Synthetic Studies on Cycloclavine, Cyclopiazonic Acid, and Other Biologically Active Indole-Containing Compounds

by

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Synthetic Studies on Cycloclavine, Cyclopiazonic Acid, and Other Biologically Active Indole-Containing Compounds

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The first section of this dissertation describes the synthesis of five indole-containing compounds used in the BoNT LC (botulinum neurotoxin light chain) SAR analysis. Our approach employs a Pd(II)-catalyzed cyclization for the formation of indole rings, which are subsequently converted to the corresponding amidines or imidazolines.

The second section describes the extension of the indole synthesis methodology through a microwave assisted IMDAF (intramolecular Diels-Alder furan) reaction. This protocol allows for a convergent and rapid preparation of 4-mono- and 3,4-disubstituted indoles. This cascade process is quite tolerant of functional groups and associated substitution patterns.

The third part we describes novel routes to the naturally occurring indole alkaloid cycloclavine and its unnatural C(5)-epimer. Key features include the rapid construction of the heterocyclic core segments by two Diels-Alder reactions. An indole annulation was accomplished by a late-stage IMDAF reaction, while the cyclopropa[*c*]indoline core of cycloclavine was derived through a stereoselective intramolecular [4+2] cycloaddition of a methylenecyclopropane.

The fourth section describes an approach towards the total synthesis of cyclopiazonic acid. A promising route to this alkaloid was established, including a rapid construction of the tricyclic indole-containing core and a stereoselective pyrrolidinone ring formation.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azoisobutyronitrile
Am	amidine
Ar	aryl
Bn	benzyl
Boc	*t*-butyloxycarbonyl
BoNT	Botulinum neurotoxin
Bs	*p*-bromobenzenesulfonyl
Bu	butyl
Bz	benzoyl
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	3,4-dihydro-2*H*-pyran
DIBAL	diisobutylaluminum hydride
DIPA	diisopropylamine
DMAP	4-dimethylaminopyridine

DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DTBMP	2,6-di-*t*-butyl-4-methylpyridine
Et	ethyl
HC	heavy chain
HMBT	*N*-hydroxymethylbenzotriazole
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphorus triamide
IBX	2-iodoxybenzoic acid
Im	imidazoline
IMDAF	intramolecular Diels-Alder furan
Imid	imidazole
LC	light chain
LDA	lithium diisopropylamide
Me	methyl
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
Ns	*p*-nitrophenylsulfonyl
PCC	pyridinium chlorochromate
Ph	phenyl
Phe	phenylalanine

phen	1,10-phenantroline
PIDA	iodosobenzene diacetate
PIFA	iodosobenzene bis(trifluoro)acetate
Piv	pivaloyl
PPA	polyphosphoric acid
Pr	propyl
PTSA	*p*-toluenesulfonic acid
pyr	pyridine
SNAP-25	25 kD synaptosomal associated protein
SNARE	soluble *N*-ethylmaleimide-sensitive factor-attached protein receptors
TADMAP	1,3-(2,2,2-triphenyl-1-acetoxyethyl)-4-(dimethylamino)pyridine
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butylhydroperoxide
TBS	*t*-butyldimethylsilyl
TBTH	tributyltin hydride
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TMG	1,1,3,3-tetramethylguanidine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl

Ts	*p*-toluenesulfonyl

1.0 SYNTHESIS OF BOTULINUM NEUROTOXIN A LIGHT CHAIN INHIBITORS

1.1 INTRODUCTION

Botulinum toxin (BoNT) is a neurotoxin protein produced by the microorganism *Clostridium botulinum*.[1,2] Even though it is among the most toxic naturally occurring substances and the most toxic protein, it is used in minute amounts in the treatment of muscle spasms as well as in cosmetics.[3,4] Furthermore, BoNTs have been recognized as potential biological weapons.[5]

BoNT was first described at the beginning of the 19th century when it was found that some bacteria cause poisoning from poorly conserved meat products. About 80 years later, *Clostridium botulinum* was isolated and later found to play a key role in blocking neuromuscular transmission.[6]

Seven serologically distinct toxin types have been described (designated A through G) with 3 subtypes of type A.[1] The toxin is biosynthesized as a single-chain polypeptide of ~150 kDa and is post-translationally cleaved to form a di-chain molecule. The two-chain polypeptide consists of a 100 kDa heavy chain (HC) joined by a disulfide bridge (Cys430-Cys454) to a 50 kDa light chain (LC) (Figure 1).[7] The LC acts as a zinc-dependent endopeptidase and attacks one of the fusion proteins at the neuromuscular junction, cleaving components of the SNARE complex and inhibiting acetylcholine release. The HC contains two functional domains, each of

~50 kDa size. The N-terminal half (H_N) is the translocation domain, known to form ion channels in lipid bilayers, whereas the C-terminal half (H_C) is the ganglioside-binding domain, which has an important role in targeting specific axon termini and in internalizing the toxin molecules into cholinergic neurons.

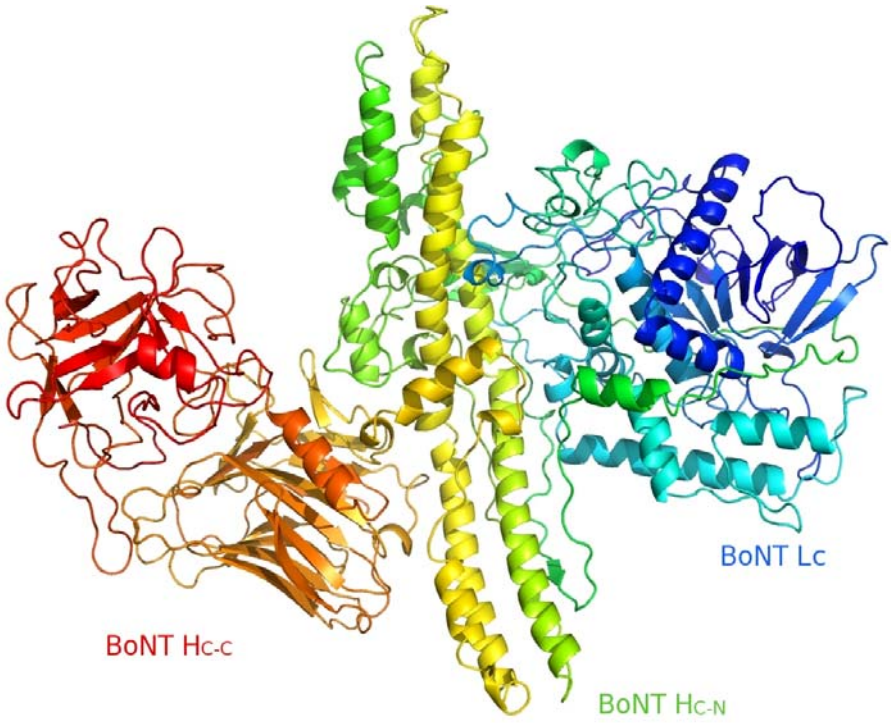


Figure 1. BoNT structure (created by PyMOL)

Following the attachment of the HC to proteins on the surface of axon terminals, the toxin is absorbed into the neuron by endocytosis. The LC is then able to leave the endocytotic vesicles and reach the cytoplasm (Figure 2).[8] Once inside, the LC proteolytically degrades SNARE proteins (SNARE: soluble *N*-ethylmaleimide-sensitive factor-attachment protein receptors). Each serotype of BoNT interacts with one of three SNARE proteins (BoNT/A and BoNT/E cleave SNAP-25 protein (25 kD synaptosomal associated protein); BoNT/B, /D, /F and /G: synaptobrevin; BoNT/C: SNAP-25 and syntaxin). The SNARE-complex is critical for

directing acetylcholine vesicles toward the neuromuscular junction and the release of neurotransmitters. Once the SNARE-complex is destroyed, the release of neurotransmitter is disabled, resulting in paralysis of muscle fibers.

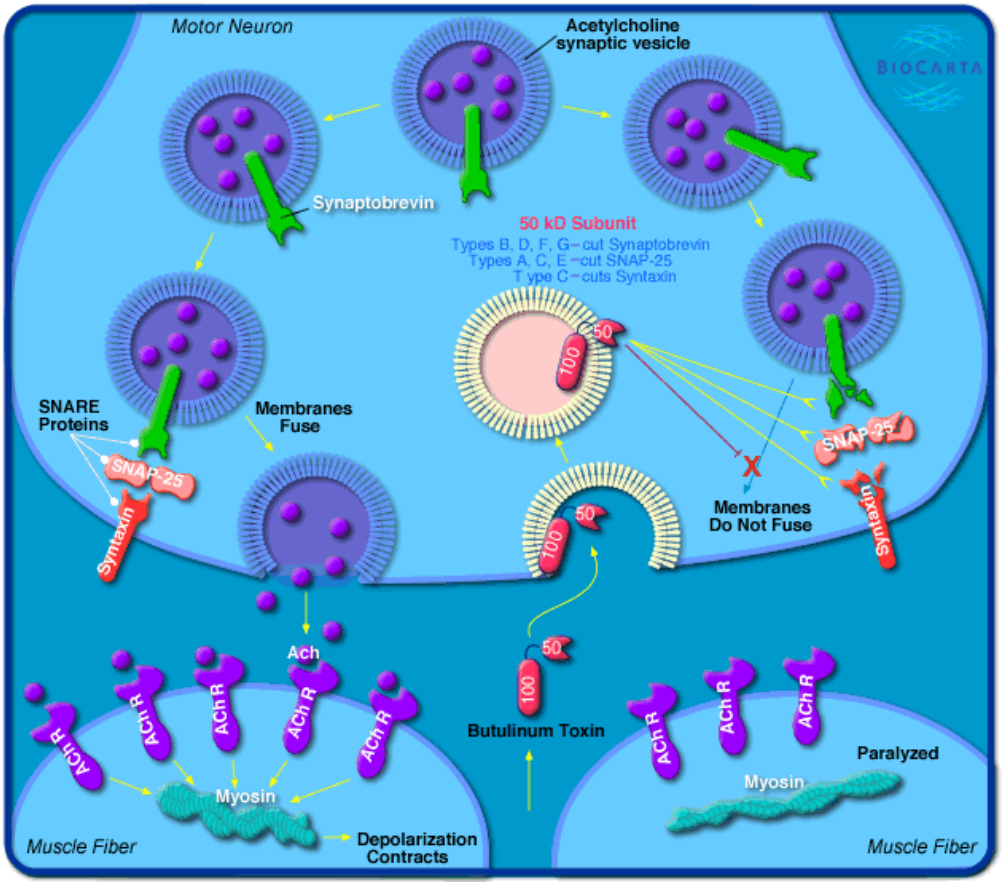


Figure 2. Mechanism of action of botulinum neurotoxins
(Reproduced from www.biocarta.com with permission)

Both HC and LC inhibitors of BoNT have previously been developed.[2,9] The initial step in BoNT poisoning is the binding of the toxin to the neuron. Thus, blocking the interaction between BoNT and the cellular receptor can inhibit nerve paralysis. Two approaches can be envisioned to accomplish the goal of antagonizing toxin-cell interactions: some molecules can coat the toxin and destroy the interaction with the cell receptor while others can bind directly to the cellular receptor, also blocking the binding of toxin. In the former case, polysialylated

gangliosides were observed to be potential ligands for BoNT/A, while some lectines were found to compete with BoNT for the cellular binding site.

The lethal effects of BoNT poisoning involve the inhibition of the synaptic signal transfer at the neuro-muscular junction. Upon endocytosis, the BoNT molecule undergoes a structural rearrangement inside the acidic compartment of the vesicle. Thus, compounds that neutralize acidic media can lengthen the time necessary for the protein to reach the cytosol. For example, the polyether ionophores nigericin and monensin were found to increase the membrane permeability to H^+ and thus act as proton shunts neutralizing the pH gradient.[10] Unfortunately, higher concentrations of these antibiotics also block synapses.[9] It has also been shown that many antimalarial drugs (aminoquinolines) are effective in antagonizing the BoNT/A-induced neuromuscular blockade.[11]

The site-specific SNARE hydrolysis is catalyzed by the BoNT/A LC, and thus another possibility for BoNT inhibition is to limit metalloprotease activity. Several small molecules were identified as inhibitors of LC metalloprotease.[2] Gussio and coworkers conducted a high-throughput screening of the National Cancer Institute Diversity Set, which provided a series of 4-aminoquinolines and led to the identification of several potent BoNT A inhibitors (michellamine B (**1-1**), Q2-15 (**1-2**) and NSC 357756 (**1-3**); Figure 3).[12] Given the presence of a critical zinc ion in the LC active site, it was speculated that the hydroxamate zinc-binding functionality, when coupled to a suitable scaffold to impart specificity, would provide potent BoNT inhibitors.[9,13] Indeed, 2,4-dichlorocinnamic hydroxamate **1-4** (Figure 3) was shown to be a good LC metalloprotease inhibitor.[13] Further analysis identified indole based analogs **1-5** – **1-7**, quinolinol **1-8**, chiral hydroxamic acid **1-9**, as well as pyrrole and thiophene containing hydroxamic acids (**1-10** and **1-11**) as very potent BoNT/A LC inhibitors.[14]

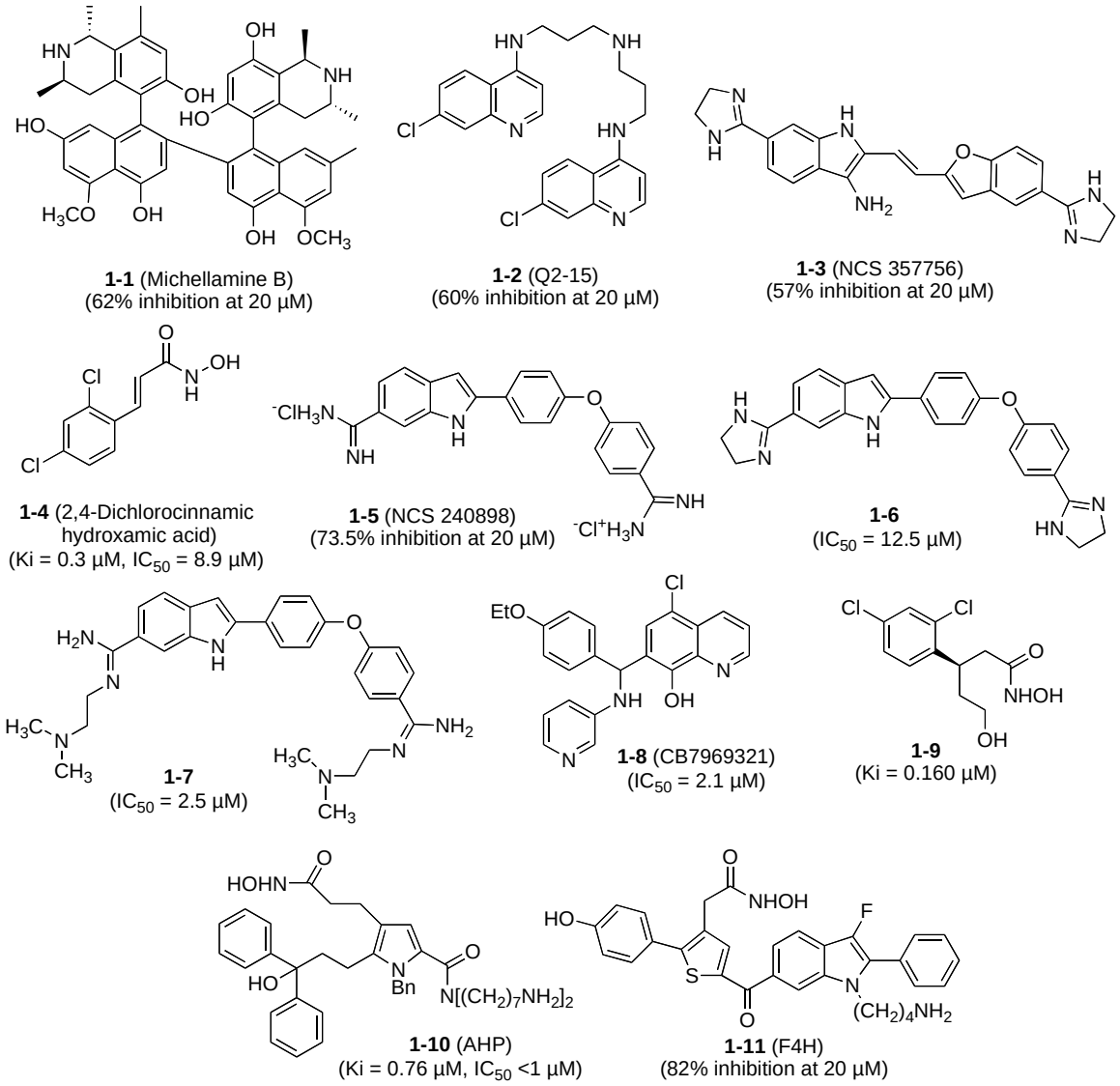


Figure 3. Small molecule inhibitors of BoNT/LC

Detailed conformational analysis together with molecular docking studies provided a model for a common pharmacophore for LC/A inhibitors.[12,15] This pharmacophore was further improved by the docking study of the peptide mimic inhibitor **1-12** developed by Schmidt and coworkers (Figure 4).[16] Comparing to the previous pharmacophore A, the newly proposed pharmacophore B contains two new components (F and G). This hypothesis revealed several new hits in NCI's Open Repository, which were assayed against LC/A. Among the four

pharmacophore components (A-C and F), which were occupied by the most potent inhibitors shown in Figure 5, component C was proposed to wedge between the side chain phenyls of Phe-162 and Phe-193. Component F was believed to be involved in hydrogen bonding with Glu-54 and Glu-63 of LC/A. While NCSs 341909 and 308574 (**1-13** and **1-14**, respectively, Figure 6) showed cytotoxicity in concentrations as low as 1-5 μM, NCS 240898 (**1-5**) was well tolerated at concentrations as high as 40 μM. Furthermore, **1-5** showed dose-dependent protection of SNAP-25 cleavage. Thus, it was chosen as a lead for a structure-activity relationship (SAR) study, with the goal to find a more potent LC/A inhibitor.

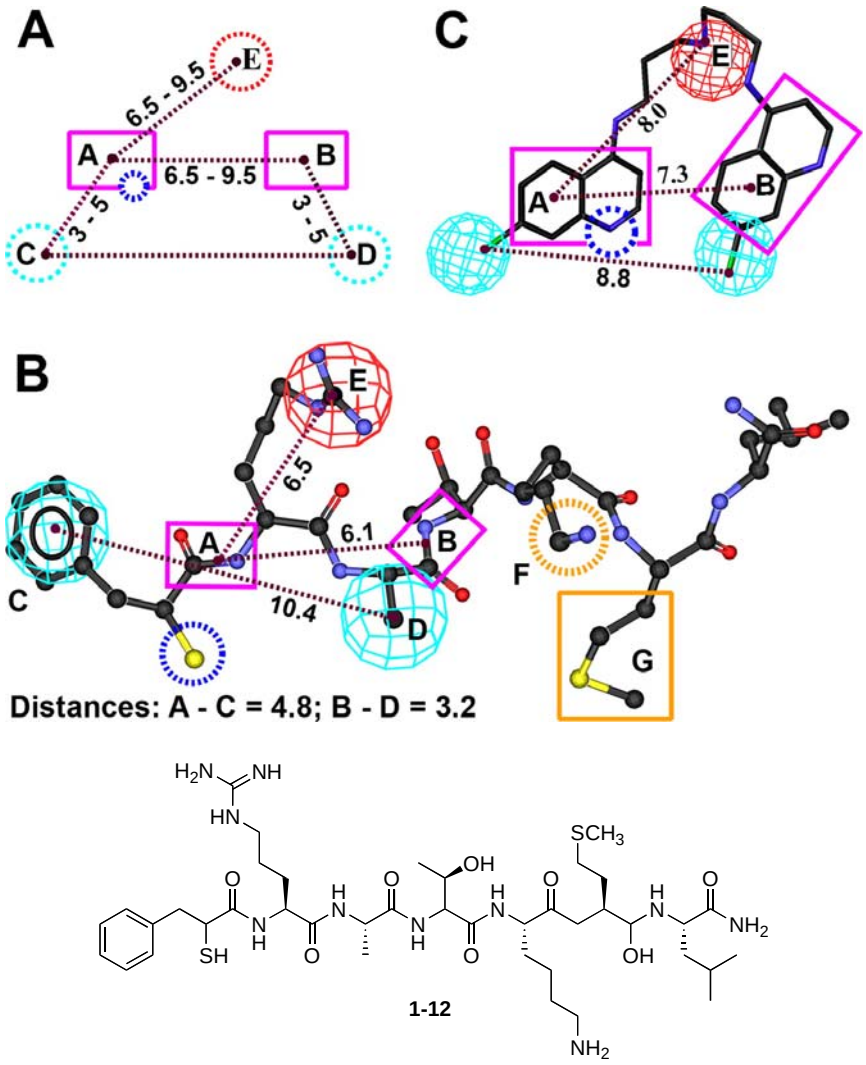


Figure 4. Proposed new pharmacophore model for LC/A

A: Components A and B represent two planar moieties, one of which contains heteroatom; C and D are two hydrophobic substituents, E is a positive ionizable substituent. **B**: The peptide mimic inhibitor (2-mercapto-3-phenylpropionyl-RATKML) was mapped to the common pharmacophore A. Components F and G represent potential new binding sites (distance unit: Å). **C**: for comparison, **1-2** (Q2-15) mapped to the common pharmacophore. (Reproduced with permission from the American Society for Biochemistry and Molecular Biology: this research was originally published in the Journal of Biological Chemistry. Burnett, J. C. et al. Inhibition of Metalloprotease of Botulinum Serotype A from a Pseudo-peptide Binding Mode to a Small Molecule that is Active in Primary Neurons. The Journal of Biological Chemistry. 2007; 282:5004-5014. © the American Society for Biochemistry and Molecuar Biology.)

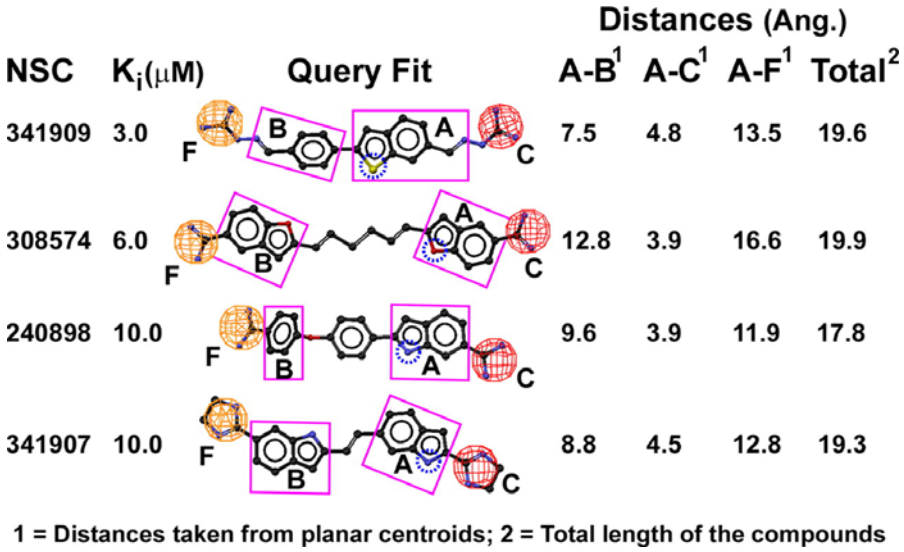


Figure 5. Non-peptidic BoNT/A LC inhibitors: Ki values and query mappings
1 = distances taken from planar centroids; 2 = total length of the compounds
(Reproduced with permission from the American Society for Biochemistry and Molecular Biology: this research was originally published in the Journal of Biological Chemistry. Burnett, J. C. et al. Inhibition of Metalloprotease of Botulinum Serotype A from a Pseudo-peptide Binding Mode to a Small Molecule that is Active in Primary Neurons. The Journal of Biological Chemistry. 2007; 282:5004-5014. © the American Society for Biochemistry and Molecuar Biology.)

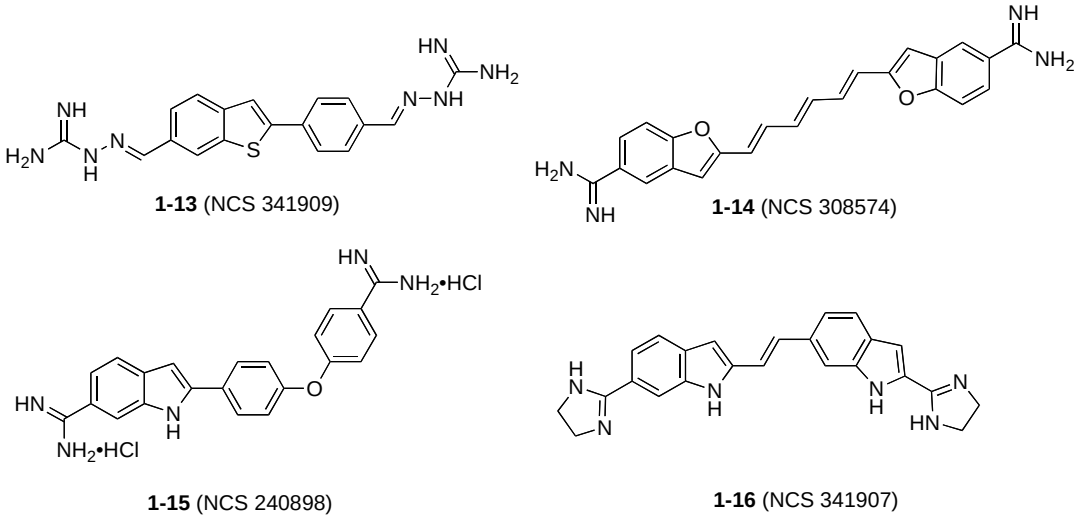


Figure 6. Structures of proposed BoNT/A LC inhibitors

1.2 RESULTS AND DISCUSION

1.2.1 BoNT/A LC Inhibitor Library Design

Compound **1-5** (NCS 240898) and its nitrogen analog **1-16** (NCS 377363, Figure 7) both exhibited 70-75% inhibition of BoNT/A LC activity at 20 μM concentration of P[167-206], the carboxy-terminal 40 residues of SNAP-25. It was hypothesized that it would be possible to improve this inhibitory activity further by modifications of the aromatic backbone: introducing either an indole (compounds **1-17 – 1-20**, Figure **7**), with amidine or imidazoline functionalities at position 5 or 6, or a thiooxadiazole moiety (**1-21**). Based on this information, the Wipf group decided to investigate the structure-activity relationship (SAR) of indole amidine type BoNT/A inhibitors and ultimately to identify more potent compounds using **1-5** and **1-16** as lead structures.

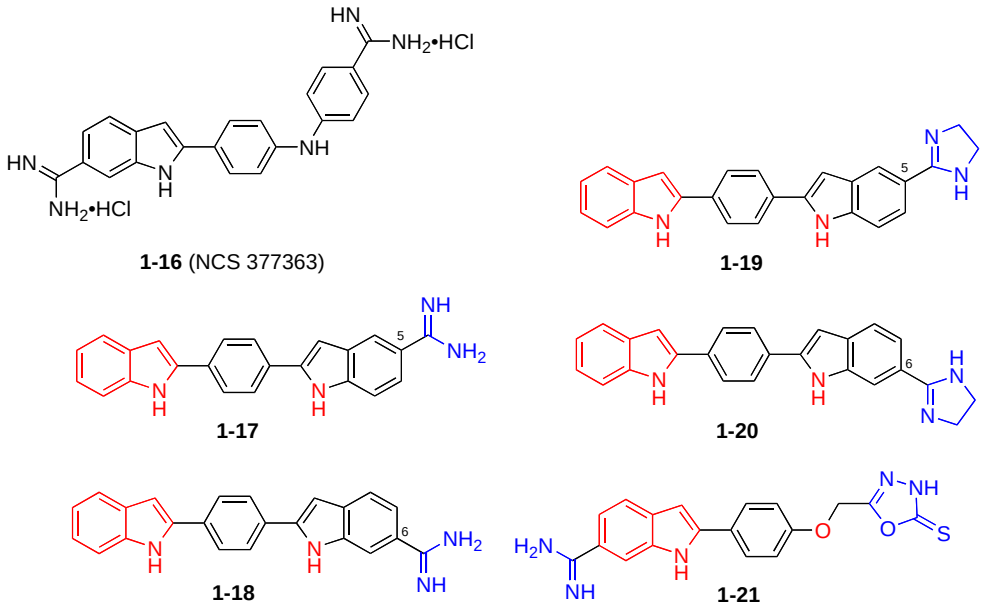
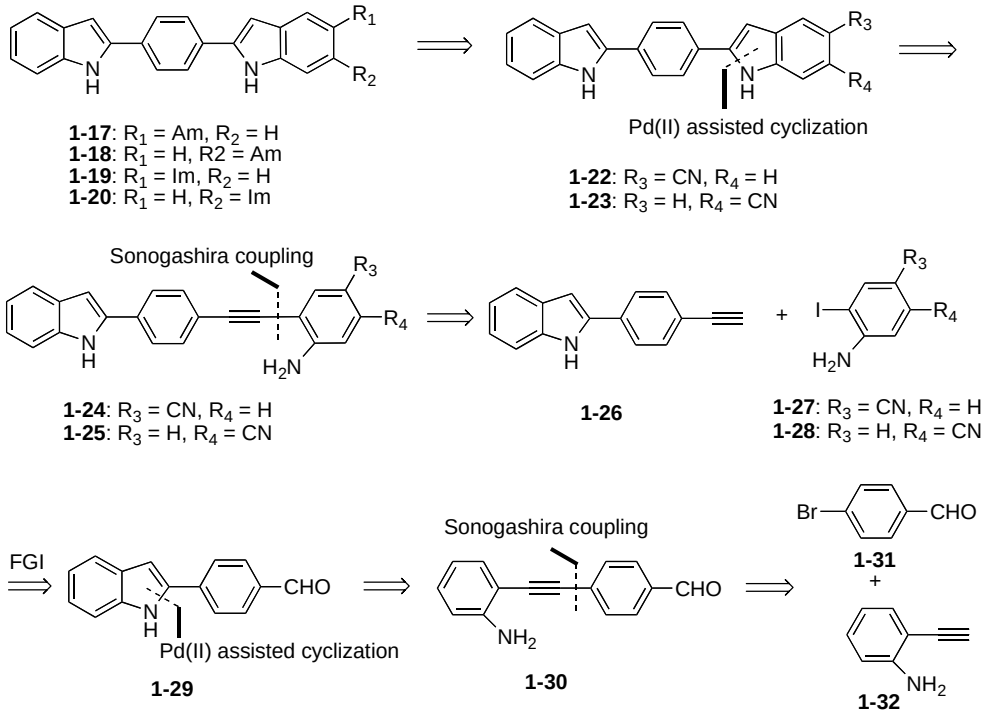


Figure 7. Proposed BoNT/A LC inhibitors and synthetic targets for SAR

1.2.2 First Generation Approach toward Analogs 1-17 – 1-20

The general features of our initial synthesis are illustrated in retrosynthetic format in Scheme 1. Although the structure of compounds **1-17** – **1-20** is quite simple, an important initial design clue for synthetic routes toward their polyaromatic framework was provided by the fact that amidine or imidazoline derivatives can be obtained from the corresponding nitriles,[17,18] thus having compounds **1-22** and **1-23** as their synthetic precursors. In the forward direction, treating nitriles **1-22** and **1-23** with hydrochloric acid in ethanol followed by treatment of the intermediate imidates with either ethylenediamine in the presence of catalytic amounts of sulfur or gaseous ammonia would be expected to afford the desired imidazolines or amidines, respectively.

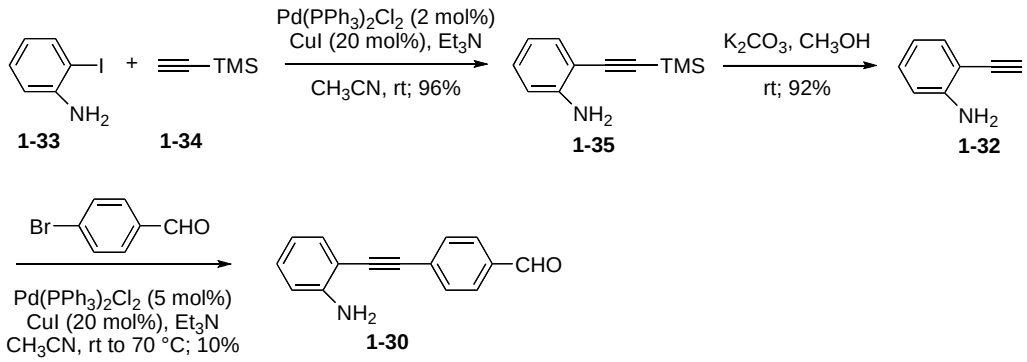


Scheme 1. Retrosynthetic analysis in the first generation approach

The synthetic challenge was now reduced to the preparation of intermediates **1-22** and **1-23**. Although a large variety of methods for indole synthesis are known,[19,20] we decided to install

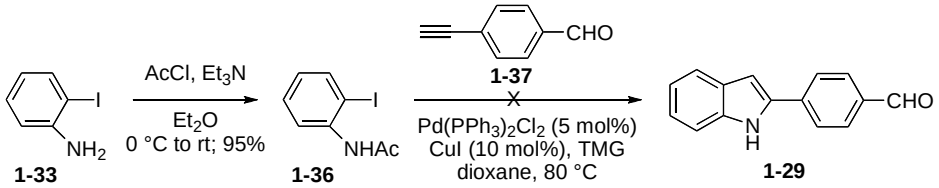
these heterocycles in two separate steps by a Sonogashira coupling followed by a Pd(II)-mediated cyclization. Retrosynthetic cleavage of the more substituted indole led us to intermediates **1-24** and **1-25**, which could easily be prepared from commercially available aminoiodobenzonitriles **1-27** and **1-28**. Through standard functional group manipulations, it is conceivable that intermediate alkyne **1-26** could be derived from aldehyde **1-29**. Another sequence of Sonogashira coupling-Pd(II)-assisted cyclization led to the commercially available *p*-bromobenzaldehyde (**1-31**) and aminoalkyne **1-32**.

Based on the retrosynthetic analysis presented above, the synthesis of compounds **1-17** – **1-20** commenced with the preparation of the intermediate **1-32** through a Sonogashira reaction using 2-iodoaniline (**1-33**) and TMS-protected acetylene **1-34** as starting materials (Scheme 2). The intermediate **1-35** was deprotected in a subsequent step and provided the aminoalkyne **1-32** in 88% overall yield.[21] When a solution of aminoalkyne **1-32,** *bis*(triphenylphosphino)palladium(II) chloride and cuprous iodide in acetonitrile was treated with *p*-bromobenzaldehyde, intermediate **1-30** was formed in only 10% yield. We believe that the initial reaction of unprotected aniline **1-32** and *p*-bromobenzaldehyde is faster and thus suppresses the Sonogashira coupling.



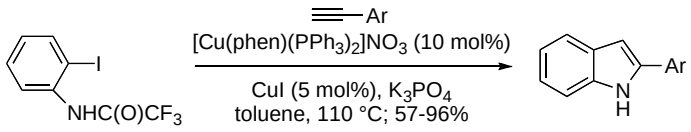
Scheme 2. Synthesis of the intermediate **1-30**

During the course of the synthesis of aldehyde **1-29**, we turned our attention to a well documented one-pot reaction for installing indole moiety.[22,23] Subjecting *N*-acylated aniline **1-36** and alkyne **1-37** to Sonogashira reaction conditions should in principle give the *N*-acylatedaminoalkyne, which subsequently undergoes intramolecular cyclization resulting in *N*-acylated indole formation (Scheme 3).[24] Unfortunately, instead of leading to the desired indole **1-29**, the reaction was very sluggish and only decomposition of the starting material was observed upon heating the reaction mixture at 80 °C.



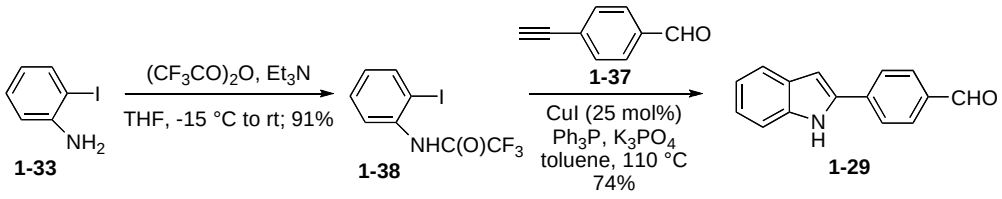
Scheme 3. Attempted domino copper-catalyzed indole formation

Surmising that a more acidic N-H bond might favor the cyclization reaction generating, under basic conditions, a stronger nitrogen nucleophile, Cacchi and coworkers recently described a similar strategy for domino indole formation using *N*-trifluoroacetyl protected 2-iodoanilines (Scheme 4).[25]



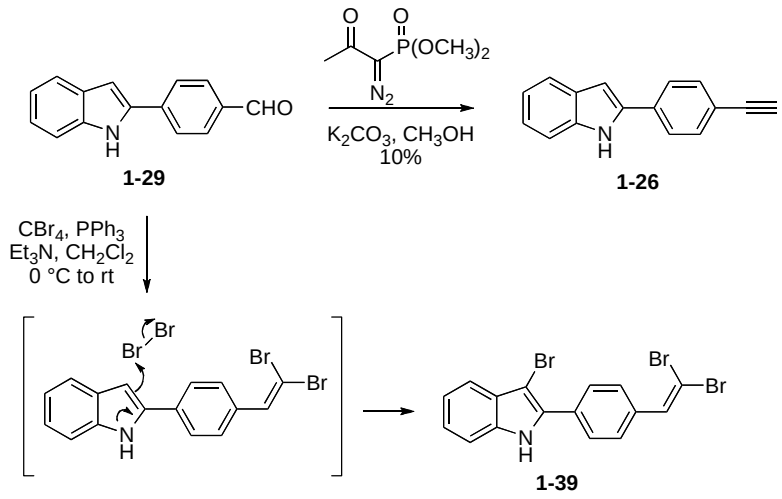
Scheme 4. 2-Arylindole formation from *o*-iodotrifluoroacetanilide

Treating *o*-iodotrifluoroacetanilide **1-38** with alkyne **1-37** in toluene, using cuprous iodide and triphenylphosphine in the presence of K_3PO_4, furnished aldehyde **1-29** in 74% yield (Scheme 5).



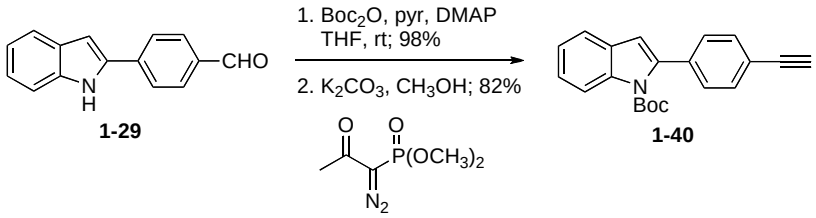
Scheme 5. Tandem copper-catalyzed Sonogashira reaction-indole formation

Initial attempts to convert **1-29** to the corresponding alkyne using Corey-Fuchs homologation[26,27] led to 3-bromo-substituted indole **1-39**, suggesting that perhaps the bromine, generated *in situ*, acted as an excellent electrophile (Scheme 6).



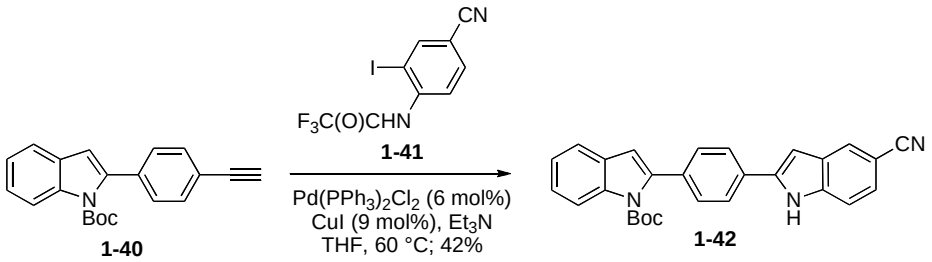
Scheme 6. Functionalization of aldehyde **1-29**

In contrast, subjecting aldehyde **1-29** to the Ohira-Bestmann modification of the Seyferth-Gilbert reaction conditions led to only a 10% isolated yield of the desired alkyne **1-26**.[28] However, using *N*-Boc-protected indole in the Ohira-Bestmann reaction furnished alkyne **1-40** in a good yield (Scheme 7).



Scheme 7. Synthesis of intermediate **1-40**

For the attachment of the second indole fragment, alkyne **1-40** was treated with 3-iodo-4-trifluoroacetamidobenzonitrile **1-41** under Sonogashira conditions to provide directly the desired cyclized product **1-42**, albeit in modest yield (Scheme 8). Interestingly, while alkyne **1-40** smoothly cyclized under Sonogashira reaction conditions, the previously attempted reaction between iodoaniline **1-36** and alkyne **1-37** (Scheme 3) was very sluggish. Importantly, the installation of the cyano group increased the acidity of the *p*-acetamide, considerably influencing the cyclization reaction.



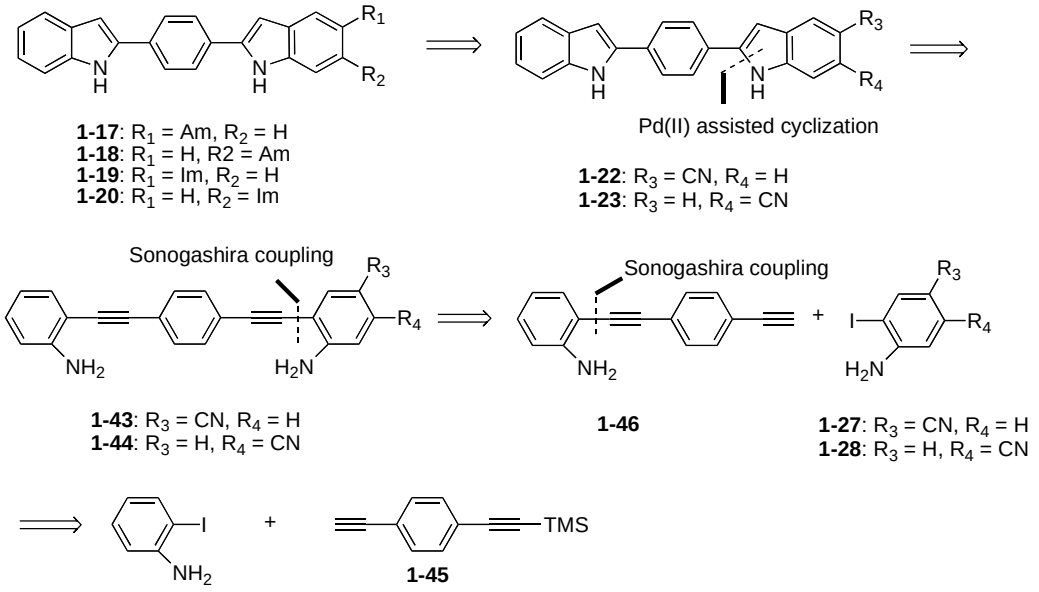
Scheme 8. Synthesis of *bis*-indole **1-42**

During the planning stages of this synthesis, the task of removing the Boc-protecting group in **1-42** was not anticipated to be problematic. Unfortunately, the seemingly straightforward deprotection of **1-42** proved to be a very difficult transformation. Many of the conventional protocols, including TFA in THF,[29] TFA (neat),[29] TFA/thioanisole,[30] NaOMe/MeOH,[31] TMSI,[32] led to decomposition of the starting material, or in the case of thermal deprotection with SiO_2 under high vacuum[33] to a very small conversion (10%).

1.2.3 Second Generation Approach towards Analogs 1-17 – 1-20

Encouraged by our success in the palladium (II)-assisted indole cyclization, we turned our attention to a related approach that bypassed an indole protection/deprotection step. We planned to achieve the construction of both indoles in a single step. Thus, our goal was to synthesize a *bis*-alkyne intermediate with two amino groups in *ortho*-positions, enabling a tandem metal-assisted cyclization.

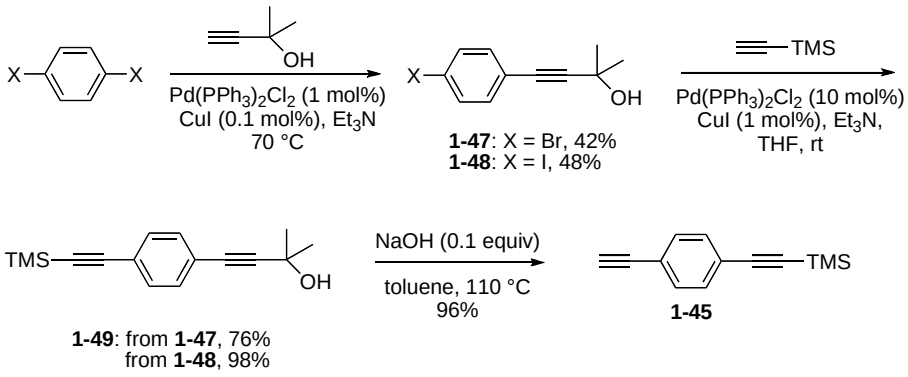
As shown in the retrosynthetic analysis (Scheme 9), our modified approach commenced with a cleavage of the *bis*-indole motif in nitriles **1-22** and **1-23**, providing the *bis*-aminoalkynes **1-43** and **1-44**.[34] These intermediates could be constructed through a double Sonogashira coupling, starting with *p*-(trimethylsilylethynyl)phenylacetylene **1-45**.[35]



Scheme 9. Second-generation approach: retrosynthetic analysis

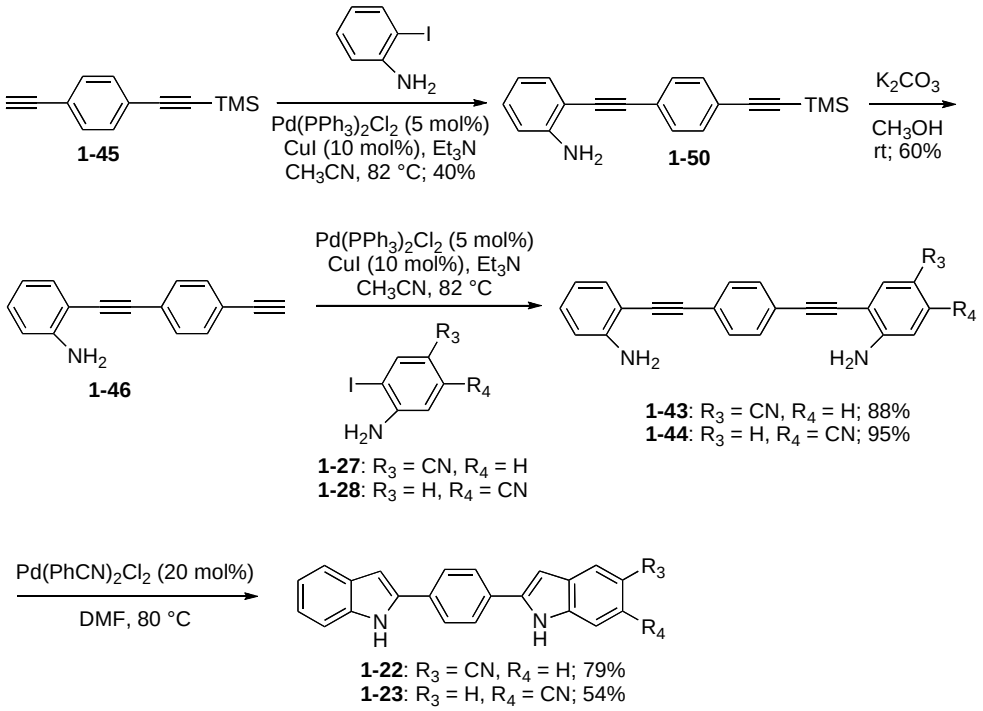
The second-generation approach towards BoNT LC inhibitors **1-17** – **1-20** commenced with the exploration of the literature protocol for the essential building block **1-45** from either

1,4-diiodobenzene or 1,4-dibromobenzene through a sequence of two Sonogashira reactions and the subsequent elimination of acetone (Scheme 10).[35]



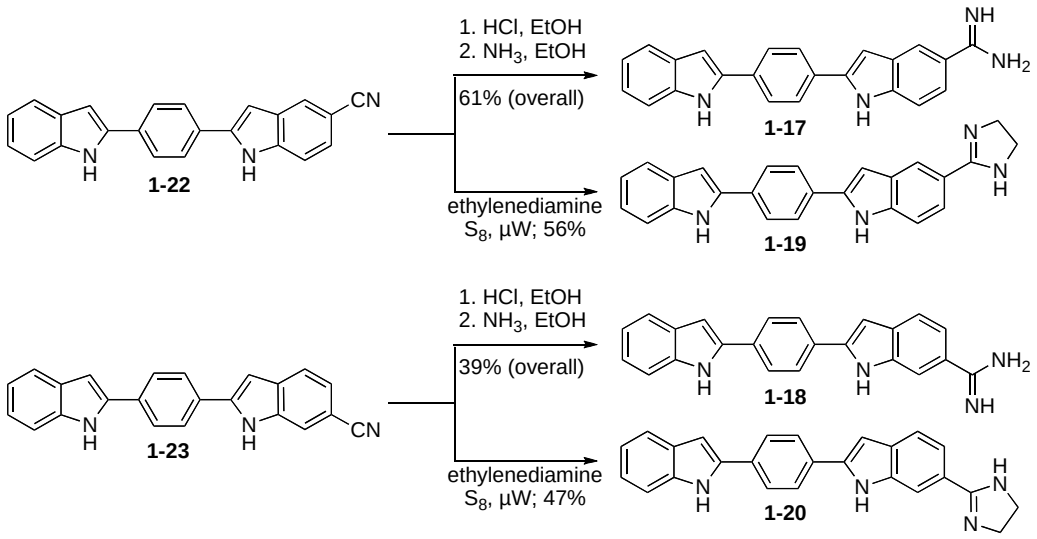
Scheme 10. Synthesis of building block **1-45**

Fragment **1-45** was subsequently coupled with 2-iodoaniline under Sonogashira reaction conditions in acetonitrile to afford intermediate **1-50** (Scheme 11). Upon treatment of **1-50** with K_2CO_3 in methanol, the terminal alkyne was deprotected, furnishing **1-46**, which set the stage to introduce the cyano-substituted benzene. Treatment of **1-46** with regioisomeric benzonitriles **1-27** and **1-28** provided the *bis*-aminoalkynes **1-43** and **1-44** in 88% and 95% yield, respectively. Exposure of **1-43** and **1-44** to 20 mol% of *bis*(benzonitrile)palladium(II) chloride in DMF at 80 °C provided **1-22** and **1-23** in 79% and 54% yield, respectively.[36]



Scheme 11. Synthesis of advanced intermediates **1-22** and **1-23**

In order to convert *bis*-indole building blocks into the corresponding amidines (**1-17**, **1-18**) or imidazolines (**1-19**, **1-20**; Scheme 12), the nitriles were treated with gaseous HCl in ethanol at room temperature for 24 h, furnishing the imidate esters.[17] These intermediates were not isolated, but by treatment with gaseous ammonia in ethanol, they were directly converted to the corresponding amidines **1-17** and **1-18**.[17,37]



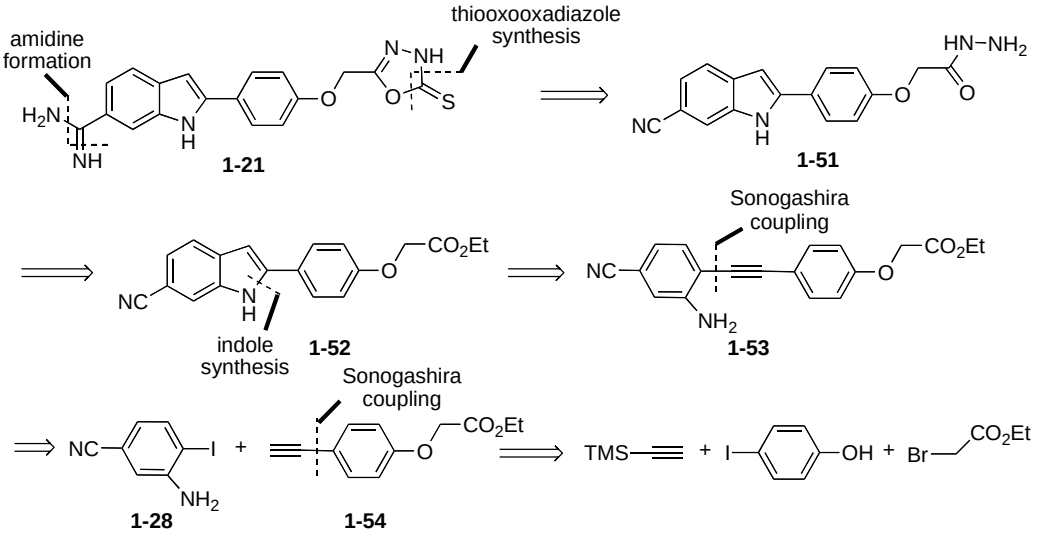
Scheme 12. Completion of synthesis of BoNT/A LC inhibitors **1-17 - 1-20**

Among several methods described in literature for imidazoline preparation from the corresponding nitriles,[38-41] we focused our attention on the reaction with ethylenediamine in the presence of elemental sulfur, because of both the simplicity of the method and the easy work-up procedure. Accordingly, nitriles **1-22** and **1-23** were converted to imidazolines **1-19** and **1-20** under microwave conditions in 56% and 47% yield, respectively.[18]

1.2.4 Synthesis of a Thiooxooxadiazole Analog 1-21

As mentioned previously, the BoNT LC contains a Zn^{2+} ion in its active site, which is shown to be critical for its proper function. In order to make a suitable inhibitor of BoNT toxin, one can imagine that binding a Zn^{2+} ion by a small molecule would impact the catalytic activity of the toxin. Accordingly, we hoped that installing the thioxooxadiazole fragment onto an indole scaffold, together with an amidine subunit, would provide a potent BoNT inhibitor. The thioxooxadiazole fragment, possessing a soft sulfur atom, was considered to interact with the soft Zn^{2+} ion, thus diminishing the BoNT activity.[42]

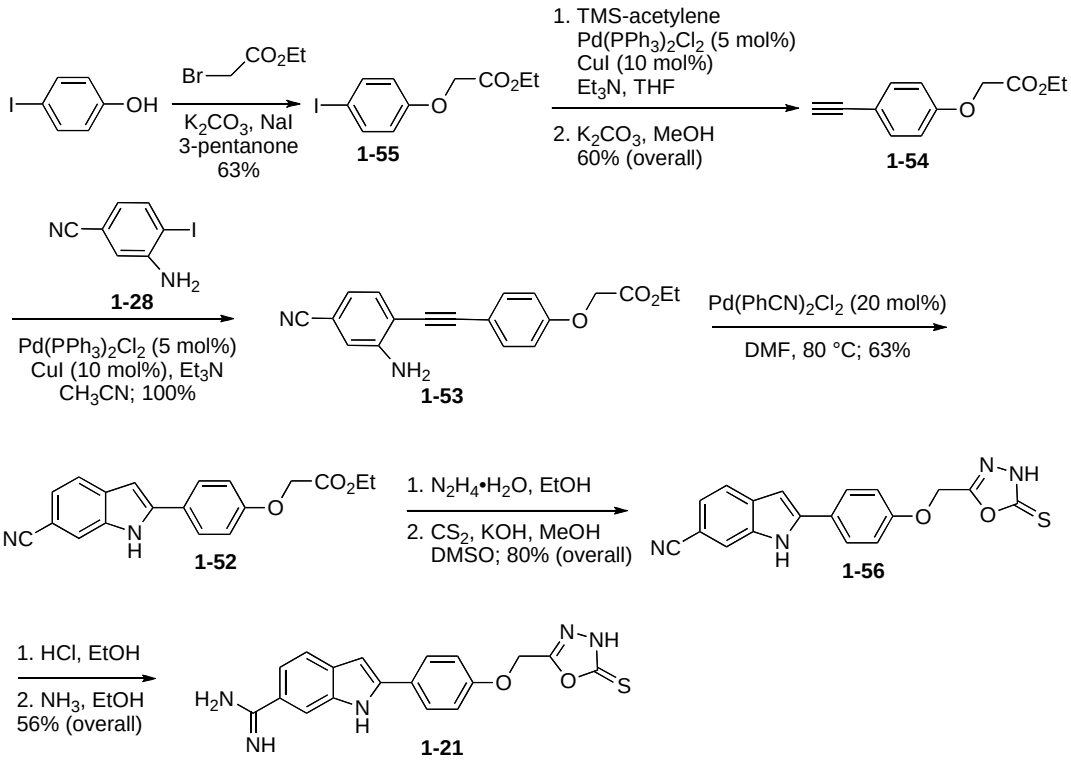
With the goal of introducing the amidine function at the last stage of our synthesis, the direct precursor to compound **1-21** was nitrile **1-51** (Scheme 13). The synthesis of the thioxooxadiazole was known[43] and thus the conversion of **1-51** into **1-21** was considered to be a feasible process. Subsequent functional group manipulation should lead to intermediate ester **1-52**. For **1-52**, the retrosynthetic disconnections mirror those applied to the synthesis of analogs **1-17**–**1-20**.



Scheme 13. Retrosynthetic analysis of **1-21**

The synthesis of thioxooxadiazole analog **1-21** (Scheme 14) commenced with *O*-alkylation of the commercially available 4-iodophenol with ethyl bromoacetate in the presence of NaI and K_2CO_3, providing ether **1-55** in 63% yield. A Sonogashira reaction with TMS-protected acetylene, followed by K_2CO_3 mediated cleavage of the TMS group, afforded **1-54** in 60% overall yield. A second Sonogashira coupling provided intermediate **1-53** in quantitative yield. The Pd(II)-mediated indole cyclization furnished the intermediate **1-52**, with both nitrile and ester functionalities, which were to be converted to amidine and thioxooxadiazole motifs, respectively.

The thioxooxadiazole ring was readily synthesized by a two-step protocol. Conversion of the ester into the corresponding hydrazide **1-51** was achieved through a reaction with hydrazine monohydrate[44] followed by a cyclization in DMSO using carbon disulfide, providing intermediate **1-56** in 80% overall yield.[43] The construction of the final amidine was accomplished by a two-step procedure: formation of the imidate ester and subsequent conversion to the amidine. Upon treating the intermediate imidate ester with gaseous ammonia in ethanol, target compound **1-21** was obtained in 56% overall yield from **1-56**.



Scheme 14. Synthesis of analog **1-21**

1.2.5 Biological Evaluation of Analogs 1-19 – 1-21

Biological evaluation[42] of compounds **1-19** – **1-21** and their comparison with other analogs previously synthesized in our group[2] revealed interesting binding properties. According

to the binding hypothesis, a 3-zone pharmacophore model was developed by Nuss and Bavari.[45] The zones can be defined as such:

Zone 1 is an aromatic planar component and one component of positive charge.

Zone 2 is also an aromatic planar component and a second component of positive charge.

Zone 3 is an aromatic planar component, which is hypothesized to occupy the BoNT/A LC S1' site, and is linked to the positively charged component of Zone 2 by a methylene tether. Results from *in vitro* testing of mono-imidazoline analogs **1-19** and **1-20** (at 20 μM concentration) indicated 26.6 (± 5.8)% and 27.4 (± 8.5)% inhibition, respectively. With respect to the 3-Zone pharmacophore (Figure 8), neither compound possesses the Zone 2 cationic charge. Moreover, neither compound occupies Zone 3.

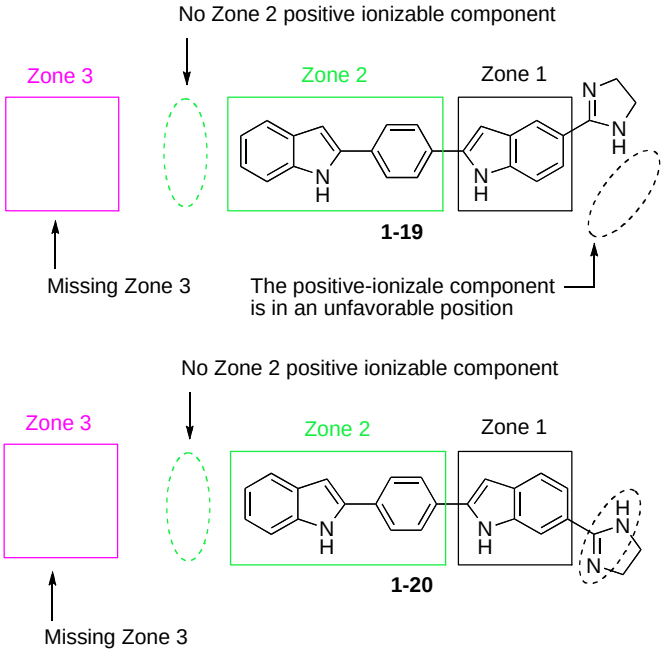


Figure 8. 3-Zone pharmacophore model for compounds **1-19** and **1-20**

Compound **1-21**, a fragment of NCS240898 containing a 5-thioxo-4,5-dihydro-1,3,4-oxadiazole (thioxooxadiazole) component, contains sulfur which might coordinate the Zn^{2+} ion. However, Zn^{2+} coordination with a constrained thioxooxadiazole ring is not trivial given the very narrow geometric window required for the Zn-S coordinate bond (distance approx. = 2.3 Å, and angle approx. = 106 - 109°).[45] No activity was observed for this compound even at 20 μM concentration. According to the 3-Zone pharmacophore (Figure 9), the sulfur atom of the thioxooxadiazole ring is unable to interact with the Zn^{2+} ion within the defined geometric parameters. Other factors that are likely contributing to the inactivity of this compound include no Zone 2 positive charge and the absence of a Zone 3 component.

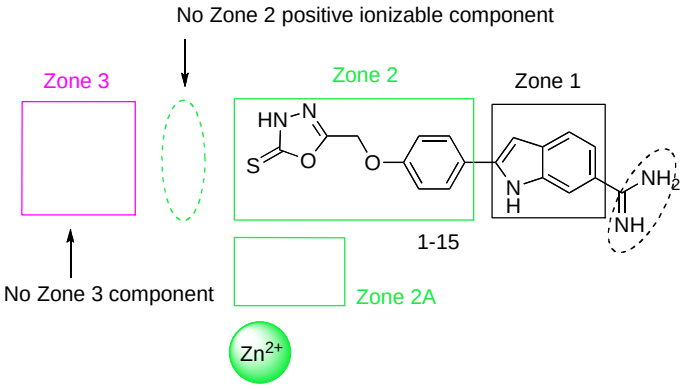


Figure 9. 3-Zone pharmacophore model for compound **1-21**

(Zone 2A added to indicate the necessary position of the Zn^{2+} coordinating substituent)

1.3 CONCLUSIONS

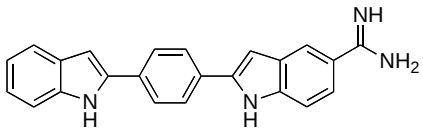
On the basis of a BoNT SAR analysis, we synthesized analogs **1-17** – **1-21**, employing a Pd(II) catalyzed cyclization for the formation of indole rings. Cyclization of both indole rings in analogs **1-17** – **1-20** (second generation approach mentioned above) offers an elegant access to

the *bis*-indole core containing two differently substituted indole rings. Amidines **1-17**, **1-18** and **1-21**, as well as imidazolines **1-19** and **1-20**, were derived from the corresponding nitriles. No activity of the nitriles **1-22** and **1-23** was observed, suggesting that a strongly basic amidine or imidazoline moiety is indeed required, either for hydrogen-bonding or ionic interactions with the receptor site at the BoNT A LC.[2] Finally, the absence of activity after the introduction of the thioxooxadiazole moiety (analog **1-21**) through a phenyloxymethylene linker at position 2 on the indole ring implies that the binding event is probably highly directional.

1.4 EXPERIMENTAL PART

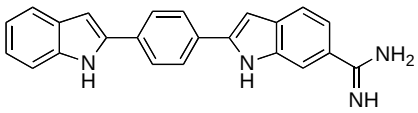
General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. Reactions carried out at -78 °C employed a dry ice/acetone bath. THF and Et_2O were dried by distillation over Na/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina filtration system. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F_{254} plates (250 μm layer thickness, particle size 0.040-0.055 mm, 230-240 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 M H_2SO_4 solution), or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1 % NaOH solution). Flash chromatography on SiO_2 was used to separate and purify the reaction crude mixtures. Microwave reactions were performed on a

Biotage Initiator microwave reactor. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance 300 instrument. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard. ^{1}H NMR spectra were run at 300, 400 or 500 MHz, and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, sept = septet, m = multiplet, br = broad, app = apparent), number of protons, and coupling constant(s). ^{13}C NMR were obtained using a proton-decoupled pulse sequence with a d1 of 3 sec, and are tabulated by observed peak. LC/MS analyses were obtained from a Helwett Packard Series 1100 MSD. RP HPLC was performed on a Gilson Series 215, using C18 column, Bio-rad Laboratories, 250 x 4.6 mm. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Infrared spectra were measured on a Nicolet AVATAR 360 FT-IR E.S.P. spectrometer (KBr or neat) or Smiths Detection IdentifyIR FT-IR spectrometer (ATR).

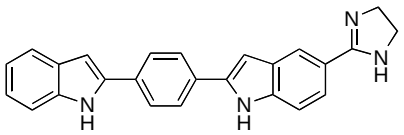


2-(4-(1*H*-Indol-2-yl)phenyl)-1*H*-indole-5-carboximidamide (1-17). A suspension of nitrile **1-22** (5.0 mg, 0.015 mmol) in ethanol (0.1 mL) was treated with gaseous HCl for 20 min at room temperature, and the mixture was stirred for 3 d. The solvent was removed under reduced pressure to afford crude imidate ester, which was used directly in the next step. A suspension of the intermediate imidate ester (6.0 mg, 0.015 mmol) in ethanol (0.5 mL) was cooled to 0 °C and treated with gaseous ammonia for 20 min. The solution was stirred for 24 h at room temperature. Solvent was removed under reduced pressure and the solid material was purified on RP HPLC (C18 column, acetonitrile/1% TFA in water, 7/3), and recrystalized from MeOH, which afforded **1-17** (3.2 mg, 61% overall yield) as a yellow solid: Mp 198-203 °C (decomp.); IR (ATR) 3410,

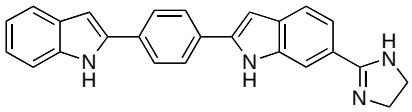
3127, 1660, 1446, 788 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 8.10 (d, 1 H, *J* = 1.2 Hz), 7.89 (app s, 4 H), 7.59 (d, 1 H, *J* = 8.7 Hz), 7.54 (d, 1 H, *J* = 8.7 Hz), 7.53 (d, 1 H, *J* = 8.4 Hz), 7.38 (d, 1 H *J* = 8.1 Hz), 7.09 (dt, 1 H, *J* = 7.2, 1.2 Hz), 7.04 (s, 1 H), 6.99 (t, 1 H, *J* = 6.9 Hz), 6.87 (s, 1 H); ^{13}C NMR (75 MHz, MeOD) δ 140.8, 140.6, 137.7, 137.2, 132.7, 130.2, 129.2, 125.5, 125.2, 121.6, 120.8, 120.3, 119.9, 119.2, 118.6, 11.5, 110.7, 99.5, 98.9; MS (ESI) *m/z* 350 ($[M+H]^+$, 9), 333 (100); HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_4$ $[M+H]^+$ 350.1531, found 350.1530.



2-(4-(1*H*-Indol-2-yl)phenyl)-1*H*-indole-6-carboximidamide (1-18). A suspension of nitrile **1-23** (26.3 mg, 0.0750 mmol) in ethanol (1.0 mL) was treated with gaseous HCl for 10 min at room temperature and the mixture was stirred for 24 h. The solvent was removed under reduced pressure to afford crude imidate ester, which was used directly in the next step. A suspension of the intermediate imidate ester in ethanol (1.0 mL) was cooled to 0 °C and treated with gaseous ammonia for 10 min. The solution was stirred for 24 h at room temperature. Solvent was removed under reduced pressure and the solid material was purified on RP HPLC (C18 column, acetonitrile/1% TFA in water, 7/3), and recrystalized from MeOH, which afforded **1-18** (10.7 mg, 39% overall yield) as a yellow solid: Mp 198 °C (decomp.); IR (ATR) 3425, 3285, 2218, 1452, 1301, 822 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 7.92-7.88 (m, 5 H), 7.73 (d, 1 H, *J* = 8.4 Hz), 7.54 (d, 1 H, *J* = 7.8 Hz), 7.44 (dd, 1 H, *J* = 8.4, 1.8 Hz), 7.40 (d, 1 H *J* = 8.4 Hz), 7.10 (dt, 1 H, *J* = 6.9, 0.9 Hz), 7.02 (s, 1 H), 7.00 (t, 1 H, *J* = 6.9 Hz), 6.89 (s, 1 H); ^{13}C NMR (75 MHz, MeOD) δ 144.2, 139.3, 138.7, 138.2, 135.5, 134.5, 131.7, 130.7, 127.4, 126.8, 123.2, 122.0, 121.4, 120.8, 119.8, 112.8, 112.3, 100.7, 100.6; MS (TOF MS ESI) *m/z* 351 $[M+H]^+$ (100), 334 (8); HRMS (TOF MS ESI) *m/z* calcd for $C_{23}H_{18}N_4$ $[M+H]^+$ 351.1610, found 351.1592.

