STUDIES TOWARDS THE TOTAL SYNTHESIS OF PALAU'AMINE: SYNTHESIS OF *TRANS*-FUSED 5,5 AZABICYCLES AND THE PHAKELLIN CORE

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To Novella Rivalti,
The queen of "I told you so"
Mi manchi tanto

ABSTRACT

The pyrrole-imidazole alkaloids (PIAs) are a family of structurally related natural products isolated from several species of marine sponges. Palau'amine, a dimeric PIA, has been a target for total synthesis ever since its isolation in 1993 due to its significant biological activity and, more importantly, its complex molecular architecture. In 2007, the structure of palau'amine was revised to incorporate a highly strained *trans*-fused azabicyclo[3.3.0]octane bicyclic system.

This thesis follows the progression of efforts that culminated in the development of a cyclization strategy for the formation of the strained *trans*-fused 5,5-bicyclic ring system. In our initial exploration, attempts to secure the *trans*-fused 5,5-ring system *via* previously established metal-mediated diamination protocols and amidyl radical cyclization were thwarted. Finally, the synthesis of the *trans*-fused core within a simple cyclic model system was enabled by the conjugate addition of a carbamate nitrogen to an ynoate which furnishes a *trans*-fused azabicyclo[3.3.0]octane bicyclic system containing an exocyclic *α,*β-unsaturated ester. The latter would act as a synthetic handle to construct the remaining right-hand side core of palau'amine.

Two particular monomeric PIAs, phakellin and phakellstatin, greatly resemble palau'amine in that they share the same ABCD tetracyclic core. The application of our conjugate addition strategy afforded the pyrrolidine A-ring, containing an exocyclic *α,*β-unsaturated ester. To access the phakellstatin core, the elaboration of that synthetic handle to the vinyl urea was achieved *via* a Curtius rearrangement. A cyclofunctionalization reaction secured the pyrazinone B-ring affording the desired tricyclic carbinolamine precursor suitable for the synthesis of phakellstatin. To access the phakellin core, the exocyclic *α,*β-unsaturated ester was elaborated, *via* a Curtius rearrangement/aza-Wittig one-pot process, to an advanced intermediate containing the complete nitrogen and carbon framework of phakellin. The cyclofunctionalization reaction with the guanidine-containing intermediate secured the pyrazinone B-ring affording the desired tricyclic carbinolamine. Unfortunately, final attempts to close the guanidine C-ring and to complete the synthesis of the natural product were however unsuccessful.

RÉSUMÉ

Les alcaloïdes de type pyrrole-imidazole (API) font partie d'une famille de produits naturels de structure similaire provenant de plusieurs espèces d'éponges marines. Parmi les API dimériques, la palau'amine a été particulièrement populaire depuis son isolation en 1993 en raison de son activité biologique significative et, surtout, en raison de son architecture moléculaire complexe. En 2007, la structure de la palau'amine a été révisée pour intégrer un système bicyclique très tendu fusionné *trans* de type azabicyclo[3.3.0]octane.

Cette thèse décrit la progression des efforts qui ont abouti à l'élaboration d'une stratégie de cyclisation pour la formation du système tendu 5,5-bicyclique fusionné *trans*. Lors de nos premières explorations, les tentatives pour obtenir ces jonctions de cycle particuliers par des protocoles déjà établis tels que la diamination métallique et la cyclisation radicalaire amidyle ont été contrecarrées. La structure a finalement été synthétisée par l'addition conjuguée d'un atome d'azote d'un carbamate à un ynoate. Cette addition a permis l'accès à un système bicyclique *trans*-fusionné azabicyclo[3.3.0]octane contenant un ester exocyclique α,β-insaturé permettant de construire la portion de droite de la palau'amine.

Deux API monomériques, la phakelline et la phakellstatine, ressemblent beaucoup à la palau'amine puisqu'ils partagent le même noyau tétracyclique ABCD. L'utilisation de la stratégie d'addition conjuguée a donné le cycle-A pyrrolidinien, contenant un ester exocyclique α,β-insaturé. La structure de base de la phakellstatine est obtenue par un réarrangement de Curtius de l'ester en urée vinylique, puis par une réaction de fonctionnalisation cyclique qui permet d'accéder au cycle B-pyrazinonien, permettant ainsi d'obtenir un précurseur tricyclique carbinolaminé. Pour accéder à la structure de la phakelline, un ester exocyclique α,β-insaturé a été élaboré par un procédé combiné Curtius/aza-Wittig, ce qui a mené à un intermédiaire contenant la structure amine et carbonée complète de la phakelline. La réaction de fonctionnalisation cyclique avec l'intermédiaire contenant de la guanidine a donné le cycle B-pyrazinonien, menant également au carbinolamine tricyclique désiré. Malheureusement, les dernières tentatives pour fermer le cycle guanidine C ont cependant échoué.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Å	angstrom
Ac	acetyl
ACCN	1,1′-azobiscyclohexanecarbonitrile
AICN	2,2′-azobisisobutyronitrile
aq.	aqueous
Ar	aryl/aromatic
atm	atmosphere
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
brsm	based on recovered starting material
BtH	1*H*-benzotriazole
Bu	butyl
Bn	benzyl
Bz	benzoyl
°C	degrees Celsius
CAN	ceric ammonium nitrate
cat.	catalytic amount of
CDI	carbonyl diimidazole
CI	chemical ionization
cm^{-1}	wavenumber
conc	concentrated
conv	conversion
COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
d	deuterium
d	doublet

d	day
δ	chemical shift
Δ	heat
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
decomp	decomposition
DIBAL	diisobutylaluminum hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
DPPA	diphenylphosphorylazide
dr	diastereomeric ratio
E	entgegen
EC_{50}	half maximum effective concentration
ee	enantiomeric excess
EDC•HCl	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EI	electron impact ionization
equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
eV	electron volt
EWG	electron-withdrawing group
FT	Fourier transform
g	gram

h	hour
HBTU	*N,N,N′,N′*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple-quantum coherence
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
i	iso
IC_{50}	half maximum inhibition concentration
IR	infrared
J	joule
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L	litre
LA	Lewis acid
LD_{50}	median lethal dose
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LTMP	lithium tetramethylpiperidide
m/z	mass to charge ratio
M	molarity
$[M]^+$	molecular ion
m	meta
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
mg	milligram

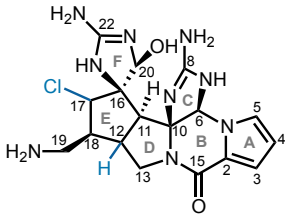
MH^+	protonated parent mass
MHz	megahertz
min	minute
mL	milliliter
μL	microliter
mmol	millimole
MNa^+	sodiated parent mass
mol	mole
Ms	mesyl, methanesulfonyl
MS	mass spectroscopy
MW	molecular weight
NBS	*N*-bromosuccinimide
ND	neodecanoate
nd	not determined
NEt_3	triethylamine
nm	nanometer
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
N.R.	no reaction
Ns	nosyl, *para*-nitrophenylsulfonyl
o	ortho
Oxone®	$2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$
p	para
pH	hydrogen ion concentration
PhH	benzene
PhMe	toluene
PG	protecting group
Ph	phenyl
PIA	pyrrole-imidazole alkaloid

PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
Py	pyridine
q	quartet
R	generic carbon substituent
R	rectus
R_f	retention factor
rt	room temperature
rxn	reaction
s	second
s	singlet
S	sinister
Ses	2-(trimethylsilyl)ethanesulfonyl
SM	starting material
T	temperature
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
T-cell	lymphocyte
Tces	trichloroethoxysulfonyl
TDI	thiocarbonyldiimidazole
Teoc	2-(trimethylsilyl)ethoxycarbonyl
Tf	triflyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatograpy

TMS	trimethylsilane
Ts	tosyl, *para*-toluenesulfonyl
Tse	tosylethyl
Tsv	tosylvinyl
UV	ultraviolet-visible
v/v	volume-to-volume ratio
w/v	weight-to-volume ratio
X	generic heteroatom or halogen substituent
Y	yield
Z	zusammen

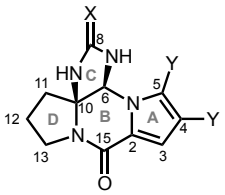
NOMENCLATURE

The numbering and ring lettering systems for palau'amine (**1.1** and **1.2**) are as follows. The numbering and ring lettering systems were used by Kinnel, Gehrken and Scheuer in their original report documenting the isolation of palau'amine. The numbering follows the same numbering as for the phakellin (**1.3**)/phakellstatin (**1.4**) family of natural products. The ring lettering system for the phakellins differs slightly in the literature but we have chosen to keep with the palau'amine ring lettering system for consistency.



1.1 palau'amine (H=α, Cl=β)

1.2 palau'amine (H=β, Cl=α)



1.3 phakellin (X=NH, Y=H)

1.4 phakellstatin (X=O, Y=H)

Chapter 1. Introduction:

Pyrrole-Imidazole Alkaloids and Palau'amine

1.1 Pyrrole-Imidazole Alkaloids

The first pyrrole-imidazole alkaloids (PIA) were isolated from marine sponges in the early 1970's[1] and thus led to the discovery of a class of natural products of unprecedented skeletal diversity with a broad range of biological profiles. The PIA family counts more than 150 natural products, which all stem from the marine alkaloid oroidin **1.5** and its congeners hymenidin **1.6** and clathrodin **1.7** (Figure **1.1**).[2]

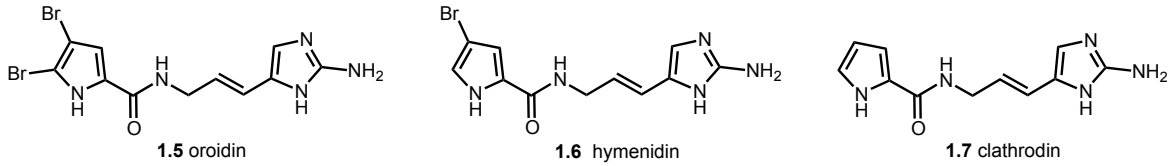


Figure 1.1 - Structure of oroidin and its congeners

Oroidin **1.5** is one of the most abundant naturally occurring members of the PIA family and can be found in concentrations as high as 1% of the sponge dry weight.[2a] Many structurally diverse PIAs exhibiting a variety of biological activities have been isolated mainly from the marine sponges of the *Agelasidae*, *Axinellidae*, *Halichondriidae*, *Hymeniacidonidae* and *Dictyonellidae* species. The structurally elaborate members of this family of natural products arise from various modes of functionalization, cyclization, and dimerization of the relatively simple oroidin-based building blocks **1.5**, **1.6** and **1.7**.

Cyclic monomeric derivatives of oroidin include cyclooroidin **1.8**,[3] agelastatin A **1.9**,[4] dibromoagelaspongin **1.10**,[5] odiline (stevensine) **1.11**,[6] the phakellins **1.3**, **1.12**, **1.13**,[1b, 7] and the isophakellins **1.14**, **1.15**.[8] Many of the natural products in the family have been isolated in varying states of bromination, demonstrating the marine sponges' ability to use hymenidin **1.6** as well as clathrodin **1.7** to construct PIAs *via* these six modes of monomeric cyclization.

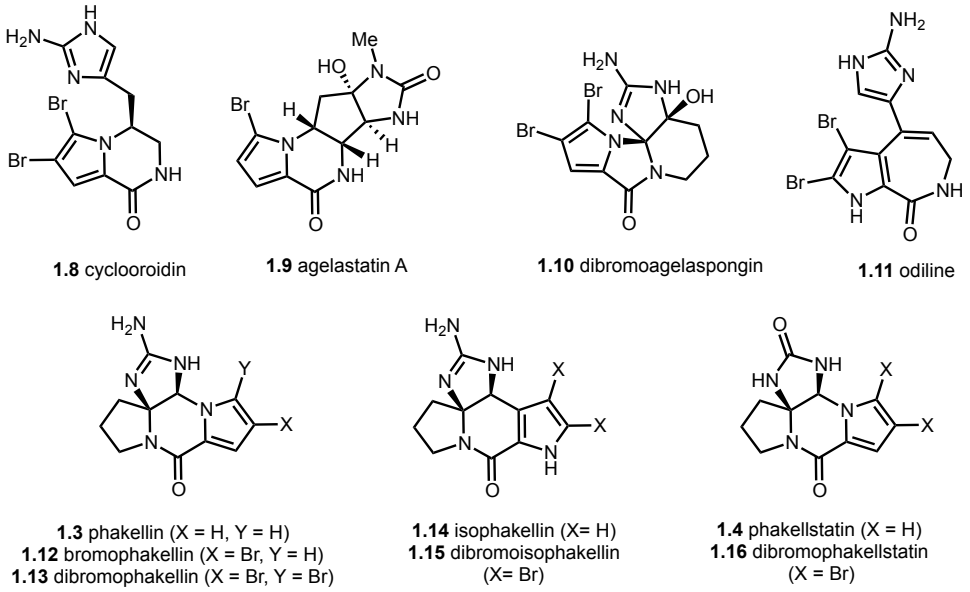


Figure 1.2 - Cyclic oroidin monomers

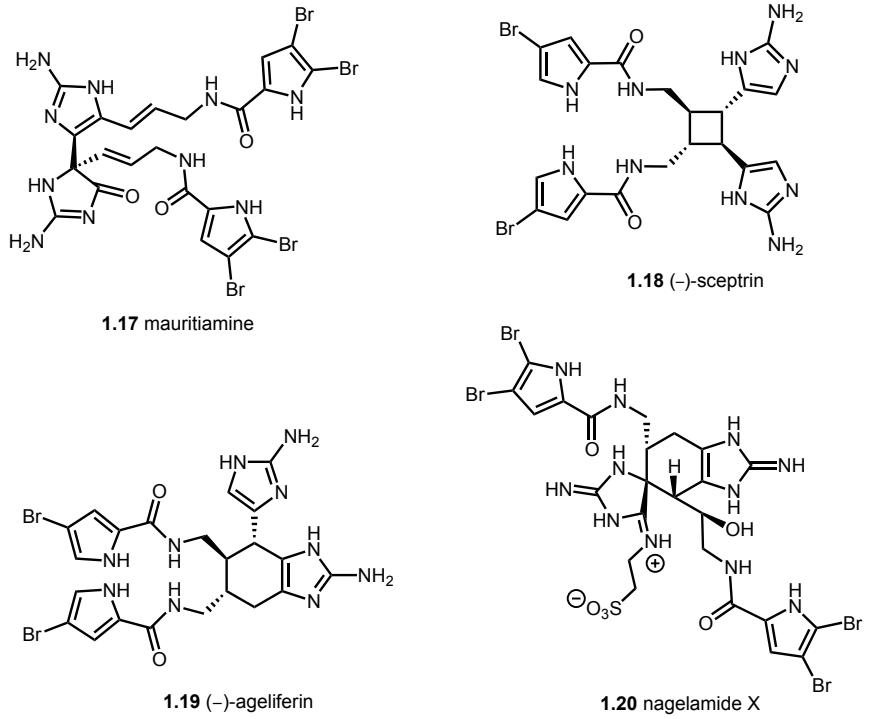
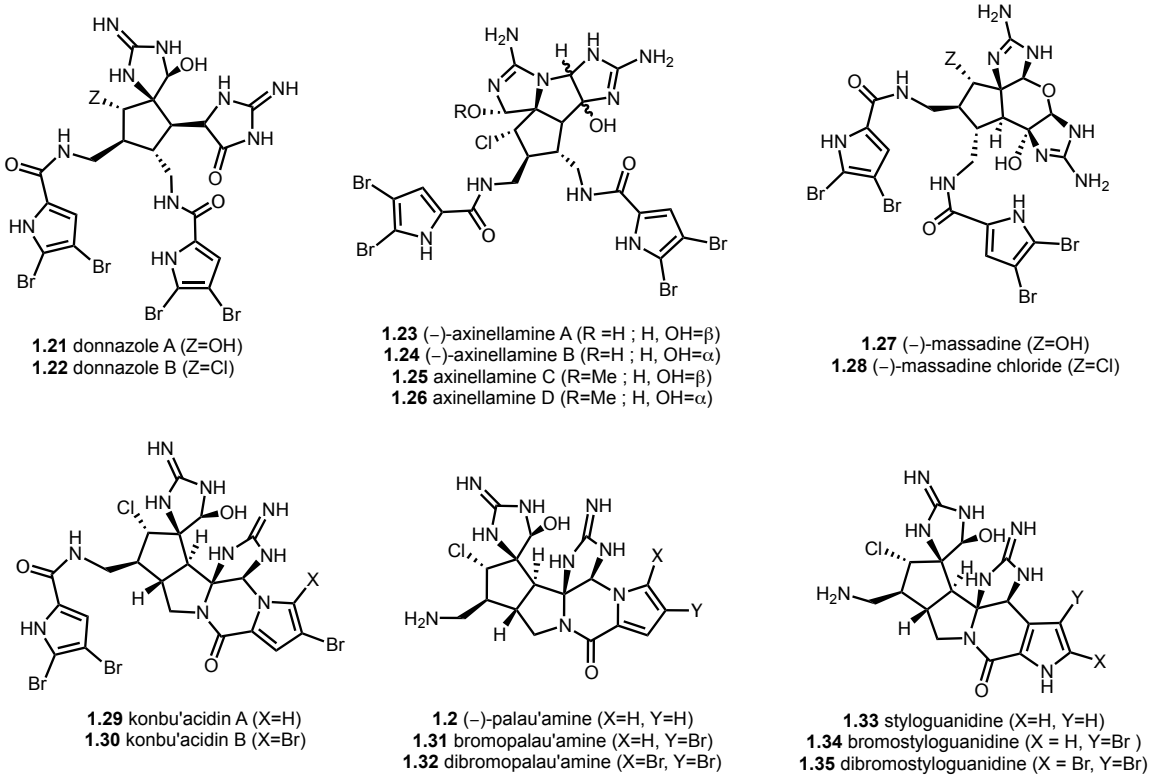


Figure 1.3 - Cyclic oroidin dimers

Furthermore, the dimerization of oroidin **1.5** leads to some of the most complex natural products known to date. The report of Faulker and Clardy in 1981[9] that revealed the structure of the first dimeric PIA, sceptrin **1.18**, which was followed by Rinehart's

isolation of the bicyclic dimer ageliferin **1.19** in 1986[10] paved the way for the discovery of a myriad of intricately complex marine small molecule natural products. For example, the head-to-head dimerization *via* the formation of a single new bond leads to mauritiamine **1.17**,[11] *via* two new bonds produces sceptrin **1.18**[9] and ageliferin **1.19**[12] or the head-to-tail dimerization forges structures such as nagelamide X **1.20**.[13] In 1993, the hexacyclic palau'amine (**1.2**) was discovered and hailed as the most architecturally complex oroidin dimer.[14] Over the next few years, other polycyclic oroidin dimers with an impressive array of functionality were isolated (Figure 1.4): the donnazoles (**1.21**, **1.22**),[15] the axinellamines (**1.23**-**1.26**),[16] the massadines (**1.27**, **1.28**),[17] the konbu'acidins (**1.29**, **1.30**),[18] the brominated palau'amines (**1.31**, **1.32**),[19] and the styloguanidines (**1.33**-**1.35**).[20] The latter two alkaloids are not true dimers in that they have undergone the loss of the pyrrole-2-carboxamide fragment resulting from a post-dimerization modification event or arise from the coupling of oroidin with a simpler non-acylated derivative. The donnazoles, massadines and axinellamines contain a highly functionalized cyclopentane core similar to the palau'amines. The konbu'acidins are the acylated analogues of the palau'amines and the styloguanidines differ from the palau'amines in the orientation of the pyrrole. Of the six modes of cyclization with monomers, only two are observed in the dimeric alkaloid series: the phakellin (**1.3**) subunit is found in the palau'amines and the konbu'acidins while the isophakellin (**1.14**) subunit is found in the styloguanidines.



1.21 donnazole A (Z=OH)
1.22 donnazole B (Z=Cl)

1.23 (–)-axinellamine A (R =H ; H, OH=β)
1.24 (–)-axinellamine B (R=H ; H, OH=α)
1.25 axinellamine C (R=Me ; H, OH=β)
1.26 axinellamine D (R=Me ; H, OH=α)

1.27 (–)-massadine (Z=OH)
1.28 (–)-massadine chloride (Z=Cl)

1.29 konbu'acidin A (X=H)
1.30 konbu'acidin B (X=Br)

1.2 (–)-palau'amine (X=H, Y=H)
1.31 bromopalau'amine (X=H, Y=Br)
1.32 dibromopalau'amine (X=Br, Y=Br)

1.33 styloguanidine (X=H, Y=H)
1.34 bromostyloguanidine (X = H, Y=Br)
1.35 dibromostyloguanidine (X = Br, Y=Br)

Figure 1.4 - Major cyclic oroidin dimers

Finally, in 2006, stylissadine A **1.36**, the ether-linked dimer of massadine **1.27**, was the first oroidin tetramer reported (Figure 1.5).[21]

Overall, marine sponges have crafted a beautiful family of alkaloids by an enantioselective cyclization, dimerization and even tetramerization of the oroidin simple building block followed by a range of both selective and seemingly random oxidation/rearrangement cascades. These fascinating molecules will continue to lure synthetic chemists to pursue their total synthesis.

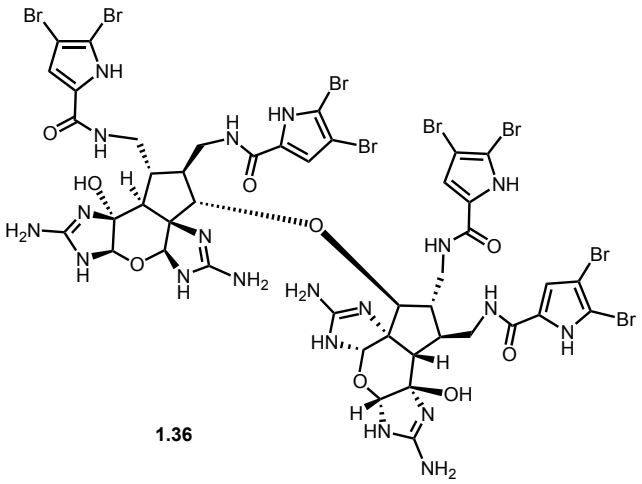
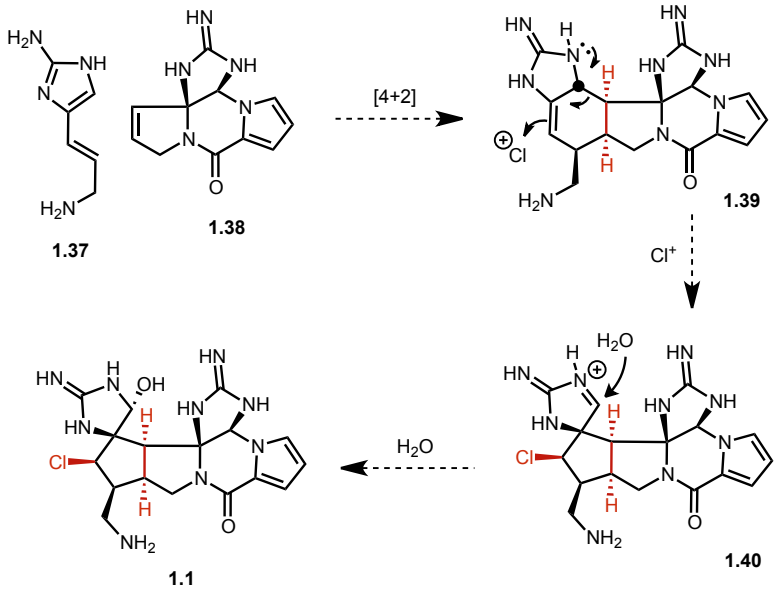


Figure 1.5 - Cyclic oroidin tetramer, stylissadine A **1.36**

1.2 Biosynthetic Origins of the Pyrrole-Imidazole Alkaloids

The entire PIA family is believed to arise in the organisms *via* biosynthetic pathways which make use of the simple metabolites such as oroidin **1.5**, clathrodin **1.6** and hymenidin **1.7**. The biosynthesis of these building blocks is not fully understood[22], however, it is obvious that dipeptides involving proline and another amino acid residue such as lysine, ornithine, histidine or arginine constitute a route for these early biosynthetic precursors.[23]

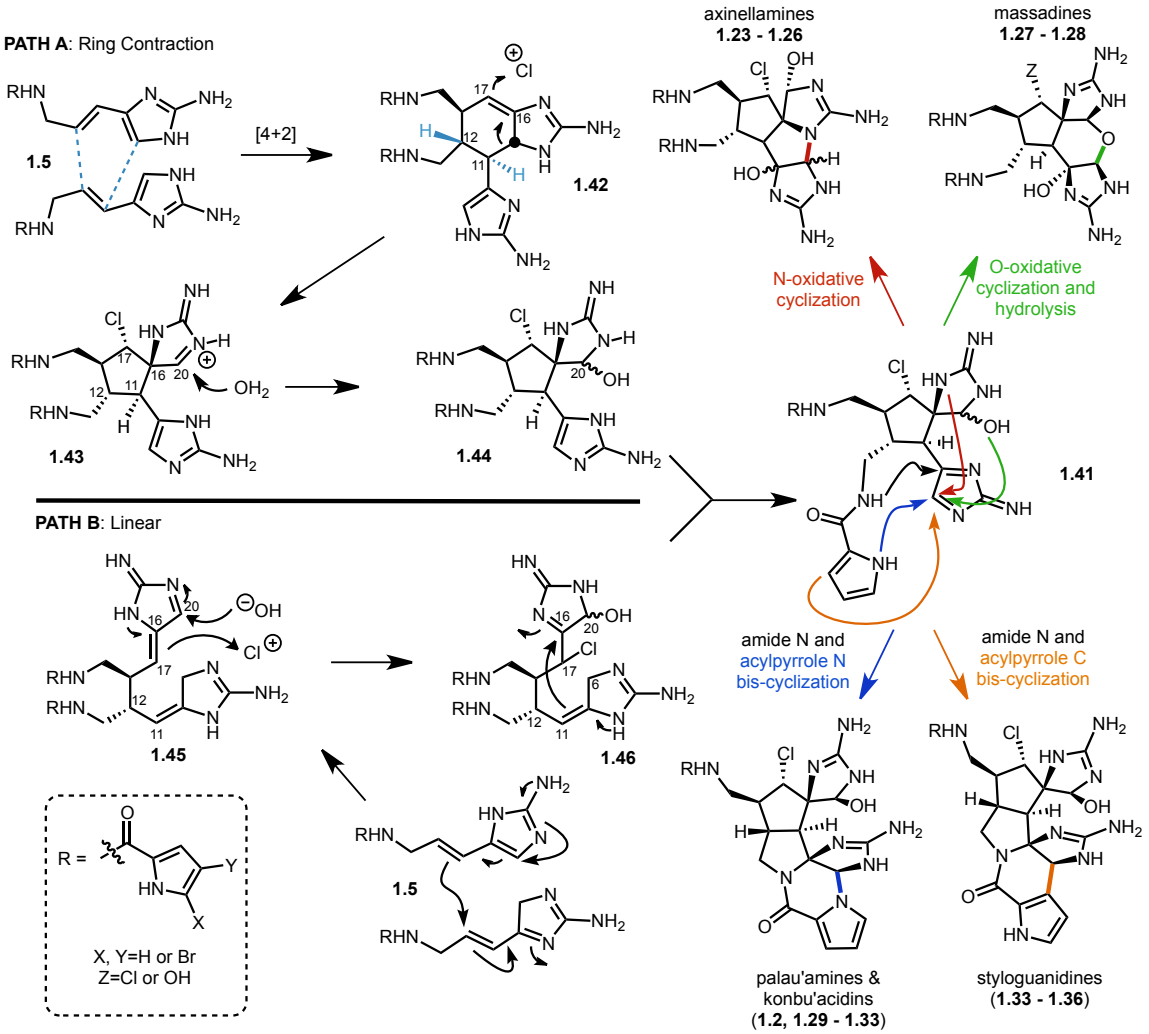
In 1998, one of the first biosynthetic proposals for the formation of major dimeric PIAs was advanced by Kinnel and Scheuer.[19] It was envisioned that a Diels-Alder cycloaddition between aminoimidazolyl propeneamine **1.37** and a hypothetical 'dihydrophakellin' dienophile **1.38** would give rise to the 5,6 *cis*-fused bicycle **1.39**. A subsequent chloroperoxidase-initiated oxidation/ring contraction event would deliver the hexacyclic core of the originally assigned structure of palau'amine **1.1**.



Scheme 1.1 - Original biosynthetic proposal for palau'amine

In 2000, Al-Mourabit and Potier proposed a universal chemical pathway for the formation of monomeric and dimeric PIA members which proved to be a landmark in the understanding of this class of alkaloids.[24] All the dimeric PIAs fit into a general chemical pathway, which begins with the enantioselective dimerization of oroidin or its congeners followed by a range of oxidation and rearrangement cascades. In 2007, when palau'amine **1.1** was recognized to possess a cyclopentane core with the same stereochemical configuration as the other congeners (*vide infra*), the biosynthetic proposal was readapted by Baran to better explain the conserved stereochemical relationship between all the dimeric members of the PIA family.[25] The hypothetical central branch point **1.41** (Scheme 1.2), dubbed "pre-axinellamine", is assembled from the dimerization and functionalization of two oroidin molecules. The first proposal (path A: ring contraction) to access "pre-axinellamine" **1.41** bears its conceptual roots in the earlier hypothesis for the genesis of the original structure of palau'amine (Scheme 1.1). Although ageliferin **1.19** was not proposed as a precursor by Kinnel and Scheuer (presumably because of the C11,C12 *cis*-relationship of the originally proposed structure of palau'amine **1.1**), the essence of the hypothesis remains valid. Two oroidin units can undergo a [4+2] cycloaddition to form the ageliferin tautomer **1.42** which furnishes "pre-axinellamine" intermediate **1.41** by reaction with an electrophilic chlorine source at C17, ring contraction *via* C11 bond migration from C20 to C16, hydration of the C20 position

and oxidation of the aminoimidazole ring. The second proposal (path B: linear) to access "pre-axinellamine" **1.41** involves the head-to-tail dimerization of oroidin tautomers generating the C18-C12 bond within intermediate **1.45**. This linear intermediate **1.45** could undergo an enzymatic chloro-hydroxylation, followed by intramolecular cyclization securing the C16-C11 bond followed by C6 oxidation to generate "pre-axinellamine" intermediate **1.41**.



Scheme 1.2 - Revised biosynthetic proposals for major PIA dimers

The "pre-axinellamine" intermediate **1.41** is hypothesized to follow one of four reaction pathways to generate the main classes of oroidin dimers. Closure of the spiro aminoimidazoline nitrogen atom onto the imine-containing amino imidazole (red arrow) leads to the axinellamines (**1.23-1.26**). Closure of the hemiaminal oxygen atom onto the adjacent aminoimidazole ring (green arrow) provides the massadines (**1.27-1.28**). The

closures of the amide nitrogen onto the aminoimidazole ring (black arrow) and either closure of the neighboring pyrrole onto the electrophilic aminoimidazole ring by the attack by the nitrogen atom (blue arrow) or the carbon atom (orange arrow) of the pyrrole furnishes the phakellin framework of the konbu'acidins (**1.29**, **1.30**) and the palau'amines (**1.2**, **1.31**, **1.32**) or the isophakellin framework that are found in the styloguanidines (**1.32**-**1.35**), respectively.

1.3 Biological Activity of Palau'amine

Palau'amine displays an array of biological activities.[19, 26] Alongside moderate antifungal and antibiotic activity together with low murine toxicity, palau'amine exhibits potent antitumor and immunosuppressive characteristics. Specifically, palau'amine is active against P-388 leukemia and A-549 lung adenocarcinoma cell lines and inhibits the mixed lymphocyte reaction at concentractions of 18 ng/mL and below, comparable to the immunosuppressant activity of cyclosporin A. Palau'amine is found to prevent the degradation of ubiquitinylated proteins, including the inhibitory-κB protein IκBα, in cell culture, which may be indicative of the potential mechanism by which these agents exhibit their exciting cytotoxic and immunosuppressive properties.[27]

The palau'amine congeners also possess a variety of biological profiles. Axinellamine A **1.23** has been shown to possess antibacterial activity against *Helicobacter pylori*, a bacterium linked to the development of duodenal ulcers and stomach cancer.[16] Styloguanidine **1.33** has been shown to be a powerful chitinase inhibitor[20] whereas konbu'acidin A **1.29** acts as an inhibitor of cyclin-dependant kinase 4.[18]

Acute Toxicity (LD_{50})	
intraperitoneal murine toxicity	13 mg/kg
Antifungal Activity	
inhibition of *Penicillium notatum* growth	24 mm zone at 50 μg/disk
Antibacterial Activity	
inhibition of *Staphylococcus aureus* growth	active at 10 μg/disk
inhibition of *Bacillus subtilus* growth	active at 10 μg/disk
Cytotoxicity (IC_{50})	
A-549 human alveolar basal epithelial cells	0.2 μg/mL
HT-29 colon carcinoma cells	2 μg/mL
KB cervical carcinoma cells	10 μg/mL
P-388 murine leukemia cells	0.1 μg/mL
Immunomodulation	
mixed lymphocyte reaction	< 18 ng/mL
murine lymphocyte assay	1.5 μg/mL

Table 1 - Biological activity for palau'amine

The monomeric cyclized PIA dibromophakellstatin **1.16** exhibits antineoplastic activity against melanoma SK-MEL-5 and colon KM20L2 cell lines with an ED_{50} of 0.11 μg/mL for both cell lines.[28] Moreover, agelastatin A **1.9** has been shown to be a potent antimetastatic agent through the inhibition of osteopontin-mediated malignant transformation and the arrest of the cell cycle and to be an inhibitor of glycogen synthase kinase-3b and might have some value in the treatment of Alzheimer's and other neurodegenerative diseases. [29] Finally, oroidin, the dominant PIA found in marine sponges, was shown to be a chemical defense deterrent against predation by coral reef fish.[30] It is believed that most PIAs play a defensive role in the sponges' ecology, however the concentrations of some PIAs are so low that they have a negligible deterrent effect. The obvious question as to why marine sponges synthesize such a large variety of complex natural products remains unanswered.

1.4 Structural Revision of Palau'amine

In 1993, Kinnel and Scheuer[14] reported the isolation of palau'amine **1.1** as an off-white amorphous solid (14 mg, 0.01% dry weight) from the marine sponge *Stylotella aurantium* collected in the Western Caroline Islands (Palau). At the time, the hexacyclic structure was the first major dimeric PIA to be isolated and was unequal in structural complexity to any other PIA isolated. It was proposed as structure **1.1** based on spectroscopic analysis and by comparison to known phakellin **1.3**, which contains the same tetracyclic subunit as palau'amine. The azabicyclo[3.3.0]octane DE ring system was unequivocally assigned as *cis*-fused, based on observed nOe correlations between H17 and H12 and H19a/b and between H11 and H18. However, the nOe correlation between H11 and H12 was surprisingly weak for a *cis*-fused ring junction. Nevertheless, H11, H12, H17 and H18 were all assigned to be on the same face of the cyclopentane E-ring core.

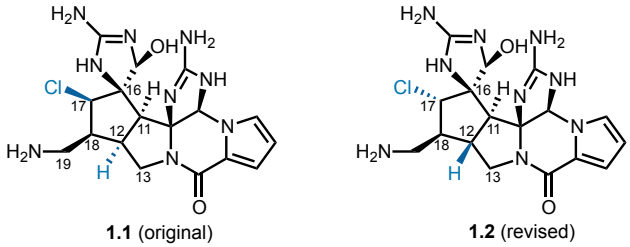


Figure 1.6 - Originally proposed (**1.1**) and revised (**1.2**) structures of palau'amine

Other major dimeric PIAs were subsequently discovered. The brominated palau'amines **1.31** and **1.32**,[19] the pyrrole-regioisomeric styloguanidines **1.33**-**1.35**,[20] and the N19-acylated congener konbu'acidin A **1.29**[18] were all structurally assigned based on direct comparison to palau'amine and were thus assigned to possess the *cis*-fused azabicyclo[3.3.0]octane ring core. In 1999, the structures of the axinellamines **1.23**-**1.26** were elucidated[16] to reveal they possessed an analogous carbon skeleton to the palau'amine congeners but incorporated a different stereoarray about the E-ring – diastereomeric at the C17 chloro and C12 ring junction stereogenic centers.[16] This raised the question from a biosynthetic perspective as to how such stereochemically different molecules are forged from molecules that comprise the same carbon skeleton. The *cis*-fused azabicyclo[3.3.0]octane ring system of palau'amine was universally accepted by the natural product community for well over a decade. The reason that the incorrect

structure of palau'amine persisted for so long is two-fold: *trans*-fused annulated five-membered rings are inherently rare in the literature[31] and the intuitive picture that a *cis*-fused 5,5-bicycle is thermodynamically more stable than the *trans*. Calculations have shown that the *trans*-fused system is significantly energetically disfavored over the *cis*-fused system by approximately 6.5 kcal/mol due to the increase in ring strain and conformational rigidity present in both rings.[25, 32]

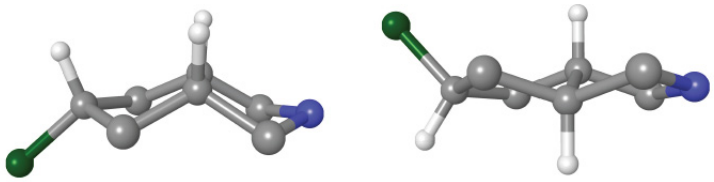


Figure 1.7 - Structural conformations of the central 3-azabicyclo[3.3.0]octane moiety in the original palau'amine configuration (left) and revised configuration (right)

The compelling story of the structural revision begins with relative configuration of the two bridgehead carbons of the central azabicyclo[3.3.0]octane ring system. The coupling constant of 14.1 Hz of the two protons, H11 and H12, was a central argument for the assignment of the junction as *cis*-fused. As a reference for the coupling constants between H11 and H12, the authors used leucodrine **1.47** whose coupling constant for the H4/H3 "analogous protons" is 12.4 Hz. Since palau'amine and leucodrine share little to no structural resemblance and there is a difference of almost 2 Hz in the coupling constant, the analogy between the two natural products is questionable.

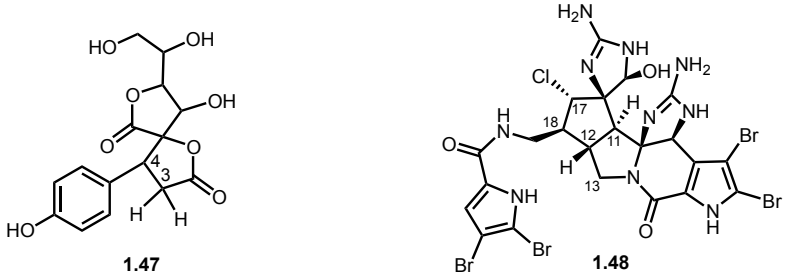
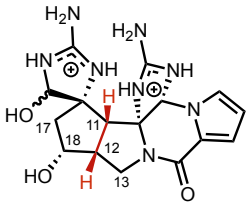


Figure 1.8 - Leucodrine **1.47** and tetrabromostyloguanidine **1.48**

In 2007, Köck[33], Quinn[21a, 34] and Matsunaga[35] called into question the structure of palau'amine. The structures of two new palau'amine congeners, tetrabromostyloguanidine **1.48** (published as carteramine A) and kondu'acidin B **1.30**, were reported as being epimeric at C12 leading to a *trans*-fused azabicyclo[3.3.0]octane

ring system and at C17 compared to the original structure of palau'amine. The ^{1}H and ^{13}C NMR data of both tetrabromostyloguanidine **1.48** and kondu'acidin B **1.30** showed that indeed both were closely related to styloguanidine **1.33** and konbu'acidin A **1.29**, however the NOESY data was in contradiction with the relative stereochemistry of the parent molecules. ROESY correlations from H18 to H11, H13α and H6 indicate that all these protons are on the same face and correlations from H12 to H17, H13β and H19 a/b suggest they are on the opposite face. This suggested that the relative stereochemistry published for the parent molecules was incorrect and since their structures were elucidated based on comparison to the published spectral data of palau'amine, it was also suggested that the relative stereochemistry for all the palau'amine congeners be revised.



1.49a/b

Figure 1.9 - Synthetic palau'amine derivatives by Overman

Furthermore, Overman and coworkers reported the synthesis of hexacyclic derivatives of palau'amine as hemiaminal epimers **1.49a/b**, which incorporated the two guanidine rings as well as the *cis*-fused azabicyclo[3.3.0]octane ring. Comparison of both ^{1}H and ^{13}C NMR of **1.49a/b** with those published for palau'amine revealed an overall close match. In sharp contrast, the H11/H12 vicinal coupling constants of **1.49a** and **1.49b** are 12.0 and 10.7 Hz, respectively whereas for palau'amine and its congeners, it is greater than 14 Hz. In addition, the NOESY spectra of **1.49a/b** revealed a strong correlation between the two ring junction protons, H11 and H12, and the absence or weak correlations for the 1,3-related pairs of protons H11/H18 and H11/H13β, respectively. This latter data contradicts the data published for palau'amine and its congeners, in which an NOE correlation between H11 and H12 was characterized as weak and correlations for H11/H13β and H11/H18 were reported. As an additional point of divergence, correlations between H13α and H18 were observed for **1.49a/b**.

In summary, a re-examination of the structure of palau'amine **1.1** prompted by the isolation of tetrabromostyloguanidine **1.48** and konbu'acidin B **1.30** as well as the

synthesis of deschloro-derivatives of palau'amine **1.49a/b** (*vide infra*) has led to a revised structure for palau'amine **1.2** and all its congeners (**1.29** and **1.31** to **1.35**).[36]

1.5 Synthetic Efforts Towards the Pyrrole-Imidazole Alkaloids

The PIA family consists of molecules with immense structural diversity and architectural complexity and thus, the synthetic efforts towards these polyheterocyclic nitrogen-rich marine alkaloids from numerous synthetic groups have led to a very prolific domain of study in chemical synthesis. While the synthesis of the simpler members of the PIA family was first accomplished in 1982, the total synthesis of the more complex dimeric natural products have only recently been realized. Furthermore, a majority of the synthetic work toward the PIAs is the subject of several reviews.[2, 29b, 37] Herein, selected accounts of the synthetic endeavors towards some members of the PIAs will be highlighted in the context of palau'amine and the construction of its key structural subunits.

1.5.1 Approaches Towards the Original Structure of Palau'amine

The original structure of palau'amine **1.1** received significant synthetic attention because of the unique stereoarray of the E-ring. The originally proposed all-*cis* stereoarray of **1.1** presented the most challenging aspect in the total synthesis of the natural product. Despite several synthetic efforts, no complete total synthesis of **1.1** has been reported. Herein, selected efforts that secured key structural subunits of **1.1** will be outlined.

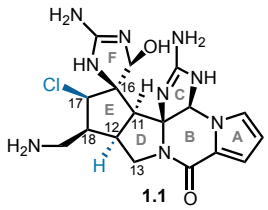
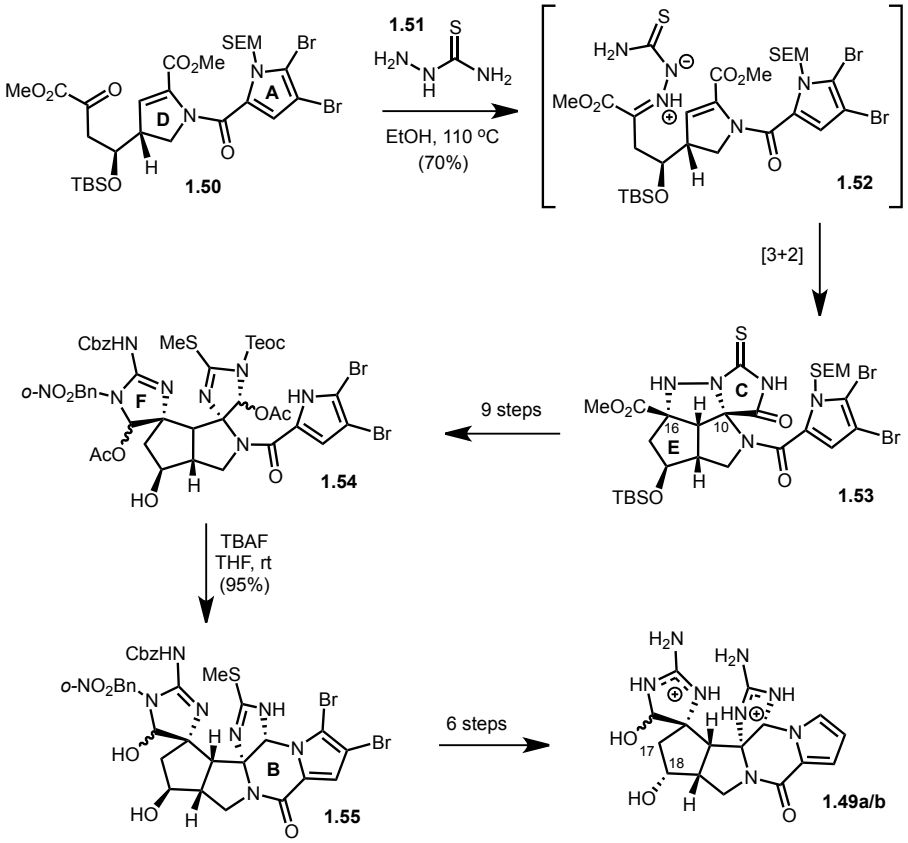


Figure 1.10 - Original structure of palau'amine (**1.1**)

1.5.1.1 Overman's Strategy

In 2007, Overman and coworkers[38] reported the synthesis of the most advanced synthetic intermediate structures (**1.49a/b**) which incorporate both guanidine functional groups and have the originally proposed *cis* configuration of the azabicyclo[3.3.0]octane

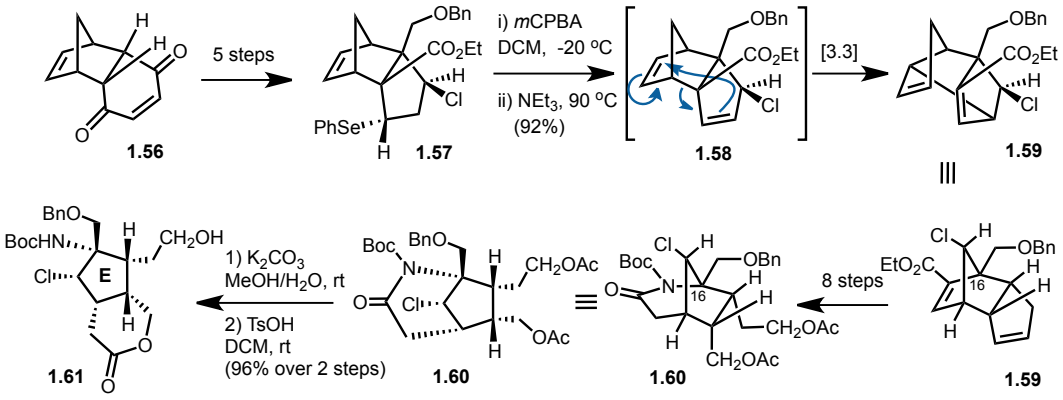
ring system. As stated previously, the comparison of the NMR data of these intermediates with the published data of palau'amine provided convincing evidence that was paramount for the structural revision of the marine alkaloids and fully supported the *trans*-configuration of the central azabicyclo[3.3.0]octane core. The strategy was to concisely forge the central *cis*-3-azabicyclo[3.3.0]octane core and the two spiro guanidine units *via* an intramolecular azomethine imine cycloaddition as to control the stereochemical relationship between the C11 and C12 ring fusion stereocenters, as well as the guanidine C10 spiro and C16 centers (Scheme 1.3). In the key sequence, thiosemicarbazide **1.51** was condensed onto *α*-ketoester **1.50** to generate azomethine imine **1.52** which undergoes a [3+2] cycloaddition afterwhich the pendant thiourea moiety cyclizes forming the spirocyclic hydantoin in tetracycle **1.53**. After both the C- and F-rings were separately constructed, the stage was set in **1.54** for a TBAF-mediated cyclization to form the ketopiperazine B-ring **1.55** and after 6 steps, heminal epimers **1.49a/b** were isolated. Only C17-chloro and the C18-aminomethylene functionalities remain to be installed on this scaffold to complete the total synthesis of **1.1**.



Scheme 1.3 - Overman's approach to original structure of palau'amine

1.5.1.2 Gin's Strategy

In 2008, Gin and coworkers[39] accessed the E-ring core of the original structure of palau'amine **1.1** through a [3.3]-sigmatropic rearrangement strategy of a bridged tricyclodecadiene. The sequence commenced with the Diels-Alder cycloadduct **1.56**, which was further elaborated to **1.57**. Selenide oxidation and elimination generated the 1,5-diene system **1.58** which spontaneously underwent a [3.3]-sigmatropic rearrangement to form the 1,5-diene isomer **1.59**. The nitrogen functionality was painstakingly installed at the sterically congested C16 quaternary carbon center *via* a Beckmann ring expansion furnishing **1.60** which was elaborated to reveal the less-strained E-ring framework **1.61**. This Diels-Alder/[3.3]-sigmatropic rearrangement strategy was used to construct a hexasubstituted cyclopentane, which maps directly onto the cyclopentane core of **1.1**, and, gratifyingly, could also be adapted to access the revised E-ring motif of **1.2** (*vide infra*).

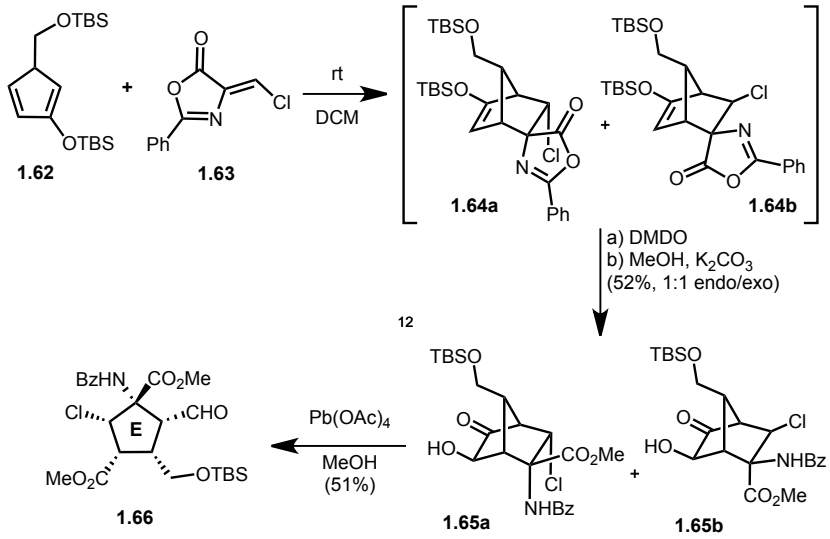


Scheme 1.4 - Gin's approach towards original E-ring core

1.5.1.3 Gleason's Strategy

In 2008, our lab[40] reported the synthesis of subunit **1.66**, the fully functionalized E-ring core with the all-*cis* stereoarray of the original structure of (+)-palau'amine **1.1**. Our strategy towards palau'amine was to devise an *exo*-selective Diels-Alder reaction of a 5-substituted cyclopentadiene with a chlorinated dienophile with a nitrogen at the α-position embedded in a heterocyclic motif, which would allow access to the guanidine F-ring. Ring opening of the newly formed cyclohexene would subsequently reveal a hexasubstituted cyclopentane in which five of the substituents are on one face of the molecule. In the forward direction, the [4+2] cycloaddition of **1.62** with

chloromethyleneoxazolone **1.63** yielded a 1:1 mixture of cycloadducts **1.64a/b** which were then subjected to enol oxidation by treatment with DMDO followed by methanolysis of the oxazolone to afford chromatographically stable and separable hydroxyl ketones **1.65a/b**. The oxidative cleavage of **1.65a** by $Pb(OAc)_4$ afforded the hexasubstituted cyclopentane **1.66**, which maps directly onto the cyclopentane core of **1.1**. We also demonstrated that a siloxy group at the 2-position greatly stabilizes 5-substituted cyclopentadienes towards [1,5]-sigmatropic shift thus allowing cyclopentadienes such as **1.62** to be used as practical and synthetically attractive diene components in Diels-Alder cycloaddition reactions.



Scheme 1.5 - Gleason's approach to original E-ring core

1.5.2 Approaches Towards the Revised Structure of Palau'amine

Since the structural revision of palau'amine at C12 and C17, a frenzy of activity has occurred in attempts to access the new stereoarray of the E-ring of the redefined target. Finally, palau'amine **1.2** succumbed to total synthesis in 2010. In addition, other related natural products equal in complexity that share the substitution pattern of the cyclopentane ring have been accessed and are also discussed in this section.

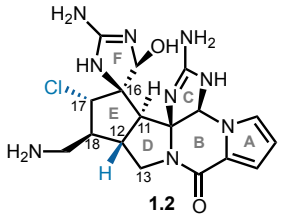
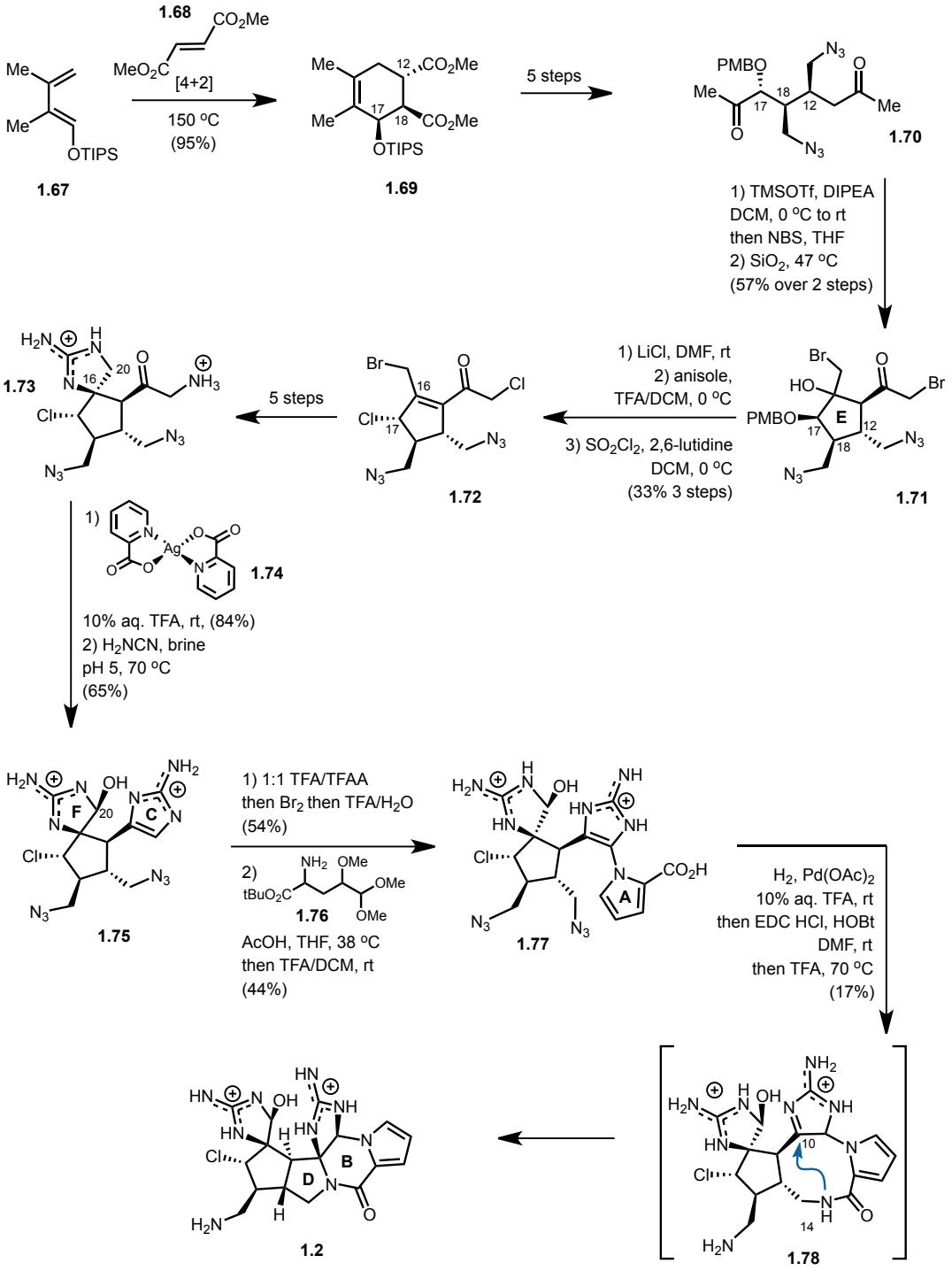


Figure 1.11 - Revised structure of palau'amine (**1.2**)

1.5.2.1 Baran's Strategy

In 2010, Baran and coworkers[41] published the first and only total synthesis of palau'amine (**1.2**). The overall approach involved accessing a highly functionalized cyclopentane construct which could be used as the foundation for the synthesis of the carbogenic skeleton of the major dimeric alkaloids **1.23**, **1.24**, **1.27** and **1.2** whose synthesis could be achieved by varying the modes of cyclization (Scheme 1.2). The synthesis commenced with a Diels-Alder reaction to furnish cycloadduct **1.69** thereby setting three of the key stereochemical relationships (C12, C17, C18) that would eventually manifest themselves in the cyclopentane core. The newly formed cyclohexene was ruptured and an intramolecular aldol addition secured the cyclopentane E-ring core as dibromide **1.71**. The installation of the chloride at C17 in **1.72** proceeded by an invertive displacement of the alcohol and also resulted in the formation of an allylic bromide which acted as a synthetic handle to install the spirocyclic guanidine at C16. A highlight of the synthesis is the strategic use of silver(II) picolinate **1.74**, a methodology that was developed in the course of this group's previous synthetic studies towards the axinellamines **1.23** and **1.24**, and one that minimizes redox adjustments and enabled the chemo- and regio-selective installation of the sensitive C-20 hemiaminal late in the synthesis. The pyrrole A-ring was introduced *via* surrogate **1.76** affording tetracyclic pyrrole-acid **1.77** and, upon reduction of the azide groups to the diamine, a macrolactamization to "macro-palau'amine" **1.78** was performed. This set the stage for the most notable feature of the total synthesis, an across-ring bond stitching of the 9-membered lactam leading to the final 5,6 BD-ring system. This transannular N14-C10 cyclization also secured the *trans*-fused azabicyclo[3.3.0]octane ring system to deliver (±)-palau'amine **1.2**. In 2011, Baran and coworkers[42] published the enantioselective total syntheses of five dimeric PIAs including (−)-palau'amine. The synthesis of the

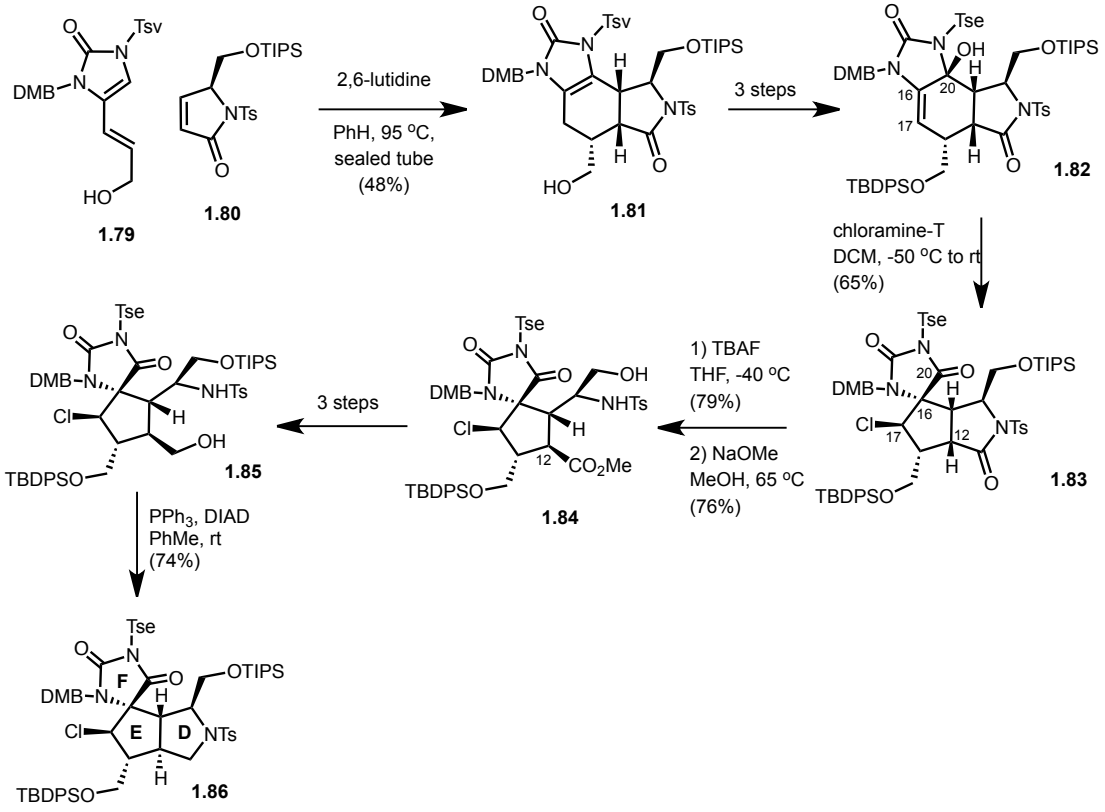
natural enantiomer of each natural product was enabled by a catalytic and stereoselective Diels-Alder reaction similar to the one described above.



Scheme 1.6 - Baran's total synthesis of (±)-palau'amine

1.5.2.2 Romo's Strategy

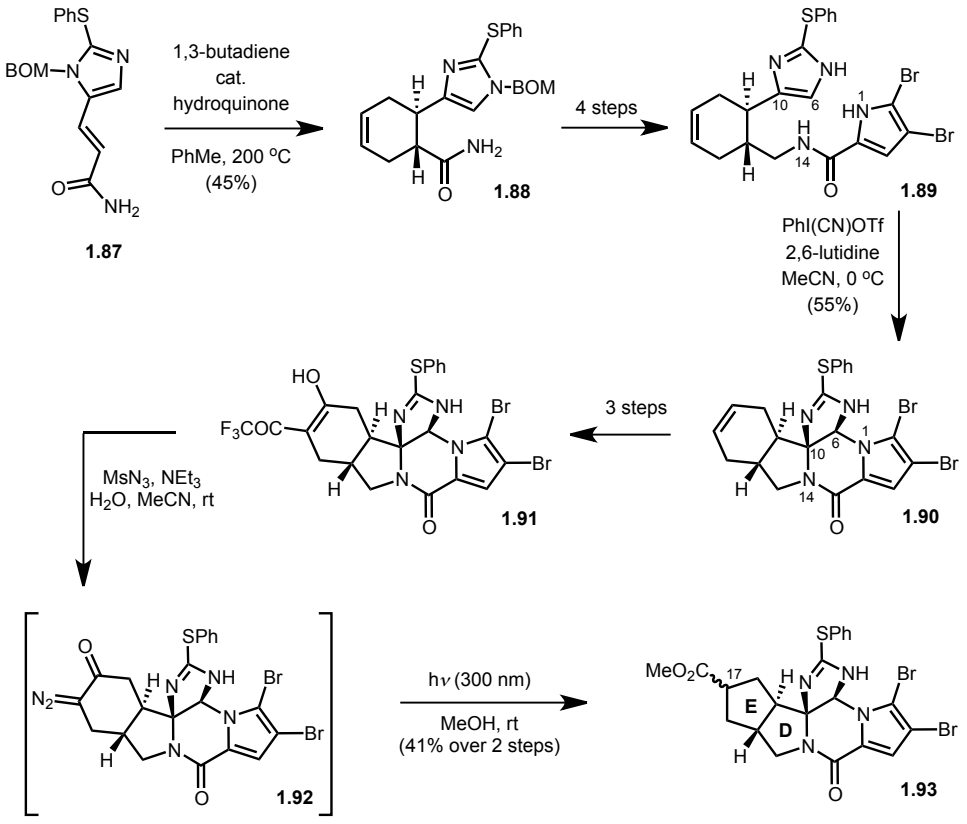
In 2008, Romo and coworkers[43] published the first synthetic route towards the azabicyclo[3.3.0]octane core that contains the crucial *trans*-ring junction. The strategy was inspired by the original biosynthetic pathway (Scheme 1.1) in which the EF-ring system is forged in a chloride-initiated oxidation/ring contraction event. The highly functionalized Diels-Alder adduct **1.81** was exposed to DMDO to afford the vinyl carbinol urea **1.82**. Treatment of **1.82** with chloramine-T allows for the formation of spirocyclic hydantoin **1.83**, supposedly *via* initial intermolecular chlorination from the convex face of vinyl hemiaminal **1.82** followed by a suprafacial 1,2-alkyl shift, a sequence which sets the stereochemistry at C16 and C17 and also forms the *cis*-fused 5,5 azabicyclic ring system. In order to correct the C12 stereocenter and access the *trans*-ring junction, a ring opening/C12-epimerization/intramolecular Mitsunobu displacement was performed thus forging the *trans*-fused azabicyclo[3.3.0]octane core in **1.86** and forming the DEF-subunit of **1.2**.



Scheme 1.7 - Romo's approach to the revised DEF-ring subunit

1.5.2.3 Feldman's Strategy

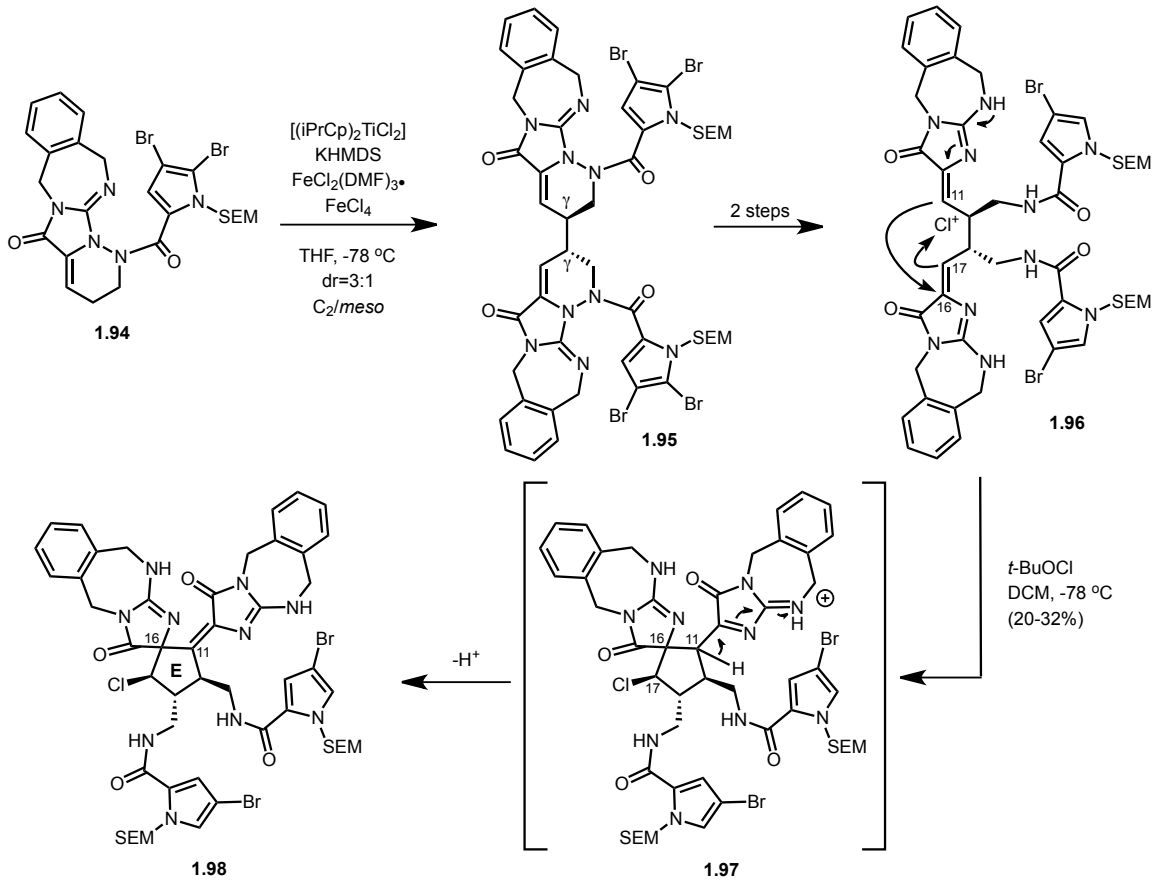
In 2010, Feldman and coworkers[44] reported a method to assemble the *trans*-azabicyclo[3.3.0]octane unit of dibromopalau'amine based on a biomimetic oxidative cyclization, similar to the hypothesis in Scheme 1.2 and greatly inspired from their synthesis of dibromophakellin (Scheme 1.18 – *vide infra*). The Diels-Alder-derived oroidin surrogate **1.89** was treated with Stang's reagent, PhI(CN)OTf, leading to the formation of pentacycle **1.89** *via* activation of the thioimidazolone and subsequent N14-C10 bond formation followed by N1-C6 ring closure. Contraction of the cyclohexene ring of the *trans*-fused system to the desired cyclopentane was accomplished *via* a photochemical Wolff rearrangement of α-diazo ketone **1.92** providing the cyclopentane **1.93** as a mixture of C17-epimers. Regrettably, the Pummerer bicyclization on a construct analogous to **1.89** featuring the requisite *trans*-cyclopentane ring was met with failure, presumably due to the high degree of torsional strain involved in the cyclization event.



Scheme 1.8 - Feldman's approach to the DE-ring junction and phakellin subunit of **1.2**

1.5.2.4 Harran's Strategy

In 2009, Harran and coworkers[45] reported the synthesis of the E-ring core through a biomimetic strategy that bears similarity to the linear biosynthetic hypothesis (Scheme 1.2). The approach capitalizes on the veiled symmetry within the PIA dimers and allows for the construction a spirocyclopentane EF-ring motif *via* a halogenative desymmetrization event. The C_2-symmetric γ,γ-dimer product **1.95** contains the entire carbon and heterocyclic skeleton of the dimeric PIAs. In the key step, when bis-alkylidene **1.96** was treated with *t*-BuOCl, an oxidative cyclization effected the formation of the C17-chloro bond as well as C11-C16 bond of spirocyclic intermediate **1.97**, which after an elimination generates the E-ring core **1.98** of the major PIA dimers. Unfortunately, the pitfalls of this strategy are that the 1,3-benzodiazepine guanidine masking groups that were intended to facilitate the oxidative spirocyclization proved to be difficult to remove and the geometry of the alkylidene at C11 and the relative stereochemistry at C16 were not assigned. More recently in 2012, Harran and coworkers[46] published the total synthesis of nonchlorinated (±)-axinellamine A *via* a biomimetic strategy, which bears great resemblance to this earlier report.

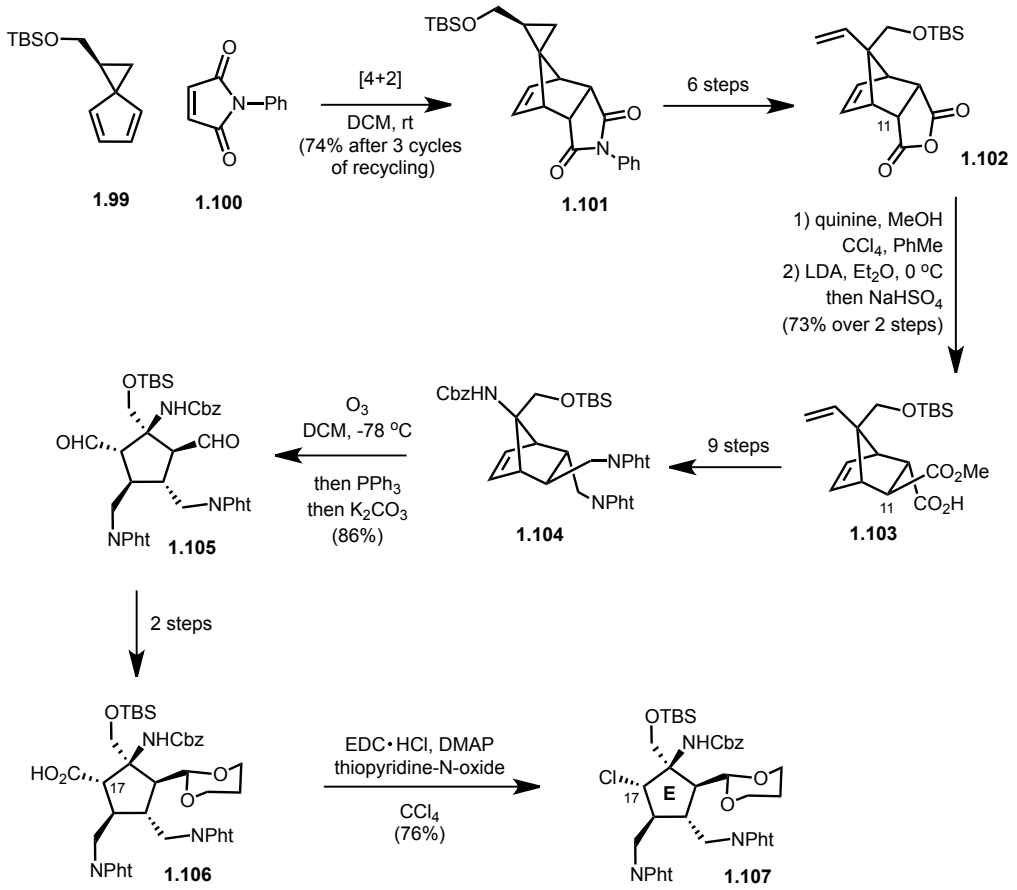


Scheme 1.9 - Harran's approach to the E-ring core

1.5.2.5 Carreira's Strategy

In 2000, Carreira and coworkers[47] disclosed the first enantioselective synthesis of the fully functionalized cyclopentane core of the axinellamines **1.23**-**1.26** which also turned out to be the common E-ring precursor for the revised structure of palau'amine. The strategy exploits a Diels-Alder cycloaddition to furnish a cycloadduct, which upon desymmetrization at an advanced stage, permits access to the persubstituted E-ring core. The Diels-Alder derived *meso*-cyclic anhydride **1.102** was desymmetrized using quinine and a selective C11-epimerization of the methyl ester gave the *trans* acid-ester **1.103**. After the installation of the three *N*-based substituents at C10, C13 and C18, the cyclohexene in **1.104** was ruptured under ozonolytic conditions to reveal the fully functionalized cyclopentane core as the thermodynamically favored *trans*-dial **1.105**. A highlight of the synthesis is the late-stage installation of the hindered chlorine at C17 *via*

homolytic cleavage of the corresponding Barton ester of **1.106**, decarboxylation and finally chlorine abstraction from the solvent. More recently, Carreira and coworkers[48] published a route to access the cyclopentane core of massadine **1.27**, which bears great resemblance to this earlier work.

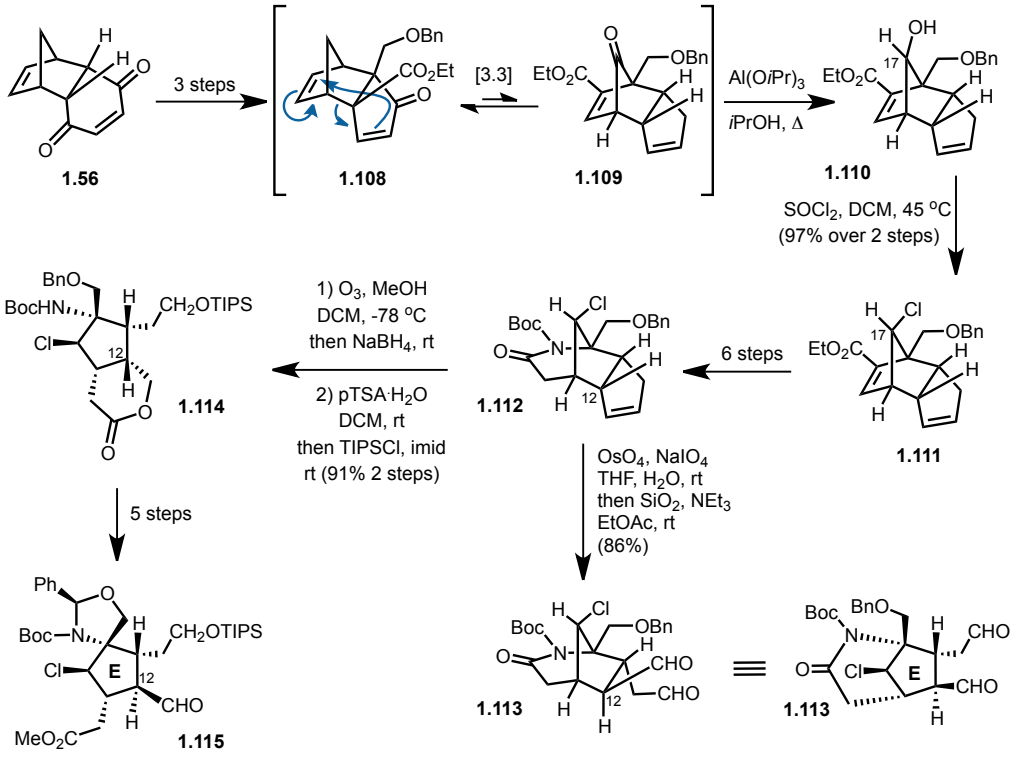


Scheme 1.10 - Carreira's approach to the E-ring core

1.5.2.6 Gin's Strategy

In 2008, in the same publication discussed in section 1.5.1.2, Gin and coworkers[39] adapted their [3.3]-sigmatropic rearrangement strategy of a bridged tricyclodecadiene to access the revised E-ring core of **1.2**. Enone **1.108**, accessed from the common intermediate hydroquinone **1.56** (Scheme 1.5), was found to exist as a dynamic mixture with its rearranged counterpart **1.109**. Subjecting the mixture to a Meerwein-Ponndorf-Verley reduction of the bridging ketone of **1.109** generated the secondary alcohol of **1.110**. Installation of the C17 chlorine with the revised

stereochemistry of **1.2** was accomplished by a retentive substitution of the hydroxyl group with a chloride to furnish **1.111**. The correction of the C12 center could be performed on either constructs **1.112** or **1.114** *via* an epimerization to generate thermodynamically favored *trans*-dial **1.113** or the spirocyclic intermediate of the E-ring core **1.115**, respectively.



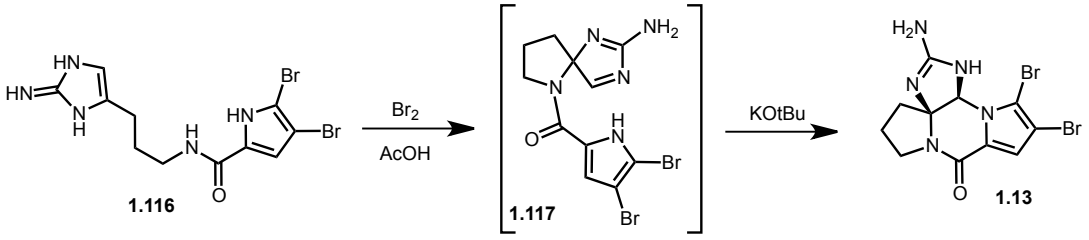
Scheme 1.11 - Gin's approach to the revised E-ring core

1.5.3 Approaches Towards the Monomeric Pyrrole-Imidazole Alkaloids

The cyclized monomeric PIAs have also received significant attention from the synthetic community due to their interesting biological activity and compact structures. The syntheses of the tetracyclic alkaloids phakellin **1.3**, phakellstatin **1.4** and brominated analogues have also provided a training ground for construction of the ABCD subunit of the palau'amine.

1.5.3.1 Büchi's Strategy

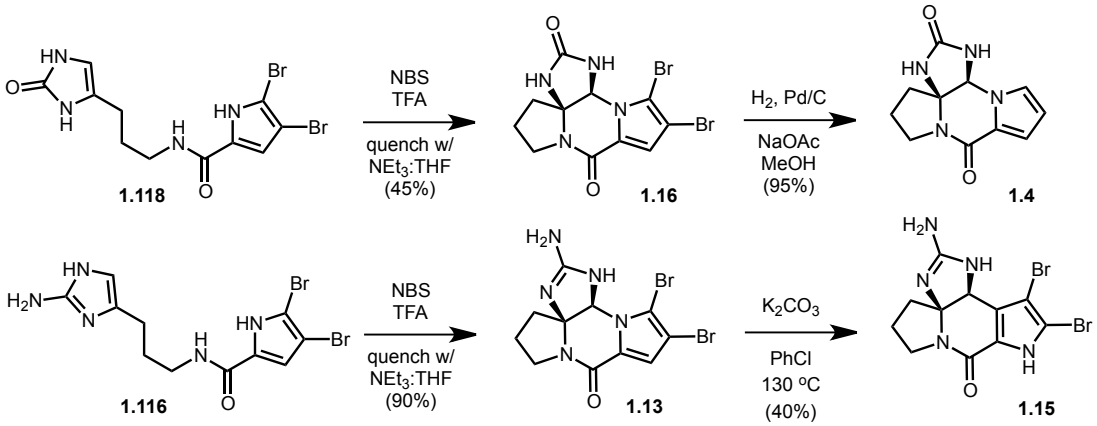
In 1982, Büchi and coworkers[49] described a biomimetic synthesis of dibromophakellin **1.13**. Dihydrooroidin **1.116** was oxidized with elemental bromine to yield unstable spirocyclic intermediate **1.117** which could be converted quantitatively to dibromophakellin **1.13** upon treatment with potassium *tert*-butoxide. This pioneering work by Büchi laid the groundwork for the bioinspired synthesis of other PIA members.



Scheme 1.12 - Büchi's total synthesis of (±)-phakellin

1.5.3.2 Horne's Strategy

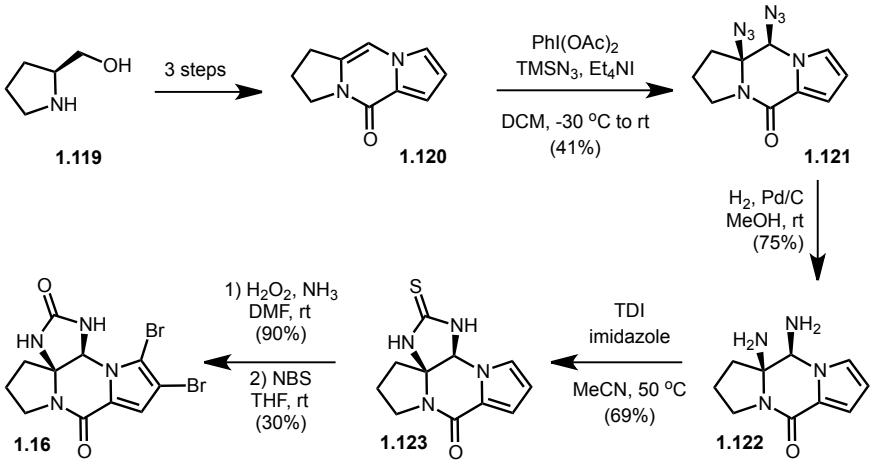
In 2002, Horne and coworkers[50] reported the concise synthesis of four monomeric PIAs based on the biomimetic oxidative cyclization originally developed by Büchi. The use of a less reactive brominating agent, NBS, in conjunction with a stronger acid, TFA, substantially increased the yield and allowed products to be obtained in both the imidazole and aminoimidazole series. Under this set of conditions, dibromophakellstatin **1.16** and dibromophakellin **1.13** were formed and were converted to phakellstatin **1.4** by simple hydrogenolysis and dibromoisophakellin **1.15** by heating in the presence of K_2CO_3 to effect the N to C rearrangement, respectively.



Scheme 1.13 - Horne's total synthesis of (±)-dibromophakellstatin, (±)-phakellstatin, (±)-dibromophakellin, (±)-dibromoisophakellin

1.5.3.3 Austin's Strategy

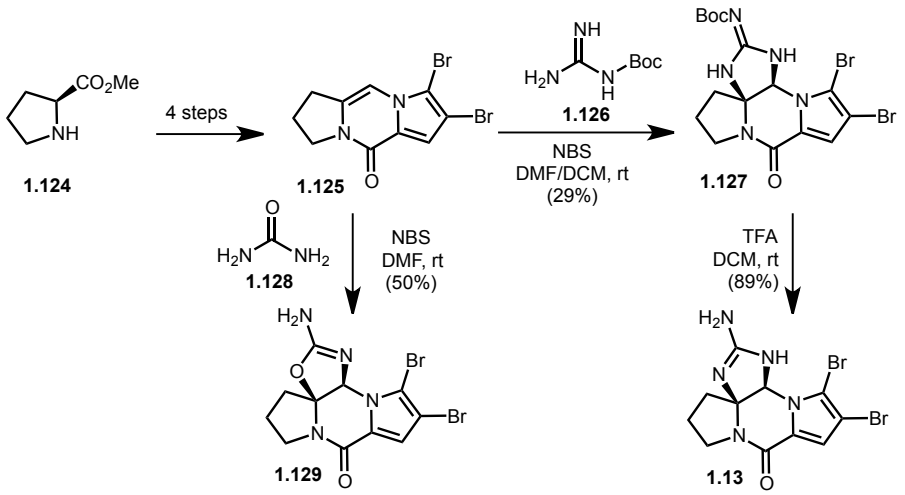
In 2004, Austin and coworkers[51] synthesized dibromophakellstatin **1.16** by late-stage incorporation of the urea C-ring employing a key *syn*-diazide intermediate. A hypervalent iodine-mediated diazidation of the alkene of dihydrodipyrrolopyrazinone **1.120** furnished diazide **1.121**. Subsequent hydrogenation to the *syn*-diamine and condensation with thiocarbonylimidazole provided tetracyclic thiourea **1.123**, which was converted to dibromophakellstatin **1.16**.



Scheme 1.14 - Austin's total synthesis of (±)-dibromophakellstatin

1.5.3.4 Tepe's Strategy

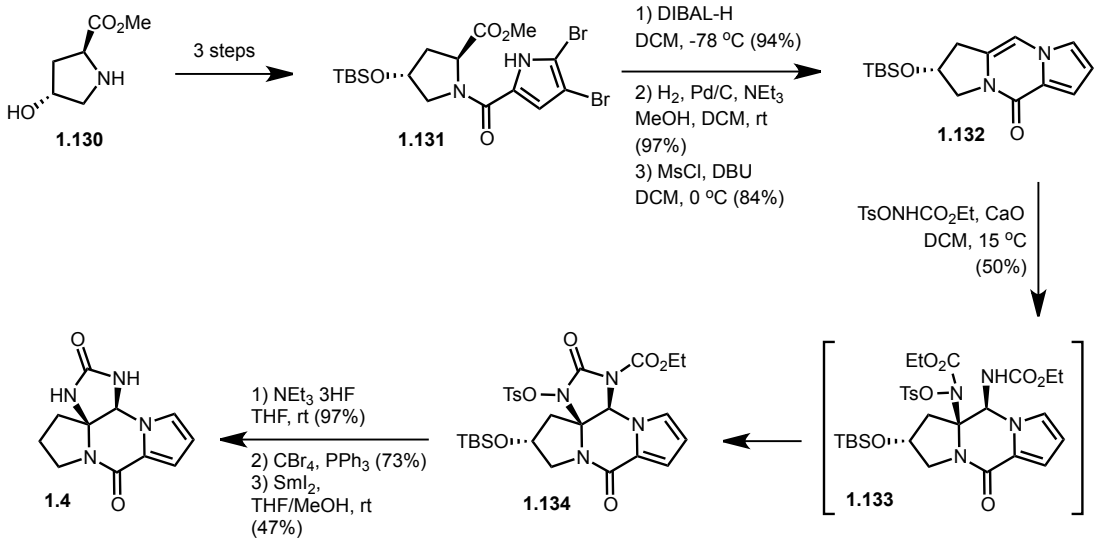
In 2011, Tepe and coworkers[52] published an expedient synthesis of dibromophakellin **1.13** *via* functionalization of an alkene of a dihydrodipyrrolopyrazinone construct – similar to Austin's strategy. The key step involves the brominium-mediated guanylation of the olefin of pyrazinone **1.125** to furnish dibromophakellin **1.13** after deprotection. The obvious extension of this methodology to access the phakellstatins proved difficult as the analogous reaction with urea has only yielded unwanted tetracyclic oxazoline **1.129**.



Scheme 1.15 - Tepe's total synthesis of (±)-dibromophakellstatin

1.5.3.5 Lindel's Strategy

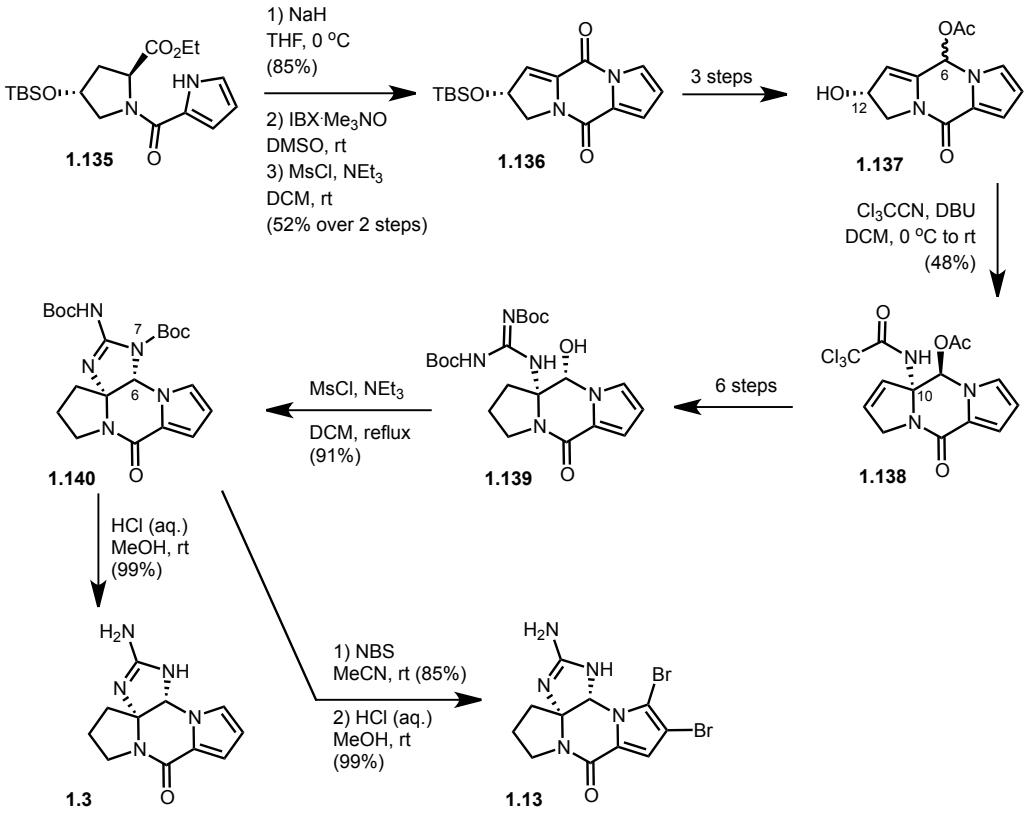
In 2007, Lindel and coworkers[28c, 53] reported the enantioselective synthesis of (−)-phakellstatin **1.4**, based on seminal work first disclosed in 2005 in which the imidazolinone C-ring is introduced *via* nitrene chemistry. Dihydrodipyrrolopyrazinone **1.132** was accessed in a straightforward fashion from hydroxy-proline derivative **1.130** whose hydroxyl functionality was protected as the TBS silyl ether to impart steric control during the C-ring formation. The key step in this strategy involves a three-component imidazolinone annulation with enamide **1.132** and two equivalents of an *in situ* generated electrophilic *N*-acyl nitrene derived from ethyl-*N*-tosyloxycarbamate and garners tetracycle **1.134** after condensation. For the endgame of the synthesis, a SmI_2 reduction concomitantly removed the chiral handle and *N*-deprotected the urea C-ring to afford (−)-phakellstatin **1.4**.



Scheme 1.16 - Lindel's total synthesis of (−)-phakellstatin

1.5.3.6 Nagasawa's Strategy

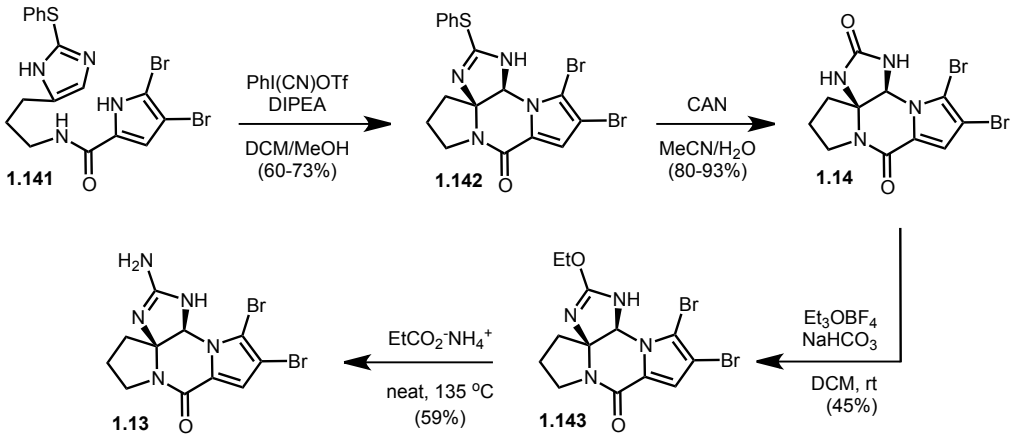
In 2009, Nagasawa and coworkers[54] reported the enantioselective synthesis of both (+)-dibromophakellin **1.13** and (+)-phakellin **1.3**. The approach was to set the stereochemistry of the guanidine C-ring *via* the transfer of the chirality from C12 to C10 using a [3.3]-sigmatropic rearrangement. Allylic alcohol **1.137** was treated with trichloroacetonitrile to afford an allylic trichloroacetimidate which underwent the enamide-type Overman rearrangement spontaneously generating aminal **1.138**. The N7-C6 cyclization of the C-ring guanidine was effected when carbinolamine **1.139** was treated with methanesulfonyl chloride thus generating the tetracyclic framework of **1.13** and **1.3**.



Scheme 1.17 - Nagasawa's total synthesis of (+)-phakellin and (+)-dibromophakellin

1.5.3.7 Feldman's Strategy

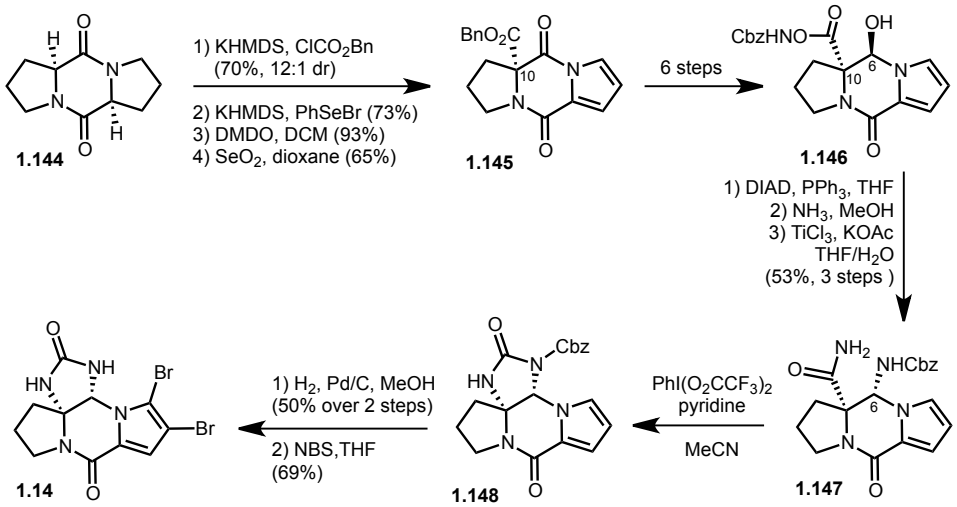
In 2007, Feldman and co-workers[55] published the concise synthesis of dibromophakellstatin **1.16**, based on a biomimetic approach in which N14-C10 and N1-C6 bonds are formed concomitantly. The key Pummerer-like oxidative cyclization was again effected using Stang's reagent to afford tetracyclic thioimidate **1.142** from thioimidazole-containing dihydrooroidin derivative **1.141**. Oxidative hydrolysis with CAN afforded dibromophakellin **1.14** which was converted to dibromophakellstatin **1.13** *via* the intermediacy of *O*-alkylated urea **1.143** according to a procedure developed by Jacobi.[56]



Scheme 1.18 - Feldman's total synthesis of (±)-dibromophakellin

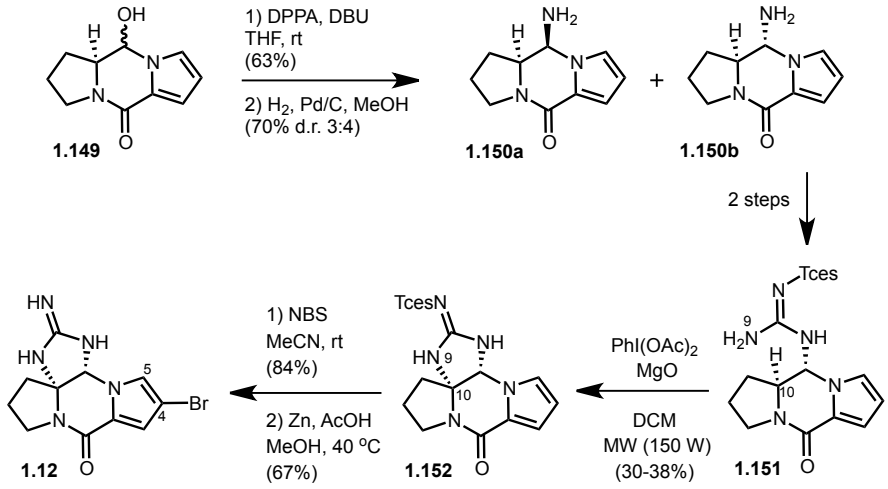
1.5.3.8 Romo's Strategy

In 2003, Romo and coworkers[57] reported the enantioselective synthesis of both (+)-dibromophakellstatin **1.14** and (+)-phakellstatin **1.4**. The strategy was based on a late-stage incorporation of the imidazolinone ring *via* an asymmetric acylative desymmetrization of C_2-symmetric diketopiperazine **1.144**, (*S,S*)-cyclo (Pro, Pro). The route commenced with the desymmetrization process entailing the acylation followed by a three step process to provide tricyclic pyrrole **1.145**. The *N*-moiety at C6 of β-aminoamide **1.147** was introduced by the application of an intramolecular Mitsunobu reaction and the formation of the cyclic urea was accomplished *via* a Hofmann rearrangement to afford dibromophakellstatin **1.14** after hydrogenolysis and bromination.



Scheme 1.19 - Romo's total synthesis of (+)-phakellstatin and (+)-dibromophakellstatin

In 2008, Romo and coworkers[58] published a concise enantioselective synthesis of (+)-bromophakellin **1.12**. The initial idea for the strategy was to form the N9-C10 bond of the cyclic guanidine moiety based on rhodium-catalyzed C-H amination chemistry previously developed by Du Bois and coworkers.[59] However it was demonstrated that a rhodium(II) catalyst was not required for the key transformation and that a simple oxidative cyclization mechanism was in operation furnishing *N*-Tces phakellin **1.152** from tricyclic guanidine **1.151**. Bromination followed by reduction, resulting in cleavage of the Tces group and loss of the C5 bromo substituent, afforded (+)-bromophakellin **1.12**.



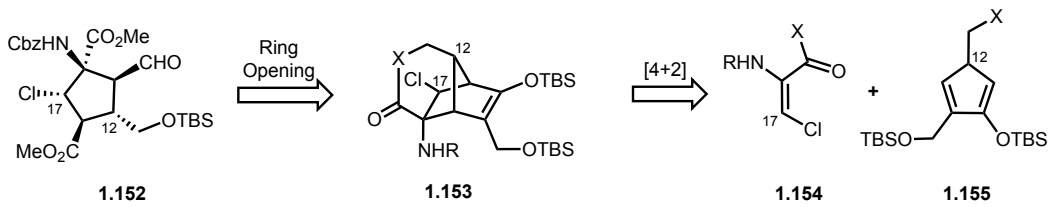
Scheme 1.20 - Romo's total synthesis of (+)-monobromophakellin

1.6 Retrosynthetic Analysis of Palau'amine

As outlined above, the main synthetic challenges in palau'amine are the construction of the hexasubstituted cyclopentane E-ring core as well as the elaboration of remaining ABCD rings which correspond to the phakellin subunit. To further complicate matters, the structural revision palau'amine has linked these two complex subunits *via* the [3.3.0]-azabicyclic ring system (ED-rings) that possesses the thermodynamically disfavored *trans*-stereochemical configuration.

In initial work, the cyclopentane core had attracted much attention from the synthetic community as it possessed most of the stereochemical complexity of palau'amine. The principal focus of our synthetic efforts towards palau'amine as well as those of Gin, Baran, Romo and Carreira discussed in the chapter has been to secure the fully decorated E-ring core early on. All these strategies employed the power of the Diels-Alder cycloaddition to ultimately access the desired cyclopentane with all five of its stereogenic centers.

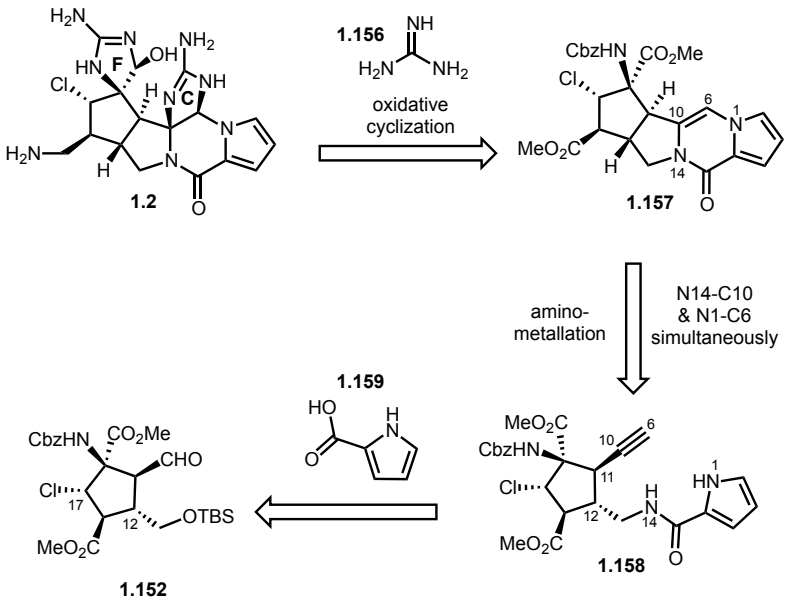
While our original Diels-Alder strategy delivered the hexasubstituted E-ring with the all-*cis* stereoarray of **1.1** (Scheme 1.5), this strategy would require revision to deal with the new stereochemistry at the C17-chloro and C12-ring junction. In our original synthetic plan, the C17 stereocenter was set during the Diels-Alder cycloaddition and was controlled from the *Z* double bond geometry of the dienophile (Scheme 1.5). Changing from a *Z* to an *E* dienophile would therefore allow access to the newly proposed C17 stereochemistry. Access to a *trans* dienophile as in **1.154** is not expected to be difficult and many synthetic options are available (Scheme 1.21). The absolute stereochemistry of the C12 stereocenter in our synthesis of the original E-ring stereoarray was set by approach of the dienophile away from the silyloxy methyl group. While it could be possible to adjust this stereocenter after cycloaddition through an oxidation-epimerization pathway, it would be more efficient to obtain the desired relative stereochemistry directly from the Diels-Alder reaction. While unlikely in an intermolecular cycloaddition, a properly devised intramolecular Diels-Alder might force the dienophile to approach the diene *syn* to the 5-substituent and deliver a tricyclic adduct such as **1.153** (Scheme 1.21). We assumed that a quick modification of our original Diels-Alder methodology could ultimately deliver cyclopentane ring core **1.152**.



1.152 **1.153** **1.154** **1.155**

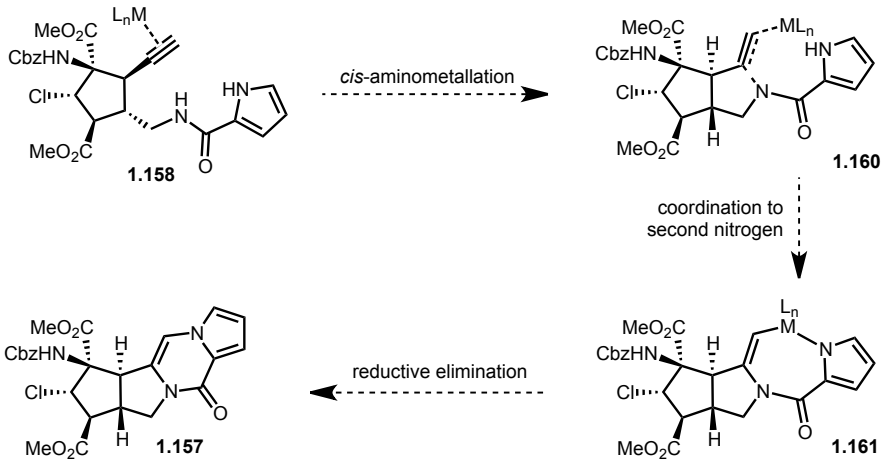
Scheme 1.21 - Retrosynthesis of revised E-ring core from an intramolecular Diels-Alder

Ever since the structural revision of palau'amine, the major synthetic challenge has shifted. In 2007, the new priority was to tackle the quintessential *trans*-fused [3.3.0]-azabicyclic ring system and a novel synthetic strategy was designed to secure the strained *trans*-fused [3.3.0]-azabicyclic ring system of the revised structure of palau'amine. It was envisaged that **1.2** could be accessed from the tetracyclic pyrazinone **1.157** *via* a late-stage incorporation of two units of guanidine **1.156** (Scheme 1.22). It was expected that the installation of the C-ring guanidine could be appended at C10 and C6 *via* some set of conditions similar to those used in the phakellin class of compounds, *vide supra*. Retrosynthetically, the ketopiperazine B-ring and the [3.3.0]-azabicyclic ring system could be stitched up in a single step in which the N14-C10 and N1-C6 bonds are formed concomitantly *via* a metal-mediated diamination reaction between the pyrrole N and the amide N and a tethered alkyne. The modern toolbox of metal-facilitated hydroamination methods to add nitrogen across non-activated unsaturated bonds received much attention in the recent literature and seemed like a tenable disconnection for palau'amine. Transition metals such as palladium, copper, nickel, platinum and gold have been used extensively in diamination and hydroamination chemistry. This transition metal must first activate the unsaturated bond towards nucleophilic attack by the first nitrogen and then become displaced by the second nitrogen nucleophile in a net M^{n+2} to M^{n} reduction. This atom-economical and expedient step was an attractive starting point for our investigation to build the B-ring of palau'amine (and by extension phakellin and phakellstatin) because much mechanistic work had already been accomplished in the fields of hydramination and diamination. Finally, **1.158** could be accessed *via* the appropriate functional group interconversion of the handles at C11 – alkynylative homologation of the aldehyde using either the Ohira-Bestmann or the Corey-Fuchs protocol – and incorporation of pyrrole carboxylic acid **1.159** at C12 on elaborated cyclopentane **1.152**.



Scheme 1.22 - Initial retrosynthetic analysis of palau'amine

There are two important considerations for the implementation of the key diamination step (Scheme 1.23). The first critical issue is that the unsaturated bond insertion into the M-N bond needs to proceed *via cis*-aminometallation to ensure proper orientation of the metal center to allow for coordination with the incoming second nitrogen as in **1.161**. The second vital consideration is that the second ring closure must be kinetically favored over premature reductive elimination of the intermediate organometallic species. The second step of the diamination is strongly dependent on the electronic nature of the second nitrogen and on the choice of the organometallic reagent. In our case, the nitrogen of the pyrrole needs to be able to coordinate to the organometallic center forming metallocycle **1.161** which upon reductive elimination of the metal would afford the desired pyrazinone B-ring in tetracyclic construct **1.157**. Achieving this would require an opportune choice of both transition metal and reaction conditions (i.e. base, solvent, additive, stoichiometry, reoxidant).



Scheme 1.23 - Proposed diamination pathway

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Chapter 2.

Trans-fused 5,5 Azabicycles: Diamination, Amidyl Radicals and Conjugate Addition

2.1 Introduction

Chapter 2 describes the gradual evolution of our synthetic strategy toward the *trans*-fused 5,5-azabicylic motif found in the revised structure of palau'amine (**1.2**). The initial route begins with an extension of previously developed diaminometalation chemistry but this approach suffered from poor substrate scope. Our route also takes a detour through amidyl radical chemistry but, once more, this method proved to be severely limited. The ultimately successful strategy to secure the targeted *trans*-fused azabicyclo[3.3.0]octane ring system was *via* a seemingly simple 1,4-conjugate addition onto an ynoate ester.

