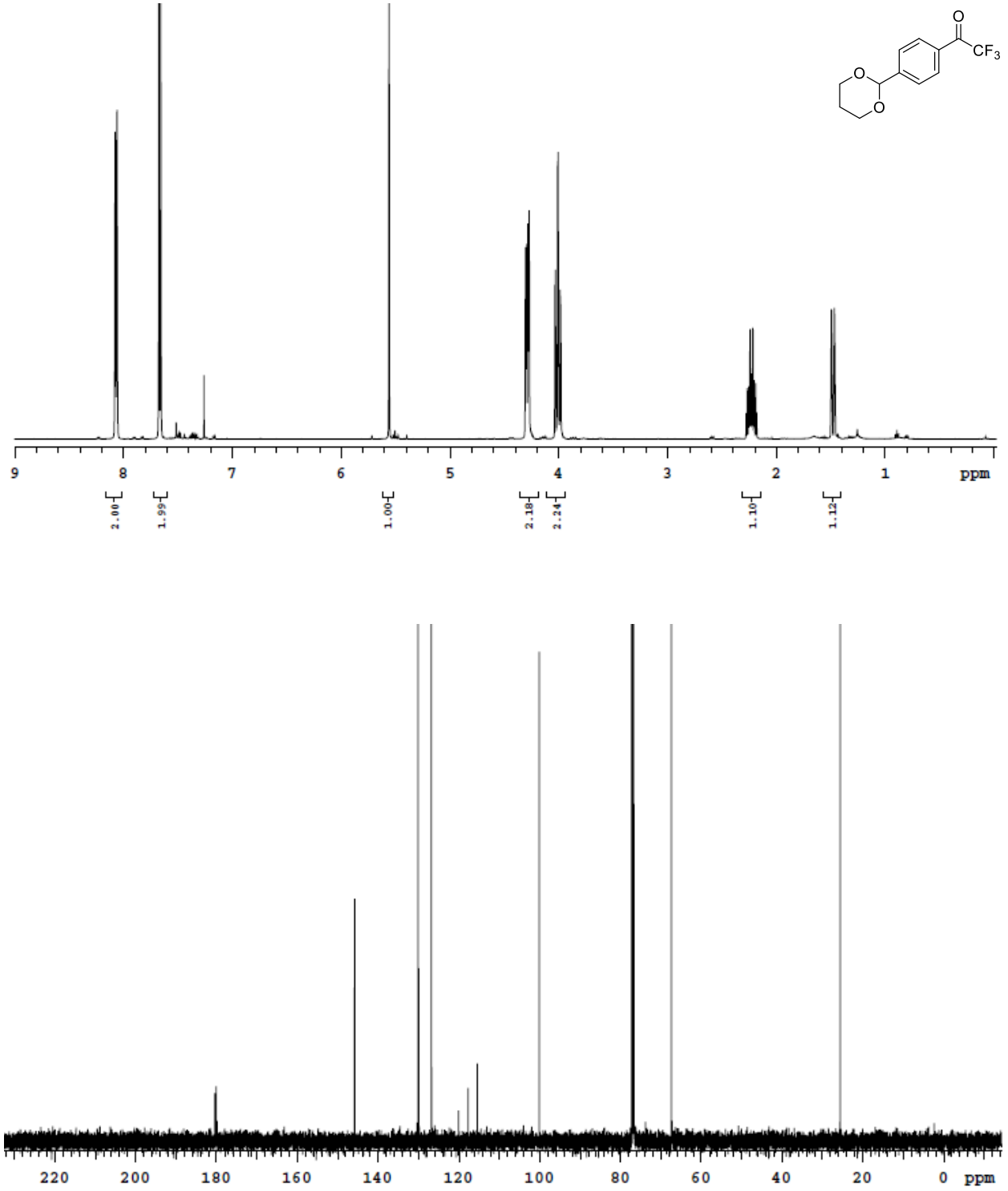


Figure 10.173: ^{1}H and ^{13}C Spectra of Compound VIII.8a