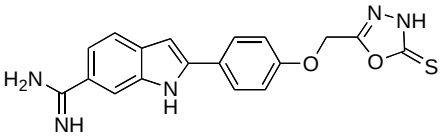


2-(4-(1*H*-Indol-2-yl)phenyl)-5-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-indole (1-19). To a solution of nitrile **1-22** (5.7 mg, 0.017 mmol) in ethylenediamine (2.0 mL) was added sulfur (0.9 mg, 0.03 mmol) and the reaction mixture was heated in the microwave for 20 min at 130 °C. To the reaction mixture was added water and the precipitate was filtered through a Buchner funnel, and rinsed with water (3 x 5 mL). The solid residue was purified by RP HPLC (C18 column, acetonitrile/1% TFA in water, 7/3) to afford **1-19** (3.6 mg, 56%) as a yellow solid: Mp 198-201 °C (decomp.); IR (neat) 3413, 3221, 2927, 1598, 1442, 1301, 792 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.26 (s, 1 H), 11.61 (s, 1 H), 10.29 (s, 1 H), 8.26 (s, 1 H), 8.00-8.03 (m, 4 H), 7.66, 7.62 (AB, 2 H, J = 8.1), 7.54 (d, 1 H, J = 7.5 Hz), 7.41 (d, 1 H, J = 8.1 Hz), 7.23 (s, 1 H), 7.11 (t, 1 H, J = 7.2 Hz), 7.01-7.07 (m, 2 H), 4.01 (s, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9, 140.3, 140.2, 137.3, 137.0, 131.9, 129.8, 128.6, 128.4, 125.8, 125.4, 121.8, 121.2, 120.1, 119.5, 113.0, 112.0, 111.3, 100.0, 99.3, 44.2; MS (TOF MS ESI) *m/z* 377 $[M+H]^+$ (100), 365 (8), 139 (10); HRMS (TOF MS ESI) *m/z* calcd for $C_{25}H_{20}N_4$ $[M+H]^+$ 377.1766, found 377.1774.

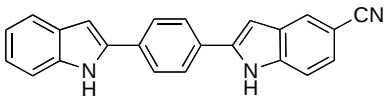


2-(4-(1*H*-Indol-2-yl)phenyl)-6-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-indole (1-20). To a solution of nitrile **1-23** (25.0 mg, 0.0660 mmol) in ethylenediamine (2.0 mL) was added sulfur (1.0 mg, 0.028 mmol). The reaction mixture was heated in a microwave reactor for 30 min at 130 °C. To the reaction mixture was added water, and the precipitate was filtered through a Buchner funnel and rinsed with water (3 x 5 mL). The solid residue was dried *in vacuo* to afford **1-20** (10.2 mg, 47%) as a yellow solid: Mp 197.6-198.3 °C (decomp.); IR (KBr) 3421, 2925, 2360,

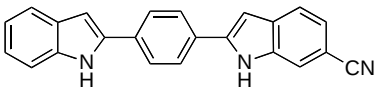
2340, 1601, 1451, 790 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (s, 1 H), 11.60 (s, 1 H), 7.99 (app s, 4 H), 7.91 (s, 1 H), 7.50-7.60 (m, 3 H), 7.42 (d, 1 H, *J* = 7.8 Hz), 7.12 (t, 1 H, *J* = 7.2 Hz), 6.96-7.07 (m, 3 H), 3.67 (s, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.5, 141.5, 137.3, 137.0, 136.3, 132.3, 131.9, 130.0, 128.6, 126.1, 125.4, 121.8, 120.1, 119.5, 119.1, 111.7, 111.3, 99.5, 99.3, 45.8; MS (TOF MS ESI) *m/z* 377 ($[M+H]^+$, 100), 290 (14); HRMS (TOF MS ESI) *m/z* calcd for $C_{25}H_{20}N_4$ $[M+H]^+$ 377.1766, found 377.1766.



2-(4-((5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-indole-6-carboximidamide (1-21). A suspension of nitrile **1-56** (7.5 mg, 0.021 mmol) in ethanol (0.5 mL) was treated with gaseous HCl for 10 min at room temperature and the mixture was stirred for 24 h. The solvent was removed under reduced pressure to afford crude imidate ester, which was used directly in the next step. A suspension of the intermediate imidate ester in ethanol (0.2 mL) was treated with gaseous ammonia for 10 min. The solution was stirred for 24 h at room temperature. Solvent was removed under reduced pressure and the solid material was purified on RP HPLC (C18 column, acetonitrile/1% TFA in water, 7/3), and recrystalized from MeOH, which afforded **1-21** (4.2 mg, 56% overall yield) as a yellow solid: Mp 232-234 °C (decomp.); IR (ATR) 3351, 3086, 3030, 1660, 1606, 1455, 1124, 1312 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.07 (bs, 1 H), 9.19 (bs, 2 H), 8.63 (bs, 2 H), 7.89 (d, 2 H, *J* = 8.7 Hz), 7.86 (s, 1 H), 7.70 (d, 1 H, *J* = 8.4 Hz), 7.42 (d, 1 H, *J* = 8.4 Hz), 7.19 (d, 2 H, *J* = 8.7), 6.97 (s, 1 H), 5.13 (s, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.3, 157.9, 142.1, 135.9, 133.0, 127.1, 124.4, 119.9, 119.6, 118.8, 115.4, 111.8, 98.3, 59.9.

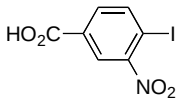


2-(4-(1*H*-Indol-2-yl)phenyl)-1*H*-indole-5-carbonitrile (1-22). To a solution of **1-43** (15.0 mg, 0.0450 mmol) in DMF (0.5 mL) was added $Pd(PhCN)_2Cl_2$ (3.4 mg, 0.0088 mmol). The mixture was heated to 80 °C for 30 min, cooled to room temperature, treated with water (1 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (1 x 20 mL), brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by chromatography on SiO_2 (50% THF/hexanes) afforded **1-22** (11.8 mg, 79%) as a yellow solid: Mp 198 °C (decomp.); IR (KBr) 3432, 2220, 1616, 790 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 11.28 (bs, 1 H), 10.75 (bs, 1 H), 8.05 (s, 1 H), 8.00 (app s, 4 H), 7.61 (d, 1 H, J = 8.4 Hz), 7.59 (d, 1 H, J = 8.1 Hz), 7.44 (d, 1 H, J = 8.4 Hz), 7.43 (d, 1 H, J = 8.1 Hz), 7.16-7.06 (m, 2 H), 7.01-6.92 (m, 2 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 139.9, 138.9, 137.3, 137.0, 131.8, 129.8, 128.6, 128.4, 125.8, 125.4, 124.3, 121.8, 120.7, 120.1, 119.5, 112.4, 111.3, 101.5, 99.4, 99.3; MS (EI) *m/z* 333 ($M^{\bullet+}$, 100), 262 (67), 183 (53), 68 (37); HRMS (EI) *m/z* calcd for $C_{23}H_{15}N_3$ 333.1266, found 333.1276.

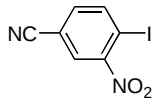


2-(4-(1*H*-Indol-2-yl)phenyl)-1*H*-indole-6-carbonitrile (1-23). A solution of **1-44** (130.0 mg, 0.3899 mmol) and $Pd(PhCN)_2Cl_2$ (31.0 mg, 0.0808 mmol) in DMF (3.9 mL) was heated to 80 °C for 1 h. After cooling the reaction mixture to room temperature, water (5 mL) was added and the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with water (1 x 20 mL) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (50% THF/hexanes) afforded **1-23** (70.1 mg, 54%) as a

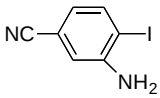
yellow solid: Mp 192 °C (decomp.); IR (KBr) 3431, 2359, 2340, 2218, 1617, 1353 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.18 (bs, 1 H), 11.60 (bs, 1 H), 8.00 (app s, 4 H), 7.84 (s, 1 H), 7.71 (d, 1 H, J = 8.1 Hz), 7.55 (d, 1 H, J = 7.8 Hz), 7.41 (d, 1 H, J = 8.1 Hz), 7.34 (d, 1 H, J = 8.1 Hz), 7.09-7.14 (m, 2 H), 6.98-7.03 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 141.6, 137.3, 137.0, 135.9, 132.1, 131.9, 129.7, 128.6, 126.1, 125.4, 122.3, 121.9, 121.0, 120.7, 120.2, 119.5, 115.8, 111.3, 102.6, 99.7, 99.4; MS (EI) *m/z* 333 ($M^{\bullet+}$, 33), 205 (100), 91 (57); HRMS (EI) *m/z* calcd for $C_{23}H_{15}N_3$ 333.1266, found 333.1256.



4-Iodo-3-nitrobenzoic acid. A solution of 4-iodobenzoic acid (10.0 g, 40.3 mmol) in a mixture of conc. H_2SO_4 (50 mL) and conc. HNO_3 (10 mL) was stirred for 20 h at room temperature. The reaction mixture was poured into ice water (100 mL) and filtered through a Buchner funnel. The solid residue was dissolved in THF, concentrated under reduced pressure and azeotropically dried with toluene (50 mL). The yellow residue was dissolved in THF (200 mL), dried (Na_2SO_4), and filtered through a pad of Celite/Florisil (1/1; v/v). After concentration under reduced pressure, the residue was dissolved in water (300 mL), extracted with EtOAc (3 x 150 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford 4-iodo-3-nitrobenzoic acid (11.8 g, 100%) as a yellow solid: Mp 212.2-215.3 °C; IR (ATR) 3086, 2834, 1685, 1521, 1353, 1297 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.42 (d, 1 H, J = 1.8 Hz), 8.32 (d, 1 H, J = 8.1 Hz), 7.97 (dd, 1 H, J = 8.1, 1.8 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.6, 154.8, 143.4, 134.5, 133.2, 126.5, 92.7; MS (EI) *m/z* 293 ($M^{\bullet+}$, 100), 92 (61), 74 (53); HRMS (EI) *m/z* calcd for $C_7H_4INO_4$ 292.9185, found 292.9174.

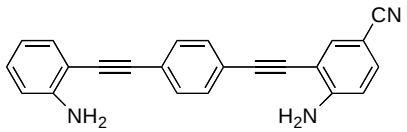


4-Iodo-3-nitrobenzonitrile. A solution of 4-iodo-3-nitrobenzoic acid (2.57 g, 8.77 mmol) in THF (25 mL) and DMF (0.3 mL) was cooled to 0 °C and oxalyl chloride (1.4 mL, 16 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. Solvent was removed *in vacuo*. The residue was re-dissolved in THF (30 mL), treated with gaseous ammonia for 5 min and stirred for 1 h at room temperature. After addition of ether (30 mL), the mixture was filtered through Celite/Florisil (1/1; v/v). The filtrate was concentrated *in vacuo* and dissolved in pyridine (25 mL) under an atmosphere of dry nitrogen. After addition of mesyl chloride (1.5 mL, 19 mmol), the mixture was stirred for 30 h at room temperature, treated with ether (20 mL), transferred to a separatory funnel with aq $NaHSO_4$ (2M solution, 150 mL), and extracted with ether (3 x 75 mL). The combined organic layers were washed with aq $NaHSO_4$ (2M solution, 50 mL), water (100 mL), brine, and dried (Na_2SO_4). Purification by chromatography on SiO_2 (5% Et_2O/toluene) gave 4-iodo-3-nitrobenzonitrile (2.08 g, 87%) as a yellow powder: Mp 121.0-124.2 °C; IR (ATR) 3086, 2233, 1705, 1526, 1342, 840 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.42 (d, 1 H, J = 8.4 Hz), 8.40 (d, 1 H, J = 2.4 Hz), 7.83 (dd, 1 H, J = 8.4, 2.1 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 143.1, 135.9, 133.2, 128.2, 116.2, 113.4, 92.5; MS (EI) *m/z* 274 ($M^{\bullet+}$, 100), 228 (73), 101 (75), 75 (51); HRMS (EI) *m/z* calcd for $C_7H_3IN_2O_2$ 273.9239, found 273.9233.



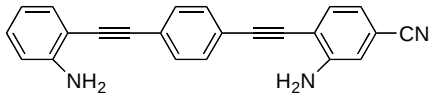
3-Amino-4-iodobenzonitrile (1-28). To a solution of 4-iodo-3-nitrobenzonitrile (2.00 g, 7.29 mmol) in EtOH (20 mL) was added glacial acetic acid (20 mL), iron powder (2.29 g, 41.0 mmol)

and conc. HCl (0.3 mL). The reaction mixture was heated at reflux for 4 h, cooled to room temperature, and treated with Na_2CO_3 slowly until gas stopped evolving. The reaction mixture was extracted with EtOAc (3 x 35 mL) and the combined organic layers were washed with water, brine and dried (Na_2SO_4). Purification by chromatography on SiO_2 (50% EtOAc/hexanes) furnished **1-28** (1.56 g, 87%) as a white solid: Mp 122-124.8 °C; IR (ATR) 3395, 3315, 2223, 1586, 1463, 1301 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.59 (d, 1 H, J = 8.7 Hz), 7.05 (d, 1 H, J = 2.7 Hz), 6.77 (dd, 1 H, J = 8.7, 3.0 Hz), 5.34 (bs, 2 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 150.1, 140.7, 121.3, 121.0, 120.3, 120.1, 79.7; MS (EI) *m/z* 244 ($M^{\bullet+}$, 100), 118 (72), 91 (63), 63 (59); HRMS (EI) *m/z* calcd for $C_7H_5IN_2$ 243.9497, found 243.9488.

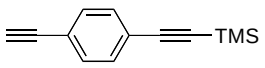


4-Amino-3-((4-((2-aminophenyl)ethynyl)phenyl)ethynyl)benzonitrile (1-43). To a solution of **1-46** (15.2 mg, 0.0700 mmol) in MeCN (0.5 mL) were added $PdCl_2(PPh_3)_2$ (2.8 mg, 0.0040 mmol), CuI (1.4 mg, 0.0073 mmol), Et_3N (50 μL, 0.35 mmol) and 4-amino-3-iodobenzonitrile (**1-27**) (17.1 mg, 0.0701 mmol). The resulting mixture was heated at reflux for 2 h, and filtered through a pad of Celite/Florisil (1:1; v/v). The pad was washed with Et_2O (3 x 5 mL) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (10 to 20 to 30% EtOAc/hexanes) afforded **1-43** (15.2 mg, 65%) as a pale yellow solid: Mp 184-186 °C (decomp.); IR (KBr) 3460, 3395, 3324, 2360, 2340, 2216, 1621, 1510, 833 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.67 (d, 1 H, J = 1.8 Hz), 7.56-7.66 (m, 4 H), 7.44 (dd, 1 H, J = 8.4, 1.8 Hz), 7.31 (dd, 1 H, J = 7.5, 0.9 Hz), 7.13 (dt, 1 H, J = 8.4, 1.2 Hz), 6.93 (d, 1 H, J = 8.7 Hz), 6.81 (d, 1 H, J = 8.1 Hz), 6.62 (dt, 1 H, J = 7.2, 0.9 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 153.8, 150.6,

137.2, 134.3, 133.0, 132.5, 132.3, 131.0, 124.8, 123.3, 120.0, 117.5, 115.2, 115.1, 107.8, 107.3, 99.5, 95.9, 94.6, 89.7, 86.8; MS (EI) *m/z* 333 ($M^{\bullet+}$, 18), 117 (45), 91 (94), 88 (100), 81 (73); HRMS (EI) *m/z* calcd for $C_{23}H_{15}N_3$ 333.1266, found 333.1259.

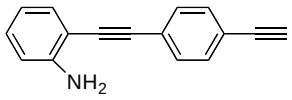


3-Amino-4-((4-((2-aminophenyl)ethynyl)phenyl)ethynyl)benzonitrile (1-44). To a solution of **1-46** (100.8 mg, 0.4639 mmol) in MeCN (3.5 mL) was added $PdCl_2(PPh_3)_2$ (16.8 mg, 0.0239 mmol), CuI (8.0 mg, 0.042 mmol), Et_3N (320 μL, 2.30 mmol) and 3-amino-4-iodobenzonitrile (**1-28**) (112.5 mg, 0.4610 mmol). The resulting mixture was heated at reflux for 4 h and filtered through a pad of Celite/Florisil (1:1; v/v). The pad was washed with Et_2O (3 x 10 mL) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (30% EtOAc/hexanes) afforded **1-44** (146.1 mg, 95%) as a yellow solid: Mp 178-180 °C; IR (KBr) 3412, 3333, 2360, 2340, 2215, 1616, 1515, 753 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.56-7.66 (m, 4 H), 7.47 (d, 1 H, *J* = 7.8 Hz), 7.29 (d, 1 H, *J* = 7.5 Hz), 7.09-7.14 (m, 2 H), 6.95 (dd, 1 H, *J* = 7.8, 1.2 Hz), 6.80 (d, 1 H, *J* = 8.1 Hz), 6.62 (t, 1 H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 150.7, 150.6, 133.8, 132.9, 132.5, 132.2, 131.0, 125.0, 123.1, 121.1, 119.5, 117.5, 117.4, 115.1, 113.6, 111.8, 107.2, 97.8, 94.6, 89.8, 87.5; MS (TOF MS ESI) *m/z* 334 $[M+H]^+$ (100); HRMS (TOF MS ESI) *m/z* calcd for $C_{23}H_{15}N_3$ $[M+H]^+$ 334.1344, found 334.1319.

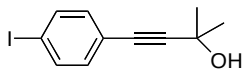


((4-Ethynylphenyl)ethynyl)trimethylsilane (1-45).[35] A solution of **1-49** (3.50 g, 13.6 mmol) in toluene (200 mL) was treated with finely powdered NaOH (90.0 mg, 2.25 mmol), heated at reflux for 2 h, and stirred at room temperature overnight. Solvent was removed under reduced

pressure and the residue was purified by chromatography on SiO_2 (hexanes) to furnish **1-45** (2.60 g, 96%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (app s, 4 H), 3.44 (s, 1 H), 0.24 (s, 9 H); MS (EI) *m/z* 199 ($M^{\bullet+}$, 31), 183 (36), 91 (100).

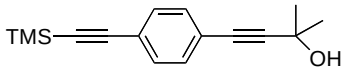


((4-Ethynylphenyl)ethynyl)trimethylsilane (1-46). To a solution of **1-50** (1.16 g, 4.00 mmol) in MeOH (60 mL) and THF (100 mL) was added K_2CO_3 (2.20 g, 16.0 mmol). The reaction mixture was stirred at room temperature for 2 h, filtered through a pad of Celite/Florisil (1/1; v/v), and washed with ether. The filtrate was concentrated *in vacuo* to afford **1-50** (0.50 g, 60%) as a white solid which was used in the next step without further characterization: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.60-7.49 (m, 4 H), 7.29 (dd, 2 H, J = 7.8, 1.5 Hz), 7.12 (dt, 1 H, J = 8.7, 1.5 Hz), 6.79 (dd, 1 H, J = 8.1, 0.6 Hz), 6.61 (dt, 1 H, J = 7.5, 1.2 Hz), 5.20 (bs, 2 H), 3.81 (s, 1 H); MS (EI) *m/z* 217 ($M^{\bullet+}$, 100), 289 (78), 274 (100), 137 (8); HRMS (EI) *m/z* calcd for $C_{19}H_{19}NSi$ 289.1287, found 289.1285.

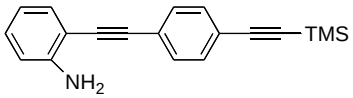


4-(4-Iodophenyl)-2-methylbut-3-yn-2-ol (1-48). To a solution of 1,4-diiodobenzene (10.2 g, 30.3 mmol) in THF (100 mL) under an atmosphere of dry nitrogen were added $Pd(PPh_3)_2Cl_2$ (0.42 g, 0.61 mmol) and CuI (0.23 g, 1.2 mmol). The reaction mixture was stirred at room temperature for 5 min, treated with triethylamine (10.6 mL, 75.8 mmol) and 2-methyl-3-butyne-2-ol (2.9 mL, 30 mmol), stirred overnight, filtered through a pad of Celite/Florisil (1/1; v/v), and washed with ether. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to provide **1-48** (4.11 g, 48%) as a

white solid: Mp 86-88 °C; IR (KBr) 3410, 2981, 2360, 2340, 1481, 1372, 1274, 1159, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 2 H, *J* = 8.4 Hz), 7.13 (d, 2 H, *J* = 8.4 Hz), 2.17 (s, 1 H), 1.62 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 133.1, 122.3, 95.2, 94.1, 81.2, 65.6, 31.4; MS (EI) *m/z* 286 ($M^{\bullet+}$, 35), 272 (12), 271 (100), 144 (25), 115 (25); HRMS (EI) *m/z* calcd for $C_{11}H_{11}OI$ 285.9855, found 285.9867.

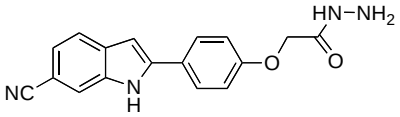


2-Methyl-4-(4-((trimethylsilyl)ethynyl)phenyl)but-3-yn-2-ol (1-49). To a solution of **1-48** (4.00 g, 14.0 mmol) in THF (45 mL) were added $Pd(PPh_3)_2Cl_2$ (0.20 g, 0.28 mmol) and CuI (0.10 g, 0.56 mmol). The reaction mixture was stirred at room temperature for 5 min, treated with triethylamine (4.9 mL, 35 mmol) and ethynyltrimethylsilane (2.1 mL, 15 mmol), stirred for 2 h at room temperature, filtered through a pad of Celite/Florisil (1/1; v/v), and washed with ether. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on SiO_2 (10% EtOAc/hexanes) to provide **1-48** (3.50 g, 98%) as a white solid: Mp 108 °C; IR (KBr) 3281, 2981, 2960, 2359, 2156, 1249, 864, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73-7.63 (m, 4 H), 2.06 (s, 1 H), 1.54 (s, 6 H), 0.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 131.4, 123.0, 122.8, 104.5, 96.1, 95.6, 81.8, 65.6, 31.4, -0.1; MS (EI) *m/z* 256 ($M^{\bullet+}$, 23), 242 (21), 241 (100), 183 (14), 68 (28); HRMS (EI) *m/z* calcd for $C_{16}H_{20}OSi$ 256.1283, found 256.1289.

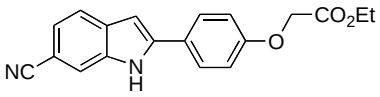


2-((4-((Trimethylsilyl)ethynyl)phenyl)ethynyl)benzenamine (1-50). To a solution of **1-45** (2.12 g, 10.7 mmol) in CH_3CN (70 mL) under an atmosphere of nitrogen were added

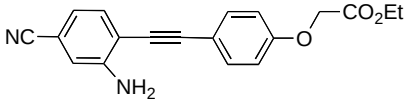
$Pd(PPh_3)_2Cl_2$ (0.38 g, 0.53 mmol) and CuI (0.22 g, 1.1 mmol). The reaction mixture was stirred for 5 min at room temperature, treated with triethylamine (7.5 mL, 53 mmol) and 2-iodoaniline (2.34 g, 10.7 mmol), heated at reflux for 2 h, cooled to room temperature, filtered through a pad of Celite/Florisil (1/1; v/v), and washed with ether. The filtrate was concentrated *in vacuo* and then purified by chromatography on SiO_2 (5% EtOAc/hexanes) to furnish **1-50** (1.16 g, 40%) as a white solid: Mp 99-101 °C; IR (KBr) 3385, 3294, 2960, 2361, 2151, 1612, 1250, 865, 837, 761 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.58-7.45 (m, 4 H), 7.29 (d, 1 H, J = 7.5 Hz), 7.11 (t, 1 H, J = 8.1 Hz), 6.79 (d, 1 H, J = 8.4 Hz), 6.61 (t, 1 H, J = 7.2 Hz), 5.19 (bs, 2 H), 0.24 (s, 9 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 150.6, 132.9, 132.7, 132.2, 131.0, 125.0, 123.5, 117.4, 115.1, 107.2, 105.6, 96.6, 94.5, 89.7, 0.0; MS (EI) *m/z* 289 ($M^{\bullet+}$, 78), 274 (100), 137 (8); HRMS (EI) *m/z* calcd for $C_{19}H_{19}NSi$ 289.1287, found 289.1285.



2-(4-(6-Cyano-1*H*-indol-2-yl)phenoxy)acetohydrazide (1-51). To a suspension of **1-52** (112.1 mg, 0.3500 mmol) in EtOH (14.2 mL) was added hydrazine monohydrate (0.50 mL, 10 mmol) and the reaction mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure and the crude product was dried *in vacuo* overnight to give **1-52** (107.0 mg, 100%) as a grey solid: Mp 270-272 °C (decomp.); IR (KBr) 3423, 3302, 3168, 2216, 1685, 1248 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.03 (s, 1 H), 9.38 (bs, 1H), 7.85 (d, 2 H, J = 9.0 Hz), 7.78 (s, 1 H), 7.65 (d, 1 H, J = 8.4 Hz), 7.31 (dd, 1 H, J = 8.4, 0.9 Hz), 7.09 (d, 2 H, J = 8.7 Hz), 6.95 (s, 1 H), 4.55 (s, 2 H), 4.35 (bs, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.5, 158.1, 141.9, 135.7, 132.1, 127.0, 124.2, 122.2, 120.8, 120.6, 115.5, 115.2, 102.0, 98.4, 66.3; MS (EI) *m/z* 306 ($M^{\bullet+}$, 30), 234 (100), 61 (33); HRMS (EI) *m/z* calcd for $C_{17}H_{14}N_4O_2$ 306.1117, found 306.1116.

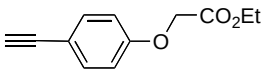


Ethyl 2-(4-(6-cyano-1*H*-indol-2-yl)phenoxy)acetate (1-52). A solution of **1-53** (115.1 mg, 0.3593 mmol) in DMF (3.6 mL) was treated with $Pd(PhCN)_2Cl_2$ (28.1 mg, 0.0733 mmol), heated at reflux for 1.5 h, and cooled to room temperature. EtOAc (10 mL) and water (10 mL) were added and the product was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on SiO_2 (30% EtOAc/hexanes) provided **1-52** (71.8 mg, 63%) as a white solid: Mp 195 °C (decomp.); IR (KBr) 3367, 2211, 1752, 1495, 1261 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 11.17 (bs, 1 H), 7.86 (d, 2 H, J = 8.7 Hz), 7.78 (s, 1 H), 7.70 (d, 1 H, J = 8.4 Hz), 7.31 (dd, 1 H, J = 8.2, 1.3 Hz), 7.08 (dt, 2 H, J = 9.0, 1.9 Hz), 6.95 (s, 1 H), 4.80 (s, 2 H), 4.22 (q, 2 H, J = 7.2 Hz), 1.26 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 169.3, 159.6, 143.1, 137.1, 133.6, 128.0, 125.8, 123.4, 121.8, 121.3, 116.4, 116.2, 104.3, 99.7, 65.9, 61.6, 14.6; MS (EI) *m/z* 320 ($M^{\bullet+}$, 100), 233 (72); HRMS (EI) *m/z* calcd for $C_{19}H_{16}N_2O_3$ 320.1161, found 320.1154.



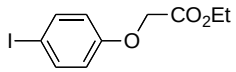
Ethyl 2-(4-((2-amino-4-cyanophenyl)ethynyl)phenoxy)acetate (1-53). A solution of **1-54** (101.0 mg, 0.4585 mmol) in CH_3CN (2.5 mL) was treated with $Pd(PPh_3)_2Cl_2$ (16.8 mg, 0.0239 mmol) and CuI (10.4 mg, 0.0546 mmol). The resulting mixture was stirred for 5 min at room temperature, treated with triethylamine (0.25 mL, 2.5 mmol) and **1-28** (124.2 mg, 0.5089 mmol), heated at reflux for next 1 h, cooled to room temperature, and filtered through Celite/Florisil (1/1; v/v). The pad was washed with ether. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on SiO_2 (20% EtOAc/hexanes) to afford **1-53** (159.2 mg,

100%) as a white solid: Mp 131-132 °C; IR (KBr) 3460, 3368, 2223, 1725, 1621, 1549, 1514, 1238 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.58-7.53 (m, 2 H), 7.42 (d, 1 H, J = 8.1 Hz), 7.12 (d, 1 H, J = 1.5 Hz), 6.99 (dt, 2 H, J = 9.0, 2.0 Hz), 6.93 (dd, 1 H, J = 7.8, 1.5 Hz), 5.61 (bs, 2 H), 4.79 (s, 2 H), 4.22 (q, 2 H, J = 7.2 Hz), 1.25 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 169.1, 159.6, 150.5, 134.0, 133.5, 120.1, 119.7, 117.3, 116.4, 116.0, 115.8, 113.0, 98.2, 84.6, 65.8, 61.7, 14.5; MS (TOF MS ESI) *m/z* 321 $[M+H]^+$ (100); HRMS (TOF MS ESI) *m/z* calcd for $C_{19}H_{16}N_2O_3$ $[M+H]^+$ 321.1239, found 321.1232.

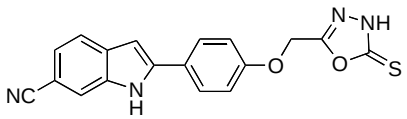


Ethyl 2-(4-ethynylphenoxy)acetate (1-54). To a solution of **1-55** (0.50 g, 1.6 mmol) in THF (3 mL) were added $Pd(PPh_3)_2Cl_2$ (21.0 mg, 0.0299 mmol) and CuI (12.0 mg, 0.0630 mmol). The resulting mixture was stirred for 5 min at room temperature, treated with triethylamine (0.34 mL, 2.5 mmol) and ethynyltrimethylsilane (0.24 mL, 1.7 mmol), stirred at room temperature for 1 h, and filtered through Celite/Florisil (1/1; v/v). The pad was washed with ether. The filtrate was concentrated *in vacuo* and the crude material was dissolved in MeOH (5 mL). After the addition of K_2CO_3 (330.1 mg, 2.450 mmol), the mixture was stirred at room temperature for 2 h. The product was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The solid residue was purified by chromatography on SiO_2 (1% EtOAc/hexanes) to afford **1-54** (171.1 mg, 60%) as a white solid: Mp 78.0-80.5 °C; IR (ATR) 3235, 1744, 1508, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, 2 H, J = 9.0 Hz), 6.86 (d, 2 H, J = 9.0 Hz), 4.63 (s, 2 H), 4.28 (q, 2 H, J = 7.2 Hz), 3.01 (s, 1 H), 1.30 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 158.1, 133.6, 115.5, 114.6,

83.3, 76.2, 65.3, 61.5, 14.1; MS (EI) *m/z* 204 ($M^{\bullet+}$, 100), 131 (48); HRMS (EI) *m/z* calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0777.



Ethyl 2-(4-iodophenoxy)acetate (1-55). To a solution of 4-iodophenol (5.00 g, 22.7 mmol) in 3-pentanone (100 mL) was added NaI (0.68 g, 4.5 mmol) followed by K_2CO_3 (9.42 g, 68.1 mmol) and ethyl bromoacetate (10.0 mL, 90.8 mmol). The reaction mixture was heated at reflux for 12 h, cooled to room temperature, and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (1% EtOAc/hexanes) gave **1-55** (4.40 g, 63%) as a white solid: Mp 57.2-59.6 °C; IR (ATR) 3067, 2972, 2929, 1739, 1211, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (dt, 2 H, *J* = 9.0, 2.0 Hz), 6.69 (dt, 2 H, *J* = 9.0, 2.0 Hz), 4.59 (s, 2 H), 4.27 (q, 2 H, *J* = 7.2 Hz), 1.30 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 157.7, 138.3, 117.0, 84.0, 65.4, 61.5, 14.1; MS (EI) *m/z* 306 ($M^{\bullet+}$, 100), 233 (36), 203 (25), 106 (18), 86 (44), 84 (73); HRMS (EI) *m/z* calcd for $C_{10}H_{11}IO_3$ 305.9753, found 305.9742.



2-(4-((5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-indole-6-carbonitrile (1-56). To a solution of **1-51** (15.8 mg, 0.0516 mmol) in DMSO (0.5 mL) was added a solution of KOH (4.9 mg, 0.050 mmol) in MeOH (0.5 mL), followed by the addition of CS_2 (0.25 mL). The reaction mixture was heated at reflux for 24 h, quenched with aq HCl (1M, 10 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water (20 mL), brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by

chromatography on SiO_2 (10 to 50% EtOAc/hexanes) gave **1-56** (13.4 mg, 80%) as a white solid: Mp 141 °C; IR (ATR) 3583, 3325, 2217, 1460, 1245, 821 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 14.71 (bs, 1 H), 12.05 (s, 1 H), 7.89 (d, 2 H, J = 8.4 Hz), 7.79 (s, 1 H), 7.66 (d, 1 H, J = 8.4 Hz), 7.32 (d, 1 H, J = 8.1 Hz), 7.20 (d, 2 H, J = 8.4 Hz), 6.98 (s, 1 H), 5.34 (s, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.0, 159.5, 157.4, 141.7, 135.7, 132.0, 127.2, 125.0, 122.2, 120.7, 115.6, 115.5, 102.3, 98.7, 59.6; MS (EI) *m/z* 348 ($M^{\bullet+}$, 13), 234 (100), 233 (36); HRMS (EI) *m/z* calcd for $C_{18}H_{12}N_4O_2S$ 348.0681, found 348.0691.

2.0 MICROWAVE ASSISTED INTRAMOLECULAR-DIELS-ALDER-FURAN APPROACH TO UNPROTECTED 4-MONOSUBSTITUTED AND 3,4-DISUBSTITUTED INDOLES

2.1 INTRODUCTION

2.1.1 Importance of Indole Containing Compounds

The indole ring is a ubiquitous motif in nature and is found in a wide array of naturally occurring alkaloids. Functionalized indoles, along with their dihydro and tetrahydro derivatives, have been of interest to organic chemists for many years due to the large number of natural products and biologically active compounds that contain these heterocycles.[46,47] Some natural indoles are simple monosubstituted derivatives, such as plant growth regulator indole-3-acetic acid **2-1** (Figure 10),[48] while others have more complex substitution pattern. Most indole alkaloids are derived from the amino acid (*S*)-tryptophan **2-2** and some of them, such as serotonin **2-3**, are involved in important biological processes and metabolic pathways. A relatively uniform fraction of ~4% of all pharmaceuticals, high-throughput screening samples, and natural products, contain an aromatic or partially saturated indole core.[49-52] Many indole-containing compounds are important drugs, such as naturally occurring vincristine **2-4**,[53] ambiguine A isonitrile **2-5**,[54] and

lysergic acid **2-6**, as well as synthetic drugs such as imitrex **2-7**,[55] zorfan ODT **2-8**,[56] cialis **2-9**,[57] requip **2-10**,[58] and the phosphoinositide 3-kinase inhibitor **2-11**[51] (Figure 10).

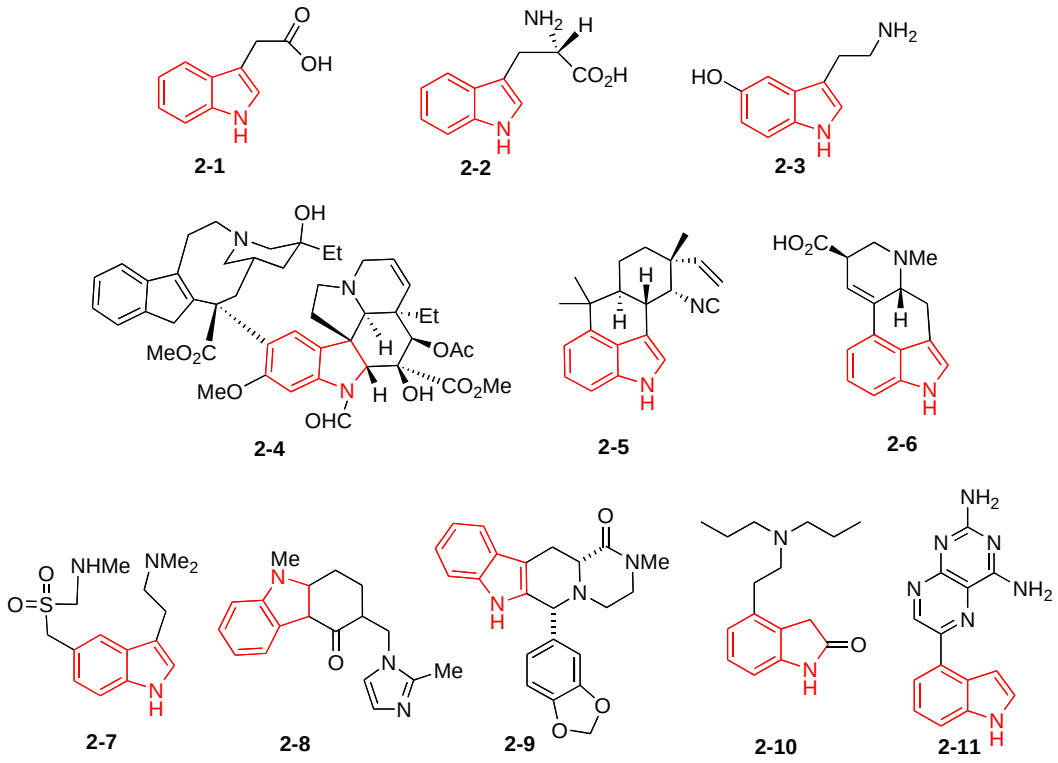


Figure 10. Representative indole-containing natural and synthetic products (indole outlined in red)

For over a hundred years, the synthesis of indoles has been a major area of focus for synthetic chemists, and many methods for indole preparation have been developed.[59] In some cases, however, specific substitution patterns remain difficult to obtain by standard indole-forming reactions.[60] Thus, the search for efficient protocols for the formation of substituted/functionalized indole scaffolds remains an important topic in the areas of synthetic and medicinal chemistry.[61]

2.1.2 Methods for Indole Synthesis

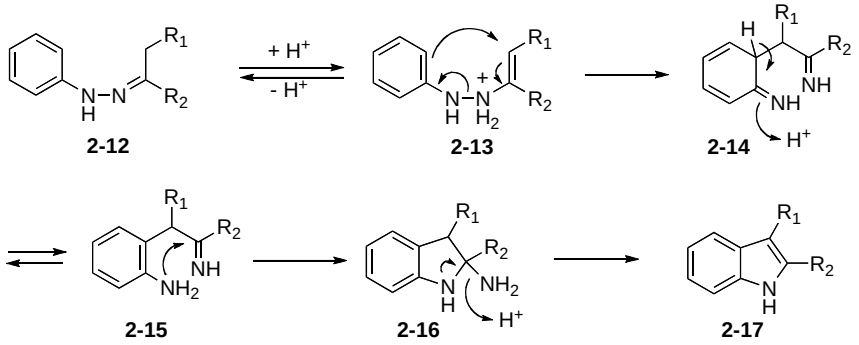
The most nucleophilic position of the indole ring is the C3 position. It is therefore relatively easy to prepare 3-substituted indoles by an electrophilic aromatic substitution reaction on an existing indole nucleus. For indoles with other substitution patterns, however, it is often necessary to assemble the ring system. Two general approaches have been outlined. The first approach is based on an aniline with a free *ortho*-position, while the second approach utilizes an *ortho*-alkylated aniline.[19]

2.1.2.1 Fischer Indole Synthesis

The Fisher indole synthesis provides a simple, efficient method for the transformation of enolizable *N*-arylhydrazones into indoles.[62] In many cases, the indolization reaction is carried out by simple heating of the ketone or aldehyde and the arylhydrazine with an appropriate acid, without isolation of the hydrazone intermediate. The catalysts that successfully lead to indolization include strong acids (e.g., PTSA, PPA, HCl, H_2SO_4), weak acids (e.g., pyridinium chloride, acetic acid), solid acids (e.g., montmorillionite KSF clay, Zeolite Y, ion exchange resins) and Lewis acids (e.g., PCl_3, $ZnCl_2$).[63]

Advantages of the Fisher indole synthesis include the tolerance of a wide range of functional groups and the use of relatively readily available starting materials.[64] One disadvantage is that unsymmetrical ketones can lead to mixtures of indoles if both substituents have enolizable α-protons. Arylhydrazones of methyl alkyl ketones, however, normally give 2-methylindoles, implying that the cyclization takes place at the more substituted alkyl group.

The mechanism of the Fisher indole synthesis is believed to involve a [3,3]-sigmatropic rearrangement of an ene-hydrazine tautomer **2-13** to a *bis*-iminobenzylketone **2-14** (Scheme 15). Cyclization and aromatization with loss of ammonia provides the indole product **2-17**.[65]



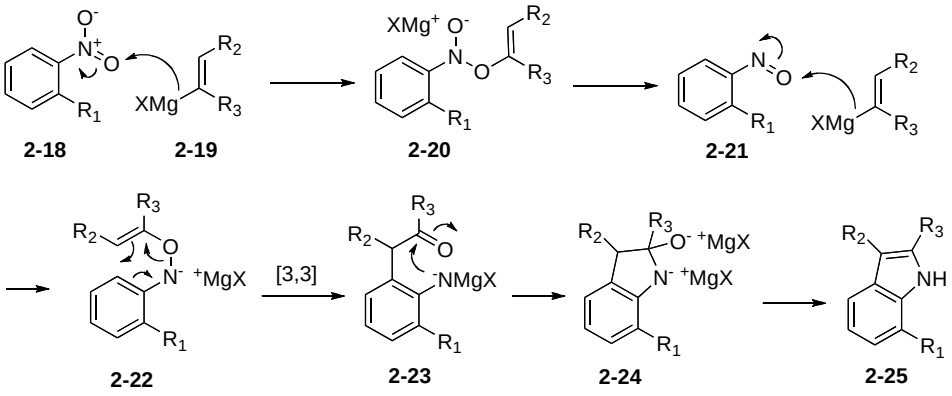
Scheme 15. Mechanism of the Fischer indole synthesis

2.1.2.2 Bartoli Synthesis

Bartoli *et al*. have described the reaction of substituted nitroarenes with an excess of vinyl Grignard reagents at low temperature to afford substituted indoles upon aqueous work-up.[66,67] The highest yields were obtained with *ortho*-substituted nitroarenes, while the absence of the *ortho*-substituent leads to very low yields of the desired indole.

The mechanism of the Bartoli reaction (Scheme 16) is believed to also involve a [3,3]-sigmatropic rearrangement as the key step.[68] The sequence begins with the addition of Grignard reagent **2-19** to the oxygen atom of the nitro group, followed by a rapid conversion to the intermediate nitrosoarene **2-21**. This intermediate is more reactive than the starting nitroarene **2-18** and quickly reacts with a second equivalent of Grignard reagent to give the *O*-alkenyl hydroxylamine **2-22**, which undergoes a [3,3]-sigmatropic rearrangement. The rearranged product **2-23** then undergoes an intramolecular attack followed by deprotonation by the third

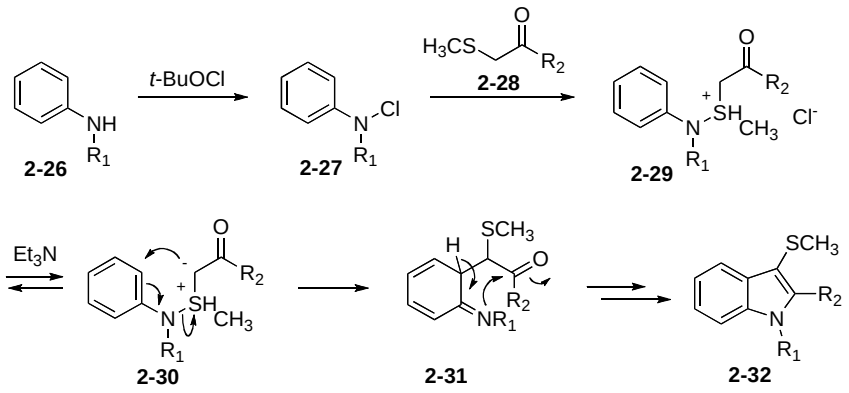
equivalent of Grignard reagent. Finally, an acidic work-up yields the 7-substituted indole **2-25** in moderate to good yields.



Scheme 16. Bartoli indole synthesis

2.1.2.3 Gassman Indole Synthesis

Another method based on *ortho*-cyclization uses a [3,2]-sigmatropic rearrangement of a sulfonium ylide. The starting material for the Gassman synthesis is an *N*-chlorinated aniline **2-27**, which is converted to sulfonium salt **2-29** by reaction with the α-keto sulfide **2-28**, thereby providing the additional carbon aroms needed to construct the indole core (Scheme 17).[69,70] In the cyclization step, a weak N-S bond (E = 111 kcal mol^{-1}) is broken and a strong C-C bond (E = 145 kcal mol^{-1}) is formed. Upon rearomatization and intramolecular nucleophilic attack, indole **2-32** is formed. The methylthio group can be removed in a subsequent step by reduction with Raney Ni.[71]

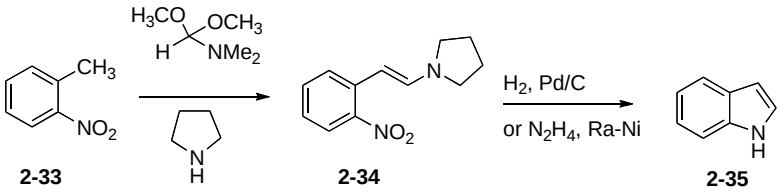


Scheme 17. Gassman indole synthesis

2.1.2.4 Leimgruber-Batcho Indole Synthesis

One of the most important and commonly used methods for the preparation of 2,3-unsubstituted indoles is the Leimgruber-Batcho indole synthesis.[72] The classical Leimgruber-Batcho reaction involves the condensation of an appropriately substituted *o*-nitrotoluene **2-33** with *N*,*N*-dimethylformamide dimethyl acetal (Scheme 18) to give the intermediate β-(dimethylamino)-2-nitrostyrene **2-34**. Reductive cyclization leads to substituted indoles **2-35**. The increased acidity of the methyl group of the *o*-nitrotoluene allows the isolation of the remarkably stable intermediate **2-34**. In an improved procedure, the formation of **2-34** uses an excess of pyrrolidine.[72,73]

The Leimgruber-Batcho reaction is capable of tolerating a large number of substituents, and this method has been extensively used for the construction of both natural products and pharmaceutically important compounds.[20,74]

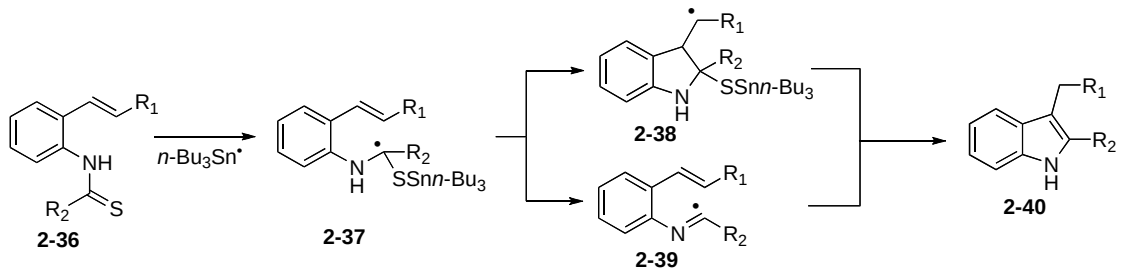


Scheme 18. Leimgruber-Batcho reaction

2.1.2.5 Fukuyama's Radical Approach to Indole

Fukuyama and coworkers have reported a mild method for indole synthesis employing a radical cyclization.[75] In this efficient and useful method 2-alkenylthioanilide was subjected to tri-*n*-butyltin hydride and AIBN in toluene at 80 °C for 5 min, resulting in clean formation of the desired indole. It was also shown that using Et_3B as a radical initiator gave excellent results in this procedure.

The sequence is believed to begin with the addition of tin radical to thioamide **2-36** (Scheme 19) to form either a C-sp^3 **2-38** or an imidoyl radical species **2-39**. Both radical species could in principle undergo a cyclization to furnish the 2,3-disubstituted indole **2-40**.[75]



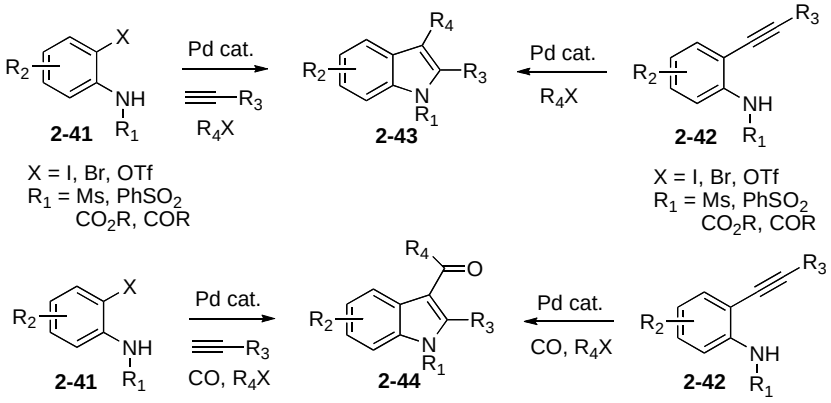
Scheme 19. Fukuyama reaction

The ease of preparation of the indole precursors, the mild cyclization conditions and the compatibility with various substituents at the 2- and 3- positions, as well as on the benzene group

make this method a very powerful addition to existing indole syntheses. It has already been utilized in numerous synthesis, including aspidophytine,[76] vinblastine[77] and strychnine.[78]

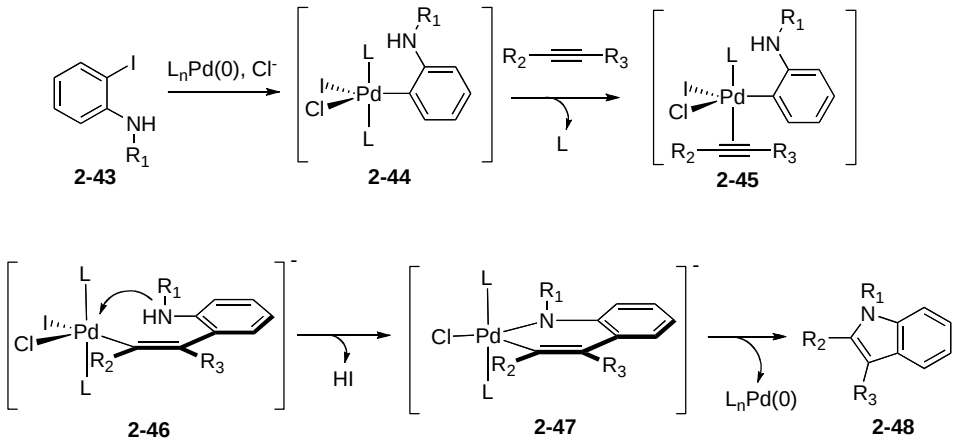
2.1.2.6 Palladium-Mediated Processes for Indole Synthesis

The palladium-catalyzed cyclization of 2-alkynylanilines **2-42** and the one-pot annulation of 2-haloanilines **2-41** with terminal alkynes have received considerable attention for the construction of indoles.[22,23,79,80] In both cases, the preparation of indoles requires reductive elimination of either an indolylpalladium intermediate, leading to substituted indoles **2-43**, or an acylindolylpalladium species, giving 3-acylindoles **2-44** (Scheme 20).



Scheme 20. Palladium-assisted reactions for indole synthesis

It was reported recently by Larock that 2-iodoanilines and disubstituted alkynes undergo one-pot Pd-catalyzed coupling to furnish 2,3-disubstituted indoles.[81] The reaction commences with the oxidative addition of the Pd(0) catalyst into the C-I bond to form intermediate **2-44**. Upon ligand exchange, intermediate **2-46** undergoes a carbopalladation process followed by reductive elimination to give substituted indoles **2-48** (Scheme 21).[82]



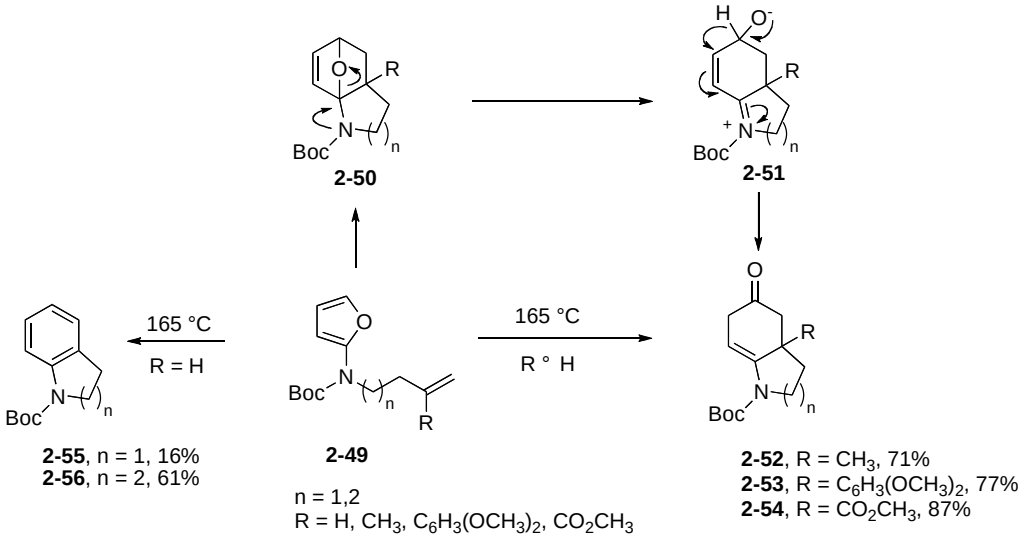
Scheme 21. Larock indole synthesis

2.1.3 Intramolecular Diels-Alder Furan (IMDAF) Reaction

The intramolecular Diels-Alder furan cycloaddition (IMDAF), popularized by Padwa[83-87] and others, represents a particularly interesting method for indole preparation, and it has successfully been applied to the synthesis of a variety of indolines. This process involves the regioselective intramolecular cycloaddition of 2-aminofurans to various dienophiles.[86]

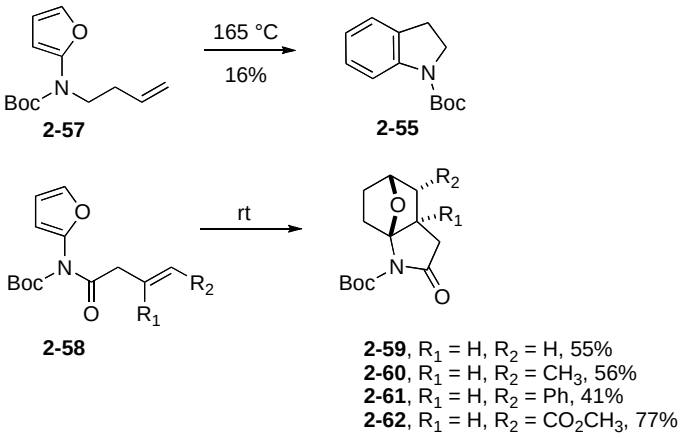
To establish the viability of the IMDAF sequence, Padwa and coworkers prepared several 2-amidofurans containing olefinic tethers from the reaction of *N*-*tert*-butylfuranyl carbamate with various alkenyl halides in the presence of base.[84] As outlined in Scheme 22, the IMDAF reaction of alkenyl-substituted furanyl carbamates proceeds via a cycloaddition/rearrangement cascade. It was shown that the initially formed oxabicyclic intermediate **2-50** undergoes a nitrogen-assisted ring opening followed by the loss of a proton to produce aza-bicyclic ketones **2-52 – 2-54**. Early studies by the Padwa group showed that when a 2-substituted olefin was used, the thermal reaction provided rearranged hexahydroindolinones **2-52 – 2-54**. On the other hand,

unsubstituted alkenyl tethers furnished dihydroindoles **2-55** and **2-56** by the thermally promoted loss of a water molecule.



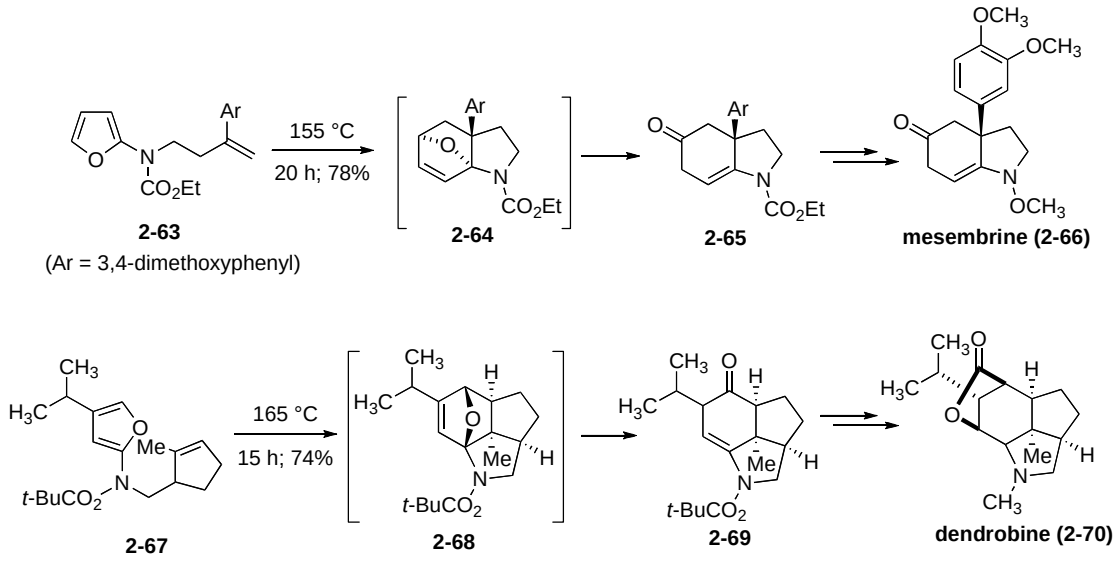
Scheme 22. Intramolecular Diels-Alder reaction of 2-amidofurans

A remarkable rate enhancement was noticed with substrates that contain an sp^2 center within the tether. These reactions proceed at lower temperature, and often lead to the isolation of the oxabicyclic intermediates (Scheme 23). The presence of the rigid amide moiety is believed to place the alkenyl dienophile in a much closer position to the furanyl π-system, thereby lowering the energy gap between the ground state and the reactive conformers.



Scheme 23. Effect of the carbonyl group present in the tether

The Padwa group successfully applied this methodology for a number of alkaloids containing a hydroindole subunit. The synthesis of the *Amaryllidaceae* alkaloid mesembrine **2-66** (Scheme 24) utilized a thermolysis of amidofuran **2-63** to establish the required quaternary center present in the natural product. A similar strategy was also used in the synthesis of dendrobine (**2-70**), where the key IMDAF reaction involved a cycloaddition of the amidofuran unit with a trisubstituted unactivated olefin, and provided the highly functionalized tricyclic ketone **2-69** in 74% yield. Further functional group transformations provided the desired alkaloid dendrobine.[88]

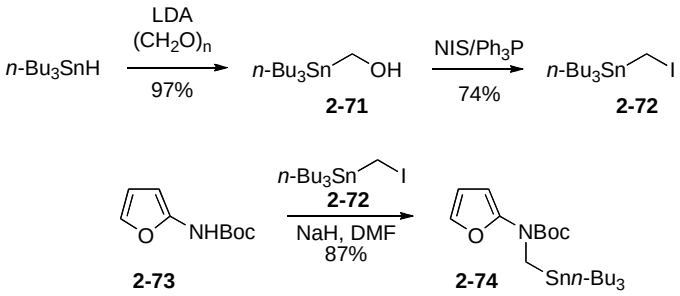


Scheme 24. Padwa's IMDAF approach to mesembrine and dendrobine

Previous work in our group focused on extending the use of 2-aminofuranes for indole synthesis.[89] Such a process would be readily possible by the strategic placement of a second, easily dehydrated oxygen functionality. To achieve this goal, it was envisioned that allylic alcohols bearing the *N*-Boc-protected 2-furanylaminomethyl fragment could be employed as starting materials. In contrast to Padwa's work where dehydration of the 6-membered ring of the indole-like fragment was an undesired reaction pathway,[84] our methodology utilizes an extensive

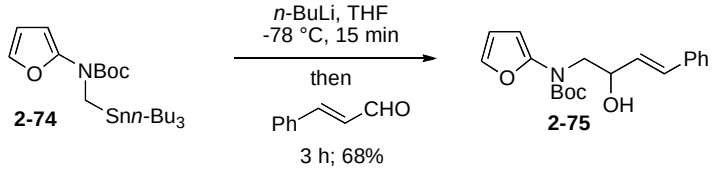
aromatization and introduces an additional hydroxyl group leading to the pyrrole portion of the target heterocycle.[90]

Appropriate furanyl olefins were envisioned to arise from an alkyllithium addition to α,β-unsaturated aldehydes. Due to the instability of alkyllithium reagents, a stannane precursor was selected, which can be transmetalated *in situ* by treatment with *n*-BuLi.[91] The stannane reagent was synthesized by a series of routine transformations (Scheme 23).[92] The tributylstannyl anion, generated by treatment of tributyltin hydride with LDA, was quenched with paraformaldehyde to afford alcohol **2-71**. Iodination of this alcohol with NIS/PPh_3 furnished the corresponding iodide **2-72**, which was subsequently coupled with *N*-Boc-protected 2-aminofuran **2-73**[86] in the presence of sodium hydride to yield stannane **2-74**.



Scheme 25. Furanyl stannane reagent preparation

With the stannane in hand, conditions for the addition to α,β-unsaturated aldehydes were explored. Treatment of **2-74** with *n*-buthyllitium in THF for 15 min at -78 °C, followed by the addition of cinnamaldehyde provided the expected addition product **2-75** in 68% yield after 3 h (Scheme 24).

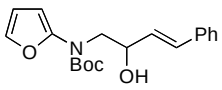
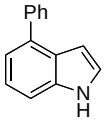


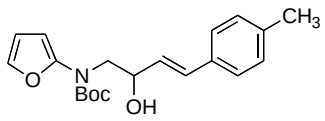
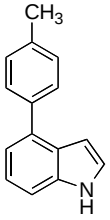
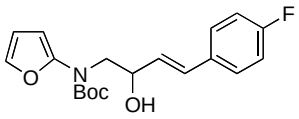
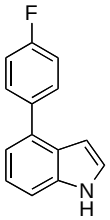
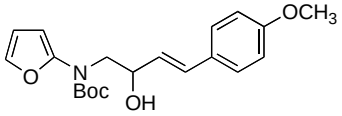
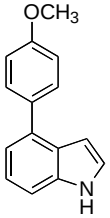
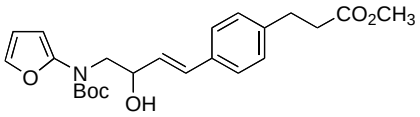
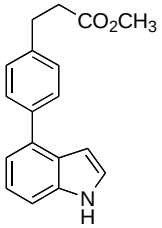
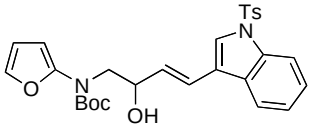
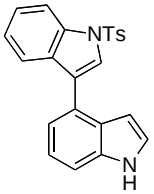
Scheme 26. Transmetallation and alkylation of cinnamaldehyde

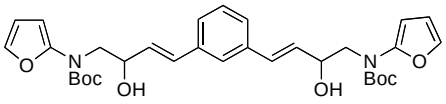
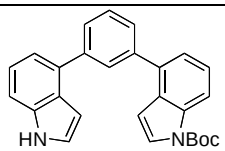
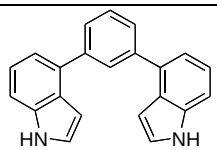
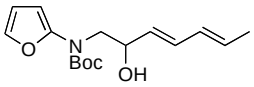
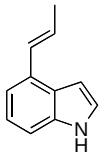
Unfortunately, heating alcohol **2-75** in toluene at reflux led to gradual decomposition instead of the desired Diels-Alder reaction. Microwave conditions, however, proved to be very efficient. When **2-75** was heated in *o*-dichlorobenzene for 20 min at 180 °C, complete consumption of the starting material was observed, and the desired 4-phenylindole (**2-76**, Table 1, entry 1) was isolated in 79% yield. Additionally, this process proceeded with complete Boc-deprotection.[93,94]

It is clear that the microwave heating is essential for the success of the IMDAF reaction. The introduction of microwave energy into a chemical reaction can lead to much higher heating rates than those that can be achieved conventionally.[95] In contrast to conventional heating, which involves a slow heat transfer from an external heating source, microwave irradiation is transferred directly by interaction of the radiation with dipoles of solvent and/or reaction components.[48,96]

Table 1. Scope of the microwave-assisted IMDAF reaction[a]

Entry	Substrate	Product	Yield (%)
1	 **2-75**	 **2-76**	79

2	 **2-77**	 **2-78**	76
3	 **2-79**	 **2-80**	83
4	 **2-81**	 **2-82**	69
5	 **2-83**	 **2-84**	77
6	 **2-85**	 **2-86**	71

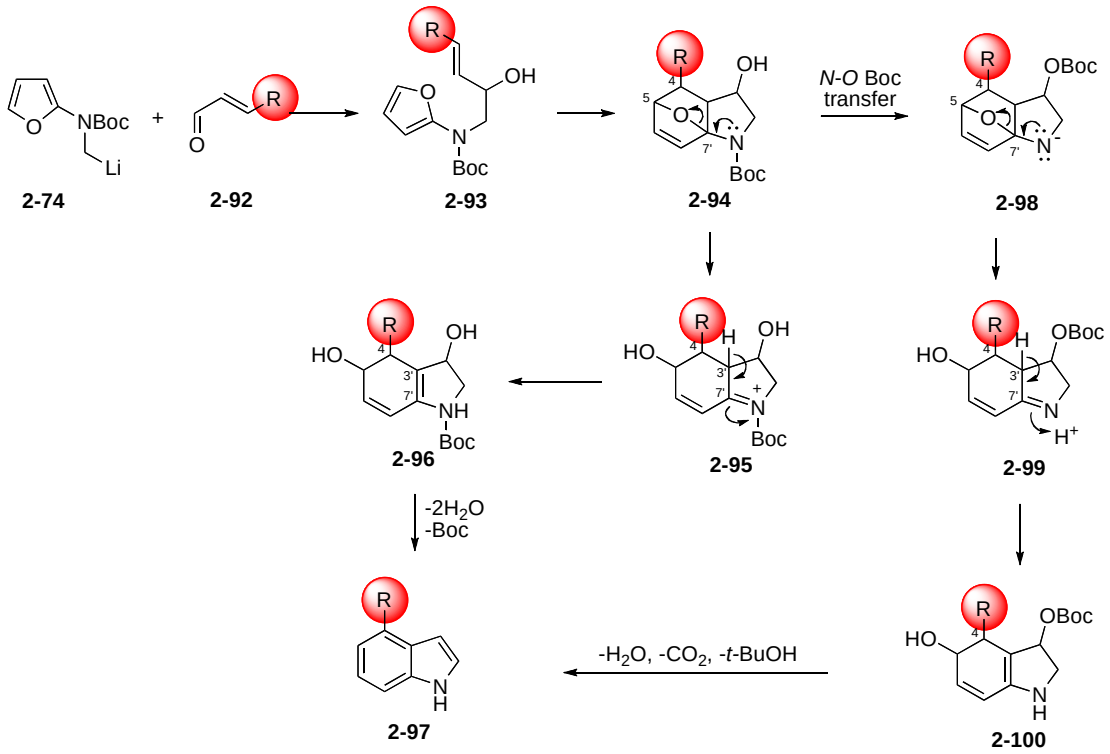
7	 **2-87**	 **2-88**	 **2-89**	61 (1.75:1)
8	 **2-90**	 **2-91**		69[b]

[a]All reactions were carried out by heating a solution of alcohol in *o*-dichlorobenzene in a microwave reactor for 20 min at 180 °C. The reaction mixture was concentrated and purified by chromatography on SiO_2 (1% EtOAc/hexanes). [b]The product **2-91** was isolated as a mixture of geometric isomers (*E*:*Z* = 7:1)

Of particular importance is the degree of structural diversity that can be accessed during this process.[90] As seen in Table 1, both electron rich *p*-anisyl (**2-81**) and electron poor *p*-fluorophenyl (**2-79**) substrates were suitable for cyclization. Carboxylic ester **2-83** was tolerated without diminishing reactivity or yield. Incorporation of an additional double bond in allylic alcohol **2-90** led to clean formation of 4-alkenyl substituted indole **2-91** in a 7:1 ratio of *E*:*Z* isomers. When symmetric bisfuran **2-87** was subjected to the Diels-Alder cascade process, diannulated products **2-88** and **2-89** were isolated in a 7:4 ratio, with no monocyclization being observed.

The straightforward construction of 4-substituted indoles presented here presumably proceeds as shown in Scheme 27. The addition of the alkyllithium reagent to the α,β-unsaturated carbonyl compound **2-92** furnishes allylic alcohol **2-93**. Upon heating, allylic aclohol **2-93** undergoes a [4+2] cycloaddition resulting in the formation of the tricyclic intermediate **2-94** bearing an alkyl or an aryl substituent at position 4. The nitrogen atom adjacent to the 5,7′-ether facilitates the opening of the ether bridge in intermediate **2-94** to give iminium ion **2-95**. The completion of the sequence requires deprotonation at position 3', water elimination, and Boc-

deprotection. This results in the formation of the *N*-unprotected 4-substituted indole **2-97**. Alternatively, the tricyclic intermediate **2-94** could undergo an *N-O* Boc-group transfer, leading to the amide **2-98**. Upon opening of the oxygen bridge followed by a proton transfer, elimination of water and CO_2 from the intermediate **2-100** leads to the formation of indole **2-97**.



