THE UNIVERSITY OF CHICAGO

STUDIES ON PALLADIUM CATALYZED FUNCTIONALIZATION OF INDOLES, SYNTHESIS OF PIPERAZINES AND RHODIUM CATALYZED BINOL ARYLATION

A DISSERTATION SUBMITTED TO

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To my wife Joanne and my parents

without whose support this would never have been possible

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LIST OF ABBREVIATIONS:

Å	angstrom
Ac	acetyl
Acac	acetylacetonate
AcOH	acetic acid
alloc	allyloxycarbonyl
anh	anhydrous
Ar	aryl
atm	atmospheres
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BIPHEP	2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
Bn	benzyl
Boc	*tert*-butylcarbonyl
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
C2	second atom counting clockwise from indole nitrogen
C3	third atom counting clockwise from indole nitrogen
C5	fifth atom counting clockwise from indole nitrogen
°C	degree Celsius
Cbz	carboxybenzyl
CDI	1,1′-carbonyldiimiazole
cod	cyclooctadiene
coe	cyclooctene
Cp	cyclopentadiene

Cp*	pentamethylcyclopentadiene
Cy	cyclohexyl
(D)-	dextrorotatory
DACH-phenyl	1,2-diaminocyclohexane-*N, N′*-bis(2-diphenylphosphinobenzoyl)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	1,2-dichloroethane
DEA	diethylamine
Diglyme	diethyl glycol dimethyl ether
DMA	dimethylacetamide
DMAP	4-dimethylamionpyridine
DMF	dimethylformamide
DMI	1,3-dimethyl-2-imiazolidinone
DMPU	*N,N′*-dimethylpropylene urea
DMSO	dimethylsulfoxide
DPEphos	(oxydi-2, 1-phenylene)bis(diphenylphosphine)
dppb	1,4-Bis(diphenylphosphino)butane
dppe	ethylenebis(diphenylphosphine)
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
dppm	1,1′-Bis(diphenylphoshino)methane
d.r.	diastereomeric ratio
E	entgegen
EDCI	*N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride
ee	enantiomeric excess

equiv	equivalents
ESI	electrospray ionization
Et	ethyl
EtOAc	ethylacetate
EtOH	ethanol
h	hours
Hex	hexanes
HPLC	high pressure liquid chromatography
HSAB	hard – soft, acid – base
HTE	high throughput experiment
i-Pr	iso-propyl
L	ligand
(L)-	levorotatory
m	meta
M	molar
MAC	masked acyl cyanide
m-CPBA	3-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minutes
MOM	methoxymethyl
MPa	megapascal
MS	molecular sieves
Ms	methylsulfonyl

$( )_n$	variable number of CH_2 groups at this position
N1	nitrogen of indole
N10	tethered amine of tryptamine
Nbd	norbornadiene
ND	not determined
NMP	N-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nuc	generic nucleophile
Ns	2-nitrobenzenesulfonyl
o	ortho
p	para
Pd(0)	palladium in its zero oxidation state
Pd(II)	palladium in its +2 oxidation state
Ph	phenyl
PhH	benzene
PHN	phenanthrene
pin	pinacol
Pyr	pyridine
quant	quantitative
QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinolin
R	variable alkyl group
(R)-	rectus
Rac	racemic
RT	ambient temperature
Rt	retention time

(S)-	sinister
S_N2	nucleophilic substitution bi-molecular
S_N2'	nucleophilic conjugate substitution
solv	solvent
TBDMS	*tert*-butyldimethylsilane
t-Bu	*tert*-butyl
temp	temperature
tert	tertiary
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMS	trimethylsilane
Tol	toluene
Ts	toluenesulfonyl
w/w	weight per weight ratio
X	variable atom
Xphos	2-dicyclohexylphosphino-2′,4 ′,6,-triisopropylbiphenyl
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Z	zusammen

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CHAPTER I

REACTION OF PALLADIUM 0 WITH PROPARGYL SPECIES AND THEIR FURTHER TRANSFORMATIONS: A LITERATURE REVIEW

> *"It is true that many transition metals are now used in organic synthesis, but it is widely recognized that palladium is the most versatile in promoting or catalyzing reactions, particularly those involving carbon-carbon bond formation, which is not always easy to achieve with other transition metals."*
>
> Jiro Tsuji, 1994[1]

I.1: Introduction

Palladium catalysis is a staple process of modern organic chemistry. There exist myriad transformations which are promoted by a palladium catalyst, and yet new applications are continuously appearing in the literature. One particular application of palladium catalysis is the interaction of palladium with propargylic compounds and the subsequent chemistry which can occur with these generated species.[2]

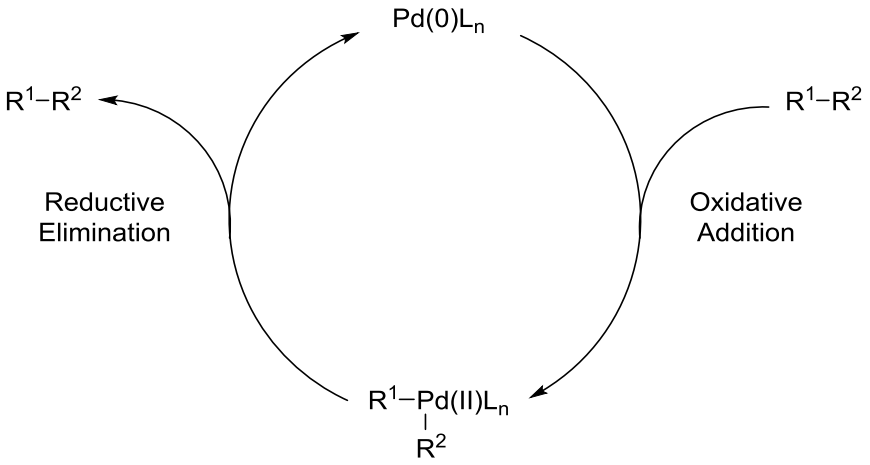
There are two different oxidation states of palladium which are usually relevant to palladium interactions with propargyl carbonates; palladium (0) and palladium (II). The oxidation state of a metal, in this case palladium, is defined as a method for classifying metal centers by assigning a formal charge to the metal center, which balances the overall charge of the

[1] Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons, Inc.: New York, NY, 1996.

[2] For reviews of Pd-catalyzed propargylation, see: (a) Bruneau, C.; Darcel, C.; Dixneuf, P. H. *Curr. Org. Chem.* **1997**, *1*, 197-218. (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley & Sons Ltd.: Chichester, West Sussex, England,2004; pp 543-562. (c) Inuki, S. *Platinum Metals Rev.* **2012**, *56*, 194-199. (d) Yoshida, M. *Chem. Pharm. Bull.* **2012**, *60*, 285-299. (e) Yoshida, M. *Heterocycles* **2013**, *87*, 1835-1864.

complex.[3] In a general sense it can be said that all interactions between a palladium catalyst and a propargylic species must include oxidative addition and reductive elimination. During oxidative addition, a palladium (0) metal center will add in an oxidative manner, generating a palladium (II) complex. The opposite of this process is reductive elimination: where a palladium (II) complex bearing at least two substituents can eliminate the substituents and reduce the metal center from palladium (II) to palladium (0) (Scheme 1).[4] This basic pattern of oxidative addition and reductive elimination is a common theme observed not only in reactions involving palladium but with many other metal catalyzed processes.

Scheme 1: Oxidative Addition and Reductive Elimination



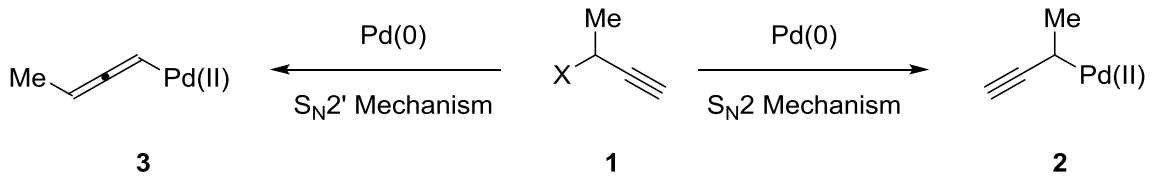
The first step, that of oxidative addition, between a propargylic compound **1** and a palladium catalyst may proceed through one of two mechanisms (Scheme 2). The first mechanism can be thought of as a simple S_N2 displacement reaction in which the palladium (0)

[3] (a) Hartwig, J. *Organotransition Metal Chemistry*; University Science Books: 2010. (b) Spessard, G. O.; Miessler, G. L. *Organometallic Chemistry: Second Edition*; Oxford University Press, Inc. 2010.

[4] (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489. (b) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.

oxidatively adds, displacing the leaving group with inversion of the stereocenter, giving propargyl palladium **2**. Alternatively the initial step can been seen as analogous to the S_N2' reaction, involving oxidative addition into the π* system of the alkyne and displacing the leaving group to generate a palladium allene **3**.

Scheme 2: General Mechanism of Oxidative Addition to a Propargylic System



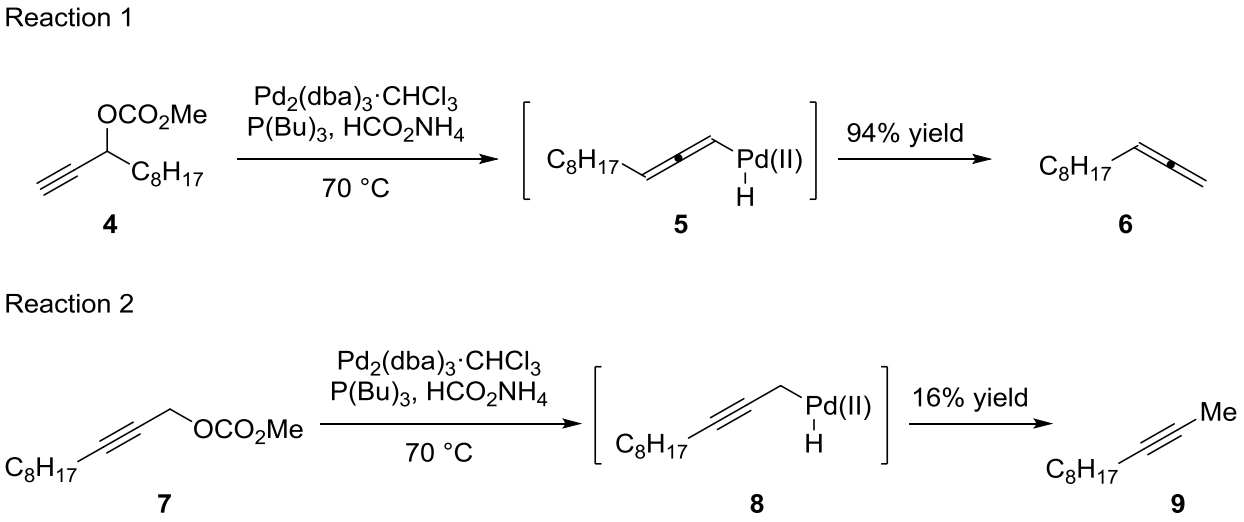
I.2: Reactions involving Propargyl Palladium Complexes

The formation of propargyl palladium species **2**, while less common than palladium allene complexes **3**, have been observed in the literature. In an early example during the formation and subsequent hydrogenation of different palladium complexes different products were observed, depending on the substitution pattern of the propargyl carbonate (Scheme 3).[5] When propargyl carbonate **4** was exposed to a palladium (0) catalyst the proposed intermediate **5** forms, which following hydrogenation of the palladium (II) center by ammonium formate, will reductively eliminate to give allene **6** (reaction 1). However with the regioisomeric propargyl methyl carbonate **7** the greater steric repulsion causes propargyl palladium complex **8** to form to some extent. Following hydrogenation and reductive elimination as before gives alkyne **9** as a minor product (reaction 2).

[5] Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis* **1987**, *1987*, 603-606.

I.2.1: Hydrogenation of Palladium Allene and Palladium Propargyl Metal Complexes

Scheme 3: Hydrogenation of Palladium Complexes



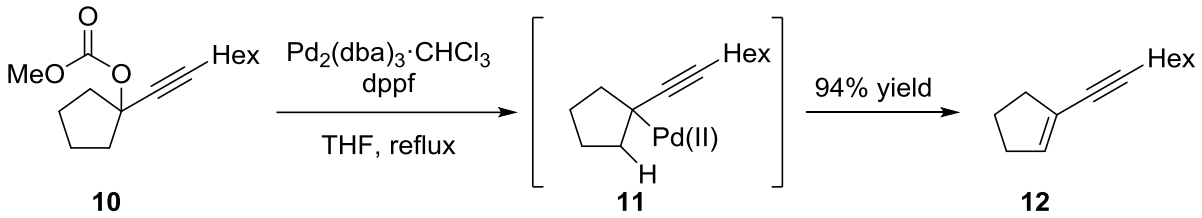
I.2.2: Formation of Alkenes by β-Hydride Elimination

When palladium oxidatively adds to a compound where the palladium center is adjacent to a sp^3 hybridized carbon[6] bearing one or more protons, there exists the possibility for β-hydride elimination; a special type of reductive elimination.[3] This property can be used to form new olefins in a molecule, or serve as a trap for metal intermediates (Scheme 4).[7] Propargyl carbonate **10** reacts with the palladium catalyst to give palladium (II) propargyl complex **11**. This can then undergo β-hydride elimination to give the conjugated ene-yne system **12** in good yield.

[6] For a review on orbital hybridization please see the following reviews and sources cited therein: (a) Carey, F. A. *Organic Chemistry: Sixth Edition*; McGraw-Hill Companies, Inc.: New York, NY, 2006. (b) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books, 2006. (c) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms: Fifth Edition*; Springer Science+Buisness Media, LLC:New York, NY, 2007.

[7] Mandai, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 7615-7618.

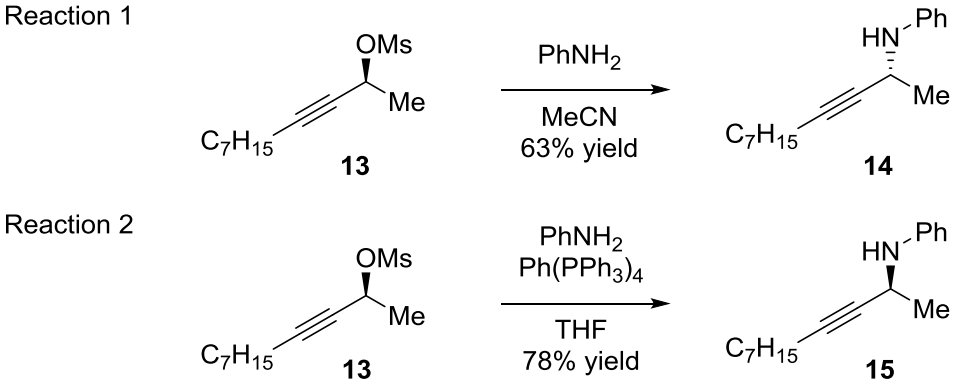
Scheme 4: β-Hydride Elimination of Palladium Propargyl Complexes



I.2.3: Mechanistic Evidence for Palladium Oxidative Addition

The S_N2 nature of the displacement of the leaving group by palladium was clearly demonstrated by Marshall and coworkers (Scheme 5).[8] When propargyl methylsulfonate **13** is reacted with aniline the expected S_N2 reaction occurs with inversion of the stereocenter to give compound **14** in good yield (reaction 1). However when the same reaction is performed in the presence of a palladium (0) catalyst the observed product is propargyl amine **15** with retention of the stereocenter. This can be explained by initial addition of palladium (0) to compound **13** and inversion of the stereocenter. This is followed by subsequent S_N2 type displacement of the palladium by aniline, again inverting the stereocenter. This double inversion gives amine **15** with overall retention of chirality at the stereocenter (reaction 2).

Scheme 5: Evidence for S_N2 Type Reaction

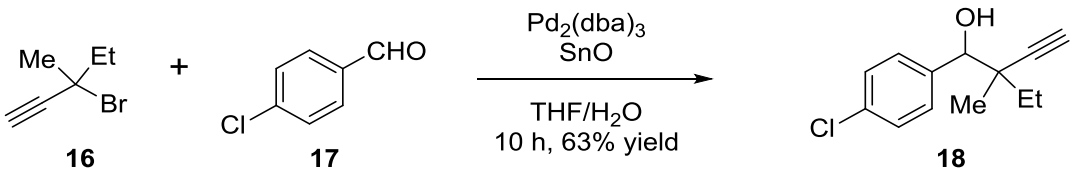


[8] Marshall, J. A.; Wolf, M. A. *The Journal of Organic Chemistry* **1996**, *61*, 3238-3239.

I.2.4: Palladium Propargyl Complex Reaction with Carbonyls

The use of a palladium (0) catalyst for the propargylation of a carbonyl, typically an aldehyde, has proven to be a highly effective method for generating homopropargylic alcohols (Scheme 6).[9] A nice example by Banerjee and Roy[9e] shows that by using a palladium catalyst with a β-SnO additive, propargyl bromide **16** can be added to arylaldehyde **17** to give products such as homopropargylic alcohol **18**. While this is a formal propargylation, it is not thought to proceed through a propargyl palladium (II) species. Rather after initial formation of palladium allene **20** followed sequentially by a transmetalation step to yield metal allene **21** which can add nucleophilically to carbonyl **22** generating observed product **23** (Scheme 7).

Scheme 6: Palladium Catalyzed Propargylation of a Carbonyl



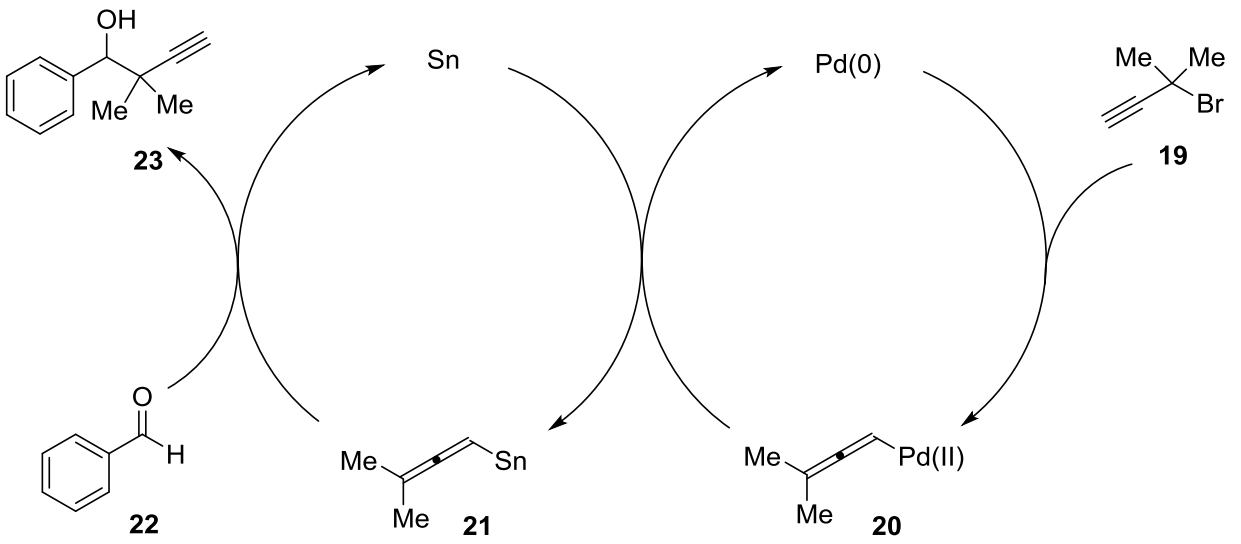
A more recent example of a formal propargylation was shown in the recent paper by Li and coworkers.[10] By combining benzyl chloride **24** with alkynyl carboxylic acid **25** under palladium mediated conditions, they were able to effect clean conversion to propargyl compound **26** throught a decarboxylative coupling process (Scheme 8). This again, does not likely involve a

[9] (a) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angewandte Chemie International Edition in English* **1996**, *35*, 878-880. (b) Marshall, J. A.; Adams, N. D. *The Journal of Organic Chemistry* **1998**, *63*, 3812-3813. (c) Marshall, J. A.; Grant, C. M. *The Journal of Organic Chemistry* **1999**, *64*, 696-697. (d) Sakamoto, T.; Takahashi, K.; Yamazaki, T.; Kitazume, T. *The Journal of Organic Chemistry* **1999**, *64*, 9467-9474. (e) Banerjee, M.; Roy, S. *Chem. Commun.* **2003**, 534-535.

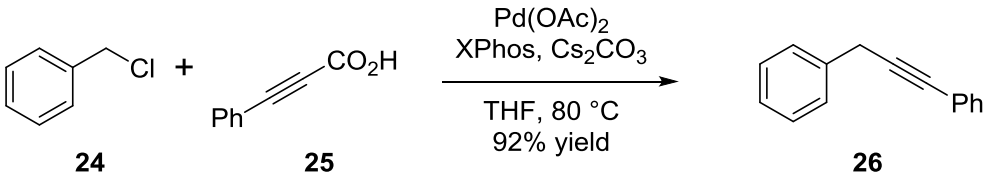
[10] Zhang, W.-W.; Zhang, X.-G.; Li, J.-H. *The Journal of Organic Chemistry* **2010**, *75*, 5259-5264.

palladium (II) propargyl species, but rather addition of a palladium (II) benzyl complex across the alkyne followed by a decarboxylative reductive elimination step.

Scheme 7: Catalytic Cycle for Homopropargylic Alcohol Formation



Scheme 8: Decarboxylative Propargyl Formation

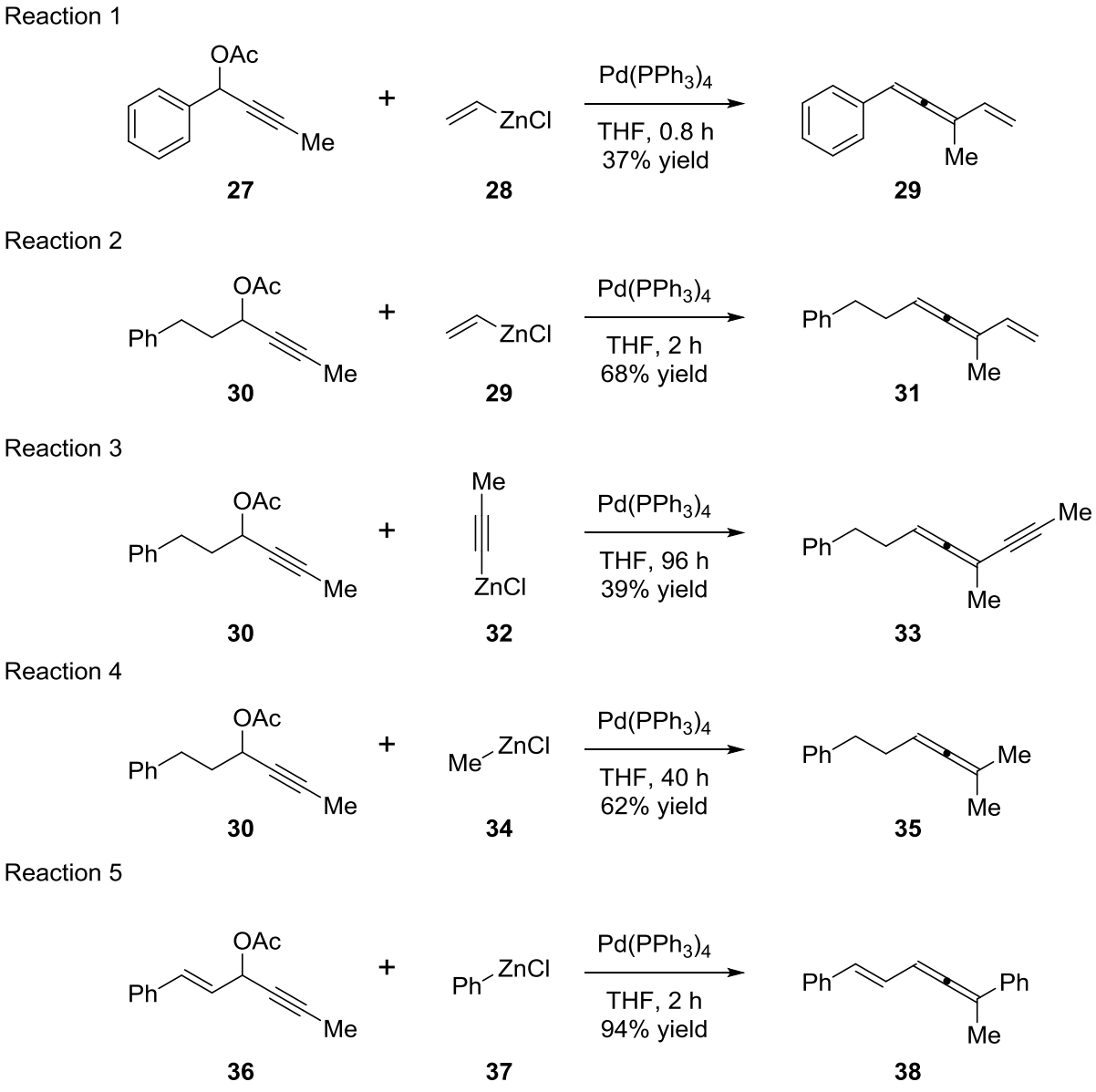


I.3: Formation and Trapping of Palladium Allene Complexes

With the addition of palladium (0) to a propargyl compound the more common reaction pathway is for the palladium (0) to add in an S_N2' type fashion and give a palladium (II) allene complex. While such complexes possess their own inherent reactivity, they can also be trapped in order to generate new compounds bearing an allene moiety. There exist a number of pathways in which the palladium allene can be trapped: transmetallation, addition across an alkene, addition across an alkyne, insertion into the palladium allene bond and reductive elimination.

I.3.1: Transmetallation of Palladium (II) Allene Complexes using Zinc

Scheme 9: Palladium (II) Allene Reaction with Organozinc



Transmetallation is a process where two different metal centers exchange ligands. In the case of palladium this can occur with a large number of different metals. A common metal used for the transmetallation of palladium (II) complexes is zinc, which is famously used in Negishi

coupling reactions[11] (Scheme 9).[12] The first example shows the coupling of propargyl acetate **27** with vinyl zinc chloride **28** to give allene **29** in modest yield (reaction 1). Along with vinyl zinc compounds, this chemistry is also compatible with propargyl zinc (reaction 3), alkyl zinc (reaction 4) and aryl zinc (reaction 5). In all cases the shown allene product is the sole product reported.

I.3.2: Transmetallation of Palladium (II) Allene Complexes using Aluminum and Tin

Other metals have also been found to be effective for participating in a transmetallation type process with palladium (II) allenes (Scheme 10).[12b] When triethyl aluminum **39** was combined with propargyl acetate **27**, the transient palladium (II) allene intermediate reacted with triethyl aluminum **39** to give an ethyl allene palladium (II) complex which after reductive elimination gave allene **40** in reasonable yield. When alkynyl aluminum **41** was combined with propargyl acetate **30** under the reaction conditions, desired product **42** was isolated in excellent yield (reaction 2). When stannyl allene **43** was used with propargyl acetate **36** corresponding product **44** does not correlate to a simple transmetallation mechanism (reaction 3). Instead the propargyl allene is isolated, indicating that a more complex reaction process is occurring. Such results are usually explained by an equilibrium existing between the palladium allene and palladium propargyl complexes. In lieu of stannyl allene **42**, stannyl allyl **46** may be used, generating compound **47** in moderate yield after 2 hours (reaction 4). For the reactions involving the stannyl coupling partners, a major side product involves reaction at the benzylic position of the allyl acetate (Scheme 11).

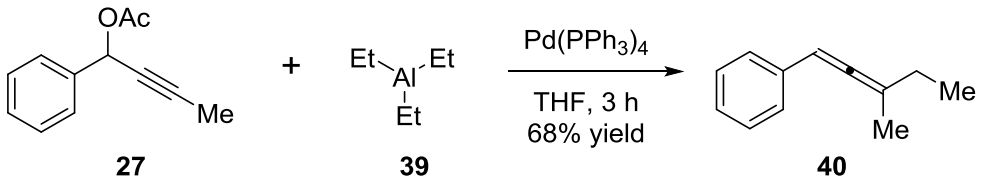
---

[11] Wang, Z. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc.: 2010.

[12] (a) Ruitenberg, K.; Kleijn, H.; Elsevier, C. J.; Mijer, J.; Vermeer, P. *Tetrahedron Lett.* **1981**, *22*, 1451-1452. (b) Keinan, E.; Bosch, E. *The Journal of Organic Chemistry* **1986**, *51*, 4006-4016. (c) Jansen, A.; Krause, N. *Synthesis* **2002**, *2002*, 1987-1992.

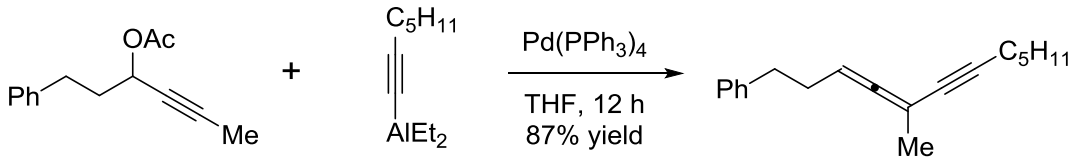
Scheme 10: Use of Alkyl Aluminum and Stannanes

Reaction 1



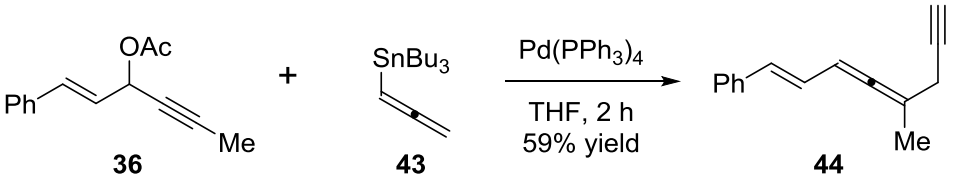
27 **39** **40**

Reaction 2



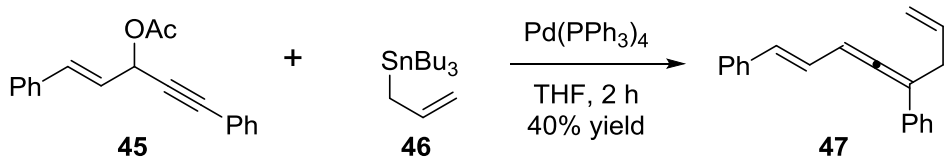
30 **41** **42**

Reaction 3



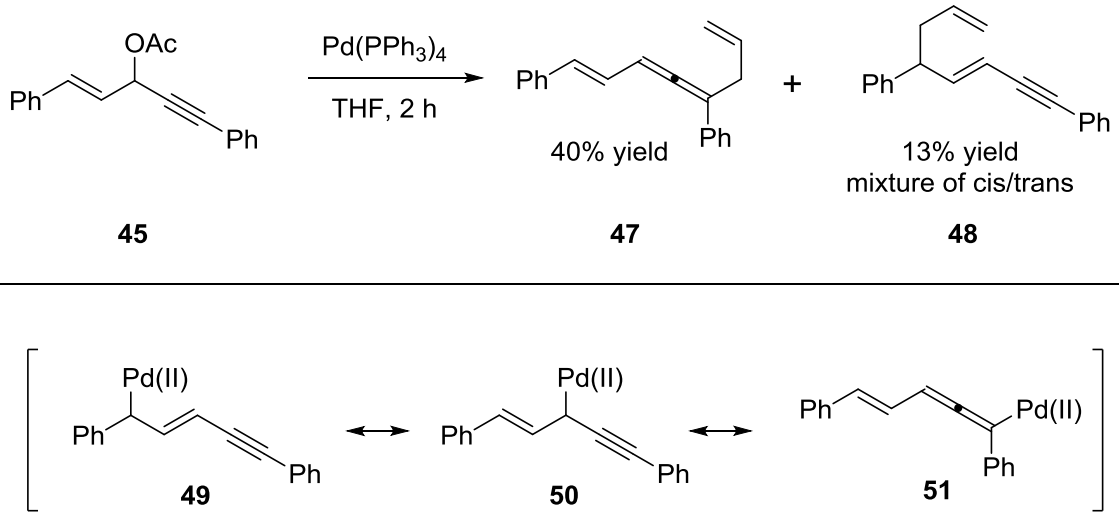
36 **43** **44**

Reaction 4



45 **46** **47**

Scheme 11: Mechanistic Rationale for Distribution of Products



I.3.3: Transmetallation of Palladium (II) Allene Complexes using Copper

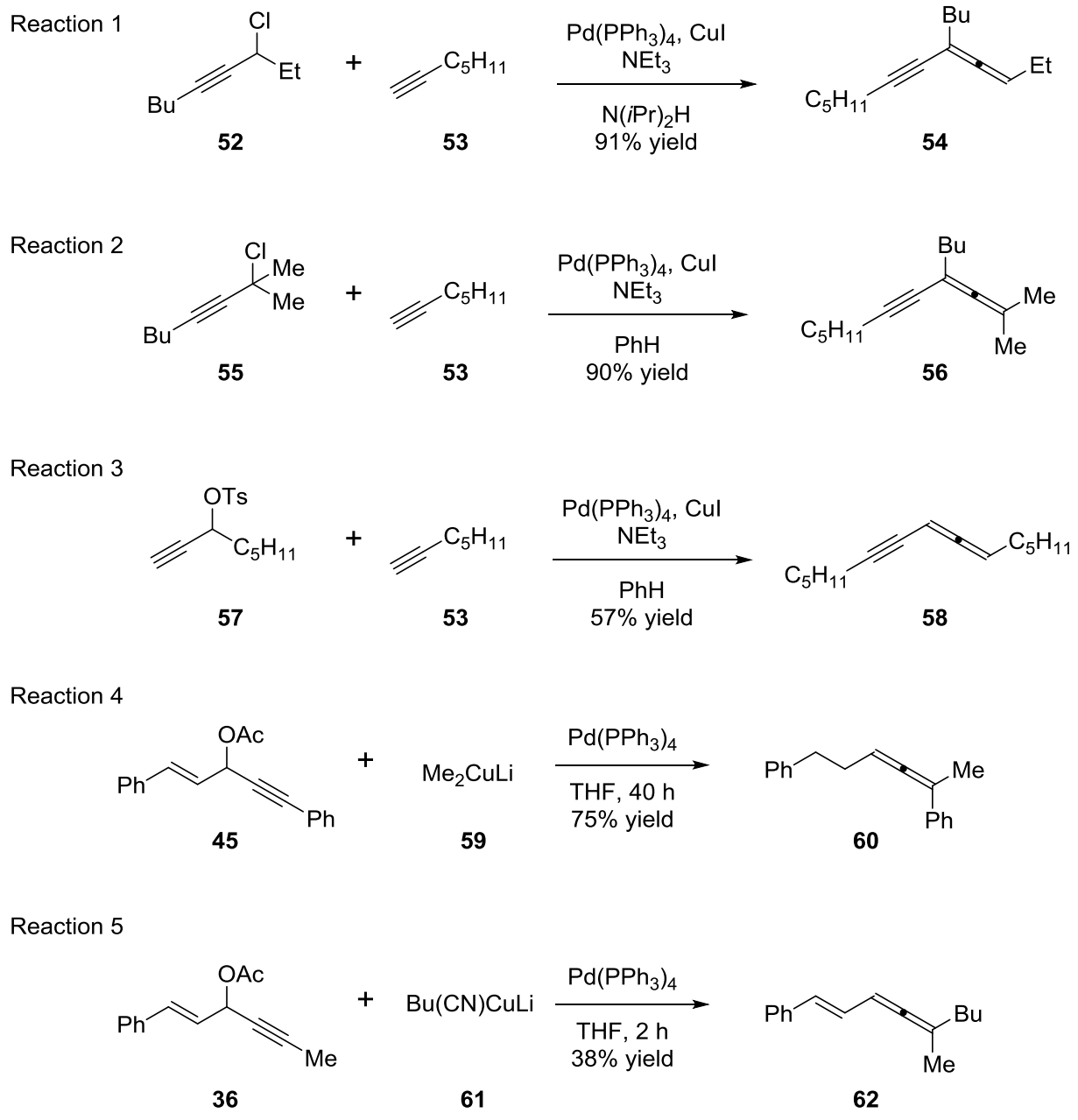
Organocuprates are another rich group of compounds which have found extensive use in transmetallation cross coupling processes, the best example of which is the Sonogashira coupling reaction.[13] Both Sonogashira type reactions and the use of a standard organocuprate are seen to be highly effective for the interception of palladium (II) allene species and the generation of substituted allenes (Scheme 12).[12b, 14] The bis-alkyl substituted propargyl halide **53** can be combined with a palladium catalyst and stoichiometric copper to give allene product **54** in excellent yield (reaction 1). The substrate scope of the reaction is quite good, tolerating trisubstituted propargyl chloride **55** and showing clean conversion to the fully substituted allene **56** (reaction 2). Propargyl tosylate **57** can also be used in this reaction, as can propargyl bromides, however, while both function as expected, the yields are somewhat lower than with

[13] (a) Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084-5121. (b) Schilz, M.; Plenio, H. *The Journal of Organic Chemistry* **2012**, *77*, 2798-2807. (c) Bakherad, M. *Appl. Organomet. Chem.* **2013**, *27*, 125-140.

[14] (a) Gueugnot, S.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 3853-3856. (b) Condon-Gueugnot, S.; Linstrumelle, G. *Tetrahedron* **2000**, *56*, 1851-1857.

the corresponding propargyl chloride (reaction 3). Both methyl **59** and butyl **61** organocuprates can be used for the cross coupling reaction (reactions 4, 5), giving the desired products **60** and **62** in good to modest yield.

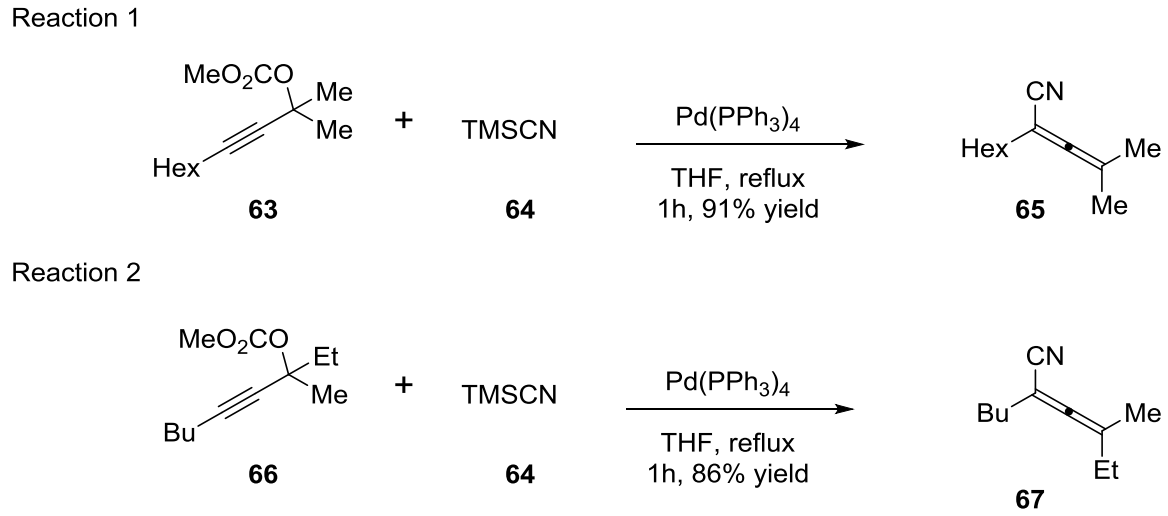
Scheme 12: Use of Organocuprates for Reaction with Palladium (II) Allenes



I.3.4: Transmetallation of Palladium (II) Allene Complexes using Silicon and Boron

A more recent development has involved the use of cyanosilanes to mediate the transfer of a cyano group to the allene via transmetallation from the silane to the palladium (II) allene complex (Scheme 13).[15] In both examples the cyano allene is isolated in excellent yield after only 1 hour.

Scheme 13: Use of Cyanosilanes

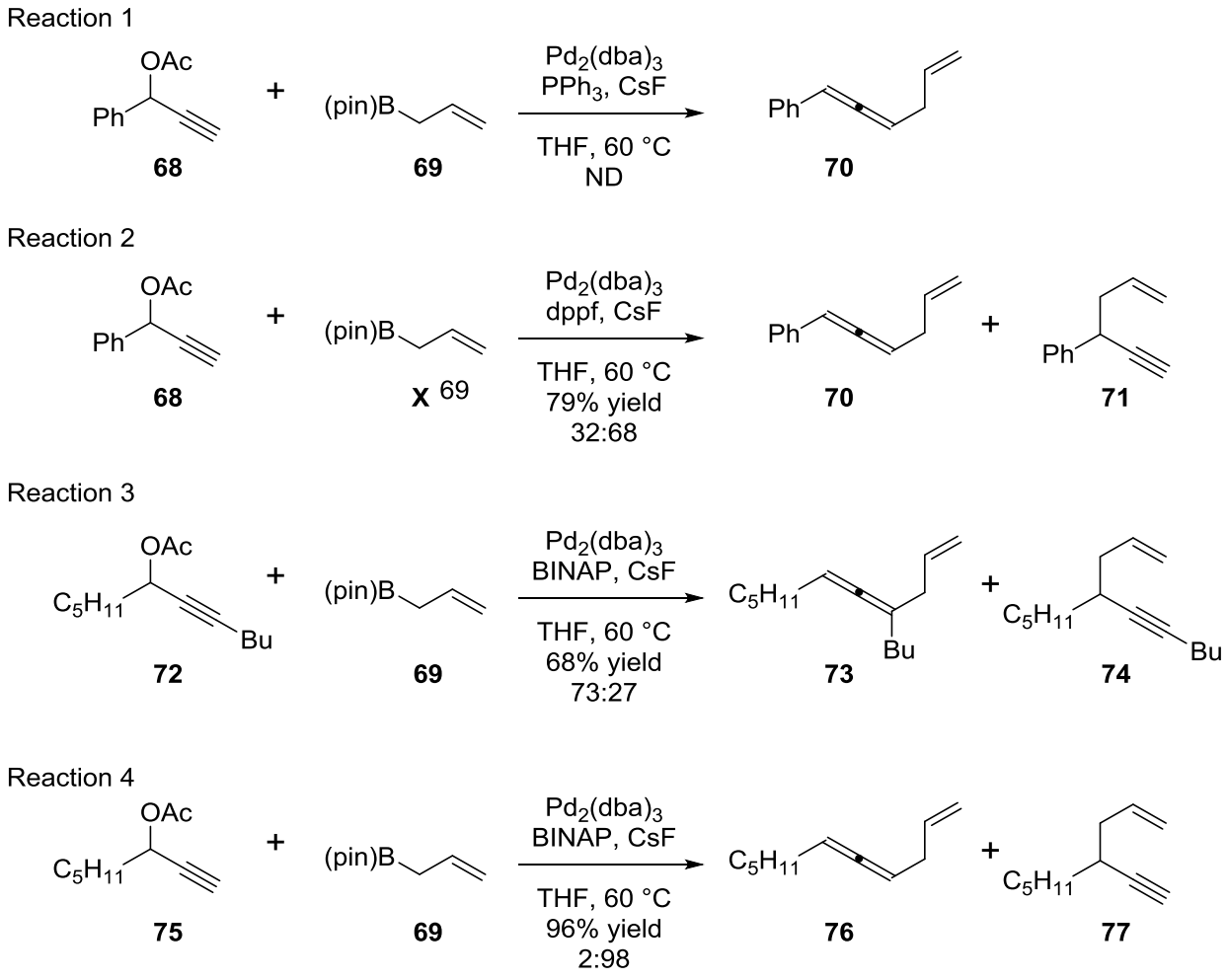


A final example of using transmetallation to trap palladium (II) allene intermediates involves the use of allyl boronates (Scheme 14).[16] When phenyl substituted propargyl acetate **68** was combined with allyl boronate **69** in the presence of a palladium catalyst, allylated allene product **70** was the only compound reported (reaction 1). However when a nearly identical reaction was carried out, with the only change being the ligand substitution of dppf for PPh_3, a 2:1 mixture of products formed, with the major product being allylated propargyl compound **71** (reaction 2). The sensitivity of this reaction to steric factors is clearly demonstrated in the next

[15] Tsuji, Y.; Taniguchi, M.; Yasuda, T.; Kawamura, T.; Obora, Y. *Org. Lett.* **2000**, *2*, 2635-2637.
[16] (a) Ma, S.; Zhang, A. *The Journal of Organic Chemistry* **2002**, *67*, 2287-2294. (b) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 8770-8773. (c) Zhang, L.; Li, X.; Liu, Y.; Zhang, D. *Chem. Commun.* **2015**, *51*, 6633-6636.

two examples. The the bis-substituted propargyl acetate is used a 3:1 mixture of products is formed, favoring allene **73** (reaction 3). However when there is no substitution at the terminal position of the alkyne, as in propargyl acetate **75**, formation of propargyl product **77** dominates the reaction (reaction 4).

Scheme 14: Palladium Catalyzed Reaction of Allyl Boronate with Propargyl Acetates

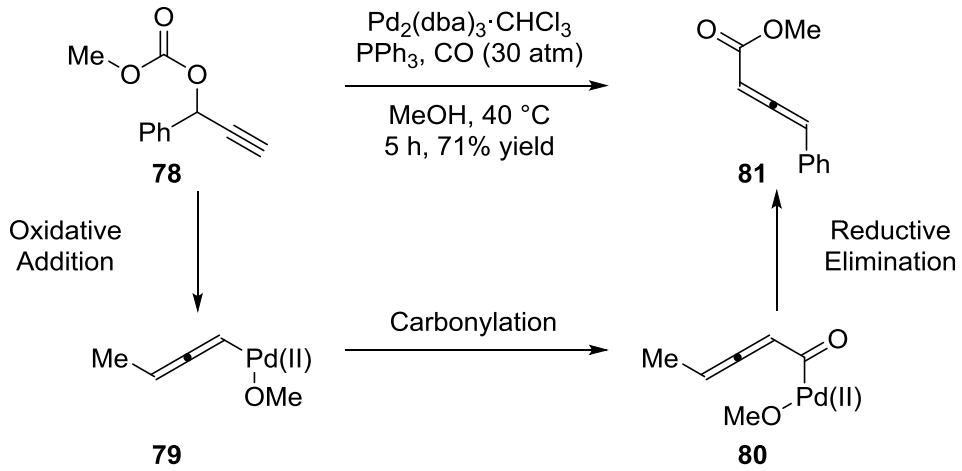


I.3.5: Carbonylation of Palladium (II) Allene Complexes

A different route for the use and functionalization of palladium allene intermediates is through reaction with carbon monoxide. It is well established that carbon monoxide can insert into a carbon – palladium bond, forming a new palladium carbonyl species which can undergo

reductive elimination and generate compounds containing an additional carbonyl moiety.[17] This type of reaction was first applied to palladium allene complexes by Tsuji and coworkers forty years ago.[18] After exposing propargyl methyl carbonate **78** to palladium under an atmosphere of carbon monoxide, carbonylated allene **81** was isolated in good yield after 5 hours. The proposed mechanism for this transformation involves initial oxidative addition, generating palladium (II) allene **79**, followed by carbonylation (inserting carbon monoxide into the palladium (II) carbon bond) and subsequent reductive elimination of complex **80** will give ester allene **81** (scheme 15).

Scheme 15: Carbonylation of Palladium (II) Allene Complex



Since this first report, the carbonylation of palladium allenes has received a significant amount of attention with a selection of different reactions shown (scheme 16).[17] When cyclohexyl propargyl methyl carbonate **82** was exposed to palladium under an atmosphere of carbon monoxide (15 atm), allen **83** formed following a similar mechanism as previously

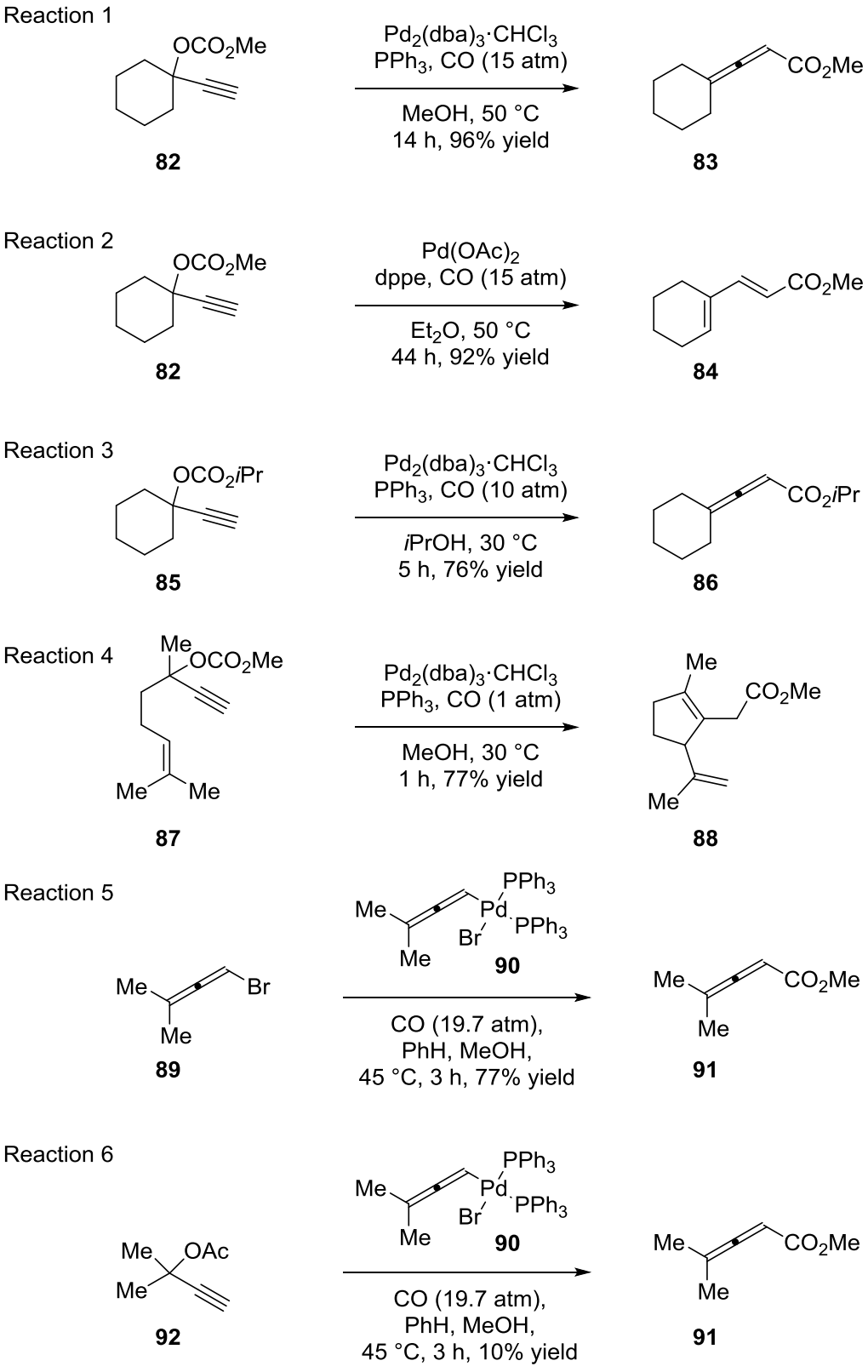
[17] (a) Tsuji, J.; Mandai, T. *J. Organomet. Chem.* **1993**, *451*, 15-21.(b) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114-4133. (c) Bakherad, M. *Appl. Organomet. Chem.* **2013**, *27*, 125-140. (d) Wu, X.-F.; Neumann, H.; Beller, M. *ChemSusChem* **2013**, *6*, 229-241. (e) Gadge, S. T.; Bhanage, B. M. *RSC Advances* **2014**, *4*, 10367-10389.
[18] Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 731-734.

described (reaction 1).[18, 19] Interestingly, when the palladium source and ligand were changed for the reaction of propargyl carbonate **82** under carbon monoxide, diene **84** was the sole isolated product (reaction 2). Presumably this diene arises from initial formation of allene **83**, followed by palladium mediated olefin isomerization,[20] generating observed diene **84**.[18]

When cyclohexyl propargyl iso-propyl carbonate **85** was exposed to the reaction conditions, with iso-propanol as solvent, the corresponding iso-propyl ester **86** is formed in good yield (reaction 3). When using an alkene tethered to propargyl carbonate **87,** after initial allene formation, an intramolecular Alder-Ene reaction[21] occurs, giving decorated cyclopentene **88** as the sole product (reaction 4).[18] Formation of allene ester **91** can be accomplished by carbonylation of allene bromide **89** using palladium (II) complex **90** as the pre-catalyst (reaction 5). Alternatively the same product can be formed by use of an appropriate propargyl acetate **92**, though the yield for the reaction is very poor (reaction 6).[22]

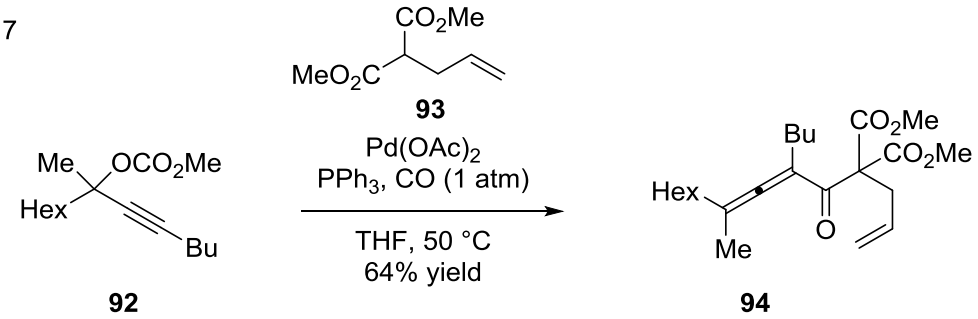
[19] For a more recent application of this chemistry see: (1) Chai, G.; Wu, S.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2011**, *133*, 3740-3743.
[20] (a) Sen, A.; Lai, T. W. *Inorg. Chem.* **1981**, *20*, 4036-4038. (b) Sen, A.; Lai, T. W. *Inorg. Chem.* **1984**, *23*, 3257-3258.
[21] (a) Alder, K.; Pascher, F.; Schmitz, A. *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1943**, *76*, 27-53. (b) Stephenson, L. M.; Mattern, D. L. *The Journal of Organic Chemistry* **1976**, *41*, 3614-3619. (c) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426-432. (d) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021-1050. (e) Paderes, G. D.; Jorgensen, W. L. *The Journal of Organic Chemistry* **1992**, *57*, 1904-1916.
[22] Trieu, N. D.; Elsevier, C. J.; Vrieze, K. *J. Organomet. Chem.* **1987**, *325*, C23-C26.

Scheme 16: Examples of CO Insertion of Palladium (II) Allene Complexes

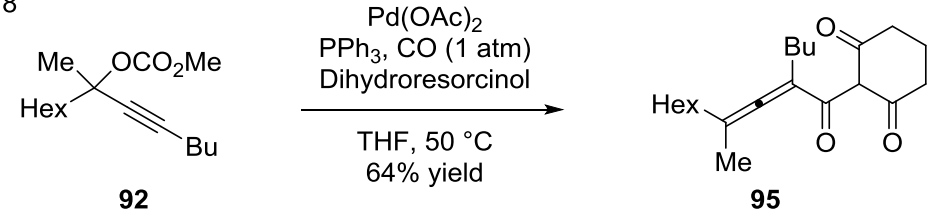


Scheme 16: continued

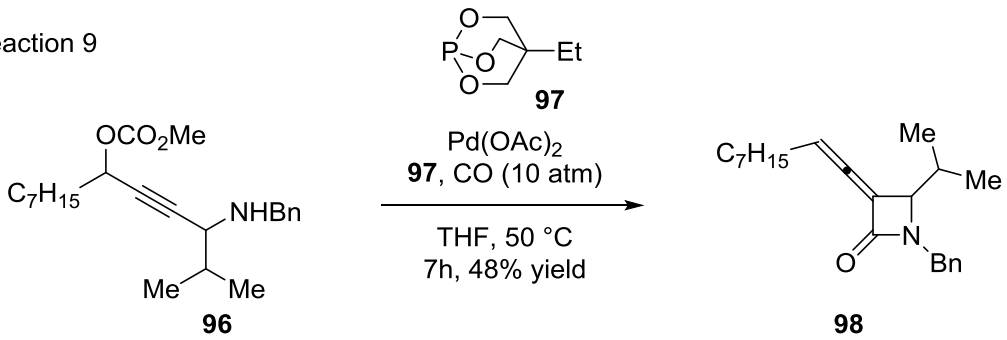
Reaction 7



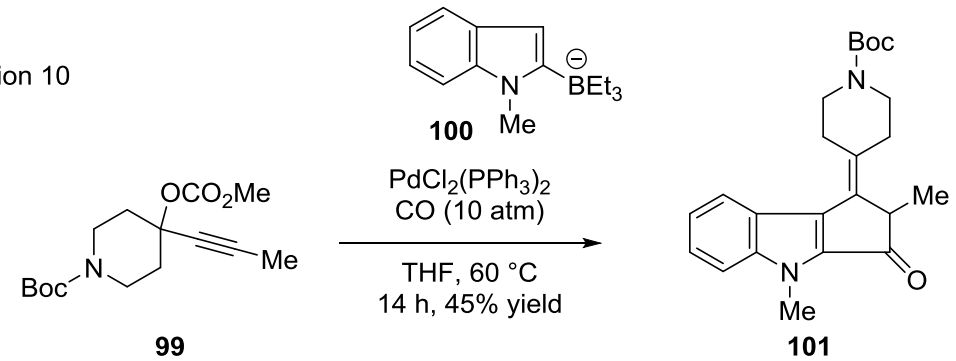
Reaction 8



Reaction 9



Reaction 10



This chemistry was also able to access ketones when a carbon nucleophile was substituted for an oxygen or amine nucleophile.[23] When 1,3-dicarbonyl compound **92** was combined with propargyl methyl carbonate **93** under carbonylative conditions ketone **94** was formed in good yield (reaction 7). A similar process was successfully employed when a cyclic 1,3-dicarbonyl was used, giving compound **95** in respectable yield (reaction 8). The mechanism for these reaction is similar to what has been previously described, with an additional step where the carbon nucleophile displaces methoxide prior to the reductive elimination step.[23]

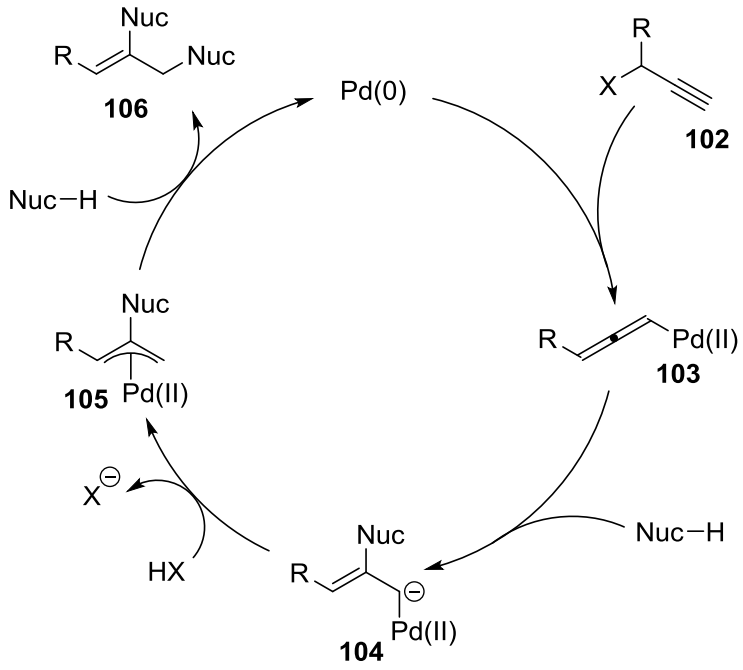
A common theme in organic chemistry is to render an intermolecular reaction intramolecular. Some advantages for doing so are that it often leads to interesting cyclic products, and due to the intramolecular nature of the reaction it is usually much faster than the intermolecular variant. This was demonstrated by Tsuji when he reported a carbonylative β-lactam formation procedure, starting from a propargyl carbonate bearing tethered nucleophilic amine **96** (reaction 9).[24] A more recent example by Ishikura nicely demonstrates both the synthetic utility of this reaction, and how relatively complex products can be quickly synthesized using this chemistry.[25] When fully substituted propargyl carbonate **99** is exposed to palladium it will presumably form the corresponding palladium (II) allene. After carbonylation the resulting complex can transmetallate with indole borane **100**. This will reductively eliminate, producing a transient indole carbonyl allene. The C3 position of indole will then add to the electrophilic central carbon of the allene, generating compound **101** after protonation and rearomatization of the indole core (reaction 10).[25]

[23] Mandai, T.; Kunitomi, H.; Higashi, K.; Kawada, M.; Tsuji, J. *Synlett* **1991**, *1991*, 697-698.
[24] Mandai, T.; Ryoden, K.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1991**, *32*, 7683-7686.
[25] Ishikura, M.; Uchiyama, H.; Matsuzaki, N. *Heterocycles*, **2001**, *55*, 1063-1070.

I.4: Nucleophilic Attack onto the Central Allene Carbon

Another method for utilizing the complexes formed from the reaction of a palladium (0) metal center and a propargyl compound is nucleophilic attack on the central carbon of the palladium (II) allene (Scheme 17). As with all allene compounds, the central carbon is electrophilic and prone to attack from nucleophiles.[26] Following oxidative addition of palladium (0) to propargyl compound **102** palladium (II) allene **103** will form. After nucleophilic attack onto the central allene carbon of palladium (II) complex **103**, the generated anion **104** is stabilized by the adjacent olefin and the palladium metal center. Following subsequent protonation of intermediate **104**, Pd-π-allyl complex **105** is formed, which can react with a second nucleophile and, after reductive elimination, provide compound **106** with regeneration of the palladium (0) catalyst.[1, 2]

Scheme 17: General Reaction of Palladium Allene with Nucleophiles at Central Carbon



[26] (a) Ma, S. *Pure Appl. Chem.* **2007**, *79*, 261-267. (b) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679-1688.

I.4.1: Use of Oxygen Based Nucleophiles

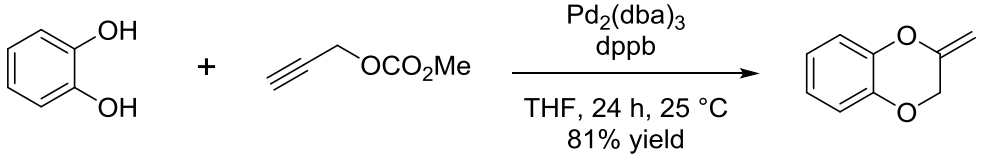
There have been a number of investigations into the use of oxygen as the primary nucleophile for the addition to the central allene carbon. One of the best studied systems employs the use of catechol (1,2-dihydroxybenzene) as both the primary and secondary nucleophile (Scheme 18).[27] The initial reaction shown has catechol **107** reacting with propargyl methyl carbonate **108** to give bicyclic compound **109** in good yield after 24 hours (reaction 1). Identical products were isolated when either propargyl carbonate **110** or **112** were used for the reaction, demonstrating a partially shared mechanism for regioisomeric propargyl carbonates (reactions 2, 3).

However, when phenyl substituted propargyl methyl carbonate **78** was utilized for the reaction, a 2:3 mixture of regioisomers **113** and **114** were isolated. The minor product **113** shows a similar substitution pattern to the previous examples with the phenyl group being adjacent to the second oxygen nucleophile of catechol **107**. The major product, compound **114**, was seen to consist solely of the Z olefin isomer, was formed in 60 % isolated yield (reaction 4). Finally the reaction of a propargyl carbonate with catechol **107** was rendered asymmetric through the use of a chiral ligand, generating **116** in excellent levels of yield and selectivity (reaction 5). In order to avoid issues of generating a mixture of products, as in reaction 4, propargyl methyl carbonate **115** was used. The advantage of this propargyl carbonate is that it does not offer the possibilities of generating regioisomers and is sufficiently sterically bulky to allow for high levels of enantioselectivity.

[27] (a) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025-9028. (b) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Eur. J. Org. Chem.* **2002**, *2002*, 1966-1971. (c) Dominczak, N.; Damez, C.; Rhers, B.; Labrosse, J.-R.; Lhoste, P.; Kryczka, B.; Sinou, D. *Tetrahedron* **2005**, *61*, 2589-2599.

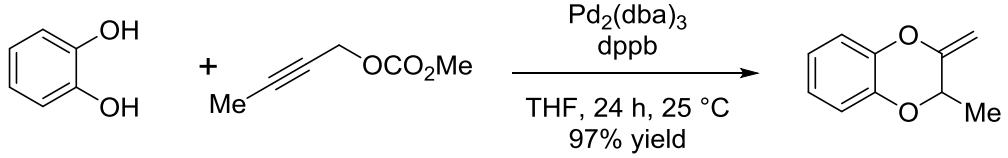
Scheme 18: Reaction of Propargyl Carbonates with Catechol

Reaction 1



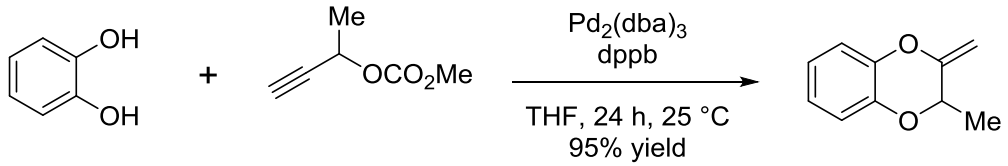
107 **108** **109**

Reaction 2



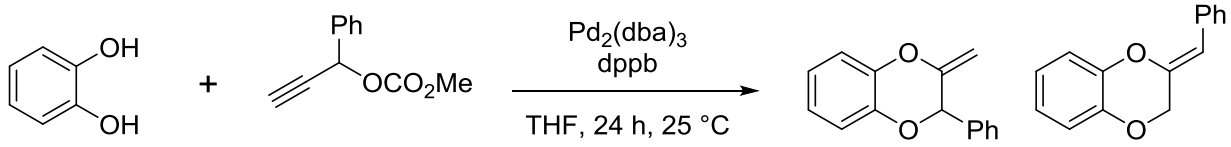
107 **110** **111**

Reaction 3



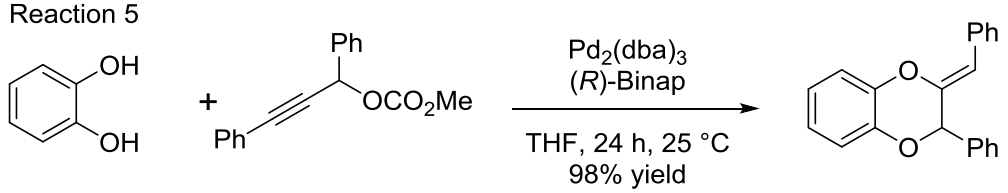
107 **112** **111**

Reaction 4



107 **78** **113** 40% yield **114** 60% yield

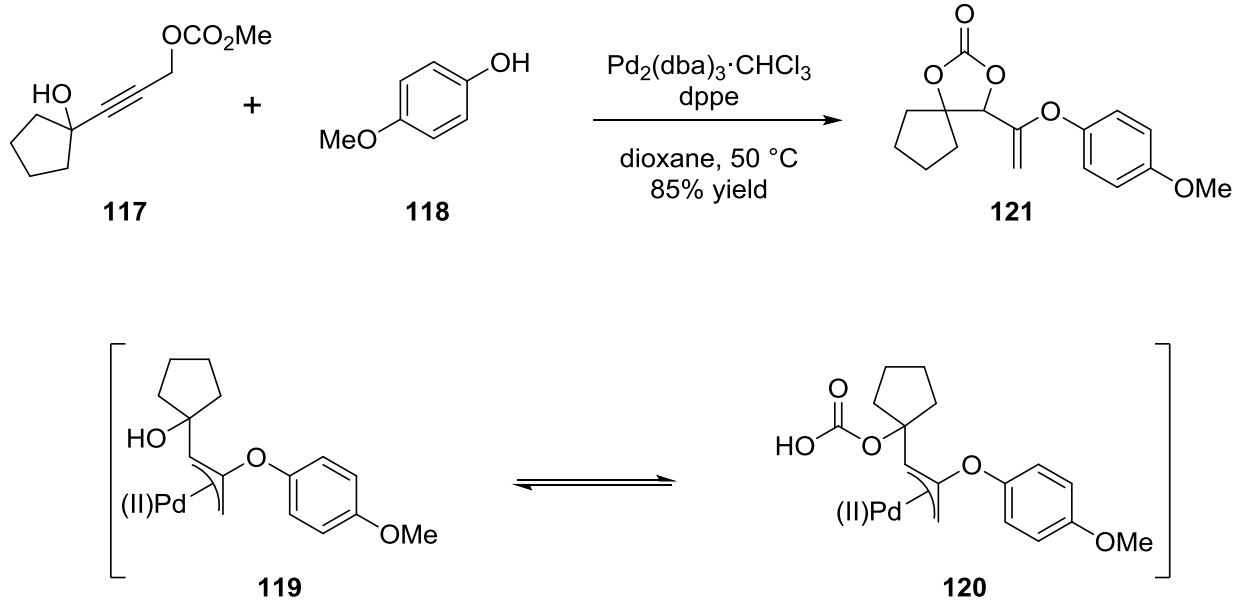
Reaction 5



107 **115** **116**

Another interesting example of using an oxygen nucleophile was reported by Yoshida and coworkers (Scheme 19).[28] By taking advantage of a carefully engineered propargyl carbonate **117**, addition of palladium (0) gives the corresponding palladium (II) allene complex. Following addition of phenol **118** to the allene, palladium-π-allyl species **119** forms. The free alcohol will form an equilibrium mixture with carbonic acid **120** by reacting with free carbon dioxide in solution which was liberated during the oxidative addition/decarboxylation step.[29] The transient carbonic acid/carbonate is then trapped intramolecularally by addition to the palladium-π-allyl species to give spirocyclized compound **122** in good yield. For some substrates the use of an atmosphere of carbon dioxide is required for good conversion to the cyclic carbonate products.

Scheme 19: Decarboxylation and CO_2 Recapture to Generate Carbonate Heterocycles



[28] (a) Yoshida, M.; Ihara, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 616-619. (b) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874-4881. (c) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron* **2005**, *61*, 4381-4393.

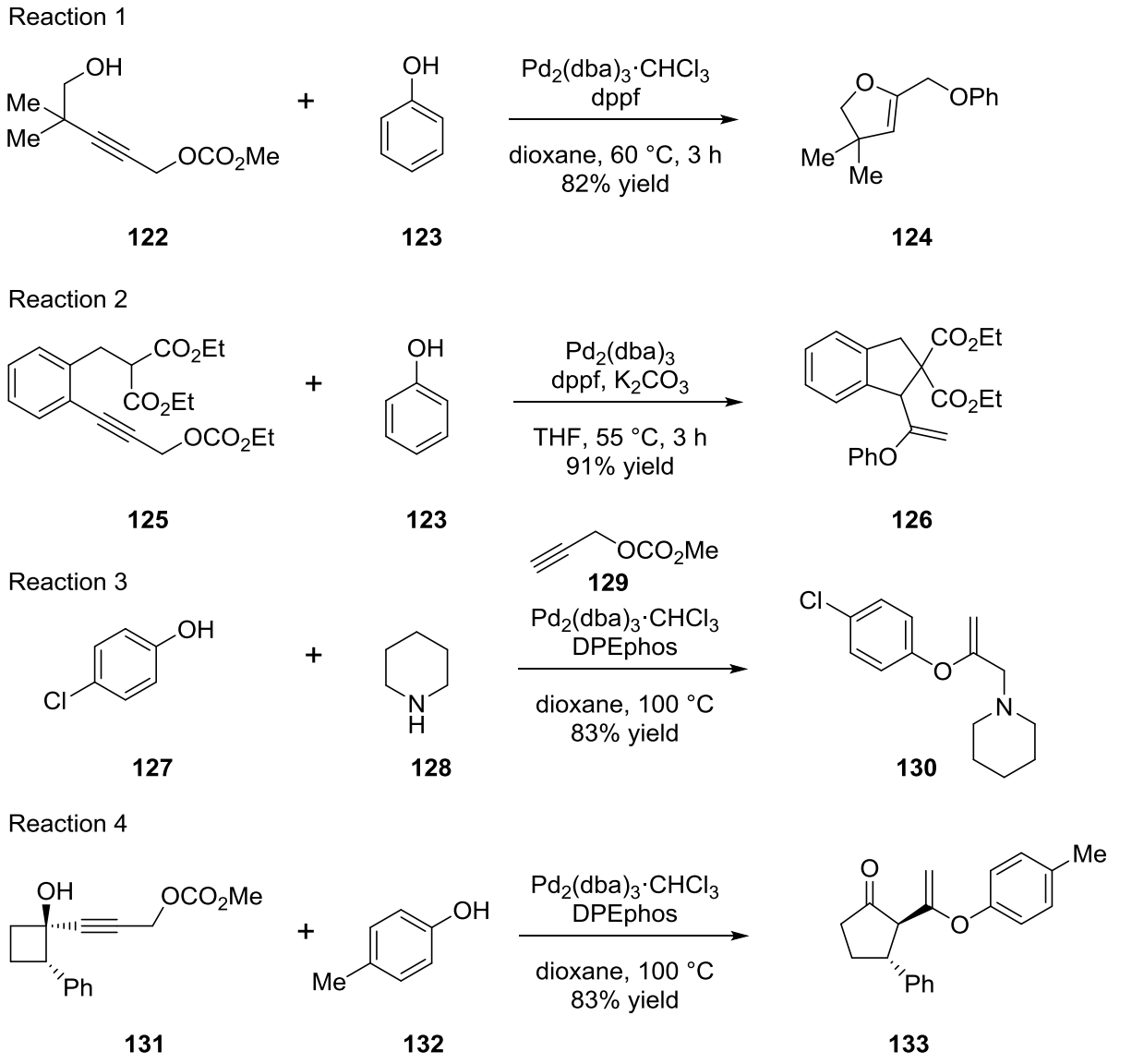
[29] Buytendyk, F. J. J.; Brinkman, R.; Mook, H. W. *Biochem. J* **1927**, *21*, 576-584.

Further developments into the use of oxygen nucleophiles for the initial bond forming reaction have led to a number of interesting transformations (Scheme 20). In a similar vein to what had been previously observed, the use of phenols as the initial nucleophile continues to prove to be a recurring theme. For alcohol tethered propargyl methyl carbonate **122,** after initial reaction with phenol **123,** ring closure is accomplished by reaction of the tethered alcohol with the palladium-π-allyl intermediate to give dihydrofuran **124** (reaction 1).[30] Following this success, Bi and coworkers published a paper which took advantage of a carbon based nucleophile tethered to propargyl ethyl carbonate **125** to afford the 6,5-fused bicyclic system **126** in good yield (reaction 2).[31]

In a pseudo three component reaction Koizumi et al. were able to combine phenol **127**, piperidine **128**, and propargyl methyl carbonate **129** to generate product **130**.[32] While all three components could simply be mixed together, in order to generate the desired compound **130** in good yield, sequential addition of the components was required (reaction 3). This selectivity between different nucleophiles is a constant trend in palladium allene chemistry and will continue to reoccur throughout this document. Finally when the cyclobutanol based propargyl methyl carbonate **131** was utilized, a net ring expansion was observed in product **133**. The reaction mechanism is hypothesized to proceed by initial addition of p-cresol **132** to the palladium (II) allene complex to give a palladium-π-allyl intermediate. This can then undergo a sigmatropic shift to reveal the ketone and reductively eliminate palladium (0), closing the catalytic cycle and producing observed compound **133** (reaction 4).

[30] Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 1861-1864.
[31] Bi, H.-P.; Guo, L.-N.; Gou, F.-R.; Duan, X.-H.; Liu, X.-Y.; Liang, Y.-M. *The Journal of Organic Chemistry* **2008**, *73*, 4713-4716.
[32] Nishioka, N.; Koizumi, T. *Tetrahedron Lett.* **2011**, *52*, 3662-3665.

Scheme 20: Additional Uses of Oxygen Based Nucleophiles



I.4.2: Use of Nitrogen Based Nucleophiles

A group of nucleophiles similar to the previously described oxygen nucleophiles are the nitrogen based nucleophiles. While the nucleophile may be a different heteroatom, in many regards the chemistry and mechanism of the reactions are identical (Scheme 21).

By tethering a sulfonamide to a propargyl benzyl alcohol **134** an intramolecular ring forming reaction can be promoted under palladium catalysis to give N-heterocycle **135** (reaction 1).[33] The reaction presumably proceeds through initial addition of the sulfonamide to the palladium (II) allene and subsequent formation of a palladium-π-allyl complex. In the absence of other nucleophiles, the formed palladium-π-allyl complex can undergo β-hydride elimination to generates diene **135** in moderate yield. Mori and coworkers went on to demonstrate that, with the use of similar scaffold **136** and the addition of methyl tolyl sulfonamide **137** to act as a second nucleophile, heterocycle **138** can be synthesized in excellent yield (reaction 2).[33] While the two nucleophiles are electronically similar, the fact that one is tethered to the propargyl carbonate means that it can out compete the other to react with the palladium (II) allene first.

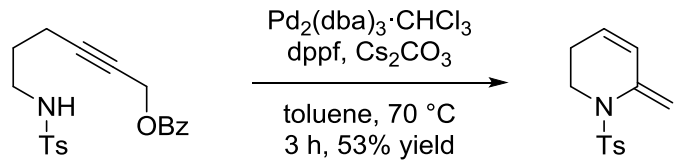
In a similar reaction to one which they had reported previously, Yoshida et al. noted that cyclobutanol based propargyl methyl carbonate **139**, upon treatment with palladium and in the presence of a suitable amide nucleophile **140**, could generate cyclopentanone **141** in modest yield (reaction 3).[34] In a final example, the reaction appears to be a simple addition of tethered secondary amide **142** over alkyne to give enamine **143** (reaction 4). However, the mechanism for this transformation is the same as for the previous examples. After oxidative addition of palladium to the propargyl carbamate **142**, nucleophilic attack of the central allene carbon by sulfonamide and subsequent ring closure by the carbamate oxygen will provide cyclic carbamate **143** in good yield.[35] While decarboxylation is expected to occur to some extent, as was noted

[33] Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499-1502.
[34] Yoshida, M.; Komatsuzaki, Y.; Nemoto, H.; Ihara, M. *Organic & Biomolecular Chemistry* **2004**, *2*, 3099-3107.
[35] (a) Alamsetti, S. K.; Persson, A. K. Å.; Jiang, T.; Bäckvall, J.-E. *Angew. Chem. Int. Ed.* **2013**, *52*, 13745-13750. (b) Alamsetti, S. K.; Persson, A. K. Å.; Bäckvall, J.-E. *Org. Lett.* **2014**, *16*, 1434-1437.

earlier, there can exist an equilibrium between the sulfonamide and the carbamate, with the latter being able to be trapped intramolecularly, generating **143**.

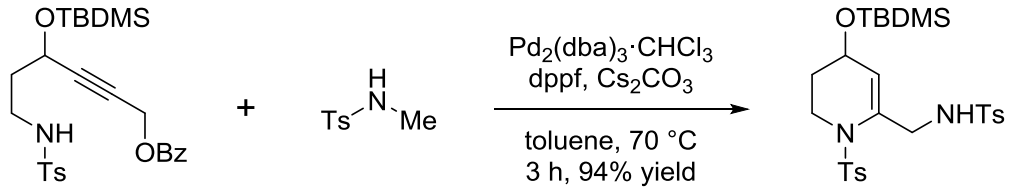
Scheme 21: Addition of Nitrogen Nucleophiles to Central Carbon of Palladium Allene

Reaction 1



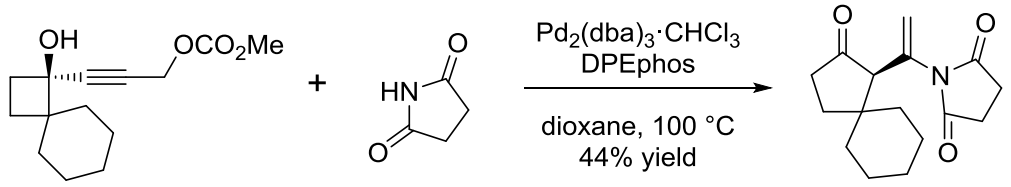
134 **135**

Reaction 2



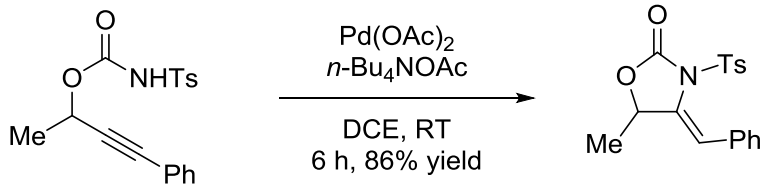
136 **137** **138**

Reaction 3



139 **140** **141**

Reaction 4



142 **143**

The manipulation and synthesis of indoles and their related compounds is of high importance to both organic and medicial chemists due to the prevalence of this privileged

heterocycle in pharmaceuticals[36] and natural products.[37] In light of their importance a number of methods have been developed to take advantage of the reactivity of propargyl carbonates with palladium catalysts in order to synthesize indoles directly (Scheme 22). Propargyl ethyl carbonate **144**, bearing a tethered phenyl amide nucleophile, reacts with piperizine **145** to give indole **146** through initial attack of the palladium allene by the tethered amide (reaction 1). The same reaction can be performed with an additional substitution on propargyl ethyl carbonate **147** to give a C2-substituted indole **148** (reaction 2).[38] When the reaction was run again, but in the presence of a carbon monoxide atmosphere (40 atm), the resulting carbonylated product **149** was isolated in modest yield after 24 hours (reaction 3).[39] Interestingly, the generated palladium allene was not intercepted by carbon monoxide to give a carbonyl allene product. Instead it appears that the palladium allene reacts first with the tethered amide and it is the palladium-π-allyl species which inserts carbon monoxide prior to reductive elimination.

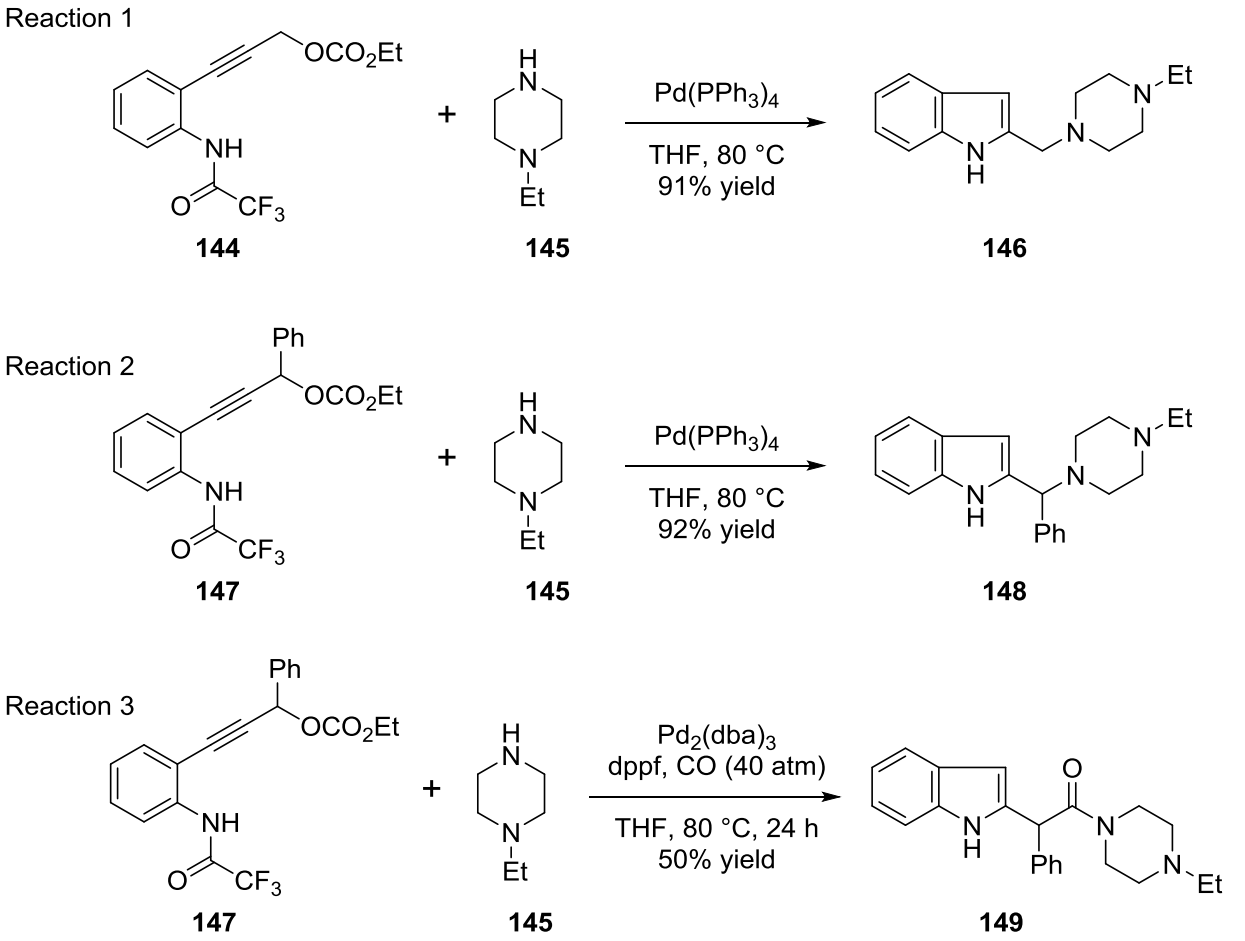
[36] (a) DeRosa, T. F. *Significant Pharmaceuticals Reported in US Patents*; Elsevier Ltd.: Oxford, UK, 2007. (b) Dhani, R.; Avinash, A.; Salenaagina, S. K.; Teja, M. V. S.; Mastanaiah, P.; Rathnam, P. R.; Silpa, V. C. *J. Chem. Pharm. Res.* **2011**, *5*, 519-523. (c) Barden, T. C.; *Top Heterocycle Chem.* **2011**, *26*, 31-46. (d) Rosse, G. *ACS Medicinal Chemistry Letters* **2012**, *3*, 953-953. (e) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A.; K.; Choi, E. H. *Molecules*, **2013**, *18*, 6620-6662.

[37] (a) Ihara, M.; Fukumoto, K. *Natural Product Reports* **1995**, *12*, 277-301. (b) Ihara, M.; Fukumoto, K. *Natural Product Reports* **1996**, *13*, 241-261. (c) Gribble, G. W.; Joule, J. A. *Progress in Heterocyclic Chemistry*; Elsevier Ltd.: Oxford, UK, 2007, Vol 18. (d) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chemistry – A European Journal* **2011**, *17*, 1388-1408. (e) Srivastava, A.; Pandeya, S. N. *International Journal of Current Pharmaceutical Review and Research* **2011**, *3*, 1-17. (f) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Natural Product Reports* **2013**, *30*, 694-752.

[38] (a) Ambrogio, I.; Cacchi, S.; Fabrizi, G.; Prastaro, A. *Tetrahedron* **2009**, *65*, 8916-8929. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Molinaro, C.; Verdiglione, R. *The Journal of Organic Chemistry* **2014**, *79*, 401-407.

[39] Cacchi, S.; Fabrizi, G.; Filisti, E. *Synlett* **2009**, *2009*, 1817-1821.

Scheme 22: Intramolecular Amide Addition to give C2-Substituted Indoles

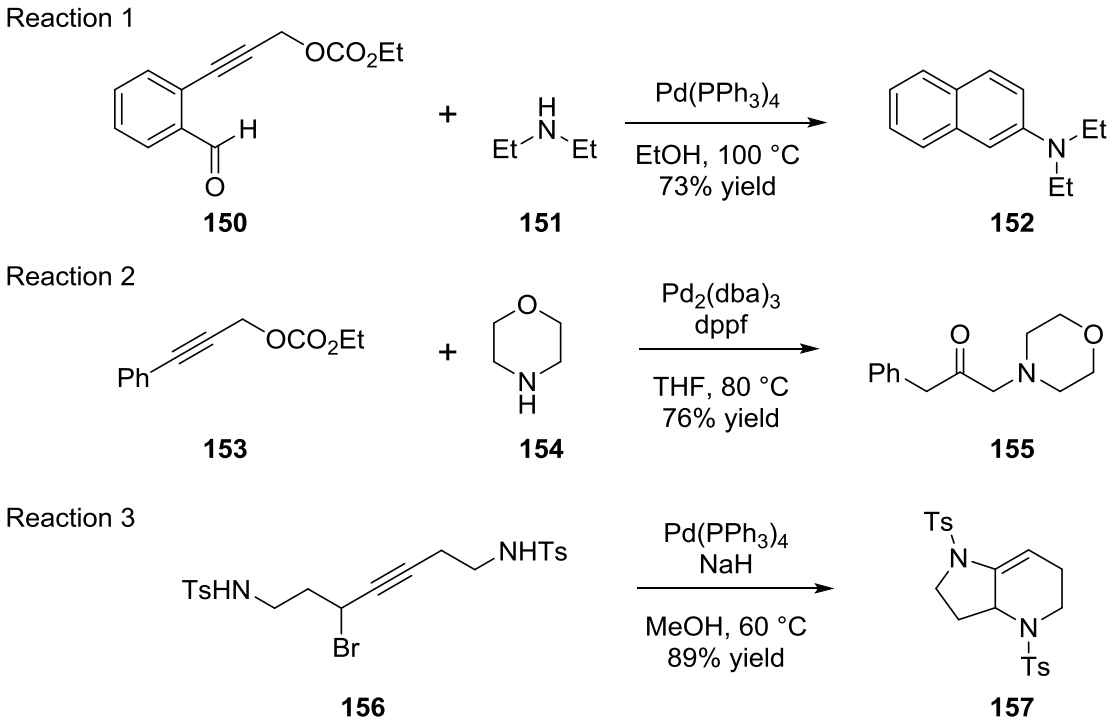


For several examples of reactions involving nitrogen addition to a palladium (II) allene the products generated are not immediately recognizable as having originated from such precursors (Scheme 23). With propargyl ethyl carbonate **150,** after oxidative addition of palladium (0) to give the palladium (II) allene, diethyl amine **151** adds to the central carbon as expected. However, instead of protonation of the generated anion and formation of a palladium-π-allyl, intramolecular addition of the anion to the aldehyde occurs. Following dehydration and aromatization naphthyl amine **152** is formed in good yield (reaction 1).[40] When propargyl ethyl carbonate **153** is combined with two equivalents of morpholine **154**, isolated product **155**

[40] Gou, F.-R.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 3418-3421.

corresponds to morpholine adding twice according to the standard mechanism. The generated enamine can tautomerize to the iminium cation, which in the presence of water can be hydrolyzed to give the observed ketone (reaction 2).[41] Another example involves propargyl bromide **156** which contains two tethered sulfonamide moieties (reaction 3). Upon oxidative addition of palladium (0) each of the sulfonamides react sequentially to give bicylic heterocycle **157** in excellent yield.[42] Selectivity for which order the sulfonamides add is irrelevant due to the careful construction of the substrate. Following oxidative addition and formation of the palladium (II) allene attack by either sulfonamide to the central allene carbon will generatae the same five membered palladium-π-intermediate.

Scheme 23: Unusual Structural Motifs



[41] Cacchi, S.; Fabrizi, G.; Filisti, E.; Goggiamani, A.; Iazzetti, A.; Maurone, L. *Organic & Biomolecular Chemistry* **2012**, *10*, 4699-4703.
[42] Ohno, H.; Okano, A.; Kosaka, S.; Tsukamoto, K.; Ohata, M.; Ishihara, K.; Maeda, H.; Tanaka, T.; Fujii, N. *Org. Lett.* **2008**, *10*, 1171-1174.

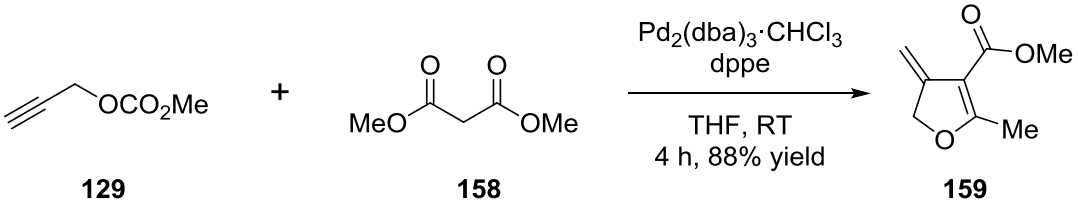
1.4.3: Use of Carbon Based Nucleophiles

While the use of hard carbon nucleophiles,[43] such as organozinc compounds, have been shown to provide allene products (Scheme 9), the use of soft carbon nucleophiles tend to proceed through reaction at the central carbon of the allene (Scheme 24).[44, 45, 3] The first report on using a soft carbon nucleophile was by Tsuji and coworkers in 1985 and demonstrated the use of 1,3-dicarbonyls as suitable bis-nucleophiles for reactions with propargyl carbonates.[46] When propargyl methyl carbonate **129** was combined with dimethyl malonate **158** under palladium catalysis, the compounds combined in a 1:1 ratio to give dihydrofuryl compound **159**, which isomerized to the furan upon acidic workup (reaction 1). While the reaction proceeded in good yield at room temperature with propargyl methyl carbonate **129** changing the leaving group to an acetate **160** or a bromide **161** required far harsher conditions and provided dihydrofuran **159** in significantly lower yields than compared to propargyl carbonate **129** (reactions 2, 3). When cyclic dicarbonyl **162** was used, expected furan **163** was isolated in good yield after acidic isomerization (reaction 4). By utilizing substituted propargyl methyl carbonate **110** and the deuterium labeled dimethyl malonate **164**, deutero-dihydrofuryl product **165** was isolated as the sole product (reaction 5). Using the information gained from the deutero labeled malonate experiment, a mechanistic rationale for this transformation is shown below (Scheme 25).

[43] (a) Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1-20. (b) Ho, T.-L. *Tetrahedron* **1985**, *41*, 3-86.
[44] For an explanation of conditions influencing inner or outer sphere reactions with palladium complexes please see the following paper and sources cited therein: Xiang, S.; Hoang, K. L. M.; He, J.; Tan, Y. J.; Liu, X.-W. *Angew. Chem. Int. Ed.* **2015**, *54*, 604-607.
[45] For general reviews on inner/outer sphere considerations see the following: (1) Rollick, K. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 1319-1330. (1) Lexa, D.; Saveant, J. M.; Schaefer, H. J.; Su Khac, B.; Vering, B.; Wang, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 6162-6177. (1) Torres, L. M.; Gil, A. F.; Galicia, L.; González, I. *J. Chem. Educ.* **1996**, *73*, 808.
[46] Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196-2198.

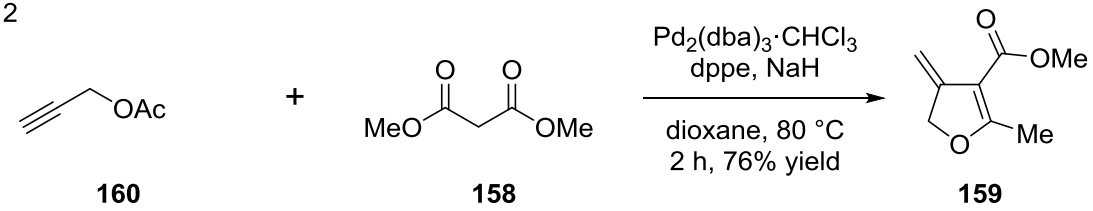
Scheme 24: Use of 1,3-Dicarbonyl Compounds as Bis-Nucleophiles

Reaction 1



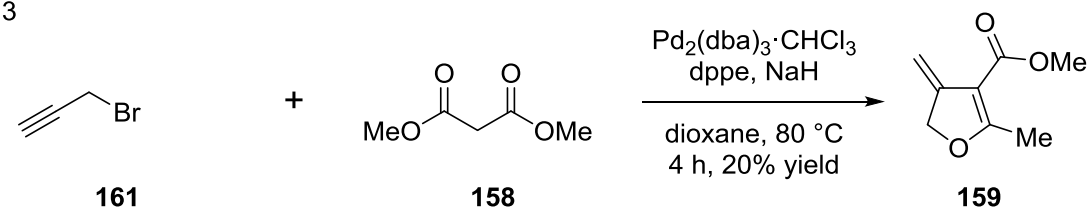
129 **158** **159**

Reaction 2



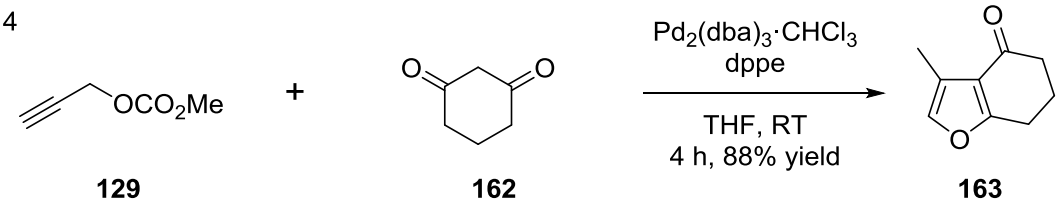
160 **158** **159**

Reaction 3



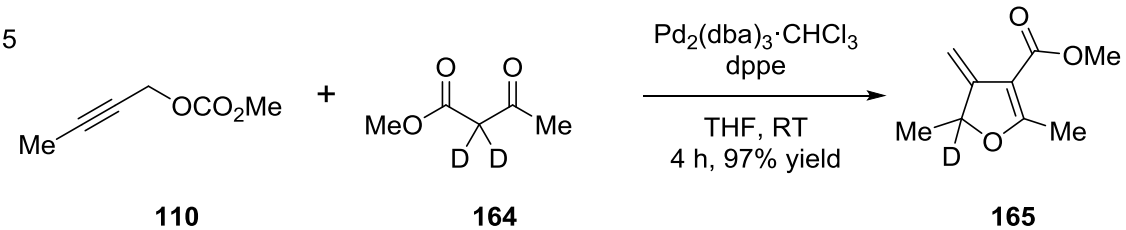
161 **158** **159**

Reaction 4



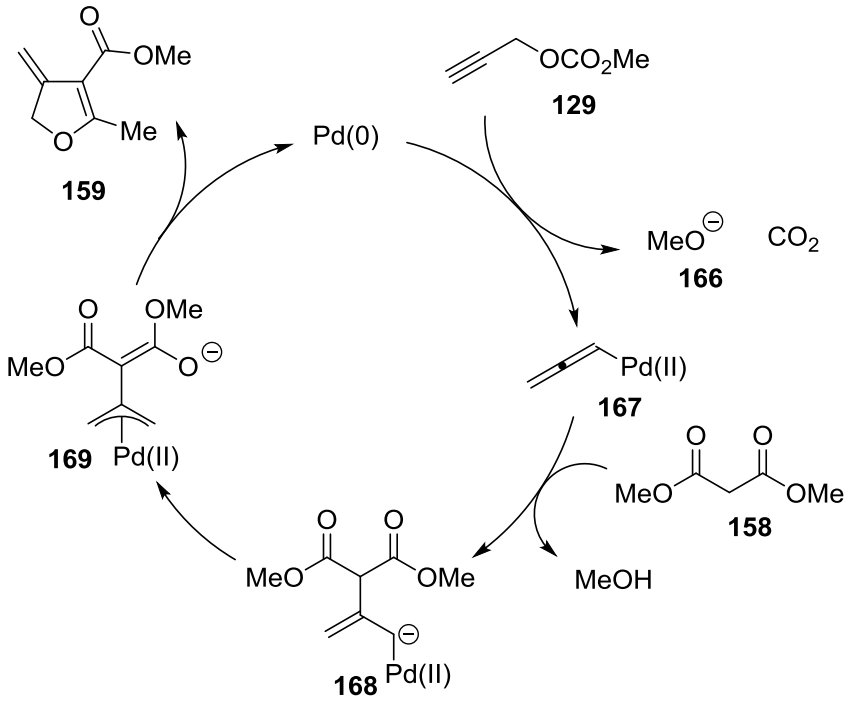
129 **162** **163**

Reaction 5



110 **164** **165**

Scheme 25: Mechanism for Dihydrofuran Synthesis

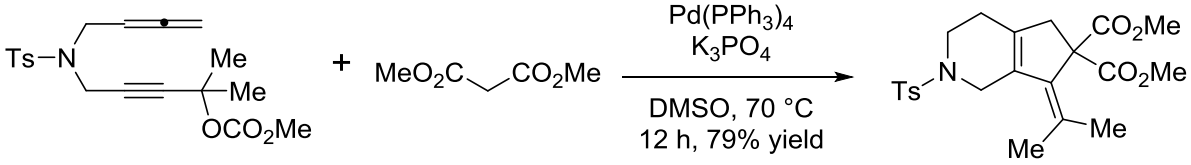


Following oxidative addition of palladium (0) to propargyl methyl carbonate **129** an equivalent of palladium (II) allene **167** and methoxide **166** are generated. Subsequent deprotonation of dimethylmalonate **158** by methoxide **166**, nucleophilic attack of the central carbon of palladium (II) allene **167** will give intermediate **168**. After protonation of the palladium carbene **168** and deprotonation of the alpha position of the malonate, palladium-π-allyl enolate intermediate **169** will form. Subsequent intramolecular attack by the oxygen will reductively eliminate palladium and give dihydrofuran **159**.[47]

[47] For a related study on synthesis of oxanes see: (1) Lifeng, G.; Xiyan, L. *Tetrahedron Lett.* **1990**, *31*, 111-114.

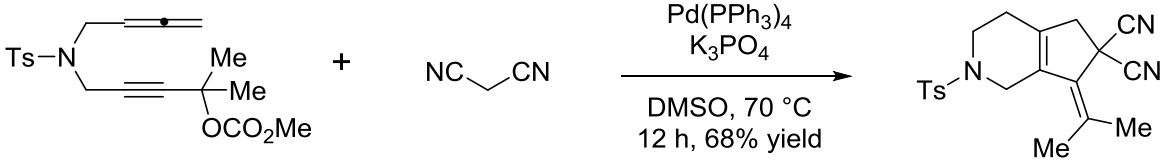
Scheme 26: Additional Examples of Carbon Nucleophiles

Reaction 1



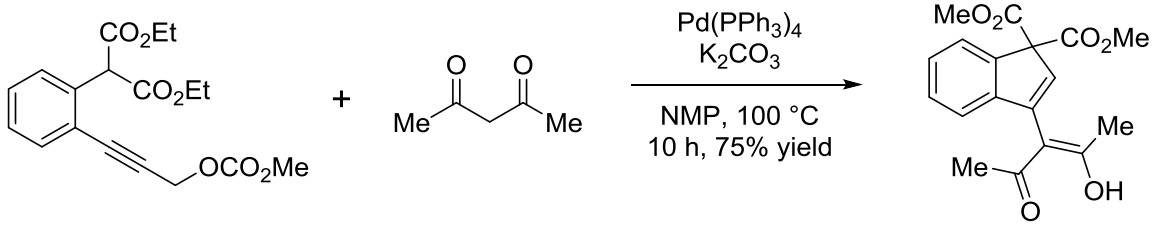
170 **158** **171**

Reaction 2



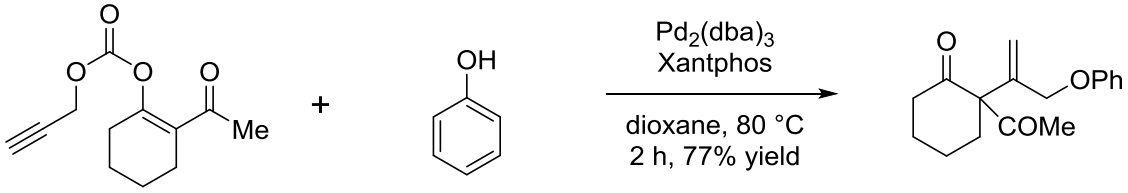
170 **172** **173**

Reaction 3



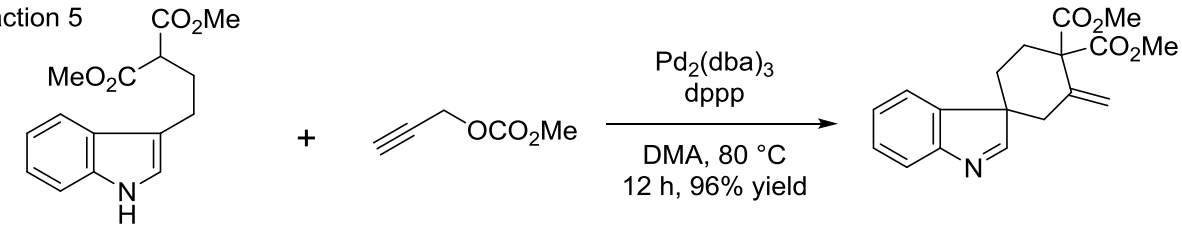
174 **175** **176**

Reaction 4



177 **123** **178**

Reaction 5



179 **129** **180**

Ma and coworkers have developed a nice method for the generation of cyclic compounds used palladium propargyl chemistry (Scheme 26, reaction 1).[48] By linking a propargyl carbonate to allene **170** they were able to effect two coupled cyclization reactions after addition of dimethyl malonate **158** to give **171** in good yield. The reaction proceeded well, not only for diketone nucleophiles by also with malononitrile **172**, a challenging substrate which has, so far, seen little utility in this field of chemistry (reaction 2). Work has also been done on the synthesis of indenes, by taking an appropriately prepared propargyl methyl carbonate **174** and reacting it with acetylacetone **175**. The substituted indene **176** is isolated in good yield, generating an all carbon ring system (reaction 3).[49]

Recently there have been two similar reports taking advantage of linking the carbon nucleophile to the propargyl through the carbonate (reaction 4).[50] After oxidative addition and decarboxylation of propargyl carbonate **177**, the formed enolate recombines with the palladium (II) allene. This step is followed by phenol **123** reacting with the palladium allyl species to give compound **178**.[50a] For a few examples there is good selectivity in respect to the order of addition, for the majority of compounds reported the selectivity is about 4:1 with the minor product corresponding to intial reaction with phenol **123**. Recently You et al. released a method for the synthesis of spirocyclized indolenines (reaction 5).[51] The spiroindolenine forms by initial addition of tethered malonate **179** to propargyl methyl carbonate **129** which, after ring closure at the indole center, generates spiroindolenine **180**.

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[48] Ye, J.; Ma, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 10809-10813.
[49] Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777-5780.
[50] (a) Schröder, S. P.; Taylor, N. J.; Jackson, P.; Franckevičius, V. *Org. Lett.* **2013**, *15*, 3778-3781. (b) Kenny, M.; Christensen, J.; Coles, S. J.; Franckevičius, V. *Org. Lett.* **2015**, *17*, 3926-3929.
[51] (1) Gao, R.-D.; Liu, C.; Dai, L.-X.; Zhang, W.; You, S.-L. *Org. Lett.* **2014**, *16*, 3919-3921.

I.5: Conclusion

The use of propargyl type compounds with palladium catalysis allows for the generation of a wide range of interesting compounds. The different possible reaction pathways for this family of transformations has inspired many different and creative ways to take advantage of the reactive intermediates formed. A key aspect of this chemistry is the ability for the chemist to select which reaction path to use for a given transformation by careful selection of reaction parameters. While there has already been a significant amount work done on investigating this set of palladium catalyzed reactions there is still more than enough room for additional work to be done over the coming years.

CHAPTER II

PALLADIUM CATALYZED C-3 FUNCTIONALIZATION OF INDOLE AND OXINDOLE BASED SUBSTRATES

II.1: Introduction:

The ubiquitous heterocycle indole[1] has long captured the attention and interest of synthetic chemists from many different groups and laboratories. This is due, in no small part, to indole's prevalence in a wide variety of biologically active natural products[2] and pharmaceutical agents.[3] Therefore it is of no surprise that there exists a pressing need for different and diverse methods for the functionalization of this fundamental heterocycle.[4] More specifically functionalization of the nucleophilic C3 position (Scheme 1) of indole, especially for C3 substituted indole, remains a desirable target.

---

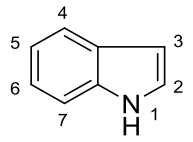
[1] (a) Saxton, J. E. *Indoles*; John Wiley and Sons, Inc.: New York, NY, 1983. (b) Sundberg, R. J. *Indoles*; Academic Press: London, UK, 1996. (c) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Malden, MA, 2000. (d) Maes, B. U. W.; Gribble, G. W. *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*; Springer-Verlag: Berlin, GE, 2010, Vol. 26.

[2] (a) Ihara, M.; Fukumoto, K. *Natural Product Reports* **1995**, *12*, 277-301. (b) Ihara, M.; Fukumoto, K. *Natural Product Reports* **1996**, *13*, 241-261. (c) Gribble, G. W.; Joule, J. A. *Progress in Heterocyclic Chemistry*; Elsevier Ltd.: Oxford, UK, 2007, Vol 18. (d) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chemistry – A European Journal* **2011**, *17*, 1388-1408. (e) Srivastava, A.; Pandeya, S. N. *International Journal of Current Pharmaceutical Review and Research* **2011**, *3*, 1-17. (f) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Natural Product Reports* **2013**, *30*, 694-752.

[3] (a) DeRosa, T. F. *Significant Pharmaceuticals Reported in US Patents*; Elsevier Ltd.: Oxford, UK, 2007. (b) Dhani, R.; Avinash, A.; Salenaagina, S. K.; Teja, M. V. S.; Mastanaiah, P.; Rathnam, P. R.; Silpa, V. C. *J. Chem. Pharm. Res.* **2011**, *5*, 519-523. (c) Barden, T. C.; *Top Heterocycle Chem.* **2011**, *26*, 31-46. (d) Rosse, G. *ACS Medicinal Chemistry Letters* **2012**, *3*, 953-953. (e) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A.; K.; Choi, E. H. *Molecules*, **2013**, *18*, 6620-6662.

[4] (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873-2920. (b) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608-9644. (c) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673-714. (d) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449-4465. (f) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215-PR283.

Scheme 27: Indole



181

II.1.1: Alkylation of Indoles

Early efforts into the alkylation of indole[5] found that after deprotonation with a strong base such as a Grignard reagent[6] or sodium amide, subsequent addition of a suitable electrophile would furnish the functionalized heterocycle. While this can be an effective method it suffers from several drawbacks. First, the use of harsh conditions to generate the nucleophilic indole anion is not amenable to many functional groups which can react either with the base or the indole anion. Additionally, the substrate scope for such transformation is generally rather limited, allowing for the use of only a few alkyl halides. A more recent example by Professor Stoltz and coworkers[7] demonstrated that C3 alkylation of the indole core can be realized under mild reaction conditions (Scheme 28). Presumably indole **182** reacts with benzyl chloride **183** in a S_N2 type mechanism[8] generating the iminium chloride. This iminium is susceptible to nucleophilic addition by the tethered arylsulfonamide, which ,following deprotonation by cesium carbonate, generates **184**.

---

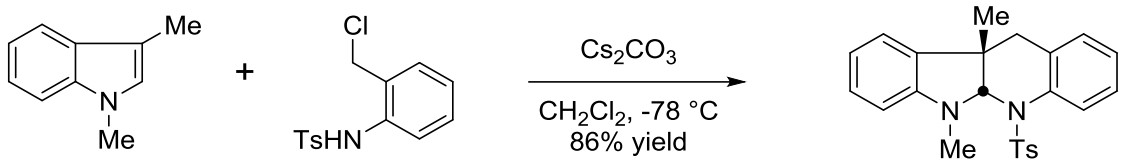
[5] (a) Hoshino, T. *Justus Liebigs Annalen der Chemie* **1933**, *500*, 35-42. (b) Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 838-840. (c) Spande, T. F.; Wilchek, M.; Witkop, B. *J. Am. Chem. Soc.* **1968**, *90*, 3256-3258.

[6] (a) Ashby, E. C. *Quarterly Reviews, Chemical Society* **1967**, *21*, 259-285. (b) Garst, J. F.; Soriaga, M. P. *Coord. Chem. Rev.* **2004**, *248*, 623-652.

[7] May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203-1205.

[8] Carey, F. A. *Organic Chemistry: Sixth Edition*; McGraw-Hill Companies, Inc.: New York, NY, 2006.

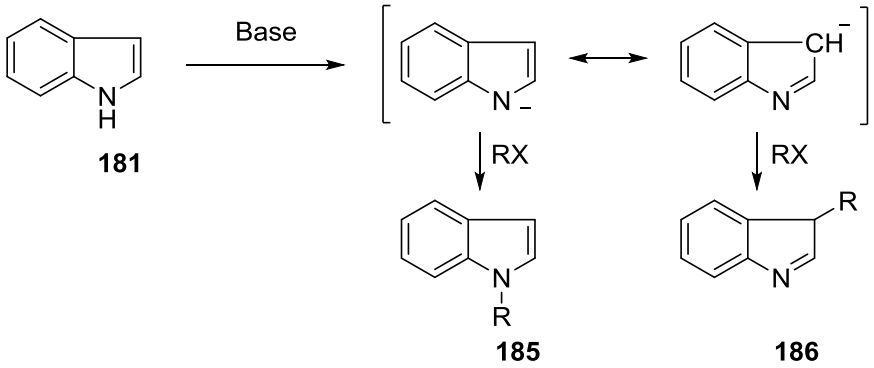
Scheme 28: Mild Indole Alkylation[7]



182 **183** **184**

However, even with this example of mild alkylation, similar examples are rare and often suffer from limited scope while the majority of methods for direct alkylation still make use of strong bases and must deal with the issues intrinsic to the use of such reagents. An additional and non-trivial concern with such methods involving deprotonation and alkylation is they often have issues of C vs N selectivity due to the ambiedent nature of indole nucleophiles (Scheme 29). These complications lead to the generation of a mixture of compounds composed of regioisomers and over alkylated products.

Scheme 29: C vs N Alkylation of Indoles

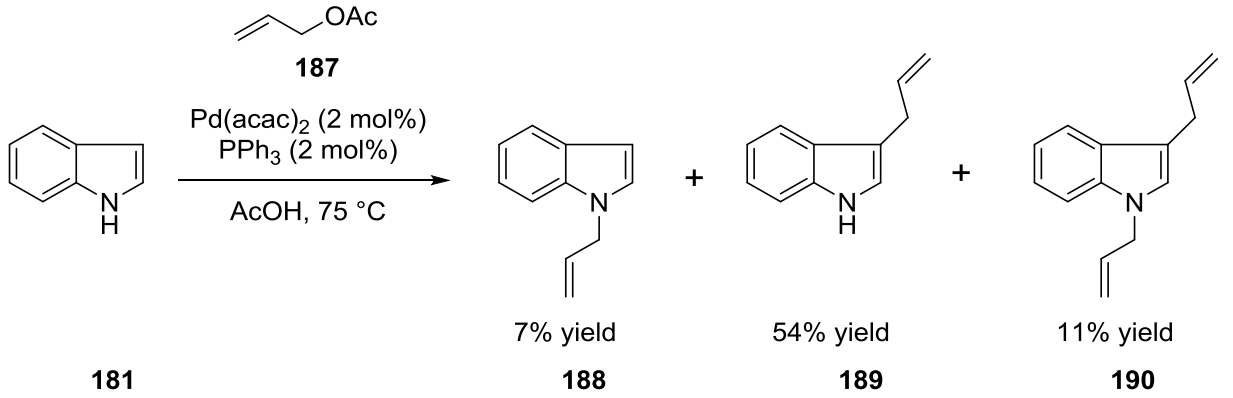


181 **185** **186**

II.1.2: Metal Catalyzed Functionalization of Indoles and Biological Significance

In an effort to overcome these limitations significant effort has been directed toward the adaptation of palladium catalyzed allylation chemistry[9] for the C3-allylation of C3-unsubstituted indoles.[10] With the pioneering work by Billups and coworkers[10a] it was demonstrated for the first time that palladium could catalyze the C3 allylation of indole (Scheme 30).

Scheme 30: Billups Allylation of Indole



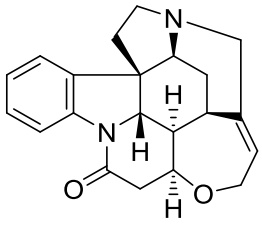
Subsequent developments into the allylation of C3-unsubstituted indoles would see the reduction of catalyst loading, increased selectivity and milder reaction conditions.[10] A far less

[9] (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140-145. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons, Inc.: New York, NY, 1996. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2944. (e) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley & Sons Ldt.: Chichester, West Sussex, England, 2004.

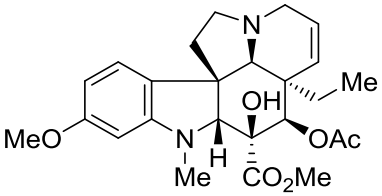
[10] For selected references see: (a) Billups, W. E.; Erkes, R. S.; Reed, L. E. *Synth. Commun.* **1980**, *10*, 147-154. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199-3202. (c) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424-1425. (d) Cheung, H. Y.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T. L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295-4298. (e) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2007**, *48*, 3963-3967. (f) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207-1210. (g) Kimura, M.; Tohyama, K.; Yamaguchi, Y.; Kohno, T. *Heterocycles*, **2010**, *80*, 787-797. (h) Cao, Z.; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H. *Org. Lett.* **2011**, *13*, 2164-2167. (i) Hoshi, T.; Sasaki, K.; Sato, S.; Ishii, Y.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2011**, *13*, 932-935. (j) Yuan, F.-Q.; Gao, L.-X.; Han, F.-S. *Chem. Commun.* **2011**, *47*, 5289-5291.

explored area is the allylation of C3 substituted indoles, a group of compounds which is simultaneously more appealing and more challenging due to the increased steric hindrance and the possibility of forming a new quaternary stereogenic center. In addition to the importance of this fundamental transformation is the synthetic utility it represents.

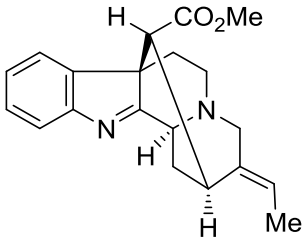
Scheme 31: Indole Alkaloids with a Fully Substituted C3 Center



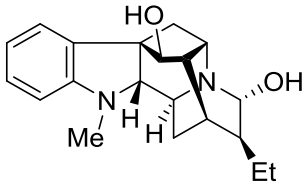
191
strychnine



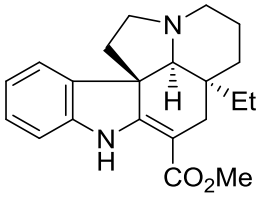
192
vindoline



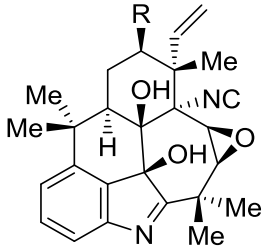
193
strictamine



194
ajmaline



195
tabersonine



196
ambiguine D: R=Cl
ambiguine J: R=H

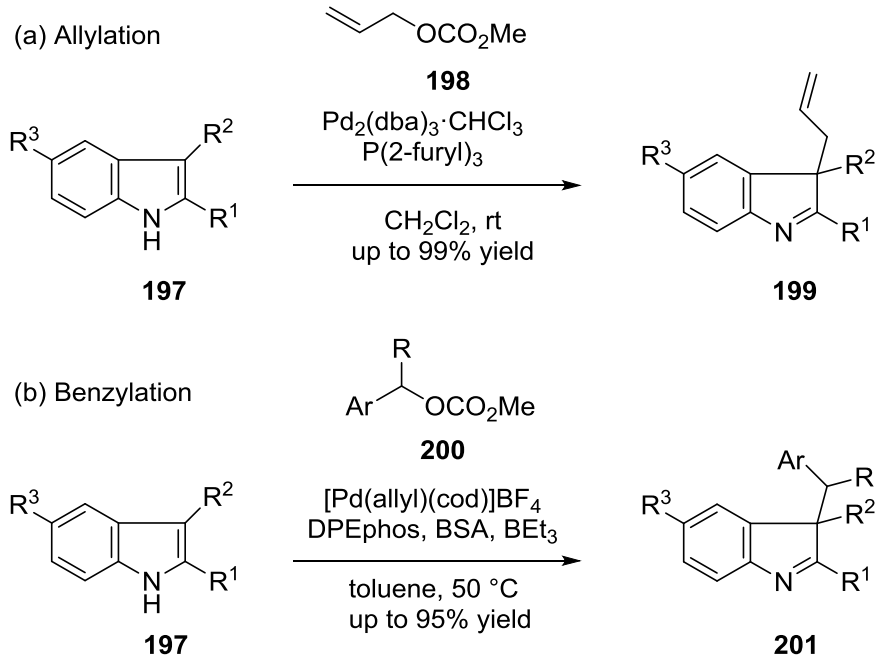
There exist myriad indole alkaloids bearing a quaternary center at the C3 position (Scheme 31), many of which are either known pharmaceutical agents or possess significant levels of bioactivity.[11] With this being the case, the developments of new, robust methods for the generation of such centers and molecules is of clear significance.

[11] Strychnine: Cannon, J. S.; Overman, L. E. *Angew. Chem. Int. Ed.* **2012**, *51*, 4288-4311. Vindoline: (1) Ando, M.; Buechi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880-6881. (b)

II.1.3: Palladium Catalyzed Intermolecular Allylation and Benzylation of Indoles

Prior to this work several excellent reports appeared in the literature demonstrating the C3 allylation of C3 substituted indole using various transition metal catalysts.[12] Of particular note is the work of Dr. Natsuko Kagawa and coworkers,[12c] who made use of an allyl methyl carbonate as the allyl source and demonstrated under a wide substrate scope under mild reaction conditions.

Scheme 32: Prior Work on Intermolecular Allylation and Benzylation



Kato, D.; Sasaki, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3685-3687. Strictamine: Schnoes, H. K.; Biemann, K.; Mokry, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *The Journal of Organic Chemistry* **1966**, *31*, 1641-1642. Ajmaline: Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998-7010. Tabersonine: (a) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998-7010. (b) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628-4641. Ambiguine: (1) Hillwig, M. L.; Zhu, Q.; Liu, X. *ACS Chemical Biology* **2014**, *9*, 372-377.

[12] (a) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592-4593. (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314-6315. (c) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381-2384. (d) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Chemical Science* **2013**, *4*, 97-102.

The field of palladium catalyzed C3 functionalized of indoles was further expanded with development of methods allowing for the analogous C3 benzylation of indoles by Dr. Ye Zhu and coworkers (Scheme 32).[13] A common theme among these methods is the use of two components for the reaction, an indole substrate bearing a free NH and an allyl or benzyl carbonate, alcohol or acetate. Given the ready access to *N*-alloc and *N*-Cbz protected indoles[14] it was hypothesized that such simple precursors could provide ready access to the same sort of C3 allylated and benzylated indoles in an intramolecular fashion. In this chapter the realization of the C3 functionalization of indoles from their *N*-alloc and *N*-Cbz protected precursors is described.[15, 16]

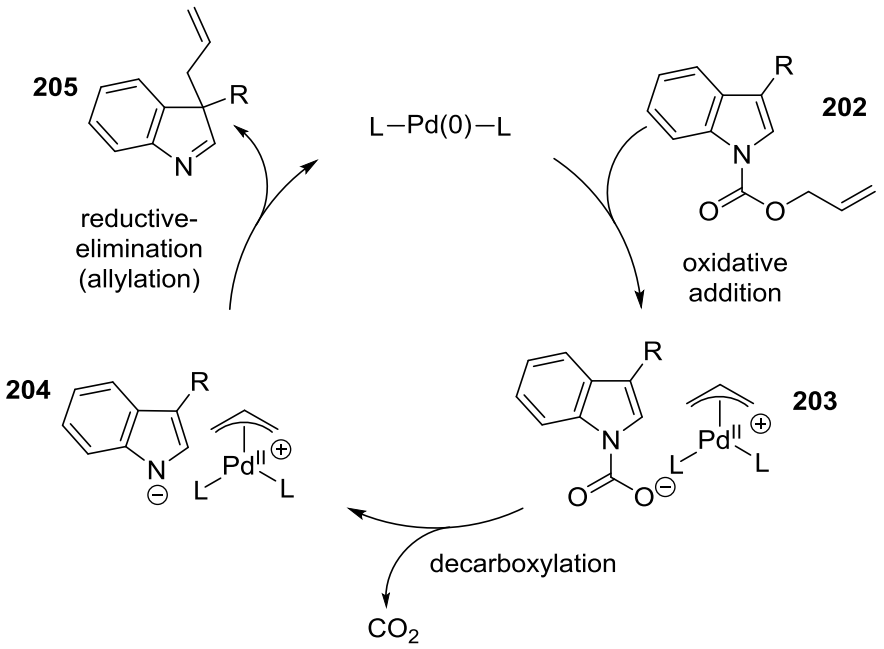
II.2: Palladium-Catalyzed Decarboxylative Allylation of *N*-Alloc Indoles

II.2.1: Mechanistic Rationale

When first examining the reaction conditions, *N*-alloc protected 2,3-dimethylindole **202** was chosen as the model substrate and prepared according to standard procedures.[13] It was envisioned that the reaction would proceed in line with current thinking on Tsuji-Trost allylation mechanisms (Scheme 33).[9]

[13] Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111-114.
[14] *N*-Alloc and *N*-Cbz indoles can be easily accessed by several methods: (a) Shingarova, I. D.; Sizova, O. S.; Preobrazhenskaya, M. N. *Chem Heterocycl Compd* **1983**, *19*, 1188-1191. (b) Weedon, A. C.; Zhang, B. *Synthesis* **1992**, 95-100. (c) Macor, J. E.; Cuff, A.; Cornelius, L. *Tetrahedron Lett.* **1999**, *40*, 2733-2736. (d) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039-10047.
[15] Montgomery, T. D.; Zhu, Y.; Kagawa, N.; Rawal, V. H. *Org. Lett.* **2013**, *15*, 1140-1143.
[16] Chen, J.; Cook, M. J. *Org. Lett.* **2013**, *15*, 1088-1091.

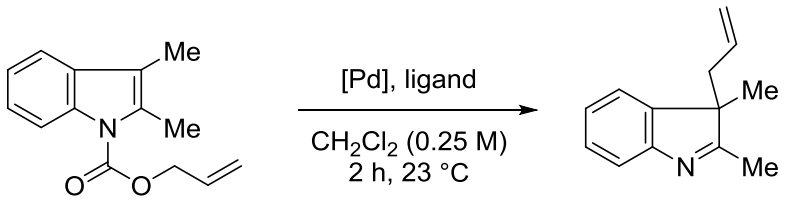
Scheme 33: Plausible Mechanism for Allylation of Indoles



With the initial oxidative addition by palladium (0) to allyl carbamate **202**, intermediate **203** will form, composed of the cationic Pd-π-allyl species and the indole carbamate anion. After loss of carbon dioxide and formation of indole anion **204**, subsequent addition of the indole nucleophile and reductive elimination will give allylated indolenine **205** with regeneration of the palladium catalyst. The advantage of this process over the intermolecular variant lies firstly in the activated indole nucleophile **203** or **204**, which should render the addition/allylation step much more facile. Secondly, the close proximity between the formed ions may keep the reactive intermediates in close proximity, again promoting a faster reaction rate. With this hypothesis in mind *N*-alloc indole **202** was synthesized and different reaction parameters were examined in order to optimize the proposed transformation (Table 1).

II.2.2: Optimization of Reaction Parameters

Table 1: Optimization of Decarboxylative Allyation



202 **205**

Entry	[Pd] (mol %)	Ligand (mol %)	Yield[a]
1	$Pd(PPh_3)_4$ (5.0)	None	78
2	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	PPh_3 (5.0)	84
3	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	P(*t*-Bu)$_2$biphenyl (5.0)	82
4	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	$P(4\text{-}C_6H_5F)_3$ (5.0)	73
5	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	P(2-furyl)$_3$ (5.0)	93
6	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	P(*t*-Bu)$_3$ (5.0)	5
7	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	dppe (5.0)	17
8	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	*rac*-BINAP (5.0)	56
9	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	P(OMe)$_3$ (5.0)	8
10	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	P(OPh)$_3$ (5.0)	2
11	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	P(2-furyl)$_3$ (15.0)	90
12	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	P(2-furyl)$_3$ (25.0)	89
13	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	P(2-furyl)$_3$ (2.5)	80
14[b]	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.5)	P(2-furyl)$_3$ (0.5)	95

[a]Isolated yield. [b]Experiment run at 3.5 M for 3 h.

Gratifyingly the initial conditions tried, using palladium-(tetrakistriphenylphosphine), gave the desired product **205** in good yield after two hours (entry 1). By changing the palladium source to $Pd_2(dba)_3{\cdot}CHCl_3$ a modest improvement to the yield was observed (entry 2). At this

point a range of different phosphine ligands were examined including electron rich aryl (entries 2,3), electron deficient aryl (entires 4,5), alkyl (entry 6), and bidentate phosphine ligands (entries 7,8).[17] Of the phosphine ligands examined the electron poor trifuryl phosphine (entry 5) gave the best conversion to desired indolenine **205**. When the even more electron deficient phosphite type ligands were used the reaction was almost completely shut down giving **205** in very poor yield (entries 9, 10). With trifuyl phosphine being the optimal ligand, different stoichiometries were explored. Increasing the ratio between ligand and palladium from 1:1 to 3:1 or 5:1 saw only a slight loss in yield (entries 11,12).

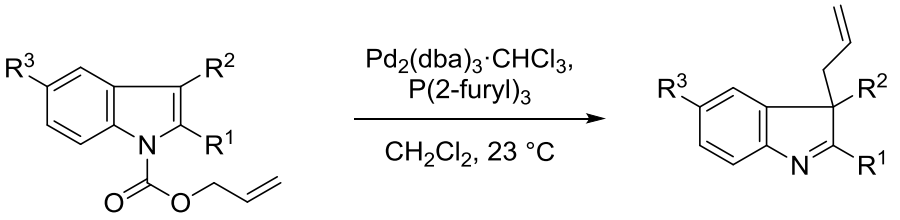
Interestingly, when the amount of ligand was decreased to half the molar amount of palladium a significant loss of yield was observed (entry 13). Taking advantage of the high solubility of the *N*-alloc substrate in dichloromethane the reaction concentration was raised from 0.5 M to 3.5 M, greatly accelerating the rate of the reaction. This increase to the reaction rate in turn allowed for the catalyst loading to be lowered to 0.5 mol percent,[18] an order of magnitude lower than had been previously described for the intermolecular variant.[19,20] With the decarboxylative allyation procedure fully optimized the substrate scope was then explored (Table 2).

II.2.3: Development of the N-Alloc Reaction Substrate Scope

After model substrate **202** *N*-alloc protected tetrahydrocarbazole **206** was subjected to the reaction conditions to give tricyclic indolenine **207** in excellent yield (entry 1). Next electron withdrawing **208** and electron donating **210** C5 substituted substrates were tested (entries 2,3).

[17] Hartwig, J. *Organotransition Metal Chemistry*; University Science Books: 2010
[18] 0.5 mole percent palladium equals 0.25 mole percent $Pd_2(dba)_3 \cdot CHCl_3$
[19] Prior examples of allylation of C3 substituted indoles were run at 5.0 mol % loading
[20] Cook and coworkers report the transformation at 1.0 mol % loading for a similar transformation

Table 2: Substrate Scope of Decarboxylative Allylation



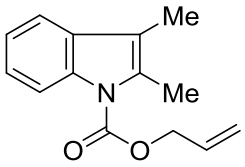
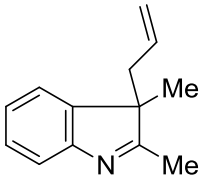
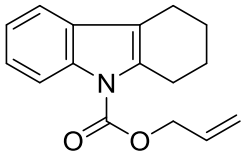
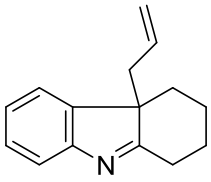
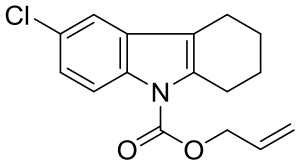
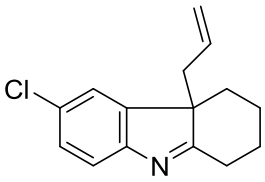
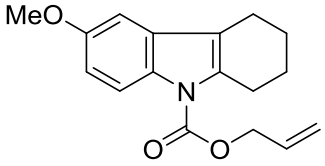
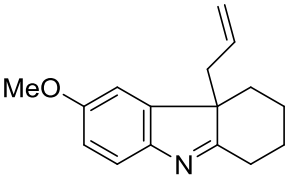
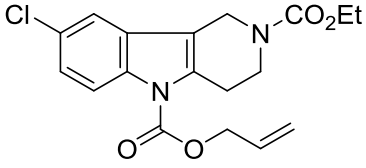
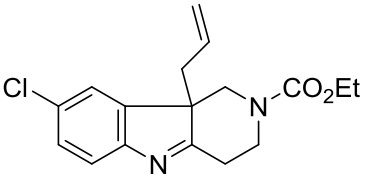
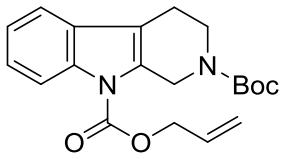
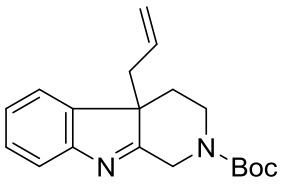
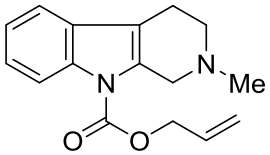
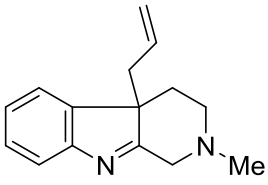
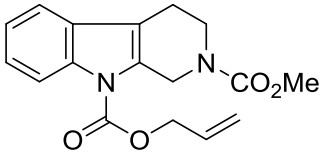
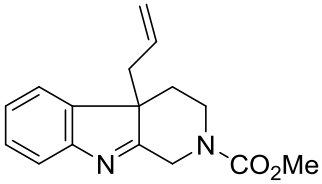
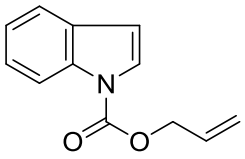
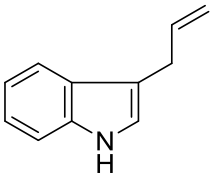
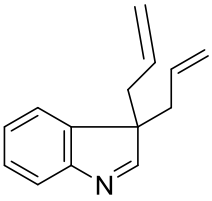
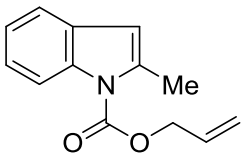
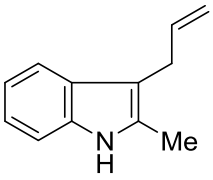
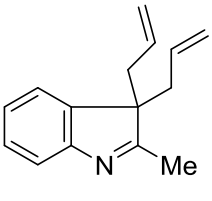
Entry	Substrate	Pd (mol %)	Time (h)	Yield (%)[a]	Product
1	 **202**	0.5	3	95	 **205**
2	 **206**	0.5	3	95	 **207**
3	 **208**	0.5	3	95	 **209**
4	 **210**	0.5	5	81	 **211**
5	 **212**	1.0	5	80	 **213**

Table 2. continued

6	 **214**	2.0	12	36	 **215**
7	 **216**	2.0	12	83	 **217**
8	 **218**	5.0	12	73	 **219**
9	 **220**	2.0	12	48/26	 **221**  **222**
10	 **223**	2.0	12	48/22	 **224**  **225**

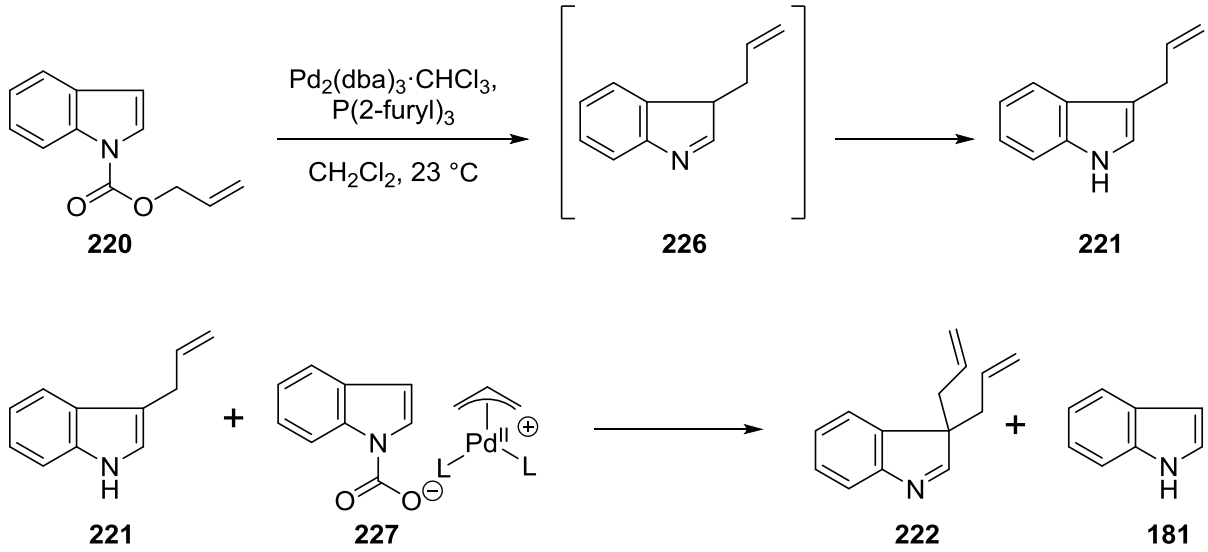
[a]Isolated yield.

While both functionalities were well tolerated, substrate **208**, bearing the electron withdrawing moiety, proved significantly more reactive. Next, *N*-alloc substituted β-

tetrahydrocarbonline **212** gave expected indolenine **213** in good yield (entry 5). When a series of γ-tetrahydrocarbolines (**214**, **216**, **218**) were examined *N*-methyl **216** and *N*-carbomethoxy **218** were well tolerated, giving expected indolenines **217** and **219** in very good yields. However when *N*-Boc γ-tetrahydrocarboline substrate **214** was exposed to the optimized conditions **215** was formed in only modest yield (entries 6-8). While the reaction conditions had worked very well for C3 substituted indoles, when C3 unsubstituted substrates (**220**, **223**) were used a mixture of products were obtained. In both cases, where the C2 group was either methyl or hydrogen, the two products were formed in about a 2:1 ratio where the desired product (**221** or **224**) is the major compound isolated (entries 9,10). This can be understood by looking at the likely mechanism for this transformation (Scheme 34).

II.2.4: C3-Unsubstituted Indole Substrates

Scheme 34: Bis-Allylation of C3-Unsubstituted Indoles Rationale

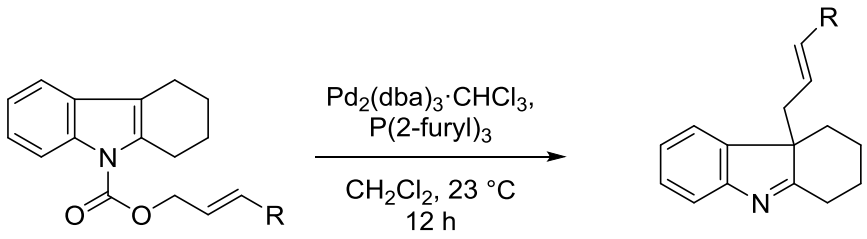


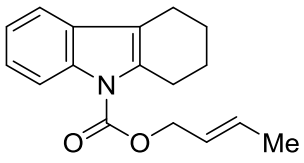
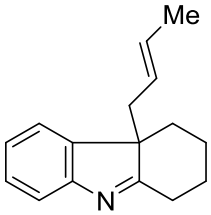
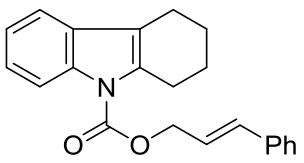
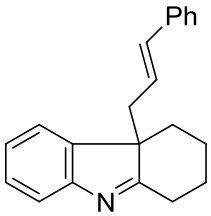
After decarboxylative allylation of indole **220** indolenine compound **226** is formed, it will immediately tautomerize to the aromatic C3 substituted indole **221**. At this point the palladium catalyst can react with another equivalent of *N*-alloc protected indole **220**, forming intermediate

227, comprising of either the indole or carbamate anion and the Pd-π-allyl cation. During this step the Pd-π-allyl can disassociate from the anionic portion and react with the C3 allylated indole **221**. This will result in the formation of one equivalent bis-allylated indolenine **222** and one equivalent indole **181** following decarboxylation and protonation. This hypothesis is well supported by the observed product distribution arising from the reaction of substrates **220** and **223**.

II.3: Palladium Catalyzed Crotylation and Cinnamylation of Indoles

Table 3: Use of Crotyl and Cinnamyl Carbamates



Entry	Substrate	Pd (mol %)	Yield (%)[a]	Product
1	 **228**	5.0	84	 **229**
2	 **230**	2.0	80	 **231**

[a]Isolated yield.

In addition to examining a range of substrates involving variations to the indole portion of the

substrate, the crotyl **228** and cinnamyl **230** indole carbamates were prepared to explore the effect of substitution on the allyl portion. As expected, both substrates provided the C3 substituted indoles in excellent yield. Additionally both **229** and **231** formed exclusively as the trans/E olefin isomer (Table 3).

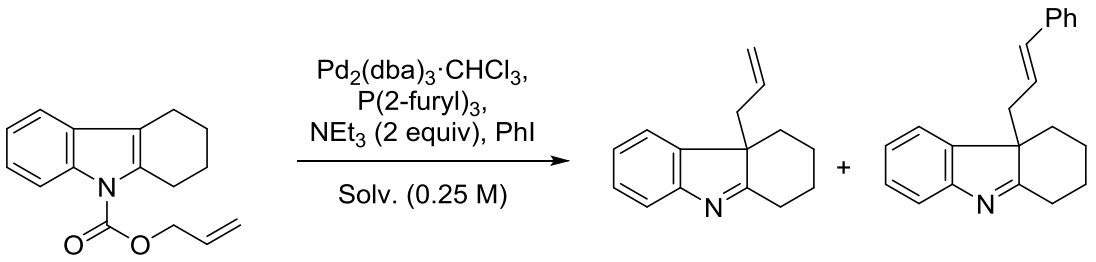
While the transformation from cinnamyl carbamate **230** into indolenine **231** was both facile and high yielding, the preparation of the cinnamyl carbamate **230** was not as trivial as the preparation of the other *N*-alloc protected indoles. In an effort to improve the process for forming cinnamylated product **231** it was hypothesized that a Mizoroki-Heck[21] reaction could be coupled to the initial Tsuji allylation reaction in a one pot procedure. It should also be noted that regardless of whether the allylation or Mizoroki-Heck reaction proceeded first, the theoretical product should remain the same (Table 4).

II.3.1: Development of One-Pot Protocol for Cinnamylation of Indoles

The initial attempt to realize this transformation involved using the previously optimized palladium and ligand combination. The standard conditions were then modified by the addition of iodobenzene and a base, triethylamine, in order to facilitate the Mizoroki-Heck reaction. Furthermore, the reaction temperature was increased for the Mizoroki-Heck reaction, and a higher boiling solvent was selected accordingly. After five hours the reaction was quenched and a mixture of C3-allyl indolenine **207** and C3-cinnamyl indolenine **231** were observed in approximately a 2:1 ratio (entry 1).

[21] (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581-581. (b) Heck, R. F.; Nolley, J. P. *The Journal of Organic Chemistry* **1972**, *37*, 2320-2322. (c) de Meijere, A.; Meyer, F. E. *Angewandte Chemie International Edition in English* **1995**, *33*, 2379-2411.

Table 4: Optimization of One Pot Protocol



206 **207** **231**

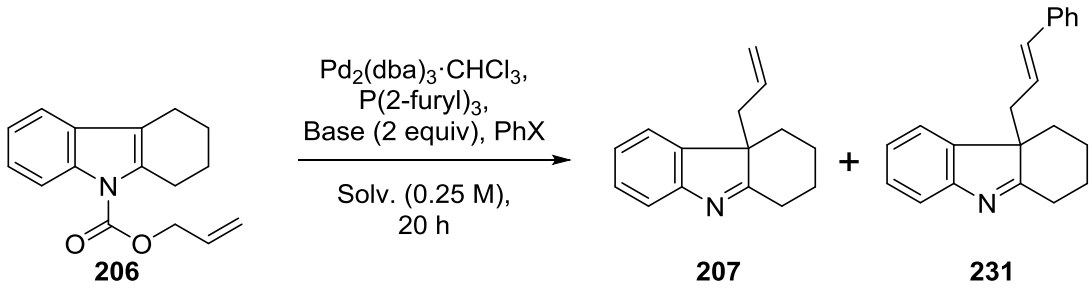
Entry	[Pd] (mol %)	Solvent	Temp (°C)	PhI (equiv.)	Time	Yield 207[a]	Yield 231[a]
1	10	MeCN	80	1.1	5	67	31
2	10	MeCN	80	1.5	5	55	42
3	10	MeCN	80	2.5	5	38	48
4	10	MeCN	80	2.0	20	8	86
5	10	MeCN	80	1.5	20	14	80
6	5	MeCN	80	1.5	20	40	60
7	2	MeCN	80	1.5	20	74	17
8	10	CH_2Cl_2	40	1.5	20	95	5

[a]NMR yield based on internal standard.

Capitalizing on this initial hit, the stoichiometry of iodobenzene was examined and the reaction time was increased to twenty hours (entries 2-4). By allowing a longer reaction time and using an increased amount of iodobenzene, the ratio between the products shifted to 1:10 in favor of desired cinnamylated compound **231**. Unfortunately the catalyst loading could not be lowered without greatly reducing the conversion to desired product **231** (entries 5-7). In an effort to determine which reaction progressed first, a lower temperature experiment was planned (entry 8). While the starting material was completely consumed, giving the C3-allyl product, very little of the C3-cinnamyl indolenine was observed, suggesting that allylation occurs before the

Mizoroki-Heck coupling. To further optimize the reaction, additional conditions were examined in an effort to improve the reaction yield (Table 5).

Table 5: Further Optimization of One Pot Protocol



206 **207** **231**

Entry	[Pd] (mol %)	Solvent	Base	Temp (°C)	PhX (equiv.)	Yield 207 [a]	Yield 231 [a]
1	10	MeCN	Na_2CO_3	80	PhI (2.0)	9	85
2	10	MeCN	K_2CO_3	80	PhI (2.0)	5	95
3	5	MeCN	K_2CO_3	80	PhBr (2.0)	49	48
4	10	Tol	K_2CO_3	80	PhI (2.0)	7	70
5	10	DMSO	K_2CO_3	80	PhI (1.1)	6	75
6	5	DMSO	K_2CO_3	100	PhI (1.4)	19	68
7	2	DMSO	K_2CO_3	100	PhI (1.4)	9	48
8	5	DMSO	K_2CO_3	100	PhBr (1.4)	16	68

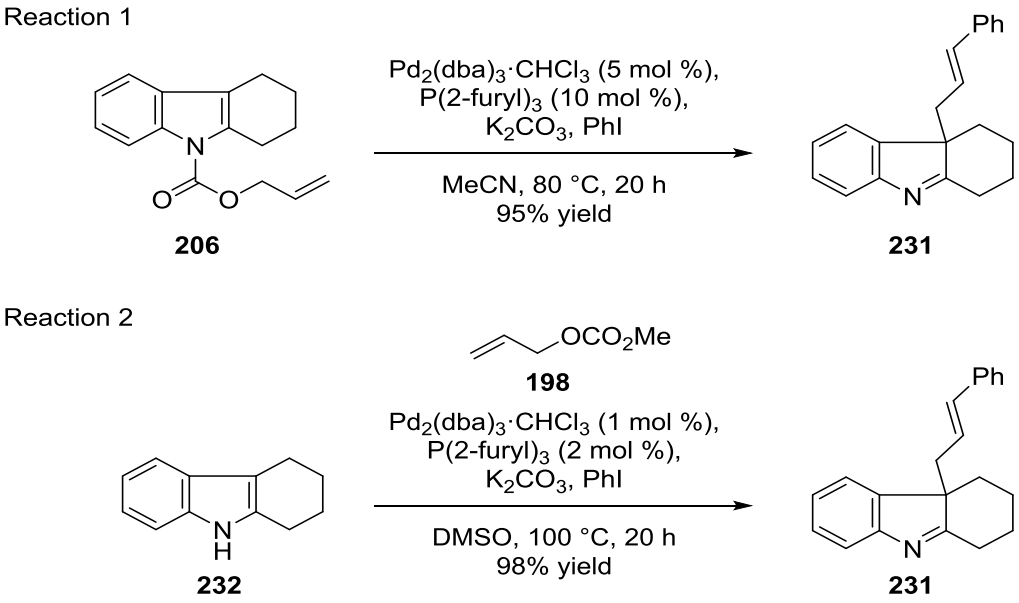
[a]NMR yield based on internal standard

By switching from triethyl amine to an inorganic base a substantitial increase in conversion to desired indolenine **231** was observed (entries 1,2). Further optimization examining different solvents, lower catalyst loadings, and substituting bromobenzene in lieu of iodobenzene failed to offer any improvement to the reaction yield (entries 3-8). With the optimized conditions (entry 2) in hand, a faster and easier route to C3-cinnamyl indolenine **231** was now available. Additionally when a slight modification to the optimized parameters was used, unprotected

indole **232** could be combined with allyl methyl carbonate **198** to give the C3-cinnamyl indolenine **231** in near quantitative yield in a three component, one pot reaction sequence (Scheme 35).

II.3.2: One-Pot Reaction and Three Component Reaction for Indole Cinnamylation

Scheme 35: Direct Access to Cinnamyl Products



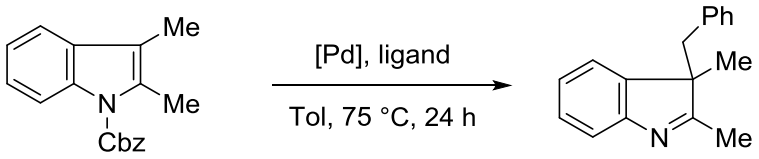
II.4: Palladium Catalyzed Benzylation of Cbz Protected Indoles

II.4.1: Background and Optimization of Reaction Parameters

With the completion of the work on the decarboxylative allylation of *N*-alloc indoles, the next step was to examine the analogous reaction involving *N*-Cbz indoles. The field of intermolecular C3 benzylation of indoles is far less explored than that of C3 allylation, with only one report appearing in the literature at the time of these studies.[13] While on first observation the *N*-Cbz protected indoles appear to be very different from the previous *N*-alloc indoles, at their core the principle thoughts behind the transformation are the same. Instead of an allyl group,

these substrates have a benzyl group which allows it to react according to a similar mechanism, in so far as both systems consist of a leaving group attached to a carbon adjacent to a π-system. At this point *N*-Cbz-2,3-dimethylindole **232** was prepared and the reaction parameters were optimized (Table 6). Initial efforts to achieve the benzylation (entry 1) gave only 8 % yield after 24 hours.

Table 6: Optimization of Decarboxylative Benzylation of N-Cbz Indoles



232 **233**

Entry	[Pd] (mol %)	Ligand (mol %)	Yield [a]
1	$Pd(PPh_3)_4$ (5.0)	None	8
2	$Pd(OAc)_2$ (5.0)	*rac*-BINAP (5.0)	4
3	Pd(allyl)Cp (5.0)	dppf (5.0)	29
4	Pd(allyl)Cp (5.0)	P(*t*-Bu)$_2$biphenyl (5.0)	15
5	Pd(allyl)Cp (5.0)	Xantphos (5.0)	72
6	Pd(allyl)Cp (5.0)	DPEphos (5.0)	85
7	[Pd(allyl)cod]BF_4 (5.0)	DPEphos (5.0)	75
8 [b]	Pd(allyl)Cp (5.0)	DPEphos (5.0)	95
9 [b]	[Pd(allyl)cod]BF_4 (5.0)	DPEphos (5.0)	93

[a]Isolated yield. [b]Experiment run for 5 h with addition of BEt_3.

In light of the difficulties of forming a Pd-π-benzyl species, due to the disruption of aromaticity, the reaction required heating to a significantly higher temperature than what had been previously required for the allylation chemistry. Palladium acetate with BINAP acting as

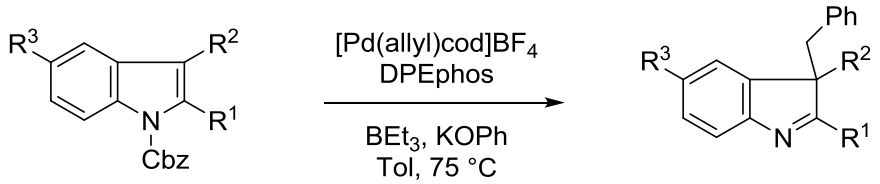
ligand gave only trace conversion to desired product **233** (entry 2). When another palladium (II) source was examined a significant improvement in yield was observed (entry 3). After screening several bidentate phosphine ligands DPEphos was found to give the best results (entries 4,7). It was found that the addition of triethyl borane was highly advantageous, decreasing the reaction time from 24 to only 5 hours, while still providing desired indolenine **233** in excellent yield. This observation of improved reaction rate was also made for the intermolecular reaction. The hypothesized rationale is that the Lewis acidic borane can stabilize some of the intermediates during the catalytic cycle, and so facilitate catalyst turnover.[13] Palladium (II) precatalysts Pd(allyl)Cp and [Pd(allyl)cod]BF_4 gave comparable levels of yield for the reaction. [Pd(allyl)cod]BF_4 was chosen as the palladium (II) precatalyst due to its ease of preparation and ease of handling compared to Pd(allyl)Cp.[22]

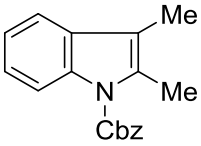
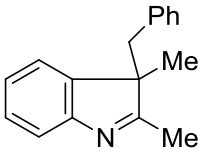
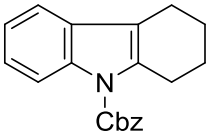
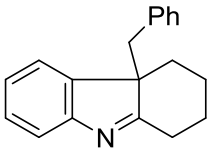
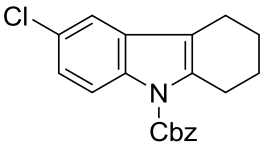
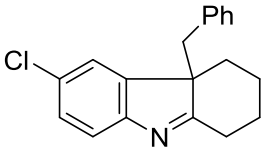
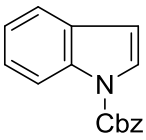
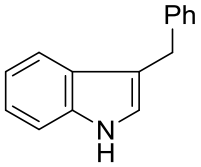
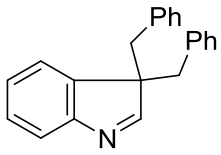
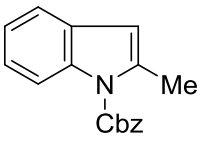
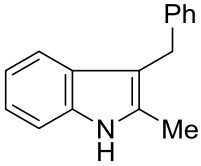
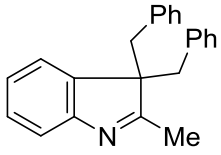
II.4.2: Investigations into Substrate Scope of Benzylation of Indoles

A focused substrate scope (Table 7) was explored for this reaction. While the optimized conditions worked very well for the initial substrate **232** (entry 1), when either **234** or **236** were subjected to the reaction conditions high catalyst loading and long reaction times were required to obtain the C3-benzyl indolenine products **235** and **237** in excellent yield (entries 2, 3). When C3-unsubstituted substrates **238** and **241** were examined, a similar result to when the related *N*-alloc substrates were examined was obtained, with a mixture of mono and di-benzylation occurring (entries 4, 5). Overall the benzylation proved to be significantly more difficult than the allylation. When other *N*-Cbz protected indoles, such as carbolines, were exposed to the reaction conditions they were found to be unreactive.

[22] Pd(allyl)Cp required storage at low temperatures due to its low sublimation point.

Table 7: Palladium Catalyzed Decarboxylative Benzylation Substrate Scope



Entry	Substrate	Pd (mol %)	Time (h)	Yield (%)[a]	Product
1	 **232**	5	5	98	 **233**
2	 **234**	10	16	97	 **235**
3	 **236**	10	16	98	 **237**
4	 **238**	5	24	35/22	 **239**  **240**
5	 **241**	5	24	40/26	 **242**  **243**

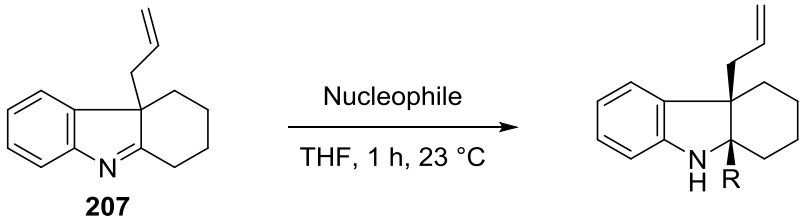
[a]Isolated yield.

II.5: Further Functionalization of Indolenines

II.5.1: Nucleophilic Addition to Indolenine Imine

With the exploration of both substrate motifs complete, the question arose on whether the generated compounds could be further functionalized. The drive behind this question linked back to the earlier statements on the prevalence of the indole core in both natural products and bioactive agents. If further functionalization was possible then this chemistry could be adapted towards the generation of a small library of compounds, which could be submitted for biological screening. The obvious sites for further functionalization were the olefin, which had already proven amenable to further modification, and the imine of the indolenine core. To this purpose a focused group of carbon based nucleophiles were added to indolenine **207** (Table 8).

Table 8: Addition of Nucleophiles to Indolenine



207

Entry	Nucleophile	R	Yield (%)[a]	Product
1[b]	AllylMgBr	Allyl	99	**244**
2	MeLi	Me	91	**245**
3	PhLi	Ph	68	**246**

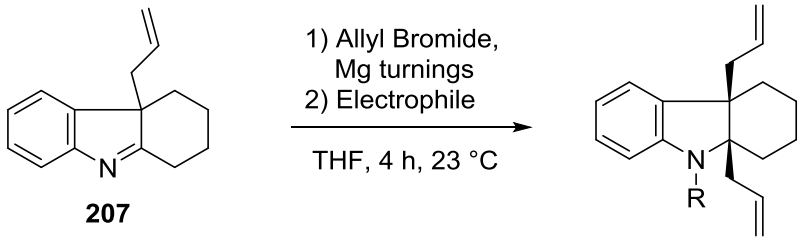
[a]NMR yield based on internal standard. [b]Grignard generated *in situ.*

Imines are well known electrophiles that will react readily with organometallic nucleophiles.[8] When allyl magnesium bromide was combined with indolenine **207**, the addition proceeded rapidly giving bis-allyl indoline **244** as a single diastereomer in quantitative yield.

Presumably the formed diastereomer is the cis-indoline, as the alternate trans-indoline would generate a highly strained trans-6,5 indoline ring system.[23,24] In addition to allyl magnesium bromide, both phenyl and methyl lithium (entries 2,3) gave indolines **245** and **246** in good yield. With such an effective protocol for addition to the indolenine it was thought that if a suitable electrophile was introduced then the anionic amine could be trapped, giving another source of diversity (Table 9).

II.5.2: Further Functionalization of Indolines Through One-Pot Reactions

Table 9: Two Step Functionalization



207

Entry	Electrophile	R	Yield (%)[a]	Product
1	Acetyl chloride	Ac	25	**247**
2	Benzoyl chloride	COPh	55	**248**
3	Methanesulfonyl chloride	SO_2Me	83	**249**
4	Methyl chloroformate	CO_2Me	52	**250**

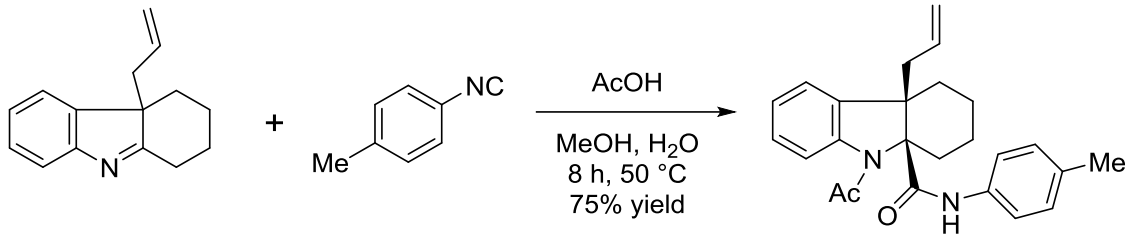
[a]Isolated yield

A series of carbonyl based electrophiles were tried, and all gave the expected *N*-protected indoline, though for some electrophiles (acetyl chloride) the yield was relatively poor (entries 1-

[23] For comparison of cis and trans fused bicyclic systems: Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books, 2006.
[24] (a) Rodriguez, J. G.; Urrutia, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 665-667. (b) Rodri´guez, J. G.; Urrutia, A. *Tetrahedron* **1998**, *54*, 15613-15618.

4). Another possible means of functionalizing the formed indolenine **207** was through the application of the Ugi reaction (Scheme 36).[25] Gratifyingly when indolenine **207** was combined with an isocyanate **251** and a carboxylic acid, the Ugi reaction proceeded exactly as expected, generating the highly substituted indoline compound **252** in good yield.

Scheme 36: Ugi Reaction



207 **251** **252**

II.6: Conclusion

Described here is a detailed method for the C3 functionalization of indoles from their *N*-alloc and *N*-Cbz precursors. This palladium catalyzed transformation can be performed with significantly lower catalyst loadings than have been previously described in similar systems. Additionally the generated products can be further decorated in one-pot fashion, either through sequential palladium catalyzed coupling reactions or via addition to the electrophile C2 center of the indolenine. This protocol therefore represents an alternate method for the generation of C3 bis-substituted indolenines and indolines under mild conditions.

[25] (a) Ugi, I. *Angewandte Chemie International Edition in English* **1962**, *1*, 8-21. (b) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.

CHAPTER III

SPIROCYCLIZATION OF INDOLE AND OXINDOLE BIS-NUCLEOPHILES

III.1: Introduction

With the successful completion of the investigation into the direct allylation and benzylation of *N*-alloc and *N*-Cbz indoles detailed in the previous chapter, other methods for functionalizing indoles were explored. By taking inspiration from both the previously described studies and the published work on the allylation of indoles using allyl methyl carbonates it was hypothesized that propargyl carbonates could serve a similar function for the propargylation of indoles.[1, 2] This would be an appealing transformation, not only from a purely academic standpoint but also due to the intrinsic differences in reactivity between alkenes and alkynes.[3] If

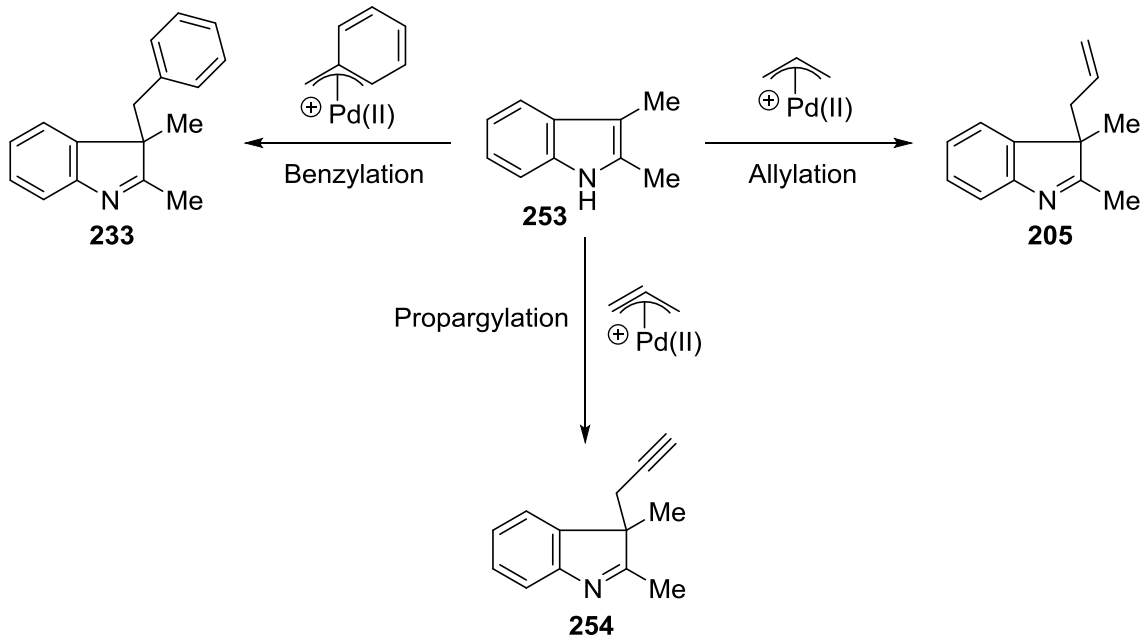
[1] For reviews of Pd-catalyzed propargylation, see: (a) Bruneau, C.; Darcel, C.; Dixneuf, P. H. *Curr. Org. Chem.* **1997**, *1*, 197-218. (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley & Sons Ltd.: Chichester, West Sussex, England,2004; pp 543-562. (c) Inuki, S. *Platinum Metals Rev.* **2012**, *56*, 194-199. (d) Yoshida, M. *Chem. Pharm. Bull.* **2012**, *60*, 285-299. (e) Yoshida, M. *Heterocycles* **2013**, *87*, 1835-1864.

[2] For reports of Pd-catalyzed propargylation see: (a) Tsuji, J.; Watanabe, H.; Miami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196-2198. (b) Tsuji, J.; Sugiura, T.; Yuhara, M.; Minami, I. *J. Chem. Soc., Chem. Commun.* **1986**, 922-924. (c) Geng, L.; Lu, X. *Tetrahedron Lett.* **1990**, *31*, 111-114. (d) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew. Chem.* **1996**, *108*, 962-963. (e) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025-9028. (f) Dominczak, N,; Damez, C.; Rhers, B.; Labrosse, J.-R.; Kryczka, B.; Sinou, D. *Tetrahedron* **2005**, *61*, 2589-2599. (g) Duan, X.-h.; Liu, X.-y.; Guo, L.-n.; Liao, M.-c.; Liu, W.-M.; Liang, Y.-m. *J. Org. Chem.* **2005**, *70*, 6980-6983. (h) Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 6705-6708. (i) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A. Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199-14223. (j) Millán, A.; Álvarez de Cienfuegos, L.; Martín-Lasanta, A.; Campaña, A. G.; Cuerva, J. M. *Adv. Synth. Catal.* **2011**, 73-78. (k) Yoshida, M.; Sugimura, C. *Tetrahedron Lett.* **2013**, *54*, 2082-2084. (l) Schröder, S. P.; Taylor, N. J.; Jackson, P.; Franckevičius, V. *Org. Lett.* **2013**, *15*, 3778-3781.

[3] For reviews on alkene and alkyne reactivity see: (a) Carey, F. A. *Organic Chemistry: Sixth Edition*; McGraw-Hill Companies, Inc.: New York, NY, 2006. (b) Carey, F. A.; Sundberg, R. J.

realized this would allow for the installation of additional functionality at the C3 position of indole, giving the chemisty control over what functional group handle was present in the final compound (Scheme 37).

Scheme 37: Palladium Catalyzed C3 Functionalization of Indoles



III.1.1: Initial Results and Reaction Exploration

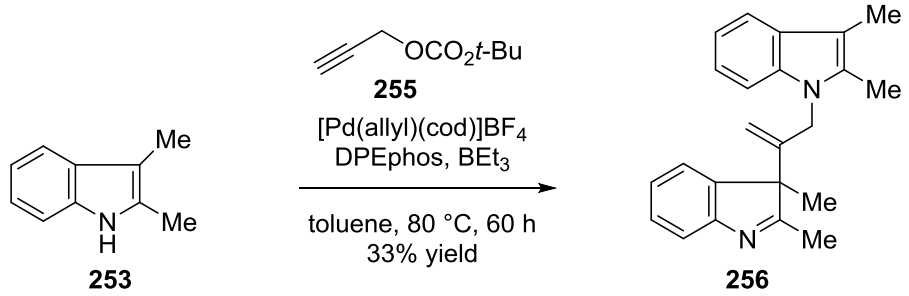
In order to determine the feasibility of this transformation, *tert*-butyl propargyl carbonate **255** was prepared and reacted with 2,3-dimethylindole **253** under conditions which had previously proven effective for the analogous allylation and benzylation reactions (Scheme 38).[4] While no reaction was initially observed, under more forcing conditions; higher catalyst loading (10 mol %) and heating to 80 °C, new compound **256** slowly formed over 60 hours. Rather than the expected C3 propargyl indolenine **254**, the formed compound **256** was a pseudo dimer

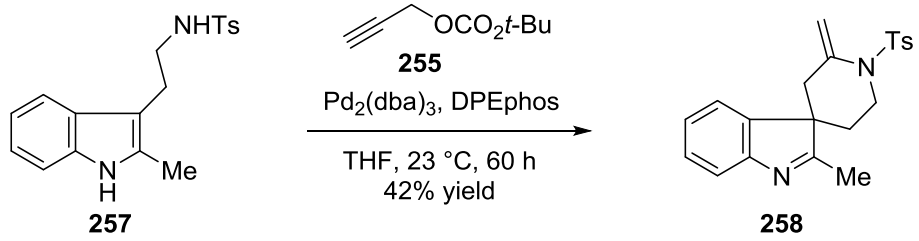
Advanced Organic Chemistry: Part A: Structure and Mechanisms: Fifth Edition; Springer Science+Buisness Media, LLC:New York, NY, 2007.

[4] Initial experiments as shown in Scheme X were performed by Dr. Ye Zhu: Zhu, Y. Ph.D. Thesis, University of Chicago, Chicago, IL, 2012.

arising from two equivalents of indole, adding 1,2 across the propargyl residue. Additionally the indole equivalents added in two different manners, one reacting at the C3 position and the other at the nitrogen. In order to capitalize on this observed reactivity it was hypothesized that an indole substrate, having in place a tethered nucleophilic moiety, could give rise to a spirocyclized compound. This hypothesis was confirmed when tosyl-tryptamine derivative **257** reacted with propargyl *tert*-butyl carbonate **255** at ambient temperature in the presence of a palladium catalyst and a bidentate phosphine ligand, affording spirocyclized indolenine **258** in modest yield after several days.

Scheme 38: Initial Experiments



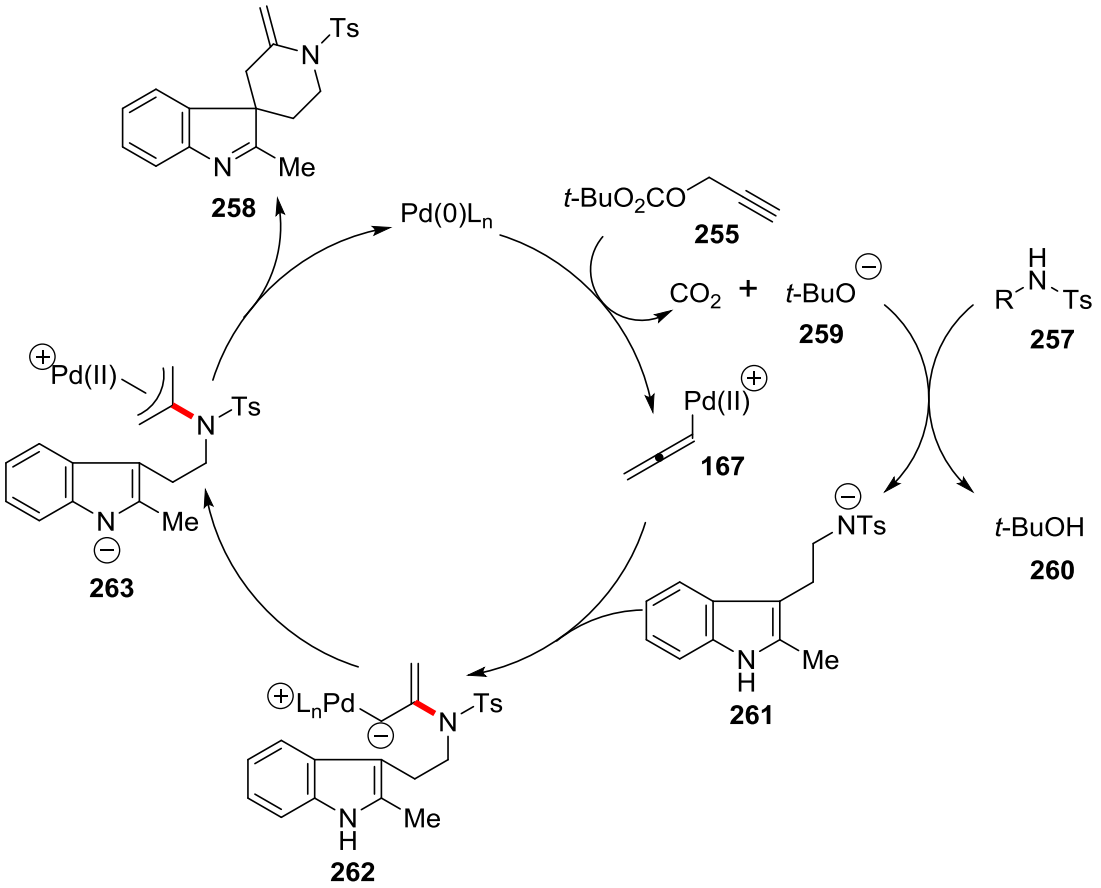


III.1.2: Mechanistic Rationale for Observed Products

This observed reactivity indicated that the reaction is proceeding through a different type of reaction mechanism than had been previously observed with the allylation and benzylation of

indoles (Scheme 38).[5] Presumably the palladium undergoes oxidative addition to *tert*-buyl propargyl carbonate **255** through an S_N2' type mechanism, generating palladium (II) allene complex **167**.[6]

Scheme 39: Proposed Catalytic Cycle



[5] (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140-145. (b) Tsuji, J.; Mandai, T. *Angew. Chem. Int. Ed.* **1995**, *34*, 2589-2612. (c) Ma, S. *Eur. J. Org. Chem.* **2004**, 1175-1183. (d) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111-122. (e) Yoshida, M. *Chem. Pharm. Bull.* **2012**, *60*, 285-299. (f) Ye, J.; Ma, S. *Acc. Chem. Res.* **2014**, *47*, 989-1000.

[6] (a) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103-1105. (b) Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis* **1987**, *1987*, 603-606. (c) Su, C.-C.; Chen, J.-T.; Lee, G.-H.; Wang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4999-5000. (d) Ogoshi, S.; Tsutsumi, K.; Kurosawa, H. *J. Organomet. Chem.* **1995**, *493*, C19-C21. (e) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367-371. (f) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687-2692.

After decarboxylation and expulsion of carbon dioxide, *tert*-butoxide anion **259** may serve as an endogenous base and deprotonate sulfonamide substrate **257** to give sulfonamide anion **261** and *tert*-butanol **260**. Deprotonation of the indole is not expected due to the relative pKa values (DMSO) of indole (21)[7] and sulfonamide (16.1).[8]

At this point nucleophilic attack by sulfonamide anion **261** onto the central carbon of the palladium (II) allene complex **167** would generate zwitterionic intermediate **262**, which may also be thought of as a palladium carbene.[9] Subsequent protonation, formally by the indole N-H, of complex **262** would form the corresponding palladium-π-allyl species **263**. Intramolecular addition to palladium-π-allyl of **263** by the C3 position of indole and reductive elimination will give spiroindolenine **258** and regenerate the palladium (0) catalyst.[10] In this chapter, the adaptation of these initial results into an efficient means of synthesizing spirocyclized indolenines and their related compounds is described.[11, 12, 13]

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[7] Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *The Journal of Organic Chemistry* **1981**, *46*, 632-635.

[8] Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T. Y.; Satish, A. V.; Whang, Y. E. *The Journal of Organic Chemistry* **1990**, *55*, 3330-3336.

[9] For examples of the nucleophilic addition to allenyl-palladium species, see: (a) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225-242. (b) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Synlett* **1996**, *1996*, 553-554.

[10] For examples of palladium-catalyzed allylic alkylation reactions, see selected reviews and papers cited therein: (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-393. (b) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089-1122. (c) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163-3186. (d) Kapdi, A. R.; Prajapati, D. *RSC Advances* **2014**, *4*, 41245-41259.

[11] Montgomery, T. D.; Nibbs, A. E.; Zhu, Y.; Rawal, V. H. *Org. Lett.* **2014**, *16*, 3480-3483.

[12] Nibbs, A. E.; Montgomery, T. D.; Zhu, Y.; Rawal, V. H. *The Journal of Organic Chemistry* **2015**, *80*, 4928-4941.

[13] During the course of these studies, two reports appeared on the propargylation of indole substrates, both utilizing a tethered alkyne for an intramolecular reaction: (a) Nemoto, T.; Zhao, Z.; Yokosaka, T.; Suzuki, Y.; Wu, R.; Hamada, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 2217-2220. (b) Iwata, A.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2014**, *50*, 298-300.

III.2: Optimization of Reaction Conditions

Given the potential of this methodology to offer new ways to access drug like spirocyclized indolenines, the reaction conditions were carefully optimized (Table 10).

III.2.1: Screening Ligands and Solvent Conditions

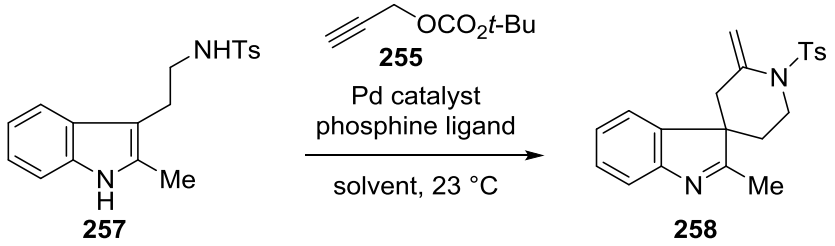
Beginning with the previously discovered conditions for the formation of spiroindolenine **258**, the reaction time was decreased from 60 to 12 hours (entry 1). As expected, the shorter reaction time lead to a decrease in the yield of the reaction, though only by four percent, demonstrating that prolonged reaction times were not overly advantageous for this chemistry. Upon changing the solvent from tetrahydrofuran (THF) to dichloromethane (CH_2Cl_2) a marked improvement to both the reaction rate and level of conversion was observed (entry 2). A number of different phosphine ligands were screened, including another bidentate ligand 1,2-bis(diphenylphosphino)butane (dppb), and a number of monodentate phosphines (entries 3-6).

The monodentate phosphines gave uniformly worse conversions, with electron rich aryl, electron deficient aryl and even the highly electron rich tri-*tert*-butyl phosphine providing inferior results than those previously obtained with DPEphos. The bidentate phosphine Xantphos performed as well as DPEphos over a prolonged reaction period, however when the reaction time was decreased it was clear that Xantphos promoted a significantly faster reaction than DPEphos (entries 7,8).

It was also observed that use of a greater excess of propargyl carbonate was mildly beneficially to the reaction. Two control experiments were performed in order to verify that this was really a catalytic reaction. It was shown that in either the absence of the catalyst or the phosphine ligand there was no conversion from tryptamine derivative **257** to spiroindolenine **258**

(entries 9,10). Other solvents were screened, including protic solvent methanol and polar aprotic solvent ethyl acetate. Both gave no conversion to spiroindolenine **258** (entries 11, 12) and chloroform gave significantly lower yield of **258** than dichloromethane (entry 13).

Table 10: Optimization of reaction conditions



257 **258**

entry	[Pd] (mol %)	ligand	solvent (M)	**255** (equiv)	time (h)	yield (%)[a]
1	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	DPEphos	THF 0.1 M	1.1	12	38
2	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	DPEphos	CH_2Cl_2 0.1 M	1.1	3.5	95
3	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	dppb	CH_2Cl_2 0.1 M	1.1	12	28
4	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	PPh_3	CH_2Cl_2 0.1 M	1.1	3.5	81
5	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	P(2-furyl)$_3$	CH_2Cl_2 0.1 M	1.1	3.5	5
6	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	P(*t*-Bu)$_3$	CH_2Cl_2 0.1 M	1.1	3.5	0
7	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	DPEphos	CH_2Cl_2 0.1 M	1.3	0.58	59
8	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	Xantphos	CH_2Cl_2 0.1 M	1.3	0.58	90
9	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	none	CH_2Cl_2 0.1 M	1.3	0.58	0
10	None	Xantphos	CH_2Cl_2 0.1 M	1.3	0.58	0
11	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	Xantphos	MeOH 0.1 M	1.3	0.58	0
12	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	Xantphos	EtOAc 0.1 M	1.3	0.58	0
13	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	Xantphos	$CHCl_3$ 0.1 M	1.3	0.58	54

Table 10. continued

14	$Pd(PPh_3)_4$ (5.0)	Xantphos	CH_2Cl_2 0.1 M	1.3	0.58	0
15	$Pd(OAc)_2$ (5.0)	Xantphos	CH_2Cl_2 0.1 M	1.3	1	0
16	$Pd(dppf)_2Cl_2$ (5.0)	Xantphos	CH_2Cl_2 0.1 M	1.3	0.58	0
17	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	Xantphos	CH_2Cl_2 0.2 M	1.3	0.66	79
18	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	Xantphos	CH_2Cl_2 0.05 M	1.3	0.66	90
19	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	Xantphos	CH_2Cl_2 0.04 M	1.3	0.66	99
20[b]	$Pd_2(dba)_3 \cdot CHCl_3$ (5.0)	Xantphos	CH_2Cl_2 0.04 M	1.3	20	68
21	$Pd_2(dba)_3 \cdot CHCl_3$ (2.4)	Xantphos	CH_2Cl_2 0.04 M	1.3	4	98[c]
22	$Pd_2(dba)_3 \cdot CHCl_3$ (1.0)	Xantphos	CH_2Cl_2 0.04 M	1.3	14	87[c]

[a]NMR yield based on internal standard. [b]Under ambient atmosphere. [c]Isolated yield.

By substituting palladium tetrakis(triphenylphosphine) into the reaction there was no conversion to expected product **258**. This was very surprising, as it had performed very similarly during the allylation work to the palladium dba complex finally selected for the substrate scope. Similarly, both palladium (II) salts tried (entries 15,16) failed to give any conversion to desired spiroindolenine **258**. It should also be noted that propargyl *tert*-butyl carbonate was chosen as the propargyl cation source because it could be easily prepared on scale, stored under ambient atmosphere and was more reactive than both propargyl methyl carbonate and propargyl acetate. With the reaction optimization proceeding well, the effect of solvent concentration was examined.

III.2.2: Concentration Effects and Rationale

Surprisingly, when the concentration was increased from 0.1 molar to 0.2 molar there was a sharp decline in the yield after 40 minutes as compared to the standard reaction (entry 17).

Even more puzzlingly was that when the reaction concentration was decreased to 0.05 molar (entry 18) and even lower to 0.04 molar (entry 19) a marked improvement was seen, with the latter concentration giving the spiroindolenine in basically quantitative yield. This result was particularly surprising due to the fact that the first two steps of the reaction are assumed to be intermolecular, and by decreasing the reaction concentration the average distance between the required reactants will increase, decreasing the likelihood of them combining and undergoing bond forming interactions. This result could not be explained by poor solubility, as at all tested concentrations, all components of the reaction were completely soluble. Closer examination of the crude ^{1}H NMR spectra revealed that at higher concentrations (> 0.05 M) a mixture of products was being formed. The vast majority of the starting material **257** was being converted into spiroindolenine **258**, some was left unreacted and small amounts were converted into unidentified oligomeric species. These oligomeric species, while never isolated and characterized, presumably formed from pseudo dimerization reactions similar to those previously observed in **256** (Scheme 38).

III.2.3: Experimental Verification of Detrimental Oligomers

It was hypothesized that such oligomers were responsible for the loss of catalyst activity at higher concentrations. To test this hypothesis an experiment was executed, a small amount of the crude unidentified oligomeric mixture was isolated and added to a reaction being performed under the optimized conditions (entry 19). Gratifyingly the reaction performed significantly worse as compared to the control, indicating that these off cycle products were somehow poisoning the catalyst or otherwise hindering the reaction. The observed increase in reaction rate at lower concentrations could now be rationalized as being due to disfavoring off cycle

intermolecular reactions, allowing for the intramolecular ring closure to dominate and give desired spirocyclized indolenine **258** in high yields.

III.2.4: Examination of Palladium Loading and Air Sensitivity

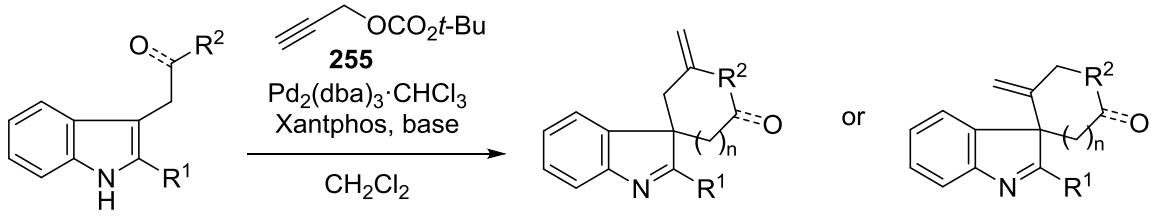
In an effort to test the robustness of this reaction, a sample was run under ambient atmosphere. While the reaction did not proceed to the same level of conversion as when run under nitrogen it did furnish spiroindolenine **258** in good yield (entry 20). The catalyst loading could be reduced to 2.4 mol % (entry 21) and even 1.0 mol % (entry 22); though significantly longer reaction times were required to achieve good yields. With the optimal conditions for the spirocyclization determined, the reaction scope in relation to the indole bis-nucleophile core was thoroughly examined (Table 11).

With the optimized substrate giving excellent yields in only four hours the next substrate to be tested involved replacing the C2 methyl group for phenyl **264**, increasing the steric bulk at this position. The reaction proceeded smoothly, giving the spiroindolenine **265** in excellent yield (entry 2). Following this success, a tryptamine bearing a 3,4-bis(methyoxy)phenyl group at the C2 position **266** also proved amenable to this chemistry, giving spiroindolenine **267** in high yield (entry 3).[14] While somewhat less reactive than toluenesulfonamide, use of methanesulfonamide as the tethered nucleophile was well tolerated, giving spiroindolenine **269** in high yield, though necessitating the use of slightly elevated temperatures and addition of a mild base (entry 4).

[14] Such a core is a key intermediate in the classic synthesis of Strychnine: Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749-4751.

III.3: Substrate Scope for Indolenine Formation

Table 11: Substrate Scope of Spirocyclization of Indole Bis-Nucleophiles



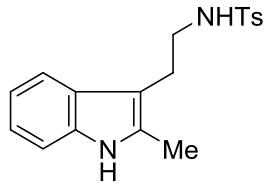
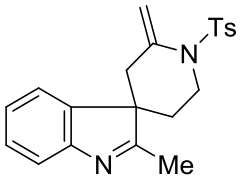
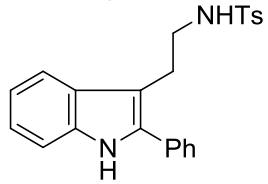
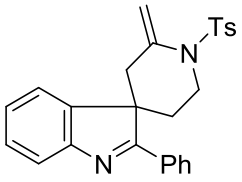
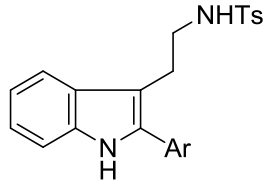
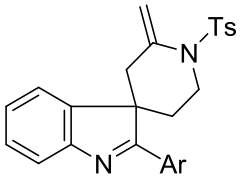
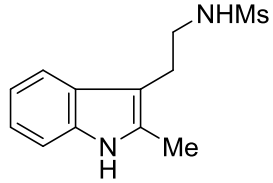
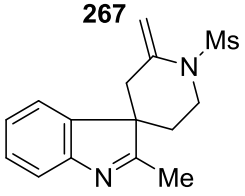
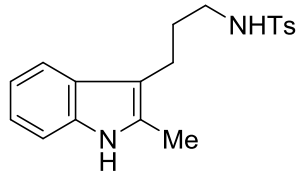
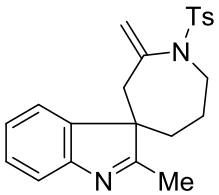
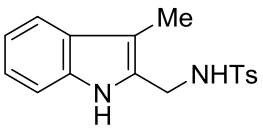
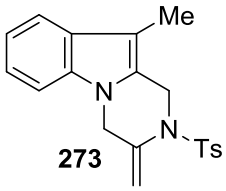
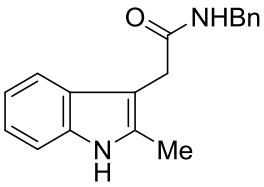
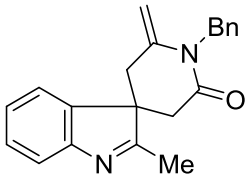
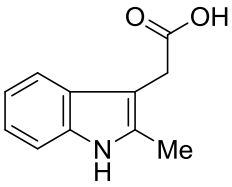
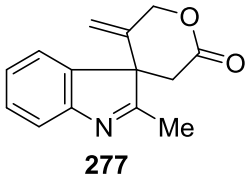
Entry	Substrate	[Pd] (mol %)	Temp. (°C)	Base	Time (h)	Yield[a]	Product
1	 **257**	2.5	23	none	4	98	 **258**
2	 **264**	5.0	23	none	2	86	 **265**
3	 **266**	5.0	23	none	0.5	80	 **267**
4	 **268**	5.0	40	NEt_3	2	93	 **269**
5	 **270**	5.0	40	NEt_3	18	52	 **271**

Table 11. continued

6	 **272**	5.0	40	none	18	60	 **273**
7	 **274**	5.0	40	$N(i\text{-}Pr)_2Et$	24	7	 **275**
8	 **276**	5.0	40	NEt_3	18	52	 **277**

[a]Isolated yield. Ar = 3,4-$(OMe)_2$Ph.

The tether length could be extended to give spirofused seven membered ring product **271** under the correct reaction conditions. It should be noted that homotryptamine analog **270** proved to be significantly less reactive than parent compound **257**, possibly due to the higher enthalpic barrier in forming seven membered rings (entry 5).[3]

III.3.1: Alternative Structural Types

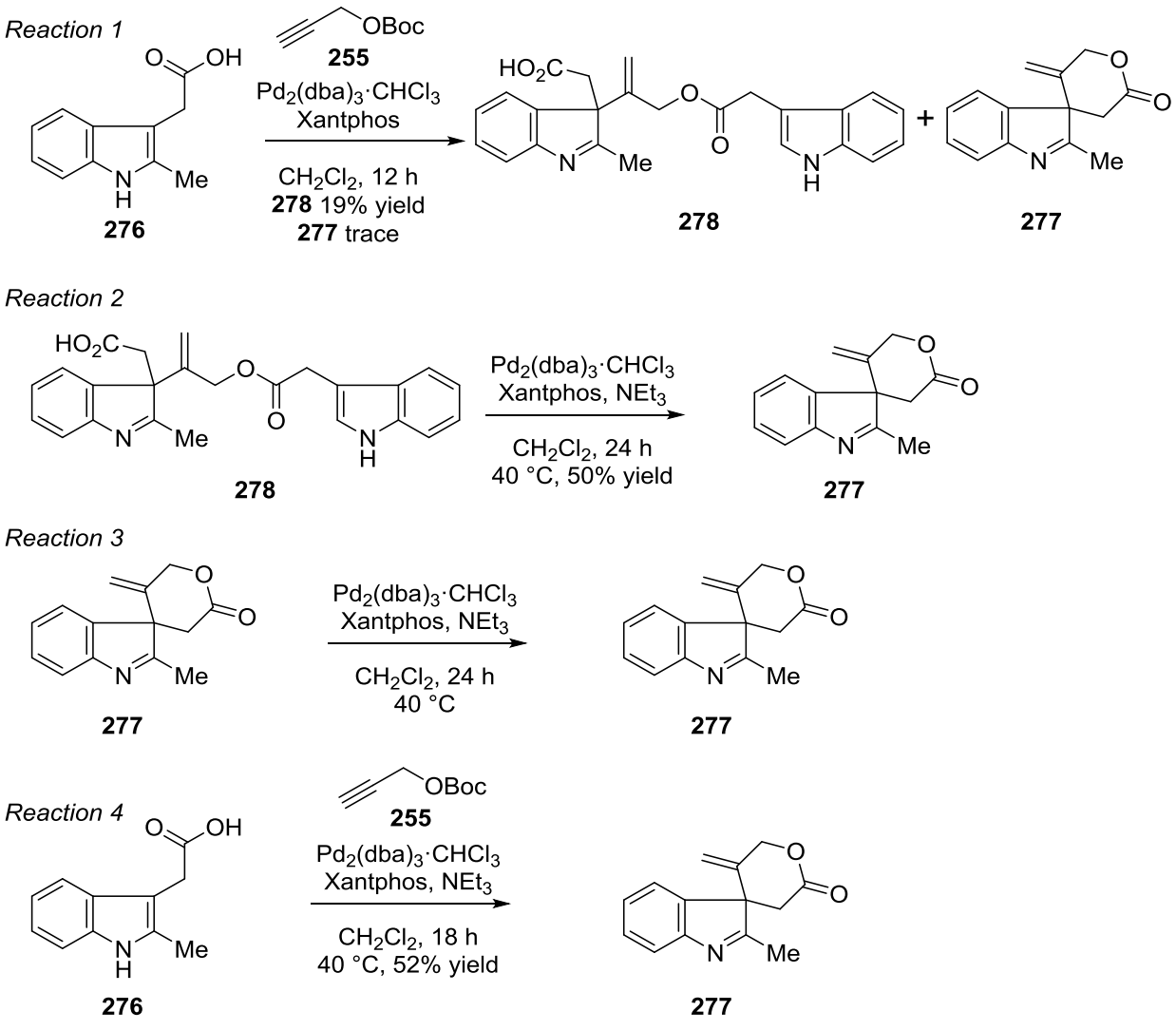
By shifting the sulfonamide tether from the C3 position to the C2 position as in indole **272**, an alternate skeletal type could be accessed (entry 6). Presumably after initial reaction at the sulfonamide nitrogen the cyclization event occurs at the indole nitrogen rather than the C3 position due to the steric repulsion of the C3 methyl group giving 6,5,6 fused tricyclic indole **273**. When a benzyl amide was substituted for sulfonamide as tethered nucleophile **274**, only a

small amount of product **275** was isolated, even with heating and addition of an exogenous base (entry 7).

III.4: Palladium Catalyzed Reaction with Additional Substrate Types

III.4.1: Initial Results for Reaction with a Tethered Carboxylic Acid Moiety

Scheme 40: Reversibility of Reaction with Indole Acetic Acid **276**



Use of indole acetic acid substrate **276** for this transformation was initially performed in the absence of triethylamine and produced only trace amounts of lactone **277**. The major isolated

component, besides recovered starting material, was pseudo-dimeric product **278**, isolated in 19% yield (Scheme 40, reaction 1). After isolating and analyzing both desired lactone **277** and pseudo-dimer **278** it was deduced that the reaction order was unlike the previous entries, where the sulfonamide reacts with the palladium allene initially, followed by ring closure onto the indole. In the case of substrate **276** it appeared that for both products the initial reaction occurred at the indole center and then the resulting intermediate subsequently reacted, either intra- or intermolecularally, to generate the desired or undesired products respectively. Due to this order of addition, both of the generated products contained an allyl carboxylate moiety, a well-known reaction partner for palladium catalyzed allylation. It was therefore hypothesized that the formed products may not be stable to the reaction conditions, and if some type of dynamic equilibrium existed between them, then this may provide a means of selecting one over the other.

III.4.2: Validation of Hypothesis and Improved Reaction Conditions

In agreement with this hypothesis, when compound **278** was exposed to a modification of the reaction conditions, in the absence of additional propargyl carbonate, a 1:1 mixture of products **277** and **278** were isolated (reaction 2). Furthermore when lactam **277** was exposed to the same conditions it proved to be completely inert. This is possibly due to the inability of the allyl carbonate to adopt an appropriate conformation to react with the palladium catalyst (reaction 3). Alternately in the absence of free carboxylic acid substrate, the population of intermolecular coupling partners available is so low that the intermolecular reaction cannot compete with the intramolecular cyclization. Regardless of the explanation, when the reaction of **276** was performed again in the presence of propargyl *tert*-butyl carbonate **255** and allowed to react for a prolonged time, at elevated temperature, in the presence of triethylamine, spiroindolenine lactam **277** was generated in good yield as the major product (reaction 4).

III.4.3: Use of C2-Unsubstituted Indole Substrates and Their Further Reactions

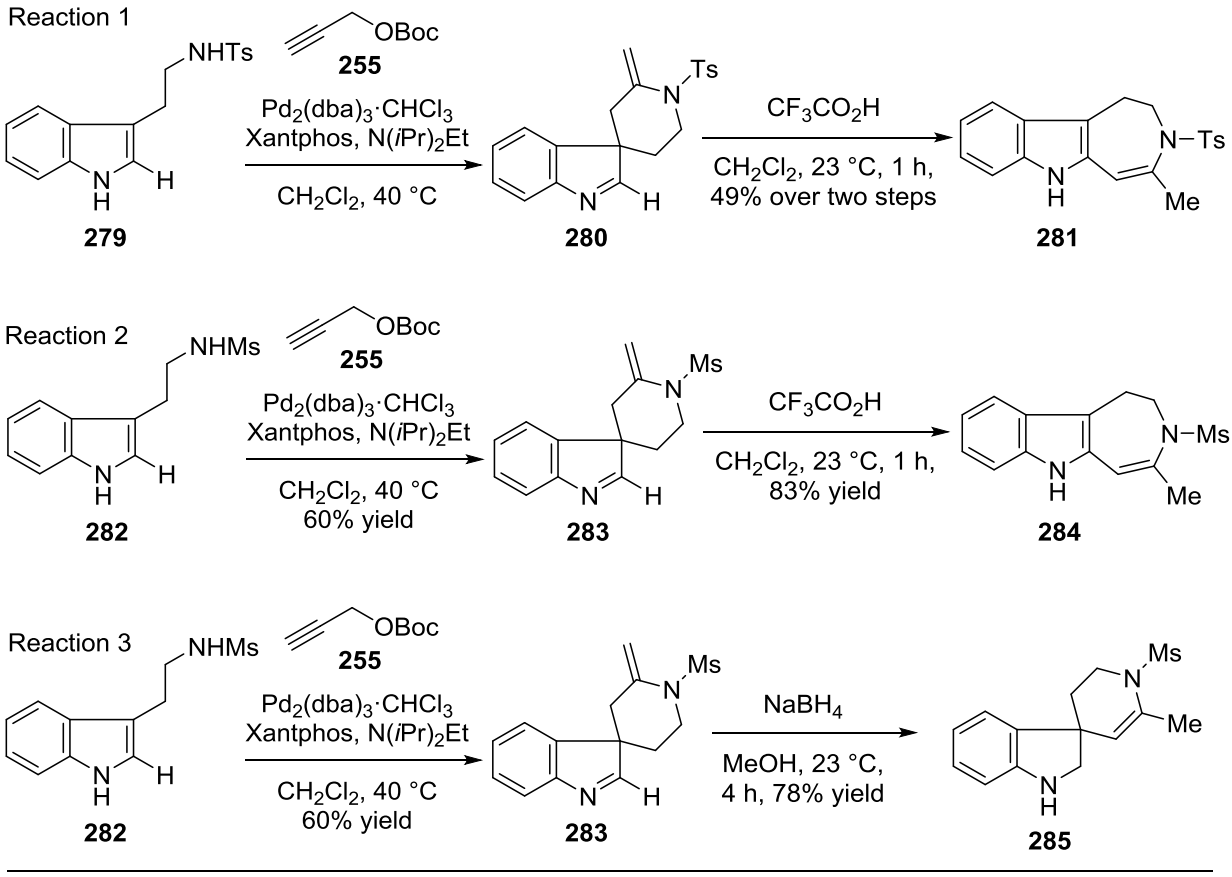
When substrates that lacked a C2 substituent were used in the spirocyclization reaction the expected spirocyclized indolenines were generated smoothly (Scheme 41). However the product of toluenesulfonamide tryptamine **279** was unstable to column conditions and would decompose over time. Taking advantage of this instability, crude spiroindolenine **280** was acidified with trifluoroacetic acid to trigger a rearrangement to fused tricyclic indole **281** (reaction 1). The rearrangement could possibly occur through a [1,5]-sigmatropic shift[15,16] or through some other non-concerted mechanism.

When methanesulfonamide substrate **282** was subjected to the same reaction conditions, it proved to be more robust than its counterpart **280** and could be isolated in decent yield. Spiroindolenine **283** could also be converted, under the same acidic conditions, into tricyclic indole compound **284** in good yield (reaction 2). Alternatively spiroindolenine **283** could be reduced with sodium borohydride to give spiroindoline **285** cleanly in acceptable yield (reaction 3). For both transformations, acidic rearrangement and reduction, the olefin completely isomerized to the thermodynamically favored endocyclic alkene shown.

[15] For related rearrangements of indole derivatives, see, : (a) Wang, T. S. T. *Tetrahedron Lett.* **1975**, *19*, 1637-1638, (b) Baran, P. S. Maimone, T. J.; Richter, J. M. *Nature*, **2007**, *446*, 404-408. (c) Zheng, C.; Wu, Q.-F.; You, S.-L. *J. Org. Chem.* **2013**, *78*, 4357-4365, and references cited therein.

[16] The rearrangement is expected to proceed in a suprafacial manner necessitating a [1,5] sigmatropic shift which is thermally allowed as opposed to the forbidden [1,3] shift. For a review on sigmatropic shifts see: Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books, 2006.

Scheme 41: Reaction of C2-Unsubstituted Indoles

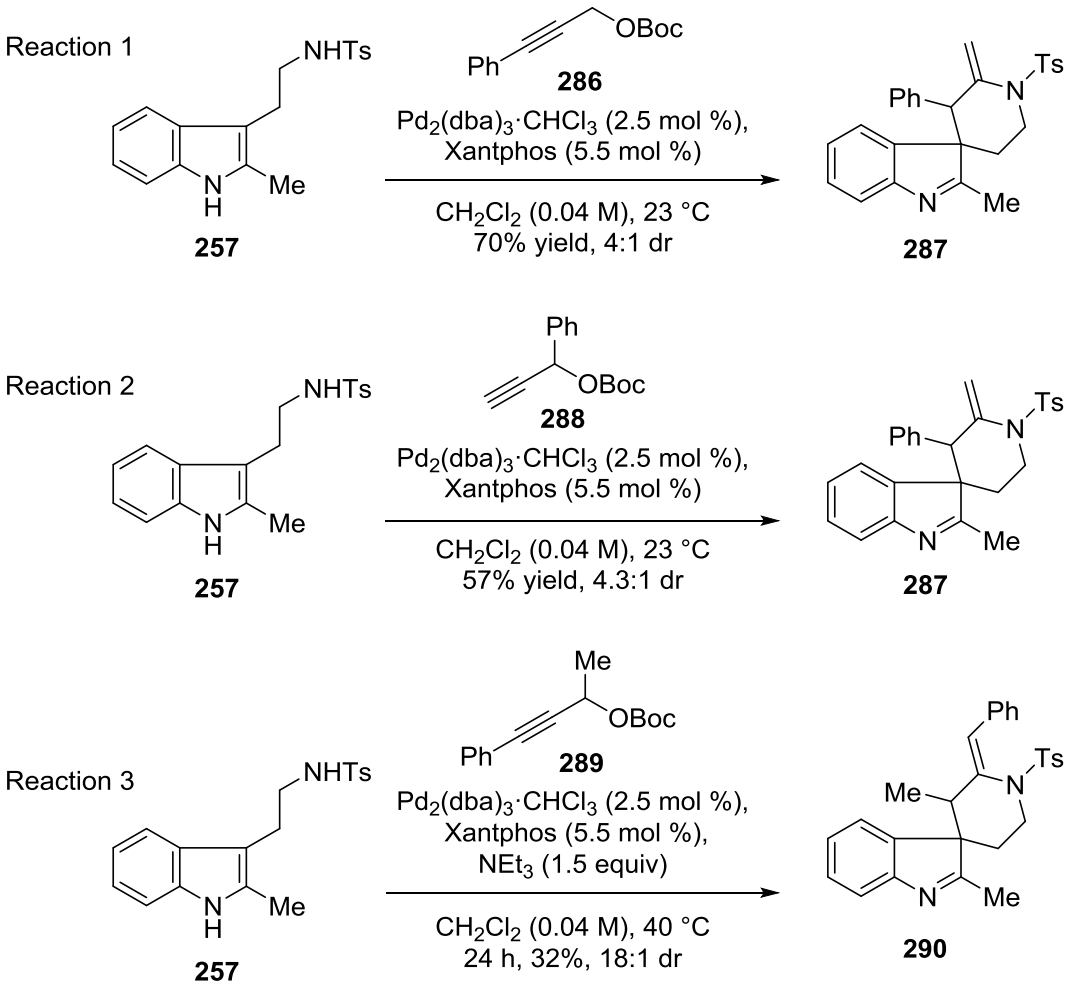


III.5: Use of Substituted Propargyl Carbonates

III.5.1: Screening of Different Propargyl Carbonates for Indolenine Formation

In an effort to further expand the substrate scope of this reaction, a number of substituted propargyl *tert*-butyl carbonates were prepared according to standard procedures. While a number of the prepared propargyl carbonates, specifically ones only bearing alkyl substituents, gave inseparable mixtures of regio- and stereoisomers, propargyl carbonates bearing aryl groups proved amenable for use in the reaction (Scheme 42).

Scheme 42: Use of Substituted Propargyl Carbonates



When terminal phenyl substituted propargyl *tert*-butyl carbonate **286** was used in a reaction with substrate **257,** a single regioisomer, **287** was isolated in good yield and with respectable levels of diastereoselectivity (reaction 1). Curiously, when the regioisomeric propargyl *tert*-butyl carbonate **288** was used for the reaction, under identical conditions, the same spiroindolenine **287** was isolated in similar levels of yield and selectivity (reaction 2). When bis-substituted propargyl *tert*-butyl carbonate **289** was used, highly substituted spiroindolenine **290** was formed in very modest yield but with an excellent level of selectivity (18:1 d.r.). This is even more remarkable given the fact that the reaction possessed the possibility of form up to eight

different isomeric compounds (reaction 3).[17] Apart from showing an increased substrate scope the results obtained lend credence to the mechanism originally proposed (Scheme 43).

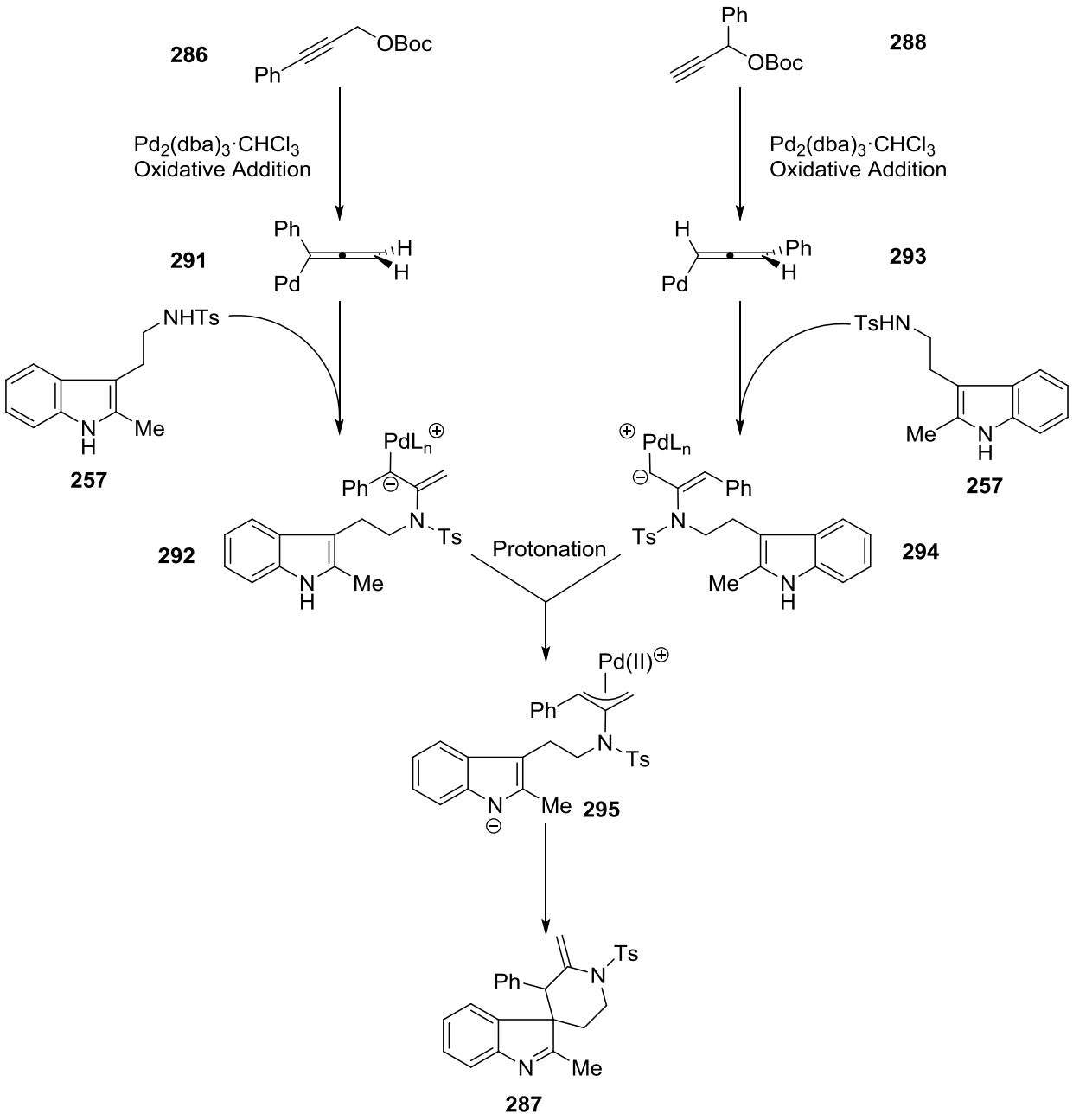
III.5.2: Stereoconvergent Synthesis of Spiroindolenine

Following oxidative addition by the palladium catalyst to 3-phenyl propargyl *tert*-butyl carbonate **286**, palladium allene **291** will form following decarboxylation. Subsequent nucleophilic attack of the central carbon of the allene by sulfonamide **257** will generate key σ-allyl intermediate **292**. Alternatively, when 1-phenyl propargyl *tert*-burtl carbonate **287** reacts with palladium the isomeric palladium allene complex **293** will be generated. Following nucleophilic addition to the central carbon of palladium allene **293** Pd-σ-allyl intermediate **294** will form. Both intermediate **292** and **294**, following protonation, will produce Pd-π-allyl complex **295**. Assuming free rotation around the nitrogen-carbon sigma bond is sufficiently fast the two states will be in equilibrium and therefore the subsequent ring closure will produce a single compound, spiroindolenine **287**.

The reason that spiroindolenine **290** forms as opposed to any other regioisomer is presumably due to a delicate balance between steric and electronic biases. This delicate balance is clearly demonstrated by comparison of spiroindolenine **287** to **290** where **287** forms the second bond to indole at the more sterically hindered benzylic position, which can better support a positive charge, and therefore can be thought of as the more electrophilic position. On the other hand during the formation of spiroindolenine **290** the second bond forming step does not occur at the benzylic position, instead giving product **290** where the aryl ring is in conjugation with the olefin.

[17] Number of possible combinations is = 2^n where n = 3.

Scheme 43: Mechanistic Rationale for Stereoconvergent Synthesis of Spiroindolenine **287**



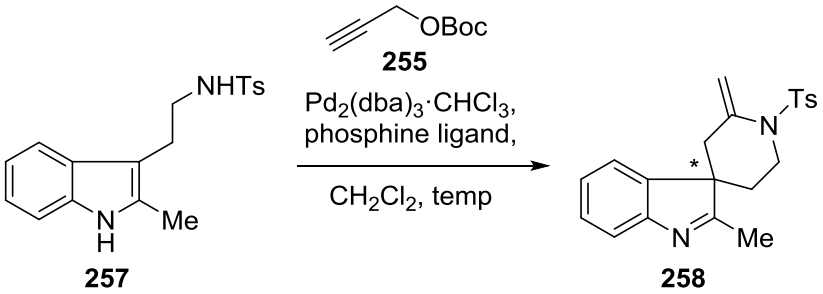
III.6: Asymmetric Variant of Decarboxylative Indole Spirocyclization

III.6.1: Screening of Chiral Phosphine Ligands

A natural progression of this work was to render the spirocyclization of indole based bis-nucleophiles asymmetric. Toward this end a number of different chiral ligands were examined, screening for good yields and high enantioselectivities (Table 12). Chiral ligand (*R*)-BINAP generated spiroindolenine **258** in good yield and low, albeit promising, levels of enantioselectivity (entry 1). Modifying the quantity of chiral ligand (entry 2), temperature (entry 3) or use of a more hindered chiral ligand (entry 4) provided only minor improvements to the level of enantioselectivity for the spirocyclization. Changing from a bis-phosphine to a mono-phosphine ligand shut the reaction down, giving no conversion to product **258** (entry 5).

Employment of BIPHEP-type ligand **296** improved the yield and gave similar levels of enantioselectivity as previously noted (entry 6). By changing the aryl component of the BIPHEP-type ligand from phenyl to furyl, a substantial increase in selectivity was observed (entry 7). Increasing the bulk of the furyl group for BIPHEP-type ligand **298** gave the highest levels of enantioselectivity observed so far. Disappointingly, the corresponding benzofuran-substituted ligand **299** gave only about half the level of enantioselectivity previously observed. With these modest levels of selectivity the reaction conditions were applied to a more sterically congested pair of indole bis-nucleophiles (Scheme 44).

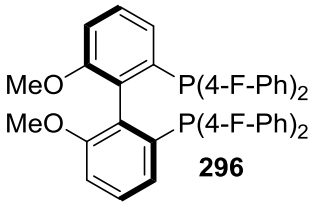
Table 12: Optimization of Asymmetric Reaction



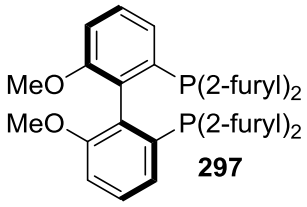
257 258

entry	ligand	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	(*R*)-BINAP	23	12	80	12
2[c]	(*R*)-BINAP	23	2	77	15
3	(*R*)-BINAP	0	16	25	16
4	(*R*)-T-BINAP	23	18	68	15
5	QUINAP	23	18	0	0
6	**296**	23	24	86	16
7	**297**	23	2	68	34
8	**298**	23	16	69	41
9	**299**	23	24	65	20

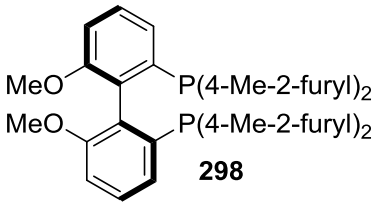
[a]Isolated yield. [b]Determined by stationary phase HPLC. [c](*R*)-BINAP (10 mol %).



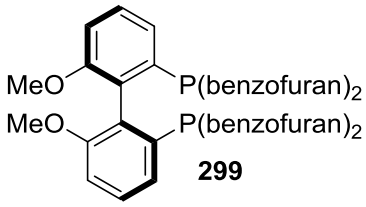
296



297



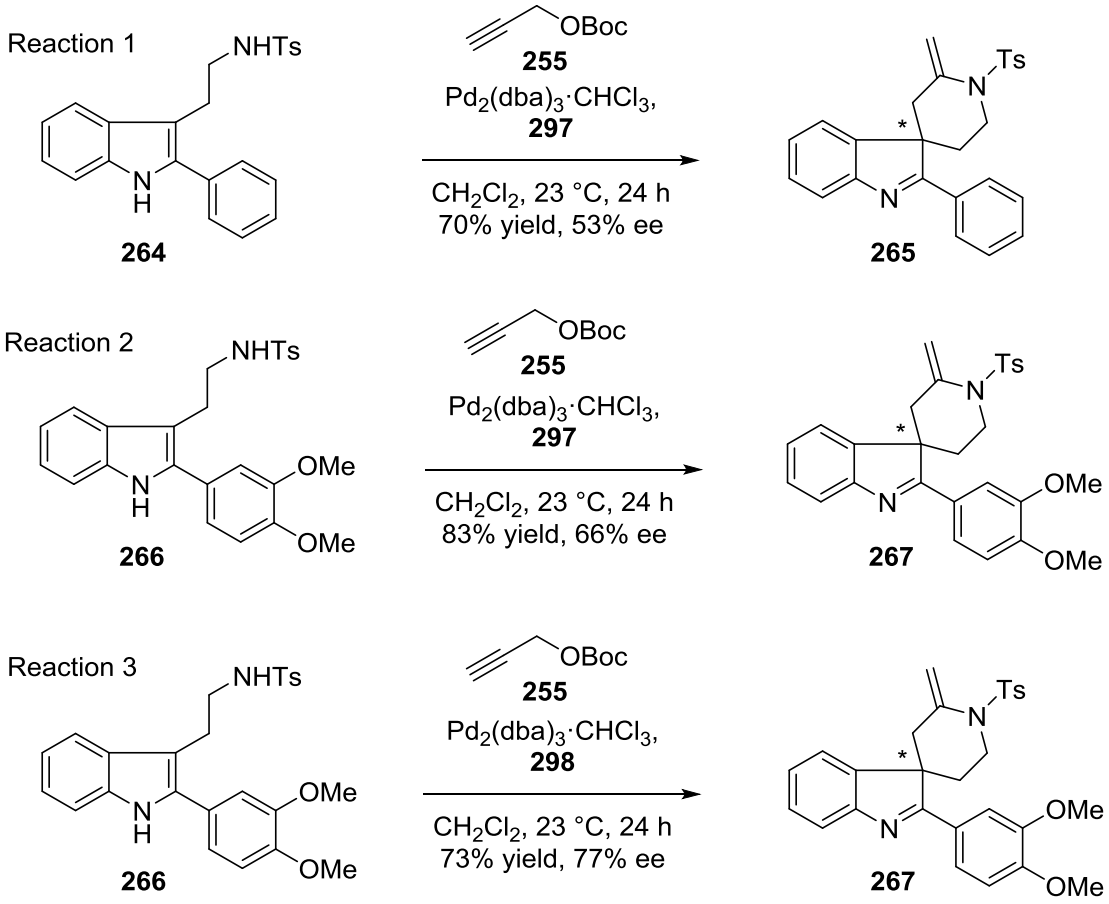
298



299

III.6.2: Use of Sterically More Hindered Substrates

Scheme 44: Use of C2-Ayrl Substituted Substrates for Asymmetric Variant



When C2-phenyl substrate **264** was used in the asymmetric reaction with BIPHEP-type ligand **297**, not only did the reaction proceed to give a good yield of spiroindolenine **265**, but reasonable levels of enantioselectivity were also obtained (reaction 1). By further increasing the size of the C2 substituent to di-methoxyphenyl **266**, even higher levels of selectivity were possible. Finally in an effort to maximize the enantioselectivity of the reaction, the most effective BIPHEP-type ligand **298** was used in conjunction with the sterically hindered substrate **266**

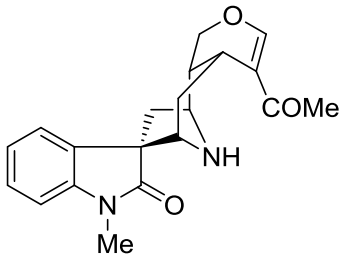
(reaction 3). After a prolonged reaction time desired spiroindolenine **267** was isolated in 73% yield and 77% ee (enantiomeric excess).[18]

III.7: Exploration and Optimization of Oxindole Based Bis-Nuclophiles

III.7.1: Background and Biological Significance

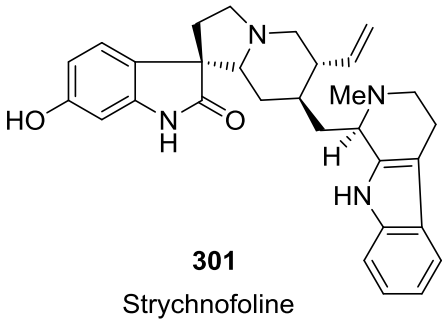
With the successful examination of indole based bis-nucleophiles it was hypothesized that oxindole based bis-nucleophiles should behave in a similar manner. The need for methods to access such interesting compounds is the same as it was for the indole based products. Such motifs are often seen in both pharmaceuticals and natural products and new enabling methods which allow easy access this class of molecules is of high synthetic and practical value (Scheme 45).[19,20]

Scheme 45: Oxindole Natural Products



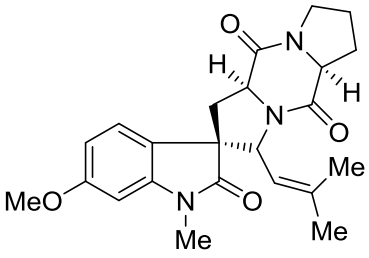
300

Alstonisine



301

Strychnofoline



302

Spirotryprostatin A

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[18] X% ee = (Y% major enantiomer) – (Z% minor enantiomer). ie 77% ee is a 88.5:11.5 ratio of major to minor enantiomers.

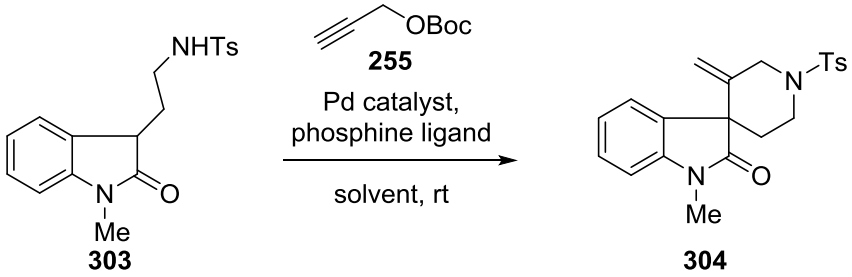
[19] (a) Elderfield, R. C.; Gilman, R. E. *Phytochemistry* **1972**, *11*, 339-343. (b) Ghendira, K.; Zeshes-Hanrot, M.; Richard, B.; Massiot, G.; Le Men-Oliver, L.; Sevener, T.; Goh, S.H. *Pyrochemistry*, **1988**, *27*, 3955-3962. (c) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651-12666. (d) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot*. **1996**, *49*, 832-835. (e) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209-2219.

[20] For a review see :Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758

While in many respects the oxindole based substrates behaved in a similar manner to the analogous indoles, their subtle differences in reactivity gave access to different structural motifs and reaction patterns than had been previously observed. For the reaction of oxindole based bisnucleophiles, *N*-methyl protected sulfonamide oxindole **303** was chosen as the model substrate and the reaction was subsequently optimized (Table 13).

III.7.2: Reaction Optimization for Spirocyclic Oxindole Formation

Table 13: Optimization of Oxindole Spirocyclization Reaction



entry	Catalyst (mol %)	ligand (mol %)	solvent	**255** (equiv)	time (h)	yield[a]
1	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	Xantphos (5.5)	CH_2Cl_2	1.3	18	83
2	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	DPEphos (5.5)	THF	1.1	0.75	83
3	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb (5.5)	THF	1.1	0.75	97[c]
4	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	none	THF	1.1	0.75	0
5	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	PPh_3 (5.5)	THF	1.1	4	0
6	$Pd(OAc)_2$ (5.0)	dppb (5.5)	THF	1.1	0.75	10
7	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb (5.5)	CH_2Cl_2	1.1	0.5	84
8	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb (5.5)	EtOAc	1.1	0.75	92
9[b]	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb (5.5)	THF	1.1	0.75	0
10	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	dppb (5.5)	THF	1.5	0.33	98
11	$Pd_2(dba)_3{\cdot}CHCl_3$ (1.0)	dppb (2.2)	THF	1.5	2	98[c]
12	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.5)	dppb (1.1)	THF	1.5	6	95[c]

[a]NMR yield based on internal standard. [b]Under ambient atmosphere. [c]Isolated yield.

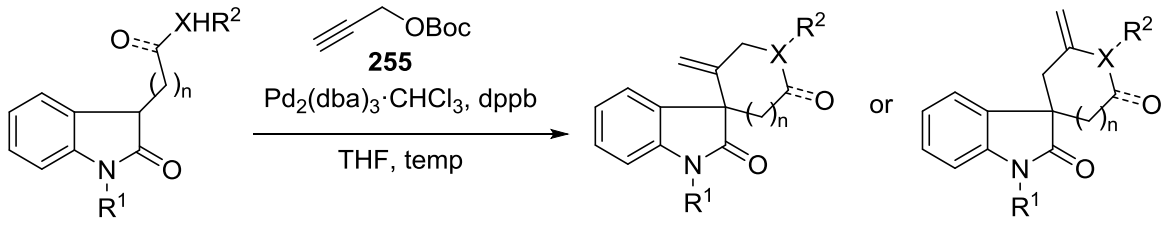
Using the optimized conditions for the spirocyclization reaction between indole bis-nucleophiles and propargyl *tert*-butyl carbonate **255**, spiro-oxindole **304** was obtained in good yield after eighteen hours (entry 1). It was additionally interesting to note that the isolated product showed an inverse order of reactivity as compared to the majority of indole based bis-nucleophiles screened. More specifically, the C3 position of the oxindole reacted first, followed by ring closure by the tethered sulfonamide nitrogen. By returning to the reaction conditions originally tried for formation of spiroindolenine **258**, a significant increase in the reaction rate was observed. By subsequently changing the ligand from DPEphos to dppb, desired spiro-oxindole **304** was isolated in basically quantitative yield after forty five minutes (entry 3). As with the spiroindolenine chemistry, in the absence of phosphine ligand the reaction did not proceed (entry 4). Similarly when mono-dentate ligand triphenyl phosphine was used the reaction was again shut down, demonstrating the need for a bi-dentate phosphine ligand (entry 5).

The use of a palladium (II) source gave only minor conversion to product **304** and neither dichloromethane nor ethyl acetate gave a better result than tetrahydrofuran (entries 7,8). When the reaction mixture was exposed to ambient atmosphere the reaction did not proceed at all, showing a much greater sensitivity to air than with the generation of spiroindolenine **258** (entry 9). Finally it was possible to lower the catalyst loading to as low as 1 mol% palladium and still have the reaction proceed to completion giving the desired spiro-oxindole **304** in quantitative yield (entries 11,12).

III.8: Substrate Scope for Oxindole Spirocyclization

With the optimized conditions in hand, the substrate scope for the decarboxylative spirocyclization of oxindole based bis-nucleophiles was explored (Table 14).

Table 14: Substrate Scope of Spiro-oxindole Formation



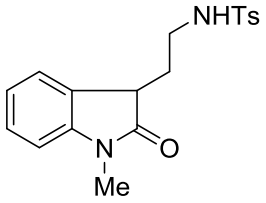
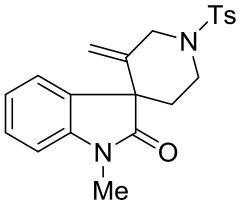
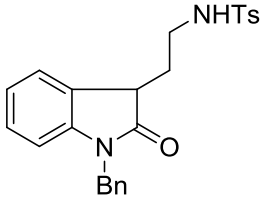
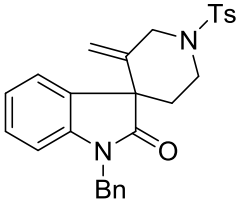
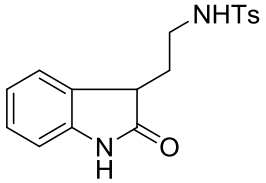
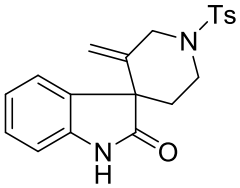
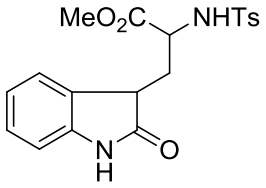
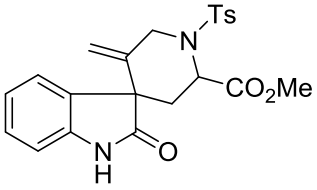
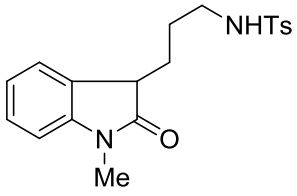
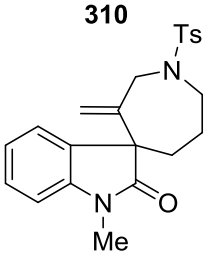
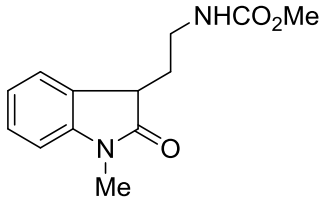
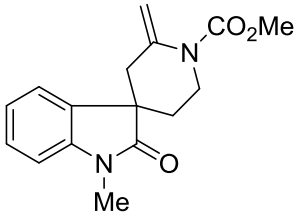
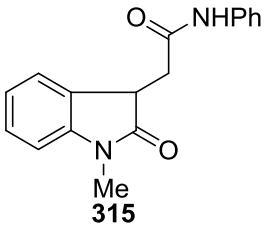
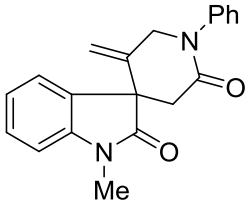
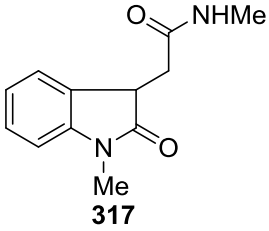
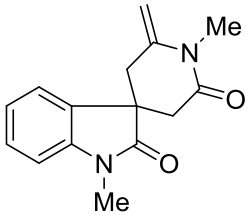
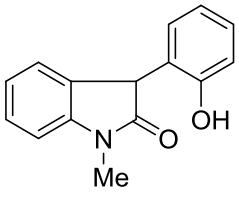
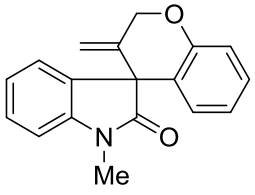
entry	substrate	conc. (M)	temp (°C)	time (h)	yield (%)[a]	product
1	 **303**	0.1	23	0.33	97	 **304**
2	 **305**	0.1	23	0.5	92	 **306**
3	 **307**	0.1	23	14	95	 **308**
4	 **309**	0.1	23	7	78[b] (59:41 dr)	 **310**
5	 **311**	0.1	23	0.33	78	 **312**

Table 14: continued

6	 **313**	0.01	50	15	68	 **314**
7	 **315**	0.01	50	0.5	77	 **316**
8	 **317**	0.01	50	0.5	73	 **318**
9	 **319**	0.1	23	0.5	95	 **320**

[a]Isolated yield. [b]Diastereomer ratio (dr) determined by ^{1}H NMR

With the successful optimization for *N*-methyl oxindole substrate **303**, *N*-benzyl oxindole **305** was exposed to the reaction conditions. As expected, the product was easily generated to give the spiro-oxindole **306** in excellent yield after 30 minutes (entry 2). In the absence of a methyl or benzyl group, the free *N*-H oxindole substrate **307** provided the expected spiro-oxindole **308** in excellent yield. The reaction of **307** was significantly more sluggish than what had been previously observed for oxindole substrates **303** and **305** (entry 3). At this point

tryptophan derivative **309** was used instead of a tryptamine derivative, in an effort to see if any diastereoselectivity could be observed. Disappointingly, while desired spiro-oxindole **310** was isolated in high yield the product formed as a nearly 1:1 mixture of diastereomers (entry 4).

III.8.1: Different Structural Motifs and Reaction Re-Optimization

In an effort to further diversify the structural motifs accessible through this method, an elongated tethered bis-nucleophile **311** was employed. As previously noted with the indole bis-nucleophiles, the reaction was far slower with the longer tether, however, the product was isolated in acceptable levels of yield, giving the interesting 7-5 spirocyclic system **312**. When carbamate oxindole **313** was exposed to the optimized reaction conditions, a significant amount of oligomeric product formed, with the desired spiro-oxindole **314** forming in only 18% yield. The oligomeric product formation could be minimized by diluting the reaction conditions, elevating the temperature and changing the order of addition. Bis-nucleophile **313** was added as a solution to a solution of the dilute catalyst, ligand and propargyl *tert*-butyl carbonate, over a period of one hour. The purpose behind these modifications was to increase the effective dilution of the starting material, therefore favoring the intramolecular ring closing reaction. These changes proved to be highly effective, increasing the yield of **314** from 18% to 68% yield (entry 6).

Of additional interest is the fact that the product formed is not the expected isomer, correlating to initial reaction at the oxindole C3 position, but rather with the initial nucleophilic attack occurring from the carbamate nitrogen. Similar conditions to those used for **313** were required of the reaction of aryl amide **315**, which gave the more typical regioisomer **316** in good yield. Interestingly, when methyl amide substrate **317** was used, spiro-oxindole **318** was isolated and once again the isomeric product was formed exclusively (entry 8). Finally, when an *o*-phenol

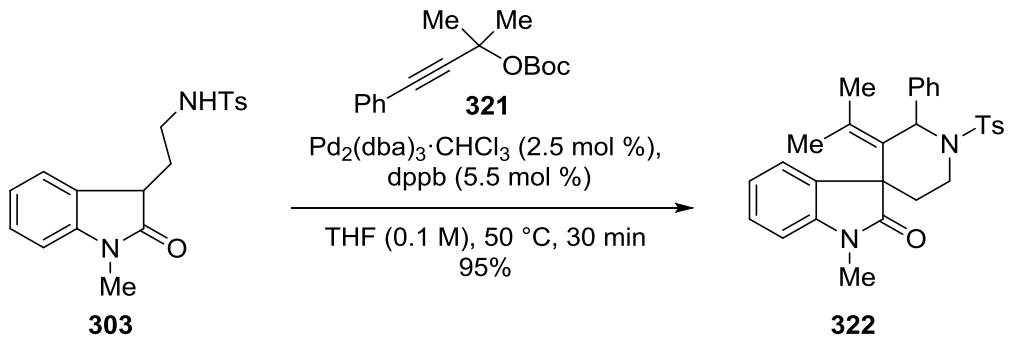
was tethered to the C3 position of *N*-methyl oxindole **319**, the reaction proceeded very smoothly to give the product **320** in near quantitative yield (entry 9).

III.9: Further Exploration of Substrate Scope and Enantioselective Variant

III.9.1: Use of Substituted Propargyl Carbonates

In an effort to further expand the substrate scope for the spirocyclization of oxindoles, a range of different substituted propargyl *tert*-butyl carbonates were reacted with oxindole **303** under the optimized reaction conditions. Unfortunately the products formed were composed of inseparable mixtures of stereo- and regioisomers. The exception to this was when the fully substituted propargyl *tert*-butyl carbonate **321** was combined with **303**. Under the reaction conditions highly decorated spiro-oxindole **322** was formed in near quantitative yield as a single diastereomer (Scheme 46).

Scheme 46: Use of Substituted Propargyl tert-Butyl Carbonates with Oxindole Bis-Nuclophiles

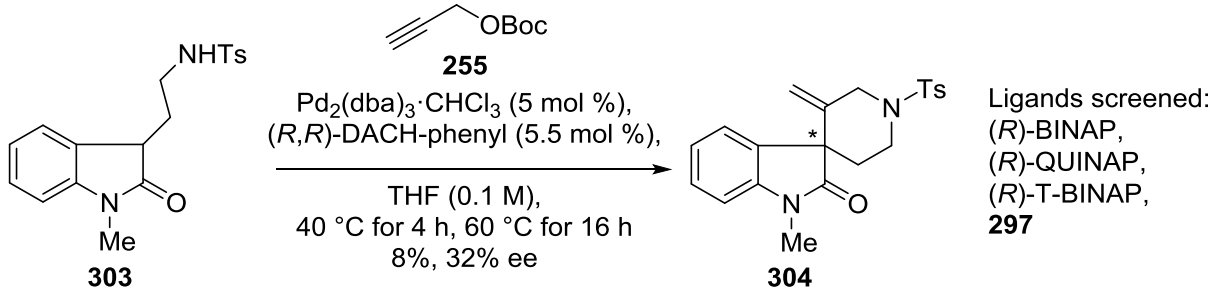


III.9.2: Development of an Enantioselective Spirocyclization of Oxindole Bis-Nucleophiles

Following the successful development of this methodology in regards to the racemic reaction, the possibilities of an enantioselective variant were explored (Scheme 47). Again demonstrating the differences between this methodology and that for the spiroindolenine formation, a screen of chiral ligands previously found effective uniformly gave no conversion to

the desired product **304**. Finally, when a DACH-phenyl ligand was used, under forcing conditions, the desired spiro-oxindole **304** was isolated in very poor yield and only modest levels of ee (32%).