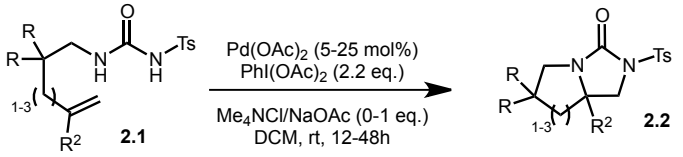
2.2 Intramolecular Diamination

Alkene diamination, initially explored in the 1970s with stoichiometric metal promoters, has experienced a resurgence in the last decade.[1] The synthesis of a saturated nitrogen heterocycle and concomitant introduction of two nitrogen functionalities across an alkene can be enabled in a very direct and efficient manner using transition metal catalysis. This section will briefly present several methods in which transition metals (palladium, copper and nickel) are employed to catalyze olefin diamination reactions for the synthesis of saturated heterocyclic compounds.[2]

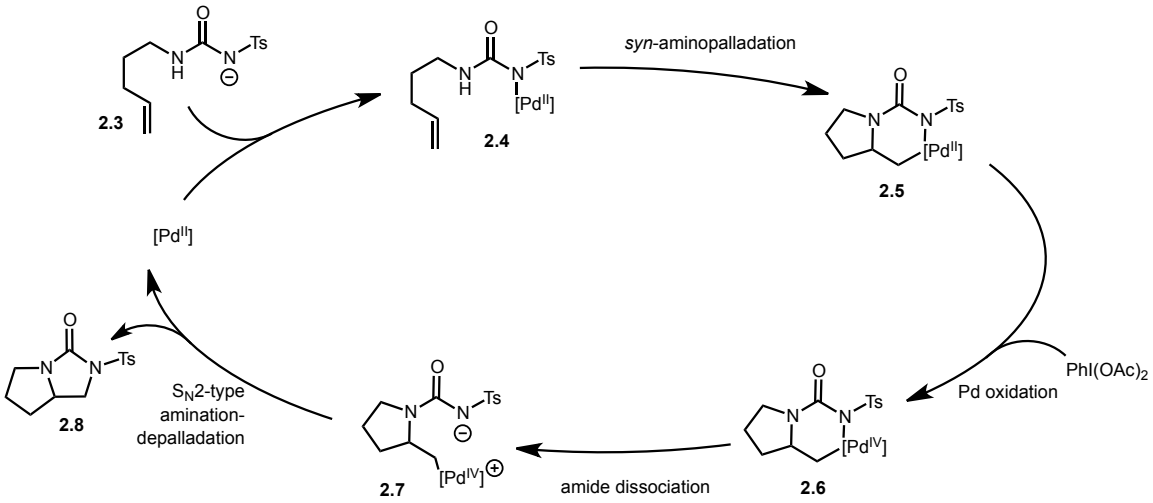
2.2.1 Palladium-Catalyzed Diamination

In 2005, Muñiz and coworkers[3] published the first catalytic intramolecular diamination of unactivated alkenes using catalytic palladium with $PhI(OAc)_2$ as a stoichiometric oxidant. This reaction generated fused 5,5-, 6,5-, and 7,5-bicyclic ureas from unsaturated *N*-tosylureas in high yields (Scheme 2.1). A mechanism was proposed to involve a $[Pd^{II}]/[Pd^{IV}]$ catalytic cycle and is shown in Scheme 2.2.[4] First, the deprotonation of the tosylamide N-H moiety occurs and is followed by coordination of the urea to palladium in **2.4** which allows the alkene to enter the coordination sphere of the palladium. Formation of palladacycle **2.5** via *syn*-aminopalladation is the rate-limiting step in the process and is followed by a rapid oxidation by $PhI(OAc)_2$ of the tetrahedral palladium(II) intermediate to a octahedral palladium(IV) species. Release of the tosylamide from the coordination sphere of the palladium generates a cationic octahedral

palladium(IV) state in **2.7**, enhancing the electrophilicity of the palladated methylene group. This permits for concomitant S_N2-type nucleophilic substitution by the tosyl amide and reductive depalladation forming cyclic urea **2.8**. This second step of the diamination is strongly dependent on the electronic nature of the second nitrogen. An electron-withdrawing sulfonyl-based group is essential to generate the required nucleophilicity to the nitrogen.



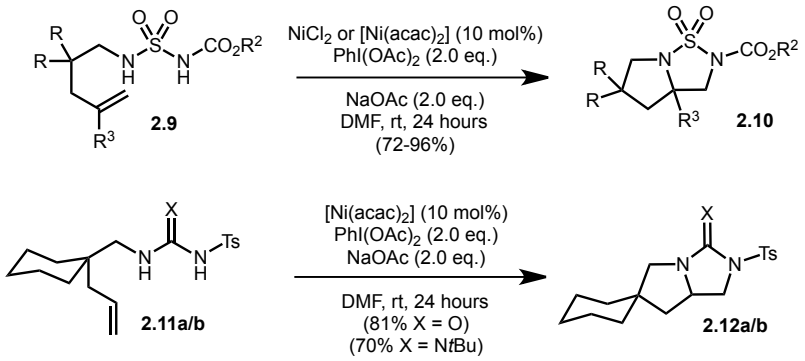
Scheme 2.1 - Pd-catalyzed diamination of unactivated alkenes



Scheme 2.2 - Proposed catalytic cycle for Pd-catalyzed intramolecular diamination

2.2.2 Nickel-Catalyzed Diamination

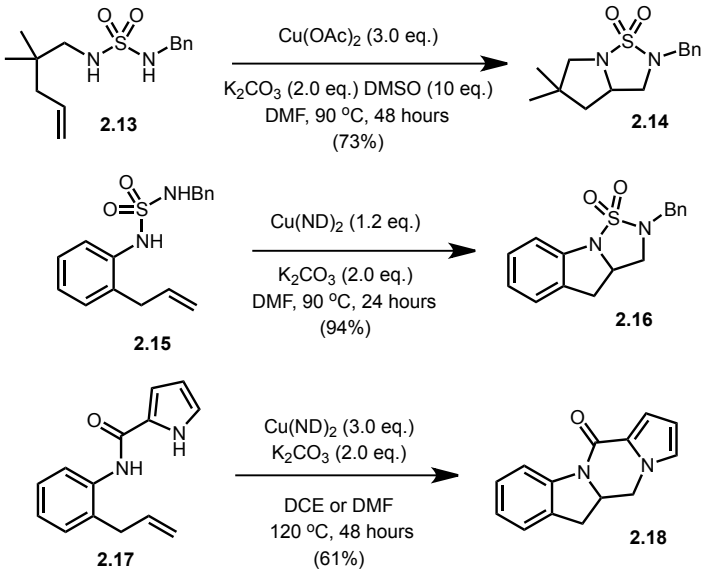
In 2007, Muñiz and coworkers[5] disclosed that nickel complexes could be used to catalyze the intramolecular diamination of unsaturated sulfamides, ureas and guanidines across terminal and 1,1-disubstituted alkenes (Scheme 2.3). The mechanism is believed to proceed analogously to the palladium-catalyzed variant: first C-N bond formation *via* aminometalation and second oxidative C_{alkyl}-N bond formation *via* [Ni^{III}] species from oxidation with $PhI(OAc)_2$.



Scheme 2.3 - Ni-catalyzed diamination of unactivated alkenes

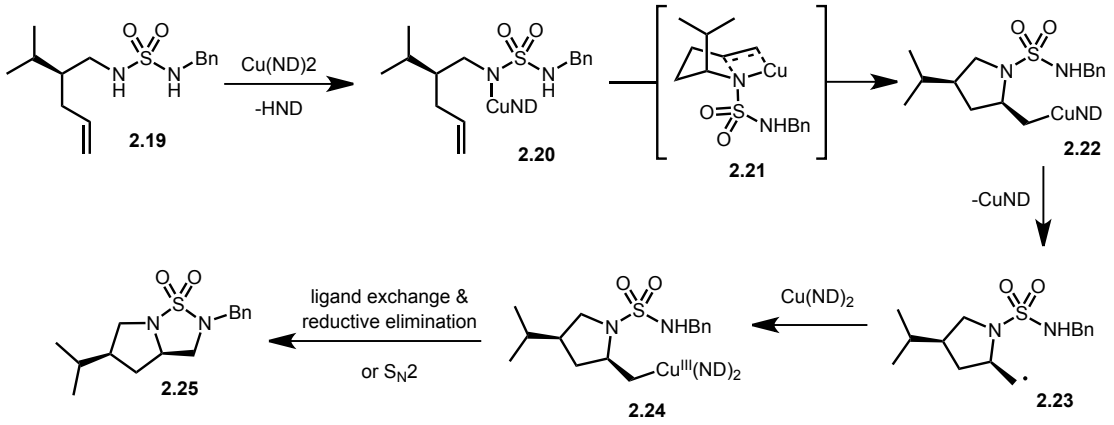
2.2.3 Copper-Promoted Diamination

In 2005, Chemler and coworkers[6] published the diamination of alkenes using less expensive copper complexes as reaction promoters. Copper(II)-promoted diaminations of unactivated alkenes with sulfamides, sulfonamides, amides and ureas enabled the synthesis of pyrrolidines and indolines (Scheme 2.4). The reactions were initially performed with $Cu(OAc)_2$ in a mixture of DMF and DMSO. However, in 2007, improved reaction conditions using $Cu(ND)_2$ in DCE or DMF were disclosed.[7] Of great interest, the pyrroloamide substrate **2.17** was shown to undergo diamination and form tetracyclic indoline **2.18**. This is, to the best of our knowledge, the first example in which a 6-membered ring is formed in the context of a diamination reaction and also in which the second nitrogen nucleophile was from a pyrrole and did not require activation by a sulfonyl group. This pyrrolo-pyrazinone motif forged in **2.18** greatly resembles the AB-ring system of palau'amine.



Scheme 2.4 - Cu-promoted diamination of unactivated olefins

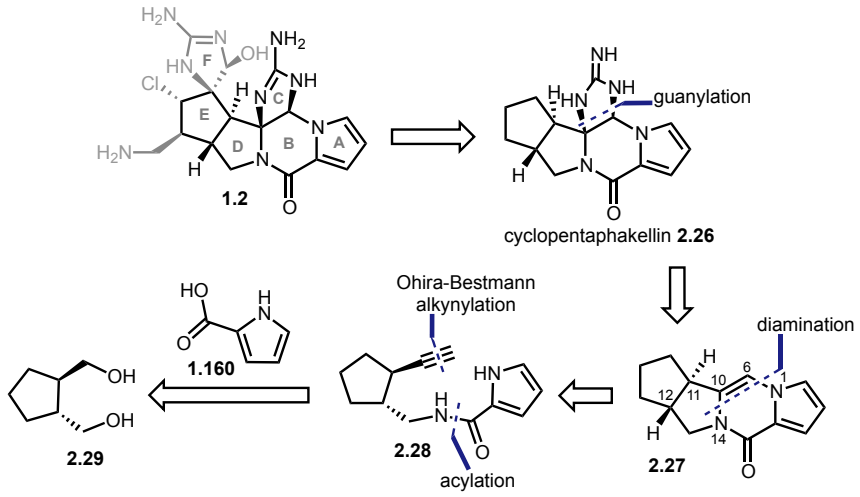
Based on reaction diastereoselectivity and isotopic labeling studies, the reaction mechanism was proposed to commence with the deprotonation of the sulfonamide nitrogen allowing for ligand exchange with the Cu(II) species. Coordination of the alkene would lead to stereoselective *cis*-aminocupration *via* transition state **2.21** forming *cis*-pyrolidine **2.22** and the unstable organocopper(II) intermediate would undergo C–[Cu(II)] bond homolysis. The resulting primary carbon radical combines with a second equivalent of [Cu(II)] to afford [Cu(III)] intermediate **2.24**. It is unclear whether, at this stage, the tethered amine would coordinate to the [Cu(III)] center which then reductively eliminates to form the new C–N bond in **2.25** or whether the amine simply displaces the [Cu(III)] in an S_N2 fashion.[8]



Scheme 2.5 - Proposed mechanism for Cu-promoted diamination

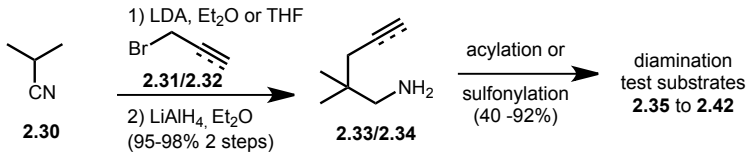
2.2.4 Extension Towards Palau'amine

Our goal was to develop an expedient route to the ABCD-ring system of palau'amine (**1.2**) whilst also tackling the *trans*-fused [3.3.0]-azabicyclic DE-ring core (Scheme 2.6). The structure of the natural product phakellin (**1.3**), with an identical ABCD-framework relative to palau'amine, was considered as the basis for a scaffold of the envisioned palau'amine model target. Fusing a simple cyclopentane (E-ring) onto the D-ring of phakellin with a *trans*-stereochemical configuration at C11 and C12 would lead to model target, cyclopentaphakellin **2.26**, mimicking the pentacyclic ring system of the revised structure of palau'amine (**1.2**). The synthesis of **2.26** would, in the context of a natural product-like molecule, require the development of novel methods to access the *trans*-fused [3.3.0]-bicyclic ring system as well as the rest of the phakellin heterocyclic ring structure. Retrosynthetically, it was envisaged that cyclopentaphakellin **2.26** could be accessed from the tetracyclic pyrazinone **2.27** *via* an oxidative incorporation of a guanidine unit. Multiple methods have recently been published that allow introduction of a guanidine C-ring onto related tricyclic pyrazinones (Schemes 1.14 to 1.16). The ketopiperazine B-ring and the [3.3.0]-azabicyclic ring system could be stitched up in a single step in which the N14-C10 and N1-C6 bonds are formed concomitantly *via* a metal-mediated diamination reaction between the pyrrole nitrogen atom and the amide nitrogen atom and a tethered alkyne. Ynamide **2.28** could be accessed from 1,2-bis(hydroxymethyl)cyclopentane **2.29** *via* functional group interconversion of each handle: at C11, an alkynylative homologation after oxidation to the corresponding aldehyde and at C12, coupling of the primary amine with pyrrole carboxylic acid **1.160**.



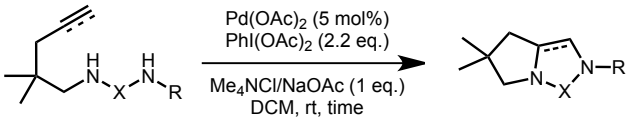
Scheme 2.6 - Retrosynthetic analysis for cyclopentaphakellin model target

We expected pyrroloamide substrates such as **2.28** to be readily prepared from 1,2-*trans*-bis(hydromethyl)cyclopentane **2.29**. However, their synthesis would require a minimum of nine steps (two steps for the diol synthesis plus seven for elaborating each arm of the cyclopentane). Given their unknown scope, we opted for a simpler acyclic ynamide model system which could help establish whether the transition metal mediated diamination methodologies could be applied to the palau'amine framework without the added strain associated with the formation of a *trans* 5,5-ring system. None of the diamination protocols published included diamine substrates tethered to unactivated alkynes; therefore, to determine whether the diamination methodologies could be extended to alkynes, both alkenyl and alkynyl diamination substrates were synthesized. The simple acyclic model system was obtained in high yields in two straightforward steps (Scheme 2.7). Isobutyronitrile **2.30** was alkylated either with allyl bromide **2.31** or propargyl bromide **2.32** and subsequent reduction with lithium aluminum hydride furnished enamine **2.33** and ynamine **2.34**, respectively, in excellent yields.[9] All diamination substrates could be easily obtained either *via* acylation or sulfonylation to access the urea subtrates **2.35**, **2.37**,[4] amides **2.36, 2.38-2.40** and sulfamides **2.41** and **2.42**, respectively. Further improvements of these procedures were made upon scale-up: the synthesis of both the enamine **2.33** and ynamine **2.34** was carried out in decagram scale and a only single column chromatography at the end of the three steps was necessary to afford the diamination substrates.



Scheme 2.7 - Synthesis of diamination test substrates

Substrates **2.35** to **2.40** were subjected to the reported palladium-catalyzed diamination conditions. In accordance with published results, *N*-tosyl urea substrate **2.35** afforded bicyclic urea **2.43** in 63% yield (Table 2.1 entry 1). Unfortunately, all other substrates tested under the same reaction conditions proved to be either unreactive or decomposed slowly over the course of the reaction. To explore whether a 5,6-bicyclic system – such as the palau'amine BD-ring system – could be forged *via* this method, the *N*-tosylglycine substrate **2.36** was evaluated as the one-carbon-extended version of the control substrate **2.35** (entry 2). Trace amounts (<5% based on ^{1}H NMR) of the desired 5,6-bicyclic system **2.44** could be observed only when the reaction was conducted for 48 hours using 20 mol% of the palladium catalyst (entry 3), suggesting that the six-membered ring annulation is a considerably more difficult process – possibly due to slow formation of a putative 7-membered ring palladacycle (analogous to **2.6** in Scheme 2.2). Olefinic pyrroloamide substrates **2.38** and **2.39** were designed to investigate whether the pyrrole nitrogen could be a competent nucleophile in the diamination process. When **2.38** was subjected to the reaction conditions, no product of a diamination process was observed and the starting material was recovered (entry 5). Pyrroloamide **2.39** was completely consumed under the reaction conditions and resulted in undefined decomposition, possibly due to side-reactions involving oxidation of the dibromopyrrole (entry 6). In order to examine whether unactivated olefins could be swapped for unactivated alkynes, alkynyl substrates **2.37** and **2.40** were also examined. No reaction was observed with alkynyl urea **2.37** (entry 4) and unsurprisingly, the use of alkynyl pyrroloamide **2.40** led to decomposition (entry 6).



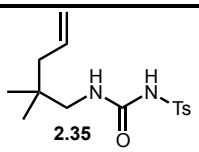
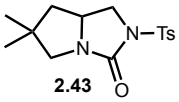
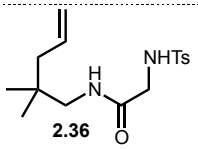
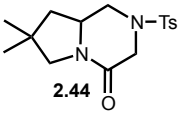
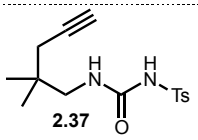
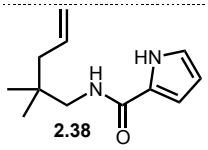
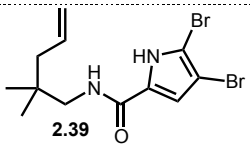
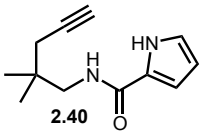
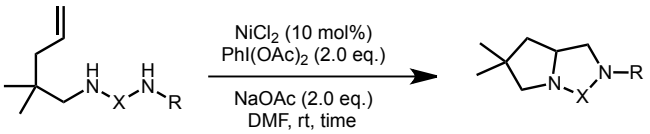
entry	diamine	time (h)	outcome
1	 **2.35**	16	 **2.43** 63% Y[a]
2	 **2.36**	48	 **2.44** n.d.[b]
3	 **2.37**	48	N.R.
4	 **2.38**	30	N.R.
5	 **2.39**	16	decomposition
6	 **2.40**	30	decomposition

Table 2.1 - Palladium-catalyzed diamination screen on urea and pyrrolyl substrates

[a] Refers to isolated yield [b] Reaction conducted with 20 mol% $Pd(OAc)_2$ and <5% of desired diamination product was detected by ^{1}H-NMR

Muñiz's nickel-catalyzed diamination protocol was quickly investigated and subsequently ruled out as a viable method. The sulfamide and urea control substrates **2.41** and **2.35** were equally reactive under the published reaction conditions and the expected bicyclic products were observed by ^{1}H NMR (Table 2.2 entries 1 and 2). However, when olefinic pyrroloamide substrate **2.38** was treated under the same reaction conditions, no diamination product was observed.



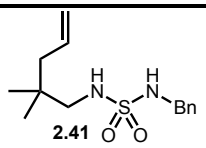
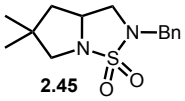
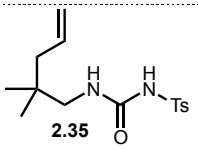
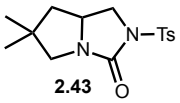
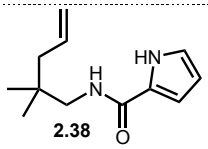
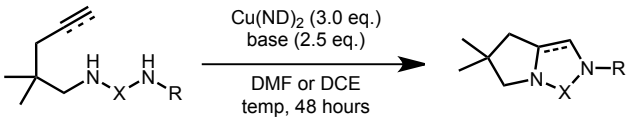
entry	diamine	time (h)	outcome
1	 **2.41**	18	 **2.45** 60%[a]
2	 **2.35**	18	 **2.43** 50%[a]
3	 **2.38**	48	N.R.

Table 2.2 - Nickel-catalyzed diamination screen on pyrrolyl substrates

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

Our attention turned next to the methodology described by Chemler and coworkers in which an organic soluble copper(II) salt, copper (II) neodecanoate [$Cu(ND)_2$], was used to mediate the diamination of vicinal amino units across unactivated alkenes. The sulfamide control substrate **2.41** was exposed to the reported reaction conditions and the pyrrolidine adduct **2.45** was isolated in 75-76% yield (Table 2.3 entry 1). In sharp contrast to the result reported with the aniline-derived amidopyrrole **2.17** (Scheme 2.4), pyrroloamide **2.38** failed to afford any desired annulation product under the standard conditions as well to other modified conditions (entries 2 to 5). A slight increase in reaction temperature led to the formation of an intractable mixture of products presumably due to the thermal decomposition of the pyrrole moiety. We reasoned that the discrepancy in reactivity between substrate **2.17** and **2.38** is purely electronic as the pK_a of the anilide NH bond in **2.17** is close to 19 while the amide NH bond in substrate **2.38** would have a value of approximately 25. The substitution of K_2CO_3 for the more organic soluble Cs_2CO_3 or for the stronger base NaH proved equally fruitless. Moreover, the use of the alkynyl substrates **2.40** and **2.42** resulted in recovery of starting material (entries 6 and 7).



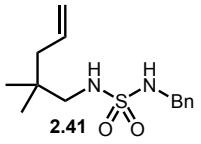
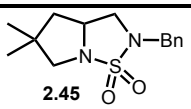
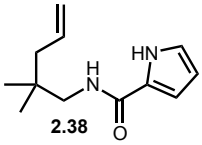
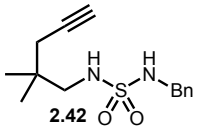
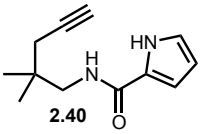
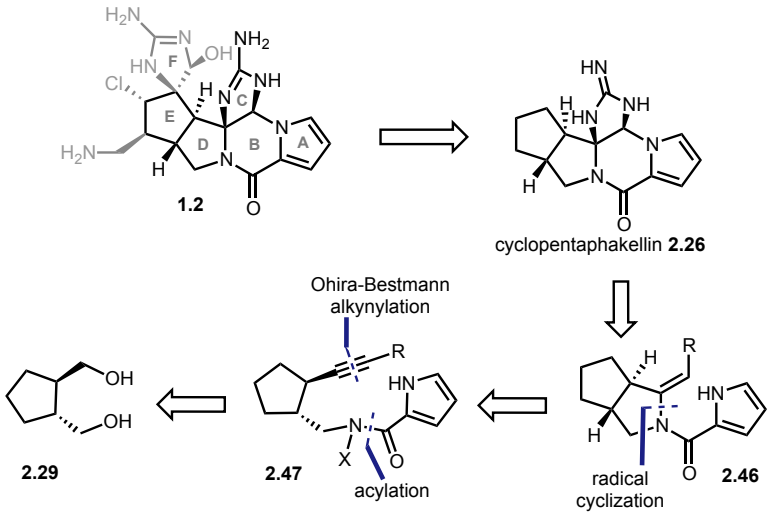
entry	diamine	base	T (°C)	outcome
1	 **2.41**	K_2CO_3	120	 **2.45** 75-76%[a]
2	 **2.38**	K_2CO_3	120	N.R.[a]
3		K_2CO_3	150	decomposition
4		Cs_2CO_3	120	N.R.
5		NaH	120	N.R.
6	 **2.42**	K_2CO_3	120	N.R.
7	 **2.40**	K_2CO_3	120	N.R.

Table 2.3 - Copper-mediated diamination screen on pyrrolyl substrates

[a] reactions conducted in both DMF and DCE

2.2.5 Revised Retrosynthesis

We reasoned that the challenges associated with our initial diamination approach could not be overcome, making the pursuit of this route untenable, and thus a major overhaul in strategy was necessary. Our concomitant N14-C10 and N1-C6 diamination strategy was perhaps over-ambitious, therefore we decided that a simpler stepwise diamination, in which we would focus first on the formation of the N14-C10 bond, was required. Retrosynthetic analysis of pentacyclic structure **2.26** suggested tricyclic intermediate **2.46** as a precursor (Scheme 2.8). The pyrazinone B-ring might be accessed *via* the addition of the pyrrole nitrogen to the exocyclic olefin and the undefined R group that might serve as a synthetic handle to also allow for the construction of the guanidine C-ring. An amidyl radical 5-*exo*-*dig* cyclization was chosen as the key step to form the *trans*-fused [3.3.0]-bicyclic ring system, as it would use a highly exothermic reaction that could potentially offset the high energy of cyclization to generate the *trans*-fused ring system.



Scheme 2.8 - Revised retrosynthetic analysis for cyclopentaphakellin model target

2.3 Amidyl Radicals

Radical initiated C-C bond forming processes found widespread use in organic synthesis during the 1980's. The synthetic utility of *C*-centered radicals is due to the facility of radical production in chain reactions, the fast rates of radical reactions in general, the ease of five-membered ring production in particular, the stability of unprotected polar functional groups to the radical reaction conditions and their ability to form bonds in sterically challenging contexts. The limitations of radical reactions reside in the kinetic reactivity of the radical, a property that often precludes their use in intermolecular reactions and sometimes rendered the regio- and stereochemical outcomes of some reactions less predictable (Figure 2.1). *N*-centered radical chemistry has most certainly not kept pace with *C*-centered radical chemistry in the intervening period. A major shortcoming was that the available precursors for *N*-based radicals were highly reactive *N*-halo- or *N*-nitrosoamides that were produced under conditions that precluded many functional groups in the substrate and often were employed in non-chain reactions that gave high radical concentrations.[10] Also, investigations into the synthetic potential of *N*-centered radicals *via* the use of new radical precursors that are available from mild reaction conditions and react cleanly in radical chain propagation steps are more recent.[11] This section will briefly introduce amidyl radicals, emphasizing their application towards cyclization with alkenes and recent applications in synthesis.

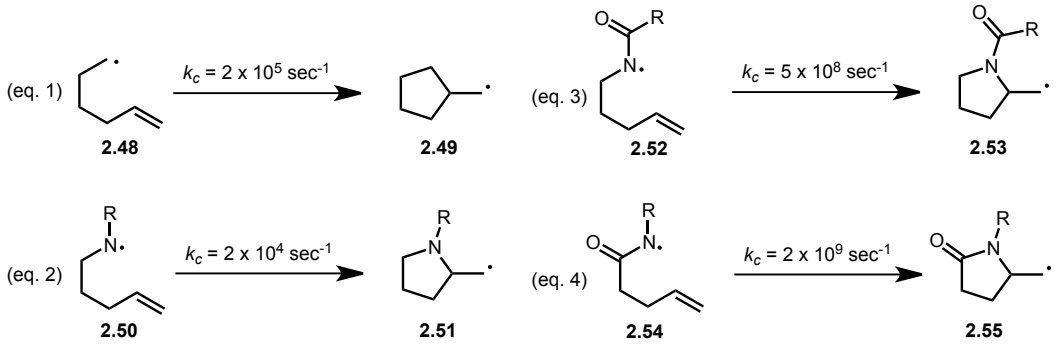
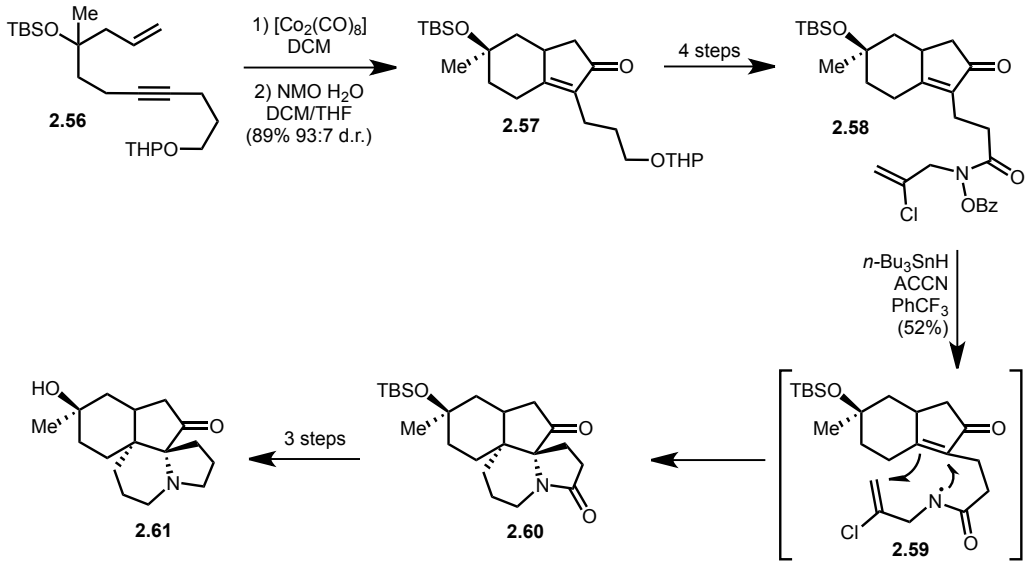


Figure 2.1 - Rate constants for 5-*exo*-trig radical cyclizations

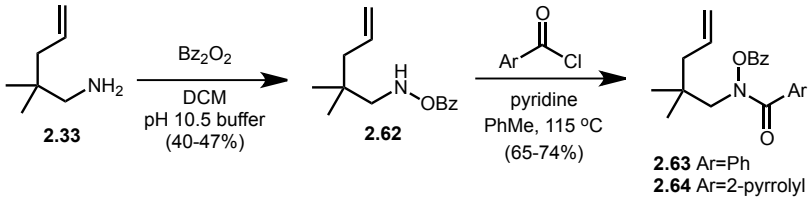
Amidyl radicals can be easily formed through homolytic cleavage of suitable functional groups appended to the nitrogen atom (i.e. *N*-hydroxypyridine-2-thione imidates,[12] thiocarbazones,[13] thiophenols,[14] benzoates[11a, 11b, 15] or xanthates[16]). These radical species are typically more electrophilic than aminyl radicals and have been found to undergo 5-*exo*-trig cyclizations at rates that are 10^5 and 10^4 times greater than *C*-centered radicals and aminyl radicals, respectively (Figure 2.1).[10] Zard and coworkers demonstrated that amidyl radicals can be synthetically useful in powerful cascade reactions to access natural products[13, 15a, 15b]. One particularly impressive example of a *N*-centered radical cascade reaction was used in a recent total synthesis of 13-deoxyserratine (Scheme 2.9). Bicyclic enone **2.57** was assembled *via* a Pauson-Khand reaction using enyne **2.56**. The *O*-benzoyl-*N*-allylhydroxamine **2.58** was chosen as the suitable amidyl radical precursor and was prepared in four straightforward steps. Treatment of **2.58** with tributylstannane and ACCN in refluxing α,α,α-trifluorotoluene created two bonds and two adjacent quaternary centers stereoselectively affording the tetracycle **2.60**. The 5-*exo*/5-*exo* cyclization cascade was discouraged over the 5-*exo*/6-*endo* by incorporating a chlorine atom on the olefinic trap which could then be removed homolytically with another equivalent of stannane. The synthesis of the natural product (**2.61**) was completed in an additional three steps.



Scheme 2.9 - Zard's approach to 13-deoxyserratine **2.61**

2.3.1 Acyclic Model System

After a brief survey of the literature, we reasoned that *N*-benzoate precursors such as **2.58** as opposed to the *N*-thio or *N*-chloro precursors would be the ideal starting point for our investigation due their greater ease of manipulation and synthesis. The synthesis of an *N*-benzoate amide precursor commencing from enamine **2.33** consisted of two steps – formation of the N-O bond by treatment of primary amine **2.33** with benzoyl peroxide in a biphasic mixture followed by acylation of *O*-benzoyl hydroxylamine **2.62** (Scheme 2.9).[17] The literature is surprisingly void of examples in which *N*-centered radicals cyclize onto alkynes therefore we first focused our attention to alkenyl *N*-benzoate amides, specifically benzamide **2.63** and 2-pyrroloamide **2.64**.



Scheme 2.10 - Synthetic route to alkenyl N-benzoate amides

Pleasingly, when a solution of tributyltin hydride was added slowly over a period of 12 hours (*via* syringe pump) to a solution of precursor **2.63** and ACCN in hot α,α,α-trifluorotoluene, benzoindolizidinone **2.65** was isolated in 30% yield (Table 2.4 entry 3). This tricyclic product presumably arises from the desired 5-*exo* radical cyclization

followed by a 6-*endo* cyclization onto the pendant phenyl ring (Scheme 2.11).[18] Such radical cascades in which a second cyclization event occurs onto an aromatic ring followed by a rearomatization is not uncommon and has even been employed as a strategy towards the synthesis of polycyclic natural products.[13a, 15c, 19]

Only when 2-pyrroloamide substrate **2.64** was treated with a stoichiometric amount of initiator, bicyclic amide **2.66** was generated in a moderate yield of 44% (entry 7). This demonstrated that the amidyl radical strategy could indeed allow for the formation of the desired pyrrolidine D-ring, albeit in a simple acyclic system. We were surprised to observe that, in this case, the 6-*endo-trig* cyclization did not occur. We reasoned that it may be potentially due to the geometry of the system: the primary carbon centered radical resulting from the initial 5-*exo* cyclization may not be in close enough proximity to the C3-position of the acylpyrrole unit and is simply quenched by the stannane.

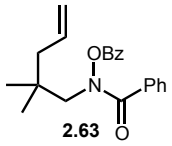
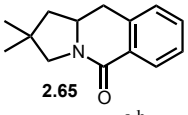
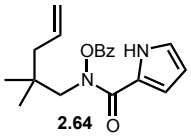
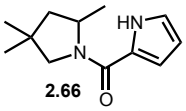
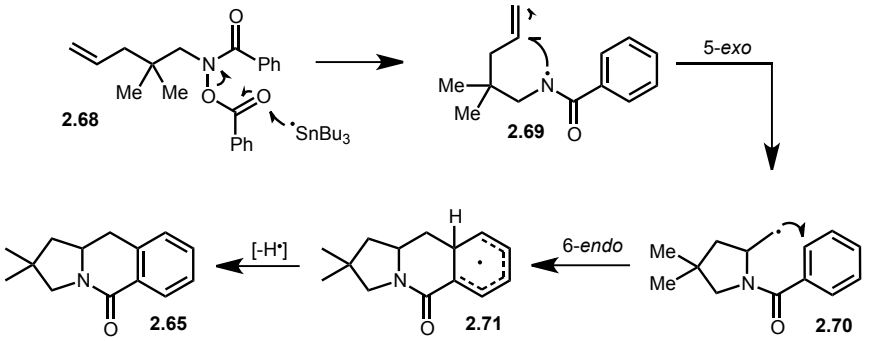
entry	benzoate	Bu_3SnH (eq.)	ACCN (eq.)	solvent	T (°C)	outcome
1	 **2.63**	2.3	0.2	PhMe	100	N.R.
2		2.2	0.2	cyclohexane	90	N.R.
3		2.3	0.2	$PhCF_3$	95	 **2.65** 33% $Y^{a,b}$
4		2.3	0.2	$PhCF_3$	105	**2.65** 20% $Y^{a,b}$
5		2.4	0.3	PhMe	120	N.R.
6	 **2.64**	2.4	0.3	$PhCF_3$	90	N.R.
7		2.5	1.2	PhMe	120	 **2.66** 44% $Y^{a,b}$

Table 2.4 - Radical cyclizations of alkenyl benzoate-derived precursors

[a]Refers to isolated yield [b]The majority of the remaining mass balance was the corresponding uncyclized reduced amide



Scheme 2.11 - Proposed mechanism for radical cascade towards tricyclic products

As expected, amidyl radicals are especially reactive. However, they suffer from one major drawback – premature quenching of the radical species. Reactions described in Table 2.4 were generally clean and resulted either in the chromatographic isolation of the cyclized product, recovered starting material or the amide product corresponding to premature quenching of the nitrogen-based radical with tributylstannane. Even though the rate constant for reaction with tributylstannane is essentially diffusion controlled, the 5-*exo* ring closure is sufficiently rapid to compete successfully under appropriate reaction conditions. It is interesting to note that the position of the carbonyl plays a critical role in the kinetics of the amidyl radical cyclization (Figure 2.2). When the carbonyl is on the outside as opposed to the inside of the nascent pyrrolidine, the rate of 5-*exo* closure is slower and because trapping of amidyl radicals with tin hydride is fast, there exists a greater risk of generating more of the amide by-product.[10, 11c, 19e, 20]

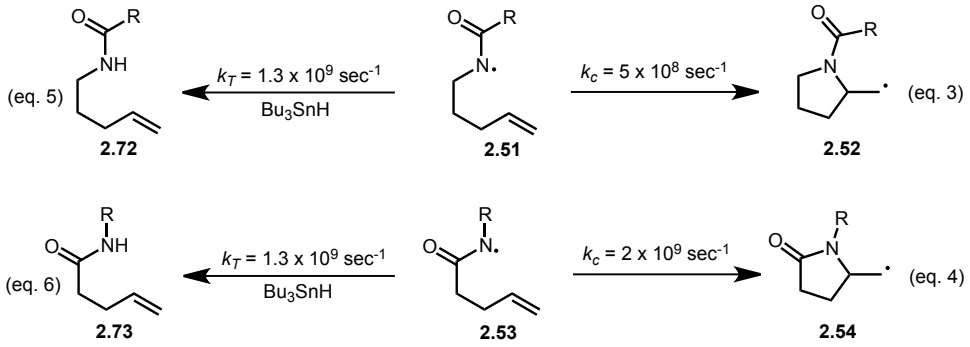
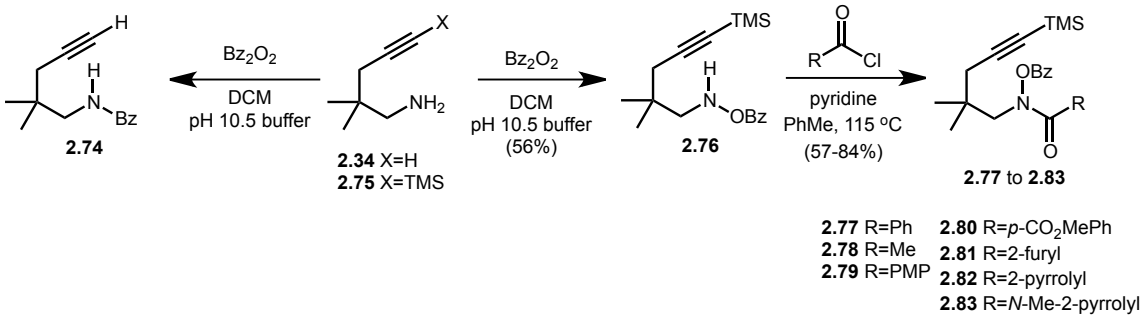


Figure 2.2 - Rate constants for cyclization (k_C) and hydrogen atom transfer (k_T)

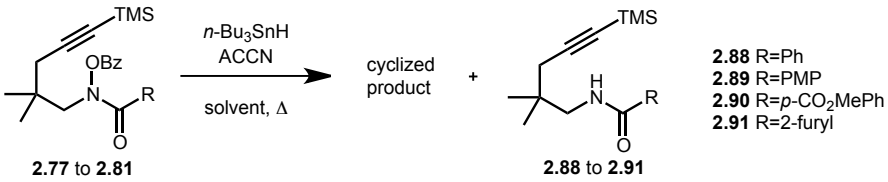
Encouraged by the above success of the 5-*exo-trig* cyclization, we decided to turn our attention to applying amidyl radicals in 5-*exo-dig* cyclizations, the desired disconnection of palau'amine (Scheme 2.8). Unexpectedly, treatment of aminoalkyne

2.34 to the conditions for *O*-benzoyl hydroxylamine formation led exclusively to the isolation of the unwanted benzamide by-product **2.74**. By contrast, using easily accessible trimethylsilyl-capped alkynylamine **2.75**,[21] alkynyl *O*-benzoyl hydroxylamine **2.76** could be accessed in moderate yield and converted to the corresponding *N*-benzoate amides **2.77** to **2.82** in good yields as shown in Scheme 2.12.



Scheme 2.12 - Synthetic route to alkynyl N-benzoate amides

When a solution of tributyltin hydride was slowly added to a solution of precursor **2.77** and ACCN in hot trifluorotoluene, tricyclic amide **2.84** was furnished in 37% yield *via* the 5-*exo*-*dig*/6-*endo*-*trig* cascade sequence (Table 2.5, entry 1). Since amidyl radical addition to alkynes has not been discussed in the literature, it was decided to investigate the influence of the nature of the amide R group on the 5-*exo*-*dig* cyclization. The acetamide derivative **2.78** failed to initiate and was not pursued (entry 2). Substrates incorporating an electron-rich aroyl moiety (entry 3) afforded more of the radical cascade product than substrates with more electron-poor aroyl groups (entry 4). The 2-furanylamide substrate **2.81** was also investigated as it served as a model substrate for the 2-pyrrolyl substrates. The amidyl radical from this benzoate precursor undergoes the 5-*exo*-*dig* cyclization but not the 6-*endo* closure, possibly due to geometrical constraints. Another possibility is that, with the benzamide derivatives **2.81**-**2.83**, the tricyclic intermediates (analogous to **2.71**) are thermodynamically stable due to high degree of delocalization of the radical and thus drive the 6-*endo* cyclization onto the phenyl ring.[12]



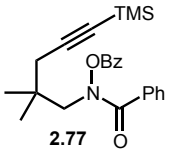
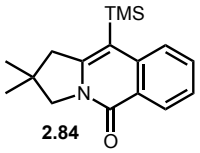
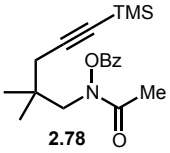
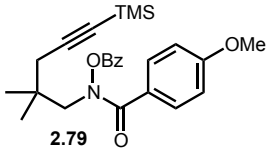
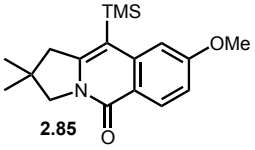
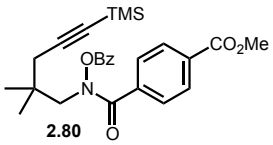
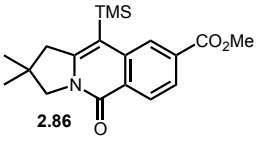
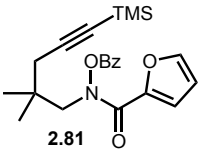
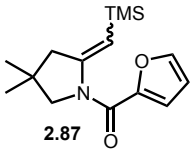
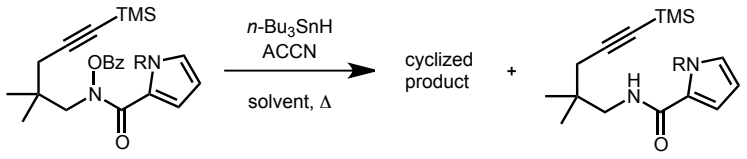
entry	benzoate	Bu_3SnH (eq.)	ACCN (eq.)	solvent	T (°C)	cyclized product
1	 **2.77**	2.6	0.6	$PhCF_3$	110	 **2.84** 37% Y[a,b]
2	 **2.78**	2.0	0.5	$PhCF_3$	95 °C	N.R.
3	 **2.79**	2.0	0.5	$PhCF_3$	110	 **2.85** 40% Y[a,b]
4	 **2.80**	2.6	0.6	$PhCF_3$	110	 **2.86** 17% Y[a,c]
5	 **2.81**	2.0	0.6	$PhCF_3$	95	 **2.87** 6% Y[a,b]

Table 2.5 - Radical cyclizations of alkynyl benzoate-derived precursors

[a]Refers to isolated yield [b]The majority of the remaining mass balance was the corresponding uncyclized reduced amide

Attempted free radical cyclizations of alkynyl pyrrolyl benzoate-derived precursor **2.82** with a free pyrrole NH failed to provide any cyclized material (Table 2.6). Under the "optimized" reaction conditions from the alkenyl 2-pyrroloamide *N*-benzoate substrate, in which a full equivalent of initiator was employed, only the amide byproduct was isolated

(Table 2.6 entries 1 to 4). The reason as to the marked difference in the outcomes of the reactions with both pyrrole-containing substrates **2.64** and **2.82** remains elusive however we reasoned that the rate of hydrogen atom transfer from the stannane likely outcompetes the initial rate of 5-*exo*-*dig* cyclization in **2.82**. In lieu of designing a route to **2.82** that incorporated a protecting group on the pyrrole nitrogen, in the interest of time, we opted to synthesize **2.83** in which a methyl group was used to cap the pyrrole nitrogen. The attempted cyclization with *N*-methylpyrrolyl substrate **2.83** afforded mainly the undesired amide product **2.94** with only a trace amount (*ca.* 4% yield) of tricyclic pyrrole **2.93** observed by ^{1}H NMR. In contrast to the cyclization reaction of **2.69** in which only the 5-*exo* cyclization occurred, with **2.87**, the formation of the pyrrolidine ring is followed by a 6-*endo*-*trig* cyclization of the vinyl radical onto the C3 position of the pyrrole. Although far from satisfactory, this procedure had some potential for optimization and it could provide the first entry into the isophakellin **1.14**/styloguanidine **1.33** skeleton in an efficient manner. Ultimately, optimization of this procedure was not pursued in light of more promising results obtained with an alternative approach that was being investigated in parallel (*vide infra*).



2.82 R=H
2.83 R=Me

2.92 R=H
2.94 R=Me

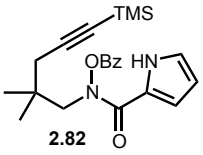
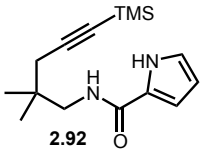
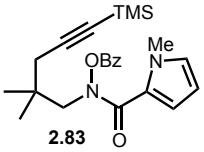
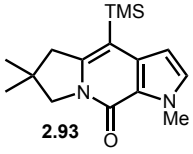
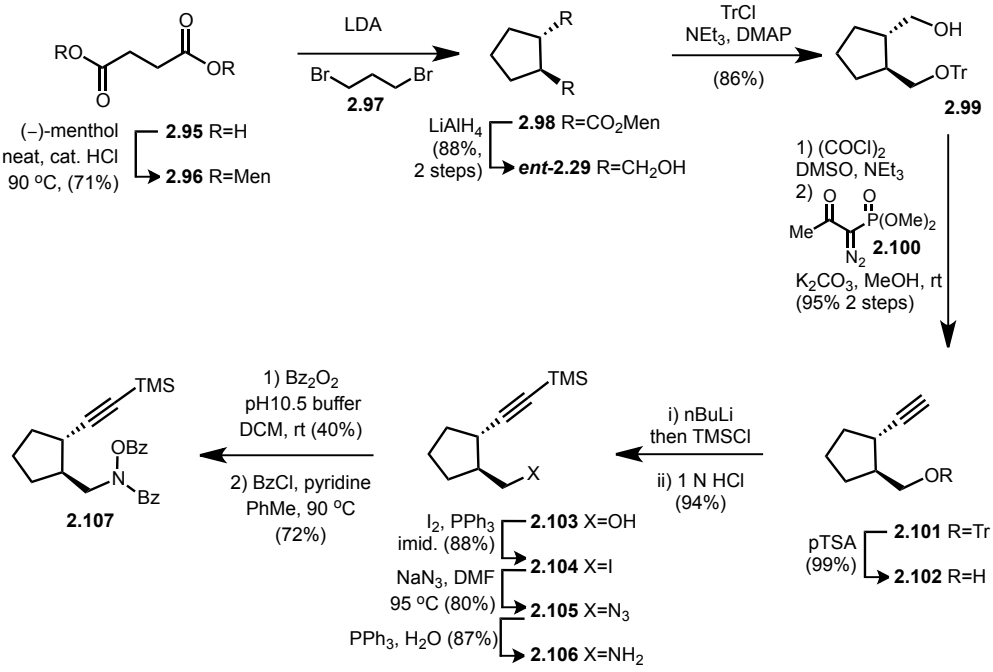
entry	benzoate	Bu_3SnH (eq.)	ACCN (eq.)	solvent	T (°C)	result
1		2.0	0.4	$PhCF_3$	95	N.R.
2		2.2	1.0	$PhCF_3$	95	 38% Y[a,b]
3		3.0	1.0	$PhCF_3$	100	**2.92** 40% Y[a,b]
4		5.0	2.0	$PhCF_3$	100	**2.92** 93% Y[a,b]
5		2.0	0.6	$PhCF_3$	95	 4% Y[a,b]

Table 2.6 - Radical cyclizations of alkynyl pyrrolyl benzoate-derived precursors
[a]Refers to isolated yield [b]The majority of the remaining mass balance was the corresponding uncyclized reduced amide

2.3.2 Cyclic Model System

With the acyclic model system, we successfully demonstrated that the amidyl cyclization approach was a viable strategy to form the desired pyrrolidine D-ring and hence stitch together the N14-C10 bond of palau'amine. Although we observed an ensuing 6-*endo* cyclization when the cyclizing nitrogen was substituted as the benzamide, the desired monocyclization event (as in retrosynthetic analysis of Scheme 2.8) occurred predominantly when the amide comprised a five-membered ring aromatic such as in **2.66** and **2.87**. We needed to investigate at this point if the amidyl radical cyclization was

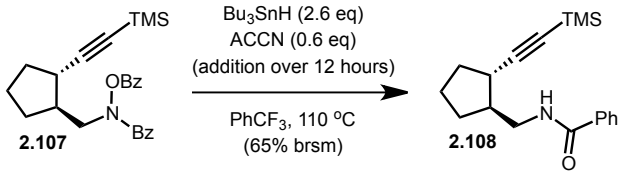
amenable to furnish the pyrrolidine ring but in the context of setting the highly strained *trans*-bicyclic system.



Scheme 2.13 - Synthesis of benzoate radical precursor **2.106**

The synthesis of our cyclic model system (Scheme 2.13) commenced with the dimenthol ester of succinic acid **2.96**, easily accessed in high yield *via* a Fischer esterification of succinic acid.[22] Due to the significant price difference between (+)-menthol and (−)-menthol, we chose to synthesize 1,2-*trans*-bis(hydroxymethyl)cyclopentane ***ent*-2.29**, which was obtained in 88% yield in a two-step procedure adapted from Yamamoto[22] and Grubbs.[23] Treatment of diester **2.96** with two equivalents of lithium diisopropylamide (LDA) formed the corresponding *s-trans*-(*E*,*E*)-enolate which was then alkylated with dibromopropane **2.97** to provide exclusively the 1,2-*trans* substituted 5-membered ring **2.98**. Following the lithium aluminum hydride reduction of diester **2.98** to diol ***ent*-2.29**, a mono-protection as the trityl ether in **2.99** allowed for the selective functionalization of one cyclopentane arm and incorporation of the terminal alkyne *via* the Ohira-Bestmann protocol.[24] Incorporating the trimethylsilyl group onto the terminal alkyne of **2.101** proved difficult, most likely due to steric factors, therefore the trityl group was removed at this stage to reveal hydroxyalkyne **2.102** which, at this point, could be easily silated. Conversion of the pendant alcohol **2.103** to the

primary amine **2.106** was achieved in 61% yield over three steps *via* a Staudinger reduction of the corresponding azide **2.105**. Finally, formation of the benzoate amide precursor **2.107** proceeded in moderate yield using the conditions developed for the acyclic model system.



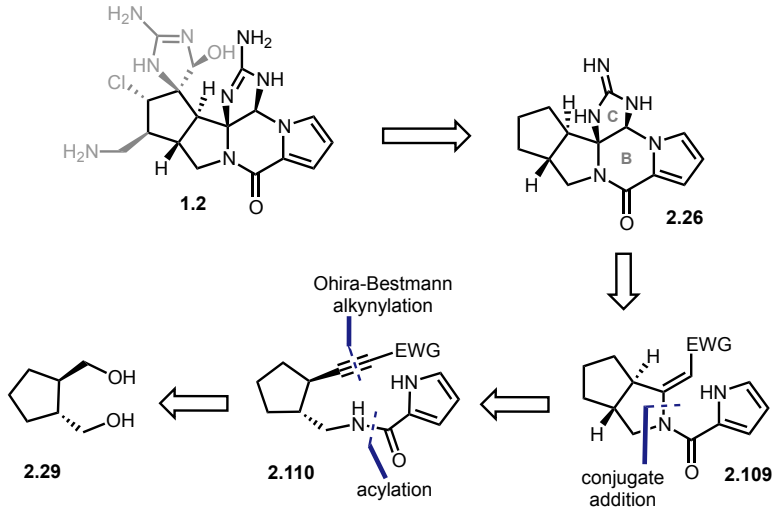
Scheme 2.14 - Attempted amidyl radical cyclization

Under the established radical cyclization conditions, amidyl radical precursor **2.107** generated solely the corresponding benzamide product **2.108** without any traces of the desired cyclized product (Scheme 2.14). This result is rationalized by the inherent strain of the *trans* conformation of the nascent bicyclic system; premature quenching from tributyltin stannane outcompetes the severely slowed rate of pyrrolidine ring formation. Although this undesired side reaction may have been minimized by using a different radical initiating reagent, optimization of this procedure was not pursued in light of more promising results obtained with an alternative approach (*vide infra*).

2.4 Conjugate Addition

We considered incorporating an electron-withdrawing group (EWG) onto the alkyne in an effort to increase its electrophilicity towards addition either in the context of the amidyl radical chemistry (R=EWG in **2.47** in Scheme 2.8) or in a more general ionic 1,4-addition of an amide nitrogen (in **2.110** in Scheme 2.15). We chose to append an ester functional moiety onto the alkyne which would serve as an EWG and would also act as a synthetic handle to allow for the construction and elaboration of the guanidine C-ring. In the literature, there are only very limited cases of intramolecular conjugate addition of nitrogen to ynoate esters and most examples have been largely been used to access pyrrolidine and piperidine motifs in heteroaromatics and polycyclic natural products.[25] From a retrosynthetic perspective, the pentacyclic structure **2.26** is simplified to tricyclic intermediate **2.109**. The pyrazinone B-ring could be accessed *via* the oxidative functionalization of the exocyclic olefin bearing the EWG group that would serve for the

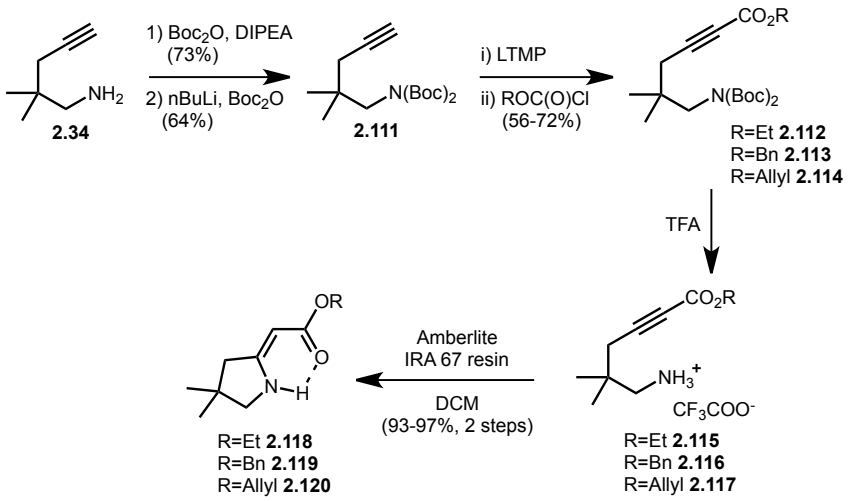
construction of the guanidine C-ring. The key step to form the *trans*-fused [3.3.0]-bicyclic ring system would be a Baldwin-favored 5-*exo*-*dig* cyclization.



Scheme 2.15 - Revised retrosynthetic analysis for cyclopentaphakellin model target

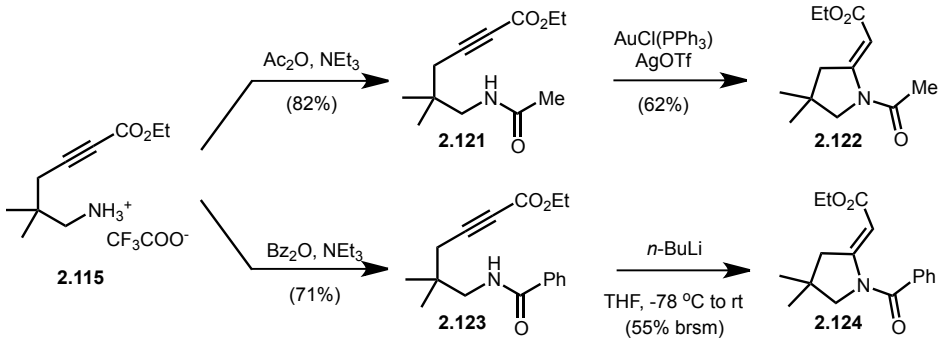
2.4.1 Acyclic Model System

To test our hypothesis on the use of an EWG as an activating group, we returned to our acyclic model system (Scheme 2.16). Installation of an ester functionality onto the terminal alkyne could only be achieved after a double protection of the primary amine **2.34** as the bis-carbamate **2.111**. Deprotonation of alkyne **2.111** with LDA followed by slow addition of a chloroformate afforded a mixture of products in which the major product was a mixed bis-carbamate resulting from the cleavage of one of the Boc groups followed by the acylation of the carbamate with a chloroformate. The use of the more bulky base lithium tetramethylpiperidide (LTMP) solved this issue and a set of 2-alkynoates (**2.112-2.114**) could be formed without further complication (Scheme 2.16). Subjection of bis-carbamates **2.112-2.114** to trifluoroacetic acid clipped off both Boc groups and neutralization of the corresponding TFA salts **2.115-2.117** with a triethylamine-bound resin afforded *Z*-*exo*-cyclic *β*-enaminoesters constructs **2.118-2.120** in excellent yields.[26] These *β*-enaminoesters adopt the thermodynamically more stable *Z*-configuration due to the intramolecular H-bonding. We were pleased to find the ester performed as an activating group for the alkyne and allowed for an easy and straightforward intramolecular cyclization to afford the desired and appropriately functionalized pyrrolidine ring system.



Scheme 2.16 - Conjugate addition of amines towards *Z*-exocyclic *β*-enaminoesters

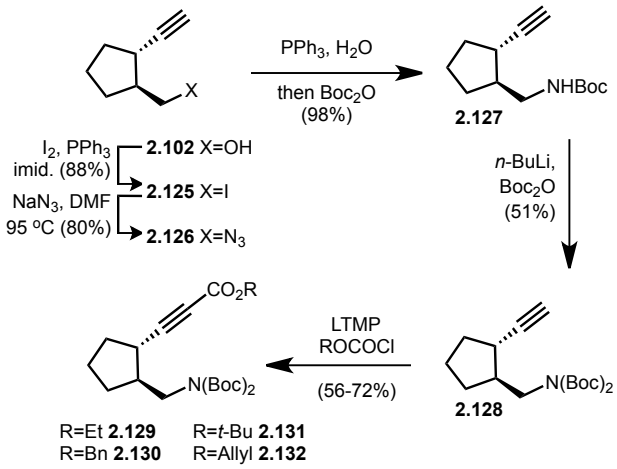
To investigate the reactivity of an amide nitrogen in this context, we sought to trap the amine as its corresponding amide (Scheme 2.17). Treatment of TFA salt **2.115** in the presence of either acetic or benzoic anhydride with triethylamine affords acetamide **2.121** and benzamide **2.123**, respectively. The 5-*exo* cyclization of **2.121** could be effected by treatment with a gold(I) species generated from the mixture of $AuCl(PPh_3)$ and silver triflate as described by Widenhoefer and coworkers[27] to furnish *E*-*exo*-cyclic *β*-enaminoester **2.122** in 62% yield. In this case, the *E*-geometry of the exocyclic olefin was dictated by steric factors.[28] Alternatively, when benzamide **2.123** was treated with equimolar amount of *n*-butyllithium, the *E*-*exo*-cyclic *β*-enaminoester **2.124** was formed in 55% yield (brsm, unoptimized), presumably *via* the 1,4-addition of the deprotonated amide to the ynoate.



Scheme 2.17 - Au-catalyzed hydroamidation and amide 1,4-addition towards *E*-exocyclic *β*-enaminoesters

2.4.2 Extension Towards Palau'amine

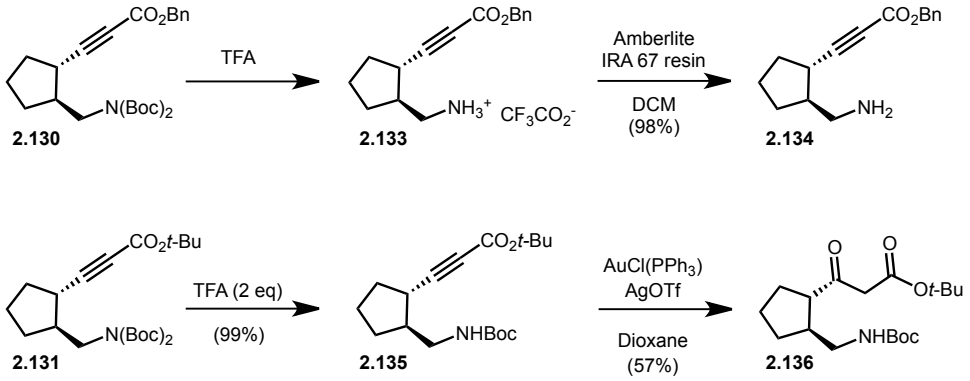
With these promising results in hand, we returned to our cyclic model system to investigate whether the conjugate addition strategy was applicable for forming the strained *trans* 5,5-azabicyclic system. We wanted to access the alkynoate esters in a similar fashion as in the acyclic model system – deprotonation and acylation of the terminal alkyne. The synthesis of this new model system construct (Scheme 2.18) was easily adapted from the dimenthol succinate model system that was used with the amidyl radical chemistry (Scheme 2.13). Hydroxyalkyne **2.102** was converted to azidoalkyne **2.126** *via* the nucleophilic displacement of the primary iodide in **2.125** with sodium azide. The *tert*-butylcarbamate **2.127** was subsequently obtained in 98% yield by one-pot Staudinger reduction/Boc protection. Following the formation the bis-carbamate **2.128**, the alkynoates **2.129**-**2.131** were formed in moderate yields by treating terminal alkyne **2.128** with LTMP and an acylating agent, either a chloroformate or di-*tert*-butyl dicarbonate.



Scheme 2.18 - Elaboration of conjugate addition precursors

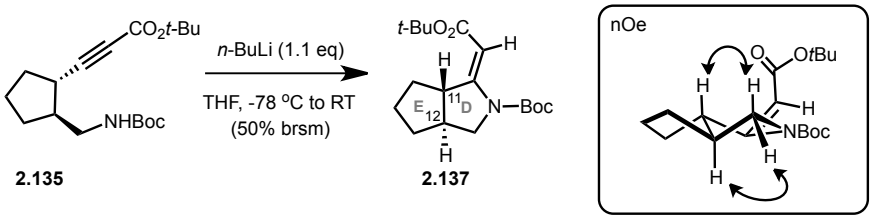
Considering that perhaps the successful 5-*exo* closures observed with the acyclic model system could be extended towards the formation of *trans*-5,5 ring systems, the same procedures were repeated on our 1,2-*trans* scaffold (Scheme 2.19). Treatment of the bis-carbamate **2.130** with trifluoroacetic acid liberated the amine from both Boc groups and quantitatively afforded the corresponding ammonium salt **2.133**. In contrast to the analogous reaction with the acyclic system, the neutralization of TFA salt **2.133** with the acid-scavenging resin did not lead to any discernible cyclization and only furnished free

amine **2.134**. Selective monodeprotection of the biscarbamate **2.131** using two equivalents of TFA afforded carbamate **2.135** which was poised to undergo the gold-catalyzed 5-*exo* hydroamidation reaction. In sharp contrast to the result obtained with our acyclic model, the internal hydration product **2.136** was obtained in 57% yield. We reasoned that the addition to the gold-activated alkyne of water present in the reaction[29] outcompeted the hydroamidation reaction and, by extension, the formation of the highly strained *trans*-5,5-azabicyle. Both outcomes of these reactions demonstrated the high degree of strain implicit in the *trans*-5,5-bicyclic system and validated the challenge associated with their preparation.



Scheme 2.19 - Failed approaches to *trans* 5,5-azabicycles

In contrast to the failures of the free amine and gold-catalyzed closure, treatment of carbamate **2.135** with an equimolar amount of *n*-butyllithium resulted in cyclization to afford *trans*-fused *E*-vinylogous carbamate **2.137** in 50% yield (brsm, unoptimized) (Scheme 2.20). The formation of the *trans*-fused product was verified by ^{1}H NMR nOe experiment where interactions allowed assignment of the bicyclic methine ring protons to either the top or bottom face of the framework. The absence of any nOe interactions between the vinyl proton of the exocyclic olefin and any protons on the E-ring suggests the *E*-configuration about the olefin.

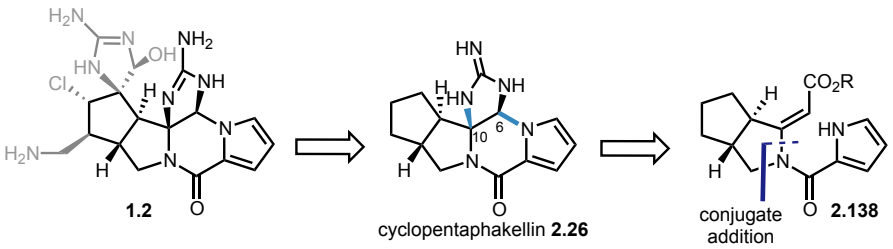


Scheme 2.20 - Intramolecular conjugate addition reaction to *trans*-fused-bicycle and key observed nOe correlations

This reaction demonstrates for the first time the feasibility of constructing the *trans*-fused [3.3.0]-bicyclic ring system using a surprisingly mild method that is operationally simple and uses an extremely common reagent such as *n*-butyllithium. Having validated our synthetic method to generate the highly strained ED-bicyclic core of the revised structure of palau'amine, we needed to address the elaboration of the rest of the right-hand side core. Although bicyclic scaffold **2.137** remains a worthy candidate for the development of the remaining right-hand side half of palau'amine, future work will aim to realize the conjugate addition reaction within a system analogous to **2.135** that already incorporates the 2-acylpyrrole subunit as to obviate the need to cleave the Boc group in **2.137** and introduce the pyrrole A-ring in subsequent steps.

2.5 Conclusion

The synthesis of the palau'amine ED-ring system was accomplished using a robust and simple protocol and allows access to the pivotal *trans*-fused azabicyclic core of the revised structure of palau'amine. Central to the success of this strategy was the development of the conditions for the 1,4-addition of a carbamate onto an ynoate ester. The cyclization event occurred smoothly with **2.135** (Scheme 2.20) and should extend to afford vinylogous carbamate **2.138** (Scheme 2.21). The next synthetic goal was the full elaboration of the ABC-rings and the formation of the N1-C6 and N9-C10 bonds (in blue). The requirement for an activated electron-deficient alkyne for the conjugate addition resulted in the incorporation of an ester functionality that we would use as a synthetic handle for the construction of the guanidine C-ring.



Scheme 2.21 - Retrosynthetic analysis for B and C-rings

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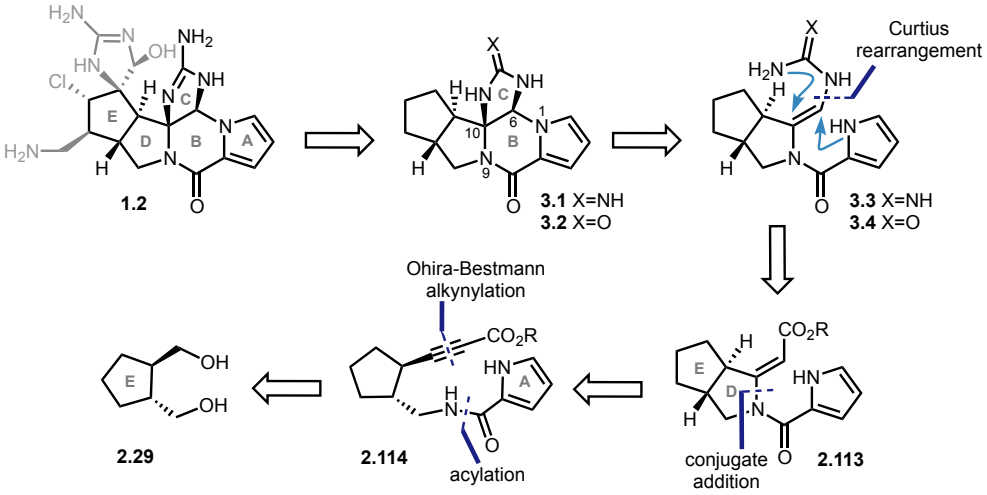
Chapter 3.

Synthetic Studies Towards the Right-Hand Side Core of Palau'amine

3.1 Introduction

After the successful attempt to effect the intramolecular cyclization of a carbamate nitrogen onto an ynoate ester, forming the key *trans* 5,5-azabicylic motif for the synthesis of the revised structure of palau'amine (see Chapter 2), we turned our attention to the remaining right-hand side portion of palau'amine. Our approach for the assembly of the ABC-ring portion was to utilize the exocyclic double bond as the reactive center where, after its appropriate functionalization, both the B-ring (N1-C6 bond formation) and C-ring (N9-C10 bond formation) could be formed simultaneously. The pendant ester component of **2.113** could be used to construct either the guanidine (X=NH, as in the palau'amine family) or even the urea (X=O, as in phakellstatin family) *via* a Curtius rearrangement (Scheme 3.1).

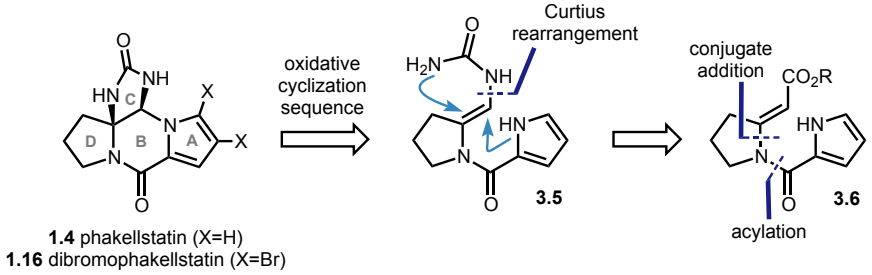


Scheme 3.1 - Retrosynthetic analysis for ABCD-core of palau'amine

3.2 Studies Towards a Phakellstatin Core

The initial strategy towards the ABC motif of palau'amine was to employ the Curtius rearrangement to access a urea such as **3.4**, perform the key cyclization reaction to access polycyclic urea such as **3.2** then, in a final sequence, convert the urea to the corresponding guanidine. This approach seemed advantageous as it would make polarity and solubility more manageable while also giving us the opportunity to probe the reactivity of the urea-derived sub-family of the PIA alkaloids. Our strategy would also allow for the expedient formation of the structurally related natural product, phakellstatin **1.4**, and its brominated congener **1.16** (Scheme 3.2). To investigate our route for the

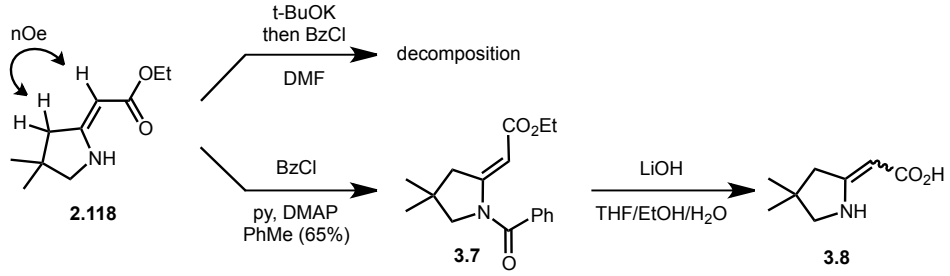
construction of the right-hand side portion of palau'amine, we decided to continue using the *gem*-dimethyl model system (Scheme 2.16). We reasoned that *Z-exo*-cyclic *β*-enaminoesters construct **2.118,** which was easily available in large quantities (>10 grams) in only a few steps, would provide valuable information as to the reactivity of these systems and would adequately mimic the real system.



Scheme 3.2 - Analogous retrosynthetic analysis for phakellstatin skeleton

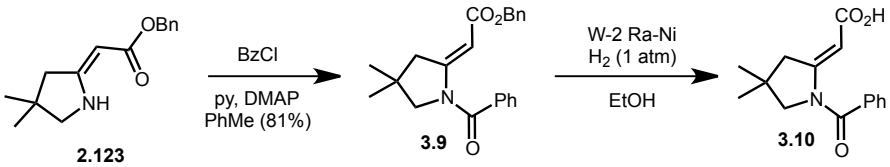
3.2.1 Incorporation of the Pyrrole A-Ring and Choice of Ester Protection

The first task in order to prepare vinylogous imide **3.6** was the acylation of the nitrogen of the enaminoester as a means to introduce the required acyl pyrrole A-ring subunit. A brief review of the literature revealed that the *N*-acylation of compounds such as **2.118** had previously been described.[1] In initial trials, the deprotonation of the pyrrolidine nitrogen of **2.118** with a hard base such as potassium *tert*-butoxide followed by trapping with a simple acyl chloride (benzoyl chloride) resulted in complete decomposition of the starting material. However, under DMAP-catalyzed conditions at elevated temperature (80 °C to 90 °C), acylation with benzoyl chloride afforded benzamide **3.7** in good yield (Scheme 3.3). In contrast to the starting enamide, nOe enhancement between the vinyl proton and the ring protons was not observed for vinylogous imide **3.7**, suggesting that, under the acylation conditions, the isomerization of exocyclic olefin had occurred.



Scheme 3.3 - Development of an acylation protocol

The choice of the protecting group for the ester came as a result of intensive investigations. When vinylogous imide **3.7** was briefly exposed to typical saponification conditions (LiOH in THF/EtOH/H_2O), hydrolysis of the ethyl ester along with cleavage of the amide bond occurred to generate the highly polar compound **3.8** in low yield. Due to the base sensitivity of the amide bond, an alternative *O*-protecting group for the vinylogous carbamate was required that could be removed under neutral conditions. We reasoned that a chemoselective hydrogenolytic cleavage of a benzyl ester in the presence of the exocyclic olefin could be achieved using Raney nickel.[2] When appropriately prepared Raney nickel from commercial sources was employed for the hydrogenolysis, the vinylogous carbamic acid **3.10** could be obtained in a modest yield of 61% without any visible hydrogenation of the exocyclic olefin (table 3.1 entry 1). Unfortunately, the reaction was repeated on a larger scale resulting in sluggish and irreproducible outcomes (entry 2). Equally dismal outcomes resulted from the use of freshly prepared Raney nickel[3] with only 31% of the desired *α,β*-unsaturated acid isolated (entry 3).

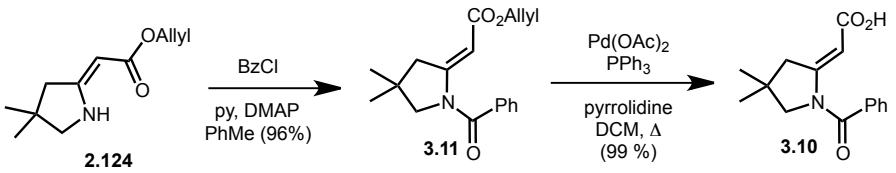


Scheme 3.4 - Access to vinylogous carbamic acid **3.10** *via* O-benzyl ester

entry	scale	W-2 Ra-Ni	rxn time	yield of **3.10**
1	50 mg	commercial	5.5 hours	61%
2	156 mg	commercial	8 hours	N.R.
3	200 mg	freshly prepared	7 hours	31%

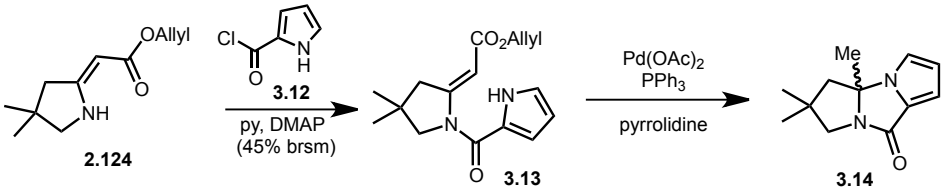
Table 3.1 - Attempted debenzylation using W-2 Raney Nickel

We then decided to investigate the allyl group for its ease of removal under mild conditions and orthogonal reactivity to many other functional groups. After careful screening (nucleophile, solvent, temperature), we successfully identified conditions to perform the desired deprotection of the vinylogous imide **3.11** using palladium acetate and triphenylphosphine with pyrrolidine as the nucleophile in refluxing dichloromethane to furnish the desired *α,β*-unsaturated acid **3.10** in excellent yield (Scheme 3.5).[4]



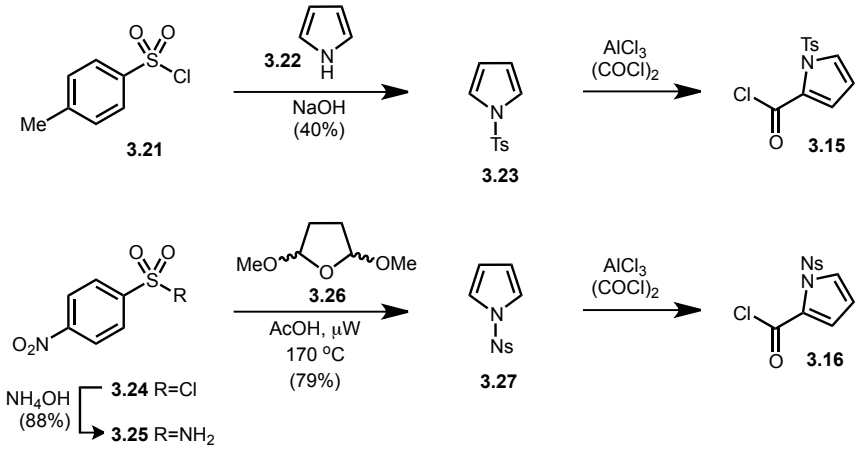
Scheme 3.5 - Access to vinylogous carbamic acid **3.10** *via* O-allyl ester

The acylation of cyclic *β*-enaminoester **2.124** with pyrrole-2-carbonyl chloride **3.12** afforded vinylogous imide **3.13** in modest yield (Scheme 3.6). The high temperature needed for the coupling to proceed may have caused some decomposition of the acylpyrrole coupling partner thereby reducing the yield. When vinylogous pyrroloamide was treated under our previously established conditions to liberate the allyl ester, tricyclic imidazolinone **3.14** was isolated as the sole product. This presumably arises from the conjugate addition of the pyrrole nitrogen to the palladium-activated *α,β*-unsaturated carboxylic acid followed by a decarboxylation.



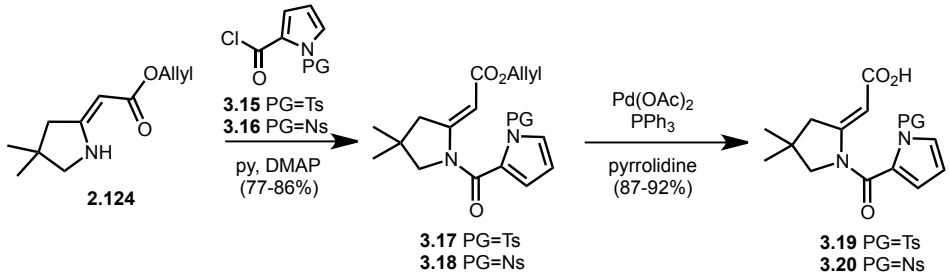
Scheme 3.6 - Observed reactivity with unprotected pyrrole intermediate **3.13**

To suppress this process, we opted to mask the nucleophilicity of the pyrrole nitrogen with a sulfonamide-based protecting group such as tosyl or nosyl, both of which can be removed under fluoride conditions.[5] The synthesis of acyl chloride **3.15** began with tosyl protection of freshly distilled pyrrole (**3.22**) with *p*-toluenesulfonyl chloride (**3.21**) to afford *N*-Ts pyrrole **3.23** in 40% yield.[6] Regioselective 2-acylation with oxalyl chloride in the presence of aluminum chloride gave an essentially quantitative yield of **3.15**.[7] The nosyl-protected acyl chloride **3.16** was prepared under similar conditions from *N*-Ns pyrrole **3.27**, prepared *via* a Clauson-Kaas reaction under microwave irradiation in 79% yield.[8]



Scheme 3.7 - Construction of *N*-sulfonamide protected acylpyrrole units

The acylation of **2.124** with both *N*-protected acyl chlorides **3.15** and **3.16** furnished vinylogous imides **3.17** and **3.18**, respectively, in excellent yield (77-86%). Deprotection of the *O*-allyl group of **3.17** and **3.18** proceeded smoothly to afford vinylogous carbamic acids **3.19** and **3.20**, respectively, in high yield (87-92%) with no visible competing decarboxylation.

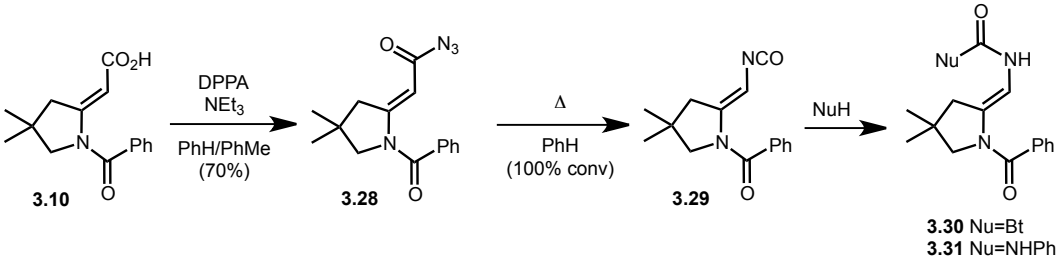


Scheme 3.7 - Vinylogous carbamic acids **3.19** and **3.20** from sulfonamide protected pyrrole

3.2.2 Curtius Rearrangement

Access to vinylogous carbamic acids **3.10**, **3.19** and **3.20** (Schemes 3.5 and 3.6) allowed for the examination of conditions to prepare vinyl urea **3.5**. It was envisioned that the urea of the C-ring of phakellstatin (**1.4**) could be introduced *via* a Curtius rearrangement of the carboxylic acid moiety in **3.10**/**3.19**/**3.20**. In initial studies, treatment of *α,β*-unsaturated acid **3.10** with DPPA in the presence of triethylamine generated chromatographically stable vinylogous carbamoyl azide **3.28** in 70% yield. After prolonged heating (85 °C for 6-7 hours), the vinyl isocyanate **3.29** was cleanly obtained and carried to the next step. Typically, isocyanates are unstable to chromatographic

purification therefore crude vinyl isocyanate **3.29** was not extensively analyzed spectroscopically but its formation could be quickly confirmed by IR spectroscopy.

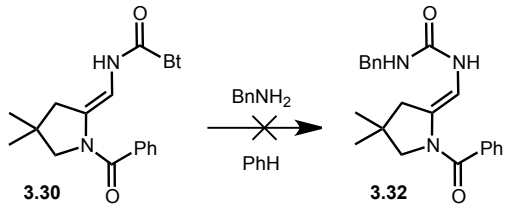


Scheme 3.8 - Curtius rearrangement sequence to vinyl urea **3.30** & **3.31**

entry	Nucleophile	solvent	temperature	outcome
1	$BnNH_2$	PhH	r.t.	decomposition
2	$BnNH_2$	THF	−78 °C to r.t	decomposition
3	EtOH	neat	reflux	N.R.
4	$PhSO_2NH_2$	THF	−78 °C to r.t	decomposition
5	Benzotriazole (BtH)	THF	reflux	**3.30** 70% Y
6	$PhNH_2$	PhMe	-15 °C to r.t	**3.31** 17% Y

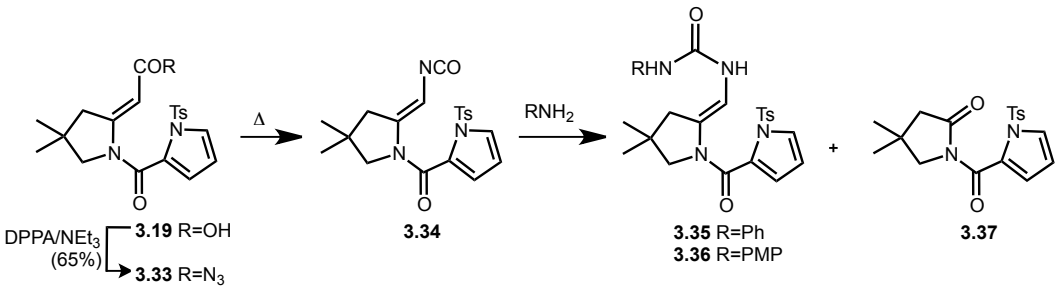
Table 3.2 – Survey of nucleophiles for formation of vinyl urea

An extensive survey of different conditions was performed including different nucleophiles (benzylamine, ethanol, benzenesulfonamide, benzotriazole, aniline), solvents (benzene, tetrahydrofuran, toluene) and temperatures (−78 °C, -15 °C, 23 °C, 80 °C) for the trapping step to form the vinyl urea. Gratifyingly, the vinyl isocyanate could be quenched with aniline to furnish vinyl urea **3.31**, albeit in a modest yield of 17% for the two steps after a recrystallization. The formation of the stable benzotriazole adduct **3.30** was encouraging since *N*-acyl benzotriazoles are reported as good acylating agents and therefore by extension, the carbamoyl benzotriazole could be used to synthesize a urea.[9] Unfortunately, attempts to form the desired urea **3.32** by displacement of the benzotriazole from **3.30** with an amine-based nucleophile by increasing the temperature resulted in the formation of intractable mixtures of unidentified products (Scheme 3.9).



Scheme 3.9 - Attempted benzotriazole exchange with benzylamine

With a somewhat successful access to aniline-derived vinyl urea **3.31**, attention was focused on the *N*-Ts pyrroloamide substrate (Scheme 3.8). Treatment of vinylogous carbamic acid **3.19** with DPPA in the presence of triethylamine provided the desired vinylogous carbamoyl azide **3.33** in 65% yield. Under the same conditions for the formation of **3.31** when acyl azide **3.33** was heated to 80 °C in benzene followed by addition of aniline, lactam **3.37** was the sole product detected by LC/MS (Table 3.3 entry 1). We reasoned that oxygen present during the reaction was responsible for the oxidative cleavage of the exocyclic olefin. In attempts to avoid the oxygen-mediated cleavage of the olefin, the procedure was altered to carry out the Curtius rearrangement in a one-pot process by running the reaction in degassed toluene and generating the isocyanate *in situ*. This change was sufficient to address the oxidation issue. However it furnished aniline-derived vinyl urea **3.35** in a disappointing 23% yield after isolation from the crude mixture by a recrystallization (entry 2). It was found that the isolation for these polar molecules was best achieved by reversed-phase chromatography. With the benzamide model system (scheme 3.8), we had discovered that aniline-based nucleophiles were the most suitable to access the desired vinyl ureas therefore we chose to perform the Curtius rearrangement sequence with anisidine as a trapping nucleophile. Furthermore, we reasoned a PMP protecting group could be removed under oxidative conditions in a final deprotection step. Gratifyingly, we were able to isolate the vinyl urea **3.36** in a synthetically useful amount (53% yield) (entry 3). Using these established conditions, the rearrangement reaction was also attempted with *p*-methoxybenzylamine as a nucleophile, since the removal of the PMB protecting group would in theory be easier than for a PMP group. However, a complex mixture of products was generated and could not be neatly separated or characterized (entry 4).

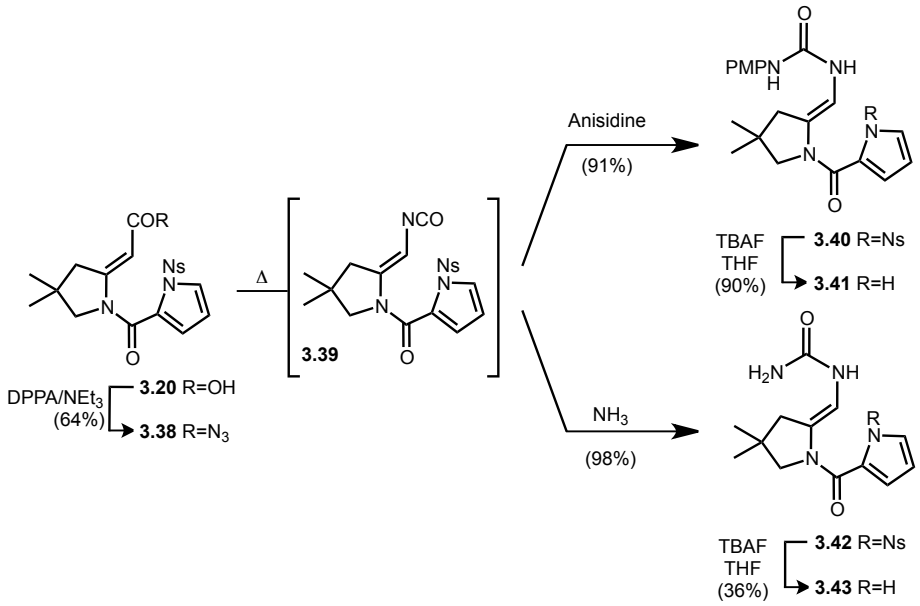


Scheme 3.10 - Curtius rearrangement sequence to vinyl urea **3.35** and **3.36**

entry	starting material	general procedure	nucleophile	outcome	purification method
1	**3.34**	A	$PhNH_2$	**3.37** [a]	--
2	**3.34**	B	$PhNH_2$	**3.35** 23% Y	recrystallization from EtOH
3	**3.34**	B	*p*-$OMePhNH_2$	**3.36** 53% Y	reversed-phase chromatography
4	**3.34**	B	*p*-$OMeBnNH_2$	complex mixture	--

Table 3.3 - Survey of nucleophiles for formation of vinyl urea **3.35** and **3.36** ; Procedure A: two-step: 1) PhH, 80 °C, 6 hours, concentrate; 2) PhMe, -15 °C then addition of nucleophile. Procedure B: one pot: i) PhMe (degassed), 80 °C, 6 hours; ii) PhMe, −78 °C then addition of nucleophile [a] as the major produt as detected by LC/MS

Unfortunately several attempts towards the removal of the tosyl protecting group on the pyrrole (conditions screened included: TBAF,[10] K_2CO_3/MeOH and Mg/NH_4Cl/MeOH) were met with no success. We had anticipated that the tosyl protecting group could be removed with a fluoride source but we found that the reaction to be very sluggish at room temperature.



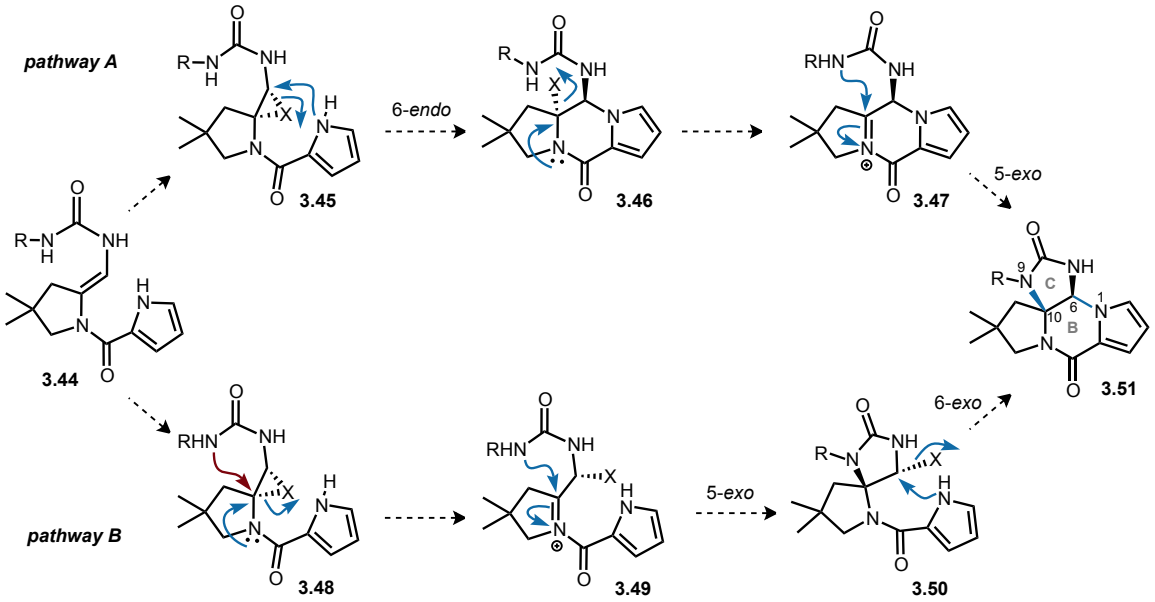
Scheme 3.11 - Curtius rearrangement sequence to PMP-urea **3.41** and primary urea **3.43**

We hypothesized that the nosyl protecting group would be easier to cleave under fluoride conditions as it would be more reactive towards nucleophilic aromatic substitution. Vinylogous carbamic acid **3.20** was treated with DPPA in the presence of triethylamine to afford vinylogous carbamoyl azide **3.38** in 64% yield (Scheme 3.11). Under our established one-pot procedure for the Curtius rearrangement, acyl azide **3.38** provided vinyl ureas **3.40** and **3.42** when the reaction was quenched with anisidine and ammonia, respectively. Gratifyingly, subjection of either **3.40** and **3.42** to nosyl deprotection using an excess of TBAF at room temperature led to the isolation of **3.41** and **3.43** after purification by reversed phase chromatography. Having devised a robust and scalable protocol for the synthesis of the pivotal cyclization precursors **3.41** and **3.43**, we changed our focus towards the projected cyclization sequence to stitch up the BC-ring motif.

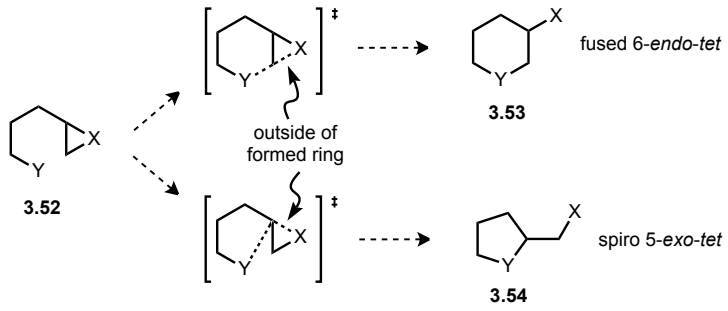
3.2.3 Cyclization Sequence

For the formation of the two remaining rings of the right-hand side core of palau'amine, we envisaged that both the N1-C6 bond (B-ring) and the N9-C10 bond (C-ring) could be formed simultaneously *via* a cyclofunctionalization reaction in which an electrophilic addition to a double bond triggers the capture of the resulting intermediate by a pendant nucleophilic group to generate a polycyclic product.[11] In our case, the

exocyclic olefin should act as the reactive center if treated with an electrophilic reagent to allow the annulation of the BC-ring motif *via* two plausible pathways (Scheme 3.12). In pathway A, the pyrrole nitrogen could open the reactive 3-membered ring in a 6-*endo* fashion which leaves an X-group at the C10 position which could act as a potential leaving group. Although the C-X bond that breaks in **3.45** is outside the newly formed ring and thusly should be considered according to Baldwin's rules[12] as an *exo*-process, the literature still refers to this cyclization as an *endo* process.[13] However, to avoid confusion, Jamison[14] and Danishefsky[15] have utilized the terms "fused" and "spiro" to describe the transition states leading to the *endo* and *exo* products, respectively (Scheme 3.13). Following the formation of the ketopiperazine B-ring *via* a fused 6-*endo*-*tet* cyclization, electron donation from the adjacent C15 amide carbonyl could then generate *N*-acyliminium **3.47** releasing the X-group from C10. Intramolecular trapping of **3.47** with the pendant urea in a 5-*exo*-*trig* cyclization would result in formation of the *syn*-fused imidazoline C-ring. Alternatively, in pathway B, we could invoke the opening of the spirocyclic 3-membered ring *via* the formation of the reactive *N*-acyliminium as in **3.48**. At this stage, the 5-*exo*-*trig* cyclization of either the distal nitrogen of the urea or the pyrrole nitrogen could occur but, from the examination of molecular models, we reasoned that the nitrogen of the pyrrole could not reach C10 due to conformation and structural rigidity of the pyrroloamide. Conversely, we cannot discount that the distal nitrogen of the pendant urea could open the 3-membered ring in a fused 5-*endo*-*tet* mode (pathway B – red arrow). We recognized that the 5-*endo* cyclization of the pendant urea onto the functionalized olefin was a Baldwin-disfavored process however, a brief survey of the literature showed that 5-*endo*-*tet* or *trig*-like cyclizations could be achieved.[16] Either arrow pushing rationale would lead to the generation of the spirocyclic imidazolinone C-ring in **3.50**. The direct nucleophilic attack in a 6-*exo*-*tet* fashion by the pyrrole nitrogen from the opposite face of the leaving group on C6 would give rise to desired ketopiperazine B-ring.



Scheme 3.12 - Potential mechanism for the formation of BC-rings

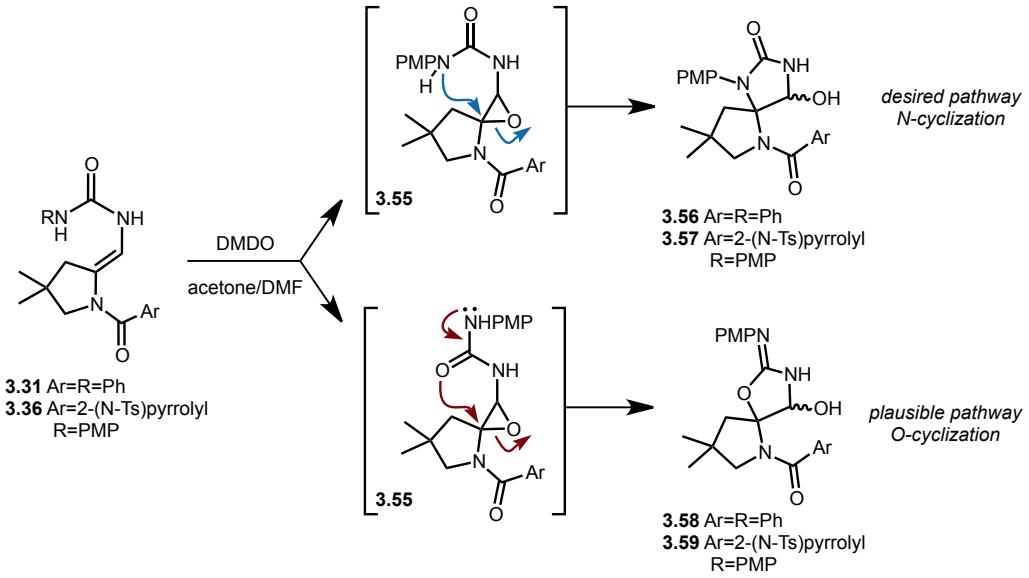


Scheme 3.13 - Baldwin's rules as they apply to intramolecular 3-membered ring opening

3.2.3.1 DMDO Cyclizations

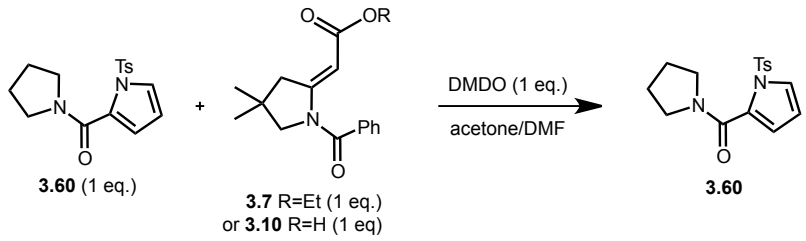
With suitable substrates in hand, we investigated cyclofunctionalization reactions in which the exocyclic olefin would be treated with a mild epoxidizing agent to be converted to the corresponding oxirane (Scheme 3.12 X=O). Before studying the cyclofunctionalization cascade sequence on a substrate with both nucleophilic partners such as **3.41** or **3.43**, we carried out test reactions with substrates containing only one nucleophilic site in order to probe the reactivity of the pendant urea. We commenced with an epoxidation reaction in which enediamine **3.31** was treated with one equivalent of dimethyldioxirane (DMDO) at −78 °C in a 10:1 mixture of acetone and DMF. LC/MS

analysis of the crude material revealed full consumption of the starting material and the mass of the major species present was consistent with the desired product **3.56**. Also, the appearance of the expected hemiaminal signal (close to 5.0 ppm)[17] in the ^{1}H NMR spectrum of the crude mixture suggested the desired oxidative cyclization had occurred. However all attempts to isolate or further characterize the putative spirocyclic hemiaminal **3.56** proved fruitless. Although we expected the participation of the distal nitrogen of the urea in the cyclofunctionalization reaction to provide hemiaminal **3.56**, we cannot discount the attack by the carbonyl oxygen to furnish the oxazolidonimine ring as in **3.58**. A urea is a bidentate nucleophile in which the oxygen of the carbonyl bears a preponderant amount of negative charge due to resonance. If we rationalize in terms of Hard-Soft theory, the epoxide generated from the functionalization of the olefin is a hard electrophile and the oxygen of the urea is more electronegative than nitrogen and is consequentially a harder nucleophile.[18] In the case of the cyclofunctionalization reaction of **3.31**, while we observed the characteristic hemiaminal signal in the ^{1}H NMR, we were unable to infer the connectivity of the formed product and we cannot disregard the possibility that cyclization *via* the oxygen had occurred (as in **3.58** in Scheme 3.14).[18b] In stark contrast to the relatively clean reaction observed with benzamide-derived enediamine **3.31**, LC/MS analysis of the crude material from the analogous reaction with **3.36** revealed a complex mixture of products that could not be separated or identified.



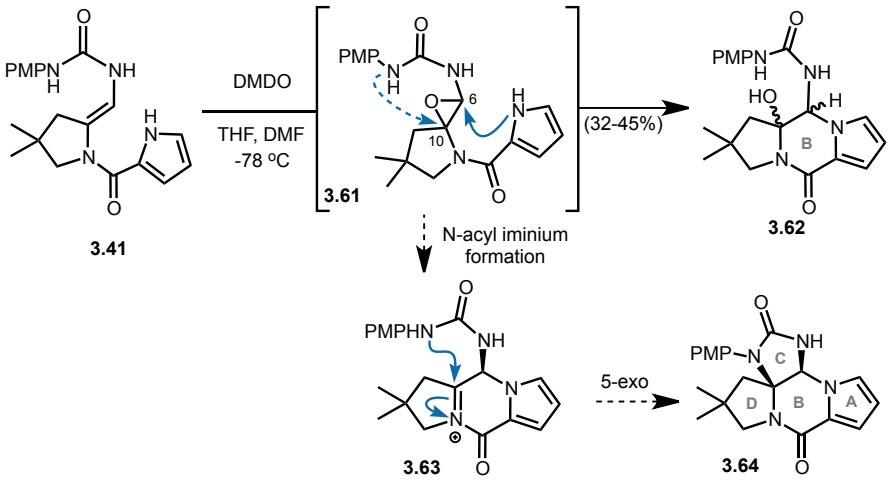
Scheme 3.14 - *N*- vs *O*-cyclization for the 5-*endo-tet* of urea **3.31** and **3.36**

We became aware of several reports in the literature indicating that pyrroles were prone to polymerization under oxidizing conditions[19] even with a relatively mild reagent such as DMDO,[20] which prompted us to further explore whether pyrrole oxidation would be a concern in the DMDO reaction with our substrates. Two competition experiments were conducted: a mixture of one equivalent of pyrroloamide **3.60** and either one equivalent of vinylogous imide **3.7** or vinylogous carbamic acid **3.10** was treated with one equivalent of DMDO. Monitoring of both reactions by LC/MS showed gradual consumption of the starting material containing the exocylic double bond (**3.7** and **3.10**); therefore we reasoned that, in the epoxidation reactions, DMDO should chemoselectively react with the electron-rich exocyclic olefin of the enediamine substrates leaving the pyrrole functionality untouched.



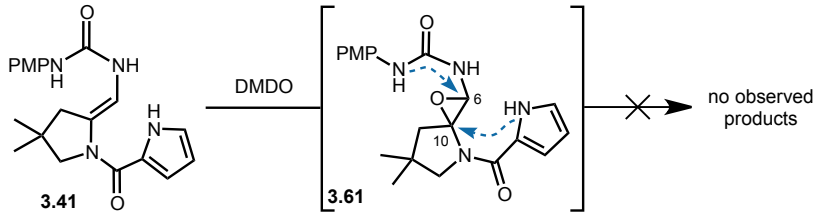
Scheme 3.15 - Competition experiment between 2-acylpyrrole **3.60** and olefins **3.7** and **3.10**

Continuing on our systematic investigation, we turned our attention to enediamine substrate **3.41** to test the nucleophilic nature of an unprotected pyrrole *N*-functionality. When enediamine **3.41** was treated with DMDO at −78 °C in a 10:1 mixture of THF and DMF, two products were isolated in a 1:1 ratio which could be only be separated by reversed phase HPLC. Both molecules exhibited similar ^{1}H and ^{13}C spectra. After extensive 2D NMR analysis (COSY, HSQC, HMBC), we were confident that the pyrrole nitrogen cyclized onto the epoxide forming the desired ketopiperidine B-ring. However no connectivity was observed between the PMP-bearing nitrogen and either the B- and D-rings. Moreover, high-resolution mass spectrometry data showed that the mass of both products were the same and consistent with the mass of the starting material incorporating an extra oxygen. We finally assigned the structure of the products as both diastereomers (1:1 ratio) of tricyclic heminal **3.62**.



Scheme 3.16 - B-ring formation *via* fused 6-*endo* epoxide opening with PMP-urea **3.41**

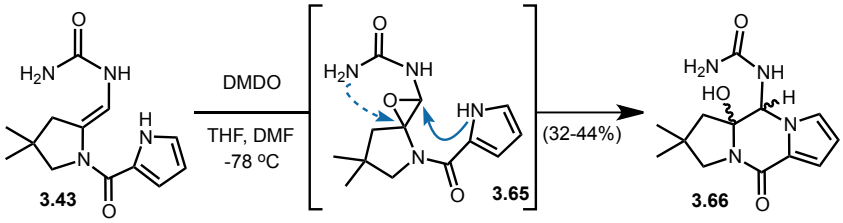
Interestingly, one could draw an alternative arrow pushing mechanism (Scheme 3.17) in which the pyrrolyl nitrogen opens the epoxide in a Baldwin-favored spiro 5-*exo*-*tet* fashion allowing the urea to potentially cyclize to a seemingly strained 4-membered ring. However, examination of hand-held molecular models suggested that the nitrogen of the pyrrole could not reach C10 due to conformation and structural rigidity of the pyrroloamide and was rather forced to cyclize at the desired C6 position.



Scheme 3.17 - Alternate arrow-pushing

At this stage, on one hand, we were pleased to find that the treatment of enediamine **3.41** with DMDO had triggered the kind of reactivity that we sought to obtain and that the reaction exhibited a high degree of regioselectivity towards the formation of the 6-membered B-ring. On the other hand, we were dismayed by the lack of reactivity of the pendant urea. The inertness of the urea could be due to the steric hindrance generated by the large PMP protecting group which could impede the approach of the nucleophile or may be attributable simply due to the low nucleophilicity of a urea further deactivated by a PMP. We hypothesized that we could increase the reactivity of the urea functionality in the desired cyclofunctionalization if the PMP group was removed. During our

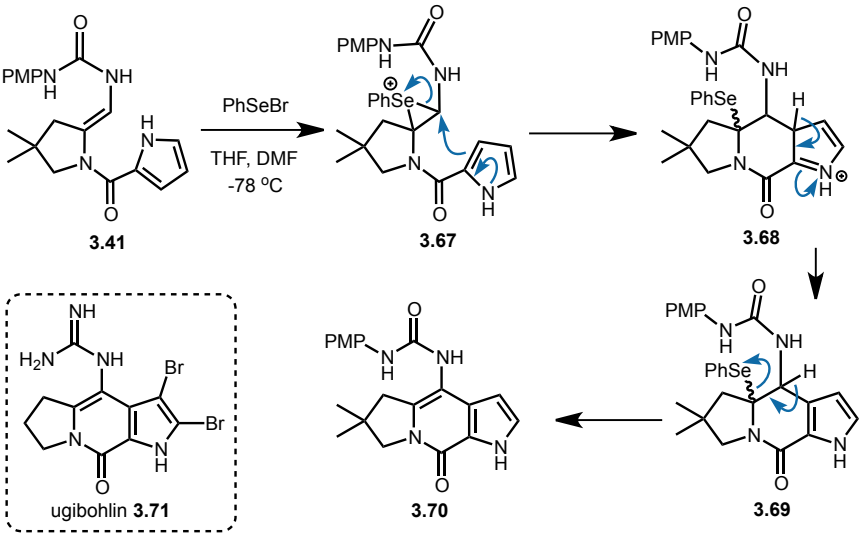
investigation into the Curtius rearrangement, we had also prepared primary urea-containing enediamine substrate **3.43** (Scheme 3.11), which was the perfect substrate to test our hypothesis. When enediamine **3.43** was treated with an equimolar amount of DMDO at −78 °C, a 1:1 mixture of diastereomers was isolated from a reversed phase column but was easily separable by reversed phase HPLC. Sadly, we observed the same reactivity pattern as with the PMP-derived enediamine substrate, indicating the low nucleophilicity of the urea was the main issue.



Scheme 3.18 - B-ring formation *via* fused 6-*endo* epoxide opening with primary urea **3.43**

3.2.3.2 Selenocyclizations

During our attempts to probe the cyclofunctionalization reaction to access the desired tetracyclic system (Scheme 3.12), a survey of alternative electrophilic reagents was conducted. One interesting result occurred when enediamine **3.41** was treated with phenylselenyl bromide at −78 °C in a 10:1 mixture of THF and DMF. The major product was isolated from the crude reaction after reversed phase chromatography. Interestingly, we noted that, upon analysis of the ^{1}H NMR, one of the pyrrole C-H protons had disappeared and the characteristic N-H peak was still visible. After extensive spectroscopic and MS analysis, the product was assigned as tricyclic compound **3.70**. A plausible mechanistic pathway for the formation of this annulation product resembles that of an electrophilic aromatic substitution involving the opening of the reactive seleniranium cation **3.67** by the C3 position of the pyrrole followed by an elimination of the phenylselenide (Scheme 3.19). In fact, the nucleophilic nature of the C3-position of the pyrrole has previously been observed both when the pyrrole is brominated at the C4 and C5 positions and unbrominated.[21] This reactivity profile could be used as an approach to access the skeletal framework of several PIA alkaloids, such as odiline **1.11**, the isophakellins **1.14-1.15**, the styloguanidines **1.33-1.35** and ugibohlin **3.71**.