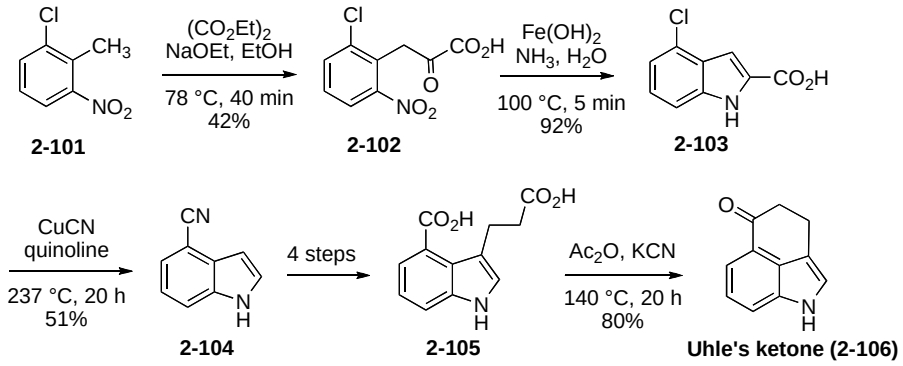
Scheme 27. Proposed mechanism for the indole formation

2.1.4 Uhle's Ketone

Uhle's ketone (**2-106**, Scheme 28) is a tricyclic compound structurally related to lysergic acid derivatives, and is a key intermediate in the synthesis of many pharmacologically active compounds.[97] It was first synthesized by Uhle in 1949 in 8 steps from 2-chloro-6-nitrotoluene.[98] Several attempts to improve the preparation of Uhle's ketone have been described,[99-101] but the

increasing importance of the synthesis of pharmacologically active compounds requires new efficient and simple ways for the synthesis of this important precursor.

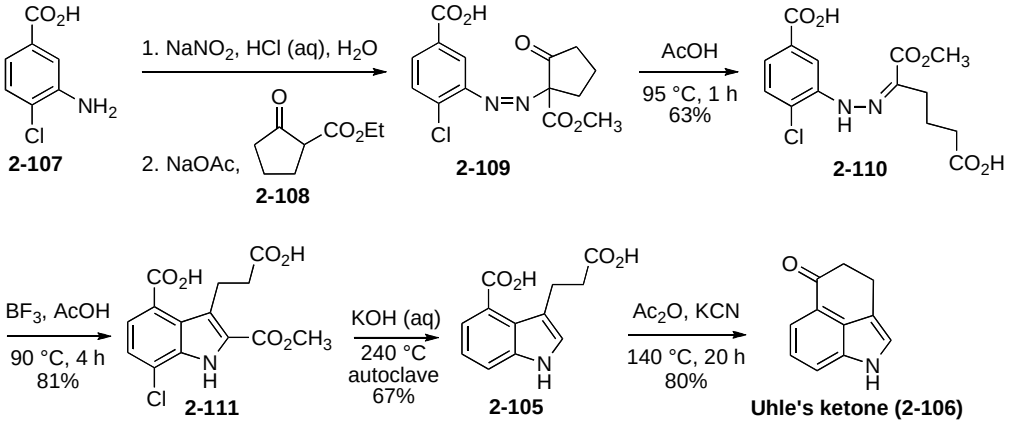
For the synthesis of Uhle's ketone, indoline derivatives or 4-substituted indole derivatives are usually employed as starting materials. While the direct cyclization at the 4-position of indole would offer an elegant way for the closure of the C ring of Uhle's ketone, the much greater nucleophilicity of the 2-position leads to the corresponding isomeric compounds.[97] To overcome this problem, Uhle prepared β-(4-carboxy-3-indole)-propionic acid **2-105** (Scheme 28), starting from 2-chloro-6-nitrotoluene **2-101**.[98] This reaction sequence introduces a carboxylic moiety at the indole 4-position through a nucleophilic substitution of chloride with copper(I) cyanide, while the indole ring is derived from the nitro group and the previously introduced three-carbon unit. After subjecting **2-105** to KCN and acetic anhydride under reflux for 20 h, Uhle obtained the corresponding ketone **2-106** in 80% yield.



Scheme 28. Uhle's approach to **2-106**

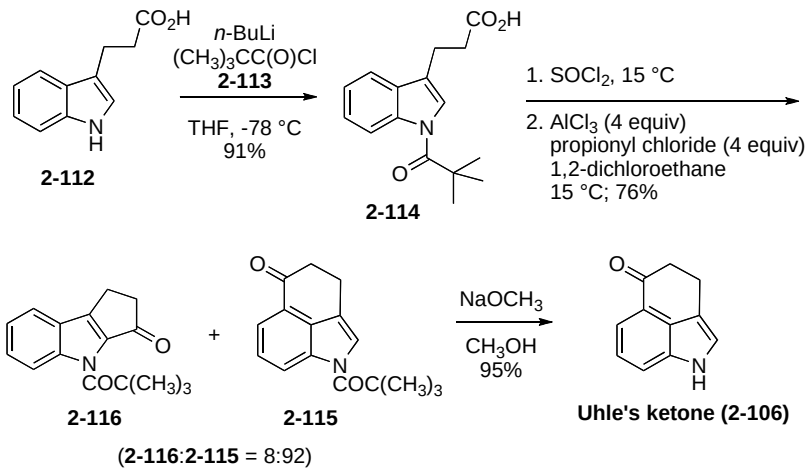
In 1972 Bowman and coworkers improved Uhle's approach to **2-106** (Scheme 29).[102] The chloroanthranilic acid **2-107** was first diazotized[103] and then coupled with ethyl 2-oxocyclopentanecarboxylate (**2-108**). Azocyclopentane **2-109** was subjected to hydrolysis to obtain hydrazono-triacid monoester **2-110**, which upon heating with BF_3 in acetic acid at 90 °C

for 4 h furnished indole **2-111** in 81% yield. Finally, selective decarboxylation of indole-2-caboxylic acid under basic conditions in the autoclave at 240 °C provided dicarboxylic acid **2-105** in 67% yield. As in the Uhle's original procedure, initial formation of a mixed anhydride with Ac_2O and a subsequent cyclization using KCN as a base, followed by an intramolecular decarboxylation of an intermediary formed α-ketoester provided **2-106** in 80% yield.



Scheme 29. Bowman's synthesis of Uhle's ketone **2-106**

Teranishi and coworkers published a facile synthesis of Uhle's ketone using a regioselective Friedel-Crafts cyclization.[97] In this work, a trimethylacetyl group was used to inhibit a cyclization at the 2-position, thus favoring the Friedel-Crafts reaction at the 4-position of the indole ring (Scheme 30). *N*-Protection of 3-(indole-3-yl)propionic acid (**2-112**) with trimethylacetyl chloride (**2-113**) and *n*-BuLi in THF at -78 °C provided **2-114** in 91% yield. This acid was converted into the corresponding chloride with thionyl chloride, and directly used in the Friedel-Crafts reaction. Treatment of **2-114** with $AlCl_3$ (4.0 equiv) and propionyl chloride (4.0 equiv) in 1,2-dichloroethane at 15 °C for 1 h gave a mixture of **2-115** and **2-116** in 76% yield and a 92:8 ratio. Subsequent removal of the trimethylacetyl group with a catalytic amount of sodium methoxide in methanol at 15 °C for 10 min gave Uhle's ketone (**2-106**) in 95% yield.



Scheme 30. Teranishi's approach to **2-106**

2.2 RESULTS AND DISCUSSIONS

2.2.1 IMDAF Cascade Process toward Indoles

Based on previous work in our group,[89] our initial goal was to extend the IMDAF methodology towards the synthesis of indoles that possess alkyl groups in the 4-position. Accordingly, we synthesized allylic alcohols with *iso*-propyl (**2-117**) or 2-methylcyclopropyl (**2-118**) substituents (Figure 11). We then subjected them to the previously described microwave conditions in order to generate 4-alkyl substituted indoles.

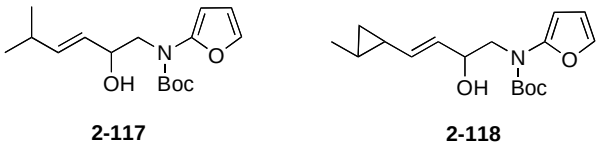
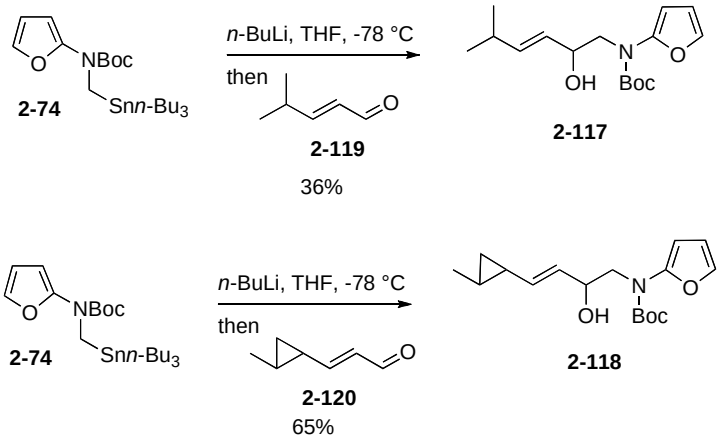


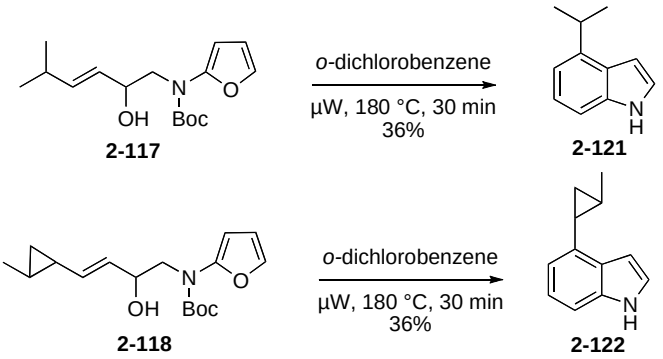
Figure 11. New precursors for the IMDAF reaction

The general strategy presented in Scheme 26 permits the construction of compounds **2-117** and **2-118**. Starting with the previously synthesized aldehydes **2-119**[104,105] and **2-120**,[104] the addition of the lithiated **2-74** in THF at -78 °C furnished alcohols **2-117** and **2-118** in 36% and 65% yield, respectively (Scheme 31).



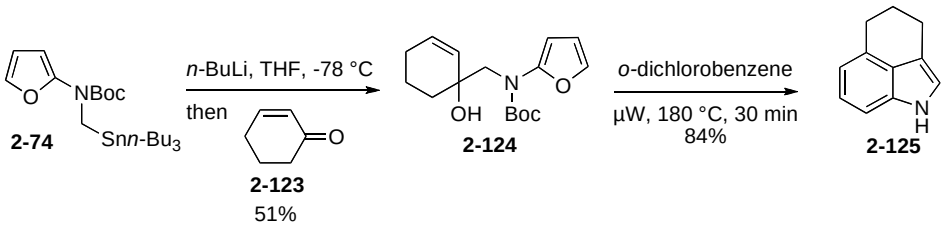
Scheme 31. Synthesis of allylic alcohols **2-117** and **2-118**

Exposing alcohols **2-117** and **2-118** to microwave conditions in *o*-dichlorobenzene for 20 min at 180 °C gave an incomplete conversion of the starting alcohols. Optimized conditions for this reaction, i.e. irradiation for 30 min at 180 °C under microwave conditions, led to complete consumption of starting materials and provided the corresponding indoles **2-121** and **2-122** in 36% and 48% yield, respectively (Scheme 32). In spite of the lower yield observed for **2-121**, the successful use of a cyclopropane-substituted compound in this reaction sequence is noteworthy.

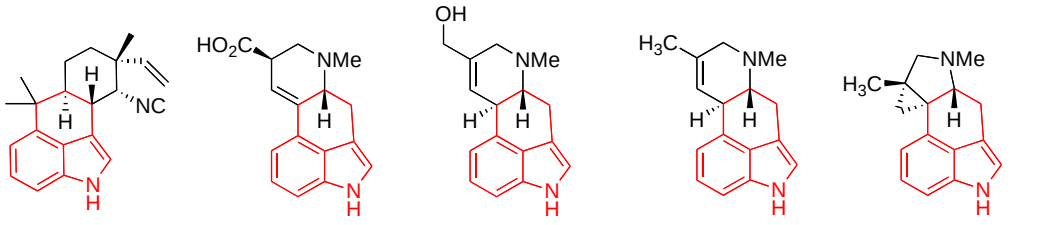


Scheme 32. IMDAF reaction on substrates **2-117** and **2-118**

We were also interested in expanding the scope of this reaction to 3,4-disubstituted indoles derived analogously from addition of the lithiated analog of **2-74** to α,β-unsaturated ketones. Treatment of the lithiated analog of **2-74** with 5 equiv of 2-cyclohexene-1-one (**2-123**) accomplished the formation of *tert*-alcohol **2-124** in 51% yield (Scheme 33). Exposure of **2-124** to the standard microwave conditions provided the cyclohexane-annulated indole **2-125** in 84% yield. Importantly, the tricyclic core **2-125** is representative of the core heterocycle of many Ergot alkaloids (Figure 12).



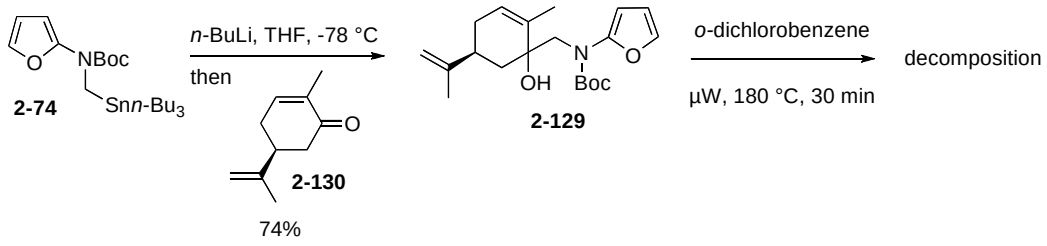
Scheme 33. Synthesis of 3,4-disubstituted indole **2-125**



Ambiguine A isonitrile (**2-5**) Lysergic acid (**2-6**) Elymoclavine (**2-126**) Agoraclavine (**2-127**) Cycloclavine (**2-128**)

Figure 12. Representative ergot alkaloids containing the tricyclic core **2-125** (outlined in red)

Notably, the presence of a hydrogen substituent at position 3′ in intermediate **2-95** (Scheme 27) was shown to be crucial for the completion of the sequence since the elimination of that hydrogen atom furnishes a cyclohexadiene intermediate, which easily rearomatizes to give the desired indole **2-97**. With an alkyl group at position 3′, aromatization is impossible in the absence of more forcing conditions. For example, when allylic alcohol **2-129** was synthesized from *S*-(+)-carvone (**2-130**) (Scheme 34), standard microwave conditions did not lead to indole product. Instead, gradual decomposition of the starting material was observed.



Scheme 34. Control experiment with allylic alcohol **2-129**

2.2.2 Attempts toward the Synthesis of 7-Azaindoles

Successful implementation of the IMDAF cascade process in the synthesis of indoles with different substitution patterns at positions 3 and 4 led us to a hypothesis that a similar strategy could be used in the synthesis of other heterocycles. Possible modifications in the structure of the original allylic alcohols and the corresponding products are shown in Figure 13.

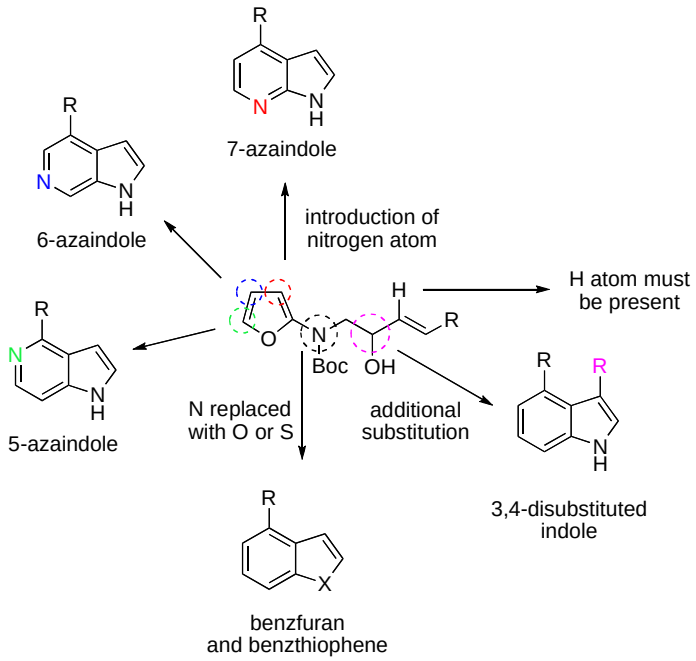


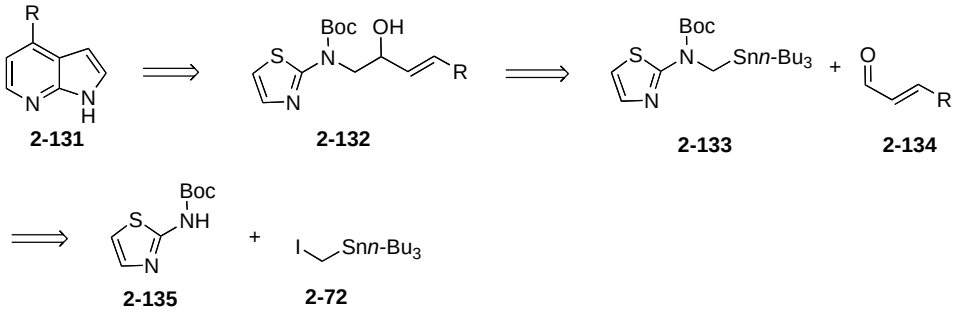
Figure 13. Summary of possible modifications to the original allylic alcohol

The incorporation of nitrogen at positions 3, 4, and 5 of the furan moiety would, in principle, allow us to synthesize 7-, 6-, and 5-azaindoles, respectively. The replacement of the oxygen atom with another heteroatom is not of any importance, since this heteroatom is being removed from the molecule in the late stage of this cascade process (Scheme 27). Finally, replacement of the N-atom from the tether with O or S, would lead us to 4-substituted benzo[*b*]furan or benzo[*b*]thiophene.

7-Azaindoles have recently attracted the interest of the chemical community and form a part of many biologically active compounds.[106] Differently acylated azaindole compounds have been reported to have analgesic and anti-inflammatory activities.[107] Azaindole derivatives were also found to possess blood pressure lowering activity, acting as effective coronary, vasodilator, cardiovascular, and hypotensive agents.

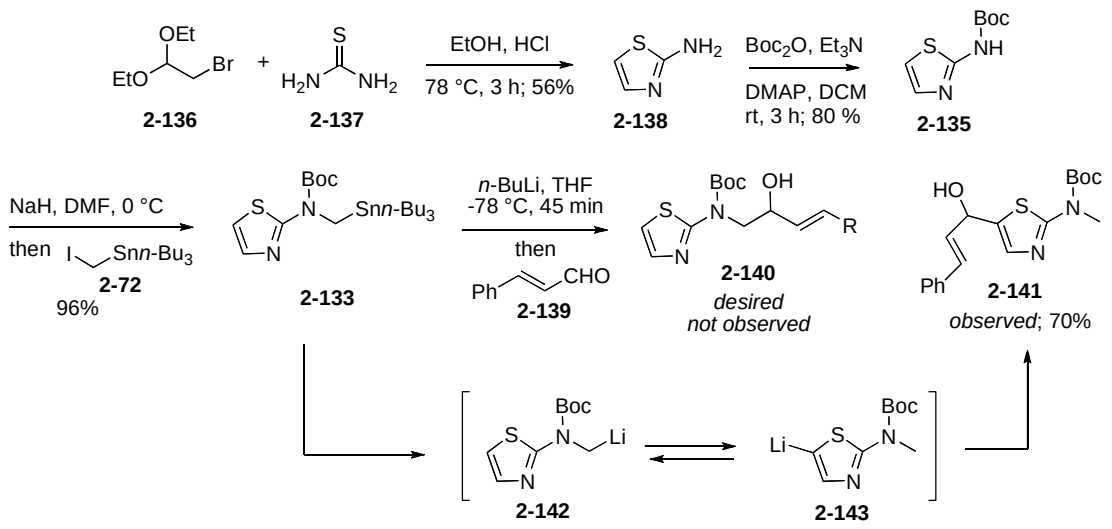
In order to test our hypothesis and apply our method to the synthesis of 7-azaindoles, we decided to start with the preparation of an allylic alcohol derived from 2-aminothiophene. As

shown in Scheme 35, we planned to synthesize the allylic alcohol **2-132** through a previously described sequence. *N*-Boc protection of 2-aminothiazole and subsequent alkylation with the known iodide **2-72** should provide the required tin reagent **2-133**. Transmetallation of **2-133** with *n*-BuLi, and coupling with α,β-unsaturated aldehyde should yield the desired alcohol **2-132**.



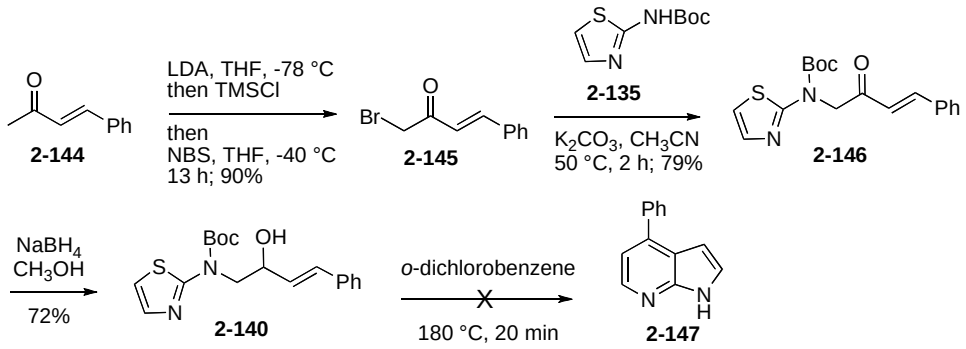
Scheme 35. Retrosynthetic plan towards 7-azaindoles through the IMDAF cascade reaction

2-Aminothiazole was prepared from bromoacetaldehyde diethylacetal **2-136** and thiourea **2-137** in 56% yield, and subsequently *N*-Boc protected in 80% yield.[108] As previously described,[86] alkylation of **2-135** with **2-72** provided the required tin reagent **2-133** (Scheme 36). Attempts to add a lithiated **2-72** to *trans*-cinnamaldehyde (**2-139**) provided alcohol **2-141** instead of the desired allylic alcohol **2-140**. Apparently, the intermediary anion **2-142** is basic enough to deprotonate the thiazole 5-position, and this proton exchange occurs faster than the addition of the electrophile. A similar observation was reported by Caldwell et al.[109]



Scheme 36. Coupling of **2-133** and *trans*-cinnamaldehyde

To circumvent this problem, we envisioned that the desired allylic alcohol could be obtained from the corresponding ketone, which could be derived from **2-135** and bromoketone **2-145** (Scheme 37). Thus, we brominated (*E*)-4-phenyl-3-butene-2-one **2-144** in a two-step procedure used by Iwasawa to obtain **2-145** in 90% yield.[110] Alkylation of thiazole **2-135** with bromide **2-145** under basic conditions gave the corresponding ketone in 79% yield.[111] Finally, ketone **2-146** was reduced with $NaBH_4$ in MeOH to provide the desired allylic alcohol **2-140** in 72% yield. Unfortunately, microwave irradiation of the solution of **2-140** in *o*-dichlorobenzene at 180 °C for 20 min did not provide the desired 7-azaindole, and only starting material was recovered.



Scheme 37. Attempts toward 4-phenyl-7-azaindole (**2-147**)

The low reactivity of thiazoles in the Diels-Alder reaction is probably due to their high aromaticity, i.e. delocalization of the π-molecular orbitals that should participate in this [4+2] cycloaddition.[112] Comparison of the bond order uniformity (i.e. the bond order deviation from an ideal bond order distribution in a ring) in few common dienes reveals the inherent stability of thiazoles in this process (Table 2). Large bond order deviation of a diene indicates more localized π-electrons, and consequently the higher reactivity of the diene in the Diels-Alder reaction. Similarly, the smaller bond order deviation of 1,3-thiazole (0.985) relative to cyclopentadiene (1.986), furan (1.290), and 1,3-oxazole (1.296) indicates stronger delocalization of π-electrons that participate in the [4+2] cycloaddition, and therefore lower reactivity.[113]

Table 2. Comparison of the bond order deviations for different dienes with the AM1 semiempirical method using Chem-3D Plus

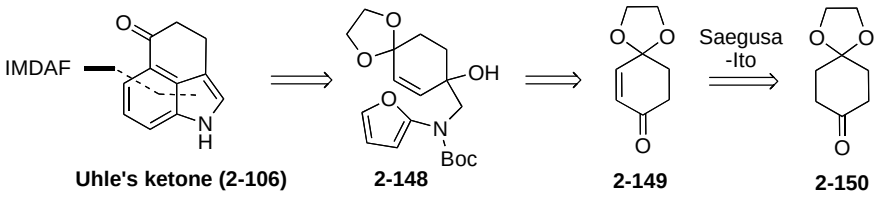
Diene	SBO[a]	ABO[b]	BDO[c]
cyclopentadiene	6.763	1.353	1.986
furane	6.738	1.348	1.290
1,3-oxazole	6.712	1.342	1.296
1,3-thiazole	6.824	1.365	0.985

[a]SBO – sum of ring bond orders; [b]ABO – average bond order; [c]BDO – sum of bond order deviation from the average ring bond order

2.2.3 Synthesis of Uhle's Ketone through IMDAF Cascade Reaction

Once we discovered a quick way to access tricycle **2-125** through the IMDAF cascade process, we hypothesized that other functionalized 2-cyclohexene-1-ones could also be used as starting materials in this reaction. As previously mentioned, Uhle's ketone is a valuable building block in the synthesis of ergot-alkaloids, and thus attracted our attention as a potential synthetic target in order to demonstrate the utility of our methodology.

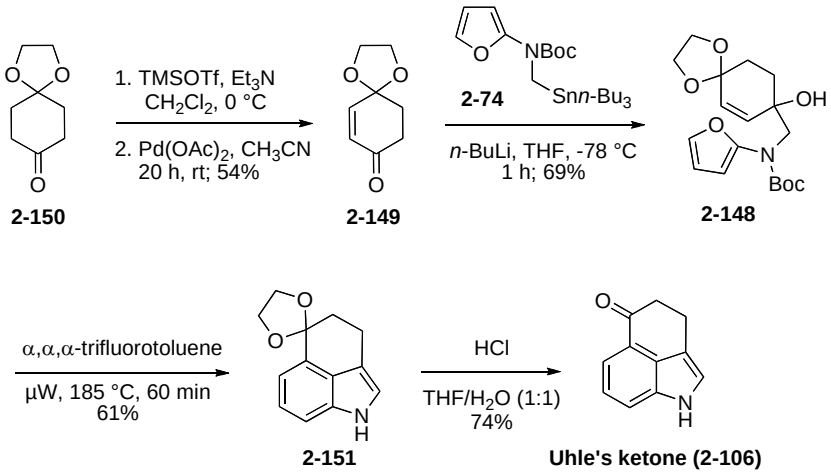
Implementing the IMDAF reaction for the construction of the indole moiety requires alcohol **2-148** as a precursor to Uhle's ketone (Scheme 38). We initially chose to use monoprotected diketone **2-149**, to avoid potential alkyl-group migration and aromatization due to the inherent reactivity and instability of the corresponding unprotected dione. Furthermore, the preparation of **2-148** would be simpler and could be achieved by the addition of the lithium reagent to **2-149**. The *α,β*-unsaturated ketone **2-149** could be derived from the commercially available **2-150** using the Saegusa-Ito protocol to install the necessary unsaturation.



Scheme 38. Proposed route towards Uhle's ketone using the IMDAF reaction

Indeed, formation of the TMS-enol ether of **2-150** under standard conditions, and treatment of this intermediate with $Pd(OAc)_2$ in CH_3CN for 20 h, afforded the desired α,β-unsaturated ketone **2-149** in 54% yield.[114,115] When **2-74** was transmetallated with *n*-BuLi and then added to a solution of **2-149** in THF at -78 °C, clean alcohol **2-148** was isolated in 69% yield. When **2-148** was heated under microwave irradiation in trifluorotoluene at 185 °C for 1 h,

2-151 was isolated in 61% yield. Finally, treatment of **2-151** with aq HCl in THF/water (1:1) at room temperature[116] gave Uhle's ketone **2-106** in 74% yield.



Scheme 39. Synthesis of Uhle's ketone **(2-106)**

Comparing to the previously published protocols for the synthesis of Uhle's ketone, our route provides a high improvement for accessing this building block. In contrast to the previously reported Uhle's and Bowman's routes, which used several steps to prepare 4-substituted indoles, our IMDAF strategy offers an opportunity for synthesizing this core in two steps, followed by a simple hydrolysis of the ketal. On the other hand, the Teranishi protocol suffers from an extensive use of environmentally harmful $SOCl_2$ as well as the large excess of $AlCl_3$, which makes the work-up procedure tedious.

2.2.4 Conclusions

We have extended the indole synthesis methodology previously developed in our group by showing that alkyl groups can also be installed in the 4-position of the indole ring. This protocol features a microwave assisted Diels-Alder cyclization of furans, which allows for a convergent

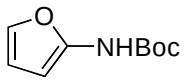
and rapid preparation of 4-monosubstituted and 3,4-disubstituted indoles. The cascade process is quite tolerant of functional groups and associated substitution patterns. Furthermore, this strategy is a convenient alternative to the standard transition metal mediated coupling processes for the synthesis of heterocycles, which yield products that are often contaminated with trace metal residues that can interfere with biological assays and therapeutic applications.

Although a similar strategy could, in principle, be used in the synthesis of other related heterocycles, we showed that the 7-azaindole core cannot be easily obtained using IMDA. This increased stability of thiazoles may be due to the higher bond order uniformity comparing to other common dienes, indicating the stronger delocalization of π-electrons that are included in the [4+2] cascade process. However, we successfully applied the previously developed IMDAF protocol in the synthesis of the synthetically valuable building block, Uhle's ketone, in 4 steps starting with the commercially available 1,4-cyclohexanedione monoethyleneketal (**2-150**).

2.3 EXPERIMENTAL PART

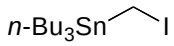
General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. Reactions carried out at -78 °C employed a dry ice/acetone bath. THF and Et_2O were dried by distillation over Na/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina filtration system. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F_{254} plates (250 μm layer thickness, particle size 0.040-0.055 mm, 230-240 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of

95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 M H_2SO_4 solution), or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1 % NaOH solution). Flash chromatography on SiO_2 was used to separate and purify the reaction crude mixtures. Microwave reactions were performed on a Biotage Initiator microwave reactor. ^1H and ^{13}C NMR were recorded on a Bruker Avance 300 instrument. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were run at 300, 400 or 500 MHz, and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, sept = septet, m = multiplet, br = broad, app = apparent), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained using a proton-decoupled pulse sequence with a d1 of 3 sec, and are tabulated by observed peak. LC/MS analyses were obtained from a Helwett Packard Series 1100 MSD. RP HPLC was obtained from Gilson Series 215, using C18 column, Bio-rad Laboratoris, 250 x 4.6 mm. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Infrared spectra were measured on a Nicolet AVATAR 360 FT-IR E.S.P. spectrometer (KBr or neat) or Smiths Detection IdentifyIR FT-IR spectrometer (ATR).



***tert*-Butyl furan-2-ylcarbamate (2-73).**[86] To a solution of 2-furoyl chloride (2.00 g, 15.3 mmol) in *t*-BuOH (16 mL) was added sodium azide (1.13 g, 17.5 mmol) and the resulting mixture was stirred at room temperature for 24 h, and then 85 °C and stirred for 16 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography on SiO_2 (10%

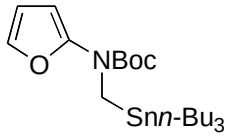
EtOAc/hexanes) to obtain **2-73** (1.26 g, 45%) as a white solid: IR (ATR) 3252, 3237, 1698, 1538, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, 1 H, *J* = 2.0, 0.8 Hz), 6.68 (s, 1 H), 6.34 (dd, 1 H, *J* = 2.8, 2.0 Hz), 6.04 (s, 1 H), 1.51 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 145.4, 136.1, 111.3, 95.1, 81.3, 28.2; HRMS (TOF MS ESI) *m/z* calcd for $C_9H_{14}NO_3$ $[M+H]^+$ 184.0974, found 1184.1006.



Tri-*n*-butyl(iodomethyl)stannane (2-72).[86] To a solution of diisopropylamine (1.05 g, 11.1 mmol) in THF (14 mL) at 0 °C was added a solution of *n*-BuLi (1.6 M solution in hexane, 6.6 mL, 11 mmol), stirred for 30 min, and treated with a solution of TBTH (2.81 g, 9.65 mmol) in THF (5.8 mL) over 30 min. The reaction mixture was stirred for 30 min at room temperature, treated with paraformaldehyde (0.42 g, 14 mmol), warmed to room temperature, and stirred for 3 h. The resulting clear and colorless solution was diluted with Et_2O (60 mL) and washed with water (35 mL). The aqueous phase was separated, and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **2-71** (3.1 g, 97%) as a colorless liquid, which was used in the next step without further purification. To a stirred solution of PPh_3 (2.57 g, 9.81 mmol) in THF (20 mL) was added dropwise a solution of NIS (2.0 g, 9.8 mmol) in THF (20 mL), and stirred at room temperature for 10 min. To this solution was added a solution of the alcohol **2-71** (2.1 g, 6.5 mmol) in THF (20 mL), and the resultant mixture was stirred at room temperature for 16 h. The reaction mixture was then poured into petrol-ether/water, organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes) gave **2-72**, which was distilled (bp 110 °C/0.1 mm Hg) to obtain **2-72** (2.1 g, 74%) as a colorless oil: IR (ATR) 2934, 2846, 1461, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.95 (s, 2 H), 1.56-

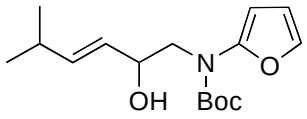
1.50 (m, 6 H), 1.33 (app sext, 6 H, J = 7.5 Hz), 1.00-0.97 (m, 6 H), 0.913 (t, 9 H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 27.2, 13.7, 10.6.

Alternatively, following the procedure used by Seitz *et al.*,[117] *n*-BuLi (1.6 M in hexanes, 72.5 mL, 115 mmol) was added at -78°C to a solution of diisopropylamine (17.7 mL, 127 mmol) in THF (230mL). The reaction mixture was stirred at 0 °C for 15 min, treated with tri-*n*-butyltin hydride (31.0 mL, 115 mmol), stirred for 30 min at 0 °C, and treated with paraformaldehyde (3.46 g, 115 mmol). The mixture was stirred for 3 h at room temperature, then cooled to -78 °C, and treated dropwise with methanesulfonyl chloride (11.8 mL, 152 mmol). The resulting mixture was stirred at room temperature for 16 h. THF was removed under reduced pressure and water was added. The resulting aqueous phase was extracted with hexanes. The combined organic layers were washed with brine and dried ($MgSO_4$), filtered and concentrated under reduced pressure. To a solution of crude (chloromethyl)tributylstannane in acetone (209 mL) was added NaI (26.9 g, 179 mmol). The resulting mixture was stirred at room temperature for 16 h. Water was added and the resulting aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes) furnished **2-72** (44.0 g, 96%) as a colorless oil.



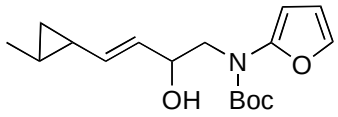
***Tert*-butyl furan-2-yl((tri-*n*-butylstannyl)methyl)carbamate (2-74).**[86] To a solution of **2-73** (0.61 g, 3.3 mmol) in DMF (4.5 mL) at 0 °C was added sodium hydride (88.0 mg, 3.67 mmol) slowly, until hydrogen gas evolution stopped. The mixture was stirred at 0 °C for 1 h, and then treated dropwise with **2-72**. The reaction mixture was stirred for 2 h at 0 °C and then partitioned

between Et_2O and saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with Et_2O, the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (hexanes) gave **2-74** (1.41 g, 87%) as a colorless liquid, which became yellowish upon storage at room temperature or in the freezer. In this case, the material needed another purification by chromatography. **2-74**: IR (ATR) 2952, 2919, 1694, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, 1 H, *J* = 2.4, 1.2 Hz), 6.33 (t, 1 H, *J* = 2.8 Hz), 5.92 (s, 1 H), 3.38 (s, 2 H), 1.50-1.40 (m, 14 H), 1.27 (app sext, 6 H, *J* = 7.2 Hz), 0.90-0.88 (m, 16 H); ^{13}C NMR (120 MHz, $CDCl_3$) δ 154.0, 150.0, 136.8, 111.1, 99.0, 81.0, 70.0, 29.0, 28.2, 27.4, 13.7, 9.7; HRMS (TOF MS ESI) *m/z* calcd for $C_{22}H_{42}NO_3Sn$ $[M+H]^+$ 488.2187, found 488.2185.



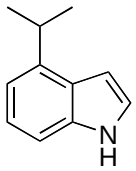
(*E*)-*tert*-Butyl furan-2-yl(2-hydroxy-5-methylhex-3-enyl)carbamate (2-117). To a solution of furanyl stannane **2-74**[90] (0.33 g, 0.60 mmol) in THF (10 mL) under nitrogen atmosphere at -78 °C was added dropwise a solution of *n*-BuLi (1.60 M in hexane, 0.43 mL, 0.69 mmol). The reaction mixture was stirred for 1 h at -78 °C, treated dropwise with a solution of aldehyde **2-119** (64.0 mg, 0.652 mmol) in THF (2 mL) over 5 min, stirred for 3 h, and quenched with saturated aq NH_4Cl (5 mL). The layers were separated, the aqueous layer was further extracted with ether (3 x 20 mL), and the combined organic layers were dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% EtOAc/hexanes) afforded **2-117** (72.3 mg, 36%) as a yellowish oil: IR (ATR) 3438, 2958, 1709, 1610, 1364, 1150, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19-7.18 (m, 1 H), 6.34 (dd, 1 H, *J* = 3.0, 2.4), 6.02 (bs, 1 H), 5.72 (dd, 1 H, *J* = 15.6, 6.6 Hz), 5.39 (ddd, 1 H, *J* = 15.6, 6.6, 0.9 Hz), 4.26-4.33 (m, 1 H), 3.57-3.71 (m, 2 H), 2.6

(bs, 1 H), 2.21-2.33 (m, 1 H), 1.44 (s, 9 H), 0.97 (d, 3 H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 140.2, 138.2, 126.5, 111.0, 101.4, 81.7, 71.7, 55.0, 30.6, 28.1, 22.1 (2 C); MS (EI) *m/z* 295 (M^+, 24), 195 (18), 134 (35), 96 (74), 57 (100); HRMS (TOF MS ESI) *m/z* calcd for $C_{16}H_{25}NO_4$ $[M+Na]^+$ 318.1681, found 318.1678.

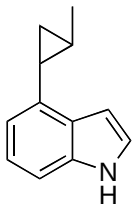


(*E*)-*tert*-Butyl furan-2-yl(2-hydroxy-4-(2-methylcyclopropyl)but-3-enyl)carbamate (2-118). To a solution of furanyl stannane **2-74** (0.30 g, 0.62 mmol) in THF (9 mL) under nitrogen atmosphere at -78 °C was added dropwise a solution of *n*-BuLi (1.60 M in hexane, 0.38 mL, 0.62 mmol). The reaction mixture was stirred for 1 h at -78 °C, treated dropwise over 5 min with a solution of aldehyde **2-120** (64.6 mg, 0.586 mmol) in THF (2 mL), stirred for 3 h, and quenched with saturated aq NH_4Cl (5 mL). The layers were separated and the aqueous layer was further extracted with ether (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on SiO_2 (1 to 5% EtOAc/hexanes) afforded **2-118** (124.2 mg, 65%) as a colorless oil: IR (ATR) 3437, 2978, 2871, 1713, 1613, 1391, 1369, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1 H), 6.34 (s, 1 H), 6.02 (s, 1 H), 5.45 (dd, 1 H, J = 15.3, 6.6 Hz), 5.28 (dd, 1 H, J = 15.3, 8.7 Hz), 4.22-4.31 (m, 1 H), 3.62-3.64 (m, 2 H), 1.48 (s, 9 H), 1.05 (d, 3 H, J = 5.7 Hz), 0.70-0.80 (m, 1 H), 0.51-0.57 (m, 1 H), 0.46-0.50 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 138.2, 137.0, 136.9, 126.5, 111.0, 101.5, 81.7, 71.8, 55.0, 28.1, 22.3, 18.4, 15.3, 15.2; MS (EI) *m/z* 307 ($M^{\bullet+}$, 4), 251 (9), 207 (34), 189 (93), 134 (49), 96 (91), 69 (42), 57 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{25}NO_4$ 307.1784, found 307.1809.

General procedure for the synthesis of 4-substituted indoles (2-121 and 2-122). A solution of the corresponding alcohol in *o*-dichlorobenzene (2.5 mL) was heated in a microwave reactor for 30 min at 180 °C. The reaction mixture was poured on a silica-gel column (packed with hexanes), and flushed with hexanes until *o*-dichlorobenzene was completely removed. Compounds **2-121** and **2-122** were purified by chromatography on SiO_2 (1-5% EtOAc/hexanes).

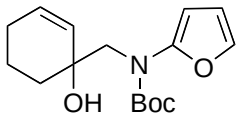


4-Isopropyl-1*H*-indole (2-121). According to the General Protocol, alcohol **2-117** (26.3 mg) was converted to the colorless oily indole **2-121** (5.1 mg, 36%): IR (ATR) 3401, 2956, 2866, 1498, 1409, 1340, 743 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 8.26 (br s, 1 H), 7.25 (d, 1 H, J = 8.1 Hz), 7.22 (t, 1 H, J = 2.7 Hz), 7.17-7.11 (m, 1 H), 6.98 (d, 1 H, J = 7.2 Hz), 6.65-6.62 (m, 1 H), 3.38 (sept, 1 H, J = 7.2 Hz), 1.38 (d, 6 H, J = 6.9 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 141.6, 136.4, 127.1, 124.0, 122.7, 115.9, 109.3, 101.4, 31.9, 23.5; MS (EI) *m/z* 159 ($M^{\bullet+}$, 100); HRMS (EI) *m/z* calcd for $C_{11}H_{13}N$ 159.1048, found 159.1047.

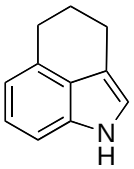


4-(2-Methylcyclopropyl)-1*H*-indole (2-122). According to the General Protocol, alcohol **2-118** (20.1 mg) was converted to the colorless oily indole **2-122** (5.4 mg, 48%): IR (ATR) 3401, 2948, 1580, 1500, 1338, 1075, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1 H), 7.23-7.21 (m, 2 H), 7.11 (app t, 1 H, J = 7.5 Hz), 6.73-6.67 (m, 2 H), 1.99-1.93 (m, 1 H), 1.28 (d, 3 H, J = 5.4

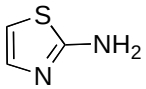
Hz), 1.28-1.16 (m, 1 H), 1.10-1.05 (m, 1 H), 0.82-0.76 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 135.5, 123.4, 122.2, 114.8, 108.2, 101.1, 22.1, 19.4, 16.6, 16.1; MS (EI) *m/z* 171 ($M^{\bullet+}$, 77), 156 (80), 86 (68), 84 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{13}N$ 171.1048, found 171.1047.



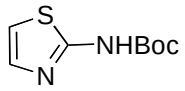
***tert*-Butyl furan-2-yl((1-hydroxycyclohex-2-enyl)methyl)carbamate (2-124).** To a solution of stannane **2-74** (250.0 mg, 0.5140 mmol) in THF (7.5 mL) under an atmosphere of nitrogen at -78 °C was added dropwise a solution of *n*-BuLi (1.60 M in hexane, 0.32 mL, 0.51 mmol). The reaction mixture was stirred for 1 h at -78 °C, treated dropwise over 5 min with a solution of 2-cyclohexane-1-one (247.1 mg, 2.570 mmol) in THF (1.5 mL), stirred for 1 h, and quenched with saturated aq NH_4Cl (5 mL). The layers were separated and the aqueous layer was further extracted with ether (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% EtOAc/hexanes) afforded **2-124** (75.6 mg, 51%) as a colorless oil: IR (ATR) 3508, 2974, 2931, 1709, 1688, 1366, 1159, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (br s, 1 H), 6.36-6.33 (m, 1 H), 6.00 (br s, 1 H), 5.82 (app dt, 1 H, *J* = 9.9, 3.0 Hz), 5.58 (d, 1 H, *J* = 9.9 Hz), 3.75 (d of AB, 1 H, *J* = 14.7, 0.9), 3.69 (d of AB, 1 H, *J* = 14.7, 1.2 Hz), 2.10-1.56 (m, 6 H), 1.44 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 138.0, 130.4, 130.1, 111.0, 101.5, 81.9, 70.7, 58.5, 33.6, 28.1, 25.2, 19.0; MS (TOF MS ES) *m/z* 316 $[M+23]^+$ (100), 242 (60), 198 (48); HRMS (TOF MS ESI) *m/z* calcd for $C_{16}H_{23}NO_4$ $[M+Na]^+$ 316.1525, found 316.1494.



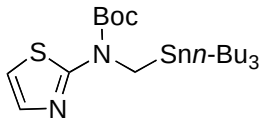
2,6,7,8-Tetrahydrobenzo[*cd*]indole (2-125). According to the General Protocol, alcohol **2-124** (25.0 mg) was converted to indole **2-125** (11.2 mg, 84%) which was isolated as a white solid: Mp 48.6-50.2 °C; IR (ATR) 3399, 2920, 2833, 1439, 1081, 1025, 745 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.92 (br s, 1 H), 7.12 (d, 1 H, *J* = 4.2 Hz), 7.06 (t, 1 H, *J* = 3.3 Hz), 6.86 (s, 1 H), 6.78 (d, 1 H, *J* = 3.3 Hz), 2.92 (t, 2 H, *J* = 3.0 Hz), 2.85 (dt, 2 H, *J* = 3.3, 0.3 Hz), 2.04 (app quint, 2 H, *J* = 3.0 Hz); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 134.5, 132.8, 127.7, 123.0, 117.7, 116.1, 114.3, 108.5, 28.0, 25.3, 22.4; MS (EI) *m/z* 157 ($M^{\bullet+}$, 100); HRMS (EI) *m/z* calcd for $C_{11}H_{11}N$ 157.0891, found 157.0894.



Thiazol-2-amine (2-138).[108] To a solution of thiourea (3.81 g, 50.0 mmol) and bromoacetaldehyde diethylacetal (9.85 g, 50.0 mmol) in EtOH (100 mL) was added aq HCl (37%, 2.5 mL), reflux for 3 h, cooled to room temperature, and concentrated to ca. 100 mL. The mixture was added to ice-water, treated with aq NaOH (10%) to adjust pH to 8-9, extracted with DCM (3 x 50 mL), washed with brine, and dried (Na_2SO_4). Purification by chromatography on SiO_2 (30% EtOAc/ hexanes) gave **2-138** (2.82 g, 56%) as an off-white solid: Mp 88.4-90.6 °C; IR (ATR) 3403, 3282, 3188, 1619, 1487 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.92 (d, 1 H, *J* = 3.5 Hz), 6.87 (br s, 2 H), 6.54 (d, 1 H, *J* = 3.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.8, 138.6, 106.5; HRMS (EI) *m/z* calcd for $C_3H_5N_2S$ $[M+H]^+$ 101.0173, found 101.0204.

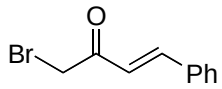


***tert*-Butyl thiazol-2-ylcarbamate (2-135).**[108] To a solution of 2-aminothiazole **2-138** (2.83 g, 28.3 mmol) in DCM (100 mL) at room temperature were added Boc_2O (6.78 g, 31.1 mmol), Et_3N (9.9 mL, 71 mmol) and DMAP (cat. amount), stirred at this temperature for 3 h, quenched with 0.1 M aq HCl (to pH 5-6), extracted with EtOAc (4 x 20 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (50% EtOAc/hexanes) gave **2-135** (3.20 g, 80%) as a white solid: Mp 87.4-86.0 °C; IR (ATR) 2975, 2934, 1709, 1566, 1288, 1249, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.42 (br s, 1 H), 7.39 (d, 1 H, *J* = 3.6 Hz), 6.89 (d, 1 H, *J* = 3.6 Hz), 1.60 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 153.0, 136.7, 112.0, 81.8, 28.3; HRMS (EI) *m/z* calcd for $C_8H_{12}N_2O_2S$ $[M+H]^+$ 201.0698, found 201.0704.

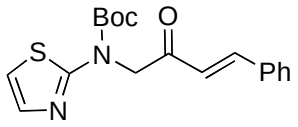


***tert*-Butyl thiazol-2-yl((tributylstannyl)methyl)carbamate (2-133).** To a solution of **2-135** (100.0 mg, 0.499 mmol) in DMF (1.0 mL) at 0 °C was added NaH (13.1 mg, 0.549 mmol) slowly, stirred at this temperature for 1 h, and then treated with Bu_3SnCH_2I (0.28 g, 0.65 mmol). After 2 h, the reaction mixture was diluted with water, extracted with EtOAc (5 x 10 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (5% EtOAc/hexanes) gave **2-133** (240.1 mg, 96%) as a colorless oil: IR (ATR) 2952, 2921, 1694, 1366, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, 1 H, *J* = 3.5 Hz), 6.89 (d, 1 H, *J* = 4.0 Hz), 3.84 (dd, 1 H, *J* = 11.0 Hz), 1.60 (s, 9 H), 1.46-1.41 (m, 6 H), 1.25 (dt, 6 H, *J* = 15.0, 7.5 Hz), 0.86 (t, 9 H, *J* = 7.5 Hz), 0.82-0.79 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

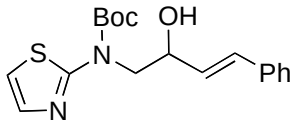
161.3, 153.2, 137.3, 113.8, 82.7, 34.1, 29.0, 28.3, 27.4, 13.7, 10.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{40}N_2O_2SSnNa$ $[M+Na]^+$ 527.1730, found 527.1748.



(*E*)-1-Bromo-4-phenylbut-3-en-2-one (2-145).[110] To a solution of DIPA (2.0 mL, 16 mmol) in THF (40 mL) at -78 °C was added *n*-BuLi (1.6 M in hexane, 10.3 mL, 16.4 mmol), stirred at 0 °C for 15 min, and then cooled to -78 °C. To this solution was added a solution of benzalacetone (**2-144**) (2.0 g, 14 mmol) in THF (5 mL), stirred at -78 °C for 1.5 h, quenched with TMSCl (1.74 mL, 13.7 mL), and stirred at room temperature for 2 h. The solvent was removed *in vacuo*. The residual suspension was filtered quickly through a pad of silica-gel, and washed with hexane (3 x 10 mL). The filtrate was concentrated *in vacuo*, and the resulting crude silyl enol ether was subjected to the next step without further purification or characterization. To a solution of silyl enol ether in THF (20 mL) at -40 °C was added NBS (3.0 g, 16 mmol), and stirred overnight at this temperature. The mixture was then poured into saturated aq $Na_2S_2O_3$, extracted with EtOAc (4 x 10 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% EtOAc/hexanes) gave **2-145** (2.76 g, 90%) as a dark liquid: IR (ATR) 2975, 1681, 1605, 1062 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 1 H, J = 16.0 Hz), 7.60 (t, 1 H, J = 1.5 Hz), 7.59 (t, 1 H, J = 2.0 Hz), 7.45-7.41 (m, 3 H), 6.97 (d, 1 H, J = 16.0 Hz), 4.10 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 145.3, 133.9, 131.1, 129.0, 128.6, 122.2, 33.0; HRMS (EI) *m/z* calcd for $C_{10}H_9Br$ 223.9837, found 223.9879.

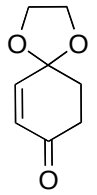


(*E*)-*tert*-Butyl 2-oxo-4-phenylbut-3-enyl(thiazol-2-yl)carbamate (2-146). To a solution of bromide **2-145** (220.0 mg, 0.9774 mmol) in acetonitrile at room temperature was added thiazole **2-135** (177.9 mg, 0.8885 mmol), followed by K_2CO_3 (245.6 mg, 1.777 mmol). The reaction mixture was heated to 50 °C for 2 h, diluted with water and EtOAc, extracted with EtOAc (4 x 5 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% EtOAc/hexanes, dry load) gave **2-146** (241.0 mg, 79%) as a yellow solid: Mp 101.0-102.8 °C; IR (ATR) 2986, 2975, 1705, 1364, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 1 H, *J* = 16.4 Hz), 7.58 (d, 1 H, *J* = 2.0 Hz), 7.56 (d, 1 H, *J* = 2.8 Hz), 7.42-7.41 (m, 3 H), 7.35 (d, 1 H, *J* = 3.2 Hz), 6.95 (br s, 1 H), 6.84 (d, 1 H, *J* = 16.0 Hz), 1.53 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 161.3, 143.7, 137.1, 134.2, 130.8, 129.0, 128.4, 122.5, 114.5, 83.6, 82.0, 54.5, 28.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_2O_3SNa$ $[M+Na]^+$ 376.1092, found 376.1072.



(*E*)-*tert*-Butyl 2-hydroxy-4-phenylbut-3-enyl(thiazol-2-yl)carbamate (2-140). To a solution of **2-146** (28.0 mg, 0.0813 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (6.2 mg, 0.16 mmol), and stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo*, diluted with water, extracted with EtOAc (3 x 5 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (20% EtOAc/hexanes) gave **2-140** (20.2 mg, 72 %) in the form of colorless oil: IR (ATR) 3400, 2975, 2816, 1700, 1152 cm^{-1}; ^1H NMR (500

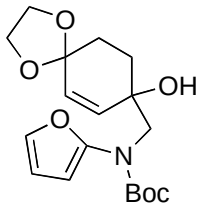
MHz, $CDCl_3$) δ 7.43 (d, 1 H, *J* = 3.5 Hz), 7.40-7.38 (m, 2 H), 7.32 (dt, 2 H, *J* = 7.0, 1.5 Hz), 7.25-7.22 (m, 1 H), 6.99 (d, 1 H, *J* = 3.5 Hz), 6.72 (d, 1 H, *J* = 16.0 Hz), 6.29 (dd, 1 H, *J* = 16.0, 6.0 Hz), 4.69 (d, 1 H, *J* = 5.5 Hz), 4.36-4.28 (m, 2 H), 1.55 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 136.7, 130.8, 129.4, 128.5, 128.3, 127.6, 126t5, 125.8, 114.6, 78.0, 72.4, 53.9, 28.1; HRMS (ESI) *m/z* calcd for $C_{18}H_{23}N_2O_3S$ $[M+H]^+$ 347.1429, found 347.1439.



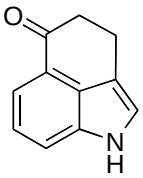
1,4-Dioxaspiro[4.5]dec-6-en-8-one (2-149).[114] To a stirred solution of 1,4-cyclohexadiene monoethylene ketal (1.19 g, 7.62 mmol) and triethylamine (3.21 mL, 22.86 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added a solution of TMSOTf (1.52 mL, 8.38 mmol) in CH_2Cl_2 (20 mL) over 10 min, stirred for 2 h, quenched with saturated aq $NaHCO_3$. Organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, filtered through a plug of SiO_2, washed with CH_2Cl_2 (50 mL), and concentrated *in vacuo* to give the corresponding TMS-enol ether, which was used crude, without further purification or characterization: ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (t, 1 H, *J* = 3.6 Hz), 3.98 (s, 4 H), 2.27 (s, 4 H), 2.22 (t, 2 H, *J* = 6.4), 1.81 (t, 2 H, *J* = 6.4 Hz), 0.19 (s, 9 H).

The solution of the intermediate TMS-enol ether (1.40 g) in CH_3CN (80 mL) was treated with $Pd(OAc)_2$ (0.54 g, 2.40 mmol) and stirred at room temperature for 14 h. The reaction mixture was then concentrated *in vacuo*, dissolved in CH_2Cl_2, washed with saturated aq $NaHCO_3$, concentrated *in vacuo*, and purified by chromatography on SiO_2 (50% EtOAc/hexanes) to provide **2-149** (0.63 g, 54%) as a yellowish oil: IR (ATR) 2958, 1676, 1217, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, 1 H, *J* = 10.0 Hz), 6.01 (d, 1 H, *J* = 10.4 Hz), 4.05 (dd, 4 H, *J* =

6.8, 4.0 Hz), 2.63 (t, 2 H, J = 6.4 Hz), 2.20 (t, 2 H, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 146.3, 130.5, 104.0, 65.0, 35.3, 32.9; HRMS (ESI) *m/z* calcd for $C_8H_{11}O_3S$ 155.0708, found 155.0734.



***tert*-Butyl furan—2—yl((8—hydroxy—1,4—dioxaspiro[4.5]dec—6—en—8yl)methyl)carbamate (2-148).** To a solution of tin reagent **2-74** (315.4 mg, 0.6487 mmol) in THF (2.5 mL) at -78 °C was added *n*-BuLi (1.6 M in hexane, 0.4 mL, 0.6 mmol), stirred at -78 °C for 1 h. To this solution was added a solution of **2-149** (100.0 mg, 0.6487 mmol) in THF (2.5 mL), stirred at this temp for 1 h, quenched with saturated aq NH_4Cl, extracted with EtOAc (4 x 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (30-50% EtOAc/hexanes) gave **2-148** (156.6 mg, 69%) as a yellowish oil: IR (ATR) 3482, 2975, 1709, 1366, 1146 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (dd, 1 H, J = 1.0 Hz), 6.33 (dd, 1 H, J = 3.0, 2.0 Hz), 6.00 (br s, 1 H), 5.78 (d, 1 H, J = 10.0 Hz), 5.61 (d, 1 H, J = 10.5 Hz), 3.99-3.91 (m, 4 H), 3.79 (d, 1 H, J = 15.0 Hz), 3.69 (d, 1 H, J = 15.0 Hz), 2.01-1.96 (m, 1 H), 1.93-1.86 (m, 2 H), 1.76-1.71 (m, 1 H), 1.44 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 138.2, 134.5, 129.2, 111.0, 105.1, 101.7, 82.3, 70.7, 64.6, 64.5, 57.4, 31.7, 30.3, 28.0; HRMS (TOF MS ESI) *m/z* calcd for $C_{18}H_{25}NO_6Na$ $[M+Na]^+$ 374.1580, found 374.1585.



3,4-Dihydrobenzo[*cd*]indol-5(1*H*)-one (2-106): A solution of **2-148** (34.0 mg, 0.0968 mmol) in trifluorotoluene (3.5 mL) was heated in the microwave oven for 60 min at 180 °C. The solvent was removed *in vacuo*, and the residue was filtered through a plug SiO_2 (20% EtOAc/hexanes) to provide **2-151** (12.7 mg, 61%) as a colorless oil, which was used in the next step without further purification.

To a solution of crude **2-151** (7.0 mg, 0.033 mmol) in water/THF (1:1; 2 mL) was added hydrochloric acid (6 M, 1 drop). The mixture was stirred at room temperature for 30 min, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (20% EtOAc/hexanes) gave Uhle's ketone **2-106** (5.6 mg, 74%) as a yellowish solid: Mp 161.2-162.4 °C (lit. mp 162-164 °C);[116] IR (ATR) 3224, 3210, 2924, 1648, 1616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (br s, 1 H), 7.62 (d, 1 H, J = 7.5 Hz), 7.55 (d, 1 H, J = 8.0 Hz), 7.30 (t, 1 H, J = 8.0 Hz), 7.09 (s, 1 H), 3.28 (t, 2 H, J = 7.5 Hz), 2.94 (t, 2 H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 134.7, 132.4, 125.9, 122.8, 120.2, 115.7, 115.6, 110.8, 39.4, 20.8; HRMS (ESI) *m/z* calcd for $C_{11}H_{10}NO$ 172.0762, found 172.0735.

3.0 TOTAL SYNTHESIS OF CYCLOCLAVINE AND 5-*EPI*-CYCLOCLAVINE

3.1 INTRODUCTION

3.1.1 Ergot Alkaloids

Ergot alkaloids comprise a notable class of indole-containing alkaloids. They are produced by fungi of the families *Clavicipitaceae* (e.g., *Claviceps* and *Neotyphodium*) and *Trichocomaceae* (including *Aspergillus* and *Penicillium*), which affect the seeds of various plants, mostly rye and other cerial grains. These natural products are striking for their molecular architecture and wide spectrum of physiological activity.[118,119] Nowadays, ergot alkaloids have found widespread clinical use, and more than 50 formulations contain natural or semisynthetic ergot alkaloids. The broad physiological effects are based mostly on their interactions with neurotransmitter receptors, resembling some important neurohumoral mediators (e.g., noradrenalin, serotonin, dopamine).[120]

The ergot alkaloid family consists of two distinct structural types which are distinguished by the nature of the functionality present in the six-membered ring D in the common tetracyclic core, called ergoline (**3-1**, Figure 14).[121] Thus, while the lysergic acid subclass has oxygenated substituents at position C(8) of the ergoline core (D-ring), the clavine subclass alkaloids features alkyl chains at that position.

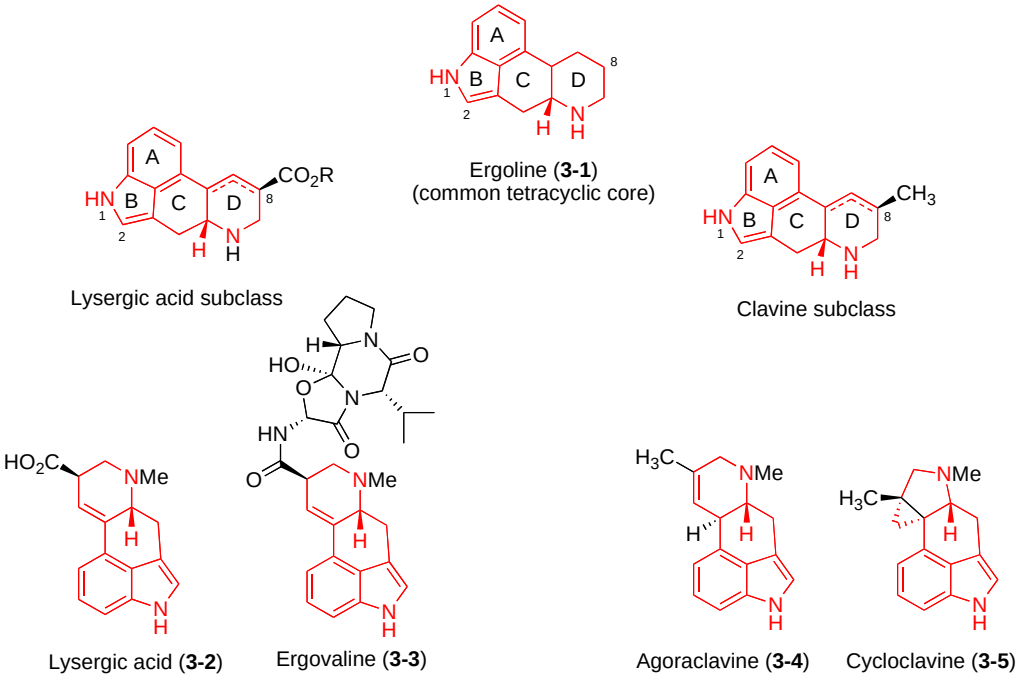


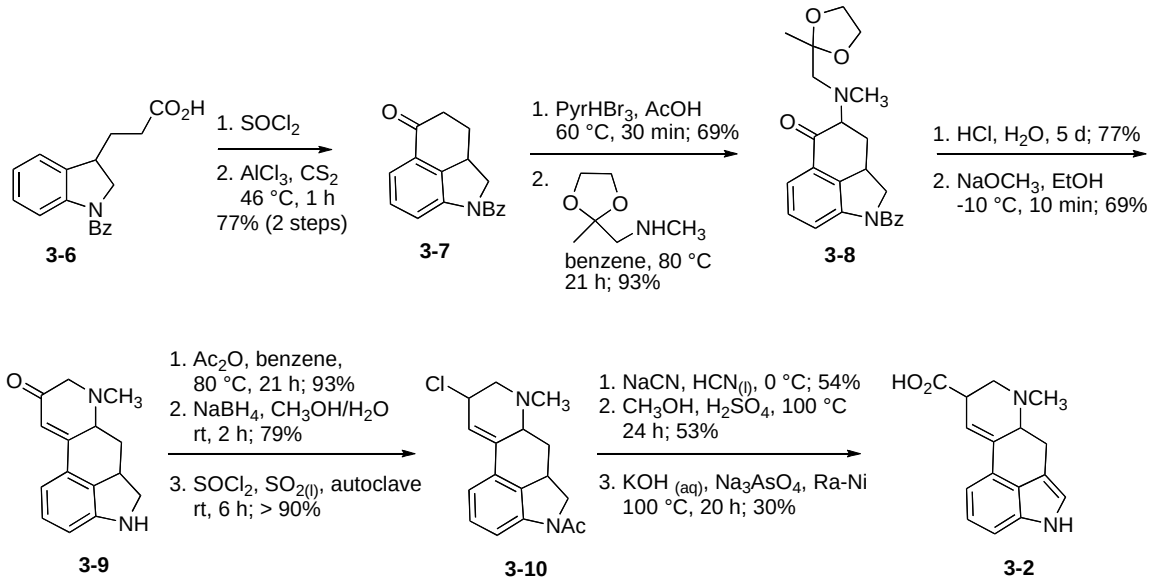
Figure 14. Ergot alkaloid sturcture types and representative examples of two subclasses (common ergoline core outlined in red)

The ergoline nucleus has been a challenging target for total synthesis with attempts dating back to the classic work of Uhle in 1949 and culminating in the synthesis of lysergic acid by Woodward and coworkers in 1954.[122,123] The total synthesis of ergot alkaloids received increasing attention in the 1980s and 1990s, and the pursuit of synthesizing these alkaloids has led to the development of new strategies for the construction of the ergoline core.[120] With a vast majority of research existing in literature regarding the synthesis of ergot alkaloids, only approaches relevant to the material contained in this dissertation will be mentioned.

3.1.2 Approaches to Ergot Alkaloids

In 1954 Woodward and coworkers published the first total synthesis of an ergot alkaloid – lysergic acid (**3-2**, Scheme 40).[123,124] Their pioneering work commences with *N*-benzoylated 3-

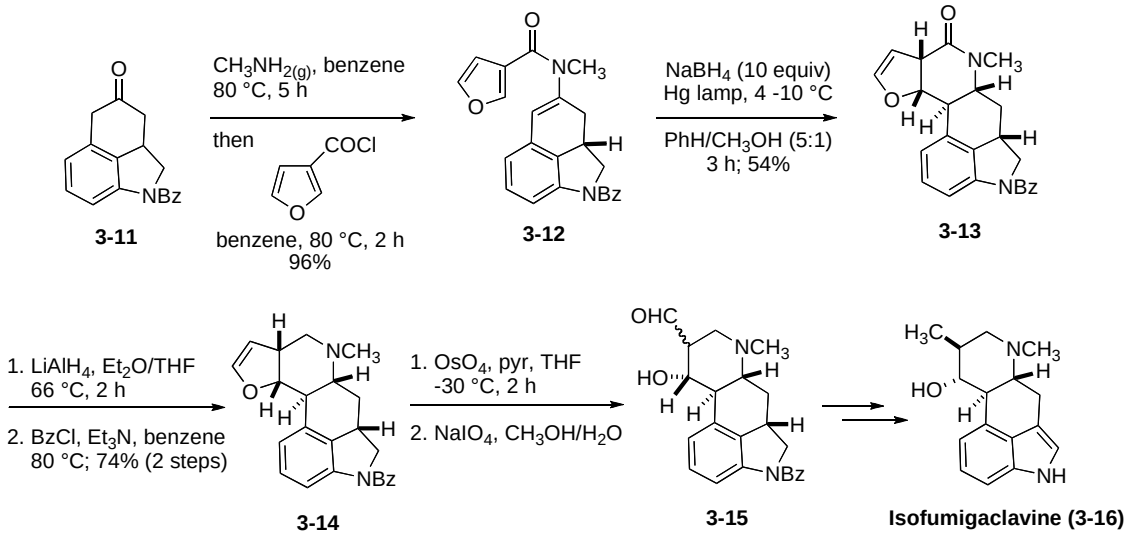
(β-carboxyetheyl)dihydroindole (**3-6**), which was converted into tricyclic ketone **3-7** through a two-step sequence. Compound **3-7** was brominated and subsequently converted to the corresponding α-aminoketone **3-8**. The synthesis of the D-ring (ergoline numbering) was completed through an intramolecular aldol reaction of the ketone derived from **3-8**. After several functional group manipulations, the necessary carboxylic group was introduced at position 8. Finally, the indole moiety was formed through a dehydrogenation step, which provided lysergic acid (**3-2**) in 30% yield.