Scheme 47: Enantioselective Reaction of Oxindole Bis-Nucleophile



III.9.3: Observations on Reactivity Patterns for Bis-Nucleophile Addition

Over the course of optimizing and screening substrates for this reaction the fact that certain substrates uniformly gave isomeric products is highly interesting. Upon examining the reported pKa values for aryl sulfonamide (16.1),[21] methyl amide (25.9),[22] phenyl amide (21.5),[23] phenol (18.0)[24] and oxindole (18.5)[25] no clear pattern emerged between pKa value and addition order. With the selectivity of palladium catalyzed alkylation of indoles, in regards to N verses C selectivity, often explained in terms of the hard – soft, acid – base (HSAB) heuristic it was thought that such considerations may apply here.[26] With the pKa values of the competing nucleophiles being so similar, conditions such as nucleophilicity, steric hindrance and HSAB

[21] Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T. Y.; Satish, A. V.; Whang, Y. E. *The Journal of Organic Chemistry* **1990**, *55*, 3330-3336.
[22] Bordwell, F. G.; Harrelson, J. A.; Lynch, T. Y. *The Journal of Organic Chemistry* **1990**, *55*, 3337-3341.
[23] Bordwell, F. G.; Ji, G. Z. *J. Am. Chem. Soc.* **1991**, *113*, 8398-8401
[24] Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *The Journal of Organic Chemistry* **1984**, *49*, 1424-1427.
[25] Bordwell, F. G.; Fried, H. E. *The Journal of Organic Chemistry* **1991**, *56*, 4218-4223.
[26] (a) Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1-20. (b) Ho, T.-L. *Tetrahedron* **1985**, *41*, 3-86.

compatibility with the generated palladium intermediates may dominate the order of the reaction. However, even with all of these competing interactions and influences, for all reactions screened absolute regioselectivity was observed, with only a single olefin isomer being observed for a specific bis-nucleophile.

III.10: Conclusion

Described here is a novel method for the palladium catalyzed formation of indolenine and oxindole spirocyclic compounds. The reactions are performed under mild conditions and generally provide the products in good to excellent yields. Furthermore the reactions are performed under low catalyst loadings, generally five mol %, and generate complex products. Not only has the basic reaction scope been explored, but investigations into modifying the propargyl *tert*-butyl carbonate and development of an enantioselective variation have been reported.

CHAPTER IV

PIPERAZINE AND LACTAM FORMATION VIA A PALLADIUM CATALYZED CYCLIZATION REACTION

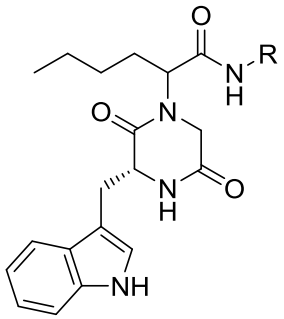
IV.1: Introduction

IV.1.1: Background into Drive for Methodology Development

A central goal in organic chemistry is the development of novel and versatile methods for the direct synthesis of complex structures. Indeed, an ideal method is one in which a chemist can simply combine basic, easily prepared and safely handled precursors in order to generate high value products in a direct fashion. Not only this, but the generated molecules should be easily isolated in good yield and give single regio- and/or stereoisomers. The difficulty of course arises due to the inherent tradeoff between ease of use and reactivity. Compounds which are stable to ambient atmospheric conditions such as oxygen and water, are generally stable because they are inherently less reactive. Furthermore when compounds are simply combined, avoiding thermodynamic mixtures of products becomes a non-trivial problem. A solution to these issues often comes from the use of a catalyst, a compound which can lower the activation energy of a chemical reaction, therefore increasing the effective reactivity of otherwise stable compounds, and organizing the reaction space and transition structures giving control over what products can be formed.

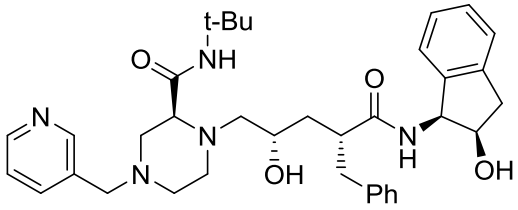
IV.1.2: Piperazine Biological and Chemical Significance

Scheme 48: Examples of Bioactive Piperazines



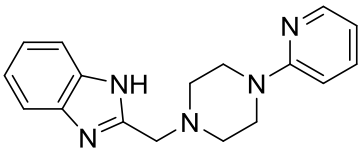
CCK-B receptor antagonist

323



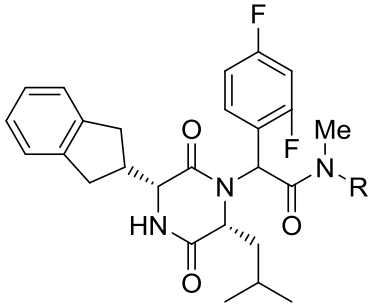
Indinavir
HIV protease inhibitor-Roche

324



ABT-724
Erectile Dysfunction-Abbot

325



WO2003053443
Oxytocyn antagonist

326

A class of structures of particular interest and importance are nitrogen containing heterocycles. The importance of the indole core has been previously described and clearly demonstrated; however another important structure is piperazine. The piperazine core is widely found in many different molecules including pharmaceuticals,[1] natural products,[2] and other drug like

[1] (a) Dua, R.; Shrizastava, S.; Sonwane, S. K.; Sricastava, S. K. *Advances in Biological Research* **2011**, *5*, 120-144. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (c) Aldeghi, M.; Malhotra, S.; Selwood, D. L.; Chan, A. W. E. *Chemical Biology & Drug Design* **2014**, *83*, 450. (d) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845.

[2] (a) Ciufolini, M. A. *Il Farmaco* **2005**, *60*, 627. (b) Nicolaou, K. C.; Chen, J. S. *Pure Appl. Chem.* **2008**, *80*, 727-742. (c) Royer, J. *Asymmetric Synthesis of Nitrogen Heterocycles*; Wiley-

compounds.[3] A selection of pharmaceutical agents bearing a central piperazine motif are shown (Scheme 48), ranging from the simplistic to the complex and displaying a wide range of activities.[4]

IV.2: Background

IV.2.1: Functionalization of Piperazine Core

Traditionally there are a number of different methods for accessing piperazines and their related compounds.[5,6] The most basic methods involve the decoration of a piperazine molecule, reactions occurring at either or both nitrogens (Scheme 49).

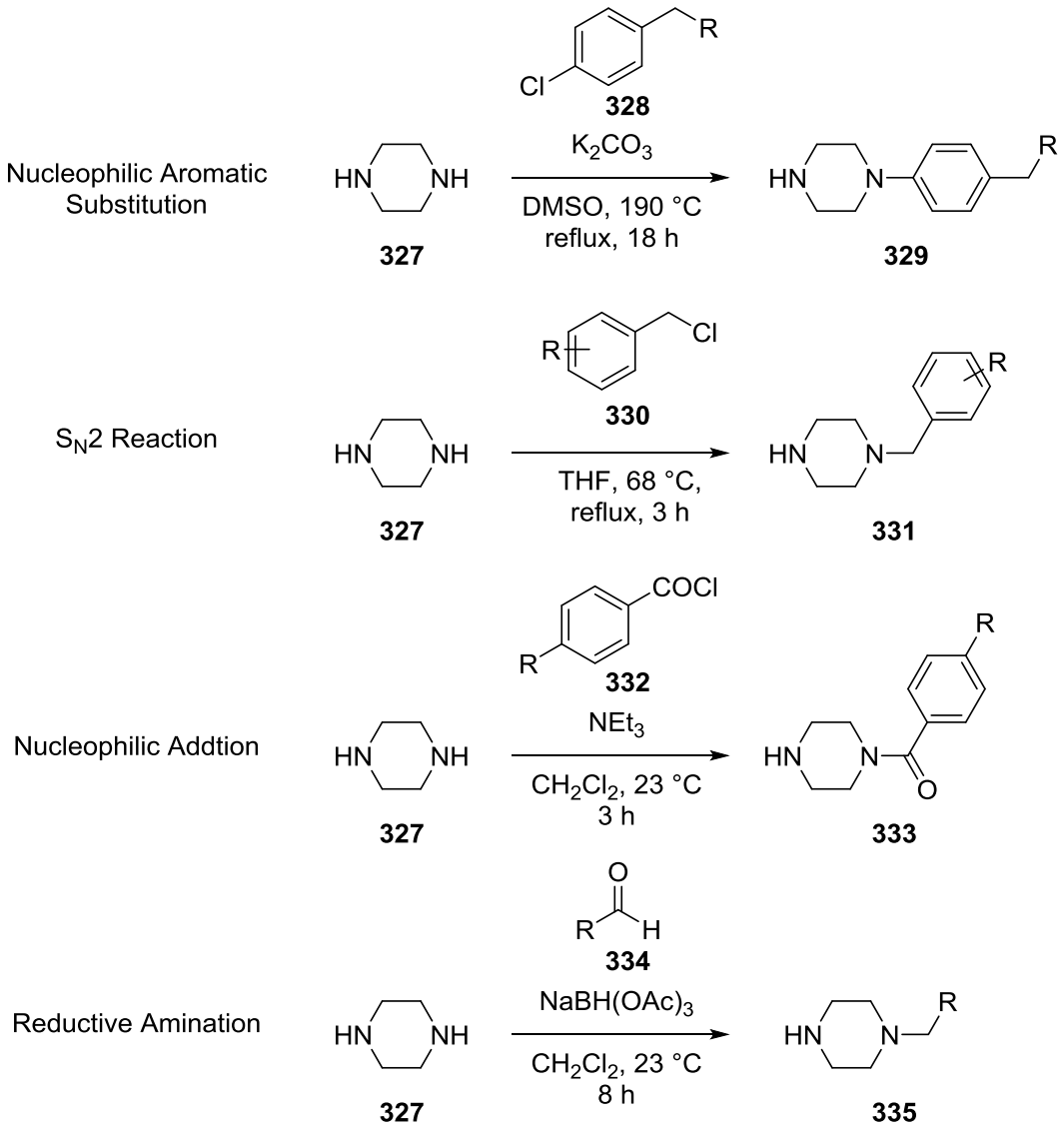
VCH Verlag GmbH & Co. KGaA: **2009**. (d) van den Broek, S. A. M. W.; Meeuwissen, S. A.; van Delft, F. L.; Rutjes, F. P. J. T. *In Metathesis in Natural Product Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: **2010**, p 45. (e) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat Chem* **2012**, *4*, 130. (f) Chen, P. Ph.D. Thesis, Simon Fraser University **2012**.

[3] (a) Asif, M. *Med. Chem.* **2012**, *2*, 151-167. (b) Minyar, P. B.; Murumkar, P. R.; Patil, P. S.; Barmade, M. A.; Bothara, K. G. *Min-Reviews in Medicinal Chemistry*, **2013**, *13*, 1607-1625. (c) Patel, R. V.; Park, S. W. *Mini-Reviews in Medicinal Chemistry*, **2013**, *13*, 1579-1601.Mordini, A.; Reginato, G.; Calamante, M.; Zani, L. *Current Topics in Medicinal Chemistry*, **2014**, *14*, 1308-1316.

[4] (a) Shiosaki, K.; Nadzan, A. M.; Garvey, D. S.; Shue, Y.-K.; Brodie, M. S.; Hooaday, M. W.; Chung, J. Y.-L.; Tufano, M.D.; May, P. D. *Peptide analog type-B CCK receptor ligands.* U.S. Patent US5340802 A1; January 29, 1993. (b) Wilkerson, W. W.; Akamike, E.; Cheatham, W. W.; Hollis, A. Y.; Collins, R. D.; DeLucca, I.; Lam, P. Y. S.; Ru, Y. *J. Med. Chem.* **1996**, *39*, 4299-4312. (c) Cowart, M. D.; Bhatia, P. A.; Daanen, J. F.; Stewart, A. O.; Patel, M. V.; Kolara, T.; Brioni, J. D.; Rohde, J. B*enzimidazoles that are useful in treating sexual dysfunction.* U.S. Patent US2002/169167 A1; March 8, 2002. (d) Borthwick, A. D.; Davies, D. E.; Exall, A. M.; Hatley, R. J. D.; Hughes, J. A.; Irving, W. R.; Livermore, D. G.; Sollis, S. L.; Nerozzi, F.; Valko, K. L.; Allen, M. J.; Perren, M.; Shabbir, S. S.; Woollard, P. M.; Price, M. A. *J. Med. Chem.* **2006**, *49*, 4159-4170.

[5] For a selection of reviews on piperazine synthesis see : (a) Kitchen, L. J.; Pollard, C. B. *J. Am. Chem. Soc.* **1947**, *69*, 854-855. (b) Henry, D. W. *J. Heterocycl. Chem.* **1966**, *3*, 503-511. (c) Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297-3312. (d) Tan, Y.; Wang, S. J.; Wang, Y. T.; Gao, B. X.; Ba, X. W. *Synth. Commun.* **2010**, *40*, 3648-3653. (e) Liu, T.; Weng, Z.; Dong, X.; Chen, L.; Ma, L.; Cen, S.; Zhou, N.; Hu, Y. *PLoS ONE* **2013**, *8*, e53636. (f) Al-Ghorbani, M.; Begum, B.; Zabiulla, A.; Mamatha, S. V.; Khanm, S. A. *Journal of Chemical and Pharmaceutical Research*, **2015**, *7*, 281-301.

Scheme 49: Reaction of Piperazine at the Nitrogen



The obvious limitation to this method is the inability to manipulate the core carbons of the piperazine, denying the possibility of additional diversification of the piperazine structure.

[6] For a selection of recent papers on piperazine synthesis see : (a) Romba, J.; Kuppert, D.; Morgenstern, B.; Neis, C.; Steinhauser, S.; Weyhermüller, T.; Hegetschweiler, K. *Eur. J. Inorg. Chem.* **2006**, *2006*, 314-328. (b) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820-1821.

This represents a significant stumbling block, as the ability to easily manipulate all positions of base materials is of great importance in medicinal chemistry.

The nitrogen of piperazine can be reacted in a number of ways. Arylation occurs though a nucleophilic aromatic substitution reaction and requires very harsh conditions. Formation of the benzyl variation is accomplished by simple reaction of piperazine **327** with a benzyl chloride **330**. Amide formation is acomplished through nucleophilic addition of the piperazine **327** to an acid chloride **332**. Various alkyl groups can be installed via *in situ* imine formation and reduction with a mild reducing agent. For all these processes over reaction, the addition of multiple equivalents to a single piperazine, presents a real limitation to the chemistry. Other methods involving cyclization of the piperazine core are detailed in (Scheme 50).

IV.2.2: Standard Methods for Piperazine Synthesis

Piperazine can be synthesized by simply reacting diamine **336** with Raney nickel,[7] giving piperazine **327** and water, which is subsequently removed by distillation (reaction 1).[8] Another method involves the reaction of ethylenediamine **337** with compound **338** via an S_N2/amide formation type mechanism to give piperazinone **339**. Piperazinone **339** can then be reduced with $LiAlH_4$ to give the substituted piperazine **340** (reaction 2).[9] A similar product can be accessed via a different method (reaction 3), involving opening of phenyl-nitro-peroxide **341** with diamine **337**, followed by reduction of the formed imine to give a 2:1 ratio of *cis/trans* isomers in modest

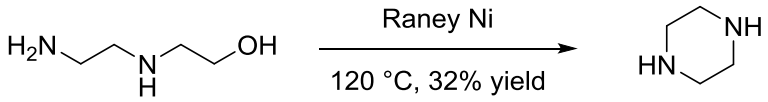
[7] (a) Fouilloux, P. *Applied Catalysis* **1983**, *8*, 1-42. (b) Yang, T.-K.; Lee, D.-S.; Haas, J. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: 2001.
[8]Kitchen, L. J.; Pollard, C. B. *J. Am. Chem. Soc.* **1947**, *69*, 854-855.
[9] Schmiesing, R. J. *Processes for the preparation of trans-1,3,4,6,7,11b-hexahydro-7-aryl-2H-pyrazino[2,1-a]isoquinolines as antidepressants, antihistaminics, and chloinergics*. U.S. Patent: 4772705 A; September 20, 1988.

yield.[10] Nitrogen can function as a nucleophile in the S_N2 displacement of a leaving group to give cyclized piperazines **345** and **348** (reactions 4,5).[11, 12]

[10] Vidal-Albalat, A.; Rodríguez, S.; González, F. V. *Org. Lett.* **2014**, *16*, 1752-1755.
[11] Huang, J.; Xu, W.; Xie, H.; Li, S. *The Journal of Organic Chemistry* **2012**, *77*, 7506-7511.
[12] Sengupta, S.; Sahu, D. P.; Chatterjee, S. K. *Liebigs Ann. Chem.* **1993**, *1993*, 437-439.

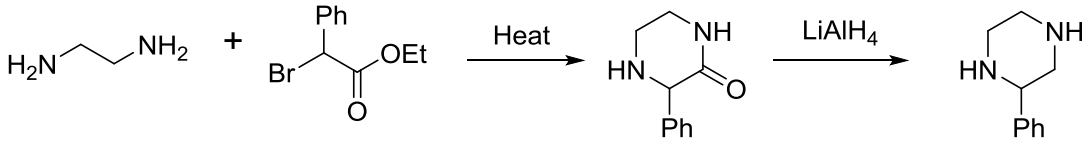
Scheme 50: Methods for Synthesis of Piperazine

Reaction 1



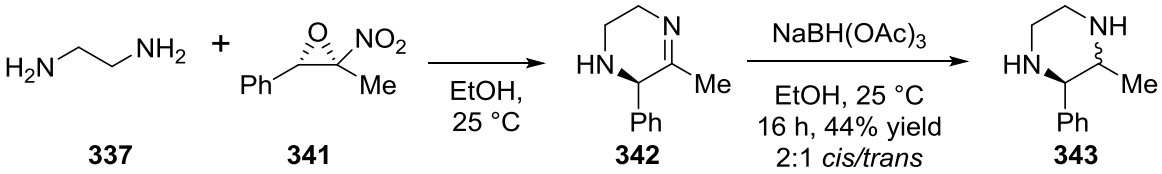
336 **327**

Reaction 2



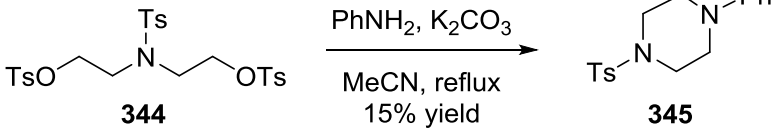
337 **338** **339** **340**

Reaction 3



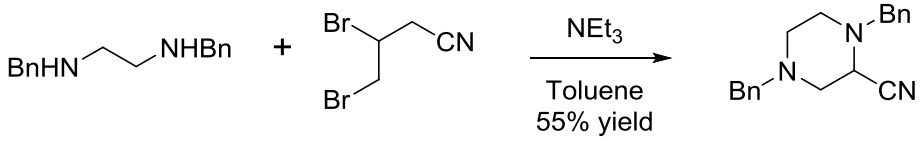
337 **341** **342** **343**

Reaction 4



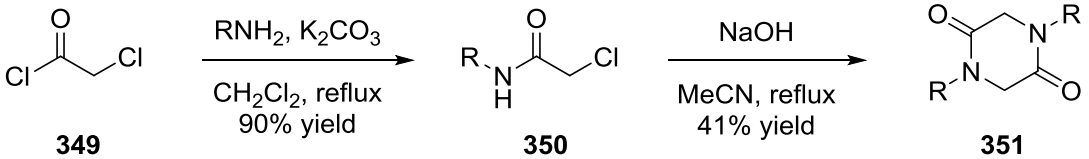
344 **345**

Reaction 5



346 **347** **348**

Reaction 6



349 **350** **351**

Reaction of an amine with α-chloro-acid chloride **349** gives α-chloro-amide **350**, which under basic conditions can dimerize to give compound **351** (reaction 6).[13] Many of these reactions require harsh reaction conditions, such as high refluxing temperatures and hazardous reagents, and provide the products in low to modest yields. Further development of methods for piperazine synthesis has been accomplished through the use of metal catalysts (Scheme 51).

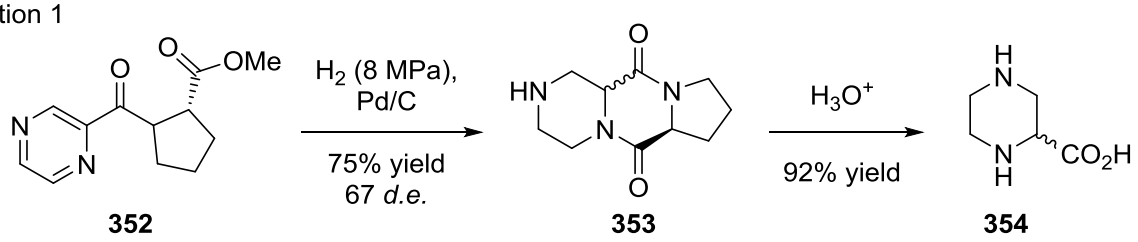
IV.2.3: Synthesis of Piperazines via Metal Catalysis

Kukula and coworkers were able to form enantioenriched piperazines via a two-step protocol.[14] After palladium mediated hydrogenation of the diazine ring and addition to the methyl ester, compound **353** was formed as a mixture of diastereomers. Following cleavage of the chiral proline auxiliary under acidic conditions, piperazine **354** was revealed in good yield and modest ee (reaction 1). In one of the most direct methods for piperazine synthesis to date Madsen et al. demonstrated that protected diamine **355** can be combined with a basic 1,2-diol to give piperazine product **356** (reaction 2).[15] The use of a palladium catalyst was shown to effectively catalyze an intramolecular amination/Heck process starting with allyl amine **357** and gave a mixture of products, with piperazine **358** being the major component of the mixture (reaction 3).[16]

[13] Cho, S.-D.; Song, S.-Y.; Kim, K.-H.; Zhao, B.-X.; Ahn, C.; Joo, W.-H.; Yoon, Y.-J.; Falck, J. R.; Shin, D.-S. *ChemInform* **2004**, *35*.
[14] Kukula, P.; Prins, R. *J. Catal.* **2002**, *208*, 404-411.
[15] Nordstrom, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034-5036.
[16] Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279-3282.

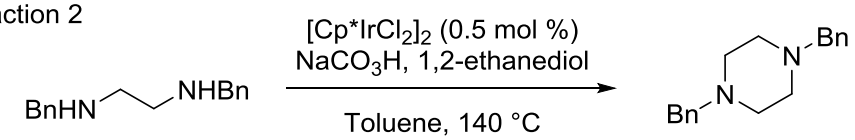
Scheme 51: Metal Catalyzed Piperazine Formation

Reaction 1



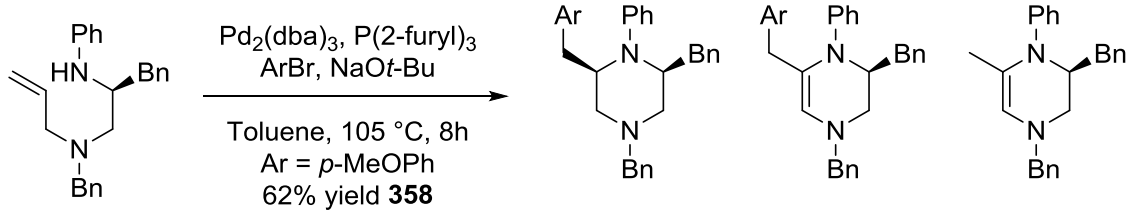
352 **353** **354**

Reaction 2



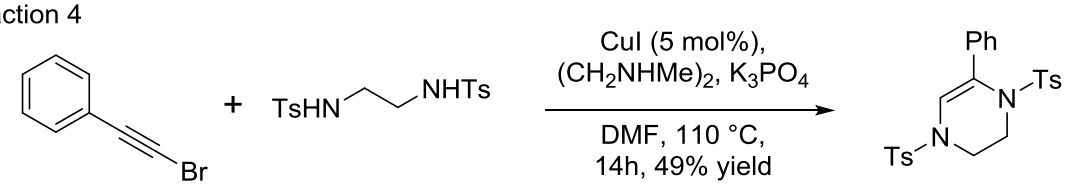
355 **356**

Reaction 3



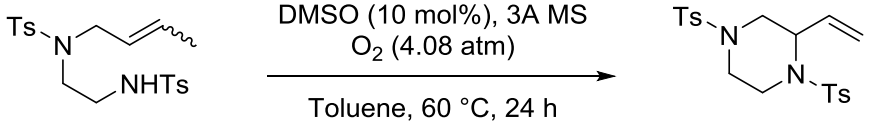
357 **358** 71% conv. **359** 7% conv. **360** 21% conv.

Reaction 4



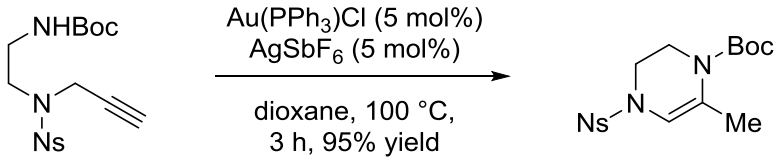
361 **362** **363**

Reaction 5



364 **365**

Reaction 6



366 **367**

In 2008 Urabe and coworkers developed a very nice method for combining halo-alkynes with bis-sulfonamides under copper catalyzed conditions.[17] The reaction is thought to proceed through initial displacement of the bromide by sulfonamide **362** followed by copper mediated ring closure to give **363** in moderate yield. Stahl et al. showed an interesting method for the palladium mediated ring closure of an allyl sulfonamide **364**.[18] Forcing conditions were required, high pressure and temperature, in order to effect this transformation in greater than ten percent yield (reaction 5). Finally the group of Prof. Nelson demonstrated the use of a tethered propargyl sulfonamide **366**, for catalyzed piperazine synthesis.[19] Indeed, under gold catalysis, the reaction gave the desired unsaturated piperazenine **367** in excellent yield (reaction 6). While all of these methods do give access to piperazines in modest to high yields, the reactions still uniformly require heating and harsh conditions. Additionally many of the examples listed have poor substrate scope, limiting their synthetic utility and only function well for specific substrates.

With the importance of the scaffold well-established, and clear need for new methods to access the piperazine core, alternative means for synthesizing piperazines is of critical importance. In this chapter a method is presented for the mild preparation of highly substituted and structurally diverse piperazines and piperazinones from simple building blocks via a high yielding palladium catalyzed transformation.[20]

IV.3: Method Discovery and Optimization

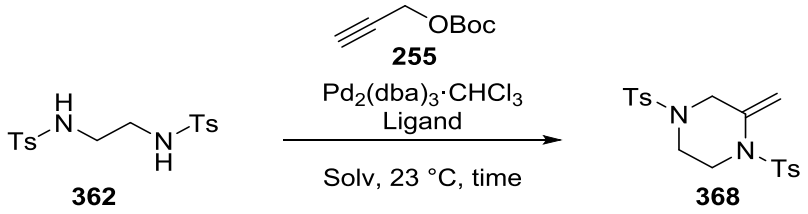
Inspiration for this chemistry came from the work previously described with indole and oxindole tethered bis-nucleophiles. The use of a sulfonamide as one of the nucleophilic partners

[17] Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820-1821.
[18] Lu, Z.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 1234-1237.
[19] James, T.; Simpson, I.; Grant, J. A.; Sridharan, V.; Nelson, A. *Org. Lett.* **2013**, *15*, 6094-6097.
[20] Montgomery, T. D.; Rawal, V. H. Paper submitted for publication, **2015**.

was key for the successful application of the spirocyclization chemistry. It was then hypothesized that the easily prepared ethyl bridged bis-toluenesulfonamide **362** could react with propargyl *tert*-butyl carbonate **255** to provide easy access to piperazine **368** bearing an exocyclic olefin moiety (Table 15).

IV.3.1: Initial Results and Examination of Solvent

Table 15: Optimization of Palladium Catalyzed Piperazine Formation



Entry	Pd (mol %)	Ligand	Solv.	Time (min)	yield (%)[a]
1	5	DPEphos	Acetone	30	71
2	5	DPEphos	MeCN	30	90
3	5	DPEphos	CH_2Cl_2/MeCN	30	10
4	5	DPEphos	CH_2Cl_2	10	>95
5	5	xantphos	CH_2Cl_2	10	>95
6	5	dppb	CH_2Cl_2	10	87
7	5	dppf	CH_2Cl_2	10	>95
8	5	dppe	CH_2Cl_2	10	NR
9	5	(R)-BINAP	CH_2Cl_2	10	NR
10	5	P(2-furyl)$_3$	CH_2Cl_2	10	>95
11	5	P(*t*-Bu)$_3$	CH_2Cl_2	10	NR
12	3	DPEphos	CH_2Cl_2	20	98[b]
13	2	DPEphos	CH_2Cl_2	110	90
14	1	DPEphos	CH_2Cl_2	240	50
15	0.5	DPEphos	CH_2Cl_2	240	NR

[a]NMR yield based on internal standard. [b]Isolated yield.

The initial reaction conditions selected gave desired product **368** in good yield after only 30 minutes. By changing the solvent to acetonitrile the yield was increased to 90% (entry 2). Surprisingly when a mixed solvent system of acetonitrile and dichloromethane was used the reaction gave a very poor yield. Thse conditions were selected due to previous success with dichloromethane as solvent (entry 3). A new and even more puzzling development occurred when dichloromethane was substituted in as the solvent; the starting material was poorly soluble, giving a heterogeneous mixture, however after ten minutes the reaction had become homogeneous and showed complete conversion to desired product **368** (entry 4).

IV.3.2: Examination of Ligands and Catalyst Loading for Piperazine Synthesis

With this exciting result in hand a range of other ligands were subsequently screened, bidentate ligands xantphos (entry 5) and dppf (bis(diphenylphosphino)ferrocene) (entry 7) giving excellent conversion to piperazine **368**. Interestingly bidentate ligands dppe (bis(diphenylphosphino)ethane) (entry 8) and (*R*)-BINAP (entry 9) failed to effect any conversion to desired product **368**. Of the monodentate ligands screened, trifuryl phosphine provided **368** in excellent yield while tri(*tert*-butyl)phosphine shut the reaction down completely (entries 10, 11). After additional experiments, the original ligand DPEphos was selected as the optimal ligand and the catalyst loading was lowered to as low as 1.0 mol% palladium catalyst. When the loading was reduced still further no conversion to desired piperazine **368** was observed after 4 hours (entry 15). A catalyst loading of 3 mol% palladium[21] was selected as representing the optimal compromise between low catalyst loading, high yield and a short reaction time.

[21] 1.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$

IV.4: Substrate Scope for Synthesis of Piperazines

A range of substrates were screened for compatibility with the reaction parameters. Substrates were selected to demonstrate the versatility of the reaction and provide examples of unique structural motifs which can be accessed through this chemistry (Table 16).

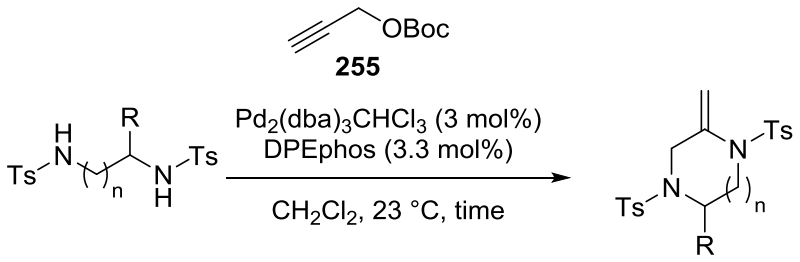
IV.4.1: Use of Symmetrical Bis-Sulfonamides

After the optimized substrate it was shown that a different bisarylsulfonamide **369** was compatible with the reaction conditions and provided piperazine **370** in excellent yield (entry 2). The alkyl linker between the two nucleophiles could be increased to propyl **371** giving easy access to the analogous seven-membered nitrogen heterocycle **372**. This heterocyclic system could also be formed with a geminal dimethyl group, generating heterocycle **374** (entries 3, 4). The ring size could be further enlarged by exposing 1,4-butyl spaced bis-sulfonamide **375** to the reaction conditions. Interestingly the larger eight membered heterocycle **376** formed more easily than the smaller seven membered heterocycle **372** (entry 5). It should be noted that this chemistry appears to be much more tolerant than that previously explored with the spirocyclization of indole and oxindole with respect to linker length.

IV.4.2: Non-Symmetrical Substrates and Regiochemical Control

At this point non-symmetrical bis-nucleophile **377** was used in the reaction. Gratifyingly **377** gave complete conversion to substituted piperazine **378** with modest levels of selectivity (3:1) (entry 6). When entioenriched bis-sulfonamide **379** was used in the reaction, the major regioisomer **380** could be cleanly isolated in high yield (entry 7).

Table 16: Substrate Scope for Palladium Catalyzed Formation of Piperazines



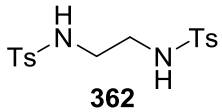
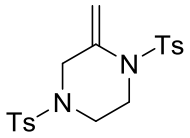
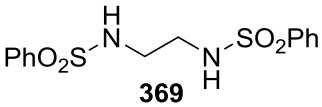
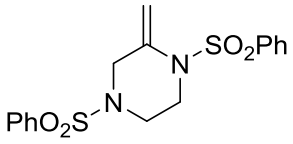
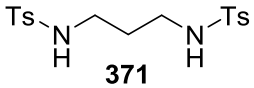
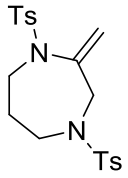
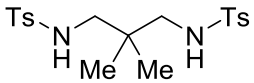
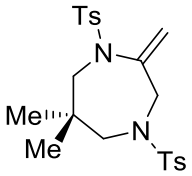
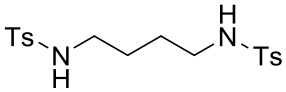
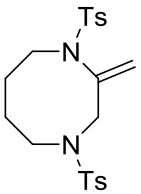
Entry	Substrate	Time	Yield[a]	Product
1	 **362**	20 min	98	 **368**
2	 **369**	20 min	93	 **370**
3	 **371**	3 h	90	 **372**
4	 **373**	90 min	98	 **374**
5	 **375**	75 min	90	 **376**

Table 16. continued

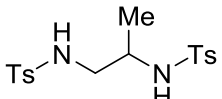
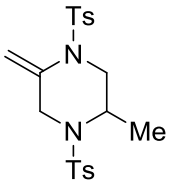
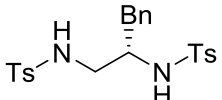
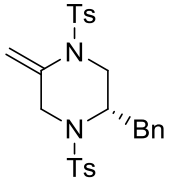
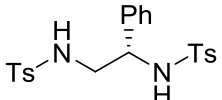
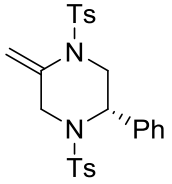
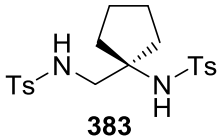
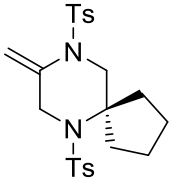
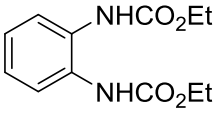
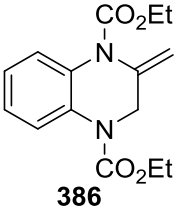
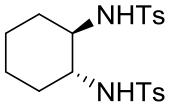
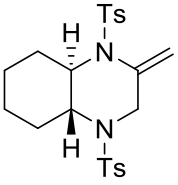
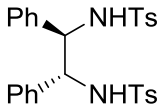
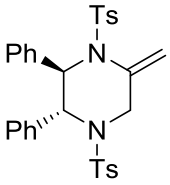
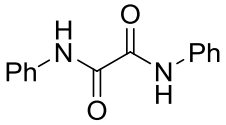
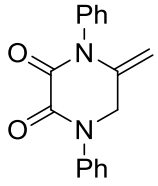
6	 **377**	3 h	97 3:1 regioisomers	 **378**
7	 **379**	15 min	80	 **380**
8	 **381**	10 min	92	 **382**
9	 **383**	45 min 50 min	98 34	 **384**
10	 **385**	45 min	95	 **386**
11	 **387**	60 min	94	 **388**

Table 16. continued

12	 **389**	60 min	94	 **390**
13	 **391**	24 h	21	 **392**

[a]Isolated yield

Excitingly, when phenyl substituted bis-sulfonamide **381** was combined with propargyl *tert*-butyl carbonate **255**, the resulting piperazine **382** formed as a single regioisomer and presumably a single enantiomer (entry 8). Like with phenyl substituted compound **382**, spirocyclized piperazine **384** was formed in near quantitative yield after only 45 minutes as a single regioisomer (entry 9).

IV.4.3: Synthesis of Fused Bicyclic Systems and Other Structural Themes

In an effort to generate different structural motifs, methyl carbamate protected diaminobenzene **385** was prepared and produced expected product **386** in only moderate yield (entry 10). Analysis of the reaction mixture showed that starting material had been fully converted into a mixture of bicyclic product **386** and unidentified oligiomeric biproducts. When bis-sulfonamide analog of (*R,R*)-cylcohexanediamine **287** was exposed to the optimized conditions the resulting fused piperazine structure **288** was isolated in excellent yield. Another entioenriched bis-sulfonamide **389** was prepared and tested, giving clean conversion to the

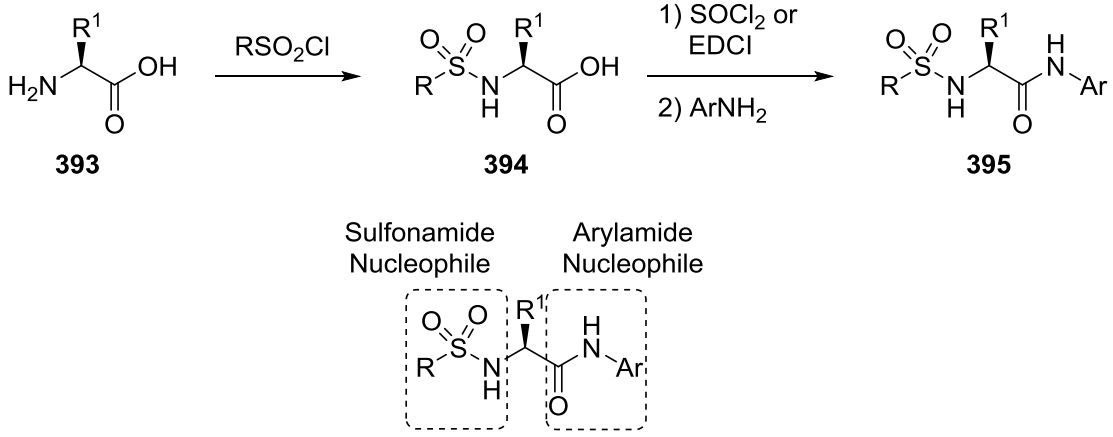
highly substituted and sterically hindered piperazine **390** in near quantitative yield (entry 12). A structurally distinct bis-nucleophile was bis-aryl amide **391**, arising from addition of aniline to oxalyl chloride. While the reaction was sluggish and only furnished 21 percent yield of desired cyclo-bisamide **392** this represents a simple method for producing another structural motif (entry 13).

IV.5: Substrate Scope for Synthesis of Piperazinones

IV.5.1: Inception and Realization of Amino Acid Substrates

While the yield of compound **392** was disappointing, it represented an important fact, aryl amides were competent nucleophiles for this reaction. With this in mind a new group of highly interesting possible substrates were envisioned, substrates based on amino acids (Scheme 52). If amino acid based substrates proved to be amenable to the reaction parameters then a wide range of substrates could be formed, bearing different substitution patterns and giving enantioenriched products.

Scheme 52: Preparation of Amino Acid Substrates



The preparation of such substrates was envisioned to proceed through a two-step process. Initial formation of the sulfonamide could be easily accomplished in the presence of the less nucleophilic carboxylic acid moiety[22] using standard conditions.[23] After purification of the resulting sulfonamide **394**, the carboxylic acid could be transformed into the aryl amide either via conversion into the acid chloride followed by addition of an aryl amine[24] or through an EDCI mediated coupling reaction.[25] The formed substrate **395** would now bear both a sulfonamide and an aryl amide nucleophilic center, as well as possibly a chiral center. Another advantage of this planned synthetic scheme is it allowed for the modulation of three positions (R, R^1 and Ar) over a two-step sequence. With a short, feasible and flexible route to these amino acid based substrates established, a number of compounds were synthesized and exposed to the optimized reaction conditions (Table 17).

IV.5.2: Substrate Scope of Reaction of Amino Acid Substrates with Propargyl Carbonate

The first attempt of reacting an amino acid based substrate with propargyl *tert*-butyl carbonates was made using modified glycine residue **396**. Glycine based substrate **396** was selected to test the concept of the proposed reaction because it possessed the simplest possible carbon skeleton. Excitingly the reaction proceeded as expected and clean conversion to piperazinone **397** was observed (entry 1). Additionally the product formed with complete regioselectivity, giving the shown regioisomer in excellent yield.

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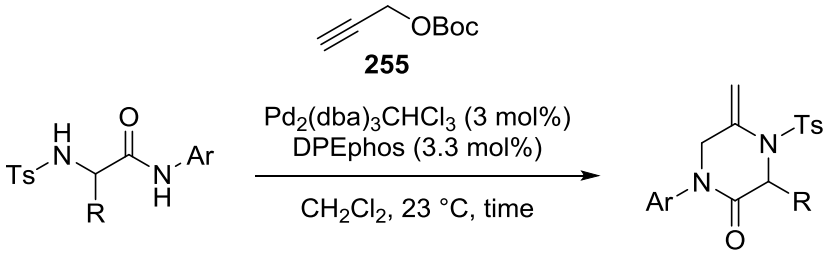
[22] For general trends on the reactivity of various nucleophiles see: Carey, F. A. *Organic Chemistry: Sixth Edition*; McGraw-Hill Companies, Inc.: New York, NY, 2006.

[23] (a) Craig, D.; Hyland, C. J. T.; Ward, S. E. *Chem. Commun.* **2005**, 3439-3441. (b) Simsek, S.; Horzella, M.; Kalesse, M. *Org. Lett.* **2007**, *9*, 5637-5639. (c) Ajani, O. O.; Familoni, O. B.; Wu, F.; Echeme, J. O.; Sujiang, Z. *International Journal of Drug Design and Discovery*, **2013**, *4*, 983-993.

[24] Aguilar-Castro, L.; Tlahuextl, M.; Tapia-Benavides, A. R.; Tlahuext, H. *Heteroat. Chem* **2003**, *14*, 247-253.

[25] Sheehan, J.; Cruickshank, P.; Boshart, G. *The Journal of Organic Chemistry* **1961**, *26*, 2525-2528.

Table 17: Substrate Scope of Palladium Catalyzed Piperazinone Formation



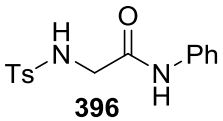
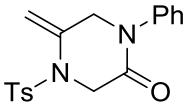
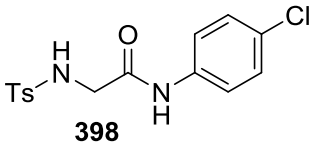
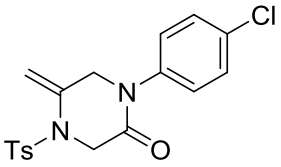
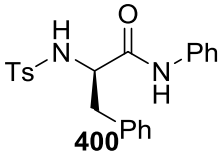
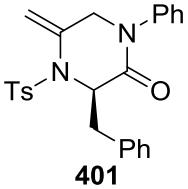
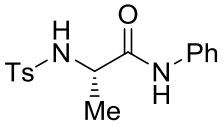
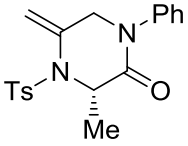
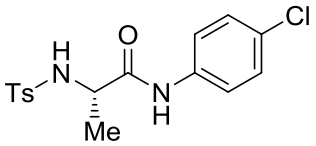
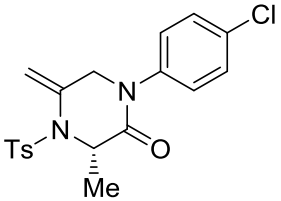
Entry	Substrate	Time	Yield[a]	Product
1	 **396**	30 min	93	 **397**
2	 **398**	90 min	99	 **399**
3	 **400**	45 min	98	 **401**
4	 **402**	4 h	98	 **403**
5	 **404**	1 h	98	 **405**

Table 17. continued

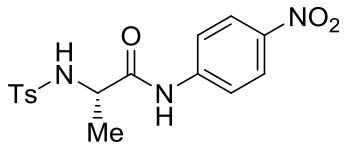
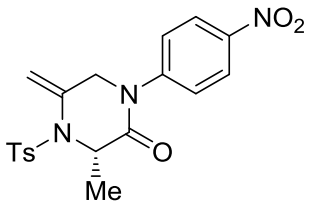
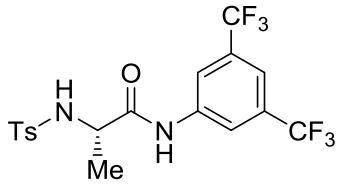
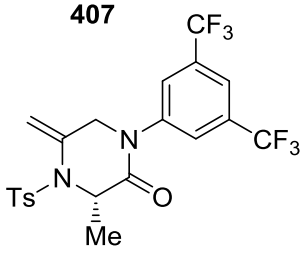
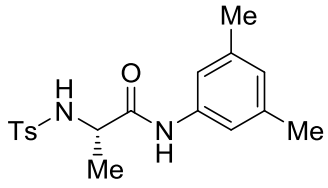
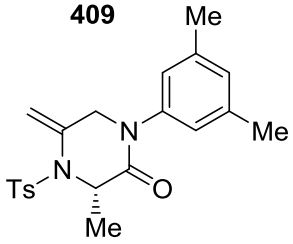
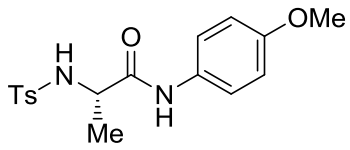
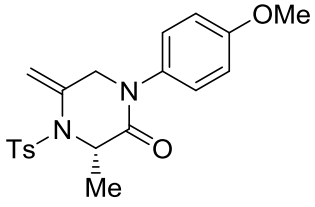
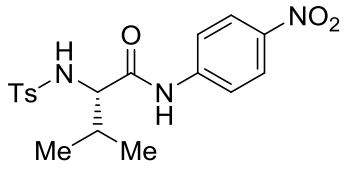
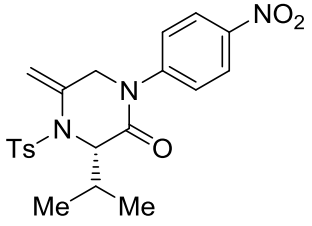
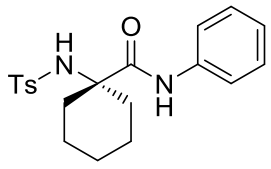
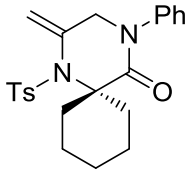
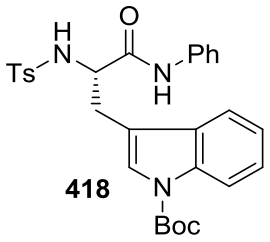
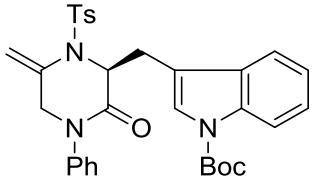
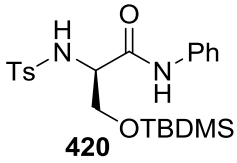
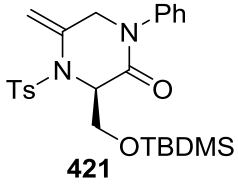
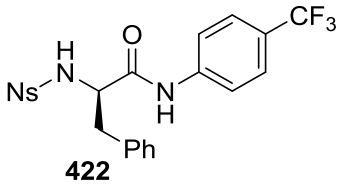
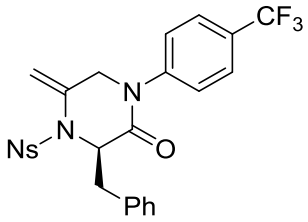
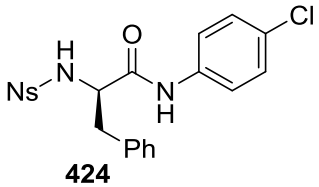
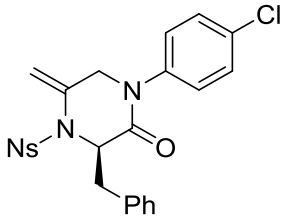
6	 **406**	1 h	97	 **407**
7	 **408**	75 min	62	 **409**
8	 **410**	5 h	61	 **411**
9	 **412**	5 h	98	 **413**
10	 **414**	36 h	85	 **415**
11	 **416**	100 min	98	 **417**

Table 17. continued

12	 **418**	3.5 h	97	 **419**
13	 **420**	5 h	97	 **421**
14	 **422**	24 h	97	 **423**
15	 **424**	28 h	99	 **425**

[a]Isolated yield

The phenyl group could be substituted for the more electron withdrawing *p*-chlorophenyl group without compromising the reaction and piperazinone **399** was isolated in quantitative yield after only ninety minutes (entry 2). Following this initial success, the modified glycine substrate was substituted for modified (D)-phenylalanine substrate **400**. The substrate proved to be perfectly compatible with the reaction conditions and the penta-substituted piperazinone **401** was generated in excellent yield (entry 3).

IV.5.3: Examination of Electronically Different Aryl Amides

Similarly, the substrate based on (L)-alanine **402** gave the methyl substituted product **403** in high yield, though a longer reaction time was required. Taking advantage of the modular nature of the synthetic route to this family of substrates, a variety of electron deficient and electron rich aryl groups were incorporated into (L)-alanine based substrates (entries 5-9). Generally the electron deficient aryl substituents gave superior results to the electron rich aryl groups. This is best demonstrated by comparing substrates **408** and **410**, with the electron defiant substrate **408** reacting in almost 1/5 the time. It should also be noted that regardless of the electronic nature of the aryl amide, perfect regiochemical control was observed with the products generated, corresponding to initial reaction at the sulfonamide nitrogen.

IV.5.4: Sterically Congested and Structurally Diverse Substrates

When a (L)-valine derived substrate was prepared it initially proved to be very poorly reactive, giving trace levels of yield, even after prolonged reaction times. This low reactivity necessitated the use of a more reactive electron deficient aryl group **414** to produce hindered piperazinone **415** in high yield (entry 10). Surprisingly the seemingly more hindered substrate **416** cleanly proceeded to desired spirocyclic compound **417** in basically quantitative yield after less than two hours (entry 11). Up to this point the substrates tried had only possessed side chain functionality which does not lend itself to further reactivity, *i.e.* aliphatic and aryl groups.

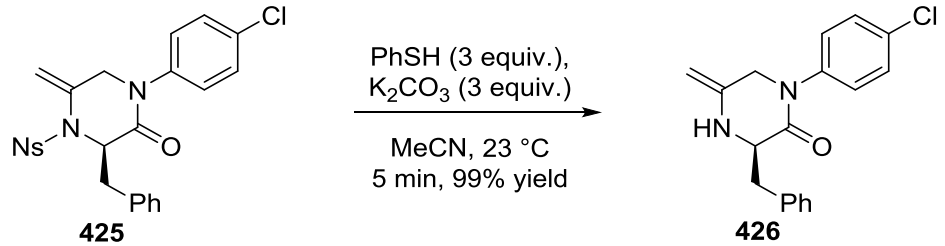
In an effort to demonstrate the selectivity/versitility of the reaction the more interesting (L)-tryptophan based substrate **418** was prepared through a three step protocol. The third step involved the selective Boc protection of the indole nitrogen; when the unprotected substrate was used no reaction was observed with complete recovery of starting material. When compound **418** was exposed to the reaction conditions clean conversion to piperazinone **419** was observed. This

shows an excellent level of selectivity, as indole is a competent nucleophile for this reaction and no spirocyclized product nor intermolecular pseudo-dimerization was observed (entry 12). With this success, (D)-serine based substrate **420** was synthesized, incorporation of a silyl group was necessary due to the poor solubility of the free alcohol in non-protic solvents and its propensity to cyclize or oligiomerize during the amide forming step. With the protected substrate in hand the reaction proceeded smoothly to give piperazinone **421** in excellent yield with the incorporation of a useful synthetic handle (entry 13).

IV.5.5: Use of Easy Cleaved Nosyl Protected Sulfonamide Substrates

Furthering the goal of developing a versatile reaction, the tosyl group could be substituted for nosyl with *p*-trifluromethylphenyl substrate **422** and *p*-chlorophenyl substrate **424**. Both substrates, while somewhat less reactive than parent tosyl compound **400**, gave the desired piperazinones (**423**, 97%) and (**425**, 99%) as single regioisomers in near quantitative yield (entries 14,15). The loss of reactivity from tosyl to nosyl may be due to the greater electron withdrawing capability of *o*-nitro benzene as compared to toluene, therefore rendering the sulfonamide less nucleophilic. The advantage of using a nosyl protecting group is that a nosyl group can be easily removed under very mild conditions (Scheme 53).

Scheme 53: Removal of Nosyl Protecting Group



425 **426**

Piperazinone **425** was stirred with potassium carbonate in acetonitrile, after the addition of thiophenol the nosyl group was quantitatively and cleanly removed to give free amine **426**. Interestingly there was no observed isomerization of the exocyclic olefin to give either the endocyclic olefin or the imine, even after aqueous workup, purification and exposure to ambient atmosphere for several days.[26] This ability to cleanly generate a free vinyl secondary amine further demonstrates the value and utility of this chemistry.

IV.6: Use of Substituted Propargyl Carbonates and Mechanistic Insights

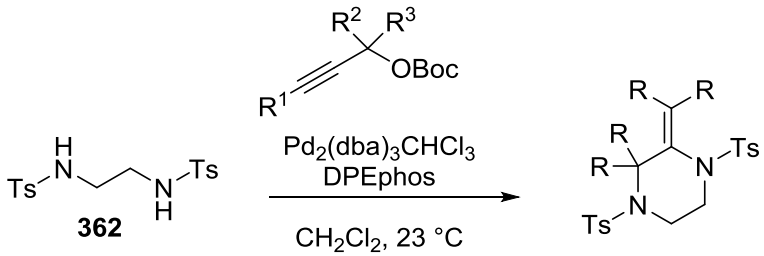
With a broad range of substitution patterns possible on both the carbon backbone and the nucleophilic nitrogens it was wondered if these bis-sulfonamide substrates would be compatible with substituted propargyl *tert*-butyl carbonates (Table 18).

IV.6.1: Mono-Substituted Propargyl Carbonates

The first propargyl *tert*-butyl carbonate screened was terminal phenyl substituted carbonate **286**. When combined with bis-sulfonamide **362**, a separable mixture of two products were formed in approximately a 1:1 ratio (entry 1). Piperazine **427** formed predominantly as the shown olefin isomer (10:1 ratio). When isomeric phenyl substituted propargyl *tert*-butyl carbonate **288** was used, a significantly faster reaction was observed, generating piperazines **427** and **428** in approximately equal amounts after 45 minutes (entry 2). Taking advantage of the fast reaction rate for propargyl *tert*-butyl carbonate **288**, the reaction was repeated at 0 °C in an attempt to selectively form a single product. Gratifyingly the reaction gave piperazine **427** as the sole isolated product as a (>20:1) mixture of olefin isomers in decent yield (entry 3).

[26] As previously observed exposure of a compound with an exocyclic olefin to trifluoroacetic acid tautomerized the olefin to the endocyclic position, see: Nibbs, A. E.; Montgomery, T. D.; Zhu, Y.; Rawal, V. H. *The Journal of Organic Chemistry* **2015**, *80*, 4928-4941.

Table 18: Piperazine Synthesis using Substituted Propargyl tert-Butyl Carbonates



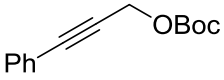
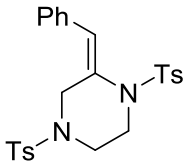
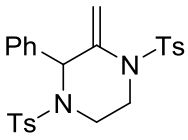
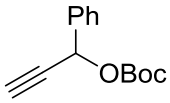
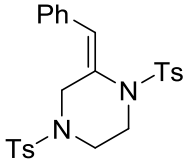
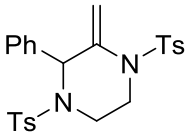
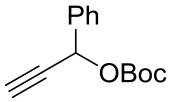
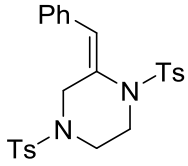
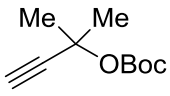
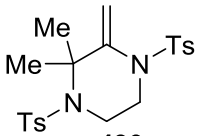
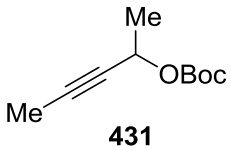
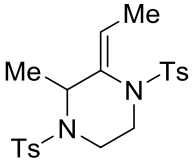
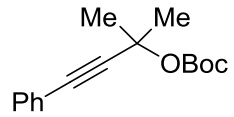
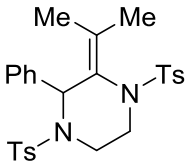
Entry	Substrate	Time	Yield[a]	Product
1	 **286**	12 h	45,45 [b]	 **427**  **428**
2	 **288**	45 min	45, 43	 **427**  **428**
3 [c]	 **288**	5 h	50	 **427**
4	 **429**	3 h	60	 **430**
5	 **431**	24 h	57	 **432**

Table 18: continued

6 [d]	 **321**	24 h	20	 **433**

[a]Isolated yield. [b]NMR yield based on internal standard. [c]Reaction run at 0 °C. [d]Reaction run at 40 °C.

IV.6.2: Bis-Substituted and Tri-Substituted Propargyl Carbonates

Germinal dimethyl substrate **429** was tested and generated a single compound **430**, in good yield after three hours (entry 4). The isomeric 1,3-bismethyl propargyl *tert*-butyl carbonate **431** was used and produced substituted piperazine **432** as a single regioisomer, presumably due to avoidance of severe allylic 1,3 strain (entry 5).[27] Finally, when the fully substituted propargyl carbonate **321** was exposed to the reaction conditions, while requiring mild heating and a long reaction time, provided the highly substituted piperazine **433** in modest yield as a single regioisomer (entry 6).

IV.6.3: Mechanistic Insights

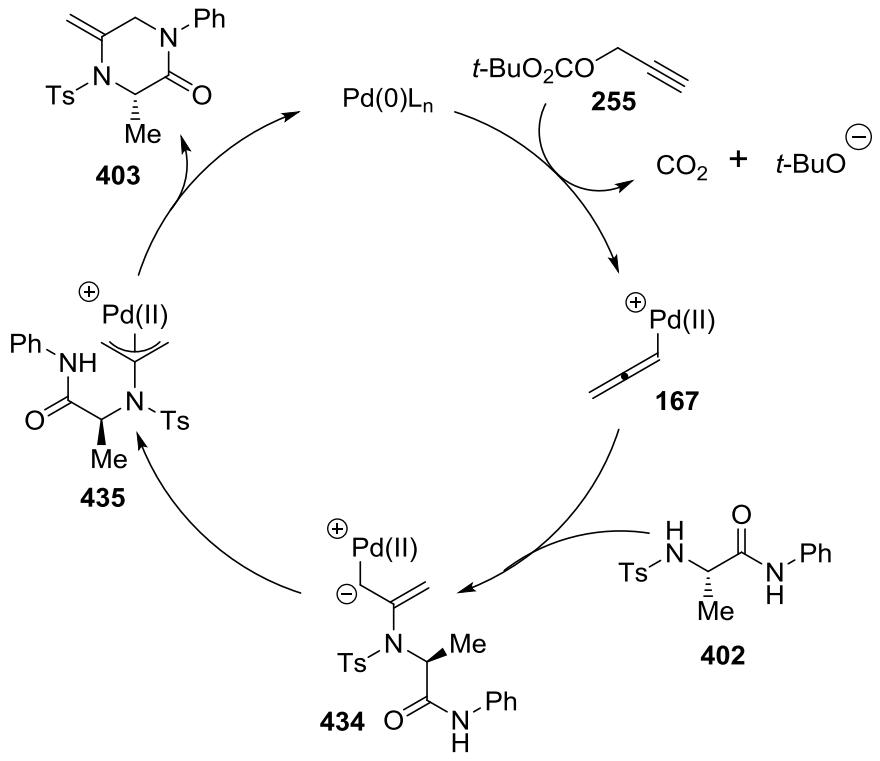
In order to rationalize the products that formed during this process a plausible mechanism, in agreement with observations and literature precedent, is presented here (Scheme 54).[28] Oxidative addition of palladium 0 to propargyl *tert*-butyl species **255** through an S_N2' type process will generate palladium allene **167** and an equivalent of tert-butoxide anion following

[27] (a) Hoggmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms: Fifth Edition*; Springer Science+Buisness Media, LLC. New York, NY, 2007.

[28] (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140-145. (b) Tsuji, J.; Mandai, T. *Angew. Chem. Int. Ed.* **1995**, *34*, 2589-2612. (c) Ma, S. *Eur. J. Org. Chem.* **2004**, 1175-1183. (d) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111-122. (e) Yoshida, M. *Chem. Pharm. Bull.* **2012**, *60*, 285-299. (f) Ye, J.; Ma, S. *Acc. Chem. Res.* **2014**, *47*, 989-1000.

decarboxylation.[29] Addition of the sulfonamide nitrogen to palladium allene **167** will give zwitterionic/palladium carbene species **434**.[30] Following protonation, formally from the amide nitrogen, palladium-π-allyl species **435** will form before being trapped by intramolecular ring closure giving piperazinone **403** and regenerating the palladium catalyst.[31]

Scheme 54: Plausible Catalytic Cycle



[29] (a) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103-1105. (b) Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis* **1987**, 603-606. (c) Su, C.-C.; Chen, J.-T.; Lee, G.-H.; Wang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4999-5000. (d) Ogoshi, S.; Tsutsumi, K.; Kurosawa, H. *J. Organomet. Chem.* **1995**, *493*, C19-C21. (e) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367-371. (f) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687-2692.

[30] For examples of the nucleophilic addition to allenyl-palladium species, see: (a) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225-242. (b) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Synlett* **1996**, *1996*, 553-554.

[31] For examples of palladium-catalyzed allylic alkylation reactions, see selected reviews and papers cited therein: (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-393. (b) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089-1122. (c) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163-3186. (d) Kapdi, A. R.; Prajapati, D. *RSC Advances* **2014**, *4*, 41245-41259.

IV.7: Conclusion

A novel method for accessing highly substituted piperazines and piperazinones has been developed. The reaction takes advantage of the ability of palladium to form a palladium (II) allene under very mild conditions which can function as a 1,2-bis-electrophile. The developed substrate scope is very broad, tolerating a wide range of substrates, functional groups and changes to all reaction components. The products generated are generally formed in good to excellent yield, at low catalyst loadings and with a high level of stereochemical control. The developed method represents a unique way of accessing these compounds which is orthogonal to current literature protocols.

CHAPTER V

EFFORTS TOWARDS A DIRECT BIS-ORTHO ARYLATION OF 2, 2′-BINAPHTHOL

V.1: Introduction

V.1.1: Background

Binaphthol is a widely used scaffold for the construction of various chiral catalysts[1] and ligands.[2] Binaphthol compounds which incorporate substitution at the 3,3′ position have found significant use as chiral catalyst scaffolds[3] extending the chiral environment further into the reaction space and generally acting as a more selective catalyst.[4] Indeed, a major class of catalysts based on this scaffold are the phosphoric acid catalysts[5]. These powerful catalysts have shown great utility and effectiveness in a wide range of reactions including the Mannich, Strecker, Diels-Alder and Nazarov reactions.[6]

[1] (a) Hatano, M.; Ishihara, K. *Synthesis* **2010**, *2010*, 3785. (b) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Organic & Biomolecular Chemistry* **2010**, *8*, 5262. (c) Parra, A.; Reboredo, S.; Martin Castro, A. M.; Aleman, J. *Organic & Biomolecular Chemistry* **2012**, *10*, 5001.

[2] For the use of BINAP as a chiral phosphine please see the following review and references cited therein: Ohkuma, T.; Kurono, N. In *Privileged Chiral Ligands and Catalysts*; Wiley-VCH Verlag GmbH & Co. KGaA: 2011, p 1-53.

[3] Li, G.; Liu, F.; Wu, M. *ARKIVOC* **2015**, 140-174.

[4] Bhadury, P. S.; Li, H. *Synlett* **2012**, *2012*, 1108.

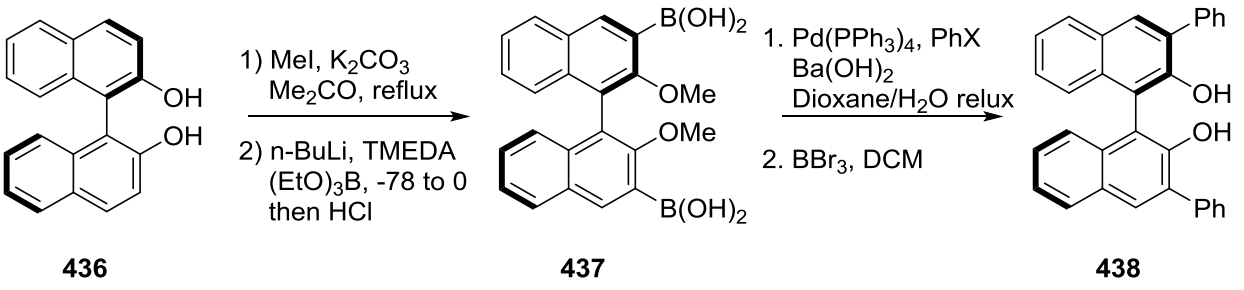
[5] For selected reviews see: (a) Akiyama, T. In *Asymmetric Synthesis II*; Wiley-VCH Verlag GmbH & Co. KGaA: 2012, p 261. (b) Mori, K.; Akiyama, T. In *Comprehensive Enantioselective Organocatalysis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2013, p 289. (c) Nagorny, P.; Sun, Z.; Winschel, G. A. *Synlett* **2013**, *24*, 661. (d) Yang, Z.-P.; Zhang, W.; You, S.-L. *The Journal of Organic Chemistry* **2014**, *79*, 7785. (e) Wu, H.; He, Y.-P.; Shi, F. *Synthesis* **2015**, *47*, 1990.

[6] (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047-9153. (b) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626-9627

V.1.2: General Literature Procedure for 3, 3′ Bis-Aryl Binaphthol Synthesis

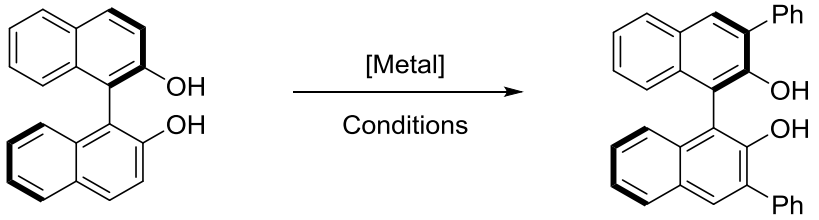
The general procedure for synthesizing a 3, 3′ bis-arylated binaphthol (Scheme 55) involves five steps,[7] beginning with the methylation of the alcohol moieties, followed by ortho-lithiation and generation of bis-boronic ester **437**. With bis-boronic ester **437** in hand a variety of aryl halides can be used in a Suzuki coupling reaction[8] and following removal of the methyl groups the desired 3,3′ bis-arylated binaphthol product is revealed.

Scheme 55: General Method for Bis-Arylation of Binaphthol



436 **437** **438**

Scheme 56: One Step Direct Bis-Arylation



436 **438**

While each of these steps is robust and generally high yielding, preparing such compounds requires a significant amount of time and the use of potentially hazardous reagents.

[7] (a) Li, B.; Chiu, P. *Eur. J. Org. Chem.* **2011**, *2011*, 3932. (b) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9266.

[8] For reviews on the Suzuki reaction see *inter aila*: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *2004*, 2419. (b) Suzuki, A. *Proceedings of the Japan Academy, Series B* **2004**, *80*, 359. (c) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6722. (d) Akiyama, T. In *Asymmetric Synthesis II*; Wiley-VCH Verlag GmbH & Co. KGaA: 2012, p 261. (e) Mora, M.; Jiménez-Sanchidrian, C.; Ruiz, J. R. *Current Organic Chemistry* **2012**, *16*, 1128-1150.

In an effort to streamline access, a direct route from binaphthol **436** to the desired 3, 3′ bis-arylated binaphthol products was envisioned involving an analogous process to the well precedented ortho arylation of phenol[9] and naphthol (Scheme 56).[10]

V.1.3: Alternate Methods

There have been two recent reports on a more direct route for accessing these compounds; the first by Liu takes advantage of a three step sequence in which directed C-H activation is utilized to generate the desired compounds in modest yields.[11] The second report, by Daugulis, offers a direct route to the bis-arylated products, however the reaction requires stoichiometric silver and only gives the product in moderate yield.[12] Additionally both reports demonstrate a very limited substrate scope and so there still exists a strong need for a general, practical method for the production of bis-arylated binaphthols.

V.2: Initial Screening of Conditions

V.2.1: Screening of Palladium Catalyzed Conditions

Initial screening for the bis-arylation of binaphthol **436** was originally investigated by Dr. Saikut Sen who examined a range of palladium catalysts and conditions. In order to verify his

[9] For examples of phenol arylation see : (a) Barton, D. H. R.; Finet, J.-P.; Giannotti, C.; Halley, F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 241. (b) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *The Journal of Organic Chemistry* **1997**, *62*, 2. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angewandte Chemie International Edition in English* **1997**, *36*, 1740. (d) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112. (e) Bedford, R. B.; Limmert, M. E. *The Journal of Organic Chemistry* **2003**, *68*, 8669. (f) Oi, S.; Watanabe, S.-i.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665. (g) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200.

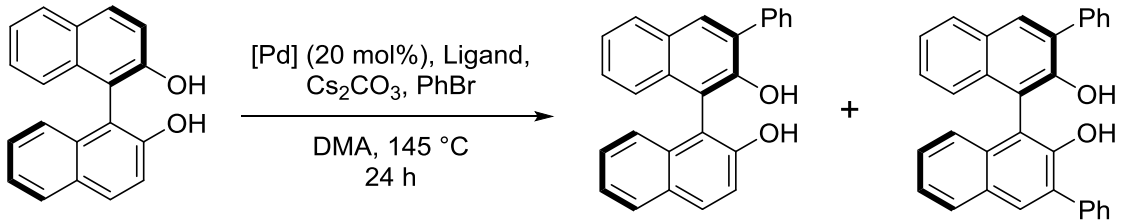
[10] For examples of naphthol arylation see the following sources and references cited therein: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Wang, H. *Chirality* **2010**, *22*, 827.

[11] (a) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 468-469.

[12] Truong, T.; Daugulis, O. *Chemical Science* **2013**, *4*, 531.

results a selection of conditions were tested (Table 19). Unfortunately neither the mono nor bis-arylated product was observed, even after extended reaction times at elevated temperature. The only observed product corresponded to the Ullmann type coupling of two bromobenzene molecules.[13]

Table 19: Palladium Catalyzed Arylation of Binaphthol



436 **439** **438**

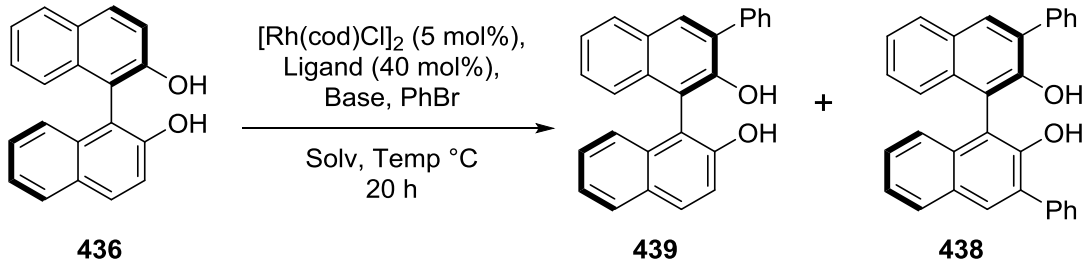
Entry	[Pd]	Ligand (equiv)	PhBr equiv	Cs_2CO_3 equiv	Yield **439**	Yield **438**
1	$Pd(PPh_3)_4$	None	6	6	0	0
2	$Pd(OAc)_2$	P(o-tolyl)$_3$ (0.2)	6	8	0	0
3	$Pd(OAc)_2$	PCy_3 (0.6)	6	8	0	0
4	$Pd(OAc)_2$	PCy_3 (0.6)	8	10	0	0

V.2.2: Initial Results Using a Rhodium Catalyst

After the unsuccessful initial investigation into the use of palladium for the transformation it was determined that a rhodium catalyst may prove to be more effective. This thought was inspired from the many reports in which a rhodium catalyst is successfully used for the ortho arylation of phenols and naphthols (Table 20).[9, 10] Starting with conditions similar to those of Inoue and coworkers[9f] both the mono and bis-arylated products were observed in the crude ^{1}H NMR spectra (entry 3), albiet in poor yields. A mixture of NMP and toluene was found to be superior to toluene, presumably due to the increased solubility of the starting materials.

[13] Fanta, P. E. *Synthesis* **1974**, *1974*, 9-21.

Table 20: Screen of Different Rhodium Catalyst Conditions



436 **439** **438**

Entry	Ligand	Base (equiv)	PhBr (equiv)	Solv (°C)	Yield **439**[a]	Yield **438**[a]
1	$P(NEt_2)_3$	K_2CO_3 (5)	4	Tol (100)	0	0
2	$P(NEt_2)_3$	K_2CO_3 (10)	8	Tol (100)	0	0
3	$P(NEt_2)_3$	K_2CO_3/Cs_2CO_3 (12)	5	Tol (110)	10	1
4	$P(NEt_2)_3$	K_2CO_3/Cs_2CO_3 (8)	6	Tol/NMP (110)	12	1
5	$P(OPh)_3$	K_2CO_3/Cs_2CO_3 (8)	6	Tol/NMP (110)	5	0
6	PPh_3	K_2CO_3/Cs_2CO_3 (8)	6	Tol/NMP (110)	0	0
7	P(*t*-Bu)$_3$	K_2CO_3/Cs_2CO_3 (8)	6	Tol/NMP (110)	28	5
8	P(2-furyl)$_3$	K_2CO_3/Cs_2CO_3 (8)	6	Tol/NMP (110)	0	0
9	PCy_3	K_2CO_3/Cs_2CO_3 (8)	6	Tol/NMP (110)	0	0
10	P(*t*-Bu)$_2$biphenyl	K_2CO_3/Cs_2CO_3 (8)	6	Tol/NMP (110)	0	0
11	$P(NEt_2)_3$	K_2CO_3 (8)	6	Tol/NMP (110)	7	0
12	$P(NEt_2)_3$	Cs_2CO_3 (8)	6	Tol/NMP (110)	17	1
13	$P(NEt_2)_3$	KOt-Bu (8)	6	Tol/NMP (110)	2	0
14	$P(NEt_2)_3$	K_3PO_4 (8)	6	Tol/NMP (110)	17	1
15	$P(NEt_2)_3$	Pyridine (8)	6	Tol/NMP (110)	0	0
16	$P(NEt_2)_3$	N(*i*-Pr)$_2$Et (8)	6	Tol/NMP (110)	0	0
17	$P(NEt_2)_3$	DMAP (8)	6	Tol/NMP (110)	0	0

[a]NMR yield based on internal standard.

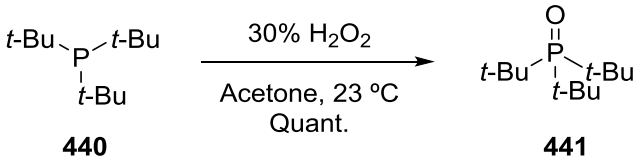
Of the ligands screened P(*t*-Bu)$_3$ (entry 7) proved to be the best for conversion to the two desired products **439** and **438**. The use of an inorganic base was critical for successful conversion to the desired products, with a mixture of potassium and cesium carbonate proving best. Interestingly, all organic bases examined failed to give any conversion to desired products **439** and **438** (entries 15-17).

V.3: Discovery and Use of Phosphine Oxides as Ligands

V.3.1: Synthesis of a Phosphine Oxide

In an attempt to capitalize on the exciting result with P(*t*-Bu)$_3$ (Table 20, entry 7) the experiment was repeated using a freshly purchased bottle P(*t*-Bu)$_3$. Disappointingly, after several attempts no reaction was observed when using the newly purchased ligand. In an effort to understand this anomaly the old bottle of P(*t*-Bu)$_3$ was examined and was determined to have mostly oxidized to the phosphine oxide P(*t*-Bu)$_3$O **441**. With this knowledge, a sample of P(*t*-Bu)$_3$ was oxidized to the corresponding phosphine oxide **441** by simple reaction with hydrogen peroxide under ambient conditions (Scheme 57).[14]

Scheme 57: Phosphine Oxidation



440 **441**

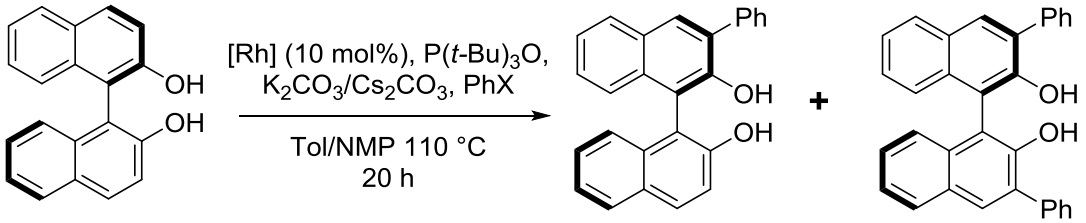
V.3.2: Use of Phosphine Oxides as Ligands

Subsequent use of the phosphine oxide in the arylation reaction showed that it was indeed the active ligand/additive. At this point in the optimization, other undesired products, were

[14] Bowden, A.; Coles, S. J.; Pitak, M. B.; Platt, A. W. G. *Inorg. Chem.* **2012**, *51*, 4379-4389.

observed in the NMR, along with the desired compounds **439** and **438**. These compounds were determined to be a variety of O-arylation products arising from undesired reaction pathways. Therefore the aryl halide and several different rhodium sources were screened (Table 21). Iodobenzene was quickly found to give superior results as compared to bromobenzene (entries 1,2), however when a greater excess was used, the level of side products generated greatly increased (entry 3).

Table 21: Screening Rhodium Sources



436 **439** **438**

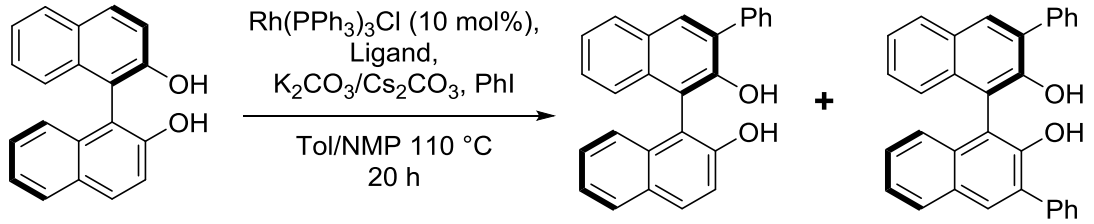
Entry	[Rh]	PhX (equiv)	Additive	Yield **439**[a]	Yield **438**[a]
1	$[Rh(cod)Cl]_2$	PhBr (8)	None	8	1
2	$[Rh(cod)Cl]_2$	PhI (8)	None	18	1
3	$[Rh(cod)Cl]_2$	PhI (12)	None	NA	NA
4	$[Rh(cod)Cl]_2$	PhI (8)	None	19	1
5	$Rh(PPh_3)Cl$	PhI (8)	None	34	6
6	$RhCO(PPh_3)_2Cl$	PhI (8)	None	32	2
7	$[Rh(C_2H_4)_2Cl]_2$	PhI (8)	None	18	2
8	$Rh(nbd)_2BF_4$	PhI (8)	None	36	11
9	$Rh(PPh_3)Cl$	PhI (8)	4 Å MS	24	1
10	$Rh(PPh_3)Cl$	PhI (8)	BEt_3 (1.1 equiv)	8	1

[a]NMR yield based on internal standard

When switching to Wilkinson's catalyst (entry 5) a significant improvement in reaction yield was observed. A further improvement was observed when cationic rhodium source $Rh(nbd)_2BF_4$ was used, giving the best conversion to **439** and **438** seen so far (entry 8). It was also noted that the addition of either molecular sieves or a borane was detrimental to the reaction (entries 9,10).

V.3.3: Control Experiments for Arylation Reaction

Table 22: Stoichiometry of Phosphine Oxide



436 **439** **438**

Entry	[Rh]	Ligand (equiv)	Yield **439** [a]	Yield **438** [a]
1	$Rh(PPh_3)_3Cl$	PPh_3O (0.4)	12	0
2	$Rh(PPh_3)_3Cl$	PPh_3O (0.2)	14	0
3	None	PPh_3O (0.2)	0	0
4	$Rh(PPh_3)_3Cl$	None	10	0
5	$Rh(PPh_3)_3Cl$	P(*t*-Bu)$_3$O (0.4)	16	<5
6	$Rh(PPh_3)_3Cl$	P(*t*-Bu)$_3$O (0.2)	36	<5
7	$Rh(PPh_3)_3Cl$	P(*t*-Bu)$_3$O (0.15)	30	<5
8 [b]	$Rh(PPh_3)_3Cl$	P(*t*-Bu)$_3$O (0.1)	42	15
9	$Rh(PPh_3)_3Cl$	P(*t*-Bu)$_3$O (0.08)	18	<5

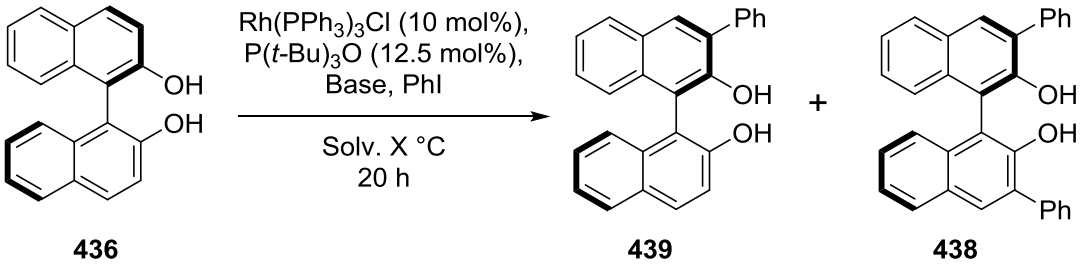
[a] NMR yield based on internal standard. [b] Isolated yield.

Before proceeding further with the optimization a number of control experiments were performed (Table 22). The reaction showed no conversion to any detectable prodcuts in the absence of rhodium (entry 3) and gave inferior yields in the absence of a phosphine oxide (entry 4). With the importance of the phosphine oxide in mind the stoichiometry of the phosphine oxide required was carefully screened for using Wilkinson's catalyst (enties 5-9). It was quickly discovered that 0.1 equivalents was optimal (entry 8) giving desired products **439** and **438** in isolatable amounts.

V.3.4: Examination of Reaction Temperature and Solvents

Continuing with the optimization of this reaction, the temperature was increased from 110 °C to 130 °C with the hopes of increasing the rate and yield of the reaction. This being the case, a new solvent would have to be selected and so several were screened (Table 23, entries 1-4). Indeed, when the similar solvent *m*-Xylenes was substituted for toluene along with NMP were used as the solvent system (entry 4), there was nearly full conversion towards desired compounds **439** and **438**. Interestingly, when the temperature was raised an additional 10 °C, the number of side reactions increased dramatically, preventing accurate characterization and showing an upper bound for the temperature of this transformation (entries 5-8).

Table 23: Increased Temperature Solvent Screen



436 **439** **438**

Entry	Base (equiv)	Solvent (M)	Temp °C	Yield **439**[a]	Yield **438**[a]
1	K_2CO_3/Cs_2CO_3 (8)	NMP (0.2 M)	130	50	<5
2	K_2CO_3/Cs_2CO_3 (8)	DMF (0.2 M)	130	46	<5
3	K_2CO_3/Cs_2CO_3 (8)	DMA (0.2 M)	130	30	<5
4[b]	K_2CO_3/Cs_2CO_3 (8)	o-Xylene/NMP (0.1 M)	130	55	30
5	K_2CO_3/Cs_2CO_3 (8)	NMP (0.2 M)	140	0	0
6	K_2CO_3/Cs_2CO_3 (8)	DMF (0.2 M)	140	ND	ND
7	K_2CO_3/Cs_2CO_3 (8)	DMA (0.2 M)	140	ND	ND
8	K_2CO_3/Cs_2CO_3 (8)	o-Xylene/NMP (0.1 M)	140	ND	ND

[a]NMR yield based on internal standard. [b]Isolated yield.

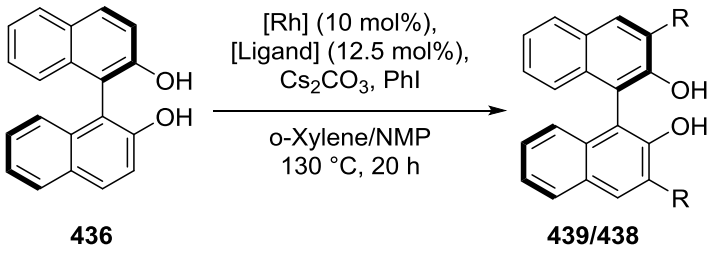
V.4: Collaboration and High Throughput Screening

V.4.1: Establishment of Collaboration and Validation Screen

At this stage, the number of different reaction parameters needing to be optimized had reached a point where the best path forward seemed to lay in automation of the optimization process. A collaboration was established with Professor Marisa Kozlowski and Dr. Rosaura Padilla-Salinas at the University of Pennsylvania in order to rapidly screen reaction conditions. Details for preparing to run the screens, determining the protocol for the high throughput robot

and collecting the raw data can be found in Dr. Rosaura Padilla-Salinas' doctoral thesis.[15] After the protocol was worked out with automated analysis by HPLC vs an internal standard it was tested with a 24 well plate looking at previously screened conditions.

Scheme 58: First Full High Throughput Screen



436 439/438

Rhodium Sources	Ligands	Additive
$Rh(PPh_3)_3Cl$	PPh_3O	None
$Rh(CO)Cl(PPh_3)_2$	$P(t\text{-}Bu)_3O$	$AgSbF_6$
$[Rh(nbd)_2]BF_4$	$P(NEt_2)_3$	
$[Rh(cod)Cl]_2$	xPhos	
$[Rh(coe)_2Cl]_2$	Davephos	
$[Rh(Cp^*)Cl_2]_2$	Buckwald Ligand	
	$P(OCH(CF_3)_2)_3$	
	$PCy_3 \cdot HBF_4$	

Gratifyingly the automated protocol was successful and while it was unable to exactly match previously determined results, the calibration experiment was deemed successful. With this proof of concept completed, a 96 well plate experiment was formulated using six rhodium catalysts, eight ligands and either the absence or presence of a silver salt (Scheme 58). The purpose of the silver salt was to exchange the halide for hexafluoroantimonate in an effort to increase the electrophilicity of the rhodium catalyst.

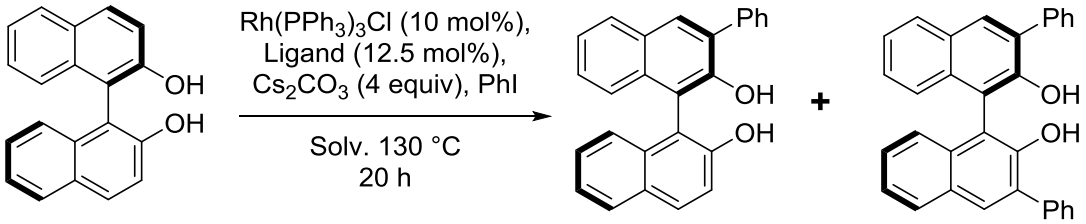
V.4.2: Screening of Conditions After HTE Results

The data after the high throughput experiment (HTE) suggested several things: that phosphine oxides were superior ligands for this reaction, that triphenylphosphine oxide performed better than all other phosphine oxides, the addition of a silver salt had the effect of

[15] Padilla-Salinas, Rosaura. Ph.D. Thesis, University of Pennsylvania, Philadelphia, PA, 2014.

increasing the yield of both the desired products the undesired of O-arylation products, and that the use of a highly dissociative counter ion such as BF_4 was advantageous. It was independently determined that only four equivalents of cesium carbonate were required for the reaction to proceed.

Table 24: Screening Phosphine Oxides and Solvents



436 **439** **438**

Entry	Ligand	Solvent (M)	Yield **439**[a]	Yield **438**[a]
1	PPh_3O	o-Xylene/NMP (0.1 M)	25	16
2	PBu_3O	o-Xylene/NMP (0.1 M)	22	13
3	PEt_3O	o-Xylene/NMP (0.1 M)	24	19
4	$P(morpholine)_3O$	o-Xylene/NMP (0.1 M)	20	14
5	$P(4\text{-}CF_3Ph)_3O$	o-Xylene/NMP (0.1 M)	24	16
6	$P(C_6F_5)_3O$	o-Xylene/NMP (0.1 M)	27	13
7	PPh_3O	Diglyme (0.1 M)	33	17
8	PPh_3O	o-Xylene/Diglyme (0.1 M)	18	16
9	PPh_3O	Diglyme/NMP (0.1 M)	23	3
10	PPh_3O	DMI (0.1M)	23	1
11	PPh_3O	o-Xylene/DMI (0.1)M	33	11
12	PPh_3O	DMPU (0.1M)	16	1
13	PPh_3O	o-Xylene/DMPU (0.1)M	36	6

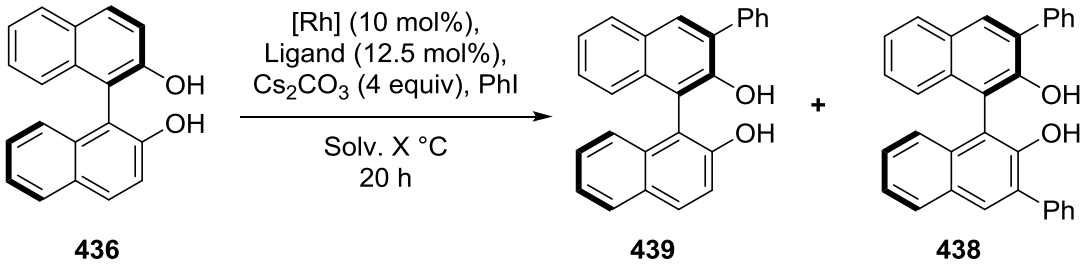
[a]NMR yield based on internal standard.

Capitalizing on the results from the HTE screen other phosphine oxides were synthesized to be screened for the reaction of binaphthol **436** with iodobenzene (Table 24). The use of alkyl phosphine oxides proved to be slightly less efficiant at promoting the reaction than the triphenyl phosphine oxide and resulted in a greater number of undesired side products (entries 2-4). The electron deficient aryl phosphine oxides (entries 5,6) gave comparable results to the control triphenyl phosphine oxide. Furthering efforts to improve both yield and selectivity a variety of solvents and solvent combinations were screened. Excitingly, solvent combonations involving the polyether solvent diglyme (entries 7-9) gave superior conversion to the desired products. Other high boiling solvents, DMI and DMPU failed to offer an advantage for coversion to desired compounds **439** and **438** over the control (entries 10-13).

V.5: Preparation and Examination of Different Phosphine Oxides

Furthering investigations into the ligand a number of phosphine oxides were prepared in a manner similar to the preparation of tri(tert-butyl)phosphine oxide **441** (Scheme 57). With a selection of phosphine oxides in hand phosphine oxides bearing different functional types were screened (Table 25). Using the rhodium source which had given the optimal results during the HTE screening, several sterically bulky (entries 3,4), electron deficient aryl (entries 5,6), bidentate (entries 7,8,11) and electron rich aryl (entries 9,10) phosphine oxides were examined. Interestingly the electron rich aryl phosphine oxides proved superior to the others screened. The sterically congested tri(*o*-anisyl)phosphine oxide gave exceptionally clean conversion to the desired products (**439** in 56% and **438** in 44%) isolated yields.

Table 25: Examination of Phosphine Oxides



436 **439** **438**

Entry	[Rh]	Ligand	Solvent (0.1 M)	Yield **439** [a]	Yield **438** [a]
1	$Rh(PPh_3)_3Cl$	PPh_3O	o-Xylene/Diglyme	32	13
2	$Rh(nbd)_2BF_4$	PPh_3O	o-Xylene/NMP	34	16
3	$Rh(nbd)_2BF_4$	XphosO	o-Xylene/NMP	9	1
4	$Rh(nbd)_2BF_4$	JohnphosO	o-Xylene/NMP	14	8
5	$Rh(nbd)_2BF_4$	$P(4\text{-}CF_4Ph)_3O$	o-Xylene/NMP	29	11
6	$Rh(nbd)_2BF_4$	$P(4\text{-}FPh)_3O$	o-Xylene/NMP	30	18
7	$Rh(nbd)_2BF_4$	$dppeO_2$	o-Xylene/NMP	13	2
8	$Rh(nbd)_2BF_4$	$dppbO_2$	o-Xylene/NMP	31	18
9	$Rh(nbd)_2BF_4$	$P(4\text{-}OMePh)_3O$	o-Xylene/NMP	25	19
10 [b]	$Rh(nbd)_2BF_4$	$P(2\text{-}OMePh)_3O$	o-Xylene/NMP	56	44
11	$Rh(nbd)_2BF_4$	$BINAPO_2$	o-Xylene/NMP	0	0

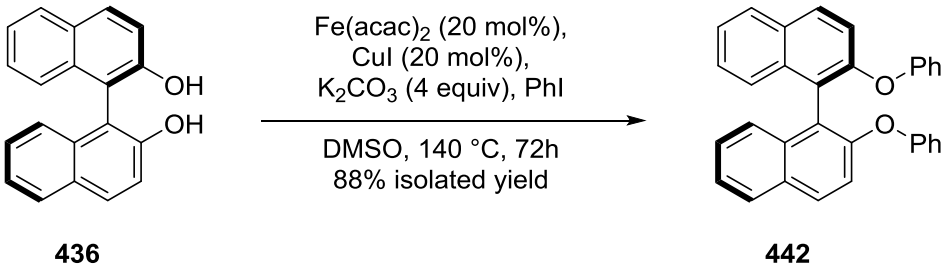
[a]NMR yield based on internal standard. [b]Isolated yield.

V.5.1: Control Experiments on Possible Product Interconversion

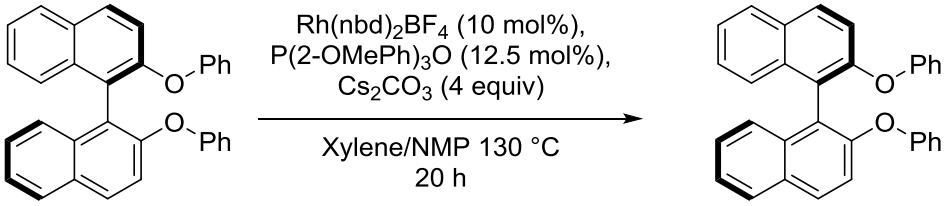
During the course of these studies the interconversion of the various products was discussed. In order to test the hypothesis that the O-arlyated compounds could interconvert with the desired *o*-arlyated products, bis-phenyl ether **442** was prepared according to standard

procedures.[16] When **442** was exposed to the optimal reaction conditions, in the absence of aryl halide, there was no reaction observed either by ^{1}H NMR analysis of the crude reaction mixture or during examination of the purified products.

Scheme 59: Control Experiment



436 **442**



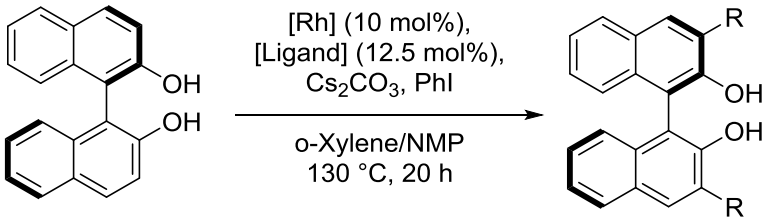
442 **442**

V.5.2: Proposed Conditions for Second HTE Screen

With the results of the most recent rounds of optimization, as well as the results from the first round screen, a second HTE screen was planned (Scheme 60). In this screen four rhodium sources were examined along with three of the best phosphine oxide ligands and three so far untested ligands. Finally four different solvent combinations were selected based on combinations which had previously proved effective for the transformation of binaphthol **435**.

[16] Qu, X.; Li, T.; Zhu, Y.; Sun, P.; Yang, H.; Mao, J. *Organic & Biomolecular Chemistry* **2011**, *9*, 5043-5046.

Scheme 60: Second Round of High Throughput Screening



436 **439/438**

Rhodium Sources	Ligands	Solvents
$Rh(PPh_3)_3Cl$	PPh_3O	o-Xylene:NMP
$[Rh(nbd)_2]BF_4$	$P(4\text{-}OMePh)_3O$	o-Xylene:Dyglyme
$[Rh(cod)_2Cl]$	$P(2\text{-}OMePh)_3O$	PhCl:Dyglyme
$[Rh(nbd)Cl]_2$	$P(o\text{-}tolyl)_3O$	PhCl:NMP
	$P(2,4,6\text{-}OMePh)_3O$	
	$P(NMe_2)_3O$	

V.5.3: Results of Second Round HTE

The results of the HTE screen showed that a number of the combinations tried gave good levels of conversion to the desired products and suppressed formation of undesired side products. Unfortunately the optimal result from the screen was the previously obtained optimal set of conditions (Table 25, entry 10). At this point, while a substantial amount of progress had been made from the initial experiments, it was determined that the conversion to desired product **438** was still not at a synthetically useful level. Additional experiments involving the use of electronically perturbed or sterically hindered aryl iodides saw conversion to products drop off severely. Finally, the reaction had been so highly tuned to binaphthol that when naphthol or phenol was substituted into the reaction no *o*-arylated products were observed after 24 hours.

V.6: Conclusion

In summary a new method for accessing 3,3′-bis-aryl-2,2′-binaphthols has been developed. This rhodium catalyzed transformation allows for the avoidance of a multi-step sequence and generation of desired compound **438** in a more time efficient manner. While additional effort and screening needs to be performed inorder to make this a general method for the bis-arylation of binaphthols it already demonstrates promise for becoming a synthetically useful transformation.

CHAPTER VI

NEW DIRECTIONS

VI.1: Development of Thiosquaramides

VI.1.1: Introduction

The hydrogen bond is defined as: the attractive interaction between two species originating from electron donation from an electronegative atom to a hydrogen atom which is itself bonded to another electronegative atom.[1] Hydrogen bonds and hydrogen bonding interactions are widely seen in both chemistry and biology and have a profound impact on both chemical reactivity and structure. A recent development in the realm of organocatalysis[2] is the use of hydrogen bond donors to activate substrates in order to facilitate enantioselective bond forming interactions.[3]

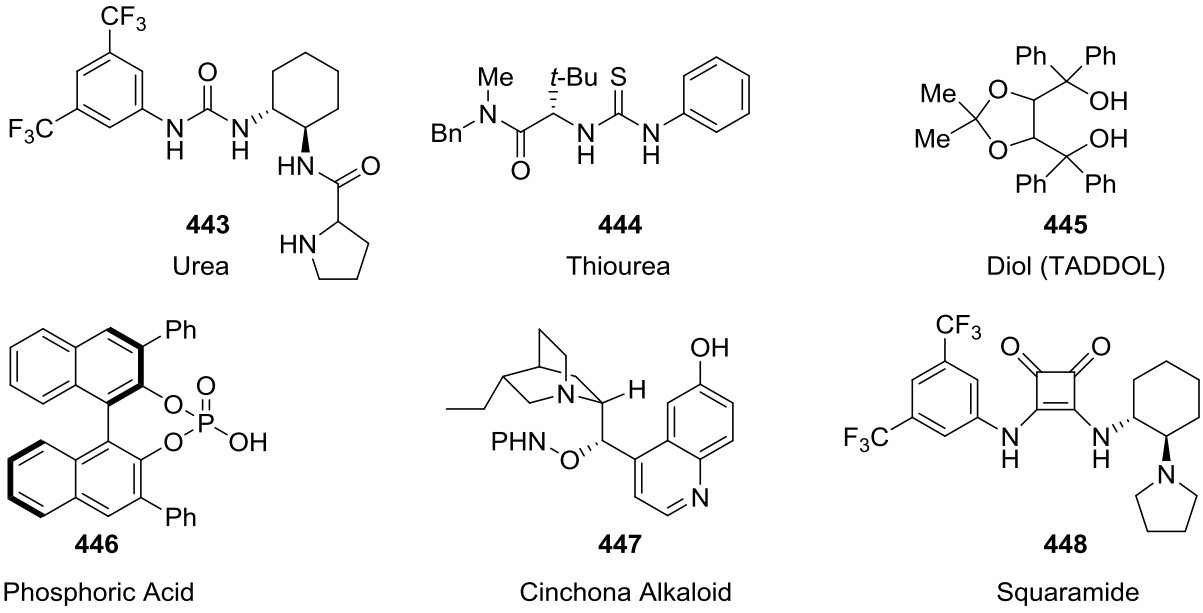
---

[1] For a selection of reviews on hydrogen bonds please see : (a) Kollman, P. A.; Allen, L. C. *Chem. Rev.* **1972**, *72*, 283-303. (b) Frey, P. A. *Magn. Reson. Chem.* **2001**, *39*, S190-S198. (c) Atkins, P.; de Paula, J. *Physical Chemistry: 8th Edition*; W. H. Freeman and Company, New York, NY, 2006. (d) Arunan, E.; Desiraju Gautam, R.; Klein Roger, A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary David, C.; Crabtree Robert, H.; Dannenberg Joseph, J.; Hobza, P.; Kjaergaard Henrik, G.; Legon Anthony, C.; Mennucci, B.; Nesbitt David, J. In *Pure Appl. Chem.* 2011; Vol. 83, p 1637. (e) Arunan, E.; Desiraju Gautam, R.; Klein Roger, A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary David, C.; Crabtree Robert, H.; Dannenberg Joseph, J.; Hobza, P.; Kjaergaard Henrik, G.; Legon Anthony, C.; Mennucci, B.; Nesbitt David, J. In *Pure Appl. Chem.* 2011; Vol. 83, p 1619.

[2] (a) Dalko, P. I. In *Enantioselective Organocatalysis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2007, p 1-17. (b) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8-27. (c) List, B. *Chem. Rev.* **2007**, *107*, 5413-5415. (d) Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178-2189. (e) Aleman, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774-793.

[3] Please see the following reviews and papers cited therein: (a) Hine, J.; Linden, S. M.; Kanagasabapathy, V. M. *The Journal of Organic Chemistry* **1985**, *50*, 5096-5099. (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289-296. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int.*

Scheme 61: Hydrogen Bonding Scaffolds



There exist several privileged scaffolds within the family of hydrogen bond donating catalysts (Scheme 61). Such scaffolds include but are not limited to ureas,[4] thioureas,[5] diols,[6]

Ed. **2006**, *45*, 1520-1543. (d) Dalko, P. I. In *Enantioselective Organocatalysis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2007, p 1-17. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743. (f) Yu, X.; Wang, W. *Chemistry – An Asian Journal* **2008**, *3*, 516-532. (g) Knowles, R. R.; Jacobsen, E. N. *Proceedings of the National Academy of Sciences* **2010**, *107*, 20678-20685.

[4] (a) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Chem. Pharm. Bull.* **2004**, *52*, 477-480. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499-2510. (c) So, S. S.; Oottikkal, S.; Badjić, J. D.; Hadad, C. M.; Mattson, A. E. *The Journal of Organic Chemistry* **2014**, *79*, 4832-4842. (d) Nickerson, D. M. Ph.D. Thesis, The Ohio State University, **2014**.

[5] (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1281. (c) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217-220. (d) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673. (e) Wittkopp, A.; Schreiner, P. R. *Chemistry – A European Journal* **2003**, *9*, 407-414. (f) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999-1010. (g) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593-601. (h) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Organic & Biomolecular Chemistry* **2013**, *11*, 7051-7071. (i) Yeung, C. S.; Ziegler, R. E.; Porco, J. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 13614-13617.

[6] (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146-146. (b) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proceedings of the National Academy of Sciences of the United States of America* **2004**, *101*, 5846-5850. (c) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem.* **2006**, *118*, 6276-6279. (d) Zhou, Y.; Shan, Z. *The*

phosphoric acids,[7] cinchona alkaloids[8] and squaramides.[9] The squaramide scaffold has proven to be a particularly powerful tool for the transformation of pro-chiral sp^2 hybridized centers into sp^3 chiral centers in a number of different reactions (Scheme 62).[10]

Journal of Organic Chemistry **2006**, *71*, 9510-9512. (e) Rueping, M.; Sugiono, E.; Moreth, S. A. *Adv. Synth. Catal.* **2007**, *349*, 759-764. (f) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2009**, *48*, 776-779. (g) Kano, T.; Shirozu, F.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 16068-16073. (h) An, W.-K.; Han, M.-Y.; Wang, C.-A.; Yu, S.-M.; Zhang, Y.; Bai, S.; Wang, W. *Chemistry – A European Journal* **2014**, *20*, 11019-11028. (i) Kim, H. Y.; Oh, K. *Synlett* **2015**, *26*, 2067-2087. (j) Klimczyk, S.; Misale, A.; Huang, X.; Maulide, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 10365-10369.

[7] For selected reviews see: (a) Akiyama, T. In *Asymmetric Synthesis II*; Wiley-VCH Verlag GmbH & Co. KGaA: 2012, p 261. (b) Mori, K.; Akiyama, T. In *Comprehensive Enantioselective Organocatalysis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2013, p 289. (c) Nagorny, P.; Sun, Z.; Winschel, G. A. *Synlett* **2013**, *24*, 661. (d) Yang, Z.-P.; Zhang, W.; You, S.-L. *The Journal of Organic Chemistry* **2014**, *79*, 7785. (e) Wu, H.; He, Y.-P.; Shi, F. *Synthesis* **2015**, *47*, 1990.

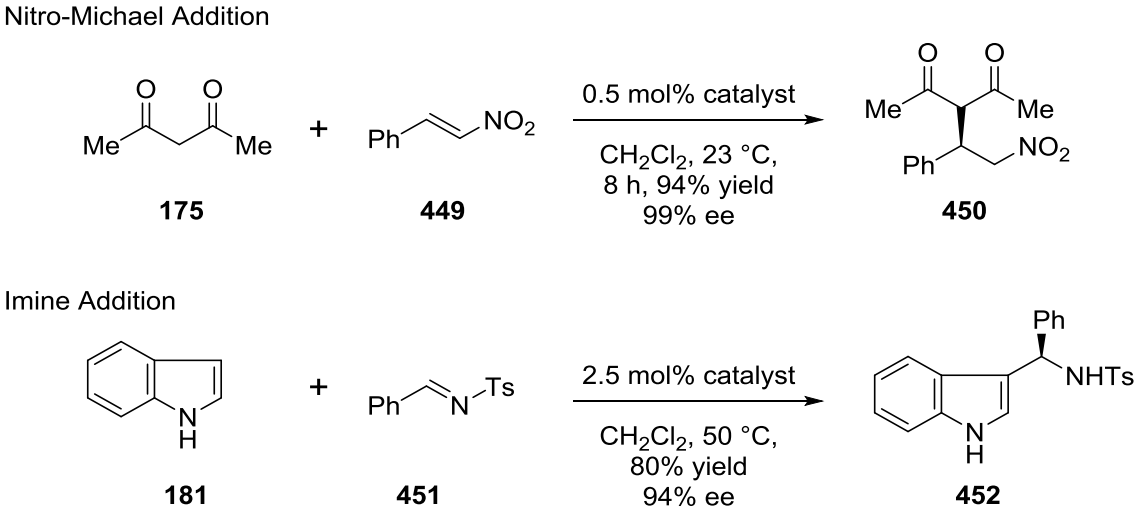
[8] (a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928-3930. (b) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422-2423. (c) Hu, X.; Wang, J.; Li, W.; Lin, L.; Liu, X.; Feng, X. *Tetrahedron Lett.* **2009**, *50*, 4378-4380. (d) Jang, H. B.; Lee, J. W.; Song, C. E. In *Cinchona Alkaloids in Synthesis and Catalysis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2009, p 197-247. (e) Li, H.; Liu, X.; Wu, F.; Tang, L.; Deng, L. *Proceedings of the National Academy of Sciences* **2010**, *107*, 20625-20629. (f) Jiang, L.; Chen, Y.-C. *Catalysis Science & Technology* **2011**, *1*, 354-365. (g) Marcelli, T. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2011**, *1*, 142-152. (h) Yeboah, E. M. O.; Yeboah, S. O.; Singh, G. S. *Tetrahedron* **2011**, *67*, 1725-1762. (i) Yang, K. S.; Rawal, V. H. *J. Am. Chem. Soc.* **2014**, *136*, 16148-16151.

[9] (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417. (b) Zhou, W.-M.; Liu, H.; Du, D.-M. *Org. Lett.* **2008**, *10*, 2817-2820. (c) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028-2031. (d) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028-2031. (e) Qian, Y.; Ma, G.; Lv, A.; Zhu, H.-L.; Zhao, J.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 3004-3006. (f) Xu, D.-Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A.-G.; Xia, A.-B.; Xu, Z.-Y. *Chemistry – A European Journal* **2010**, *16*, 4177-4180. (g) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153-156. (h) Yang, W.; Du, D.-M. *Chem. Commun.* **2011**, *47*, 12706-12708. (i) Yang, W.; Du, D.-M. *Adv. Synth. Catal.* **2011**, *353*, 1241-1246. (j) He, H.-X.; Du, D.-M. *RSC Advances* **2013**, *3*, 16349-16358. (k) Wang, H.; Wang, Y.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2013**, *2013*, 4844-4851. (l) Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 16050-16053. (m) Manoni, F.; Connon, S. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 2628-2632. (n) Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627-3648. (o) Nair, D. K.; Menna-Barreto, R. F. S.; da Silva Junior, E. N.; Mobin, S. M.; Namboothiri, I. N. N. *Chem. Commun.* **2014**, *50*, 6973-6976.

[10] For a review on orbital hybridization please see the following reviews and sources cited therein: (a) Carey, F. A. *Organic Chemistry: Sixth Edition*; McGraw-Hill Companies, Inc.: New

The first reported use of a chiral squaramide involved addition of acetylacetone **175** to β-nitrostyrene **449** in a nitro-Michael type reaction (Scheme 62).[9a] Addition to imines, particularly imines connected to a hydrogen bond acceptor moiety, have also proven to be good substrates for squaramide catalysis.[9c] In a similar fashion to the addition to imines, the nucleophilic addition to ketones has been reported, though generally the ketone requires an α-carbonyl to improve the ability of the squaramide to coordinate to the substrate.[11] The classic Michael addition reaction[10a,c] has proven amenable to squaramide catalysis, providing chiral beta-keto substituted products.[9l]

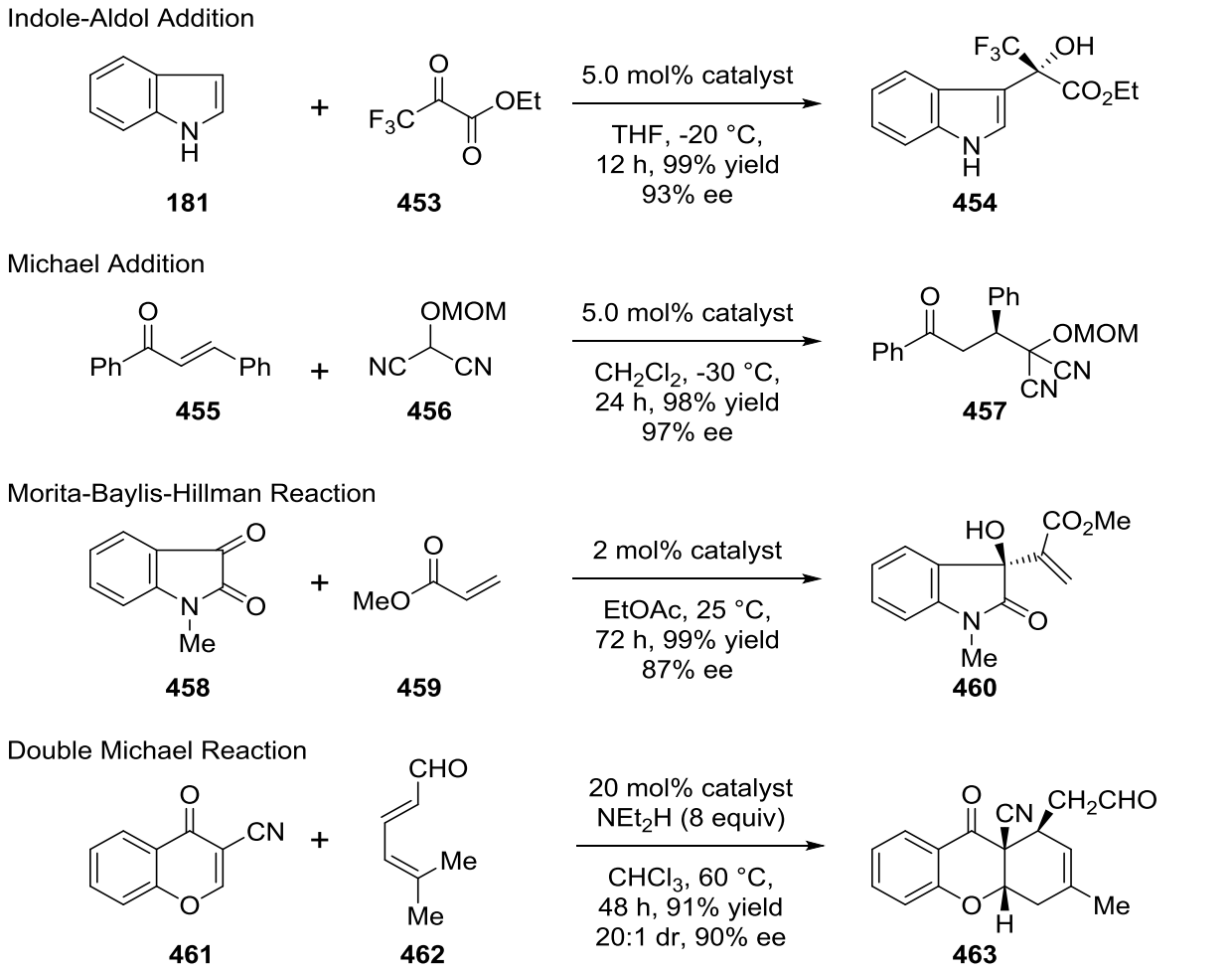
Scheme 62: Squaramide Catalyzed Reactions



York, NY, 2006. (b) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books, 2006. (c) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms: Fifth Edition*; Springer Science+Buisness Media, LLC:New York, NY, 2007.

[11] Han, X.; Liu, B.; Zhou, H.-B.; Dong, C. *Tetrahedron: Asymmetry* **2012**, *23*, 1332-1337.

Scheme 62: continued



Another reaction class catalyzed by squaramides is the Morita-Baylis-Hillman reaction,[12] when isatin **458** is combined with an enone **459** desired allylic alcohol **460** forms in good yield and ee.[13] Multi-reaction cascades have been successfully promoted by a squaramide catalyst, for

[12] (a) Zhao, M.-X.; Wei, Y.; Shi, M. In *The Chemistry of the Morita-Baylis-Hillman Reaction*; The Royal Society of Chemistry: 2011, p 1-78. (b) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659-6690.

[13] Qian, J.-Y.; Wang, C.-C.; Sha, F.; Wu, X.-Y. *RSC Advances* **2012**, *2*, 6042-6048.

example, a double Michael reaction sequence promoted by *in-situ* imine formation leads to product **463** formed with excellent enantio- and diastereo control.[14]

VI.1.2: Conception and Synthesis of Thiosquaramides

While the use of squaramide as a chiral scaffold has inspired numerous groups to develop new enantioselective reactions, the core structure of squaramide has yet to be modified for use in asymmetric catalysis. An obvious means of modifying the nature of the squaramide core is to convert a squaramide into a thiosquaramide.[15] While conversion of squaric acid derivatives into their respective thio forms was first investigated over thirty years ago there has been surprisingly little research done over the subsequent years. A notable example of recent development in this field has been the preparation of achiral bis-aryl thiosquaramides for use in anion transportation by Jolliffe and coworkers.[16]

A possible advantage of thiosquaramide catalysts lies in the increased acidity of the core amines. As the N-H bond polarizes (becomes more acidic) it becomes a better hydrogen bond donor.[17] This conjecture is supported by computational studies which predict that

[14] Albrecht, Ł.; Cruz Acosta, F.; Fraile, A.; Albrecht, A.; Christensen, J.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 9088-9092.

[15] (a) Seitz, G.; Mann, K.; Schmiedel, R. *Chemiker-Zeitung*, **1975**, *99*, 332. (b) Gerecht, B.; Kämpchen, T.; Köhler, K.; Massa, W.; Offermann, G.; Schmidt, R. E.; Seitz, G.; Sutrisno, R. *Chem. Ber.* **1984**, *117*, 2714-2729. (c) Köhler, K.; Massa, W.; Offermann, G.; Seitz, G.; Sutrisno, R. *Chem. Ber.* **1985**, *118*, 1903-1916. (d) Müller, M.; Heileman, M. J.; Moore, H. W.; Schaumann, E.; Adiwidjaja, G. *Synthesis* **1997**, *1997*, 50-52.

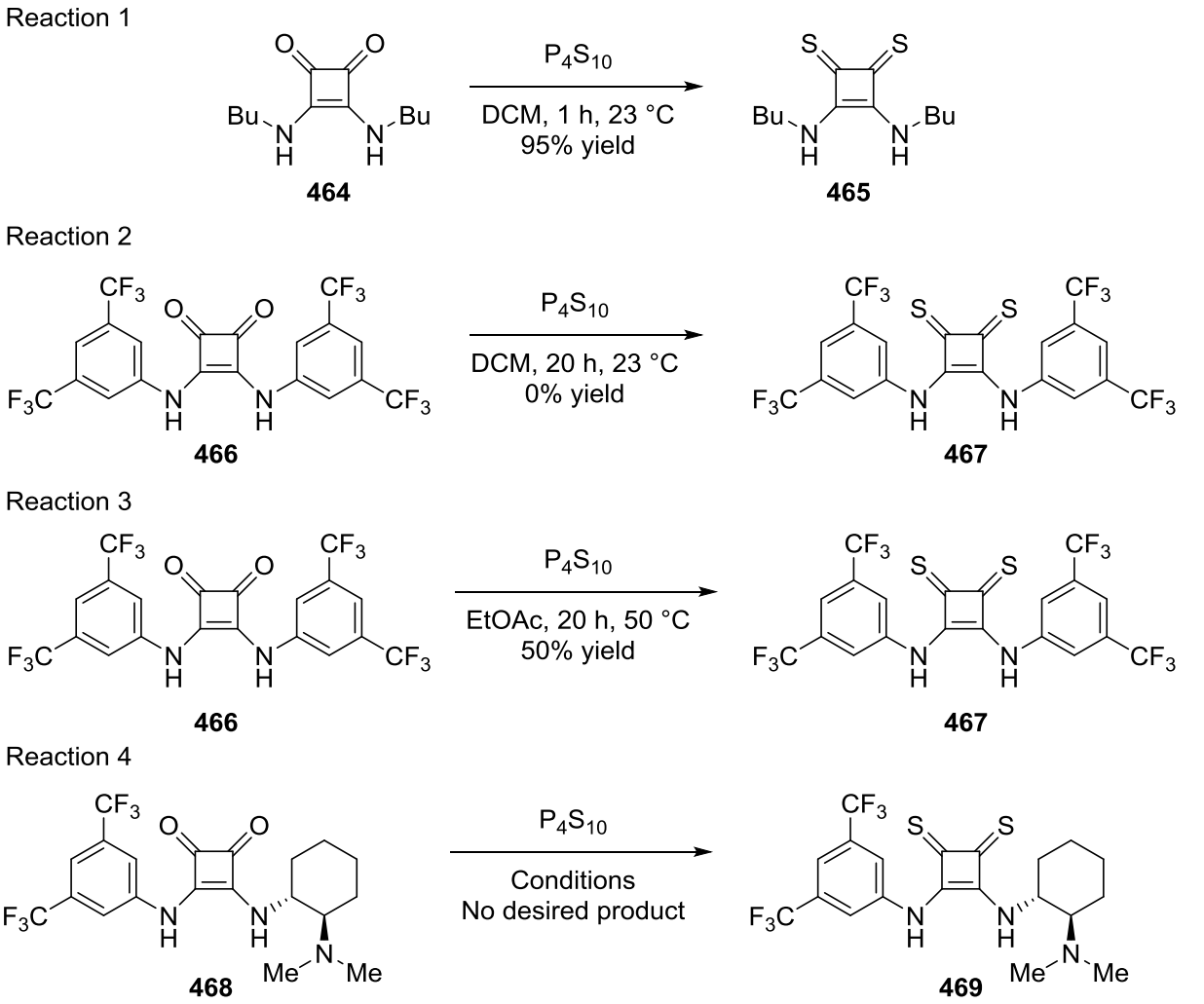
[16] (a) Busschaert, N.; Elmes, R. B. P.; Czech, D. D.; Wu, X.; Kirby, I. L.; Peck, E. M.; Hendzel, K. D.; Shaw, S. K.; Chan, B.; Smith, B. D.; Jolliffe, K. A.; Gale, P. A. *Chemical Science* **2014**, *5*, 3617-3626. (b) Elmes, R. B. P.; Busschaert, N.; Czech, D. D.; Gale, P. A.; Jolliffe, K. A. *Chem. Commun.* **2015**, *51*, 10107-10110.

[17] Thioamides tend to be more acidic than amides, please see: (a) Bordwell, F. G.; Fried, H. E. *The Journal of Organic Chemistry* **1991**, *56*, 4218-4223. (b) Bordwell, F. G.; Ji, G. Z. *J. Am. Chem. Soc.* **1991**, *113*, 8398-8401.

thiosquaramides will act as excellent hydrogen bond donors.[18] Another possible advantage relates to the predicted improved solubility of a thiosquaramide catalyst as compared to a squaramide, which are generally poorly soluble in non-protic solvents.

VI.1.3: Initial Attempts and Results

Scheme 63: Preparation of Symmetrical Thiosquaramides



The most obvious and direct approach for accessing thiosquaramides would be to simply convert a squaramide into the corresponding thiosquaramide. Methods for synthesizing

[18] Lu, T.; Wheeler, S. E. *Chemistry – A European Journal* **2013**, *19*, 15141-15147.

structurally diverse squaramides are well documented. Beginning with a simple substrate, several different conditions were attempted in order to form and isolate chiral thiosquaramide **469** (Scheme 63).

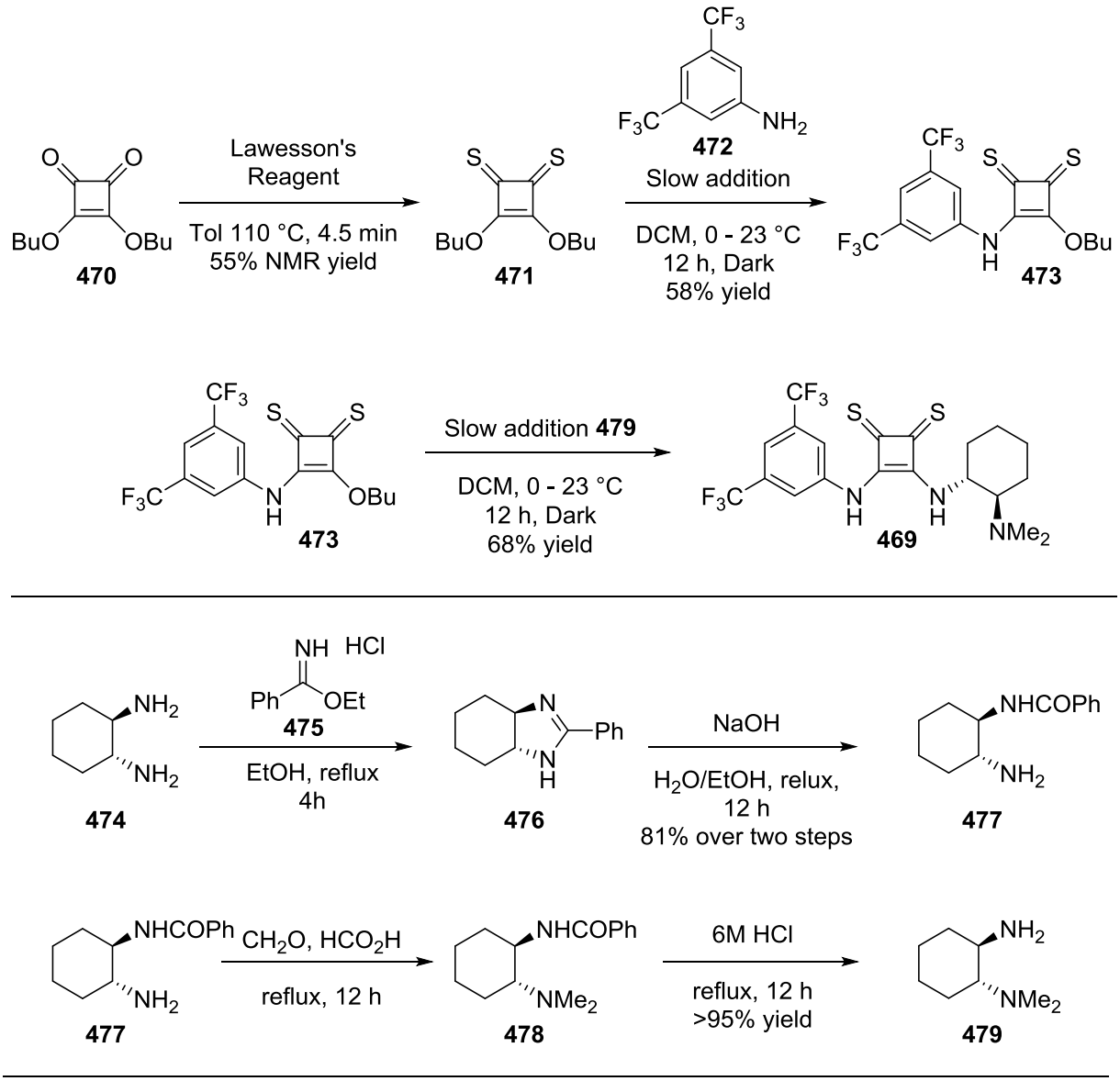
Beginning with relatively electron rich alkyl substituted squaramide **464**, the use of P_4S_{10} proved sufficient to cleanly convert squaramide **464** into thiosquaramide **465**. Disappointingly when the bis-aryl squaramide **466** was tested, it proved completely unreactive to the previously used reaction conditions. To facilitate conversion of squaramide **466** into desired thiosquaramide **467**, harsher conditions were required, including heating to 50 °C for a prolonged reaction time (reaction 2, 3). With methods for the thionation of both symmetrical squaramides **465** and **467** determined, both sets of conditions were applied to chiral squaramide **468**. Disappointingly, all thionating conditions tried produced no significant conversion to thiosquaramide **469** (reaction 4). After encountering persistent difficulties for the direct conversion of a squaramide into a thiosquaramide, a less direct route to such compounds was employed (Scheme 64).

After a significant amount of optimization and experimentation, a route was devised which for the first time, gave rise to a thiosquaramide compound bearing an additional amine moiety. The intial reaction of dibutyl squarate **470** was carried out with Lawesson's reagent[19] at 110 °C. Following conversion of squarate **470** into thiosquarate **471**, the partial purified compound was dissolved in dichloromethane and aniline **472** was added to provide half thiosquaramide **473** in modest yield. The right half of the molecule was synthesized according to a known protocol to produce *N*,*N*-dimethyl-(*R*,*R*)-diaminocylohexane **479** in good yield after

[19] (a) Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, *2003*, 1929-1958. (b) In *Name Reactions*; Springer Berlin Heidelberg: 2006, p 348-349. (c) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210-5278.

several steps.[20] Chiral amine **479** was carefully combined with thiosquaramide **473** to produce chiral thiosquaramide catalyst **469** in acceptable yield.

Scheme 64: Stepwise Approach to Thiosquaramides

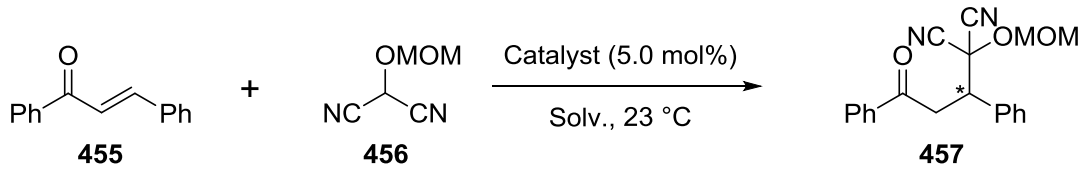


[20] Suez, G.; Bloch, V.; Nisnevich, G.; Gandelman, M. *Eur. J. Org. Chem.* **2012**, *2012*, 2118-2122.

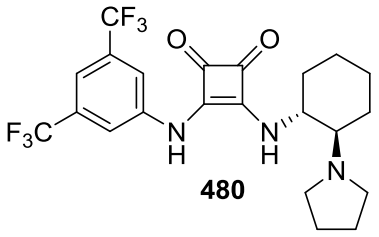
VI.1.4: Calibration Studies using Thiosquaramide

With newly developed thiosquaramide **469** in hand a number of different reactions were selected to determine if thiosquaramide **469** possessed any level of catalytic activity (Table 26).

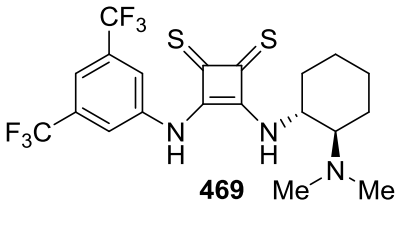
Table 26: Calibration of Thiosquaramide Using MAC Addition



Entry	Catalyst	Additive	Solvent	Yield (%) [a]	ee (%) [b]
1	-	NEt_3	CH_2Cl_2	95	0
2	-	-	CH_2Cl_2	0	-
3 [c]	**480**	-	CH_2Cl_2	81	91
4	**469**	-	CH_2Cl_2	0	-
5	**469**	-	Tol	0	-
6	**469**	-	DCE	0	-
7	**469**	-	Hex	0	-



480



469

[a]NMR yield based on internal standard. [b]ee determined by chiral HPLC. [c]Literature result.

The addition of a masked acyl cyanide (MAC) to chalcone has been established as a high yielding reaction promoted by chiral bifunctional squaramide catalyst **480** and was chosen as a first test for thiosquaramide **469**.[91] Conversion of chalcone **455** into compound **457** proceeded smoothly in the presence of trimethylamine (entry 1). It was also seen that in the absence of

either a catalyst or amine base the reaction failed to give any conversion to desired product **457**. The known literature reaction is reported to provide product in good yield and excellent levels of selectivity.[21] Several solvents were screened for use with thiosquaramide **469** (entries 4-7). Disappointingly all of the conditions tried failed to provide any level of conversion to desired product **457**.

VI.1.5: Attenuation of Tertiary Amine and Use of Acidic Substrates

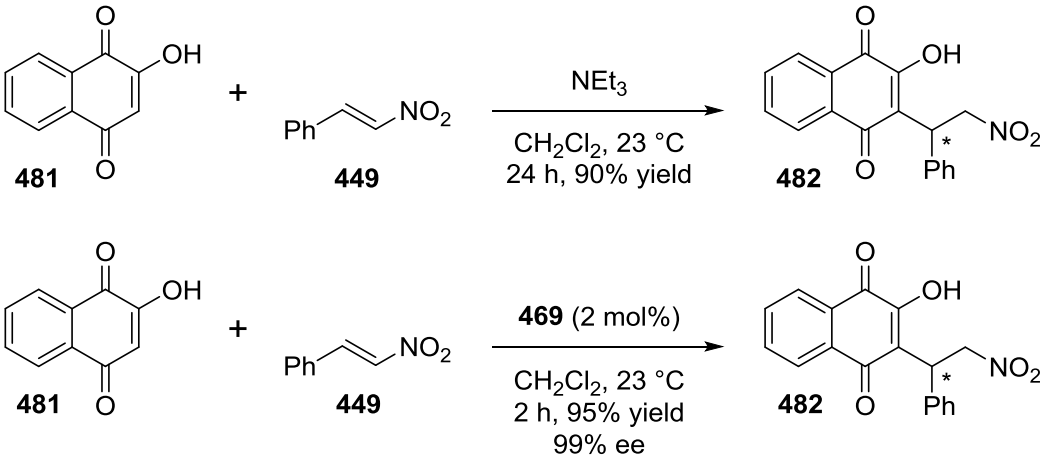
While the previous set of experiments failed to provide any conversion to product **457**, an interesting insight into how thiosquaramide **469** functioned was obtained. Addition of MAC reagent **456** to chalcone **455** gave desired product **457** only in the presence of a basic amine moiety. This led to the hypothesis that thiosquaramide **469** was sufficiently acidic to either protonate or otherwise attenuate the ability of the tethered tertiary amine to function as a base. This would account for the complete lack of a reaction for the MAC addition and potentially by using a more acidic substrate thiosquaramide **469** could function as a hydrogen bonding catalyst (Scheme 65).

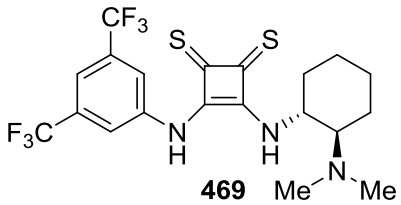
Addition of 2-hydroxy-1,4-naphthaquinone **481** (lawsone) to β-nitrostyrene **449** is a known transformation[22] which has been successfully rendered asymmetric using a squaramide catalyst.[23] The reaction has been reported to give good yield and selectivity (96% yield, 97% ee) and is compatable with a variety of substrates. This reaction was chosen as a calibration study

[21] The reaction was performed and gave near complete conversion to product, however the ee was not determined as the experiment was only to validate the technique being used.
[22] Barcia, J. C.; Otero, J. M.; Estévez, J. C.; Estévez, R. J. *Synlett* **2007**, *2007*, 1399-1402.
[23] (1) Yang, W.; Du, D.-M. *Adv. Synth. Catal.* **2011**, *353*, 1241-1246. (2) Kasaplar, P.; Rodríguez-Escrich, C.; Pericàs, M. A. *Org. Lett.* **2013**, *15*, 3498-3501. (3) Zhou, E.; Liu, B.; Dong, C. *Tetrahedron: Asymmetry* **2014**, *25*, 181-186.

due to the high acidity of lawsone **481** (pKa = 4).[24] After promoting the racemic reaction with trimethylamine, thiosquaramide **469** was used to catalyze this transformation. Excitingly thiosquaramide **469** catalyzed a rapid conversion of lawesone **481** into desired compound **482** in excellent yield. After analysis by chiral HPLC the reaction was seen to give practically a single enantiomer (99% ee). The rate acceleration, as compared to the run using trimethylamine and the ability of thiosquaramide **469** to impart high levels of selectivity demonstrated conclusively that developed thiosquaramide **469** is a chiral hydrogen bonding catalyst. To further explore the ability of thiosquaramide catalyst **469** to promote reactions involving acidic substrates, a second calibration experiment was devised. In a similar fashion to the previous example, the reaction selected had already proved ameinable to squaramide catalysis (Scheme 66).[25]

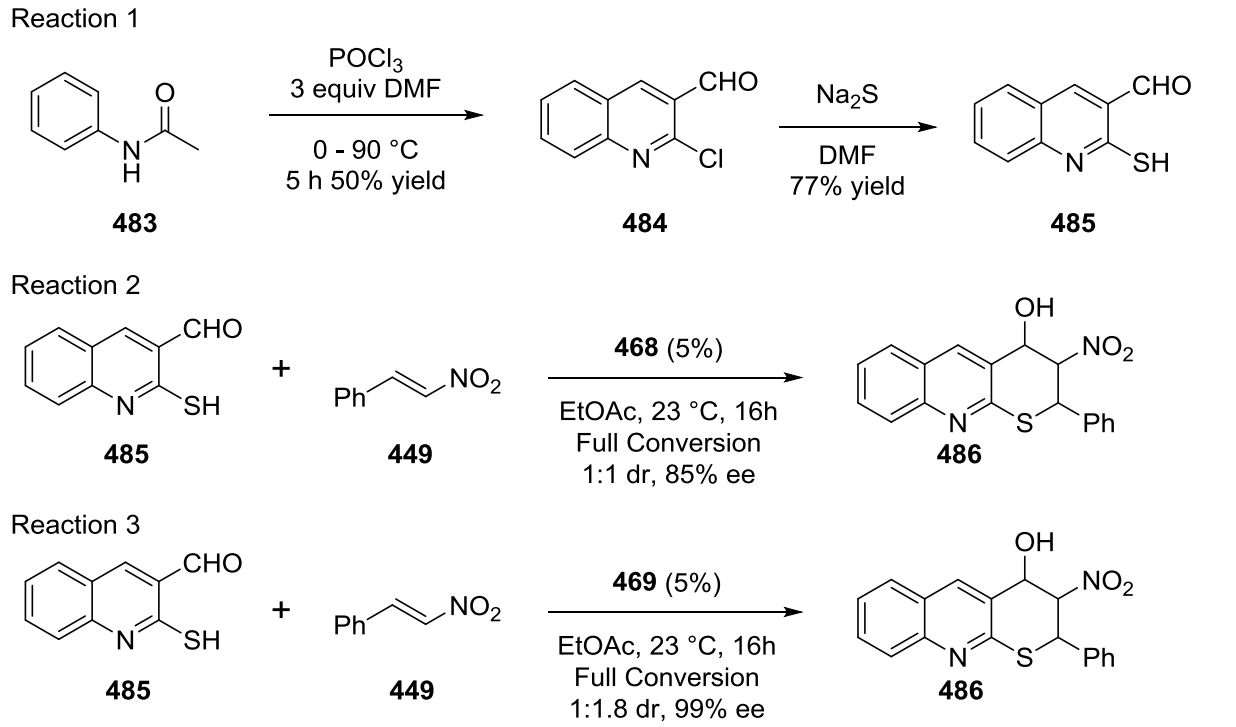
Scheme 65: Addition of 2-Hydroxy-1,4-Naphthaquinone to β-Nitrostyrene

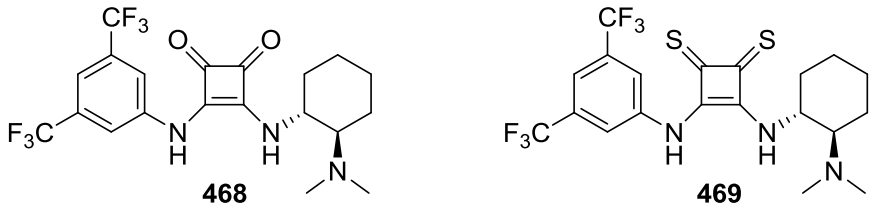




[24] Ashnagar, A.; Shiri, A. *International Journal of ChemTech Research*, **2011**, *3*, 1941-1944.
[25] Wu, L.; Wang, Y.; Song, H.; Tang, L.; Zhou, Z.; Tang, C. *Adv. Synth. Catal.* **2013**, *355*, 1053-1057.

Scheme 66: Direct Comparison Between Squaramides and Thiosquaramides for Catalyzing a Tandem Michael-Henry Reaction





Compound **485** can be synthesized according to a two-step process starting with phenyl acetamide **483** and dimethyl formamide (DMF). Resulting compound **484** is then transformed into aryl-thiol via a simple nucleophilic aromatic substitution reaction, giving substrate **485** in reasonable yield (reaction 1). When aryl-thiol **485** was combined with β-nitrostyrene **449** in the presence of squaramide **468**, tricylic compound **486** was isolated in excellent levels of conversion and enantioselectivity (reaction 2). When analogous thiosquaramide **469** was used for

the reaction similar levels of conversion were observed but significantly higher levels of diastereoselectivity and enantioselectivity were obtained (reaction 3). This direct comparison demonstrates that under appropriate reaction conditions a thiosquaramide catalyst can outperform a squaramide catalyst.

VI.1.6: Conclusion of Thiosquaramide

In summary, a novel class of hydrogen bond donating catalysts has been developed and shown to have unique properties not shared with typical squaramide catalysts. Thiosquaramides seem to be less basic than corresponding squaramides but when used with a suitably acidic substrate they can give comparable or superior levels selectivity. Additionally, thiosquaramides are significantly more soluble, qualitatively, than squaramide catalysts. With these initial results, further development into this field is expected to occur in the near future.

VI.2: Palladium Catalyzed Carbonylative Arylation of Indole

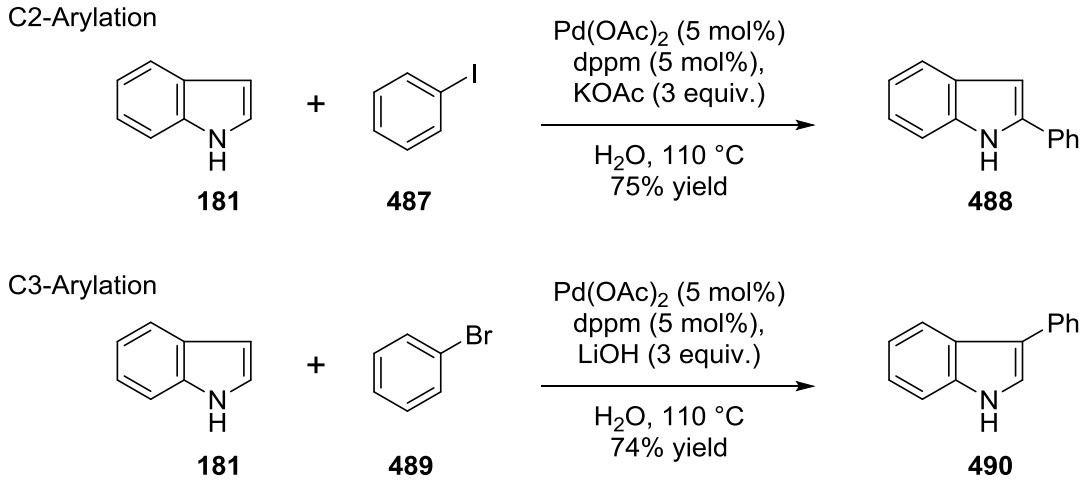
VI.2.1: Introduction

The functionalization of indoles remains an area of chemistry which commands interest from both a scientific viewpoint and a practical one. In chapters II and III the C3 functionalization of indoles and oxindoles is addressed in a certain amount of depth. While investigating the allylation of indole it was hypothesized that a carbonylative arylation of the C3 position could be possible. The palladium catalyzed arylation of indoles has been reported in the literature for both the C2[26] and the C3[27] position of the indole ring (Scheme 67). It was thought

[26] For examples of palladium catalyzed arylation of C2 position of indole see : (a) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1473-1476. (b) Joucla, L.; Batail, N.; Djakovitch, L. *Adv. Synth. Catal.* **2010**, *352*, 2929-2936. (c) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990-12993. (d) Malmgren, J.; Nagendiran, A.; Tai, C.-W.; Bäckvall, J.-E.; Olofsson, B. *Chemistry – A European Journal* **2014**, *20*, 13531-13535.

that this sort of process could be modified to perform a carbonylative arylation of indole, giving access to new classes of compounds.[28]

Scheme 67: Palladium Catalyzed Functionalization of Indole

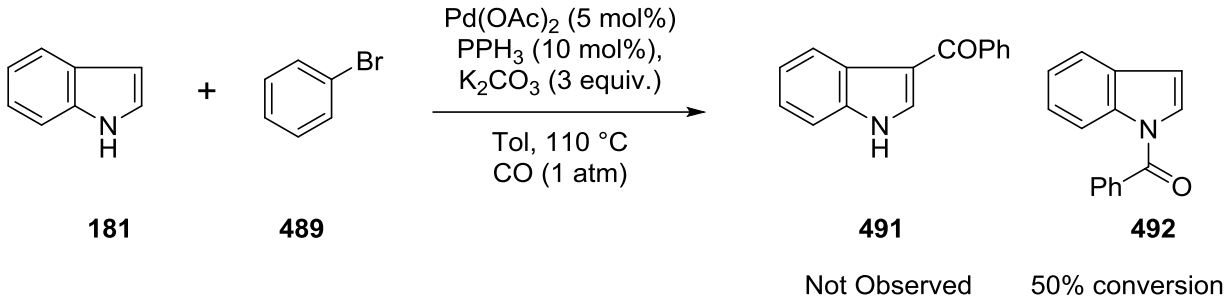


In an effort to realize a carbonylative arylation of the C3 position of indole, a modification of a procedure by Rossi and coworkers was used with the addition of a carbon monoxide atmosphere.[27c] Surprisingly the major identifiable product from the reaction mixture corresponded to a reaction at the *N*1 position of indole giving aryl amide **492** (Scheme 68).

[27] For examples of palladium catalyzed arylation of C3 position of indole see : (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897-2900. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050-8057. (c) Bellina, F.; Benelli, F.; Rossi, R. *The Journal of Organic Chemistry* **2008**, *73*, 5529-5535. (d) Chen, Y.; Guo, S.; Li, K.; Qu, J.; Yuan, H.; Hua, Q.; Chen, B. *Adv. Synth. Catal.* **2013**, *355*, 711-715. (e) Chen, S.; Liao, Y.; Zhao, F.; Qi, H.; Liu, S.; Deng, G.-J. *Org. Lett.* **2014**, *16*, 1618-1621.

[28] For examples of palladium catalyzed carbonylation please see the following reviews and sources sited therein: (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons, Inc.: New York, NY, 1996. (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley & Sons Ldt.: Chichester, West Sussex, England, 2004.

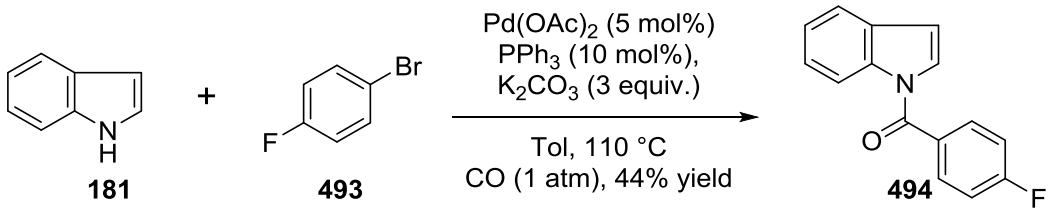
Scheme 68: *N*-Reactivity of Indole



VI:2.2: Reaction Optimization

While product **492** is not particularly interesting it was thought that this chemistry could provide access to a wider range of products that cannot be accessed through commercially available acid chlorides. To demonstrate this practicality indole **181** was combined with 4-fluro-bromobenzene **493** under a carbon monoxide atmosphere to give *N*-carbonyl product **494** in moderate yield (Scheme 69).

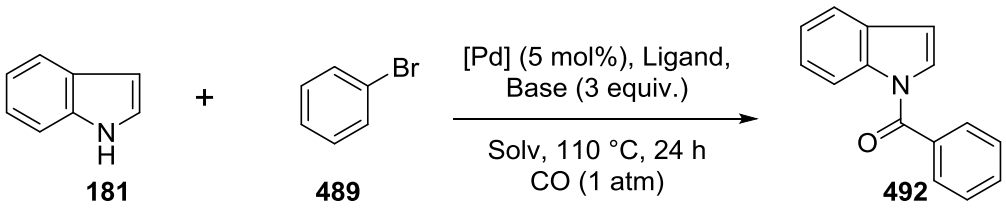
Scheme 69: Reaction with 4-Fluro-Bromobenzene



With this concept now established, a short optimization of the reaction conditions was carried out, screening a variety of ligands and catalysts (Table 27). While several other palladium sources were screened, none managed to show greater conversion to desired product **492** than the original palladium acetate (entries 1-4). Following this it was deduced that an electron rich trialkyl phosphine (entry 6) gave the optimal result out of the ligands screened (entries 5-8).

Finally by increasing the amount of bromobenzene added to the reaction mixture complete conversion to desired compound **492** was realized (entries 9, 10).

Table 27: Optimization of Conditions for Carbonylation



Entry	[Pd]	Ligand	Equiv. PhBr	Solv.	Yield[a]
1	$Pd(OAc)_2$	PPh_3	1.2	Tol	55
2	$Pd(PPh_3)_4$	None	1.2	Tol	20
3	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3	1.2	Tol	37
4	$[Pd(allyl)cod]BF_4$	PPh_3	1.2	Tol	14
5	$Pd(OAc)_2$	$P(2\text{-furyl})_3$	1.2	Tol	16
6	$Pd(OAc)_2$	$P(t\text{-Bu})_3$	1.2	Tol	67
7	$Pd(OAc)_2$	$P(OPh)_3$	1.2	Tol	9
8	$Pd(OAc)_2$	$P(NEt_2)_3$	1.2	Tol	34
9	$Pd(OAc)_2$	$P(t\text{-Bu})_3$	1.5	Tol	94
10	$Pd(OAc)_2$	$P(t\text{-Bu})_3$	1.8	Tol	>99

[a]NMR yield based on internal standard.

This optimized transformation creates the possibility for the easy generation of a range of different indole derivatives under palladium catalysis conditions.[29]

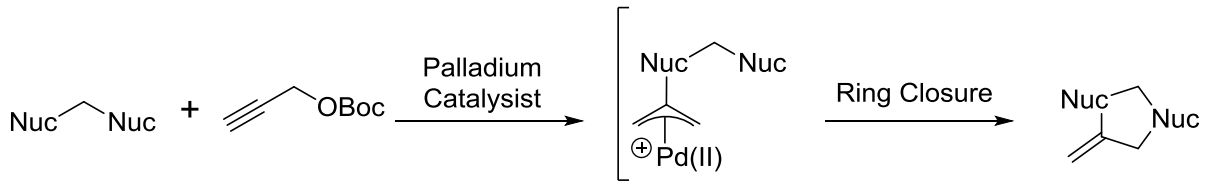
[29] A similar transformation has been since reported in the literature: Fang, W.; Deng, Q.; Xu, M.; Tu, T. *Org. Lett.* **2013**, *15*, 3678-3681.

VI.3: Palladium Catalyzed Reaction of Propargyl *tert*-Butyl Carbonate With 1,2-Bis-Nucleophiles

VI.3.1: Introduction

Following the successful application of the palladium mediated coupling of a propargyl carbonate with a bis-nuclophile, further applications of the chemistry were considered. During the examination of such reactions, as detailed in chapter IV, the reaction proved compatible with ethyl, propyl and even butyl spaced nucleophiles giving access to six, seven and eight membered heterocycles. This left the question of whether the chemistry could be adapted for the synthesis of a five membered heterocycle; and if so what nucleophiles would prove compatible with the reaction conditions (Scheme 70).

Scheme 70: Envisioned Palladium Catalyzed Ring Formation



495 **255** **496** **497**

Similar to piperazines and piperazinones, five membered heterocyclic compounds are of great interest to chemists due to their appearance in pharmaceuticals and natural products.[30] Certain structures such as: imidazolidine,[31] thiazolidine,[32] γ-lactam[33] and pyrrolidine[34] are

[30] (a) In *Chem Heterocycl Compd*; John Wiley & Sons, Inc.: 2008, p 213-222. (b) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein Journal of Organic Chemistry* **2011**, *7*, 442-495. (c) Lopchuk, J. M. In *Prog. Heterocycl. Chem.*; Gordon, W. G., John, A. J., Eds.; Elsevier: 2014; Vol. Volume 26, p 151-192. (d) Yet, L. In *Prog. Heterocycl. Chem.*; Gordon, W. G., John, A. J., Eds.; Elsevier: 2014; Vol. Volume 26, p 237-277.

[31] For selected references see : (a) Ferm, R. J.; Riebsomer, J. L. *Chem. Rev.* **1954**, *54*, 593-613. (b) Fernández-Bolaños, J. G.; Zafra, E.; López, O.; Robina, I.; Fuentes, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3011-3023. (c) Al-Raqa, S. Y.; ElSharief, A. M. S.; Khalil, S. M. E.; Al-

common and important motifs, making the development of novel methods for accessing them of critical importance.

VI.3.2: Initial Experiments and Bis-Nucleophile Selection

A number of bis-nucleophiles were prepared and exposed to reaction conditions similar to those previously used during the spirocyclization reaction of indoles (Scheme 71). The substrates were chosen based on their predicted or measured acidity. A qualitative pattern had been seen during the previous work, where it was observed that nucleophiles with pKa values between 22 and 17 were compatible with the reaction conditions.[35]

Amri, A. M. *Heteroat. Chem* **2006**, *17*, 634-647. (d) Liu, H.; Yang, Z.; Pan, Z. *Org. Lett.* **2014**, *16*, 5902-5905.

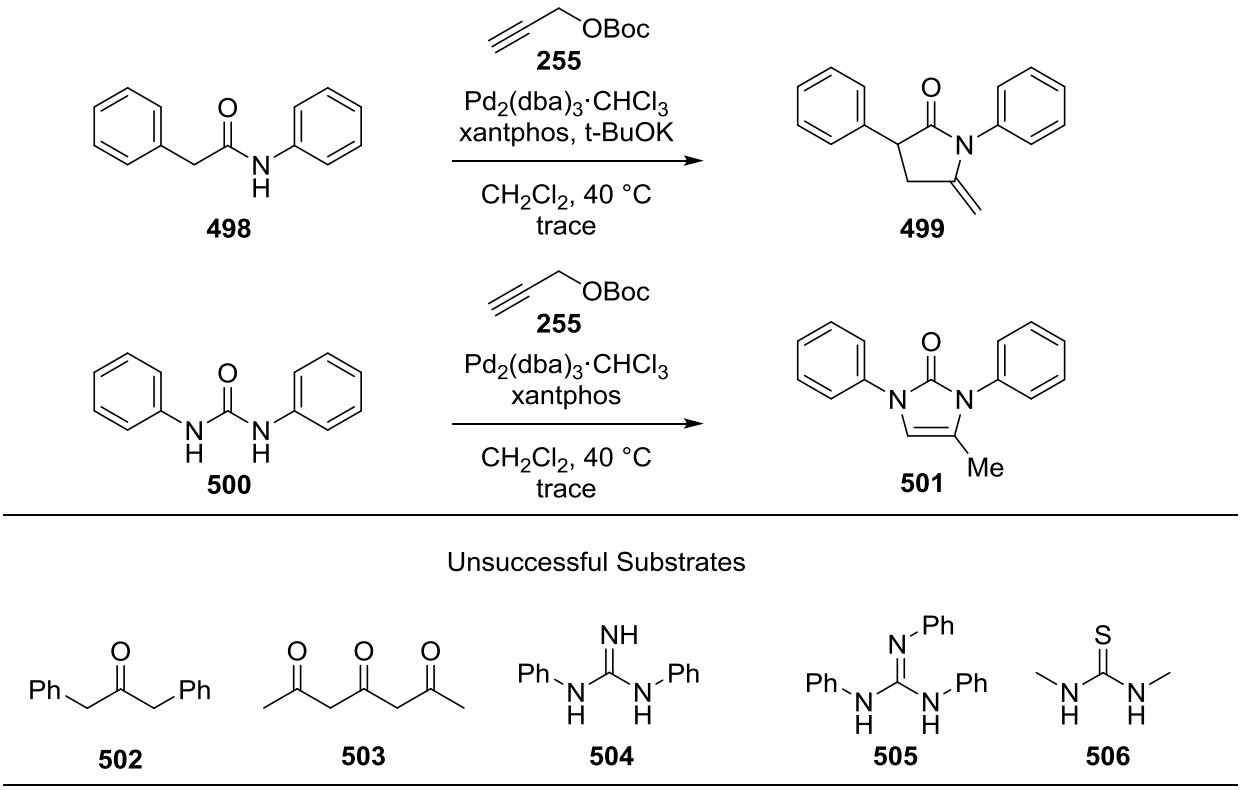
[32] For selected references see : (a) Schmolka, I. R.; Spoerri, P. E. *The Journal of Organic Chemistry* **1957**, *22*, 943-946. (b) Nishida, S.; Maruoka, H.; Yoshimura, Y.; Goto, T.; Tomita, R.; Masumoto, E.; Okabe, F.; Yamagata, K.; Fujioka, T. *J. Heterocycl. Chem.* **2012**, *49*, 303-309. (c) Stojanovic, M.; Markovic, R.; Kleinpeter, E.; Baranac-Stojanovic, M. *Organic & Biomolecular Chemistry* **2012**, *10*, 575-589. (d) Jain, V. S.; Vora, D. K.; Ramaa, C. S. *Biorg. Med. Chem.* **2013**, *21*, 1599-1620.

[33] For selected references see : (a) Chatterjee, B. G.; Sahu, D. P. *The Journal of Organic Chemistry* **1977**, *42*, 3162-3165. (b) Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *The Journal of Organic Chemistry* **1991**, *56*, 2603-2605. (c) Kumar, K. R. R.; Basappa; Rangappa, K. S.; Mallesha, H. *J. Heterocycl. Chem.* **2003**, *40*, 607-609.
(4) Aszodi, J.; Rowlands, D. A.; Mauvais, P.; Collette, P.; Bonnefoy, A.; Lampilas, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2489-2492. (e) Poulsen, T. B.; Dickmeiss, G.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem.* **2008**, *120*, 4765-4768.

[34] For selected references see : (a) Dolfini, J. E.; Dolfini, D. M. *Tetrahedron Lett.* **1965**, *6*, 2053-2058. (b) Machinaga, N.; Kibayashi, C. *The Journal of Organic Chemistry* **1991**, *56*, 1386-1393. (c) K.-I. Fujita, T. Fujii, R. Yamaguchi, *Org. Lett.*, **2004**, *6*, 3525-3528. (d) Bertrand, M. B.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457-460. (e) Nishida, S.; Maruoka, H.; Yoshimura, Y.; Goto, T.; Tomita, R.; Masumoto, E.; Okabe, F.; Yamagata, K.; Fujioka, T. *J. Heterocycl. Chem.* **2012**, *49*, 303-309. (f) Duris, A.; Barber, D. M.; Sanganee, H. J.; Dixon, D. J. *Chem. Commun.* **2013**, *49*, 2777-2779. (g) Barber, D. M.; Ďuriš, A.; Thompson, A. L.; Sanganee, H. J.; Dixon, D. J. *ACS Catalysis* **2014**, *4*, 634-638.(h) Bhat, C.; Tilve, S. G. *RSC Advances* **2014**, *4*, 5405-5452.

[35] For a detailed scheme showing different nucleophiles tested please see the supporting information of: Nibbs, A. E.; Montgomery, T. D.; Zhu, Y.; Rawal, V. H. *The Journal of Organic Chemistry* **2015**, *80*, 4928-4941.

Scheme 71: Different Bis-Nucleophiles Screened

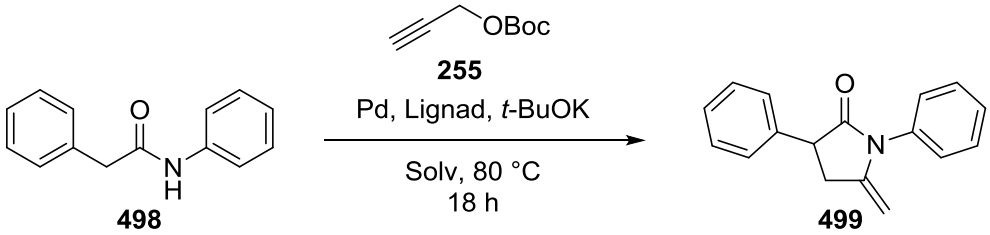


Of the substrates screened the formation of any amount of desired cyclic product was only observed for substrates **498** and **500**. When phenyl benzylamide **498** were used a small amount of desired product **499** was observed in the crude mixture by ^{1}H NMR. Diphenyl urea **500** also gave trace amounts of cyclic product **501** after exposure to the reaction conditons. Of additional interest was the fact that heterocyclic structure **501** appeared to have undergone olefin isomerization following ring closure to give the endocyclic olefin product. Five other substrates were combined with propargyl *tert*-butyl carbonate **255** under palladium catalyst conditions and all failed to affect any amount of cyclized product. With these primary results in hand a number of conditions were examined to optimize the cyclization of amide **498** to lactam **499**.

VI.3.3: Screening Conditions for **499** Synthesis

With the initial conditions giving very poor yield a number of different solvents (entries 1-4) were screened.[36] Only the chlorinated solvents (DCE and CH_2Cl_2) gave any appreciable conversion to desired product **499**. A focused selection of other bidentate ligands were examined (entries 5-7), again giving no particular improvement for conversion to **499**.

Table 28: Initial Screening of Conditions

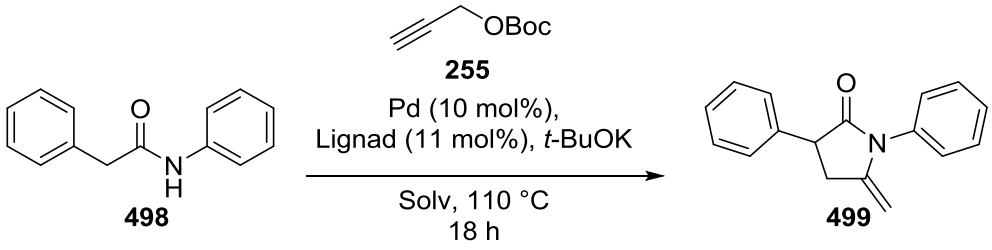


Entry	Pd	Ligand	Solv.	Conversion[a]
1	$Pd_2(dba)_3{\cdot}CHCl_3$	xantphos	MeCN	NR
2	$Pd_2(dba)_3{\cdot}CHCl_3$	xantphos	DCE	<5%
3	$Pd_2(dba)_3{\cdot}CHCl_3$	xantphos	Tol	Trace
4	$Pd_2(dba)_3{\cdot}CHCl_3$	xantphos	Dioxane	NR
5	$Pd_2(dba)_3{\cdot}CHCl_3$	DPEphos	DCE	trace
6	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	DCE	trace
7	$Pd_2(dba)_3{\cdot}CHCl_3$	dppf	DCE	trace
8	$Pd(PPh_3)_4$	xantphos	DCE	NR
9	$Pd(OAc)_2$	xantphos	DCE	5%
10	$[Pd(allyl)cod]BF_4$	xantphos	DCE	6%

[a]Conversion determined by ^{1}H NMR

[36] $Conversion = \left(\frac{X}{Y}\right) * 100$ where x = ^{1}H integration of **X** and y = ^{1}H integration of **X**.

Table 29: Second Round of Screening



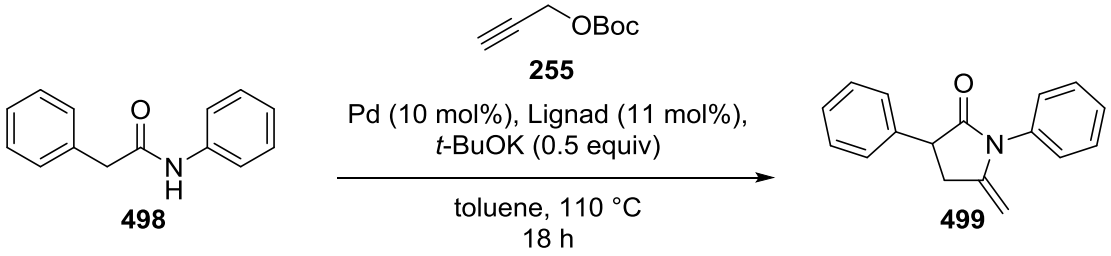
Entry	Pd	Ligand	Solv	Equiv Base	Conversion [a]
1	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	Tol	1.1	51
2	$Pd_2(dba)_3 \cdot CHCl_3$	Xantphos	Tol	1.1	48
3	$Pd_2(dba)_3 \cdot CHCl_3$	dppe	Tol	1.1	NR
4	$Pd_2(dba)_3 \cdot CHCl_3$	(R)-BINAP	Tol	1.1	39
5	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	Tol	0.1	50
6	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	Tol	0.5	53
7	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	Tol	1.5	37
8	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	DMF	0.5	NR
9	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	Pyr.	0.5	NR
10	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	Dioxane	0.5	trace
11	$Pd(PPh_3)_4$	DPEphos	Tol	0.5	10

[a]Conversion determined by ^1H NMR

When palladium (II) salts were examined, clear and quantifiable conversion to lactam **499** was observed in the crude reaction mixture (entries 8-10). Due to the low conversions obtained, the reaction temperature was increased to 110 °C and the catalyst loading was increased from (5 mol%) to (10 mol%) palladium (Table 29) in order to facilitate conversion to **499**. Gratifyingly, the higher temperature and catalyst loading provided a significantly improved conversion of amide **498** into lactam **499** after 18 hours (entry 1). Additional ligands were

screened with none providing any improvement from DPEphos (entries 2-4). The amount of base was examined next and it was determined that a half equivalent was optimal for conversion to lactam **499** (entries 5-7). A selection of high boiling solvents was screened, as well as another palladium (0) source (entries 8-11). None of these modifications offered an advantage, with many simply shutting the reaction down. In an effort to find conditions which would promote a high yielding method, a final set of parameters were examined (Table 30).

Table 30: Screen of Conditions for Synthesis of Lactam **498**



Entry	Pd	Ligand	Conversion[a]
1	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	61
2	$Pd_2(dba)_3 \cdot CHCl_3$	NiXantphos	11
3	$Pd_2(dba)_3 \cdot CHCl_3$	*t*-Buxantphos	NR
4	$Pd_2(dba)_3 \cdot CHCl_3$	Trost Ligand	NR
5[b]	$Pd_2(dba)_3 \cdot CHCl_3$	DPEphos	49
6	$Pd(OAc)_2$	DPEphos	6
7	$Pd(OAc)_2$	DPEphos (2 eq)	24
8	$Pd(OTf)_2$	DPEphos	8
9	$Pd(OTf)_2$	DPEphos (2 eq)	49
10	$[Pd(allyl)cod]BF_4$	DPEphos	54

[a]Conversion determined by ^1H NMR. [b]Benchtop toluene used.

With rigorous degassing of the solvent, using standard freeze-pump-thaw techniques, lactam **499** was generated in 61% conversion (entry 1).[37] Both modified xantphos ligands used (entries 2,3) failed to provide good levels of conversion to γ-lactam **499**. Furthermore, use of Trost's chiral ligand showed no reaction after 18 h (entry 4).[38] When the reaction was run using non-degassed and non-anhydrous solvent, a significant loss of yield was observed (entry 5). Several palladium (II) salts were screened again, with both palladium acetate and palladium triflate failing to give satisfactory conversion to desired lactam **499** (entries 6-9). When palladium source [Pd(allyl)cod]BF_4 was examined (entry 10) it gave reasonable conversion to desired product **499** but was still inferior to the prior result (entry 1).

VI.3.4: Conclusion for Palladium Catalyzed 5-Membered Ring Formation

A number of different 1,3-bis-nucleophiles were examined for the possibility of forming various five membered rings through a similar process to the six membered ring formation previously described. Unlike the previously explored conditions the five membered ring formation reaction proved much more challenging, requiring high temperature and catalyst loadings in order to access these compounds in a satisfactory manner. A number of conditions were examined to catalyze this transformation, looking at palladium source, ligand, solvent and amount of base used. These results will act as a firm foundation for additional investigations into this transformation, hopefully resulting in a useful method for accessing five membered cyclic compounds.

[37] See reference and sources cited therein: Guerrero-Sanchez, C.; Keddie, D. J.; Saubern, S.; Chiefari, J. *ACS Combinatorial Science* **2012**, *14*, 389-394.
[38] Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422.

VI.4: Use of (Phenylthio)nitromethane for Nucleophilic Addition Reactions

VI.4.1: Introduction

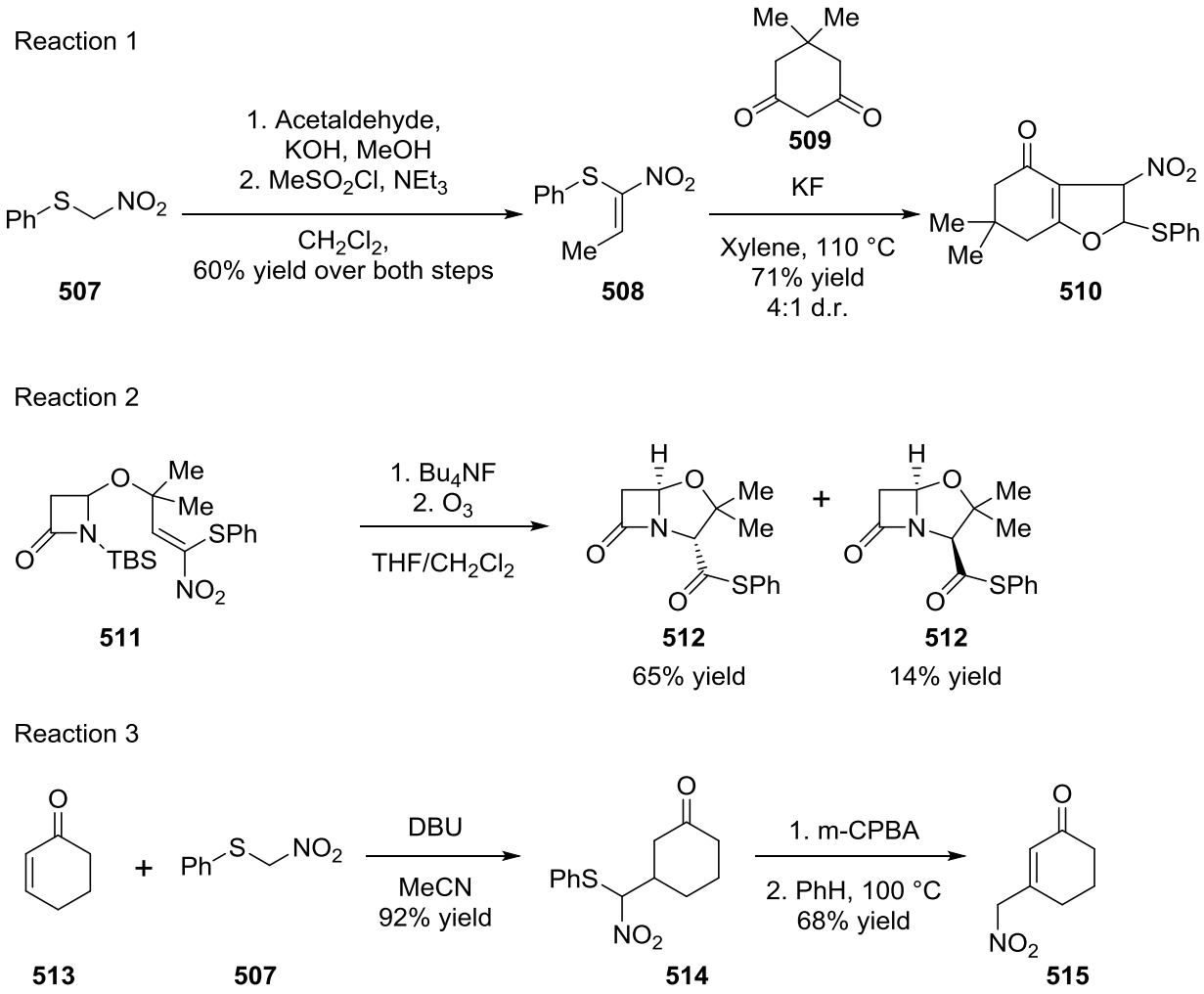
A staple reaction in the field of hydrogen bonding catalysis is the addition of a nucleophile to an electrophile which can accept one or more hydrogen bonds.[2,3] To this end a number of nucleophiles have been adapted for use with hydrogen bond donating catalysts including carbon, sulfur, and phosphorous based nucleophiles.[4-9] Of continuing interest in this field is the addition of novel nucleophilic compounds, or the use of Umpolung synthons.[39] An interesting nucleophile from the literature is (phenylthio)nitromethane **507**. First reported by Kharasch in 1951,[40] it has seen only sporadic application as a nucleophilic species over the subsequent years (Scheme 72).

In the first example, after condensation of **507** with acetaldehyde and subsequent dehydration, electrophilic species **508** is isolated in moderate yield. Carbon nucleophile dimedone **509** is added to compound **508** and the reaction is heated to 110 °C. Following a domino nitro-Michael, Aldol sequence dihydrofuryl compound **510** is isolated in good yield (reaction 1).[41] Reaction two shows TBS protected β-lactam **511**, which when treated with a fluoride source (TBAF) liberates the lactam anion that then adds intramolecularly to the tethered nitro olefin. Subsequent ozonolysis of the anionic nitro gives diastereomeric 4,5-bicyclic structure **512** in good yield.[42, 43]

---

[39] For examples of Umpolung reactivity see the following review and sources cited therein: Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511-3522.
[40] Kharasch, N.; Cameron, J. L. *J. Am. Chem. Soc.* **1951**, *73*, 3864-3867.
[41] Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1978**, 362-363.
[42] Barrett, A. G. M.; Graboski, G. G.; Sabat, M.; Taylor, S. J. *The Journal of Organic Chemistry* **1987**, *52*, 4693-4702.

Scheme 72: Literature uses of (Phenylthio)nitromethane **507**



A more recent example involves the addition of (phenylthio)nitromethane**507** to cyclohexenone **513** generating compound **514**. Following oxidation of the thioether to the sulfoxide, elimination and thermal isomerization substituted cyclohexenone **515** is isolated in good yield over three steps (reaction 3).[44] Other studies have investigated methods for generating (phenylthio)nitromethane,[45] as well as measuring its pKa.[46] In an effort to expand the scope of

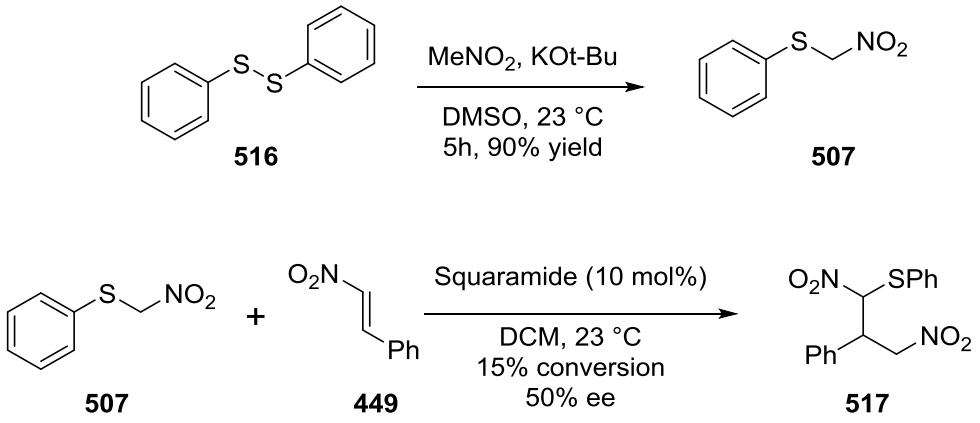
[43] For a similar transformation see: Barrett, A. G. M.; Flygare, J. A.; Spilling, C. D. *The Journal of Organic Chemistry* **1989**, *54*, 4723-4726.
[44] Baranczak, A.; Sulikowski, G. A. *Org. Lett.* **2012**, *14*, 1027-1029.
[45] Blanco, G. A.; Baumgartner, M. T. *Tetrahedron Lett.* **2011**, *52*, 7061-7063.

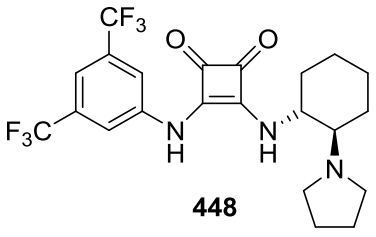
nucleophiles used for hydrogen bonding catalysis (phenylthio)nitromethane **507** was synthesized and screened for addition to β-nitrostyrene using a chiral squaramide catalyst (Scheme 73).

VI.4.2: Addition of (Phenylthio)nitromethane to β-Nitrostyrene

(Phenylthio)nitromethane **507** was easily synthesized from diphenyl disulfide **516** and isolated in excellent yield. The reaction between (phenylthio)nitromethane **507** and β-nitrostyrene **449** resulted in the isolation of the major diastereomer in poor yield but promising levels of enantioselectivity. Inspired by this initial result a small screen of chiral squaramides was examined in an effort to optimize the reaction (Table 31).

Scheme 73: Initial Results for Addition of β-Nitrostyrene

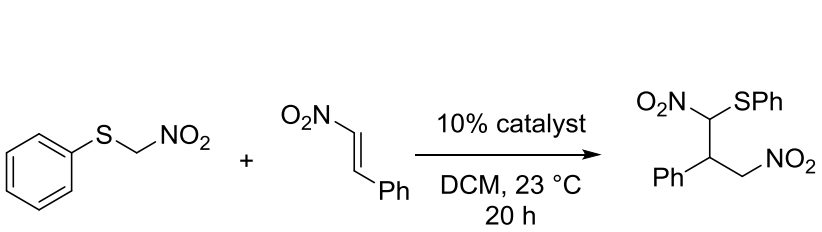




[46] (a) Bordwell, F. G.; Bartmess, J. E. *The Journal of Organic Chemistry* **1978**, *43*, 3101-3107. (b) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1994**, *116*, 8885-8889. (c) Bernasconi, C. F.; Kittredge, K. W. *The Journal of Organic Chemistry* **1998**, *63*, 1944-1953.

The chiral squaramides screened for the reaction of (phenylthio)nitromethane **507** with β-nitrostyrene **449** only involved modification to the right hand portion of the squaramide core. When the pyrrolidine portion of squaramide **448** was substituted for dibenzylamine **518** no conversion to the product was observed (entry 1). Subsequently changing one of the benzyl groups to a methyl group provided product **517** in 14% conversion as a 1:1 mixture of diastereomers and with poor levels of enantioselectivity (entry 2).

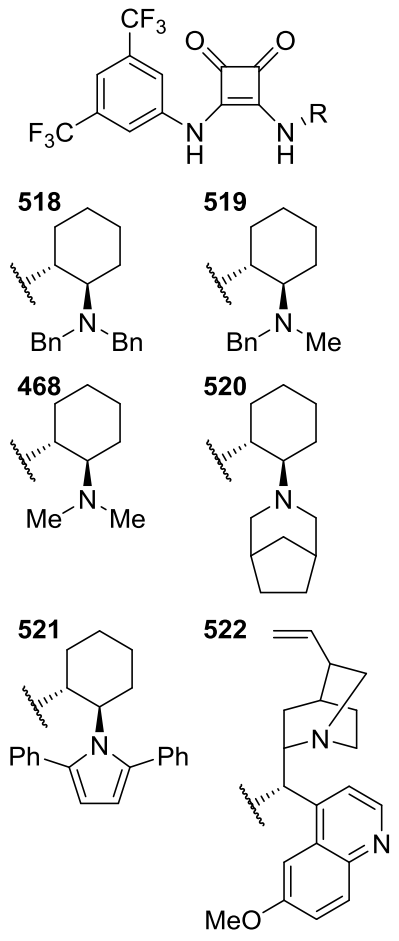
Table 31: Initial Results for Addition of β-Nitrostyrene



507 **449** **517**

Entry	Catalyst	Conv.	dr	ee
1	**518**	0	ND	ND
2	**519**	14	1:1	20
3	**468**	30	9:1	42
4	**520**	20	1:1	30
5	**521**	0	ND	ND
6	**522**	35	>20:1	-20

[a]Conversion determined by ^{1}H NMR. [b]ee determined by HPLC



The dimethyl amine squaramide **468** provided **517** in higher, though still modest levels of conversion and showed decent diastereo- and enantioselectivity (entry 3). Squaramide **520** failed

to offer any improvement to the reaction yield or selectivity and squaramide **521** did not catalyze the reaction to any extent (entries 4,5). Finally the cinchona alkaloid derived squaramide **522** gave compound **517** in almost perfect d.r. (>20:1) but disappointing levels of selectivity (entry 6).

VI.4.3: Conclusion of Investigations into Reactions using (Phenylthio)nitromethane

The use of (phenylthio)nitromethane **507** as a nucleophile for asymmetric addition to electrophiles, such as β-nitrostyrene **449**, offers the possibility of expanding the current scope of hydrogen bond catalyzed processes. Additionally the ability of this nucleophile to introduce new functionality though both a nitro and thioether moiety may serve as useful functional group handles. Reported here is the initial screening for rendering this reaction asymmetric involving the screening of seven different hydrogen bond donating squaramide catalysts.

CHAPTER VII

EXPERIMENTAL SECTION

VII.1: General Information

Reactions were run in oven-dried glassware under N_2 atmosphere. Reactions were monitored by TLC on Whatman silica gel 60 Å F254 plates or EMD Millipore silica gel 60 Å F254 plates, visualized by UV florescence quenching (254 nm), I_2/SiO_2 and staining with $KMnO_4$, *p*-anisaldehyde, Vanillin, Seebach's or Cerium-Ammonium-Molybdate (CAM) staining solution. Flash column chromatography was performed on SiliCycle SiliaFlash silica gel (40-63 µm). NMR spectra were measured on Bruker DRX, DMX and SMP spectrometers at 50 MHz for ^1H spectra and 125 MHz for ^{13}C spectra. ^1H spectra were calibrated from internal standard TMS (δ 0.00) or solvent resonance (Chloroform: 7.26, DMSO: 2.50, Acetone: 2.05, Toluene: 2.08 and Methanol: 3.31). ^{13}C spectra were calibrated from solvent resonance (Chloroform: 77.0, DMSO: 39.52, Acetone: 206.26, Toluene: 20.43 and Methanol: 49.00). NMR data are reported as: chemical shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad signal), coupling constant (Hz) and integration. High-resolution mass spectral analysis (HRMS) was measured on Agilent Technologies 6224 TOF LC/MS (positive electrospray ionization). Standard mass spectral analysis (MS) was measured on Agilent Technologies 6130 LC/MS. Enantiomeric excess (ee) was determined by chiral HPLC analysis using an HPLC instrument with a Chiralcel OD-H or ChiralPak AD-H or AS-H column (25 mm x 10 mm, 4.6 µm partical size, 1.0 mL/min flow rate) equipped with a guard column, employing a mixture of *iso*-propanol and hexanes. IR spectra were measured on

Nicolet 6700 FTIR spectrometer. Melting points were measured using a capillary melting point apparatus.

Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether (Et_2O), toluene (PhMe), benzene (PhH), Acetonitrile (MeCN) and Dimethylformamide (DMF) were purified by passage over activated alumina, using an Innovative Technology, Inc. Puresolv solvent purification system. All other solvents were purchased from commercially sources and used as received.

Unless otherwise noted all chemicals were purchased from commercial sources and used as received.

Procedure for Calculation of NMR Yield: The crude reaction mixture was concentrated *in vaccuo*, and the residue was dissolved in an appropriate deuterated solvent (approx. 1 mL). To this solution was added 1,3,5-trimethoxybenzene (0.33 equiv.), followed by stirring until all solids were completely dissolved. An aliquot was removed and subjected to ^{1}H NMR analysis (d1 relaxation time is set to 5) wherein the integration value of the 1,3,5-trimethoxybenzene signal at δ 6.08 (s, 3H) was compared to the integration values of several peaks corresponding to the desired product. With this information the NMR yield was determined by using the following equations:

$$NMR\ yield = \frac{P}{SM}$$

$$P = \frac{3x}{y} * mmol\ of\ (1,3,5 - trimethyoxybenzene)$$

P = calculated mmol of product; SM = mmol of starting material; x = a normalized average of three aromatic signals corresponding to the product; y = integration value of 1,3,5-trimethyoxybenzene peak at δ 6.08.

VII.2: Experimental Section – Chapter II[1]

General Procedure for Preparation of *N*-alloc Indoles[2]

Prepared according to a modified protocol from Jacquemard and coworkers.[3] A solution of indole substrate in anh. THF, maintained under a positive pressure of nitrogen was cooled to 0 °C in an ice water bath. To this stirred solution 60% NaH was added portionwise over five minutes. After addition of NaH was complete the reaction was allowed to stir an additional 30 minutes at 0 °C under nitrogen, at which time allyl chloroformate was carefully added dropwise via syringe. After completion of addition the reaction flask was allowed to warm to ambient temperature (23 °C). After consumption of starting material, as determined by TLC analysis, the reaction mixture was diluted with diethyl ether and carefully quenched with 1M aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3x). The combined organic extracts were combined, washed with brine, dried over anh. $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography to yield the desired product.

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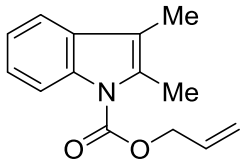
[1] Supporting information is reproduced with permission from: Montgomery, T. D.; Zhu, Y.; Kagawa, N.; Rawal, V. H. *Org. Lett.* **2013**, *15*, 1140-1143.

[2] All non-commercially available indoles were prepared via Fisher indole synthesis using well established procedures.

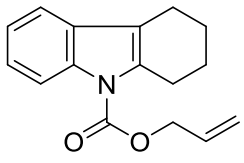
[3] Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039-10047.



202

***N*-alloc-2,3-dimethyl-indole (202):** Prepared according to the general method using 2,3-dimethyl-indole (0.50 g, 3.44 mmol), 60% w/w NaH (0.21 g, 5.17 mmol), allyl chloroformate (0.46 mL, 4.3 mmol) in anh. DMF (16 mL). Purified by flash column chromatography (30:1 Hexanes:EtOAc) to yield **202** (0.69 g, 3.0 mmol, 87% yield) as a white solid.

Analytical data for **202**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 – 8.03 (m, 1H), 7.41 (dd, *J* = 6.1, 2.8 Hz, 1H), 7.25 – 7.20 (m, 2H), 6.15 – 6.00 (m, 1H), 5.51 – 5.40 (m, 1H), 5.38 – 5.30 (m, 1H), 4.93 – 4.89 (m, 2H), 2.54 (s, 3H), 2.18 (s, 3H). Analytical data match those found in the literature.[4]

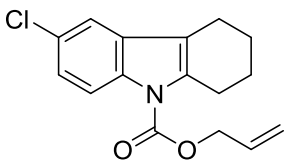


206

***N*-alloc-1,2,3,4-tetrahydrocarbazole (206):** Prepared according to the general method using 1,2,3,4-tetrahydrocarbazole (171 mg, 1.0 mmol), 60% w/w NaH (80 mg, 2.0 mmol), allyl chloroformate (0.32 mL, 3.0 mmol) in anh. DMF (2 mL). Purified by flash column chromatography (30:1 Hexanes:EtOAc) to yield **206** (0.24 g, 0.94 mmol, 94% yield) as a white solid.

[4] Chen, J.; Cook, M. J. *Org. Lett.* **2013**, *15*, 1088-1091.

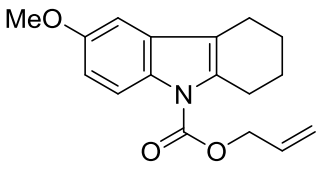
Analytical data for **206**: ^{1}H NMR (500 MHz, Acetone) δ 8.13 (d, *J* = 7.4 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.26 – 7.16 (m, 2H), 6.08 (ddd, *J* = 11.6, 10.4, 5.8 Hz, 1H), 5.46 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.35 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.91 (dt, *J* = 5.8, 1.3 Hz, 2H), 3.01 (d, *J* = 6.2 Hz, 2H), 2.65 (t, *J* = 6.1 Hz, 2H), 1.90 (dd, *J* = 7.5, 3.3 Hz, 2H), 1.86 – 1.78 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.59, 123.59, 122.73, 122.72, 117.58, 115.51, 67.15, 25.68, 23.56, 22.20, 21.10. Analytical data match those found in the literature.[4]



208

***N*-alloc-9-chloro-1,2,3,4-tetrahydrocarbazole (208):** Prepared according to the general method using 9-chloro-1,2,3,4-tetrahydrocarbazole (206 mg, 1.0 mmol), 60% w/w NaH (80 mg, 2.0 mmol), allyl chloroformate (0.21 mL, 2.0 mmol) in anh. DMF (2 mL). Purified by flash column chromatography (30:1 Hexanes:EtOAc) to yield **208** (0.24 g, 0.83 mmol, 83% yield) as a solid.

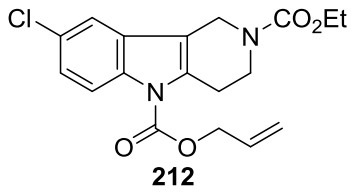
Analytical data for **208**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.19 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.07 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.46 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.35 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.93 – 4.87 (m, 2H), 3.00 (ddd, *J* = 6.2, 4.2, 2.0 Hz, 2H), 2.60 (ddd, *J* = 8.0, 4.0, 2.0 Hz, 2H), 1.88 (dt, *J* = 6.2, 3.8 Hz, 2H), 1.82 (dt, *J* = 5.1, 3.5 Hz, 2H).



210

***N*-alloc-9-methoxy-1,2,3,4-tetrahydrocarbazole (210):** Prepared according to the general method using 9-methoxy-1,2,3,4-tetrahydrocarbazole (141 mg, 0.7 mmol), 60% w/w NaH (56 mg, 1.4 mmol), allyl chloroformate (0.15 mL, 1.4 mmol) in anh. DMF (1.4 mL). Purified by flash column chromatography (30:1 Hexanes:EtOAc) to yield **210** (158 mg, 0.55 mmol, 79% yield) as a solid.

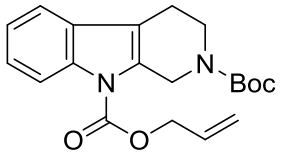
Analytical data for **210**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 1H), 6.84 (dd, *J* = 7.6, 2.4 Hz, 2H), 6.07 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.45 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.33 (ddd, *J* = 10.4, 2.4, 1.2 Hz, 1H), 4.91 – 4.86 (m, 2H), 3.85 (s, 3H), 2.99 (ddd, *J* = 6.2, 4.3, 2.0 Hz, 2H), 2.60 (ddd, *J* = 6.1, 4.1, 2.1 Hz, 2H), 1.91 – 1.85 (m, 2H), 1.84 – 1.78 (m, 2H).



212

***N*-alloc-9-chloro-(N3-carboethoxy)-β-carboline (212):** Prepared according to the general method using 9-chloro-(N3-carboethoxy)-β-carboline (106 mg, 0.38 mmol), 60% w/w NaH (45 mg, 1.12 mmol), allyl chloroformate (0.06 mL, 0.54 mmol) in anh. THF (8 mL). Purified by flash column chromatography (5:1 Hexanes:EtOAc) to yield **212** (109 mg, 0.30 mmol, 79% yield) as a white solid.

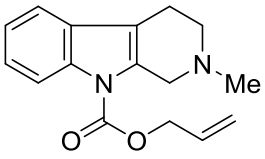
Analytical data for **212**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.19 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.18 – 5.95 (m, 1H), 5.46 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.38 (dd, *J* = 10.4, 1.0 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 2H), 4.54 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 3.09 (s, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.06, 128.69, 124.13, 119.95, 119.39, 116.61, 112.40, 67.71, 61.68, 40.52, 14.76.



214

***N*-alloc-(N2-tert-butyl-carbamate)-γ-carboline (214):** Prepared according to the general method using (N2-tert-butyl-carbamate)-γ-carboline (138 mg, 0.6 mmol), 60% w/w NaH (68 mg, 1.69 mmol), allyl chloroformate (0.09 mL, 0.8 mmol) in anh. THF (12 mL). Purified by flash column chromatography (10:1 Hexanes:EtOAc) to yield **214** (118 mg, 0.38 mmol, 63% yield) as a white solid.

Analytical data for **214**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.32 – 7.23 (m, 2H), 6.08 (ddt, *J* = 16.4, 10.5, 5.9 Hz, 1H), 5.48 (d, *J* = 16.8 Hz, 1H), 5.36 (d, *J* = 10.3 Hz, 1H), 4.92 (d, *J* = 5.5 Hz, 2H), 4.83 (s, 2H), 3.73 (s, 2H), 2.73 (s, 2H), 1.50 (s, 9H).

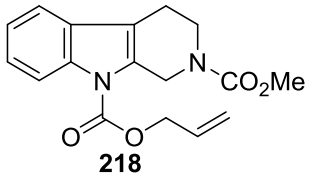


216

***N*-alloc-(N2-methyl)-γ-carboline (216):** Prepared according to the general method using (N2-methyl)-γ-carboline (186 mg, 1.0 mmol), 60% w/w NaH (112 mg, 2.81 mmol), allyl chloroformate (0.14 mL, 1.34 mmol) in anh. THF (16 mL). Purified by flash column chromatography (EtOAc to 50:1 EtOAc:NEt_3) to yield **216** (172 mg, 0.64 mmol, 64% yield) as a solid.

Analytical data for **216**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 9.0 Hz, 2H), 6.08 (dq, *J* = 10.7, 6.0 Hz, 1H), 5.46 (d, *J* = 17.2 Hz, 1H), 5.36

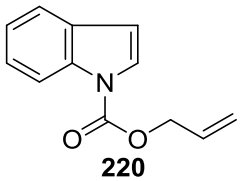
(d, *J* = 10.3 Hz, 1H), 4.91 (d, *J* = 5.7 Hz, 2H), 3.90 (s, 2H), 2.78 (s, 4H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.49, 129.27, 123.86, 122.91, 119.43, 117.86, 115.53, 67.38, 54.11, 51.53, 45.48, 21.38.



218

***N*-alloc-(N2-carbomethoxy)-γ-carboline (218):** Prepared according to the general method using (N2-carbomethoxy)-γ-carboline (137 mg, 0.6 mmol), 60% w/w NaH (68 mg, 1.69 mmol), allyl chloroformate (0.09 mL, 0.8 mmol) in anh. THF (12 mL). Purified by flash column chromatography (15:1 Hexanes:EtOAc) to yield **218** (119 mg, 0.38 mmol, 63% yield) as a solid.

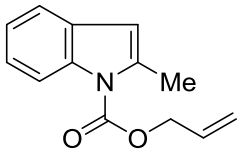
Analytical data for **218**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 24.6 Hz, 1H), 7.38 (s, 1H), 7.30 – 7.22 (m, 2H), 5.48 (d, *J* = 17.2 Hz, 1H), 5.37 (d, *J* = 10.4 Hz, 1H), 4.92 (d, *J* = 4.8 Hz, 2H), 4.87 (s, 2H), 3.76 (s, 5H), 2.72 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.30, 131.38, 129.03, 124.35, 123.13, 119.69, 117.87, 115.57, 67.65, 52.85, 43.90, 40.92, 20.97.



220

***N*-alloc-2-methyl-indole (220):** Prepared according to the general method using indole (186 mg, 1.59 mmol), 60% w/w NaH (179 mg, 4.47 mmol), allyl chloroformate (0.23 mL, 2.13 mmol) in anh. THF (25 mL). Purified by flash column chromatography (30:1 Hexanes:EtOAc) to yield **220** (0.30 g, 1.48 mmol, 93% yield) as a white solid.

Analytical data for **220**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 5.5 Hz, 1H), 7.58 (d, *J* = 3.6 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.27 (m, 1H), 7.25 – 7.19 (m, 1H), 6.55 (dd, *J* = 3.8, 0.7 Hz, 1H), 6.02 (ddt, *J* = 17.1, 10.5, 5.8 Hz, 1H), 5.42 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.31 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.86 (d, *J* = 5.8 Hz, 2H). Analytical data match those found in the literature.[3]



223

***N*-alloc-2-methyl-indole (223):** Prepared according to the general method using 2-methyl-indole (656 mg, 5.0 mmol), 60% w/w NaH (562 mg, 14.05 mmol), allyl chloroformate (0.71 mL, 6.7 mmol) in anh. THF (50 mL). Purified by flash column chromatography (12:1 Hexanes:EtOAc) to yield **223** (1.00 g, 4.65 mmol, 93% yield) as a white solid.

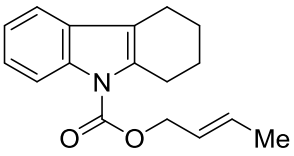
Analytical data for **223**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.18 – 7.13 (m, 1H), 7.11 (td, *J* = 7.4, 1.2 Hz, 1H), 6.16 – 6.12 (m, 1H), 5.91 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1H), 5.31 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1H), 5.20 (ddd, *J* = 10.4, 2.4, 1.2 Hz, 1H), 4.71 – 4.68 (m, 2H), 2.44 (d, *J* = 1.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.75, 137.74, 136.66, 131.82, 129.76, 123.47, 123.03, 119.72, 119.25, 115.79, 108.68, 67.38, 16.91.

General Procedure for Preparation of Crotyl and Cinnamyl Indole Carbamates

Prepared according to a modified protocol from Macor and coworkers.[5] A dry round bottomed flask was charged 1,2,3,4-tetrahydrocarbazole **X,** DMAP, CDI and dissolved in anh. acetonitrile (MeCN). The reaction flask was fitted with a reflux condenser and was subsequently heated to reflux in an oil bath for eight hours. To the refluxing solution was added the appropriate alcohol

[5] Macor, J. E.; Cuff, A.; Cornelius, L. *Tetrahedron Lett.* **1999**, *40*, 2733-2736.

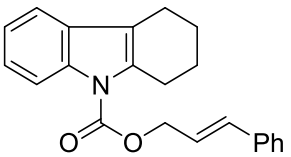
all at once and the solution was allowed to stir under reflux for an additional ten hours. The reaction was then cooled to ambient temperature (23 °C) and concentrated *in vacuo*. The residue was redissolved in dichloromethane, washed with water (3x), brine, dried over anh. $MgSO_4$ and concentrated *in vaccuo*. The residue was purified by flash column chromatography to yield the desired products.



228

***N*-crotyloxy-1,2,3,4-tetrahydrocarbazole (228):** Prepared according to the general method using 1,2,3,4-tetrahydrocarbazole (342 mg, 2.0 mmol), CDI (487 mg, 3.0 mmol), crotyl alcohol (0.34 mL, 4.0 mmol) and DMAP (24.4 mg, 0.2 mmol) in anh. MeCN (6.0 mL). Purified by flash column chromatography (18:1:1 Hexanes:CH_2Cl_2:Toluene) to yield **228** (81 mg, 0.30 mmol, 15% yield) as a solid.

Analytical data for **228**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.12 (m, 2H), 5.91 (tt, *J* = 13.0, 6.5 Hz, 1H), 5.74 (dtd, *J* = 7.7, 6.6, 1.1 Hz, 1H), 4.87 – 4.77 (m, 2H), 2.99 (t, *J* = 5.9 Hz, 2H), 2.62 (t, *J* = 5.9 Hz, 2H), 1.94 – 1.84 (m, 2H), 1.81 (ddd, *J* = 12.6, 6.2, 2.3 Hz, 2H), 1.76 (d, *J* = 6.5 Hz, 3H).



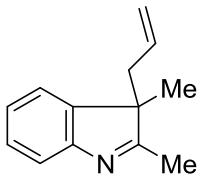
230

***N*-cinnamyloxy-1,2,3,4-tetrahydrocarbazole (230):** Prepared according to the general method using 1,2,3,4-tetrahydrocarbazole (342 mg, 2.0 mmol), CDI (344 mg, 2.12 mmol), cinnamyl alcohol (383 mg, 2.86 mmol) and DMAP (6.1 mg, 0.05 mmol) in anh. MeCN (7.2 mL). Purified by flash column chromatography (18:1:1 Hexanes:CH_2Cl_2:Toluene) to yield **230** (444 mg, 1.34 mmol, 67% yield) as a solid.

Analytical data for **230**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.31 – 7.26 (m, 2H), 7.21 (dtd, *J* = 13.5, 7.4, 3.8 Hz, 3H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.36 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.97 (dd, *J* = 6.6, 1.2 Hz, 2H), 2.96 (dd, *J* = 8.0, 4.1 Hz, 2H), 2.59 – 2.55 (m, 2H), 1.82 (ddd, *J* = 8.0, 5.7, 2.7 Hz, 2H), 1.79 – 1.72 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.01, 136.16, 135.88, 135.73, 135.22, 130.23, 128.78, 128.40, 126.88, 123.72, 122.86, 122.72, 121.02, 119.13, 117.80, 117.71, 117.40, 115.68, 110.49, 67.24, 25.82, 23.68, 23.45, 23.36, 22.31, 21.21. Analytical data match those found in the literature.[4]

General Procedure for Palladium Catalyzed Decarboxylation Allylation

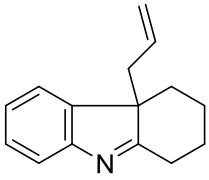
N-alloc indole substrate, $Pd_2(dba)_3{\cdot}CHCl_3$ and P(2-furyl)$_3$ were added to an oven-dried 16x100 borosilicate test tube, sealed with a rubber septa, purged 3x with N_2 and maintained under a positive pressure of N_2. To this anh. CH_2Cl_2 was added and the reaction was allowed to stir until the starting material was consumed, as determined by TLC analysis. At which point the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to yield the desired products.



205

3-allyl-2,3-dimethyl-3H-indole (205): Prepared according to the general procedure using *N*-alloc indole **202** (229 mg, 1.00 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.6 mg, 2.5 μmol), P(2-furyl)$_3$ (1.2 mg, 5.0 μmol), and CH_2Cl_2 (0.33 mL) at 23 °C for 3 h. Purified by flash column chromatography (5:2 Hexanes:EtOAc) to afford **205** (176 mg, 0.95 mmol, 95% yield) as a white solid.

Analytical data for **205**: R_f 0.23 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, J=7.65 Hz, 1H), 7.30 (td, J=1.20, 7.55 Hz, 1H), 7.26 (d, J=7.10 Hz, 1H), 7.18 (td, J=0.70, 7.40 Hz, 1H), 5.15 (ddt, J=7.05, 9.65, 17.45 Hz, 1H), 4.94 (dd, J=1.35, 16.95 Hz, 1H), 4.86 (dd, J=0.75, 10.10 Hz, 1H), 2.62 (dd, J=6.35, 13.90 Hz, 1H), 2.41 (dd, J=7.95, 13.90 Hz, 1H), 2.25 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.4, 154.2, 143.3, 132.4, 127.6, 124.9, 121.7, 119.7, 117.9, 57.4, 41.1, 21.8, 15.9. ^{1}H NMR match those reported in the literature.[6]



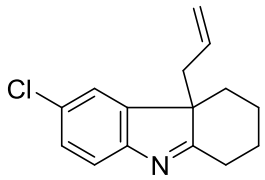
207

4a-allyl-2,3,4,4a-tetrahydro-1H-carbazole (207): Prepared according to the general procedure using *N*-alloc indole **206** (255 mg, 1.00 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.6 mg, 2.5 μmol), P(2-furyl)$_3$ (1.2 mg, 5.0 μmol), and CH_2Cl_2 (0.33 mL) at 23 °C for 3 h. Purified by flash column

[6] Kagawa N.; Malerich, J. P.; Rawal V. H. *Org. Lett.* **2008**, *10*, 2381-2384.

chromatography (5:1 Hexanes:EtOAc) to afford **207** (201 mg, 0.95 mmol, 95% yield) as a white solid.

Analytical data for **207**: R_f 0.49 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J=7.70 Hz, 1H), 7.31 (td, J=1.25, 7.50 Hz, 1H), 7.29 (dd, J=0.65, 5.55 Hz, 1H), 7.18 (td, J=1.00, 7.40 Hz, 1H), 5.17 (ddt, J=7.22, 9.70, 17.35 Hz, 1H), 4.94 (dq, J=1.35, 3.20, 16.95 Hz, 1H), 4.84 (dq, J=0.90, 1.85, 10.00 Hz, 1H), 2.88 (dm, J=13.15 Hz, 1H), 2.64 (dt, J=1.10, 3.60 Hz, 1H), 2.61 (dt, J=1.10, 6.70 Hz, 1H), 2.55-2.52 (m, 1H), 2.36 (dq, J=2.45, 5.70, 13.45 Hz, 1H), 2.19 (dm, J=15.35 Hz, 1H), 1.84 (qt, 3.75, 13.75, 27.55 Hz, 1H), 1.68 (dm, J=14.05 Hz, 1H), 1.43 (qt, J=4.25, 13.35, 26.7 Hz, 1H), 1.16 (td, J=4.15, 13.55 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.8, 154.9, 144.6, 132.2, 127.6, 124.6, 121.9, 120.1, 117.9, 57.6, 37.6, 37.0, 30.2, 28.8, 21.1. ^{1}H NMR match those reported in the literature.[6]

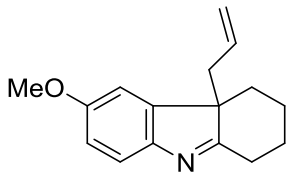


209

4a-allyl-6-chloro-2,3,4,4a-tetrahydro-1H-carbazole (209): Prepared according to the general procedure using *N*-alloc indole **208** (290 mg, 1.00 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mg, 2.5 μmol), P(2-furyl)$_3$ (1.2 mg, 5.0 μmol), and CH_2Cl_2 (0.33 mL) at 23 °C for 3 h. Purified by flash column chromatography (5:2 Hexanes:EtOAc) to afford **209** (233 mg, 0.95 mmol, 95% yield) as an off white solid.

Analytical data for **209**: R_f 0.26 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J=8.15 Hz, 1H), 7.31-7.27 (m, 2H), 5.18 (ddt, J=6.95, 10.00, 17.05 Hz, 1H), 4.98 (dd,

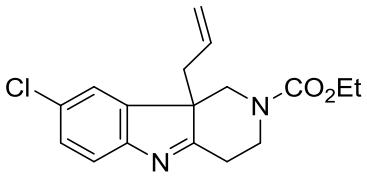
J=1.20, 17.00 Hz, 1H), 4.90 (dd, J=0.95, 10.05 Hz, 1H), 2.88 (dm, J=13.25 Hz, 1H), 2.59 (dd, J=2.85, 8.20 Hz, 2H), 2.54 (td, J=5.70, 13.35 Hz, 1H), 2.34 (dq, J=2.45, 5.25, 13.45 Hz, 1H), 2.22 (dm J=12.95 Hz, 1H), 1.84 (qt, J=3.70, 13.70, 27.50 Hz, 1H), 1.70 (dm, J=14.15 Hz, 1H), 1.44 (qt, J=4.25, 13.35, 26.70 Hz, 1H), 1.18 (td, J=4.20, 13.55 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 89.4, 153.5, 146.4, 131.6, 130.6, 127.8, 122.4, 121.0, 118.5, 58.2, 37.5, 36.9, 30.1, 28.8, 21.0. ^{1}H NMR match those reported in the literature.[6]



211

3-allyl-2,3-dimethyl-3H-indole (211): Prepared according to the general procedure using *N*-alloc indole **210** (285 mg, 1.00 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mg, 2.5 µmol), P(2-furyl)$_3$ (1.2 mg, 5.0 µmol), and CH_2Cl_2 (0.33 mL) at 23 °C for 5 h. Purified by flash column chromatography (5:2 Hexanes:EtOAc) to afford **211** (195 mg, 0.81 mmol, 81% yield) as a solid.

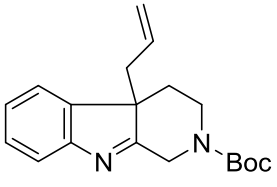
Analytical data for **211**: R_f 0.20 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, J=0.90, 7.95 Hz, 1H), 6.86-6.84 (m, 2H), 5.19 (ddt, J=7.35, 9.70, 17.00 Hz, 1H), 4.96 (dq, J=1.35, 3.25, 17.00 Hz, 1H), 4.88 (dq, J=0.90, 2.85, 10.05 Hz, 1H), 3.83 (s, 3H), 2.84 (dm, J=13.20 Hz, 1H), 2.58 (dd, J=1.05, 7.00 Hz, 2H), 2.53 (td, J=5.65, 13.40 Hz, 1H), 2.32 (dq, J=2.45, 5.65, 13.40 Hz, 1H), 2.18 (dm, 13.15, 1H), 1.82 (qt, J=3.75, 13.70, 27.45 Hz, 1H), 1.68 (dm J=14.05 Hz, 1H), 1.42 (qt, J=4.30, 13.35, 26.70 Hz, 1H), 1.18 (td, J=4.15, 13.55 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.7, 157.6, 148.6, 146.2, 132.2, 120.2, 117.96, 112.1, 108.8, 57.8, 55.7, 37.7, 37.0, 30.1, 28.9, 21.1. ^{1}H NMR match those reported in the literature.[6]



213

ethyl-9b-allyl-8-chloro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(9bH)-carboxylate (213): Prepared according to the general procedure using *N*-alloc indole **212** (363 mg, 1.00 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5.2 mg, 5.0 μmol), P(2-furyl)$_3$ (2.3 mg, 10.0 μmol), and CH_2Cl_2 (0.33 mL) at 23 °C for 5 h. Purified by flash column chromatography (5:2 Hexanes:EtOAc) to afford **213** (255 mg, 0.80 mmol, 80% yield) as an off white solid.

Analytical data for **213**: R_f 0.22 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J=8.20 Hz, 1H), 7.15 (dd, J=2.05, 8.20 Hz, 1H), 7.10 (d, J=1.90 Hz, 1H), 5.12 (ddt, J=7.05, 10.00, 17.30 Hz, 1H), 4.75 (d, J=17.00 Hz, 1H), 4.71 (d, J=10.15 Hz, 1H), 4.64-4.50 (s, br, 1H), 4.50-4.36 (s, br, 1H), 4.12 (t, J=6.70 Hz, 2H), 2.58 (dm, J=12.85 Hz, 1H), 2.50-2.42 (m, 2H), 2.34 (td, J=3.30, 12.45 Hz, 1H), 2.26 (dd, J=8.85, 14.15 Hz, 1H), 1.88 (d, J=13.05 Hz, 1H), 1.14 (t, J=14.15 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.11, 128.7, 128.5, 128.3, 127.8, 127.6, 127.6, 127.59, 127.41, 127.4, 127.39, 125.0, 124.8, 124.6, 118.3, 61.4, 36.3, 20.2, 20.1, 19.9. ^{1}H NMR match those reported in the literature.[6]

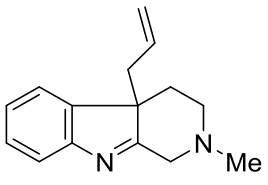


215

tert-butyl-4a-allyl-4,4a-dihydro-1H-pyrido[3,4-b]indole-2(3H)-carboxylate (215): Prepared according to the general procedure using *N*-alloc indole **214** (178 mg, 0.50 mmol),

$Pd_2(dba)_3 \cdot CHCl_3$ (5.2 mg, 5.0 μmol), P(2-furyl)$_3$ (2.3 mg, 10.0 μmol), and CH_2Cl_2 (2.0 mL) at 23 °C for 12 h. Purified by flash column chromatography (5:2 Hexanes:EtOAc) to afford **215** (56 mg, 0.18 mmol, 36% yield) as a solid.

Analytical data for **215**: R_f 0.10 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J=7.65 Hz, 1H), 7.37 (td, J=1.00, 7.55 Hz, 1H), 7.34 (dd, J=0.50, 7.40 Hz, 1H), 7.25 (t, J=1.45 Hz, 1H), 5.18 (ddt, J=7.35, 9.65, 16.95 Hz, 1H), 4.98 (dd, J=1.25, 16.95 Hz, 1H), 4.91 (dd, J=0.85, 10.05 Hz, 1H), 3.98 (d, J=14.55 Hz, 1H), 3.31 (s, br, 1H), 2.69 (dd, J=6.55, 13.80 Hz, 1H), 2.59 (dd J=7.50, 13.10 Hz, 1H), 2.32 (dt, J=2.75, 13.70 Hz, 1H), 1.51-1.40 (m, 3H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 143.3, 131.4, 128.1, 125.6, 122.2, 121.0, 118.8, 56.1, 36.9, 28.4. ^{1}H NMR match those reported in the literature.[6]

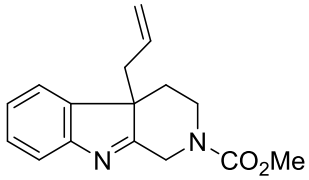


217

4a-allyl-2-methyl-2,3,4,4a-tetrahydro-1H-pyrido[3,4-b]indole (217): Prepared according to the general procedure using *N*-alloc indole **216** (135 mg, 0.50 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5.2 mg, 5.0 μmol), P(2-furyl)$_3$ (2.3 mg, 10.0 μmol), and CH_2Cl_2 (2.0 mL) at 23 °C for 12 h. Purified by flash column chromatography (1:1 EtOAc:Hexanes to 10:1:0.5 EtOAc:Hexanes:NEt_3) to afford **217** (94 mg, 0.42 mmol, 83% yield) as a solid.

Analytical data for **217**: R_f 0.35 (10:1:0.5 EtOAc:MeOH:NEt_3), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J=7.60 Hz, 1H), 7.36-7.31 (m, 2H), 7.22 (t, J=7.35 Hz, 1H), 5.16 (ddt, J=7.25, 9.75, 17.00 Hz, 1H), 4.94 (dq, J=1.30, 3.05, 17.00 Hz, 1H), 4.87 (d, J=10.05 Hz, 1H), 3.74 (d, J=11.95 Hz, 1H), 3.22 (d, J=12.00 Hz, 1H), 2.78 (dm, J=12.35 Hz, 1H), 2.69-2.62 (m, 2H), 2.58

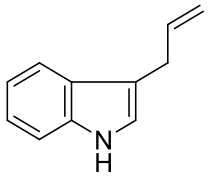
(td, J=7.65, 13.85 Hz, 1H), 2.45 (s, 3H), 2.26 (dt, J=2.15, 13.50 Hz, 1H), 1.52 (td, J=4.55, 13.10 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.5, 155.0, 143.9, 131.6, 127.9, 125.2, 122.1, 120.9, 118.4, 55.9, 55.6, 50.1, 45.3, 37.2, 34.7. HRMS (ESI) calcd for $(C_{15}H_{19}N_2)^+$ $[M+H]^+$: 227.1543, found: 227.1532.



219

methyl-4a-allyl-4,4a-dihydro-1H-pyrido[3,4-b]indole-2(3H)-carboxylate (219): Prepared according to the general procedure using *N*-alloc indole **218** (157 mg, 0.50 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (12.9 mg, 12.5 µmol), P(2-furyl)$_3$ (5.8 mg, 25.0 µmol), and CH_2Cl_2 (2.0 mL) at 23 °C for 12 h. Purified by flash column chromatography (5:2 Hexanes:EtOAc) to afford **219** (99 mg, 0.37 mmol, 73% yield) as a solid.

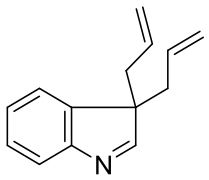
Analytical data for **219**: R_f 0.14 (2:1 Hexanes:EtOAc), ^{1}H NMR (500 MHz, DMSO, 340 K): δ 7.65 (d, J=7.00 Hz, 1H), 7.16 (dq, J=2.05, 6.80, 8.80 Hz, 1H), 7.06-7.01 (m, 2H), 5.08 (ddt, J=6.80, 10.10, 17.55 Hz, 2H), 4.78-4.71 (m, 2H), 3.85 (s, 1H), 3.72 (d, J=14.50 Hz, 1H), 3.51 (s, 3H), 2.93 (dq, J-3.20, 12.30, 15.55 Hz, 1H), 2.28 (dd, J=6.80, 13.95 Hz, 1H), 2.18 (dd, J=7.50, 13.95 Hz, 1H), 1.81 (dt, J=3.00, 13.50 Hz, 1H), 1.08 (td, J=5.05, 12.45 Hz, 1H). ^{13}C NMR (125 MHz, DMSO, 340 K): δ 181.0, 143.2, 131.3, 128.2, 125.6, 122.2, 121.2, 118.9, 56.1, 53.0, 45.7, 39.4, 36.9, 35.0. HRMS (ESI) calcd for $(C_{16}H_{19}N_2O_2)^+$ $[M+H]^+$: 271.1441, found: 271.1430.



221

3-allyl-1H-indole (221): Prepared according to the general procedure using *N*-alloc indole **220** (101 mg, 0.50 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5.2 mg, 5.0 μmol), P(2-furyl)$_3$ (2.3 mg, 10.0 μmol), and CH_2Cl_2 (2.0 mL) at 23 °C for 12 h. Purified by flash column chromatography (5:1 Hexanes:EtOAc) to afford **221** (38 mg, 0.24 mmol, 48% yield) as an off white solid.

Analytical data for **221**: R_f 0.53 (3:1 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (s, br, 1H), 7.60 (dd, J=0.50, 7.45 Hz, 1H), 7.34 (dt, J=0.85, 8.10 Hz, 1H), 7.18 (td, J=1.10, 7.05 Hz, 1H), 7.10 (td, J=1.10, 7.30 Hz, 1H), 6.97 (d, J=2.30 Hz, 1H), 6.07 (ddt, J=6.45, 10.10, 17.00 Hz, 1H), 5.16 (dq, J=1.80, 3.60, 17.05 Hz, 1H), 5.06 (dq, J=1.30, 3.30, 10.05 Hz, 1H), 3.52 (dq, J=1.40, 2.50, 6.40 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 136.5, 127.5, 127.1, 121.7, 119.3, 119.2, 115.3, 114.6, 111.1, 29.9. ^{1}H NMR match those reported in the literature.[7]



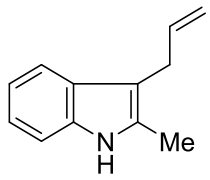
222

3,3-diallyl-3H-indole (222): Prepared according to the general procedure using *N*-alloc indole **220** (101 mg, 0.50 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5.2 mg, 5.0 μmol), P(2-furyl)$_3$ (2.3 mg, 10.0 μmol),

[7] Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592-4593.

and CH_2Cl_2 (2.0 mL) at 23 °C for 12 h. Purified by flash column chromatography (5:1 Hexanes:EtOAc) to afford **222** (26 mg, 0.13 mmol, 26% yield) as an off white solid.

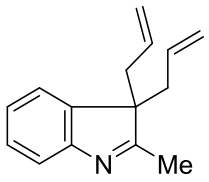
Analytical data for **222**: R_f 0.28 (3:1 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.62 (d, J=7.65 Hz, 1H), 7.35 (td, J=1.30, 7.40 Hz, 1H); 7.31 (d, J=6.90 Hz, 1H), 7.26 (t, J=6.00 Hz, 1H), 5.44 (ddt, J=7.15, 9.95, 17.10 Hz, 2H), 5.01 (dd, J=1.55, 16.95 Hz, 2H), 4.96 (dd, J=0.90, 10.10 Hz, 2H), 2.59-2.50 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 155.6, 141.4, 132.4, 129.0, 128.4, 128.0, 126.0, 122.3, 121.2, 118.7, 38.6. HRMS (ESI) calcd for $(C_{14}H_{16}N)^+$ $[M+H]^+$: 198.1277, found: 198.1266.



224

3-allyl-2-methyl-1H-indole (224): Prepared according to the general procedure using *N*-alloc indole **223** (108 mg, 0.50 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5.2 mg, 5.0 µmol), P(2-furyl)$_3$ (2.3 mg, 10.0 µmol), and CH_2Cl_2 (2.0 mL) at 23 °C for 12 h. Purified by flash column chromatography (5:1 Hexanes:EtOAc) to afford **224** (41 mg, 0.24 mmol, 48% yield) as a white solid.

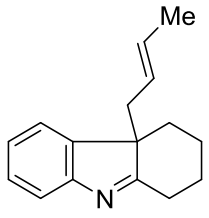
Analytical data for **224**: R_f 0.50 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, br, 1H), 7.49 (d, J=7.65 Hz, 1H), 7.24 (d, J=8.10 Hz, 1H), 7.10 (td, J=1.30, 7.05 Hz, 1H), 7.06 (td, J=1.25, 7.60 Hz, 1H), 5.96 (ddt, J=6.10, 10.05, 17.05 Hz, 1H), 5.05 (dq, J=1.85, 3.65, 17.00 Hz, 1H), 4.98 (dq, J=1.55, 3.55, 10.05 Hz, 1H), 3.44 (dt, J=1.50, 6.15 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 135.2, 131.3, 128.8, 119.7, 119.2, 118.2, 114.4, 110.2, 109.3, 28.6, 11.6. ^{1}H NMR match those reported in the literature.[7]



225

3,3-diallyl-2-methyl-3H-indole (225): Prepared according to the general procedure using *N*-alloc indole **223** (108 mg, 0.50 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5.2 mg, 5.0 µmol), P(2-furyl)$_3$ (2.3 mg, 10.0 µmol), and CH_2Cl_2 (2.0 mL) at 23 °C for 12 h. Purified by flash column chromatography (5:1 Hexanes:EtOAc) to afford **225** (23 mg, 0.11 mmol, 22% yield) as a white solid.

Analytical data for **225**: R_f 0.35 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J=7.65 Hz, 1H), 7.31 (td, J=1.20, 7.55 Hz, 1H), 7.27 (d, J=7.25 Hz, 1H), 7.20 (td, J=0.70, 7.35 Hz, 1H), 5.11 (ddt, J=6.30, 7.90, 20.70 Hz, 2H), 4.94 (d, J=16.90 Hz, 2H), 4.84 (d, J=10.05 Hz, 2H), 2.68 (dd, J=6.30, 15.80 Hz, 2H), 2.45 (dd, J=7.90, 13.90 Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.0, 141.2, 132.1, 127.9, 125.0, 122.2, 119.8, 118.1, 61.8, 40.3, 16.6. HRMS (ESI) calcd for $(C_{15}H_{18}N)^+$ $[M+H]^+$: 212.1434, found: 212.1428.

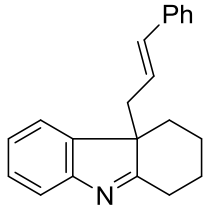


229

4a-(but-2-enyl)-2,3,4,4a-tetrahydro-1H-carbazole (229): Prepared according to the general procedure using *N*-alloc indole **228** (81 mg, 0.30 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (7.8 mg, 7.5 µmol), P(2-furyl)$_3$ (3.5 mg, 15 µmol), and CH_2Cl_2 (1.2 mL) at 23 °C for 12 h. Purified by flash column

chromatography (5:1 Hexanes:EtOAc) to afford **229** (58 mg, 0.25 mmol, 84% yield) as an off white solid.

Analytical data for **229**: R_f 0.23 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J=7.70 Hz, 1H), 7.32 (td, J=1.30, 7.55 Hz, 1H), 7.28 (dd, J=0.55, 7.35 Hz, 1H), 7.18 (td, J=1.05, 7.45 Hz, 1H), 5.42-5.34 (m, 1H), 4.87-4.81 (m, 1H), 2.88 (dm, J=12.90 Hz, 1H), 2.58-2.51 (m, 2H), 2.45 (dd, J=7.90, 13.95 Hz, 1H), 2.35 (dm, J=13.25 Hz, 1H), 2.21-2.18 (m, 1H), 1.82 (qt, J=3.70, 13.65, 27.40 Hz, 1H), 1.67 (dm, J=14.05 Hz, 1H), 1.48 (d, J=6.45 Hz, 3H), 1.42 (qt, J=4.15, 13.35, 26.95 Hz, 1H), 1.13 (td, J=4.15, 13.55 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.6, 127.5, 124.52, 124.5, 121.9, 120.1, 36.8, 36.4, 30.2, 28.9, 21.1, 17.8. ^{1}H NMR match those reported in the literature.[6]

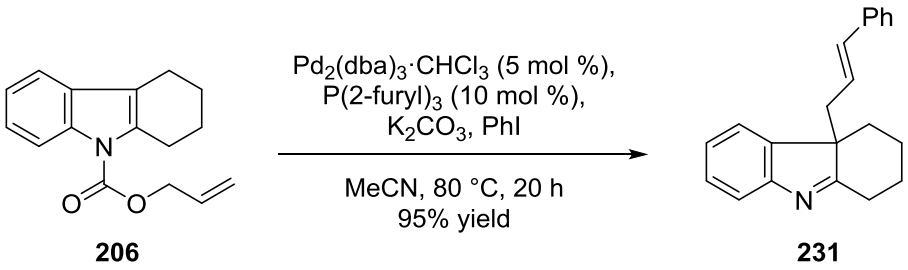


231

4a-cinnamyl-2,3,4,4a-tetrahydro-1H-carbazole (231): Prepared according to the general procedure using *N*-alloc indole **230** (331 mg, 1.00 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (10.4 mg, 10.0 µmol), P(2-furyl)$_3$ (4.6 mg, 20.0 µmol), and CH_2Cl_2 (0.33 mL) at 23 °C for 12 h. Purified by flash column chromatography (5:2 Hexanes:EtOAc) to afford **231** (230 mg, 0.80 mmol, 80% yield) as a white solid.

Analytical data for **231**: R_f 0.24 (5:2 Hexanes:EtOAc), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (dd, J=0.90, 7.25 Hz, 1H), 7.34-7.31 (m, 2H), 7.24-7.14 (m, 6H), 6.32 (d, J=15.70 Hz, 1H), 5.64 (dt, J=7.85, 15.65 Hz, 1H), 2.90 (dm, J=13.25 Hz, 1H), 2.80 (ddd, J=1.35, 6.90, 13.95 Hz, 1H),

2.64-2.58 (m, 2H), 2.43 (dq, J=2.40, 5.40, 13.45 Hz, 1H), 2.22 (dm, J=11.00 Hz, 1H), 1.87 (qt, J=3.75, 13.7, 27.45 Hz, 1H), 1.72 (dm, J=14.05 Hz, 1H), 1.45 (qt, J=4.25, 13.35, 26.70 Hz, 1H), 1.18 (td, J=4.10, 13.55 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 144.7, 137.1, 133.2, 128.4, 127.8, 127.3, 126.2, 124.7, 124.0, 122.1, 120.3, 57.9, 36.7, 30.2, 28.9, 21.2. ^{1}H NMR match those reported in the literature.[6]



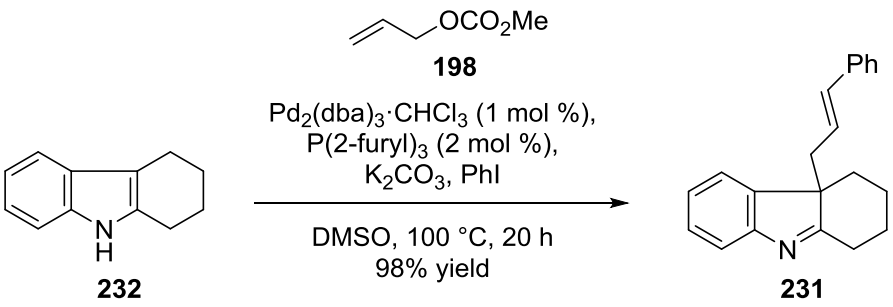
206 **231**

Procedure for Direct Synthesis of: 4a-cinnamyl-2,3,4,4a-tetrahydro-1H-carbazole (231) from *N*-Alloc Protected Substrate 206

N-alloc 1,2,3,4-tetrahydrocarbazole **206** (127 mg, 0.50 mmol), $Pd_2(dba)_3$·$CHCl_3$, (26 mg, 25.0 µmol) P(2-furyl)$_3$ (12 mg, 50.0 µmol) and K_2CO_3 (138 mg, 1.0 mmol) were added to an oven-dried 16x100 borosilicate test tube, sealed with a rubber septa, purged 3x with N_2 and maintained under a positive pressure of N_2. To this anh. MeCN (2.0 mL) was added, followed by PhI (204 mg, 1.0 mmol) and the heterogeneous reaction mixture was then heated to 80 °C in an oil bath with stirring. After the starting material had been consumed (20 h), as determined by TLC analysis, the reaction mixture was allowed to cool to ambient temperature (23 °C) and was diluted with diethyl ether (15 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic extracts were washed with bring, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was

purified by flash column chromatography (5:2 Hexanes : EtOAc) to afford **231** (136 mg, 0.48 mmol, 95% yield) as a white solid.

Analytical data match those previously reported in this document.



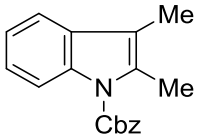
Procedure for Direct Synthesis of: 4a-cinnamyl-2,3,4,4a-tetrahydro-1H-carbazole (231) from 1,2,3,4-Tetrahydrocarbazole (232) and Allyl Methyl Carbonate (198)

1,2,3,4-tetrahydrocarbazole **232** (86 mg, 0.50 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$, (5 mg, 5.0 µmol) P(2-furyl)$_3$ (2 mg, 10.0 µmol) and K_2CO_3 (138 mg, 1.0 mmol) were added to an oven-dried 16x100 borosilicate test tube, sealed with a rubber septa, purged 3x with N_2 and maintained under a positive pressure of N_2. To this anh. DMSO (2.0 mL) was added, followed by sequential addition of allyl methyl carbonate **198** (81 mg, 0.7 mmol) and PhI (143 mg, 0.7 mmol). The reaction mixture was then heated to 100 °C in an oil bath for 20 h. After completion of the reaction the reaction mixture was allowed to cool to ambient temperature (23 °C) and diluted with diethyl ether (15 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic extracts were washed with bring, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (5:2 Hexanes : EtOAc) to afford **231** (141 mg, 0.49 mmol, 98% yield) as a white solid.

Analytical data match those previously reported in this document.

General Procedure for Preparation of *N*-Cbz Indoles

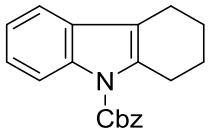
Prepared according to a modified protocol from Jacquemard and coworkers.[3] A solution of indole substrate in anh. THF, maintained under a positive pressure of nitrogen was cooled to 0 °C in an ice water bath. To this stirred solution 60% NaH was added portionwise over five minutes. After addition of NaH was complete the reaction was allowed to stir an additional 30 minutes at 0 °C under nitrogen, at which time benzyl chloroformate was carefully added dropwise via syringe. After completion of addition the reaction flask was allowed to warm to ambient temperature (23 °C). After consumption of starting material, as determined by TLC analysis, the reaction mixture was diluted with diethyl ether and carefully quenched with 1M aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3x). The combined organic extracts were combined, washed with brine, dried over anh. $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography to yield the desired product.



232

***N*-Cbz-2,3-dimethyl-indole (232):** Prepared according to the general method using 2,3-dimethyl-indole (0.5 g, 3.44 mmol), 60% w/w NaH (0.21 g, 5.17 mmol), benzyl chloroformate (0.64 mL, 4.48 mmol) in anh. DMF (18 mL). Purified by flash column chromatography (3:1 Hex:PhH + 2% CH_2Cl_2) to give **232** (817 mg, 2.92 mmol, 85% yield) as a yellow oil which crystalized on standing to give a white crystalline solid.

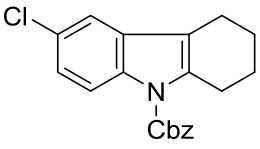
Analytical data for **232**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 6.0, 3.4 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.44 – 7.34 (m, 4H), 7.24 – 7.20 (m, 2H), 5.45 (s, 2H), 2.53 (s, 3H), 2.18 (d, *J* = 0.7 Hz, 3H); Analytical data match those found in the literature.[8]



234

***N*-Cbz-1,2,3,4-tetrahydrocarbazole (234):** Prepared according to the general method using 1,2,3,4-tetrahydrocarbazole (171 mg, 1.0 mmol), 60% w/w NaH (60 mg, 1.5 mmol), benzyl chloroformate (0.28 mL, 2.0 mmol) in anh. DMF (5 mL). Purified by flash column chromatography (15:1 Hexanes:EtOAc) to give **234** (162 mg, 0.53 mmol, 53% yield) as a colorless oil.

Analytical data for **234**: ^{1}H NMR (500 MHz, Acetone) δ 8.11 (d, *J* = 7.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.32 (m, 4H), 7.19 (dddd, *J* = 4.2, 3.4, 1.9, 0.8 Hz, 2H), 5.39 (s, 2H), 2.95 (t, *J* = 6.0 Hz, 2H), 2.58 (d, *J* = 5.8 Hz, 2H), 1.84 – 1.76 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.00, 135.79, 135.68, 135.45, 130.15, 128.80, 128.66, 128.64, 128.61, 128.57, 128.41, 123.69, 122.81, 117.64, 117.42, 115.60, 68.35, 25.78, 23.62, 22.23, 21.15. Analytical data match those found in the literature.[8]

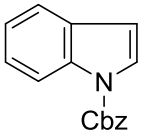


236

[8] Park, I.-K.; Suh, S.-E.; Lim, B.-Y.; Cho, C.-G. *Org. Lett.* **2009**, *11*, 5454-5456.

***N*-Cbz-9-chloro-1,2,3,4-tetrahydrocarbazole (236):** Prepared according to the general method using 9-chloro-1,2,3,4-tetrahydrocarbazole (206 mg, 1.0 mmol), 60% w/w NaH (112 mg, 2.81 mmol), benzyl chloroformate (0.20 mL, 1.34 mmol) in anh. THF (10 mL). Purified by flash column chromatography (15:1 Hexanes:EtOAc) to give **236** (326 mg, 0.96 mmol, 96% yield) as a colorless oil which solidified on standing.

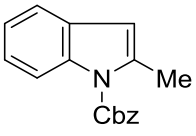
Analytical data for **236**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.39 – 7.33 (m, 3H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.10 (dd, *J* = 8.8, 2.2 Hz, 1H), 5.37 (s, 2H), 2.90 (t, *J* = 6.1 Hz, 2H), 2.49 (ddd, *J* = 6.0, 4.2, 2.2 Hz, 2H), 1.83 – 1.71 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.59, 137.10, 135.20, 134.11, 131.37, 128.82, 128.74, 128.63, 128.36, 123.50, 117.30, 116.74, 116.49, 68.56, 25.75, 23.42, 22.04, 20.95.



238

***N*-Cbz-indole (238):** Prepared according to the general method using indole (586 mg, 5.0 mmol), 60% w/w NaH (0.56 g, 14.05 mmol), benzyl chloroformate (0.95 mL, 6.7 mmol) in anh. THF (50 mL). Purified by flash column chromatography (12:1 Hexanes:EtOAc) to give **238** (1.19 g, 4.75 mmol, 95% yield) as a solid.

Analytical data match those found in the literature.[9]



241

[9] Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *The Journal of Organic Chemistry* **2006**, *71*, 4255-4261.

***N*-Cbz-2-methyl-indole (241):** Prepared according to the general method using 2-methyl-indole (656 mg, 5.0 mmol), 60% w/w NaH (0.56 g, 14.05 mmol), benzyl chloroformate (0.95 mL, 6.7 mmol) in anh. THF (50 mL). Purified by flash column chromatography (12:1 Hexanes:EtOAc) to give **241** (1.33 g, 5.00 mmol, >99% yield) as a solid.

Analytical data for **241**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.06 (m, 1H), 7.53 – 7.47 (m, 2H), 7.45 – 7.37 (m, 4H), 7.19 (ddd, *J* = 6.5, 4.5, 1.6 Hz, 2H), 6.37 – 6.31 (m, 1H), 5.46 (s, 2H), 2.59 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.47, 128.91, 128.83, 128.71, 128.48, 124.65, 122.83, 119.09, 117.39, 115.28, 68.48, 9.70, 9.68.

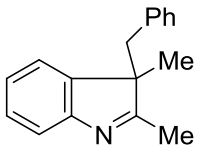
Procedure for Synthesis of [Pd(C_3H_5)cyclooctadiene]BF_4 Precatalyst

Prepared according to a procedure by White.[10] A oven dried round bottomed flask is charged with [(C_3H_5)Pd_2Cl_2] (500 mg, 1.37 mmol) and $AgBF_4$ (533 mg, 2.74 mmol). The flask is sealed with a rubber septum and anh. CH_2Cl_2 (14 mL) is added via syringe, the reaction suspension is then wrapped in aluminum foil and set stirring at a high rate under nitrogen for fifteen minutes. At this point 1,5-cyclooctadiene (0.55 mL, 4.47 mmol) is added via syringe and the mixture is allowed to stir an additional two minutes. The solid material is removed by vacuum filtration and washed with CH_2Cl_2. The filtrate is then diluted with diethyl ether (50 mL), additional diethyl ether is added until a precipitate forms. The precipitate is collected by vacuum filtration and washed with diethylether. The filtrate is then redissoloved in CH_2Cl_2, diethyl ether is added until a precipitate forms and collected by vacuum filtration to provide [Pd(allyl)cod]BF_4 (941 mg, 2.74 mmol, 78% yield) as a lusterless grey solid.

General Procedure for Palladium Catalyzed Decarboxylative Benzylation

[10] White, D. A.; Doyle, J. R.; Lewis, H. In *Inorg. Synth.*; John Wiley & Sons, Inc.: 2007, p 55-65.

N-Cbz indole substrate, [Pd(allyl)cod]BF_4, DPEphos, and KOPh were added to an oven-dried 16x100 borosilicate test tube, sealed with a rubber septa, purged 3x with N_2 and maintained under a positive pressure of N_2. To this anh. toluene was added, followed by the addition of a 1M BEt_3 solution. The reaction mixture was heated to 75 °C in an oil bath. After consumption of starting material, as determined by TLC analysis, the reaction mixture was allowed to cool to ambient temperature (23 °C), concentrated *in vacuo* and the resulting residue was purified by flash column chromatography to yield the desired products.