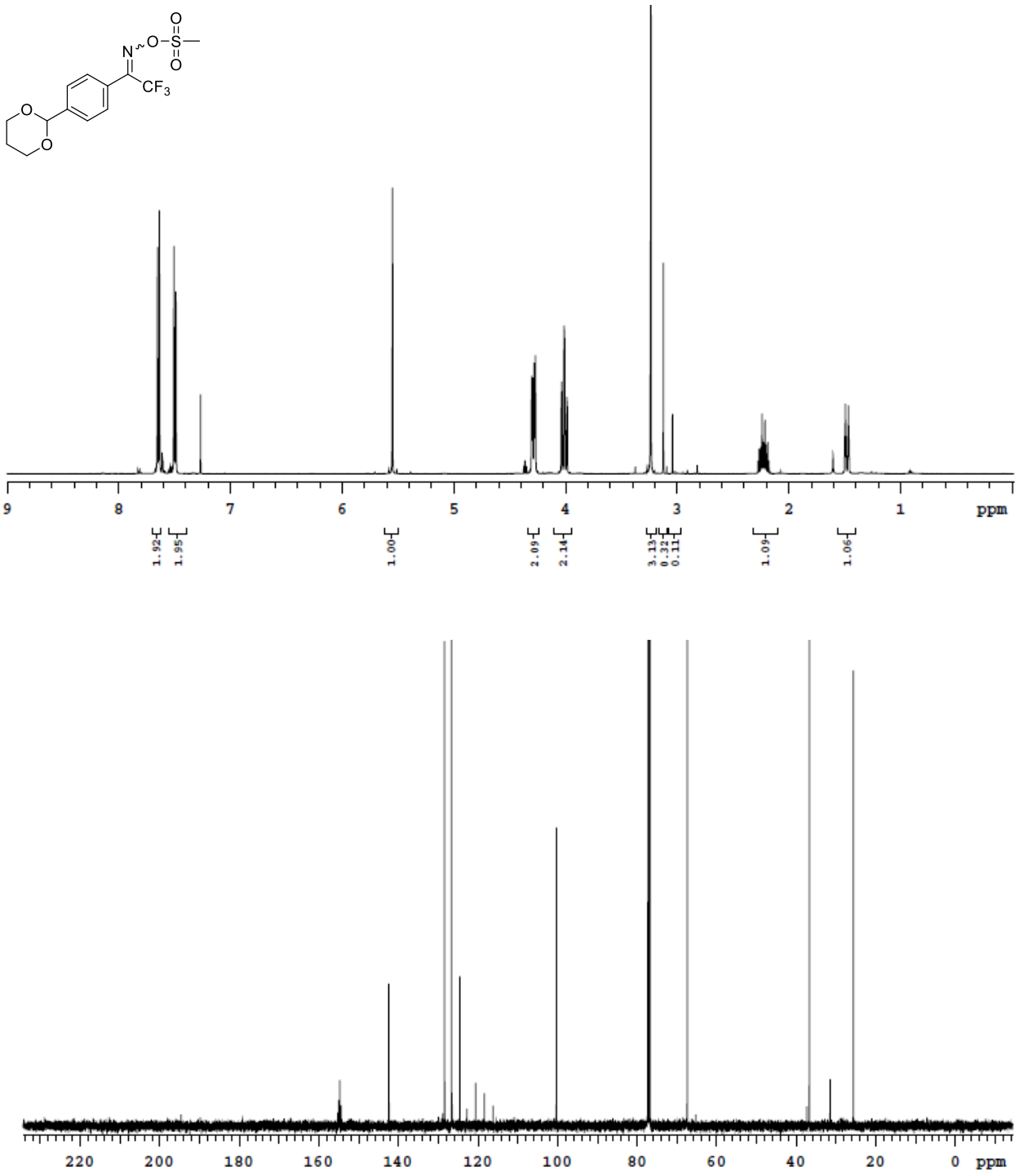


Figure 10.174: ^{1}H and ^{13}C Spectra of Compound VIII.8

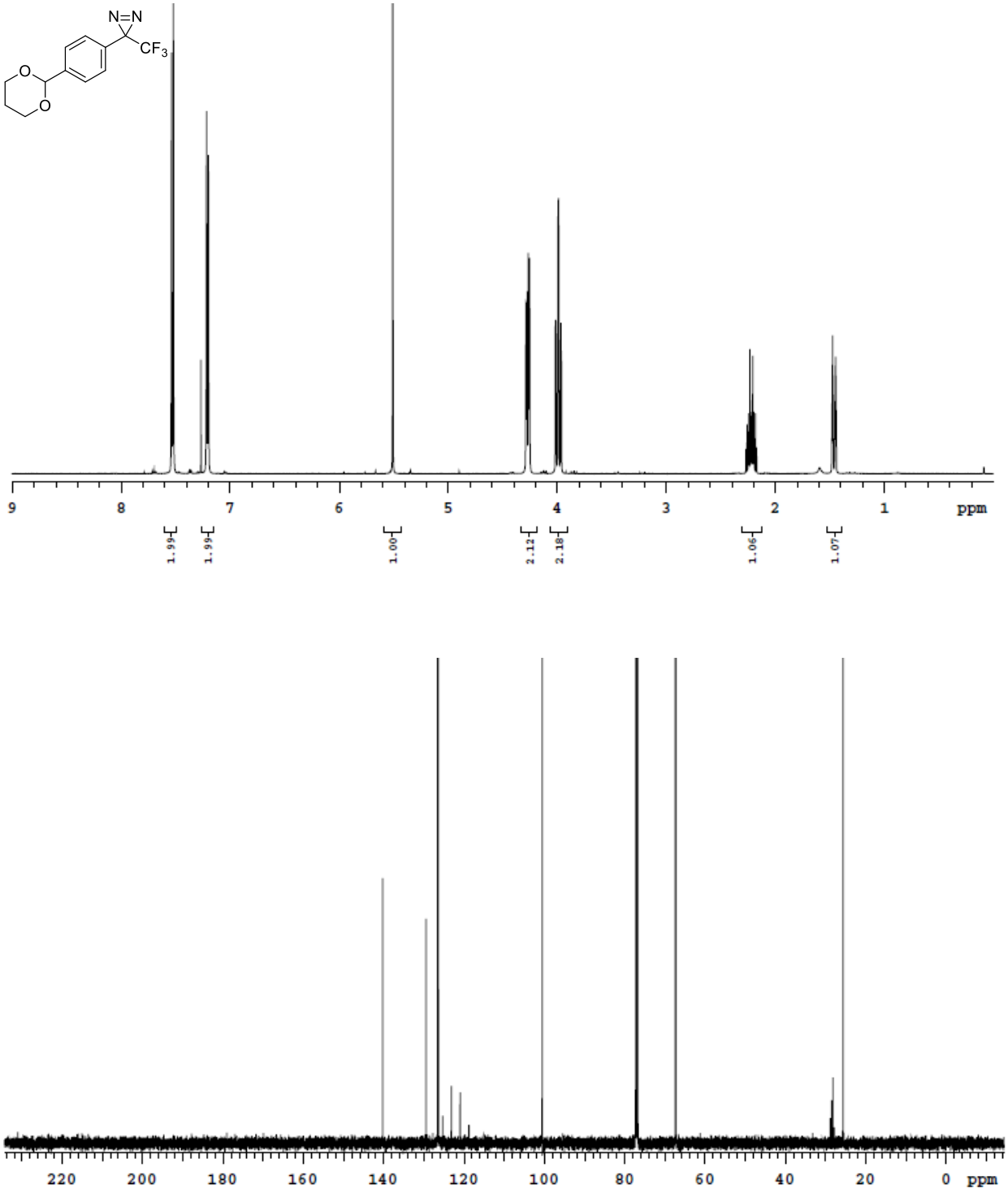