Scheme 40. Woodward's approach to lysergic acid **(3-2)**

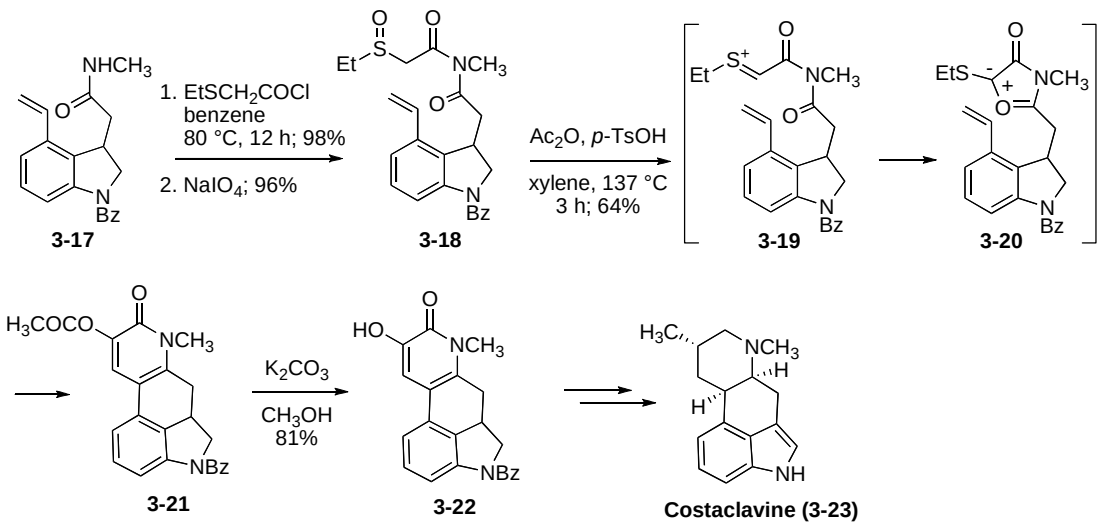
A unique approach by Ninomiya and coworkers features a reductive photocyclization of a furan enamide for the construction of the ergoline D-ring, followed by a glycol formation and oxidative cleavage of the dihydrofuran ring.[125] Initial coupling of **3-11** with furan-3-carbonyl chloride afforded enamide **3-12** in 96% yield (Scheme 41). Elaboration of the D-ring was achieved by irradiation of enamide **3-12** in the presence of excess of $NaBH_4$, which afforded the pentacyclic amide **3-13** in 54% yield. Subsequent functional group transformations led to **3-15**, a

direct precursor to isofumigaclavine **3-16**. Similar to Woodward's approach, the indole moiety was established through a late stage dehydrogenation of the indoline core.



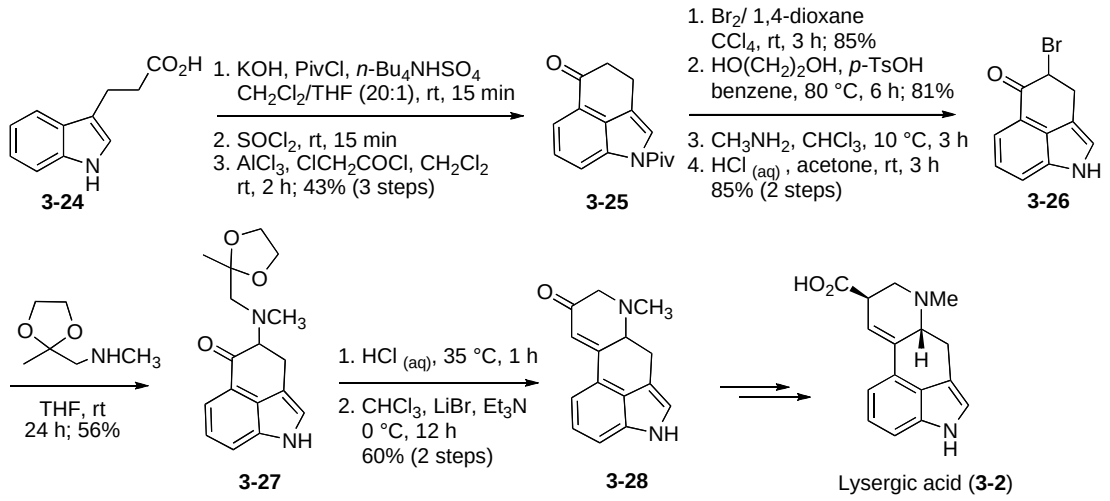
Scheme 41. Reductive photocyclization approach to clavine alkaloids by Ninomiya

The recent synthesis of costaclavine (**3-23**) reported by Padwa employs the Pummerer cyclization-deprotonation-cycloaddition cascade reaction of imidosulfoxides (Scheme 42).[126] Starting with the known amide **3-17**, the authors prepared imidosulfoxide **3-18** in 94% yield over two steps. When **3-18** was subjected to the Pummerer-deprotonation conditions, tetracyclic intermediate **3-21** was isolated in 64% yield. This interesting transformation presumably involves the formation of the isomüchnone **3-20**, followed by an intramolecular 1,3-dipolar cycloaddition, thus allowing the rapid construction of the D-ring. Several additional functional group conversions, including the indoline oxidation in the last step, led to the completion of (±)-**3-23**.



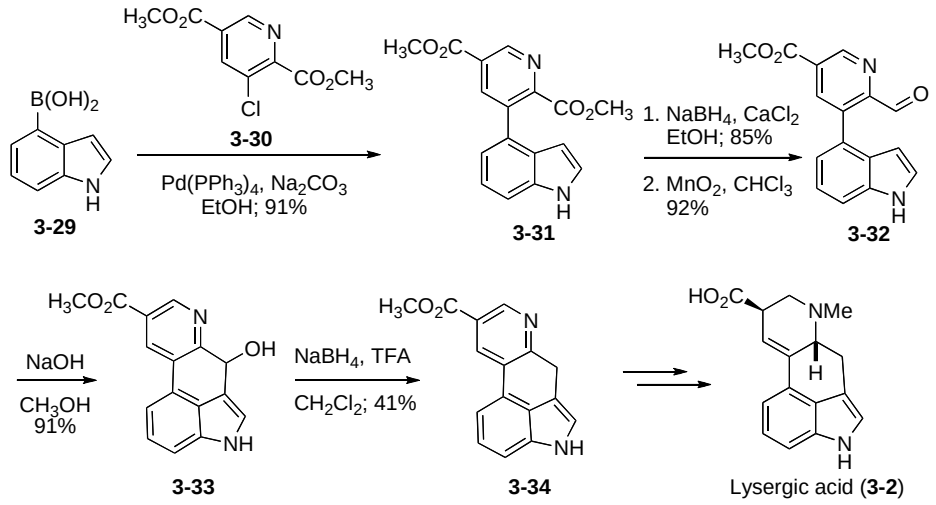
Scheme 42. Padwa's cycloaddition approach to ergot alkaloids

In the recent synthesis of lysergic acid reported by Szántay,[127] the D-ring of the ergoline core was formed by an intramolecular aldol reaction, similar to the Woodward's approach. However, the Szántay group employed Uhle's ketone, possessing the necessary indole moiety, thus avoiding the low yielding indoline oxidation in the last step. Elaboration of 3-indolepropionic acid (**3-24**) into *N*-unprotected 4-bromo-Uhle's ketone (**3-26**),[128] followed by an S_N2 displacement of the secondary bromide and a ketal deprotection afforded a diketone, a direct precursor to **3-28**. The enantiomers of (±)-**3-28** were further separated using (–)-dibenzoyl-L-tartaric acid, which, after several additional steps, allowed the completion of (+)-lysergic acid (**3-2**).



Scheme 43. Szántay's synthesis of lysergic acid

In 2004, Hendrickson and Wang reported a 10-step synthesis of (±)-lysergic acid (**3-2**).[129] Following the initial Suzuki coupling of boronic acid **3-29** and *m*-chloropyridine **3-30**, the diester **3-31** was selectively converted into aldehyde **3-32**, which under basic conditions allowed for the synthesis of the entire core of the lysergic acid. A few additional manipulations provided the desired acid **3-2** in a 6:1 ration with its *cis*-isomer isolysergic acid.

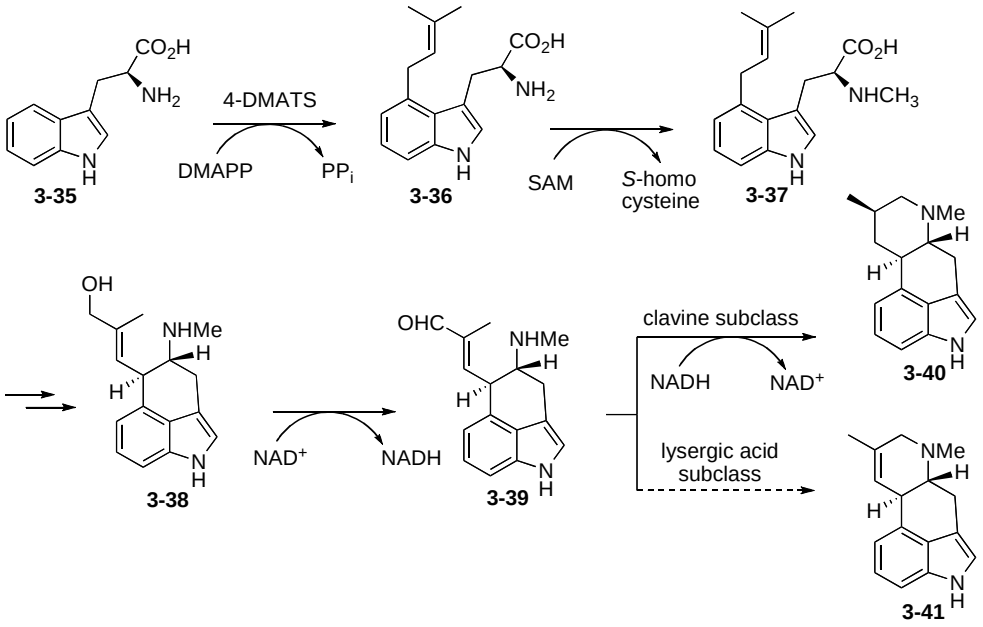


Scheme 44. Hendrickson's approach to the ergoline core

3.1.3 Biosynthetic Relationship of Ergot Alkaloids

Based on the information obtained from gene clusters, significant progress has been made in the identification of the biosynthetic pathways towards ergot alkaloids. Functions of six out of seven genes found in all known ergot alkaloid clusters have been proven experimentally. Their roles were assigned to reaction steps from L-tryptophan to festuclavine (**3-40**) or agoraclavine (**3-41**).[119,130]

The biosynthesis of ergot alkaloids begins with the prenylation of L-tryptophan (**3-35**) at position C(4) of the indole ring in the presence of dimethylallyl pyrophosphate (DMAPP). This reaction is catalyzed by the prenyltransferase 4-dimethylallyltryptophane synthase (4-DMATS). The product of 4-DMATS is further methylated at the amino group by (*S*)-adenosyl methionine, resulting in the formation of *N*-methyl dimethylallyl tryptophane **3-37**.



Scheme 45. Proposed biosynthesis of ergot alkaloids

The next detected intermediate in the biosynthesis of ergot alkaloids is chanoclavine-I (**3-38**). Although no direct proof of this transformation exists, it is believed that it includes at least three steps: decarboxylation, stereoselective cyclization, and hydroxylation of one methyl group of the dimethylallyl unit. Further oxidation of the primary alcohol by a short-chain dehydrogenase/reductase (SDR) in the presence of NAD^+ yields chanoclavine-I aldehyde (**3-39**), the presence of which has been proven by feeding experiments with isotopically labeled precursors.[131]

Chanoclavine-I aldehyde is the branch point in the biosynthesis of ergot alkaloids. While in the synthesis of the clavine subclass of ergot alkaloids chanoclavine-I aldehyde undergoes reductive cyclization and olefin reduction, the synthesis of the D-ring in the lysergic acid subclass is believed to proceed without the reduction of alkene, thus enabling the subsequent allylic oxidation and the introduction of the oxygenated substituent at C(8).

3.1.4 Cycloclavine

Cycloclavine (**3-5**, Figure 15) was first isolated in 1969 from the seeds of the African morning glory (*Ipomea hildebrandtii*) by Hoffman and co-workers.[132] On the basis of spectroscopic data and an X-ray crystallographic analysis of its methobromide salt, these investigators were able to establish the absolute configuration of all stereocenters. Later, other research groups found cycloclavine among other ergot alkaloids in different *Aspergillus* and *Argyrea* fungi.[133,134]

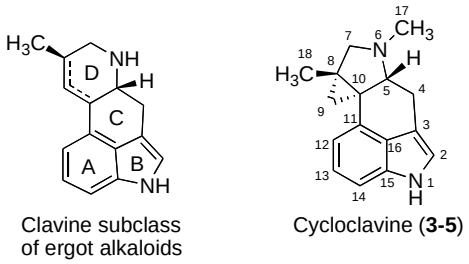


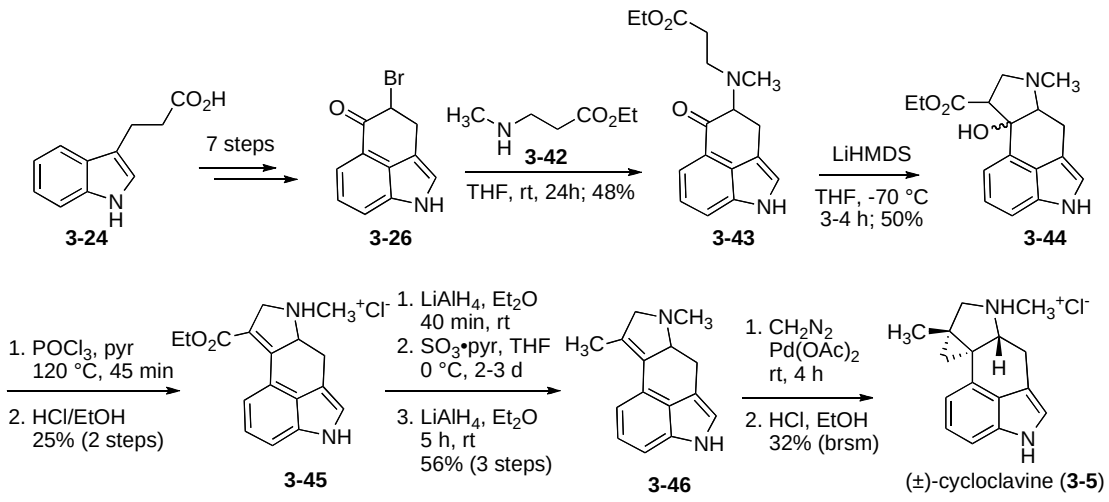
Figure 15. Structure of cycloclavine (**3-5**)

In spite of its small size ($C_{16}H_{18}N_2$, MW = 238), possessing only sixteen carbon atoms, cycloclavine has a very interesting structure. Its compact molecular framework displays three contiguous stereogenic centers, two of which are fully substituted and part of a cyclopropane ring, thus posing a respectable synthetic challenge.[135]

In contrast to other ergot alkaloids of the clavine subclass with a 6-membered D-ring in the ergoline core, cycloclavine contains an additional C(8)-C(10) bridge, making this molecule unique among other members of this family. Although no significant biological activity has been reported to date, the total synthesis of this remarkable ring system is an attractive venture.

3.1.5 Previous Work on the Total Synthesis of Cycloclavine

In 2008, Szántay and coworkers reported the first total synthesis of (±)-cycloclavine (Scheme 46).

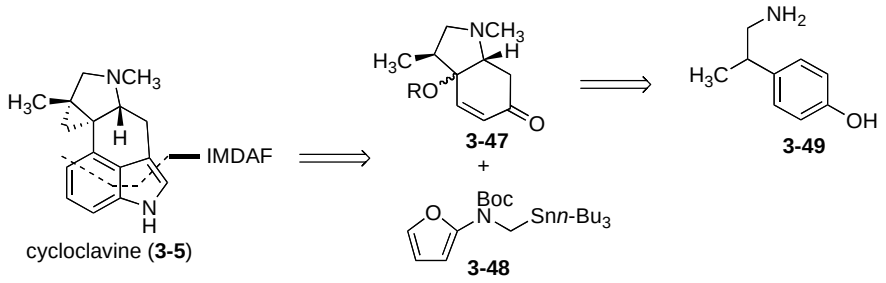


Scheme 46. Szántay's approach to (±)-cycloclavine

The initial S_N2 displacement of 4-bromo-Uhle's ketone (**3-26**), which was synthesized according to the previously mentioned route (Scheme 43) with ethyl 3-*N*-methylaminopropanoate (**3-42**) afforded amine **3-43**. An intramolecular aldol reaction under basic conditions provided hydroxyester **3-44** as a 65:35 inseparable mixture of isomers, which was subsequently subjected to water elimination with $POCl_3$ in pyridine, which gave **3-45**, isolated as a hydrochloride salt in 25% yield.

From this intermediate, the construction of the target molecule required the complete reduction of the allylic ester, as well as the installation of the necessary cyclopropane moiety. Thus, ester reduction followed by an oxidation/reduction sequence, furnished 8-methyl-*D*-norergoline **3-46** in 56% yield. The final cyclopropanation, although a straightforward transformation, proved to be very challenging and was achieved by using diazomethane in the presence of $Pd(OAc)_2$ as a catalyst. (±)-Cycloclavine was isolated as a hydrochloride salt in 22% yield (32% brsm). Accordingly, this total synthesis features 14 steps and an overall yield of 0.2% for the longest linear sequence.

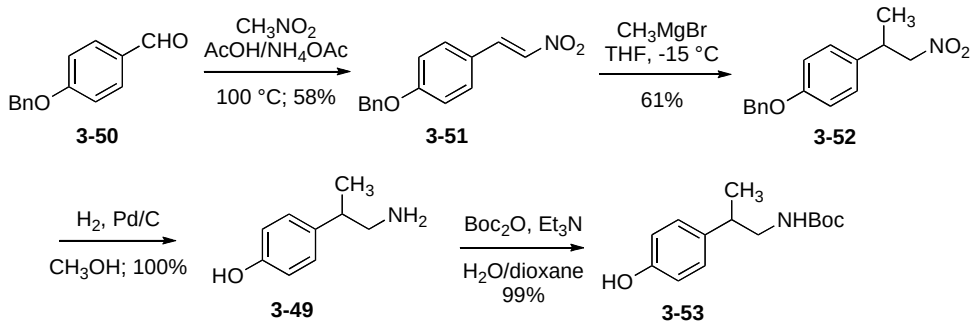
Our group joined this arena shortly before the first total synthesis of cycloclavine was published. Dr. Timmons, a former Wipf group member, evaluated a new strategy towards cycloclavine, based on two key steps: the oxidative cyclization of a methyl tyramine, and the construction of an indole by an intramolecular furan Diels-Alder reaction (Scheme 47).[89]



Scheme 47. Oxidative cyclization/IMDAF approach to cycloclavine

Since the development of the oxidative cyclization of tyrosine to hydroindoles by Wipf and coworkers in 1992,[136] it has been used in the total synthesis of three members of the Stemona alkaloid family: stenine,[137] tuberostemonine,[138] and sessilifoliamide C.[139] In addition, this approach seemed attractive for the possible construction of the hydroindoline part of the cycloclavine scaffold. With this in mind, a direct precursor to the hydroindole moiety would be methyl tyramine (**3-49**).

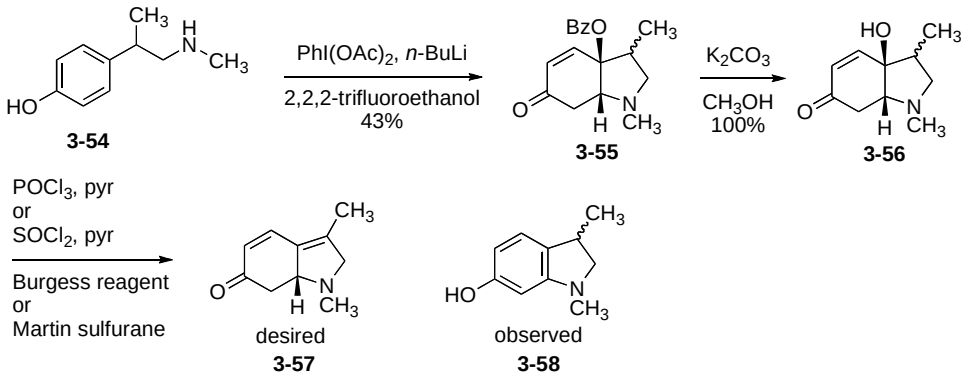
The requisite methyl tyramine (**3-49**) was synthesized from 4-benzyloxybenzaldehyde (**3-50**) and nitromethane (Scheme 48). The corresponding nitrostyrene **3-51** was isolated in 58% yield and subjected to the conjugate addition of methyl magnesium bromide. A hydrogenative deprotection of the benzyl ether and a reduction of the nitro group afforded the desired methyl tyramine (**3-49**) in 61% yield over 2 steps. Final Boc-protection of the primary amine gave the corresponding carbamate **3-53**.



Scheme 48. Synthesis of *N*-Boc protected methyl tyramine **(3-53)**

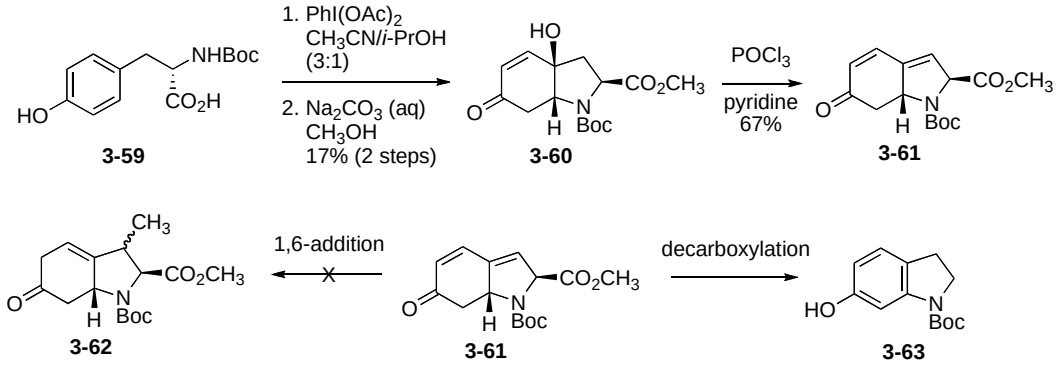
Exposure of methyl tyramine **3-53** to standard oxidative cyclization conditions using iodosobenzene diacetate (PIDA) as the oxidant did not provide any desired product. Changing the oxidant to iodosobenzene bis(trifluoroacetate) (PIFA) or oxone did not improve the results, and in all cases complex reaction mixtures were obtained with no detectable quantities of the desired product.

After considerable reaction optimization, it was found that *N*-benzoyl protected methyl tyramine (**3-54**) underwent an oxidative cyclization process, giving the desired hydroindole **3-55** in 43% yield (Scheme 48). At this stage, elimination of the benzoate group to form the diene **3-57** would have furnished the required scaffold for the hydroindoline system of cycloclavine. Unfortunately, benzoate removal under thermal and π-allyl palladium conditions proved to be unsuccessful. Although the alcohol could be unmasked quantitatively by treatment of the benzoate ester with K_2CO_3 in methanol, all attempts to dehydrate **3-56** to the resulting diene **3-57** resulted in the formation of phenol **3-58**.



Scheme 49. Attempts towards diene **3-57**

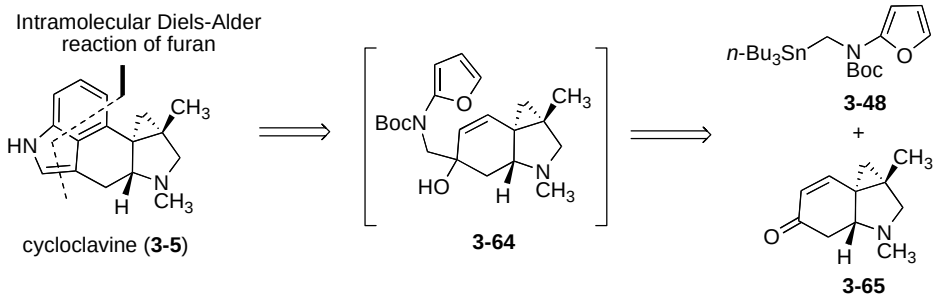
In the revised strategy, following the established protocol, hydroindoline **3-60** was accessed in one pot from Boc-protected L-tyrosine **3-59**. Gratifyingly, the exposure of **3-60** to $POCl_3$ in pyridine yielded the desired diene **3-61** in 67%. Unfortunately, all attempts to install the necessary methyl group at C(8) (ergot alkaloid numbering) through a 1,6-conjugate addition using a variety of copper salts were unsuccessful. Similarly, all trials to decarboxylate the methyl ester through a vinylogous Krapcho elimination with LiCl in DMSO, or through an oxidation-decarboxylation sequence yielded either a very complex mixture of products or an undesired phenol **3-63**.



Scheme 50. Oxidative cyclization of Boc-L-tyrosine and elaboration of the diene **3-61**

3.2 RESULTS AND DISSCUSION

On the basis of our previous success in indole ring formation summarized in Chapter 2.2, we decided to apply the IMDAF strategy to install the indole portion of cycloclavine (Scheme 51). It was anticipated that indoline **3-65** should be the precursor for the cascade process. Indeed, as we have shown previously, the 1,2-addition of the tin-lithium exchanged product of stannane **3-48** to an α,β-unsaturated ketone should provide an allylic tertiary alcohol, which under previously optimized conditions cyclizes to give an indole. According to our retrosynthetic plan, we assumed that the stability of the cyclopropane moiety in the hydroindoline intermediate **3-64** was sufficient to allow a thermal [4+2] process,[90] leading us to the idea of constructing the indole portion of cycloclavine in the last step of our synthesis.

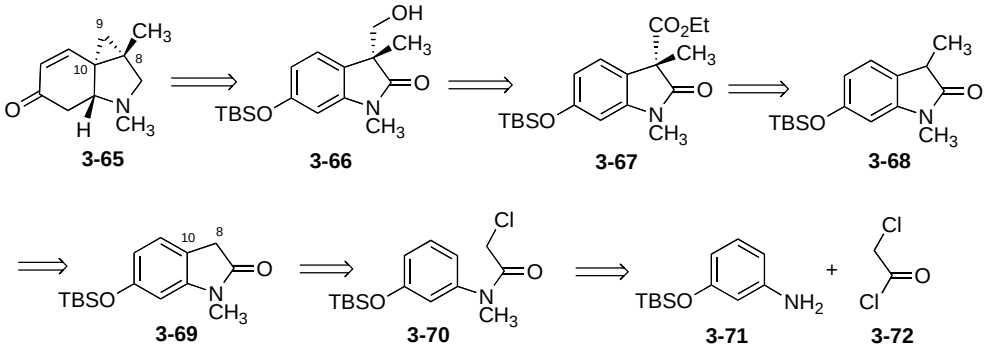


Scheme 51. Strategy for the indole formation in our synthesis of cycloclavine

3.2.1 1st Generation Approach: Cascade TBS-Deprotection/Cyclopropanation Process

Initially, we envisioned that the retrosynthetic disassembly of tricyclic ketone **3-65** furnished the reduced and protected intermediate **3-66** as a potential precursor. If successful, this maneuver would accomplish the formation of the cyclopropane ring in the late stage of the synthesis and allow a quick access to a higher level of molecular complexity starting from a seemingly simple

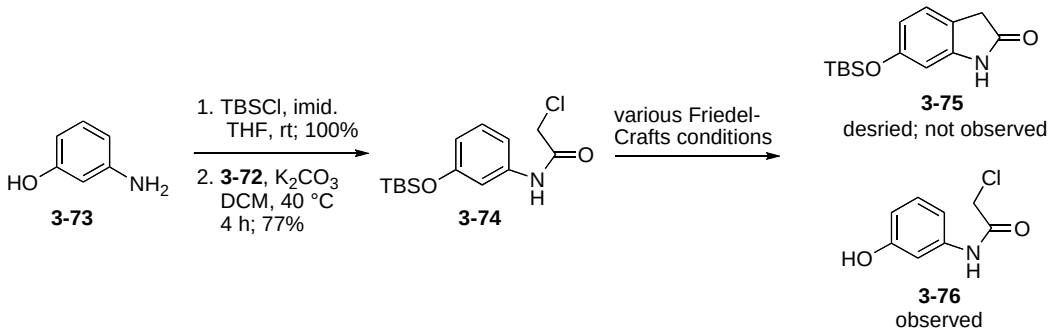
precursor. Although we feared that the strained cyclopropane ring would be difficult to form, we also had much confidence in this cyclization method, since the results of numerous experiments underscored its utility for the construction of cyclopropanes.[140]



Scheme 52. Retrosynthetic approach to **3-65**: tandem TBS-deprotection/cyclopropanation

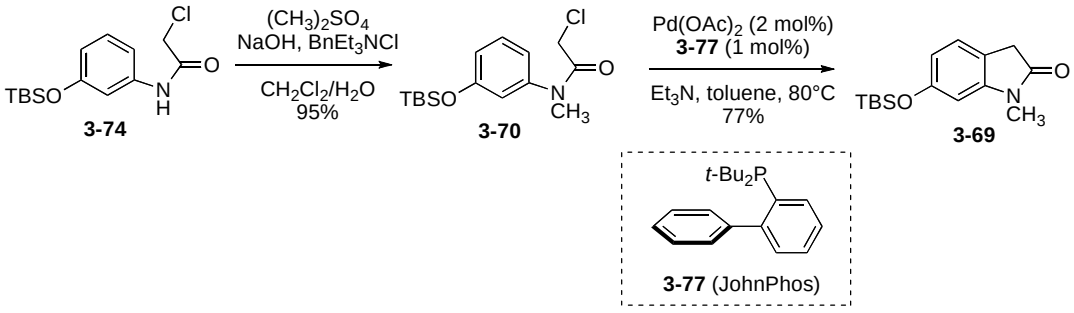
The primary alcohol group, an essential element for the conversion of **3-67** to **3-66**, was derived from the ester moiety in **3-67**. Based on the Vedejs' procedure, it was anticipated that the ester moiety could be stereoselectively introduced in a two-step protocol employing an *O*-acylation of lactam **3-68**, followed by an enantioselective TADMAP-catalyzed carboxyl migration.[141] Finally, lactam **3-69** could be further simplified by cleavage of the C(8)-C(10) bond, through an intramolecular Friedel-Crafts reaction. Intermediate **3-70**, a direct precursor to **3-69**, could be traced retrosynthetically to the commercially available chloroacetyl chloride (**3-72**) and TBS-protected 3-aminophenol (**3-71**).

Our approach to cycloclavine began with the *tert*-butyldimethylsilyl protection of 3-aminophenol and the conversion of aniline **3-71** to its *N*-acylated analog **3-74** (Scheme 53). Intermediate **3-74** was exposed to several standard conditions previously described for an intramolecular Friedel-Crafts reaction.[142,143] Unfortunately, all attempts to induce cyclization were unsuccessful, and instead of cyclized product **3-75**, TBS-deprotection was observed.



Scheme 53. Attempted formation of 2-indolinone **3-69**

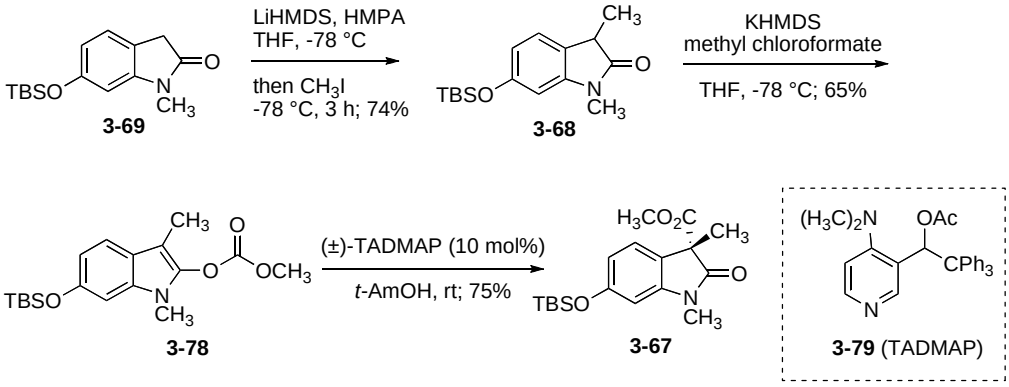
In 2005, Hennessy and Buchwald reported a synthesis of 2-oxindoles via palladium-catalyzed C-H activation of α-chloroacetanilides.[144] Although initial attempts to induce cyclization of **3-74** following the Buchwald protocol failed, we found that when the *N*-methylated amide **3-70**, obtained in 95% yield from **3-74**, was heated in toluene in the presence of a catalytic amount of $Pd(OAc)_2$ and phosphine catalyst **3-77**, the desired cyclized product **3-69** was generated in 77% yield. *N*-Methylation was certainly a required step in our synthesis, and a simple change in order of steps gratifyingly afforded indolinone **3-69**, easily prepared in multigram quantities following this protocol.



Scheme 54. Synthesis of indolinone **3-69** via Pd-catalyzed C-H activation

We were now in a position to address the installation of methyl and carboxyl groups at position C(8). As mentioned before, it was anticipated that this could be achieved by treating the anion with methyl iodide, followed by an *O*-acylation and an acyl-transfer using Vedejs'

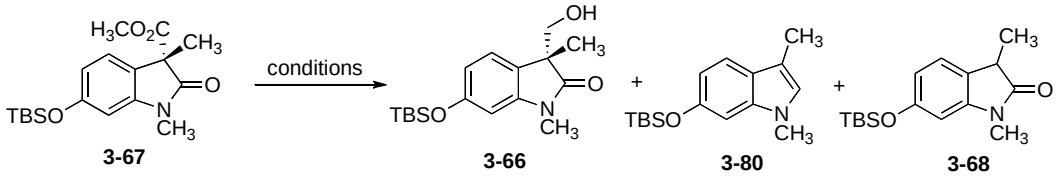
protocol.[141] When **3-69** was treated with LiHMDS in THF at -78 °C in the presence of HMPA, followed by the addition of methyl iodide, **3-68** was isolated in 74% yield (Scheme 55). After successful *O*-acylation of **3-68** with methyl chloroformate, a critical stage of the synthesis had been reached. Although the acyl transfer could be performed in a stereoselective fashion, we decided to first use (±)-TADMAP (**3-79**) in this transformation to check its feasibility. Indeed, treatment of **3-78** with (±)-TADMAP in the solution of *t*-AmOH resulted in the formation of **3-67** in 75% yield.



Scheme 55. Introduction of methyl- and methoxycarbonyl groups at C(8)

As discussed previously, the use of an ester moiety represented an important feature of the synthesis, since its conversion to the primary alcohol would lead to the cyclization precursor that would enable cyclopropane formation. This tactic would install another quaternary stereocenter and allow the formation of the intermediate dienone in an enantioselective fashion. Unfortunately, all attempts toward a selective reduction of the ester function led to either loss of the ester or a complete reduction to the corresponding indole (Table 3).

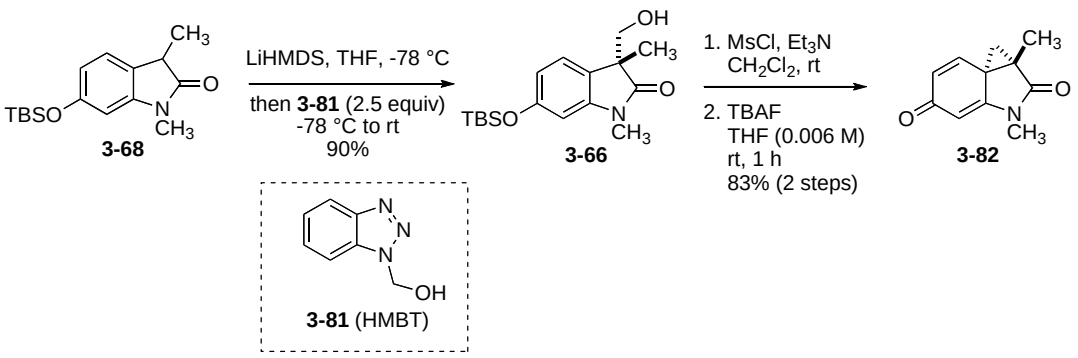
Table 3. Attempts toward reduction of ester **3-67**



3-67 **3-66** **3-80** **3-68**

Entry	Conditions	Result
1	$LiAlH_4$ (1 equiv), THF, -78 °C	**3-68**
2	DIBAL (1 equiv), THF, -78 °C	**3-80** (6%) + **3-68** (52%)
3	DIBAL (1.2 equiv), toluene, -78 °C (12 h)	**3-68** (34%)
4	$LiBH_4$ (1 equiv), THF, -78 to 0 °C to rt	**3-80** (23%) + **3-68** (43%)
5	BH_3 (2 equiv), THF, -78 to 0 °C; then 66 °C, 2 h	Decomposition during heating

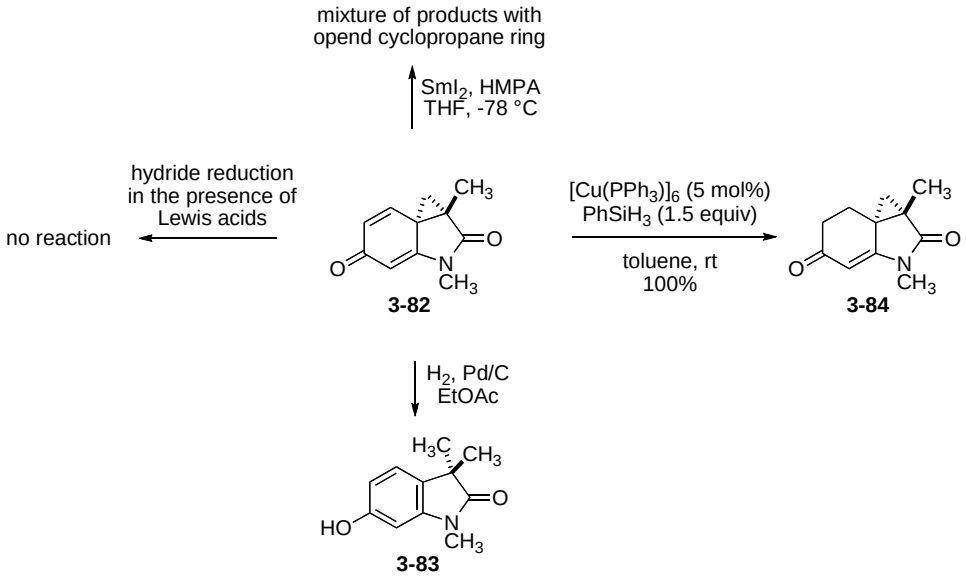
The lack of success in the ester reduction forced us to identify another way to install the necessary hydroxymethyl moiety. Hydroxymethylbenzotriazol (**3-81**), developed by Katrizky's group[145] and used as an efficient source of formaldehyde by Bischoff,[146] appeared to be particularly attractive. Indeed, treating **3-68** with LiHMDS in THF at -78 °C, followed by the addition of a suspension of **3-81** in THF, furnished the desired alcohol **3-66** in 90% yield. From this intermediate, the construction of the cyclopropane ring required only a hydroxyl group activation, followed by a TBS-deprotection. Primary alcohol **3-66** was converted to the corresponding mesylate in high yield. Treatment of this mesylate with TBAF in THF (0.1 M) resulted in a complex mixture of products. In contrast, under high dilution conditions (0.006 M), TBAF promoted a silyl ether cleavage, with a concomitant intramolecular alkylation to give **3-82**.[147]



Scheme 56. Synthesis of **3-82**: tandem TBS-deprotection/cyclopropane formation

We were now at the stage of a very challenging transformation. A selective reduction of the cross-conjugated dienone **3-82** would provide the desired enone **3-65**, a direct precursor for the key IMDAF reaction. Only a few literature reports of selective reductions of this type had been reported, but in all cases the starting material did not contain labile moieties as in **3-82**. Thus, this transformation was a concern, but we hoped that we could effect it by taking advantage of Lewis acidic reducing agents and the electron-donating properties of the β-amino substituent. However, in spite of considerable experimentation, our attempts to regioselectively reduce the trisubstituted alkene in **3-82** proved to be unsuccessful (Scheme 57). Hydride reductions in the presence of Lewis acids ($NH_4Br/NaBH_3CN$, $BF_3•Et_2O/Et_3SiH$, $Me_3OBF_4/NaBH_4$)[148] led only to the recovered starting material. Under hydrogenation conditions (H_2, Pd/C), formation of the corresponding phenol **3-83** was observed with concomitant opening of the cyclopropane ring. When **3-82** was subjected to SmI_2/HMPA reduction,[149] opening of the cyclopropane ring was detected. These observations indicated that the more substituted double bond in **3-82** was difficult to reduce chemoselectively, which, on the other hand, was expected, given the fact that this olefin is a part of a conjugated enamide moiety. In addition, the cross-conjugated dienone increases the reactivity of the cyclopropane ring, favoring its opening under hydrogenation conditions.

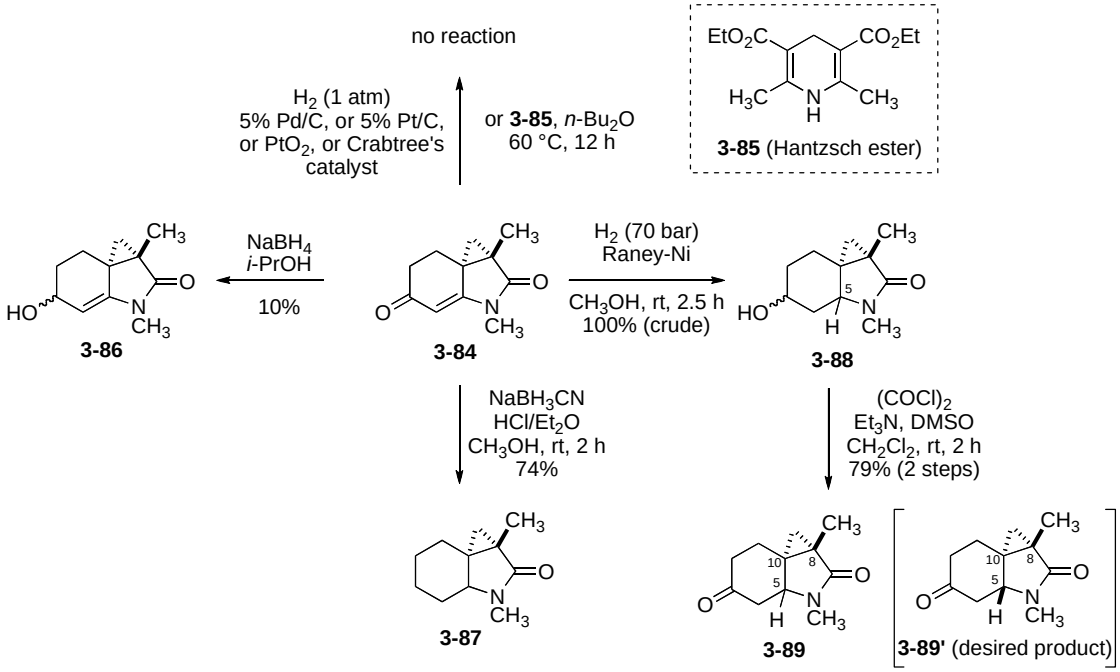
The next obvious step was a selective reduction of the less substituted olefin in the cross-conjugated dienone **3-82**, hoping that, after a successful reduction of the intermediate enamide, introduction of the unsaturation at C(11)-C(16) would be feasible. Using conditions reported by Lipshutz, dienone **3-82** was selectively reduced with Stryker's reagent and $PhSiH_3$ in toluene, and the corresponding enamide **3-84** was isolated in quantitative yield.[150]



Scheme 57. Attempts toward selective reduction of dienone **3-82**

As stated before, partial reduction of dienone **3-82** diminishes the reactivity of the cyclopropane ring. This gave us an opportunity to thoroughly investigate conditions for the reduction of the alkene present in **3-84** (Scheme 58). Initial attempts towards hydrogenation led only to the isolation of starting material.[151] A similar result was obtained when Hantzsch ester (**3-85**) was used as a hydride source.[152] Metal hydrides, on the other hand, led to the reduction of the keto-group, giving either a mixture of allylic alcohols with the double bond intact (in the case of $NaBH_4$/*i*-PrOH) or completely reduced **3-87 (**in the case of $NaBH_3CN$ under acidic conditions). To our surprise, when **3-84** was subjected to hydrogenation under high pressure (70 bar), using

Raney-Ni as a catalyst, a mixture of diastereomeric alcohols **3-88** was isolated in quantitative yield. Oxidation of **3-88** under the Swern conditions provided the desired ketone **3-89** in 79% yield as a single diastereomer.



Scheme 58. Attempts toward enamide reduction and synthesis of **3-89**

Reduction of the enamide **3-84** to the corresponding alcohol **3-88**, and its subsequent oxidation to provide **3-89** need an additional comment. Although successful, the reduction-oxidation sequence from **3-84** to **3-89** provided only one diastereomer, but we were not able to ascertain the relative configuration at C(5) in **3-89** at this point. Based on the Newman projection of **3-84**, we hypothesized that the cyclopropane moiety would shield the α-face from hydrogen delivery (Figure 16). If our hypothesis was correct, the reduction-oxidation sequence would provide the desired diastereomer of **3-89**, in which hydrogen atom at C(5) and the methyl group at C(8) are on the same face of the hydroindoline core. In other words, the hydrogen delivery should occur selectively from the β-face, leading to the desired stereochemistry at C(5). Hoping

that our rationale was valid and that the stereochemistry at C(5)-C(10) in **3-89** was *trans* as in **3-89'**, we continued with our journey towards cycloclavine.

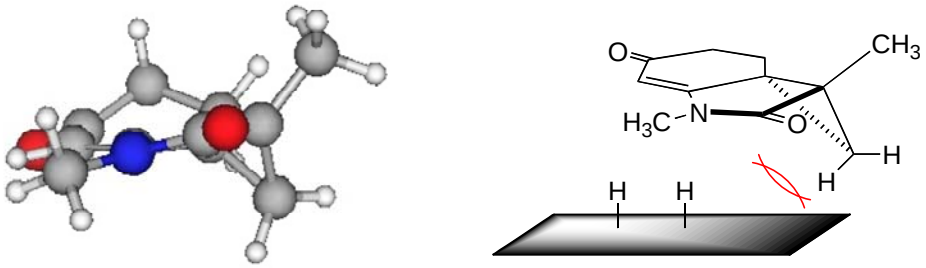
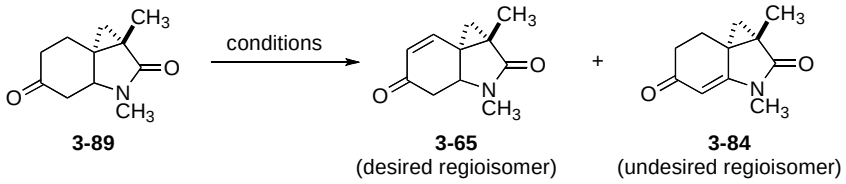


Figure 16. Newman projection of **3-84** and disfavored hydrogen delivery from the α-face

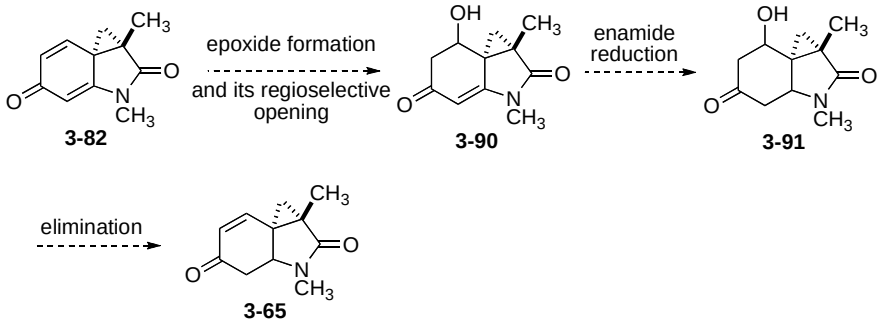
Following our previously mentioned plan, we next attempted to install the necessary unsaturation at C(11)-C(16) (cycloclavine numbering) in **3-89** (Scheme 59). Accordingly, we subjected **3-89** to several conditions for the formation of the corresponding silyl enol ether, followed by the $Pd(OAc)_2$-assisted oxidation (Saegusa-Ito protocol).[115] Treating **3-89** with either HMDS[153] or LiTMP[154] as a base, followed by the addition of a slight excess of TMSI (1.2–1.5 equiv), and then subjecting the intermediate TMS-enol ether to the Saegusa-Ito conditions provided the undesired regioisomer **3-84** as a sole product. On the other hand, heating the mixture of **3-89**, TMSOTf (5 equiv) and Et_3N (5 equiv) in acetonitrile at reflux for 2.5 h,[155] followed by the oxidation with $Pd(OAc)_2$ in DMSO led to the formation of both regioisomers **3-65** and **3-84** in 1:2 ratio (93% combined yield), favoring the formation of the more substituted alkene **3-84**. Using Mukaiyama's reagent[156] or IBX in DMSO[157] led to the exclusive formation of the undesired isomer **3-84** in 45% and 66% yields respectively.



Scheme 59. Formation of the α,β-unsaturated ketone **3-65**

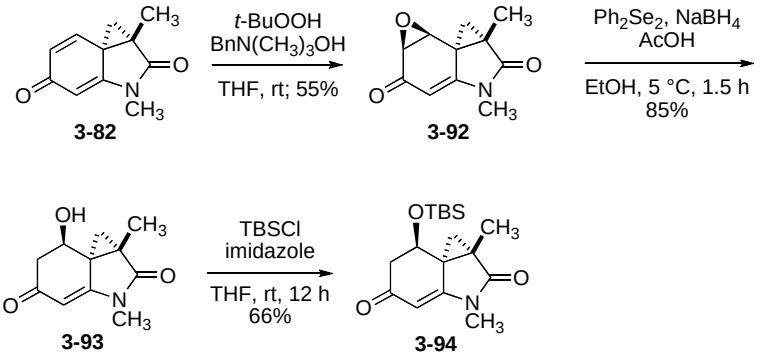
The strong preference for the formation of the undesired regioisomer **3-84** under kinetic conditions could be partly attributed to the rigid nature of **3-89** (i.e. the fused ring system with a cyclopropane moiety and a quaternary center), which might prevent the approach of the base from the seemingly less hindered side. In addition, the electron-withdrawing nature of the nitrogen atom at the β-position probably increases the acidity of the α-proton at C(4). Under thermodynamic conditions, however, the preference for the formation of the undesired regioisomer **3-84** probably lies in the fact that the double bond is a part of an extended conjugated system, thus favoring the formation of the enamide.

In order to address the problem associated with the regioselective introduction of the alkene, we decided to make a major modification to our synthetic strategy. The successful synthesis of dienone **3-82** and the more reactive nature of the less substituted alkene led us to a hypothesis that, perhaps, this alkene unit could be protected as an epoxide, which would, after a successful reduction of the enamide moiety, provide a handle for the formation of the desired enone **3-65** (Scheme 60).



Scheme 60. Modification of the initial strategy toward **3-65**

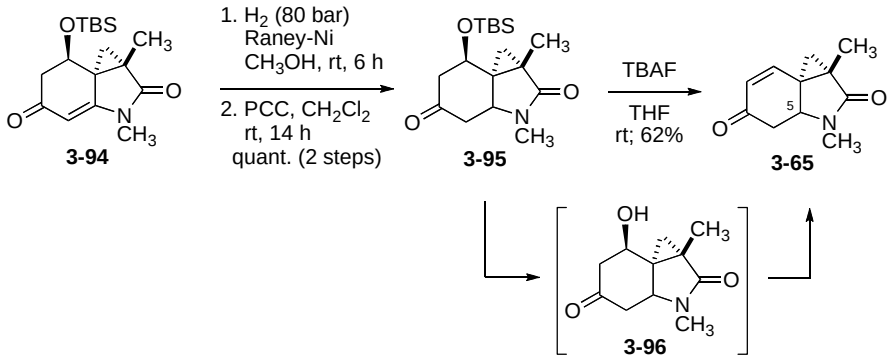
Accordingly, epoxidation of **3-82** with *tert*-butyl hydroperoxide (TBHP) in THF[158] provided monoepoxide **3-92** as a sole regio- and stereoisomer (Scheme 61). Following the procedure of Miyashita and coworkers,[159] **3-92** was regioselectively opened with Na[PhSeB(OEt)$_3$] in EtOH, furnishing β-hydroxy ketone **3-93** in 85% yield. Thus, the disubstituted alkene in **3-82** was masked as a secondary alcohol. Further protection of the secondary alcohol with TBSCl in DMF provided **3-94** in 66% yield. This additional protection was necessary since the reduction of the enamide fragment under previously mentioned conditions (Raney-Ni, H_2 (80 bar), 6 h, rt) also leads to the formation of a secondary alcohol.



Scheme 61. Masking the less substituted olefin in **3-82** as an alcohol

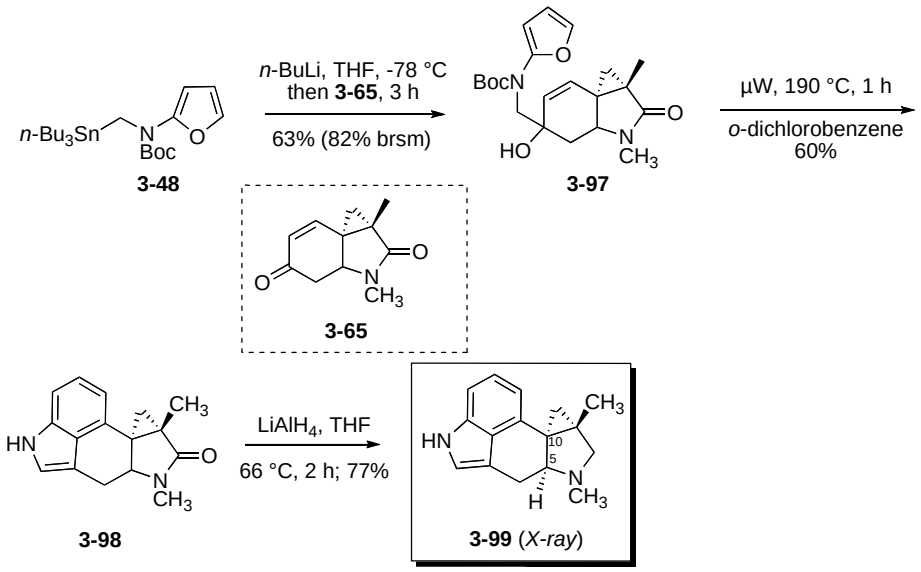
Hydrogenation of **3-94** followed by PCC oxidation afforded **3-95** in quantitative yield. As stated before, the hydrogen delivery in this step was assumed to occur from the β-face since it

was expected that the fused cyclopropane ring would block the α-attack. Exposure of **3-95** to a TBAF solution in THF promoted the β-elimination of the intermediary formed hydroxyketone and furnished the α,β-unsaturated ketone **3-65'** in 62% yield.



Scheme 62. Formation of the desired enone

After tin-lithium exchange of stannane **3-48** followed by a 1,2-addition to **3-65'** in THF, a single isomer of the tertiary alcohol **3-97** was obtained in 63% yield (Scheme 63). When **3-97** was heated in *o*-dichlorobenzene at 190 °C for 1 h under microwave irradiation, a cyclized product **3-98** was isolated in 60% yield. Finally, after exposure of lactam **3-98** to $LiAlH_4$ in THF at reflux, we were pleased to see the formation of the final product **3-99**.



Scheme 63. Synthesis of 5-*epi*-cycloclavine (**3-99**)

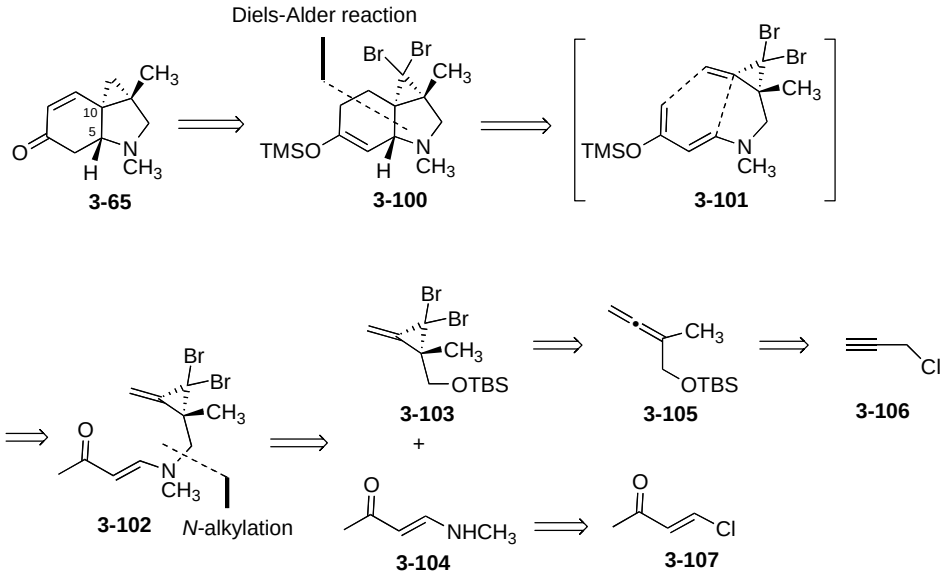
Unfortunately, the analytical data of **3-99** did not match those of cycloclavine. An X-ray analysis of **3-99** confirmed the *cis*-configuration at the C(5)-C(10) ring fusion of the indoline substructure. Such a stereochemical outcome, which comes from the hydrogenation step, revealed the strong substrate preference for the delivery of hydrogen from the α-face. This was surprising, since not only the hydrogenation of the TBS-ether **3-95**, but also the deoxygenated analog **3-84**, provided a sole hydrogenation isomer. Comparison of the ^{1}H NMR data for **3-84** and **3-95** confirmed the same stereochemistry at C(5), which was assigned to be *trans* with respect to the C(8)-CH_3 group, based on the X-ray analysis of 5-*epi*-cycloclavine (**3-99**).

These substrate preferences, in addition to the difficulties in reducing the trisubstituted alkene in dienone **3-82**, required a complete redesign of our retrosynthetic approach.

3.2.2 2nd Generation Approach: Formation of the Indoline Core *via* a [4+2] Cycloaddition

The main feature of our new strategy is the introduction of the C(5)-C(10) *trans*-hydroindole by an intramolecular methylenecycopropane Diels-Alder reaction, which is presented in a retrosynthetic format in Scheme 64. Disconnection of dibromide **3-100**, a direct precursor to **3-65**, furnishes intermediate **3-102**. Such transformation would be used to set two stereocenters in our synthesis of cycloclavine and to construct the hydroindoline core in one step. Although a few cases of the intramolecular [4+2] cycloaddition of unsubstituted methylenecyclopropane and other simple derivatives (such as perfluoromethylenecyclopropane, 2,2-difluoromethylenecyclopropane, and methyl 2-chloro-2-cyclopropylidene acetate) have been described in literature,[160-163] there is only one prior report of an intramolecular, high-pressure Diels-Alder reaction with this strain-activated dienophile.[164] This intramolecular [4+2] cycloaddition of an exocyclic olefin with the diene portion of **3-102** would be expected to afford the *trans*-C(5)-C(10) TMS-enol ether **3-100**, which, after conventional functional group manipulations, could be converted to the desired enone **3-65**. The synthetic problem is now reduced to the construction of amide **102**, and it was anticipated that this objective could be achieved by merging β-aminovinyl ketone **3-104**[165] and the primary bromide derived from the TBS-protected alcohol **3-103**.

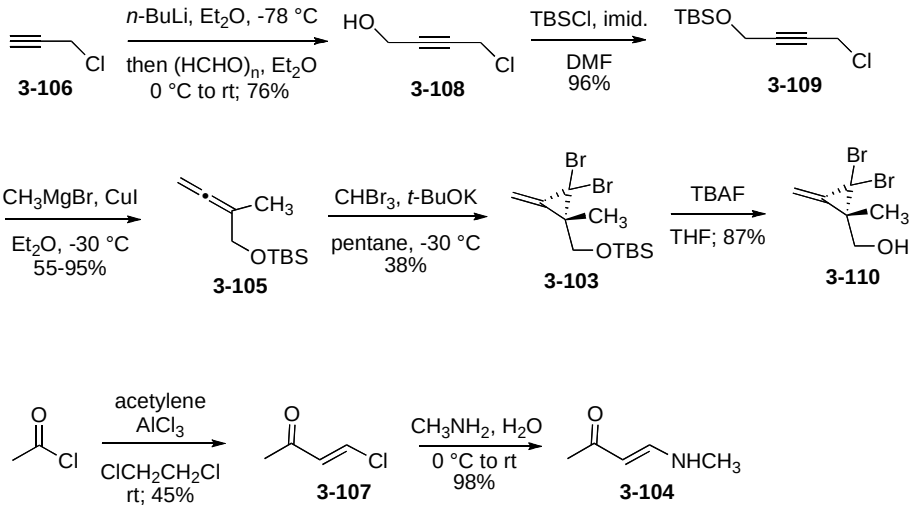
On the basis of Kuivila's pioneering work in the 1960s,[166] olefin **3-103**, the projected dienophile component for the Diels-Alder reaction, could conceivably be derived from allene **3-105** by a selective dibromocyclopropanation of the more electron-rich double bond, which in turn could be obtained from propargylic chloride, a process previously described in literature.[167]



Scheme 64. Retrosynthetic analysis of **3-65**: cycloaddition approach

Our cycloaddition approach toward the cycloclavine precursor **3-65** commenced with the conversion of acetyl chloride into *β*-chlorovinyl ketone **3-107**. In this simple transformation, acetylene gas was bubbled through a solution of acetyl chloride in dichloroethane in the presence of $AlCl_3$ to furnish **3-107** in 45% yield. Exposure of **3-107** to methylamine resulted in an addition-elimination process, which provided **3-104** in 98% yield after overnight extraction using diethyl ether.

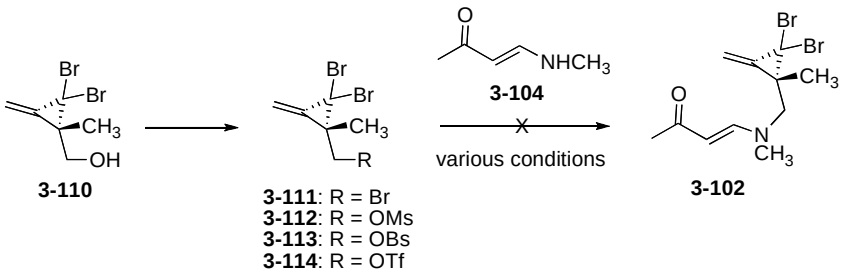
The synthesis of fragment **3-103** started with a previously well-established protocol.[168] Treatment of propargylic chloride with stoichiometric amounts of *n*-BuLi, followed by the addition of formaldehyde, provided propargylic alcohol **3-108** in 76% yield. After protection of the hydroxyl group in the form of a *tert*-butyldimethylsilyl ether, propargylic chloride **3-109** was converted into the allene **3-105** with MeMgBr in the presence of CuI. However, the allene was isolated in variable yields, depending on the scale and the quality of CuI.



Scheme 65. Synthesis of intermediates **3-104** and **3-110**

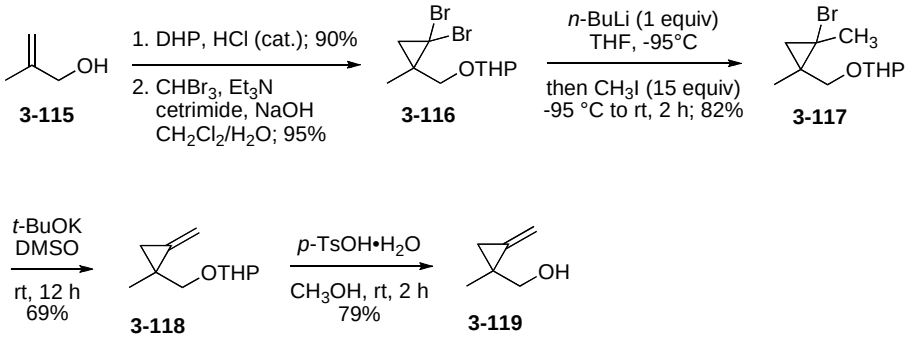
One of the challenging tasks remaining for the synthesis of **3-65** was the chemoselective cyclopropanation of the more substituted double bond in the allene intermediate **3-105**. Although allenes can successfully be cyclopropanated,[169-171] only a few chemoselective examples are available in the literature. As previously mentioned, using the Kuivila procedure and exposure of the allene intermediate to one equivalent of $CHBr_3$ in the presence of *t*-BuOK in pentane resulted in the formation of the desired dibromocyclopropane **3-103** in modest yield. Finally, TBS-deprotection of the primary alcohol furnished dibromocyclopropylmethyl alcohol **3-110** with the required exocyclic olefin fragment.

With the two requisite coupling components in hand, the next step was the union of fragments **3-110** and **3-104**. This seemingly straightforward transformation proved to be very difficult. Several conditions, including various leaving groups (OMs, OBs, OTf, Br) in **3-110** as well as different bases (NaH, *n*-BuLi, Et_3N), were examined, but none of them gave rise to the desired coupling product **3-102**. Instead, decomposition of **3-110** was observed.



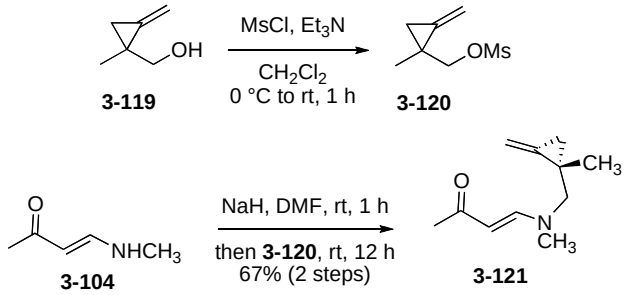
Scheme 66. Attempted coupling of **3-104** and **3-110**

At this stage, another major overhaul of our synthetic strategy was clearly needed. We believed that the failure of our previous approach could partly be attributed to the reactive nature of the dibromocyclopropyl intermediates (**3-111 – 3-114**), which decompose under the basic conditions used for the attempted coupling. In order to overcome this problem, we decided to synthesize the corresponding methylenecyclopropyl derivative **3-118** (Scheme 67). The main feature of this route is the transformation of the corresponding dibromocyclopropyl moiety to the desired olefin, the necessary dienophile for the Diels-Alder reaction, prior to the coupling with the vinylogous amide **3-104**. Accordingly, *β*-methallyl alcohol **3-115** was THP-protected and converted to dibromocyclopropane **3-116** under phase transfer conditions in 86% overall yield. Exposure of **3-116** to *n*-BuLi (1 equiv) at -95 °C in THF and subsequent treatment of the monobromo-monolithiated intermediate with CH_3I furnished the tertiary bromide **3-117**. When **3-117** was treated with *t*-BuOK in DMSO at room temperature, a clean conversion to the corresponding dehydrobrominated product **3-118** was observed. Finally, THP-deprotection with *p*-TsOH•H_2O in CH_3OH provided the desired cyclopropylmethylidene alcohol **3-119**.



Scheme 67. Synthesis of cyclopropylmethylidene alcohol **3-119**

Conversion of this alcohol to the corresponding mesylate **3-120**, followed by the *N*-alkylation of the anion of vinylogous amide **3-104** cleanly provided the desired coupling product **3-121** in 67% yield from **3-119**. As we had hypothesized, the presence of the dibromocyclopropane moiety in **3-110** was apparently the cause of the failure of the attempted coupling with **3-104** under basic conditions.

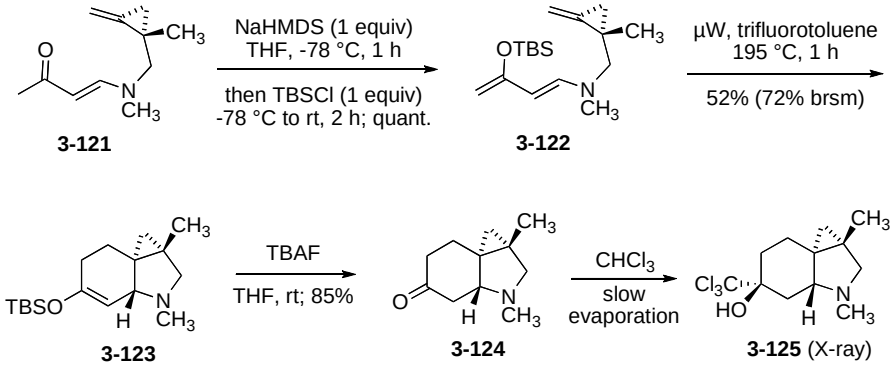


Scheme 68. Coupling between **3-120** and **3-104**

With this coupling product in hand, we set out to convert **3-121** into the corresponding TBS-enol ether (Scheme 69). Formation of the silyloxy diene was originally met with some problems. Common bases, such as LiHMDS, LDA, or KHMDS gave either no reaction or very complex mixtures of products, as evidenced by ^{1}H NMR. Gratifyingly, treatment of **3-121** with NaHMDS (1 equiv) in THF, followed by TBSCl trapping of the enolate provided a clean conversion of **3-121** to **3-122** in quantitative yield.[172] It is worth mentioning that, although

several procedures employ an aqueous work-up followed by a TBS-enol ether purification by chromatography on SiO_2,[173-175] **3-122** was found to be very easily hydrolyzed, to the extent that even a TLC-analysis could not be used to monitor the reaction progress.

The crude Diels-Alder precursor **3-122** was smoothly converted to the indoline **3-123** by microwave irradiation in α,α,α-trifluorotoluene at 195 °C for 1 h. The tricyclic ketone **3-124** was isolated in 85% yield after removal of the TBS group with TBAF.



Scheme 69. Intramolecular Diels-Alder reaction of TBS-enol ether **3-122**

The configuration of **3-124** could not be assigned from ^{1}H NMR or 2D NMRs due to overlap of the indicative proton signals. However, after slow evaporation of the chloroform solution of **3-124**, a chloroform adduct **3-125** was obtained as a crystalline compound, the X-ray crystallographic analysis of which confirmed the desired *trans*-configuration at the indoline ring fusion bond. Thus, the configuration at C(5) in **3-124** was unambiguously assigned to be *cis* with respect to the methyl group at C(8).