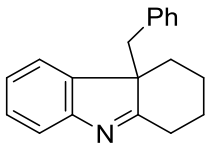


233

3-benzyl-2,3-dimethyl-3H-indole (233): Prepared according to the general procedure using *N*-Cbz indole **232** (140 mg, 0.50 mmol), [Pd(allyl)cod]BF_4 (8.6 mg, 25.0 µmol), DPEphos (16 mg, 27.5 µmol), KOPh (3.6 mg, 27.5 µmol), BEt_3 (1.0 M in Tol) (0.55 mL, 0.55 mmol) and Toluene (1.0 mL) at 75 °C for 5 h. Purified by flash column chromatography (10:1 Hexanes:EtOAc) to afford **233** (115 mg, 0.49 mmol, 98% yield) as a white amorphous solid.

Analytical data for **233**: R_f 0.23 (5:2 Hexanes:EtOAc), ^{1}H NMR(500MHz): δ 7.42 (d, J=7.60 Hz, 1H), 7.26 (td, J=0.95, 7.50 Hz, 1H), 7.14 (t, J=7.15 Hz, 1H), 7.12-7.08 (m, 3H), 7.04 (d, J=7.30 Hz, 1H), 6.79 (dd, J=1.40, 7.05 Hz, 2H), 3.16 (d, J=13.50 Hz, 1H), 2.84 (d, J=13.55 Hz, 1H), 2.33 (s, 3H), 1.37 (s, 3H). ^{13}C NMR(125MHz): δ 186.2, 154.2, 143.0, 136.1, 129.4, 127.7, 127.6, 126.6, 124.5, 122.6, 119.8, 58.4, 42.7, 21.9, 16.2. ^{1}H NMR matches reported values.[11]

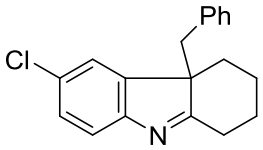
[11] Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111-114.



235

4a-benzyl-2,3,4,4a-tetrahydro-1H-carbazole (235): Prepared according to the general procedure using *N*-Cbz indole **234** (153 mg, 0.50 mmol), [Pd(allyl)cod]BF_4 (17.2 mg, 50.0 µmol), DPEphos (32 mg, 55.0 µmol), KOPh (7.3 mg, 55.0 µmol), BEt_3 (1.0 M in Tol) (0.55 mL, 0.55 mmol) and Toluene (1.0 mL) at 75 °C for 16 h. Purified by flash column chromatography (10:1 Hexanes:EtOAc) to afford **235** (127 mg, 0.48 mmol, 97% yield) as a white amorphous solid.

Analytical data for **235**: R_f 0.22 (5:2 Hexanes:EtOAc), ^{1}H NMR(500MHz): δ 7.46 (d, J=7.70 Hz, 1H), 7.26 (td, J=1.15, 7.60 Hz, 1H), 7.12 (td, J=0.80, 7.40 Hz, 1H), 7.08-7.04 (m, 4H), 6.77 (dd, J=2.05, 7.50 Hz, 2H), 3.20 (d, 13.50 Hz, 1H), 2.98 (d, J=13.55 Hz, 1H), 2.92 (dm, J=13.15 Hz, 1H), 2.76 (td, J=5.65, 13.3 Hz, 1H), 2.46 (dd, J=2.55, 13.55 Hz, 1H), 2.27 (dm, J=13.15 Hz, 1H), 2.02 (qt, J=3.70, 13.80, 27.50 Hz, 1H), 1.77 (d, J=14.00 Hz, 1H), 1.47 (qt, J=4.10, 13.35, 26.65 Hz, 1H), 1.18 (td, J=3.95, 13.65 Hz, 1H). ^{13}C NMR(125MHz): δ 188.5, 154.9, 144.2, 136.2, 129.5, 127.8, 127.6, 126.6, 124.3, 122.7, 120.1, 58.6, 39.1, 30.7, 29.2, 21.4. ^{1}H NMR matches reported values.[11]

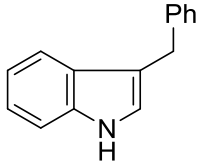


237

4a-benzyl-6-chloro-2,3,4,4a-tetrahydro-1H-carbazole (237): Prepared according to the general procedure using *N*-Cbz indole **236** (170 mg, 0.50 mmol), [Pd(allyl)cod]BF_4 (17.2 mg,

50.0 µmol), DPEphos (32 mg, 55.0 µmol), KOPh (7.3 mg, 55.0 µmol), BEt_3 (1.0 M in Tol) (0.55 mL, 0.55 mmol) and Toluene (1.0 mL) at 75 °C for 16 h. Purified by flash column chromatography (10:1 Hexanes:EtOAc) to afford **237** (145 mg, 0.49 mmol, 98% yield) as a white amorphous solid.

Analytical data for **237**: R_f 0.21 (5:2 Hexanes:EtOAc), ^{1}H NMR(500MHz): δ 7.35 (d, J=8.20 Hz, 1H), 7.23 (dd, J=2.05, 8.20 Hz, 1H), 7.10 (m, 3H), 7.01 (d, J=1.90 Hz, 1H), 6.78 (m, 2H), 3.18 (d, J=13.60 Hz, 1H), 3.00 (d, J=13.60 Hz, 1H), 2.92 (d, J=13.10 Hz, 1H), 2.76 (td, J=5.20, 13.35 Hz, 1H), 2.43 (dq, J=2.40, 5.05, 13.55 Hz, 1H), 2.28 (dm, J=13.20 Hz, 1H), 2.00 (qt, J=3.65, 13.75, 27.50 Hz, 1H), 1.78 (d, J=13.84 Hz, 1H), 1.46 (qt, J=4.10, 13.35, 26.65 Hz, 1H), 1.18 (td, J=4.05, 13.65 Hz, 1H). ^{13}C NMR(125MHz): δ 189.0, 146.0, 135.7, 130.2, 129.4, 127.9, 127.8, 126.8, 123.2, 120.9, 59.2, 39.05, 39.04, 37.0, 30.7, 29.1, 21.3; HRMS calcd for $(C_{19}H_{19}ClN)^+$: 296.1201 found: 296.1184.

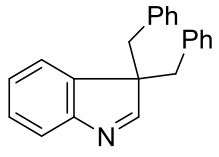


239

3-benzyl-1H-indole (239): Prepared according to the general procedure using *N*-Cbz indole **238** (126 mg, 0.50 mmol), [Pd(allyl)cod]BF_4 (8.6 mg, 25.0 µmol), DPEphos (16 mg, 27.5 µmol), KOPh (3.6 mg, 27.5 µmol), BEt_3 (1.0 M in Tol) (0.55 mL, 0.55 mmol) and Toluene (1.0 mL) at 75 °C for 24 h. Purified by flash column chromatography (30:1 Hexanes:EtOAc) to afford **239** (36 mg, 0.18 mmol, 35% yield) as a white amorphous solid.

Analytical data for **239**: R_f 0.47 (5:2 Hexanes:EtOAc), ^{1}H NMR(500MHz): δ 7.95 (s, br., 1H), 7.52 (d, J=7.90 Hz, 1H), 7.36 (d, J=8.10 Hz, 1H), 7.30-7.25 (m, 4H), 7.18 (t, J=7.10 Hz, 2H),

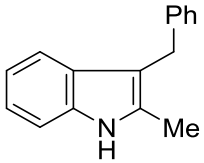
7.08 (t, J=7.65 Hz, 1H), 6.92 (s, 1H), 4.12 (s, 2H). ^{13}C NMR(125MHz): δ 141.2, 128.7, 128.3, 127.5, 125.9, 122.3, 122.1, 119.4, 119.2, 115.9, 111.1, 31.6. ^{1}H NMR matches reported values.[11]



240

4a-cinnamyl-2,3,4,4a-tetrahydro-1H-carbazole (240): Prepared according to the general procedure using *N*-Cbz indole **238** (126 mg, 0.50 mmol), [Pd(allyl)cod]BF_4 (8.6 mg, 25.0 μmol), DPEphos (16 mg, 27.5 μmol), KOPh (3.6 mg, 27.5 μmol), BEt_3 (1.0 M in Tol) (0.55 mL, 0.55 mmol) and Toluene (1.0 mL) at 75 °C for 24 h. Purified by flash column chromatography (30:1 Hexanes:EtOAc) to afford **240** (33 mg, 0.11 mmol, 22% yield) as a white amorphous solid.

Analytical data for **240**: R_f 0.31 (5:2 Hexanes:EtOAc), ^{1}H NMR(500MHz): δ 8.12 (s, 1H), 7.36-7.34 (m, 1H), 7.32-7.30 (m, 1H), 7.24 (d, J=3.90 Hz, 2H), 7.10 (t, J=2.85 Hz, 6H), 6.89 (dm, J=3.10 Hz, 4H), 3.22 (d, J=13.40 Hz, 2H), 3.11 (d, J=13.40 Hz, 2H). ^{13}C NMR(125MHz): δ 177.0, 140.8, 136.0, 129.8, 127.93, 127.9, 126.7, 125.6, 122.8, 121.1, 63.0, 41.6. ^{1}H NMR matches reported values.[11]

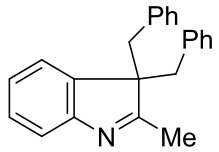


242

4a-cinnamyl-2,3,4,4a-tetrahydro-1H-carbazole (242): Prepared according to the general procedure using *N*-Cbz indole **241** (133 mg, 0.50 mmol), [Pd(allyl)cod]BF_4 (8.6 mg, 25.0 μmol),

DPEphos (16 mg, 27.5 µmol), KOPh (3.6 mg, 27.5 µmol), BEt_3 (1.0 M in Tol) (0.55 mL, 0.55 mmol) and Toluene (1.0 mL) at 75 °C for 24 h. Purified by flash column chromatography (40:1 Hexanes:EtOAc) to afford **242** (44 mg, 0.20 mmol, 40% yield) as an off white amorphous solid.

Analytical data for **242**: R_f 0.51 (5:2 Hexanes:EtOAc), ^{1}H NMR(500MHz): δ 7.78 (s, br., 1H), 7.38 (d, J=7.85 Hz, 1H), 7.27 (dd, J=0.55, 7.95 Hz, 1H), 7.25-7.20 (m, 4H), 7.16-7.13 (m, 1H), 7.10 (td, J=1.10, 7.05 Hz, 1H), 7.02 (td, J=1.10, 7.70 Hz, 1H), 4.07 (s, 2H), 2.39 (s, 3H). ^{13}C NMR(125MHz): δ 131.7, 129.0, 128.3, 128.28, 125.7, 121.0, 119.3, 118.4, 118.3, 110.1, 30.1, 11.8. ^{1}H NMR matches reported values.[11]



243

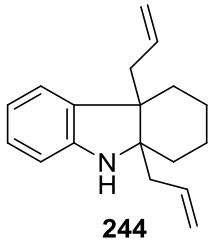
4a-cinnamyl-2,3,4,4a-tetrahydro-1H-carbazole (243): Prepared according to the general procedure using *N*-Cbz indole **241** (140 mg, 0.50 mmol), [Pd(allyl)cod]BF_4 (8.6 mg, 25.0 µmol), DPEphos (16 mg, 27.5 µmol), KOPh (3.6 mg, 27.5 µmol), BEt_3 (1.0 M in Tol) (0.55 mL, 0.55 mmol) and Toluene (1.0 mL) at 75 °C for 24 h. Purified by flash column chromatography (40:1 Hexanes:EtOAc) to afford **243** (41 mg, 0.13 mmol, 26% yield) as an off white amorphous solid.

Analytical data for **243**: R_f 0.26 (5:2 Hexanes:EtOAc), ^{1}H NMR(500MHz): δ 7.24 (d, J=7.35 Hz, 1H), 7.21 (td, J=1.15, 7.20 Hz, 1H), 7.14 (td, J=1.20, 7.30 Hz, 1H), 7.09-7.02 (m, 7H), 6.75 (dd, J=1.00, 7.40 Hz, 4H), 3.35 (d, J=13.60 Hz, 2H), 3.06 (d, J=13.60 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR(125MHz): δ 84.0, 140.5, 135.8, 129.4, 127.9, 127.8, 126.7, 124.3, 123.6, 119.8, 64.0, 42.3, 17.4; HRMS calcd for $(C_{23}H_{22}N)^+$: 312.1747 found: 312.1739.

General Procedure for Addition of Nucleophiles to Indolenine 207.

Method A: Indoline **207** and freshly crushed magnesium ribbon were added to an oven-dried 16x100 borosilicate test tube, sealed with a rubber septa, purged 3x with N_2 and maintained under a positive pressure of N_2. To this anh. THF was added via syringe followed by careful addition of alkyl, alkenyl or aryl halide. The reaction mixture was allowed to stir at ambient temperature until starting material had been consumed, as determined by TLC analysis. Following consumption of the starting material the reaction mixture was diluted with diethyl ether and carefully quenched with sat. $NaHCO_3$ (aq) solution. The organic phase was separated and the aqueous phase was washed with diethyl ether (x2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified as needed by flash column chromatography to yield the desired products.

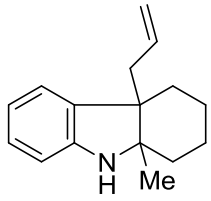
Method B: Indoline **207** was added to an oven-dried 16x100 borosilicate test tube, sealed with a rubber septa, purged 3x with N_2 and maintained under a positive pressure of N_2. To this anh. THF was added via syringe followed by careful addition of commercially procured organometallic reagent solution. The reaction mixture was allowed to stir at ambient temperature until starting material had been consumed, as determined by TLC analysis. Following consumption of the starting material the reaction mixture was diluted with diethyl ether and carefully quenched with sat. $NaHCO_3$ (aq) solution. The organic phase was separated and the aqueous phase was washed with diethyl ether (x2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified as needed by flash column chromatography to yield the desired products.



244

4a-allyl-9a-allyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole (244): Prepared according to general method A using indolenine **207** (106 mg, 0.5 mmol), magnesium (30 mg, 1.2 mmol), allyl bromide (48 µL, 0.55 mmol) in THF (2 mL) at ambient temperature. Pure after aqueous workup to yield **244** (123 mg, 0.48 mmol, 97% yield) as an oil.

Analytical data for **244**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 5.95 – 5.82 (m, 1H), 5.68 (tdd, *J* = 14.9, 5.8, 4.1 Hz, 1H), 5.17 (d, *J* = 1.2 Hz, 1H), 5.14 (dd, *J* = 5.7, 4.7 Hz, 1H), 5.01 – 4.95 (m, 1H), 4.95 – 4.86 (m, 1H), 3.57 (dd, *J* = 102.9, 34.0 Hz, 1H), 2.43 (dtd, *J* = 33.1, 13.3, 7.5 Hz, 3H), 2.06 (dd, *J* = 12.8, 7.8 Hz, 2H), 1.74 – 1.64 (m, 1H), 1.46 (dddd, *J* = 25.2, 17.9, 12.5, 4.5 Hz, 3H), 1.37 – 1.19 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.94, 135.50, 134.74, 127.17, 123.68, 118.72, 118.28, 117.12, 110.57, 68.23, 49.79, 40.40, 36.17, 32.72, 30.71, 22.14, 22.02. LCMS (ESI) calcd for $(C_{18}H_{24}N)^{+}$ $[M+H]^{+}$: 254.2, found: 254.2.

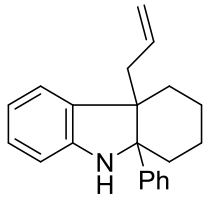


245

4a-allyl-9a-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole (245): Prepared according to general method B using indolenine **207** (53 mg, 0.25 mmol), MeLi (1.6 M in THF) (0.24 mL,

0.38 mmol) in THF (1 mL) at ambient temperature. ^{1}H NMR analysis of crude reaction mixture revealed conversion to **245** which was determined to have formed in 68% NMR yield.

Analytical data for **245**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 – 7.00 (m, 1H), 6.97 – 6.93 (m, 1H), 6.72 (td, *J* = 7.4, 1.0 Hz, 1H), 6.62 (ddd, *J* = 7.7, 0.9, 0.5 Hz, 1H), 5.63 (dddd, *J* = 23.4, 10.1, 8.3, 6.3 Hz, 1H), 4.98 – 4.94 (m, 1H), 4.88 (ddd, *J* = 3.2, 2.4, 1.4 Hz, 1H), 2.40 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.10 (d, *J* = 13.3 Hz, 1H), 1.99 (dd, *J* = 13.3, 8.3 Hz, 1H), 1.55 – 1.45 (m, 4H), 1.45 – 1.42 (m, 1H), 1.29 (d, *J* = 4.6 Hz, 4H), 1.23 – 1.19 (m, 2H).



246

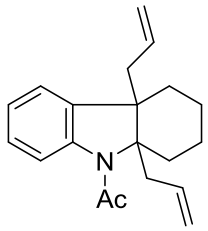
4a-allyl-9a-phenyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole (246): Prepared according to general method B using indolenine **207** (53 mg, 0.25 mmol), PhLi (1.6 M in THF) (0.24 mL, 0.38 mmol) in THF (1 mL) at ambient temperature. ^{1}H NMR analysis of crude reaction mixture revealed complete conversion to **246** which was determined to have formed in 68% NMR yield.

Analytical data for **246** matches ^{1}H spectra from the literature.[4]

General Procedure for One-Pot of Nucleophile and *N*-Anion Capture.

Indolenine **207** and freshly crushed magnesium ribbon were added to an oven-dried 16x100 borosilicate test tube, sealed with a rubber septa, purged 3x with N_2 and maintained under a positive pressure of N_2. To this anh. THF was added via syringe followed by careful addition of allyl bromide. The reaction mixture was allowed to stir at ambient temperature for 70 minutes.

At which point an electrophile was added via syringe to the reaction mixture dropwise. The reaction was allowed to continue stirring at ambient temperature until starting material was consumed, as determined by TLC analysis. Following consumption of the starting material the reaction mixture was diluted with diethyl ether and carefully quenched with sat. $NaHCO_3$ (aq) solution. The organic phase was separated and the aqueous phase was washed with diethyl ether (x2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to yield the desired products.

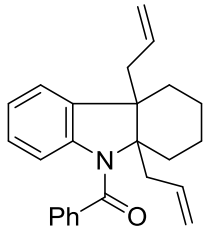


247

4a-allyl-9a-allyl-2,3,4,4a,9,9a-hexahydro-1-acetyl-carbazole (247): Prepared according to general method A using indolenine **207** (106 mg, 0.5 mmol), magnesium (30 mg, 1.2 mmol), allyl bromide (48 µL, 0.55 mmol), acetyl chloride (59 µL, 0.55 mmol) in THF (2 mL) at ambient temperature. Purified by flash column chromatography (19:1 to 5:1 Hexanes:EtOAc) to yield **247** (41 mg, 0.14 mmol, 24% yield) as a foam.

Analytical data for **247**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.1 Hz, 1H), 7.16 (td, *J* = 7.9, 1.3 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.01 (td, *J* = 7.4, 1.0 Hz, 1H), 6.05 – 5.94 (m, 1H), 5.90 (tdd, *J* = 15.8, 9.5, 6.2 Hz, 1H), 5.11 (s, 1H), 5.09 (d, *J* = 5.6 Hz, 1H), 5.01 – 4.92 (m, 2H), 2.55 (dd, *J* = 14.7, 6.4 Hz, 1H), 2.46 (dd, *J* = 15.1, 7.4 Hz, 1H), 2.44 – 2.36 (m, 6H), 1.81 – 1.69 (m, 2H), 1.67 – 1.58 (m, 1H), 1.48 (dddd, *J* = 16.9, 12.6, 8.0, 3.9 Hz, 2H), 1.36 – 1.27 (m, 2H). ^{13}C

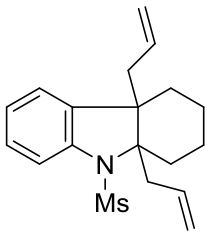
NMR (126 MHz, $CDCl_3$) δ 169.36, 141.77, 135.48, 134.66, 126.80, 123.23, 123.03, 117.94, 116.65, 116.52, 49.39, 39.19, 30.27, 25.44, 21.80, 21.23. LCMS (ESI) calcd for $(C_{20}H_{26}NO)^+$ $[M+H]^+$: 296.2, found: 296.1.



248

4a-allyl-9a-allyl-2,3,4,4a,9,9a-hexahydro-1-benzoyl-carbazole (248): Prepared according to general method A using indolenine **207** (42 mg, 0.2 mmol), magnesium (23 mg, 0.96 mmol), allyl bromide (20 µL, 0.22 mmol), benzoyl chloride (35 µL, 0.30 mmol) in THF (2 mL) at ambient temperature. Purified by flash column chromatography (19:1 to 5:1 Hexanes:EtOAc) to yield **248** (39 mg, 0.11 mmol, 55% yield) as a foam.

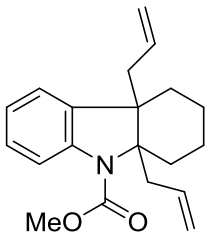
Analytical data for **248**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.32 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.10 (d, *J* = 7.0 Hz, 1H), 6.97 (s, 1H), 6.63 – 6.53 (m, 1H), 5.95 (ddt, *J* = 17.3, 10.1, 7.5 Hz, 1H), 5.80 – 5.68 (m, 1H), 5.26 – 5.15 (m, 2H), 5.05 – 5.01 (m, 1H), 4.98 – 4.91 (m, 1H), 2.59 – 2.45 (m, 2H), 2.41 (dd, *J* = 13.3, 7.7 Hz, 1H), 2.16 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.06 (d, *J* = 13.6 Hz, 1H), 1.82 (dd, *J* = 12.8, 5.5 Hz, 1H), 1.58 – 1.47 (m, 3H), 1.37 – 1.23 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.52, 134.85, 133.99, 130.83, 128.92, 128.02, 119.06, 117.76, 115.48, 69.01, 48.90, 39.88, 33.41, 21.94, 21.49. LCMS (ESI) calcd for $(C_{25}H_{28}NO)^+$ $[M+H]^+$: 358.2, found: 358.2.



249

4a-allyl-9a-allyl-2,3,4,4a,9,9a-hexahydro-1-methanesulfonyl-carbazole (249): Prepared according to general method A using indolenine **207** (42 mg, 0.2 mmol), magnesium (23 mg, 0.96 mmol), allyl bromide (20 µL, 0.22 mmol), methane sulfonyl chloride (25 µL, 0.30 mmol) in THF (2 mL) at ambient temperature. Purified by flash column chromatography (19:1 to 5:1 Hexanes:EtOAc) to yield **249** (55 mg, 0.17 mmol, 83% yield) as a foam.

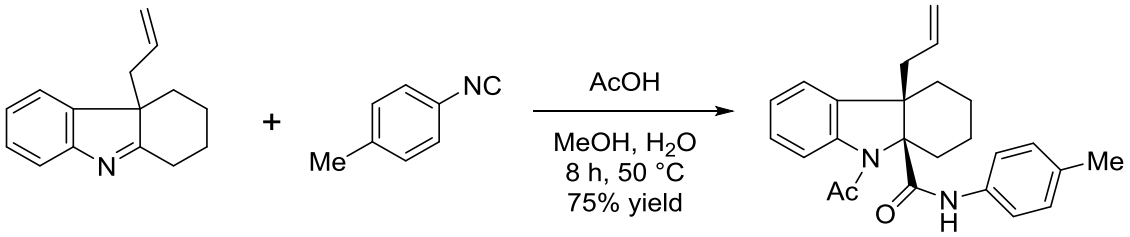
Analytical data for **249**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 1H), 7.21 (td, *J* = 8.1, 1.4 Hz, 1H), 7.14 – 7.08 (m, 1H), 7.01 (td, *J* = 7.4, 0.9 Hz, 1H), 6.16 (ddt, *J* = 13.7, 10.0, 6.8 Hz, 1H), 5.63 (td, *J* = 17.0, 7.3 Hz, 1H), 5.13 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.05 (ddd, *J* = 12.0, 10.6, 1.9 Hz, 2H), 4.95 (d, *J* = 16.9 Hz, 1H), 3.10 (s, 3H), 2.97 (dd, *J* = 15.2, 6.6 Hz, 1H), 2.73 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.43 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.29 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.17 (s, 2H), 1.94 (dd, *J* = 12.2, 7.2 Hz, 3H), 1.60 (ddd, *J* = 15.1, 9.4, 3.9 Hz, 1H), 1.51 – 1.41 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.05, 134.12, 127.71, 123.20, 122.45, 118.11, 117.51, 114.15, 40.41, 39.15, 33.17, 22.04, 21.10. LCMS (ESI) calcd for $(C_{19}H_{26}NO_2S)^+$ $[M+H]^+$: 332.1, found: 332.1.



250

4a-allyl-9a-allyl-2,3,4,4a,9,9a-hexahydro-1-carbomethoxy-carbazole (250): Prepared according to general method A using indolenine **207** (42 mg, 0.2 mmol), magnesium (23 mg, 0.96 mmol), allyl bromide (20 µL, 0.22 mmol), methyl chloroformate (25 µL, 0.30 mmol) in THF (2 mL) at ambient temperature. Purified by flash column chromatography (19:1 to 5:1 Hexanes:EtOAc) to yield **250** (33 mg, 0.11 mmol, 53% yield) as a foam.

Analytical data for **250**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.9 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.13 (dd, *J* = 7.4, 0.8 Hz, 1H), 6.96 (td, *J* = 7.4, 1.0 Hz, 1H), 5.86 (dddd, *J* = 17.2, 14.8, 8.5, 5.2 Hz, 2H), 5.07 (d, *J* = 10.2 Hz, 2H), 5.02 (dd, *J* = 12.2, 1.9 Hz, 1H), 4.95 (dd, *J* = 10.1, 2.0 Hz, 1H), 3.82 (s, 3H), 2.65 (dd, *J* = 14.9, 6.9 Hz, 1H), 2.56 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.43 – 2.34 (m, 2H), 1.88 – 1.79 (m, 1H), 1.73 – 1.61 (m, 2H), 1.48 – 1.39 (m, 3H), 1.39 – 1.21 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.18, 134.75, 127.27, 122.41, 117.66, 116.76, 116.24, 77.26, 77.00, 76.75, 73.09, 52.03, 49.57, 38.85, 31.56, 21.56, 21.16. LCMS (ESI) calcd for $(C_{20}H_{26}NO_2)^+$ $[M+H]^+$: 312.1, found: 312.1.



207 **251** **252**

4a-allyl-9a-(4-tolylamide)-2,3,4,4a,9,9a-hexahydro-1-acetyl-carbazole (252): Indolenine **207** was added to a 16x100 test tube which was equipped with a magnetic stir bar. To this was added THF (1.0 mL) and allowed to stir under ambient atmosphere and temperature conditions. To the reaction mixture was added one drop of H_2O (distilled) as dispensed by a pasture pipette. Following this *p*-tolylisonitrile (0.05 mL, 0.4 mmol) and acetic acid (0.05 mL, 0.4 mmol) were

added via syringe, the reaction vessel was capped, heated to 50 °C and the reaction was allowed to stir for an additional 8 h. The reaction mixture was cooled to ambient temperature, diluted with diethyl ether and carefully quenched with sat. $NaHCO_3$ (aq) solution. The organic phase was separated and the aqueous phase was washed with diethyl ether (x2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (15:1 to 3:1 Hexanes:EtOAc) to yield **252** (58 mg, 0.15 mmol, 75% yield).

Analytical data for **252**: R_f: (0.41, 2:1 Hexanes:EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.17 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.14 – 7.09 (m, 3H), 5.66 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 5.01 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.92 (dd, *J* = 17.0, 1.7 Hz, 1H), 2.67 (ddd, *J* = 12.3, 7.2, 4.5 Hz, 1H), 2.51 – 2.33 (m, 5H), 2.30 (s, 3H), 1.99 – 1.87 (m, 2H), 1.86 – 1.76 (m, 2H), 1.62 – 1.57 (m, 1H), 1.54 – 1.43 (m, 1H), 1.22 – 1.13 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.40, 134.36, 133.31, 129.48, 128.17, 124.37, 123.90, 120.54, 119.04, 118.95, 43.75, 31.33, 25.69, 20.82, 20.70, 19.21. LCMS (ESI) calcd for $(C_{25}H_{19}N_2O_2)^+$ $[M+H]^+$: 389.2, found: 389.1.

VII.3: Experimental Section – Chapter III[12]

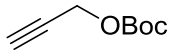
General Procedure for *tert*-Butyl Propargyl Carbonates.

Method A: Prepared according to Chalasani and coworkers.[13] To a solution of propargyl alcohol in anh. CH_2Cl_2 maintained under a positive pressure of nitrogen was added N(*i*-Pr)$_2$Et and

[12] Supporting information is reproduced with permission from: (a) Montgomery, T. D.; Nibbs, A. E.; Zhu, Y.; Rawal, V. H. *Org. Lett.* **2014**, *16*, 3480-3483. (b) Nibbs, A. E.; Montgomery, T. D.; Zhu, Y.; Rawal, V. H. *The Journal of Organic Chemistry* **2015**, *80*, 4928-4941.
[13] Chalasani, D.; Li, J.; Jackson, N. M.; Payne, M.; Lucht, B. L. *J. Power Sources* **2012**, *15*, 67-73.

DMAP. The reaction mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate was either added portionwise over two min or dropwise as a solution in CH_2Cl_2. The reaction mixture was slowly warmed to ambient temperature (23 °C) over 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water, 10% aq. HCl, sat. aq. $NaHCO_3$, and brine. The organic layer was then dried over anh. $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired product.

Method B: Prepared according to Štambask and coworkers.[14] To a suspension of 60% w/w NaH in THF maintained under a positive pressure of nitrogen was added the propargyl alcohol. This mixture was allowed to stir at ambient temperature for 30 min and was then cooled to 0 °C. To this mixture was added a solution of Boc_2O in THF over 1 h, and the mixture was allowed to warm to ambient temperature. After consumption of the starting material, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine. The organic layer was dried with anh. $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired product.



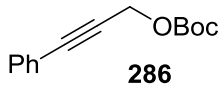
255

***tert*-butyl prop-2-yn-1-yl carbonate** (**255**): Prepared according to method A. To a solution of propargyl alcohol (1.7 mL, 30 mmol) in anh. CH_2Cl_2 (2.5 mL) maintained under a positive pressure of nitrogen was added N(*i*-Pr)$_2$Et (13.1 mL, 75 mmol) and DMAP (366 mg, 3 mmol). The reaction mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (8.51 g, 39 mmol) was added portionwise over two minutes. The reaction mixture was slowly warmed to ambient

[14] Štambask, J., Malkov, A. V., Kočovsk, P., *Collect. Czech. Chem. Commun.* **2008**, *73*, 705–732.

temperature over 3 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (10 mL), 10% aq. HCl (10 mL), aq. $NaHCO_3$ (10 mL) and brine. The organic layer was then dried over anh. $MgSO_4$ and concentrated *in vacuo*. Purified by filtration over a short plug of SiO_2 to afford **255** (3.33 g, 71%) as a colorless liquid.

Analytical data match those reported in the literature.[13]

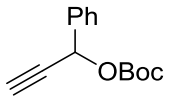


286

***tert*-butyl (3-phenylprop-2-yn-1-yl) carbonate** (**286**): Step 1: Prepared according to procedure by Panteleev and coworkers.[15] $Pd(PPh_3)_2Cl_2$ (35 mg, 50 µmol) and CuI (19 mg, 0.1 mmol) were suspended in NEt_3 (20 mL, 0.275 M) under a positive pressure of nitrogen. To this suspension was added iodobenzene (560 µL, 5.0 mmol) and propargyl alcohol (320 µL, 5.5 mmol). The reaction was stirred for 16 h at ambient temperature. Any precipitate matter was removed by filtration through a plug of Celite™, which was then washed with NEt_3 (2 x 10 mL). The reaction mixture was passed through a plug of silica and concentrated *in vacuo*. This residue was used without further purification. Step 2: Prepared according to Method B using 60% w/w NaH (320 mg, 8.0 mmol) in THF (15 mL), the unpurified Sonogashira product (5.0 mmol) as a solution in THF (10 mL), and Boc_2O (982 mg, 4.5 mmol) in THF (25 mL). Purified by flash column chromatography (10% EtOAc/Hexanes) to afford **286** (929 mg, 73% over both steps) as a red/brown liquid.

[15] Panteleev, J.; Huang, R. Y.; Lui, E. K. J.; Lautens, M. *Org. Lett.* **2011**, *13*, 5314-5317.

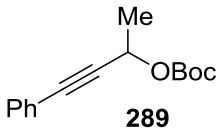
Analytical data (^{1}H NMR, ^{13}C NMR, and HRMS) match those reported in the literature.[16]



288

***tert*-butyl (1-phenylprop-2-yn-1-yl) carbonate** (**288**): Prepared according to Method A using 1-phenylprop-2-yn-1-ol (920 µL, 7.57 mmol), Boc_2O (2.2 g, 9.9 mmol), N(*i*-Pr)$_2$Et (3.3 mL, 18.9 mmol), DMAP (93 mg, 0.76 mmol), and CH_2Cl_2 (640 µL). Purified by flash column chromatography (10% EtOAc/Hexanes) to afford **288** (1.54 g, 88%) as a red/brown liquid.

Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) match those reported in the literature.[16]

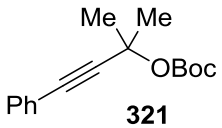


289

***tert*-butyl (4-phenylbut-3-yn-2-yl) carbonate (289):** Prepared according to Method A using 4-phenyl-3-butyn-2-ol (1.11 mL, 7.6 mmol), Boc_2O (2.2 g, 9.9 mmol), N(*i*-Pr)$_2$Et (3.3 mL, 18.9 mmol), DMAP (93 mg, 0.76 mmol), and CH_2Cl_2 (0.64 mL) for 16 h. Purified by filtration over a short plug of SiO_2 to afford **289** (2.01 g, 99%) as a pale yellow liquid.

Analytical data for **289**: ^{1}H NMR (500 MHz, $CDCl_3$): δ7.46 – 7.41 (m, 2H), 7.33 – 7.27 (m, 3H), 5.50 (q, *J* = 6.7 Hz, 1H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 131.6, 128.3, 128.0 (x2), 122.1, 87.0, 84.8, 82.2, 63.4, 27.6, 27.5 (x3), 21.3; HRMS (ESI) calcd for $(C_{15}H_{18}O_3Na)^+$ $[M+Na]^+$: 269.1148, found: 269.1152.

[16] Yamamoto, H.; Nishiyama, M.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 8369-8373.



321

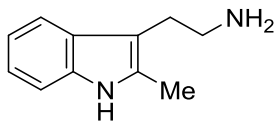
***tert*-butyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate** (**321**): Step 1: Prepared according to a procedure by Li and coworkers.[17] To a 125-mL flame-dried RBF was added $HNEt_2$ (125 mL), PhBr (7.6 mL, 60 mmol), 2-methyl-3-butyn-2-ol (4.9 mL, 50 mmol), PPh_3 (197 mg, 0.75 mmol), CuI (95 mg, 0.5 mmol), and $Pd(OAc)_2$ (56 mg, 0.25 mmol). The mixture was sparged with N_2 for 30 min, then the RBF was fitted with a reflux condenser and sparged for an additional 5 min. The reaction was allowed to reflux for 22 h. After cooling to ambient temperature, the mixture was concentrated *in vacuo*. Purified by flash column chromatography (10% EtOAc/Hexanes) to afford the Sonogashira product (6.98 g, 87%) as a tan solid. Analytical data (^{1}H NMR and ^{13}C NMR) match those reported in the literature.17 ^{1}H NMR spectrum is provided to demonstrate purity. Step 2: Prepared according to Method B using Sonogashira product (1.76 g, 11 mmol), 60% w/w NaH (840 mg, 21 mmol), Boc_2O (2.29 g, 10.5 mmol), and THF (110 mL). Purified by flash column chromatography (10% EtOAc/Hexanes) and the method by Basel and Hassner[18] (for the destruction of excess Boc_2O) to afford **321** (1.67 g, 61%) as a light yellow solid.

Analytical data for **321**: mp: 46-47 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 – 7.40 (m, 2H), 7.33 – 7.27 (m, 3H), 1.78 (s, 6H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.3, 131.6 (x2), 128.2, 128.1 (x2), 122.6, 89.9, 84.0, 81.8, 73.7, 28.9 (x2), 27.7 (x3); HRMS (ESI) calcd for $(C_{16}H_{20}O_3Na)^+$ $[M+Na]^+$: 283.1305, found: 283.1294.

Preparation of 2-Methyl Tryptamines

[17] Li, Y.; Zou, H.; Gong, J.; Xiang, J.; Luo, T.; Quan, J.; Wang, G.; Yang, Z. *Org. Lett.*, **2007**, *9*, 4057–4060.
[18] Basel, Y.; Hassner, A. *Synthesis* **2001**, 550-551.

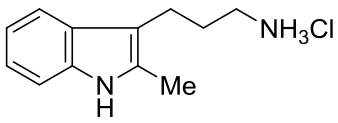
Prepared according to a modified procedure by Bowman and coworkers.[19] To a solution of phenyl hydrazine in absolute EtOH was added ketone dropwise. The flask was fitted with a condenser, heated to reflux, and was monitored by TLC. The reaction was then allowed to cool to ambient temperature and was concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 and washed with water. The aqueous layer was separated and washed with CH_2Cl_2. The combined organic layers were washed with brine, dried over anh. $MgSO_4$ or anh. Na_2SO_4 and concentrated *in vacuo*. The residue was purified by trituration or used without further purification.



523

2-(1*H*-indol-3-yl)ethanamine (**523**): Prepared according to the general procedure using phenyl hydrazine (1.08 mL, 10.0 mmol), EtOH (50 mL), and 5-chloro-2-pentanone (1.69 g, 14.0 mmol) at 80 °C for 4 h. The resulting white solid **523** (1.428 g, 82%) was analytically pure and was used without further purification.

Analytical data match those reported in the literature.[19]



524

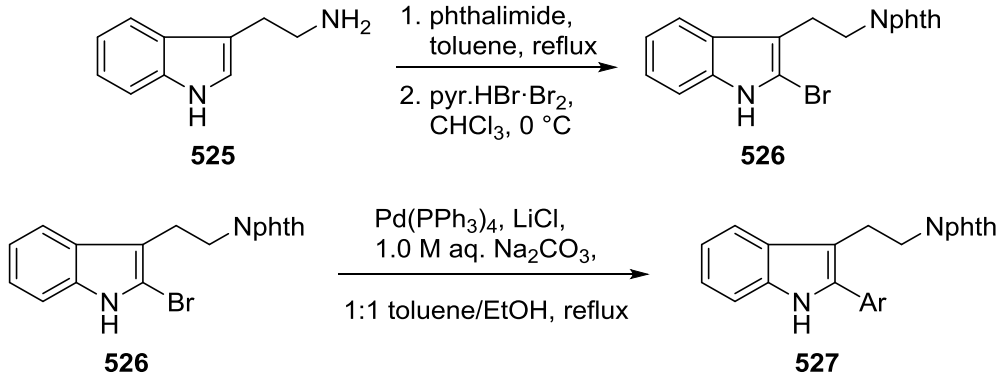
3-(2-methyl-1*H*-indol-3-yl)propan-1-amine hydrochloride (**524**): Prepared according to the general procedure using phenyl hydrazine (1.8 mL, 18 mmol), EtOH (60 mL), and 6-chloro-2-

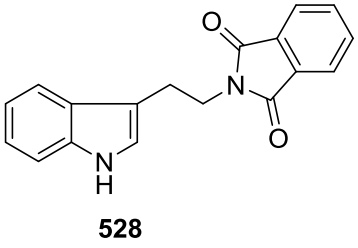
[19] Bowman, M. D.; Schmink, J. R.; McGowan, C. M.; Kormos, C. M.; Leadbeater, N. E. *Org. Process Res. Dev.* **2008**, *12*, 1078-1088.

hexanone (2 mL, 15 mmol) at 80 °C for 24.5 h. Purified by trituration from CH_2Cl_2/Et_2O to afford **524** (1.42 g, 42%) of a pale-yellow shiny solid.

Analytical data for **524**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.09 (br s, 3H), 7.43 (d, J = 7.7 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 6.91 (td, J = 7.5, 1.1 Hz, 1H), 2.82 – 2.72 (m, 2H), 2.69 (t, J = 7.5 Hz, 2H), 2.32 (s, 3H), 1.84 (p, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, DMSO) δ 135.2, 131.6, 128.0, 119.9, 118.0, 117.3, 110.3, 108.8, 38.6, 28.3, 20.6, 11.2; HRMS (ESI) calcd for $(C_{12}H_{16}N_2)H^+$ $[M+H]^+$: 189.1386, found: 189.1377.

Preparation of 2-Aryl Tryptamines





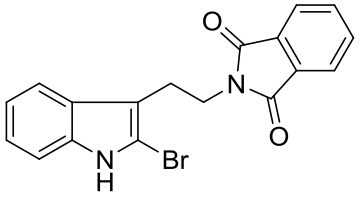
528

2-(2-(1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (**528**): Prepared according to a procedure by Feng and coworkers.[20] To a 250-mL RBF was added tryptamine (4.81 g, 30 mmol), phthalic anhydride (4.58 g, 30.9 mmol), and toluene (176 mL). The RBF was fitted with a reflux condenser and brought to reflux. After 13 h, the reaction mixture was cooled and concentrated *in*

[20] Feng, P.; Fan, Y.; Xue, F.; Liu, W.; Li, S.; Shi, Y. *Org. Lett.* **2011**, *13*, 5827-5829.

vacuo. Purified by trituration from CH_2Cl_2/Hexanes to afford **528** (7.77 g, 89%) as a light-yellow solid.

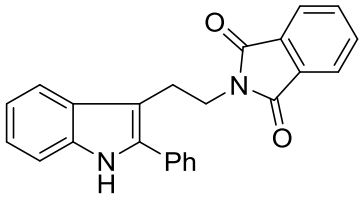
^{1}H NMR and ^{13}C NMR analytical data match those reported in the literature.[20] HRMS (ESI) calcd for $(C_{18}H_{14}N_2O_2)H^+$ $[M+H]^+$: 291.1128, found: 291.1129.



526

2-(2-(2-bromo-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (**526**): Prepared according to a procedure by Feng and coworkers.[20] To a 100-mL RBF was added **528** (1.76 g, 6.07 mmol) and $CHCl_3$/THF (1:1, 0.1 M). The mixture was cooled to –10 °C in a bath. Pyridinium tribromide (2.04 g, 6.37 mmol) was added portionwise over the course of 1 min. The reaction progress was monitored by TLC. After 1 h, the reaction was quenched with sat. aq. $Na_2S_2O_3$. The mixture was stirred for 30 min, then extracted three times with CH_2Cl_2 and dried over anh. $MgSO_4$. Purified by trituration from CH_2Cl_2 and Hexanes to afford **526** (1.93 g, 86%) as a sand-colored solid.

^{1}H and ^{13}C NMR analytical data match those reported in the literature.[20] HRMS data match those reported in the literature.[21]

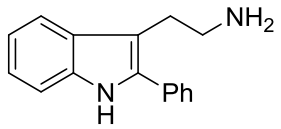


529

[21] Gerasyuto, Aleksey I.; Hsung, Richard P.; Sydorenko, Nadiya; Zificsak, Craig A. *Org. Biomol. Chem.* **2005**, 3, 2140 – 2144.

2-(2-(2-phenyl-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (**529**): Prepared according to a procedure by Chu and coworkers.[22] To a 100-mL flask was added bromoindole **529** (877 mg, 2.38 mmol), phenylboronic acid (363 mg, 2.98 mmol), PhMe/EtOH (1:1, 60 mL), 1.0 M aq. $Na_2CO_3 \cdot H_2O$ (6 mL), and LiCl (303 mg, 7.14 mmol). The mixture was sparged with N_2 for 25 min, then $Pd(PPh_3)_4$ (138 mg, 119 μmol) was added and the mixture was brought to reflux. After 2.5 h, the reaction mixture was cooled to ambient temperature, then filtered through anh. Na_2SO_4 and concentrated. Purified by flash column chromatography (15→30% EtOAc/Hexanes) to afford **529** (572 mg, 66%) as a yellow solid.

Analytical data match those reported in the literature.[23]

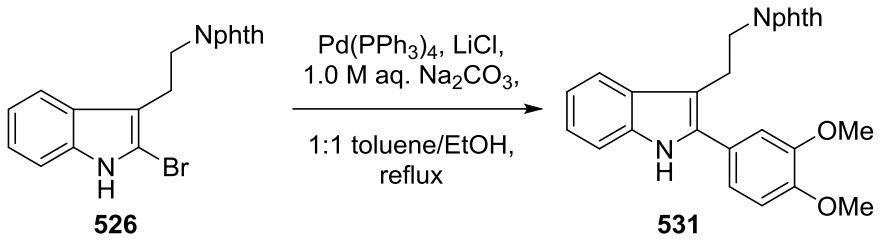


530

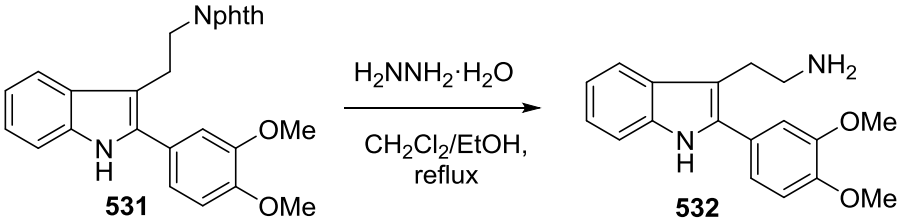
2-(2-phenyl-1*H*-indol-3-yl)ethanamine (**SI-6**): To a 100-mL RBF was added **SI-5** (572 g, 1.56 mmol), CH_2Cl_2/MeOH (1:1, 31 mL), and 50-60% hydrazine hydrate (1.5 mL). After heating to reflux for 13.5 h, the milky-white heterogeneous reaction mixture was cooled to ambient temperature, vacuum-filtered and the filtrate was concentrated *in vacuo*. Purified by flash column chromatography (10→50% MeOH/CH_2Cl_2) to afford **SI-6** (371 mg, quant.) as a tan residue.

Analytical data match those reported in the literature.[24]

[22] Chu, L.; Fisher, M. H.; Goulet, M. T.; Wyratt, M. J. *Tetrahedron Lett.* **1997**, *38*, 3871-3874.
[23] Kolundzic, F.; Noshi, M. N.; Tjandra, M.; Movassaghi, M.; Miller, S. J. *J. Am. Chem. Soc.* **2011**, *133*, 9104-9111.
[24] Preciado, S.; Mendive-Tapia, L.; Albericio, F.; Lavilla, R. *J. Org. Chem.*, **2013**, *78*, 8129-8135.



Step 1 [**2-(2-(2-(3,4-dimethoxyphenyl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione** (**531**)]: Prepared according to a procedure by Chu and coworkers.[25] To a 100-mL flask was added bromoindole **526** (675 mg, 1.83 mmol), 3,4-dimethoxyphenylboronic acid (417 mg, 2.29 mmol), PhMe/EtOH (1:1, 46 mL), 1.0 M aq. $Na_2CO_3 \cdot H_2O$ (4.6 mL), and LiCl (233 mg, 5.49 mmol). The mixture was sparged with N_2 for 30 min, then $Pd(PPh_3)_4$ (106 mg, 91.5 μmol) was added. The mixture was purged for an additional 15 min, then brought to reflux. After 6 h, the reaction mixture was cooled to ambient temperature. The reaction mixture was diluted with EtOAc, and the aqueous layer was removed. The organic layer was washed three times with 1.0 M NaOH, once with brine, and dried over anh. $MgSO_4$. The residue was used without further purification.



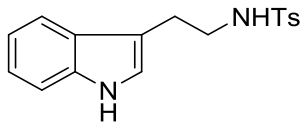
Step 2 [**2-(2-(3,4-dimethoxyphenyl)-1*H*-indol-3-yl)ethanamine** (**532**)]: To the above residue of **531** was added CH_2Cl_2/MeOH (1:1, 37 mL), and 50-60% hydrazine hydrate (1.7 mL). After heating to reflux for 16 h, the reaction mixture was cooled to ambient temperature and the brown heterogeneous mixture was vacuum filtered using a fritted funnel. The filtrate was concentrated,

[25] Chu, L.; Fisher, M. H.; Goulet, M. T.; Wyratt, M. J. *Tetrahedron Lett.* **1997**, *38*, 3871-3874.

then diluted with 1.0 M NaOH. The mixture was extracted four times with 4:1 $CHCl_3$/i-PrOH and dried over anh. Na_2SO_4. The residue was used without further purification.

Preparation of C-3 Alkyl Sulfonamides

To a solution of tryptamine in anh. CH_2Cl_2 maintained under a positive pressure of nitrogen was added NEt_3 and cooled to 0 °C. To the stirred solution was added tosyl or mesyl in one portion and the reaction was allowed to slowly warm to ambient temperature. The reaction was allowed to stir an additional 12 h. The solution was then diluted with CH_2Cl_2, washed with 10% aq. HCl, aq. $NaHCO_3$, and brine. The organic layer was passed through a plug of silica, which was washed with CH_2Cl_2. The combined organic layers were dried over anh. $MgSO_4$ or anh. Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography to give the desired products.

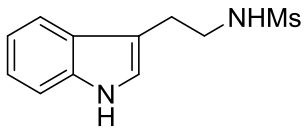


279

***N*-(2-(1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide** (**279**): Prepared according to the general procedure using tryptamine (2.4 g, 15 mmol), CH_2Cl_2 (24 mL), NEt_3 (2.3 mL, 16.5 mmol), and TsCl (3.43 g, 18 mmol) for 16 h at 0→23 °C. Purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford **279** (4.13 g, 88%) as a pale orange solid.

Analytical data match those reported in the literature.[26]

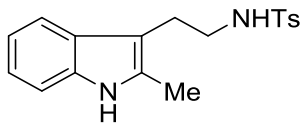
[26] Priebbenow, D.; Henderson, L. C.; Pfeffer, F. M.; Sterwart, S. G. *J. Org. Chem.* **2010**, *75* 1787–1790.



282

***N*-(2-(1*H*-indol-3-yl)ethyl)methanesulfonamide** (**282**): Prepared according to the general procedure using tryptamine (801 mg, 5 mmol), CH_2Cl_2 (8.3 mL), NEt_3 (840 µL, 6 mmol), and MsCl (0.46 mL, 6 mmol) for 12 h at 23 °C. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **282** (0.792 g, 66%) as a brown solid.

Analytical data for **282**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.14 (ddd, *J* = 8.1, 6.8, 1.0 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 4.26 (t, *J* = 5.3 Hz, 1H), 3.47 (q, *J* = 6.4 Hz, 2H), 3.06 (t, *J* = 6.5 Hz, 2H), 2.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.4, 126.9, 122.7, 122.4, 119.7, 118.5, 111.6, 111.4, 43.2, 40.1, 26.1; HRMS (ESI) calcd for $(C_{11}H_{14}N_2O_2S)H^+$ $[M+H]^+$: 239.0849, found: 239.0850.

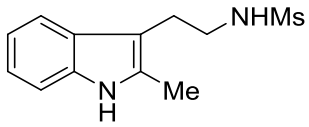


257

4-methyl-*N*-(2-(2-methyl-1*H*-indol-3-yl)ethyl)benzenesulfonamide (**257**): Prepared according to the general procedure using 2-methyltryptamine **523** (4.37 g, 25.1 mmol), CH_2Cl_2 (41.8 mL), NEt_3 (4.24 mL, 30.2 mmol), and TsCl (5.76 g, 30.2 mmol) for 12 h at 23 °C. Purified by flash column chromatography (25% EtOAc/Hexanes) to afford **257** (4.62 g, 53% over two steps) as a white solid.

Analytical data match those reported in the literature.[27]

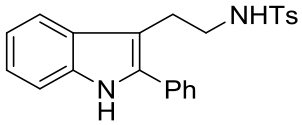
[27] Righi, M.; Topi, F.; Bartolucci, S.l Bedini, A.; Piersanti, G.; Spadoni, G. *J. Org. Chem.* **2012**, *77*, 6351-6357.



268

***N*-(2-(2-methyl-1*H*-indol-3-yl)ethyl)methanesulfonamide** (**268**): Prepared according to the general procedure using 2-methyltryptamine **523** (871 mg, 5 mmol), CH_2Cl_2 (8.33 mL), NEt_3 (840 µL, 6 mmol), and MsCl (460 µL, 6 mmol) for 12 h at 23 °C. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **268** (548 mg, 43% over two steps) as a yellow oil/amorphous solid.

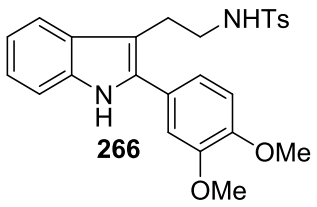
Analytical data for **268**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.08 (td, *J* = 7.5, 1.4 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 4.47 (t, *J* = 6.3 Hz, 1H), 3.27 (q, *J* = 6.6 Hz, 2H), 2.89 (t, *J* = 6.8 Hz, 2H), 2.67 (s, 3H), 2.29 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$): δ 135.1, 132.6, 128.0, 121.0, 119.2, 117.4, 110.4, 106.9, 43.3, 39.5, 24.9, 11.4; HRMS (ESI) calcd for $(C_{12}H_{16}N_2O_2S)H^+$ $[M+H]^+$: 253.1005, found: 253.1004.



264

4-methyl-*N*-(2-(2-phenyl-1*H*-indol-3-yl)ethyl)benzenesulfonamide (**264**): Prepared according to the general procedure using 2-phenyltryptamine **530** (286 mg, 1.21 mmol), CH_2Cl_2 (2 mL), NEt_3 (354 µL, 2.54 mmol), and TsCl (254 mg, 1.33 mmol) for 14 h at 23 °C. Purified by flash column chromatography (20→25% EtOAc/Hexanes) to afford **264** (282 mg, 60% over two steps) as an off-white solid.

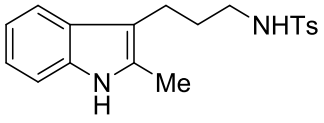
Analytical data match those reported in the literature.[28]



266

***N*-(2-(2-(3,4-dimethoxyphenyl)-1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide** (**266**): Prepared according to the general procedure using unpurified 2-aryltryptamine **532** (1.83 mmol), CH_2Cl_2 (3 mL), NEt_3 (307 µL, 2.20 mmol), and TsCl (383 mg, 2.01 mmol) for 18 h at 23 °C. Purified by flash column chromatography (0→3% MeOH/CH_2Cl_2) to afford **266** (267 mg, 32% over three steps) as a tan powder.

Analytical data for **266**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.78 (t, *J* = 5.4 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.40 – 7.34 (m, 3H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.12 (s, 1H), 7.10 – 7.01 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.03 – 2.88 (m, 4H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 148.8, 148.4, 137.7, 135.7, 134.8, 129.5 (x2), 128.5, 126.5 (x2), 125.2, 121.2, 120.0, 118.7, 117.8, 112.0, 111.4, 111.0, 107.1, 55.6, 55.5, 43.3, 25.4, 20.9; HRMS (ESI) calcd for $(C_{25}H_{26}N_2O_4S)H^+$, $[M+H]^+$: 451.1686, found: 451.1684.



270

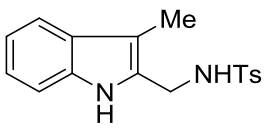
4-methyl-*N*-(3-(2-methyl-1*H*-indol-3-yl)propyl)benzenesulfonamide (**270**): Prepared according to the general procedure using 2-methylhomotryptamine **524** (658 mg, 2.93 mmol), CH_2Cl_2 (4.9 mL), NEt_3 (857 µL, 6.15 mmol), and TsCl (614 mg, 322 mmol) for 17 h at 23 °C.

[28] Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *Chem. Sci.* **2012**, *3*, 3170-3174.

Purified by flash column chromatography (CH_2Cl_2) to afford **270** (853 mg, 85%) as an off-white shiny solid.

^{1}H NMR and HRMS analytical data match those reported in the literature.[29] ^{13}C NMR (125 MHz, $CDCl_3$): δ143.2, 136.8, 135.2, 131.2, 129.6 (x2), 128.3, 126.9 (x2), 120.8, 119.0, 117.7, 110.3, 110.2, 43.0, 30.0, 21.4, 21.1, 11.4.

Preparation of C2-Tethered Sulfonamide



272

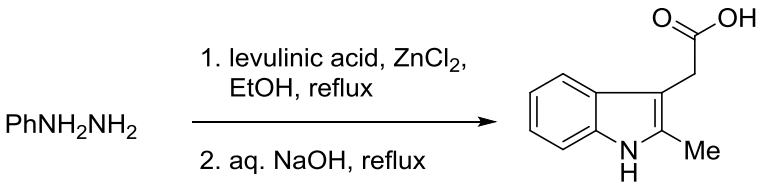
4-methyl-*N*-((3-methyl-1*H*-indol-2-yl)methyl)benzenesulfonamide (**272**): Prepared according to a modified procedure by Bandini and coworkers.[30] To a 50-mL RBF was added 3-methyl-1*H*-indole-2-carbaldehyde (300 mg, 2.07 mmol) and $TsNH_2$ (532 mg, 3.11 mmol). The RBF was fitted with a reflux condenser greased at the joint, purged with N_2, and toluene (4.5 mL) and $Ti(OEt)_4$ (868 µL, 4.14 mmol) was added down the inside walls of the reflux condenser. An additional volume of toluene (4.5 mL) was washed down the inside walls of the reflux condenser. The reaction mixture was stirred at 120 °C for 4 h. After cooling to ambient temperature, the volatiles were concentrated *in vacuo*. The RBF containing the bright red-orange residue was purged with N_2, diluted with THF (8.6 mL) and MeOH (8.6 mL), and cooled with an ice/water bath. $NaBH_4$ (313 mg, 8.28 mmol) was added, and the reaction was warmed to room temperature overnight. After 14.5 h, the reaction mixture was cooled with an ice/water bath and quenched with water. The solvent was removed *in vacuo* and the resulting residue was diluted

[29] Yadav, J. S.; Reddy, B. V. S.; Satheesh, G. N. *Syn. Lett.* **2009**, *5*, 727-730.
[30] Bandini, M.; Gualandi, A.; Monari, M.; Romaniello, A.; Savoia, D.; Tragni, M. *J. Organomet. Chem.* **2011**, *696*, 338-347.

with water and extracted three times with CH_2Cl_2. The combined organic layers were washed twice with water, back-extracted once with CH_2Cl_2, washed once with brine, and dried over anh. Na_2SO_4. Purified by flash column chromatography (20→30% EtOAc/Hexanes) to afford **272** (383 mg, 59%) as a light orange-yellow solid.

Analytical data for **272**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 5.08 (br s, 1H), 4.20 (d, *J* = 6.2 Hz, 2H), 2.37 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 136.5, 135.8, 129.7 (x2), 128.7, 128.5, 127.0 (x2), 122.4, 119.2, 118.7, 110.9, 109.4, 38.4, 21.5, 8.2; HRMS (ESI) calcd for $(C_{17}H_{18}N_2O_2S)H^+$ $[M+H]^+$: 315.1162, found: 315.1159.

Preparation of Indole Acetic Acid Derivatives



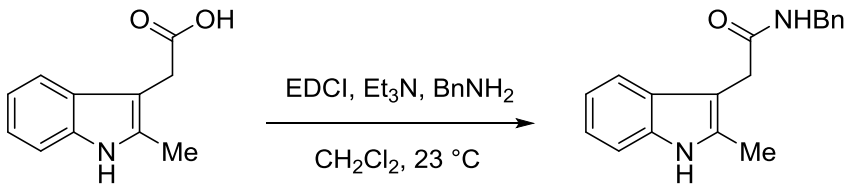
276

2-(2-methyl-1*H*-indol-3-yl)acetic acid (**276**) (Step 1): Prepared according to a procedure by Bullock and Fox.[31] Phenyl hydrazine (4.9 mL, 50 mmol), EtOH (36 mL), levulinic acid (5.1 mL, 50 mmol), and 18.0 M H_2SO_4 (4 mL) were heated to reflux. After 24 h, the mixture was cooled to ambient temperature and the EtOH was concentrated *in vacuo*. The residue was dissolved in EtOAc, washed once with water, three times with 1.0 M HCl, three times with water, once with brine, and dried over anh. Na_2SO_4. Purified by flash column chromatography (25→30% EtOAc/Hexanes) to provide a mixture of pyridazinone and indole ethyl acetate, which was used

[31] Bullock, M. W.; Fox, S. W. *J. Am. Chem. Soc.* **1951**, *73*, 5155-5157.

without further purification. Step 2: The residue from the first step was diluted with water (50 mL), NaOH added (6.0 g, 150 mmol), and the mixture brought to reflux. After 21 h, the reaction mixture was acidified with 1.0 M HCl to pH = 1, then extracted four times with CH_2Cl_2. The combined organic layers were washed once with water, once with brine, and dried over anh. Na_2SO_4 to afford 1.55 g of the indole acetic acid as a reddish-brown solid. The combined aqueous layers were filtered and washed with water and Hexanes to produce an additional 1.19 g of product, affording a combined 2.74 g of **276** (29% over two steps).

Analytical data for **276**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.06 (br s, 1H), 10.82 (s, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 6.99 (ddd, J = 8.0, 7.0, 1.3 Hz, 1H), 6.93 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 3.56 (s, 3H), 2.50 (p, J = 1.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.1, 135.0, 132.9, 128.3, 120.0, 118.2, 117.5, 110.3, 103.9, 29.9, 11.2; HRMS (ESI) calcd for $(C_{11}H_{11}NO_2)H^+$ $[M+H]^+$: 190.0863, found: 190.0862.



276 **274**

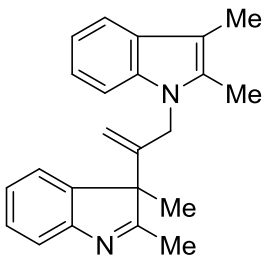
***N*-benzyl-2-(2-methyl-1*H*-indol-3-yl)acetamide** (**274**): To a 100-mL RBF was added indole acetic acid **276** (1.19 g, 6.29 mmol) and CH_2Cl_2 (21 mL). NEt_3 (1.9 mL, 13.8 mmol) was added to the mixture, then EDCI (1.45 mg, 7.55 mmol) after five min. The mixture was allowed to stir for 20 min, then benzyl amine (714 μL, 6.92 mmol) was added. After 18 h, the reaction mixture was poured into a separatory funnel and washed with 1.0 M NaOH twice and once with water. The combined aqueous layers were back-extracted once with CH_2Cl_2. The combined organic

layers were washed with brine and dried over anh. Na_2SO_4. Purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford **274** (1.40 g, 80%) as an orange-yellow solid.

Analytical data for **274**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.15 (m, 4H), 7.15 – 7.00 (m, 4H), 6.06 (t, *J* = 6.1 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 3.71 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 138.2, 135.4, 133.4, 128.4 (x2), 128.1, 127.2 (x3), 121.5, 119.8, 117.6, 110.5, 104.3, 43.2, 32.2, 11.5; HRMS (ESI) calcd for $(C_{18}H_{18}N_2O)H^+$ $[M+H]^+$: 279.1492, found: 279.1489.

General Procedure for the Pd-Catalyzed Spirocylization of Indole-based Bis-Nucleophiles

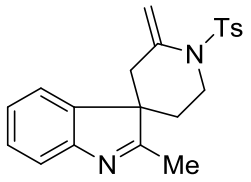
Indole substrate (0.20 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5.0 µmol, 5 mol % Pd) and Xantphos (6 mg, 11 µmol) were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape or parafilm. The test tube was purged with N_2, anh. CH_2Cl_2 (5 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. Exogenous base (0.30 mmol) was added to this mixture if required, and the mixture was either heated or maintained at ambient temperature as indicated. After 15 min, propargyl *tert*-butyl carbonate **1** (0.26 mmol) was added to the reaction mixture. After consumption of starting material as judged by TLC, the reaction was filtered through a pipet plug of Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired products.



256

3-(3-(2,3-dimethyl-1*H*-indol-1-yl)prop-1-en-2-yl)-2,3-dimethyl-3*H*-indole (**256**): Prepared according to the general procedure using 2,3-dimethylindole (73 mg, 0.50 mmol), propargyl carbonate **255** (85.9 mg, 0.55 mmol), [Pd(allyl)cod]BF_4 (17 mg, 50 µmol), DPEphos (30 mg, 55 µmol), and toluene (5 mL) at 80 °C for 18 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **256** (54 mg, 33%) as a yellow solid.

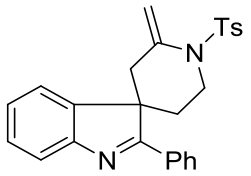
Analytical data for **256**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.36 – 7.31 (m, 2H), 7.05 (tt, *J* = 7.2, 5.5 Hz, 2H), 6.82 – 6.77 (m, 1H), 5.27 (t, *J* = 1.7 Hz, 1H), 4.27 (t, *J* = 2.0 Hz, 1H), 3.87 (dt, *J* = 18.5, 2.0 Hz, 1H), 3.73 (dt, *J* = 18.4, 1.8 Hz, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 2.07 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.1, 155.0, 143.7, 143.3, 136.0, 132.1, 128.5, 128.5, 126.0, 121.8, 120.6, 120.6, 118.8, 117.9, 111.6, 108.2, 106.8, 61.8, 43.1, 20.0, 15.7, 9.4, 8.8; HRMS (ESI): Mass calcd for $(C_{23}H_{24}N_2)H^+$ $[M+H]^+$: 329.2012; found: 329.2011.



258

2-methyl-2'-methylene-1'-tosylspiro[indole-3,4'-piperidine] (**258**): Prepared according to the general procedure using sulfonamide **257** (66 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3 mg, 2.5 µmol), Xantphos (3 mg, 5.5 µmol), and anh. CH_2Cl_2 (5 mL) at 23 °C for 4 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **258** (72 mg, 98%) as a white solid.

Analytical data for **258**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.38 (ap d, *J* = 8.0 Hz, 3H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.13 (td, *J* = 7.5, 1.2 Hz, 1H), 5.34 (d, *J* = 1.5 Hz, 1H), 4.89 (d, *J* = 1.7 Hz, 1H), 4.34 – 4.25 (m, 1H), 3.79 – 3.68 (m, 1H), 2.48 (s, 3H), 2.34 (dt, *J* = 13.4, 1.7 Hz, 1H), 2.09 (s, 3H), 1.96 (ddd, *J* = 13.6, 12.1, 4.8 Hz, 1H), 1.80 (dd, *J* = 13.4, 1.6 Hz, 1H), 1.31 – 1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.1, 153.9, 143.9, 141.9, 138.3, 137.5, 129.8 (x2), 128.3, 127.4 (x2), 124.8, 123.4, 120.4, 112.6, 55.9, 43.3, 36.4, 29.3, 21.5, 15.8; HRMS (ESI): Mass calcd for $C_{21}H_{22}N_2O_2S$ [M]: 366.1402; found: 366.1402.

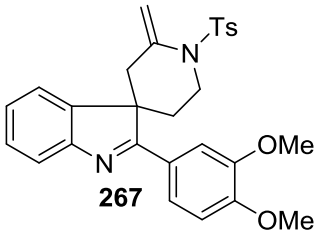


265

2-phenyl-2'-methylene-1'-tosylspiro[indole-3,4'-piperidine] (**265**): Prepared according to the general procedure using sulfonamide **264** (78 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), Xantphos (6 mg, 11 μmol), and CH_2Cl_2 (5 mL) at 23 °C for 2 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **265** (74 mg, 86%) as a white crystalline solid.

Analytical data for **265**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.43 – 7.34 (m, 5H), 7.19 (tt, *J* = 7.5, 1.3 Hz, 1H), 5.43 (d, *J* = 1.7 Hz, 1H), 4.93 (d, *J* = 1.8 Hz, 1H), 4.36 (ddd, *J* = 14.3, 5.0, 2.9 Hz, 1H), 3.88 – 3.79 (m, 1H), 2.90 (dt, *J* = 13.8, 1.9 Hz, 1H), 2.52 (s, 3H), 2.46 – 2.37 (m, 1H), 1.96 (dt, *J* = 14.0, 1.6 Hz, 1H), 1.38 – 1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.1, 153.3, 143.6, 143.1, 138.0, 137.6, 132.6, 130.4, 129.9 (x2), 128.4, 128.4,

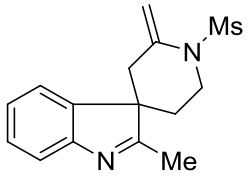
128.1 (x2), 127.2 (x2), 125.3, 123.8, 121.4, 113.4, 56.2, 43.2, 36.7, 29.8, 21.7; HRMS (ESI): Mass calcd for $(C_{26}H_{24}N_2O_2S)H^+$ $[M+H]^+$: 429.1631; found: 429.1628.



267

2-(3,4-dimethoxyphenyl)-2'-methylene-1'-tosylspiro[indole-3,4'-piperidine] (**267**): Prepared according to the general procedure using sulfonamide **266** (90 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 µmol), Xantphos (6 mg, 11 µmol), and CH_2Cl_2 (5 mL) at 23 °C for 30 min. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **267** (78 mg, 80%) as a white solid.

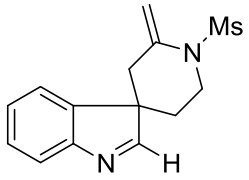
Analytical data for **267**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 – 7.85 (m, 3H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.19 – 7.11 (m, 2H), 6.77 (dd, *J* = 8.5, 0.8 Hz, 1H), 5.32 (d, *J* = 1.6 Hz, 1H), 4.92 (d, *J* = 1.8 Hz, 1H), 4.36 (ddd, *J* = 14.1, 5.2, 2.8 Hz, 1H), 4.00 (s, 3H), 3.99 – 3.96 (m, 1H), 3.97 (s, 3H), 3.07 (dt, *J* = 13.8, 2.0 Hz, 1H), 2.62 – 2.53 (m, 1H), 2.53 (s, 3H), 2.01 (d, *J* = 14.0 Hz, 1H), 1.38 (dd, *J* = 14.1, 3.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.2, 153.3, 151.4, 149.2, 143.7, 143.5, 138.5, 137.6, 129.9 (x2), 128.3, 127.4 (x2), 125.2, 124.8, 123.5, 121.3, 121.1, 113.1, 111.4, 109.9, 56.1, 55.9, 55.8, 43.3, 37.6, 30.7, 21.7; HRMS (ESI): Mass calcd for $(C_{28}H_{28}N_2O_4S)H^+$ $[M+H]^+$: 489.1843; found: 489.1843.



269

2-methyl-2'-methylene-1'-(methylsulfonyl)spiro[indole-3,4'-piperidine] (**269**): Prepared according to the general procedure using sulfonamide **268** (50 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5 μmol), Xantphos (6 mg, 11 μmol), and CH_2Cl_2 (5 mL) at 40 °C for 2 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **269** (54 mg, 93%) as a yellow solid.

Analytical data for **269**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 5.30 (s, 1H), 4.90 (s, 1H), 4.20 (dt, *J* = 13.3, 4.2 Hz, 1H), 3.66 (ddd, *J* = 14.9, 12.3, 3.2 Hz, 1H), 3.16 (s, 3H), 2.79 (d, *J* = 13.4 Hz, 1H), 2.33 (s, 3H), 2.22 (td, *J* = 12.5, 4.7 Hz, 1H), 2.05 (d, *J* = 13.4 Hz, 1H), 1.45 (d, *J* = 13.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.2, 154.0, 141.7, 139.3, 128.4, 124.8, 123.4, 120.5, 109.1, 56.0, 42.8, 39.3, 37.8, 30.3, 16.1; HRMS (ESI): Mass calcd for $(C_{15}H_{18}N_2O_2S)H^+$ $[M+H]^+$: 291.1162; found: 291.1163.

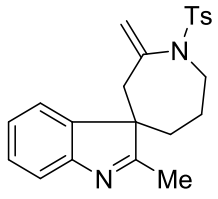


283

2'-methylene-1'-(methylsulfonyl)spiro[indole-3,4'-piperidine] (**283**): Prepared according to the general procedure using sulfonamide **282** (47 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5 μmol), Xantphos (6 mg, 11 μmol), DIPEA (39 mg,

0.3 mmol), and CH_2Cl_2 (5 mL) at 40 °C for 40 min. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **283** (34 mg, 60%) as a yellow solid.

Analytical data for **283**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.68 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.32 – 7.26 (m, 1H), 5.29 (s, 1H), 4.96 (s, 1H), 4.00 (ddd, *J* = 13.4, 6.9, 4.3 Hz, 1H), 3.80 (ddd, *J* = 13.3, 8.2, 4.1 Hz, 1H), 3.14 (s, 3H), 2.51 (d, *J* = 13.6 Hz, 1H), 2.46 (d, *J* = 13.6 Hz, 1H), 2.00 – 1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 154.7, 141.3, 140.2, 128.7, 126.4, 122.4, 121.7, 109.3, 56.3, 44.3, 39.6, 37.5, 30.0; HRMS (ESI): Mass calcd for $(C_{14}H_{16}N_2O_2S)H^+$ $[M+H]^+$: 277.1005; found: 277.1001.

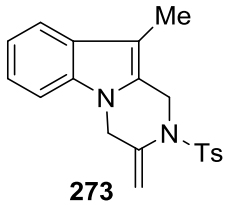


271

2'-methyl-2-methylene-1-tosylspiro[azepane-4,3'-indole] (**271**): Prepared according to the general procedure using sulfonamide **270** (68 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 µmol), Xantphos (6 mg, 11 µmol), and CH_2Cl_2 (5 mL) at 40 °C for 18 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **271** (40 mg, 52%) as a yellow solid.

Analytical data for **271**: ^{1}H NMR (500 MHz, $CDCl_3$): δ7.75 (d, *J* = 7.9 Hz, 2H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.22 (s, 1H), 4.69 (s, 1H), 4.04 (dt, *J* = 12.8, 4.7 Hz, 1H), 3.53 (ddd, *J* = 13.2, 10.3, 3.3 Hz, 1H), 2.46 (s, 3H), 2.36 (d, *J* = 13.7 Hz, 1H), 2.22 – 2.15 (m, 1H), 2.18 (s, 3H), 2.09 – 1.99 (m, 1H), 1.93 (d, *J* = 13.9 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.37 (dd, *J* = 14.1, 6.2 Hz, 1H); ^{13}C NMR (125 MHz,

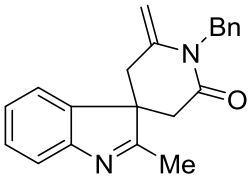
$CDCl_3$): δ 185.7, 154.1, 143.7, 142.3, 140.5, 129.6 (x2), 128.1, 127.4 (x3), 124.5, 124.2, 120.3, 115.1, 57.9, 48.9, 39.7, 33.8, 23.8, 21.5, 16.0; HRMS (ESI): Mass calcd for $(C_{22}H_{24}N_2O_2S)H^+$ $[M+H]^+$: 381.1631; found: 381.1629.



273

4a-methyl-3-methylene-2-tosyl-2,3,4,4a-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**273**): Prepared according to the general procedure using sulfonamide **272** (63 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), Xantphos (6 mg, 11 μmol), and CH_2Cl_2 (5 mL) at 40 °C for 18 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **273** (42 mg, 60%) as a white solid.

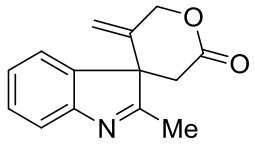
Analytical data for **273**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 5.56 (s, 1H), 5.11 (s, 1H), 4.93 (s, 2H), 4.42 (s, 2H), 2.26 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 136.4, 129.0 (x2), 128.3, 127.0 (x3), 126.4, 121.4, 119.3, 118.7, 109.1, 107.9, 106.0, 44.5, 43.4 (x2), 21.2, 8.2; IR (film) 1645, 1467, 1347, 1164, 1090, 730, 674, 547 cm^{-1}; HRMS (ESI): Mass calcd for $(C_{20}N_{20}N_2O_2S)H^+$ $[M+H]^+$: 353.1318; found: 353.1315.



275

1'-benzyl-2-methyl-2'-methylenespiro[indole-3,4'-piperidin]-6'-one (**275**): Prepared according to the general procedure using indole acetamide **274** (56 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5.0 µmol), Xantphos (6 mg, 11.0 µmol), NEt_3 (40 uL, 0.3 mmol), and CH_2Cl_2 (5.0 mL) at 40 °C for 24 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **275** (11 mg, 17%) as a yellow solid.

Analytical data for **275**: ^{1}H NMR (500 MHz, $CDCl_3$): δ7.56 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.28 (m, 6H), 7.16 – 7.09 (m, 2H), 5.19 (d, *J* = 15.3 Hz, 1H), 5.12 (d, *J* = 15.3 Hz, 1H), 4.61 (t, *J* = 1.5 Hz, 1H), 4.20 (s, 1H), 2.94 (d, *J* = 17.6 Hz, 1H), 2.86 (d, *J* = 14.5 Hz, 1H), 2.58 (dd, *J* = 17.6, 2.3 Hz, 1H), 2.38 (dd, *J* = 14.5, 2.2 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ182.5, 167.3, 153.8, 140.8, 140.2, 136.8, 128.7, 128.7 (x2), 127.4 (x2), 127.4, 125.6, 122.3, 120.5, 96.1, 46.5, 37.8, 36.7, 29.7, 16.2; HRMS (ESI): Mass calcd for $(C_{21}H_{20}N_2O)H^+$ $[M+H]^+$: 317.1648; found: 317.1649.

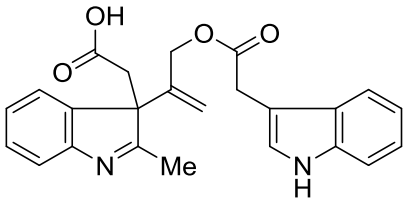


277

2-methyl-5'-methylene-5',6'-dihydrospiro[indole-3,4'-pyran]-2'(3'*H*)-one (**277**): Prepared according to the general procedure using indole acetic acid **276** (38 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 µmol), Xantphos (6 mg, 11 µmol), NEt_3 (30 mg, 0.3 mmol), and CH_2Cl_2 (5 mL) at 40 °C for 16 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **277** (24 mg, 52%) as a yellow oil.

Analytical data for **277**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.25 – 7.20 (m, 2H), 5.16 (s, 1H), 5.02 (d, *J* = 13.6 Hz, 1H), 5.02 (d, *J* = 13.6 Hz, 1H), 4.55

(d, *J* = 1.2 Hz, 1H), 2.81 (d, *J* = 15.3 Hz, 1H), 2.64 (d, *J* = 15.3 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.0, 154.1, 144.0, 137.8, 128.9, 126.5, 121.7, 120.6, 115.0, 71.2, 59.5, 35.6, 16.0; HRMS (ESI): Mass calcd for $(C_{14}H_{13}NO_2)H^+$ $[M+H]^+$: 228.1019; found: 228.1019.



278

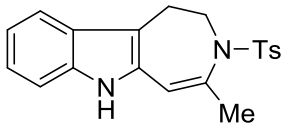
(*S*)-2-(2-methyl-3-(3-(2-(2-methyl-1*H*-indol-3-yl)acetoxy)prop-1-en-2-yl)-3*H*-indol-3-yl)acetic acid (**278**): Prepared according to the general procedure using indole acetic acid **276** (38 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), Xantphos (6 mg, 11 μmol), and CH_2Cl_2 (5 mL) at 23 °C for 18 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **278** (22.4 mg, 27%) as a yellow liquid.

Analytical data for **278**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.43 (m, 2H), 7.22 – 7.17 (m, 2H), 7.12 – 7.03 (m, 4H), 4.95 – 4.90 (m, 2H), 4.55 (s, 2H), 3.64 (s, 2H), 3.56 (s, 2H), 2.30 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 169.8, 150.0, 135.1, 132.9, 132.8, 128.4, 128.3, 121.3, 121.2, 119.6, 119.6, 118.0, 117.9, 110.3, 110.2, 105.1, 104.1, 103.7, 62.9, 30.2, 30.0, 11.6; IR (film): 3398, 3057, 2922, 1743, 1673, 1463, 1170, 742 cm^{-1}; HRMS (ESI): Mass calcd for $(C_{25}H_{24}N_2O_4)H^+$ $[M+H]^+$: 417.1809; found: 417.1808.

General Procedure for the Sigmatropic Rearrangement of Spiroindolenines

To a solution of indolenine (0.20 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (91 mg, 0.80 mmol). This was allowed to stir for 1 h at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with sat. aq. $NaHCO_3$ (10 mL) and brine. The organic

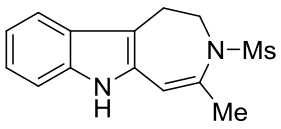
layer was concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired products.



281

4-methyl-3-tosyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole (**281**): Prepared according to the general procedure using sulfonamide **279** (63 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5 µmol), Xantphos (6 mg, 11 µmol), and CH_2Cl_2 (5 mL) at 40 °C for 4 h. After the reaction was cooled to ambient temperature, TFA (80 µL, 1.0 mmol) was added and the reaction was stirred at 23 °C for 1 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **281** (34 mg, 49% over two steps) as a yellow solid.

Analytical data for **281**: ^{1}H NMR (500 MHz, DMSO) δ 10.76 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.06 (s, 1H), 3.74 (br s, 2 H), 3.13 (t, *J* = 5.4 Hz, 2H), 2.32 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 143.3, 138.0, 136.8, 135.1, 130.3, 129.6 (x2), 128.2, 126.4 (x2), 121.6, 118.5, 117.9, 112.1, 111.4, 110.6, 48.2, 27.1, 22.4, 20.8; HRMS (ESI) calcd for $(C_{20}H_{20}N_2O_2S)H^+$: 353.1318, found: 353.1315.



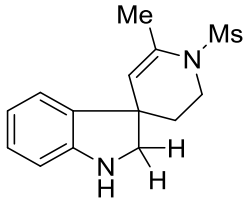
284

4-methyl-3-(methylsulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole (**284**): Prepared according to the general procedure using spiroindolenine **283** (30 mg, 0.11 mmol), CH_2Cl_2 (2

mL), and TFA (0.04 mL, 0.44 mmol) at 23 °C for 1 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **284** (25 mg, 83%) as a yellow solid.

Analytical data for **284**: ^{1}H NMR (500 MHz, ($CDCl_3$): δ 7.74 (br s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.11 (s, 1H), 3.79 (t, *J* = 5.6 Hz, 2H), 3.28 (t, *J* = 5.7 Hz, 2H), 2.82 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 137.3, 135.2, 130.4, 128.3, 121.7, 118.5, 118.0, 111.9, 111.3, 110.7, 47.6, 40.9, 27.0, 22.1; HRMS (ESI) calcd for $(C_{14}H_{16}N_2O_2S)H^+$: 277.1005, found: 277.1003.

Reduction of Spiroindolenine



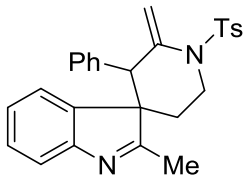
285

6'-methyl-1'-(methylsulfonyl)-2',3'-dihydro-1'*H*-spiro[indoline-3,4'-pyridine] (**285**): To a solution of spiroindolenine **283** (37 mg, 0.13 mmol) in MeOH (0.7 mL) was added $NaBH_4$ (6 mg, 0.15 mmol). This mixture was allowed to stir at 23 °C for 4 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (10 mL), brine, and dried over anh. $MgSO_4$. The organic layer was concentrated *in vacuo*. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **285** (30 mg, 78%) as a colorless liquid.

Analytical data for **285**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (tt, *J* = 7.7, 1.1 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.75 (tt, *J* = 7.4, 0.9 Hz, 1H), 6.69 – 6.65 (m, 1H), 5.01 (s, 1H), 3.97 – 3.89 (m, 1H), 3.76 (br s, 1H), 3.56 – 3.48 (m, 1H), 3.45 (d, *J* = 9.0 Hz, 1H), 3.29 (d, *J* = 9.0 Hz, 1H), 3.03 (s, 3H), 2.17 (s, 3H), 2.09 – 2.01 (m, 1H), 1.82 (ddd, *J* = 13.5, 9.8, 3.0 Hz, 1H); ^{13}C NMR (125

MHz, $CDCl_3$): δ 150.4, 135.6, 134.8, 128.1, 123.2, 119.1, 116.5, 110.0, 60.4, 45.5, 44.8, 40.7, 33.9, 22.6; HRMS (ESI) calcd for $(C_{14}H_{18}N_2O_2S)H^+$: 279.1162, found: 279.1162.

General Procedure for the Pd-catalyzed Spirocyclization of Indole-based Bis-nucleophiles. Tryptamine sulfonamide **8** (0.20 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5.0 µmol, 5 mol % Pd) and Xantphos (6 mg, 11 µmol) were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape or parafilm. The test tube was purged with N_2, anhydrous CH_2Cl_2 (5 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. After 15 min *tert*-butyl propargyl carbonate **5** (0.26 mmol) was added to the reaction mixture. After consumption of starting material as judged by TLC, the reaction was filtered through a pipet plug of Celite™ and concentrated. The residue was purified by flash column chromatography to give the desired products.

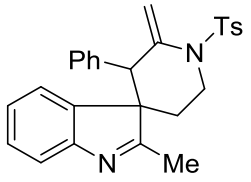


287

2-methyl-2'-methylene-3'-phenyl-1'-tosylspiro[indole-3,4'-piperidine] (**287**): Prepared according to the general procedure using sulfonamide **257** (66 mg, 0.20 mmol), propargyl carbonate **287** (60 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5.0 µmol), Xantphos (6 mg, 11.0 µmol), and anh. CH_2Cl_2 (5 mL) at 23°C for 24 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **287** (59 mg, 70%, 4:1 dr) as an off-white solid.

Analytical data for **287**: mp: 78-80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (major): 7.94 – 7.85 (m, 2H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.53 – 7.43 (m, 3H), 7.41 (td, *J* = 7.6, 1.1 Hz, 1H), 7.27 – 7.20 (m,

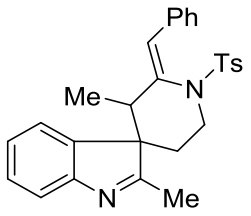
1H), 7.10 – 7.01 (m, 2H), 6.95 (t, *J* = 7.7 Hz, 2H), 6.29 (br s, 2H), 5.50 (d, *J* = 1.7 Hz, 1H), 4.53 (ddd, *J* = 14.6, 5.2, 2.0 Hz, 1H), 3.90 (ddd, *J* = 14.7, 13.4, 3.1 Hz, 1H), 3.43 (s, 1H), 2.53 (s, 3H), 2.19 (td, *J* = 13.3, 5.1 Hz, 1H), 1.91 (d, *J* = 0.9 Hz, 3H), 1.14 (ddd, *J* = 13.4, 3.2, 2.2 Hz, 1H). ^{13}C NMR analytical data and HRMS data match those reported below.



287

2-methyl-2'-methylene-3'-phenyl-1'-tosylspiro[indole-3,4'-piperidine] (**287**): Prepared according to the general procedure using sulfonamide **257** (66 mg, 0.20 mmol), propargyl carbonate **288** (60 mg, 0.26 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5.0 µmol), Xantphos (6 mg, 11.0 µmol), and anh. CH_2Cl_2 (5 mL) at 23°C for 18 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **287** (51 mg, 57%, 4.3:1 dr) as an off-white solid.

Analytical data for **287**: mp: 78-80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (major): 7.92 – 7.86 (m, 2H), 7.70 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.41 (td, *J* = 7.7, 1.1 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.09 – 7.00 (m, 2H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.29 (br s, 2H), 5.51 (d, *J* = 1.7 Hz, 1H), 4.60 (d, *J* = 1.9 Hz, 1H), 4.53 (ddd, *J* = 14.5, 5.2, 2.0 Hz, 1H), 3.90 (ddd, *J* = 14.6, 13.3, 3.1 Hz, 1H), 3.43 (s, 1H), 2.52 (s, 3H), 2.19 (td, *J* = 13.3, 5.2 Hz, 1H), 1.91 (s, 3H), 1.71 (dt, *J* = 14.4, 4.0 Hz, 1H), 1.14 (dt, *J* = 13.3, 2.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.2, 155.0, 154.9, 144.0, 143.9, 142.1, 139.6, 138.0, 135.2, 129.8, 129.6, 129.5, 128.7, 128.6, 128.3, 128.1, 128.0, 127.8, 127.6, 127.3, 127.2, 125.1, 124.7, 124.5, 121.0, 120.8, 120.0, 116.5, 60.8, 53.4, 51.5, 43.1, 43.1, 32.2, 32.2, 31.5, 29.7, 22.0, 21.6, 15.6; HRMS (ESI): Mass calcd for $(C_{27}H_{27}N_2O_2S)^+$ $[M+H]^+$: 443.1788; found: 443.1789.



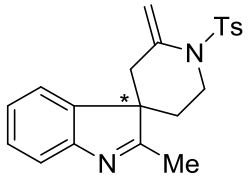
290

2'-benzylidene-1,3'-dimethyl-1'-tosylspiro[indoline-3,4'-piperidin]-2-one (**290**): Prepared according to the general procedure using sulfonamide **257** (66 mg, 0.20 mmol), propargyl carbonate **289** (64 mg, 0.26 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5.0 µmol), Xantphos (6 mg, 11.0 µmol), triethylamine (30 mg, 0.3 mmol) and anh. CH_2Cl_2 (5 mL) at 40°C for 24 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **290** (29.4 mg, 32%, 18:1 dr) as a pale-yellow oil.

Analytical data for **290**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, min), 7.55 (d, *J* = 7.6 Hz, 1H, maj), 7.52 (d, *J* = 8.3 Hz, 2H, maj), 7.40 (dd, *J* = 7.5, 2.0 Hz, 2H, maj), 7.34 (d, *J* = 7.4 Hz, 1H, maj), 7.33 – 7.29 (m, 1H, maj), 7.26 – 7.22 (m, *J* = 1.4 Hz, 2H, maj), 7.20 (d, *J* = 7.8 Hz, min), 7.11 (d, *J* = 8.4 Hz, 2H, maj), 7.05 (t, *J* = 7.5 Hz, 1H, maj), 6.96 (t, *J* = 7.5 Hz, min), 6.70 (d, *J* = 7.4 Hz, min), 6.48 (d, *J* = 7.7 Hz, min), 6.26 (s, 1H, maj), 5.45 (d, *J* = 7.0 Hz, min), 4.35 (dd, *J* = 5.0, 15.0 Hz, min), 4.28 (dd, *J* = 14.7, 3.5 Hz, 1H, maj), 3.79 – 3.71 (m, 1H, maj), 3.09 – 2.97 (m, 1H, maj), 2.65 (s, min), 2.57 (s, min), 2.42 – 2.32 (m, 1H, maj), 2.37 (s, 3H, maj), 2.15 (s, 3H, maj), 1.77 (dd, *J* = 6.9, 2.0 Hz, min), 1.13 (d, *J* = 13.3 Hz, 1H, maj), 0.53 (d, *J* = 6.7 Hz, 3H, maj); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.22, 155.03, 143.53, 139.24, 137.16, 136.40, 135.05, 129.29 (x2), 129.00 (x2), 128.63, 128.29 (x2), 128.25, 127.83 (x2), 127.58, 124.73, 123.82, 120.54, 63.00, 44.23, 38.88, 30.86, 21.45, 15.37, 11.94; HRMS (ESI): Mass calcd for $(C_{28}H_{29}N_2O_2S)^+$ $[M+H]^+$:457.1944; found: 457.1947.

General Procedure for the Enantioselective Pd-catalyzed Spirocyclization of Indole-Based Bis-Nucleophiles.

Tryptamine sulfonamide **257** (0.20 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5.0 µmol, 5 mol % Pd) and chiral ligand (11 µmol) were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape or parafilm. The test tube was purged with N_2, anhydrous CH_2Cl_2 (5 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. After 15 min *tert*-butyl propargyl carbonate **255** (0.26 mmol) was added to the reaction mixture. After consumption of starting material as judged by TLC, the reaction was filtered through a pipet plug of Celite™ and concentrated. The residue was purified by flash column chromatography to give the desired products.

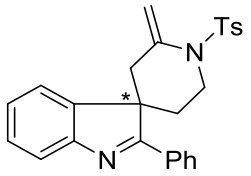


258

2-methyl-2'-methylene-1'-tosylspiro[indole-3,4'-piperidine] (**258**): Prepared according to the general procedure using tryptamine **257** (66 mg, 0.20 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5 µmol), 2,2'-Bis(di-2-(4-methylfuranyl)phosphino)-6,6'-dimethoxy-1,1'-biphenyl (6 mg, 11 µmol) and CH_2Cl_2 (5 mL) at ambient temperature for 16 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **258** (51 mg, 69%, 41% ee) as a white solid.

Analytical data (^{1}H NMR , ^{13}C NMR, and HRMS) match those previously reported in the document. A ^{1}H NMR spectrum is provided to demonstrate purity. Enantiomeric ratio was

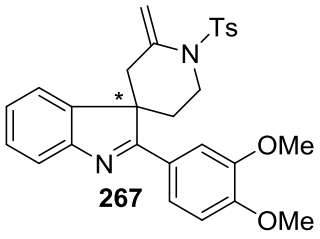
measured by HPLC (Chiralpak AD-H, 25% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 10.30, Rt_2 = 16.4).



265

2'-methylene-2-phenyl-1'-tosylspiro[indole-3,4'-piperidine] (**265**): Prepared according to the general procedure using tryptamine **264** (39 mg, 0.10 mmol), propargyl carbonate **255** (20 mg, 0.13 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (3 mg, 2.5 µmol), 2,2'-Bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (3 mg, 5.5 µmol), and anh. CH_2Cl_2 (2.5 mL) at ambient temperature for 18 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **265** (30 mg, 70%, 53% ee) as a white solid.

Analytical data (**(**^{1}H NMR ,^{13}C NMR, and HRMS) match those previously reported in the document. A ^{1}H NMR spectrum is provided to demonstrate purity. Enantiomeric ratio was measured by HPLC (Chiralcel OD-H, 2.5% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 34.8, Rt_2 = 38.2).



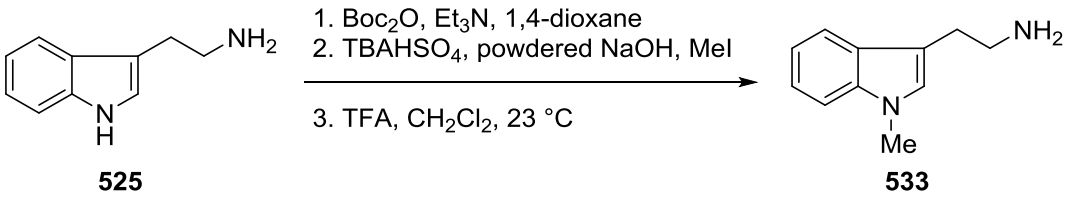
267

2-(3,4-dimethoxyphenyl)-2'-methylene-1'-tosylspiro[indole-3,4'-piperidine] (**267**): Prepared according to the general procedure using tryptamine **266** (45 mg, 0.10 mmol), propargyl carbonate **255** (20 mg, 0.13 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (3 mg, 2.5 µmol), 2,2'-Bis(di-2-(4-methylfuranyl)phosphino)-6,6'-dimethoxy-1,1'-biphenyl (3 mg, 5.5 µmol), and anh. CH_2Cl_2 (2.5

mL) at ambient temperature for 24 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **267** (36 mg, 73%, 77% ee) as a white solid.

Analytical data (^{1}H NMR , ^{13}C NMR, and HRMS) match those previously reported in the document. A ^{1}H NMR spectrum is provided to demonstrate purity. Enantiomeric ratio was measured by HPLC (Chiralcel AD-H, 10% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 24.3, Rt_2 = 57.4).

Preparation of *N*^{1}-alkyl Tryptamines and Tryptamine Derivatives:



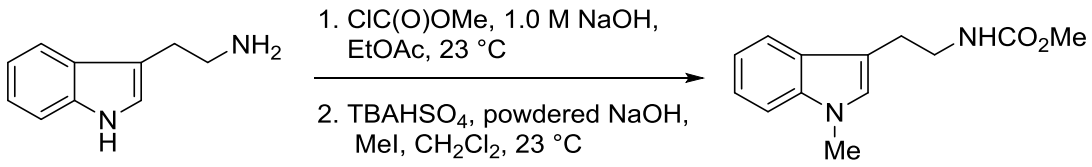
525 **533**

2-(1-methyl-1*H*-indol-3-yl)ethanamine (**533**) Step1: Prepared according to Feldman and co-workers.[32] To a 250-mL RBF was added tryptamine **525** (3.52 g, 22 mmol), 1,4-dioxane (18.3 mL), and Et_3N (6.13 mL, 44 mmol). A solution of Boc_2O (4.37 g, 20 mmol) in 1,4-dioxane (18.3 mL) was added dropwise via addition funnel over 10 min. After 18 h, the mixture was poured into a separatory funnel, diluted with CH_2Cl_2, and washed three times with 1.0 M aq. HCl. The organic layer was backextracted once with CH_2Cl_2, and the combined organic layers were washed once with brine, dried over anh. Na_2SO_4, and concentrated *in vacuo*. The dark red-brown residue was used without further purification. Step 2: Prepared according to Song and co-workers.[33] To a 250-mL RBF containing unpurified Boc-tryptamine was added CH_2Cl_2 (110 mL), $TBAHSO_4$ (1.49 g, 4.39 mmol), powdered NaOH (10.6 g, 26.5 mmol), and MeI (2.74 mL, 44 mmol). The mixture was stirred for 15 h, then diluted with water and stirred vigorously for 30 min. The organic layer was separated, washed three times with water, and backextracted once

[32] Feldman, K. S.; Ngernmeesri, P. *Org. Lett.* **2010**, *12*, 4502-4505.

with CH_2Cl_2. The combined organic layers were washed once with brine, dried over anh. Na_2SO_4, and concentrated *in vacuo*. Purified by flash column chromatography (20% EtOAc/Hexanes) to remove most of the $TBAHSO_4$. The resulting residue was used without further purification. Step 3: Prepared according to a modified procedure by Song and co-workers.[33] To a 500-mL RBF containing *N*-methyl Boc tryptamine was added CH_2Cl_2 (100 mL). This solution was cooled with an ice/water bath and a solution of 50/50 v/v TFA/CH_2Cl_2 (15.3 mL) was added dropwise over 30 min via an addition funnel. The reaction mixture was stirred for ten min at 0 °C, then the ice/water bath was removed and the reaction mixture was allowed to warm to ambient temperature. After 16.5 h, the reaction mixture was cooled with an ice/water bath and slowly neutralized with sat. aq. $NaHCO_3$. The resulting mixture was poured into a separatory funnel and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2, washed once with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford **533** (2.82 g, 82%) as a dark-brown solid foam.

Analytical data (^{1}H NMR and ^{13}C NMR) match those reported in the literature.[34] A ^{1}H NMR spectrum is provided to demonstrate purity.



525 **534**

methyl (2-(1*H*-indol-3-yl)ethyl)carbamate (**534**): Step 1: Prepared according to a procedure by Fong and Copp.**Error! Bookmark not defined.** To a mixture of tryptamine (3.20 g, 20 mmol) in

[33] Song, H.; Yang, J.; Chen, W.; Qin, Y. *Org. Lett.* **2006**, *8*, 6011-6014.
[34] Lygin, A. V.; de Meijere, A. *Eur. J. Org. Chem.* **2009**, 5138-5141.

EtOAc (40 mL) was added 1.0 M NaOH (25 mL) and methyl chloroformate (2 mL, 26 mmol). After 14 h at ambient temperature (23 °C), the reaction mixture was poured into a separatory funnel. The organic layer was separated, washed once with water, dried over anh. Na_2SO_4 and concentrated *in vacuo*. The residue was used without further purification. Step 2: Prepared according to Method B with tryptamine carbamate (20 mmol), CH_2Cl_2 (100 mL), $TBAHSO_4$ (1.36 g, 4 mmol), powdered NaOH (9.6 g, 400 mmol), and MeI (2.5 mL, 40 mmol) at ambient temperature for 19 h. After this time, analysis by TLC indicated that the reaction had not gone to completion. Additional powdered NaOH (9.6 g, 400 mmol) was added. TLC after an additional 9 h indicated that the reaction had gone to completion. The reaction mixture was diluted with water and poured into a separatory funnel. The organic layer as separated and washed twice with 1.0 M HCl. The organic layer was washed once with brine and dried over anh. Na_2SO_4. Purified by flash column chromatography (3→4% MeOH/CH_2Cl_2) to afford **534** (2.65 g, 57%) as a red-orange oil that solidified on standing.

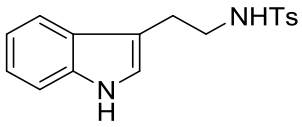
Analytical data (^{1}H NMR and ^{13}C NMR) match those reported in the literature.[35] A ^{1}H NMR spectrum is provided to demonstrate purity.

General Method for Preparation of C-3-Alkyl Sulfonamides.

To a solution of tryptamine (5 mmol) in anh. CH_2Cl_2 (8 mL) maintained under a positive pressure of nitrogen was added NEt_3 (10.0 mmol) and cooled to 0 °C. To the stirred solution was added tosyl or mesyl chloride (5.5 mmol) in one portion and the reaction was allowed to slowly warm to ambient temperature. The reaction was allowed to stir an additional 12 h. The solution was then diluted with CH_2Cl_2 (10 mL), washed with 10% aq. HCl (2 x 10 mL), aq. $NaHCO_3$ (15

[35] Yang, Y.; Jiang, X.; Qing, F. *J. Org. Chem.* **2012**, *77*, 7538-7547.

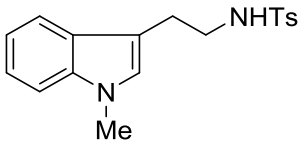
mL), and brine. The organic layer was passed through a plug of silica, which was washed with CH_2Cl_2 (3 x 15 mL). The combined organic portions were dried over anh. $MgSO_4$ or anh. Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired products.



279

***N*-(2-(1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide** (**279**): Prepared according to the general procedure using tryptamine (2.4 g, 15 mmol), CH_2Cl_2 (24 mL), Et_3N (2.3 mL, 16.5 mmol), and TsCl (3.43 g, 18 mmol) for 16 h at 0→rt. Purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford **279** (4.13 g, 88%) as a pale orange solid.

Analytical data (^{1}H NMR,^{13}C NMR) match those reported in the literature.[36] A ^{1}H NMR spectrum is provided to demonstrate purity.



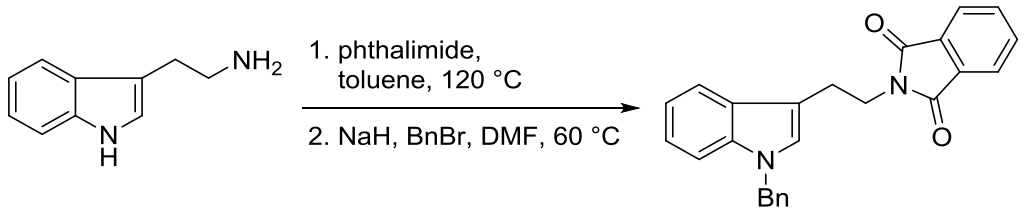
535

4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)benzenesulfonamide (**535**): Prepared according to the general procedure using tryptamine **279** (310 mg, 1.63 mmol), CH_2Cl_2 (8.2 mL), NEt_3 (450 µL, 3.3 mmol), and TsCl (370 mg, 2.0 mmol) for 12 h at ambient temperature. Purified by

[36] Priebbenow, D.; Henderson, L. C.; Pfeffer, F. M.; Sterwart, S. G. *J. Org. Chem.* **2010**, *75*, 1787–1790.

flash column chromatography (20 % EtOAc/Hexanes) to afford **535** (1.01 g, 62 % over two steps) as a yellow oil.

Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) match those reported in the literature.[37] A ^{1}H NMR spectrum is provided to demonstrate purity.



525 **536**

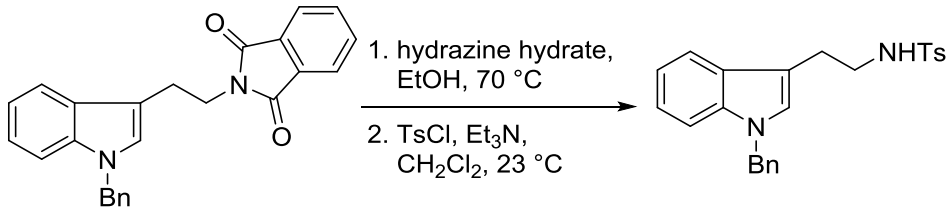
***N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide 536:**

Step 1: Prepared according to a procedure by Feng and coworkers.[20] To a 250-mL RBF was added tryptamine (4.81 g, 30 mmol), phthalic anhydride (4.58 g, 30.9 mmol), and toluene (176 mL). The RBF was fitted with a reflux condenser and brought to reflux. After 13 h, the reaction mixture was cooled and concentrated *in vacuo*. Purified by trituration from CH_2Cl_2 and Hexanes to afford tryptamine phthalimide (7.77 g, 89%) as a light-yellow solid after three triturations. Analytical data (^{1}H NMR, ^{13}C NMR) match those reported in the literature.[20] A ^{1}H NMR spectrum is provided to demonstrate purity. HRMS (ESI) calcd for $(C_{18}H_{15}N_2O_2)^+$ $[M+H]^+$: 291.1128, found: 291.1129.

Step 2: Prepared according to Zhai and coworkers.[38] To a suspension of 60% w/w NaH (488 mg, 12.2 mmol) in DMF (87 mL) was added a solution of tryptamine phthalimide (2.61 g, 6.12 mmol) in DMF (44 mL). Benzyl bromide (2.5 mL, 20.8 mmol) was added to the mixture, which

[37] Lozano, O.; Blessley, G.; Martinez del Campo, T.; Thompson, A. L.; Giuffred, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 8105-8109.
[38] Liu, Y.; Luo, S.; Fu, X.; Fang, Zhuang, Z.; Xiong, W.; Jia, Z.; Zhai, H. *Org. Lett.* **2006**, *8*, 115-118.

was then heated at 60 °C for 14.5 h. At this point, TLC indicated incomplete consumption of starting material, so additional NaH (488 mg, 12.2 mmol) was added. After an additional 2 h, the reaction was cooled to ambient temperature. The mixture was poured over $NaHCO_3$, into EtOAc, washed five times with water, once with brine, and dried over anh. Na_2SO_4. The orange-sherbert-colored solid was used without further purification.

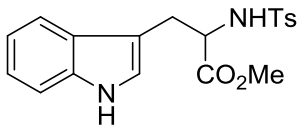


536 **537**

Step 3: The protected tryptamine (6.12 mmol) was dissolved in EtOH (100 mL) and heated to 70 °C. After 10 min, 50-60% hydrazine hydrate (1.9 mL) added. After 18.5 h, the mixture was cooled to ambient temperature and filtered through a cotton plug. The filtrate was diluted with 1.0 M aq. NaOH and extracted three times with 4:1 $CHCl_3$/*i*-PrOH and dried over anh. Na_2SO_4. The solvent was concentrated to afford a light yellow oil, which was used without further purification. Step 4: Prepared according to the general procedure using unpurified tryptamine precursor (6.12 mmol), CH_2Cl_2 (9.9 mL), NEt_3 (938 µL, 6.73 mmol), and TsCl (1.4 g, 7.34 mmol) for 17.5 h at ambient temperature. Purified by flash column chromatography (30→40% EtOAc/Hexanes) to afford **537** (2.05 g, 83% over two steps) as an off-white solid.

Analytical data for **537**: mp: 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.28 – 7.24 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.19 – 7.16 (m, 1H), 7.10 (d, *J* = 6.8 Hz, 2H), 7.05 (ddd, *J* = 7.8, 7.0, 1.0 Hz, 1H), 6.86 (s, 1H), 5.25 (s, 2H), 4.33 (t, *J* = 6.1 Hz, 1H), 3.28 (q, *J* = 6.5 Hz, 2H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.39 (s, 3H);

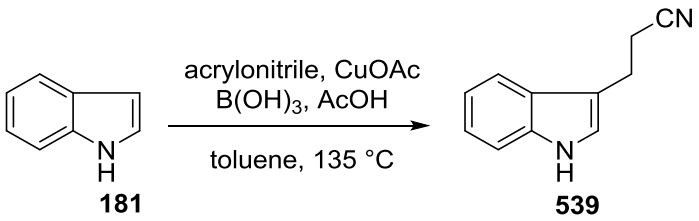
^{13}C NMR (125 MHz, $CDCl_3$): δ 143.0, 137.3, 136.8, 136.6, 129.4 (x2), 128.5 (x2), 127.5, 127.4, 126.8 (x2), 126.7 (x2), 126.4, 121.7, 119.0, 118.6, 110.7, 109.7, 49.7, 43.1, 25.3, 21.3; HRMS (ESI) calcd for $(C_{24}H_{25}N_2O_2S)^+$ $[M+H]^+$: 405.1631, found: 405.1624.



538

methyl 3-(1*H*-indol-3-yl)-2-(4-methylphenylsulfonamido)propanoate (**538**): Prepared according to the general procedure using (*L*)-tryptophan methyl ester hydrochloride (2.0 g, 7.9 mmol), CH_2Cl_2 (15.7 mL), Et_3N (3.3 mL, 23.6 mmol), and TsCl (1.65 g, 8.6 mmol) for 12 h at ambient temperature. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **538** (2.05 g, 70%) as a white powder.

Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) match those reported in the literature.[39] A ^{1}H NMR spectrum is provided to demonstrate purity.



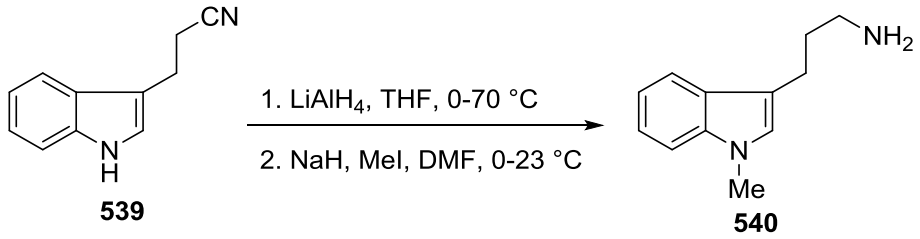
181 **539**

4-methyl-*N*-(3-(1-methyl-1*H*-indol-3-yl)propyl)benzenesulfonamide (**539**): Step 1: Prepared according to a modified procedure by Kuehne and coworkers.[40] To a 20-mL Ace Glass pressure tube was added indole (4.69 g, 40 mmol), acrylonitrile (4.4 mL, 66.8 mmol), $Cu(OAc)_2$ (80 mg, 0.4 mmol), $B(OH)_3$ (25 mg, 0.4 mmol), and toluene (2.9 mL). The vessel was sealed and heated

[39] Priebbenow, D.; Sterwart, S. G.; Pfeffer, F. M.; *Tetrahedron Lett.*, **2012**, *53*, 1468-1471.
[40] Kuehne, M.; Cowen, S. D.; Zu, F.; Borman, L. S. *J. Org. Chem.* **2001**, *66*, 5303-5316.

to 135 °C behind a blast shield. After 48 h, the reaction was cooled to ambient temperature. The reaction mixture was poured into a separatory funnel, diluted with water, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over anh. Na_2SO_4. Purified by flash column chromatography (10→20% EtOAc/Hexanes) to afford the nitrile (4.24 g, 62%) an off-white solid.

Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) matched those reported in the literature.[41] A ^{1}H NMR spectrum is provided to demonstrate purity.

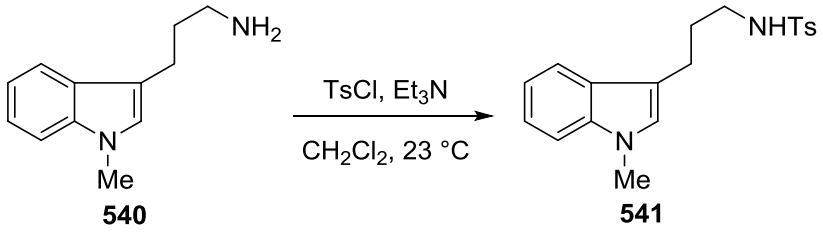


539 **540**

Step 2 [**3-(1*H*-indol-3-yl)propan-1-amine**]: Prepared according to a modified procedure by Kuehne and coworkers.[40] To a 200 mL RBF fitted with a reflux condenser under a positive pressure of nitrogen was added lithium aluminum hydride (25.9 mL of 1.0 M solution in THF, 25.9 mmol) and cooled to 0 °C. A solution of the nitrile (2.0 g, 11.8 mmol) in THF (35.6 mL) was added to the cooled reaction flask dropwise via cannula over 10 minutes. The reaction flask was then warmed to room temperature, heated to reflux using an oil bath and allowed to reflux for 5 h. The reaction mixture was then allowed to cool to room temperature and was worked up using the Fieser method. The resulting residue was purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford the amine (1.05 g, 51% yield) as yellow oil. The oil was used without further purification.

[41] Pedras, M. S. C.; Minic, Z.; Thongbam, P. D.; Bhaskar, V.; Montaut, S. *Phytochemistry* **2010**, *71*, 1952-1962.

Step 3 [**3-(1-methyl-1*H*-indol-3-yl)propan-1-amine** (**540**)]: Prepared according to a modified procedure by Meijere and coworkers.[34] To a solution of the crude amine (0.42 g, 2.4 mmol) in DMF (6 mL) 60% w/w NaH (116 mg, 2.9 mmol) was added portion-wise over 5 minutes. This was allowed to stir at ambient temperature for 30 minutes under a positive pressure of nitrogen. To the stirring solution was added a solution of MeI (0.18 mL, 2.9 mmol) in DMF (6 mL) dropwise over 15 minutes. The resulting solution was allowed to stir for an additional 18 h. The reaction solution was poured into water and diluted with CH_2Cl_2. The organic layer was separated and washed 5 times with H_2O, once with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/Hexanes) to afford the alkylated homotryptamine (0.31 g, 68%) as a pale-yellow oil.



540 **541**

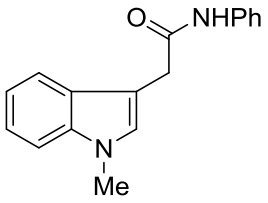
Step 4 **[4-methyl-*N*-(3-(1-methyl-1H-indole-3-yl)propyl)benzenesulfonamide 541:** Prepared according to the general procedure using the homotryptamine precursor (0.23 g, 1.2 mmol), CH_2Cl_2 (2.4 mL), Et_3N (0.2 mL, 1.44 mmol), and TsCl (0.27 g, 1.44 mmol) for 18 h at ambient temperature. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **541** (0.23 g, 59%) as a yellow oil.

Analytical data for **541**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.46 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.31 – 7.24 (m, 3H), 7.21 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.07 (ddt, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.76 (s, 1H), 4.41 (br s, 1H), 3.72 (s, 3H), 3.01 (q, *J* = 6.6 Hz, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.41 (s, 3H), 1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 137.0, 129.6 (x2),

127.6, 127.1 (x3), 126.4, 121.5, 118.7, 118.6, 113.3, 109.2, 42.8, 32.5, 29.9, 21.9, 21.5; HRMS (ESI) calcd for $(C_{19}H_{23}N_2O_2S)^+$ $[M+H]^+$: 343.1475, found: 343.1475.

General Method for Preparation of Indole 3-Acetamides.

To a 100-mL RBF was added indole acetic acid and CH_2Cl_2. Et_3N was added, then EDCI. The mixture was allowed to stir for a few min, and then the amine was added. Upon consumption of starting material, the reaction was diluted with water. The mixture was poured into a separatory funnel and washed with 1.0 M NaOH several times, brine, and dried over anh. Na_2SO_4. The residue was purified by flash column chromatography to give the desired products.

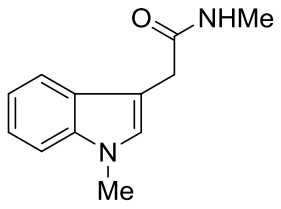


542

2-(1-methyl-1*H*-indol-3-yl)-*N*-phenylacetamide (**542**): Prepared according to the general procedure using 1-methyl-3-indoleacetic acid (1.89 g, 10 mmol), CH_2Cl_2 (33 mL), NEt_3 (3.1 mL, 22 mmol), EDCI (2.3 g, 12 mmol), and aniline (1 mL, 11 mmol) for 15 h at ambient temperature. Purified by flash column chromatography (0→2% MeOH/CH_2Cl_2) to afford **542** (1.20 g, 45%) as a tan solid.

Analytical data (^{1}H NMR and ^{13}C NMR) match those reported in the literature.[42] A ^{1}H NMR spectrum is provided to demonstrate purity.

[42] Shao, J.; Huang, X.; Wang, S.; Liu, B.; Xu, B. *Tetrahedron* **2012**, *68*, 573-579.



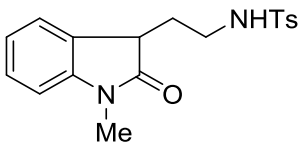
543

***N*-methyl-2-(1-methyl-1*H*-indol-3-yl)acetamide** (**543**): Prepared according to the general procedure using 1-methyl-3-indoleacetic acid (1.89 g, 10 mmol), CH_2Cl_2 (33 mL), NEt_3 (3.1 mL, 22 mmol), EDCI (2.3 g, 12 mmol), and $MeNH_2$ (5.5 mL, 2.0 M in THF) for 18 h at ambient temperature. Purified by flash column chromatography (5→30% MeOH/CH_2Cl_2) to afford **543** (1.06 g, 52%) as an orange-brown solid.

Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) match those reported in the literature.[43] A ^{1}H NMR spectrum is provided to demonstrate purity.

General Procedure for Indole Oxidation.

To a solution of tryptamine in DMSO at ambient temperature (23 °C) was added 12.1 M HCl dropwise. After the oxidation was completed, the reaction mixture was neutralized with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and dried over anh. $MgSO_4$ or anh. Na_2SO_4. The organic extract was then concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired products.

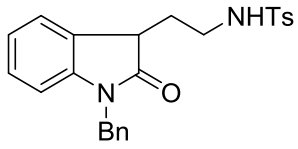


303

[43] Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815-10818.

4-methyl-*N*-(2-(1-methyl-2-oxoindolin-3-yl)ethyl)benzenesulfonamide (**303**): Prepared according to the general procedure using sulfonamide **535** (320 mg, 1.0 mmol), DMSO (1.7 mL 24.3 mmol), and 12.1 M HCl (3.4 mL, 41.6 mmol) at ambient temperature. Methanol (1 mL) to keep solids solubilized. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **303** (170 mg, 55%) as a white solid.

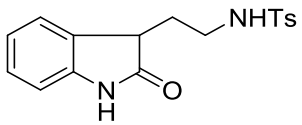
Analytical data for **303**: mp: 132-133 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 5.52 (br s, 1H), 3.45 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.26 (ddd, *J* = 12.8, 7.1, 5.6 Hz, 1H), 3.22 – 3.11 (m, 1H), 3.19 (s, 3H), 2.42 (s, 3H), 2.25 – 2.16 (m, 1H), 1.91 (dddd, *J* = 14.3, 8.8, 7.1, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 143.9, 143.1, 137.2, 129.6, 128.2 (x2), 128.2, 127.0 (x2), 123.6, 122.7, 108.2, 43.5, 40.9, 30.3, 26.2, 21.4.; HRMS (ESI) calcd for $(C_{18}H_{21}N_2O_3S)^+$ $[M+H]^+$: 345.1267, found: 345.1253.



305

***N*-(2-(1-benzyl-2-oxoindolin-3-yl)ethyl)-4-methylbenzenesulfonamide** (**305**): Prepared according to the general procedure using sulfonamide **537** (331 mg, 0.82 mmol), DMSO (291 µL, 4.09 mmol), and 12.1 M HCl (676 µL, 8.18 mmol) at ambient temperature for 24 h. Analysis by TLC indicated reaction was not yet complete, so additional DMSO (291 µL, 4.09 mmol) and 12.1 M HCl (676 µL, 8.18 mmol) were added to the reaction mixture, which was stirred for an additional 10 h. Purified by flash column chromatography (40% EtOAc/Hexanes) to afford **305** (279 mg, 81%) as an off-white solid.

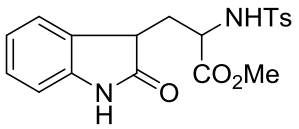
Analytical data for **305**: mp: 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.23 (m, 7H), 7.22 – 7.13 (m, 2H), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H), 6.76 – 6.68 (m, 1H), 5.57 – 5.46 (m, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 4.85 (d, *J* = 15.6 Hz, 1H), 3.55 (dd, *J* = 8.7, 5.1 Hz, 1H), 3.37 – 3.25 (m, 1H), 3.20 (ddt, *J* = 12.8, 7.1, 5.7 Hz, 1H), 2.42 (s, 3H), 2.25 (ddt, *J* = 14.4, 7.1, 5.5 Hz, 1H), 1.95 (dddd, *J* = 14.0, 8.5, 7.0, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 143.0, 142.9, 137.1, 135.6, 129.5 (x2), 128.6 (x2), 128.1, 128.0, 127.5, 127.1 (x2), 126.9 (x2), 123.8, 122.6, 109.1, 43.6, 43.2, 40.6, 30.5, 21.3; HRMS (ESI) calcd for $(C_{24}H_{22}N_2O_2SNa)^+$ $[M–H_2O+Na]^+$: 425.1300, found: 425.1300.



307

4-methyl-*N*-(2-(2-oxoindolin-3-yl)ethyl)benzenesulfonamide (**307**): Prepared according to the general procedure using sulfonamide **279** (1.12 g, 3.56 mmol), DMSO (909 µL, 12.8 mmol), and 12.1 M HCl (1.06 mL, 12.8 mmol) at ambient temperature for 22 h. Purified by flash column chromatography (10% MeOH/CH_2Cl_2) to afford **307** (768 g, 65%) as a light purple solid.

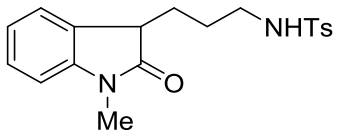
Analytical data for **307**: mp 160-161 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.39 (s, 1H), 7.69 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 3.43 (t, *J* = 6.7 Hz, 1H), 3.35 (br s, 1 H), 2.93 – 2.81 (m, 2H), 2.38 (s, 3H), 1.91 (ddt, *J* = 13.3, 8.8, 6.7 Hz, 1H), 1.81 (ddt, *J* = 13.3, 8.5, 6.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 178.5, 142.6, 142.5, 137.5, 129.6 (x2), 129.1, 127.7, 126.4 (x2), 123.8, 121.2, 109.2, 42.5, 40.0, 30.3, 20.9; HRMS (ESI) calcd for $(C_{17}H_{18}N_2O_3S)^+$ $[M+H]^+$: 331.1111, found: 331.1094.



309

methyl 3-(1-methyl-2-oxoindolin-3-yl)-2-(4-methylphenylsulfonamido)propanoate (**309**): Prepared according to the general procedure using sulfonamide **538** (1.9 g, 5.0 mmol), DMSO (8.5 mL, 120 mmol), and 12.1 M HCl (17 mL, 205 mmol) at ambient temperature for 12 h. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **309** (1.3 g, 66%) as a white solid.

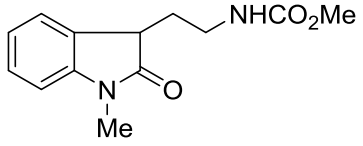
Analytical data for **309**: mp: 97-98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (br s, min), 8.59 (br s, maj), 7.78 (d, J = 8.2 Hz, maj), 7.64 (d, J = 8.2 Hz, min), 7.33 (d, J = 7.5 Hz, min), 7.30 (d, J = 8.0 Hz, maj), 7.23 (d, J = 6.7 Hz, 2H), 7.20 (d, J = 7.0 Hz, 2H), 7.08 – 7.02 (m, 2H), 6.90 (d, J = 7.8 Hz, maj), 6.87 (d, J = 7.7 Hz, min), 6.41 (d, J = 10.1 Hz, min), 6.15 (d, J = 8.8 Hz, maj), 4.30 (td, J = 9.1, 5.0 Hz, maj), 4.22 (td, J = 9.9, 4.2 Hz, min), 3.72 – 3.66 (m, 1H), 3.62 (dd, J = 7.9, 3.3 Hz, 1H), 3.46 (s, maj), 3.43 (s, min), 2.41 (s, maj), 2.38 (s, min), 2.33 (ddd, J = 14.4, 9.2, 3.7 Hz, maj), 2.19 (ddd, J = 14.1, 8.2, 4.9 Hz, min); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 171.4, 143.6, 143.3, 141.8, 141.3, 137.0, 136.7, 129.6, 129.4, 128.8, 128.3, 128.2, 127.3, 127.1, 124.4, 123.8, 122.6, 122.4, 110.3, 110.1, 53.9, 53.7, 52.4, 52.3, 42.7, 42.2, 34.1, 32.4, 21.5, 21.4; HRMS (ESI) calcd for $(C_{19}H_{21}N_2O_5S)^+$ $[M+H]^+$: 389.1166, found: 389.1159.



311

4-methyl-*N*-(3-(1-methyl-2-oxoindolin-3-yl)propyl)benzenesulfonamide (**311**): Prepared according to the general procedure using unpurified tryptamine **541** (0.23 g, 0.67 mmol), DMSO (1.2 mL, 16.1 mmol), and 12.1 M HCl (2.3 mL, 27.5 mmol) at ambient temperature for 12 h. Purified by flash column chromatography (50% EtOAc/Hexanes) to afford **311** (0.16 g, 68%) as a brown solid.

Analytical data for **311**: mp: 129-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.24 (m, 3H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.85 (t, *J* = 6.2 Hz, 1H), 3.42 (t, *J* = 6.0 Hz, 1H), 3.16 (s, 3H), 2.99 – 2.84 (m, 2H), 2.42 (s, 3H), 2.02 – 1.84 (m, 2H), 1.61 – 1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 144.2, 143.2, 137.0, 129.6 (x2), 128.5, 128.0, 127.0 (x2), 123.7, 122.5, 108.0, 44.7, 42.9, 27.3, 26.1, 25.8, 21.5; HRMS (ESI) calcd for $(C_{19}H_{23}N_2O_3S)^+$ $[M+H]^+$: 359.1424, found: 359.1408.

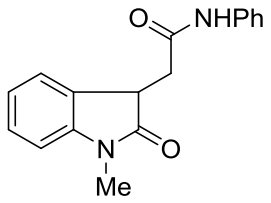


313

methyl (2-(1-methyl-2-oxoindolin-3-yl)ethyl)carbamate (**313**): Prepared according to the general procedure using tryptamine **354** (1.43 g, 6.16 mmol), DMSO (2.2 mL, 30.8 mmol), and 12.1 M HCl (5.1 mL, 61.6 mmol) at ambient temperature for 21 h. Purified by flash column chromatography (40→50% EtOAc/Hexanes), followed by trituration with CH_2Cl_2/Et_2O to afford **313** (515 mg, 34%) as a light gray powder.

Analytical data for **313**: mp: 98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.27 (m, 2H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.27 (br s, 1H), 3.65 (s, 3H), 3.48 (t, *J* = 6.7 Hz, 1H), 3.46 – 3.34 (m, 2H), 3.21 (s, 3H), 2.25 – 2.16 (m, 1H), 2.03 (dt, *J* = 14.0, 7.1 Hz, 1H);

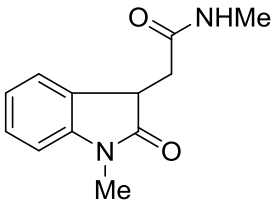
^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 157.0, 144.0, 128.5, 128.0, 123.8, 122.6, 108.0, 51.9, 43.4, 38.5, 30.6, 26.1; HRMS (ESI) calcd for $(C_{13}H_{17}N_2O_3)^+$ [M +H]$^+$: 249.1234, found: 249.1232.



315

2-(1-methyl-2-oxoindolin-3-yl)-*N*-phenylacetamide (**315**): Prepared according to the general procedure using tryptamine **542** (1.02 g, 3.86 mmol), DMSO (1.4 mL, 19.3 mmol), and 12.1 M HCl (3.2 mL, 38.6 mmol) at ambient temperature for 16 h. Purified by flash column chromatography (2.5% MeOH/CH_2Cl_2) to afford **315** (849 mg, 79%) as a straw-colored solid.

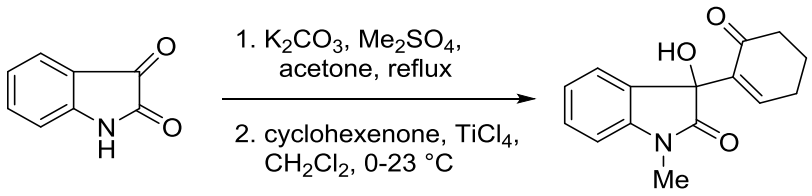
Analytical data for **315**: mp: 58-59 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.06 (br s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.29 (m, 4H), 7.16 – 7.06 (m, 2H), 6.87 (d, *J* = 7.7 Hz, 1H), 3.96 (t, *J* = 6.7 Hz, 1H), 3.27 (s, 3H), 3.05 (dd, *J* = 15.8, 7.8 Hz, 1H), 2.79 (dd, *J* = 15.7, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 168.6, 143.7, 138.1, 128.9 (x2), 128.3, 128.1, 124.2, 124.1, 123.0, 119.9 (x2), 108.2, 42.2, 38.4, 26; HRMS (ESI) calcd for $(C_{17}H_{14}N_2ONa)^+$ [M–H_2O+Na]$^+$: 285.1004, found: 285.1015.



317

***N*-methyl-2-(1-methyl-2-oxoindolin-3-yl)acetamide** (**317**): Prepared according to the general procedure using indole acetamide **543** (1.06 g, 5.24 mmol), DMSO (1.9 mL, 26.2 mmol), and 12.1 M HCl (4.4 mL, 52.4 mmol) at ambient temperature for 26.5 h. Purified by flash column chromatography (5→10% MeOH/CH_2Cl_2) to afford **317** (589 mg, 52%) as a pale-yellow powder.

Analytical data for **317**: mp: 157-158 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.30 (t, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.52 (br s, 1H), 3.87 (t, *J* = 6.8 Hz, 1H), 3.23 (s, 3H), 2.91 – 2.83 (m, 1H), 2.87 (d, *J* = 4.7 Hz, 3 H), 2.58 (dd, *J* = 15.5, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 170.7, 143.8, 128.4, 128.1, 124.1, 122.6, 108.0, 42.2, 37.0, 26.3, 26.2; HRMS (ESI) calcd for $(C_{12}H_{15}N_2O_2)^+$ $[M+H]^+$: 219.1128, found: 219.1129.

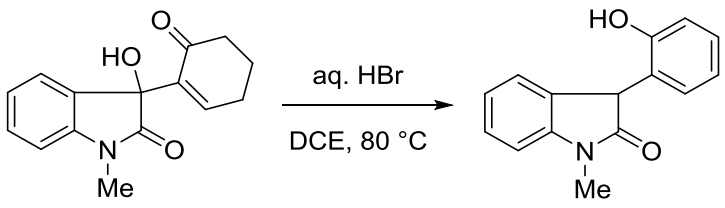


544 **545**

Step 1 **3-hydroxy-1-methyl-3-(6-oxocyclohex-1-en-1-yl)indolin-2-one** (**545**)]: Prepared according to a procedure by Basavaiah and co-workers.[44] To a 250-mL RBF was added isatin **544** (2.94 g, 20 mmol), Na_2CO_3 (5.30 g, 50 mmol), acetone (100 mL), and Me_2SO_4 (2.85 mL, 30 mmol). The RBF was fitted with a reflux condenser and heated at reflux for 42.5 h. After cooling to ambient temperature, the bright-orange suspension was vacuum-filtered and the filtrate was concentrated. Purified by flash column chromatography (0→2.5% EtOAc/Hexanes) to afford methyl isatin (2.92 g) as a bright red-orange oil that consisted of a mixture of product and some Me_2SO_4. The residue was used without further purification.

[44] Basavaiah, D.; Roy, S.; Das, U. *Tetrahedron* **2010**, *66*, 5612-5622.

Step 2: The 100-mL RBF containing the aforementioned methyl isatin was purged with N_2 and anh. CH_2Cl_2 (20 mL) and cyclohexenone (1.94 mL, 20 mmol) were added. The mixture was cooled with an ice/water bath and $TiCl_4$ (20 mL, 1.0 M in CH_2Cl_2) was added. The reaction was allowed to warm to ambient temperature. After 3.5 h, the reaction mixture was cooled with an ice/water bath and quenched with water, extracted three times with CH_2Cl_2, and dried over anh. Na_2SO_4, The combined organic layers were reduced *in vacuo*. Purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford the hydroxyoxindole (1.68 g, 33% over two steps) as a light-yellow solid foam. A ^{1}H NMR spectrum is provided to demonstrate purity.



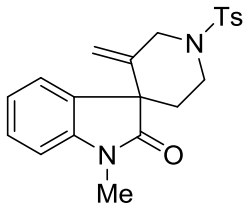
545 **319**

Step 3 **3-(2-hydroxyphenyl)-1-methylindolin-2-one** (**319**): To a 100-mL RBF containing the hydroxyoxindole (852 mg, 3.31 mmol) was added 1,2-dichloroethane (3.3 mL) and 48% aq. HBr (1.9 mL). The reaction mixture was refluxed for 15.5 h, then cooled to ambient temperature. The reaction mixture was diluted with water, extracted three times with CH_2Cl_2, and the combined organic layers were dried over anh. Na_2SO_4 and concentrated *in vacuo*. Purified by flash column chromatography (50-75% EtOAc/Hexanes) to afford **319** (551 mg, 70%) as an off-white solid.

Analytical data (^{1}H NMR and ^{13}C NMR) match those reported in the literature.[44] A ^{1}H NMR spectrum is provided to demonstrate purity.

General Procedure for the Pd-catalyzed Spirocyclization of Oxindole-based Bis-nucleophiles.

Oxindole substrate 6 (0.20 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5.0 µmol, 5 mol % Pd) and dppb (5 mg, 11 µmol) were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape or parafilm. The test tube was purged with N_2, anhydrous THF (2 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. The reaction was either heated or maintained at ambient temperature (23 °C) as indicated. After 15 min the propargyl *tert*-butyl carbonate 5 (0.30 mmol) was added to the reaction mixture. After consumption of starting material as judged by TLC, the reaction mixture was filtered through a pipet plug of Celite™ and concentrated. The residue was purified by flash column chromatography to give the desired products.

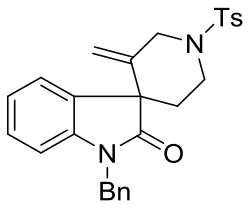


304

1-methyl-3'-methylene-1'-tosylspiro[indoline-3,4'-piperidin]-2-one (**304**): Prepared according to the general procedure using oxindole **303** (69 mg, 0.20 mmol), propargyl carbonate **255** (47 mg, 0.30 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2 mg, 2 µmol), dppb (2 mg, 4.4 µmol), and anh. THF (2 mL) at ambient temperature for 20 min. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **304** (75 mg, 98%) as a white solid.

Analytical data for **304**: mp: 194 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.72 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.31 (ddd, *J* = 8.1, 6.9, 2.1 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.06 (s, 1H), 4.55 (s, 1H), 4.28 (dd, *J* = 12.8, 1.7 Hz, 1H), 3.88 (d, *J* = 12.7 Hz, 1H), 3.79 (dq, *J* = 9.8, 2.4 Hz, 1H), 3.42 (td, *J* = 12.4, 2.9 Hz, 1H), 3.10 (s, 3H), 2.46 (s, 3H), 2.19 (td,

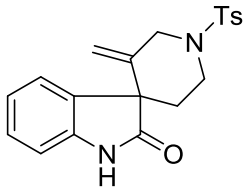
J = 13.2, 4.8 Hz, 1H), 1.78 (dt, *J* = 13.7, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ176.7, 143.5, 143.2, 139.3, 133.7, 130.5, 129.7 (x2), 128.5, 127.7 (x2), 124.3, 122.7, 114.2, 108.3, 51.1, 49.6, 41.6, 34.0, 26.0, 21.5; HRMS (ESI): Mass calcd for $(C_{21}H_{23}N_2O_3S)^+$ $[M+H]^+$: 383.1424; found: 383.1429.



306

1-benzyl-3'-methylene-1'-tosylspiro[indoline-3,4'-piperidin]-2-one (**306**): Prepared according to the general procedure using oxindole **305** (84 mg, 0.20 mmol), propargyl carbonate **255** (47 mg, 0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), dppb (5 mg, 11 μmol) and anh. THF (2 mL) at ambient temperature for 30 min. Purified by flash column chromatography (20→30% EtOAc/Hexanes) to afford **306** (85 mg, 92%) as a white solid foam.

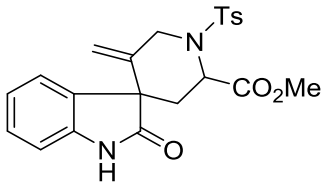
Analytical data for **306**: mp: 158-159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.73 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.21 (m, 3H), 7.18 (td, *J* = 7.6, 1.6 Hz, 1H), 7.16 – 7.12 (m, 2H), 7.12 – 7.04 (m, 2H), 6.71 (d, *J* = 7.8 Hz, 1H), 5.10 (s, 1H), 4.83 (d, *J* = 15.8 Hz, 1H), 4.74 (d, *J* = 15.8 Hz, 1H), 4.59 (s, 1H), 4.32 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.91 (d, *J* = 12.7 Hz, 1H), 3.83 (ddt, *J* = 11.9, 4.6, 2.2 Hz, 1H), 3.46 (td, *J* = 12.3, 2.8 Hz, 1H), 2.45 (s, 3H), 2.25 (ddd, *J* = 13.9, 12.7, 4.9 Hz, 1H), 1.85 (dt, *J* = 13.8, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 176.8, 143.6, 142.3, 139.4, 135.5, 133.6, 130.5, 129.7 (x2), 128.7 (x2), 128.4, 127.7 (x2), 127.5, 126.7 (x2), 124.4, 122.8, 114.5, 109.3, 51.0, 49.7, 43.1, 41.7, 34.0, 21.5; HRMS (ESI): Mass calcd for $(C_{27}H_{26}N_2O_3SNa)^+$ $[M+Na]^+$: 481.1556; found: 481.1557.



308

3'-methylene-1'-tosylspiro[indoline-3,4'-piperidin]-2-one (**308**): Prepared according to the general procedure using oxindole **307** (66 mg, 0.20 mmol), propargyl carbonate **255** (47 mg, 0.30 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5 µmol), dppb (5 mg, 11 µmol), and anh. THF (2 mL) at ambient temperature for 14 h. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **308** (70 mg, 95%) as a white solid.

Analytical data for **308**: mp: 205-207 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.75 (br s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.24 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.83 (d, *J* = 7.7 Hz, 1H), 5.08 (s, 1H), 4.59 (s, 1H), 4.28 (dd, *J* = 12.9, 1.5 Hz, 1H), 3.88 (dd, *J* = 12.9, 1.4 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.42 (td, *J* = 12.4, 2.9 Hz, 1H), 2.47 (s, 3H), 2.20 – 2.10 (m, 1H), 1.83 (dt, *J* = 13.8, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 178.7, 143.6, 140.3, 139.1, 133.9, 131.2, 129.7 (x2), 128.5, 127.8 (x2), 124.8, 122.8, 114.6, 109.8, 51.4, 49.6, 41.6, 34.0, 21.6; HRMS (ESI): Mass calcd for $(C_{20}H_{21}N_2O_3S)^+$ $[M+H]^+$: 369.1267; found: 369.1266.

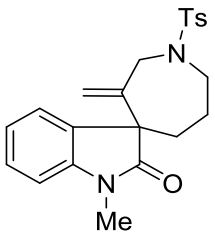


310

methyl 5'-methylene-2-oxo-1'-tosylspiro[indoline-3,4'-piperidine]-2'-carboxylate (**310**): Prepared according to the general procedure using oxindole **309** (78 mg, 0.20 mmol), propargyl carbonate **255** (47 mg, 0.30 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5 µmol), dppb (5 mg, 11 µmol), and

anh. THF (2 mL) at ambient temperature for 8 h. Purified by flash column chromatography (5→50% EtOAc/Hexanes) to afford diastereomer **310 major** (41 mg, 48%) as a white solid, mp: 213-214 °C, and diastereomer **310 minor** (25 mg, 30%) as a white solid. mp: 213-214 °C; Analytical data for **310 major**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (br s, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.20 (m, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.06 (s, 1H), 4.72 – 4.65 (m, 1H), 4.63 (s, 1H), 4.24 (d, *J* = 13.5 Hz, 1H), 4.13 (d, *J* = 13.5 Hz, 1H), 3.77 (s, 3H), 2.49 – 2.44 (m, 1H), 2.46 (s, 3H), 2.20 (ddd, *J* = 14.1, 4.6, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.8, 171.4, 143.8, 140.3, 138.4, 134.5, 131.2, 129.6 (x2), 128.7, 128.3 (x2), 124.6, 122.8, 115.1, 110.2, 54.9, 52.6, 51.4, 48.9, 36.1, 21.6; HRMS (ESI): Mass calcd for $(C_{22}H_{23}N_2O_5S)^+$ $[M+H]^+$: 427.1322; found: 427.1327.

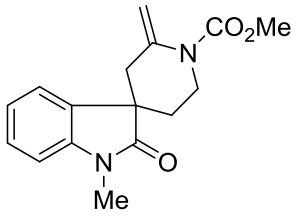
Analytical data for **310 minor**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (br s, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.24 (td, *J* = 7.8, 1.3 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 5.04 (s, 1H), 4.89 (d, *J* = 6.2 Hz, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.51 (s, 1H), 4.38 (d, *J* = 15.0 Hz, 1H), 3.67 (s, 3H), 2.52 – 2.48 (m, 1H), 2.48 (s, 3H), 2.17 (dd, *J* = 14.2, 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 169.9, 143.4, 140.6, 138.6, 137.5, 130.7, 129.5 (x2), 128.8, 127.6 (x2), 124.6, 122.7, 114.2, 110.0, 53.3, 52.3, 51.2, 46.0, 34.4, 21.5; HRMS (ESI): Mass calcd for $(C_{22}H_{23}N_2O_5S)^+$ $[M+H]^+$: 427.1322; found: 427.1324.



312

1'-methyl-3-methylene-1-tosylspiro[azepane-4,3'-indolin]-2'-one (**312**): Prepared according to the general procedure using oxindole **311** (61 mg, 0.17 mmol), propargyl carbonate **255** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4 mg, 4.3 µmol), dppb (4 mg, 9.4 µmol), and anh. THF (1.7 mL) at ambient temperature for 20 min. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **312** (53 mg, 78%) as a white solid.

Analytical data for **312**: mp: 161 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.73 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 5.25 (s, 1H), 4.61 (s, 1H), 4.42 (dd, *J* = 14.0, 1.5 Hz, 1H), 3.92 (d, *J* = 13.9 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.17 (s, 3H), 2.97 (ddd, *J* = 12.5, 8.4, 3.6 Hz, 1H), 2.46 (s, 3H), 2.16 – 2.07 (m, 2H), 2.04 – 1.91 (m, 1H), 1.85 – 1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ178.6, 144.1, 143.2, 142.9, 136.3, 133.8, 129.7 (x2), 128.1, 127.3 (x2), 124.3, 122.8, 119.9, 108.2, 55.3, 51.9, 48.9, 35.0, 26.3, 24.4, 21.5; HRMS (ESI): Mass calcd for $(C_{22}H_{25}N_2O_3S)^+$ $[M+H]^+$: 397.1580; found: 397.1592.

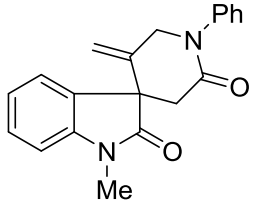


314

methyl 1-methyl-2'-methylene-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate (**314**): To a 50-mL RBF was added $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 µmol) and dppb (5 mg, 11 µmol). The flask was purged with N_2 and anh. THF (20 mL) was added. After 5 min, propargyl carbonate **255** (47 mg, 0.30 mmol) was added, then stirred at ambient temperature for 5 min. After heating to 50 °C for 15 min, a solution of oxindole **313** (50 mg, 0.20 mmol) in THF (1 mL) was added dropwise

via syringe pump over 1 h. After 15 h, the reaction was cooled to ambient temperature, filtered over a Celite™ pipet plug, and concentrated *in vacuo*. Purified by flash column chromatography (40% EtOAc/Hexanes) to afford **314** (39 mg, 68%) as an amber residue. NOTE: Exocyclic olefin product slowly isomerizes to endocyclic olefin product at ambient temperature; purified **314** is stored at –78 °C to slow/halt this process.

Analytical data for **314**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.20 (s, 1H), 4.93 (s, 1H), 4.22 (dt, *J* = 13.4, 5.2 Hz, 1H), 3.78 (s, 3H), 3.67 (ddd, *J* = 13.6, 9.8, 3.7 Hz, 1H), 3.23 (s, 3H), 2.73 (d, *J* = 13.6 Hz, 1H), 2.23 (d, *J* = 13.6 Hz, 1H), 2.12 (ddd, *J* = 14.0, 9.7, 4.5 Hz, 1H), 1.67 (dt, *J* = 13.7, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 155.2, 142.7, 139.1, 132.8, 128.1, 123.9, 122.3, 109.3, 108.1, 52.8, 46.7, 41.2, 39.3, 32.0, 26.3; HRMS (ESI): Mass calcd for $(C_{16}H_{19}N_2O_3)^+$ $[M+H]^+$: 287.1390; found: 287.1392.

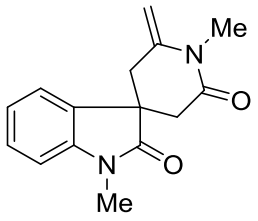


316

1-methyl-5'-methylene-1'-phenylspiro[indoline-3,4'-piperidine]-2,2'-dione (**316**): To a 50-mL RBF was added oxindole **315** (56 mg, 0.20 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), and dppb (5 mg, 11 μmol). The flask was purged with N_2 and anh. THF (20 mL) was added. The flask was immediately immersed in a 50 °C oil bath. After heating for 15 min, propargyl carbonate **255** (47 mg, 0.30 mmol) was added in one portion. After 30 min, the reaction mixture was cooled to ambient temperature, filtered over a Celite™ pipet plug, and concentrated *in*

vacuo. Purified by flash column chromatography (50→70% EtOAc/Hexanes) to afford **316** (49 mg, 77%) as an off-white solid foam. mp: 63-64 °C; NOTE: Exocyclic olefin product slowly isomerizes to endocyclic olefin product at ambient temperature; purified **316** is stored at –78 °C to slow/halt this process.

Analytical data for **316**: ^{1}H NMR (500 MHz, $CDCl_3$): δ7.50 – 7.40 (m, 4H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.28 – 7.23 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 5.14 (s, 1H), 4.83 (d, *J* = 14.5 Hz, 1H), 4.79 (s, 1H), 4.35 (d, *J* = 14.5 Hz, 1H), 3.26 (s, 3H), 2.96 (d, *J* = 16.3 Hz, 1H), 2.79 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.1, 167.6, 143.1, 142.1, 139.5, 130.6, 129.2 (x2), 128.8, 127.0, 126.0 (x2), 123.9, 123.1, 113.2, 108.6, 55.2, 52.4, 40.5, 26.4; HRMS (ESI): Mass calcd for $(C_{20}H_{19}N_2O_2)^+$ $[M+H]^+$: 319.1441; found: 319.1437.

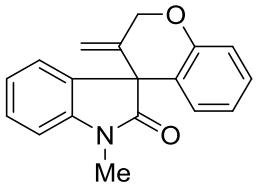


318

1,1'-dimethyl-2'-methylenespiro[indoline-3,4'-piperidine]-2,6'-dione (**318**): To a 50-mL RBF was added oxindole **317** (44 mg, 0.20 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), and dppb (5 mg, 11 μmol). The flask was purged with N_2 and anh. THF (20 mL) was added. The flask was immediately immersed in a 50 °C oil bath. After heating for 15 min, propargyl carbonate **255** (47 mg, 0.30 mmol) was added in one portion. After 30 min, the reaction mixture was cooled to ambient temperature, filtered over a Celite™ pipet plug, and concentrated *in vacuo*. Purified by

flash column chromatography (0→5% MeOH/CH_2Cl_2) to afford **318** (37 mg, 73%) as an amber residue that slowly crystallized on standing.

Analytical data for **318**: mp: 139-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.32 (td, *J* = 7.7, 1.3 Hz, 1H), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H), 6.96 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 4.52 (t, *J* = 1.7 Hz, 1H), 4.20 (t, *J* = 1.6 Hz, 1H), 3.34 (s, 3H), 3.25 (s, 3H), 3.05 (d, J = 17.4 Hz, 1H), 3.03 (dt, *J* = 14.5, 1.8 Hz, 1H), 2.49 (dd, *J* = 17.3, 2.8 Hz, 1H), 2.41 (dd, *J* = 14.6, 2.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.0, 167.0, 142.6, 141.6, 130.7, 128.7, 123.2, 122.8, 108.4, 94.5, 45.0, 39.1, 37.2, 29.6, 26.4; HRMS (ESI): Mass calcd for $(C_{15}H_{17}N_2O_2)^+$ $[M+H]^+$: 257.1285; found: 257.1277.

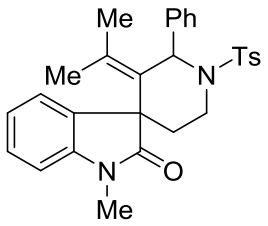


320

1'-methyl-3-methylenespiro[chroman-4,3'-indolin]-2'-one (**320**): Prepared according to the general procedure using oxindole **319** (48 mg, 0.20 mmol), propargyl carbonate **255** (47 mg, 0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), dppb (5 mg, 11 μmol), and anh. THF (2 mL) at ambient temperature for 20 min. Purified by flash column chromatography (10→30% EtOAc/Hexanes) to afford **320** (52 mg, 95%) as a pale-yellow powder.

Analytical data for **320**: mp: 97-98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (td, *J* = 7.7, 1.3 Hz, 1H), 7.14 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1H), 7.02 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.95 (td, *J* = 8.3, 1.0 Hz, 2H), 6.73 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 6.41 (dd, *J* = 7.8, 1.7 Hz, 1H), 5.35 (dd, *J* = 11.9, 1.3 Hz, 1H), 5.17 (d, *J* = 1.3 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.65 (s,

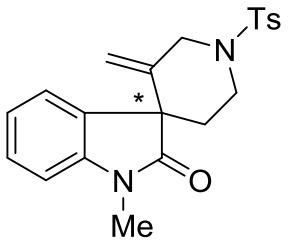
1H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 155.6, 144.5, 139.3, 132.3, 128.8, 128.7, 127.9, 125.5, 123.3, 121.8, 121.1, 117.4, 113.6, 108.2, 68.4, 55.5, 26.6; HRMS (ESI): Mass calcd for $(C_{18}H_{16}NO_2)^+$ $[M+H]^+$: 278.1176; found: 278.1165.



322

1-methyl-2'-phenyl-3'-(propan-2-ylidene)-1'-tosylspiro[indoline-3,4'-piperidin]-2-one (**322**): Prepared according to the general procedure using oxindole **303** (69 mg, 0.20 mmol), propargyl carbonate **321** (78 mg, 0.30 mmol, as a 0.30 M solution in THF), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), dppb (5 mg, 11 μmol), and anh. THF (2 mL) at 50 °C for 30 min. Purified by flash column chromatography (20→25% EtOAc/Hexanes) to afford **322** (92 mg, 95%) as an amorphous bright orange-yellow solid foam.

Analytical data for **322**: ^{1}H NMR (500 MHz, $CDCl_3$): δ7.53 (t, *J* = 7.1 Hz, 3H), 7.44 – 7.37 (m, 2H), 7.36 – 7.29 (m, 4H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 4.14 – 4.07 (m, 1H), 3.16 (s, 3H), 2.64 – 2.53 (m, 2H), 2.45 – 2.39 (m, 2H), 2.36 (s, 3H), 1.53 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ177.5, 144.1, 142.9, 136.8, 131.4 (x2), 129.4 (x2), 129.0, 128.4, 128.2 (x2), 127.9, 126.9 (x2), 124.8, 123.2, 122.3, 107.9, 94.3, 82.7, 55.5, 39.9, 38.6, 32.0, 26.0, 24.6, 23.8, 21.3; HRMS (ESI): Mass calcd for $(C_{29}H_{31}N_2O_3S)^+$ $[M+H]^+$: 487.2050; found: 487.2052.



X

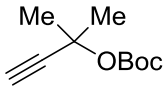
1-methyl-3'-methylene-1'-tosylspiro[indoline-3,4'-piperidin]-2-one (**304***): Prepared according to a modification of the general procedure using oxindole **303** (69 mg, 0.20 mmol), propargyl carbonate **255** (47 mg, 0.30 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5.0 μmol), (*R*,*R*)-DACH-phenyl (7 mg, 11 μmol), and anh. THF (2 mL) at 40 °C for 4 h, followed by heating to 60 °C for 16 h. Purified by flash column chromatography (25% EtOAc/Hexanes) to afford **304*** (6 mg, 8%, 32% ee) as a white solid.

Analytical data (^{1}H NMR, ^{13}C NMR, and HRMS) match those previously reported in this document. A ^{1}H NMR spectrum is provided to demonstrate purity. Enantiomeric ratio was measured by HPLC (Chiralpak AS-H, 10% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 22.8, Rt_2 = 26.0).

VII.4: Experimental Section – Chapter IV

General Method: Prepared according to a modified procedure from Chalasani and coworkers[13] as we have previously described. To a solution of propargyl alcohol in anh. CH_2Cl_2 maintained under a positive pressure of nitrogen was added N(*i*-Pr)$_2$Et and DMAP. The reaction mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate was either added portionwise over two min or dropwise as a solution in CH_2Cl_2. The reaction mixture was slowly warmed to ambient temperature over 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water, 10% aq. HCl, sat. aq. $NaHCO_3$, and brine. The organic layer was then dried over anh. $MgSO_4$

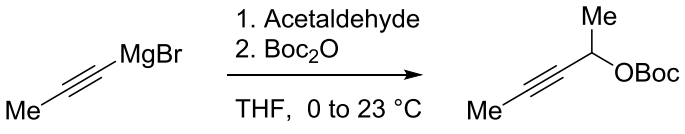
and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired product.



428

***tert*-butyl (2-methylbut-3-yn-2-yl) carbonate** (**428**): Prepared according to Štambask and coworkers.[4] To a suspension of 60% w/w NaH (0.62 g, 15.5 mmol) in THF (40 mL) maintained under a positive pressure of nitrogen was added 2-methyl-3-butyn-ol (1.02 mL, 10.5 mmol). This mixture was allowed to stir at ambient temperature for 30 min and was then cooled to 0 °C. To this mixture was added a solution of Boc_2O (2.18 g, 10.0 mmol) in THF (60 mL) over 1 h by syringe pump. Following completion of the addition the mixture was allowed to warm to ambient temperature and stir for 16 h. After consumption of the starting material, as determined by TLC, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine. The combined organic layer was dried with anh. $MgSO_4$, passed through a short plug of SiO_2 and concentrated *in vacuo* to afford **428** (1.05 g, 57%) as a colorless liquid.

Analytical data match those reported in the literature.[16]



546 **430**

***tert*-butyl (pent-3-yn-2-yl) carbonate (430):** Prepared according to Tamaru and coworkers.[45] To a dry round bottomed flask equipped with a stirbar under an atmosphere of nitrogen a solution of 1-propynylmagnesium bromide (0.5 M in THF, 10 mmol) was added via syringe. The solution was cooled to 0 °C and acetaldehyde (0.85 mL, 15 mmol) was added dropwise over five minutes. The reaction mixture was allowed to warm to ambient temperature and stir for an additional 2 h. At which time di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) was added to the reaction mixture and allowed to stir an additional 16 h. The mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 and washed with water. This was back extracted two times with CH_2Cl_2 and the combined organic layers were washed with brine and dried over $MgSO_4$. The solution was passed through a plug of silica and concentrated *in vacuo* to give **430** (1.18 g, 64% yield over two steps) as a clear oil.

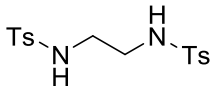
Analytical data for **430**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 – 5.09 (m, 1H), 1.83 (dd, J = 2.3, 1.0 Hz,), 1.48 (s, 9H), 1.47 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.60, 82.35, 81.56, 77.44, 63.64, 27.74, 21.71 (x3), 3.55; HRMS (ESI) calcd for $(C_{10}H_{17}O_3)^+$ $[M+H]^+$: 185.1172, found: 185.1167.

Preparation of Bis-Sulfonamide Substrates

General Method: Based on the protocol of Urabe and coworkers[46]. To a solution of diamine in anhydrous pyridine (0.2 M) cooled to 0 °C was added sulfonyl chloride portion wise over 5 minutes. The solution was then sealed, purged three times with nitrogen and allowed to warm to ambient temperature. The reaction mixture was allowed to stir for an additional 18 h. The

[45] Tamaru, Y.; Kimura, M.; Tanaka, S.; Kure, S.; Yoshida, Z.-i. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2838.
[46] Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820.

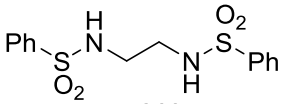
solution was poured into water (six times the volume of pyridine used) and stirred for 5 min. The formed precipitate was collected by vacuum filtration and subsequently washed two times with water and four times with diethyl ether. The solid was then collected and dried *in vacuo* to give the desired product.



362

***N,N′*-Bis(*p*-toluenesulfonyl)ethylenediamine (362):** Prepared according to the general method using ethylenediamine (0.67 mL, 10 mmol), tosyl chloride (3.91 g, 20.5 mmol) and pyridine (50 mL). Purified by vacuum filtration and washing with diethyl ether to afford **362** (2.47 g, 67% yield) as an off white solid.

Analytical data matched those reported in the literature.[47]

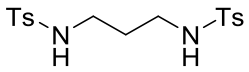


369

***N,N′*-Bis(phenylsulfonyl)ethylenediamine (369):** Prepared according to the general method using ethylenediamine (0.10 mL, 1.5 mmol), benzenesulfonyl chloride (0.39 mL, 3.08 mmol), and pyridine (7.5 mL). Purified by vacuum filtration and washing with diethyl ether to afford **369** (295 mg, 58% yield) as a white solid.

Analytical data matched those reported in the literature.[48]

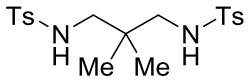
[47] Romba, J.; Kuppert, D.; Morgenstern, B.; Neis, C.; Steinhauser, S.; Weyhermüller, T.; Hegetschweiler, K. *Eur. J. Inorg. Chem.* **2006**, *2006*, 314.
[48] Khazaei, A.; Rostami, A.; Mahboubifar, M. *Catal. Commun.* **2007**, *8*, 383.



371

***N,N′*-Bis(*p*-toluenesulfonyl)1,3-propylenediamine (371):** Prepared according to the general method using 1,3-propylenediamine (0.17 mL, 2.0 mmol), tosyl chloride (782 mg, 4.1 mmol) and pyridine (6.7 mL). Purified by vacuum filtration and washing with diethyl ether to afford **371** (114 mg, 16% yield) as an off white solid.

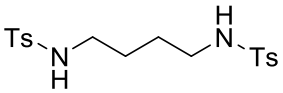
Analytical data matched those reported in the literature.[49]



373

N,N'-(2,2-dimethylpropane-1,3-diyl)bis(4-methylbenzenesulfonamide) (373): Prepared according to the general method using 2,2-dimethyl-1,3-propanediamine (0.12 mL, 1.0 mmol), tosyl chloride (391 mg, 2.05 mmol) and pyridine (5 mL). Isolated by extraction into EtOAc followed by subsequent washing with water to afford a yellow oil after concentration *in vaccuo*. The crude material was purified by flash column chromatography to give **373** (0.27 g, 66% yield) as a yellow amorphous solid.

Analytical data matched those reported in the literature.[50]

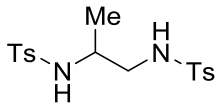


375

[49] Tan, Y.; Wang, S. J.; Wang, Y. T.; Gao, B. X.; Ba, X. W. *Synth. Commun.* **2010**, *40*, 3648.
[50] Burkhart, A.; Fischer, J.; Mondrzyk, A.; Ritter, H. *Macromol. Chem. Phys.* **2014**, *215*, 421.

***N,N'*-Bis(*p*-toluenesulfonyl)1,4-diaminobutane (375):** Prepared according to the general method using 1,4-diaminobutane (0.20 mL, 2.0 mmol), tosyl chloride (782 mg, 4.1 mmol) and pyridine (10 mL). Purified by vacuum filtration and washing with diethyl ether to afford **375** (401 mg, 51% yield) as a white solid.

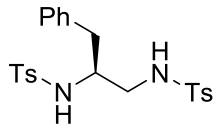
Analytical data matched those reported in the literature.[51]



377

N,N'-(propane-1,2-diyl)bis(4-methylbenzenesulfonamide) (377): Prepared according to the general method using 1,2-diaminopropane (0.09 mL, 1.0 mmol), tosyl chloride (391 mg, 2.05 mmol) and pyridine (5 mL). Diluted with water and extracted with EtOAc (2x), the organic layer was subsequently washed with 1M HCl, brine, dried over $MgSO_4$ and concentrated *in vaccuo*. Residual pyridine was removed azeotropically by dissolving the residue in toluene and removal of solvent *in vacuo* to afford **377** (222 mg, 58% yield) as an off white solid.

Analytical data matched those reported in the literature.[52]



379

(S)-N,N'-(3-phenylpropane-1,2-diyl)bis(4-methylbenzenesulfonamide) (379): Step 1: A dry round bottomed flask was charged with L-Phenylalaninamide (500 mg, 3.04 mmol), followed by

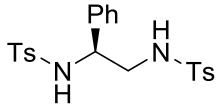
[51] Khanjin, N. A.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 2028.
[52] Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3784.

addition of THF (16 mL) via syringe. The reaction flask was then purged 3x N_2 and cooled to 0 °C in an ice water bath. After 30 minutes lithium aluminum hydride (1.0 M in THF) (6.1 mL, 6.08 mmol) was added dropwise over 15 minutes via syringe. Following the addition the reaction flask was equipped with a reflux condenser, purged 3x N_2 and heated to reflux for 12 h. After cooling to ambient temperature residual lithium aluminum hydride was quenched using standard Fieser workup protocol: The reaction mixture was cooled to 0 °C followed by slow addition of water (0.25 mL). After frothing had stopped 15% $NaOH_{(aq)}$ (0.25 mL) was added dropwise, followed by water (0.75 mL). The reaction mixture was then allowed to warm to ambient temperature and left stirring for 30 minutes. At this point anh. $MgSO_4$ was added and the heterogeneous mixture was filtered over Celite. After removal of solvent *in vacuo* a yellow oil was isolated which solidified on standing. The crude NMR showed most of the material had been reduced to the diamine and was taken on without purification.

Step 2: Prepared according to the general method using crude diamine (396 mg, 2.63 mmol), tosyl chloride (1.03 g, 5.40 mmol) and pyridine (13 mL). Diluted with water and extracted with EtOAc (2x), the organic layer was subsequently washed with 1M HCl, brine dried over $MgSO_4$ and concentrated *in vaccuo*. Residual pyridine was removed azeotropically by dissolving the residue in toluene and removal of solvent *in vacuo* to afford **379** (450 mg, 38% yield) as a white solid.

Analytical data for **379**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.17 – 7.03 (m, 5H), 6.84 (d, *J* = 7.2 Hz, 2H), 5.60 (t, *J* = 6.4 Hz, 1H), 5.36 (d, *J* = 7.2 Hz, 1H), 3.35 (dd, *J* = 11.8, 5.1 Hz, 1H), 3.00 (dd, *J* = 11.8, 6.6 Hz, 2H), 2.73 (dd, *J* = 13.9, 6.9 Hz, 1H), 2.57 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.38 (s, 3H), 2.37 (s, 3H); 13C NMR (126 MHz, $CDCl_3$) δ 143.31, 143.23, 136.48, 136.35, 136.28, 129.62 (x2), 129.53

(x2), 128.96 (x2), 128.45 (x2), 127.03 (x2), 126.89 (x2), 126.50 (x2), 54.76, 46.29, 38.35, 21.37; HRMS (ESI) calcd for $(C_{23}H_{27}N_2O_4S_2)^+$ $[M+H]^+$: 459.1407, found: 459.1408.



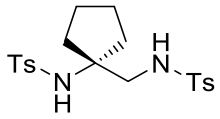
381

(S)-N,N'-(1-phenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (381): Step 1: A dry round bottomed flask was charged with (2S)-2-Amino-2-phenylethanamide (1.00 g, 6.66 mmol), followed by addition of THF (33 mL) via syringe. The reaction flask was then purged 3x N_2 and cooled to 0 °C in an ice water bath. After 30 minutes lithium aluminum hydride (1.0 M in THF) (13.3 mL, 13.3 mmol) was added dropwise over 15 minutes via syringe. Following the addition the reaction flask was equipped with a reflux condenser, purged 3x N_2 and heated to reflux for 12 h. After cooling to room temperature residual lithium aluminum hydride was quenched using standard Fieser workup protocol: The reaction mixture was cooled to 0 °C followed by slow addition of water (0.5 mL). After frothing had stopped 15% $NaOH_{(aq)}$ (0.5 mL) was added dropwise, followed by water (1.5 mL). The reaction mixture was then allowed to warm to ambient temperature and left stirring for 30 minutes. At this point anh. $MgSO_4$ was added and the heterogeneous mixture was filtered over Celite. After removal of solvent *in vacuo* a yellow oil was isolated. The crude NMR showed most of the material had been reduced to the diamine and the oil was taken on without purification.

Step 2: Prepared by dissolving the crude diamine (739 mg, 5.42 mmol) in CH_2Cl_2 (30 mL) and the solution was then transferred to a dry round bottomed flask and sealed under N_2. The flask was cooled to 0 °C in an ice water bath and NEt_3 (1.88 mL, 13.56 mmol) was added via syringe. Tosyl chloride (2.12 g, 11.12 mmol) was added as a solution in CH_2Cl_2 (14 mL) and added

dropwise over the course of 3 h. The resulting mixture was allowed to warm to ambient temperature and stir for an additional 12 h. The reaction mixture was then diluted with CH_2Cl_2 and washed with sat. $NaCO_3H$, water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow residue. The residue was purified by flash column chromatography (1:1 to 0:1 Hex:CH_2Cl_2) to afford **381** (981 mg, 41% yield) as a pale yellow amorphous solid.

Analytical data for **381**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 3H), 7.04 (t, *J* = 10.5 Hz, 6H), 6.94 (d, *J* = 7.0 Hz, 2H), 4.41 – 4.31 (m, 1H), 3.11 (dd, *J* = 13.6, 8.1 Hz, 1H), 3.06 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.33 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.18, 142.89, 137.37, 136.75, 136.39, 129.45 (x2), 129.07 (x2), 128.49 (x2), 128.21 (x2), 127.50, 126.84 (x2), 126.76 (x2), 126.47, 57.33, 47.82, 21.16; HRMS (ESI) calcd for ($C_{22}H_{25}N_2O_4S_2$) + [M+H]+: 445.1250, found: 445.1243.



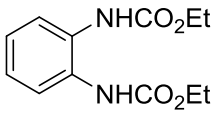
383

4-methyl-N-((1-((4-methylphenyl)sulfonamido)cyclopentyl)methyl)benzenesulfonamide (383): Step 1: A dry round bottomed flask was charged with 1-aminocyclopentane-1-carboxamide (500 mg, 3.90 mmol), followed by addition of THF (20 mL) via syringe. The reaction flask was then purged 3x N_2 and cooled to 0 °C in an ice water bath. After 30 minutes lithium aluminum hydride (1.0 M in THF) (7.8 mL, 7.80 mmol) was added dropwise over 15 minutes via syringe. Following the addition the reaction flask was equipped with a reflux condenser, purged 3x N_2 and heated to reflux for 12 h. After cooling to room temperature residual lithium aluminum hydride was quenched using standard Fieser workup protocol: The

reaction mixture was cooled to 0 °C followed by slow addition of water (0.30 mL). After frothing had stopped 15% $NaOH_{(aq)}$ (0.30 mL) was added dropwise, followed by water (0.90 mL). The reaction mixture was then allowed to warm to ambient temperature and left stirring for 30 minutes. At this point anh. $MgSO_4$ was added and the heterogeneous mixture was filtered over Celite. After removal of solvent *in vacuo* a clear oil was isolated. The crude NMR showed most of the material had been reduced to the diamine and the oil was taken on without purification.

Step 2: Prepared by dissolving the crude diamine (256 mg, 2.24 mmol) in CH_2Cl_2 (4 mL) and the solution was then transferred to a dry round bottomed flask and sealed under N_2. The flask was cooled to 0 °C in an ice water bath and NEt_3 (0.78 mL, 5.60 mmol) was added via syringe. Tosyl chloride (875 mg, 4.59 mmol) was added as a solution in CH_2Cl_2 (6 mL) and added dropwise over the course of 1h. The resulting mixture was allowed to warm to ambient temperature and stir for an additional 12 h. The reaction mixture was then diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The residue was purified by flash column chromatography (8:1 to 3:1 Hex:EtOAc) to afford **383** (1.13 g, 51% yield) as a white amorphous solid.

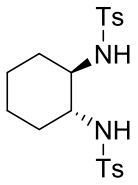
Analytical data for **383**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 3.4 Hz, 2H), 7.74 (d, J = 3.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 5.75 (t, J = 6.8 Hz, 1H), 5.58 (s, 1H), 3.08 (d, J = 6.9 Hz, 2H), 2.41 (s, 3H), 2.40 (s, 3H), 1.71 – 1.63 (m, 2H), 1.61 – 1.54 (m, 2H), 1.51 – 1.37 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.13, 143.07, 139.36, 137.04, 129.56 (x2), 129.52 (x2), 126.86 (x2), 126.68 (x2), 67.36, 49.60, 35.89, 31.42, 22.54 (x2), 21.36, 13.85; HRMS (ESI) calcd for ($C_{20}H_{27}N_2O_4S_2$) + [M+H]+: 423.1407, found: 423.1400.



385

diethyl 1,2-phenylenedicarbamate (385): Prepared according to a protocol by Conconi and coworkers.[53] A dry round bottomed flask was charged with 1,2-diamnobenzene (216 mg, 2.0 mmol), THF (13 mL) and NEt_3 (1.11 mL, 8.0 mmol). To this solution ethyl chloroformate (0.76 mL, 8.0 mmol) was added dropwise, following the addition, the reaction flask was fitted with a reflux condenser and heated to reflux under N_2 for 1 h. The reaction mixture was then allowed to cool to ambient temperature and the heterogeneous mixture was filtered over celite and the filtrate was washed with Et_2O. The combined organic solution was concentrated *in vacuo* to afford **385** (504 mg, 2.0 mmol, >99% yield).

Analytical data matched those reported in the literature.[53]



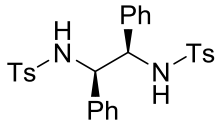
387

N,N'-((1R,2R)-cyclohexane-1,2-diyl)bis(4-methylbenzenesulfonamide) (387): Prepared according to a protocol by Stones and coworkers.[54] A dry round bottomed flask was charged with (1*R*, 2*R*)-(-)-diaminocyclohexane (228 mg, 2.0 mmol), followed by addition of CH_2Cl_2 (2

[53] Conconi, M. T.; Marzaro, G.; Urbani, L.; Zanusso, I.; Di Liddo, R.; Castagliuolo, I.; Brun, P.; Tonus, F.; Ferrarese, A.; Guiotto, A.; Chilin, A. *European Journal of Medicinal Chemistry* **2013**, *67*, 373.
[54] Stones, G.; Tripoli, R.; McDavid, C. L.; Roux-Duplatre, K.; Kennedy, A. R.; Sherrington, D. C.; Gibson, C. L. *Organic & Biomolecular Chemistry* **2008**, *6*, 374.

mL) and stirred until solids are dissolved. N(*i*Pr)$_2$Et (2.2 mL, 12.8 mmol) was added via syringe followed by addition of tosyl chloride (782 mg, 4.1 mmol) all at once. The reaction mixture was then stirred for an additional 12 h at ambient temperature. The reaction was quenched by the addition of 10% HCl and the diluted with Et_2O. The aqueous phase was separated and extracted 3 x with Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue expanded into a white amorphous solid (770 mg, 1.82 mmol, 91% yield) after prolonged exposure to high vacuum, affording **387** and required no further purification.

Analytical data matched those reported in the literature.[54]



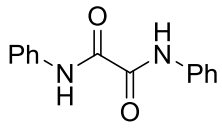
389

N,N'-((1R,2R)-1,2-diphenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (389): Prepared according to a protocol by Giuffredi and coworkers.[55] A dry round bottomed flask was charged with (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (250 mg, 1.18 mmol), followed by addition of THF (8 mL), this was stirred under nitrogen until all solids dissolved. The reaction mixture was cooled to 0 °C and triethyl amine (0.13 mL, 0.9 mmol) was added via syringe. After stirring 1 minute tosyl chloride (245 mg, 1.28 mmol) was added portionwise over 2 minutes. After stirring for an additional 2 h the reaction mixture was diluted with CH_2Cl_2 and quenched with $NaCO_3H$ (aq). The aqueous layer was extracted 3 times with CH_2Cl_2, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting

[55] Giuffredi, G. T.; Purser, S.; Sawicki, M.; Thompson, A. L.; Gouverneur, V. *Tetrahedron: Asymmetry* **2009**, *20*, 910.

residue was purified by flash chromatography (2% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to afford **389** (614 mg, 24% yield) as a white solid.

Analytical data matched those reported in the literature.[56]



391

N1,N2-diphenyloxalamide (391): Prepared according to a protocol by Wang and coworkers.[57] To a suspension of sodium bicarbonate (428 mg, 5.1 mmol) in THF (4.2 mL) under nitrogen atmosphere oxalyl chloride (0.21 mL, 2.5 mmol) was added via syringe. Aniline (0.46 mL, 5.1 mmol) was added dropwise to the stirring suspension over 5 minutes and the reaction was allowed to stir for an additional 1 h. The reaction was then quenched by addition of water, the formed precipitate was isolated by vacuum filtration, washed with water and dried under high vacuum for 24 h. The procedure afforded **391** (433 mg, 72% yield) as a white solid and required no further purification.

Analytical data matched those reported in the literature.[57]

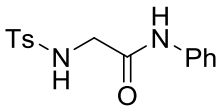
Preparation of Amino Acid Based Substrates

General Method: Step 1: Based on the protocol by Ajani and coworkers.[58] To a flask charged with amino acid (1.0 equiv.) and $NaHCO_3$ (2.1 equiv.) water (0.8 M) is added and the suspension

[56] Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61.
[57] Cotton, F. A.; Liu, C. Y.; Murillo, C. A.; Villagrán, D.; Wang, X. *J. Am. Chem. Soc.* **2003**, *125*, 13564.
[58] Ajani, O. O.; Familoni, O. B.; Wu, F.; Echeme, J. O.; Sujiang, Z. *International Journal of Drug Design and Discovery*, **2013**, *4*, 983-993.

is set stirring at a high rate. The suspension is then cooled to 0 °C and after 20 min sulfonyl chloride (1.2 equiv.) is added portion-wise over five minutes. The reaction vessel is then sealed under nitrogen and allowed to slowly warm to ambient temperature. The mixture is then stirred for 4 to 18 h after which it is carefully quenched with 10% HCl. Upon acidification the formed precipitate is isolated by vacuum filtration and washed with 2.2 pH buffer solution (746 mg KCl, 1.56 mL 10% HCl in 50 mL water). Unless otherwise indicated the crude material is taken on without further purification.

Step 2: Based on the protocol by Aguilar-Castro and coworkers.[59] The crude product isolated previously was dissolved in THF (0.1 M), cooled to 0 °C and sealed under nitrogen. To this $SOCl_2$ (2.32 equiv.) was added dropwise over five minutes and then the solution was allowed warm to ambient temperature and stirred for 1 h. The reaction mixture was then concentrated *in vacuo* to remove excess $SOCl_2$, the resulting residue was redissolved in THF (0.1 M) and aniline (1.1 equiv.) was added dropwise over 5 minutes. The reaction mixture was allowed to stir at ambient temperature until starting material was consumed as determined by TLC. The reaction mixture was then diluted with EtOAc and water. The aqueous layer was extracted three times with EtOAc and the combined organic layers were then washed with $NaHCO_3$ (aq), brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to give the desired compounds.

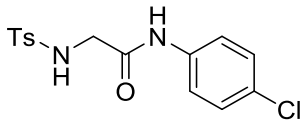


396

[59] Aguilar-Castro, L.; Tlahuextl, M.; Tapia-Benavides, A. R.; Tlahuext, H. *Heteroat. Chem* **2003**, *14*, 247.

2-((4-methylphenyl)sulfonamido)-N-phenylacetamide (396): Prepared according to the general method using glycine (375 mg, 5.0 mmol), tosyl chloride (1.14 g, 6.0 mmol), $NaHCO_3$ (1.11 g, 10.5 mmol) and water (6.2 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (280 mg), $SOCl_2$ (0.21 mL, 2.83 mmol), aniline (0.12 mL, 1.34 mmol) and THF (12 mL) were stirred for 3 h at ambient temperature. Purified by flash column chromatography (9:1 to 4:1 Hexanes:EtOAc) to afford **396** (98.4 mg, 0.32 mmol, 26% yield over two steps) as a white solid.

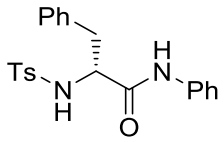
Analytical data for **396**: ^{1}H NMR (500 MHz, Acetone) δ 9.17 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.23 (m, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.79 (s, 1H), 3.76 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, Acetone) δ 167.09, 144.36, 139.48, 130.57 (x2), 129.61 (x2), 128.11 (x2), 124.70 (x2), 120.43 (x2), 47.20, 21.45; HRMS (ESI) calcd for $(C_{15}H_{17}N_2O_3S)^+$ $[M+H]^+$: 305.0954, found: 305.0960.



398

N-(4-chlorophenyl)-2-((4-methylphenyl)sulfonamido)acetamide (398): Prepared according to the general method using glycine (375 mg, 5.0 mmol), tosyl chloride (1.14 g, 6.0 mmol), $NaHCO_3$ (1.11 g, 10.5 mmol) and water (6.2 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (280 mg), $SOCl_2$ (0.21 mL, 2.83 mmol), 4-chloroaniline (0.12 mL, 1.34 mmol) and THF (12 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 4:1 Hexanes:EtOAc) to afford **398** (74.2 mg, 0.32 mmol, 18% yield over two steps) as a white solid.

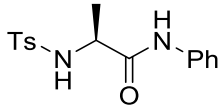
Analytical data for **398**: ^{1}H NMR (500 MHz, Acetone) δ 9.31 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.9 Hz, 2H), 7.41 – 7.34 (m, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 6.82 (s, 1H), 3.76 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, Acetone) δ 168.05, 145.05, 139.08, 131.24 (x3), 130.21 (x3), 128.78 (x3), 122.63, 47.93, 22.11; HRMS (ESI) calcd for $(C_{15}H_{16}ClN_2O_3S)^+$ $[M+H]^+$: 339.0565, found: 339.0558.



400

(R)-2-((4-methylphenyl)sulfonamido)-N,3-diphenylpropanamide (400): Prepared according to the general method using (*D*)-phenylalanine (826 mg, 5.0 mmol), tosyl chloride (1.14 g, 6.0 mmol), $NaHCO_3$ (1.11 g, 10.5 mmol) and water (6.0 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (723 mg), $SOCl_2$ (0.38 mL, 5.25 mmol), aniline (0.23 mL, 2.49 mmol) and THF (23 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 4:1 Hexanes:EtOAc) to afford **400** (475 mg, 1.19 mmol, 53% yield over two steps) as a fluffy white solid.

Analytical data matched those reported in the literature.[60]



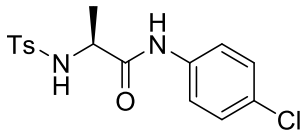
402

(S)-2-((4-methylphenyl)sulfonamido)-N-phenylpropanamide (402): Prepared according to the general method using (*L*)- alanine (445 mg, 5.0 mmol), tosyl chloride (1.14 g, 6.0 mmol), K_2CO_3

[60] Gou, S.; Judeh, Z. M. A. *Chirality* **2011**, *23*, 105.

(1.45 g, 10.5 mmol) and water (6.0 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (105 mg), $SOCl_2$ (0.08 mL, 1.0 mmol), aniline (0.05 mL, 0.47 mmol) and THF (1.2 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **402** (104 mg, 0.33 mmol, 75 % yield over two steps) as a white solid.

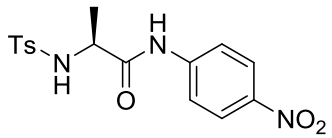
Analytical data for **402**: ^{1}H NMR (500 MHz, Acetone) δ 9.11 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.22 (m, 4H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.75 (s, 1H), 4.00 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.31 (s, 3H), 1.29 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Acetone) δ 170.65, 144.18, 140.16, 139.50, 130.40 (x2), 129.46 (x2), 128.00 (x2), 124.59 (x2), 120.40, 54.05, 21.34, 19.56; HRMS (ESI) calcd for $(C_{16}H_{19}N_2O_3S)^+$ $[M+H]^+$: 319.1111, found: 319.1116.



404

(S)-N-(4-chlorophenyl)-2-((4-methylphenyl)sulfonamido)propanamide (404): Prepared according to the general method using (L)- alanine (891 mg, 10.0 mmol), tosyl chloride (2.10 g, 11.0 mmol), K_2CO_3 (2.90 g, 21.0 mmol) and water (12.0 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (122 mg), $SOCl_2$ (0.08 mL, 1.16 mmol), 4-chloroaniline (70 mg, 0.55 mmol) and THF (5 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **404** (38 mg, 0.11 mmol, 22 % yield over two steps) as a white solid.

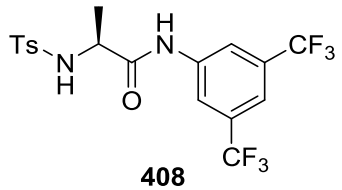
Analytical data for **404**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.30 (dd, *J* = 8.0, 0.5 Hz, 2H), 7.25 (d, *J* = 9.2 Hz, 2H), 5.19 (d, *J* = 7.5 Hz, 1H), 3.91 (t, *J* = 7.2 Hz, 1H), 2.40 (s, 3H), 1.30 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.20, 144.46, 135.67, 130.06 (x2), 129.61 (x2), 128.96 (x2), 127.26 (x2), 121.19 (x2), 53.27, 21.52, 18.56; HRMS (ESI) calcd for $(C_{16}H_{18}ClN_2O_3S)^+$ $[M+H]^+$: 353.0721, found: 353.0723.



406

(S)-2-((4-methylphenyl)sulfonamido)-N-(4-nitrophenyl)propanamide (406): Prepared according to the general method using (L)- alanine (445 mg, 5.0 mmol), tosyl chloride (1.14 g, 6.0 mmol), K_2CO_3 (1.45 g, 10.5 mmol) and water (6.0 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (105 mg), $SOCl_2$ (0.08 mL, 1.0 mmol), 4-nitroaniline (69 mg, 0.47 mmol) and THF (1.2 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **406** (98 mg, 0.27 mmol, 63 % yield over two steps) as a white solid.

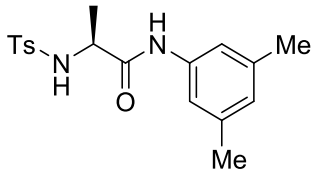
Analytical data for **406**: ^{1}H NMR (500 MHz, Acetone) δ 9.68 (s, 1H), 8.20 (d, *J* = 9.2 Hz, 2H), 7.79 (d, *J* = 9.3 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 4.13 – 3.99 (m, 1H), 2.30 (s, 3H), 1.32 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Acetone) δ 171.68, 145.42, 144.32, 138.79, 130.46 (x3), 128.06 (x2), 125.47 (x2), 120.15 (x2), 54.34, 21.33, 19.16; HRMS (ESI) calcd for $(C_{16}H_{18}N_3O_5S)^+$ $[M+H]^+$: 364.0962, found: 364.0958.



408

(S)-N-(3,5-bis(trifluoromethyl)phenyl)-2-((4-methylphenyl)sulfonamido)propanamide (408): Prepared according to the general method using (L)- alanine (445 mg, 5.0 mmol), tosyl chloride (1.14 g, 6.0 mmol), K_2CO_3 (1.45 g, 10.5 mmol) and water (6.0 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (105 mg), $SOCl_2$ (0.08 mL, 1.0 mmol), 3,5-bis(trifluoromethyl)aniline (0.08 mL, 0.47 mmol) and THF (1.2 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **408** (54 mg, 0.54 mmol, 28 % yield over two steps) as a white solid.

Analytical data for **408**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.98 (s, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.60 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.21 (d, *J* = 7.1 Hz, 1H), 3.96 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.41 (s, 3H), 1.32 (d, *J* = 7.1 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.17, 169.56, 145.07, 138.70, 130.19 (x3), 127.29 (x4), 122.14, 119.64, 53.32 (x2), 29.69, 21.47, 18.19; HRMS (ESI) calcd for $(C_{18}H_{17}F_6N_2O_3S)^+$ $[M+H]^+$: 455.0859, found: 455.0854.

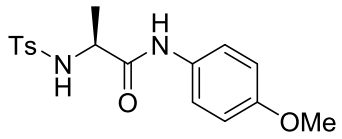


410

(S)-N-(3,5-dimethylphenyl)-2-((4-methylphenyl)sulfonamido)propanamide (410): Prepared according to the general method using (L)- alanine (445 mg, 5.0 mmol), tosyl chloride (1.14 g, 6.0 mmol), K_2CO_3 (1.45 g, 10.5 mmol) and water (6.0 mL) for 16 h. A portion of the crude

material was taken on to the next step. The crude solid (105 mg), $SOCl_2$ (0.08 mL, 1.0 mmol), 3,5-bis(methyl)aniline (0.06 mL, 0.47 mmol) and THF (1.2 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **410** (50 mg, 0.14 mmol, 34 % yield over two steps) as a white solid.

Analytical data for **410**: ^{1}H NMR (500 MHz, Acetone) δ 8.93 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.11 (s, 2H), 6.77 (s, 1H), 6.71 (s, 1H), 3.98 (s, 1H), 2.33 (s, 3H), 2.23 (s, 6H), 1.28 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, Acetone) δ 170.47, 144.17, 139.29, 138.94, 138.92, 130.42 (x2), 128.00 (x3), 126.20 (x2), 118.24 (x2), 54.05, 21.41, 21.36, 19.58; HRMS (ESI) calcd for $(C_{18}H_{23}N_2O_3S)^+$ $[M+H]^+$: 319.1111, found: 319.1116.

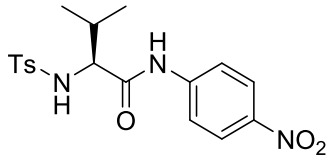


412

(S)-N-(4-methoxyphenyl)-2-((4-methylphenyl)sulfonamido)propanamide (412): Prepared according to the general method using (L)- alanine (891 mg, 10.0 mmol), tosyl chloride (2.10 g, 11.0 mmol), K_2CO_3 (2.90 g, 21.0 mmol) and water (12.0 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (122 mg), $SOCl_2$ (0.08 mL, 1.16 mmol), p-anisidine (68 mg, 0.55 mmol) and THF (5 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **412** (38 mg, 0.11 mmol, 22 % yield over two steps) as a white solid.

Analytical data for **412**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 4H), 6.80 (d, *J* = 8.9 Hz, 2H), 5.52 (d, *J* = 7.7 Hz, 1H), 3.93 (d, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 2.38 (s, 3H), 1.30 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.97,

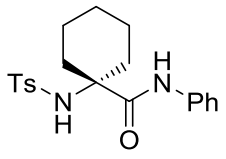
156.47, 144.04, 129.94 (x2), 127.21 (x3), 121.85 (x2), 114.03 (x2), 55.68, 55.42, 53.17, 21.63, 18.86; HRMS (ESI) calcd for $(C_{17}H_{21}N_2O_3S)^+$ $[M+H]^+$: 349.1217, found: 349.1222.



414

(S)-3-methyl-2-((4-methylphenyl)sulfonamido)-N-(4-nitrophenyl)butanamide (414): Prepared according to the general method using (L)- valine (469 mg, 4.0 mmol), tosyl chloride (839 mg, 4.4 mmol), K_2CO_3 (1.16 g, 8.4 mmol) and water (4.8 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (250 mg), $SOCl_2$ (0.15 mL, 2.07 mmol), 4-nitroaniline (140 mg, 1.0 mmol) and THF (5 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **414** (161 mg, 0.41 mmol, 45 % yield over two steps) as a white solid.

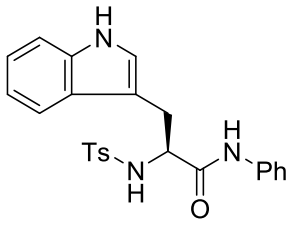
Analytical data for **414**: ^{1}H NMR (500 MHz, Acetone) δ 9.63 (s, 1H), 8.18 (d, *J* = 9.2 Hz, 2H), 7.78 – 7.62 (m, 4H), 7.33 – 7.13 (m, 2H), 6.67 (d, *J* = 9.0 Hz, 1H), 3.76 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.18 (s, 3H), 0.96 (dd, *J* = 10.9, 6.8 Hz, 7H); ^{13}C NMR (126 MHz, Acetone) δ 170.82, 145.14, 144.07, 130.22 (x3), 128.12 (x3), 125.43 (x2), 120.04 (x2), 64.06, 32.31, 21.22, 19.48, 18.39; HRMS (ESI) calcd for $(C_{18}H_{22}N_3O_5S)^+$ $[M+H]^+$: 392.1275, found: 392.1264.



416

1-((4-methylphenyl)sulfonamido)-N-phenylcyclohexane-1-carboxamide (416): Prepared according to the general method using 1-aminocyclohexanecarboxylic acid (573 mg, 4.0 mmol), tosyl chloride (839 mg, 4.4 mmol), K_2CO_3 (1.16 g, 8.4 mmol) and water (4.8 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (193 mg), $SOCl_2$ (0.11 mL, 1.51 mmol), aniline (0.07 mL, 0.72 mmol) and THF (6.5 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **416** (131 mg, 0.35 mmol, 54 % yield over two steps) as a white amorphous solid.

Analytical data for **416**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.23 (t, J = 7.9 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 5.96 (s, 1H), 2.32 (s, 3H), 1.96 (s, 4H), 1.49 – 1.38 (m, 3H), 1.31 – 1.19 (m, 3H); C^{13} NMR (126 MHz, $CDCl_3$) δ 172.00, 143.53, 138.76, 137.74, 129.59 (x2), 128.96, 128.62 (x2), 128.15, 126.91 (x2), 124.19, 120.29 (x2), 63.25, 33.25, 24.86, 21.39, 21.27; HRMS (ESI) calcd for $(C_{20}H_{25}N_2O_3S)^+$ $[M+H]^+$: 373.1580, found: 373.1578.



547

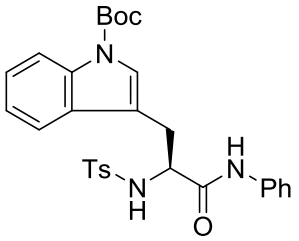
(S)-3-(1H-indol-3-yl)-2-((4-methylphenyl)sulfonamido)-N-phenylpropanamide (547): Step 1: Prepared according a protocol Simsek and coworkers.[61] To an oven-dried borosilicate test tube (*L*)-tryptophan (408 mg, 2.0 mmol) is suspended/dissolved in H_2O/THF (9:1 ratio, 4.4 mL) and set rapidly stirring. To this is added NEt_3 (0.58 mL, 4.2 mmol) and the reaction tube is cooled to

[61] Simsek, S.; Horzella, M.; Kalesse, M. *Org. Lett.* **2007**, *9*, 5637.

0 °C in an ice water bath. After 15 minutes tosyl chloride (381 mg, 2.0 mmol) is added portion-wise over 15 minutes and the reaction is allowed to warm to ambient temperature. After consumption of starting material as determined by TLC the mixture was washed 2x with Et_2O, acidified with 1M HCl and then extracted 3x with EtOAc. The combined EtOAc extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude ^{1}H NMR matched known spectra[25] and was taken on without further purification.

Step 2: Prepared by charging a dry round bottomed flask with the crude tosyl protected product (717 mg), DCC (413 mg, 2.0 mmol, 1 equiv.) 80% 1-hydroxybenzenetriazole hydrate (34 mg, 0.2 mmol, 0.1 equiv.), purged 2x with nitrogen and disolved in anh. TFH (10 mL). To this mixture aniline (0.18 mL, 2.0 mmol, 1 equiv.) was added dropwise over 15 minutes. The reaction mixture was allowed to stir at ambient temperature for 16 h, the mixture was then concentrated *in vacuo* to give a residue which was purified by flash column chromatography (1:1 Hex:CH_2Cl_2 to 1:9 MeOH:CH_2Cl_2) to give **547** (633 mg, 1.4 6 mmol, 73% yield over two steps) as an off white solid.

Analytical data for **547**: ^{1}H NMR (500 MHz, Acetone) δ 9.96 (s, 1H), 9.19 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.47 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.15 (d, *J* = 2.1 Hz, 1H), 7.10 (dd, *J* = 11.6, 4.5 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.98 – 6.94 (m, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 4.27 (dd, *J* = 14.7, 7.6 Hz, 1H), 3.34 (dd, *J* = 14.5, 6.5 Hz, 1H), 3.15 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, Acetone) δ 169.62, 143.00, 138.45, 137.41, 136.67, 129.26 (x2), 128.61 (x2), 127.46 (x2), 126.87, 124.05 (x2), 123.90, 121.31, 119.88 (x2), 118.78, 118.35, 111.41, 109.35, 58.29, 20.66; HRMS (ESI) calcd for $(C_{24}H_{24}N_3O_3S)^+$ $[M+H]^+$: 434.1533, found: 434.1515.

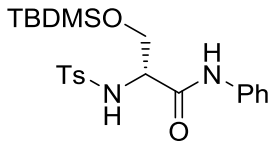


418

tert-butyl (S)-3-(2-((4-methylphenyl)sulfonamido)-3-oxo-3-(phenylamino)propyl)-1H-indole-1-carboxylate (418): Step 3: Selective protection of the indole nitrogen was accomplished by following a modified procedure from Chalasani and coworkers.[13] To an oven dried borosilicate test tube charged with **547** (127 mg, 0.29 mmol) is added DMAP (4-dimethylamino pyridine) (4 mg, 0.03 mmol) and sealed under N_2. The solids were then dissolved in anh. CH_2Cl_2 (3.0 mL) followed by addition of N(*i*Pr)$_2$Et (0.13 mL, 0.73 mmol) and then cooled to 0 °C in an ice water bath. Boc_2O (63 mg, 0.29 mmol) was dissolved in anh. CH_2Cl_2 (1.0 mL) and added dropwise over 90 minutes via syringe to the solution. Following addition the reaction mixture was allowed to warm to ambient temperature and stirred an additional 12 h. The reaction mixture was then diluted with CH_2Cl_2 and subsequently washed with 0.5 M $HCl_{(aq)}$, water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (9:1-5:2 Hex:EtOAc) to give **418** (33 mg, 0.06 mmol, 22% yield, 78% BRSM) as a white amorphous solid.

Analytical data for **418**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.04 (s, 1H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.25 (m, 5H), 7.11 (dd, *J* = 13.8, 6.9 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 5.24 (d, *J* = 6.2 Hz, 1H), 4.03 (dt, *J* = 8.7, 5.6 Hz, 1H), 3.30 (dd, *J* = 14.8, 4.9 Hz, 1H), 2.97 (dd, *J* = 14.8, 8.8 Hz, 1H), 2.27 (s, 3H), 1.65 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.45, 143.99, 137.04, 129.35 (x2), 128.92 (x2), 126.71 (x2), 124.79 (x2), 124.62 (x2), 124.50,

122.78 (x2), 120.20 (x2), 118.61 (x2), 115.32 (x2), 114.32, 83.87, 57.06, 28.16 (x3), 21.56; HRMS (ESI) calcd for $(C_{29}H_{32}N_3O_5S)^+$ $[M+H]^+$: 534.3057, found: 534.3059.



420

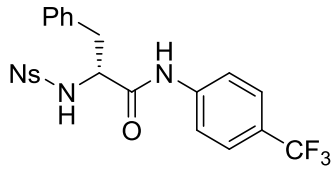
(R)-3-((tert-butyldimethylsilyl)oxy)-2-((4-methylphenyl)sulfonamido)-N-phenylpropanamide (420): Step 1: Prepared according a modified protocol from Craig and coworkers.[62] To a round bottomed flask charged with (*D*)-serine (210 mg, 2.0 mmol) was added tosyl chloride (496 mg, 2.6 mmol) EtOAc (4.8 mL) and water (1.4 mL). The suspension was set rapidly stirring and 2.0 M $NaOH_{(aq)}$ (2.7 mL, 5.4 mmol) was added dropwise over 3 h at ambient temperature. After addition the reaction mixture was allowed to stir for an additional hour. At this point the layers were separated and the aqueous layer was acidified with $HCl_{(conc)}$ and precipitate was isolated by vacuum filtration. The precipitate was washed with water and dried to give the crude tosyl protected intermediate.

Step 2: The crude product (0.27 g, 1.0 mmol) was dissolved in anh. THF (20 mL) and cooled to 0 °C in an ice water bath. To this mixture imidazole (170 mg, 2.5 mmol) was added and the reaction mixture was sealed under N_2. TBDMSCl (166 mg, 1.1 mmol) was added portion-wise over 20 min, after completion of addition the reaction was purged with N_2, allowed to warm to ambient temperature and stir an additional 12 h. The mixture was then diluted with EtOAc, washed with 1M HCl, water and brine, and concentrated *in vacuo*. The resulting residue was taken on without further purification.

[62] Craig, D.; Hyland, C. J. T.; Ward, S. E. *Chem. Commun.* **2005**, 3439.

Step 3: Prepared according to the general method using crude residue from the previous step (234 mg), $SOCl_2$ (0.11 mL, 1.46 mmol), aniline (0.06 mL, 0.69 mmol) and THF (6.3 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (4:1 to 3:1 Hexanes:CH_2Cl_2) to afford **420** (100 mg, 0.32 mmol, 51 % yield) as an off white amorphous solid.

Analytical data for **420**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 2H), 7.35 – 7.28 (m, 3H), 7.12 (t, *J* = 7.4 Hz, 1H), 5.72 (d, *J* = 5.4 Hz, 1H), 4.12 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.72 (ddd, *J* = 7.2, 5.5, 3.9 Hz, 1H), 3.54 (dd, *J* = 10.1, 7.3 Hz, 1H), 2.42 (s, 3H), 0.87 (s, 9H), 0.06 (d, *J* = 4.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.11, 144.26, 137.10, 130.00 (x2), 129.02 (x2), 127.32 (x2), 124.73 (x2), 119.89 (x2), 63.21, 57.51, 25.76 (x3), 21.52, 18.13, -5.51, -5.56; HRMS (ESI) calcd for $(C_{22}H_{32}N_2O_4SSiNa)^+$ $[M+Na]^+$: 471.1744, found: 471.1736.

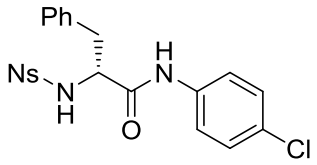


422

(R)-2-((4-nitrophenyl)sulfonamido)-3-phenyl-N-(4-(trifluoromethyl)phenyl)propanamide (422): Prepared according to the general method using (*D*)-phenylalanine (1.65 g, 10.0 mmol), 2-nitrosulfonyl chloride (2.66 g, 12.0 mmol), K_2CO_3 (2.90 g, 21 mmol) and water (12.0 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (0.60 g), $SOCl_2$ (0.29 mL, 3.98 mmol), 4-(trifluoromethyl)aniline (0.24 mL, 1.90 mmol) and THF (65 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1

to 5:2 Hexanes:EtOAc) to afford **422** (244 mg, 0.49 mmol, 29 % yield over two steps) as a yellow amorphous solid.

Analytical data for **422**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.10 – 7.91 (m, 1H), 7.77 – 7.70 (m, 1H), 7.67 – 7.56 (m, 4H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.08 – 7.02 (m, 2H), 6.98 (t, *J* = 6.9 Hz, 3H), 6.49 (d, *J* = 5.4 Hz, 1H), 4.48 – 4.22 (m, 1H), 3.38 (dd, *J* = 14.2, 4.7 Hz, 1H), 2.99 (dd, *J* = 14.2, 10.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.04, 146.85, 140.04, 134.88, 133.86, 133.25, 132.18, 131.02, 128.93 (x2), 128.54, 127.21, 126.03, 126.00, 125.97, 125.88, 125.00, 122.84, 119.87 (x2), 60.71, 38.19; HRMS (ESI) calcd for $(C_{22}H_{19}F_3N_3O_5S)^+$ $[M+H]^+$: 494.0992, found: 494.0991.



424

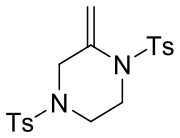
(R)-N-(4-chlorophenyl)-2-((4-nitrophenyl)sulfonamido)-3-phenylpropanamide (424): Prepared according to the general method using (*D*)-phenylalanine (1.65 g, 10.0 mmol), 2-nitrosulfonyl chloride (2.66 g, 12.0 mmol), K_2CO_3 (2.90 g, 21 mmol) and water (12.0 mL) for 16 h. A portion of the crude material was taken on to the next step. The crude solid (2.74 g), $SOCl_2$ (1.33 mL, 18.2 mmol), 4-chloroaniline (1.10 g, 8.6 mmol) and THF (200 mL) were stirred for 16 h at ambient temperature. Purified by flash column chromatography (9:1 to 5:2 Hexanes:EtOAc) to afford **424** (1.24 g, 2.69 mmol, 35 % yield over two steps) as a yellow amorphous solid.

Analytical data for **424**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.03 – 7.92 (m, 1H), 7.73 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.69 – 7.58 (m, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 5H), 6.39 (d, *J* = 5.7 Hz, 1H), 4.34 – 4.18 (m, 1H), 3.33 (dd, *J* = 14.2, 4.8

Hz, 1H), 2.96 (dd, J = 14.1, 9.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.52, 146.94, 135.47, 134.95, 133.80, 133.17, 132.34, 130.99, 129.86, 128.95, 128.85, 128.58, 127.21, 125.86, 121.54 (x2), 60.48, 38.32, 31.49, 22.56, 14.02; HRMS (ESI) calcd for $(C_{21}H_{19}ClN_3O_5S)^+$ $[M+H]^+$: 460.0728, found: 460.0726.

General Procedure for the Pd-catalyzed Piperizine Formation

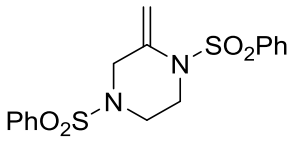
General Method: Diamine substrate (1 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.015 equiv., 3 mol % Pd) and DPEphos (0.033 equiv.) were added to a oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was purged with nitrogen, anhydrous CH_2Cl_2 (0.1 M) was added and the mixture was maintained under a positive pressure of nitrogen. In the case of a heterogeneous mixture sonication was used to break up larger particles of insoluble substrate. After 2 min *tert*-butyl propargyl carbonate **255** (1.3 equiv.) was added to the reaction mixture via syringe. The test tube was purged again with nitrogen. After consumption of starting material as judged by TLC, the reaction was concentrated and purified by flash column chromatography to give the desired products.



368

2-methylene-1,4-ditosylpiperazine (368): Prepared according to the general method using **362** (184 mg, 0.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mg, 2.5 μmol), DPEphos (3.2 mg, 5.5 μmol), propargyl carbonate **255** (102 mg, 0.65 mmol) in CH_2Cl_2 (5.0 mL) for 12 h. Purified by flash column chromatography (9:1 to 3:1 Hexanes:EtOAc) to afford **368** (165 mg, 0.43 mmol, 85% yield) as a white solid.

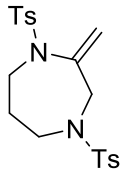
Analytical data for **368**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 5.11 (d, *J* = 0.6 Hz, 1H), 4.96 (d, *J* = 0.7 Hz, 1H), 3.79 – 3.63 (m, 2H), 3.36 (s, 2H), 3.09 – 2.99 (m, 2H), 2.45 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.09, 143.97, 136.73 (x2), 136.05 (x2), 129.75, 129.69 (x2), 127.73 (x2), 127.15 (x2), 110.30, 49.61, 45.87, 44.68, 21.52, 21.46; HRMS (ESI) calcd for $(C_{19}H_{23}N_2O_4S_2)^+$ $[M+H]^+$: 407.1094, found: 407.1099.



370

2-methylene-1,4-bis(phenylsulfonyl)piperazine (370): Prepared according to the general method using **369** (68 mg, 0.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.1 mg, 3.0 μmol), DPEphos (3.6 mg, 6.6 μmol), propargyl carbonate **255** (41 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 20 min. Purified by flash column chromatography (9:1 to 3:1 Hexanes:EtOAc) to afford **370** (70 mg, 0.19 mmol, 93% yield) as a white solid.

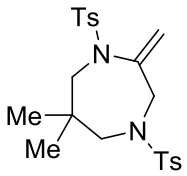
Analytical data for **370**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.66 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.57 – 7.46 (m, 3H), 7.42 (t, *J* = 7.8 Hz, 2H), 5.16 (s, 1H), 5.00 (s, 1H), 3.76 – 3.66 (m, 2H), 3.35 (s, 2H), 3.11 – 2.94 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.89, 133.21 (x2), 133.06 (x2), 129.18 (x2), 129.13 (x2), 127.66 (x2), 127.04 (x2), 110.92, 49.48, 45.95, 44.58; HRMS (ESI) calcd for $(C_{17}H_{19}N_2O_4S_2)^+$ $[M+H]^+$: 461.1563, found: 461.1552.



372

2-methylene-1,4-ditosyl-1,4-diazepane (372): Prepared according to the general method using **371** (111 mg, 0.3 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.6 mg, 4.5 µmol), DPEphos (5.3 mg, 9.9 µmol), propargyl carbonate **255** (61 mg, 0.39 mmol) in CH_2Cl_2 (3.0 mL) for 3 h. Purified by flash column chromatography (9:1 to 3:1 Hexanes:EtOAc) to afford **372** (110 mg, 0.27 mmol, 90% yield) as an off white amorphous solid.

Analytical data for **372**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.2, 0.9 Hz, 2H), 7.63 (dd, *J* = 8.2, 0.9 Hz, 2H), 7.36 – 7.21 (m, 4H), 5.13 (s, 1H), 5.03 (s, 1H), 3.77 (s, 2H), 3.65 – 3.57 (m, 2H), 3.30 – 3.21 (m, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 1.94 – 1.82 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.65, 143.42, 141.34, 136.37 (x2), 135.90, 129.69 (x2), 129.58, 127.41 (x2), 126.98 (x2), 112.73, 53.38, 47.80, 47.59, 28.97, 21.43, 21.38; HRMS (ESI) calcd for $(C_{20}H_{25}N_2O_4S_2)^+$ $[M+H]^+$: 421.1250, found: 421.1265.

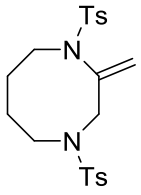


374

6,6-dimethyl-2-methylene-1,4-ditosyl-1,4-diazepane (374): Prepared according to the general method using **373** (82 mg, 0.2 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (3.1 mg, 3.0 µmol), DPEphos (3.6 mg, 6.6 µmol), propargyl carbonate **255** (41 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 1.5 h. Purified

by flash column chromatography (9:1 to 3:1 Hexanes:EtOAc) to afford **374** (87 mg, 0.19 mmol, 98% yield) as an off white amorphous solid.

Analytical data for **374**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 7.9 Hz, 2H), 7.29 (dd, J = 7.4, 6.9 Hz, 4H), 5.13 (s, 1H), 4.81 (s, 1H), 3.66 (s, 2H), 3.35 (s, 2H), 2.98 (s, 2H), 2.41 (s, 6H), 1.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.74, 143.45, 140.79, 136.13, 135.47, 129.68 (x2), 129.57 (x2), 127.32 (x2), 127.06 (x2), 112.42, 58.16, 56.86, 53.50, 36.27, 24.21 (x2), 21.43, 21.39; HRMS (ESI) calcd for ($C_{22}H_{29}N_2O_4S_2$) + [M+H]+: 449.1563, found: 449.1584.

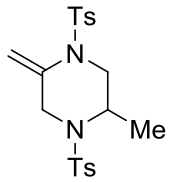


376

2-methylene-1,4-ditosyl-1,4-diazocane (376): Prepared according to the general method using **375** (119 mg, 0.3 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4.6 mg, 4.5 µmol), DPEphos (5.3 mg, 9.9 µmol), propargyl carbonate **255** (61 mg, 0.39 mmol) in CH_2Cl_2 (3.0 mL) for 75 min. Purified by flash column chromatography (6:1 to 4:1 Hexanes:EtOAc) to afford **376** (117 mg, 0.27 mmol, 90% yield) as an off white solid.

Analytical data for **376**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 10.5, 8.3 Hz, 4H), 7.36 – 7.22 (m, 4H), 5.46 (s, 1H), 4.57 (s, 1H), 3.91 (s, 2H), 3.48 (d, *J* = 5.5 Hz, 2H), 3.39 (d, *J* = 5.1 Hz, 2H), 2.42 (d, *J* = 2.0 Hz, 6H), 1.82 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.55, 143.22, 136.36, 129.70 (x2), 129.44 (x2), 127.68 (x2), 126.84 (x2), 119.29, 55.63 (x2), 50.78 (x2), 48.38

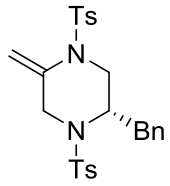
(x2), 27.91, 22.19, 21.44; HRMS (ESI) calcd for $(C_{21}H_{27}N_2O_4S_2)^+$ $[M+H]^+$: 435.1407, found: 435.1415.



378

2-methyl-5-methylene-1,4-ditosylpiperazine (378): Prepared according to the general method using **377** (77 mg, 0.2 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (3.1 mg, 3.0 µmol), DPEphos (3.6 mg, 6.6 µmol), propargyl carbonate **255** (41 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 3 h at 0 °C. Purified by flash column chromatography (9:1 to 3:1 Hexanes:EtOAc) to afford **378** (82 mg, 0.19 mmol, 97% yield) as a white solid.

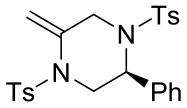
Analytical data for **378**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dt, *J* = 16.5, 8.2 Hz, 4H), 7.51 (d, *J* = 8.2 Hz, 0H), 7.34 – 7.23 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 0H), 5.24 (s, 0H), 5.13 (s, 0H), 5.02 (s, 1H), 4.66 (s, 1H), 4.11 – 3.99 (m, 1H), 3.91 (d, *J* = 12.1 Hz, 0H), 3.78 (d, *J* = 14.2 Hz, 1H), 3.72 (d, *J* = 14.2 Hz, 1H), 3.56 (dd, *J* = 12.8, 4.6 Hz, 1H), 3.34 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.43 (d, *J* = 12.6 Hz, 6H), 2.36 (s, 0H), 1.30 (d, *J* = 6.8 Hz, 0H), 1.23 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.09, 144.06, 143.68, 136.61, 135.84, 129.70 (x2), 129.64, 129.52 (x2), 127.63 (x2), 127.29 (x2), 127.23, 127.18, 114.46, 102.89, 50.42, 50.09, 49.85, 49.32, 49.21, 46.41, 21.48, 21.46, 17.93; HRMS (ESI) calcd for $(C_{20}H_{25}N_2O_4S_2)^+$ $[M+H]^+$: 421.1250, found: 421.1265.



380

(S)-2-benzyl-5-methylene-1,4-ditosylpiperazine (380): Prepared according to the general method using **379** (92 mg, 0.2 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (3.1 mg, 3.0 μmol), DPEphos (3.6 mg, 6.6 μmol), propargyl carbonate **255** (41 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 15 min. Purified by flash column chromatography (9:1 to 3:1 Hexanes:EtOAc) to afford **380** (79 mg, 0.16 mmol, 80% yield) as a white solid.

Analytical data for **380**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.27 – 7.22 (m, 7H), 5.11 (s, 1H), 4.72 (s, 1H), 4.06 (dd, J = 9.3, 4.3 Hz, 1H), 3.76 – 3.67 (m, 2H), 3.67 – 3.62 (m, 1H), 3.08 – 2.94 (m, 3H), 2.42 (d, J = 7.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.12, 143.78, 136.90, 136.74, 129.75 (x2), 129.67 (x2), 129.57 (x2), 128.70 (x2), 127.39 (x3), 127.26 (x2), 126.87 (x2), 103.38, 56.00, 47.25, 46.50, 38.47, 21.54, 21.51; HRMS (ESI) calcd for $(C_{26}H_{29}N_2O_4S_2)^+$ $[M+H]^+$: 497.1563, found: 497.1564.

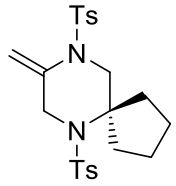


382

(S)-2-phenyl-5-methylene-1,4-ditosylpiperazine (382): Prepared according to the general method using **381** (133 mg, 0.3 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.6 mg, 4.5 μmol), DPEphos (5.3 mg, 9.9 μmol), propargyl carbonate **255** (61 mg, 0.39 mmol) in CH_2Cl_2 (3.0 mL) for 10 min. Purified

by flash column chromatography (6:1 to 3:1 Hexanes:CH_2Cl_2) to afford **382** (134 mg, 0.28 mmol, 92% yield) as an off white amorphous solid.

Analytical data for **382**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.28 (m, 5H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.01 – 4.97 (m, 1H), 4.95 (s, 1H), 4.52 (s, 1H), 4.08 (d, *J* = 15.1 Hz, 1H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.84 (dd, *J* = 13.5, 6.8 Hz, 1H), 3.75 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.09, 143.76, 138.15, 136.64, 135.73, 135.19, 129.62, 129.59, 128.65, 127.93, 127.45, 127.25, 126.57, 100.21, 57.94, 48.69, 47.83, 21.48; HRMS (ESI) calcd for $(C_{25}H_{27}N_2O_4S_2)^+$ $[M+H]^+$: 483.1407, found: 483.1410.

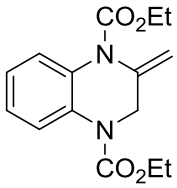


384

8-methylene-6,9-ditosyl-6,9-diazaspiro[4.5]decane (384): Prepared according to the general method using **383** (106 mg, 0.25 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.9 mg, 3.8 µmol), DPEphos (4.5 mg, 8.3 µmol), propargyl carbonate **255** (52 mg, 0.33 mmol) in CH_2Cl_2 (2.5 mL) for 45 min. Purified by flash column chromatography (9:1 to 4:1 Hexanes:EtOAc) to afford **384** (113 mg, 0.25 mmol, 98% yield) as a white amorphous solid.

Analytical data for **384**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 5.02 (s, 1H), 4.58 (s, 1H), 3.95 (s, 2H), 3.47 (s, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 2.25 – 2.17 (m, 2H), 1.80 (t, J = 8.8 Hz, 4H), 1.60 – 1.52 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.19, 143.17, 137.72, 129.72 (x2), 129.59 (x2),

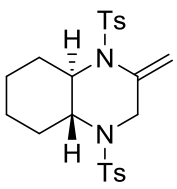
127.19 (x3), 126.90 (x3), 100.72, 69.32, 53.04, 49.46, 34.94 (x2), 23.18 (x2), 21.52, 21.43; HRMS (ESI) calcd for $(C_{23}H_{28}N_2O_4S_2Na)^+$ $[M+Na]^+$: 483.1388, found: 483.1384.



386

diethyl 2-methylene-2,3-dihydroquinoxaline-1,4-dicarboxylate (386): Prepared according to the general method using **385** (50 mg, 0.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.1 mg, 3.0 μmol), DPEphos (3.6 mg, 6.6 μmol), propargyl carbonate **255** (41 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 50 min. Purified by flash column chromatography (9:1 to 3:1 Hexanes:EtOAc) to afford **386** (19 mg, 0.07 mmol, 34% yield) as a white solid.

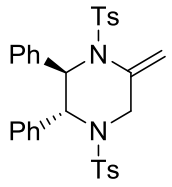
Analytical data for **386**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.41 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.12 (pd, *J* = 7.4, 1.4 Hz, 2H), 5.38 (s, 1H), 4.93 (s, 1H), 4.46 (d, *J* = 1.1 Hz, 2H), 4.26 (qdd, *J* = 7.1, 3.2, 1.0 Hz, 4H), 1.32 (qd, *J* = 7.1, 1.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.42, 139.99, 133.11, 124.97, 124.84, 124.68, 124.39, 123.79, 62.60, 62.30, 52.59, 51.06, 14.51, 14.27, 7.34; HRMS (ESI) calcd for $(C_{15}H_{18}N_2O_4Na)^+$ $[M+Na]^+$: 313.1159, found: 313.1152.



388

(4aR,8aR)-2-methylene-1,4-ditosyldecahydroquinoxaline (388): Prepared according to the general method using **387** (65 mg, 0.15 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.4 mg, 2.3 μmol), DPEphos (2.7 mg, 5.0 μmol), propargyl carbonate **255** (31 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) for 45 min. Purified by flash column chromatography (9:1 to 3:1 Hexanes:EtOAc) to afford **388** (67 mg, 0.15 mmol, 95% yield) as a yellow oil.

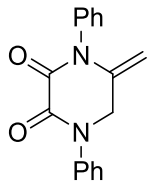
Analytical data for **388**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.32 (dd, *J* = 8.0, 0.6 Hz, 2H), 7.25 (dd, *J* = 8.0, 0.5 Hz, 2H), 5.35 (d, *J* = 2.3 Hz, 1H), 4.99 (d, *J* = 1.9 Hz, 1H), 4.04 (dt, *J* = 14.3, 2.4 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.74 (d, *J* = 14.3 Hz, 1H), 2.92 (td, *J* = 11.1, 3.3 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 2.37 (d, *J* = 13.9 Hz, 1H), 2.05 (d, *J* = 12.8 Hz, 1H), 1.76 – 1.63 (m, 3H), 1.43 – 1.30 (m, 2H), 1.19 – 1.07 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.91, 143.31, 138.46, 136.53, 136.26, 129.66, 129.62, 128.24, 127.62, 127.02, 126.86, 113.21, 63.87, 60.08, 51.72, 33.64, 29.66, 25.25, 24.03, 21.53, 21.43.; HRMS (ESI) calcd for $(C_{23}H_{29}N_2O_4S_2)^+$ $[M+H]^+$: 461.1563, found: 461.1552.



390

(2R,3R)-5-methylene-2,3-diphenyl-1,4-ditosylpiperazine (390): Prepared according to the general method using **389** (52 mg, 0.1 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (1.6 mg, 1.5 μmol), DPEphos (1.8 mg, 3.3 μmol), propargyl carbonate **255** (20 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) for 60 min. Purified by flash column chromatography (6:1 to 3:1 Hexanes:EtOAc) to afford **389** (52 mg, 0.09 mmol, 94% yield) as a white amorphous solid.

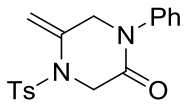
Analytical data for **389**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.46 (m, 2H), 7.37 (ddd, *J* = 6.7, 4.3, 1.5 Hz, 5H), 7.25 – 7.20 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.93 (d, *J* = 0.7 Hz, 4H), 6.02 (s, 1H), 5.66 (s, 1H), 4.98 (s, 1H), 4.60 (s, 1H), 3.96 (d, *J* = 13.7 Hz, 1H), 3.86 (d, *J* = 13.7 Hz, 1H), 2.33 (d, *J* = 7.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.74, 143.18, 139.77, 139.15, 135.24, 129.38 (x2), 129.25 (x2), 128.93 (x2), 128.72 (x2), 127.72 (x3), 127.68 (x2), 127.24 (x2), 126.92 (x2), 126.90 (x2), 126.14 (x2), 100.76, 64.15, 62.85, 46.64, 21.41; HRMS (ESI) calcd for $(C_{31}H_{31}N_2O_4S_2)^+$ $[M+H]^+$: 559.1720, found: 559.1710.



392

5-methylene-1,4-diphenylpiperazine-2,3-dione (392): Prepared according to the general method using **391** (102 mg, 0.42 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4.6 mg, 4.5 μmol), DPEphos (5.3 mg, 9.9 μmol), propargyl carbonate **255** (86 mg, 0.55 mmol) in CH_2Cl_2 (4.2 mL) for 24 h. Purified by flash column chromatography (9:1 to 0:1 Hexanes:EtOAc) to afford **392** (25 mg, 0.09 mmol, 21% yield) as a white solid.

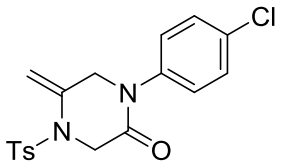
Analytical data for **392**: ^{1}H NMR (500 MHz, MeOD) δ 7.37 – 7.32 (m, 2H), 7.30 – 7.22 (m, 5H), 7.16 – 7.08 (m, 3H), 4.64 (d, *J* = 0.4 Hz, 2H), 4.52 (d, *J* = 1.5 Hz, 1H), 3.96 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (126 MHz, MeOD) δ 157.35, 140.94, 138.80, 130.89 (x2), 130.36 (x2), 129.99 (x2), 129.25 (x2), 128.76 (x2), 126.14 (x2), 99.70, 52.92; HRMS (ESI) calcd for $(C_{17}H_{15}N_2O_2)^+$ $[M+H]^+$: 279.1128, found: 279.1122.



397

5-methylene-1-phenyl-4-tosylpiperazin-2-one (397): Prepared according to the general method using **396** (65 mg, 0.15 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.4 mg, 2.3 µmol), DPEphos (2.7 mg, 5.0 µmol), propargyl carbonate **255** (31 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) for 30 min. Purified by flash column chromatography (6:1 to 4:1 Hexanes:EtOAc) to afford **397** (48 mg, 0.14 mmol, 93% yield) as a white solid.

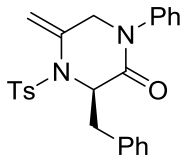
Analytical data for **397**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.38 (qd, *J* = 9.3, 7.0 Hz, 5H), 6.78 (dd, *J* = 8.0, 1.1 Hz, 2H), 4.28 (d, *J* = 1.1 Hz, 1H), 4.17 (s, 2H), 4.13 (s, 2H), 3.73 (s, 1H), 2.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.43, 144.60, 139.67, 136.46, 130.02 (x2), 129.61 (x2), 128.60 (x2), 128.20 (x2), 128.07 (x2), 95.60, 49.75, 47.82, 21.51; HRMS (ESI) calcd for $(C_{18}H_{19}N_2O_3S)^+$ $[M+H]^+$: 343.1111, found: 343.1118.



399

1-(4-chlorophenyl)-5-methylene-4-tosylpiperazin-2-one (399): Prepared according to the general method using **398** (34 mg, 0.1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (1.6 mg, 1.5 µmol), DPEphos (1.8 mg, 3.3 µmol), propargyl carbonate **255** (20 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) for 90 min. Purified by flash column chromatography (8:1 to 3:1 Hexanes:EtOAc) to afford **399** (38 mg, 0.1 mmol, 99% yield) as a white solid.

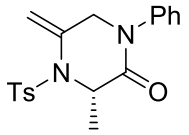
Analytical data for **399**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.43 – 7.29 (m, 4H), 6.73 (d, *J* = 8.5 Hz, 2H), 4.31 (s, 1H), 4.17 (s, 2H), 4.12 (s, 2H), 3.75 (s, 1H), 2.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.46, 144.65, 139.65, 134.88, 134.59, 130.03 (x2), 129.93 (x2), 129.67 (x3), 128.09 (x2), 95.62, 49.73, 47.76, 21.52; HRMS (ESI) calcd for $(C_{18}H_{18}ClN_2O_3S)^+$ $[M+H]^+$: 377.0721, found: 377.0720.



401

(R)-3-benzyl-5-methylene-1-phenyl-4-tosylpiperazin-2-one (401): Prepared according to the general method using **400** (79 mg, 0.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.1 mg, 3.0 μmol), DPEphos (3.6 mg, 6.6 μmol), propargyl carbonate **255** (41 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 45 min. Purified by flash column chromatography (6:1 to 4:1 Hexanes:EtOAc) to afford **401** (85 mg, 0.20 mmol, 98% yield) as a white solid.

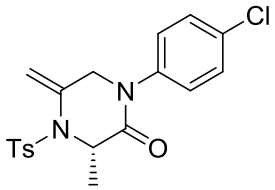
Analytical data for **401**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.22 (m, 10H), 6.56 (dd, *J* = 7.8, 1.4 Hz, 2H), 4.80 (ddd, *J* = 7.6, 4.8, 1.7 Hz, 1H), 4.44 (dd, *J* = 16.9, 1.7 Hz, 1H), 4.08 (s, 1H), 3.82 (d, *J* = 16.8 Hz, 1H), 3.50 (s, 1H), 3.39 (dd, *J* = 14.0, 7.7 Hz, 1H), 3.29 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.84, 144.03, 140.01, 136.70, 136.19, 129.71, 129.70 (x2), 129.45, 129.43 (x3), 128.58 (x2), 128.39, 128.00 (x2), 127.80 (x2), 127.13, 94.69, 59.28, 43.57, 38.15, 21.41; HRMS (ESI) calcd for $(C_{25}H_{25}N_2O_3S)^+$ $[M+H]^+$: 433.1580, found: 433.1586.



403

(S)-3-methyl-5-methylene-1-phenyl-4-tosylpiperazin-2-one (403): Prepared according to a modification of the general method using **402** (20 mg, 0.07 mmol). To this 1 mL of a prepared stock solution ($Pd_2(dba)_3 \cdot CHCl_3$ (3.1 mg, 3.0 µmol), DPEphos (3.6 mg, 6.6 µmol) in CH_2Cl_2 (3 mL)) was added followed by propargyl carbonate **255** (14 mg, 0.09 mmol) and stirred for 4 h. Purified by flash column chromatography (6:1 to 4:1 Hexanes:EtOAc) to afford **403** (22 mg, 0.07 mmol, 98% yield) as a white solid.

Analytical data for **403**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.29 (m, 5H), 6.47 (d, *J* = 5.4 Hz, 2H), 4.70 (qd, *J* = 7.2, 1.8 Hz, 1H), 4.63 (dd, *J* = 16.9, 1.6 Hz, 1H), 4.29 (d, *J* = 16.8 Hz, 1H), 4.19 (s, 1H), 3.55 (s, 1H), 2.49 (s, 3H), 1.66 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.95, 144.16, 139.88, 136.57, 135.99, 129.89 (x2), 129.44 (x2), 128.40, 128.10 (x2), 127.85 (x2), 94.55, 54.37, 42.72, 21.46, 17.84; HRMS (ESI) calcd for $(C_{19}H_{21}N_2O_3S)^+$ $[M+H]^+$: 357.1267, found: 357.1271.

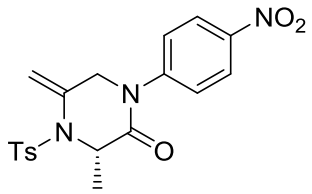


405

(S)-1-(4-chlorophenyl)-3-methyl-5-methylene-4-tosylpiperazin-2-one (405): Prepared according to the general method using **404** (16 mg, 0.05 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.8 mg, 0.8 µmol), DPEphos (0.9 mg, 1.6 µmol), propargyl carbonate **255** (10 mg, 0.07 mmol) in CH_2Cl_2

(0.5 mL) for 60 min. Purified by flash column chromatography (8:1 to 3:1 Hexanes:EtOAc) to afford **405** (21 mg, 0.05 mmol, 98% yield) as a white solid.

Analytical data for **405**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.33 (dd, *J* = 7.9, 0.6 Hz, 2H), 7.29 (dd, *J* = 8.8, 0.8 Hz, 2H), 6.42 (d, *J* = 8.3 Hz, 2H), 4.69 (dddd, *J* = 8.2, 7.2, 6.4, 1.0 Hz, 1H), 4.66 – 4.57 (m, 1H), 4.27 (dd, *J* = 16.8, 0.8 Hz, 1H), 4.21 (s, 1H), 3.56 (d, *J* = 0.8 Hz, 1H), 2.48 (s, 3H), 1.64 (dd, *J* = 7.2, 0.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.98, 144.33, 139.69, 135.90, 135.47, 134.96, 134.38, 129.89, 129.75 (x2), 129.56 (x2), 127.88 (x2), 94.59, 54.33, 42.61, 21.48, 17.75; HRMS (ESI) calcd for $(C_{19}H_{20}ClN_2O_3S)^+$ $[M+H]^+$: 391.0878, found: 391.0879.

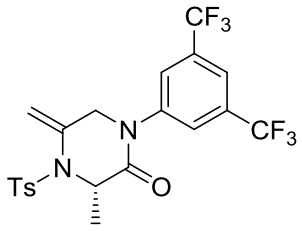


407

(S)-3-methyl-5-methylene-1-(4-nitrophenyl)-4-tosylpiperazin-2-one (407): Prepared according to the general method using **406** (33 mg, 0.1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (1.6 mg, 1.5 μmol), DPEphos (1.8 mg, 3.3 μmol), propargyl carbonate **255** (20 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) for 60 min. Purified by flash column chromatography (8:1 to 3:1 Hexanes:EtOAc) to afford **407** (35 mg, 0.1 mmol, 97% yield) as a white solid.

Analytical data for **407**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 4.72 (qd, *J* = 7.2, 1.7 Hz, 1H), 4.66 (d, *J* = 17.1 Hz, 1H), 4.30 (m, 1H), 4.28 (d, *J* = 1.4 Hz, 1H), 3.54 (s, 1H) 2.51 (s, 3H), 1.65 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.90, 147.43, 144.40, 142.35, 139.51, 135.86,

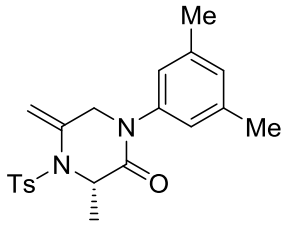
129.93 (x2), 129.60 (x2), 127.89 (x2), 124.79 (x2), 94.89, 54.29, 42.54, 21.51, 17.63; HRMS (ESI) calcd for $(C_{19}H_{20}N_3O_5S)^+$ $[M+H]^+$: 402.1118, found: 402.1118.



409

(S)-1-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-5-methylene-4-tosylpiperazin-2-one (409): Prepared according to the general method using **408** (59 mg, 0.15 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.3 mg, 2.2 µmol), DPEphos (2.4 mg, 4.5 µmol), propargyl carbonate **255** (31 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) for 75 min. Purified by flash column chromatography (8:1 to 3:1 Hexanes:EtOAc) to afford **409** (39 mg, 0.09 mmol, 62% yield) as a white solid.

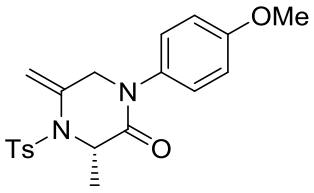
Analytical data for **409**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.99 (s, 2H), 4.77 (qd, *J* = 7.2, 1.7 Hz, 1H), 4.69 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.33 (dt, *J* = 17.0, 1.7 Hz, 1H), 4.28 (d, *J* = 1.8 Hz, 1H), 3.46 (d, *J* = 1.9 Hz, 1H), 2.46 (s, 3H), 1.69 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.00, 144.79, 139.64, 137.96, 133.28, 133.00, 129.92 (x2), 129.17, 127.92 (x2), 127.33 (x2), 123.69, 122.49, 121.52, 94.80, 54.30, 42.50, 21.29, 17.78; HRMS (ESI) calcd for $(C_{21}H_{19}F_6N_2O_3S)^+$ $[M+H]^+$: 493.1015, found: 493.1016.



411

(S)-1-(3,5-dimethylphenyl)-3-methyl-5-methylene-4-tosylpiperazin-2-one (411): Prepared according to the general method using **410** (23 mg, 0.07 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (1.1 mg, 1.0 µmol), DPEphos (1.2 mg, 2.2 µmol), propargyl carbonate **255** (14 mg, 0.09 mmol) in CH_2Cl_2 (1.0 mL) for 5 h. Purified by flash column chromatography (4:1 to 3:1 Hexanes:EtOAc) to afford **411** (15 mg, 0.04 mmol, 61% yield) as a white solid.

Analytical data for **411**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.90 (s, 1H), 6.63 (br. s, 1H), 5.90 (s, 1H), 5.46 (s, 1H), 4.73 (tt, *J* = 7.1, 3.5 Hz, 1H), 2.45 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 1.52 (d, *J* = 1.1 Hz, 3H), 1.46 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.91, 143.84, 136.04, 130.15 (x2), 129.70 (x4), 127.23 (x4), 103.89 (x2), 54.46 (x2), 21.58, 21.10, 16.76, 16.73; HRMS (ESI) calcd for $(C_{21}H_{25}N_2O_3S)^+$ $[M+H]^+$: 385.1580, found: 385.1581.

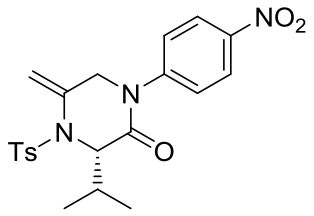


413

(S)-1-(4-methoxyphenyl)-3-methyl-5-methylene-4-tosylpiperazin-2-one (6i413 Prepared according to the general method using **412** (32 mg, 0.1 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (1.6 mg, 1.5 µmol), DPEphos (1.8 mg, 3.3 µmol), propargyl carbonate **255** (20 mg, 0.13 mmol) in CH_2Cl_2

(1.0 mL) for 5 h. Purified by flash column chromatography (8:1 to 3:1 Hexanes:EtOAc) to afford **413** (34 mg, 0.1 mmol, 98% yield) as a white solid.

Analytical data for **413**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 9.1 Hz, 2H), 6.39 (d, *J* = 8.2 Hz, 2H), 4.69 (tt, *J* = 7.2, 3.6 Hz, 1H), 4.62 (dd, *J* = 16.9, 1.8 Hz, 1H), 4.28 (dt, *J* = 16.8, 1.8 Hz, 1H), 4.18 (s, 1H), 3.78 (s, 3H), 3.59 (t, *J* = 1.6 Hz, 1H), 2.48 (s, 3H), 1.65 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.13, 159.22, 144.08, 139.98, 135.84, 129.84 (x2), 129.00 (x2), 127.82 (x2), 114.68 (x2), 94.41, 55.37 (x2), 54.36, 42.68, 21.45, 17.81; HRMS (ESI) calcd for $(C_{20}H_{23}N_2O_4S)^+$ $[M+H]^+$: 387.1373, found: 387.1378.

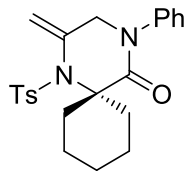


415

(S)-3-isopropyl-5-methylene-1-(4-nitrophenyl)-4-tosylpiperazin-2-one (415): Prepared according to the general method using **414** (117 mg, 0.3 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4.6 mg, 4.5 μmol), DPEphos (5.3 mg, 9.9 μmol), propargyl carbonate **255** (61 mg, 0.39 mmol) in CH_2Cl_2 (3.0 mL) for 36 h. Purified by flash column chromatography (6:1 to 2:1 Hexanes:EtOAc) to afford **415** (110 mg, 0.26 mmol, 85% yield) as a yellow oil.

Analytical data for **415**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 4.72 (d, *J* = 17.5 Hz, 1H), 4.29 (d, *J* = 17.5 Hz, 1H), 4.24 – 4.16 (m, 2H), 3.51 (s, 1H), 2.50 (s, 3H), 2.39 – 2.24 (m, 1H), 1.17 (t, *J* = 7.1

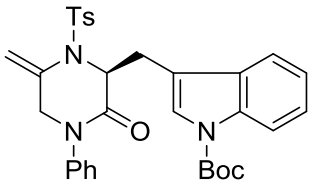
Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.29, 147.31, 144.30, 142.60, 139.62, 135.95, 129.93 (x2), 129.56 (x2), 127.89 (x2), 124.69 (x2), 94.50, 63.73, 43.36, 29.91, 21.50, 20.01, 19.52; HRMS (ESI) calcd for $(C_{21}H_{24}N_3O_5S)^+$ $[M+H]^+$: 430.1431, found: 430.1411.



417

2-methylene-4-phenyl-1-tosyl-1,4-diazaspiro[5.5]undecan-5-one (417): Prepared according to the general method using **416** (37 mg, 0.1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (1.6 mg, 1.5 μmol), DPEphos (1.8 mg, 3.3 μmol), propargyl carbonate **255** (20 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) for 100 min. Purified by flash column chromatography (9:1 to 4:1 Hex:EtOAc) to afford **417** (40 mg, 0.1 mmol, 98% yield) as a white amorphous solid.