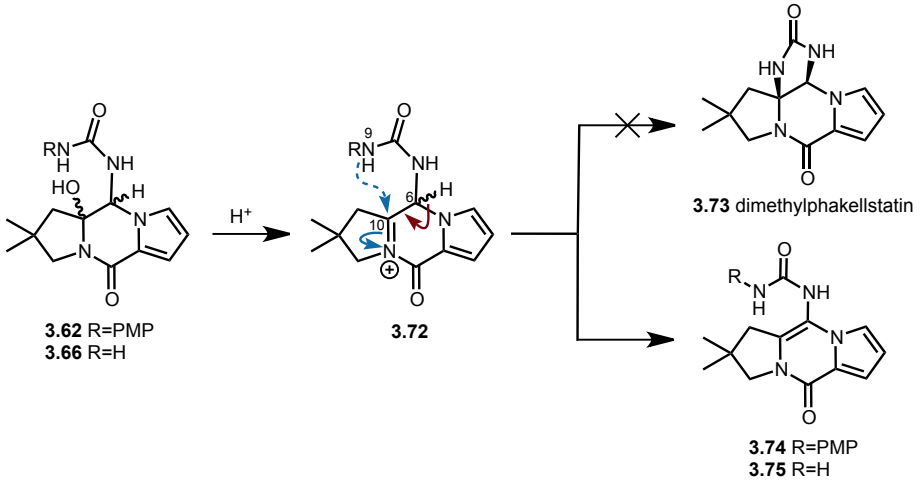
Scheme 3.19 - B-ring formation *via* 6-*endo* seleniranium opening

This chemodivergent mode of attack of the pyrrole – N vs C – can be rationalized by Pearson's Hard-Soft Acid-Base theory. The nitrogen of the pyrrole is more electronegative than the carbon at the 3-position and consequently a harder nucleophile. In the case of the DMDO reaction (*vide supra*), the reaction of the olefin with DMDO generates a hard electrophile thus favoring *N*-cyclization as the mode of attack, resulting in the formation of structures such as **3.62** and **3.66**. In contrast, the seleniranium cation generated from the reaction of the olefin and phenylselenyl bromide is a soft electrophile which favors C-cyclization as the mode of attack, generating structure **3.70**.

3.2.4 *N*-Acyliminium Formation

At this stage, we had developed an efficient strategy to access the B-ring motif of the phakellstatin and isophakellin series of natural products based on a cyclofunctionalization reaction in which the chemoselectivity is controlled by the choice of reagent. Unfortunately, the N9-C10 bond could not be formed in this process, however we anticipated that the activation of the hemiaminal could induce the cyclization of the imidazoline *via* the formation of the *N*-acyliminium.[22] A brief review of the literature on the synthesis of the monomeric PIA alkaloids revealed that the cyclization of the C-ring could be effected *via* the trapping of the *in-situ* generated acyliminium ion **3.72** (Scheme 3.20).[23] This annulation strategy had previously been described in the context of the formation of phakellin (Scheme 1.20) in which a pendant guanidine cyclizes in a similar

5-*exo* fashion.[23a] We hypothesized that, analogously to the guanidine cyclization, the urea should also close onto the iminium to form the desired tetracyclic scaffold **3.73**.



Scheme 3.20 - *N*-acyliminium formation from hemiaminals **3.62** and **3.66**

entry	S.M.	acid (eq.)	solvent	outcome
1	**3.62**	PPTS (0.5 then 1)	MeCN-d_3 +DMF-d_4	N.R.
2	**3.62**	TFA (0.5)	MeCN-d_3 +DMF-d_4	decomp
3	**3.62**	CSA (0.5)	MeCN-d_3 +DMF-d_4	**3.74** 96% Y
4	**3.66**	CSA (0.5)	MeCN-d_3 +DMF-d_4	**3.75** 67% Y
5	**3.66**	AcOD (xs)	DMF-d_4	**3.75** 75% Y

Table 3.4 – Survey of acids for acyliminium cyclization

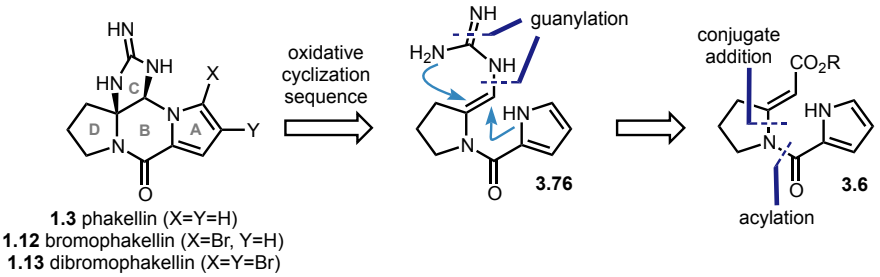
To promote the dehydration of the hemiaminal moiety, thus generating the reactive *N*-acyliminium as to form the desired N9-C10 bond, a variety of Brønsted acids were screened. Both ends of the reactivity spectrum were quickly identified: while no perceptible reaction was observed when carbinolamine **3.62** was treated with one equivalent of pyridinium *p*-toluenesulfonate (PPTS), **3.62** undergoes rapid decomposition when subjected to a substoichiometric amount of TFA. Unfortunately, with camphorsulfonic acid (CSA), we observed a competitive pathway in which the elimination of the proton at the C6 aminal position led the formation of the undesired by-product, ketene aminal **3.74** (Scheme 3.20, red arrow). As before, we rationalized that the PMP group on the urea was the main cause for the inertness of the pendant urea in the

cyclization due to the steric hindrance and the poor nucleophilicity of the phenyl urea. Furthermore, we were encouraged by Kishi and coworkers's seminal report on the total synthesis of (±)-saxitoxin in which the construction of an imidazoline ring was constructed by trapping an iminium ion with a primary urea under acidic conditions.[24] To test the reactivity of our primary urea in the intramolecular acyliminium cyclization, tricyclic hemiaminal **3.66** was subjected to the same conditions (CSA and AcOH) as with **3.62**. Once more, we found that the closure of the urea onto the acyliminium was outcompeted by the elimination of the proton at the C6 aminal position furnishing the undesired by-product **3.75**.

In light of these results, further investigations toward the direct construction of the phakellstatin core were not pursued. Activation of the olefin in tricyclic ketene aminals such as **3.74** and **3.75** was not attempted. However, further exploration of these reactivity avenues is warranted. Our investigations towards the synthesis of phakellstatin showed that the desired ketopiperazine B-ring could be formed regioselectively in a cyclofunctionalization reaction. However all our efforts to induce the stepwise the bis-annulation sequence (scheme 3.12) were thwarted by the low reactivity of the urea. Our efforts were refocused on an alternative approach still centered upon the late-stage oxidative cyclization with a more nucleophilic guanidine motif instead of a urea.

3.3 Studies Towards a Phakellin Core

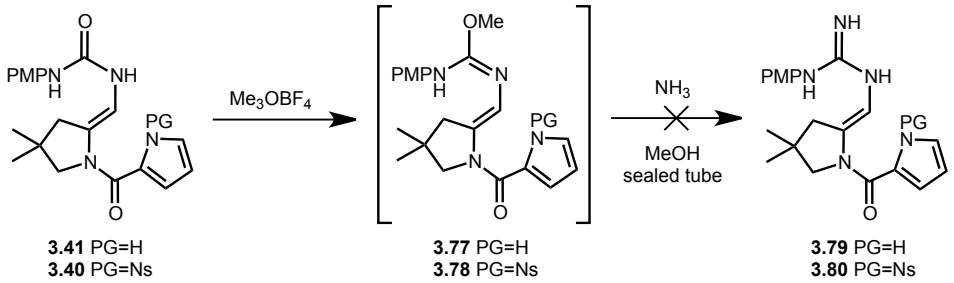
Our revised strategy towards the ABC motif of palau'amine was to directly access the guanidine-containing tetracyclic structure **3.2** from the vinyl guanidine **3.4** by employing our established cyclofunctionalization protocol with DMDO. We anticipated that the earlier incorporation of a guanidine group would help to overcome the reactivity issues that we encountered with the urea substrates. This strategy would also allow for the expedient formation of the structurally related natural product, phakellin **1.3**, and its brominated congeners **1.12** and **1.13** (Scheme 3.21). We chose to adapt our route starting from the *Z-exo*-cyclic *β*-enaminoesters constructs (Scheme 2.16) and to develop an expedient method to arrive at the target cyclization precursor **3.76** with the pivotal guanidine functional group.



Scheme 3.21 - Retrosynthetic analysis for phakellin

3.3.1 Conversion of Urea to Guanidine

It was envisioned that the urea moiety in **3.40** or **3.41** could be interconverted directly to the guanidine *via* the intermediacy of an *O*-alkyl pseudourea. This workaround approach based on the precedents of Kishi[24a, 24b] and Jacobi[25] in the saxitoxin area has been applied to the total synthesis of other natural products[26] including dibromophakellin **1.13**.[27] Treatment of **3.41** with Meerwein's reagent (Me_3OBF_4) and sodium bicarbonate in ethyl acetate generated a complex mixture of products that could not be neatly separated or characterized (Scheme 3.22). It was not clear whether the *O*-alkylation of the nucleophilic carbonyl oxygen in urea **3.41** would be a chemoselective process and thus we considered that the other potentially nucleophilic sites in **3.41** might be interfering and leading to unidentified products. The alkylation reaction of urea **3.40** with Meerwein's salt and sodium bicarbonate in dichloromethane resulted in inconsistent outcomes that provided only unintelligible or inconclusive data. Treatment of **3.40** with Meerwein's salt with proton sponge as a base in dichloromethane cleanly generated the desired alkylamidine as confirmed by ^{1}H NMR and LC/MS; however, all attempts to isolate pseudourea **3.78** (either *via* normal or reversed phase chromatography) were unsuccessful. In order to avoid the isolation of the unstable *O*-methylamidine, we tried to trap this intermediate as the desired guanidine **3.80** by direct treatment with a methanolic solution of ammonia in a sealed tube. Unfortunately, after some experimentation, the one-pot two-step sequence failed to furnish any detectable amount of the desired product.

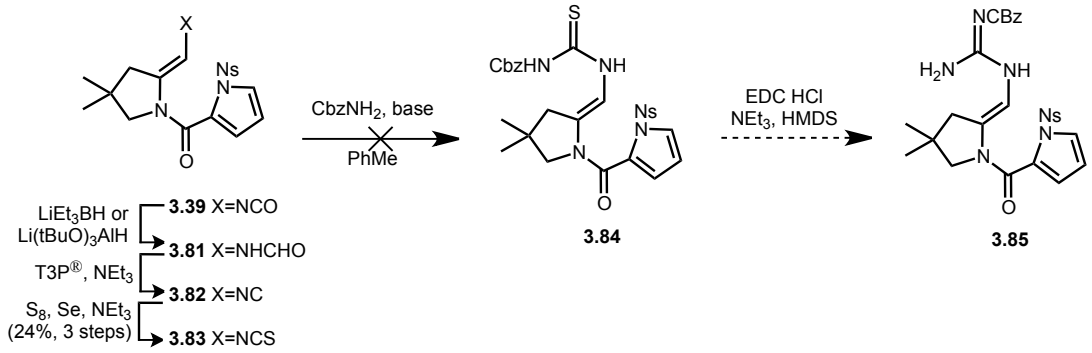


Scheme 3.22 - Attempts to access guanidine **3.79** and **3.80** *via* O-methyl pseudourea

3.3.2 Introduction of Guanidine *via* Thiourea

At this point, due to the problems associated with the instability of the pseudourea, we designed a workaround to access the analogous thiourea **3.84** which we believed could be easier to convert to the desired guanidine **3.85**.[23b, 28] One of the well-known methods to access guanidines is from the treatment of an EWG-containing thiourea with EDC and an amine. The first task in order to prepare thiourea **3.84** was the incorporation of the sulfur. The direct thionation of the carbonyl of the urea in **3.41** using a reagent such Lawesson's reagent could not be achieved in a chemoselective manner in the presence of the carbonyl of the amide.[29] Therefore, a synthetically laborious route to build in the thiourea – adapted from Hart[30] – was necessary and consisted of a stepwise excision of the oxygen and incorporation of the sulfur (Scheme 3.23). The reduction of vinyl isocyanate **3.39** to the corresponding vinyl formamide **3.81** using a solution of lithium triethylborohydride proved to be inconsistent and poorly reproducible. After screening several other reductants ($NaBH_4$, $LiAlH_4$, $HSiCl_3/NEt_3$), we found that the milder reducing agent, lithium tri(*t*-butoxy)aluminium hydride, afforded the desired vinyl formamide **3.81** as the major product; however, no drastic improvement in the yield was ever obtained. The dehydration of the formamide to vinyl isonitrile **3.82** proved to be equally problematic under standard conditions ($TsCl/NEt_3$,[30] $POCl_3$[31]). We discovered that T3P® (propylphosphonic anhydride), a reagent commonly used as a mild coupling reagent in peptide synthesis and as a water scavenger,[32] cleanly generated the desired vinyl isonitrile **3.82** without the need for further purification. Reaction of isocyanides with elemental sulfur is the most straightforward method for the preparation of isothiocyanates but the reaction of aromatic isocyanides is reported to be very sluggish. We opted to try the protocol developed by Fujiwara[33] in which isonitriles in the presence

triethylamine and a catalytic amount of elemental selenium generate *in-situ* the isoselenocyanate (RNCSe), which then undergoes the Se-S exchange reaction with elemental sulfur to furnish the desired isothiocyanate (RNCS). Exposure of vinyl isonitrile **3.82** to these conditions provided the anticipated vinyl isothiocyanate **3.83** as the sole product in good yield. Although the whole 3-step procedure was streamlined to provide the desired vinyl isothiocyanate **3.83**, albeit in low overall yield (24% over the 3 steps), our investigation towards the formation of Cbz-derived thiourea **3.81** was unsuccessful. All attempts to quench the isothiocyanate **3.83** with benzylcarbamate pretreated with a base such as sodium hydride or *n*-butyllithium resulted in the formation of a complex mixture of unidentified products. In light of more promising results obtained with an alternative approach (*vide infra*) that was being investigated in parallel, we quickly abandoned this strategy.

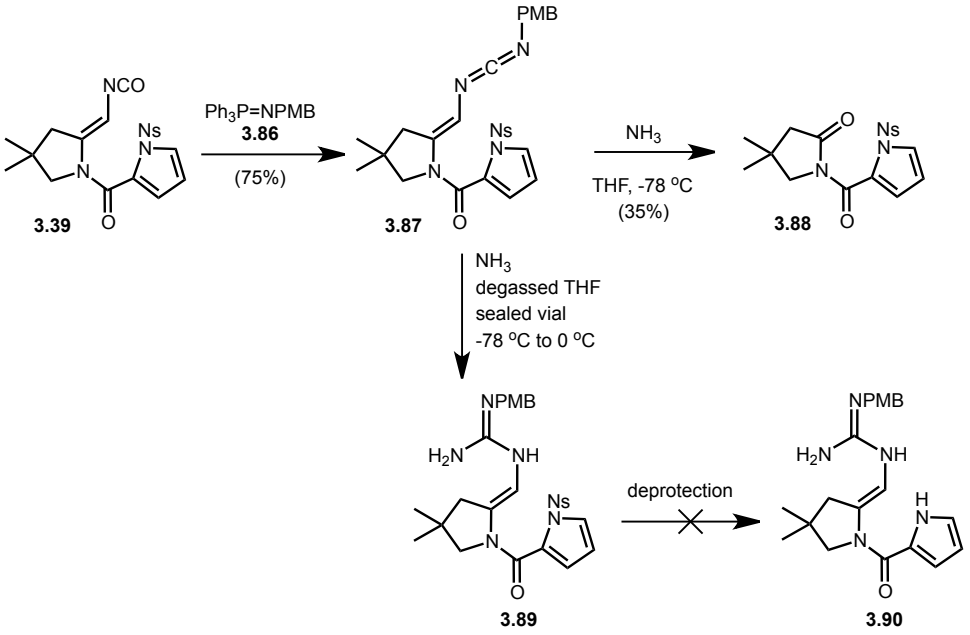


Scheme 3.23 - Attempts to access guanidine **3.85** *via* thiourea **3.84**

3.3.3 Sequential Curtius Rearrangement/Aza-Wittig

Given the disheartening results obtained thus far with the strategies aimed at forming vinyl guanidine construct **3.76** (Scheme 3.21), it was decided to attempt the formation of the guanidine moiety in a more direct approach using a vinyl carbodiimide as a gateway to the desired vinyl guanidine. This synthetic approach to guanidines has been extensively used in natural product synthesis.[34] The required carbodiimide is formed from the aza-Wittig reaction of the isocyanate with a phosphazene. We chose the PMB-substituted phosphazene **3.86** as a coupling partner for the aza-Wittig reaction with isocyanate **3.39** because we envisaged that the PMB protecting group could be easily cleaved from the guanidine in a final deprotection step. The coupling of vinyl isocyanate **3.39** and PMB-phosphazene **3.86** cleanly afforded the chromatographically stable

carbodiimide **3.87** in 75% yield. In a first attempt to access the target guanidine **3.89**, ammonia was carefully condensed dropwise into a solution of carbodiimide **3.87** at −78 °C but only pyrrolidinone **3.88**, most likely the product from oxidative cleavage of the exocyclic olefin, was isolated from the reaction. In our studies with the urea constructs (Table 3.3), oxidative cleavage of the olefin had also been a problem. However, it was quickly rectified by carefully degassing the reaction mixture before running the Curtius rearrangement. In subsequent attempts to access the target guanidine **3.89**, ammonia was carefully bubbled into a degassed solution of carbodiimide **3.87** at −78 °C for a few minutes (1-3 minutes, depending on scale). We also found that conducting the reaction in a round-bottomed microwave vial proved operationally beneficial as after the addition of ammonia, the vial could be sealed and allowed to warm to 0 °C without any concerns about the internal pressure of the reaction. After the reaction mixture was cooled back to −78 °C, the tube was unsealed and allowed to warm to room temperature under an atmosphere of argon. LC/MS and HRMS analysis the crude residue confirmed a single product and the isotopic pattern of the significant mass cluster was consistent with vinyl guanidine **3.89**. Unfortunately, **3.89** proved to be unstable and any attempt at purification (normal and reversed phase chromatography) resulted in the complete loss of material, presumably *via* decomposition during the workup and purification.

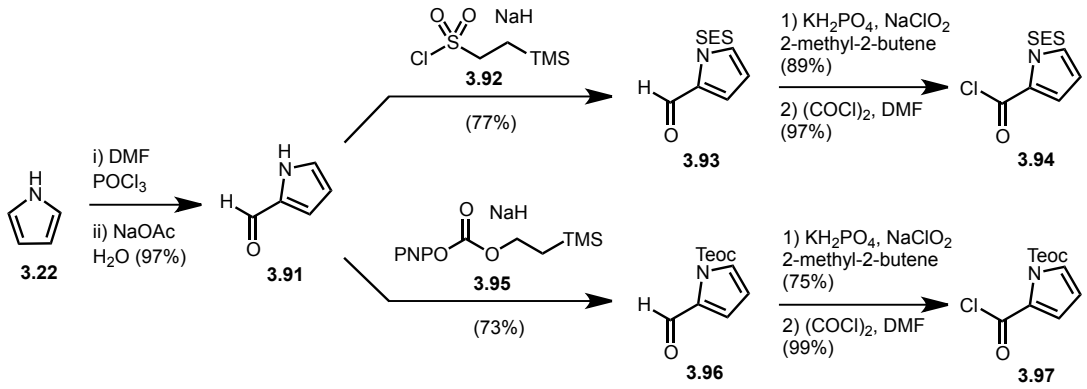


Scheme 3.24 - Elaboration of isocyanate **3.39** to vinyl guanidine **3.89**

To access our key target cyclization precursor such as **3.90**, we need to cleave the nosyl protecting group from the pyrrole. Considering the trapping of the carbodiimide with ammonia was a clean reaction, we opted to access the *N*-deprotected pyrroloamide **3.90** in a one-pot process without any work-up of the unstable intermediate **3.86**. After complete conversion of **3.87** to **3.89** (reaction monitored by LC/MS), subjection of **3.89** to a variety of conditions for nosyl-cleavage (TBAF, TBAF•(*t*BuOH)$_4$,[35] 2-mercaptoethanol) resulted in a slow decomposition of the starting material or no reaction. In contrast to the ease of nosyl-deprotection observed with the urea construct (Scheme 3.11), we were unable to liberate the pyrrole nitrogen from its nosyl protecting group at a late-stage just prior to the cyclofunctionalization reaction in the presence of the guanidine. Therefore we chose to examine a new protecting group which would be easier to cleave under mild conditions using a source of fluoride.

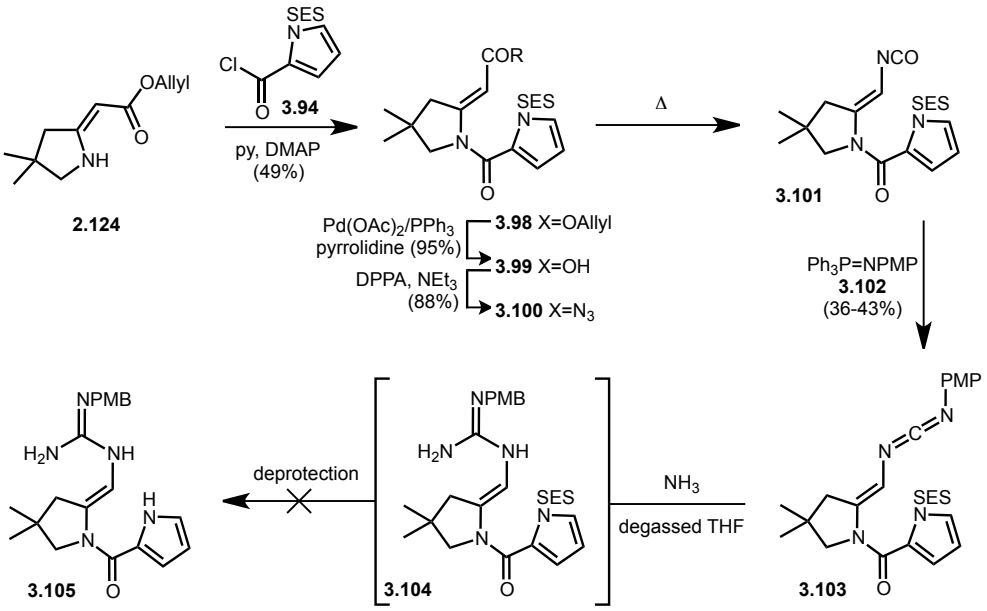
After a brief review of the literature, we chose to synthesize in parallel two separate systems each incorporating a different protecting group. The sulfonamide-based SES and carbamate-based Teoc fit the bill. Although their use as pyrrole protecting groups is quite limited,[23b, 36] both were compatible with the synthetic transformations of our route and mild conditions were used for their removal.

Since we had previously been successful in coupling β-enaminoesters with *N*-protected acylpyrrole units *via* an acylation with acyl chlorides (Scheme 3.6), we proceeded to the synthesis of acyl chlorides **3.94** and **3.97**, which began with 1*H*-pyrrole-2-carboxaldehyde **3.91** – easily accessible on large scale (>30 grams) from the Vilsmeier-Haack reaction of pyrrole **3.22** (Scheme 3.25).[37] Treatment of **3.91** with sodium hydride and either 2-trimethylsilylethanesulfonyl chloride **3.92**[38] or nitrophenyl 2-(trimethylsilyl)ethyl carbonate **3.95**[39] effected the SES and Teoc protection of the pyrrole nitrogen to afford aldehydes **3.93** and **3.96**, respectively. The corresponding carboxylic acids were obtained from the Pinnick oxidations of the respective aldehyde and converted to the acyl chlorides **3.94** and **3.97** in nearly quantitative yield by exposure to oxalyl chloride and catalytic dimethylformamide.[23b]



Scheme 3.25 - Construction of *N*-SES and *N*-Teoc protected acylpyrrole units

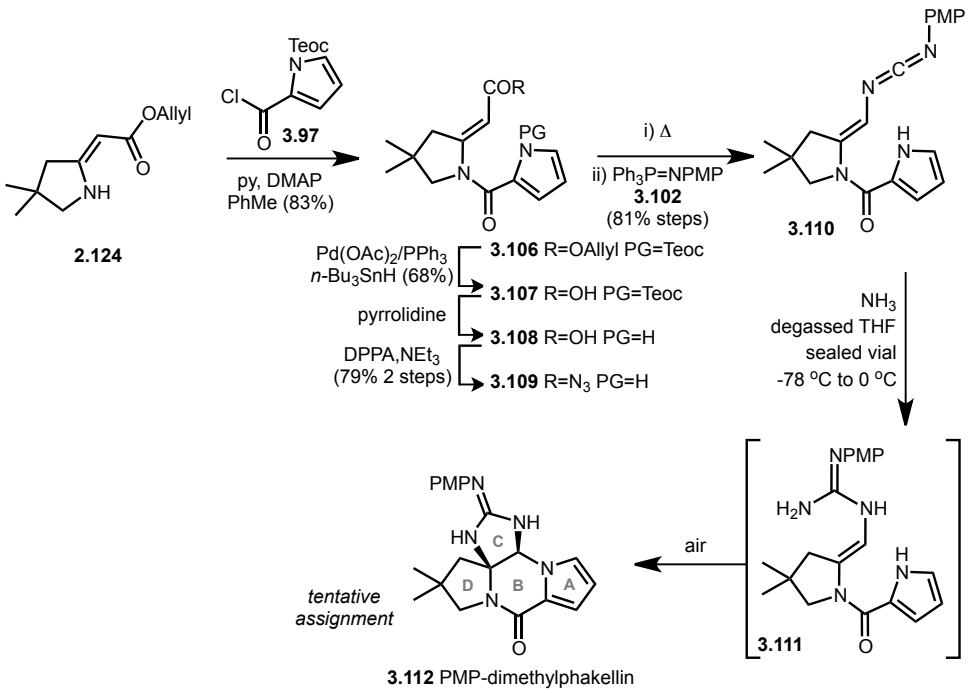
The acylation of **2.124** with *N*-SES acyl chloride **3.94** furnished vinylogous imide **3.98** in modest yield (Scheme 3.26). Deprotection of the *O*-allyl group of vinylogous imide **3.98** proceeded smoothly to afford, in 95% yield, vinylogous carbamic acid **3.99** which was treated with DPPA and triethylamine to produce vinylogous carbamoyl azide **3.100**. The Curtius rearrangement occured readily upon mild heating of **3.100** in toluene to furnish isocyanate **3.101**. Surprisingly, treatment of isocyanate **3.101** with PMB-derived phosphazene **3.86** led to the formation of an unidentified product with no traces of the desired carbodiimide whereas the reaction of isocyanate **3.101** with PMP-derived phosphazene **3.102** afforded carbodiimide **3.103** as the major product, albeit in low yield (36-43%). As done previously, ammmonia was bubbled into a solution of carbodiimide **3.103** in degassed THF to cleanly afford vinyl guanidine **3.104**. We tried to identify conditions (TBAF, TBAF•(tBuOH)$_4$[35], HF buffered in pyridine) to remove the sulfonamide protecting group but, unfortunately these resulted only in the decomposition of the starting material.



Scheme 3.26 - Elaboration of *N*-SES construct **3.98** to vinyl guanidine **3.105**

When we investigated the analogous route with the Teoc protecting group on the pyrrole, we made a surprising discovery (Scheme 3.27). The coupling of **2.124** with *N*-Teoc acyl chloride **3.97** afforded vinylogous imide **3.106** in good yield. When the deprotection of the *O*-allyl group was attempted using the previously established conditions (Pd^0 and pyrrolidine), the only isolated product was the Teoc-adduct of pyrrolidine. This suggested that the excess amount of the nucleophile used to trap the allyl group also cleaved the Teoc from the pyrrole. This unprecedented method for Teoc cleavage, though initially undesired, eventually proved beneficial. After screening several other nucleophiles for the Pd^0-catalyzed deallylation (morpholine, HCO_2H/NEt_3, dimedone), we found that the use of tributyltin hydride[40] afforded the desired vinylogous carbamic acid **3.107** in moderate yield. At this stage, treatment of pyrroloamide **3.107** with pyrrolidine at room temperature cleanly effected the Teoc-cleavage to provide the more polar vinylogous carbamic acid **3.108**. We hypothesized that the free NH of the unprotected pyrrole would not interfere in the elaboration of **3.108** to the desired carbodiimide. The formation of the vinylogous carbamoyl azide **3.109** using DPPA and triethylamine proceeded smoothly. We found that running the Curtius rearrangement and the aza-Wittig in one pot to be operationally simpler and higher yielding, most likely due to the strict requirement for anaerobic reaction conditions. After

mild heating of **3.109** in degassed toluene effected the rearrangement to the corresponding isocyanate, PMP-derived phosphazene **3.102** was added and stirring was continued at room temperature to afford carbodiimide **3.110** as the major product, in excellent yield (81%). Next, ammonia was bubbled into a degassed solution of carbodiimide for 2 minutes until the volume of the reaction mixture increased slightly. The vial was sealed and the reaction was stirred at −78 °C then warmed to 0 °C at which point a white precipitate formed, presumably the insoluble and polar guanidine. After the reaction had cooled back down to −78 °C, the vial was unsealed and the reaction mixture was allowed to warm to room temperature open to air. LC/MS analysis of the crude reaction prior to warming revealed full consumption of the starting material and the mass of the major species present was consistent with the desired guanidine product **3.111**. In initial trials, we performed the ammonia reaction in an NMR tube and monitored the formation of the guanidine, however the ^{1}H NMR of guanidine **3.111** was not pristine. All attempts to isolate the desired cyclization precursor **3.111** by conventional methods were thwarted by the propensity of the material to slowly react upon exposure to ambient air. When we monitored the reaction as it warmed to room temperature under air by LC/MS, we tracked the consumption of the guanidine and the clean formation of two new products. After purification by reversed-phase chromatography, the major product isolated appeared consistent by ^{1}H NMR as well as by HRMS with tetracycle **3.112**. The chemical shifts of the two sets of protons on the D-ring and the hemiaminal proton at the junction of the B/C-rings were clearly identifiable in the ^{1}H NMR spectrum and seemed reasonably consistent with the NMR data of the natural product. Although the evidence gathered strongly supports the indicated structural assignment, the minute amount of product obtained prevented an exhaustive spectroscopic characterization and this assessment must be considered tentative.



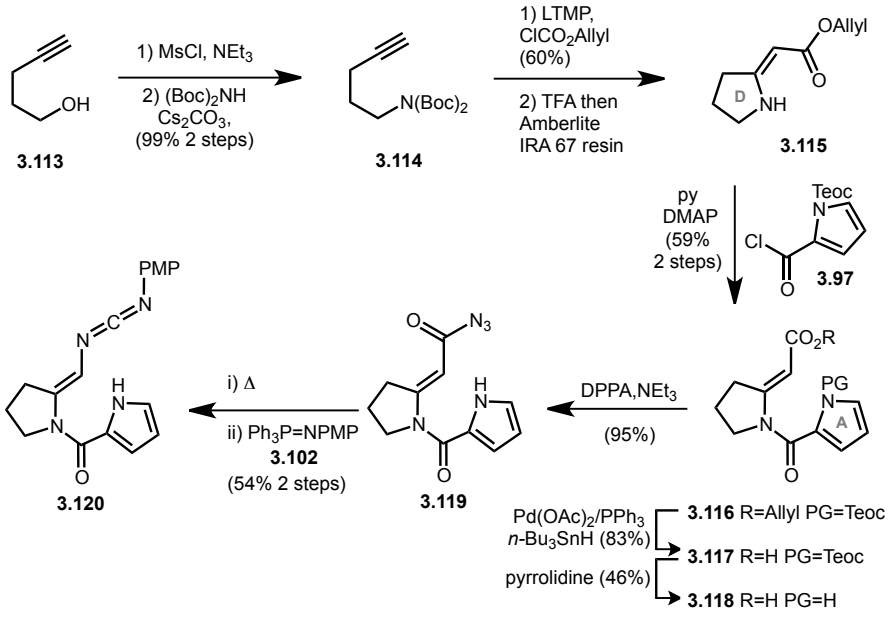
Scheme 3.27 - Elaboration of *N*-Teoc construct **3.106** to PMP-dimethylphakellin **3.112**

3.3.4 Efforts Towards the Total Synthesis of (±)-Phakellin

At this stage, we embarked on the total synthesis of phakellin (**1.3**) in order to apply and validate our strategy used in the gem-dimethyl model system (Scheme 3.27) but would also allow for the direct comparison of spectroscopic data with that of the natural product.

Our racemic synthesis of phakellin (Scheme 3.28) commenced with the formation of bis-carbamate **3.114**, accessible in straightforward fashion from commercially available 4-pentynol **3.113** *via* the intermediacy of a primary mesylate.[41] Deprotonation of the terminal alkyne of **3.114** with LTMP followed by addition of allyl chloroformate furnished the desired ynoate. We reasoned that the Baldwin favored 5-*exo*-*dig* conjugate addition of the free amine onto the ynoate should still proceed even without the Thorpe-Ingold effect as in **2.124**. As expected, upon treatment with an excess of trifluoroacetic acid to cleave both Boc-protecting groups and stirring of the resulting TFA salt with the acid-scavenging triethylamine-bound resin, the desired conjugate addition occurred and yielded the desired D-ring fragment **3.115** of phakellin. The coupling of the *Z*-*exo*-cyclic

β-enaminoesters **3.115** with *N*-Teoc pyrrole 2-acyl chloride **3.97** allowed for the introduction of the pyrrole A-ring and provided bicyclic vinylogous imide **3.116** in reasonable yield (59% over 2 steps). Next, both protecting groups were removed sequentially: treatment of vinylogous imide **3.116** to *in-situ* formed Pd^0 followed by addition of tributylstannane liberated the *O*-allyl group then subjection to pyrrolidine cleaved the Teoc group from the pyrrole nitrogen. Conversion of vinylogous carbamic acid **3.118** to carbamoyl azide **3.119** with DPPA and triethylamine proceeded smoothly in 95% yield. The one-pot Curtius rearrangement/aza-Wittig was performed under the same condition as for the formation of **3.110**. As the progress of the aza-Wittig reaction proved impossible to monitor by TLC, it was necessary to concentrate an aliquot of the reaction mixture and to determine, by IR, full consumption of the isocyanate (2278 cm^{-1}) and conversion to the carbodiimide (2111 cm^{-1}). Unfortunately, after extensive experimentation, the PMP-derived carbodiimide **3.120** could only be isolated in a modest yield of 54%.

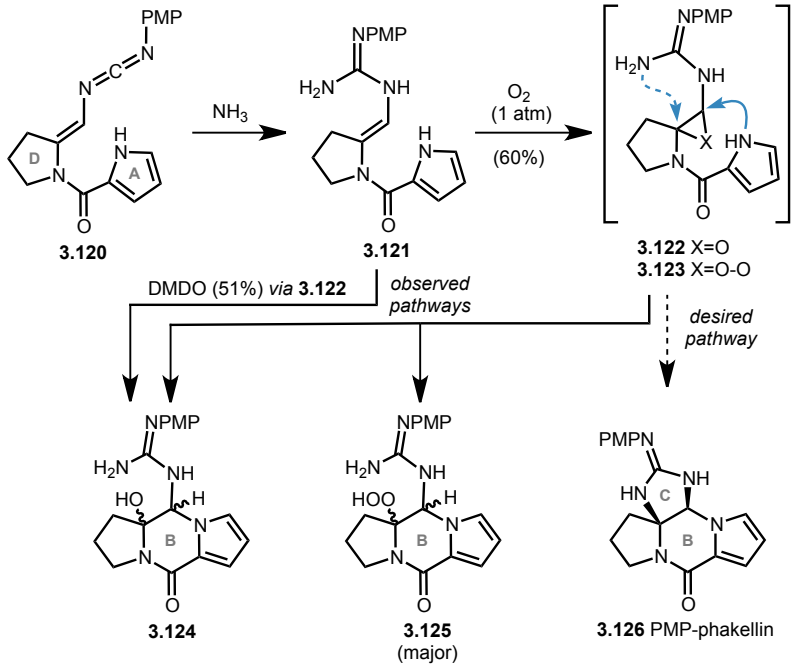


Scheme 3.28 - Synthesis of vinyl carbodiimide **3.120** from 4-pentynol **3.113**

At this stage, the final nitrogen needed to be introduced to complete the nitrogen skeleton of phakellin. As previously with **3.110** (Scheme 3.27), vinyl carbodiimide **3.120** was completely converted to vinyl guanidine **3.121** upon treatment with gaseous

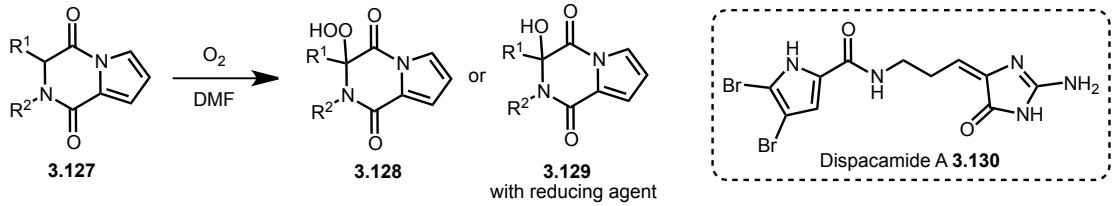
ammonia under a strictly inert atmosphere (Scheme 3.29). Upon warming the reaction to room temperature under argon, a white precipitate formed and LC/MS analysis of the crude reaction mixture confirmed a single product whose mass was consistent with guanidine **3.121**. When O_2 was bubbled into the reaction mixture, the white precipitate quickly disappeared and LC/MS data showed that the guanidine had been entirely consumed and that two new products formed exclusively. The purification by reversed-phase chromatography of the major products allowed for the separation of the two major compounds. The ^{1}H NMR spectra of both of these new products were difficult to interpret, however we noted that the spectra were very similar: both contained all the correct shifts for the 3 sets of protons on the D-ring as well as the pyrrole protons of the A-ring however the characteristic C6 aminal proton signal was absent. Moreover, LC/MS data confirmed that neither compound was the desired fully-cyclized product, PMP-phakellin **3.126**, but instead showed that one of the compounds had a mass of the starting material incorporating an one extra oxygen while the other isolated compound had a mass consistent with the addition of two extra oxygen atoms therefore both products were tentatively assigned as **3.124** and **3.125**, respectively. A plausible mechanistic rationale for the formation of these products could be advanced: the reaction of molecular oxygen with electron-rich enediamine generated a putative perepoxide such as **3.123** which is opened by the pyrrole nitrogen securing the pyrazinone B-ring and affords **3.125** with the pendant peroxide at C10 as the major product. Although minor amounts of the corresponding carbinolamine **3.124** could also be isolated from the reaction mixture, the formation of the desired PMP-phakellin tetracycle **3.126** was not observed. We had reasoned that in the case of the gem-dimethyl substrate **3.112** (Scheme 3.27), the final cyclization event securing the C-ring guanidine had occurred under the conditions for purification (reversed-phase chromatography with MeCN/H_2O with 0.1% formic acid). By contrast, when the analogous carbodiimide **3.120** was subjected to identical reaction and purification conditions, tricyclic compounds **3.124** and **3.125** were the only products isolated. Alternatively, optimization of the epoxidation of the enediamine was investigated in an attempt to control the unwarranted overoxidation product, **3.125**. As in our sequence with the ureas (Schemes 3.16 and 3.18), DMDO, instead of molecular oxygen, was used to effect the controlled epoxidation of the exocyclic olefin after the

formation of the guanidine **3.121**. However, this did not result in any significant improvements as the desired tricyclic carbinolamine **3.124** was only isolated in 51% yield.



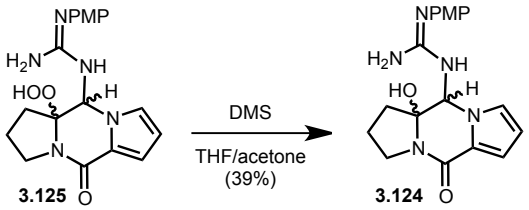
Scheme 3.29 - Formation of B-ring *via* fused-6-*endo* epoxide opening with PMP-guanidine **3.121**

Although the oxygen-mediated oxidation/cyclization process of our enediamine species **3.121** seemed surprising (Scheme 3.29), the air oxidation within the context of the PIA family had previously been reported by Al-Mourabit (Scheme 3.30).[42] In particular, in synthetic efforts to toward acyclic monomeric PIA dispacamide A **3.130**, Al-Mourabit had discovered that the aerobic peroxidation at the α-position of α-aminoacids acylated with pyrrolecarboxylic acid proceeded with triplet oxygen under neutral conditions to provide peroxides such as **3.128** and that the oxidation in the presence of a reducing agent afforded the corresponding carbinolamine derivative **3.129**.



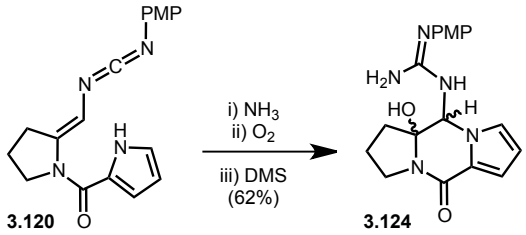
Scheme 3.30 - Diketopiperazine oxidation reported by Al-Mourabit

Moreover, to verify the identity of the tricyclic "perhemiaminal" **3.125** but also to steer clear of the unknown reactivity pattern of the peroxide, we attempted the conversion of **3.125** to **3.124** *via* the reduction of the hydroperoxide functionality to the corresponding alcohol. Pleasingly, dimethyl sulfide (DMS) was able to effect the reduction to the desired carbinolamine **3.124**, albeit in a low yield of 39% (Scheme 3.31).



Scheme 3.31 - Reduction of "perhemiaminal" **3.125** to heminal **3.124**

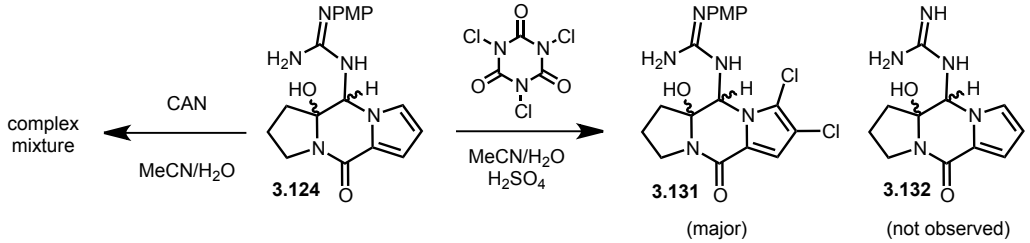
Although far from satisfactory, this procedure to access tricyclic carbinolamine **3.124** had potential for optimization and could provide a more efficient entry into the projected *N*-acyliminium precursor for the synthesis of phakellin. We reasoned that the formation of the guanidine, B-ring cyclization and reduction of the resulting peroxide could all be effected in a one-pot process. Gratifyingly, the reaction starting with vinyl carbodiimide **3.120** was easily telescoped to provide tricyclic guanidine **3.124** in good yield – 62% overall after 3 steps (Scheme 3.32).



Scheme 3.32 - Telescoped reaction of vinyl carbodiimide **3.120** to tricyclic hemiaminal **3.124**

We hypothesized that the liberation of the guanidine from the *p*-methoxyphenyl (PMP) protecting group could solve the problem with reactivity. The deprotection of the PMP functionality from an amine nitrogen is reported to occur *via* oxidative dearylation with ceric ammonium nitrate.[43] Most reports describe the oxidative removal at low pH usually with a large excess of CAN. Moreover, in Feldman's synthesis of dibromophakellstatin and dibromophakellin (Scheme 1.18), CAN (in a refluxing mixture of acetonitrile and water) was used in the oxidative hydrolysis of thioimidate-containing

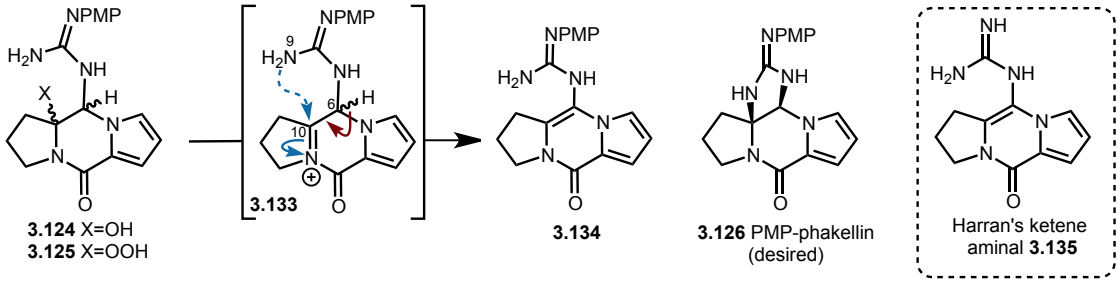
advanced intermediate **1.142** to the tetracyclic urea, dibromophakellstatin (**1.14**). This key step suggested that these types of pyrrolopyrazinones are stable to harsh oxidative conditions such as CAN and that our oxidative deprotection could proceed in an analogous fashion. Unfortunately, all our attempts to cleave the PMP protecting group prior to the final cyclization event were met with failure (Scheme 3.33). A brief survey of different conditions was performed: no discernable reaction occurred upon treatment with two equivalents of CAN at room temperature or at 80 °C. However, an intractable mixture was obtained using five equivalents of CAN at 95 °C, likely due to decomposition from pyrrole oxidation. An alternative procedure was also attempted in which trichloroisocyanuric acid (TCCA) is used as the oxidant in the deprotection of the PMP group.[44] When carbinolamine **3.124** was treated with a slight excess of TCCA at room temperature in a mixture of water and acetonitrile, tricyclic dichloropyrrole **3.131** was isolated as the sole product. The LC/MS data indicated the incorporation of two chlorine atoms onto our starting material. However the minute amount of product obtained prevented an exhaustive spectroscopic characterization and this characterization must be considered tentative. In retrospect, given that TCCA has been reported to be an efficient reagent for the chlorination of unsaturated compounds including aromatic and heteroaromatic systems,[45] this outcome is not surprising.



Scheme 3.33 - Failed PMP-deprotection of heminaminal **3.124**

The strategy for the final annulation step involved the Baldwin-favored 5-*exo*-*dig* of the pendant guanidine onto the putative *N*-acyliminium **3.133** (Scheme 3.34). It seemed reasonable to anticipate that generating the reactive *N*-acyliminium could again be achieved by dehydration of the hemiaminal moiety as had been observed before with the urea series (Scheme 3.20). We had reasoned that the pendant guanidine would be more nucleophilic than the analogous urea and thus the cyclization should proceed hopefully without any interference from the elimination of the C6 proton as was

previously observed. In initial experiments, we resorted to examine tricyclic peroxide **3.125** to garner some information about the potential reactivity of this substrate. Treatment with TFA (Table 3.5 entry 1) led to the exclusive formation of the C6 proton elimination product **3.134** *via* the formation of putative iminium **3.133** formed from the expulsion of the hydrogen peroxide anion. The structural assignment for ketene aminal **3.134** was based upon ^{1}H NMR comparison with the free guanidine derivative **3.135** prepared by Harran.[46] We had reasoned that the judicious choice of solvents would aid in the stabilization of the positive charge of the putative *N*-acyliminium **3.133** and would thus favor the closure of the guanidine ring. The same reactivity was observed when peroxide **3.125** was treated with the milder acid, formic acid, in a mixture of acetonitrile, water and trifluoroethanol (TFE). Interestingly, in contrast to what was observed with the analogous urea **3.66**, no noticeable reaction was detected when carbinolamine **3.124** was treated with a large excess of d_4-acetic acid.



Scheme 3.34 - Formation N-acyliminium from **3.124** and **3.125** to access PMP-phakellin

entry	S.M.	Brønsted or Lewis acid (eq.)	solvent	outcome
1	**3.125**	TFA (xs)	MeCN-d_3 +DMSO-d_6	**3.134** (n.d.)
2	**3.125**	HCO_2H (0.5 then 1)	MeCN/H_2O/TFE	**3.134** (41%)
3	**3.124**	AcOD (xs)	MeCN-d_3 +DMSO-d_6	N.R. (83% rec SM)
4	**3.124**	$B(O_2CCF_3)_3$ (10)	TFA	**3.134** (98%)

Table 3.5 – Survey of acids for acyliminium cyclization

Furthermore, we were encouraged by DuBois and coworkers's report of the first generation total synthesis of (+)-saxitoxin in which the construction of the guanidine ring was secured by trapping an iminium ion with a guanidine under Lewis acidic conditions.[47] Following the established protocol, carbinolamine **3.124** was exposed to

freshly prepared boron tris(trifluoroacetate) in TFA, which led to the clean and near quantitative conversion to the ketene aminal **3.134** (Table 3.5 entry 4). Once again, we found that the closure of the pendant guanidine onto the acyliminium was outcompeted by the elimination of the proton at the C6 aminal position furnishing the undesired by-product **3.134**. Although our studies with these tricyclic carbinolamine structures (Schemes 3.20 and 3.34) have demonstrated their propensity to undergo a competitive reaction manifold and may suggest that a revision of our retrosynthetic analysis may be required, these systems remain worthy candidates for the development of an efficient approach to key functionalities found in the PIAs.

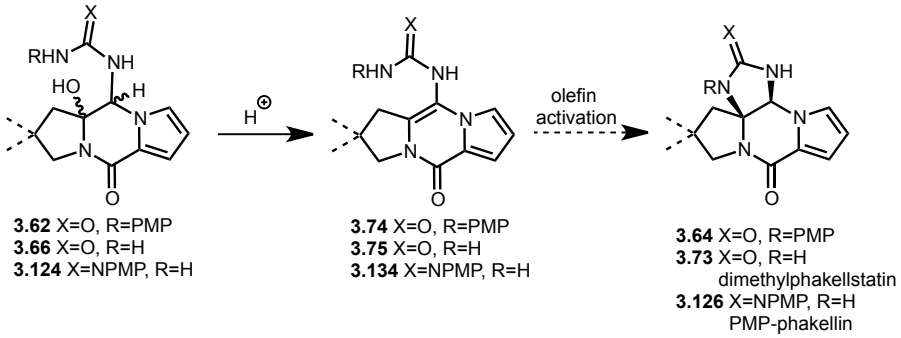
The synthesis of the 5,6,5-tricyclic core of phakellin was accomplished from a cyclofunctionalization reaction forging the pyrazinone B-ring from an advanced intermediate containing both the A and D rings. The synthetic route had to be optimized to avoid the presence of oxygen until required at the cyclofuntionalization step. The last ring, the guanidine C-ring, was to be formed from a 5-*exo* cyclization onto an *N*-acyliminium. This bond disconnection turned out to be a dead-end due to the competing C6 proton elimination process and unfortunately, this last ring was not formed despite many attempts.

3.4 Conclusion and Future Directions

A novel route towards the tetracyclic natural product phakellin **1.3** was developed. The synthesis featured the application of a conjugate addition of a free amine to an ynoate ester to construct the pyrrolidine D-ring. The *N*-Teoc pyrrole A-ring was introduced in a straightforward fashion *via* a coupling reaction. After the sequential removal of the protecting groups, the resultant vinylogous carbamic acid was converted to the corresponding carbamoyl azide which set the stage for the one-pot Curtius rearrangement/aza-Wittig reaction generating the PMP-derived vinyl carbodiimide. The formation of the guanidine was followed by a molecular oxygen-mediated cyclofunctionalization reaction which regioselectively formed the desired pyrazinone B-ring. The resulting peroxide could be subsequently reduced to the tricyclic carbinolamine. At this stage, it was anticipated that the cyclization of the pendant guanidine would occur in a 5-*exo* fashion onto an *N*-acyliminium generated from the carbinolamine under acidic

conditions. Initial results with our gem-dimethyl model system (Scheme 3.27) strongly suggested that the desired C-ring cyclization had occurred. Unfortunately, all attempts at the formation of the N9-C10 bond securing the desired final ring of the phakellin structure were thwarted.

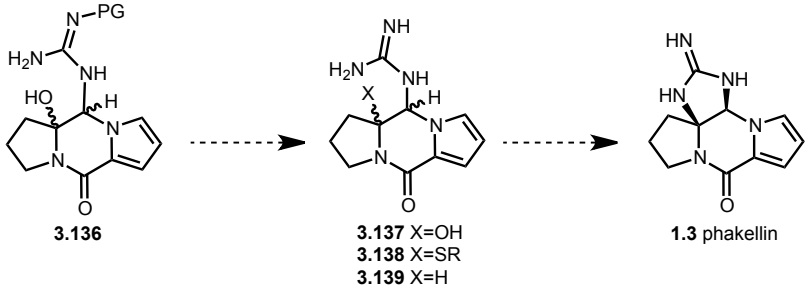
Future investigations toward the closure of the guanidine C-ring could be pursued. In this chapter (sections 3.2.4 and 3.3.4), it was demonstrated that tricyclic ketene aminals such as **3.74**, **3.75** and **3.134** could be readily accessed under acidic conditions *via* the elimination of the C6 proton. The closure of the C-ring guanidine could be promoted by the activation of the C6-C10 olefin (Scheme 3.35). Although electrophilic activation of the unsaturation with a source of halonium might prove to be difficult due to the presence of the pyrrole,[48] a direct metal-mediated activation would be a more *via*ble avenue to pursue.[49]



Scheme 3.35 - C-ring formation *via* olefin activation of ketene aminal

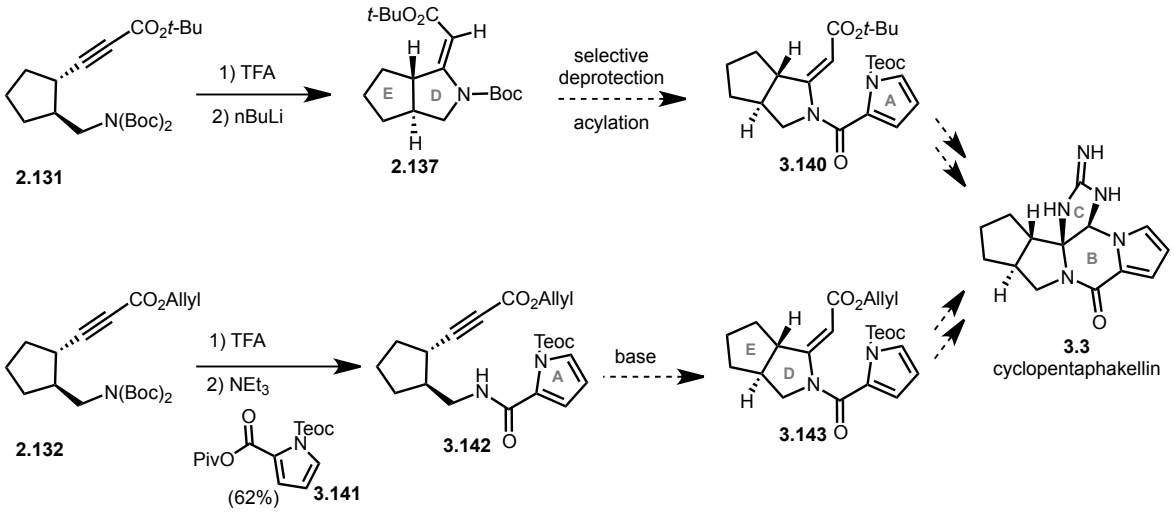
Having established a practical method to transform vinylogous carbamic acid **3.118** into functionalized guanidine **3.121**, a substrate capable of undergoing a facile guanidine cyclization sequence could be accessed with either of the following changes. Firstly, an alternative protecting group for the guanidine that can be more easily removed than *p*-methoxyphenyl would be highly attractive. Secondly, with carbinolamine **3.137** (Scheme 3.36), a screen of Lewis acids could be undertaken to assess whether, under Lewis acidic conditions, generation of the *N*-acyliminium would allow for the guanidine cyclization to occur. Thirdly, similarly to work by Gin and coworkers,[23b] we could adapt our route to incorporate a more convenient synthetic handle (i.e., a thioether as in **3.138**, Scheme 3.36) at the C10 position that could be chemoselectivity activated at a later stage to generate the required *N*-acyliminium for the guanidine cyclization. Lastly, a C−H

amination strategy for the N9-C10 disconnection reminiscent of work by Romo and coworkers[23a] (Scheme 1.20) could be envisioned. The reduction of hemiaminal to the saturated pyrrolopyrazinone tricyclic core **3.139** (Scheme 3.36) would lead to development of conditions for the guanidine cyclization.



Scheme 3.36 - Second generation approaches to the C-ring formation

Furthermore, in future efforts, our strategy to construct the ABCD-ring framework needs to be applied to the cyclic model system (Scheme 2.20) and finally to the total synthesis of palau'amine. We envisage that we could access the desired ADE-ring framework in either of two ways (Scheme 3.37). The application of our ynoate conjugate addition approach led the formation of the desired *trans*-fused azabicyclo[3.3.0]octane **2.137** which could be utilized directly to access tricyclic system **3.140** following selective deprotection of the *tert*-butyl carbamate and subsequent acylation with the A-ring pyrrole unit. Alternatively, the earlier introduction of the pyrrole A-ring *via* the coupling of the mixed anhydride **3.141** with the corresponding TFA salt of **2.132** has only recently been achieved in 62% yield. The strategy to access the *trans*-fused bicycle within tricyclic vinylogous imide **3.143** would involve the conjugate addition of an amide to the ynoate. With either tricyclic system **3.140** or **3.143**, future efforts will involve accessing the cyclopentaphakellin **3.3** by the application of our strategy towards phakellin. Application of these new methods will hopefully culminate in the total synthesis of this structurally complex natural product.



Scheme 3.37 - Potential routes to complete ABCDE-ring framework

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CONTRIBUTIONS TO KNOWLEDGE

1. The synthesis of *trans*-fused azabicyclo[3.3.0]octane bicyclic system of palau'amine was achieved by the conjugate addition of a carbamate nitrogen to an ynoate, within the context of a cyclic model system **2.137**.

   In order to access the phakellstatin series of natural products, an approach to elaborate the resulting exocyclic *α,β*-unsaturated ester from the conjugate addition approach to the vinyl ureas **3.40** and **3.42** *via* a Curtius rearrangement was developed.

2. To secure the pyrazinone ring found in phakellstatin, a novel cyclofunctionalization reaction using DMDO was established yielding regioselective access to the desired tricyclic carbinolamines **3.62** and **3.66**.

   To access the phakellin and palau'amine right-hand side core, an expedient method to elaborate the exocyclic *α,β*-unsaturated ester, *via* a one-pot Curtius rearrangement/aza-Wittig, to vinyl carbodiimide **3.120** was developed. Conditions were established to furnish the desired guanidine in advanced intermediate **3.121** which contains the all the requisite nitrogen atoms in phakellin.

3. A molecular oxygen-mediated cyclofunctionalization reaction with the guanidine-containing intermediate was developed to efficiently secure the pyrazinone ring found in phakellstatin and to afford the desired tricyclic carbinolamine **3.124**.

Chapter 4.

Experimental Procedures

General Procedures: All non-aqueous reactions were carried out in flame- or oven-dried (120 ºC) glassware fitted with rubber septa under a positive pressure of argon with magnetic stirring, unless otherwise noted. Liquids and solutions were transferred *via* syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation at ~15 Torr (water aspirator or Buchi V-700 diaphragm vacuum pump). Analytical thin layer chromatography (TLC) was performed using glass-backed silica gel $60F_{254}$ (Merck, 250 μm thickness). Plates were visualized under UV light (at 254 nm) and/or by staining with ceric ammonium molybdate or potassium permanganate followed by heating. Flash column chromatography was carried out using 60Å Silica Gel (230-400 mesh) (Silicycle) as a stationary phase with reagent grade solvents. Reactions were monitored by HPLC-MS on reversed phase column, using acetonitrile/water/0.1% formic acid as the mobile phase.

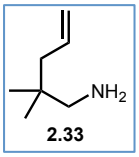
Materials: Tetrahydrofuran and diethyl ether were purified by distillation from sodium benzophenone ketyl radical under a nitrogen atmosphere. Toluene, dichloromethane, triethylamine, diisopropylamine were purified by distillation from calcium hydride under a dry air atmosphere. Methanol was stored over activated 3Å molecular sieves. Dimethylsulfoxide was purified by distillation from calcium hydride under a argon atmosphere and stored over activated 4Å molecular sieves. Under certain circumstances, dichloromethane, acetonitrile, toluene, dimethylformamide, tetrahydrofuran, methanol may have also been obtained from a Innovative Technology Pure Solv MD-7 solvent system passing HPLC or reagent grade solvents through activated alumina or activated 5Å molecular sieves. Ethyl acetate, hexanes, acetone and chloroform were used without purification. Where noted, solvents were deoxygenated by carrying out a freeze-pump-thaw cycle three times. Deuterated solvents were purchased from either Aldrich or Cambridge Isotopes and used as received, with the exception of deuterated chloroform which was stored over activated 4Å molecular sieves. Alkyl halides and chloroformates were passed through basic alumina prior to use. Alkylation substrates were dried via azeotropic removal of water using dry toluene. *n*-Butyllithium was titrated with a solution of *sec*-butanol in toluene using 2,2'-dipyridyl as an indicator in diethylether. Other chemicals were purchased from Aldrich, Acros or Strem and used as received without

further purification unless otherwise noted.

Instrumentation: Microwave reactions were performed using a Biotage Initiator instrument. Infrared (IR) spectra were obtained using a Bruker alpha Platinum ATR. Proton and carbon-13 were obtained on Varian 200, 300, 400, 500 MHz or Bruker 400, 500 MHz spectrometers. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (7.27 ppm), benzene-d^6 (7.16 ppm), CD_3OD (3.31 ppm), acetone-d^6 (2.05 ppm) or DMSO-d^6 (2.50 ppm). ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sex (sextet), m (multiplet), br s (broad singlet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), ddd (doublet of doublets of doublets). Deuteriobenzene (benzene-d^6), deuteriochloroform ($CDCl_3$), CD_3OD, or DMSO-d^6 served as internal standard (128.30 ppm, 77.23 ppm, 49.00 ppm, or 39.50 ppm respectively) for all ^{13}C spectra. HPLC analysis and purification were conducted on an Agilent 1200 Series instrument equipped with VWD-detector, octadecyl-functionalized silica-gel HPLC column (Agilent, Zorbax SB-C18 250 mm x 9.4 mm, 5 μm), UV detection at 210, 254 and 280 nm. High-resolution mass spectra were obtained by Dr. Nadim Saade and Dr. Alexander Wahba (McGill University, Chemistry Department).

4.1 Trans-fused 5,5-Azabicyles: Diamination, Amidyl Radicals and Conjugate Addition

4.1.1 Acyclic Model System Substrates

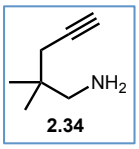


2.33

2,2-Dimethylpent-4-en-1-amine. To a stirred solution of diisopropylamine (5.9 mL, 0.040 mol, 1.2 eq.) in 120 mL of THF cooled to −78 °C was added a 2.27 M solution of *n*-BuLi in hexanes (16.2 mL, 0.037 mol, 1.1 eq.) dropwise. The reaction mixture was stirred at −78 °C for 15mins. Isobutyronitrile (3.0 mL, 0.33 mol, 1.0 eq.) was added in 1 portion at −78 °C. The reaction mixture was stirred at −78 °C for 1h. Allyl bromide (5.8 mL, 0.067 mol, 2.0 eq.) was added in several portions at −78 °C. The reaction was allowed to warm to 20 °C overnight then was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and most of the solvent was removed under reduced pressure on ice to yield 2,2-dimethylpent-4-enenitrile (3.82 g) as a yellow solution of in diethyl ether (concentration determined by ^{1}H NMR) that could be used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.81 (m, 1H), 5.17 (m, 2H), 2.25 (d, J = 7.3 Hz, 2H), 1.33 (s, 6H). Spectral data match literature values.

To a slurry of lithium aluminum hydride (4.96 g, 0.131 mol, 4.0 eq.) in diethyl ether (50 mL) at 0 °C was added a solution of the crude nitrile (0.33 mol, 1.0 eq.) in diethyl ether (50 mL) over 30 min. The reaction was allowed to warm to 20 °C overnight then cooled to 0 °C. Water (5.0 mL, initially added dropwise), 15% aqueous sodium hydroxide (5.0 mL) and water (15.0 mL) were sequentially added with vigorous stirring. The reaction mixture was then filtered, and the resulting filter cake washed thoroughly with diethyl ether. The filtrate was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure on ice to yield the product (3.59 g, 0.037 mol, 95% over 2 steps) as a yellow oil. NMR (400 MHz, $CDCl_3$) δ 5.83-5.77 (m, 1H), 5.04-4.99 (m, 2H), 2.44 (s, 2H), 1.96 (d, *J* = 7.0, 2H), 1.45 (br, 2H), 0.84 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 116.9, 111.6, 52.57, 43.99, 34.83, 24.55. HRMS (ESI) calcd for

C7H16N [M+H] 114.1277; found 114.1280.

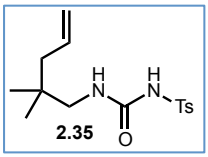


2.34

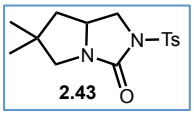
2,2-Dimethylpent-4-yn-1-amine. To a stirred solution of diisopropylamine (6.0 mL, 0.40 mol, 1.2 eq.) in 120 mL of diethyl ether cooled to −78 °C was added a 2.50 M solution of *n*-BuLi in hexanes (14.7 mL, 0.037 mol, 1.1 eq.) dropwise. The reaction mixture was stirred at −78 °C for 15mins. Isobutyronitrile (3.0 mL, 0.033 mol, 1.0 eq.) was added in 1 portion at −78 °C. The reaction mixture was stirred at −78 °C for 1h. Propargyl bromide (7.4 mL of a 80% wt. solution in toluene, 0.050 mol, 1.5 eq.) was added in several portions at −78 °C. The reaction was allowed to warm to 20 °C overnight then was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and most of the solvent was removed under reduced pressure on ice to yield a dark brown solution of 2,2-dimethylpent-4-ynenitrile contaminated with propargyl bromide in diethyl ether and toluene (concentration determined by ^{1}H NMR) but could be used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (d, J = 2.5 Hz, 2H), 2.18 (t, J = 2.5 Hz, 1H), 1.44 (s, 6H).

To a slurry of lithium aluminum hydride (3.8 g, 0.10 mol, 3.0 eq.) in diethyl ether (100 mL) at 0 °C was added a solution of the crude nitrile (0.033 mol, 1.0 eq.) in diethyl ether (100 mL) over 30 min. The reaction was allowed to warm to 20 °C overnight then cooled to 0 °C. Water (3.8 mL, initially added dropwise), 15% aqueous sodium hydroxide (3.8 mL) and water (11.4 mL) were sequentially added with vigorous stirring. The reaction mixture was then filtered, and the resulting filter cake washed thoroughly with diethyl ether. The filtrate was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure on ice to yield a solution of the amine (5.34 g, 0.032 mol determined by ^{1}H NMR, 98% over 2 steps) in diethyl ether and toluene. The material could be used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 2H), 2.15 (d, J = 2.4 Hz, 2H), 2.00 (t, J = 2.4 Hz, 1H), 0.95 (s, 6H).

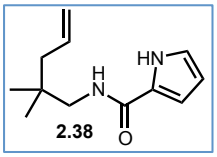
4.1.2 Diamination Substrates



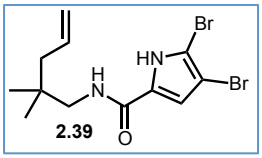
***N*-((2,2-Dimethylpent-4-en-1-yl)carbamoyl)-4-methylbenzenesulfonamide.** To a stirred solution of **2.33** (566 mg, 5.003 mmol, 1.0 eq.) in DCM (10 mL) cooled to 0 °C was added *p*-toluenesulfonyl isocyanate (0.84 mL, 5.50 mmol, 1.1 eq.). The reaction was allowed to warm to 20 °C and stirred for 1h after which the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield the product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 6.63 (br s, 1H), 5.82-5.74 (m, 1H), 5.10-4.95 (m, 2H), 3.04 (d, J = 6.2 Hz, 2H), 2.44 (s, 3H), 1.88 (d, J = 7.3 Hz, 2H), 0.82 (s, 6H). Spectral data match literature values.[1]



6,6-Dimethyl-2-tosyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one. To a stirred solution of $Pd(OAc)_2$ (4.5 mg, 0.0200 mmol, 0.05 eq.) and $PhI(OAc)_2$ (258 mg, 0.800 mmol, 2.0 eq.) in DCM (5 mL) were added **2.35** (124 mg, 0.400 mmol, 1.0 eq.), Me_4NCl (44 mg, 0.400 mmol, 1 eq.) and NaOAc (33 mg, 0.400 mmol, 1 eq.). The reaction mixture was allowed to stir for 16h at 20 °C then quenched with saturated solution of sodium thiosulfate. Ethyl acetate and water were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (1:3:3 mixture of diethyl ether:DCM:hexanes as eluent) to yield the product (78 mg, 2.510 mmol, 63%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.03 (dd, J = 8.7, 9.3 Hz, 1H), 3.92 (m, 1H), 3.63 (m, 1H), 3.29 (d, J = 11.3 Hz, 1H), 2.77 (d, J = 11.3 Hz, 1H), 2.42 (s, 3H), 1.78 (dd, J = 6.1, 12.4 Hz, 1H), 1.31 (dd, J = 9.2, 12.4 Hz, 1H), 1.07 (s, 3H), 0.99 (s, 3H). Spectral data match literature values.[1]

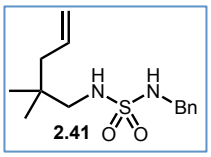


***N*-(2,2-Dimethylpent-4-en-1-yl)-1*H*-pyrrole-2-carboxamide.** To a stirred solution of pyrrole-2-carboxylic acid (516 mg, 4.644 mmol, 1.05 eq.) and triethylamine (1.54 mL, 11.05 mmol, 2.5 eq.) in DCM (60 mL) was added hydroxybenzotriazole hydrate (657 mg, 4.861 mmol, 1.1 eq.) and EDC•HCl (923 mg, 4.861 mmol, 1.1 eq.). The reaction mixture was allowed to stir for 10 mins at 20 °C then **2.33** (500 mg, 4.423 mmol, 1.0 eq.) was added. The reaction mixture was allowed to stir overnight at 20 °C and then quenched with water and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, saturated ammonium chloride solution and brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield the product (780 mg, 3.804 mmol, 86%) as a white solid. IR (neat) ν = 3240, 3074, 2960, 1619, 1560, 1521, 1324, 1195, 1130, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (br s, 1H), 6.95-6.93 (m, 1H), 6.56-6.54 (m, 1H), 6.26-6.24 (m, 1H), 5.96 (br s, 1H), 5.96-5.85 (m, 1H), 5.14-5.09 (m, 2H), 3.29 (d, *J* = 6.5 Hz, 2H), 2.07 (d, *J* = 7.5 Hz, 2H), 0.97 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 135.2, 126.1, 121.6, 117.5, 109.6, 108.2, 48.8, 44.8, 35.2, 25.1; HRMS (ESI) calcd for C12H18N2NaO [M+Na] 229.1315; found 229.1315.



4,5-Dibromo-*N*-(2,2-dimethylpent-4-en-1-yl)-1*H*-pyrrole-2-carboxamide. To a stirred solution of **2.33** (300 mg, 2.650 mmol, 1.0 eq.) and triethylamine (0.92 mL, 6.62 mmol, 2.5 eq.) in DMF (6 mL) was added 4,5-dibromo-2-(trichloroacetyl)pyrrole (1.08 g, 2.915 mmol, 1.1 eq.) and DMAP (40 mg, 0.327 mmol, 0.1 eq.). The reaction was allowed to stir at 20 °C for 48h then quenched with brine and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and brine, dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10 to 20% ethyl acetate in hexanes) to yield the product (370 mg, 1.060 mmol, 40%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.71 (br s, 1H), 6.54 (s, 1H), 6.00-5.97 (m, 1H), 5.88-5.84 (m, 1H), 5.10-5.08 (m, 2H), 3.32 (d, *J* = 4.4

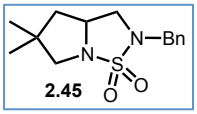
Hz, 2H), 2.03 (d, J = 4.6 Hz, 2H), 0.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 135.0, 126.9, 117.7, 111.6, 106.1, 99.3, 49.1, 45.0, 35.1, 25.1. HRMS (ESI) calcd for C12H17Br2N2O [M+H] 362.9702; found 362.9699.



2.41

***N*-Benzyl-*N'*-2,2-dimethylpent-4-enyl-sulfamide.** To a stirred solution of benzylamine (1.00 mL, 9.32 mmol, 1.0 eq.) in DCM (10 mL) cooled to 0 °C was added dropwise chlorosulfonic acid (0.19 mL, 2.796 mmol, 0.3 eq.). The reaction was allowed to stir for 30mins at 0 °C then for 30mins at 20 °C and after which the reaction mixture was filtered. The filter cake was suspended in toluene (10 mL) and PCl_5 (580 mg, 2.796 mmol, 0.3 eq.) was added. The reaction was stirred at reflux (115 °C) for 1h then cooled to 20 °C after which the solvent was removed under reduced pressure to afford benzylsulfamoyl chloride (575 mg, 2.768 mmol, 99%) as a brown syrup which was dissolved in toluene (28mL) to give a 0.1M solution.

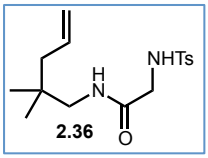
To a stirred solution of **2.33** (129 mg, 1.140 mmol, 1.0 eq.) and triethylamine (0.32 mL, 2.280 mmol, 2.0 eq.) in toluene (7 mL) cooled to 0 °C was added a 0.1 M solution of benzylsulfamoyl chloride in toluene (18.0 mL, 1.800 mmol, 1.58 eq.) dropwise. The reaction was allowed to warm to 20 °C overnight after which the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield the product (210 mg, 0.684 mmol, 65%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 5.80-5.73 (m, 1H), 5.08-5.02 (m, 2H), 4.41 (br s, 1H), 4.22 (d, J = 6.0 Hz, 2H), 4.04 (br s, 1H), 2.74 (d, J = 4.8 Hz, 2H), 1.96 (d, J = 4.2 Hz, 2H), 0.88 (s, 6H). HRMS (ESI) calcd for C14H22N2NaO2S [M+Na] 305.1294; found 305.1294. Spectral data match literature values.[2]



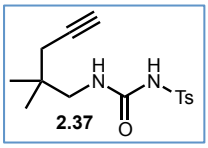
2.45

2-Benzyl-5,5-dimethylhexahydropyrrolo[1,2-*b*][1,2,5]thiadiazole 1,1-dioxide. To a stirred solution of K_2CO_3 (60 mg, 0.426 mmol, 2.5 eq.) and a 60% w/w solution of $Cu(ND)_2$ (346 mg, 0.511 mmol, 3.0 eq.) in DCE (1.8 mL) was added **2.41** (48 mg, 0.170 mmol, 1.0 eq.). The reaction mixture was allowed to stir for 48h at 120 °C then cooled to 20 °C and diluted with diethyl ether and water. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined

organic layers were washed with saturated EDTA solution, 10% NaOH solution then brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 30% ethyl acetate in hexanes as eluent) to yield the product (36 mg, 0.07 mmol, 76%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 4.43 (d, *J* = 13.2 Hz, 1H), 4.06 (m, 1H), 3.81 (d, *J* = 13.2 Hz, 1H), 3.27 (d, *J* = 9.2 Hz, 1H), 3.14 (m, 1H), 2.96 (d, *J* = 9.2 Hz, 1H), 1.83 (m, 1H), 1.46 (m, 1H), 1.17 (s, 3H), 1.12 (s, 3H). Spectral data match literature values. [2]

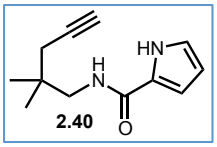


***N*-(2,2-Dimethylpent-4-en-1-yl)-2-(4-methylphenylsulfonamido)acetamide.** To a stirred solution of **2.33** (150 mg, 1.33 mmol, 1.0 eq.), diisopropylethylamine (0.70 mL, 4.0 mmol, 3.0 eq.) and N-tosyl glycine (305 mg, 1.33 mmol, 1 eq.) in DMF (3 mL) was added HBTU (554 mg, 1.46 mmol, 1.1 eq.). The reaction was allowed to stir at 20 °C overnight then quenched with brine and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with 0.1 N HCl, saturated aq. sodium bicarbonate solution, water and brine, dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 45 to 55% ethyl acetate in petroleum ether) to yield the product (363 mg, 1.12 mmol, 83%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.41 (br s, 1H), 5.85-5.73 (m, 1H), 5.27 (t, *J* = 6.2 Hz, 1H), 5.09-5.02 (m, 2H), 3.56 (d, *J* = 6.3 Hz, 2H), 3.07 (d, *J* = 6.3 Hz, 2H), 2.43 (s, 3H), 1.95 (d, *J* = 7.5 Hz, 2H), 0.86 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 144.2, 135.5, 134.6, 130.0, 127.2, 117.8, 49.0, 45.9, 44.4, 34.7, 24.8, 21.6. HRMS (ESI) calcd for C16H24N2NaO3S [M+Na] 347.1400; found 347.1397.



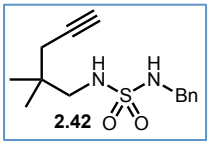
***N*-((2,2-Dimethylpent-4-yn-1-yl)carbamoyl)-4-methylbenzenesulfonamide.** To a stirred solution of the HCl salt of **2.34** (145 mg, 0.98 mmol, 1.0 eq.) and triethylamine (0.15 mL, 1.08 mmol, 1.1 eq.) in DCM (5 mL) cooled to 0 °C was added *p*-toluenesulfonyl isocyanate

(0.84 mL, 5.5 mmol, 1.1 eq.). The reaction was allowed to warm to 20 °C overnight after which the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield the product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.62 (br s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.67 (br s, 1H), 3.16 (d, *J* = 6.4 Hz, 2H), 2.45 (s, 3H), 2.04-2.00 (m, 3H), 0.92 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 144.9, 136.6, 130.0, 126.9, 81.0, 70.8, 49.3, 34.7, 29.5, 24.6, 21.6. HRMS (ESI) calcd for C15H20N2NaO3S [M+Na] 331.1087; found 331.1091.



2.40

***N*-(2,2-Dimethylpent-4-yn-1-yl)-1*H*-pyrrole-2-carboxamide.** To a stirred solution of pyrrole-2-carboxylic acid (393 mg, 3.537 mmol, 1.05 eq.) and triethylamine (1.64 mL, 11.79 mmol, 3.5 eq.) in DCM (50 mL) was added hydroxybenzotriazole hydrate (501 mg, 3.710 mmol, 1.1 eq.) and EDC•HCl (711 mg, 3.710 mmol, 1.1 eq.). The reaction mixture was allowed to stir for 10 mins at 20 °C then 2,2-dimethylpent-4-yn-1-amine hydrochloride (498 mg, 3.373 mmol, 1.0 eq.) was added. The reaction mixture was allowed to stir overnight at 20 °C and then quenched with water and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, saturated ammonium chloride solution and brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to yield the product (681 mg, 3.331 mmol, 99%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (br s, 1H), 6.93-6.91 (m, 1H), 6.55-6.52 (m, 1H), 6.24-6.22 (s, 1H), 6.16 (br s, 1H), 3.37 (d, *J* = 6.4 Hz, 2H), 2.18 (d, *J* = 2.4 Hz, 2H), 2.10-2.07 (m, 1H), 0.94 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 125.9, 121.8, 109.5, 108.6, 81.9, 70.8, 48.4, 35.1, 29.9, 25.0. HRMS (ESI) calcd for C12H17N2O [M+H] 205.1335; found 205.1335

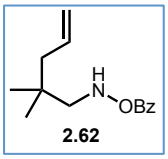


2.42

***N*-Benzyl-*N'*-2,2-dimethylpent-4-enyl-sulfamide.** To a stirred solution of HCl salt of **2.34** (203 mg, 1.375 mmol, 1.0 eq.) and triethylamine (0.57 mL, 4.11 mmol, 3.0 eq.) in toluene (10 mL) cooled to 0 °C was

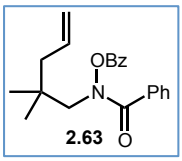
added a 0.187 M solution of benzylsulfamoyl chloride in toluene (11.8 mL, 2.200 mmol, 1.6 eq.) dropwise. The reaction was allowed to warm to 20 °C overnight after which the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield the product (354 mg, 1.265 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.24 (m, 5H), 4.63 (br s, 1H), 4.43 (br s, 1H), 4.22 (d, *J* = 2.1 Hz, 2H), 2.87 (d, *J* = 6.9 Hz, 2H), 2.11 (d, *J* = 2.4 Hz, 2H), 2.00 (t, *J* = 2.5 Hz, 1H), 0.97 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 128.8, 128.7, 128.1, 128.0, 81.3, 70.96, 52.2, 47.3, 33.9, 29.4, 24.8; HRMS (ESI) calcd for C14H22N2NaO2S [M+Na] 305.1294; found 305.1294

4.1.3 Amidyl Radical Substrates

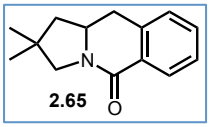


2.62

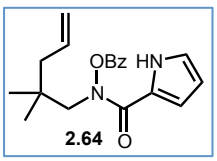
***O*-Benzoyl-*N*-(2,2-dimethylpent-4-en-1-yl)hydroxylamine.** To a stirred solution **2.33** (150 mg, 1.325 mmol, 1.0 eq.) in DCM (7 mL) and pH 10.5 aq. buffer (7 mL) was added benzoyl peroxide (322 mg, 1.329 mmol, 1.0 eq.). The reaction was allowed to stir for overnight at 20 °C. Water and DCM were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, saturated ammonium chloride solution and brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (60% toluene in petroleum ether) to yield the product (105 mg, 0.451 mmol, 34%) as a white solid. *Rf* = 0.22 (50% toluene in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.44, 2H), 5.92-5.79 (m, 1H), 5.19-5.02 (m, 2H), 2.93 (s, 2H), 2.11 (d, *J* = 7.5, 2H), 1.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.21, 134.93, 133.53, 129.52, 128.75, 128.28, 117.96, 62.17, 45.21, 34.48, 25.96. LRMS (ESI) calcd for C14H19NaNO2 [M+Na] 256.13; found 256.1.



***N*-(Benzoyloxy)-*N*-(2,2-dimethylpent-4-en-1-yl)benzamide.** To a stirred solution of **2.62** (60 mg, 0.257 mmol, 1.0 eq.) and pyridine (42 µL, 0.514 mmol, 2.0 eq.) in toluene (4 mL) was added benzoyl chloride (30 µL, 0.257 mmol, 1.0 eq.). The reaction was allowed to stir at reflux (115 °C) for 3h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to yield the product (72 mg, 0.213 mmol, 83%) as a white solid. *Rf* = 0.45 (5% ethyl acetate in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2H), 7.69-7.54 (m, 3H), 7.45-7.24 (m, 5H), 5.94-5.73 (m, 1H), 5.06-4.96 (m, 2H), 3.78 (br, 2H), 2.15 (d, *J* = 7.4 Hz, 2H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.56, 164.97, 134.67, 134.45, 133.90, 129.94, 128.95, 128.23, 128.19, 127.06, 118.11, 58.70, 45.16, 35.93, 25.72.



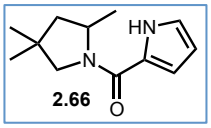
2,2-Dimethyl-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1*H*)-one. To a solution of **2.63** (60 mg, 0.178 mmol, 1.0 eq.) heated at 90 °C in degassed α,α,α-trifluorotoluene (5 mL) was added a solution of ACCN (10 mg, 0.004 mmol, 0.2 eq.) and tributyltin hydride (111 µL, 0.410 mmol, 2.3 eq.) in degassed α,α,α-trifluorotoluene (5 mL) at a rate of 0.42 mL/hour *via* syringe pump. The reaction mixture was cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 20% ethyl acetate in hexanes) to yield the tricyclic product (12.7 mg, 0.05899 mmol, 33%) and the amide by-product (16.8 mg, 0.077 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 1H), 7.59-7.31 (m, 2H), 7.17 (d, *J* = 7.2 Hz, 1H), 4.06 (m, 1H), 3.55 (d, *J* = 12 Hz, 1H), 3.42 (d, *J* = 12 Hz, 1H), 2.96 (dd, *J* = 10.8 Hz, *J* = 4.2 Hz, 1H), 2.83 (t, *J* = 14.2 Hz, 1H), 2.00 (m, 1H), 1.65 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 136.8, 131.4, 127.6, 127.1, 127.0, 57.7, 56.0, 47.5, 35.1, 27.5, 27.4.



***N*-(Benzoyloxy)-*N*-(2,2-dimethylpent-4-en-1-yl)-1*H*-pyrrole-2-carboxamide.** To a stirred suspension of pyrrole-2-carboxylic acid (100 mg, 0.901 mmol, 1.0 eq.) in toluene (5 mL) were added DMF (7

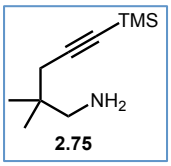
μL, 0.090 mmol, 0.1 eq.) and thionyl chloride (330 μL, 4.135 mmol, 5.0 eq.). The reaction was allowed to stir at 75 °C for 1h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude acyl chloride could be used directly in the next step without further purification.

To a stirred solution of **2.62** (60 mg, 0.257 mmol, 1.0 eq.) and pyridine (42 μL, 0.514 mmol, 2.0 eq.) in toluene (4 mL) was added pyrrole-2-carbonyl chloride (68 mg, 0.514 mmol, 2.0 eq.). The reaction mixture was allowed to stir at reflux (115 °C) for 3h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether) to yield the product (59 mg, 0.179 mmol, 70%) as a white solid. *Rf* = 0.19 (5% ethyl acetate in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.63 (br s, 1H), 8.13 (d, *J* = 6.8 Hz, 2H), 7.70 (t, *J* = 6.8 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 2H), 6.91 (br s, 1H), 6.59 (br s, 1H), 6.09 (m, 1H), 5.88-5.81 (m, 1H), 5.05-5.00 (m, 2H), 4.00-3.00 (br, 2H), 2.14 (d, *J* = 7.2 Hz, 2H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.89, 162.28, 134.82, 134.77, 130.22, 129.32, 127.55, 123.16, 122.52, 118.03, 113.86, 110.66, 58.62, 45.13, 35.99, 25.70; HRMS (ESI) calcd for C19H23N2O3 [M+H] 327.17032; found 327.16969.



2.66

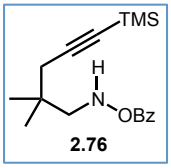
(1*H*-Pyrrol-2-yl)(2,4,4-trimethylpyrrolidin-1-yl)methanone. To a solution of **2.64** (60 mg, 0.179 mmol, 1.0 eq.) heated at 125 °C in degassed toluene (5 mL) was added a solution of ACCN (67 mg, 0.276 mmol, 1.5 eq.) and tributyltin hydride (125 μL, 0.461 mmol, 2.5 eq.) in degassed toluene (5 mL) at a rate of 0.42 mL/hour *via* syringe pump. The reaction mixture was cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 17.5% to 22.5% ethyl acetate in hexanes) to yield the bicyclic product (17 mg, 0.082 mmol, 44%) and the amide by-product (19 mg, 0.092 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 6.93 (br s, 1H), 6.54 (br s, 1H), 6.27 (br s, 1H), 4.36 (br s, 1H), 3.70 (AB, *J* = 9.2 Hz, 1H), 3.43 (AB, *J* = 9.2 Hz, 1H), 1.92 (m, 1H), 1.65 (m, 1H), 1.26 (s, 3H), 1.16 (s, 3H), 0.98 (s, 3H).



2,2-Dimethyl-5-(trimethylsilyl)pent-4-yn-1-amine. To a stirred solution of diisopropylamine (6.0 mL, 0.041 mol, 1.3 eq.) in 80 mL of diethyl ether cooled to −78 °C was added a 2.42 M solution of *n*-BuLi in hexanes (15.6 mL, 0.038 mmol, 1.2 eq.) dropwise. The reaction mixture was stirred at −78 °C for 15mins. Propargyl bromide (3.5 mL of 80% wt. solution in toluene, 0.031 mmol, 1.0 eq.) was added in several portions at −78 °C. The reaction mixture was stirred at −78 °C for 1h. Chlorotrimethylsilane (4.4 mL, 0.035 mol, 1.1 eq.) was added in several portions at −78 °C. The reaction was allowed to warm to 20 °C overnight then was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure on ice to yield a dark brown solution of (3-bromoprop-1-yn-1-yl)trimethylsilane in diethyl ether (84% w/w) and toluene that was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 2H), 0.16 (s, 9H). Spectral data match literature values.[3]

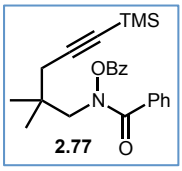
To a stirred solution of diisopropylamine (4.4 mL, 0.031 mol, 1.2 eq.) in diethyl ether (80 mL) cooled to −78 °C was added a 2.42 M solution of *n*-BuLi in hexanes (11.4 mL, 0.027 mol, 1.1 eq.) dropwise. The reaction mixture was stirred at −78 °C for 15mins. Isobutyronitrile (2.24 mL, 0.025 mol, 1.0 eq.) was added in 1 portion at −78 °C. The reaction mixture was stirred at −78 °C for 1h. TMS-propargyl bromide (7.03 g of 84% w/w solution in diethyl ether, 0.030 mol, 1.2 eq.) was added in several portions at −78 °C. The reaction was allowed to warm to 20 °C overnight then was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure on ice to yield a dark brown solution of 2,2-dimethyl-5-(trimethylsilyl)pent-4-ynenitrile in diethyl ether and toluene that was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 2H), 1.43 (s, 6H), 0.17 (s, 9H).

To a slurry of lithium aluminum hydride (3.5 g, 0.094 mol, 3.0 eq.) in diethyl ether (100 mL) at 0 °C was added a solution of the crude nitrile (31.4 mmol, 1.0 eq.) in diethyl ether (20 mL) over 30 min. The reaction was allowed to warm to 20 °C overnight then cooled to 0 °C. Water (3.5 mL, initially added dropwise), 15% aqueous sodium hydroxide (3.5 mL) and water (11.5 mL) were sequentially added with vigorous stirring. The reaction mixture was then filtered, and the resulting filter cake washed thoroughly with diethyl ether. The filtrate was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure on ice to yield a solution of the amine (6.51 g, 0.0250 mol determined by NMR, 99% over 3 steps) in diethyl ether and toluene. The material could be used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 2H), 2.12 (s, 2H), 0.93 (s, 6H), 0.14 (s, 9H).



2.76

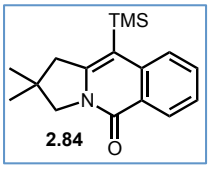
***O*-Benzoyl-*N*-(2,2-dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)hydroxylamine.** To a stirred solution of **2.75** (430 mg, 2.348 mmol, 1.0 eq.) in DCM (20 mL) and pH 10.5 aq. buffer (20 mL) was added benzoyl peroxide (570 mg, 2.348 mmol, 1.0 eq.). The reaction was allowed to stir for 48h at 20 °C. Water and DCM were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, saturated ammonium chloride solution and brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 60% to 100% toluene in petroleum ether as eluent) to yield the product (398 mg, 1.315 mmol, 56%) as a yellow oil. *Rf* = 0.51 (10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 8.03 (d, *J* = 12.0 Hz, 2H), 7.59 (t, *J* = 6.8 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 3.02 (br s, 2H), 2.31 (s, 2H), 1.11 (2, 6H), 0.12 (s, 9H); HRMS (ESI) calcd for C17H26O2NSi [M+H] 304.17273; found 304.17315.



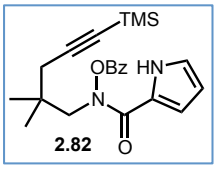
2.77

***N*-(Benzoyloxy)-*N*-(2,2-dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)benzamide.** To a stirred solution of **2.76** (61 mg, 0.201 mmol, 1.0 eq.) and pyridine (33 µL, 0.402 mmol, 2.0 eq.) in toluene (4 mL) was added benzoyl chloride (26 µL, 0.221 mmol, 1.1 eq.). The reaction was allowed to stir at reflux

(120 °C) for 4h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 3% to 5% ethyl acetate in petroleum ether) to yield the product (51 mg, 0.125 mmol, 63%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 6.8 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.32-7.26 (m, 2H), 4.13-3.24 (br, 2H), 2.36 (br s, 2H), 1.12 (s, 6H), -0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.26, 164.35, 134.16, 133.52, 130.70, 129.83, 128.63, 128.19, 127.96, 126.77, 104.21, 87.21, 56.85, 35.78, 31.71, 25.31, -0.18; HRMS (ESI) calcd for C24H30NO3Si [M+H] 408.19895; found 408.19948.



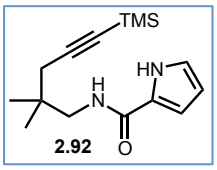
2,2-Dimethyl-10-(trimethylsilyl)-2,3-dihydropyrrolo[1,2-*b*]isoquinolin-5(1*H*)-one. To a solution of **2.77** (60 mg, 0.180 mmol, 1.0 eq.) heated at 125 °C in degassed toluene (5 mL) was added a solution of ACCN (67 mg, 0.276 mmol, 1.5 eq.) and tributyltin hydride (125 µL, 0.450 mmol, 2.5 eq.) in toluene (5 mL) at a rate of 0.42 mL/hour *via* syringe pump. The reaction mixture was cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 17.5% to 22.5% ethyl acetate in hexanes) to yield the amide by-product (19 mg, 0.092 mmol, 50%, *Rf* = 0.47 (20% ethyl acetate in hexanes)) and the bicyclic product (17 mg, 0.082 mmol, 44%) and. *Rf* = 0.32 (20% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.6 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 7.0 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 3.89 (s, 2H), 2.94 (s, 2H), 1.19 (s, 6H), 0.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.68, 149.13, 141.06, 131.26, 127.72, 126.64, 125.21, 125.19, 106.56, 77.22, 59.21, 48.26, 35.96, 26.56, 2.6; HRMS (ESI) calcd for C17H24ONSi [M+H] 286.16217; found 286.16167.



***N*-(Benzoyloxy)-*N*-(2,2-dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)-1*H*-pyrrole-2-carboxamide.** To a stirred suspension of pyrrole-2-carboxylic acid (100 mg, 0.900 mmol, 1.0 eq.) in toluene (5 mL) were added DMF (7 µL, 0.090 mmol, 0.1 eq.) and thionyl chloride (330 µL, 4.500 mmol, 5.0 eq.). The reaction was allowed to stir at 75 °C for 1h then cooled to 20 °C and the solvent

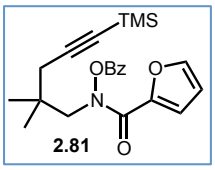
was removed under reduced pressure. The crude acyl chloride could be used directly in the next step without further purification.

To a stirred solution of **2.76** (200 mg, 0.659 mmol, 1.0 eq.) and pyridine (106 μL, 1.318 mmol, 2.0 eq.) in toluene (8 mL) was added pyrrole-2-carbonyl chloride (85 mg, 0.660 mmol, 1.0 eq.). The reaction was allowed to stir at reflux (115 °C) for 3h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether) to yield the product (190 mg, 0.479 mmol, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (br s, 1H), 8.14 (d, *J* = 7.2 Hz, 2H), 7.69 (t, *J* = 6.4 Hz, 2H), 7.54 (t, *J* = 8.2 Hz, 2H), 6.91 (br s, 1H), 6.57 (br s, 1H), 6.07 (m, 1H), 4.80-4.30 (br s, 1H), 3.60-3.20 (br s, 1H), 2.48-2.17 (br, 2H), 1.11 (s, 6H), -0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.58, 161.82, 134.44, 130.14, 128.97, 127.32, 122.80, 122.32, 113.68, 110.50, 104.39, 87.18, 56.34, 35.93, 31.67, 25.13, -0.23; HRMS (ESI) calcd for C22H29N2O3Si [M+H] 397.19420; found 397.19322.



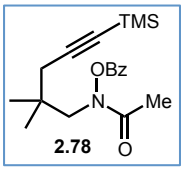
2.92

***N*-(2,2-Dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)-1*H*-pyrrole-2-carboxamide.** To a solution of **2.82** (45 mg, 0.113 mmol, 1.0 eq.) heated at 105 °C in degassed α,α,α-trifluorotoluene (4 mL) was added a solution of ACCN (55 mg, 0.276 mmol, 2 eq.) and tributyltin hydride (152 μL, 0.567 mmol, 5.0 eq.) in α,α,α-trifluorotoluene (4 mL) at a rate of 0.4 mL/hour *via* syringe pump. The reaction mixture was cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 17.5% to 22.5% ethyl acetate in hexanes) to yield the amide by-product (29.2 mg, 0.105 mmol, 93%). *Rf* = 0.26 (25% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (br s, 1H), 6.58 (br s, 1H), 6.27-6.19 (m, 2H), 3.37 (d, *J* = 6.0 Hz, 2H), 2.21 (s, 2H), 1.03 (s, 6H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 125.9, 122.0, 109.4, 108.8, 104.6, 87.3, 48.5, 35.3, 31.3, 25.1, 0.2; HRMS (ESI) calcd for C15H25O7N2Si [M+H] 277.17307; found 277.17264.

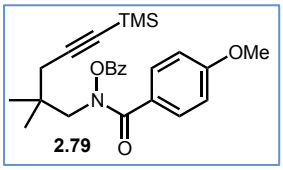


***N*-(Benzoyloxy)-*N*-(2,2-dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)furan-2-carboxamide.** To a stirred suspension of 2-furoic acid (500 mg, 4.461 mmol, 1.0 eq.) in toluene (10 mL) were added DMF (100 µL, 1.338 mmol, 0.3 eq.) and thionyl chloride (1.3 mL, 17.8 mmol, 4.0 eq.). The reaction was allowed to stir at 90 °C for 1h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude acyl chloride could be used directly in the next step without further purification.

To a stirred solution of **2.76** (398 mg, 1.311 mmol, 1.0 eq.) and pyridine (211 µL, 2.622 mmol, 2.0 eq.) in toluene (8 mL) was added furanyl-2-carbonyl chloride (205 mg, 1.574 mmol, 1.2 eq.). The reaction was allowed to stir at 90 °C for 4h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether) to yield the product (272 mg, 0.684 mmol, 61%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 8.12 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 6.4 Hz, 2H), 7.54 (t, *J* = 8.2 Hz, 2H), 6.91 (br s, 1H), 7.40 (s, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 6.36 (m, 1H), 2.36 (br, 2H), 1.55 (s, 2H), 1.11 (s, 6H), -0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.60, 159.06, 145.40, 145.29, 134.41, 130.12, 128.90, 127.06, 117.66, 111.52, 104.27, 87.23, 56.68, 35.87, 31.72, 25.32, -0.22; HRMS (ESI) calcd for C22H28NO4Si [M+H] 398.17821; found 398.17881.

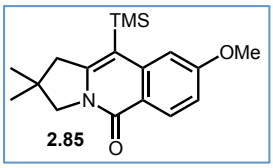


***N*-(Benzoyloxy)-*N*-(2,2-dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)acetamide.** To a stirred solution of **2.76** (130 mg, 0.428 mmol, 1.0 eq.) and pyridine (70 µL, 0.857 mmol, 2.0 eq.) in toluene (12 mL) was added acetyl chloride (46 µL, 0.642 mmol, 1.5 eq.). The reaction was allowed to stir at 80 °C for 4h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (15% ethyl acetate in petroleum ether) to yield the product (85 mg, 0.246 mmol, 57%) as a white solid. *Rf* = 0.20 (10% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ, 8.09 (d, *J* = 8.0 Hz, 2H), 7.66 (m, 1H), 7.50 (m, 2H), 4.00-3.34 (br, 2H), 2.28 (br s, 2H), 2.03 (br s, 3H), 1.05 (s, 6H), -0.08 (s, 9H).



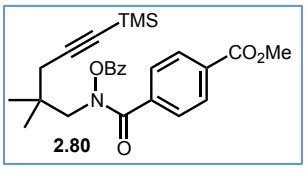
***N*-(Benzoyloxy)-*N*-(2,2-dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)-4-methoxybenzamide.** To a stirred solution of *p*-methoxybenzoic acid (500 mg, 3.286 mmol, 1.0 eq.) in toluene (5 mL) was added thionyl chloride (1.2 mL, 16.4 mmol, 5.0 eq.). The reaction was allowed to stir at 100 °C for 4h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude acyl chloride could be used directly in the next step without further purification.

To a stirred solution of **2.76** (128 mg, 0.422 mmol, 1.0 eq.) and pyridine (70 µL, 0.844 mmol, 2.0 eq.) in toluene (10 mL) was added *p*-anisoyl chloride (108 mg, 0.633 mmol, 1.5 eq.). The reaction was allowed to stir at 80 °C for 4h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% ethyl acetate in petroleum ether) to yield the product (126 mg, 0.288 mmol, 68%) as a white solid. *Rf* = 0.35 (20% ethyl acetate in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ, 7.93 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.60 (m, 1H), 7.42 (t, *J* = 6.4 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 2.38 (br s, 2H), 1.11 (s, 6H), -0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.05, 164.04, 161.50, 134.13, 132.84, 130.21, 129.88, 128.65, 126.93, 125.44, 114.12, 113.25, 104.33, 87.11, 56.95, 55.22, 35.77, 31.66, 25.27, -0.17; HRMS (ESI) calcd for C25H31NNaO4Si [M+Na] 460.9015; found 460.1928.



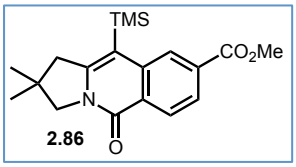
8-Methoxy-2,2-dimethyl-10-(trimethylsilyl)-2,3-dihydropyrrolo[1,2-*b*]isoquinolin-5(1*H*)-one. To a solution of **2.79** (62.3 mg, 0.1424 mmol, 1.0 eq.) heated at 110 °C in degassed α,α,α-trifluorotoluene (5 mL) was added a solution of ACCN (17 mg, 0.070 mmol, 0.5 eq.) and tributyltin hydride (83 µL, 0.313 mmol, 2.2 eq.) in α,α,α-trifluorotoluene (5 mL) at a rate of 0.4 mL/hour *via* syringe pump. The reaction mixture was cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 20% to 40% ethyl acetate in hexanes) to yield the bicyclic product (17 mg, 0.082 mmol, 44%) and the amide by-product (19 mg, 0.092 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 1H), 7.18 (s, 1H), 6.99 (t, *J* = 6.6 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 2H), 2.92 (s, 2H), 1.19 (s,

6H), 0.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.03, 161.83, 150.01, 142.68, 129.53, 119.10, 114.10, 108.71, 105.93, 59.09, 55.33, 48.32, 35.99, 26.56, 2.57.



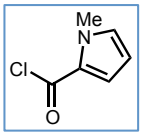
Methyl 4-((benzoyloxy)(2,2-dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)carbamoyl)benzoate. To a stirred solution of 4-(methoxycarbonyl)benzoic acid (145 mg, 0.805 mmol, 1.0 eq.) in toluene (7 mL) were added DMF (6 µL, 0.0805 mmol, 0.1 eq.) and thionyl chloride (0.30 mL, 4.024 mmol, 5.0 eq.). The reaction was allowed to stir at 90 °C for 4h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude acyl chloride could be used directly in the next step without further purification.

To a stirred solution of **2.76** (142 mg, 0.468 mmol, 1.0 eq.) and pyridine (113 µL, 1.404 mmol, 3.0 eq.) in toluene (8 mL) was added methyl 4-(chlorocarbonyl)benzoate (140 mg, 0.702 mmol, 1.5 eq.). The reaction was allowed to stir at 90 °C for 5h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (7.5% ethyl acetate in hexanes) to yield the product (183 mg, 0.393 mmol, 84%). *Rf* = 0.34 (20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ, 7.96 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 2.36 (br s, 2H), 1.13 (s, 6H), -0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 164.3, 137.8, 134.4, 131.9, 129.9, 129.8, 129.2, 128.7, 127.9, 126.4, 104.0, 87.3, 56.8, 52.3, 35.7, 31.7, 25.3, -0.2; HRMS (ESI) calcd for C26H31NNaO5Si [M+Na] 488.1864; found 488.1874.



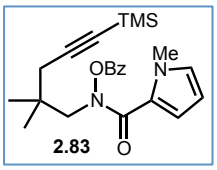
Methyl 2,2-dimethyl-5-oxo-10-(trimethylsilyl)-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline-8-carboxylate. To a solution of **2.80** (61 mg, 0.131 mmol, 1.0 eq.) heated at 95 °C in degassed α,α,α-trifluorotoluene (4 mL) was added a solution of ACCN (19 mg, 0.078 mmol, 0.6 eq.) and tributyltin hydride (92 µL, 0.341 mmol, 2.6 eq.) in α,α,α-trifluorotoluene (5 mL) at a rate of 0.4 mL/hour *via* syringe pump. The reaction mixture was cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 20% to 30% ethyl acetate in hexanes) to yield the tricyclic product (6 mg, 0.017 mmol, 17%) and

the amide by-product (35 mg, 0.100 mmol, 73%). *Rf* = 0.15 (25% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 3.90 (s, 3H), 2.96 (s, 2H), 1.21 (s, 6H), 0.44 (s, 9H).



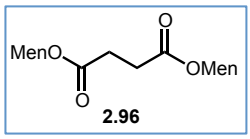
1-Methyl-1*H*-pyrrole-2-carbonyl chloride. To a stirred solution of pyrrole-2-carboxylic acid methyl ester (600 mg, 4.795 mmol, 1.0 eq.) in DMF (40 mL) cooled to 0 °C was added 60% w/w suspension of sodium hydride (384 mg, 9.590 mmol, 2.0 eq.). The reaction was allowed to stir at 0 °C for 1h. Methyl iodide (600 μL, 9.590 mmol, 2.0 eq.) was added and the reaction was allowed to stir overnight while warming to 20 °C. The reaction was quenched with water and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, 0.1M HCl solution and brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 5% to 10% ethyl acetate in hexanes as eluent) to yield the product (610 mg, 4.384 mmol, 91%). *Rf* = 0.74 (40% ethyl acetate in hexanes + 1% acetic acid). To a stirred solution of N-methyl pyrrole-2-carboxylic acid methyl ester (600 mg, 4.312 mmol, 1.0 eq.) in THF (6 mL) and MeOH (6 mL) was added a 2.15M aqueous solution of KOH (740 mg, 13.189 mmol, 3 eq.). The reaction was allowed to stir at 20 °C for 16h. The reaction mixture was acidified to pH 2 with 1M HCl solution and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, 0.1M HCl solution and brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 20% ethyl acetate in hexanes + 1% acetic acid as eluent) to yield the product (492 mg, 3.932 mmol, 63%). *Rf* = 0.74 (40% ethyl acetate in hexanes + 1% acetic acid); IR (neat) ν = 2924, 1667, 1434, 1327, 1265, 1125, 1053, 725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14-7.13 (m, 1H), 6.87-6.86 (m, 1H), 6.19-6.17 (m, 1H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 130.7, 121.7, 120.0, 108.4, 37.09; HRMS (ESI) calcd for C6H7NNaO2 [M+Na] 148.0369; found 148.0367.

To a stirred solution of N-methyl pyrrole-2-carboxylic acid (145 mg, 1.16 mmol, 1.0 eq.) in toluene (15 mL) were added DMF (10 µL, 0.12 mmol, 0.1 eq.) and thionyl chloride (0.42 mL, 5.79 mmol, 5.0 eq.). The reaction was allowed to stir at 80 °C for 4h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude acyl chloride could be used directly in the next step without further purification.



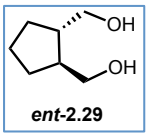
***N*-(Benzoyloxy)-*N*-(2,2-dimethyl-5-(trimethylsilyl)pent-4-yn-1-yl)-1-methyl-1*H*-pyrrole-2-carboxamide.** To a stirred solution of **2.76** (164 mg, 0.540 mmol, 1.0 eq.) and pyridine (130 µL, 1.621 mmol, 3.0 eq.) in toluene (10 mL) was added N-methyl pyrrole-2-carbonyl chloride (116 mg, 0.810 mmol, 1.5 eq.). The reaction was allowed to stir at 90 °C for 12h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (7.5% ethyl acetate in hexanes) to yield the product (160 mg, 0.390 mmol, 72%). *Rf* = 0.35 (10% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ, 8.04 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 6.69-6.51 (m, 2H), 5.93-5.90 (m, 1H), 3.86 (s, 3H), 2.35 (br, 2H), 1.09 (s, 6H), -0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.89, 163.82, 134.11, 129.97, 128.73, 128.27, 122.74, 115.42, 107.2, 104.51, 87.03, 56.50, 36.77, 35.78, 31.64, 25.23, -0.19; HRMS (ESI) calcd for C23H31N2O3Si [M+H] 411.20985; found 411.21061.

4.1.4 Cyclic Model system – Radical Substrates



Bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) succinate. To a neat mixture of (−)-menthol (33.47 g, 0.21 mol, 2.0 eq.) and succinic acid (12.65 g, 0.11 mol, 1.0 eq.) was added concentrated HCl (500 µL, 6.00 mmol, 0.05 eq.). The reaction mixture was stirred at 90 °C for 48h then cooled to 20 °C and diluted with diethyl ether and saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with saturated sodium bicarbonate solution, water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under

reduced pressure to yield a crude yellow oil. The residue was then dissolved in boiling methanol and cooled to -30 °C. The resulting solid was collected to afford the product (53.7 g, 0.14 mol, 65 %) as white crystals. IR (neat) ν = 2952, 2926, 2868, 1730, 1213, 1165, 983 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.88 (td, J = 6.5, 4.5 Hz, 2H), 2.46 (m, 4H), 2.05 (m, 4H), 1.47-1.35 (m, 6H), 1.21-1.12 (m, 2H), 1.11-0.22 (m, 26H); ^{13}C NMR (125 MHz, C_6D_6) δ171.3, 73.8, 47.1, 41.0, 34.1, 31.1, 29.2, 26.3, 23.4, 21.8, 20.6, 16.3; HRMS (ESI) calcd for C24H43O4 [M+H] 395.31559; found 395.31535.

