STRATEGIES FOR THE CONCISE SYNTHESIS OF THE AKUAMMILINE ALKALOIDS

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ABSTRACT

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The akuammiline alkaloids are an intriguing class of natural products that display an array of biological activities and structural diversity. Despite being known for over 125 years, it is surprising that these complex monoterpene indole alkaloids have only recently elicited sustained interest from the synthetic community, especially given the storied history of this broad family in the development of the art of total synthesis, and, in particular, heterocyclic chemistry. This dissertation details our efforts to address these deficiencies through work initially directed at the unique akuammiline alkaloid scholarisine A, ultimately yielding a concise and enantiospecific preparation of this challenging target. Hereafter, we showcase our studies aiming to extend these advances to the akuammiline class as whole, through the development of a readily generalizable approach to this alkaloid family.

Thus, Chapter 1 will serve to introduce this exciting class of alkaloids, beginning with the details of their proposed biosynthesis, followed by a summary of the diverse biological activities they display. Lastly, the reported synthetic approaches to this family will be described, starting with a select number of early efforts and culminating in the few, but impressive examples of completed total syntheses that have recently appeared.

Next, Chapter 2 will detail the evolution of our synthetic approach to the highly rearranged akuammiline alkaloid scholarisine A, a strategy guided throughout by a key pyrone Diels–Alder logic. That discussion will include out early attempts to fashion its

characteristic framework through intramolecular Diels–Alder approaches and how those efforts informed the development of our eventual synthetic solution based on an intermolecular process. Finally, it will be demonstrated that advances made during our early work have led to a method with potential utility in both natural product synthesis and the assembly of medicinally-relevant building blocks.

Finally, in Chapter 3, our efforts to develop a general approach to the akuammiline alkaloids will be described, studies that initially focused on the prototypical member of this class, strictamine. These efforts have culminated in a concise and readily scalable route to a number of advanced tetracyclic intermediates, empowered by a number of methodological advances. These intermediates, many embodying all the carbon atoms of strictamine and related targets, are poised for a final ring formation to complete their total syntheses. In addition, we disclose promising discoveries that should allow for broad access to akuammiline class, having identified facile means to transition from the strictamine series to other subfamilies.

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LIST OF ABBREVIATIONS

ACCN	1,1'-azobis(cyclohexanecarbonitrile)
AIBN	azobisisobutyronitrile
BHT	2,6-di-*tert*-butyl-4-methylphenol
brsm	based on recovered starting material
Bt	1-benzotriazole
BTPP	*tert*-Butylimino-tri(pyrrolidino)phosphorane
COD	1,4-cyclooctadiene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino)pyrine
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
HAT	hydrogen-atom transfer
HRMS	high-resolution mass spectrometry
IMDA	intramolecular Diels–Alder
IR	infrared

LR	Lawesson's reagent
LRMS	low-resolution mass spectrometry
***m*CPBA**	*meta*-chloroperbenzoic acid
MeOH	methanol
Ms	methanesulfonyl
MS	molecular sieves
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ns	2-nitrobenzenesulfonyl
***o*-DCB**	1,2-dichlorobenzene
pin	pinacolato
PMP	1,2,2,6,6-pentamethylpiperidine
PPTS	pyridinium p-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
Ra-Ni	Raney nickel
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl

TBS *tert*-butyldimethylsilyl

TEMPO 2,2,6,6-Tetramethylpiperidine 1-oxyl

Tf trifluoromethanesulfonyl

TFA trifluoroacetic acid

TFAA trifluoroacetic anhydride

THF tetrahydrofurn

TIPB 1,3,5-triisopropylbenzene

TMG *N,N,N',N'*-tetramethylguanidine

TMS trimethylsilyl

Ts p-toluenesulfonyl

UV ultraviolet

VT-NMR variable temperature nuclear magnetic resonance

ACKNOWLEDGMENTS

Reflecting back on the past five years or so, it is something of an ambivalent experience – a simultaneous combination of relief at having made it to the end of the slog that is a Ph.D. in organic chemistry, disappointment in not having achieved all the naïve (and truthfully unrealistic) goals set by my younger self, and an inner sense of accomplishment in what five years of effort has culminated in. As many before me have expressed, likely more eloquently, this has been a war of attrition – man versus molecule if you will – with many an emotional up and down. Unquestionably, me surviving to tell this tale would have been near impossible without the help of the many people listed below – thank you.

Naturally, I'd like to express my sincerest thanks to my advisor, Professor Scott Snyder, for everything he has done over the course of these past five years. Scott as a mentor is exceptionally good at nurturing and steering his students to develop their talents, and I feel that under his tutelage I have grown into an independent, creative and dare I say imposing organic chemist. I feel like the extremely high standards you set in problem selection and the bar for their solutions has taught me to be uncompromising (inasmuch as is possible) when it comes to quality and scholarship. But beyond simply guiding me through my chemical education, I truly appreciate the time Scott has invested in helping to prepare me for my chosen academic career path. The many occasions he has shared his insights into the ins-and-outs of being a young PI in organic chemistry, be it from the grant writing perspective, expert tips on presenting, or the review and hiring process, all will undoubtedly be invaluable later on in my own academic career.

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CHAPTER 1

THE AKUAMMILINE ALKALOIDS: BACKGROUND, BIOSYNTHESIS AND PREVIOUS SYNTHETIC APPROACHES.

1.1 Introduction

The akuammiline alkaloids are an incredibly intriguing class of natural products that have long been known within the scientific community.[1] Indeed, its inaugural member, echitamine (**1**) was isolated in 1875,[2] and in the ensuing decades dozens of additional members have been obtained, many with unique structures and several, as will be defined shortly, having promising biological activity. Collectively, these alkaloids are isolated from various species of plants of the *Apocynaceae* family which are typically found in tropical regions of both Africa and Asia. In fact, the name of the family itself derives from the native Ghanaian word for the tree *Picralima klaineana*, "akuamma", which led the early isolation chemist T. Henry to name some of the first alkaloids he isolated from its seeds as akuammine[3] (**2**, 1927) and akuammiline[4] (**3**, 1932), the latter of which has since encompassed the entire group.

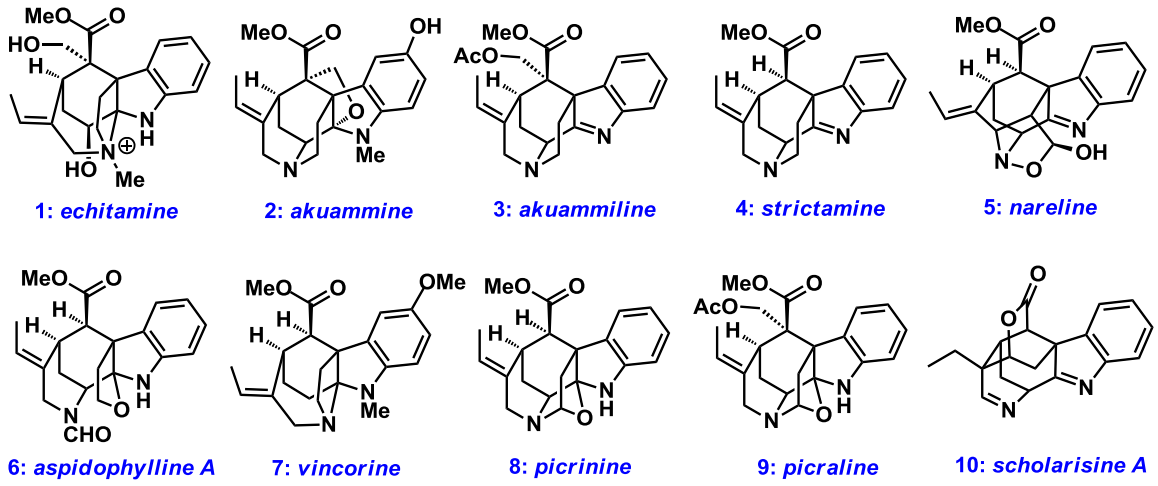


Figure 1. The diverse structures of a representative cross section of the akuammiline alkaloids.

These early investigations of the akuammiline family were likely stimulated by the fact that the seeds of *Picralima klaineana* had long been used in traditional, local medicines as a treatment for malaria, as well as by the relatively large quantities of certain family

members available from the natural sources, which facilitated structure proof in an era with minimal spectroscopy. Indeed, in more recent years, further investigations by various groups have uncovered a great diversity of structure within the class and a promising array of biological activity for the akuammilines, including anticancer, antibacterial, anti-inflammatory, antiviral and antimalarial activity.[1b] It is somewhat surprising, therefore, especially in light of the rich history of monoterpene indole alkaloids in the development of organic synthesis, and specifically heterocyclic chemistry, that their complex structures had remained an unanswered synthetic challenge until very recent times.

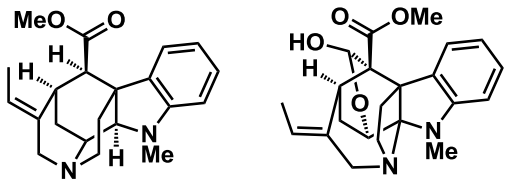
Globally, this opening chapter will serve to introduce this exciting class of alkaloids, beginning with the details of their proposed biosynthesis, followed by a summary of the diverse biological activities they display. Finally, the reported synthetic approaches to this family will be described, starting with a select number of early efforts and culminating in the few, but impressive examples of completed total syntheses that have recently appeared, largely empowered by creative strategies for forging hindered, polycyclic systems.