Remarkably, the aforementioned intramolecular Diels-Alder reaction provided, after TBS deprotection with TBAF, **3-124** as a sole diastereomer. Although the desired diastereomer was isolated and its structure confirmed by an X-ray crystallographic analysis, this reaction needed an additional analysis. As shown in Figure 17, there are two possible transition states (***exo*-3-122**

and ***endo*-3-122**). The ***exo*-3-122** transition state, which would ultimately lead to the undesired ketone **3-124'**, suffers from the syn-pentane interaction between *N*-CH_3 group and the cyclopropane ring. On the other hand, in ***endo*-3-122** *N*-CH_3 group is pointed away from the cyclopropane ring, thus avoiding this unfavorable interaction. Furthermore, there is an additional steric repulsion between the hydrogen atom at C(5) and one of the hydrogen atoms on the cyclopropane fragment in ***exo*-3-122**, while in ***endo*-3-122** cyclopropane ring is placed on the opposite side of the C(5)-H atom. Indeed, a computational analysis suggests that the energy for the *endo*-transition state ***endo*-3-122** leading to **3-124** is 6.8 kcal/mol lower than the transition state ***exo*-3-122** (Figure 18).[176]

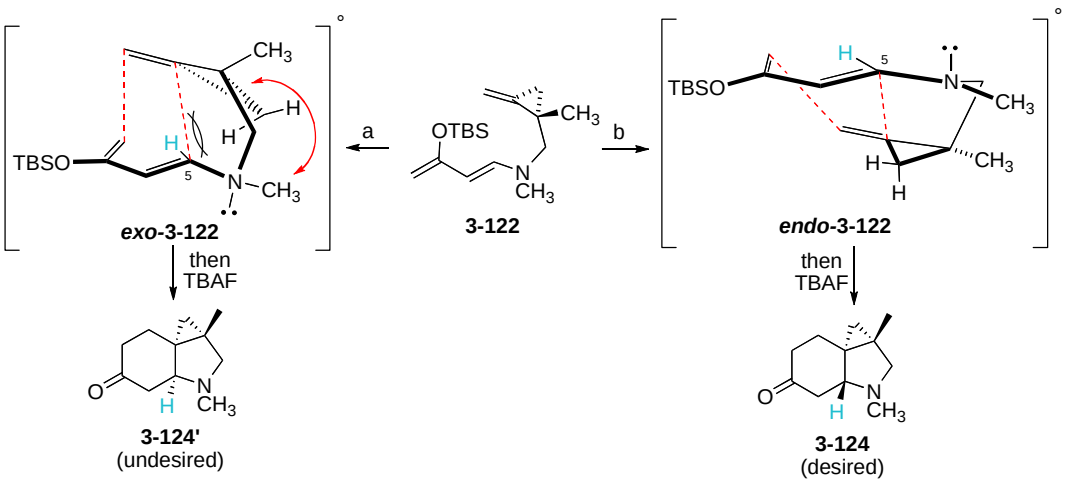


Figure 17. Possible transition states for the Diels-Alder reaction

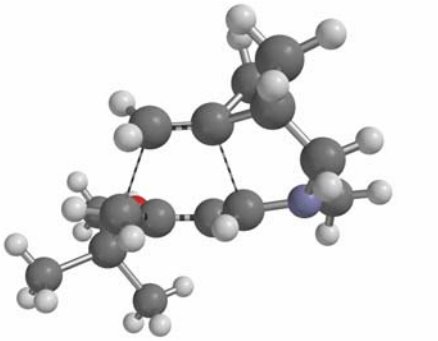
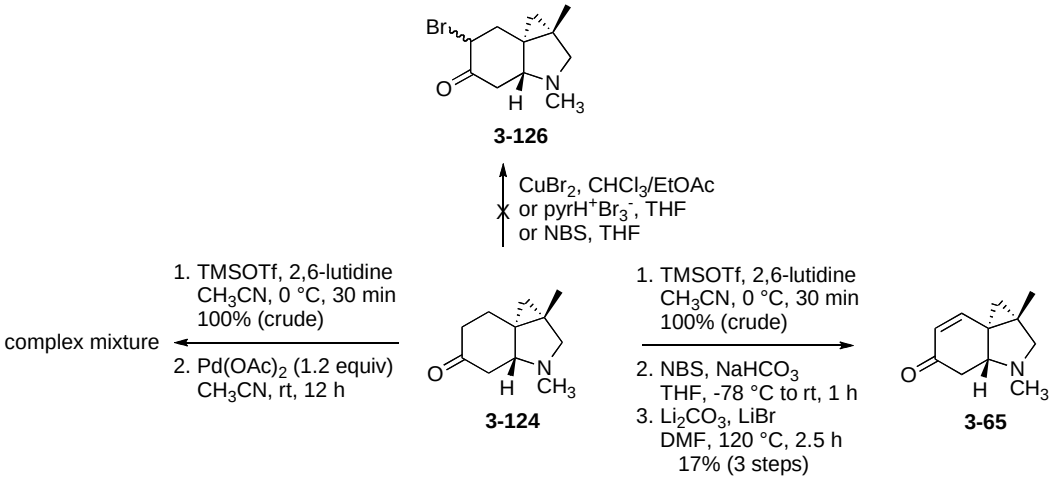


Figure 18. Transition state ***endo*-3-122**

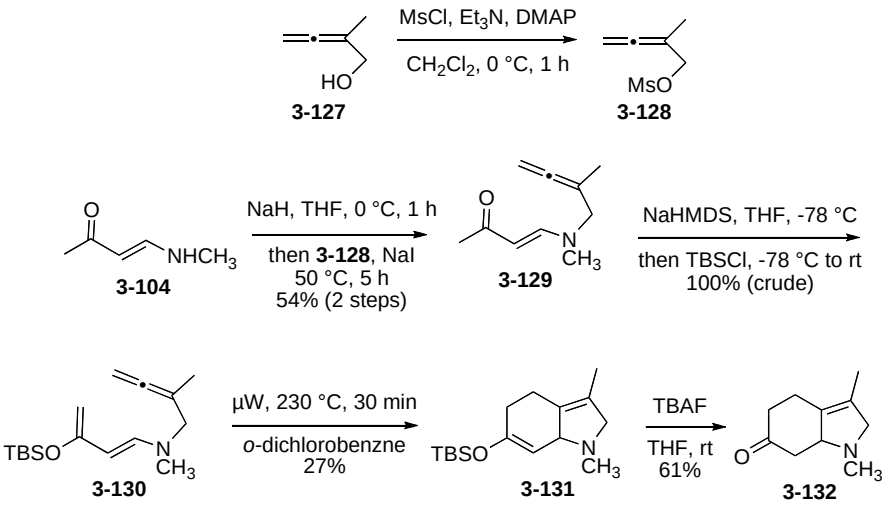
Encouraged with this result, we next attempted to install the required unsaturation at C(11)-C(16). Once again we were met with less than desirable reactivity issues. The formation of the corresponding silyl enol ether, followed by a Pd-catalyzed oxidation (Saegusa-Ito protocol) did not provide any isolable product, probably due to competing side reactions involving the basic amine moiety. Several conditions ($CuBr_2$ in $CHCl_3$/EtOAc,[177] $PyrH^+Br_3^-$ in THF,[178] or NBS in THF) were screened towards the regioselective α-bromination of ketone **3-124**. In all cases, however, only starting material was recovered. Interestingly, when the corresponding TMS-enol ether was exposed to NBS in THF, and then treated with Li_2CO_3 and LiBr in DMF at 120 °C, the desired enone was isolated as the sole regioisomer, although only in 17% yield.



Scheme 70. Attempts towards the synthesis of **3-65**

As we encountered difficulties in the successful formation of **3-65**, we decided to elaborate an additional approach by postponing the introduction of the cyclopropane ring. We hoped that if a double bond was present at C(8)-C(10), the introduction of an additional unsaturation should be facilitated by an extended resonance (Scheme 71). Consequently, a mesylation of the allylic alcohol **3-127** and subsequent *N*-alkylation of the anion of **3-104**, provided the coupling product **3-129**. Following our previously developed strategy, **3-129** was

treated with NaHMDS in THF and quenched with TBSCl, which afforded TBS-enol ether **3-130**. When **3-130** was heated in *o*-dichlorobenzene for 30 min at 230 °C under microwave irradiation, the cyclization product **3-131** was obtained. Finally, TBS deprotection by TBAF in THF provided the desired ketone **3-132** in 61% yield.

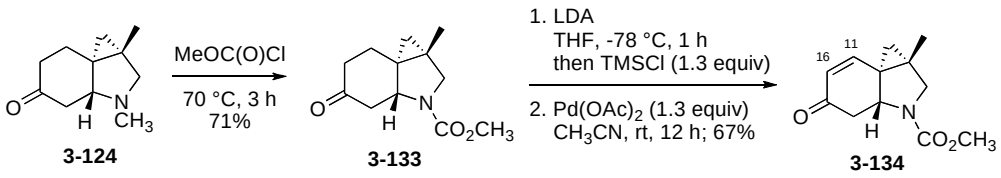


Scheme 71. Alternative approach: synthesis of **3-132**

Unfortunately, **3-132** proved to be very unstable, slowly decomposing at room temperature even under vacuum. This could partly be attributed to the reactive nature of **3-132** towards air and oxygen. Furthermore, exposing **3-132** to the same reaction conditions as described previously for the preparation of **3-65** (Scheme 70), yielded a complex mixture of products.

Having demonstrated the success in the preparation of **3-124**, but faced with a problematic dehydrogenation to the corresponding enone **3-65**, we investigated an additional strategy. We envisioned that a protection of the indolinone nitrogen atom as a carbamate could give the desired enone, without obvious side reactions. Accordingly, we decided to circumvent the problem by a dealkylative protection of the tertiary amine as a carbamate. Indeed, when **3-**

124 was heated at reflux for 3 h in methyl chloroformate, the corresponding carbamate **3-133** was isolated in 71% yield.[179] Further treatment of **3-133** under Saegusa-Ito oxidation conditions (LDA, TMSCl, -78 °C, then $Pd(OAc)_2$) served to cleanly introduce the desired double bond at the C(11)-C(16) position of **3-134**.

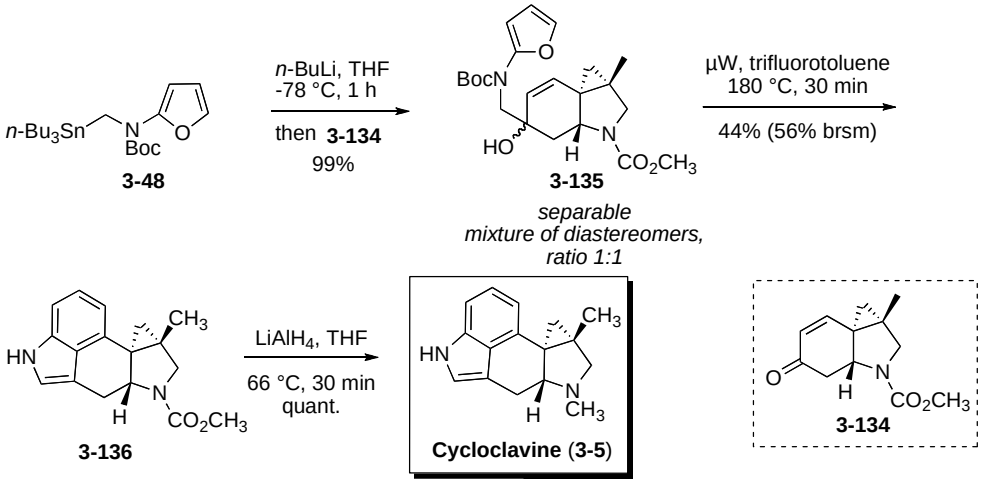


Scheme 72. Dealkylative protection of **3-124** and the formation of enone **3-134**

Treatment of enone **3-134** with the tin-lithium exchange product of stannane **3-48** led to the formation of two diastereomeric tertiary alcohols **3-135** in a 1:1 ratio (Scheme 73). Although these two diastereomeric alcohols can be separated by chromatography on SiO_2, we did not determine their relative configurations. Instead, we subjected both diastereomers separately to the microwave-promoted IMDAF cyclization in trifluorotoluene at 190 °C. Surprisingly, only one diastereomer (R_f = 0.35, 50% EtOAc/hexanes) exhibited the expected reactivity, furnishing indole **3-136** in 44% yield. Another diastereomer (R_f = 0.52, 50% EtOAc/hexanes) was unreactive under these conditions. Extended heating under microwave conditions at 210 °C led to a complete decomposition of the alcohol, with no detected product of cyclization. The reason for such a big difference in reactivities of the two stereoisomeric alcohols is probably due to the different steric hindrance of the C(8)-methyl group and the cyclopropyl methylene unit. The C(5)-hydrogen atom and the C(8)-methyl group at the β-face of **3-134** are not too close to the reacting C(11)-C(16) olefinic bond, favoring the furan approach from this side during the Diels-Alder reaction. On the other hand, fused cyclopropane ring probably blocks the α-face of **3-134**,

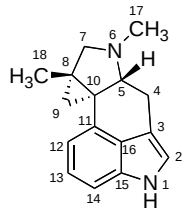
disfavoring the furan α-approach during the [4+2]-cycloaddition. However, this assumption requires more detailed analysis in order to determine the nature of the reacting isomer.

Finally, reduction of the carbamate with $LiAlH_4$ in THF provided (±)-cycloclavine (**3-5**) in quantitative yield. The spectroscopic data for **3-5** (Tables 4 and 5) were consistent with the previously reported data for the natural compound.



Scheme 73. Synthesis of (±)-cycloclavine (**3-5**)

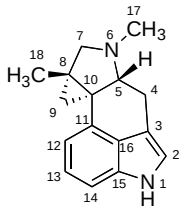
Table 4. ^{1}H NMR comparison of Santay's synthetic cycloclavine[180] and **3-5**



Cycloclavine (**3-5**)

atom #	Santay's synthetic cycloclavine ^{1}H NMR, $CDCl_3$, 300 MHz δ [ppm], multiplicity (J)	Our synthetic cycloclavine ^{1}H NMR, $CDCl_3$, 700 MHz δ [ppm], multiplicity (J)
1	7.95, s (8.4 Hz)	7.92, br s
2	6.87, d (2.0 Hz)	6.91, s
4	3.12, dd (13.2, 4.3 Hz) 2.58, ddd (13.2, 11.6, 2.0 Hz)	3.15, dd (14.0, 4.2 Hz) 2.61, t (12.6 Hz)
5	2.76, dd (11.6, 4.3 Hz)	2.79, dd (11.2, 3.5 Hz)
7	3.14, d (9.0 Hz) 2.38, d (9.0 Hz)	3.17, d (9.1 Hz) 2.42, d (8.4 Hz)
9	1.58, d (3.6 Hz) 0.46, d (3.6 Hz)	1.61, d (2.8 Hz) 0.46, d (3.5 Hz)
12	6.80, d (7.0 Hz)	6.84, d (7.0 Hz)
13; 14	7.15-7.00, m	7.15, d (8.4 Hz); 7.10, t (7.7 Hz)
17	2.34, s	2.37, s
18	1.68, s	1.70, s

Table 5. ^{13}C NMR comparison of Szantay's synthetic cycloclavine[180] and **3-5**



Cycoclavine (**3-5**)

atom #	Santay's synthetic cyclcoclavine ^{13}C NMR, $CDCl_3$, 75 MHz δ [ppm]	Our synthetic cycloclavine ^{13}C NMR, $CDCl_3$, 175 MHz δ [ppm]
2	118.3	118.1
3	113.5	113.2
4	25.1	24.9
5	69.9	69.9
7	65.8	65.6
8	29.9	34.3
9	24.2	24.2
10	28.0	27.8
11	135.6	135.4

12	110.6	110.3
13	123.1	122.9
14	108.1	107.9
15	133.8	133.5
16	129.0	128.7
17	40.1	39.9
18	16.7	16.5

3.2.3 Conclusions

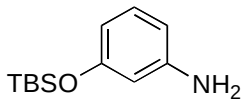
The Ergot alkaloids have represented important synthetic targets for decades and many creative approaches towards the total syntheses of these molecules have been described in literature. Herein, we have developed novel synthetic routes to the ergot alkaloid cycloclavine (**3-5**) as well as the unnatural 5-*epi*-cycloclavine (**3-99**). The total syntheses proceed in 14 steps and 1.2% overall yield for **3-5**, and in 17 steps and 2.3% overall yield for **3-99**. The main feature of both syntheses is a rapid construction of the indole moieties through the allylic alcohol-IMDAF reaction. Based on the previous research in our group and the results described in the Chapter 2 of this thesis, we were able to synthesize the indole portion of cycloclavine and 5-*epi*-cycloclavine by the application of the cascade IMDAF reaction in the late stages of these two

routes, showing the high tolerance of a usually sensitive cyclopropane unit. In the course of the synthesis of 5-*epi*-cycloclavine we observed the high preference of the tricyclic vinylogous amide **3-94** towards the α-hydrogen delivery during the Ra-Ni catalyzed hydrogenation, which ultimately led to the undesired stereochemistry at C(5). In a different approach we have developed a new strategy for the formation of the cycloclavine's indoline core through a novel and highly stereoselective intramolecular Diels-Alder reaction of methylenecyclopropane, which led to the formation of only one diastereomeric ketone **3-124** with the desired configuration at C(5). In this route, the introduction of a necessary unsaturation at C(11)-C(16) was highly regioselective, giving **3-134** as a sole isomer. Finally, the addition of lithiated **3-48** provided two stereoisomeric tertiary allylic alcohols, the only one of which underwent the IMDAF cyclization and the desired indole ring formation. The carbamate functional group, introduced to protect the sensitive tertiary amine, was converted to the required *N*-methyl amine by $LiAlH_4$ reduction.

3.3 EXPERIMENTAL PART

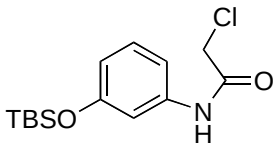
General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. Reactions carried out at -78 °C employed a dry ice/acetone bath. THF and Et_2O were dried by distillation over Na/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina filtration system. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F_{254} plates (250 μm layer thickness, particle size 0.040-0.055 mm, 230-240 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of

95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 M H_2SO_4 solution), or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1 % NaOH solution). Flash chromatography on SiO_2 was used to separate and purify the reaction crude mixtures. Microwave reactions were performed on a Biotage Initiator microwave reactor. ^1H and ^{13}C NMR were recorded on a Bruker Avance 300 instrument. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were run at 300, 400 or 500 MHz, and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, sept = septet, m = multiplet, br = broad, app = apparent), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained using a proton-decoupled pulse sequence with a d1 of 3 sec, and are tabulated by observed peak. LC/MS analyses were obtained from a Helwett Packard Series 1100 MSD. RP HPLC was obtained from Gilson Series 215, using C18 column, Bio-rad Laboratoris, 250 x 4.6 mm. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Infrared spectra were measured on a Nicolet AVATAR 360 FT-IR E.S.P. spectrometer (KBr or neat) or Smiths Detection IdentifyIR FT-IR spectrometer (ATR).

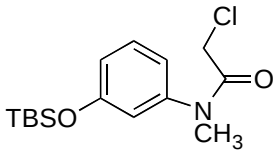


3-(*tert*-Butyldimethylsilyloxy)benzenamine (3-71).[181] To a solution of imidazole (4.00 g, 58.6 mmol) and 3-aminophenol (4.00 g, 36.6 mmol) in THF (100 mL) was added *tert*-butyldimethylsilyl chloride (7.18 g, 47.6 mmol). The reaction mixture was rapidly stirred at room temperature overnight, poured into water (150 mL), extracted with ether (3 x 50 mL),

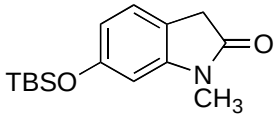
washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (30% EtOAc/hexane) gave **3-71** (8.2 g, 100%) as a colorless oil: IR (ATR) 3466, 3369, 2926, 2855, 1591, 1489, 1191, 976, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (app t, 1 H, *J* = 8.1 Hz), 6.32 (app dt, 2 H, *J* = 8.1, 1.8 Hz), 6.24 (app t, 1 H, *J* = 2.4 Hz), 3.63 (br s, 2 H), 1.05 (s, 9 H), 0.26 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 147.6, 129.8, 110.2, 108.4, 106.9, 25.6, 18.0, -4.5; MS (EI) *m/z* 223 ($M^{\bullet+}$, 31), 166 (100), 86 (33), 84 (52); HRMS (EI) *m/z* calcd for $C_{12}H_{21}NOSi$ 223.1392, found 223.1386.



***N*-(3-(*tert*-Butyldimethylsilyloxy)phenyl)-2-chloroacetamide (3-74).** To a mixture of **3-71** (1.00 g, 4.50 mmol) and potassium carbonate (0.74 g, 5.4 mmol) in CH_2Cl_2 (7 mL) was added dropwise chloroacetyl chloride (0.61 g, 5.4 mmol). The reaction mixture was heated to 40 °C for 4 h, cooled to room temperature, poured into ice water (30 mL), and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was crystallized from ether/hexane to provide **3-71** (1.04 g, 77%) as a white solid: Mp 71.8-72.5 °C; IR (ATR) 3286, 2928, 1673, 1554, 1224, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (br s, 1 H), 7.24-7.18 (m, 2 H), 7.06 (d, 1 H, *J* = 7.8 Hz), 6.67 (dd, 1 H, *J* = 7.8, 1.5 Hz), 4.18 (s, 2 H), 1.00 (s, 9 H), 0.23 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 156.3, 137.7, 129.7, 116.9, 112.8, 112.0, 42.9, 25.6, 18.2, -4.5; MS (EI) *m/z* 299 ($M^{\bullet+}$, 73), 242 (75), 84 (100), 75 (68); HRMS (EI) *m/z* calcd for $C_{14}H_{22}ClNO_2Si$ 299.1108, found 299.1112.

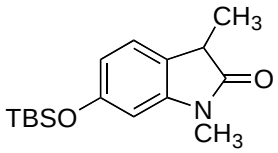


***N*-(3-(*tert*-Butyldimethylsilyloxy)phenyl)-2-chloro-*N*-methylacetamide (3-70).** To a solution of **3-74** (0.70 g, 2.3 mmol) in CH_2Cl_2 (21 mL) was added Me_2SO_4 (1.00 mL, 10.0 mmol), followed by benzyltriethylammonium chloride (0.22 g, 0.90 mmol). A solution of NaOH (1.7 mL of 50% in water) was added dropwise over 10 min. The reaction mixture was stirred at room temperature overnight, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (20% EtOAc/hexane) furnished **3-70** (0.69 g, 95%) as a white solid: Mp 40.0-42.1 °C; IR (ATR) 2950, 1679, 1584, 1483, 1221, 908, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, 1 H, *J* = 8.1 Hz), 6.84 (app dt, 2 H, *J* = 7.8, 1.2 Hz), 6.71 (t, 1 H, *J* = 2.1 Hz), 3.87 (s, 2 H), 3.28 (s, 3 H), 0.98 (s, 9 H), 0.21 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 156.9, 143.6, 130.6, 120.3, 119.8, 118.8, 41.4, 37.8, 25.5, 18.1, -4.5; MS (EI) *m/z* 313 ($M^{\bullet+}$, 10), 199 (80), 150 (57), 122 (100), 65 (75); HRMS (EI) *m/z* calcd for $C_{15}H_{24}NO_2SiCl$ 313.1265, found 313.1273.



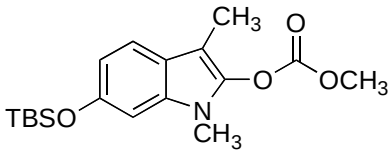
6-(*tert*-Butyldimethylsilyloxy)-1-methylindolin-2-one (3-69). To a flame-dried flask was added palladium acetate (1.4 mg, 0.0062 mmol), followed by 2-(di-*tert*-butylphosphino)biphenyl (**3-77**) (1.3 mg, 0.0044 mmol) and **3-70** (100.0 mg, 0.3150 mmol). The flask was evacuated and refilled with nitrogen three times. Triethylamine (65 μL, 4.7 mmol) was added, followed by toluene (0.3 mL). The mixture was placed into a preheated oil bath (80 °C), stirred for 4 h, quenched with

water (10 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water (25 mL), brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (20% EtOAc/hexane) gave **3-69** (67.6 mg, 77%) as a white solid: Mp 70.2-72.3 °C; IR (ATR) 2926, 1713, 1700, 1368, 970, 837, 798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, 1 H, *J* = 8.1 Hz), 6.49 (dd, 1 H, *J* = 8.1, 2.1 Hz), 6.34 (d, 1 H, *J* = 2.4 Hz), 3.46 (s, 1 H), 3.18 (s, 3 H), 1.01 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 155.9, 146.3, 124.7, 116.8, 113.1, 101.4, 35.3, 26.2, 25.7, 18.2, -4.4; MS (EI) *m/z* 277 ($M^{\bullet+}$, 37), 220 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{23}NO_2Si$ 277.1498, found 277.1492.

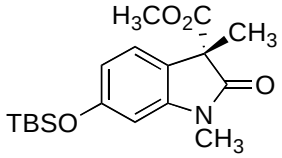


6-(*tert*-Butyldimethylsilyloxy)-1,3-dimethylindolin-2-one (3-68). To a solution of **3-69** (2.60 g, 9.37 mmol) in THF (20 mL), cooled to -78 °C, was added a solution of LiHMDS (1.72 g, 10.3 mmol) in THF (10 mL), followed by HMPA (5.0 mL). The mixture was stirred at -78 °C for 1 h. Methyl iodide (8.70 mL, 140 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 3 h, quenched with saturated aqueous NH_4Cl and extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (5% EtOAc/hexanes) provided **3-68** as a colorless liquid (2.64 g, 96%): IR (ATR) 2952, 2928, 1713, 1614, 1373, 1249, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, 1 H, *J* = 7.8 Hz), 6.49 (dd, 1 H, *J* = 8.1, 2.1 Hz), 6.32 (d, 1 H, *J* = 2.1 Hz), 3.35 (q, 1 H, *J* = 7.2 Hz); 3.15 (s, 1 H), 1.42 (d, 3 H, *J* = 7.5 Hz), 0.99 (s, 9 H), 0.21 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 155.9, 145.1, 123.8, 123.1, 113.0, 101.2,

40.1, 26.1, 25.7, 18.2, 15.6, -4.4; MS (EI) *m/z* 291 ($M^{\bullet+}$, 65), 290 (90), 234 (100), 73 (49); HRMS (EI) *m/z* calcd for $C_{16}H_{25}NO_2Si$ 291.1655, found 291.1647.

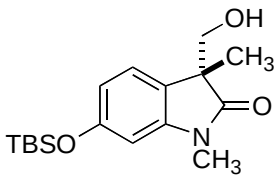


6-(*tert*-Butyldimethylsilyloxy)-1,3-dimethyl-1*H*-indol-2-yl methyl carbonate (3-78). To a solution of KHMDS (41.0 mg, 0.206 mmol) in THF (0.25 mL) at -78 °C was added a solution of **3-68** (50.0 mg, 0.171 mmol) in THF (0.35 mL), stirred at -78 °C for 1 h, and then transferred to a solution of methyl chloroformate (20.0 mg, 0.206 mmol) in THF (0.4 mL) at -78 °C. This solution was allowed to warm to room temperature, quenched with water, extracted with EtOAc (3 x 5 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% EtOAc/hexanes) gave **3-78** (39.1 mg, 65%) as a colorless oil: IR (ATR) 2952, 2934, 1772, 1232, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 1 H, J = 8.8 Hz), 6.71 (s, 1 H), 6.69 (d, 1 H, J = 6.0 Hz), 3.98 (s, 3 H), 3.51 (s, 3 H), 2.16 (s, 3 H), 1.03 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 151.5, 138.3, 133.3, 121.1, 119.2, 113.6, 99.9, 96.1, 56.1, 28.2, 25.8, 18.2, 7.2, -4.4; MS (EI) *m/z* 350 ($M^{\bullet+}$, 49), 349 (99), 306 (52), 290 (100).



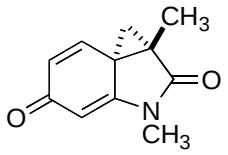
Methyl 6-(*tert*-butyldimethylsilyloxy)-1,3-dimethyl-2-oxoindoline-3-carboxylate (3-67). To a solution of **3-78** (34.4 mg, 0.0984 mmol) in *t*-amyl alcohol (1 mL) was added TADMAP (4.3 mg, 0.0098 mmol), stirred at room temperature for 36 h, and quenched with methyl iodide (1

mL). The solution was concentrated under reduced pressure, and purified by chromatography on SiO_2 (10% EtOAc/hexanes) to obtain **3-67** (24.7 mg, 75%) as a colorless oil: IR (ATR) 2950, 2934, 1718, 1612, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 1 H, *J* = 7.8 Hz), 6.50 (dd, 1 H, *J* = 7.8, 1.8 Hz), 6.36 (d, 1 H, *J* = 2.1 Hz), 3.66 (s, 3 H), 3.22 (s, 3 H), 1.64 (s, 3 H), 1.00 (s, 9 H), 0.23 (s, 3 H), 0.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 170.6, 156.8, 144.7, 123.6, 122.4, 113.5, 101.6, 54.4, 52.9, 26.5, 25.6, 20.3, 18.1, -4.4 (2C); MS (TOF ESI) *m/z* 350 (35), 349 (M^+, 31), 290 (100).

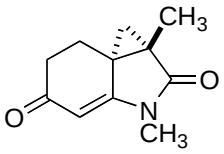


6-(*tert*-Butyldimethylsilyloxy)-3-(hydroxymethyl)-1,3-dimethylindolin-2-one (3-66). A solution of LiHMDS (52.0 mg, 0.311 mmol) in THF (0.6 mL) was cooled to -78 °C, treated with a solution of **3-68** (30.0 mg, 0.103 mmol) in THF (0.2 mL), and stirred for 1 h. After the addition of a suspension of 1*H*-benzotriazole-1-methanol (**3-81**) (30.0 mg, 0.201 mmol) in THF (1 mL), the reaction mixture was stirred for 2 h, quenched with water, warmed up to room temperature, and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with aqueous NaOH (10 mL, 1 M solution), brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (30 to 50% hexane/ EtOAc) afforded **3-66** (30.1 mg, 91%) as a white solid: Mp 109.3-110.0 °C; IR (ATR) 3423, 2924, 2881, 1687, 1610, 1381, 1247, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, 1 H, *J* = 7.8 Hz), 6.52 (dd, 1 H, *J* = 8.1, 2.1 Hz), 6.38 (d, 1 H, *J* = 2.1 Hz), 3.80 (d, 1 H, *J* = 10.8 Hz), 3.69 (d, 1 H, *J* = 10.8 Hz),3.18 (s, 3 H), 1.38 (s, 3 H), 1.00 (s, 9 H), 0.23 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 156.3, 144.7, 123.9, 123.2, 113.3, 101.5, 67.7, 49.4, 26.2, 25.6, 19.1, 18.1, -4.4. MS (ESI) *m/z* 344 ($[M+Na]^+$,

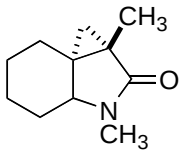
100), 304 (90), 290 (48); HRMS (ESI) *m/z* calcd for $C_{17}H_{27}NO_3SiNa$ ([M+Na]$^+$) 344.1658, found 344.1652.



(1a*S,7a*S**)-1a,3-Dimethyl-1*H*-cyclopropa[*c*]indole-2,5(1a*H*,3*H*)-dione (3-82)**. To a solution of **3-66** (200.0 mg, 0.6221 mmol) in CH_2Cl_2 (5.5 mL) was added triethylamine (0.26 mL, 1.8 mmol) followed by methanesulfonyl chloride (96 μL, 1.2 mmol). The mixture reaction was stirred at room temperature for 30 min, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure to provide crude mesylate, which was used in the next step without further purification. A solution of crude mesylate (301.1 mg, 0.7535 mmol) in THF (50 mL) was treated with a solution of TBAF (0.68 mL, 1 M solution in THF, 0.68 mmol), stirred at room temperature for 1 h, and the reaction mixture was filtered through a pad of SiO_2 (pretreated with TEA). The filtrate was concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% acetone/chloroform) afforded **3-66** (79.1 mg, 83%) as a white crystalline solid: Mp 107.8-108.7 °C; IR (ATR) 3286, 2933, 1733, 1632, 1569, 1364, 1064, 853 cm^{-1}; ^{1}H NMR (300 MHz, MeOD) δ 6.92 (d, 1 H, *J* = 9.9 Hz), 6.38 (dd, 1 H, *J* = 9.9, 1.5 Hz), 5.83 (d, 1 H, *J* = 1.5 Hz), 2.98 (s, 3 H), 2.09 (d, 1 H, *J* = 3.9 Hz), 1.96 (d, 1 H, *J* = 3.9 Hz), 1.57 (s, 3 H); ^{13}C NMR (75 MHz, MeOD) δ 189.4, 177.5, 165.4, 143.7, 131.7, 103.6, 40.2, 38.8, 35.9, 26.6, 11.3; MS (EI) *m/z* 189 ($M^{\bullet+}$, 100), 161 (47), 132 (56), 63 (77); HRMS (EI) *m/z* calcd for $C_{11}H_{11}NO_2$ 189.0790, found 189.0789.

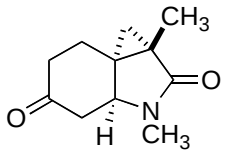


(1a*S,7a*R**)-1a,3-Dimethyl-6,7-dihydro-1*H*-cyclopropa[*c*]indole-2,5(1a*H*,3*H*)-dione (3-84)**. To a solution of Stryker's reagent (156.0 mg, 0.07928 mmol) in toluene (21 mL) was added triphenylsilane (0.3 mL, 2.37 mmol), followed by **3-82** (300.0 mg, 1.585 mmol). The reaction mixture was stirred for 2 h at room temperature, filtered through Celite, and concentrated *in vacuo*. Purification by chromatography on SiO_2 (2% to 30% to 50% EtOAc/hexanes) gave vinylogous amide **3-84** (323.6 mg, 100%) as a white solid: Mp 102-104.3 °C; IR (ATR) 2933, 1720, 1591, 1463, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (s, 1 H), 2.92 (s, 3 H), 2.66-2.61 (m, 2 H), 2.39-2.28 (m, 1 H), 1.76-1.69 (m, 1 H), 1.41 (s, 3 H), 1.32 (d, 1 H, J = 4.2 Hz), 1.70 (d, 1 H, J = 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 177.0, 164.3, 101.3, 36.8, 30.0, 29.8, 29.1, 26.2, 24.4, 10.3; HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0941.



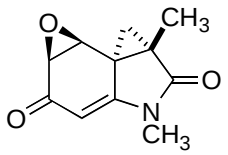
(1a*S,7a*R**)-1a,3-Dimethylhexahydro-1*H*-cyclopropa[*c*]indol-2(1a*H*)-one (3-87)**. To a solution of **3-84** (100.0 mg, 0.5229 mmol) in MeOH (5 mL) at room temperature was added a solution of HCl in Et_2O (5 ml, 2 M HCl in Et_2O), followed by sodium cyanoborohydride (150.0 mg, 2.615), and stirred at room temperature for 2 h. The reaction mixture was quenched with water, extracted with Et_2O (5 x 20 mL), combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (50% EtOAc/hexanes) gave **3-87** (69.3 mg, 74%) as a colorless oil: IR (ATR) 2934, 2928, 2854, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.11 (dd, 1 H, J = 11.4, 3.0), 2.66 (s, 3 H), 2.00-1.88 (m, 3

H), 1.77 (dt, 1 H, *J* = 12.3, 2.7), 1.61 (s, 1 H), 1.56-1.41 (m, 3 H), 1.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 62.8, 33.2, 29.8, 29.1, 28.0, 26.8, 26.2, 24.9, 23.1, 10.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{18}NO$ ($[M+H]^+$) 180.1388, found 180.1350.

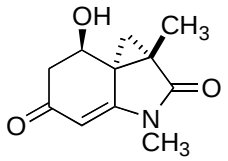


(1a*S,3a*S**,7a*R**)-1a,3-Dimethyltetrahydro-1*H*-cyclopropa[*c*]indole-2,5(1a*H*,3*H*)-dione (3-89).** To a solution of **3-84** (300.0 mg, 1.569 mmol) in CH_3OH (15 mL) was added slurry of Raney-Ni (600.0 mg of 50% slurry of Raney-Ni in water, rinsed with CH_3OH (3 x 10 mL)), and subjected to hydrogenation (70 bar) at room temperature for 2.5 h. The reaction was filtered through Celite, washed with EtOAc, and concentrated *in vacuo*. Purification on SiO_2 (50% EtOAc/hexanes) gave alcohol **3-88** (280.0 mg, 78%) as an inseparable mixture of diastereomers in a form of a colorless oil, which was used in the next step without further characterization. To a solution of oxalyl chloride (88 μL, 1.0 mmol) in CH_2Cl_2 (1.5 mL) at -78 ºC was added DMSO (110 μL, 1.54 mmol) in CH_2Cl_2 (0.4 mL), and stirred for 5 min at -78 ºC. To this solution was added a solution of **3-88** (100.0 mg, 0.512 mmol) in CH_2Cl_2 (0.4 mL), and stirred for 1 h. To this solution was added Et_3N (285 μL, 2.05 mmol), slowly warmed to room temperature, quenched with saturated aqueous of $NaHCO_3$, and extracted with CH_2Cl_2 (3 x 10 mL). Combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on SiO_2 (5% to 10% CH_3OH/CH_2Cl_2) afforded **3-89** (76.0 mg, 79%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (t, 1 H, *J* = 6.6 Hz), 2.80 (dd, 1 H, *J* = 15.0, 6.3), 2.68 (s, 3 H), 2.52-2.23 (m, 4 H), 1.81-1.75 (m, 1 H), 1.30 (s, 3 H), 0.89 (d, 1 H, *J* = 4.5

Hz), 0.82 (d, 1 H, J = 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 175.8, 60.3, 43.6, 38.8, 29.0, 27.3, 26.8, 25.4, 23.8, 11.5; HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO_2$ 193.1103, found 193.1099.

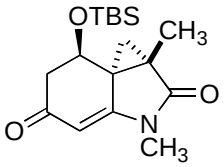


(4a*S,5a*S**,5b*S**,6a*S**)-2,6a-Dimethyl-4a,5a,6,6a-tetrahydro-1*H*-cyclopropa[*c*]oxireno[2,3-*e*]indole-1,4(2*H*)-dione (3-92).** To a solution of dienone **3-82** (25.0 mg, 0.132 mmol) in THF (0.5 mL) at 0 °C was added sequentially a solution of TBHP (5-6 M in decane, 26.0 μL, 0.132 mmol) and Triton-B (40% solution in MeOH, 3 drops). The reaction mixture was warmed to room temperature and stirred for 3 days, quenched with saturated aqueous Na_2SO_3, and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% acetone/chloroform) gave epoxide **3-92** (15.0 mg, 55%) as a colorless oil: IR (ATR) 1733, 1601, 1591, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (d, 1 H, J = 1.8 Hz), 3.61 (dd, 1 H, J = 3.9, 1.5 Hz), 3.42 (d, 1 H, J = 3.9 Hz), 2.93 (s, 3 H), 1.67 (s, 3 H), 1.61 (d, 1 H, J = 4.8 Hz), 1.39 (d, 1 H, J = 4.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 176.6, 174.9, 158.6, 97.7, 53.6, 50.9, 30.8, 30.4, 26.3, 11.3; MS (ESI) *m/z* 205 (42), 176 (33), 86 (87), 84 (100); HRMS (ESI) *m/z* calcd for $C_{11}H_{11}NO_3$ 205.0739, found 205.0728.



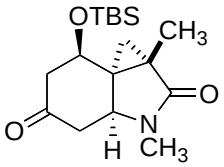
(1a*S,7*R**,7a*S**)-7-Hydroxy-1a,3-dimethyl-6,7-dihydro─1*H*─cyclopropa[*c*]indole─2,5(1a*H*,3*H*)-dione (3-93).** Sodium borohydride (55.3 mg, 1.46 mmol) was slowly added, under nitrogen

atmosphere, to a suspension of diphenyl diselenide (228.2 mg, 0.7311 mmol) in EtOH (4 mL) at room temperature. After a vigorous evolution of hydrogen had ceased and the $NaBH_4$ was consumed, the faint yellow solution of $Na[PhSeB(OEt)_3]$ was cooled to 0 °C, and glacial acetic acid (14 μL, 0.24 mmol) was added. The resulting mixture was stirred for 5 min, and then treated with a solution of epoxyketone **3-92** (100.0 mg, 0.4873 mmol) in EtOH (3 mL). The mixture was stirred at 0 °C for 75 min, then diluted with EtOAc (10 mL), washed with half-saturated brine (2 x 10 mL), extracted with EtOAc, and the combined organic layers were concentrated *in vacuo*. Purification by chromatography on SiO_2 (5 to 10% acetone/chloroform) gave alcohol **3-93** (84 mg, 85%) as a white crystalline solid: Mp 161.2-162.4 °C; IR (ATR) 3420, 1731, 1591, 1441, 1210, 1010 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 5.46 (s, 1 H), 4.31 (br s, 1 H), 4.25 (br s, 1 H), 2.92 (s, 3 H), 2.78 (dd, 1 H, J = 9.9, 1.5 Hz), 2.61 (d, 1 H, J = 10.2 Hz), 1.96 (s, 1 H), 1.48 (app s, 4 H), 1.36 (d, 1 H, J = 3.6 Hz); ^{13}C NMR (acetone-d_6, 125 MHz) δ 195.3, 177.5, 162.5, 101.7, 69.3, 61.0, 47.3, 36.3, 26.7, 21.3, 15.0, 11.5; MS (ESI) *m/z* 208 ($[M+H]^+$, 12), 207 (87), 192 (58), 164 (41), 163 (65), 134 (43); HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0885.



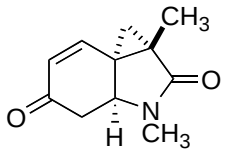
(1a*S,7*R**,7a*S**)-7-((*tert*-Butyldimethylsilyl)oxy)-1a,3-dimethyl-6,7-dihydro-1*H*-cyclopropa[*c*]indole-2,5(1a*H*,3*H*)-dione (3-94).** A solution of *tert*-butyldimethylsilyl chloride (107.6 mg, 0.7139 mmol), alcohol **3-93** (74.0 mg, 0.357 mmol) and imidazole (97.2 mg, 1.42 mmol) in DMF (1.5 mL) was stirred for 5 h, diluted with water, extracted with EtOAc (5 x 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (50%

EtOAc/hexane) gave **3-94** (76.0 mg, 66%) as a white solid: IR (ATR): 2928, 2853, 1728, 1610, 1077, 1075 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 5.48 (s, 1 H), 4.41 (t, 1 H, *J* = 3.0 Hz), 2.94 (s, 3 H), 2.82 (dd, 1 H, *J* = 16.2, 2.4 Hz), 2.80 (br s, 1 H), 2.63 (dd, 1 H, *J* = 16.2, 2.4 Hz), 1.52 (d, 1 H, *J* = 4.2 Hz), 1.46 (s, 3 H), 1.35 (d, 1 H, *J* = 4.2 Hz), 0.82 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 194.3, 176.9, 161.9, 101.0, 70.7, 47.3, 36.5, 30.2, 28.9, 26.4, 26.1, 18.4, 11.4, -4.0, -4.5; MS (EI) *m/z* 322 (18), 306 (32), 266 (50), 264 (76), 265 (88), 222 (86%), 148 (95), 75 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{27}NO_3Si$ 321.1760, found 321.1751.

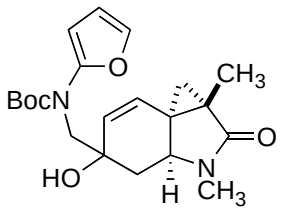


(1a*S,3a*S**,7*R**,7a*S**)-7-((*tert*-Butyldimethylsilyl)oxy)-1a,3-dimethyltetrahydro-1*H*-cyclopropa[*c*]indole-2,5(1a*H*,3*H*)-dione (3-95).** To a suspension of Raney-Ni (50% slurry in water, 45 mg, rinsed with MeOH (2 x 3 mL)) in MeOH (0.8 mL), was added TBS-protected alcohol **3-95** (40.0 mg, 0.123 mmol) in MeOH (1.0 mL). The reaction mixture was subjected to hydrogenation for 8 h (room temperature, 80 bar), filtered through Celite, concentrated *in vacuo*, and used crude in the next step without further purification. To a solution of the intermediate alcohol in CH_2Cl_2 (3.0 mL) was added PCC (45.0 mg, 0.209 mmol). The mixture was stirred at room temperature for 14 h, filtered through Celite, concentrated *in vacuo* and purified by chromatography on SiO_2 (5% acetone/chloroform) to obtain ketone **3-95** (39.8 mg, 100%) as a colorless liquid: IR (ATR) 2928, 2950, 1718, 1675, 1098, 1055, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.34 (dd, 1 H, *J* = 5.7, 3.3 Hz), 3.62 (dd, 1 H, *J* = 9.0, 5.4 Hz), 2.82-2.52 (m, 4 H), 2.74 (s, 3 H), 1.46 (s, 3 H), 1.19 (d, 1 H, *J* = 3.9 Hz), 0.91 (d, 1 H, *J* = 4.2 Hz), 0.85 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 206.6, 175.8, 68.4, 58.5, 48.5, 42.5, 33.6, 29.8, 27.6, 25.7, 24.5, 17.8, 13.5, -4.2, -4.9; MS (ESI) *m/z* 315 (51), 314 (100), 146 (71), 115 (44), 77 (34); HRMS (ESI) *m/z* calcd for $C_{17}H_{29}NO_3SiNa$ ($[M+Na]^+$) 346.1814, found 346.1831.

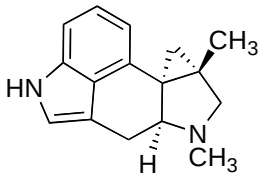


(1a*S,3a*S**,7a*S**)-1a,3-Dimethyl-3a,4-dihydro-1*H*-cyclopropa[*c*]indole-2,5(1a*H*,3*H*)-dione (3-65).** A solution of TBAF (1 M in THF, 0.40 mL, 0.40 mmol) was added to a solution of ketone **3-95** (85.0 mg, 0.263 mmol) in THF (2.5 mL) at room temperature, stirred for 2 h, diluted with water, extracted with EtOAc (3 x 5 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (20% acetone/chloroform) gave enone **3-65** (31.1 mg, 62%) as an off-white solid: Mp 117.2-119.0 °C; IR (ATR) 3286, 2917, 1666, 1606, 1401, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (d, 1 H, *J* = 6.0 Hz), 6.19 (d, 1 H, *J* = 6.0 Hz), 3.86 (dd, 1 H, *J* = 6.9, 3.3 Hz), 3.02 (dd, 1 H, *J* = 9.0, 3.3), 2.79 (s, 3 H), 2.27 (dd, 1 H, *J* = 9.3, 7.2 Hz), 1.45 (s, 3 H), 1.33 (d, 1 H, *J* = 3.0 Hz), 1.30 (d, 1 H, *J* = 2.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 173.9, 148.1, 130.2, 58.3, 43.1, 35.0, 30.4, 28.6, 27.3, 12.6; MS (EI) *m/z* 191($M^{\bullet+}$, 23), 148 (51), 91 (100), 77 (82); HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0947.



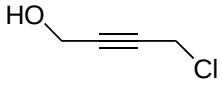
***tert*-Butyl furan-2-yl(((1a*S**,3a*S**,7a*S**)-5-hydroxy-1a,3-dimethyl-2-oxo─1a,2,3,3a,4,5-hexahydro-1*H*-cyclopropa[*c*]indol-5-yl)methyl)carbamate (3-97).** To a solution of stannane **3-48**

(85.7 mg, 0.176 mmol) in THF (1.0 mL) at -78 °C was slowly added a solution of *n*-BuLi (1.6 M in hexane, 110 μL, 0.176 mmol). The reaction mixture was stirred at this temperature for 1 h, than treated with a solution of enone **3-65** (67.4 mg, 0.352 mmol) in THF (1.0 mL) over 10 min, stirred at -78 °C for 2 h, quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (20 to 50% acetone/chloroform) gave recovered enone **3-65** (13.7 mg) and the desired alcohol **3-97** (43.6 mg, 63%, 82% brsm) in the form of yellow oil, as a single diastereomer: IR (ATR) 3362, 2972, 2926, 1668, 1364, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 1 H, *J* = 1.5 Hz), 6.37 (dd, 1 H, *J* = 3.3, 2.1 Hz), 6.03 (d, 1 H, *J* = 3.0 Hz), 5.78 (dd, 1 H, *J* = 9.9, 1.2 Hz), 5.28 (d, 1 H, *J* = 10.2 Hz), 3.84 (d, 1 H, *J* = 15.0 Hz), 3.74 (s, 1 H), 3.71 (d, 1 H, *J* = 15.0 Hz), 3.37 (dd, 1 H, *J* = 12.0, 4.2 Hz), 2.66 (s, 3 H), 2.59 (dd, 1 H, *J* = 12.6, 3.0 Hz), 1.44 (s, 9 H), 1.29 (s, 3 H), 1.00 (d, 1 H, *J* = 4.8 Hz), 0.96 (d, 1 H, *J* = 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 149.2, 138.2, 134.0, 127.7, 111.3, 101.6, 82.5, 72.8, 57.7, 56.0, 38.1, 32.3, 29.5, 28.0, 27.1, 26.2, 12.2; MS (EI) *m/z* 388 ($M^{\bullet+}$, 29), 288 (45), 270 (46), 193 (91), 192 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{28}N_2O_5$ 388.1998, found 388.1990.



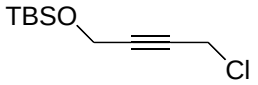
***tert*-Butyl furan-2-yl(((1a*S**,3a*S**,7a*S**)-5-hydroxy-1a,3-dimethyl-2-oxo─1a,2,3,3a,4,5-hexahydro-1*H*-cyclopropa[*c*]indol-5-yl)methyl)carbamate (5-*epi*-Cycloclavine, 3-99).** A solution of alcohol **3-97** (23.0 mg, 0.0592 mmol) in *o*-dichlorobenzene (1.5 mL) was heated in the microwave reactor (190 °C, 30 min), then poured onto a pad of SiO_2, eluted with chloroform (to remove the solvent), and then with 50% acetone/chloroform to obtain crude **3-98** (8.9 mg, 60%),

which was used in the next step without further characterization. To a suspension of $LiAlH_4$ (12.0 mg, 0.320 mmol) in THF (0.2 mL) was added a suspension of intermediate **3-98** (8.9 mg, 0.035 mmol) in THF (0.2 mL). The reaction mixture was heated at 66 °C for 2 h, treated with water (12 μL), 15% aqueous NaOH (12 μL), and then water (36 μL), extracted with EtOAc (3 x 4 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (20 to 50% acetone/chloroform) gave 5-*epi*-cycloclavine **3-99** (6.4 mg, 77%) as a white solid: Mp 148-150 °C; IR (ATR) 3286, 3176, 2928, 2915, 1599, 1437, 1014 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) 8.04 (br s, 1 H), 7.15-7.10 (m, 2 H), 6.92 (dd, 1 H, *J* = 1.8 Hz), 6.58 (dd, 1 H, *J* = 6.6, 0.6 Hz), 3.47 (dd, 1 H, *J* = 10.8, 6.0 Hz), 3.01 (dd, 1 H, *J* = 14.4, 6.0 Hz), 2.98 (d, 1 H, *J* = 8.4 Hz), 2.66 (d, 1 H, *J* = 9.0 Hz), 2.59 (ddd, 1 H, *J* = 16.2, 11.4, 1.8 Hz), 2.48 (s, 3 H), 1.57 (d, 1 H, *J* = 3.0 Hz), 1.12 (s, 3 H), 1.11 (d, 1 H, *J* = 4.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.3, 130.5, 127.4, 122.9, 118.1, 112.9, 111.7, 107.6, 62.9, 59.8, 35.8, 35.4, 33.2, 20.1, 18.6, 14.9; MS (AP) *m/z* 239 ($[M+H]^+$, 43), 208 (100); HRMS (AP) *m/z* calcd for $C_{16}H_{19}N_2$ ($[M+H]^+$) 239.1548, found 239.1540.

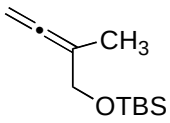


4-Chlorobut-2-yn-1-ol (3-108). To a solution of propargyl chloride (4.85 mL, 65.8 mmol) in diethyl ether (125 mL) at -78 °C was added *n*-BuLi (1.6 M solution in hexane, 47 mL, 65.8 mmol) dropwise. The reaction mixture was stirred at -78 °C for 2 hours, and then transferred to a solution of paraformaldehyde (2.08 g, 65.8 mmol) in diethyl ether (14 mL) via cannula at 0°C. The mixture was warmed up to room temperature, stirred for 14 hours, quenched with water (50 mL), and extracted with diethyl ether (4 x 150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, which gave **3-108**

(5.32 g, 76%) as a brownish oil, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) 4.34-4.25 (m, 2 H), 4.16 (dt, 2 H, J = 12.6, 2.4 Hz), 1.90 (t, 1 H, J = 5.7 Hz).

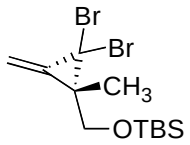


***tert*-Butyl(4-chlorobut-2-ynyloxy)dimethylsilane (3-109).** A solution of **3-108** (5.32 g, 50.9 mmol), TBSCl (9.98 g, 66.2 mmol), and imidazole (5.2 g, 76 mmol) in DMF (100 mL) was stirred at room temperature for 12 h, poured into water (100 mL), and extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (10% EtOAc/hexanes) gave the desired chloride **3-109** (10.70 g, 96%) as a colorless liquid: IR (ATR) 2928, 1950, 1260, 1079, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (app t, 2 H, J = 2.1 Hz), 4.17 (app t, 2 H, J = 2.1 Hz), 0.91 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.2, 79.4, 51.7, 30.5, 25.8, 18.3, -5.2; MS (EI) *m/z* 218 ($M^{\bullet+}$, 12), 161 (36), 125 (35), 95 (39), 93 (100), 84 (45); HRMS (EI) *m/z* calcd for $C_{10}H_{19}ClOSi$ 218.0894, found 218.0888.

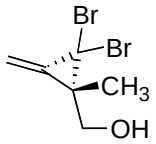


***tert*-Butyldimethyl(2-methylbuta-2,3-dienyloxy)silane (3-105).** A solution of methyl magnesium bromide (3M solution in ether, 11.5 mL, 34.3 mmol) in ether (30 mL) was cooled to -30 °C, treated with cuprous iodide (2.60 g, 13.7 mmol), and stirred at -30 °C for 1 h. To the black colored mixture was added **3-109** (3.0 g, 13.7 mmol) dropwise over 30 min. The reaction mixture was stirred at -30 °C for 1 h, slowly warmed to room temperature, quenched with saturated aqueous NH_4Cl (30 mL), and extracted with diethyl ether (4 x 75 mL). The combined

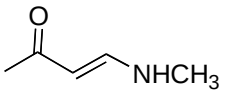
organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (5% EtOAc/hexanes) gave **3-105 (**1.4 g, 55%) as a colorless oil: IR (ATR) 2926, 1962, 1252, 1072, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67-4.64 (m, 2 H), 4.12-4.10 (m, 2 H), 1.71-1.69 (m, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 98.7, 74.8, 65.1, 25.9, 18.4, 15.2, -5.3.



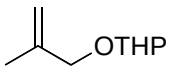
***tert*-Butyl((2,2-dibromo-1-methyl-3-methylenecyclopropyl)methoxy)dimethylsilane (3-103).** To a solution of **3-105** (1.40 g, 7.06 mmol) in pentane (6 mL) was added dropwise bromoform (1.78 g, 7.06 mmol). The reaction mixture was cooled to -20 °C, stirred at this temperature for 3 h, during which time potassium *tert*-butoxide was added portion wise (0.91 g, 5.80 mmol), stirred for additional 2 h, quenched with water, and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on SiO_2 (hexanes) gave **3-103** (1.02 g, 38%) as a colorless oil: IR (ATR) 2926, 1461, 1250, 1090, 833, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (s, 1 H), 5.50 (d, 1 H, J = 0.6 Hz), 3.79, 3.73 (AB, 2 H, J = 18.3 Hz), 1.51 (s, 3 H), 0.93 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 109.0, 68.9, 36.9, 30.6, 25.8, 20.4, 18.3, -5.3.



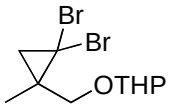
((2,2-Dibromo-1-methyl-3-methylenecyclopropyl)methanol (3-110). To a solution of **3-103** (1.00 g, 2.70 mmol) in THF (8 mL) was added a solution of TBAF (1M solution in THF, 8.1 mL 8.1 mmol). The reaction mixture was stirred at room temperature for 10 min, quenched with water (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on SiO_2 (30% EtOAc/hexanes) gave **3-110** (0.61 g, 87%) as an colorless oil: IR (ATR) 3285, 2925, 1416, 1017, 1003, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (bs, 1 H), 5.55 (app d, 1 H, J = 0.9 Hz), 3.81 (app d, 2 H, J = 2.4 Hz), 2.04 (bs, 1 H), 1.58 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 109.8, 69.0, 37.3, 30.2, 20.2; MS (EI) *m/z* 241 (16), 227 (37), 67 (100); HRMS (EI) *m/z* calcd for $C_5H_5Br_2O$ 238.8707, found 238.8701.



(*E*)-4-(Dimethylamino)but-3-en-2-one (3-104). To acetylacetaldehyde dimethyl acetal (5.30 mL, 37.8 mmol), freshly distilled prior to use (bp 67 °C, 12 mm Hg), was added a solution of methylamine (2 M solution in methanol, 21.0 mL, 42.7 mmol) in one portion. The reaction mixture was stirred at room temperature for 12 h, and concentrated under reduced pressure. The resulting oil was purified by bulb-to-bulb distillation (0.25 mm, oven temperature 80-95°C) to afford **3-104** (3.75 g, 100%) as a light-yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.8-9.6 (br, 1 H), 6.60 (dd, 1 H, J = 12.9, 7.2 Hz), 4.97 (d, 1 H, J = 7.2 Hz), 2.95 (d, 3 H, J = 13.0 Hz), 2.02 (s, 3 H).

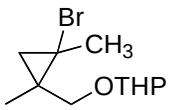


Synhtesis of 2-(2-Methylallyloxy)tetrahydro-2*H*-pyran. To a stirred solution of alcohol *β*-methallyl alcohol (30.0 g, 0.416 mol) and 3,4-dihydro-2*H*-pyran (35.0 g, 0.416 mol) were added several drops of concentrated aq HCl. The reaction mixture was stirred at room temperature for 3 h, quenched with a saturated solution of $NaHCO_3$, extracted with EtOAc, and concentrated *in vacuo* to obtain the title compound (58.4 g, 90%) as a colorless liquid: IR (ATR) 2939, 2868, 1647, 1200, 1118, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.98 (br s, 1 H), 4.87 (br s, 1 H), 4.62 (t, 1 H, *J* = 3.3 Hz), 4.12 (d, 1 H, *J* = 12.6 Hz), 3.88 (d, 1 H, *J* = 12.0 Hz), 3.86-3.83 (m, 1 H), 3.54-3.47 (m, 1 H), 1.87-1.79 (m, 1 H), 1.74 (s, 3 H), 1.79-1.49 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 111.6, 97.6, 70.6, 62.0, 30.5, 25.4, 19.6, 19.3.

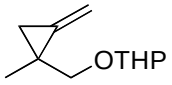


2-((2,2-Dibromo-1-methylcyclopropyl)methoxy)tetrahydro-2*H*-pyran (3-116). To a solution of 2-(2-methylallyloxy)tetrahydro-2*H*-pyran (10.0 g, 64.0 mmol), bromoform (11.20 mL, 128.0 mmol), cetrimide (1.10 g, 3.02 mmol) and triethylamine (10 drops) in dichloromethane (20 mL) was added a solution of sodium hydroxide (41.0 g, 1.02 mol) in water (41 mL) at -20 °C. The reaction mixture was vigorously stirred with a mechanical stirrer for 24 h, dilute with water (150 mL), and extracted with CH_2Cl_2 (5 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in hexane (30 mL), stirred at room temperature for 15 min, filtered, and concentrated *in vacuo*. Purification by chromatography on SiO_2 (2-5% EtOAc/hexane) gave **3-116** (20.0 g, 95%) as a yellowish, oily, inseparable mixture of diastereomers: IR (ATR) 2937, 2866, 1446, 1351, 1200, 1120, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68-4.64 (m, 1 H), 3.96-3.86 (m, 2 H), 3.56-3.47 (m, 2 H), 1.91-

1.46 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.8, 98.6, 73.5, 73.2, 62.3, 61.9, 36.1, 35.7, 32.8, 32.7, 30.6, 30.4, 29.7, 29.2, 25.4, 21.1 (2 C), 19.5, 19.1; MS (ESI) *m/z* 331 (33), 329 (68), 327 (66), 229 (99), 228 (83), 227 (55), 226 (97), 225 (100), 85 (81); HRMS (EI) *m/z* calcd for $C_{10}H_{16}O_2Br_2$ 325.9517, found 325.9511.

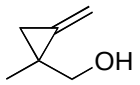


2-((2-Bromo-1,2-dimethylcyclopropyl)methoxy)tetrahydro-2*H*-pyran (3-117). To a magnetically stirred solution of **3-116** (10.0 g, 30.4 mmol) in THF (60 mL) at -95 °C was added a solution of *n*-BuLi (1.6 M in hexane, 19.0 mL, 30.4 mmol). The reaction mixture was stirred for 25 min, treated with MeI (5.7 mL, 0.092 mol) over 5 min, warm to room temperature over 2 h, quenched with water (20 mL), extracted with EtOAc (6 x 20 mL), washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (5 % EtOAc/hexanes) gave **3-117** (6.61 g, 82%) in the form of yellowish liquid, as an inseparable mixture of diastereomers, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70-4.50 (m, 1 H), 3.94-3.76 (m, 2 H), 3.62-3.21 (m, 2 H), 1.90-1.84 (m, 4 H), 1.74-1.49 (m, 6 H), 1.46 (s, 1 H), 1.45 (s, 1 H), 1.32-1.20 (m, 2 H).

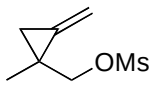


2-((1-Methyl-2-methylenecyclopropyl)methoxy)tetrahydro-2*H*-pyran (3-118). To a solution of potassium *t*-butoxide (0.96 g, 8.7 mmol) in DMSO (50 mL) at room temperature was added a solution of **3-117** (1.80 g, 6.91 mmol) in DMSO (14 mL). The reaction mixture was stirred for 12 h, quenched with water (50 mL), and extracted with pentane (5 x 20 mL) and EtOAc (5 x 20 mL). The combined organic layers were washed with water (50 mL), brine, dried (Na_2SO_4), and

concentrated *in vacuo*. Purification by chromatography on SiO_2 (2% to 5% EtOAc/hexanes) gave **3-118** (0.46 g, 69%) as a colorless, oily mixture of diastereomers: IR (ATR) 2939, 2898, 1446, 1349, 1118, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (ddt, 1 H, *J* = 7.8, 2.7, 0.9 Hz), 5.34 (br s, 1 H), 4.65 (dt, 1 H, *J* = 9.6, 3.3 Hz), 3.90-3.83 (m, 1 H), 3.68-3.58 (m, 1 H), 3.53-3.46 (m, 1 H), 3.33-3.20 (m, 1 H), 1.89-1.51 (m, 6 H), 1.25 (s, 3 H), 1.21-1.12 (m, 1 H), 1.04-0.99 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 139.6, 102.6, 102.5, 98.4, 97.9, 73.3, 72.6, 62.3, 61.9, 30.7, 30.6, 25.5 (2 C), 20.2, 20.0, 19.8 (2 C), 19.6, 19.4, 15.7, 15.2.

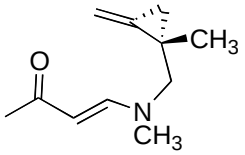


(1-Methyl-2-methylenecyclopropyl)methanol (3-119). To a solution of **3-118** (4.00 g, 21.9 mmol) in MeOH (60 mL) at room temperature was added *p*-toluenesulfonic acid monohydrate (0.90 g, 4.7 mmol). The reaction mixture was stirred for 18 h. The solvent was slowly distilled off (oil bath temp. 80-85 °C), and the residue was separated between water (5 mL) and Et_2O (5 mL), and extracted with diethyl ether (5 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification on SiO_2 (2 to 5 to 15% Et_2O/pentane) gave **3-119** (1.65 g, 79%) as a colorless oil: IR (ATR) 3362 (bs), 2969, 1446, 1375, 1025, 885 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 5.41 (dt, 1 H, *J* = 2.4, 0.9 Hz), 5.32 (bs, 1 H), 3.43 (s, 2 H), 2.14 (s, 1 H), 1.22 (s, 3 H), 1.05 (dt, 1 H, *J* = 8.7, 2.1 Hz), 0.95 (dt, 1 H, *J* = 8.4, 2.1 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 140.6, 102.9, 69.1, 23.1, 19.7, 15.3.

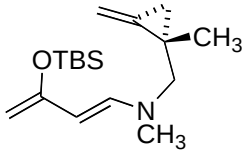


(1-Methyl-2-methylenecyclopropyl)methyl methanesulfonate (3-120). To a solution of **3-119** (0.88 g, 9.0 mmol) in CH_2Cl_2 (45 mL) at 0 °C was added triethylamine (3.70 mL, 26.3 mmol)

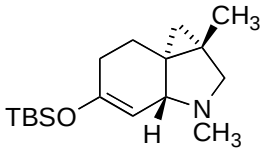
and mesyl chloride (1.00 mL, 12.9 mmol). The reaction mixture was stirred for 1 h, quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (5 x 50 mL), washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and the resulting mesylate **3-120** was used crude in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (t, 1 H, *J* = 2.7 Hz), 5.38 (app s, 1 H), 3.12 (d, 2 H, *J* = 0.6 Hz), 2.98 (d, 3 H, *J* = 0.3 Hz), 1.28-1.24 (m, 1 H), 1.25 (s, 3 H), 1.13-1.10 (m, 1 H).



(*E*)-4-(Methyl((1-methyl-2-methylenecyclopropyl)methyl)amino)but-3-en-2-one (3-121). To a slurry of NaH (120.1 mg, 5.003 mmol) in DMF (10.0 mL) at room temperature was added a solution of amide **3-104** (0.23 g, 2.3 mmol) in DMF (10.0 mL). The reaction mixture was stirred for 30 min at this temperature, cooled to 0 °C, and a solution of (1-methyl-2-methylenecyclopropyl)methyl methanesulfonate (0.53 g, 3.0 mmol) in DMF (10.0 mL) was added dropwise. The mixture was stirred at room temperature for 24 h, quenched with water, and extracted with EtOAc (5 x 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (50% EtOAc/hexanes) afforded **3-121** (286.3 mg, 67%) as a yellowish oil: IR (ATR) 3531 (bs), 2963, 1653, 1593, 1552, 1357, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 1 H, *J* = 12.9 Hz), 5.40-5.37 (m, 2 H), 5.04 (d, 1 H, *J* = 12.6 Hz), 3.28 (d, 1 H, *J* = 13.8 Hz), 2.96 (d, 1 H, 14.1 Hz), 2.79 (br s, 3 H), 2.05 (s, 3 H), 1.05 (s, 3 H), 1.03-1.00 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 152.1, 138.8, 104.0, 96.6, 77.2, 64.5, 35.6, 28.0, 19.6, 15.3; MS (ESI) *m/z* 202 ($[M+Na]^+$,100), 156 (18), 180 (18); HRMS (ESI) *m/z* calcd for $C_{11}H_{17}NONa$ $[M+Na]^+$ 202.1208, found 202.1209.

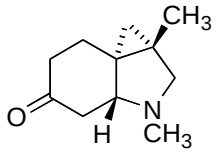


(*E*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methyl-*N*-((1-methyl-2-methylenecyclopropyl)methyl) buta-1,3-dien-1-amine (3-122). To a solution of NaHMDS (0.42 g, 2.3 mmol) in THF (2.5 mL) at -78 °C was added a solution of **3-121** (0.41 g, 2.3 mmol) in THF (1.5 mL) over a period of 30 min. The resulting clear yellow solution was stirred for 1 h at -78 °C, treated with a solution of *tert*-butylchlorodimethylsilane (0.36 g, 2.4 mmol) in THF (1.5 mL) over a period of 5 min, slowly warmed to room temperature, and concentrated under reduced pressure to provide crude **3-122** (0.67 g, 100%) as an orange thick oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, 1 H, *J* = 13.2 Hz), 5.40 (d, 1 H, *J* = 14.4 Hz), 4.79 (d, 1 H, *J* = 13.2 Hz), 3.92 (s, 1 H), 3.83 (s, 1 H), 3.14 (d, 1 H, *J* = 14.1 Hz), 2.86 (d, 1 H, *J* = 14.1 Hz), 2.73 (s, 3 H), 1.11 (s, 3 H), 0.99 (app s, 11 H), 0.21 (app s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 140.6, 140.1, 103.4, 94.1, 85.3, 63.2, 36.2, 26.0, 20.5, 20.1, 18.3, 15.5, -4.5 (2 C).

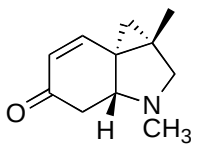


***tert*-Butyl furan-2-yl(((1a*S**,3a*S**,7a*S**)-5-hydroxy-1a,3-dimethyl-2-oxo─1a,2,3,3a,4,5-hexa-hydro-1*H*-cyclopropa[*c*]indol-5-yl)methyl)carbamate (3-123).** A solution of crude **3-122** (0.67 g, 4.0 mmol) in trifluorotoluene (7 mL) was heated under microwave irradiation at 195 °C for 1 h, concentrated *in vacuo*, and purified by chromatography on SiO_2 (30 to 50% EtOAc/hexane) to obtain vinylogous amide **3-122** (0.11 g) and the desired silyl enol ether **3-123** (0.35 g, 52%, 72% brsm) as a light yellow liquid: IR (ATR) 2928, 1646, 1250, 1180, 1159, 865 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (br s, 1 H), 3.04 (d, 1 H, *J* = 8.7 Hz), 2.69 (br s, 1 H),

2.23 (s, 3 H), 2.21-2.12 (m, 3 H), 1.95 (dt, 1 H, *J* = 12.0, 6.3 Hz), 1.41-1.34 (m, 1 H), 1.15 (s, 3 H), 0.92 (app s, 10 H), 0.16 (s, 3 H), 0.15 (s, 3 H), -0.19 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 104.9, 67.2, 66.1, 40.2, 33.5, 30.9, 25.7, 24.8, 24.3, 18.0, 16.4, 15.1, -4.3, -4.7; MS (EI) *m/z* 294 (14), 292 (100), 250 (27), 97 (34), 83 (34), 73 (48), 57 (73); HRMS (EI) *m/z* calcd for $C_{17}H_{31}NOSi$ 293.2175, found 293.2187.