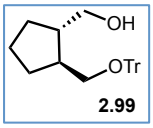


ent-2.29

(1*S*,2*S*)-Cyclopentane-1,2-diyldimethanol. To a stirred solution of diisopropylamine (21.2 mL, 0.153 mmol, 2.2 eq.) in THF (100 mL) cooled to −78 °C was added a 2.42 M solution of *n*-BuLi in hexanes (60.0 mL, 0.146 mmol, 2.1 eq.) dropwise. The reaction mixture was stirred at −78 °C for 15mins. A solution of **2.96** (27.4 g, 0.070 mol, 1.0 eq.) in THF (80 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1h. A solution of 1,3-dibromopropane (6.3 mL, 0.062 mol, 0.9 eq.) in THF (80 mL) was added dropwise at −78 °C. The reaction was stirred for 1h at −78 °C then stirred for 1h at 20 °C for 3h. The reaction mixture was 1.0 M HCl and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with 0.1 M HCl, water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure on ice to yield a crude yellow oil that could be used directly in the next step without further purification. ^{1}H NMR (300 MHz, C_6D_6) δ 4.90 (td, *J* = 10.7 Hz, *J* = 4.3 Hz, 2H), 3.40-3.29 (m, 2H), 2.17-2.00 (m, 4H), 2.00-1.78 (m, 4H), 1.55-1.34 (m, 6H), 1.26-1.10 (m, 2H), 0.95-0.60 (m, 8H), 0.90 (d, *J* = 7.0 Hz, 6H), 0.85 (d, *J* = 7.0 Hz, 6H), 0.77 (d, *J* = 6.4 Hz, 6H). Spectral data match literature values.[4]

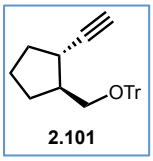
To a slurry of lithium aluminum hydride (5.2 g, 0.14 mol, 2.2 eq.) in diethyl ether (200 mL) at 0 °C was added a solution of the crude diester (0.062 mol, 1.0 eq.) in diethyl ether (100 mL) over 30mins. The reaction was allowed stir while warming to 20 °C overnight then cooled to 0 °C. Water (5.2 mL, initially added dropwise), 15% aqueous sodium hydroxide (5.2 mL) and water (15.6 mL) were sequentially added with vigorous stirring. The reaction mixture was then filtered, and the resulting filter cake washed thoroughly

with diethyl ether. The filtrate was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 2% to 10% methanol in dichloromethane as eluent) to yield the product (7.15 g, 0.055 mmol, 88% over 2 steps) as a pale yellow oil. *Rf* = 0.32 (5% methanol in DCM); IR (neat) ν = 3280, 2944, 2867, 1449, 1330, 1061, 1015 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 4.82 (brs, 2H), 3.63 (dd, *J* = 6.4 Hz and 4.0 Hz, 2H), 3.24 (t, *J* = 9.6 Hz, 2H), 1.70 (m, 2H), 1.52 (m, 2H), 1.30 (m, 2H), 1.0 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ = 66.3, 48.2, 29.6, 23.7; HRMS (ESI) calcd for C7H14O2 [M+H] 131.10273; found 131.10567.



2.99

((1*S*,2*S*)-2-((Trityloxy)methyl)cyclopentyl)methanol. To a solution of ***ent*-2.29** (7.0 g, 0.054 mol, 1.0 eq.) in DCM (250 mL) was added triethylamine (11.2 mL, 0.081 mmol, 1.5 eq.), 4-dimethylaminopyridine (73 mg, 0.600 mmol, 0.1 eq.) and trityl chloride (15.0 g, 0.054 mol, 1 eq.). The reaction mixture was allowed to stir for 4 days at 20 °C then diluted with DCM and water. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 35% ethyl acetate in hexanes as eluent) to yield the product (17.22 g, 0.0462 mol, 86%) as a pale yellow oil. *Rf* = 0.38 (20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.44 (m, 5H), 7.34-7.21 (m, 10H), 3.59-3.46 (m, 2H), 3.33 (dd, *J* = 4.5 Hz, 1H), 2.99 (m, 1H), 2.88 (t, *J* = 8.7 Hz, 1H), 1.92-1.85 (m, 1H), 1.79-1.67 (m, 3H), 1.56-1.46 (m, 2H), 1.30-1.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 128.7, 127.9, 127.1, 87.6, 68.0, 67.1, 47.4, 44.6, 30.3, 29.9, 24.1; HRMS (ESI) calcd for C26H28O2Na [M+Na] 395.19815; found 395.19880.

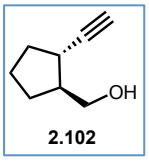


2.101

((((1*S*,2*S*)-2-Ethynylcyclopentyl)methoxy)methanetriyl)tribenzene. To a stirred solution of oxalyl chloride (310 µL, 3.623 mmol, 1.1 eq.) in DCM (20 mL) cooled to −78 °C was added a solution of DMSO (280 µL, 3.942 mmol, 1.2 eq.) in DCM (10 mL) dropwise. The reaction mixture was stirred at −78 °C for

15mins. A solution of **2.99** (1.210 g, 3.248 mmol, 1.0 eq.) in DCM (10 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 30mins. Triethylamine (2.30 mL, 0.0163 mol, 5.0 eq.) was added in one portion at −78 °C. The reaction was stirred for 20mins at −78 °C then warmed to 20 °C and exposed to air for 1h. The reaction mixture was quenched with a saturated ammonium chloride solution and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure on ice to yield a yellow oil that could be used directly in the next step without further purification.

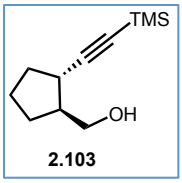
To a solution of the crude aldehyde in methanol (40 mL) was added potassium carbonate (900 mg, 6.512 mmol, 2.0 eq.) followed by freshly prepared dimethyl (1-diazo-2-oxopropyl)phosphonate[5] (770 mg, 4.008 mmol, 1.2 eq.). The reaction mixture was stirred overnight at 20 °C then quenched with water and diethyl ether. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes as eluent) to yield the product (1.19 g, 3.24 mmol, 99%) as a pale yellow oil. *Rf* = 0.74 (20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.44 (m, 5H), 7.32-7.21 (m, 10H), 3.11-3.06 (m, 2H), 2.5 (m, 1H), 2.21 (m, 1H), 2.04 (s, 1H), 2.03-1.97 (m, 1H), 1.88-1.85 (m, 1H), 1.72-1.54 (m, 3H), 1.43-1.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 128.7, 127.7, 126.8, 88.3, 86.3, 68.0, 65.2, 47.6, 33.6, 33.0, 28.9, 24.1; HRMS (ESI) calcd for C27H26ONa [M+Na] 389.18759; found 398.18811.



2.102

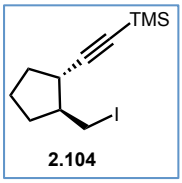
((1*S*,2*S*)-2-Ethynylcyclopentyl)methanol. To a stirred solution of **2.101** (8.38 g, 0.023 mol, 1.0 eq.) in methanol (130 mL) and DCM (90 mL) was added *p*-toluene sulfonic acid monohydrate (435 mg, 2.287 mmol, 0.1 eq.) in one portion. The reaction mixture was stirred at 20 °C for 6h then quenched with a saturated sodium bicarbonate solution and diluted with ethyl acetate and water. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine, dried with anhydrous

magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 15% to 35% ethyl acetate in hexanes as eluent) to yield the product (2.29 g, 0.0032 mol, 81%) as a clear oil. *Rf* = 0.26 (20% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74-3.61 (m, 2H), 2.40-2.31 (m, 1H), 2.20-1.96 (m, 3H), 1.91-1.81 (m, 1H), 1.80-1.56 (m, 4H), 1.72-1.54 (m, 3H), 1.40-1.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.8, 68.7, 65.7, 49.6, 33.6, 33.0, 28.2, 24.0; HRMS (ESI) calcd for C8H12ONa [M+Na] 147.07804; found 147.07799.



2.103

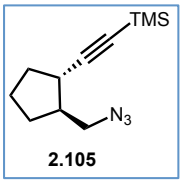
((1*S*,2*S*)-2-((Trimethylsilyl)ethynyl)cyclopentyl)methanol. To a stirred solution of **2.102** (103 mg, 0.829 mmol, 1.0 eq.) in THF (6 mL) cooled to −78 °C was added a 2.496 M solution of *n*-BuLi in hexanes (765 µL, 1.909 mmol, 2.3 eq.) dropwise. The reaction mixture was stirred at −78 °C for 45mins. Chlorotrimethylsilane (262 µL, 2.064 mmol, 2.5 eq.) was added in several portions at −78 °C. The reaction was allowed to warm to 20 °C overnight then a 1M aqueous solution of HCl (1 mL) was added at 20 °C and the reaction was allowed to stir for 10mins. The reaction was diluted with water and diethyl ether and water. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, saturated sodium bicarbonate solution and brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 5% to 20% ethyl acetate in hexanes as eluent) to yield the product (154 mg, 0.784 mmol, 94%). *Rf* = 0.50 (20% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75-3.61 (m, 2H), 2.40-2.31 (m, 1H), 2.08-1.94 (m, 2H), 1.89-1.79 (m, 2H), 1.77-1.57 (m, 3H), 1.39-1.22 (m, 1H), 0.51 (s, 9H).



2.104

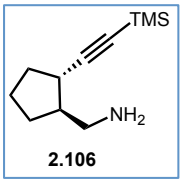
(((1*S*,2*S*)-2-(Iodomethyl)cyclopentyl)ethynyl)trimethylsilane. To a solution of iodine (327 mg, 1.288 mmol, 1.5 eq.) in DCM (8 mL) was added triphenylphosphine (361 mg, 1.376 mmol, 1.6 eq.) in small portions. To the bright yellow reaction mixture was added imidazole (177 mg, 2.599 mmol, 2.0 eq.) followed by a solution of **2.103** (169 mg, 0.861 mmol, 1.0 eq.)

in DCM (2 mL). The reaction mixture was stirred at 20 °C for 3h then was quenched with a saturated sodium bicarbonate solution and a saturated sodium thiosulfate solution and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (100% pentane as eluent) to yield the product (230 mg, 0.751 mmol, 88%). *Rf* = 0.63 (100% pentane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.56-3.44 (m, 1H), 3.28-3.19 (m, 1H), 2.39-2.23 (m, 2H), 2.19-2.05 (m, 1H), 2.03-1.95 (m, 2H), 1.80-1.60 (m, 2H), 1.38-1.20 (m, 2H), 0.15 (s, 9H).



2.105

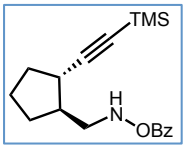
(((1*S*,2*S*)-2-(Azidomethyl)cyclopentyl)ethynyl)trimethylsilane. To a solution of **2.104** (585 mg, 1.910 mmol, 1.0 eq.) in dimethylformamide (20 mL) was added sodium azide (186 mg, 2.861 mmol, 1.5 eq.). The reaction mixture was stirred at 95 °C for 4h. Ethyl acetate and water were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, a solution of 5% aqueous sodium bicarbonate, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (1% ethyl acetate in hexanes as eluent) to yield the product (334 mg, 1.509 mmol, 80%) as a clear oil. *Rf* = 0.34 (100% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51-3.42 (m, 1H), 3.31-3.24 (m, 1H), 2.39-2.32 (m, 2H), 2.19-2.10 (m, 1H), 2.09-2.01 (m, 1H), 1.96-1.87 (m, 1H), 1.78-1.60 (m, 3H), 1.41-1.35 (m, 1H), 0.15 (s, 9H).



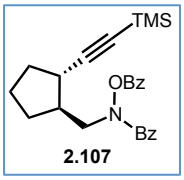
2.106

((1*S*,2*S*)-2-((Trimethylsilyl)ethynyl)cyclopentyl)methanamine. To a solution of **2.105** (334 g, 1.509 mmol, 1.0 eq.) in THF (12 mL) and water (2 mL) was added triphenylphosphine (475 mg, 1.819 mmol, 1.05 eq.) in one portion. The reaction mixture was allowed to stir at 20 °C for 16h then the solvent was removed under reduced pressure then coevaporated twice with toluene. The crude material was purified by flash column chromatography on silica gel

(4% MeOH in DCM + 0.5% NEt_3 as eluent) to yield the product (258 mg, 1.321 mmol, 87%) as a clear oil. *Rf* = 0.42 (4% methanol in dichloromethane with 1% triethylamine); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79-2.82 (m, 1H), 2.70-2.62 (m, 1H), 2.28-2.21 (m, 1H), 2.06-1.84 (m, 3H), 1.76-1.56 (m, 3H), 1.28-1.19 (m, 1H), 0.15 (s, 9H).



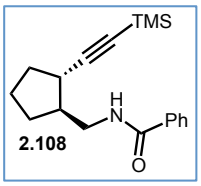
***O*-Benzoyl-*N*-(((1*S*,2*S*)-2-((trimethylsilyl)ethynyl)cyclopentyl)methyl)hydroxylamine.** To a stirred solution of **2.106** (193 mg, 0.988 mmol, 1.0 eq.) in DCM (5 mL) and pH 10.5 aq. buffer (5 mL) was added benzoyl peroxide (240 mg, 0.991 mmol, 1.0 eq.). The reaction was allowed to stir for overnight at 20 °C. Water and DCM were added. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 0% to 1.5% ethyl acetate in toluene) to yield the product (123 mg, 0.390 mmol, 40%) as a white solid. *Rf* = 0.46 (2.5% ethyl acetate in toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 3.39-3.34 (m, 1H), 3.12-3.07 (m, 1H), 2.37-2.35 (m, 1H), 2.21-2.17 (m, 1H), 2.06-1.98 (m, 2H), 1.76-1.63 (m, 3H), 1.41-1.37 (m, 1H), 0.12 (s, 9H).



2.107

***N*-(Benzoyloxy)-*N*-(((1*S*,2*S*)-2-((trimethylsilyl)ethynyl)cyclopentyl)methyl)benzamide.** To a stirred solution of **2.106** (38 mg, 0.120 mmol, 1.0 eq.) and pyridine (30 µL, 0.361 mmol, 3.0 eq.) in toluene (2 mL) was added benzoyl chloride (21 µL, 0.181 mmol, 1.5 eq.). The reaction was allowed to stir at 90 °C for 4h then cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 15% ethyl acetate in hexanes) to yield the product (36 mg, 0.086 mmol, 72%) as a white solid. *Rf* = 0.22 (10% ethyl acetate in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.5 Hz, 2H), 7.64 (d, J = 7.0Hz, 2H, 7.60 (t, J = 6.5 Hz, 1H), 7.45 (m, 5H), 4.12-4.05 (m, 1H), 4.06-3.78 (m, 1H), 2.45-2.34 (m, 2H), 2.11-1.97 (m, 2H), 1.78-1.60 (m, 3H), 1.42-1.38 (m,

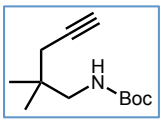
1H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 164.3, 134.2, 133.6, 130.8, 129.9, 128.7, 128.1, 127.9, 126.9, 84.7, 52.7, 45.7, 35.6, 33.6, 33.6, 30.1, 23.9, 0.2.



2.108

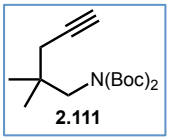
***N*-(((1*S*,2*S*)-2-((Trimethylsilyl)ethynyl)cyclopentyl)methyl)benzamide.** To a solution of **2.107** (46.5 mg, 0.1108 mmol, 1.0 eq.) heated at 100 °C in degassed α,α,α-trifluorotoluene (3 mL) was added a solution of ACCN (16.2 mg, 0.0663 mmol, 0.6 eq.) and tributyltin hydride (78 µL, 0.289 mmol, 2.6 eq.) in degassed α,α,α-trifluorotoluene (3 mL) at a rate of 0.30 mL/hour *via* syringe pump. The reaction mixture was cooled to 20 °C and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes as eluent) to yield the amide product (17.2 mg, 0.0574 mmol, 61%) and starting material (6.4 mg, 0.0153 mmol, 14%). *Rf* = 0.22 (20% ethyl acetate in hexanes); IR (neat) ν = 3322, 2957, 2165, 1705, 1638, 1577, 1247, 838, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.0 Hz, 2H), 7.50 (q, *J* = 5.0 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 6.76 (br s, 1H), 3.85-3.81 (m, 1H), 3.34-3.29 (m, 1H), 2.35 (q, *J* = 9.0 Hz, 1H), 2.20-2.12 (m, 2H), 1.97-1.95 (m, 1H), 1.77-1.66 (m, 4H), 1.37-1.35 (m, 1H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 134.7, 131.4, 130.2, 128.6, 128.5, 127.0, 126.9, 110.5, 85.8, 46.7, 45.1, 36.8, 34.4, 30.2, 23.9, 0.1; HRMS (ESI) calcd for C18H26ONSi [M+H] 300.17782; found 300.17743.

4.1.5 Conjugate Addition Substrates



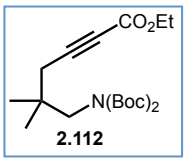
***Tert*-butyl (2,2-dimethylpent-4-yn-1-yl)carbamate.** To a stirred solution of diisopropylethylamine (3.2 mL, 0.019 mol, 1.2 eq.) and di-*tert*-butyl dicarbonate (3.6 g, 0.016 mol, 1.0 eq.) in DCM (30 mL) cooled to 0 °C was added a solution of crude 2,2-dimethylpent-4-yn-1-amine (2.6 g, 0.016 mol, 1.0 eq.) in DCM (10 mL) dropwise. The reaction mixture was stirred overnight at 20 °C. The resulting orange solution was diluted with saturated ammonium chloride and DCM and washed with water. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash column

chromatography on silica gel (8% ethyl acetate in hexanes) to yield the product (3.45 g, 0.016 mmol, 87%) as a yellow oil. *Rf* = 0.33 (10% ethyl acetate in hexanes); IR (neat) ν = 3310, 2966, 1694, 1511, 1365, 1246, 1164, 629 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (br s, 1H), 3.05 (d, *J* = 6.9 Hz, 2H), 2.09 (d, *J* = 2.7 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 2H), 1.46 (s, 9H), 0.96 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 81.7, 79.1, 70.4, 49.7, 34.9, 29.4, 28.37, 24.6; (ESI) calcd for C12H21NNaO2 [M+Na] 234.1464; found 234.1469.



2.111

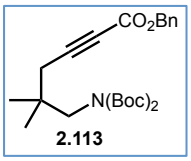
***Tert*-butyl *N*-[(tert-butoxy)carbonyl]-N-(2,2-dimethylpent-4-yn-1-yl)carbamate.** To a stirred solution of *tert*-butyl (2,2-dimethylpent-4-yn-1-yl)carbamate (19.86 g, 0.093 mol, 1.0 eq.) in THF (500 mL) cooled to −78 °C was added a 2.64 M solution of *n*-BuLi in hexanes (39.0 mL, 0.10 mol, 1.1 eq.) dropwise. The reaction mixture was stirred at −78 °C for 1h. A solution of di-*tert*-butyl dicarbonate (24.7 g, 0.11 mol, 1.0 eq.) in THF (100 mL) was slowly added into the reaction flask dropwise. The reaction was allowed to warm to 20 °C overnight then was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 1% to 2.5% ethyl acetate in hexanes as eluent) to yield the product (25.18 g, 0.081 mol, 86%) as a yellow oil. *Rf* = 0.62 (15% ethyl acetate in hexanes); IR (neat) ν = 2977, 1738, 1699, 1395, 1366, 1332, 1245, 1171, 1124, 853, 629 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (s, 2H), 2.16 (d, *J* = 3.0 Hz, 2H), 2.02 (t, *J* = 3.0 Hz, 1H), 1.52 (s, 18H), 1.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ157.7, 82.2, 70.3, 54.4, 36.3, 30.4, 28.0, 24.8; HRMS (ESI) calcd for C17H29NNaO4 [M+Na] 334.19888; found 334.19878.



2.112

Ethyl 6-{bis[(tert-butoxy)carbonyl]amino}-5,5-dimethylhex-2-ynoate. To a stirred solution of 2,2,6,6-tetramethylpiperidine (1.3 mL, 0.0077 mol, 1.6 eq.) in THF (60 mL) cooled to −78 °C was added a 2.50

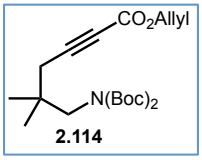
M solution of *n*-BuLi in hexanes (2.9 mL, 0.0072 mol, 1.5 eq.) dropwise. The mixture was suspended above the cooling bath and allowed to reach room temperature, then recooled to −78 °C. A solution of **2.111** (1.5 g, 0.0048 mmol, 1.0 eq.) in THF (20 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1h. Ethyl chloroformate (920 µL, 0.00964 mol, 2.0 eq.) was added in one portion at −78 °C. The reaction was stirred at −78 °C for 1h then was allowed to warm to 20 °C and stirred for 30mins. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to yield the product (1.37 g, 3.57 mmol, 74%) as a yellow oil. *Rf* = 0.47 (15% ethyl acetate in hexanes); IR (neat) ν = 2978, 1738, 1702, 1366, 1243, 1169, 1069, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.2 Hz, 2H), 3.58 (s, 2H), 2.31 (s, 2H), 1.47 (s, 18H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 153.7, 87.1, 82.5, 75.1, 61.7, 54.5, 36.7, 20.4, 28.0, 25.0; HRMS (ESI) calcd for C20H33NNaO2 [M+Na] 406.2200; found 406.2213.



2.113

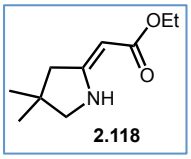
Benzyl 6-{bis[(tert-butoxy)carbonyl]amino}-5,5-dimethylhex-2-ynoate. To a stirred solution of 2,2,6,6-tetramethylpiperidine (250 µL, 1.481 mmol, 1.6 eq.) in THF (15 mL) cooled to −78 °C was added a 2.50 M solution of *n*-BuLi in hexanes (580 µL, 1.450 mmol, 1.5 eq.) dropwise. The mixture was suspended above the cooling bath and allowed to reach room temperature, then recooled to −78 °C. A solution of **2.111** (300 mg, 0.963 mmol, 1.0 eq.) in THF (2 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 45mins. Benzyl chloroformate (185 µL, 1.926 mmol, 2.0 eq.) was added in one portion at −78 °C. The reaction was stirred at −78 °C for 1h then was allowed to warm to 20 °C and stirred for 30mins. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether

and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to yield the product (252 mg, 0.566 mmol, 60%) as a yellow oil. *Rf* = 0.40 (10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 5H), 5.18 (s, 2H), 3.59 (s, 2H), 2.31 (s, 2H), 1.46 (s, 18H), 1.08 (s, 6H).



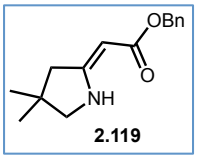
2.114

Prop-2-en-1-yl 6-{bis[(tert-butoxy)carbonyl]amino}-5,5-dimethylhex-2-ynoate. To a stirred solution of 2,2,6,6-tetramethylpiperidine (4.4 mL, 0.026 mol, 1.6 eq.) in of THF (300 mL) cooled to −78 °C was added a 2.60 M solution of *n*-BuLi in hexanes (9.1 mL, 0.024 mol, 1.5 eq.) dropwise. The mixture was suspended above the cooling bath and allowed to reach room temperature, then recooled to −78 °C. A solution of **2.111** (5.0 g, 0.016 mol, 1.0 eq.) in THF (50 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 20mins. A solution of allyl chloroformate (3.4 mL, 0.032 mol, 2.0 eq.) in 50 mL of THF was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1h then was allowed to warm to 20 °C and stirred for 30mins. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 2% to 5% ethyl acetate in hexanes as eluent) to yield the product (4.9 g, 0.012 mmol, 78%) as a yellow oil. *Rf* = 0.23 (5% ethyl acetate in hexanes); IR (neat) ν = 2974, 2935, 1735, 1649, 1456, 1394, 1327, 1276, 1256, 1158, 1132, 993, 845, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99-5.82 (m, 1H), 5.34 (d, *J* = 16.5 Hz, 1H), 5.26 (d, *J* = 9.3 Hz, 1H), 4.63 (d, *J* = 5.7 Hz, 2H), 3.59 (s, 2H), 2.31 (s, 2H), 1.49 (s, 18H), 1.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 153.4, 131.3, 119.1, 87.8, 82.5, 74.8, 66.2, 54.5, 36.7, 30.4, 27.9, 24.9; HRMS (ESI) calcd for C21H33NNaO6 [M+Na] 418.22001; found 418.21879.



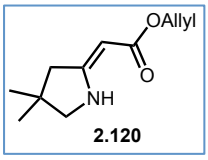
2.118

(*Z*)-Ethyl 2-(4,4-dimethylpyrrolidin-2-ylidene)acetate. To **2.112** (950 mg, 2.477 mmol, 1.0 eq.) was added trifluoroacetic acid (3 mL, 0.039 mol, 15.8 eq.) in several portions at 20 °C. The reaction mixture was allowed to stir at 20 °C for 10mins. The reaction mixture was concentrated under reduced pressure, dissolved in 10 mL of toluene and reconcentrated. The resultant oil was dissolved in DCM (20 mL) and 3 scoops of Amberlite IRA-67 free base resin were added. The slurry was stirred at 20 °C for 40mins then filtered. The filtrate was concentrated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to yield the product (330 mg, 1.800 mmol, 73%) as a yellow oil. *Rf* = 0.32 (10% ethyl acetate in hexanes); IR (neat) ν = 2978, 2229, 1707, 1688, 1436, 1392, 1365, 1343, 1245, 1225, 1172, 11229, 887, 853, 780, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 4.48 (s, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.22 (s, 2H), 2.33 (s, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 166.3, 77.1, 59.7, 58.4, 46.8, 37.0, 26.7, 14.7; HRMS (ESI) calcd for C10H17NNaO2 [M+Na] 206.1151; found 206.1155.



2.119

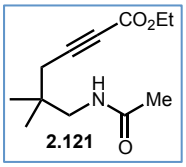
(*Z*)-Benzyl 2-(4,4-dimethylpyrrolidin-2-ylidene)acetate. To a solution of **2.113** (613 mg, 1.376 mmol, 1.0 eq.) in DCM (2 mL) cooled to 0 °C was added trifluoroacetic acid (2 mL, 0.026 mol, 19 eq.) in several portions. The reaction mixture was allowed to warm to 20 °C then stirred at 20 °C for 5mins. The reaction mixture was concentrated under reduced pressure, dissolved in toluene (10 mL) and reconcentrated. The resultant oil was dissolved in DCM (10 mL) and 3 scoops of Amberlite IRA-67 free base resin were added. The slurry was stirred at 20 °C for 35mins then filtered. The filtrate was concentrated under reduced pressure to yield the product (300 mg, 1.223 mmol, 89%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 5.11 (s, 2H), 4.57 (s, 1H), 3.24 (s, 2H), 2.35 (s, 2H), 1.13 (s, 6H).



2.120

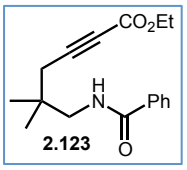
(*Z*)-Allyl 2-(4,4-dimethylpyrrolidin-2-ylidene)acetate. To a solution of **2.114** (2.33 g, 0.00589 mol, 1.0 eq.) in DCM (15 mL) cooled to 0 °C was added trifluoroacetic acid (3.5 mL, 0.046 mol, 7.7 eq.) in several portions. The reaction mixture was allowed to warm to 20 °C then stirred at 20 °C for

10mins. The reaction mixture was concentrated under reduced pressure, dissolved in toluene (10 mL) and reconcentrated. The resultant oil was dissolved in DCM (25 mL) and 3 scoops of Amberlite IRA-67 free base resin were added. The slurry was stirred at 20 °C for 1h then filtered. The filtrate was concentrated under reduced pressure to yield the product (1.11 g, 0.0057 mol, 97%) as an oil that slowly crystallized. IR (neat) ν = 3374, 2958, 1727, 1659, 1297, 1141, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (brs, 1H), 6.02-5.89 (m, 1H), 5.29 (d, *J* = 17.1Hz, 1H), 5.17 (d, *J* = 10.5, 1H), 4.56 (d, *J* = 5.7, 2H), 4.53 (s, 1H), 3.23 (s, 2H), 2.35 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 166.6, 133.8, 116.9, 76.8, 63.3, 59.8, 46.9, 37.0, 26.7; HRMS (ESI) calcd for C11H18NO2 [M+H] 196.1332; found 196.1334.

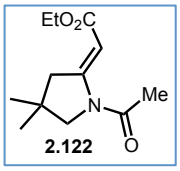


2.121

Ethyl 6-acetamido-5,5-dimethylhex-2-ynoate. To a solution of **2.112** (205 mg, 0.535 mmol, 1 eq.) in DCM (1 mL) cooled to 0 °C was added trifluoroacetic acid (3.0 mL, 39.0 mmol, 74 eq.) in several portions. The reaction mixture was allowed to warm to 20 °C then stirred at 20 °C for 5mins. The reaction mixture was concentrated under reduced pressure, dissolved in toluene (10 mL) and reconcentrated. To a solution of the resultant oil in DCM (1 mL) cooled to 0 °C, was added acetic anhydride (2.0 mL, 21.1 mmol, 40 eq.) in one portion followed by triethylamine (2.0 mL, 14.4 mmol, 27 eq.) dropwise. The reaction mixture was allowed to warm to 20 °C over a period of 3h. The reaction mixture was quenched with water and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (70% ethyl acetate in hexanes as eluent) to yield the product (101 mg, 0.448 mmol, 85%) as an oil. *Rf* = 0.3 (70% ethyl acetate in hexanes); IR (neat) ν = 3302, 2964, 2230, 1705, 1652, 1549, 1467, 1368, 1246, 1205, 1069, 1036, 1010, 848, 752, 596 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (brs, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.20 (d, *J* = 6.50 Hz, 2H), 2.27 (s, 2H), 2.01 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 153.7, 86.6, 75.3, 61.9, 48.7, 35.4, 29.9, 25.0, 23.3, 14.0; HRMS (ESI) calcd for C12H19NaNO3 [M+Na] 248.1257; found 247.1258.

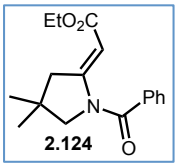


Ethyl 6-benzamido-5,5-dimethylhex-2-ynoate. To a solution of **2.112** (205 mg, 0.535 mmol, 1 eq.) in DCM (2 mL) cooled to 0 °C was added trifluoroacetic acid (2.0 mL, 26.1 mmol, 47 eq.) in several portions. The reaction mixture was allowed to warm to 20 °C then stirred at 20 °C for 5mins. The reaction mixture was concentrated under reduced pressure, dissolved in toluene (10 mL) and reconcentrated. To a solution of the resultant oil in DCM (1 mL) cooled to 0 °C, was added benzoic anhydride (1.3 g, 0.0056 mol, 10 eq.) in one portion followed by triethylamine (1.0 mL, 6.7 mmol, 12 eq.) dropwise. The reaction mixture was allowed to warm to 20 °C over a period of 4h. The reaction mixture was quenched with water and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 20% to 35% ethyl acetate in in hexanes as eluent) to yield the product (115 mg, 0.400 mmol, 71%) as a white solid. *Rf* = 0.125 (20% ethyl acetate in hexanes); IR (neat) ν = 3338, 2964, 2231, 1705, 1641, 1602, 1578, 1540, 1491, 1467, 1450, 1251, 1175, 1071, 1024848, 711, 648 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.3 Hz, 2H), 7.51-7.44 (m, 3H), 6.42 (brs, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.45 (d, *J* = 6.5 Hz, 2H), 2.37 (s, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 153.6, 133.6, 131.6, 130.2, 128.6, 128.5, 126.9, 86.5, 75.5, 61.9, 49.1, 35.8, 30.1, 25.1, 14.0; HRMS (ESI) calcd for C17H21NaNO3 [M+Na] 310.1414; found 310.1415.



(*E*)-Ethyl 2-(1-acetyl-4,4-dimethylpyrrolidin-2-ylidene)acetate. To a solution of **2.121** (100 mg, 0.444 mmol, 1 eq.) in 1,4-dioxane (450 µL) was added $Au(PPh_3)Cl$ (11 mg, 0.022 mmol, 0.05 eq.) and silver(I) triflate (6 mg, 0.022 mmol, 0.05 eq.). The reaction mixture was degassed *via* 3 cycles of freeze-pump-thaw then stirred at 60 °C for 18h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (25% ethyl acetate in in hexanes as eluent) to yield the product (56.1 mg, 0.2490 mmol, 56%). *Rf* = 0.76 (60% ethyl acetate in hexanes); IR (neat) ν = 2960, 1688, 1610, 1379, 1319, 1154, 1122, 1106, 1043, 854 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82

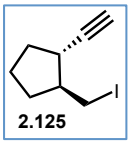
(br s, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.40 (s, 2H), 2.95 (s, 2H), 2.09 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.0, 156.5, 100.1, 62.9, 59.4, 45.6, 35.0, 26.2, 25.6, 14.4; HRMS (ESI) calcd for C12H19NaNO3 [M+Na] 248.1257; found 247.1260.



2.124

(*E*)-Ethyl 2-(1-benzoyl-4,4-dimethylpyrrolidin-2-ylidene)acetate. To a solution of **2.123** (30 mg, 0.104 mmol, 1 eq.) in THF (2 mL) cooled to −78 °C was added a 2.50 M solution of *n*-BuLi in hexanes (46 µL, 0.114 mmol, 1.1 eq.) dropwise. The reaction mixture was stirred at −78 °C for 3h then at 0 °C for 2h. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 5mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by preparative thin layer chromatography (25% ethyl acetate in hexanes as eluent) to yield the starting material (10.1 mg, 0.0351 mmol, 35%)) and the product (11.3 mg, 0.0393 mmol, 57% brsm). IR (neat) ν = 2958, 1669, 1612, 1392, 1363, 1115, 853, 718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ δ 7.47-7.41 (m, 5H), 6.71 (s, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.38 (s, 2H), 3.03 (s, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 168.7, 156.8, 136.7, 130.6, 128.6, 126.8, 101.1, 64.6, 59.5, 45.9, 35.5, 25.8, 14.4. HRMS (ESI) calcd for C17H21NNaO3 [M+Na] 310.1414; found 310.1415.

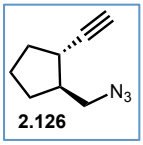
4.1.6 Cyclic Model system – Conjugate Addition Substrates



2.125

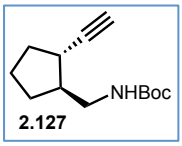
(1*S*,2*S*)-1-Ethynyl-2-(iodomethyl)cyclopentane. To a solution of iodine (7.02 g, 0.0277 mol, 1.5 eq.) in DCM (180 mL) cooled to 0 °C was added triphenylphosphine (7.74 g, 0.0295 mol, 1.6 eq.) in small portions. To the bright yellow reaction mixture was added imidazole (3.77 g, 0.0553 mol, 3.0 eq.) followed by a solution of **2.102** (2.29 g, 0.0184 mol, 1.0 eq.) in DCM (20 mL). The

reaction mixture was stirred at 0 °C for 1h and for 10h at 20 °C then was quenched with a saturated sodium bicarbonate solution and a saturated sodium thiosulfate solution and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (100% hexanes as eluent) to yield the product (3.76 g, 16.06 mmol, 87%) as a clear oil. *Rf* = 0.45 (100% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52-3.38 (m, 1H), 3.29-3.24 (m, 1H), 2.36-2.28 (m, 1H), 2.17-2.07 (m, 2H), 2.00-1.82 (m, 2H), 1.80-1.60 (m, 3H), 1.40-1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.4, 69.1, 48.8, 36.6, 33.6, 32.4, 23.2, 12.2 ; LRMS (EI) calcd for C8H11I [M+] 233.99; found 233.9.



2.126

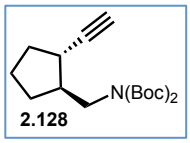
(1*S*,2*S*)-1-(Azidomethyl)-2-ethynylcyclopentane. To a solution of **2.125** (3.76 g, 0.0161 mol, 1.0 eq.) in dimethylformamide (150 mL) was added sodium azide (1.6 g, 0.0241 mol, 1.5 eq.). The reaction mixture was stirred at 70 °C for 4.5h and at 20 °C for 1.5h. Ethyl acetate and water were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, a solution of saturated sodium bicarbonate, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (1.5% ethyl acetate in hexanes as eluent) to yield the product (2.4 g, 0.016 mol, 99%) as a clear oil. *Rf* = 0.46 (5% ethyl acetate in hexanes); IR (neat) ν = 3300, 2960, 2091, 1450, 1264, 633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (dd, *J* = 7.2, 4.9 Hz, 1H), 3.33 (dd, *J* = 6.9, 5.4 Hz,1H), 2.34-2.28 (m, 1H), 2.16-2.10 (m, 2H), 1.98-1.91 (m, 2H), 1.80-1.63 (s, 3H), 1.40-1.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.7, 68.8, 54.4, 47.1, 33.7, 33.2, 29.3, 23.7; HRMS (ESI) calcd for C8H11N3Na [M+Na] 172.08507; found 172.08442.



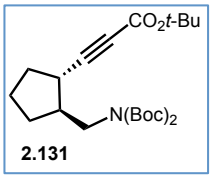
2.127

***Tert*-butyl (((1*S*,2*S*)-2-ethynylcyclopentyl)methyl)carbamate.** To a solution of **2.126** (2.4 g, 0.016 mol, 1.0 eq.) in THF (150 mL) and water (35 mL) was added triphenylphosphine (4.43 g, 0.0169 mol, 1.05 eq.) in one portion. The reaction mixture was stirred at 20 °C overnight then cooled to 0 °C. A

solution of di-*tert*-butyl dicarbonate (5.3 g, 0.024 mol, 1.5 eq.) in DCM (50 mL) was added and the reaction was allowed to stir overnight while warming to 20 °C. The reaction mixture was diluted with DCM and water. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 50% DCM in hexanes to 100% DCM as eluent) to yield the product (3.35 g, 0.0150 mol, 93%) as a clear oil. *Rf* = 0.21 (60% DCM in hexanes); IR (neat) ν = 3307, 2963, 1689, 1509, 1391, 1248, 1164, 952, 872, 779, 623 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (br s, 1H), 3.11 (t, 2H), 2.33-2.22 (m, 1H), 2.11 (s, 1H), 2.09-1.98 (m, 2H), 1.96-1.80 (m, 1H), 1.44 (s, 9H), 1.37-1.30 (m, 1H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 86.7, 68.9, 47.5, 44.4, 34.3, 33.5, 29.5, 28.4, 23.7; HRMS (ESI) calcd for C13H21NNaO2 [M+Na] 247.14700; found 247.14634.



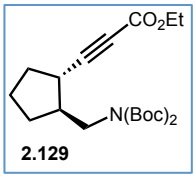
2.128



2.131

Tert-butyl N-[(tert-butoxy)carbonyl]-N-[(2-ethynylcyclopentyl)methyl]carbamate and **Tert-butyl 3-[2-({bis[(tert-butoxy)carbonyl]amino}methyl)cyclopentyl]prop-2-ynoate.** To a solution of **2.127** (3.35g, 0.015 mmol, 1.0 eq.) in THF (200 mL) cooled to −78 °C was added a 2.50 M solution of *n*-BuLi in hexanes (6.6 mL, 0.0165 mol, 1.1 eq.) dropwise. The reaction mixture was stirred at −78 °C for 1h. A solution of di-*tert*-butyl dicarbonate (3.9 g, 0.018 mol, 1.2 eq.) in THF (50 mL) was added dropwise at −78 °C. The reaction mixture was allowed to stir overnight while warming to 20 °C. The reaction mixture was quenched with a saturated solution of ammonium chloride and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 5% ethyl acetate in hexanes as eluent) to yield **2.128** (2.38 g, 0.00736 mol, 49%) and **2.130** (1.7 g, 0.0040 mol, 27%). **tert-butyl N-[(tert-butoxy)carbonyl]-N-[(2-ethynylcyclopentyl)methyl]carbamate 2.128** *Rf* = 0.40 (10% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (dd, *J*

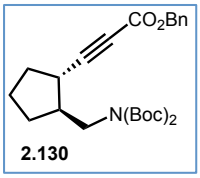
= 6.3, 6.9 Hz, 1H), 3.59 (dd, *J* = 7.2, 7.8 Hz, 1H), 2.39-2.20 (m, 2H), 2.10-1.85 (m, 1H), 2.02 (s, 1H), 1.89-1.76 (m, 1H), 1.75-1.60 (m, 3H), 1.54 (s, 18H), 1.36-1.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 87.6, 82.2, 68.3, 49.6, 46.8, 34.0, 33.3, 29.7, 28.1, 23.7; HRMS (ESI) calcd for C18H29O4NNa [M+Na] 346.19943; found 346.19887. **tert-butyl 3-[2-({bis[(tert-butoxy)carbonyl]amino}methyl)cyclopentyl]prop-2-ynoate 2.131** *Rf* = 0.18 (10% ethyl acetate in hexanes); IR (neat) ν = 2979, 2229, 1699, 1477, 1393, 1367, 1346, 1271, 1256, 1160, 1129, 847, 752, 736, 704, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72-3.67 (m, 1H), 3.63-3.58 (m, 1H), 2.51-2.46 (m, 1H), 2.41-2.36 (m, 1H), 1.87-1.65 (m, 3H), 1.52 (s, 18H), 1.47 (s, 9H), 1.34-1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 152.7, 89.5, 82.6, 82.3, 74.5, 49.4, 46.5, 33.7, 32.8, 29.9, 28.1, 28.0, 24.1; HRMS (ESI) calcd for C23H37NNaO6 [M+Na] 446.2513; found 446.2520.



2.129

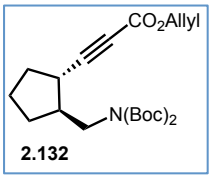
Ethyl 3-[2-({[(tert-butoxy)carbonyl][1-(tert-butoxy)ethenyl]amino}methyl)cyclopentyl]prop-2-ynoate. To a stirred solution of 2,2,6,6-tetramethylpiperidine (220 µL, 1.304 mmol, 1.3 eq.) in THF (15 mL) cooled to −78 °C was added a 2.50 M solution of *n*-BuLi in hexanes (480 µL, 1.202 mmol, 1.2 eq.) dropwise. A solution of **2.128** (324 mg, 1.001 mmol, 1.0 eq.) in THF (3 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1h. Ethyl chloroformate (170 µL, 1.803 mmol, 1.8 eq.) was added in one portion at −78 °C. The reaction was stirred at −78 °C for 30mins then was allowed to warm to 20 °C and stirred for 30mins. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to yield the product (174 mg, 0.440 mmol, 44%). *Rf* = 0.33 (10% ethyl acetate in hexanes); IR (neat) ν = 3371, 2958, 2870, 1656, 1599, 1490, 1365, 1296, 1220, 1141, 1094, 1047, 865, 778, 621, 543 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (q, J = 7.5 Hz, 2H), 3.74-3.62 (m, 2H), 2.56 (q, *J* = 8.5 Hz, 1H), 2.41 (sex, *J* = 8.2 Hz, 1H), 2.12-2.07 (m, 1H), 1.90-1.63 (m,

3H), 1.53 (s, 18H), 1.41-1.33 (m, 1H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 152.8, 92.0, 82.4, 73.2, 61.6, 49.4, 46.5, 33.7, 29.8, 28.1, 24.1, 14.1; HRMS (ESI) calcd for C21H33NNaO6 [M+Na]418.2200; found418.2212.



2.130

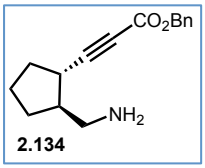
Benzyl 3-[2-({[(tert-butoxy)carbonyl][1-(tert-butoxy)ethenyl]amino}methyl)cyclopentyl]prop-2-ynoate. To a stirred solution of 2,2,6,6-tetramethylpiperidine (215 µL, 1.274 mmol, 1.6 eq.) in THF (10 mL) cooled to −78 °C was added a 2.24 M solution of *n*-BuLi in hexanes (526 µL, 1.194 mmol, 1.5 eq.) dropwise. The mixture was suspended above the cooling bath and allowed to reach room temperature, then recooled to −78 °C. A solution of **2.128** (254 mg, 0.785 mmol, 1.0 eq.) in THF (5 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1h. Benzyl chloroformate (150 µL, 1.570 mmol, 2.0 eq.) in THF (50 mL) was added in one portion at −78 °C. The reaction was stirred at −78 °C for 1h then was allowed to warm to 20 °C and stirred for 35mins. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to yield the product (198 mg, 0.432 mmol, 56%). *Rf* = 0.41 (15% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.16 (s, 2H), 3.71-3.60 (m, 2H), 2.54 (m, 1H), 2.38 (m, 1H), 2.12-2.06 (m, 1H), 1.85-1.65 (m, 4H), 1.40-1.22 (m, 2H).



2.132

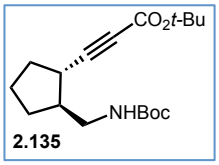
Allyl 3-[2-({[(tert-butoxy)carbonyl][1-(tert-butoxy)ethenyl]amino}methyl)cyclopentyl]prop-2-ynoate. To a stirred solution of 2,2,6,6-tetramethylpiperidine (1.70 mL, 0.0102 mol, 1.6 eq.) in THF (75 mL) cooled to −78 °C was added a 2.54 M solution of *n*-BuLi in hexanes (3.8 mL, 0.0096 mol, 1.5 eq.) dropwise. The mixture was suspended above the cooling bath and allowed to reach room temperature, then recooled to −78 °C. A solution

of **2.128** (2.06 g, 6.37 mmol, 1.0 eq.) in THF (20 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1h. Allyl chloroformate (1.4 mL, 12.7 mmol, 2.0 eq.) in THF (25 mL) was added in one portion at −78 °C. The reaction was stirred at −78 °C for 2h then was allowed to warm to 20 °C and stirred for 1h. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 3% to 6% ethyl acetate in hexanes as eluent) to yield the product (1.83 g, 4.49 mmol, 71%). *Rf* = 0.41 (15% ethyl acetate in hexanes); IR (neat) ν = 2977, 2229, 1709, 1688, 1392, 1366, 1240, 1172, 1130, 854, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96-5.86 (m, 1H), 5.34 (d, J = 16.0 Hz, 1H), 5.26 (d, J = 9.2 Hz, 1H), 4.62 (d, J = 6.0Hz, 2H), 3.73-3.60 (m, 2H), 2.54 (q, J = 8.3 Hz, 1H), 2.40 (sex, J = 8.0 Hz, 1H), 2.12-2.03 (m, 1H), 1.90-1.64 (m, 4H), 1.54 (s, 18H), 1.37-1.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.11, 152.8, 131.4, 119.1, 92.6, 82.4, 72.9, 66.2, 49.4, 46.4, 33.7, 32.8, 29.8, 28.1, 24.1; HRMS (ESI) calcd for C22H33O6NNa [M+Na] 430.22001; found 430.21980.

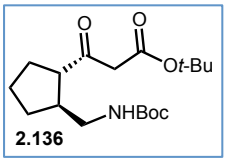


2.134

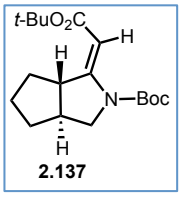
Benzyl 3-((1*S*,2*S*)-2-(aminomethyl)cyclopentyl)propiolate. To a solution of **2.130** (198 mg, 0.433 mmol, 1 eq.) in DCM (500 μL) cooled to 0 °C was added trifluoroacetic acid (1.0 mL, 13.1 mmol, 30 eq.) in several portions. The reaction mixture was allowed to warm to 20 °C then stirred at 20 °C for 10mins. The reaction mixture was concentrated under reduced pressure, dissolved in toluene (10 mL) and reconcentrated. The resultant oil was dissolved DCM (20 mL) and 2 scoops of Amberlite IRA-67 free base resin were added. The slurry was stirred at 20 °C for 1h then filtered. The filtrate was concentrated under reduced pressure to yield the product (77.3 mg, 0.3004 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 5H), 5.17 (s, 2H), 2.86-2.79 (m, 1H), 2.69-2.61 (m, 1H), 2.44-2.39 (m, 1H), 2.08-1.60 (m, 5H), 1.34-0.8 (m, 2H).



Tert-butyl 3-((1S,2S)-2-(((tert-butoxycarbonyl)amino)methyl)cyclopentyl)propiolate. To a solution of **2.131** (160 mg, 0.378 mmol, 1.0 eq.) in DCM (5 mL) was added trifluoroacetic acid (60 µL, 0.756 mmol, 2.0 eq.). The reaction mixture was stirred at 20 °C for 5mins, concentrated under reduced pressure then coevaporated with toluene. The crude material was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to yield the product (122 mg, 0.377 mmol, 99%) as a clear oil. *Rf* = 0.17 (10% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (br s, 1H), 3.20-3.13 (m, 2H), 2.42-2.36 (m, 1H), 2.14-1.99 (m, 2H), 1.88-1.65 (m, 4H), 1.47 (s, 9H), 1.42 (s, 9H), 1.37-1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ156.1, 153.0, 89.3, 82.9, 79.2, 74.8, 47.3, 44.2, 34.0, 32.8, 29.6, 28.4, 28.0, 24.1.



***Tert*-butyl 3-((1*R*,2*R*)-2-(aminomethyl)cyclopentyl)-3-oxopropanoate.** To a solution of **2.135** (100 mg, 0.309 mmol, 1 eq.) in 1,4-dioxane (300 µL) was added $Au(PPh_3)Cl$ (7.6 mg, 0.015 mmol, 0.05 eq.) and silver(I) triflate (4 mg, 0.015 mmol, 0.05 eq.). The reaction mixture was degassed via 3 cycles of freeze-pump-thaw then stirred at 60 °C for 12h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (20% ethyl acetate in in hexanes as eluent) then repurified by flash column chromatography on silica gel (2% acetonitrile in chloroform as eluent) to yield the product (56.1 mg, 0.1643 mmol, 56%). *Rf* = 0.48 (20% ethyl acetate in hexanes); IR (neat) ν = 3367, 2975, 1701, 1512, 1391, 1248, 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (br s, 1H), 3.40 (s, 2H), 3.15-3.04 (m, 2H), 2.76-2.71 (m, 1H), 2.43-2.38 (m, 1H), 2.03-1.62 (m, 4H), 1.45 (s, 9H), 1.42 (s, 9H), 1.38-1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 166.7, 156.2, 81.9, 79.1, 55.8, 49.8, 44.6, 42.1, 30.3, 30.1, 28.4, 28.3, 28.0, 24.9. HRMS (ESI) calcd for C18H31NNaO5 [M+Na] 364.2094; found 364.2109.

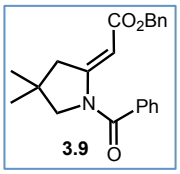


2.137

(3a*R*,6a*R*,*E*)-*Tert*-butyl 1-(2-(*tert*-butoxy)-2-oxoethylidene)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate. To a solution of **2.135** (219 mg, 0.677 mmol, 1.0 eq.) in THF (7 mL) cooled to −78 °C was added a 2.24 M solution of *n*-BuLi in hexanes (363 μL, 0.812 mmol, 1.2 eq.) dropwise. The reaction mixture was allowed to warm to 0 °C and stirred for 7h. The reaction mixture was quenched with a saturated solution of ammonium chloride and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 5% to 10% ethyl acetate in hexanes as eluent) to yield the product (40.5 mg, 0.125 mmol, 25% brsm unoptimized). *Rf* = 0.11 (10% ethyl acetate in hexanes); IR (neat) ν = 2967, 1701, 1618, 1377, 1353, 1128, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (s, 1H), 3.77 (dd, J = Hz, 1H), 3.10 (dd, J = Hz, 1H), 2.64-2.49 (m, 1H), 2.46-2.36 (m, 1H), 2.10-1.55 (m, 3H), 1.69-1.61 (m, 1H), 1.48 (s, 9H), 1.43 (s, 9H), 1.38-1.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 154.1, 152.3, 100.0, 81.3, 78.9, 56.1, 50.8, 48.2, 28.2, 28.2, 27.3, 25.4, 24.2; HRMS (ESI) calcd for C18H29O4NNa [M+Na] 346.19888; found 346.19858.

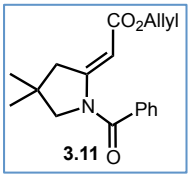
4.2 Synthetic Studies Towards the Right-Hand Side Core of Palau'amine

4.2.1 Benzamide-derived Substrates



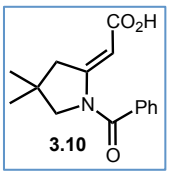
3.9

(*E*)-Benzyl 2-(1-benzoyl-4,4-dimethylpyrrolidin-2-ylidene)acetate. To a solution of **2.123** (830 mg, 3.383 mmol, 1.0 eq.), pyridine (410 µL, 5.075 mmol, 1.5 eq.) and a catalytic amount of 4-dimethylamino pyridine in toluene (50 mL) was added benzoyl chloride (470 µL, 4.060 mmol, 1.2 eq.) in one portion. The reaction mixture was stirred overnight at 60 °C, cooled to 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 20% ethyl acetate in hexanes as eluent) to yield the product (950 mg, 2.719 mmol, 81%) as a white solid. *Rf* = 0.32 (20% ethyl acetate in hexanes); IR (neat) ν = 2957, 1670, 1610, 1364, 1327, 1272, 1156, 1109, 850, 790, 734, 695, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.43 (m, 5H), 7.40-7.33 (m, 5H), 6.82 (s, 1H), 5.17 (s, 2H), 3.43 (s, 2H), 3.10 (s, 2H), 1.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.5, 157.4, 136.8, 136.7, 130.71, 128.5, 128.0, 127.9, 126.9, 100.7, 65.4, 64.7, 46.1, 35.6, 25.9; HRMS (ESI) calcd for C22H22O3N [M+H] 348.16052; found 348.16016.

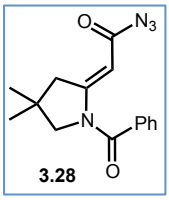


3.11

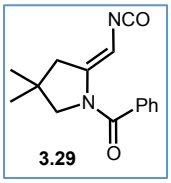
(*E*)-Allyl 2-(1-benzoyl-4,4-dimethylpyrrolidin-2-ylidene)acetate. To a solution of **2.120** (415 mg, 2.125 mmol, 1.0 eq.), pyridine (260 µL, 3.188 mmol, 1.5 eq.) and a catalytic amount of 4-dimethylamino pyridine in toluene (25 mL) was added benzoyl chloride (300 µL, 2.550 mmol, 1.2 eq.) in one portion. The reaction mixture was stirred overnight at 70 °C, cooled to 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 20% ethyl acetate in hexanes as eluent) to yield the product (610 mg, 2.037 mmol, 96%) as a white solid. *Rf* = 0.28 (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.42 (m, 5H), 6.72 (s, 1H), 5.99-5.90 (m, 1H), 5.31 (d, *J* = 16.0 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 4.60 (d, *J* = 7 Hz, 2H), 3.41 (s, 2H), 3.06 (s, 2H), 1.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 168.3, 157.3, 136.7, 132.8, 130.7, 128.6, 126.9, 117.5, 110.6, 64.6, 64.3, 46.0, 35.5, 25.8.



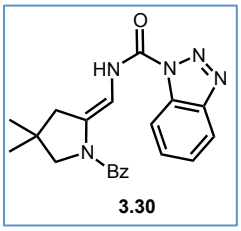
(*E*)-2-(1-Benzoyl-4,4-dimethylpyrrolidin-2-ylidene)acetic acid. A solution of palladium acetate (19 mg, 0.082 mmol, 0.05 eq.) and triphenylphosphine (88 mg, 0.334 mmol, 0.2 eq.) in DCM (10 mL) was heated at reflux for 2h then cooled to 20 °C. A solution of **3.11** (494 mg, 1.650 mmol, 1.0 eq.) and pyrrolidine (210 µL, 2.475 mmol, 1.5 eq.) in DCM (20 mL) were then added and heating at reflux was continued for 5.5h. The reaction mixture was then cooled to 20 °C and was quenched with 0.1 M HCl solution and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with 0.1 M HCl solution, water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The product (424 mg, 1.635 mmol, 99%) could be used directly in the next step without further purification. IR (neat) ν = 2958, 1675, 1594, 1365, 1336, 1277, 1162, 1136, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.44 (m, 5H), 6.61 (s, 1H), 3.43 (s, 2H), 3.05 (s, 2H), 1.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 159.1, 136.5, 130.9, 128.8, 128.6, 127.0, 100.12, 64.6, 46.4, 35.5, 25.8; HRMS (ESI) calcd for C15H18O3N [M+H] 260.12812; found 260.12801.



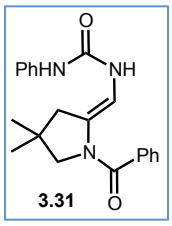
(*E*)-2-(1-Benzoyl-4,4-dimethylpyrrolidin-2-ylidene)acetyl azide. To a solution of **3.10** (25 mg, 0.964 mmol, 1.0 eq.) in benzene (3.5 mL) cooled to 0-5 °C was added triethylamine (15 µL, 0.964 mmol, 1.0 eq.) and diphenylphosphoryl azide (22 µL, 0.964 mmol, 1.0 eq.). The reaction mixture was allowed to stir while warming to 20 °C. After 3h, the reaction mixture was quenched with water and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (15% diethyl ether in hexanes as eluent) to yield the product (21.0 mg, 0.0739 mmol, 74%). *Rf* = 0.38 (20% diethyl ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 5H), 6.58 (s, 1H), 3.45 (s, 2H), 3.10 (s, 2H), 1.10 (s, 6H).



(*E*)-(2-(Isocyanatomethylene)-4,4-dimethylpyrrolidin-1-yl)(phenyl)methanone. A solution of **3.28** (108 mg, 0.380 mmol, 1.0 eq.) in benzene (2 mL) was stirred at 70 °C for 6h then cooled to 20 °C and concentrated under reduced pressure. The product (98 mg, 0.379 mmol, 99%) could be used directly in the next step without further purification. IR (neat) ν = 2960, 2261, 1638, 1600, 1489, 1397, 1385, 1320, 1270, 1181, 1160, 1085, 965, 787 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.26 (m, 6H), 3.38 (s, 2H), 2.55 (s, 2H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 138.9, 136.9, 128.5, 126.7, 104.4, 65.3, 43.1, 35.7, 25.6.

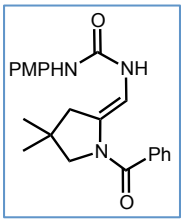


(*E*)-*N*-((1-Benzoyl-4,4-dimethylpyrrolidin-2-ylidene)methyl)-1*H*-benzo[*d*][1,2,3]triazole-1-carboxamide. A solution of **3.28** (50 mg, 0.176 mmol, 1.0 eq.) in benzene (2 mL) was stirred at 75 °C for 5h then cooled to 20 °C and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes as eluent) to yield the product (100 mg, 0.266 mmol, 70%) as an off-white solid. *Rf* = 0.26 (30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 10.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.90 (br, 2H), 7.63 (t, *J* = 8.4 Hz, 1H), 7.51-7.41 (m, 5H), 3.45 (s, 2H), 2.60 (s, 2H), 1.14 (s, 6H).



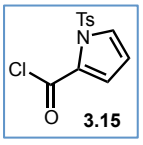
(*E*)-1-((1-Benzoyl-4,4-dimethylpyrrolidin-2-ylidene)methyl)-3-phenylurea. A solution of **3.28** (73 mg, 0.257 mmol, 1.0 eq.) in benzene (5 mL) was stirred at 90 °C for 3h then cooled to 20 °C and concentrated under reduced pressure. To a solution of the crude material in toluene (5 mL) cooled to -15 °C was added aniline (28 µL, 0.308 mmol, 1.2 eq.) in one portion. The reaction mixture was allowed to stirred while warming to 20 °C overnight then concentrated under reduced pressure. The residue was then dissolved in boiling ethanol and cooled to -30 °C. The resulting solid was collected to afford the product (15 mg, 0.049 mmol, 17%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO) δ 8.55 (s, 1H), 7.95 (br s, 1H), 7.69 (d, *J* = 10.8 Hz, 1H), 7.44-7.37 (m, 7H), 7.27 (t, *J* = 7.5 Hz, 2H),

6.95 (t, *J* = 7.5 Hz, 1H), 3.31 (s, 2H), 2.36 (s, 2H), 1.00 (s, 6H); LRMS (ESI) calcd for C21H23N3O [M+H] 350.19; found 350.12.



(*E*)-1-((1-Benzoyl-4,4-dimethylpyrrolidin-2-ylidene)methyl)-3-phenylurea. A solution of **3.28** (157 mg, 0.552 mmol, 1.0 eq.) in toluene (14 mL) was degassed *via* 3 cycles of freeze-pump-thaw. The reaction mixture was then stirred at 95 °C for 4.5h after which point, it was cooled to 20 °C then to −78 °C. *p*-Anisidine (78 mg, 0.635 mmol, 1.15 eq.) was then added as solution (also degassed via 3 cycles of freeze-pump-thaw) in toluene (4 mL). The reaction mixture was allowed to stir while warming to 20 °C overnight and was concentrated under reduced pressure. The residue was then dissolved in boiling ethanol and cooled to -30 °C. The resulting solid was collected to afford the product (15 mg, 0.049 mmol, 17%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO) δ 8.40 (d, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.69-7.65 (m, 1H), 7.50-7.38 (m, 5H), 7.33-7.30 (m, 2H), 6.87-6.82 (m, 2H), 3.71 (s, 3H), 3.29 (s, 2H), 2.37 (s, 2H), 1.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 154.8, 130.4, 128.8, 128.2, 127.0, 120.0, 119.9, 114.5, 114.1, 55.6, 42.0, 36.0, 35.8, 25.8, 21.6.

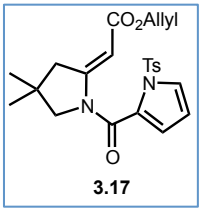
4.2.2 N-Tosyl Pyrrole-derived Substrates



1-Tosyl-1*H*-pyrrole-2-carbonyl chloride. To a solution of pyrrole (9.70 g, 0.145 mol, 1 eq.) in dichloroethane (100 mL) cooled to 0 °C was added NaOH (18g, 450 mmol, 3 eq.) followed by tosyl chloride (35.00 g, 0.184 mol, 1.2 eq.). The reaction mixture was allowed to warm to 20 °C and stirred for 36h. The reaction mixture was poured into water (500 mL) then concentrated under reduced pressure to remove the DCM. The remaining liquid was diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was then dissolved in boiling ethanol and cooled to -30 °C. The resulting solid was collected to afford the product (12.00 g, 0.054 mol, 39%) as dark crystals. IR (neat) ν = 3140,

1360, 1181, 1057, 1033, 754, 671, 588, 539 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.17 (t, *J* = 2.25 Hz, 1H), 6.31 (t, *J* = 2.25 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ145.0, 136.2, 130.0, 126.9, 120.7, 113.5, 21.6; HRMS (ESI) calcd for C11H11NNaO2S [M+Na] 244.0403; found 244.0410.

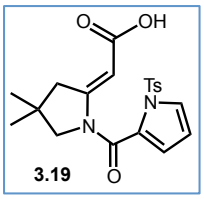
To a solution of aluminum chloride (1.5 g, 0.011 mol, 5.0 eq.) in dichloroethane (25 mL) cooled to 0 °C was added oxalyl chloride (0.98 mL, 11.3 mmol, 5.0 eq.) slowly. The reaction mixture was stirred for 20mins after which a solution of **3.23** (500 mg, 2.260 mmol, 1 eq.) in dichloroethane (5 mL) was added portionwise. The black solution was stirred for 30mins at 0 °C then stirred for 1h at 20 °C. The reaction mixture was poured onto ice water and allowed to stir for 20mins after which diethyl ether was added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The product (555 mg, 1.956 mmol, 87%) could be used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.87 (m, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.49-7.47 (m, 1H), 7.36 (d, J = 8.4 Hz, 2H), 6.43 (t, J = 3.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 133.4, 131.8, 129.7, 128.7, 111.2, 21.8.



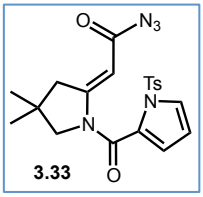
3.17

(*E*)-Allyl 2-(4,4-dimethyl-1-(1-tosyl-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetate. To a solution of **2.124** (320 mg, 1.639 mmol, 1.0 eq.), pyridine (200 µL, 2.458 mmol, 1.5 eq.) and a catalytic amount of 4-dimethylamino pyridine in toluene (20 mL) was added a solution of **3.15** (555 mg, 1.956 mmol, 1.2 eq.) in toluene (5 mL). The reaction mixture was stirred overnight at 75 °C, cooled to 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes as eluent) to yield the product (582 mg, 1.315 mmol, 81%) as a white solid. *Rf* = 0.33 (20% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 7.23-7.21 (m, 1H), 6.95 (s, 1H), 6.33-6.32 (m, 1H), 6.27 -6.25 (m, 1H), 6.05-5.93 (m, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.2 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 3.41 (s, 2H), 3.06 (s, 2H), 2.41 (s, 3H), 1.11 (s,

6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 162.5; 156.93, 145.6, 135.2, 132.9, 129.9, 129.2, 128.0, 123.0, 117.7, 114.3, 122.3, 11.8, 64.4, 64.1, 46.2, 35.4, 25.8, 21.7; HRMS (ESI): *m/z* calcd. for C23H27N2O5S [(M+H)] = 443.16352, found = 443.16310.

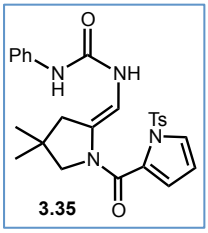


(*E*)-2-(4,4-Dimethyl-1-(1-tosyl-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetic acid. A solution of palladium acetate (10 mg, 0.046 mmol, 0.05 eq.) and triphenylphosphine (10 mg, 0.184 mmol, 0.2 eq.) in DCM (20 mL) was heated at reflux for 1.5h then cooled to 20 °C. A solution of **3.17** (408 mg, 0.922 mmol, 1.0 eq.) and pyrrolidine (150 µL, 1.844 mmol, 2.0 eq.) in DCM (5 mL) were then added and heating at reflux was continued for 6h. The reaction mixture was then cooled to 20 °C and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes with 1% acetic acid as eluent) to yield the product (320 mg, 0.795 mmol, 86%) as a white solid. *Rf* = 0.24 (20% ethyl acetate in hexanes with 1% acetic acid); IR (neat) ν = 2960, 1677, 1597, 1366, 1337, 1170, 1153, 1132, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.26-7.24 (m, 1H), 6.90 (s, 1H), 6.36-6.34 (m, 1H), 6.28-6.26 (m, 1H), 3.44 (s, 2H), 3.06 (s, 2H), 2.41 (s, 3H), 1.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 162.5, 158.6, 145.6, 135.1, 129.9, 129.0, 128.0, 123.2, 114.5, 112.2, 100.3, 64.1, 46.5, 35.4, 25.9, 21.7. HRMS (ESI): *m/z* calcd. for C20H22N2NaO5S [(M+Na)] =425.1142, found = 425.1152.

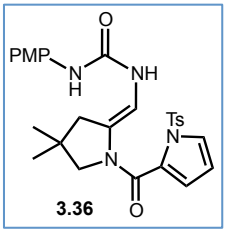


(*E*)-2-(4,4-Dimethyl-1-(1-tosyl-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetyl azide. To a solution of the crude **3.19** (250 mg, 0.621 mmol, 1.0 eq.) in benzene (10 mL) and toluene (10 mL) cooled to 0 °C was added triethylamine (690 µL, 4.970 mmol, 8.0 eq.) slowly. Diphenylphosphoryl azide (535 µL, 2.485 mmol, 4.0 eq.) was added dropwise and the reaction mixture was allowed to stir while warming to 20 °C. After 5h, the reaction mixture was quenched with water and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by

flash column chromatography on silica gel (gradient of 5% to 25% diethyl ether in hexanes as eluent) to yield the product (202 mg, 0.473 mmol, 76%) as a white solid. *Rf* = 0.19 (20% diethyl ether in hexanes); IR (KBr pellet) ν = 2961, 2130, 1675, 1462, 1366, 1330, 1170, 1150, 1067, 1046, 907, 729, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.25-7.23 (m, 1H), 6.80 (s, 1H), 6.36-6.34 (m, 1H), 6.28-6.26 (m, 1H), 3.45 (s, 2H), 3.09 (s, 2H), 2.41 (s, 3H), 1.12 (s, 6H).



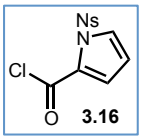
(*E*)-1-((4,4-Dimethyl-1-(1-tosyl-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)methyl)-3-phenylurea. In a round bottom flask already equipped with a reflux condenser, a solution of **3.33** (78 mg, 0.182 mmol, 1.0 eq.) in toluene (6 mL) was degassed *via* 3 cycles of freeze-pump-thaw. The reaction mixture was then stirred at 70 °C for 6h after which point, it was cooled to 20 °C then to −78 °C. Aniline (20 μL, 0.219 mmol, 1.2 eq.) was then added in one portion *via* syringe. The reaction mixture was allowed to stir while warming to 20 °C overnight and was concentrated under reduced pressure. An aliquot (30 mg) of the crude material was purified by preparative thin layer chromatography (25% ethyl acetate in toluene as eluent) to yield the product (*Rf* = 0.44 (25% ethyl acetate in toluene)). The crude material was repurified by semi-preparative HPLC (20 to 80% acetonitrile in water, 18 min gradient). The fractions containing the desired product were concentrated under reduced pressure then lyophilized to yield the urea as white fluffy solid (4.0 mg). IR (neat) ν = 3356, 2919, 2496, 1647, 1599, 1552, 1500, 1465, 1406, 1370, 1174, 1152, 671, 592 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.09 (br s, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.39 (m, 4H), 7.32-7.24 (m, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.37-6.35 (m, 2H), 6.32-6.30 (m, 1H), 3.33 (s, 2H), 2.47 (s, 2H), 2.43 (s, 3H). 1.13 (s, 6H); HRMS (APCI): *m/z* calcd. for C26H28N4O4S [(M+H)] = 493.19040, found = 493.18800.



(*E*)-1-((4,4-Dimethyl-1-(1-tosyl-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)methyl)-3-(4-methoxyphenyl)urea. In a round bottom flask already equipped with a reflux condenser, a solution of **3.33** (202 mg, 0.473 mmol, 1.0 eq.) in toluene (15 mL) was degassed *via* 3 cycles of freeze-pump-thaw. The reaction mixture was then stirred at 85 °C for

6h after which point, it was cooled to 20 °C then to −78 °C. A solution of *p*-anisidine (60 mg, 0.48 mmol, 1.02 eq.) in toluene (5 mL) (also degassed via 3 cycles of freeze-pump-thaw) was then added. The reaction mixture was allowed to stir while warming to 20 °C overnight and was concentrated under reduced pressure. The residue was then dissolved in boiling ethanol and cooled to -30 °C. The resulting solid was collected to afford the product (131 mg, 0.251 mmol, 53%) as an off-white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.10 (br s, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.36-7.31 (m, 3H), 6.83 (d, J = 8.5 Hz, 2H), 6.40-6.38 (m, 1H), 6.35-6.32 (m, 1H), 3.76 (s, 3H), 3.34 (s, 2H), 2.48 (s, 2H), 2.42 (s, 3H). 1.13 (s, 6H); HRMS (ESI) calcd for C27H30N4NaO5S [M+Na] 545.1829; found 545.1841.

4.2.3 N-Nosyl Pyrrole-derived Substrates

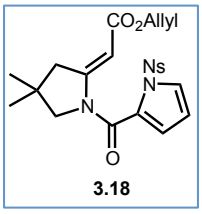


3.16

1-Nosyl-1*H*-pyrrole-2-carbonyl chloride. In a 10-20 mL microwave vial fitted with a stir bar, 2,5-dimethoxytetrahydrofuran (0.923 g, 6.990 mmol, 1.25 eq.) and 4-nitrobenzenesulfonamide (1.13 g, 5.59 mmol, 1.0 eq.) were suspended in glacial acetic acid (14 mL). The solution was heated by microwave to 150 ºC and held at that temperature for 30mins then cooled to 20 °C. The reaction mixture was poured into ice water at which point a greyish white solid begins to precipitate. The slurry was filtered and the solid was thoroughly dried overnight under high vacuum. The product **3.27** (1.10 g, 4.36 mmol, 79%) could be used directly in the next step without further purification. IR (neat) ν = 1524, 1372, 1350, 1190, 1169, 1065, 866, 855, 729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.7 Hz, 2H), 8.02 (d, *J* = 8.7 Hz, 2H) 7.16 (t, *J* = 2.3 Hz, 2H), 6.36 (t, *J* = 2.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 150.6, 144.4, 128.1, 124.6, 120.9, 114.8; HRMS (APCI): *m/z* calcd. for C10H7N2O4S [(M+H)] = 251.01320, found = 251.01323.

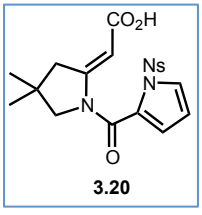
To a solution of aluminum chloride (4.10 g, 0.0307 mol, 5.0 eq.) in dichloroethane (80 mL) cooled to 0 °C was added oxalyl chloride (2.6 mL, 0.031 mol, 5.0 eq.) slowly. The reaction mixture was stirred for 30mins after which **3.27** (1.55 g, 6.14 mmol, 5.0 eq.) was added portionwise. The black solution was stirred for 30mins at 0 °C then stirred for 6h at 20 °C. The reaction mixture was poured onto ice water and allowed to stir for 20mins

after which diethyl ether was added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give a crude dark solid (1.7 g, 5.4 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.7 Hz, 2H), 8.25 (d, *J* = 8.7 Hz, 2H), 7.95 (m, 1H), 7.52 (m, 1H), 6.50 (m, 1H).



3.18

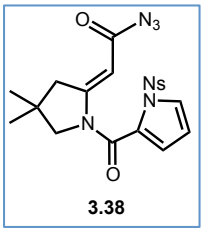
(*E*)-Allyl 2-(4,4-dimethyl-1-(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetate. To a solution of **2.124** (707 mg, 3.621 mmol, 1.0 eq.), pyridine (580 µL, 7.242 mmol, 2.0 eq.) and 4-dimethylamino pyridine (40 mg, 0.362 mmol, 0.1 eq.) in toluene (20 mL) was added a solution of **3.16** (1.70 g, 5.43 mmol, 1.5 eq.) in toluene (30 mL). The reaction mixture was stirred overnight at 80 °C, cooled to 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 0% to 5% ethyl acetate in toluene as eluent) to yield the product (1.44 g, 3.04 mmol, 85%) as a white solid. *Rf* = 0.27 (3% ethyl acetate in toluene); IR (neat) ν = 3110, 2960, 1671, 1614, 1371, 1346, 1184, 1154, 1119, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.4 Hz, 2H), 8.23 (d, *J* = 5.4 Hz, 2H), 7.32-7.30 (m, 1H), 6.91 (s, 1H), 6.43-6.41 (m, 1H), 6.36-6.33 (m, 1H), 6.03-5.93 (m, 1H), 5.35 (d, *J* = 17.4 Hz, 1H), 5.24 (d, *J* = 10.5 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 3.46 (s, 2H), 3.06 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 153.4, 131,.3, 119.1, 87.8, 82.5, 74.8, 66.2, 54.5, 36.7, 30.4, 27.9, 24.9; HRMS (ESI): *m/z* calcd. for C22H23KN3O7S [(M+K)] = 512.0888, found = 512.0894.



3.20

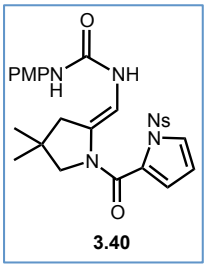
(*E*)-2-(4,4-Dimethyl-1-(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetic acid. A solution of palladium acetate (242 mg, 1.079 mmol, 0.05 eq.) and triphenylphosphine (1.13 g, 4.31 mmol, 0.2 eq.) in DCM (200 mL) was heated at reflux for 2h then cooled to 20 °C. A solution of **3.18** (10.2 g, 0.021 mol, 1.0 eq.) and pyrrolidine (3.5 mL, 0.043 mol, 2.0 eq.) in DCM (150 mL) were then added and heating at reflux was continued for 12mins. The reaction mixture was then cooled to 20 °C and concentrated

under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 15% to 40% ethyl acetate in hexanes with 1% acetic acid as eluent) to yield the product as a white solid still contaminated with traces of toluene and chloroform. *Rf* = 0.27 (30% ethyl acetate in hexanes with 1% acetic acid); IR (neat) ν = 2960, 1673, 1598, 1534, 1367, 1340, 1270, 1153, 1131, 854, 740, 681 cm^{-1}; ^{1}H NMR (400 MHz, acetone) δ 8.51 (d, *J* = 5.4 Hz, 2H), 8.37 (d, *J* = 5.4 Hz, 2H), 7.58 (d, *J* = 5.2 Hz, 1H), 6.90 (s, 1H), 6.71 (d, *J* = 5.2 Hz, 1H), 6.47 (t, *J* = 3.4 Hz, 1H), 3.58 (s, 2H), 3.02 (s, 2H), 1.14 (s, 6H); ^{13}C NMR (75 MHz, acetone) δ 168.5, 161.7, 157.1, 151.2, 144.0, 128.9, 128.1, 124.5, 124.2, 115.8, 112.7, 100.3, 63.9, 45.8, 35.3, 24.8; HRMS (ESI): *m/z* calcd. for C19H19NaN3O7S [(M+Na)] = 456.0836, found = 456.0838.



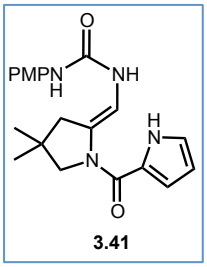
3.38

(*E*)-2-(4,4-Dimethyl-1-(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetyl azide. To a solution of the crude **3.20** (0.021 mol, 1.0 eq.) in benzene (150 mL) and toluene (150 mL) cooled to 0 °C was added triethylamine (24.0 mL, 0.172 mol, 8.0 eq.) slowly. Diphenylphosphoryl azide (18.5 mL, 0.086 mol, 4.0 eq.) was added dropwise and the reaction mixture was allowed to stir while warming to 20 °C. After 6h, the reaction mixture was quenched with water and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 20% to 60% diethyl ether in hexanes then 20% ethyl acetate + 10% diethyl ether in hexanes as eluent) to yield the product (8.8 g, 0.019 mol, 89% over 2 steps) as white needles. *Rf* = 0.19 (40% diethyl ether in hexanes); IR (KBr pellet) ν = 3110, 2961, 2134, 1675, 1599, 1534, 1371, 1183, 740, 620 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.0 Hz, 2H), 8.20 (d, *J* = 5.6 Hz, 2H), 7.32 (d, *J* = 4.8 Hz, 1H), 6.78 (s, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 6.35 (t, *J* = 6.4 Hz, 1H), 3.49 (s, 2H), 3.09 (s, 2H), 1.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 161.9, 159.4, 150.8, 143.6, 129.5, 129.0, 124.0, 116.0, 112.9, 102.0, 64.4, 46.8, 35.7, 25.7.



3.40

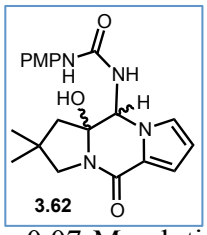
(*E*)-1-((4,4-Dimethyl-1-(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)methyl)-3-(4-methoxyphenyl)urea. In a 3-neck round bottom flask already equipped with a reflux condenser, a solution of **3.38** (674 mg, 1.470 mmol, 1.0 eq.) in toluene (42 mL) was degassed *via* 3 cycles of freeze-pump-thaw. The reaction mixture was then stirred at 85 °C for 6h after which point, it was cooled to 20 °C then to −78 °C. A solution of *p*-anisidine in toluene (10 mL) (also degassed *via* 3 cycles of freeze-pump-thaw) was then added. The reaction mixture was allowed to stir while warming to 20 °C overnight and was concentrated under reduced pressure. The crude material was purified by reversed-phase column chromatography on C-18 silica gel (gradient of 35% to 100% acetonitrile in water as eluent). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the product (740 mg, 1.337 mmol, 91%) as an orange fluffy solid. IR (KBr pellet) ν = 2960, 1673, 1598, 1534, 1367, 1340, 1270, 1153, 1131, 854, 740, 681 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 8.47 (d, *J* = 8.7 Hz, 2H), 8.40 (s, 1H), 8.29 (d, *J* = 9.6 Hz, 2H), 7.87 (d, *J* = 10.8 Hz, 1H), 7.67 (d, *J* = 10.5 Hz, 1H), 7.56 (d, *J* = 4.5 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 1H), 6.58 (d, *J* = 4.8 Hz, 1H), 6.43 (t, *J* = 3.2 Hz, 1H), 3.69 (s, 3H), 3.36 (s, 2H), 2.37 (s, 2H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, DMSO) δ 158.6, 154.8, 152.3, 151.1, 143.7, 133.2, 130.4, 129.6, 125.2, 124.0, 122.7, 119.9, 115.3, 114.5, 113.3, 112.2, 64.0, 55.6, 42.2, 35.8, 25.8; HRMS (ESI): *m/z* calcd. for C26H27NaN5O7S [(M+Na)] = 576.1523, found = 576.1518.



3.41

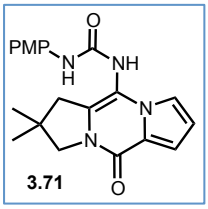
(*E*)-1-((4,4-Dimethyl-1-(1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)methyl)-3-(4-methoxyphenyl)urea. To a solution of **3.40** (1.12 g, 2.03 mmol, 1.0 eq.) in THF (60 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (10.0 mL, 10.1 mmol, 5.0 eq.) dropwise. The reaction mixture was allowed to stir at 20 °C for 7mins. The reaction mixture was concentrated under reduced pressure onto celite. The crude material was purified by reversed-phase column chromatography on C-18 silica gel (gradient of 20% to 100% acetonitrile in water as eluent). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the

product (670 mg, 1.819 mmol, 90%) as an orange fluffy solid. IR (KBr pellet) ν = 3291, 2962, 1627, 1597, 1563, 1514, 1421, 1412, 1244, 1229, 1137, 830, 766 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 11.47 (s, 1H), 8.36 (s, 1H), 7.96 (d, *J* = 10.4 Hz, 1H), 7.57 (d, *J* = 10.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.57 (s, 1H), 6.13 (s, 1H), 3.71 (s, 2H), 3.68 (s, 3H), 2.33 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (125 MHz, DMSO) δ 159.3, 154.6, 152.4, 133.4, 126.5, 124.3, 122.2, 119.8, 114.5, 112.6, 110.8, 109.4, 63.1, 55.6, 41.6, 36.1, 26.2; HRMS (ESI) calcd for C20H24NaN4O3 [M+Na] 391.1741; found 391.1740.

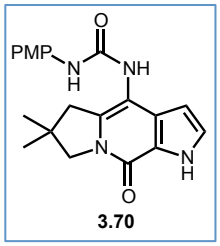


1-(5a-Hydroxy-7,7-dimethyl-10-oxo-5,5a,6,7,8,10-hexahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazin-5-yl)-3-(4-methoxyphenyl)urea. To a solution of **3.41** (40 mg, 0.108 mmol, 1.0 eq.) in THF (3.25 mL) and DMF (0.65 mL) cooled to −78 °C was added a 0.07 M solution of dimethyl dioxirane (1.55 mL, 0.108 mmol, 1.0 eq.) dropwise. The reaction mixture was allowed to stir at −78 °C for 20mins. The reaction mixture was concentrated under reduced pressure onto celite. The crude material was purified by reversed-phase column chromatography on C-18 silica gel (gradient of 20% to 100% acetonitrile in water as eluent). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the desired product as a mixture of diasteriomers. This mixture could be separated by semi-preparative HPLC (20 to 80% acetonitrile in water, 18 min gradient). The fractions containing the separated diasteriomers were concentrated under reduced pressure then lyophilized to yield the diasteriomers both as white fluffy solids (5.3 mg and 13.3 mg, 0.013 mmol and 0.035 mmol, 44% total). Compound A: ^{1}H NMR (500 MHz, DMSO) δ 8.21 (s, 1H), 7.24 (d, *J* = 10.0 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 1H), 7.00-6.99 (m, 1H), 7.22 (d, *J* = 10.0 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.64-6.63 (m, 1H), 6.12-6.11 (m, 1H), 5.83 (d, *J* = 10.0 Hz, 1H), 3.67 (s, 3H), 3.41 (d, *J* = 11.5 Hz, 1H), 3.35 (d, *J* = 11.5 Hz, 1H), 2.24 (d, *J* = 13.5 Hz, 1H), 1.89 (d, *J* = 13.5 Hz, 1H), 1.25 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 157.4, 154.8, 154.6, 133.1, 124.6, 123.5, 120.0, 114.4, 112.3, 109.9, 91.9, 65.3, 57.4, 55.6, 49.8, 36.2, 29.5, 29.1; HRMS (ESI) calcd for C20H24NaN4O4 [M+Na] 407.1690; found 407.1696. Compound B: ^{1}H NMR (500

MHz, DMSO) δ 8.99 (s, 1H), 7.33 (d, *J* = 9.0 Hz, 2H), 7.11 (br s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.80 (s, 1H), 6.65-6.64 (m, 1H), 6.13 (t, *J* = 3.5 Hz, 2H), 5.73 (d, *J* = 9.5 Hz, 1H), 3.69 (s, 3H), 3.47 (d, *J* = 11.0 Hz, 1H), 3.33 (d, *J* = 11.0 Hz, 1H), 2.04 (d, *J* = 13.5 Hz, 1H), 1.94 (d, *J* = 13.5 Hz, 1H), 1.20 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 156.7, 155.2, 154.9, 133.2, 124.2, 121.4, 120.1, 114.5, 112.9, 109.4, 90.3, 67.4, 57.2, 55.6, 51.5, 36.7, 28.9, 28.0; HRMS (ESI) calcd for C20H24NaN4O4 [M+Na] 407.1690; found 407.1696.

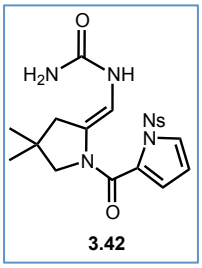


1-(7,7-Dimethyl-10-oxo-6,7,8,10-tetrahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazin-5-yl)-3-(4-methoxyphenyl)urea. To a solution of **3.62** (4.5 mg, 0.0117 mmol, 1.0 eq.) in d_3-acetonitrile (400 μL) and d_4-DMF (100 μL) was added a 0.06 M solution of camphorsulfonic acid (100 μL, 0.00585 mmol, 0.5 eq.). The reaction mixture was allowed to stand in an NMR tube for 4h. After which point, the reaction mixture was concentrated under reduced pressure and purified by semi-preparative HPLC (20 to 80% acetonitrile in water, 18 min gradient). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the desired product as a white fluffy solid (4.1 mg, 0.0112 mmol, 96%); ^{1}H NMR (400 MHz, DMSO) δ 8.94 (brs, 1H), 8.37 (brs, 1H), 7.33 (d, *J* = 9.0 Hz, 2H), 7.11 (brd, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.80 (s, 1H), 6.64 (d, *J* = 1.5 Hz, 1H), 6.13 (t, *J* = 3.5 Hz, 2H), 5.73 (d, *J* = 9.5 Hz, 1H), 3.69 (s, 3H), 3.40 (dd, *J* = 59.5 Hz, 11.0 Hz, 2H), 1.99 (dd, *J* = 39.5 Hz, 13.5. Hz, 2H), 1.20 (s, 3H), 1.06 (s, 3H); HRMS (ESI) calcd for C20H22NaN4O3 [M+Na] 389.1584; found 389.1573.



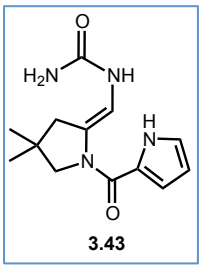
1-(6,6-Dimethyl-9-oxo-5,6,7,9-tetrahydro-1*H*-pyrrolo[2,3-*f*]indolizin-4-yl)-3-(4-methoxyphenyl)urea. To a solution of **3.41** (15 mg, 0.0407 mmol, 1 eq.) in 3.0 mL of THF (3 mL) and DMF (300 μL) cooled to −78 °C was added phenylselenyl bromide (10 mg, 0.0407 mmol, 1.0 eq.) in one portion. The reaction mixture was allowed to stir for 1h at −78 °C then quenched with methanol and concentrated under reduced pressure onto celite. The crude material was purified by reversed-phase column chromatography on C-18 silica gel (gradient of 20% to 100% acetonitrile in water as eluent). The fractions

containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the desired product which was repurified by semi-preparative HPLC (20 to 80% acetonitrile in water, 18 min gradient). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the desired product (6.4 mg, 0.0175 mmol, 43% total). ^{1}H NMR (500 MHz, DMSO) δ 11.9 (s, 1H), 8.33 (s, 1H), 7.73 (s, 1H), 7.30 (d, *J* = 9.5 Hz, 2H), 7.22 (t, *J* = 2.75 Hz, 1H), 6.81 (d, *J* = 20.0 Hz, 2H), 6.21 (t, *J* = 2.25 Hz, 1H), 3.77 (s, 2H), 3.67 (s, 3H), 2.74 (s, 2H), 1.11 (s, 6H) ; ^{13}C NMR (125 MHz, DMSO) δ 154.6, 154.1, 153.1, 136.5, 133.6, 131.1, 127.0, 122.9, 120.4, 114.3, 108.9, 101.1, 59.8, 55.6, 43.6, 37.3, 26.6; LRMS (LCMS) calcd for C20H23N4O3 [M+H] 367.18 ; found 367.17.

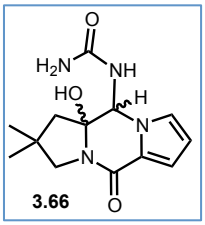


3.42

(*E*)-1-((4,4-Dimethyl-1-(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)methyl)urea. In a 3-neck round bottom flask already equipped with a reflux condenser, a solution of **3.38** (1.64 g, 3.58 mmol, 1.0 eq.) in toluene (100 mL) was degassed *via* 3 cycles of freeze-pump-thaw. The reaction mixture was then stirred at 85 °C for 6h after which point, it was cooled to 20 °C. Under a high flow of argon, the reflux condenser was swapped for a cold-finger condenser then the reaction mixture was cooled to −78 °C. Ammonia was added to the reaction mixture dropwise for 15mins. The reaction mixture was allowed to stir while warming to 20 °C overnight and was concentrated under reduced pressure. The orange fluffy material (1.47 g, 3.28 mmol, 92%) could be used directly in the next step without further purification. IR (neat) ν = 3342, 2959, 1655, 1623, 1531, 1465, 1408, 1373, 1348, 1224, 1183, 1151, 854, 740, 623 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 8.48 (d, J = 9.0 Hz, 2H), 8.30 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 10.5 Hz, 1H), 7.57-7.55 (m, 1H), 6.57-6.56 (m, 1H), 6.46-6.43 (m, 1H), 5.83 (br s, 2H), 3.34 (s, 2H), 2.34 (s, 2H), 1.05 (s, 6H); ^{13}C NMR (125 MHz, DMSO) δ 158.5, 155.7, 151.2, 143.7, 130.6, 129.6, 125.2, 123.9, 121.6, 115.2, 113.3, 113.1, 64.0, 42.2, 35.8, 25.8; HRMS (ESI): *m/z* calcd. for C19H22NaN5O6S [(M+H)] = 448.12853, found = 448.12834.

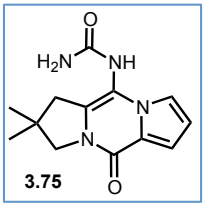


(*E*)-1-((4,4-Dimethyl-1-(1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)methyl)urea. To a solution of **3.42** (500 mg, 1.117 mmol) in THF (30 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (4.5 mL, 4.50 mmol, 4.0 eq.) dropwise. The reaction mixture was allowed to stir at 20 °C for 25mins. The reaction mixture was concentrated under reduced pressure onto celite. The crude material was purified by reversed-phase column chromatography on C-18 silica gel (gradient of 20% to 80% acetonitrile in water as eluent). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the product (118 mg, 0.450 mmol, 40%) as a white fluffy solid. IR (neat) ν = 3278, 2952, 1650, 1589, 1533, 1421, 1349, 1323, 1219, 1198, 1177, 1132, 1113, 1059, 861, 772, 690 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 11.41 (s, 1H), 6.93-6.91 (m, 1H), 6.57-6.56 (m, 1H), 6.14 (q, *J* = 3.5 Hz, 1H), 5.73 (s, 1H), 3.70 (s, 2H), 2.30 (s, 2H), 1.08 (s, 6H); ^{13}C NMR (125 MHz, DMSO) δ 159.2, 155.7, 126.6, 123.2, 122.1, 112.4, 111.8, 109.3, 63.1, 41.7, 36.1, 26.2; HRMS (ESI) calcd for C14H19N4O2 [M+H] 263.15025; found 263.15032.

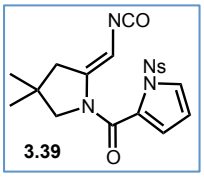


1-(5a-Hydroxy-7,7-dimethyl-10-oxo-5,5a,6,7,8,10-hexahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazin-5-yl)urea. To a solution of **3.43** (45.6 mg, 0.174 mmol, 1.0 eq.) in THF (3.25 mL) and DMF (650 μL) cooled to −78 °C was added a 0.09 M solution of dimethyl dioxirane (1.93 mL, 0.174 mmol, 1.0 eq.) dropwise. The reaction mixture was allowed to stir at −78 °C for 25mins. The reaction mixture was concentrated under reduced pressure onto celite. The crude material was purified by reversed-phase column chromatography on C-18 silica gel (gradient of 20% to 100% acetonitrile in water as eluent). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the desired product as a mixture of diasteriomers. This mixture could be separated by semi-preparative HPLC (0% to 30% acetonitrile in water, 18 min gradient). The fractions containing the separated diasteriomers were concentrated under reduced pressure then lyophilized to yield the diasteriomers both as white fluffy solids (7.0 mg and 6.1 mg, 0.025 mmol and 0.022 mmol, 27% total). Compound A: ^{1}H NMR (400 MHz, DMSO) δ 7.02 (d, J = 10.0 Hz, 1H), 6.93-6.92 (m, 1H), 6.61-6.60 (m, 1H),

6.11-6.09 (m, 1H), 5.76-5.73 (m, 1H), 5.64 (br s, 1H), 3.38 (d, *J* = 11.2 Hz, 1H), 3.31 (d, *J* = 11.2 Hz, 1H), 2.18 (d, *J* = 13.6 Hz, 1H), 1.84 (d, *J* = 13.2 Hz, 1H), 1.24 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 157.6, 157.4, 124.3, 123.6, 112.0, 109.8, 92.0, 65.5, 57.3, 49.8, 36.2, 29.5, 29.1; LRMS (LCMS) calcd for C13H18N4O3 [M+H] 279.15; found 279.2. Compound B: ^{1}H NMR (400 MHz, DMSO) δ 6.94 (d, J = 9.6 Hz, 1H), 6.71-6.69 (m, 1H), 6.63-6.61 (m, 1H), 6.17 (s, 1H), 6.13-6.11 (m, 1H), 5.63-5.60 (m, 1H), 3.45 (d, *J* = 10.8 Hz, 1H), 3.33 (d, *J* = 10.8 Hz, 1H), 1.99 (d, *J* = 14.0 Hz, 1H), 1.90 (d, *J* = 13.8 Hz, 1H), 1.19 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 158.4, 156.8, 124.2, 121.2, 112.8, 109.1, 90.4, 67.7, 57.1, 51.5, 36.7, 28.9, 27.9; LRMS (LCMS) calcd for C13H18N4O3 [M+H] 279.15; found 279.2.

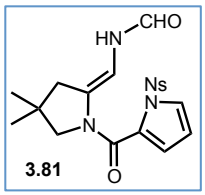


1-(7,7-Dimethyl-10-oxo-6,7,8,10-tetrahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazin-5-yl)urea. To a solution of **3.63** (1.7 mg, 0.0061 mmol, 1.0 eq.) in d_4-DMF (100 μL) and d_6-DMSO (100 μL) was added a d_4-acetic acid (400 μL). The reaction mixture was allowed to stand in an NMR tube for 4h. After which point, the reaction mixture was concentrated under reduced pressure and purified by semi-preparative HPLC (0% to 30% acetonitrile in water, 18 min gradient). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the desired product as a white fluffy solid (1.2 mg, 0.0045 mmol, 75%). ^{1}H NMR (500 MHz, DMSO) δ 8.57 (br s, 1H), 7.16 (s, 1H), 6.84-6.83 (m, 1H), 6.50-6.49 (m, 1H), 6.28 (br s, 2H), 3.64 (s, 2H), 2.62 (s, 2H), 1.11 (s, 6H); ^{13}C NMR (125 MHz, DMSO) δ 157.2, 153.9, 124.3, 115.7, 111.6, 109.2, 58.9, 41.8, 37.2, 26.3; HRMS (ESI) calcd for C13H15N4O2 [M+H] 259.12005; found 259.12012.

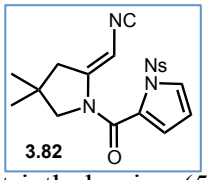


(*E*)-(2-(Isocyanatomethylene)-4,4-dimethylpyrrolidin-1-yl)(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrol-2-yl)methanone. In a round bottom flask already equipped with a reflux condenser, a solution of **3.38** (358 mg, 0.781 mmol, 1.0 eq.) in toluene (20 mL) was degassed *via* 3 cycles of freeze-pump-thaw. The reaction mixture was then stirred at 85 °C for 6h after which point, it was cooled to 20 °C and concentrated under reduced pressure. IR (neat) ν = 2959, 2257, 1640,

1465, 1401, 1370, 1172, 1150, 1082, 1049, 813, 741, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H), 7.27-7.16 (m, 2H), 6.37-6.35 (m, 1H), 6.33-6.31 (m, 1H), 3.44 (s, 2H), 2.57 (s, 2H), 1.13 (s, 6H).

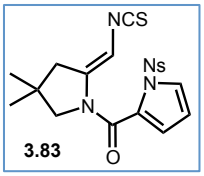


(*E*)-*N*-((4,4-Dimethyl-1-(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)methyl)formamide. To a solution of **3.39** (242 mg, 0.562 mmol, 1.0 eq.) in THF (6 mL) cooled to −78 °C was added dropwise a 1.0 M solution of lithium triethylborohydride in THF (562 µL, 0.562 mmol, 1 eq.). The reaction mixture was stirred at −78 °C for 1h, quenched at −78 °C with a saturated sodium bicarbonate solution then allowed to reach room temperature. The reaction mixture was diluted with diethyl ether and water and the layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water and dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 30% to 80% ethyl acetate in hexanes as eluent) to yield the product (142 mg, 0.328 mmol, 59%). *Rf* = 0.32 (60% ethyl acetate in hexanes); IR (neat) ν = 3286, 2960, 1655, 1630, 1531, 1404, 1374, 1348, 1177, 1151, 732, 681, 621, 590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.7 Hz, 2H), 8.24 (d, *J* = 8.7 Hz, 2H), 8.17 (s, 1H), 7.95 (br s, 1H), 7.23-7.21 (m, 1H), 6.39-6.34 (m, 2H), 3.40 (s, 2H), 2.43 (s, 2H), 1.17 (s, 6H); LRMS (LCMS) calcd for C19H21N4O6S [M+H] 433.1; found 433.3.



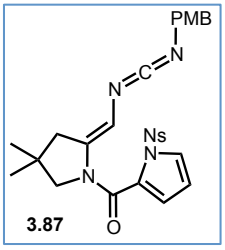
(*E*)-(2-(Isocyanomethylene)-4,4-Dimethylpyrrolidin-1-yl)(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrol-2-yl)methanone. To a solution of **3.81** (142 mg, 0.343 mmol, 1.0 eq.) in acetonitrile (5 mL) was added triethylamine (50 µL, 0.376 mmol, 1.1 eq.) and, dropwise, a 50%wt. solution of T3P in ethyl acetate (230 µL, 0.376 mmol, 1.1 eq.). The reaction mixture was stirred at 20 °C for 1.5h, quenched with a saturated sodium bicarbonate solution then diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure to

afford the isonitrile (134 mg, 0.331 mmol, 99%) which could be used directly in the next step without further purification. LRMS (LCMS) calcd for C19H19N4O5S [M+H] 415.1; found 415.2.



3.83

(*E*)-(2-(Isothiocyanatomethylene)-4,4-dimethylpyrrolidin-1-yl)(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrol-2-yl)methanone. To a solution of **3.82** (134 mg, 0.331 mmol, 1.0 eq.) in THF (5 mL) was added triethylamine (140 µL, 0.993 mmol, 3 eq.), elemental selenium (3 mg, 0.033 mmol, 0.05 eq.) and elemental sulfur (93 mg, 0.363, 1.1 eq.). The reaction mixture was stirred at reflux overnight then cooled to 20 °C and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 2% to 30% ethyl acetate in hexanes as eluent) to yield the product (60 mg, 0.134 mmol, 40%). *Rf* = 0.20 (10% ethyl acetate in hexanes); IR (neat) ν = 2970, 2117, 1729, 1654, 1531, 1399, 1372, 1349, 1228, 1216, 1182, 1151, 1072, 737, 620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H), 7.31-7.29 (m, 2H), 6.41-6.39 (m, 1H), 6.34-6.32 (m, 1H), 3.48 (s, 2H), 2.66 (s, 2H), 1.14 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 144.2, 143.7, 129.5, 129.0, 124.3, 123.5, 115.4, 112.8, 103.1, 64.9, 43.9, 35.9, 25.7; HRMS (ESI): *m/z* calcd. for C19H19KN4O5S2 [(M+H)] = 447.07914, found = 447.07903.

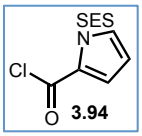


3.87

(*E*)-(2-(((((4-Methoxybenzyl)imino)methylene)amino)methylene)-4,4-dimethylpyrrolidin-1-yl)(1-((4-nitrophenyl)sulfonyl)-1*H*-pyrrol-2-yl)methanone. To a solution of **3.39** (700 mg, 1.626 mmol, 1.0 eq.) in degassed toluene (30 mL) was added a solution of **3.83** (776 mg, 1.951 mmol, 1.2 eq.) in toluene (10 mL). The reaction mixture was stirred for 40h at 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 12% to 30% ethyl acetate in hexanes as eluent) to yield the product (676 mg, 1.230 mmol, 75%). *Rf* = 0.17 (20% ethyl acetate in hexanes); IR (neat) ν = 22958, 2116, 1632, 1531, 1512, 1463, 1402, 1375, 1246, 1177, 1151, 1085, 813, 738, 680, 620, 590, 572 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 9.0 Hz, 2H), 8.27 (d, J = 9.0 Hz, 2H), 7.61 (br s, 1H), 7.29-7.27 (m,

3H), 6.93 (d, J = 8.5 Hz, 2H), 6.36 (m, 1H), 6.34-6.43 (m, 1H), 4.44 (s, 2H), 3.84 (s, 3H), 3.41 (s, 2H), 2.55 (s, 2H), 1.11 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 159.1, 150.7, 143.9, 139.2, 136.5, 130.4, 129.5, 128.8, 124.3, 122.9, 114.7, 114.0, 112.7, 64.8, 55.3, 50.3, 42.7, 35.4, 25.7. HRMS (ESI): *m/z* calcd. for C27H27N5NaO6S [(M+Na)] = 572.1574, found = 572.1564.

4.2.4 N-SES Pyrrole-derived Substrates



3.94

1-((2-(Trimethylsilyl)ethyl)sulfonyl)-1*H*-pyrrole-2-carbonyl chloride. In a 3-neck round-bottom flask equipped with a condenser and a thermometer (from a side joint), to a solution of vinyltrimethylsilane (19.4 mL, 0.13 mol, 1.0 eq.) and *t*-butyl peroxybenzoate (0.5 mL, 2.5 mmol, 0.02 eq.) in methanol (50 mL) was added a solution of sodium bisulfite (25.0 g, 0.24 mol, 1.8 eq.) in water (50 mL). The reaction mixture was heated at an internal temperature of 50 °C for 70h during which a white precipitate formed. The reaction mixture was cooled to 20 °C and the solvent was removed under reduced pressure then coevaporated twice with methanol (100 mL). The crude material was suspended in methanol (100 mL) and after vigorous stirring (10mins), the solution was filtered over a pad of celite (this operation was performed twice). The combined filtrates were concentrated under reduced pressure to afford sodium 2-(trimethylsilyl)ethanesulfonate (33.0 g, 0.162 mmol, 83%). The material could be used directly in the next step without further purification. ^{1}H NMR (300 MHz, DMSO) δ 2.32-2.26 (m, 2H), 0.82-0.76 (m, 2H), -0.05 (s, 9H). Spectral data match literature values.[6]

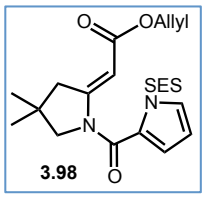
To the sulfonate salt (10.0 g, 0.049 mol, 1 eq.) cooled to 0 °C was added thionyl chloride (27.6 mL, 0.381 mol, 7.8 eq.) dropwise *via* an addition funnel followed by DMF (1.37 mL, 17.8 mmol, 0.38 eq.) dropwise *via* syringe. The reaction mixture was allowed to stir while warming to 20 °C overnight then was concentrated under reduced pressure. The crude material was suspended in hexanes (100 mL) and after vigorous stirring (15mins), the solution was filtered. The filter cake was rinsed with additional hexanes (75 mL) and the combined filtrates were concentrated under reduced pressure to afford 2-(trimethylsilyl)ethanesulfonyl chloride **3.92** (6.5 g, 0.032 mol, 66%). ^{1}H NMR (300 MHz,

$CDCl_3$) δ 3.63-3.58 (m, 2H), 1.33-1.29 (m, 2H), 1.13 (s, 9H). Spectral data match literature values.[6]

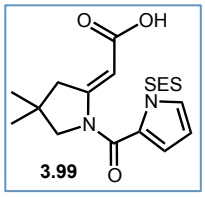
To a solution of pyrrole-2-carboxaldehyde (2.2 g, 0.023 mol, 1.0 eq.) in THF (60 mL) cooled to 0 °C was added a 60% wt dispersion of NaH in mineral oil (1.1 g, 0.028 mmol, 1.2 eq.) in small portions. The reaction mixture was stirred for 30mins at 20 °C, cooled back to 0 °C then a solution of **3.92** (6.5 g, 0.032 mol, 1.4 eq.) in THF (20 mL) was added dropwise *via* addition funnel. The reaction mixture was stirred overnight while warming to 20 °C then quenched with a saturated solution of ammonium chloride and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine and dried with anhydrous magnesium sulfate and the solvent was removed under reduced. The crude material was purified by flash column chromatography on silica gel (gradient of 5% to 15% ethyl acetate in hexanes as eluent) to yield the product (4.57 g, 0.0176 mmol, 77%) as a yellow oil. *Rf* = 0.5 (20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.56 (t, J = 1.2 Hz, 1H), 7.22 (t, J = 2.1 Hz, 1H), 6.42 (t, 3.3 Hz, 1H), 3.74-3.68 (m, 2H), 0.95-0.89 (m, 2H), 0.03 (s, 9H).

To a solution of N-SES-pyrrole-2-carboxaldehyde **3.93** (967 mg, 3.727 mmol, 1.0 eq.) in *t*-BuOH (15 mL) and H_2O (5 mL) was added a 2.0 M solution of 2-methyl-2-butene (12.0 mL, 0.024 mol, 6.5 eq.), sodium dihydrogen phosphate (2.23 g, 0.0186 mol, 5.0 eq.) and sodium chlorite (1.69 g, 0.0186 mol, 5.0 eq.) sequentially. The reaction mixture was stirred for 2h at 20 °C then diluted with ethyl acetate, water and pH 6.0 buffer. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine and dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give 1-((2-(trimethylsilyl)ethyl)sulfonyl)-1*H*-pyrrole-2-carboxylic acid (940 mg, 3.413 mmol, 92%) as a white solid. IR (neat) ν = 2960, 1690, 1446, 1364, 1217, 1162, 1153, 838, 756 cm^{-1}; ^{1}H NMR (300 MHz, acetone) δ 7.50-7.49 (m, 1H), 7.17-7.15 (m, 1H), 6.36-6.34 (m, 1H), 4.06-4.01 (m, 2H), 0.99-0.95 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, acetone) δ 205.4, 160.1, 129.9, 123.2, 109.7, 51.1, 9.9, -2.9; HRMS (ESI): *m/z* calcd. for C10H16NSSi [(M+H)] = 274.05748, found = 274.05726.

To a solution of 1-((2-(trimethylsilyl)ethyl)sulfonyl)-1*H*-pyrrole-2-carboxylic acid (423 mg, 1.536 mmol, 1.0 eq.) and DMF (3 drops) in DCM (10 mL) cooled to 0 °C was added oxalyl chloride (190 µL, 2.150 mmol, 1.4 eq.). The reaction mixture was stirred for 5mins at 0 °C then 3h at 20 °C then was concentrated under reduced pressure. The crude acyl chloride **3.94** could be used directly in the next step without further purification.

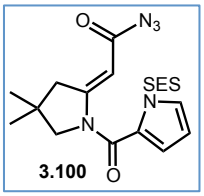


(*E*)-Allyl 2-(4,4-dimethyl-1-(1-((2-(trimethylsilyl)ethyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetate. To a solution of **2.124** (250 mg, 1.280 mmol, 1.0 eq.), pyridine (515 µL, 6.402 mmol, 5.0 eq.) and 4-dimethylamino pyridine (16 mg, 0.128 mmol, 0.1 eq.) in toluene (10 mL) was added a solution of freshly prepared acyl chloride **3.94** in toluene (6 mL) and chloroform (1 mL). The reaction mixture was stirred overnight at 80 °C, cooled to 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 5% to 13% ethyl acetate in hexanes as eluent) to yield the product (378 mg, 0.835 mmol, 65%) as a white solid. *Rf* = 0.25 (10% ethyl acetate in hexanes); IR (neat) ν = 2957, 1671, 1598, 1362, 1340, 1159, 1130, 834, 739, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.20 (m, 1H), 6.90 (s, 1H), 6.45-6.44 (m, 1H), 6.24-6.22 (m, 1H), 6.00-5.91 (m, 1H), 5.30 (d, *J* = 17.0 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.57 (d, *J* = 6.1 Hz, 2H), 3.68-3.65 (m, 2H), 3.47 (s, 2H), 3.01 (s, 2H), 1.06 (s, 6H), 0.96-0.93 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 162.4, 156.8, 132.8, 128.7, 125.3, 117.6, 115.3, 110.1, 101,1, 64.6, 64.4, 52.8, 46.1, 35.6, 25.6, 10.3, -2.0. HRMS (ESI): *m/z* calcd. for C21H32N2NaO5SSi [(M+Na)] = 475.1693, found =475.1691.