Figure 10.175: ^{1}H and ^{13}C Spectra of Compound VIII.9

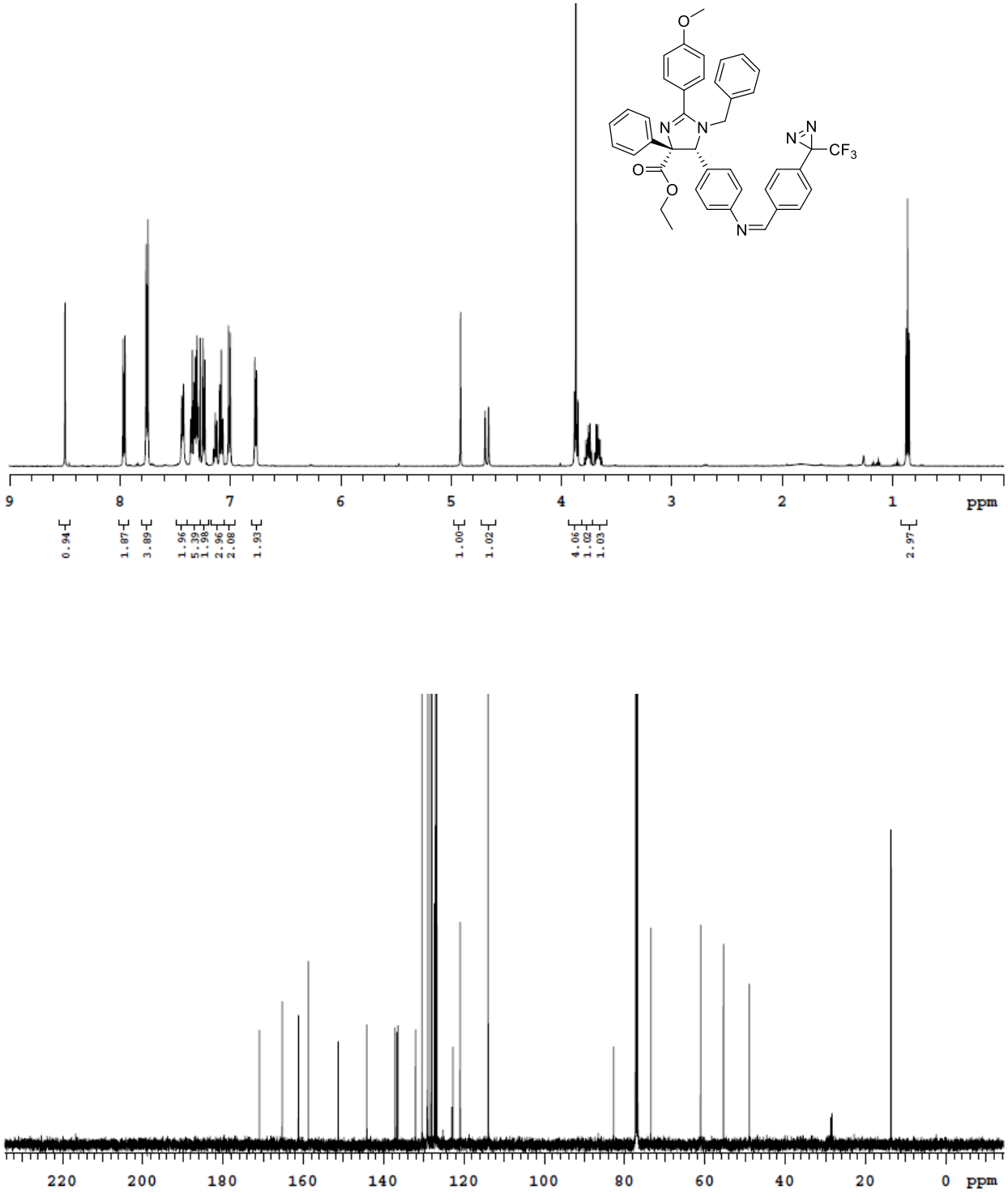