1.2 Biological Activity and Biosynthesis

1.2.1 Biological Activity

The akuammiline class as a whole exhibits a wide variety of biological activities that range from anticancer, antibacterial, anti-inflammatory, antiviral, antitussive to antimalarial activity.[1b] In particular, the earliest known member of the collection, echitamine chloride (**1**), displays impressive antitumor activity,[5] while apsidophylline A (**6**) reverses multi-drug resistance in drug-resistant KB cells.[6] Equally interesting,

derivatives of picraline[7] (**9**) have been found to inhibit the Na^+-glucose co-transporter SGLT2,[8] which has been validated as a possible target for the treatment of type II diabetes and has been the source of many recent clinical candidates from a number of leading pharmaceutical companies.[9] The related molecule picrinine[10] (**8**) displays CNS depressant activity,[11] while its less oxidized homologue strictamine[12] (**4**) displays monoamine-oxidase antagonist activity[13] as well as antiviral activities against both the herpes simplex virus and adenovirus.[14] In addition, both **4** and nareline (**5**) inhibit nuclear factor-κB (NF-κB), a target which regulates gene expression in immune and inflammatory responses.[15] Finally, cathafoline (**11**, Figure 2) displays vasorelaxant activity,[16] while corymine (**12**) behaves as an antagonist towards the glycine receptor and thus is CNS active.[17] Noteworthy, too, is the fact that the alkaloidal leaf extract of the evergreen tree *Alstonia scholaris*, known to contain a range of akuammiline alkaloids, has recently undergone successful phase I clinical trials in China for the treatment of respiratory ailments.[18] Indeed, to have such a range of activities within a given class is impressive, and argues strongly that a comprehensive codification of biological properties and advanced understanding of structure-function relationships could be of broad value in the design of even more potent materials.

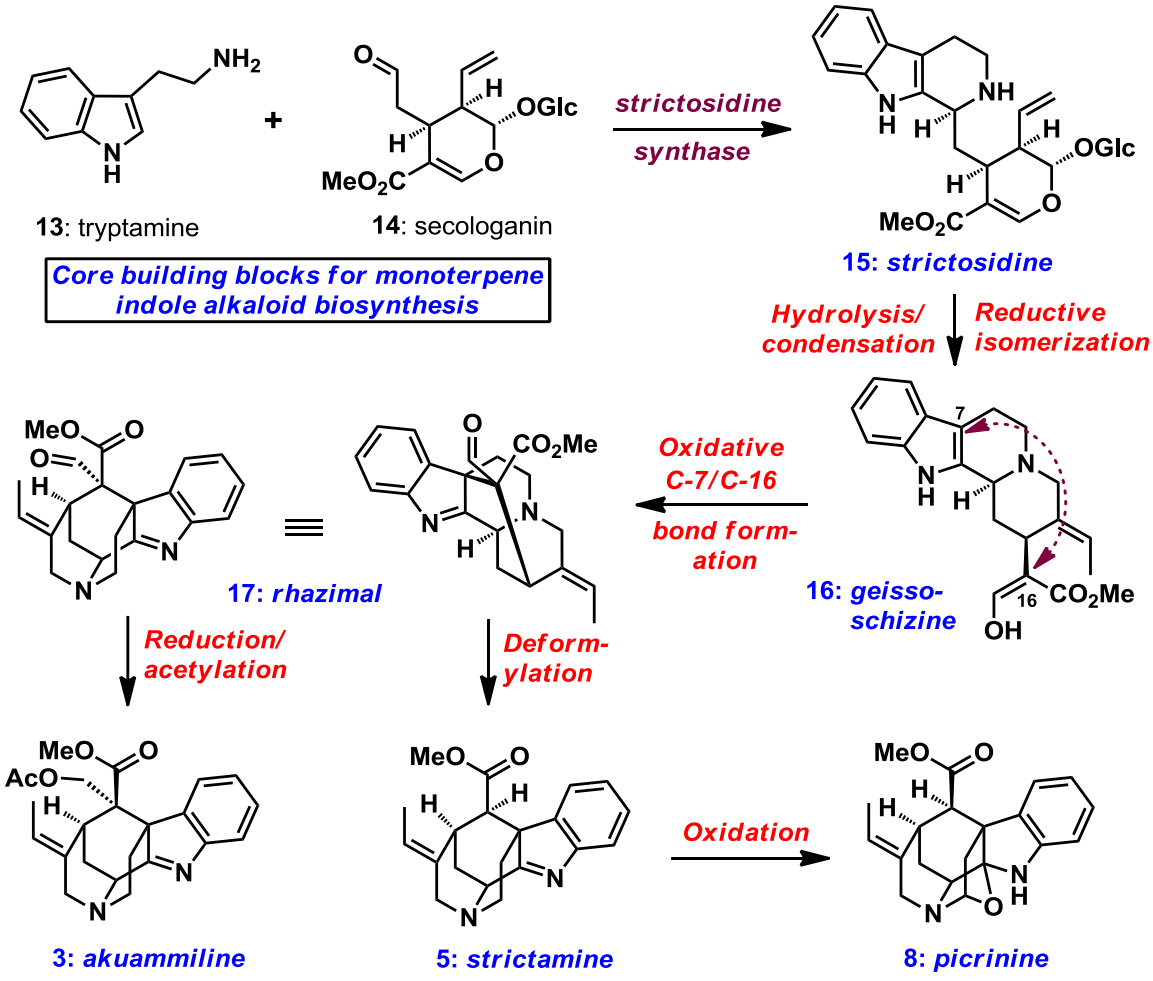


11: *cathafoline* **12: *corymine***

Figure 2. Additional bioactive alkaloids of the akuammiline class.

1.2.2 Biosynthesis

As monoterpene indole alkaloids, the akuammilines are biosynthetically thought to arise via the initial pathways common to this broad class of natural products. Thus, their biosynthesis begins with the formation of strictosidine (**15**) through a biosynthetic Pictet-Spengler reaction as achieved between the monoterpene glycoside, secologanin (**14**), and tryptamine (**13**), catalyzed by the enzyme strictosidine synthase.[1b]



Scheme 1. Proposed biosynthesis for the akuammiline alkaloids via the key biosynthetic precursor geissoschizine (**16**).

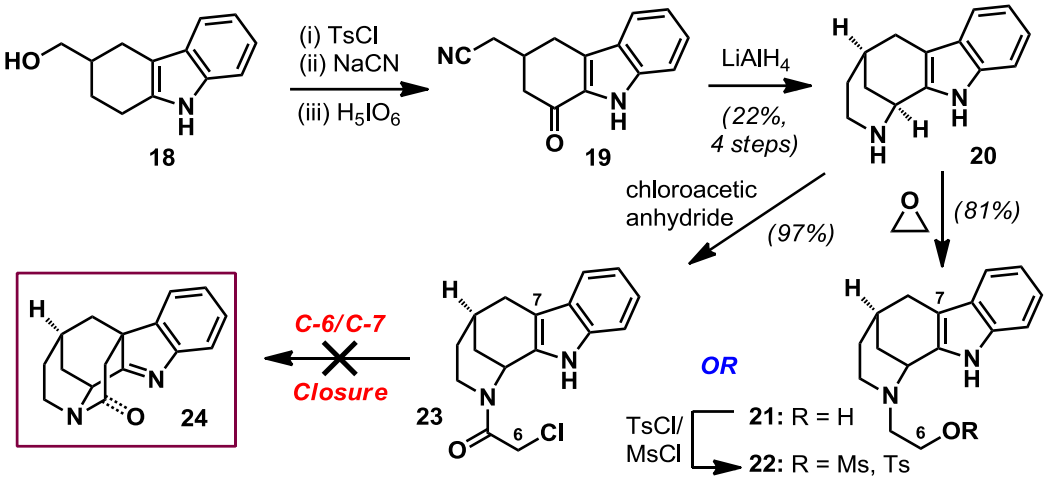
With all of the necessary carbon atoms installed through this one operation, subsequent hydrolysis, condensation, and reduction reactions deliver the natural product and important biosynthetic intermediate, geissoschizine (**16**). From **16**, a subsequent oxidative bond formation between the C-7/C-16 positions establishes the characteristic akuammiline framework in the form of rhazimal[19] (**17**), from which the great diversity of structures in Figures 1 and 2 can be accessed through oxidative tailoring and/or rearrangement.[1b]

1.3 Synthetic Studies in the Akuammiline Class

Prior to 2009, synthetic efforts towards the akuammiline class were relatively sparse, with no completed syntheses and only a select number of studies, many driven by possible biogenetic hypotheses. By contrast, the last five years have seen a large body of work appear, no doubt driven by the complex structures and promising biological activities noted above. These studies have culminated in nine completed total syntheses and one formal synthesis, of five different targets within the class. Aside from our own efforts, which are the subject of this dissertation, these successful syntheses will be presented in the ensuing section, along with a few select early studies, focusing our discussions on the key strategies and tactics that each employed in order to form the characteristic cage frameworks that epitomize the family. Although a few other synthetic studies using model compounds to address questions in the akuammiline realm have been conducted,[20] their discussion we will be deferred to Chapters 2 and 3 in those cases where they are relevant to key design considerations.