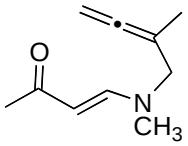


(1a*S,3a*R**,7a*R**)-1a,3-Dimethylhexahydro-1*H*-cyclopropa[*c*]indol-5(1a*H*)-one (3-124).** To a solution of **3-123** (450.0 mg, 1.533 mmol) in THF (11 mL) was added a solution of TBAF (1 M solution in THF, 1.53 mL, 1.53 mmol). The reaction mixture was stirred for 2 h at room temperature, filtered through Celite and concentrated *in vacuo*. Purification by chromatography on SiO_2 (50% EtOAc/hexanes) gave **3-124** (234.0 mg, 85%) as a colorless oil: IR (ATR) 2920, 2851, 1710, 1446, 1256 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.05 (d, 1 H, *J* = 9.0 Hz), 2.61 (ddd, 1 H, *J* = 12.5, 3.5, 1.5 Hz), 2.49-2.39 (m, 2 H), 2.32-2.21 (m, 3 H), 2.19 (s, 3 H), 1.96 (dt, 1 H, *J* = 13.0, 5.0 Hz), 1.52 (ddd, 1 H, *J* = 13.0, 6.5, 2.0 Hz), 1.19 (s, 3 H), 1.16 (d, 1 H, *J* = 3.5 Hz), 0.05 (d, 1 H, *J* = 3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0, 68.1, 65.0, 45.3, 40.6, 39.3, 33.3, 25.6, 25.1, 16.6, 15.1; MS (EI) *m/z* 179 ($M^{\bullet+}$, 11), 178 (40), 92 (100), 86 (39), 84 (63); HRMS (EI) *m/z* calcd for $C_{17}H_{11}NO$ 179.1310, found 179.1307.

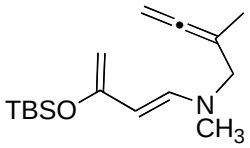


(1a*S,3a*R**,7a*S**)-1a,3-Dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopropa[*c*]indol-5(1a*H*)-one (3-65).** To a solution of **3-124** (120.0 mg, 0.6694 mmol) in acetonitrile (4 mL) at 0 °C was added

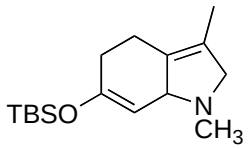
2,6-lutidine (156 μL, 1.34 mmol), followed by TMSOTf (158 μL, 0.870 mmol), warmed to room temperature over 2 h, and quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (5 x 5 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), concentrated *in vacuo* to obtain the corresponding TMS-enol ether (168.0 mg, 100%), which was used crude in the next step, without further purification or characterization. To a solution of TMS-enol ether (65.0 mg, 0.294 mmol) in THF (2.0 mL) at -78 °C was added powdered $NaHCO_3$ (30.0 mg, 0.310 mmol) followed by NBS (55.0 mg, 0.310 mmol), slowly warmed to room temperature over 1 h, quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O (4 x 10 mL) and CH_2Cl_2 (1 x 10 mL). Combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude bromide (61.0 mg, 0.23 mmol), which was dissolved in DMF (8 mL), and treated with LiBr (60.0 mg, 0.697 mmol) and Li_2CO_3 (51.2 mg, 0.697 mmol). The reaction mixture was heated at 120 °C for 2.5 h, poured into brine, and extracted with Et_2O (3 x 10 mL) and CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (50% EtOAc/hexanes) gave **3-65** (7.0 mg, 17%, three steps) as a yellowish oil: IR (ATR) 2934, 2846, 1664, 1571, 1165, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, 1 H, J = 9.5 Hz), 6.07 (d, 1 H, J = 10.0 Hz), 3.07 (d, 1 H, J = 8.5 Hz), 2.71 (dd, 1 H, J = 15.5, 4.0 Hz), 2.58 (d, 1 H, J = 13.0 Hz), 2.30 (d, 1 H, J = 14.5 Hz), 2.24 (s, 3 H), 2.17 (d, 1 H, J = 8.5 Hz), 1.31 (s, 3 H), 1.26 (s, 1 H), 0.44 (d, 1 H, J = 4.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 150.8, 130.1, 64.9, 64.0, 41.4, 39.0, 35.3, 29.2, 19.5, 15.0; HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1124.



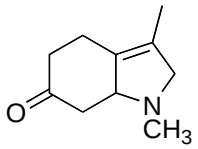
(*E*)-4-(Methyl(2-methylbuta-2,3-dienyl)amino)but-3-en-2-one (3-129). To a stirred solution of allenyl alcohol **3-127** (1.6 g, 19 mmol), DMAP (216.0 mg, 1.768 mmol) and triethylamine (4.0 mL, 28 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added mesyl chloride (1.50 mL, 20.0 mmol), stirred for 60 min, diluted with CH_2Cl_2 (20 mL), and quenched with aquoeus HCl (1 M solution, 20 mL). The organic layer was washed saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated *in vacuo*, to give mesylate **3-128** (683.5 mg) as a yellowish oil. To a suspension of NaH (104.0 mg, 4.333 mmol) in THF (34 mL) was added a solution of vinylogous amide **3-104** (0.42 g, 4.2 mmol) in THF (4 mL) dropwise at 0 °C, and the resulting mixture was stirred for 1 h. To this solution was added a solution of mesylate **3-128** (683.5 mg, 4.210 mmol) in THF (4 mL) dropwise, NaI (120.0 mg, 0.8001 mmol) in one portion at 0 °C, and stirred at 50 °C for 5 h. After the reaction mixture was cooled to room temperature, a saturated aqueous solution of NH_4Cl was added, extracted with Et_2O (3 x 5 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (50% EtOAc/hexanes) gave the desired coupling product **3-129** (1.00 g, 54%, 2 steps) as a yellowish oil: IR (ATR) 2934, 1651, 1558, 1355 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 1 H, J = 12.8 Hz), 5.08 (d, 1 H, J = 12.8 Hz), 4.72 (dd, 2 H, J = 6.0, 2.8 Hz), 3.73 (s, 2 H), 2.76 (s, 3 H), 2.09 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 195.4, 152.1, 96.8, 94.7, 75.8, 61.1, 34.8, 28.2, 15.7; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}NO$ $[M+H]^+$ 166.1232, found 166.1225.



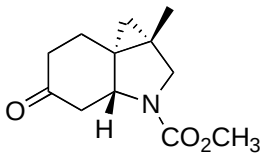
(*E*)-3-(*tert*-Butyldimethylsilyloxy)─*N*─methyl─*N*─(2-methylbuta-2,3-dienyl)buta-1,3-dien-1-amine (3-130). To a solution of NaHMDS (1.04 g, 5.70 mmol) in THF (6.5 mL) at -78 °C was added a solution of **3-129** (924.0 mg, 5.701 mmol) in THF (6.5 mL) over 30 min. The resulting clear yellow solution was stirred for 1 h at -78 °C, treated with a solution of *tert*-butylchlorodimethylsilane (902.0 mg, 5.986 mmol) in THF (6.5 mL) over a period of 5 min, slowly warmed to room temperature, and concentrated under reduced pressure to provide **3-130** (1.59 g, 100%) as an orange thick oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, 1 H, *J* = 13.2 Hz), 4.81 (d, 1 H, *J* = 13.2 Hz), 4.66 (dd, 2 H, *J* = 5.6, 2.4 Hz), 3.92 (s, 1 H), 3.84 (s, 1 H), 3.56 (dd, 1 H, *J* = 2.0 Hz), 2.67 (s, 3 H), 1.62-1.56 (m, 5 H), 0.98 (s, 3 H), 0.92 (d, 1 H, *J* = 4.4 Hz).



6-(*tert*-Butyldimethylsilyloxy)-1,3-dimethyl-2,4,5,7a-tetrahydro-1*H*-indole (3-131). A solution of **3-130** (1.59 g, 5.69 mmol) in *o*-dichlorobenzene (15 mL) was heated in portions (3 mL) in a microwave oven at 230 °C for 30 min. The reaction mixture was purified by chromatography on SiO_2, (hexanes, then 50% EtOAc/hexanes) to obtain **3-131** (434.4 mg, 27 %) as a yellow oil: IR (ATR) 2952, 2928, 1655, 1172, 867, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (dd, 1 H, *J* = 2.5 Hz), 3.63 (d, 1 H, *J* = 12.5 Hz), 3.62 (s, 1 H), 2.53 (d, 1 H, *J* = 13.5 Hz), 2.43 (s, 3 H), 2.22-2.05 (m, 3 H), 1.64 (s, 3 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 131.7, 126.2, 104.6, 69.3, 66.4, 40.2, 30.5, 25.6, 21.2, 17.9, 11.4, -4.3, -4.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{30}NOSi$ $[M+H]^+$ 280.2097, found 280.2099.

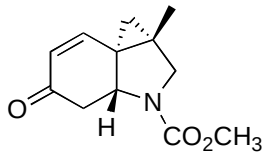


1,3-Dimethyl-4,5,7,7a-tetrahydro-1*H*-indol-6(2*H*)-one (3-132). To a solution of **3-131** (144.8 mg, 0.5181 mmol) in THF (3.5 mL) was added a solution of TBAF (1.0 M in THF, 0.52 mL, 0.52 mmol), and stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*, and then purified by chromatography on SiO_2 (25% acetone/chloroform) to give **3-132** (52.5 mg, 61%) in the form of yellowish oil: IR (ATR) 2918, 1705, 1620, 1359 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (dd, 1 H, *J* = 13.0, 3.5 Hz), 3.46 (m, 1 H), 3.26 (dt, 1 H, *J* = 12.5, 7.0, 0.5 Hz), 2.80-2.74 (m, 2 H), 2.44 (s, 3 H), 2.40-2.32 (m, 3 H), 2.20-2.13 (m, 2 H), 1.69 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 129.9, 129.1, 71.9, 66.6, 49.1, 40.3, 39.9, 21.9, 11.5; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}NO$ $[M+H]^+$ 166.1232, found 166.1195.



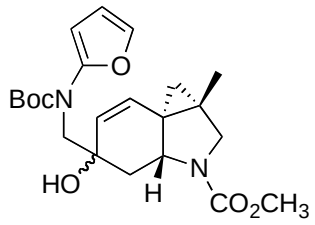
(1a*S,3a*R**,7a*R**)-Methyl 1a-methyl-5-oxohexahydro-1*H*-cyclopropa[*c*]indole-3(3a*H*)-carboxylate (3-133).** A solution of ketone **3-124** (50.0 mg, 0.279 mmol) in methyl chloroformate (3.0 mL) was heated to 70 °C for 3 h, quenched with water (3 mL), and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extracts were washed with water, brine, and dried (Na_2SO_4). Purification by chromatography on SiO_2 (20% hexanes/EtOAc) provided **3-133** (44.2 mg, 71%) as a yellow solid: Mp 79.1-81.0 °C; IR (ATR) 2958, 2859, 1696, 1437, 1349, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.71-3.66 (m, 2 H); 3.65 (s, 3 H); 3.37 (d, 1 H, *J* = 13.2 Hz), 3.27 (dd, 1 H, *J* = 10.0, 0.8 Hz), 2.53 (dddd, 1 H, *J* = 15.2, 5.2, 1.6 Hz), 2.44-2.35 (m, 2 H), 2.04 (ddt, 1 H, *J* = 13.2, 5.2, 1.2 Hz), 1.55 (ddd, 1 H, *J* = 13.2, 7.2, 2.0 Hz), 0.81 (d, 1 H, *J* = 3.6 Hz), 0.30

(d, 1 H, J = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 157.0, 60.5, 57.1, 52.1, 46.6, 40.2, 34.5, 25.0, 24.4, 17.9, 14.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO_3Na$ $[M+Na]^+$ 246.1106, found 246.1090.



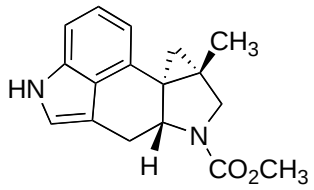
(1a*S,3a*R**,7a*S**)-Methyl 1a—methyl—5-oxo—1a,2,4,5—tetrahydro-1*H*-cyclopropa[*c*]indole-3(3a*H*)-carboxylate (3-134).** To a solution of diisopropylamine (13 µL, 0.097 mmol) in THF (0.4 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 60 µL, 0.097 mmol). The reaction mixture was stirred at this temperature for 15 min, cooled to -78 °C, and treated with a solution of **3-133** (18.0 mg, 0.0810 mmol) in THF (0.3 mL). The mixture was stirred for 60 min, treated with TMSCl (20.0 µL, 0.158 mmol), stirred at -78 °C for 1.5 h, concentrated *in vacuo*, diluted with hexane, and filtered through a pad of SiO_2. The pad was washed with hexanes (4 x 1 mL) and EtOAc (1 x 1 mL), and concentrated *in vacuo*. The crude material was dissolved in acetonitrile (1.5 mL), and treated with $Pd(OAc)_2$ (23.5 mg, 0.105 mmol) for 10 h at room temperature, filtered through a pad of Celite, washed with EtOAc (3 x 5 mL), and concentrated under reduced pressure. Purification by chromatography on SiO_2 (50% EtOAc/hexane) provided enone **3-134** (12.0 mg, 67%) as a yellow solid: Mp 95.4-97.2 °C; IR (ATR) 2950, 2872, 1709, 1674, 1661, 1348, 1195 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, 1 H, J = 9.6 Hz), 6.10 (d, 1 H, J = 9.6 Hz), 3.88 (dd, 1 H, J = 13.6, 3.6 Hz), 3.74 (d, 1 H, J = 10.0 Hz), 3.68 (s, 3 H), 3.51 (d, 1 H, J = 14.4 Hz), 3.20 (d, 1 H, J = 10.0 Hz), 2.49 (dd, 1 H, J = 16.0, 13.6 Hz), 1.36 (s, 3 H), 1.28 (d, 1 H, J = 4.8 Hz), 0.58 (d, 1 H, J = 4.4 Hz); ^{13}C NMR (120 MHz, $CDCl_3$) δ 198.7, 157.1,

148.2, 130.8, 58.0, 55.6, 52.3, 43.3, 35.3, 27.7, 19.3, 14.3; HRMS (AP) *m/z* calcd for $C_{12}H_{16}NO_3$ ($[M+H]^+$) 222.1130, found 222.1136.

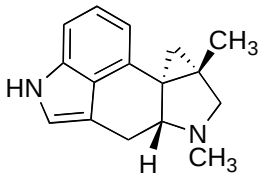


(1a*S,3a*R**,7a*S**)-Methyl 5-(((*tert*-butoxycarbonyl)(furan−2−yl)amino)methyl)-5-hydroxy-1a-methyl-1a,2,4,5-tetrahydro-1*H*-cyclopropa[*c*]indole-3(3a*H*)-carboxylate (3-135).** To a solution of furanyl stannane **3-48** (114.3 mg, 0.2350 mmol) in anhydrous THF (0.3 mL) at -78 °C was added a solution of *n*-BuLi (1.60 M in hexanes, 146 μL, 0.235 mmol) dropwise over 5 min. The reaction mixture was stirred for an additional 30 min at -78 °C, then a solution of enone **3-134** (40.0 mg, 0.181 mmol) in THF (0.2 ml) was added dropwise over 2 min. The resulting mixture was stirred for 1 h at -78 °C, diluted with EtOAc (3 mL), and quenched with saturated aqueous NH_4Cl (4 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (50% EtOAc/hexane) to obtain **3-135-a** (38.1 mg, 51%) as a colorless oil (single diastereomer), and **3-135-b** (36.1 mg, 48%) as a colorless oil (single diastereomer). **3-135-a**: R_f = 0.52 (50% EtOAc/hexanes); IR (ATR) 3465, 2977, 1696, 1364, 1150, 1148 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18-7.17 (m, 1 H), 6.35-6.34 (m, 1 H), 6.07 (br s, 1 H), 5.69-5.65 (m, 2 H), 3.84-3.58 (m, 4 H), 3.63 (s, 3 H), 3.42 (d, 1 H, *J* = 12.5 Hz), 3.07 (d, 2 H, *J* = 10.0 Hz), 1.85 (app t, 1 H, *J* = 12.5 Hz), 1.45 (s, 9 H), 1.23 (s, 3 H), 0.86 (d, 1 H, *J* = 4.5 Hz), 0.34 (d, 1 H, *J* = 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 157.2, 149.1, 138.1, 131.2, 127.8, 111.0, 101.5, 82.3, 74.6, 60.3, 55.9, 52.0, 37.8, 35.2, 28.1, 26.1, 21.0, 19.5, 14.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{30}N_2O_6Na$ ($[M+Na]^+$) 441.2002, found 441.1959. **3-**

135-b: R_f = 0.35 (50% EtOAc/hexanes); IR (ATR) 3463, 2978, 2952, 1700, 1357, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 1 H), 6.33 (d, 1 H, *J* = 1.5 Hz), 6.01 (s, 1 H), 5.68 (d, 1 H, *J* = 9.5 Hz), 5.60 (d, 1 H, *J* = 9.5 Hz), 3.79-3.66 (m, 4 H), 3.65 (s, 3 H), 3.14 (d, 1 H, *J* = 10.5), 2.88 (br s, 1 H), 1.67 (t, 1 H, *J* = 12.0 Hz), 1.43 (s, 9 H), 1.22 (s, 3 H), 0.80 (d, 1 H, *J* = 4.0 Hz), 0.24 (d, 1 H, *J* = 4.0 Hz) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 138.1, 130.0, 129.3, 111.0, 101.9, 82.0, 73.9, 60.3, 59.0, 56.9, 56.4, 52.0, 38.3, 35.2, 28.0, 25.6, 18.5, 14.2, 14.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{30}N_2O_6Na$ ($[M+Na]^+$) 441.2002, found 441.2000.



(1a*S,3a*R**,9b*S**)—Methyl 1a—methyl-1a,2,3a,4—tetrahydro—1*H*—cyclopropa[*c*]indolo[4,3-*ef*]indole-3(6*H*)-carboxylate (3-136).** A solution of alcohol **3-135-b** (23.0 mg, 0.0549 mmol) in trifluorotoluene (2.5 mL) was heated under microwave irradiation (180 °C, 30 min), concentrated *in vacuo*, and then purified by chromatography on SiO_2 (10-15% acetone/chloroform) to obtain starting allylic alcohol **3-135-b** (4.8 mg), and the desired indole **3-136** (6.8 mg, 44%, 56% brsm) as colorless oil: IR (ATR) 3324, 2949, 1680, 1441, 1113 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.98 (br s, 1 H), 7.17 (d, 1 H, *J* = 8.4 Hz), 7.09 (dd, 1 H, *J* = 8.4, 7.0 Hz), 6.93 (s, 1 H), 6.86 (d, 1 H, *J* = 7.0 Hz), 4.06 (br d, 1 H, *J* = 9.8 Hz), 3.80 (br d, 1 H, *J* = 9.1 Hz), 3.79-3.70 (br, 1 H), 3.72 (s, 3 H), 3.43 (d, 1 H, *J* = 9.8 Hz), 2.82-2.78 (m, 1 H), 1.76 (s, 3 H), 1.16 (d, 1 H, *J* = 4.2 Hz), 0.62 (d, 1 H, *J* = 4.2 Hz); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.6, 133.9, 133.3, 128.4, 122.8, 118.5, 112.9, 110.2, 108.5, 62.4, 57.1, 52.2, 35.3, 27.0, 26.5, 24.8, 16.2; HRMS (APCI) *m/z* calcd for $C_{17}H_{18}N_2O_2$ 282.1368, found 282.1398.



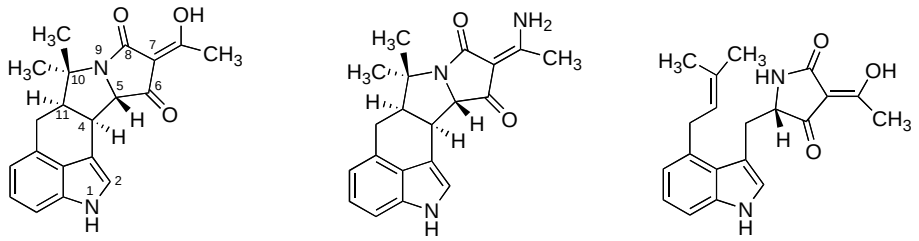
(1a*S,3a*R**,9b*S**)─1a,3─Dimethyl─1a,2,3,3a,4,6─hexahydro─1*H*-cyclopropa[*c*]indolo[4,3-*ef*]indole (Cycloclavine, 3-5).** A suspension of $LiAlH_4$ (1.4 mg, 0.041 mmol) in THF (0.2 mL) was treated with a solution of carbamate **3-136** (2.5 mg, 0.088 mmol) in THF (0.2 mL), heated to 66 °C for 30 min, and cooled to room temperature. After sequential addition of water (1.4 μL), 15% aqueous NaOH (1.4 μL), and water (4.5 μL), the mixture was filtered through Celite, and concentrated *in vacuo*. Purification by chromatography on SiO_2 (20% acetone/chloroform) gave cycloclavine (**3-5**, 2.3 mg, 100%) as a white solid: Mp 153.2-155.3 °C (acetone/chloroform); IR (ATR) 2921, 2798, 1591, 1590, 1441, 1150 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.92 (bs, 1 H), 7.15 (d, 1 H, *J* = 8.4 Hz), 7.10 (app t, 1 H, *J* = 7.7 Hz), 7.91 (s, 1 H), 6.84 (d, 1 H, *J* = 7.0 Hz), 3.17 (d, 1 H, *J* = 9.1 Hz), 3.15 (dd, 1 H, *J* = 14.0, 4.2 Hz), 2.79 (dd, 1 H, *J* = 11.2, 3.5 Hz), 2.61 (t, 1 H, *J* = 12.6 Hz), 2.42 (d, 1 H, *J* = 8.4 Hz), 2.37 (s, 3 H), 1.70 (s, 3 H), 1.61 (d, 1 H, *J* = 2.8 Hz), 0.46 (d, 1 H, *J* = 3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 133.5, 128.7, 122.9, 118.1, 113.2, 110.3, 107.9, 69.6, 65.6, 39.9, 34.3, 27.8, 24.9, 24.2, 16.5; HRMS (APCI) *m/z* calcd for $C_{16}H_{19}N_2$ ($[M+H]^+$) 239.1548, found 239.1572.

4.0 PROGRESS TOWARD THE TOTAL SYNTHESIS OF α-CYCLOPIAZONIC ACID

4.1 INTRODUCTION

4.1.1 Cyclopiazonic acid: Structure and Biological Activity

α-Cyclopiazonic acid (CPA, **4-1**, Figure 19) is an indole-tetramic acid mycotoxin produced by the molds of genera *Aspergillus* and *Penicillium*.[131,182] These molds can grow on many food substrates, such as cheese and meat. Therefore, this toxin can contaminate a variety of agricultural commodities and food sources.[183] CPA was first isolated by Holzapfel in 1968 from stored grain and cereal products infected by *Penicillium cyclopium* Westling.[184] The structure of cyclopiazonic acid was established by interpretation of its spectroscopic data; while the absolute stereochemistry was confirmed by a circular dichroism (CD) analysis. In 1970, two other metabolites related structurally to α-CPA were isolated: cyclopiazonic acid imine (**4-2**) and *bis*-seco-dehydrocyclopiazonic acid (β-cyclopiazonic acid, **4-3**).[185]



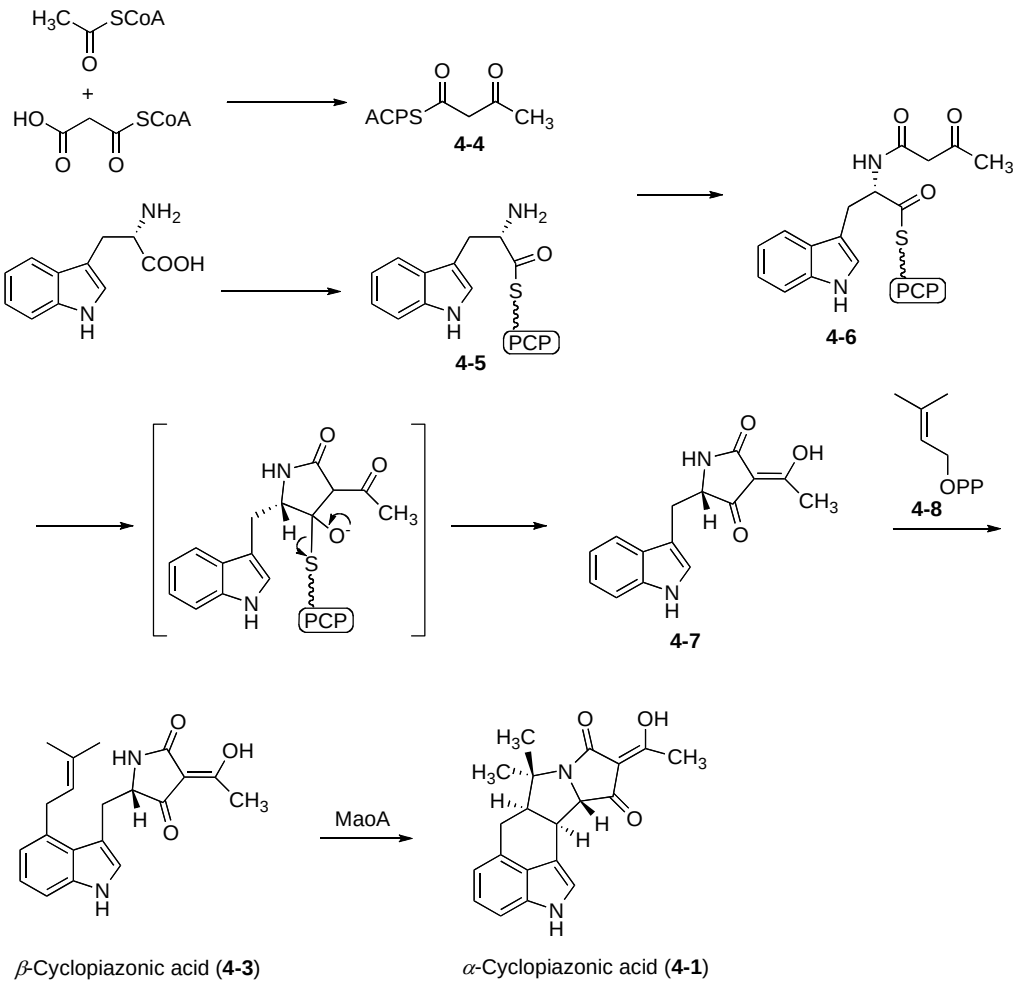
α-Cyclopiazonic acid (**4-1**) Cyclopiazonic acid imine (**4-2**) β-Cyclopiazonic acid (**4-3**)

Figure 19. Cyclopiazonic acid **(4-1)** and its two related family members

The most striking feature of α-cyclopiazonic acid is a pentacyclic array containing a 3,4-disubstituted indole and a highly substituted tetramic acid residue, together with a central *cis*-ring fusion.

The toxicity of α-cyclopiazonic acid is attributed to its ability to alter normal intracellular calcium flux through the specific inhibition of sarcoplasmic or endoplasmic reticulum Ca^{2+}-dependent ATPase (SERCA), which are essential for calcium uptake in muscles.[186,187] Recent evidence shows that α-CPA inhibits the calcium pump by blocking the calcium access channel and immobilizing four transmembrane helices of the ATPase. Furthermore, CPA induces various pathological lesions in test animals.[188]

Biosynthetically, cyclopiazonic acid is derived from *L*-tryptophan (Scheme 74). This was established by feeding studies using radiolabeled substrates.[189] The first stable intermediate in this biosynthetic pathway is *cyclo*-acetoacetyl-*L*-tryptophan (cAATrp, **4-7**), derived from *L*-tryptophan, acetyl-CoA, and malonyl-CoA. After the initial condensation of acetyl-CoA and malonyl-CoA, the acetoacetyl moiety becomes tethered on ACP (acyl carrier protein). Further substitution at the carbonyl carbon of the ACP-bound acetylacetone **4-4** by PCP-bound indole **4-5** (PCP – peptidyl carrier protein) leads to the cAATrp precursor **4-6**. The tetramic acid portion of cAATrp is formed through a Dieckman condensation, a process which ultimately leads to the formation of non-petide bound cAATrp (**4-7**).[131]



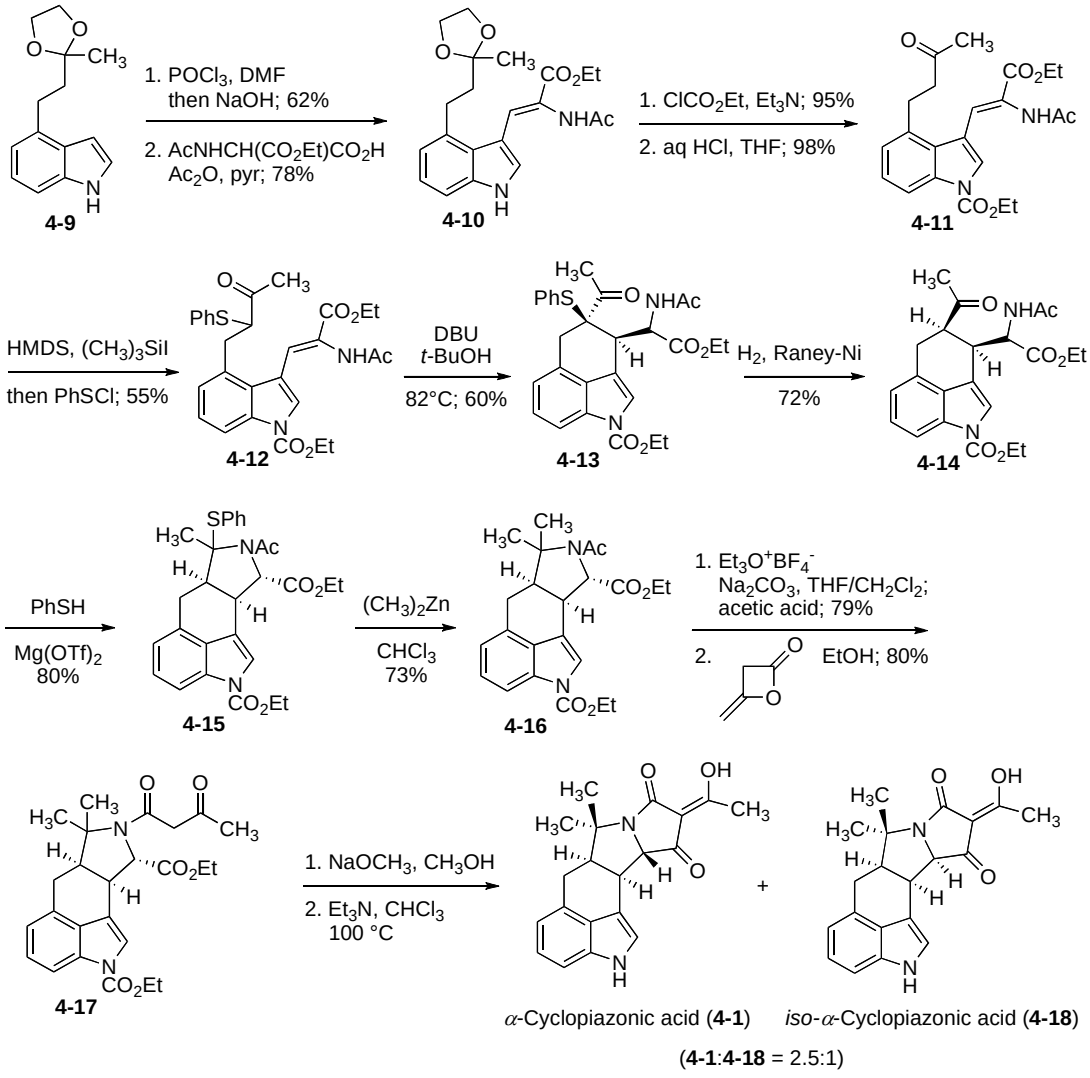
Scheme 74. Biosynthesis of α-cyclopiazonic acid **4-1**

Conversion of cAATrp to β-cyclopiazonic acid involves alkylation of the C(4) position of the Trp indole ring by DMAPP (dimethylallyl pyrophosphate, **4-8**), a reaction catalyzed by dimethylallyl transferase.[190] The final step in the biosynthesis of α-cyclopiazonic acid is the dehydrogenation of β-CPA, which results in an intramolecular ring closure. The enzyme involved in this conversion is an FAD-dependent oxidoreductase (Mao A).[191]

4.1.2 Previous Work on the Total Synthesis of Cyclopiazonic Acid

The synthetic community has been intrigued by cyclopiazonic acid's interesting structural features and its biological activity for decades. Although the structure of CPA was known since 1968, only three racemic and one asymmetric syntheses have been published to date.

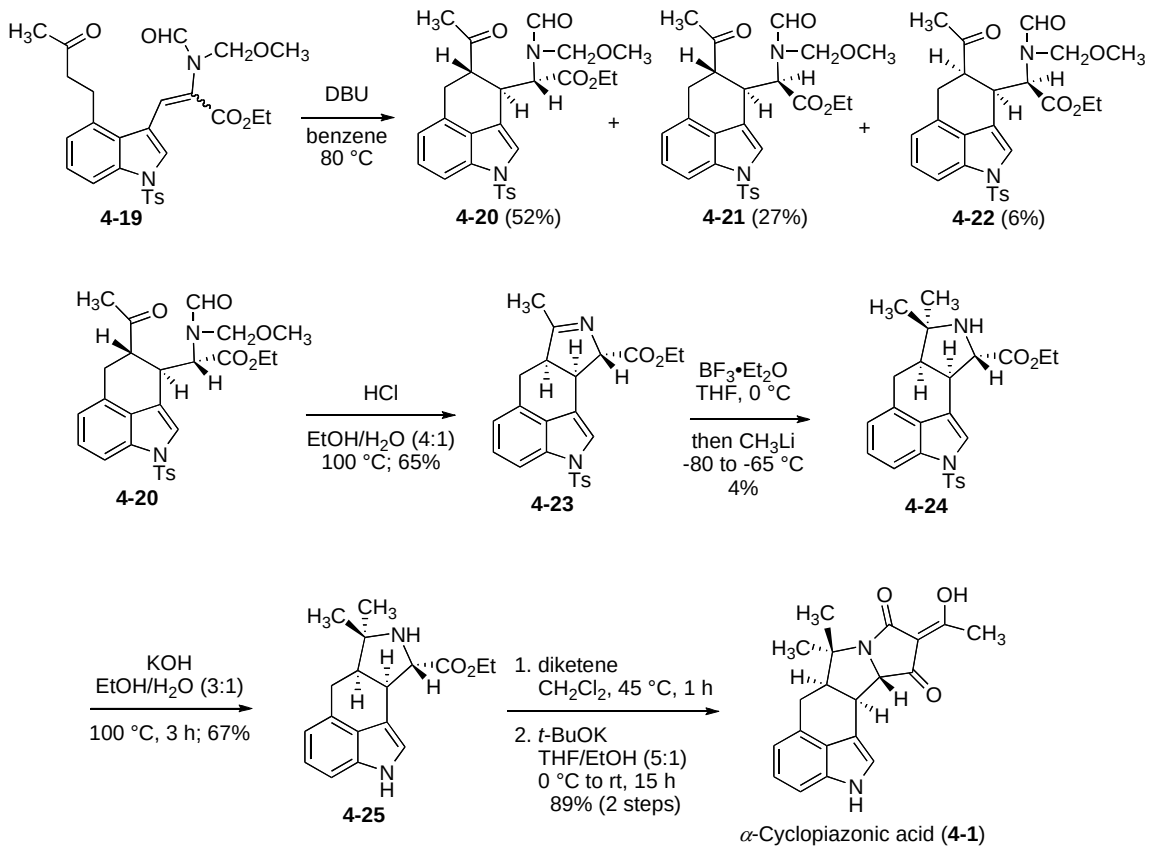
In 1984 Kozikowski and Greco reported the first racemic total synthesis of α-cyclopiazonic acid (Scheme 75).[192]



Scheme 75. Kozikowski's total synthesis of α-CPA **(4-1)**

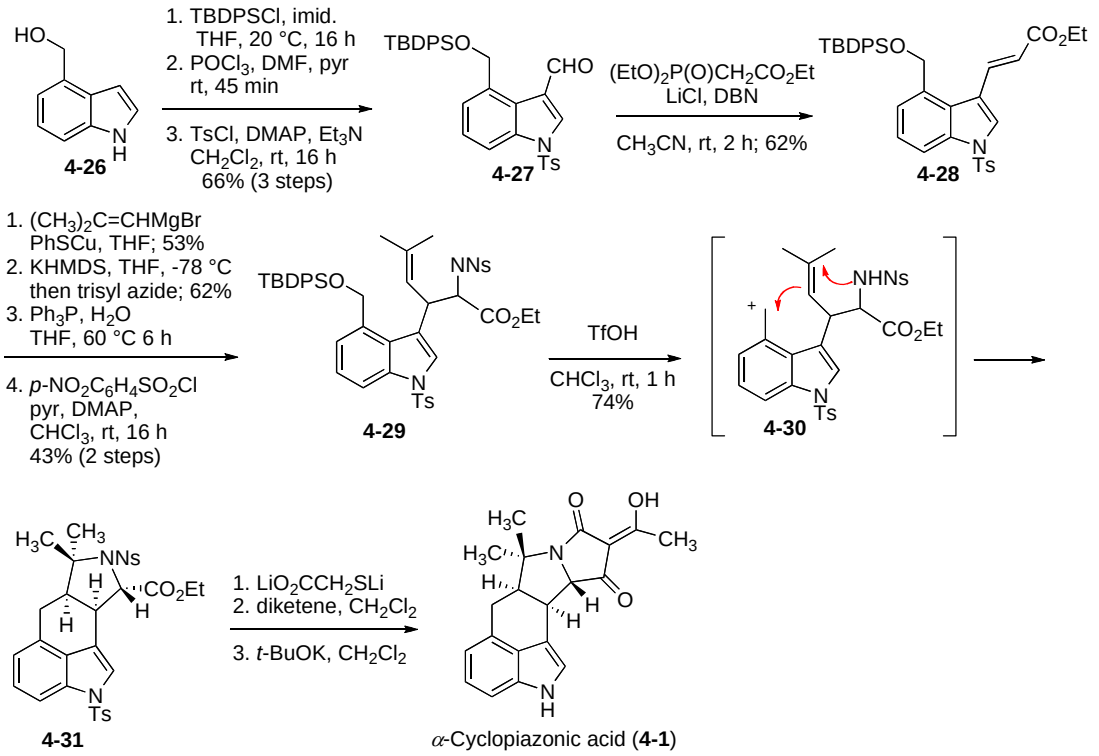
Indole **4-9** was prepared from 4-indolcarbaldehyde in 5 steps. Subsequent Vilsmeier-Haack reaction with $POCl_3$ and DMF, followed by a condensation with 2-acetamidomalonic acid monoethyl ester provided indole **4-10**, which was after an indole protection-acetal deprotection transformed to ketone **4-11**. In order to obtain tricyclic indole **4-13**, ketone **4-11** was first α-sulfenylated via its thermodynamic silyl enol ether, and then subjected to an intramolecular Michael reaction with DBU. Interestingly, while an X-ray analysis of **4-13** revealed that the two carbon appendages are *trans*, a subsequent Raney-Ni desulfurization led exclusively to the *cis* product **4-14**. This intermediate was further treated with $Mg(OTf)_2$ and thiophenol to effect D-ring formation and the synthesis of the α-phenylthio amide **4-15**. When **4-15** was exposed to the excess of dimethylzinc in chloroform, the thiophenyl substitution provided **4-16** in 73% yield. Finally, the *N*-acetyl deprotection with Meerwein's reagent, followed by the treatment of the free amine with diketene provided **4-17**, a direct precursor to α-cyclopiazonic acid. This intermediate was exposed to methanolic sodium methoxide, which resulted in the formation of *iso*-α-cyclopiazonic acid (**4-18**). To complete the synthesis, the authors isomerized **4-18** to **4-1** with Et_3N in chloroform, which provided a 2.5:1 mixture of **4-1** and the *iso*-compound **4-18**.

Similar to Kozikowski's approach, Natsume's synthesis utilizes a Michael addition for the construction of C-ring (Scheme 76).[193] However, due to the higher temperature for the cyclization reaction, a mixture of tricyclic stereoisomers **4-20**, **4-21**, and **4-22** was obtained in 8.7:4.5:1 ratio. Exposure of **4-20** to aqueous HCl, 2-methyl-1-pyrroline **4-23** was formed in 65% yield. The necessary *gem*-dimethyl moiety was introduced through an addition of CH_3Li in the presence of $BF_3 \bullet Et_2O$. After the tosyl group deprotection, the tetramic acid was elaborated using diketene, thus completing the synthesis of α-cyclopiazonic acid (**4-1**).



Scheme 76. Natsume's approach to **4-1**

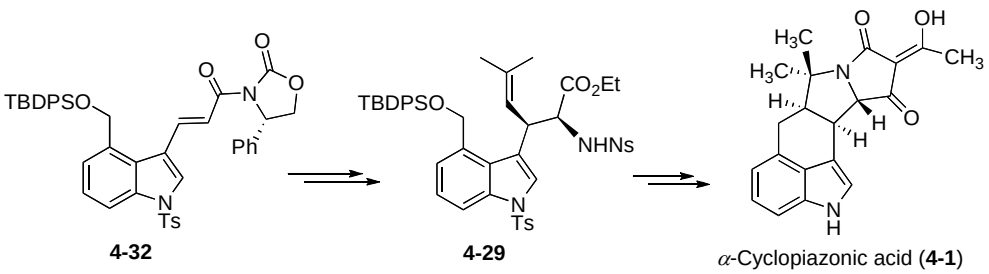
In 2005, Haskins and Knight reported a synthesis of α-cyclopiazonic acid through an implementation of an interesting cationic cascade reaction (Scheme 77).[194] Starting with indole-4-methanol **4-26**, aldehyde **4-27** was synthesized through an *O*-TBDPS protection, formylation under standard Vilsmeier conditions, and protection of the indole nitrogen by tosylation. Aldehyde **4-27** was further homologated by a Horner-Wadsworth-Emmons reaction, which yielded unsaturated ester **4-28**. Exposure of this ester to a Michael addition of 2-methylpropenylmagnesium bromide in the presence of phenylthiocopper, followed by a treatment with KHMDS and trisyl azide, engendered introduction of the necessary nitrogen functionality. Conversion into the corresponding free amino-ester was achieved under Staudinger conditions. Finally, *N*-nosylation gave the desired precursor **4-29**.



Scheme 77. Haskins and Knight's synthesis of **4-1**

Exposure of **4-29** to triflic acid in $CHCl_3$ cleanly provided the advanced tetracyclic **4-31**, presumably through an intermediate **4-30**, with the desired stereochemistry. Final deprotection of the secondary amine, followed by the previously reported procedure for the formation of the tetramic acid (diketene in CH_2Cl_2, and the subsequent exposure to *t*-BuOK) led smoothly to α-CPA (**4-1**).

Improvement of the Knight synthesis by Beyer and coworkers led to the first asymmetric total synthesis of α-CPA (Scheme 78).[195] 1,4-Addition of isopropenylcuprate to the chiral indolyl acrylic acid **4-32**, followed by a 1,2-addition of trisyl azide (*dr* 98:2), provided the bicyclic intermediate **4-29** in enantiomerically pure form. Further elaboration according to the Knight route led to the formation of **4-1**.



Scheme 78. Beyer's asymmetric synthesis of **4-1**

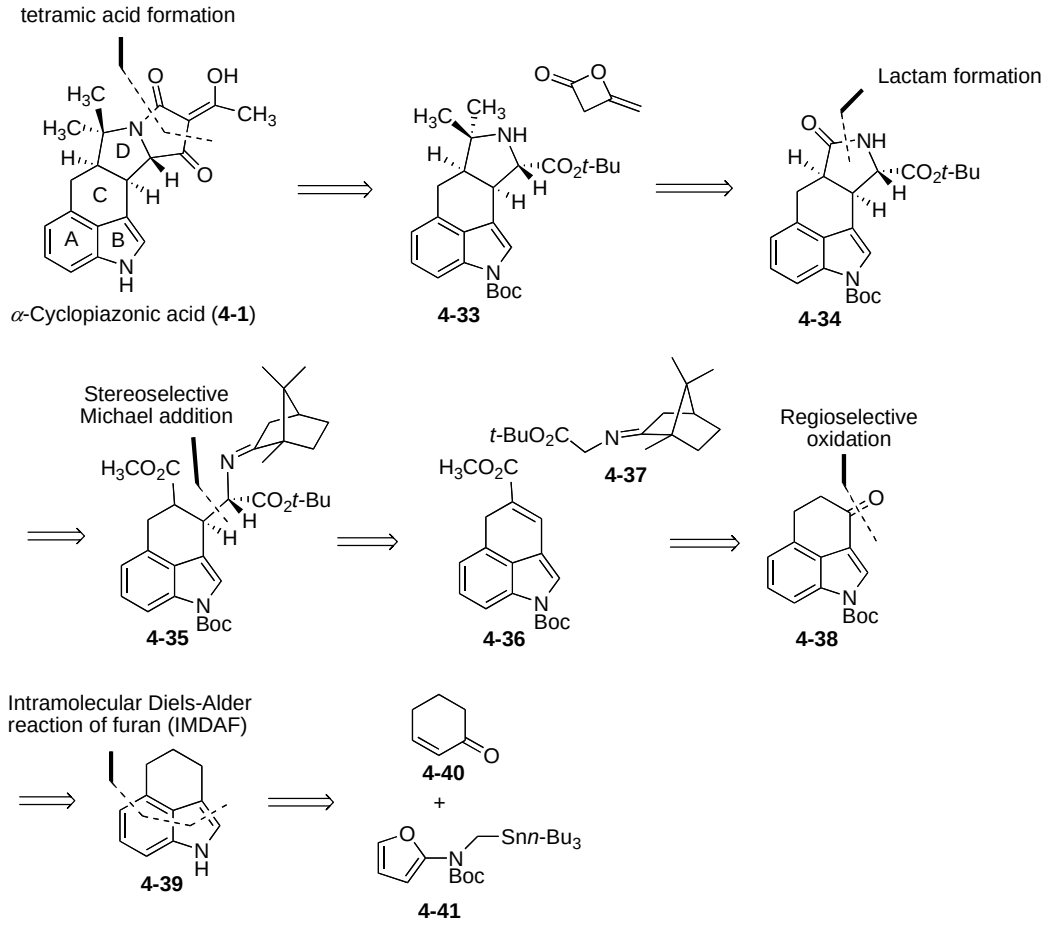
4.2 RESULTS AND DISCUSSION

4.2.1 Retrosynthetic Analysis of Cyclopiazonic acid (4-1)

After our success in the formation of the tricyclic indole **4-39** through an intramolecular furan Diels-Alder reaction (IMDAF), described in Chapter 2 of this thesis, and the successful implementation of this methodology in the synthesis of cycloclavine (Chapter 3), our attention turned to the related alkaloid cyclopiazonic acid (**4-1**).

Retrosynthetically, we envisioned that the formation of the tricyclic indole **4-39** through an IMDAF cascade could provide the part of the core structure of cyclopiazonic acid (Scheme 79). As in previous syntheses of this alkaloid, the initial disconnection was the tetramic acid formation, which could be accessed via a coupling of **4-33** with diketene. The requisite dimethylamine could be derived from the corresponding lactam **4-34**. The required stereochemistry at the C-D ring junction could be revealed following a stereoselective 1,4-addition of the camphor-derived *t*-butylglycine imine **4-37** to the α,β-unsaturated ester **4-36**, which could be synthesized from the corresponding ketone **4-38**. This ketone could further be

simplified to 2-cyclohexen-1-one (**4-40**) and stannane **4-41**, through an IMDAF cascade reaction followed by a regioselective oxidation of the tricyclic intermediate **4-39**.

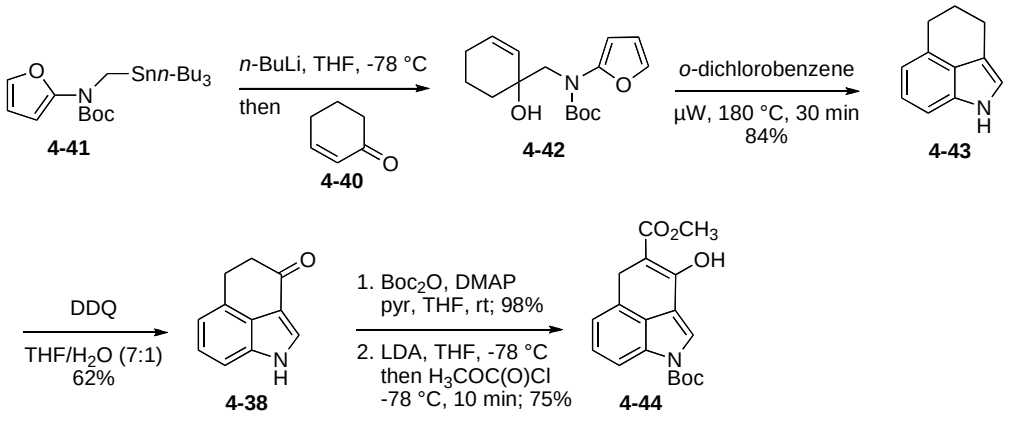


Scheme 79. Retrosynthetic analysis of cyclopiazonic acid **(4-1)**

4.2.2 Progress towards the Total Synthesis of Cyclopiazonic Acid

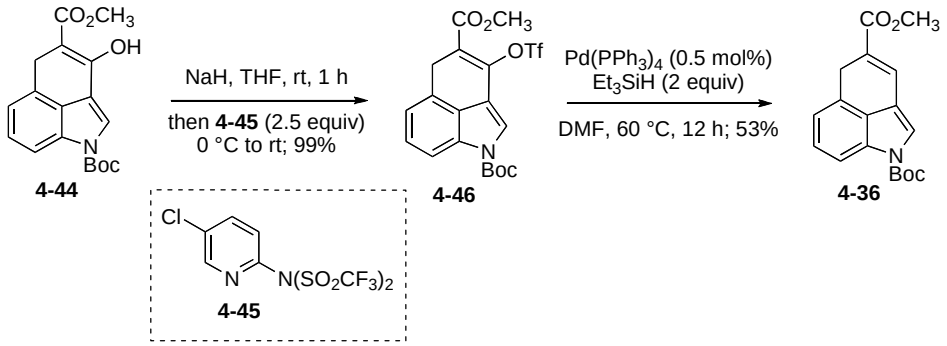
Our synthetic approach commences with the previously described coupling of 2-cyclohexene-1-one (**4-40**) and the lithiated analog of stannane **4-41** (Scheme 80). Alcohol **4-42** was cyclized under microwave conditions in *o*-dichlorobenzne or trifluorotoluene at 180 °C to provide **4-39** in 84% yield. Regioselective oxidation of the tricyclic indole **4-39** with DDQ in a mixture of water

and THF at room temperature,[196] followed by an *N*-Boc protection of the indole provided desired ketone **4-38**. When **4-38** was exposed to basic conditions (LDA, THF, -78 °C), and then treated with methyl cyanoformate (4 equiv), a formation of the enol **4-44** was observed in 75% yield. It is interesting to note that **4-44** exists in the enol form, and no ketone tautomer was observed by a ^{1}H NMR analysis at room temperature.



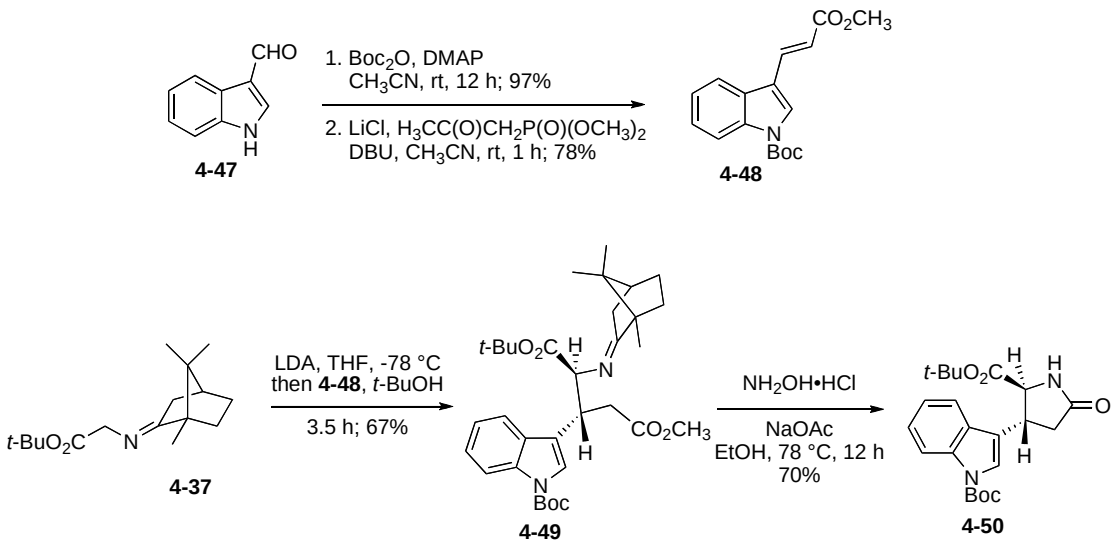
Scheme 80. Synthesis of the tricyclic ester **4-44**

Attempts towards the preparation of **4-36** through a three-step sequence (enol reduction, secondary alcohol mesylation, elimination)[197] from **4-44** failed, probably due to the inherent reactivity of the intermediary formed mesylate, which could not be isolated. Alternatively, triflation of the enol **4-44** with *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) in the presence of NaH, followed by the $Pd(PPh_3)_4$-assisted reduction with Et_3SiH in DMF provided **4-36** in 53% yield (2 steps).[198]



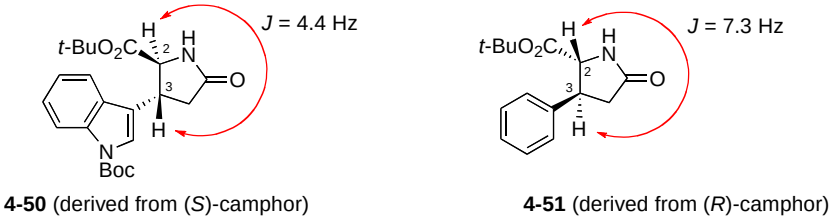
Scheme 81. Reduction of the enol **4-44**

With **4-36** in hand, we were now in a position to explore the construction of the D-ring through a stereoselective Michael addition followed by lactamization. In 1991, Kanemasa and coworkers reported a highly diastereoselective Michael addition of lithiated camphor imines of glycine esters to α,β-unsaturated esters to synthesize optically pure 5-oxopyrrolidine-2-carboxylates.[199,200] In order to test the viability of this approach, we first synthesized the oxopyrrolidine carboxylate on model system **4-48** (Scheme 82). Accordingly, indole-3-carbaldehyde (**4-47**) was *N*-protected and homologated to **4-48** through the Horner-Wadsworth-Emmons reaction. Michael addition of the lithium enolate, formed *in situ* by treating **4-37** with LDA at -78 °C, to the α,β-unsaturated ester **4-48** resulted in the formation of **4-49** in 67% yield. The camphor chiral auxiliary was readily removed by heating the adduct **4-49** at reflux with hydroxylamine hydrochloride and sodium acetate in EtOH, which provided **4-50** in 70% yield.



Scheme 82. Diastereoselective Michael addition of **4-49** to model system **4-48**

^{1}H NMR analysis of **4-50** revealed a discrepancy with regard to the configuration at the pyrrolidinone ring (Figure 20). The H-atom at C(2) of the pyrrolidinone moiety in **4-50** appeared as dublet (δ 4.30 ppm) with J = 4.4 Hz. However, in *t*-butyl (2*R*)-3-phenyl-5-oxopyrrolidine-2-carboxylate (**4-51**), synthesized by Kanemasa and coworkers using the same method, the corresponding C(2)-H appears as dublet (δ 4.03 ppm) with a coupling constant J = 7.3 Hz, indicating the desired *trans*-stereochemistry.

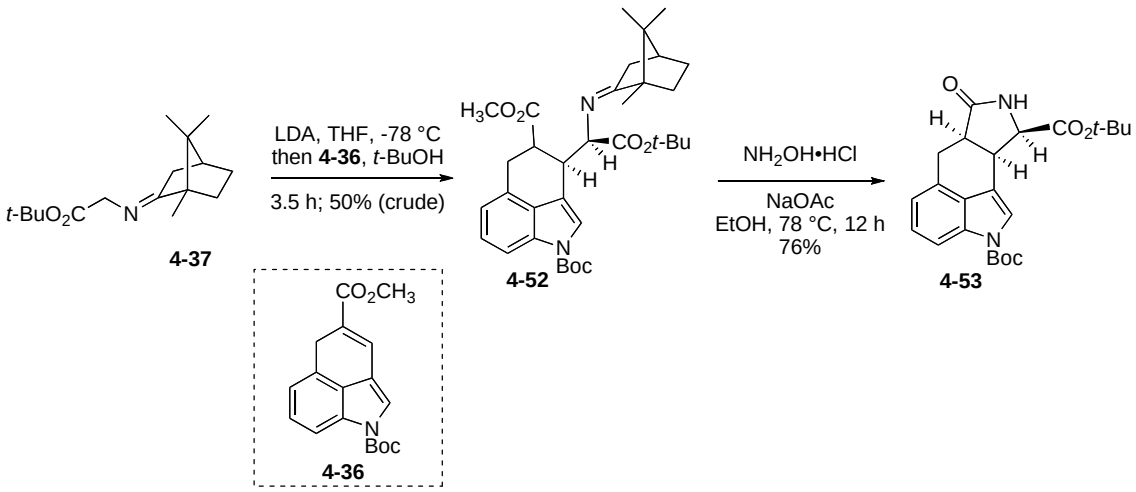


4-50 (derived from (*S*)-camphor) **4-51** (derived from (*R*)-camphor)

Figure 20. Comparison of the coupling constant $J_{H2\text{-}H3}$ in **4-50** and **4-51**

Having succeeded in the synthesis of the required pyrrolidinone ring in the model system, but keeping in mind the previously mentioned inconsistency with regard to the stereochemical outcome of this process, we decided to subject **4-36** to the same reaction conditions for the

Michael addition. Treatment of **4-37**, prepared from (*S*)-camphor and *t*-butyl glycinate,[201] with LDA at -78 °C in THF, followed by the addition of **4-36** and *t*-BuOH provided **4-52** (Scheme 83). Again, the camphor chiral auxiliary was removed by heating the adduct **4-52** at reflux with hydroxylamine hydrochloride and sodium acetate in EtOH, providing **4-53** in 76% yield.



Scheme 83. Enolate addition to **4-36** and formation of the tetracyclic **4-53**

Comparison of the ^{1}H NMR data for **4-53** with **4-31** (an advanced intermediate in the Knight synthesis of cyclopiazonic acid),[194] as well as with *iso*-cyclopiazonic acid (**4-18**, synthesized by Beyer *et al*)[195] indicated a *cis*-relationship between H(4) and H(5) in **4-53** (Figure 21; cyclopiazonic acid numbering).

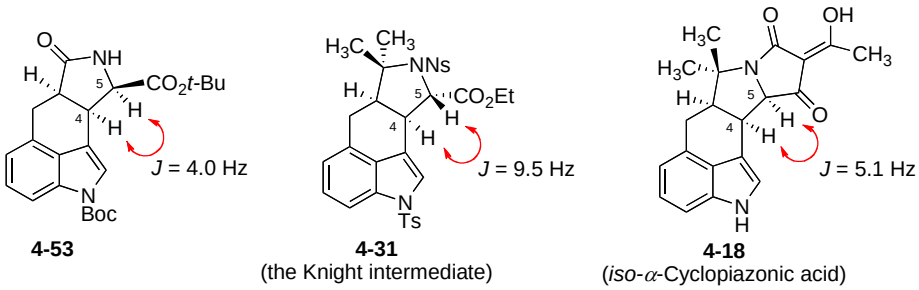


Figure 21. Comparison of the $J_{H4\text{-}H5}$ coupling constant in **4-53**, **4-31**, and **4-18**

This inconsistency with the previously reported data could reflect the effect of the α-substituent as a part of the ring in the starting α,β-unsaturated ester, which enforces a *Z*-geometry of the olefin. Although the Kanemasa model suggests the formation of the desired *trans*-configuration between H(4) and H(5) (Figure 22), it is possible that the α-substituent introduces an additional strain in the transition state, thus favoring a disruption of the chelation between Li and imine N-atom (Figure 21). Or, perhaps more importantly, the steric hindrance introduced by the α-substituent might disfavor the coordination of the α,β-unsaturated ester from the α-face of the camphor-auxiliary, thus exposing the *re*-face of the enolate to the reaction with the electrophile.

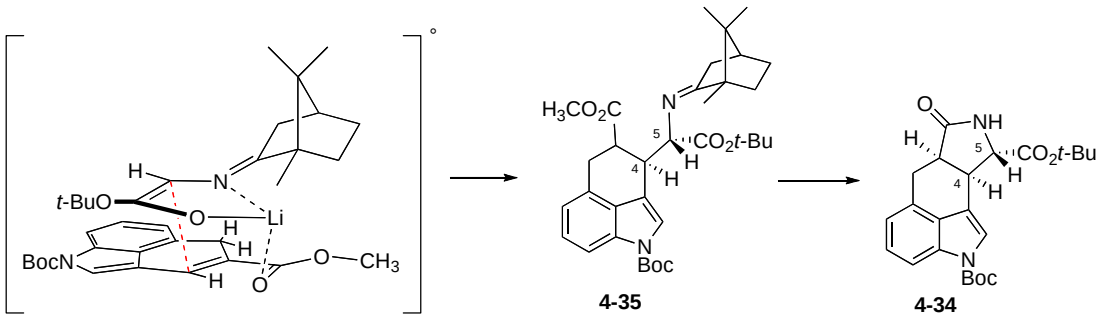
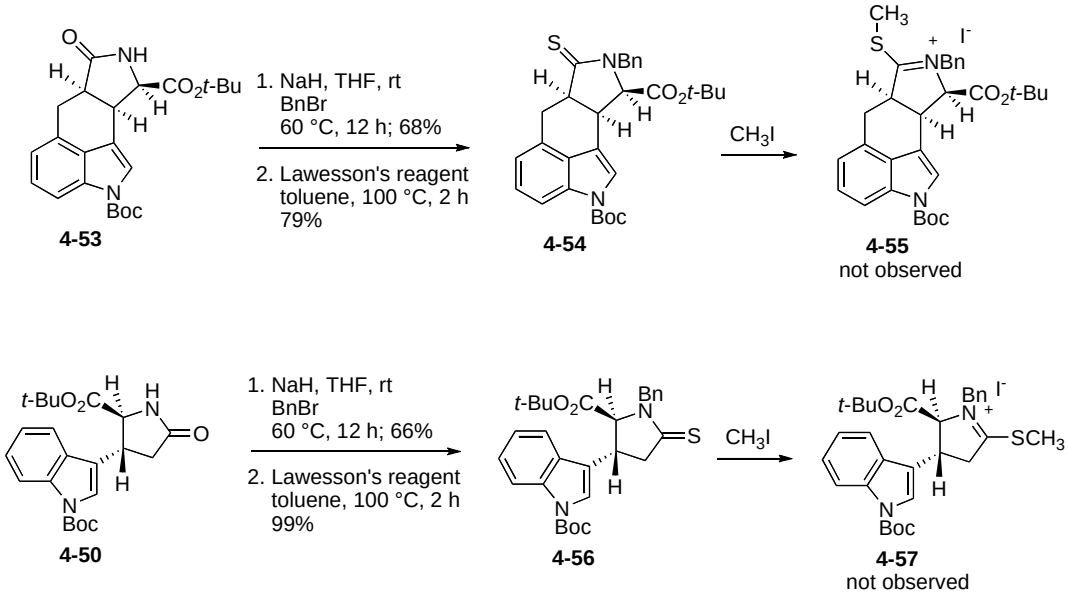


Figure 22. Kanemasa's transition state for the Michael addition

Although the configuration at the pyrrolidinone ring was not correctly set in the Michael addition step, we surmised that it would be possible to change the configuration at C(5) in the later stage of the synthesis through a thermodynamic equilibration with *t*-BuOK/*t*-BuOH. According to our earlier plan, we were now in a position to convert the previously synthesized lactam into a 2,2-dimethylamine.

In 2008, Renaud and coworkers developed an efficient method for the synthesis of *gem*-2,2-disubstituted tertiary amines from the corresponding lactams or amides.[202] This protocol is based on the reaction of thioiminium ions, easily prepared from lactams and amides with

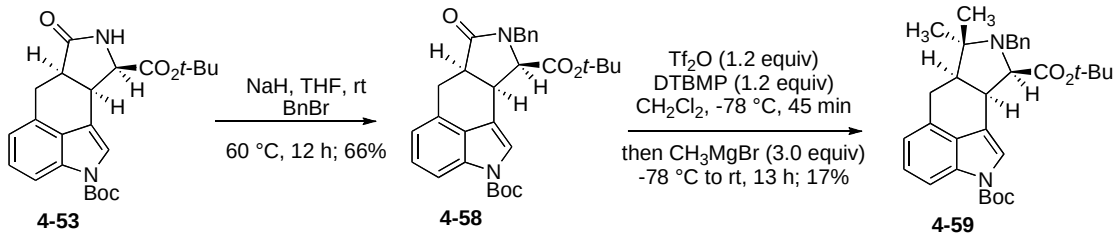
organometallic reagents such allylmagnesium, benzylmagnesium, and primary alkylcerium reagents. Following this protocol, we converted **4-53**, after a benzyl protection, to the corresponding thiolactam **4-54** (Scheme 84). Unfortunately, when **4-54** was exposed to CH_3I, no *S*-methylation was observed, and only starting material was recovered in this reaction. Similarly, the exposure of **4-56**, derived form **4-50** in a two-step sequence (*N*-benzylation followed by the lactam conversion to the thiolactam) to the methylation conditions did not give rise to desired thioiminium salt **4-57**. Instead, starting thiolactam was the only observed material.



Scheme 84. Attempts towards the formation of the thioiminium salts **4-55** and **4-57**

Another procedure for reductive alkylation of lactams with Grignard or organolithium reagents was reported by Huang and coworkers.[203] In this direct one pot transformation, a lactam is activated with triflic anhydride, and then treated with an appropriate Grignard or organolithium reagent. Following this procedure, *N*-benzyl protected **4-53** was first treated with Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), and then with a solution of CH_3MgBr (Scheme 85). After a lot of experimentation, we found that **4-58** could be converted to

the corresponding amine **4-59** following this protocol, and warming the reaction mixture to room temperature over 12 h. Seemingly successful, this transformation provided amine **4-59** in only 17% yield, as confirmed by ^{1}H NMR and HRMS analyses. However, the reaction conditions were found to be irreproducible, and this protocol was finally abandoned.



Scheme 85. One-pot conversion of **4-53** to 2,2-dimethylamine **4-59**

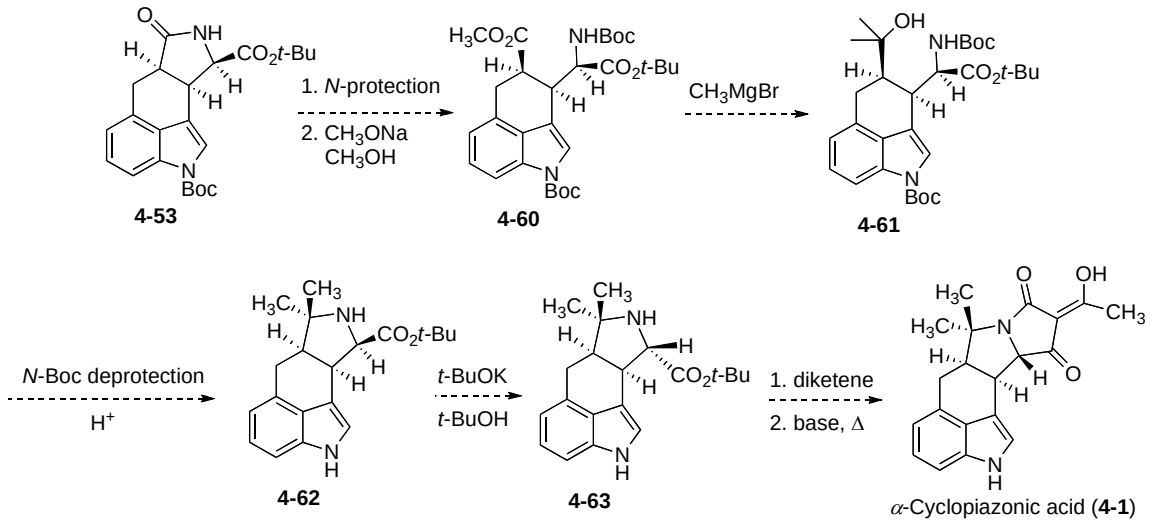
We also explored an alternative route, which relied on a cyclopropanation of the amide carbonyl moiety.[204,205] Once installed, the cyclopropane ring could generate the required *gem*-dimethyl amine through a hydrogenolysis step. However, several protocols aimed at the cyclopropanation of the amide carbonyl failed, and only starting material was observed and recovered.

This inherent stability of the amide carbonyl in **4-53** or the thioamide thiocarbonyl in **4-54** might originate from steric hindrance. The amide group of the tetrasubstituted pyrrolidinone ring in **4-53** could be difficult to access by nucleophiles, such as Grignard or organotitanium reagents, thus leading to either no reaction or very low yielding process.