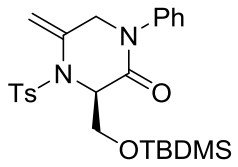
Analytical data for **417**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.31 (dd, *J* = 13.6, 5.3 Hz, 5H), 6.54 (d, *J* = 7.8 Hz, 2H), 4.75 (d, *J* = 1.3 Hz, 2H), 4.15 – 4.09 (m, 1H), 3.62 – 3.57 (m, 1H), 2.47 (s, 5H), 2.07 – 2.00 (m, 2H), 1.72 – 1.59 (m, 5H), 1.47 – 1.29 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.04, 143.91, 141.17, 137.47, 129.80 (x2), 129.23 (x2), 128.27 (x3), 127.95 (x2), 92.42, 63.84, 45.62 (x2), 33.32 (x2), 25.42, 21.45, 21.32; HRMS (ESI) calcd for $(C_{23}H_{26}N_2O_3SNa)^+$ $[M+Na]^+$: 433.1556, found: 433.1560.



419

tert-butyl (S)-3-((6-methylene-3-oxo-4-phenyl-1-tosylpiperazin-2-yl)methyl)-1H-indole-1-carboxylate (419): Prepared according to the general method using **418** (32 mg, 0.06 mmol), palladium and phosphine added as a solution (0.5 mL of $Pd_2(dba)_3 \cdot CHCl_3$ (3.6 mg, 3.6 µmol), DPEphos (4.2 mg, 8.0 µmol) in 2.0 mL CH_2Cl_2), propargyl carbonate **255** (13 mg, 0.08 mmol) in CH_2Cl_2 (0.5 mL) for 3.5 h. Purified by flash column chromatography (9:1 to 4:1 Hex:EtOAc) to afford **419** (33 mg, 0.06 mmol, 97% yield) as a white amorphous solid.

Analytical data for **419**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.54 (s, 1H), 7.39 – 7.27 (m, 4H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.59 (d, *J* = 6.1 Hz, 2H), 4.87 – 4.78 (m, 1H), 4.50 (dd, *J* = 16.7, 1.6 Hz, 1H), 4.11 (s, 1H), 3.94 (d, *J* = 16.7 Hz, 1H), 3.53 (s, 1H), 3.46 (dd, *J* = 14.9, 7.3 Hz, 1H), 3.39 (dd, *J* = 14.9, 4.6 Hz, 1H), 2.42 (s, 3H), 1.69 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.23, 149.47, 144.10, 140.03, 136.86, 135.39, 130.10, 129.56 (x2), 129.51, 128.47 (x2), 128.15, 127.85 (x2), 124.67, 124.56, 122.76, 119.14, 115.24, 115.20, 94.88, 83.67, 58.37, 43.77, 31.57, 28.25 (x3), 22.63, 21.51, 14.08; HRMS (ESI) calcd for $(C_{32}H_{34}N_3O_5SNa)^+$ $[M+Na]^+$: 572.2214, found: 572.2208.

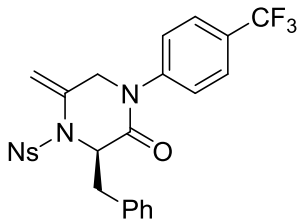


421

(R)-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-methylene-1-phenyl-4-tosylpiperazin-2-one (421): Prepared according to the general method using **420** (16 mg, 0.05 mmol), palladium and phosphine added as a solution (0.5 mL of $Pd_2(dba)_3 \cdot CHCl_3$ (3.2mg, 3.2 µmol), DPEphos (3.6 mg, 3.2 µmol) in 2.0 mL CH_2Cl_2), propargyl carbonate **255** (13 mg, 0.08 mmol) in CH_2Cl_2 (0.5

mL) for 5 h. Purified by flash column chromatography (9:1 to 4:1 Hex:EtOAc) to afford **421** (17 mg, 0.05 mmol, 97% yield) as a white amorphous solid.

Analytical data for **421**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 5H), 6.52 (s, 2H), 4.87 (d, *J* = 16.3 Hz, 1H), 4.62 (dd, *J* = 16.4, 1.3 Hz, 1H), 4.53 (d, *J* = 2.0 Hz, 1H), 4.37 (dd, *J* = 10.2, 3.0 Hz, 1H), 4.10 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.50 (s, 1H), 2.48 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.90, 144.06, 140.59, 136.99, 136.16, 129.86 (x2), 129.45 (x2), 128.36), 128.17 (x2), 127.82 (x2, 94.14, 67.31, 60.07, 46.10, 25.75 (x3), 21.47, 18.06, -5.67, -5.72; HRMS (ESI) calcd for $(C_{25}H_{34}N_2O_4SSiNa)^+$ $[M+Na]^+$: 509.1901, found: 509.1904.

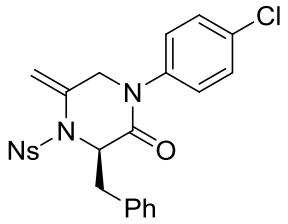


423

(R)-3-benzyl-5-methylene-4-((4-nitrophenyl)sulfonyl)-1-(4-(trifluoromethyl)phenyl)piperazin-2-one (423): Prepared according to the general method using **422** (109 mg, 0.22 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.4 mg, 3.3 μmol), DPEphos (3.9 mg, 7.3 μmol), propargyl carbonate **255** (45 mg, 0.29 mmol) in CH_2Cl_2 (2.2 mL) for 24 h. Purified by flash column chromatography (1:1 to 1:0 CH_2Cl_2:Hexanes) to afford **423** (113 mg, 0.21 mmol, 97% yield) as a white solid.

Analytical data for **423**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.68 – 7.59 (m, 2H), 7.58 – 7.49 (m, 1H), 7.22 – 7.09 (m, 7H), 5.00 – 4.89 (m, 1H), 4.55 (d, *J* = 16.5 Hz, 1H), 4.20 (s, 1H), 4.03 (d, *J* = 16.5 Hz, 1H), 3.65 (s, 1H), 3.31 (t, *J* = 6.5

Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.94, 140.41, 140.21, 135.87, 133.99, 132.57, 132.04, 131.26, 130.92, 130.61, 129.37 (x2), 129.11, 128.51 (x2), 127.25, 126.89 (x2), 124.70, 124.58, 122.53, 95.24, 60.86, 43.53, 37.66; HRMS (ESI) calcd for $(C_{25}H_{21}F_3N_3O_5S)^+$ $[M+H]^+$: 532.1149, found: 532.1149.



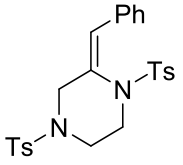
425

(R)-3-benzyl-1-(4-chlorophenyl)-5-methylene-4-((4-nitrophenyl)sulfonyl)piperazin-2-one (425): Prepared according to the general method using **424** (92 mg, 0.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.1 mg, 3.0 μmol), DPEphos (3.6 mg, 6.6 μmol), propargyl carbonate **255** (41 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 28 h. Purified by flash column chromatography (2:1 CH_2Cl_2:Hexanes to 1% MeOH in CH_2Cl_2) to afford **425** (100 mg, 0.20 mmol, 99% yield) as a white solid.

Analytical data for **425**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.62 (ddd, *J* = 9.6, 7.5, 1.4 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.20 – 7.07 (m, 5H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.96 – 4.88 (m, 1H), 4.53 (dd, *J* = 16.5, 1.7 Hz, 1H), 4.18 (s, 1H), 4.00 (d, *J* = 16.5 Hz, 1H), 3.73 – 3.63 (m, 1H), 3.30 (dd, *J* = 6.5, 4.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.95, 140.35, 135.96, 135.60, 134.49, 133.93, 132.63, 132.01, 131.21, 129.99, 129.78 (x2), 129.38 (x2), 128.48 (x2), 127.21, 124.57, 95.05, 60.86, 43.51, 37.66, 31.14, 22.28; HRMS (ESI) calcd for $(C_{24}H_{21}ClN_3O_5S)^+$ $[M+H]^+$: 498.0885, found: 498.0883.

General Procedure for the Pd-Catalzed Piperizine Formation with Substituted Propargyl Carbonates.

General Method: Diamine substrate **362** (1 equiv.), $Pd_2(dba)_3 \cdot CHCl_3$ (0.015 equiv., 3 mol % Pd) and DPEphos (0.033 equiv.) were added to a oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was purged with nitrogen, anhydrous CH_2Cl_2 (0.1 M) was added and the mixture was maintained under a positive pressure of nitrogen. In the case of a heterogeneous mixture sonication was used to break up larger particles of insoluble substrate. After 2 min the substituted propargyl carbonate **2** (1.3 equiv.) was added to the reaction mixture via syringe. The test tube was purged again with nitrogen. After consumption of starting material as judged by TLC, the reaction was concentrated and purified by flash column chromatography to give the desired products.



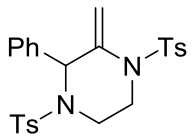
427

(Z)-2-benzylidene-1,4-ditosylpiperazine (427): Prepared according to the general method using **362** (74 mg, 0.2 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (3.1 mg, 3.0 µmol), DPEphos (3.6 mg, 6.6 µmol), propargyl carbonate **288** (60 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 45 min. Purified by flash column chromatography (8:1 to 4:1 Hexanes:EtOAc) to afford **427** (43 mg, 0.09 mmol, 45% yield, 10:1 mixture of olefin isomers) as a yellow solid.

Prepared according to a modification of the general method using **362** (37 mg, 0.1 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (1.6 mg, 1.5 µmol), DPEphos (1.8 mg, 3.3 µmol), propargyl carbonate **288** (30

mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) for 5 h. Prior to addition of propargyl carbonate the reaction mixture was cooled to 0 °C for 30 min. Purified by flash column chromatography (8:1 to 4:1 Hexanes:EtOAc) to afford **427** (24 mg, 0.05 mmol, 50% yield, 20:1 mixture of olefin isomers) as a yellow solid.

Analytical data for **427**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, min), 7.59 (d, *J* = 10.0 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, min), 7.36 (d, *J* = 7.7 Hz, min), 7.28 (m, 5H), 7.25 – 7.06 (m, 6H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.74 (s, min), 6.50 (s, 1H), 3.85 – 3.66 (m, 2H), 3.55 (s, 1H), 3.16 – 2.97 (m, 1H), 2.43 (s, 3H), 2.39 (s, min), 2.26 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.98, 143.63, 136.36, 133.92, 132.56, 131.01, 129.79 (x2), 129.69, 129.65, 129.21, 129.14 (x2), 128.90 (x2), 128.73, 128.63, 127.99 (x2), 127.84, 127.73 (x2), 127.57, 127.56 (x2), 127.26, 50.93, 46.95, 46.28, 44.44, 44.13, 21.52, 21.36; HRMS (ESI) calcd for $(C_{25}H_{27}N_2O_4S_2)^+$ $[M+H]^+$: 483.1407, found: 483.1405.

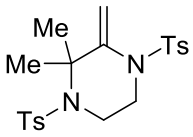


428

2-methylene-3-phenyl-1,4-ditosylpiperazine (428): Prepared according to the general method using **362** (74 mg, 0.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.1 mg, 3.0 μmol), DPEphos (3.6 mg, 6.6 μmol), propargyl carbonate **288** (60 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 45 min. Purified by flash column chromatography (8:1 to 4:1 Hexanes:EtOAc) to afford **428** (43 mg, 0.09 mmol, 45% yield) as a white solid.

Analytical data for **428**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.16 (m, 7H), 5.40 (s, 1H), 5.31 (s, 1H), 4.72 (s, 1H), 3.57 (m,

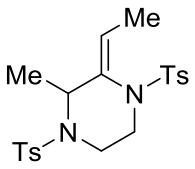
1H), 3.48 (m, 2H), 3.39 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.96, 137.54, 137.33, 129.80 (x2), 129.48 (x2), 128.53 (x3), 127.46 (x2), 127.45 (x2), 127.41 (x2), 126.26 (x2), 105.61 (x2), 62.77 (x2), 44.06, 42.96, 21.53; HRMS (ESI) calcd for $(C_{25}H_{27}N_2O_4S_2)^+$ $[M+H]^+$: 483.1407, found: 483.1411.



430

(Z)-2-ethylidene-3-methyl-1,4-ditosylpiperazine (430): Prepared according to the general method using **362** (55 mg, 0.15 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.4 mg, 2.3 μmol), DPEphos (2.7 mg, 5.0 μmol), propargyl carbonate **429** (37 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) for 24 h. Purified by flash column chromatography (8:1 to 4:1 Hexanes:EtOAc) to afford **430** (37 mg, 0.09 mmol, 57% yield) as a white amorphous solid.

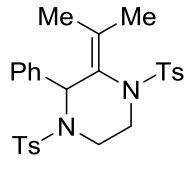
Analytical data for **430**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.29 (m, 2H), 7.28 – 7.18 (m, 2H), 5.60 (d, *J* = 6.9 Hz, 1H), 4.51 (d, *J* = 6.9 Hz, 1H), 3.58 (dt, *J* = 13.4, 2.9 Hz, 1H), 3.47 (dt, *J* = 13.6, 3.0 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.02 – 2.94 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.86, 143.44, 137.31, 137.05, 133.79, 129.68 (x2), 129.67 (x2), 127.52 (x2), 127.15 (x2), 125.48, 55.29, 46.56, 39.44, 21.49, 21.46, 17.91, 13.97; HRMS (ESI) calcd for $(C_{21}H_{27}N_2O_4S_2)^+$ $[M+H]^+$: 483.1407, found: 483.1411.



432

2,2-dimethyl-3-methylene-1,4-ditosylpiperazine (432): Prepared according to the general method using **362** (74 mg, 0.2 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (3.1 mg, 3.0 µmol), DPEphos (3.6 mg, 6.6 µmol), propargyl carbonate **431** (48 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) for 3 h. Purified by flash column chromatography (8:1 to 4:1 Hexanes:EtOAc) to afford **432** (52 mg, 0.12 mmol, 60% yield) as a white solid.

Analytical data for **432**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 4 H), 7.27 (dd, *J* = 4.3, 3.8 Hz, 4 H), 5.30 (d, *J* = 1.5 Hz, 1 H), 5.03 (d, *J* = 1.5 Hz, 1 H), 3.62 – 3.57 (m, 2 H), 3.54 (t, *J* = 5.1 Hz, 2 H), 2.43 (d, *J* = 2.3 Hz, 6 H), 1.43 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.96, 143.98, 143.96, 143.16, 129.60 (x2), 129.55 (x2), 127.56 (x2), 126.85 (x3), 107.86, 65.25, 47.58, 42.40, 26.63 (x2), 21.50, 21.44; HRMS (ESI) calcd for $(C_{21}H_{27}N_2O_4S_2)^+$ $[M+H]^+$: 435.1407, found: 435.1411.



433

2-phenyl-3-(propan-2-ylidene)-1,4-ditosylpiperazine (433): Prepared according to the general method using **362** (37 mg, 0.1 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (1.6 mg, 1.5 µmol), DPEphos (1.8 mg, 3.3 µmol), propargyl carbonate **321** (34 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) for 24 h at 40 °C.

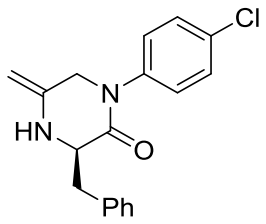
Purified by flash column chromatography (8:1 to 3:1 Hexanes:EtOAc) to afford **433** (10 mg, 0.02 mmol, 20% yield) as a clear oil.

Analytical data for **433**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.25 (m, 5H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.16 (dd, *J* = 8.2, 1.4 Hz, 2H), 5.16 (t, *J* = 5.7 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.33 (q, *J* = 6.4 Hz, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.50, 143.31, 131.58 (x3), 129.72 (x2), 129.58 (x2), 128.56 (x2), 128.21 (x2), 127.52 (x2), 127.22 (x2), 121.98, 90.57, 84.20, 57.31, 47.98, 44.52, 30.70 (x2), 21.49, 21.41; HRMS (ESI) calcd for $(C_{27}H_{31}N_2O_4S_2)^+$ $[M+H]^+$: 511.1720, found: 511.1709.

General Procedure for the Removal of Nosyl Group

General Method: Based on the protocol by Floreancig and coworkers.[63] **425** (1.0 equiv.) and K_2CO_3 (3 equiv.) are added to a dry borosilicate test tube which is then covered with a rubber septa and purged with nitrogen. Anhydrous MeCN (0.11 M) is then added via syringe and the suspension is set stirring at a high rate to prevent K_2CO_3 from settling. To this PhSH (3 equiv.) is added by syringe all at once, within five minutes a color change is noted and SM is consumed as monitored by TLC. The reaction mixture is diluted with CH_2Cl_2 and washed with water. The aqueous layer is extracted 2 times with CH_2Cl_2, the combined organic layers are then washed with brine, dried over $MgSO_4$ and concentrated *in vaccuo*. The residue is then purified by flash column chromatography to afford the desired compounds.

[63] Jung, H. H.; Floreancig, P. E. *The Journal of Organic Chemistry* **2007**, *72*, 7359.



426

(R)-3-benzyl-1-(4-chlorophenyl)-5-methylenepiperazin-2-one (426): Prepared according to the general method using **425** (50 mg, 0.1 mmol), K_2CO_3 (42 mg, 0.3 mmol), PhSH (0.03 mL, 0.3 mmol) in MeCN (1 mL) for 5 min. Purified by flash column chromatography (2:1 CH_2Cl_2:Hexanes to 1% MeOH in CH_2Cl_2) to afford **426** (47 mg, 0.1 mmol, 99% yield) as a white solid.

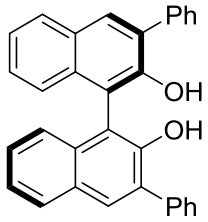
Analytical data for **426**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.30 – 7.24 (m, 3H), 7.06 (d, *J* = 8.6 Hz, 2H), 4.06 (s, 1H), 3.88 (dd, *J* = 8.3, 4.0 Hz, 1H), 3.74 (d, *J* = 14.7 Hz, 1H), 3.66 (d, *J* = 14.7 Hz, 1H), 3.62 (s, 1H), 3.37 (dd, *J* = 13.8, 3.9 Hz, 1H), 3.15 (dd, *J* = 13.8, 8.3 Hz, 1H) 1.74 (br. s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.24, 144.62, 137.46, 136.36, 134.00, 130.07 (x2), 129.90 (x2), 129.58 (x2), 128.72 (x2), 126.96, 92.07, 61.03, 47.40, 37.61; HRMS (ESI) calcd for $(C_{18}H_{18}ClN_2O)^+$ $[M+H]^+$: 313.1102, found: 313.1105.

VII.5: Experimental Section – Chapter V

Procedure for the Rh-Catalyzed *O*-Arylation of Binaphthol

2,2′-binanphthol **436** (72 mg, 0.25 mmol), $Rh(nbd)_2BF_4$ (9 mg, 25 µmol), tris(*o*-anisyl)phosphine oxide (11 mg, 31 mmol) and $CsCO_3$ (326 mg, 1.0 mmol) were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. *o*-xylene (1.75 mL) and anh. NMP (0.75 mL)

were added, and the mixture was maintained under a positive pressure of nitrogen. PhI (0.17 mL, 1.5 mmol) was added via syringe all at once, black electrical tape was placed over the septum and the reaction vessel was purged 3x with N_2. The heterogeneous reaction mixture was heated in an oil bath to 130 °C and allowed to stir for 20 h. After completion of the reaction the mixture was cooloed to ambient temperature, diluted with 20 mL Et_2O and carefully quenched with 2 mL HCl (12.1 M). The biphasic mixture was vigorously stirred under ambient conditions for 30 minutes, after which the phases were separated. The aqueous layer was extracted with Et_2O (3x), the organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Excess *o*-xylene was removed as an azeotropic mixture with methanol. The crude residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR to obtain NMR yields. Following analysis the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (20:1 Hexanes:EtOAc to 4:1 Hexanes:EtOAc) to give the desired products.

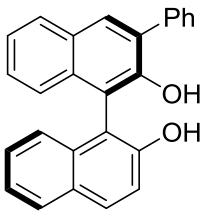


438

3,3′-Diphenyl-1,1′-bi-2,2′-naphthol (438): Isolated **438** (48 mg, 10.9 mmol, 44% yield) as a white solid.

Analytical data matched those reported in the literature.[64]

[64] Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082-6083.



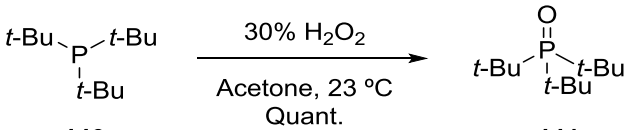
439

3-phenyl-1,1′-bi-2,2′-naphthol (439): Isolated **439** (54 mg, 14.5 mmol, 56% yield) as a white solid.

Analytical data matched those reported in the literature.[65]

General Procedure for Phosphine Oxidation

Prepared according to a procedure by Bowden and coworkers.[66] Phosphine was added to a round bottom flask followed by addition of acetone. H_2O_2 (30%) was added to the stirring solution dropwise over five minutes. The reaction flask was capped and allowed to stir at ambient temperature overnight. The solvent was then removed *in vacuo* and the aqueous residue was diluted with CH_2Cl_2. The oranic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was removed *in vaccuo* to reveal the desired product.



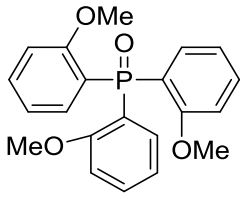
440 **441**

Tri-*tert*-butyl-phosphine oxide (441): Prepared according to the standard method using P(*t*-Bu)$_3$ (1M in toluene) (2 mL, 2.0 mmol), H_2O_2 (30%, 0.25 mL, 2.32 mmol) and acetone (16 mL).

[65] Harada, T.; Kanda, K. *Org. Lett.* **2006**, *8*, 3817-3819.
[66] Bowden, A.; Coles, S. J.; Pitak, M. B.; Platt, A. W. G. *Inorg. Chem.* **2012**, *51*, 4379-4389.

Isolated product **441** (434 mg, 2.0 mmol, 99% yield) was deemed sufficiently pure and used as is.

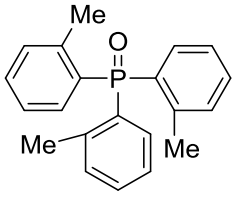
Analytical data matched those reported in the literature.[66]



548

Tris(*o*-anisyl)phosphine oxide (548): Prepared according to the standard method using tris(*o*-anisylphenyl)phosphine (176 mg, 0.5 mmol), H_2O_2 (30%, 0.1 mL, 1.0 mmol) and dichloromethane (3.6 mL). Isolated product **548** was deemed sufficiently pure and used as is.

Analytical data matched those reported in the literature.[67]

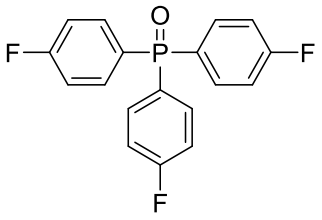


549

Tris(*o*-tolyl)phosphine oxide (549): Prepared according to the standard method using 2- tris(*o*-tolyl)phosphine oxide (238 mg, 0.5 mmol), H_2O_2 (30%, 0.1 mL, 1.0 mmol) and dichloromethane (3.6 mL). Isolated product **549** was deemed sufficiently pure and used as is.

Analytical data matched those reported in the literature.[68]

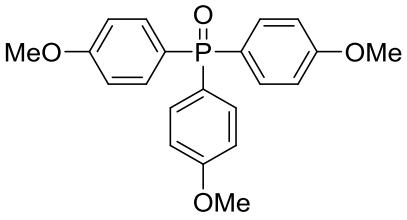
[67] Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413-3422.



550

Tris(*p*-fluorophenyl)phosphine oxide (550): Prepared according to the standard method using Tris(*p*-fluorophenyl)phosphine (316 mg, 0.5 mmol), H_2O_2 (30%, 0.1 mL, 1.0 mmol) and dichloromethane (3.6 mL). Isolated product **550** was deemed sufficiently pure and used as is.

Analytical data matched those reported in the literature.[68]

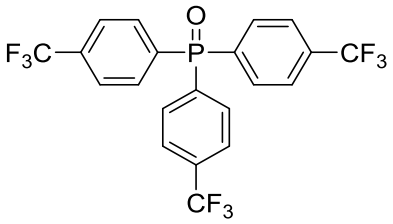


551

Tris(*p*-anisylphenyl)phosphine oxide (551): Prepared according to the standard method using tris(*p*-anisylphenyl)phosphine (176 mg, 0.5 mmol), H_2O_2 (30%, 0.1 mL, 1.0 mmol) and dichloromethane (3.6 mL). Isolated product **551** was deemed sufficiently pure and used as is.

Analytical data matched those reported in the literature.[68]

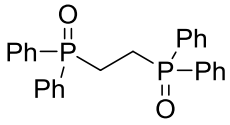
[68] Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. *The Journal of Organic Chemistry* **2011**, *76*, 6749-6767.



552

Tris(*p*-trifluoromethyl-phenyl)phosphine oxide (552): Prepared according to the standard method using Tris(*p*-trifluoromethyl-phenyl)phosphine (233 mg, 0.5 mmol), H_2O_2 (30%, 0.1 mL, 1.0 mmol) and dichloromethane (3.6 mL). Isolated product **552** (229 mg, 0.48 mmol, 95% yield) was deemed sufficiently pure and used as is.

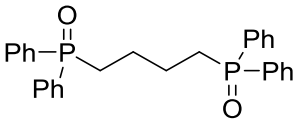
Analytical data matched those reported in the literature.[69]



553

Ethylenebis(diphenylphosphine) oxide (553): Prepared according to the standard method using ethylenebis(diphenylphosphine) (199 mg, 0.5 mmol), H_2O_2 (30%, 0.2 mL, 1.1 mmol) and dichloromethane (3.6 mL). Isolated product **553** was deemed sufficiently pure and used as is.

Analytical data matched those reported in the literature.[69]

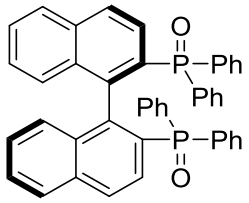


554

[69] Busacca, C. A.; Raju, R.; Grinberg, N.; Haddad, N.; James-Jones, P.; Lee, H.; Lorenz, J. C.; Saha, A.; Senanayake, C. H. *The Journal of Organic Chemistry* **2008**, *73*, 1524-1531.

1,4-bis(diphenylphosphino)butane oxide (554): Prepared according to the standard method using 1,4-bis(diphenylphosphino)butane (213 mg, 0.5 mmol), H_2O_2 (30%, 0.2 mL, 1.1 mmol) and dichloromethane (3.6 mL). Isolated product **554** was deemed sufficiently pure and used as is.

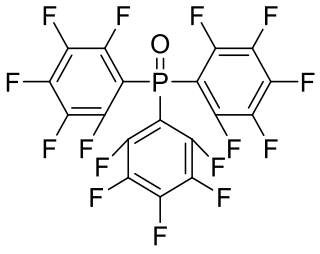
Analytical data matched those reported in the literature.[69]



555

(R)-(+)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine) oxide (555): Prepared according to the standard method using (R)-(+)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine) (311 mg, 0.5 mmol), H_2O_2 (30%, 0.2 mL, 1.1 mmol) and dichloromethane (3.6 mL). Isolated product **555** was deemed sufficiently pure and used as is.

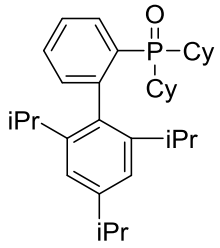
Analytical data matched those reported in the literature.[69]



556

Tris(pentafluorophenyl)phosphine oxide (556): Prepared according to the standard method using Tris(pentafluorophenyl)phosphine (266 mg, 0.5 mmol), H_2O_2 (30%, 2.5 mL, 2.55 mmol) and petroleum ether (15 mL) at 60 °C. Isolated product **556** was deemed sufficiently pure and used as is.

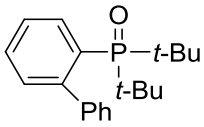
Analytical data matched those reported in the literature.[70]



557

2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl oxide (557): Prepared according to the standard method using 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (238 mg, 0.5 mmol), H_2O_2 (30%, 0.1 mL, 1.0 mmol) and dichloromethane (3.6 mL). Isolated product **557** was deemed sufficiently pure and used as is.

Analytical data matched those reported in the literature.[71]

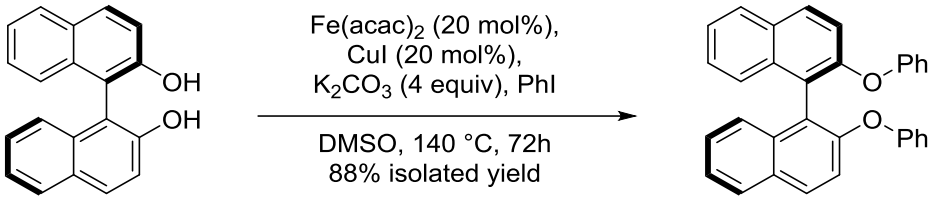


558

(2-biphenyl)di-*tert*-butylphosphine oxide (558): Prepared according to the standard method using (2-biphenyl)di-*tert*-butylphosphine (149 mg, 0.5 mmol), H_2O_2 (30%, 0.1 mL, 1.0 mmol) and dichloromethane (3.6 mL). Isolated product **558** was deemed sufficiently pure and used as is.

Analytical data matched those reported in the literature.[69]

[70] Furin, G. G.; Krupoder, S. A.; Rezvukhin, A. I.; Kilina, T. M.; Yakobson, G. G. *J. Fluorine Chem.* **1983**, *22*, 345-375.
[71] Zhang, D.; Celaje, J. A.; Agua, A.; Doan, C.; Stewart, T.; Bau, R.; Selke, M. *Org. Lett.* **2010**, *12*, 3100-3103.



435 **442**

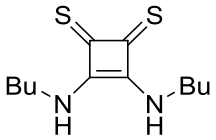
O, O′-di-phenyl-1,1′-bi-2,2′-naphthol (438): Prepared according to the procedure by Qu and coworkers.[72] 2,2′-binaphthol (143 mg, 0.5 mmol), $Fe(acac)_2$ (25 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol) and K_2CO_3 (276 mg, 2.0 mmol) were added to a dry round bottom flask equipped and sealed with a rubber stopper. Anh. DMSO (5 mL) and PhI (0.14 mL, 1.2 mmol) were added via syringe and the reaction was heated to 140 °C in an oil bath for 72 h. After the reaction mixture had cooled to ambient temperature it was diluted with Et_2O and water. The organic layer was washed with water, 1M HCl, brine and dried over $MgSO_4$. The reaction was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography to yield **442** (193 mg, 0.44 mmol, 88% yield).

VII.6: Experimental Section – Chapter VI

General Method for Synthesizing Symmetrical Thiosquaramides

Squaramide and P_4S_{10} are added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh CH_2Cl_2 (0.75 mL) was added and the mixture was maintained under a positive pressure of nitrogen. Following consumption of the starting material, as determined by TLC analysis, excess P_4S_{10} was quenched with MeOH and the reaction was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to give the desired compounds.

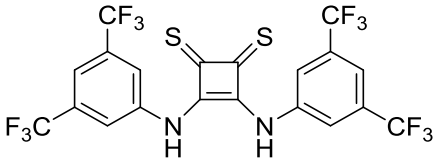
[72] Qu, X.; Li, T.; Zhu, Y.; Sun, P.; Yang, H.; Mao, J. *Organic & Biomolecular Chemistry* **2011**, *9*, 5043-5046.



465

Dibutyl thiosquaramide (465): Prepared according to the standard method using dibutyl squaramide (45 mg, 0.2 mmol), P_4S_{10} (112 mg, 0.2 mmol) and CH_2Cl_2 (5 mL). The reaction was stirred for 1 h at 23 °C. Purified by flash column chromatography (2:1 Hexanes:EtOAc to EtOAc) to give **465** (49 mg, 0.20 mmol, 99% yield).

Analytical data matched those reported in the literature.[73]

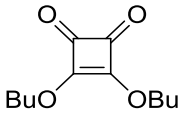


467

Di(3,5-bis(trifluoromethyl)phenyl) thiosquaramide (467): Prepared according to the standard method using Di(3,5-bis(trifluoromethyl)phenyl) squaramide (134 mg, 0.25 mmol), P_4S_{10} (333 mg, 0.75 mmol) and EtOAc (6 mL). The reaction was stirred for 20 h at 50 °C. Purified by flash column chromatography (CH_2Cl_2 to 9:1:0.1 CH_2Cl_2:MeOH:NH_4Cl) to give **467**(71 mg, 0.12 mmol, 50% yield).

Analytical data matched those reported in the literature.[74]

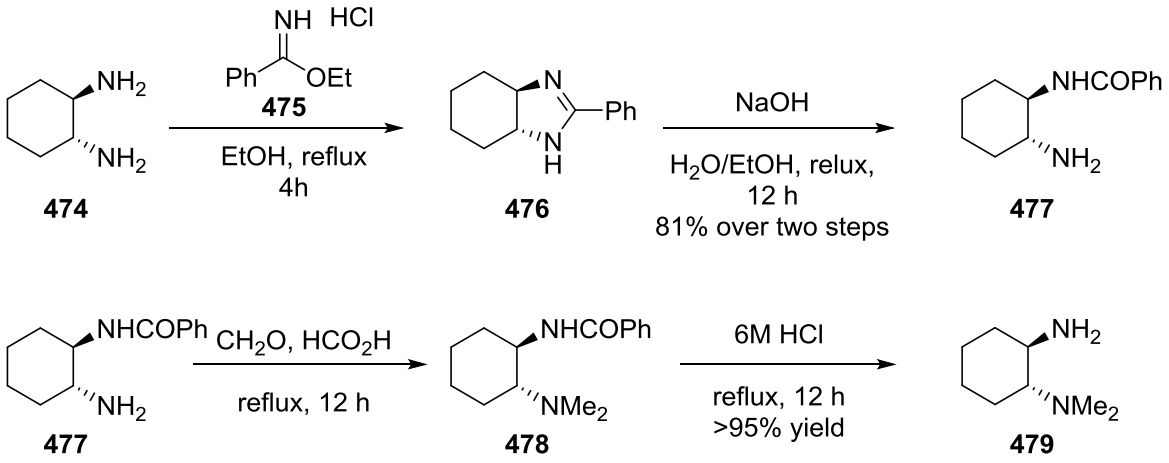
[73] Frauenhoff, G. R.; Takusagawa, F.; Busch, D. H. *Inorg. Chem.* **1992**, *31*, 4002-4007.
[74] Busschaert, N.; Elmes, R. B. P.; Czech, D. D.; Wu, X.; Kirby, I. L.; Peck, E. M.; Hendzel, K. D.; Shaw, S. K.; Chan, B.; Smith, B. D.; Jolliffe, K. A.; Gale, P. A. *Chemical Science* **2014**, *5*, 3617-3626.



470

Dibutyl Squarate (470): Prepared according to a procedure based on the work of Zhou and coworkers.[75] Squaric acid (2.85 g, 25 mmol) is added to a dry round bottom flask equipped with a Dean-Stark trap and reflux condenser. Anh toluene (14.3 mL) is added to the reaction flask followed by addition of n-butanol (14.3 mL). The reaction mixture is heated to reflux (125 °C) for 18 h. After cooling to ambient temperature the reaction mixture is concentrated *in vacuo*. The resulting residue is dissolved in CH_2Cl_2 and washed with water (3x). The organic layer is washed with brine, dried over $MgSO_4$ and passed through a plug of silica gel. The plug is washed with (4:1 Hexanes:EtOAc) and the combined organic layers are reduced *in vacuo* to give **470** (4.74 g, 21 mmol, 84% yield) as a clear oil.

Analytical data matched those reported in the literature.[75]



[75] Zhou, H.-B.; Zhang, J.; Lü, S.-M.; Xie, R.-G.; Zhou, Z.-Y.; Choi, M. C. K.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron* **2001**, *57*, 9325-9333.

(1R,2R)-N1,N1-dimethylcyclohexane-1,2-diamine (479): Prepared according to a procedure by Suez and coworkers.[76] Step 1: Ethyl benzimidate hydrochloride (1.14 g, 6.15 mmol) and (1R,2R)-cyclohexane-1,2-diamine (0.6 mL, 5.0 mmol) are added to a dry round bottom flask equipped with a relux condenser and ethanol (6 mL) was added. The reaction mixture was heated to reflux for 4 h, at which point it was allowed to cool to ambient temperature. 1M NaOH was added to the reaction mixture and was vigorously shaken. The mixture was diluted with 20:1 CH_2Cl_2:MeOH and the organic phase was separated, washed with brine and dried over $MgSO_4$. The resulting residue was taken on without further purification.

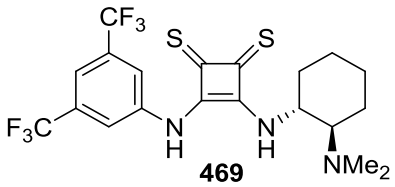
Step 2: Crude **476** (867 mg, 4.33 mmol) was added to a dry round bottom flask equipped with a relux condenser and 1:1 EtOH:H_2O (16 mL) was added. The reaction mixture was heated to reflux for 12 h, at which point it was allowed to cool to ambient temperature. The reaction mixture was reduced *in vacuo* and the resulting aqueous mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give **477** (0.89 g, 4.06 mmol, 88% yield) as a white solid.

Analytical data matches that found in the literature.[76]

Step 3: **477** (218 mg, 1.0 mmol), formic acid (0.19 mL, 5 mmol) and 37% formaldehyde (0.23 mL, 3.1 mmol) were added to a round bottom flask equipped with a reflux condenser. Water (4 mL) was added and the reaction mixture was heated to reflux for 8 h. After cooling to ambient temperature 1M NaOH is added until the reaction pH > 11. The mixture was extracted with CH_2Cl_2, washed with brine and dried over anh $MgSO_4$. The solvent was removed *in vacuo* and the residue was taken on without further purification.

[76] Suez, G.; Bloch, V.; Nisnevich, G.; Gandelman, M. *Eur. J. Org. Chem.* **2012**, *2012*, 2118-2122.

Step 4: **478** (492 mg, 2.0 mmol) was added to a round bottom flask equipped with a reflux condenser and 6 M HCl (12 mL) was added. The reaction was heated to reflux for 16 h. After cooling to ambient temperature the reaction mixture was cooled to -10 °C for 20 minutes. The precipitate was collected by vacuum filtration and the filtrate was basified with 1M NaOH. The basic solution (pH > 10) was extracted with CH_2Cl_2 and the organic phase was washed with brine, dried over anh $MgSO_4$ and concentrated *in vacuo* to give **479** (276 mg, 1.98 mmol, 97% yield) as an oil.



469

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((1*R*,2*R*)-2-(dimethyl)cyclohexyl)amino)

cyclobut-3-ene-1,2-dithione (469): Step 1. Lawesson's Reagent (1.62 g, 4.0 mmol) was added to an oven-dried round bottom flask. The flask was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, toluene (40 mL) was added and maintained under a positive pressure of nitrogen. The heterogeneous suspension was set stirring at a moderate rate and heated to 110 °C in an oil bath. Dibutyl squarate **470** (0.91 mL, 4.0 mmol) was added via syringe all at once and the reaction was monitored by TLC. After consumption of starting material, as determined by TLC analysis, the reaction was quenched with methanol and concentrated *in vacuo*. Excess Lawesson's reagent was removed by passage through a plug of silica and conversion to **471** was determined by ^{1}H NMR (2.32 mmol, 58% yield) using 1,3,5-trismethoxybenzene as an internal standard. Crude **471** was taken onto the next step without further purification.

Analytical data for **471:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (t, *J* = 6.7 Hz, 2H), 1.91 – 1.82 (m, 2H), 1.51 – 1.45 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). HRMS for $(C_{12}H_{19}O_2S_2)^+$ calcd: 259.0821, found: 259.0819.

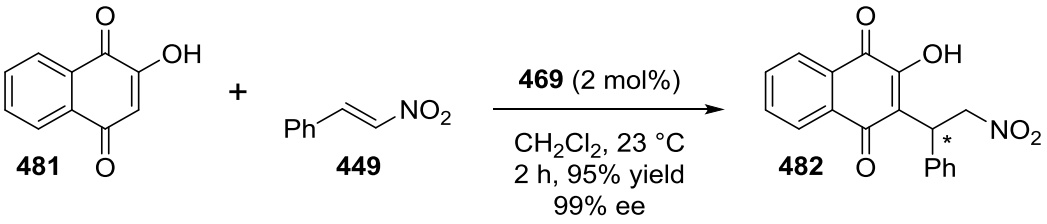
Step 2: Crude **471** (2.32 mmol) was added to an oven-dried round bottom flask. The flask was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. CH_2Cl_2 (23 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. The reaction mixture was then covered in aluminum foil and cooled to 0 °C in an ice water bath. 3,5-bis(trifluoromethyl)aniline (0.36 mL, 2.32 mmol) is added dropwise via a syringe and after completion of addition the reaction mixture is allowed to warm to ambient temperature and stir 12 h. The reaction mixture is concentrated *in vacuo* and the resulting residue is purified by flash column chromatography (20:1 Hexanes:CH_2Cl_2 to 10:1 CH_2Cl_2:MeOH) to give **473** (550 mg, 1.34 mmol, 58% yield) as an amorphous yellow solid.

Analytical data for **473**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.85 (s, 2H), 7.72 (s, 1H), 5.31 (t, *J* = 6.5 Hz, 2H), 1.94 – 1.86 (m, 2H), 1.50 (dd, *J* = 15.1, 7.5 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.57, 170.16, 137.80, 133.56, 119.51, 118.75, 75.44, 32.03, 18.54, 13.44. HRMS for $(C_{16}H_{14}F_6NOS_2)^+$ calcd: 414.0416, found: 414.0412.

Step 3: **473** (389 mg, 0.94 mmol) and K_2CO_3 (274 mg, 1.04 mmol) were added to an oven-dried round bottom flask. The flask was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. CH_2Cl_2 (5 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. To this **479** (147 mg, 1.04 mmol) is added dropwise as a solution and the reaction is allowed to stir until starting material is consumed, by

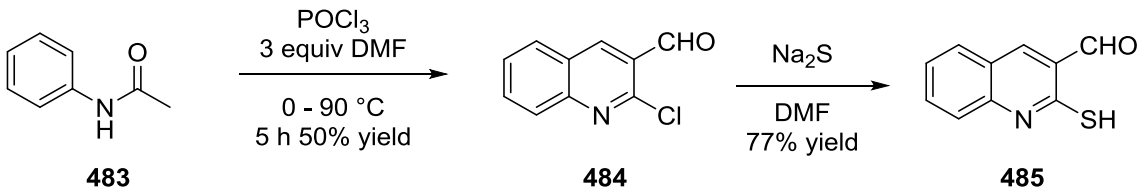
TLC analysis. The solvent is removed *in vacuo* and the material is purified to give **469** as a yellow amorphous solid.

Analytical data for **469:** IR: 1132 cm^{-1} (thione stretch), 1175 cm^{-1} (thione stretch), 1277 cm^{-1} (N-H stretch). ^{1}H NMR (500 MHz, DMSO) δ 7.91 (s, 2H), 7.70 (d, *J* = 10.3 Hz, 1H), 7.50 (s, 2H), 5.42 (s, 1H), 3.34 (s, 1H), 2.75 (s, 6H), 1.78 (d, *J* = 62.0 Hz, 3H), 1.59 (s, 1H), 1.45 (d, *J* = 9.4 Hz, 1H), 1.29 (dd, *J* = 19.3, 8.8 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) Compound **469** did not resonate under a variety of conditions. HRMS for $(C_{20}H_{22}F_6N_2S_2)^+$ calcd: 482.1154, found 482.1150.



2-hydroxy-3-(2-nitro-1-phenylethyl)naphthalene-1,4-dione (482): Lawsone (35 mg, 0.2 mmol), β-nitrostyrene (30 mg, 0.2 mmol) and **469** (2 mg, 4.0 μmol) were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. CH_2Cl_2 (0.50 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. After consumption of starting material, as determined by TLC analysis, solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography (9:1 to 1:1 Hexanes:EtOAc) to provide **482** (62 mg, 0.19 mmol, 95% yield, 99% ee).

^{1}H data matches that found in the literature.[77] Rf: 0.14 in 5:2 Hexanes:EtOAc. Enantiomeric ratio was measured by HPLC (Chiralpak AD-H, 8% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 35.2, Rt_2 = 40.6).



483 **484** **485**

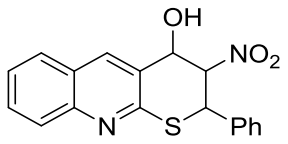
2-mercaptoquinoline-3-carboxaldehyde (485): Step 1: Prepared according to a protocol based on the work of Gupta and coworkers.[78] Acetanilide (0.48 g, 3.55 mmol) was added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. DMF (0.62 mL, 10 mmol) was added, the reaction mixture was cooled to 0 °C and the mixture was maintained under a positive pressure of nitrogen. $POCl_3$ (4 mL, 43 mmol) was added dropwise over 20 minutes, after completion of addition the reaction mixture was heated to 90 °C and stirred for 13 h. The hot solution was poured onto crushed ice **very carefully** (extremely exothermic) and stirred manually for 10 minutes until ice melted. The crude precipitate was purified by recrystallization from acetonitrile.

Step 2: Chloroquinoline **484** (479 mg, 2.5 mmol) and Na_2S (293 mg, 3.75 mmol) were added to an oven-dried round bottom flask. The flask was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. DMF (0.62 mL, 10 mmol) was added, and the mixture was maintained under a positive pressure of nitrogen. After 2 hours the mixture was poured onto crushed ice, acidified with acetic acid and the precipitate was collected by

[77] Yang, W.; Du, D.-M. *Adv. Synth. Catal.* **2011**, *353*, 1241-1246.
[78] Parmar, N.; Labana, B.; Barad, H.; Kant, R.; Gupta, V. *Monatsh Chem* **2014**, *145*, 1179-1189.

vacuum filtration. The precipitate was washe with water and gave **485** (364 mg, 1.92 mmol, 77% yield from **484**) as an organge solid.

Analytical data matches that found in the literature.[79]



486

2H-thiopyrano[2,3-β]quinolone (486): Mercaptoquinoline **485** (30 mg, 0.16 mmol), β-nitrostyrene (28 mg, 0.19 mmol) and **469** (6 mg, 12 µmol) were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. EtOAc (1.0 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. The reaction was allowed to run for 16 h, at which point solvent was removed *in vacuo* and the residue was purified by flash column chromatography (7:1 to 3:1 Hexanes:EtOAc). Product **486** (53 mg, 0.16 mmol, >98% yield, 1.18 d.r., 99% ee).

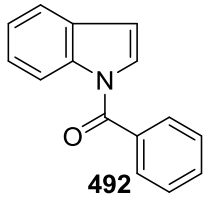
^{1}H data matches those found in the literature.[80] Enantiomeric ratio was measured by HPLC (Chiralpak AD-H, 8% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 35.2, Rt_2 = 40.6).

General Procedure for N-Carbonylation of Indole

Indole, palladium catalyst and K_2CO_3 were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was

[79] Prakash Naik, H. R.; Bhojya Naik, H. S.; Ravikumar Naik, T. R.; Raghavendra, M.; Aravinda, T.; Lamani, D. S. *Phosphorus, Sulfur, and Silicon and the Related Elements* **2009**, *184*, 460-470.
[80] Wu, L.; Wang, Y.; Song, H.; Tang, L.; Zhou, Z.; Tang, C. *Adv. Synth. Catal.* **2013**, *355*, 1053-1057.

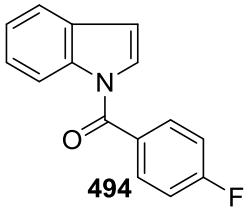
purged 3x with CO, anh. solvent was added, and the mixture was maintained under a positive pressure of CO. Bromobenzene was then added to the reaction mixture and it was heated with stirring. After starting material had been consumed, as determined by TLC analysis, the reaction mixture was allowed to cool to ambient temperature and was diluted with CH_2Cl_2. The organic solution was washed with water, brine, dried over anh $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to yield the desired products.



492

***N*-H-indol-1-ylphenyl-methanone (492):** Prepared according to the general method using indole (117 mg, 1.0 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), P(*t*-Bu)$_3$ (1M in toluene, 0.1 mL, 0.1 mmol), K_2CO_3 (435 mg, 3.0 mmol), PhBr (0.16 mL, 1.5 mmol) and toluene (4 mL). After 24 h the reaction mixture was analyzed by ^{1}H NMR and clean conversion to **492** (94% NMR yield) was observed.

Analytical data matches those found in the literature.[81]



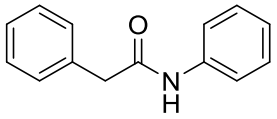
494

***N*-H-indol-1-yl(4-fluorophenyl)-methanone (494):** Prepared according to the general method using indole (117 mg, 1.0 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (27 mg, 0.1 mmol),

[81] Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137-3139.

K_2CO_3 (429 mg, 3.0 mmol), 4-fluorobromobenzene (0.13 mL, 1.2 mmol) and toluene (4 mL). After 24 h the residue was purified by flash column chromatography to give **494** (105 mg, 0.44 mmol, 44% yield).

Analytical data matches those found in the literature.[82]



498

***N*-phenyl-benzeneacetamide (498):** Aniline (2.74 mL, 30.0 mmol) was added to an oven-dried round bottom flask. The flask was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. CH_2Cl_2 (50.0 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. Phenyl acetylchloride (2.64 mL, 20.0 mmol) was added dropwise and the mixture was allowed to stir at ambient temperature for 12 h. The reaction was quenched by addition of 10% HCl (1.2 M) and the mixture was then extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over anh $MgSO_4$ and reduced *in vacuo*. The resulting residue was recrystallized from hot EtOAc to give **498** (2.81 g, 13.3 mmol, 67% yield) as an off white solid.

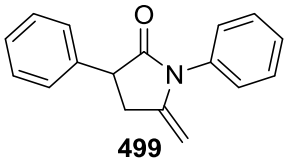
Analytical data matches those found in the literature.[83]

General Method for 5-Membered Heterocycle Synthesis

Substrate, $Pd_2(dba)_3 \cdot CHCl_3$, xantphos and potassium *tert*-butoxide were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with

[82] Fang, W.; Deng, Q.; Xu, M.; Tu, T. *Org. Lett.* **2013**, *15*, 3678-3681.
[83]Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672-17673.

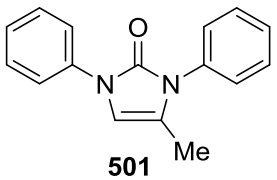
Teflon tape. The test tube was purged 3x with N_2, anh. solvent was added, and the mixture was maintained under a positive pressure of N_2. Propargyl *tert*-butyl carbonate **255** was added via syringe and the reaction has heated as required. Following consumption of the starting material, as judged by TLC, or 24 hours, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to give the desired products.



499

***N*-phenyl-3-phenyl-5-methylene-γ-lactam (499):** Prepared according to the general method using acetamide **498** (106 mg, 0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (13 mg, 12.5 µmol), xantphos (16 mg, 27.5 µmol), KO*t*-Bu (84 mg, 0.75 mmol), propargyl *tert*-butyl carbonate (102 mg, 0.65 mmol) and CH_2Cl_2 (8 mL). Purified by flash column chromatography (20:1 to 6:1 Hexanes:EtOAc) to provide **499**.

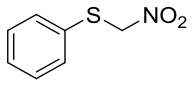
Analytical data for (**449**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (t, *J* = 7.7 Hz, 2H), 7.36 (ddd, *J* = 9.9, 8.4, 3.9 Hz, 5H), 7.31 – 7.27 (m, 3H), 4.26 (q, *J* = 1.6 Hz, 1H), 4.21 (dd, *J* = 3.6, 1.9 Hz, 1H), 3.96 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.37 (ddt, *J* = 16.3, 10.0, 1.8 Hz, 1H), 2.98 (ddt, *J* = 16.3, 5.5, 1.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.43, 168.51, 129.07, 128.64, 128.54, 128.50, 127.91, 127.81, 127.60, 127.32, 127.27, 126.55, 123.85, 122.63. HRMS for $(C_{17}H_{16}NO)^+$ calcd: 250.1226, found 250.1219.



501

1,3-dihydro-4-methyl-1,3-diphenyl-2H-imidazol-2-one (501): Prepared according to the general method using 1,3-diphenylurea (106 mg, 0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (13 mg, 12.5 µmol), xantphos (16 mg, 27.5 µmol), propargyl *tert*-butyl carbonate (102 mg, 0.65 mmol) and CH_2Cl_2 (8 mL). Purified by flash column chromatography (20:1 to 6:1 Hexanes:EtOAc) to provide **501**.

Analytical data matches those found in the literature.[84] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2H), 7.48 (t, *J* = 7.9 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.37 (t, *J* = 7.0 Hz, 3H), 7.25 – 7.19 (m, 1H), 6.48 (d, *J* = 1.4 Hz, 1H), 2.01 (d, *J* = 1.4 Hz, 3H).



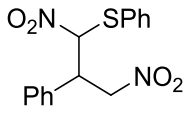
507

Phenylthionitromethane (507): Compound was synthesized following a protocol by Blanco and coworkers.[85] Potassium *tert*-butoxide (294 mg, 2.62 mmol) is added to an oven dried round bottom flask and is sealed under nitrogen. DMSO (12 mL) is added via syringe and the mixture is stirred at ambient temperature until the majority of the solids have dissolved. Nitromethane (0.11 mL, 1.95 mmol) is added via syringe and the reaction mixture is allowed to stir for an additional five minutes. Diphenyldisulfide (218 mg, 1.0 mmol) is added all at once, the flask is resealed and purged with nitrogen. The mixture is allowed to stir for five hours, followed by quenching with 1M NH_4NO_3 solution (70 mL). The solution is then acidified to pH=4, extracted with dichloromethane (3x) and the combined organic extracts are dried over $MgSO_4$. The

[84] Motamandi, A.; Remizova, L. A.; Fornenkova, T. N.; Favorskaya, I. A. *Zhurnal Organicheskoi Khimii* **1981**, *18*, 977-980.
[85] Blanco, G. A.; Baumgartner, M. T. *Tetrahedron Lett.* **2011**, *52*, 7061-7063.

solution is concentrated *in vacuo* and the residue is purified by flash column chromatography (1:0 to 10:1 Hexanes:CH_2Cl_2) to give **507** (152 mg, 0.9 mmol, 90% yield) as a yellow solid.

Analytical data matches those found in the literature.[85]



517

1-nitro-1-thiophenyl-2-phenyl-3-nitro-propane (517): Phenylthionitromethane **507** (25 mg, 0.15 mmol), β-nitrostyrene (15 mg, 0.1 mmol) and squaramide catalyst (0.01 mmol) were added to an oven-dried 16x100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape. The test tube was purged 3x with N_2, anh. CH_2Cl_2 (1 mL) was added, and the mixture was maintained under a positive pressure of N_2 for 20 h. After completion of the reaction solvent was removed *in vacuo* and the residue was purified by flash column chromatography (10:1 to 3:1 Hexanes:EtOAc).

Analytical data for **517**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.36 – 7.31 (m, 2H), 7.25 – 7.21 (m, 2H), 5.84 (d, *J* = 10.2 Hz, 1H), 5.79 (d, *J* = 7.3 Hz, 0H), 5.13 (dd, *J* = 13.4, 4.8 Hz, 1H), 4.97 (dd, *J* = 7.8, 2.6 Hz, 1H), 4.94 (d, *J* = 8.6 Hz, 0H), 4.38 (q, *J* = 7.2 Hz, 0H), 4.23 (ddd, *J* = 10.1, 8.6, 4.8 Hz, 1H). Enantiomeric ratio was measured by HPLC (Chiralpak AD-H, 8% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 35.2, Rt_2 = 40.6).^{1}H NMR of **206** (500 MHz, $CDCl_3$)

APPENDIX

^{1}H NMR, ^{13}C NMR, ^{31}P NMR AND CHIRAL HPLC SPECTRA

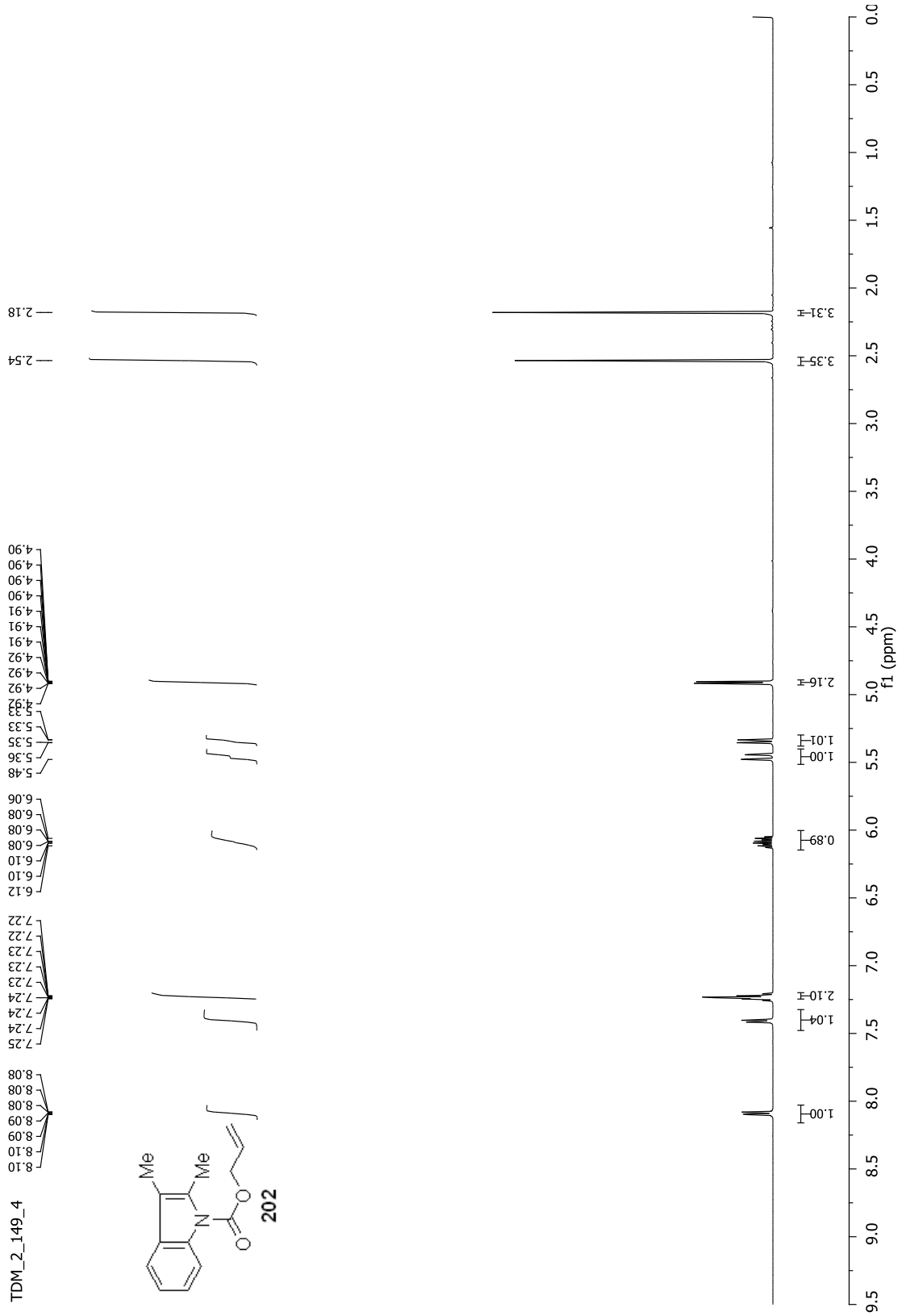


Figure 1. ^{1}H NMR Spectrum of **202** (500 MHz, $CDCl_3$)

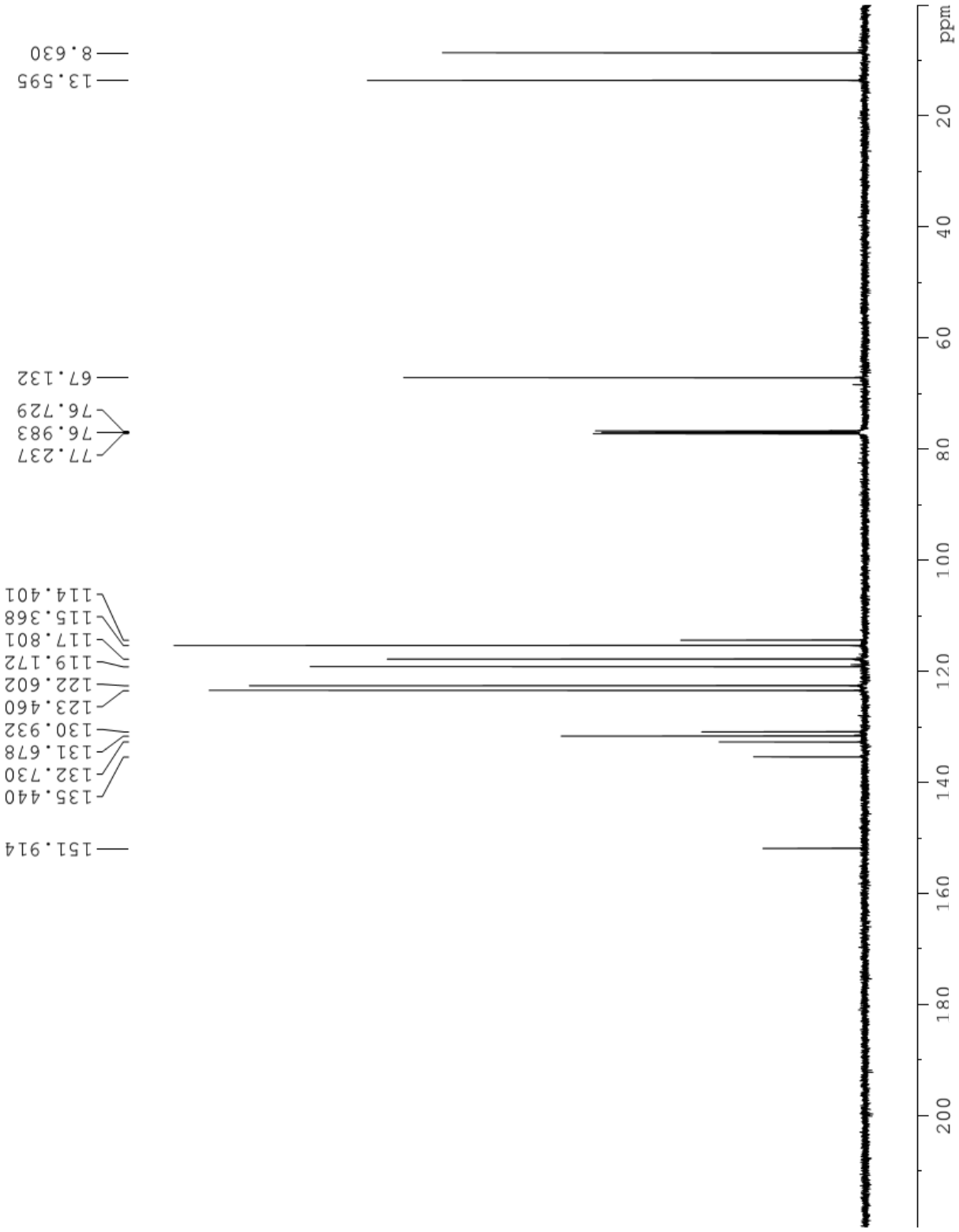


Figure 2. ^{13}C NMR Spectrum of **202** (125 MHz, $CDCl_3$)

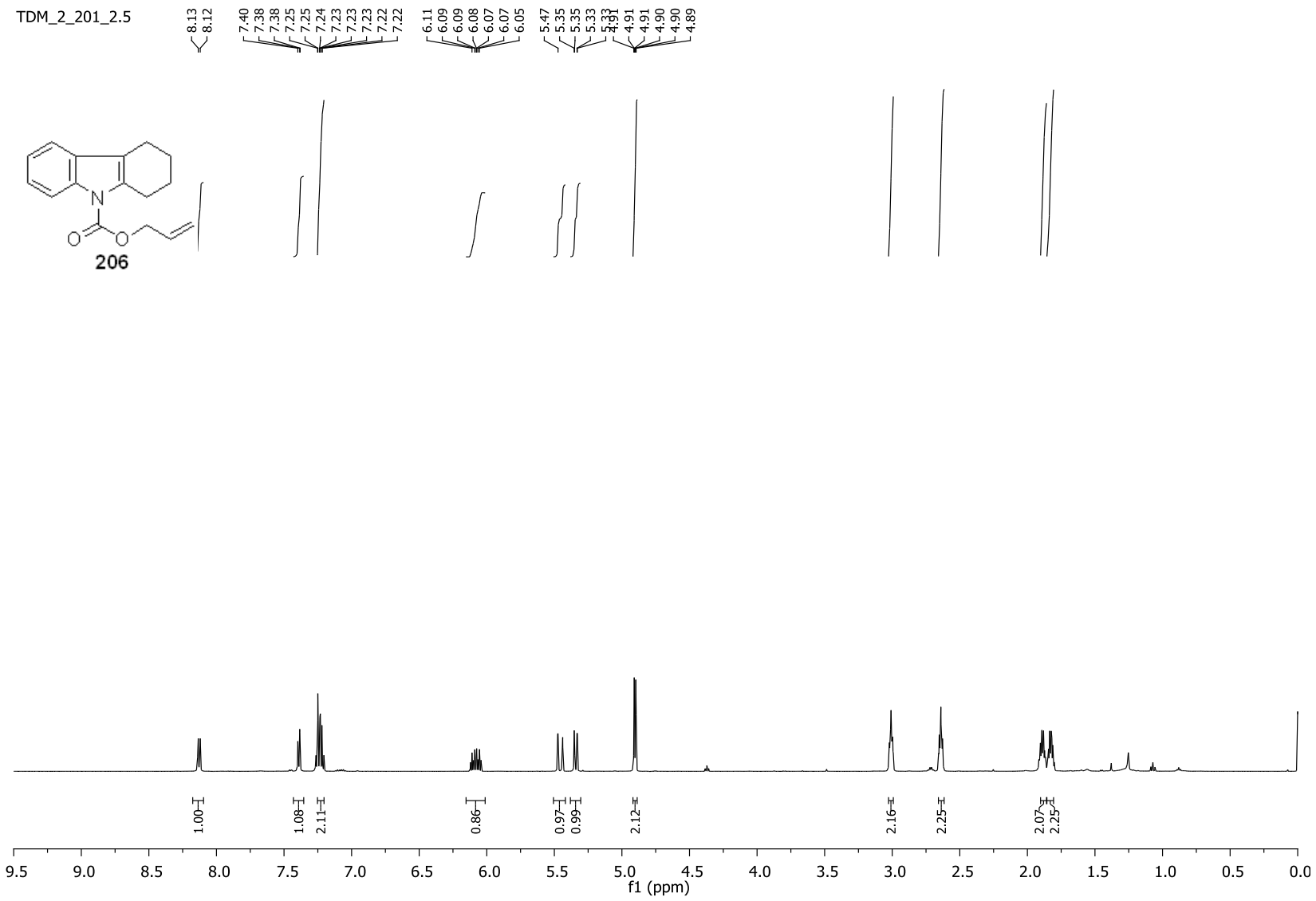


Figure 3. ^{1}H NMR Spectrum of **206** (500 MHz, $CDCl_3$)

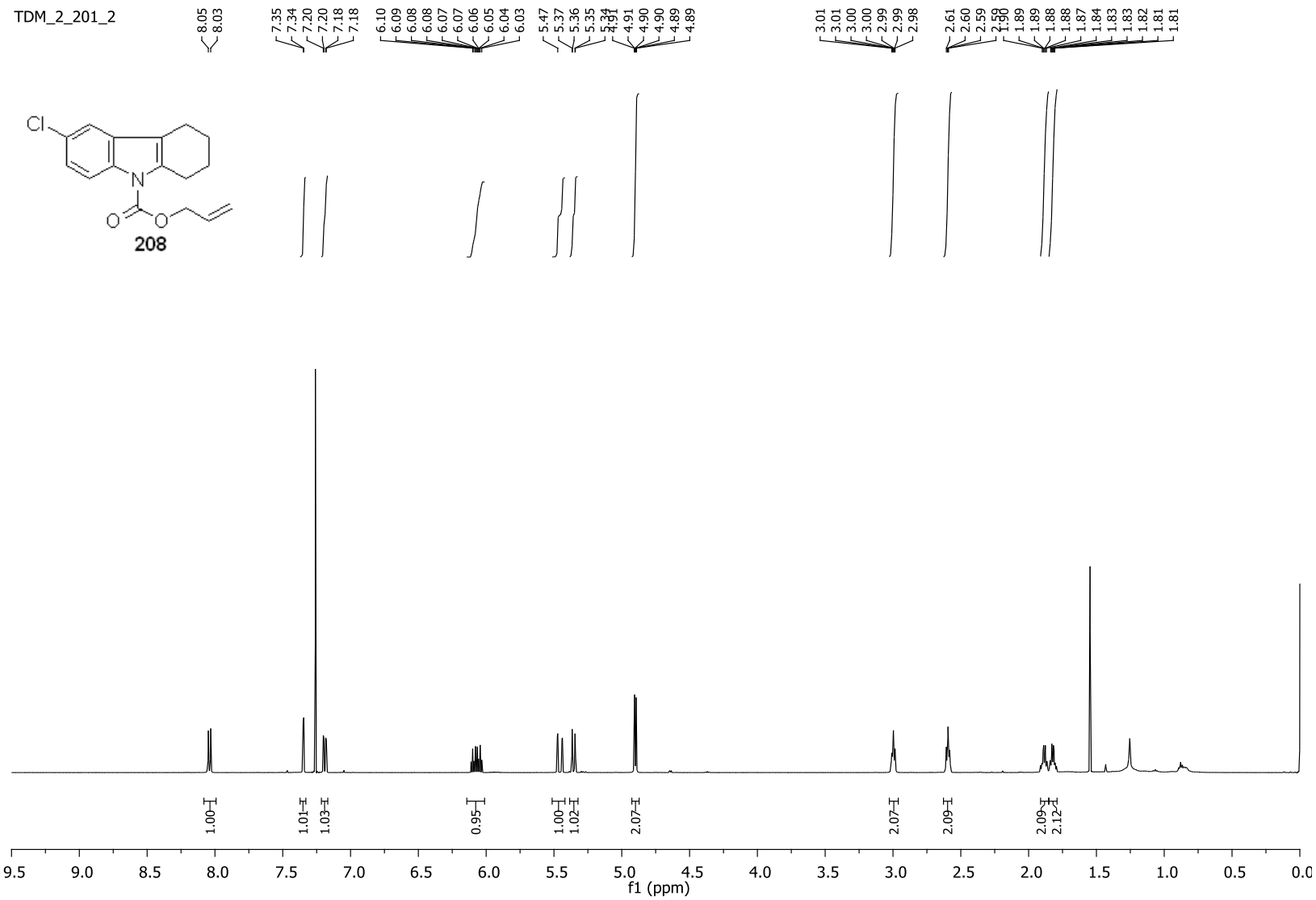


Figure 4. ^{1}H NMR Spectrum for **208** (500 MHz, $CDCl_3$)

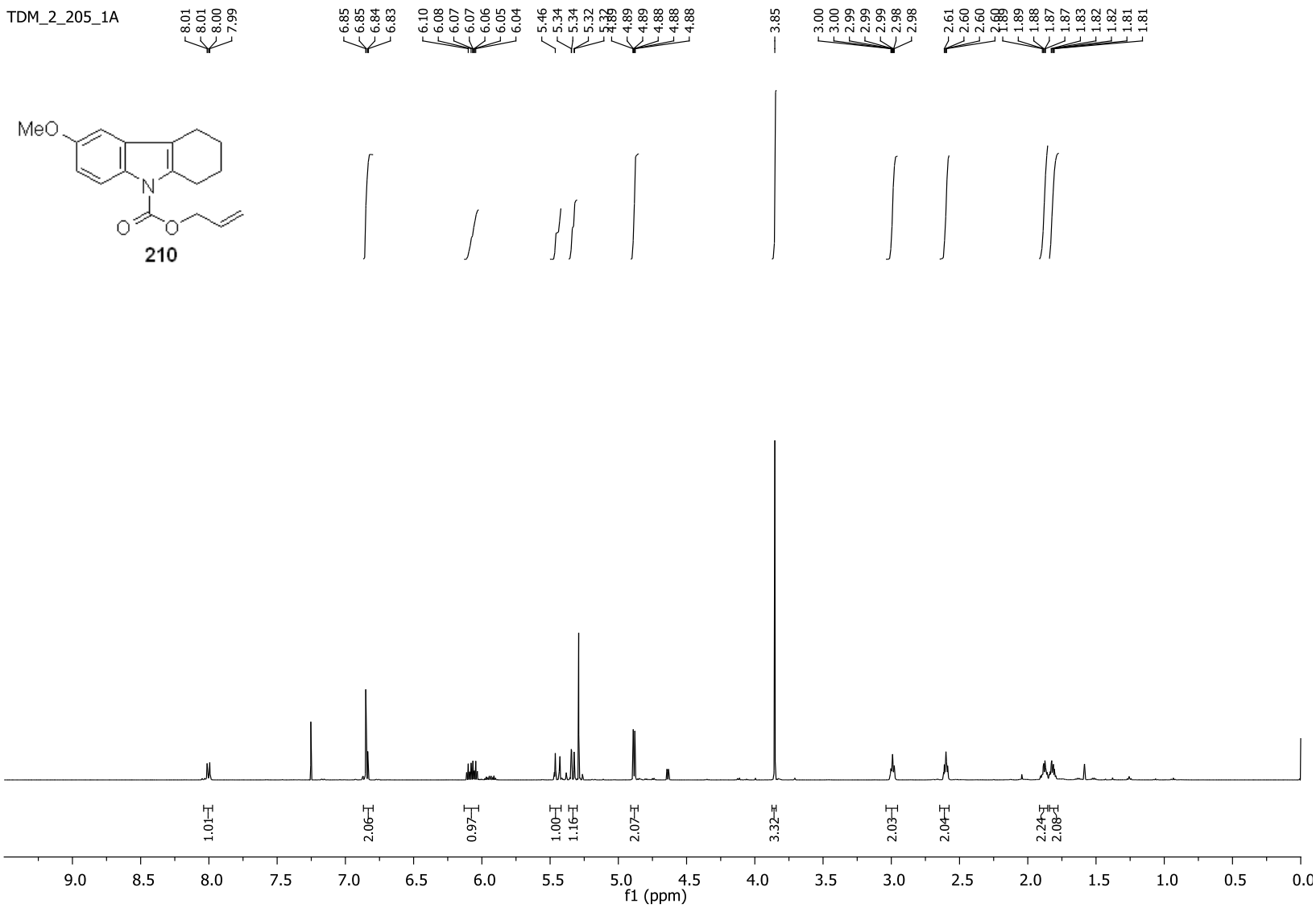


Figure 5. ^{1}H NMR Spectrum for **210** (500 MHz, $CDCl_3$)

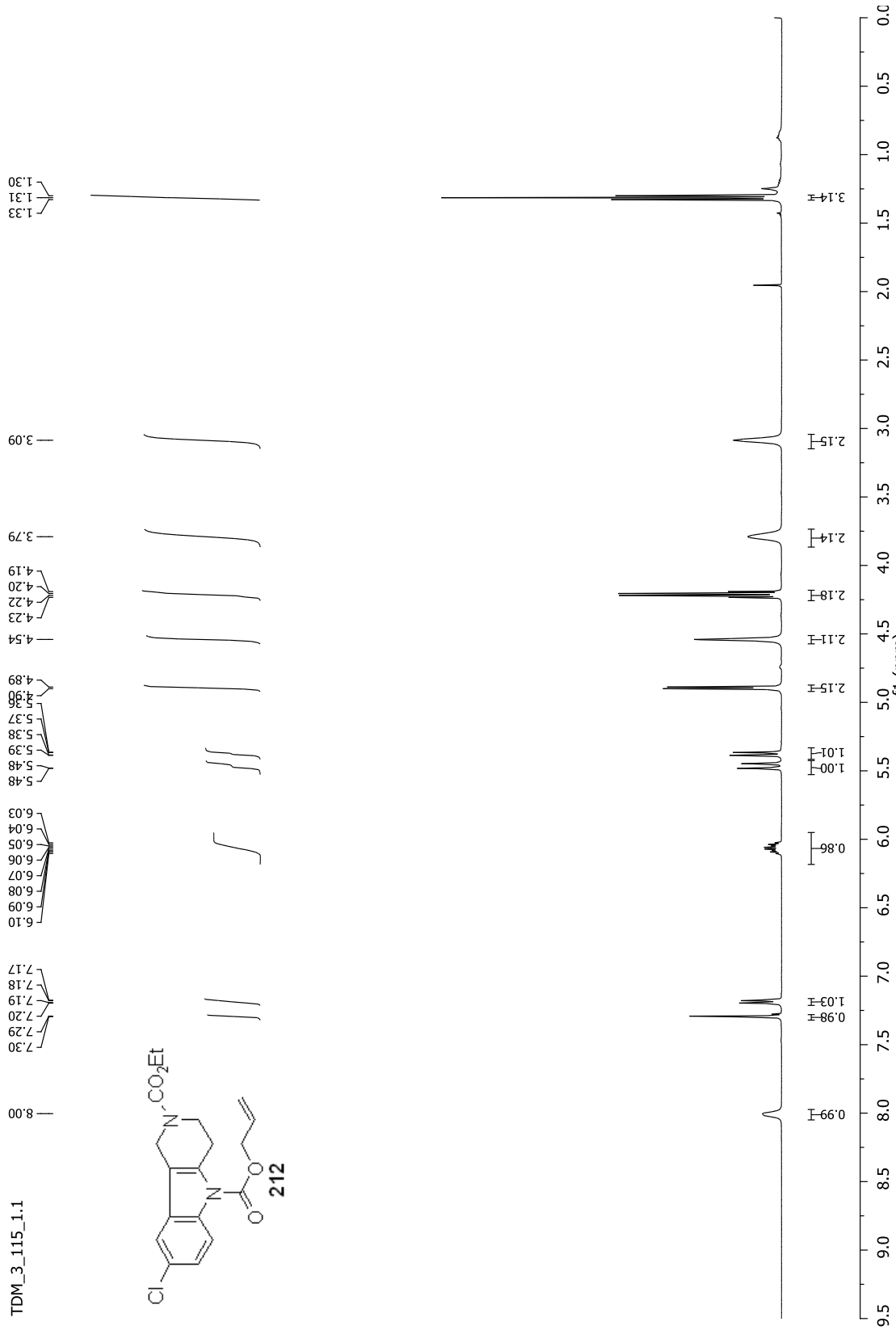


Figure 6. ^{1}H NMR Spectrum for **212** (500 MHz, $CDCl_3$)

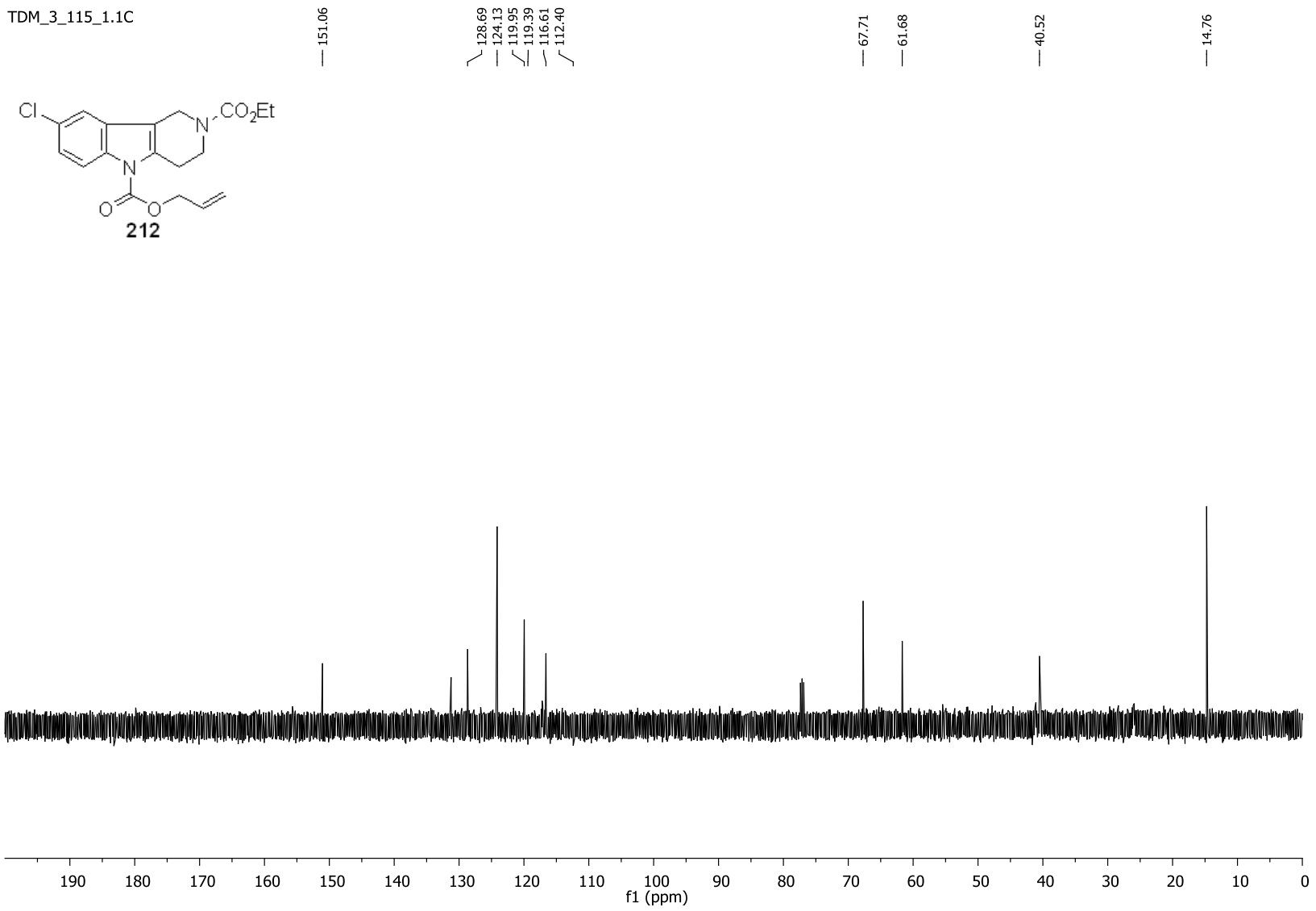


Figure 7. ^{13}C NMR Spectrum for **212** (500 MHz, $CDCl_3$)

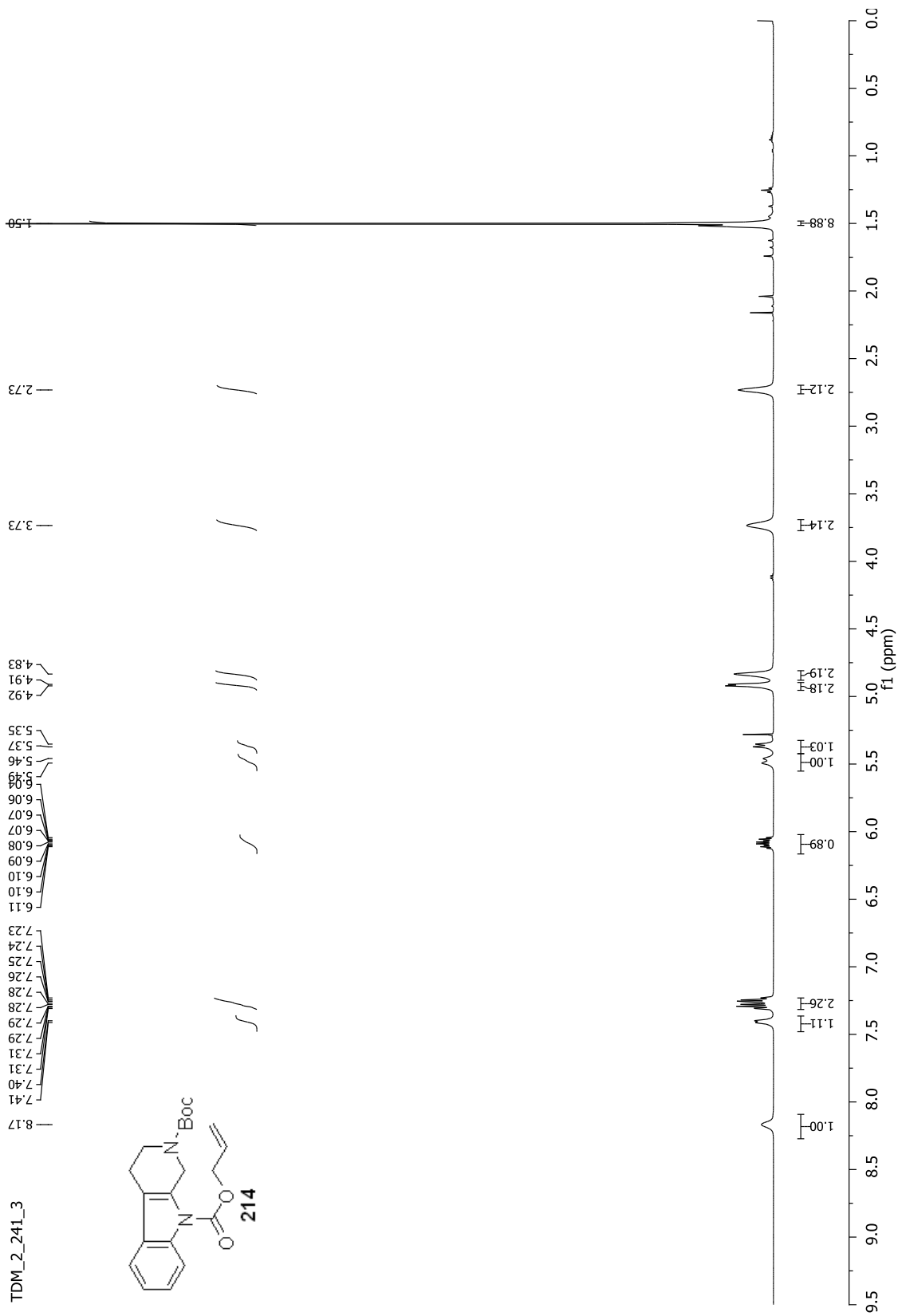


Figure 8. ^{1}H NMR Spectrum for **214** (500 MHz, $CDCl_3$)

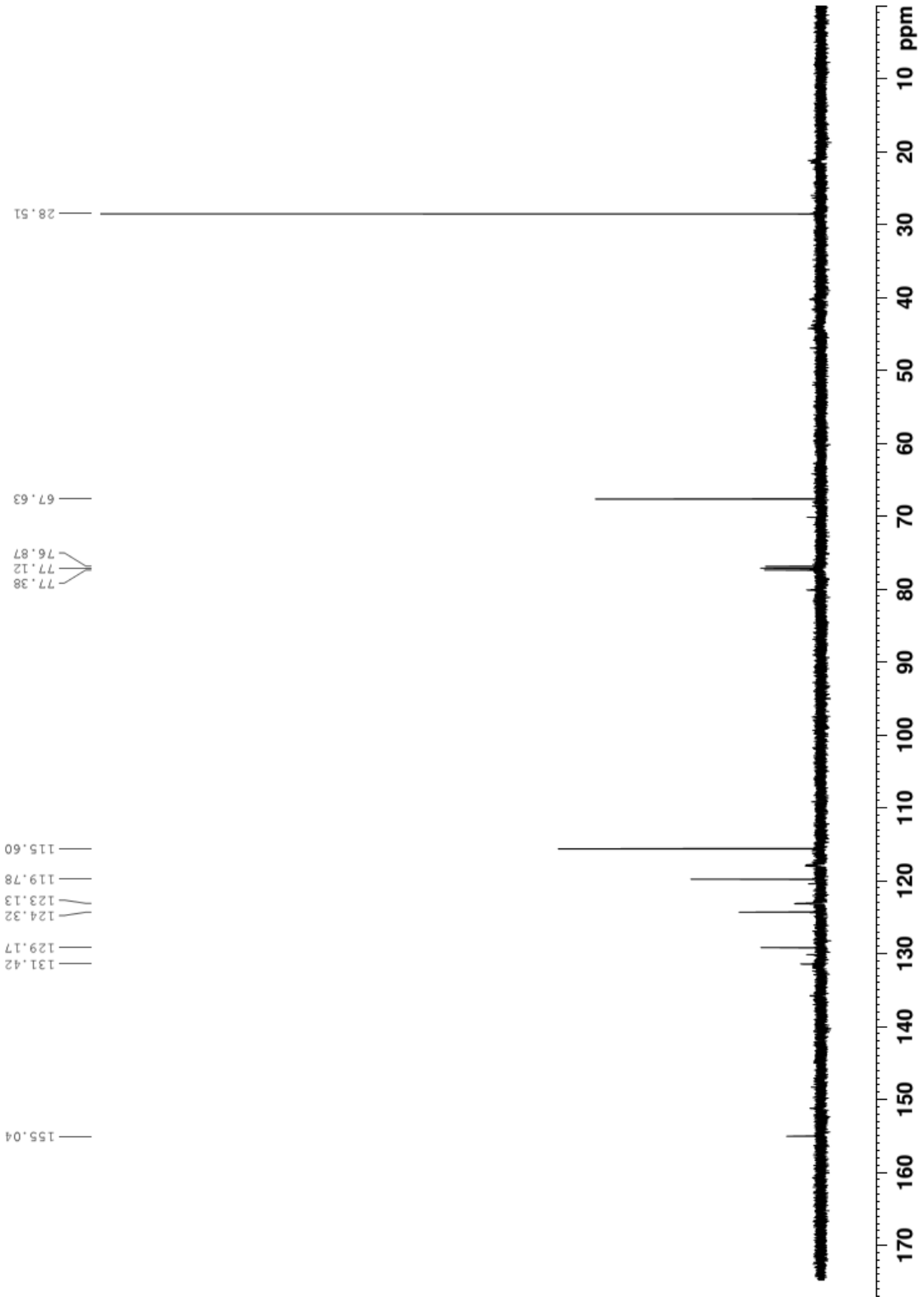


Figure 9. ^{1}H NMR Spectrum for **214** (500 MHz, $CDCl_3$)

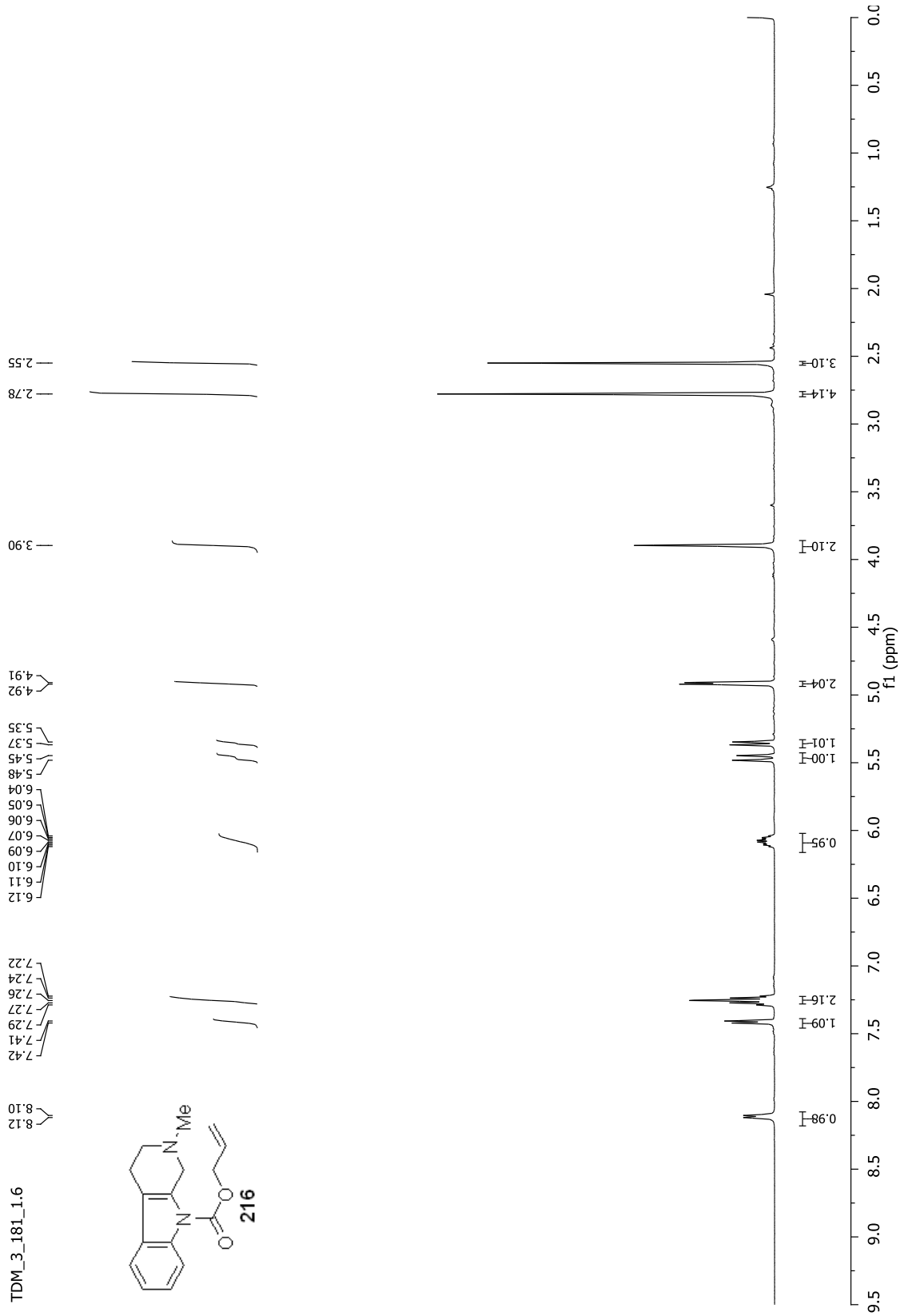


Figure 10. ^{1}H NMR Spectrum for **216** (500 MHz, $CDCl_3$)

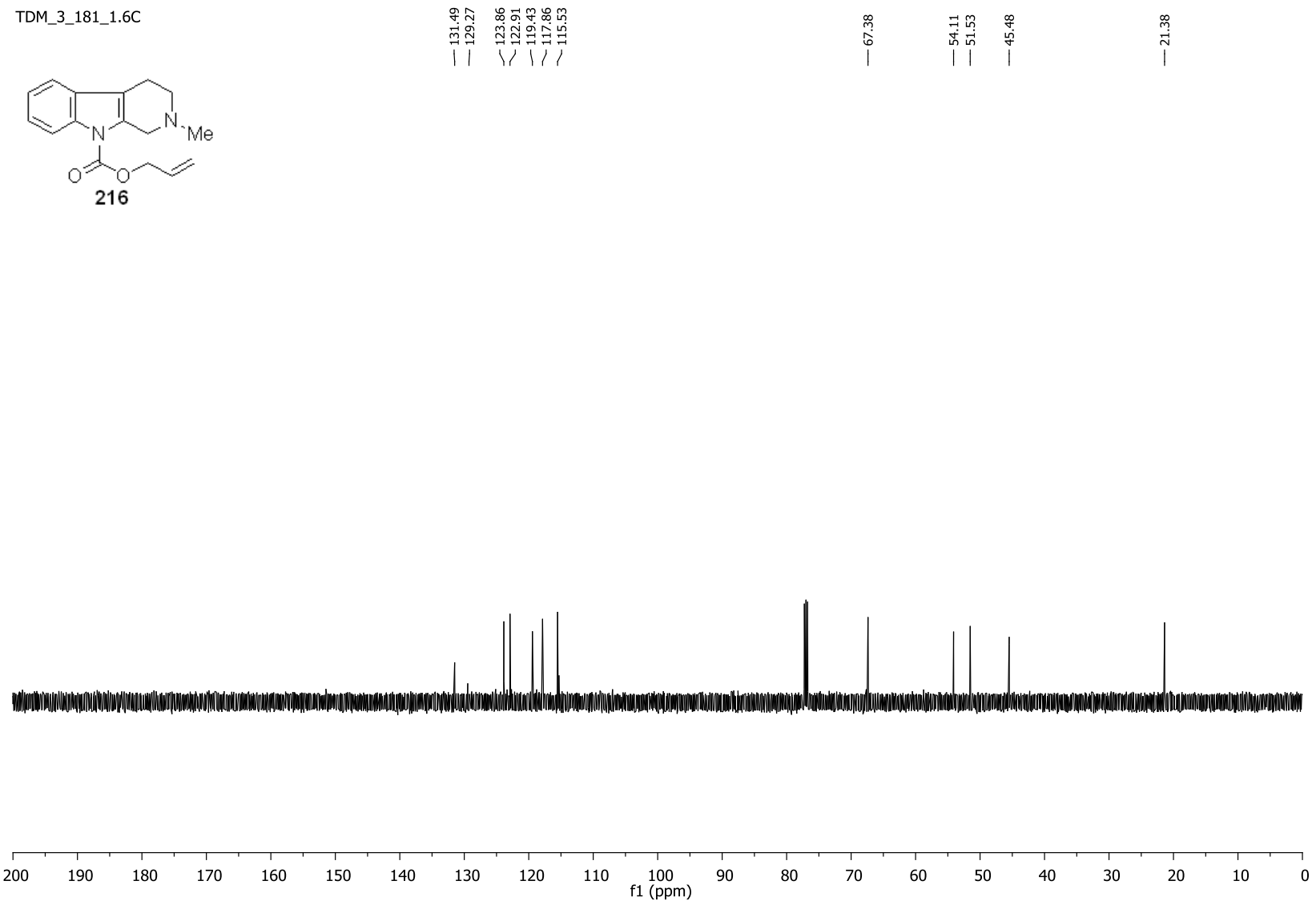


Figure 11. ^{13}C NMR Spectrum for **216** (125 MHz, $CDCl_3$)

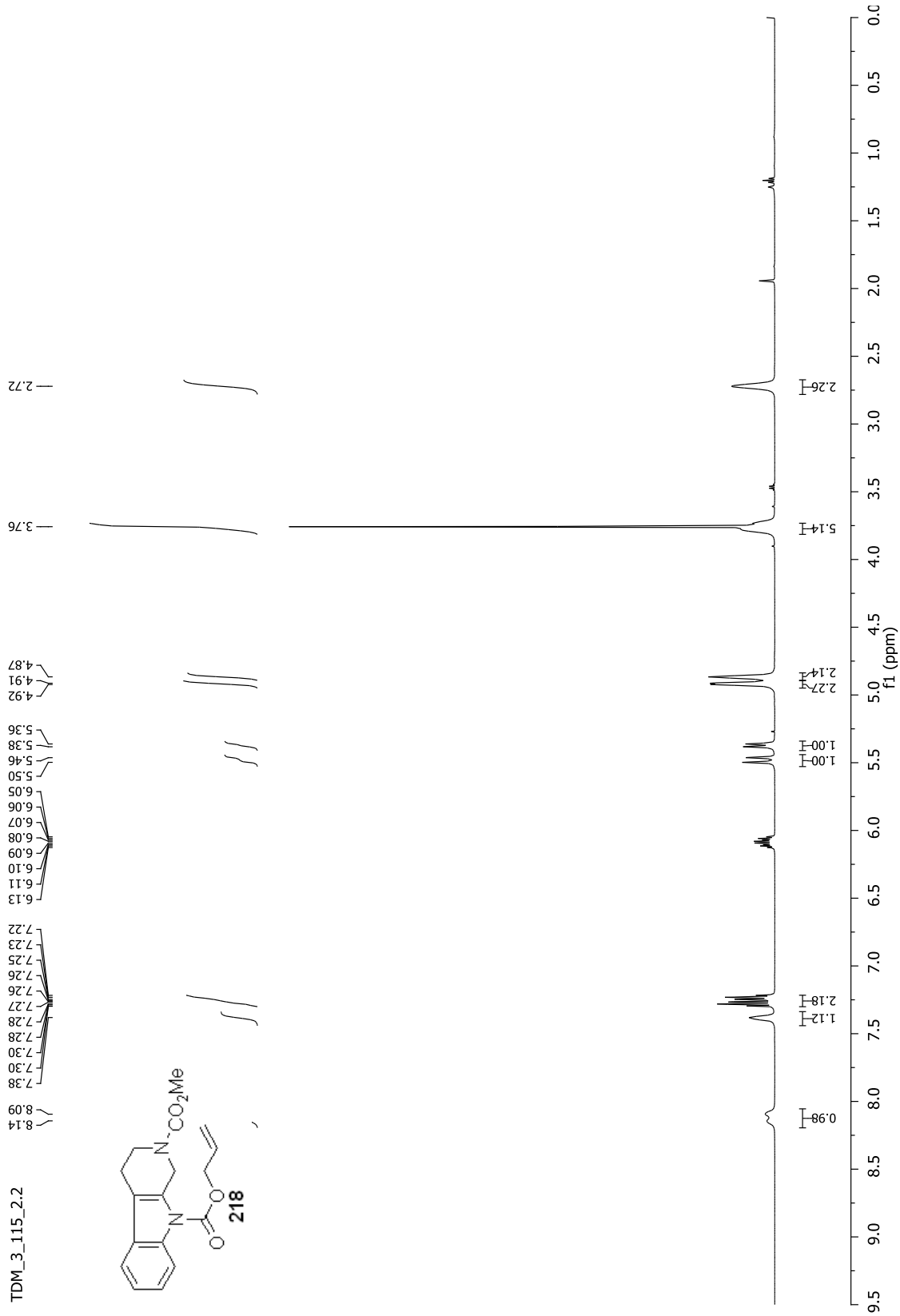


Figure 12. ^{1}H NMR Spectrum for **218** (500 MHz, $CDCl_3$)

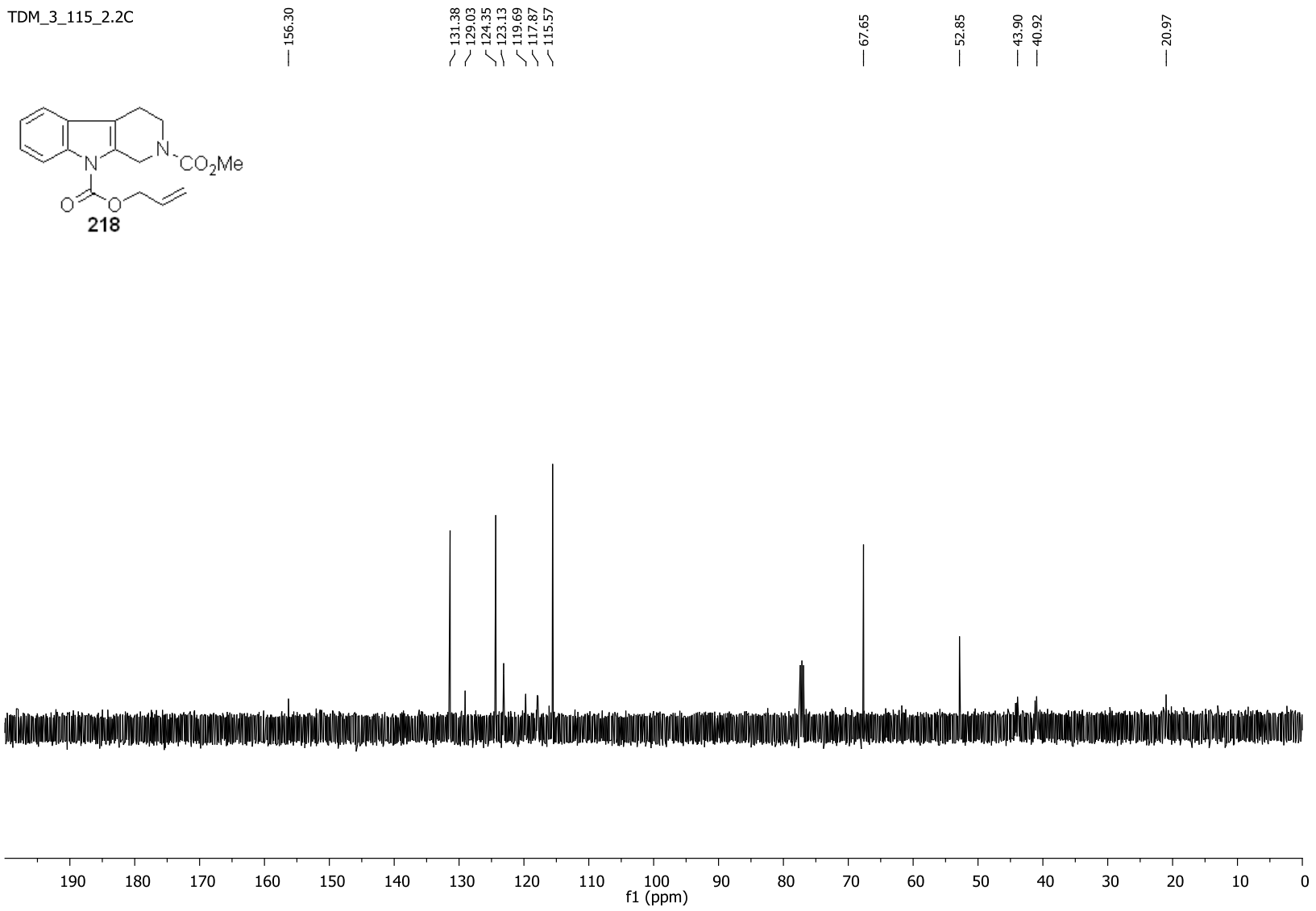


Figure 13. ^{13}C NMR Spectrum for **218** (125 MHz, $CDCl_3$)

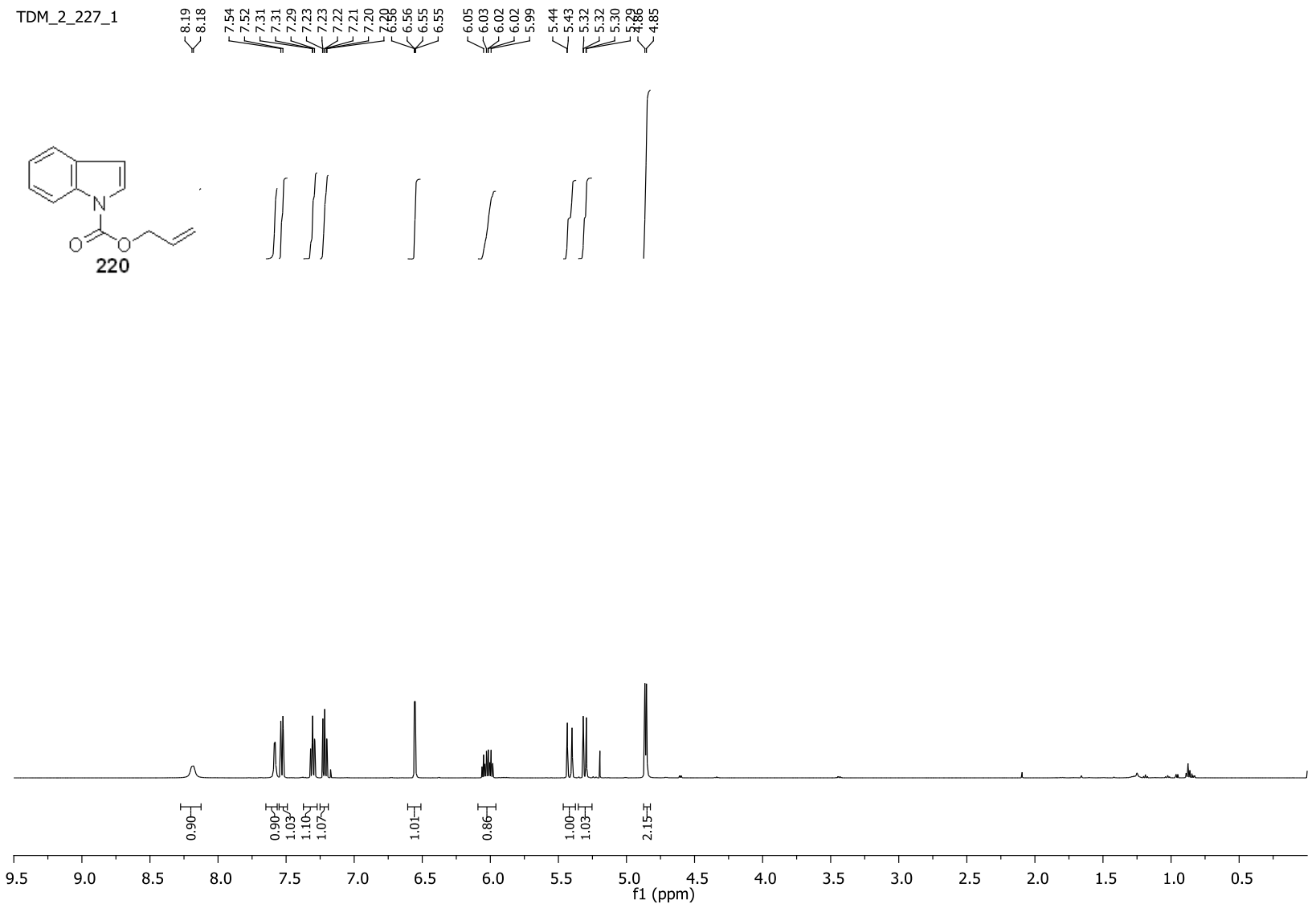


Figure 14. ^{1}H NMR Spectrum for **220** (500 MHz, $CDCl_3$)

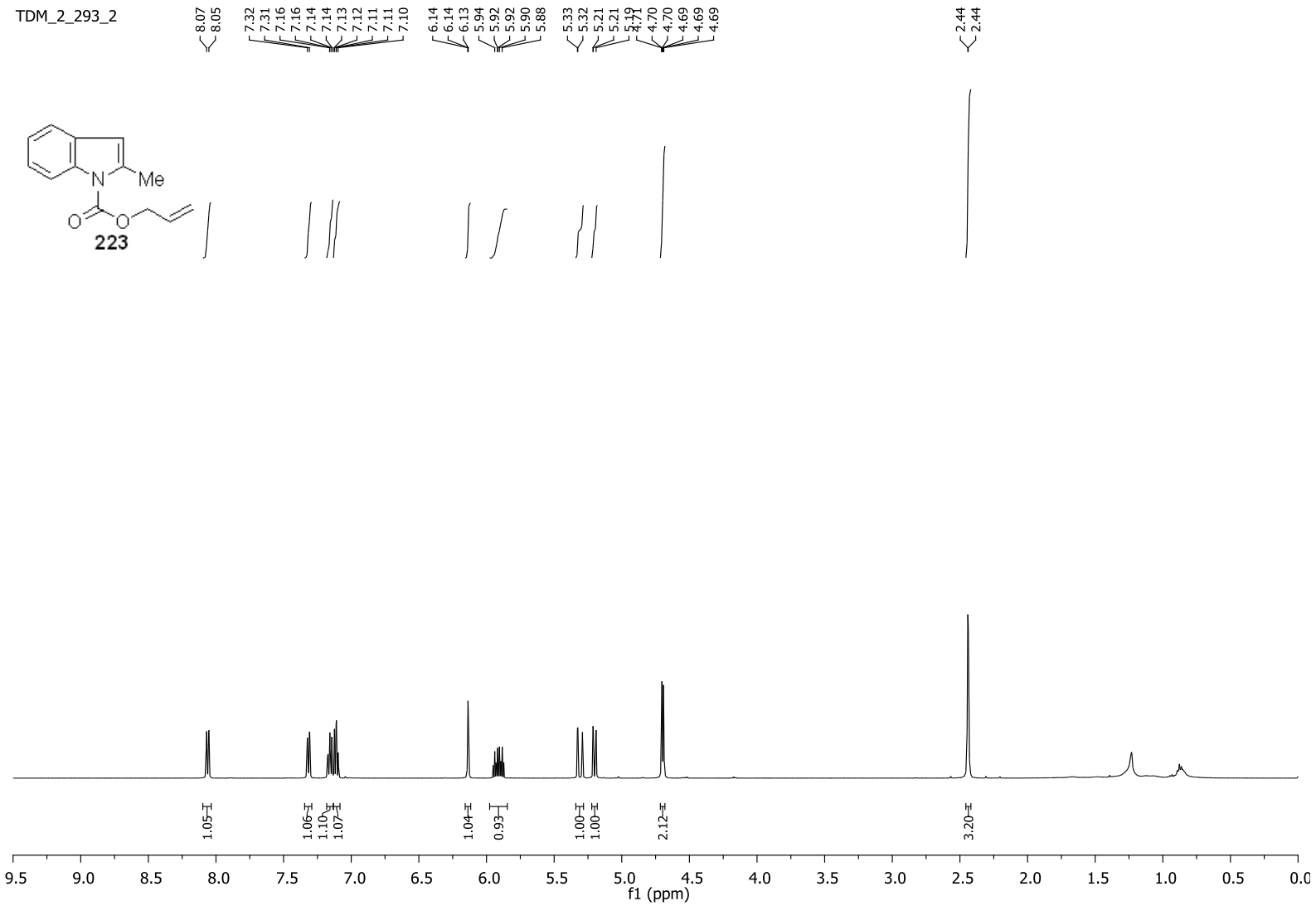


Figure 15. ^{1}H NMR Spectrum for **223** (500 MHz, $CDCl_3$)

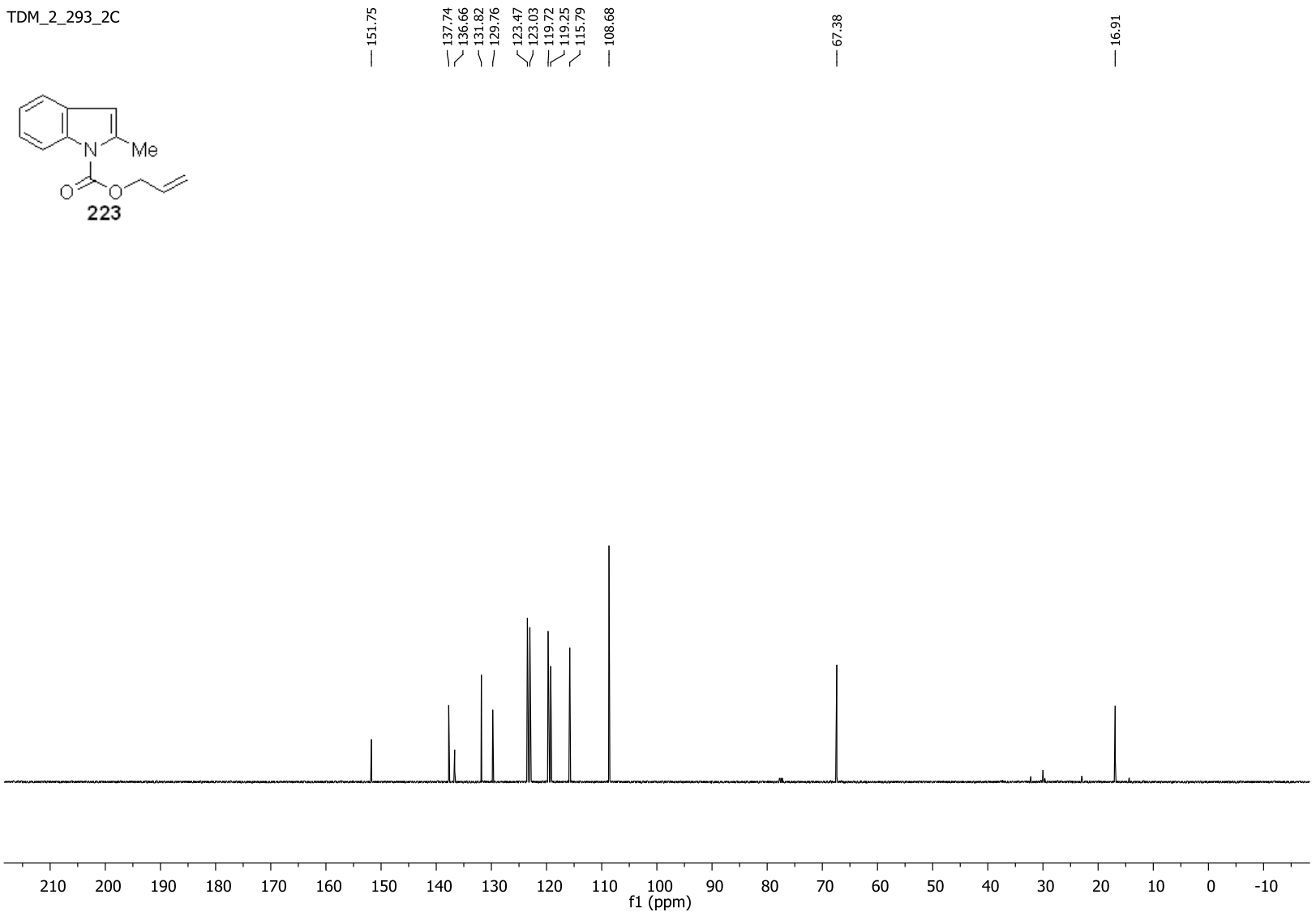


Figure 16. ^{13}C NMR Spectrum for **223** (125 MHz, $CDCl_3$)

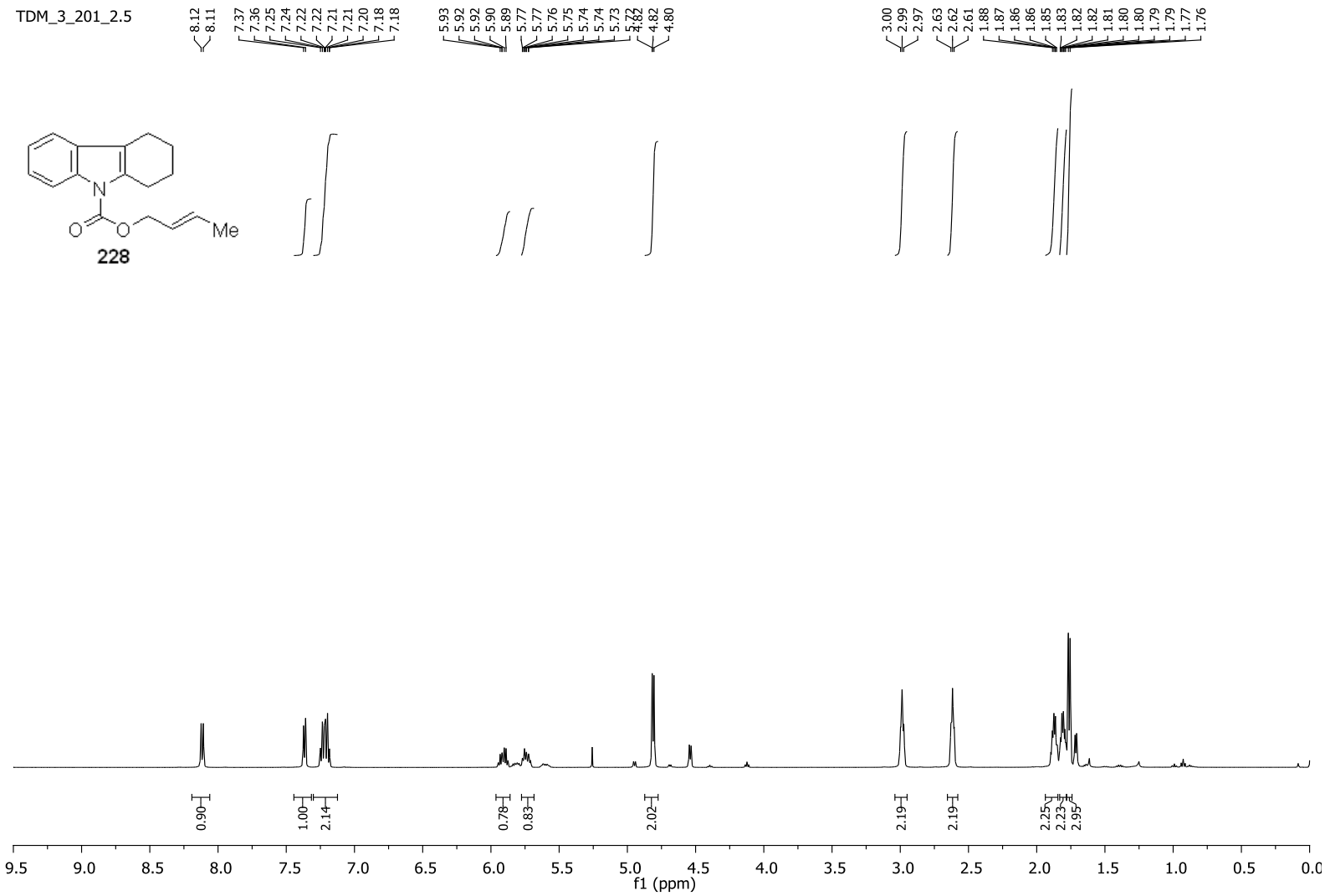


Figure 17. ^{1}H NMR Spectrum for **228** (500 MHz, $CDCl_3$)

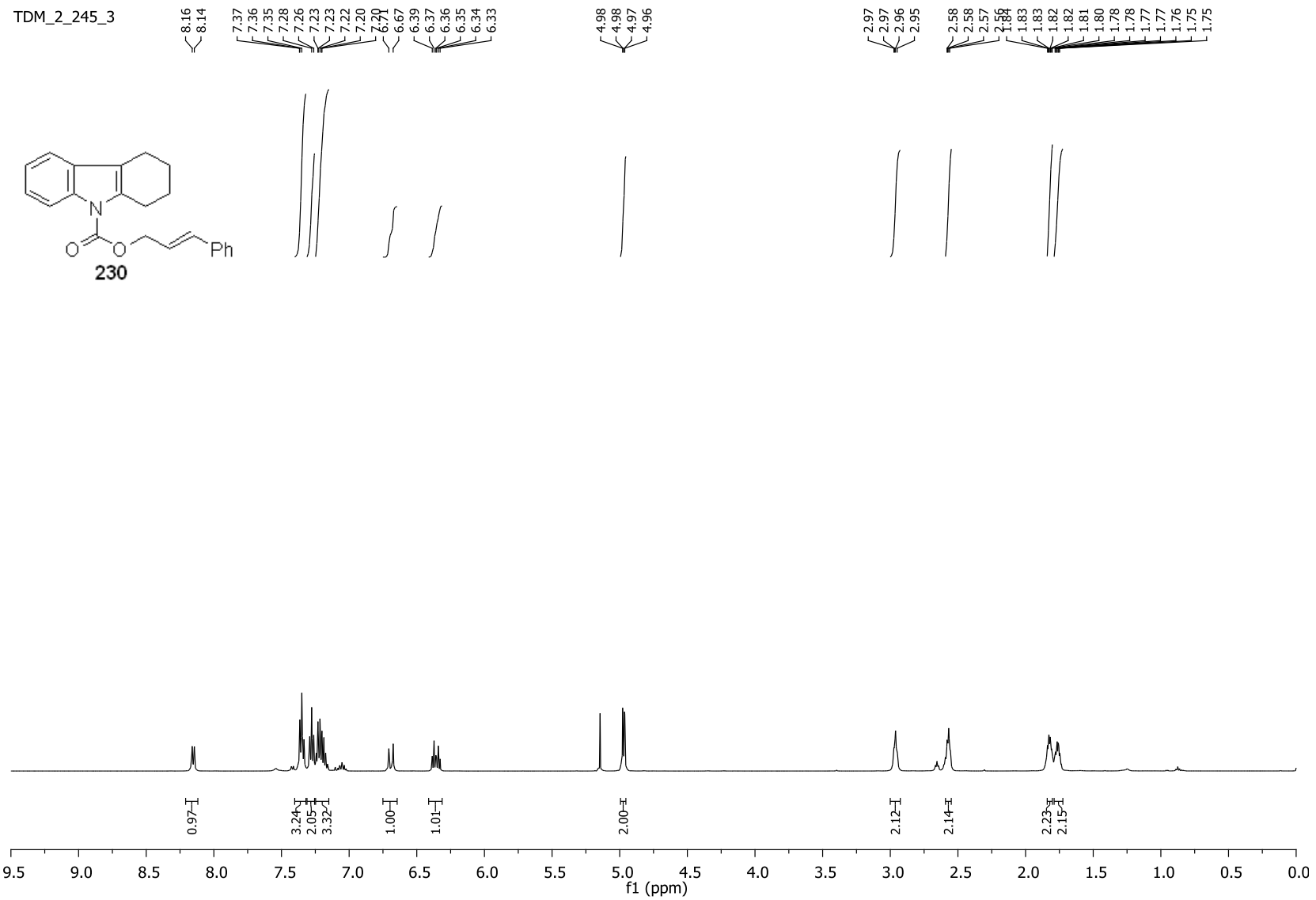


Figure 18. ^{1}H NMR Spectrum for **230** (500 MHz, $CDCl_3$)

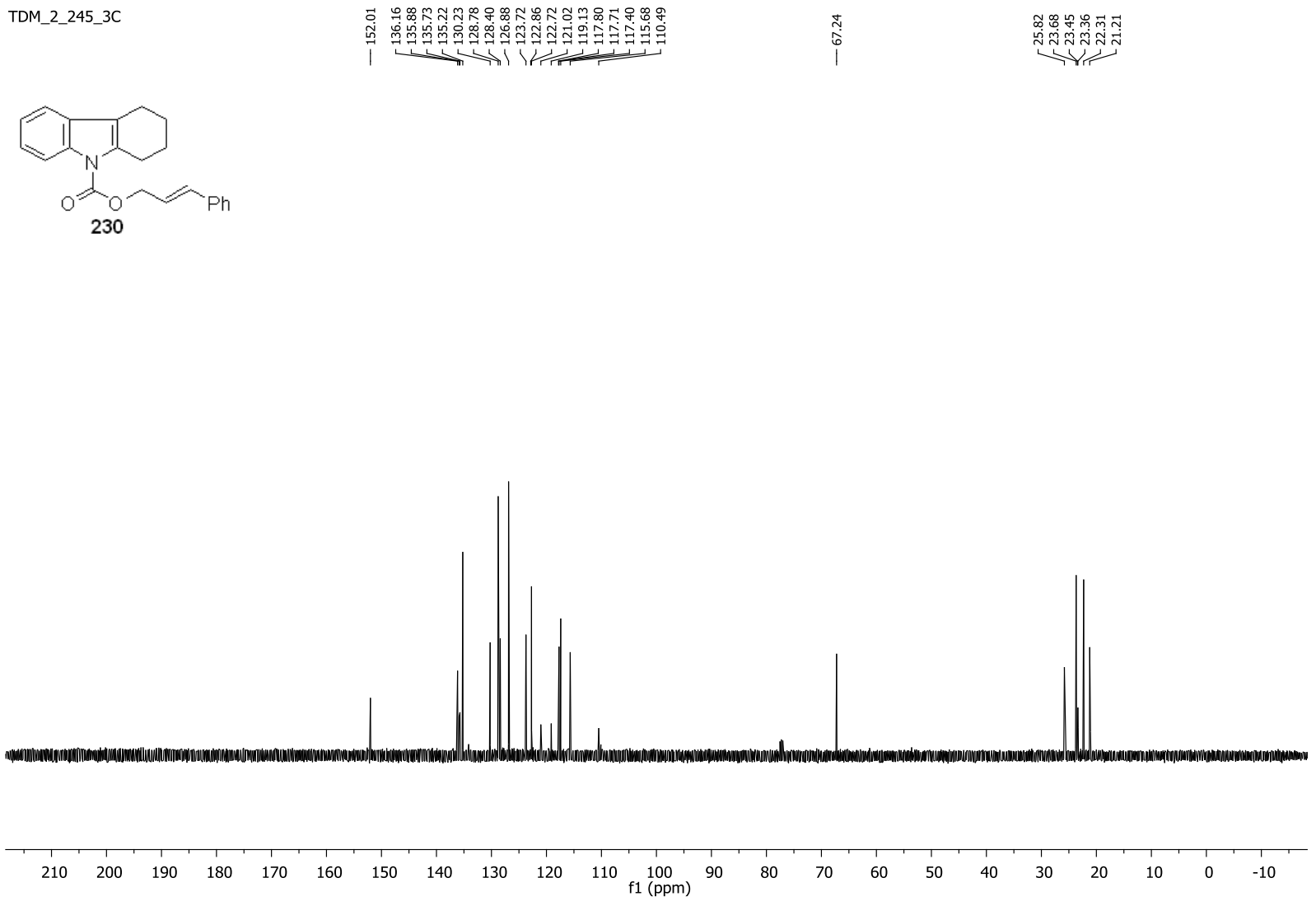


Figure 19. ^{13}C NMR Spectrum for **230** (125 MHz, $CDCl_3$)

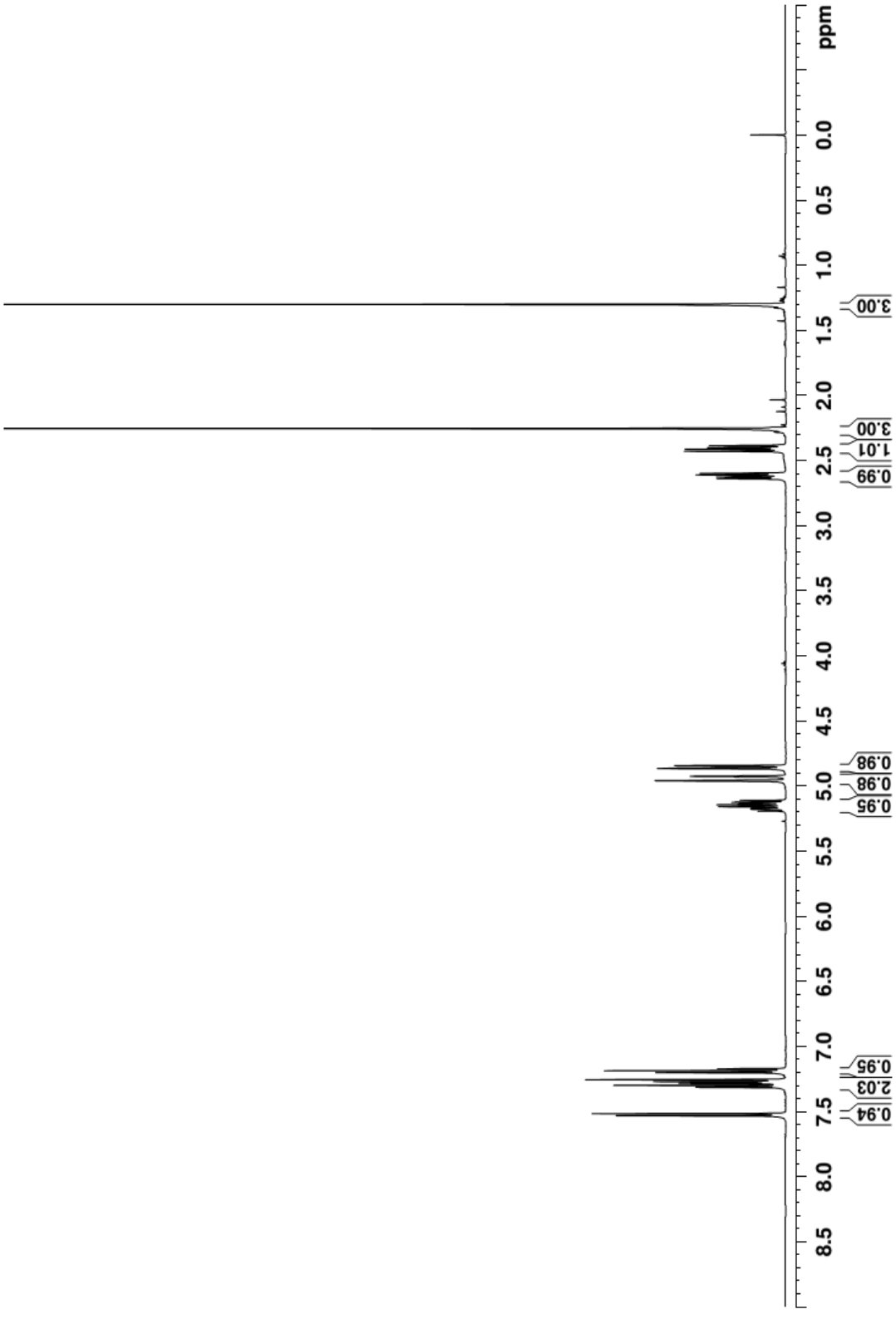


Figure 20. ^{1}H NMR Spectrum for **205** (500 MHz, $CDCl_3$)

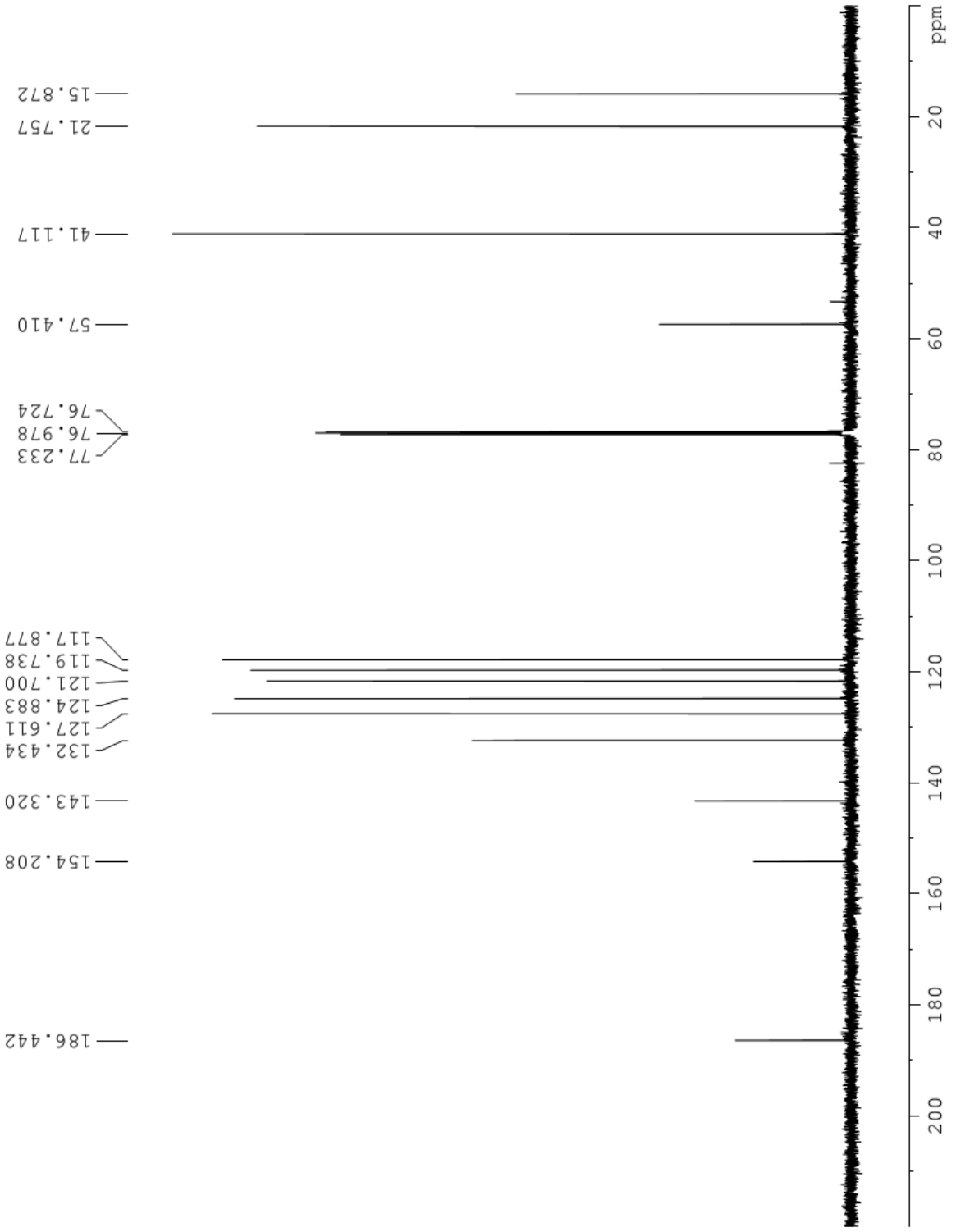


Figure 21. ^{13}C NMR Spectrum for **205** (125 MHz, $CDCl_3$)

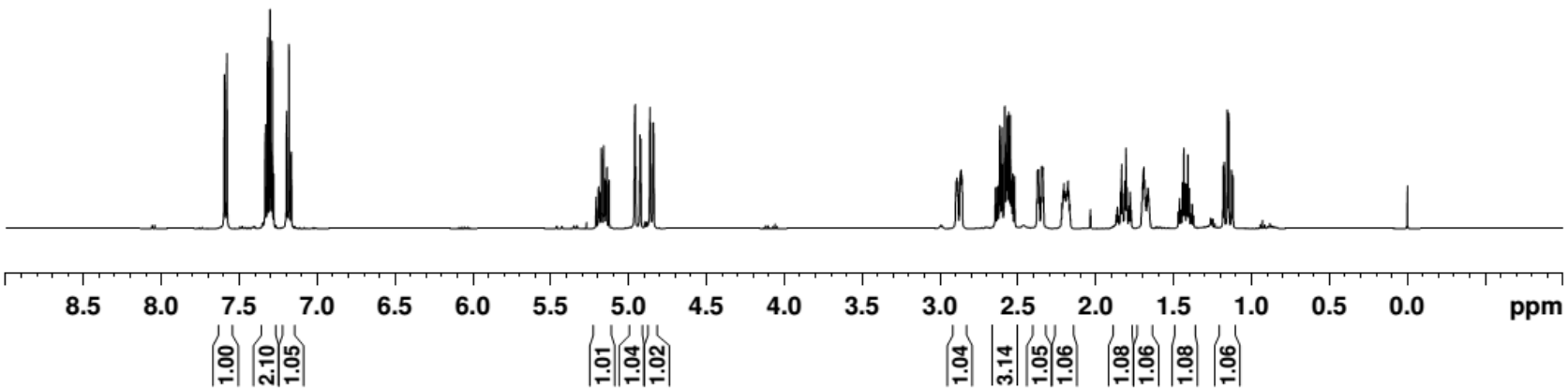


Figure 22. ^{1}H NMR Spectrum for **207** (500 MHz, $CDCl_3$)

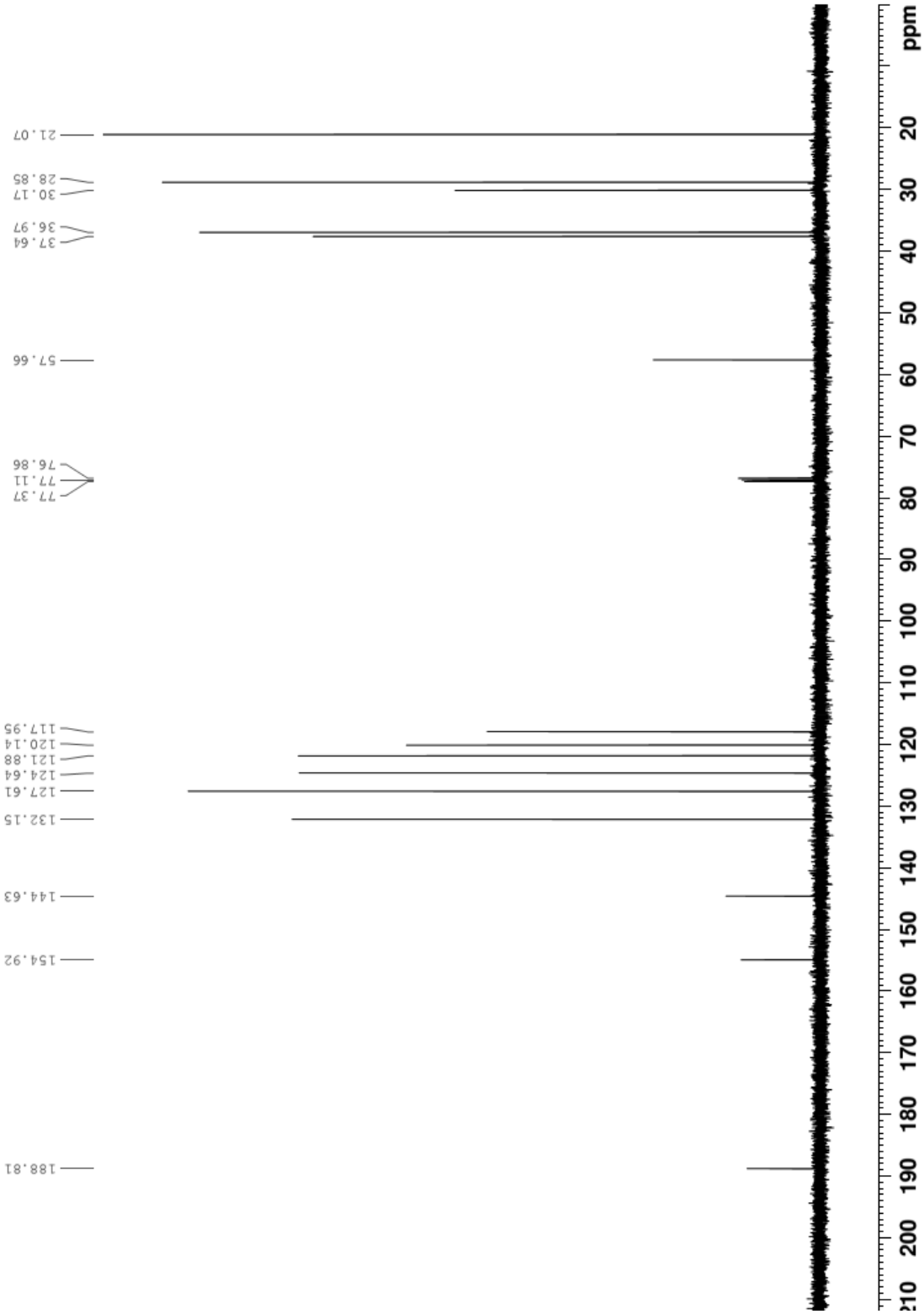


Figure 23. ^{13}C NMR Spectrum for **207** (125 MHz, $CDCl_3$)

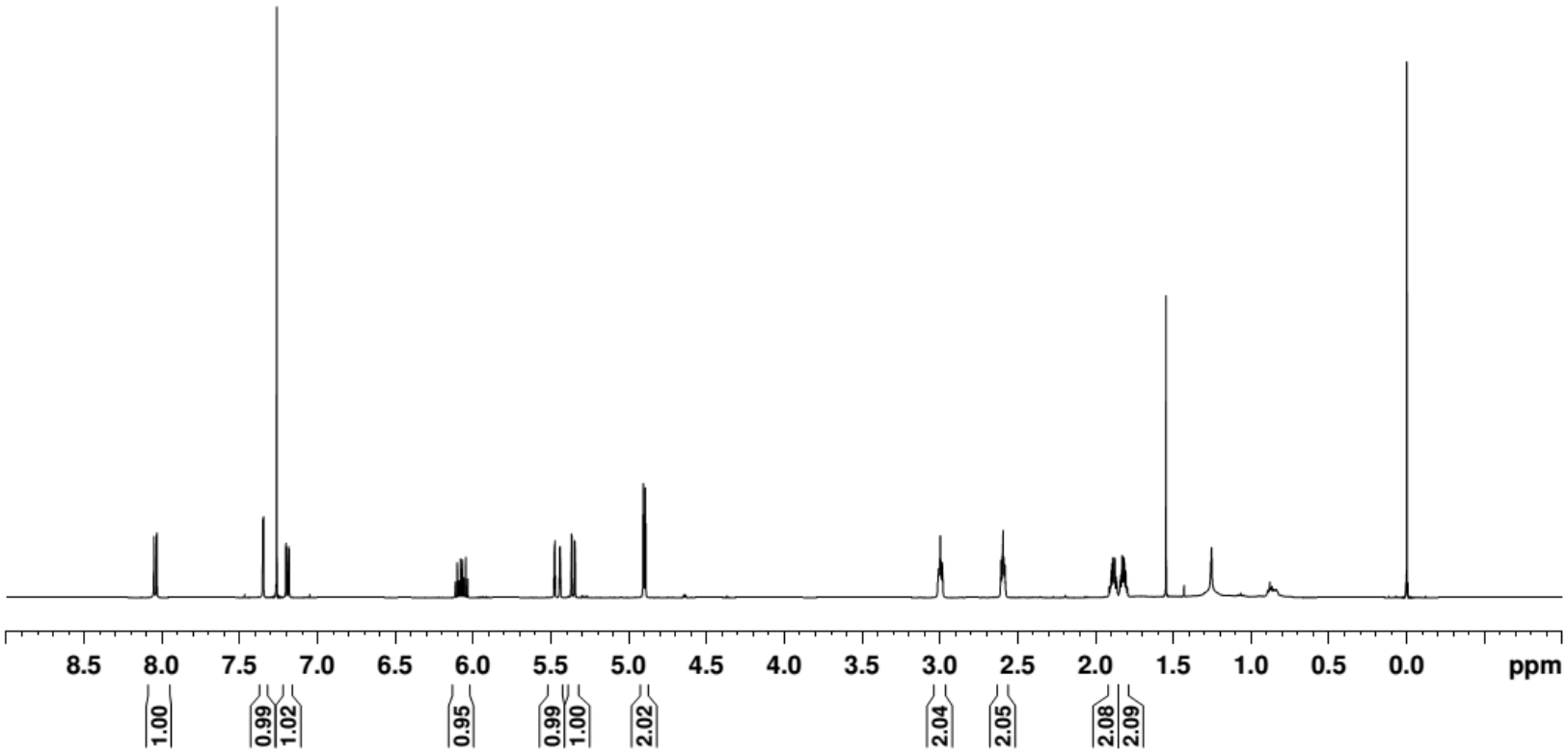


Figure 24. ^{1}H NMR Spectrum for **209** (500 MHz, $CDCl_3$)

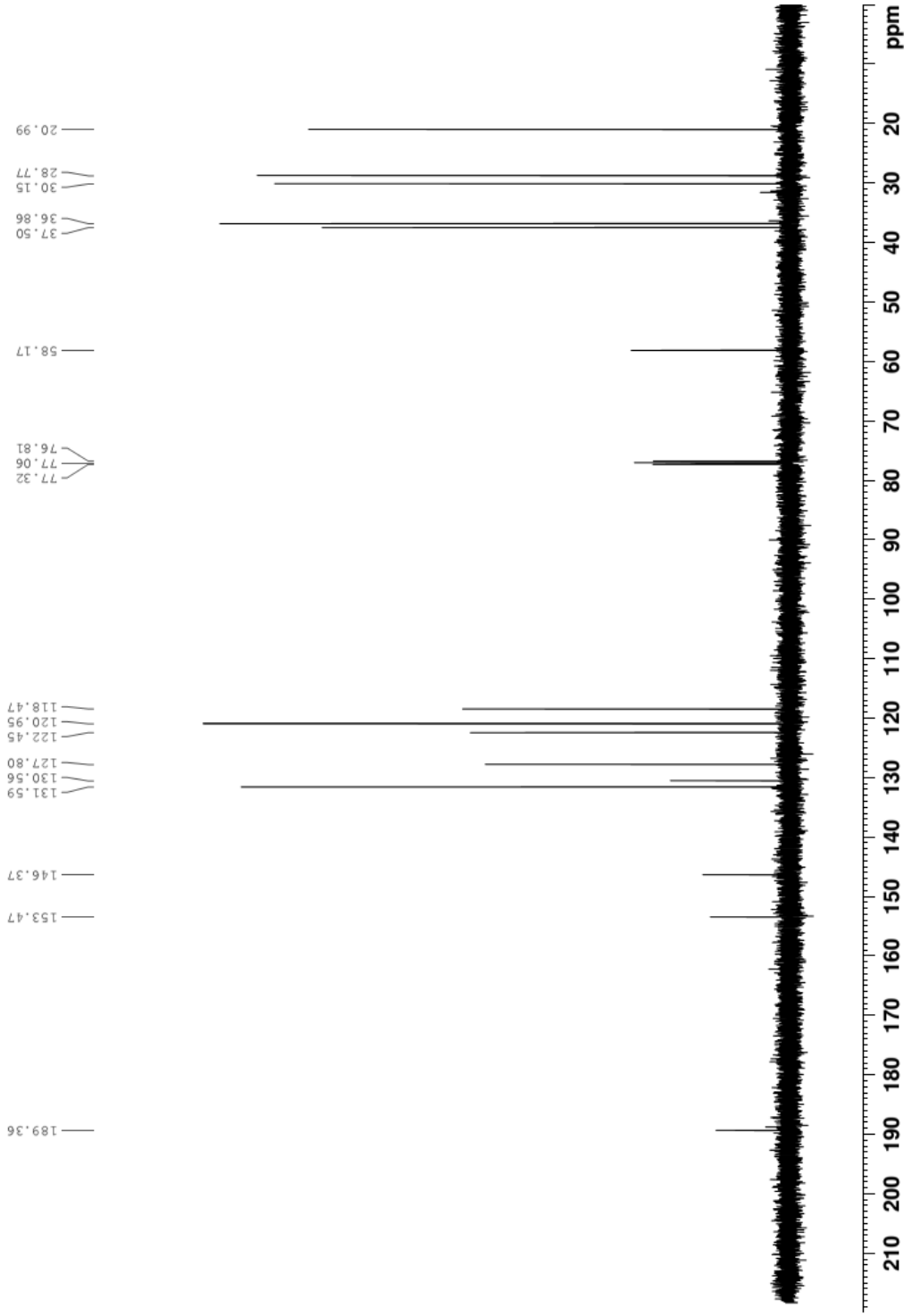


Figure 25. ^{13}C NMR Spectrum for **209** (125 MHz, $CDCl_3$)

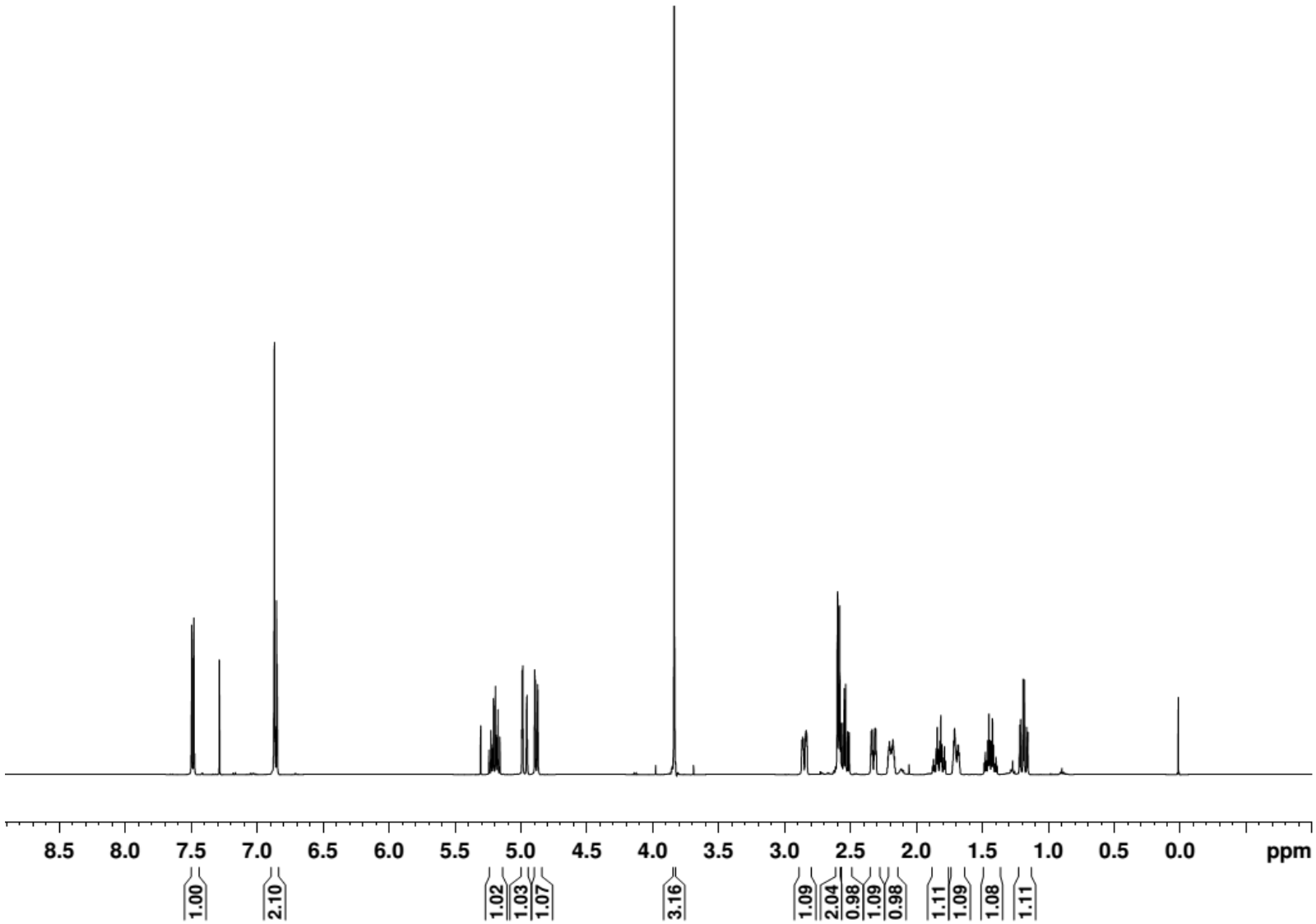


Figure 26. ^{1}H NMR Spectrum for **211** (500 MHz, $CDCl_3$)

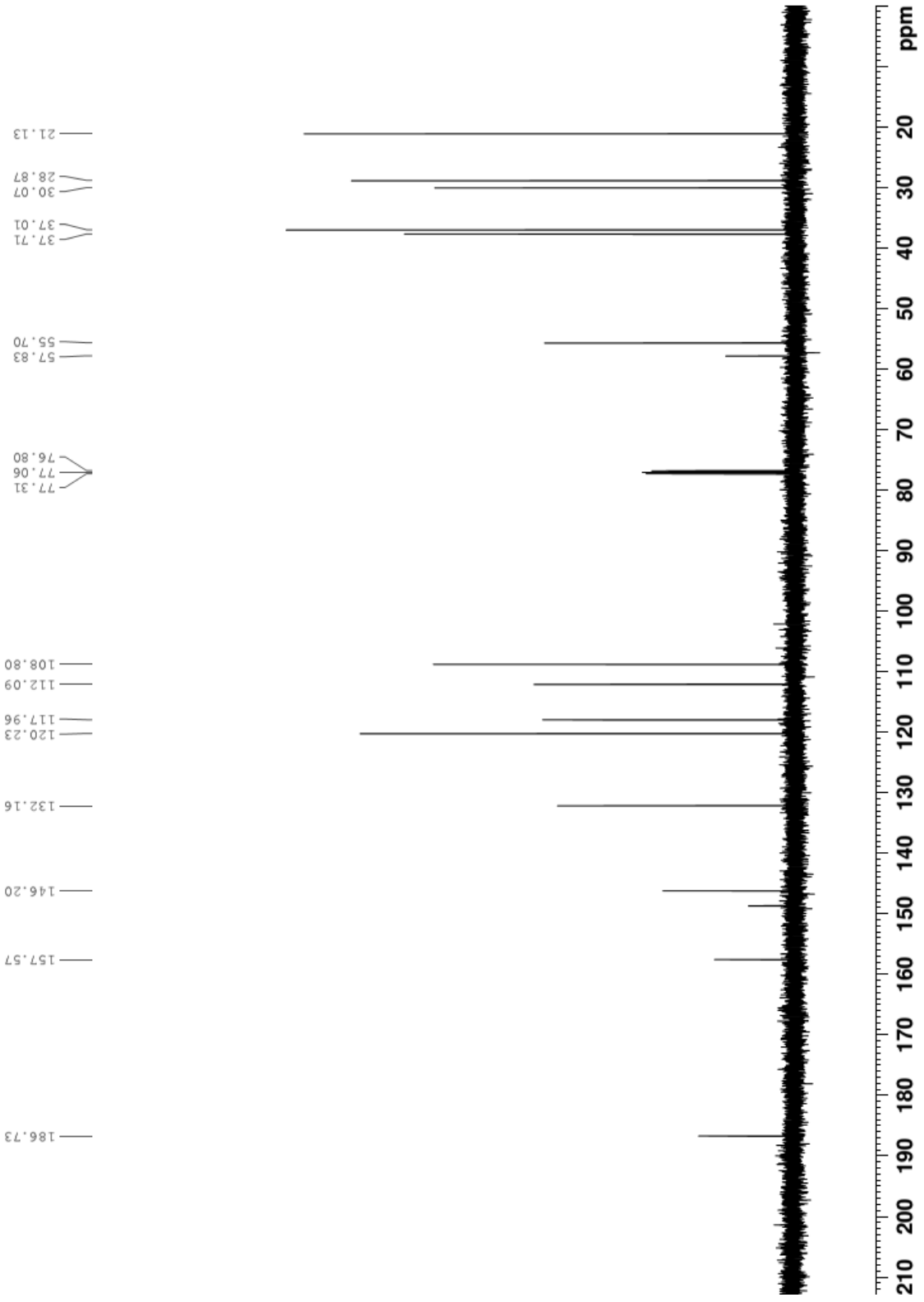


Figure 27. ^{13}C NMR Spectrum for **211** (125 MHz, $CDCl_3$)

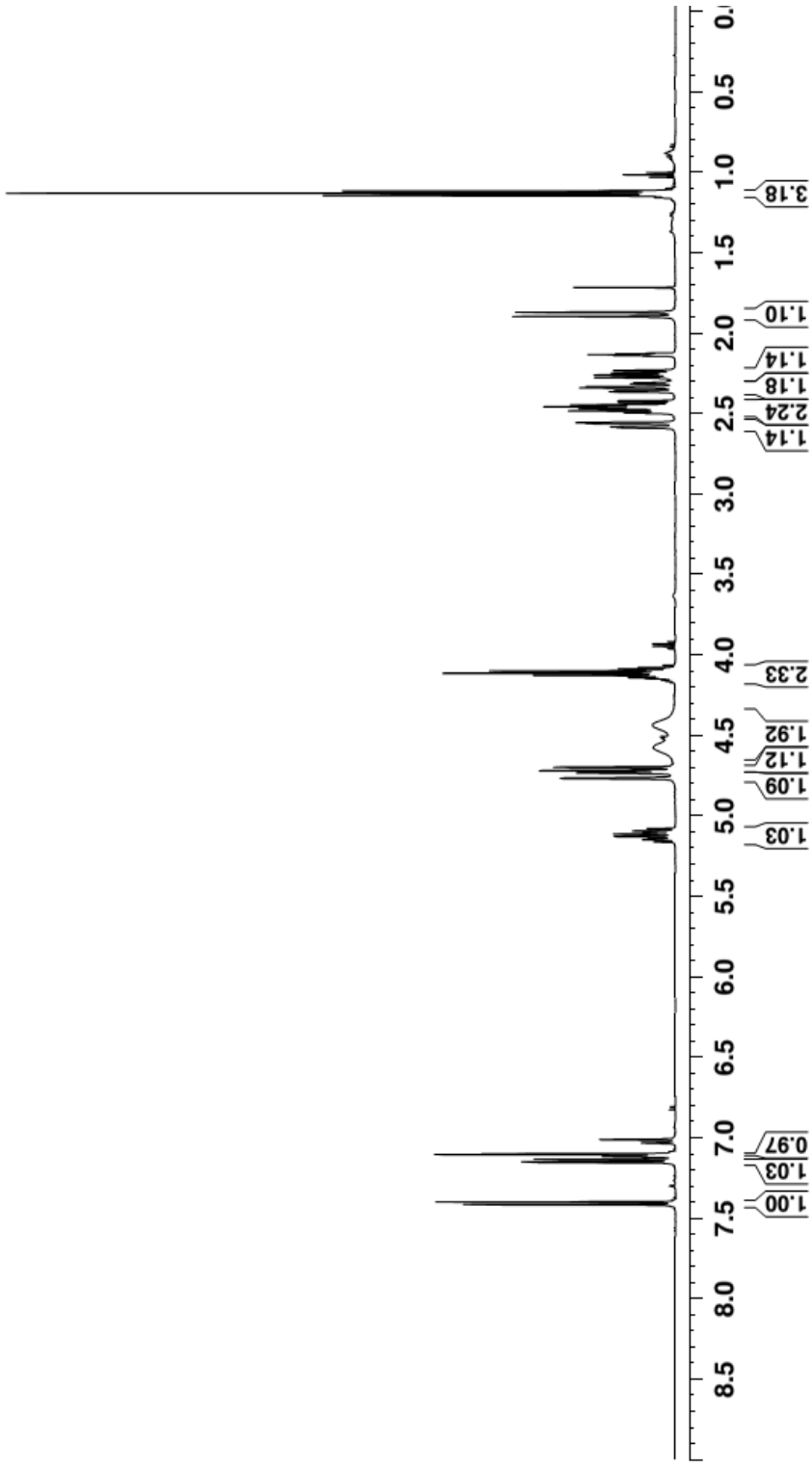


Figure 28. ^{1}H NMR Spectrum for **213** (500 MHz, $CDCl_3$)

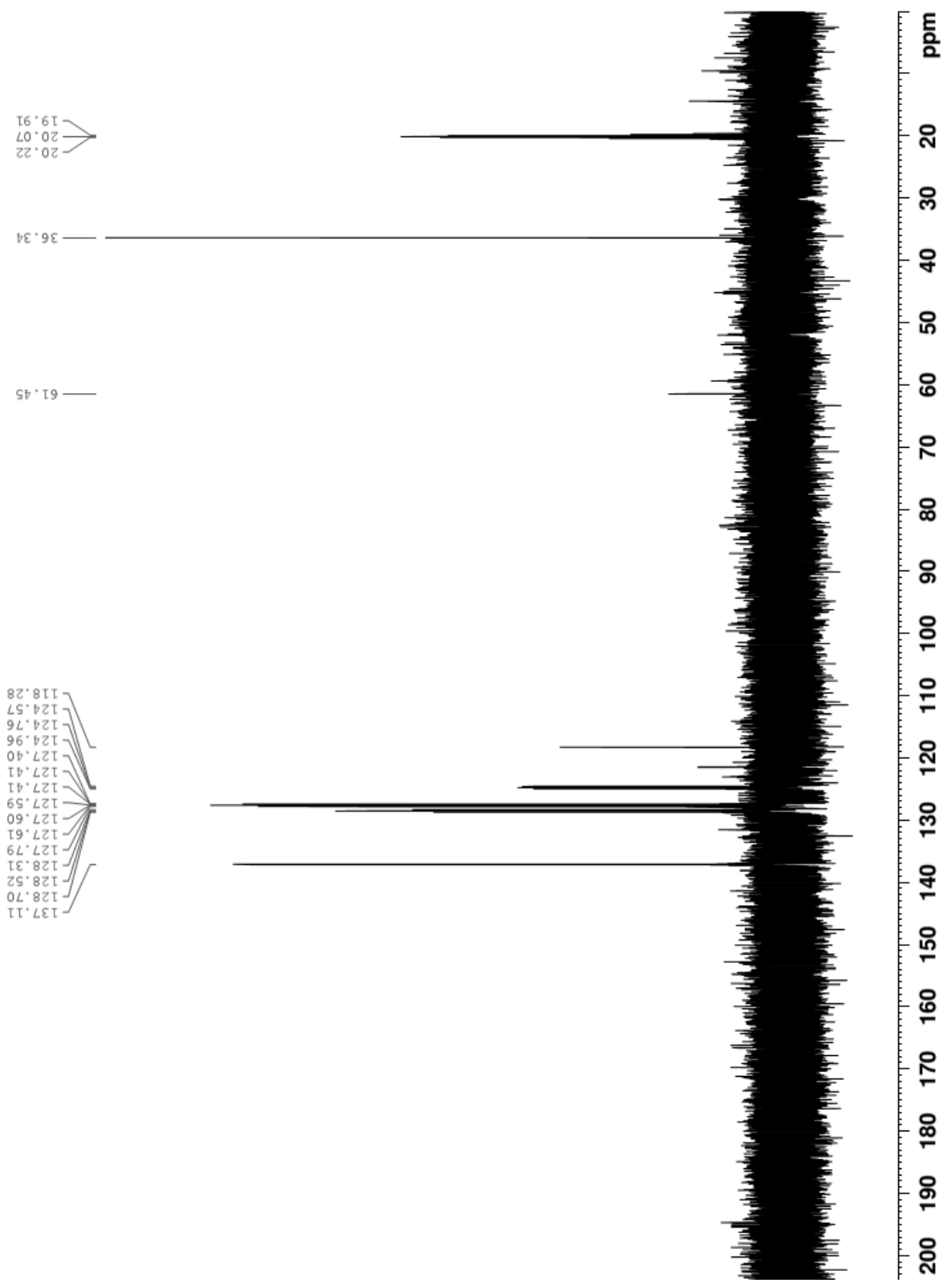


Figure 29. ^{13}C NMR Spectrum for **213** (125 MHz, $CDCl_3$)

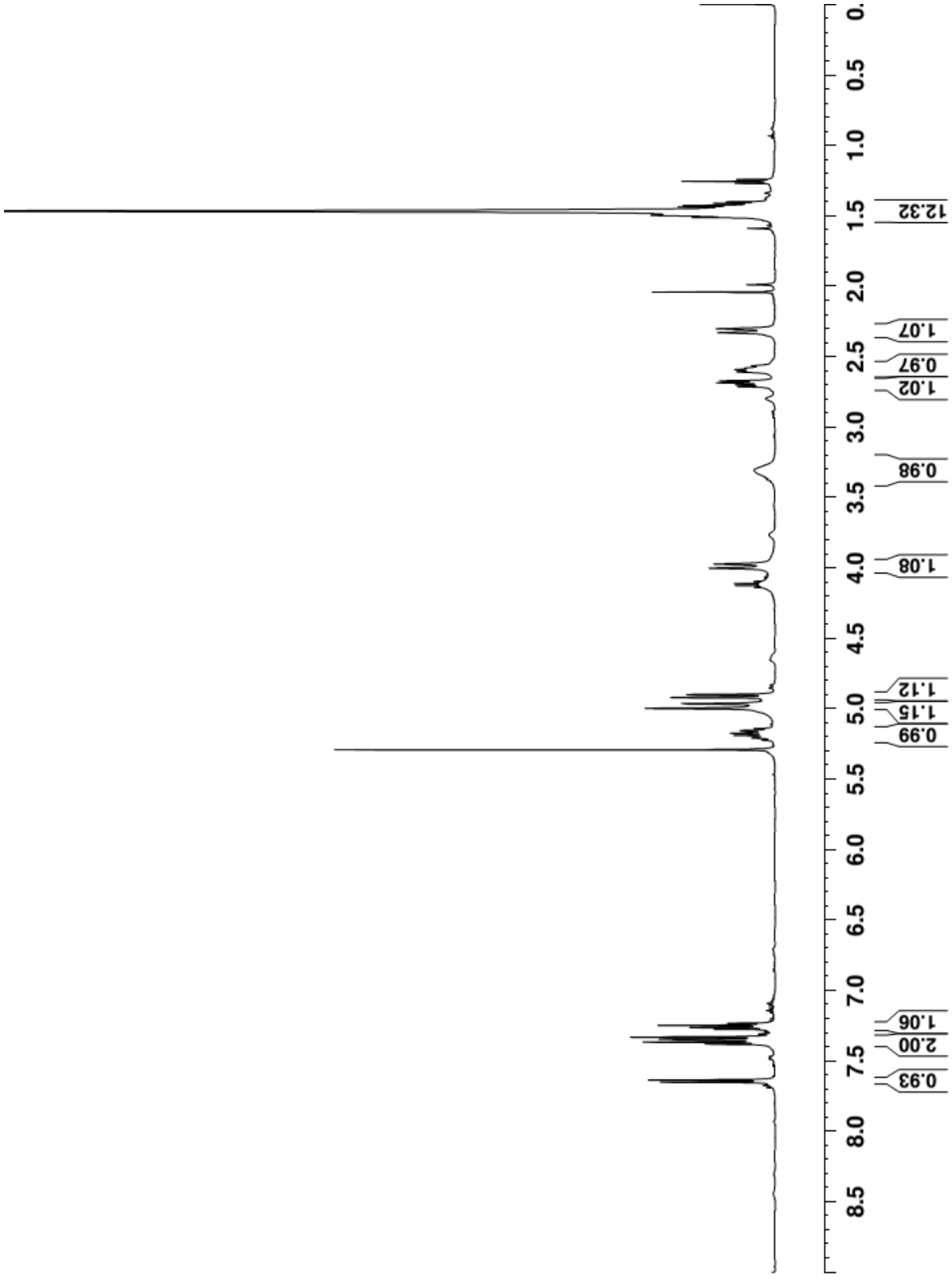


Figure 30. ^{1}H NMR Spectrum for **215** (500 MHz, $CDCl_3$)

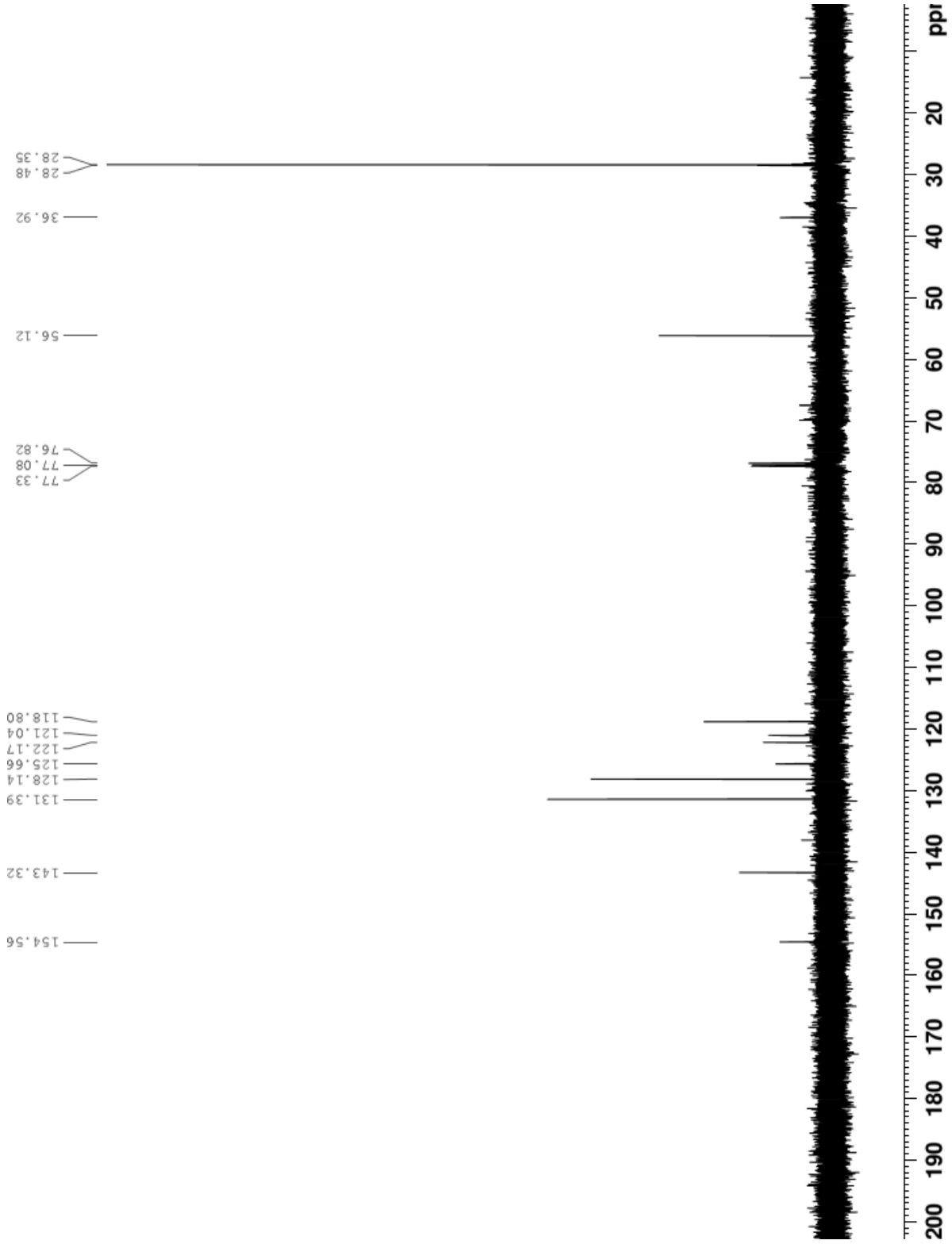


Figure 31. ^{1}H NMR Spectrum for **215** (125 MHz, $CDCl_3$)

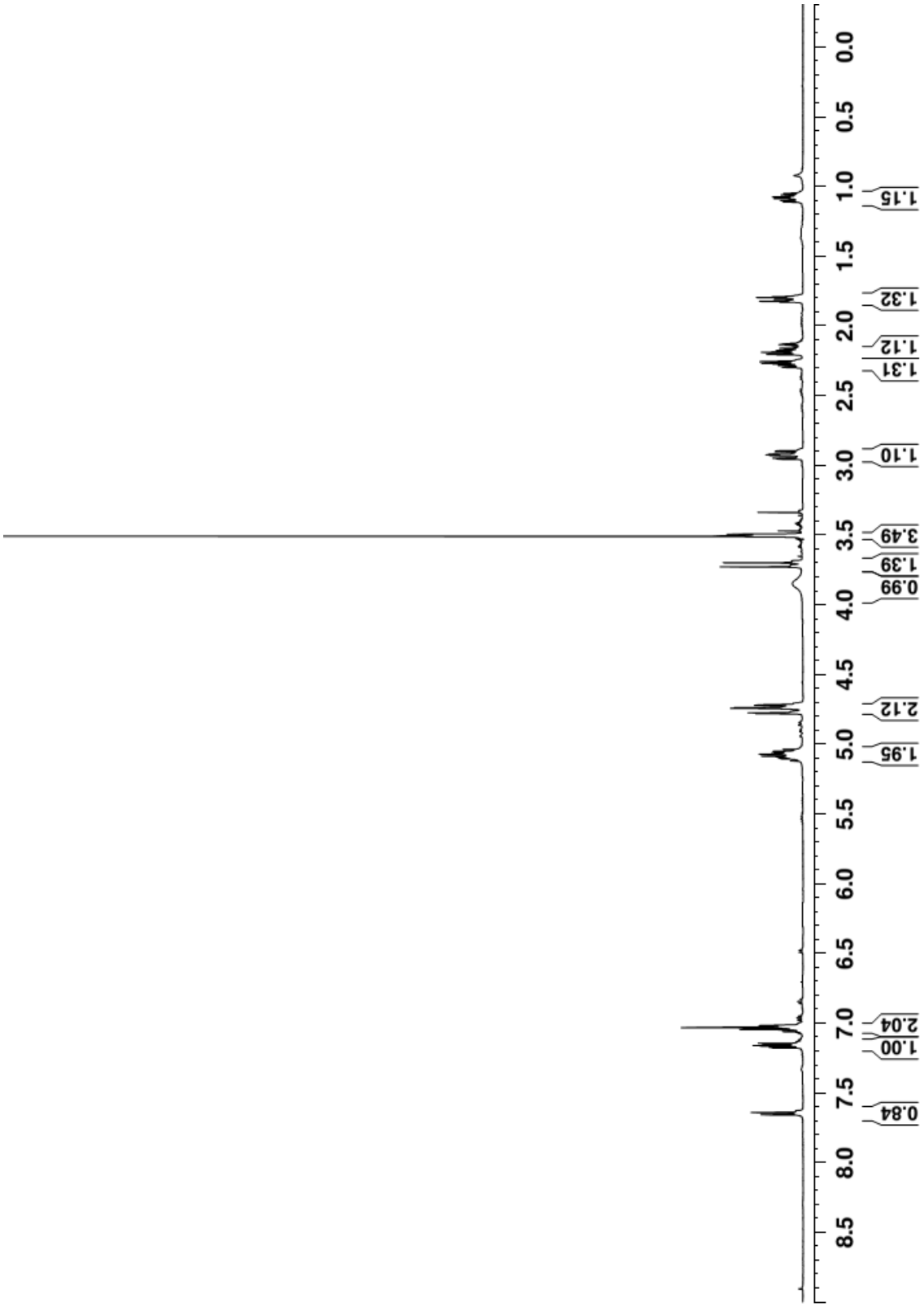


Figure 32. ^{1}H NMR Spectrum for **219** (500 MHz, $CDCl_3$)

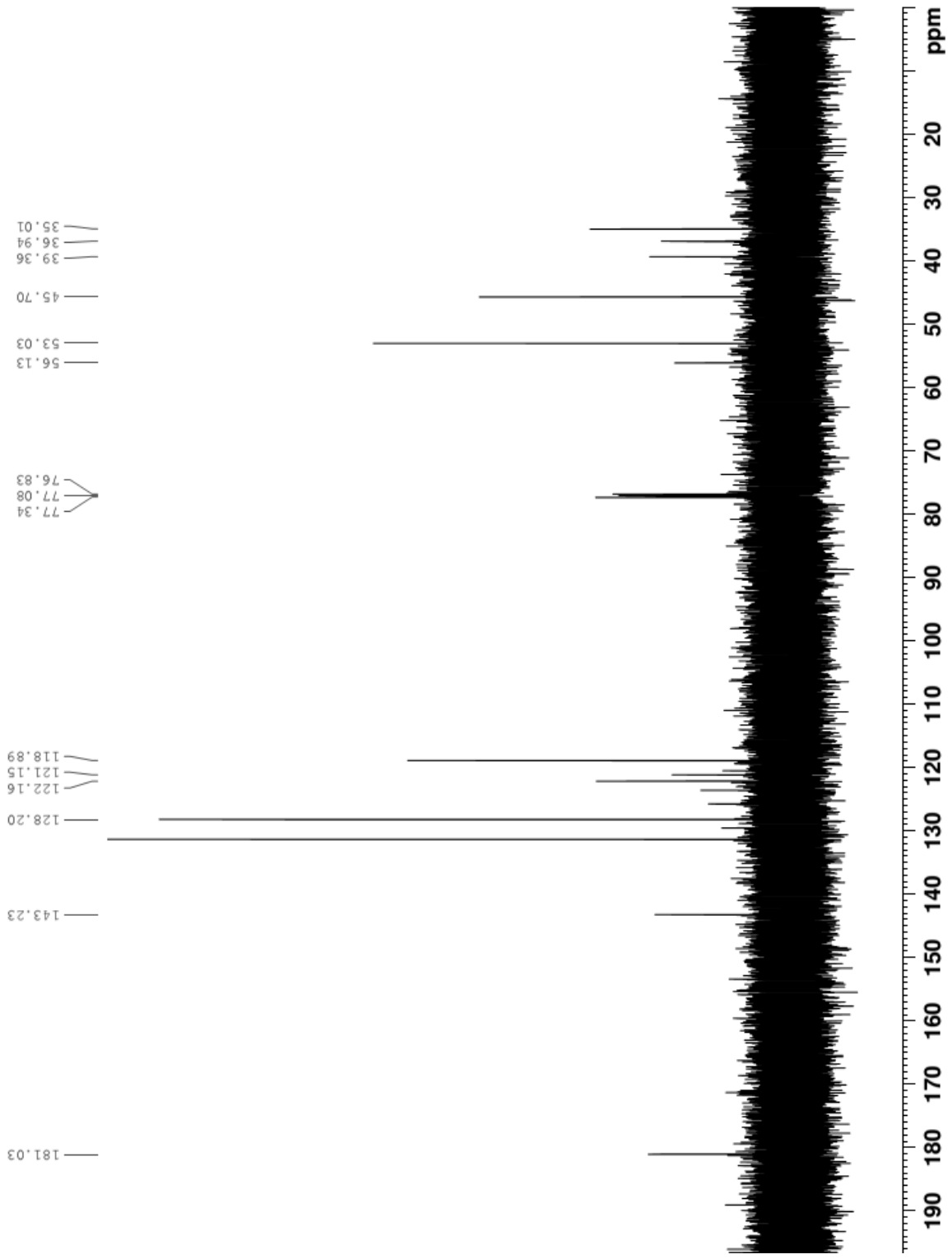


Figure 33. ^{13}C NMR Spectrum for **219** (125 MHz, $CDCl_3$)

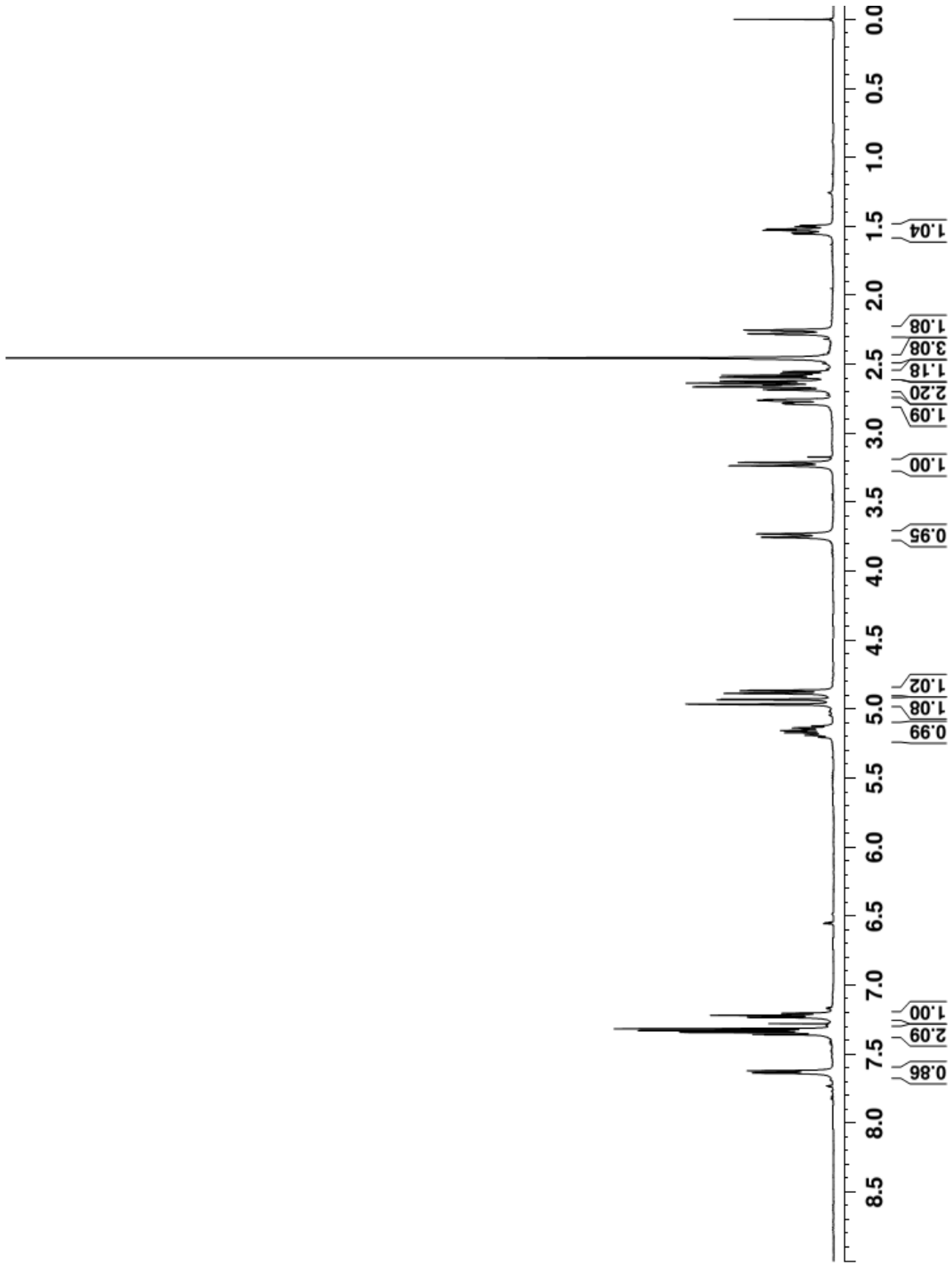


Figure 34. ^{1}H NMR Spectrum for **217** (500 MHz, $CDCl_3$)

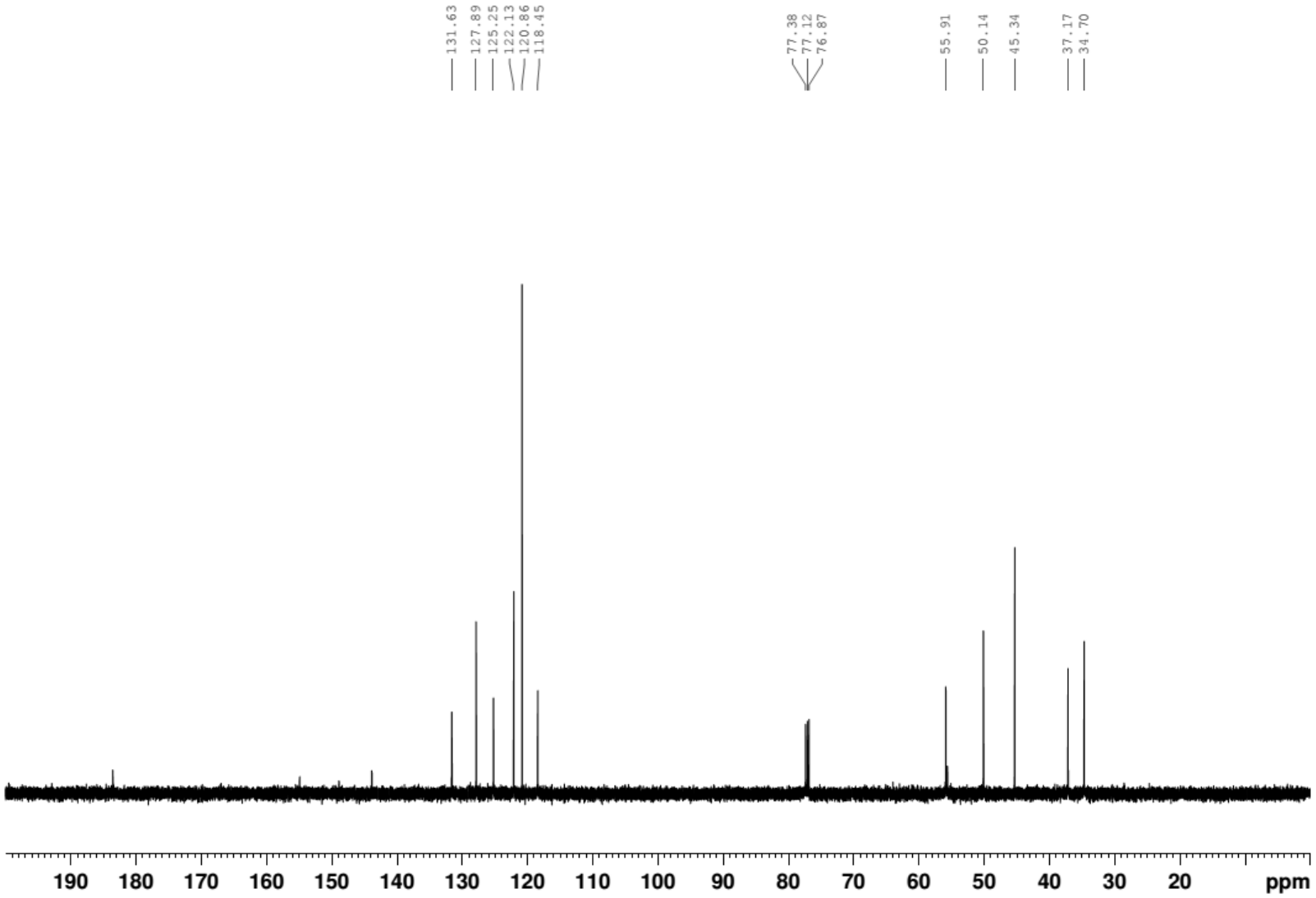


Figure 35. ^{13}C NMR Spectrum for **217** (125 MHz, $CDCl_3$)

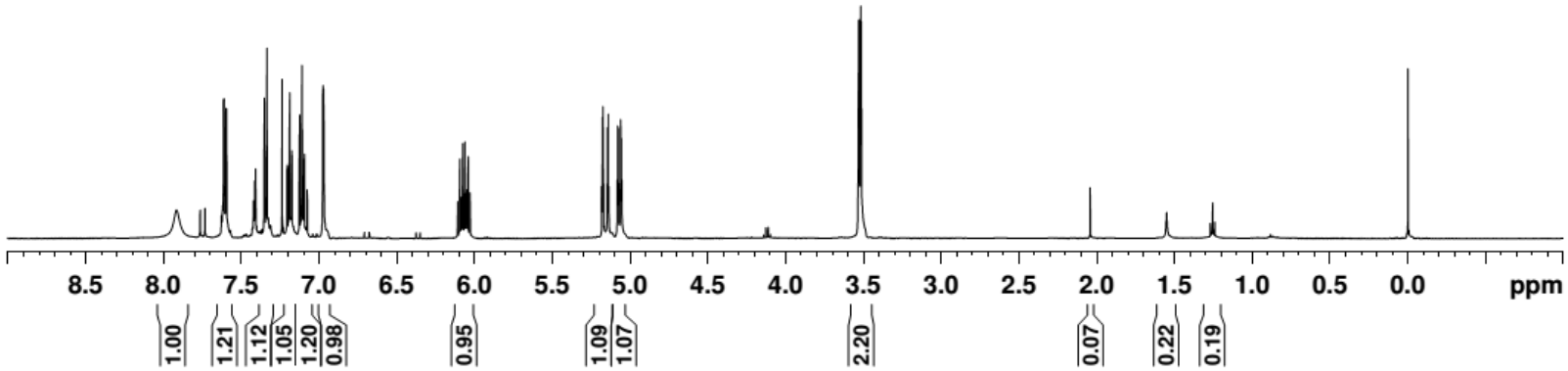


Figure 36. ^{1}H NMR Spectrum for **221** (500 MHz, $CDCl_3$)

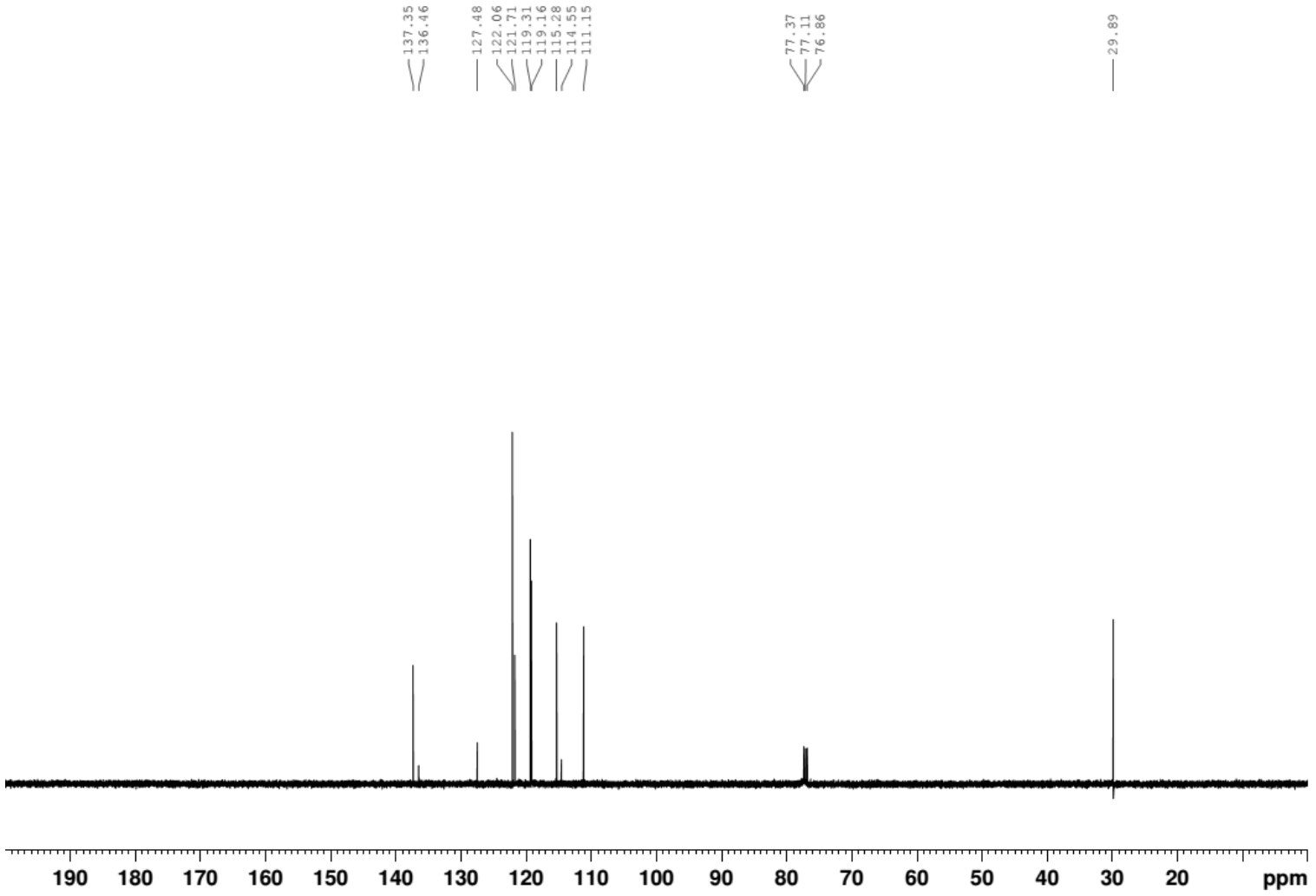


Figure 37. ^{13}C NMR Spectrum for **221** (125 MHz, $CDCl_3$)

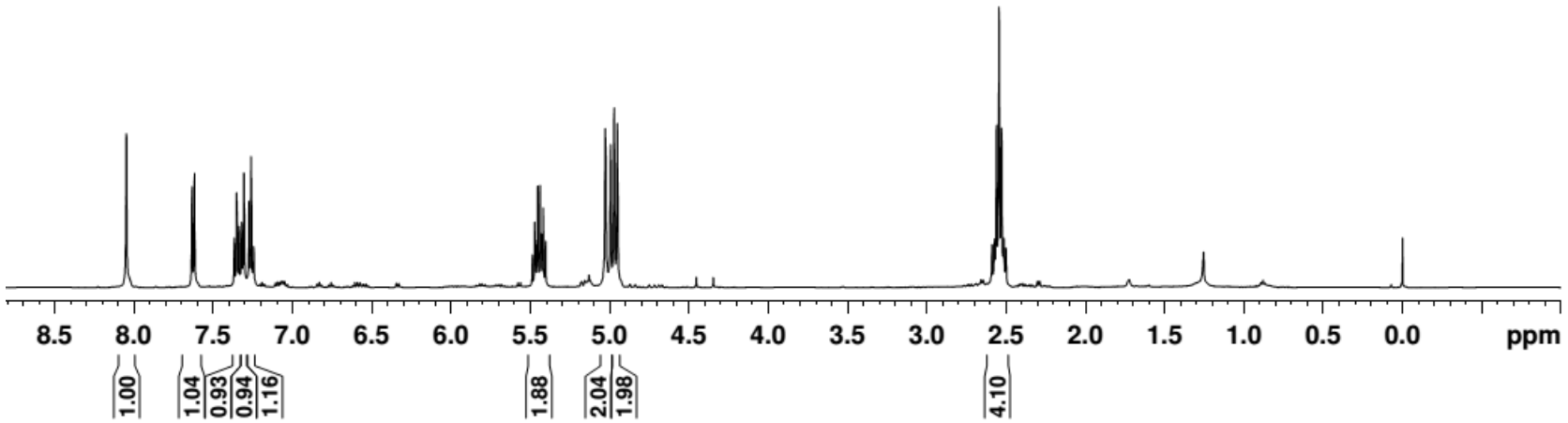


Figure 38. ^{1}H NMR Spectrum for **222** (500 MHz, $CDCl_3$)

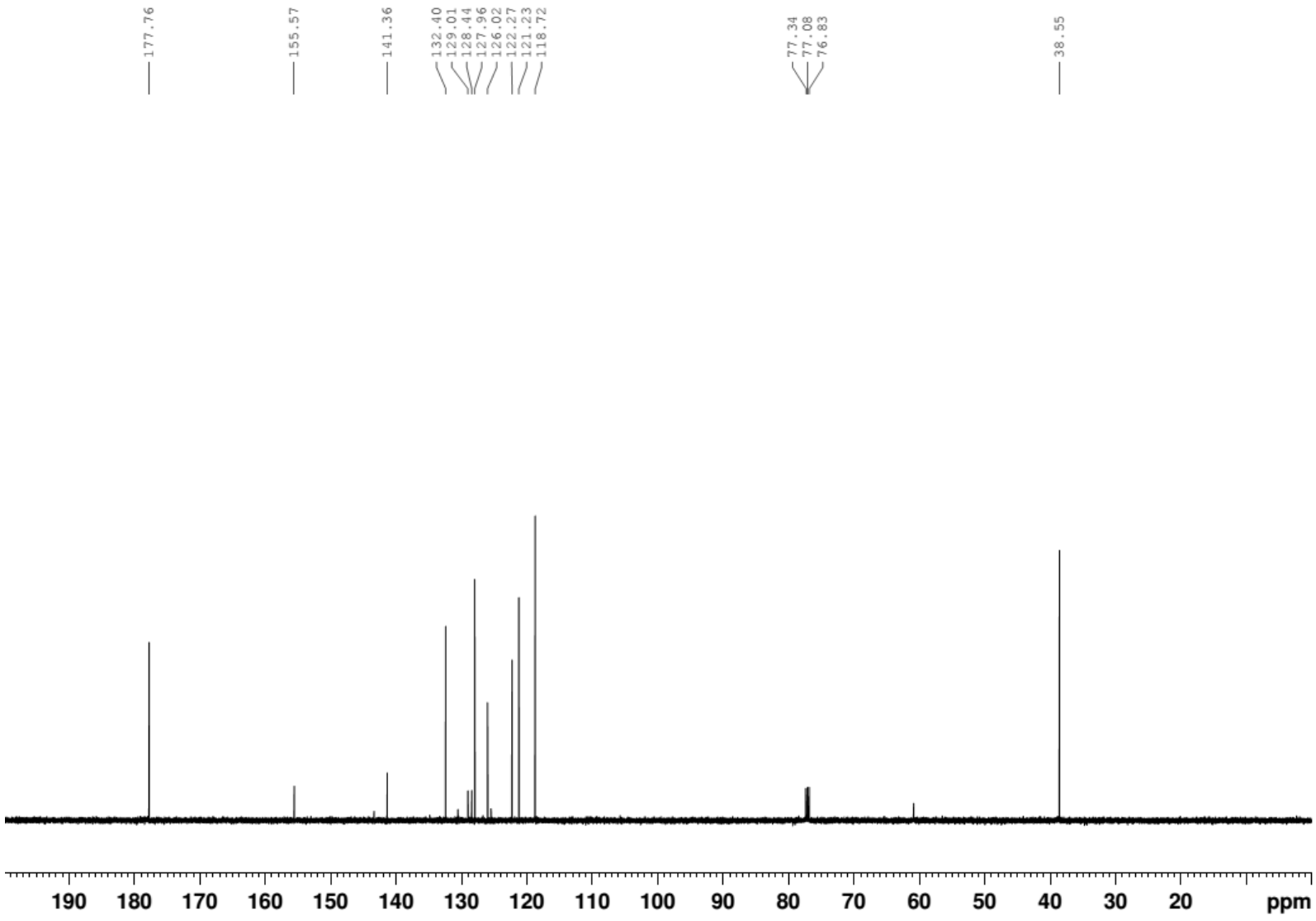


Figure 39. ^{13}C NMR Spectrum for **222** (125 MHz, $CDCl_3$)

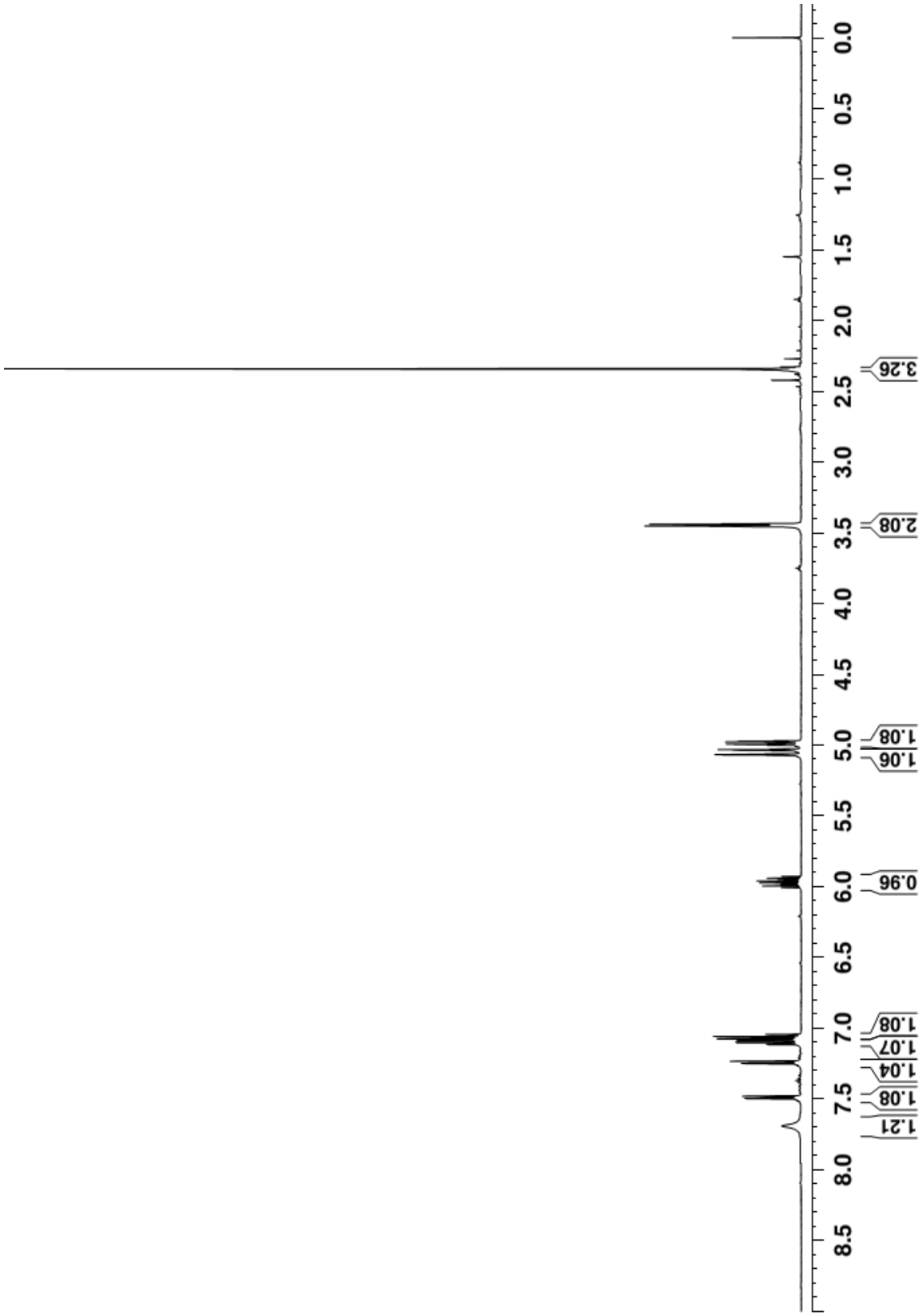


Figure 40. ^{1}H NMR Spectrum for **224** (500 MHz, $CDCl_3$)

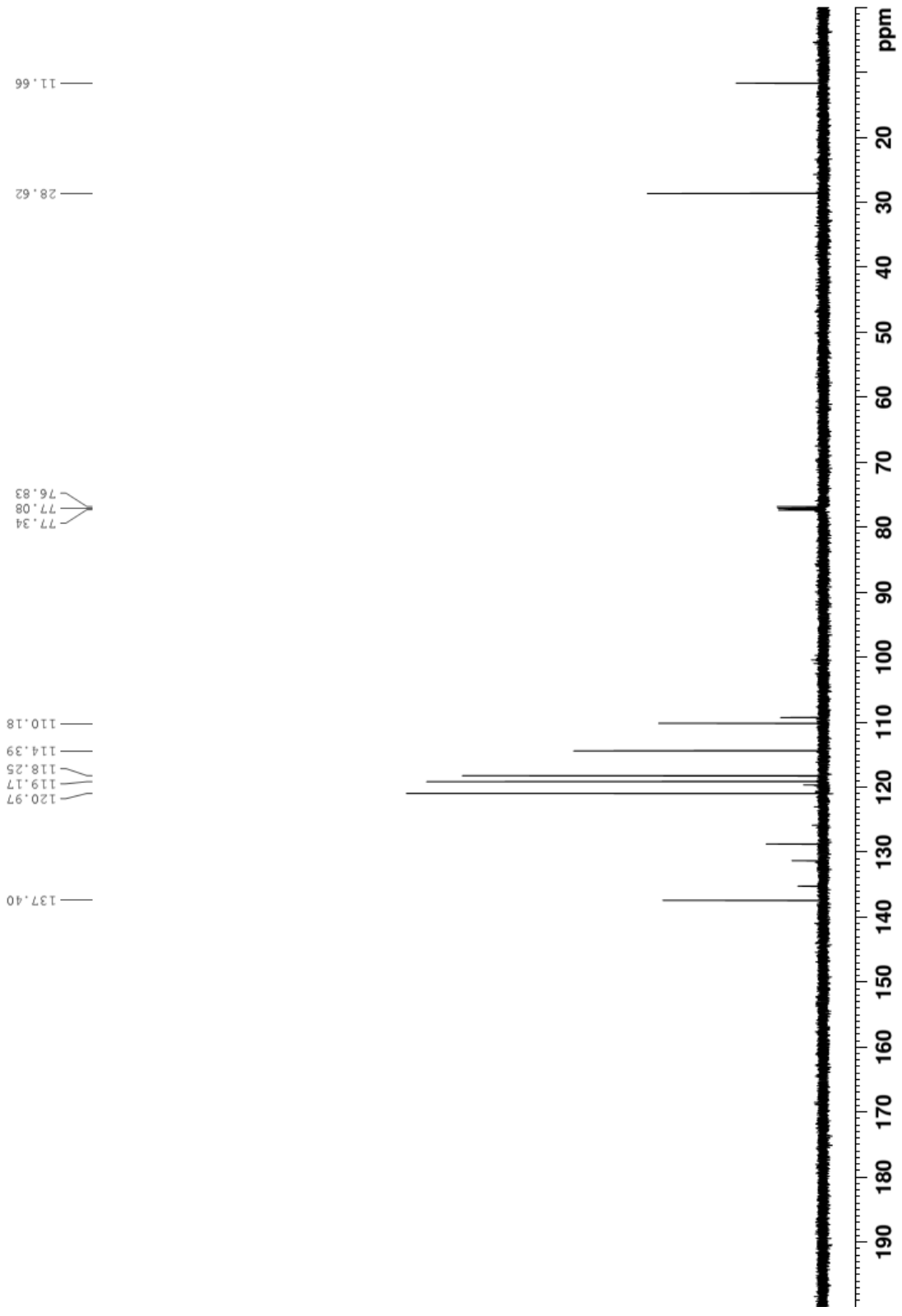


Figure 41. ^{13}C NMR Spectrum for **224** (125 MHz, $CDCl_3$)

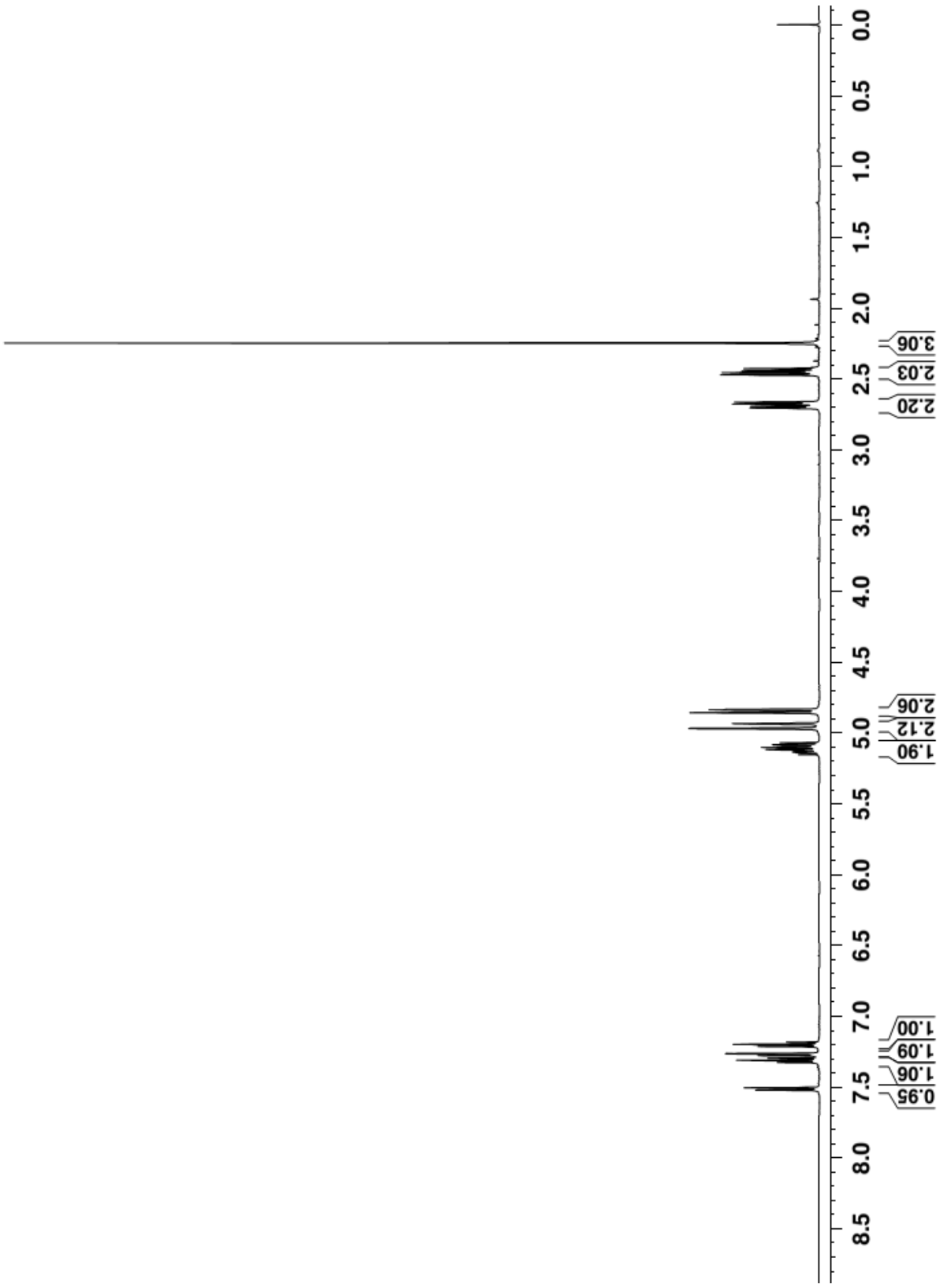


Figure 42. ^{1}H NMR Spectrum for **225** (500 MHz, $CDCl_3$)

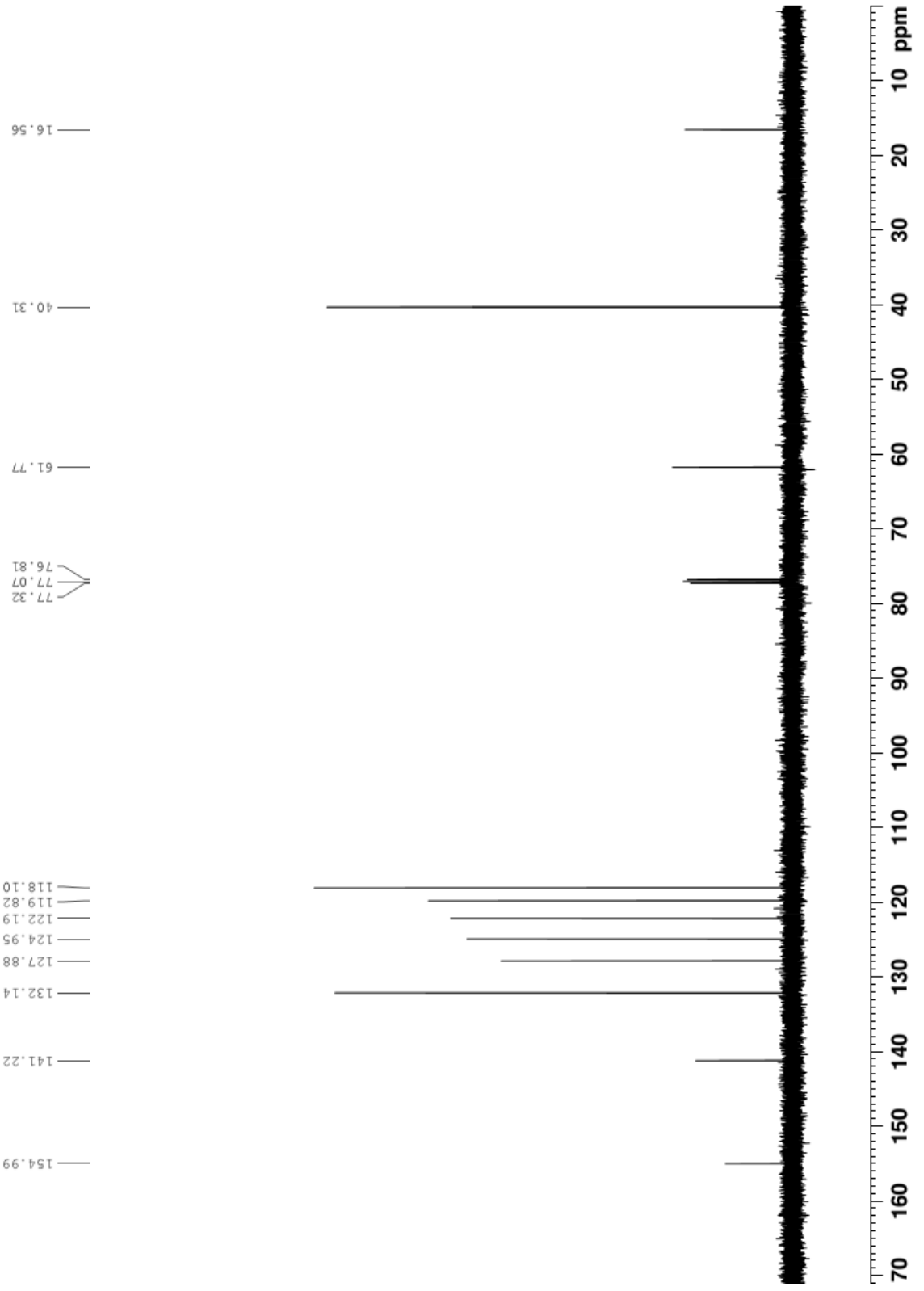


Figure 43. ^{13}C NMR Spectrum for **225** (125 MHz, $CDCl_3$)

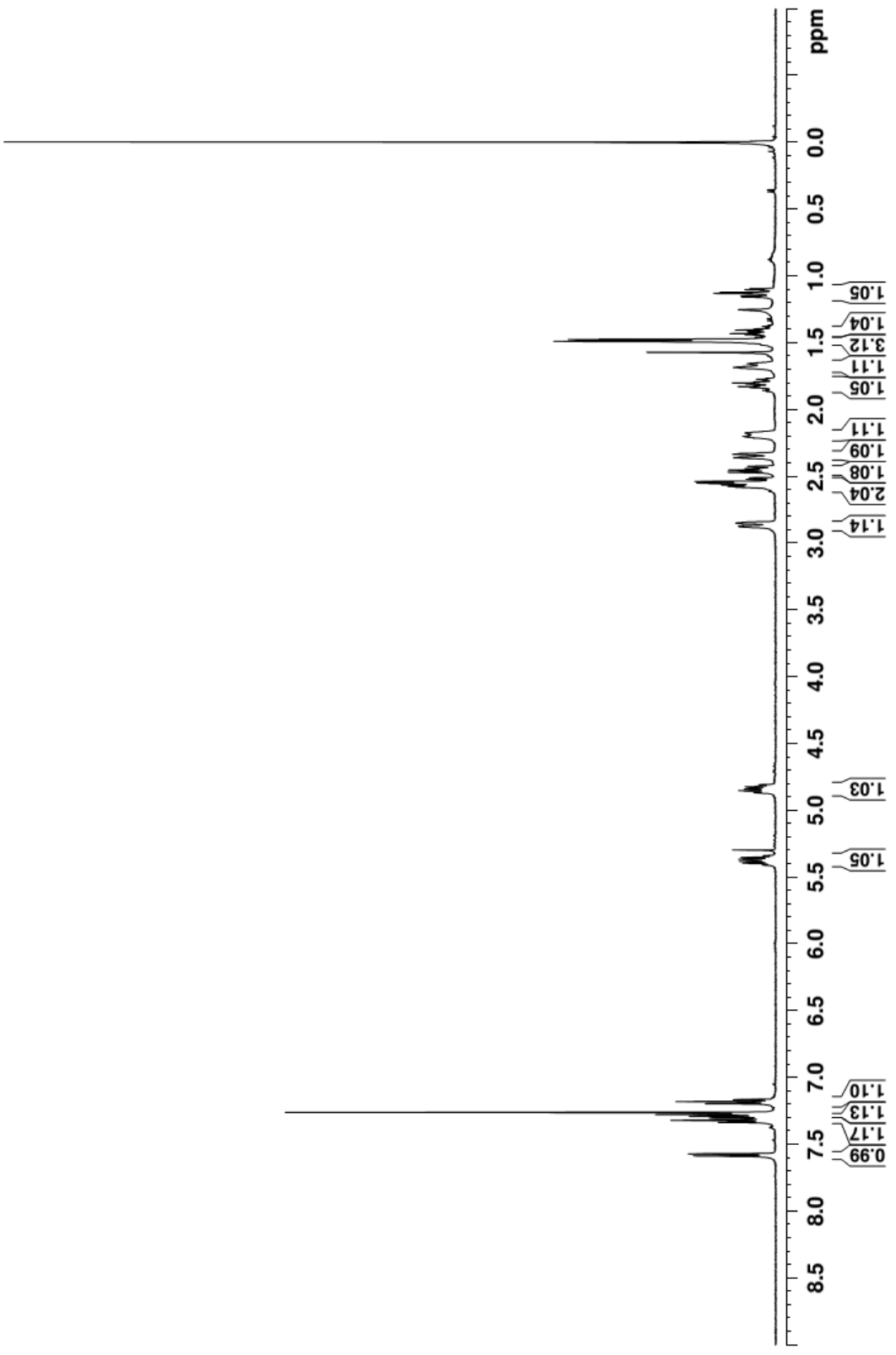


Figure 44. ^{1}H NMR Spectrum for **229** (500 MHz, $CDCl_3$)

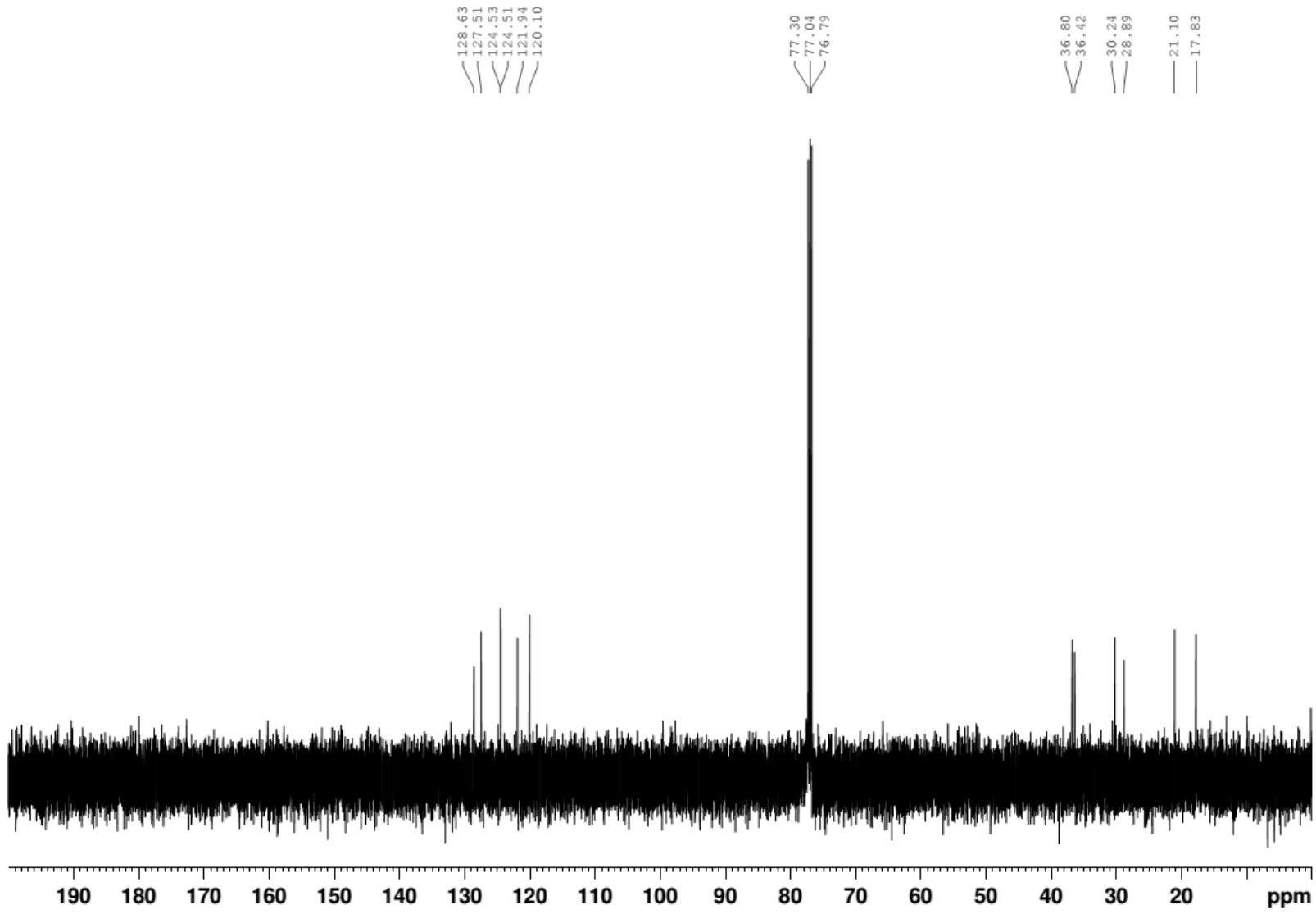


Figure 45. ^{13}C NMR Spectrum for **229** (125 MHz, $CDCl_3$)

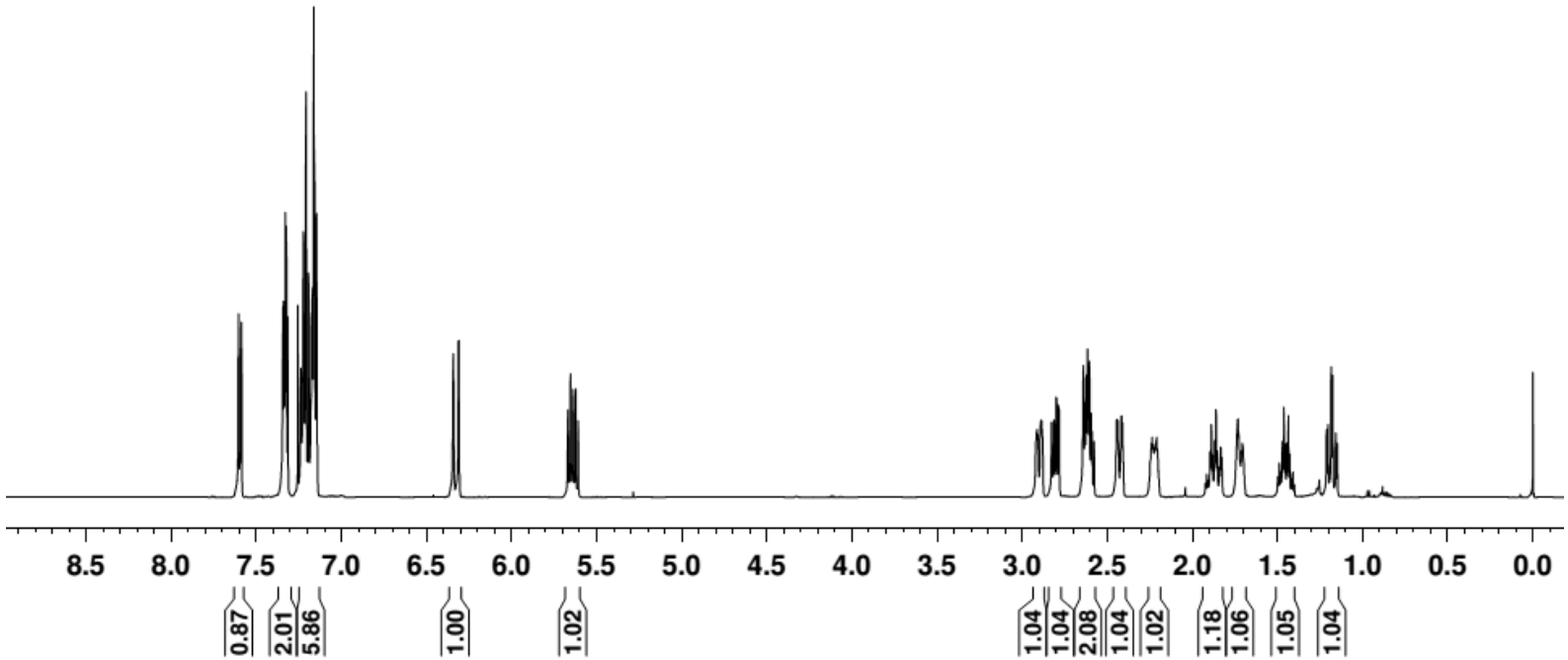


Figure 46. ^{1}H NMR Spectrum for **231** (500 MHz, $CDCl_3$)

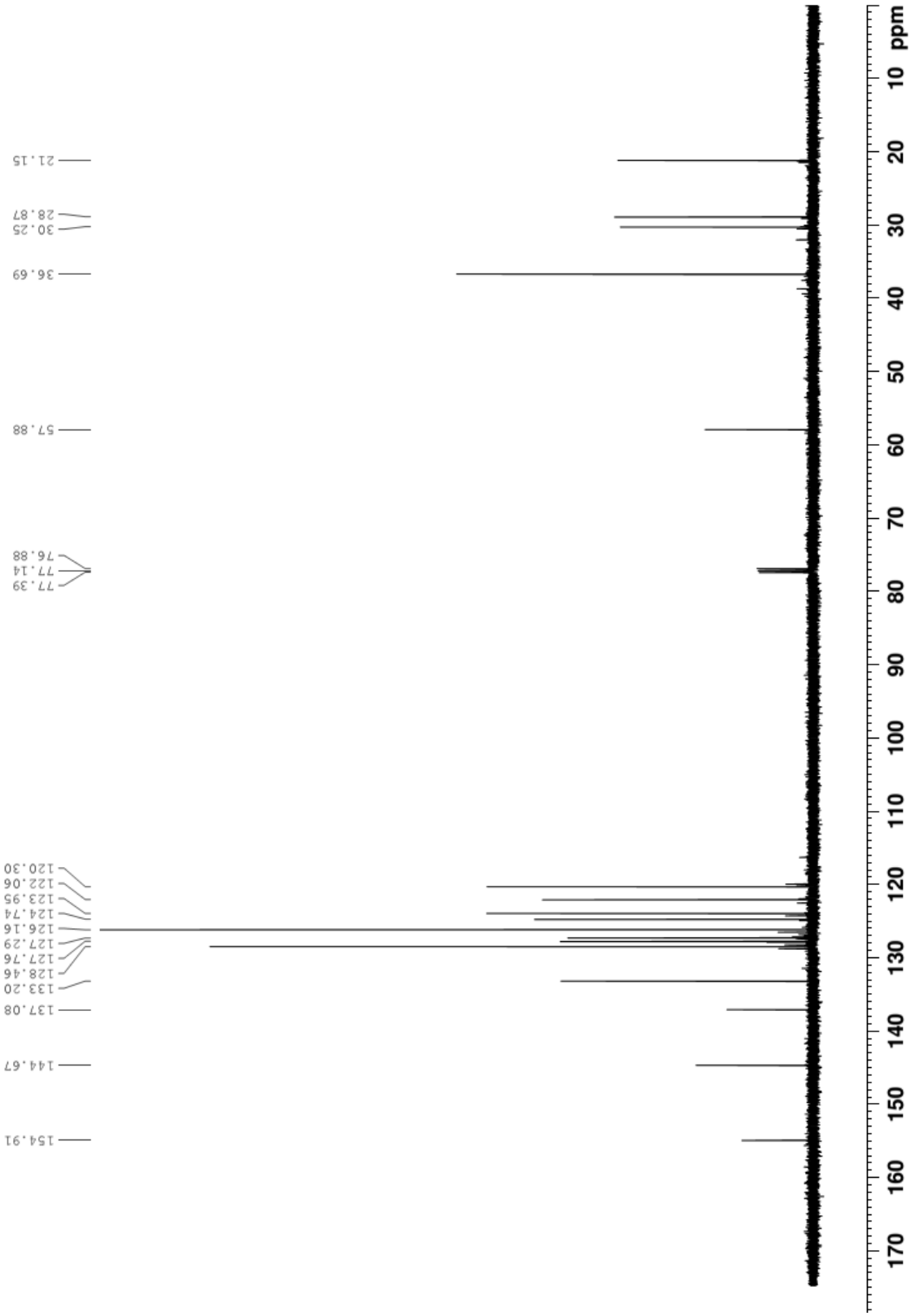


Figure 47. ^{13}C NMR Spectrum for **231** (125 MHz, $CDCl_3$)

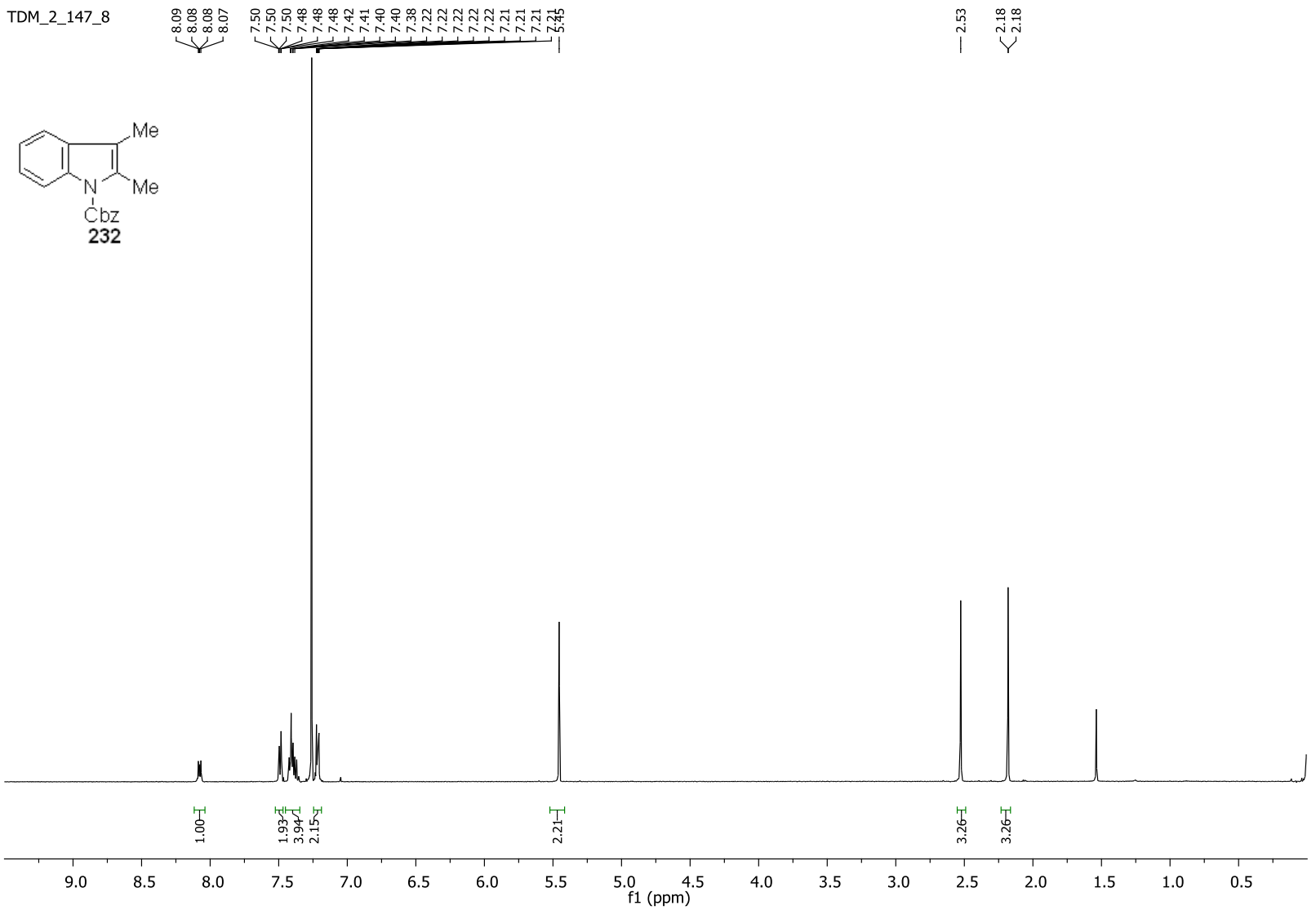


Figure 48. ^{1}H NMR Spectrum for **232** (500 MHz, $CDCl_3$)

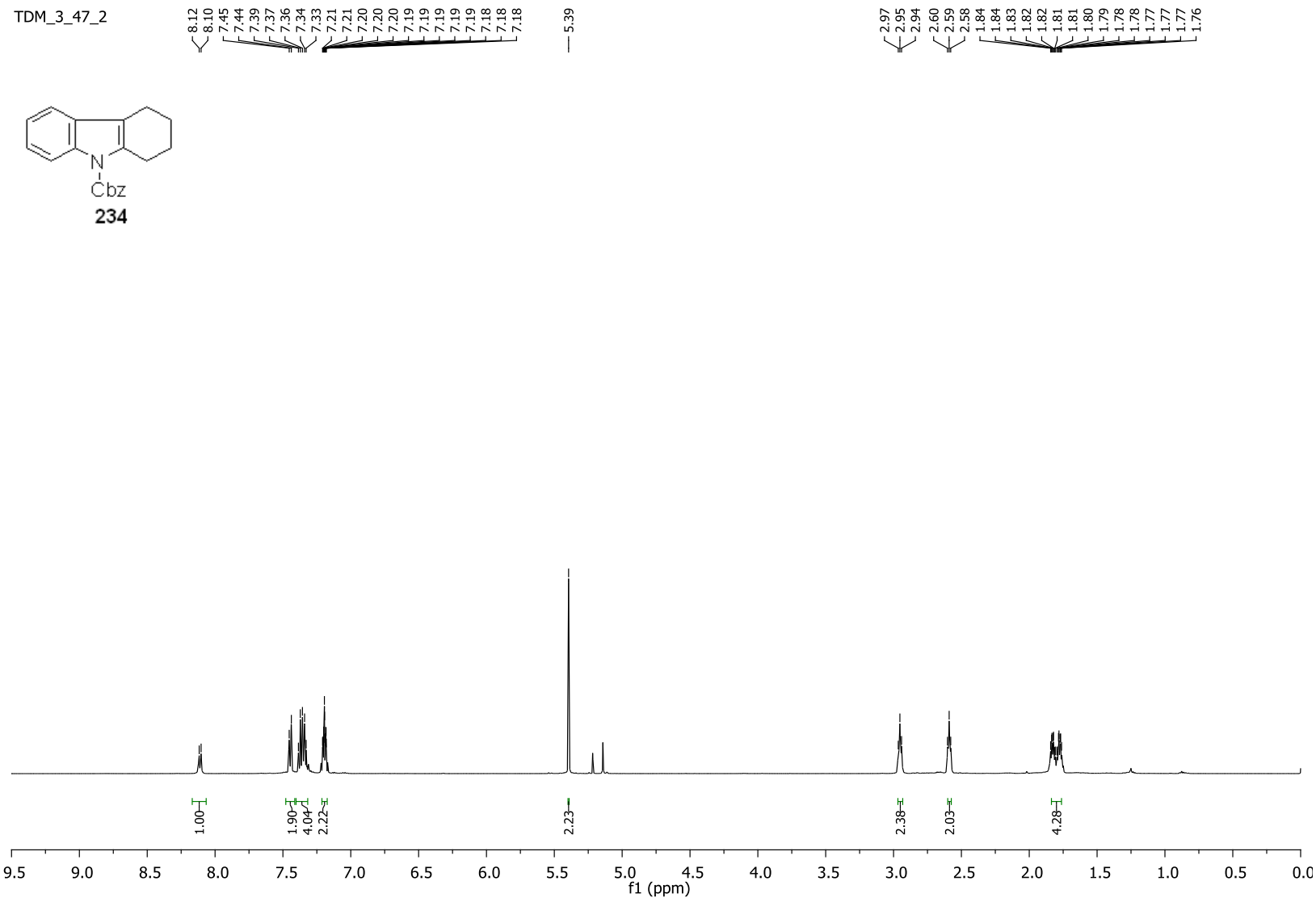


Figure 49. ^{1}H NMR Spectrum for **234** (500 MHz, $CDCl_3$)