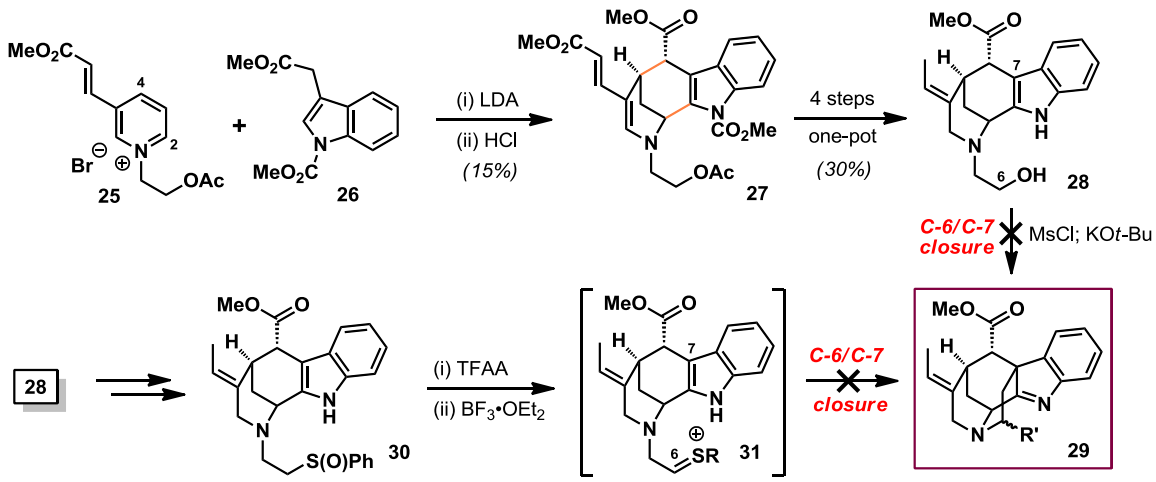
1.3.1 Early Synthetic Efforts

The first significant synthetic work towards this class was published in 1972 and 1973 in studies conducted by Dolby and co-workers.[21] These efforts were focused on the preparation of the core framework of the akuammiline alkaloids (**24**), a goal they realized as being key to accessing the family as a whole (Scheme 2). Specifically, they aimed to secure access to this core structure through intramolecular alkylation at the β-position of indole **22** (C-7 in akuammiline numbering) with a C-6 electrophile. As shown, the requisite tricyclic precursor **20** was prepared in short order from indole **18** through fairly standard chemistry, whereafter introduction of a hydroxyethyl substituent onto the secondary amine of **20** yielded **21**, setting the stage for the planned intramolecular alkylation. Unfortunately, conversion of alcohol **21** to the corresponding tosylate or mesylate (**22**) resulted in polymerization, while conversion of **18** to chloroacetate (**23**), followed by treatment with sodium hydride also proved incapable of effecting the desired C-6/C-7 closure. The former outcome was rationalized through the possible formation of an aziridinium intermediate from sulfonates **22** which may preclude the desired closure, and presages the types of challenges that many future investigators would face in attempting to construct the constrained systems of the class.



Scheme 2. Early, unsuccessful studies by Dolby targeting the akuammiline core through C-6/C-7 closure.

Indeed, extensive studies later undertaken by Bosch and Bennasar explored the same C-6/C-7 disconnection in greater detail.[22] As shown in Scheme 3, they were able to assemble a functionalized tricyclic intermediate in the form of **28**, similar to that of Dolby, through application of their pyridinium salt alkylation methodology.[23] In that key event, attack of the enolate derived from the readily accessed indole-3-acetate **26** onto C-4 of pyridinium salt **25**, followed by acidic work-up and concomitant Mannich reaction at the indole α-position gave structure **27**, albeit in moderate yield (15%). Following its conversion into an appropriate ethylidene chain and subsequent alcohol deprotection, they arrived at key intermediate **28** embodying all the carbon atoms required to access strictamine (**4**). However, despite subsequent functionalization of the hydroxyl group of **28** into a series of sulfonates and thionium ion precursors (e.g. **30**→**31**), they were unable to forge the final C-6/C-7 bond. Similarly, alternate radical modes of closure (not shown) were investigated with no success.

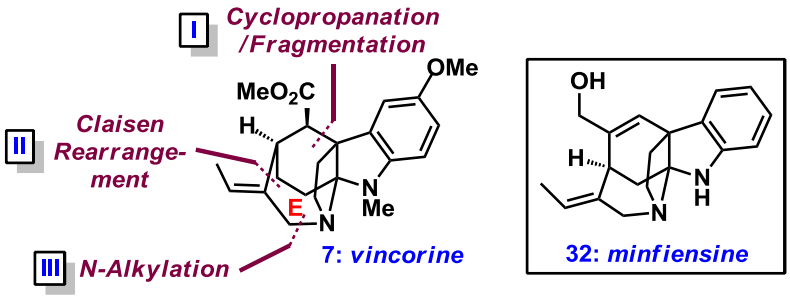


Scheme 3. More elaborate explorations of a C-6/C-7 closure undertaken by Bosch and Bennasar.

Collectively, therefore, these early studies point to the difficulties in effecting cage closure through a C-6/C-7 manifold. Indeed, as the ensuing sections will show, more recent solutions have avoided this clearly troublesome disconnection which these early studies highlighted effectively in a number of different formats.

1.3.2 Total Syntheses of Vincorine (7)

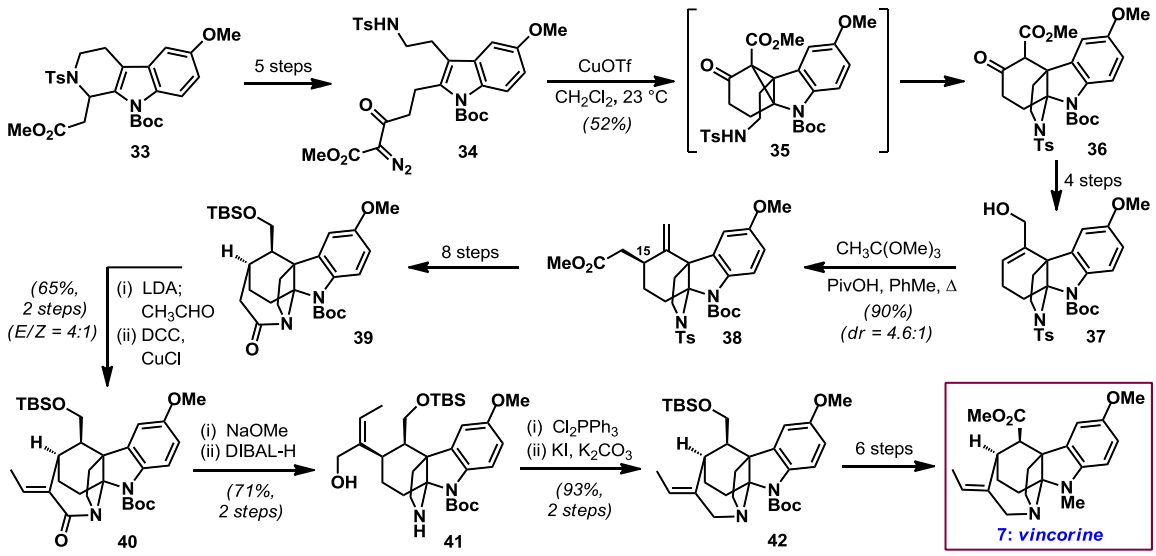
As already mentioned, no completed synthesis of an akuammiline alkaloid was reported until 2009, when the total synthesis of (±)-vincorine (**7**) was achieved by Qin and co-workers.[24] Strategically, this group aimed to apply their impressive indole cyclopropanation/fragmentation methodology which they had deployed in a number of other contexts [such as a preparation[25] of the related *Strychnos* alkaloid, minfiensine (**32**, inset, Scheme 4)] to attempt a synthesis of this pyrroloindoline alkaloid. As additional key disconnections, they aimed to complete the pentacyclic framework of **7** through a final E-ring formation via intramolecular *N*-alkylation, utilizing side-chain electrophile that had been installed through a Claisen-type rearrangement.



Scheme 4. Key strategic disconnections employed in the Qin synthesis of vincorine (**7**)

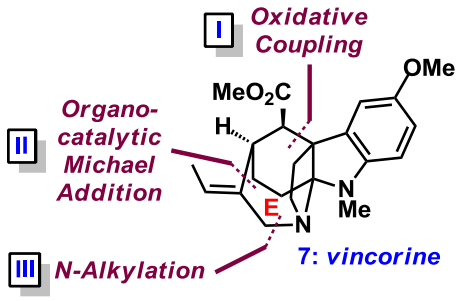
In the event, beginning with the readily available tetrahydro-β-carboline **33**, they were able to access tricyclic pyrroloindoline **36** in 52% yield through the application of their copper-catalyzed cyclopropanation/fragmentation protocol to diazoketone **34** (via intermediate **35**). From tricycle **36**, they were able to advance to allylic alcohol **37**, which, when subjected to standard Johnson–Claisen conditions, afforded ester **38** in 90% yield with the observed diastereoselectivity favoring the desired C-15 epimer (4.6:1). Elaboration to lactam **39**, followed by installation of the ethylidene chain delivered **40**, containing all the carbon atoms and the full pentacyclic structure of the final target (**7**). From this material, a somewhat circuitous, but necessary,[i] lactam opening/reduction/ reclosure sequence (via **41** and **42**) gave (±)-vincorine (**7**) in a total of 31 steps from known **33** (35 steps from commercial materials).

[i] The lactam could not be reduced in the presence of the ethylidene side-chain.



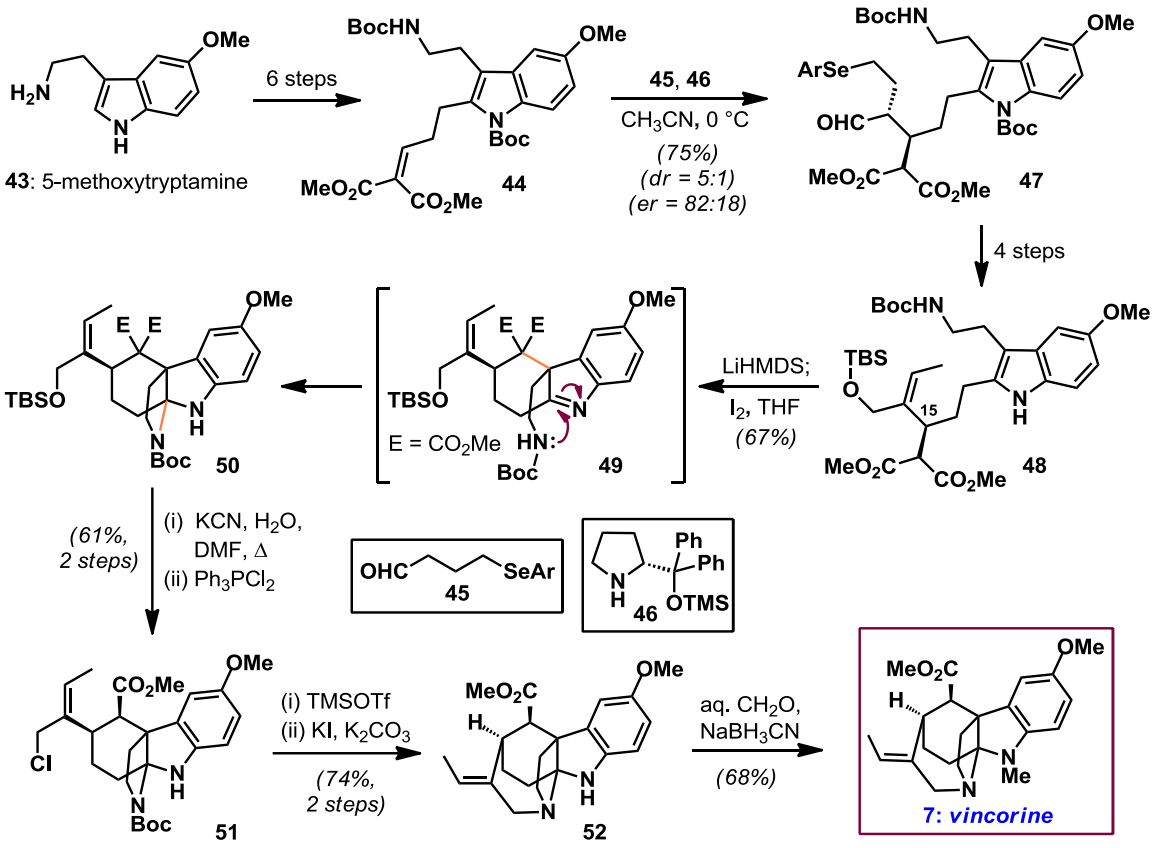
Scheme 5. The Qin synthesis of vincorine (**7**).