4.2.3 Future Directions

To complete the synthesis of α-cyclopiazonic acid, we propose using **4-53** as a key advanced intermediate (Scheme 86). Protection of the amide nitrogen atom, followed by a basic hydrolysis

of the lactam would provide aminoester **4-60**. Addition of the CH_3MgBr to this intermediate should lead to tertiary alcohol **4-61**, with the *gem*-dimethyl moiety installed. If **4-61** is subjected to acidic conditions, double *N*-Boc-deprotection is expected, with a concomitant pyrrolidine formation.[206] At this point, we propose the ester group isomerization at C(5), in order to decrease the steric hindrance on the α-face of the pyrrolidinone ring in **4-62**. Finally, treatment of **4-63** with diketene, followed by *t*-BuOK-induced tetramic acid formation, as previously shown, would lead to desired α-cyclopiazonic acid (**4-1**).

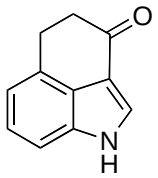


Scheme 86. Proposed route for the completion of cyclopiazonic acid

4.3 EXPERIMENTAL PART

General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. Reactions carried out at -78 °C employed a dry ice/acetone bath. THF and Et_2O were dried by distillation over Na/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina filtration system. Unless

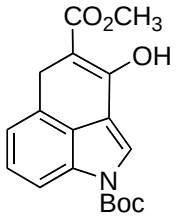
otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F_{254} plates (250 μm layer thickness, particle size 0.040-0.055 mm, 230-240 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 M H_2SO_4 solution), or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1 % NaOH solution). Flash chromatography on SiO_2 was used to separate and purify the reaction crude mixtures. Microwave reactions were performed on a Biotage Initiator microwave reactor. ^1H and ^{13}C NMR were recorded on a Bruker Avance 300 instrument. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were run at 300, 400 or 500 MHz, and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, sept = septet, m = multiplet, br = broad, app = apparent), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained using a proton-decoupled pulse sequence with a d1 of 3 sec, and are tabulated by observed peak. LC/MS analyses were obtained from a Helwett Packard Series 1100 MSD. RP HPLC was obtained from Gilson Series 215, using C18 column, Bio-rad Laboratoris, 250 x 4.6 mm. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Infrared spectra were measured on a Nicolet AVATAR 360 FT-IR E.S.P. spectrometer (KBr or neat) or Smiths Detection IdentifyIR FT-IR spectrometer (ATR).



4,5-Dihydrobenzo[*cd*]indol-3(1*H*)-one (4-38).[207] To a solution of tricyclic indole **4-39** (378.1 mg, 2.404 mmol) in THF/water (21 mL THF + 3 mL water) at 0 °C under Ar, was added a solution of DDQ (1.09 g, 4.81 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 2 h, concentrated under reduced pressure, diluted with EtOAc (10 mL), and extracted with EtOAc (6 x 20 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3, brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (20% acetone/chloroform) gave **4-38** (257.2 mg, 62 %) as an off-white solid: Mp 189-190 °C; IR (ATR) 3086, 3037, 1629, 1599, 1521 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.78 (br s, 1 H), 7.74 (d, 1 H, J = 2.8 Hz), 7.32 (d, 1 H, J = 8.0 Hz), 7.25 (app t, 1 H, J = 8.0 Hz), 7.12 (dd, 1 H, J = 6.8, 0.8 Hz), 3.38 (app t, 2 H, J = 6.8 Hz), 2.91 (app t, 2 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.9, 133.7, 129.1 (2), 124.2 (2), 118.5, 114.0, 109.3, 39.8, 27.6; HRMS (TOF ESI) *m/z* calcd for $C_{10}H_{18}NO$ $[M+H]^+$ 172.0762, found 172.0766.

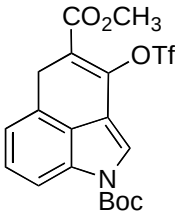
***tert*-Butyl 3-oxo-4,5-dihydrobenzo[*cd*]indole-1(3*H*)-carboxylate.**[207] To a solution of **4-38** (257.1 mg, 1.502 mmol) in THF (15 mL) were added DMAP (183.5 mg, 1.502 mmol), pyridine (121 μL, 1.50 mmol) and Boc_2O (393.3 mg, 1.802 mmol), and stirred at room temperature for 13 h. The reaction mixture was diluted with EtOAc (15 mL), washed with 1.0 M aqueous HCl, and extracted with EtOAc (4 x 15 mL). The combined organic layers were washed with brine, dried

(Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 ($CHCl_3$) gave *tert*-butyl 3-oxo-4,5-dihydrobenzo[*cd*]indole-1(3*H*)-carboxylate (398.5 mg, 98%) as a white solid: Mp 109.4-110.6 °C; IR (ATR) 3286, 1728, 1676, 1556, 1247, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.07 (s, 1 H), 7.86 (d, 1 H, *J* = 8.0 Hz), 7.33 (t, 1 H, *J* = 7.2 Hz), 7.16 (dd, 1 H, *J* = 7.2, 0.4 Hz), 3.33 (app t, 2 H, *J* = 6.8 Hz), 2.86 (app t, 2 H, *J* = 6.8 Hz), 1.69 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.6, 149.3, 133.5, 129.8, 129.3, 125.9, 124.3, 120.7, 116.6, 113.0, 85.1, 40.0, 28.0, 27.4; HRMS (TOF ESI) *m/z* calcd for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1297, found 272.1287.

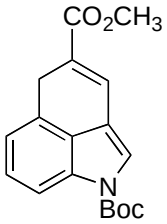


1-*tert*-Butyl 4-methyl 3-hydroxybenzo[*cd*]indole-1,4(5*H*)-dicarboxylate (4-44). To a stirred solution of diisopropylamine (0.109 mL, 0.774 mmol) in THF (2 mL) at -10 °C was added *n*-BuLi (1.6 in hexanes, 0.461 mL, 0.737 mmol), stirred for 20 min, and cooled to -78 °C. To this solution was added a solution of *tert*-butyl 3-oxo-4,5-dihydrobenzo[*cd*]indole-1(3*H*)-carboxylate (100.0 mg, 0.3686 mmol) in THF (2 mL), stirred for 30 min, treated with methyl cyanoformate (100.0 μL, 1.260 mmol), and stirred at -78 °C for 45 min. The reaction was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (4 x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% EtOAc/hexanes) gave **4-44** (78.2 mg, 75%) as a white solid: Mp 156.6-158.2 °C; IR (ATR) 2975, 2950, 1728, 1374, 1245, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 12.51 (s, 1 H), 7.70-7.60 (br s, 1 H), 7.67 (s, 1 H), 7.26 (t, 1 H, *J* = 8.0 Hz), 7.02 (d, 1 H, *J* = 7.2 Hz), 3.96 (s, 2 H), 3.86 (s, 3 H), 1.69 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.9,

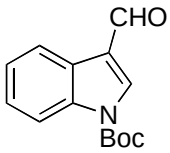
162.0, 149.5, 133.7, 129.0, 128.4, 126.2, 120.8, 120.3, 113.3, 112.4, 97.5, 84.1, 51.7, 28.7, 28.1; HRMS (TOF ESI) *m/z* calcd for $C_{18}H_{19}NO_5Na$ $[M+Na]^+$ 352.1161, found 352.1199.



1-*tert*-Butyl 4-ethyl 3-(((trifluoromethyl)sulfonyl)oxy)benzo[*cd*]indole-1,4(5*H*)-dicarboxylate (4-46). To a suspension of NaH (291.7 mg, 12.16 mmol) in THF (2 mL) at 0 °C was added a solution of **4-44** (727.9 mg, 2.210 mmol) in THF (6 mL), and stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, treated with a solution of Comins reagent (2.13 g, 5.41 mmol) in THF (5 mL), and stirred at room temperature for 2.5 h. The reaction mixture was slowly transferred to a cold saturated aqueous NH_4Cl (25 mL), and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (5% EtOAc/ hexanes) gave **4-46** (1.01 g, 99%) as an off-white solid: IR (ATR) 2975, 1735, 1718, 1232, 1197 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1 H), 7.54 (s, 1 H), 7.32 (t, 1 H, J = 8.0 Hz), 7.06 (dd, 1 H, J = 7.5, 0.5 Hz), 4.36 (s, 2 H), 3.89 (s, 3 H), 1.69 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 149.2, 144.9, 133.7, 128.6, 127.3, 126.8, 120.8, 120.4, 119.9, 118.5 (q, J = 318 Hz), 113.1, 112.1, 84.9, 52.3, 33.5, 28.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NO_7SF_3$ $[M+H]^+$ 462.0834, found 462.0802.

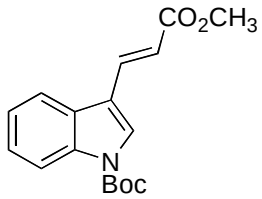


1-*tert*-Butyl 4-methyl benzo[*cd*]indole-1,4(5*H*)-dicarboxylate (4-36). To the solution of **4-46** (370.0 mg, 0.8019) in DMF (5.7 mL) were added $Pd(PPh_3)_4$ (43.7 mg, 0.0379 mmol) and Et_3SiH (250 μL, 1.56 mmol), heated to 60 °C for 2 h, diluted with water, and extracted with EtOAc (6 x 10 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10% EtOAc/hexanes) gave **4-36** (133.1 mg, 53%) as colorless oil: IR (ATR) 3286, 2982, 2947, 1724, 1702, 1364, 1128 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.67 (d, 1 H, *J* = 2.0 Hz), 7.66 (d, 1 H, *J* = 2.0 Hz), 7.46 (br s, 1 H), 7.26 (app t, 1 H, *J* = 7.6 Hz), 7.05 (dd, 1 H, *J* = 7.2, 0.4 Hz), 4.02 (s, 2 H), 3.80 (s, 3 H), 1.66 (s, 9 H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 167.3, 129.6, 129.5, 128.7, 126.9, 121.8, 121.0, 116.3, 113.0, 84.3, 52.1, 29.6, 28.2.

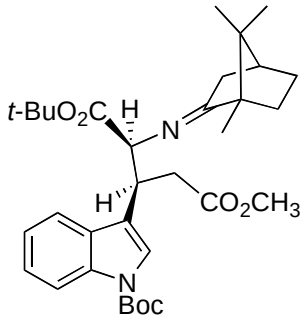


***tert*-Butyl 3-formyl-1*H*-indole-1-carboxylate.**[208] To a stirred solution of 3-indolecarbaldehyde (2.00 g, 13.8 mmol) in acetonitrile (25 mL) were added Boc_2O (3.91 g, 17.9 mmol) and DMAP (168.3 mg, 1.378 mmol), and stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc (10 mL), sequentially washed with 1.0 M aqueous HCl (5 mL), water, brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10 EtOAc/hexanes) gave the *tert*-Butyl 3-formyl-1*H*-indole-1-carboxylate (3.28 g, 97%) as a white solid: IR (ATR) 3059, 2816, 1741, 1676, 1357, 1131, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ

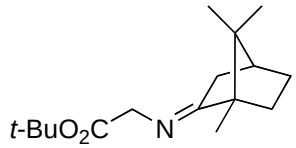
10.12 (s, 1 H), 8.30 (d, 1 H, *J* = 6.8 Hz), 8.25 (s, 1 H), 8.16 (d, 1 H, *J* = 7.6 Hz), 7.43 (dt, 1 H, *J* = 7.6, 1.6 Hz), 7.39 (dt, 1 H, *J* = 7.6, 1.2 Hz), 1.72 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.7, 148.7, 136.5, 135.9, 126.0 (2C), 124.5, 122.1, 121.5, 115.1, 85.6, 28.0; HRMS (TOF ESI) *m/z* calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1041.



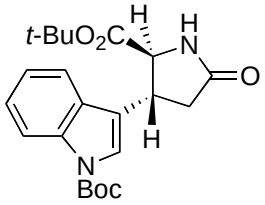
(*E*)-*tert*-Butyl 3-(3-methoxy-3-oxoprop-1-enyl)-1*H*-indole-1-carboxylate (4-48).[209] To a solution of LiCl (112.3 mg, 2.650 mmol) in CH_3CN (15 mL) at room temperature was added trimethyl phosphonoacetate (0.38 mL, 2.6 mmol), followed by DBU (0.39 mL, 2.6 mmol). To this mixture was added a solution of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (0.50 g, 2.0 mmol) in acetonitrile (2 mL), stirred at room temperature for 1 h, and diluted with Et_2O (20 mL). The organic layer was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (15% EA/ hexanes) gave **4-48** (0.48 g, 78%) as a white solid: Mp 82.4-85.6 °C; IR (ATR) 3059, 2975, 1713, 1359, 1142, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, 1 H, *J* = 8.0 Hz), 7.82-7.87 (m, 3 H), 7.39 (t, 1 H, *J* = 7.2 Hz), 7.34 (t, 1 H, *J* = 7.6 Hz), 6.56 (d, 1 H, *J* = 16.4 Hz), 3.83 (s, 3 H), 1.69 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 149.1, 136.6, 136.2, 128.7, 127.8, 125.2, 123.6, 120.2, 116.9, 116.7, 115.5, 84.7, 51.6, 28.1; HRMS (TOF ESI) *m/z* calcd for $C_{17}H_{19}NO_4Na$ $[M+Na]^+$ calcd 324.1212, found 324.1215.



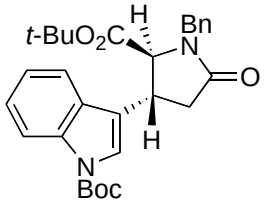
(*Z*)-1-*tert*-Butyl 5-methyl 3-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylideneamino)pentanedioate (4-49). To a solution of DIPA (151 μL, 1.07 mmol) in THF (1 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 667 μL, 1.07 mmol), stirred at room temperature for 15 min, and cooled to -78 °C. To this solution were added imine **4-37** (300.0 mg, 1.130 mmol) as a solution in THF (1 mL), then *t*-BuOH (100 μL, 1.07 mmol) as a solution in THF (0.5 mL), and indole **4-48** (321.5 mg, 1.067 mmol) as a solution in THF (1 mL), in this order. The reaction mixture was stirred at -78 °C for 3.5 h, quenched with water, and extracted with EtOAc (5 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (20% EtOAc/hexanes) gave **4-49** (429.2 mg, 67%) as a colorless oil: IR (ATR) 3027, 2934, 1728, 1366, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11 (br s, 1 H), 7.68 (d, 1 H, J = 7.2 Hz), 7.38 (br s, 1 H), 7.32-7.22 (m, 3 H), 4.23-4.12 (m, 1 H), 4.13 (d, 1 H, J = 6.0 Hz), 3.54 (s, 2 H), 3.53 (s, 1 H), 2.97-2.84 (m, 2 H), 2.22 (dt, 1 H, J = 16.8, 4.0 Hz), 1.90-1.73 (m, 3 H), 1.65 (s, 9 H), 1.36 (s, 3 H), 1.32 (s, 9 H), 1.02 (s, 3 H), 0.89 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.3, 172.8, 170.1, 149.6, 135.2, 129.9, 124.3, 123.1, 122.4, 120.8, 119.3, 115.1; HRMS (TOF ESI) *m/z* calcd for $C_{33}H_{47}N_2O_6$ $[M+H]^+$ 567.3434, found 567.3427.



***tert*-Butyl 2-((*Z*)-((1*R*,4*S*)-1,7,7─trimethylbicyclo[2.2.1]heptan─2─ylidene)amino)acetate (4-37).** To a solution of (*S*)-camphor (2.00 g, 13.1 mmol) in DME (20 mL) at room temperature was added a mixture of P_2S_5 (5.8 g, 26 mmol) and $NaHCO_3$ (5.8 g, 71 mmol) slowly (in 1.5 g portions), and stirred at room temperature for 30 min. The solution was heated to 90 °C slowly, and then the rest of the $P_2S_5/NaHCO_3$ mixture was added at 90 °C. The mixture was stirred at this temperature for 1 h, then cooled to room temperature, poured into ice-water (70 mL), stirred for 30 min, and filtered off. The residue (yellowish thick liquid) was dissolved in toluene, concentrated *in vacuo*. This procedure was repeated 3 times, to obtain crude (*S*)-thiocamphor (1.23 g, 56%), which was used in the next step without further purification or characterization. To a solution of *t*-butyl glycinate (1.0 g, 7.6 mmol) in toluene (12.5 mL) was added thiocamphor (1.23 g, 7.31 mmol) in one portion. The mixture was heated to 110 °C for 14 h, concentrated *in vacuo*, and purified by column chromatography on SiO_2 (20% EtOAc/hexanes) to obtain **4-37** (1.28 g, 70%) as a yellowish oil: IR (ATR) 2956, 2885, 1735, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.03 (d, 1 H, *J* = 16.5 Hz), 3.96 (d, 1 H, *J* = 16.5 Hz), 2.30 (dt, 1 H, *J* = 17.0, 3.5 Hz), 1.95 (t, 1 H, *J* = 4.5 Hz), 1.88-1.83 (m, 1 H), 1.80 (d, 1 H, *J* = 17.0 Hz), 1.68 (dt, 1 H, *J* = 12.5, 4.5 Hz), 1.48-1.40 (m, 1 H), 1.45 (s, 9 H), 1.21 (ddd, 1 H, *J* = 13.0, 9.5, 4.5 Hz), 1.01 (s, 3 H), 0.93 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.0, 169.5, 80.9, 54.7, 54.1, 47.2, 43.8, 35.6, 31.9, 28.1, 27.4, 19.6, 18.9, 11.2; HRMS (TOF ESI) *m/z* calcd for $C_{16}H_{28}NO_2$ $[M+H]^+$ 266.2120, found 266.2115.

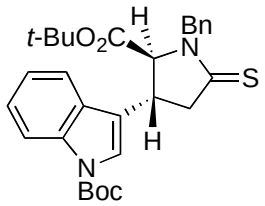


***tert*-Butyl 3-(2-(*tert*-butoxycarbonyl)-5-oxopyrrolidin-3-yl)-1*H*-indole-1-carboxylate (4-50).** To a solution of **4-49** (200.0 mg, 0.3529 mmol) in EtOH (1 mL) were added hydroxylamine hydrochloride (49.0 mg, 0.706 mmol) and sodium acetate trihydrate (96.0 mg, 0.706 mmol), heated to reflux for 12 h, cooled to room temperature, and then concentrated *in vacuo*. Purification by chromatography on SiO_2 (20% EtOAc/hexanes) gave **4-50** (98.6 mg, 70%) as a white solid: IR (ATR) 3301, 2975, 1713, 1702, 1698, 1359, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, 1 H, *J* = 7.2 Hz), 7.62 (d, 1 H, *J* = 7.6 Hz), 7.53 (s, 1 H), 7.38 (t, 1 H, *J* = 7.6 Hz), 7.29 (t, 1 H, *J* = 7.2 Hz), 6.30 (br s, 1 H), 4.30 (d, 1 H, *J* = 4.4 Hz), 3.98-3.93 (m, 1 H), 2.92 (dd, 1 H, *J* = 17.6, 9.6 Hz), 2.65 (dd, 1 H, *J* = 17.2, 5.6 Hz), 1.69 (s, 9 H), 1.51 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8, 170.4, 149.4, 135.9, 128.6, 124.8, 122.7, 122.4, 120.9, 118.8, 115.6, 83.9, 82.8, 61.8, 36.0, 35.4, 28.1, 27.9; HRMS (TOF ESI) *m/z* calcd for $C_{22}H_{29}N_2O_5$ $[M+H]^+$ 401.2076, found 401.2079.



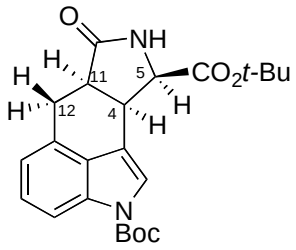
***tert*-Butyl 3-(1-benzyl-2-(*tert*-butoxycarbonyl)-5-oxopyrrolidin-3-yl)-1*H*-indole-1-carboxylate.** To a suspension of NaH (1.5 mg, 0.062 mmol) in THF (0.2 mL) at room temperature was added **4-50** (25.0 mg, 0.0624 mmol), stirred at room temperature for 15 min, and then treated with benzyl bromide (7.4 μL, 0.062 mmol). The mixture was heated to reflux for 5 h, cooled to

room temperature, diluted with EtOAc (5 mL), and slowly quenched with water. After extraction with EtOAc (4 x 5 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification on SiO_2 (30% EtOAc/hexanes) gave *tert*-butyl 3-(1-benzyl-2-(*tert*-butoxycarbonyl)-5-oxopyrrolidin-3-yl)-1*H*-indole-1-carboxylate (20.1 mg, 66%) as a white solid: IR (ATR) 2973, 1724, 1696, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, 1 H, *J* = 7.8 Hz), 7.42-7.16 (m, 9 H), 5.04 (d, 1 H, *J* = 14.7 Hz), 4.09 (d, 1 H, *J* = 14.7 Hz), 3.95 (d, 1 H, *J* = 3.0 Hz), 3.75 (dt, 1 H, *J* = 9.3, 3.0 Hz), 3.08 (dd, 1 H, *J* = 17.1, 9.3 Hz), 2.68 (dd, 1 H, *J* = 17.1, 3.9 Hz), 1.67 (s, 9 H), 1.47 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 170.2, 149.4, 135.5, 128.6 (2C), 128.5, 127.8, 124.8, 122.6, 121.9, 121.2, 118.7, 115.5, 83.9, 82.7, 65.6, 45.8, 36.1, 33.1, 28.2, 27.9.



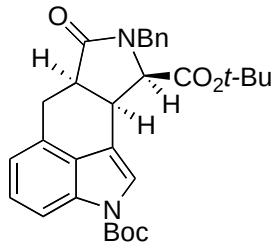
***tert*-Butyl 3—((2*R*)—1—benzyl-2-(*tert*-butoxycarbonyl)-5-thioxopyrrolidin-3-yl)-1*H*-indole-1-carboxylate (4-56).** To a solution of *tert*-butyl 3-(1-benzyl-2-(*tert*-butoxycarbonyl)-5-oxopyrrolidin-3-yl)-1*H*-indole-1-carboxylate (20.0 mg, 0.0408 mmol) in toluene (1.5 mL) was added Lawesson's reagent (10.7 mg, 0.0265 mmol), heated to 100 °C for 2 h, and cooled to room temperature. The reaction mixture was concentrated *in vacuo*, and purified by column chromatography (15% EtOAc in hexanes) to obtain **4-56** (19.0 mg, 92%) as a white solid: IR (ATR) 3059, 2978, 1726, 1452, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, 1 H, *J* = 8.0 Hz), 7.39-7.17 (m, 10 H), 4.41 (d, 1 H, *J* = 14.8 Hz), 4.23 (d, 1 H, *J* = 3.2 Hz), 3.81 (dt, 1 H, *J* = 8.4, 2.8 Hz), 3.63 (dd, 1 H, *J* = 17.6, 8.4 Hz), 3.35 (dd, 1 H, *J* = 17.6, 3.2 Hz), 1.68 (s, 9 H), 1.48 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.4, 168.5, 149.4, 135.7, 134.2, 128.7, 128.6, 128.4,

128.1, 124.8, 122.6, 122.1, 120.3, 118.5, 115.5, 84.0, 83.3, 72.2, 50.7, 49.4, 35.2, 28.1, 27.9; HRMS (TOF ESI) *m/z* calcd for $C_{29}H_{35}N_2O_4S$ $[M+H]^+$ 507.2318, found 507.2333.

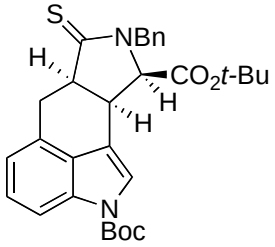


(6a*R*,9*S*,9a*R*)-Di-*tert*-butyl 7-oxo-6,6a,7,8,9,9a-hexahydro-2*H*-isoindolo[4,5,6-*cd*]indole-2,9-dicarboxylate (4-53). To a solution of diisopropylamine (8.9 μL, 0.064 mmol) in THF (0.1 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 39.5 μL, 0.063 mmol), stirred for 15 min, and cooled to -78 °C. To this solution was added a solution of imine **4-37** (16.7 mg, 0.063 mmol) in THF (0.1 mL), *t*-BuOH (6.0 μL, 0.063 mmol), and a solution of **4-36** (19.8 mg, 0.063 mmol) in THF (0.1 mL). This mixture was stirred at -78 °C for 3 h, warmed to -30 °C for 45 min, quenched with saturated aqueous NH_4Cl, extracted with EtOAc (4 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography on SiO_2 (10-15% EtOAc/hexanes) gave the corresponding indole **4-35** (21.8 mg, 84%) as colorless oil, which was subjected to the next step directly, without further characterization. To a solution of **4-35** (48.9 mg, 0.0845 mmol) in EtOH (0.3 mL) were added hydroxylamine hydrochloride (11.7 mg, 0.169 mmol) and sodium acetate trihydrate (23.0 mg, 0.169 mmol), heated 80 °C for 12 h, and then concentrated *in vacuo*. Purification by chromatography on SiO_2 (20% EtOAc/hexanes) gave **4-53** (26.6 mg, 76%) as a white solid: Mp 97.8-98.9 °C; $[\alpha]_D$ –29.2 (*c* 0.59, $CHCl_3$); IR (ATR) 3107, 3059, 2975, 1717, 1700, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.79 (br s, 1 H), 7.54 (s, 1 H), 7.27 (t, 1 H, *J* = 8.0 Hz), 7.07 (d, 1 H, *J* = 7.5 Hz), 6.10 (s, 1 H), 4.14 (C(5)-H, d, 1 H, *J* = 4.0 Hz), 3.93 (C(4)-H, ddd, 1 H, *J* = 7.0, 4.5, 1.0 Hz), 3.28, 3.22 (C(12)-H and C(12)-H', d of AB, 2 H, *J*

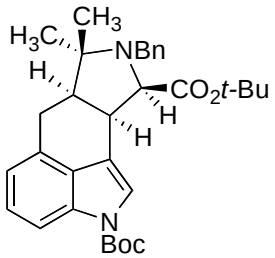
= 17.0, 6.5 Hz), 3.10 (C(11)-H, app q, 1 H, *J* = 6.5 Hz), 1.68 (s, 9 H), 1.58 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9, 170.1, 149.9, 133.0, 128.0, 127.6, 125.3, 121.3, 120.3, 115.7, 112.9, 83.7, 82.9, 61.6, 40.3, 36.4, 28.1, 28.0, 25.1; HRMS (TOF ESI) *m/z* calcd for $C_{23}H_{28}N_2O_5$ $[M+H]^+$ 413.2076, found 413.2070.



(6a*R*,9*S*,9a*R*)-Di-*tert*-butyl 7-oxo-6,6a,7,8,9,9a-hexahydro─2*H*-isoindolo[4,5,6-*cd*]indole-2,9-dicarboxylate (4-58). To a suspension of NaH (0.7 mg, 0.03 mmol) in THF (0.3 mL) at room temperature was added a solution of **4-53** (11.9 mg, 0.0288 mmol) in THF (0.3 mL), stirred at room temperature for 15 min, and then treated with benzyl bromide (3.5 μL, 0.029 mmol). The mixture was heated to 66 °C for 2 h, cooled to room temperature, diluted with EtOAc (5 mL), and slowly quenched with water. After extraction with EtOAc (4 x 5 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification on SiO_2 (30% EtOAc/hexanes) gave **4-58** (11.4 mg, 79%) as a white solid: Mp 62.4-64.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (s, 1 H), 7.28 (t, 1 H), 7.20-7.10 (m, 5 H), 6.77 (d, 1 H, *J* = 7.5 Hz), 4.96 (d, 1 H, *J* = 14.5 Hz), 3.96 (d, 1 H, *J* = 15.0 Hz), 3.80 (s, 1 H), 3.80-3.79 (m, 1 H), 3.47 (dd, 1 H, *J* = 16.5, 3.0 Hz), 3.33-3.29 (m, 1 H), 3.16 (dd, 1 H, *J* = 17.0, 6.5 Hz), 1.68 (s, 9 H), 1.51 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.8, 169.7, 149.8, 135.4, 133.0, 128.2, 127.9, 127.5, 125.5, 120.6, 116.0, 112.8, 83.6, 82.7, 65.2, 45.8, 40.4, 35.2, 28.2, 28.0, 24.9; HRMS (TOF ESI) *m/z* calcd for $C_{30}H_{35}N_2O_5$ $[M+H]^+$ 503.2546, found 503.2562.



(6a*R*,9*S*,9a*R*)-Di-*tert*-butyl 7-thioxo-6,6a,7,8,9,9a─hexahydro─2*H*-isoindolo[4,5,6-*cd*]indole-2,9-dicarboxylate (4-54). To a solution of **4-58** (11.0 mg, 0.0219 mmol) in toluene (1.0 mL) was added Lawesson's reagent (5.7 mg, 0.014 mmol), heated to 100 °C for 12 h, and cooled to room temperature. The reaction mixture was concentrated *in vacuo*, and purified by column chromatography (15% EtOAc/hexanes) to obtain **4-54** (8.8 mg, 77%) as a white solid: IR (ATR) 2975, 2934, 1726, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.79 (br s, 1 H), 7.30 (t, 1 H, *J* = 7.5 Hz), 7.23 (t, 1 H, *J* = 7.5 Hz), 7.17-7.13 (m, 3 H), 7.10 (br s, 1 H), 6.85 (s, 1 H), 6.83 (s, 1 H), 5.78 (d, 1 H, *J* = 14.5 Hz), 4.28 (d, 1 H, *J* = 15.0 Hz), 4.10 (d, 1 H, *J* = 2.5 Hz), 3.91 (dt, 1 H, *J* = 6.0, 2.0 Hz), 3.79 (17.0, 4.0 Hz), 3.59 (ddt, 1 H, *J* = 5.5, 4.5, 1.5 Hz), 3.30 (dd, 1 H, *J* = 16.5, 6.0 Hz), 1.69 (s, 9 H), 1.54 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.1, 168.1, 149.7, 134.1, 132.9, 128.3 (2C), 128.1 (2C), 128.0, 125.6, 120.8, 120.7, 115.2, 112.7, 83.6, 83.4, 70.5, 51.4, 50.9, 37.2, 28.2, 28.1, 28.0; HRMS (TOF ES) *m/z* calcd for $C_{30}H_{35}N_2O_4S$ $[M+H]^+$ 519.2318, found 519.2301.



(6a*R*,9*S*,9a*R*)-Di-*tert*-butyl 8-benzyl─7,7-dimethyl─6,6a,7,8,9,9a─hexahydro─2*H*-isoindolo-[4,5,6-*cd*]indole-2,9-dicarboxylate (4-59). A solution of amide **4-58** (20.0 mg, 0.0398 mmol)

and 2,6-di-*tert*-butyl-4-methylpyridine (9.8 mg, 0.048 mmol) in CH_2Cl_2 (0.4 mL) at -78 °C was treated with Tf_2O (7.9 μL, 0.048 mmol), and stirred at -78 °C for 45 min. A solution of CH_3MgBr (1.0 M in ether, 120 μL, 0.119 mmol) was added dropwise to the resultant mixture, warmed slowly to room temperature, and stirred for 13 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (5 x 2 mL), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by preparative TLC (20% EtOAc/hexanes) gave **4-59** (3.4 mg, 17%) as colorless oil, along with the recovered starting material **4-58** (18.7 mg). **4-59**: ^{1}H NMR (400 MHz, $CDCl_3$): 7.55 (s, 1 H), 7.32-7.22 (m, 6 H), 7.18 (d, 1 H, J = 2.8 Hz), 7.02 (d, 1 H, J = 7.2 Hz), 3.98 (d, 1 H, J = 14.4 Hz), 3.65 (d, 1 H, J = 14 Hz), 3.58-3.51 (m, 2 H), 3.45 (dt, 1 H, J = 6.4, 3.2 Hz), 3.15 (dd, 1 H, J = 16.8, 6.8 Hz), 2.95 (dd, 1 H, J = 16.8, 4.8 Hz), 2.58 (dd, 1 H, J = 12.4, 6.4 Hz), 1.67 (s, 9 H), 1.35 (s, 9 H), 1.30 (s, 3 H), 0.80 (s, 3 H); HRMS (ESI) *m/z* calcd for $C_{32}H_{41}N_2O_4$ $[M+H]^+$ 517.3066, found 517.3052.

APPENDIX A

X-RAY DATA

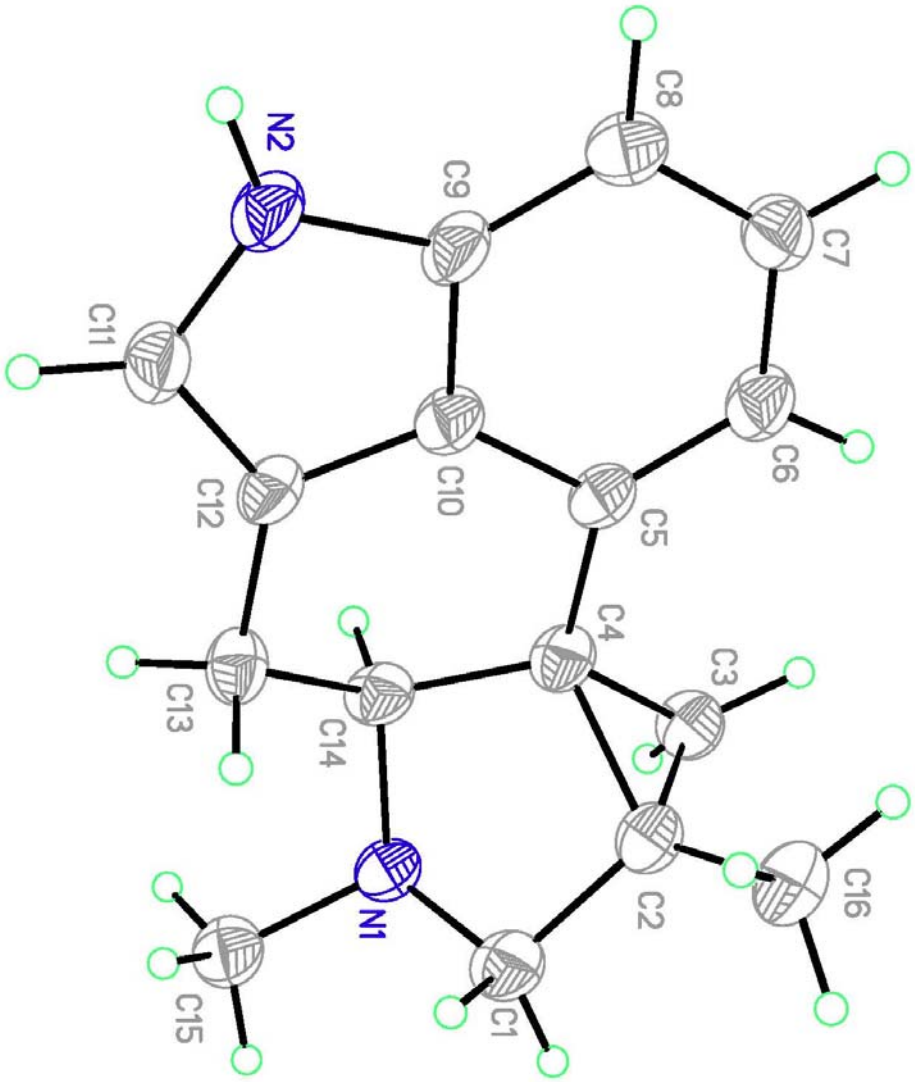


Figure 23. X-ray structure of 3-99

Table 6. Crystal data and structure refinement for **3-99**

Identification code	fp1215s	
Empirical formula	C16 H18 N2	
Formula weight	238.32	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.871(5) Å	a= 90°.
	b = 18.239(11) Å	b= 101.954(11)°.
	c = 8.966(5) Å	g = 90°.
Volume	1259.2(13) $Å^3$	
Z	4	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	512	
Crystal size	0.18 x 0.14 x 0.03 mm^3	
Theta range for data collection	2.23 to 25.00°.	
Index ranges	-9<=h<=9, -21<=k<=21, -10<=l<=10	
Reflections collected	9489	
Independent reflections	2225 [R(int) = 0.1244]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9978 and 0.9867	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2225 / 0 / 164	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0745, wR2 = 0.1806	
R indices (all data)	R1 = 0.1336, wR2 = 0.2023	
Extinction coefficient	0.010(4)	
Largest diff. peak and hole	0.286 and -0.262 $e.Å^{-3}$	

Table 7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3-99** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	-1045(3)	-6393(2)	-3037(3)	42(1)
C(1)	238(4)	-6988(2)	-2862(4)	48(1)
N(2)	-505(3)	-5960(2)	3762(3)	46(1)
C(2)	1839(4)	-6688(2)	-1818(4)	45(1)
C(3)	2241(4)	-5890(2)	-2096(4)	46(1)
C(4)	1165(4)	-6064(2)	-914(3)	40(1)
C(5)	1871(4)	-5907(2)	738(3)	38(1)
C(6)	3512(4)	-5689(2)	1450(4)	47(1)
C(7)	3919(4)	-5552(2)	3043(4)	48(1)
C(8)	2703(4)	-5626(2)	3955(4)	47(1)
C(9)	1032(4)	-5838(2)	3251(4)	41(1)
C(10)	622(4)	-5977(2)	1674(4)	40(1)
C(11)	-1803(4)	-6161(2)	2533(4)	45(1)
C(12)	-1133(4)	-6179(2)	1215(4)	39(1)
C(13)	-1861(4)	-6403(2)	-414(4)	42(1)
C(14)	-799(4)	-6027(2)	-1506(3)	41(1)
C(15)	-2828(4)	-6623(2)	-3691(4)	53(1)
C(16)	3258(4)	-7218(2)	-1111(4)	57(1)

Table 8. Bond lengths [Å] and angles [°] for **3-99**

N(1)-C(15)	1.466(4)
N(1)-C(1)	1.470(4)
N(1)-C(14)	1.503(4)
C(1)-C(2)	1.508(5)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
N(2)-C(11)	1.388(4)
N(2)-C(9)	1.398(4)
N(2)-H(2A)	0.8700
C(2)-C(16)	1.513(5)
C(2)-C(3)	1.522(5)
C(2)-C(4)	1.553(5)
C(3)-C(4)	1.521(4)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(4)-C(5)	1.498(4)
C(4)-C(14)	1.528(5)
C(5)-C(6)	1.375(4)
C(5)-C(10)	1.424(4)
C(6)-C(7)	1.420(5)
C(6)-H(6A)	0.9400
C(7)-C(8)	1.389(5)
C(7)-H(7A)	0.9400
C(8)-C(9)	1.390(5)
C(8)-H(8A)	0.9400
C(9)-C(10)	1.406(5)
C(10)-C(12)	1.407(5)
C(11)-C(12)	1.391(5)
C(11)-H(11A)	0.9400
C(12)-C(13)	1.510(4)
C(13)-C(14)	1.571(4)
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800

C(14)-H(14A)	0.9900
C(15)-H(15A)	0.9700
C(15)-H(15B)	0.9700
C(15)-H(15C)	0.9700
C(16)-H(16A)	0.9700
C(16)-H(16B)	0.9700
C(16)-H(16C)	0.9700

C(15)-N(1)-C(1)	114.2(3)
C(15)-N(1)-C(14)	115.1(3)
C(1)-N(1)-C(14)	106.0(2)
N(1)-C(1)-C(2)	105.4(3)
N(1)-C(1)-H(1A)	110.7
C(2)-C(1)-H(1A)	110.7
N(1)-C(1)-H(1B)	110.7
C(2)-C(1)-H(1B)	110.7
H(1A)-C(1)-H(1B)	108.8
C(11)-N(2)-C(9)	109.1(3)
C(11)-N(2)-H(2A)	125.5
C(9)-N(2)-H(2A)	125.5
C(1)-C(2)-C(16)	118.5(3)
C(1)-C(2)-C(3)	114.9(3)
C(16)-C(2)-C(3)	121.3(3)
C(1)-C(2)-C(4)	105.0(3)
C(16)-C(2)-C(4)	123.5(3)
C(3)-C(2)-C(4)	59.3(2)
C(4)-C(3)-C(2)	61.4(2)
C(4)-C(3)-H(3A)	117.6
C(2)-C(3)-H(3A)	117.6
C(4)-C(3)-H(3B)	117.6
C(2)-C(3)-H(3B)	117.6
H(3A)-C(3)-H(3B)	114.7
C(5)-C(4)-C(3)	120.2(3)
C(5)-C(4)-C(14)	118.4(3)
C(3)-C(4)-C(14)	114.7(3)
C(5)-C(4)-C(2)	124.0(3)

C(3)-C(4)-C(2)	59.3(2)
C(14)-C(4)-C(2)	106.4(3)
C(6)-C(5)-C(10)	116.7(3)
C(6)-C(5)-C(4)	129.4(3)
C(10)-C(5)-C(4)	113.9(3)
C(5)-C(6)-C(7)	120.8(3)
C(5)-C(6)-H(6A)	119.6
C(7)-C(6)-H(6A)	119.6
C(8)-C(7)-C(6)	122.4(3)
C(8)-C(7)-H(7A)	118.8
C(6)-C(7)-H(7A)	118.8
C(7)-C(8)-C(9)	117.5(3)
C(7)-C(8)-H(8A)	121.2
C(9)-C(8)-H(8A)	121.2
C(8)-C(9)-N(2)	134.2(3)
C(8)-C(9)-C(10)	120.3(3)
N(2)-C(9)-C(10)	105.5(3)
C(9)-C(10)-C(12)	110.4(3)
C(9)-C(10)-C(5)	122.3(3)
C(12)-C(10)-C(5)	127.4(3)
N(2)-C(11)-C(12)	109.5(3)
N(2)-C(11)-H(11A)	125.2
C(12)-C(11)-H(11A)	125.2
C(11)-C(12)-C(10)	105.5(3)
C(11)-C(12)-C(13)	133.9(3)
C(10)-C(12)-C(13)	120.5(3)
C(12)-C(13)-C(14)	109.9(3)
C(12)-C(13)-H(13A)	109.7
C(14)-C(13)-H(13A)	109.7
C(12)-C(13)-H(13B)	109.7
C(14)-C(13)-H(13B)	109.7
H(13A)-C(13)-H(13B)	108.2
N(1)-C(14)-C(4)	103.1(2)
N(1)-C(14)-C(13)	113.0(3)
C(4)-C(14)-C(13)	113.3(3)
N(1)-C(14)-H(14A)	109.1

C(4)-C(14)-H(14A)	109.1
C(13)-C(14)-H(14A)	109.1
N(1)-C(15)-H(15A)	109.5
N(1)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
N(1)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(2)-C(16)-H(16A)	109.5
C(2)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(2)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 9. Anisotropic displacement parameters ($Å^2x10^3$) for **3-99**

The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	45(2)	51(2)	34(2)	-5(1)	15(1)	-1(1)
C(1)	55(2)	55(2)	40(2)	-3(2)	20(2)	-4(2)
N(2)	42(2)	65(2)	35(2)	1(1)	17(1)	2(1)
C(2)	44(2)	54(2)	41(2)	-2(2)	20(2)	-3(2)
C(3)	49(2)	62(2)	34(2)	-1(2)	21(2)	-10(2)
C(4)	43(2)	46(2)	35(2)	1(2)	18(2)	-2(2)
C(5)	42(2)	44(2)	32(2)	0(1)	16(2)	1(2)
C(6)	43(2)	59(2)	43(2)	1(2)	19(2)	-1(2)
C(7)	41(2)	62(2)	41(2)	-2(2)	12(2)	-6(2)
C(8)	52(2)	60(2)	32(2)	0(2)	13(2)	0(2)
C(9)	40(2)	53(2)	36(2)	0(2)	19(2)	2(2)
C(10)	42(2)	47(2)	33(2)	0(2)	15(2)	0(2)
C(11)	38(2)	56(2)	45(2)	1(2)	16(2)	-4(2)
C(12)	40(2)	46(2)	34(2)	0(2)	16(2)	3(2)
C(13)	36(2)	51(2)	41(2)	7(2)	13(2)	-1(2)
C(14)	50(2)	46(2)	32(2)	-1(2)	15(2)	-3(2)
C(15)	51(2)	71(3)	38(2)	-6(2)	13(2)	-3(2)
C(16)	50(2)	65(3)	61(3)	-5(2)	24(2)	4(2)

Table 10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)

	x	y	z	U(eq)
H(1A)	492	-7123	-3852	58
H(1B)	-191	-7422	-2413	58
H(2A)	-629	-5917	4700	55
H(3A)	3436	-5720	-1726	56
H(3B)	1643	-5666	-3056	56
H(6A)	4373	-5629	874	56
H(7A)	5054	-5406	3497	57
H(8A)	2998	-5536	5009	57
H(11A)	-2958	-6268	2584	54
H(13A)	-3083	-6257	-702	50
H(13B)	-1799	-6937	-509	50
H(14A)	-1155	-5507	-1650	50
H(15A)	-2865	-6855	-4671	79
H(15B)	-3586	-6198	-3826	79
H(15C)	-3215	-6969	-3009	79
H(16A)	3487	-7553	-1886	86
H(16B)	2890	-7494	-309	86
H(16C)	4307	-6947	-686	86

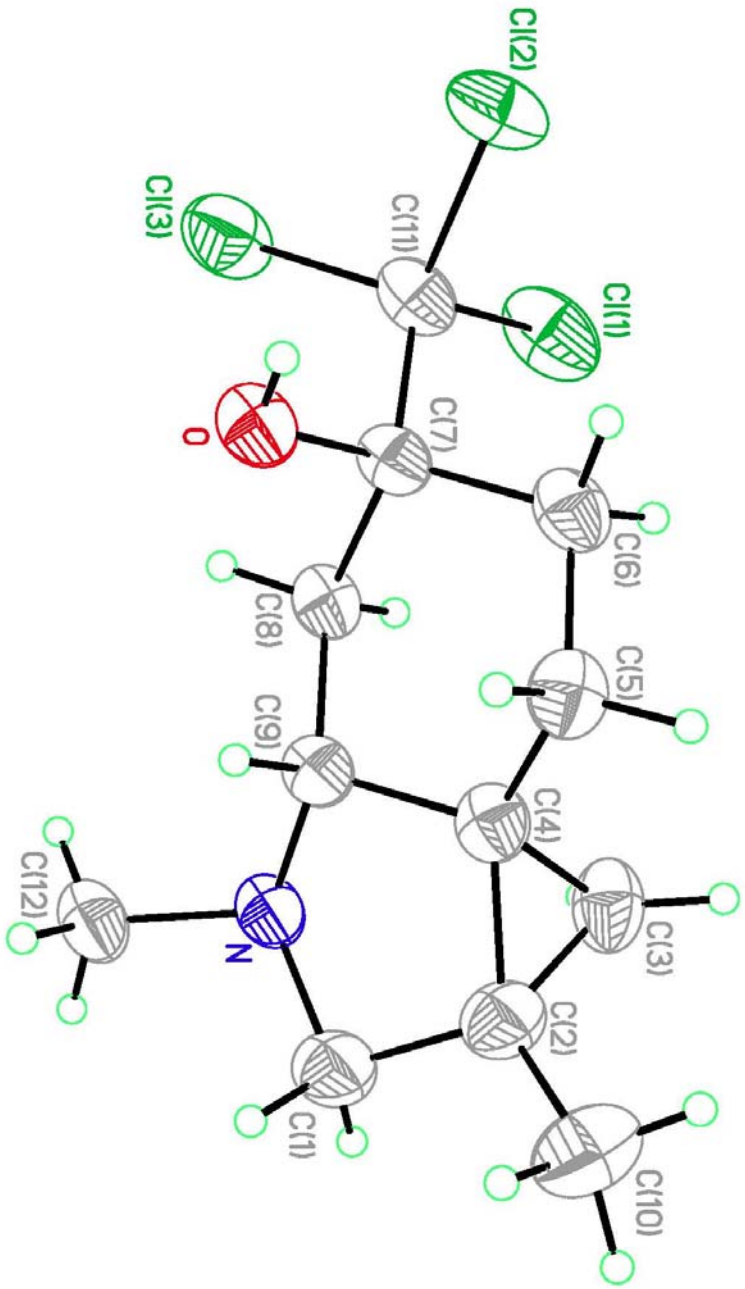


Figure 24. X-ray structure of 3-125

Table 11. Crystal data and structure refinement for 3-125

Identification code	fp12411s	
Empirical formula	C12 H18 Cl3 N O	
Formula weight	298.62	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.816(3) Å	α 90°
	b = 10.136(3) Å	β 97.281(7)°
	c = 17.731(6) Å	γ 90°
Volume	1393.4(8) $Å^3$	
Z	4	
Density (calculated)	1.424 Mg/m^3	
Absorption coefficient	0.642 mm^{-1}	
F(000)	624	
Crystal size	0.39 x 0.06 x 0.03 mm^3	
Theta range for data collection	2.32 to 27.49°.	
Index ranges	-9<=h<=10, -13<=k<=13, -23<=l<=23	
Reflections collected	13105	
Independent reflections	3200 [R(int) = 0.0473]	
Completeness to theta = 27.49°	100.0 %	
Absorption correction	Multi-scan (Sadabs)	
Max. and min. transmission	0.9810 and 0.7879	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3200 / 0 / 226	
Goodness-of-fit on F^2	0.995	
Final R indices [I>2sigma(I)]	R1 = 0.0474, wR2 = 0.1034	
R indices (all data)	R1 = 0.0736, wR2 = 0.1143	
Largest diff. peak and hole	0.372 and -0.291 $e.Å^{-3}$	

Table 12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3)

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O	8363(2)	5206(2)	1907(1)	36(1)
N	6947(2)	2807(2)	3705(1)	35(1)
Cl(1)	7121(1)	1936(1)	703(1)	58(1)
C(1)	5507(4)	3269(3)	4109(2)	44(1)
Cl(2)	7786(1)	4545(1)	182(1)	50(1)
C(2)	4084(3)	3694(2)	3494(1)	42(1)
Cl(3)	10370(1)	3190(1)	1175(1)	55(1)
C(3)	3786(4)	2724(3)	2846(2)	44(1)
C(4)	4966(3)	3895(2)	2799(1)	35(1)
C(5)	4613(4)	4881(2)	2167(1)	38(1)
C(6)	5454(3)	4389(3)	1487(1)	38(1)
C(7)	7378(3)	4079(2)	1687(1)	31(1)
C(8)	7709(3)	3127(2)	2367(1)	32(1)
C(9)	6856(3)	3665(2)	3025(1)	31(1)
C(10)	2682(5)	4571(4)	3716(2)	60(1)
C(11)	8111(3)	3467(2)	982(1)	39(1)
C(12)	8593(4)	2901(3)	4190(2)	43(1)

Table 13. Bond lengths [Å] and angles [°] for 3-125

O-C(7)	1.405(2)
O-H(1O)	0.80(3)
N-C(12)	1.457(3)
N-C(9)	1.480(3)
N-C(1)	1.485(3)
Cl(1)-C(11)	1.776(2)
C(1)-C(2)	1.517(4)
C(1)-H(1A)	0.90(3)
C(1)-H(1B)	0.97(2)
Cl(2)-C(11)	1.783(2)
C(2)-C(4)	1.501(3)
C(2)-C(3)	1.508(4)
C(2)-C(10)	1.501(4)
Cl(3)-C(11)	1.777(3)
C(3)-C(4)	1.513(3)
C(3)-H(3A)	0.92(2)
C(3)-H(3B)	0.97(2)
C(4)-C(9)	1.499(3)
C(4)-C(5)	1.500(3)
C(5)-C(6)	1.528(3)
C(5)-H(5A)	0.92(2)
C(5)-H(5B)	0.94(3)
C(6)-C(7)	1.534(3)
C(6)-H(6A)	0.88(2)
C(6)-H(6B)	0.96(3)
C(7)-C(8)	1.540(3)
C(7)-C(11)	1.568(3)
C(8)-C(9)	1.516(3)
C(8)-H(8A)	0.95(2)
C(8)-H(8B)	0.91(2)
C(9)-H(9)	0.97(2)
C(10)-H(10A)	0.92(4)
C(10)-H(10B)	0.99(3)

C(10)-H(10C)	0.97(4)
C(12)-H(12A)	0.99(2)
C(12)-H(12B)	0.95(3)
C(12)-H(12C)	0.95(3)

C(7)-O-H(1O)	115(2)
C(12)-N-C(9)	112.96(18)
C(12)-N-C(1)	111.2(2)
C(9)-N-C(1)	104.25(18)
N-C(1)-C(2)	106.0(2)
N-C(1)-H(1A)	107.9(16)
C(2)-C(1)-H(1A)	112.0(15)
N-C(1)-H(1B)	111.5(14)
C(2)-C(1)-H(1B)	110.4(14)
H(1A)-C(1)-H(1B)	109(2)
C(4)-C(2)-C(3)	60.34(16)
C(4)-C(2)-C(1)	104.9(2)
C(3)-C(2)-C(1)	112.9(2)
C(4)-C(2)-C(10)	124.1(2)
C(3)-C(2)-C(10)	122.6(3)
C(1)-C(2)-C(10)	118.3(3)
C(4)-C(3)-C(2)	59.60(15)
C(4)-C(3)-H(3A)	114.9(15)
C(2)-C(3)-H(3A)	116.6(15)
C(4)-C(3)-H(3B)	121.2(14)
C(2)-C(3)-H(3B)	121.6(14)
H(3A)-C(3)-H(3B)	113(2)
C(2)-C(4)-C(9)	107.38(19)
C(2)-C(4)-C(3)	60.06(16)
C(9)-C(4)-C(3)	116.7(2)
C(2)-C(4)-C(5)	130.1(2)
C(9)-C(4)-C(5)	112.67(19)
C(3)-C(4)-C(5)	120.6(2)
C(4)-C(5)-C(6)	108.4(2)
C(4)-C(5)-H(5A)	111.1(15)
C(6)-C(5)-H(5A)	110.3(15)

C(4)-C(5)-H(5B)	111.9(14)
C(6)-C(5)-H(5B)	108.8(14)
H(5A)-C(5)-H(5B)	106(2)
C(7)-C(6)-C(5)	113.03(19)
C(7)-C(6)-H(6A)	107.5(15)
C(5)-C(6)-H(6A)	110.1(15)
C(7)-C(6)-H(6B)	108.7(14)
C(5)-C(6)-H(6B)	108.7(15)
H(6A)-C(6)-H(6B)	109(2)
O-C(7)-C(6)	112.57(18)
O-C(7)-C(8)	105.12(17)
C(6)-C(7)-C(8)	111.83(19)
O-C(7)-C(11)	107.49(18)
C(6)-C(7)-C(11)	110.06(18)
C(8)-C(7)-C(11)	109.56(17)
C(9)-C(8)-C(7)	109.29(18)
C(9)-C(8)-H(8A)	112.8(12)
C(7)-C(8)-H(8A)	106.7(12)
C(9)-C(8)-H(8B)	109.1(15)
C(7)-C(8)-H(8B)	109.8(14)
H(8A)-C(8)-H(8B)	109.1(18)
N-C(9)-C(4)	104.70(17)
N-C(9)-C(8)	115.74(18)
C(4)-C(9)-C(8)	111.38(18)
N-C(9)-H(9)	110.2(12)
C(4)-C(9)-H(9)	107.9(12)
C(8)-C(9)-H(9)	106.7(12)
C(2)-C(10)-H(10A)	113(2)
C(2)-C(10)-H(10B)	110.1(16)
H(10A)-C(10)-H(10B)	105(3)
C(2)-C(10)-H(10C)	112(2)
H(10A)-C(10)-H(10C)	109(3)
H(10B)-C(10)-H(10C)	107(3)
C(7)-C(11)-Cl(1)	112.16(16)
C(7)-C(11)-Cl(3)	111.27(15)
Cl(1)-C(11)-Cl(3)	107.61(12)

C(7)-C(11)-Cl(2)	111.26(15)
Cl(1)-C(11)-Cl(2)	107.56(12)
Cl(3)-C(11)-Cl(2)	106.72(13)
N-C(12)-H(12A)	111.5(14)
N-C(12)-H(12B)	112.1(14)
H(12A)-C(12)-H(12B)	112(2)
N-C(12)-H(12C)	110.7(17)
H(12A)-C(12)-H(12C)	108(2)
H(12B)-C(12)-H(12C)	102(2)

Symmetry transformations used to generate equivalent atoms:

Table 14. Anisotropic displacement parameters ($Å^2x10^3$) for **3-125**

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O	47(1)	26(1)	34(1)	3(1)	-1(1)	-3(1)
N	42(1)	31(1)	30(1)	3(1)	0(1)	-8(1)
Cl(1)	91(1)	38(1)	43(1)	-12(1)	-2(1)	-3(1)
C(1)	51(2)	45(2)	39(1)	3(1)	9(1)	-13(1)
Cl(2)	67(1)	53(1)	32(1)	10(1)	6(1)	11(1)
C(2)	43(2)	42(1)	43(1)	4(1)	11(1)	-8(1)
Cl(3)	51(1)	75(1)	41(1)	1(1)	5(1)	21(1)
C(3)	40(2)	37(1)	52(2)	5(1)	-5(1)	-8(1)
C(4)	37(1)	30(1)	37(1)	0(1)	2(1)	-3(1)
C(5)	37(1)	32(1)	44(1)	4(1)	1(1)	2(1)
C(6)	44(2)	34(1)	34(1)	6(1)	-3(1)	1(1)
C(7)	40(1)	26(1)	28(1)	-1(1)	3(1)	-2(1)
C(8)	37(1)	26(1)	32(1)	2(1)	-1(1)	1(1)
C(9)	39(1)	23(1)	31(1)	2(1)	3(1)	-6(1)
C(10)	52(2)	65(2)	68(2)	7(2)	24(2)	-3(2)
C(11)	49(2)	34(1)	31(1)	1(1)	-1(1)	4(1)
C(12)	49(2)	41(2)	35(1)	3(1)	-6(1)	-7(1)

Table 15. Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2x 10 3) for **3-125**

	x	y	z	U(eq)
H(1A)	5180(30)	2590(30)	4385(14)	41(7)
H(1B)	5860(30)	4000(20)	4446(14)	46(7)
H(3A)	2750(30)	2780(20)	2542(14)	39(7)
H(3B)	4240(30)	1830(20)	2892(13)	42(7)
H(5A)	5040(30)	5700(20)	2316(13)	40(7)
H(5B)	3420(30)	4990(20)	2016(13)	39(7)
H(6A)	5360(30)	4990(20)	1127(13)	36(6)
H(6B)	4870(30)	3610(30)	1294(13)	44(7)
H(8A)	8930(30)	3048(18)	2484(12)	24(5)
H(8B)	7250(30)	2320(20)	2234(13)	40(7)
H(9)	7390(30)	4510(20)	3158(11)	25(5)
H(10A)	1870(50)	4790(30)	3310(20)	95(13)
H(10B)	2020(40)	4100(30)	4077(16)	65(9)
H(10C)	3150(50)	5370(40)	3970(20)	90(12)
H(12A)	8840(30)	3820(20)	4363(13)	42(6)
H(12B)	9510(30)	2530(20)	3956(14)	41(7)
H(12C)	8590(30)	2360(30)	4629(17)	57(8)
H(1O)	8160(40)	5830(30)	1637(16)	59(9)

Table 16. Hydrogen bonds for **3-125** [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O-H(1O)...N#1	0.80(3)	2.09(3)	2.849(3)	159(3)

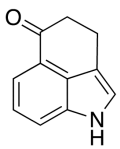
Symmetry transformations used to generate equivalent atoms:

#1 -x+3/2,y+1/2,-z+1/2

APPENDIX B

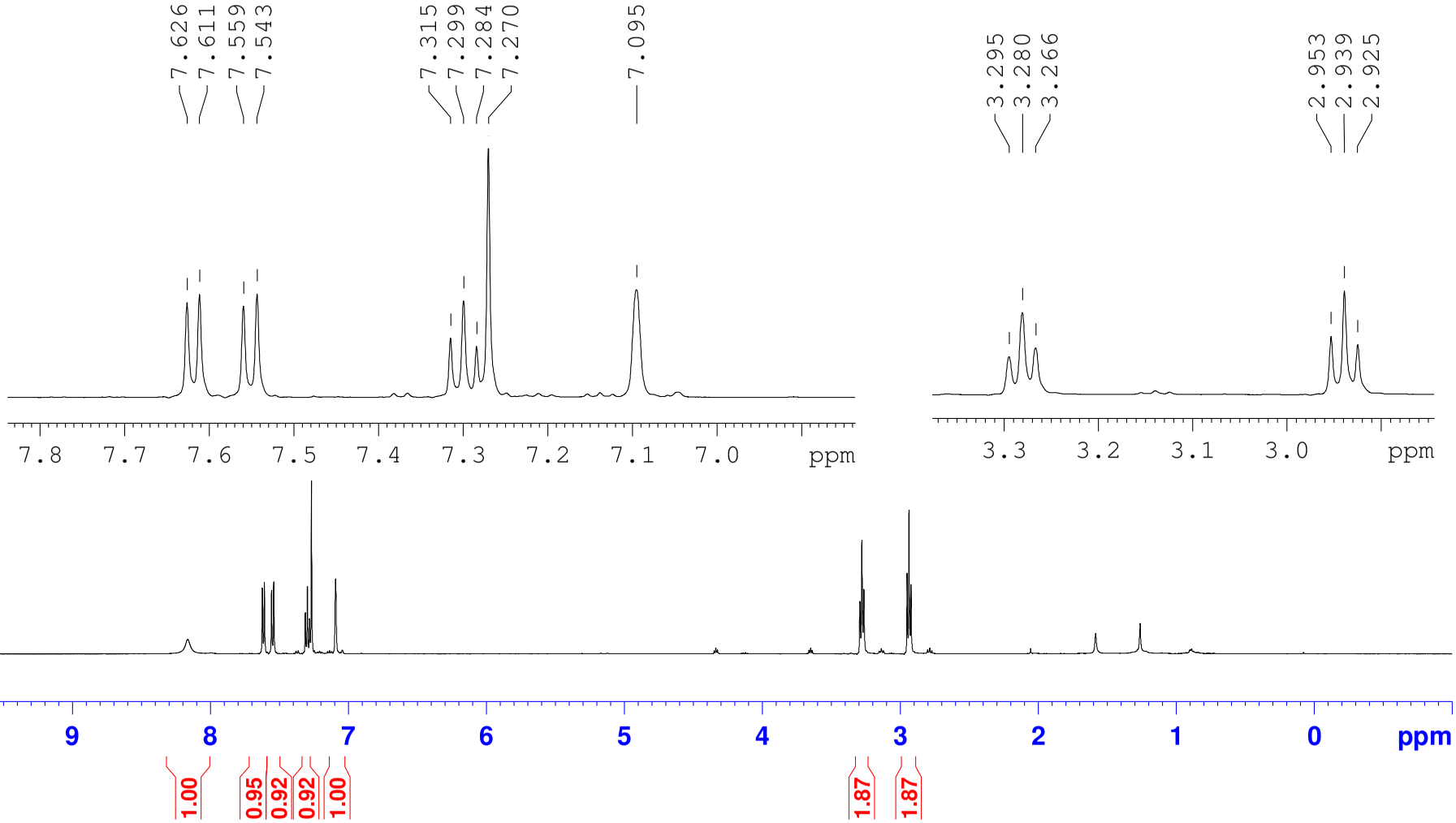
SELECTED NMR DATA

frp-11-085, cdcl3, 500



2-103

8.163
7.626
7.611
7.559
7.543
7.315
7.299
7.284
7.270
7.095
3.295
3.280
3.266
2.953
2.939
2.925



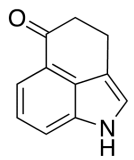
frp-11-085, cdcl3, 500

198.60

134.74
132.37
125.90
122.80
120.22
115.74
115.58
110.79

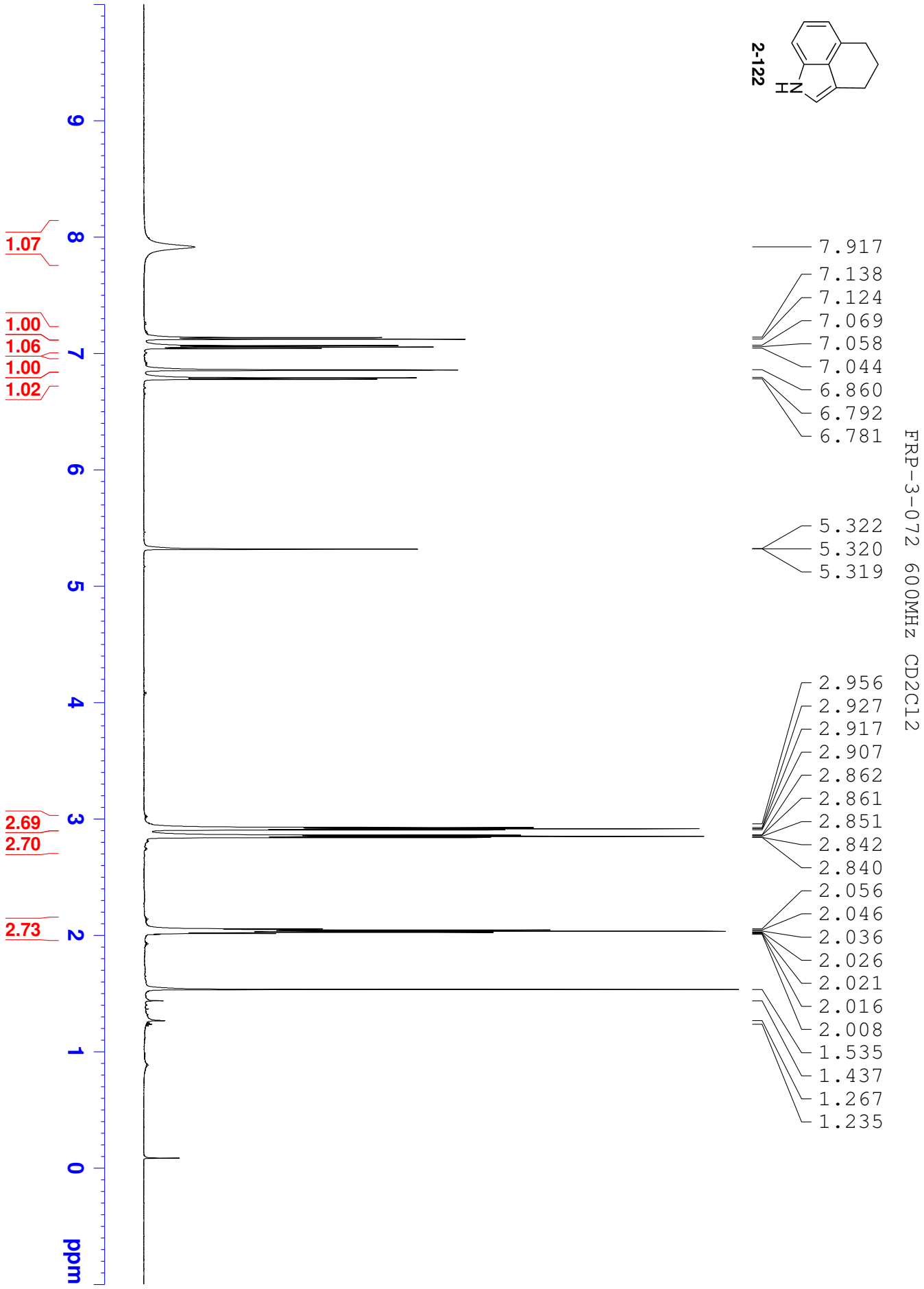
39.40

20.78

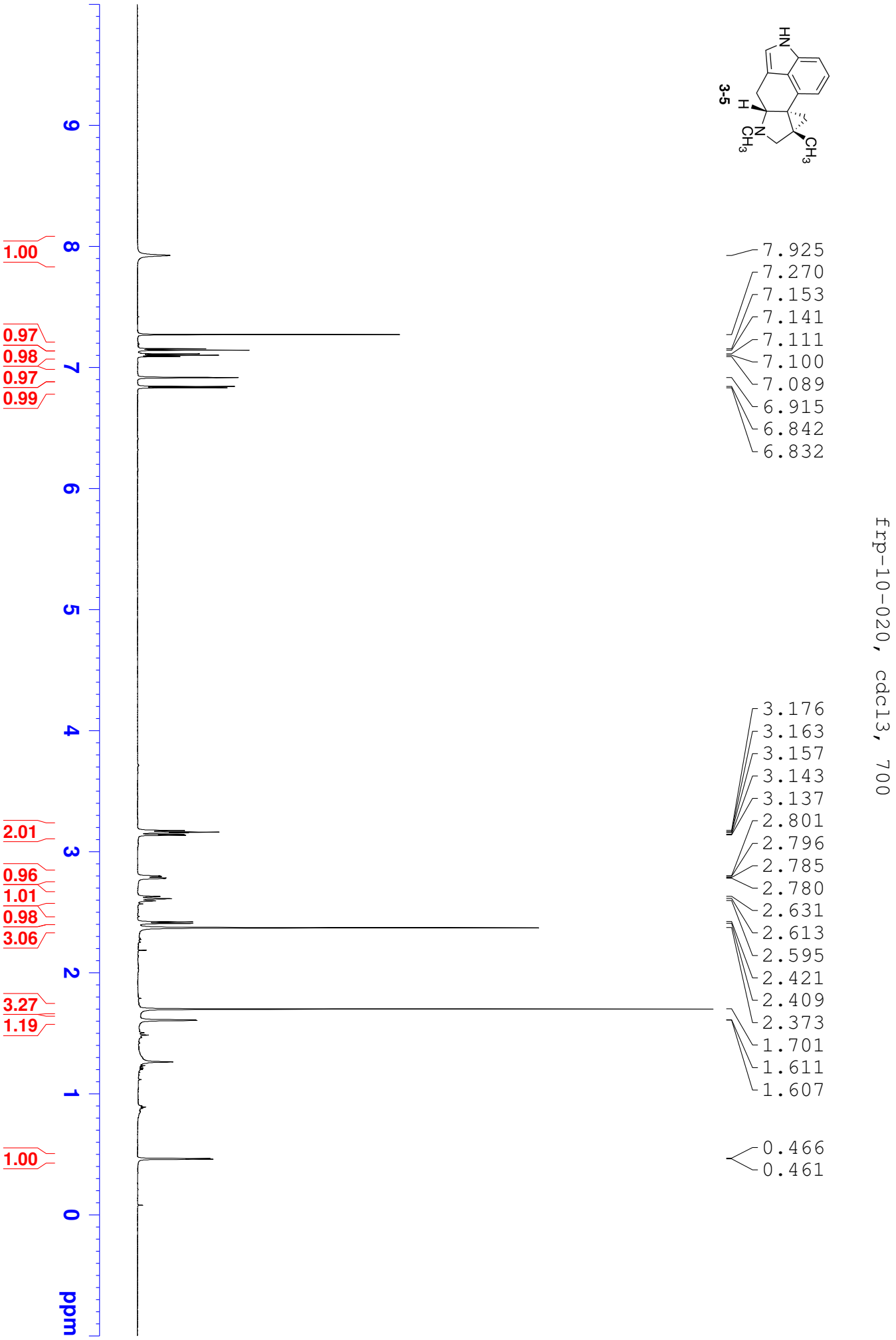


2-103

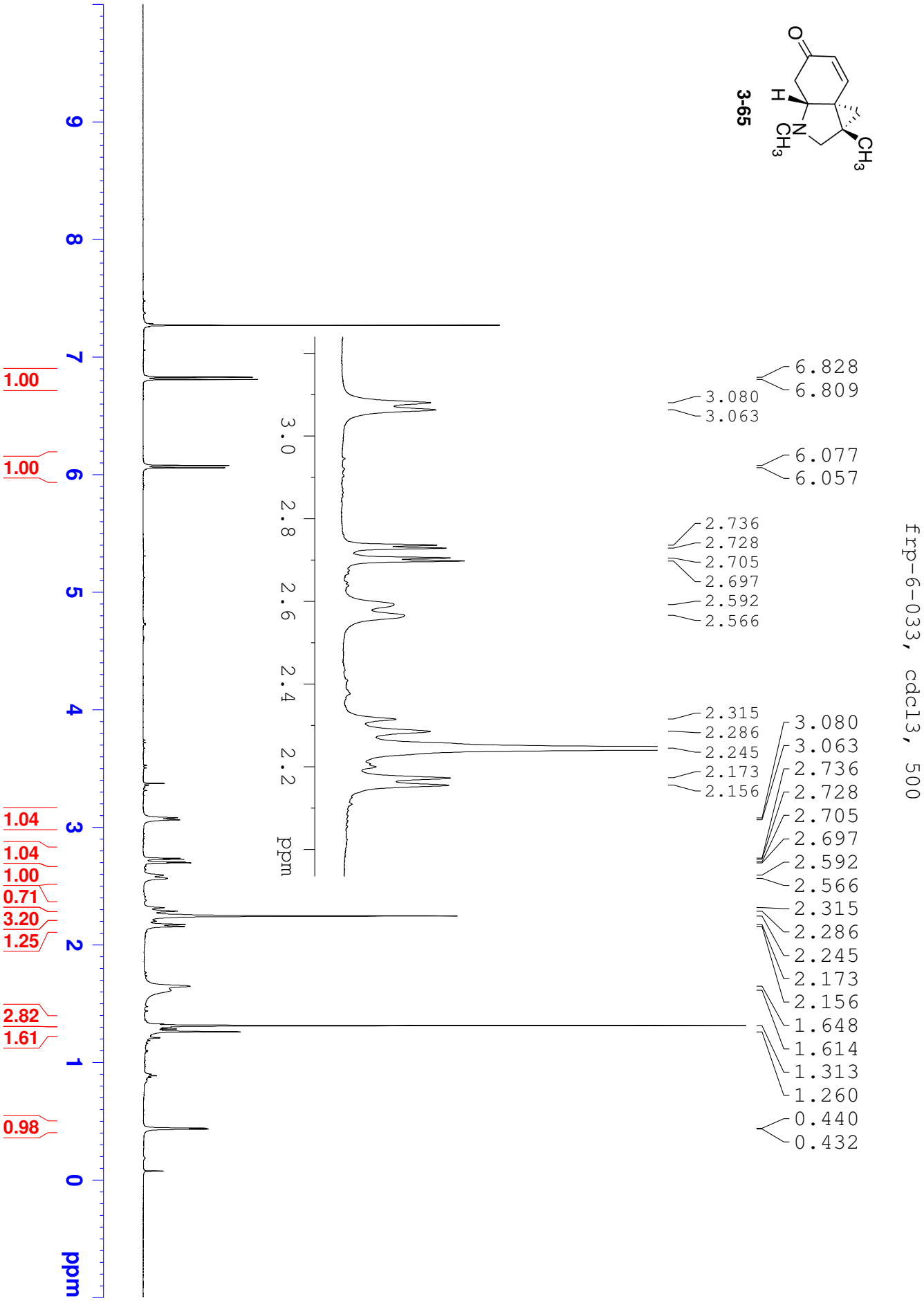
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