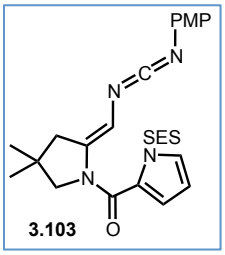
(*E*)-2-(4,4-Dimethyl-1-(1-((2-(trimethylsilyl)ethyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetic acid A solution of palladium acetate (2 mg, 0.009 mmol, 0.05 eq.) and triphenylphosphine (10 mg, 0.037 mmol, 0.2 eq.) in DCM (3 mL) was heated at reflux for 2h then cooled to 20 °C. A solution of **3.98** (70 mg, 0.155 mmol, 1.0 eq.) and pyrrolidine (30 µL, 0.310 mmol, 2.0 eq.) in DCM (2 mL) was added. The reaction mixture was stirred for 15mins at reflux, cooled to 20 °C then concentrated under reduced pressure.

The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 30% ethyl acetate in hexanes with 1% acetic acid as eluent) to yield the product (55 mg, 0.133 mmol, 86%). *Rf* = 0.43 (30% ethyl acetate in hexanes with 1% acetic acid); IR (neat) ν = 2956, 1669, 1598, 1361, 1339, 1201, 1154, 1129, 833, 738, 697, 551 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.24 (m, 1H), 6.89 (s, 1H), 6.50-6.48 (m, 1H), 6.28-6.26 (m, 1H), 3.75-3.69 (m, 2H), 3.52 (s, 2H), 3.04 (s, 2H), 1.10 (s, 6H), 1.03-0.97 (m, 2H), 0.07 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 156.7, 135.1, 128.6, 128.1, 125.5, 115.5, 110.2, 100.5, 64.7, 53.0, 46.4, 35.6, 25.7, 10.3, -2.0 ; HRMS (ESI): *m/z* calcd. for C18H28NaN5O5SiS [(M+Na)] = 435.1380, found =435.1388.



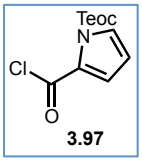
3.100

(*E*)-2-(4,4-Dimethyl-1-(1-((2-(trimethylsilyl)ethyl)sulfonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetyl azide. To a solution of **3.99** (227 mg, 0.550 mmol, 1.0 eq.) in benzene (5 mL) and toluene (5 mL) cooled to 0 °C was added triethylamine (611 µL, 4.40 mmol, 8.0 eq.). Diphenylphosphoryl azide (440 µL, 2.201 mmol, 4.0 eq.) was added dropwise and the reaction mixture was allowed to stir while warming to 20 °C. After 7h, the reaction mixture was quenched with water and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was concentrated onto silica with triethylamine (2 mL) then purified by flash column chromatography on silica gel (gradient of 5% to 20% diethyl ether in hexanes as eluent) to yield the product (210 mg, 0.480 mmol, 88%) as a white solid. *Rf* = 0.46 (20% diethyl ether in hexanes); IR (neat) ν = 2957, 2130, 1669, 1595, 1394, 1335, 1153, 1153, 1066, 832, 740, 552 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.24 (m, 1H), 6.80 (s, 1H), 6.50-6.49 (m, 1H), 6.28-6.26 (m, 1H), 3.72-3.67 (m, 2H), 3.53 (s, 2H), 3.07 (s, 2H), 1.10 (s, 6H), 1.02-0.97 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 162.4, 159.6, 128.3, 125.7, 115.7, 110.2, 101.7, 64.7, 52.9, 46.8, 35.8, 25.6, 10.3, -2.0.



(*E*)-(2-(((((4-Methoxyphenyl)imino)methylene)amino)methylene)-4,4-dimethylpyrrolidin-1-yl)(1-((2-(trimethylsilyl)ethyl)sulfonyl)-1*H*-pyrrol-2-yl)methanone. A solution of **3.100** (210 mg, 0.480 mmol, 1.0 eq.) in degassed toluene (5 mL) was heated at 85 °C for 6h. The reaction mixture was cooled to 20 °C then the solvent was removed under reduced pressure to afford the isocyanate **3.101**. IR (neat) ν = 2957, 2257, 1637, 1401, 1383, 1176, 1157, 833, 759, 580 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.17 (m, 2H), 6.41-6.40 (m, 1H), 6.26-6.24 (m, 1H), 3.74-3.69 (m, 2H), 3.48 (s, 2H), 2.54 (s, 2H), 1.09 (s, 6H), 1.02-0.97 (m, 2H), 0.07 (s, 9H). To a solution of the crude isocyanate in toluene (5 mL) was added a solution of 4-methoxy-*N*-(triphenylphosphoranylidene)aniline (232 mg, 0.576 mmol, 1.2 eq.) in toluene (2 mL). The reaction mixture was stirred for 20h at 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 2% to 20% ethyl acetate in hexanes as eluent) to yield the product (108 mg, 0.210 mmol, 43% over 2 steps). *Rf* = 0.48 (20% ethyl acetate in hexanes); IR (neat) ν = 2958, 2116, 1632, 1581, 1403, 1383, 1243, 1174, 1155, 829, 730, 553 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.21-7.20 (m, 1H), 7.04 (d, J = 7.2 Hz, 2H), 6.82 (d, J = 7.2 Hz, 2H), 6.42-6.41 (m, 1H), 6.25-6.23 (m, 1H), 3.79 (s, 3H), 3.75-3.71 (m, 2H), 3.49 (s, 2H), 2.62 (s, 2H), 1.07 (s, 6H), 1.01-0.97 (m, 2H), 0.06 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.0, 138.0, 136.9, 132.3, 128.9, 124.8, 124.7, 114.7, 114.6, 110.9, 110.0, 65.19, 55.5, 52.7, 43.1, 35.6, 25.6, 10.3, -2.0; HRMS (ESI): *m/z* calcd. for C25H34N4NaO4SSi [(M+Na)] = 537.1962, found =537.1981.

4.2.5 N-Teoc Pyrrole-derived Substrates



2-(Trimethylsilyl)ethyl 2-(chlorocarbonyl)-1*H*-pyrrole-1-carboxylate. To a solution of 4-nitrophenyl chloroformate (6.88 g, 0.034 mol, 1.0 eq.) in DCM (50 mL) cooled to 0 °C was added a solution of pyridine (3.0 mL, 0.037 mol, 1.1 eq.) and 2-(trimethylsilyl)ethanol (4.0 g, 0.034 mol, 1.0 eq.) dropwise *via* addition funnel. The cloudy solution was stirred overnight while warming to 20 °C then

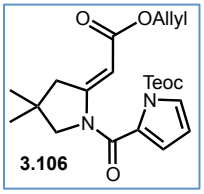
quenched with 1M HCl solution and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water and dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give the crude 4-nitrophenyl (2-(trimethylsilyl)ethyl) carbonate **3.95** (9.39 g). The material could be used directly in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.0 Hz, 2H), 7.36 (d, *J* = 7.0 Hz, 2H), 4.40-4.36 (m, 2H), 1.17-1.13 (m, 2H), 0.08 (s, 9H). Spectral data match literature values.[7]

To a solution of pyrrole-2-carboxaldehyde **3.91** (520 mg, 5.468 mmol, 1.2 eq.) in THF (15 mL) cooled to 0 °C was added a 60% wt dispersion of NaH in mineral oil (240 mg, 5.924 mmol, 1.3 eq.) in small portions. The reaction mixture was stirred for 30mins at 0 °C then a solution of 4-nitrophenyl (2-(trimethylsilyl)ethyl) carbonate **3.95** (1.30 g, 4.56 mmol, 1.0 eq.) in THF (5 mL) was added. The reaction mixture was stirred overnight while warming to 20 °C then diluted with ethyl acetate and filtered over a short pad of celite. Brine was added and the layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine and dried with anhydrous magnesium sulfate and the solvent was removed under reduced. The crude material was purified by flash column chromatography on silica gel (gradient of 30% to 70% DCM in hexanes as eluent) to yield the product **3.96** (935 mg, 3.907 mmol, 72%). *Rf* = 0.45 (60% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.4 (s, 1H), 7.48-7.47 (m, 1H), 7.23-7.20 (m, 1H), 6.32-6.30 (m, 1H), 4.55-4.49 (m, 2H), 1.22-1.16 (m, 2H), 0.10 (s, 9H). HRMS (ESI): *m/z* calcd. for C11H17N1O3SiNa [(M+Na)] = 262.08699, found = 262.08614. Spectral data match literature values.[8]

To a solution of N-Teoc-pyrrole-2-carboxaldehyde **3.96** (935 mg, 3.907 mmol, 1.0 eq.) in *t*-BuOH (15 mL) and H_2O (4 mL) was added a 2.0 M solution of 2-methyl-2-butene (12.0 mL, 0.025 mol, 6.5 eq.), sodium dihydrogen phosphate (2.34 g, 0.0195 mol, 5.0 eq.) and sodium chlorite (1.76 g, 0.0195 mol, 5.0 eq.) sequentially. The reaction mixture was stirred for 4h at 20 °C then diluted with ethyl acetate, water and pH 6.0 buffer. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine and dried with anhydrous magnesium

sulfate and the solvent was removed under reduced pressure to give the crude 1-((2-(trimethylsilyl)ethoxy)carbonyl)-1*H*-pyrrole-2-carboxylic acid (1.07 g). The material could be used directly in the next step without further purification. The crude material was purified by flash column chromatography on silica gel (gradient of 30% to 70% DCM in hexanes as eluent) to yield the product (935 mg, 3.91 mmol, 72%). *Rf* = 0.45 (60% ethyl acetate in hexanes); IR (neat) ν = 2954, 1753, 1686, 1557, 1452, 1338, 1279, 1279, 1249, 1174, 1101, 1058, 1012, 834, 745, 695, 597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 1H), 7.44-7.43 (m, 1H), 6.32 (t, *J* = 3.6 Hz, 1H), 4.59-4.55 (m, 2H), 1.22-1.20 (m, 2H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 152.7, 127.5, 127.4, 126.3, 112.0, 68.9, 17.5, -1.6; HRMS (ESI): *m/z* calcd. for C11H17NO4SiNa [(M+Na)] = 278.08191, found = 278.08125.

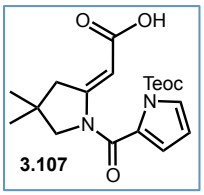
To a solution of 1-((2-(trimethylsilyl)ethoxy)carbonyl)-1*H*-pyrrole-2-carboxylic acid (2.70 g, 0.0106 mol, 1.3 eq.) and 4 drops of DMF in DCM (25 mL) cooled to 0 °C was added oxalyl chloride (1.4 mL, 0.016 mmol, 2.0 eq.). The reaction mixture was stirred for 40mins at 0 °C then 1h at 20 °C then was concentrated under reduced pressure. The crude acyl chloride **3.97** could be used directly in the next step without further purification.



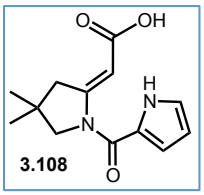
(*E*)-2-(Trimethylsilyl)ethyl 2-(2-(2-(allyloxy)-2-oxoethylidene)-4,4-dimethylpyrrolidine-1-carbonyl)-1*H*-pyrrole-1-carboxylate.

To a solution of **2.124** (1.58 g, 8.09 mmol, 1.0 eq.), pyridine (2.0 mL, 24.3 mmol, 3.0 eq.) and 4-dimethylamino pyridine (100 mg, 0.809 mmol, 0.1 eq.) in toluene (40 mL) was added a solution of freshly prepared acyl chloride **3.94** in toluene (15 mL). The reaction mixture was stirred overnight at 85 °C, cooled to 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 5% to 16% ethyl acetate in toluene as eluent) to yield the product (2.89 g, 6.68 mmol, 83%) as a white solid. *Rf* = 0.15 (10% ethyl acetate in hexanes); IR (neat) ν = 2956, 1749, 1701, 1678, 1409, 1370, 1342, 1302, 1248, 1152, 1111, 1051, 1026, 992, 930, 766 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.26 (m, 1H), 6.72 (br s, 1H), 6.41-6.39 (m, 1H), 6.26-6.24 (m, 1H), 5.99-5.92 (m, 1H), 5.30 (d, *J* = 17.0 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.61 (d, *J* = 6.1 Hz, 2H), 4.42-4.40 (m, 2H), 3.34 (s, 2H), 3.05 (s, 2H), 1.13-1-09 (m, 8H), 0.07 (s, 9H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 168.4, 163.3, 156.7, 149.6, 132.9, 128.6, 121.7, 117.4, 114.0, 111.5, 100.1, 67.1, 64.3, 63.3, 46.2, 35.2, 26.0, 17.5, -1.6; HRMS (ESI): *m/z* calcd. for C22H32N2NaO5Si [(M+Na)] = 455.1973, found = 455.1962.

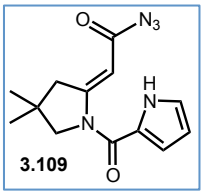


(*E*)-2-(4,4-Dimethyl-1-(1-((2-(trimethylsilyl)ethoxy)carbonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetic acid. A solution of palladium acetate (33 mg, 0.147 mmol, 0.05 eq.) and triphenylphosphine (160 mg, 0.589 mmol, 0.2 eq.) in DCM (20 mL) was heated at reflux for 2h then cooled to 20 °C. Sequentially, a solution of **3.106** (1.3 g, 3.0 mmol, 1.0 eq.) in DCM (5mL) and tributyltin hydride (970 µL, 3.61 mmol, 1.2 eq.) were added. The reaction mixture was stirred for 3h at 20 °C then quenched with 0.1M HCl solution and saturated ammonium chloride solution and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 25% ethyl acetate in hexanes with 1% acetic acid as eluent) to yield the product (760 mg, 1.936 mmol, 64%). *Rf* = 0.16 (20% ethyl acetate in hexanes with 1% acetic acid); IR (neat) ν = 2957, 1749, 1678, 1598, 1410, 1393, 1368, 1305, 1165, 1122, 1050, 855, 836, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.28 (m, 1H), 6.52 (br s, 1H), 6.43-6.42 (m, 1H), 6.26 (m, 1H), 4.44-4.40 (m, 2H), 3.38 (s, 2H), 3.04 (s, 2H), 1.13-1.09 (m, 8H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 163.3, 158.6, 149.5, 128.4, 121.8, 114.3, 111.5, 99.3, 67.1, 63.3, 46.5, 35.1, 26.0, 17.5, -1.6; HRMS (ESI): *m/z* calcd. for C19H28NaN2O5Si [(M+Na)] = 415.1660, found = 415.1654.

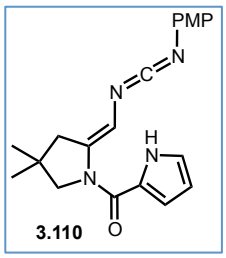


(*E*)-2-(4,4-Dimethyl-1-(1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetic acid. To a solution of **3.107** (198 mg, 0.496 mmol, 1.0 eq.) in DCM (10 mL) was added pyrrolidine (100 µL, 1.240 mmol, 2.5 eq.). The reaction mixture was allowed to stir at 20 °C for 4.5h then the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 2% to 12% methanol in DCM as

eluent) to yield the product (150 mg) as a white solid. *Rf* = 0.24 (6% methanol in DCM); IR (neat) ν = 3291, 2919, 1676, 1637, 1576, 1392, 1370, 1338, 1293, 12`9, 1162, 1135, 850, 778, 702 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 11.72 (s, 1H), 11.48 (br s, 1H), 7.04 (s, 1H), 6.86 (s, 1H), 6.78 (s, 1H), 6.20 (s, 1H), 3.81 (s, 2H), 2.92 (s, 2H), 1.07 (s, 6H); ^{13}C NMR (125 MHz, DMSO) δ 161.8, 158.4, 125.8, 124.2, 124.0, 114.8, 110.0, 99.6, 63.5, 45.6, 35.9, 25.9; HRMS (ESI) calcd for C12H17N2O3 [M+H] 249.12337; found 249.12314.



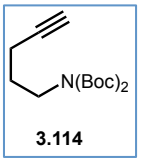
(*E*)-2-(4,4-Dimethyl-1-(1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetyl azide. To a solution of the crude **3.108** (0.504 mmol, 1.0 eq.) in benzene (6 mL) and toluene (6 mL) cooled to 0 °C was added triethylamine (560 µL, 4.032 mmol, 8.0 eq.). Diphenylphosphoryl azide (405 µL, 2.016 mmol, 4.0 eq.) was added dropwise and the reaction mixture was allowed to stir while warming to 20 °C. After 6h, the reaction mixture was quenched with water and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 20% to 50% diethyl ether in hexanes as eluent) to yield the product (109 mg, 0.399 mmol, 79% over 2 steps) as a white solid. *Rf* = 0.20 (20% diethyl ether in hexanes); IR (neat) ν = 3282, 2960, 2127, 1649, 1572, 1421, 1393, 1372, 1334, 1194, 1180, 1134, 1110, 1083, 1069, 1056, 952, 829, 802, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (br s, 1H), 7.08 (s, 1H), 7.01 (s, 1H), 6.73 (s, 1H), 6.31 (d, J = 5.4 Hz, 1H), 3.85 (s, 2H), 3.09 (s, 2H), 1.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 161.5, 161.0, 125.5, 123.8, 114.6, 110.8, 100.6, 63.9, 46.2, 36.2, 26.1; HRMS (ESI) calcd for C13H14N5O2 [M-H] 272.11530; found 272.11536.



(*E*)-(2-(((((4-Methoxyphenyl)imino)methylene)amino)methylene)-4,4-dimethylpyrrolidin-1-yl)(1*H*-pyrrol-2-yl)methanone. A solution of **3.109** (109 mg, 0.399 mmol, 1.0 eq.) in degassed toluene (7 mL) was heated at 80 °C for 6h. The reaction mixture was cooled to 20 °C

then the solvent was removed under reduced pressure to afford the isocyanate. IR (neat) ν = 3283, 2956, 2262, 1593, 1413, 1345, 1181, 1165, 1129, 1057, 1010, 962, 759, 606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (br s, 1H), 7.40 (s, 1H), 7.00 (s, 1H), 6.61 (s, 1H), 6.30-6.28 (m, 1H), 3.80 (s, 2H), 2.54 (s, 2H), 1.16 (s, 6H). To a solution of the crude isocyanate in toluene (5 mL) was added a solution of 4-methoxy-*N*-(triphenylphosphoranylidene)aniline (153 mg, 0.399 mmol, 1.0 eq.) in toluene (2 mL). After 3.5h, the reaction mixture was concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 5% to 25% ethyl acetate in hexanes as eluent) to yield the product (113 mg, 0.322 mmol, 81% over 2 steps) as a white solid. *Rf* = 0.30 (20% ethyl acetate in hexanes); IR (neat) ν = 3271, 2956, 2110, 1584, 1508, 1409, 1343, 1241, 1177, 1129, 1032, 829, 732, 645, 577 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (br s, 1H), 7.70 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.00 (s, 1H), 6.82 (d, J = 8.8 Hz, 2H), 6.62 (s, 1H), 6.29 (m, 1H), 3.80 (s, 2H), 2.62 (s, 2H), 1.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 156.9, 139.4, 137.1, 132.6, 126.0, 124.7, 122.0, 114.6, 112.8, 110.3, 109.5, 64.0, 55.5, 42.5, 35.9, 26.2; HRMS (ESI) calcd for C20H22N4NaO2 [M+Na] 373.1635; found 373.1634.

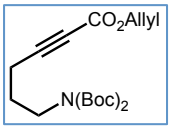
4.2.6 Route towards (±)-phakellin



3.114

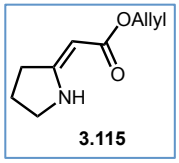
***Tert*-butyl N-[(tert-butoxy)carbonyl]-N-(pent-4-yn-1-yl)carbamate.** To a stirred solution of 4-pentynol (3.3 mL, 0.035 mol, 1.0 eq.) and triethylamine (7.3 mL, 0.053 mol, 1.5 eq.) in toluene (30 mL) and DCM (20 mL) cooled to 0 °C was added mesyl chloride (3.0 mL, 0.039 mol, 1.1 eq.) dropwise. The reaction mixture was stirred at 0 °C for 1h then at 20 °C for 3h. The resulting solution was quenched with water and diluted with DCM. The organic phase was washed with water and dried over anhydrous magnesium sulfate, filtered. The solvent was removed under reduced pressure to yield pent-4-yn-1-yl methanesulfonate (5.7 g, 0.035 mol, 100%) as a clear liquid that could be used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (t, *J* = 6.0 Hz, 2H), 3.03 (s, 2H), 2.37 (td, *J* = 2.8 Hz, *J* = 6.4 Hz, 2H), 2.02-1.95 (m, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.1, 69.8, 68.2, 37.3, 27.8, 14.7

To a stirred solution of pent-4-yn-1-yl methanesulfonate (5.7 g, 0.035 mol, 1.0 eq.) and cesium carbonate (13.7 g, 0.042 mol, 1.2 eq.) in DMF (50 mL) was added a solution of $(Boc)_2NH$[9] (7.62 g, 0.035 mmol, 1.0 eq.) in DMF (20 mL) portionwise. The reaction mixture was stirred overnight at 70 °C. The reaction mixture was cooled to 20 °C then diluted with ethyl acetate and water. The organic phase was washed with water then brine and dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 5% to 15% ethyl acetate in hexanes as eluent) to yield the product (9.81 g, 0.034 mol, 99%). *Rf* = 0.29 (5% ethyl acetate in hexanes); IR (neat) ν = 3277, 2979, 1789, 1696, 1455, 1393, 1279, 1173, 1139, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (t, *J* = 5.1 Hz, 2H), 2.21 (td, *J* = 2.1 Hz, *J* = 5.1 Hz, 2H), 1.95 (t, *J* = 2.1 Hz, 1H), 1.80 (p, *J* = 5.1 Hz, 2H), 1.51 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 83.5, 82.3, 68.6, 45.6, 28.1, 27.8, 16.1; HRMS (ESI) calcd for C15H25O4NNa [M+Na] 306.16758; found 306.16665.



Prop-2-en-1-yl 6-{bis[(tert-butoxy)carbonyl]amino}-5,5-dimethylhex-2-ynoate. To a stirred solution of 2,2,6,6-tetramethylpiperidine (9.8 mL, 0.058 mol, 1.6 eq.) in THF (500 mL) cooled to −78 °C was added a 2.54 M solution of *n*-BuLi in hexanes (20.0 mL, 0.050 mol, 1.5 eq.) dropwise. The mixture was suspended above the cooling bath and allowed to reach room temperature, then recooled to −78 °C. A solution of **3.114** (10.2 g, 0.036 mol, 1.0 eq.) in THF (100 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 30mins. A solution of allyl chloroformate (7.7 mL, 0.072 mol, 2.0 eq.) in THF (50 mL) was added dropwise at −78 °C. The reaction was stirred at −78 °C for 3h then was allowed to warm to 20 °C and stirred for 1.5h. The reaction mixture was quenched with saturated ammonium chloride solution and the mixture was vigorously stirred for 20mins. Diethyl ether and water were added. The layers were separated, and the aqueous layer was extracted with diethyl ether and the combined organic layers were washed with water, brine, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 4% to 10% ethyl acetate in hexanes as eluent) to yield the product (7.84 g, 0.0213 mol, 60%) as

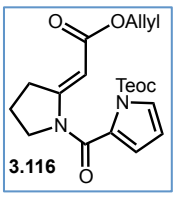
an oil. *Rf* = 0.32 (10% ethyl acetate in hexanes); IR (neat) ν = 2979, 2237, 1789, 1789, 17111, 1393, 1366, 1240, 1137, 1109, 891, 781 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96-5.86 (m, 1H), 5.35 (d, *J* = 16 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.64 (d, *J* = 5.6 Hz, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H), 1.86 (p, *J* = 7.2 Hz, 2H), 1.51 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 152.4, 131.3, 119.2, 88.7, 82.6, 73.1, 66.3, 45.5, 28.1, 27.1, 16.4; (ESI) calcd for C19H29NO6Na [M+Na] 390.18871; found 390.18772.



3.115

(*Z*)-Allyl 2-(pyrrolidin-2-ylidene)acetate. To a solution of prop-2-en-1-yl 6-{bis[(tert-butoxy)carbonyl]amino}-5,5-dimethylhex-2-ynoate (6.7 g, 0.018 mol) in DCM (5 mL) cooled to 0 °C was added trifluoroacetic acid (11 mL, 144.7 mmol, 8.0 eq.) in several portions. The reaction mixture was allowed to stir at 0 °C for 40mins then at 20 °C for 1h. The reaction mixture was concentrated under reduced pressure, dissolved in 20 mL of toluene and reconcentrated to afford the TFA salt of allyl 6-aminohex-2-ynoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (brs, 1H), 7.92 (br, 2H), 5.96-5.86 (m, 1H), 5.36 (d, *J* = 16.0 Hz, 1H), 5.29 (d, *J* = 10.0 Hz, 1H), 4.65 (d, *J* = 6.0 Hz, 2H), 3.13 (br, 2H), 2.50 (t, *J* = 6.8 Hz, 2H), 1.99 (p, *J* = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 130.6, 119.7, 87.1, 74.0, 67.1, 39.3, 24.9, 15.7.

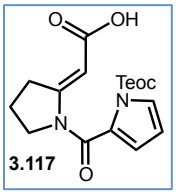
The resultant oil was dissolved DCM (85 mL) and 8 scoops of Amberlite IRA-67 free base resin were added. The slurry was stirred vigorously at 20 °C for 1h then filtered. The filtrate was concentrated under reduced pressure to yield the product (2.15 g, 0.0128 mol, 70%) as an oil. IR (neat) ν = 3366, 2943, 2873, 1657, 1591, 1493, 1287, 1228, 1138, 1051, 1029, 988, 925, 778, 639 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.97 (brs, 1H), 5.95-5.86 (m, 1H), 5.22 (d, *J* = 16.0 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.81 (s, 1H), 4.71 (d, *J* = 4.4 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.91 (t, *J* = 7.2 Hz, 2H), 1.07 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 166.9, 133.8, 116.9, 76.2, 63.3, 47.1, 32.2, 22.0; (ESI) calcd for C9H14NO2 [M+H] 168.10191; found 168.10162.



3.116

(*E*)-2-(Trimethylsilyl)ethyl 2-(2-(2-(allyloxy)-2-oxoethylidene)pyrrolidine-1-carbonyl)-1*H*-pyrrole-1-carboxylate. To a solution of **3.115** (4.58 g, 0.0213 mol, 1.0 eq.), pyridine (7.0 mL, 0.084 mol, 4.0 eq.) and 4-dimethylamino pyridine (250 mg, 2.1 mmol, 0.1 eq.) in

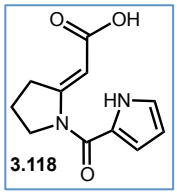
toluene (80 mL) was added a solution of freshly prepared acyl chloride **3.97** in toluene (50 mL) portionwise. The reaction mixture was stirred overnight at 80 °C, cooled to 20 °C then concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 2% to 3% ethyl acetate in toluene as eluent) to yield the product (5.0 g, 0.012 mol, 59%) as a white solid. *Rf* = 0.15 (10% ethyl acetate in hexanes); IR (neat) ν = 2953, 1747, 1677, 1611, 11558, 1408, 1376, 1344, 1302, 1248, 1144, 1116, 1050, 930, 837, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 1H), 6.53 (br s, 1H), 6.41 (m, 1H), 6.23 (t, *J* = 3.6 Hz, 1H), 5.97-5.87 (m, 1H), 5.29 (dd, *J* = 17.4 Hz, *J* = 1.6 Hz, 1H), 5.19 (dd, *J* = 10.2 Hz, *J* = 1.2 Hz, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 4.41-4.36 (m, 2H), 3.61 (t, *J* = 7.2 Hz, 2H), 3.25-3.23 (td, *J* = 7.8 Hz, *J* = 2.0 Hz, 2H), 1.91 (p, *J* = 7.6 Hz, 2H), 1.07 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 163.0, 156.9, 149.5, 132.9, 128.6, 121.7, 117.3, 114.3, 111.5, 99.1, 67.0, 64.2, 51.2, 32.1, 21.6, 17.5, -1.6; HRMS (ESI): *m/z* calcd. for C20H29N2O5Si [(M+H)] = 405.18402, found = 405.18329.



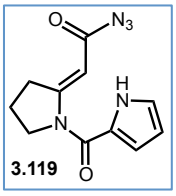
3.117

(*E*)-2-(1-(1-((2-(Trimethylsilyl)ethoxy)carbonyl)-1*H*-pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetic acid. A solution of palladium acetate (148 mg, 0.659 mmol, 0.05 eq.) and triphenylphosphine (648 mg, 2.639 mmol, 0.2 eq.) in DCM (100 mL) was heated at reflux for 1.5h then cooled to 20 °C. A solution of **3.116** (5.0 g, 0.012 mol, 1.0 eq.) and tributyltin hydride (4.0 mL, 0.015 mmol, 1.2 eq.) in DCM were then added. The reaction mixture was stirred for 2h at 20 °C then quenched with 0.1M HCl solution and saturated ammonium chloride solution and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 12% to 20% ethyl acetate in hexanes with 1% acetic acid as eluent) to yield the product (3.65 g, 0.010 mol, 81%). IR (neat) ν = 2954, 1745, 1674, 1595, 1556, 1408, 1372, 1343, 1301, 1249, 1210, 1162, 1048, 835, 730, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 1H), 6.43 (m, 1H), 6.31 (br s, 1H), 6.22 (m, 1H), 5.97-5.87 (m, 1H), 4.40-4.36 (m, 2H), 3.64 (t, *J* = 7.2 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H), 1.90 (p, *J* = 7.2 Hz,

2H), 1.09-1.045 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 163.0, 158.7, 149.5, 128.4, 121.9, 114.6, 111.6, 98.4, 67.0, 51.2, 32.4, 21.4, 17.4, -1.6 ; HRMS (ESI): *m/z* calcd. for C17H24N2O5NaSi [(M+Na)] = 387.1347, found = 387.1356.

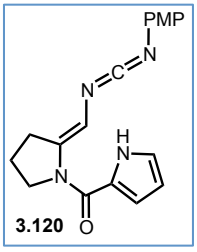


(*E*)-2-(1-(1*H*-Pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetic acid. To a solution of **3.117** (3.42 g, 0.094 mol, 1.0 eq.) in DCM (150 mL) was added pyrrolidine (3.0 mL, 0.037 mol, 3.9 eq.). The reaction mixture was allowed to stir at 20 °C for 4h then the solvent was removed under reduced pressure. The crude material was purified by reversed-phase column chromatography on C-18 silica gel (gradient of 5% to 100% methanol in water as eluent). The fractions containing the desired product were combined, concentrated under reduced pressure then lyophilized to yield the crude product. The crude was repurified by flash column chromatography on silica gel (gradient of 2% to 15% methanol in DCM as eluent) to yield the product (935 mg, 4.246 mmol, 45%) as a white solid. *Rf* = 0.42 (5% methanol in DCM); IR (neat) ν = 3286, 2925, 1635, 1579, 1535, 1379, 1332, 1215, 1161, 1129, 748 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 11.71 (s, 1H), 11.44 (s, 1H), 7.03-7.01 (m, 1H), 6.81-6.78 (m, 2H), 6.20-6.17 (m, 1H) 4.03 (t, *J* = 7.0 Hz, 2H), 3.07 (t, *J* = 7.0 Hz, 2H), 1.89 (p, *J* = 7.0 Hz, 2H), 1.09-1.045 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ169.8, 161.6, 158.9, 125.9, 124.1, 114.8, 110.0, 98.6, 51.9, 31.6, 22.6; HRMS (ESI) calcd for C11H12N2NaO3 [M+Na] 243.0740 ; found 243.0737.



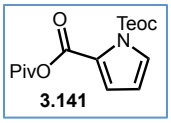
(*E*)-2-(1-(1*H*-Pyrrole-2-carbonyl)pyrrolidin-2-ylidene)acetyl azide. A solution of **3.118** (127 mg, 0.577 mmol, 1.0 eq.) in THF (10 mL) was degassed *via* 3 cycles of freeze-pump-thaw then cooled to 0 °C and triethylamine (642 µL, 4.616 mmol, 8.0 eq.) was added. Diphenylphosphoryl azide (464 µL, 2.308 mmol, 4.0 eq.) was added dropwise and the reaction mixture was allowed to stir while warming to 20 °C. The reaction mixture was allowed to stir for 7h then the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 20% to 60% ethyl acetate in hexanes as eluent) to yield the product (124 mg, 0.506 mmol, 87%) as a white solid. *Rf* = 0.43 (30% ethyl acetate in hexanes); IR (neat) ν = 3296, 2128,

1668, 1632, 1418, 1381, 1330, 1187, 1134, 1086, 1065, 770, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (br s, 1H), 7.08-7.05 (m, 1H), 6.98-6.94 (m, 1H), 6.85-6.73 (m, 1H), 6.34-6.30 (m, 1H) 4.14 (t, *J* = 7.1 Hz, 2H), 3.07 (dt, *J* = 7.7 Hz, *J* = 1.8 Hz 2H), 2.07 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 161.2, 161.1, 125.6, 123.6, 114,5, 110.9, 99.8, 51.8, 32.2, 22.5. HRMS (ESI) calcd for C11H10N5O2 [M-H] 244.0840 ; found 244.0836.

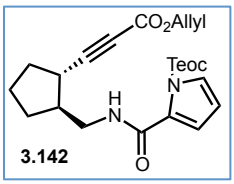


3.120

(*E*)-(2-(((((4-Methoxyphenyl)imino)methylene)amino)methylene)pyrrolidin-1-yl)(1*H*-pyrrol-2-yl)methanone. A solution of **3.125** (124 mg, 0.506 mmol, 1.0 eq.) in toluene (10 mL) was degassed *via* 3 cycles of freeze-pump-thaw then heated at 80 °C for 5.5h. An aliquot of the reaction mixture was concentrated under reduced pressure to afford the isocyanate. IR (neat) ν = 3310, 2976, 2278, 1589, 1540, 1409, 1232, 1126, 1059, 961, 818, 788, 764, 594 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (br s, 1H), 7.39-7.38 (m, 1H), 7.03-7.01 (m, 1H), 6.67-6.66 (m, 1H), 6.32 (q, *J* = 1.5 Hz, 1H), 4.12 (t, *J* = 6.8 Hz, 2H), 2.67 (td, *J* = 7.6, 2.2 Hz, 2H), 2.05 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 140.0, 125.8, 122.16, 112.9, 110.5, 103.0, 51.7, 28.6, 22.6. The reaction mixture was cooled to 20 °C and a solution of 4-methoxy-*N*-(triphenylphosphoranylidene)aniline (213 mg, 0.556 mmol, 1.1 eq.) in degassed toluene (3 mL). The reaction mixture was allowed to stir overnight at 20 °C then the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 30% ethyl acetate in hexanes as eluent) to yield the product (62 mg, 0.192 mmol, 38% over 2 steps) as a white solid. *Rf* = 0.24 (20% ethyl acetate in hexanes); IR (neat) ν = 3276, 2955, 2111, 1583, 1540, 1508, 1410, 1243, 1191, 1129, 1058, 1032, 830, 739, 642, 571 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (br s, 1H), 7.59 (t, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.92-6. 90 (m, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 6.58-6.56 (m, 1H), 6.22-6.20 (m, 1H), 4.02 (t, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 7.0 Hz, 2H), 1.94 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ160.1, 157.0, 139.4, 137.1, 132.6, 126.0, 124.7, 122.1, 114.6, 112.8, 110.4, 108.8, 55.5, 51.8, 28.4, 22.7; HRMS (APCI) calcd for C18H19N4O2 [M+H] 323.15025 ; found 323.14965.



Pivalic 1-((2-(trimethylsilyl)ethoxy)carbonyl)-1*H*-pyrrole-2-carboxylic anhydride. To a solution of 1-((2-(trimethylsilyl)ethoxy)carbonyl)-1*H*-pyrrole-2-carboxylic acid (285 mg, 1.116 mmol, 1.0 eq.) in DCM (10 mL) cooled to 0 °C was added N,N-diisopropylethylamine (293 µL, 1.674 mmol, 1.5 eq.) and pivaloyl chloride (150 µL, 1.227 mmol, 1.1 eq.). The reaction mixture was allowed to warm to 20 °C while stirring (over 3h) then quenched with water and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water and dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude anhydride could be used directly in the next step without further purification.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.06 (m, 1H), 6.28 (m, 1H), 4.51-4.47 (m, 2H), 1.34 (s, 9H), 1.22-1.18 (m, 2H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 154.8, 149.7, 129.5, 125.2, 124.0, 110.9, 67.5, 39.9, 26.6, 17.3, -1.6.



2-(Trimethylsilyl)ethyl 2-((((1*S*,2*S*)-2-(3-(allyloxy)-3-oxoprop-1-yn-1-yl)cyclopentyl)methyl)carbamoyl)-1*H*-pyrrole-1-carboxylate. To a solution of **2.132** (80 mg, 0.196 mmol, 1 eq.) in DCM (800 µL) cooled to 0 °C was added trifluoroacetic acid (1 mL, 13.0 mmol, 66 eq.) in several portions. The reaction mixture was stirred at 0 °C for 20 mins then at 20 °C for 1h. The reaction mixture was concentrated under reduced pressure, dissolved in toluene (10 mL) and reconcentrated. To a solution of the resultant oil (81 mg) in DCM (8 mL) cooled to 0 °C, was added a solution of crude anhydride **3.141** (1.116 mmol, 5.7 eq.) in DCM (2 mL) in one portion followed by triethylamine (300 µL, 1.960 mmol, 10 eq.) dropwise. The reaction mixture was allowed to warm to 20 °C while stirring overnight. The reaction mixture was quenched with water and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM and the combined organic layers were washed with water, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (gradient of 10% to 35% ethyl acetate in hexanes as eluent) to yield the product (58 mg, 0.130 mmol, 67%) as a brownish oil. *Rf* = 0.16 (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (brs, 1H), 7.37 (m, 1H), 7.01 (m,

1H), 6.21 (m, 1H), 5.96-5.88 (m, 1H), 5.29 (d, J = 17.1Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 4.64 (d, J = 5.7, 2H), 4.48 (m, 2H), 3.52 (m, 2H), 2.55 (q, J = 8.5 Hz, 1H), 2.33 (sex, J = 7.5 Hz, 2H), 2.20-2.09 (m, 1H), 2.06-1.97 (m, 1H), 1.84-1.72 (m, 3H), 1.45-1.41 (m, 1H), 1.19-1.17 (m, 2H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 153.5, 151.2, 131.3, 130.2, 125.3, 120.9, 119.2, 110.9, 92.4, 73.3, 67.2, 66.3, 47.0, 43.1, 34.3, 32.9, 29.9, 24.2, 17.5, -1.5; LRMS (LCMS) calcd for C23H33N2O5Si [M+H] 445.21 ; found 445.30.

[1] J. Streuff, C. H. Hovelmann, M. Nieger, K. Muniz, *J. Am. Chem. Soc.* **2005**, *127*, 14586-14587.

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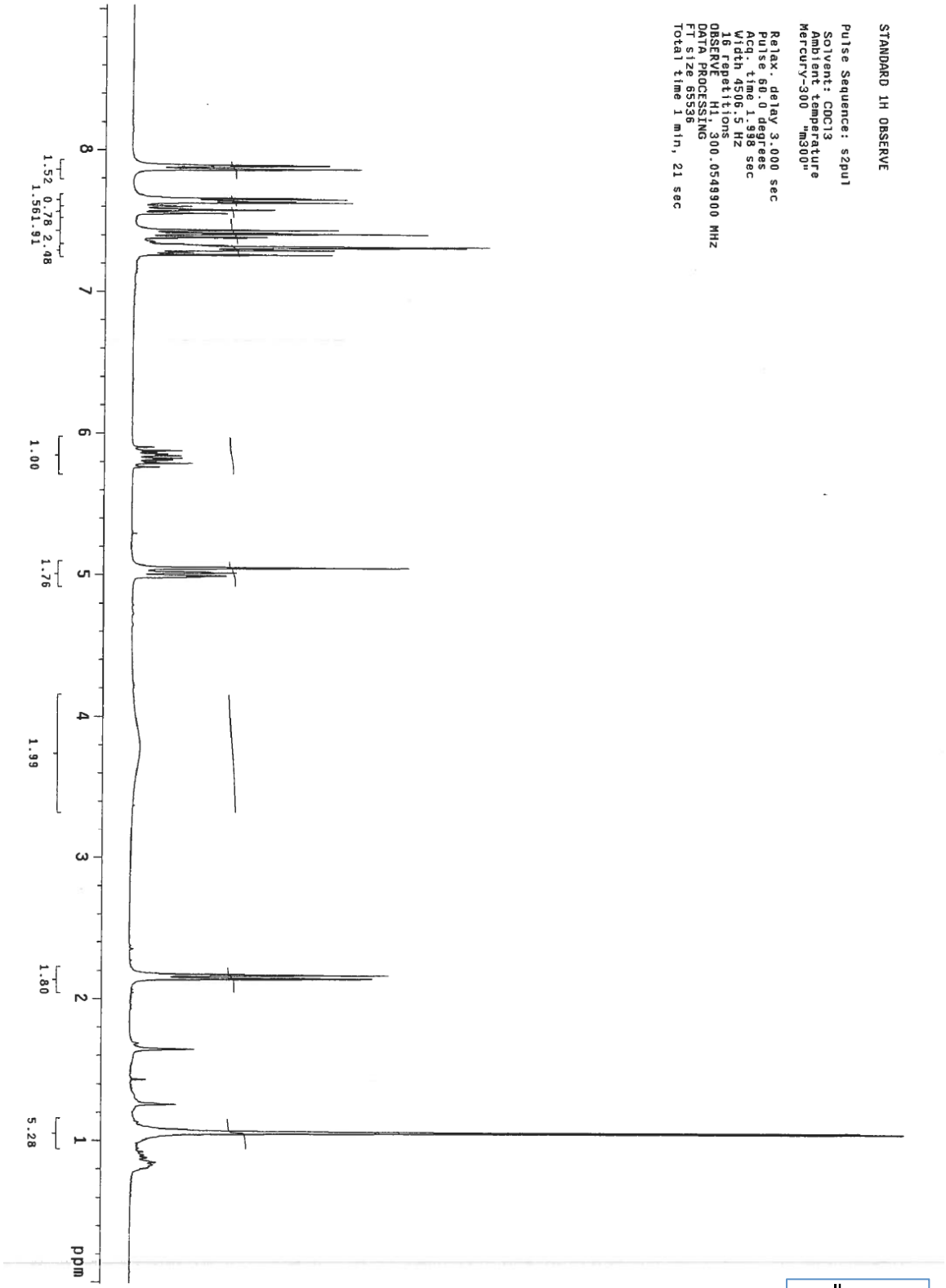
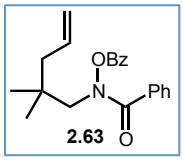
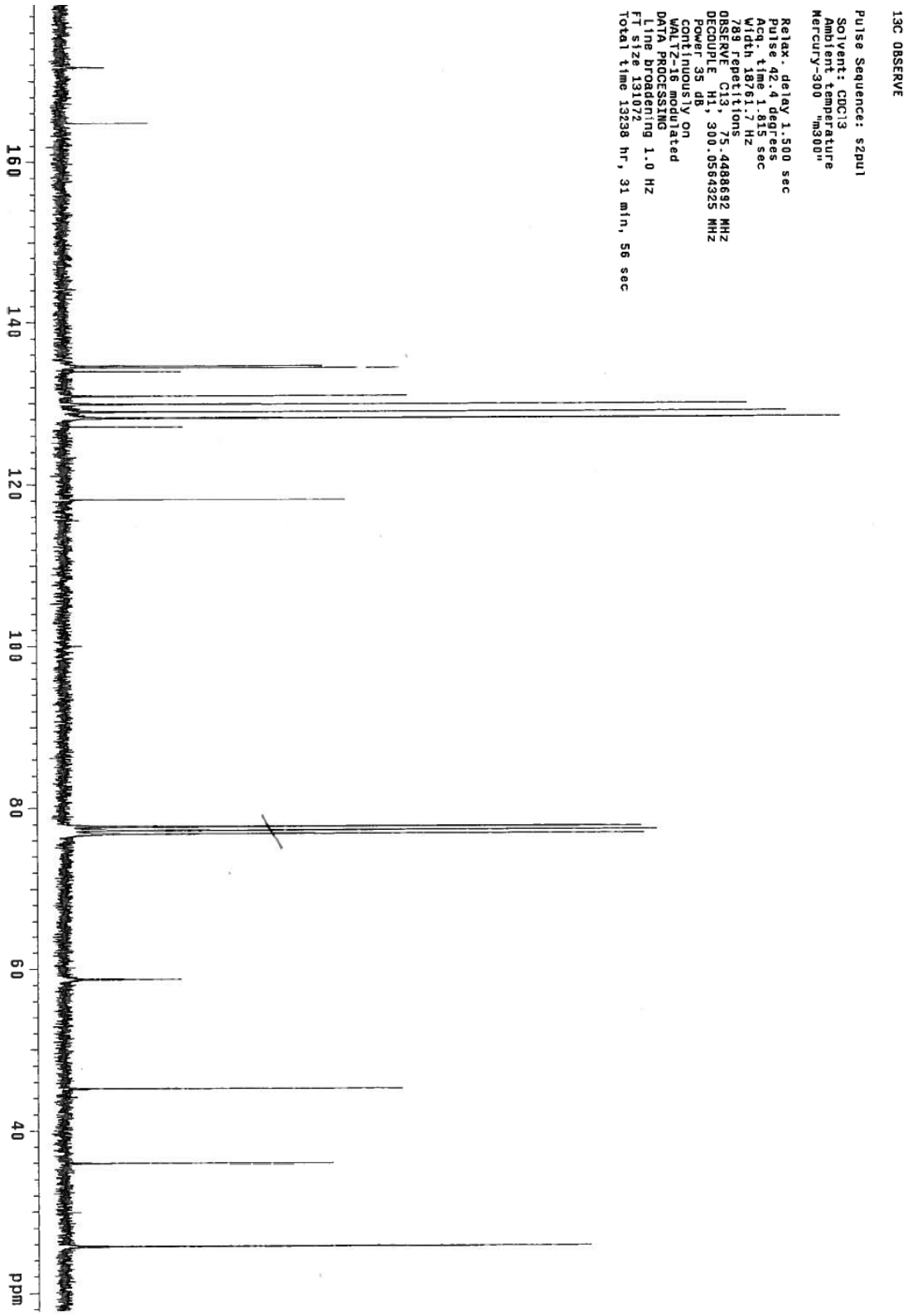
Chapter 5.

Selected Spectral Data

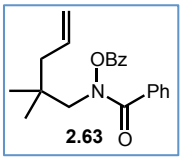


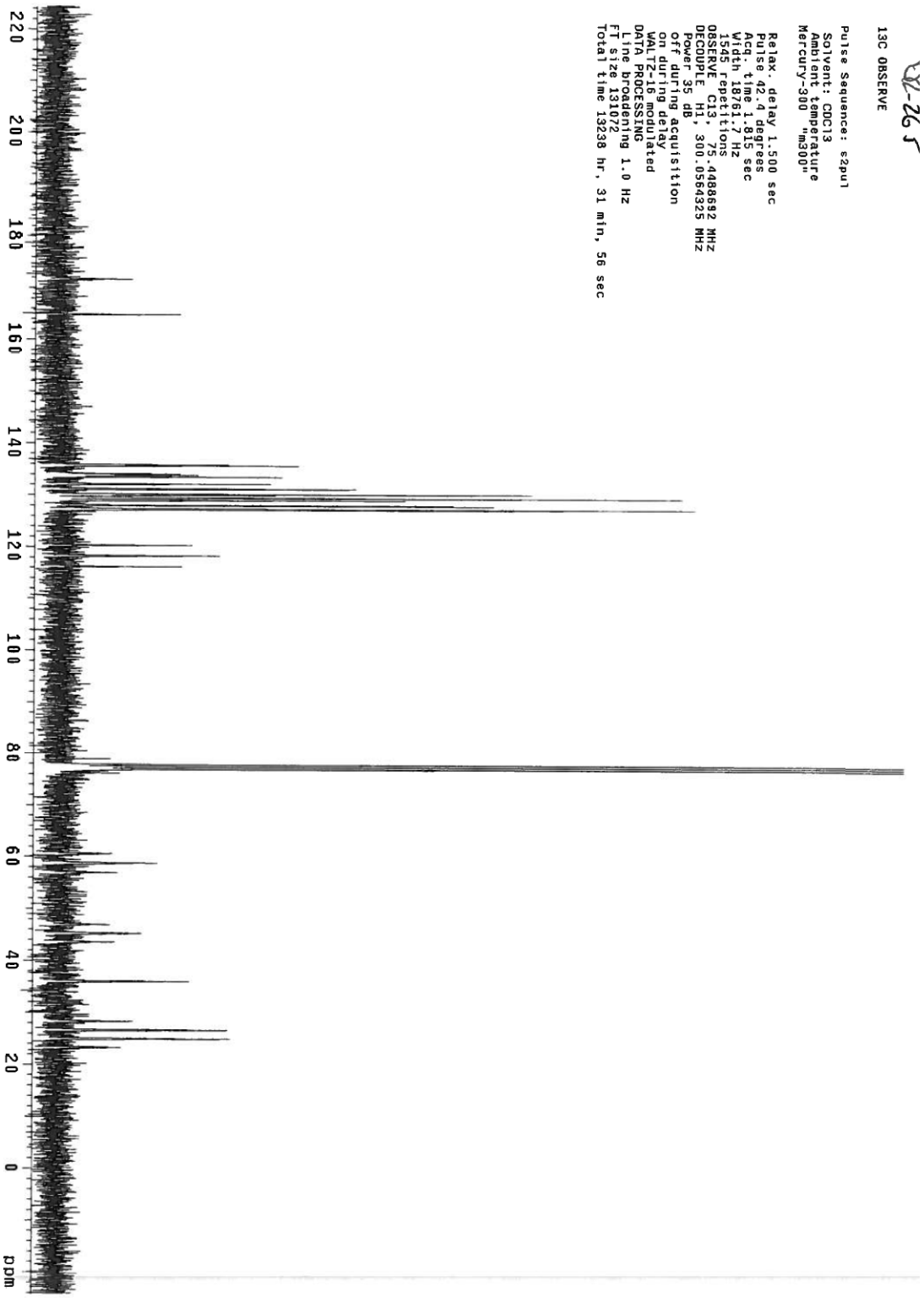
Spectrum A. 1 - ^{1}H NMR spectrum of **2.63**



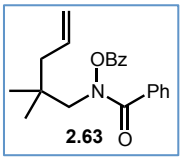


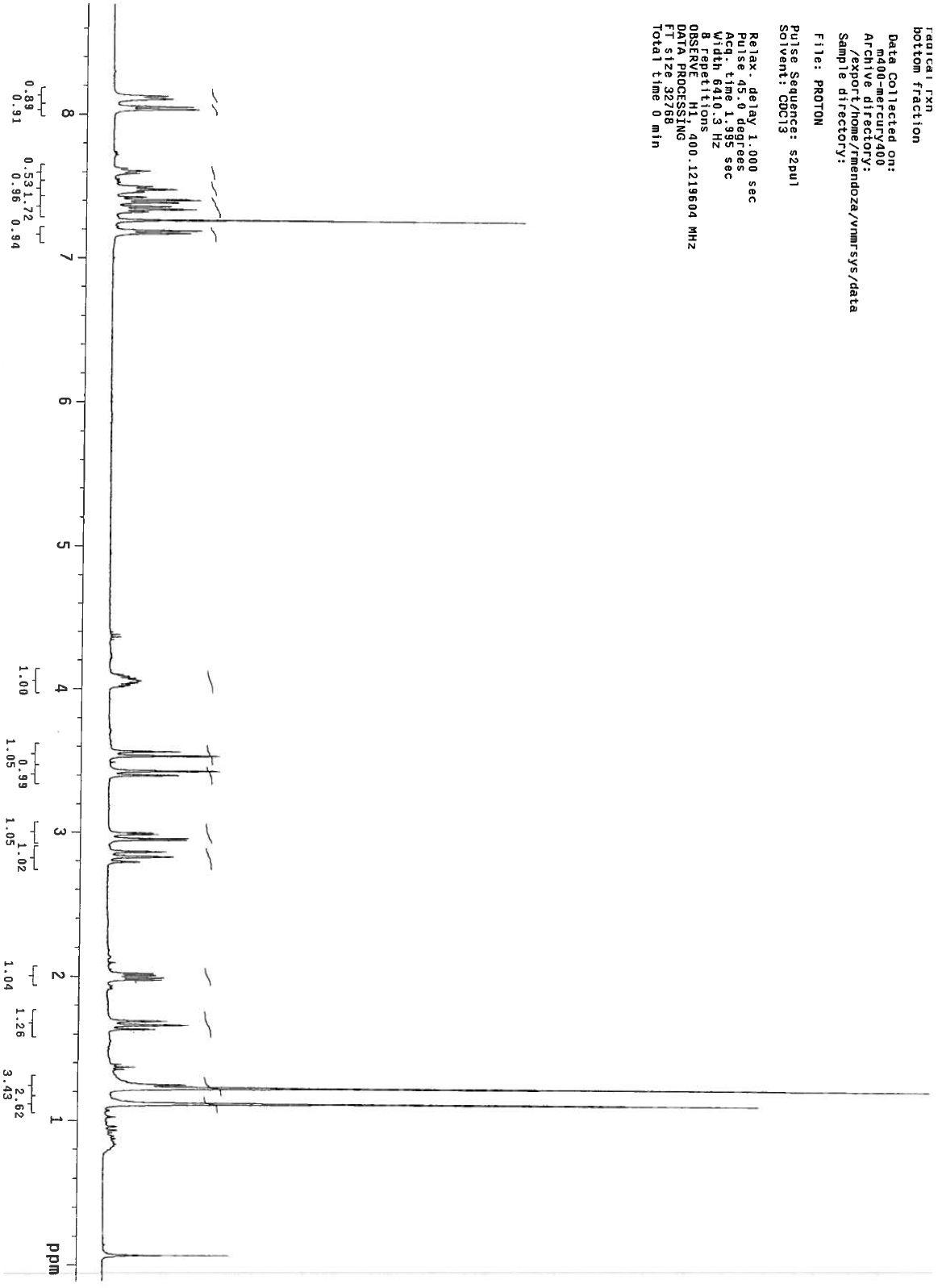
Spectrum A. 2 - ^{13}C NMR spectrum of **2.63**



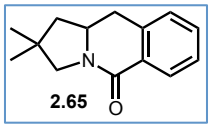


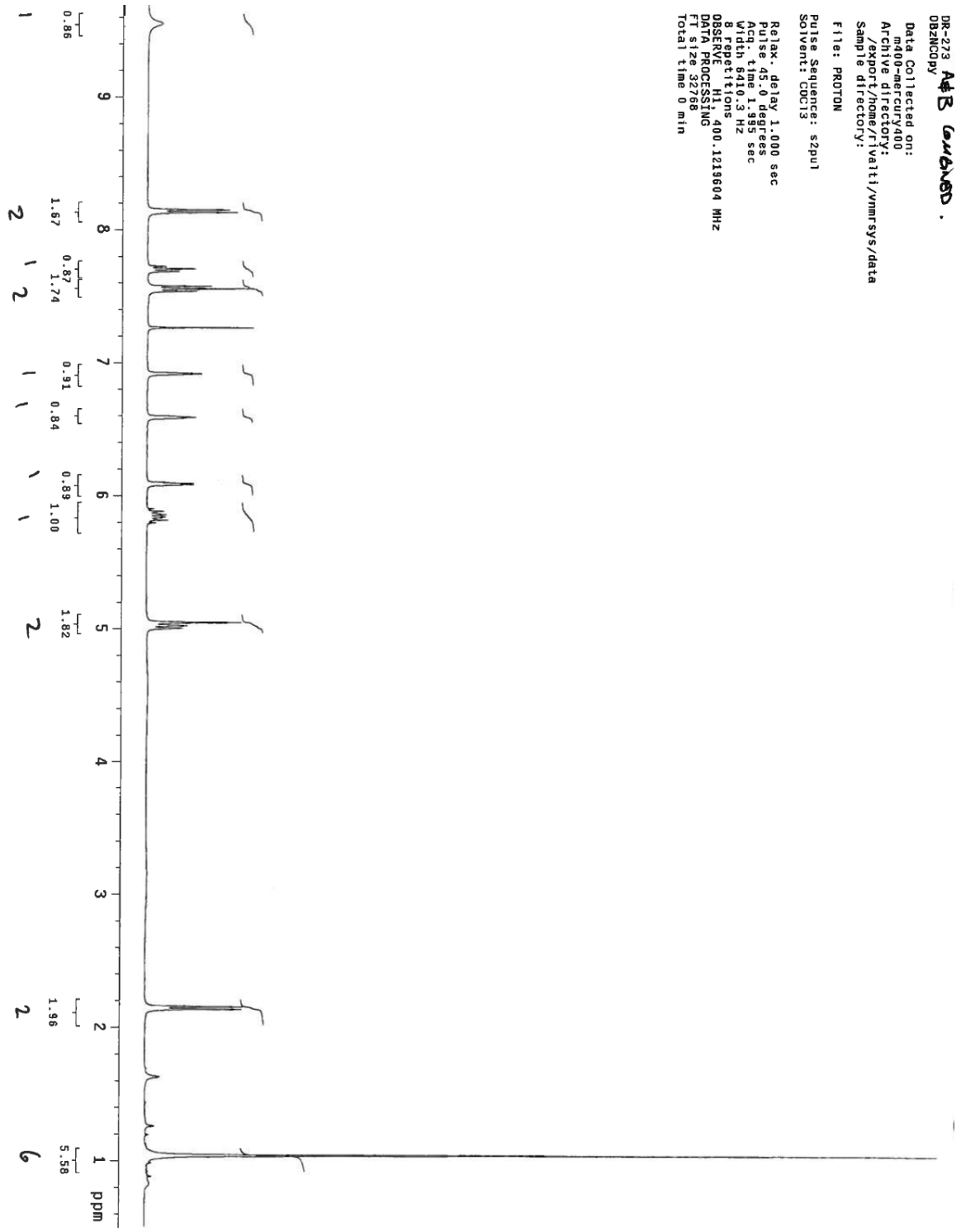
Spectrum A. 3 - ^{1}H coupled ^{13}C spectrum of **2.63**





Spectrum A. 4 - ^{1}H NMR spectrum of **2.65**





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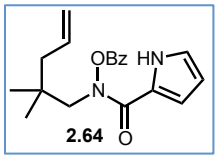
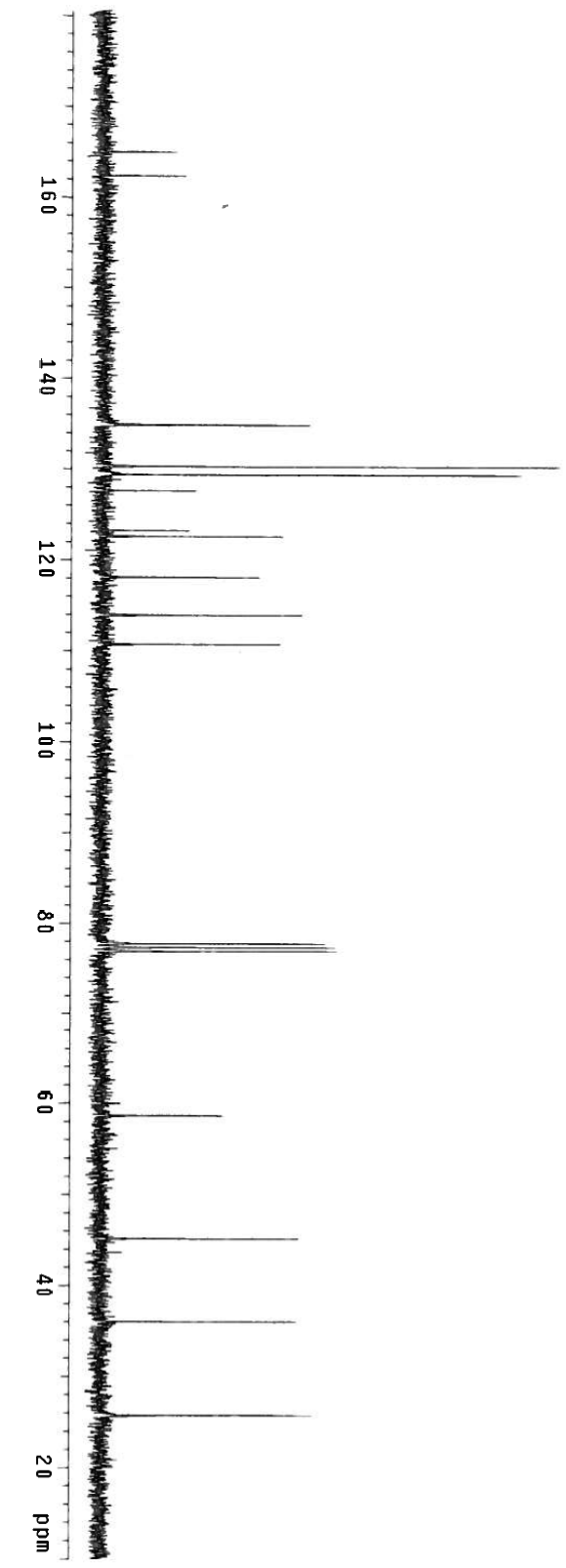
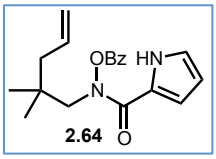
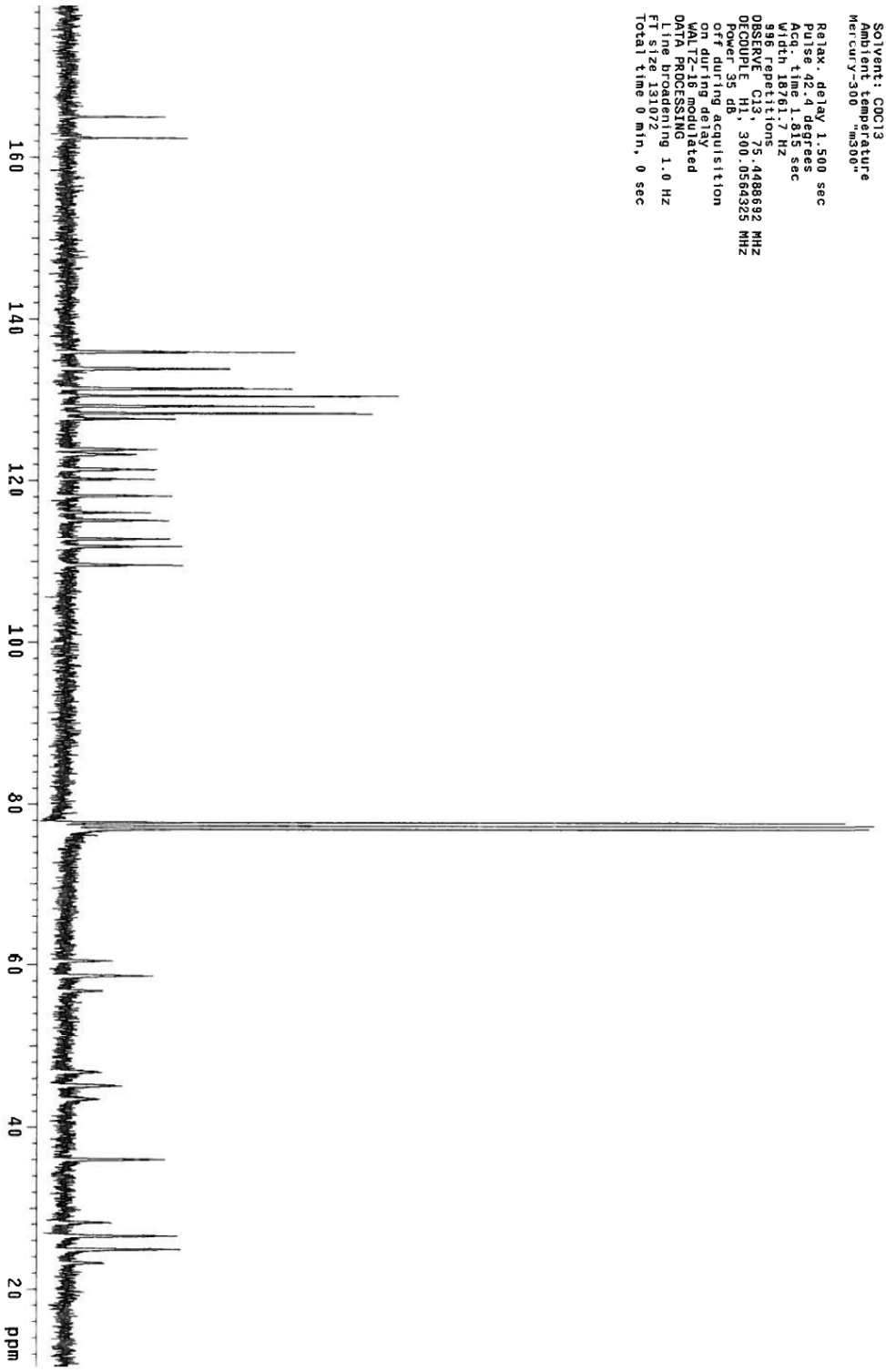


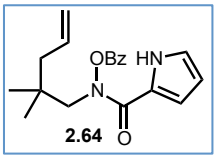


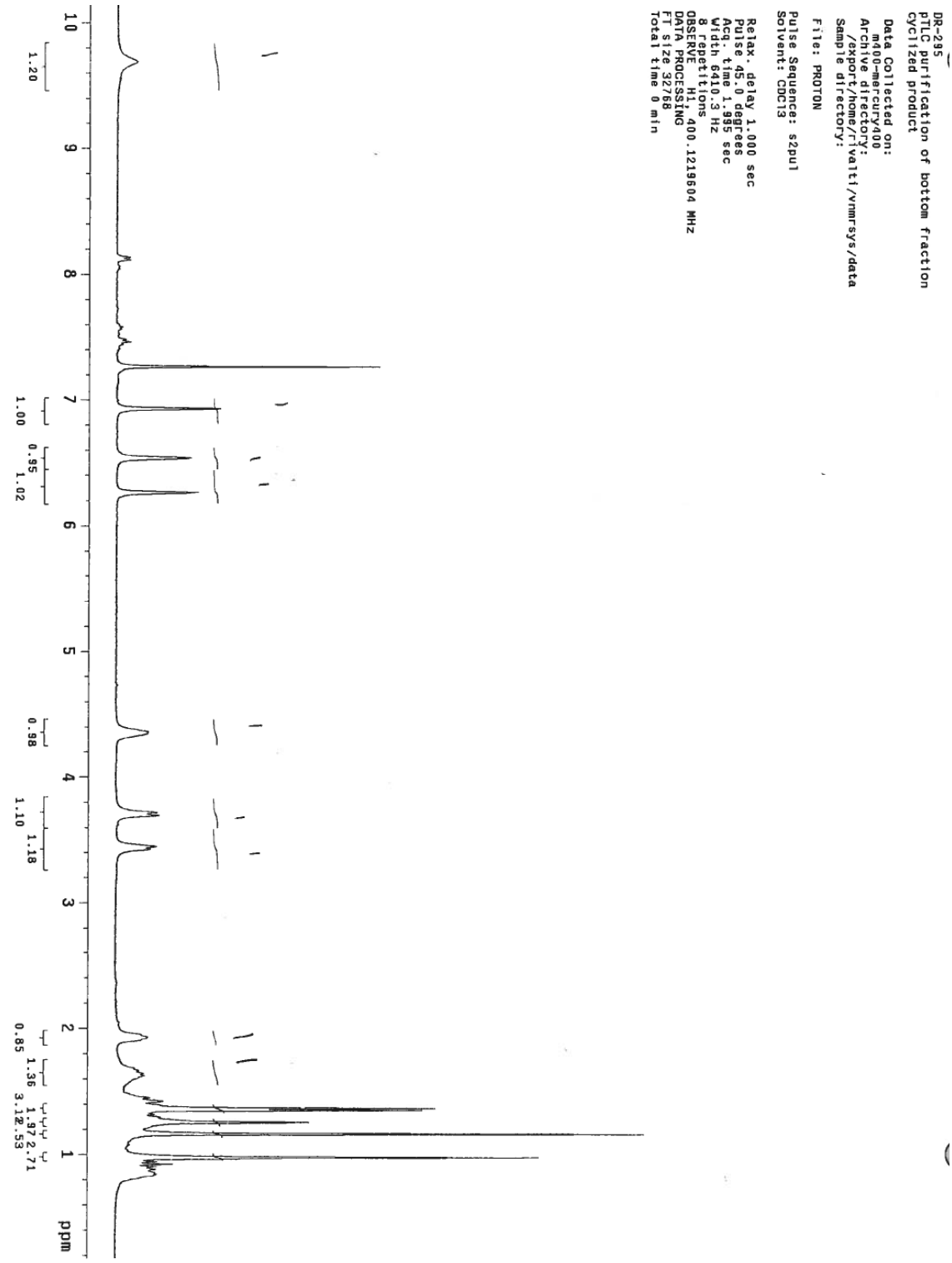
Spectrum A. 6 - ^{13}C NMR spectrum of **2.64**



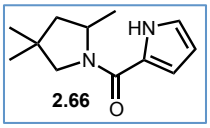


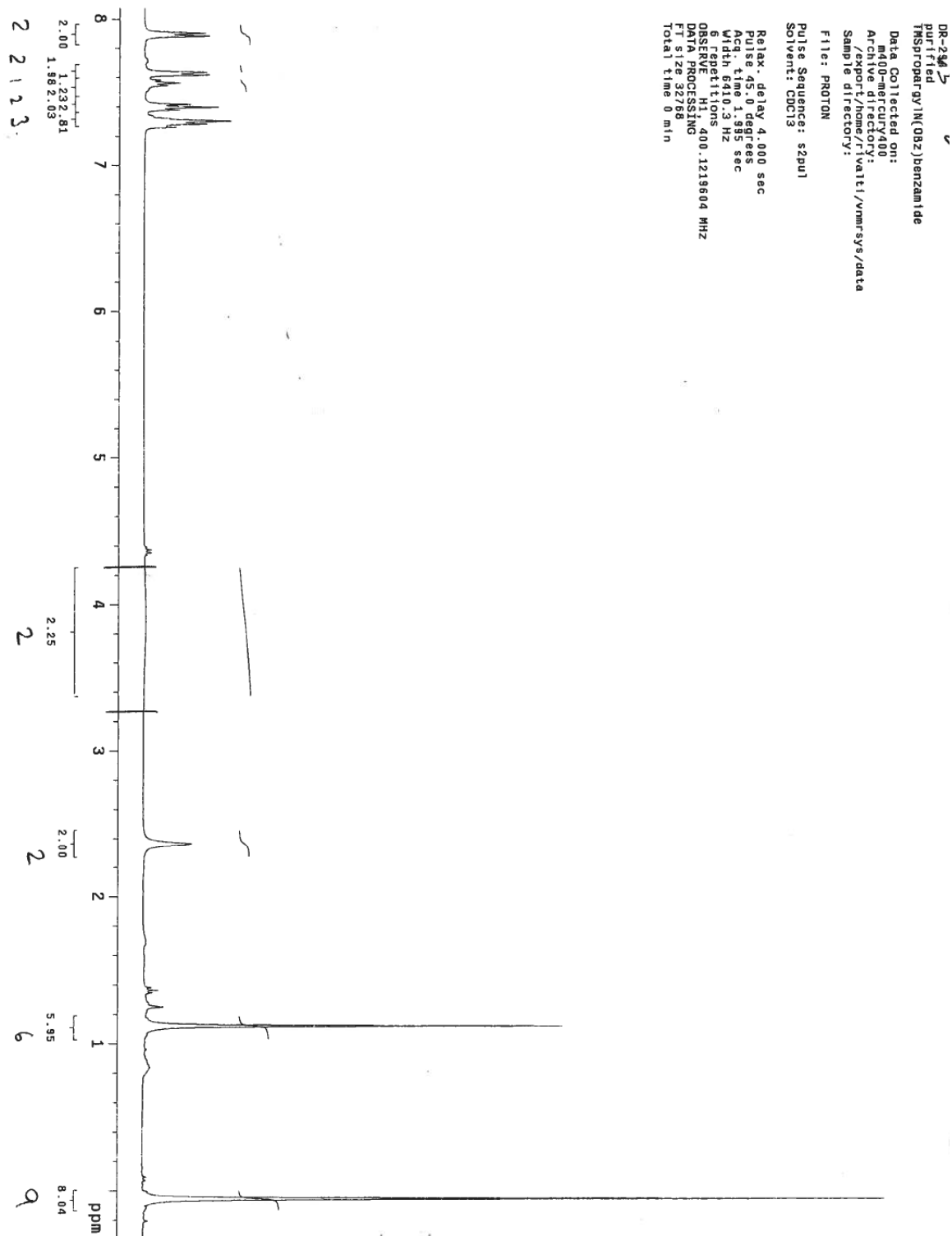
Spectrum A. 7 - ^{1}H coupled ^{13}C spectrum of **2.64**



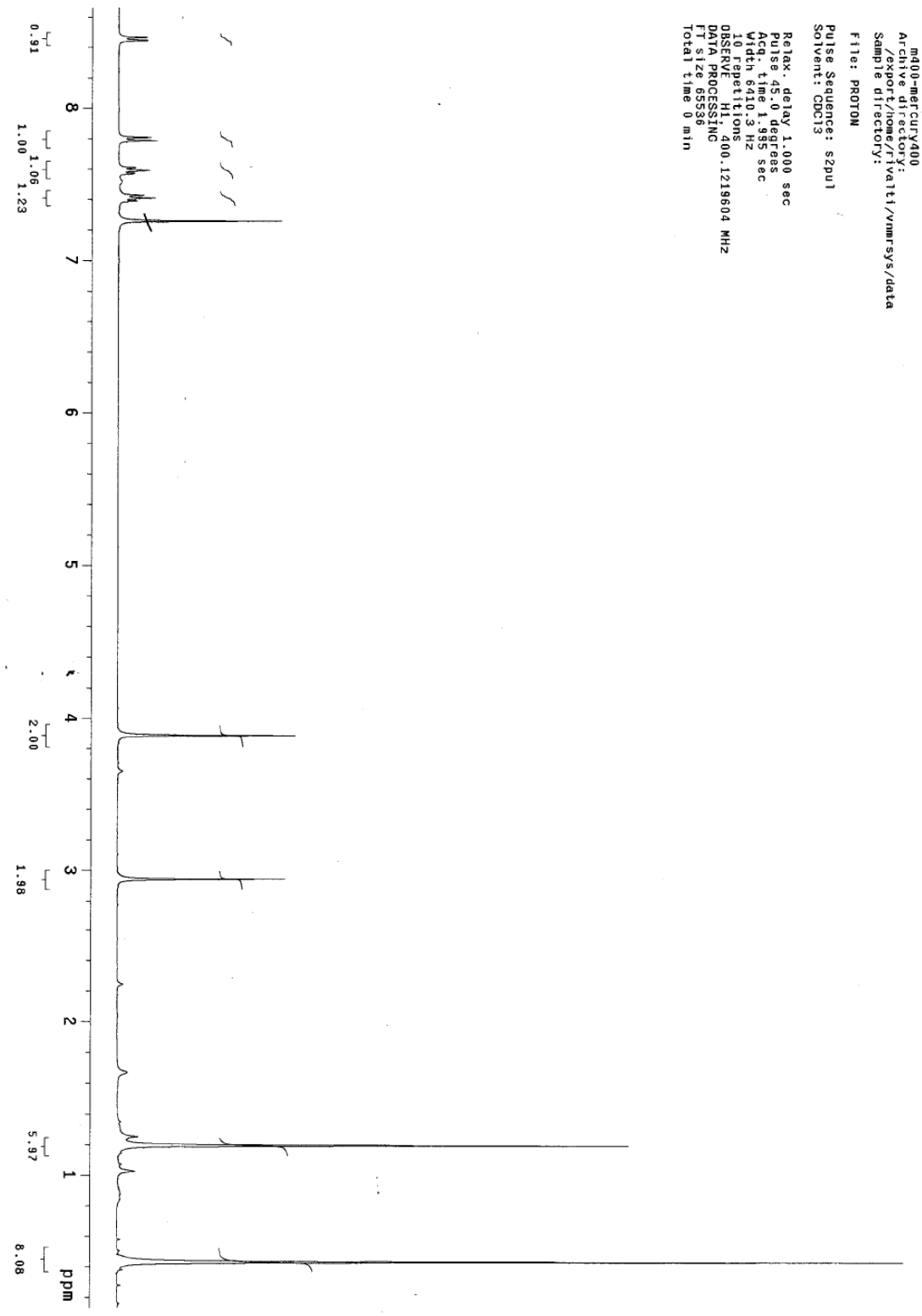


Spectrum A. 8 - ^{1}H NMR spectrum of **2.66**

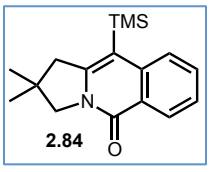


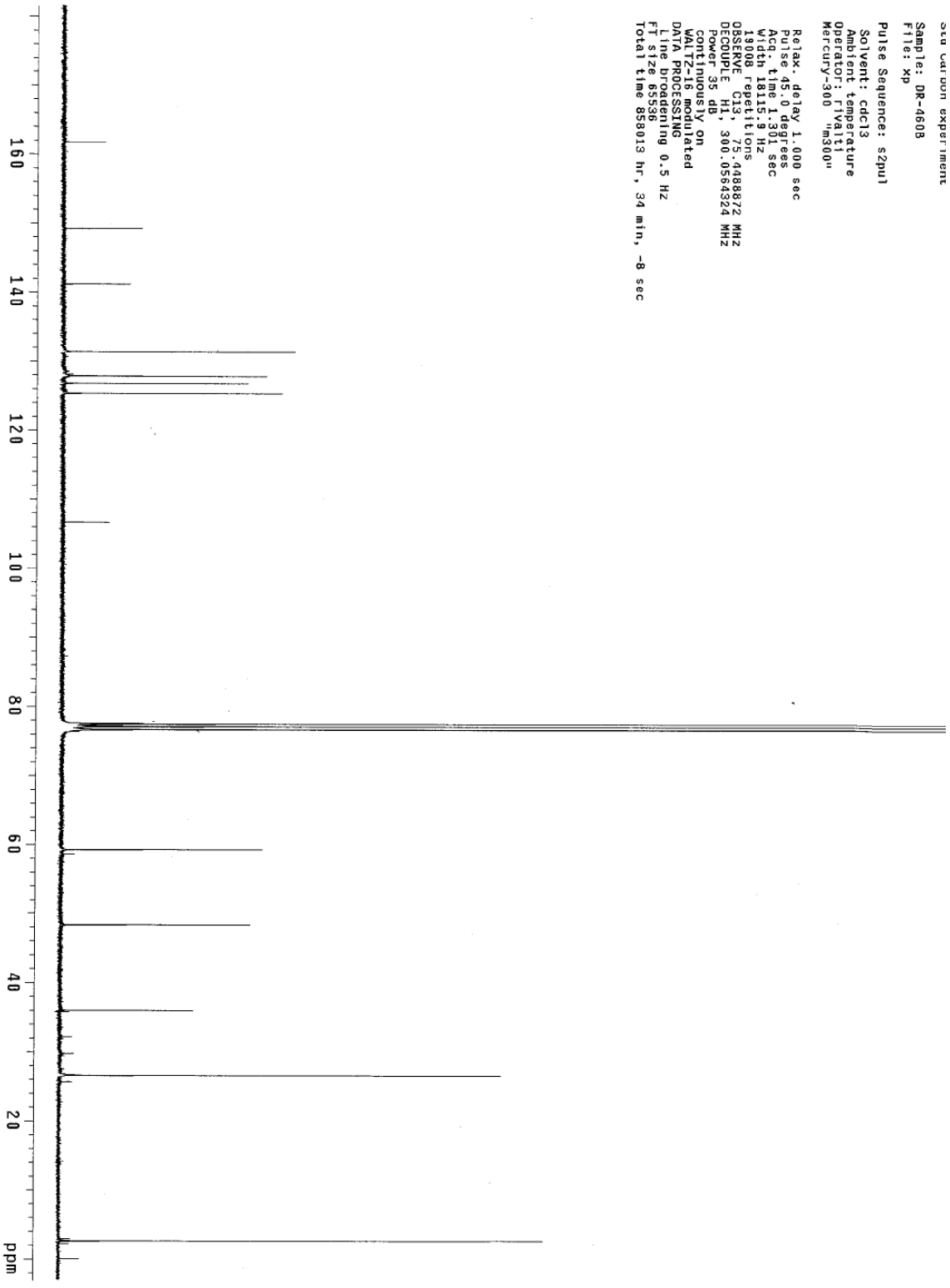


Spectrum A. 9 - ^{1}H NMR spectrum of **2.77**

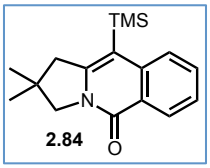


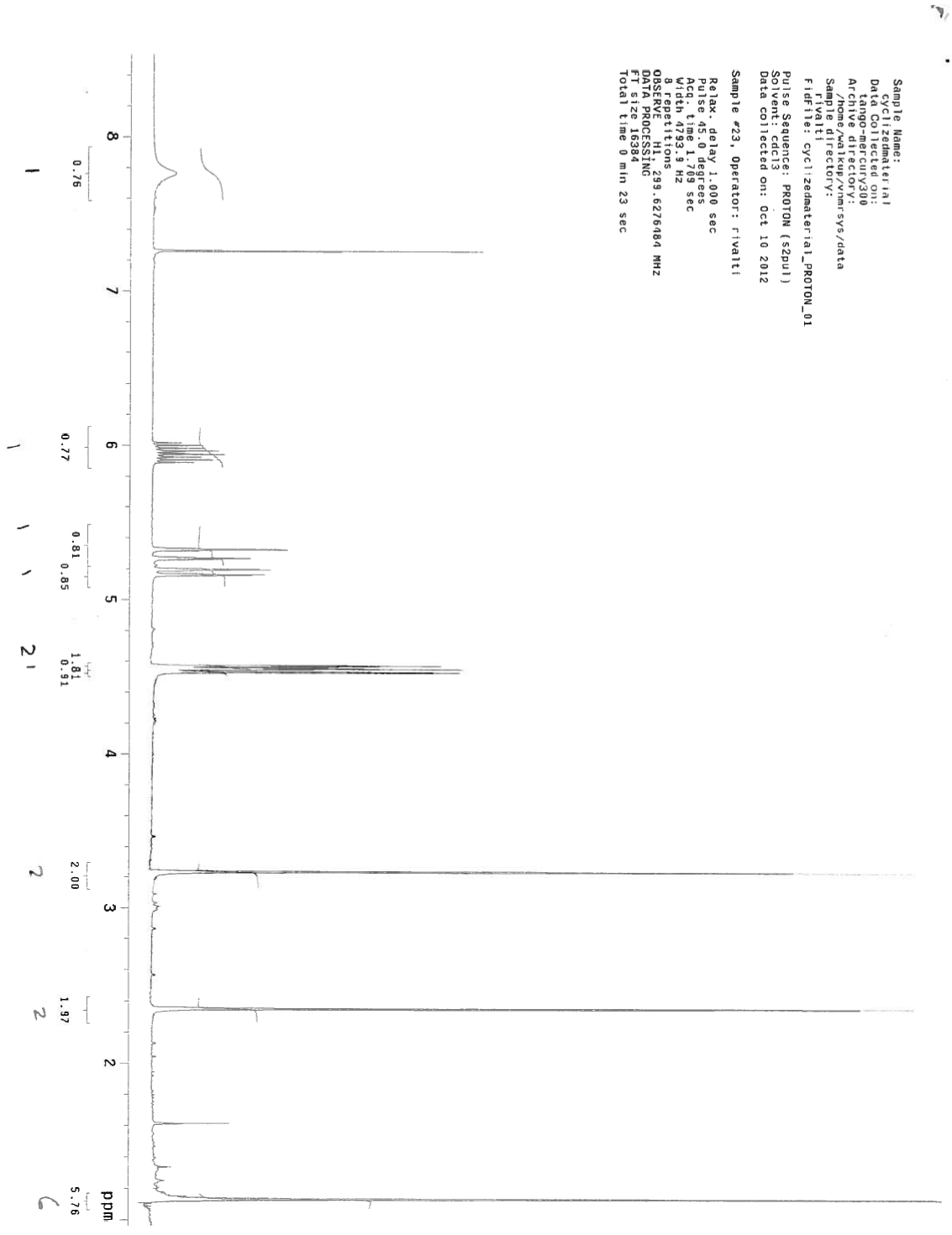
Spectrum A. 10 - ^{1}H NMR spectrum of **2.84**



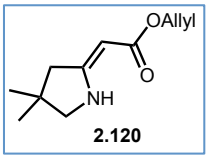


Spectrum A. 11 - ^{13}C NMR spectrum of **2.84**

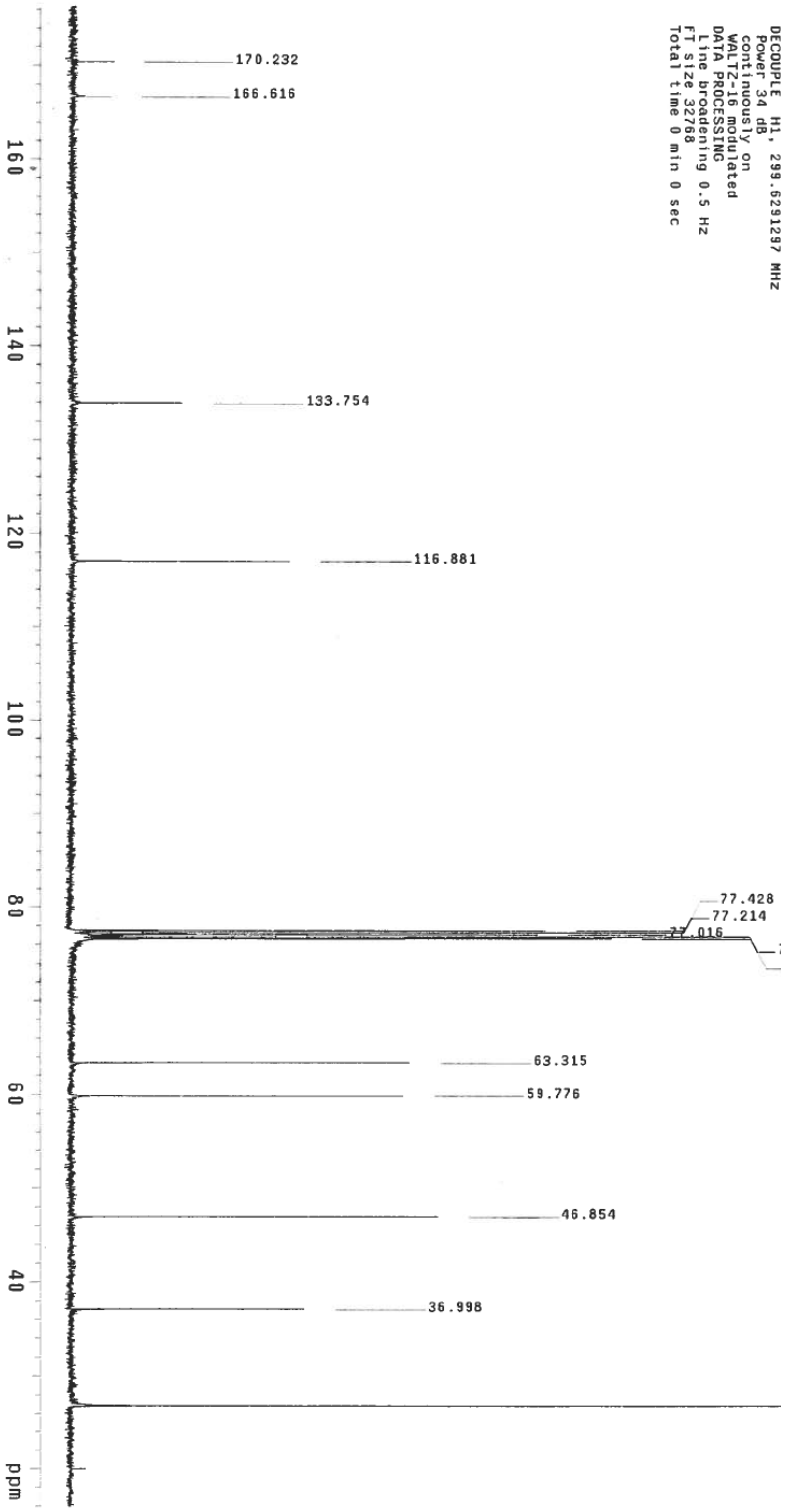




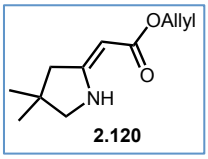
Spectrum A. 12 - ^{1}H NMR spectrum of **2.120**

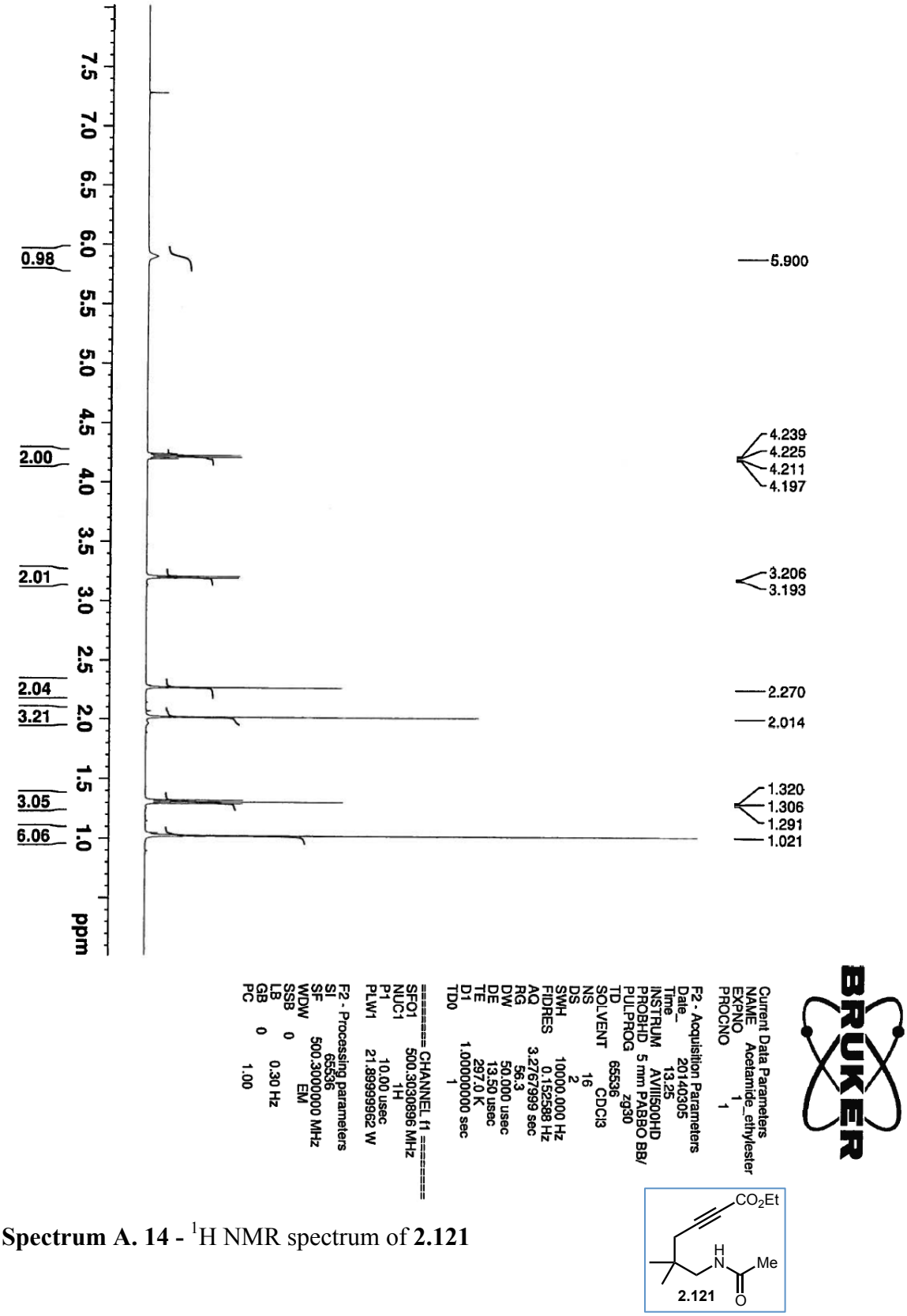


2.120

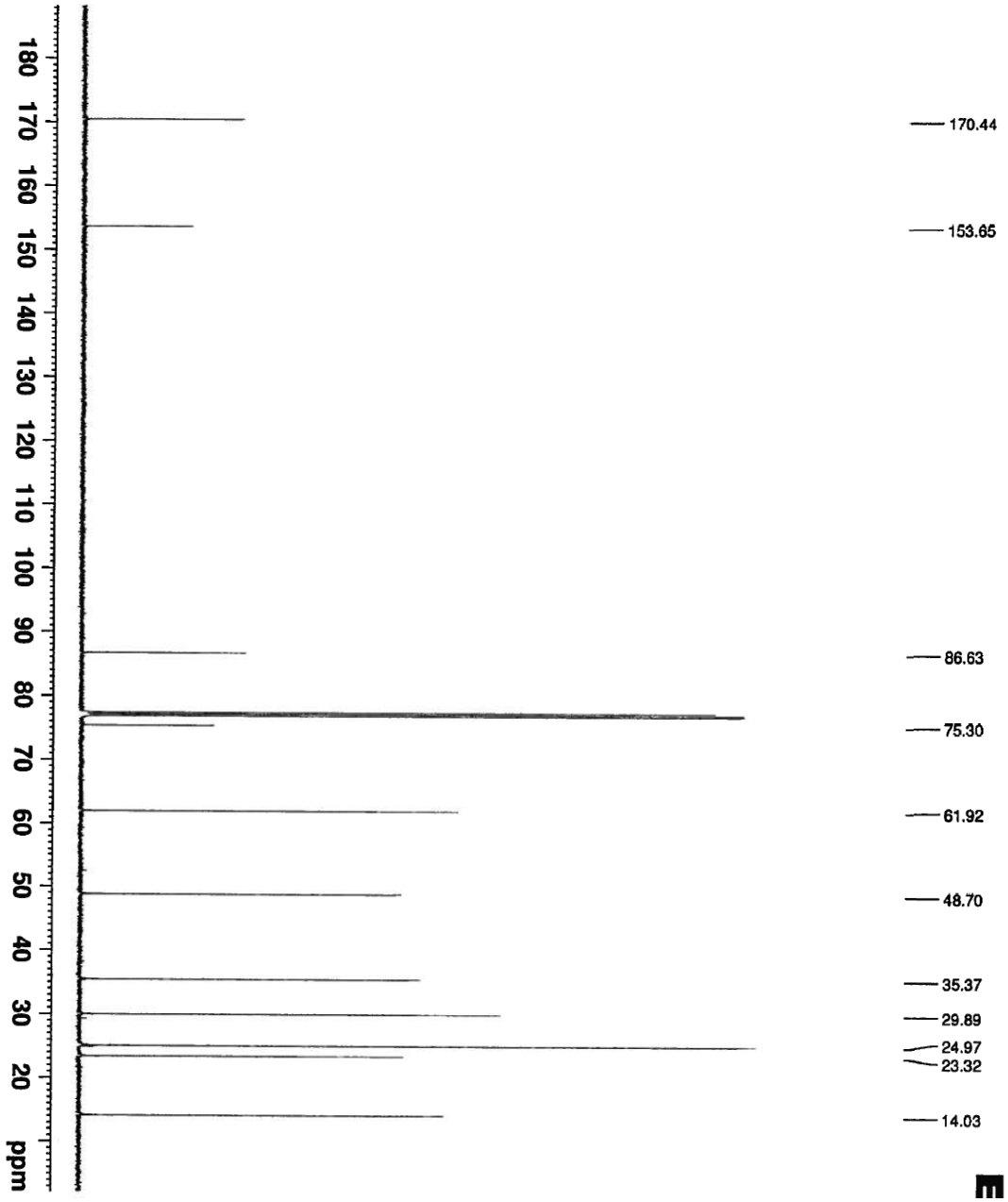


Spectrum A. 13 - ^{13}C NMR spectrum of **2.120**

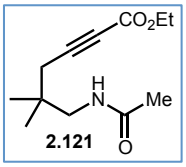


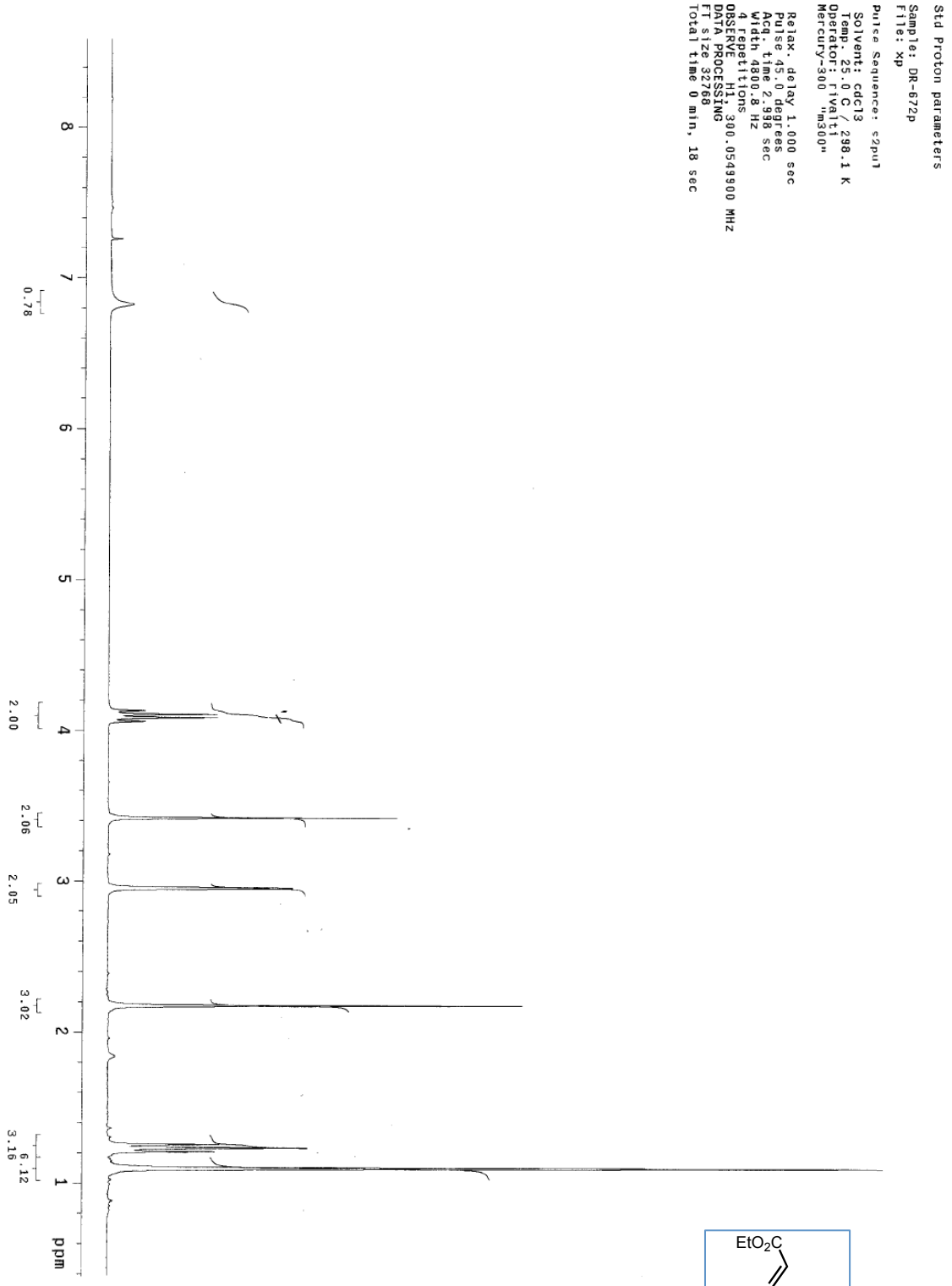


Spectrum A. 14 - ^{1}H NMR spectrum of **2.121**



Spectrum A. 15 - ^{13}C NMR spectrum of **2.121**





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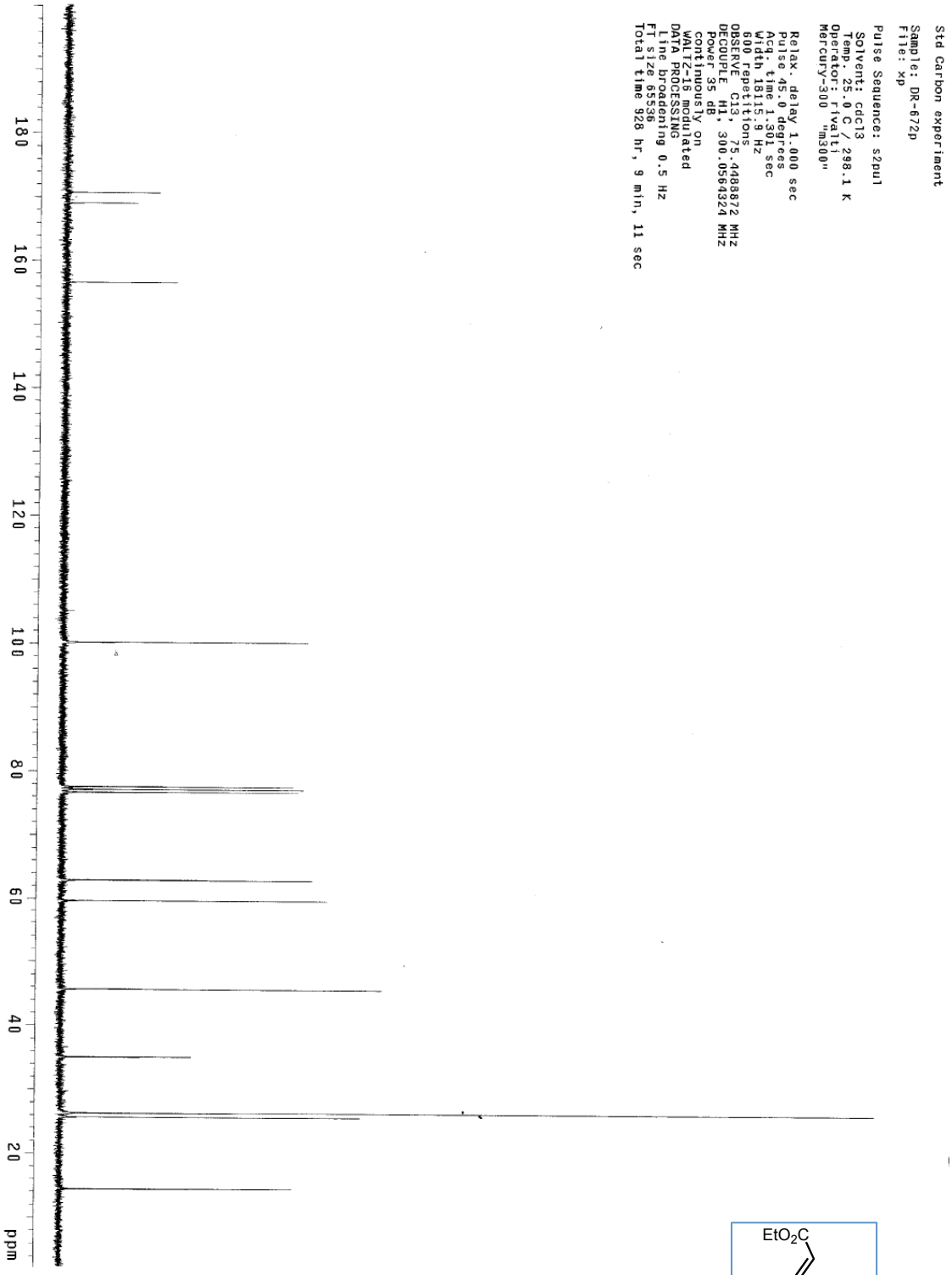
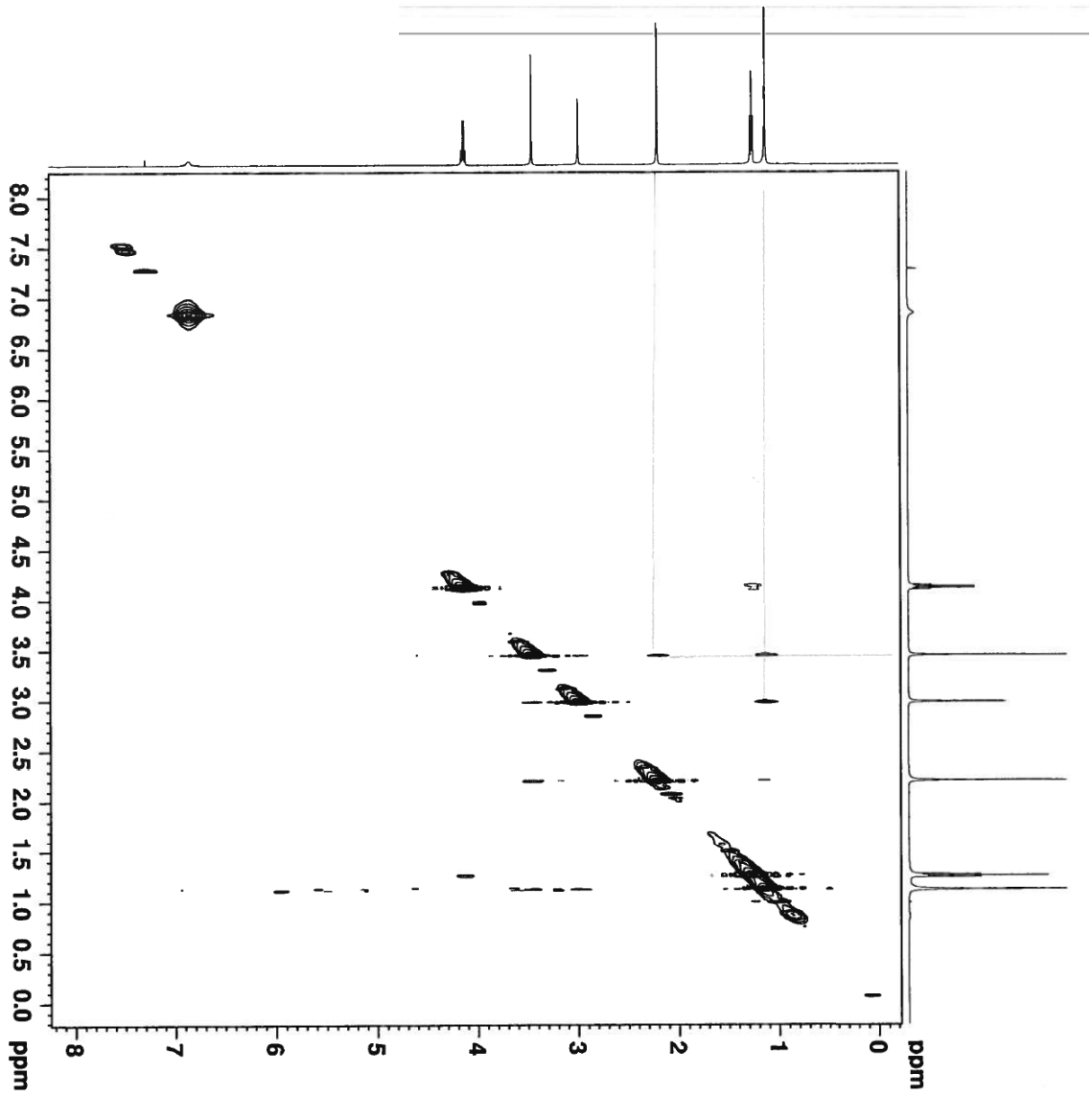
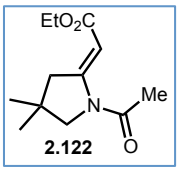
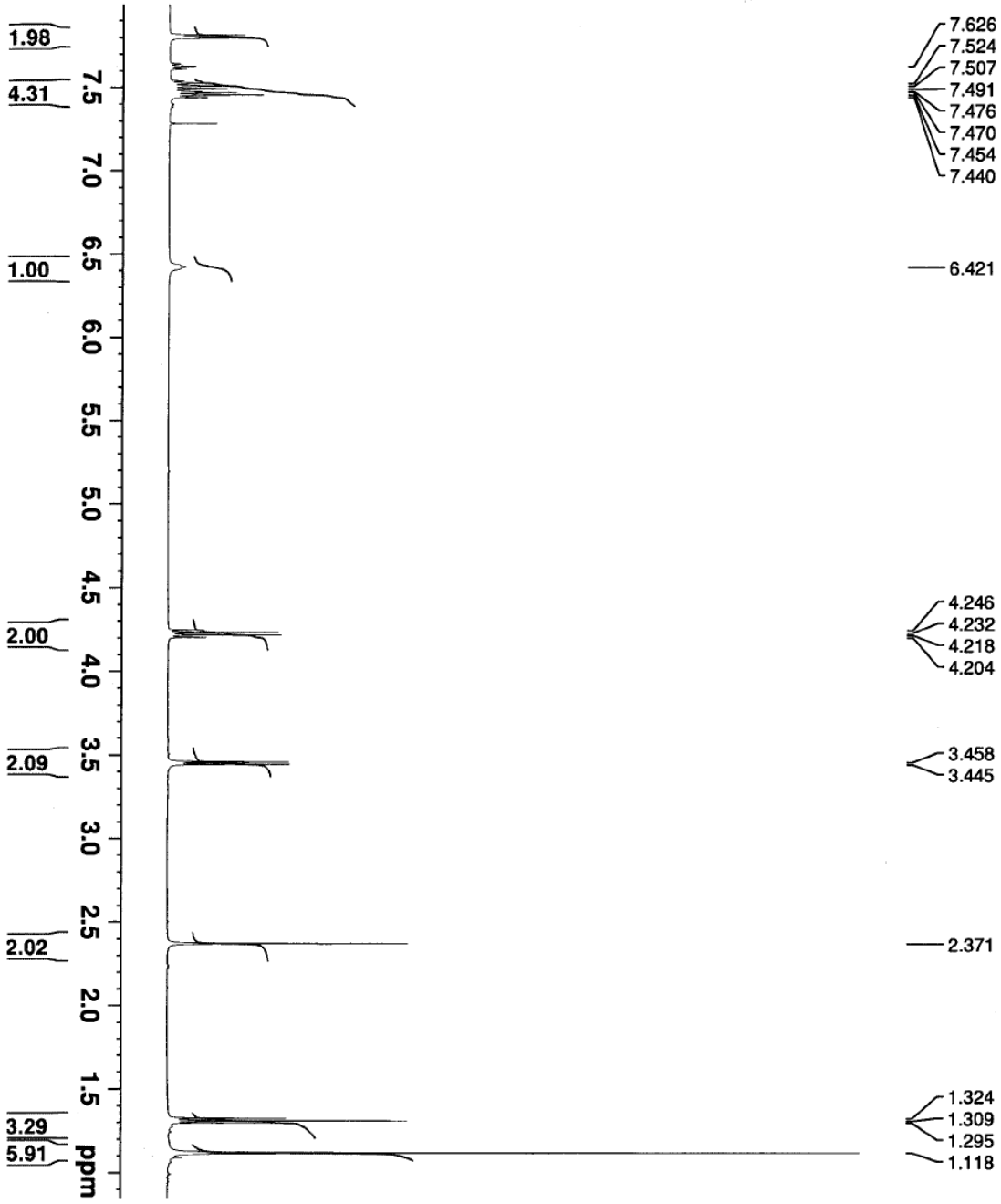