Their work, however, would not be the only effort to this compound, and since their inaugural synthesis, two other reports have issued of completed endeavors. The first of these came in 2012 when the Ma group published their own total synthesis of vincorine (**7**), one which was likely influenced by the Qin precedent since they also adopted a final *N*-alkylation approach to E-ring closure (Scheme 6).[26] In their case, however, to prepare the requisite alkylation precursor they aimed to utilize their impressive oxidative coupling methodology (originally developed by Baran et al.),[27] previously applied to alkaloids of the communesin family,[28] by employing a substrate like **48** (Scheme 7).



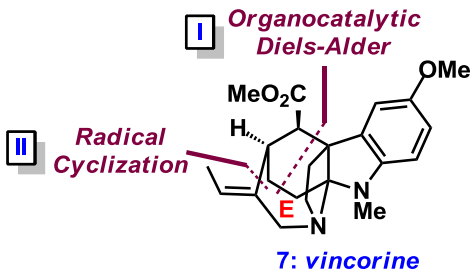
Scheme 6. Key strategic disconnections employed in the Ma synthesis of vincorine (**7**)

Thus, in the forward sense, from commercially available 5-methoxytryptamine (**43**) they were able to fashion a requisite malonylidene subtarget (**44**) in relatively short order through a series of homologations and appropriate oxidation state adjustments (Scheme 7). Then, from malonate **44**, they were able to install a precursor to the C-15 side-chain via an asymmetric Michael addition of aldehyde **45** as catalyzed by chiral prolinol **46**. This process yielded adduct **47** in 75% yield which, in turn, could be transformed into malonate **48**, bearing the requisite *E*-ethylidene group, in a few short steps**.** This advanced material contained all the carbon atoms of the target structure and, crucially, a lone stereocenter at C-15 that would dictate the installation of the remaining stereocenters in the key oxidative coupling process. In that process, treatment of **48** with LiHMDS followed by I_2 at –40 °C delivered the desired pyrroloindoline **50** as a single diastereomer in 67% yield via a presumed indolenine intermediate (**49**). From **50**, a few functional group interconversions led to allylic chloride **51**, which afforded the complete framework of **7** under alkylation conditions similar to those used by Qin.[24] Straighforward reductive methylation of the resulting pentacycle (**52**) then completed an impressive synthesis of (–)-vincorine (**7**) in 18 steps from commercial materials.



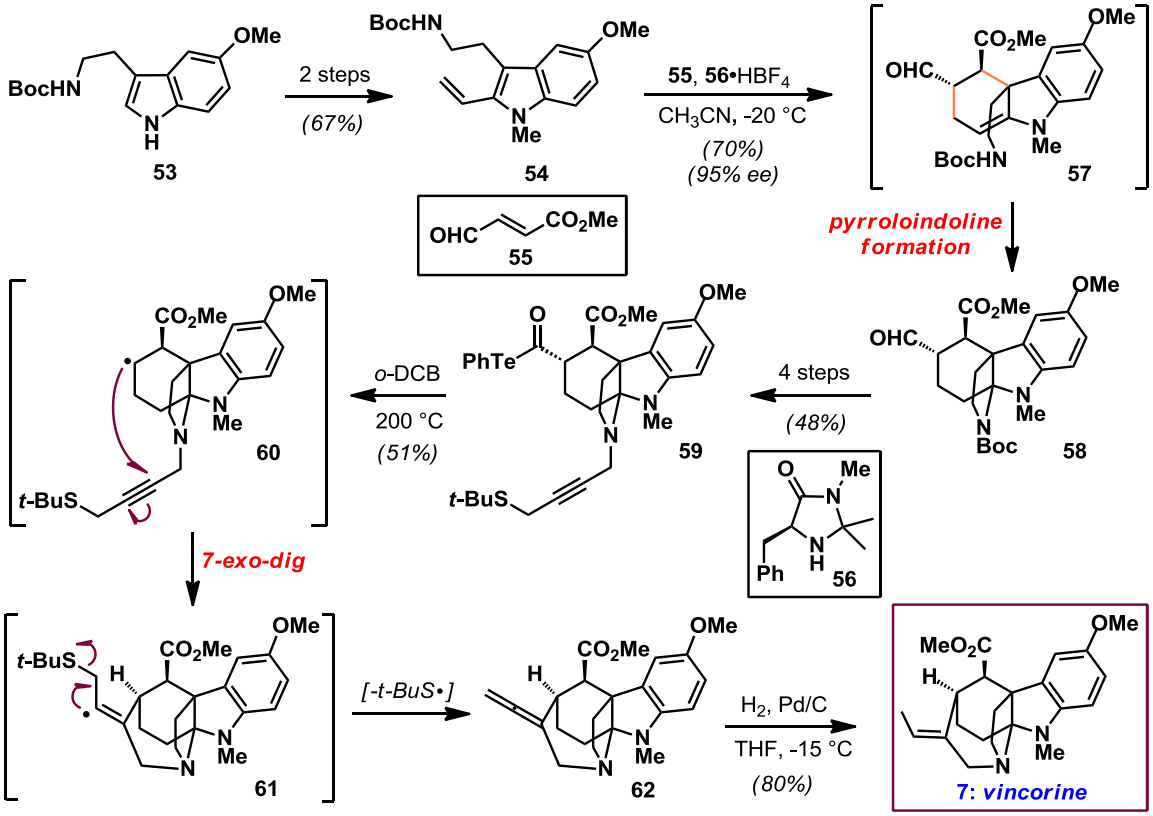
Scheme 7. The Ma synthesis of (-)-vincorine (**7**).

The final vincorine synthesis to be detailed is that by MacMillan and Horning, which was published in 2013.[29] Conceptually, their approach differs from both those of the Qin and Ma syntheses since the final bond formation event is seen to occur between the C-15 and C-20 positions through a radical cyclization/fragmentation process, a strategy the MacMillan group had already successfully applied to the synthesis of minfiensine (**32**, Scheme 8).[30]



Scheme 8. Key strategic disconnections employed in the MacMillan synthesis of vincorine (**7**)

For the formation of their required radical precursor for this application (**59**), they employed an organocatalytic Diels–Alder reaction between readily prepared 2-vinyl indole **54** and enal dienophile **55** (Scheme 9). This reaction proceeded in high yield and enantioselectivity, delivering the requisite pyrroloindoline core (**58**) which could, in a few short steps, ultimately be transformed into radical cyclization precursor **59**. The carefully chosen acyl telluride of **59** (based on only moderate success with several other initiating groups) allowed for thermolytic generation of the desired radical (**60**), delivering the targeted allene **62** in 51% yield through the planned 7-exo-dig cyclzation/β-fragementation sequence (**60**→**61**→**62**). From here, partial reduction of the allene of **62** to the requisite *E*-ethylidene with H_2 and Pd/C proceeded smoothly at low temperature to give (–)-vincorine in only 9 steps from commercial **53**.

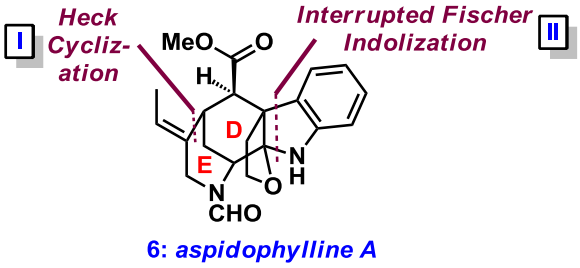


Scheme 9. The MacMillan synthesis of (-)-vincorine (**7**).

As an overall concluding remark, it is intriguing to note that in each of these syntheses, the teams were able to productively utilize past approaches toward other alkaloids to fashion this member of the akuammiline class, though in the majority additional tailoring of that approach was needed given the challenges posed by vincorine's intricate framework.