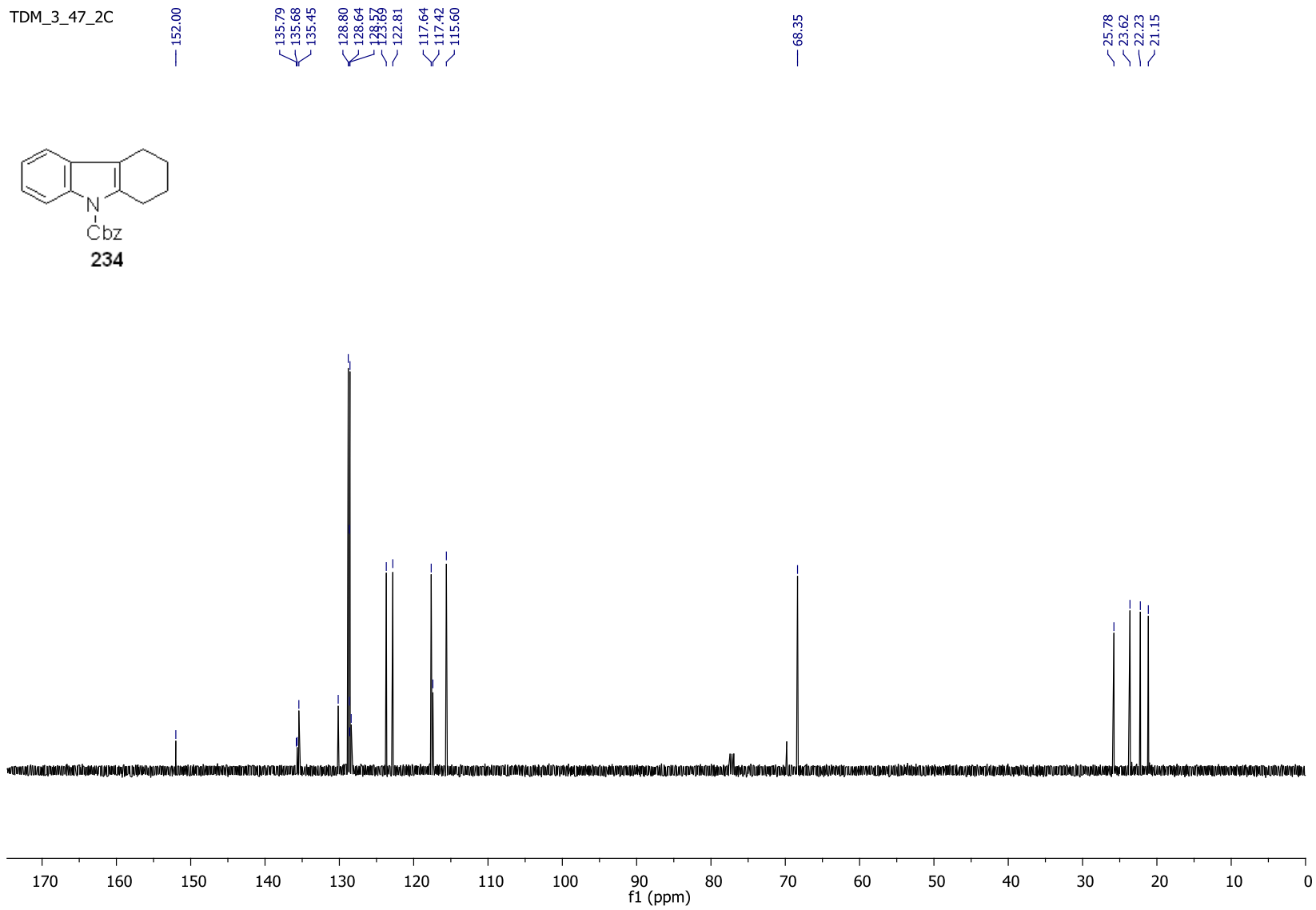


Figure 50. ^{13}C NMR Spectrum for **234** (125 MHz, $CDCl_3$)

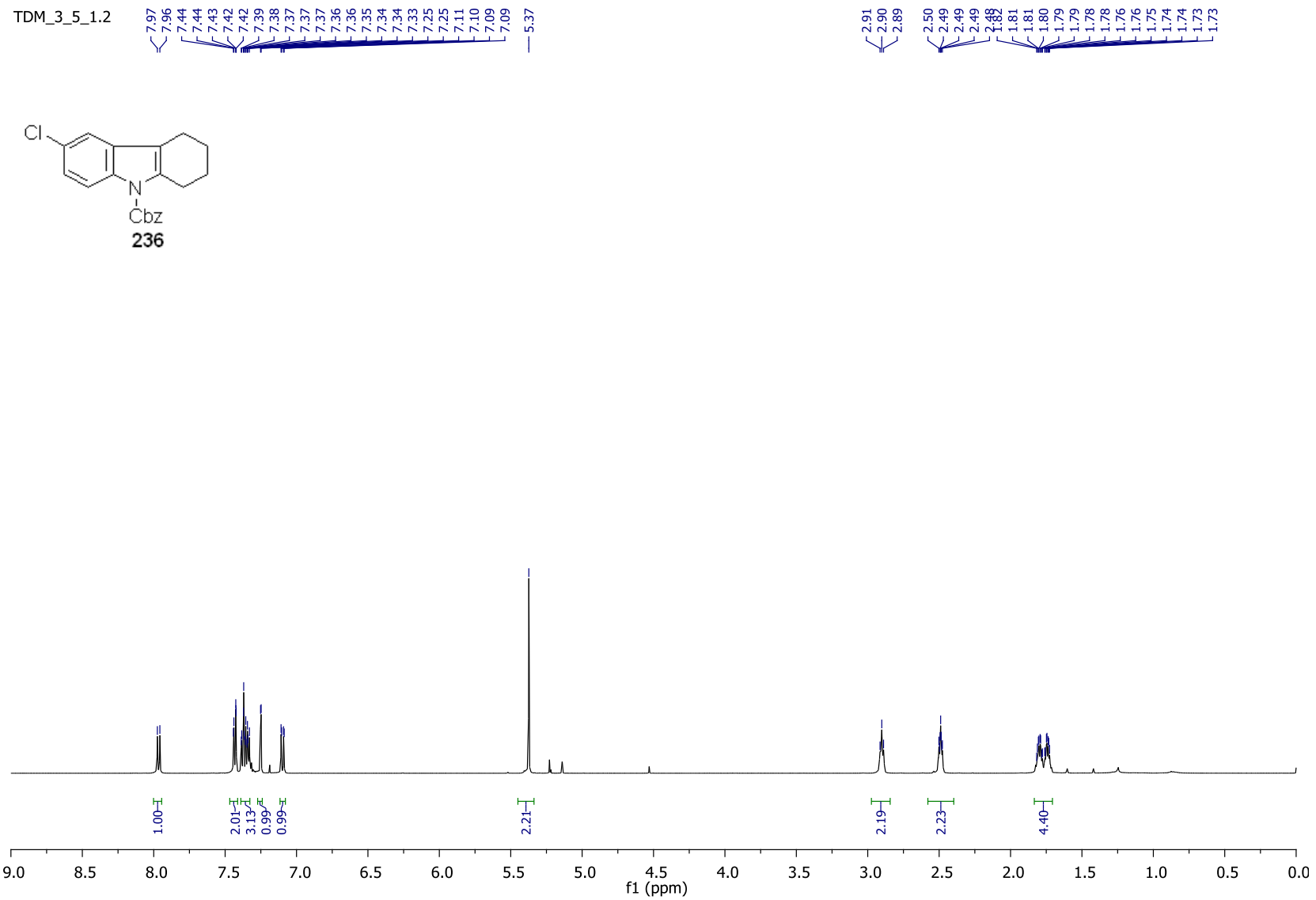


Figure 51. ^{1}H NMR Spectrum for **236** (500 MHz, $CDCl_3$)

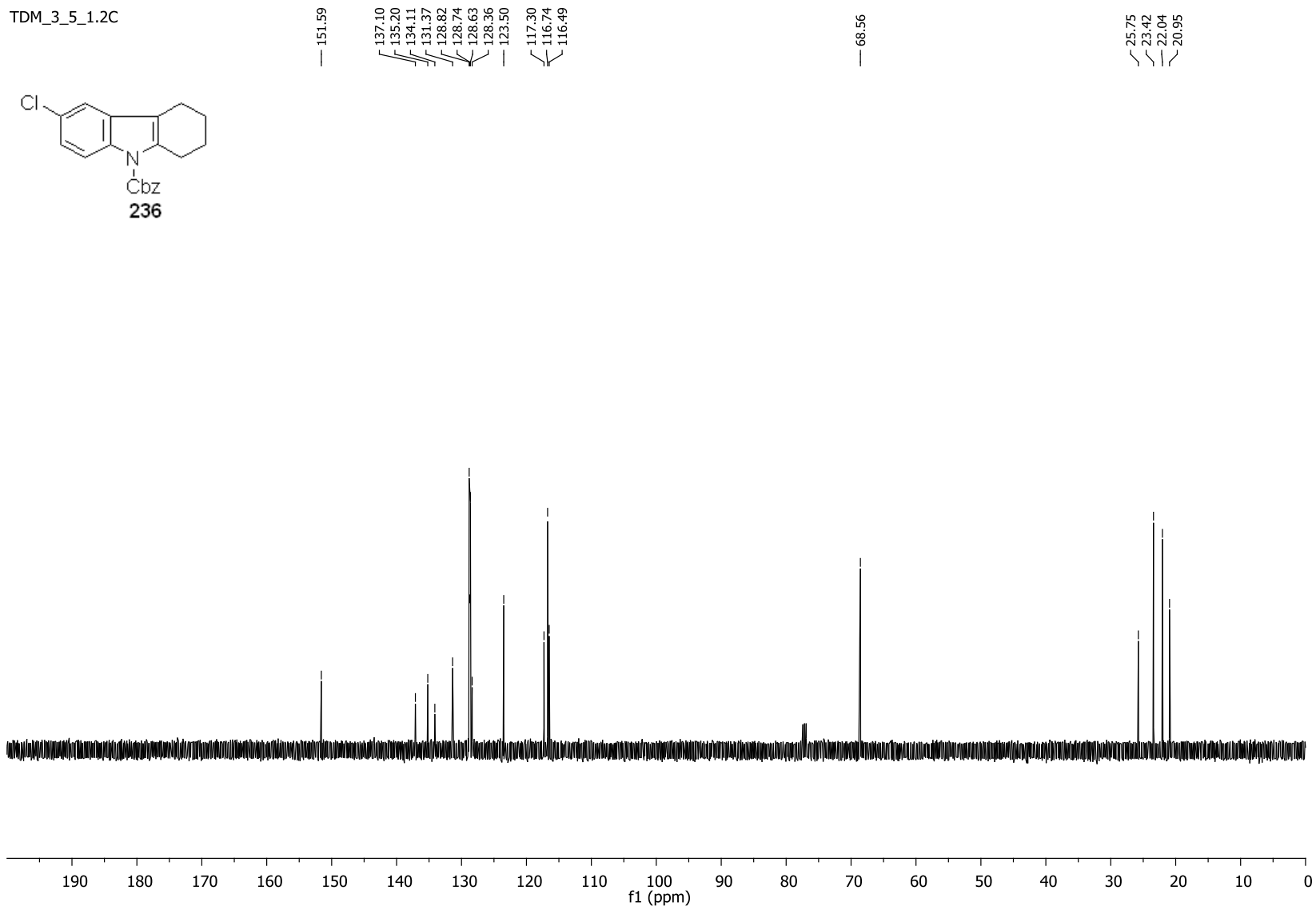


Figure 52. ^{13}C NMR Spectrum for **236** (125 MHz, $CDCl_3$)

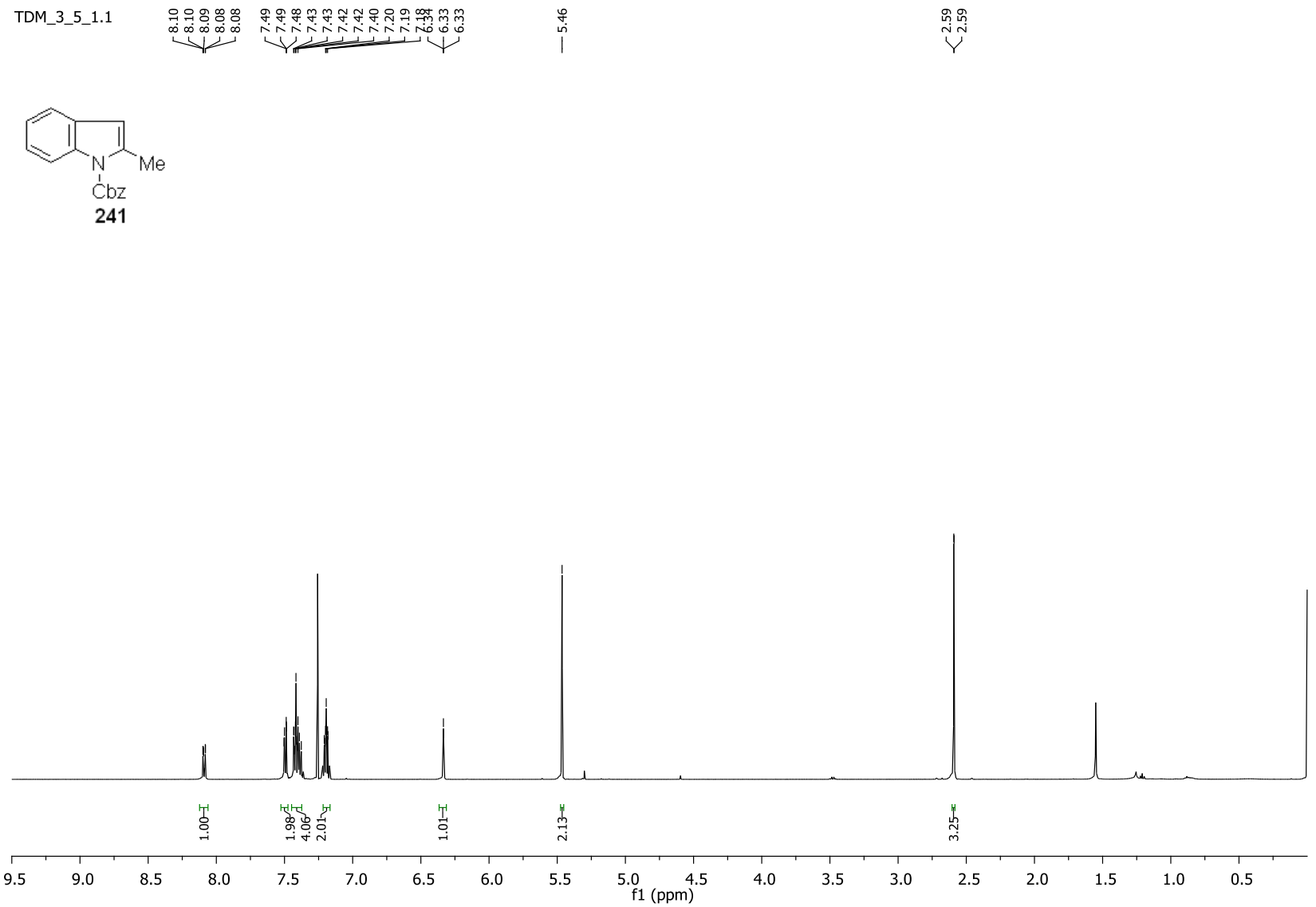


Figure 53. ^{1}H NMR Spectrum for **241** (500 MHz, $CDCl_3$)

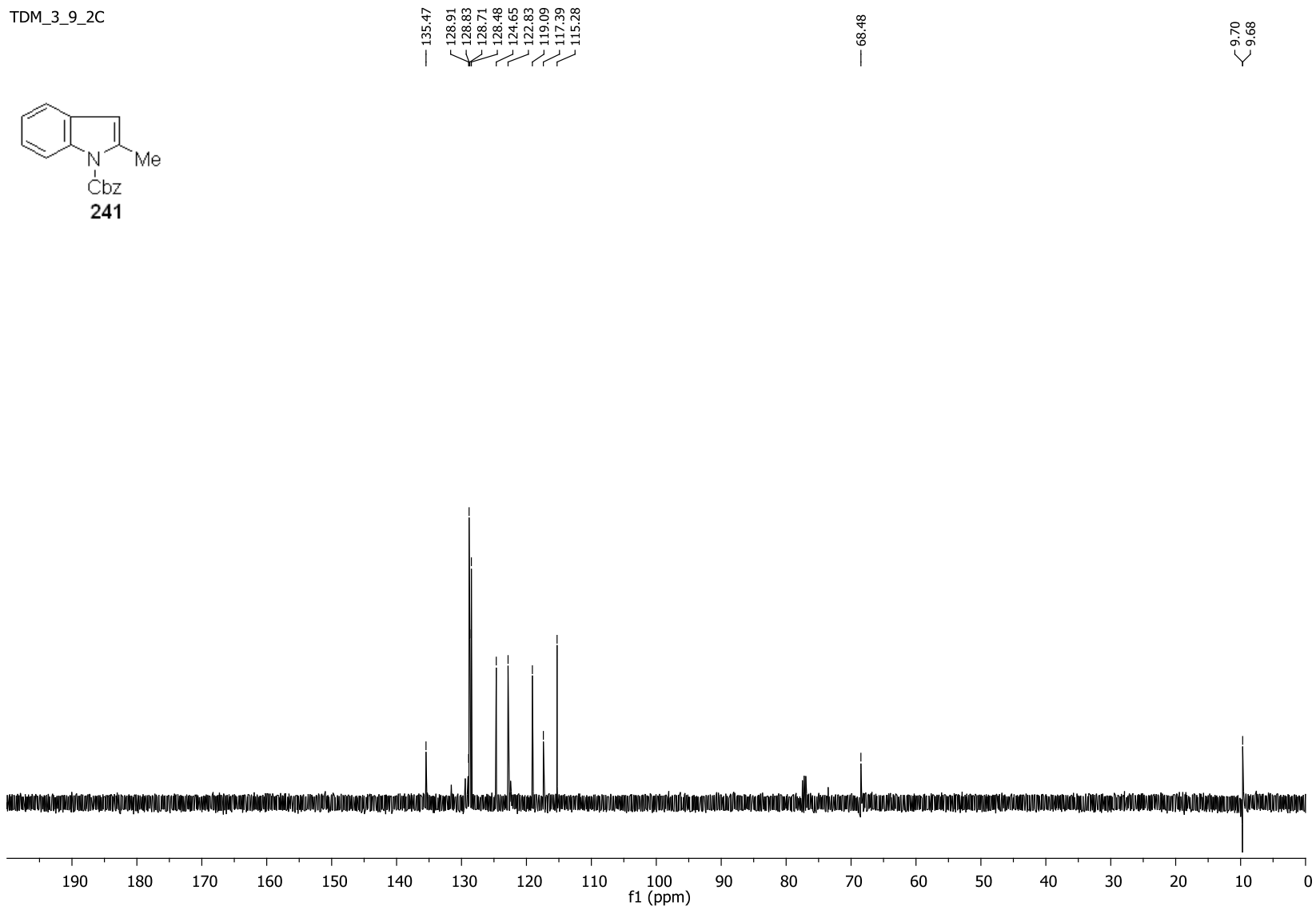


Figure 54. ^{13}C NMR Spectrum for **241** (125 MHz, $CDCl_3$)

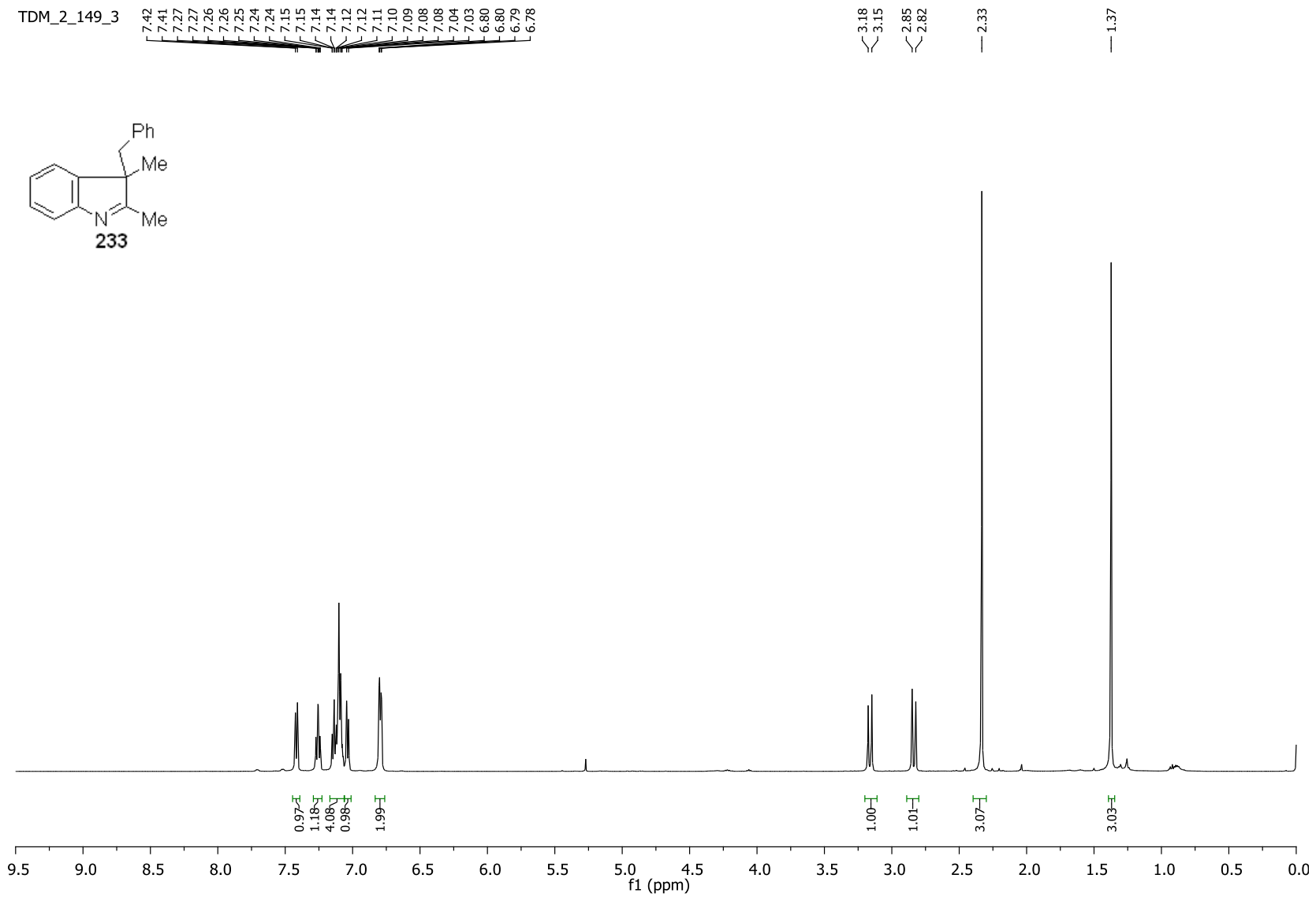


Figure 55. ^{1}H NMR Spectrum for **233** (500 MHz, $CDCl_3$)

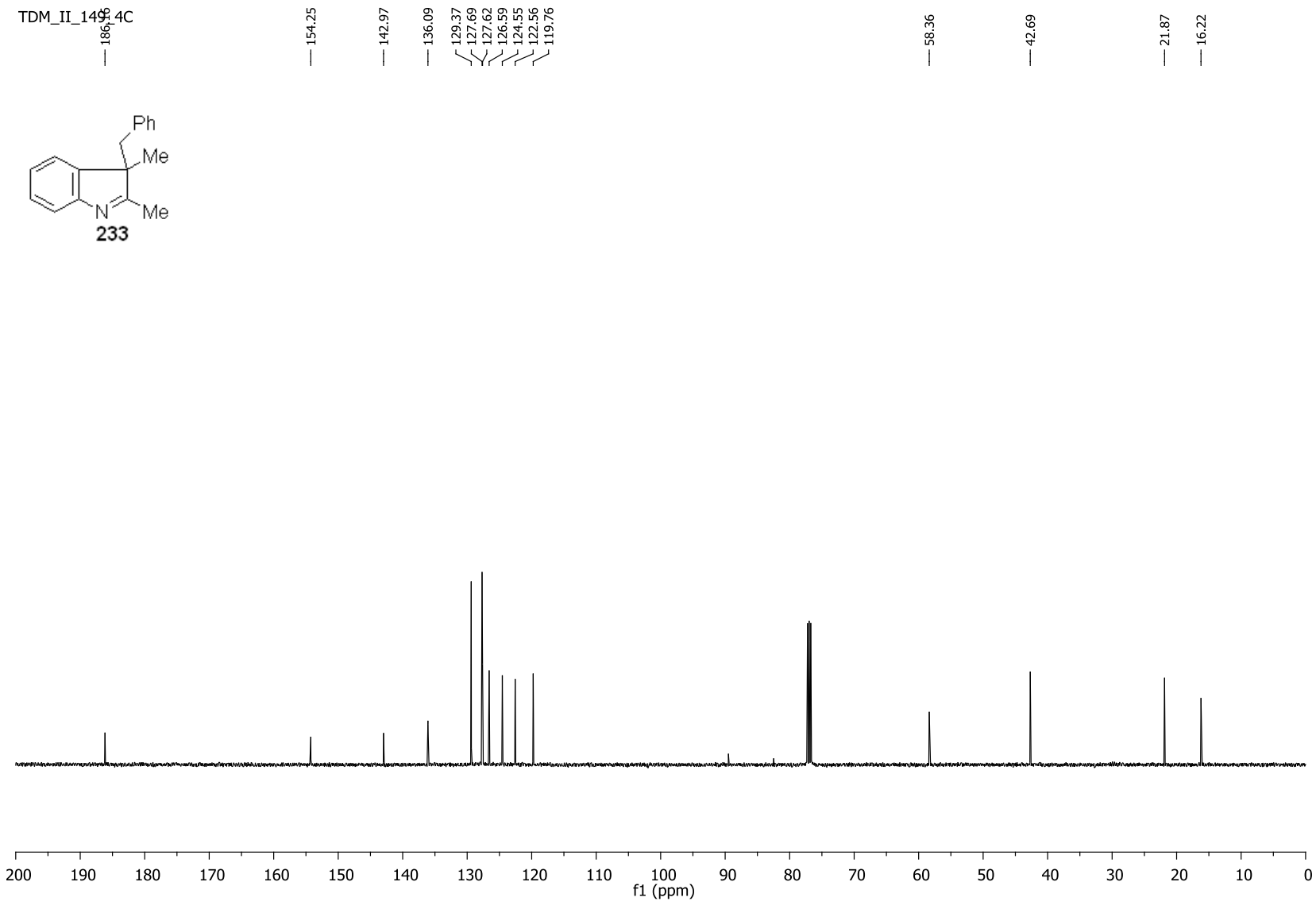


Figure 56. ^{13}C NMR Spectrum for **233** (125 MHz, $CDCl_3$)

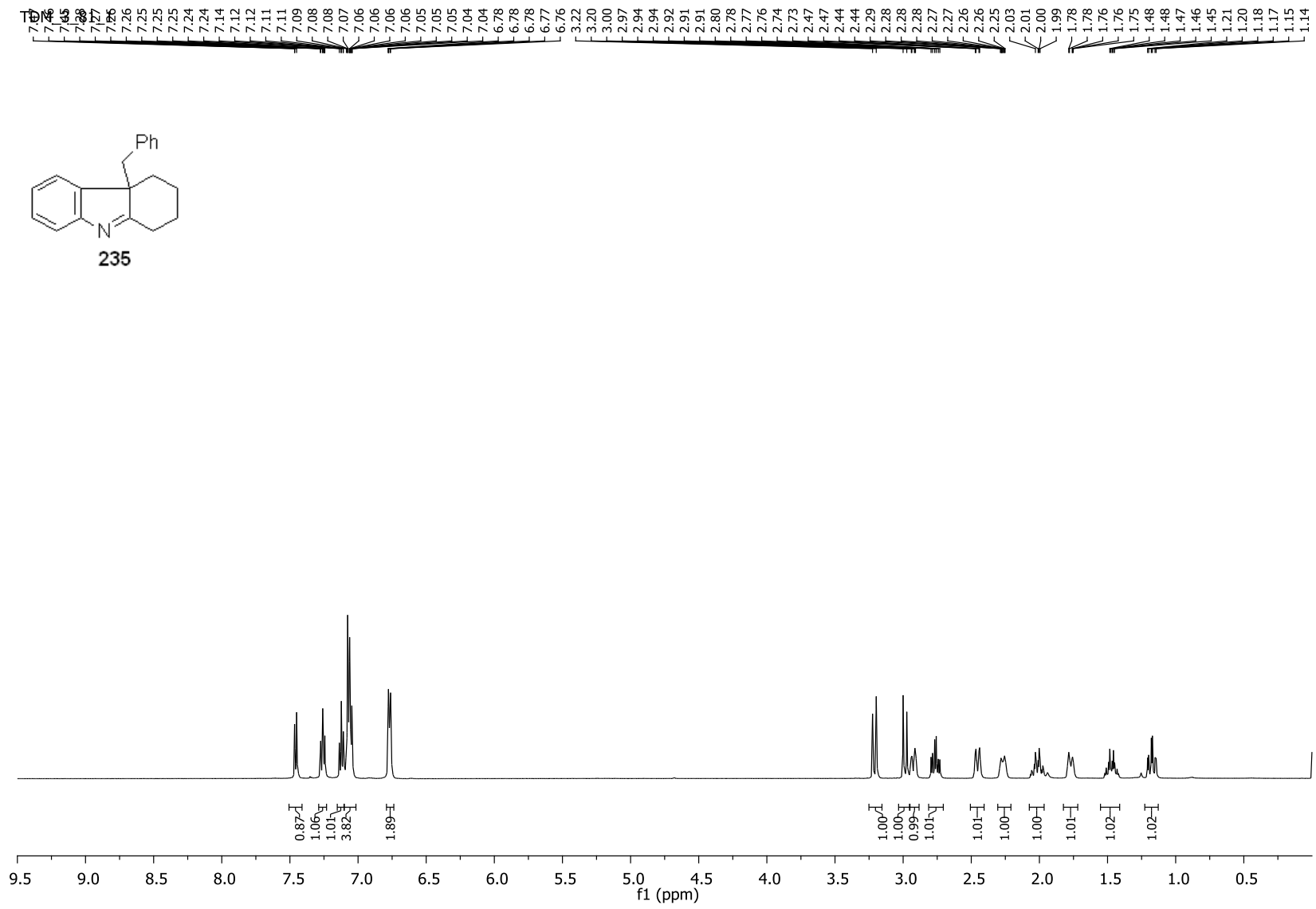


Figure 57. ^{1}H NMR Spectrum for **235** (500 MHz, $CDCl_3$)

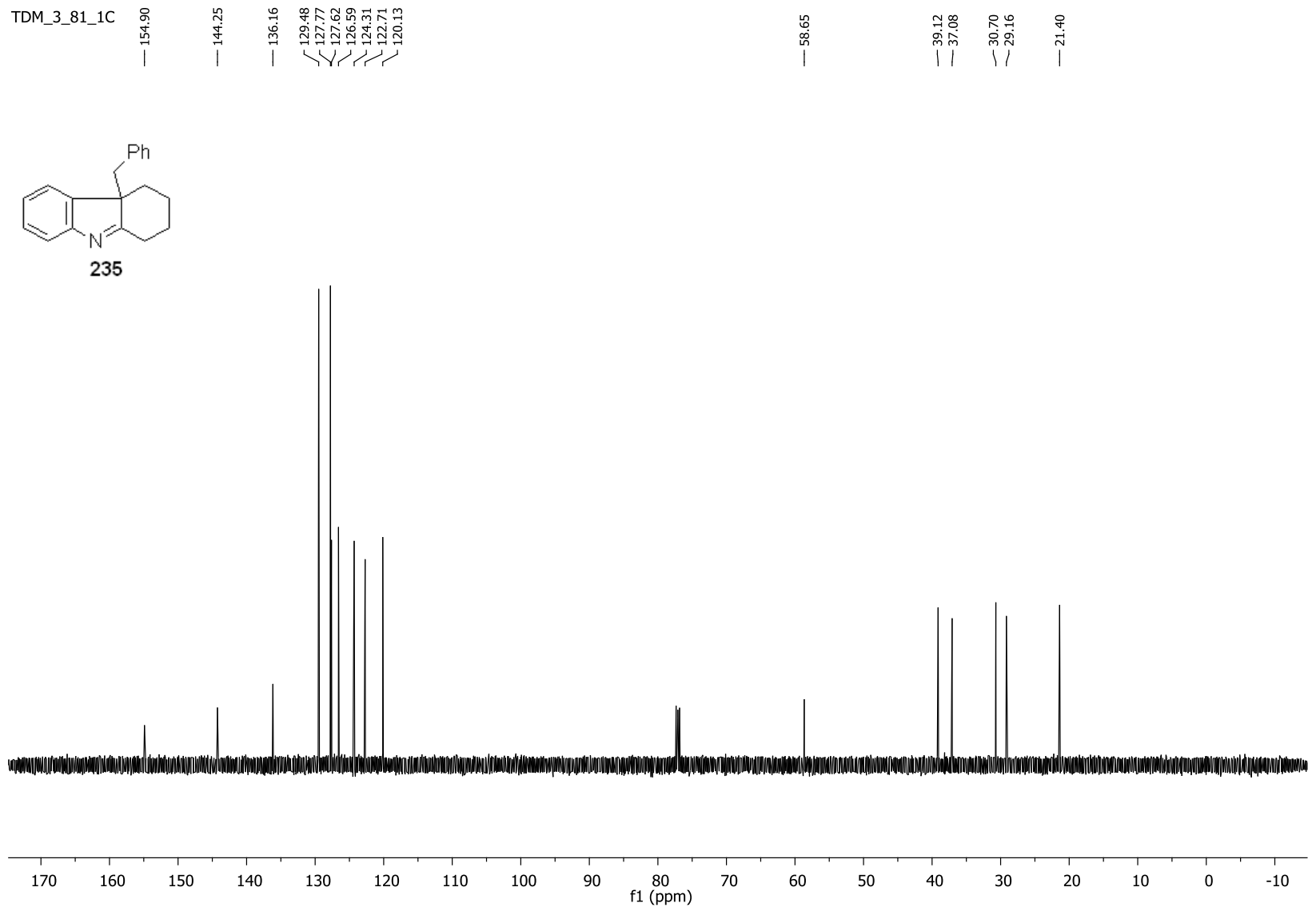


Figure 58. ^{13}C NMR Spectrum for **235** (125 MHz, $CDCl_3$)

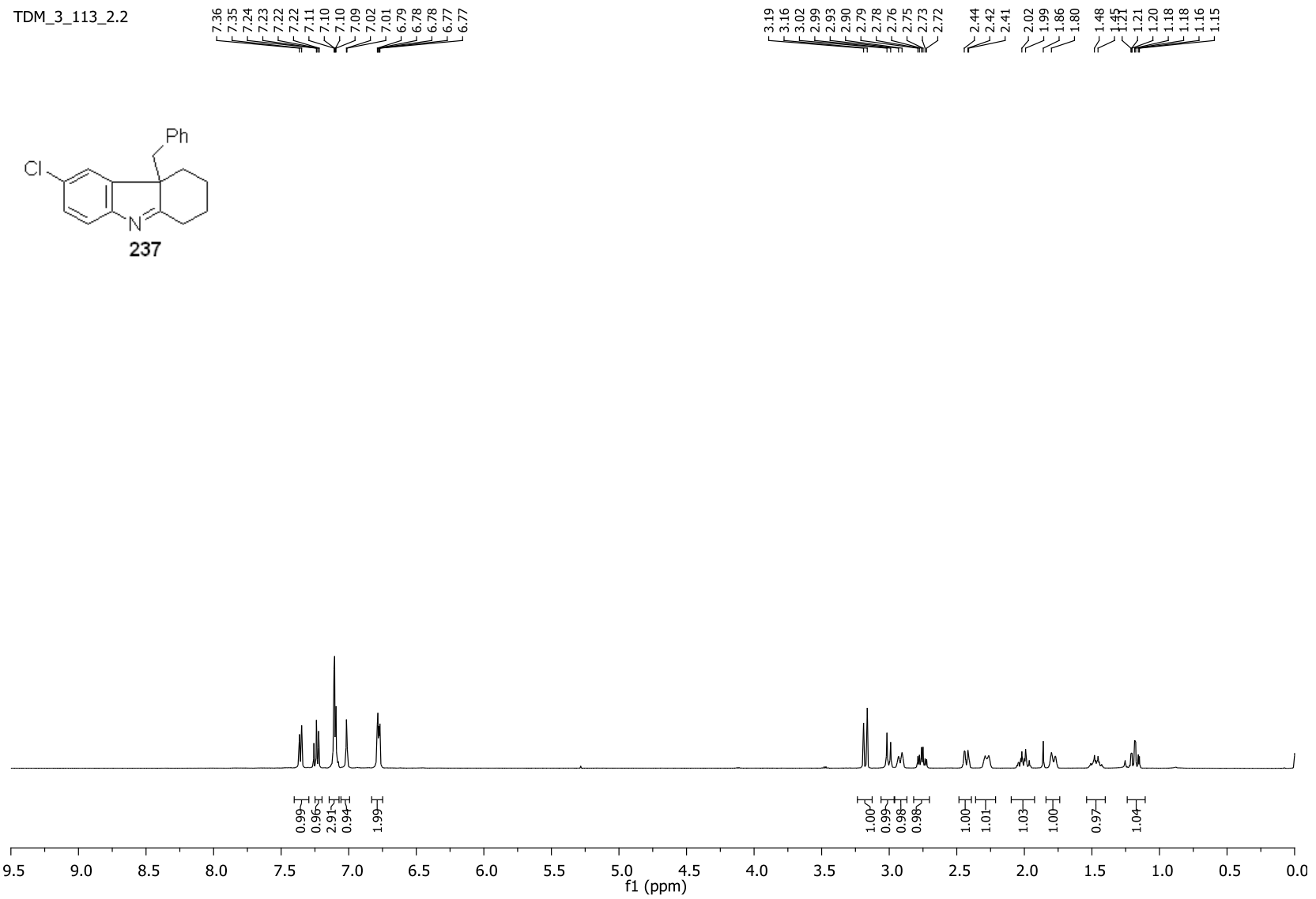


Figure 59. ^{1}H NMR Spectrum for **237** (500 MHz, $CDCl_3$)

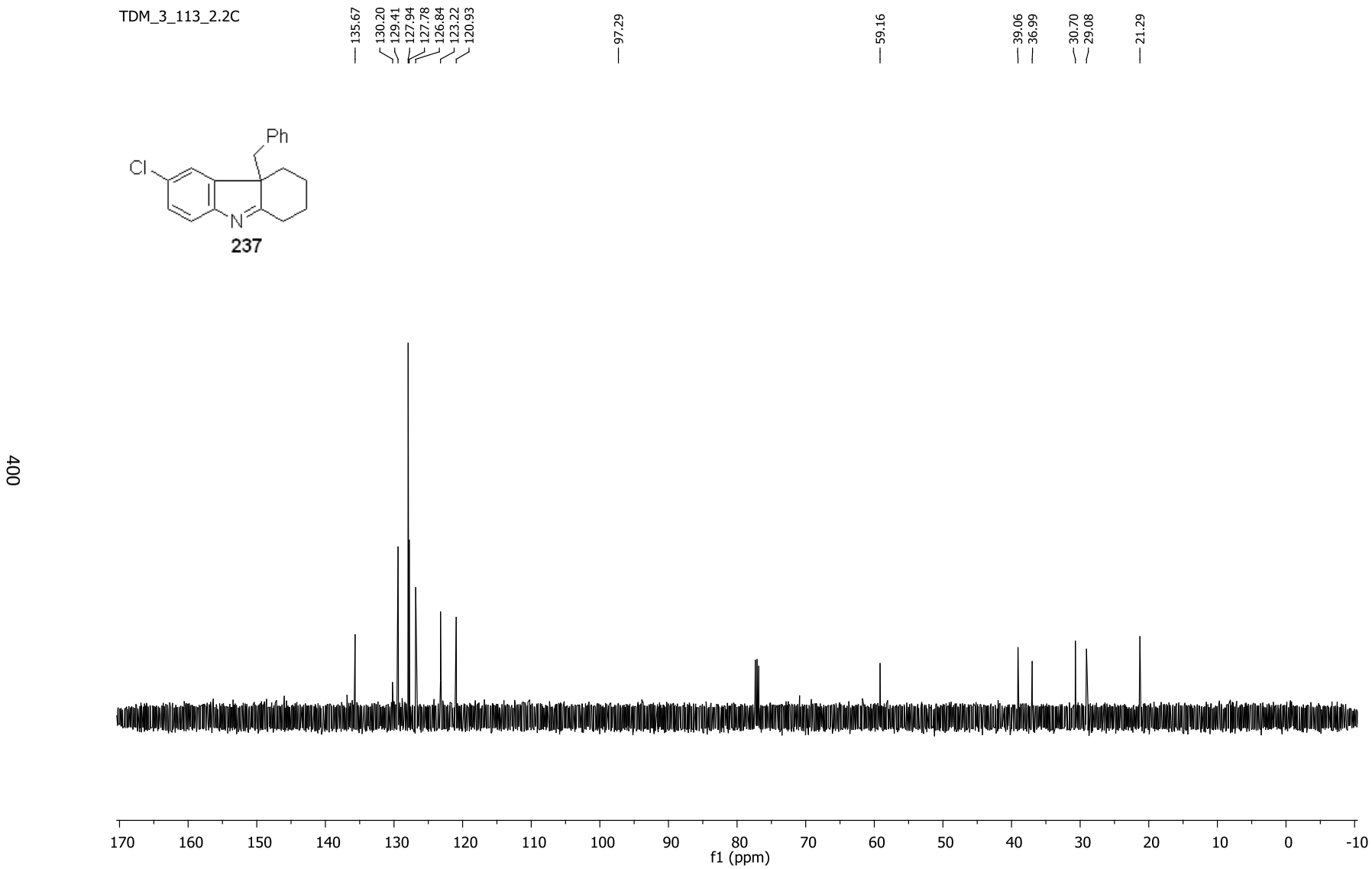


Figure 60. ^{13}C NMR Spectrum for **237** (125 MHz, $CDCl_3$)

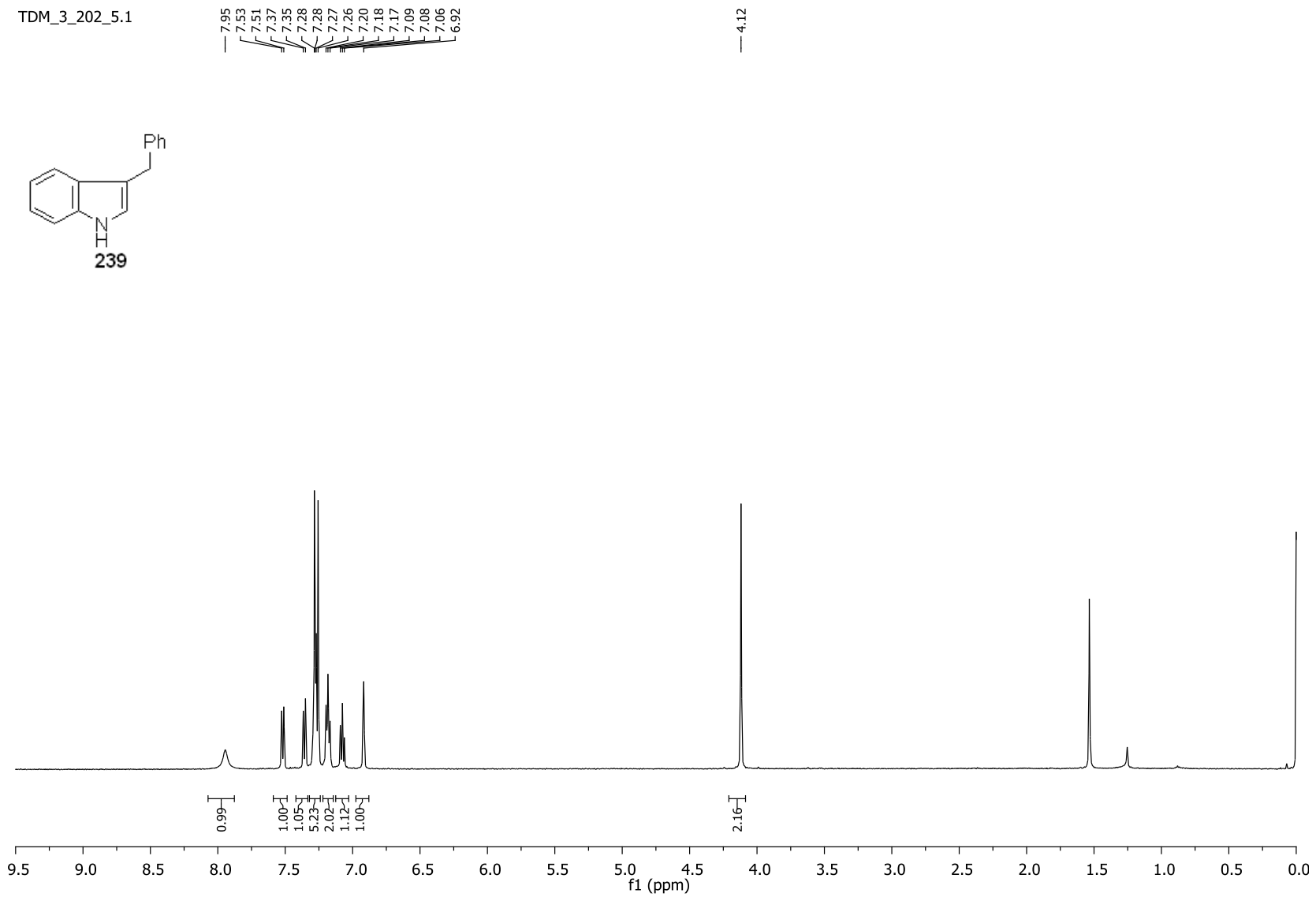


Figure 61. ^{1}H NMR Spectrum for **239** (500 MHz, $CDCl_3$)

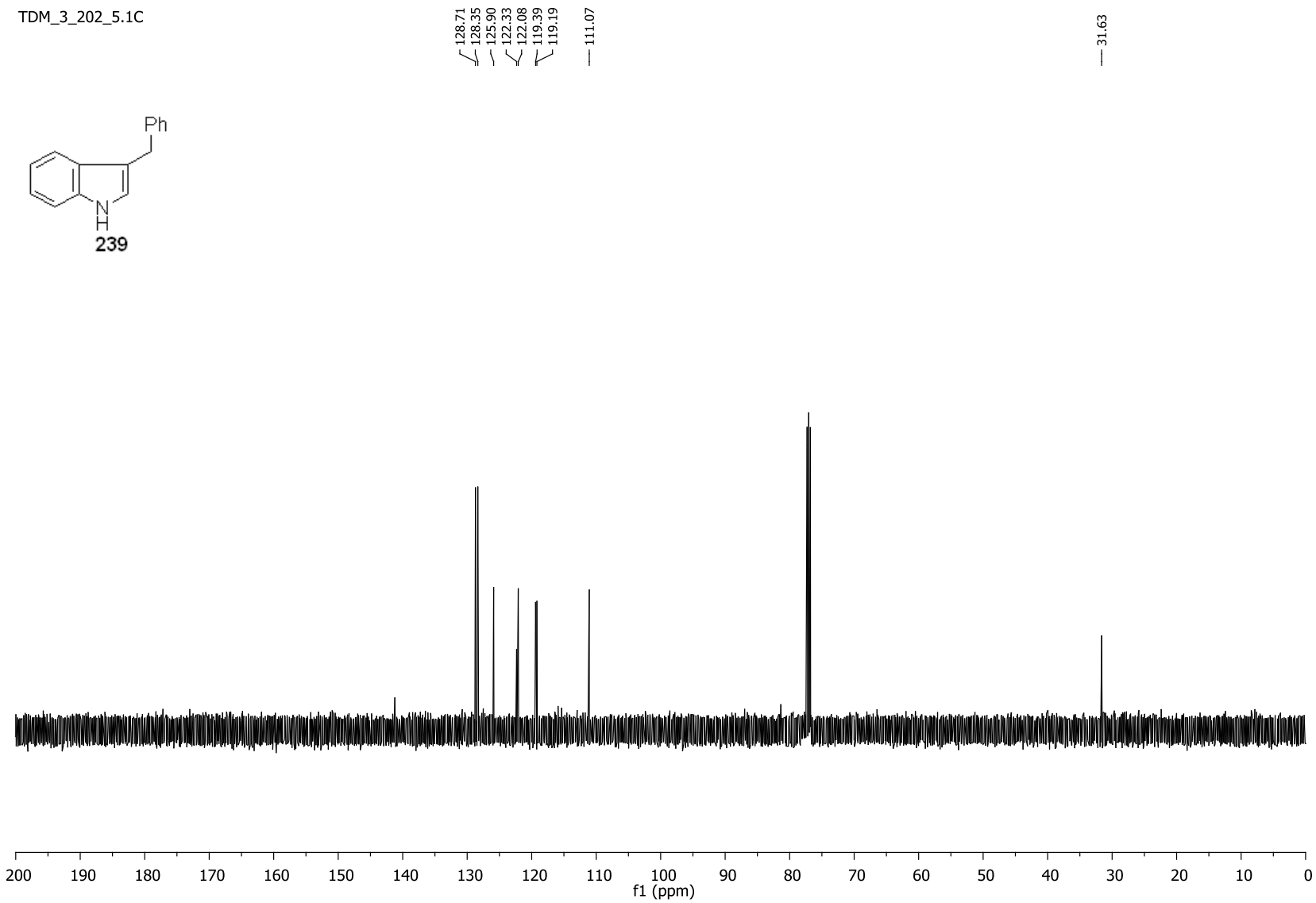


Figure 62. ^{13}C NMR Spectrum for **239** (125 MHz, $CDCl_3$)

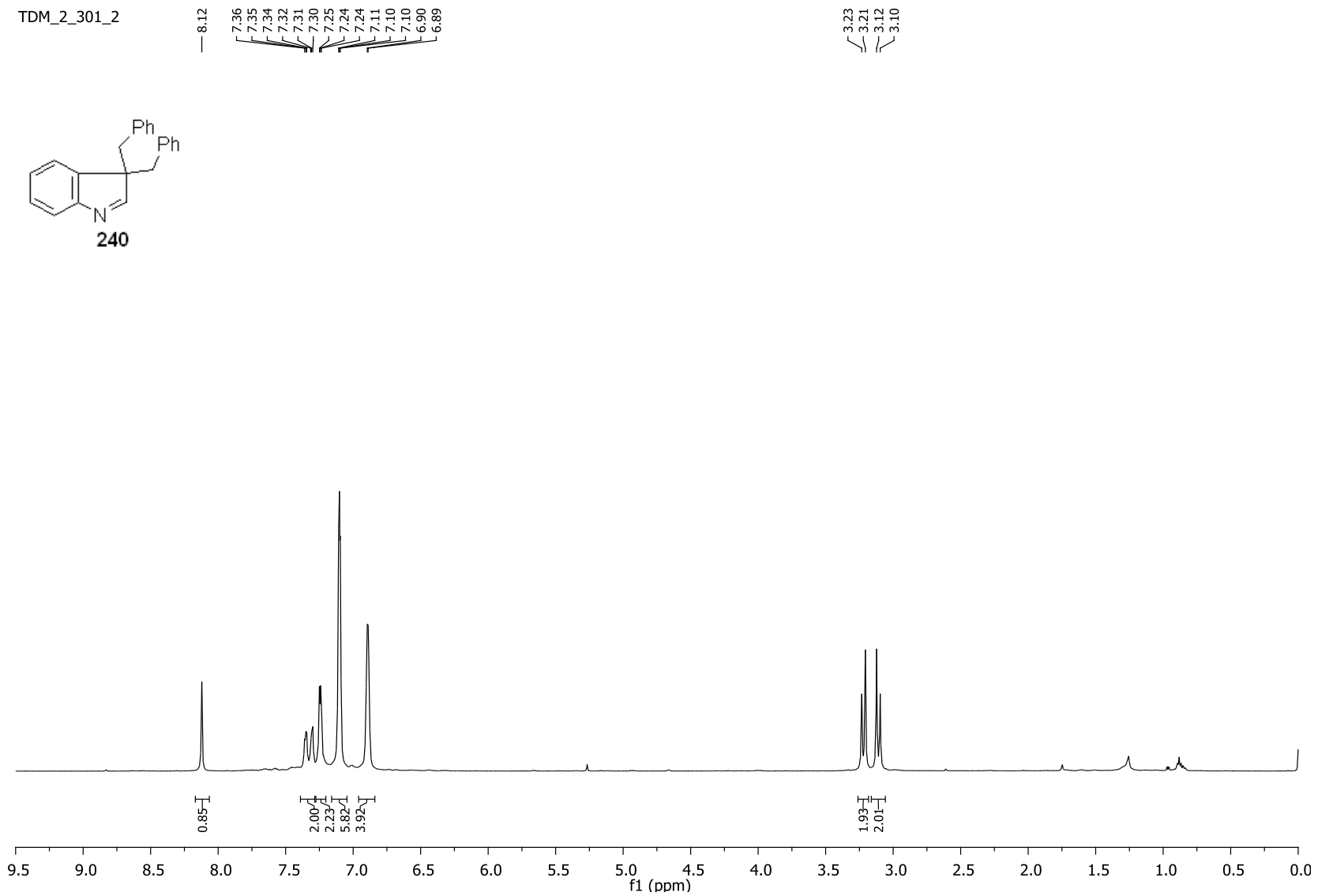


Figure 63. ^{1}H NMR Spectrum for **240** (500 MHz, $CDCl_3$)

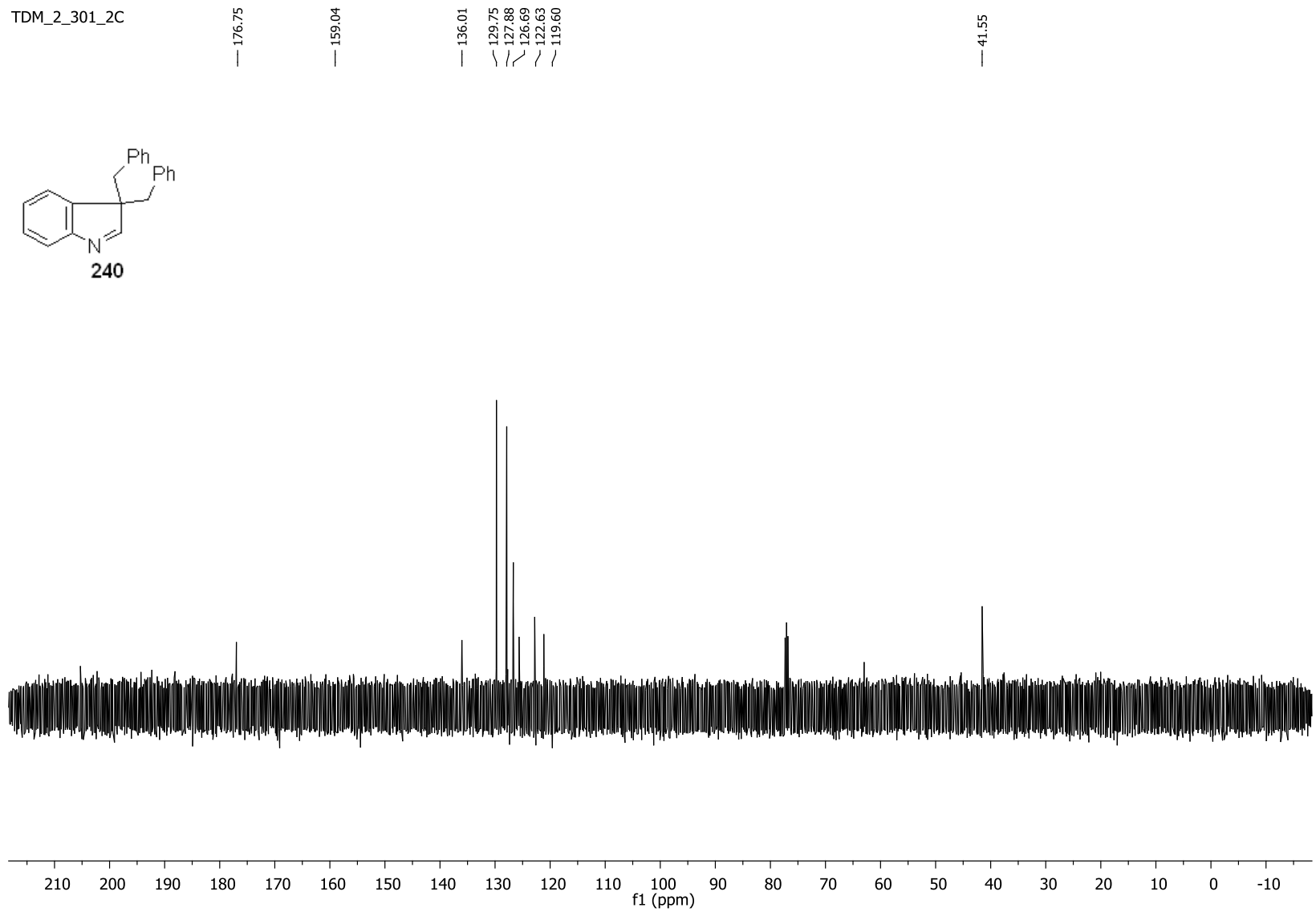


Figure 64. ^{13}C NMR Spectrum for **240** (125 MHz, $CDCl_3$)

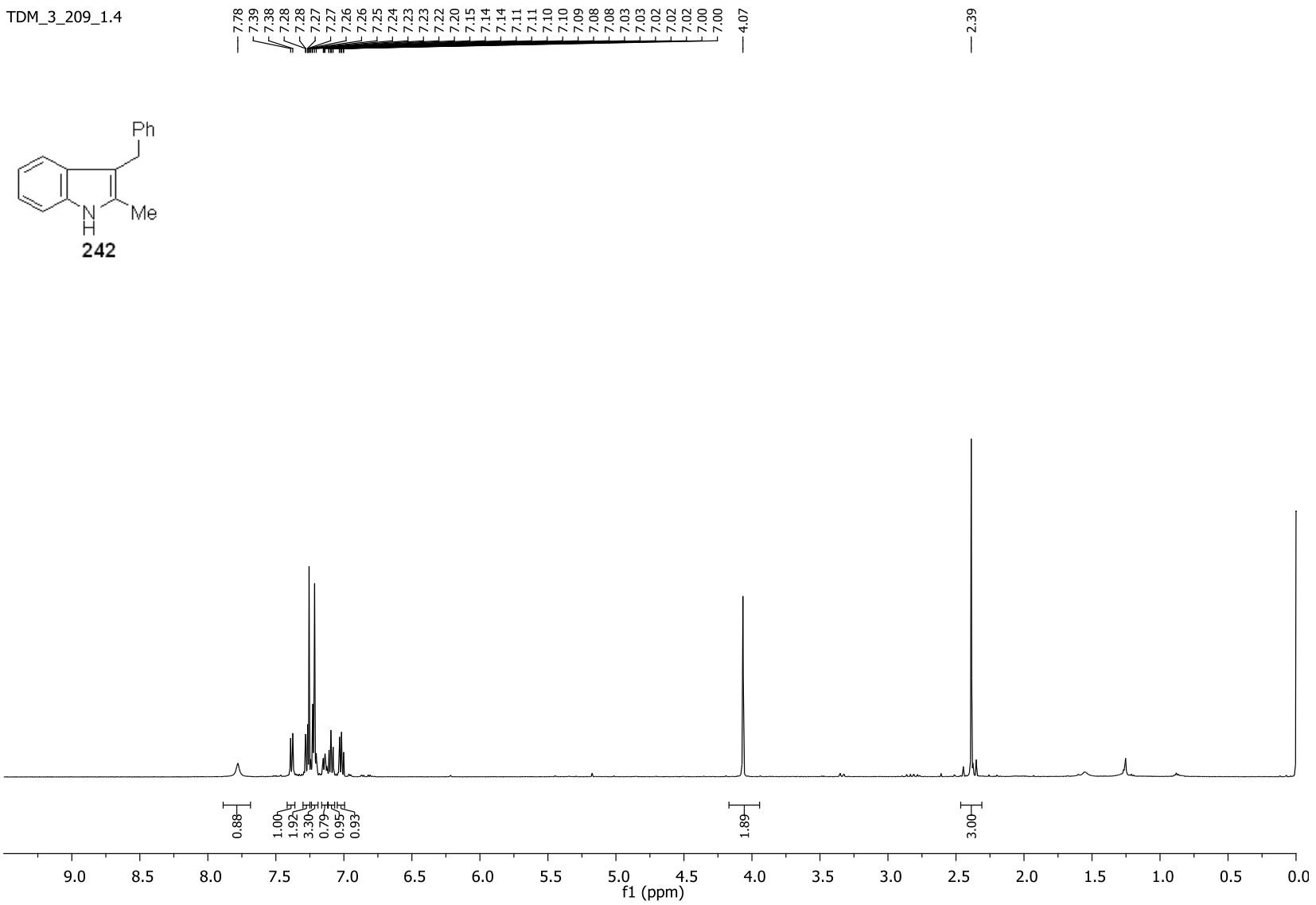


Figure 65. ^{1}H NMR Spectrum for **242** (500 MHz, $CDCl_3$)

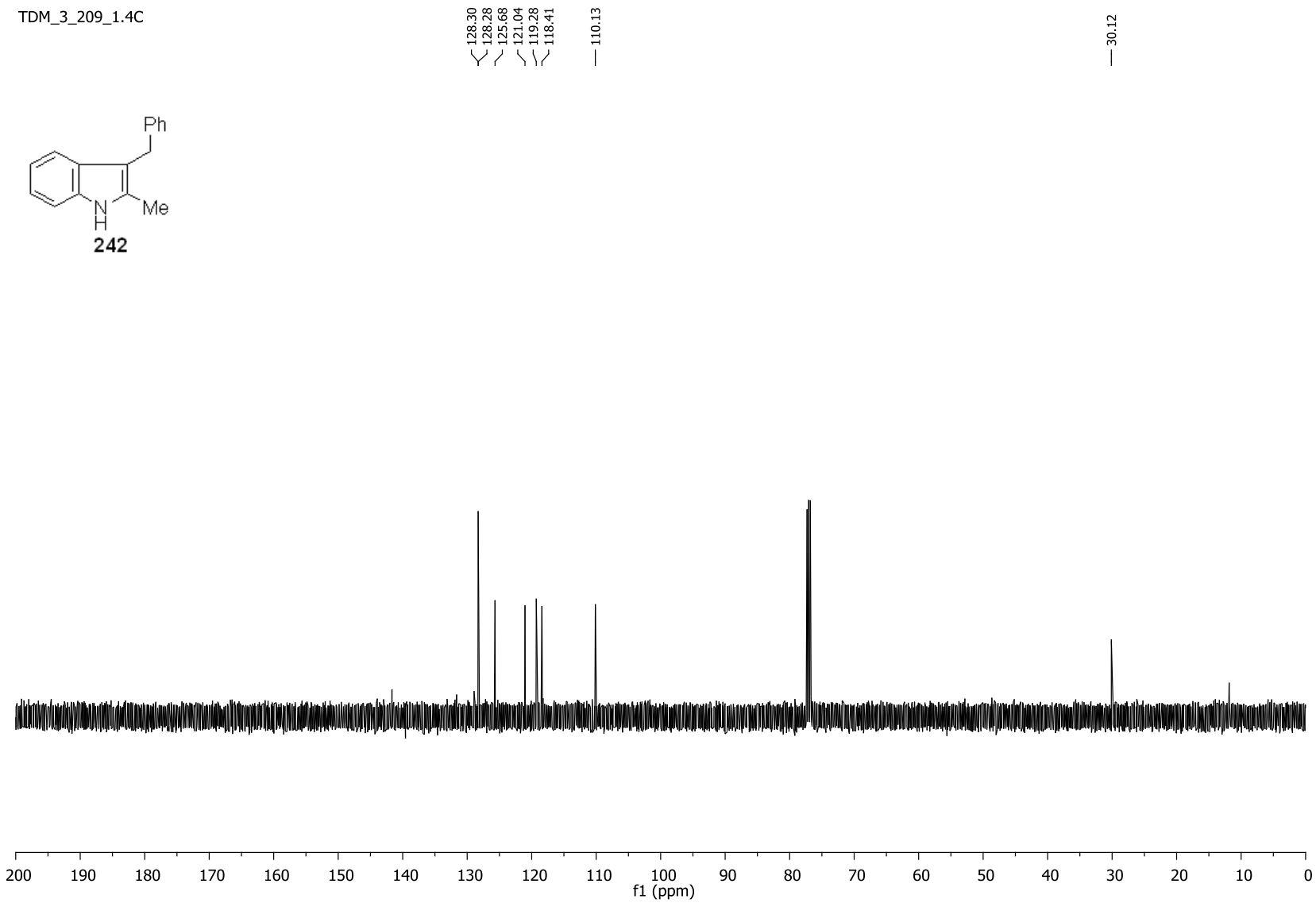


Figure 66. ^{13}C NMR Spectrum for **242** (125 MHz, $CDCl_3$)

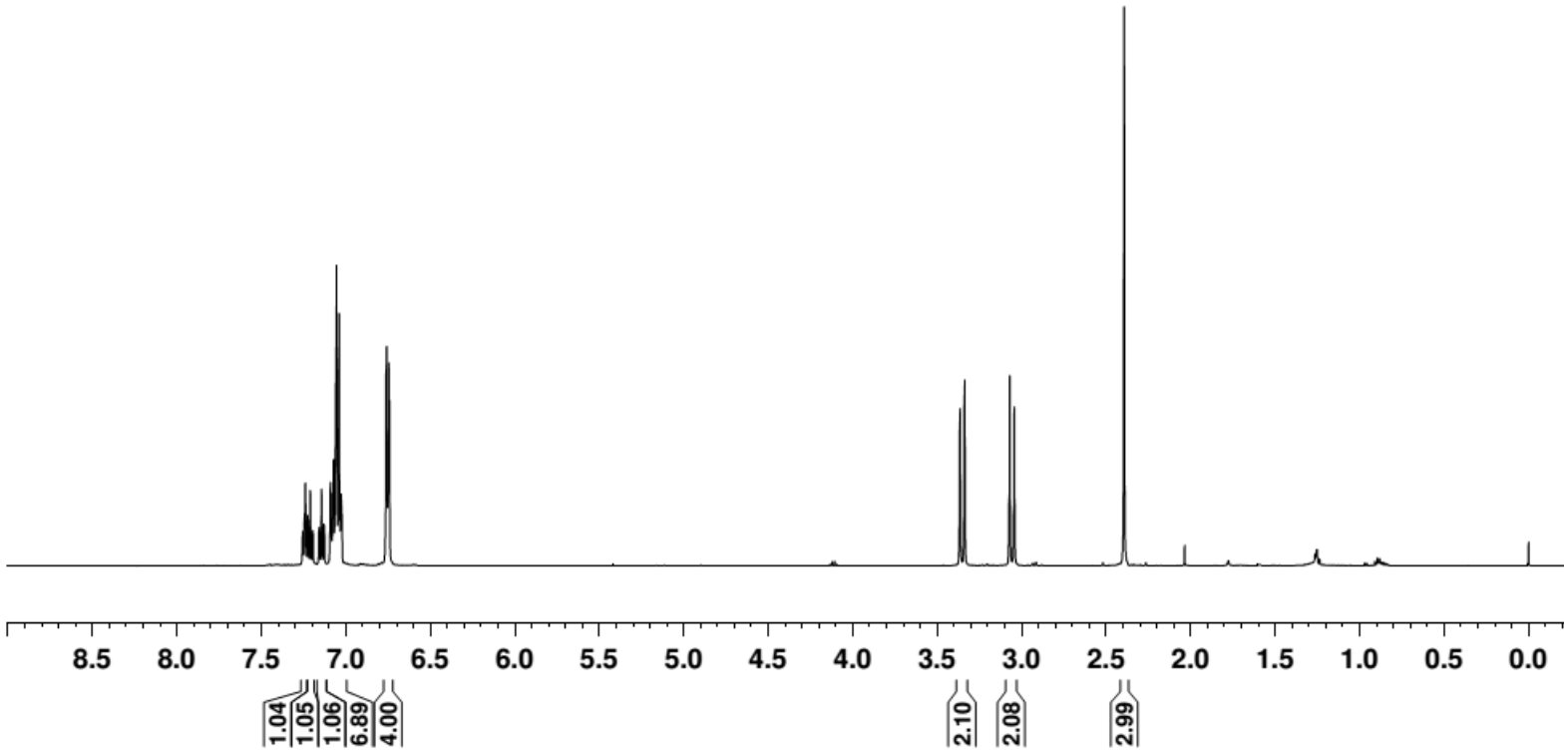


Figure 67. ^{1}H NMR Spectrum for **243** (500 MHz, $CDCl_3$)

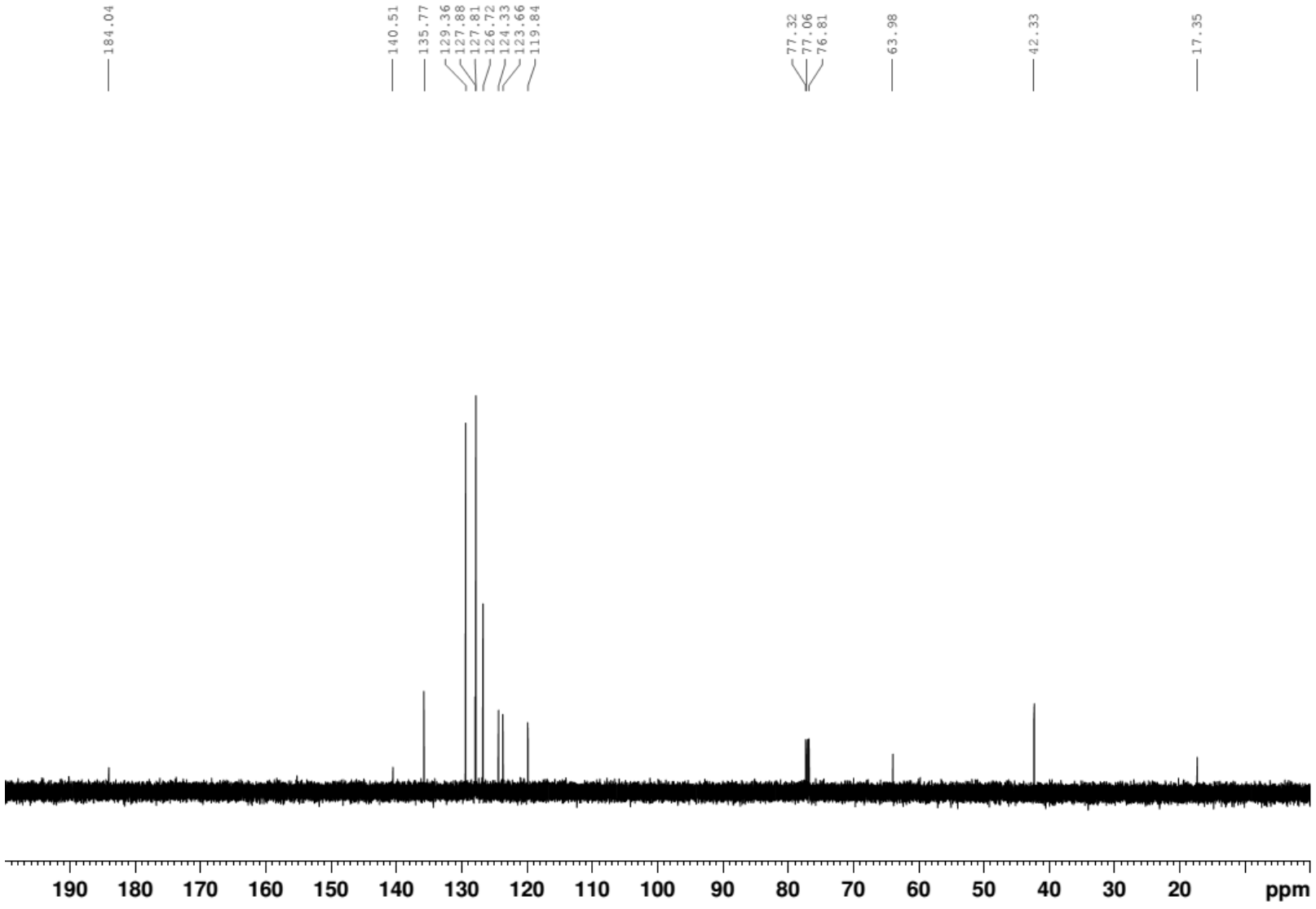


Figure 68. ^{13}C NMR Spectrum for **243** (125 MHz, $CDCl_3$)

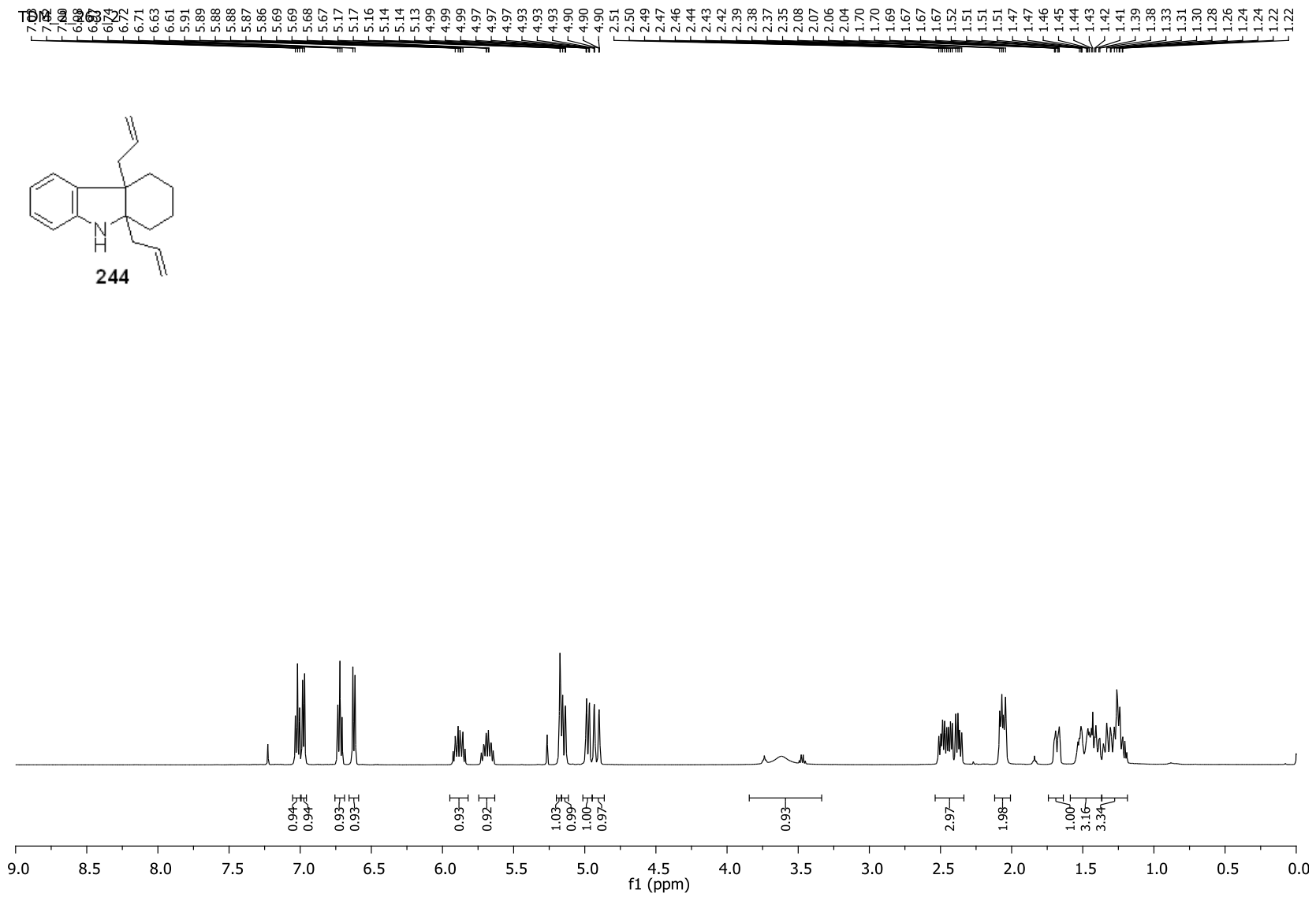


Figure 69. ^{1}H NMR Spectrum for **244** (500 MHz, $CDCl_3$)

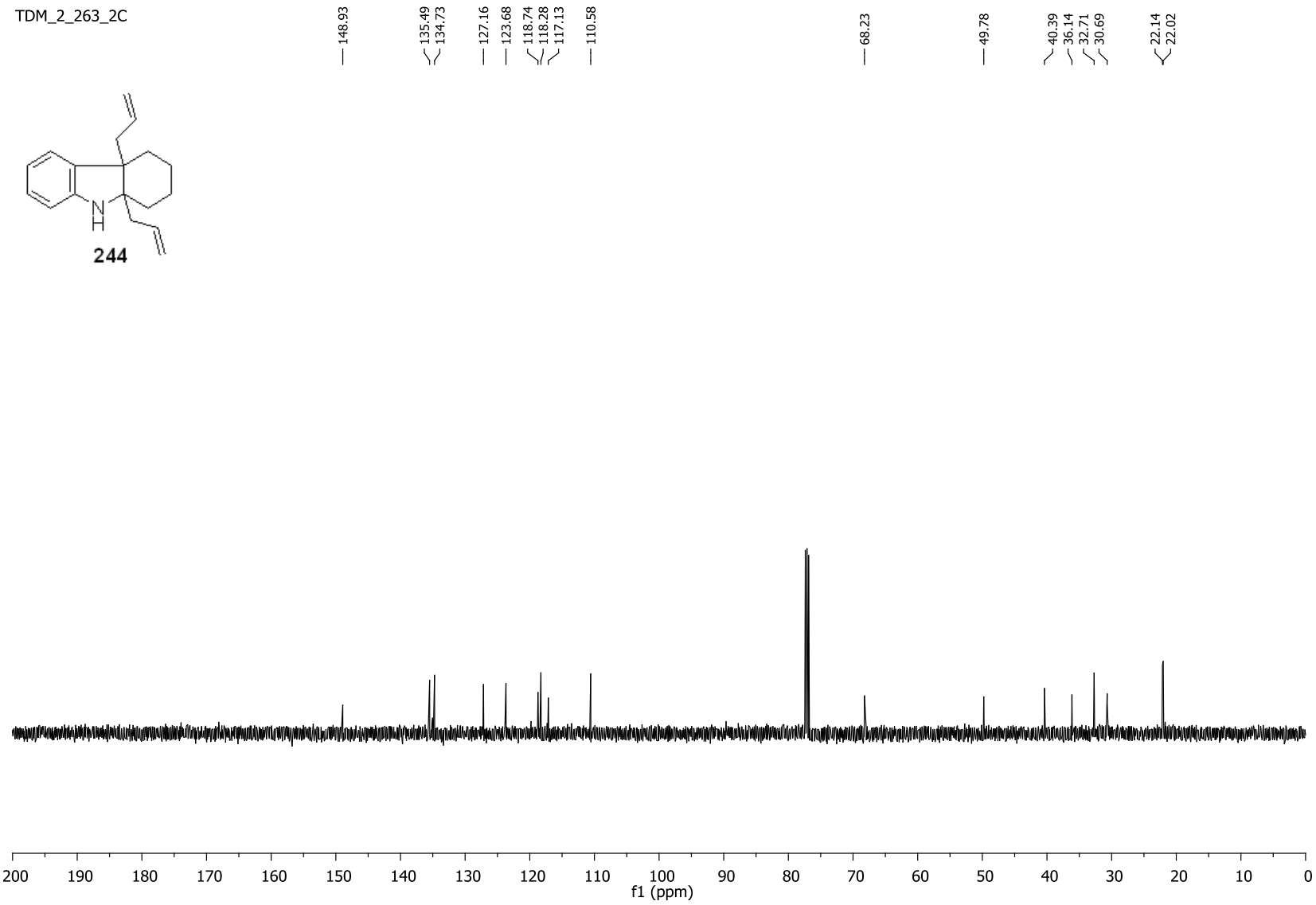


Figure 70. ^{13}C NMR Spectrum for **244** (125 MHz, $CDCl_3$)

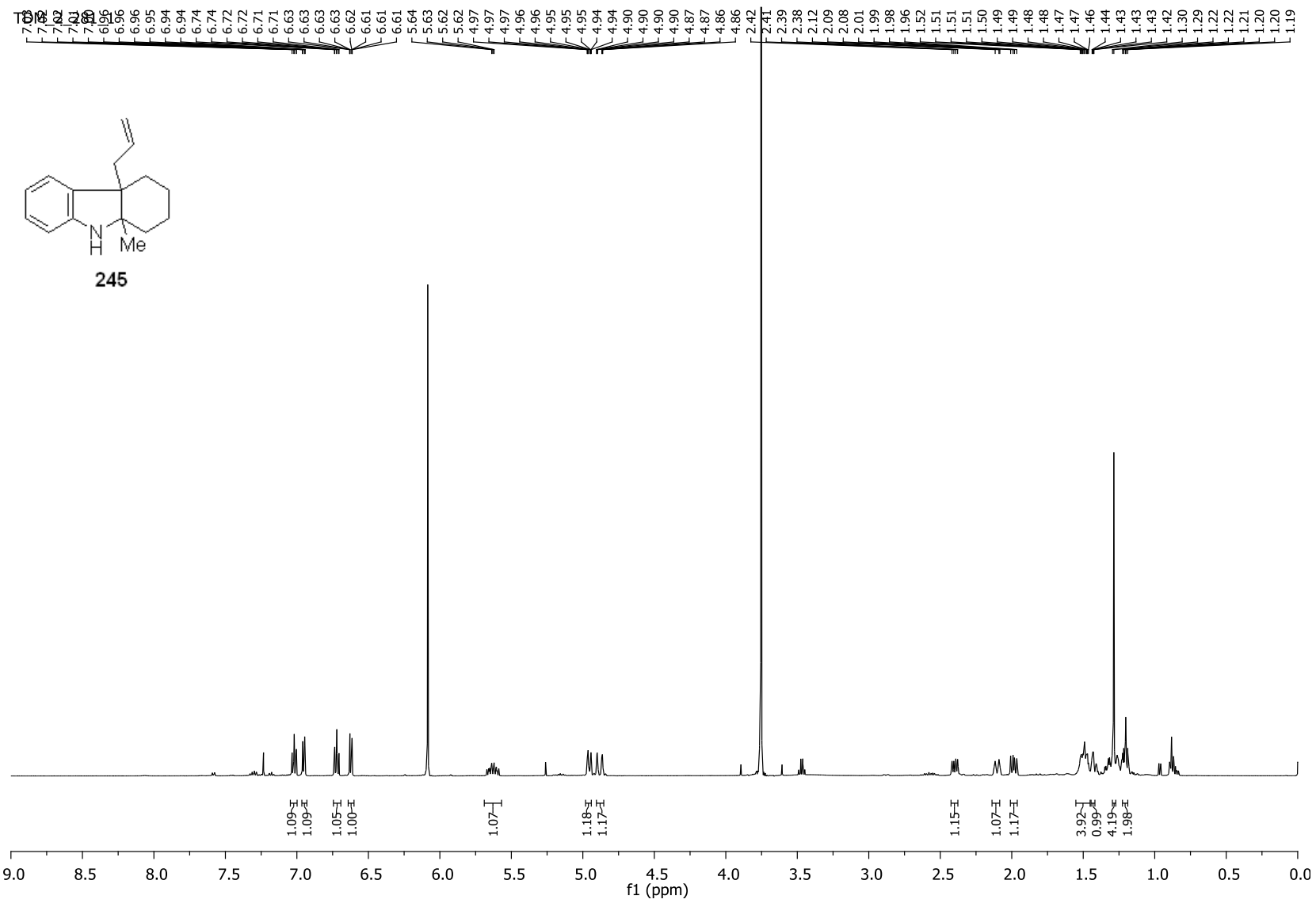


Figure 71. ^{1}H NMR Spectrum for **245** (500 MHz, $CDCl_3$)

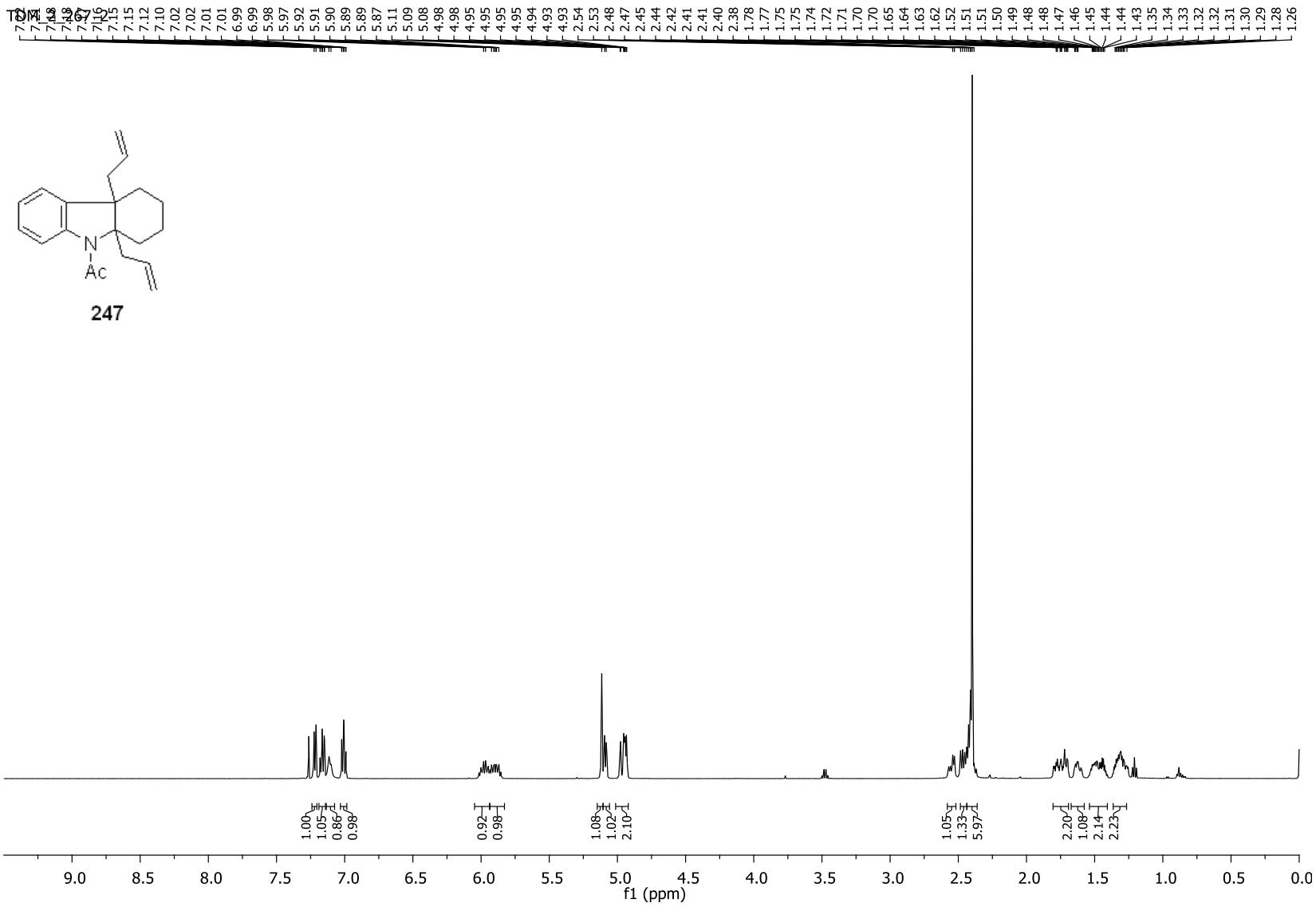


Figure 72. ^{1}H NMR Spectrum for **247** (500 MHz, $CDCl_3$)

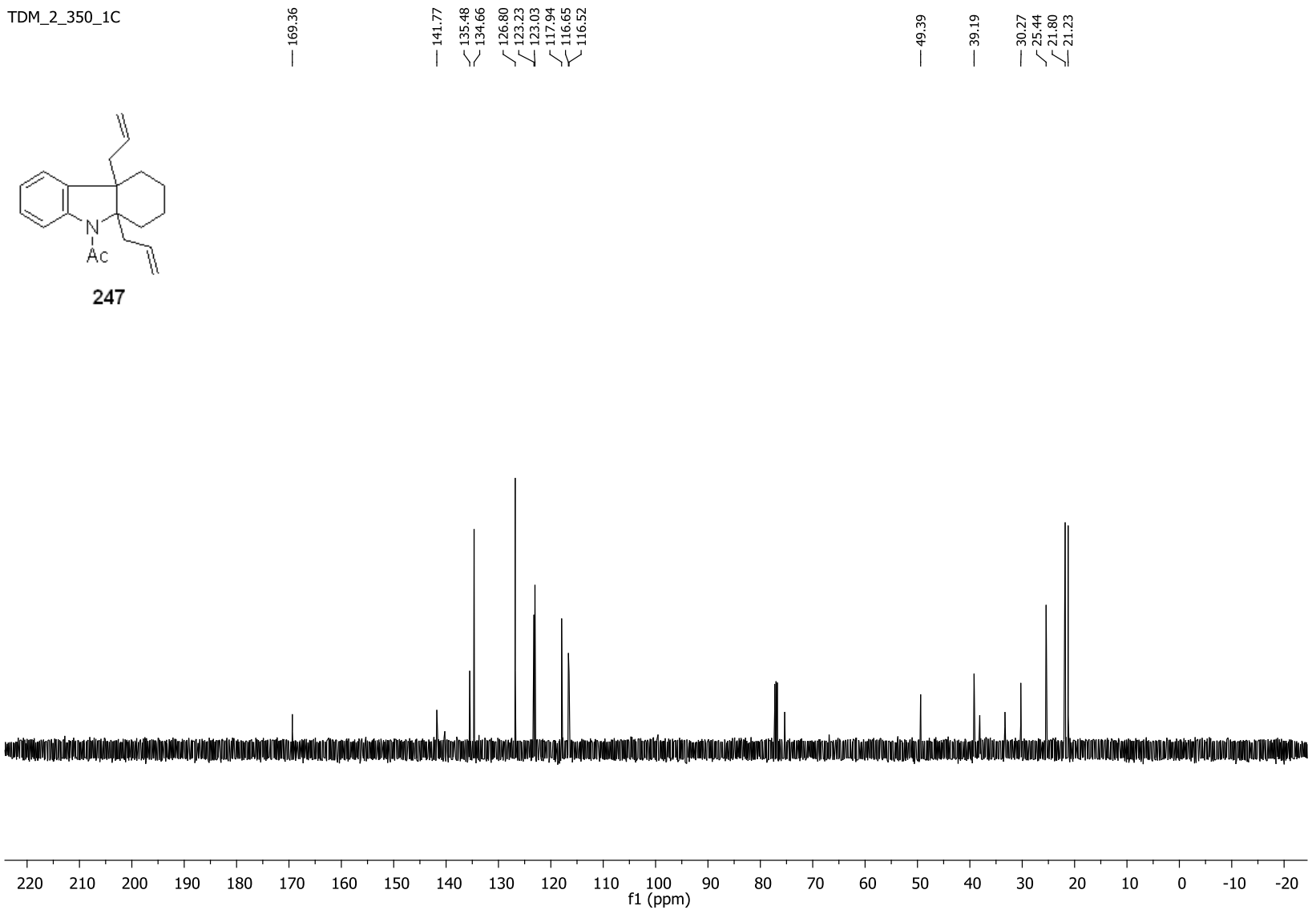


Figure 73. ^{13}C NMR Spectrum for **244** (125 MHz, $CDCl_3$)

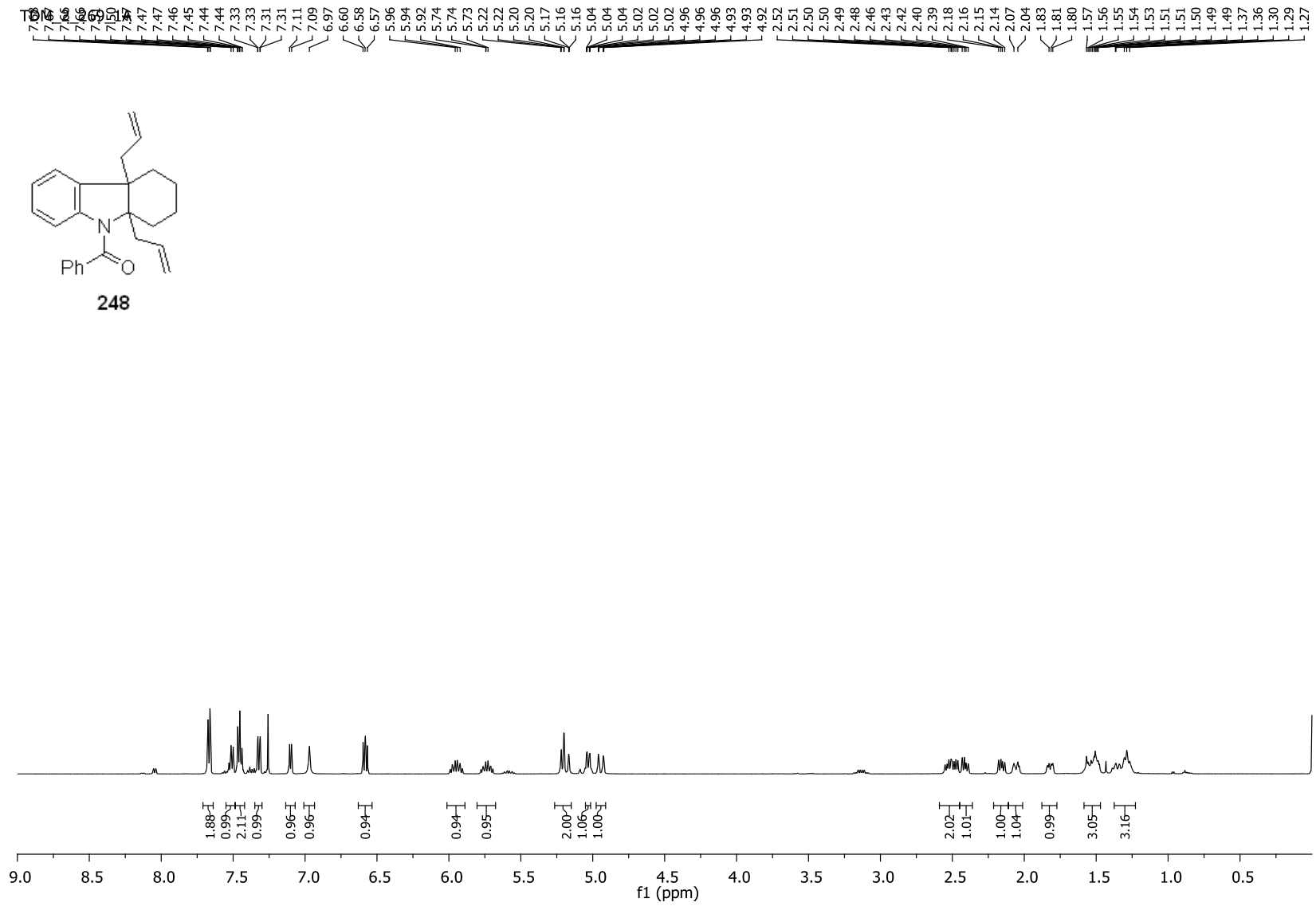


Figure 74. ^{1}H NMR Spectrum for **248** (500 MHz, $CDCl_3$)

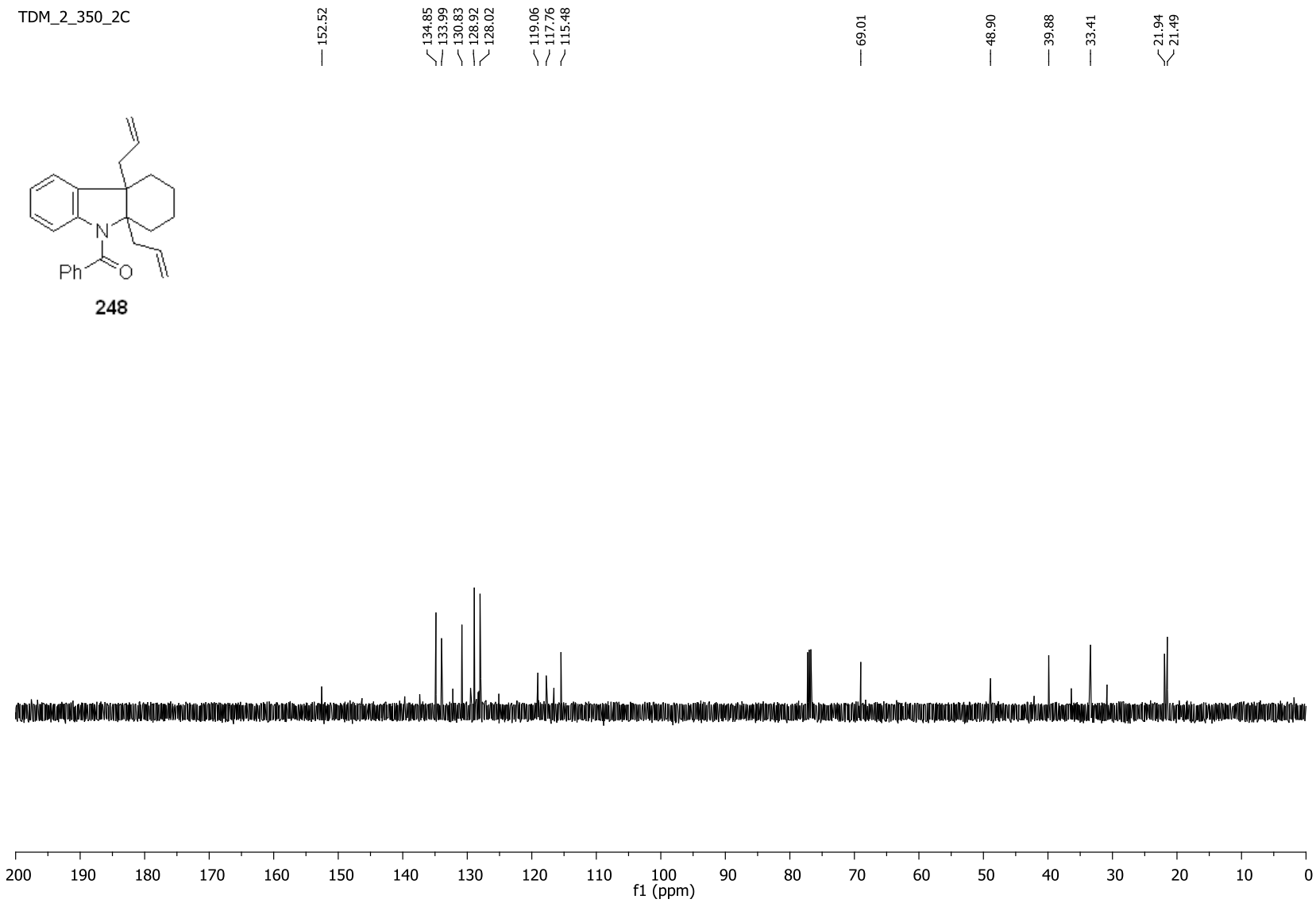


Figure 75. ^{13}C NMR Spectrum for **244** (125 MHz, $CDCl_3$)

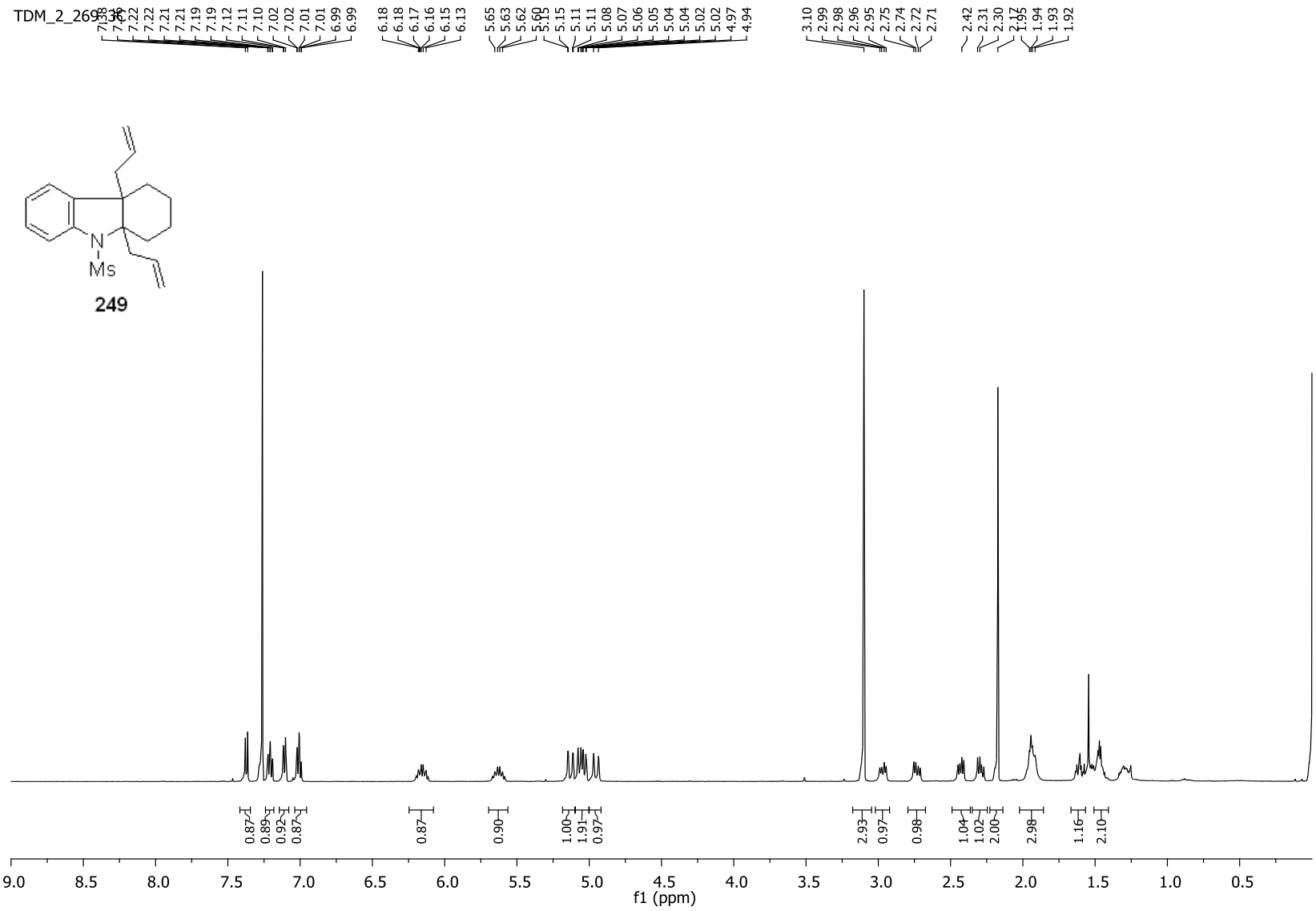


Figure 76. ^{1}H NMR Spectrum for **249** (500 MHz, $CDCl_3$)

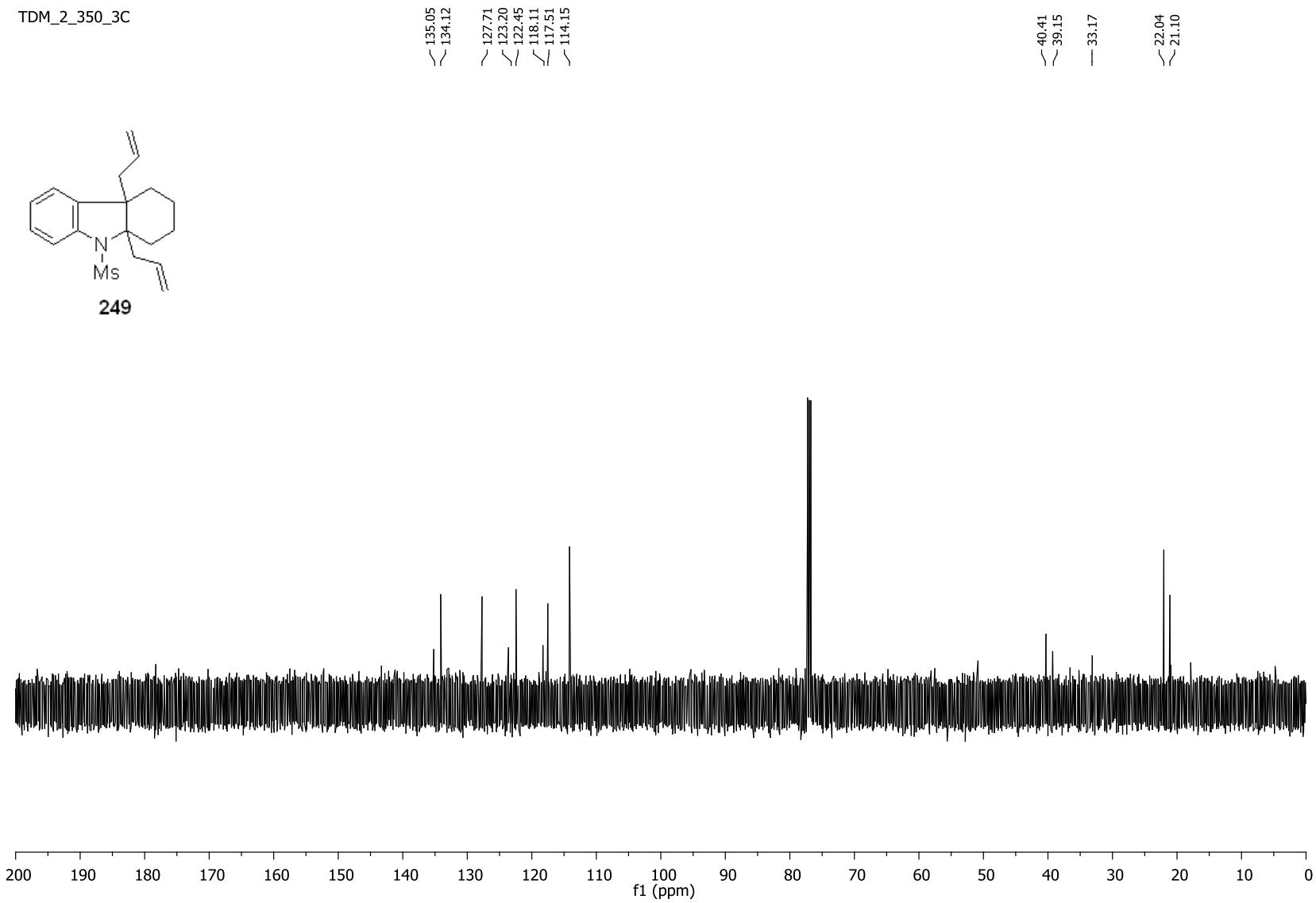


Figure 77. ^{13}C NMR Spectrum for **244** (125 MHz, $CDCl_3$)

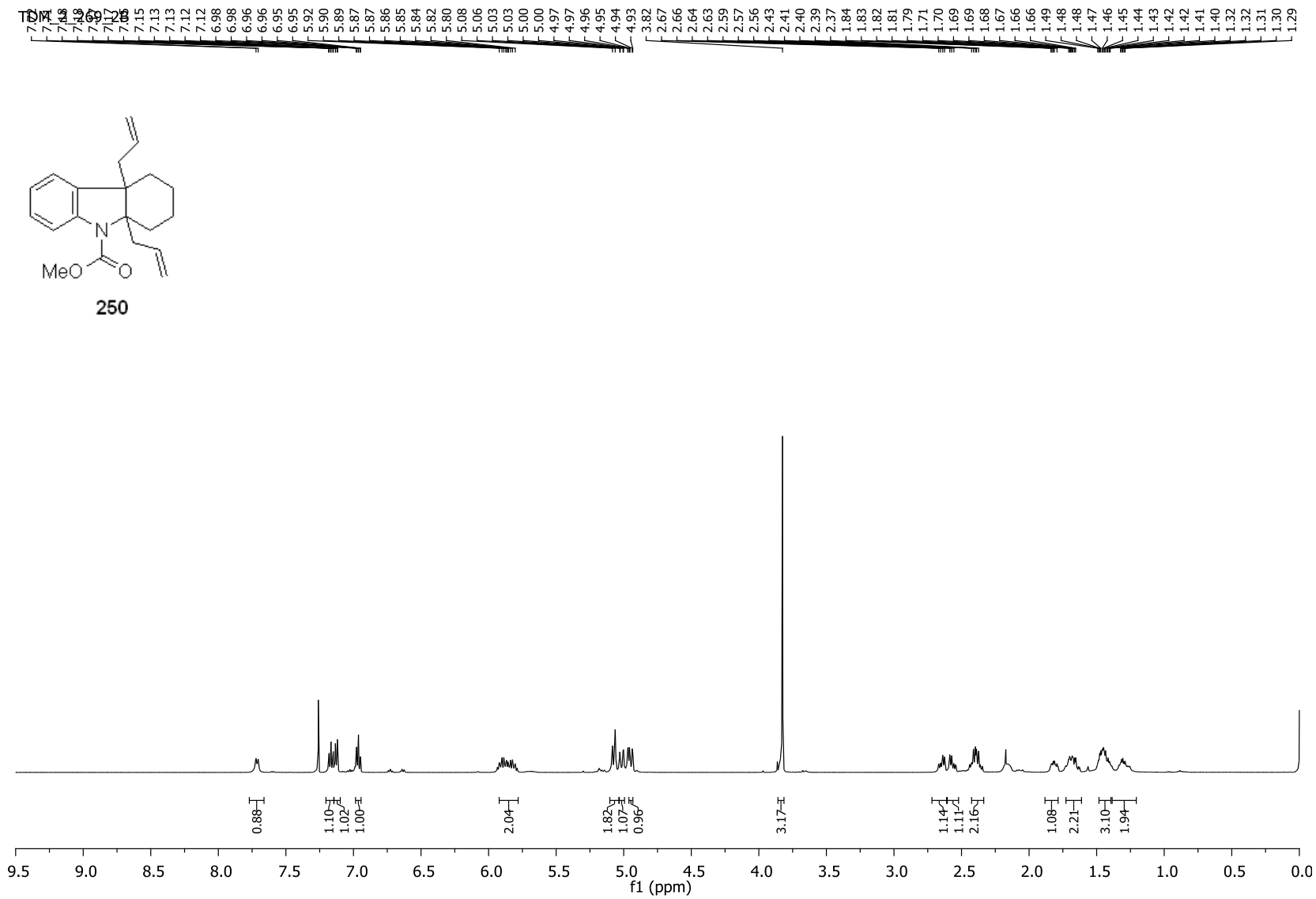


Figure 78. ^{1}H NMR Spectrum for **250** (500 MHz, $CDCl_3$)

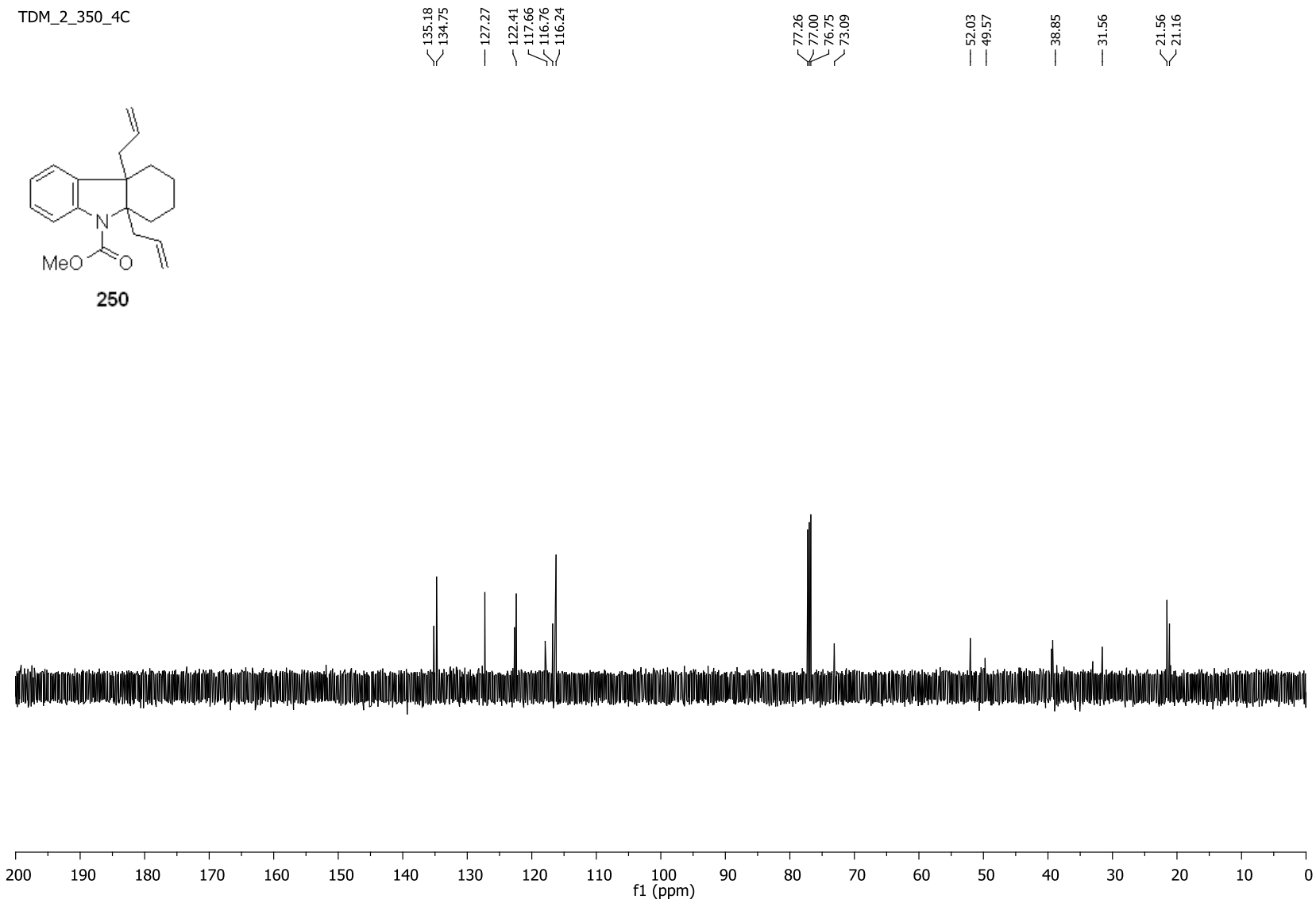


Figure 79. ^{13}C NMR Spectrum for **244** (125 MHz, $CDCl_3$)

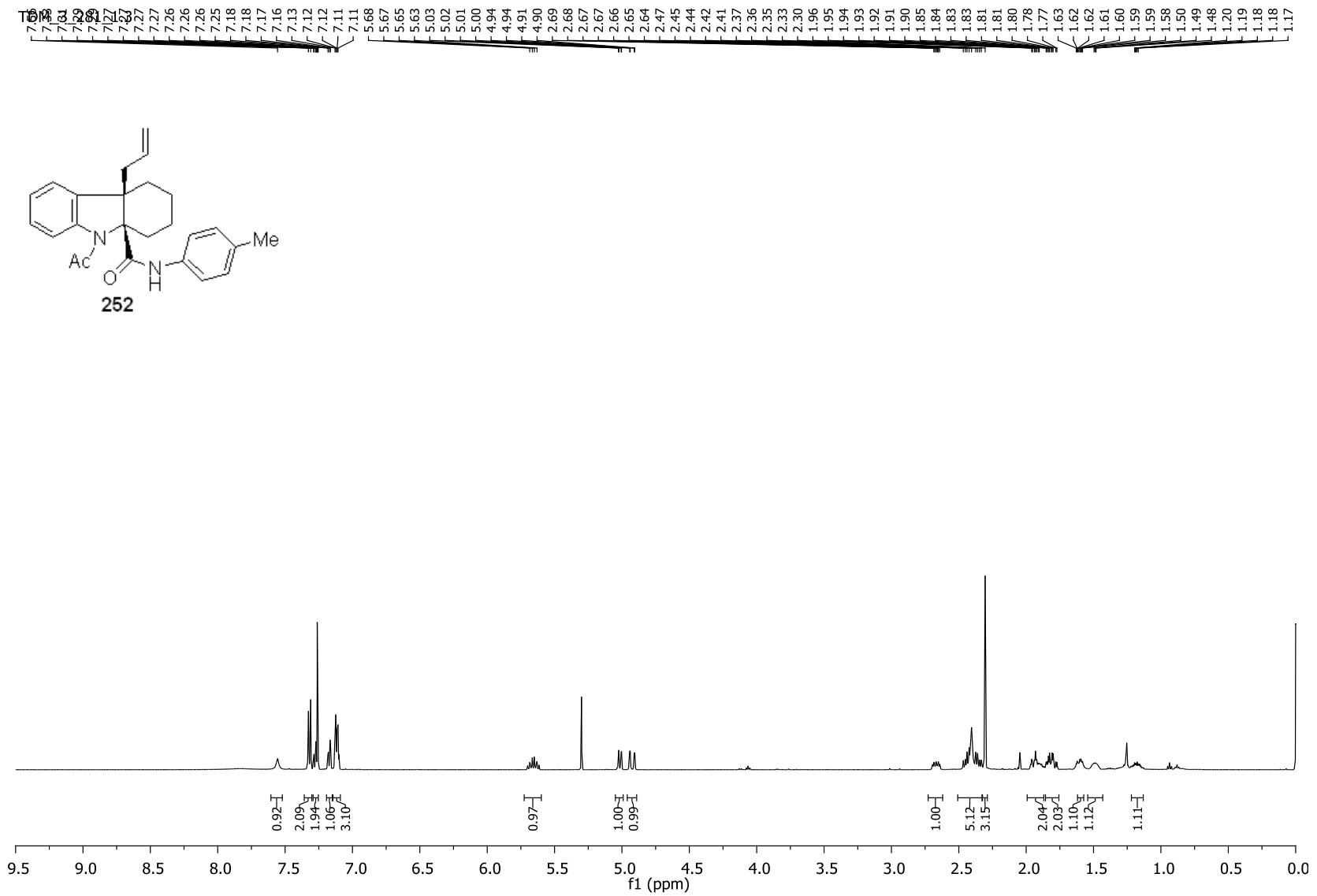


Figure 80. ^{1}H NMR Spectrum for **252** (500 MHz, $CDCl_3$)

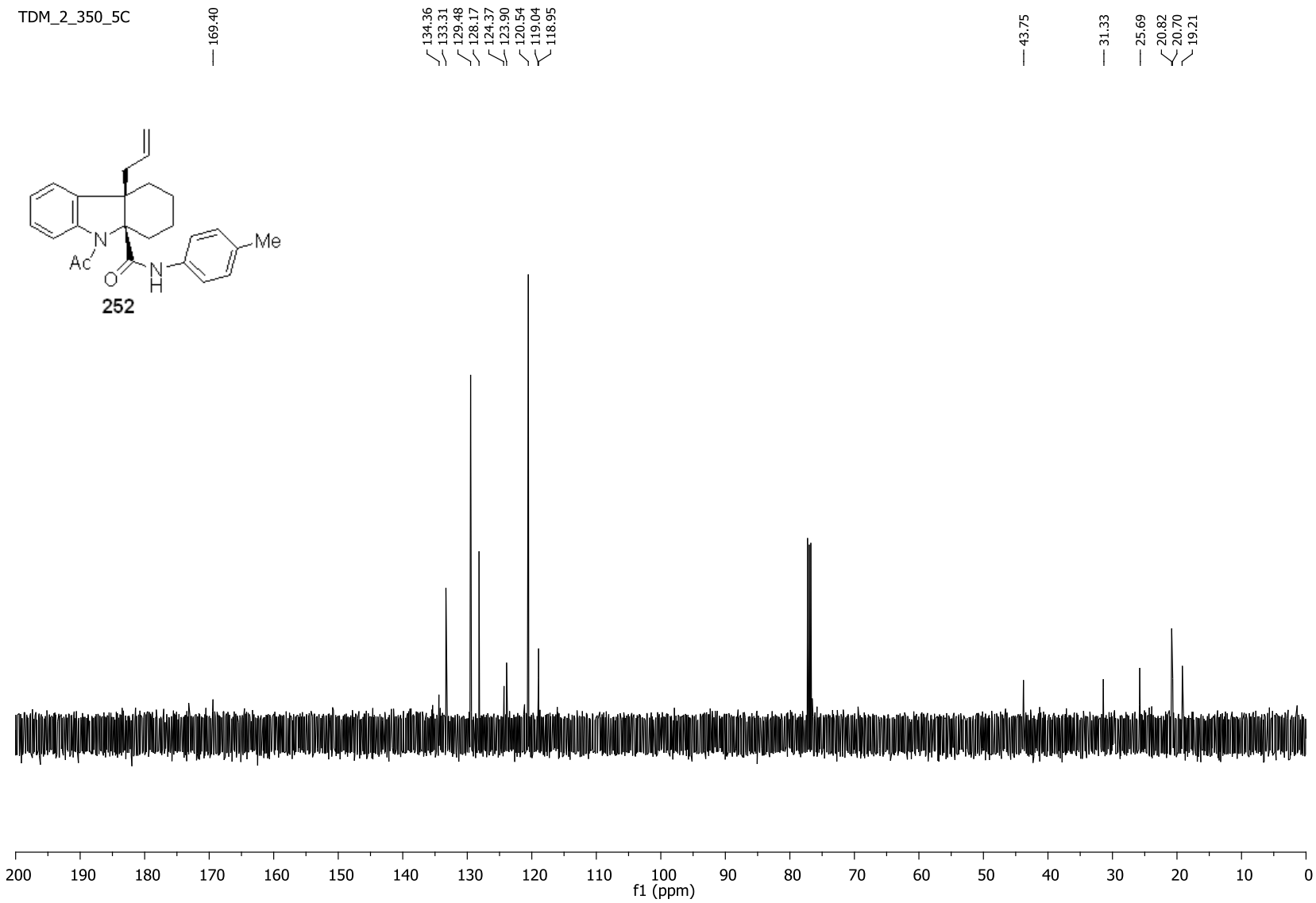


Figure 81. ^{13}C NMR Spectrum for **244** (125 MHz, $CDCl_3$)

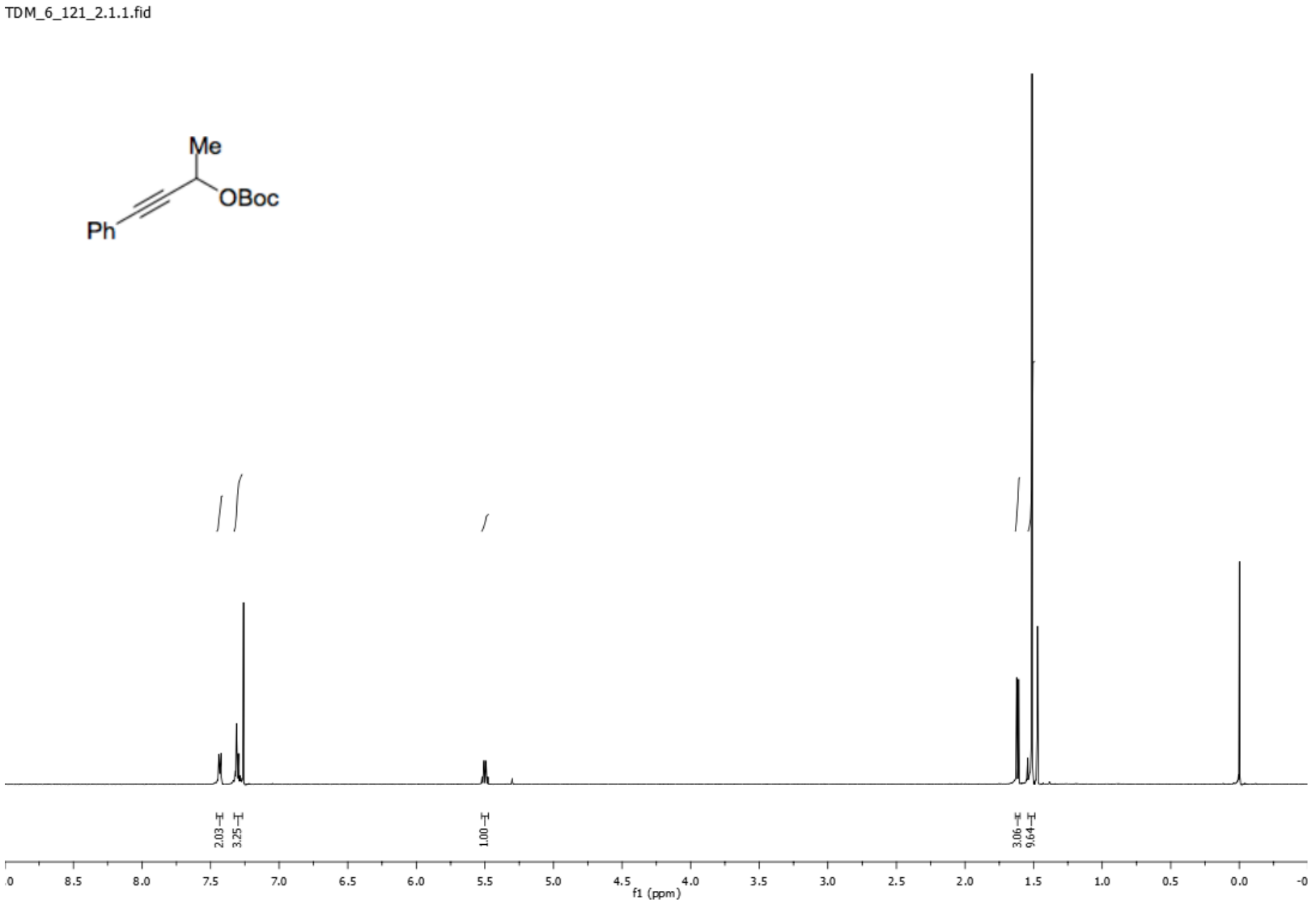


Figure 82. ^{1}H NMR Spectrum for **289** (500 MHz, $CDCl_3$)

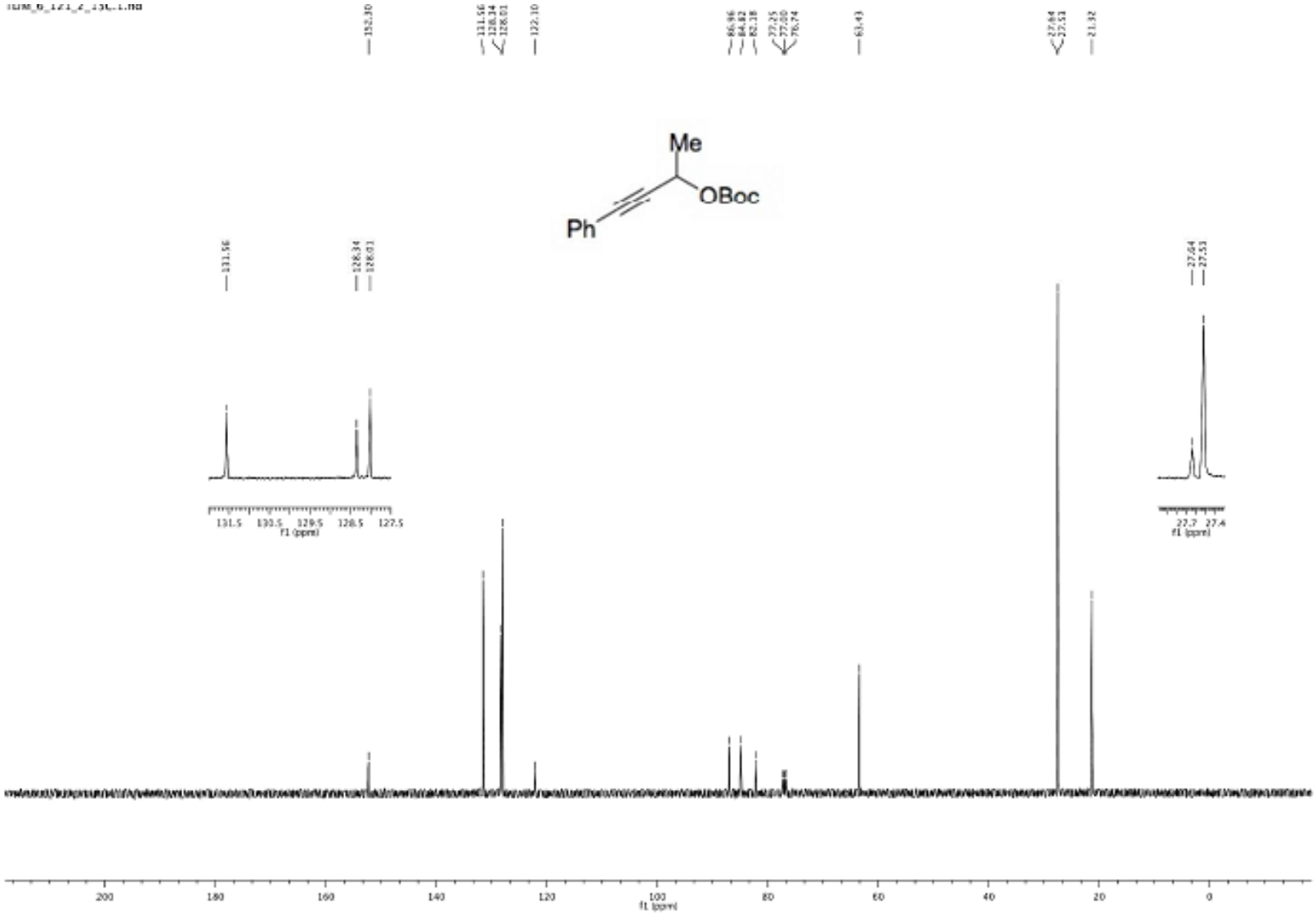


Figure 83. ^{13}C NMR Spectrum for **289** (125 MHz, $CDCl_3$)

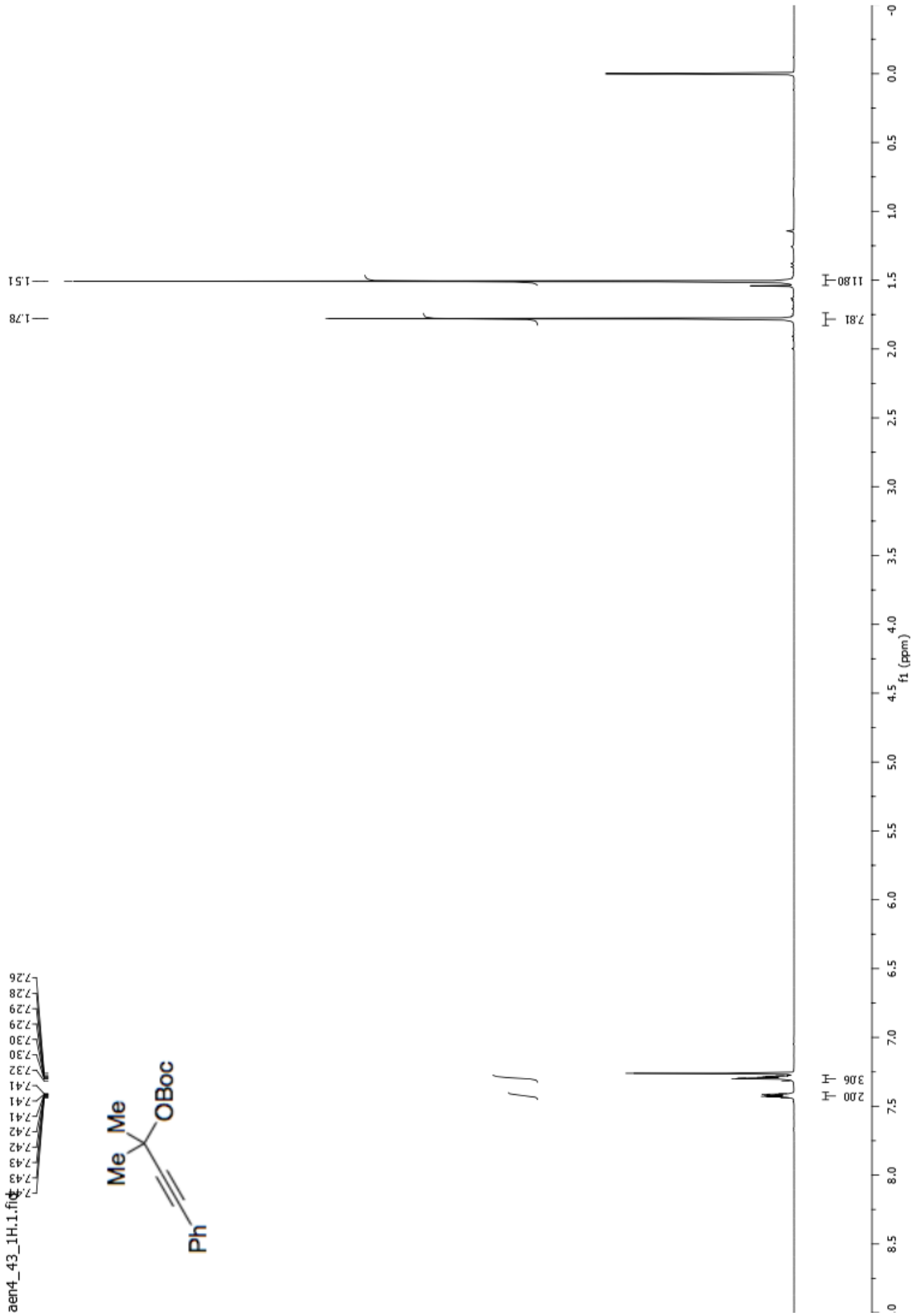


Figure 84. ^{1}H NMR Spectrum for **321** (500 MHz, $CDCl_3$)

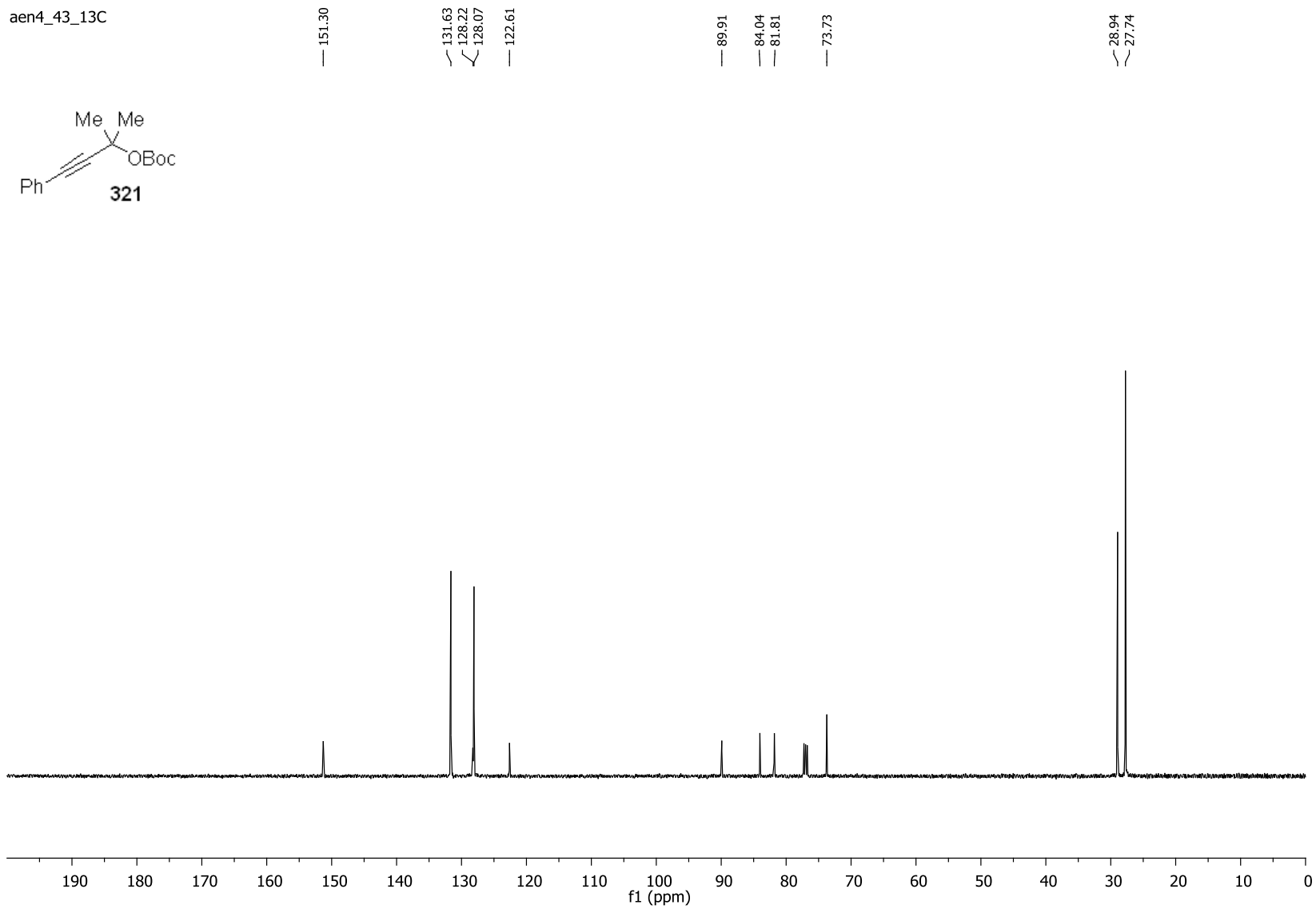


Figure 85. ^{13}C NMR Spectrum for **321** (125 MHz, $CDCl_3$)

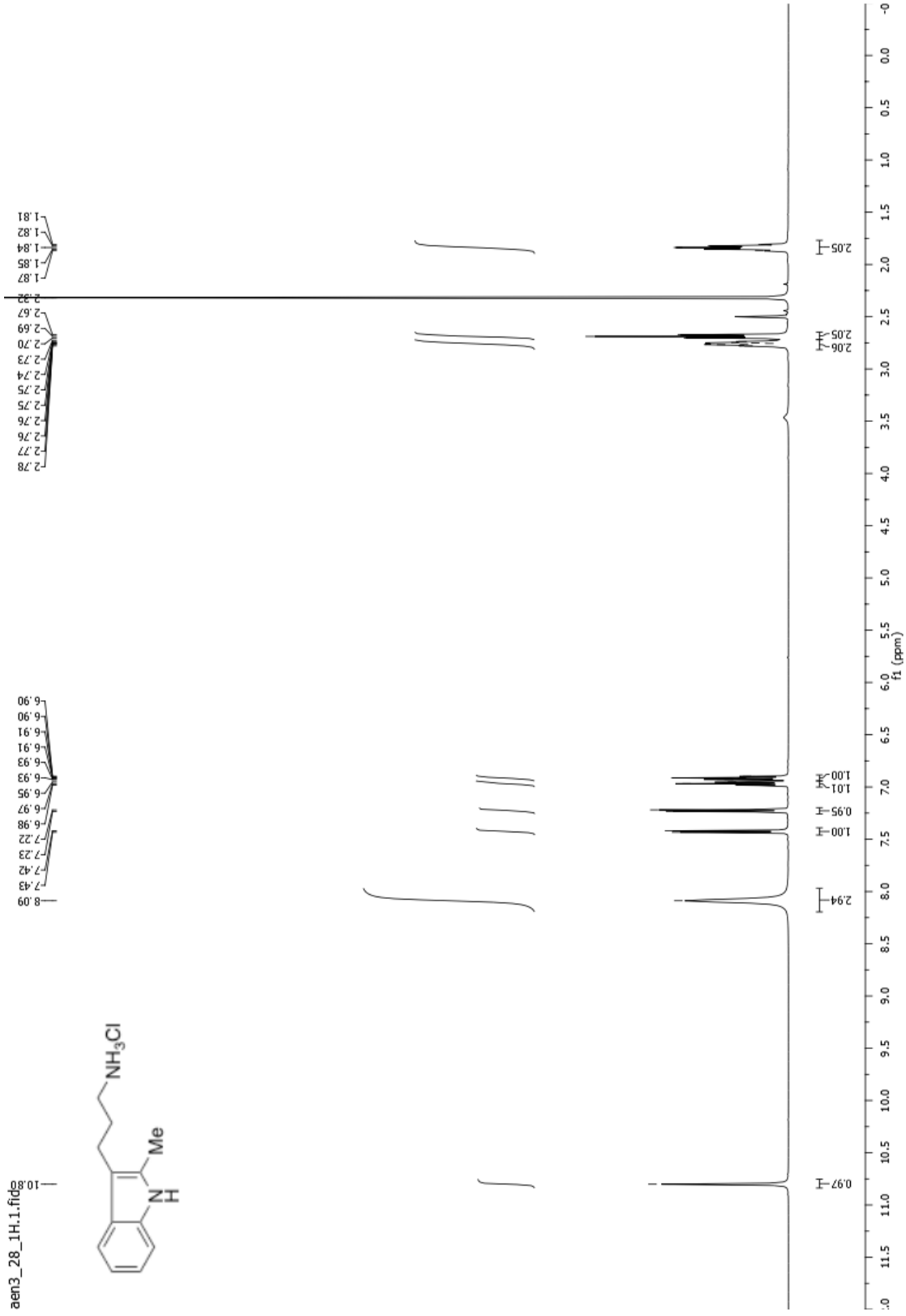


Figure 86. ^{1}H NMR Spectrum for **524** (500 MHz, $CDCl_3$)

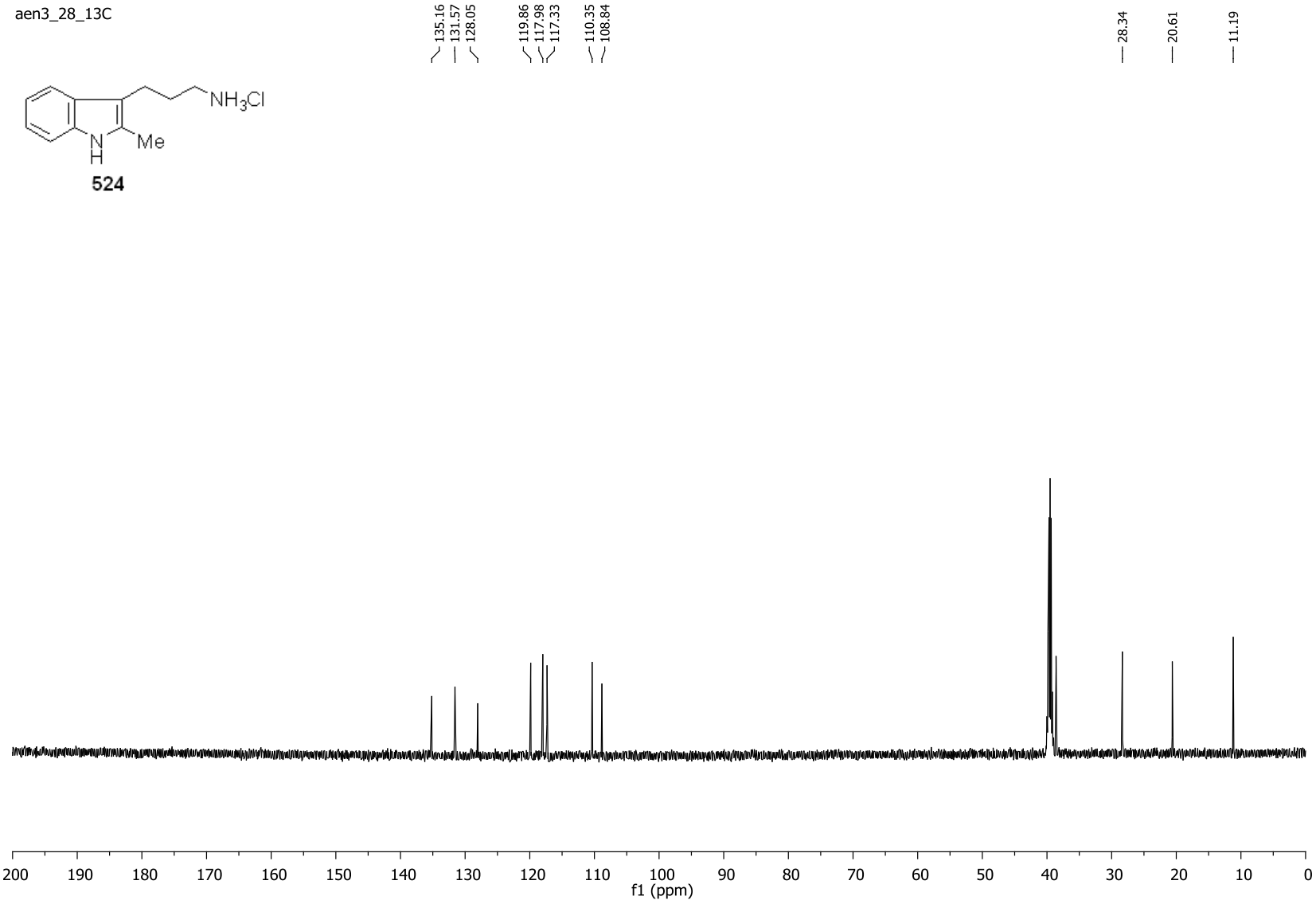


Figure 87. ^{13}C NMR Spectrum for **524** (125 MHz, $CDCl_3$)

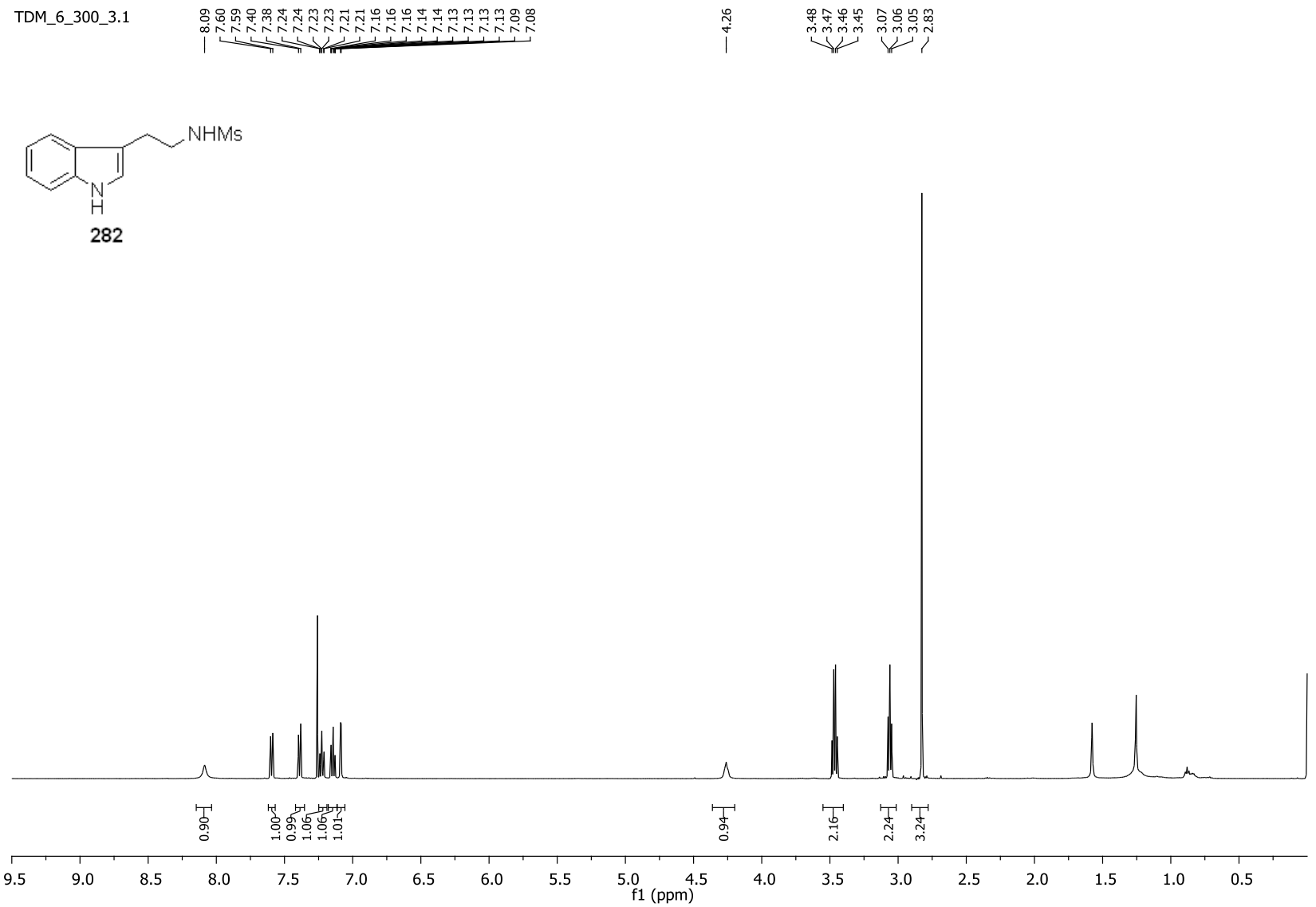


Figure 88. ^{1}H NMR Spectrum for **282** (500 MHz, $CDCl_3$)

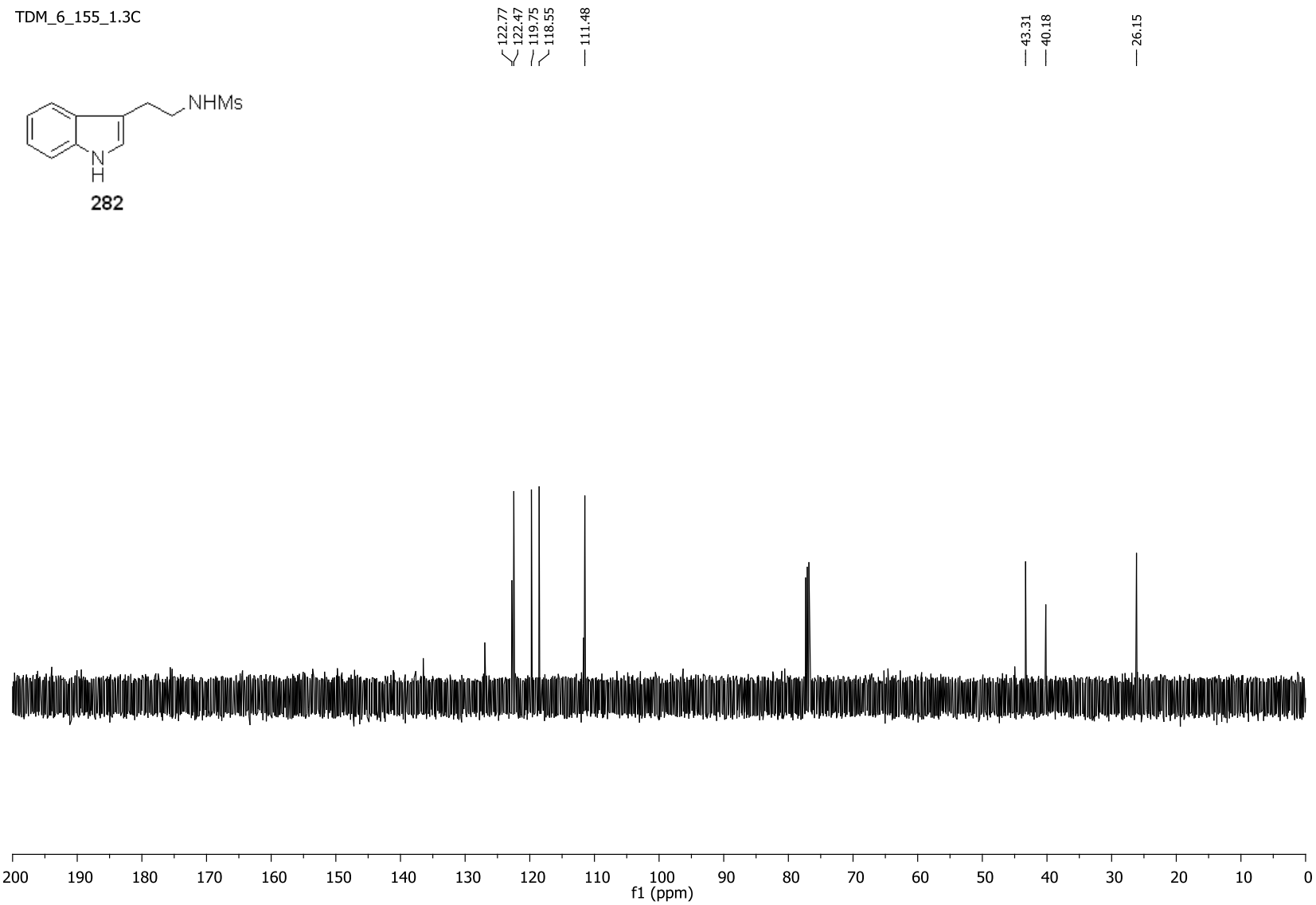


Figure 89. ^{13}C NMR Spectrum for **282** (125 MHz, $CDCl_3$)

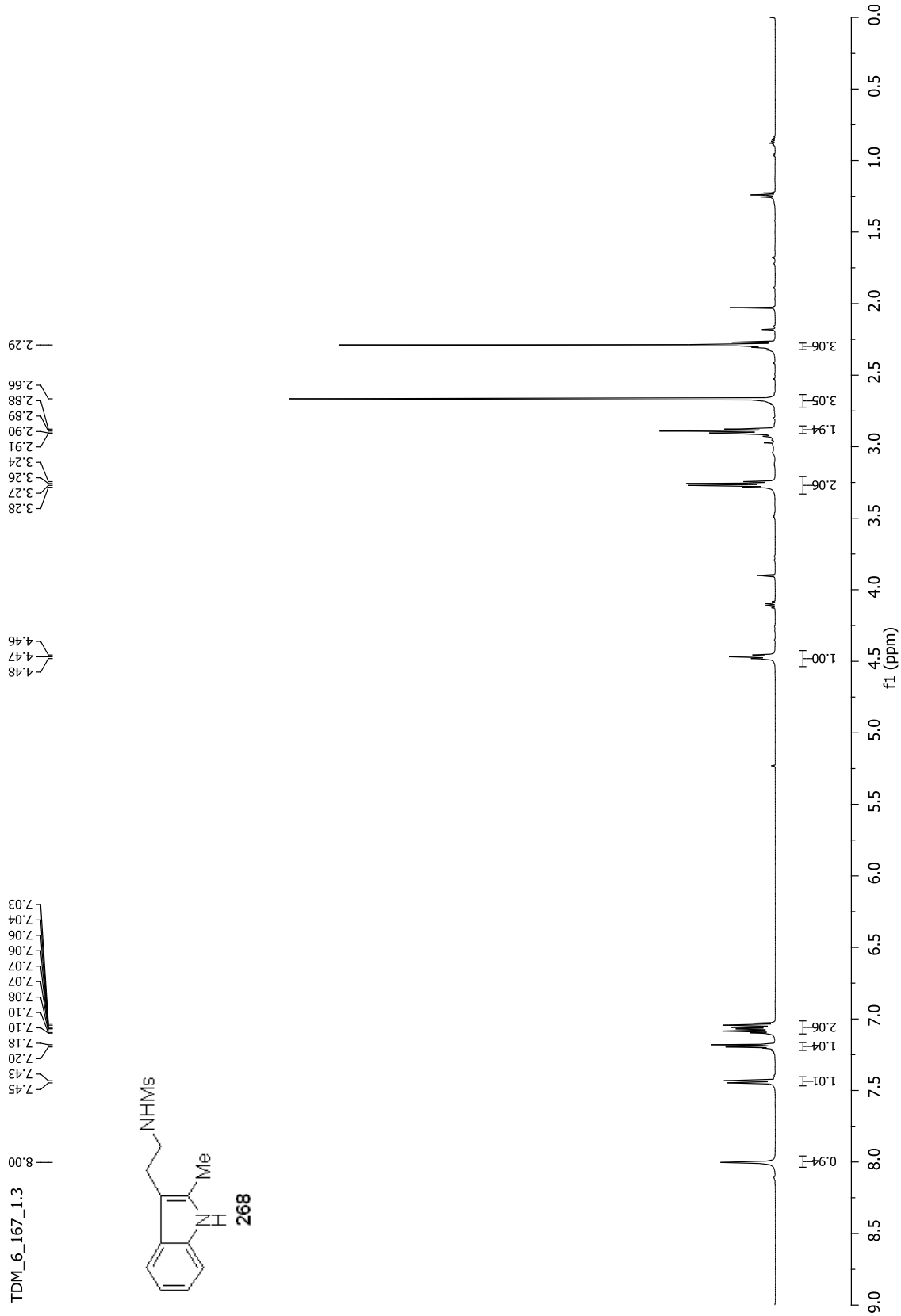


Figure 90. ^{1}H NMR Spectrum for **268** (500 MHz, $CDCl_3$)

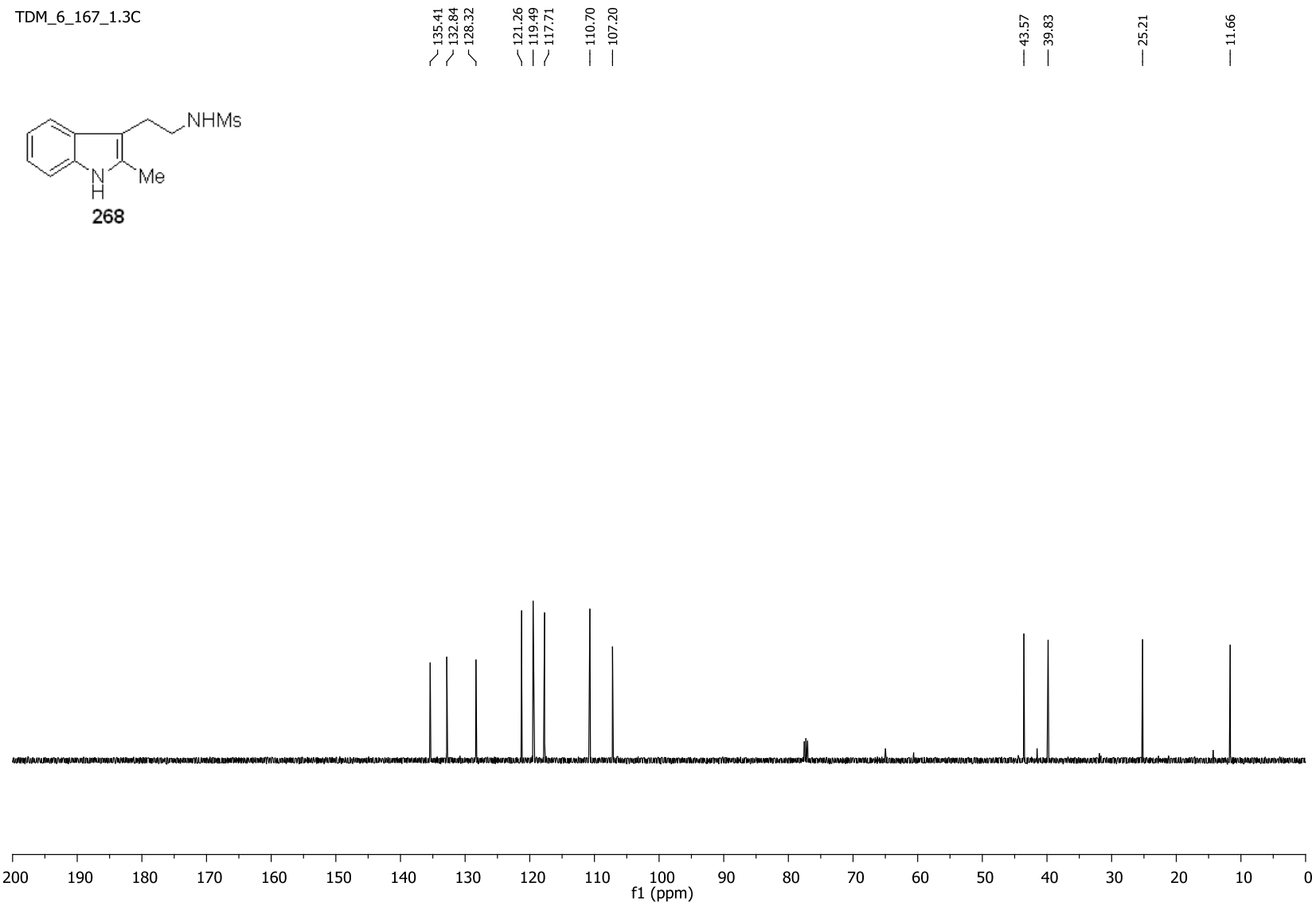


Figure 91. ^{13}C NMR Spectrum for **268** (125 MHz, $CDCl_3$)

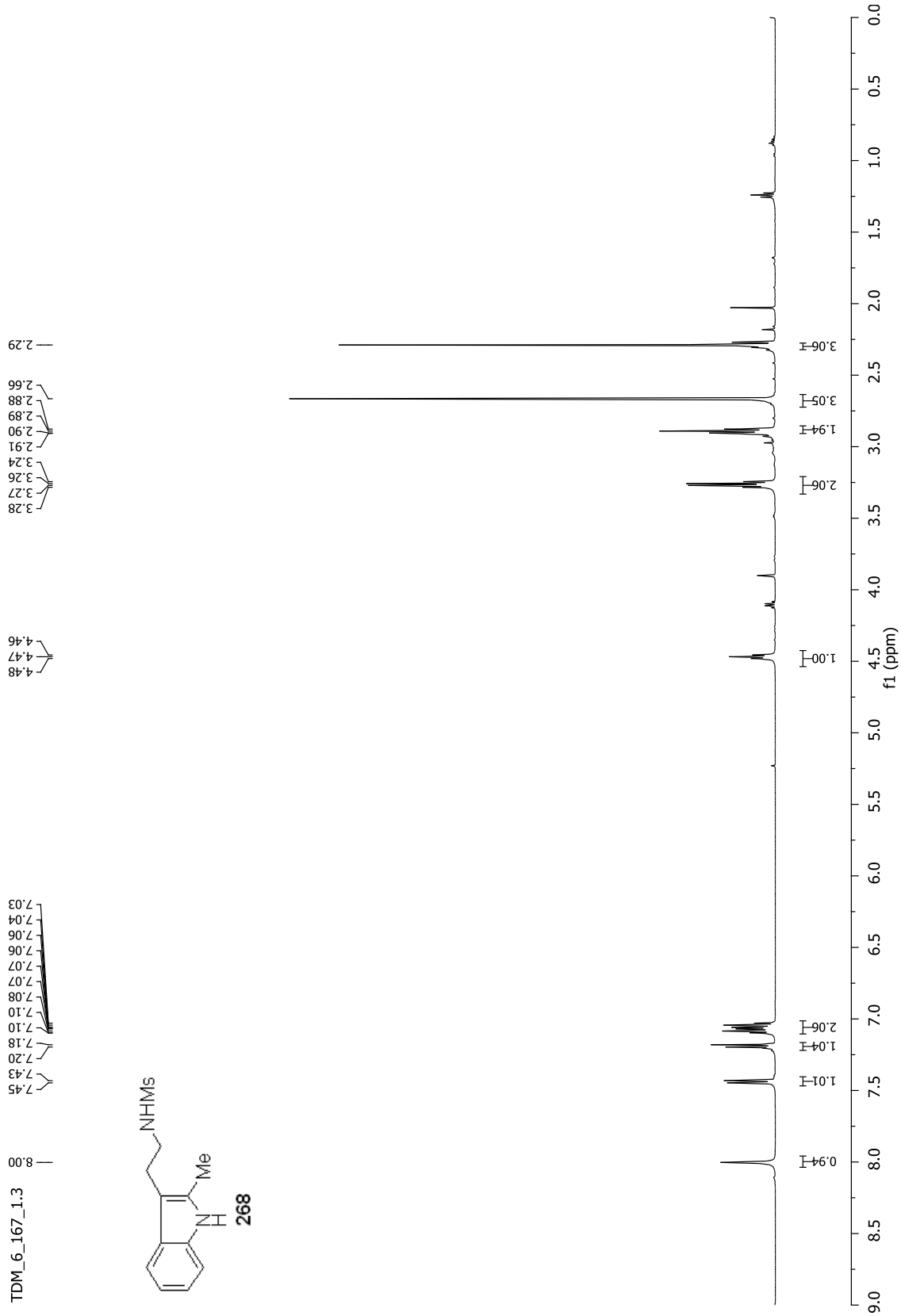


Figure 92. ^{1}H NMR Spectrum for **268** (500 MHz, $CDCl_3$)

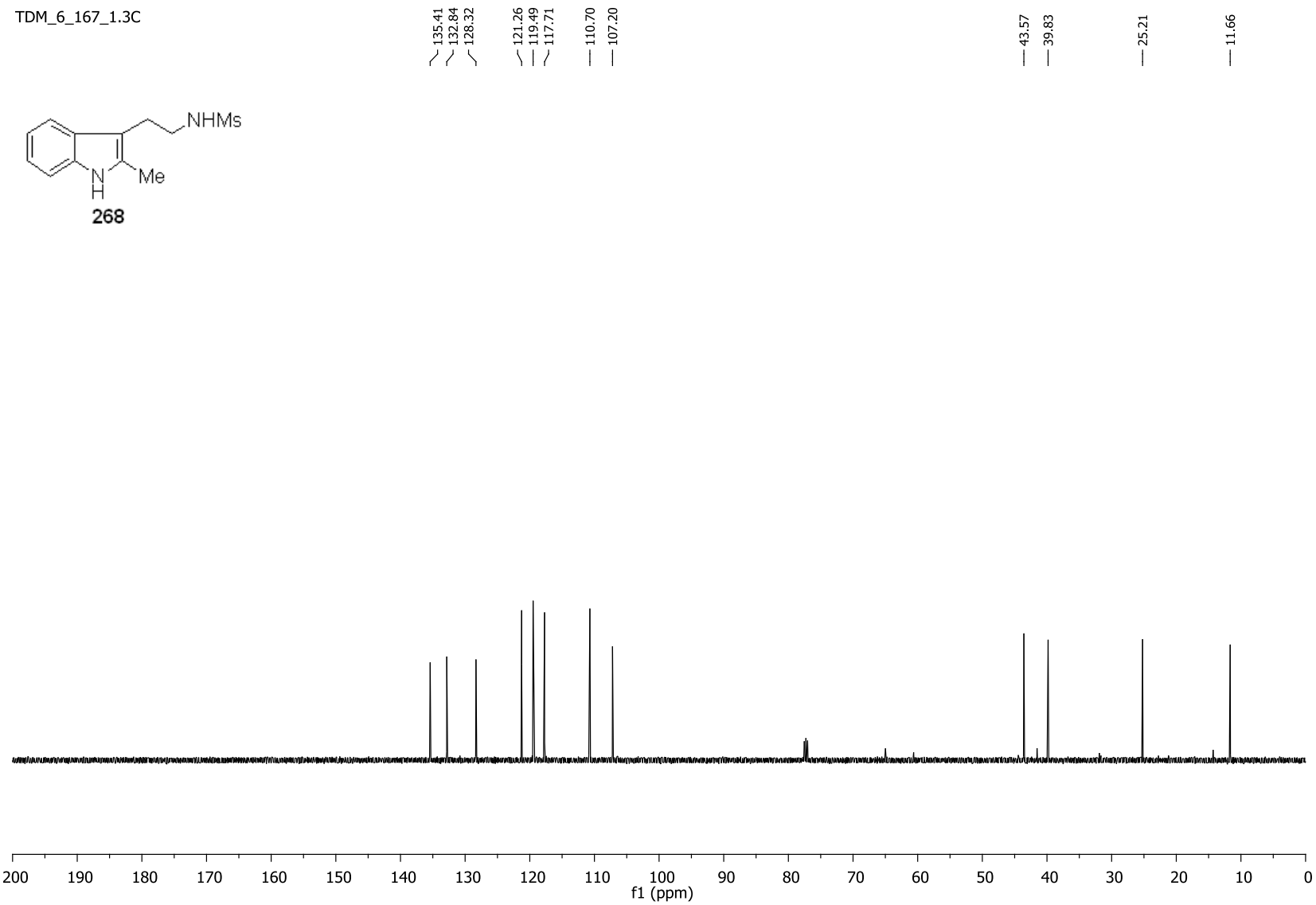


Figure 93. ^{13}C NMR Spectrum for **268** (125 MHz, $CDCl_3$)

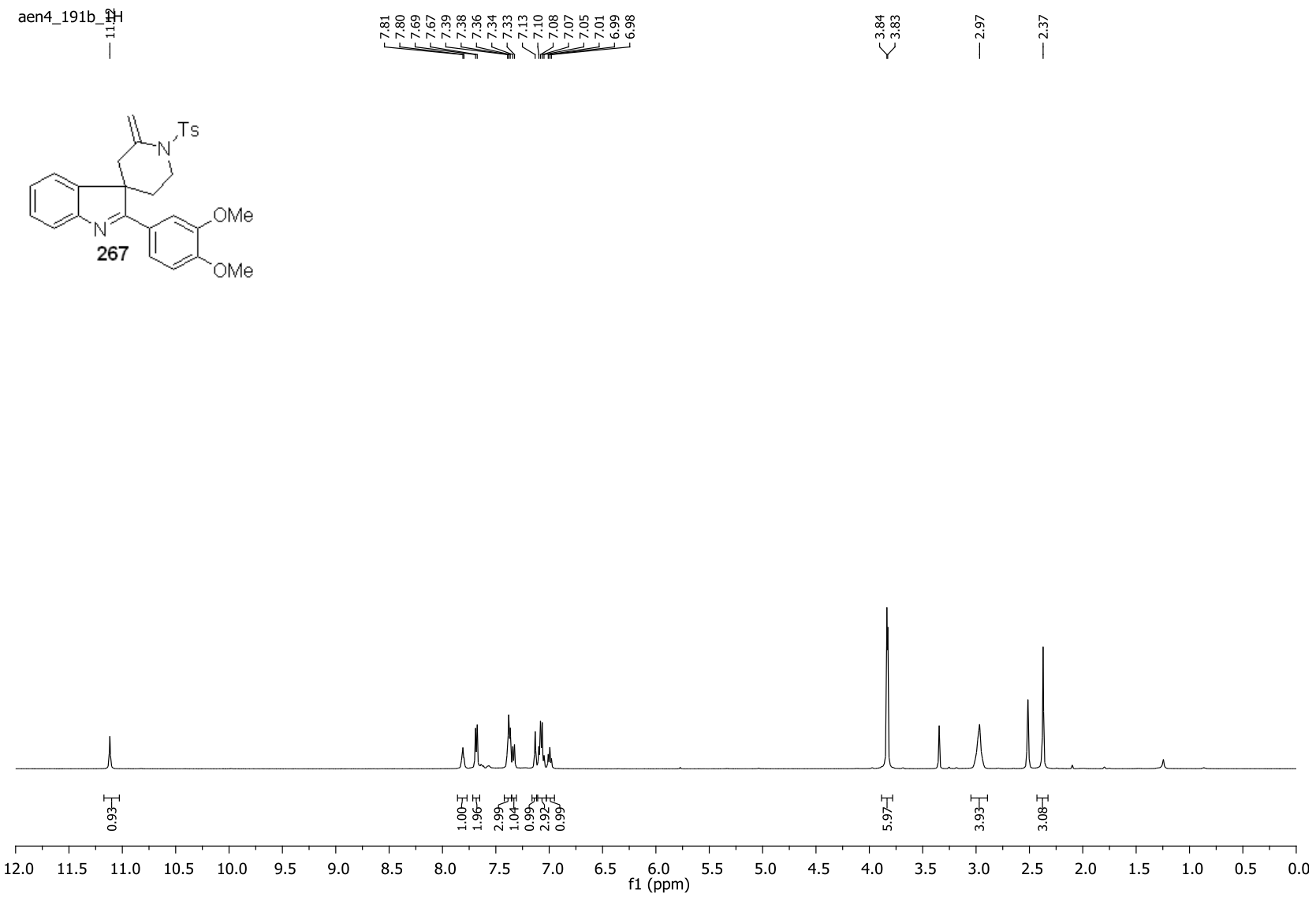


Figure 94. ^{1}H NMR Spectrum for **267** (500 MHz, DMSO)

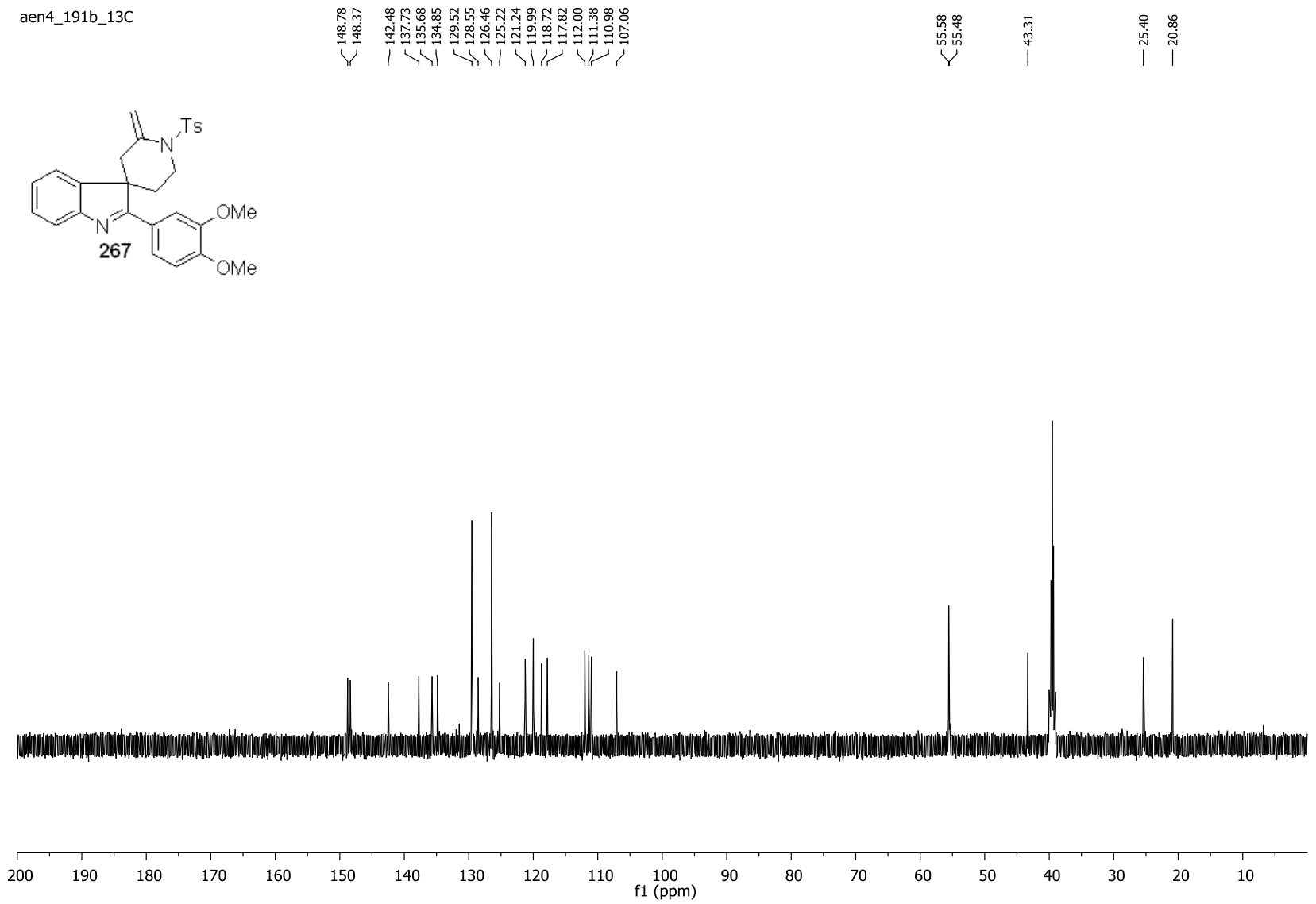


Figure 95. ^{13}C NMR Spectrum for **267** (125 MHz, DMSO)

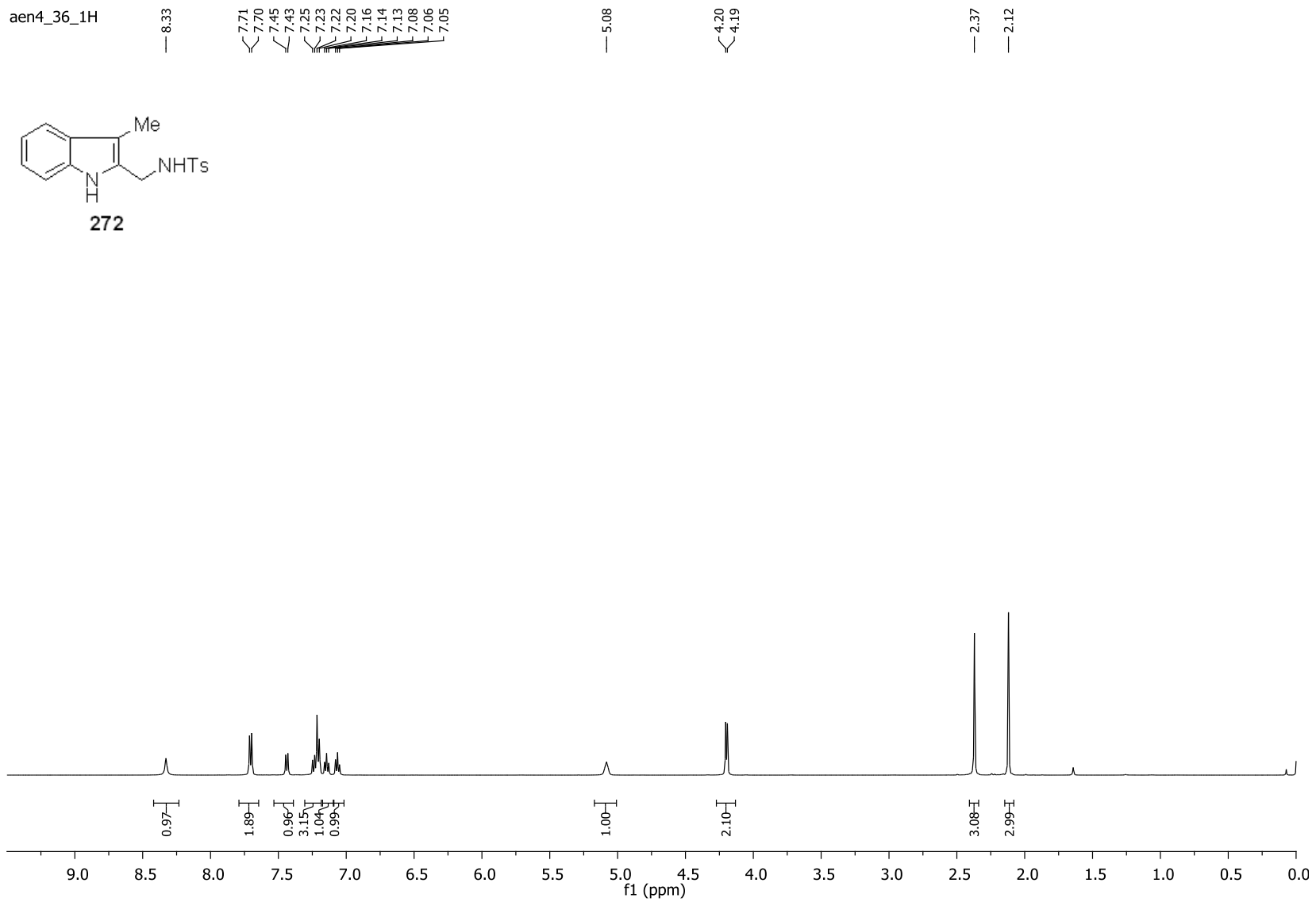


Figure 96. ^{1}H NMR Spectrum for **272** (500 MHz, DMSO)

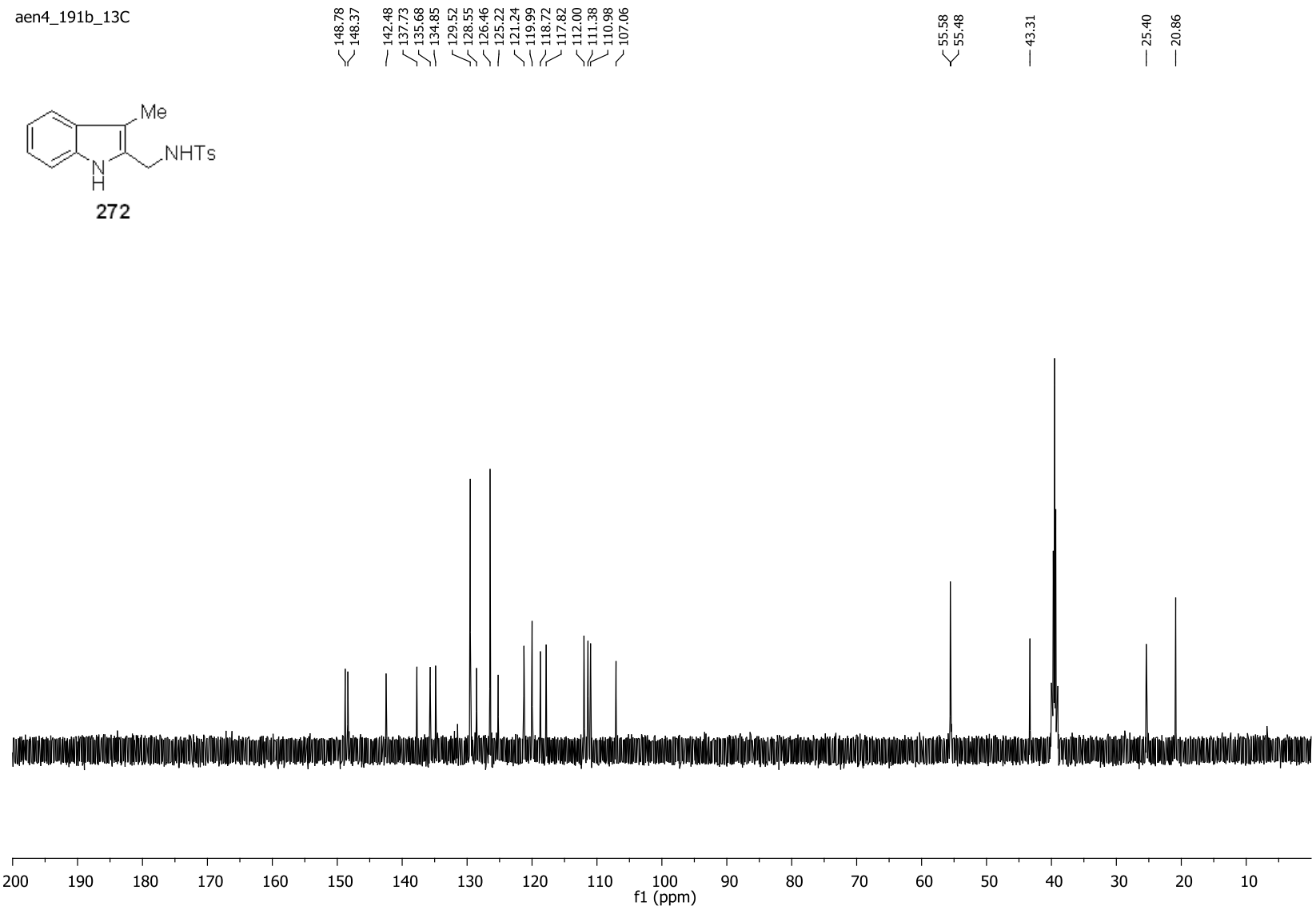


Figure 97. ^{13}C NMR Spectrum for **272** (125 MHz, DMSO)

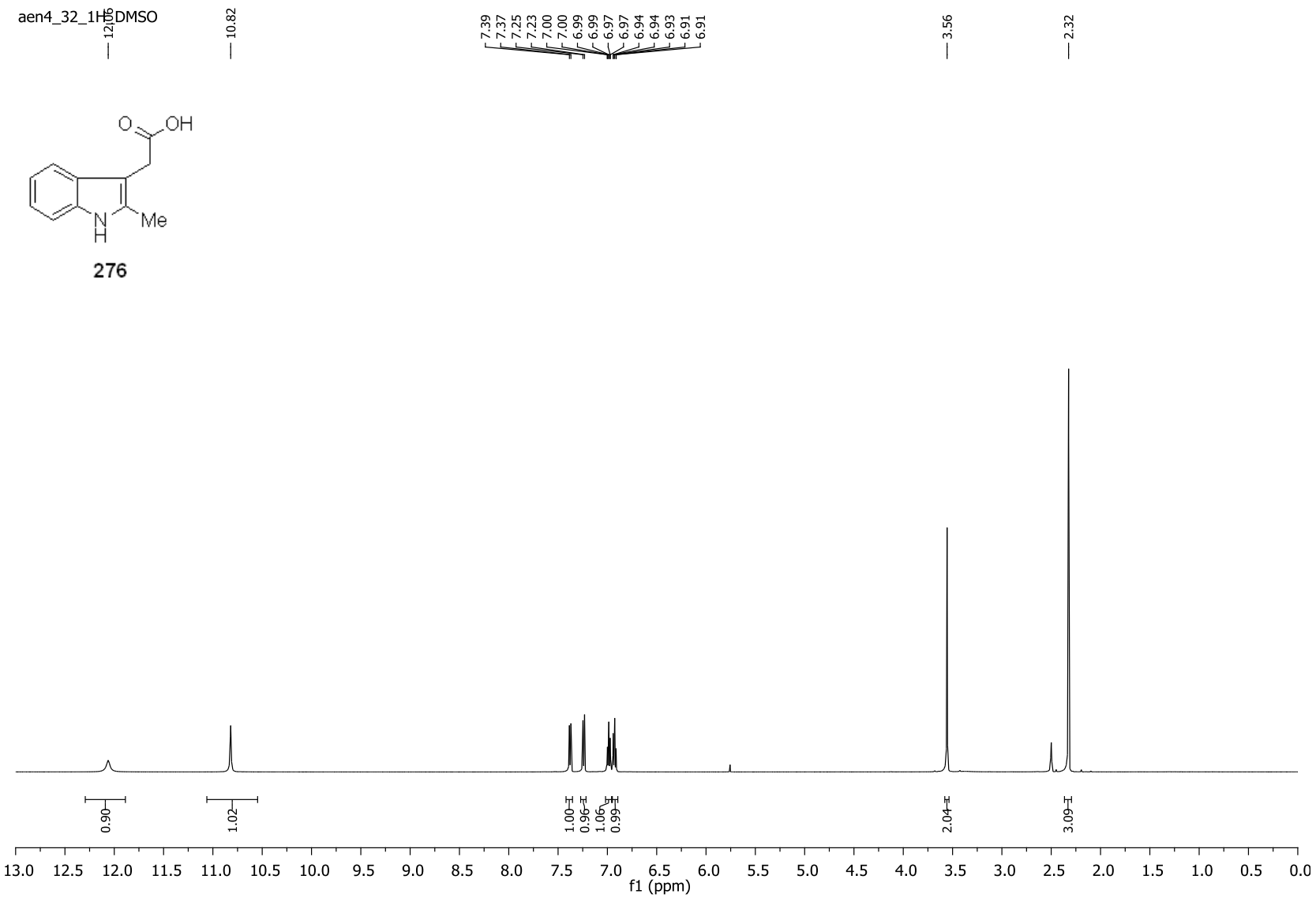


Figure 98. ^{1}H NMR Spectrum for **276** (500 MHz, DMSO)

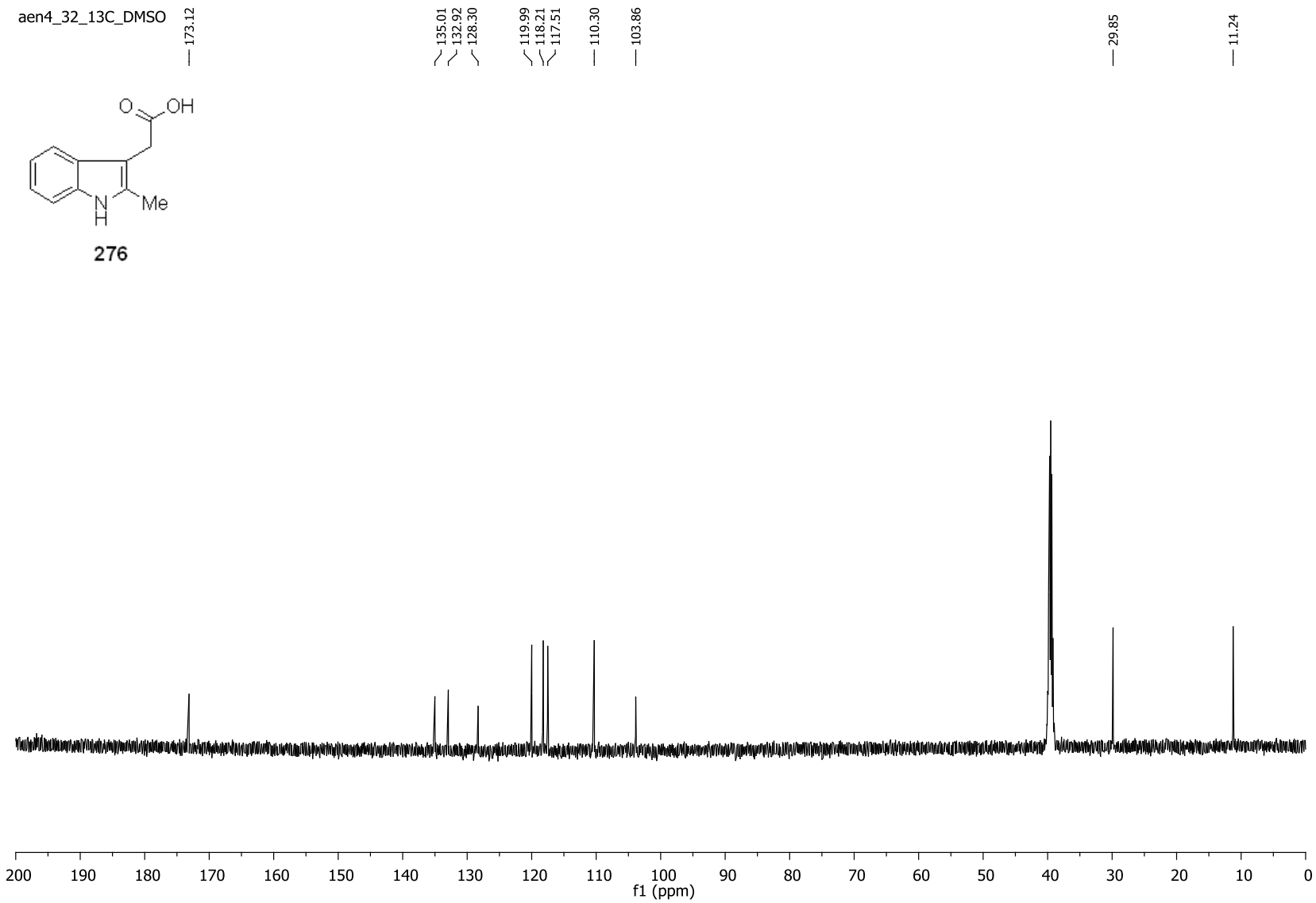


Figure 99. ^{13}C NMR Spectrum for **276** (125 MHz, DMSO)

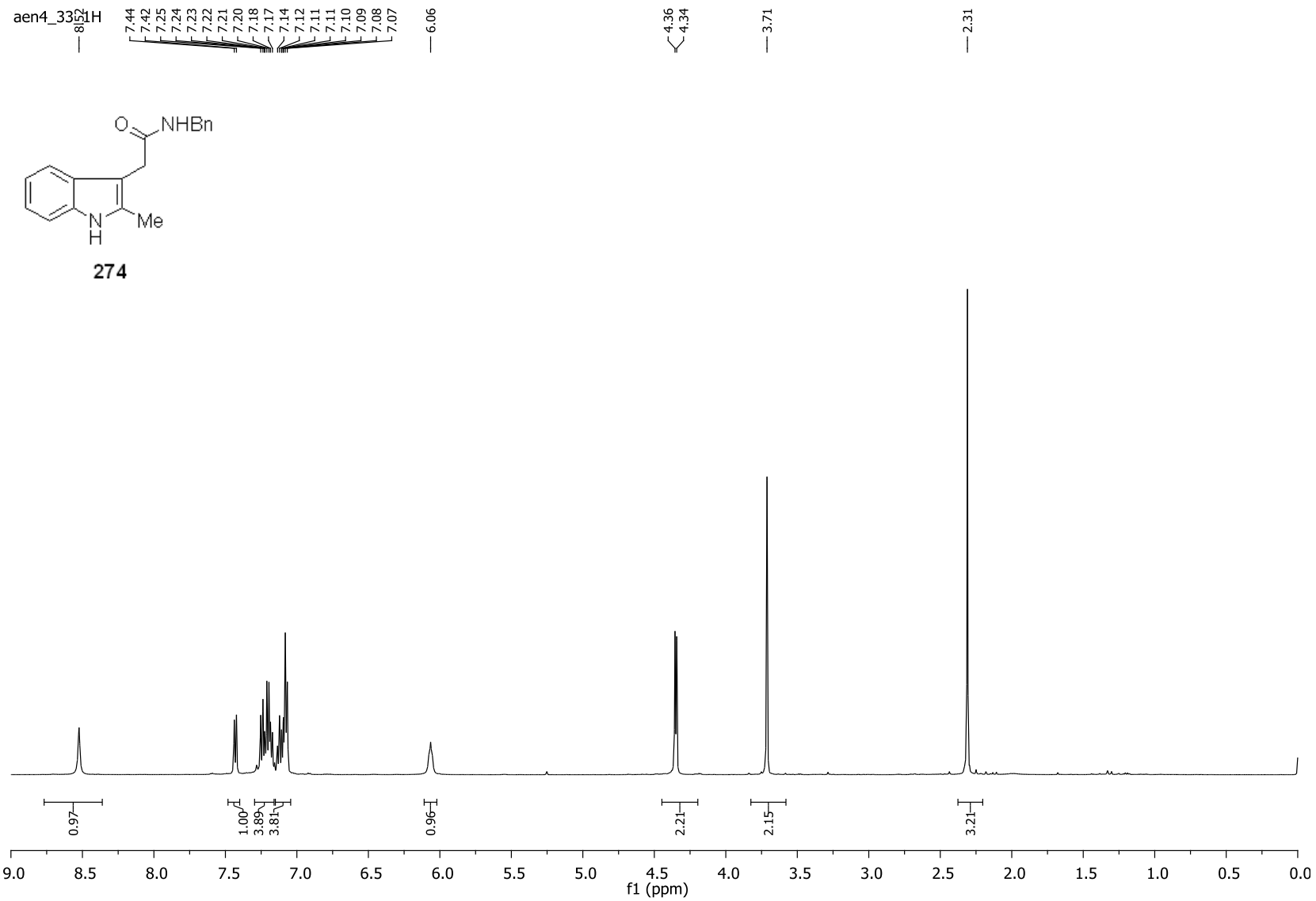


Figure 100. ^{1}H NMR Spectrum for **274** (500 MHz, $CDCl_3$)

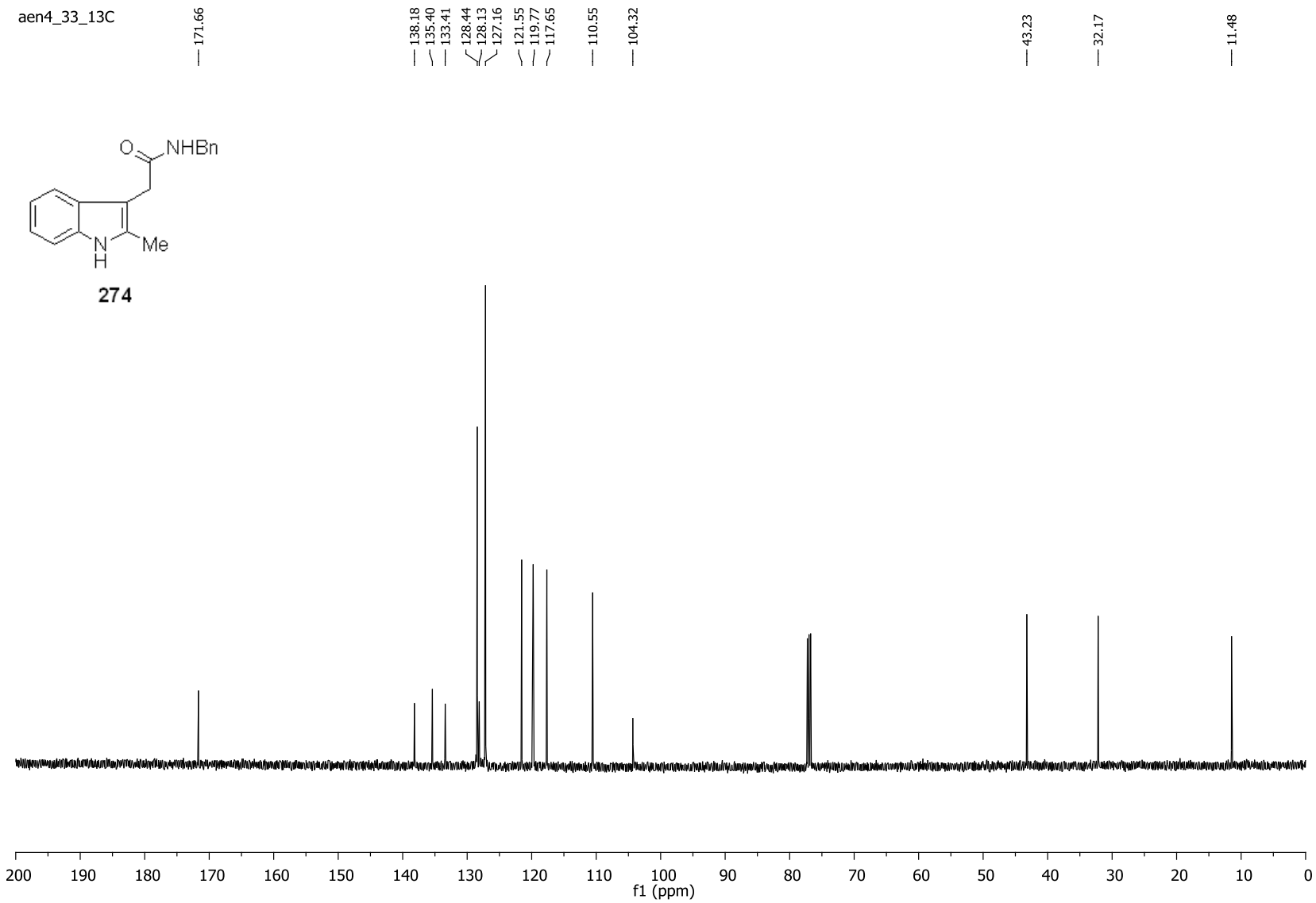


Figure 101. ^{13}C NMR Spectrum for **274** (125 MHz, $CDCl_3$)

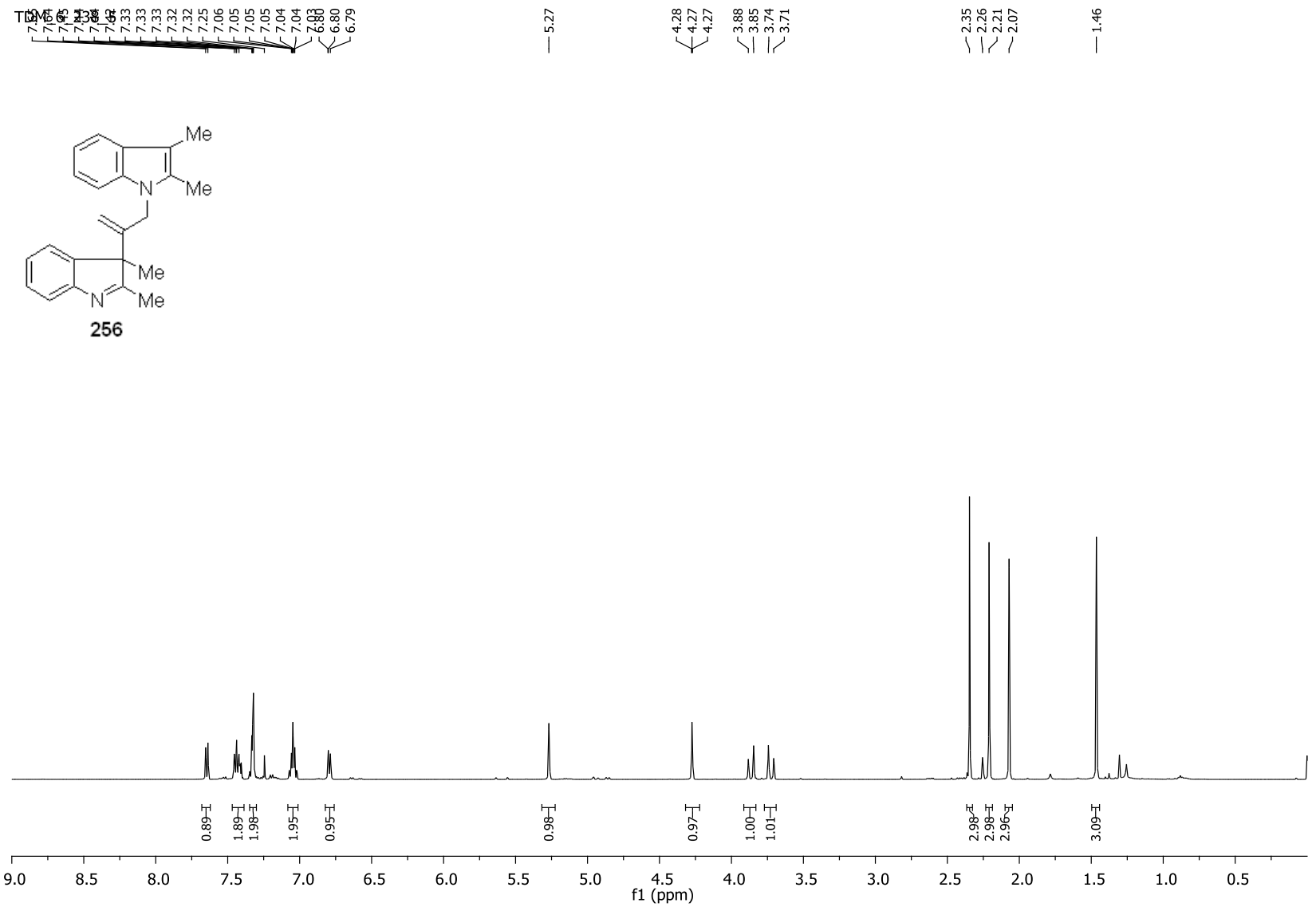


Figure 102. ^{1}H NMR Spectrum for **256** (500 MHz, $CDCl_3$)

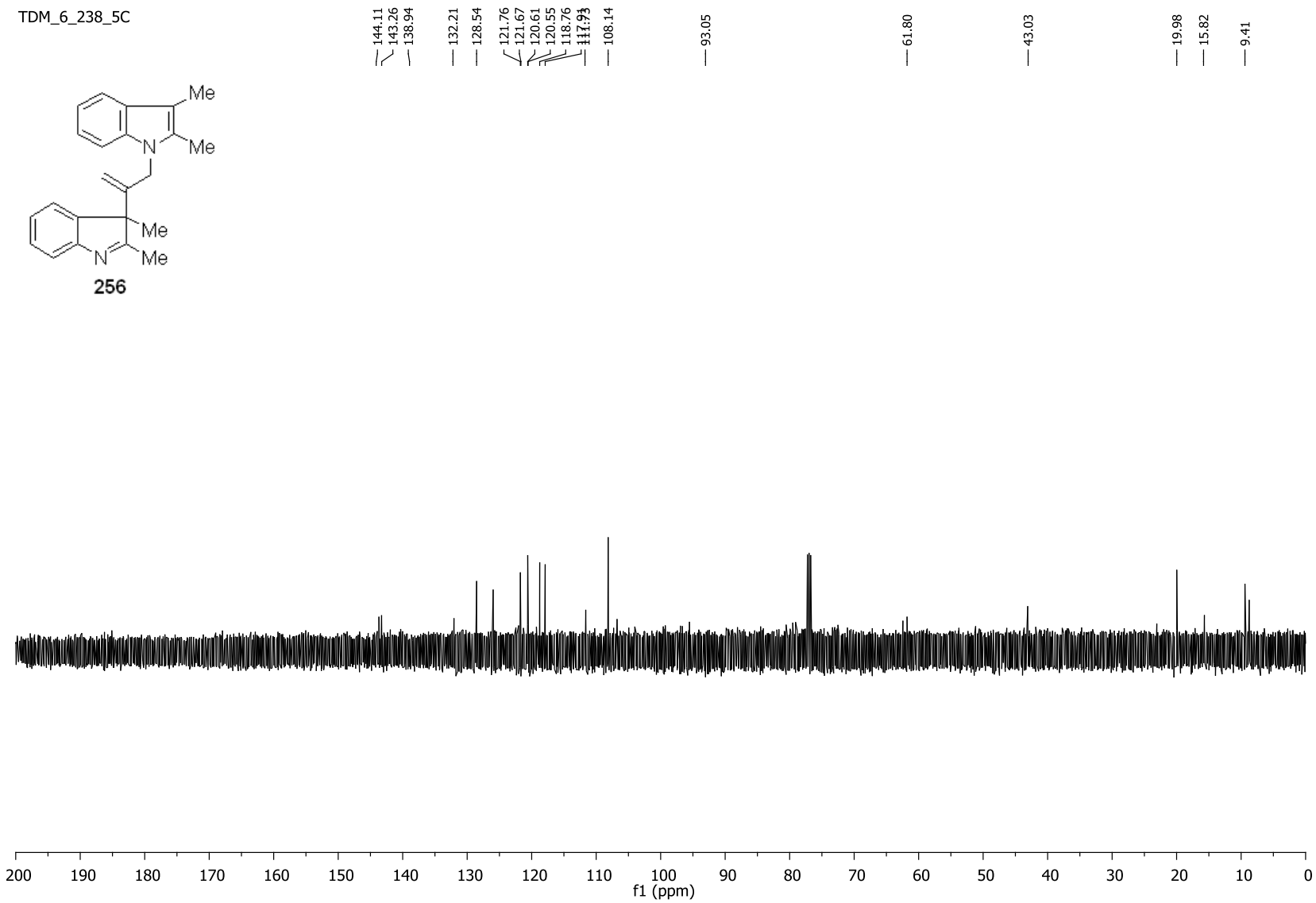


Figure 103. ^{13}C NMR Spectrum for **256** (125 MHz, $CDCl_3$)

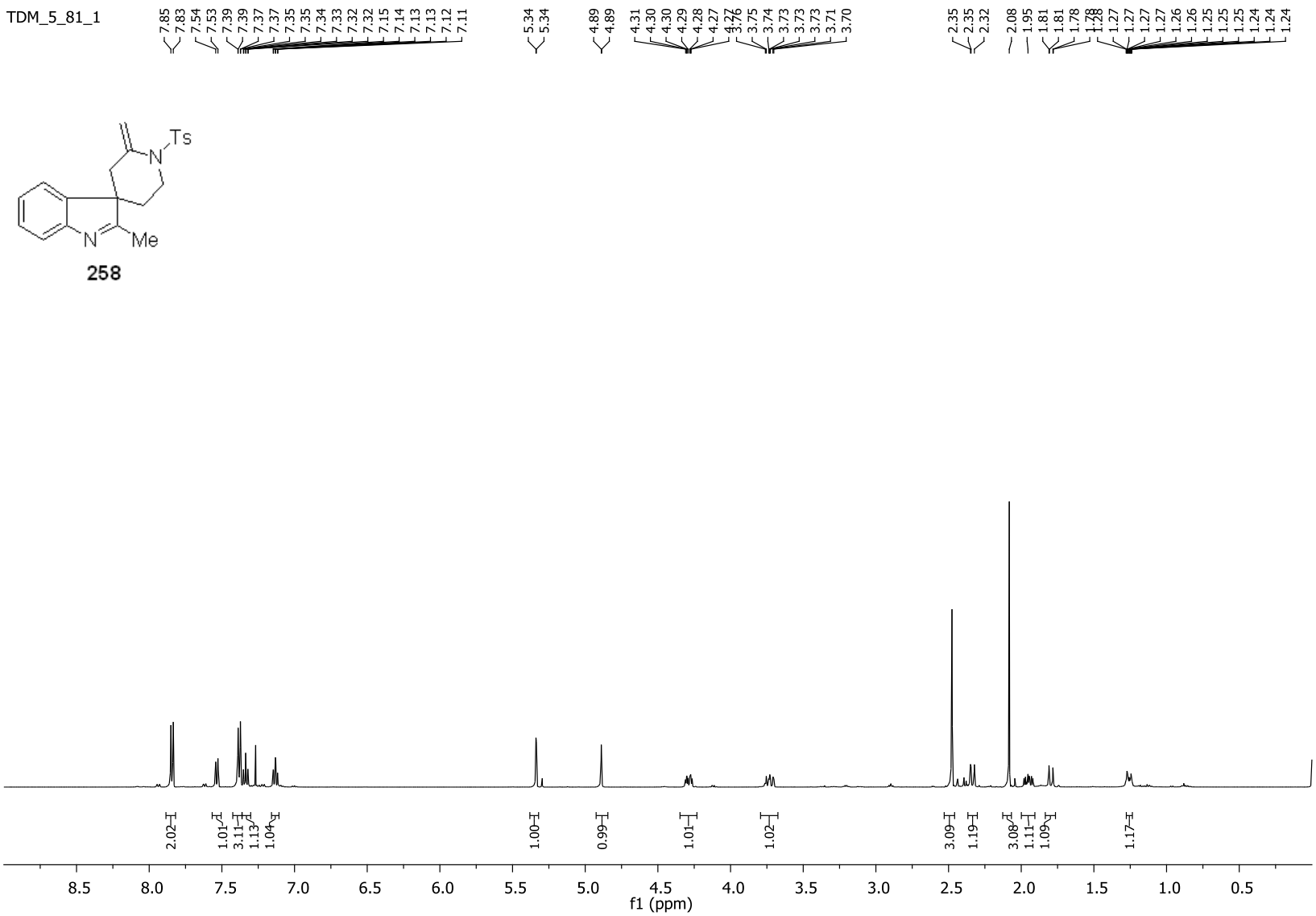


Figure 104. ^{1}H NMR Spectrum for **258** (500 MHz, $CDCl_3$)

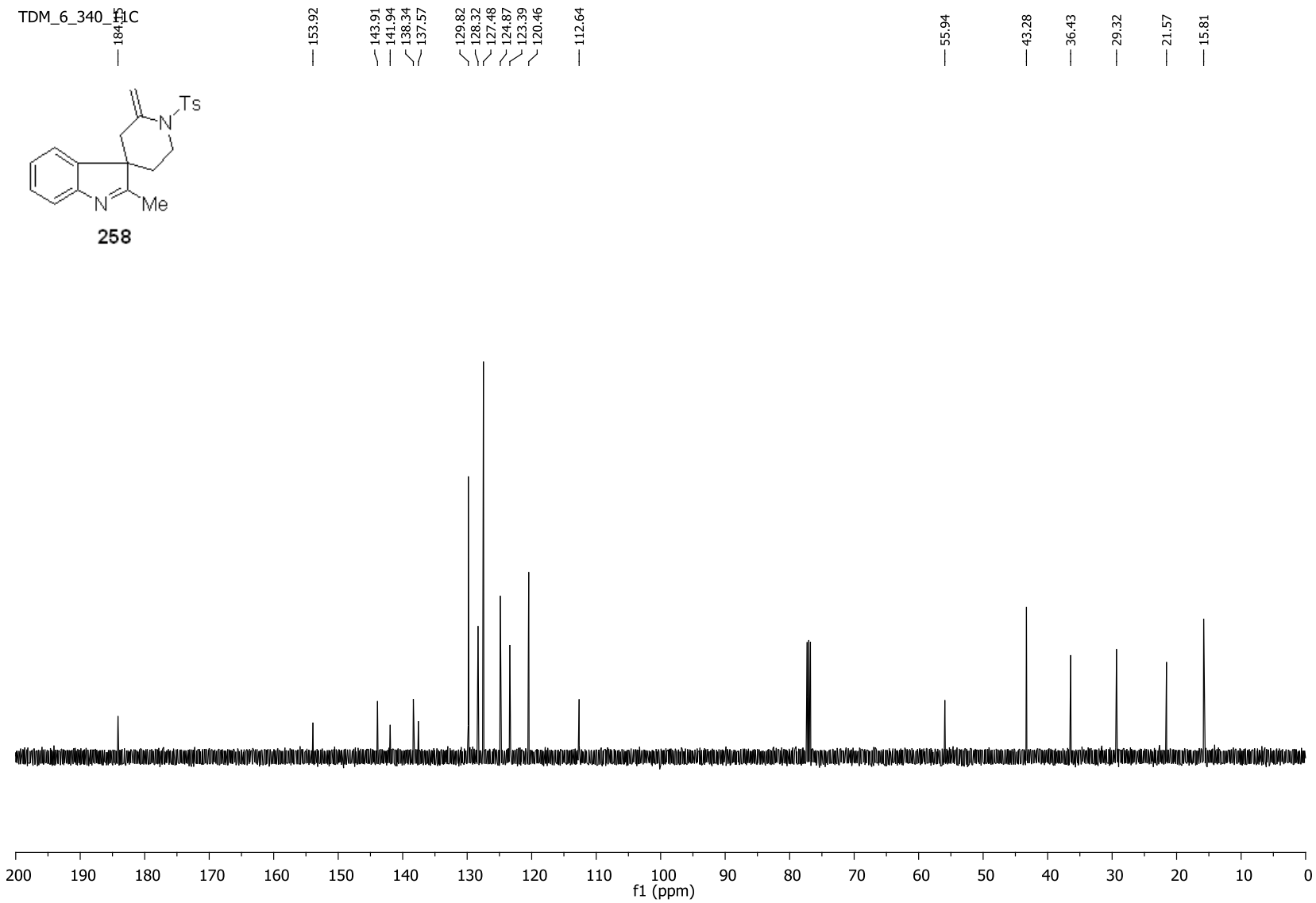


Figure 105. ^{13}C NMR Spectrum for **258** (125 MHz, $CDCl_3$)

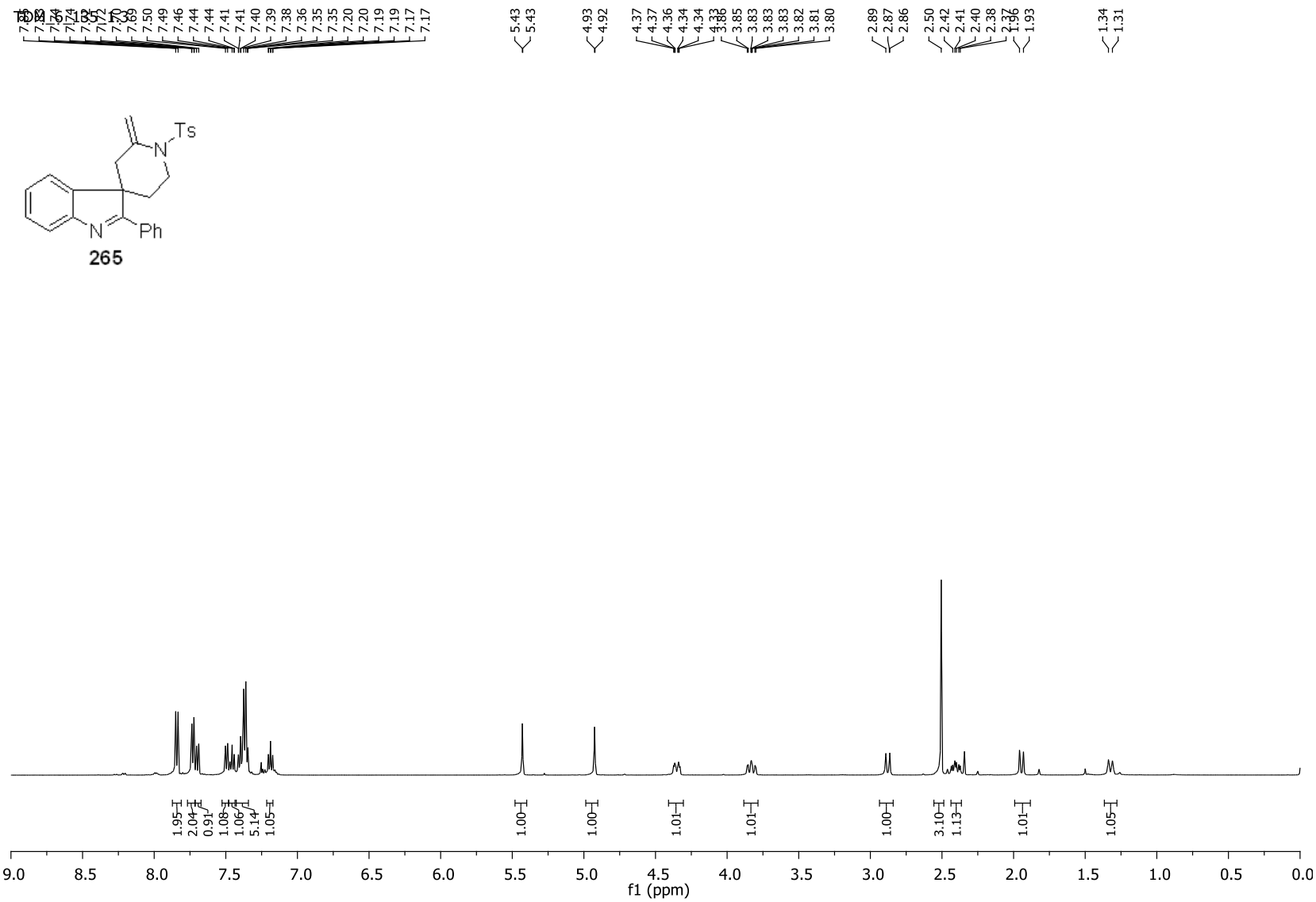


Figure 106. ^{1}H NMR Spectrum for **265** (500 MHz, $CDCl_3$)

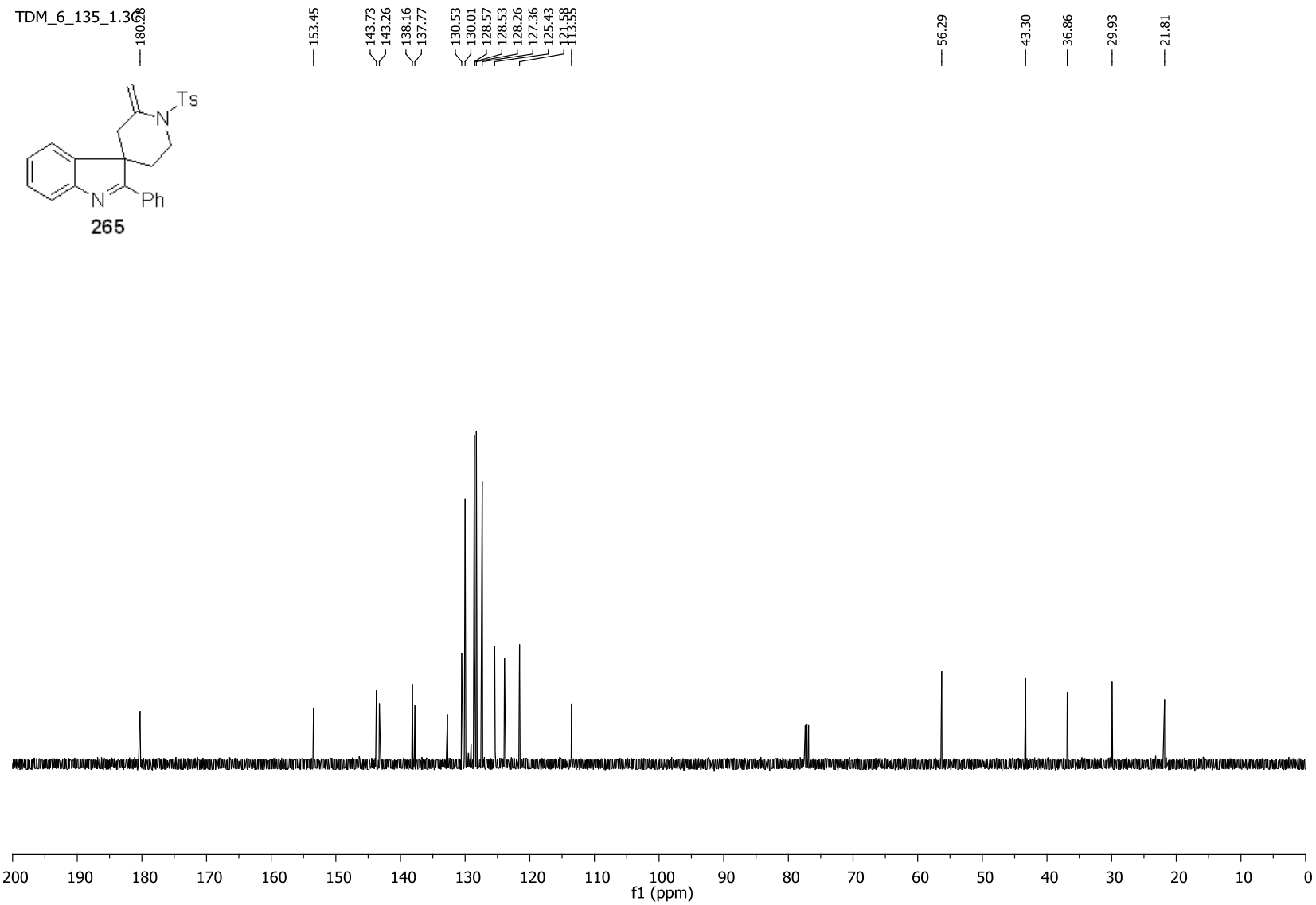


Figure 107. ^{13}C NMR Spectrum for **265** (125 MHz, $CDCl_3$)

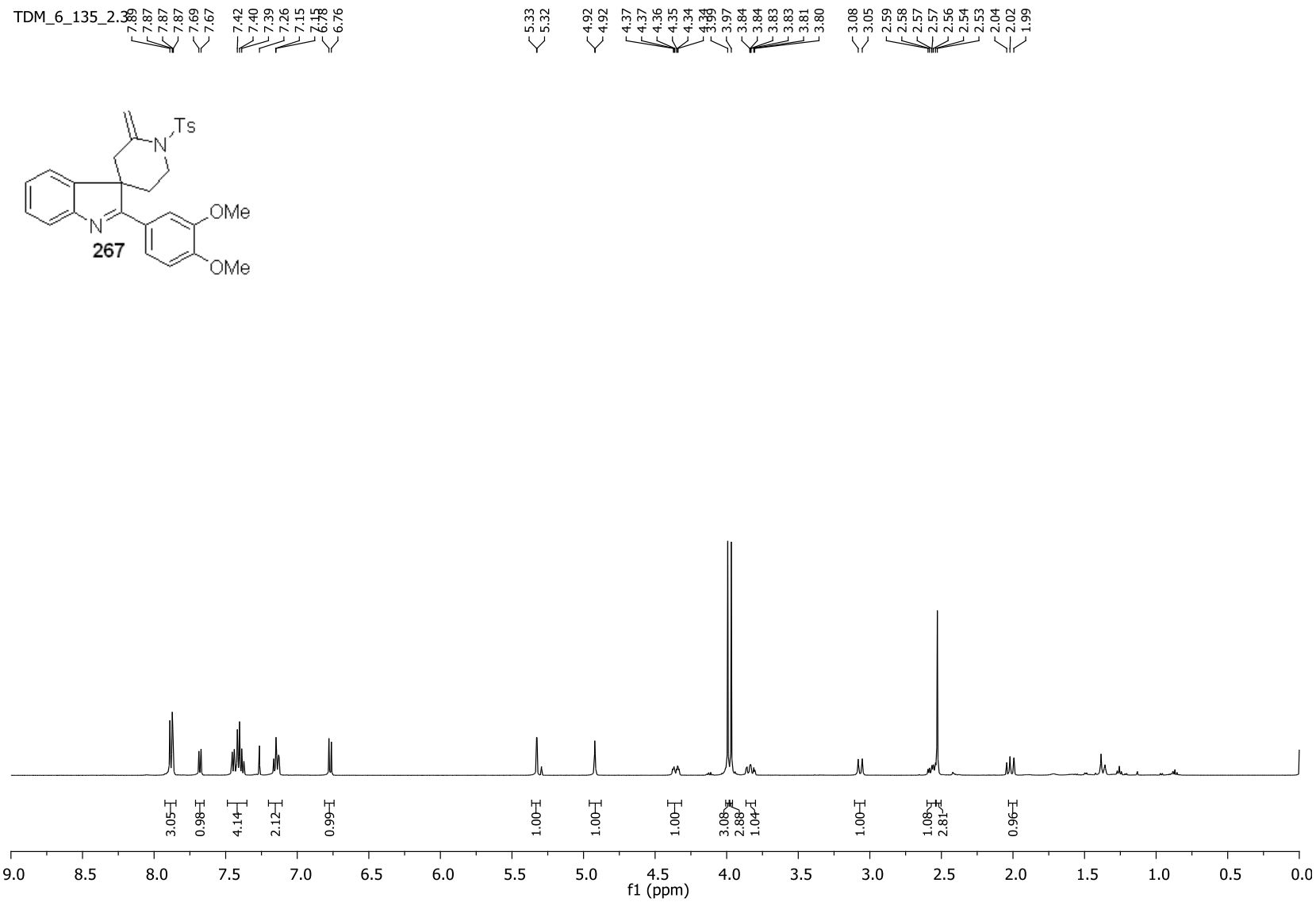


Figure 108. ^{1}H NMR Spectrum for **267** (500 MHz, $CDCl_3$)

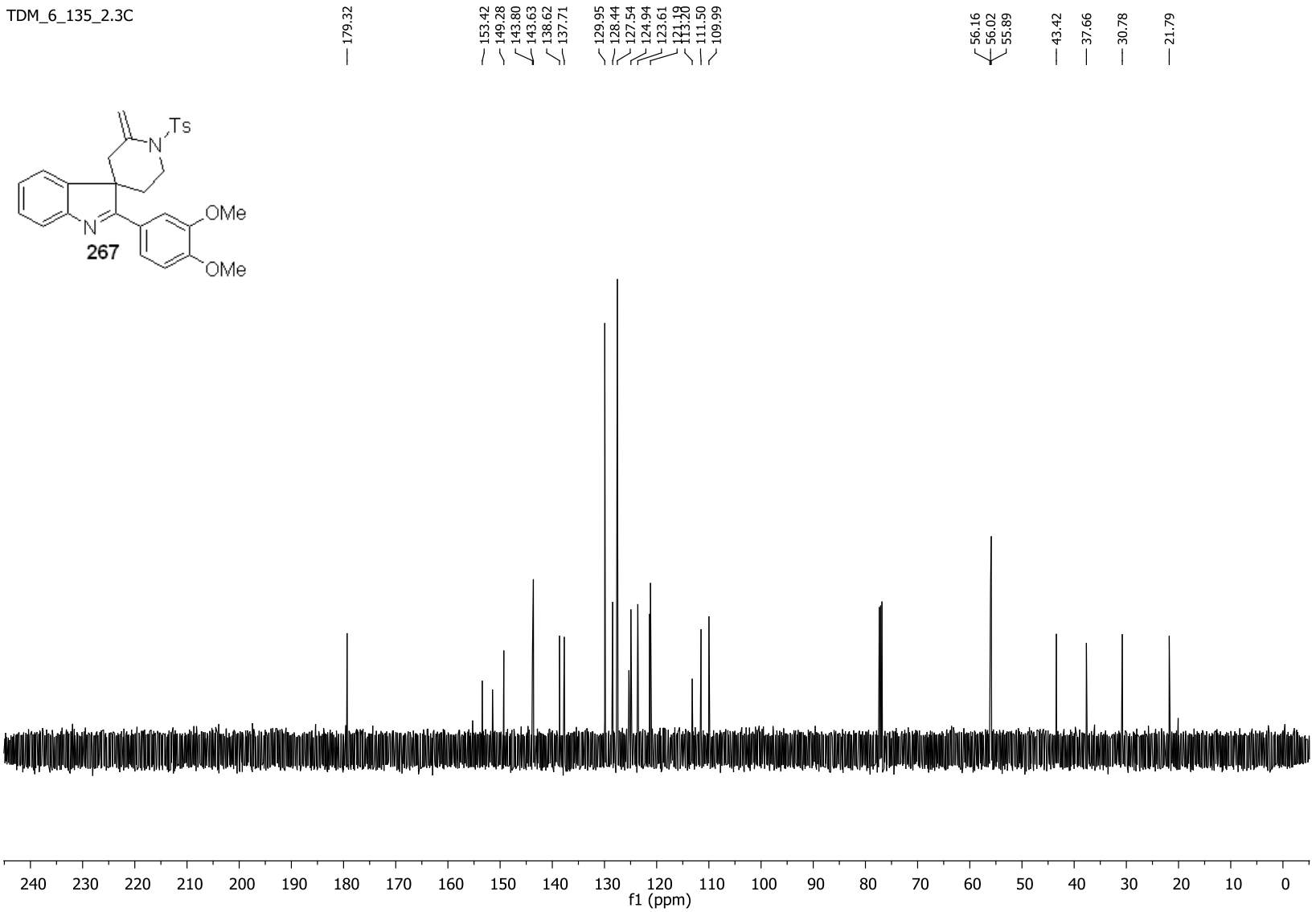


Figure 109. ^{13}C NMR Spectrum for **267** (125 MHz, $CDCl_3$)

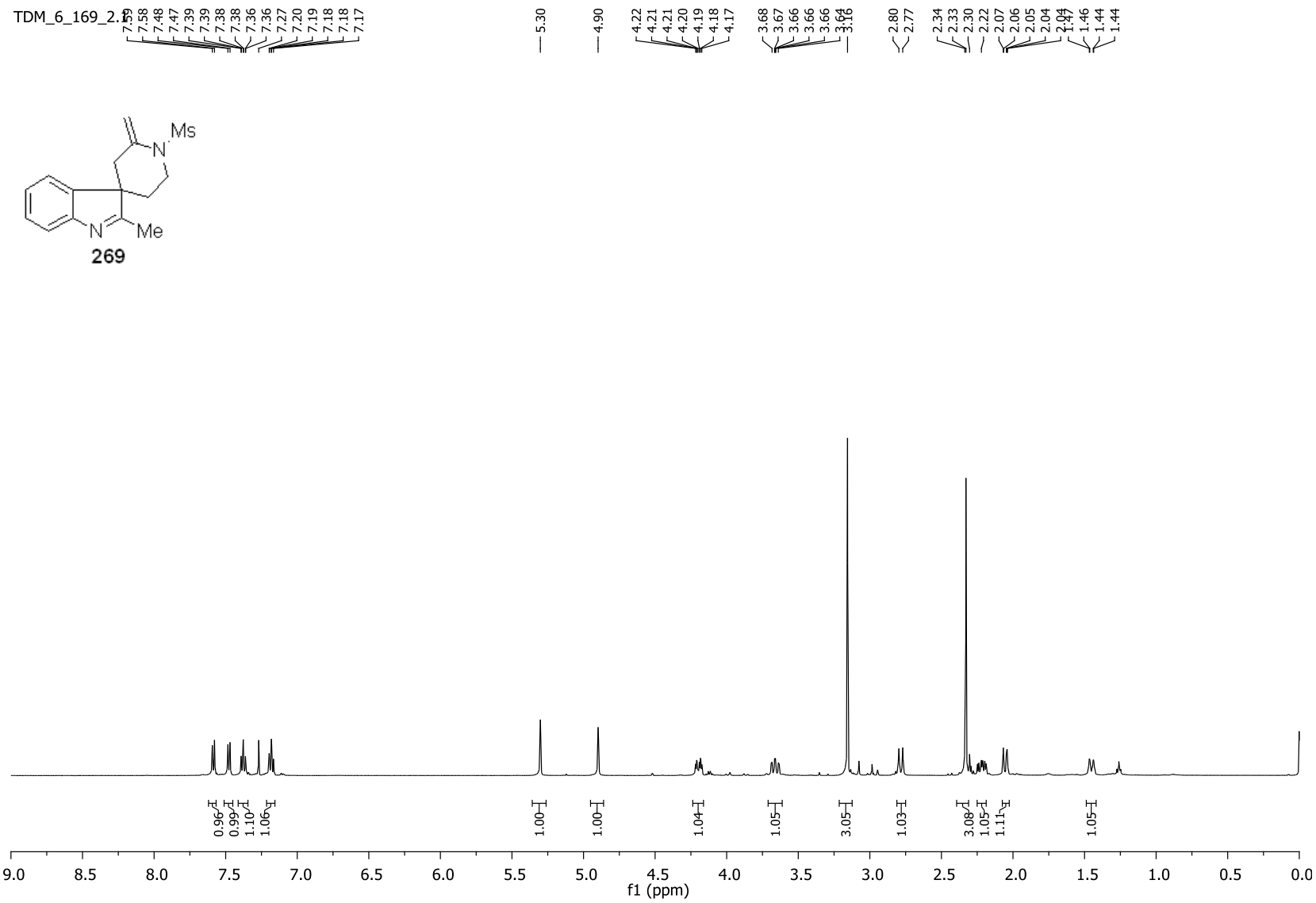


Figure 110. ^{1}H NMR Spectrum for **269** (500 MHz, $CDCl_3$)

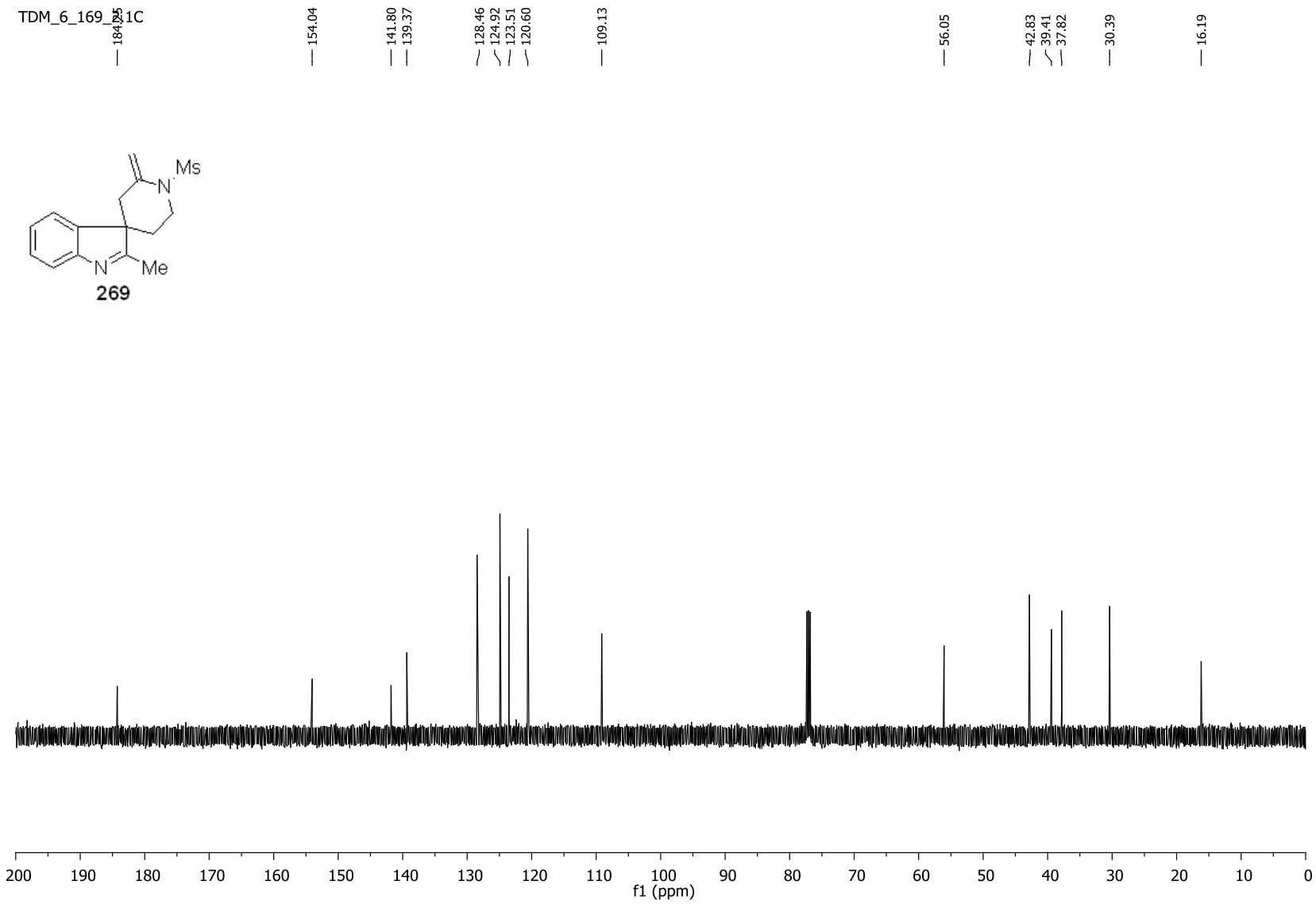


Figure 111. ^{13}C NMR Spectrum for **269** (125 MHz, $CDCl_3$)