Figure 10.176: gHMQC Spectra of Compound VIII.9

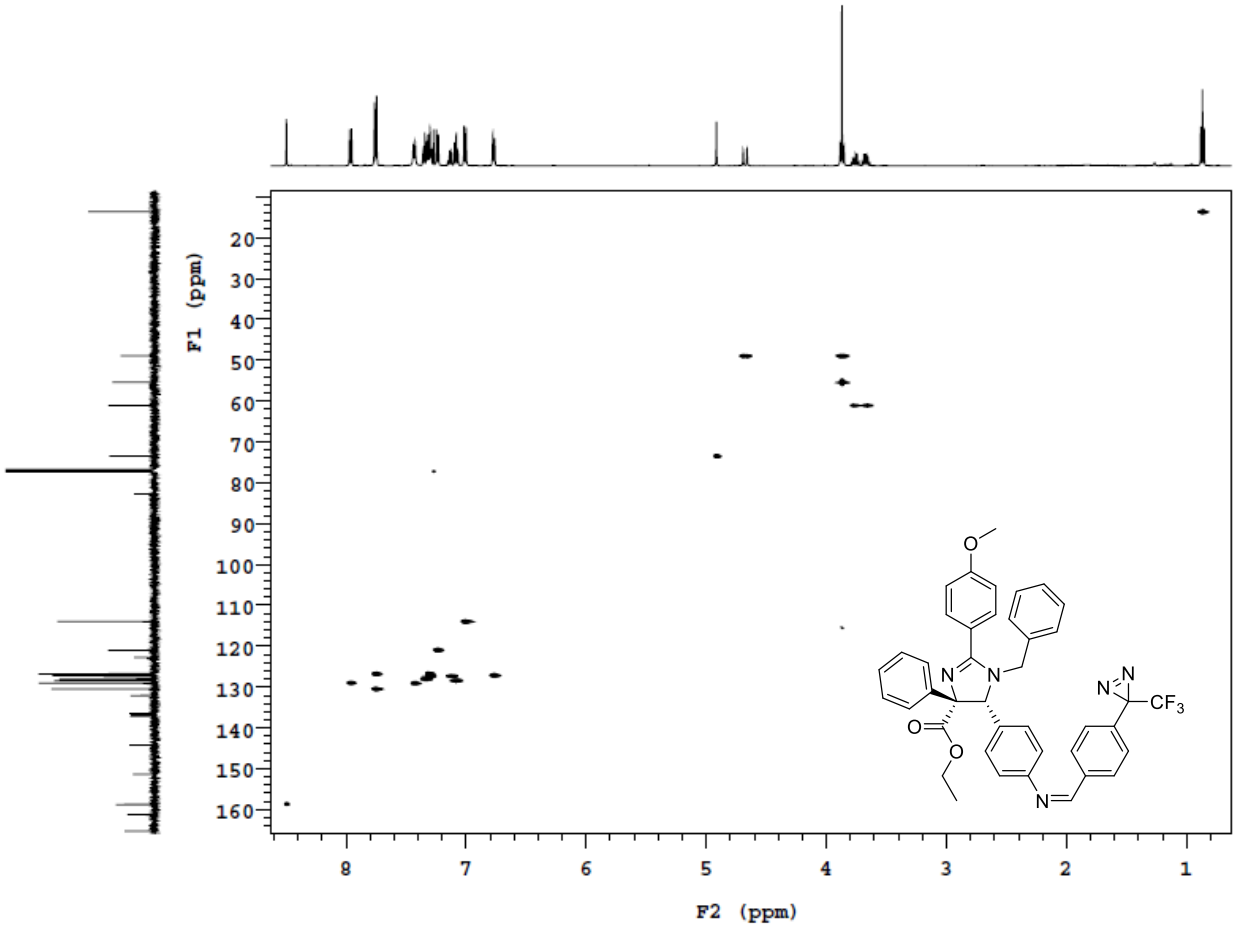
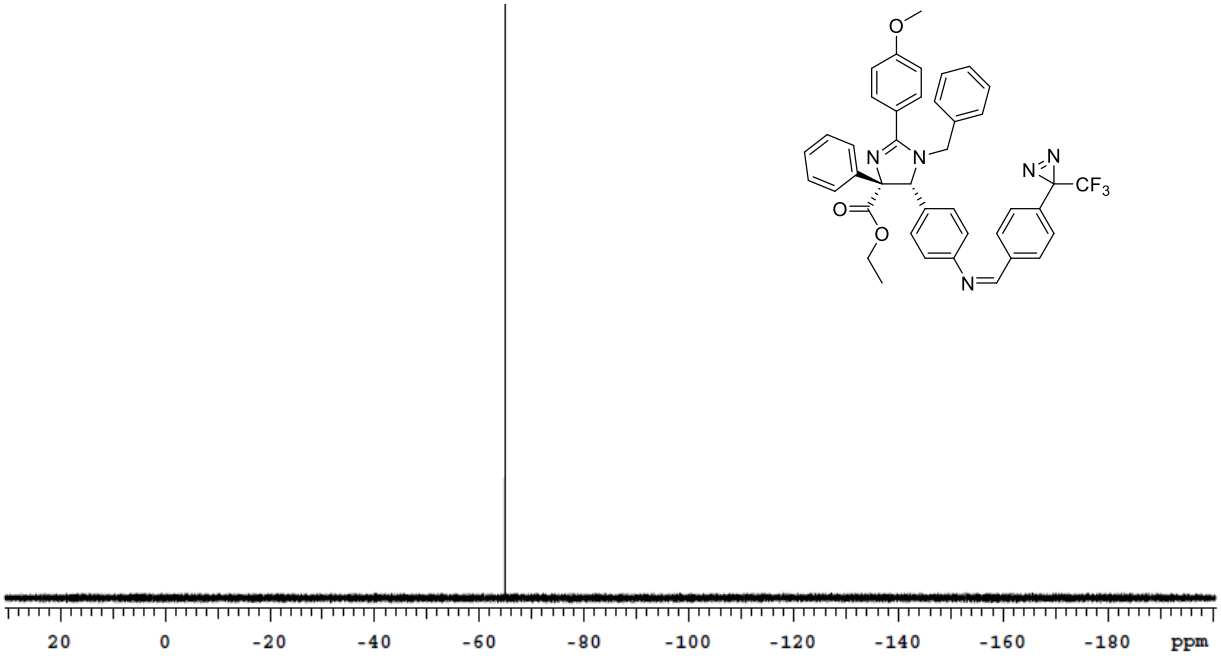


Figure 10.177: ^{19}F Spectra of Compound VIII.9



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