*1.3.3 Total Syntheses of (±)-Aspidophylline A (**6**)*

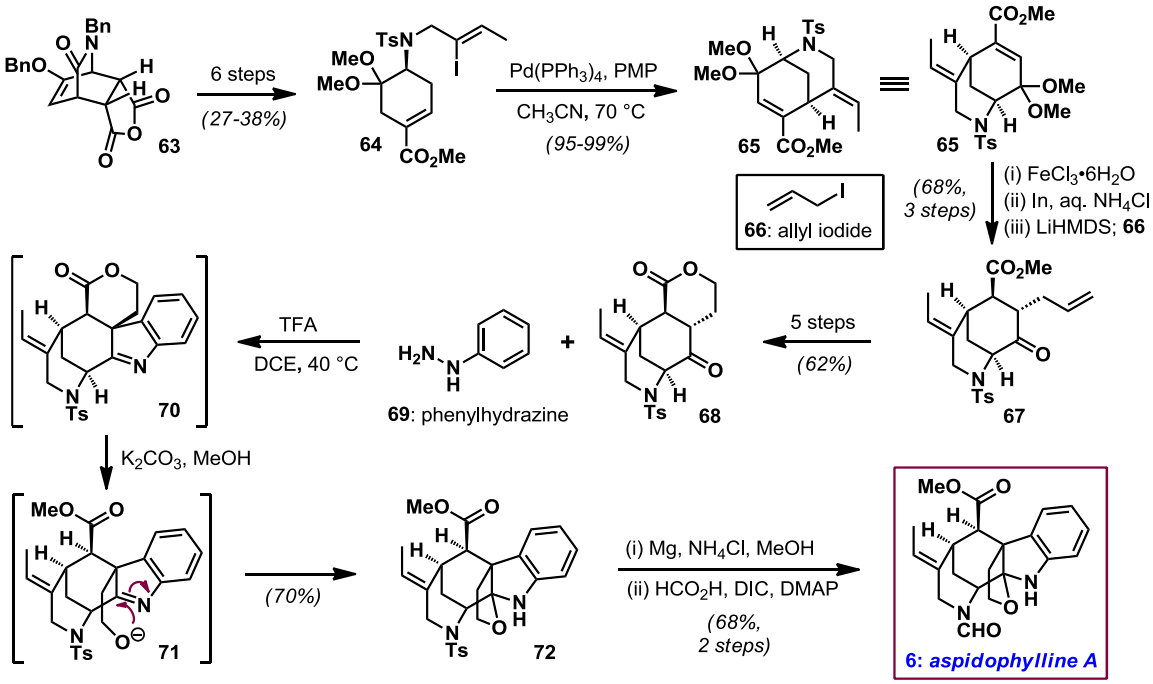
Like vincorine, aspidophylline A (**6**) has proven to be a popular akuammiline target, with three total syntheses reported to date. As with vincorine, in **6** the indolenine portion of the typical akuammiline framework is trapped with a heteroatom, in this case an oxygen to form a furanoindoline, with the nitrogen atom bearing one less bond to the core framework as a result. The first total synthesis of **6** was published by Garg and co-workers in 2011,[31] and centered upon the use of their group's interrupted Fischer indolization process[32] to form the furanoindoline portion of the molecule, wherein initial indolenine formation would be followed by a planned closure of a pendant alcohol to complete this structural motif (Scheme 10).



Scheme 10. Key strategic disconnections employed in the Garg synthesis of aspidophylline A (**6**).

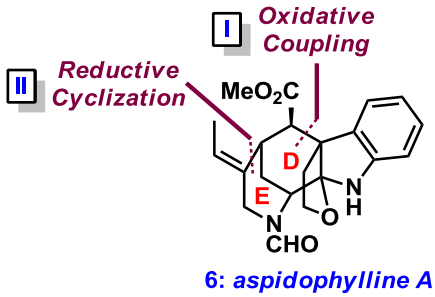
As shown in Scheme 11, the preparation of the putative ketone precursor for such a process began with known pyridone Diels–Alder adduct **63**, the functionality of which was manipulated into that of enoate ester **64** through a series of steps. The Garg group then

found that the D/E-ring system of **6** could be efficiently constructed via an intramolecular Heck process with **64**, delivering ketal **65** in near quantitative yield. Following protecting group and redox adjustments, **65** afforded a ketone which could be stereoselectively allylated to give **67**. Based on some initial exploration, they ultimately chose to advance **67** into a lactone (**68**) to apply the key reaction process. Pleasingly, this compound smoothly underwent the desired Fischer indolization, whereafter a one-pot lactone methanolysis simultaneously formed the furanoindoline and methyl ester to furnish **72** in 70% overall yield. Two straightforward steps to install the *N*-formyl group then completed the synthesis of (±)-**6** in 18 steps from known **63**.



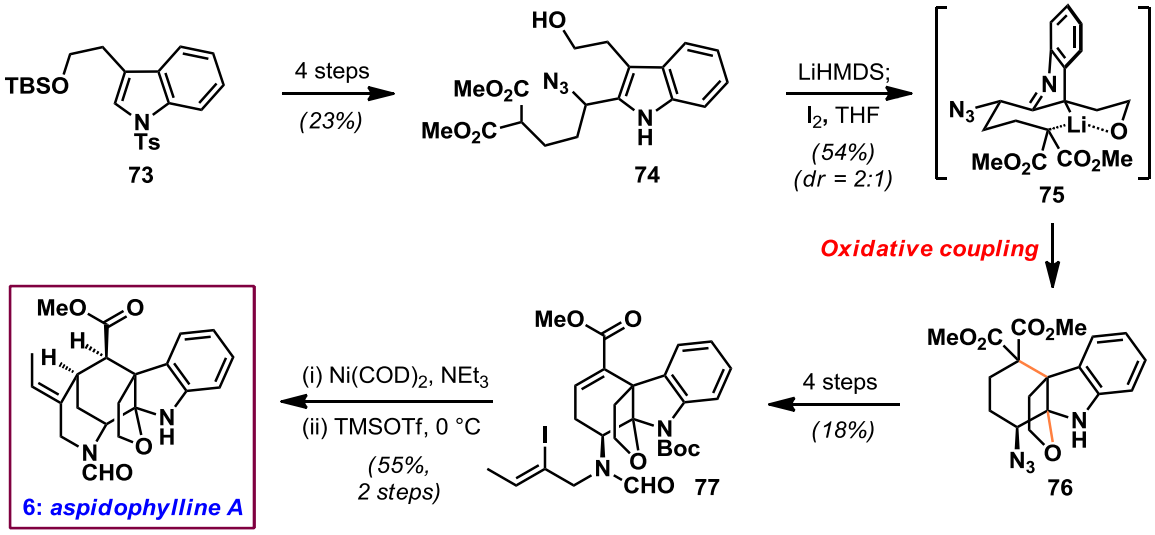
Scheme 11. The Garg synthesis of aspidophylline A (**6**).

Susequently, in 2014, the Ma and Zhu groups simultaneously published their own syntheses of (±)-aspidophylline A. In the Ma work,[33] the team showcased an extension of the oxidative coupling chemistry which they previously utilized to access pyrroloindoline **50** en route to vincorine (Scheme 7); in this case they aimed to target the furanoindoline core of **6** (Scheme 12). As the final bond-forming event, an E-ring closure through a reductive metal-mediated process was envisaged.



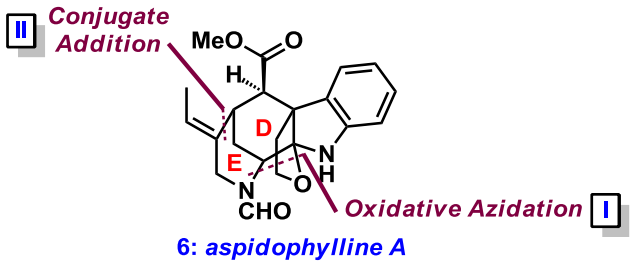
Scheme 12. Key strategic disconnections employed in the Ma synthesis of aspidophylline A (**6**).

Beginning with protected tryptophol **73**, the desired oxidative coupling precursor **74** was prepared in 4 simple steps. After some experimentation, it was found that the key transformation could be effected in moderate yield and diastereoselectivity under conditions very similar to those used in their vincorine synthesis (LiHMDS; I_2) to yield furanoindoline **76**. Interestingly, the desired oxidative coupling required the free hydroxyl of **74** to proceed, an observation they rationalize through the intermediacy of a chelated alkoxide intermediate **75**, not possible for *O*-protected congeners of **74**. From furanoindoline **76**, they were able to advance to an E-ring precursor in the form of vinyl iodide **77**. Pleasingly, the team were able to use this material to complete the core structure of **6** through a Ni(0)-mediated reductive coupling, a process previously utilized by Cook in the preparation of several monoterpene indole alkaloids.[34] A final *N*-Boc deprotection then delivered the natural product [(±)-**6**] in 15 steps from known **73**.



Scheme 13. The Ma synthesis of aspidophylline A (**6**).

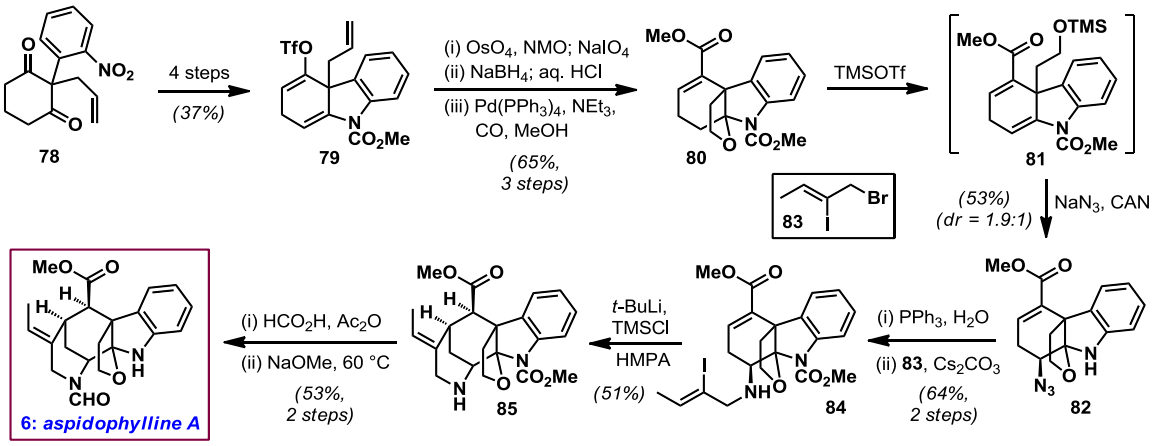
The Zhu group's concurrently published synthesis of aspidophylline A utilized a conceptually similar E-ring closure to finish the target.[35] Their assembly of the required precursor was fundamentally different, however, relying on an oxidative azidation process first described in the context of **6** during Shi's model studies (Scheme 14).[20h]



Scheme 14. Key strategic disconnections employed in the Zhu synthesis of aspidophylline A (**6**).