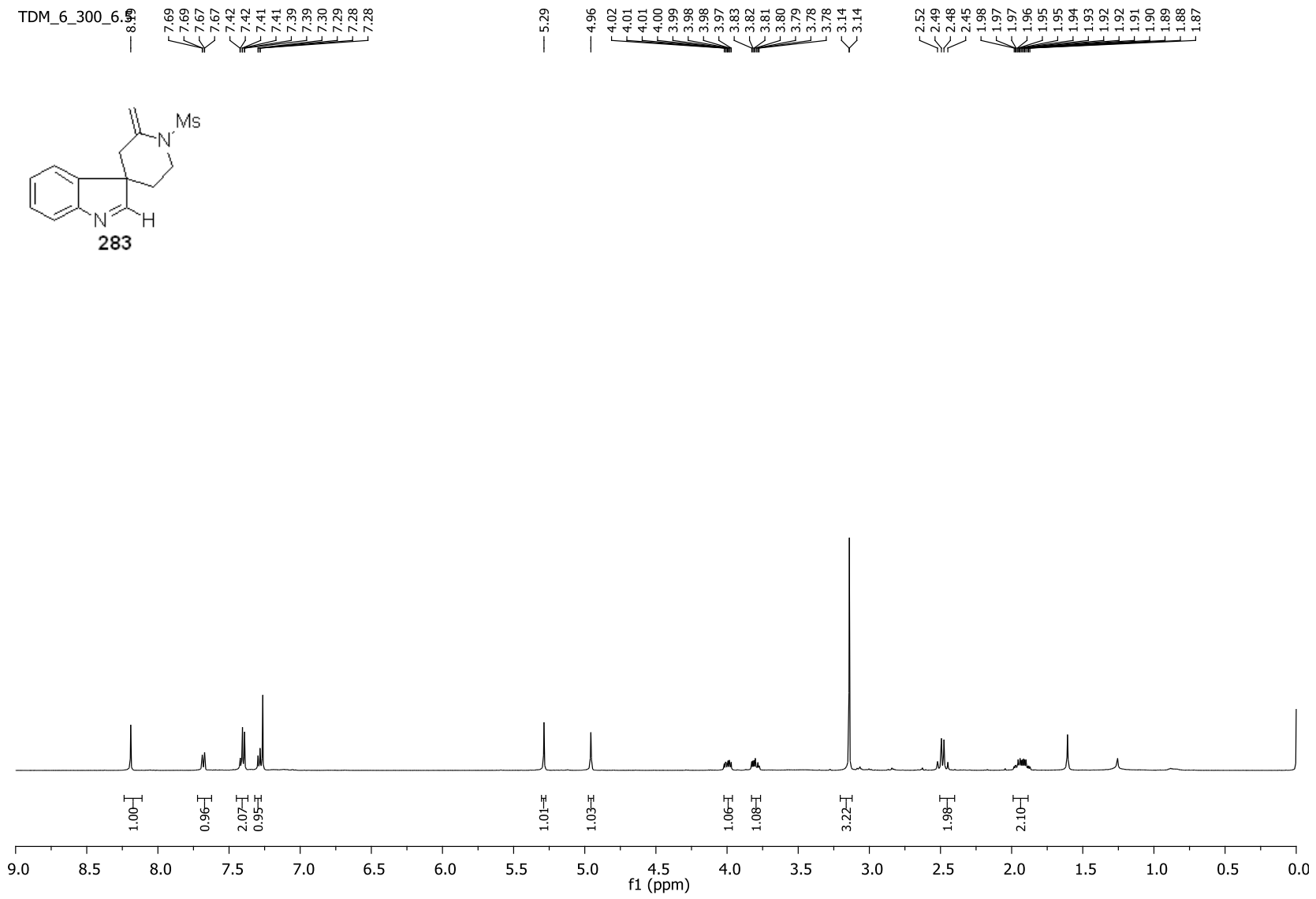


Figure 112. ^{1}H NMR Spectrum for **283** (500 MHz, $CDCl_3$)

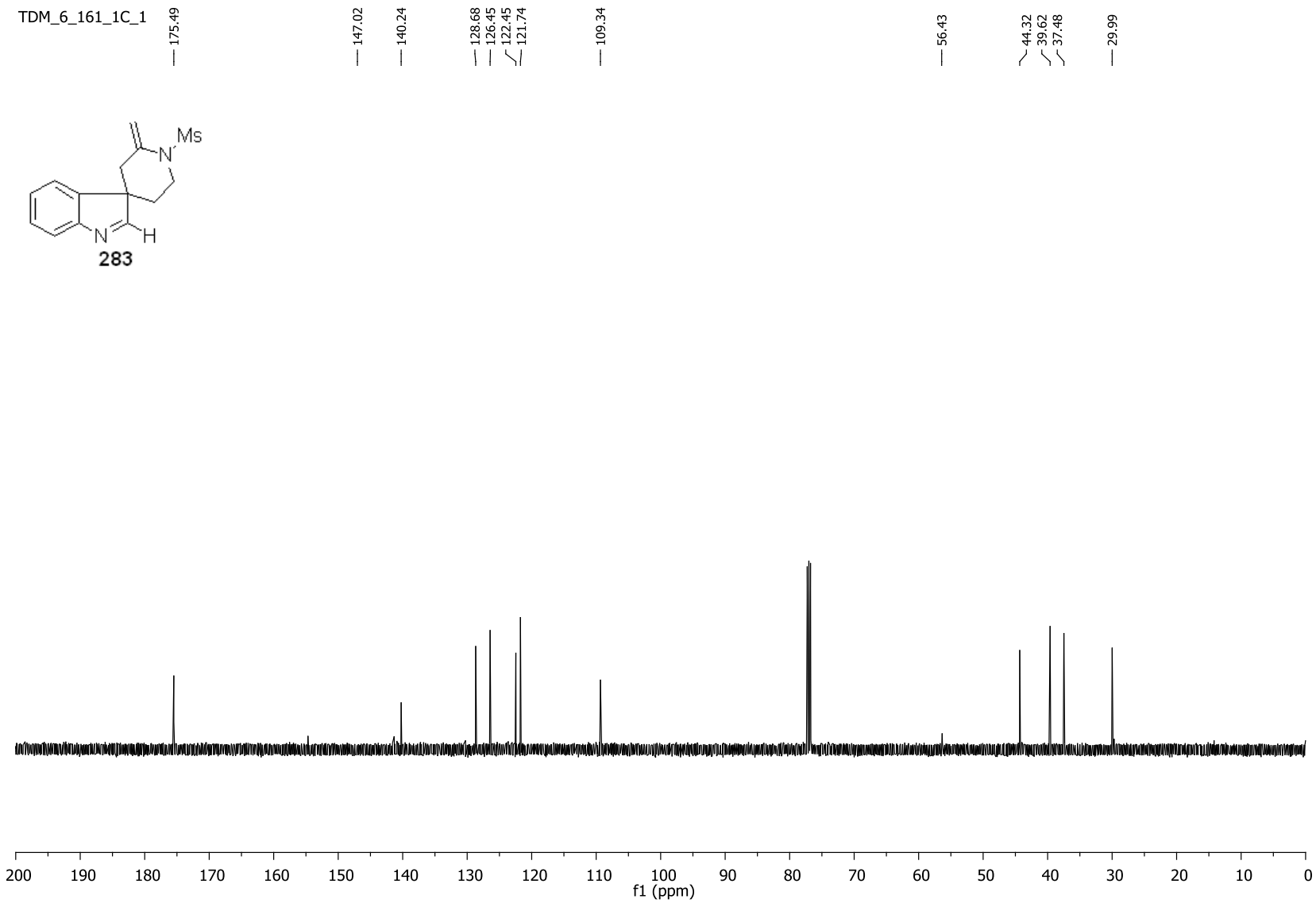


Figure 113. ^{13}C NMR Spectrum for **283** (125 MHz, $CDCl_3$)

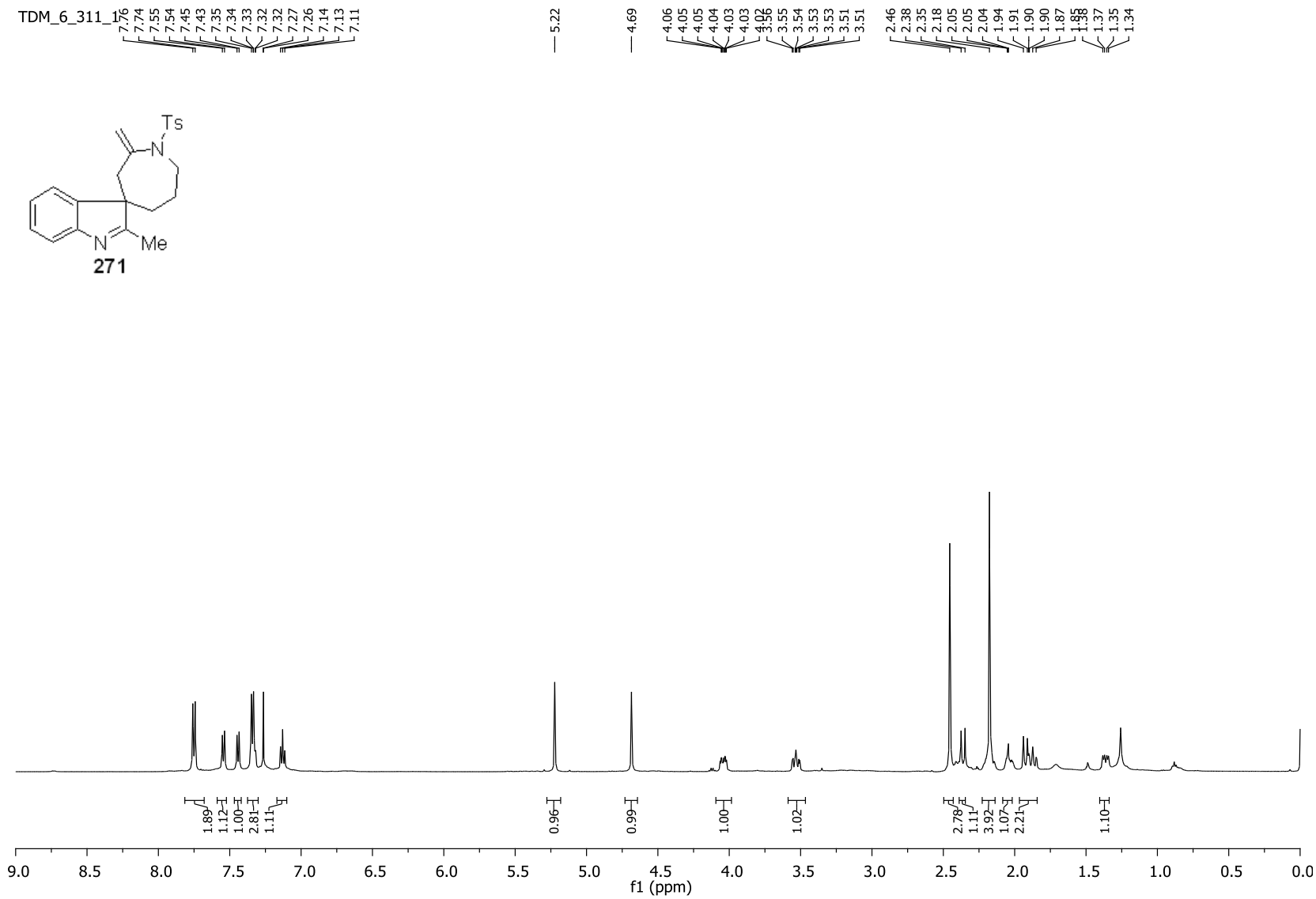


Figure 114. ^{1}H NMR Spectrum for **271** (500 MHz, $CDCl_3$)

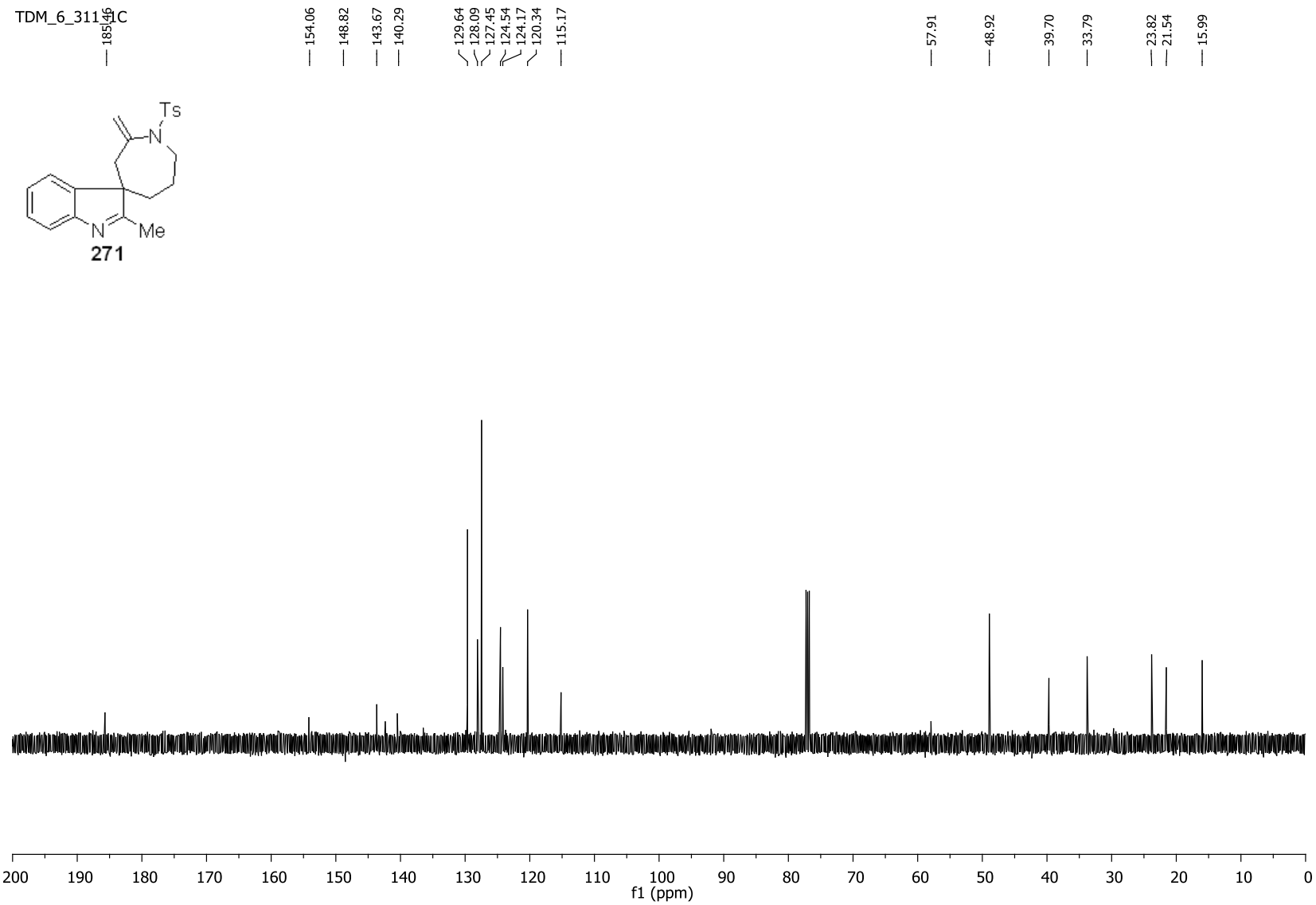


Figure 115. ^{13}C NMR Spectrum for **271** (125 MHz, $CDCl_3$)

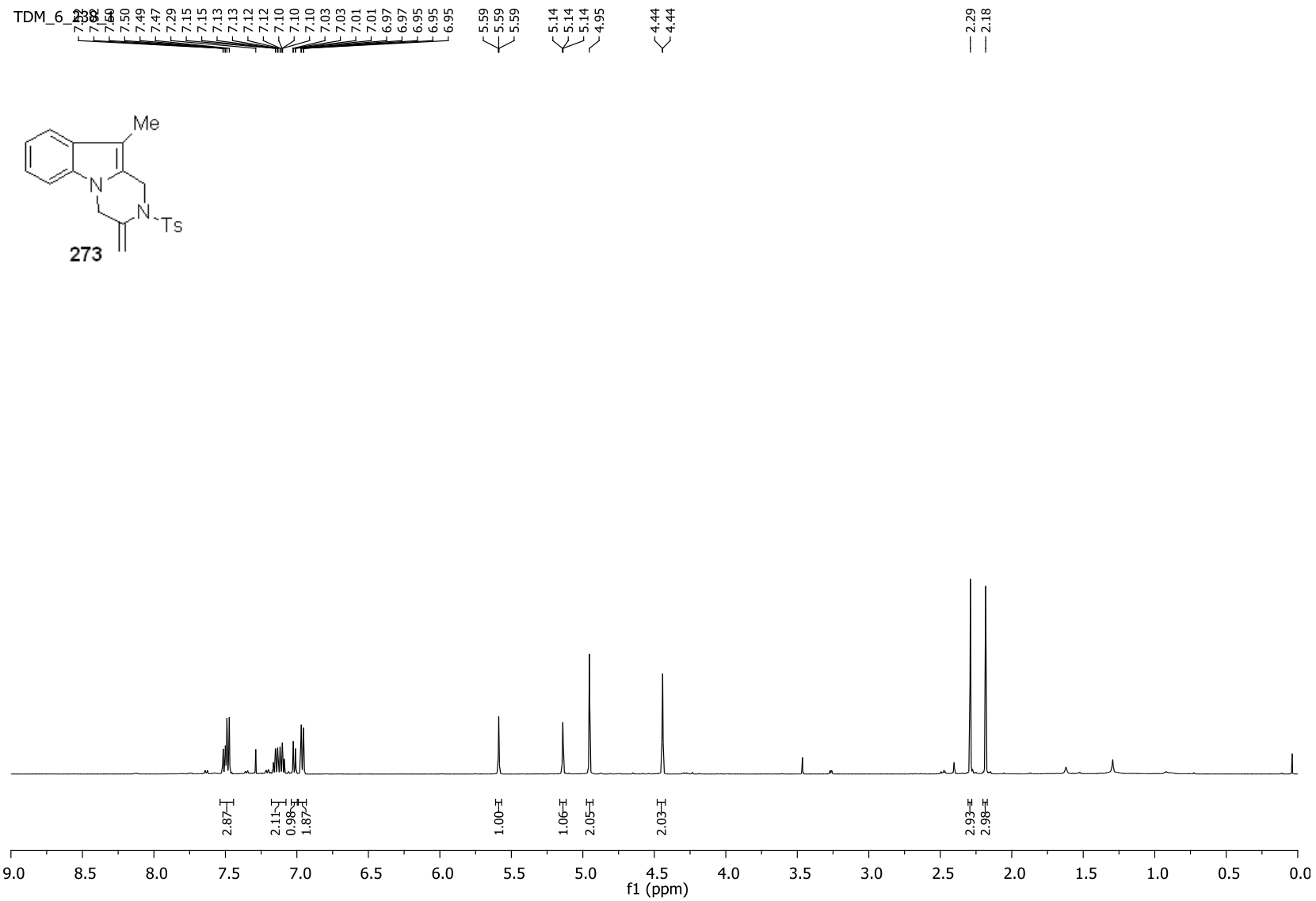


Figure 116. ^{1}H NMR Spectrum for **273** (500 MHz, $CDCl_3$)

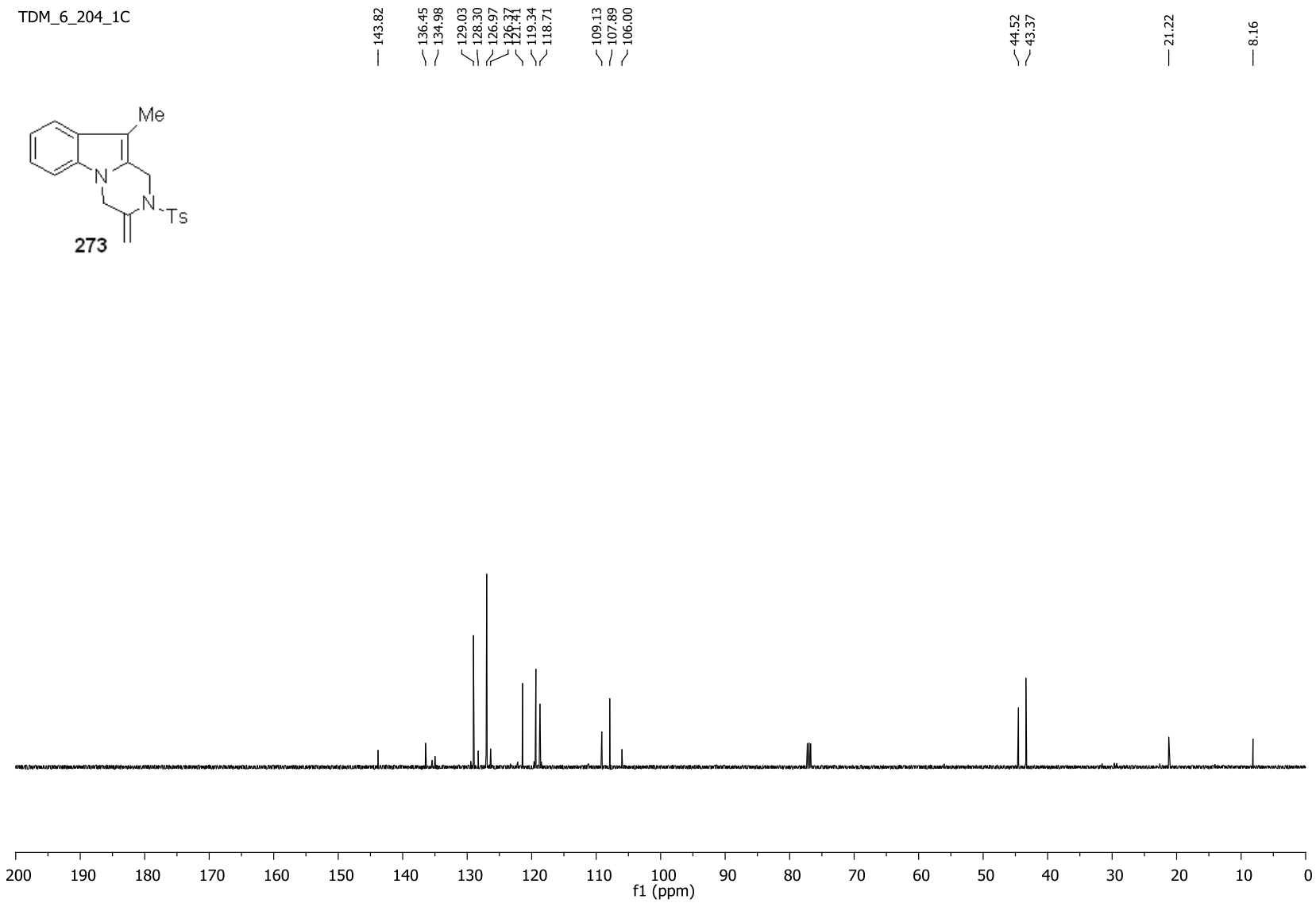


Figure 117. ^{13}C NMR Spectrum for **273** (125 MHz, $CDCl_3$)

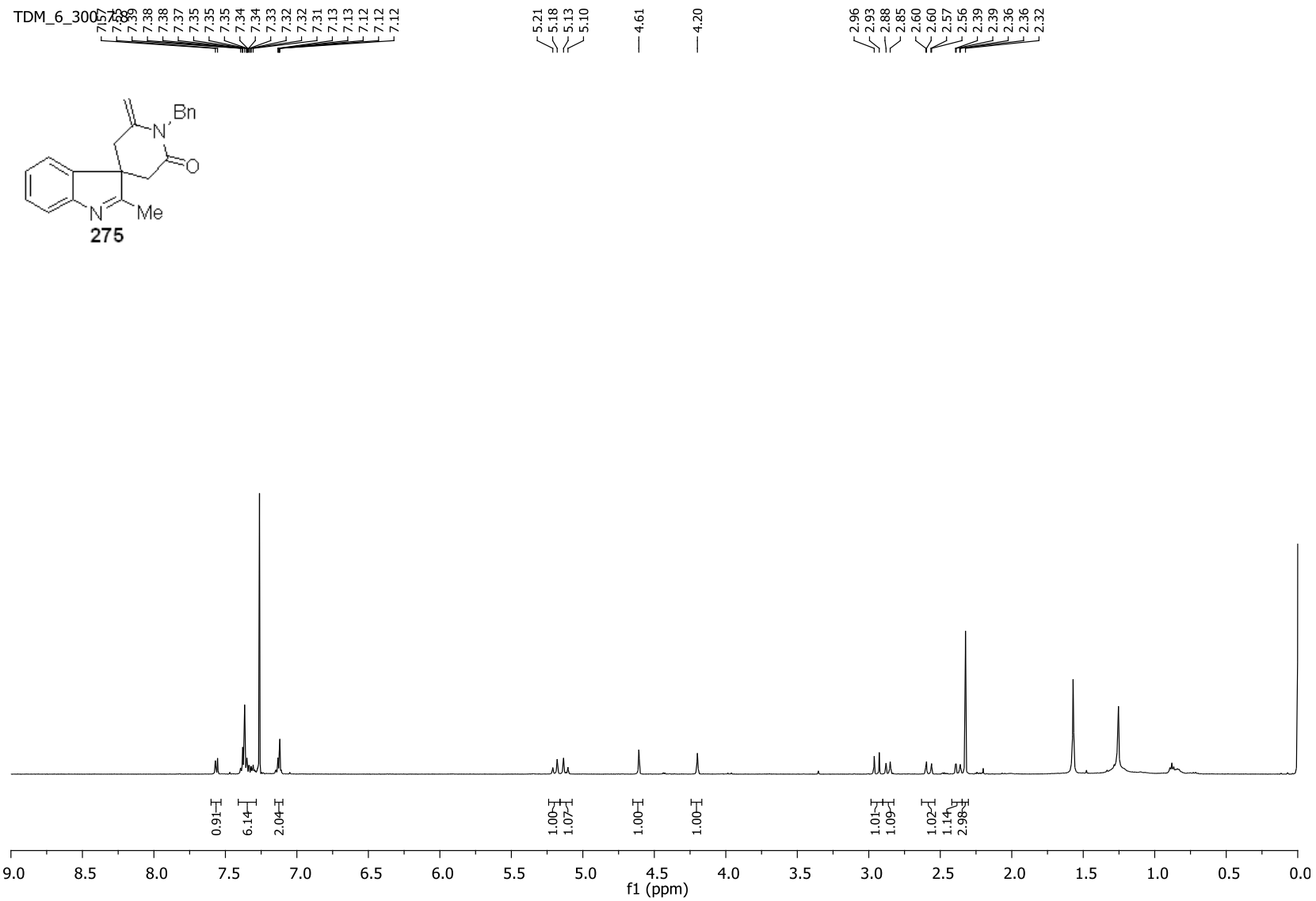


Figure 118. ^{1}H NMR Spectrum for **275** (500 MHz, $CDCl_3$)

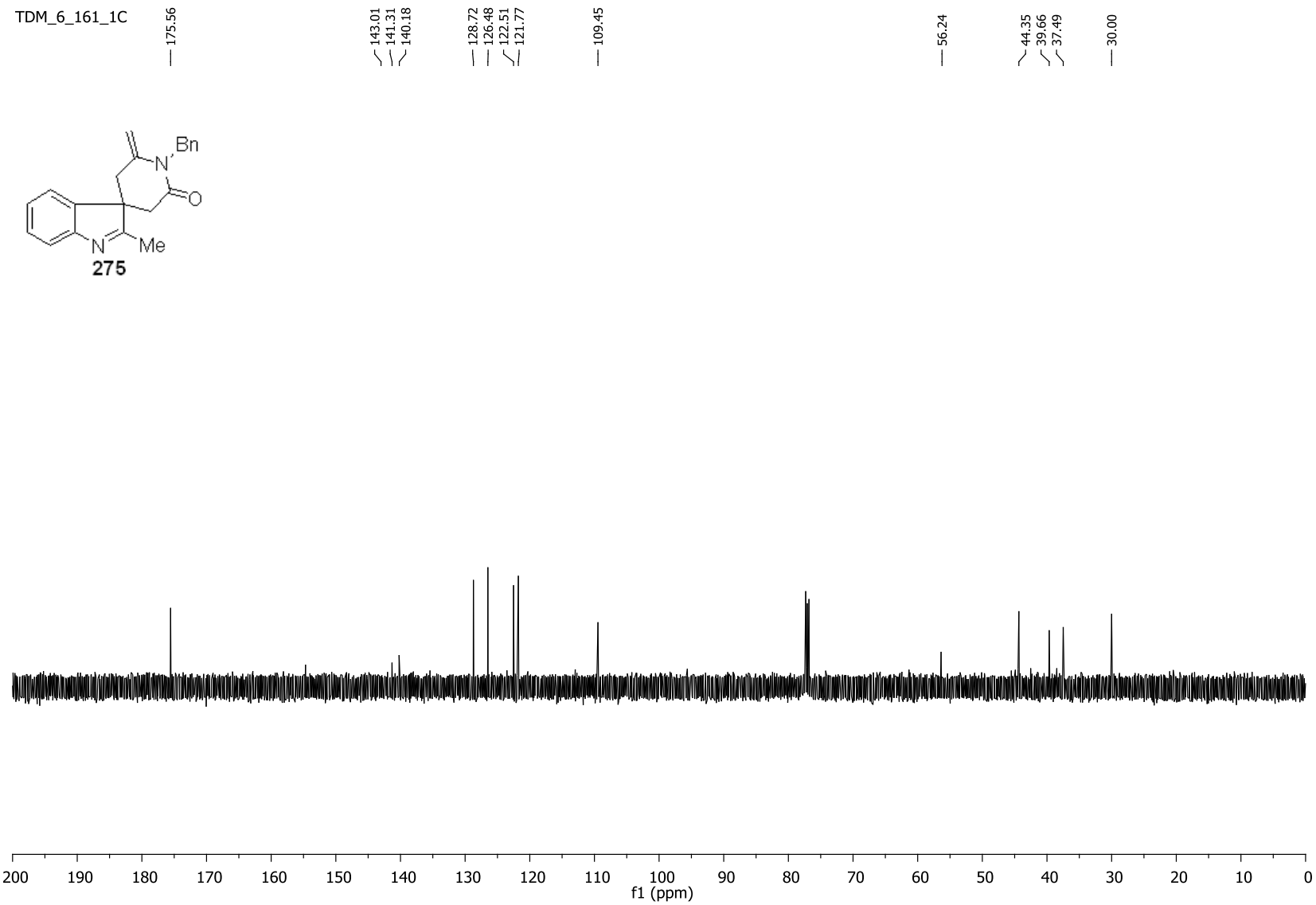


Figure 119. ^{13}C NMR Spectrum for **275** (125 MHz, $CDCl_3$)

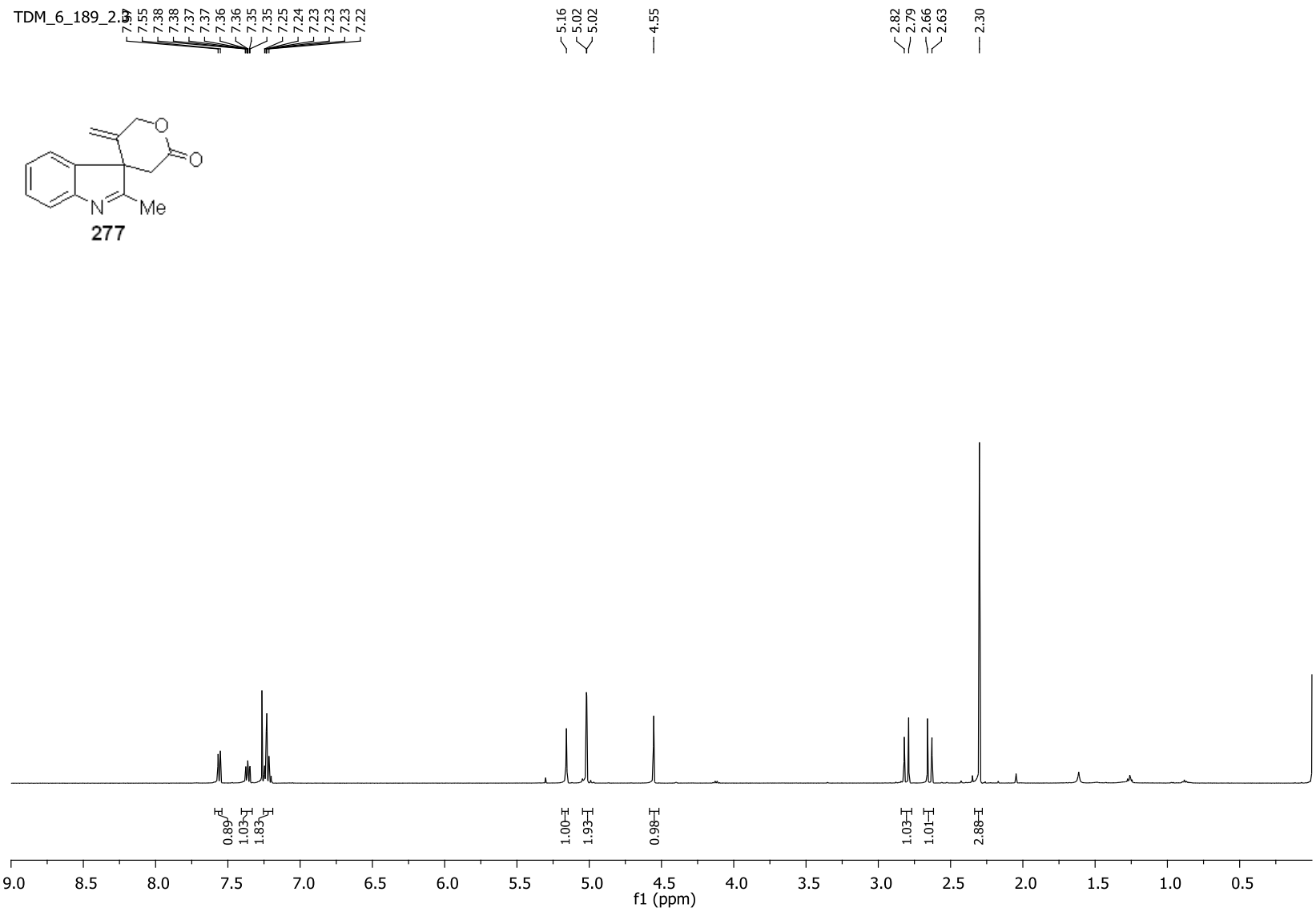


Figure 120. ^{1}H NMR Spectrum for **277** (500 MHz, $CDCl_3$)

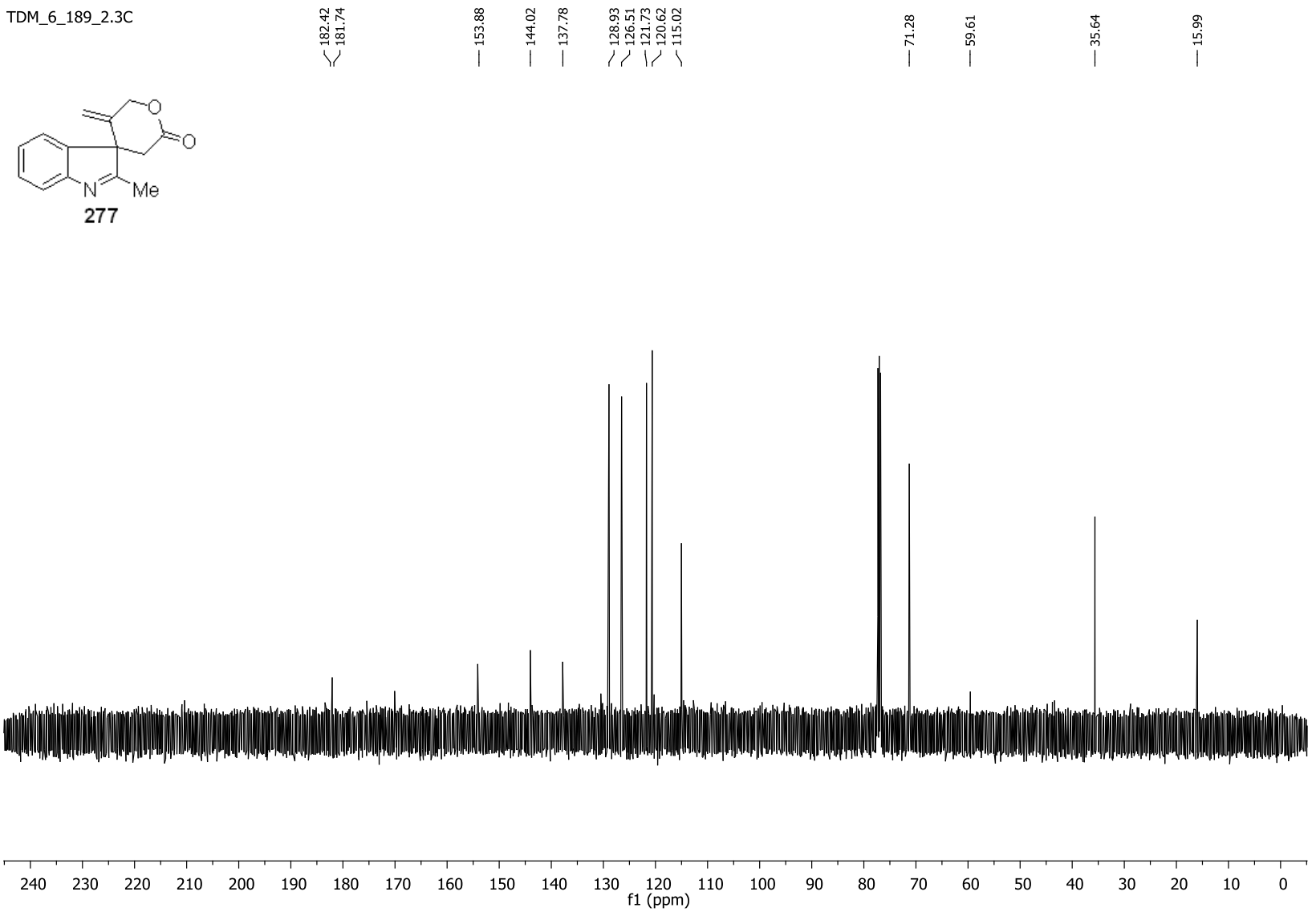


Figure 121. ^{13}C NMR Spectrum for **277** (125 MHz, $CDCl_3$)

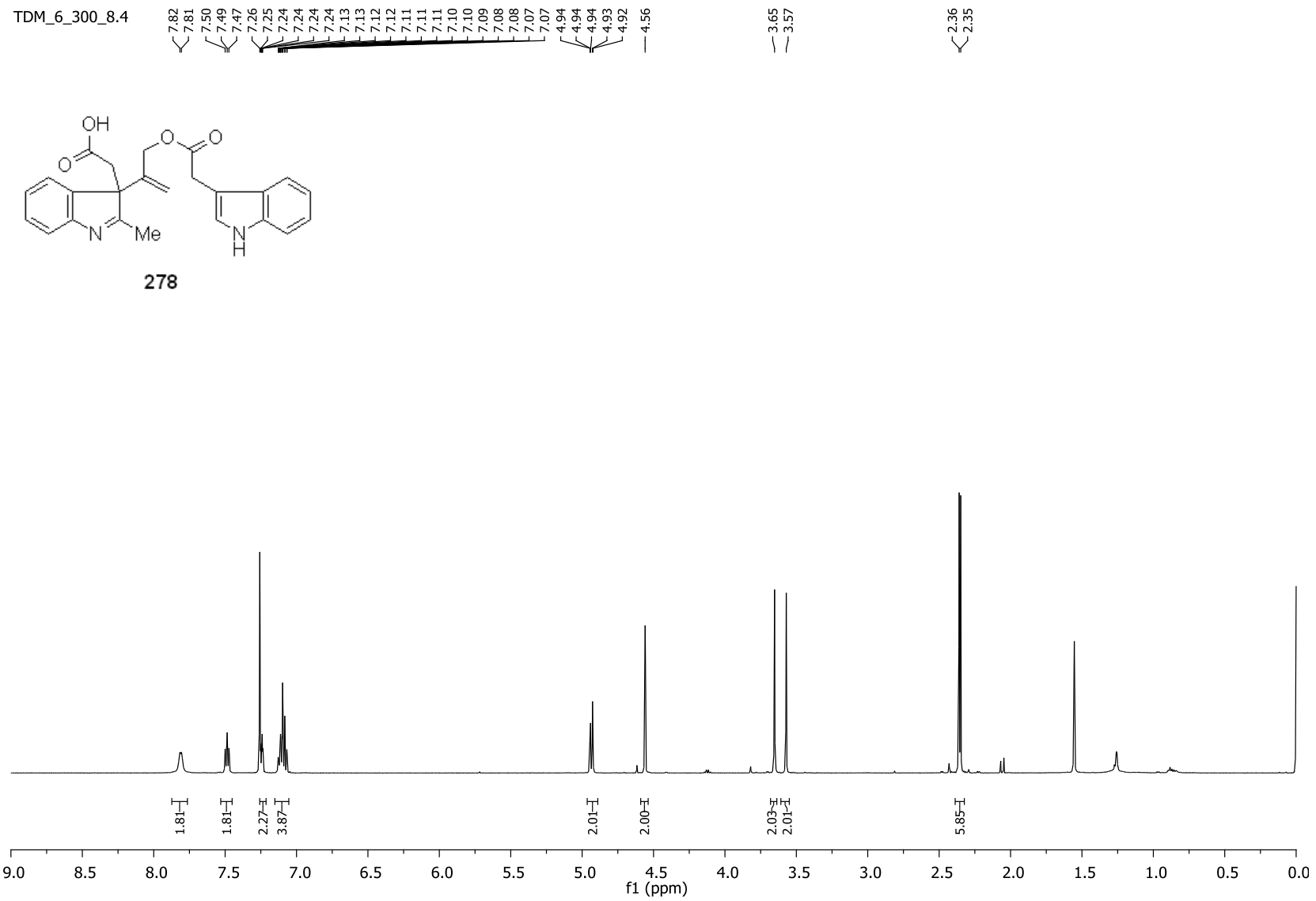


Figure 122. ^{1}H NMR Spectrum for **278** (500 MHz, $CDCl_3$)

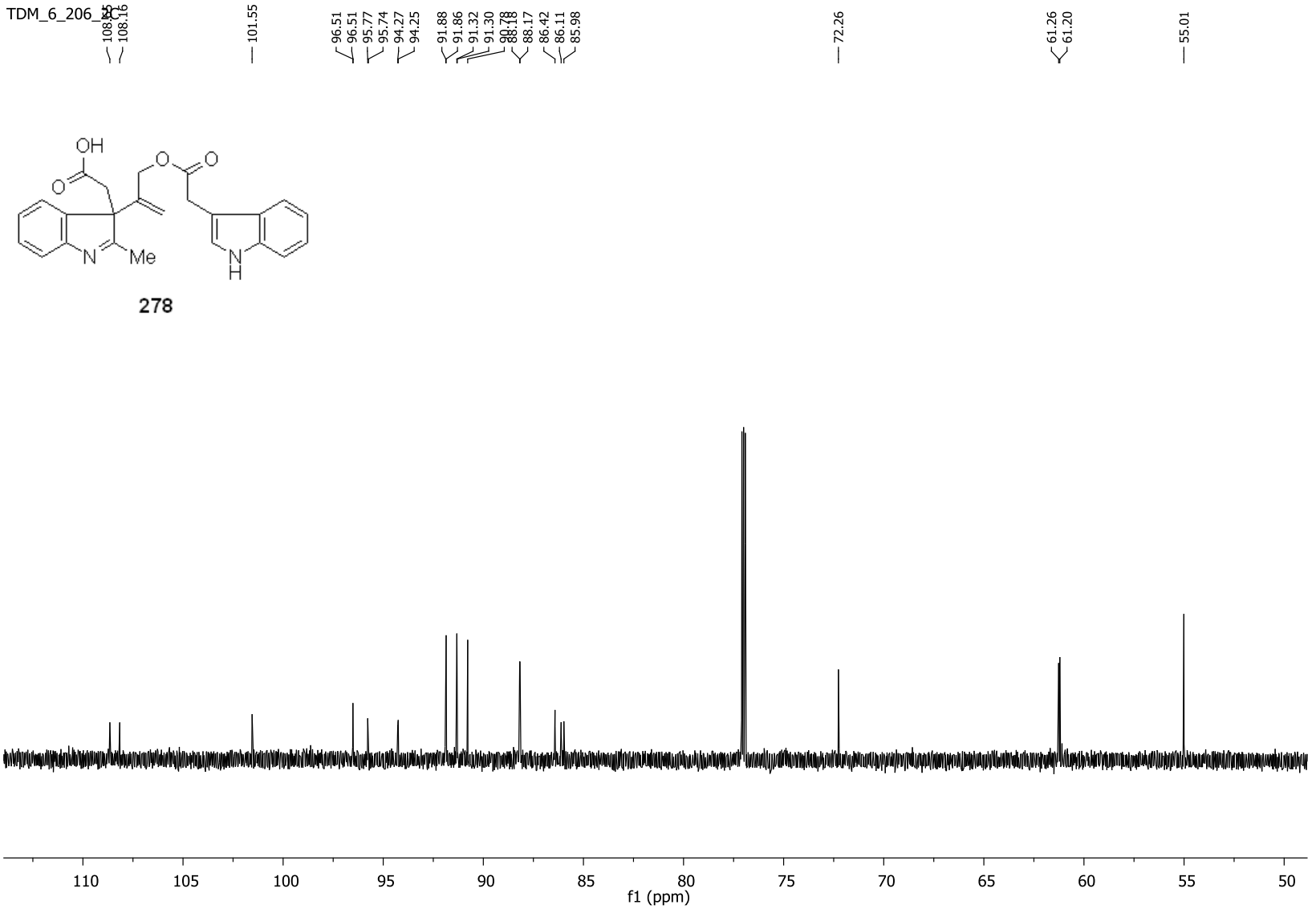


Figure 123. ^{13}C NMR Spectrum for **278** (125 MHz, $CDCl_3$)

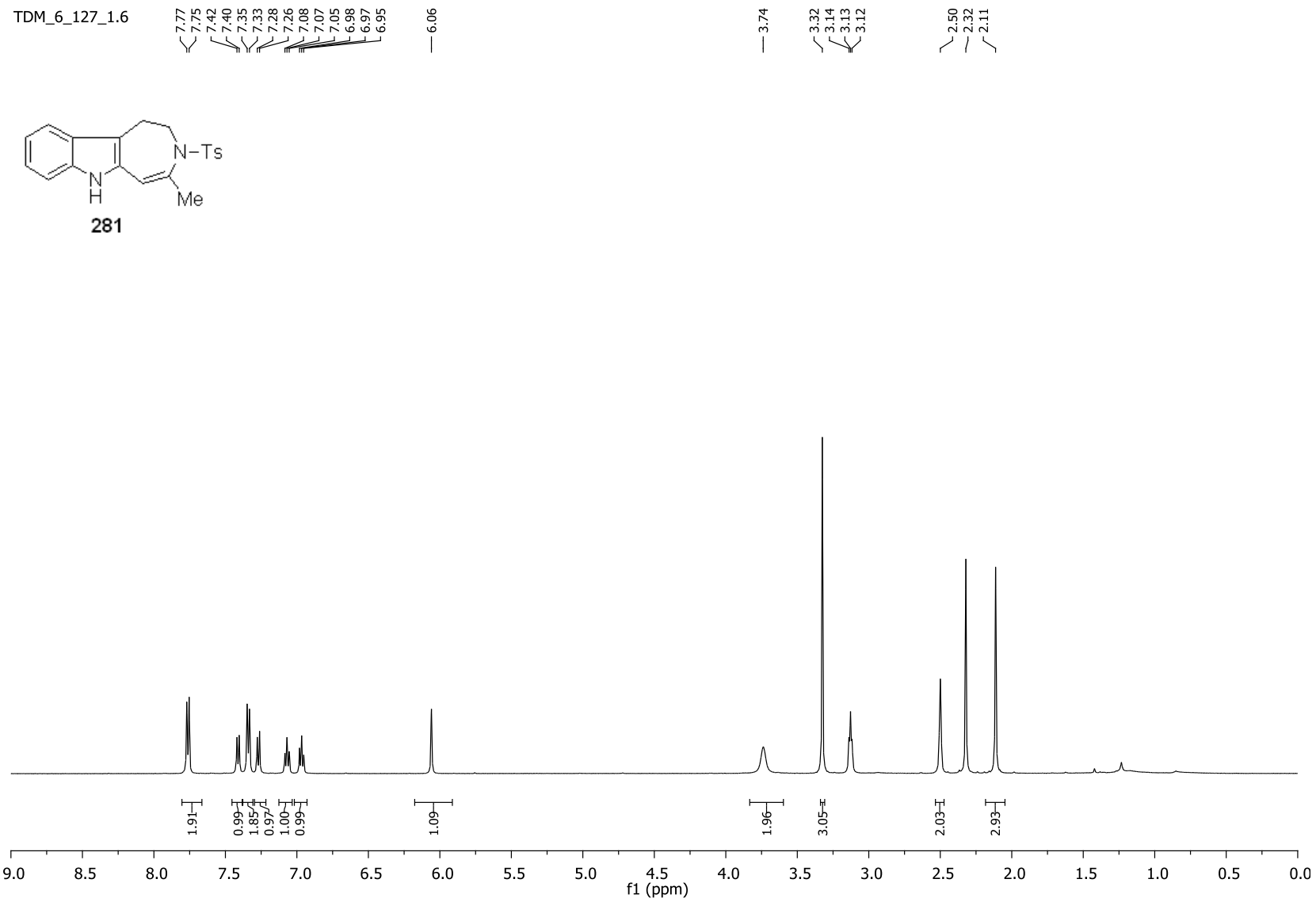


Figure 124. ^{1}H NMR Spectrum for **281** (500 MHz, $CDCl_3$)

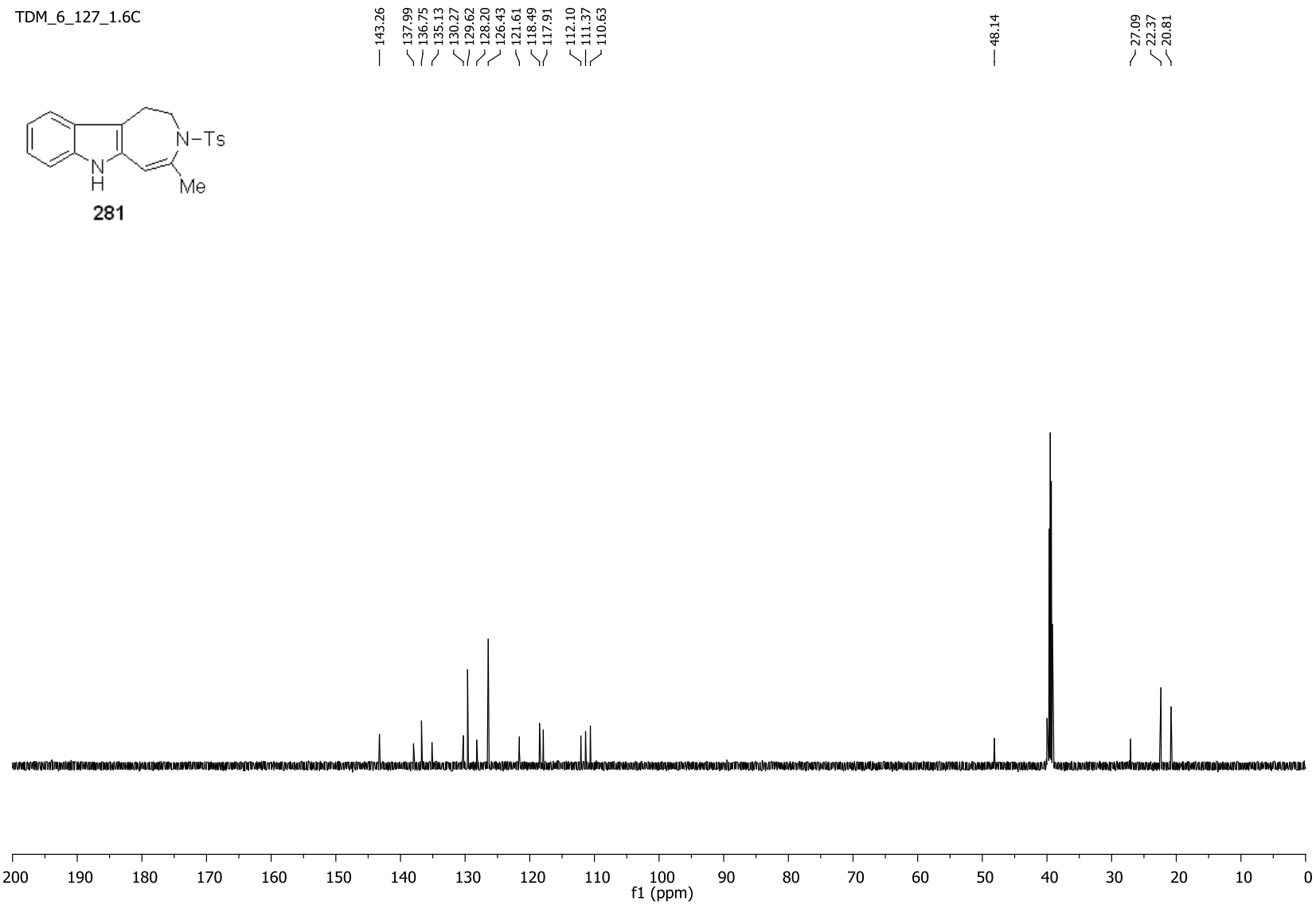


Figure 125. ^{13}C NMR Spectrum for **281** (125 MHz, $CDCl_3$)

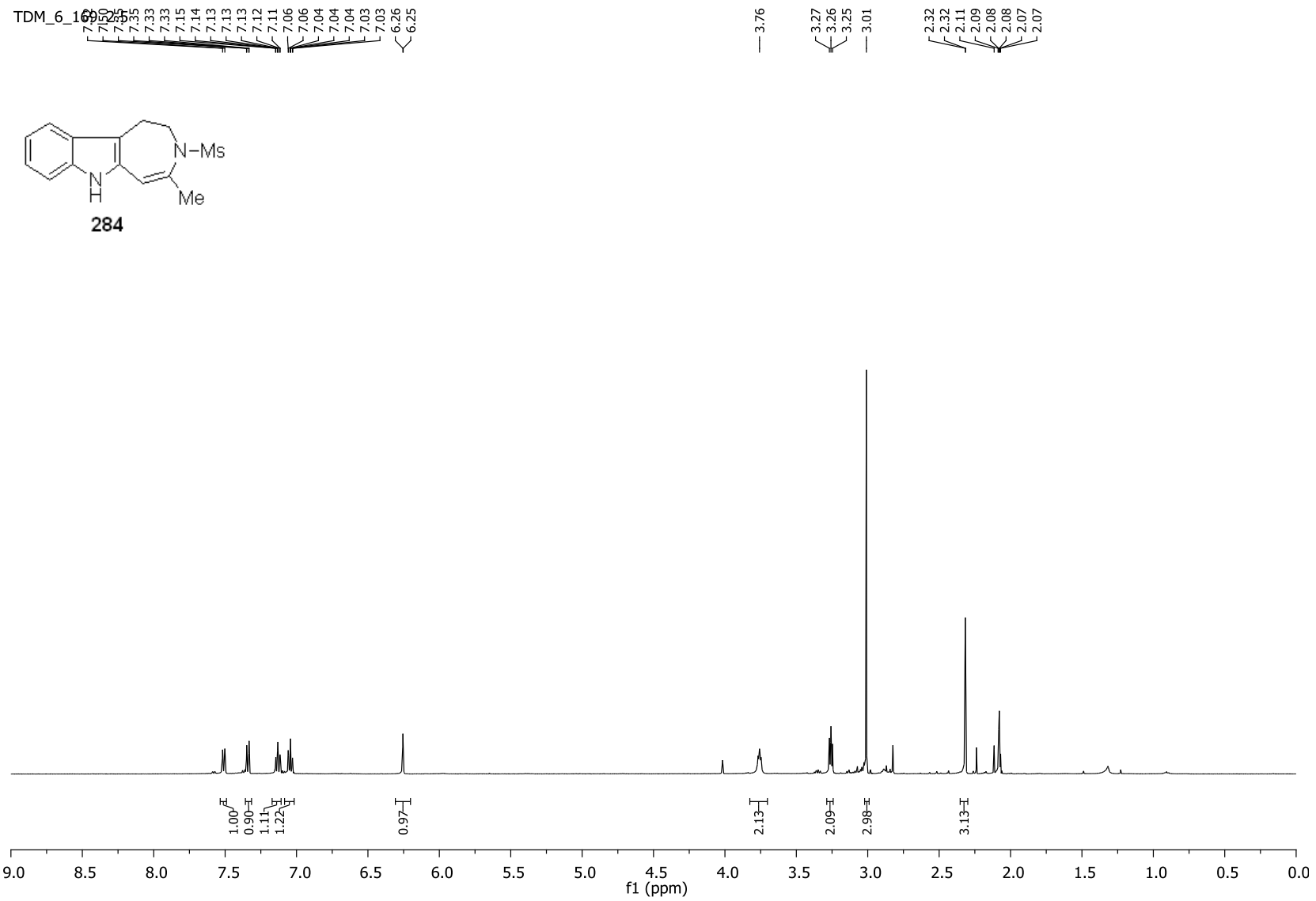


Figure 126. ^{1}H NMR Spectrum for **284** (500 MHz, $CDCl_3$)

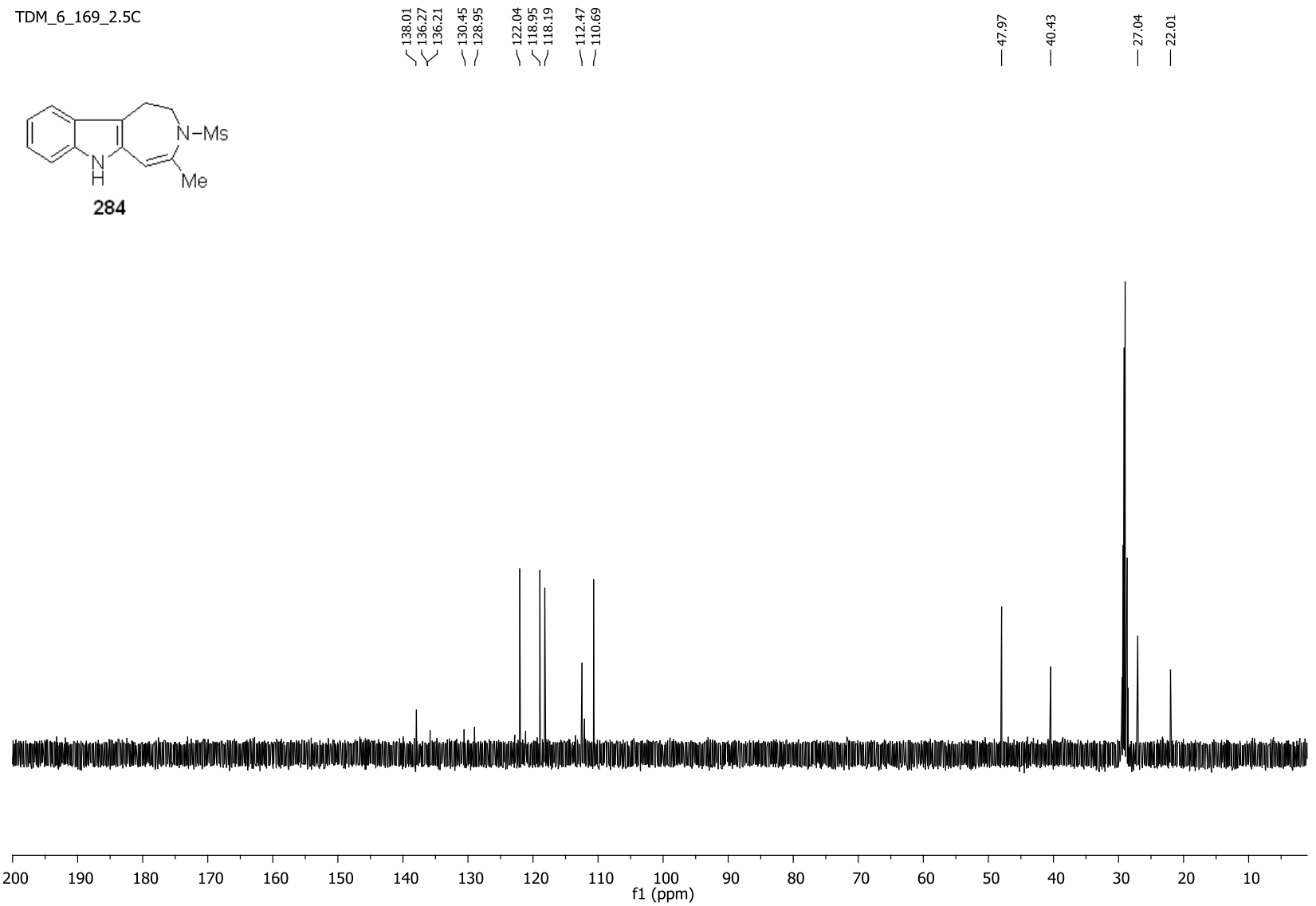


Figure 127. ^{13}C NMR Spectrum for **284** (125 MHz, $CDCl_3$)

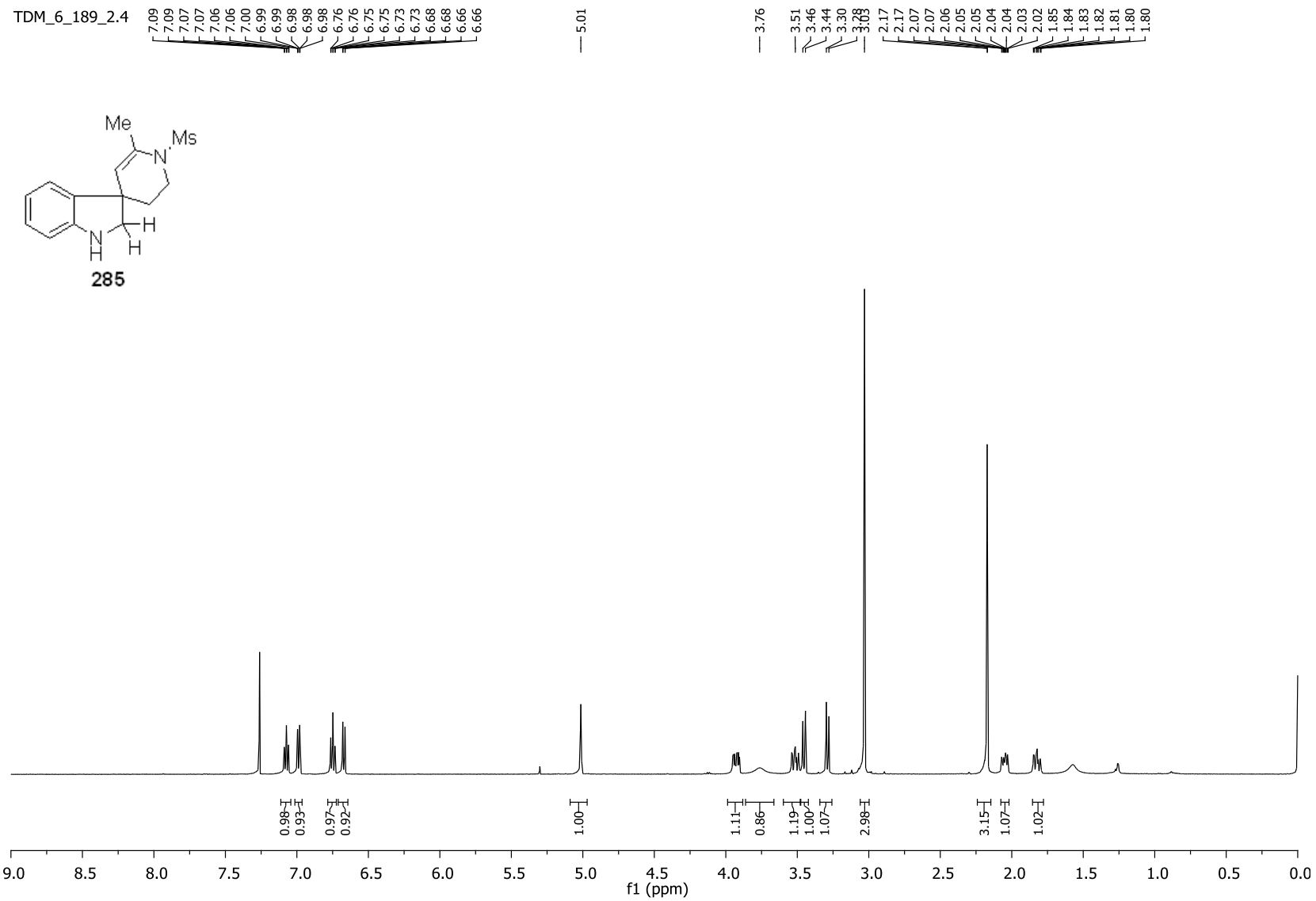


Figure 128. ^{1}H NMR Spectrum for **285** (500 MHz, $CDCl_3$)

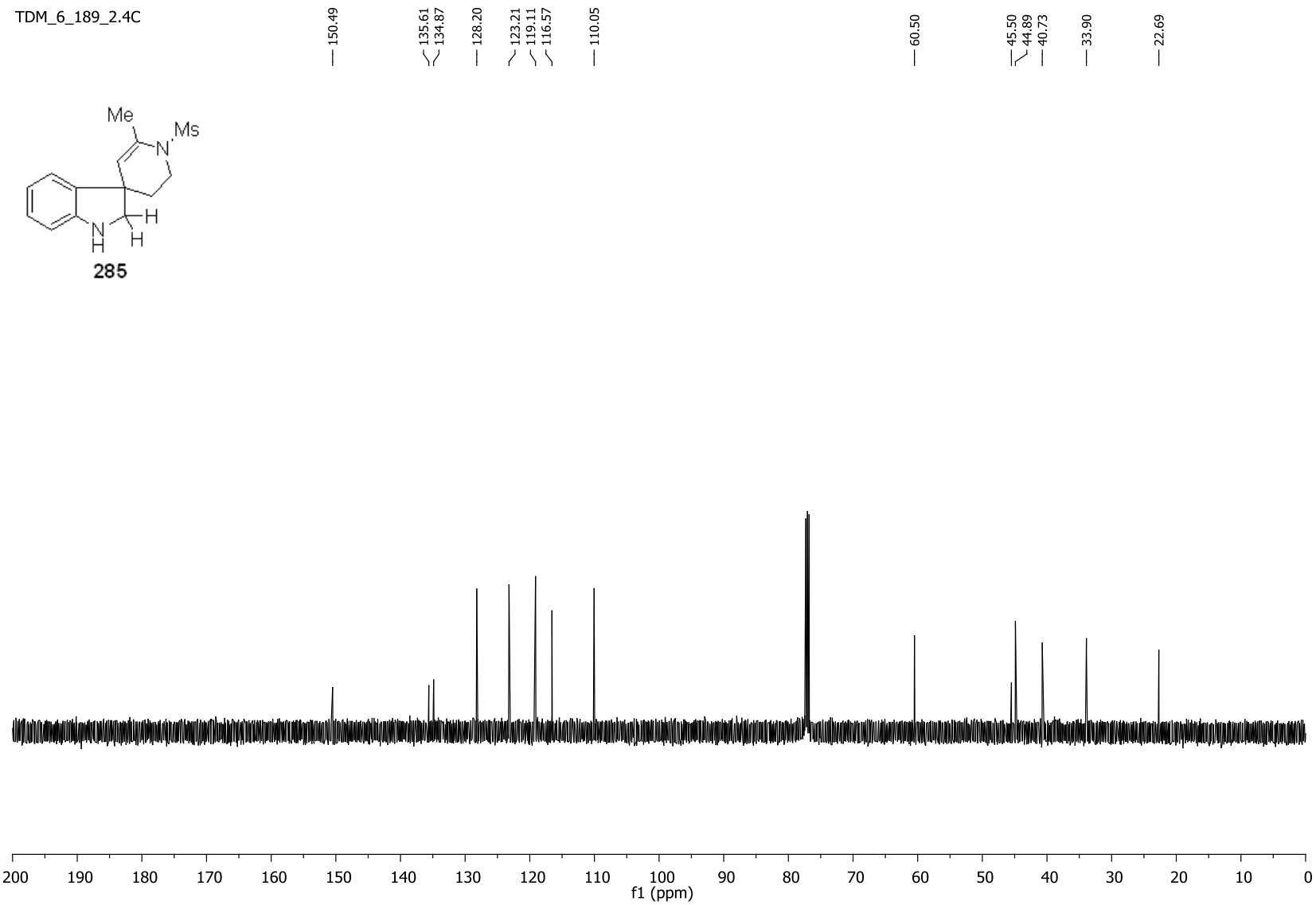


Figure 129. ^{13}C NMR Spectrum for **285** (125 MHz, $CDCl_3$)

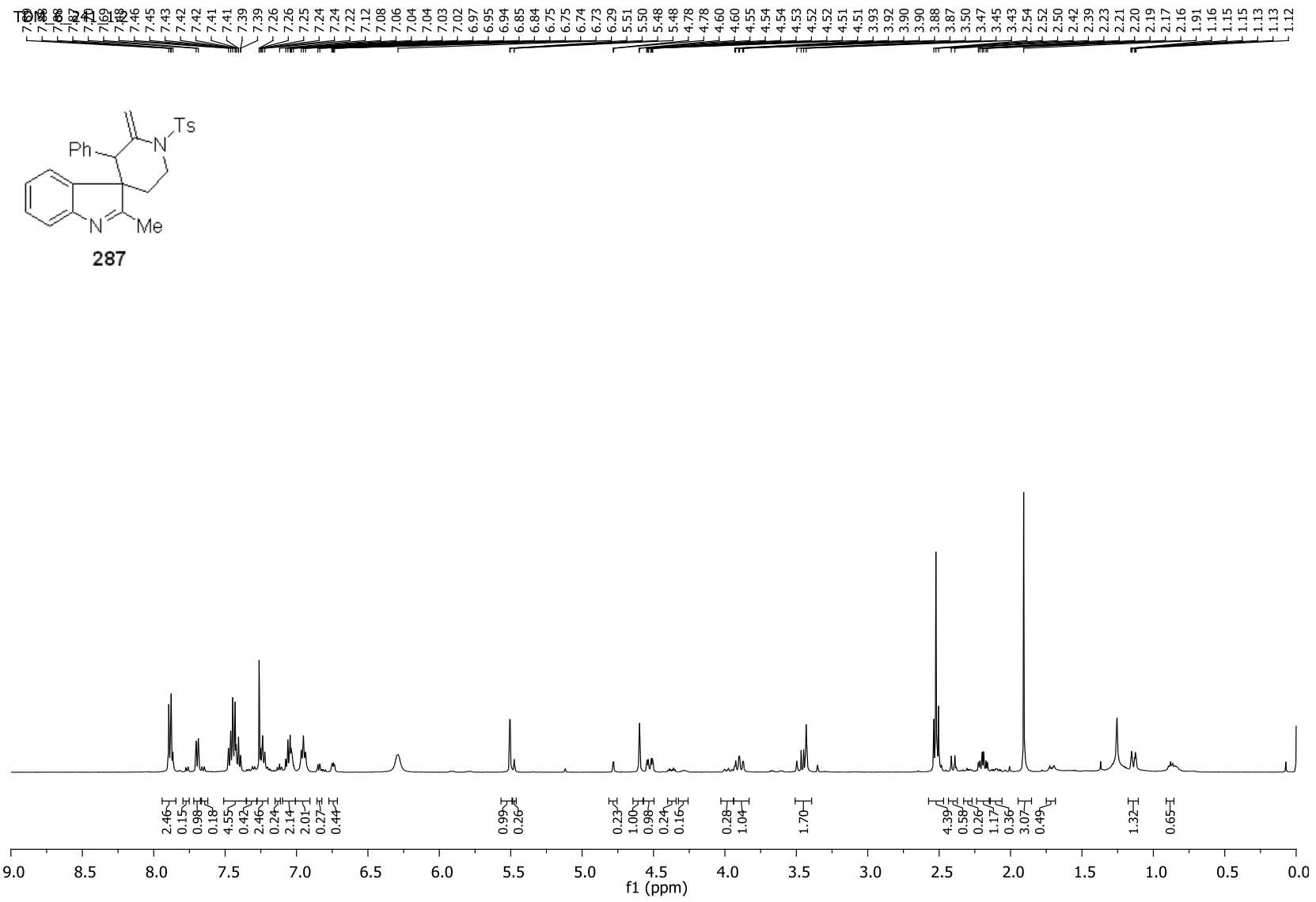


Figure 130. ^{1}H NMR Spectrum for **287** (500 MHz, $CDCl_3$)

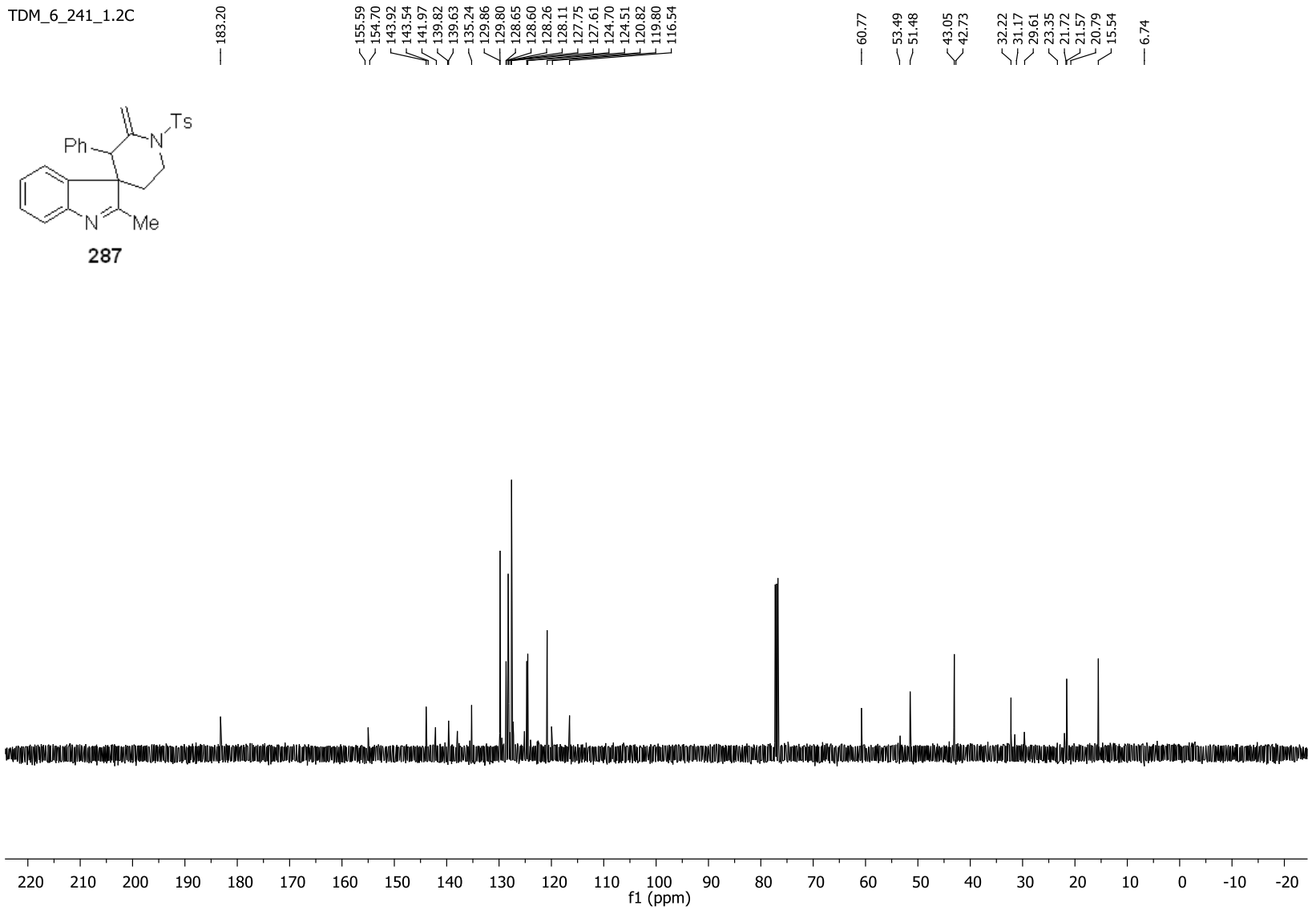


Figure 131. ^{13}C NMR Spectrum for **287** (125 MHz, $CDCl_3$)

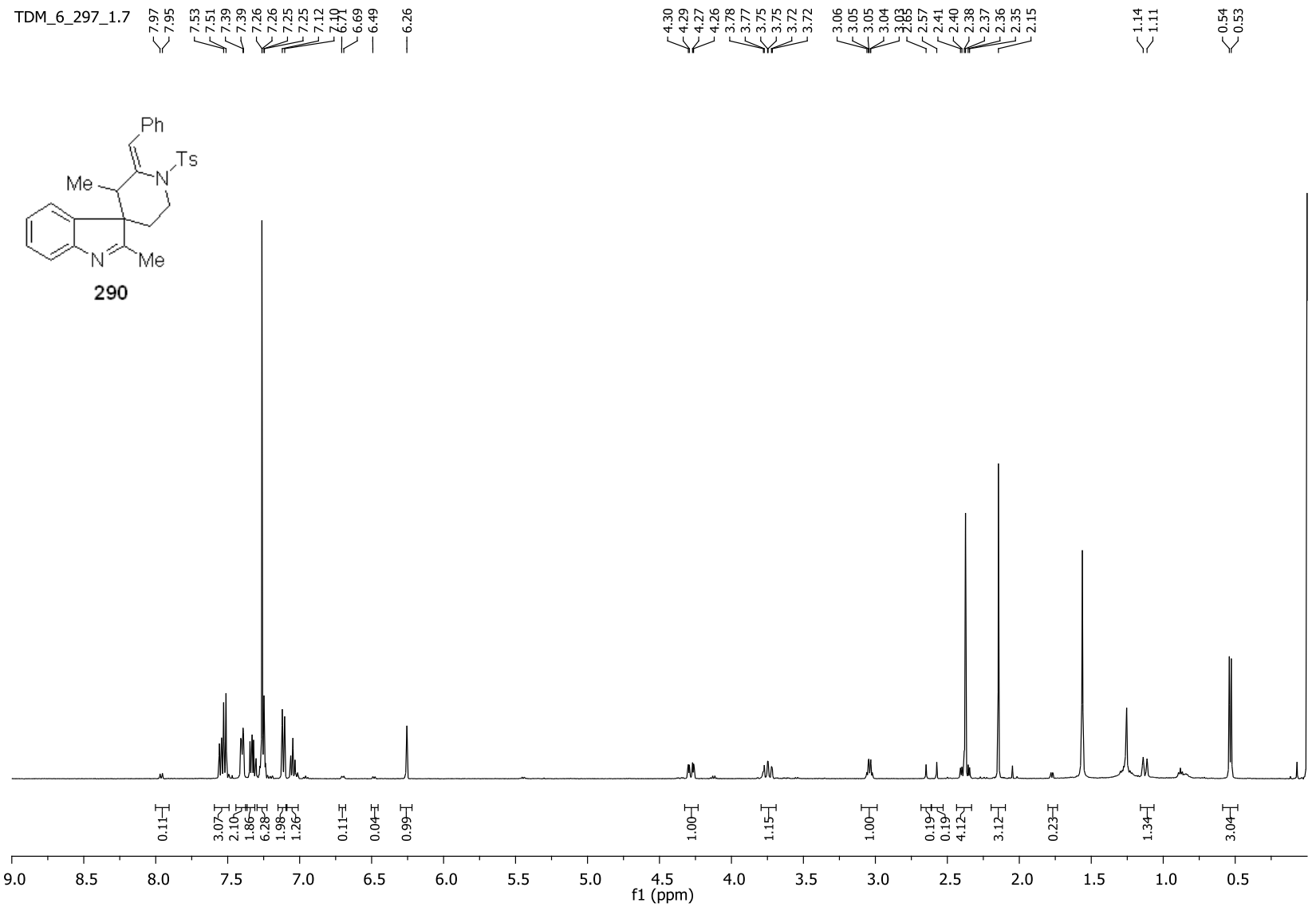


Figure 132. ^{1}H NMR Spectrum for **290** (500 MHz, $CDCl_3$)

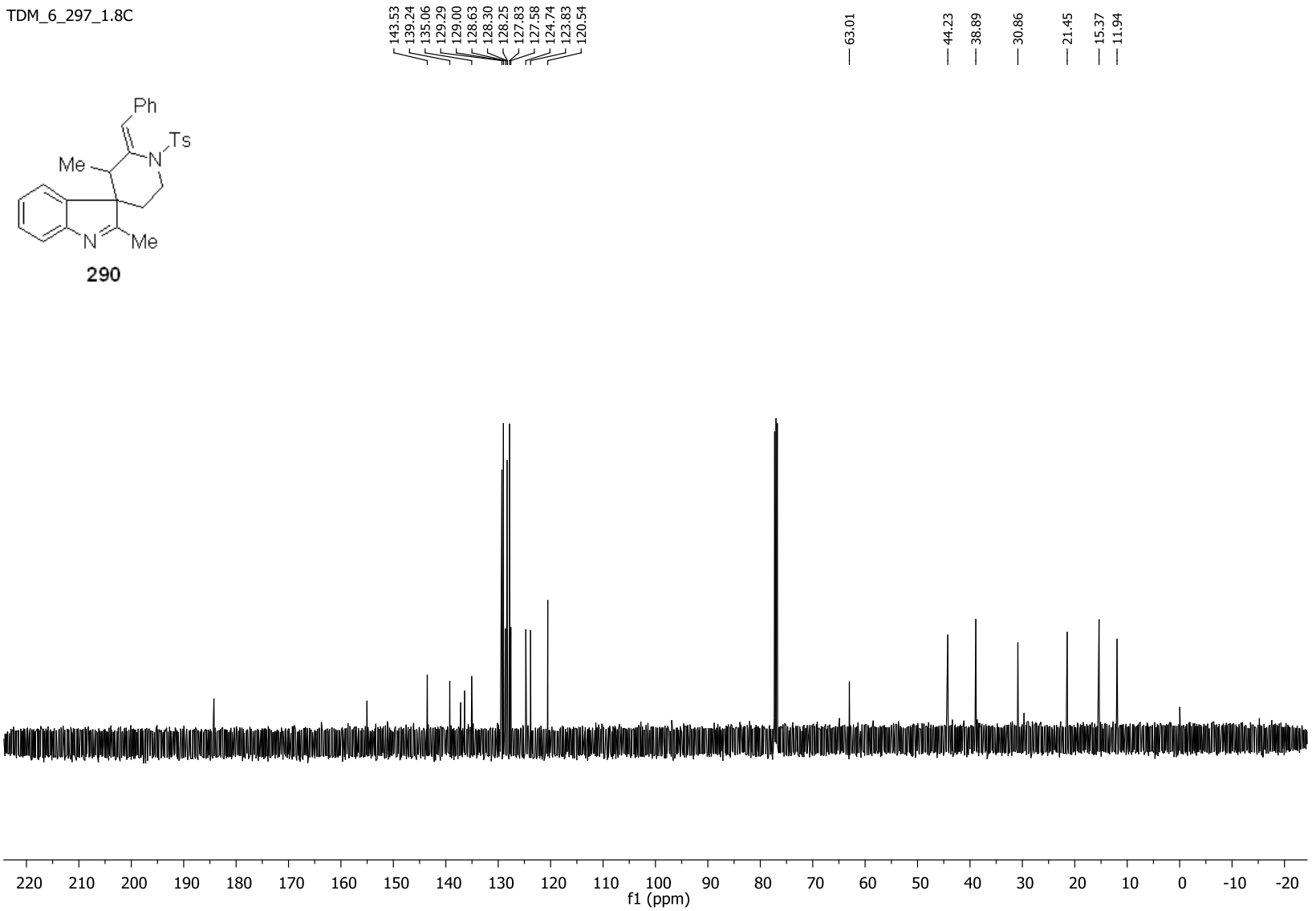
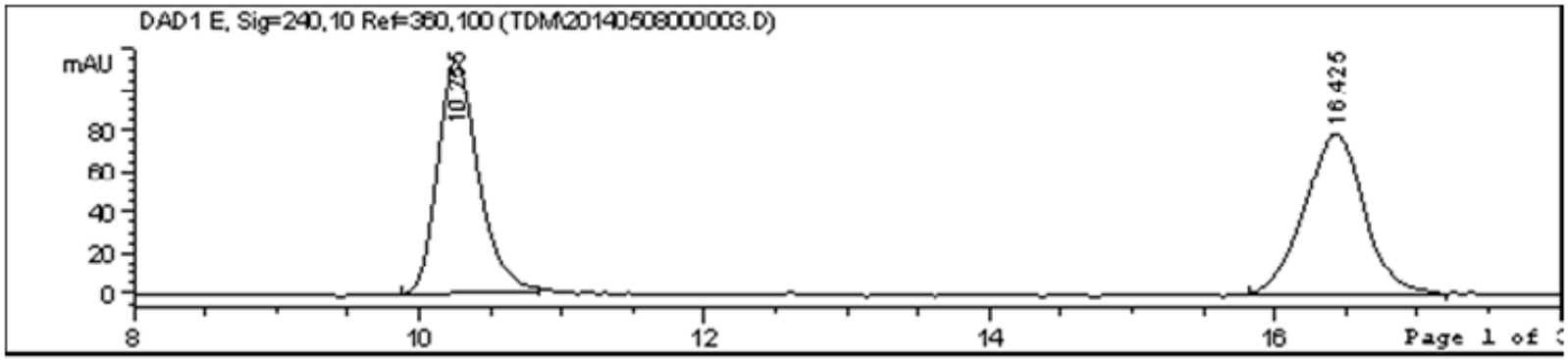


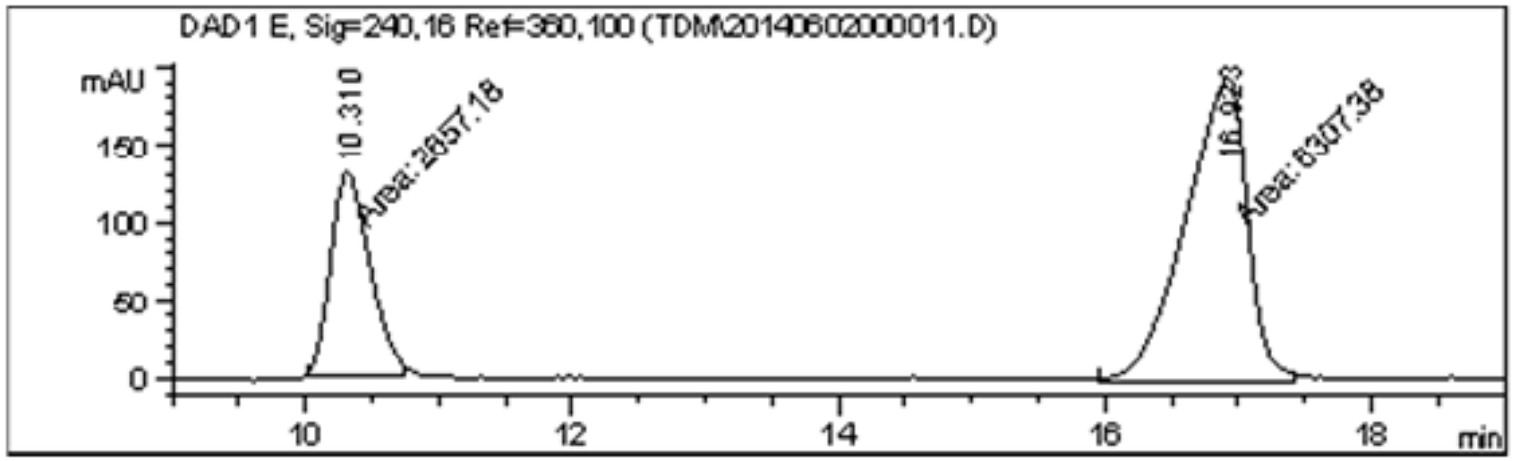
Figure 133. ^{13}C NMR Spectrum for **290** (125 MHz, $CDCl_3$)



Signal 5: DAD1 E, Sig=240,10 Ref=360,100

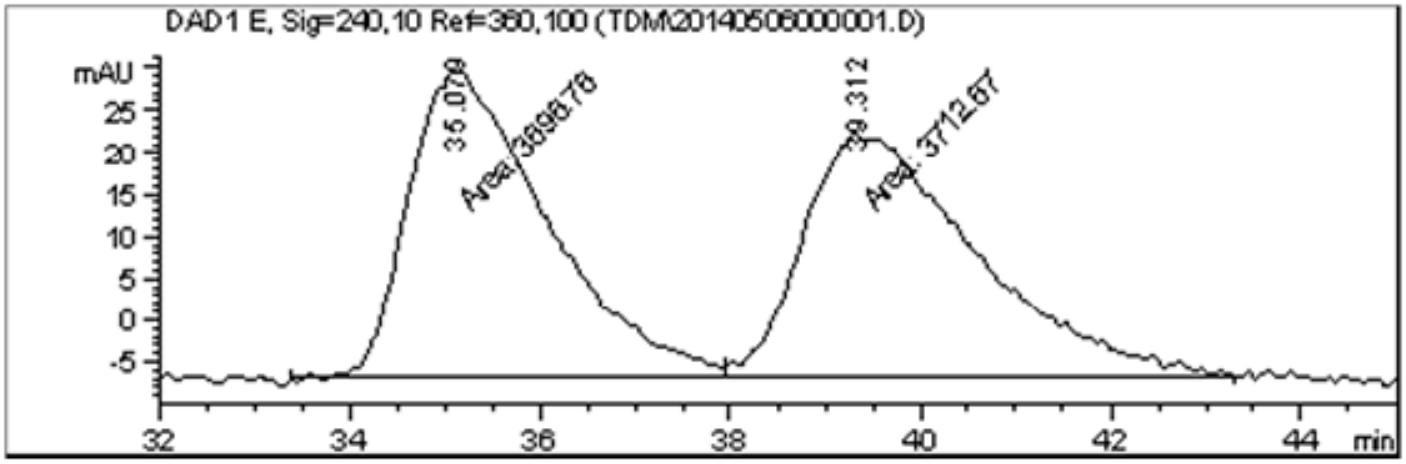
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.255	BB	0.3072	2271.97729	114.67167	49.6920
2	16.425	BB	0.4150	2300.13696	79.15520	50.3080

Figure 134. HPLC of **258** (Chiralpak AD-H)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.310	MM	0.3410	2657.17993	129.88083	29.6409
2	16.923	MM	0.5367	6307.37891	195.87837	70.3591

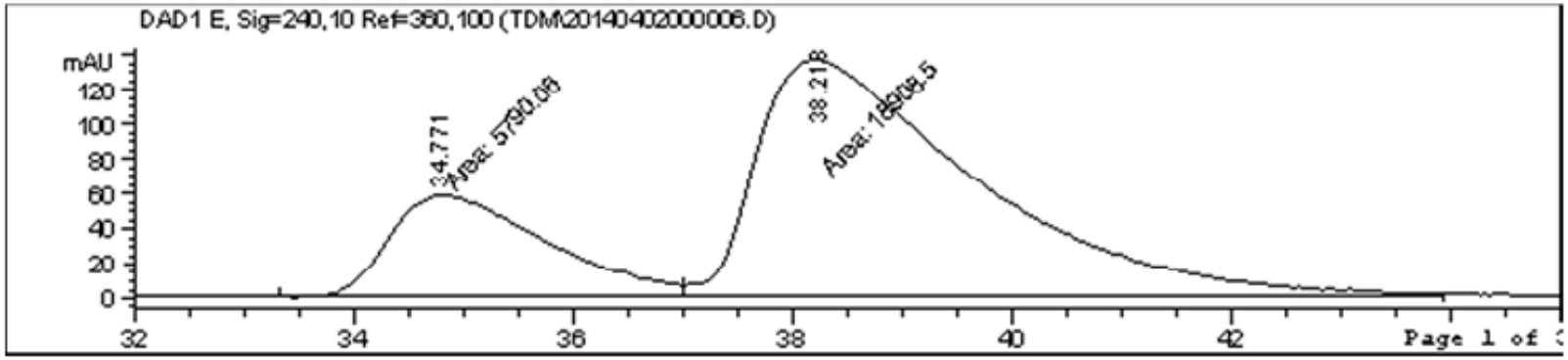
Figure 135. HPLC of **258** (Chiralpak AD-H)



Signal 5: DAD1 E, Sig=240,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.079	MF	1.6935	3696.75977	36.38289	49.8926
2	39.312	FM	2.1189	3712.66992	29.20232	50.1074

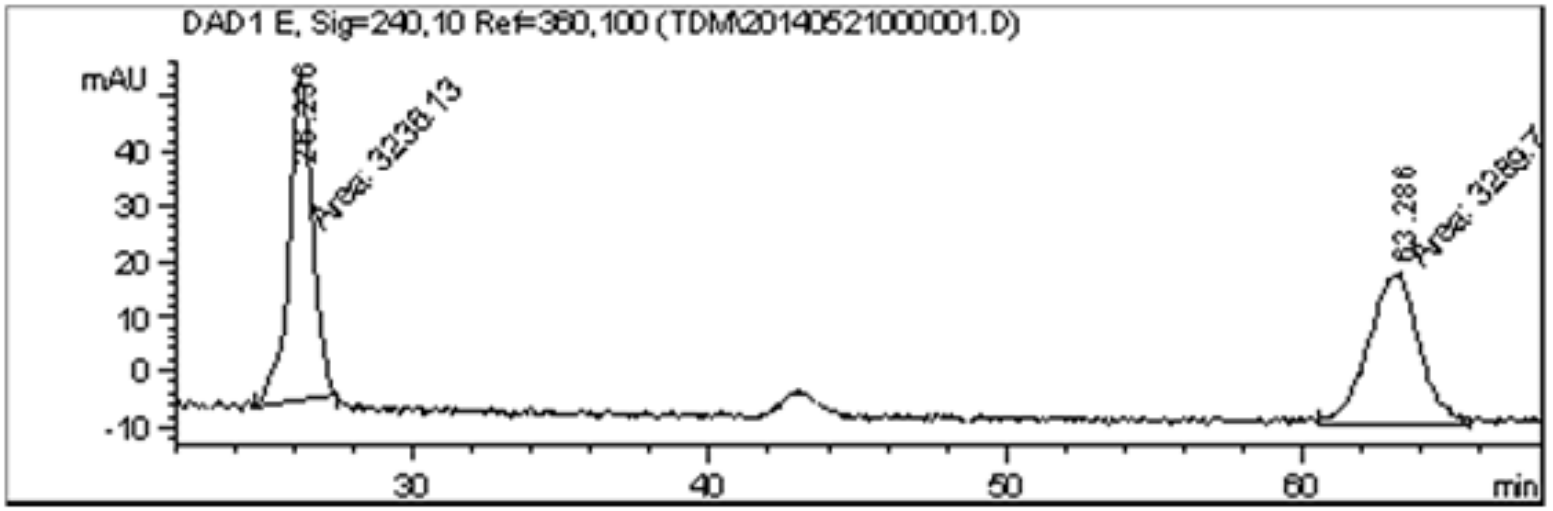
Figure 136. HPLC of **265** (Chiralpak OD-H)



Signal 5: DAD1 E, Sig=240,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.771	MF	1.6724	5790.05664	57.70059	23.4429
2	38.218	FM	2.3036	1.89085e4	136.80405	76.5571

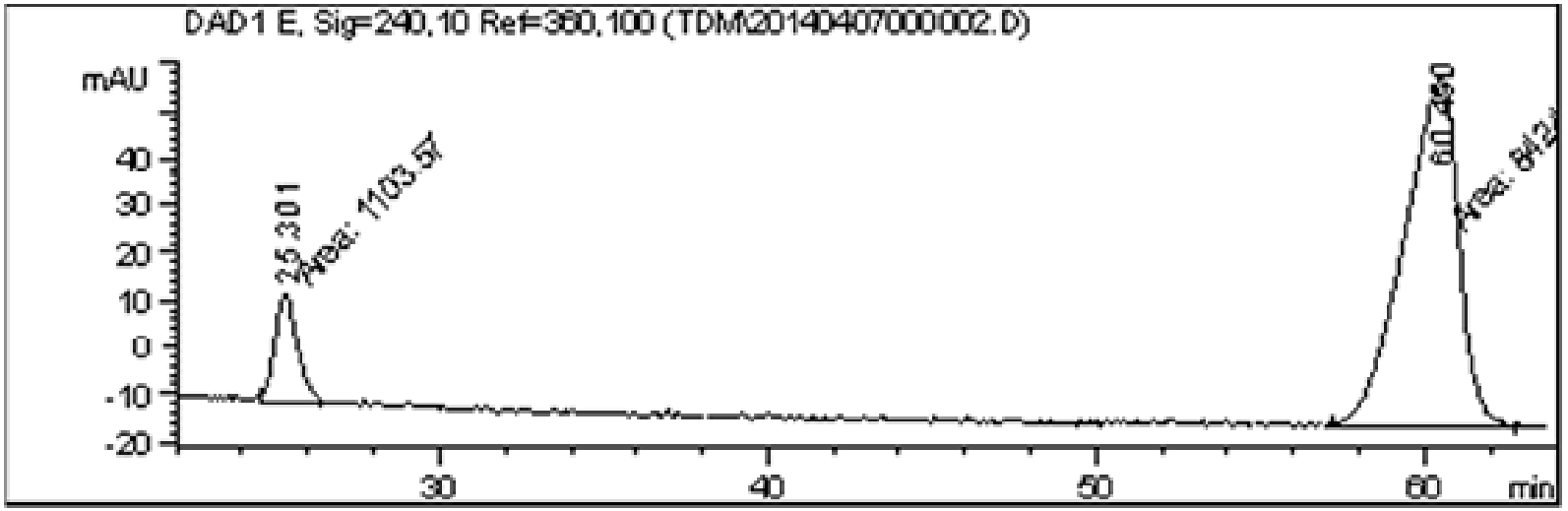
Figure 137. HPLC of **265** (Chiralpak OD-H)



Signal 5: DAD1 E, Sig=240,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.236	MM	0.9222	3236.12939	58.48884	49.5892
2	63.286	MM	1.9968	3289.74219	27.45779	50.4108

Figure 138. HPLC of **267** (Chiralpak AD-H)



Signal 5: DAD1 E, Sig=240,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.301	MM	0.7923	1103.57019	23.21464	11.5823
2	60.450	MM	1.9139	8424.49219	73.36197	88.4177

Figure 139. HPLC of **267** (Chiralpak AD-H)

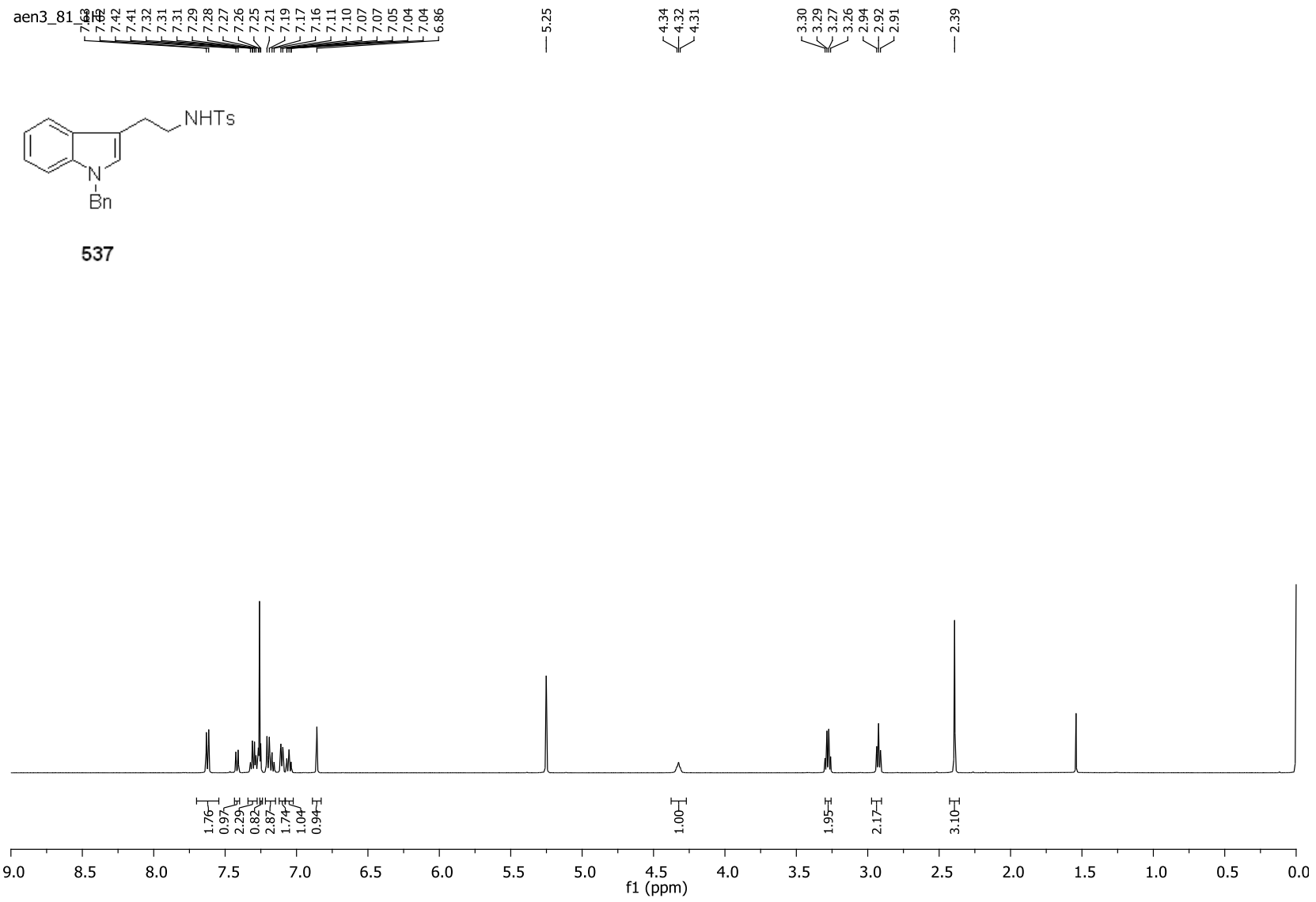


Figure 140. ^{1}H NMR Spectrum for **537** (500 MHz, $CDCl_3$)

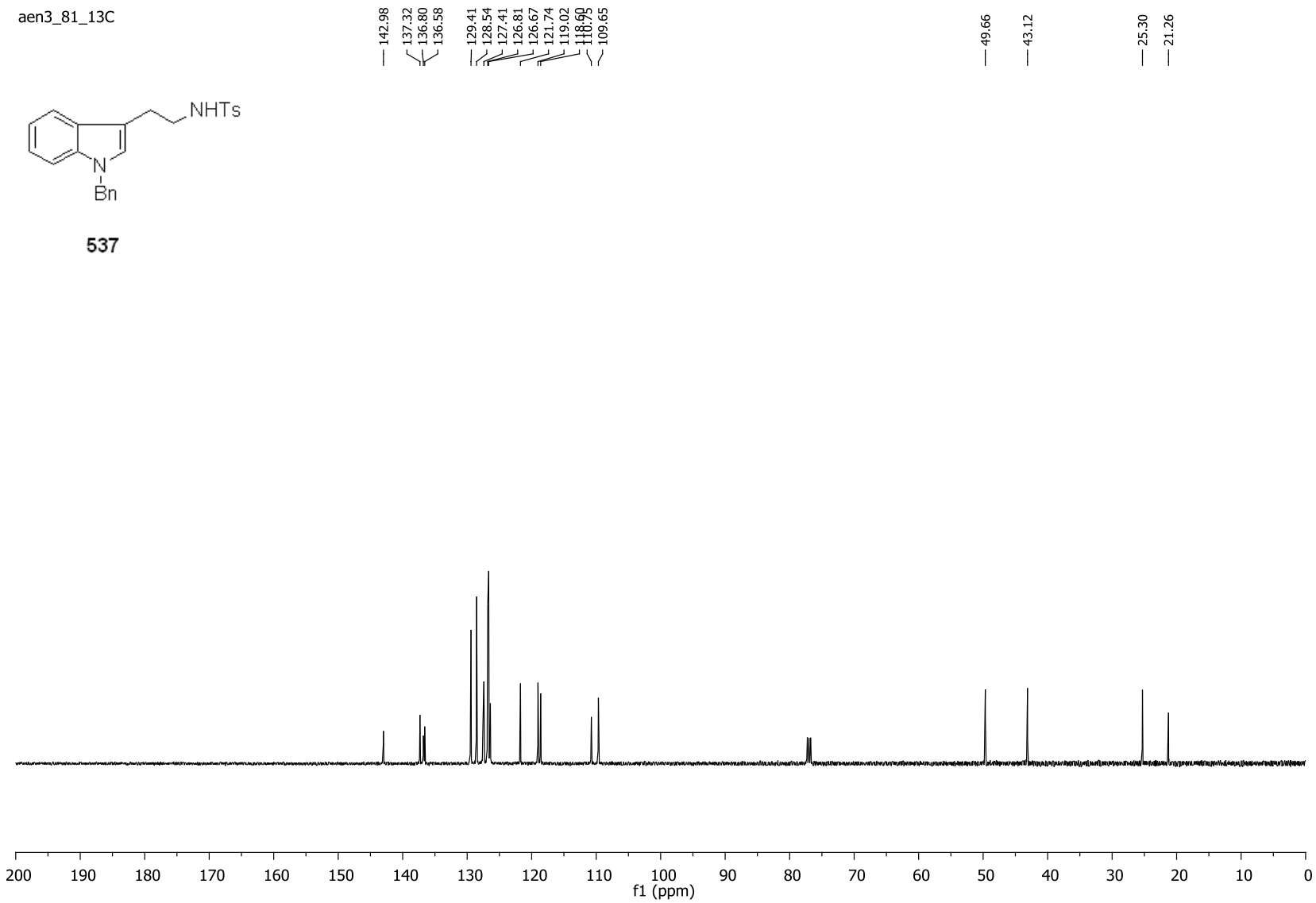


Figure 141. ^{13}C NMR Spectrum for **537** (125 MHz, $CDCl_3$)

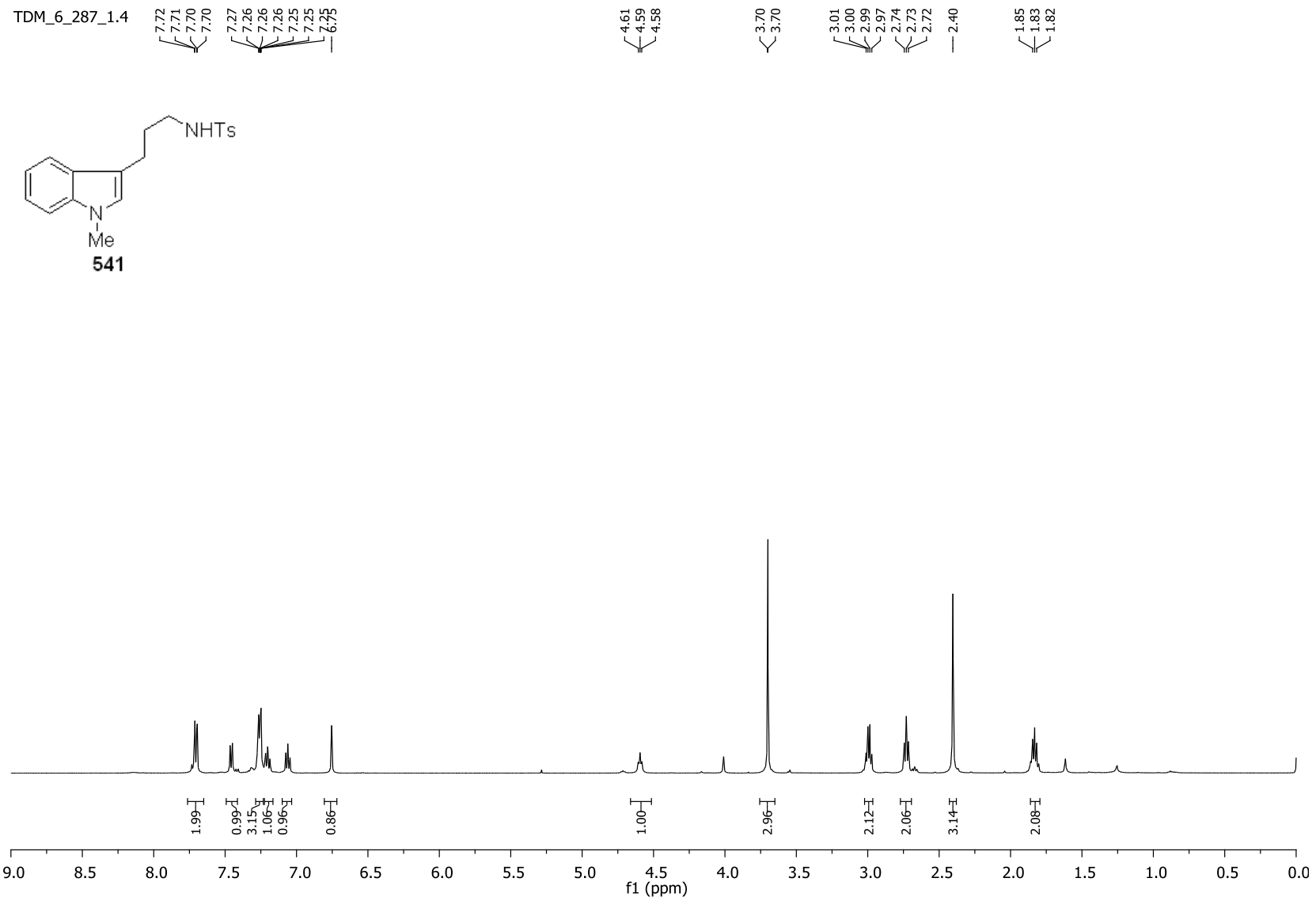


Figure 142. ^{1}H NMR Spectrum for **541** (500 MHz, $CDCl_3$)

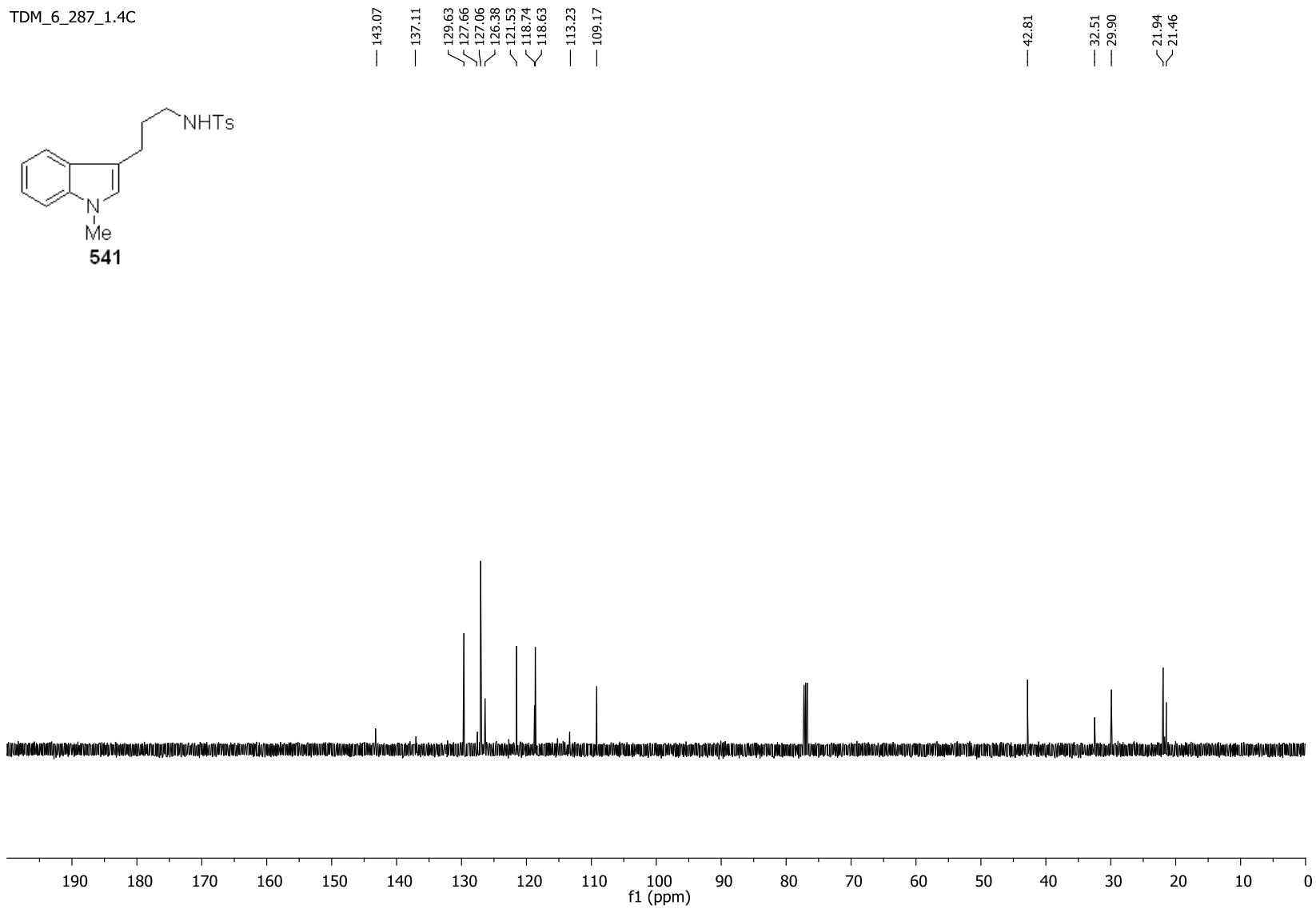


Figure 143. ^{13}C NMR Spectrum for **541** (125 MHz, $CDCl_3$)

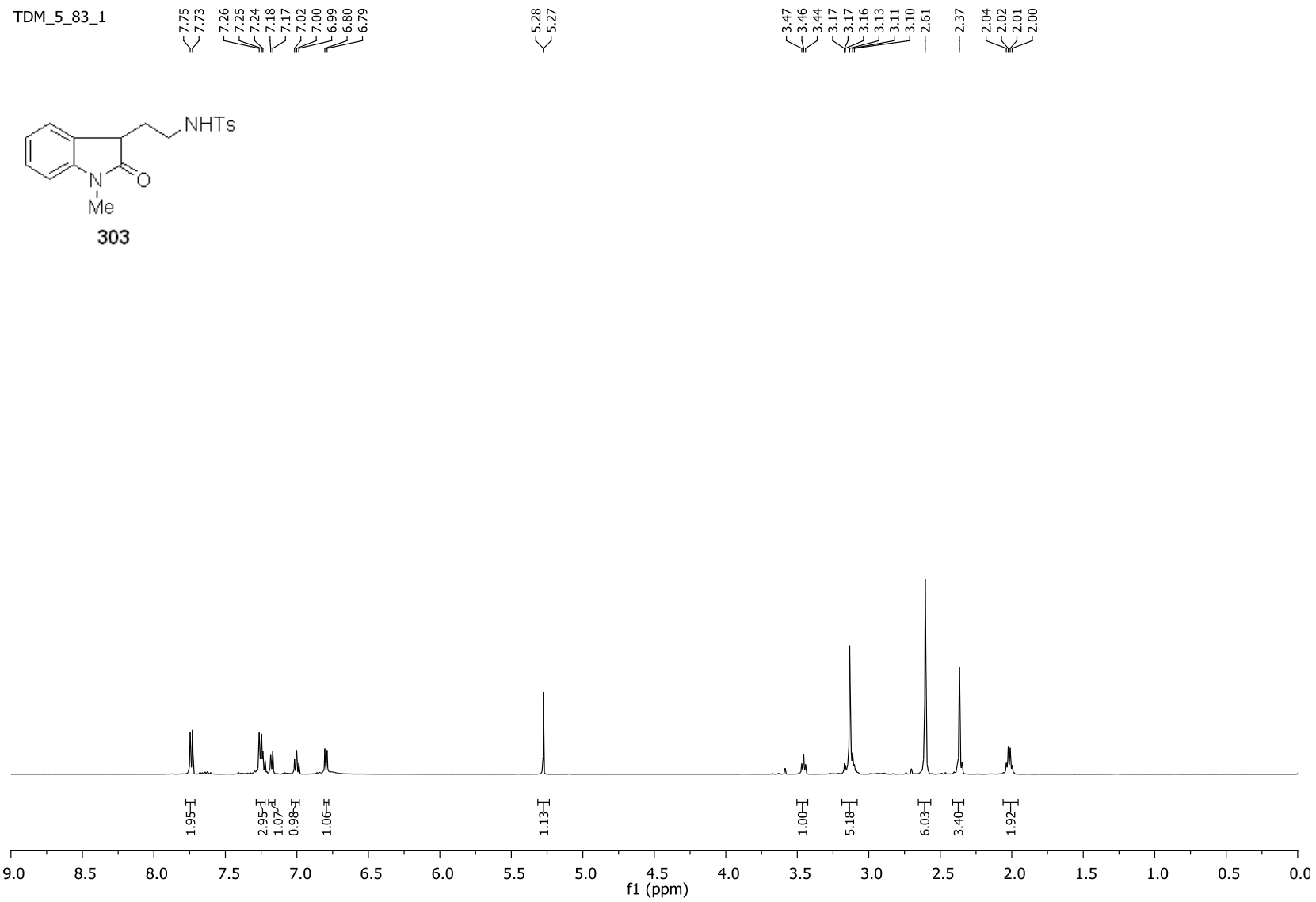


Figure 144. ^{1}H NMR Spectrum for **303** (500 MHz, $CDCl_3$)

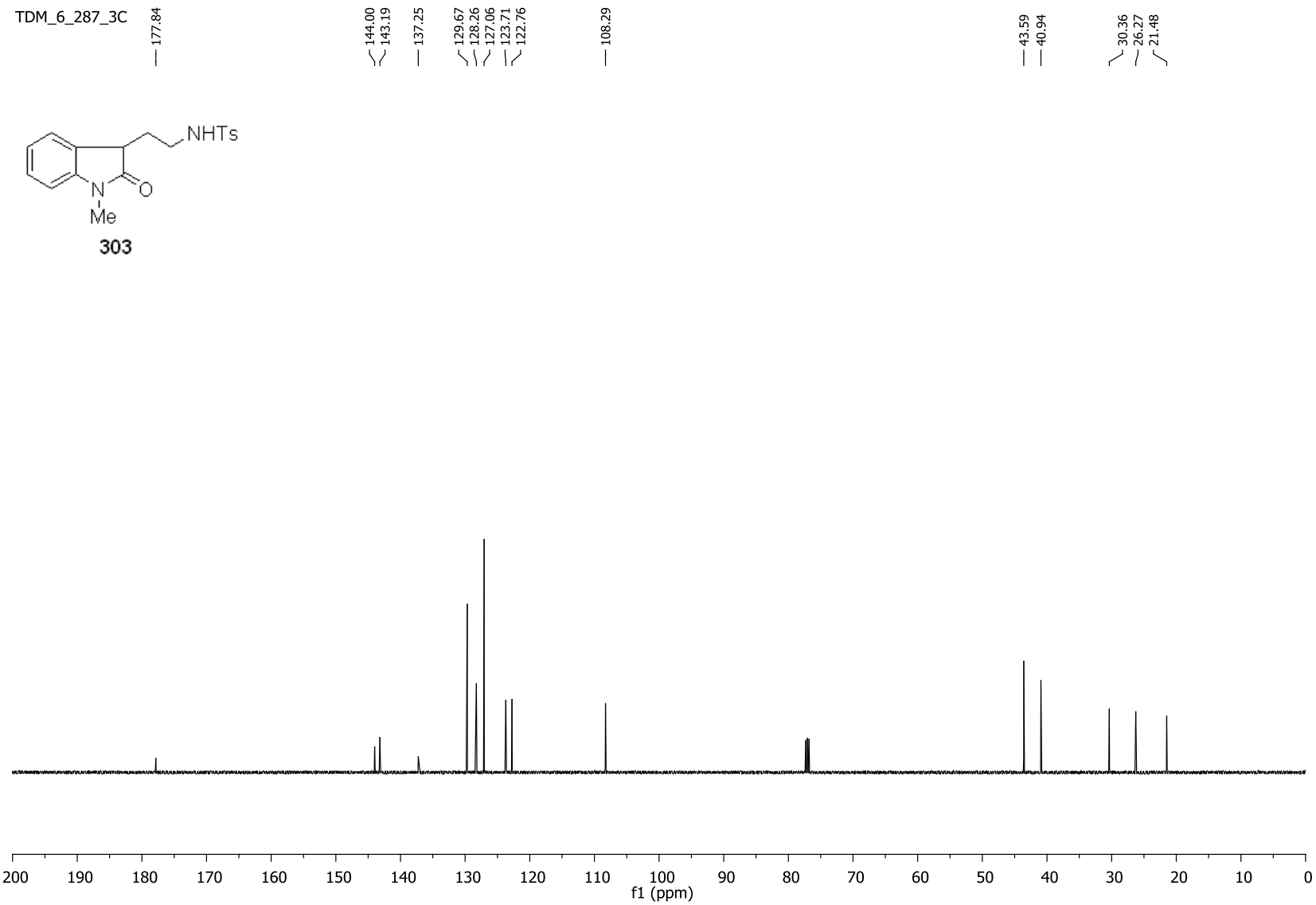


Figure 145. ^{13}C NMR Spectrum for **303** (125 MHz, $CDCl_3$)

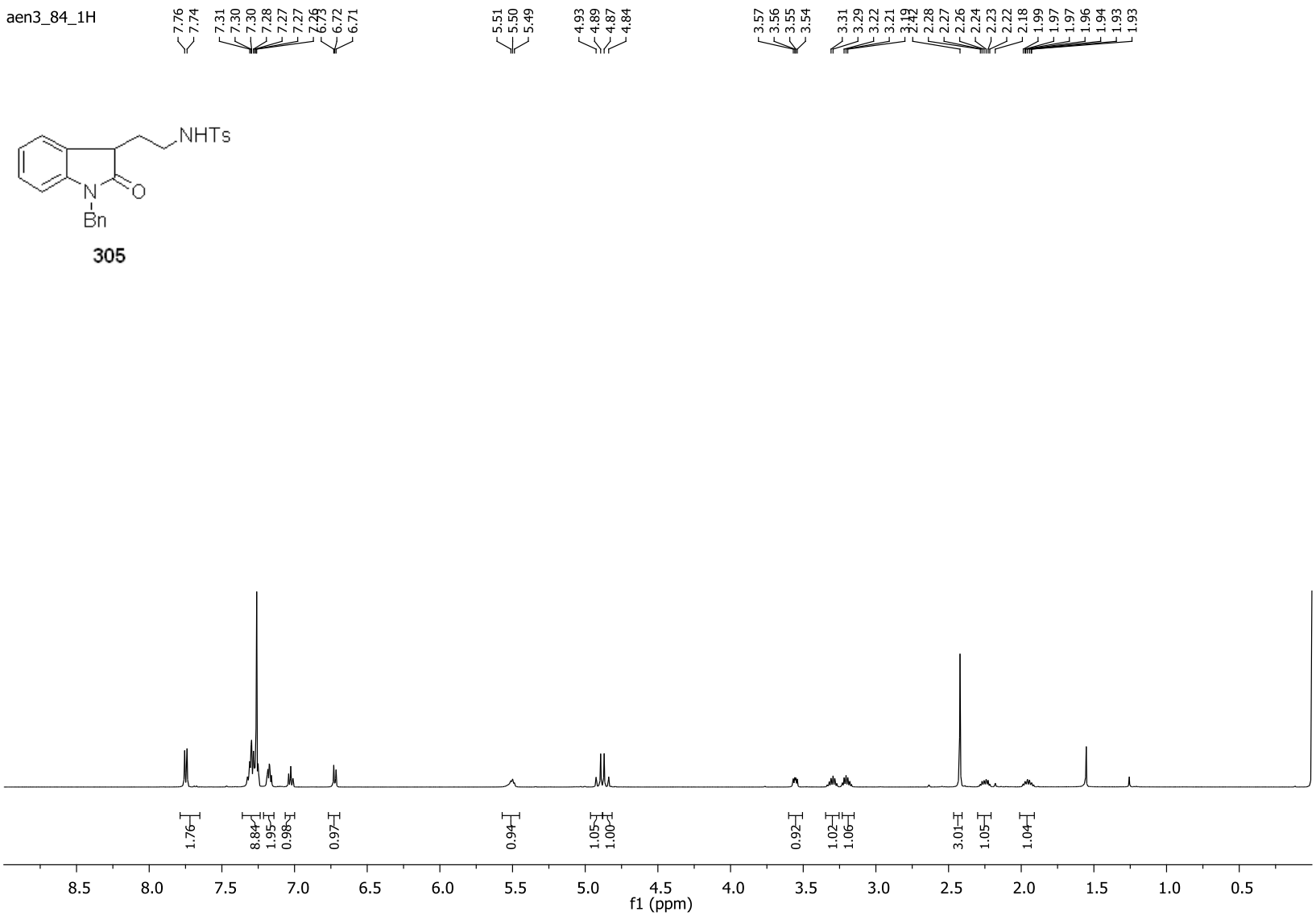


Figure 146. ^{1}H NMR Spectrum for **305** (500 MHz, $CDCl_3$)

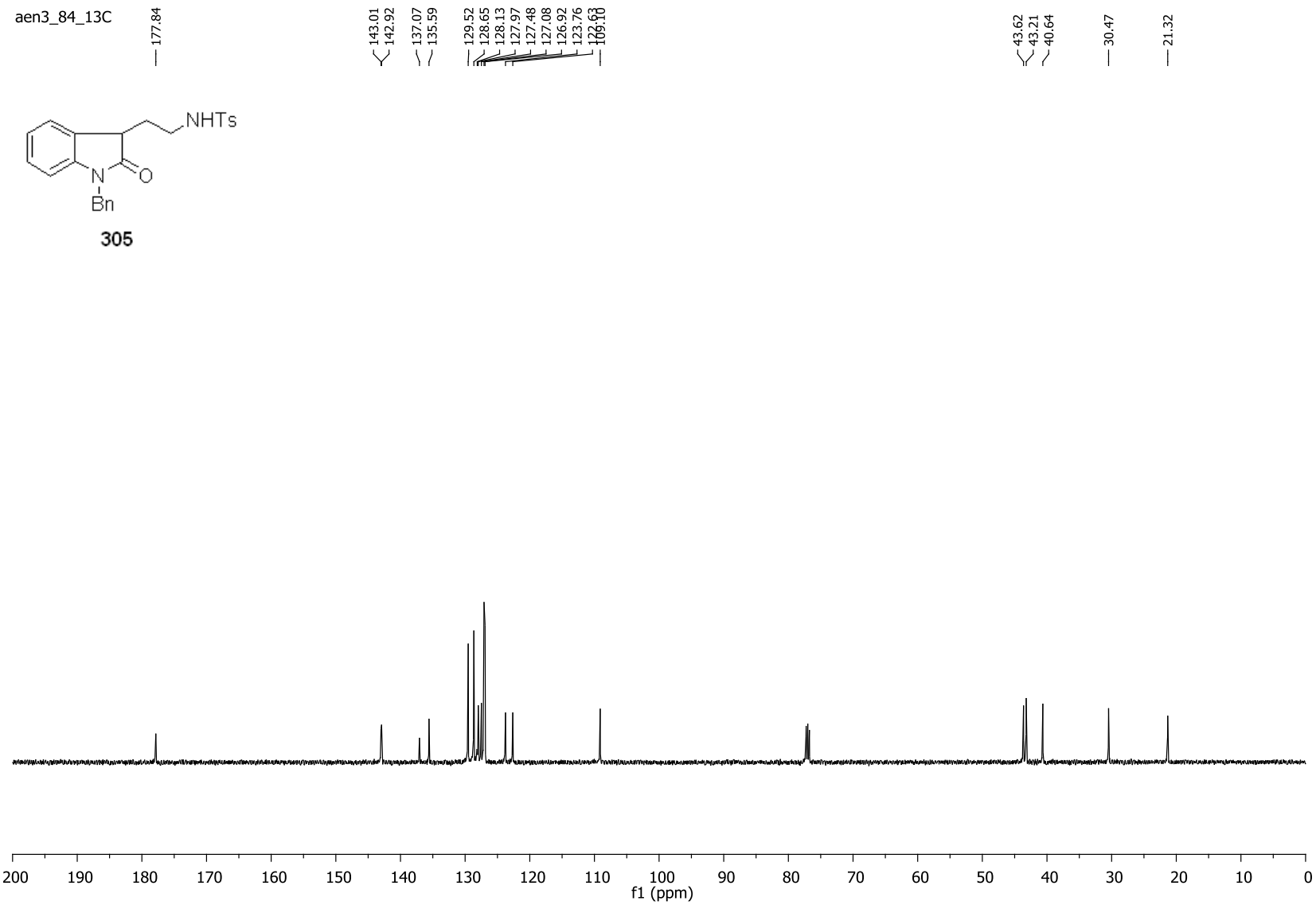


Figure 147. ^{13}C NMR Spectrum for **305** (125 MHz, $CDCl_3$)

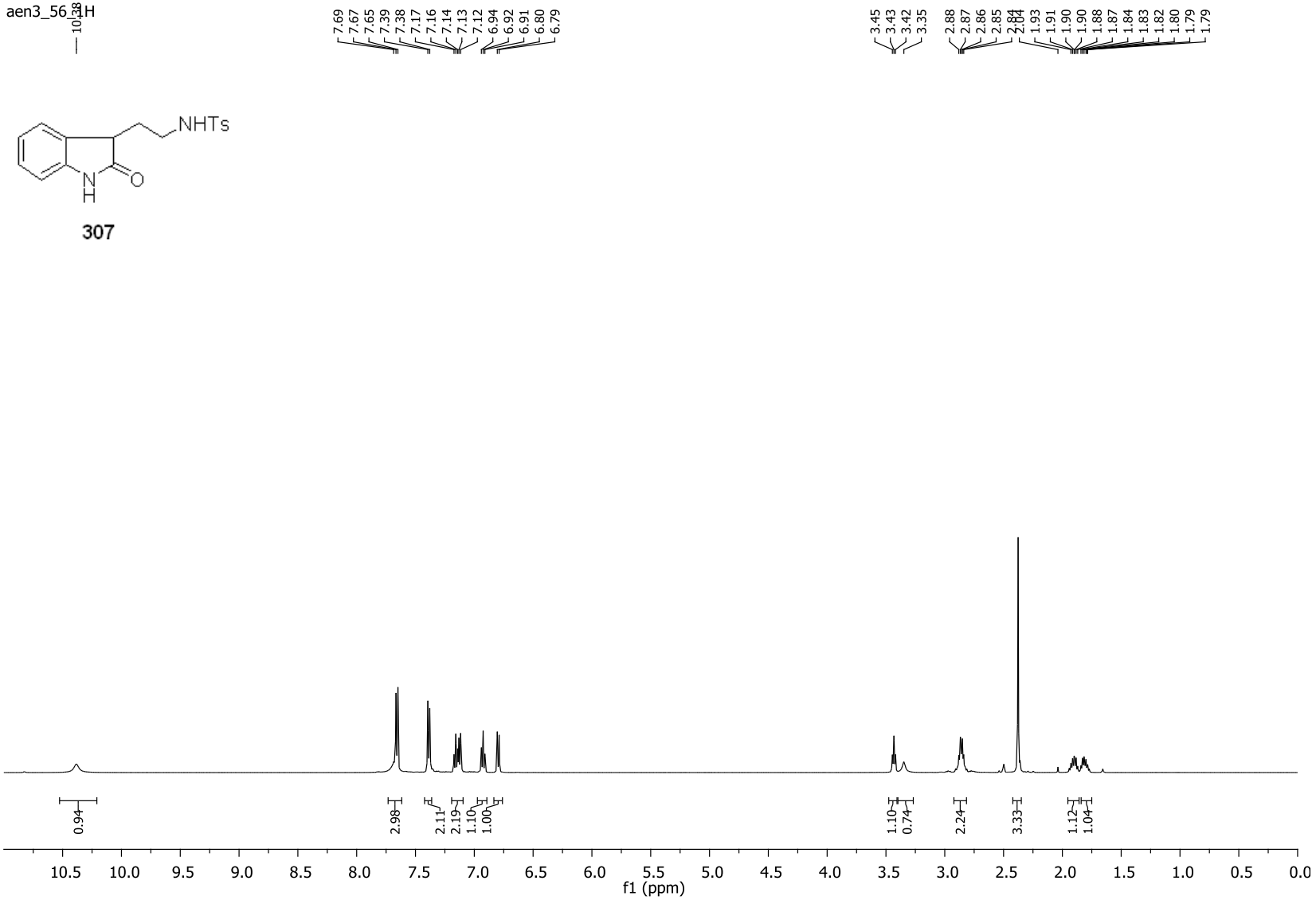


Figure 148. ^{1}H NMR Spectrum for **307** (500 MHz, $CDCl_3$)

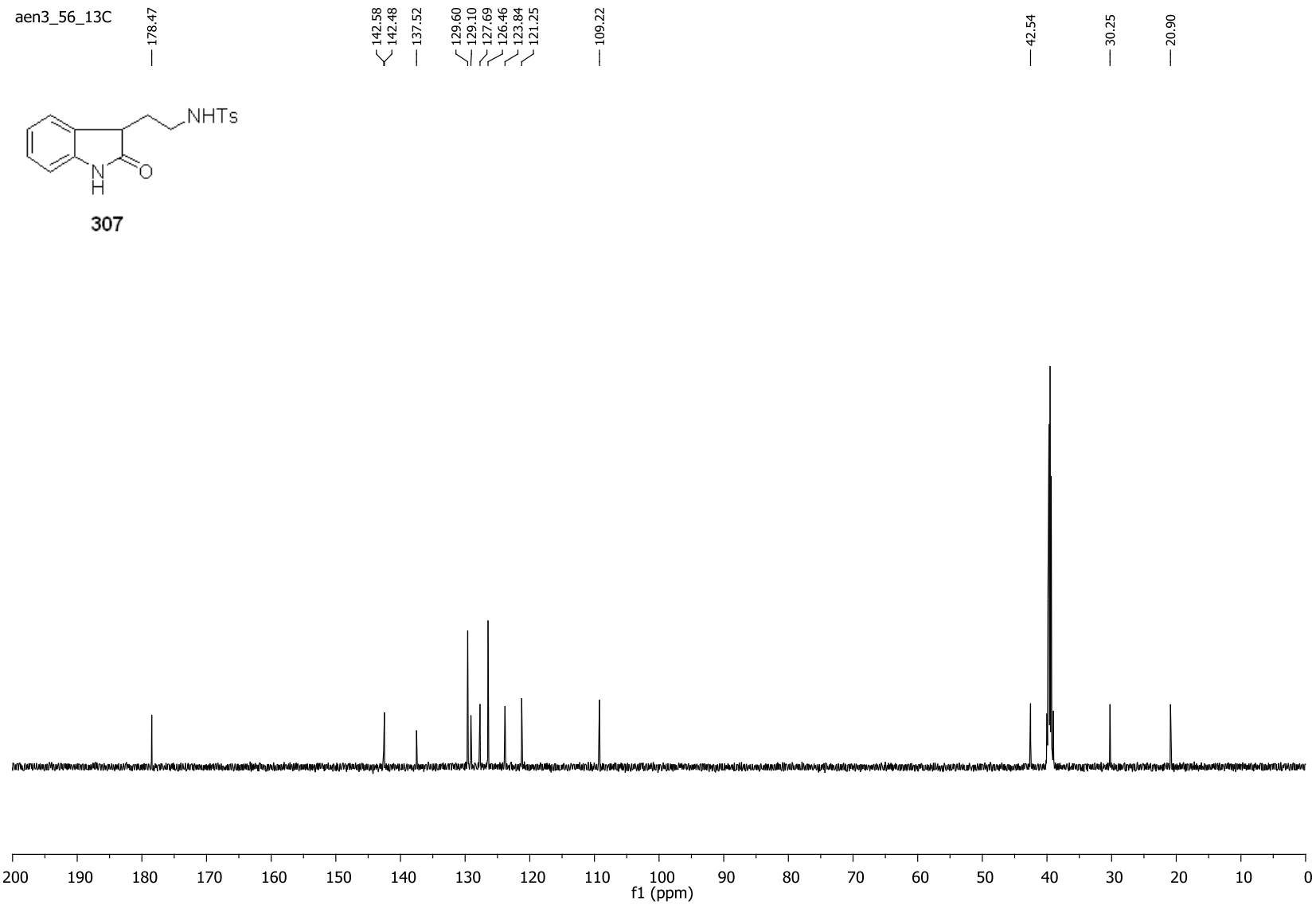


Figure 149. ^{13}C NMR Spectrum for **307** (125 MHz, $CDCl_3$)

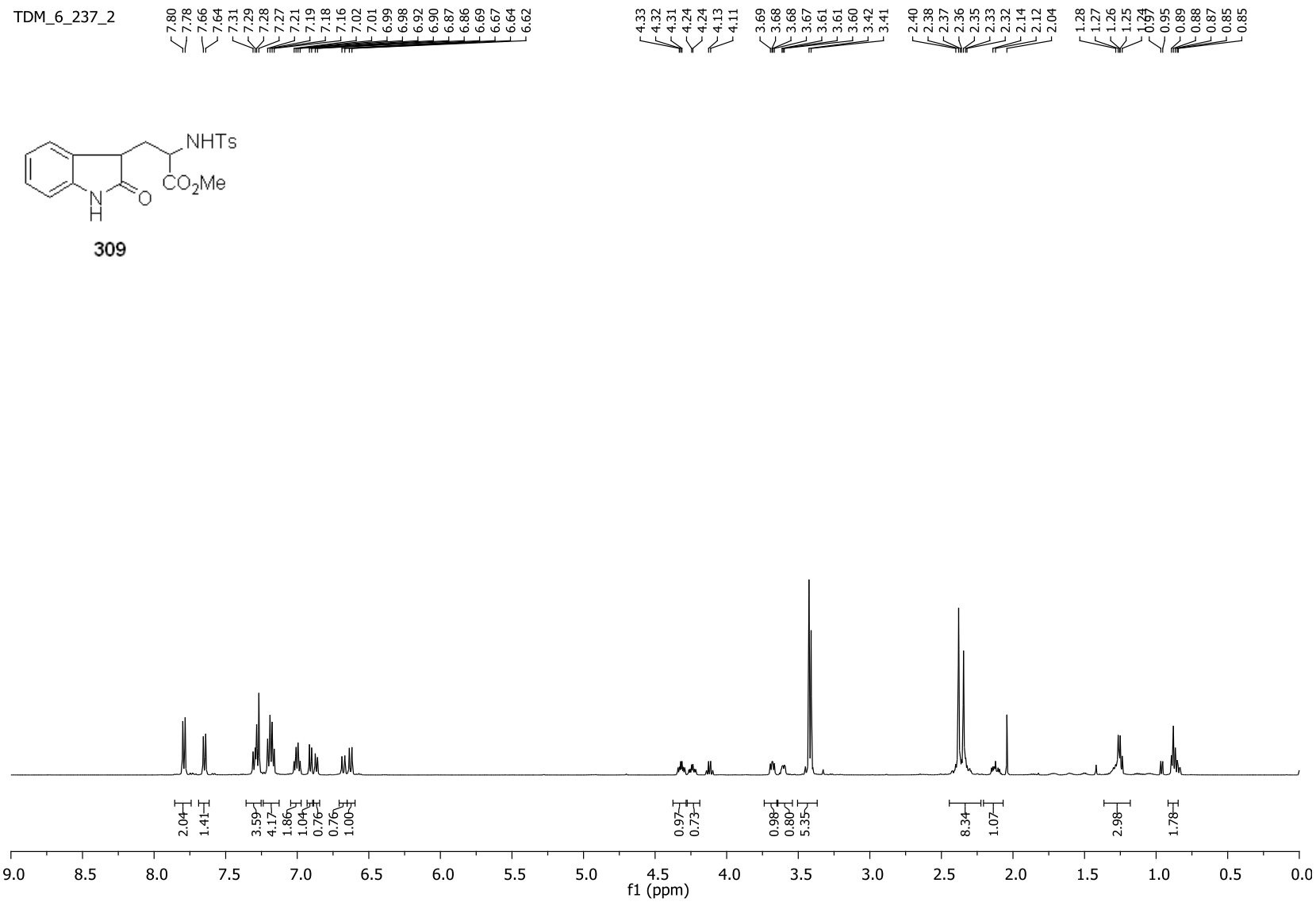


Figure 150. ^{1}H NMR Spectrum for **309** (500 MHz, $CDCl_3$)

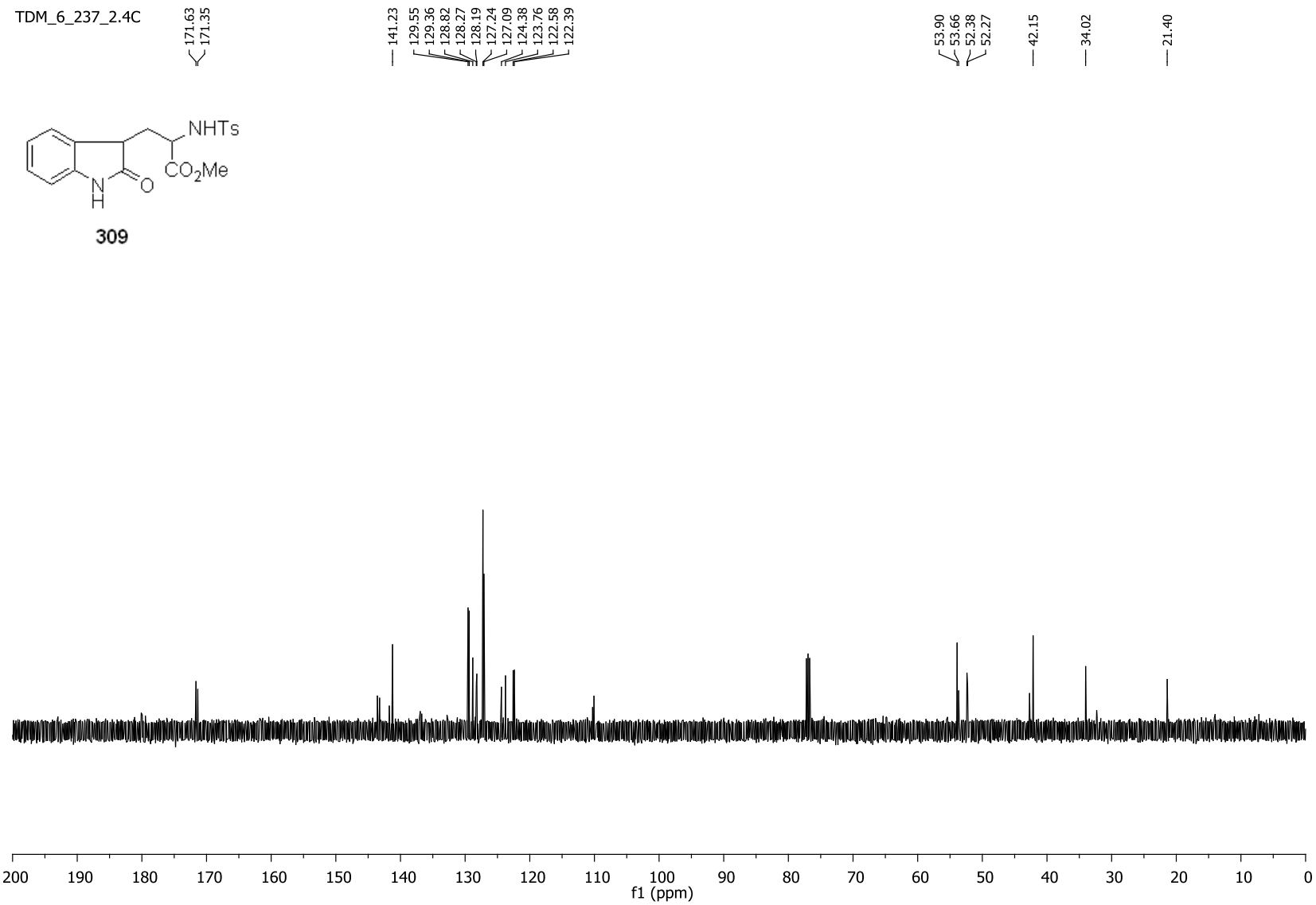


Figure 151. ^{13}C NMR Spectrum for **309** (125 MHz, $CDCl_3$)

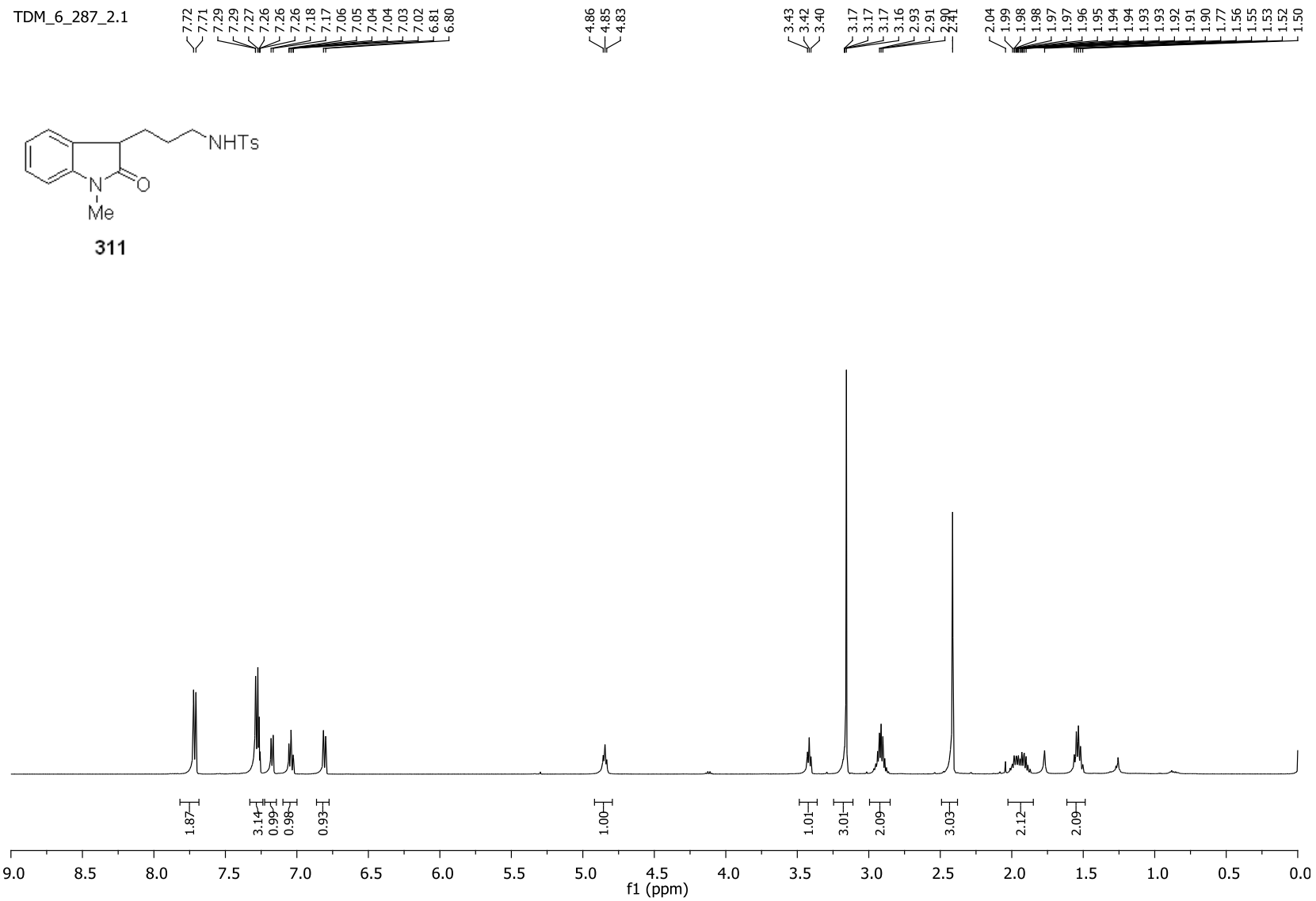


Figure 152. ^{1}H NMR Spectrum for **311** (500 MHz, $CDCl_3$)

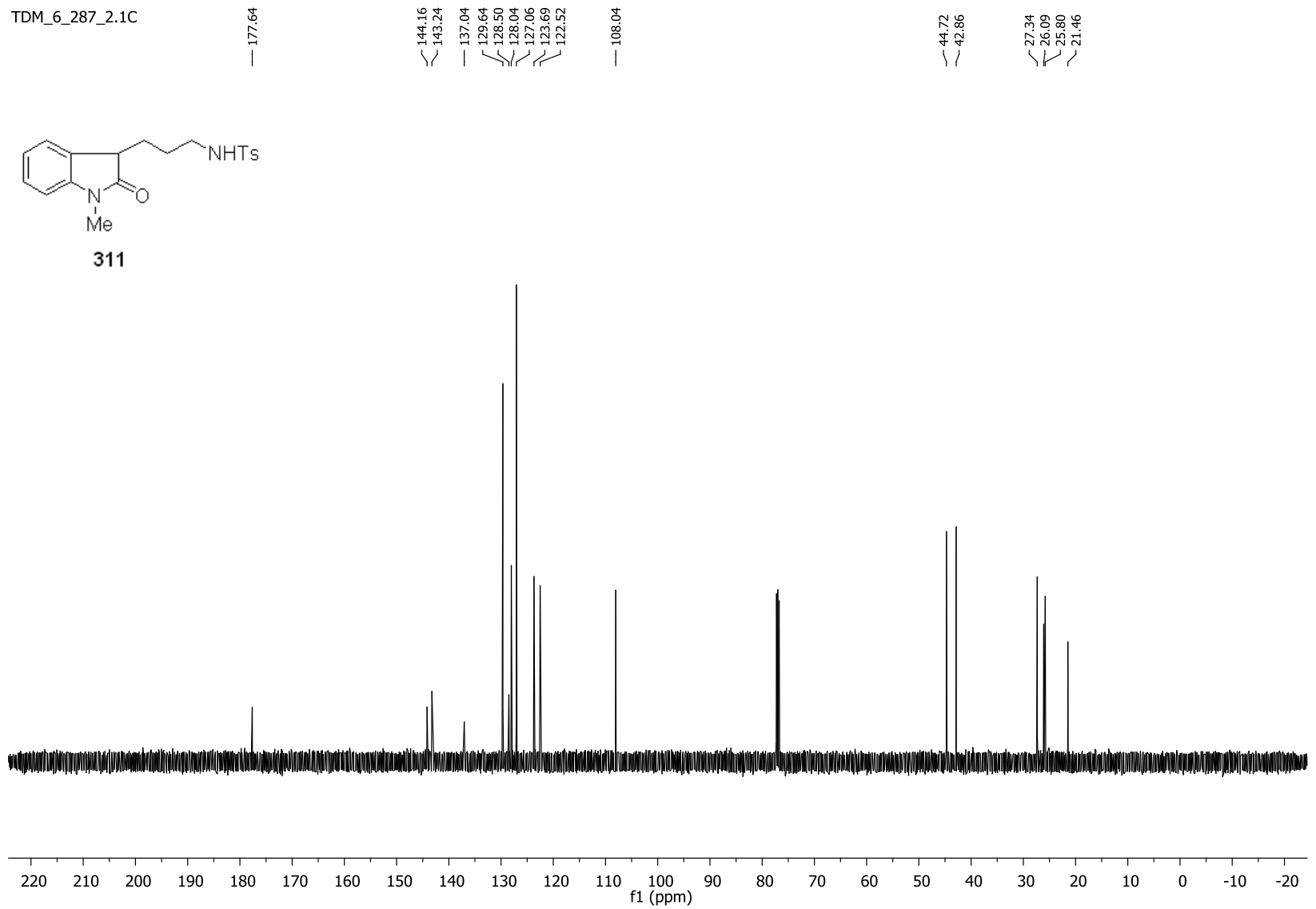


Figure 153. ^{13}C NMR Spectrum for **311** (125 MHz, $CDCl_3$)

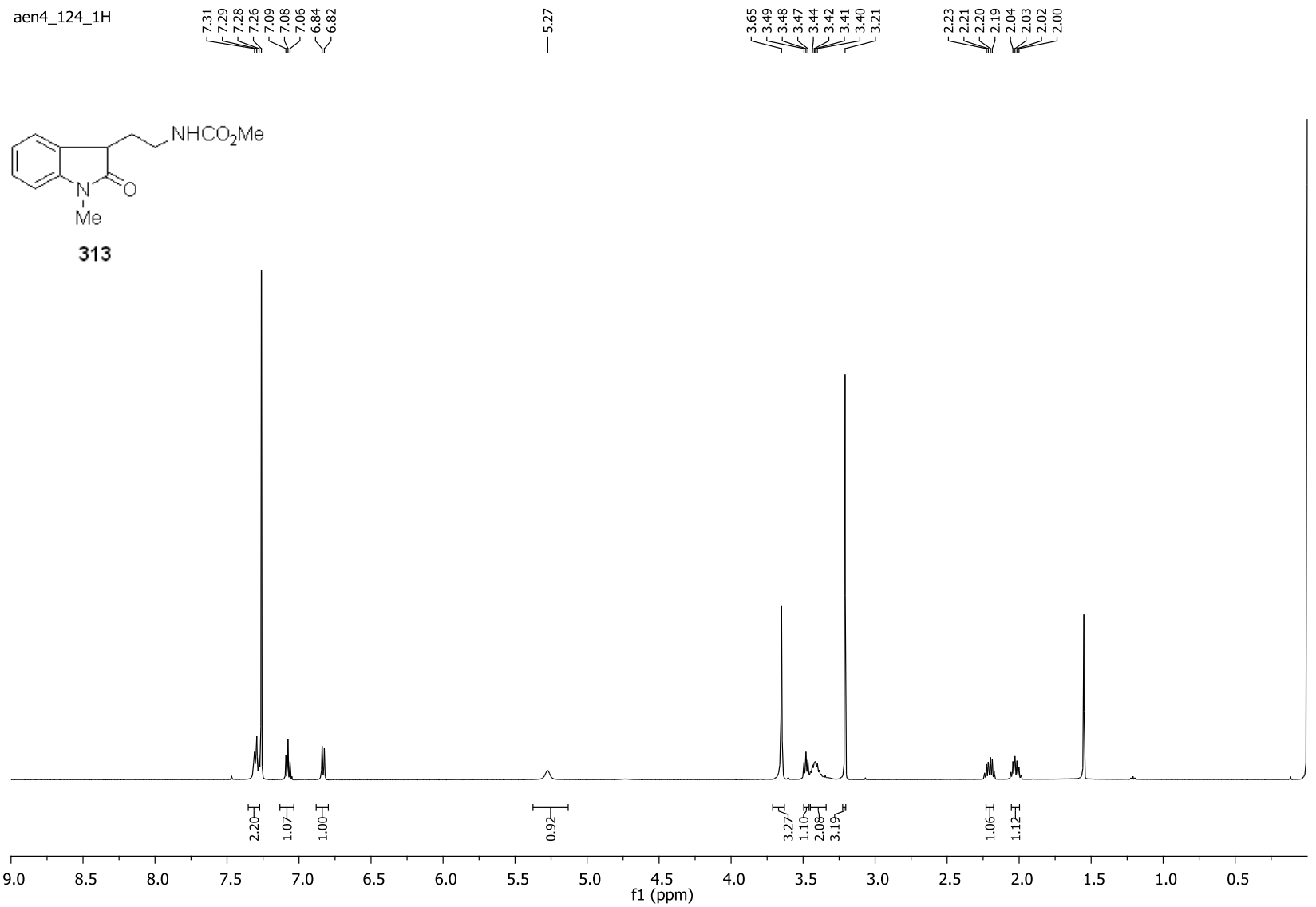


Figure 154. ^{1}H NMR Spectrum for **313** (500 MHz, $CDCl_3$)

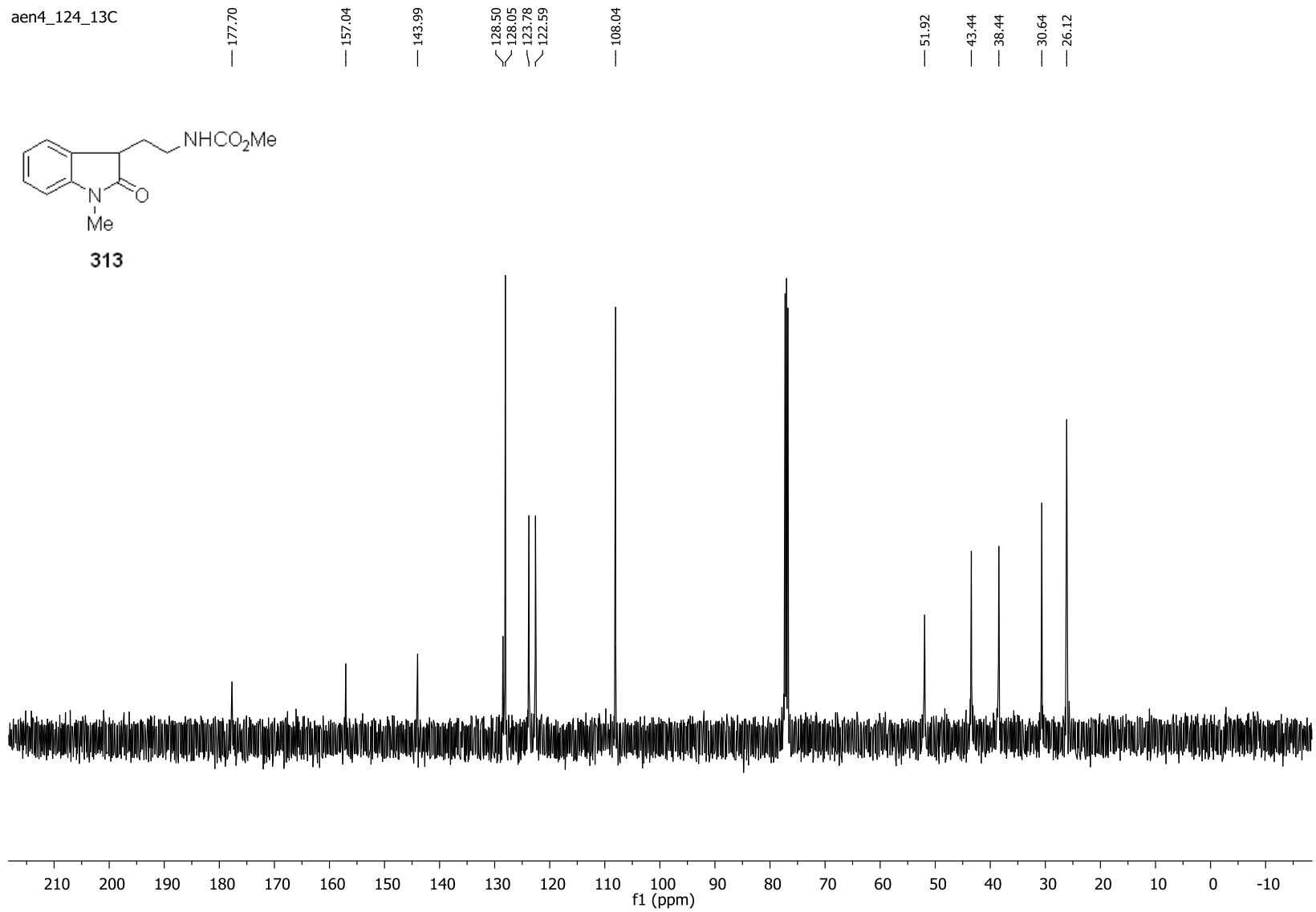


Figure 155. ^{13}C NMR Spectrum for **313** (125 MHz, $CDCl_3$)

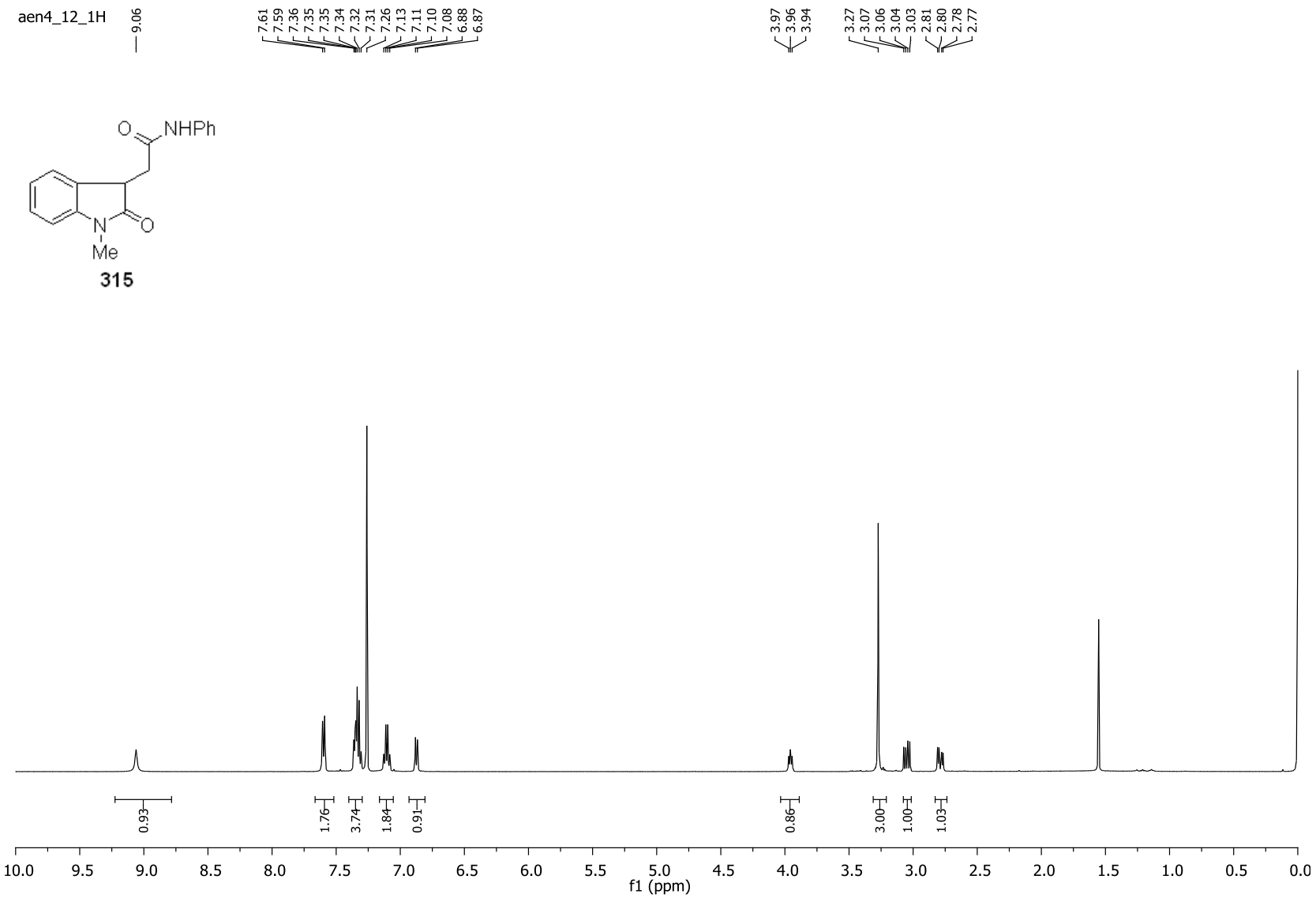


Figure 156. ^{1}H NMR Spectrum for **315** (500 MHz, $CDCl_3$)

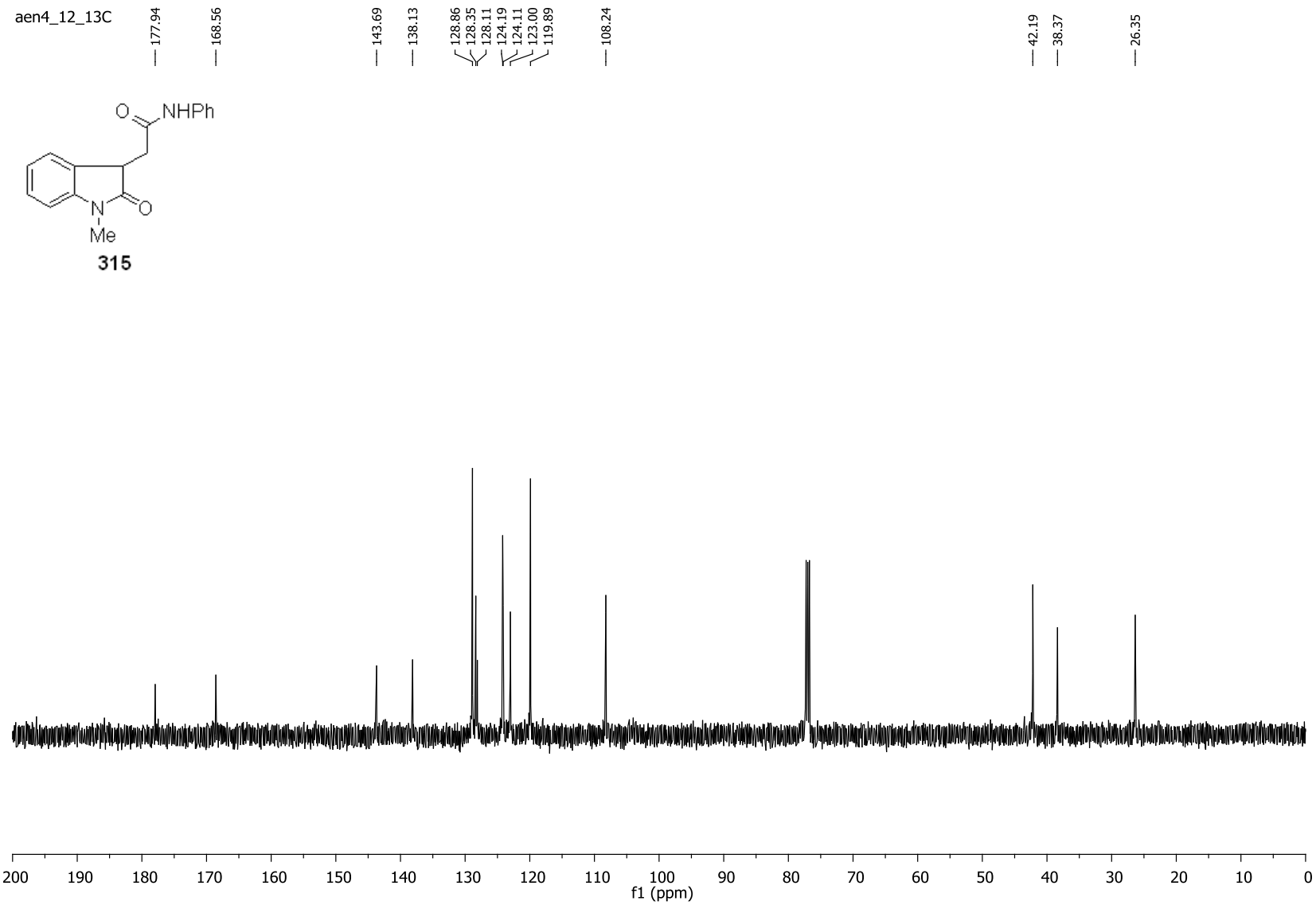


Figure 157. ^{13}C NMR Spectrum for **315** (125 MHz, $CDCl_3$)

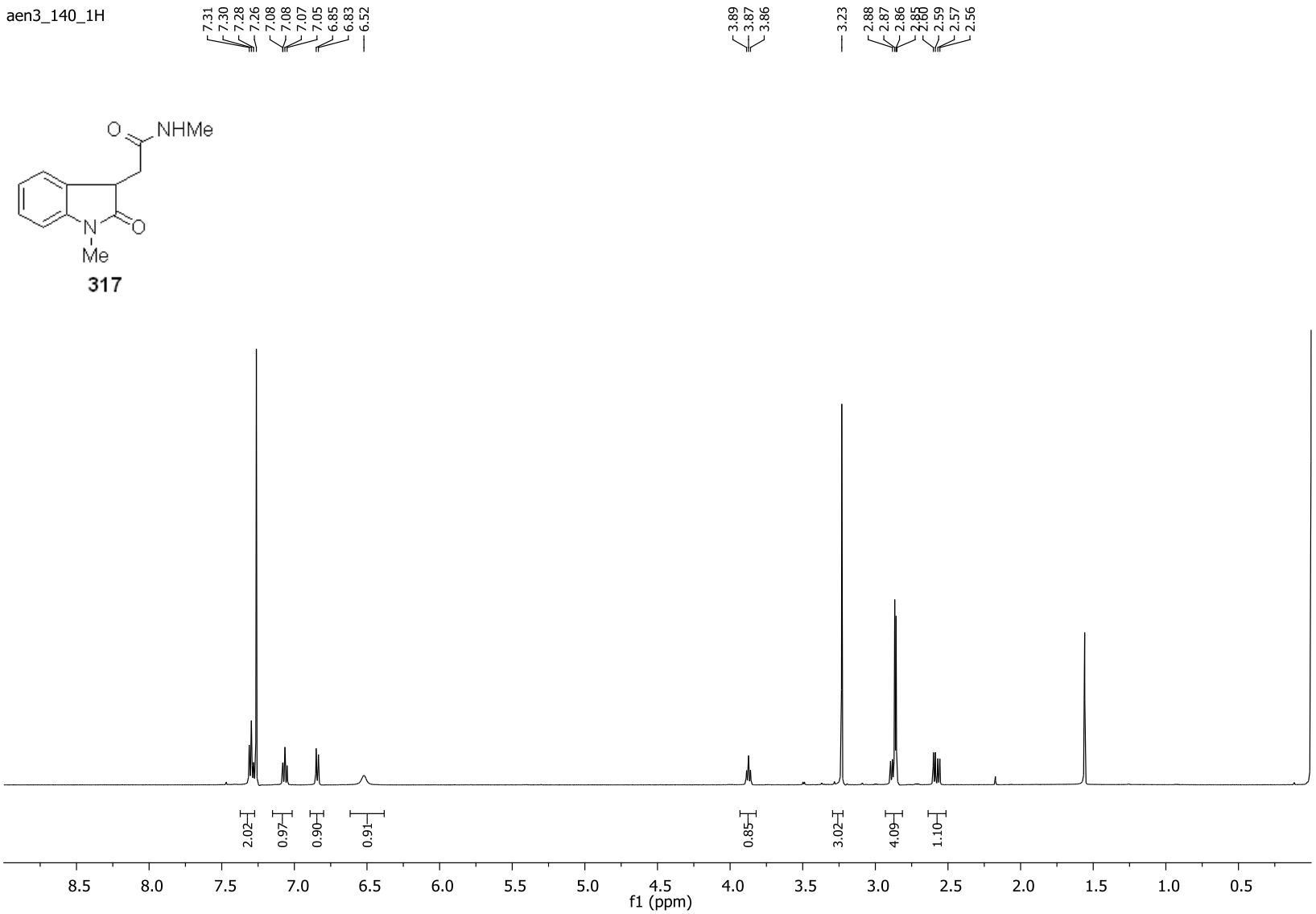


Figure 158. ^{1}H NMR Spectrum for **317** (500 MHz, $CDCl_3$)

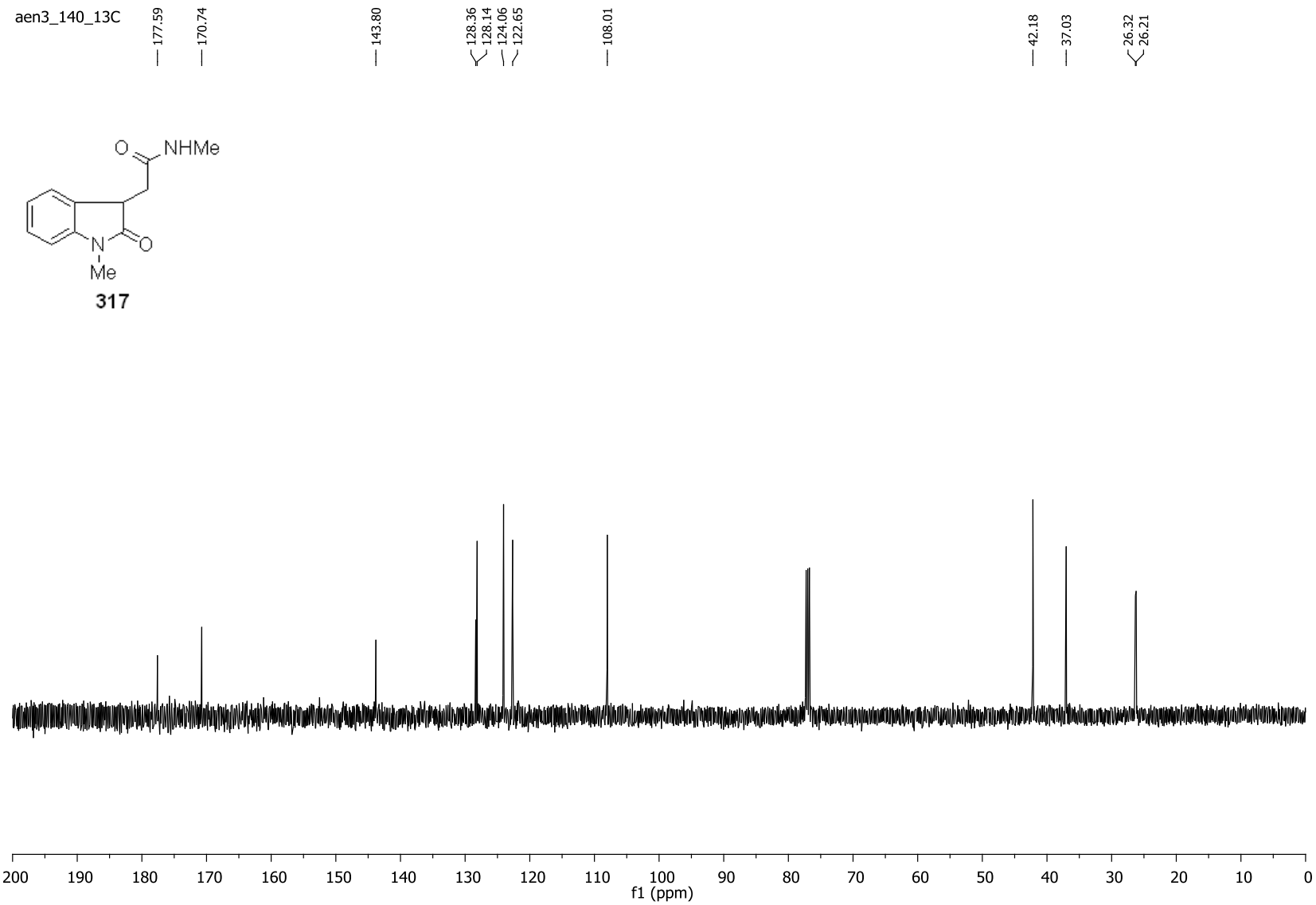
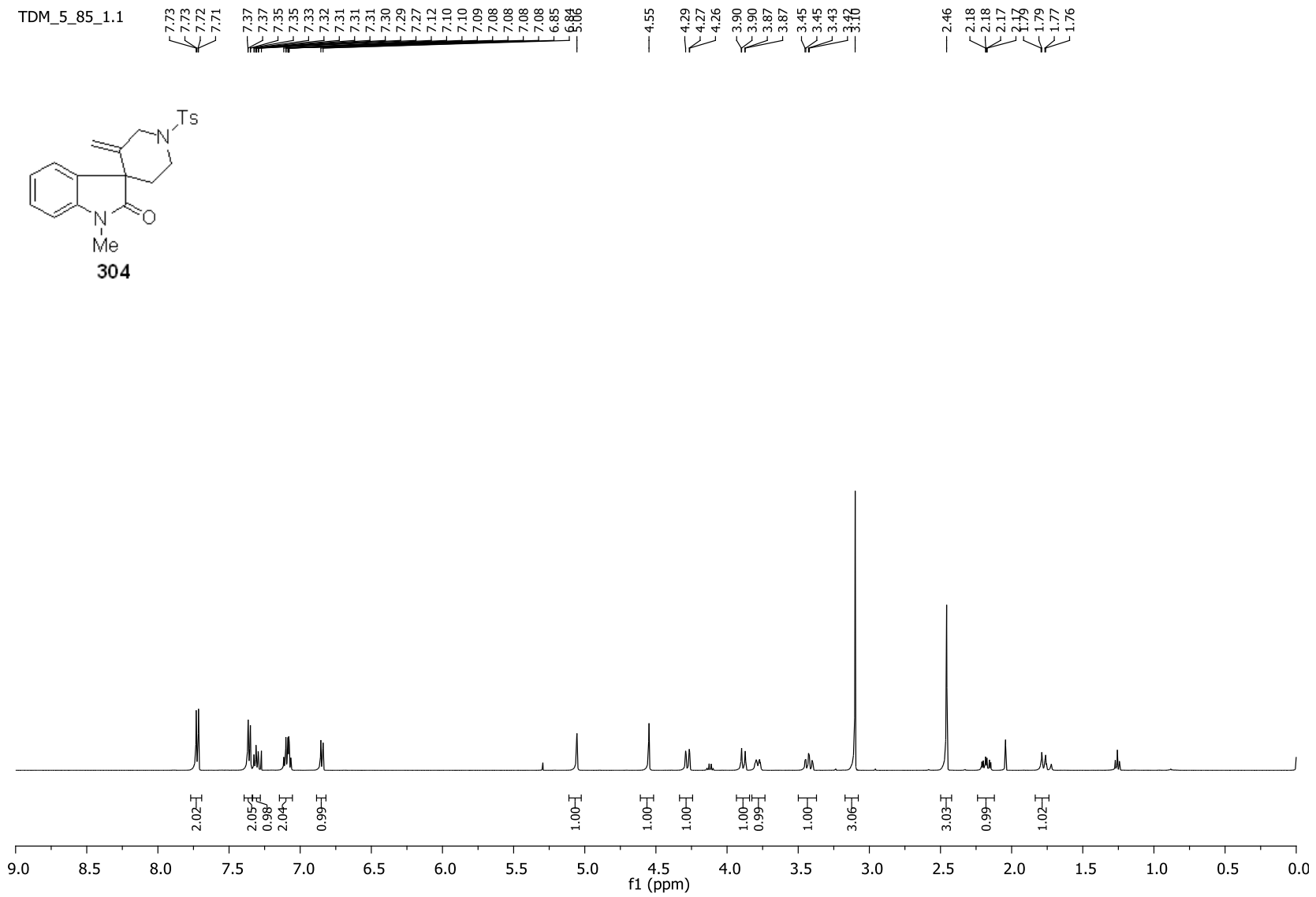


Figure 159. ^{13}C NMR Spectrum for **317** (125 MHz, $CDCl_3$)



500

Figure 160. ^{1}H NMR Spectrum for **304** (500 MHz, $CDCl_3$)

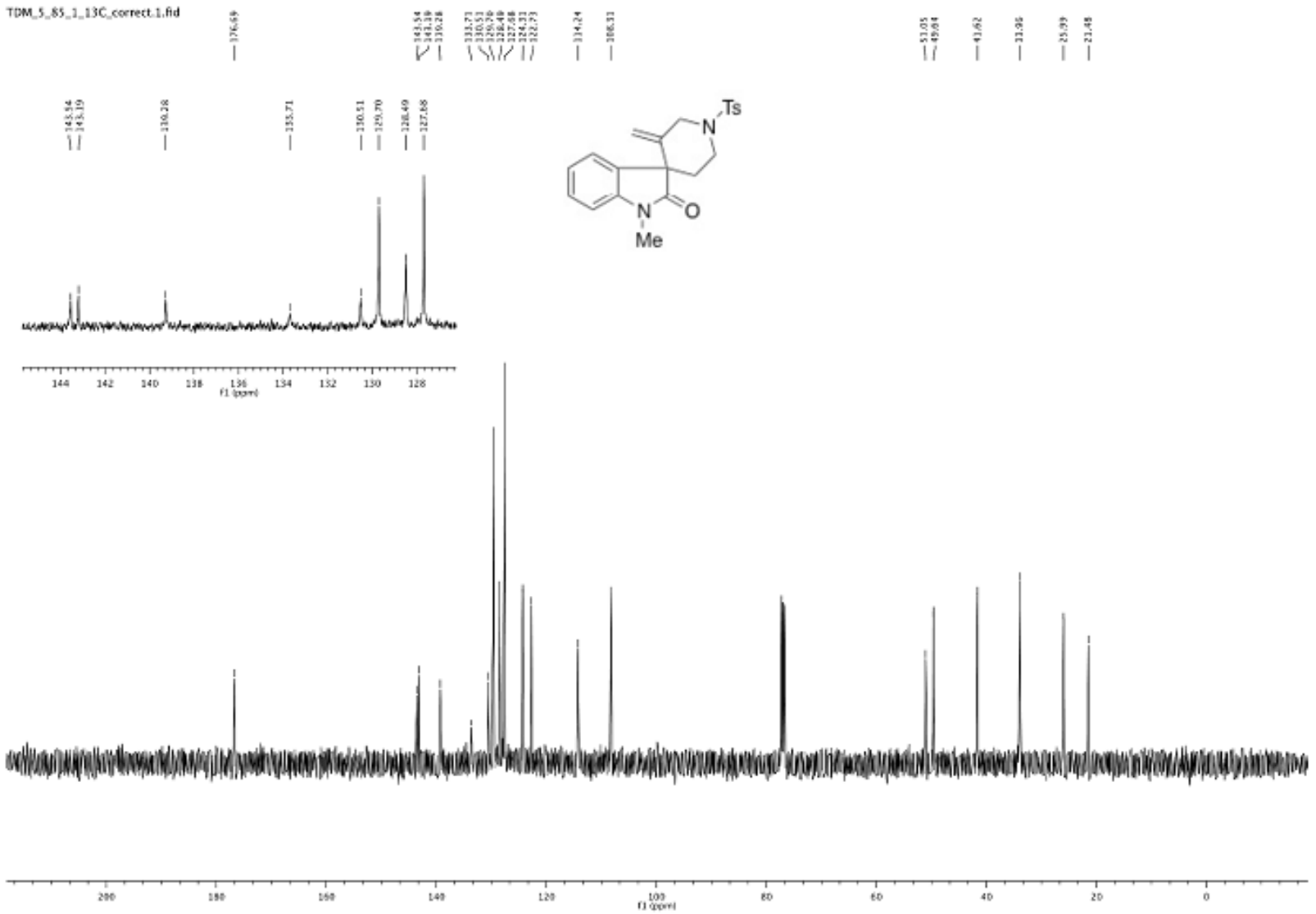


Figure 161. ^{13}C NMR Spectrum for **304** (125 MHz, $CDCl_3$)

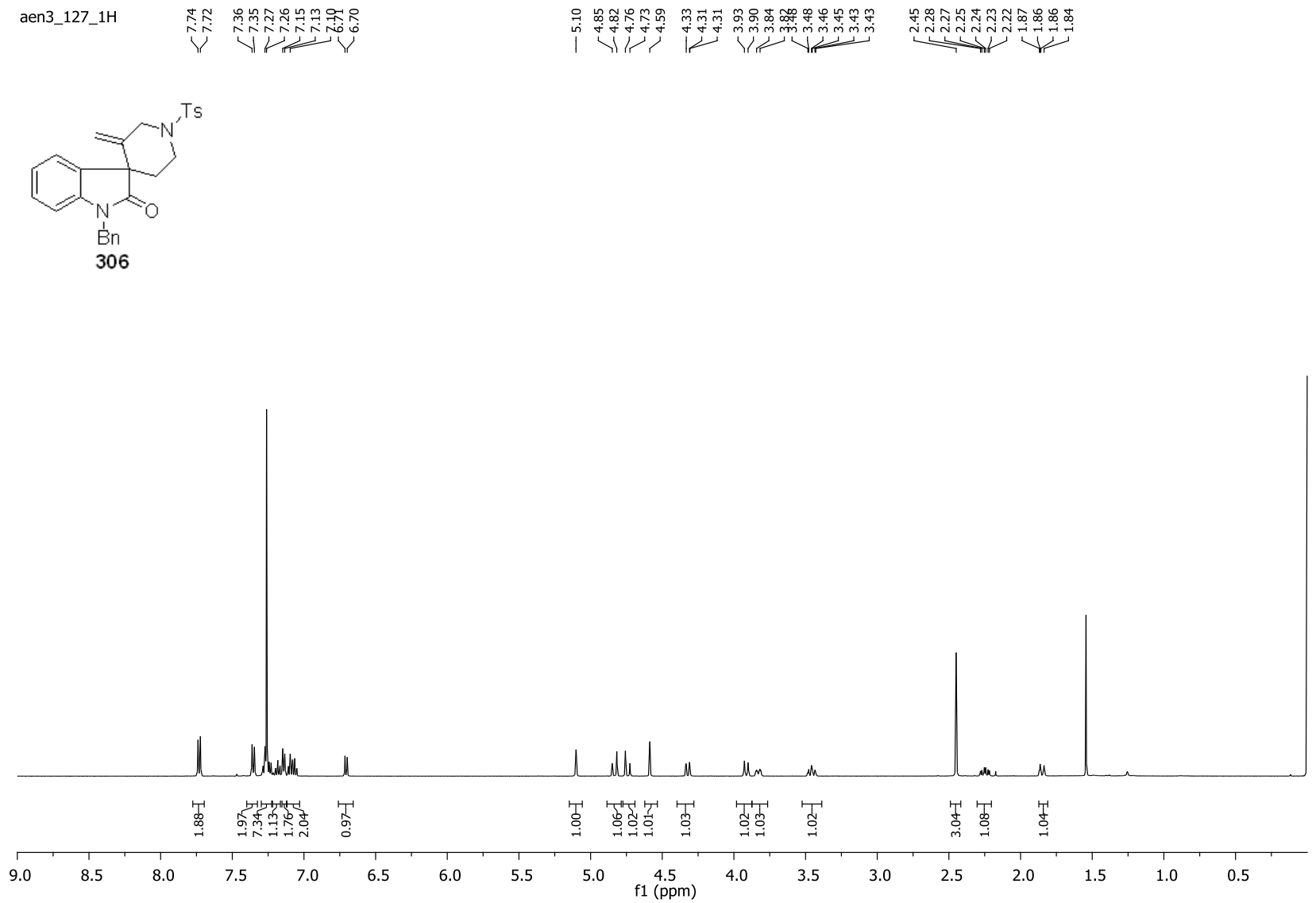


Figure 162. ^{1}H NMR Spectrum for **306** (500 MHz, $CDCl_3$)

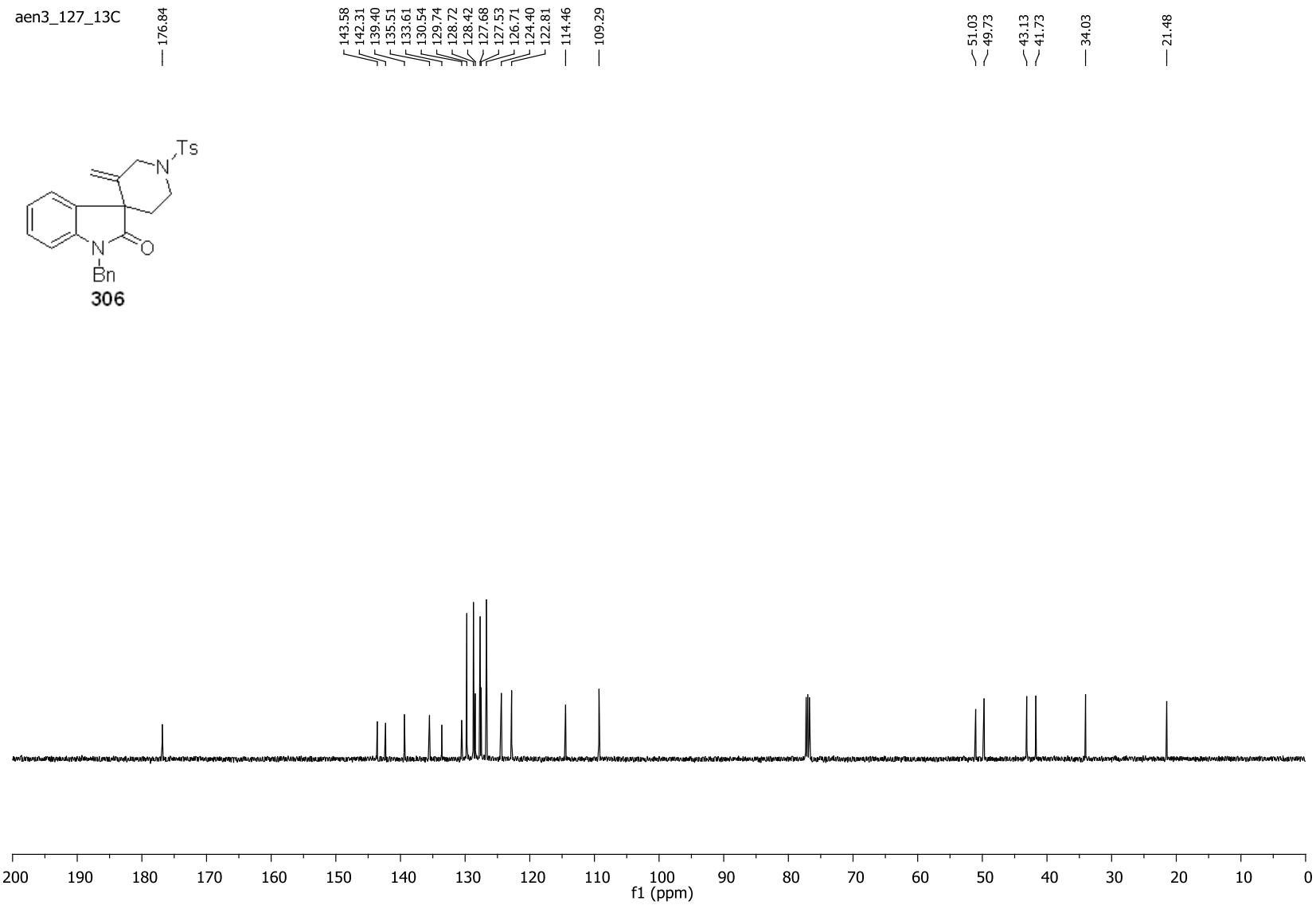


Figure 163. ^{13}C NMR Spectrum for **306** (125 MHz, $CDCl_3$)

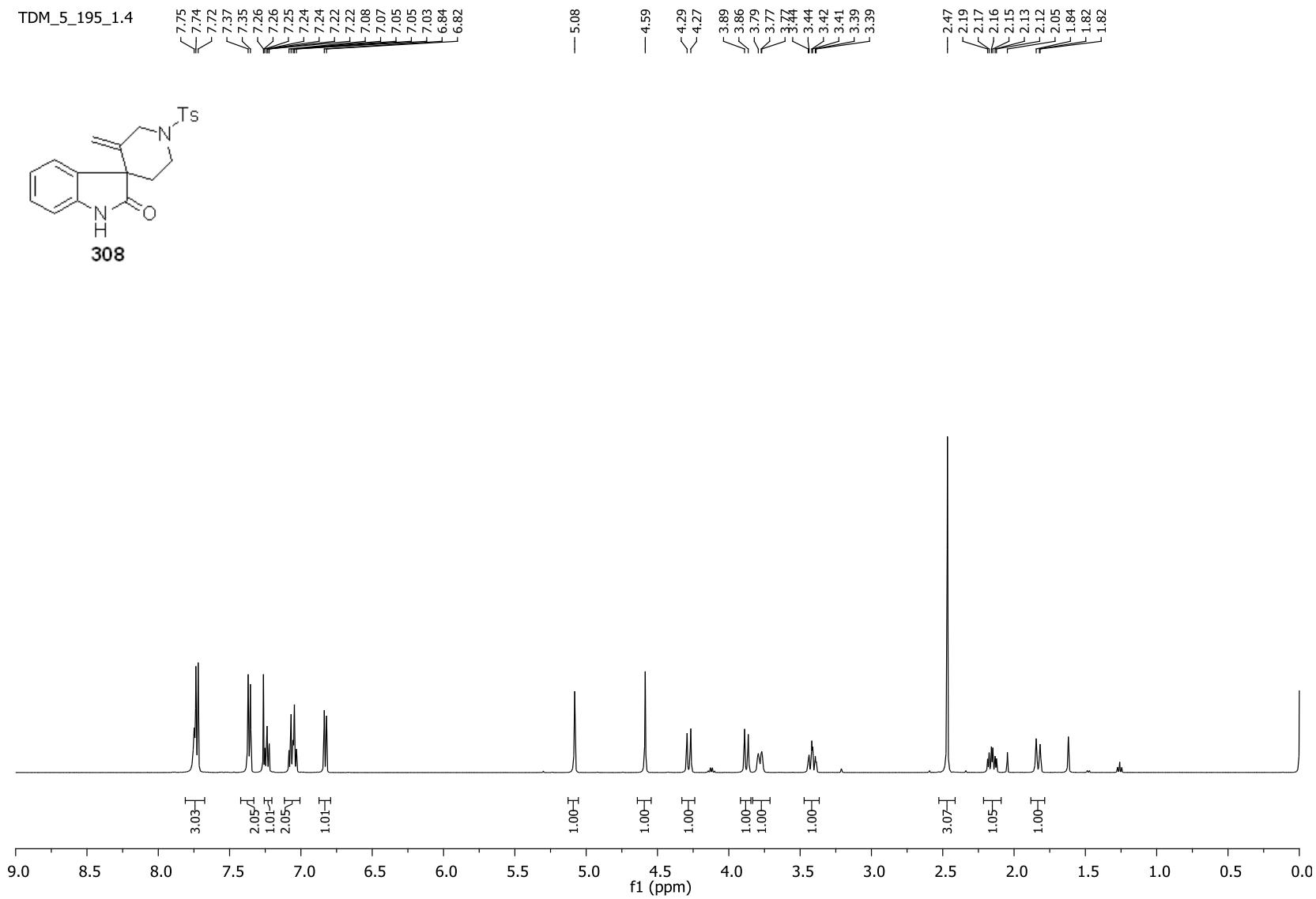


Figure 164. ^{1}H NMR Spectrum for **308** (500 MHz, $CDCl_3$)

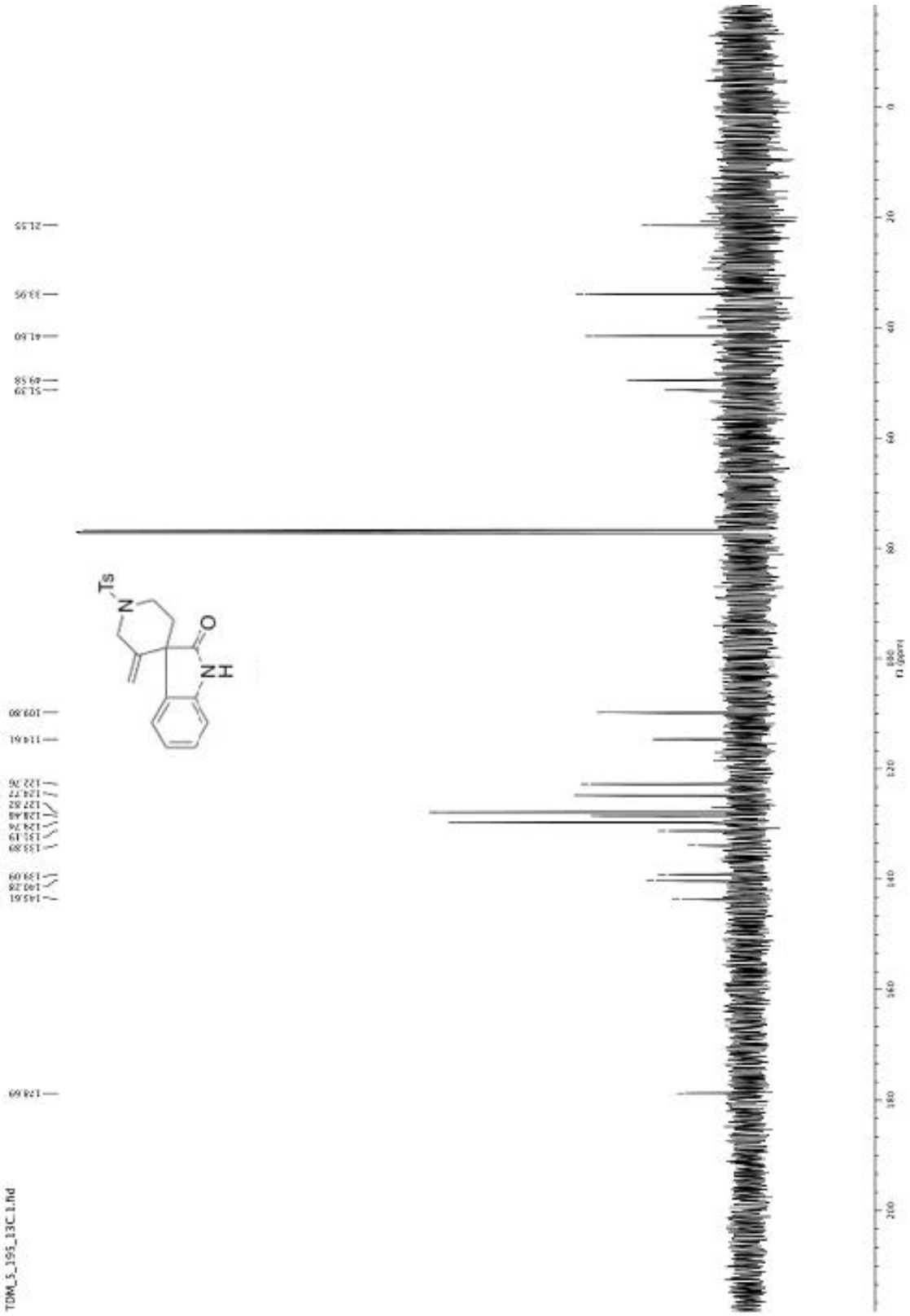


Figure 165. ^{13}C NMR Spectrum for **308** (125 MHz, $CDCl_3$)

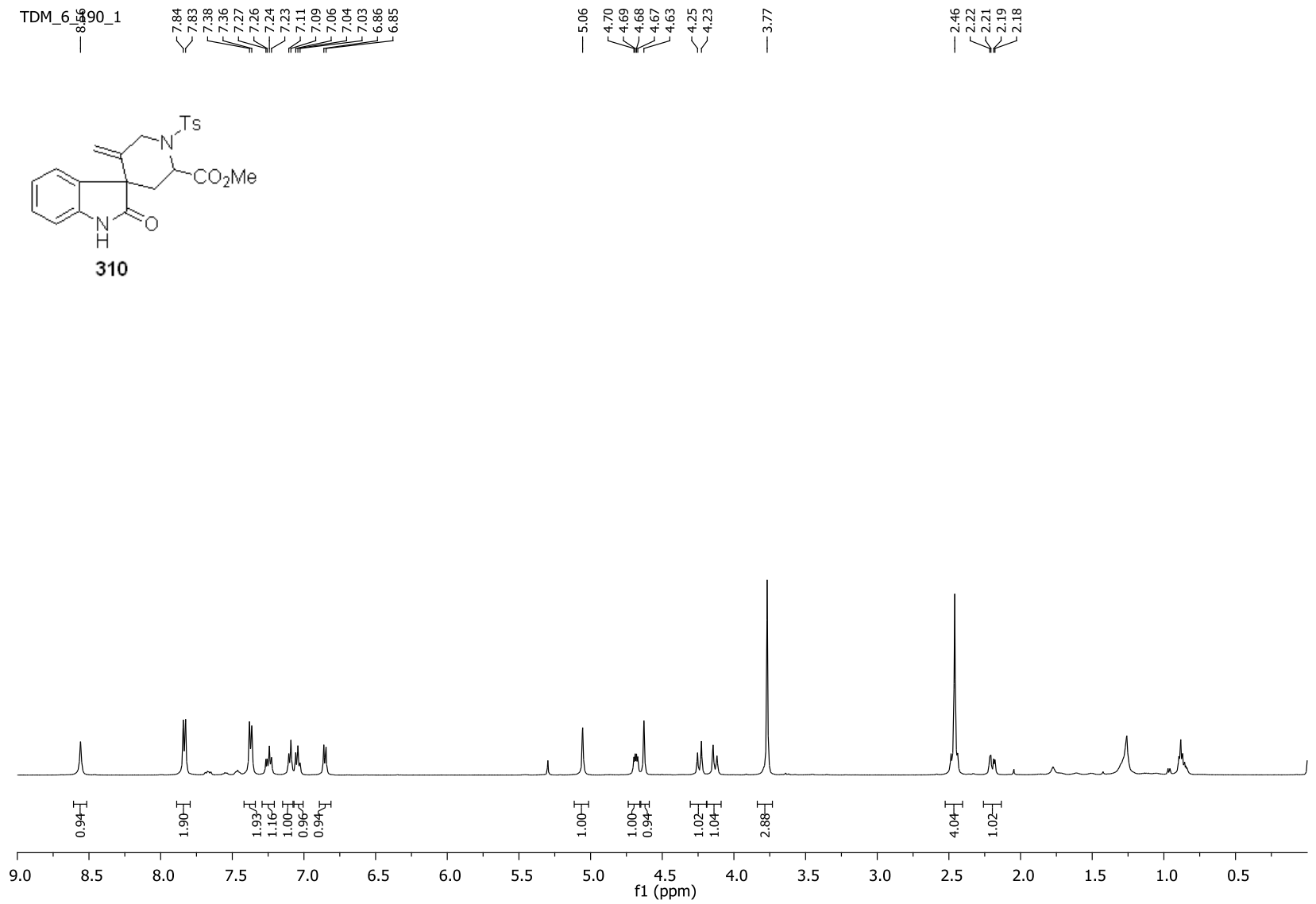


Figure 166. ^{1}H NMR Spectrum for **310** (500 MHz, $CDCl_3$)

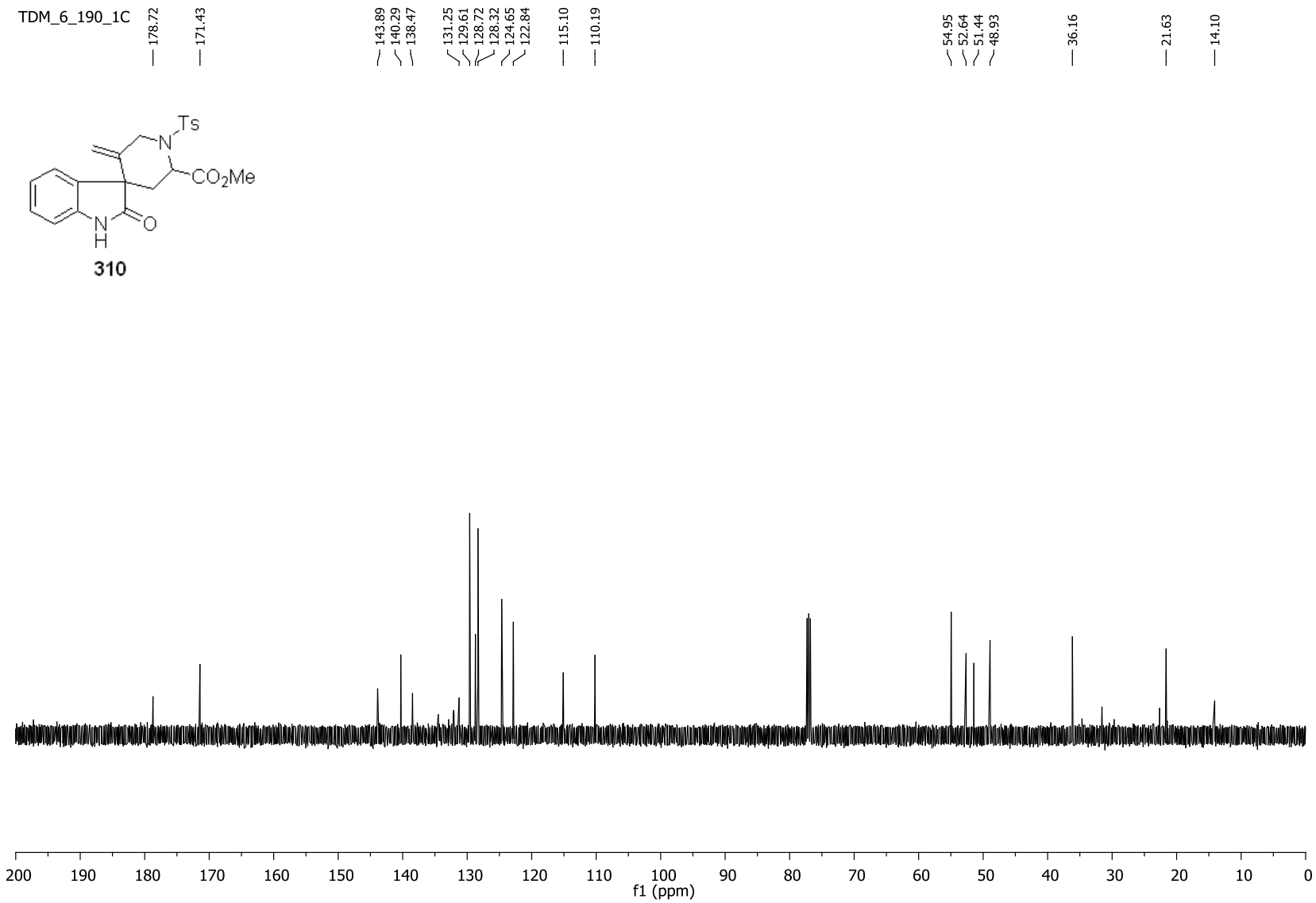


Figure 167. ^{13}C NMR Spectrum for **310** (125 MHz, $CDCl_3$)

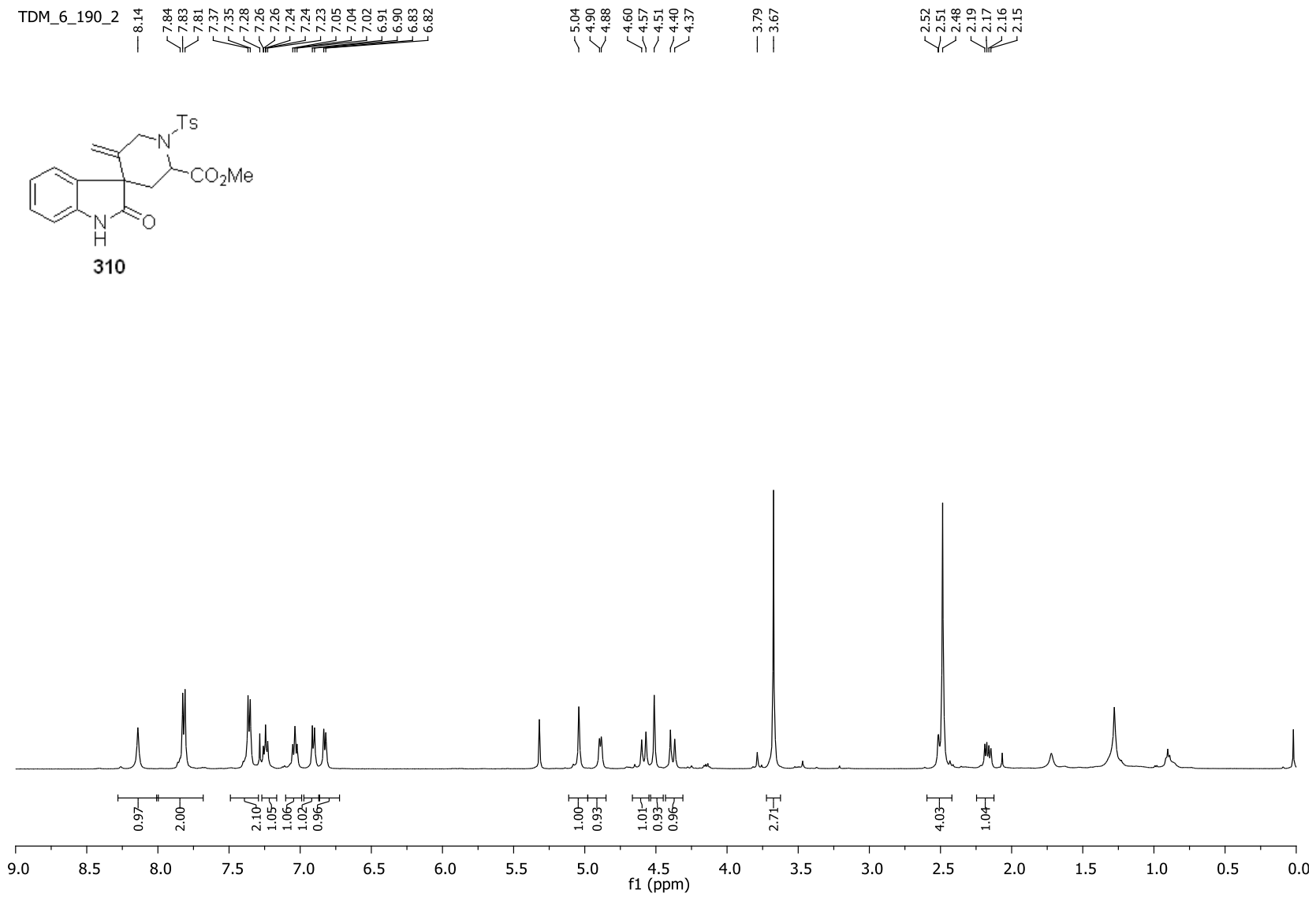


Figure 168. ^{1}H NMR Spectrum for **310** (500 MHz, $CDCl_3$)

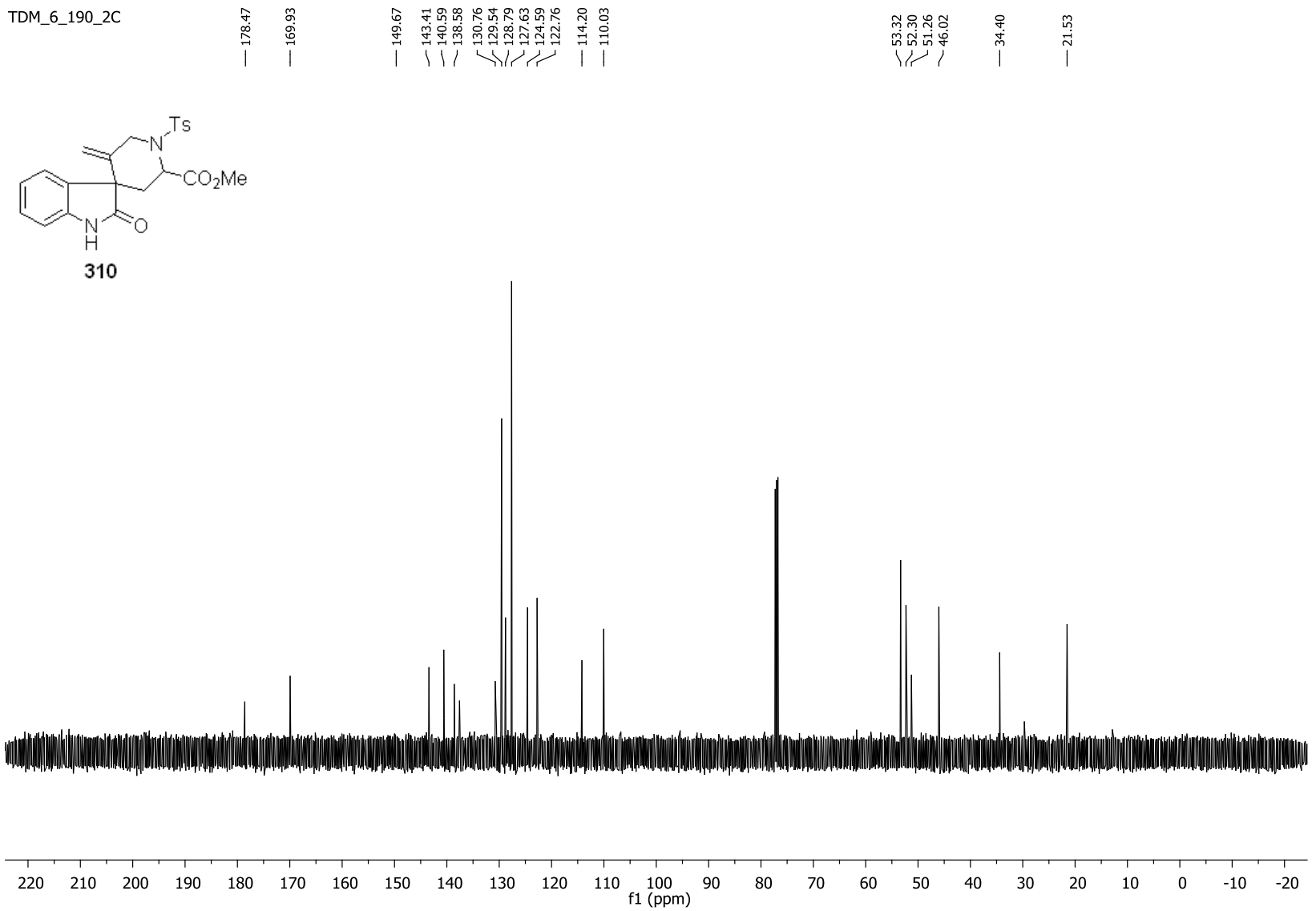


Figure 169. ^{13}C NMR Spectrum for **310** (125 MHz, $CDCl_3$)

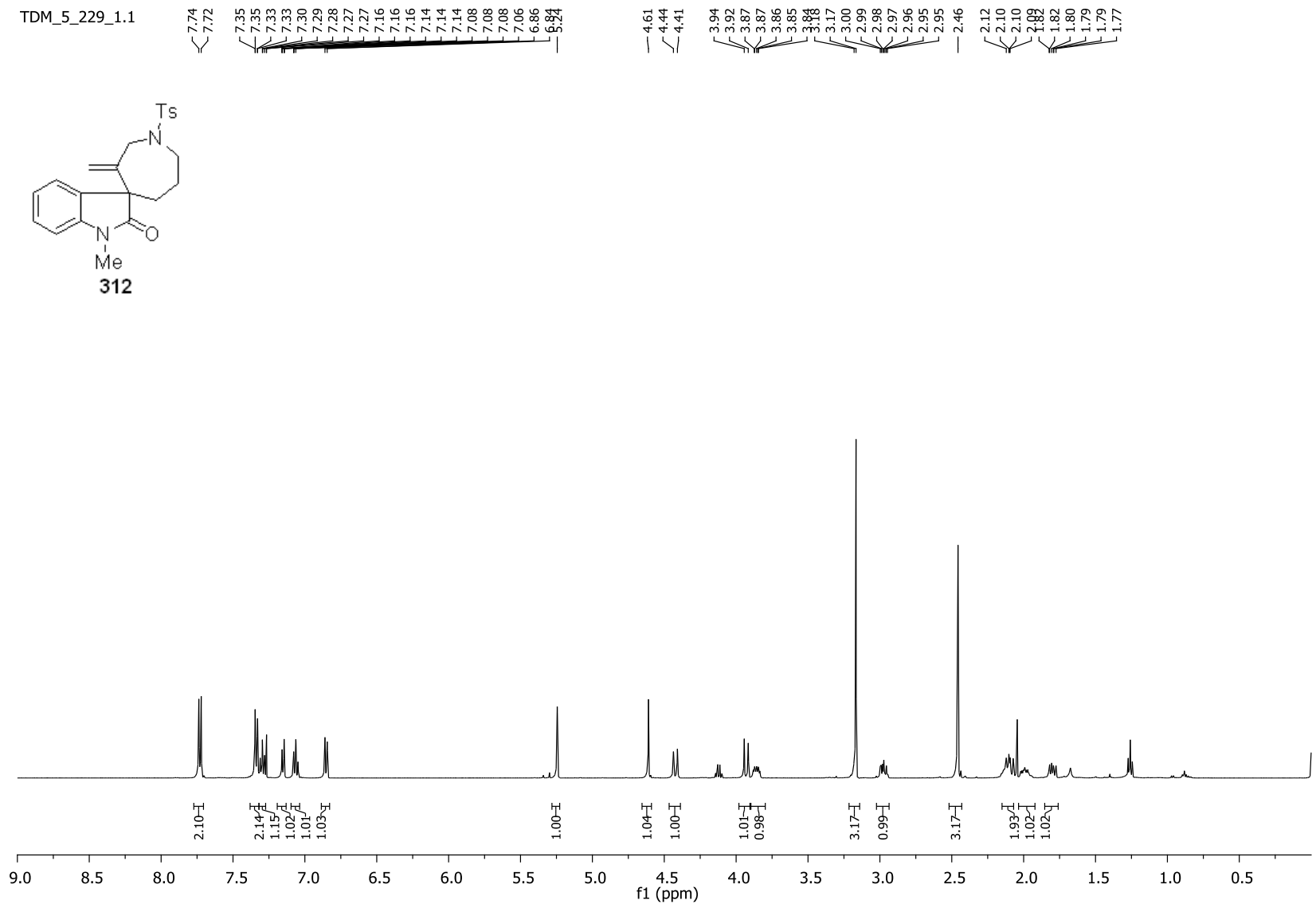


Figure 170. ^{1}H NMR Spectrum for **312** (500 MHz, $CDCl_3$)

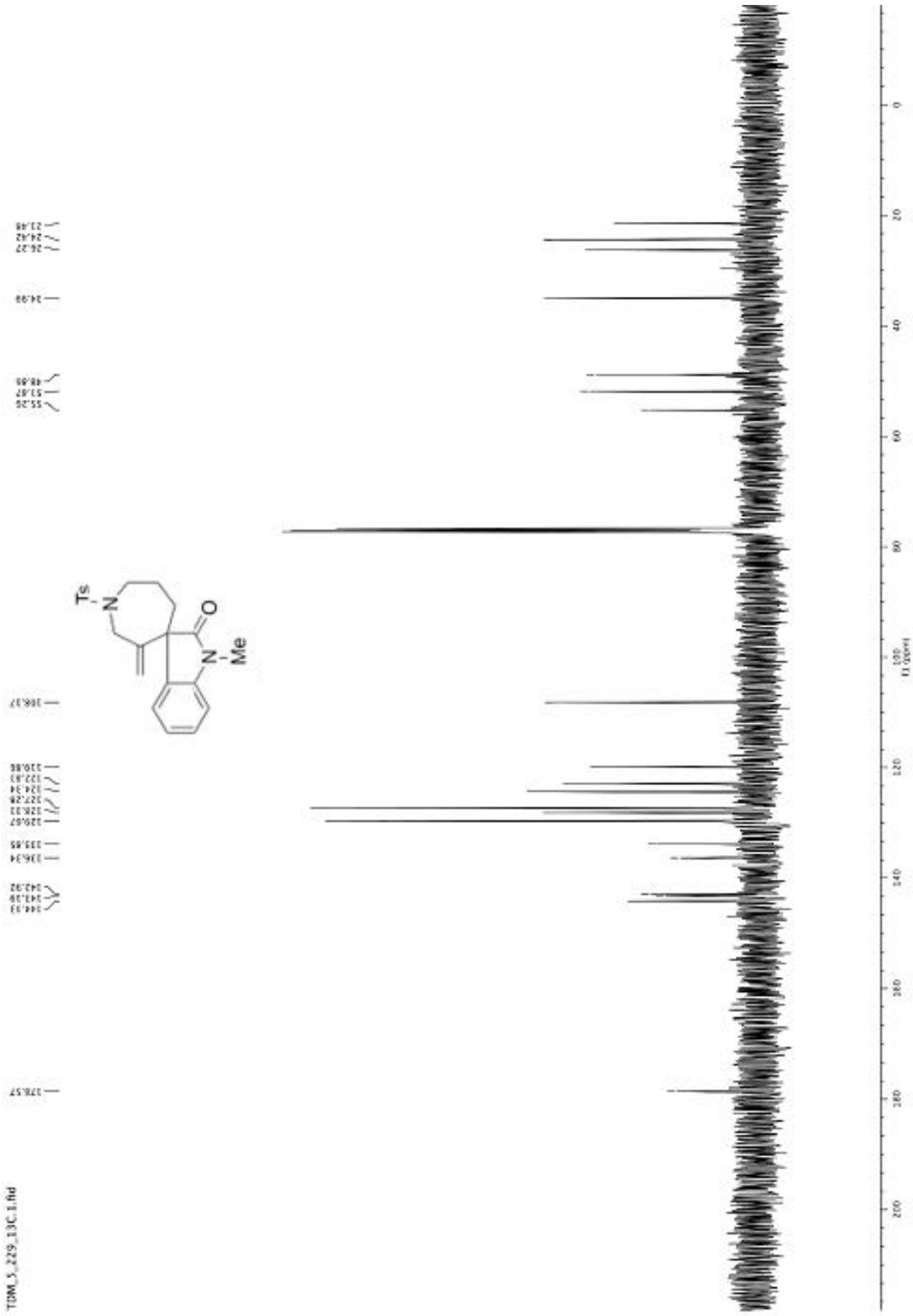


Figure 171. ^{13}C NMR Spectrum for **312** (125 MHz, $CDCl_3$)

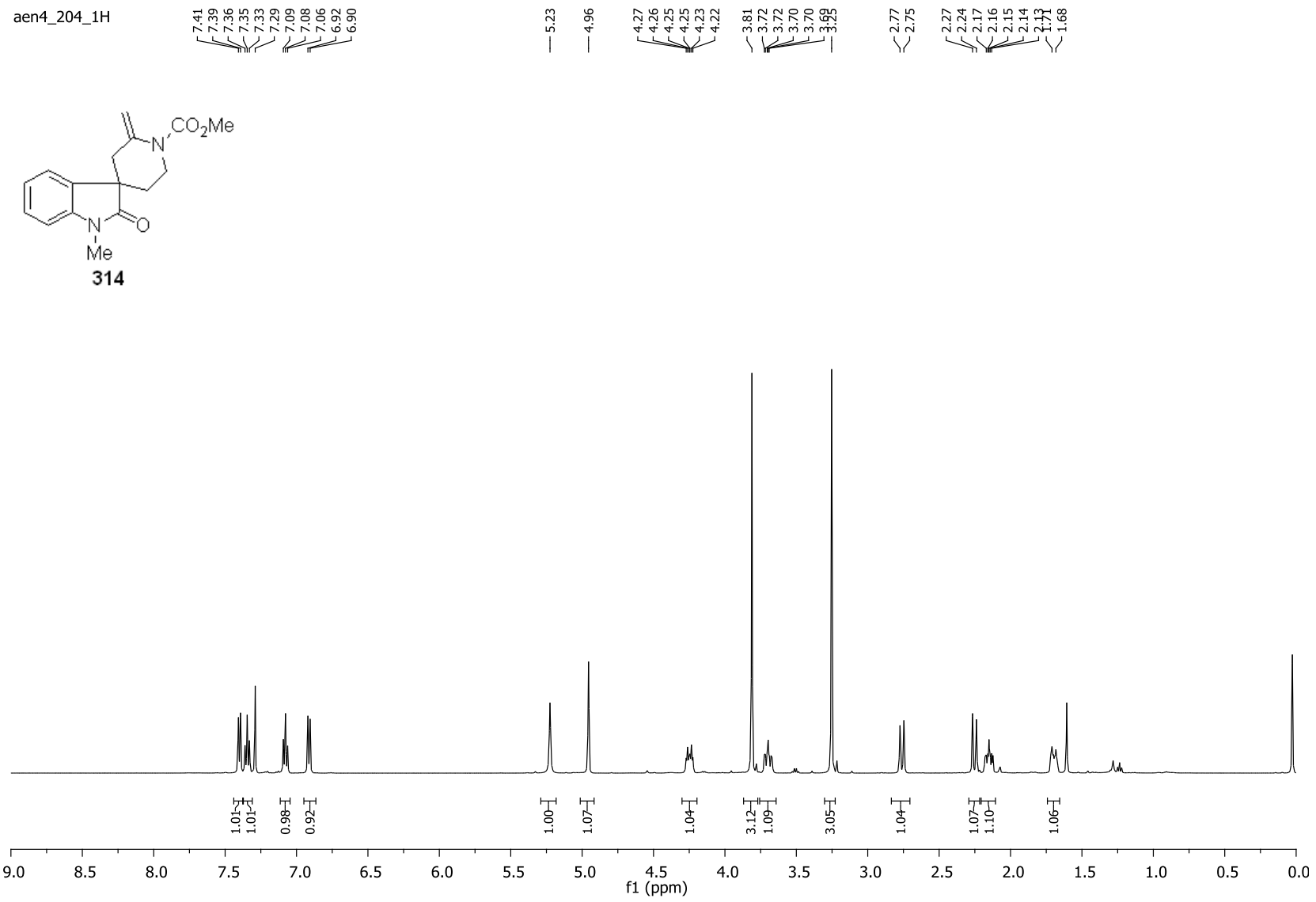


Figure 172. ^{1}H NMR Spectrum for **314** (500 MHz, $CDCl_3$)

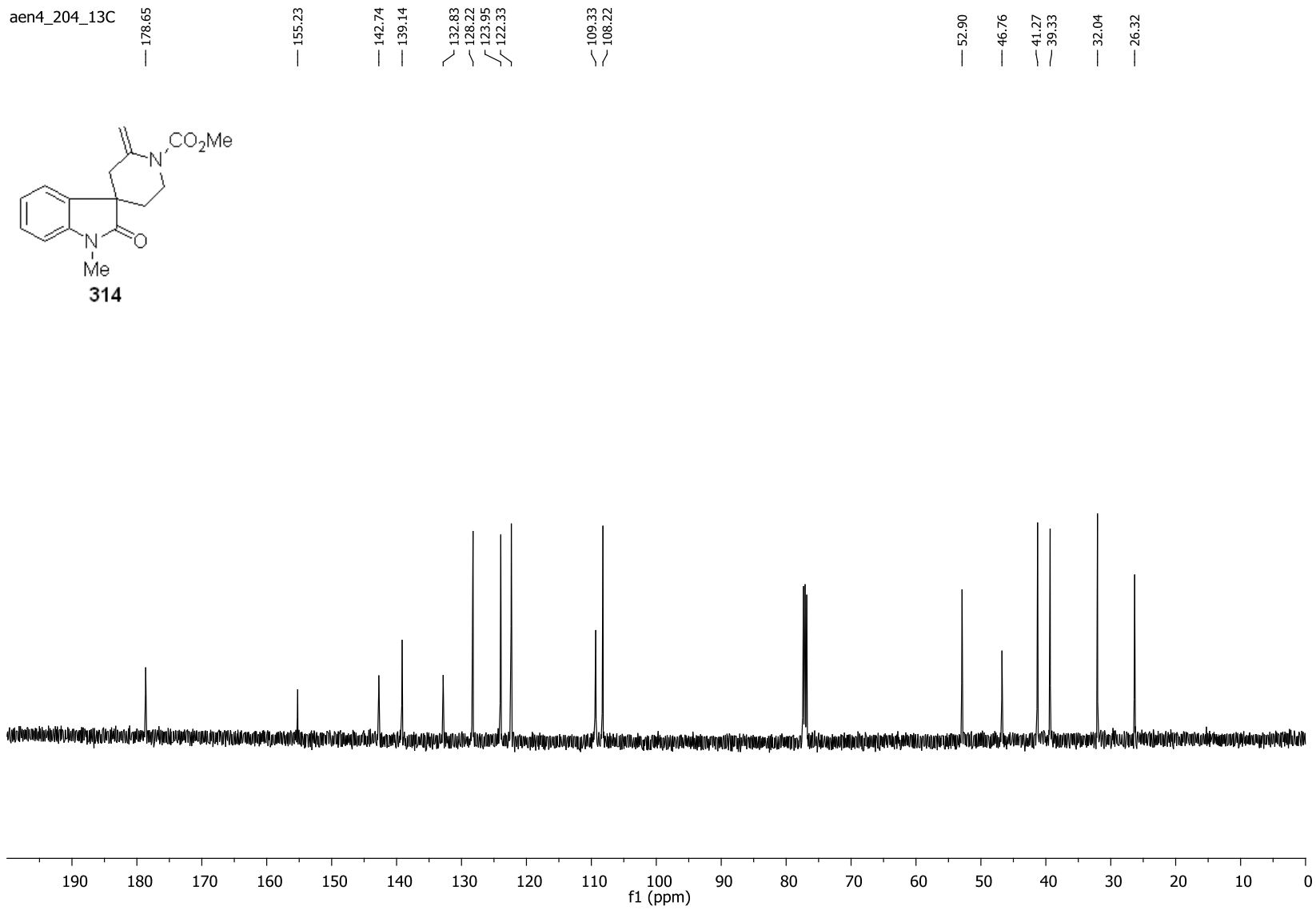


Figure 173. ^{13}C NMR Spectrum for **314** (125 MHz, $CDCl_3$)

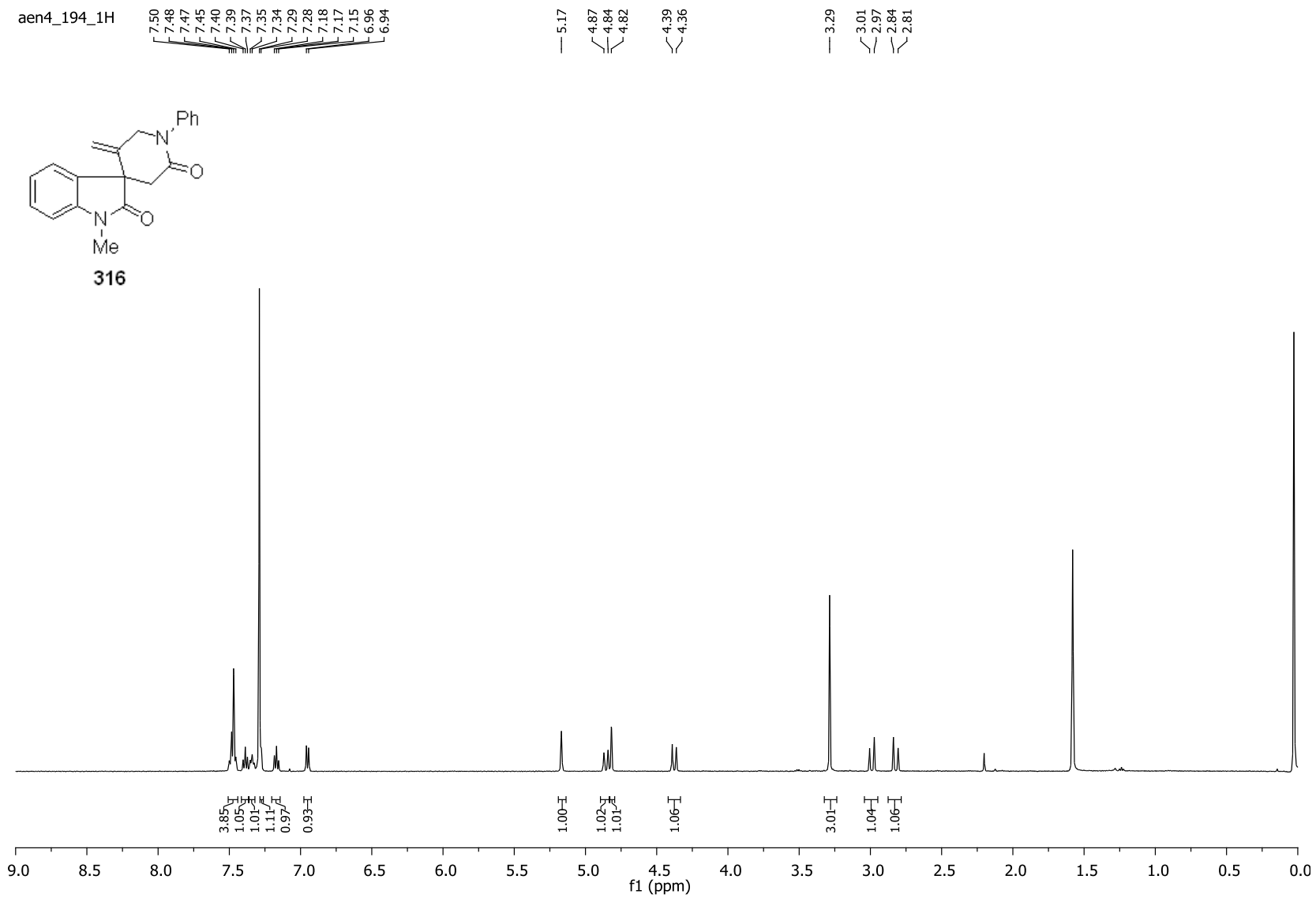


Figure 174. ^{1}H NMR Spectrum for **316** (500 MHz, $CDCl_3$)

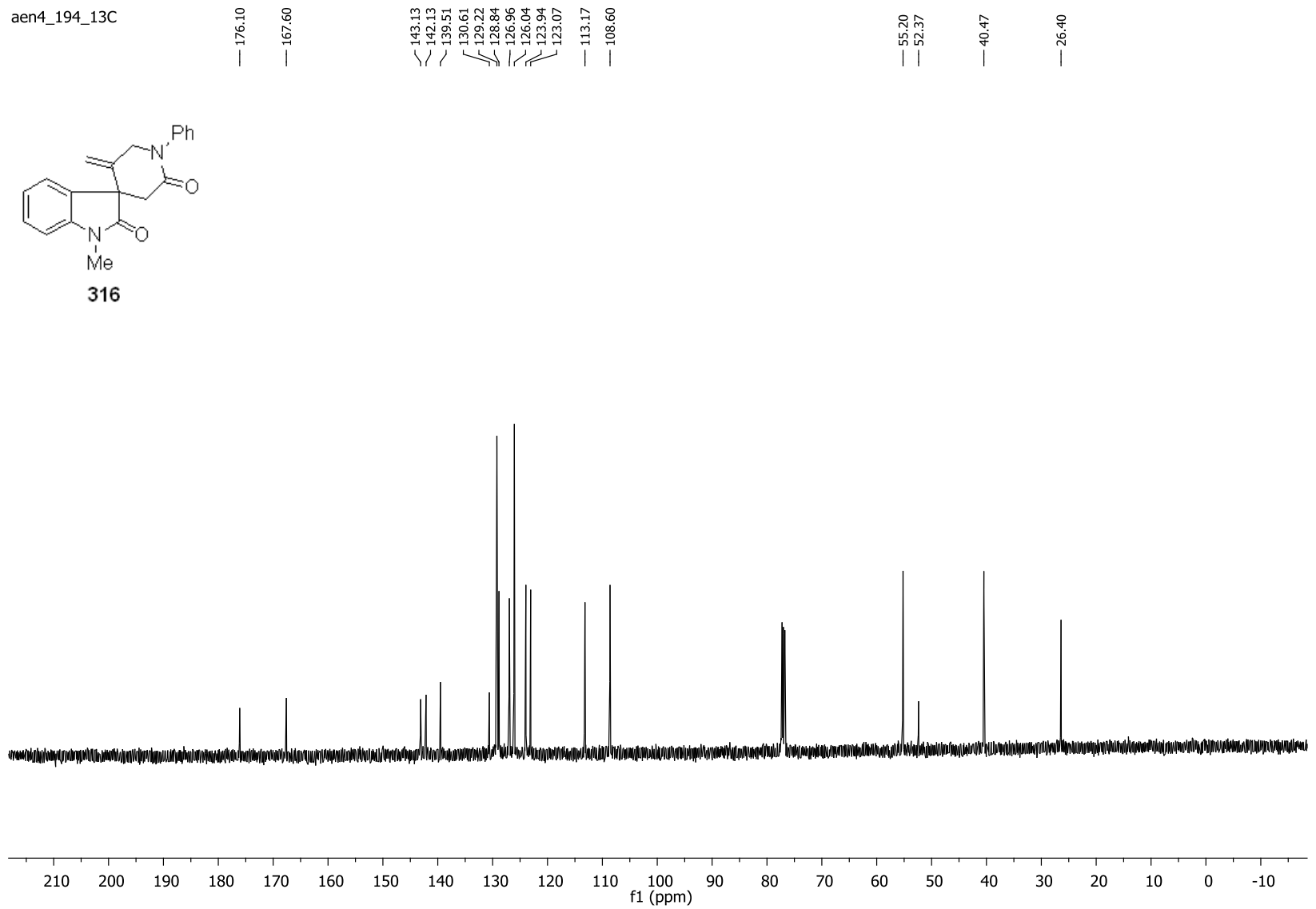


Figure 175. ^{13}C NMR Spectrum for **316** (125 MHz, $CDCl_3$)