Spectrum A. 17 - ^{13}C NMR spectrum of **2.122**

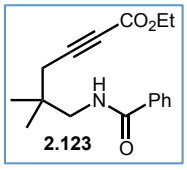


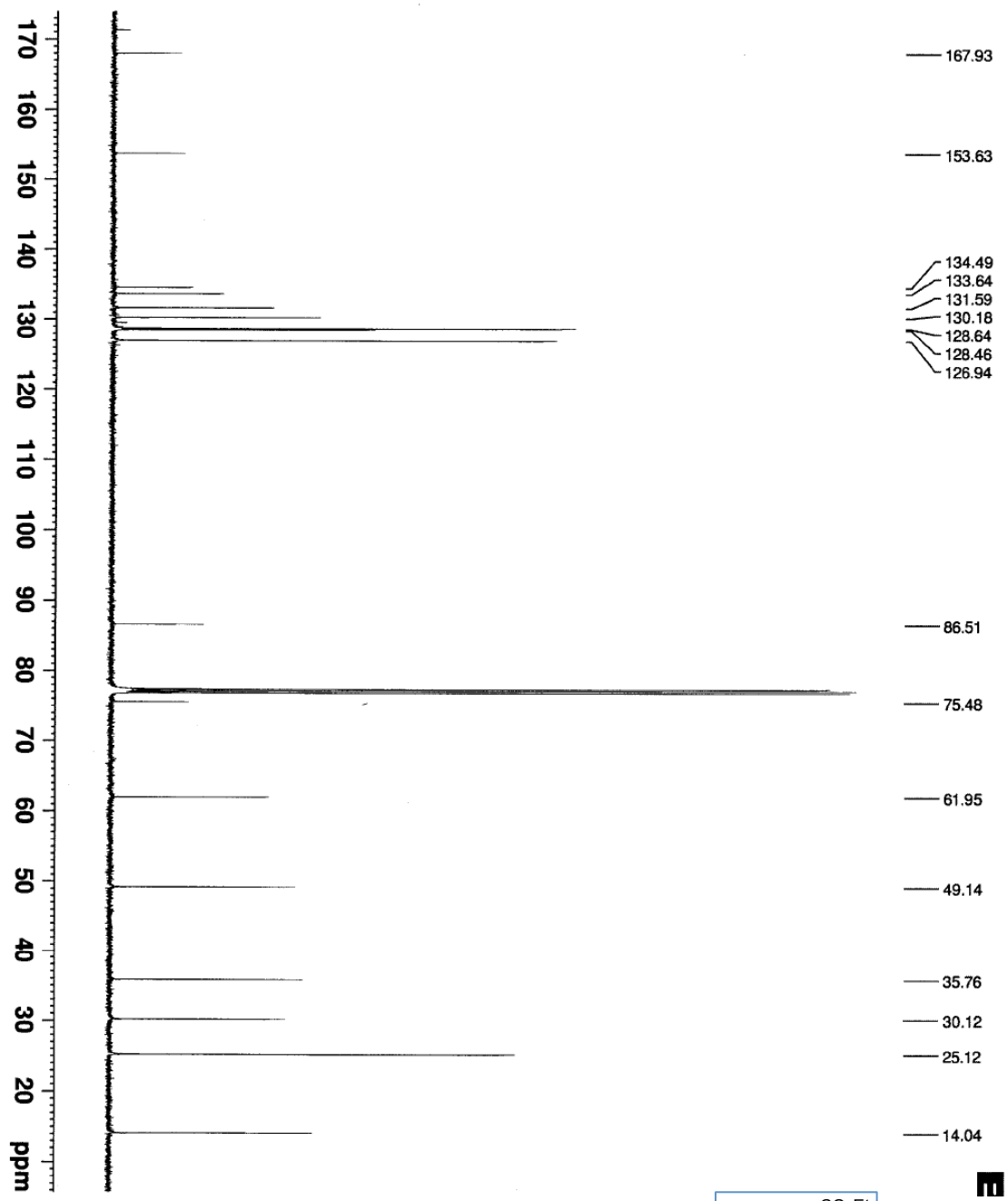
Spectrum A. 18 - NOESY spectrum of **2.122**



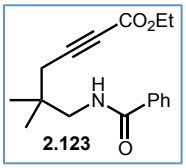


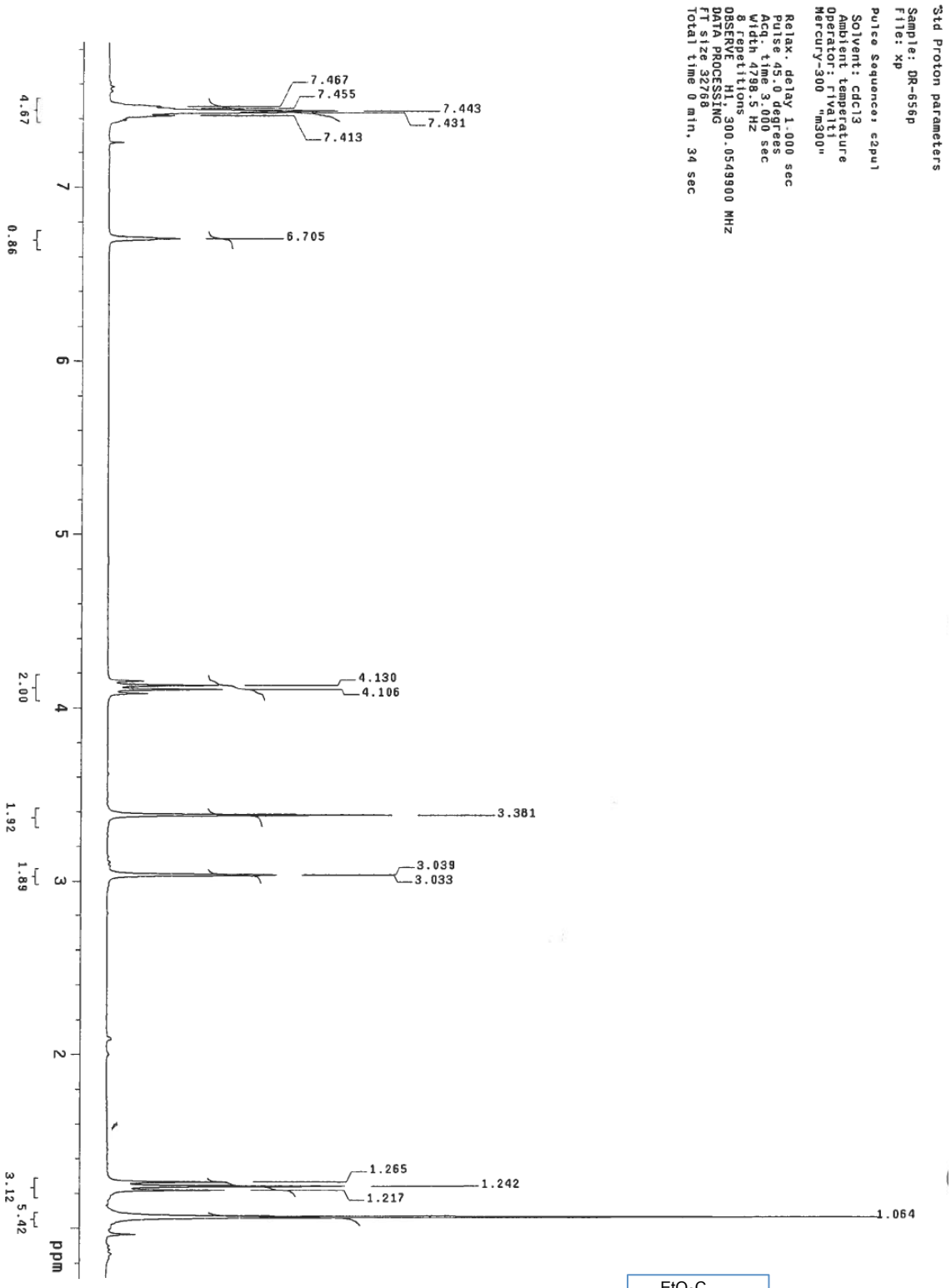
Spectrum A. 19 - ^{1}H NMR spectrum of **2.123**



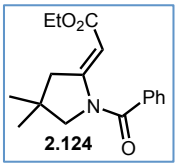


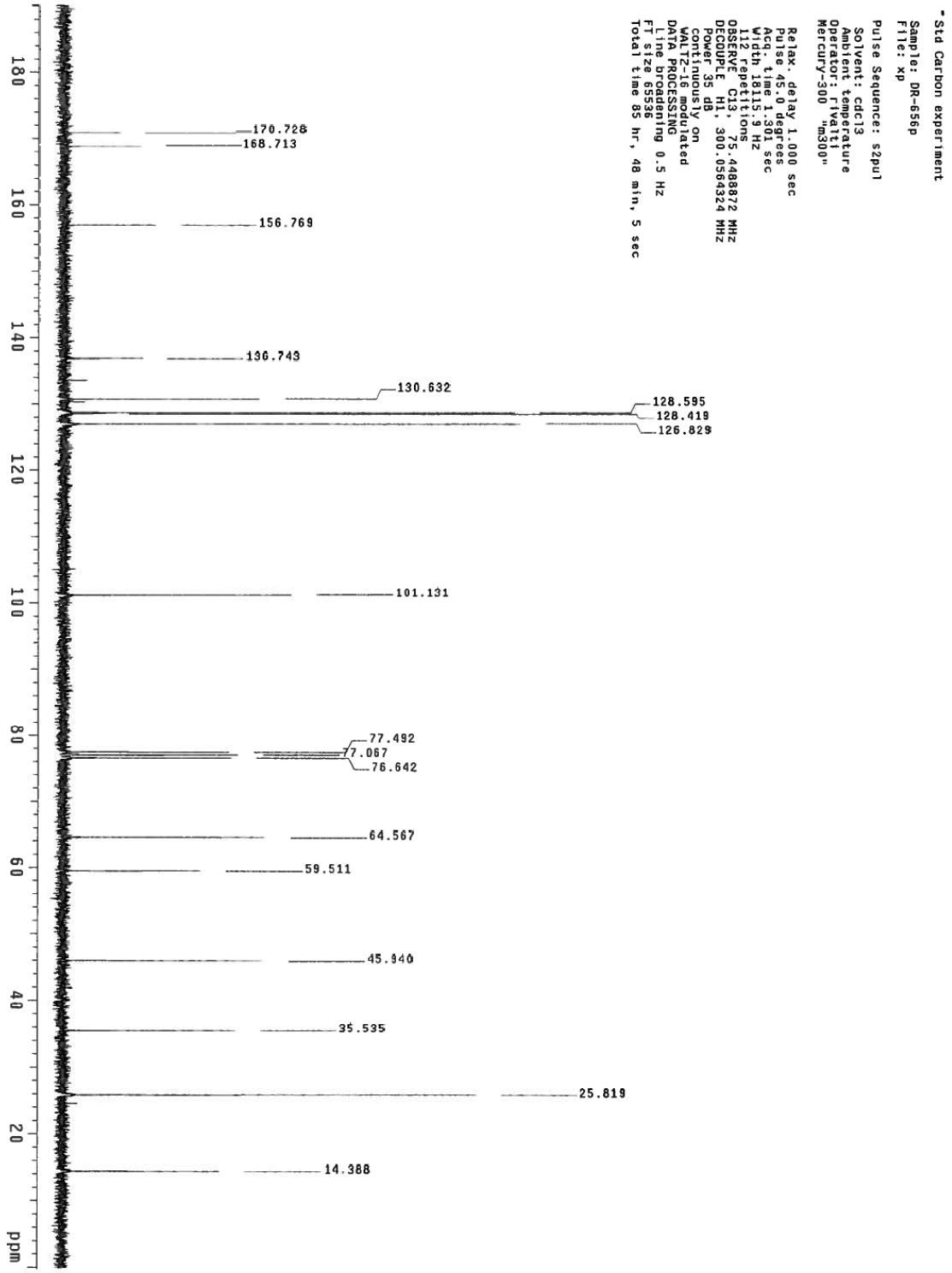
Spectrum A. 20 - ^{13}C NMR spectrum of **2.123**



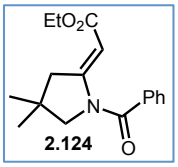


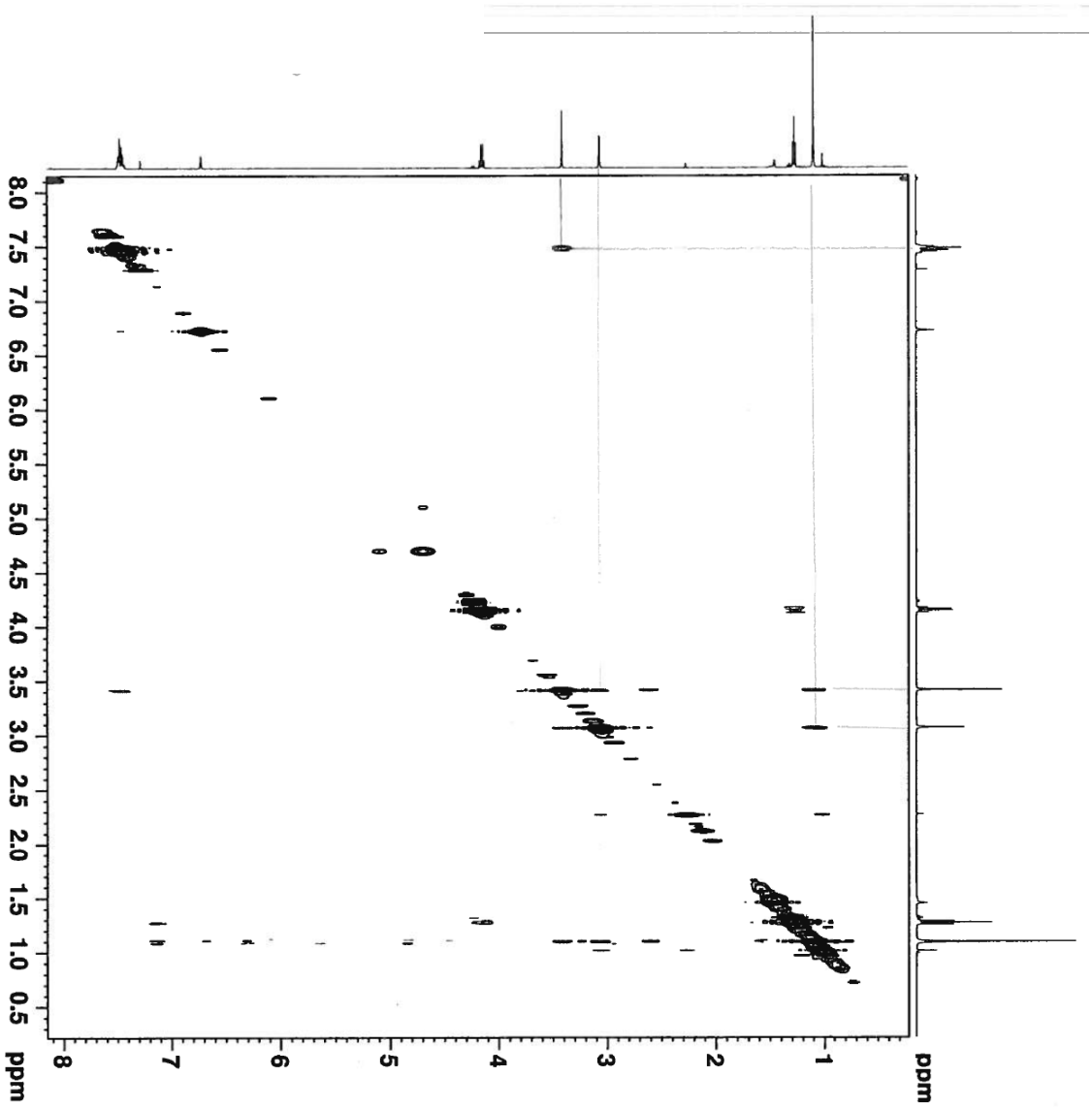
Spectrum A. 21 - ^{1}H NMR Spectrum of **2.124**



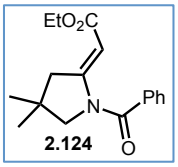


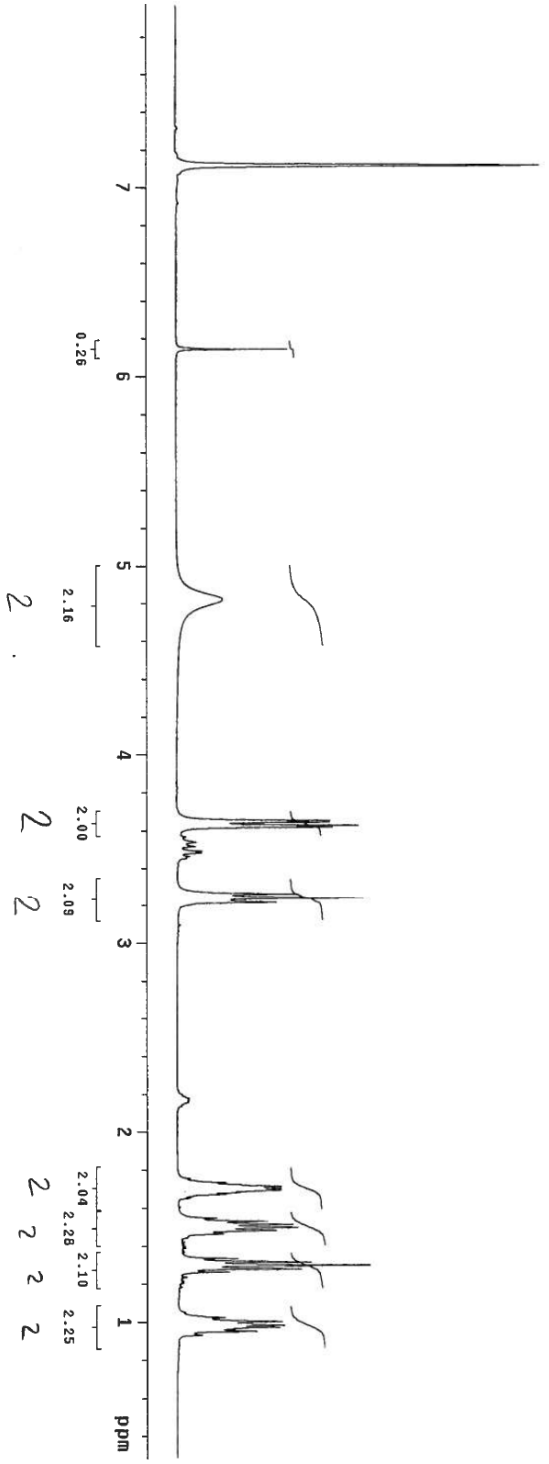
Spectrum A. 22 - ^{13}C NMR spectrum of **2.124**

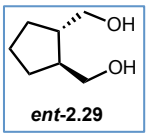




Spectrum A. 23 - NOESY spectrum of **2.124**

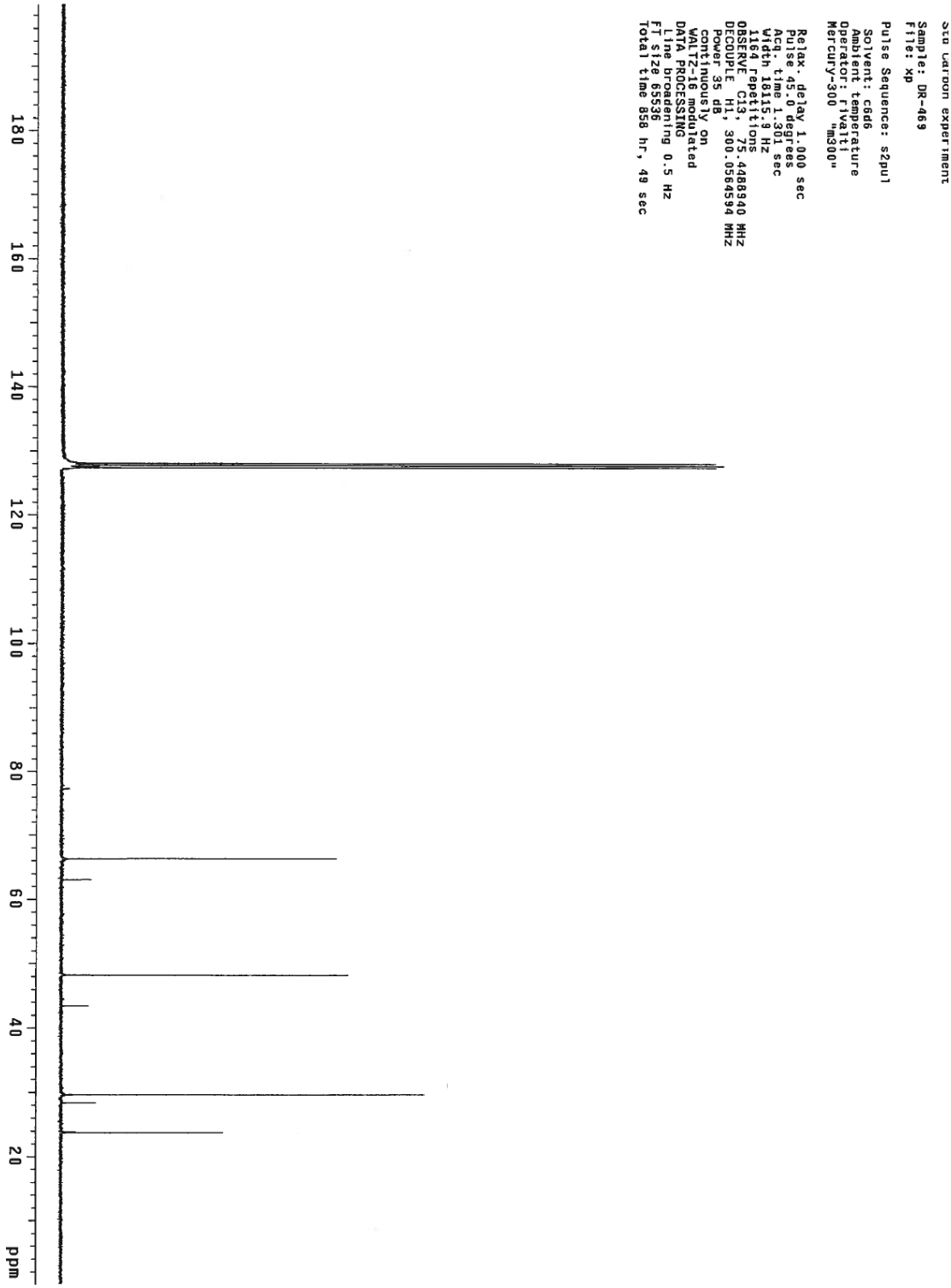




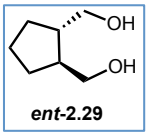


ent-**2.29**

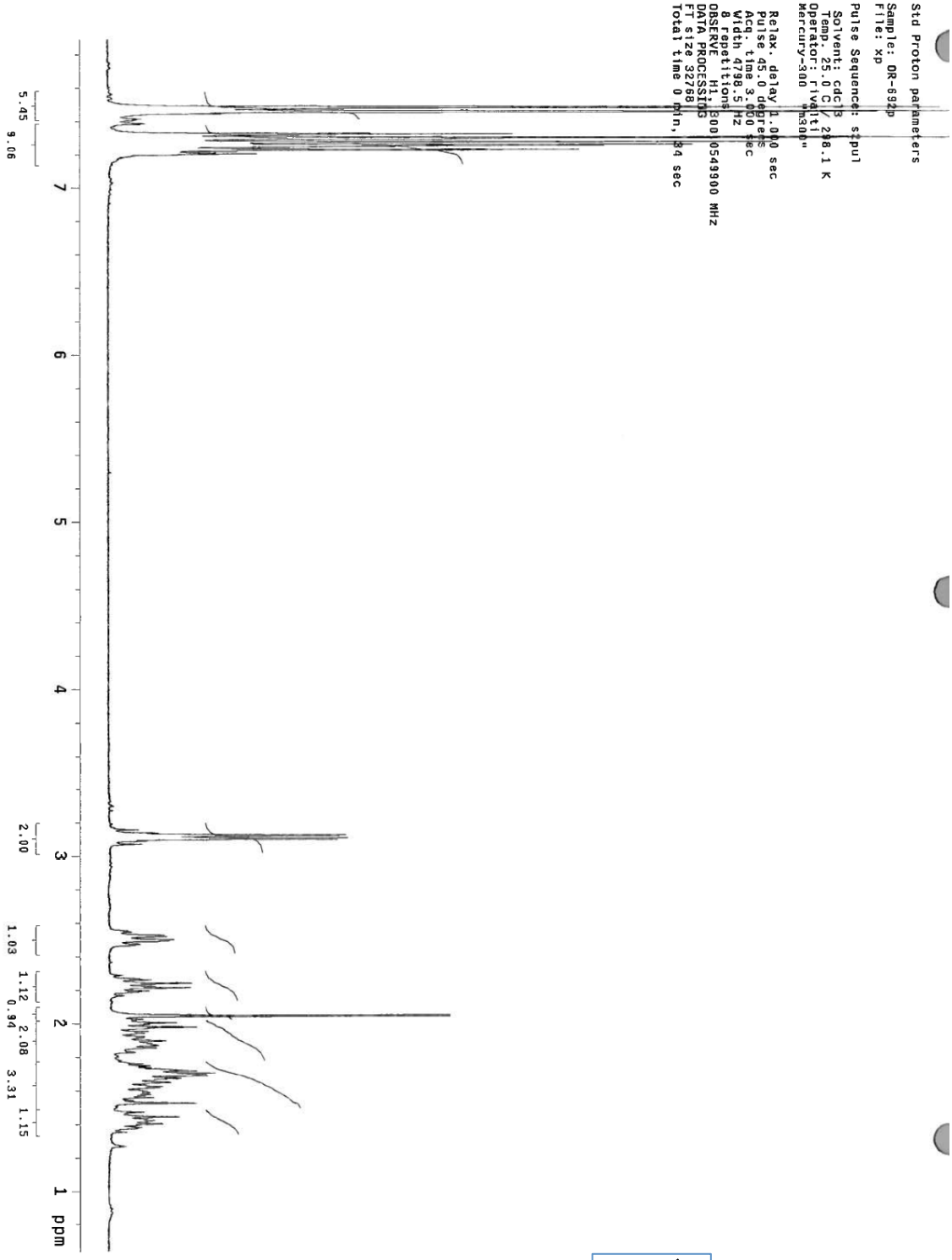
Spectrum A. 24 - ^{1}H NMR spectrum of *ent*-**2.29**



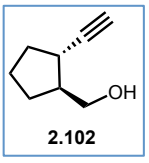
Spectrum A. 25 - ^{13}C NMR spectrum of *ent*-**2.29**



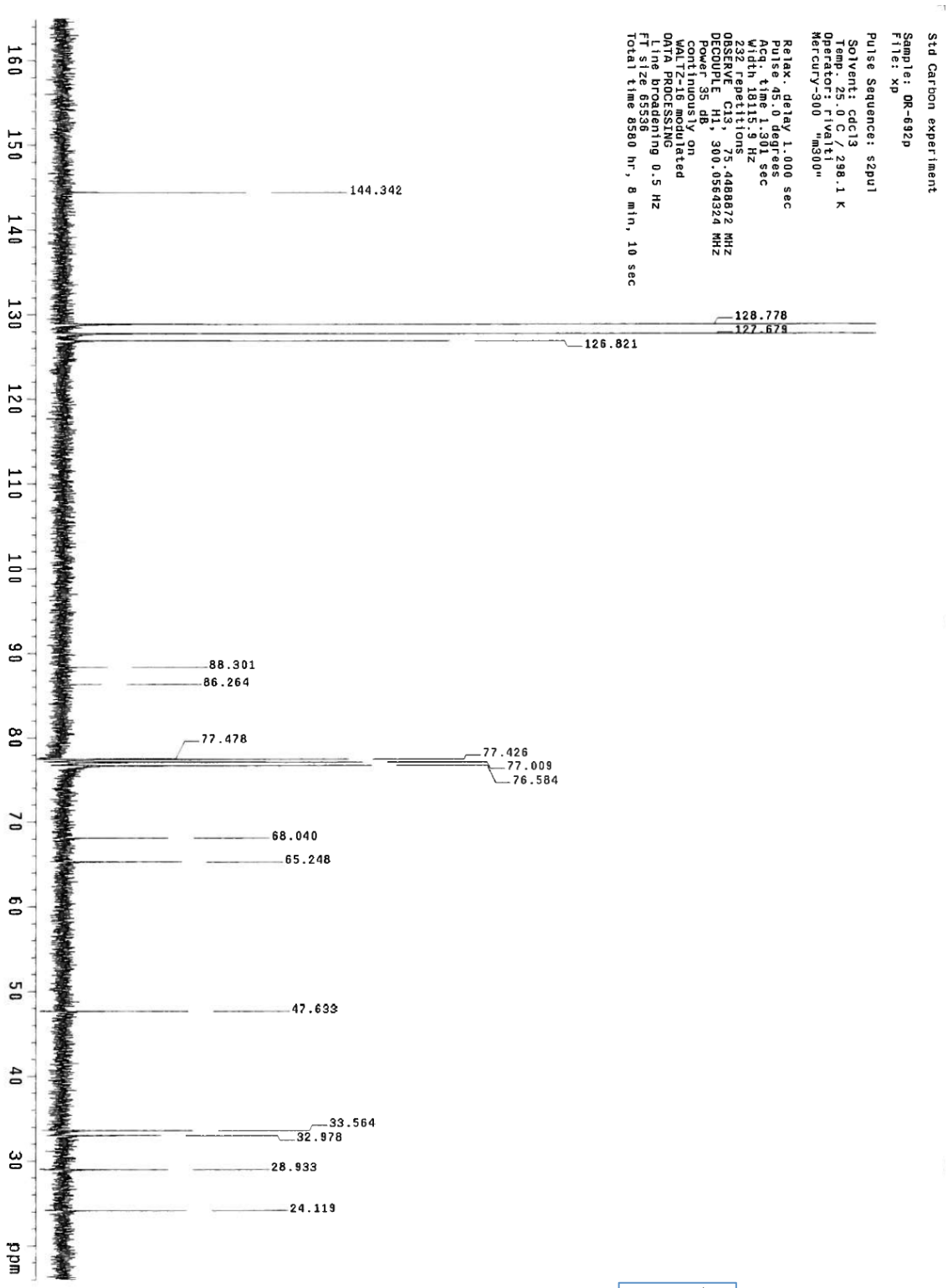
***ent*-2.29**



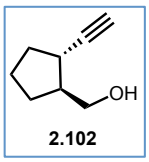
Spectrum A. 26 - ^{1}H NMR spectrum of **2.102**



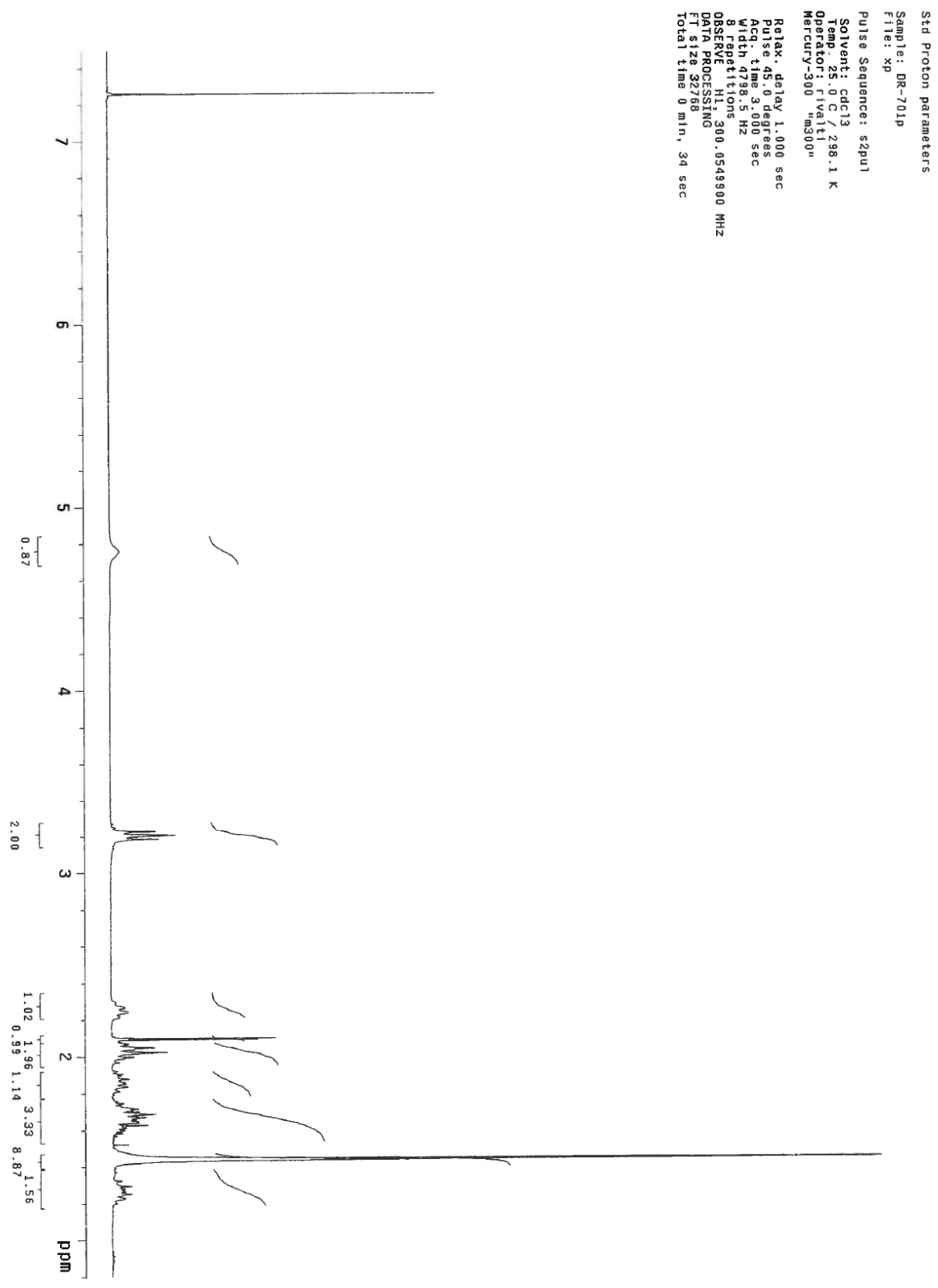
2.102



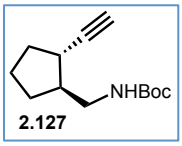
Spectrum A. 27 - ^{13}C NMR spectrum of **2.102**

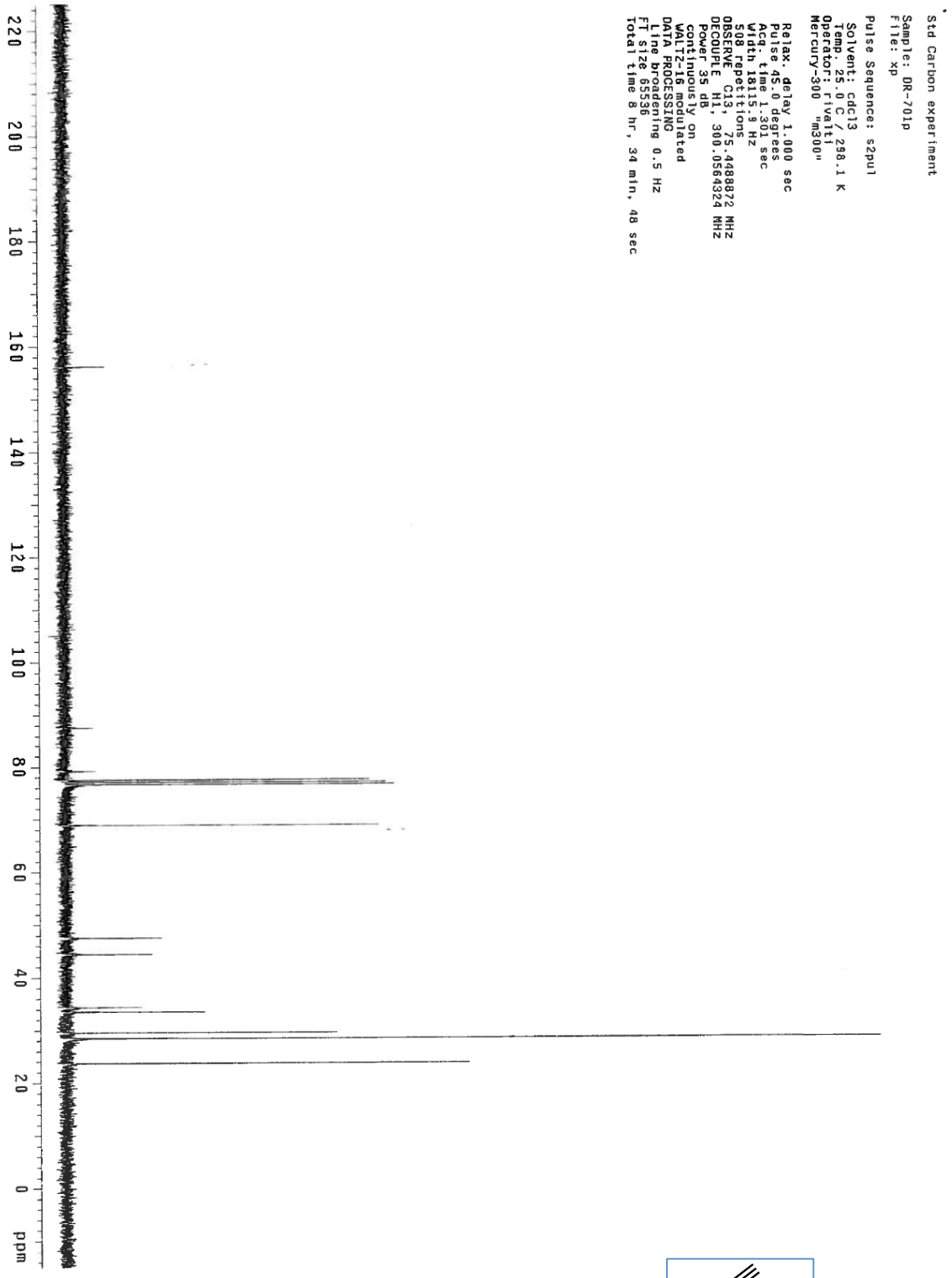


2.102

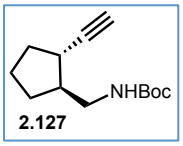


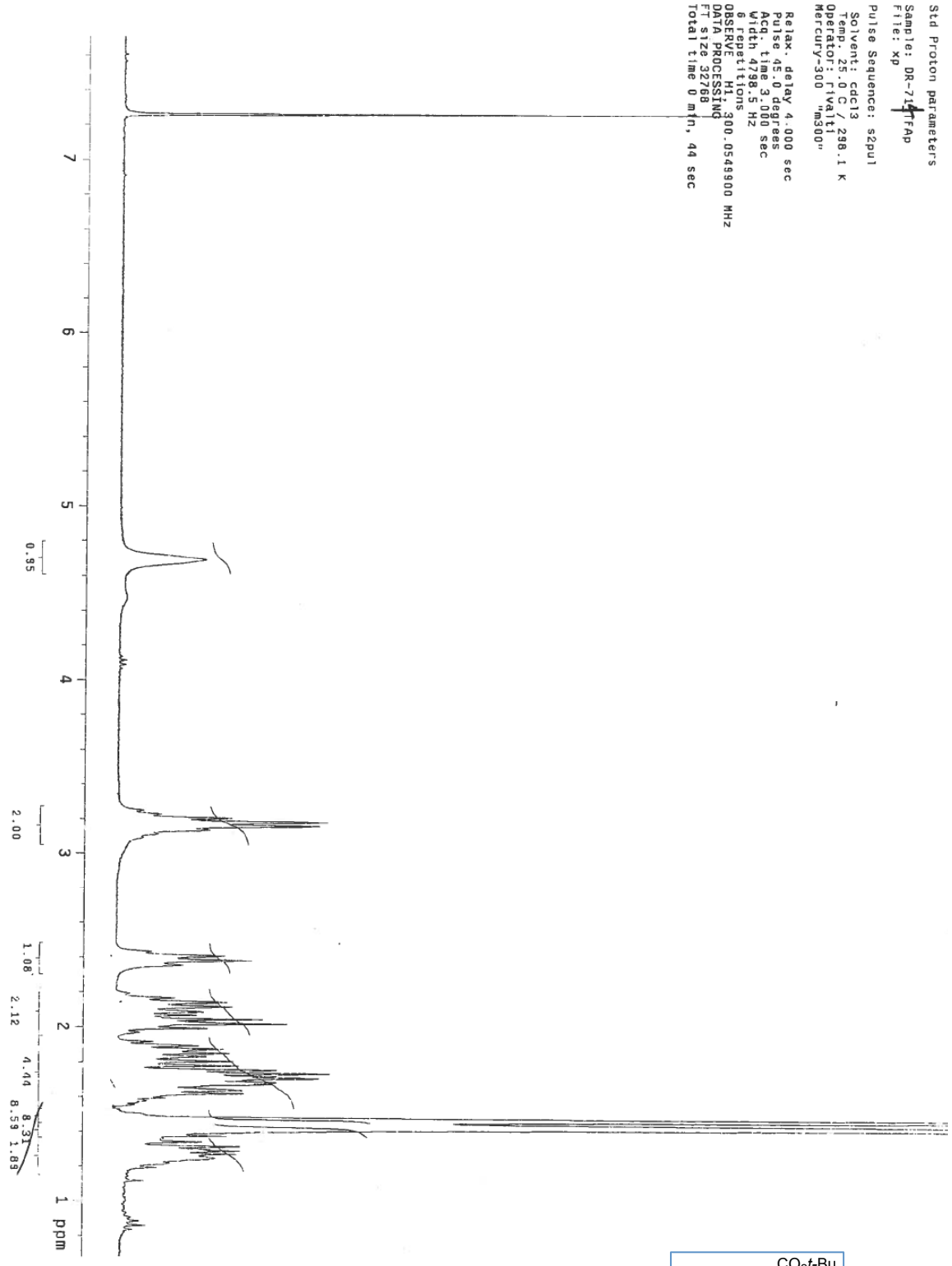
Spectrum A. 28 - ^{1}H NMR spectrum of **2.127**



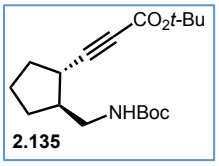


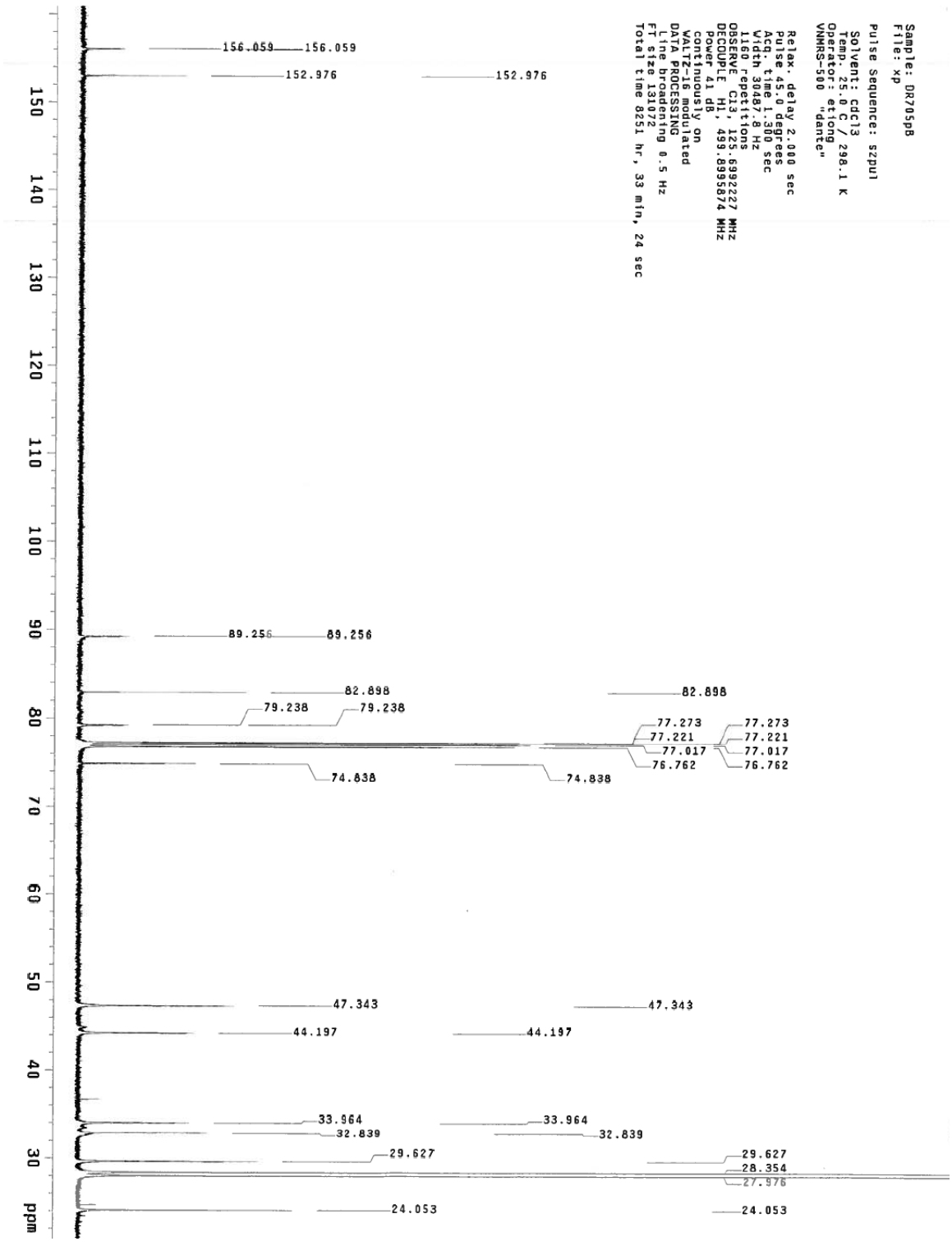
Spectrum A. 29 - ^{13}C NMR spectrum of **2.127**



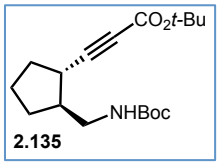


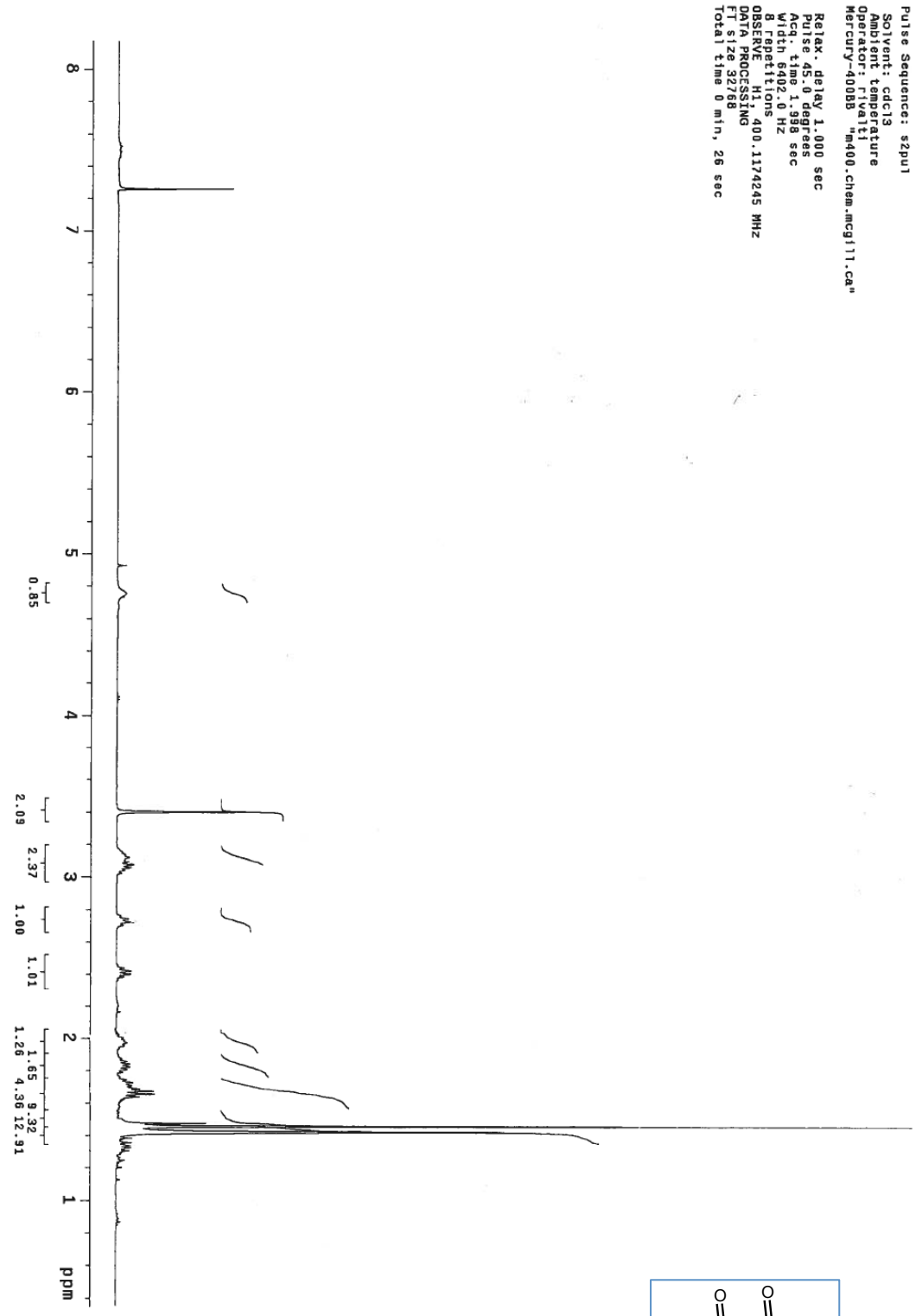
Spectrum A. 30 - ^{1}H NMR spectrum of **2.135**



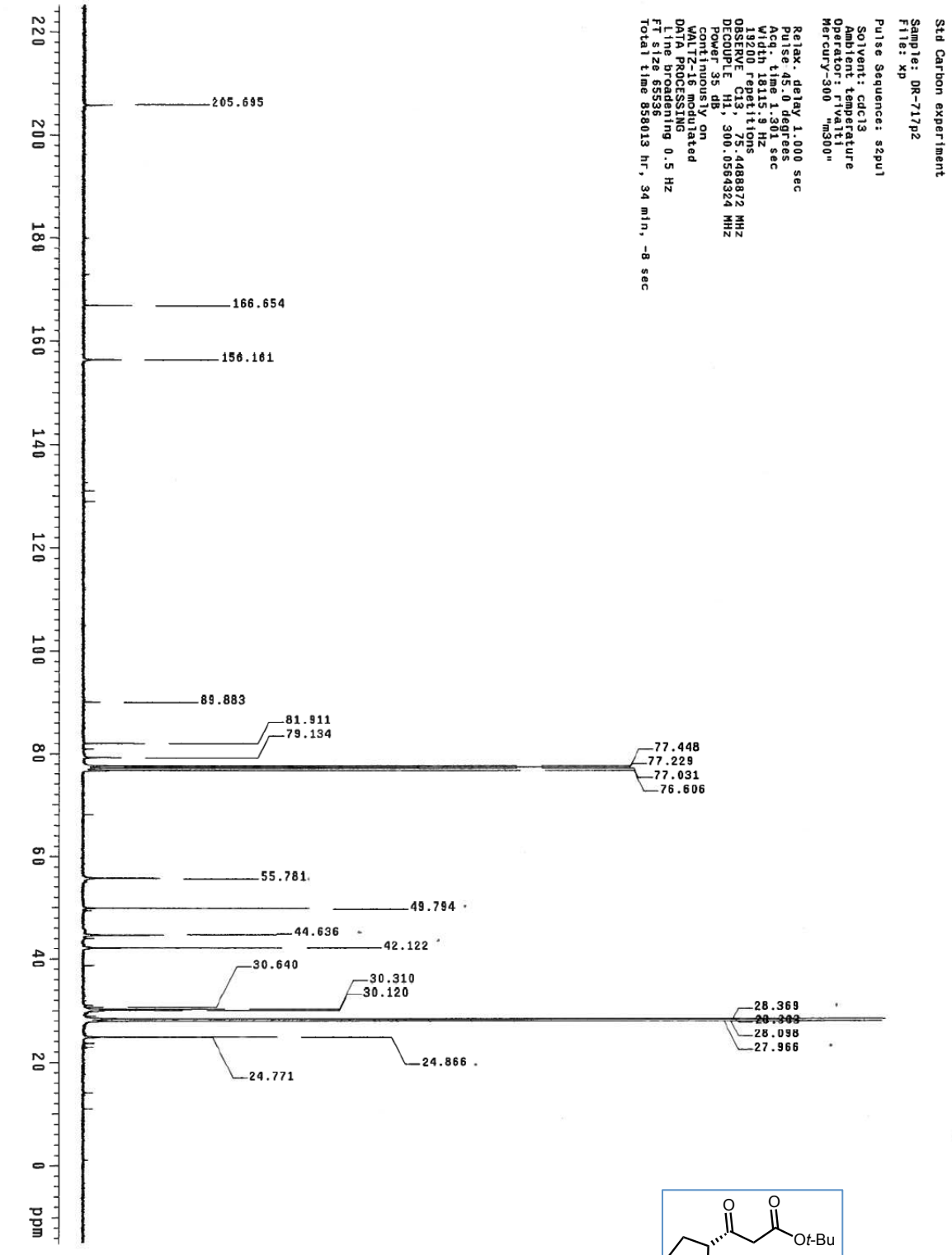


Spectrum A. 31 - ^{13}C NMR spectrum of **2.135**

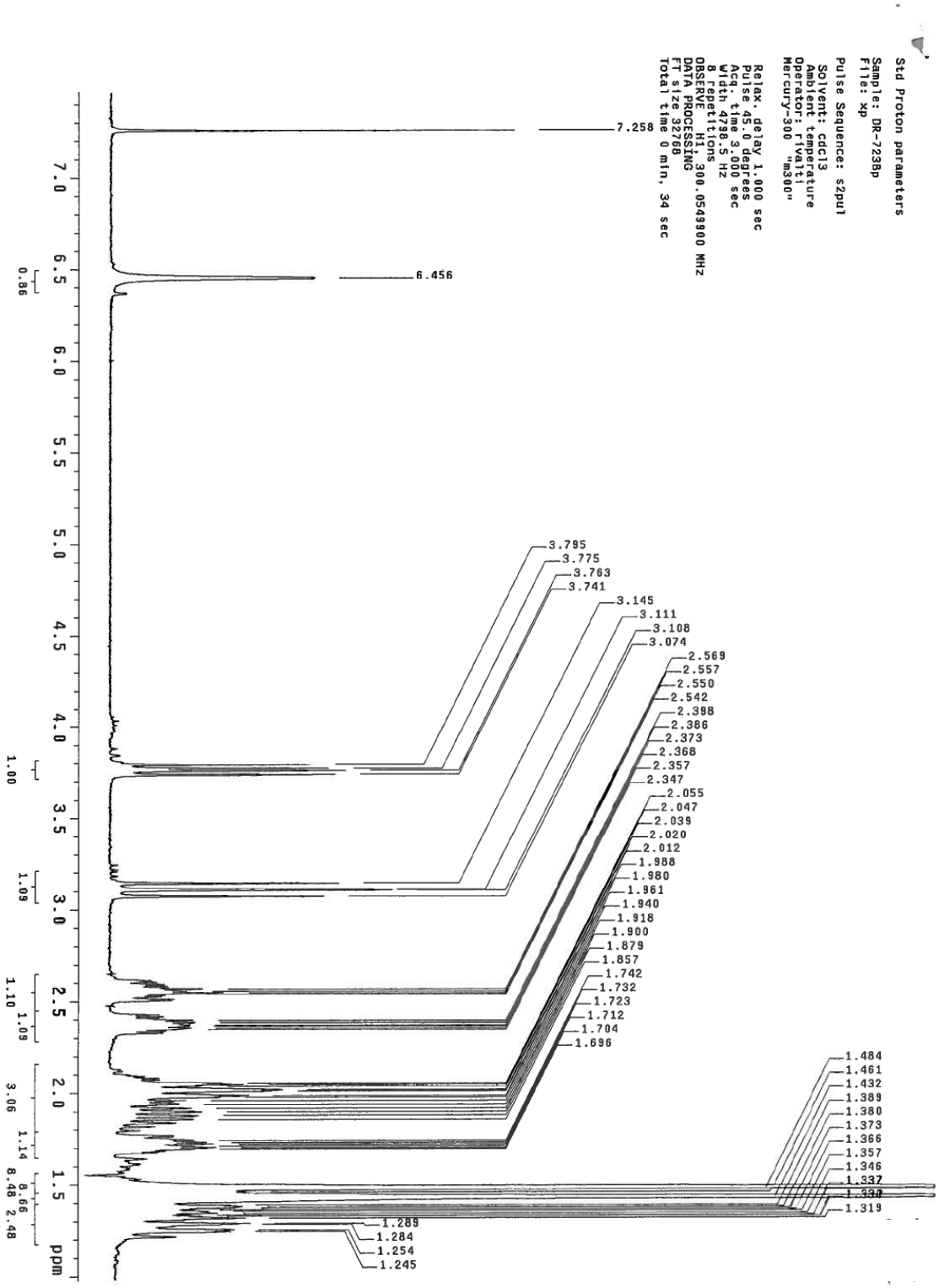


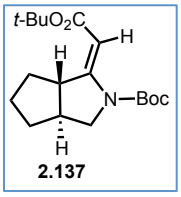


Spectrum A. 32 - ^{1}H NMR spectrum of **2.136**

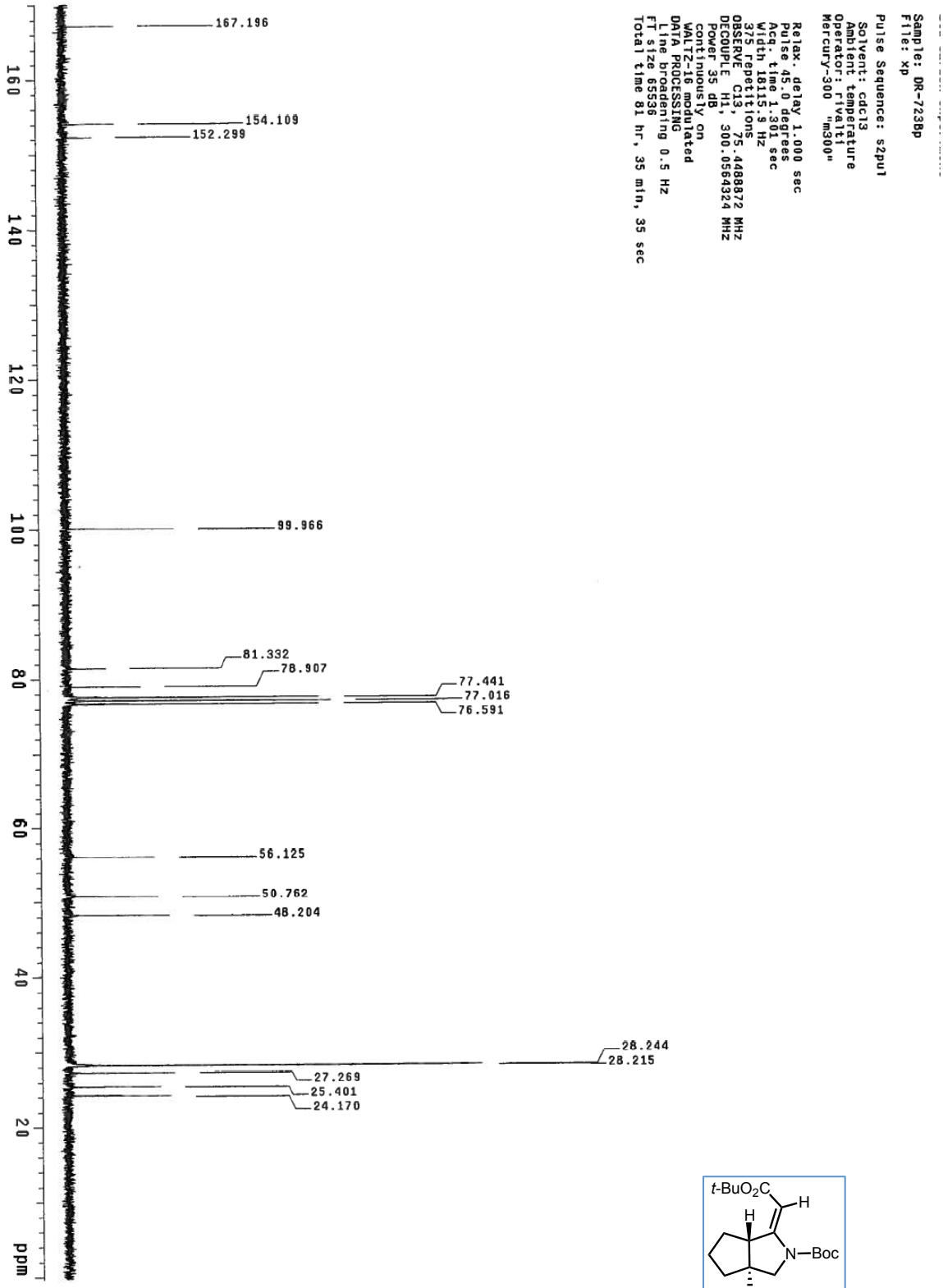


Spectrum A. 33 - ^{13}C NMR spectrum of **2.136**

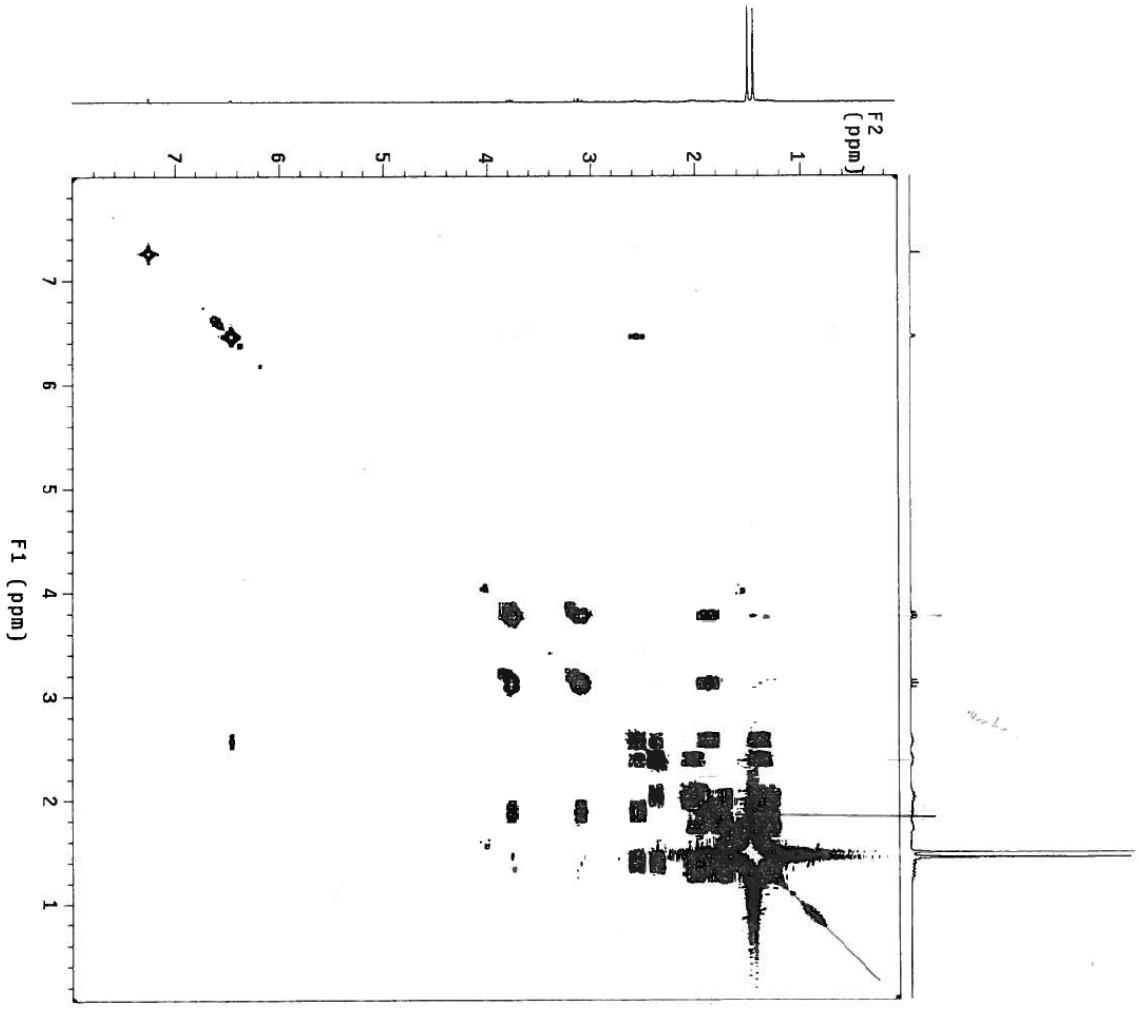




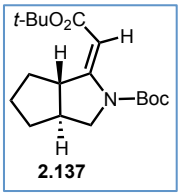
Spectrum A. 34 - ^{1}H NMR spectrum of **2.137**



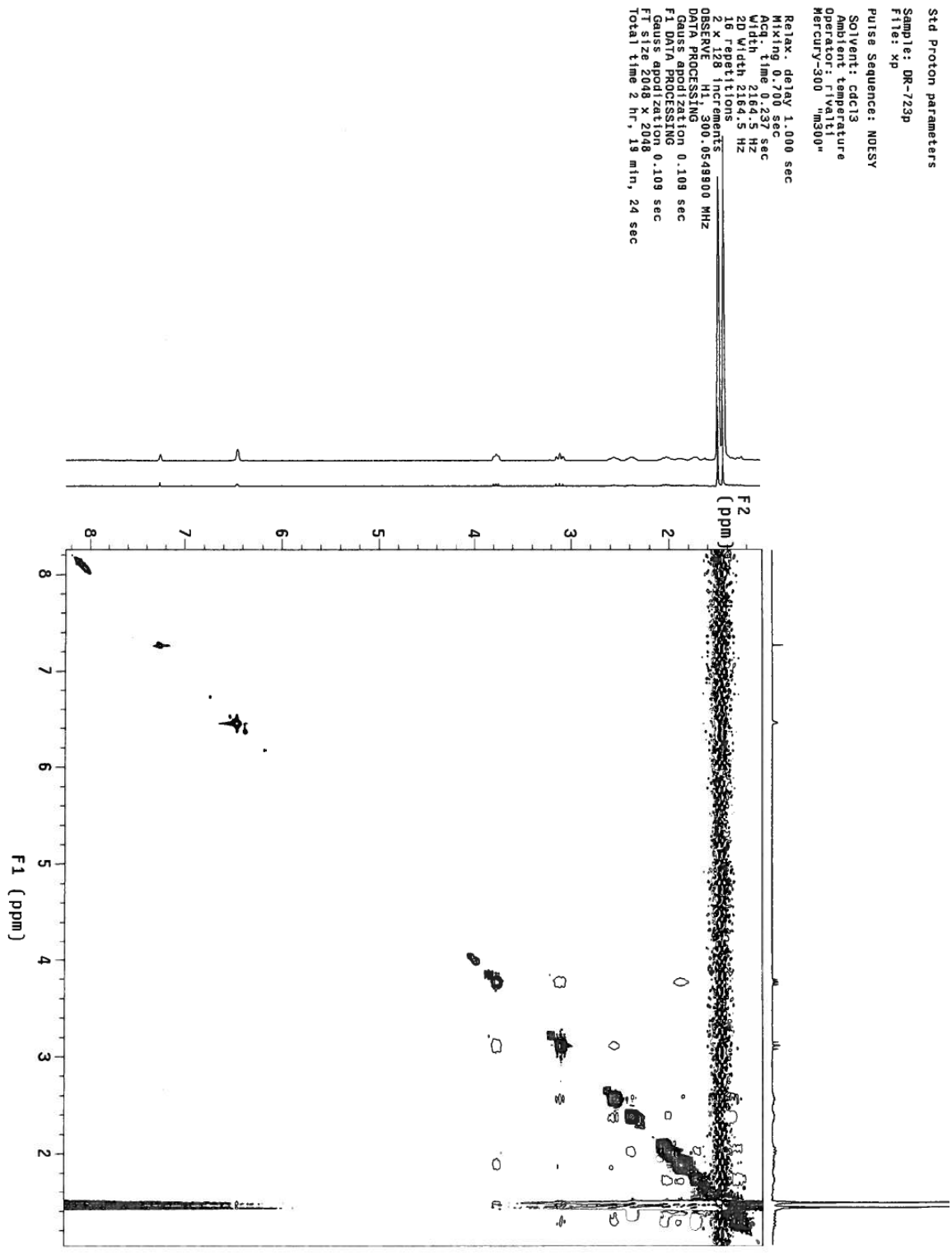
Spectrum A. 35 - ^{13}C NMR spectrum of **2.137**



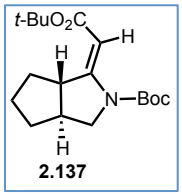
Spectrum A. 36 - COSY spectrum of **2.137**

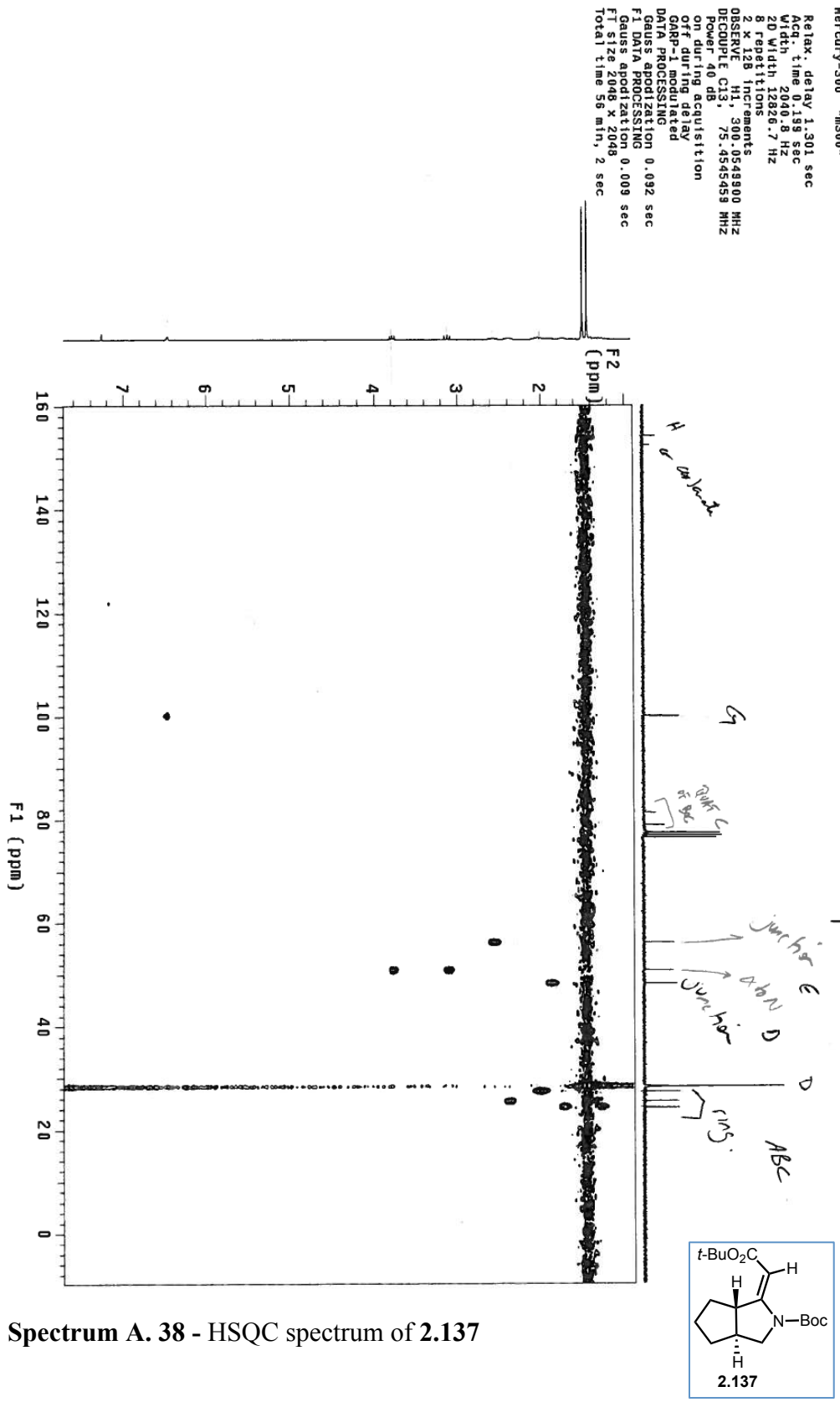


2.137

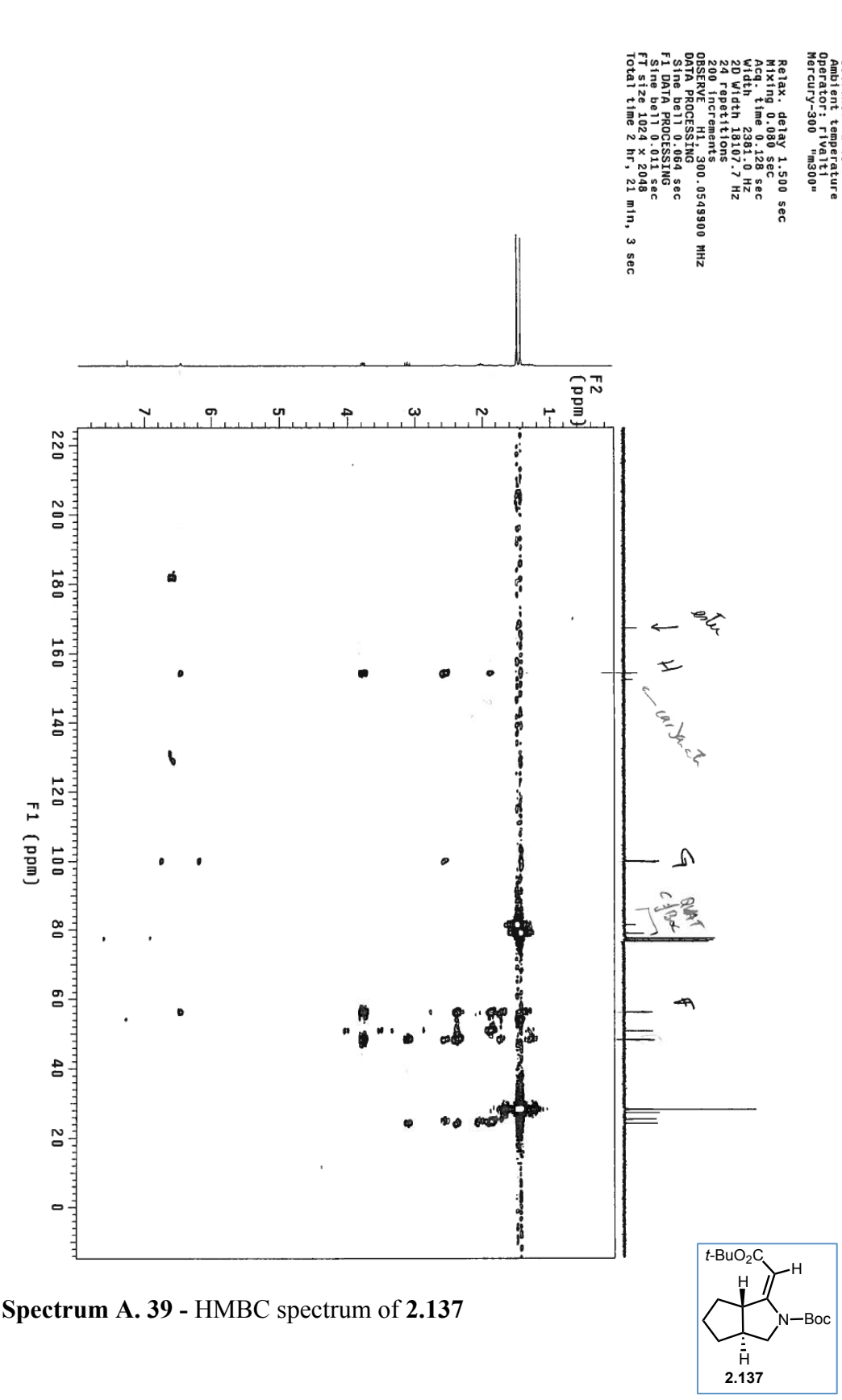


Spectrum A. 37 - NOESY spectrum of **2.137**

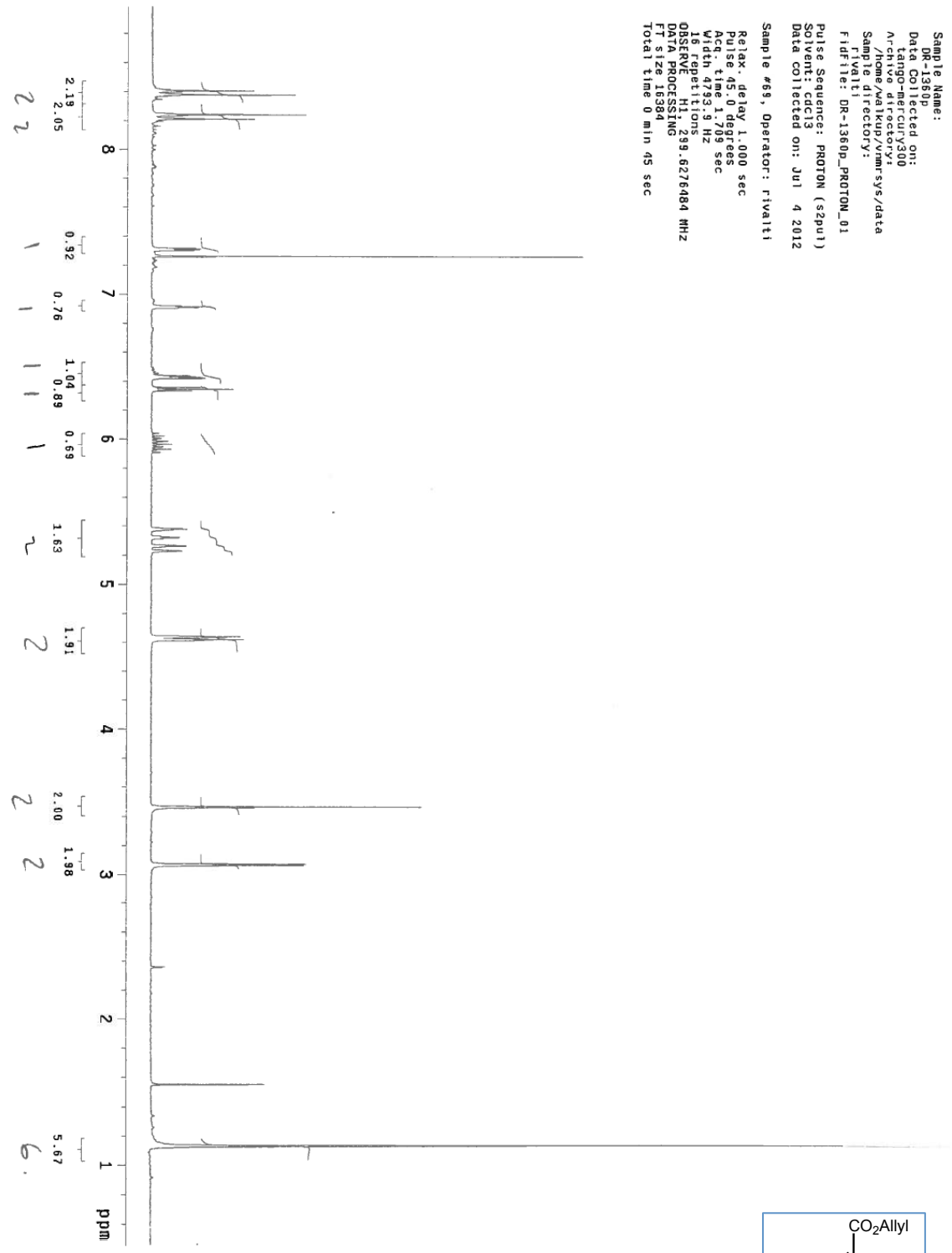




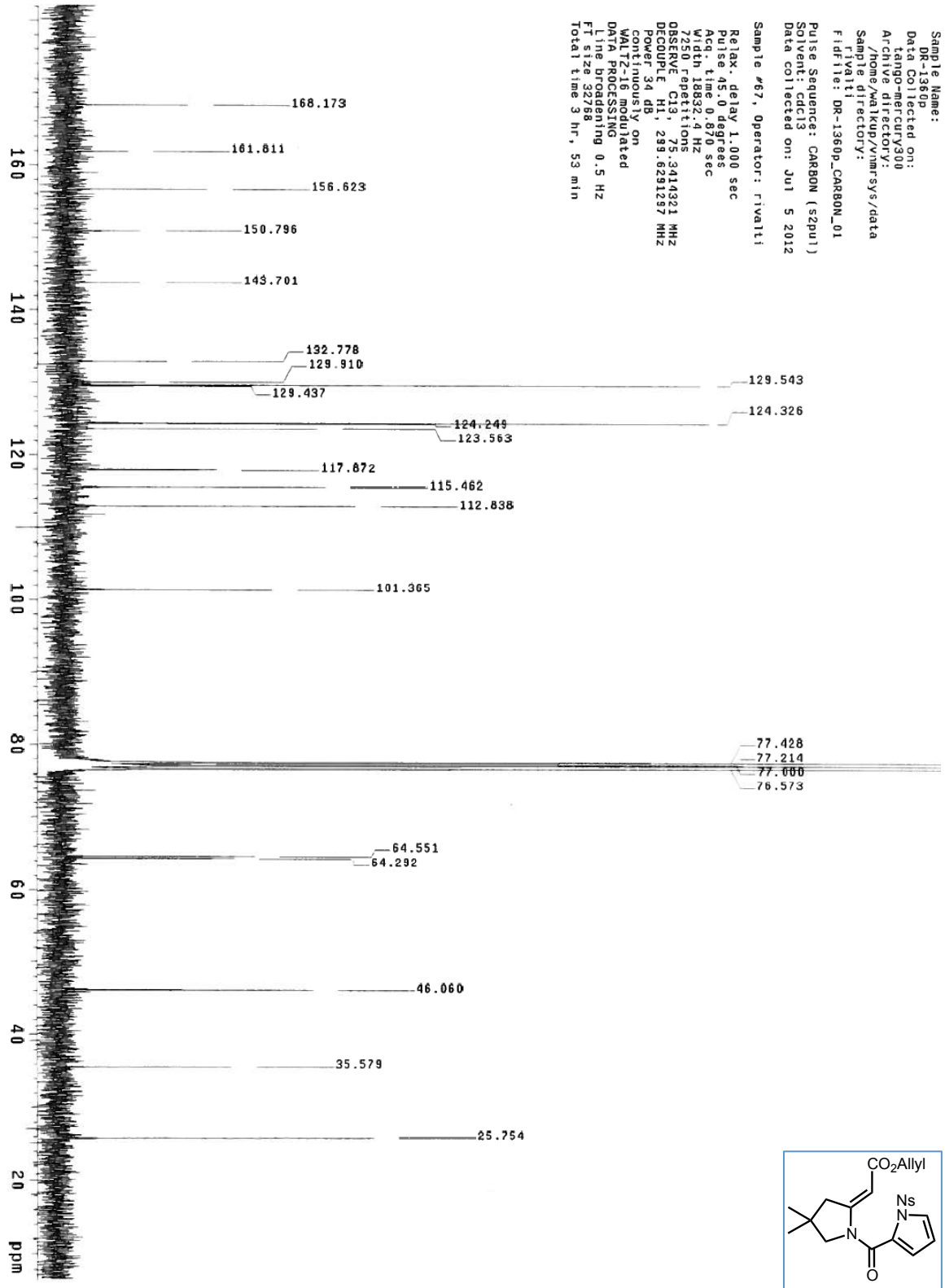
Spectrum A. 38 - HSQC spectrum of **2.137**



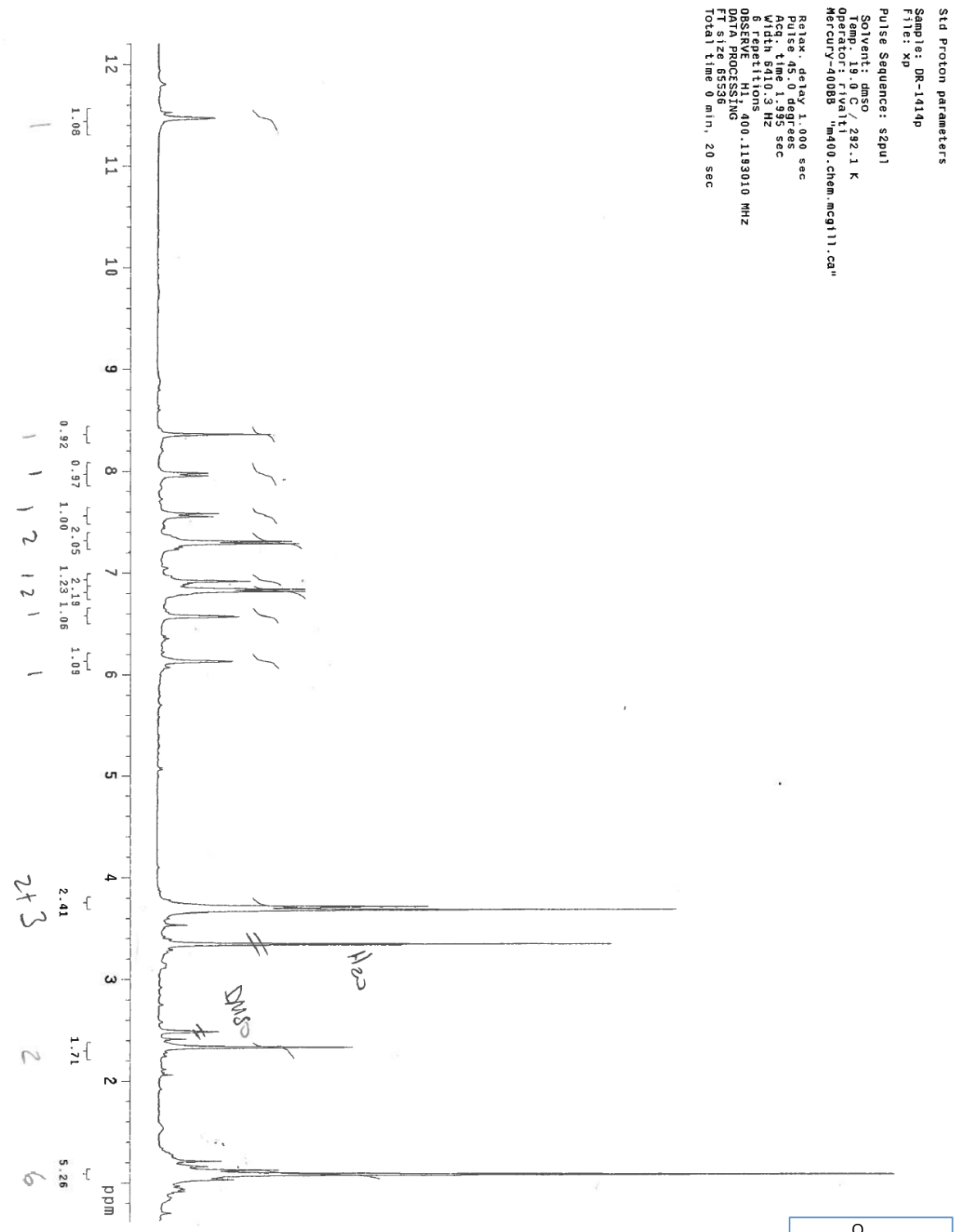
Spectrum A. 39 - HMBC spectrum of **2.137**



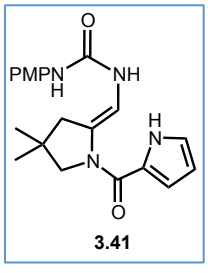
Spectrum A. 40 - ^{1}H NMR spectrum of **3.18**



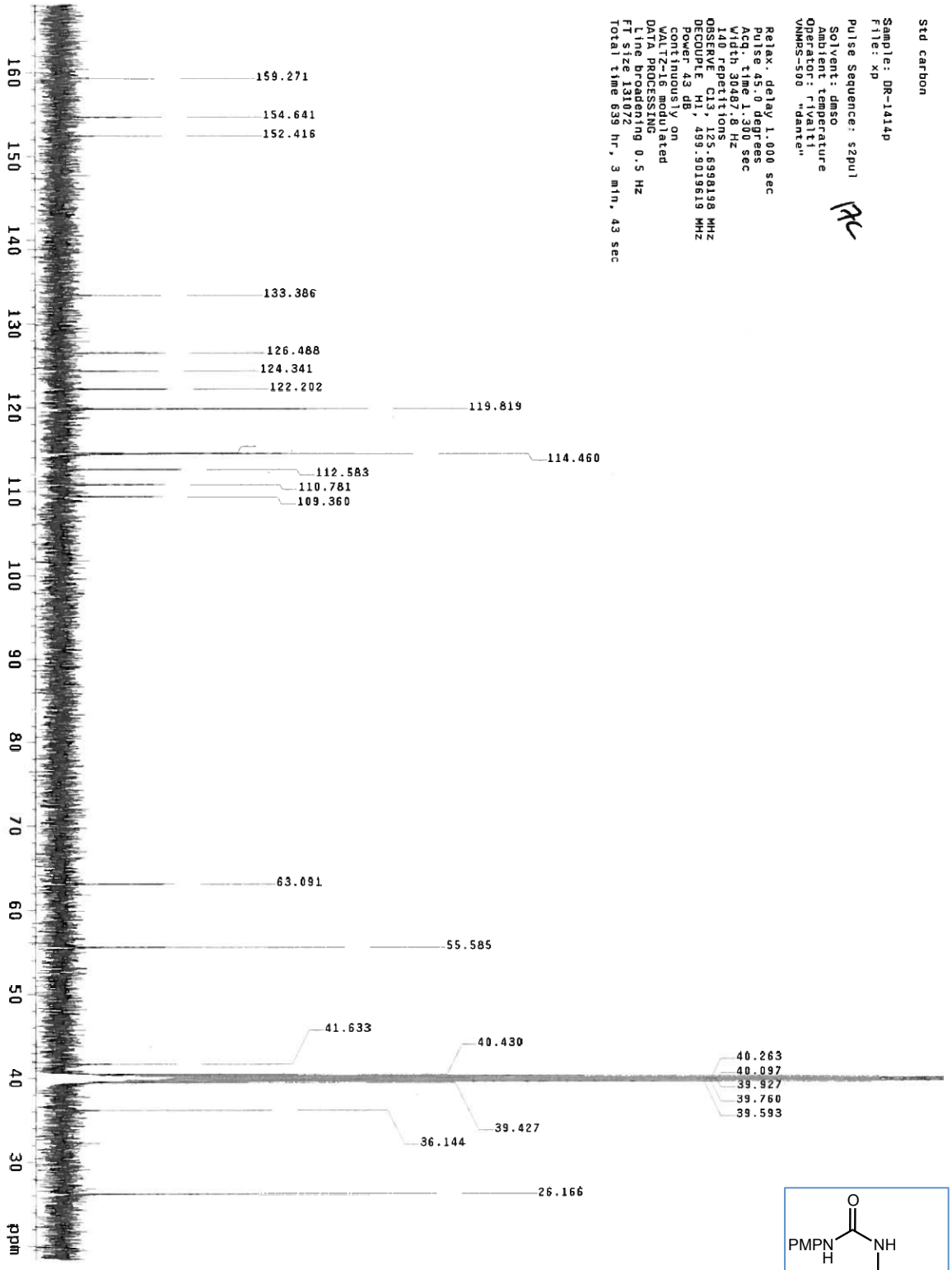
Spectrum A. 41 - ^{13}C NMR spectrum of **3.18**



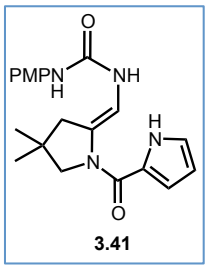
Spectrum A. 42 - ^{1}H NMR spectrum of **3.41**



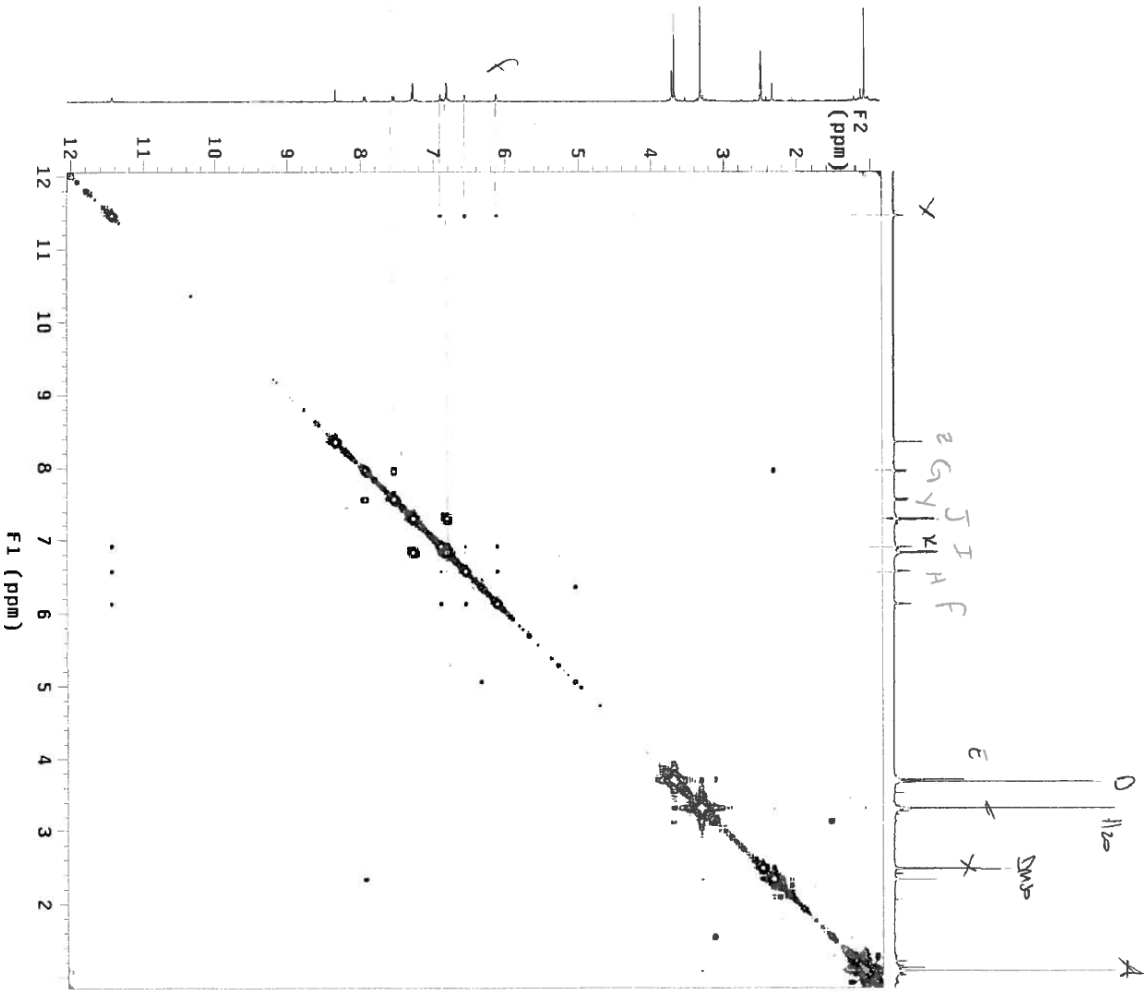
3.41



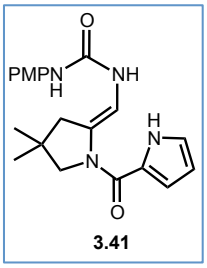
Spectrum A. 43 - ^{13}C NMR spectrum of **3.41**

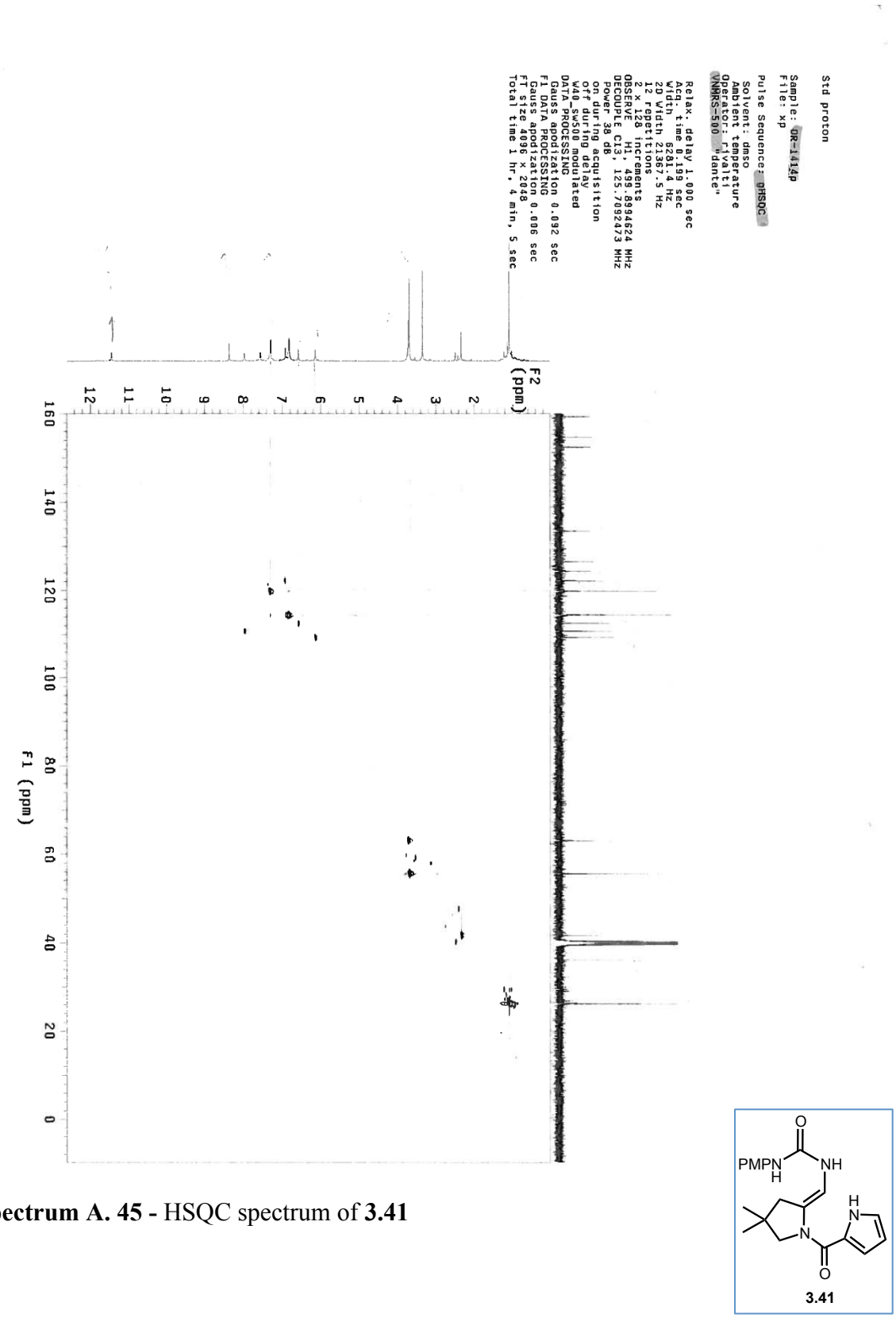


3.41

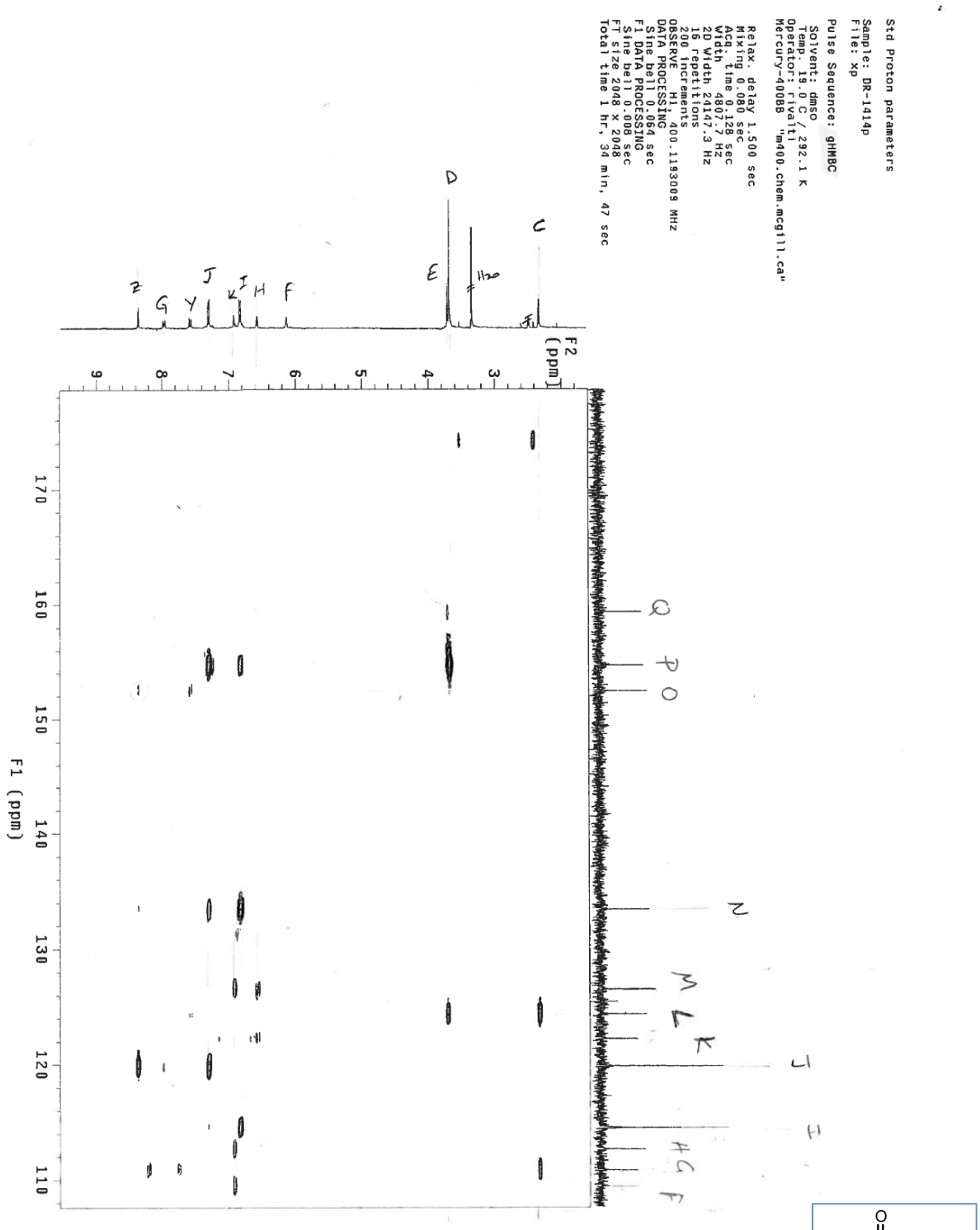


Spectrum A. 44 - COSY spectrum of **3.41**

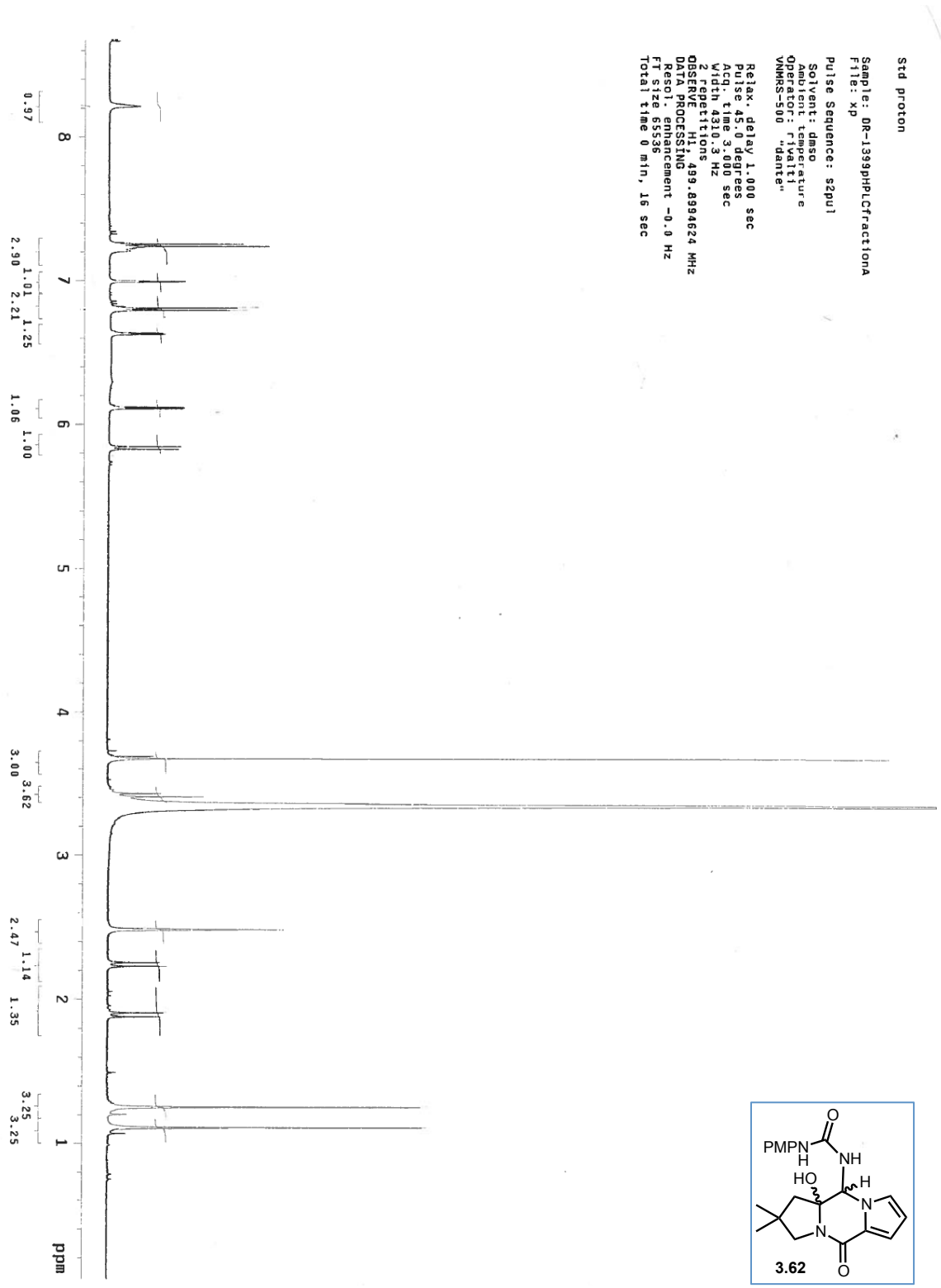




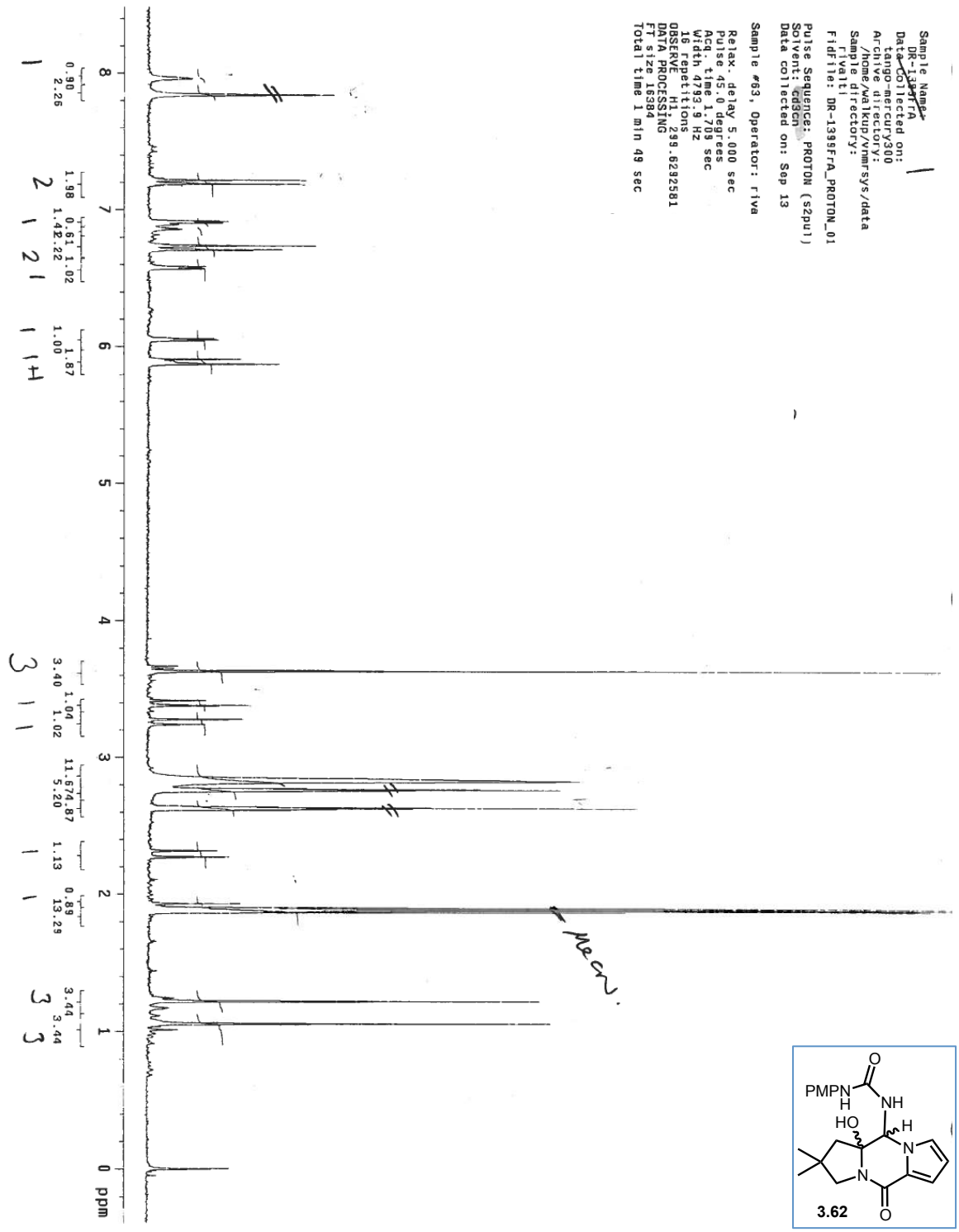
Spectrum A. 45 - HSQC spectrum of **3.41**