The Zhu team began with readily available diketone **78**, which, through mono-functionalization was able to be advanced to carbamate **79** through a series of steps. From **79**, carefully orchestrated formation and subsequent manipulation of the furanoindoline **80** allowed for the installation of a critical azide handle through a CAN-mediated oxidative azidation, delivering **82** via the intermediacy of enecarbamate **81**. Azide **82** could then be advanced to enoate ester **84**, an intermediate very similar to that employed by Ma (cf. **77**).

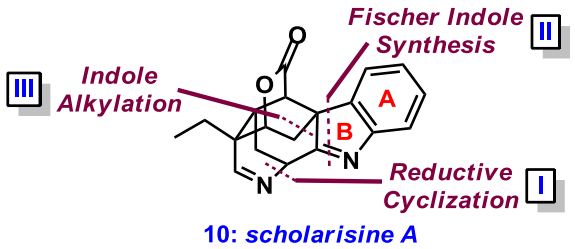
In this case, these investigators found that formation of the corresponding vinyllithium from **84** resulted in an intramolecular 1,4-addition that could secure the full carbon framework of **6** in the form of **85**. In this transformation, the free amine of **84**, was crucial for the success of the process, as its tosyl- or formyl-protected variants were unproductive under a range of conditions. Two final operations from secondary amine **85** then delivered (±)-aspidophylline A in 14 steps from known **78**.



Scheme 15. The Zhu synthesis of aspidophylline A (**6**).

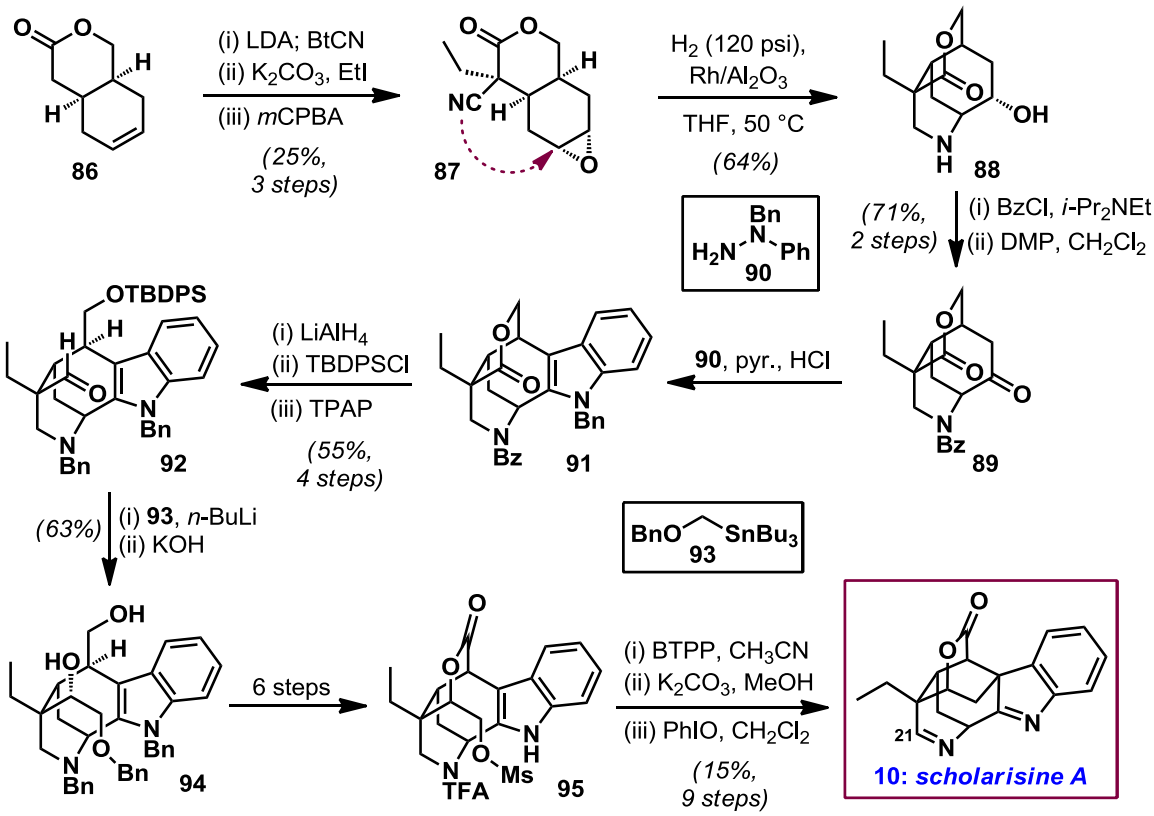
*1.3.4 The Smith Synthesis of (+)-Scholarisine A (**10**)*

In 2012, the Smith group published an enantioselective total synthesis[36] of the structurally unique akuammiline alkaloid scholarisine A (**10**).[37] These investigators aimed to construct the cage framework of **10** through 3 key bond constructions: 1) an initial reductive cyclization to fashion part of the carbocyclic core, 2) a Fischer indole synthesis to install the A/B ring system, and 3) a late-stage indole alkylation to complete the cage structure (Scheme 16).



Scheme 16. Key strategic disconnections employed in the Smith synthesis of scholarisine A (**10**).

These efforts began with the readily available enantiopure lactone **86** that, through a series of alkylations and epoxidations, was advanced to reductive cyclization precursor **87**. Nitrile **87** could then be treated with Rh/Al_2O_3 and a high pressure of H_2 to effect nitrile reduction and concomitant cyclization onto the epoxide to fashion the [3.3.1]-bicycle of **10** in the form of **88**. This material was subsequently advanced to ketone **89** through 2 straightforward operations. From **89**, like Garg, the Smith team employed a Fischer indole synthesis with **90** to install the requisite indole moiety in the form of **91**. A series of subsequent functional group manipulations then delivered aldehyde **92** which was subjected to a highly diastereoselective addition of an organolithium derived from stannane **93**. With all the carbon atoms of scholarisine A now in place in the form of **94**, conversion to an appropriate mesylate **96** set the stage for the final bond closure, which was effected upon base treatment to complete the cage framework via alkylation at the indole β-position (C-7). A final oxidation state adjustment formed the C-21 imine, completing the first synthesis of **10** in 20 steps from **86** (25 steps from commercial materials).

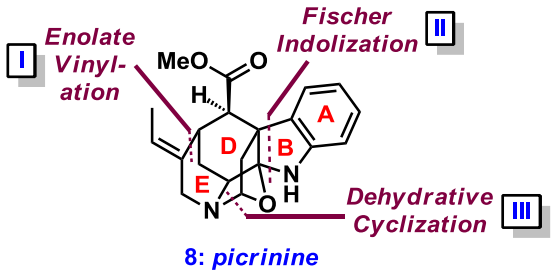


Scheme 17. The Smith synthesis of scholarisine A (**10**).

Aside from Smith's studies, the only other published work towards scholarisine A has issued from the Higuchi group.[20f] This team successfully modelled the formation of an indolenine within a compact cage through an intramolecular oxidative coupling, not dissimilar to the operation employed by Ma in the syntheses outlined in Sections 1.3.2 and 1.3.3. Brief discussion of this approach will be deferred to Chapter 2.

*1.3.5 The Garg Synthesis of (±)-Picrinine (**8**)*

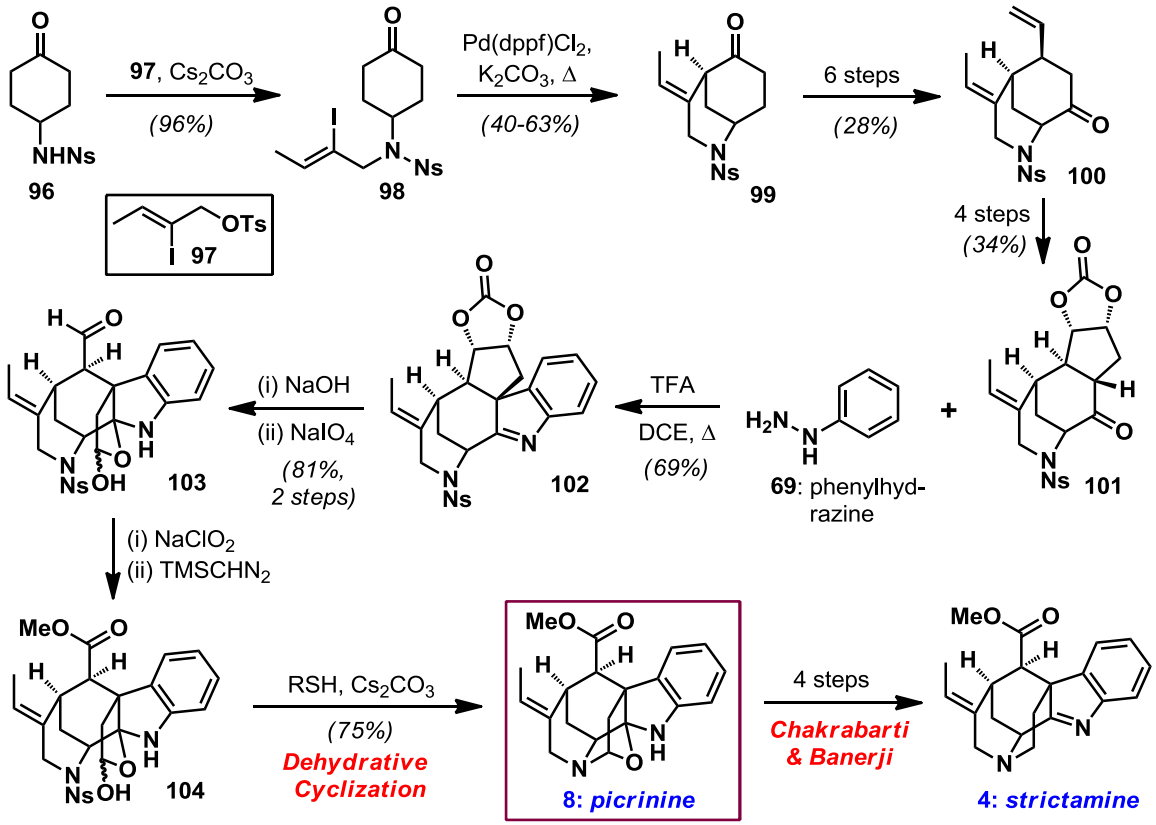
The final synthesis to have appeared as of the writing of this document (June 2014) is that of picrinine (**8**) in work conducted by the Garg group.[38] This achievement is significant because all previously achieved syntheses focused on akuammiline targets that were either pyrrolo- or furanoindolines (**7** or **6**), or were highly rearranged (**10**). No examples of the preparation of the prototypical akuammiline substructure had been achieved. For this intriguing target, the Garg group aimed to utilize the same strategy they had successfully applied to the synthesis of aspidophylline A (**6**), relying on a Fischer indolization to form the masked indolenine A/B structure at its core, after which careful orchestration of bond forming processes would fashion the double hemiaminal ether of **8** (Scheme 18).