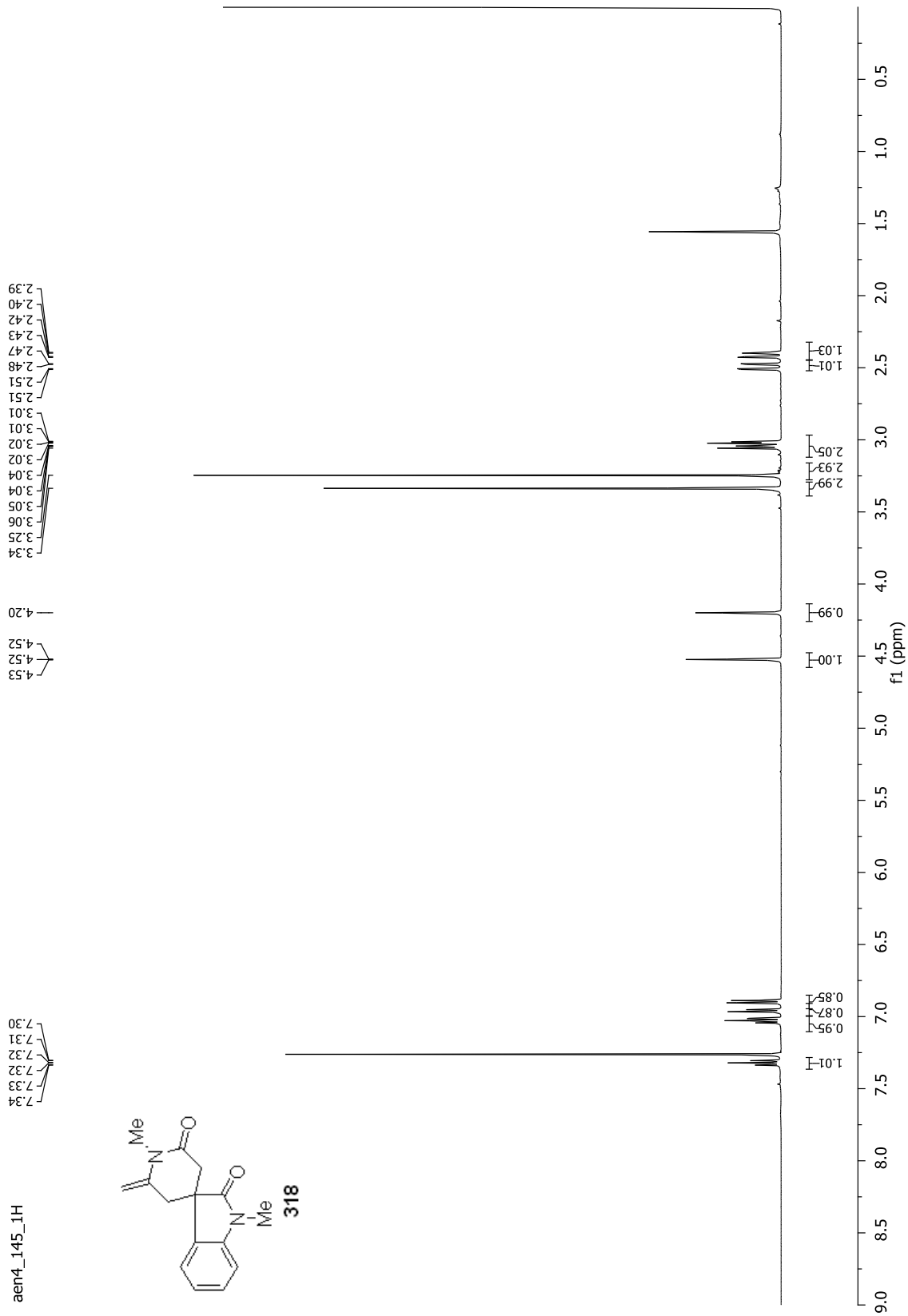


Figure 176. ^{1}H NMR Spectrum for **318** (500 MHz, $CDCl_3$)

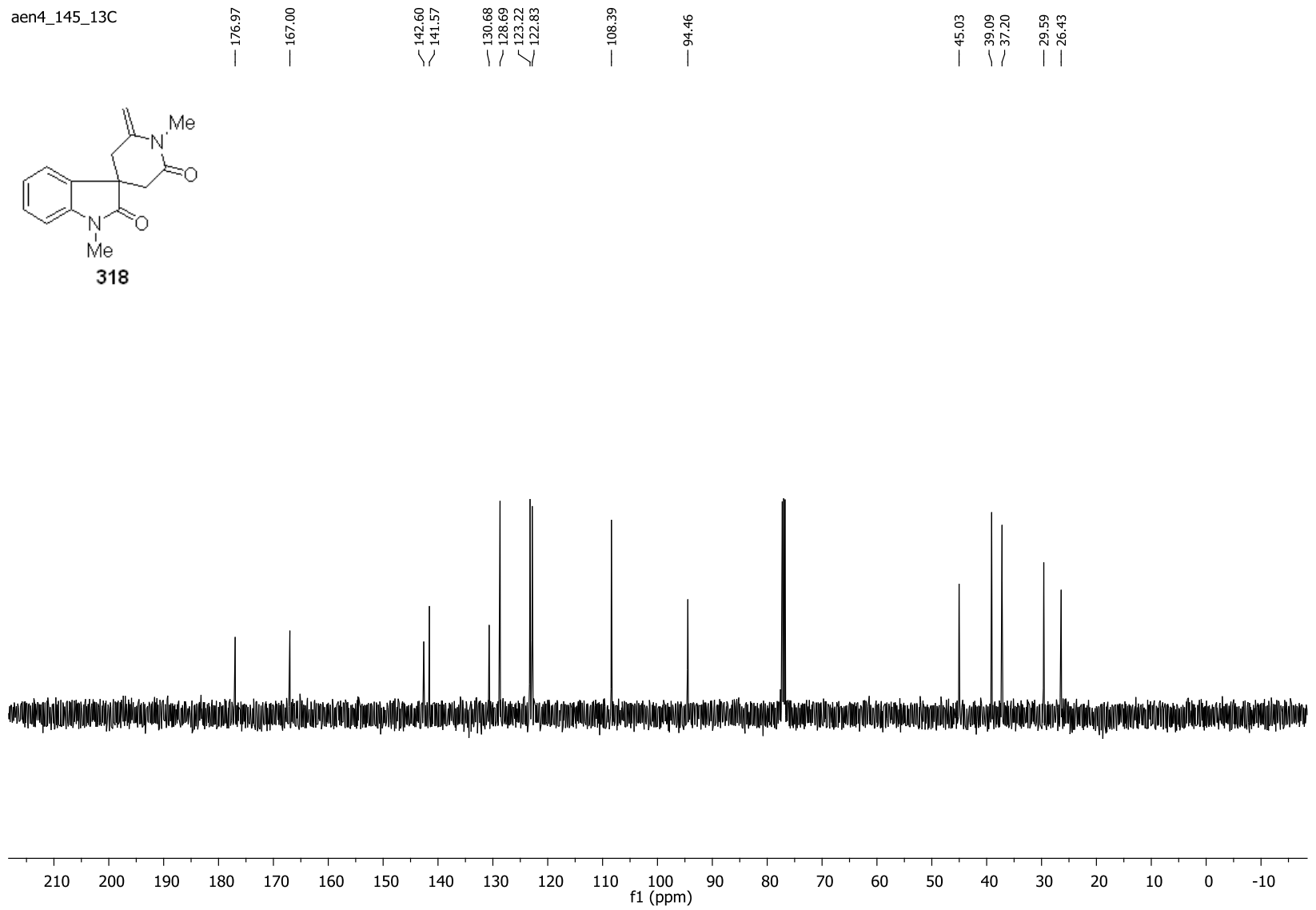


Figure 177. ^{13}C NMR Spectrum for **318** (125 MHz, $CDCl_3$)

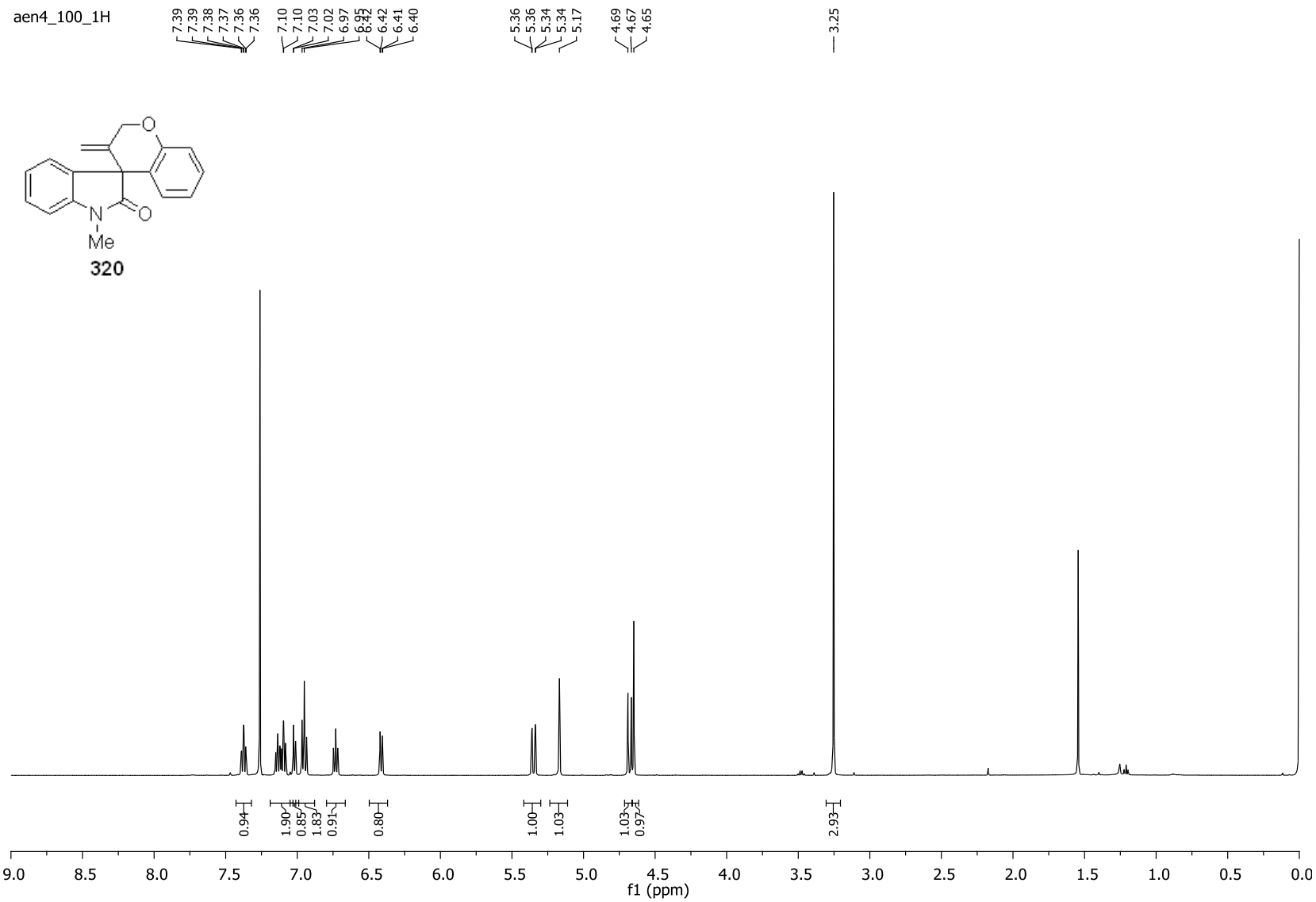


Figure 178. ^{1}H NMR Spectrum for **320** (500 MHz, $CDCl_3$)

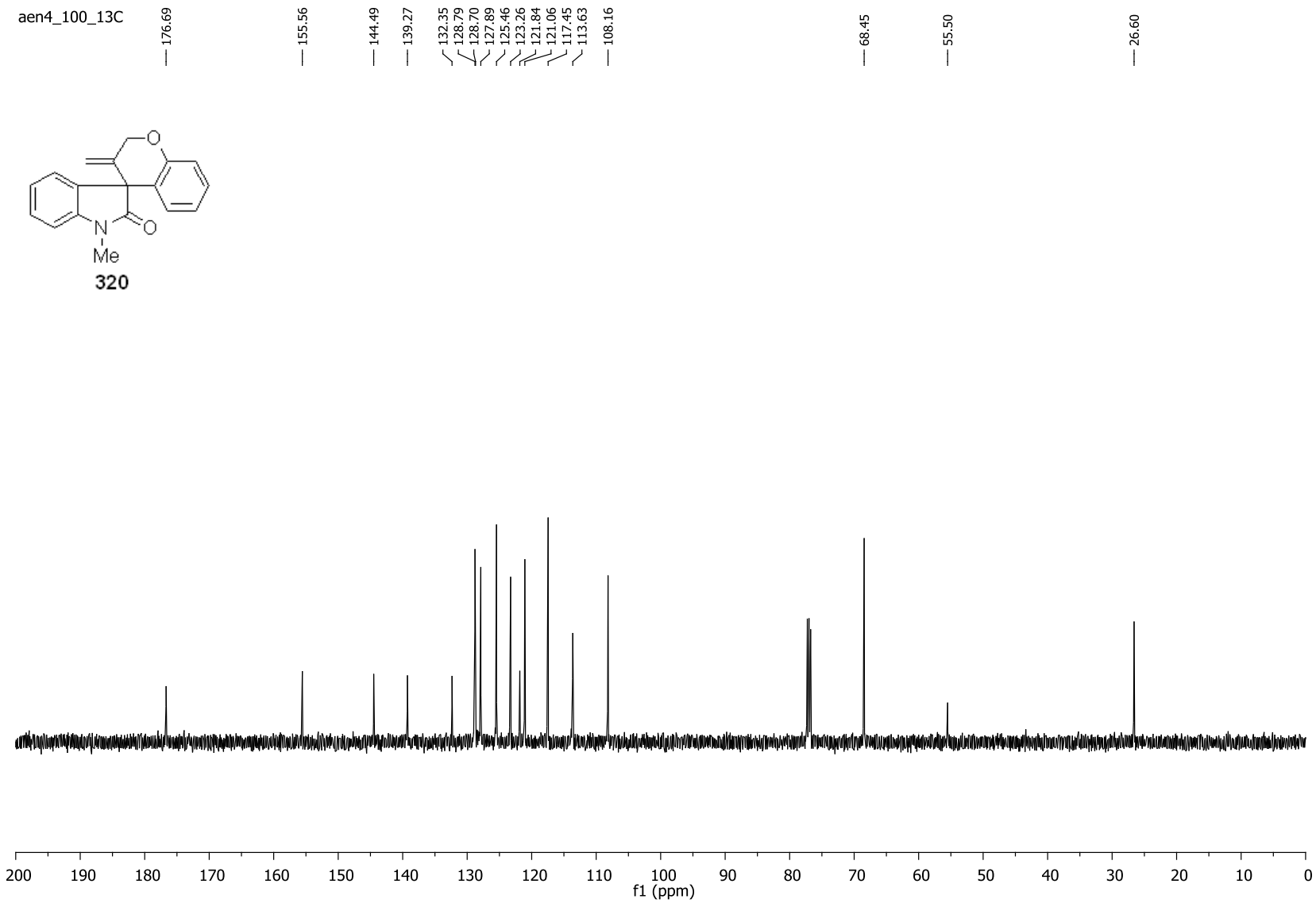


Figure 179. ^{13}C NMR Spectrum for **320** (125 MHz, $CDCl_3$)

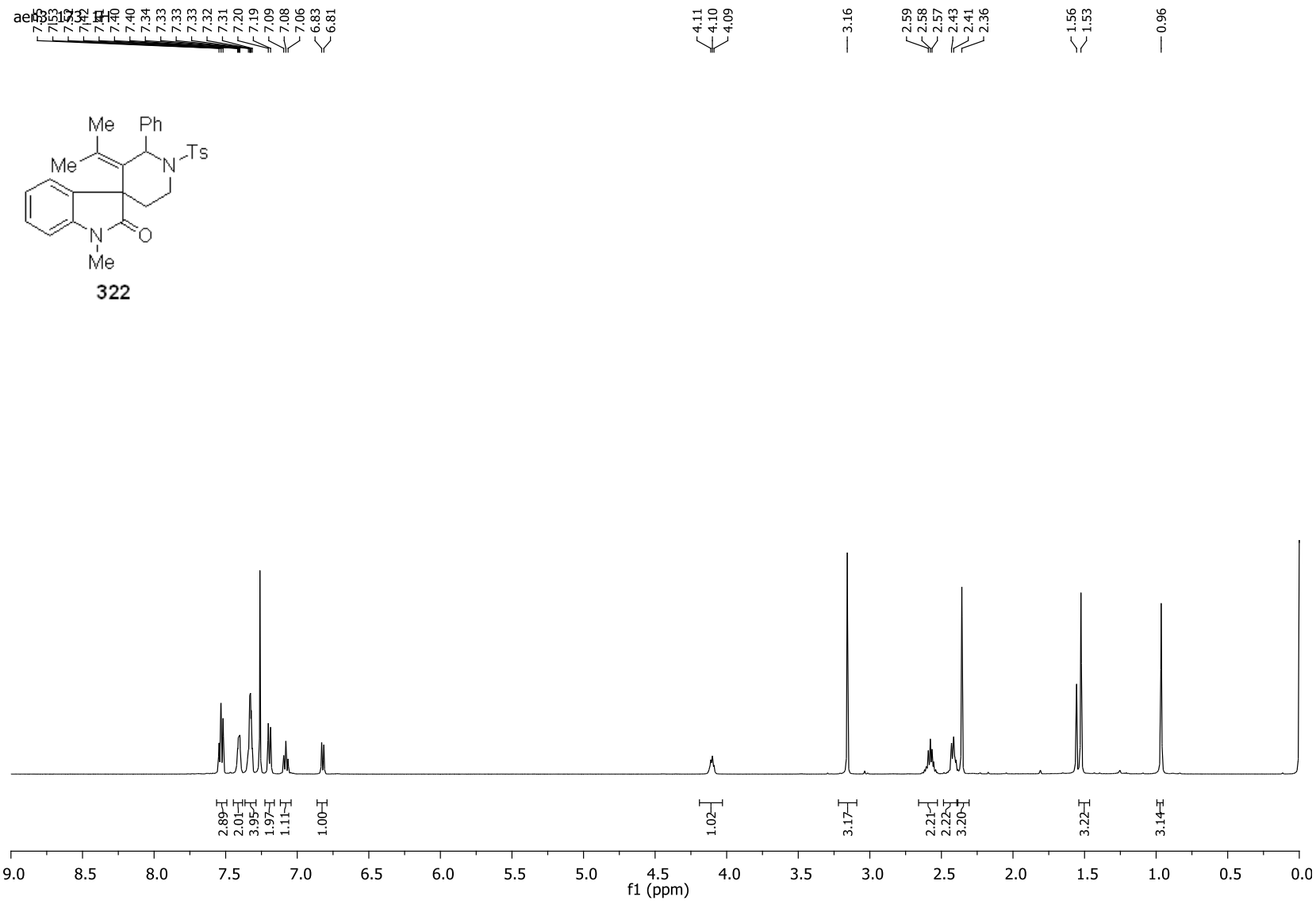


Figure 180. ^{1}H NMR Spectrum for **322** (500 MHz, $CDCl_3$)

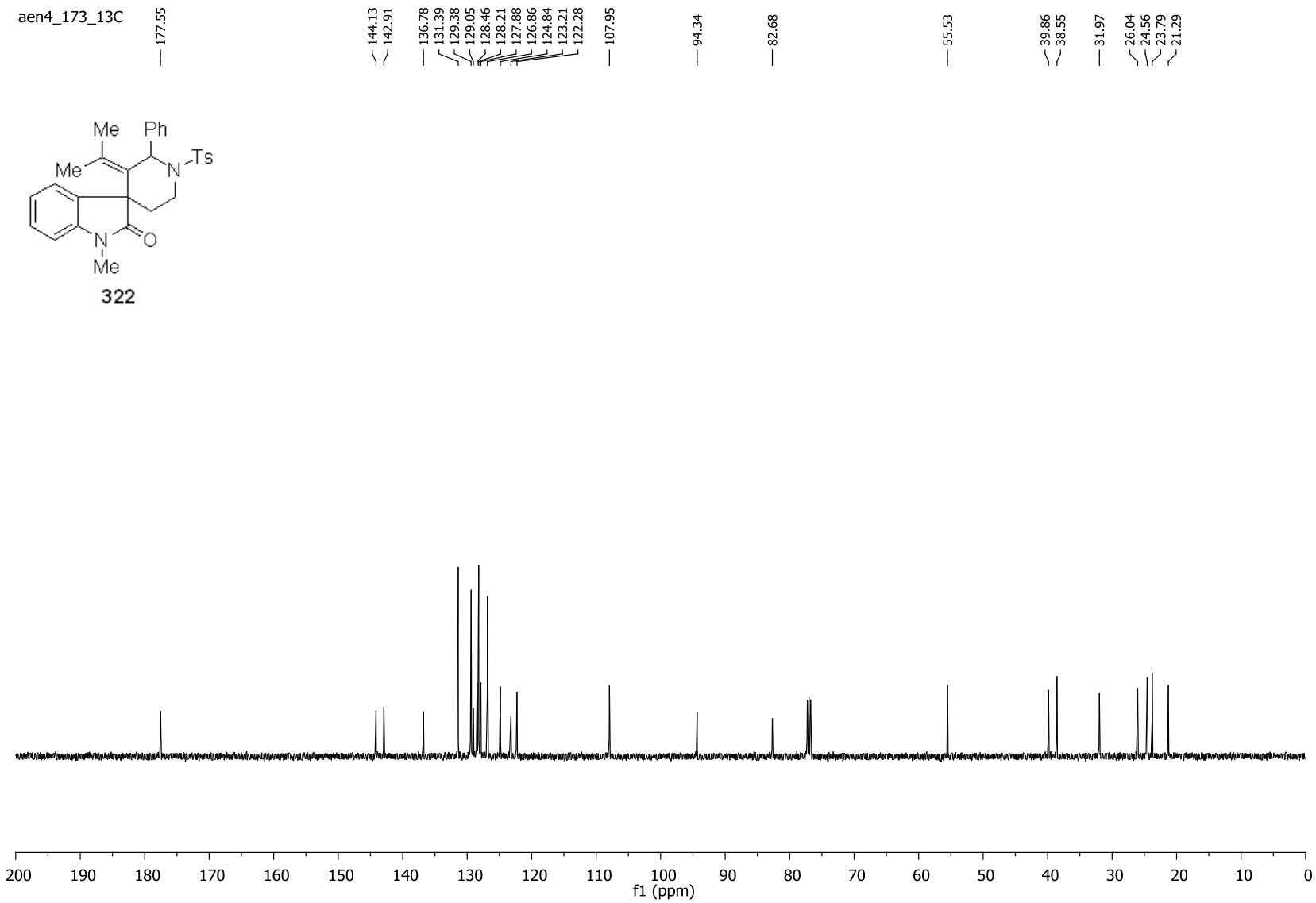
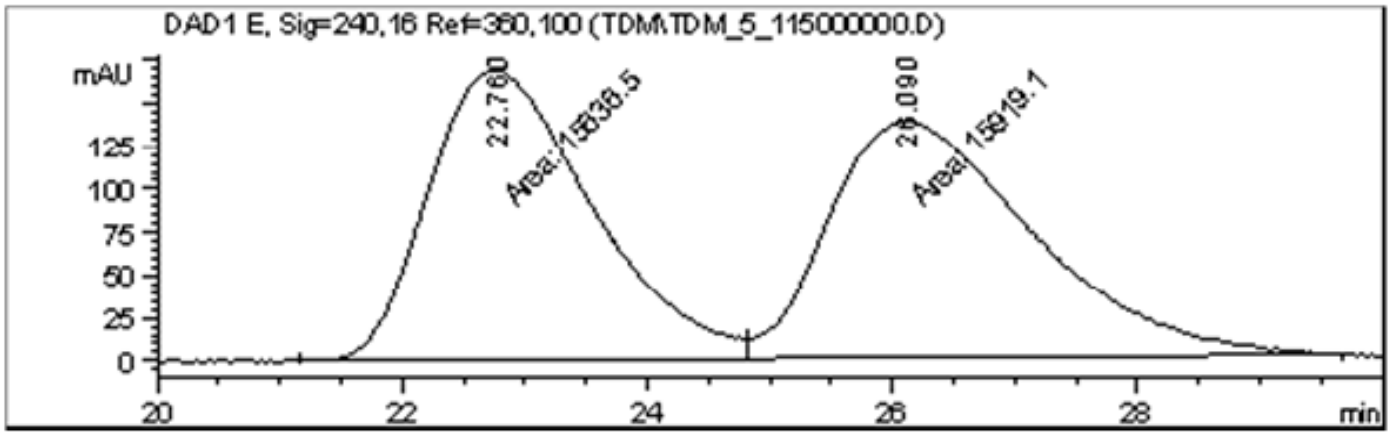


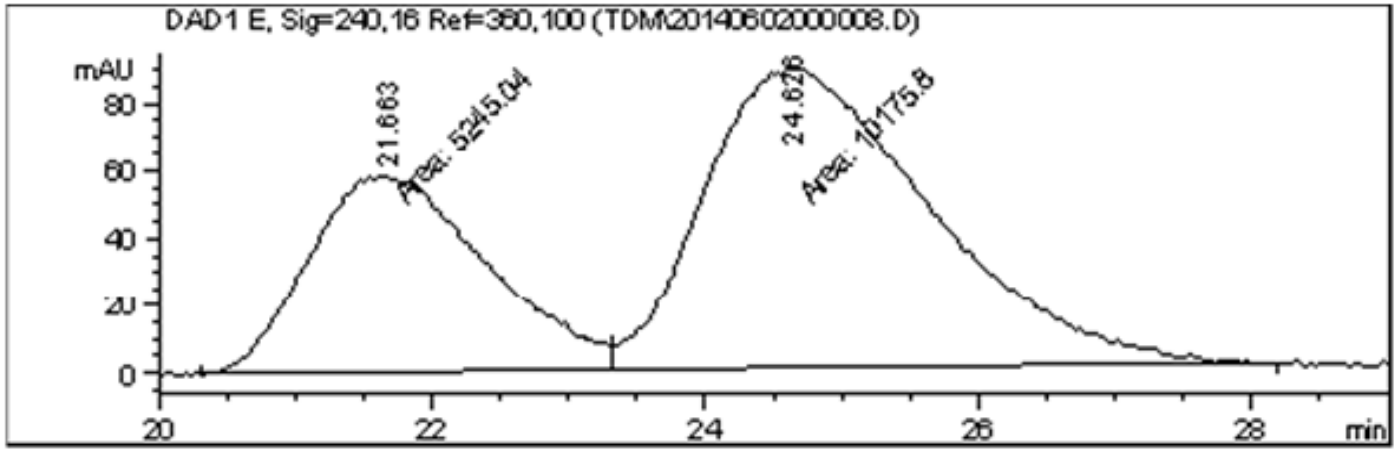
Figure 181. ^{13}C NMR Spectrum for **322** (125 MHz, $CDCl_3$)



Signal 5: DAD1 E, Sig=240,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.760	MF	1.5455	1.56365e4	168.62160	49.5522
2	26.090	FM	1.9268	1.59191e4	137.69661	50.4478

Figure 182. HPLC of **304** (Chiralpak AS-H)



Signal 5: DAD1 E, Sig=240,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.663	MF	1.5086	5245.03711	57.94570	34.0126
2	24.626	FM	1.9127	1.01758e4	88.67045	65.9874

Figure 183. HPLC of **304** (Chiralpak AS-H)

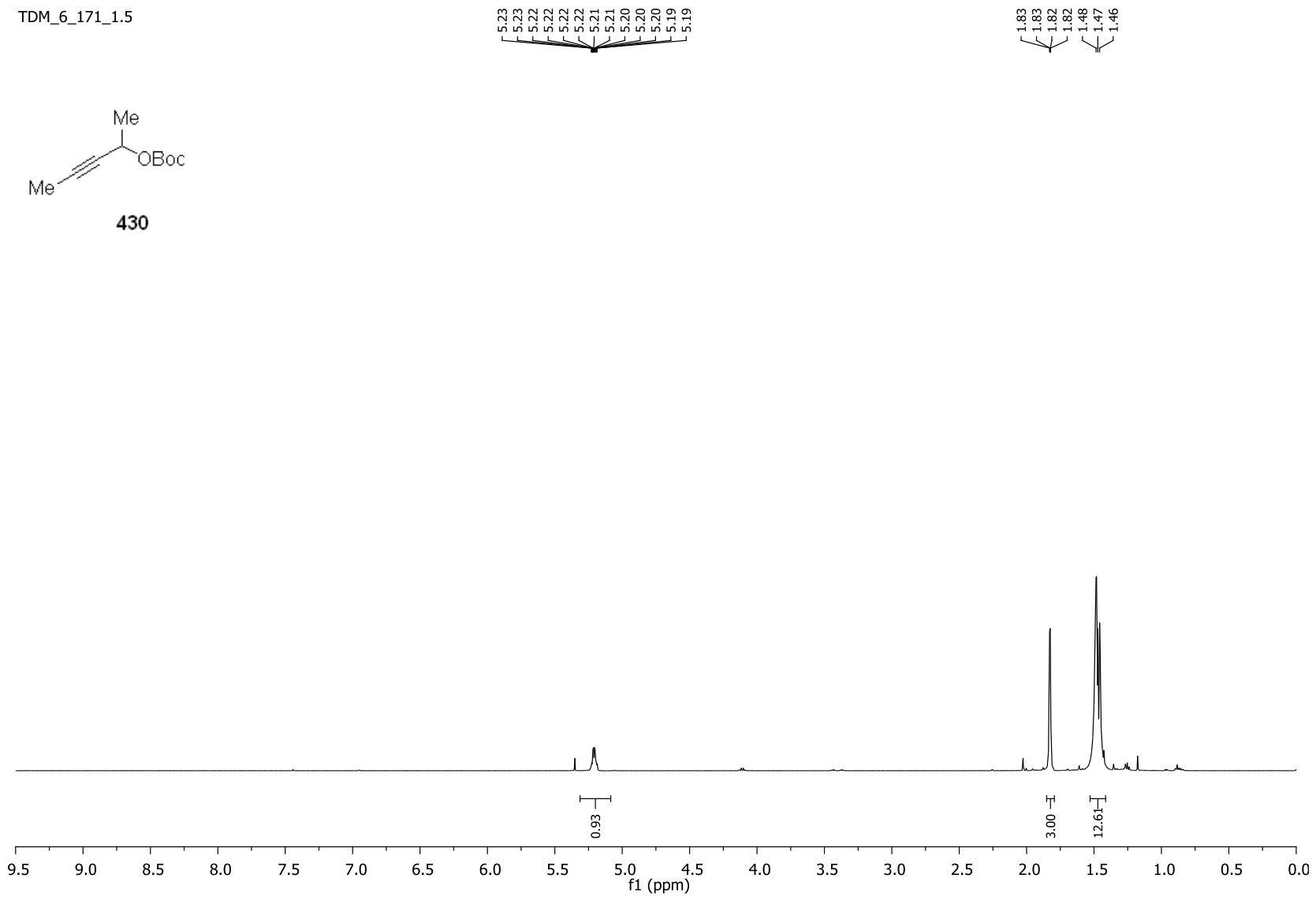


Figure 184. ^{1}H NMR Spectrum for **430** (500 MHz, $CDCl_3$)

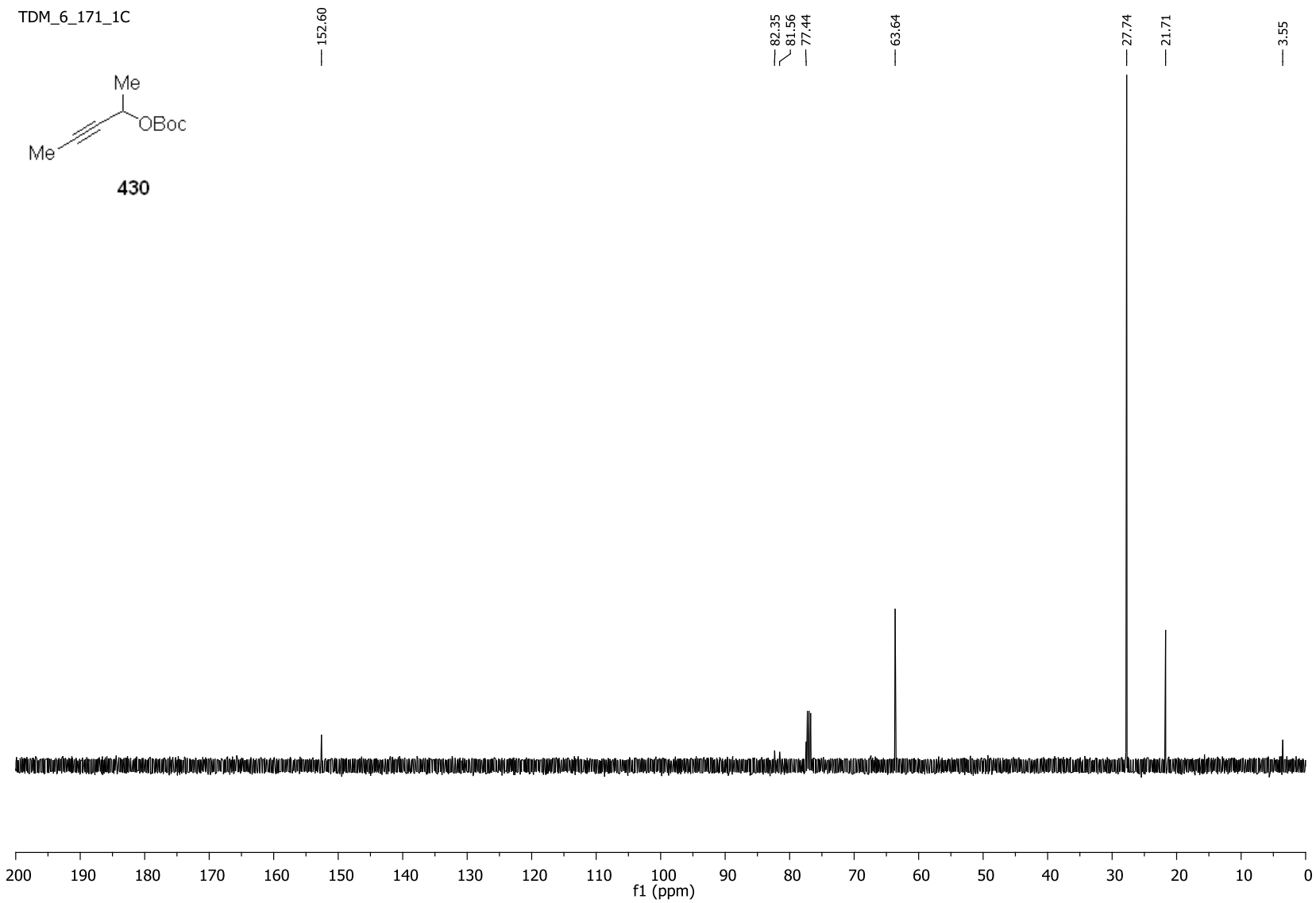


Figure 185. ^{13}C NMR Spectrum for **430** (125 MHz, $CDCl_3$)

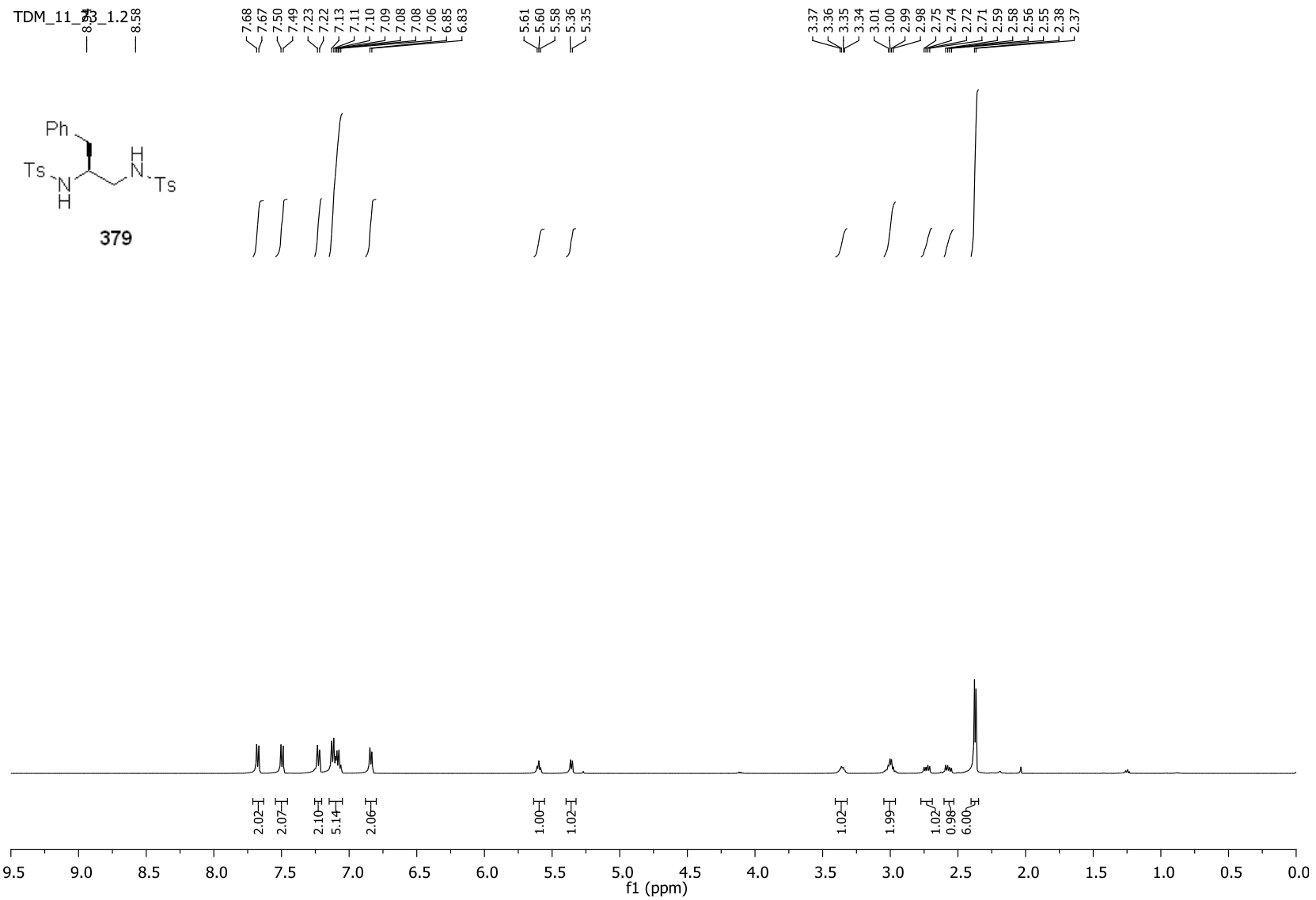


Figure 186. ^{1}H NMR Spectrum for **379** (500 MHz, $CDCl_3$)

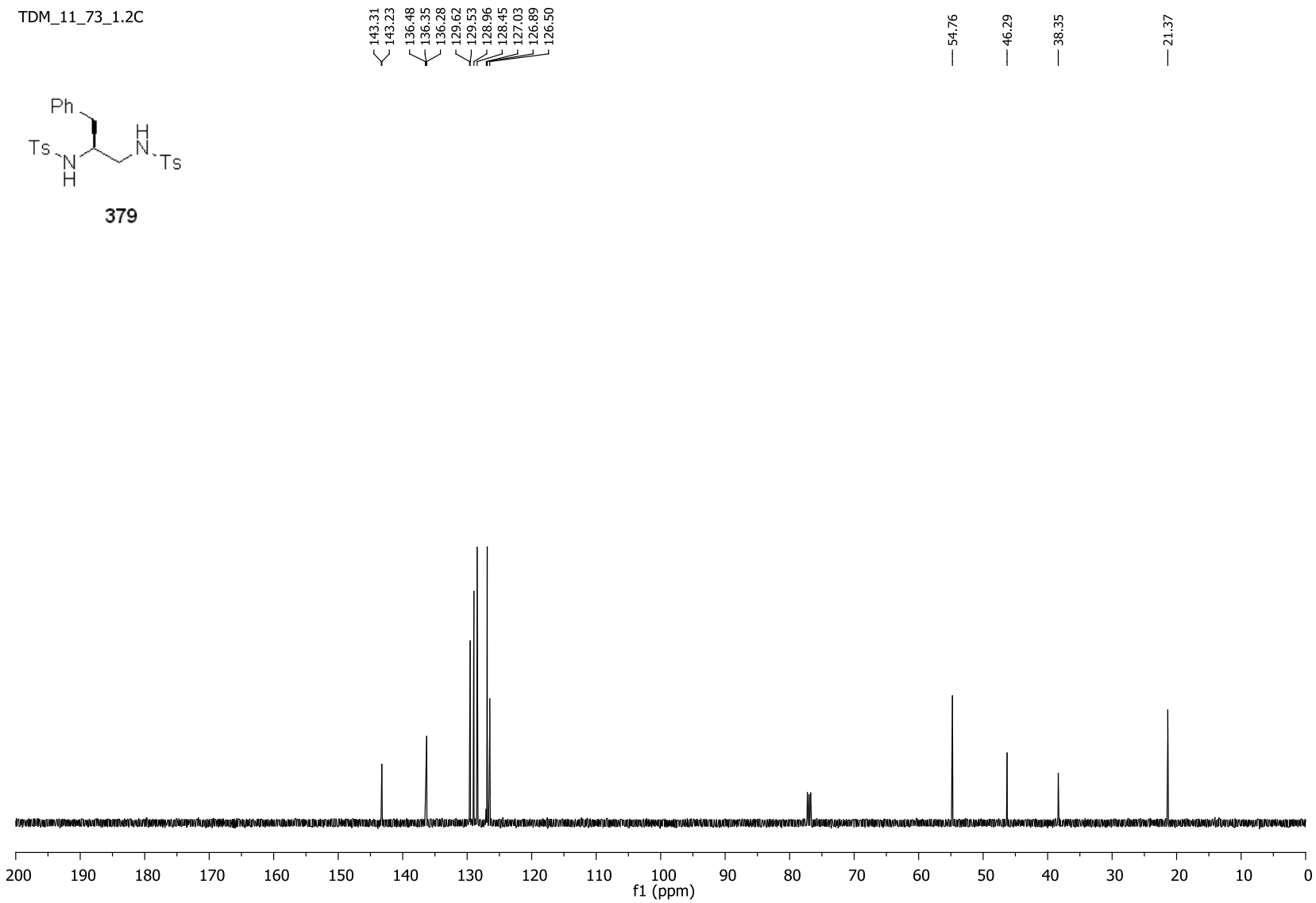


Figure 187. ^{13}C NMR Spectrum for **379** (125 MHz, $CDCl_3$)

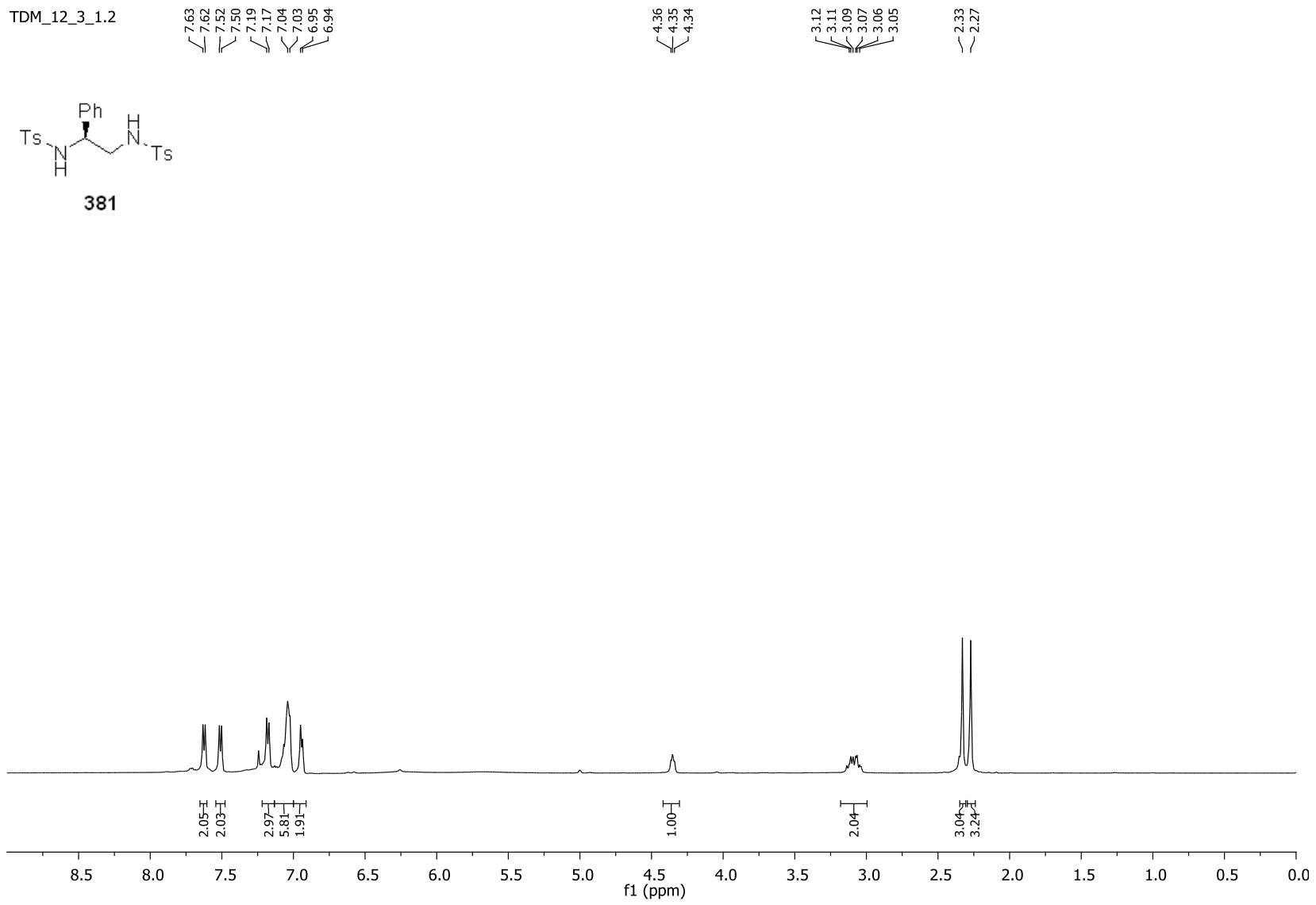


Figure 188. ^{1}H NMR Spectrum for **381** (500 MHz, $CDCl_3$)

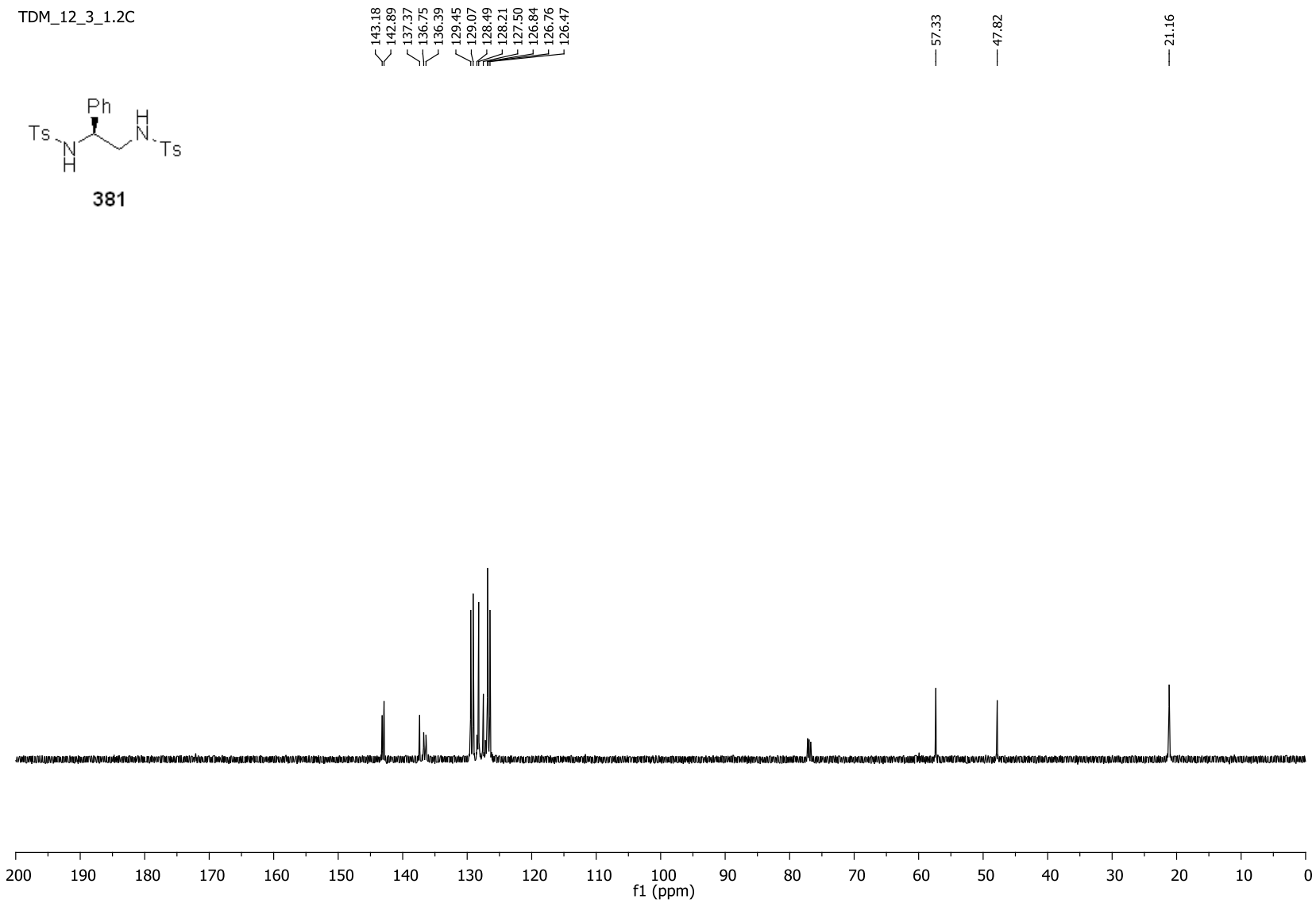


Figure 189. ^{13}C NMR Spectrum for **381** (125 MHz, $CDCl_3$)

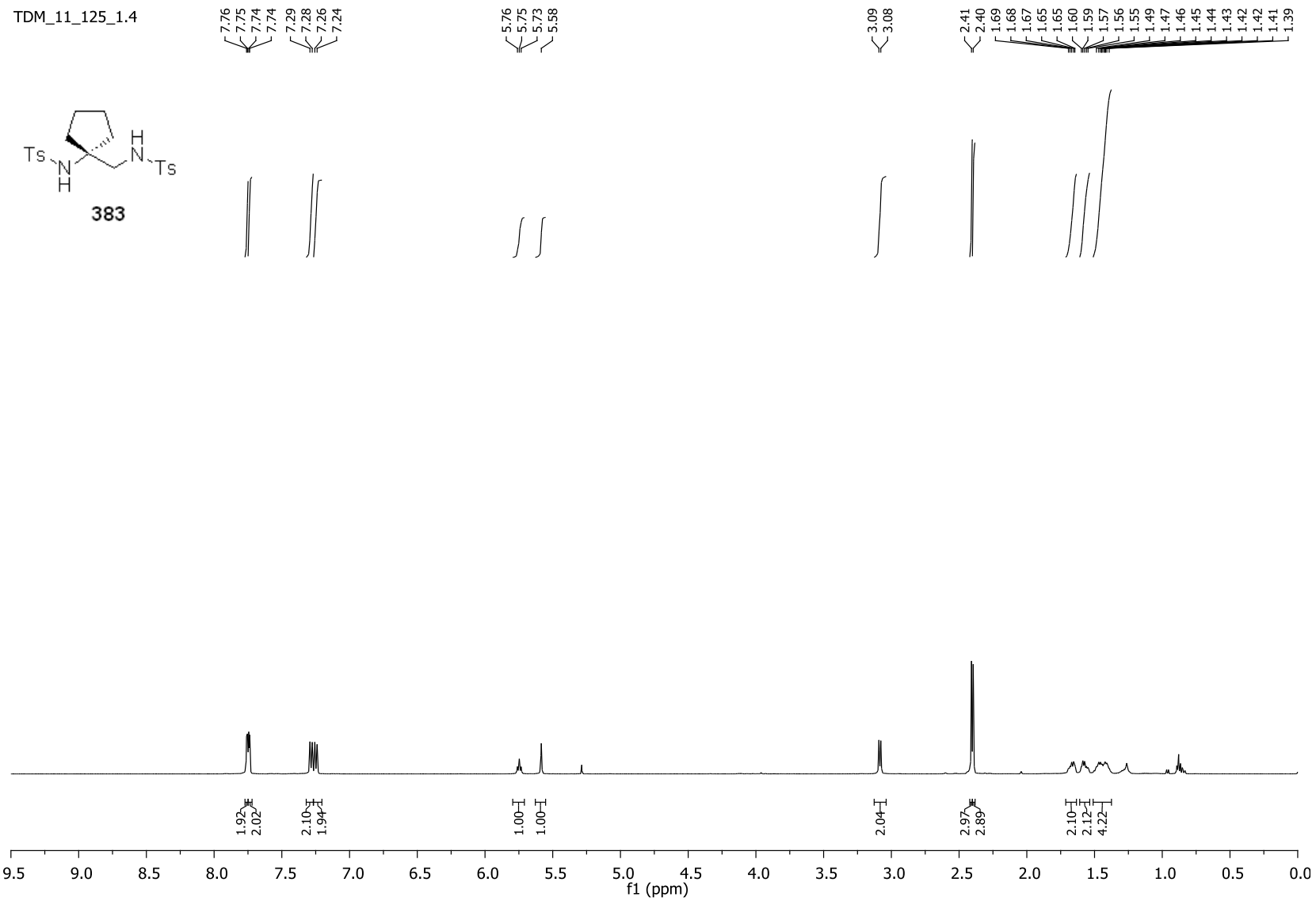


Figure 190. ^{1}H NMR Spectrum for **136** (500 MHz, $CDCl_3$)

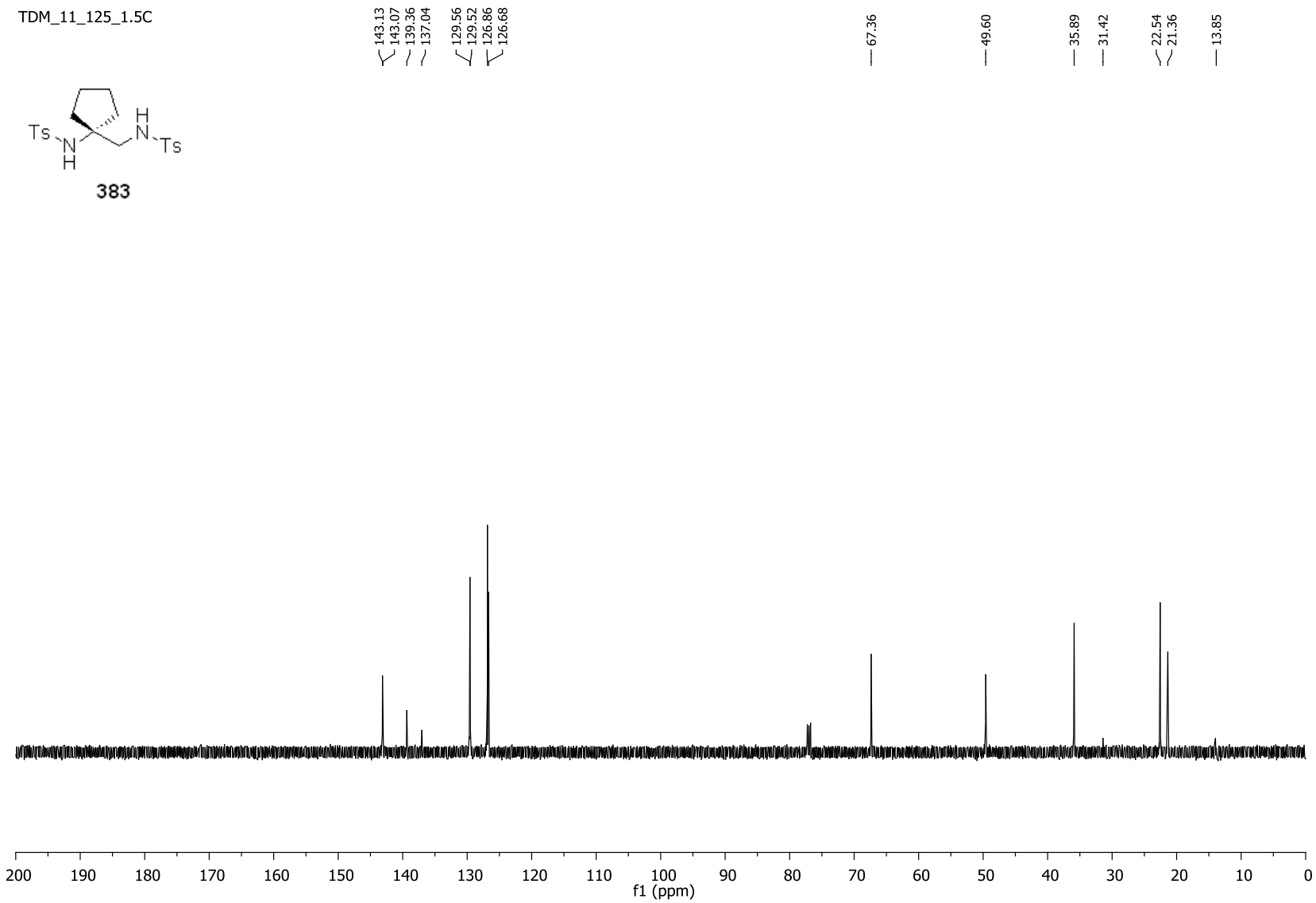


Figure 191. ^{13}C NMR Spectrum for **383** (125 MHz, $CDCl_3$)

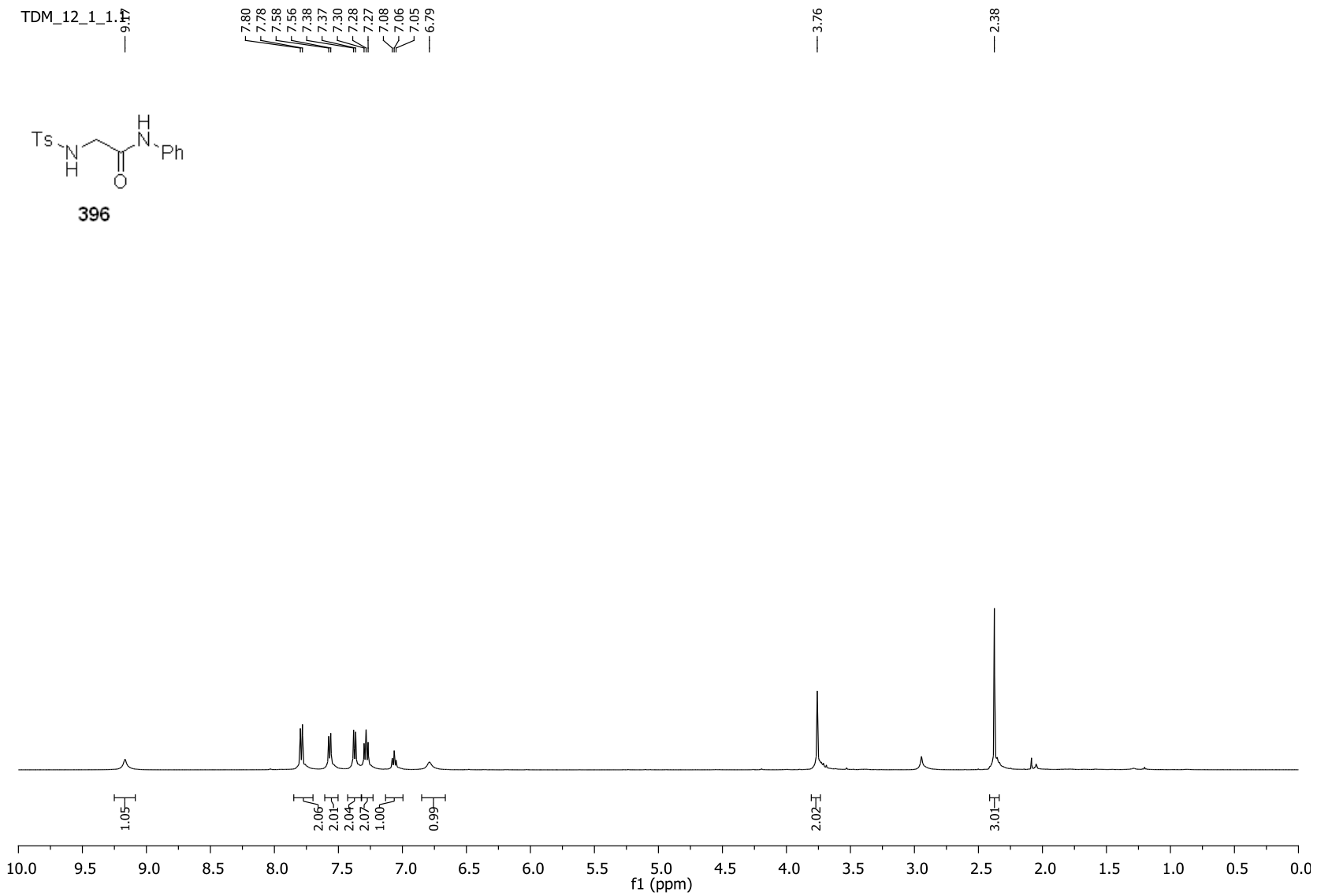


Figure 192. ^{1}H NMR Spectrum for **396** (500 MHz, $CDCl_3$)

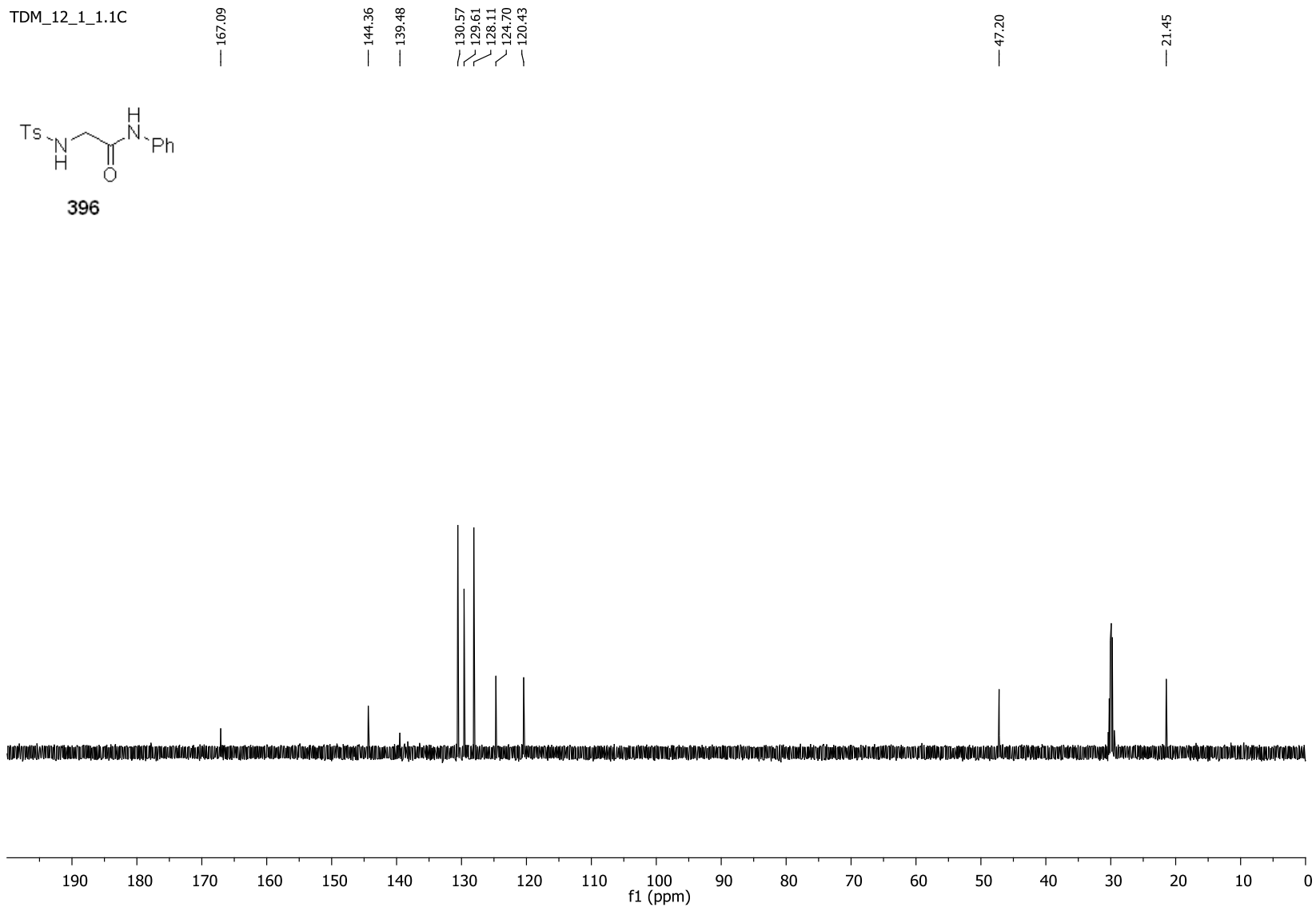


Figure 193. ^{13}C NMR Spectrum for **396** (125 MHz, $CDCl_3$)

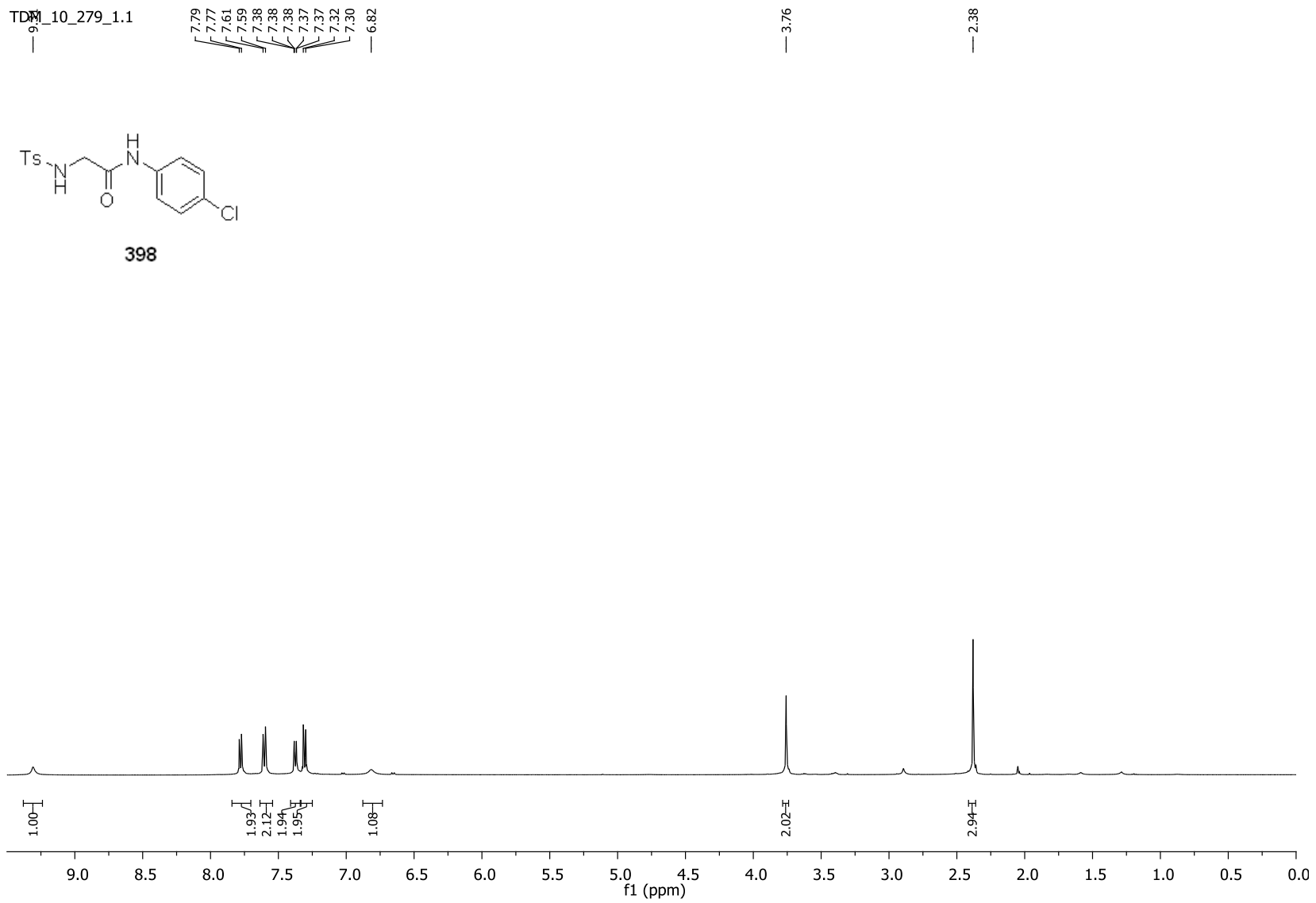


Figure 194. ^{1}H NMR Spectrum for **398** (500 MHz, $CDCl_3$)

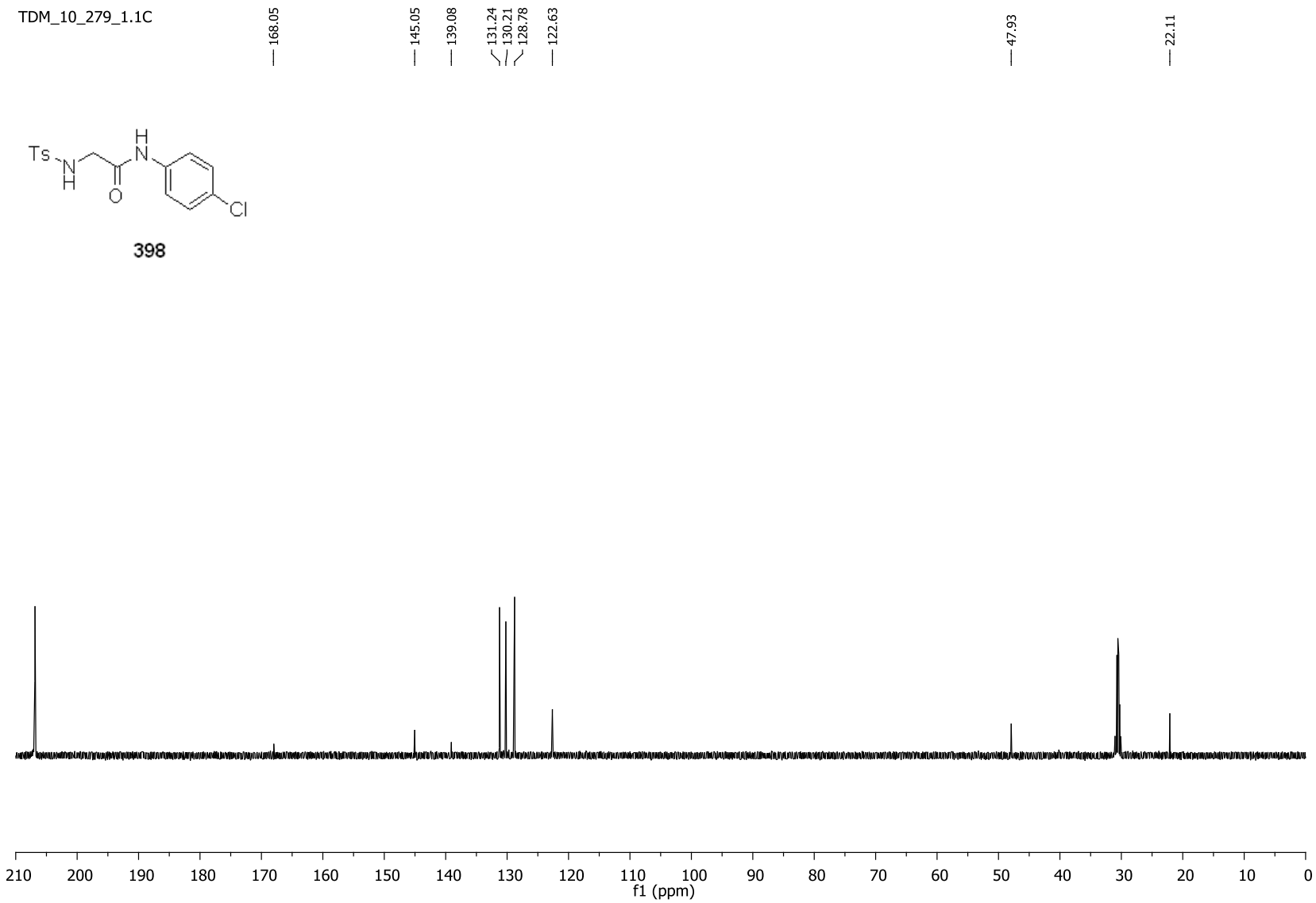


Figure 195. ^{13}C NMR Spectrum for **398** (125 MHz, $CDCl_3$)

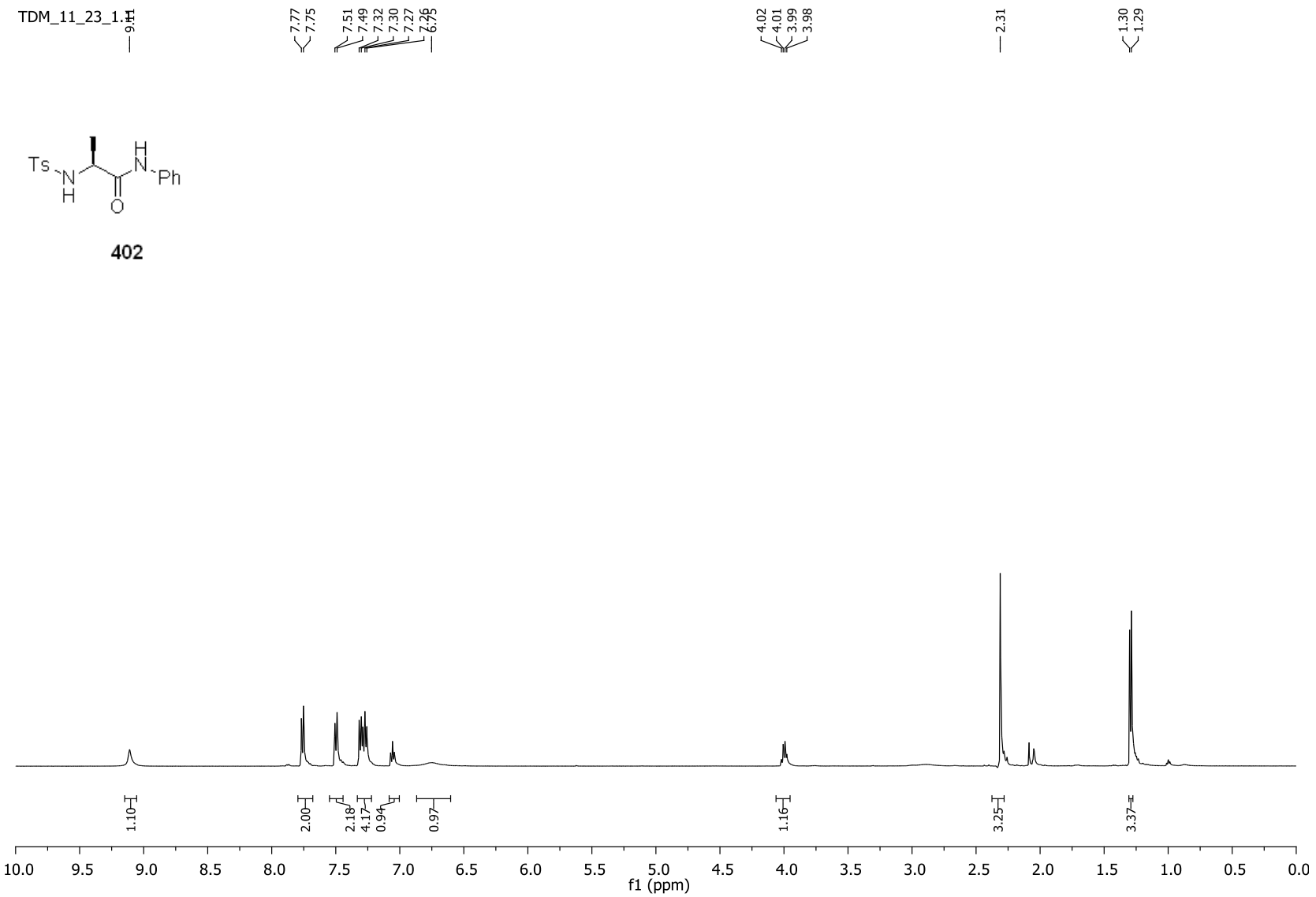


Figure 196. ^{1}H NMR Spectrum for **402** (500 MHz, $CDCl_3$)

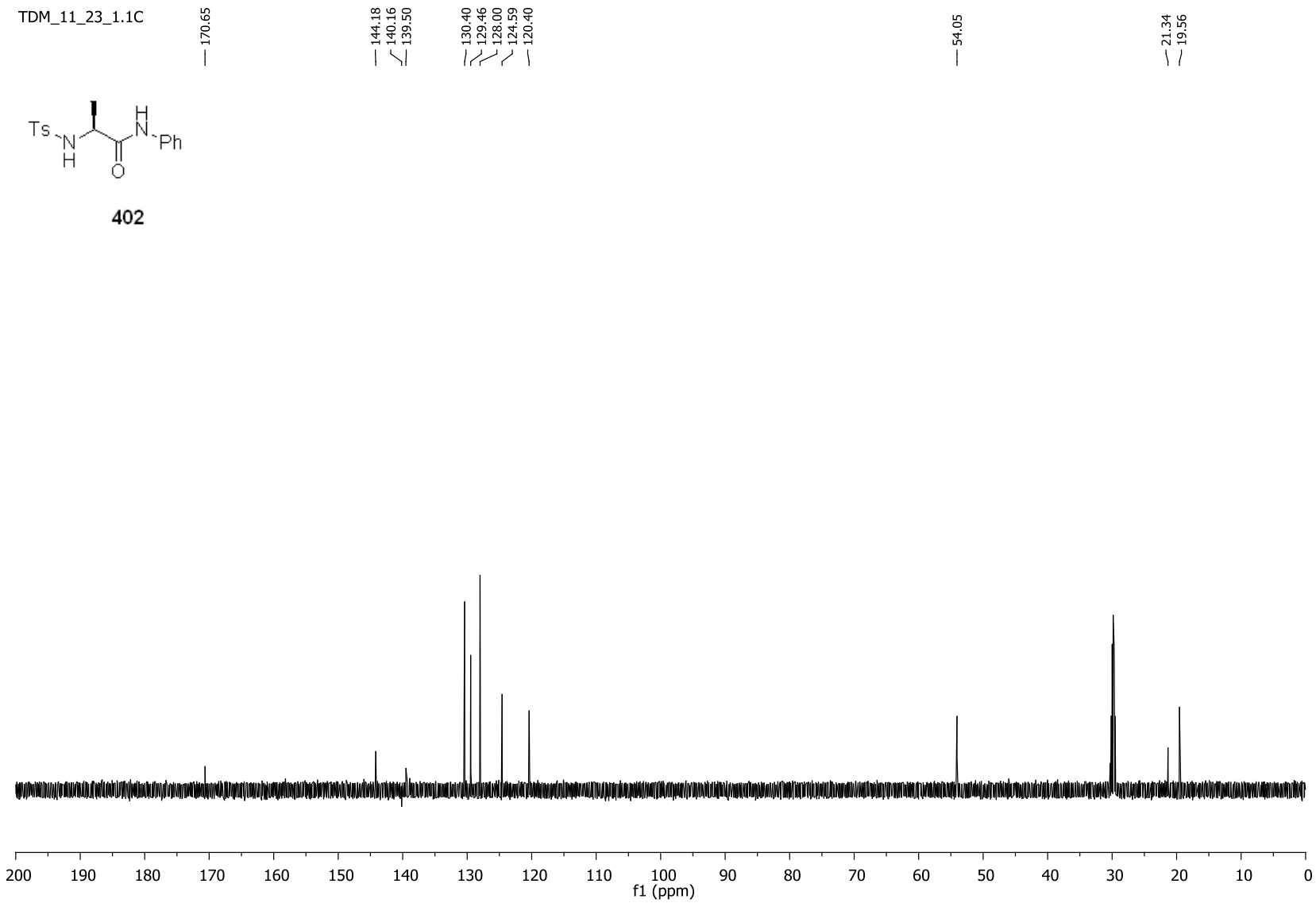


Figure 197. ^{13}C NMR Spectrum for **402** (125 MHz, $CDCl_3$)

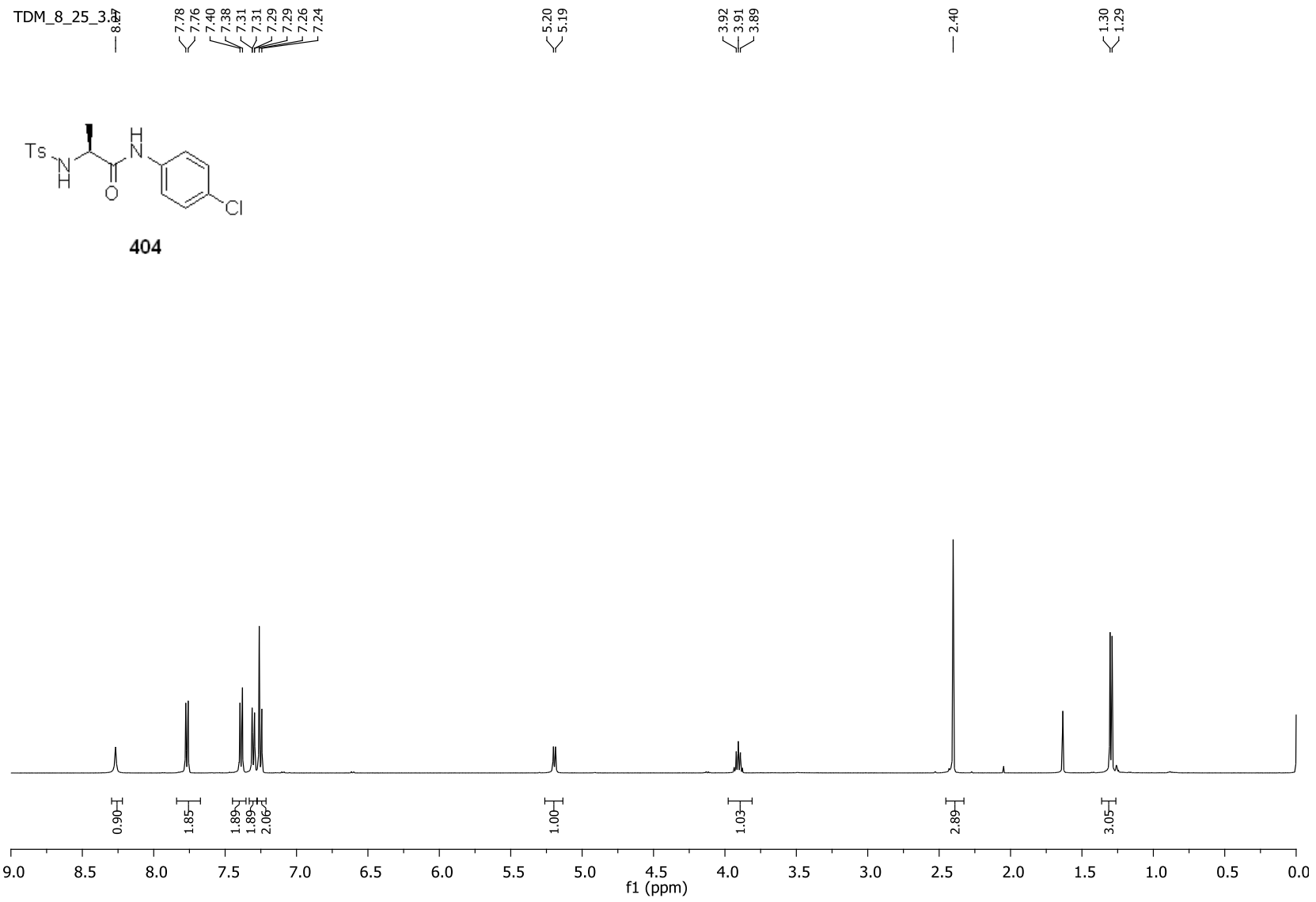


Figure 198. ^{1}H NMR Spectrum for **404** (500 MHz, $CDCl_3$)

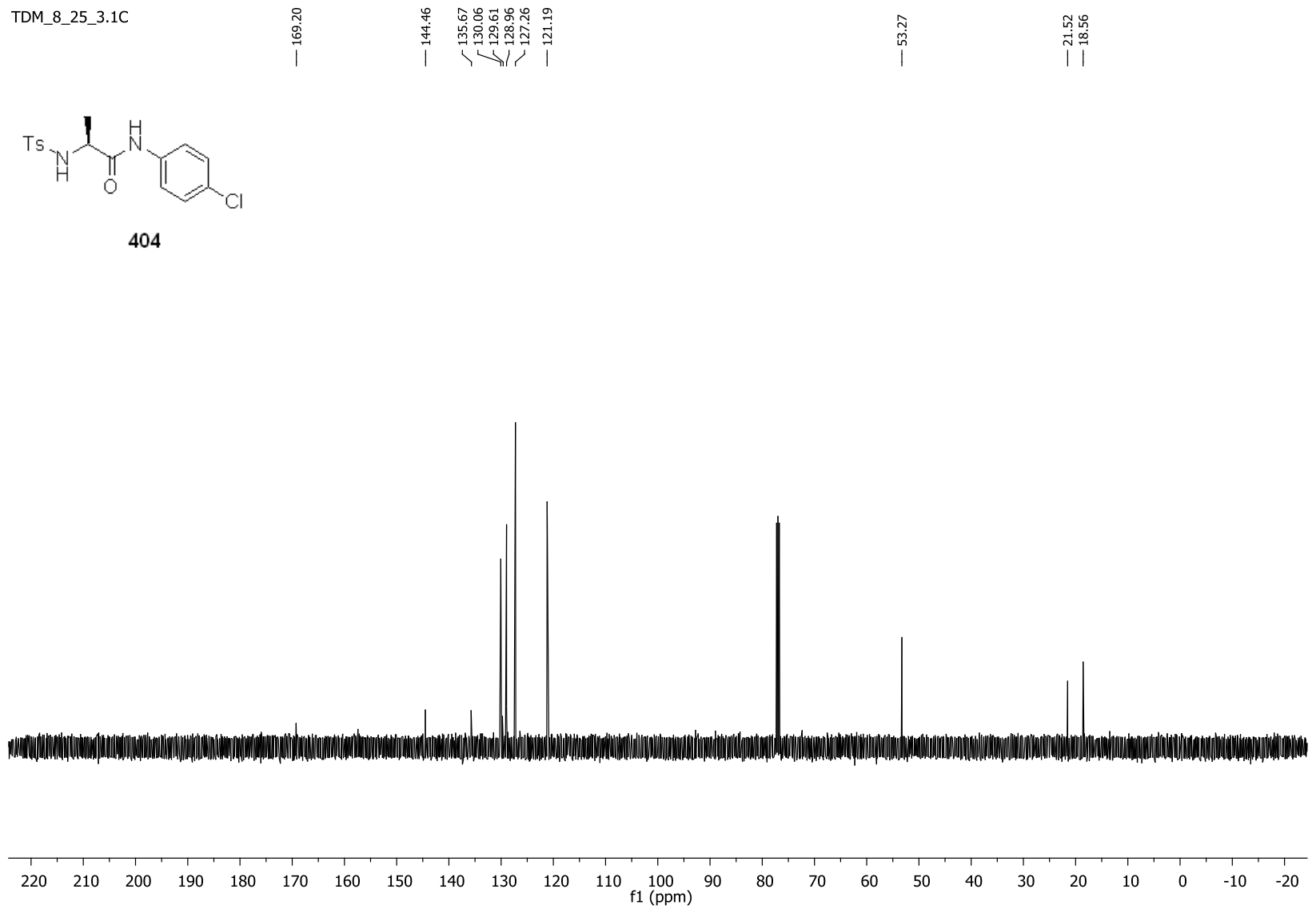


Figure 199. ^{13}C NMR Spectrum for **404** (125 MHz, $CDCl_3$)

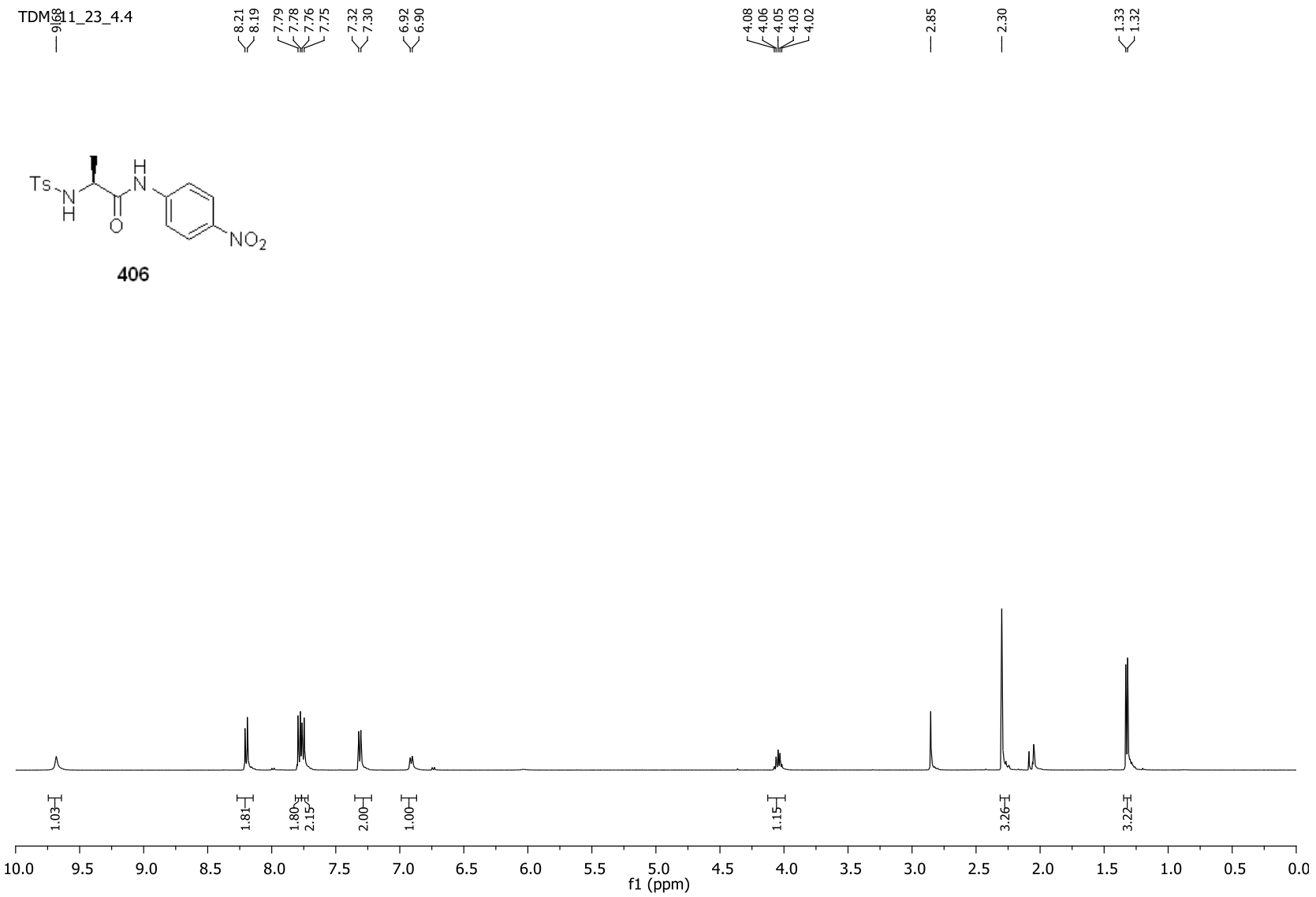


Figure 200. ^{1}H NMR Spectrum for **406** (500 MHz, $CDCl_3$)

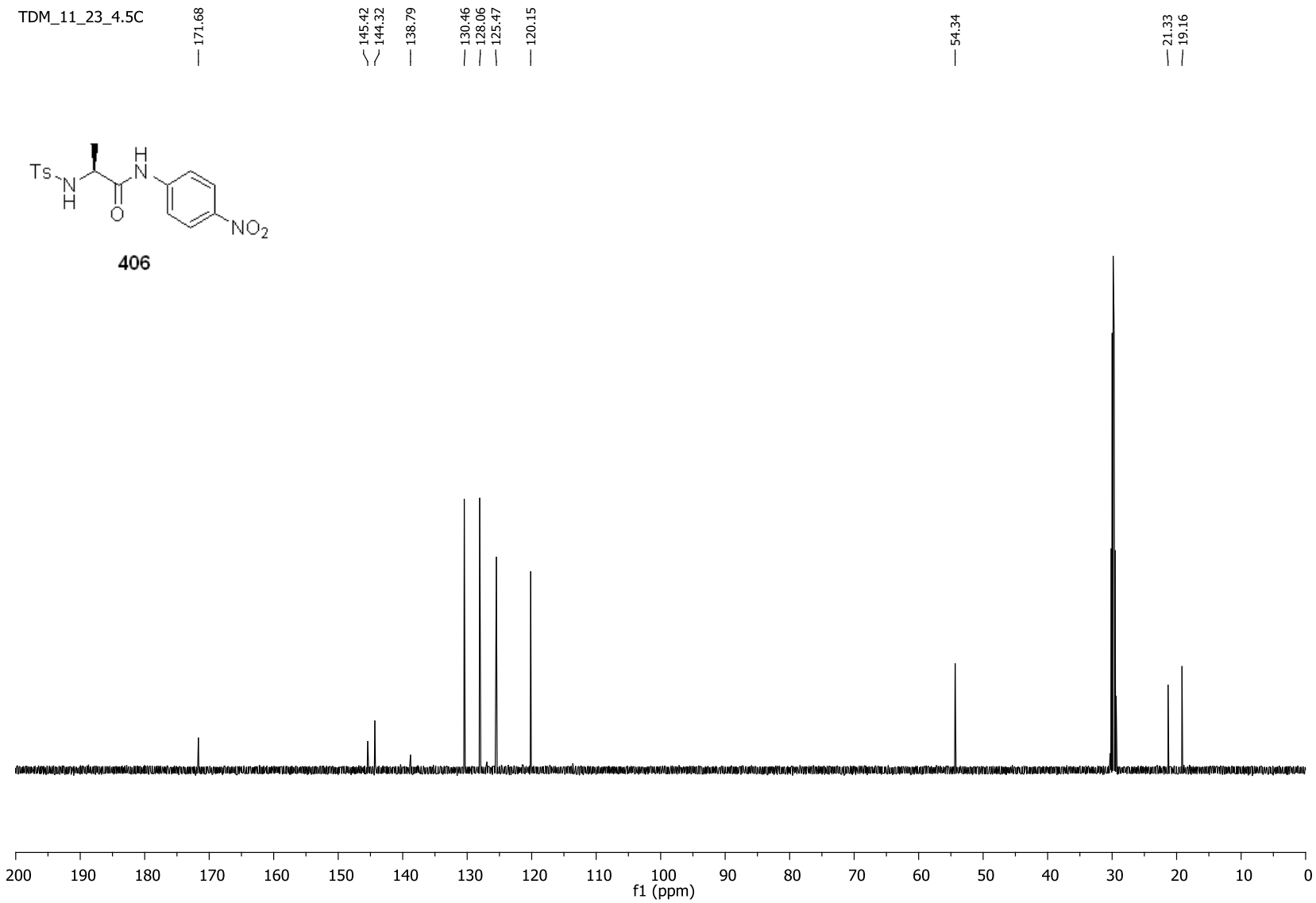


Figure 201. ^{13}C NMR Spectrum for **406** (125 MHz, $CDCl_3$)

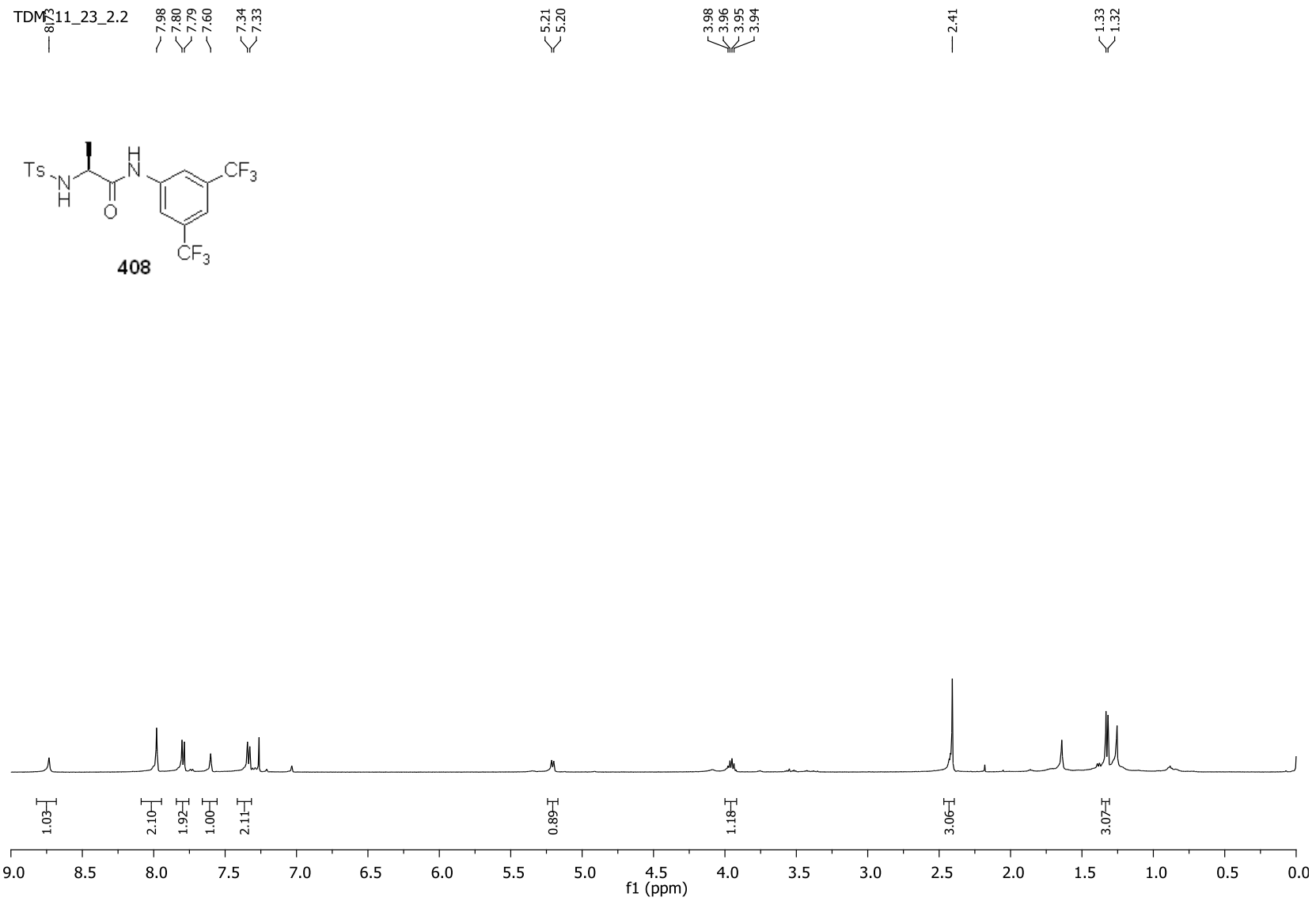


Figure 202. ^{1}H NMR Spectrum for **408** (500 MHz, $CDCl_3$)

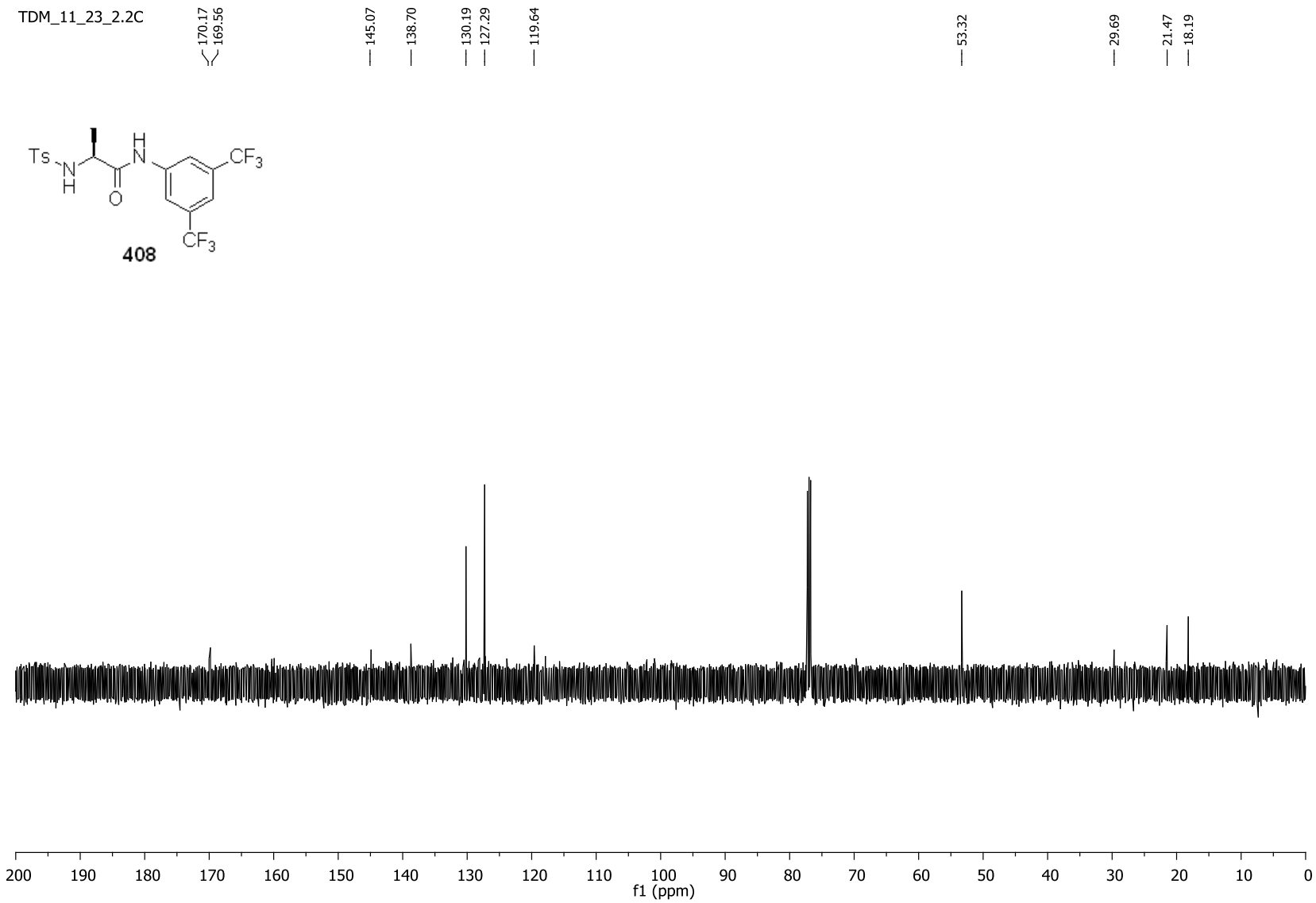


Figure 203. ^{13}C NMR Spectrum for **408** (125 MHz, $CDCl_3$)

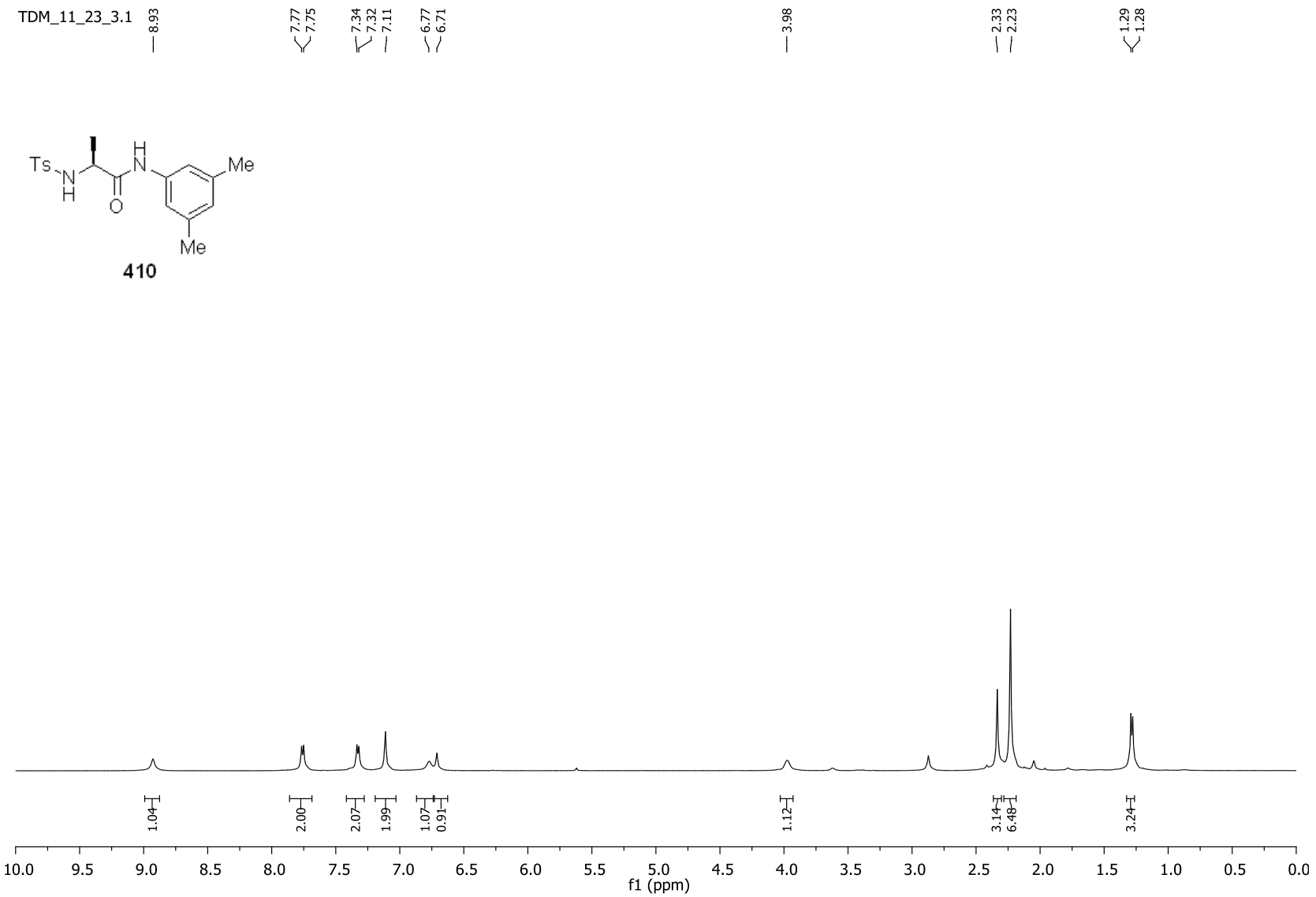


Figure 204. ^{1}H NMR Spectrum for **410** (500 MHz, $CDCl_3$)

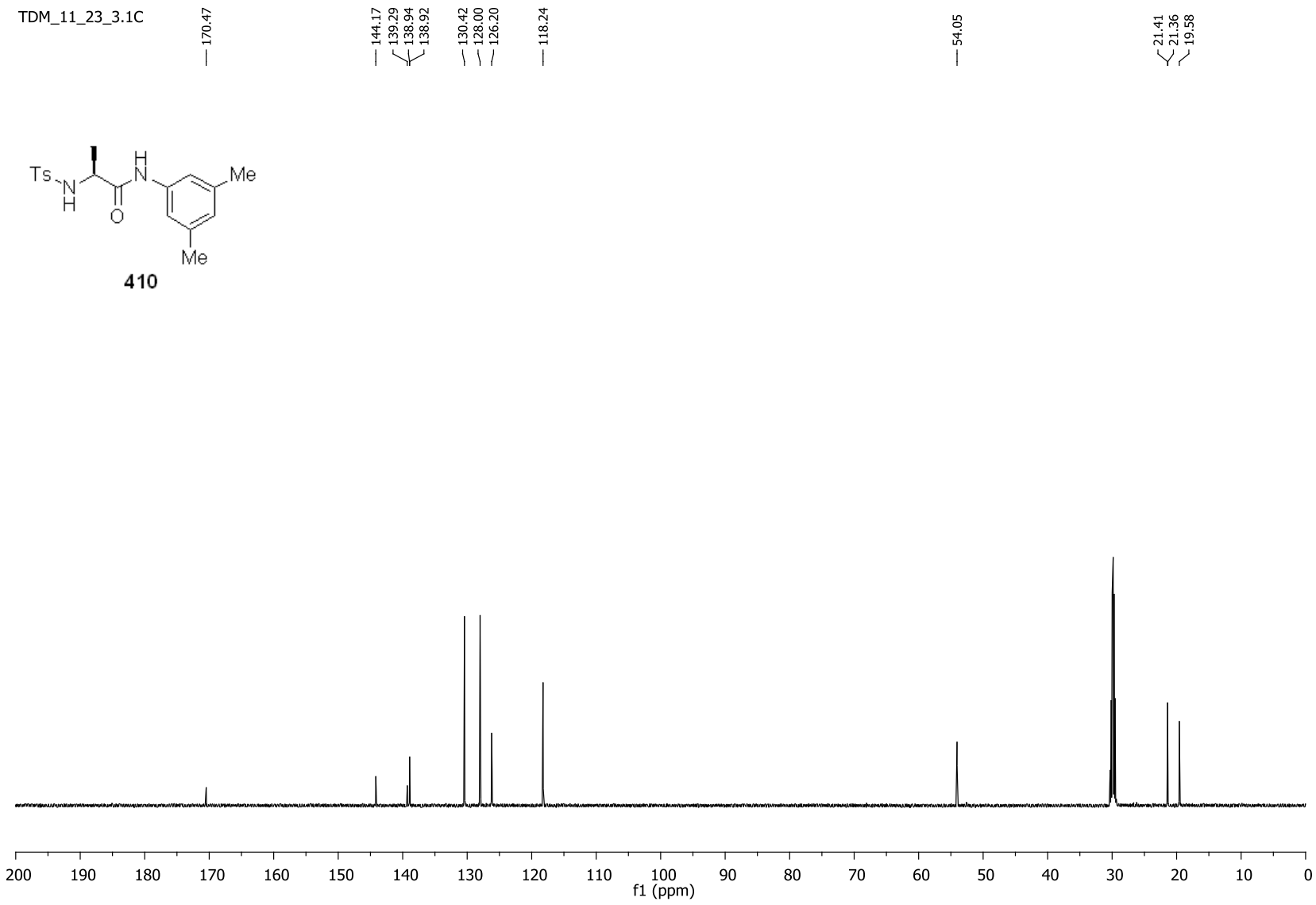


Figure 205. ^{13}C NMR Spectrum for **410** (125 MHz, $CDCl_3$)

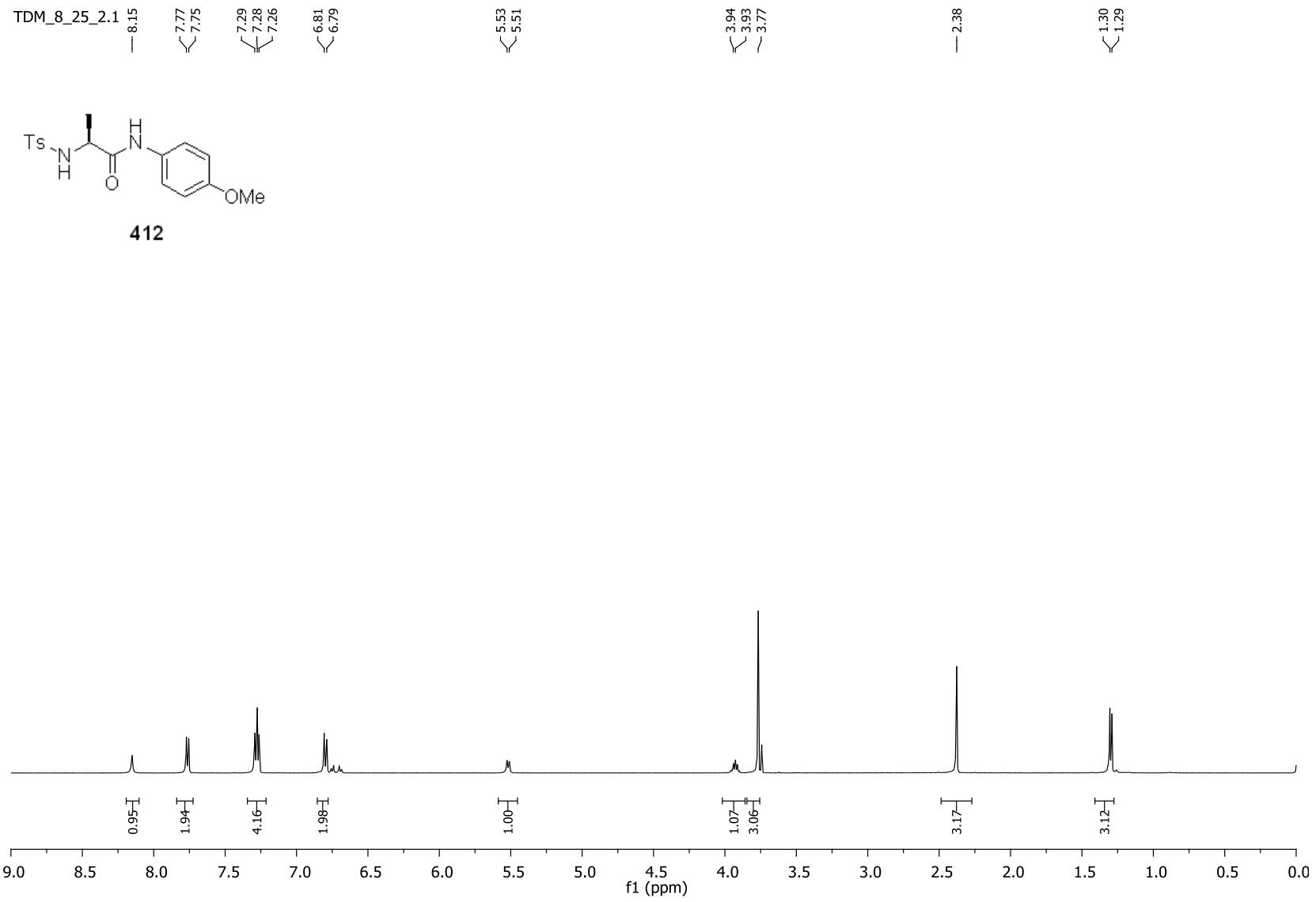


Figure 206. ^{1}H NMR Spectrum for **412** (500 MHz, $CDCl_3$)

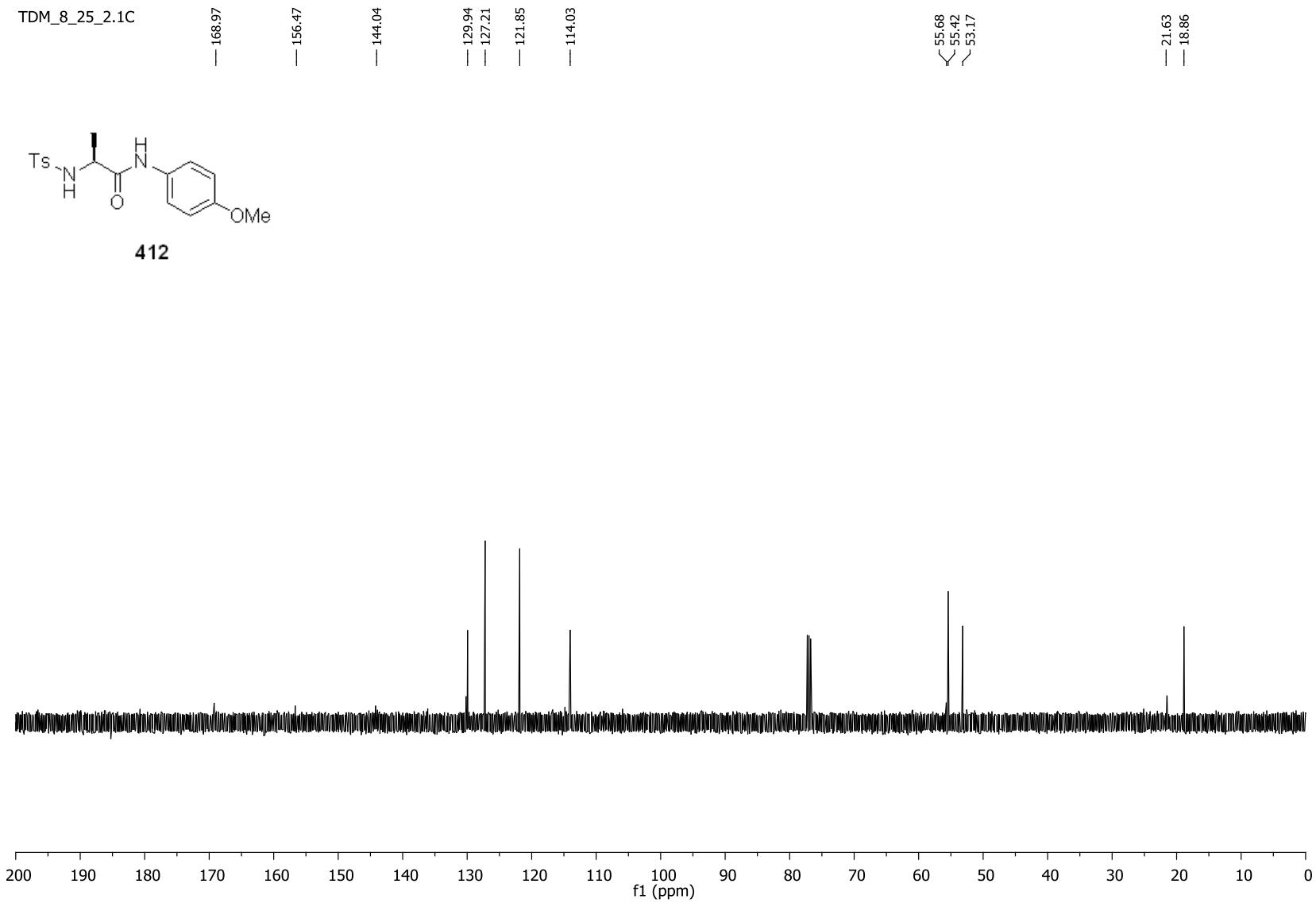


Figure 207. ^{13}C NMR Spectrum for **412** (125 MHz, $CDCl_3$)

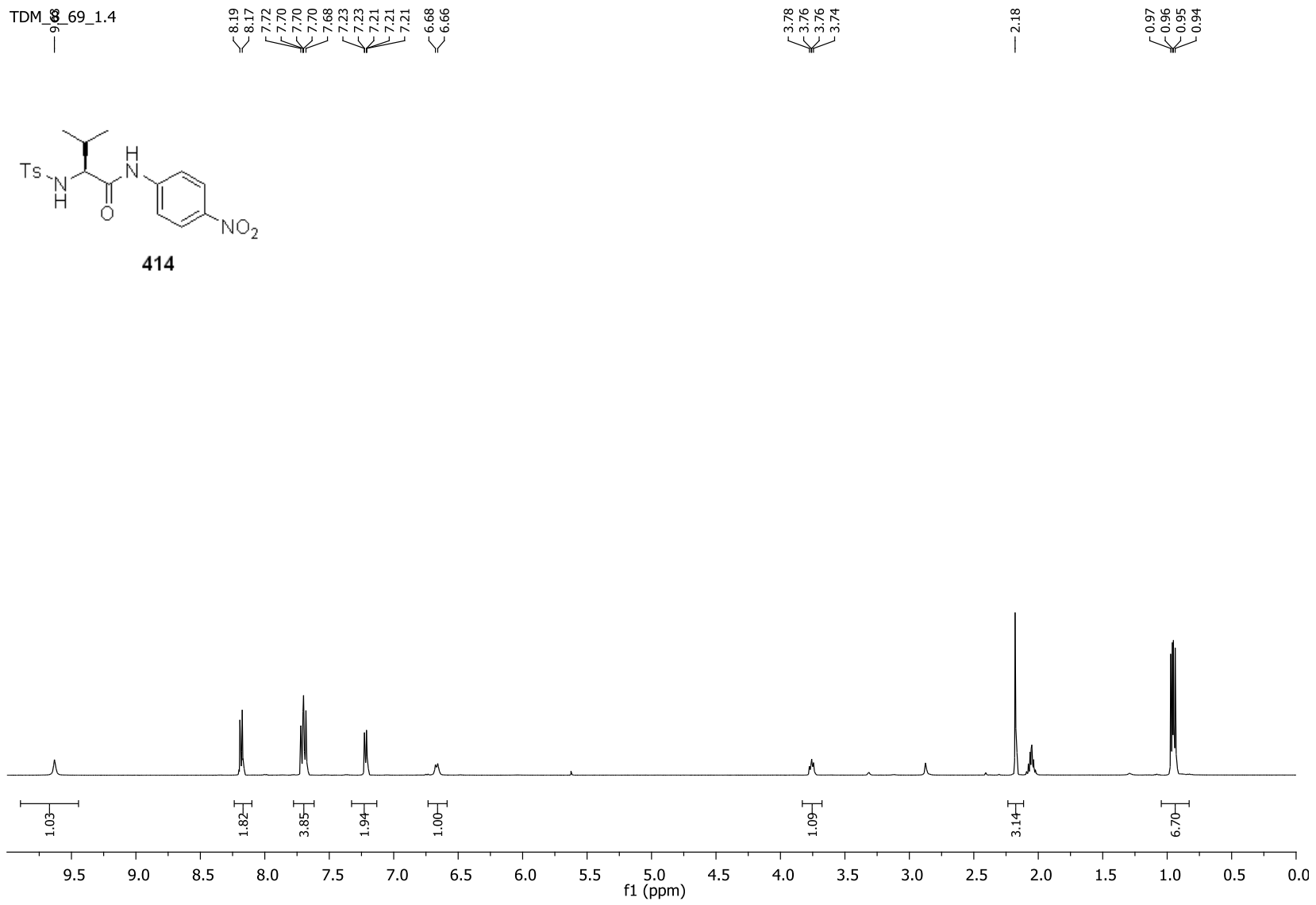


Figure 208. ^{1}H NMR Spectrum for **414** (500 MHz, $CDCl_3$)

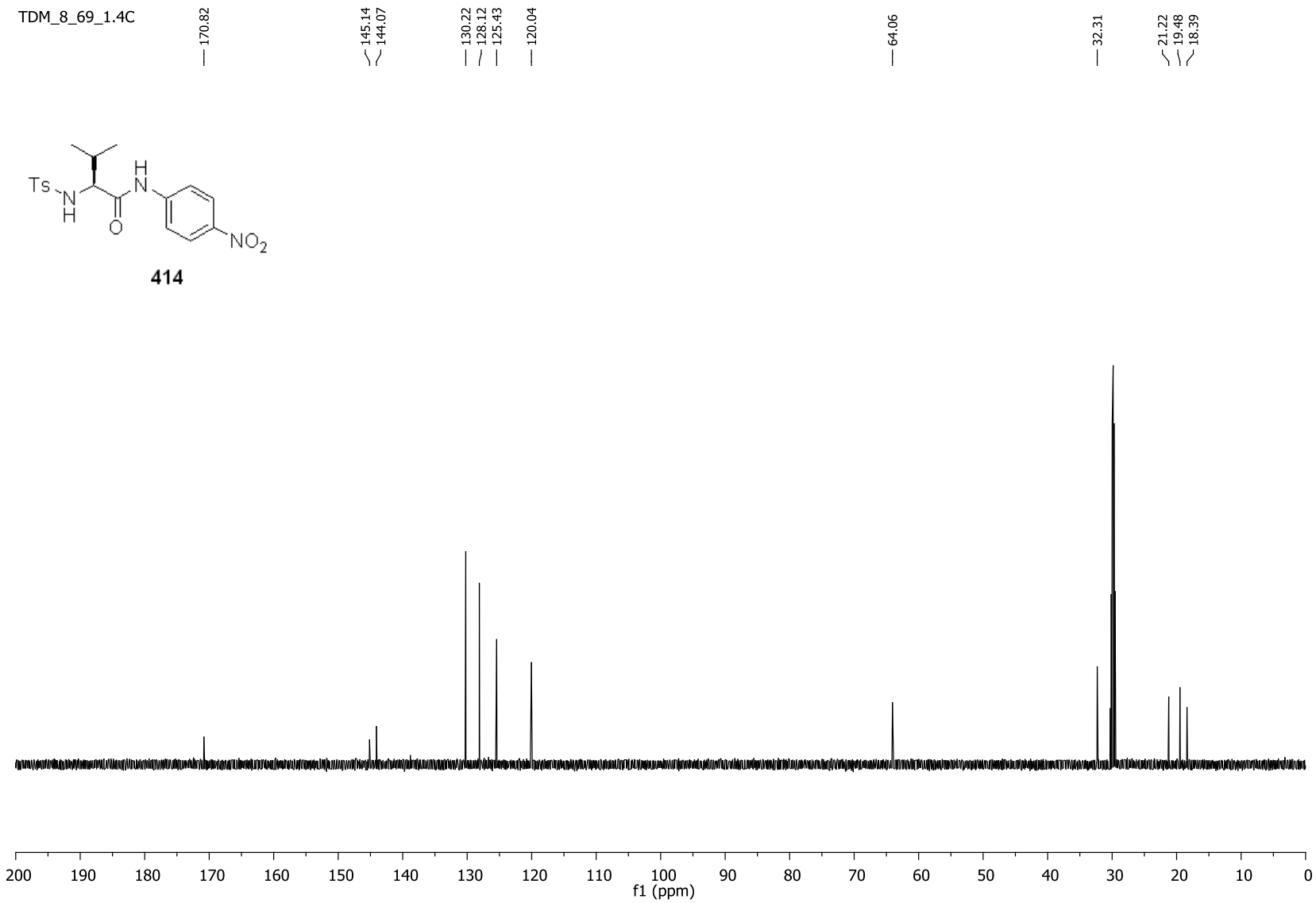


Figure 209. ^{13}C NMR Spectrum for **414** (125 MHz, $CDCl_3$)

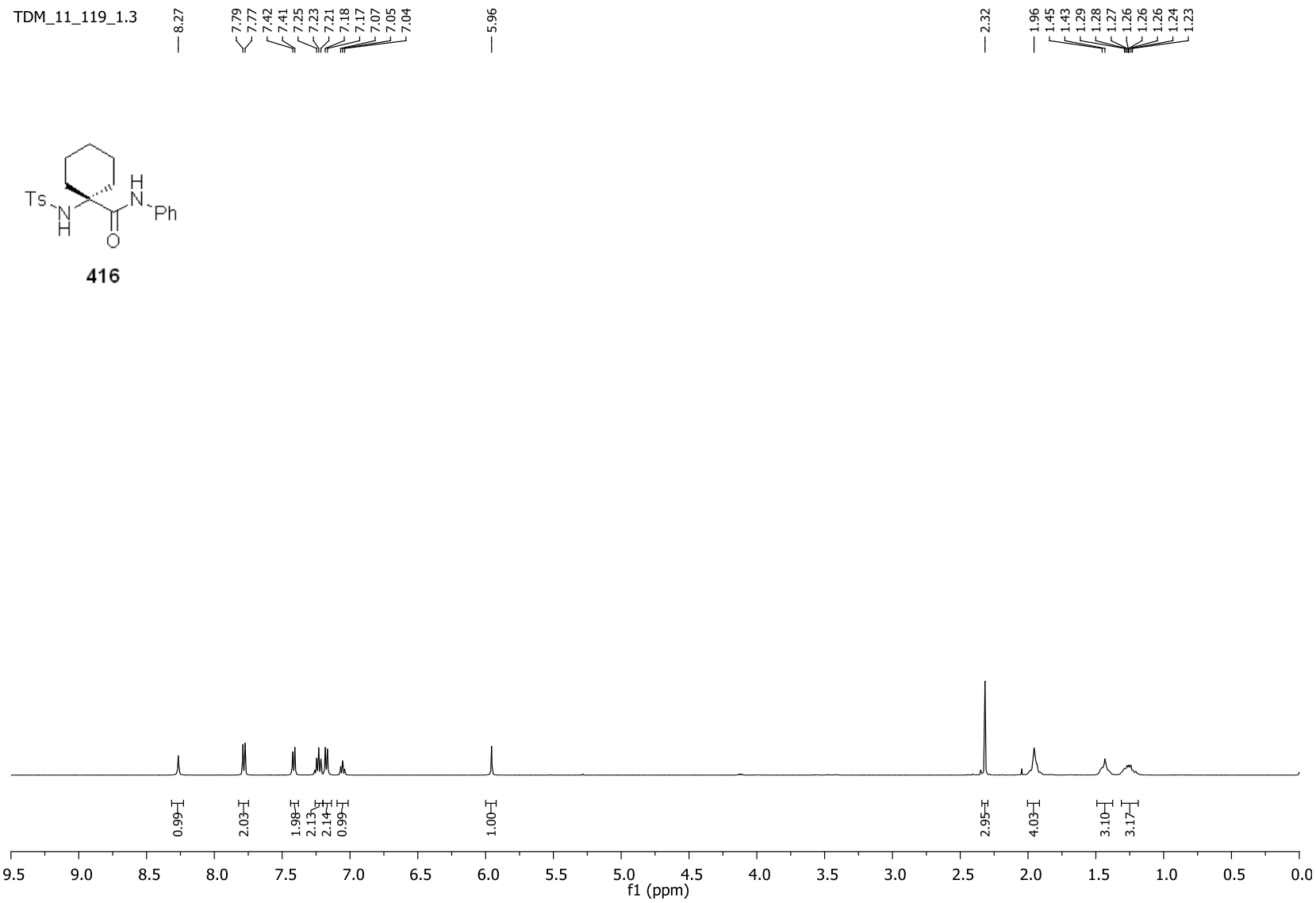


Figure 210. ^{1}H NMR Spectrum for **416** (500 MHz, $CDCl_3$)

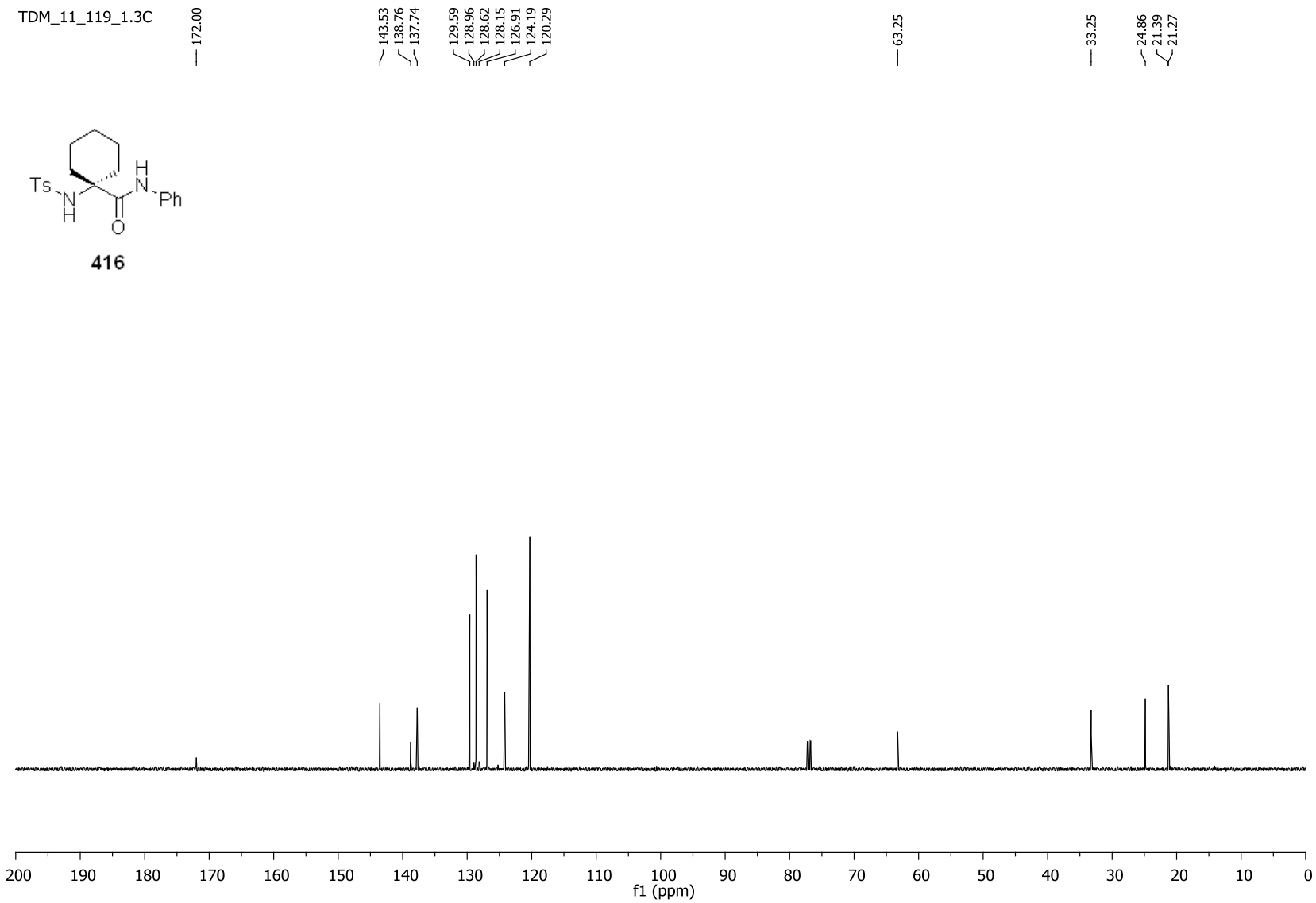
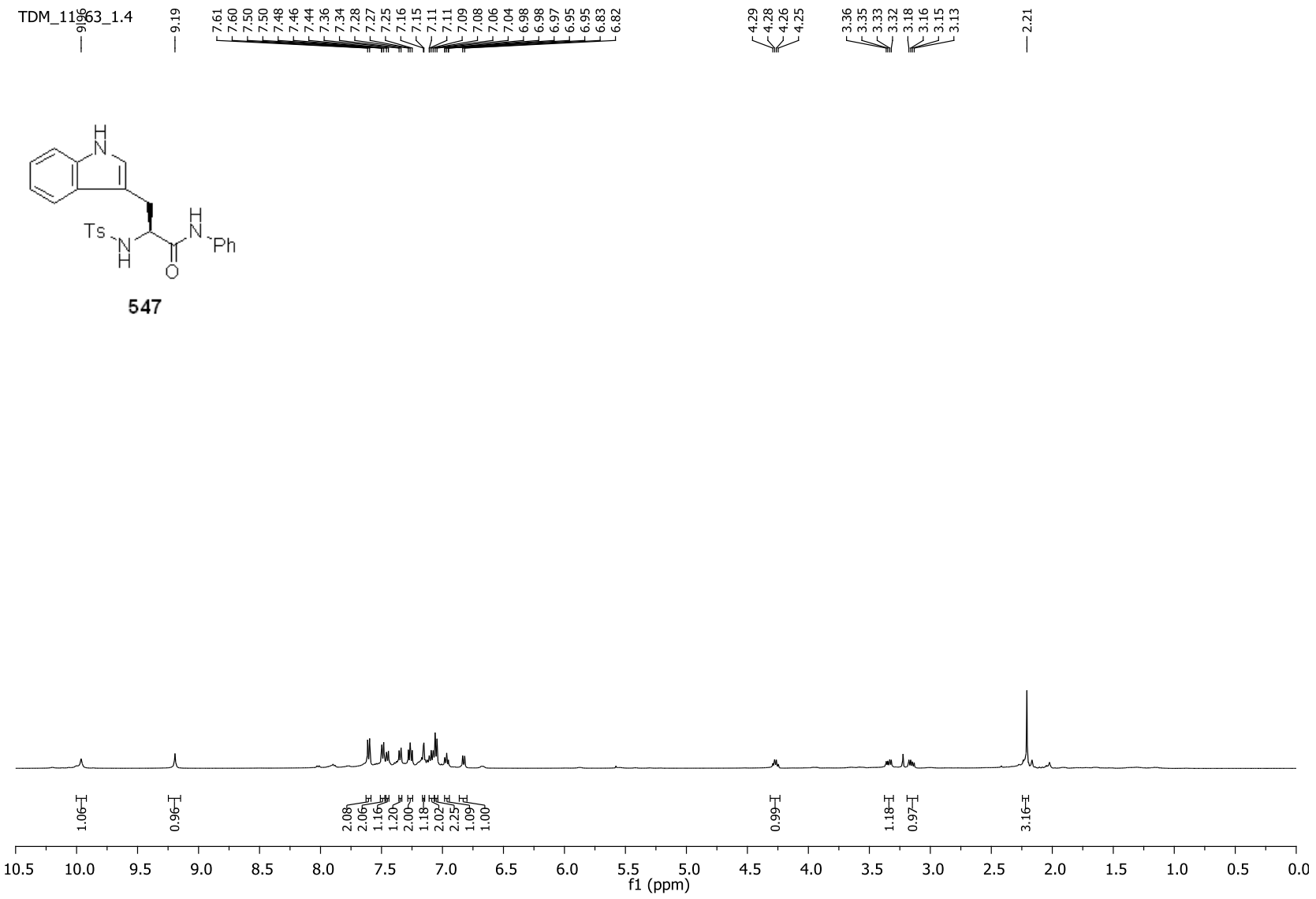


Figure 211. ^{13}C NMR Spectrum for **416** (125 MHz, $CDCl_3$)



547

Figure 212. ^{1}H NMR Spectrum for **547** (500 MHz, $CDCl_3$)

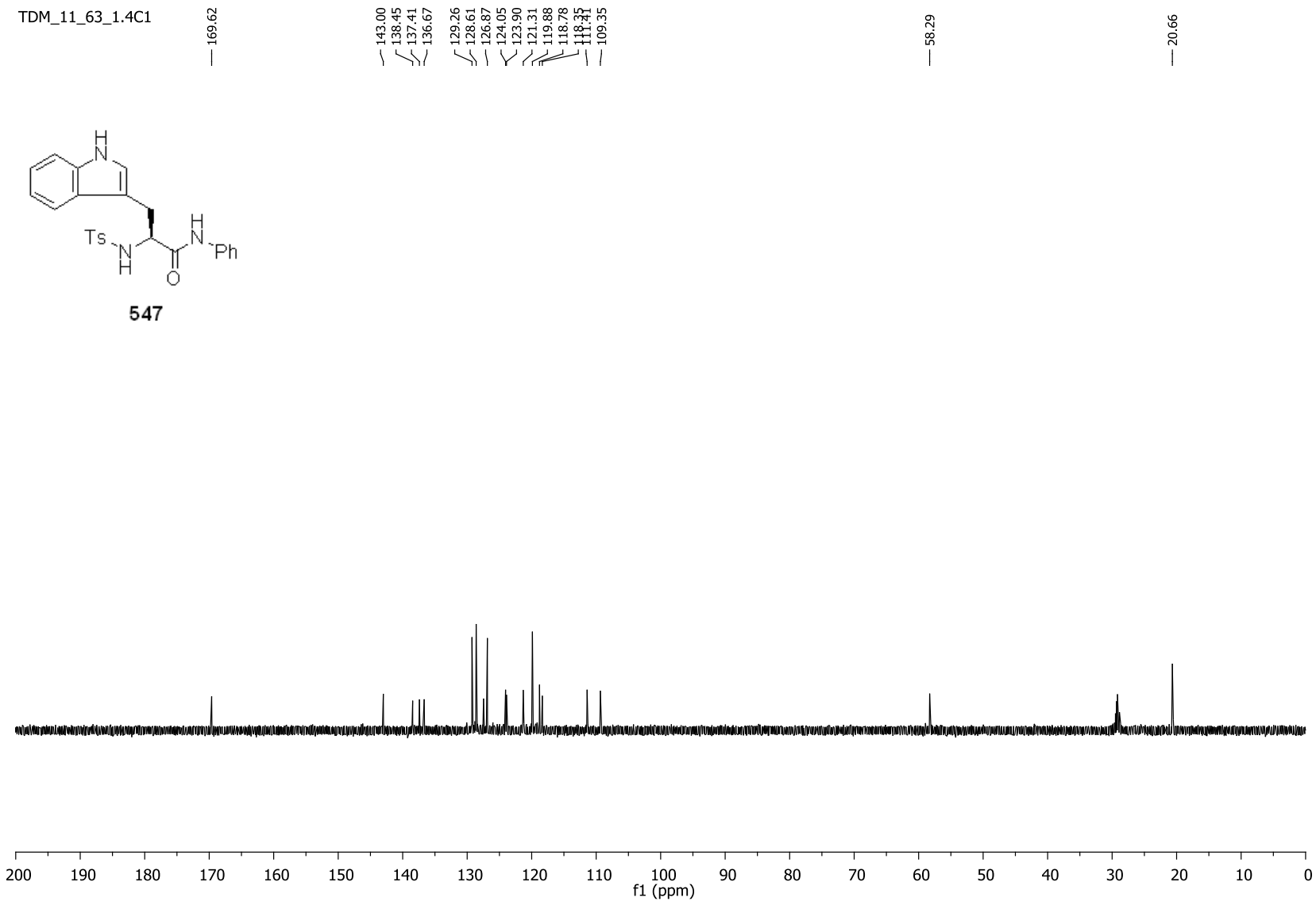


Figure 213. ^{13}C NMR Spectrum for **547** (125 MHz, $CDCl_3$)

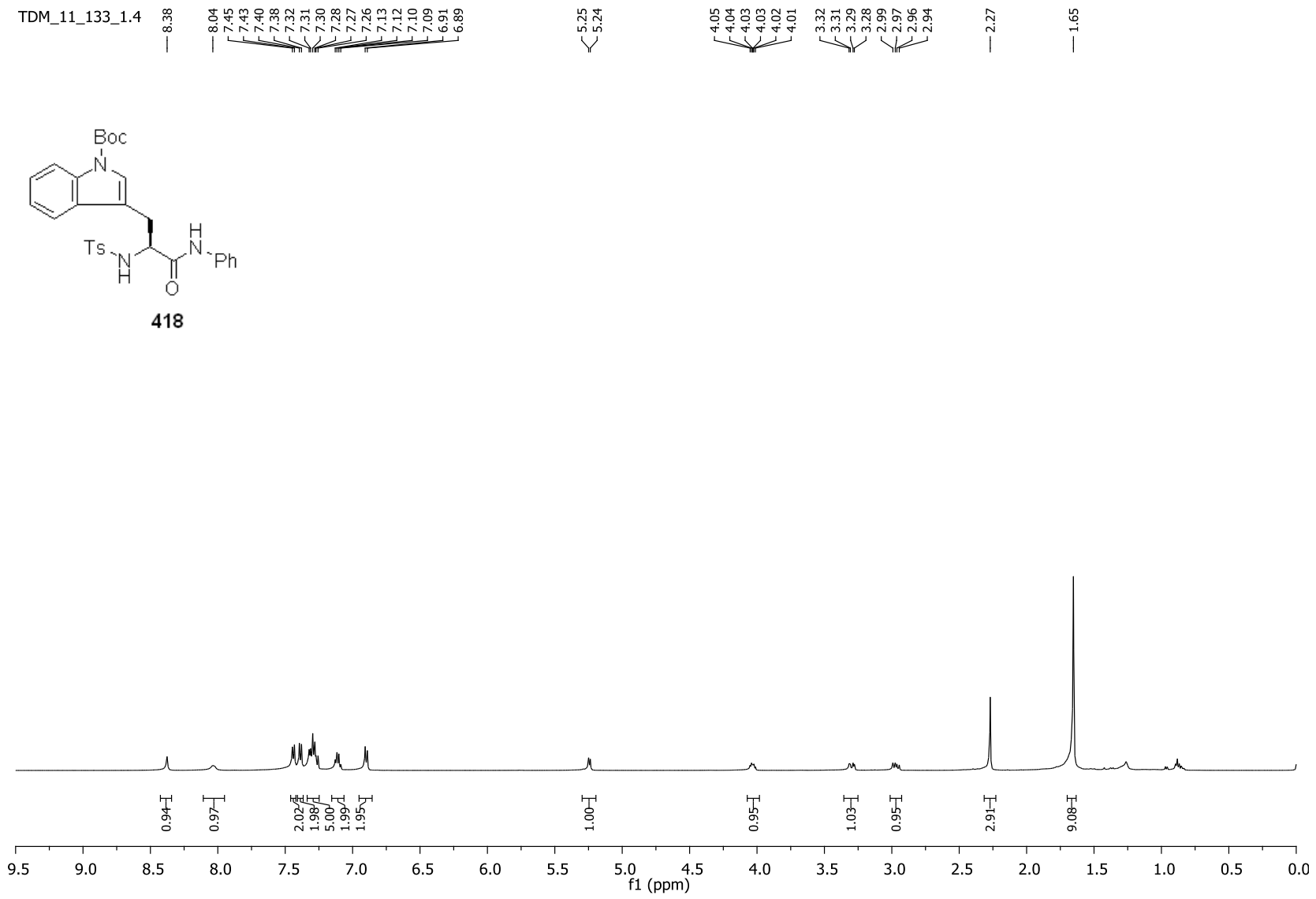


Figure 214. ^{1}H NMR Spectrum for **418** (500 MHz, $CDCl_3$)

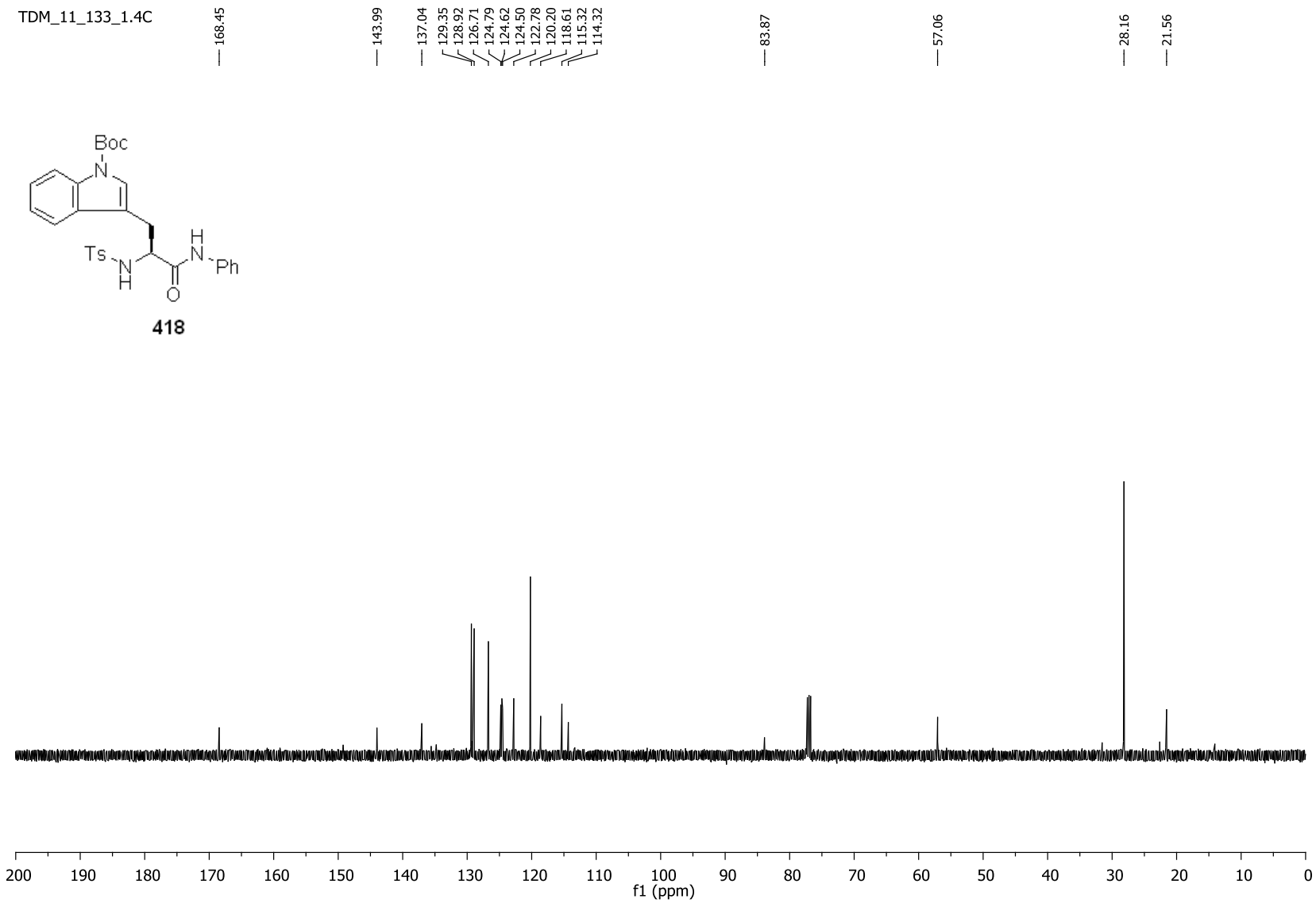


Figure 215. ^{13}C NMR Spectrum for **418** (125 MHz, $CDCl_3$)

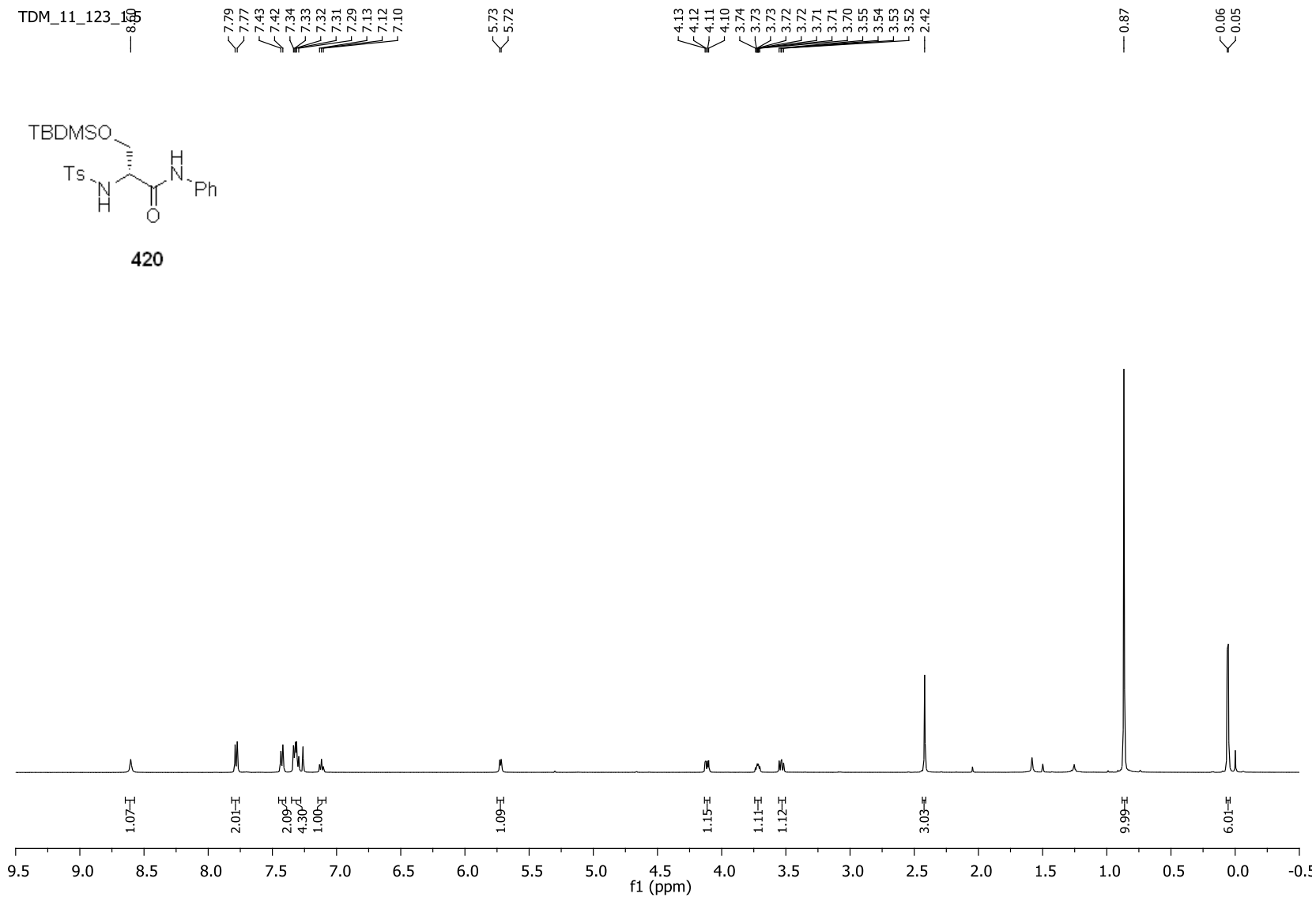


Figure 216. ^{1}H NMR Spectrum for **420** (500 MHz, $CDCl_3$)

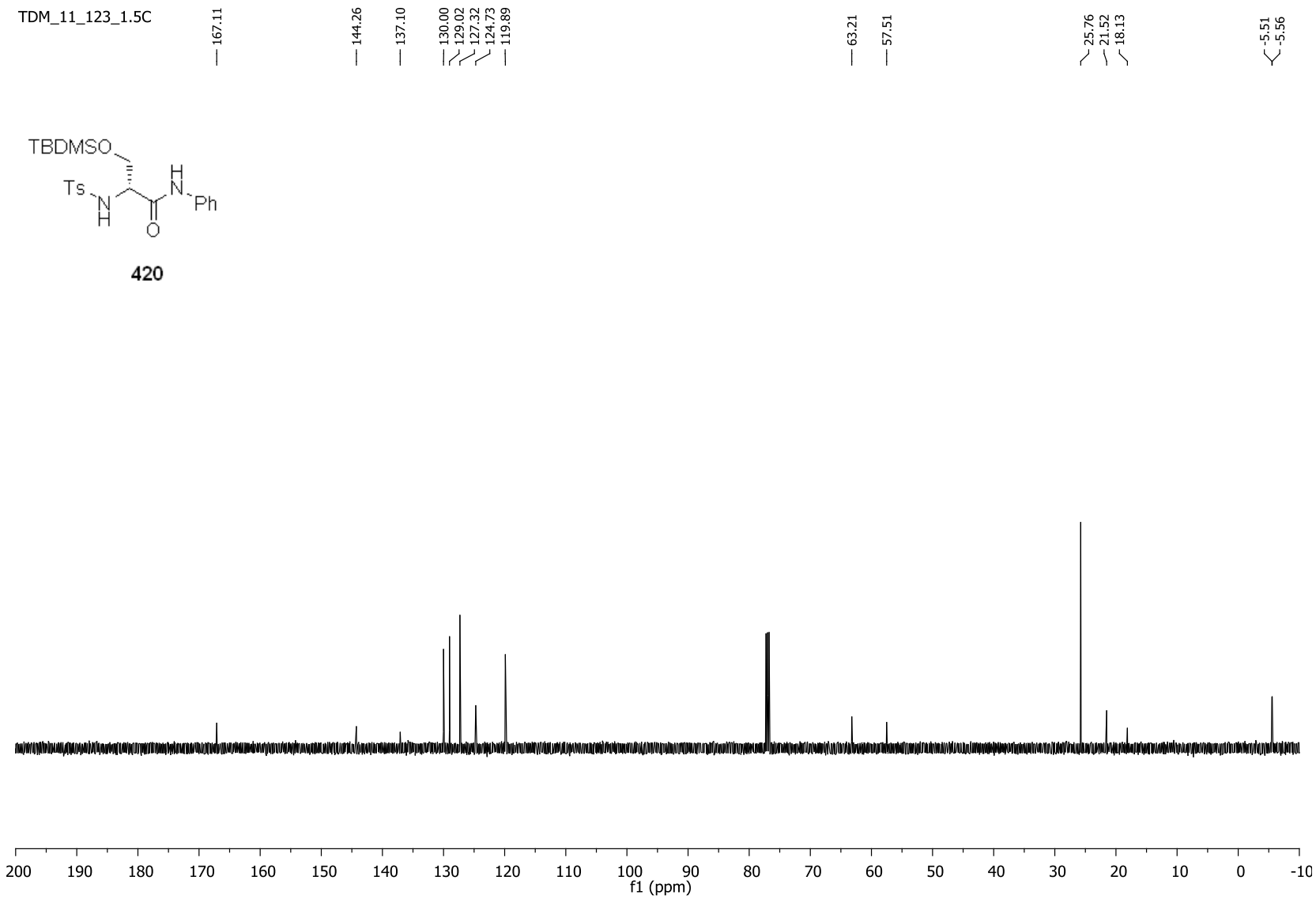


Figure 217. ^{13}C NMR Spectrum for **420** (125 MHz, $CDCl_3$)

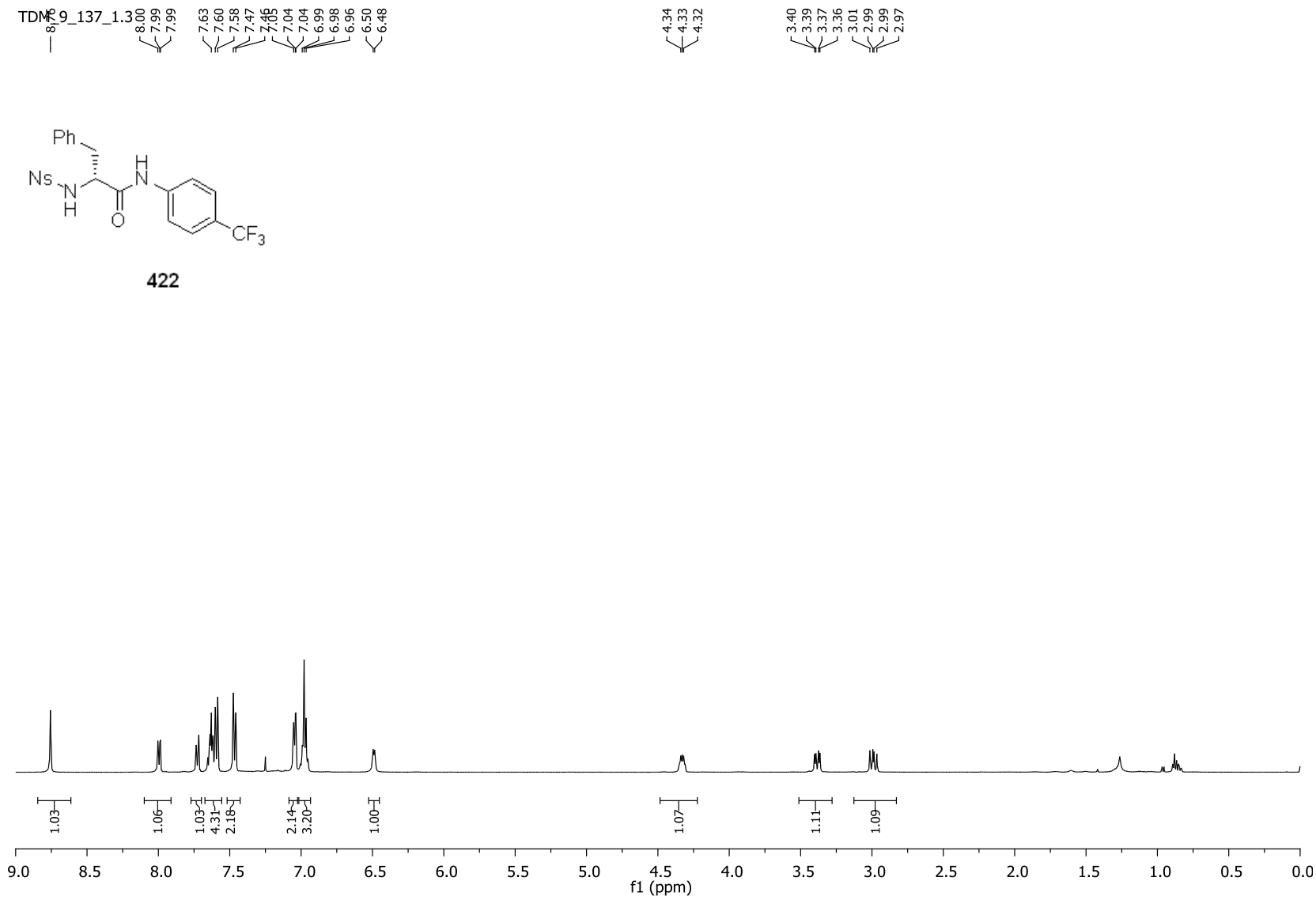


Figure 218. ^{1}H NMR Spectrum for **422** (500 MHz, $CDCl_3$)

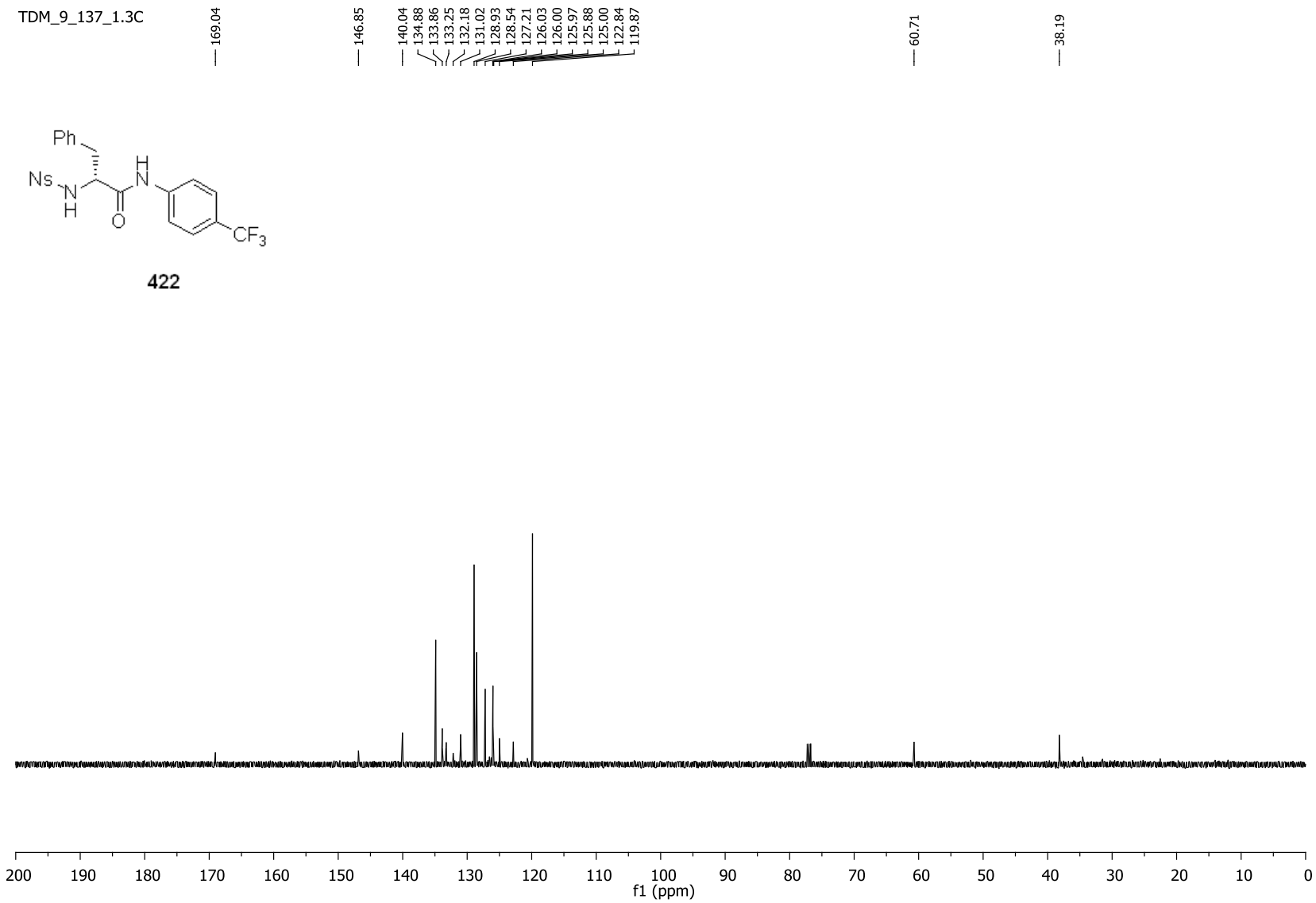


Figure 219. ^{13}C NMR Spectrum for **422** (125 MHz, $CDCl_3$)

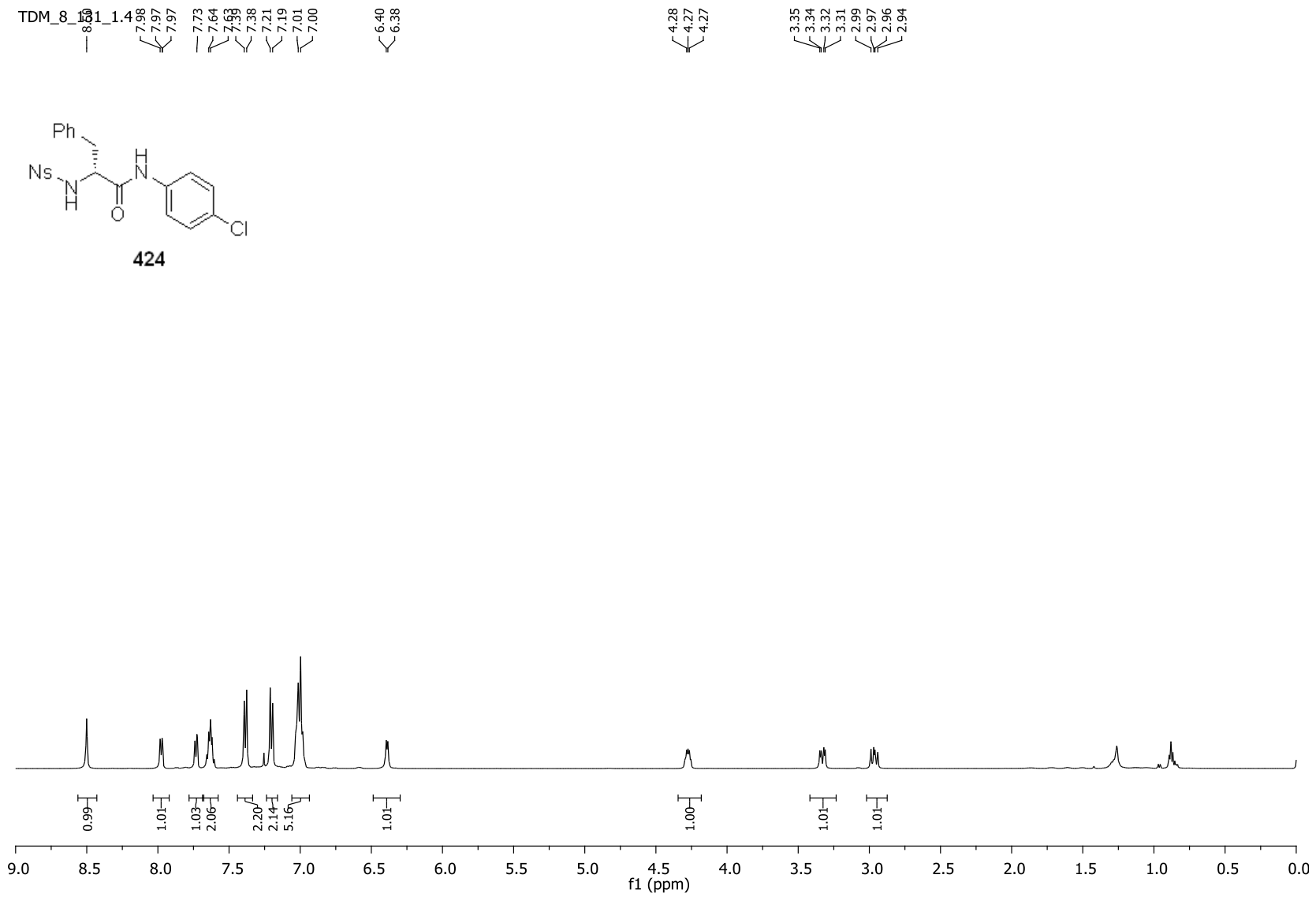


Figure 220. ^{1}H NMR Spectrum for **424** (500 MHz, $CDCl_3$)

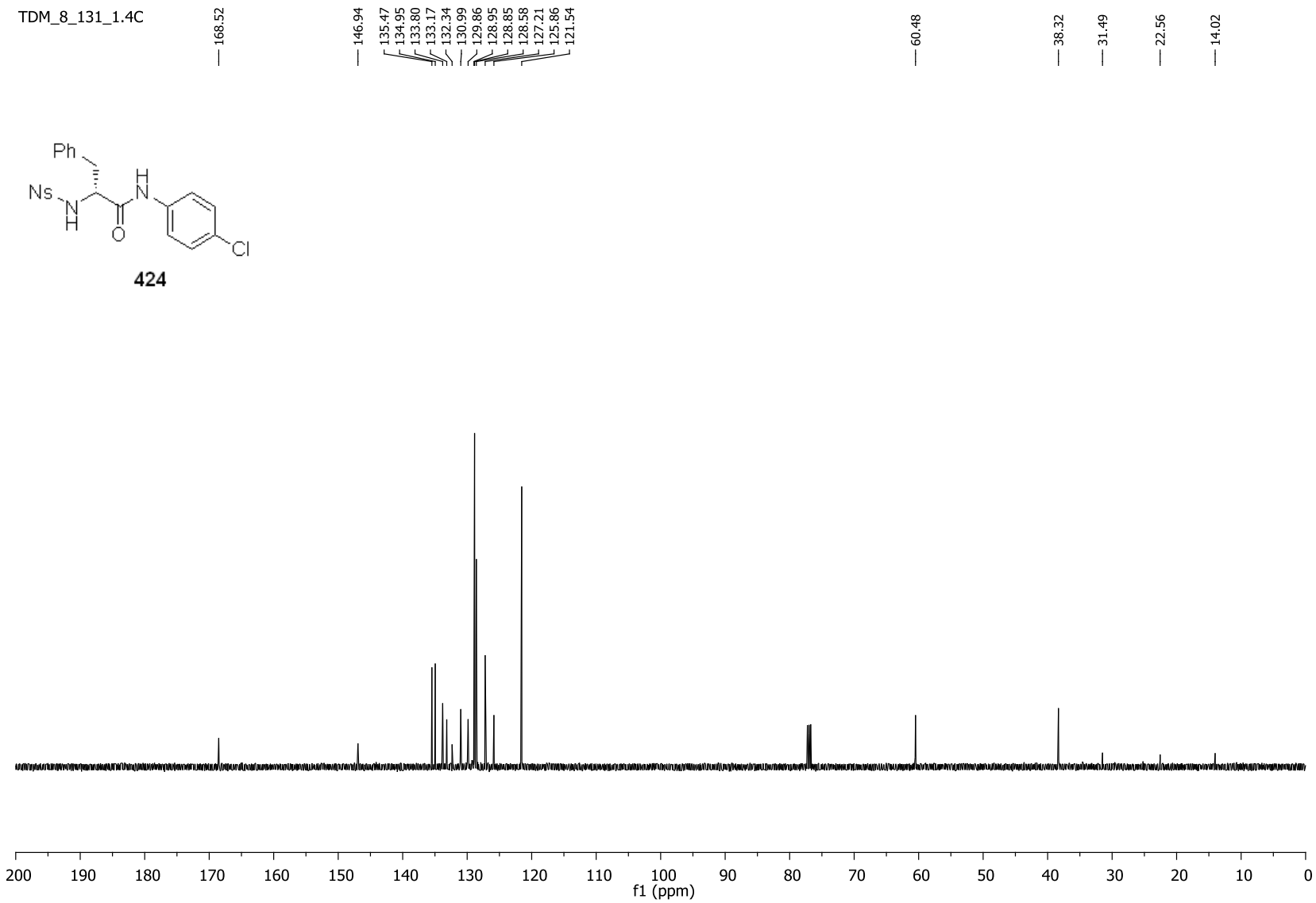


Figure 221. ^{13}C NMR Spectrum for **424** (125 MHz, $CDCl_3$)

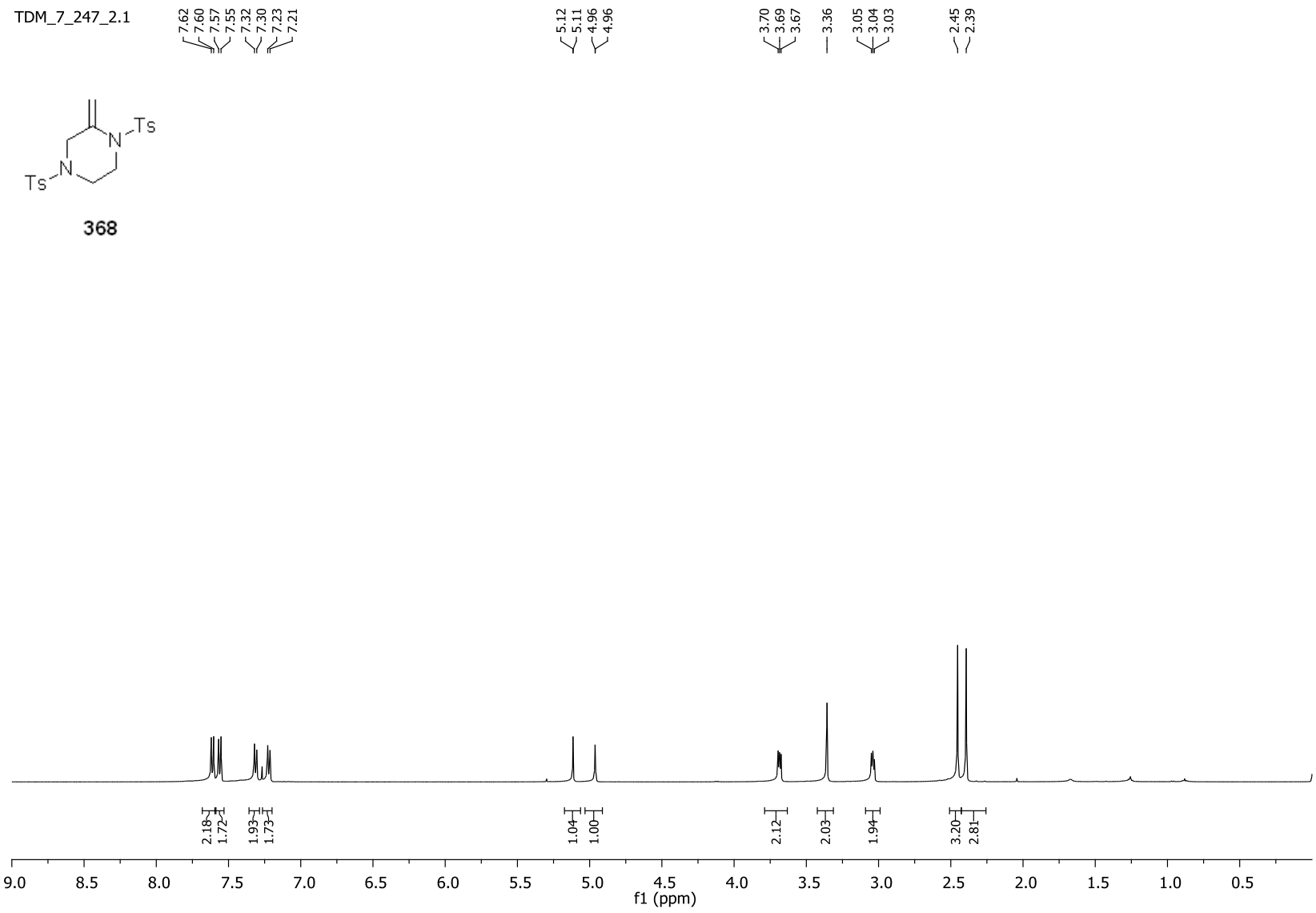


Figure 222. ^{1}H NMR Spectrum for **368** (500 MHz, $CDCl_3$)

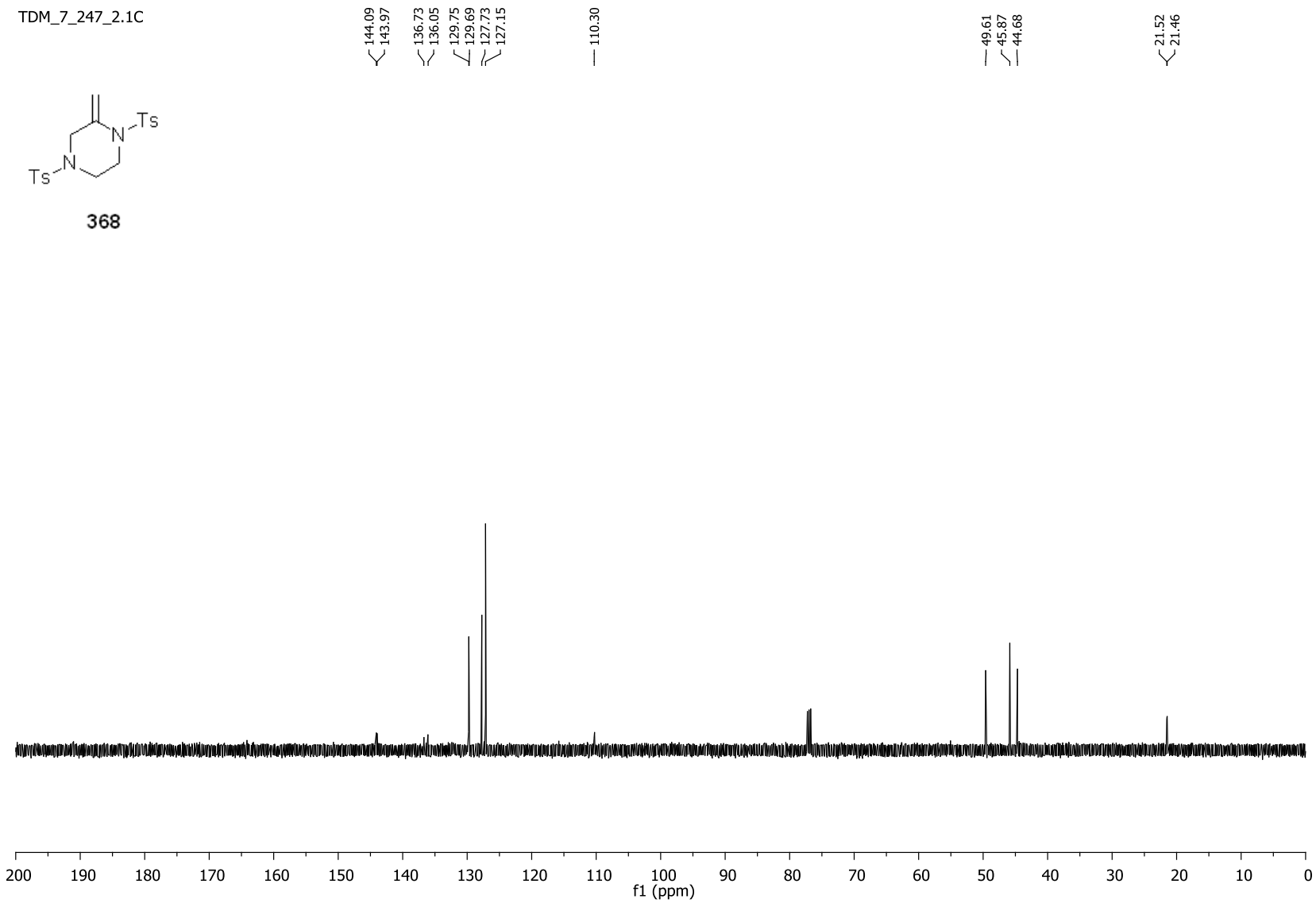


Figure 223. ^{13}C NMR Spectrum for **368** (125 MHz, $CDCl_3$)

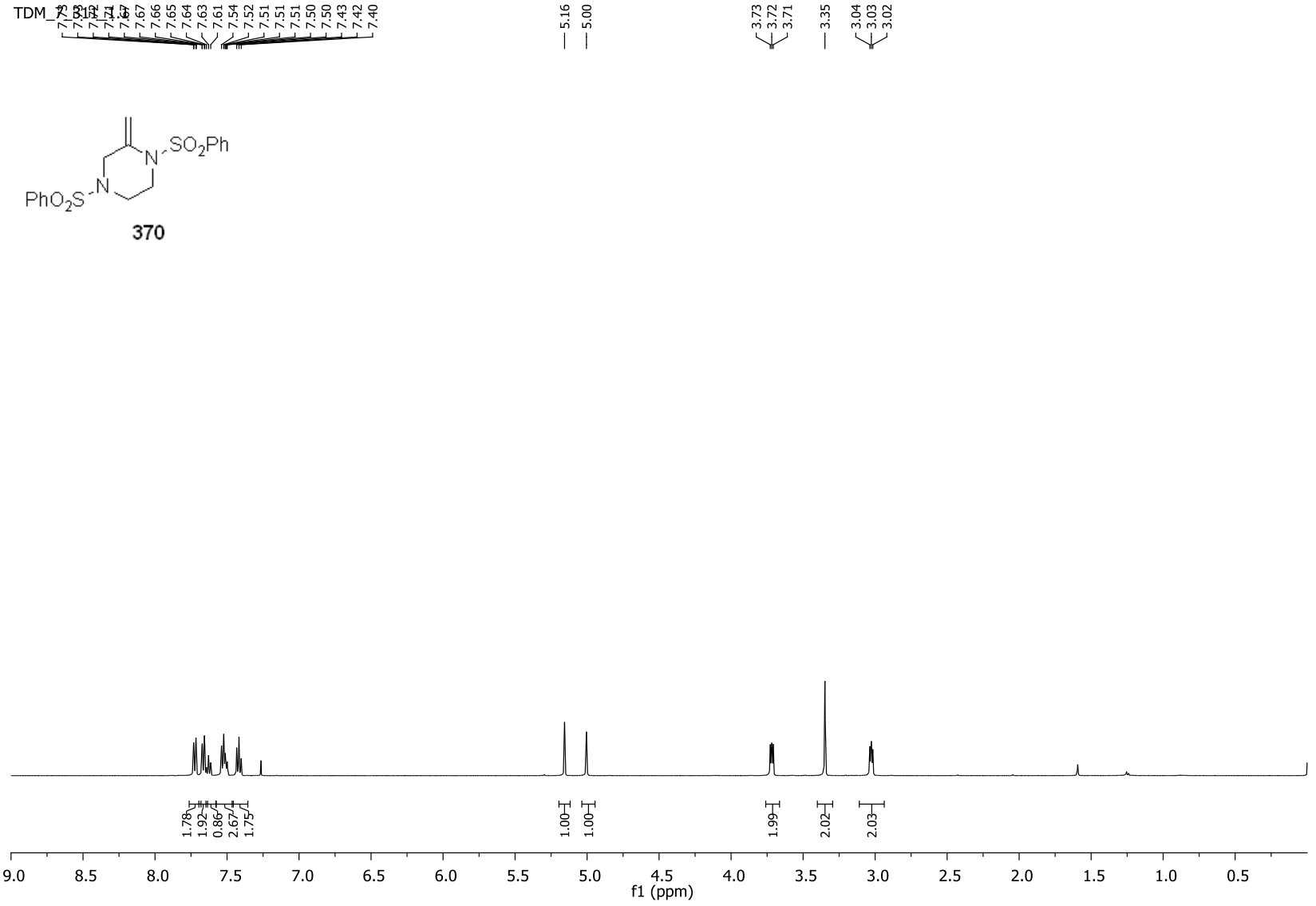


Figure 224. ^{1}H NMR Spectrum for **370** (500 MHz, $CDCl_3$)

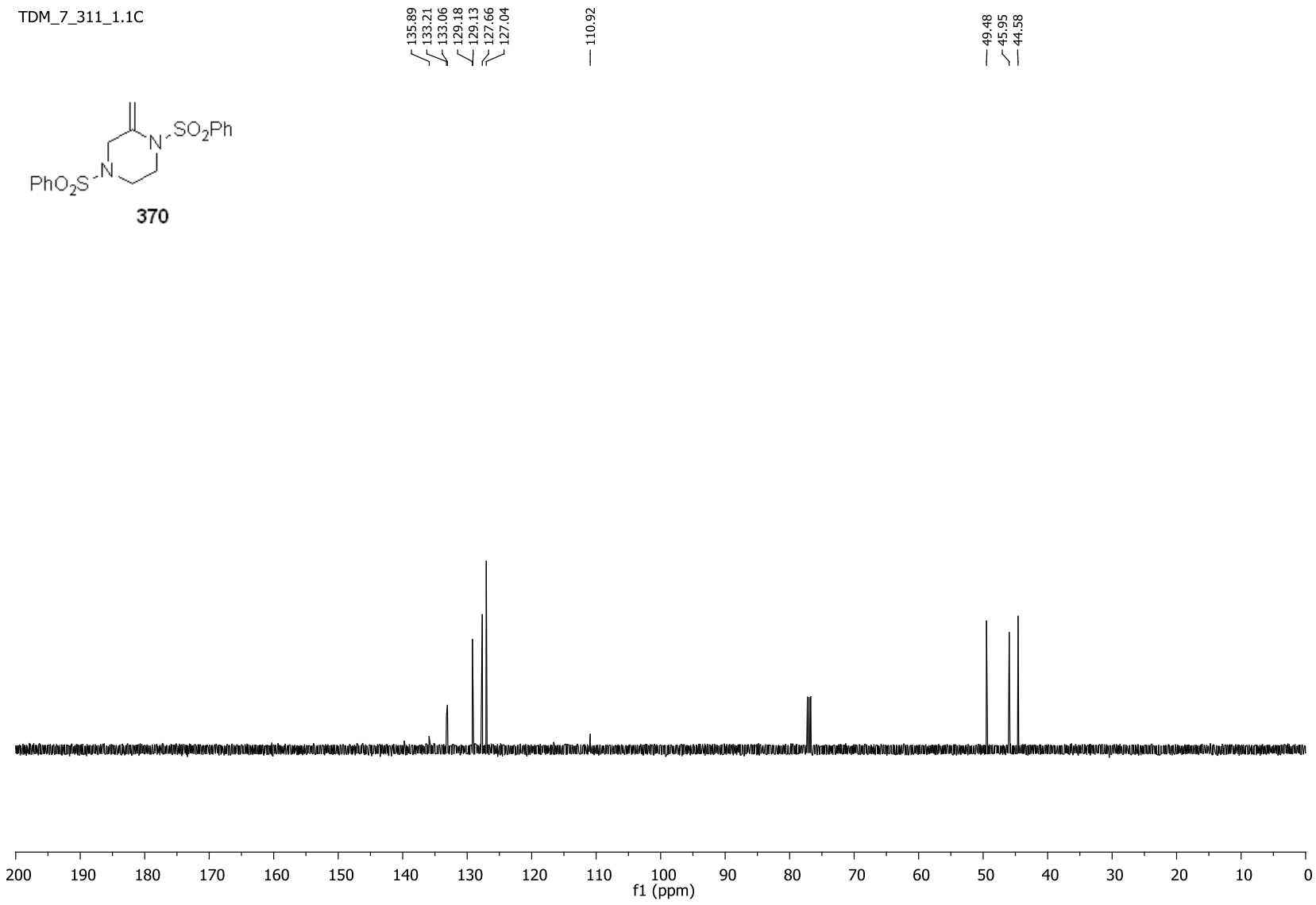


Figure 225. ^{13}C NMR Spectrum for **370** (125 MHz, $CDCl_3$)

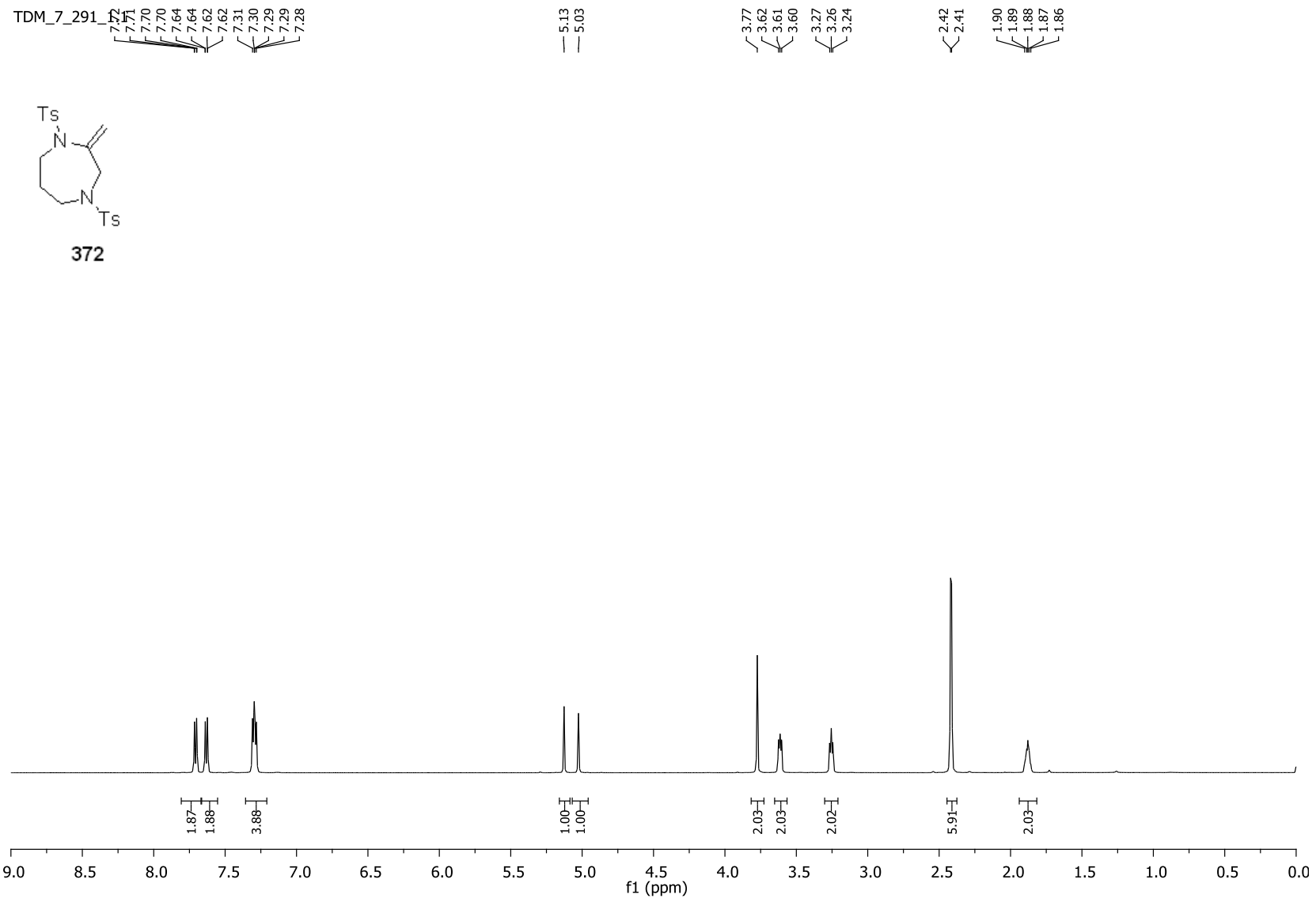


Figure 226. ^{1}H NMR Spectrum for **372** (500 MHz, $CDCl_3$)

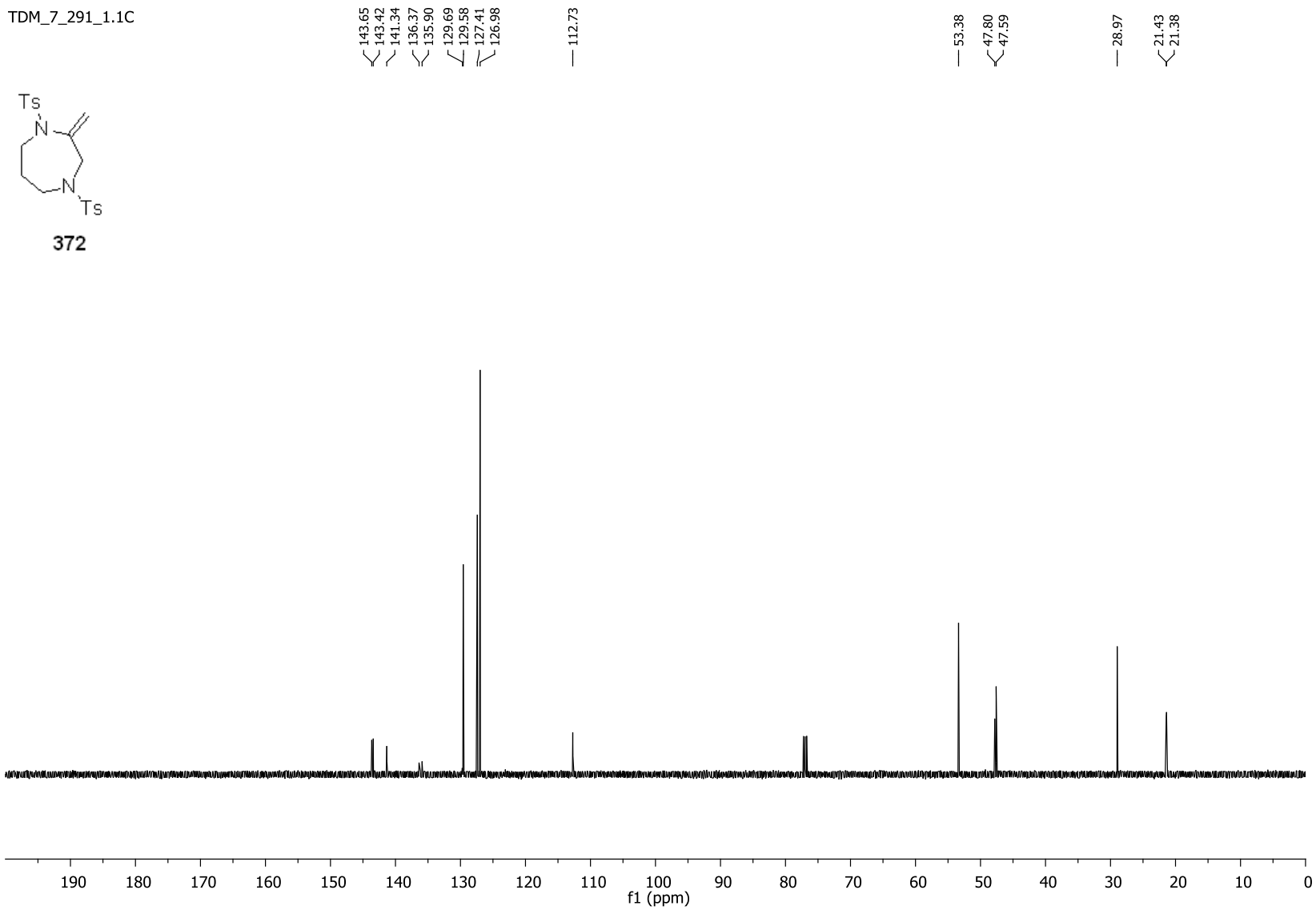


Figure 227. ^{13}C NMR Spectrum for **372** (125 MHz, $CDCl_3$)

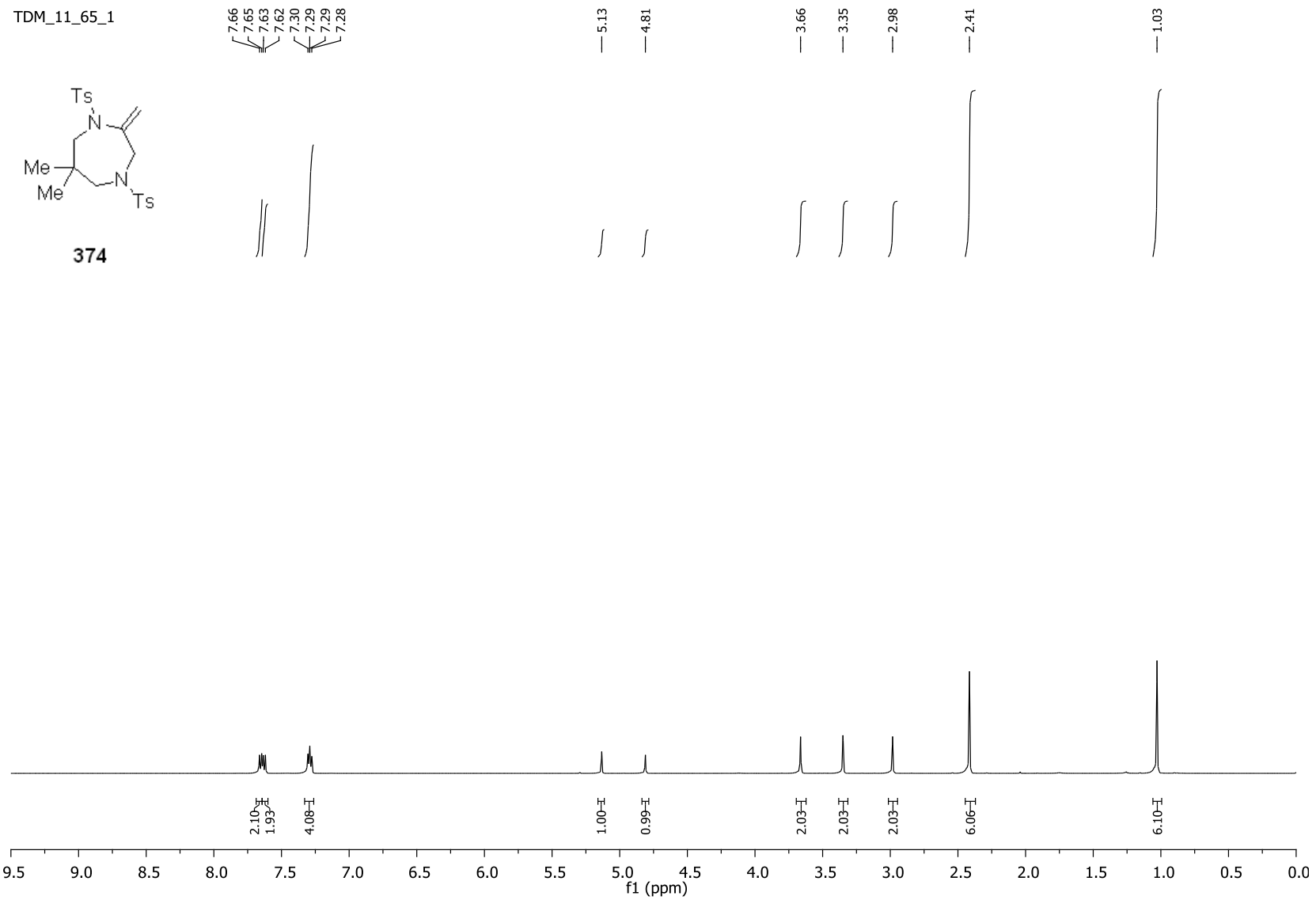


Figure 228. ^{1}H NMR Spectrum for **374** (500 MHz, $CDCl_3$)

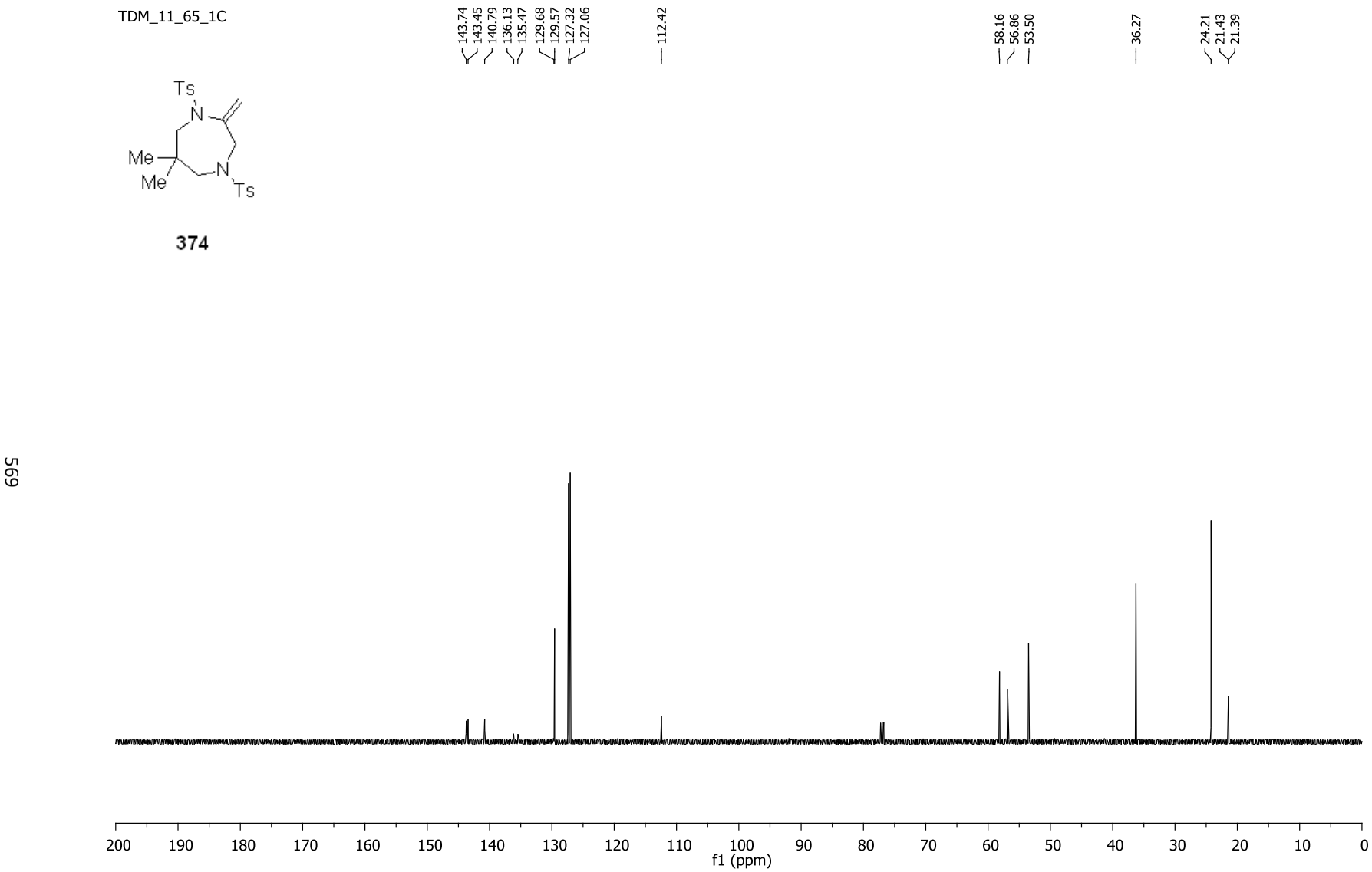


Figure 229. ^{13}C NMR Spectrum for **374** (125 MHz, $CDCl_3$)

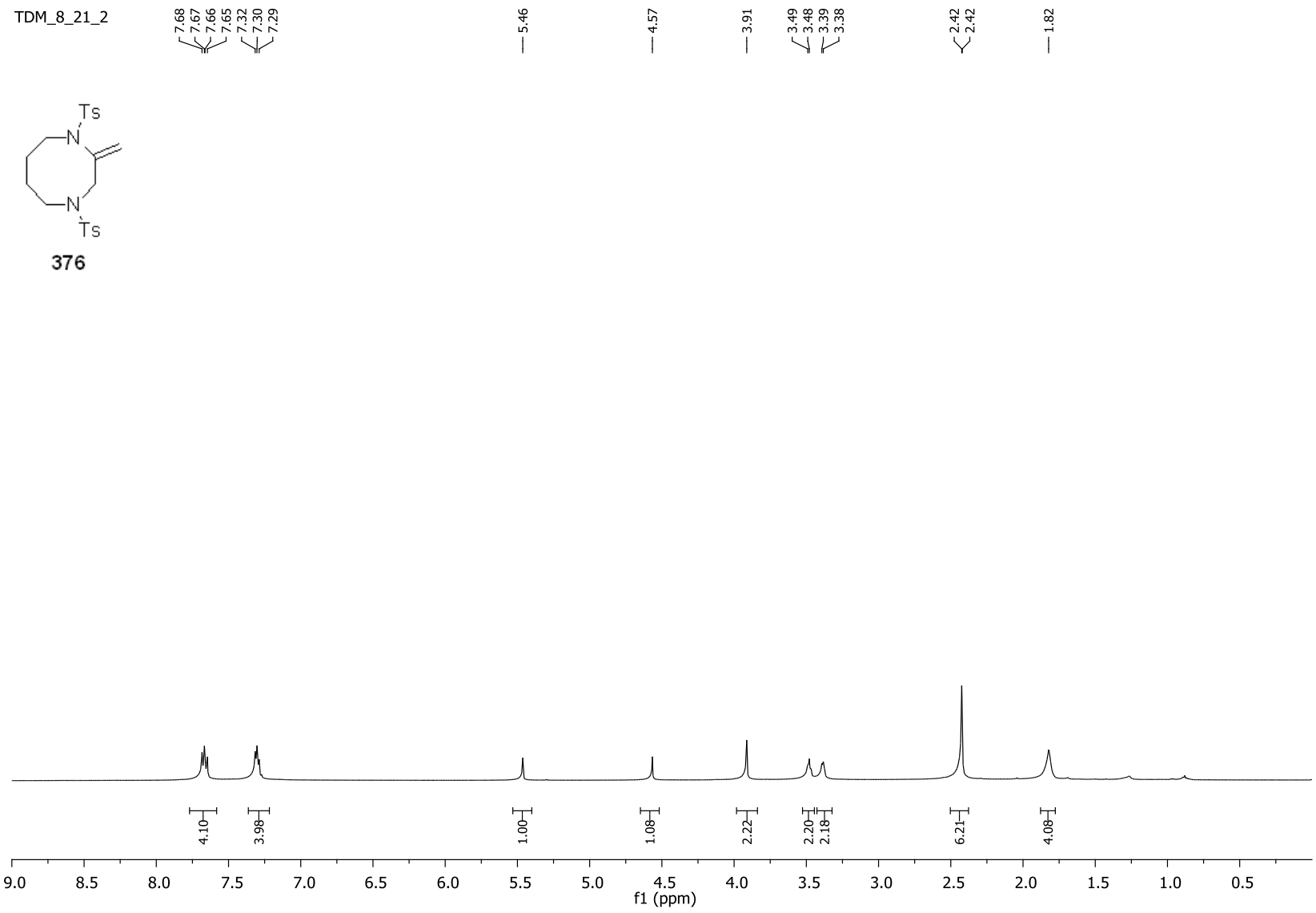


Figure 230. ^{1}H NMR Spectrum for **376** (500 MHz, $CDCl_3$)

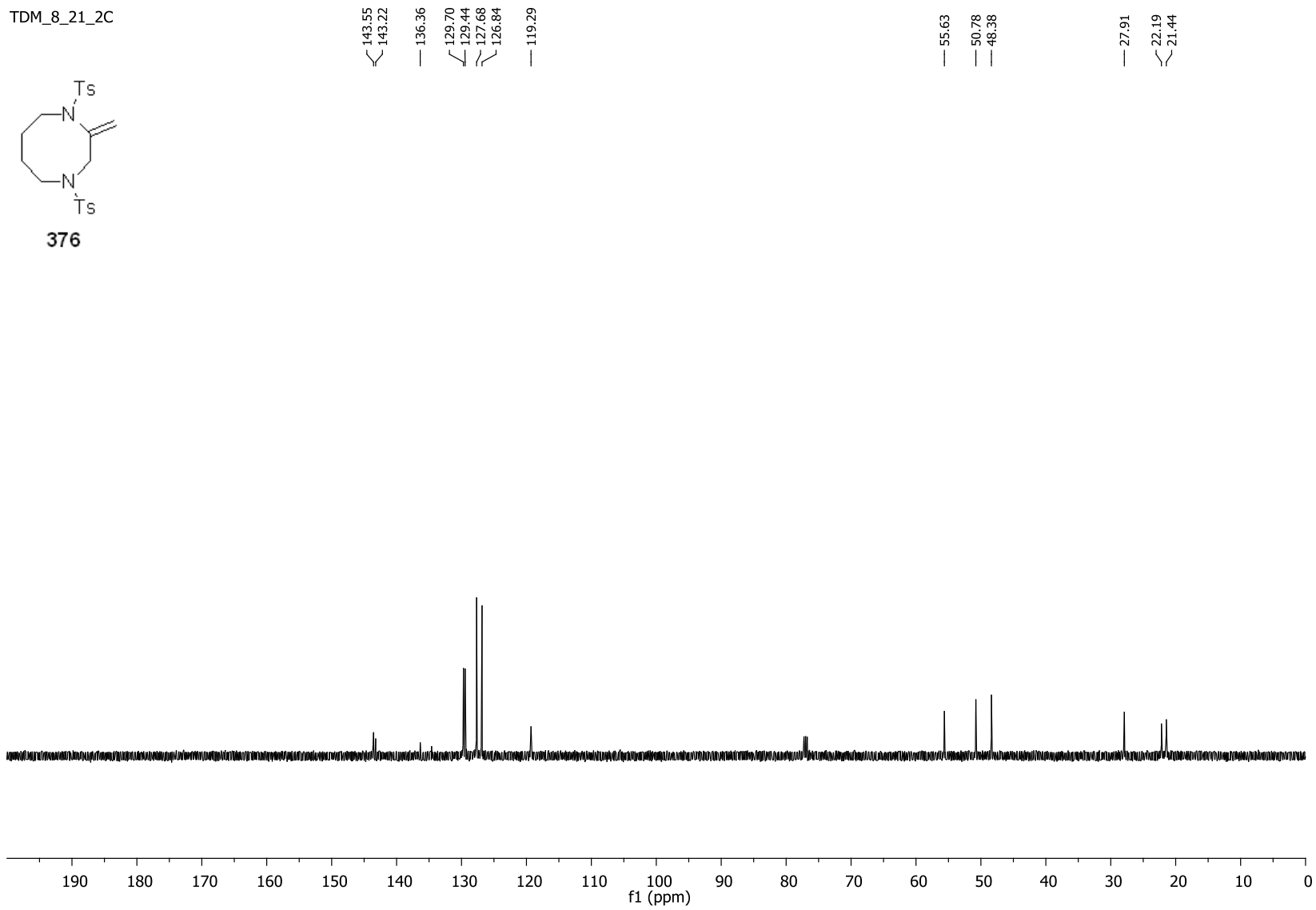
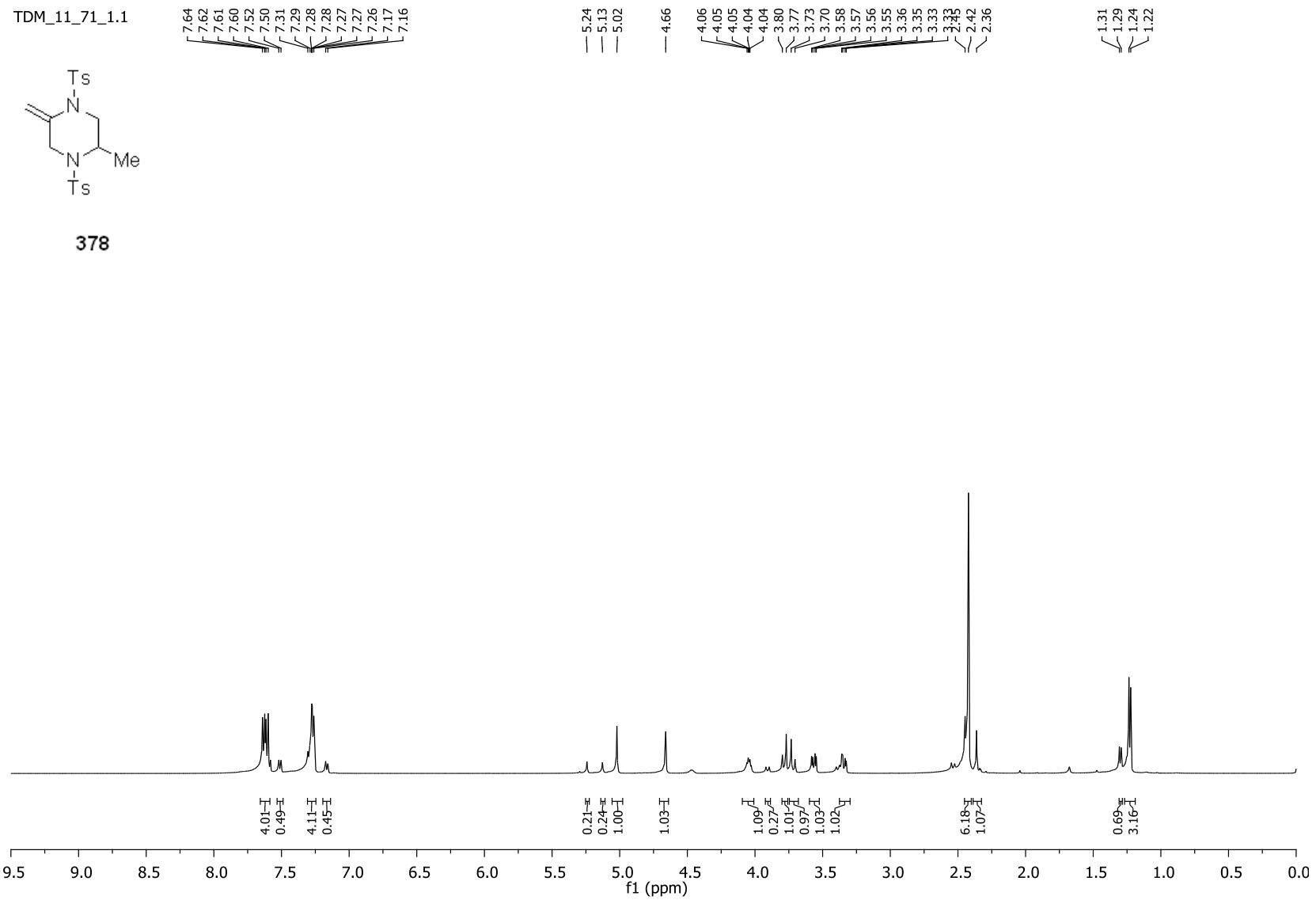


Figure 231. ^{13}C NMR Spectrum for **376** (125 MHz, $CDCl_3$)



378

Figure 232. ^{1}H NMR Spectrum for **378** (500 MHz, $CDCl_3$)

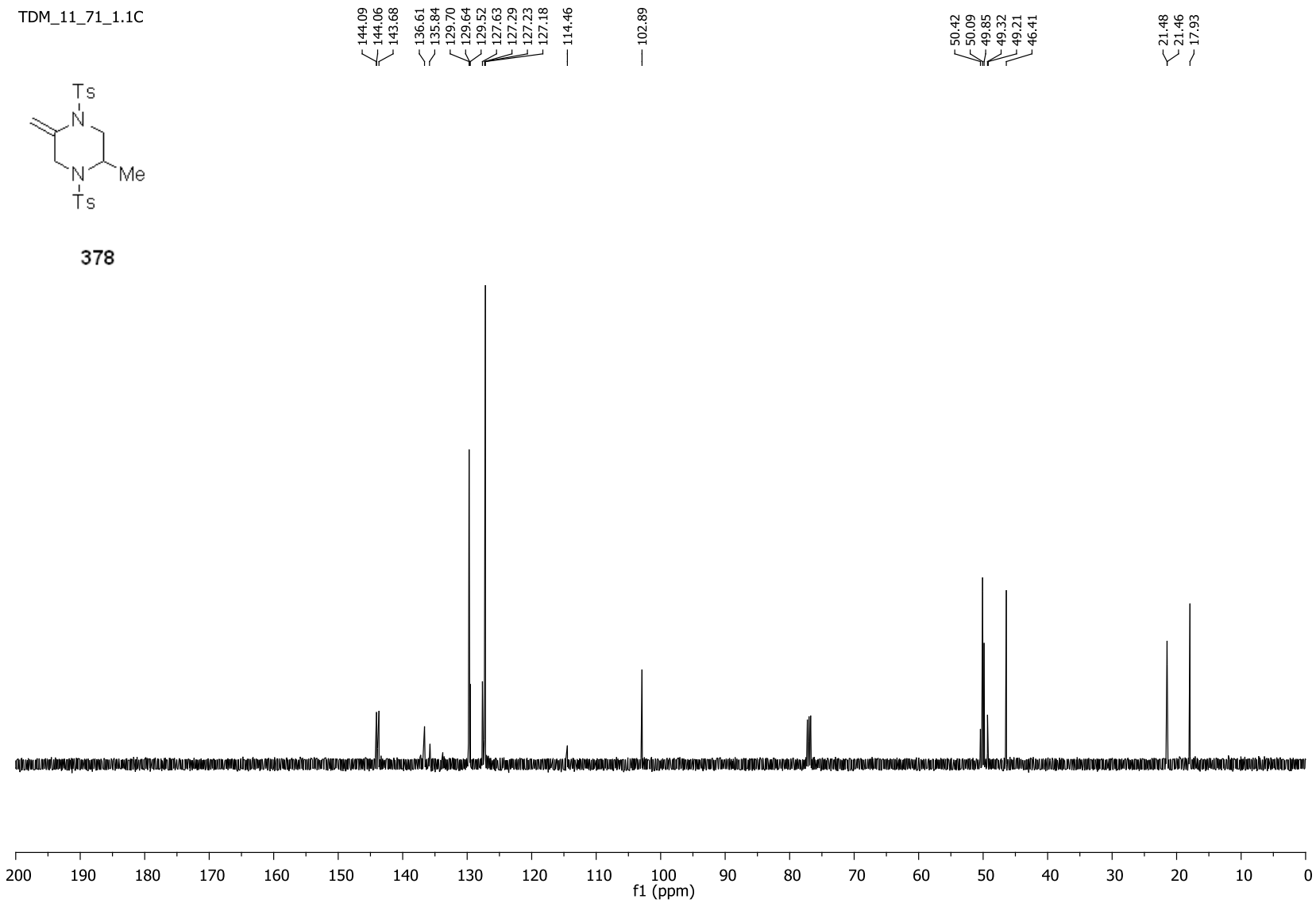


Figure 233. ^{13}C NMR Spectrum for **378** (125 MHz, $CDCl_3$)

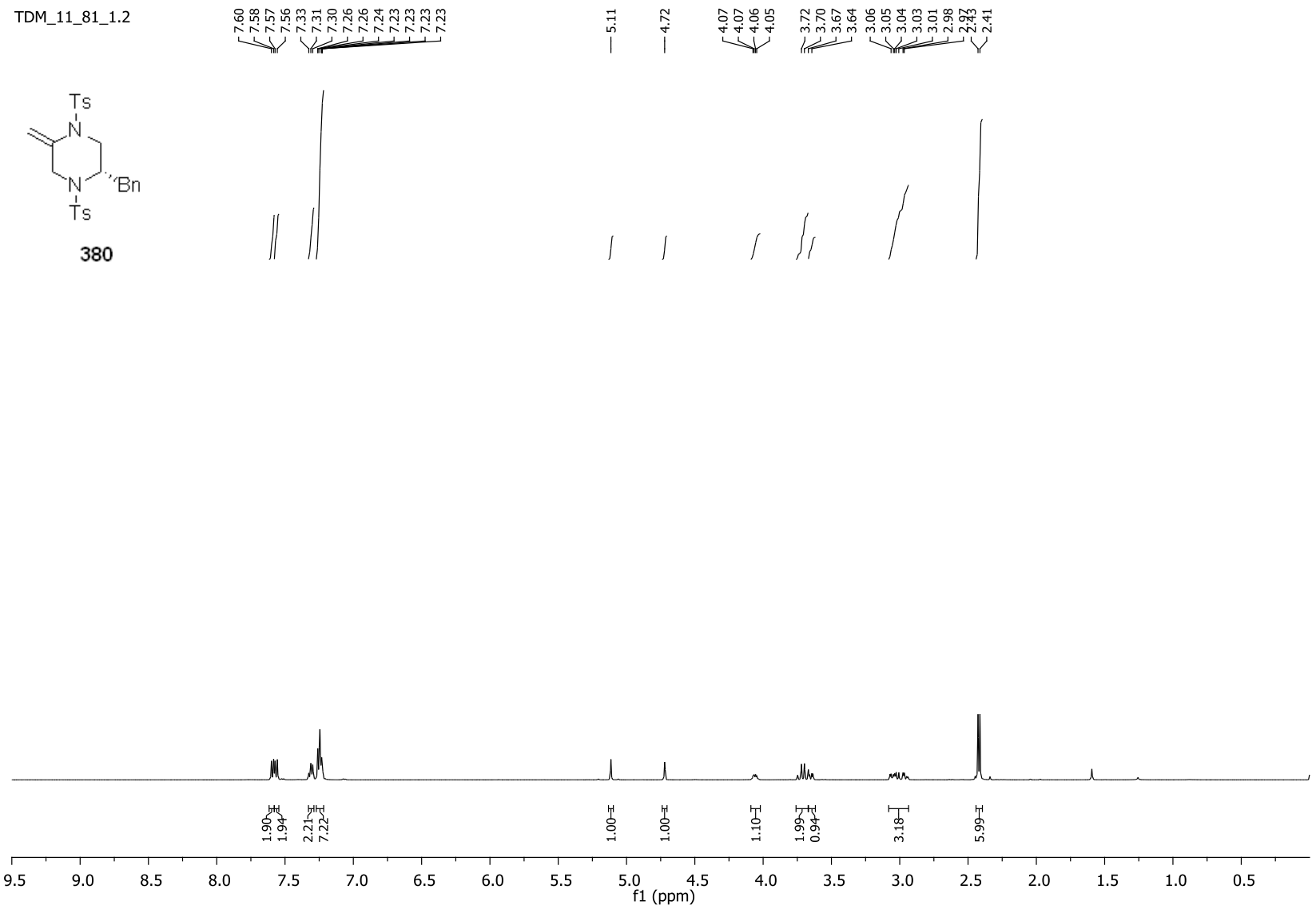


Figure 234. ^{1}H NMR Spectrum for **380** (500 MHz, $CDCl_3$)

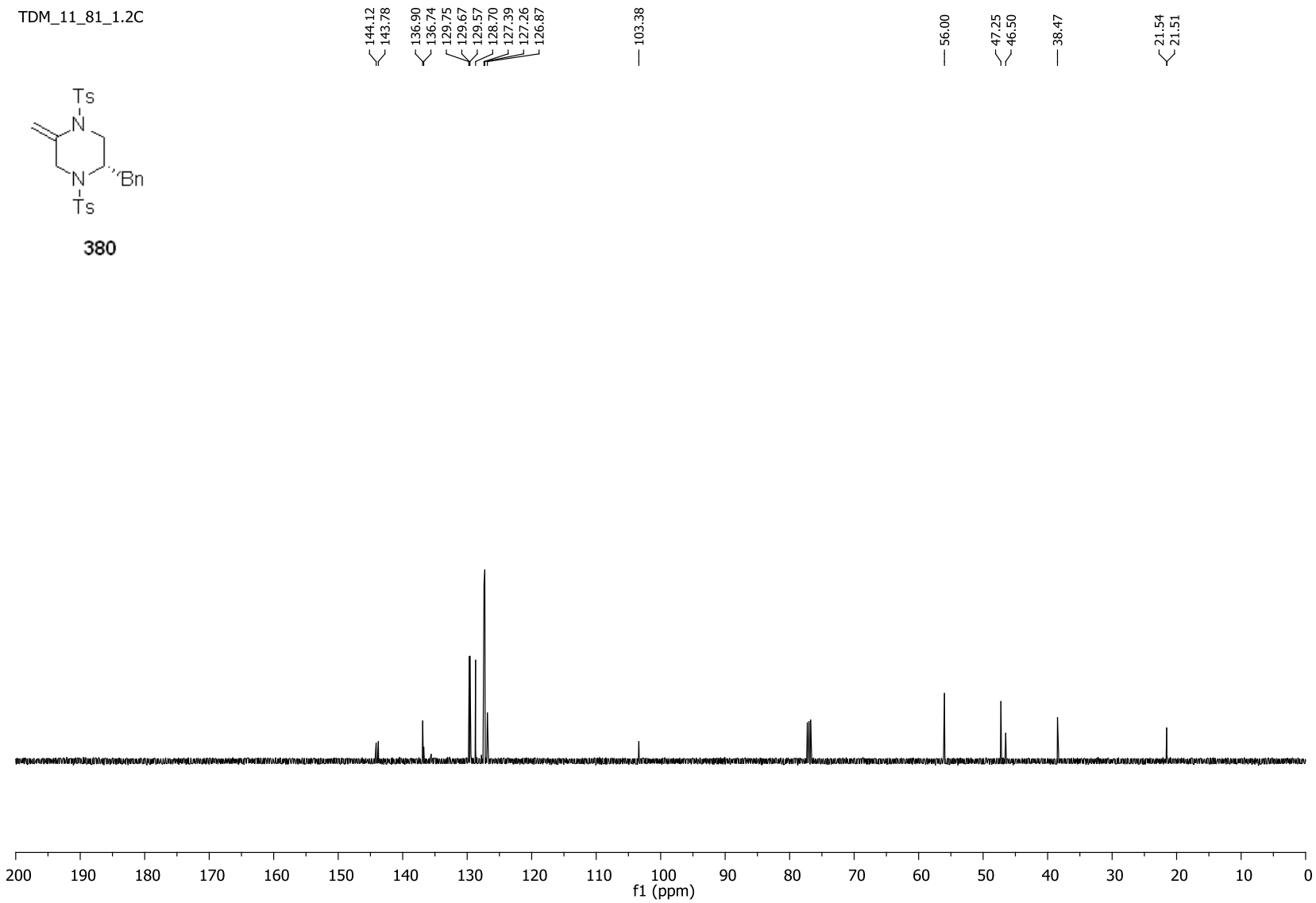


Figure 235. ^{13}C NMR Spectrum for **380** (125 MHz, $CDCl_3$)

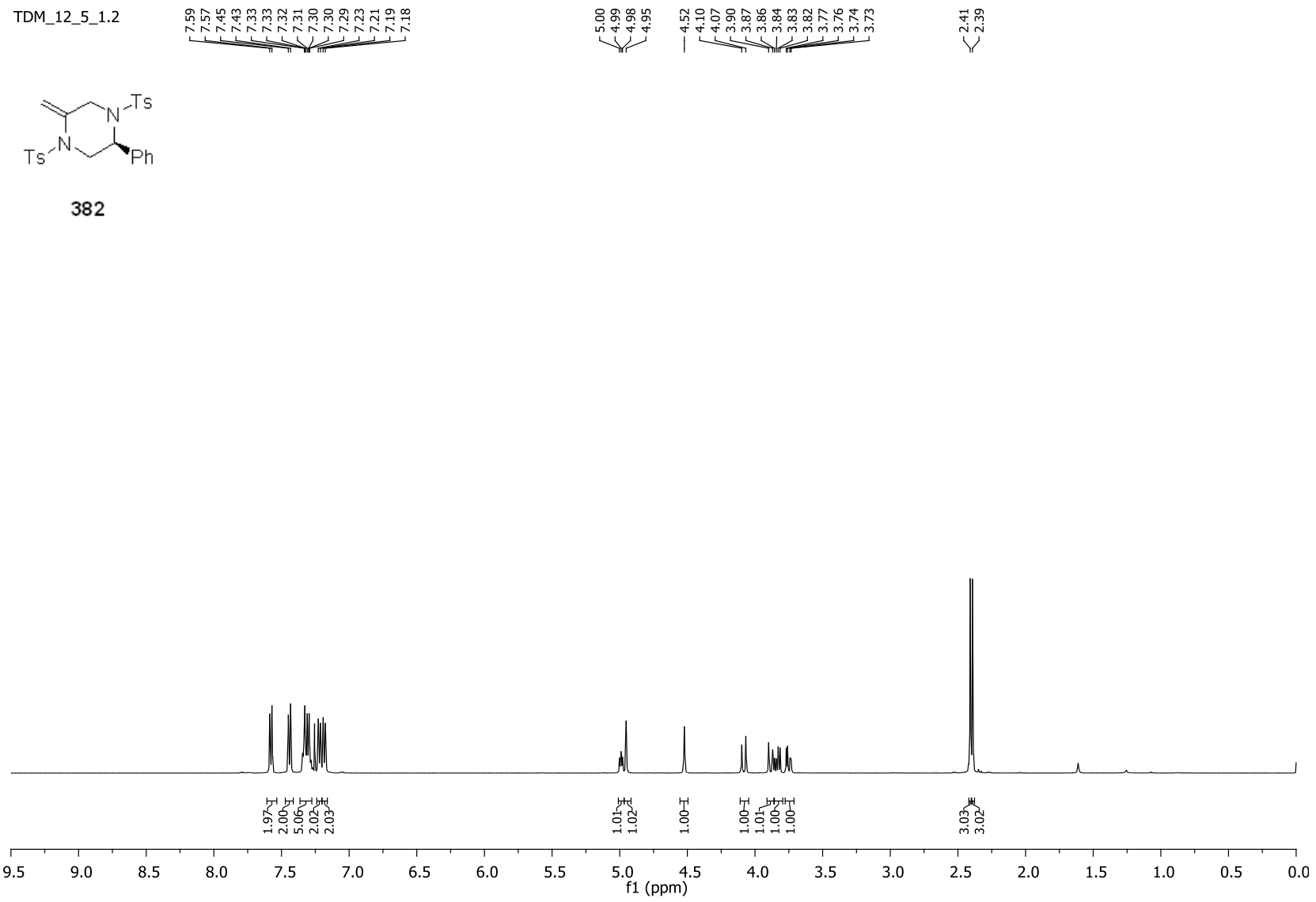


Figure 236. ^{1}H NMR Spectrum for **382** (500 MHz, $CDCl_3$)

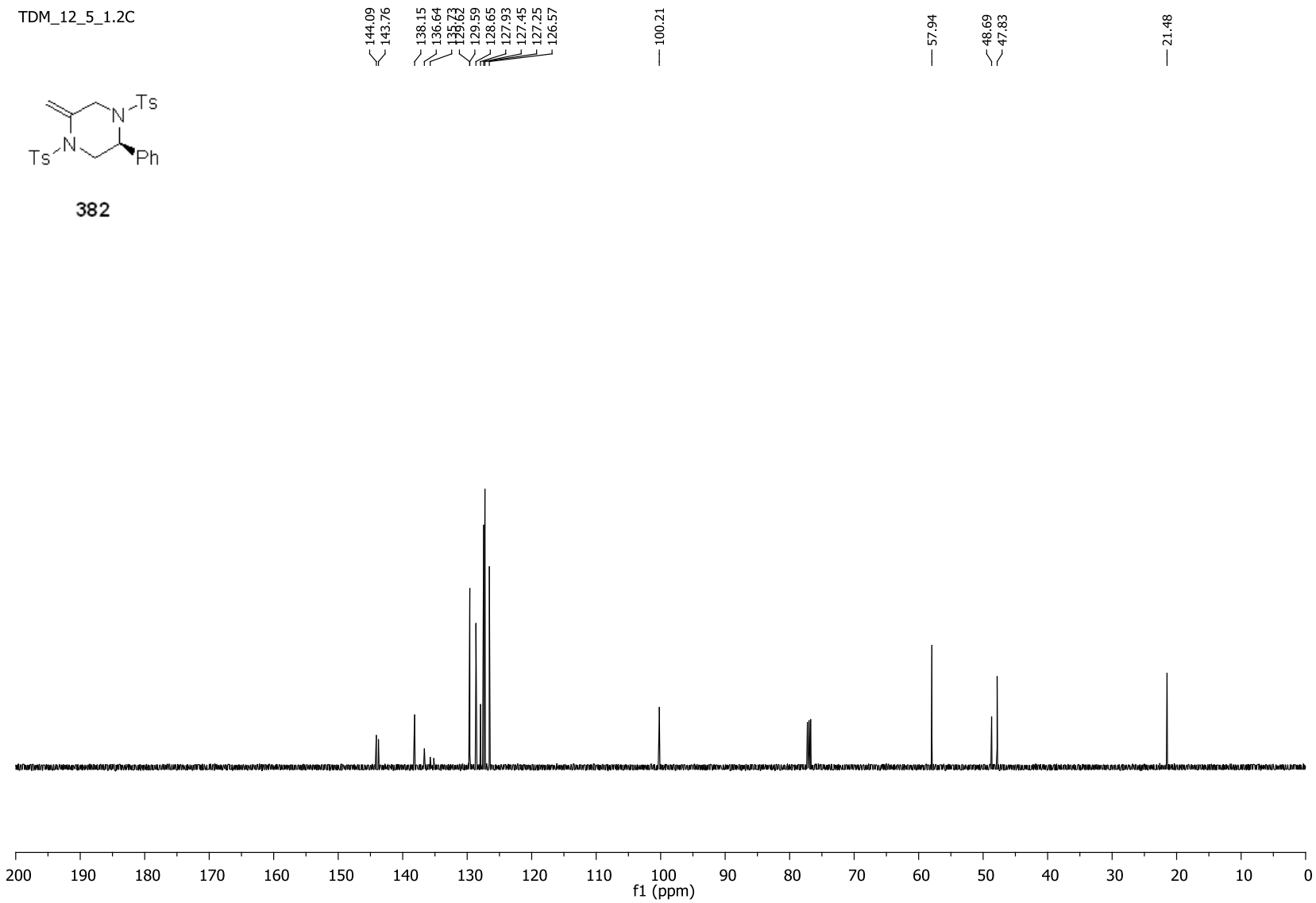


Figure 237. ^{13}C NMR Spectrum for **382** (125 MHz, $CDCl_3$)