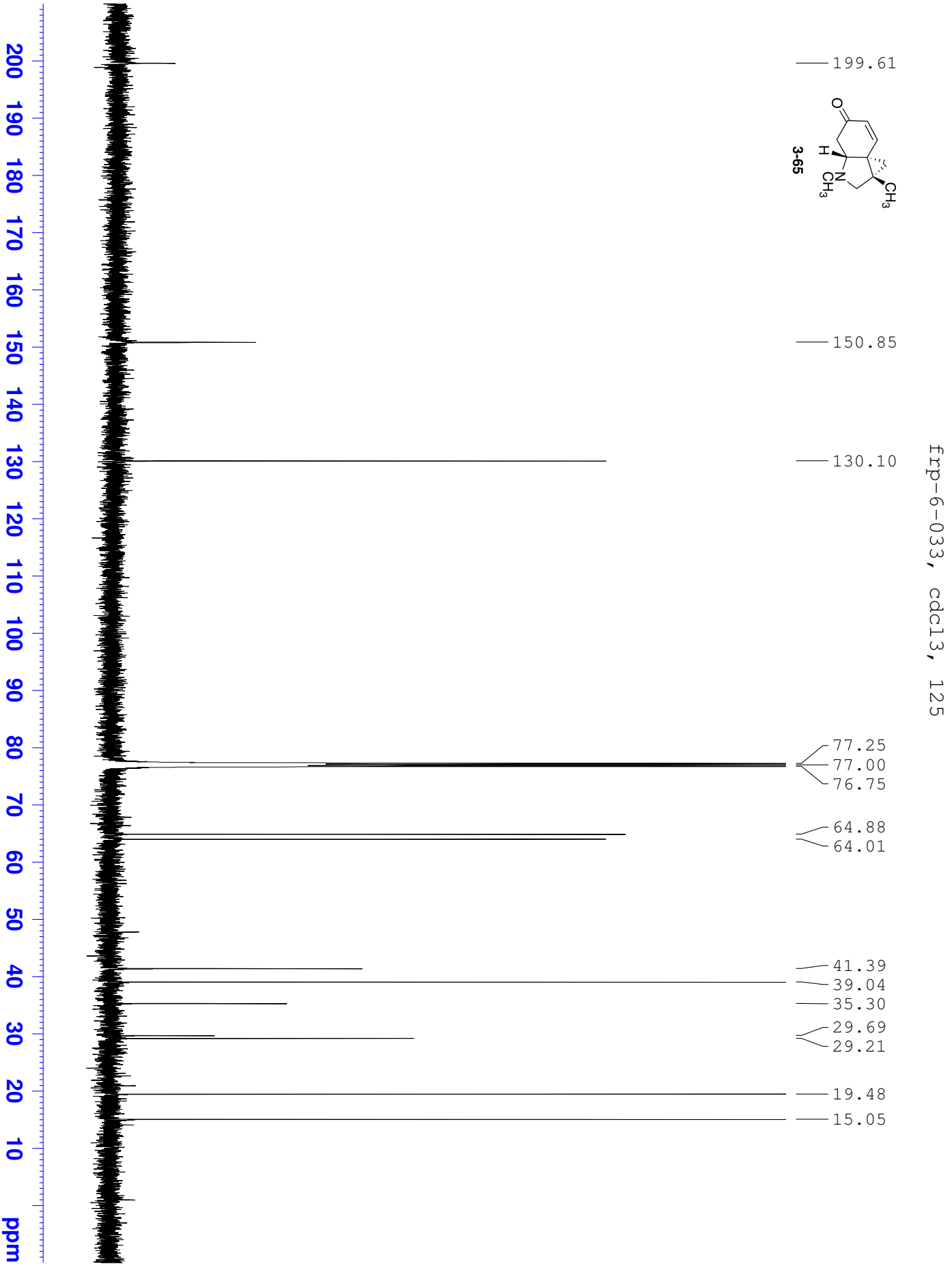

2-122
7.917
7.138
7.124
7.069
7.058
7.044
6.860
6.792
6.781
5.322
5.320
5.319
2.956
2.927
2.917
2.907
2.862
2.861
2.851
2.842
2.840
2.056
2.046
2.036
2.026
2.021
2.016
2.008
1.535
1.437
1.267
1.235
1.07
1.00
1.06
1.00
1.02
2.69
2.70
2.73
FRP-3-072 600MHz CD2Cl2
ppm

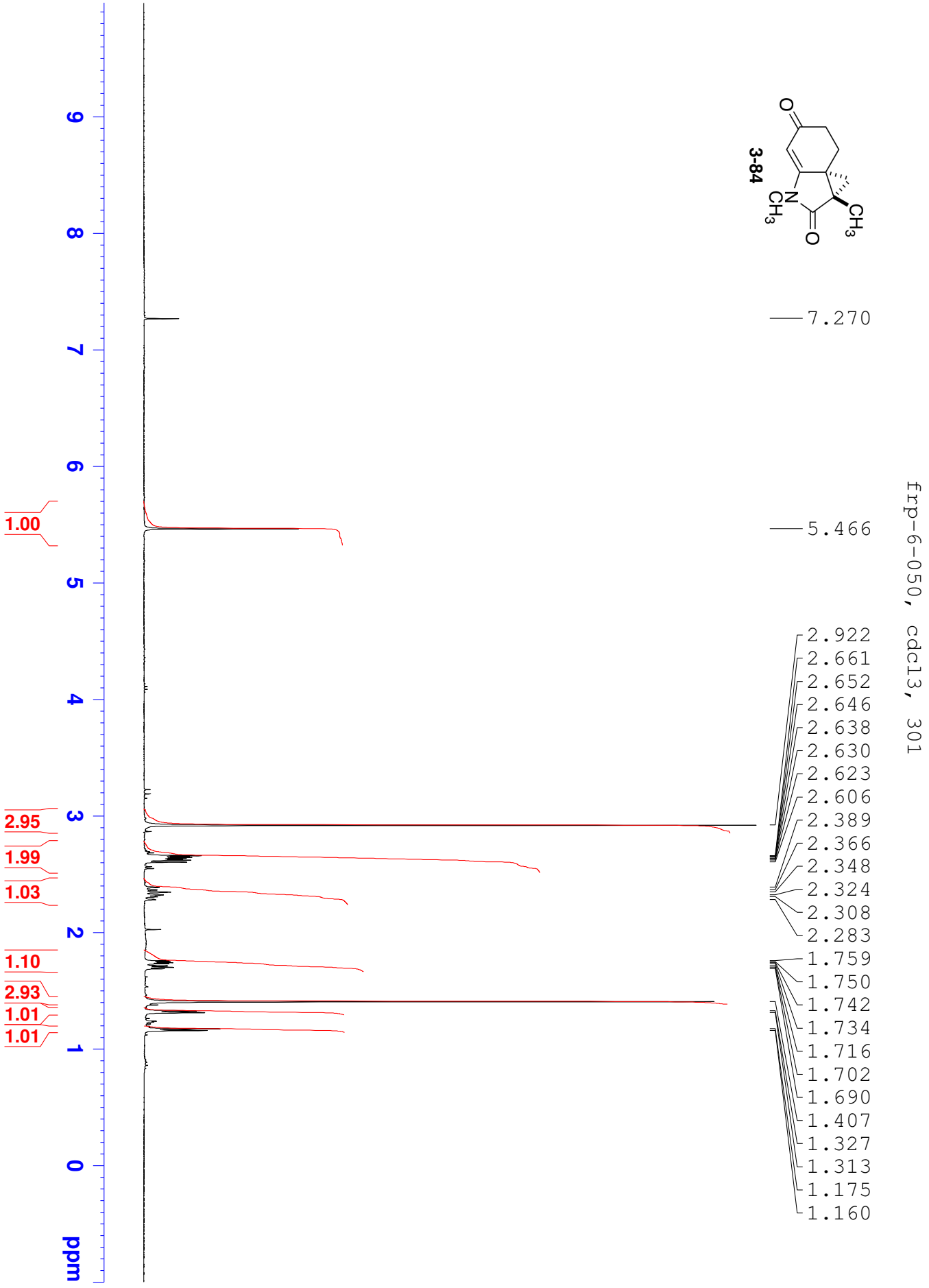
2-122
N
H
frp-3-072, CD2Cl2, 150MHz
134.48
132.79
127.70
123.04
117.69
116.15
114.26
108.49
54.36
54.19
54.00
53.83
53.65
28.05
25.35
22.43
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


3-5
HN
H
N
CH3
CH3
7.925
7.270
7.153
7.141
7.111
7.100
7.089
6.915
6.842
6.832
3.176
3.163
3.157
3.143
3.137
2.801
2.796
2.785
2.780
2.631
2.613
2.595
2.421
2.409
2.373
1.701
1.611
1.607
0.466
0.461
1.00
0.97
0.98
0.97
0.99
2.01
0.96
1.01
0.98
3.06
3.27
1.19
1.00
ppm
frp-10-020, cdcl3, 700

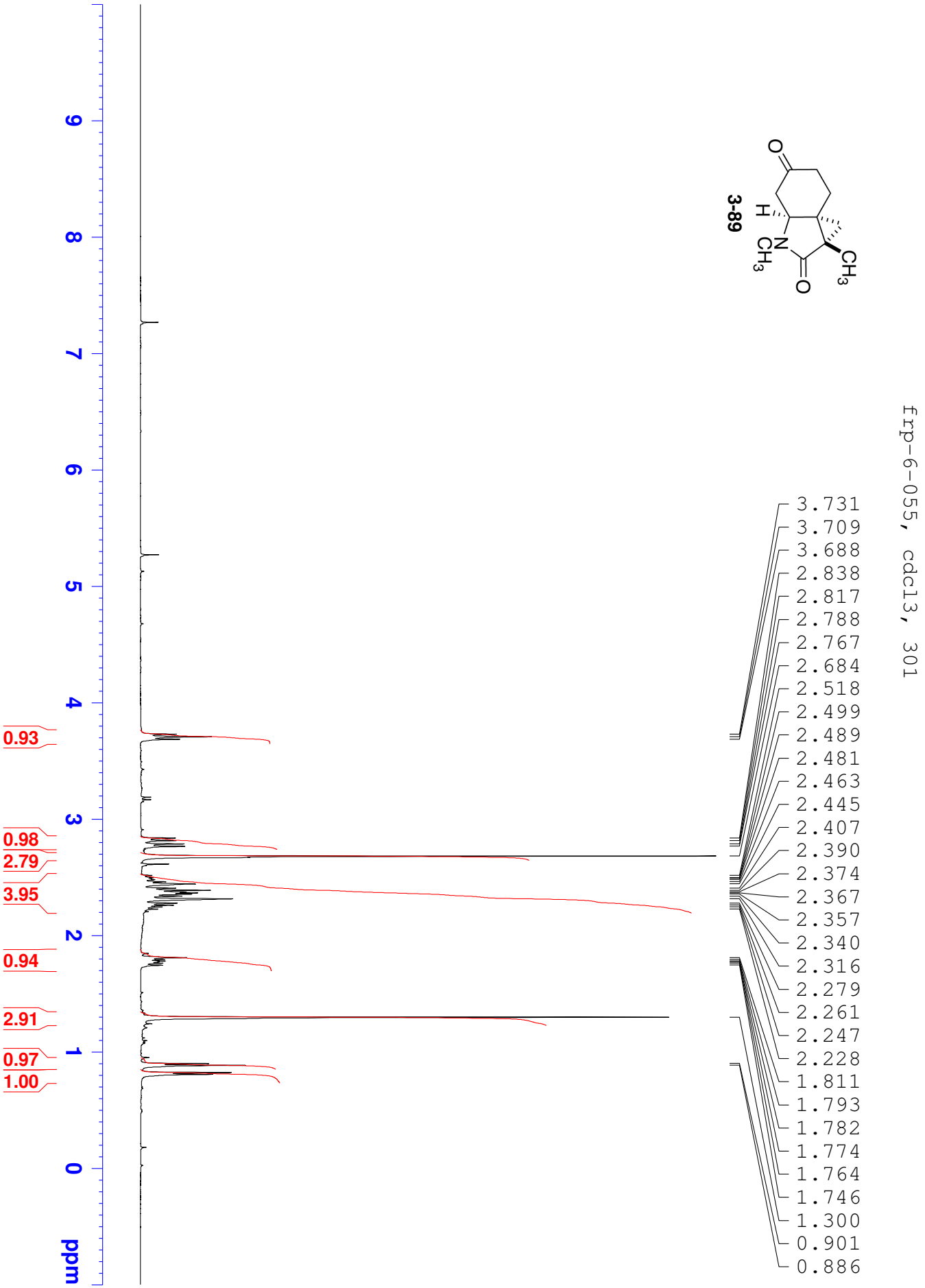
3-5
HN
H
N
CH3
CH3
135.40
133.53
128.66
122.90
118.06
113.24
110.35
107.91
77.18
77.00
76.82
69.59
65.56
39.90
34.35
27.77
24.93
24.20
16.47
frp-10-020, cdcl3, 700
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


3-65
frp-6-033, cdc13, 500
6.828
6.809
3.080
3.063
6.077
6.057
2.736
2.728
2.705
2.697
2.592
2.566
2.315
2.286
2.245
2.173
2.156
1.648
1.614
1.313
1.260
0.440
0.432
1.00
1.00
1.04
1.04
1.00
0.71
3.20
1.25
2.82
1.61
0.98
ppm

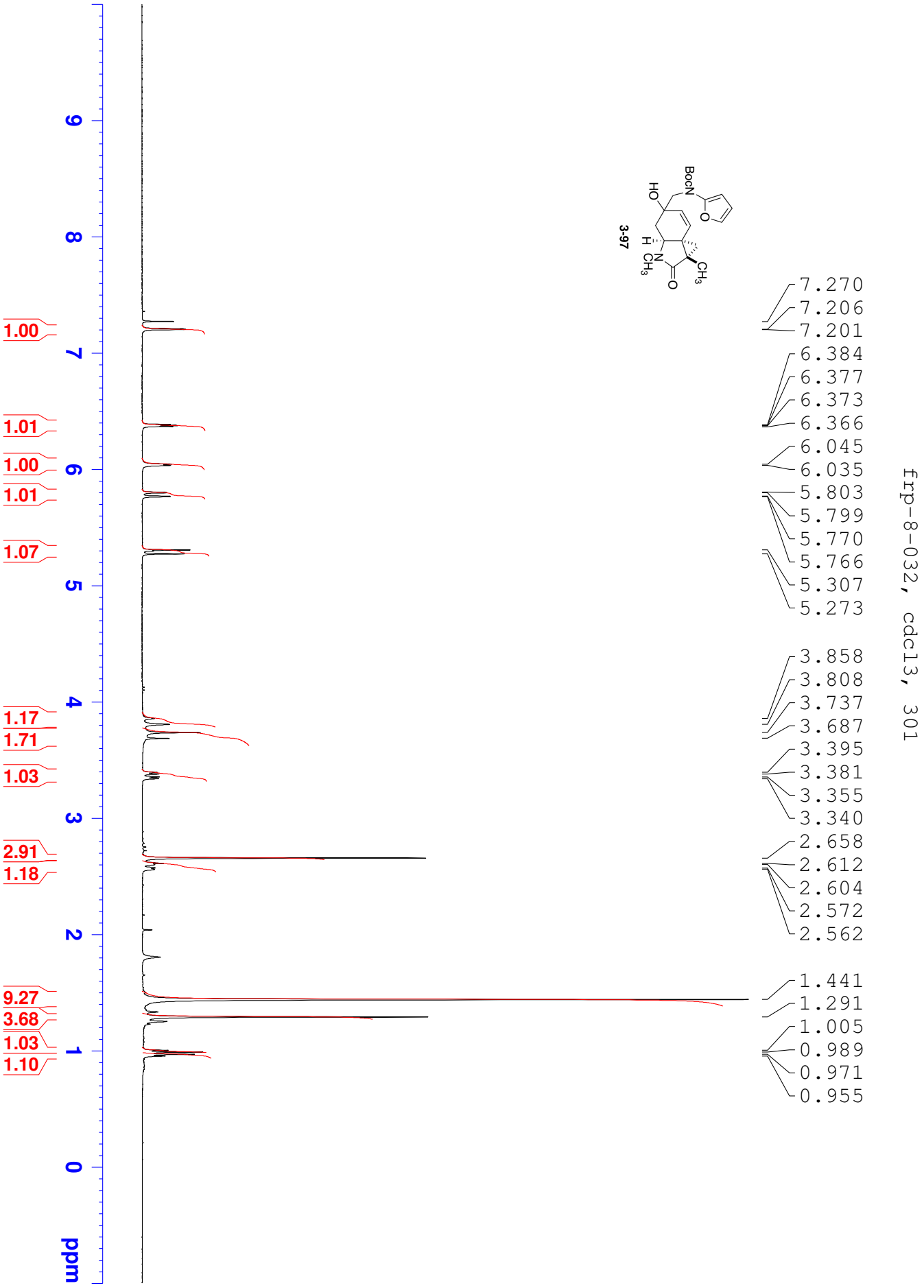

199.61
150.85
130.10
77.25
77.00
76.75
64.88
64.01
41.39
39.04
35.30
29.69
29.21
19.48
15.05
3-65
frp-6-033, cdcl3, 125
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

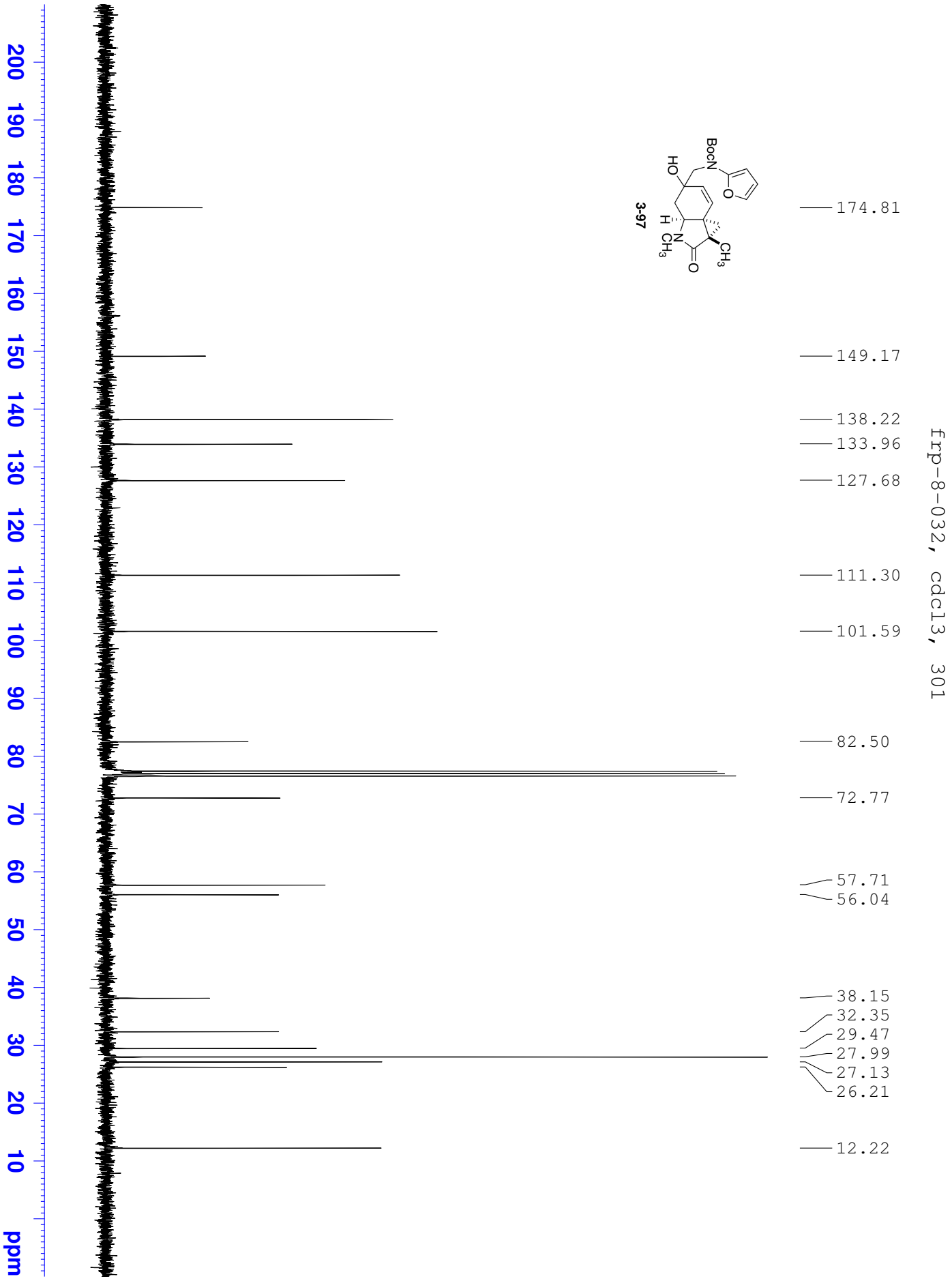

3-84
7.270
5.466
2.922
2.661
2.652
2.646
2.638
2.630
2.623
2.606
2.389
2.366
2.348
2.324
2.308
2.283
1.759
1.750
1.742
1.734
1.716
1.702
1.690
1.407
1.327
1.313
1.175
1.160
1.00
2.95
1.99
1.03
1.10
2.93
1.01
1.01
ppm
frp-6-050, cdc13, 301

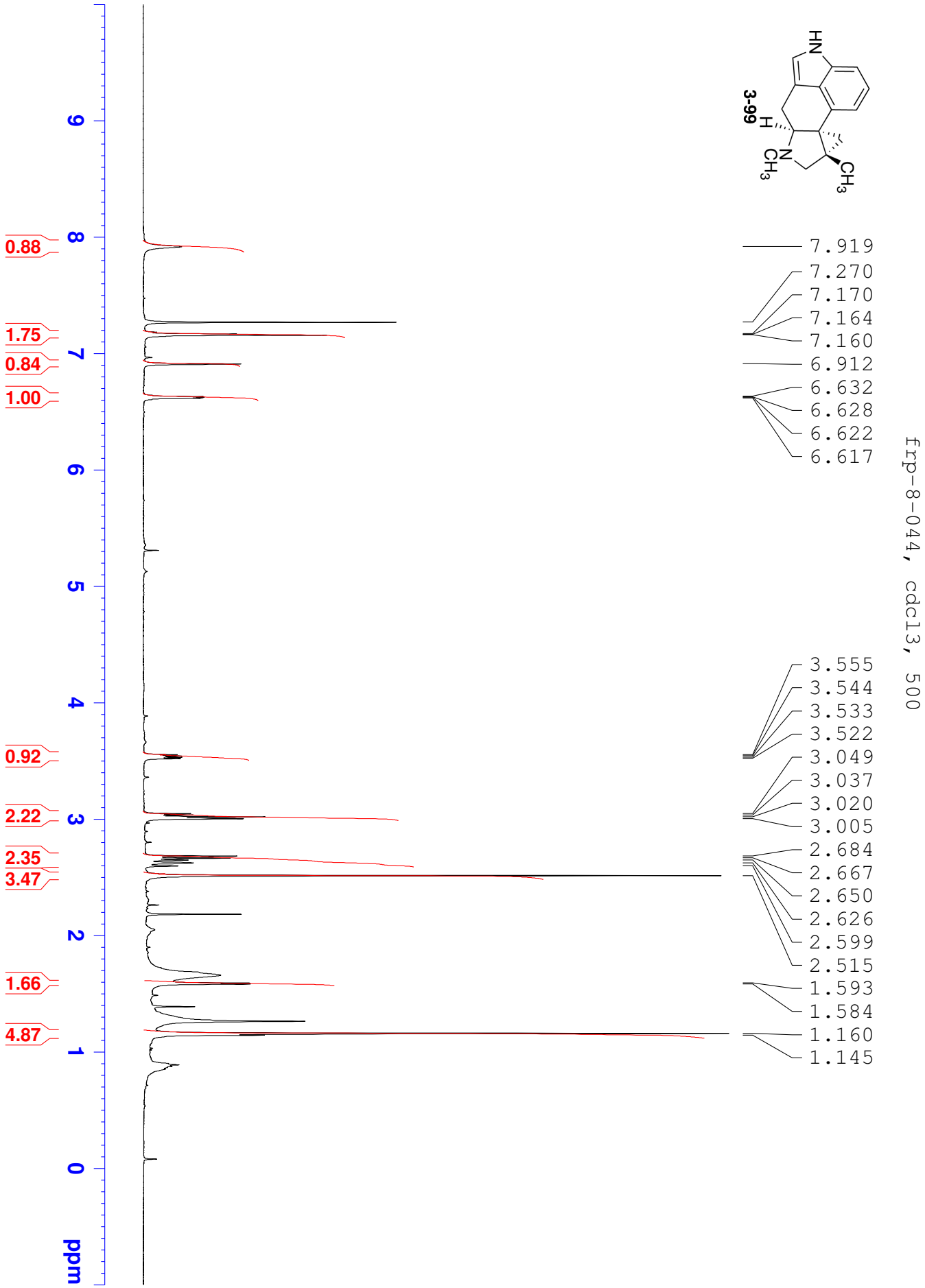
197.10
177.02
164.26
101.33
36.81
30.01
29.77
29.08
26.15
24.42
10.30
3-84
frp-6-050, cdcl3, 301
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

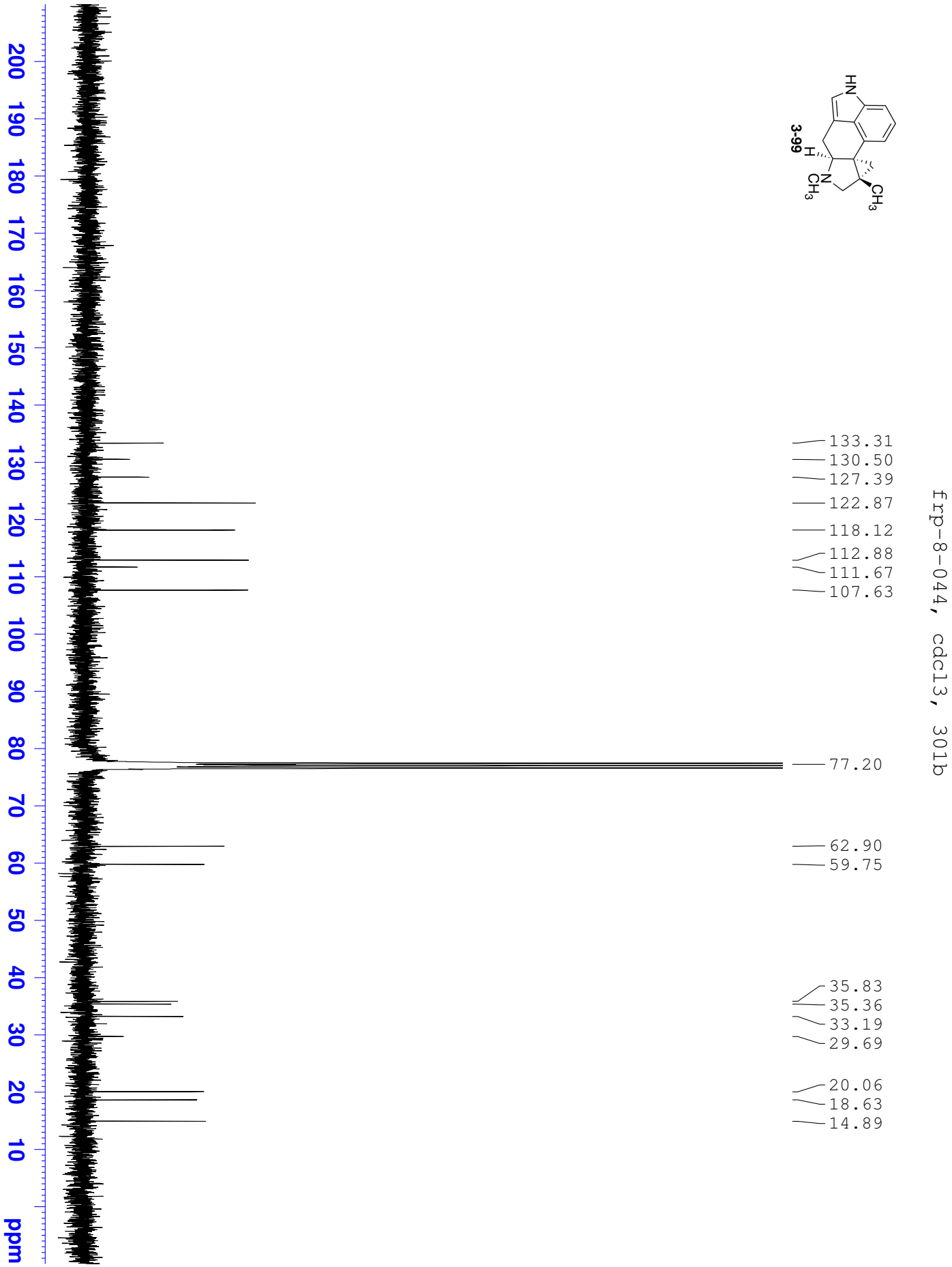

3-89
frp-6-055, cdc13, 301
3.731
3.709
3.688
2.838
2.817
2.788
2.767
2.684
2.518
2.499
2.489
2.481
2.463
2.445
2.407
2.390
2.374
2.367
2.357
2.340
2.316
2.279
2.261
2.247
2.228
1.811
1.793
1.782
1.774
1.764
1.746
1.300
0.901
0.886
0.93
0.98
2.79
3.95
0.94
2.91
0.97
1.00
ppm

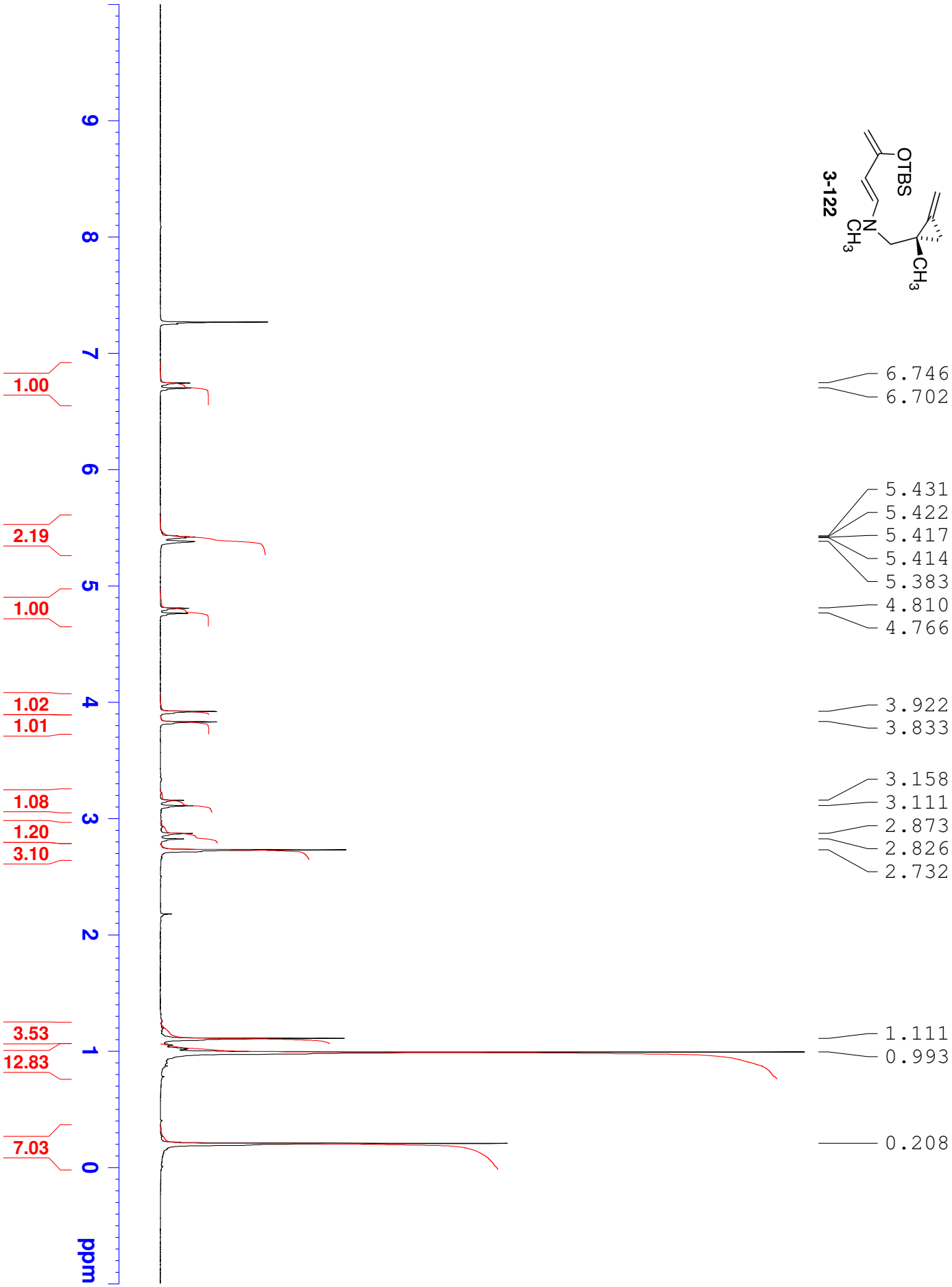
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
208.54
175.80
77.43
77.01
76.58
60.32
43.64
38.84
29.02
27.34
26.78
25.41
23.81
11.53
3-89
frp-6-055, cdcl3, 301

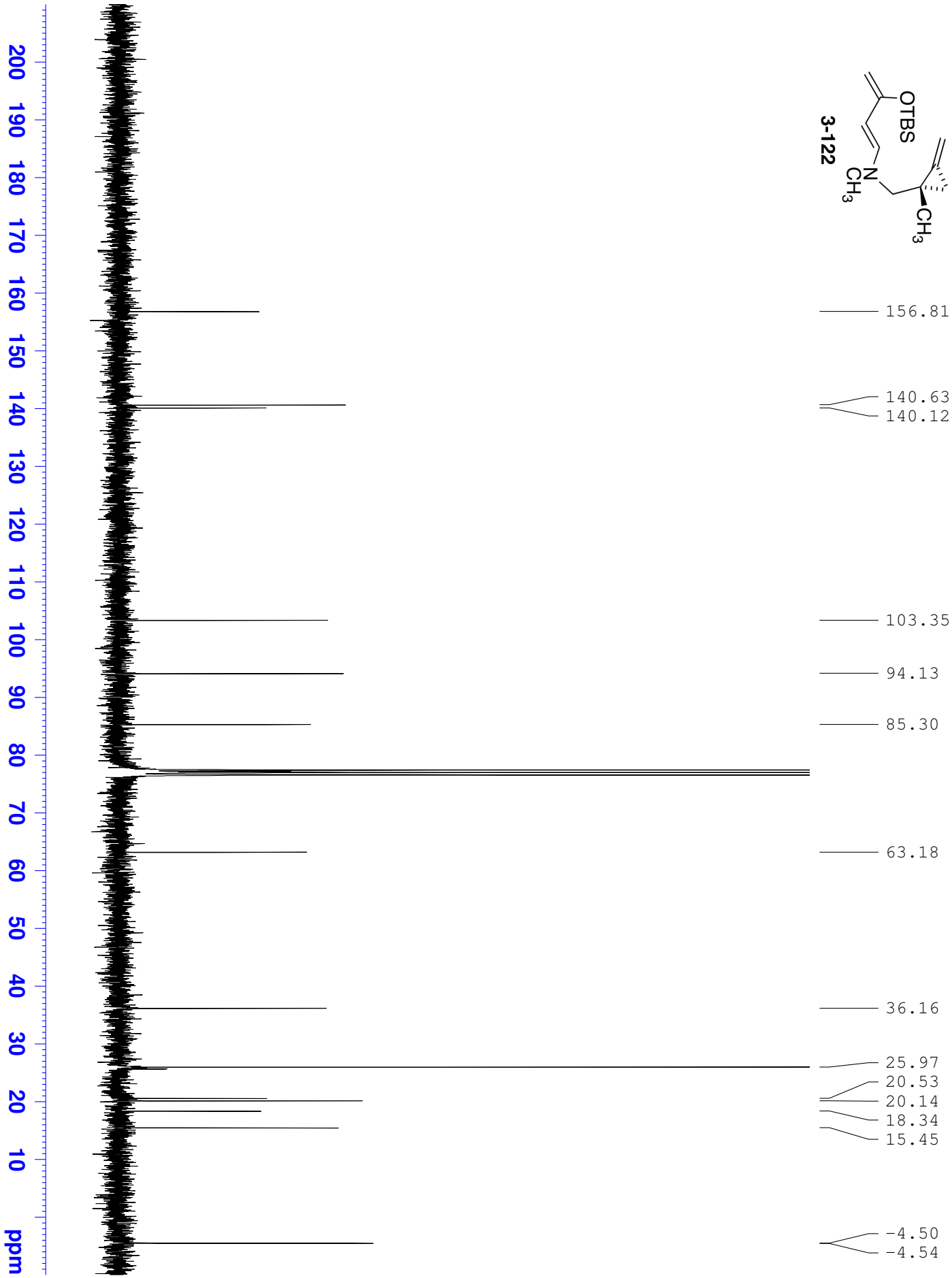

frp-8-032, cdcl3, 301
7.270
7.206
7.201
6.384
6.377
6.373
6.366
6.045
6.035
5.803
5.799
5.770
5.766
5.307
5.273
3.858
3.808
3.737
3.687
3.395
3.381
3.355
3.340
2.658
2.612
2.604
2.572
2.562
1.441
1.291
1.005
0.989
0.971
0.955
1.00
1.01
1.00
1.01
1.07
1.17
1.71
1.03
2.91
1.18
9.27
3.68
1.03
1.10
ppm
3-97

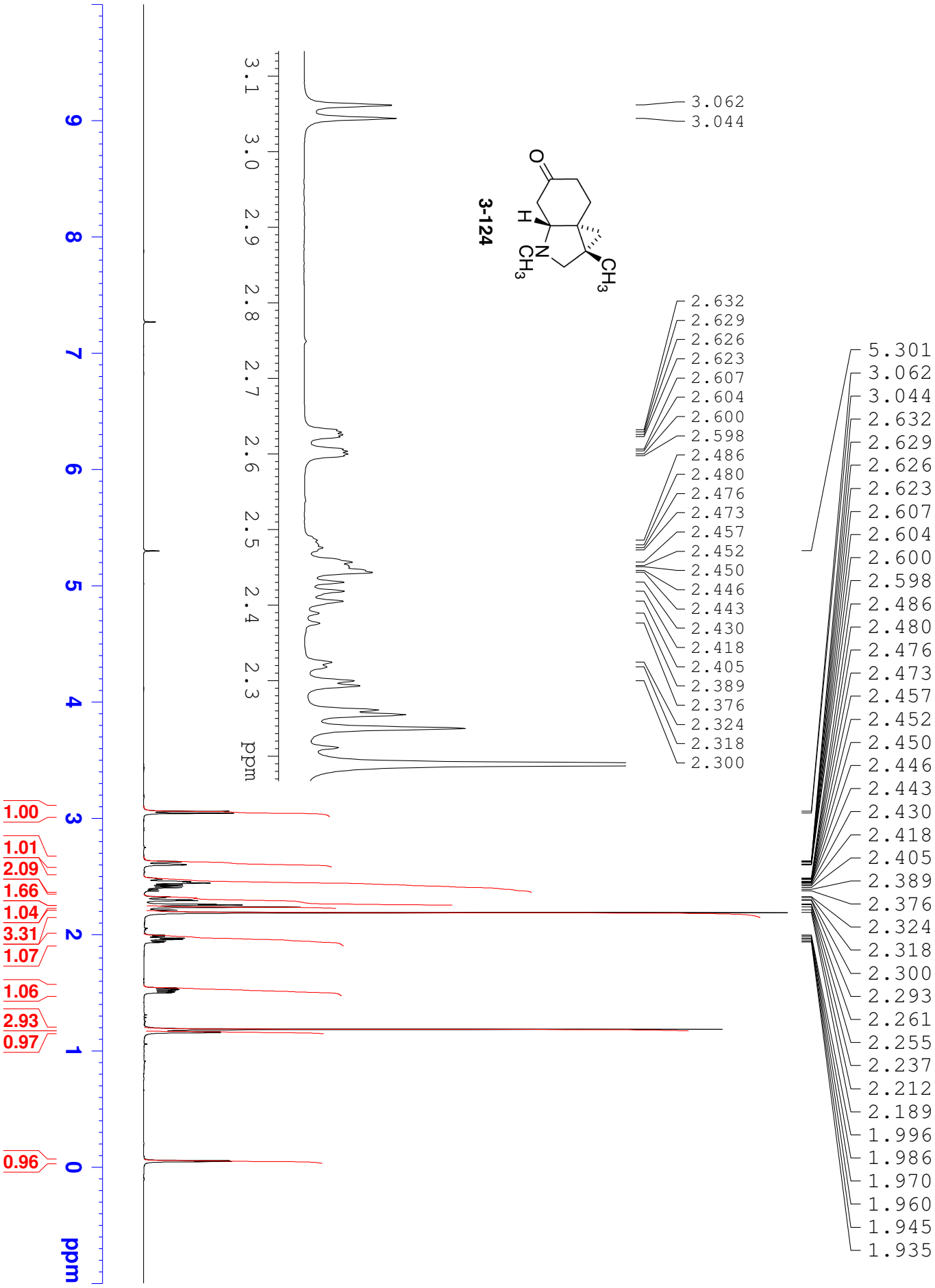

3-97
BocN
HO
H
N
CH3
CH3
O
O
174.81
149.17
138.22
133.96
127.68
111.30
101.59
82.50
72.77
57.71
56.04
38.15
32.35
29.47
27.99
27.13
26.21
12.22
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
frp-8-032, cdc13, 301


3-99
HN
H
N
CH3
CH3
7.919
7.270
7.170
7.164
7.160
6.912
6.632
6.628
6.622
6.617
3.555
3.544
3.533
3.522
3.049
3.037
3.020
3.005
2.684
2.667
2.650
2.626
2.599
2.515
1.593
1.584
1.160
1.145
0.88
1.75
0.84
1.00
0.92
2.22
2.35
3.47
1.66
4.87
ppm
frp-8-044, cdcl3, 500

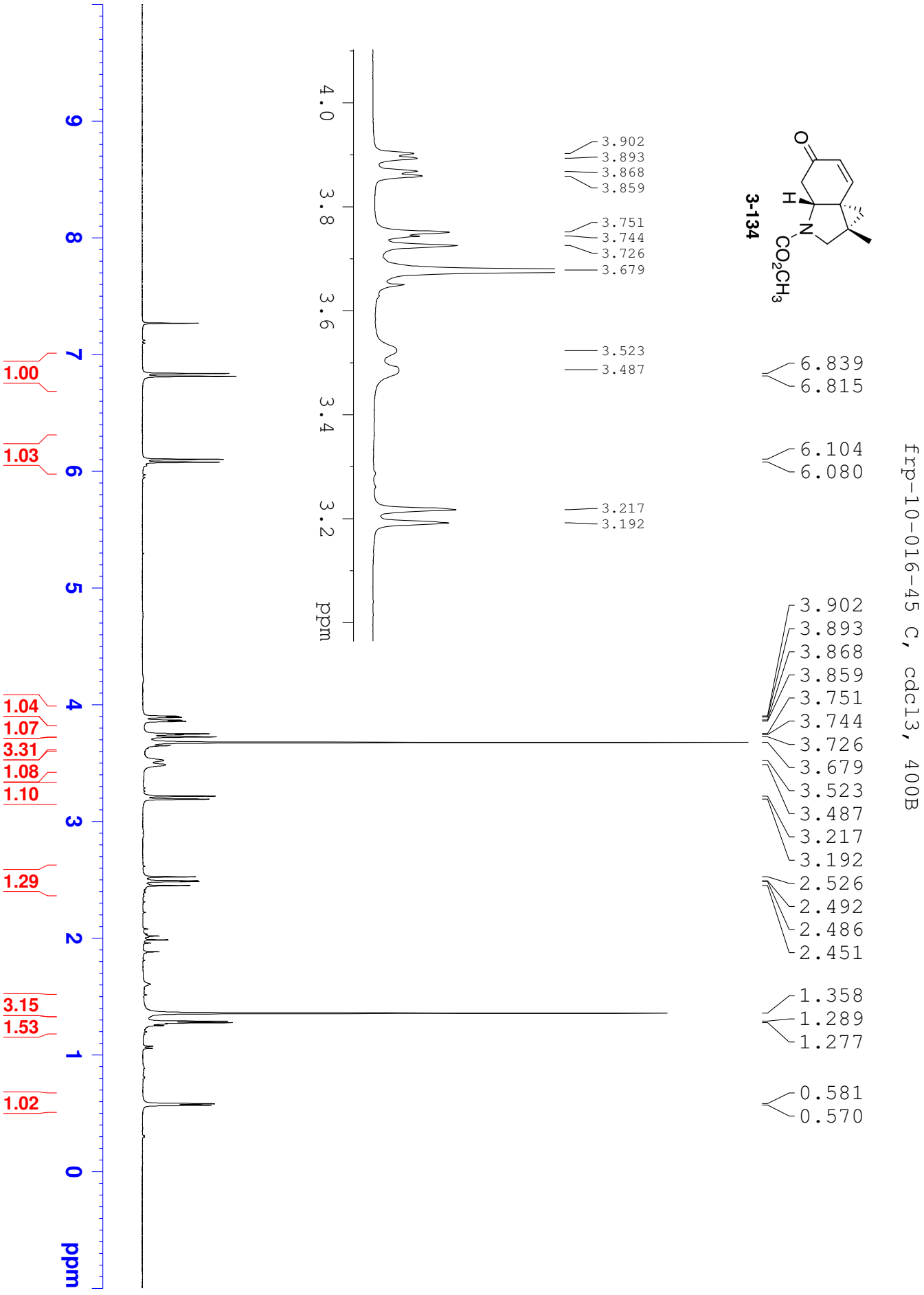

3-99
HN
H
N
CH3
CH3
133.31
130.50
127.39
122.87
118.12
112.88
111.67
107.63
77.20
62.90
59.75
35.83
35.36
33.19
29.69
20.06
18.63
14.89
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
frp-8-044, cdcl3, 301b

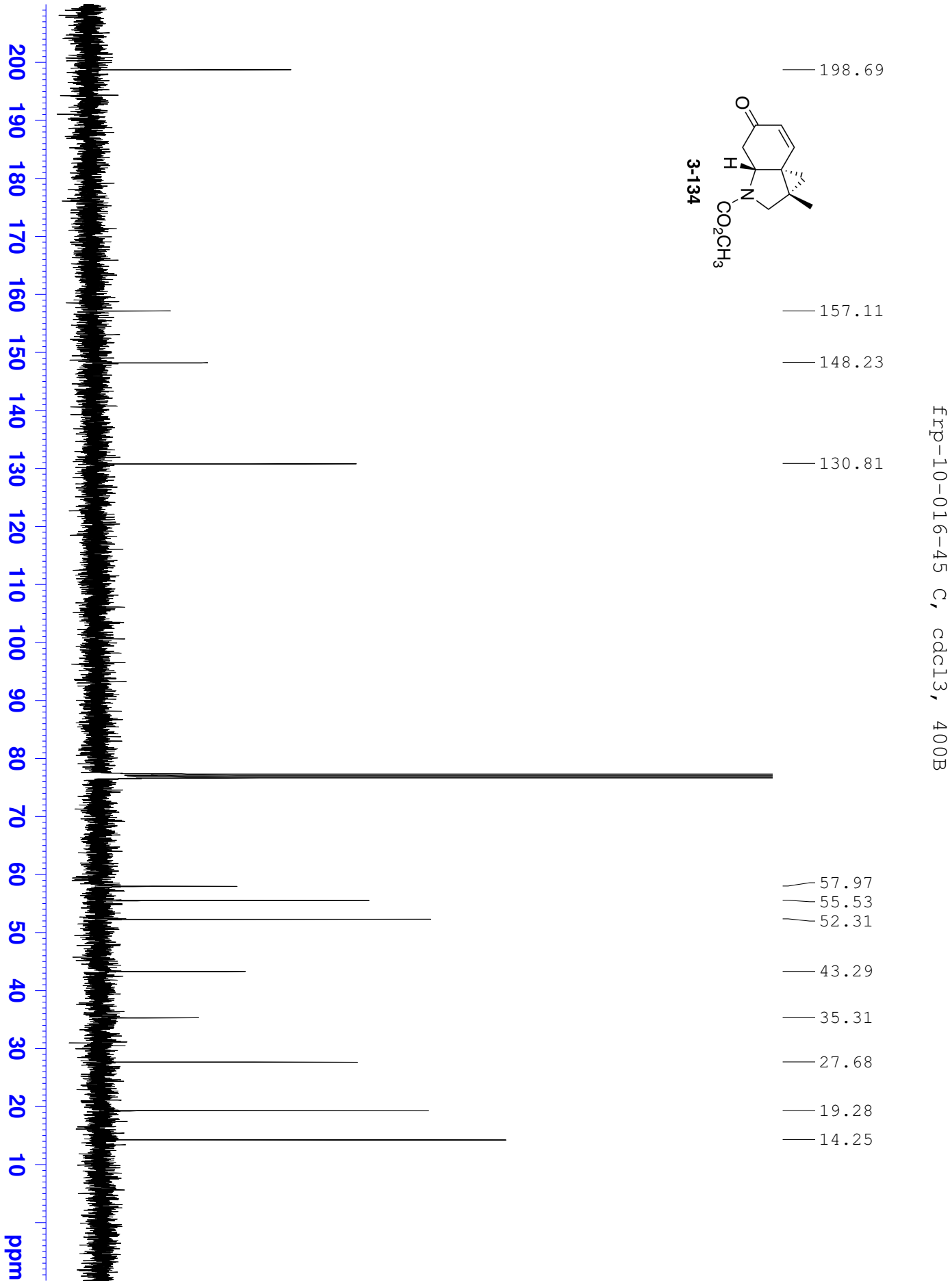

3-122
OTBS
N
CH3
CH3
6.746
6.702
5.431
5.422
5.417
5.414
5.383
4.810
4.766
3.922
3.833
3.158
3.111
2.873
2.826
2.732
1.111
0.993
0.208
1.00
2.19
1.00
1.02
1.01
1.08
1.20
3.10
3.53
12.83
7.03
ppm

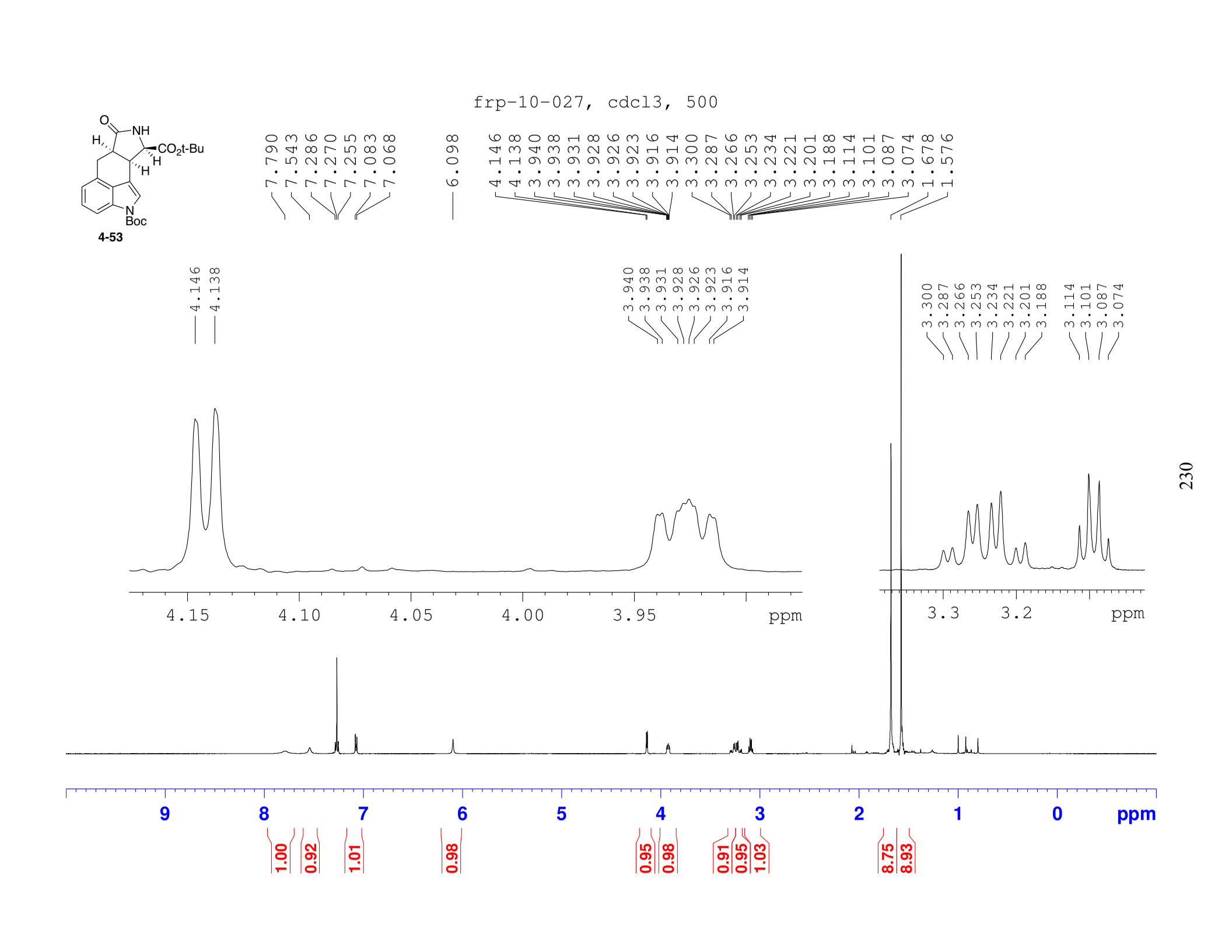

3-122
OTBS
N
CH3
CH3
156.81
140.63
140.12
103.35
94.13
85.30
63.18
36.16
25.97
20.53
20.14
18.34
15.45
-4.50
-4.54
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

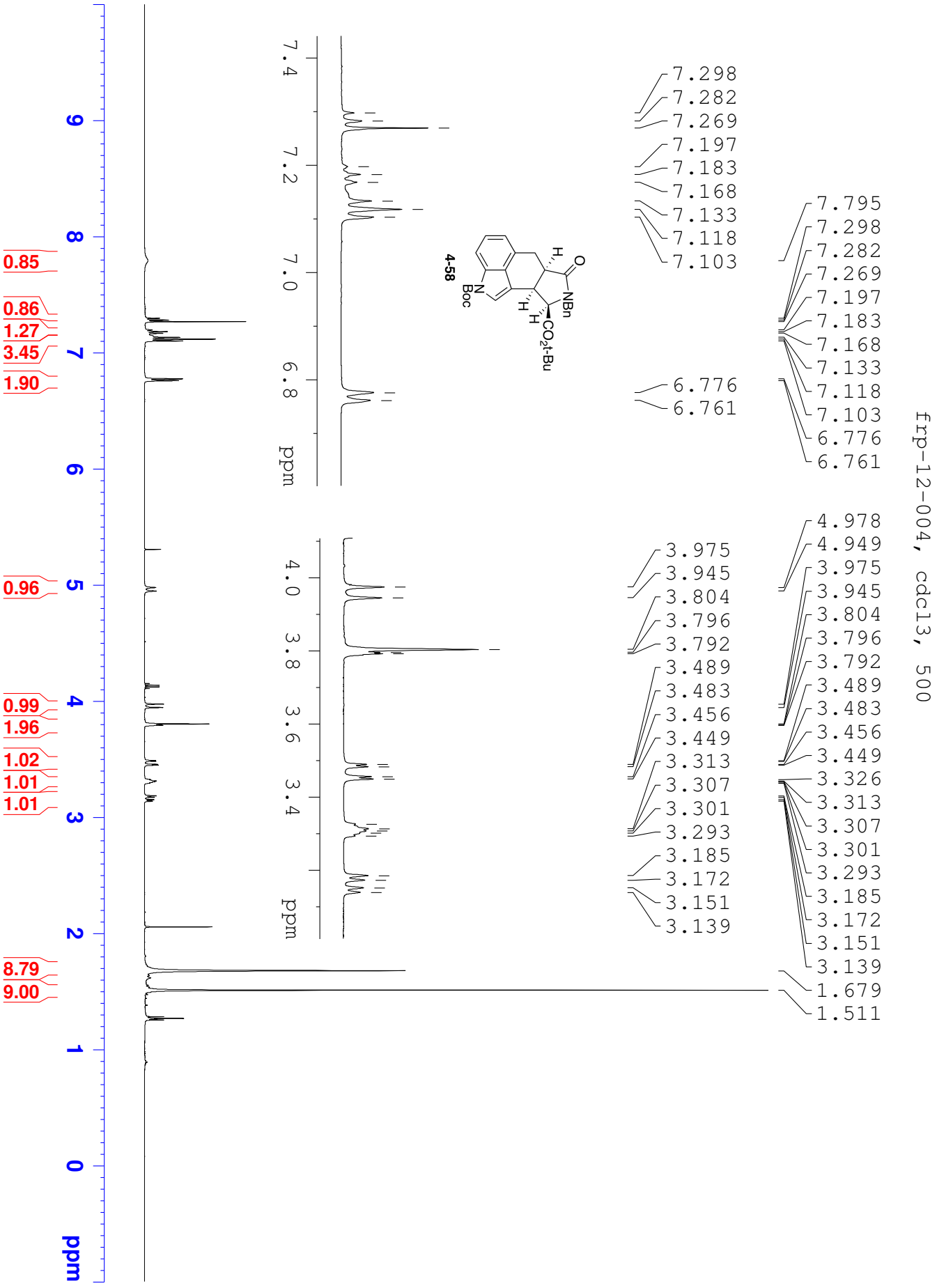

3-124
3.062
3.044
2.632
2.629
2.626
2.623
2.607
2.604
2.600
2.598
2.486
2.480
2.476
2.473
2.457
2.452
2.450
2.446
2.443
2.430
2.418
2.405
2.389
2.376
2.324
2.318
2.300
5.301
3.062
3.044
2.632
2.629
2.626
2.623
2.607
2.604
2.600
2.598
2.486
2.480
2.476
2.473
2.457
2.452
2.450
2.446
2.443
2.430
2.418
2.405
2.389
2.376
2.324
2.318
2.300
2.293
2.261
2.255
2.237
2.212
2.189
1.996
1.986
1.970
1.960
1.945
1.935
1.00
1.01
2.09
1.66
1.04
3.31
1.07
1.06
2.93
0.97
0.96
ppm

210.99
68.11
65.04
45.34
40.58
39.28
33.29
25.61
25.13
16.60
15.07
frp-6-020, cdcl3, 500
3-124
O
H
N
CH3
CH3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


3-134
frp-10-016-45 C, cdc13, 400B
ppm
1.00
1.03
1.04
1.07
3.31
1.08
1.10
1.29
3.15
1.53
1.02
6.839
6.815
6.104
6.080
3.902
3.893
3.868
3.859
3.751
3.744
3.726
3.679
3.523
3.487
3.217
3.192
2.526
2.492
2.486
2.451
1.358
1.289
1.277
0.581
0.570


198.69
157.11
148.23
130.81
57.97
55.53
52.31
43.29
35.31
27.68
19.28
14.25
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
3-134
frp-10-016-45 C, cdcl3, 400B


frp-10-027, cdcl3, 500
4-53
7.790
7.543
7.286
7.270
7.255
7.083
7.068
6.098
4.146
4.138
3.940
3.938
3.931
3.928
3.926
3.923
3.916
3.914
3.300
3.287
3.266
3.253
3.234
3.221
3.201
3.188
3.114
3.101
3.087
3.074
1.678
1.576
4.15
4.10
4.05
4.00
3.95
ppm
3.3
3.2
ppm
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.92
1.01
0.98
0.95
0.98
0.91
0.95
1.03
8.75
8.93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4-58
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CO2t-Bu
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7.183
7.168
7.133
7.118
7.103
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6.761
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3.975
3.945
3.804
3.796
3.792
3.489
3.483
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3.449
3.326
3.313
3.307
3.301
3.293
3.185
3.172
3.151
3.139
1.679
1.511
0.85
0.86
1.27
3.45
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ppm

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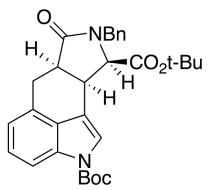

4-58

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120.65
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112.76
83.57
82.74
65.24
60.37
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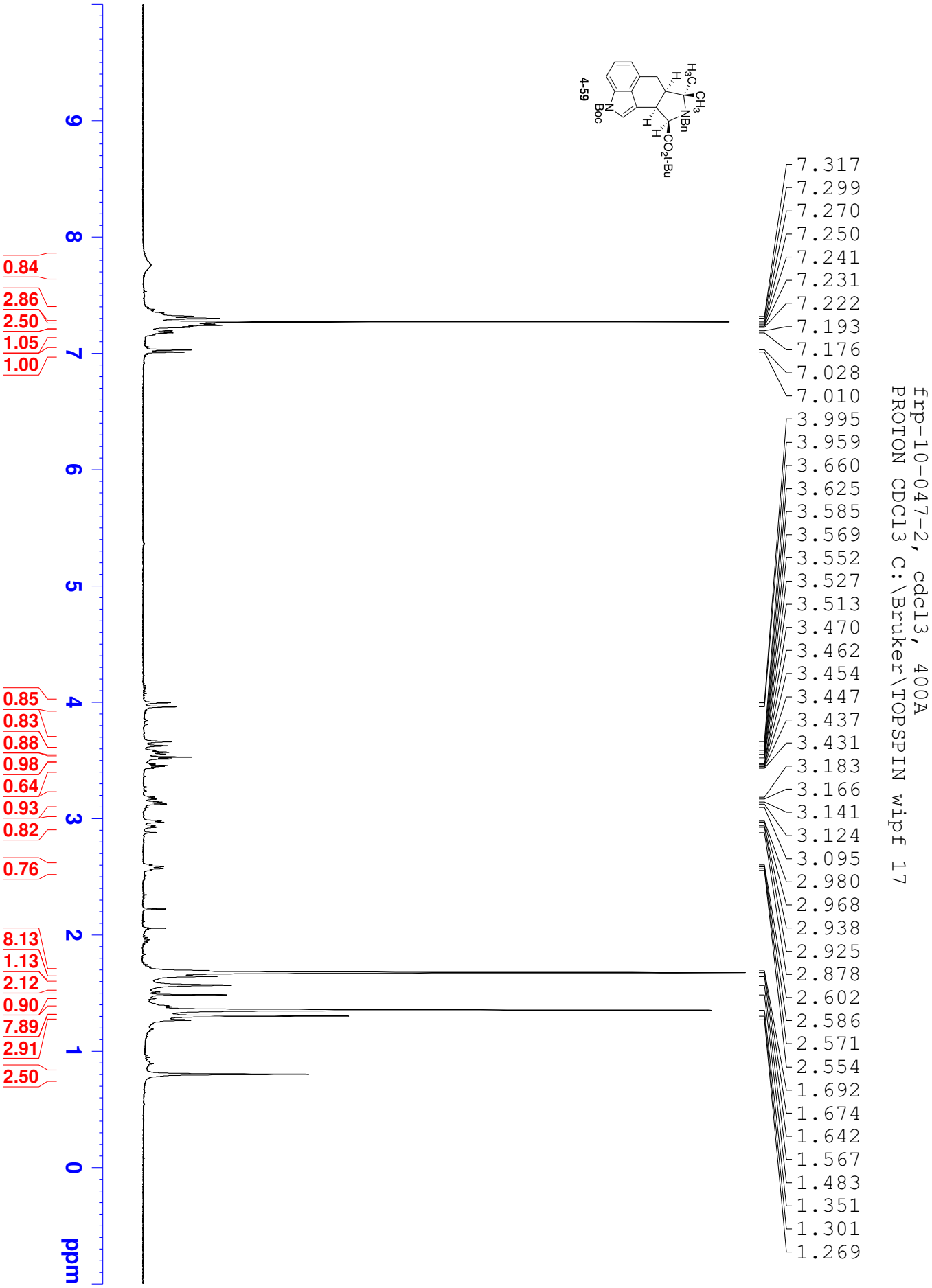
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1.692
1.674
1.642
1.567
1.483
1.351
1.301
1.269
0.84
2.86
2.50
1.05
1.00
0.85
0.83
0.88
0.98
0.64
0.93
0.82
0.76
8.13
1.13
2.12
0.90
7.89
2.91
2.50
ppm

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[7] Image of 3bta (R. C. Stevens, D. B. Lacy (1998) Crystal structure of Botulinum Neurotoxin serotype A Nat. Struct. Biol. 5:898-902) created with PyMOL

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