Scheme 18. Key strategic disconnections employed in the Garg synthesis of picrinine (**8**).

In line with their previous synthesis template, the initial D/E-ring construction was achieved through an intramolecular enolate vinylation of **98**, providing material which then could be elaborated through several steps to Fischer indole synthesis substrate **101** (Scheme 19). Here, the carbonate-protected diol of **101** would serve as a convenient precursor to a dialdehyde species upon oxidative cleavage. Fischer indolization of **101** gave the desired indolenine **102**, the masked dialdehyde of which could then be unveiled to give hydroxy furanoindoline **103**, poised for final ring closure. Following oxidation and esterification to

104, this key event was nicely achieved through a one-pot deprotection/dehydration sequence that ultimately yielded (±)-picrinine (**8**) in 18 steps from known and commercially available **96** (20 steps from standard chemical suppliers).[ii]



Scheme 19. The Garg total synthesis of picrinine (**8**) and formal synthesis of strictamine (**4**).

Additionally, this work constituted a formal synthesis of the less oxidized congener strictamine (**4**), based on the four step conversion of natural **8** to **4** as reported by Banerji and Chakrabarti in 1984.[39]

[ii] Ketone **96** is available from only one supplier, Aurora Fine Chemicals, at high cost.

1.4 Conclusions

Thus, after a large period of inactivity, chemists have rallied over the last five years to produce many appealing synthetic solutions to the akuammiline class of alkaloids. This resurgence of interest has undoubtedly been driven by the rich diversity of structure and biological activity this family holds, as well as the opportunity for synthetic innovation such complex architectures afford in forging challenging bonds and chiral centers within their highly compact frames. Indeed, as arguably one of the last synthetic frontiers within such a storied class of natural products as the monoterpene indole alkaloids, they remain one where synthetic chemists can make substantial contributions to pave the way for new biomedical studies of the natural alkaloids as well as previously inaccessible synthetic derivatives. As will be seen in the following chapters, it was these attractive features that drew our attention to the akuammiline alkaloids as compelling targets for total synthesis, and afforded the opportunity to develop a number of strategies and tactics distinct from those defined in this chapter.

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CHAPTER 2

A CONCISE TOTAL SYNTHESIS OF

(+)-SCHOLARISINE A

2.1. Introduction

As can be gleaned from the examples laid out in Chapter 1, the akuammiline class of alkaloids presents an array of intriguing structures for which creative synthetic solutions have only recently begun to appear.[1] Indeed, within this class, scholarisine A (**1**, Figure 1) is one of the more unique members given its possession of a highly rearranged, compact, cage-like structure distinct from other akuammilines.[2] This framework imparts a great deal of strain to the molecule, which, along with its labile imine and lactone functional groups, as well as a number of tertiary and quaternary stereocenters, renders scholarisine A (**1**) a daunting synthetic target. As such, we were drawn to the challenge posed by its unprecedented architecture and, coupled with an interest in its unexplored biological potential, decided to initiate a total synthesis program seeking to deliver **1** in a concise and efficient fashion.

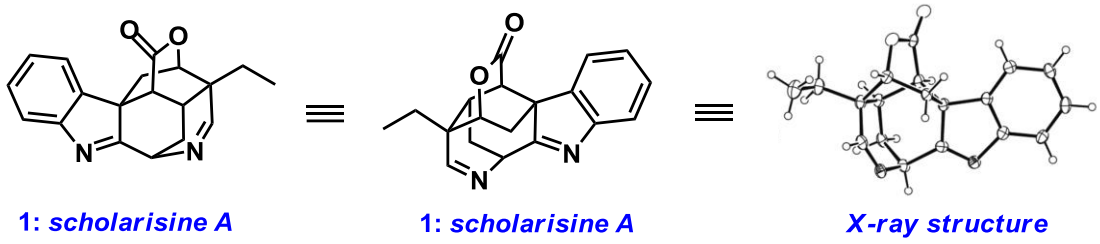


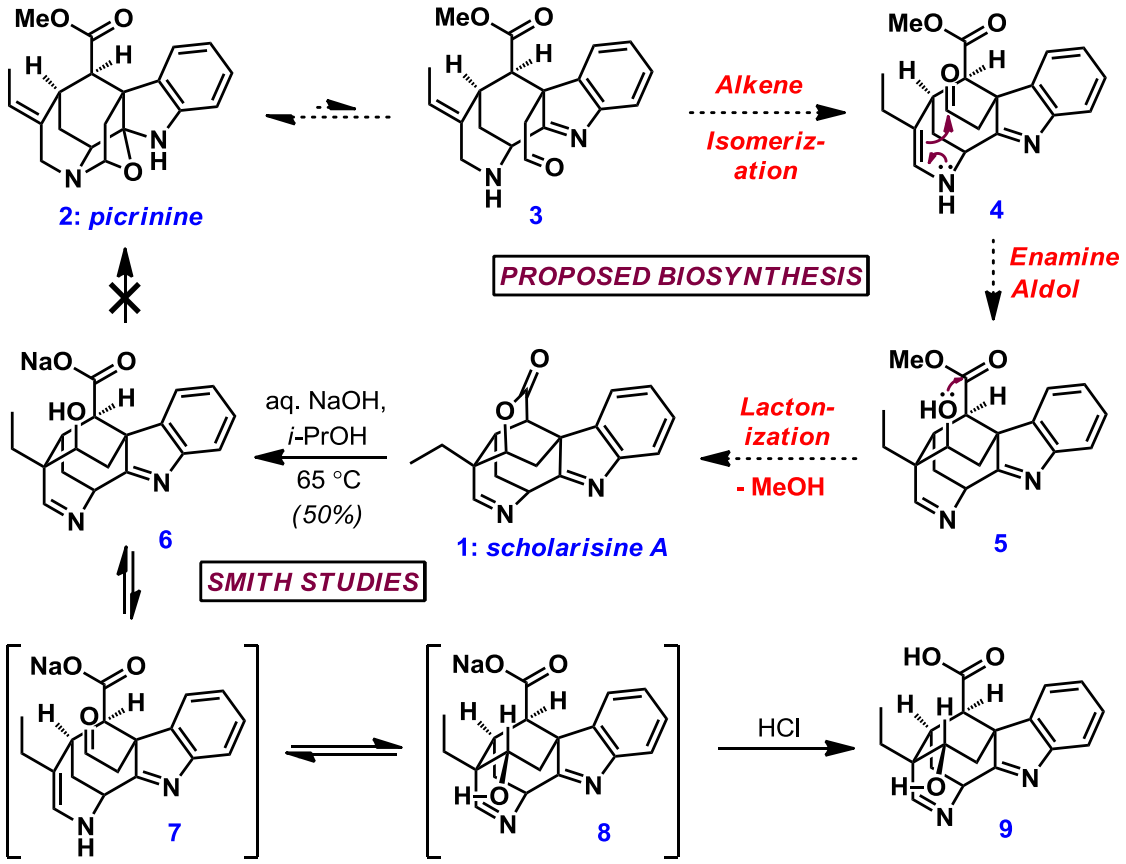
Figure 1. Scholarisine A (**1**) shown in two orientations and X-ray structure obtained by Smith *et al.*[3]

This chapter will detail the evolution of our synthetic approach to scholarisine A (**1**), beginning with a brief summary of its isolation and proposed biosynthesis. That discussion will be followed by a description of our early attempts to fashion its characteristic framework and how those efforts guided the development of our eventual synthetic solution. Finally, it will be demonstrated that advances made during our early

work have led to a method with potential utility in both natural product synthesis and the assembly of medicinally-relevant building blocks.

2.2. Isolation and Proposed Biosynthesis

Scholarisine A (**1**, Scheme 1) was isolated in 2008 by Luo and co-workers from the leaves of the evergreen tree *Alstonia scholaris*, a rich source of akuammiline alkaloids that has been used in traditional Chinese medicine for the treatment of respiratory ailments.[2] Its unique structure was assigned through a combination of advanced 1D and 2D NMR techniques, buttressed by IR and HRMS data. Biosynthetically, **1** is thought to derive from picrinine (**2**), an alkaloid also isolated in *Alstonia scholaris*, through a series of rearrangements as delineated in the top half of Scheme 1.