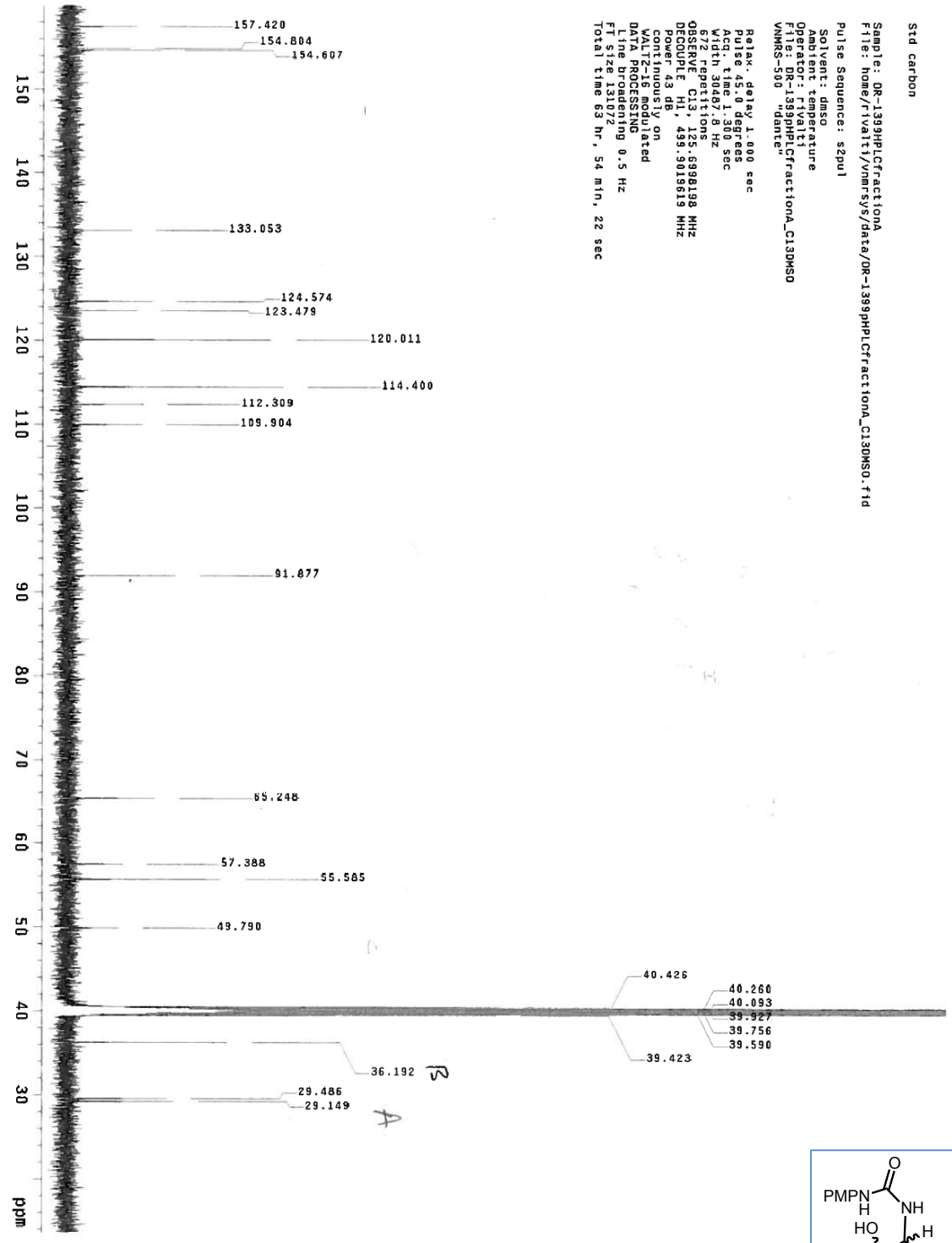
Spectrum A. 46 - HMBC spectrum of **3.41**



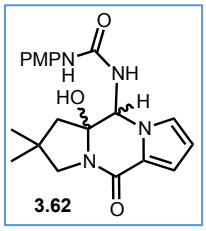
Spectrum A. 47 - ^{1}H NMR spectrum of **3.62** (diasteriomer A) in d_6-DMSO

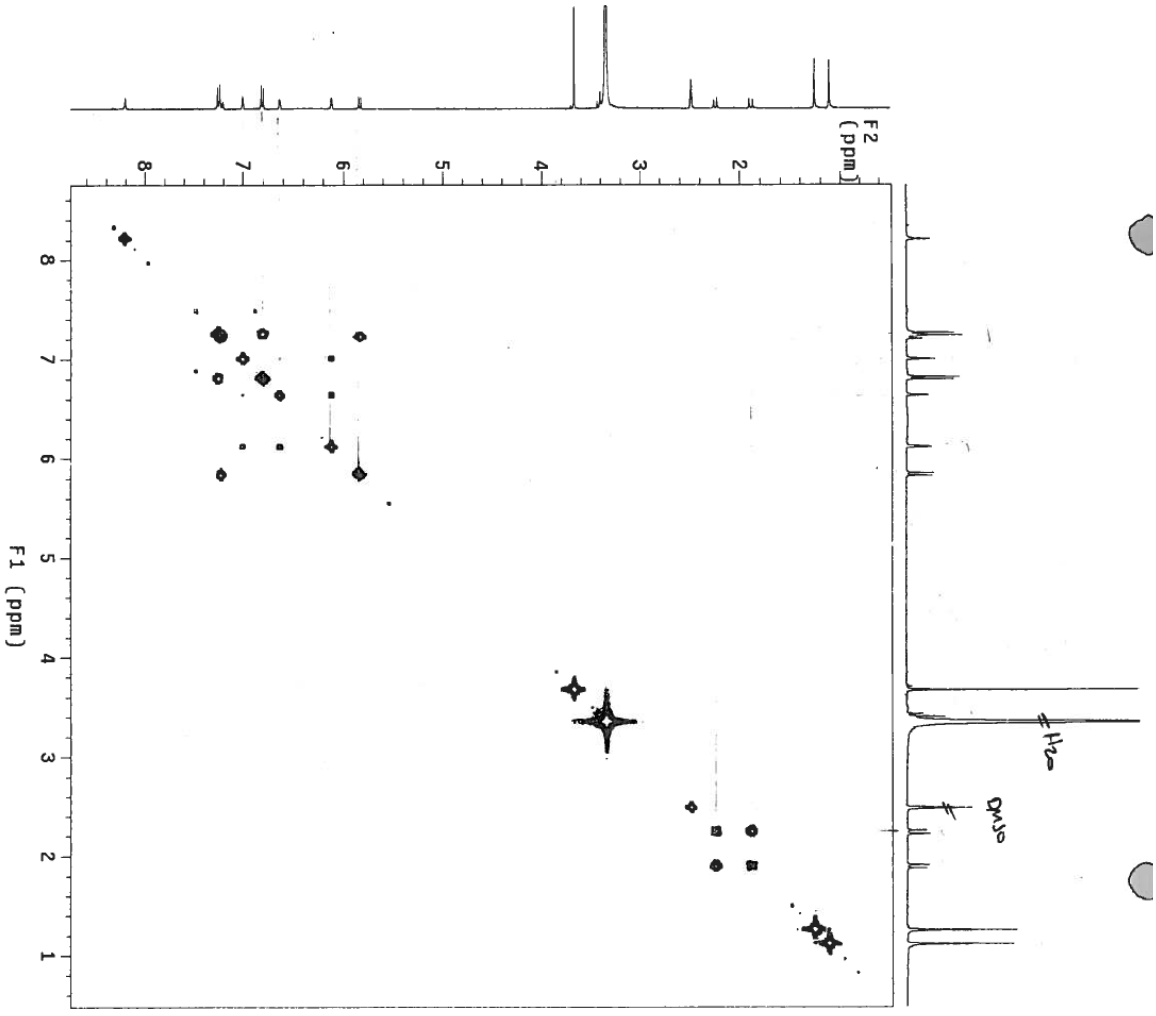


Spectrum A. 48 - ^{1}H NMR spectrum of **3.62** (diasteriomer A) in d_3-MeCN

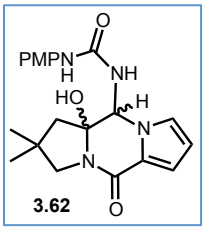


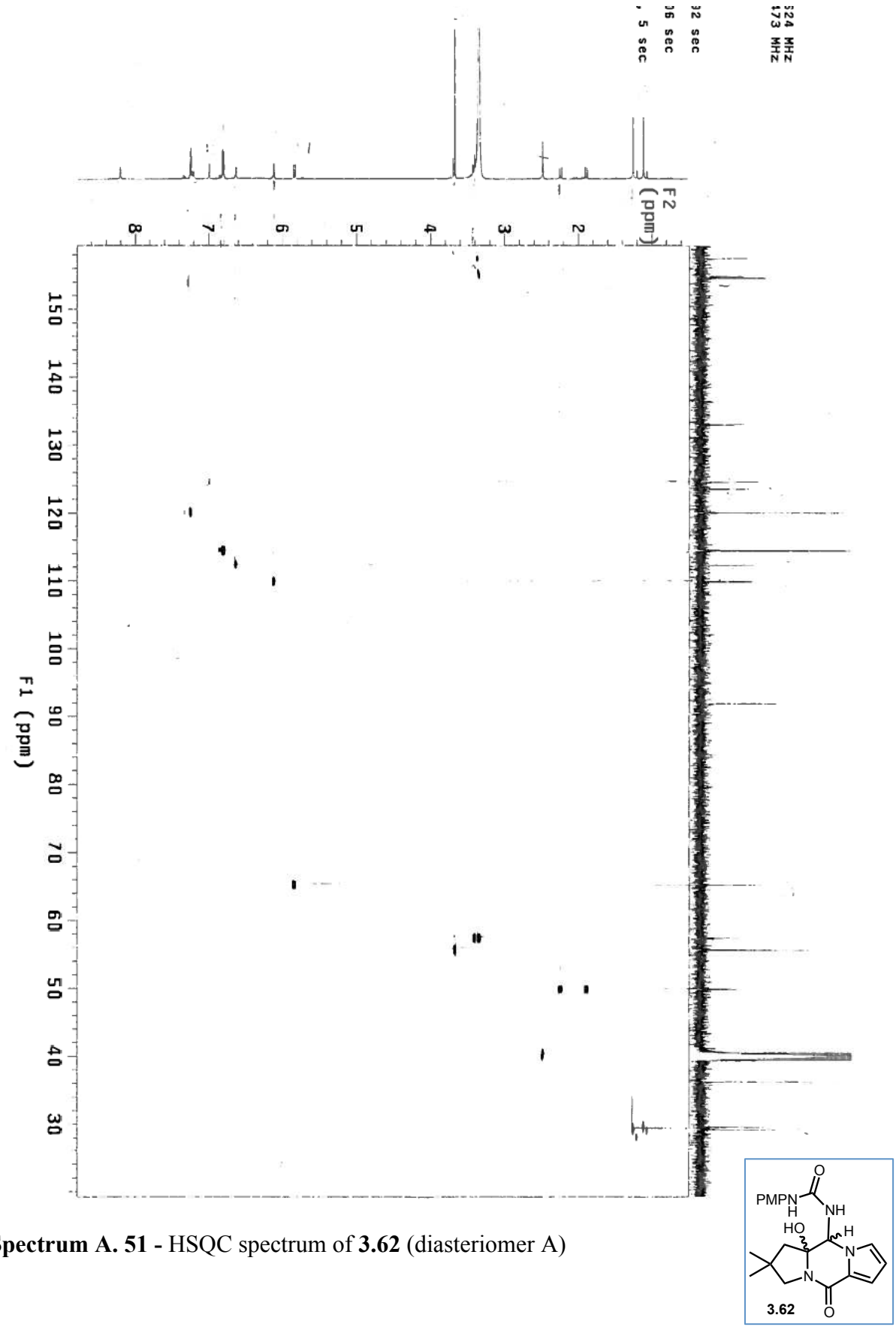
Spectrum A. 49 - ^{13}C NMR spectrum of **3.62** (diasteriomer A)



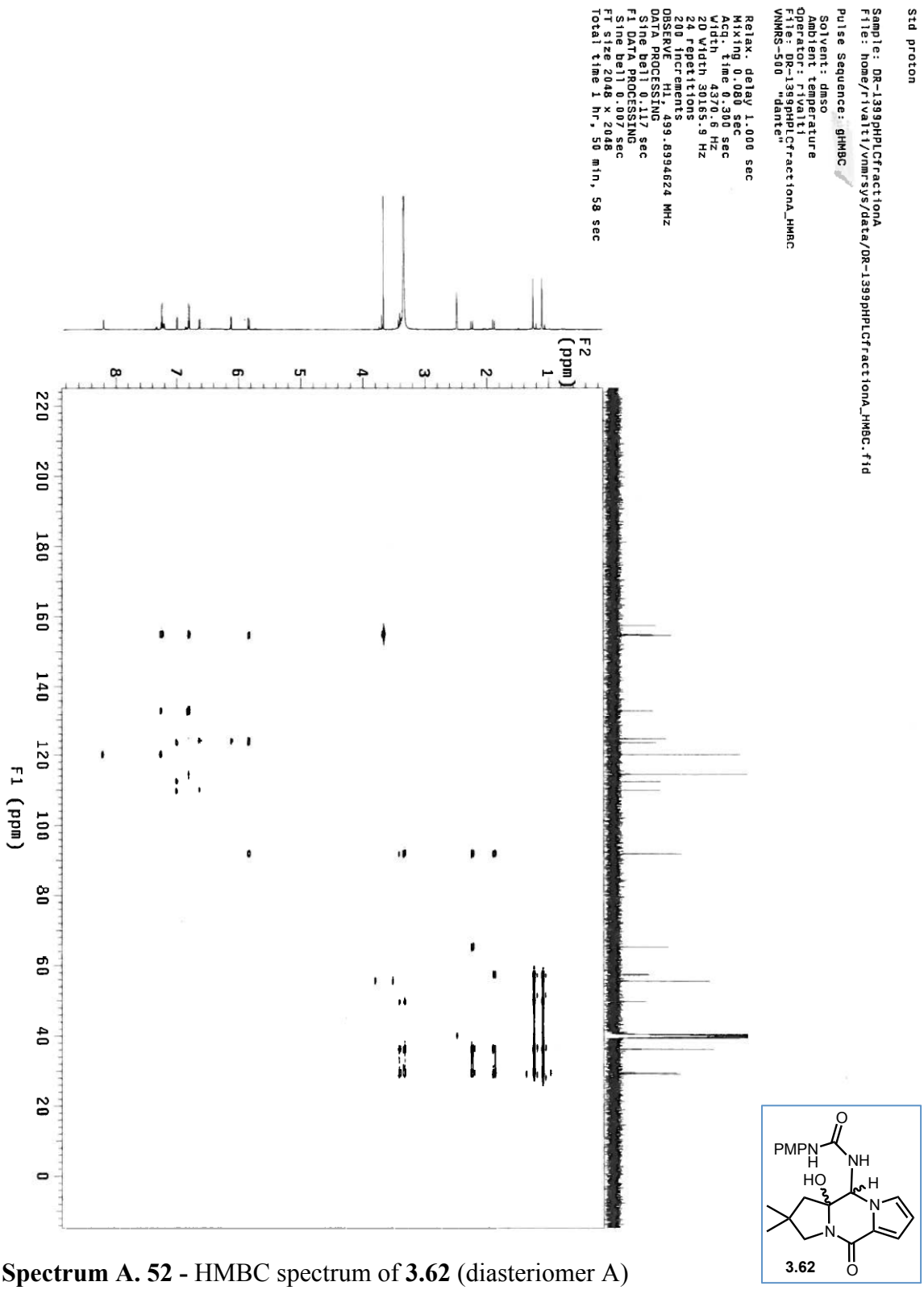


Spectrum A. 50 - COSY spectrum of **3.62** (diasteriomer A)

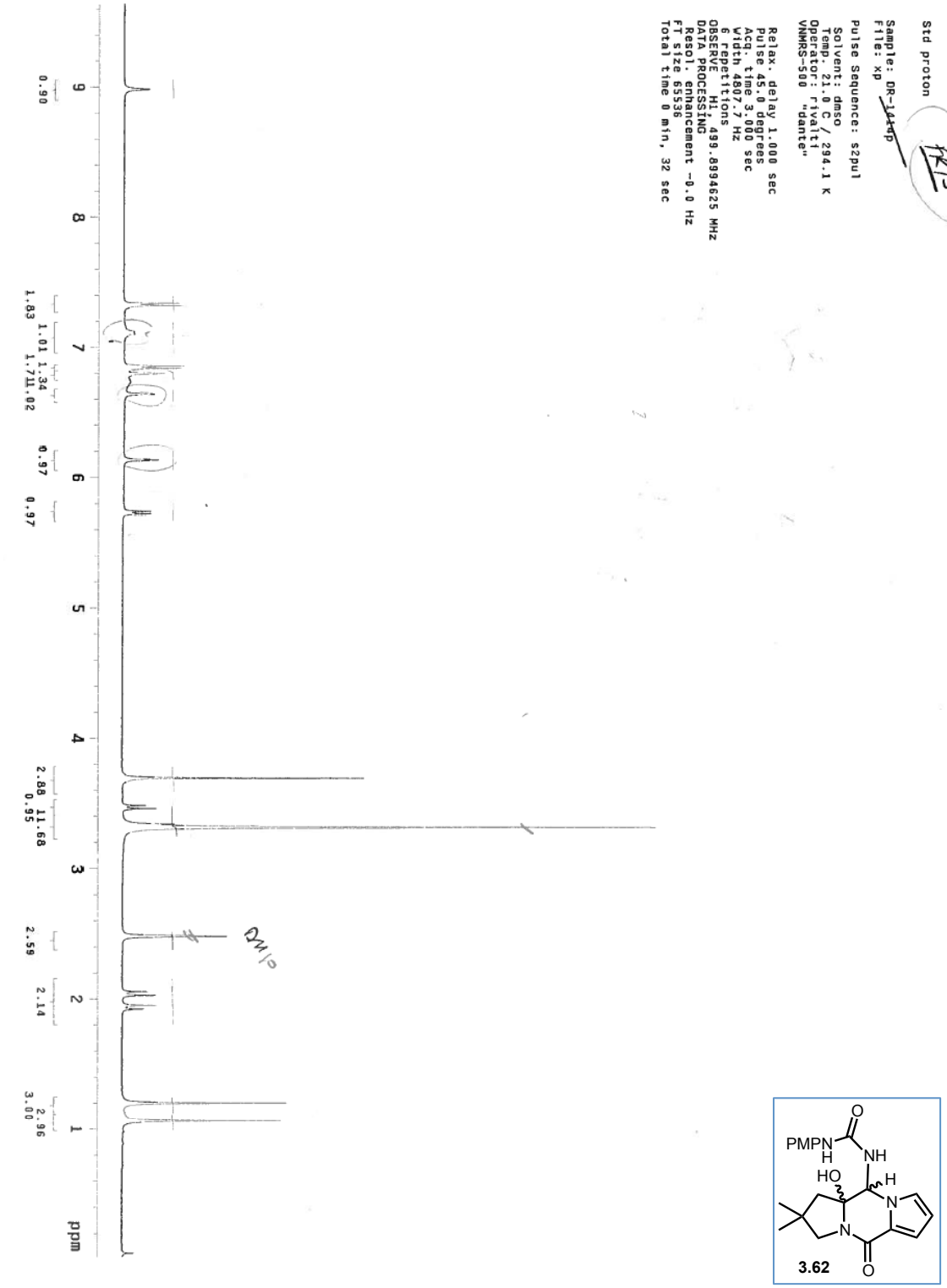




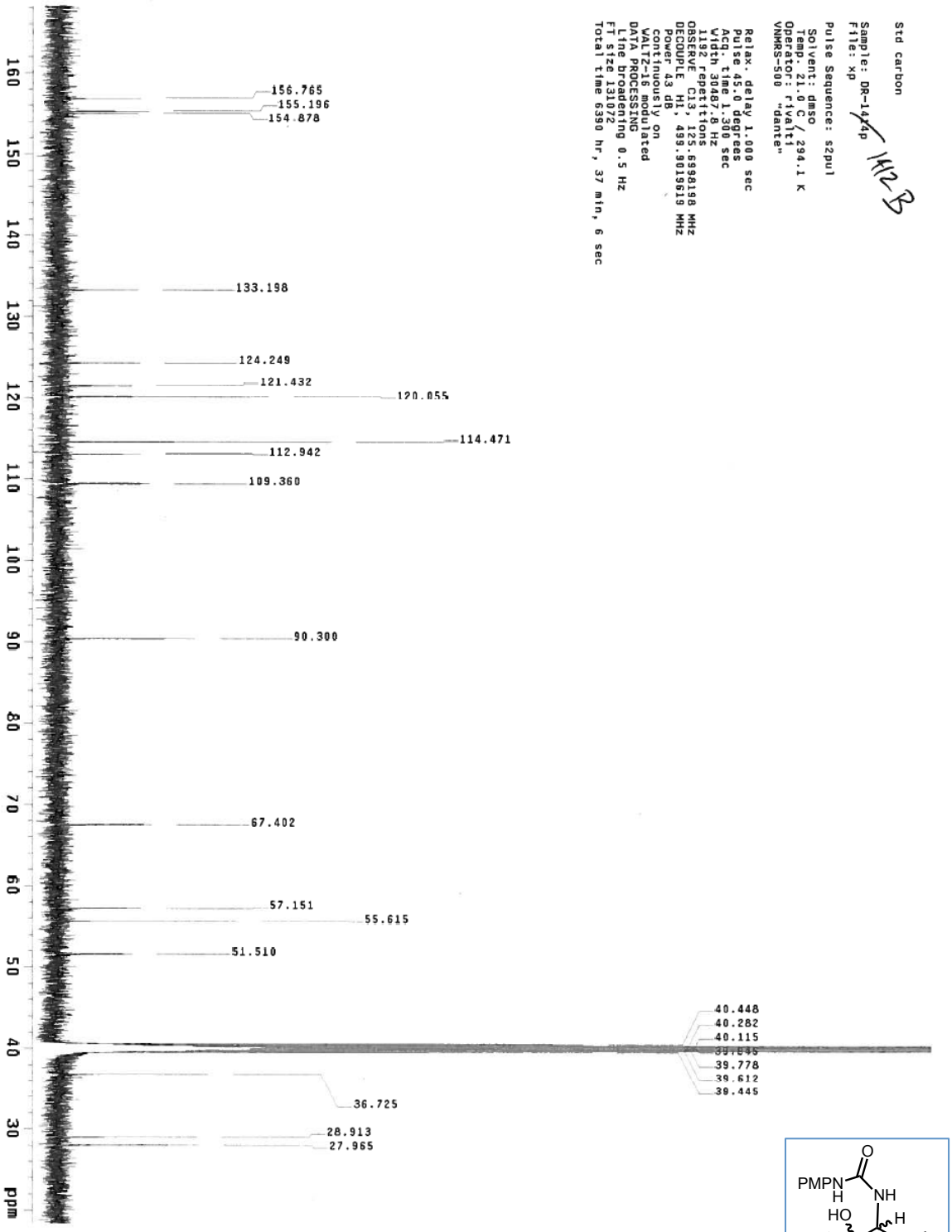
Spectrum A. 51 - HSQC spectrum of **3.62** (diasteriomer A)



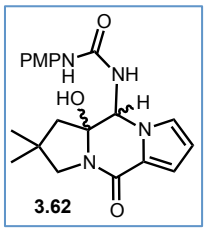
Spectrum A. 52 - HMBC spectrum of **3.62** (diasteriomer A)

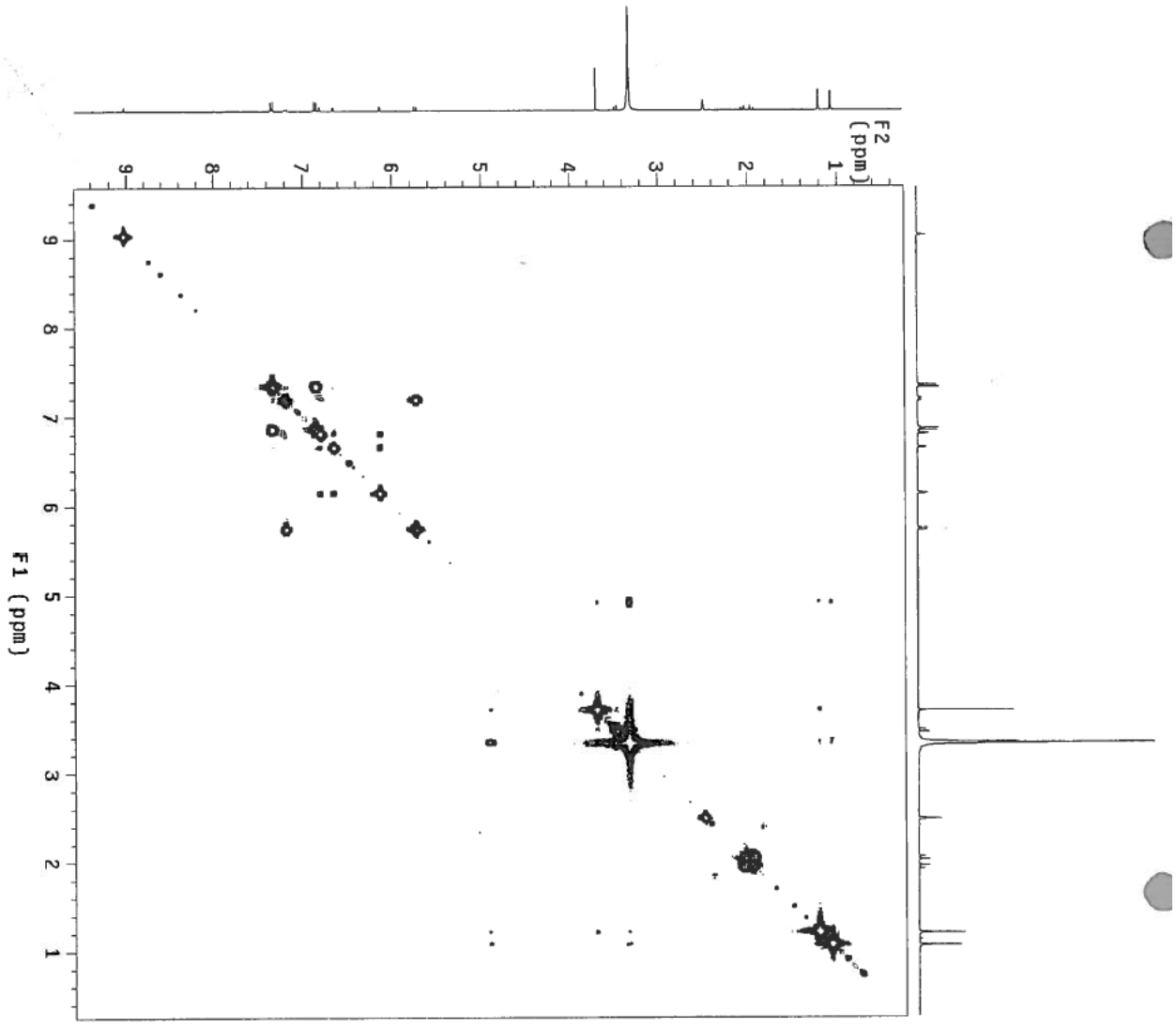


Spectrum A. 53 - ^{1}H NMR spectrum of **3.62** (diasteriomer B)

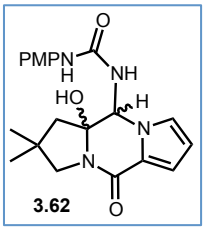


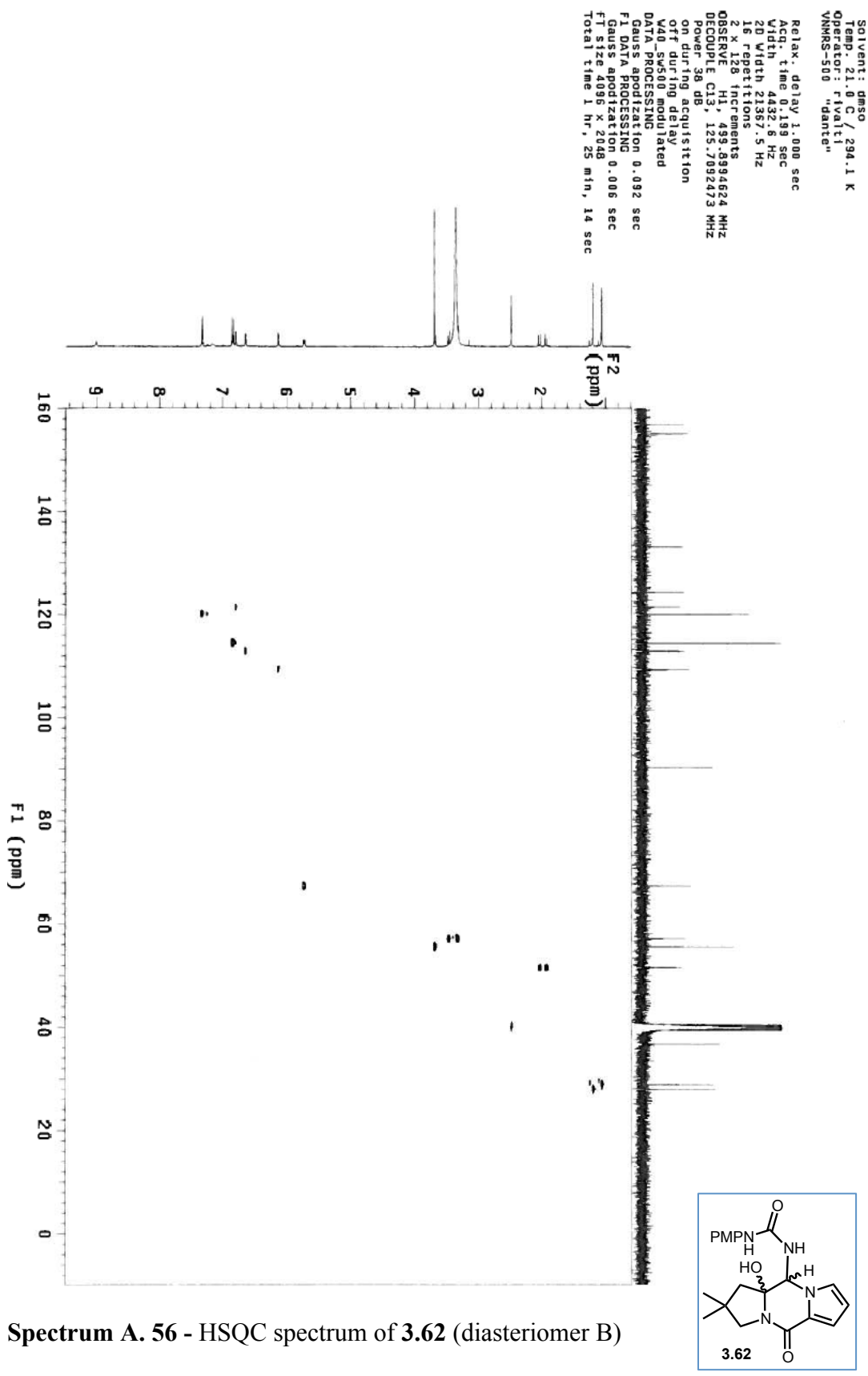
Spectrum A. 54 - ^{13}C NMR spectrum of **3.62** (diasteriomer B)



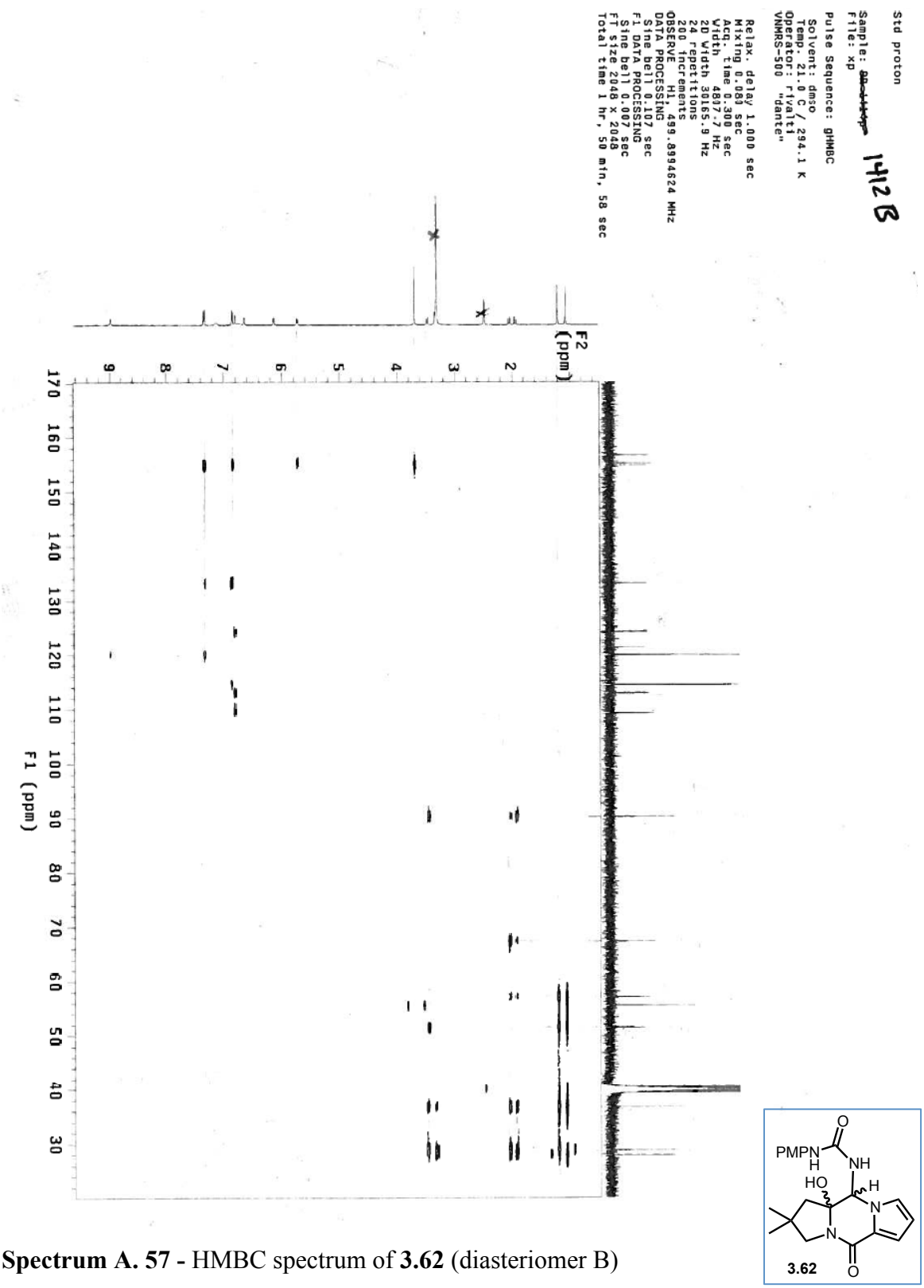


Spectrum A. 55 - COSY spectrum of **3.62** (diasteriomer B)

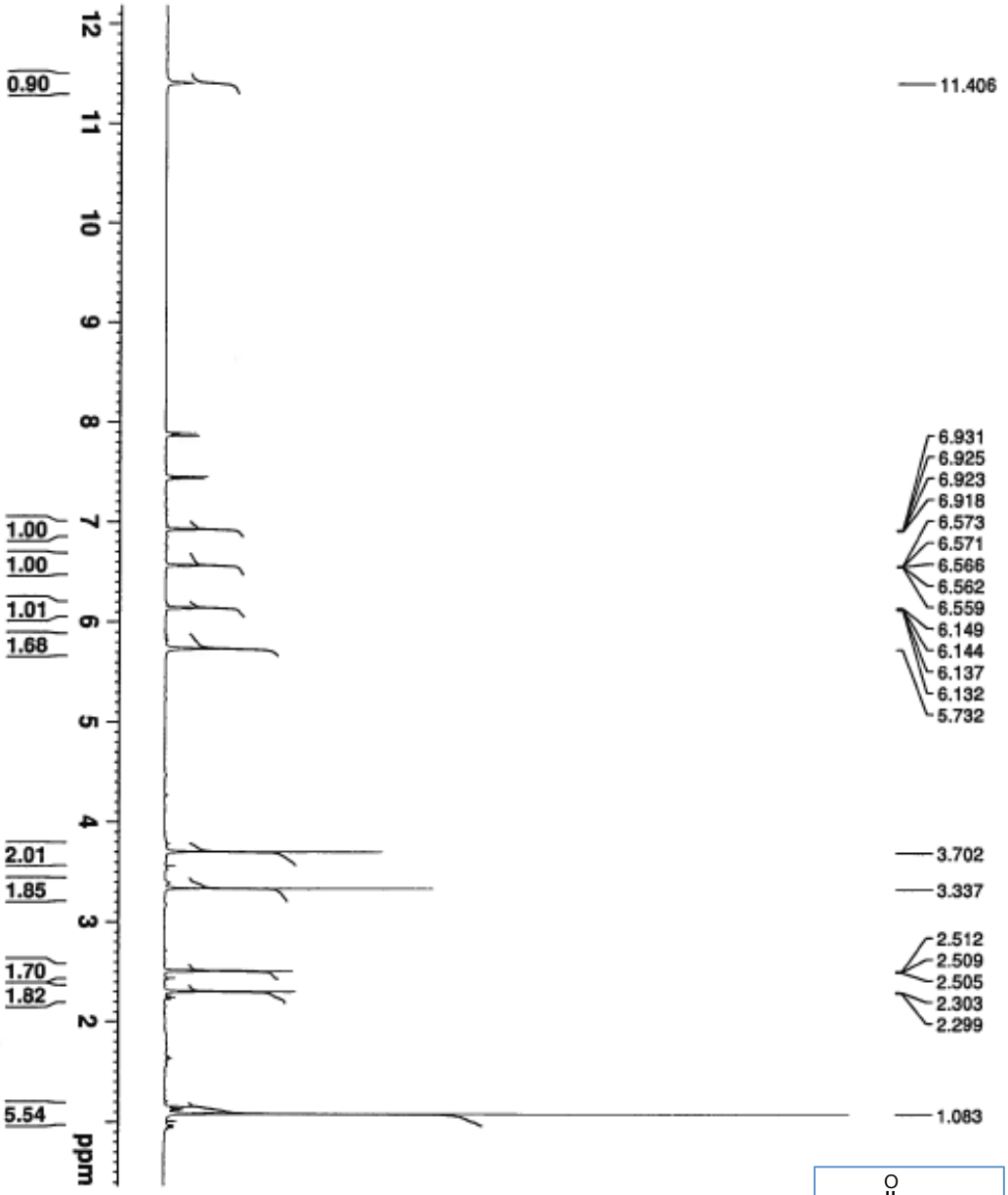




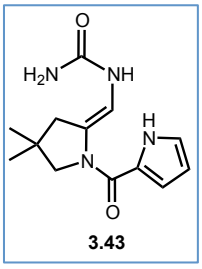
Spectrum A. 56 - HSQC spectrum of **3.62** (diasteriomer B)



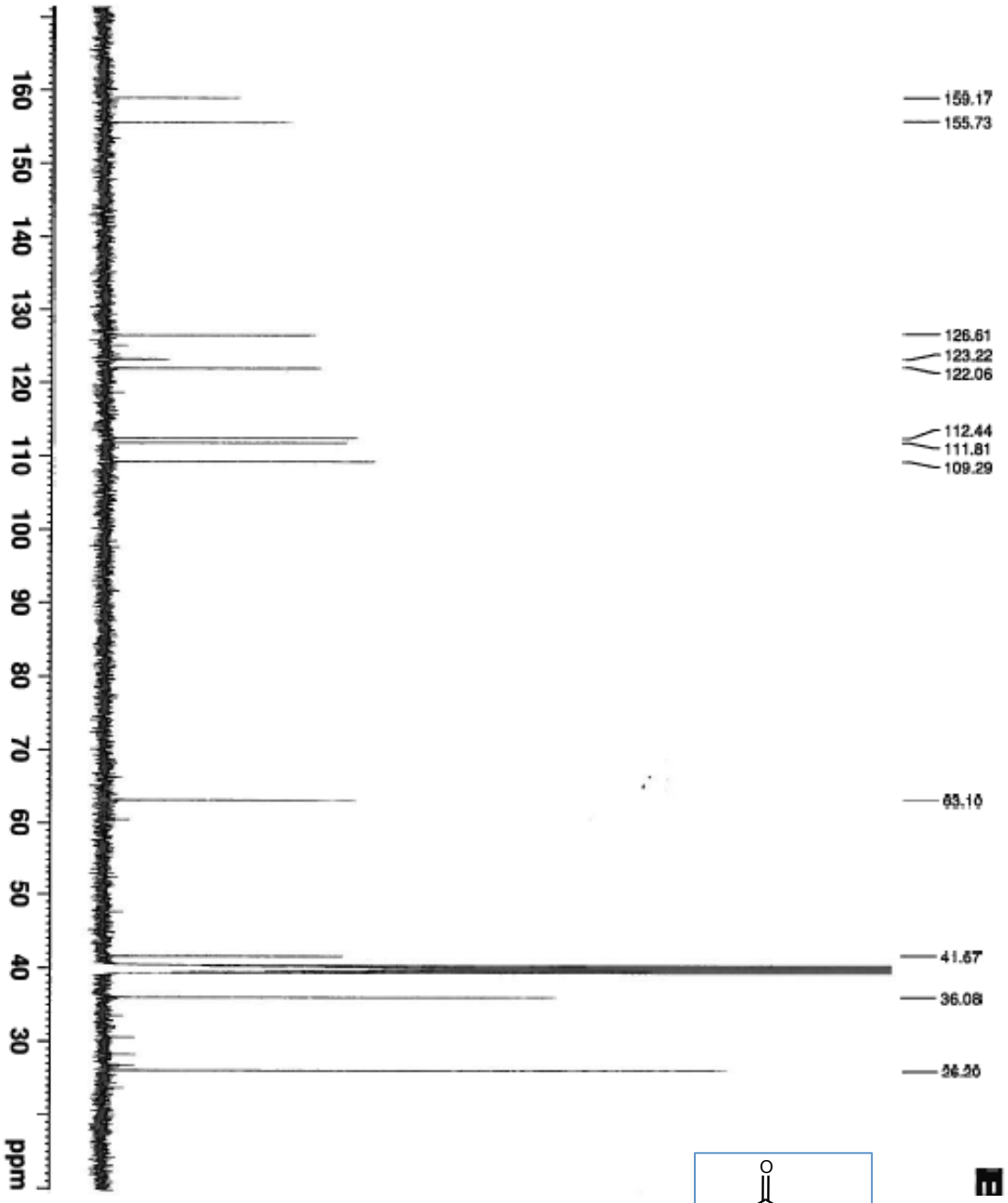
Spectrum A. 57 - HMBC spectrum of **3.62** (diasteriomer B)



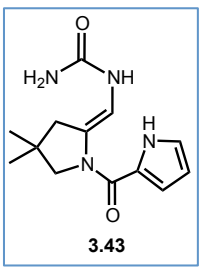
Spectrum A. 58 - ^{1}H NMR spectrum of **3.43**



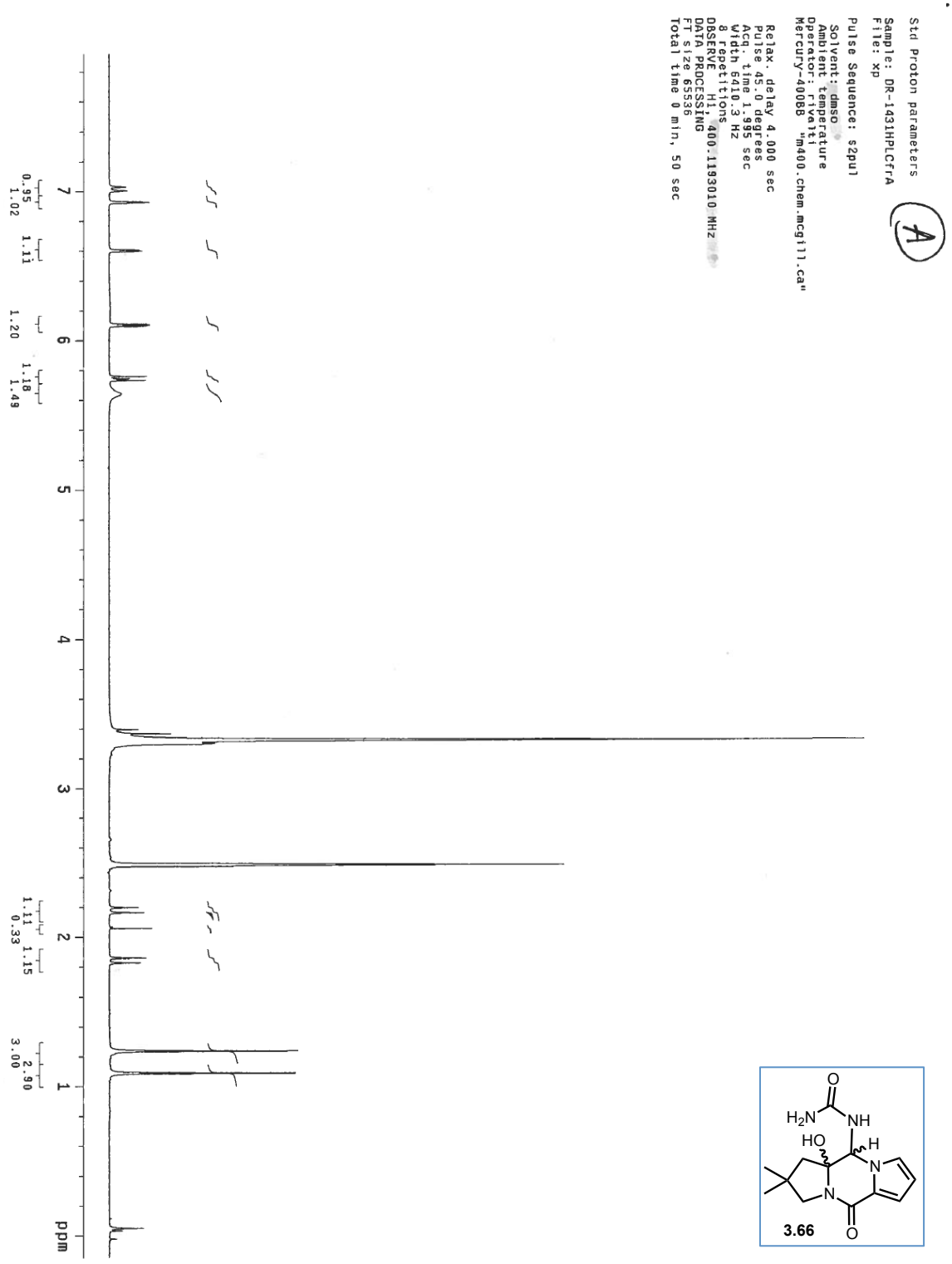
3.43



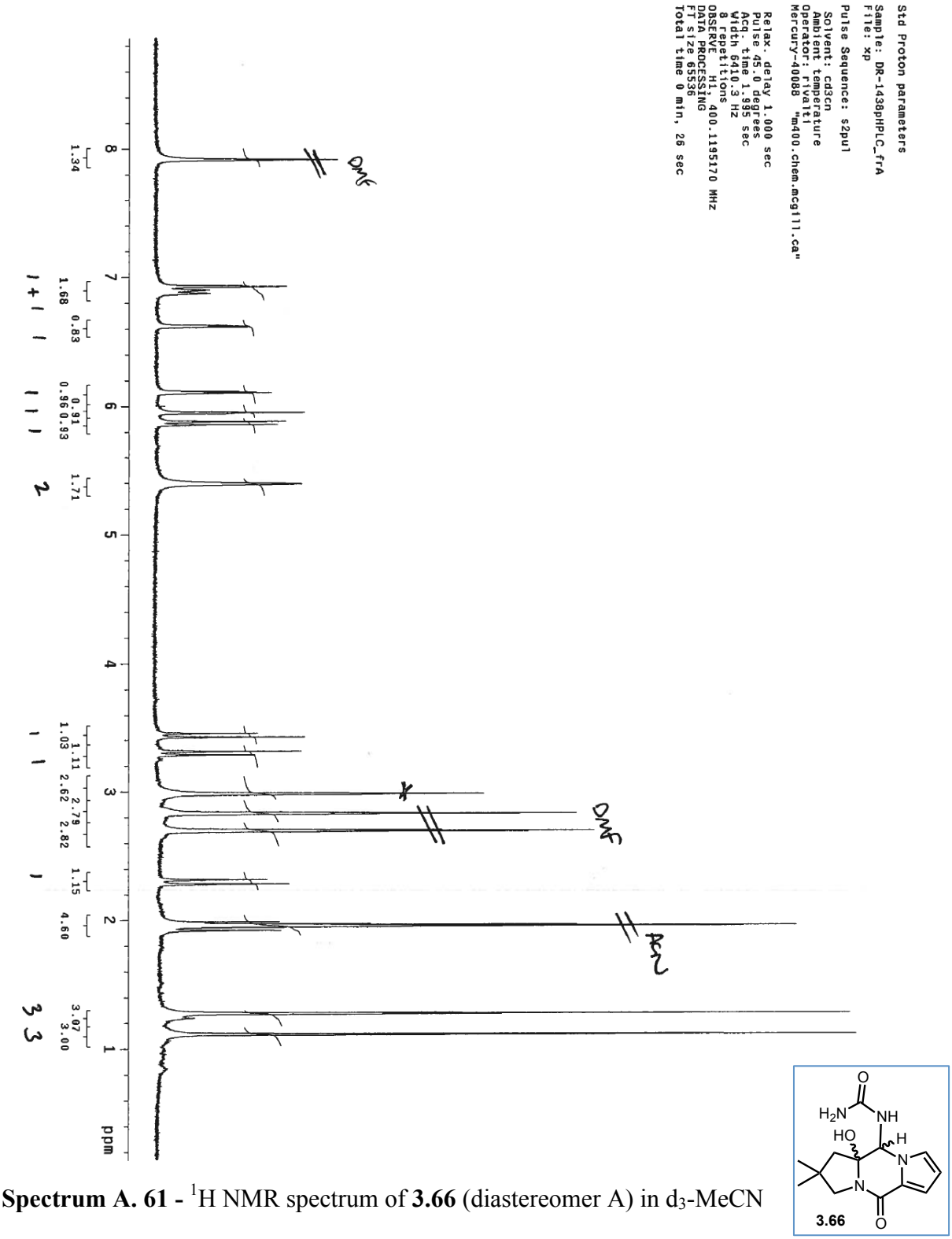
Spectrum A. 59 - ^{13}C NMR spectrum of **3.43**



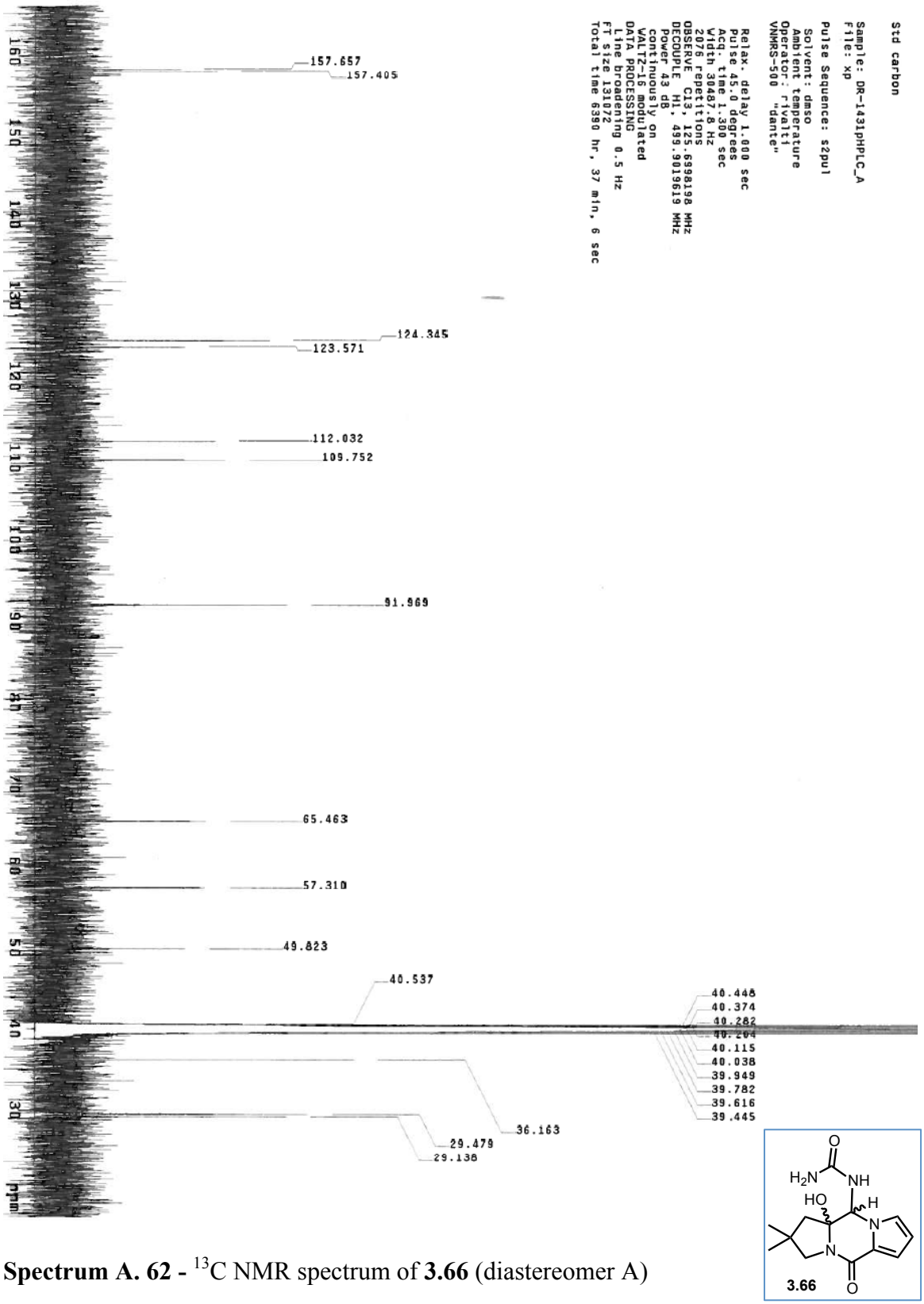
3.43



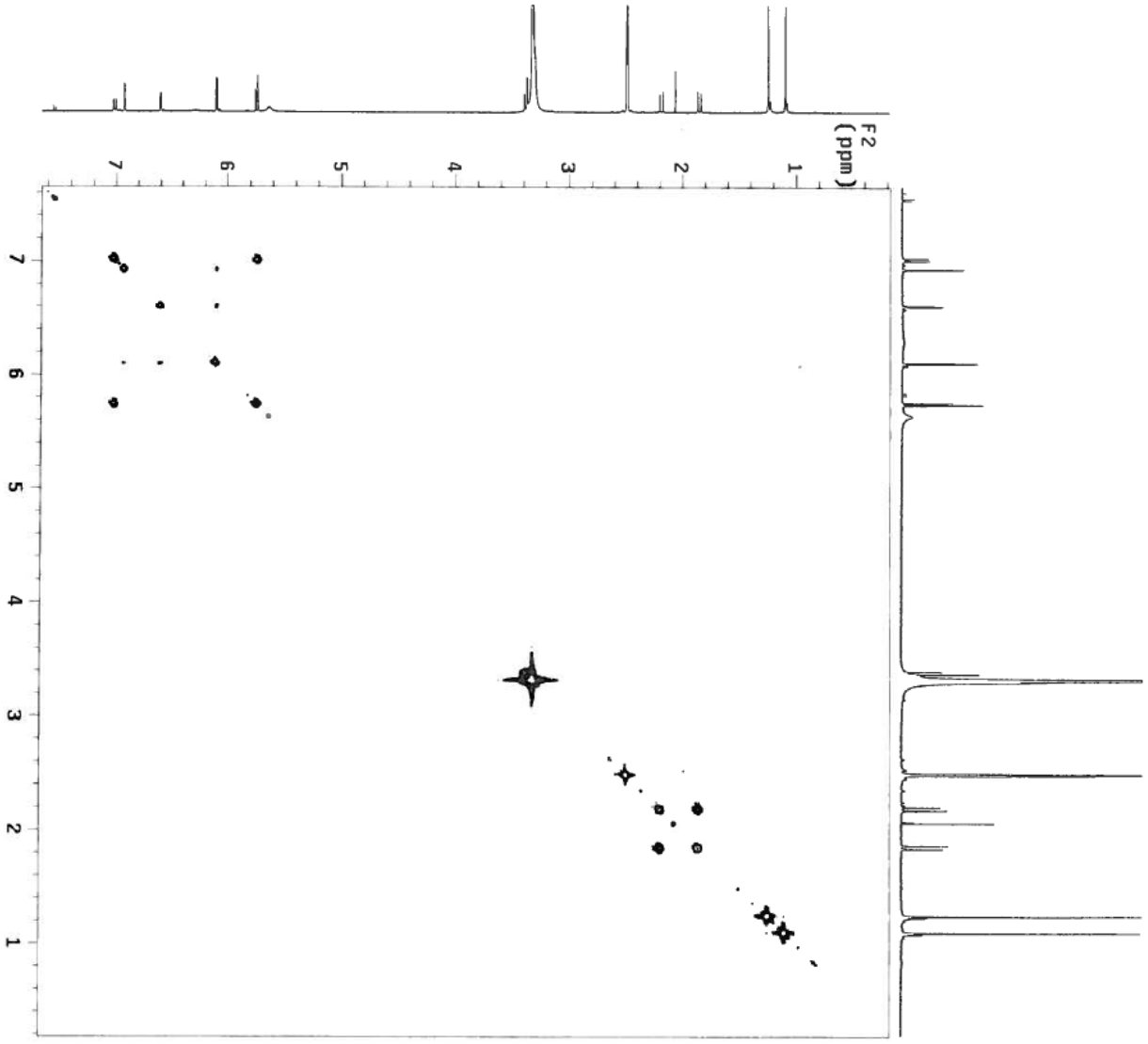
Spectrum A. 60 - ^{1}H NMR spectrum of **3.66** (diastereomer A) in d_6-DMSO



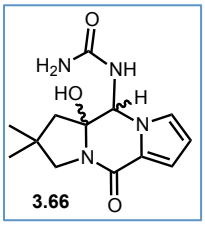
Spectrum A. 61 - ^{1}H NMR spectrum of **3.66** (diastereomer A) in d_3-MeCN

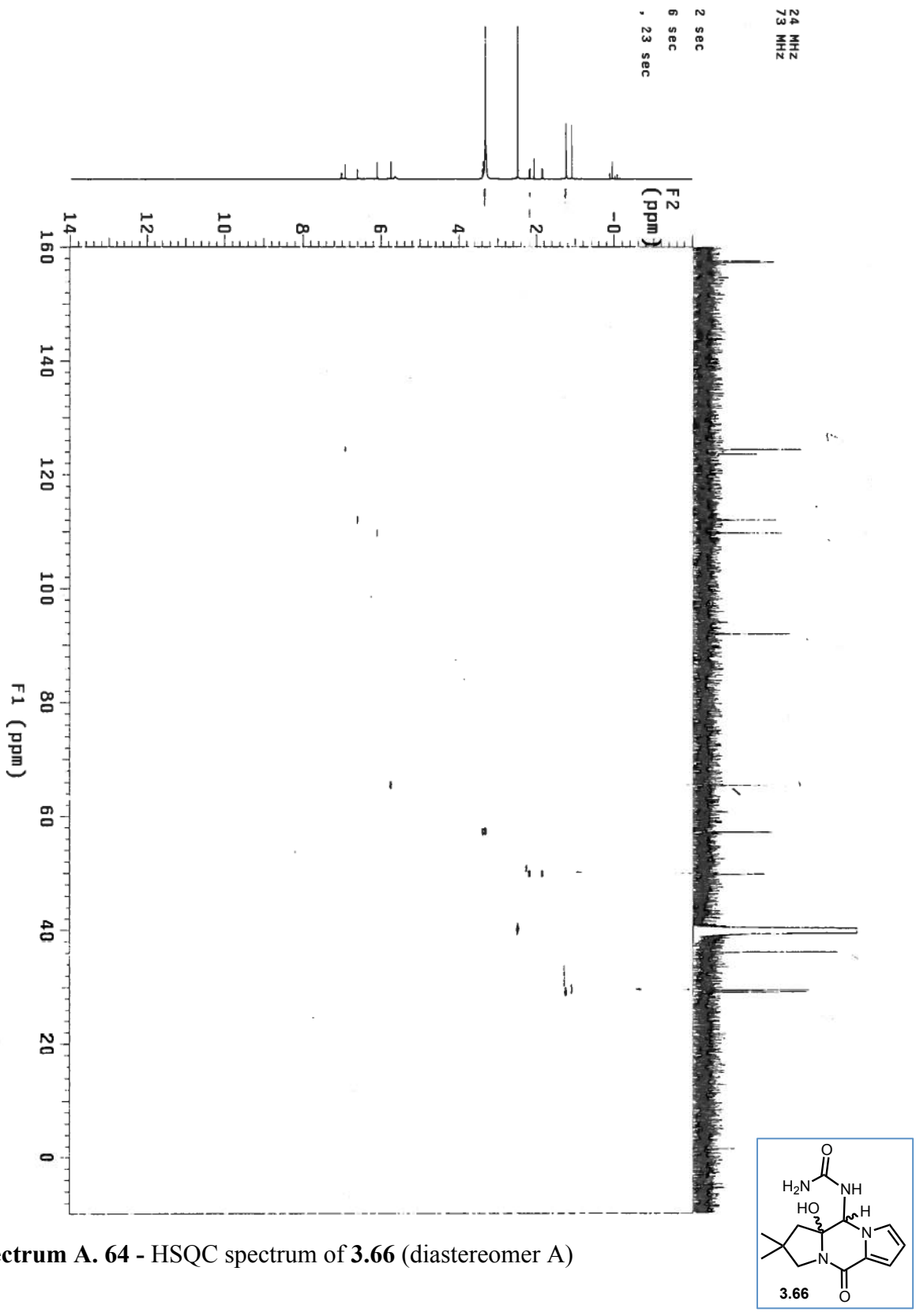


Spectrum A. 62 - ^{13}C NMR spectrum of **3.66** (diastereomer A)

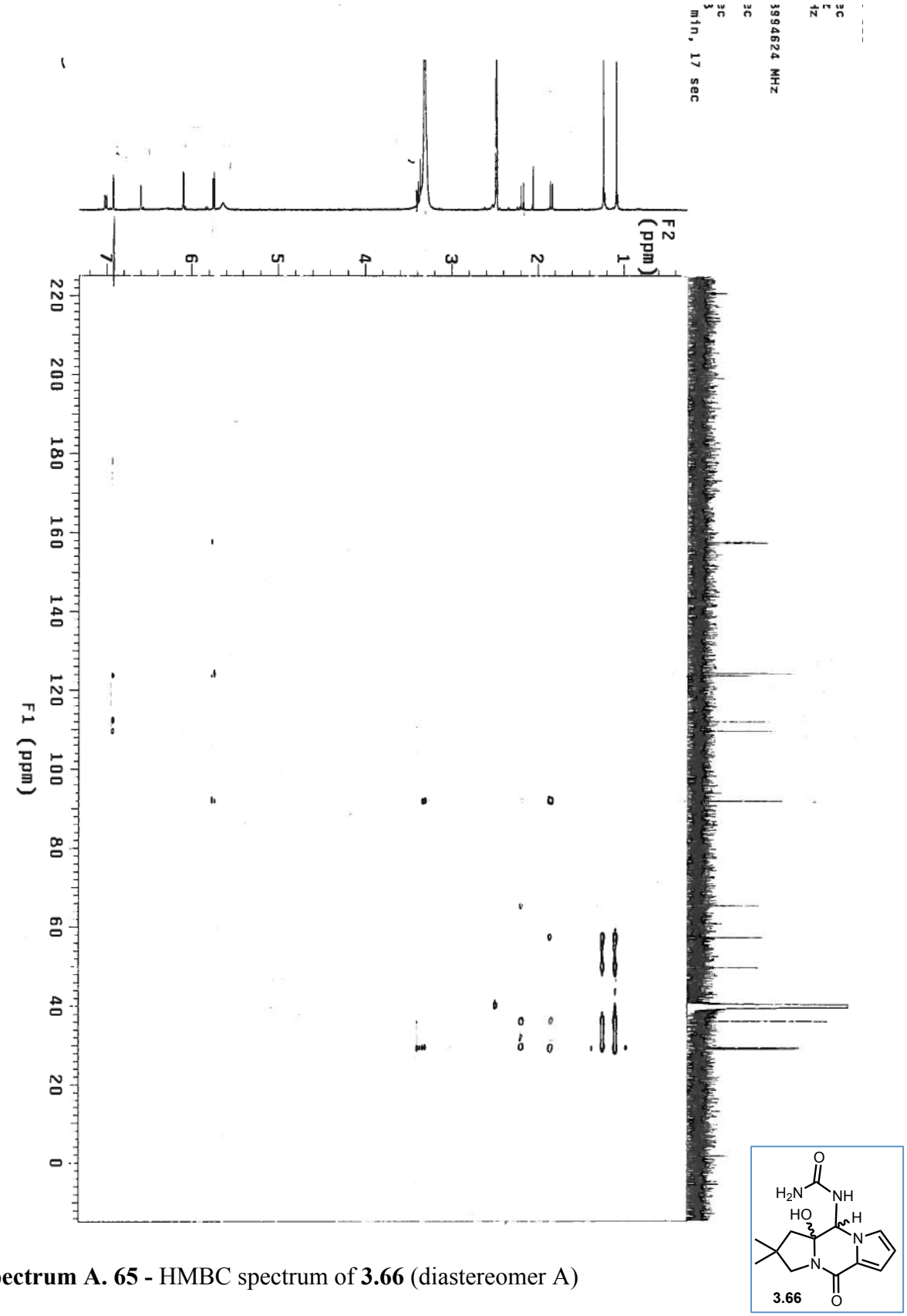


Spectrum A. 63 - COSY spectrum of **3.66** (diastereomer A)

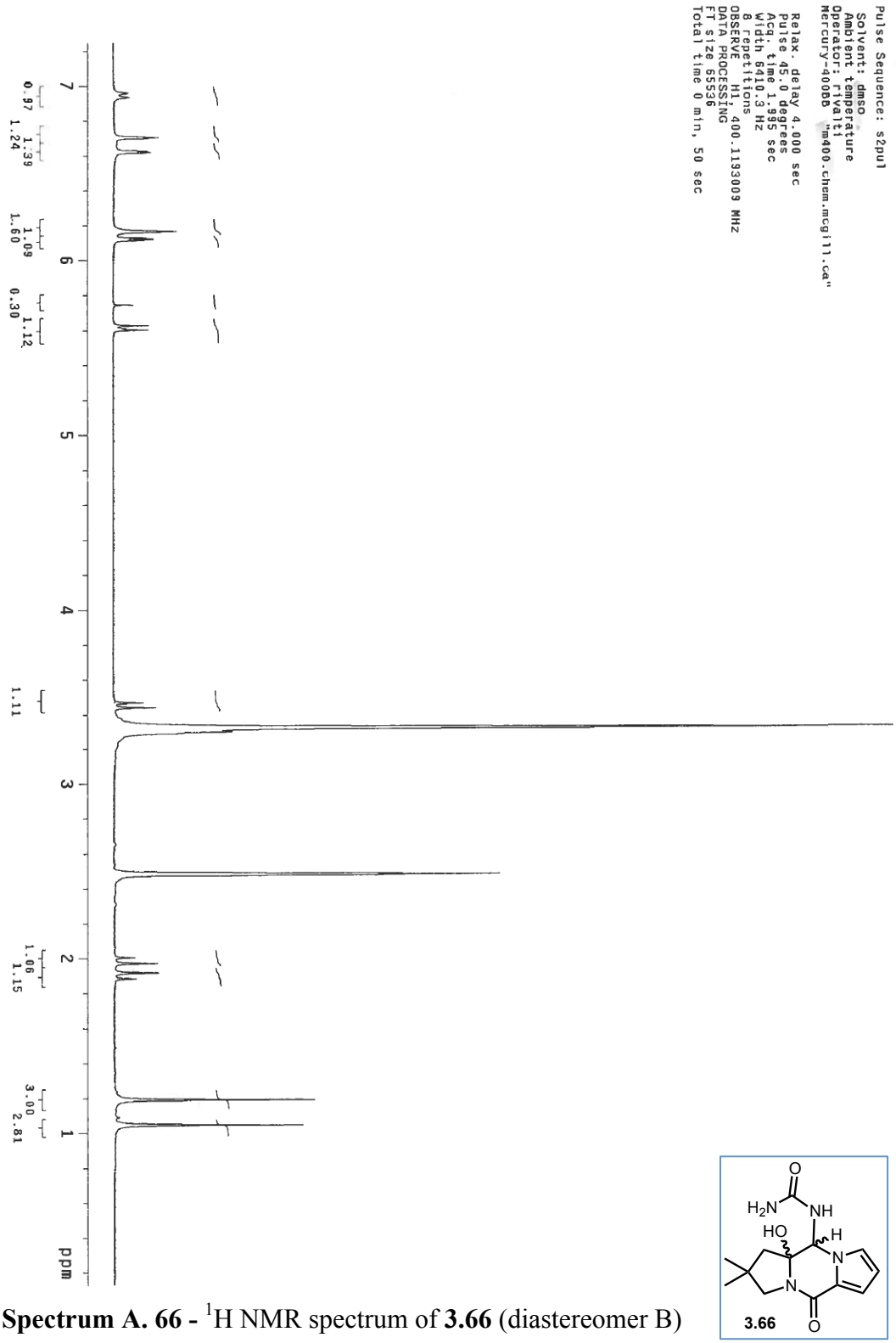




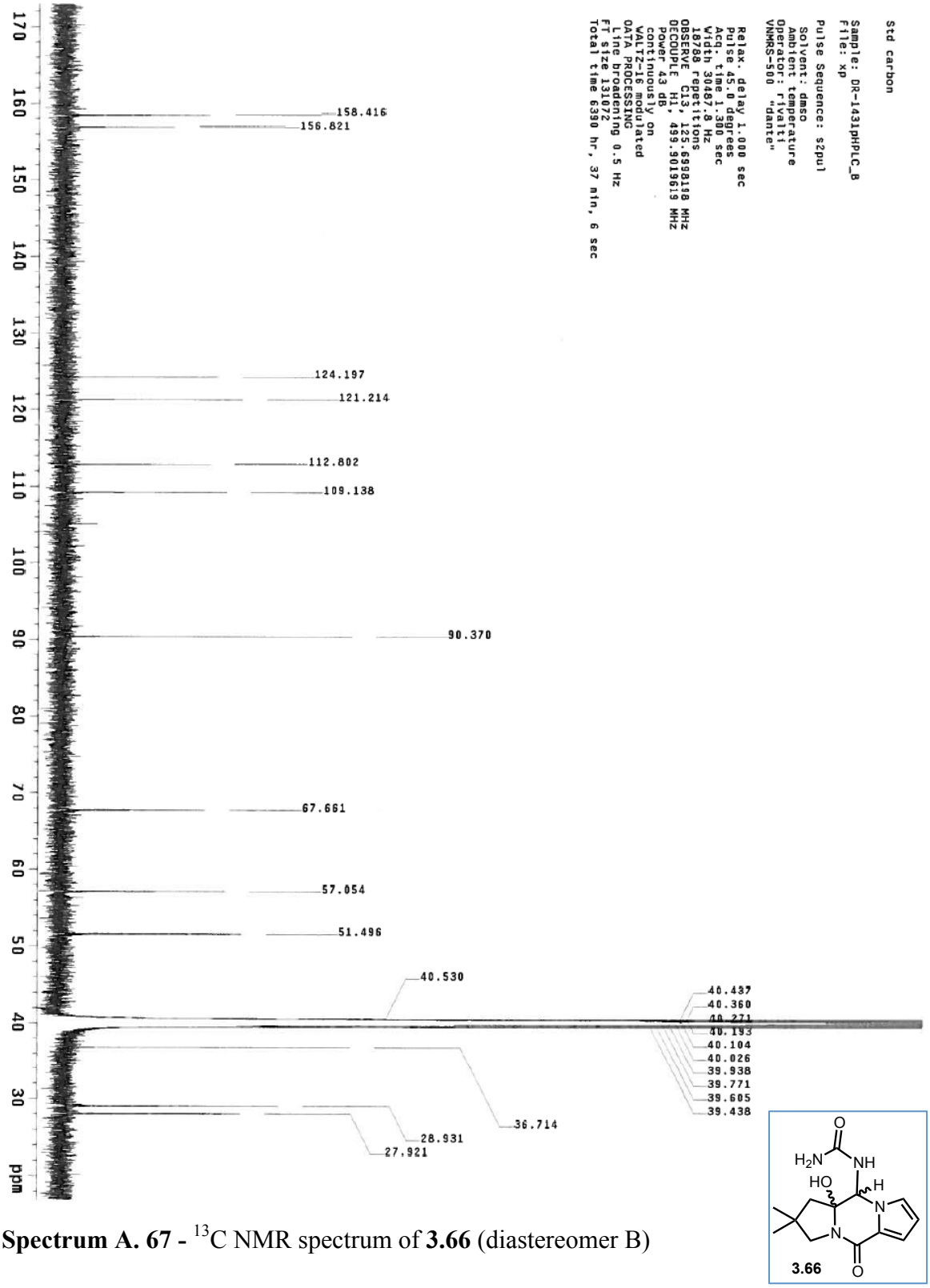
Spectrum A. 64 - HSQC spectrum of **3.66** (diastereomer A)



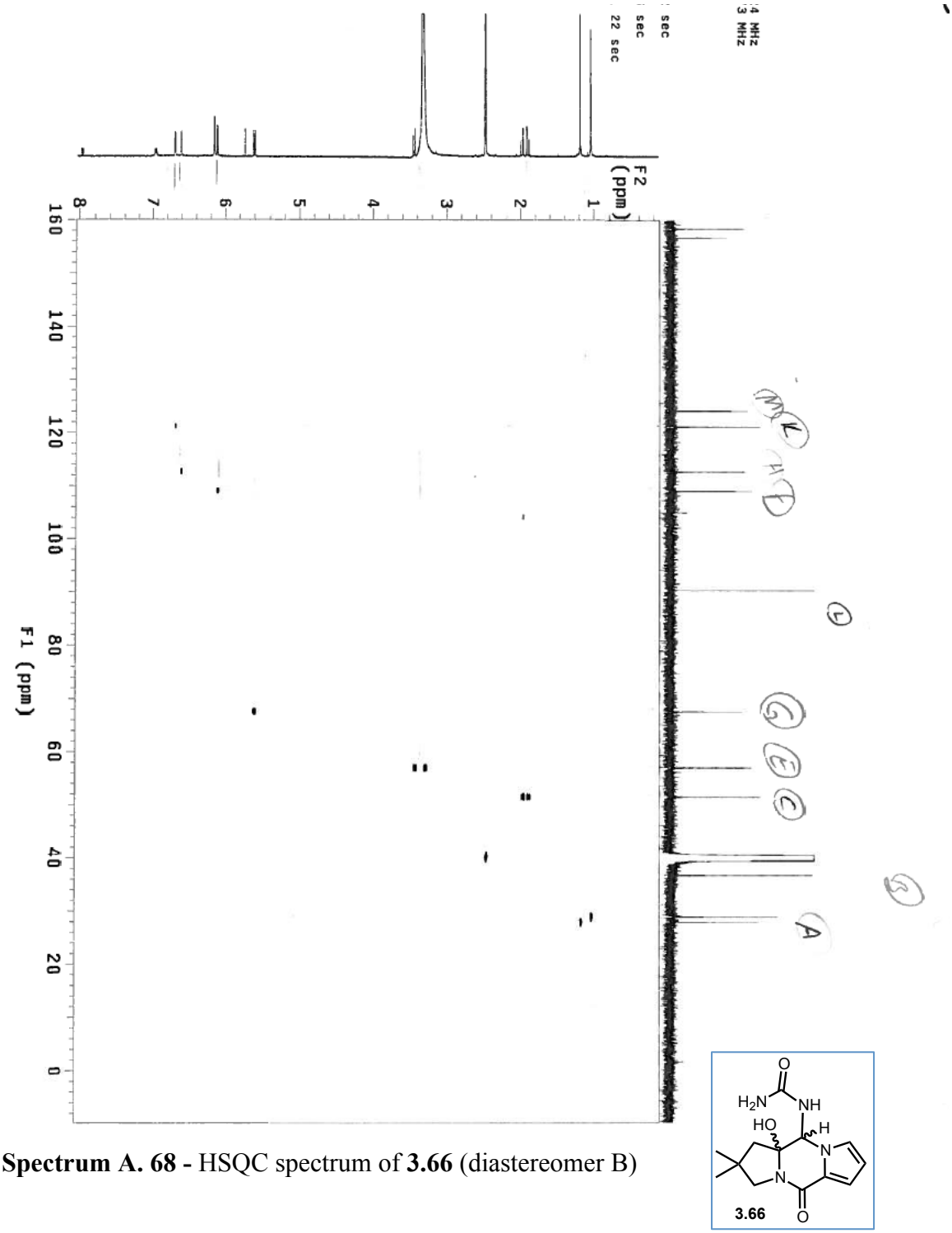
Spectrum A. 65 - HMBC spectrum of **3.66** (diastereomer A)



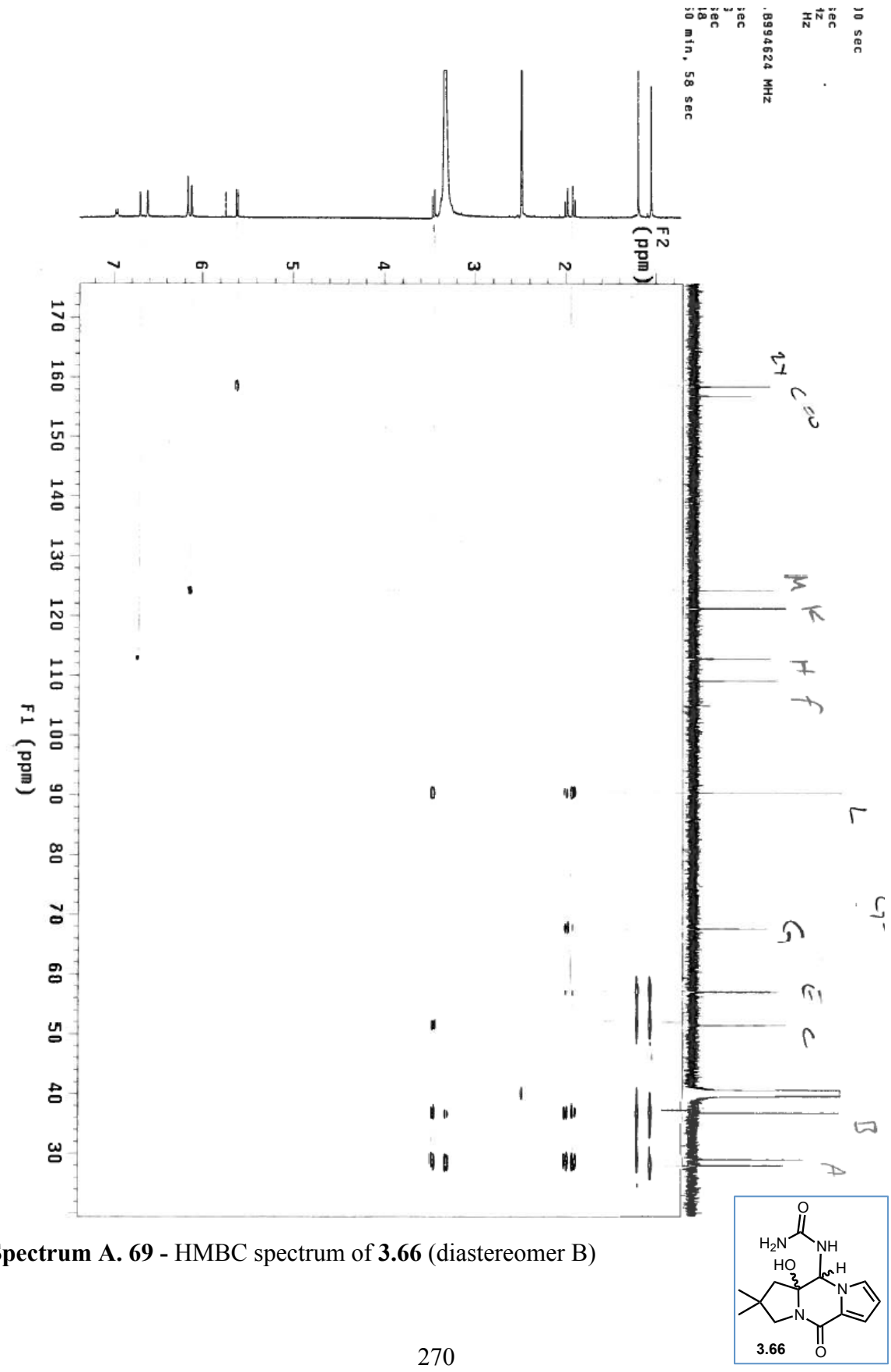
Spectrum A. 66 - ^{1}H NMR spectrum of **3.66** (diastereomer B)



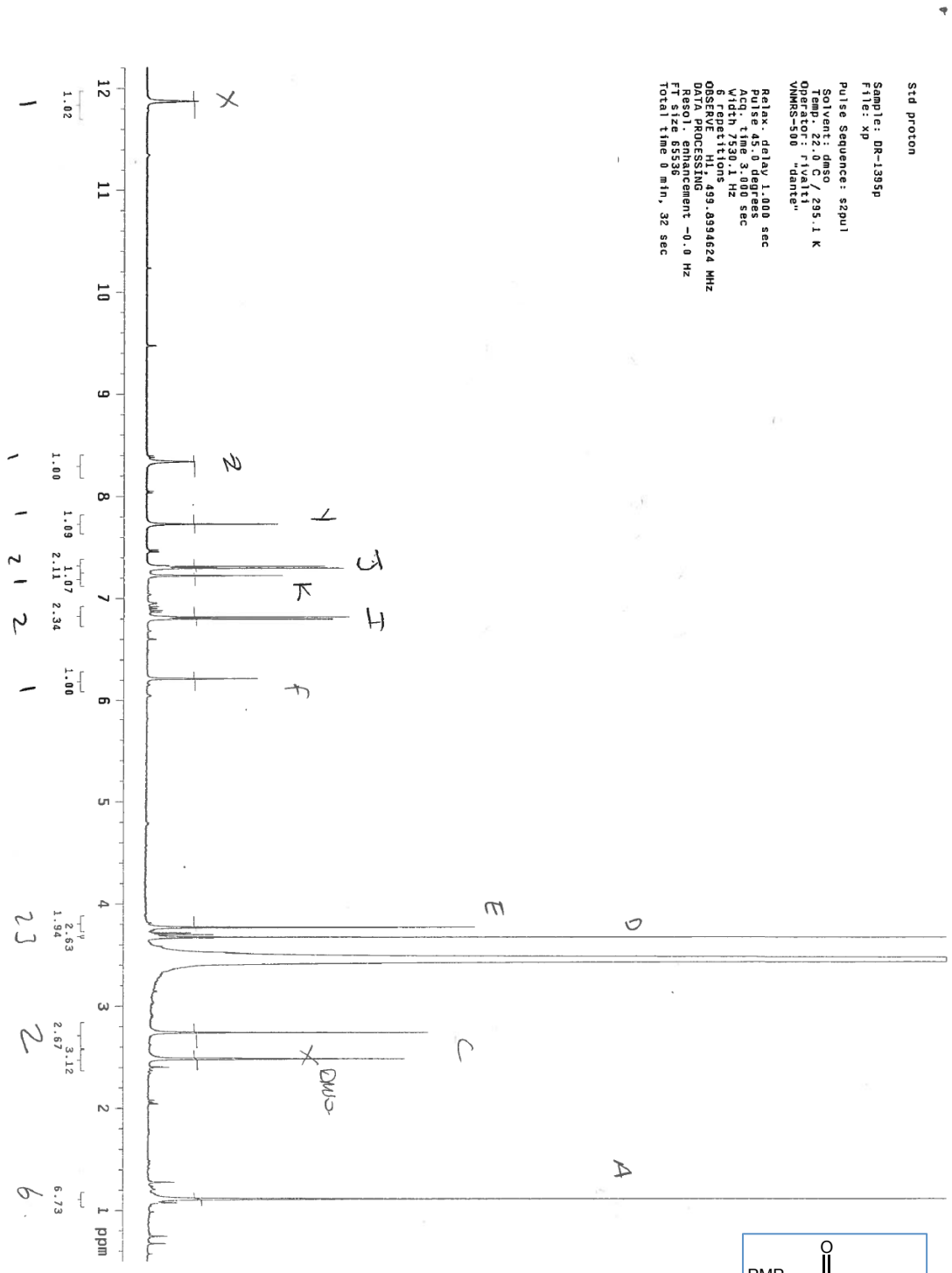
Spectrum A. 67 - ^{13}C NMR spectrum of **3.66** (diastereomer B)



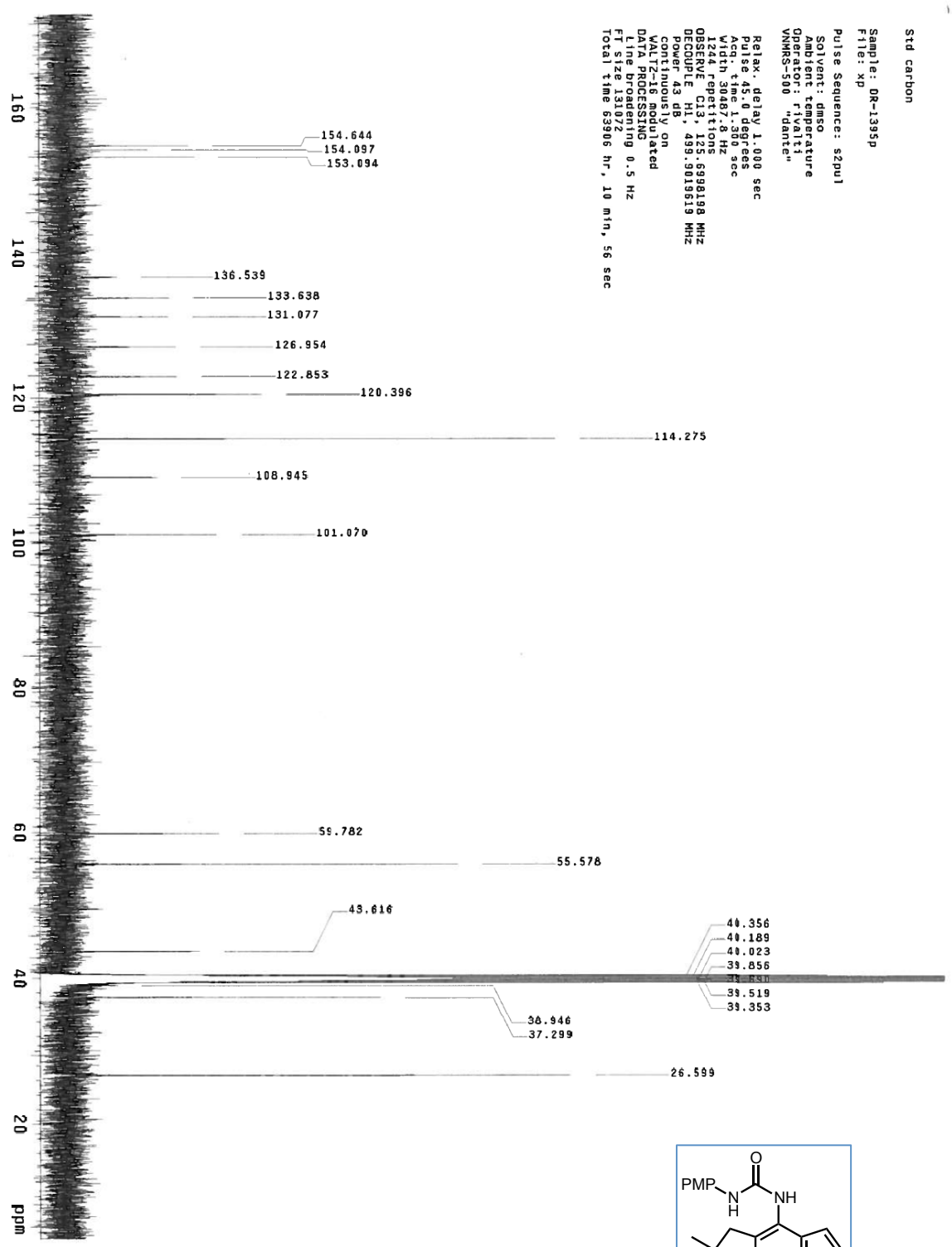
Spectrum A. 68 - HSQC spectrum of **3.66** (diastereomer B)



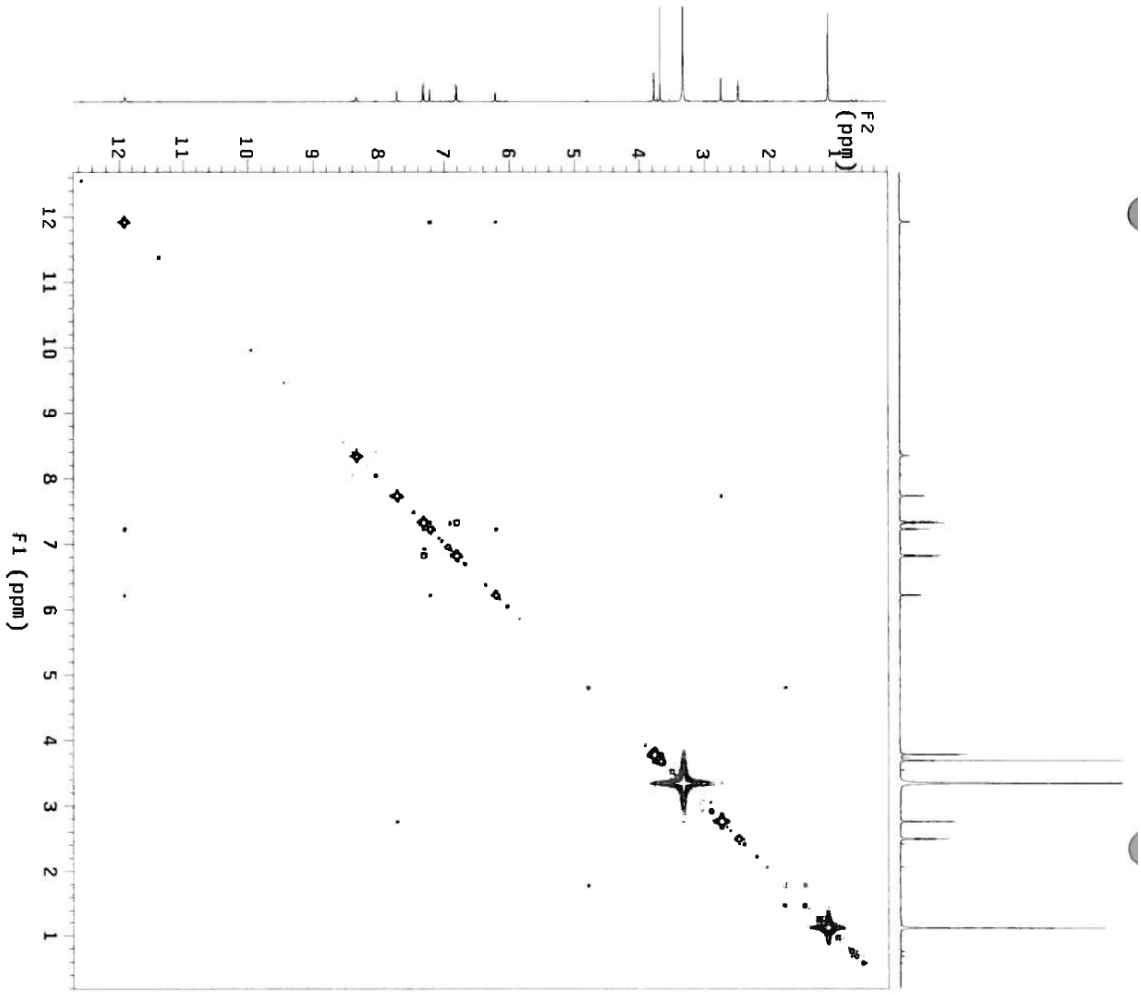
Spectrum A. 69 - HMBC spectrum of **3.66** (diastereomer B)



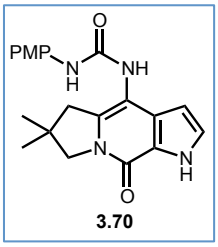
Spectrum A. 70 - ^{1}H NMR spectrum of **3.70**



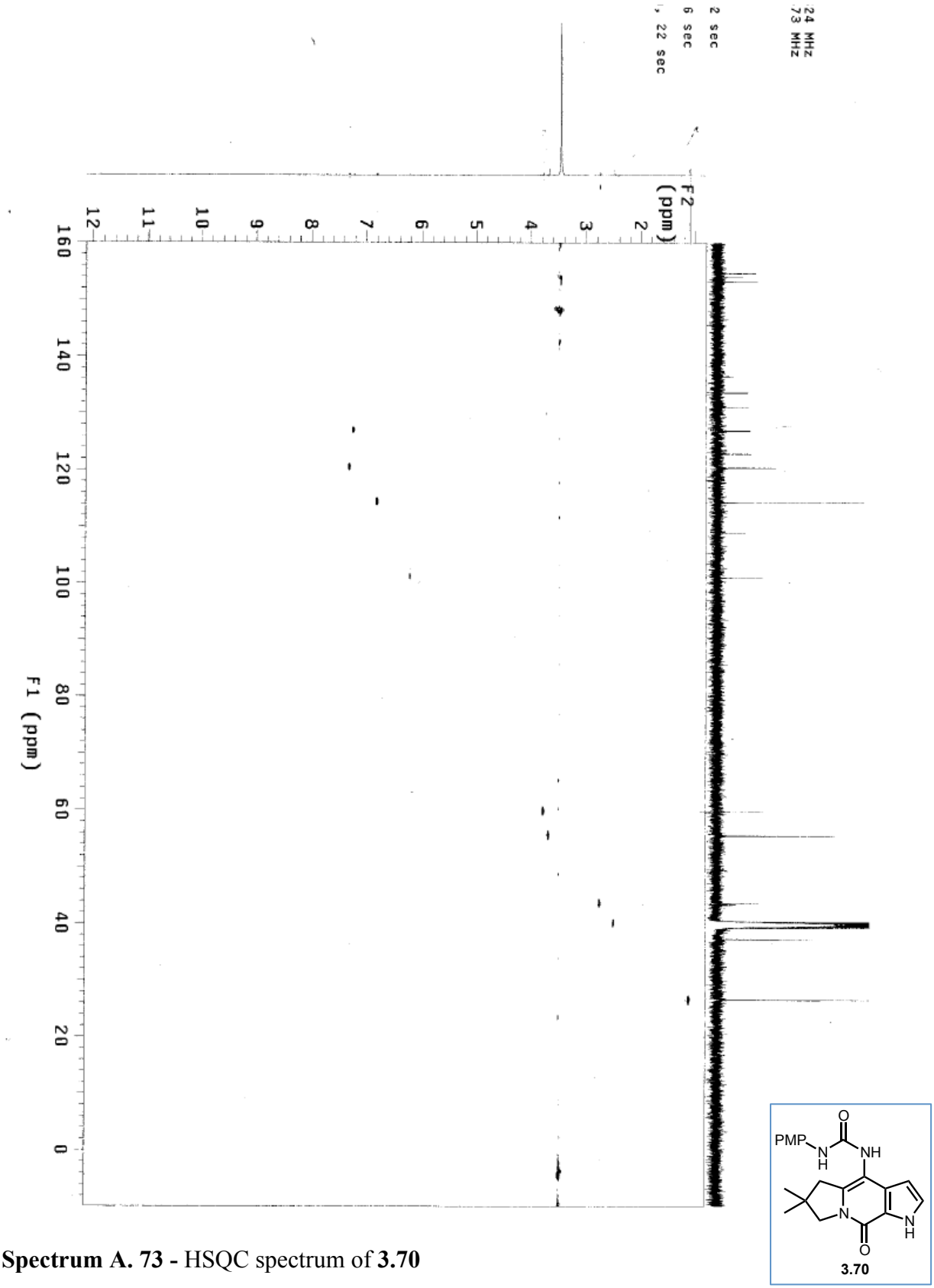
Spectrum A. 71 - ^{13}C NMR spectrum of **3.70**



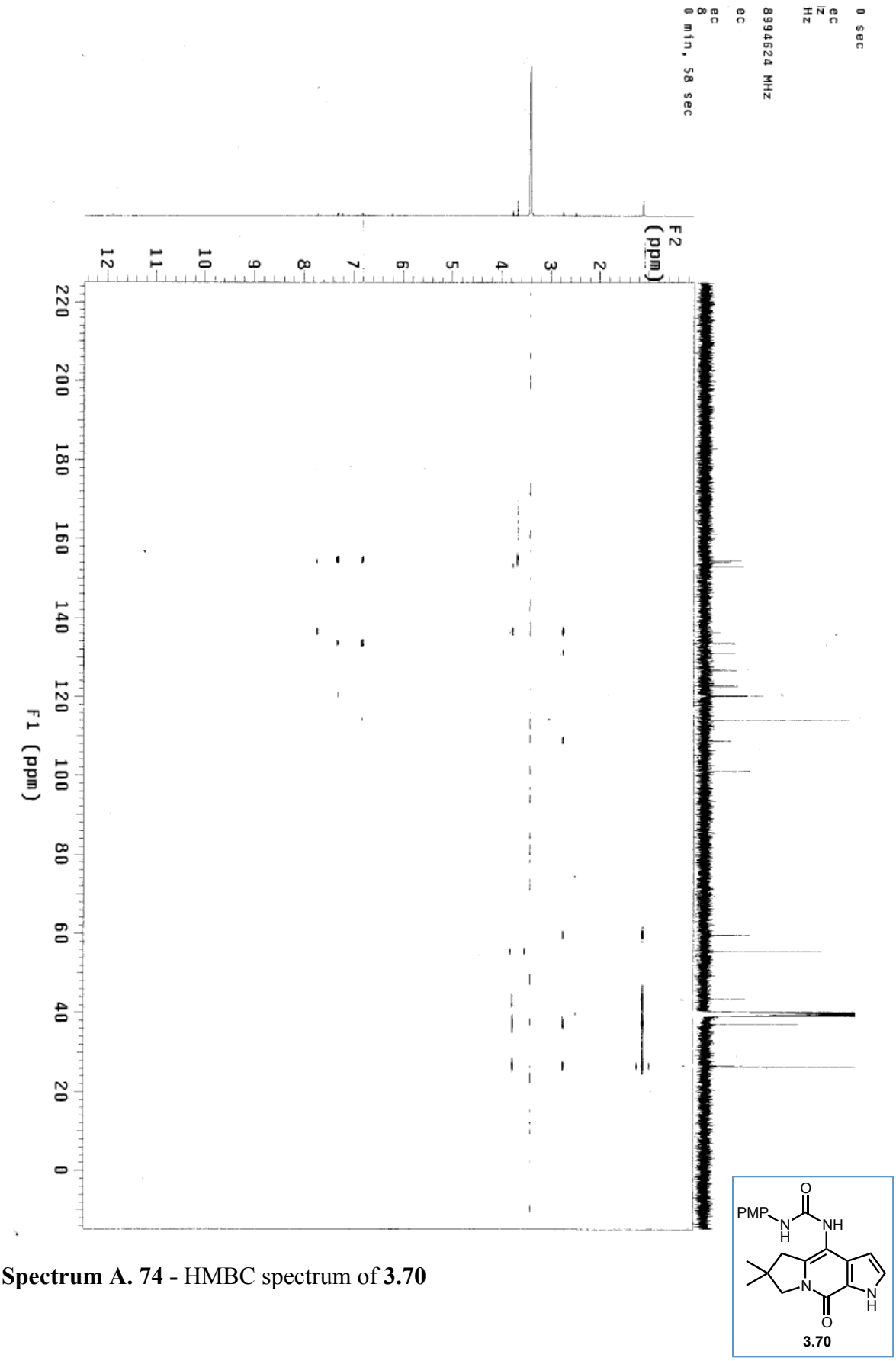
Spectrum A. 72 - COSY spectrum of **3.70**