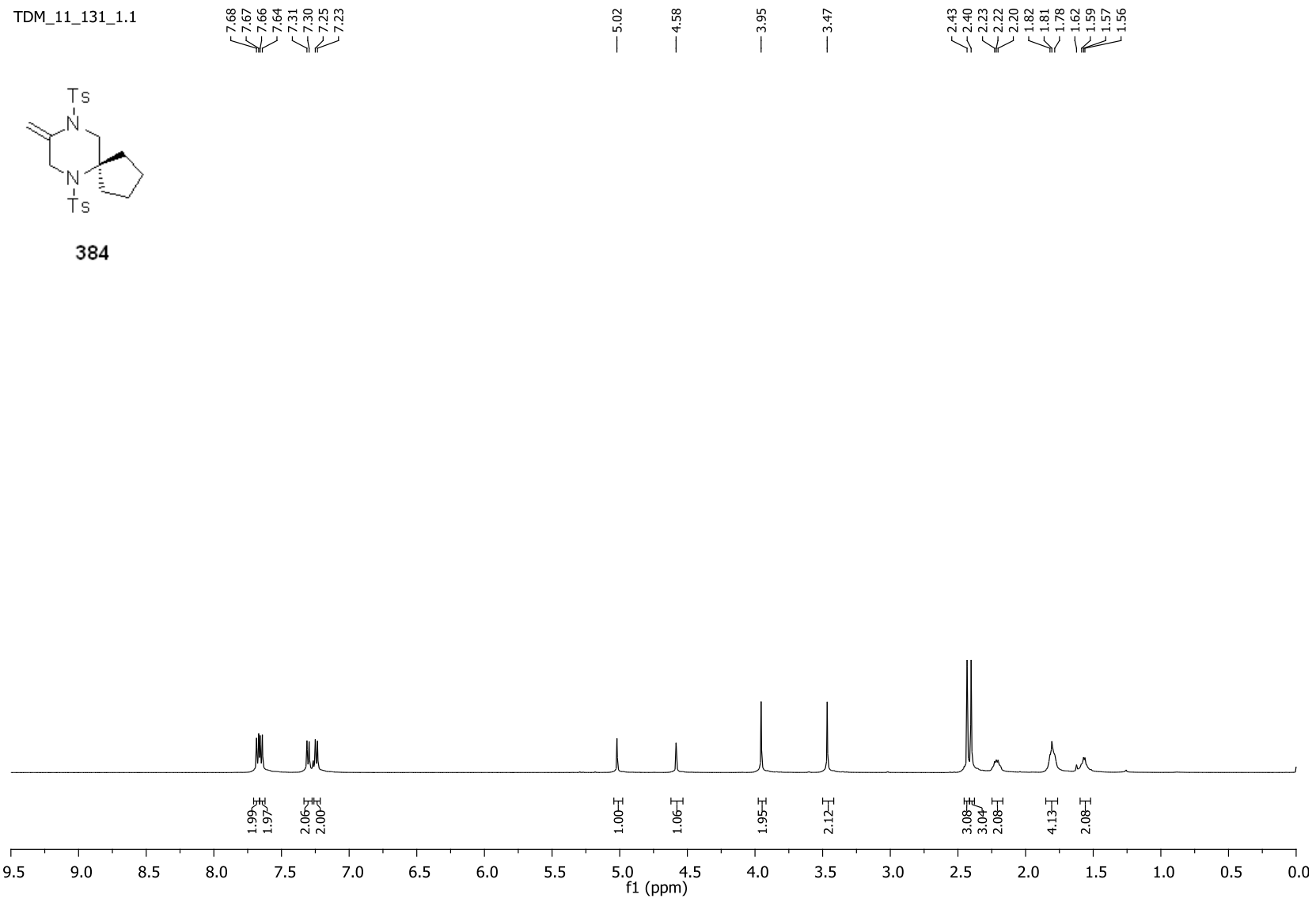


Figure 238. ^{1}H NMR Spectrum for **384** (500 MHz, $CDCl_3$)

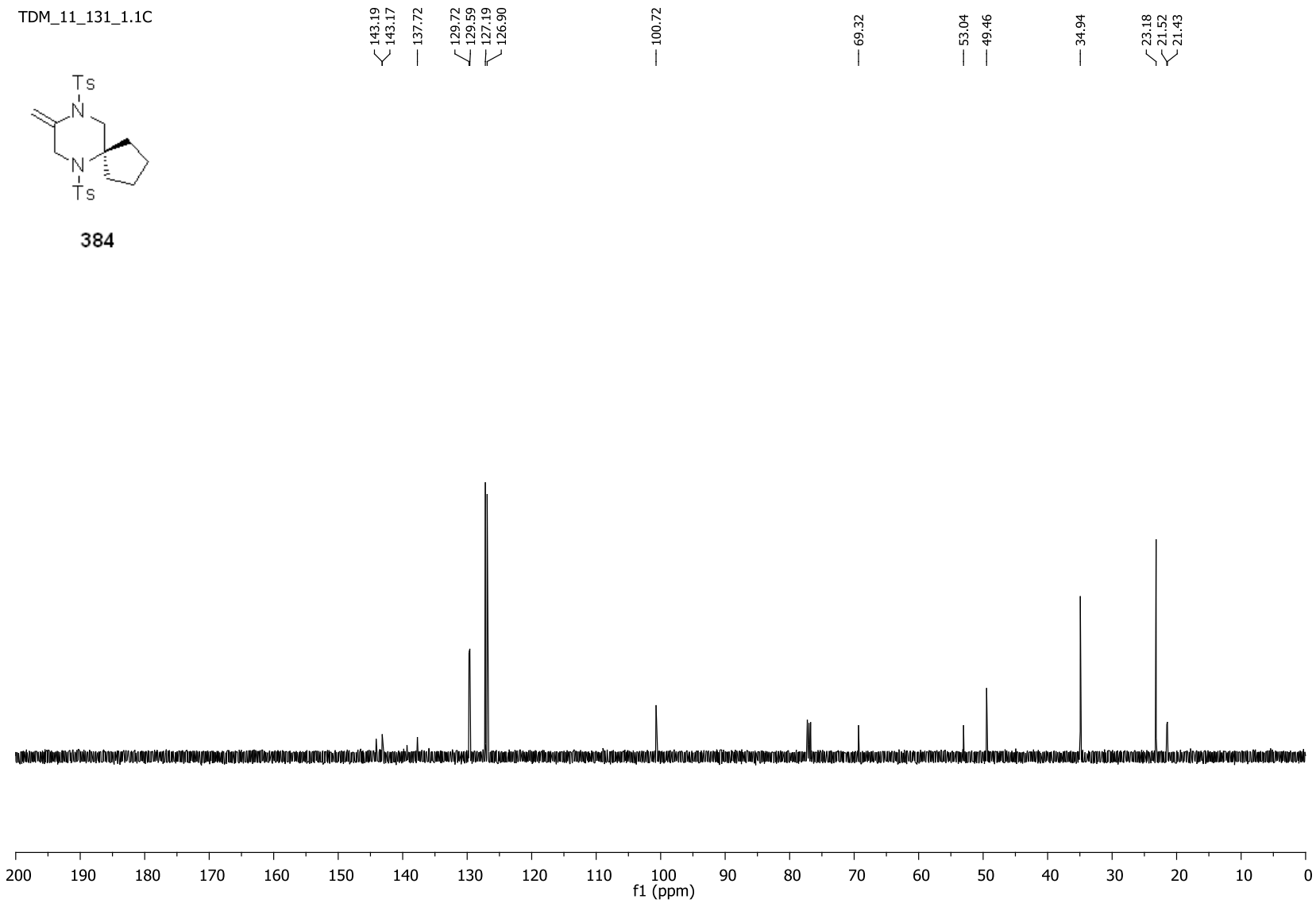


Figure 239. ^{13}C NMR Spectrum for **384** (125 MHz, $CDCl_3$)

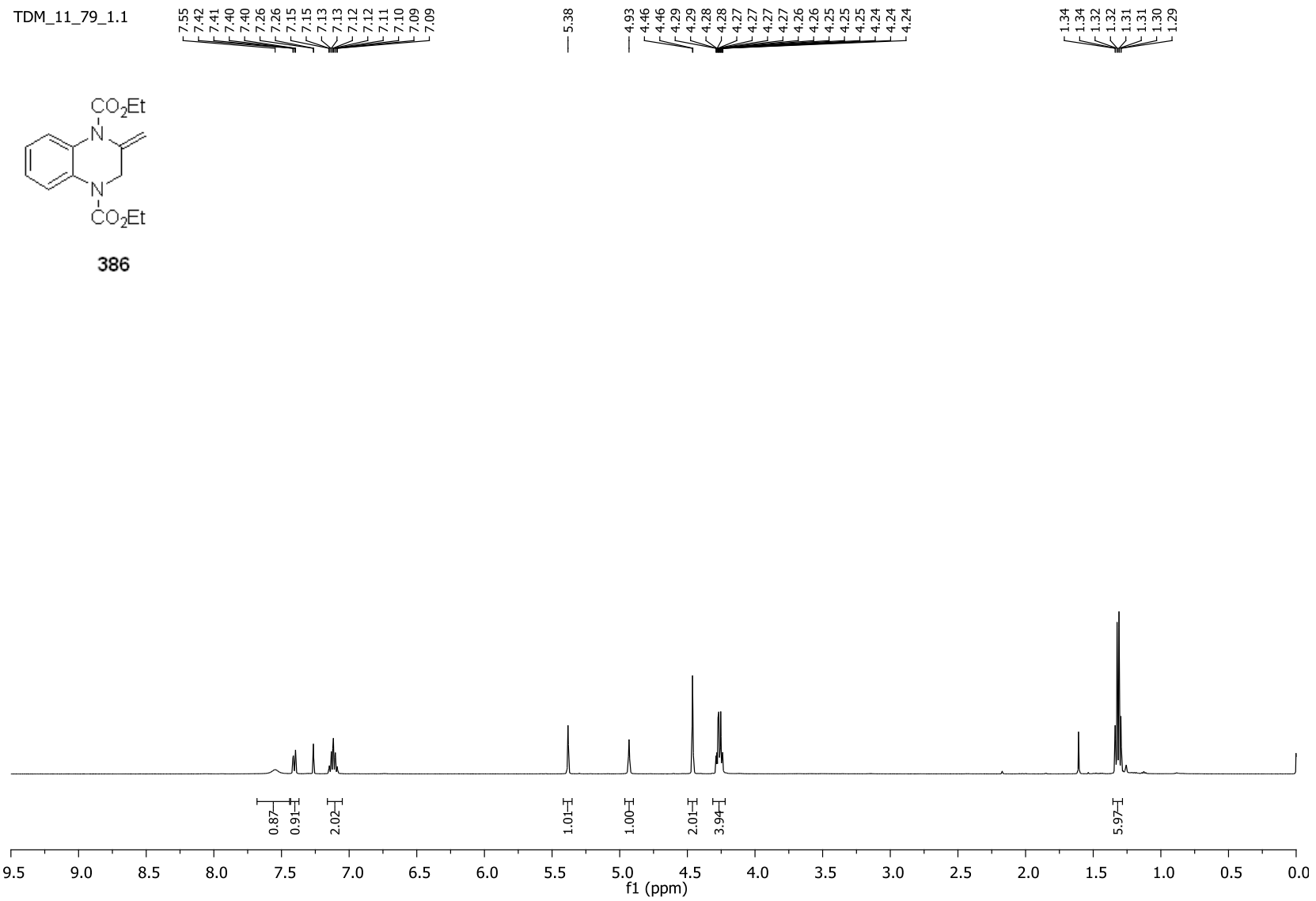


Figure 240. ^{1}H NMR Spectrum for **386** (500 MHz, $CDCl_3$)

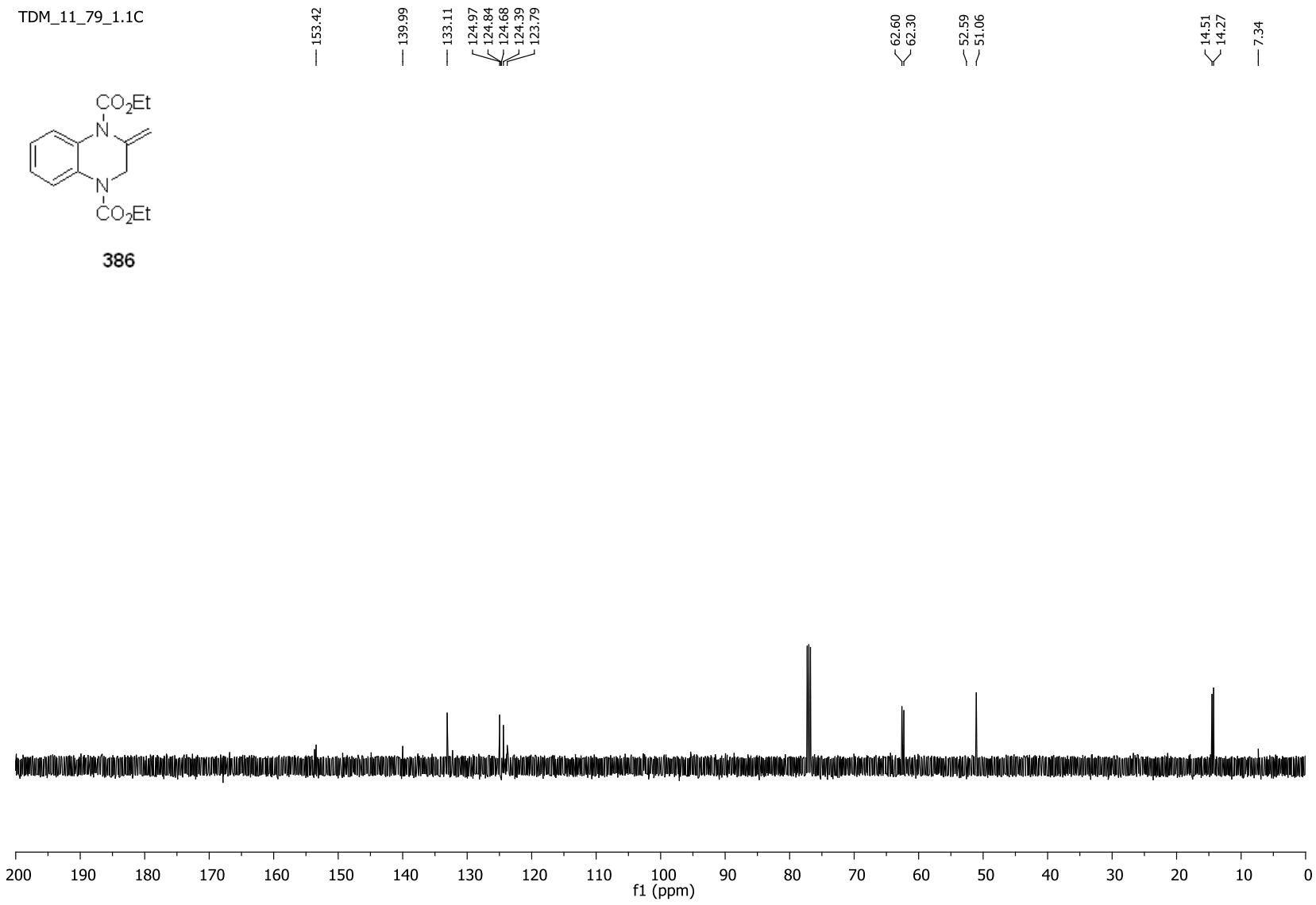


Figure 241. ^{13}C NMR Spectrum for **386** (125 MHz, $CDCl_3$)

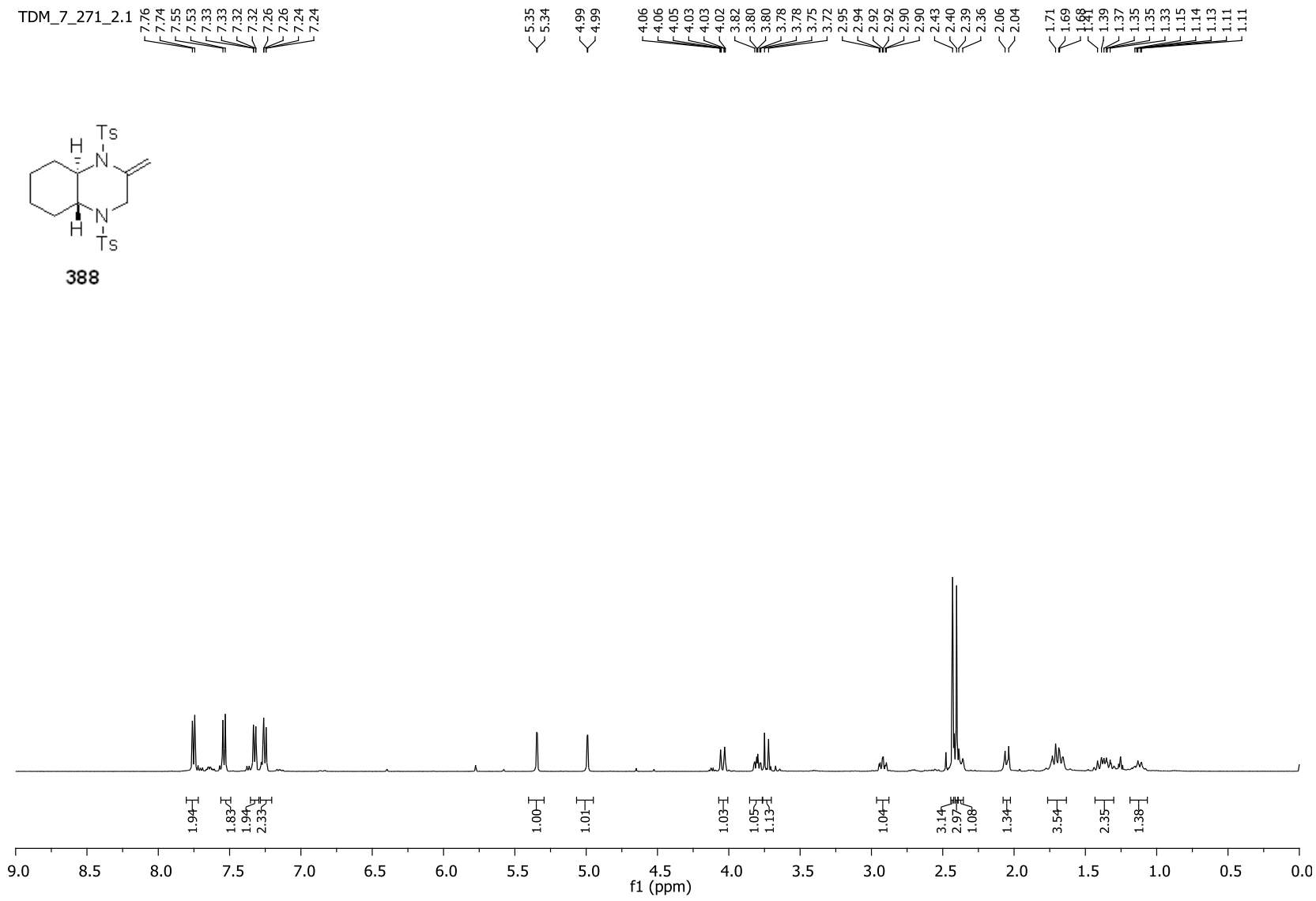


Figure 242. ^{1}H NMR Spectrum for **388** (500 MHz, $CDCl_3$)

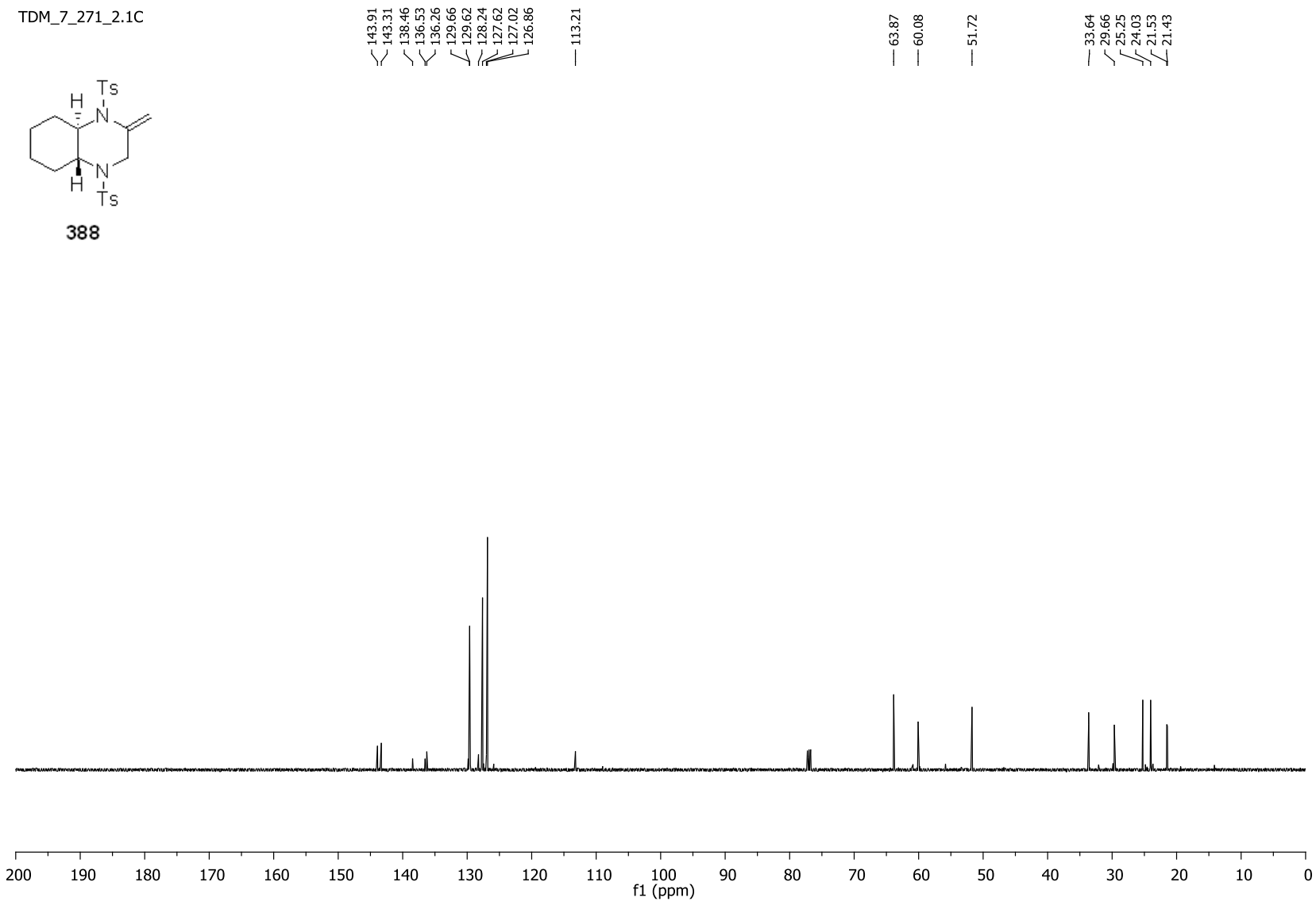


Figure 243. ^{13}C NMR Spectrum for **388** (125 MHz, $CDCl_3$)

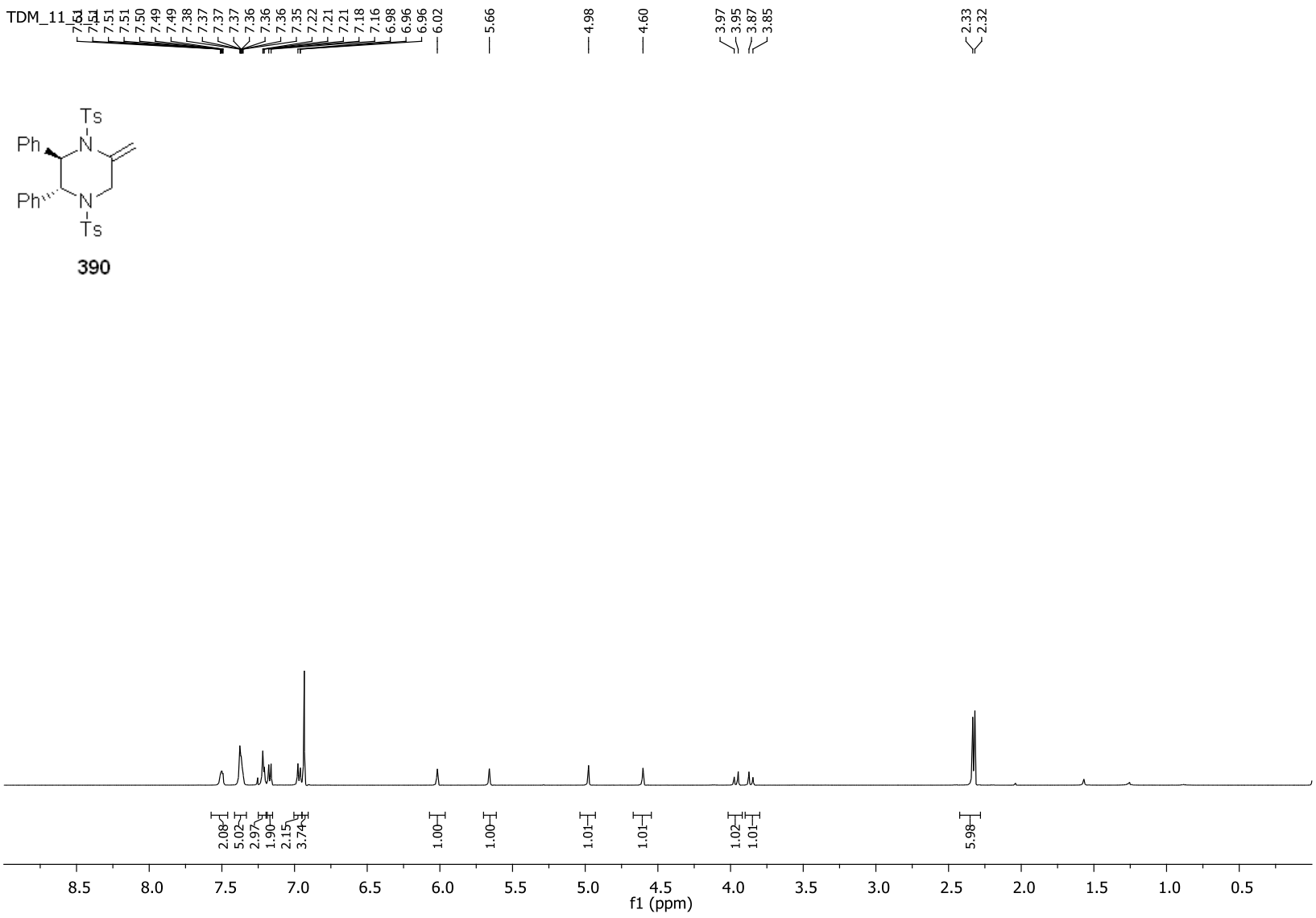


Figure 244. ^{1}H NMR Spectrum for **390** (500 MHz, $CDCl_3$)

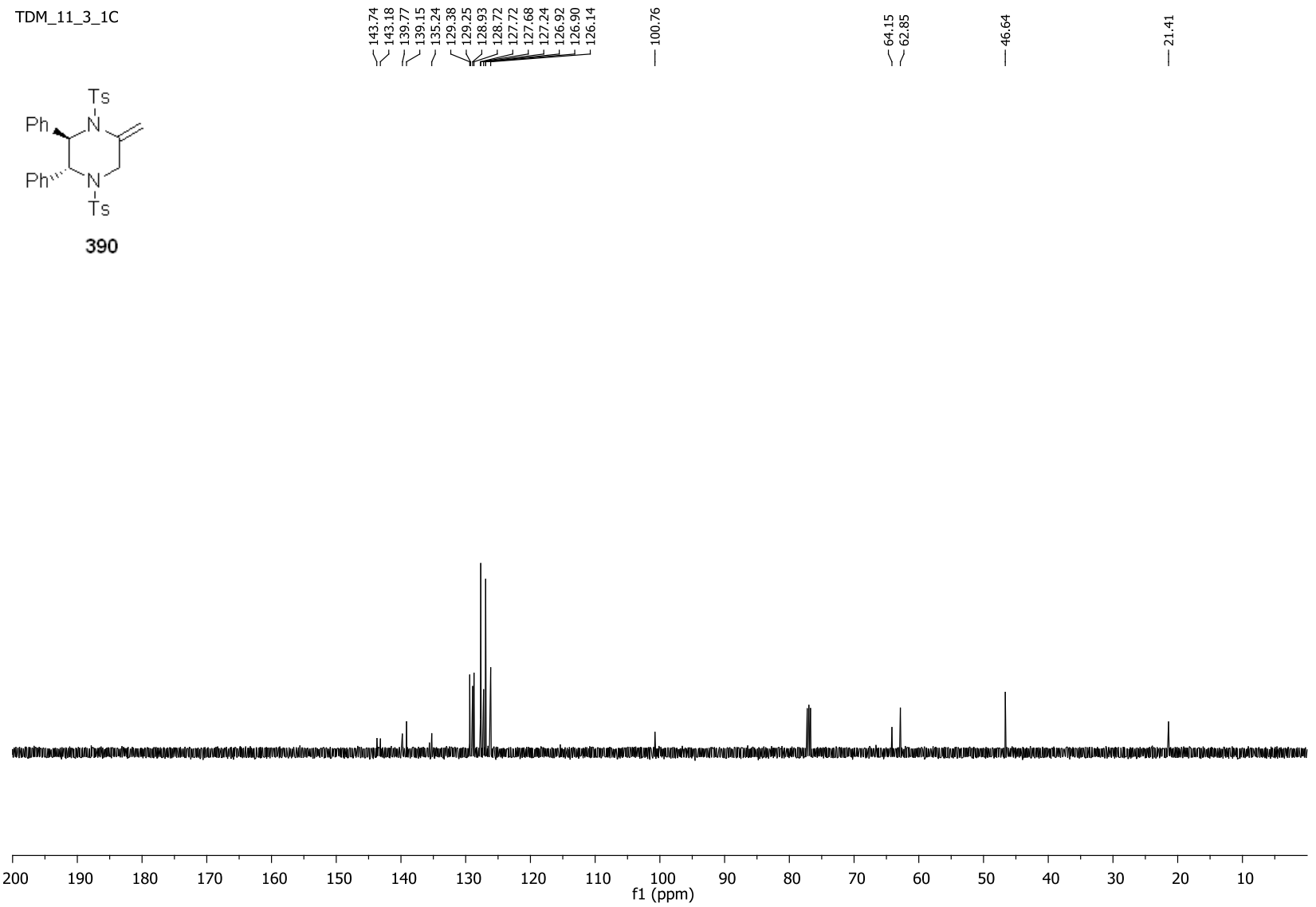


Figure 245. ^{13}C NMR Spectrum for **390** (125 MHz, $CDCl_3$)

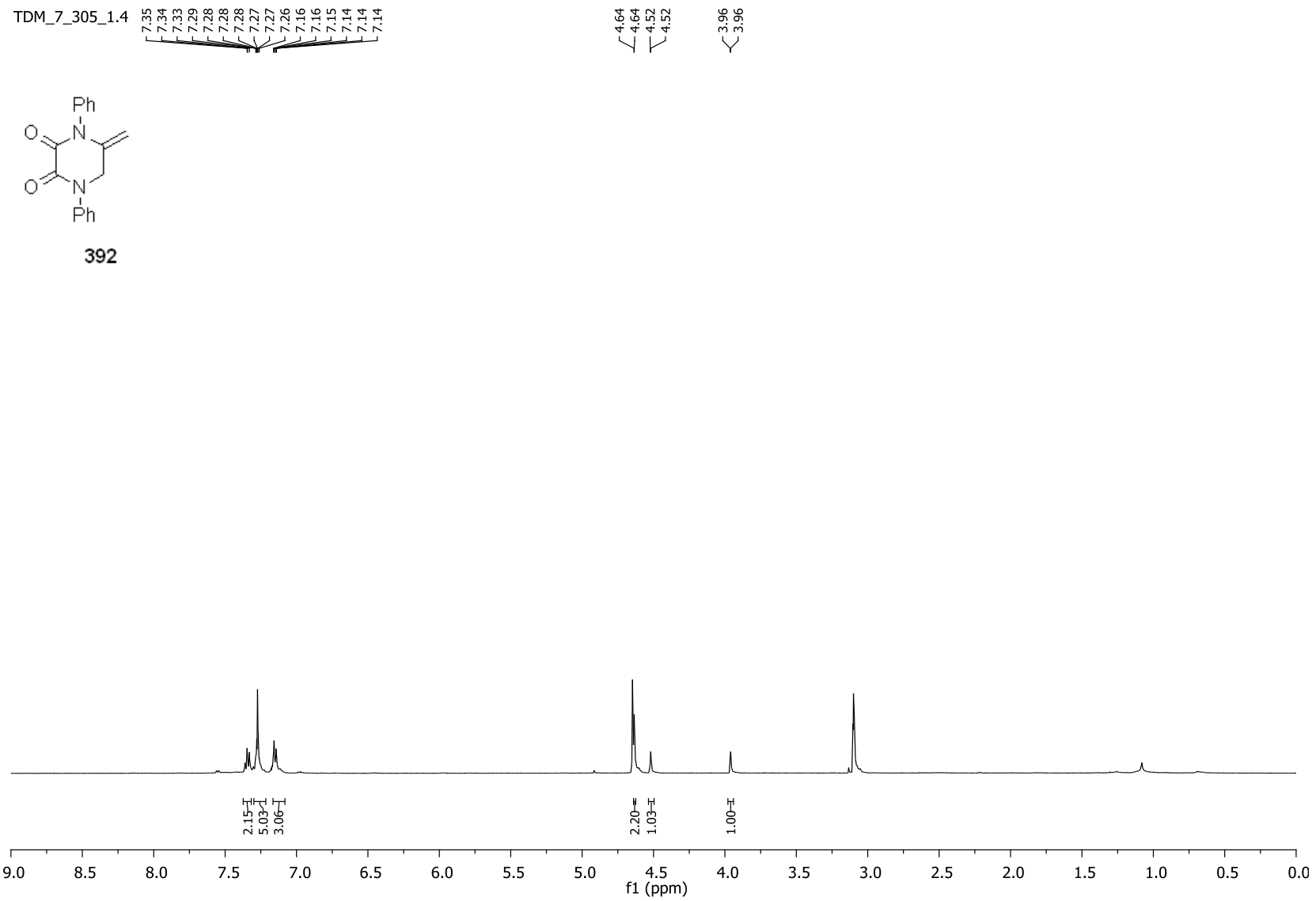


Figure 246. ^{1}H NMR Spectrum for **392** (500 MHz, $CDCl_3$)

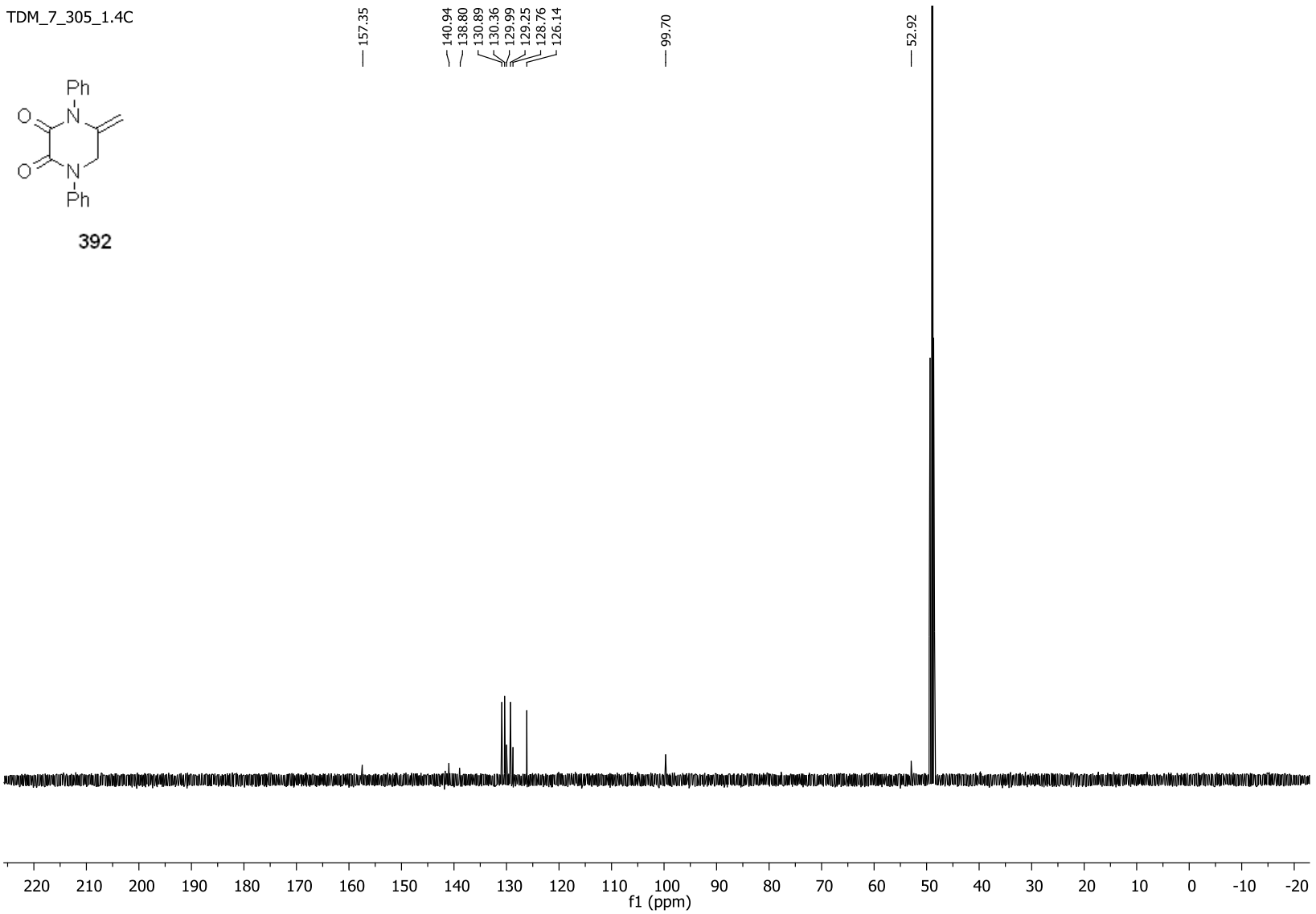


Figure 247. ^{13}C NMR Spectrum for **392** (125 MHz, $CDCl_3$)

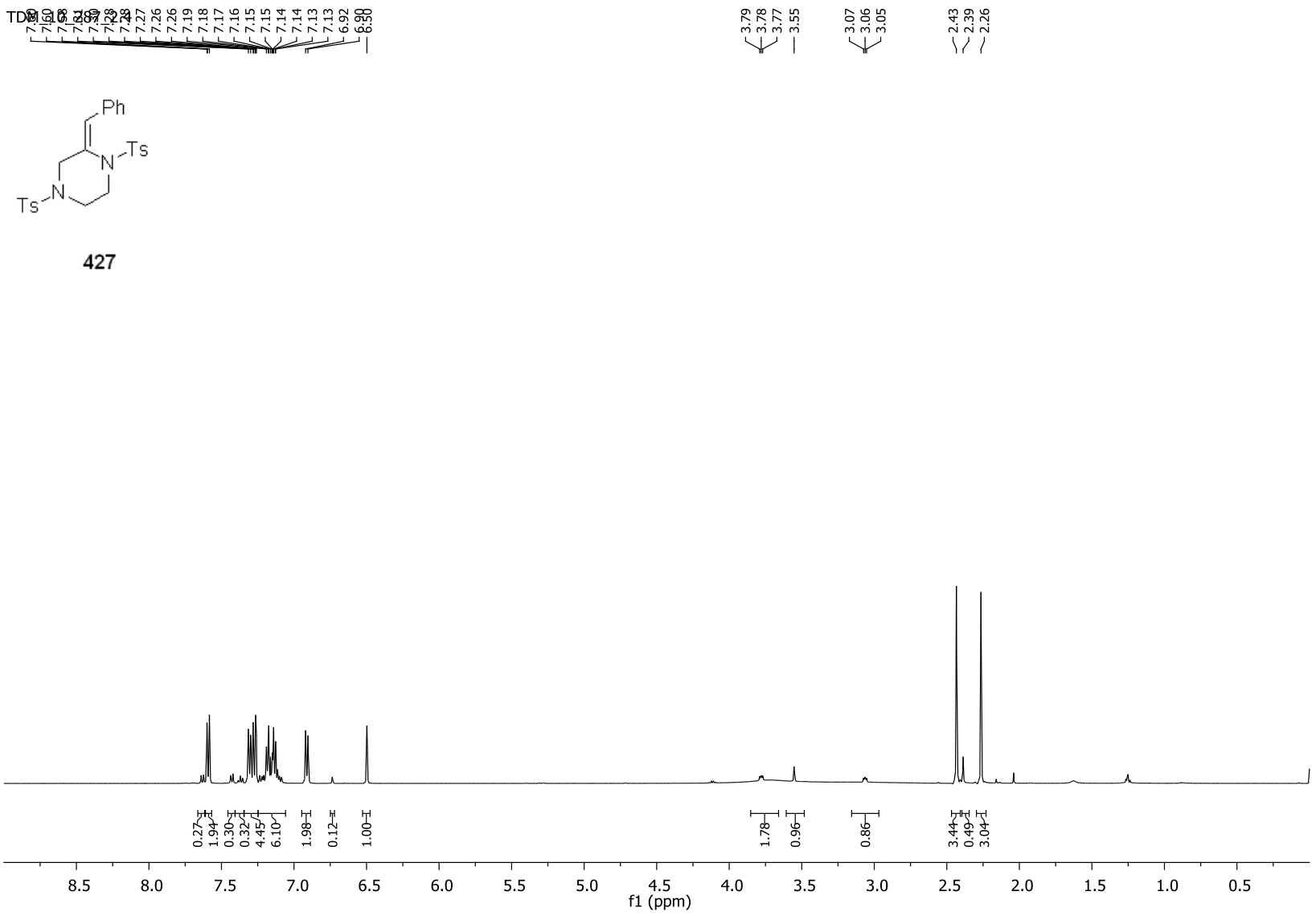


Figure 248. ^{1}H NMR Spectrum for **427** (500 MHz, $CDCl_3$)

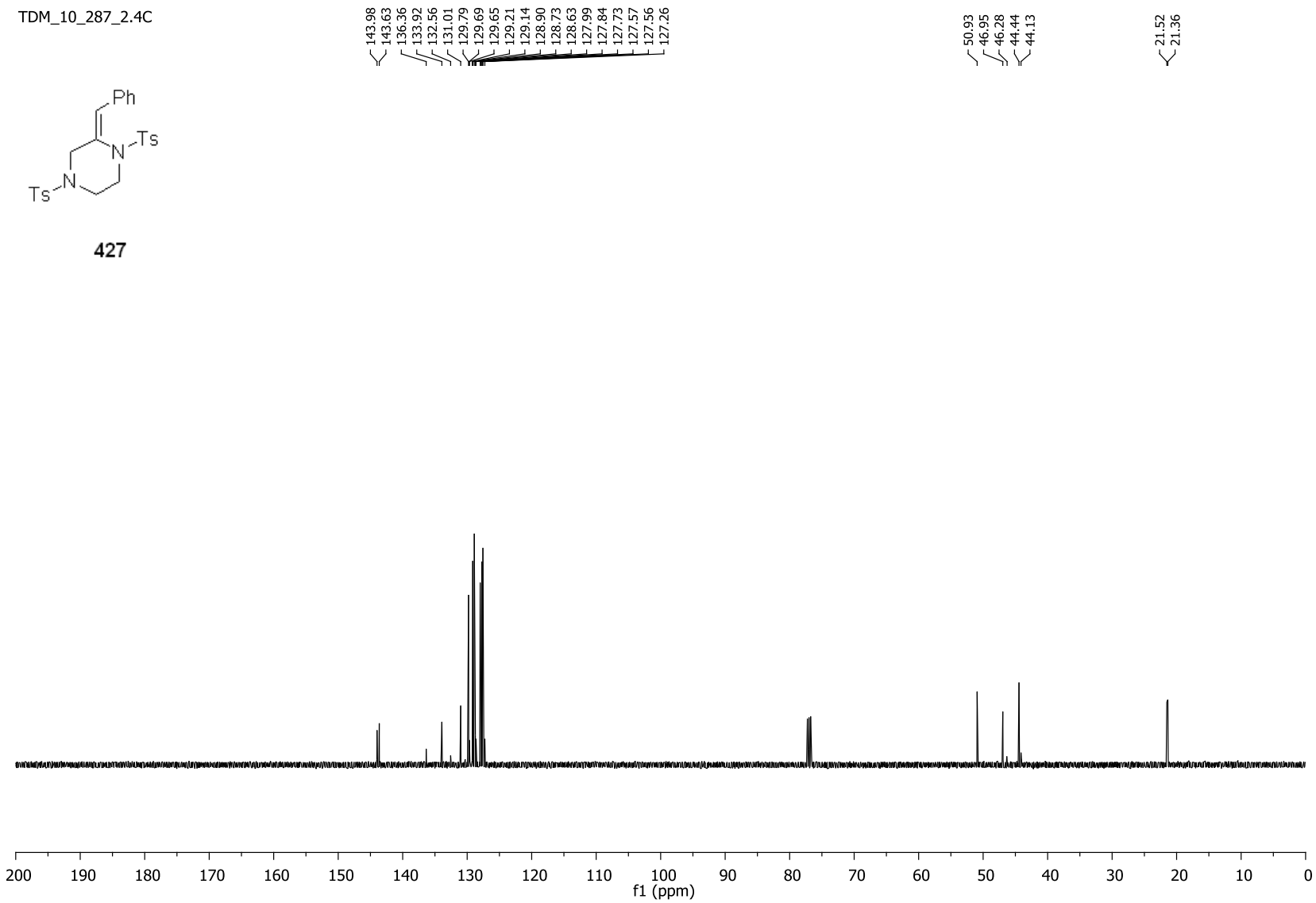


Figure 249. ^{13}C NMR Spectrum for **427** (125 MHz, $CDCl_3$)

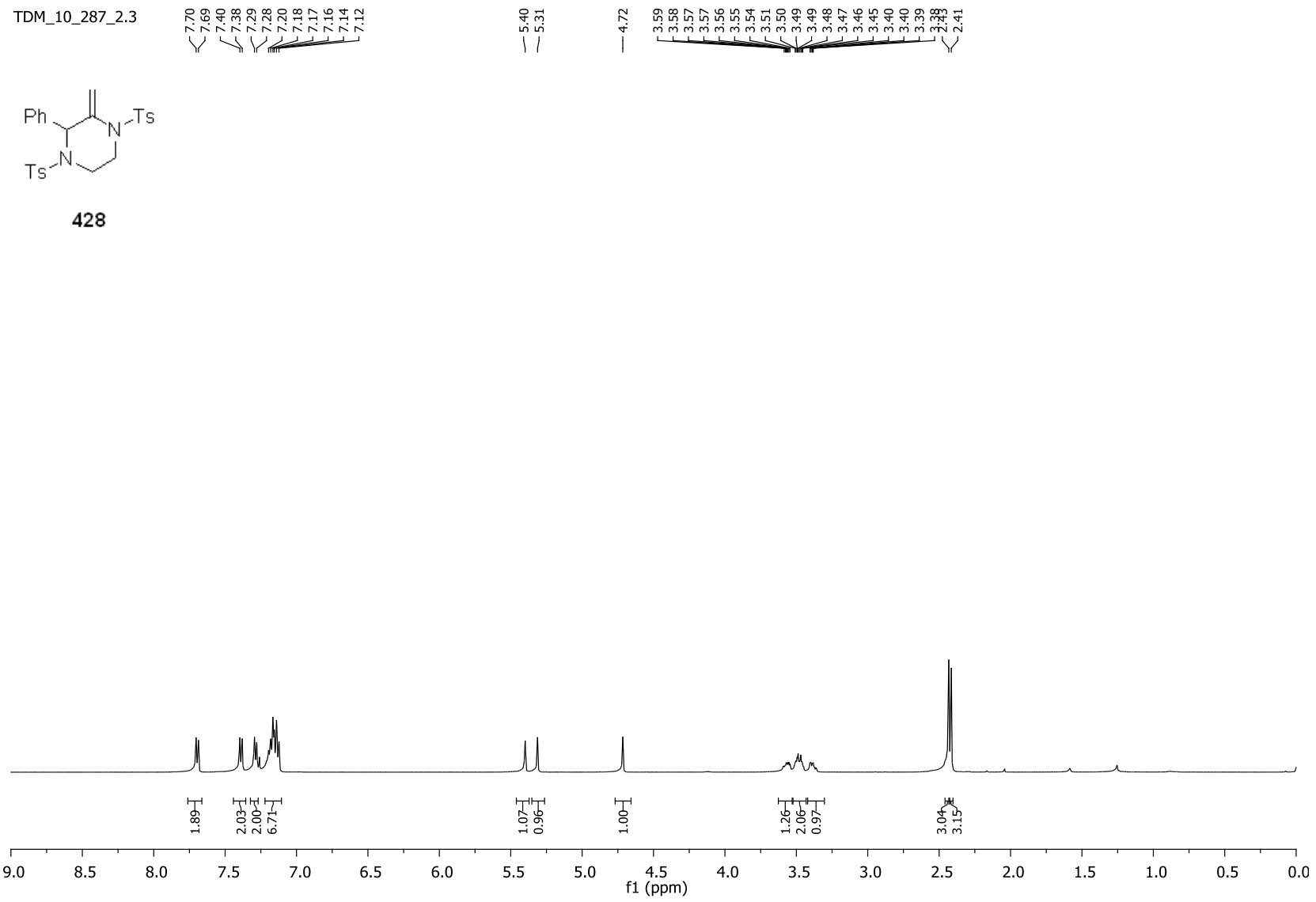


Figure 250. ^{1}H NMR Spectrum for **428** (500 MHz, $CDCl_3$)

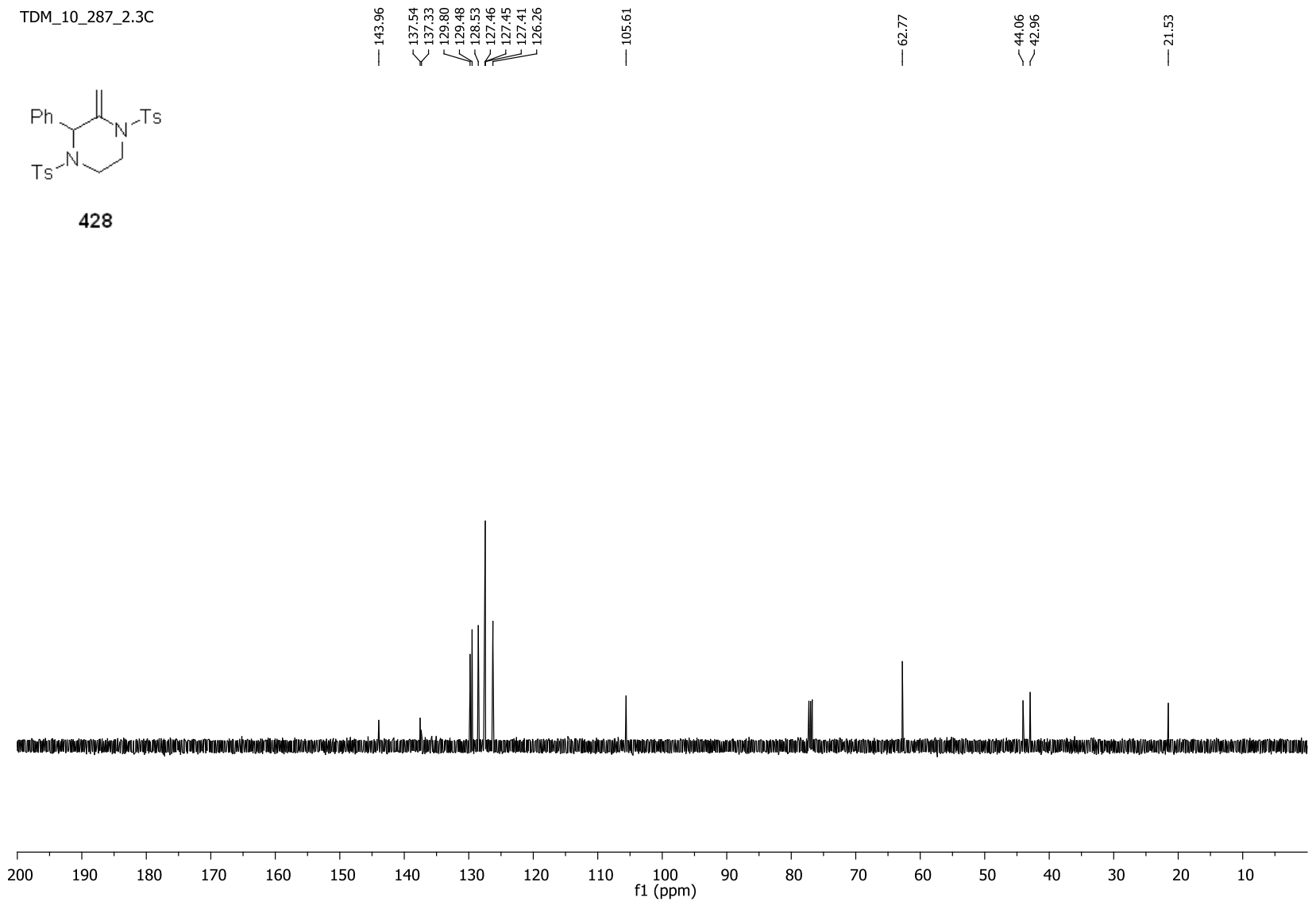


Figure 251. ^{13}C NMR Spectrum for **428** (125 MHz, $CDCl_3$)

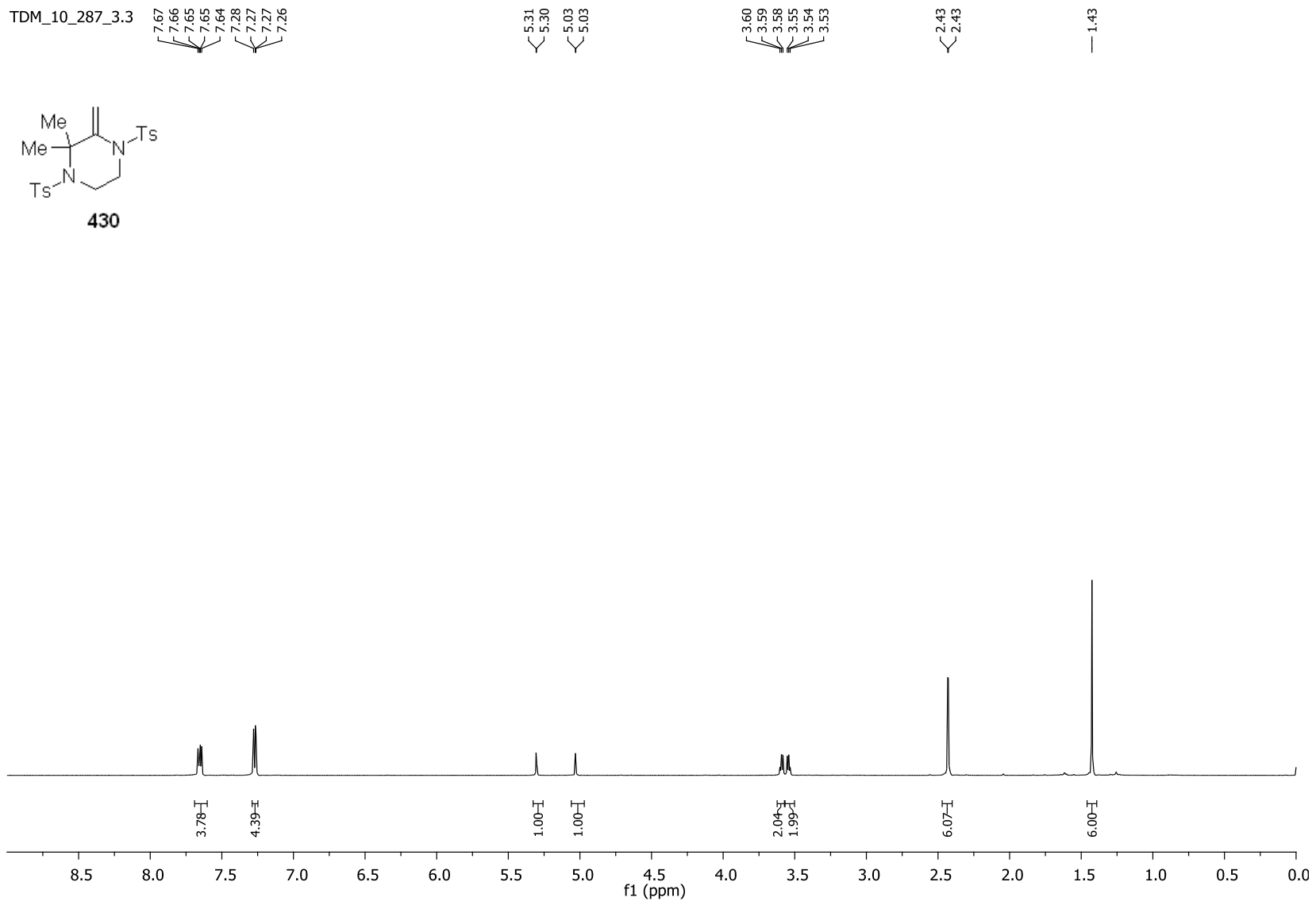


Figure 252. ^{1}H NMR Spectrum for **430** (500 MHz, $CDCl_3$)

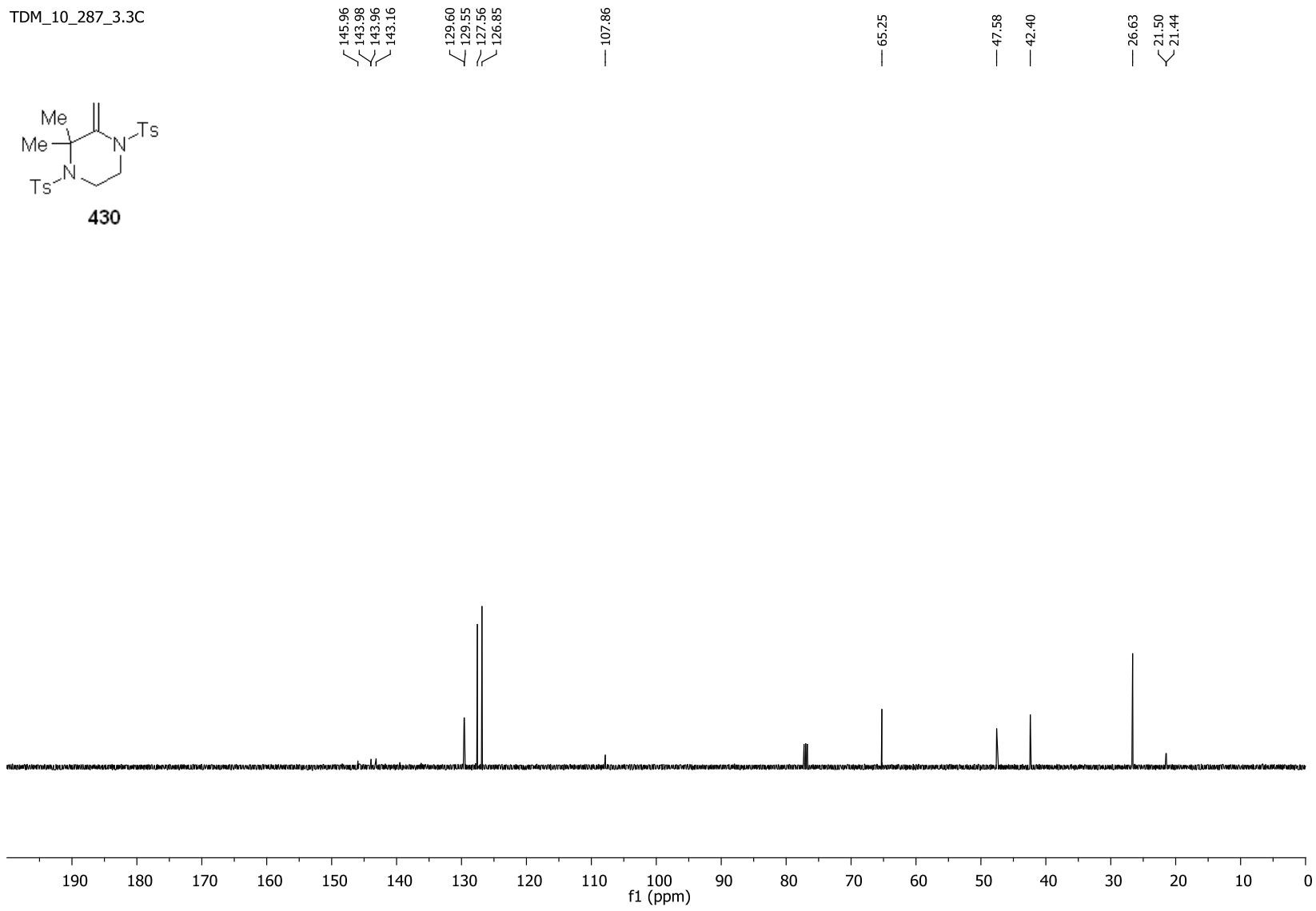
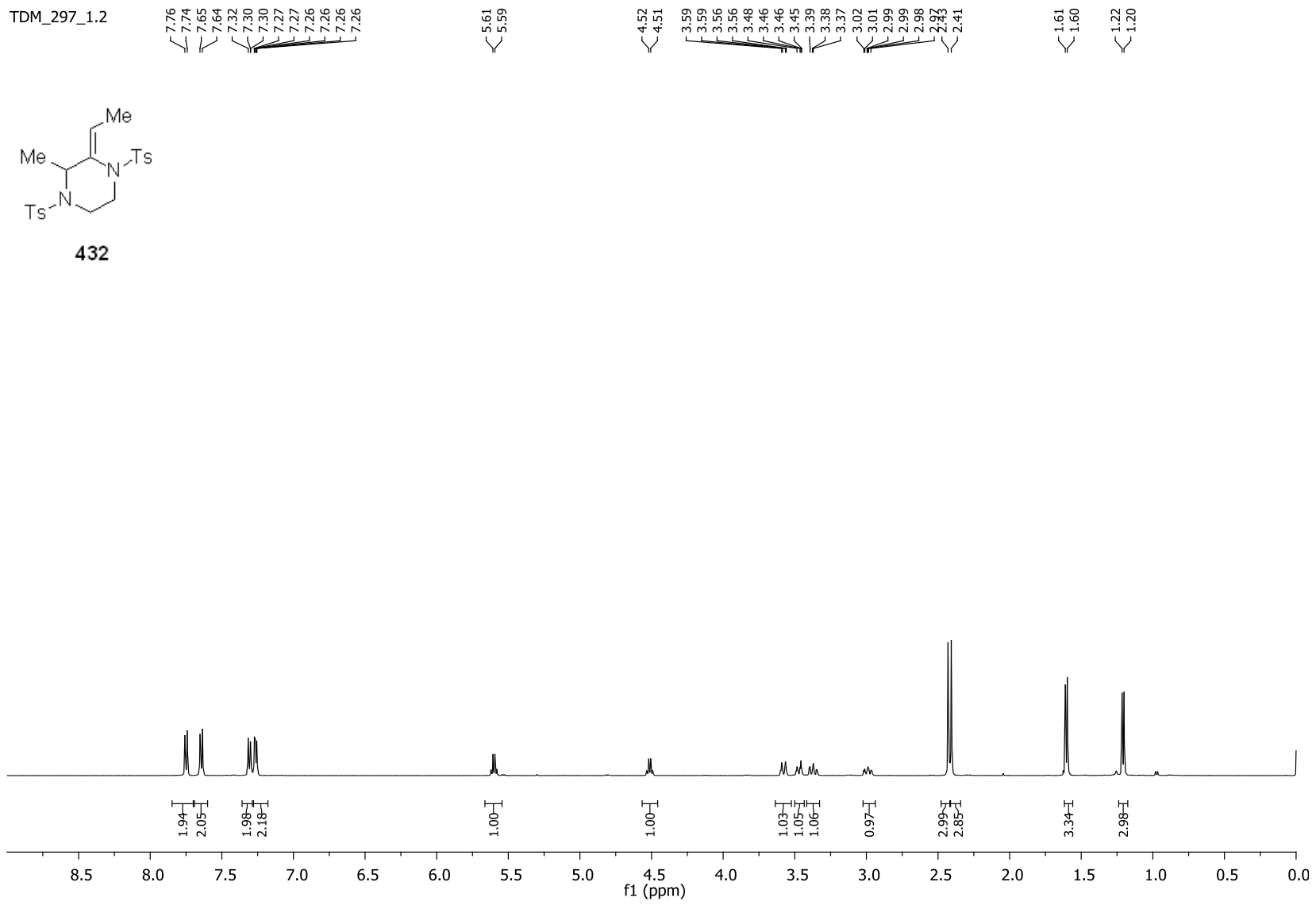


Figure 253. ^{13}C NMR Spectrum for **430** (125 MHz, $CDCl_3$)



432

Figure 254. ^{1}H NMR Spectrum for **432** (500 MHz, $CDCl_3$)

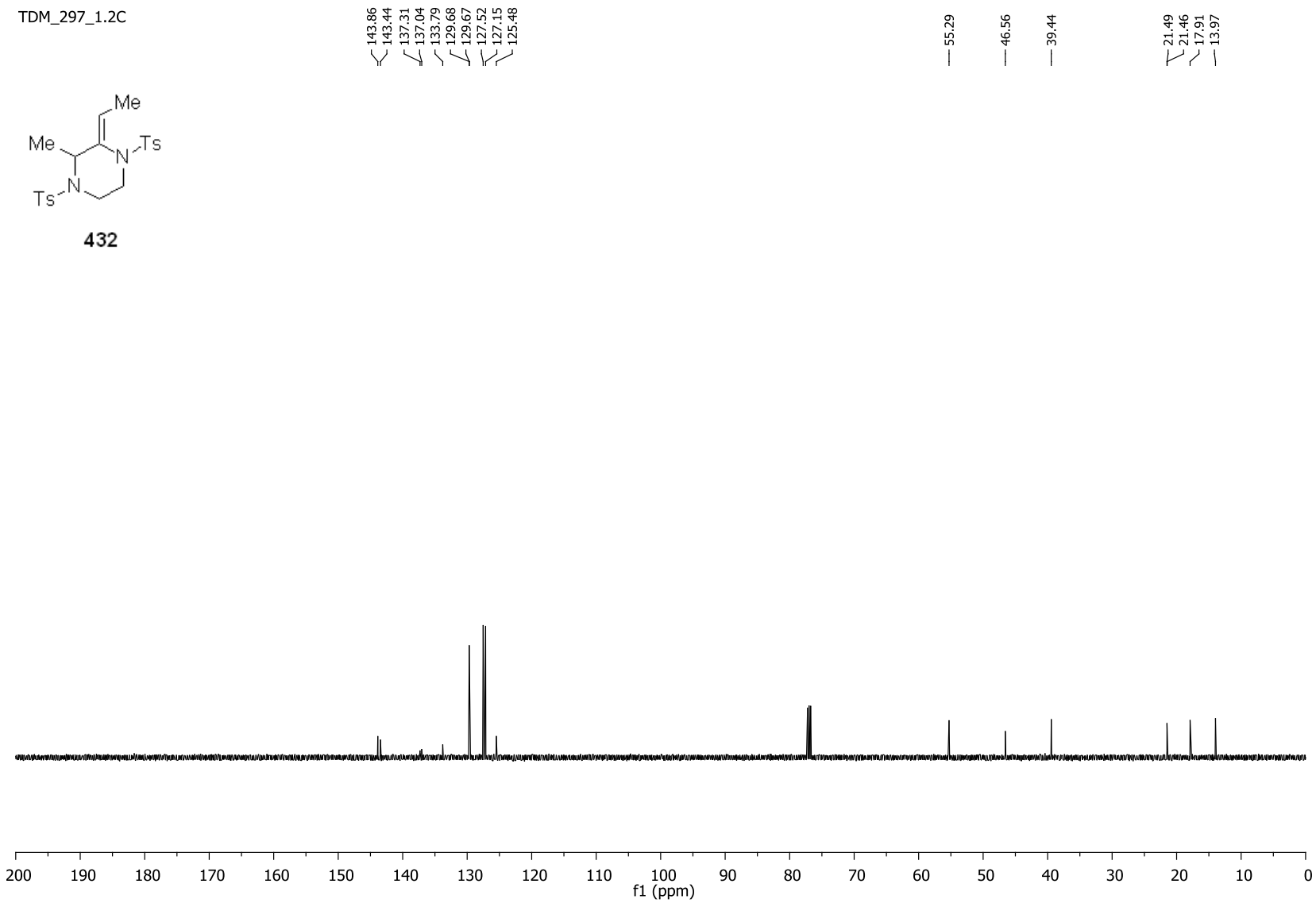


Figure 255. ^{13}C NMR Spectrum for **432** (125 MHz, $CDCl_3$)

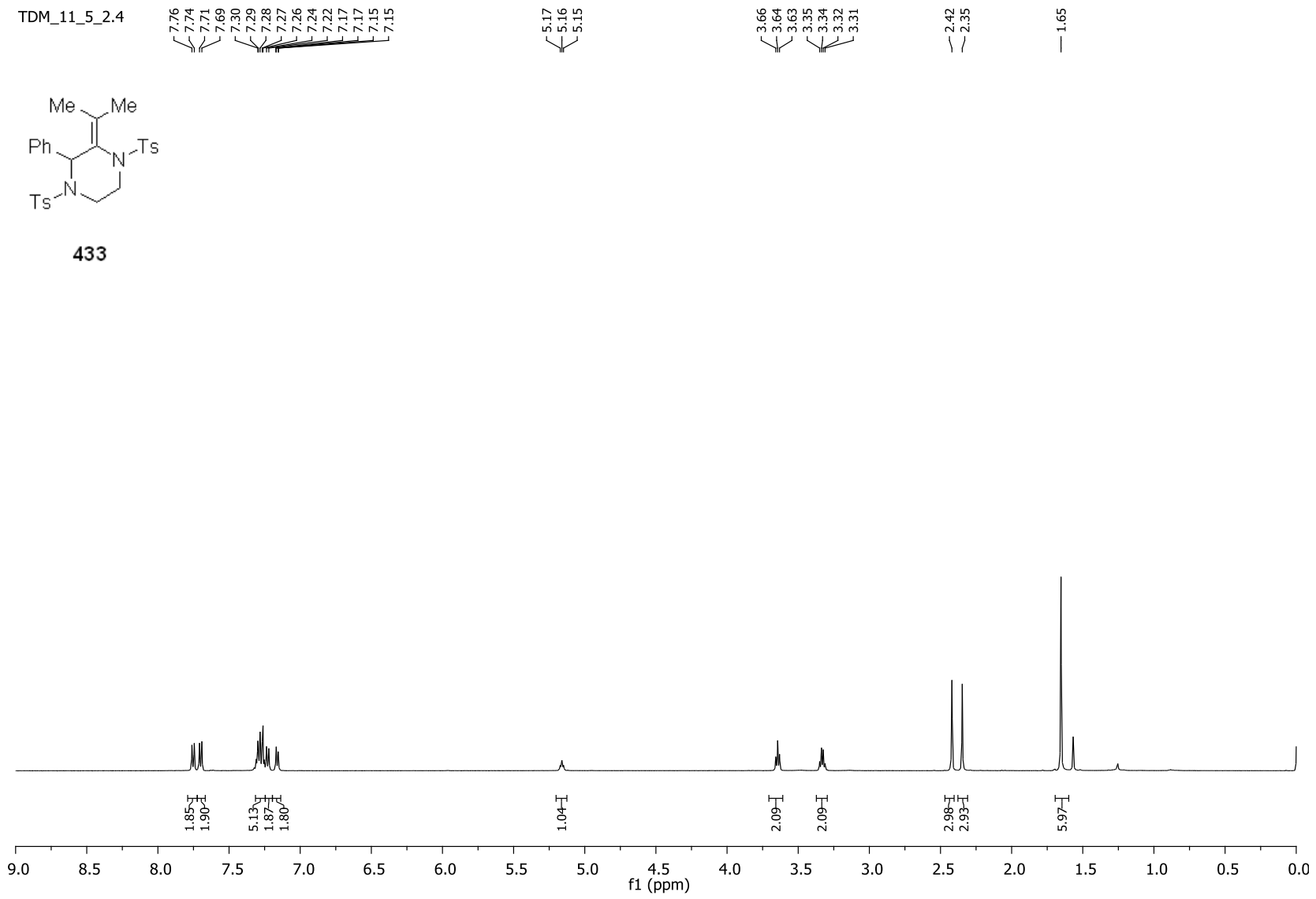


Figure 256. ^{1}H NMR Spectrum for **433** (500 MHz, $CDCl_3$)

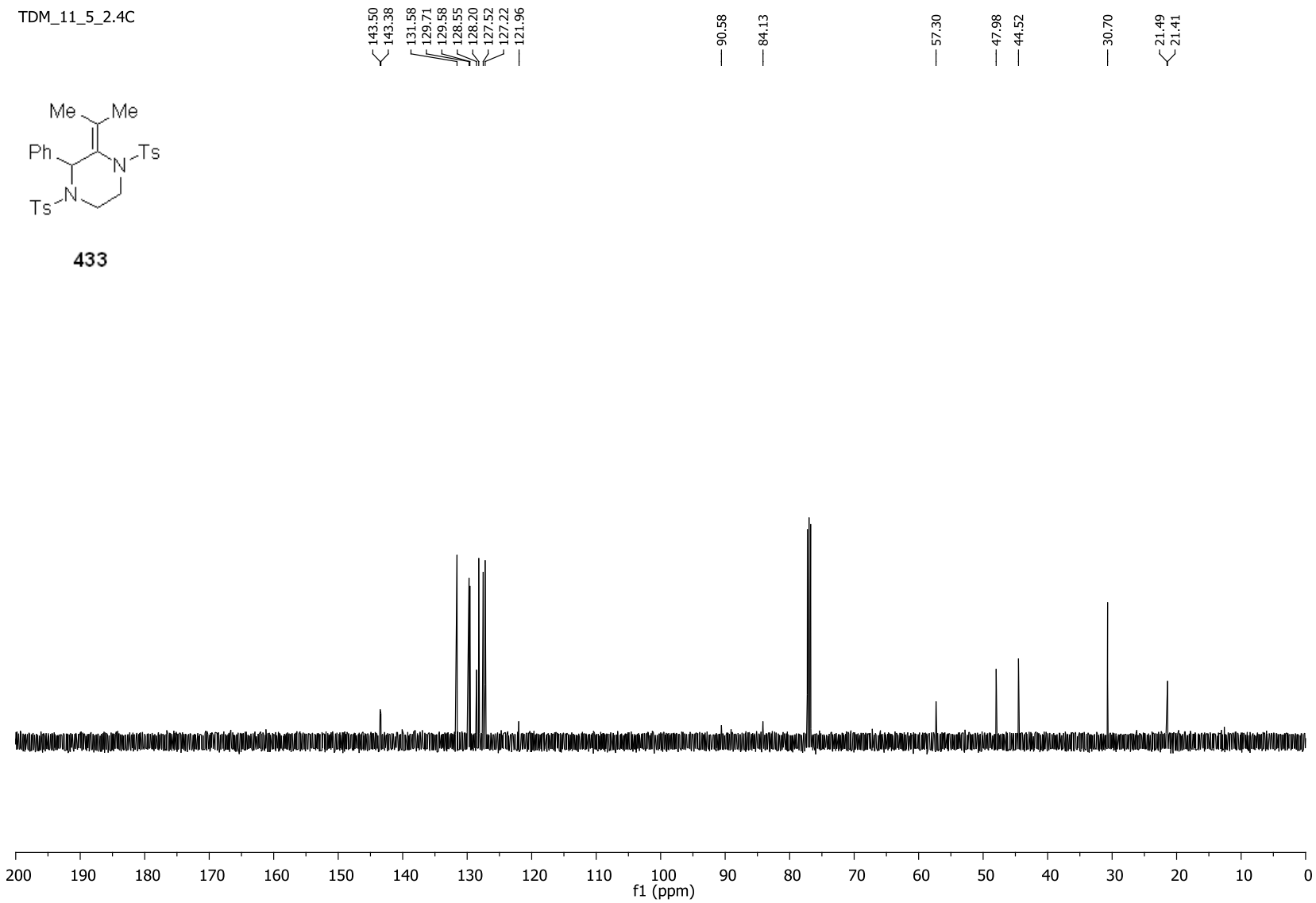


Figure 257. ^{13}C NMR Spectrum for **433** (125 MHz, $CDCl_3$)

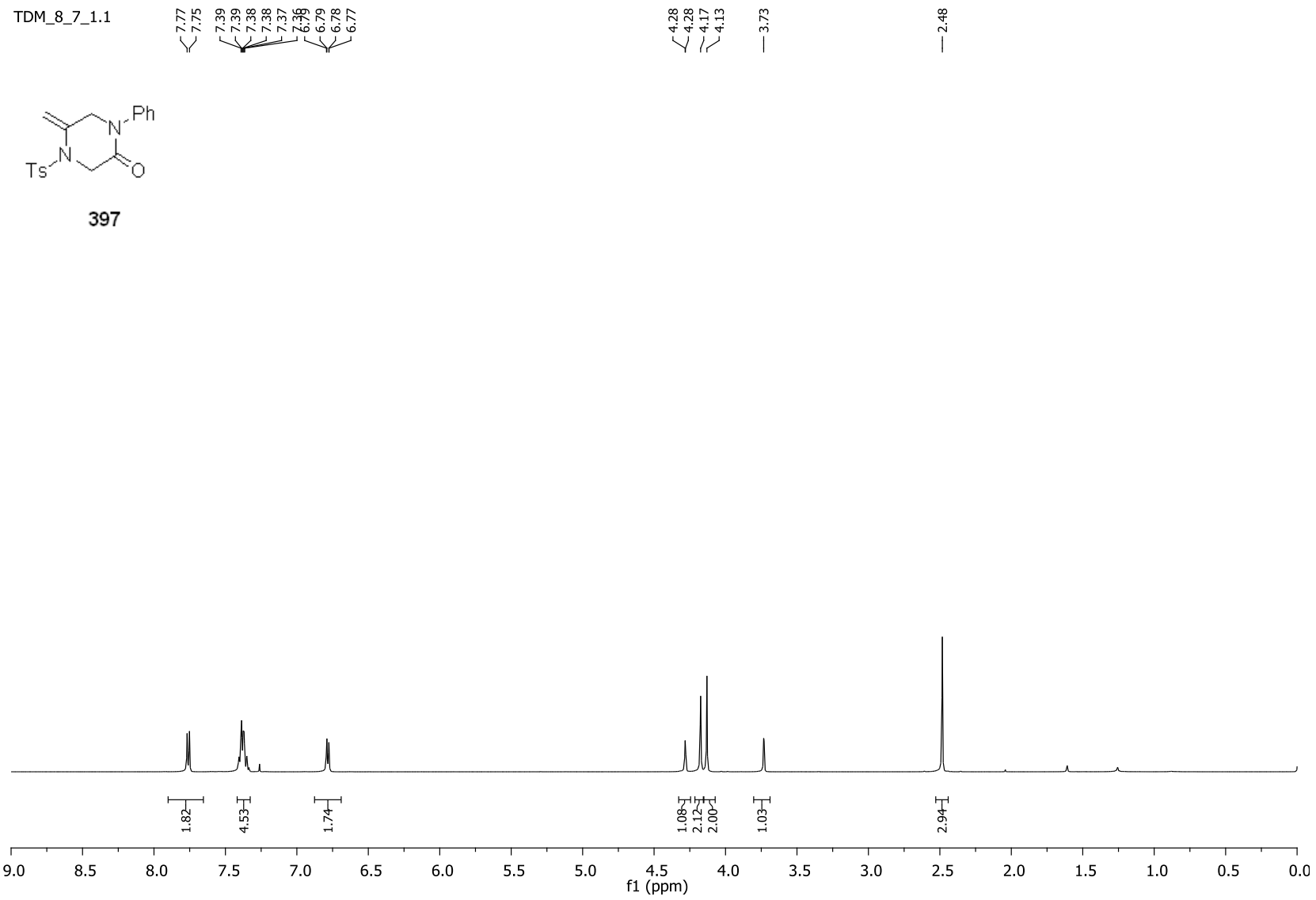


Figure 258. ^{1}H NMR Spectrum for **397** (500 MHz, $CDCl_3$)

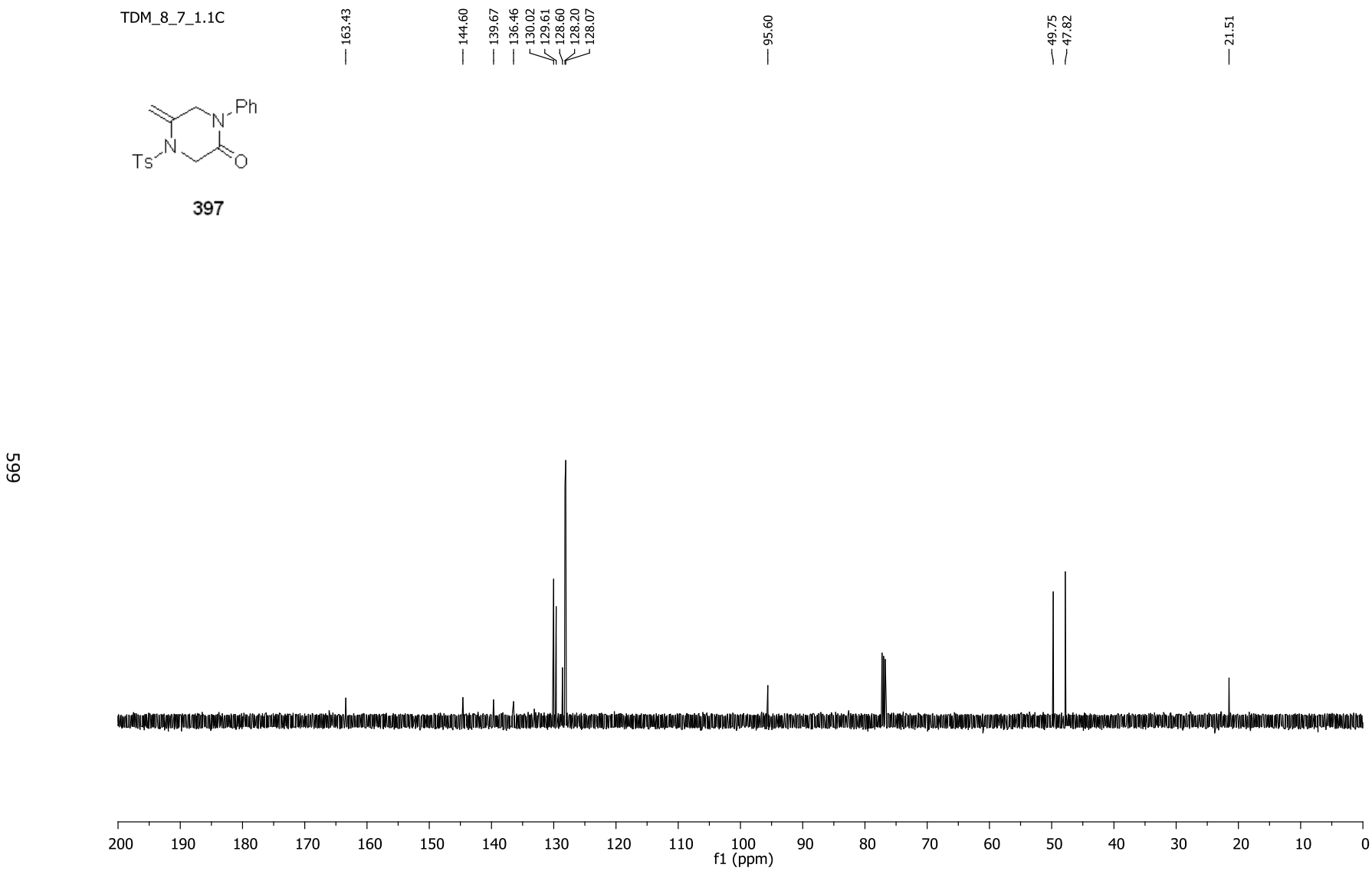


Figure 259. ^{13}C NMR Spectrum for **397** (125 MHz, $CDCl_3$)

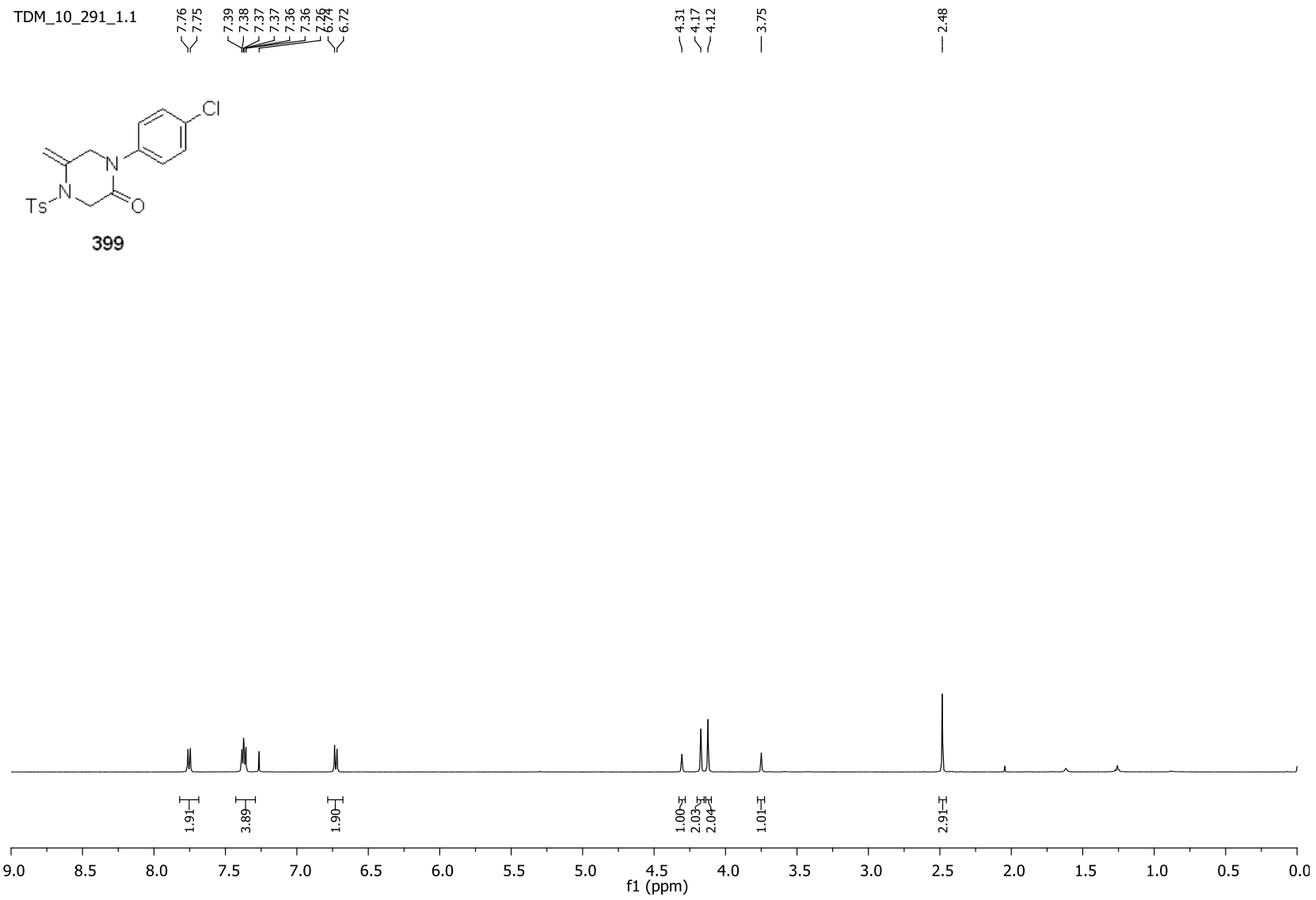


Figure 260. ^{1}H NMR Spectrum for **399** (500 MHz, $CDCl_3$)

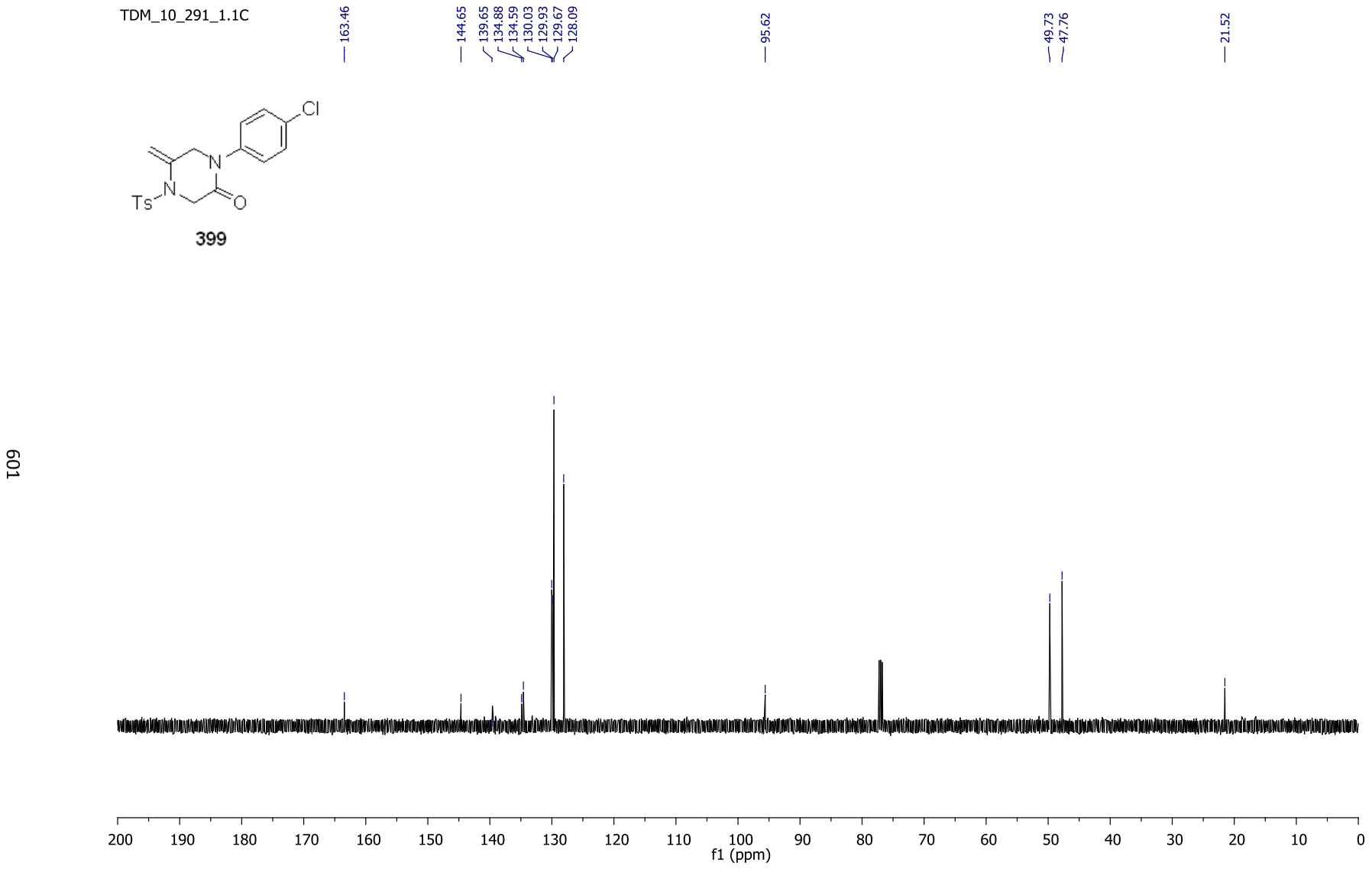


Figure 261. ^{13}C NMR Spectrum for **399** (125 MHz, $CDCl_3$)

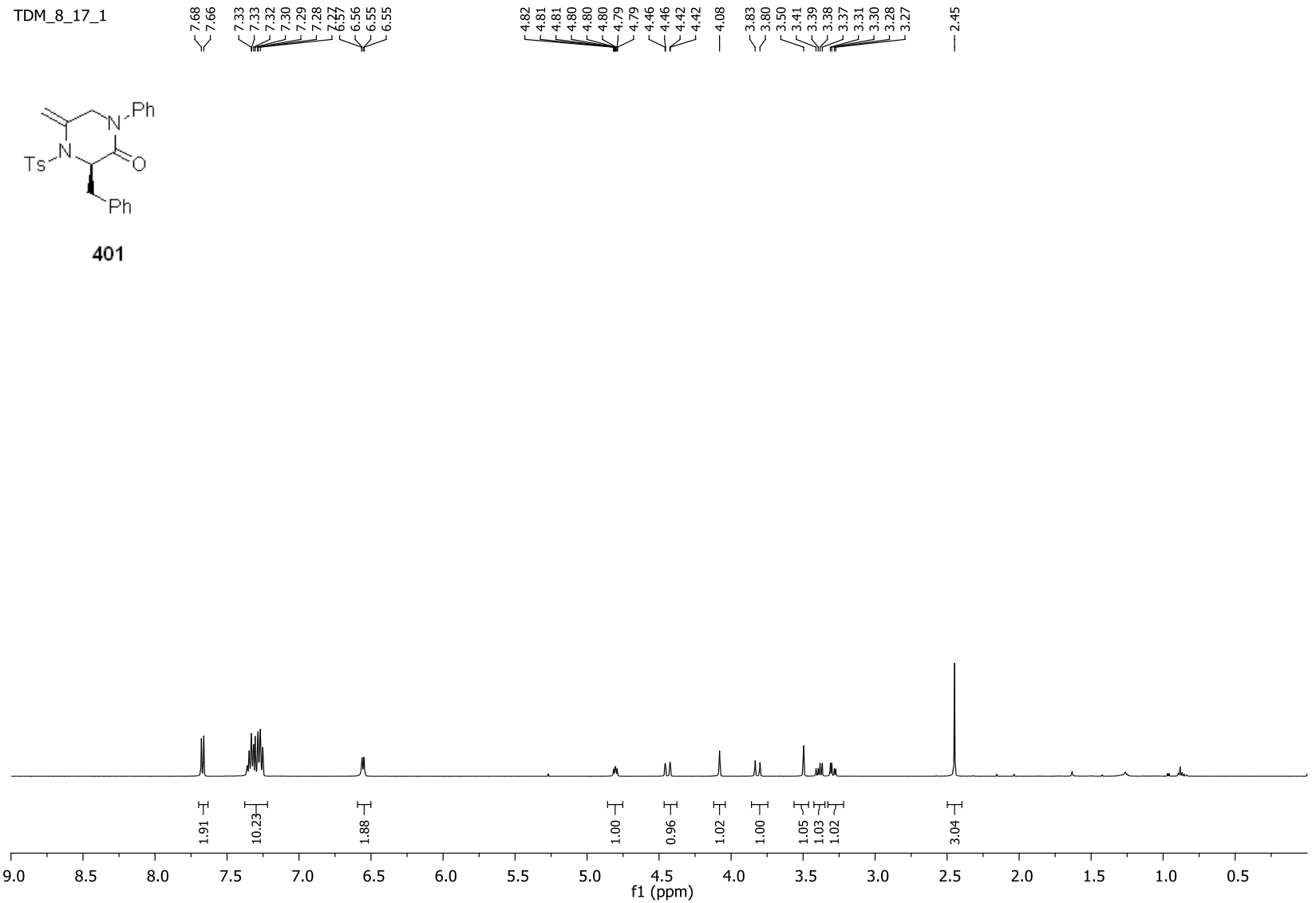


Figure 262. ^{1}H NMR Spectrum for **401** (500 MHz, $CDCl_3$)

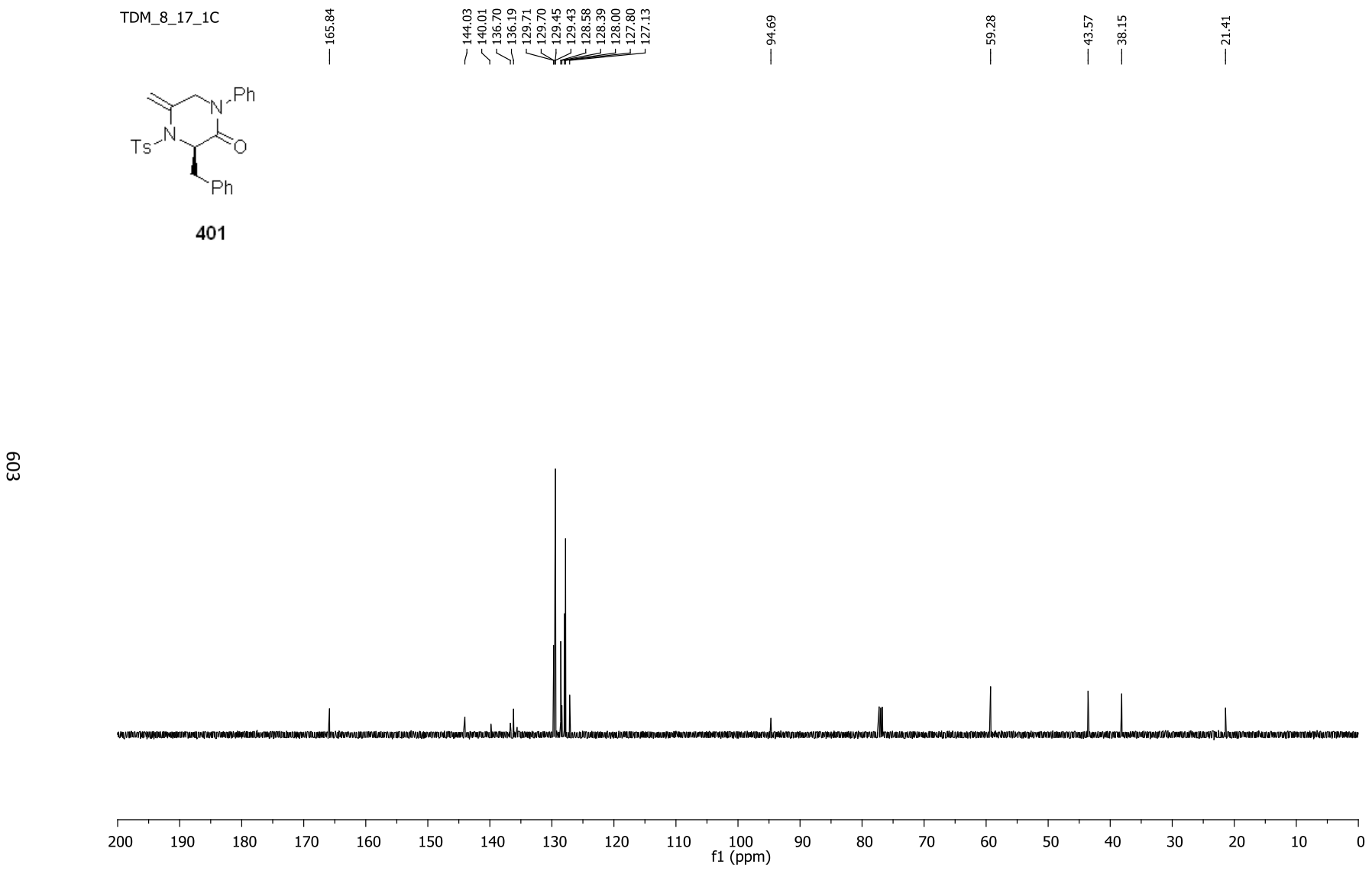


Figure 263. ^{13}C NMR Spectrum for **401** (125 MHz, $CDCl_3$)

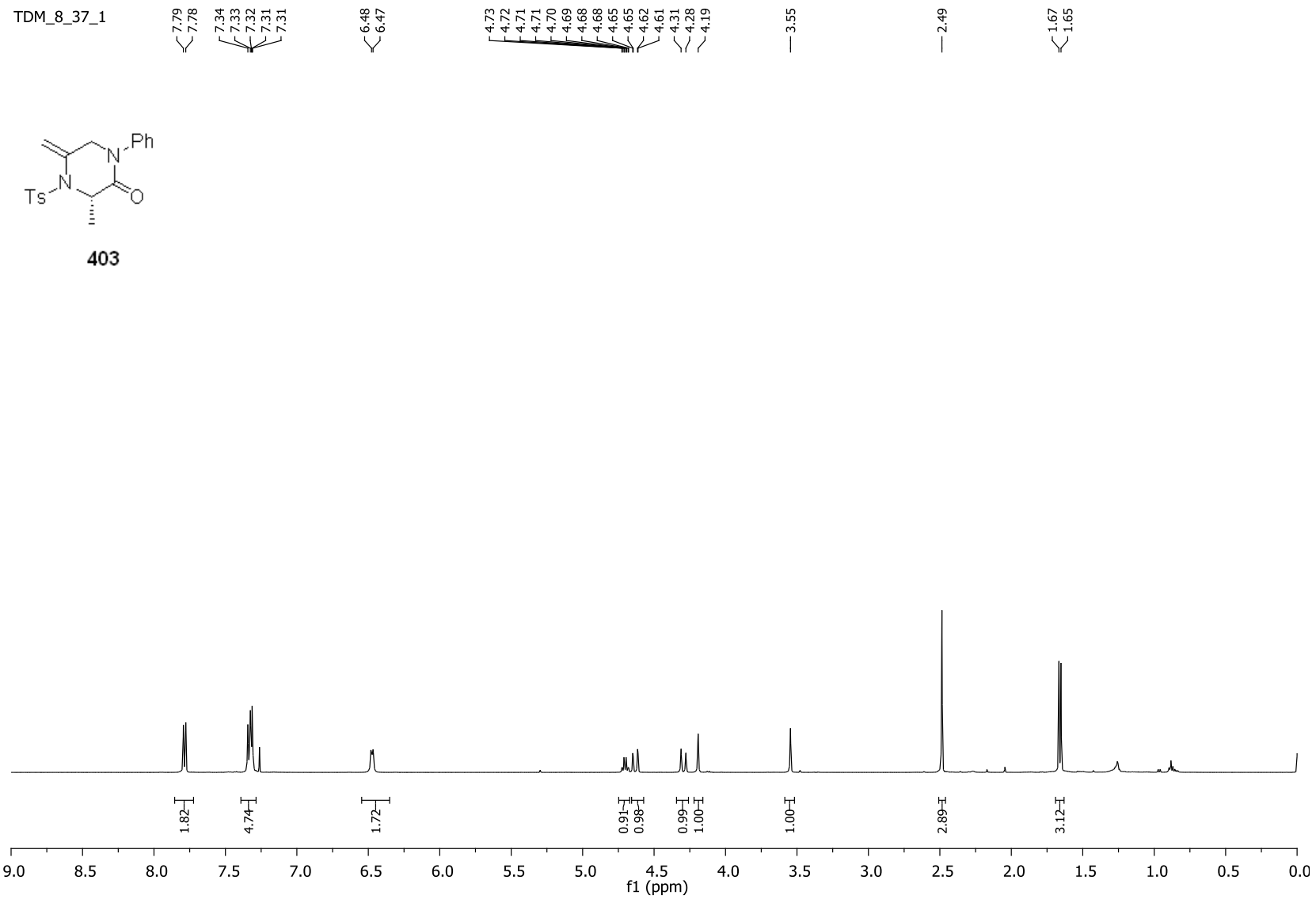


Figure 264. ^{1}H NMR Spectrum for **403** (500 MHz, $CDCl_3$)

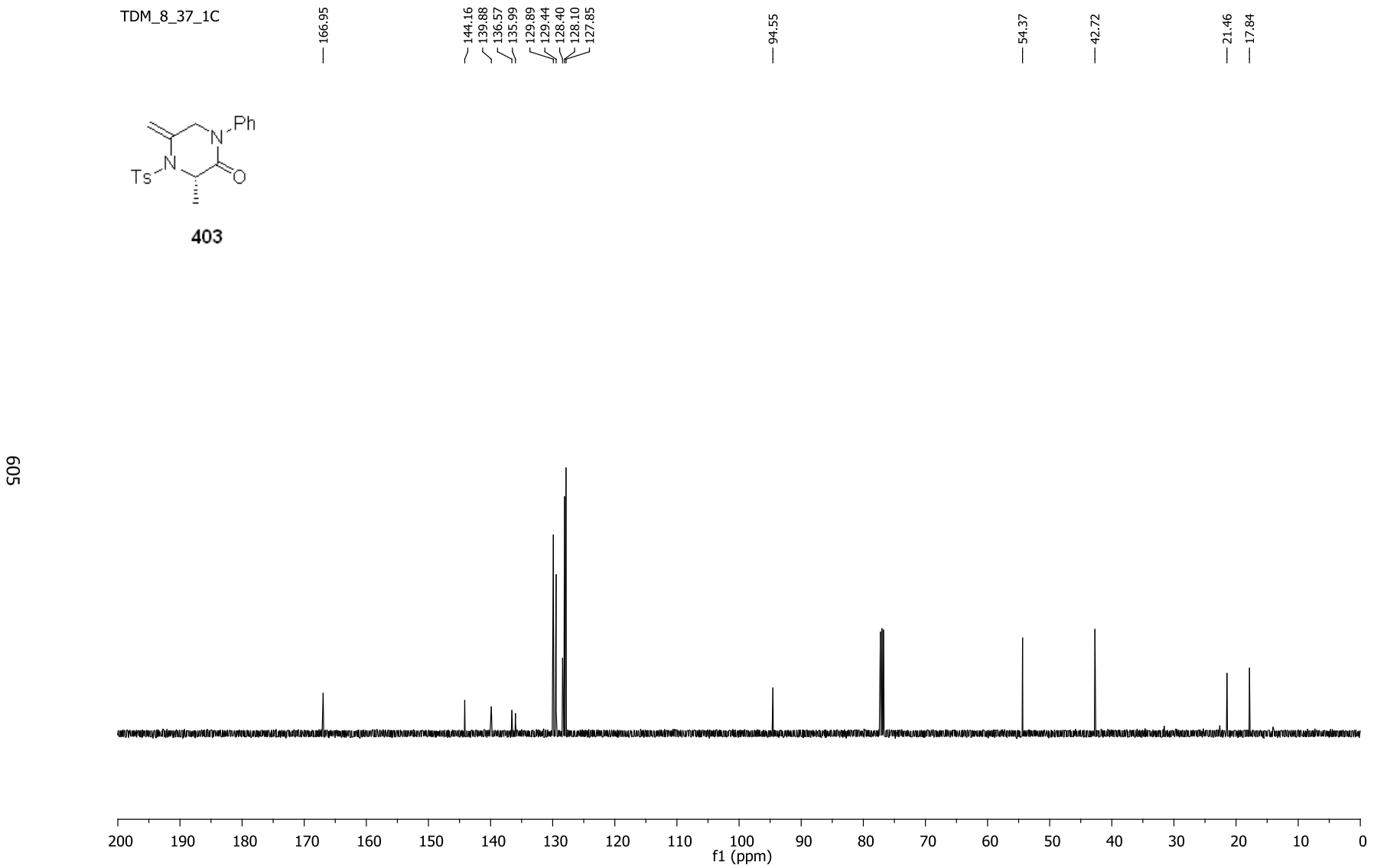


Figure 265. ^{13}C NMR Spectrum for **403** (125 MHz, $CDCl_3$)

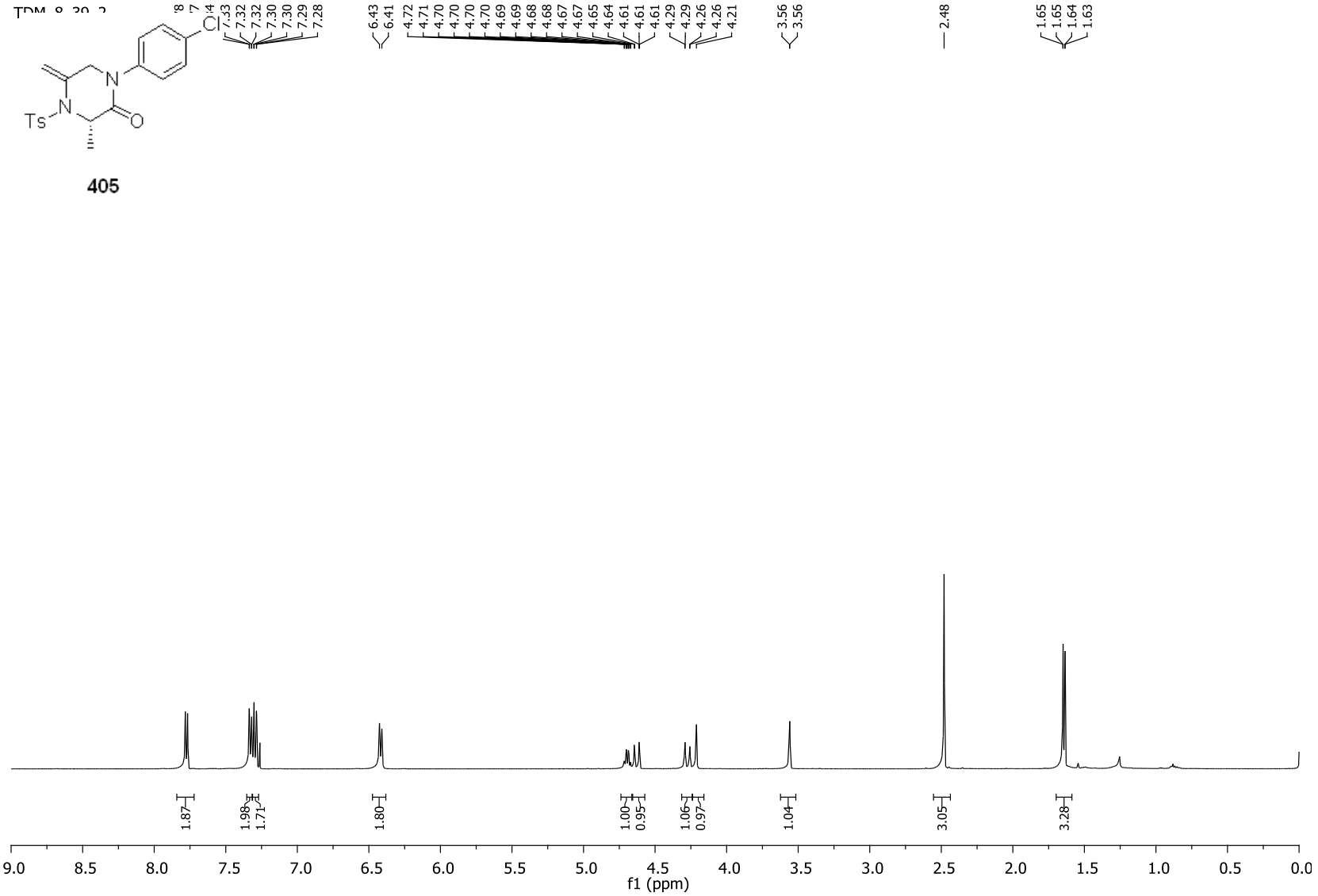


Figure 266. ^{1}H NMR Spectrum for **405** (500 MHz, $CDCl_3$)

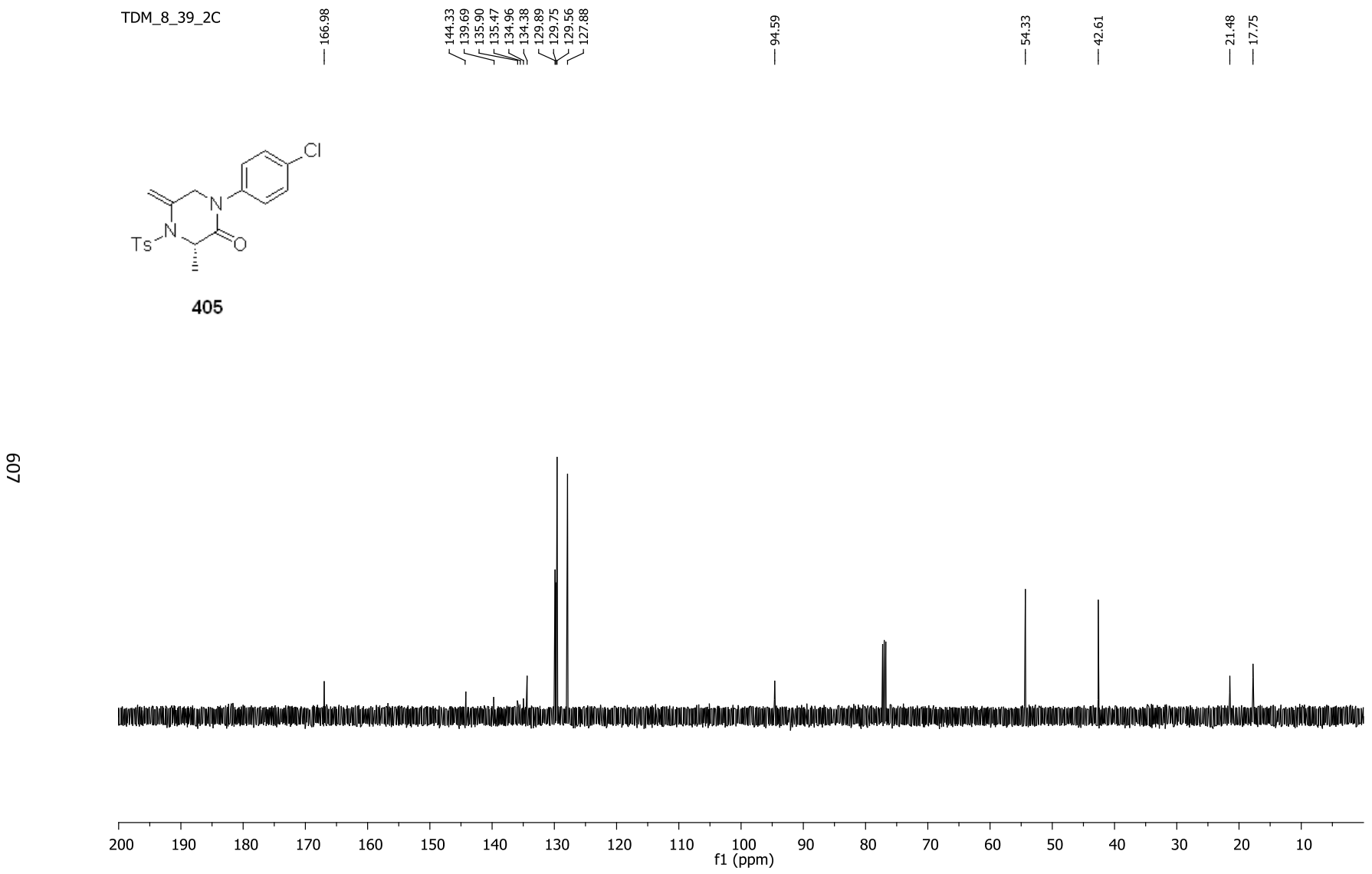
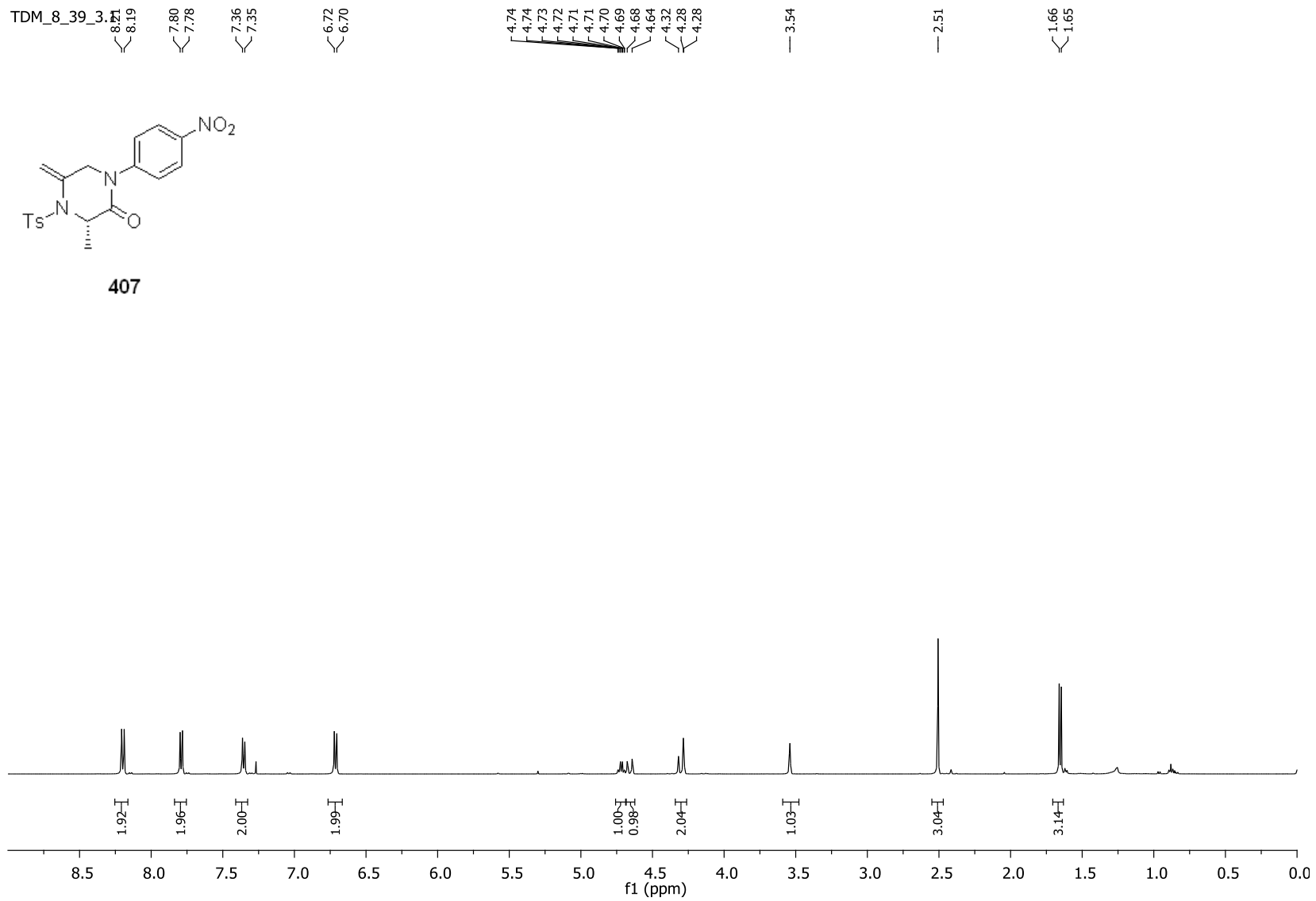


Figure 267. ^{13}C NMR Spectrum for **405** (125 MHz, $CDCl_3$)



407

Figure 268. ^{1}H NMR Spectrum for **407** (500 MHz, $CDCl_3$)

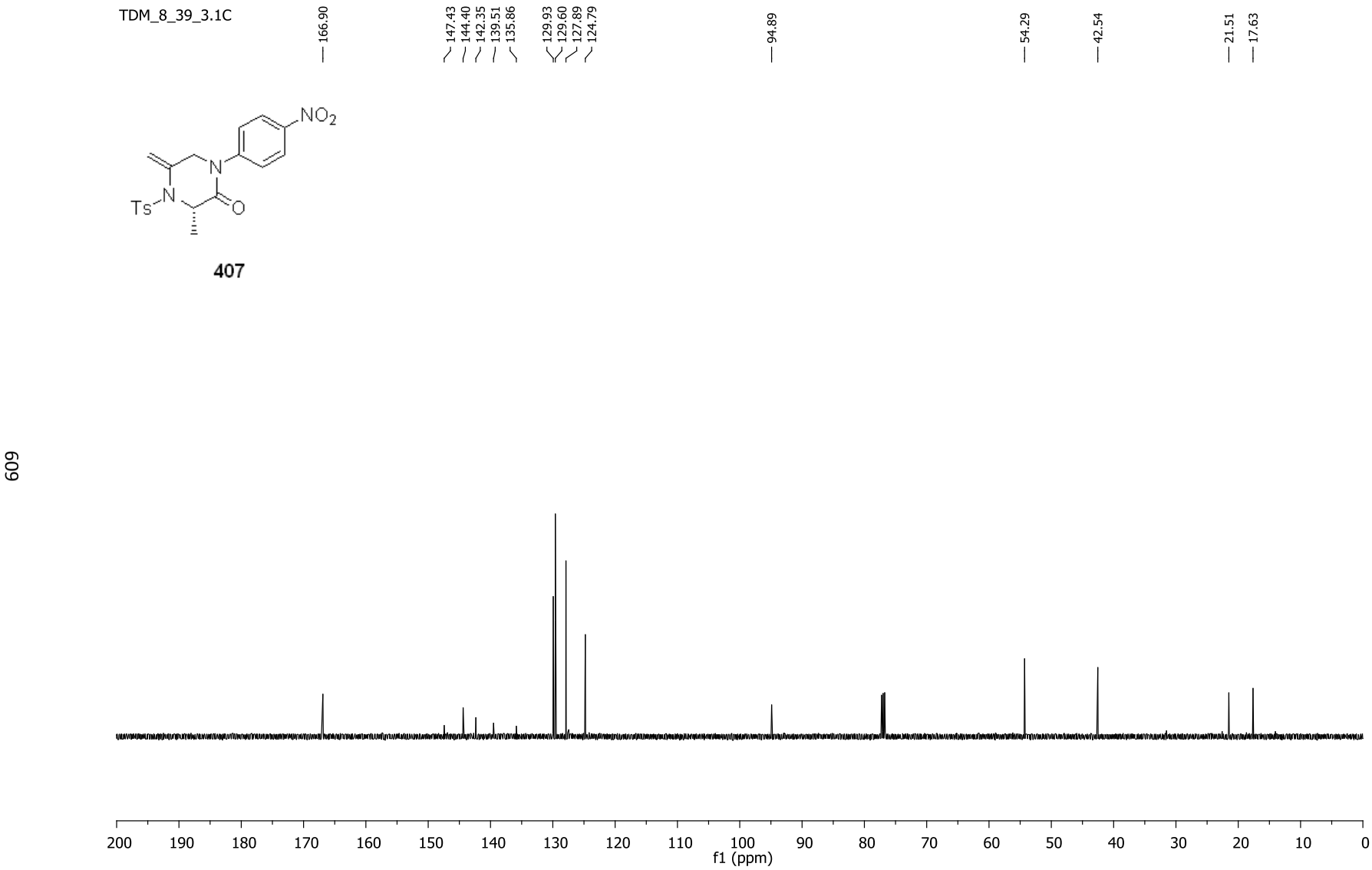
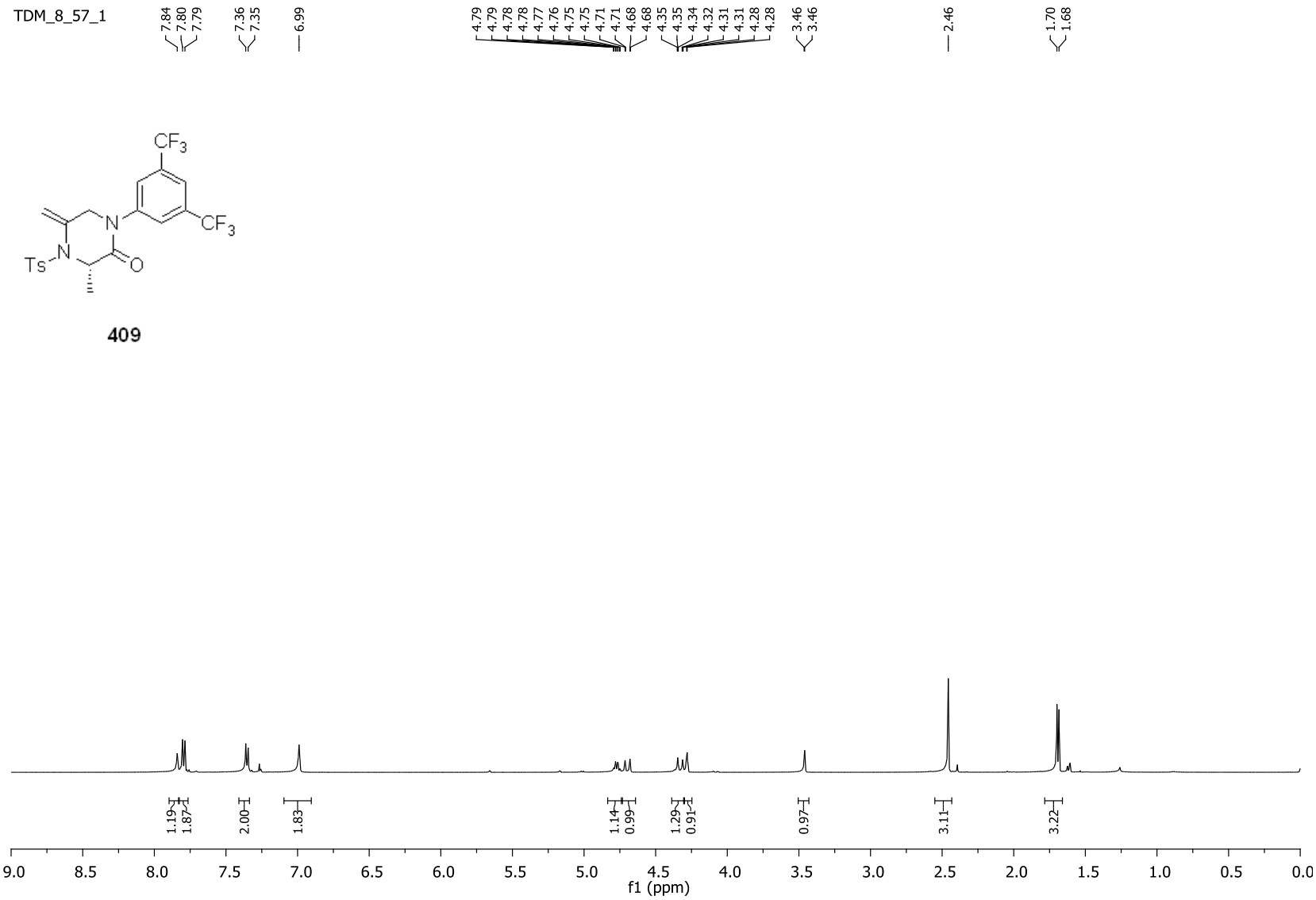


Figure 269. ^{13}C NMR Spectrum for **407** (125 MHz, $CDCl_3$)



409

Figure 270. ^{1}H NMR Spectrum for **409** (500 MHz, $CDCl_3$)

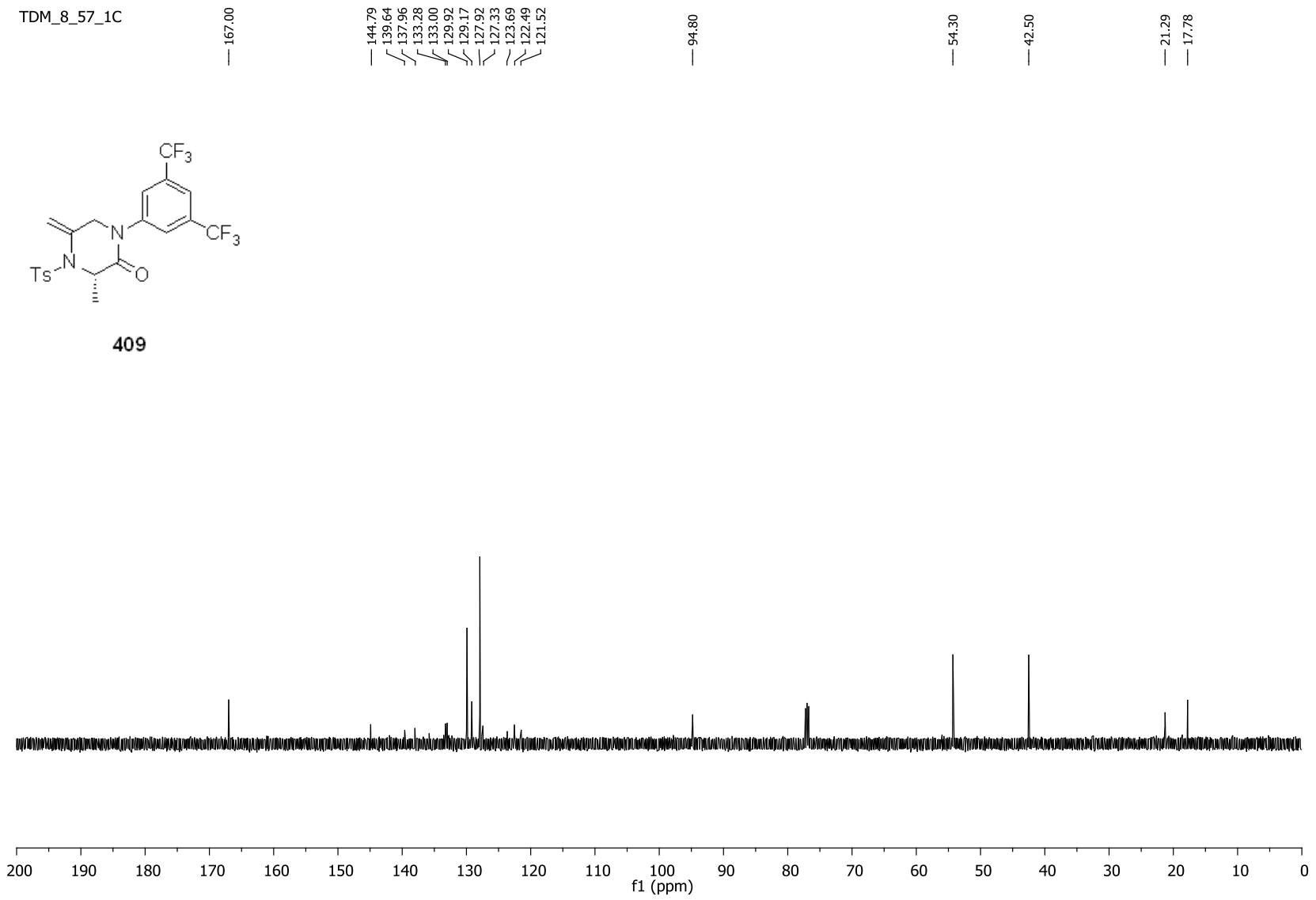


Figure 271. ^{13}C NMR Spectrum for **409** (125 MHz, $CDCl_3$)

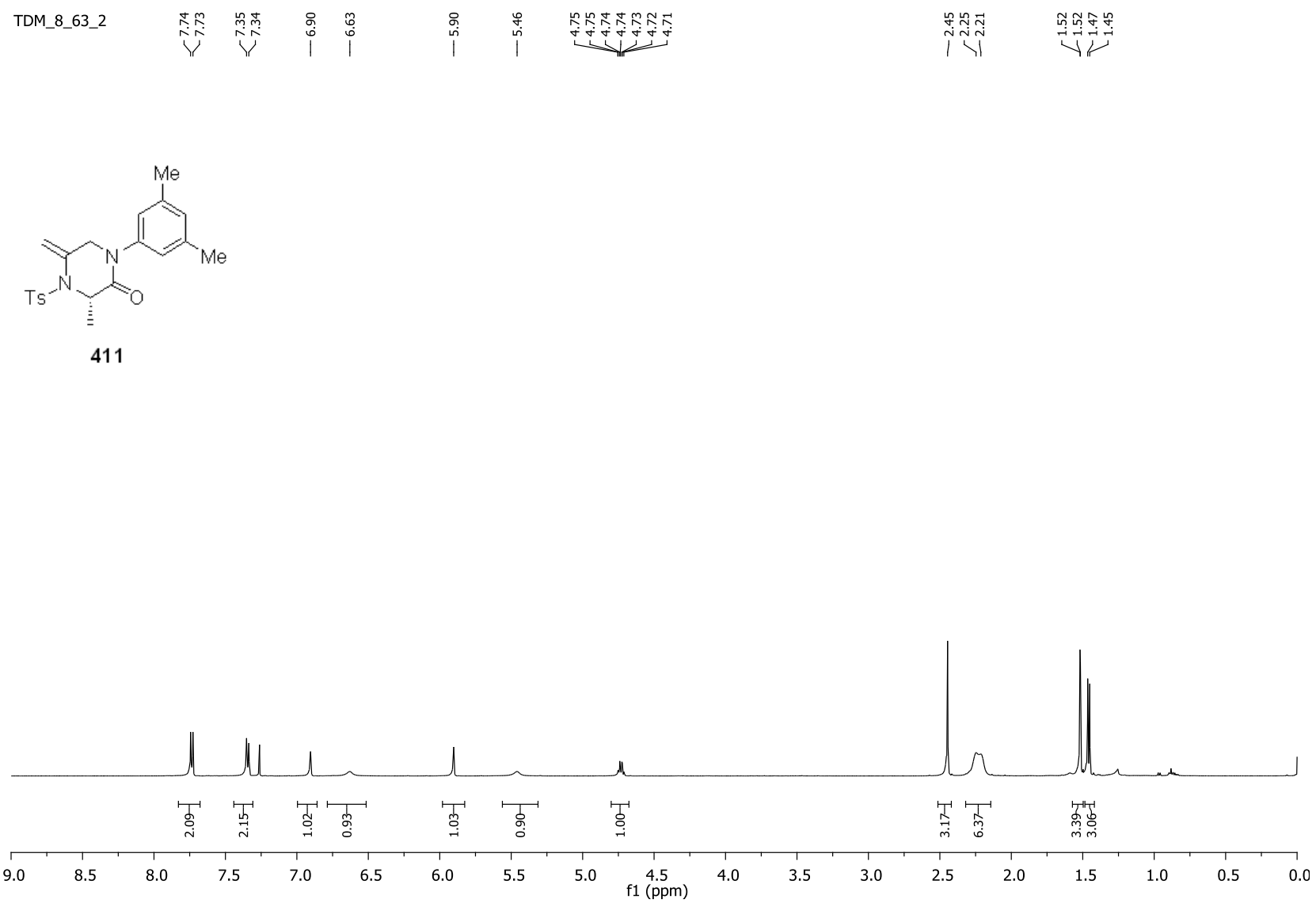


Figure 272. ^{1}H NMR Spectrum for **411** (500 MHz, $CDCl_3$)

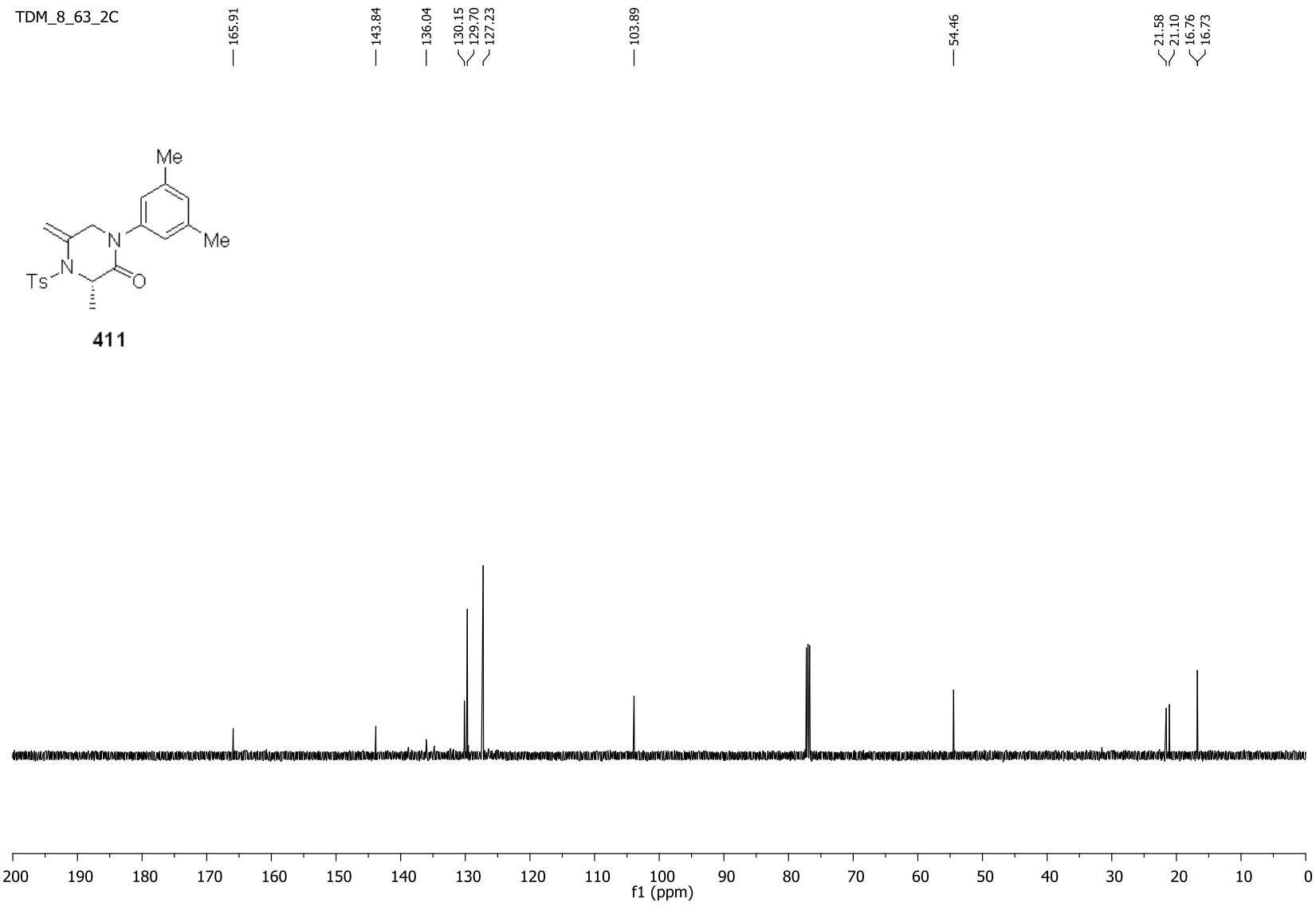


Figure 273. ^{13}C NMR Spectrum for **411** (125 MHz, $CDCl_3$)

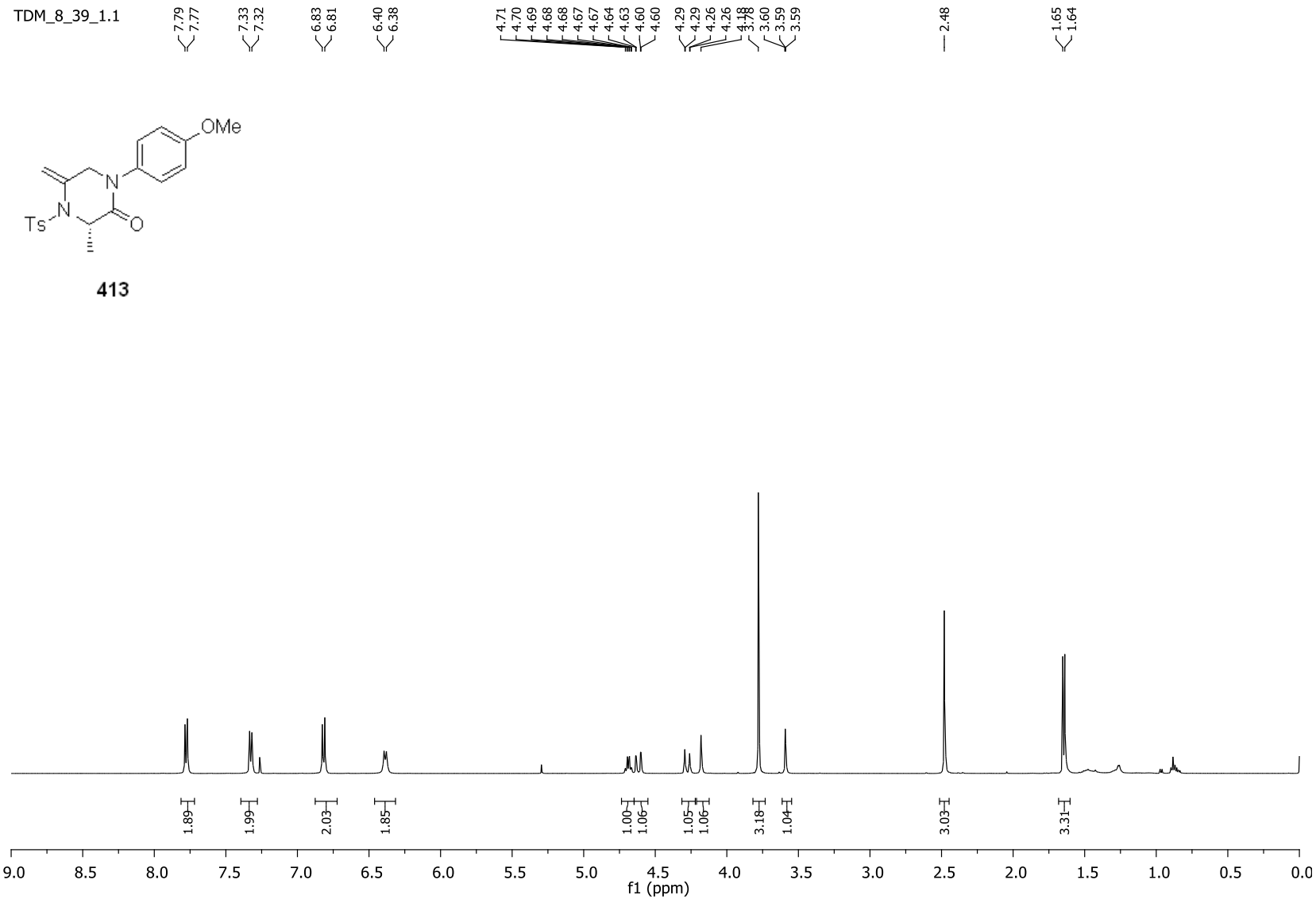


Figure 274. ^{1}H NMR Spectrum for **413** (500 MHz, $CDCl_3$)

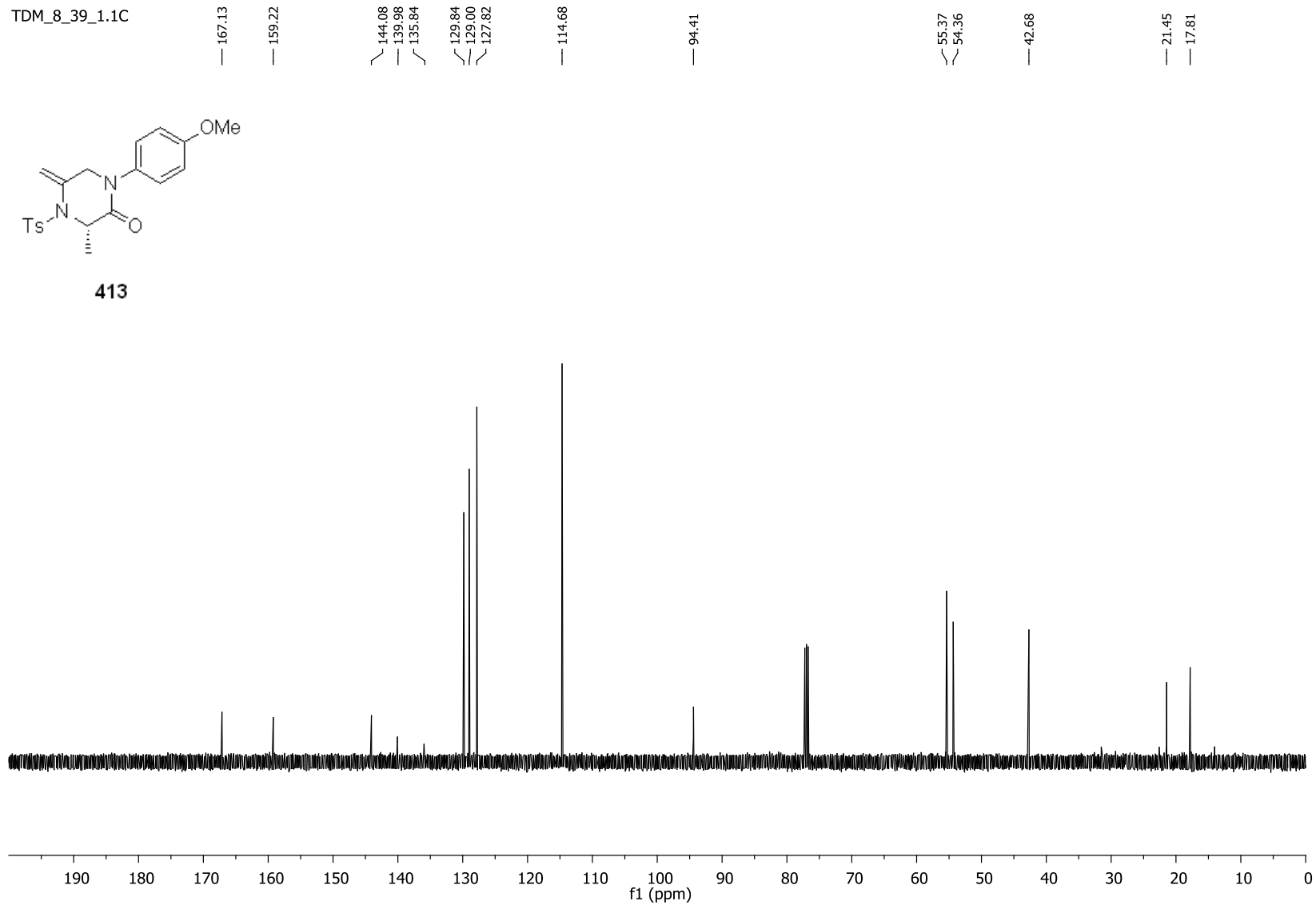


Figure 275. ^{13}C NMR Spectrum for **413** (125 MHz, $CDCl_3$)

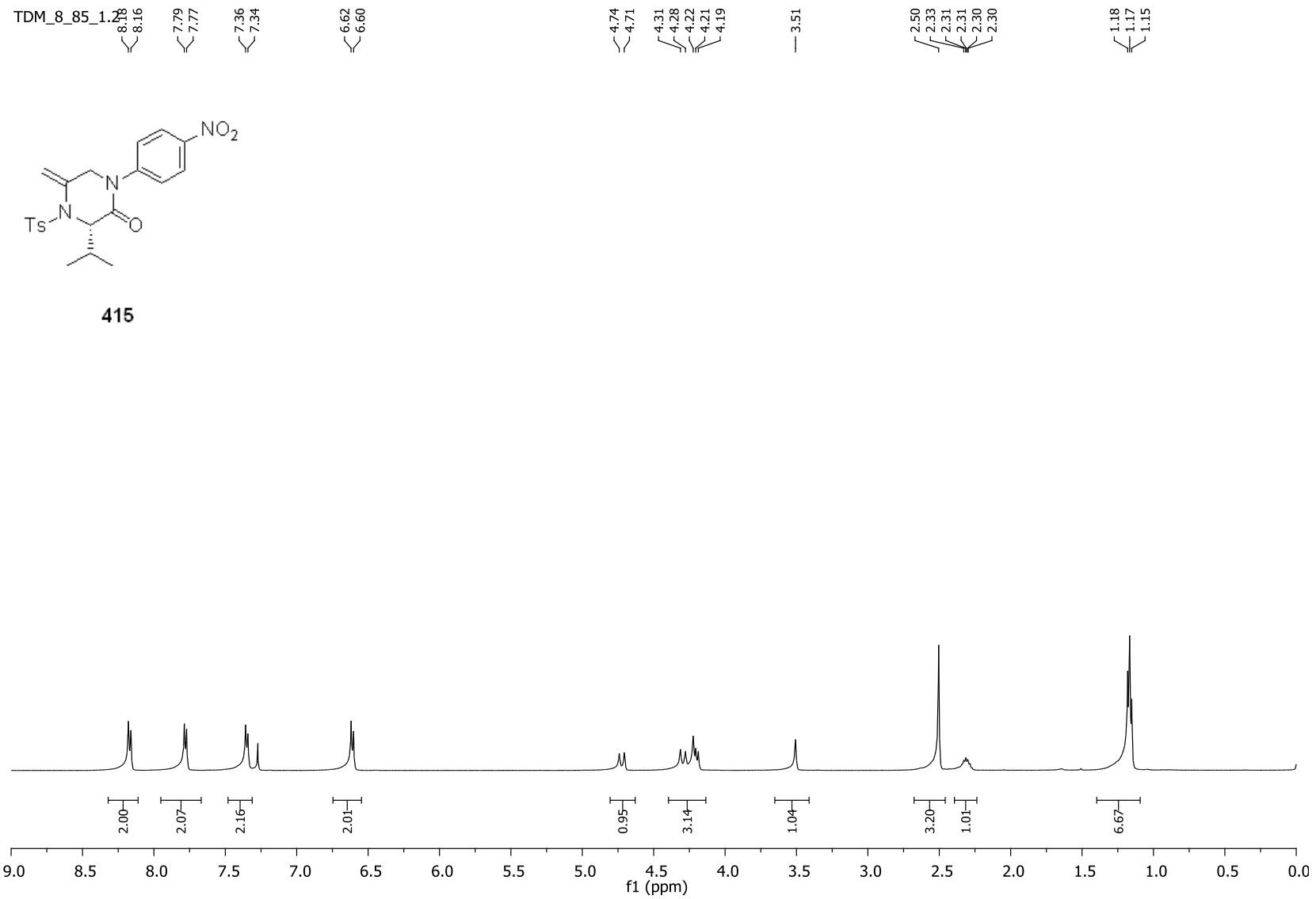


Figure 276. ^{1}H NMR Spectrum for **415** (500 MHz, $CDCl_3$)

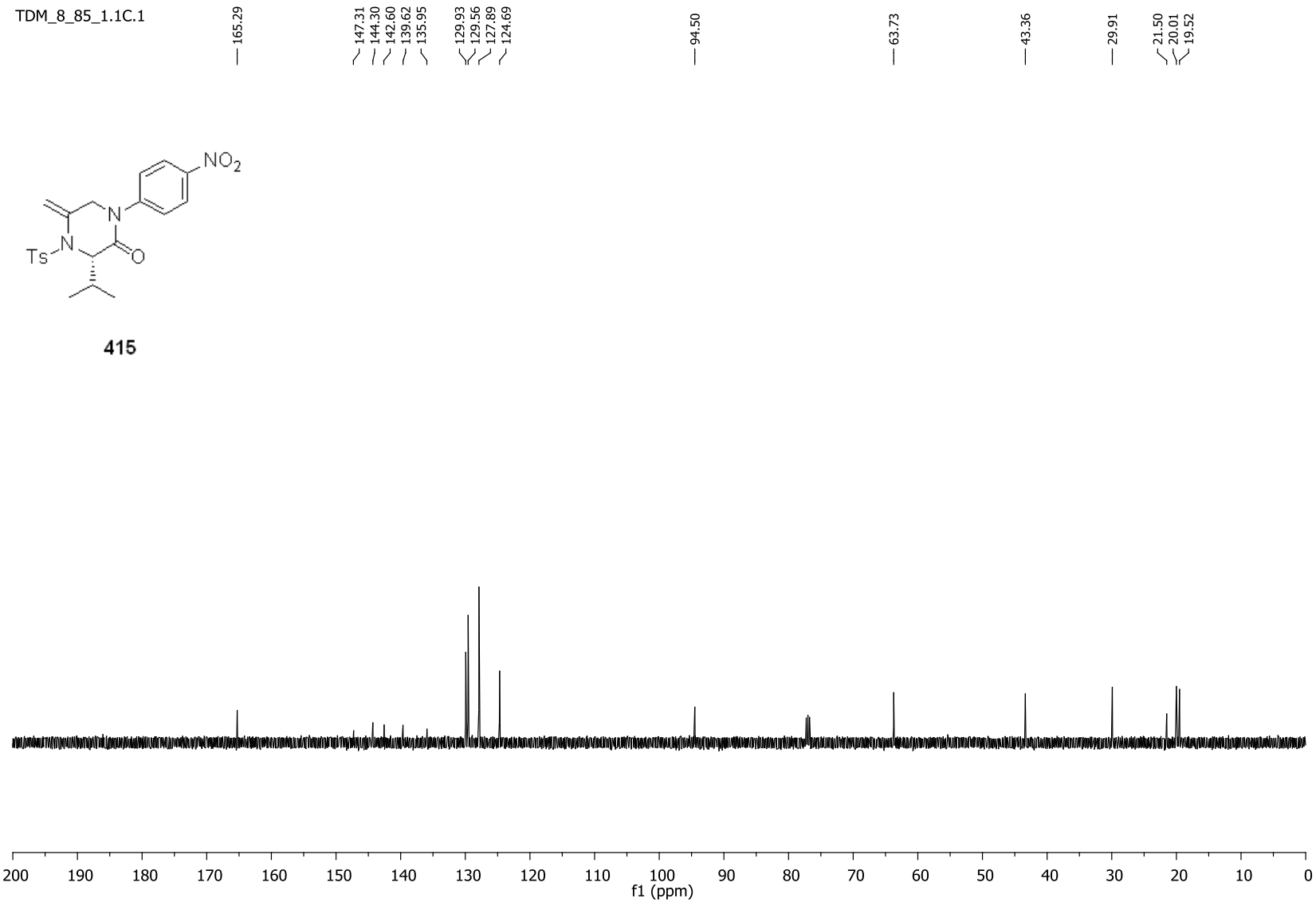


Figure 277. ^{13}C NMR Spectrum for **415** (125 MHz, $CDCl_3$)

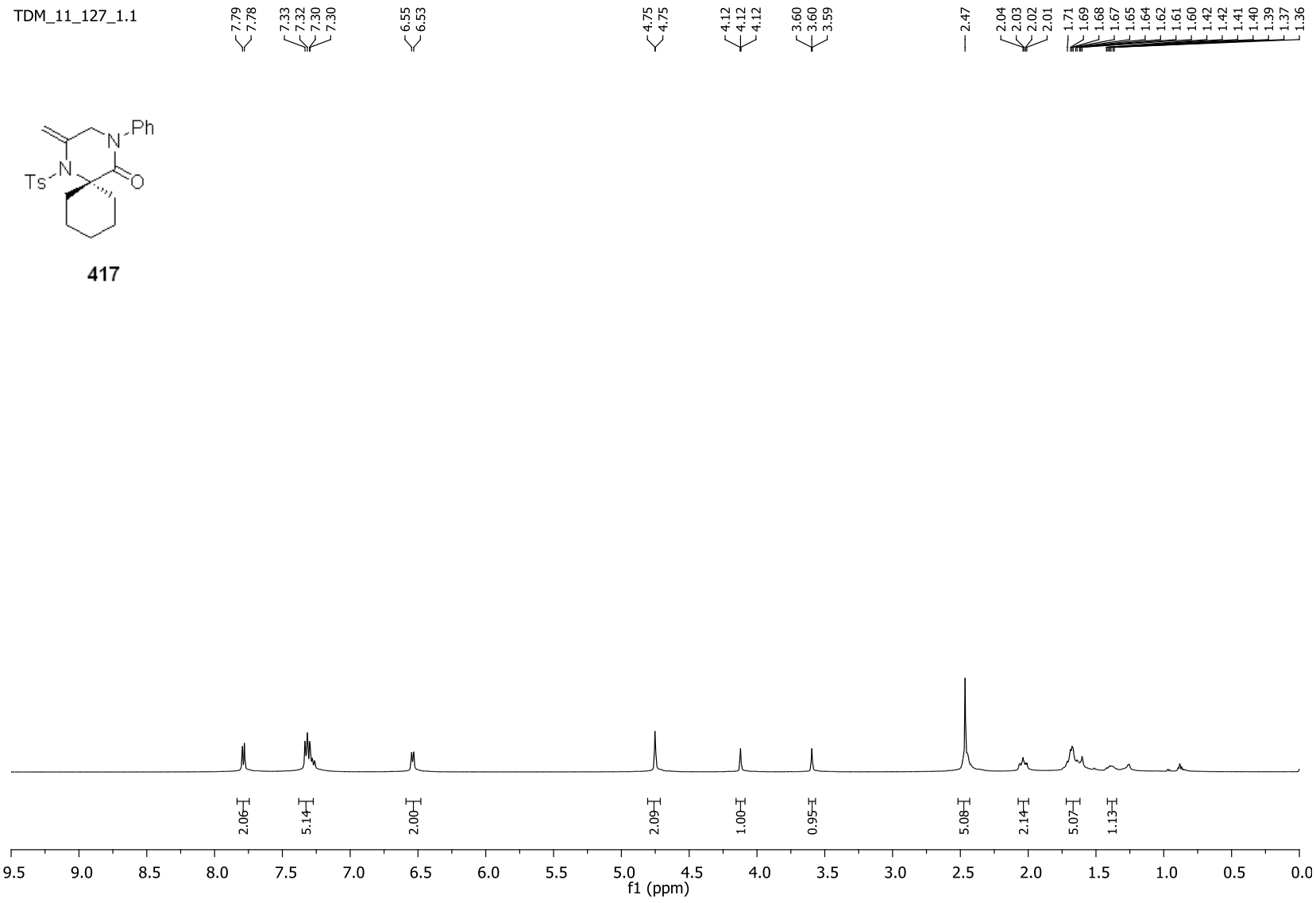


Figure 278. ^{1}H NMR Spectrum for **417** (500 MHz, $CDCl_3$)

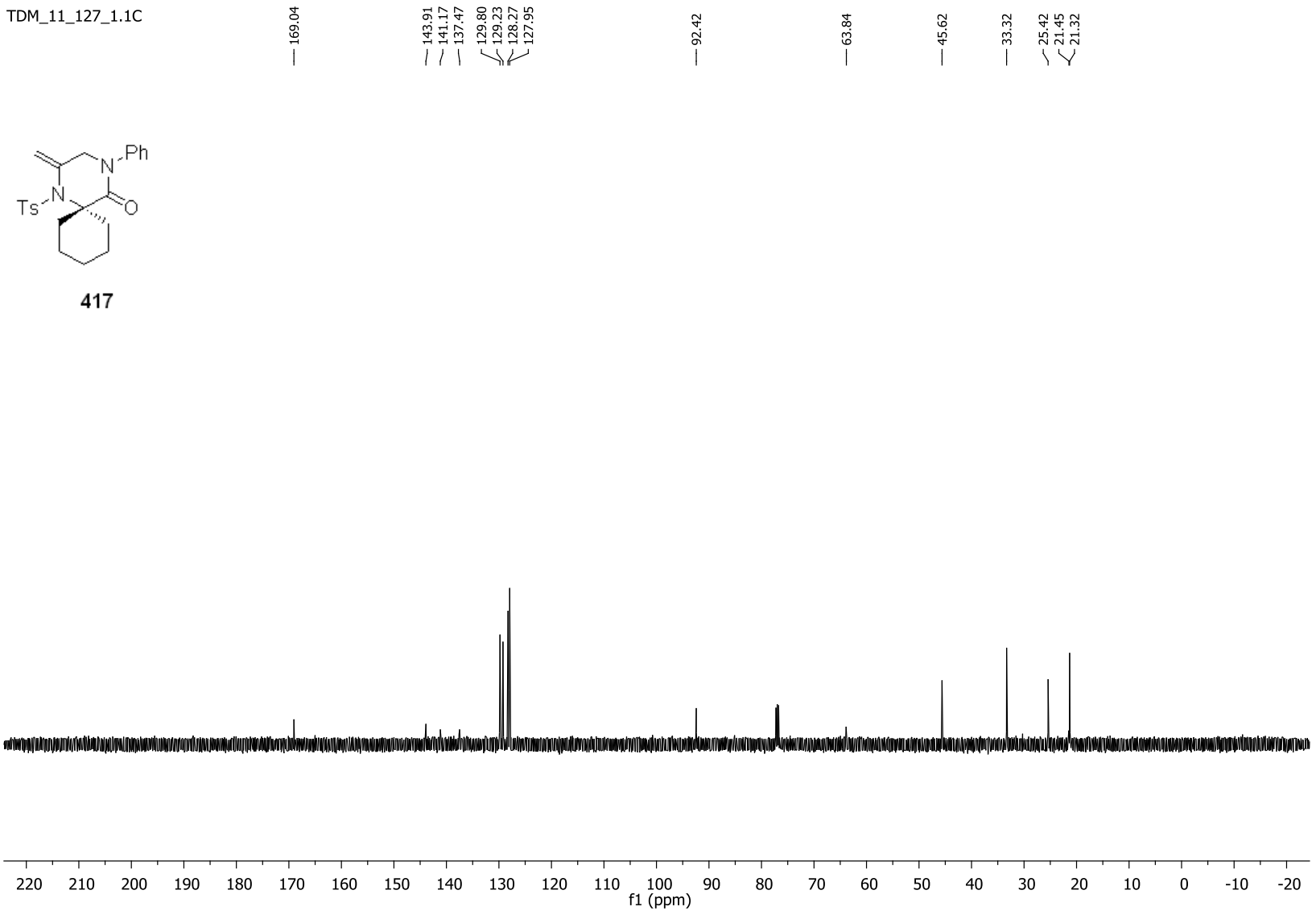


Figure 279. ^{13}C NMR Spectrum for **417** (125 MHz, $CDCl_3$)

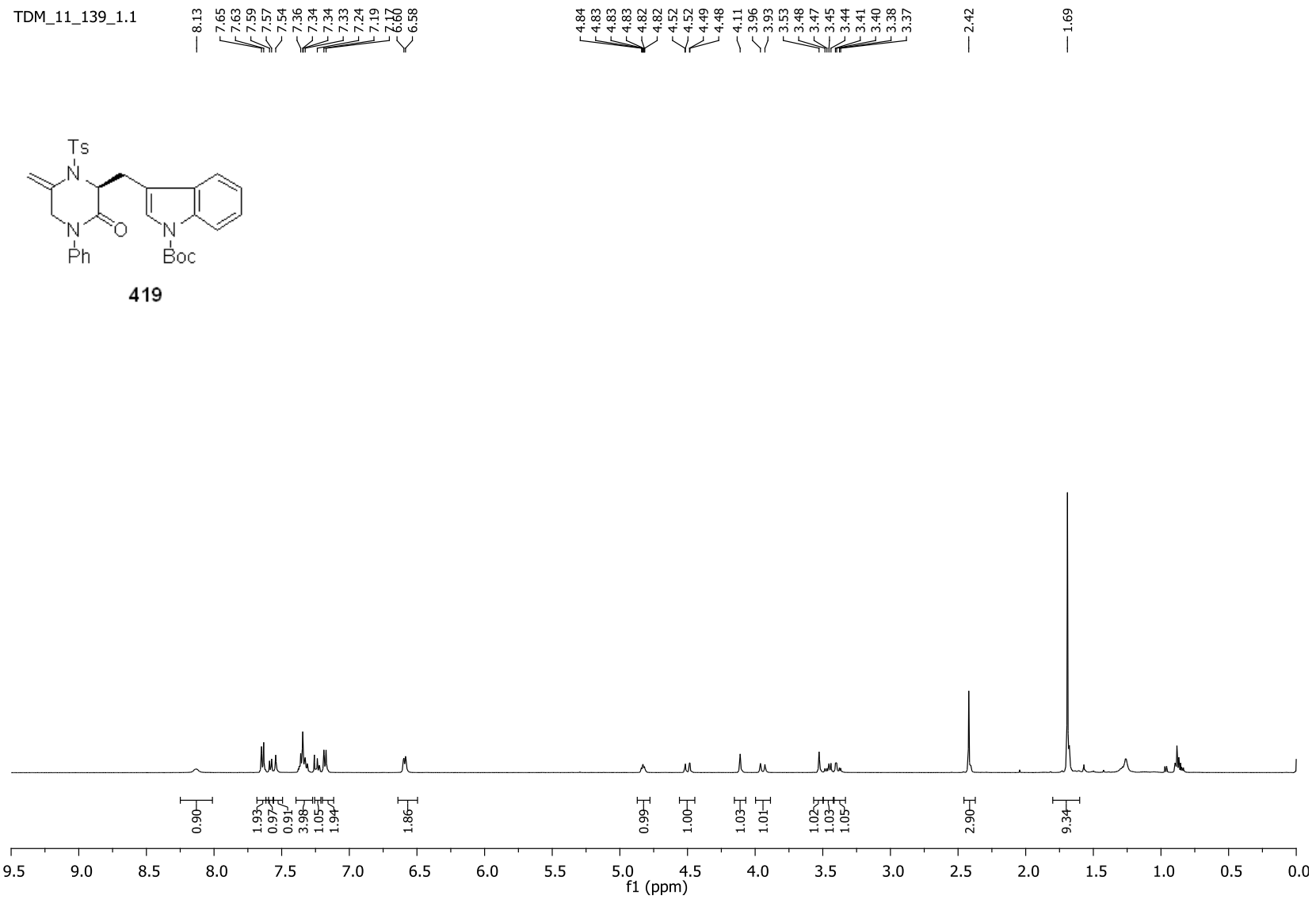


Figure 280. ^{1}H NMR Spectrum for **419** (500 MHz, $CDCl_3$)

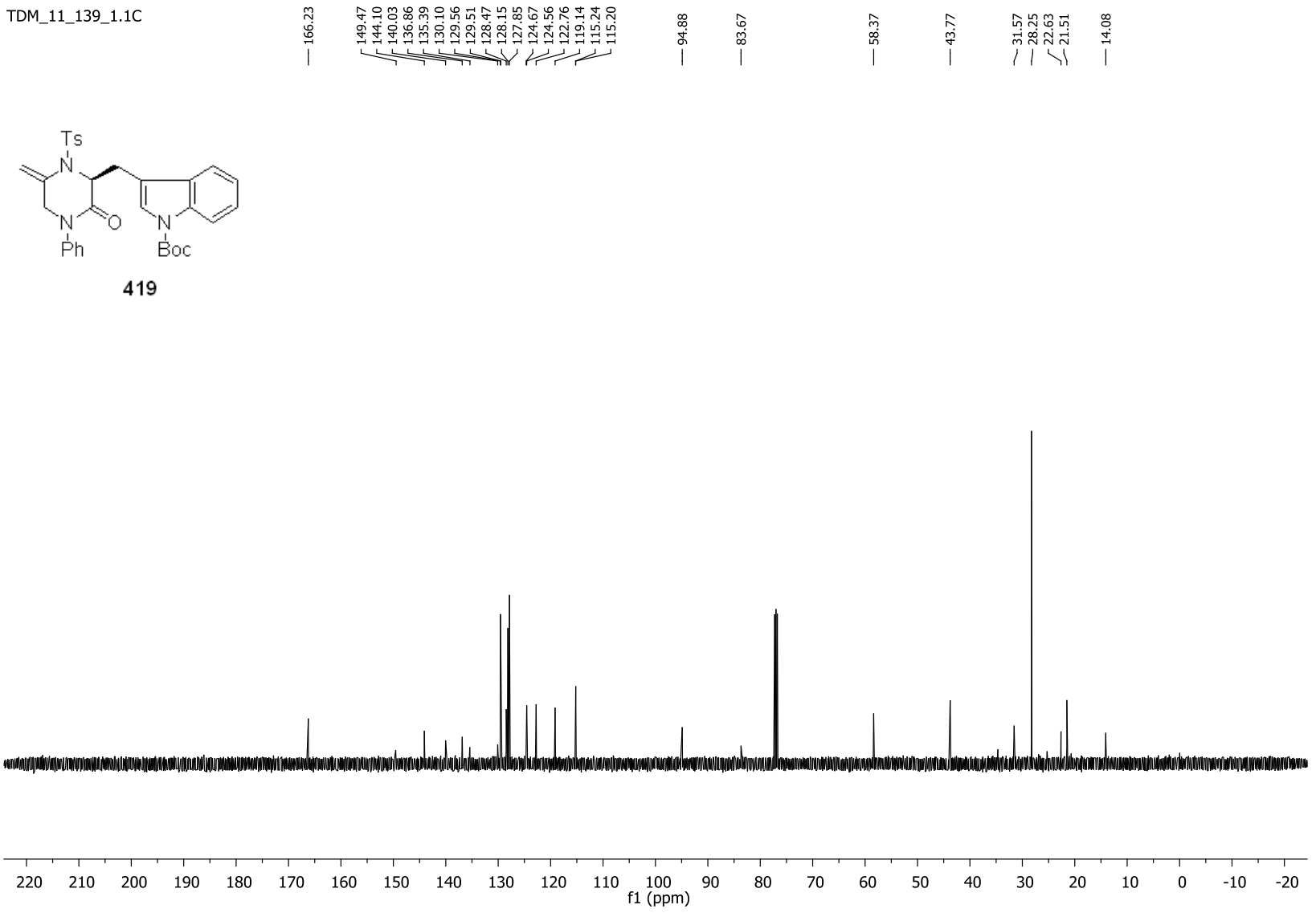


Figure 281. ^{13}C NMR Spectrum for **419** (125 MHz, $CDCl_3$)

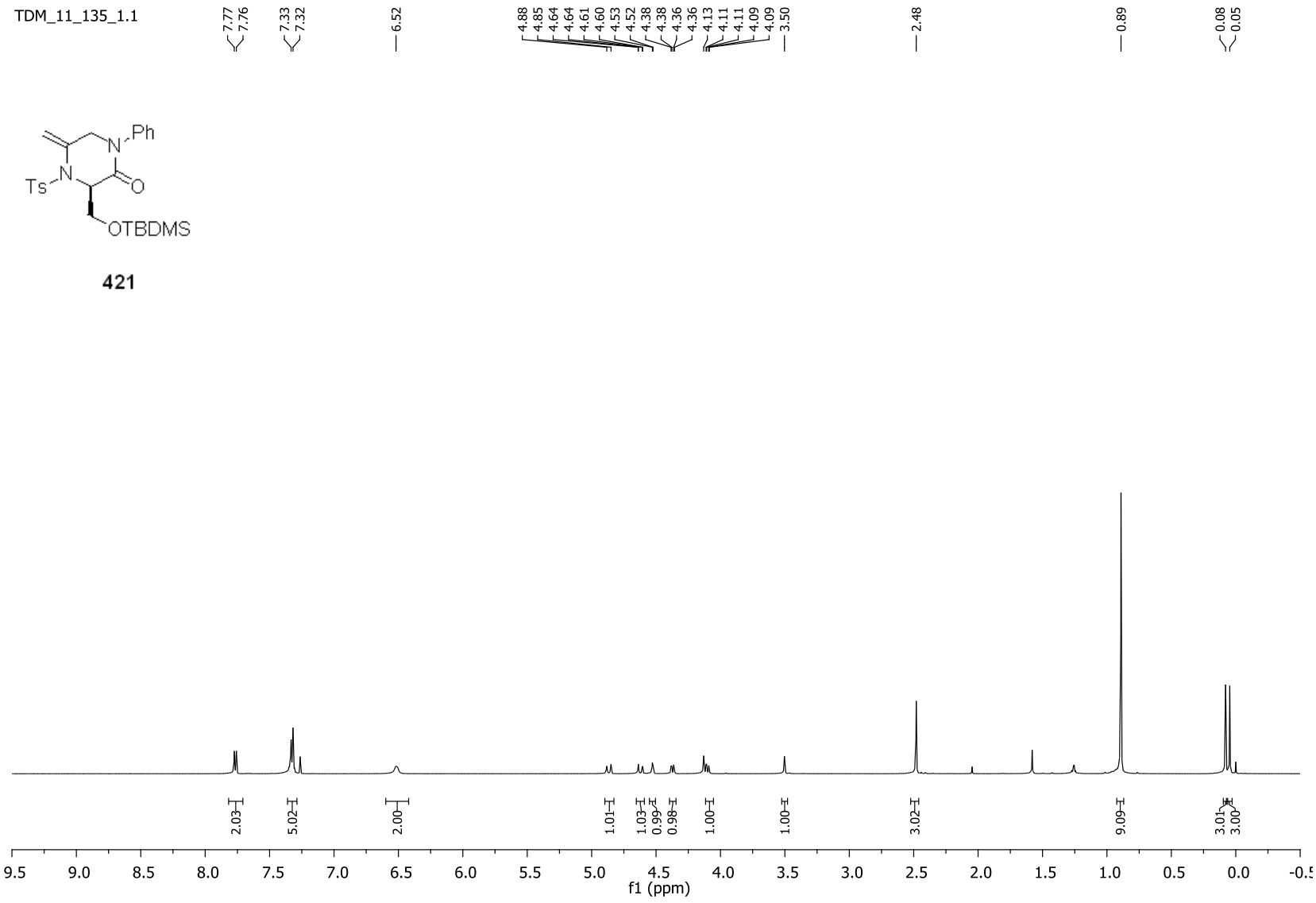


Figure 282. ^{1}H NMR Spectrum for **421** (500 MHz, $CDCl_3$)

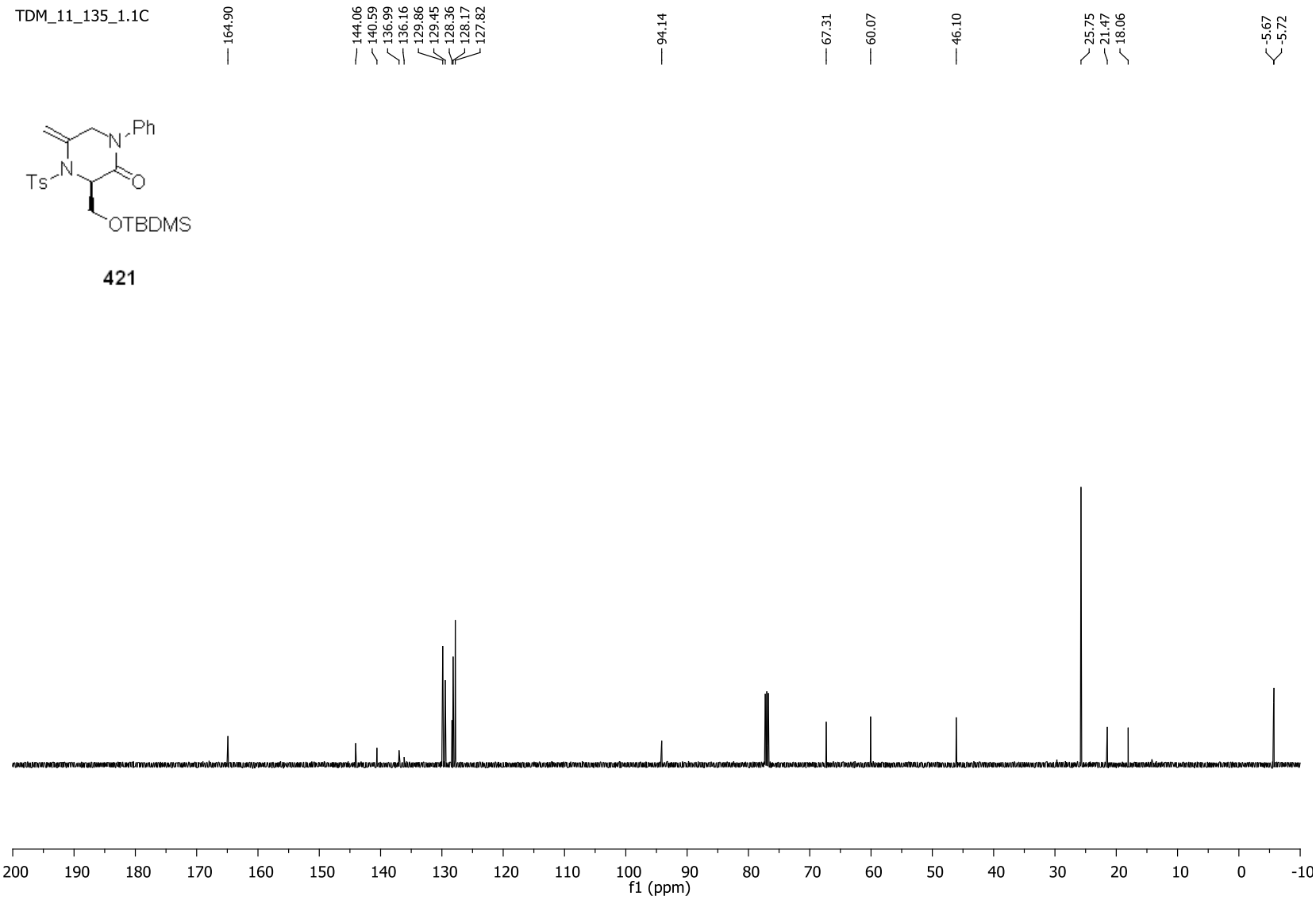


Figure 283. ^{13}C NMR Spectrum for **421** (125 MHz, $CDCl_3$)

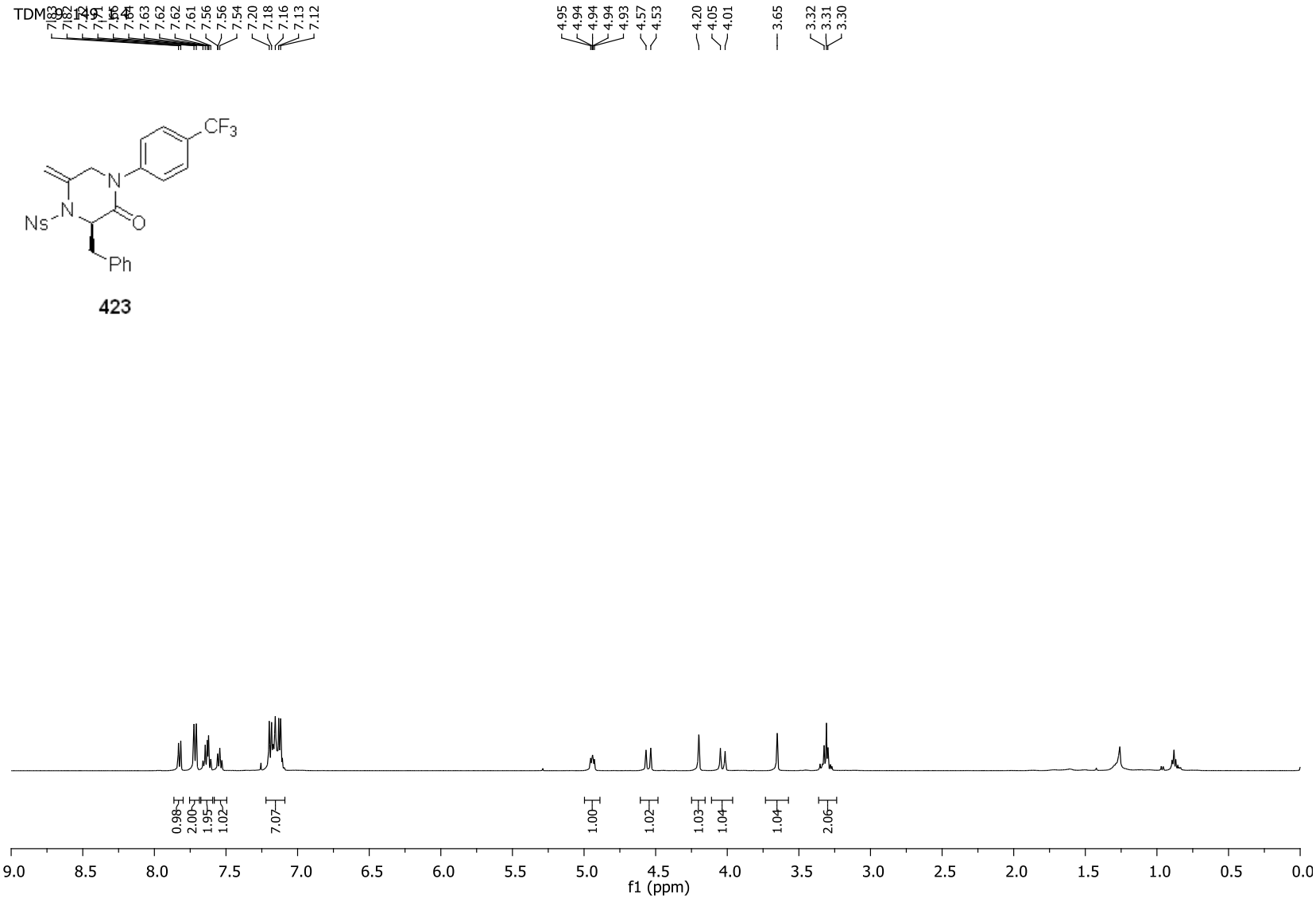


Figure 284. ^{1}H NMR Spectrum for **423** (500 MHz, $CDCl_3$)

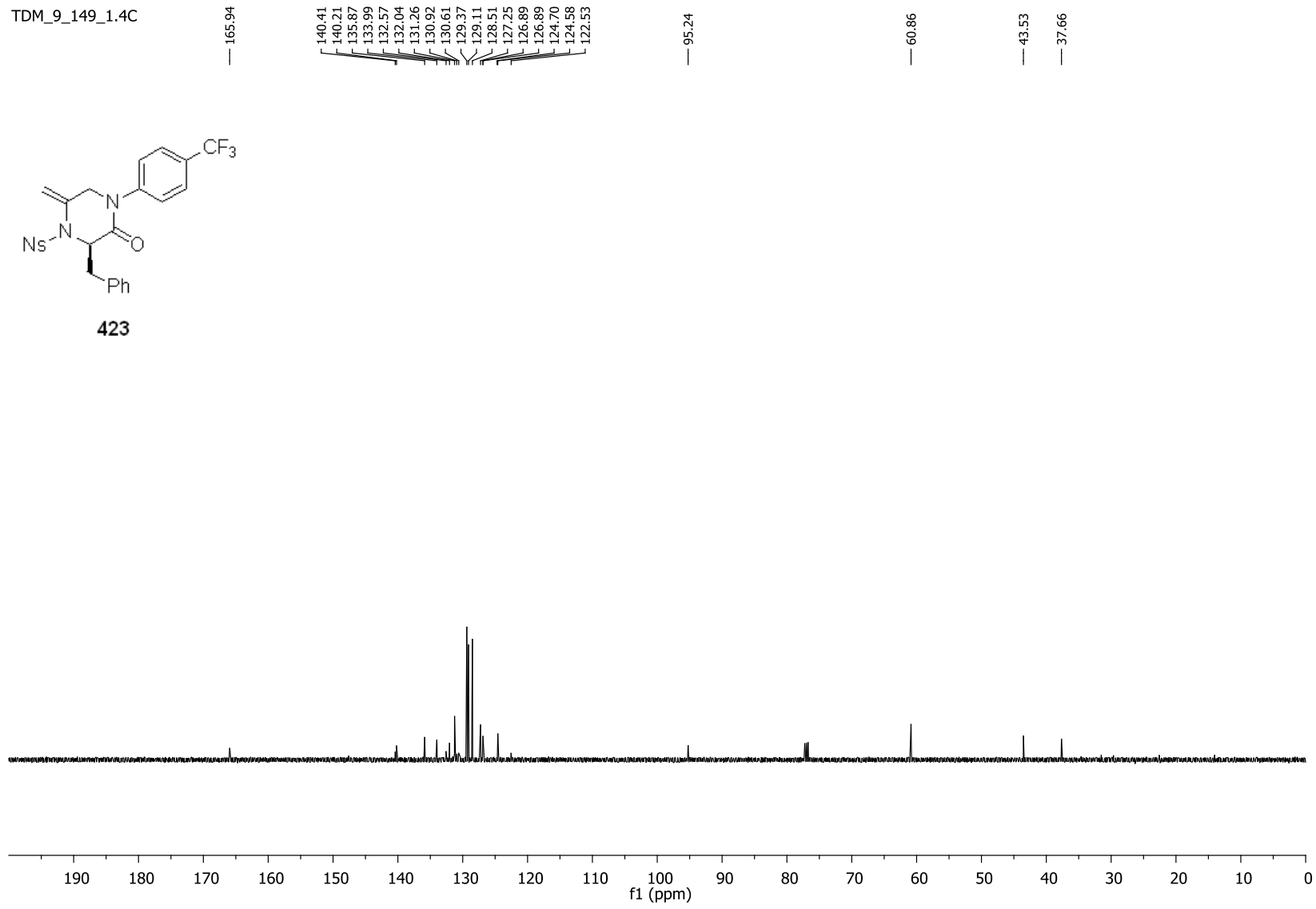
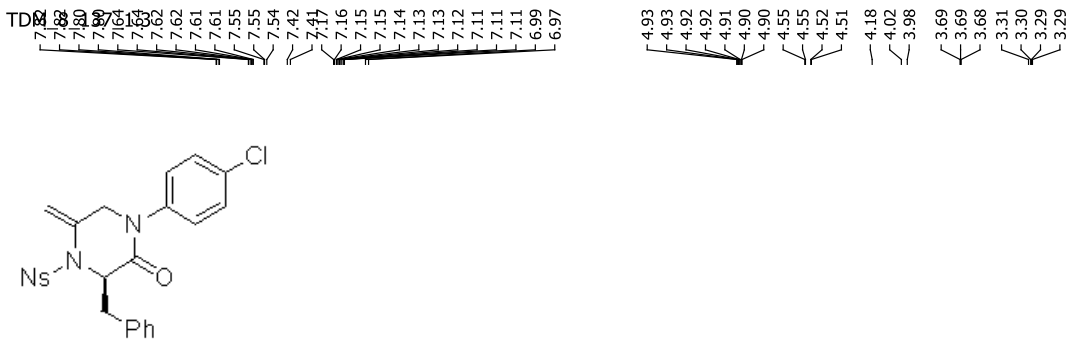


Figure 285. ^{13}C NMR Spectrum for **423** (125 MHz, $CDCl_3$)



425

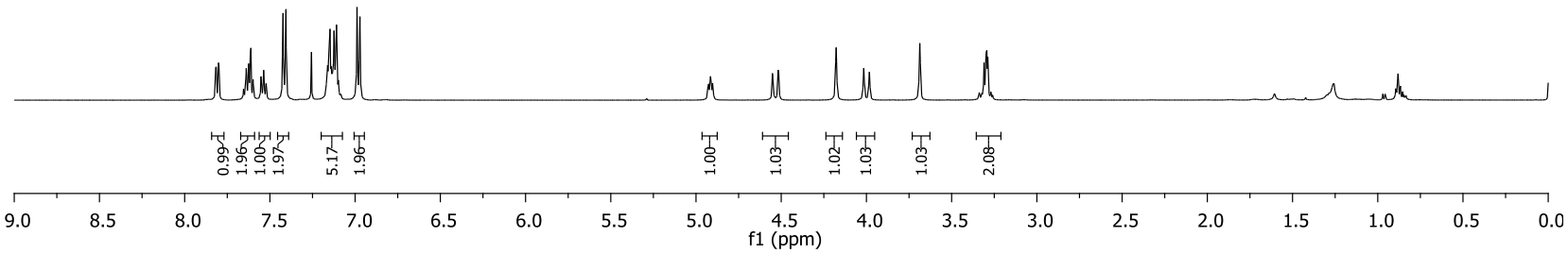


Figure 286. ^{1}H NMR Spectrum for **425** (500 MHz, $CDCl_3$)

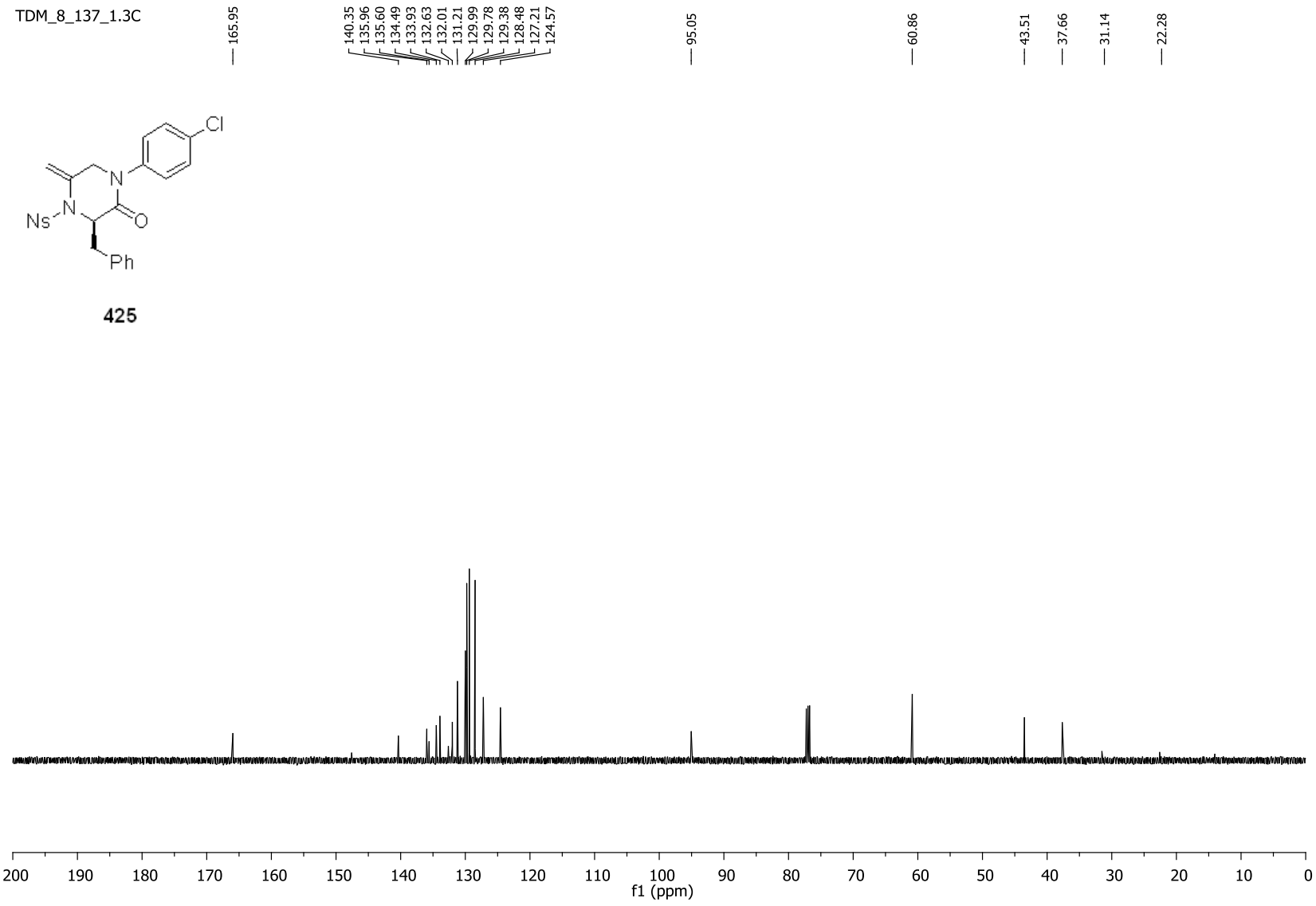


Figure 287. ^{13}C NMR Spectrum for **425** (125 MHz, $CDCl_3$)

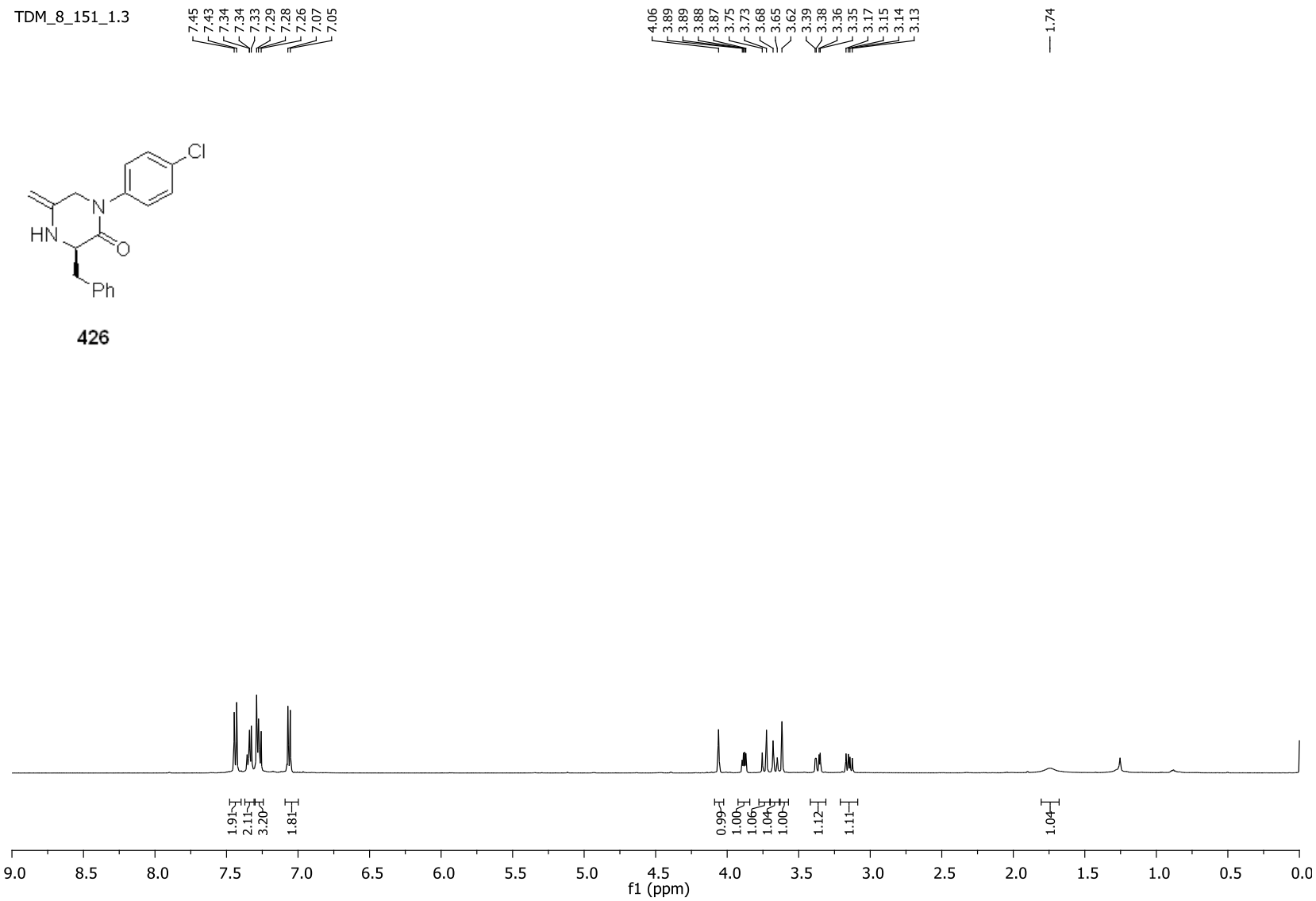


Figure 288. ^{1}H NMR Spectrum for **426** (500 MHz, $CDCl_3$)

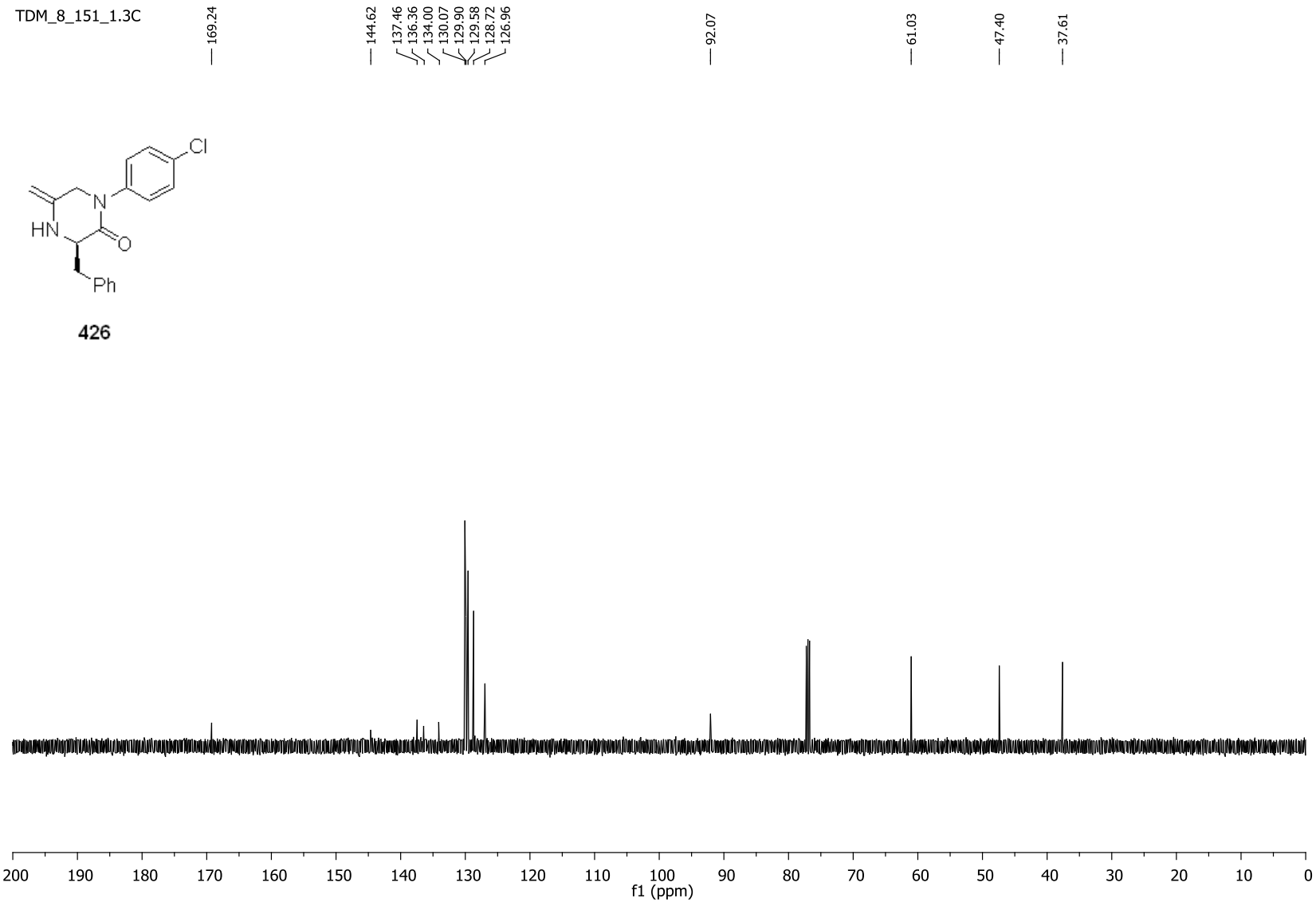


Figure 289. ^{13}C NMR Spectrum for **426** (125 MHz, $CDCl_3$)

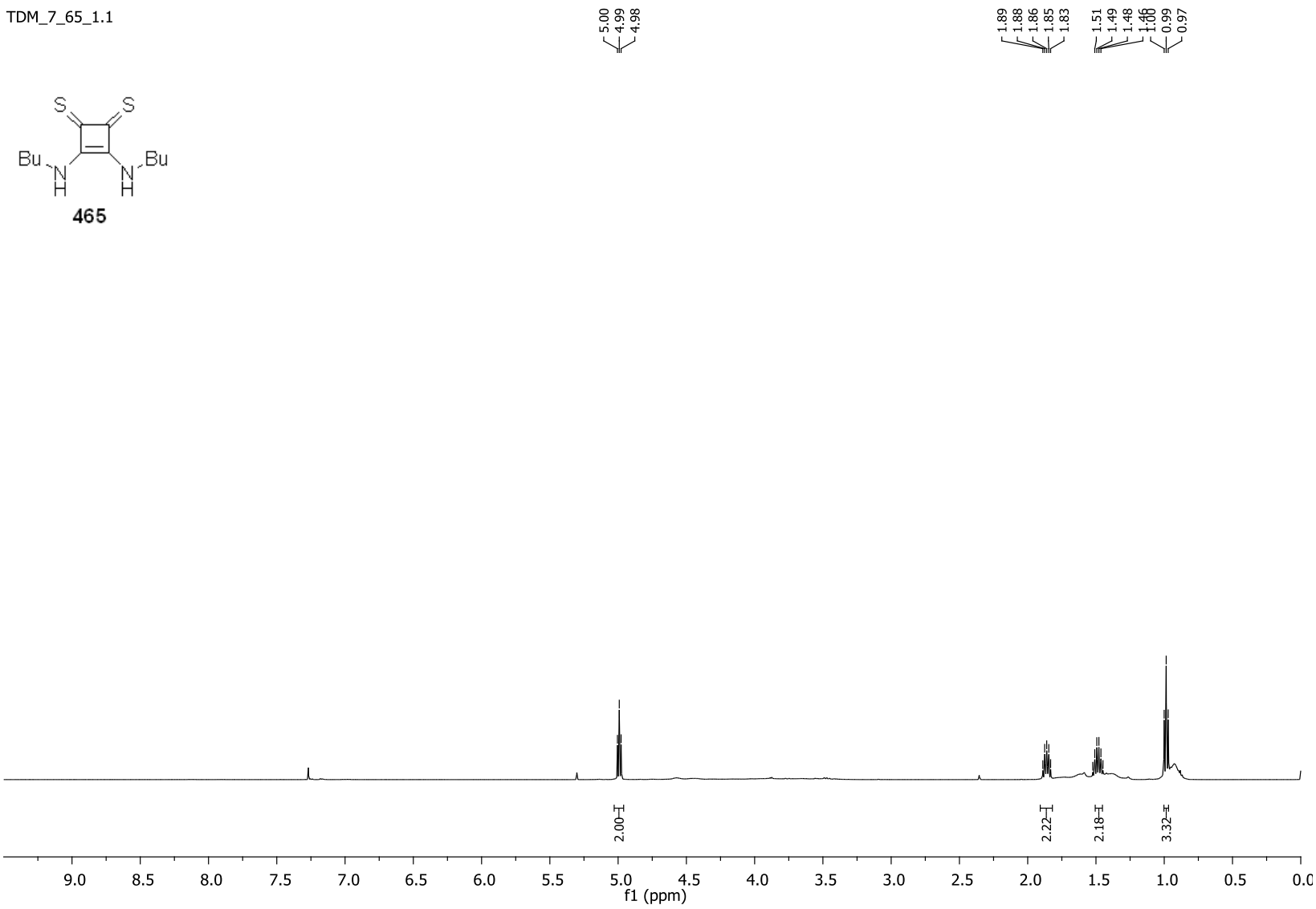


Figure 290. ^{1}H NMR Spectrum for **465** (500 MHz, $CDCl_3$)

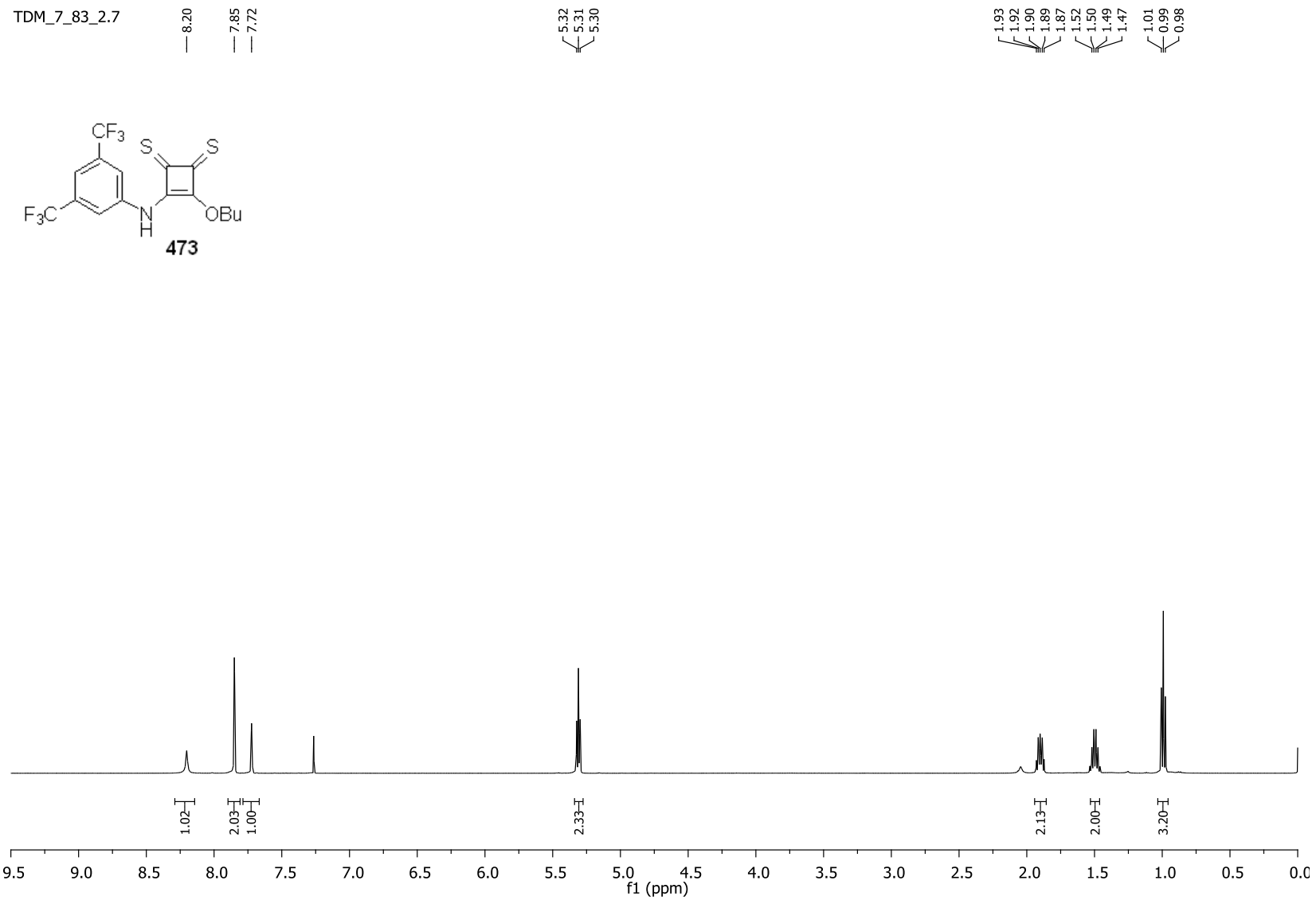


Figure 291. ^{1}H NMR Spectrum for **473** (500 MHz, $CDCl_3$)

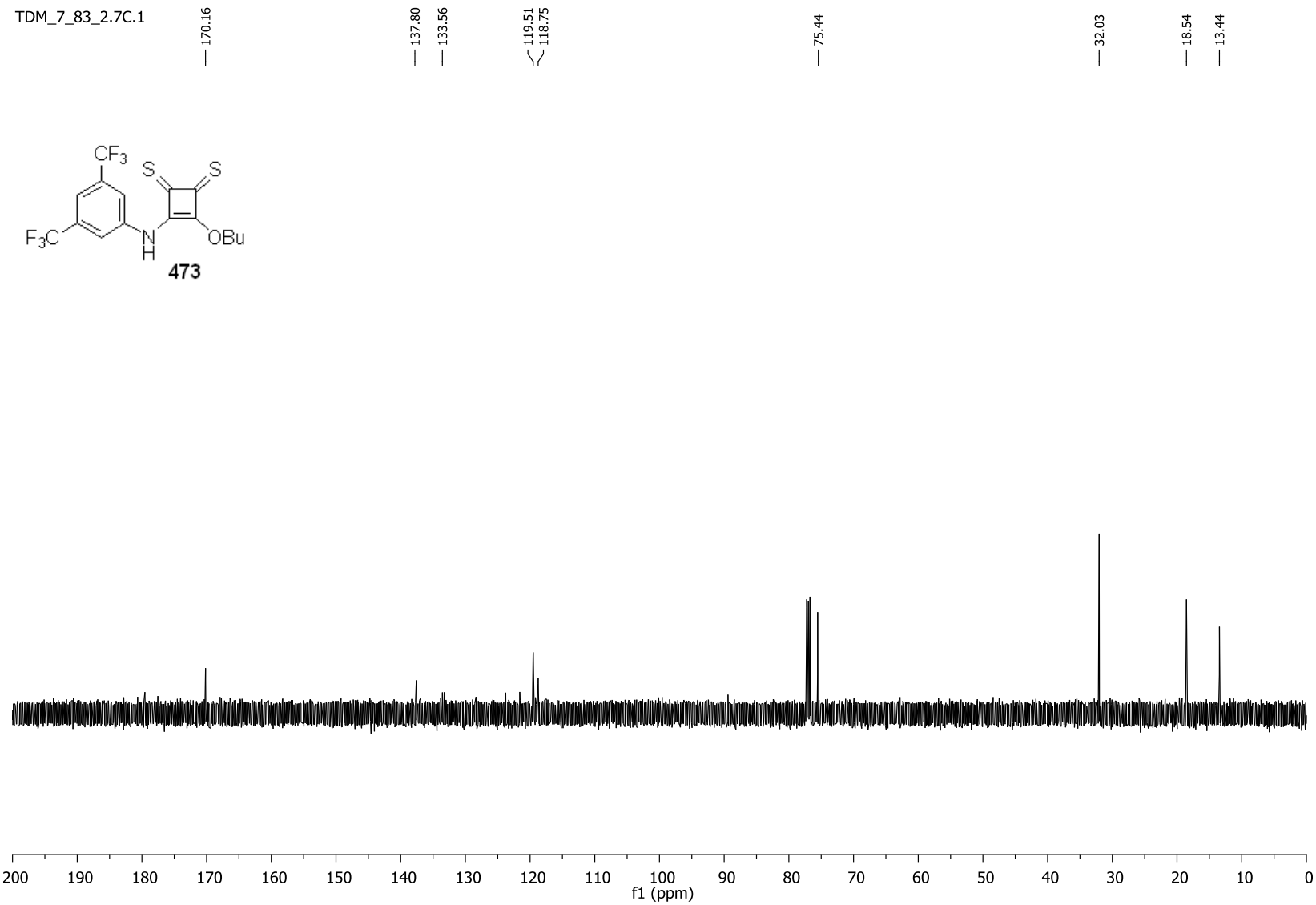


Figure 292. ^{13}C NMR Spectrum for **473** (125 MHz, $CDCl_3$)

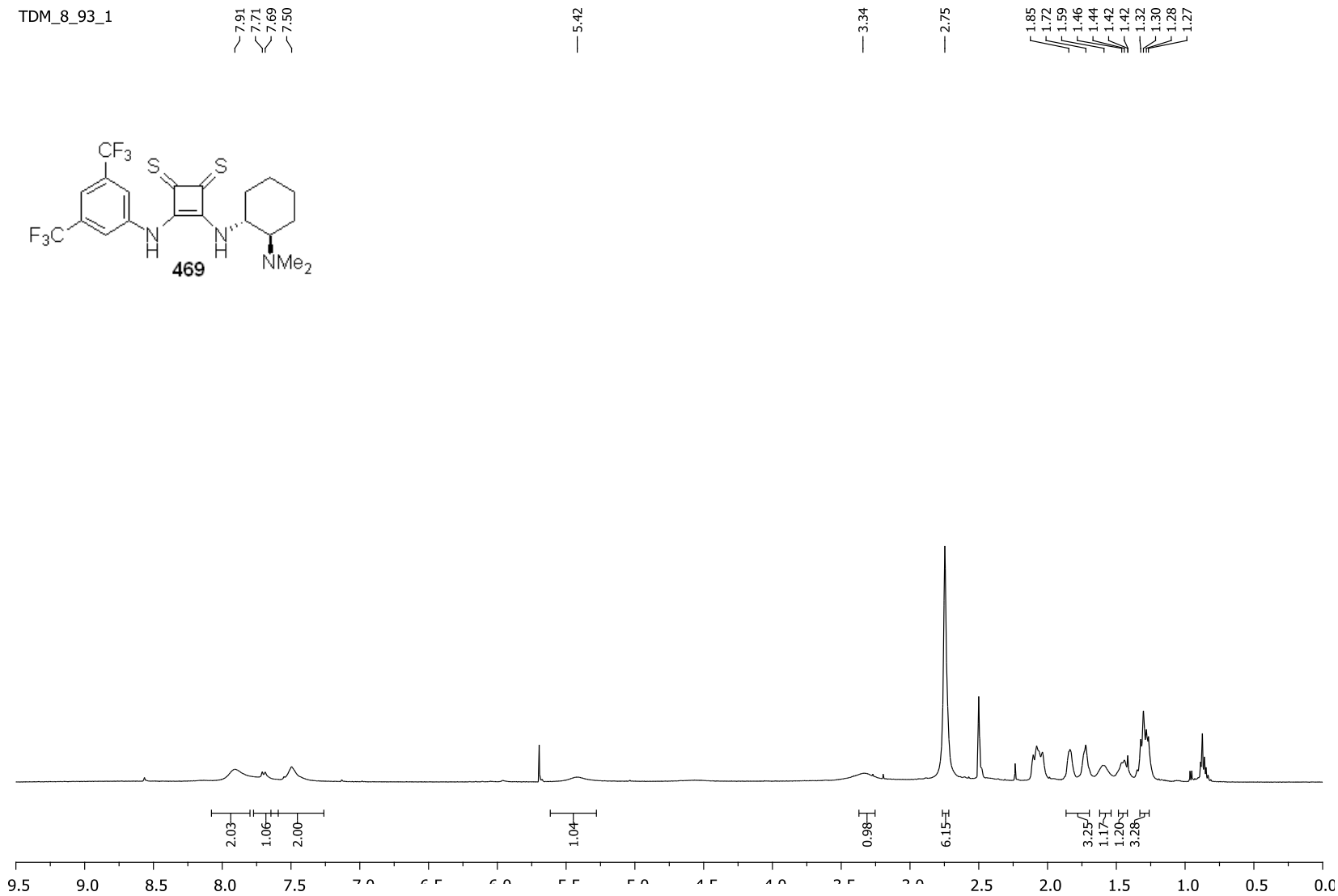
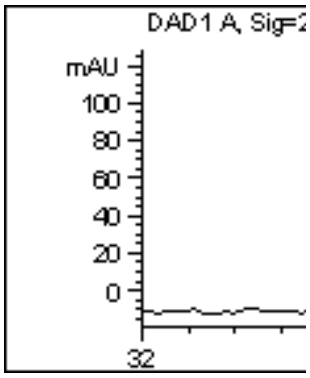


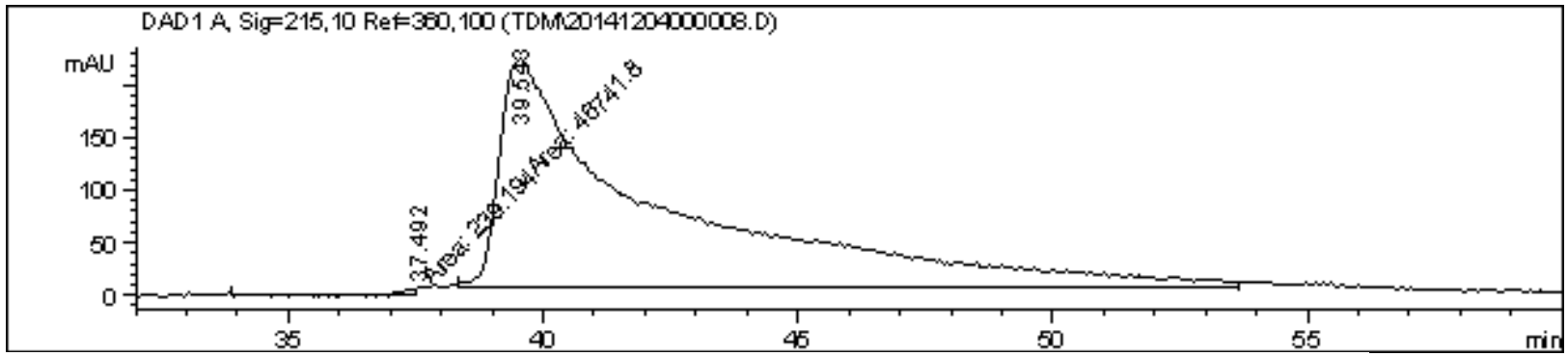
Figure 293. ^{1}H NMR Spectrum for **469** (500 MHz, $CDCl_3$)



Signal 1: DAD1 A, Sig=215,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.165	MF	1.8247	1.46298e4	133.62671	52.7381
2	40.496	FM	2.4822	1.31106e4	88.03092	47.2619
Totals :				2.77404e4	221.65763	

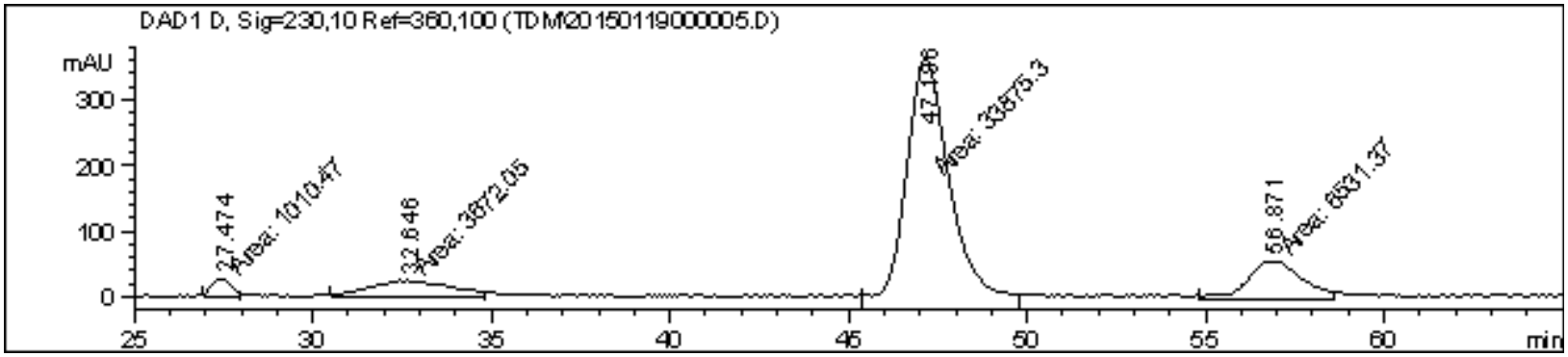
Figure 294. HPLC Trace for **482** (Racemic)



Signal 1: DAD1 A, Sig=215,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.492	MM	0.6164	239.19391	6.46775	0.5091
2	39.543	MM	3.5805	4.67418e4	217.57870	99.4909
Totals :				4.69810e4	224.04645	

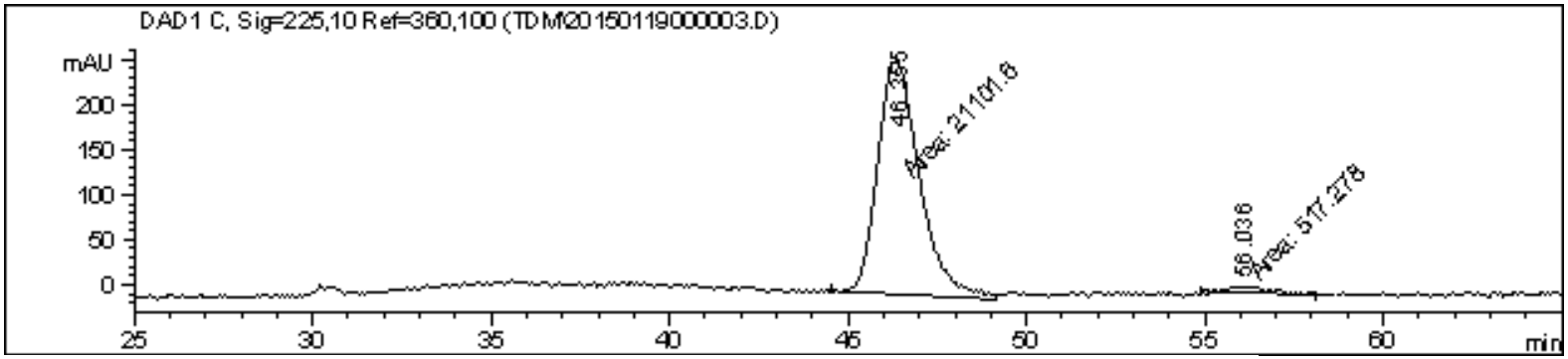
Figure 295. HPLC Trace for **482** (Chiral)



Signal 4: DAD1 D, Sig=230,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.474	MM	0.6310	1010.46753	26.68872	2.2410
2	32.646	MM	2.5666	3672.04932	23.84519	8.1440
3	47.186	MM	1.4819	3.38753e4	380.98285	75.1295
4	56.871	MM	1.7947	6531.36914	60.65465	14.4855
Totals :				4.50892e4	492.17141	

Figure 296. HPLC Trace for **486** (**468** catalyst)



Signal 3: DAD1 C, Sig=225,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	46.355	MM	1.3558	2.11016e4	259.40057	97.6073
2	56.036	MM	1.1604	517.27789	7.42959	2.3927
Totals :				2.16188e4	266.83016	

Figure 297. HPLC Trace for **486** (**469** catalyst)

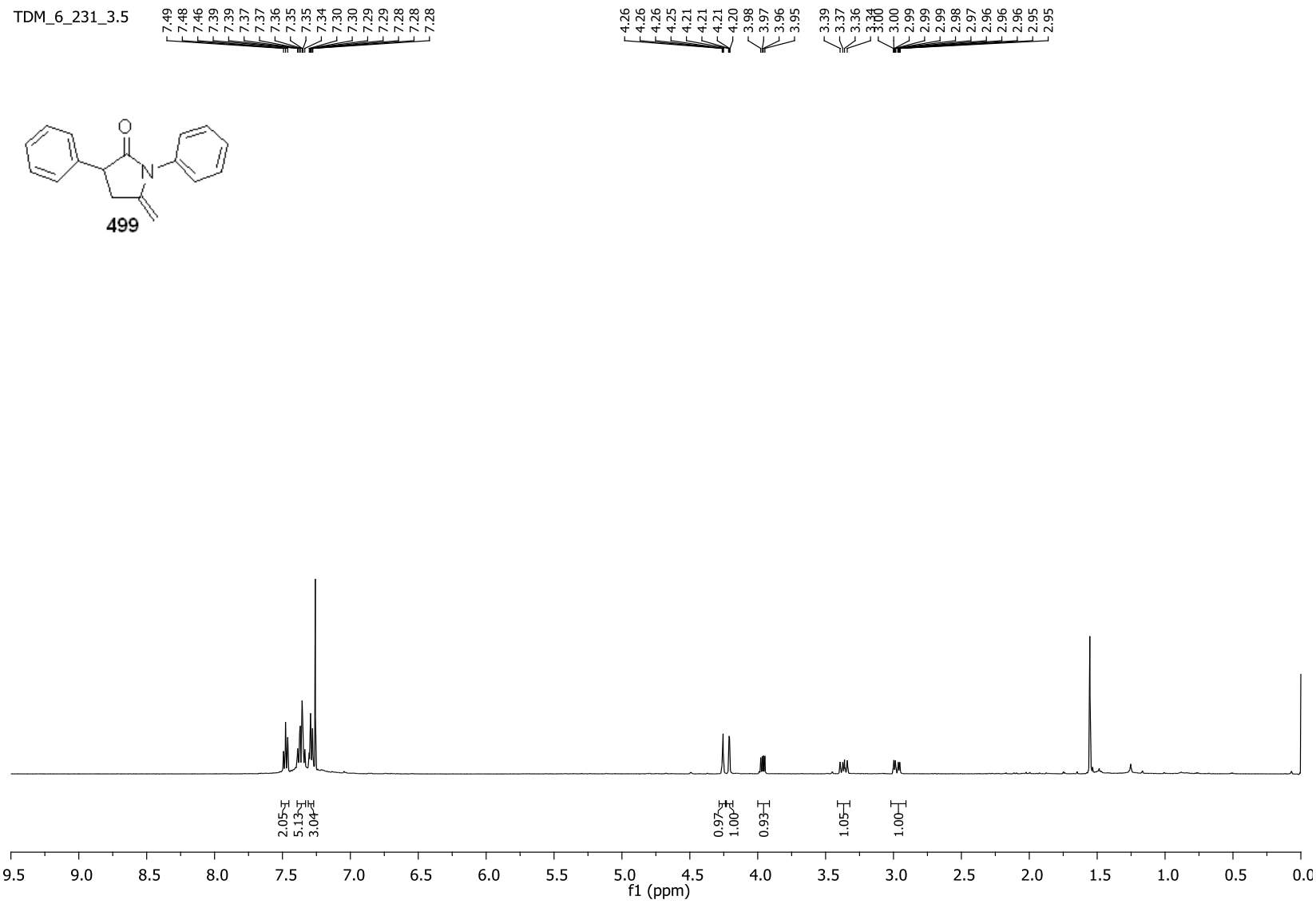


Figure 298. ^{1}H NMR Spectrum for **499** (500 MHz, $CDCl_3$)

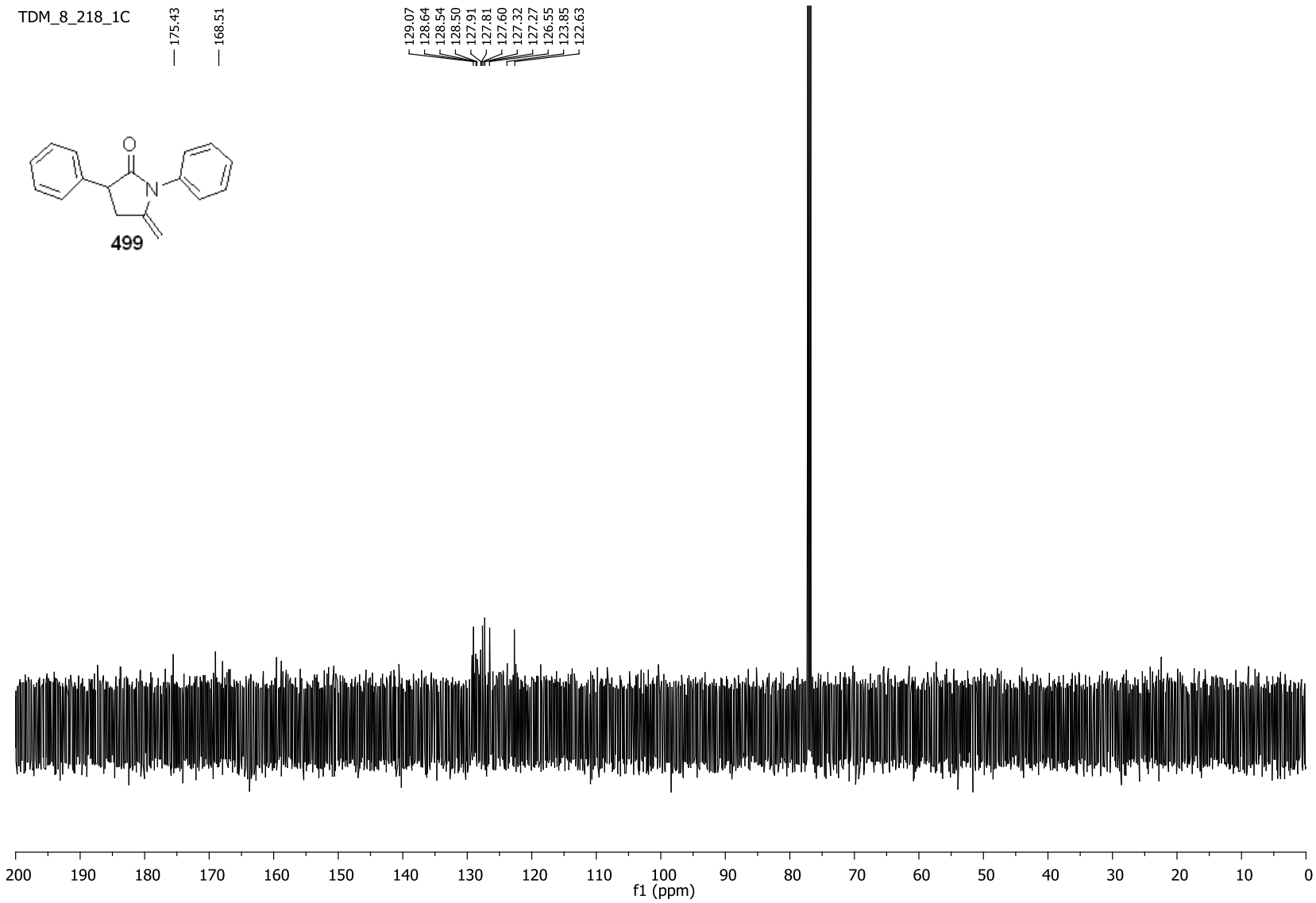


Figure 299. ^{13}C NMR Spectrum for **499** (125 MHz, $CDCl_3$)

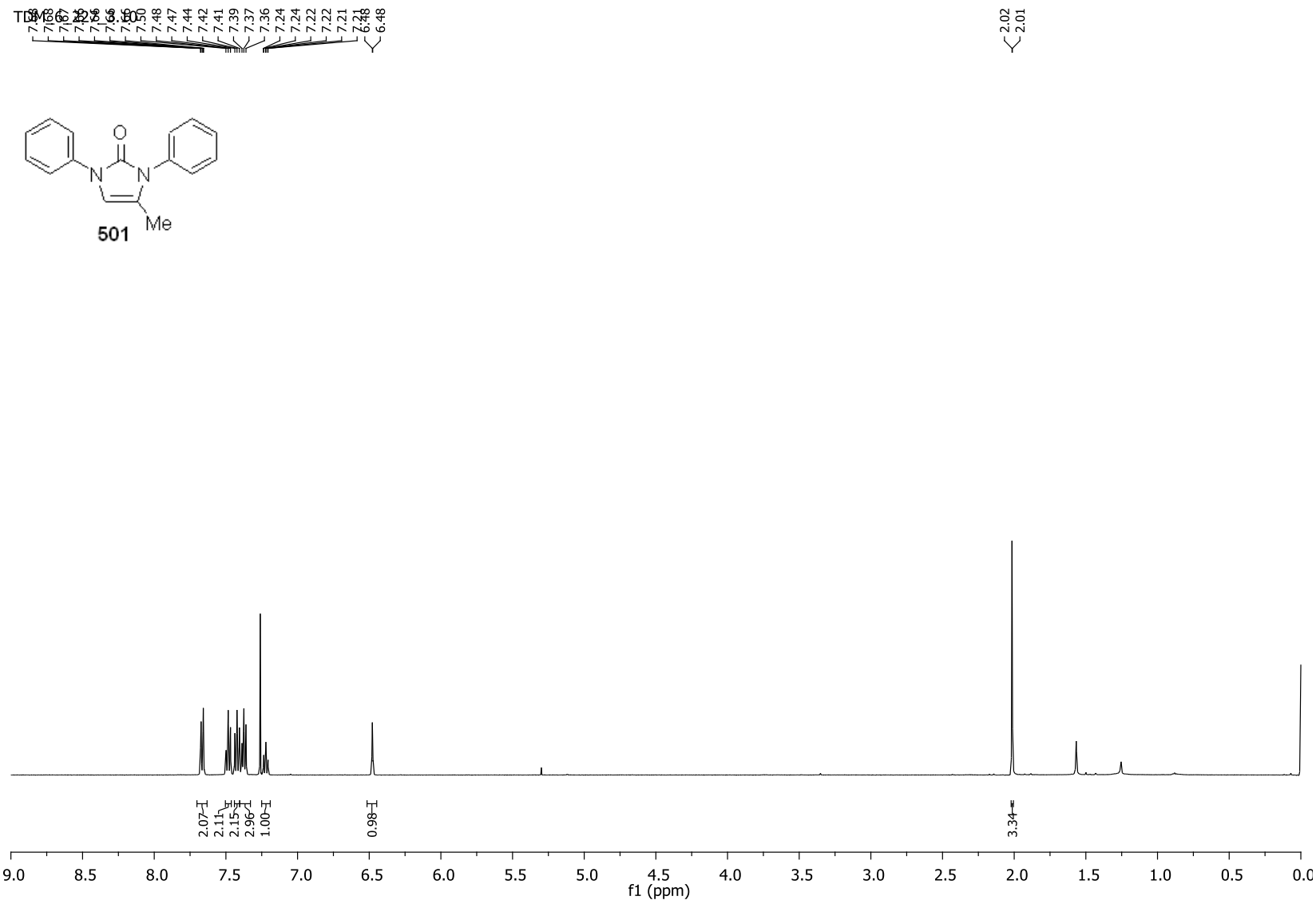
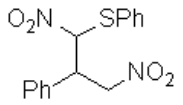


Figure 300. ^{1}H NMR Spectrum for **501** (500 MHz, $CDCl_3$)



517

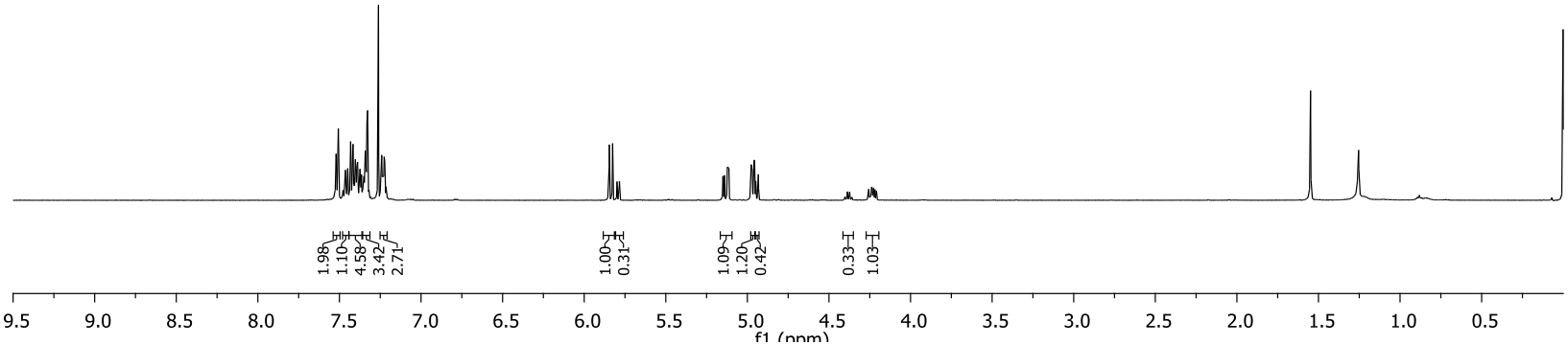
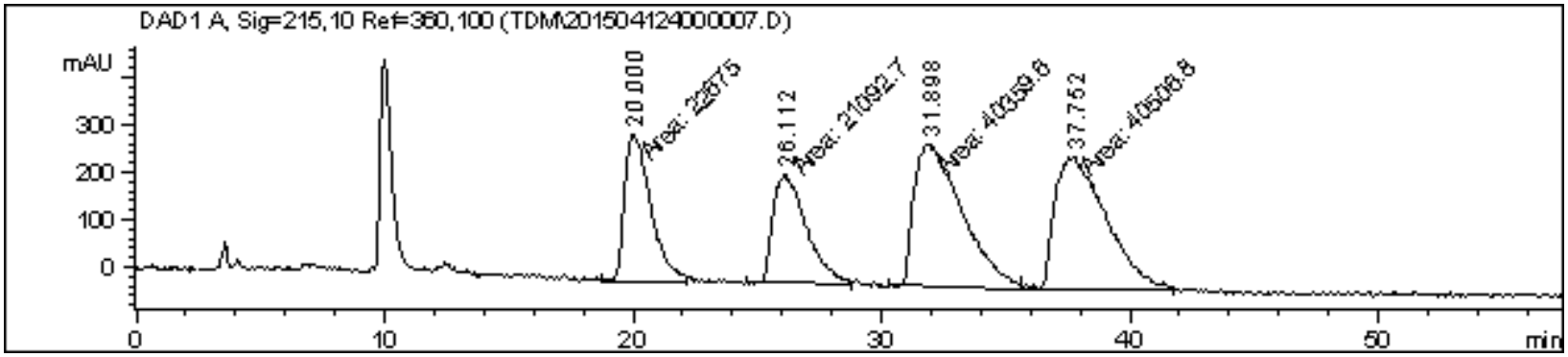


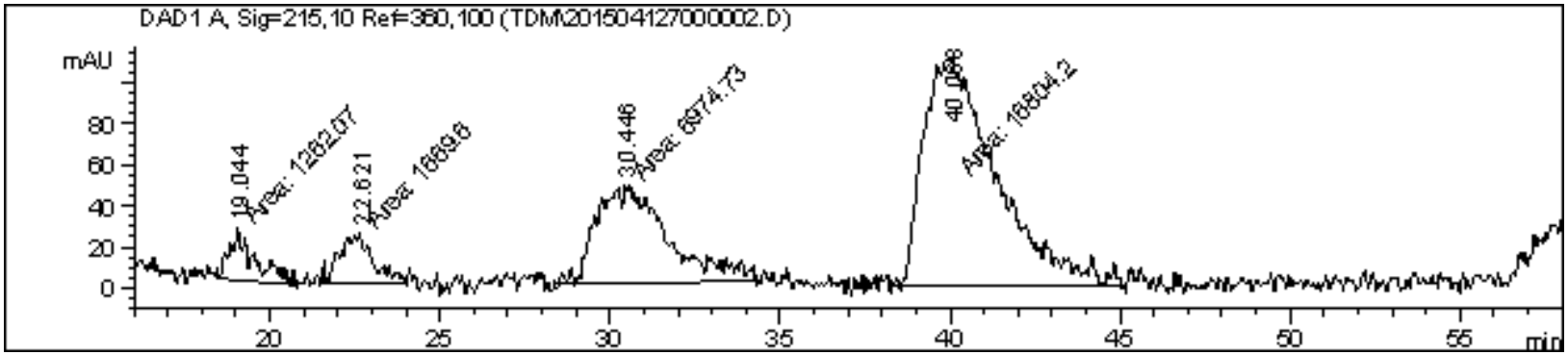
Figure 301. ^{1}H NMR Spectrum for **517** (500 MHz, $CDCl_3$)



Signal 1: DAD1 A, Sig=215,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.000	MM	1.2127	2.26750e4	311.62494	18.1933
2	26.112	MM	1.5397	2.10927e4	228.32159	16.9237
3	31.898	MM	2.2449	4.03596e4	299.64145	32.3825
4	37.752	MM	2.4043	4.05068e4	280.79099	32.5006
Totals :				1.24634e5	1120.37897	

Figure 302. HPLC Trace for **517** (Racemic)



Signal 1: DAD1 A, Sig=215,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.044	MM	0.8310	1262.07227	25.31153	4.7250
2	22.621	MM	1.1160	1669.60046	24.93384	6.2507
3	30.446	MM	2.4320	6974.73389	47.79809	26.1122
4	40.068	MM	2.4987	1.68042e4	112.08745	62.9121
Totals :				2.67106e4	210.13090	

Figure 303. HPLC Trace for **517** (Chiral)