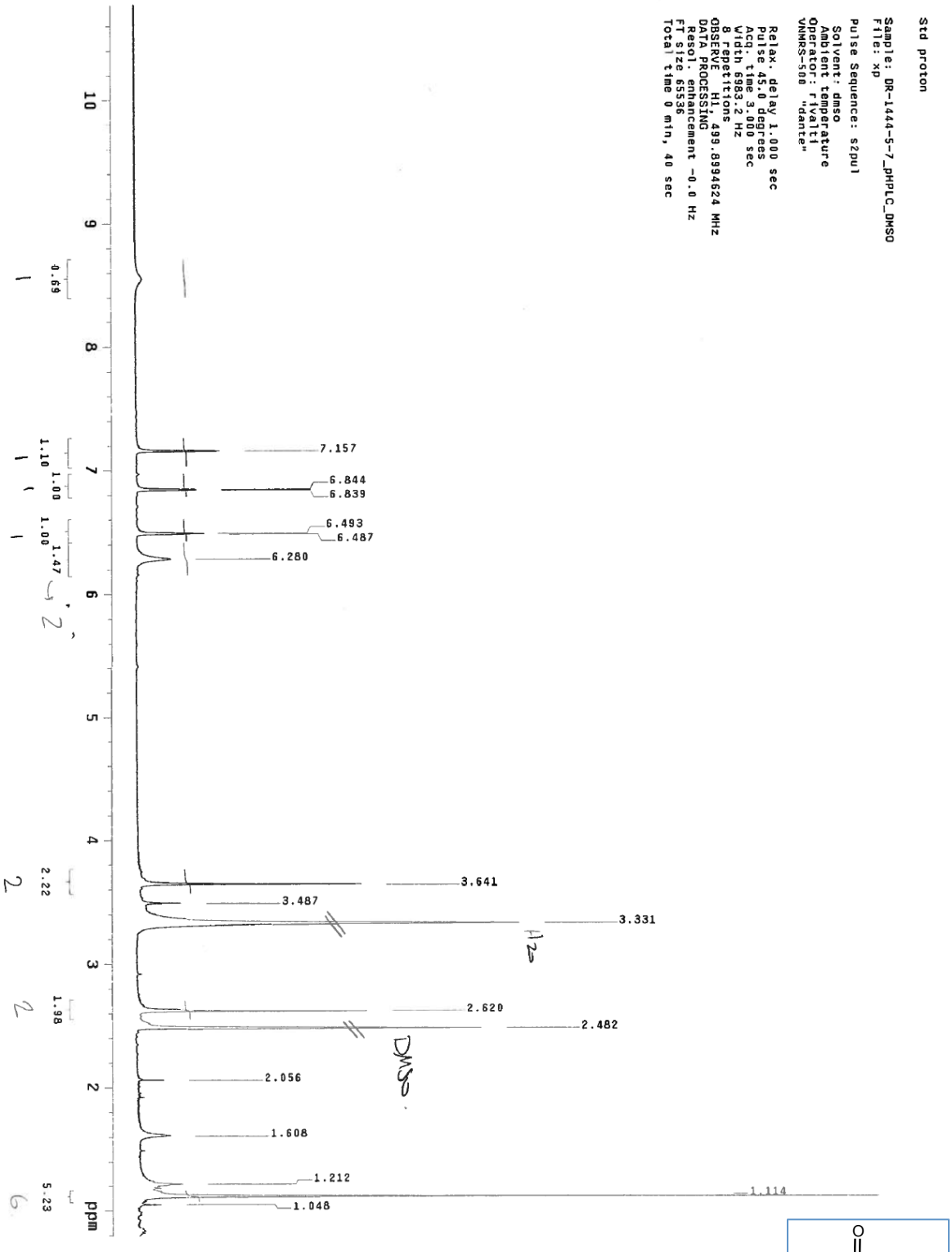
3.70

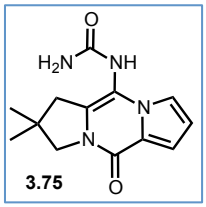


Spectrum A. 73 - HSQC spectrum of **3.70**

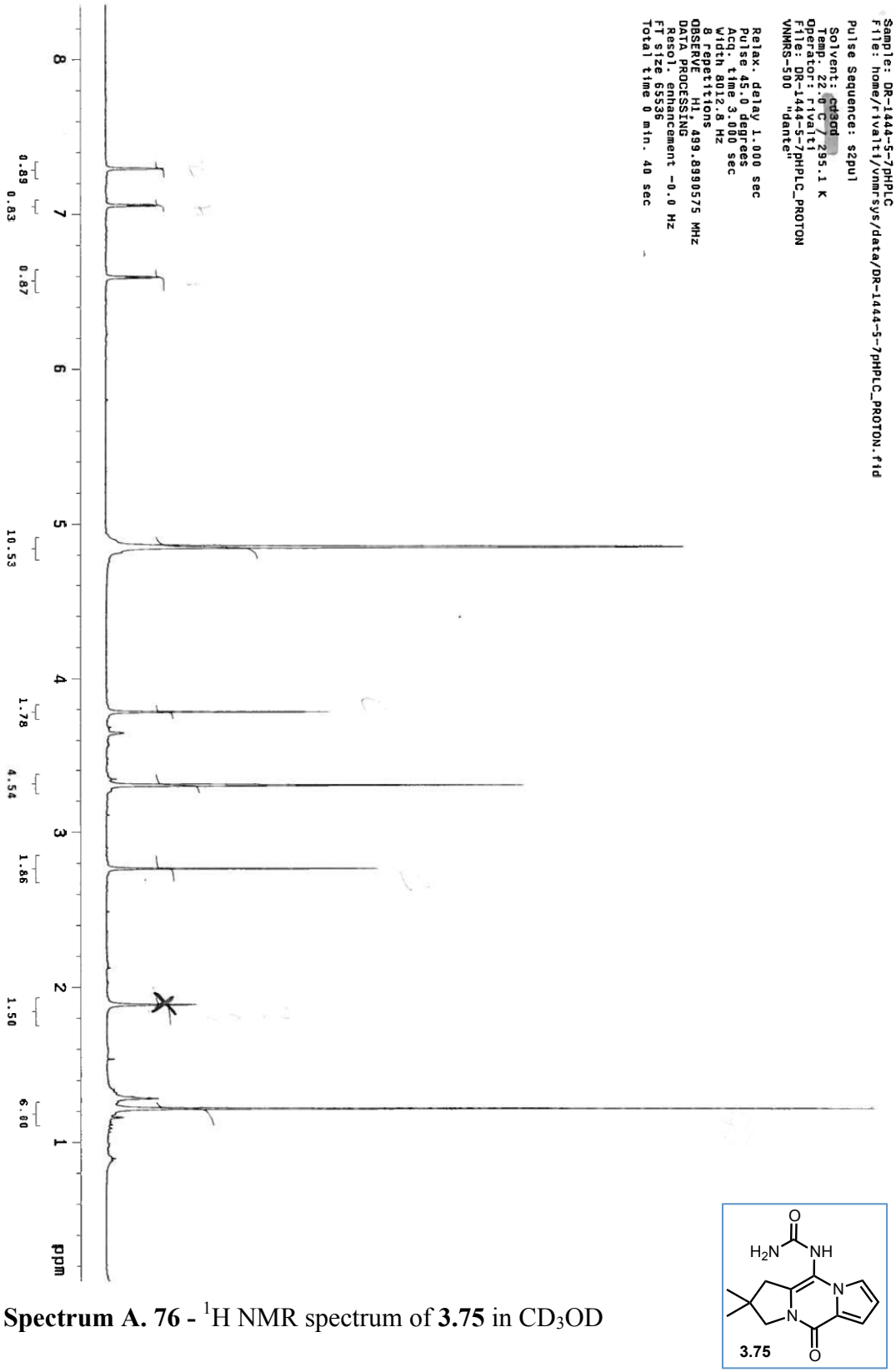


Spectrum A. 74 - HMBC spectrum of **3.70**

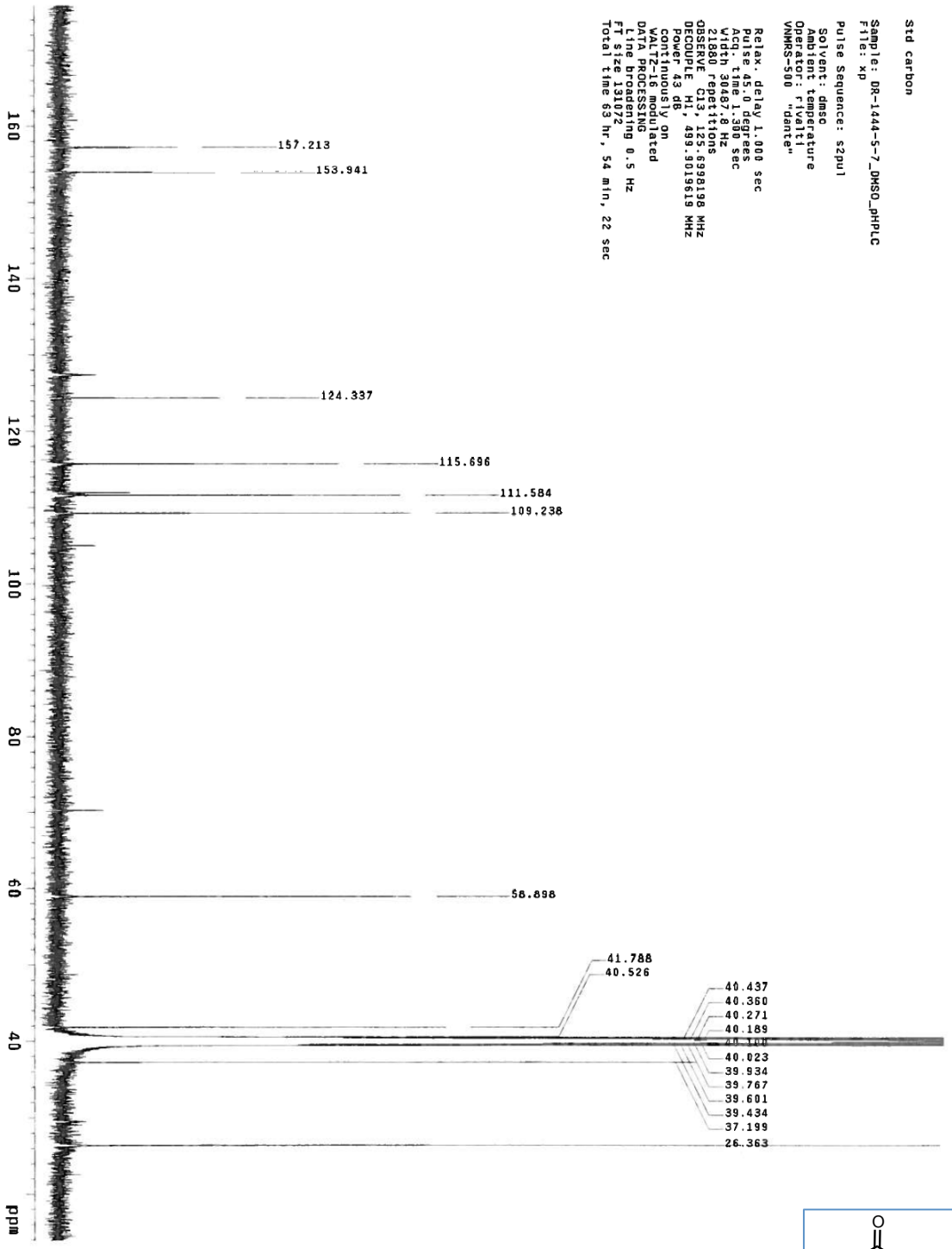


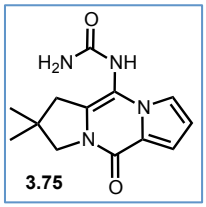


Spectrum A. 75 - ^{1}H NMR spectrum of **3.75** in d_6-DMSO

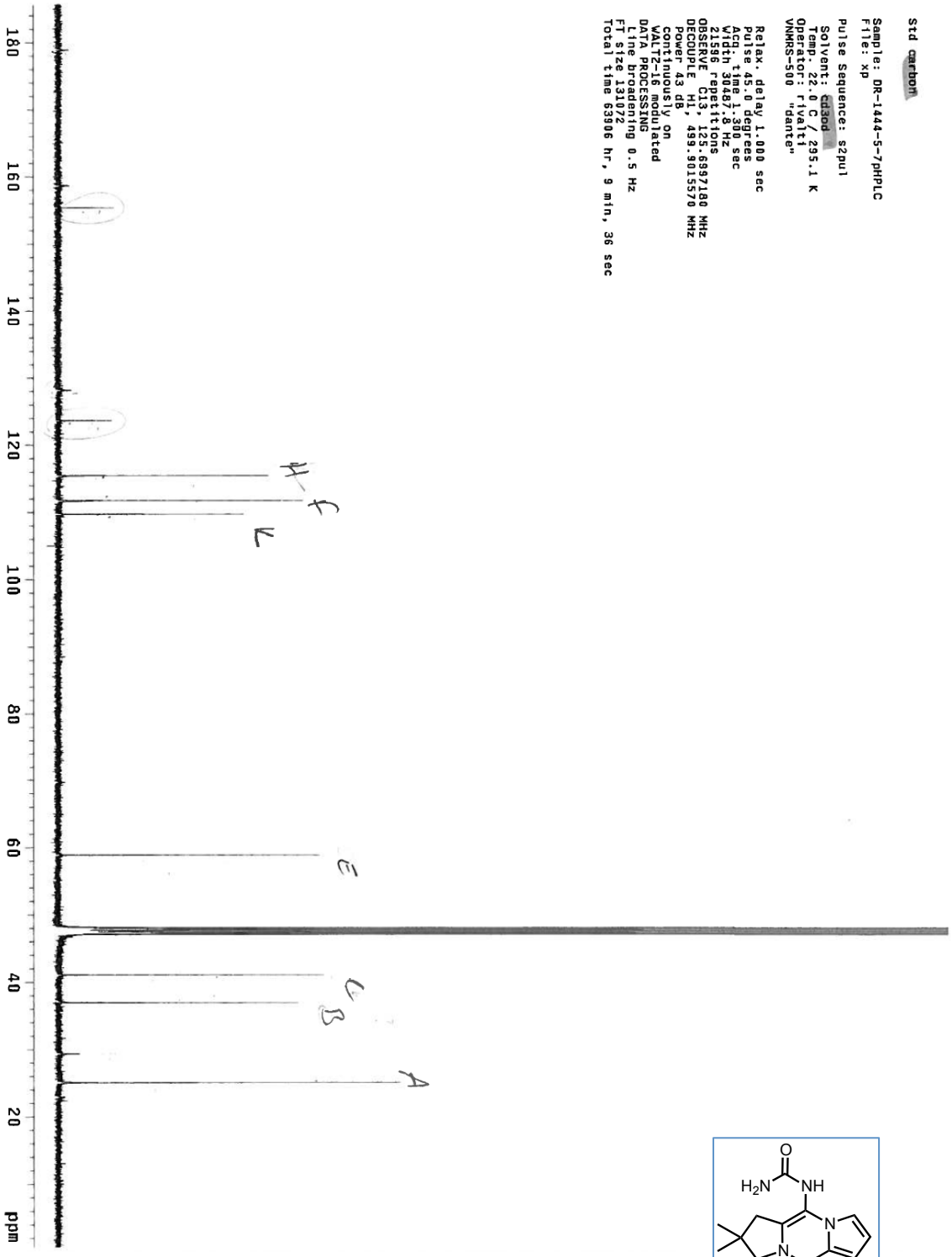


Spectrum A. 76 - ^{1}H NMR spectrum of **3.75** in CD_3OD

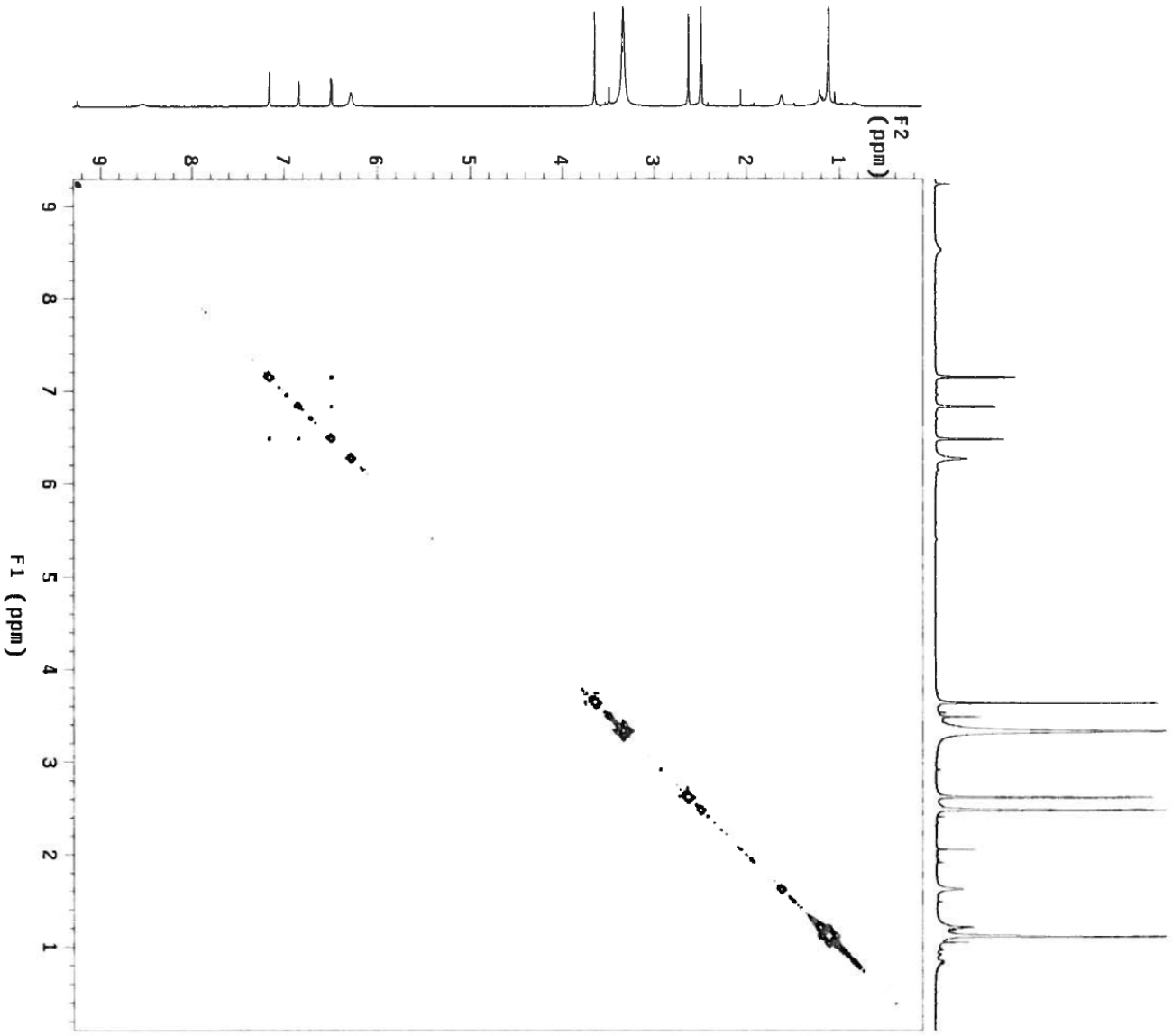




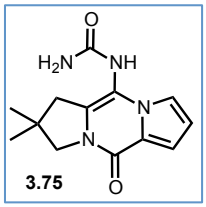
Spectrum A. 77 - ^{13}C NMR spectrum of **3.75** in d_6-DMSO

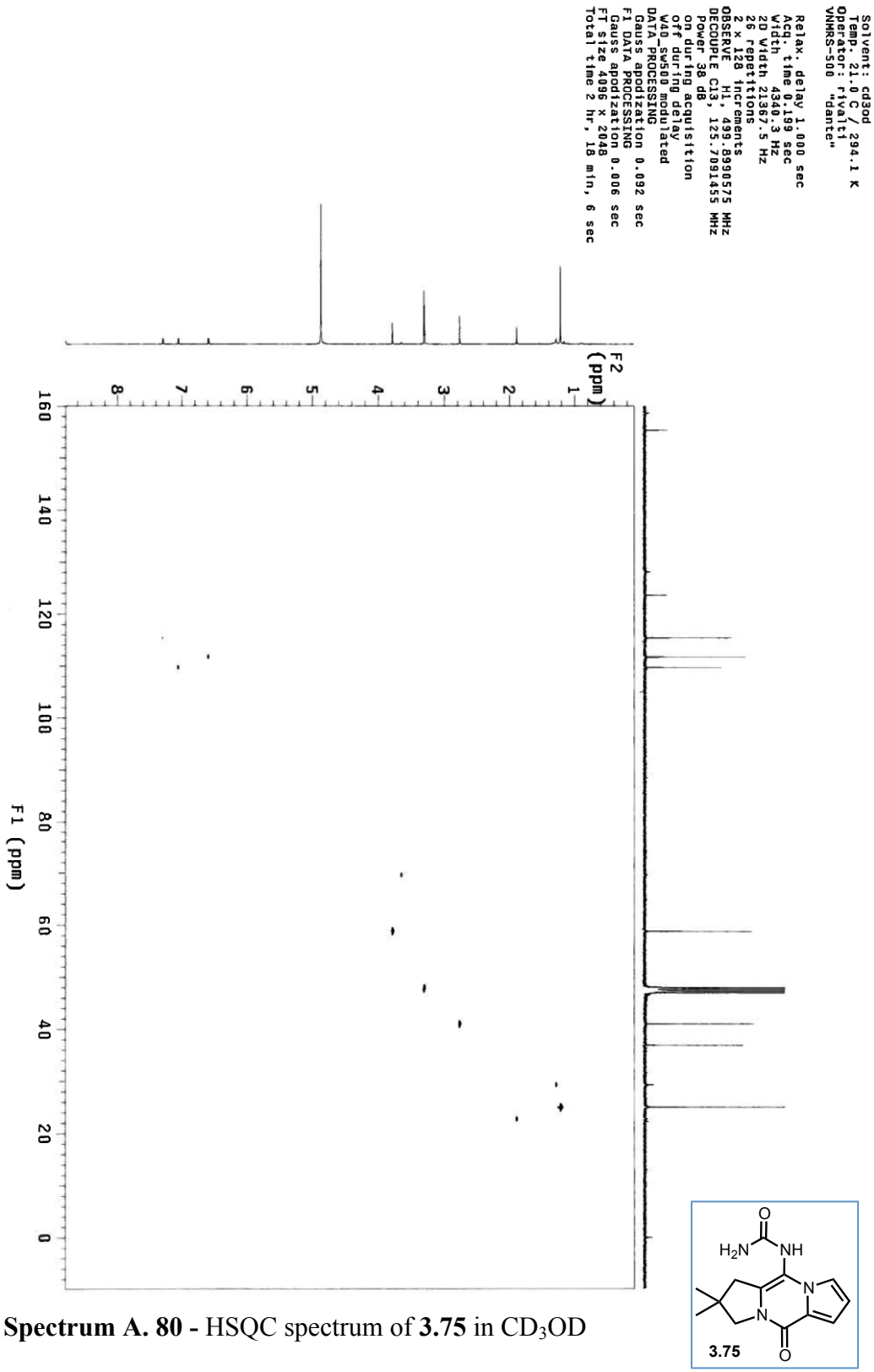


Spectrum A. 78 - ^{13}C NMR spectrum of **3.75** in CD_3OD

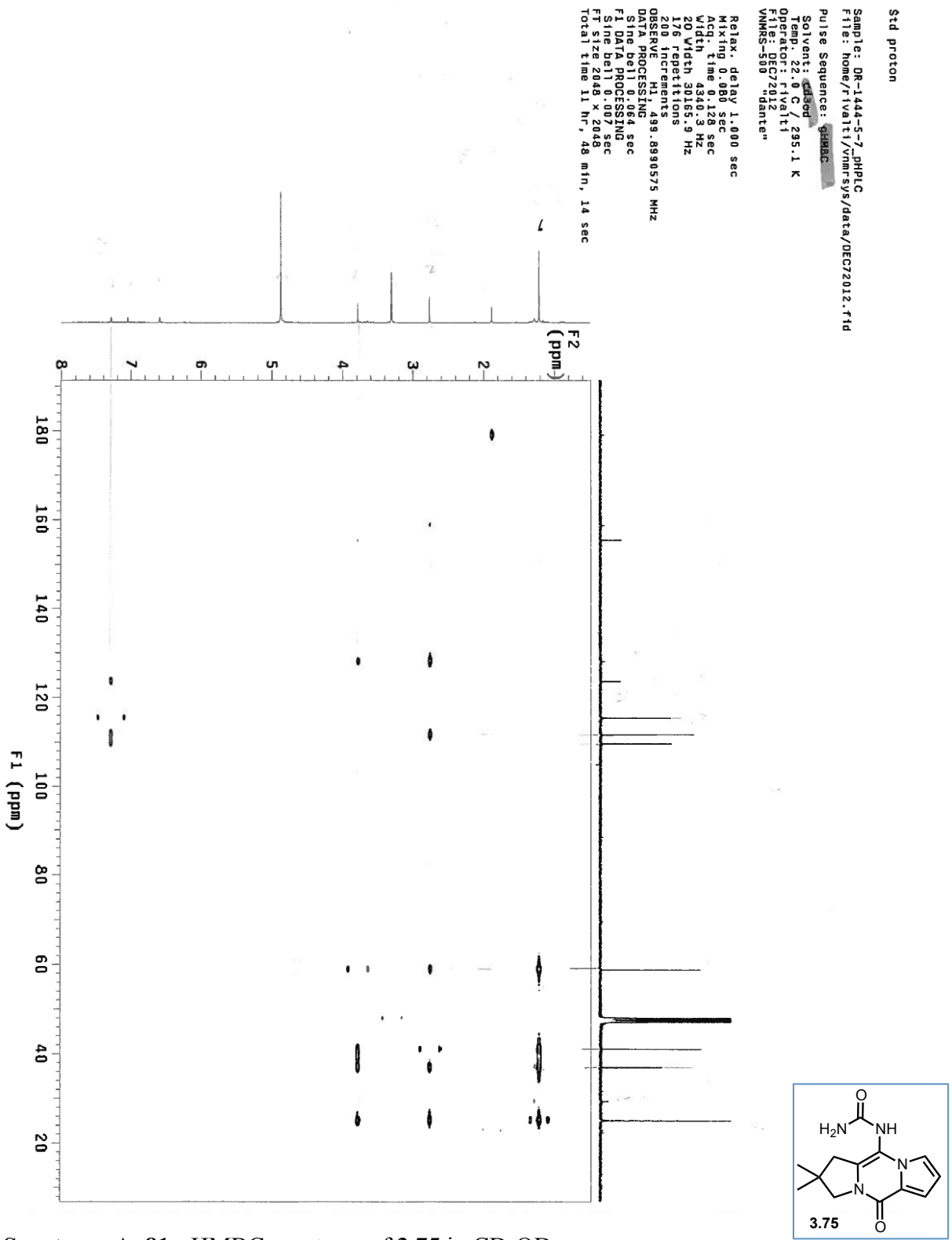


Spectrum A. 79 - COSY spectrum of **3.75** in d_6-DMSO

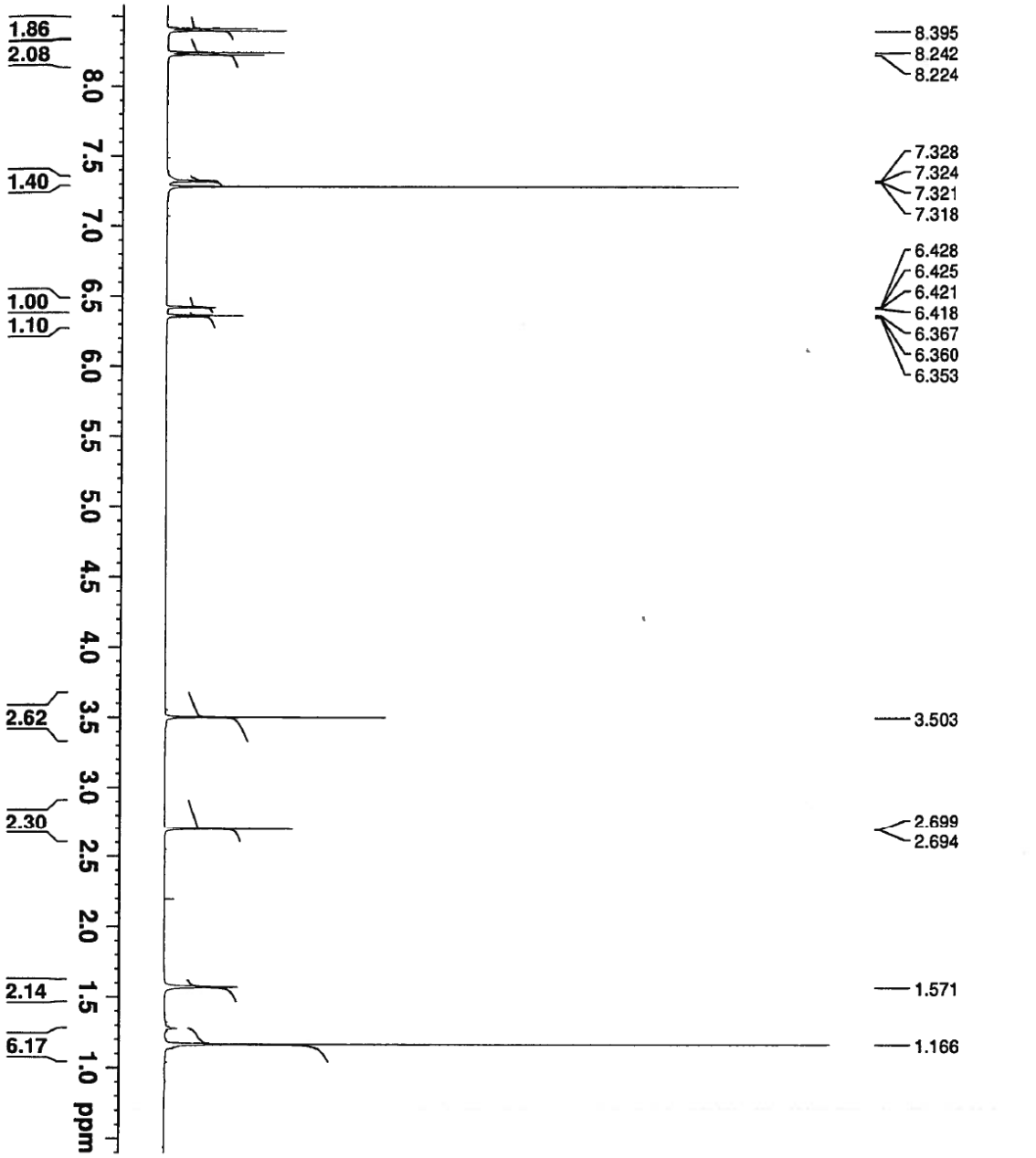




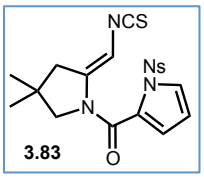
Spectrum A. 80 - HSQC spectrum of **3.75** in CD_3OD

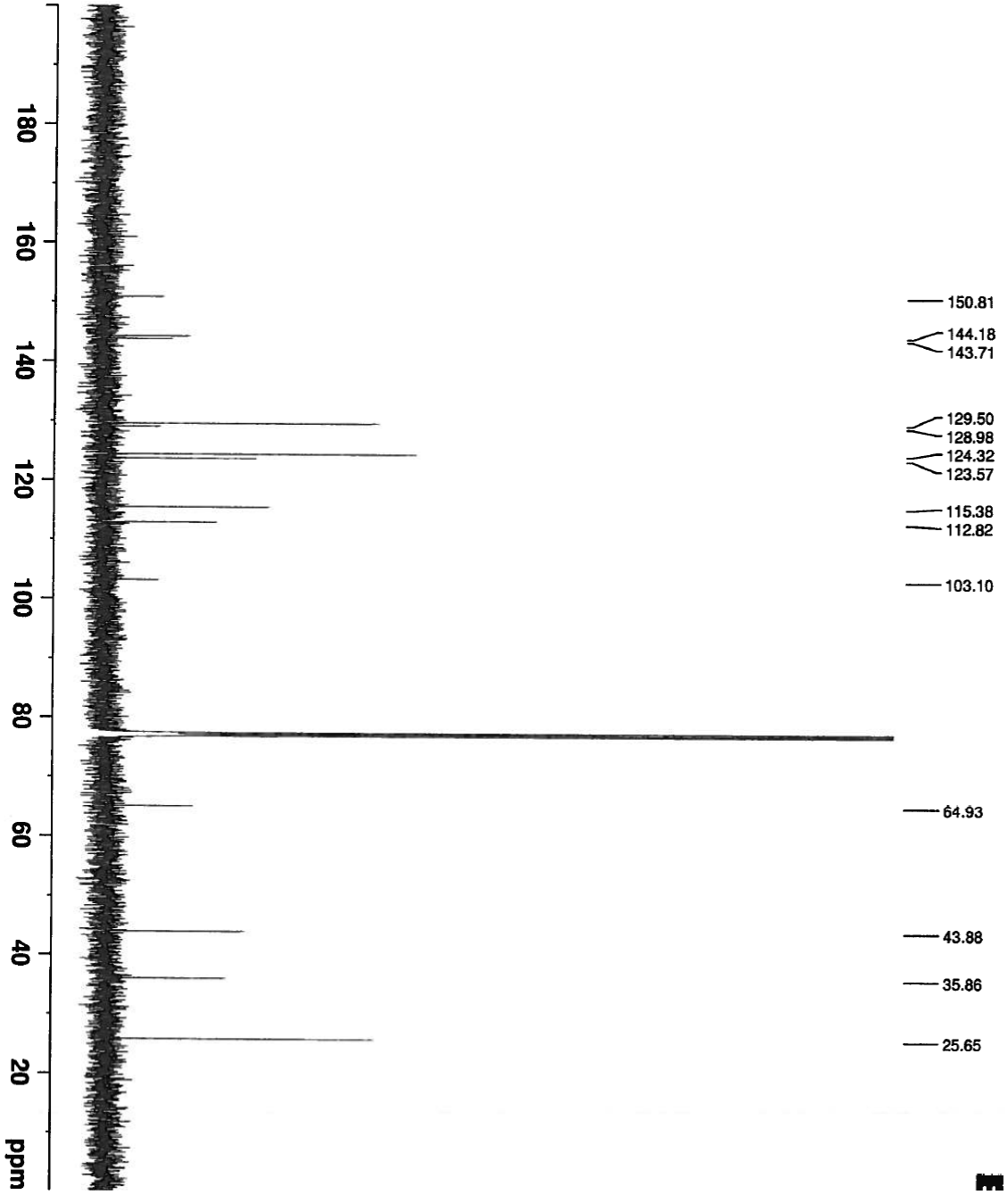


Spectrum A. 81 - HMBC spectrum of **3.75** in CD_3OD

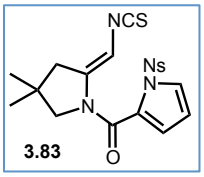


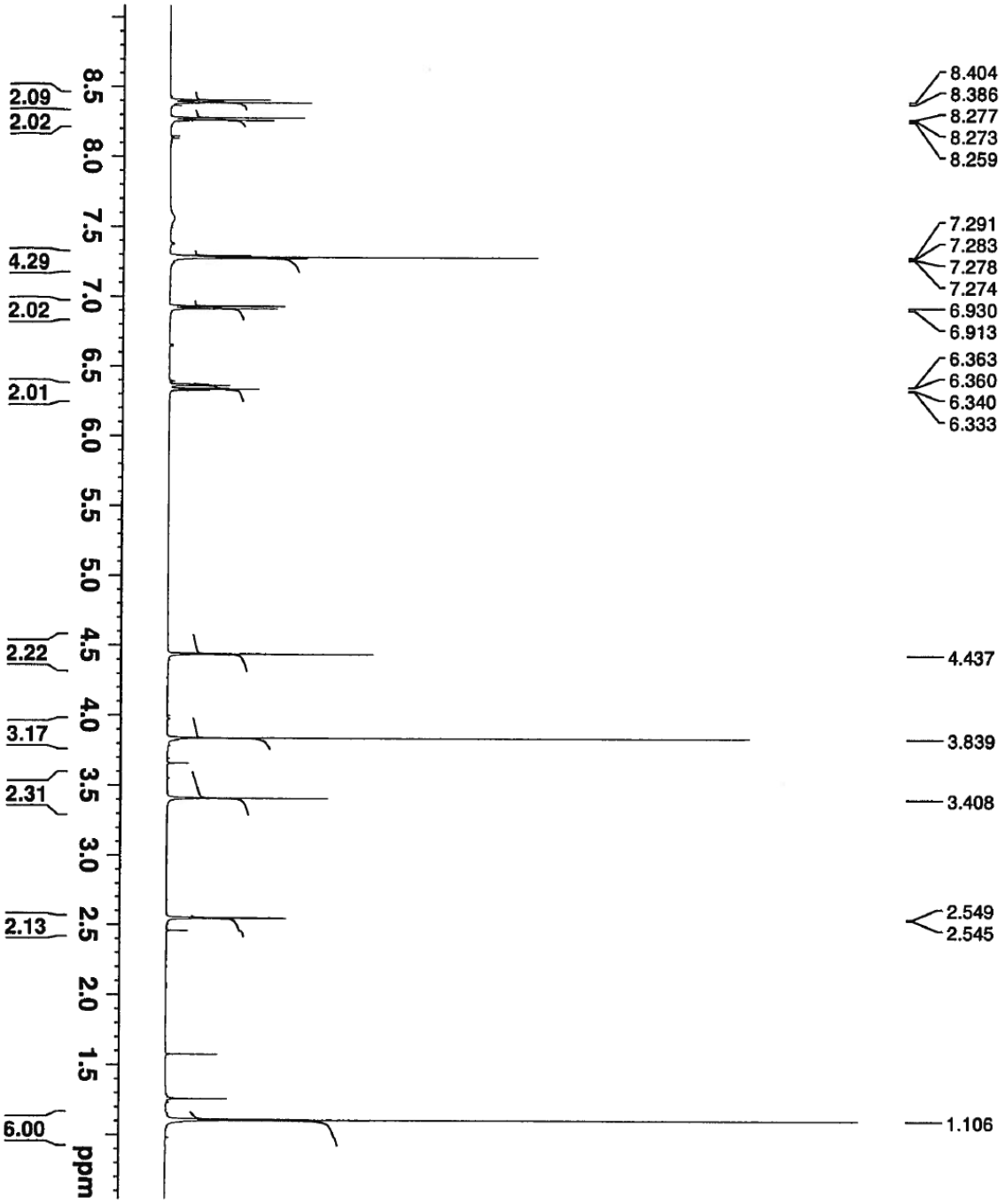
Spectrum A. 82 - ^{1}H NMR spectrum of **3.83**



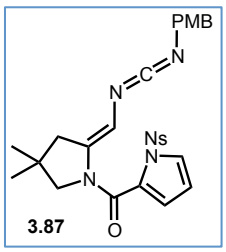


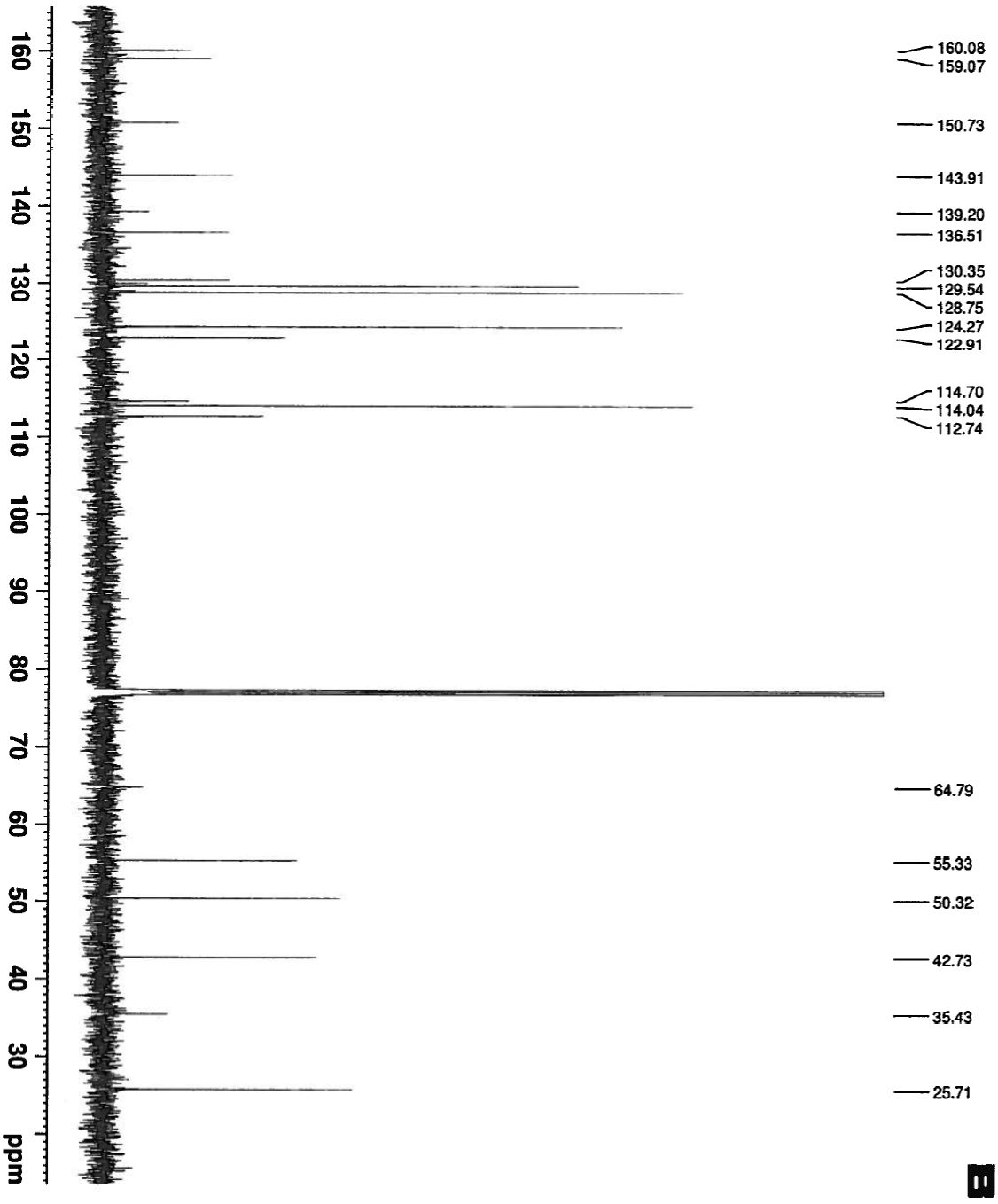
Spectrum A. 83 - ^{13}C NMR spectrum of **3.83**



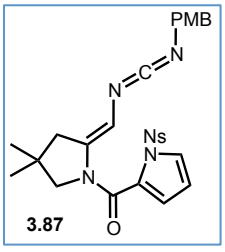


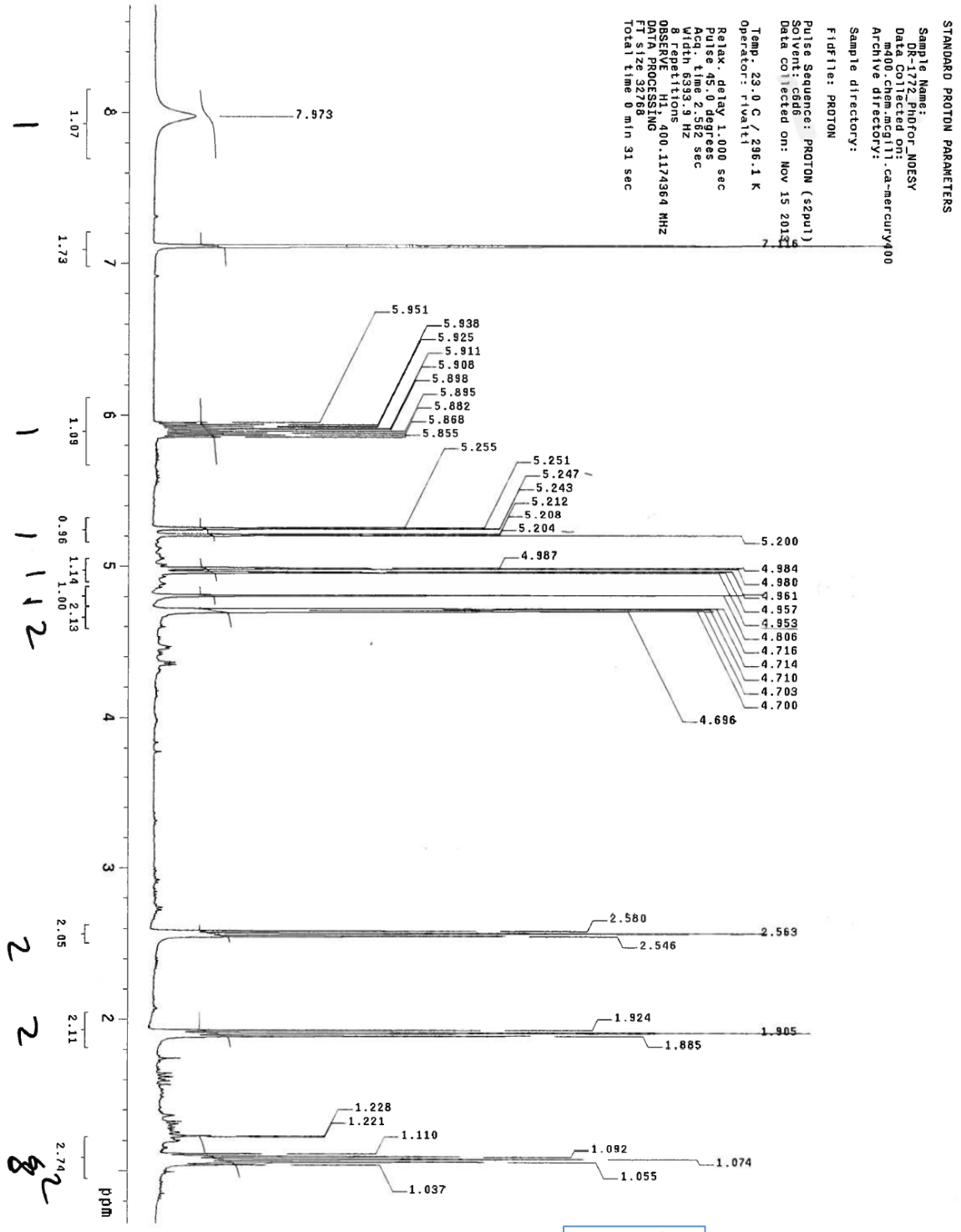
Spectrum A. 84 - ^{1}H NMR spectrum of **3.87**



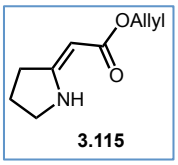


Spectrum A. 85 - ^{13}C NMR spectrum of **3.87**

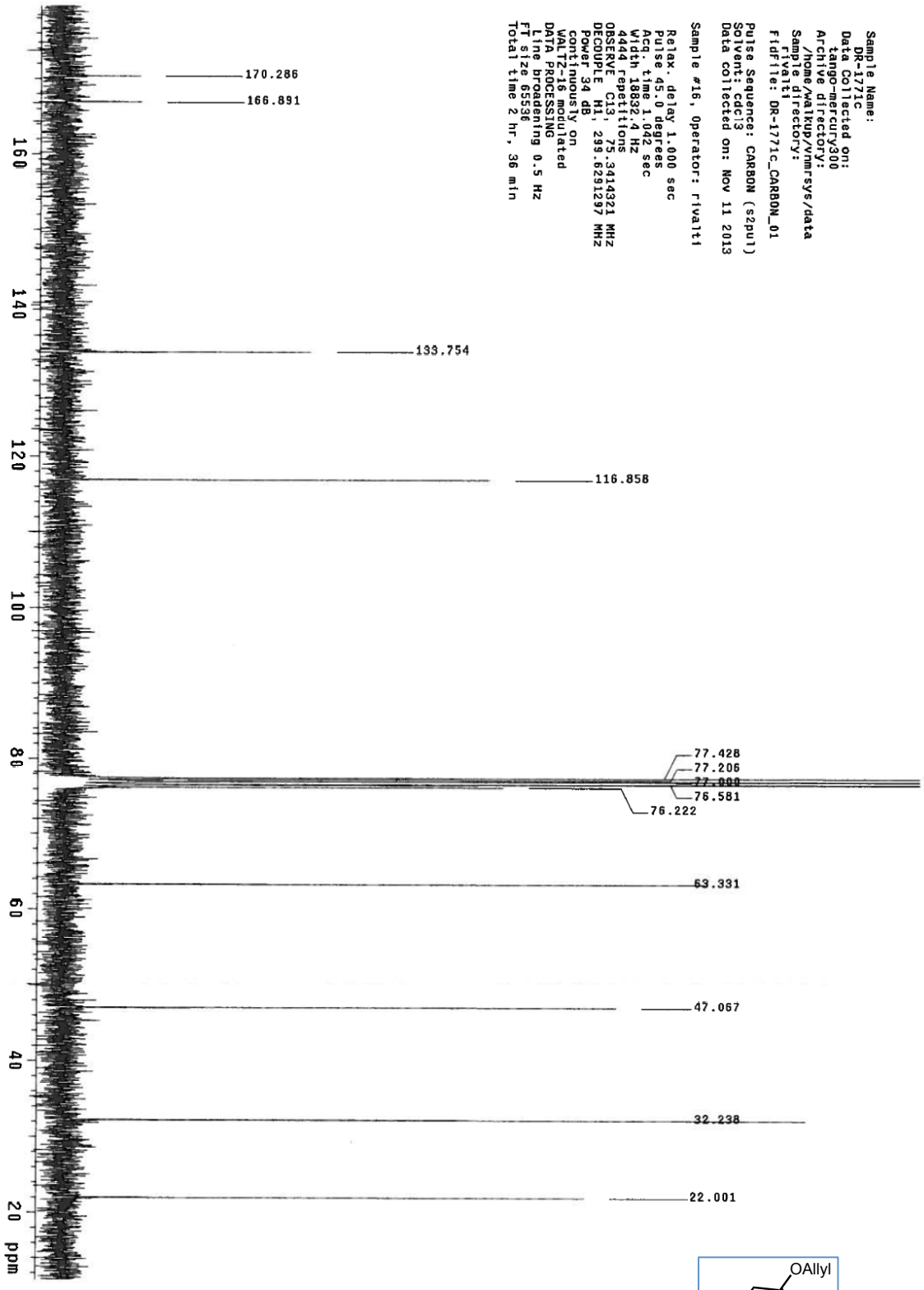




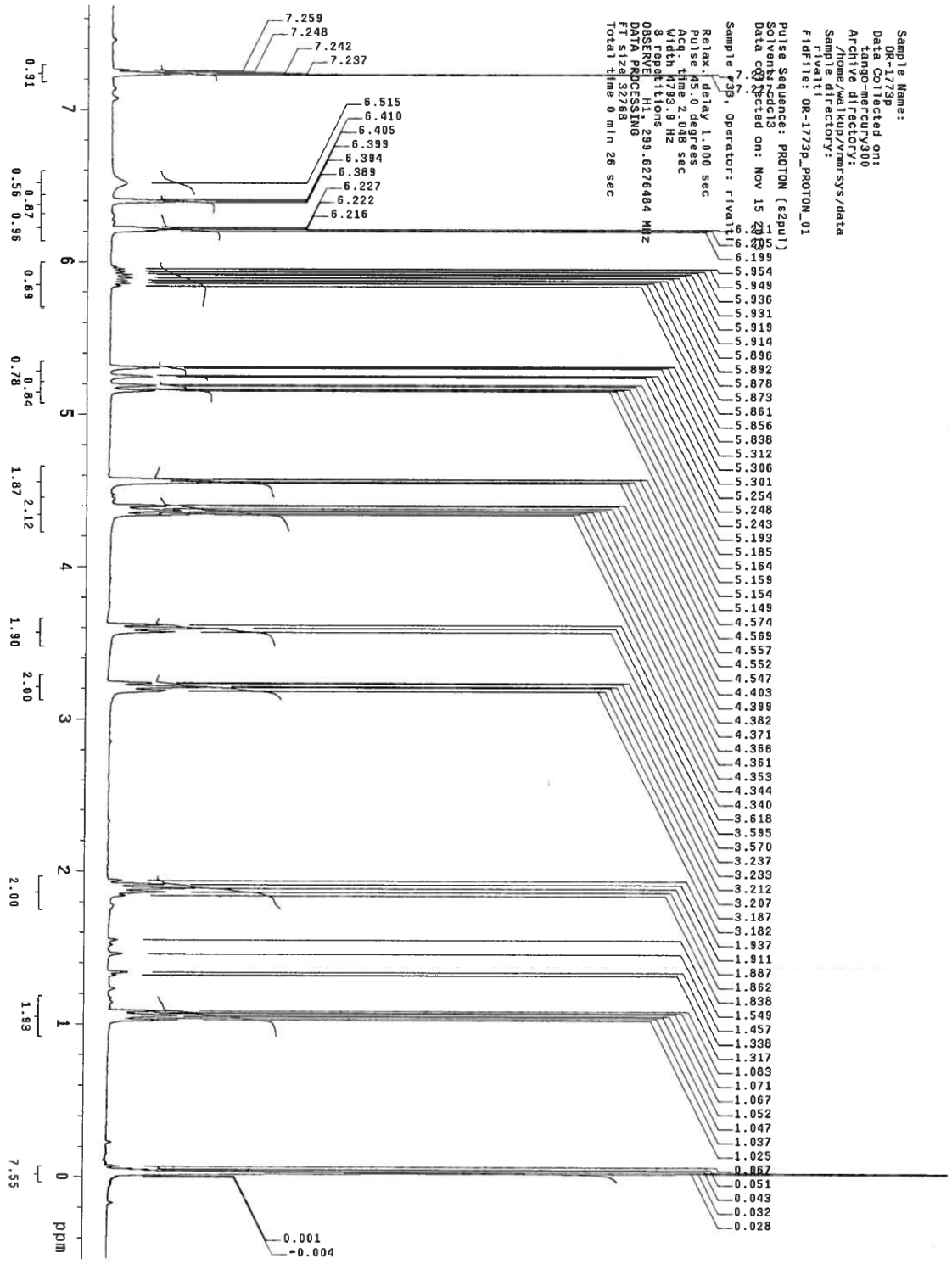
Spectrum A. 86 - ^{1}H NMR spectrum of **3.115**



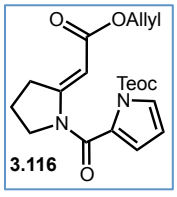
3.115

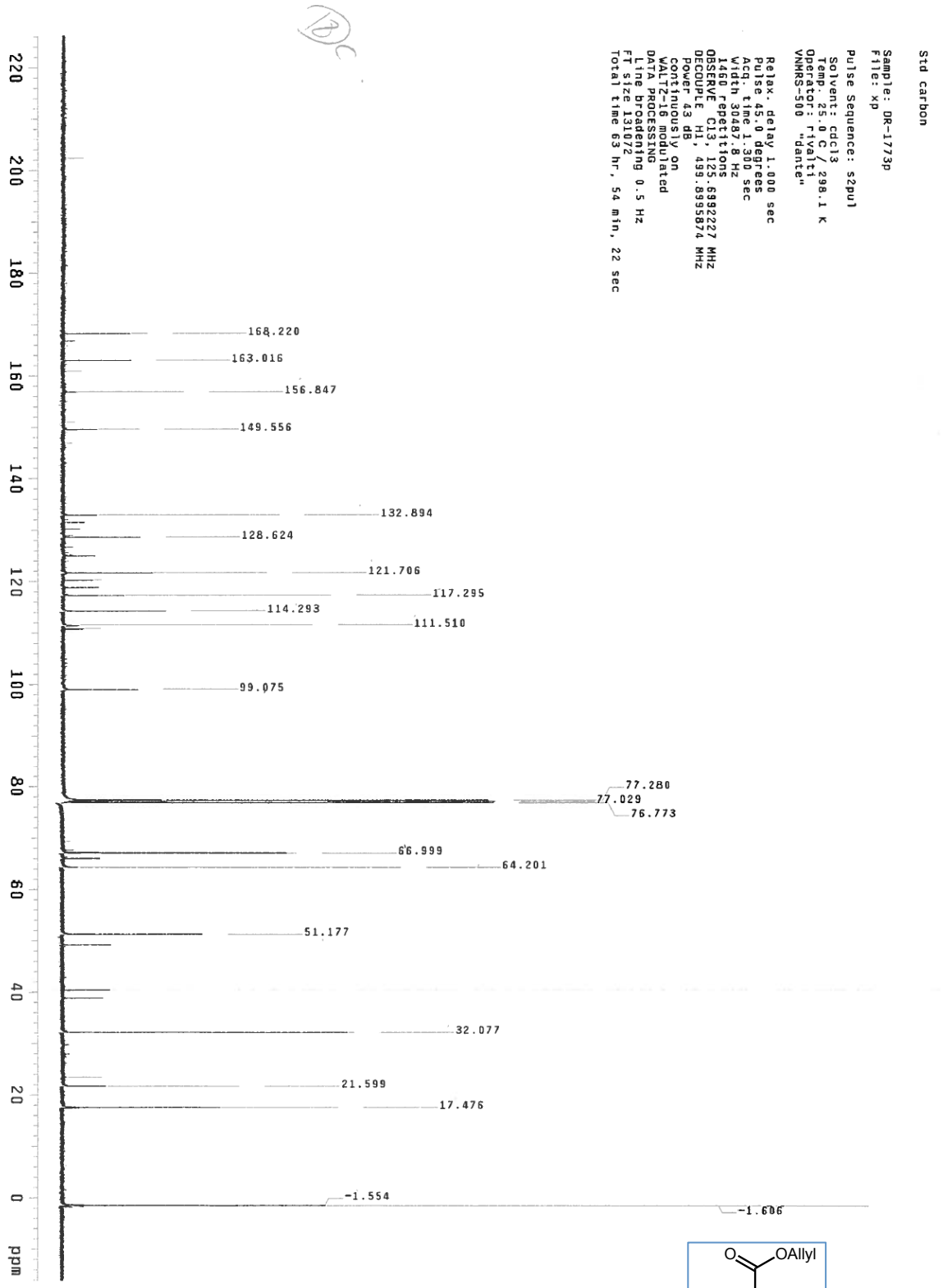


Spectrum A. 87 - ^{13}C NMR spectrum of **3.115**

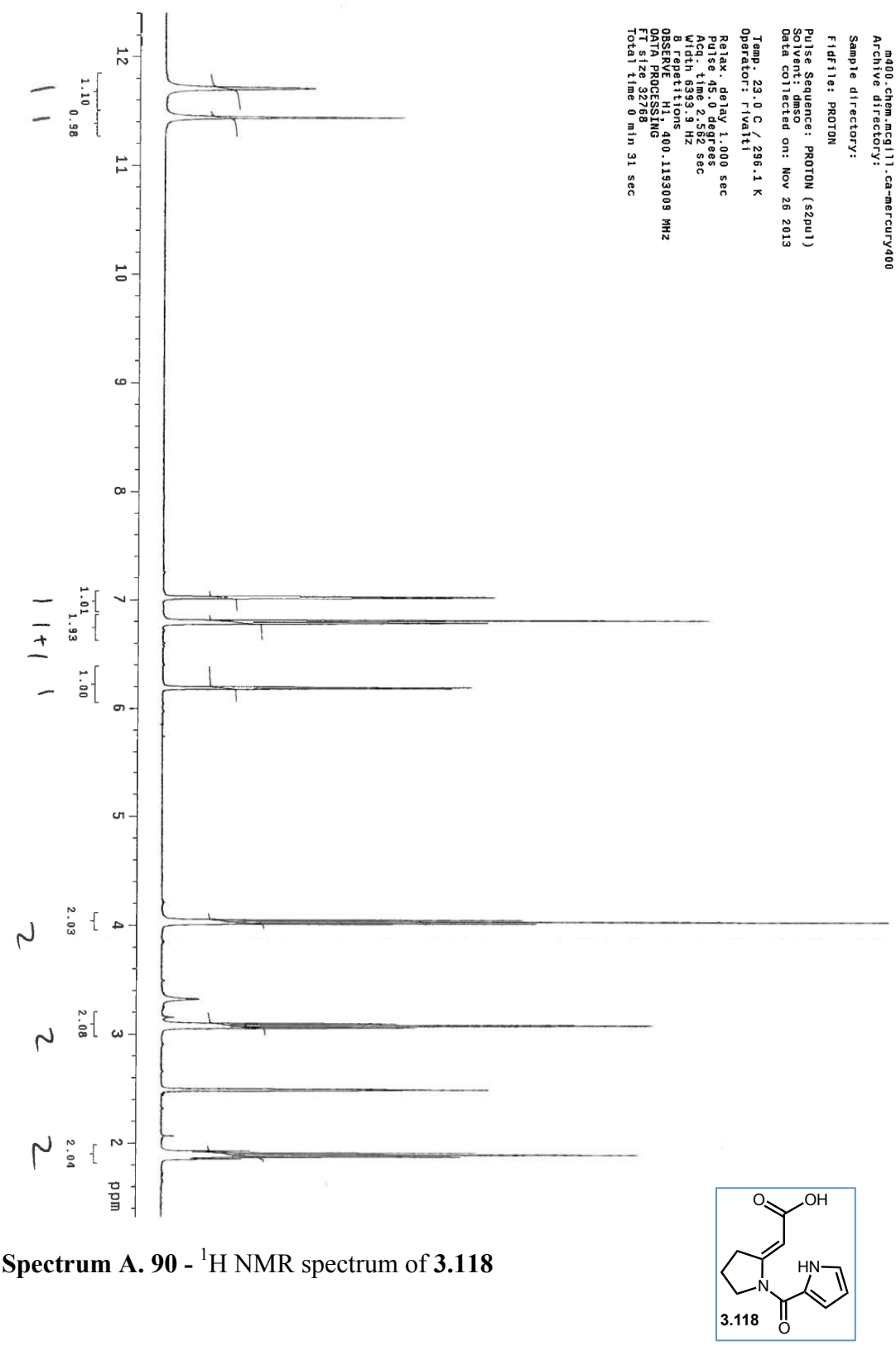


Spectrum A. 88 - ^{1}H NMR spectrum of **3.116**

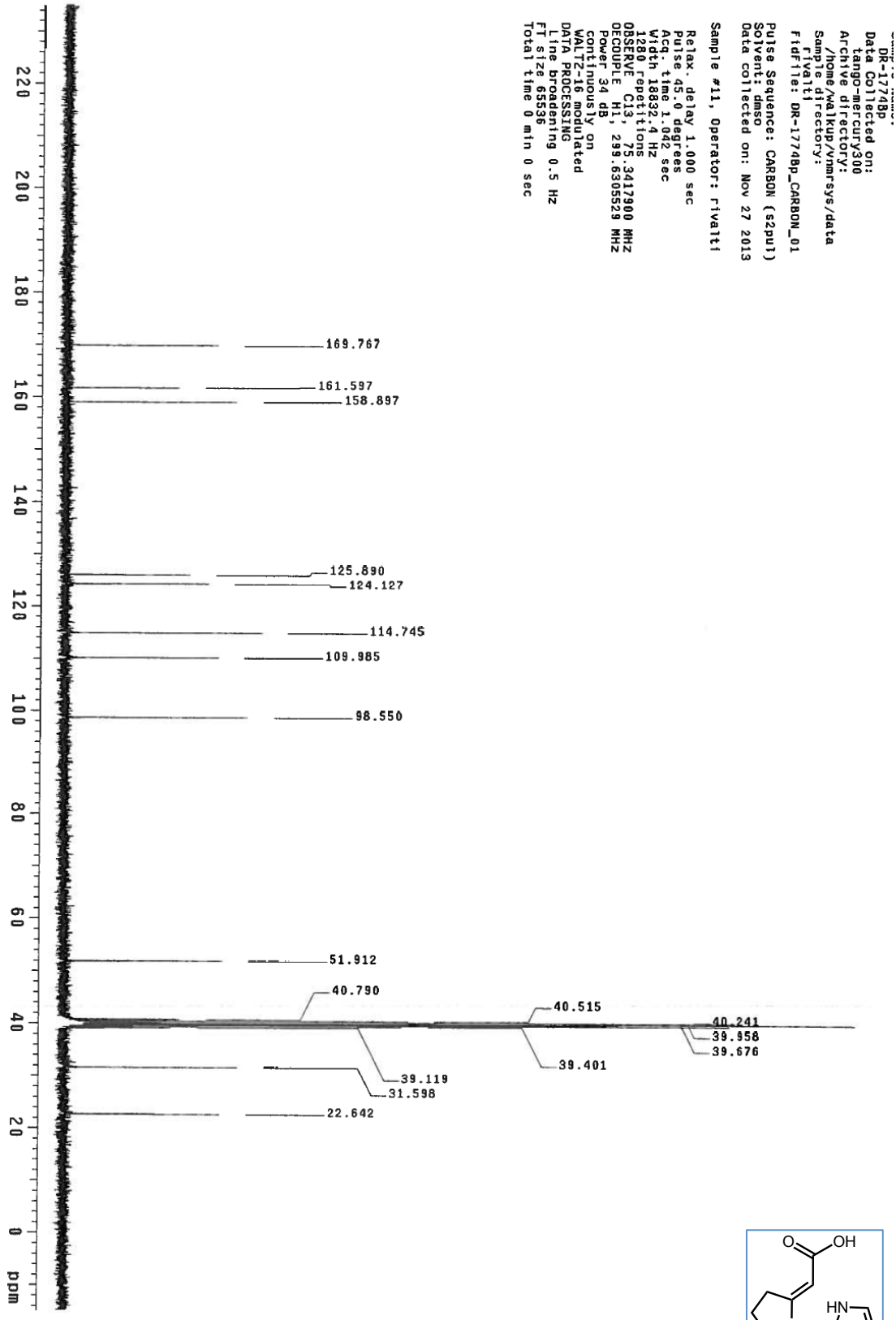




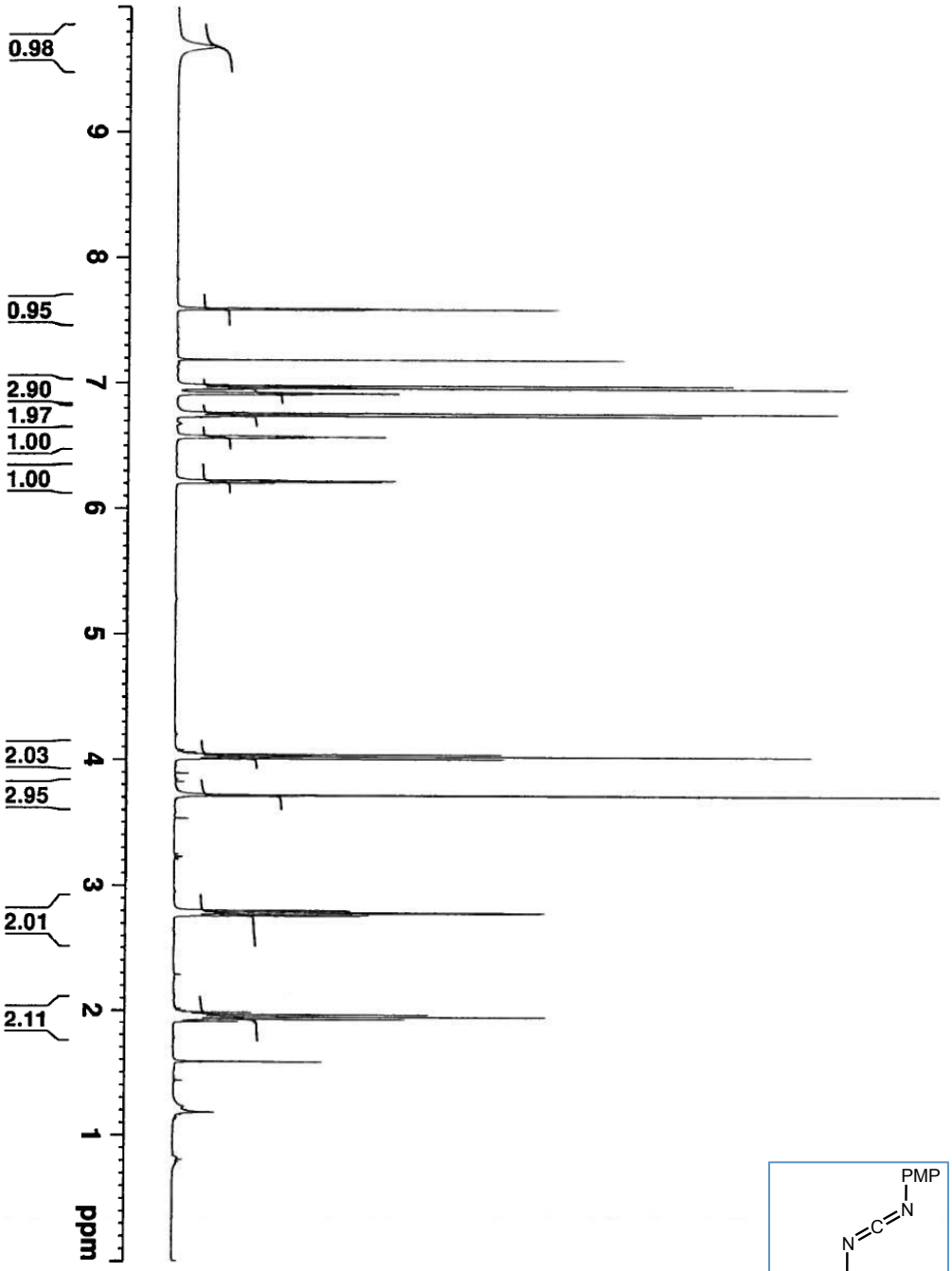
Spectrum A. 89 - ^{13}C NMR spectrum of **3.116**

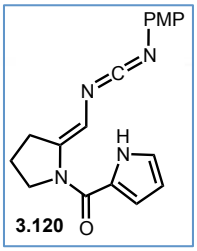


Spectrum A. 90 - ^{1}H NMR spectrum of **3.118**

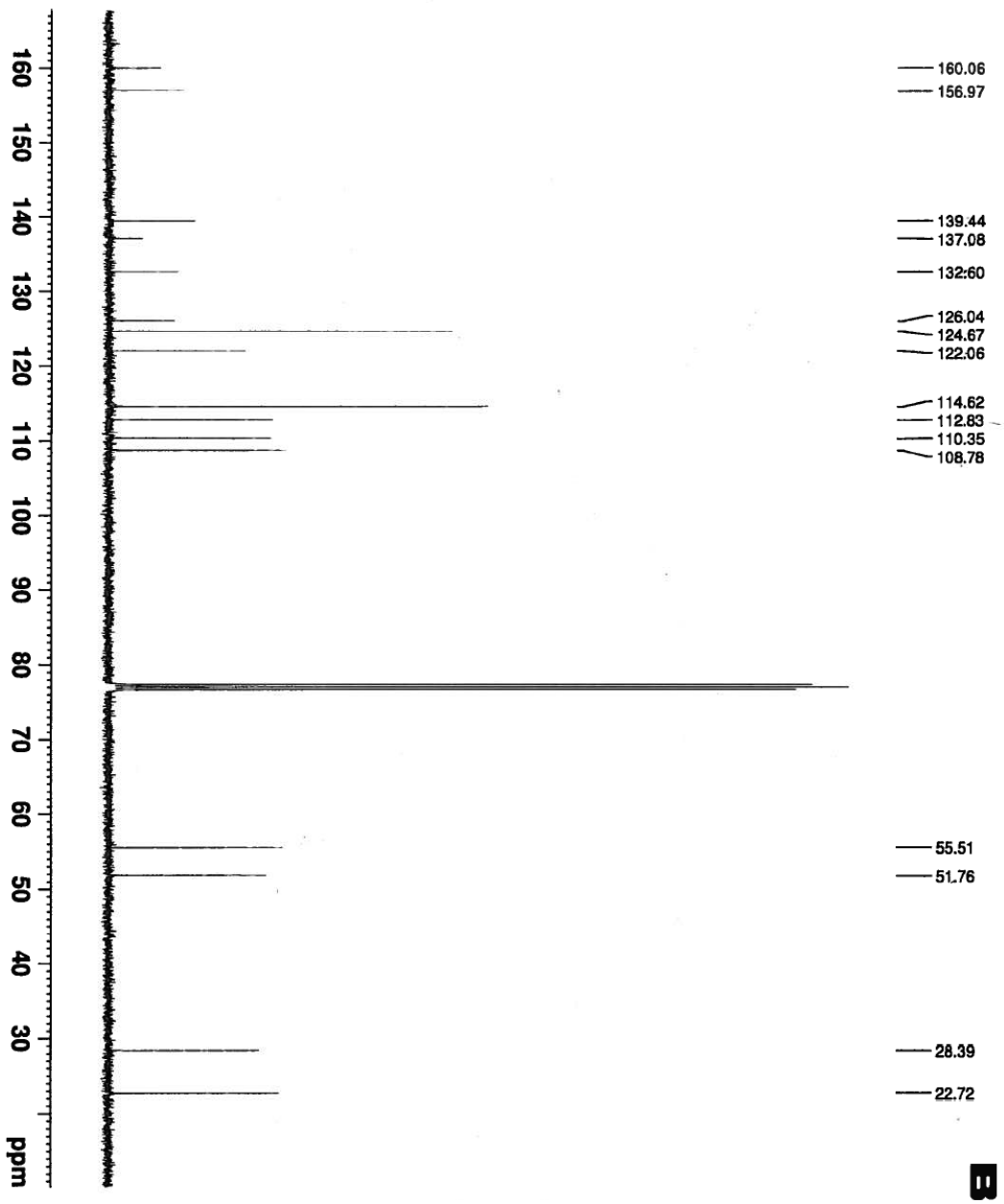


Spectrum A. 91 - ^{13}C NMR spectrum of **3.118**

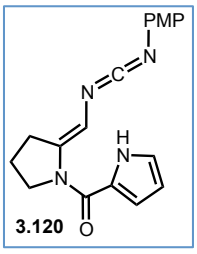


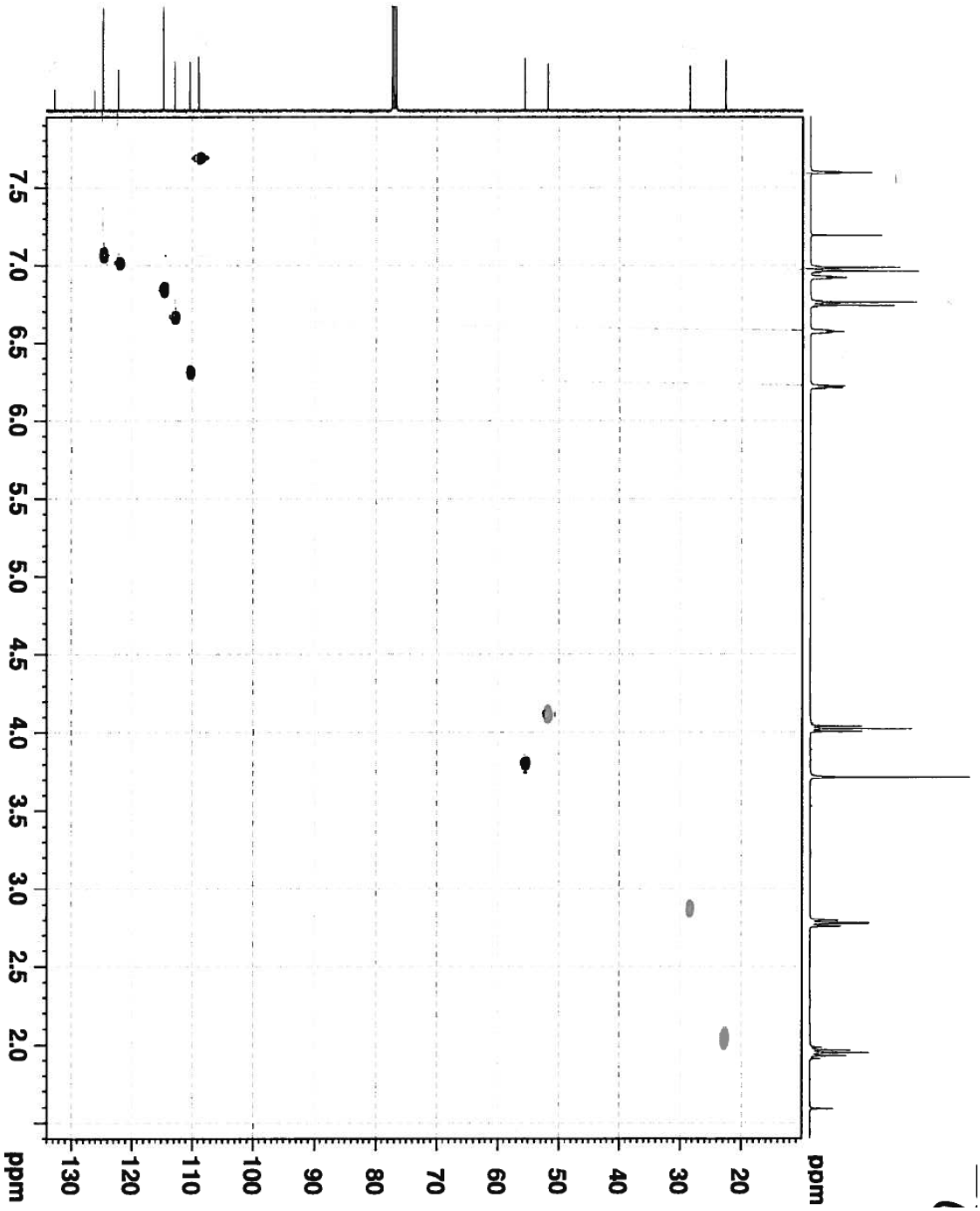


Spectrum A. 92 - ^{1}H NMR spectrum of **3.120**

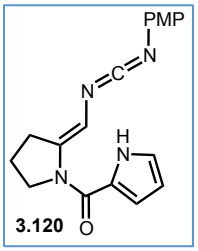


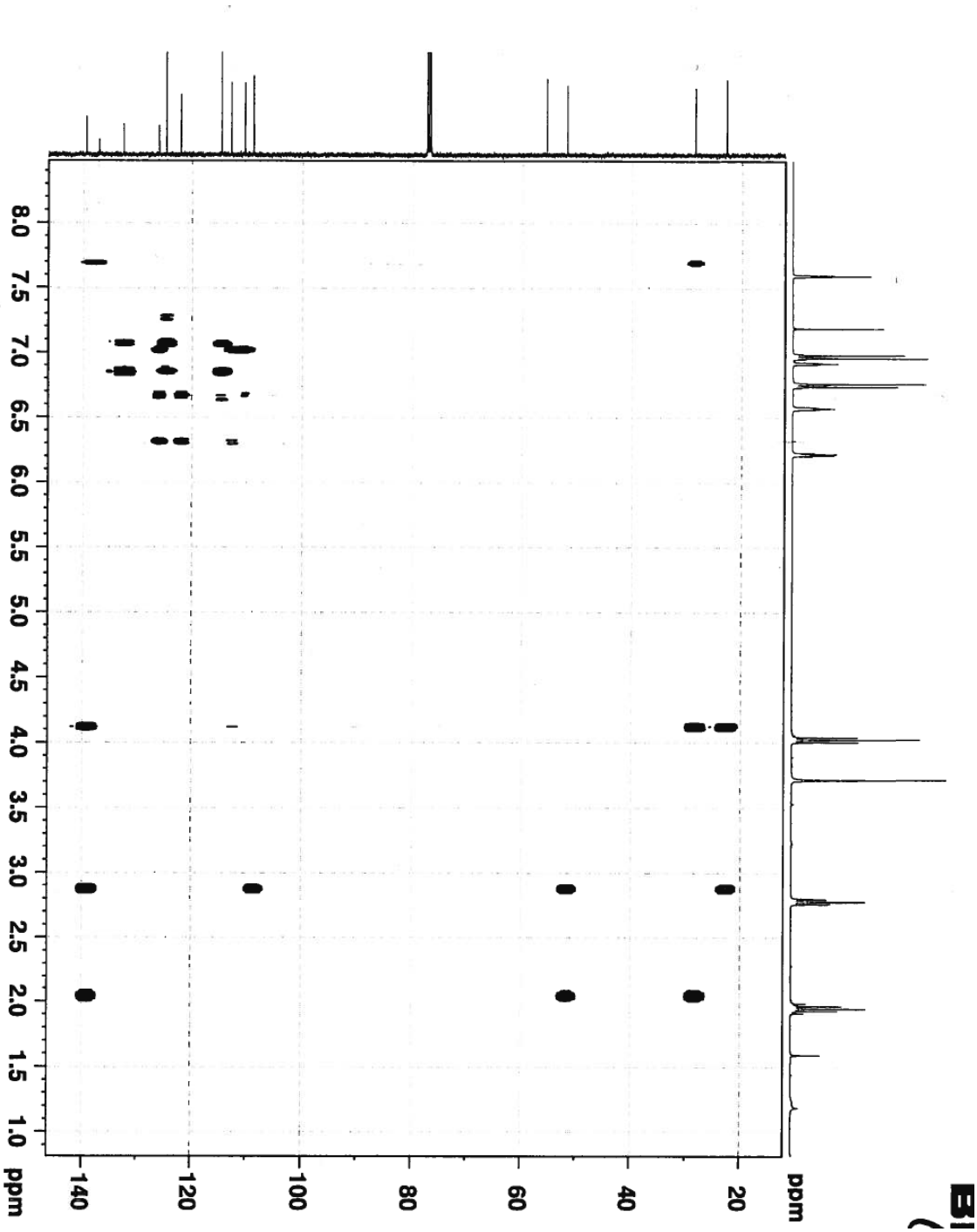
Spectrum A. 93 - ^{13}C NMR spectrum of **3.120**



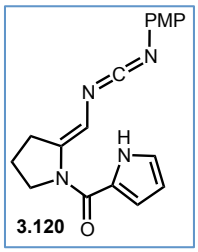


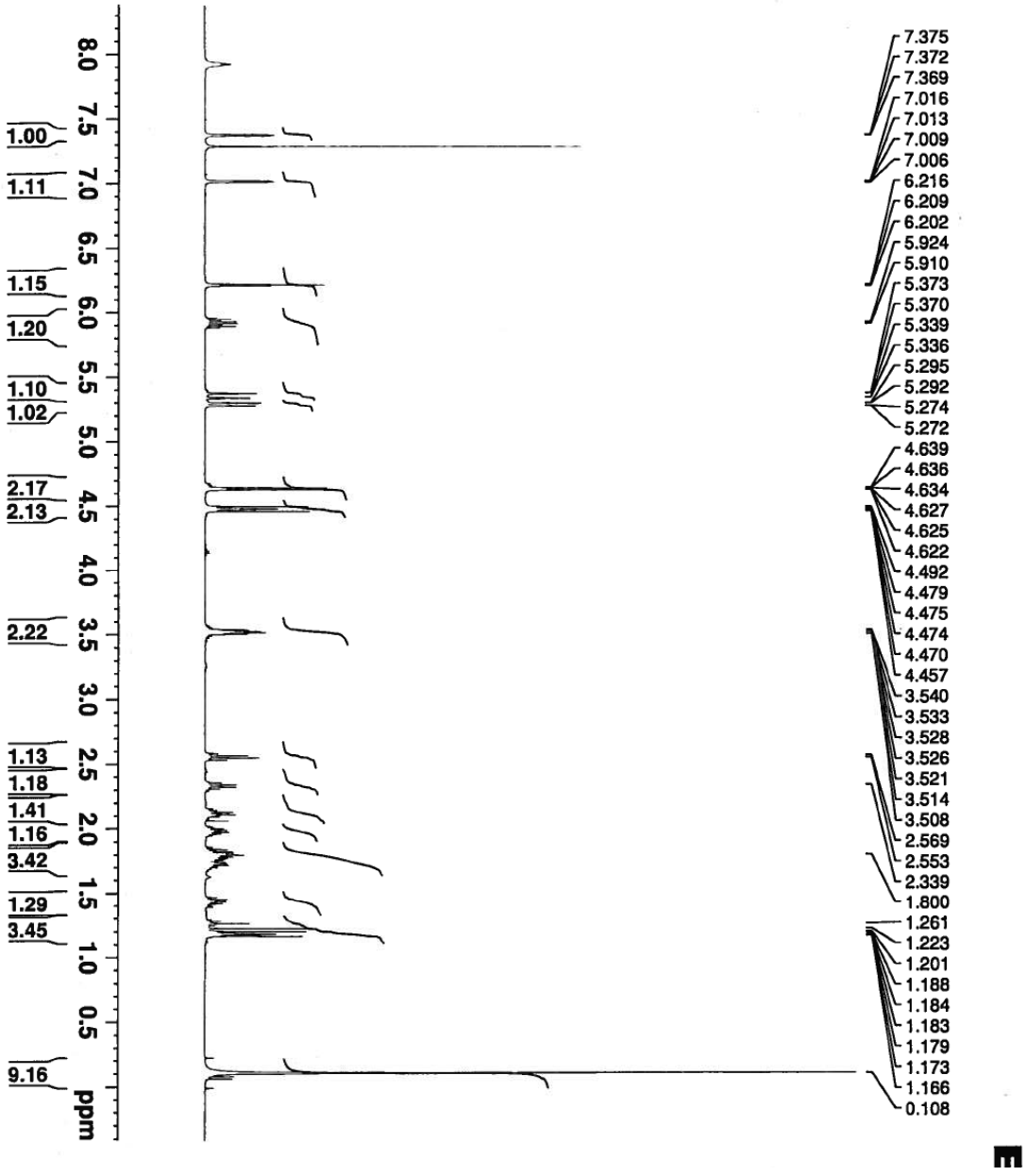
Spectrum A. 94 - HSQC spectrum of **3.120**



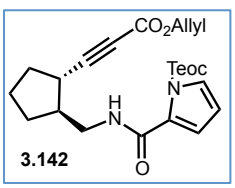


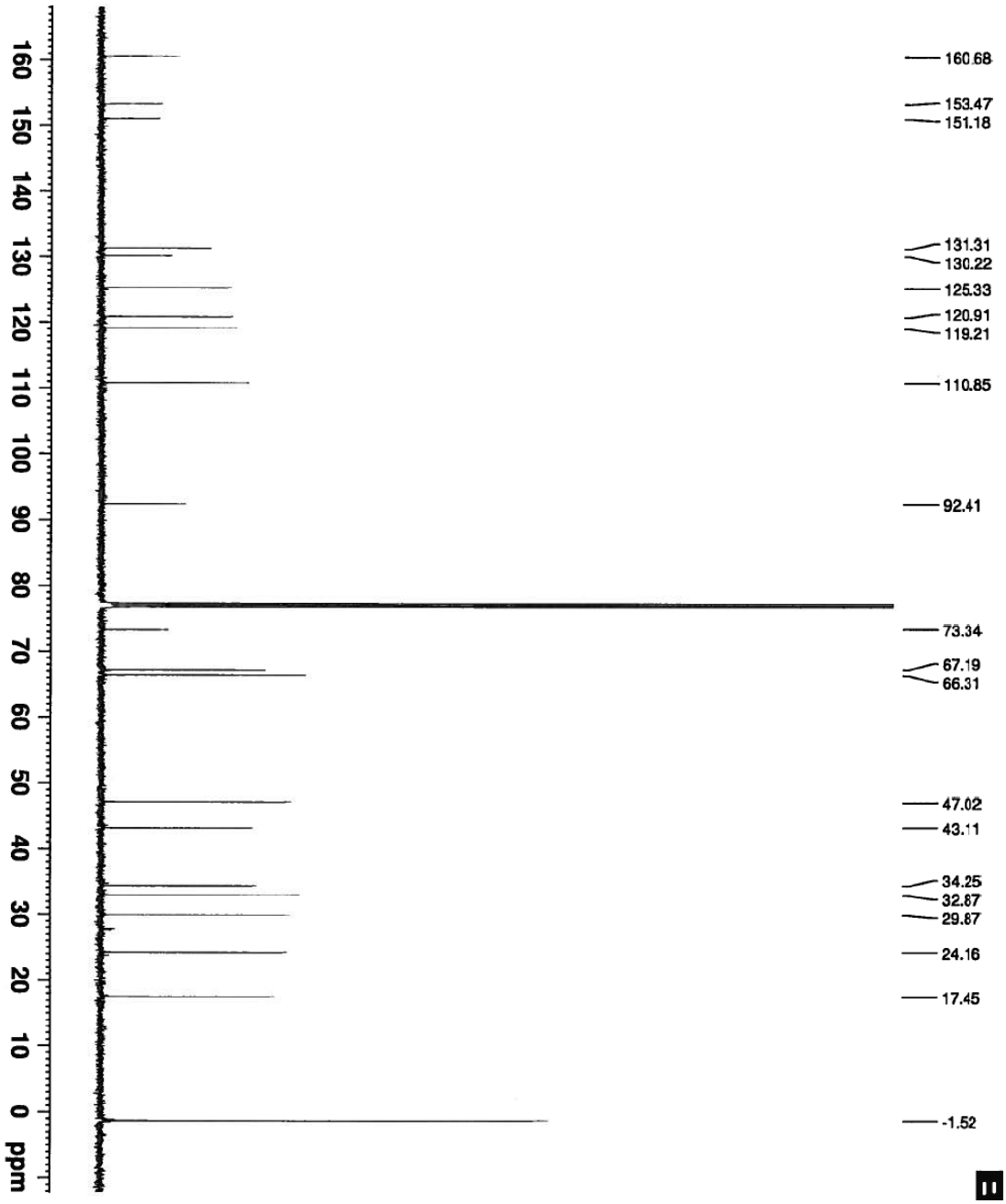
Spectrum A. 95 - HMBC spectrum of **3.120**



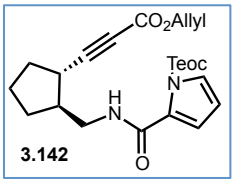


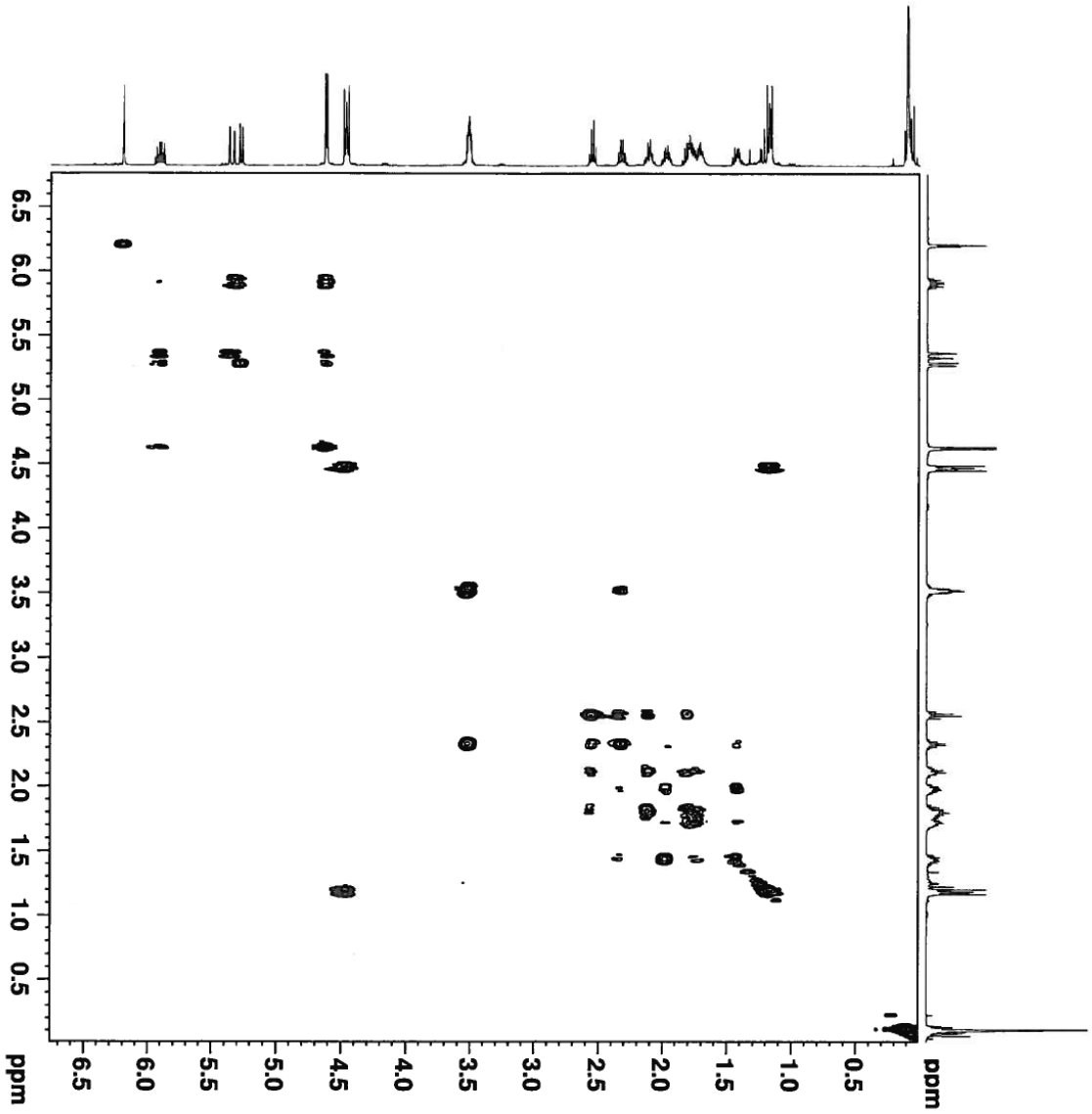
Spectrum A. 96 - ^{1}H NMR spectrum of **3.142**



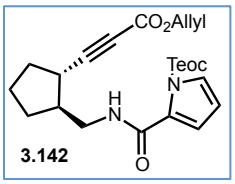


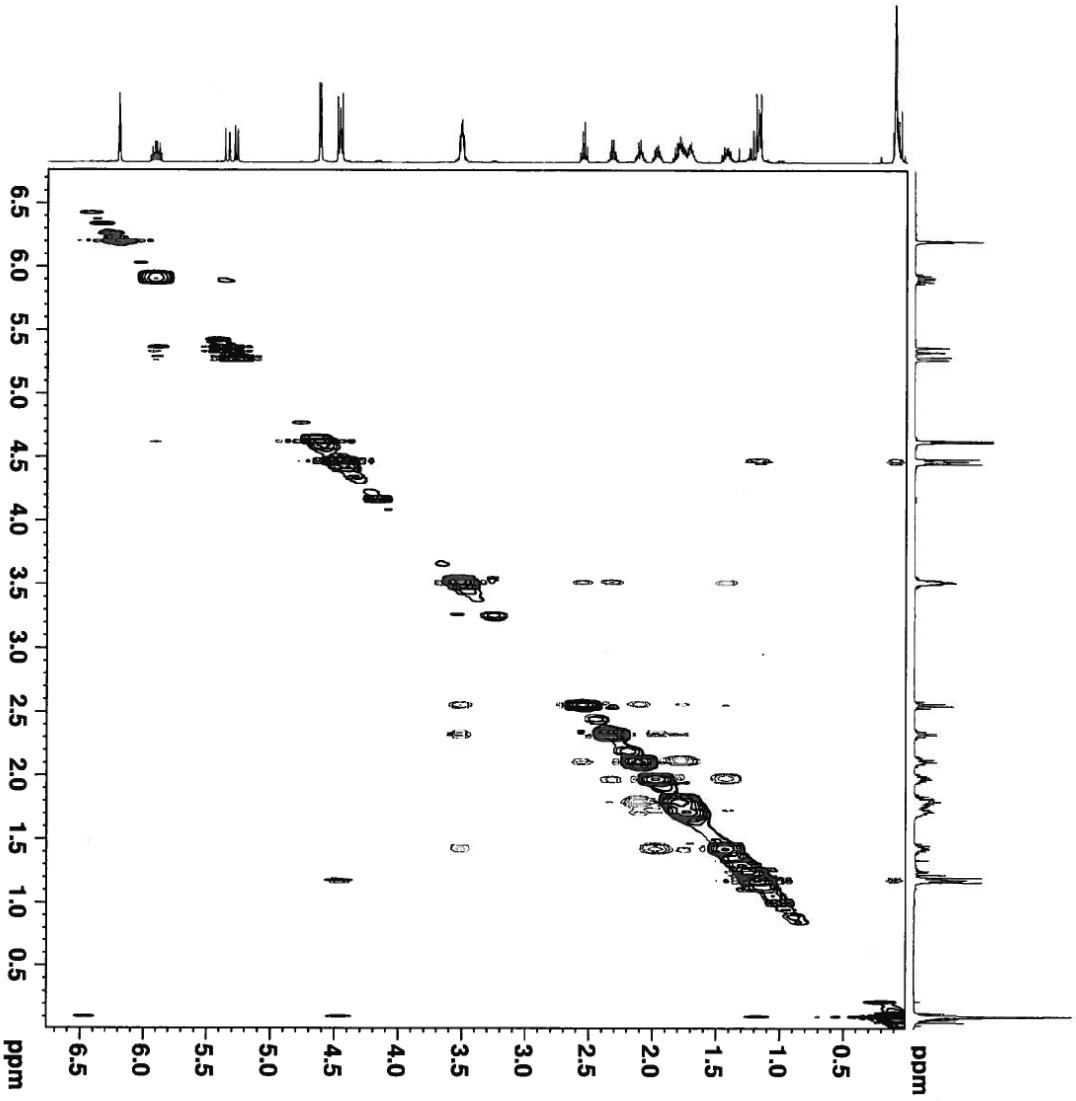
Spectrum A. 97 - ^{13}C NMR spectrum of **3.142**



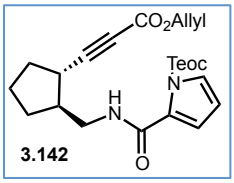


Spectrum A. 98 - COSY spectrum of **3.142**





Spectrum A. 99 - NOESY spectrum of **3.142**



Natural Product Synthesis

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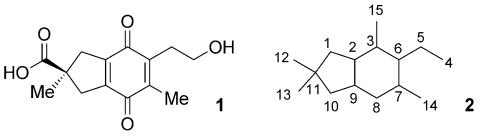
A Concise Total Synthesis of (*R*)-Puraquinonic Acid**

*Erica A. Tiong, Daniel Rivalti, Benjamin M. Williams, and James L. Gleason**

In memory of Robert E. Ireland (1929–2012)

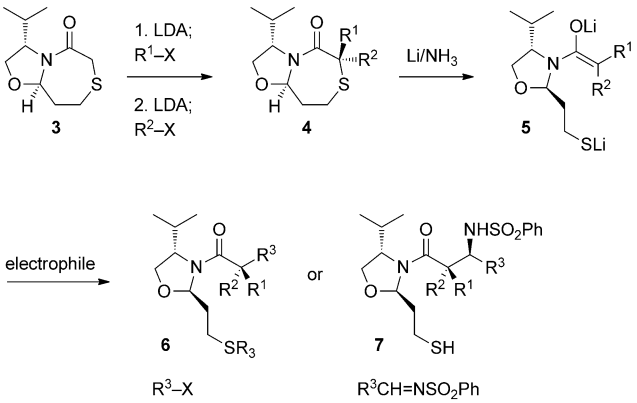
The construction of quaternary carbon stereocenters is among the most difficult challenges in synthesis, one which is compounded when two or more groups at the stereocenter are similar in size and electronics.[1] Puraquinonic acid (**1**, Scheme 1), a 15-norilludalane fungal metabolite, which was



Scheme 1. Structure of (*R*)-puraquinonic acid and the illudalane skeleton.

isolated from mycelial cultures of *Mycena Pura* and which possesses mild differentiation-inducing activity towards HL-60 cells,[2] is an intriguing example of a molecule containing a challenging quaternary stereocenter. The majority of illudalane sesquiterpenoids contain geminal dimethyl groups at C11, which are either prochiral or diastereotopic.[3] In contrast, in the structure of **1**, one of the methyl groups of the geminal dimethyl groups has undergone oxidation resulting in a new quaternary stereocenter. Importantly, the stereodefining groups in **1**, the methyl and hydroxyethyl groups, are far removed from the stereocenter and offer only a minimum of electronic differentiation. Thus, while **1** may appear at first glance to be a simple molecule, its synthesis in enantiopure form is a significant challenge. Indeed, while an efficient 10-step synthesis of racemic **1** has been reported,[4] the only enantioselective synthesis of **1** exceeds 30 steps in length.[5]

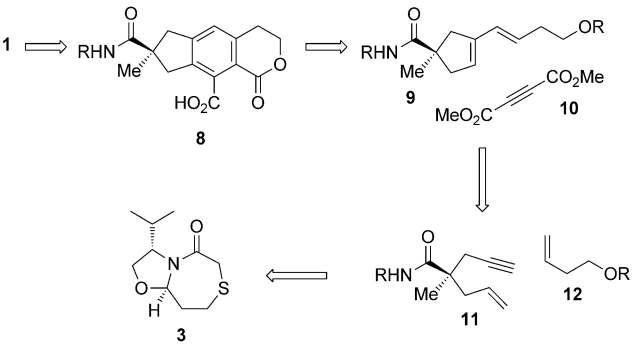
We have previously developed a method for the formation of quaternary stereocenters based on the stereoselective generation and alkylation of α,α-disubstituted amide enolates from easily prepared bicyclic thioglycolate lactam **3** (Scheme 2).[6,7] Sequential double alkylation of bicyclic lactam **3** followed by a dissolving metal reduction results in stereoselective formation of an α,α-disubstituted enolate (**5**), where the enolate geometry is regulated by the combination of the conformation of the starting bicycle and the configuration of the α-stereocenter. The resulting enolate possesses



Scheme 2. A bicyclic lactam auxiliary for selective quaternary stereocenter formation. LDA = lithium diisopropylamide.

a C_2-pseudosymmetric auxiliary and undergoes highly diastereoselective alkylations (**6**) and Mannich additions (**7**).[6c,8] Importantly, the stereoselectivity of enolate generation and subsequent alkylation is based on the order of alkylation and not the size of the substituents, such that quaternary stereocenters bearing three groups of nearly identical size (e.g. ethyl, propyl, and allyl) can be formed with excellent stereoselectivity. We felt that this method would be ideal for the synthesis of **1**, because it would allow for an early-stage introduction of the quaternary stereocenter.

Our retrosynthetic analysis (Scheme 3) suggested that the quinoid ring in **1** might be generated by oxidation of a Diels–Alder adduct of dimethyl acetylenedicarboxylate **10** and diene **9**. Diene **9** could be envisaged as coming from a tandem ring-closing ene–yne/diene–ene cross metathesis of 1,6-enyne **11** and 3-buten-1-ol.[9] Finally, we fully expected that **11** could be generated stereoselectively through a dialkylation/reduction/alkylation sequence using thioglycolate lactam **3**. Impor-



Scheme 3. Retrosynthetic approach to (*R*)-puraquinonic acid.

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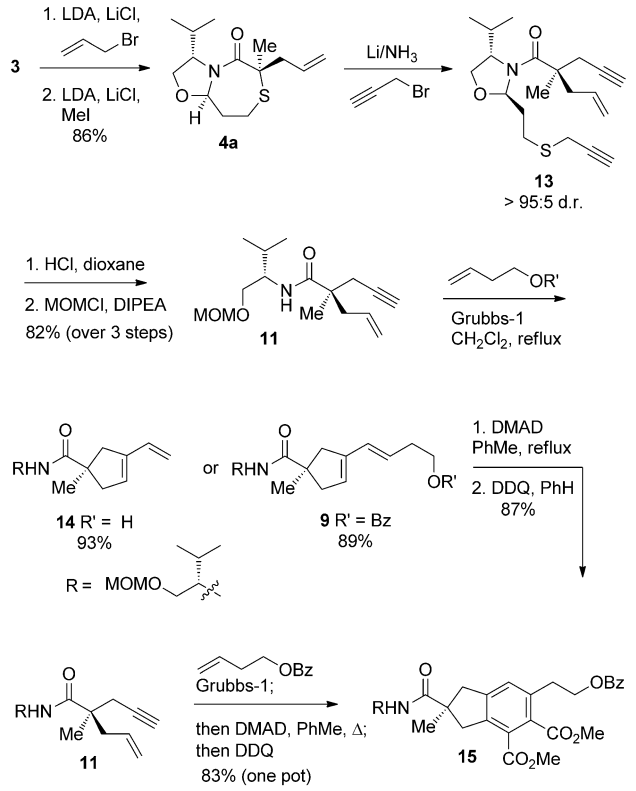
tantly, in this design, a quaternary stereocenter bearing two groups of similar size and similar electronics (allyl and propargyl) would be set at an early stage, and the stereochemistry would be transmuted through the subsequent metathesis and Diels–Alder sequences to eventually produce the distally differentiated quaternary stereocenter.

Diels–Alder precursor **9** was prepared in six steps from bicyclic lactam **3** in 63% overall yield. Sequential alkylation of **3** with allyl bromide followed by methyl iodide provided **4a** in 86% yield as a single stereoisomer (Scheme 4). Reductive

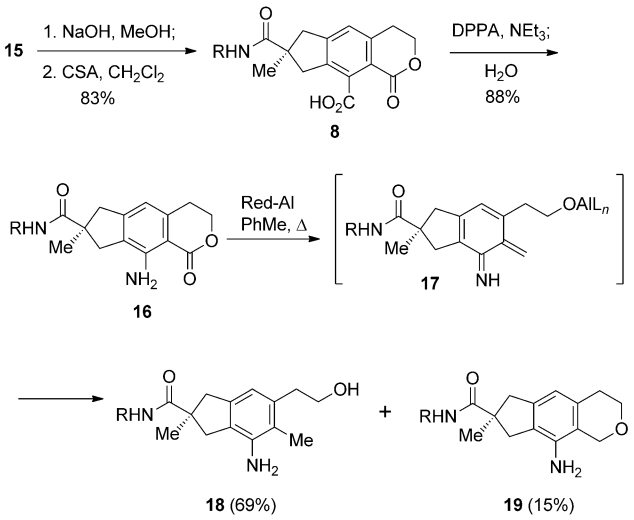


Scheme 4. Formation of the quaternary carbon stereocenter and a metathesis/Diels–Alder sequence. MOMCl = methoxymethyl chloride, DIPEA = *N,N*-diisopropylethylamine, Grubbs-1 = Grubbs catalyst of the first generation, DMAD = dimethyl acetylenedicarboxylate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

enolization of **4a** using lithium in ammonia followed by addition of propargyl bromide formed the desired quaternary stereocenter in > 95:5 d.r.[10] The aminal in **13** was hydrolyzed to simplify subsequent NMR spectra (by eliminating amide rotamers) and also to excise the additional propargyl group to avoid possible complications in subsequent metathesis and Diels–Alder chemistry. Treatment with aq. 1M HCl in dioxane at 23°C afforded selective cleavage of the aminal without affecting the amide. Protection of the resulting primary alcohol with methoxymethyl chloride and Hünig's base afforded metathesis precursor **11** in 82% yield over three steps. Attempted ring-closing ene–yne/diene–ene cross metathesis[9] of **11** with 3-buten-1-ol using either Grubbs first- or second-generation catalysts afforded only intramolecular ene–yne metathesis product **14** and the homodimer of 3-buten-1-ol with no cross-metathesis product observed.[11] However, subjection of the benzoate ester of 3-buten-1-ol to the metathesis conditions allowed the formation of cross-metathesis product **9** in 89% yield as a single *E* isomer.

Diels–Alder cycloaddition of diene **9** with dimethyl acetylenedicarboxylate proceeded readily in refluxing toluene without need for Lewis acid catalysts. The resulting diastereomeric mixture of 1,4-cyclohexadienes was directly oxidized with DDQ in benzene to afford arene **15** in 87% yield. Given the need for an ester-protecting group in the metathesis step, we attempted to develop a cascade sequence using the 3-buten-1-yl ester of acetylene dicarboxylic acid, which would undergo the metathesis sequence followed by Diels–Alder cycloaddition. Unfortunately, all attempts at this cascade resulted only in isolation of simple ring-closing product **14**. However, we were able to develop an efficient one-pot process. Conducting the metathesis reaction in dichloromethane followed by a solvent switch to toluene and addition of DMAD followed by treatment with DDQ afforded **15** in 83% yield from **11.**

To differentiate the two methyl esters, **15** was subjected to global saponification to reveal a diacid alcohol, which underwent lactonization using catalytic camphor sulfonic acid in dichloromethane to afford **8** in 83% yield (Scheme 5). To set

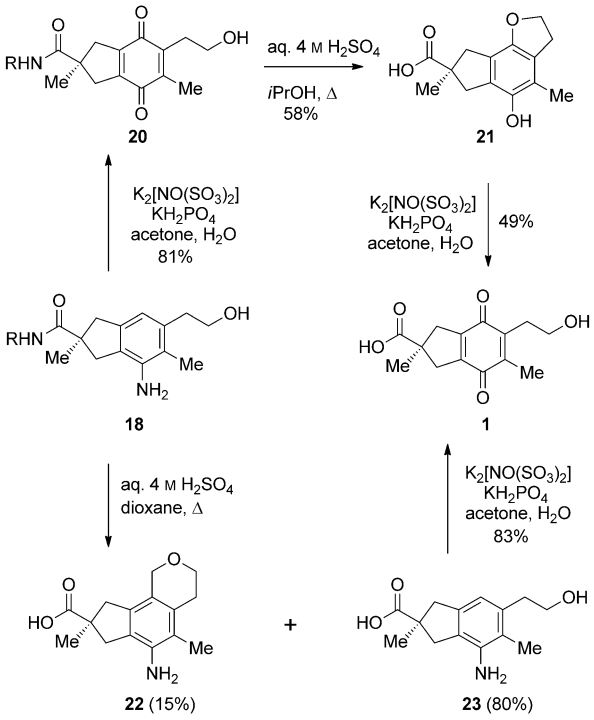


Scheme 5. Core functionalization. CSA = camphor sulfonic acid, DPPA = diphenylphosphorylazide, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.

the stage for eventual oxidation to the quinone, the remaining carboxylic acid was transformed into an amine through a Curtius rearrangement. Treatment of **8** with diphenylphosphorylazide followed by aqueous hydrolysis afforded **16** in 88% yield. In a model system, we noted that oxidation of a related aniline to the corresponding quinone could only be achieved when the ring did not bear any electron-withdrawing groups, and thus we sought to reduce the lactone in **16**. We were pleased to find that treatment of **16** with Red-Al in toluene at reflux reduced the lactone to the desired methyl group, thereby affording **18** in 69% yield. Importantly, as long as a large excess of hydride was not employed, the reaction

proceeded without any noticeable reduction of the secondary amide. The reduction was accompanied by the formation of a small amount of dihydropyran **19** (15%). That this was a by-product and not an intermediate on the reduction pathway was supported by the fact that resubmission of **19** to the reduction conditions only resulted in slow reduction of the amide. We presume that the reduction of the lactone to the methyl occurs via an *ortho*-iminoquinone methide intermediate (**17**), which is not easily formed from **19** owing to poor orbital alignment.

To complete the synthesis of **1**, all that was seemingly required was to oxidize to the quinone and remove the chiral auxiliary. Oxidation of **18** could be easily achieved by using Fremy's salt in water/acetone to give the valinol amide of puraquinonic acid (Scheme 6). However, hydrolysis of **20** with



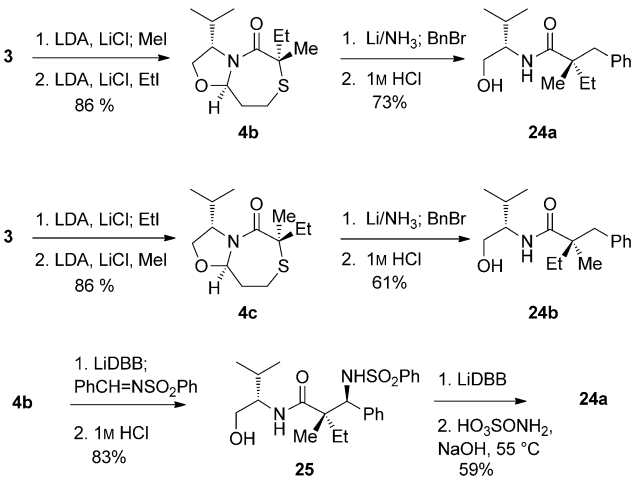
Scheme 6. Completion of the synthesis of puraquinonic acid.

aq. 4 M H_2SO_4 in dioxane at reflux failed to provide the natural product. Although the residual auxiliary was hydrolyzed, the quinone had undergone reductive etherification with the pendant hydroxyethyl group affording **21** in low yield (Scheme 6). Switching the co-solvent from dioxane to isopropanol improved the yield of **21**, but did not solve the reduction problem. Reduction of quinone dimethyl acetals under acidic conditions has been reported, with the most likely reduction source being hydride donation by released methanol,[12] and in the present case, we presume that dioxane and isopropanol can also fill this role. Unfortunately, conducting the hydrolysis without organic co-solvents was inefficient owing to insolubility. Ultimately, hydroquinone ether **21** could be transformed to puraquinonic acid (**1**) by oxidation with Fremy's salt. However, overall this final sequence was inefficient owing to the need to re-oxidize.

An improved route could be achieved by hydrolyzing the auxiliary first. Heating of **18** at reflux in aq. 4 M H_2SO_4/dioxane afforded the desired carboxylic acid **23** in 80% yield. This reaction was accompanied by the formation of dihydropyran **22** in 15% yield, presumably arising from electrophilic aromatic substitution with the formaldehyde released during MOM group cleavage. Finally, the aniline could be cleanly oxidized to the quinone to afford **1** in 83% yield.

Quinone **1** had identical ^1H, ^{13}C NMR, and IR spectroscopic characteristics to those reported.[13] However, the measured specific rotation of $+1.5$ ($c = 0.3$, $CHCl_3$) was opposite to that expected. Based on our methodology, we expected that the synthesis beginning with reduction and alkylation of **3** would ultimately produce (*R*)-**1**, as depicted. In contrast, Clive et al. reported that their synthesis of (*S*)-**1**, wherein the quaternary stereocenter was established via an Evans aldol followed by a radical cyclization, resulted in a positive rotation.[5,14]

Given the discrepancy between our observed rotation and the prior assignment, we reconfirmed the stereochemical outcome of our alkylation sequence. We initially assigned the stereochemistry of the alkylation sequence by comparing the optical rotation of an alkylation product to literature data.[6] As noted above, we have recently extended our enolate chemistry to include Mannich additions to benzenesulfonyl-protected imines.[8] Fortuitously, the stereochemistry of Mannich addition products was assigned unambiguously by X-ray crystallography, and we reasoned that a deamination process would allow direct comparison to products **24a** and **24b** formed from a standard alkylation sequence (Scheme 7). Thus, reduction of Me/Et-substituted lactam **4b** followed by addition to the benzylsulfonylimine of benzaldehyde and subsequent acetal hydrolysis afforded Mannich addition product **25** as reported. The stereochemistry of **25** was reconfirmed by X-ray crystallography and found to be consistent with our prior assignment. Direct hydrogenolytic deamination of **25** proved to be difficult.[15] However a two-step deamination could be achieved by desulfonylation with LiDBB followed by deamination via in situ formation of



Scheme 7. Stereochemical proof for alkylation chemistry. LiDBB = lithium di-*tert*-butylbiphenylide.

a monoalkyl diazene by using hydroxylamine *O*-sulfonic acid.[16] The deamination product proved to be identical to **24a**, which is the major product derived from reduction and alkylation of **4b** with benzyl bromide followed by partial aminal hydrolysis, and was clearly different than **24b**, which is the product derived from an identical sequence on lactam **4c**. This result confirmed that our original assignment of stereochemistry of the alkylation sequence was correct and strongly supports the conclusion that we have prepared (*R*)-puraquinonic acid. We presume that the source of discrepancy between our observed rotation and the literature lies in the small absolute value for rotation, which may render the determination of sign within the error limits of standard polarimetry on small samples.

In conclusion, the stereoselective synthesis of (*R*)-puraquinonic acid has been accomplished in an efficient 12 steps and 20% overall yield. This is the first application of our bicyclic thioglycolate lactam method towards the synthesis of a natural product and highlights the ability to fashion quaternary stereocenters that possess groups with very little steric or electronic difference. In the context of puraqinonic acid, the bicyclic lactam allowed the preparation of a stereocenter bearing allyl and propargyl units, which, through a metathesis and Diels–Alder sequence, could be transmuted to set the deceptively difficult stereochemistry of the natural product.

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