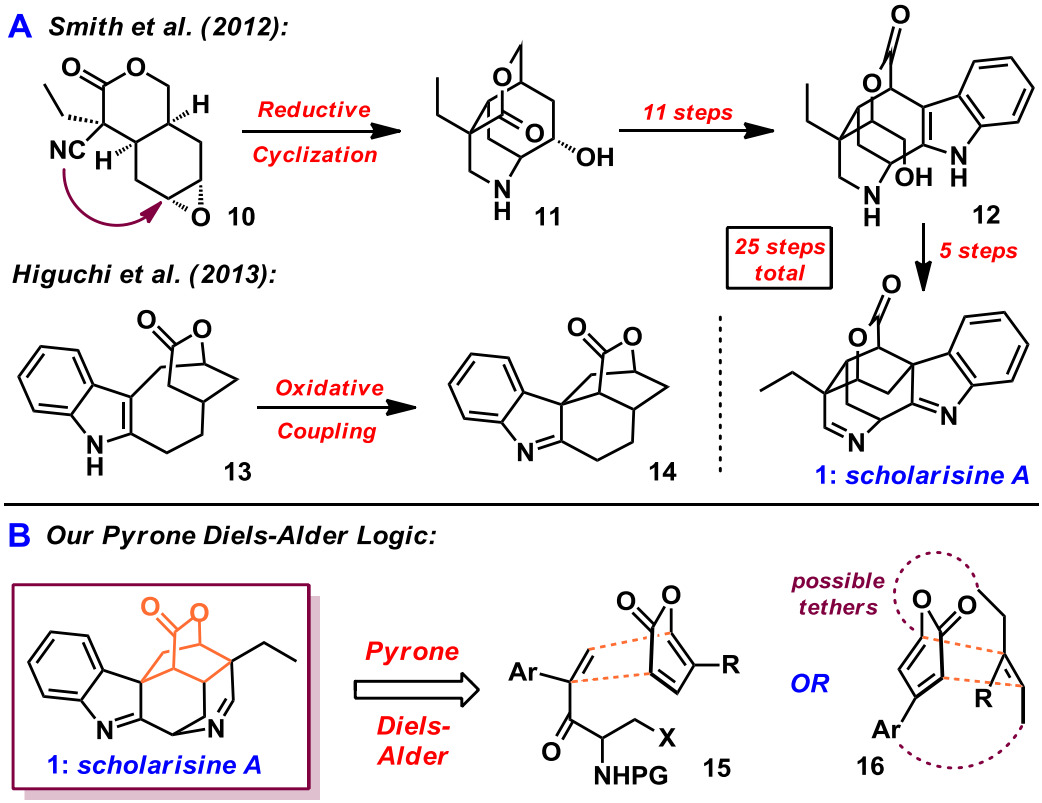
Scheme 1. Proposed biosynthesis of scholarisine A (**1**) and retrobiosynthetic studies by Smith *et. al.*

As indicated, the open aldehyde form of picrinine (**3**, possibly an equilibrium amount) first undergoes olefin isomerization to generate a nucleophilic enamine (**4**); this species then attacks the aldehyde in an aldol fashion to generate the imine of scholarisine A and a secondary alcohol in the form of **5**. The resulting hydroxyl group then engages the proximal ester to form the characteristic [2.2.2]-bicyclic lactone to give **1**. Indeed, the "retro-biosynthetic" studies undertaken by Smith and co-workers[3b] as part of their attempts to transform **1** into other akuammiline scaffolds lends credence to the enamine aldol portion (**4**→**5**) of the proposed sequence (lower half of Scheme 1). These investigators found that upon treatment of **1** with aqueous NaOH at elevated temperature, followed by acidic work-up, they obtained hydroxy acid **9** (~50% yield), a material that is epimeric at C-5 with respect to the seco-acid form of **1**. This transformation, proceeding from the initially formed carboxylate **6**, implies the reversibility of the biosynthetic aldol closure (**6**→**7**→**8**) along with the intermediacy of an enamine aldehyde species **8** (cf. **4**). To date, however, the Smith team has been unable to advance any further in the retro-biosynthetic direction to attain structures like **2**, possibly due to the contrathermodynamic alkene isomerization proving difficult to overcome.

2.3. Our Synthetic Approach to Scholarisine A: Pyrone Diels–Alder Logic

When we began our work towards this complex target in the fall of 2010, the synthetic studies towards **1** discussed in Chapter 1 (and summarized in part A of Scheme 2 below) had not yet appeared (i.e. the Smith total synthesis[3] from 2012 and the Higuchi model studies[4] from 2013). Thus, without any synthetic precedent to inform our retrosynthetic analysis in terms of possible pitfalls or especially effective disconnections, we considered in detail the unique architecture of scholarisine A and in particular the cage

framework at its core – a feature we felt to be the most challenging aspect of its structure. Mindful of our aforementioned goal to deliver **1** in a concise, efficient and hopefully scalable fashion, we were drawn to the notion that its [2.2.2]-bicyclic lactone (highlighted in orange) could arise directly from a pyrone Diels–Alder reaction of the type shown in Scheme 2B – a strategy fully distinct, as it turned out, from both the eventual Smith and Higuchi approaches. Indeed, this insight guided both our early, failed efforts towards scholarisine A and our later, ultimately successful synthetic strategy laid out in the following sections.

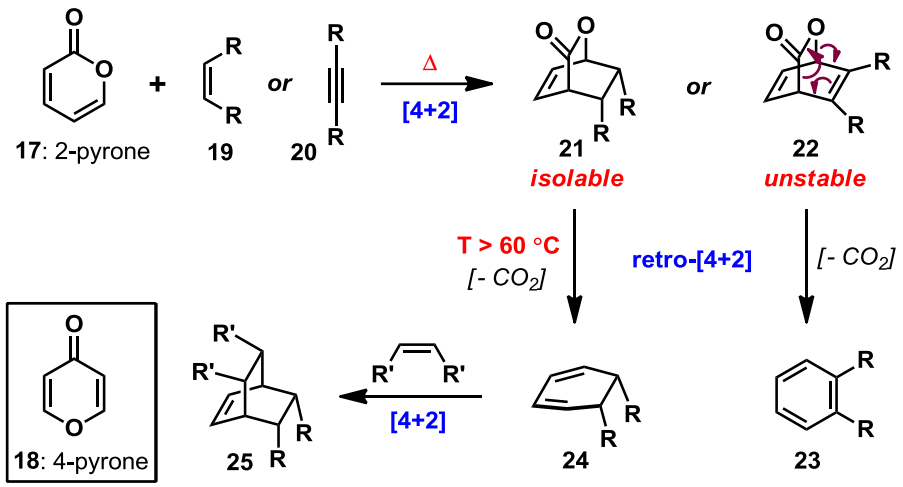


Scheme 2. (**A**) Summary of earlier Smith and Higuchi approaches; (**B**) Our pyrone Diels-Alder-inspired approach to the cage architecture of **1**.

Before describing those studies, however, a brief introduction to the Diels–Alder chemistry of 2-pyrones is warranted, especially given the central position this reaction

would ultimately hold in our synthetic strategy towards scholarisine A (*vide infra*). The topic has been the subject of a number of comprehensive reviews,[5] and the purpose of this short introduction is to provide appropriate background with respect to the utility and challenges associated with pyrone Diels–Alder chemistry, particularly as relates to our intended use in fashioning the bicyclic lactone core of **1** (Scheme 2B).

The 2-pyrone heterocyclic ring system (**17**, Scheme 3) contains a 1,3-diene (as opposed to its 4-pyrone isomer **18**) and thus is capable of engaging in Diels–Alder reactions with both alkene (**19**) and alkyne (**20**) dienophiles. Indeed, this reactivity has been known since 1931, when seminal studies by Diels and Alder showed pyrones to be competent dienes for the process which bears their names.[6] Diels–Alder reactions with 2-pyrone (**17**) initially yield oxabicyclooctenes (**21**) and oxabicyclooctadienes (**22**) with appropriate alkenes and alkynes, respectively (Scheme 3). In the latter case, these strained species are highly labile and readily lose CO_2 through a retro-[4+2] process driven by the formation of more stable aromatic systems (**23**); indeed, this transformation forms the basis for the most common use of pyrone Diels–Alder chemistry and has been exploited countless times in the synthesis of natural products, pharmaceuticals and materials to assemble complex aromatic ring systems.[5a]

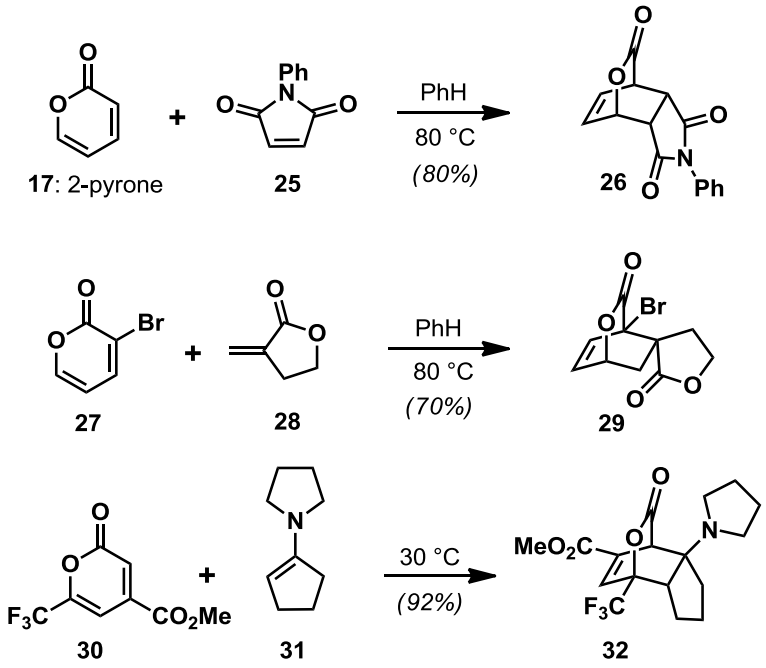


Scheme 3. General principles of 2-pyrone Diels-Alder reactions with alkene (**19**) and alkyne (**20**) dienophiles.

On the other hand, oxabicyclooctenes (**21**) – the structure that our pyrone Diels–Alder reaction would target – can often be isolated, though these materials too are thermally labile, losing CO_2 at temperatures as low as 60 °C in some cases to give diene products (**24**) (although more typically above 100 °C), themselves able to undergo further Diels–Alder chemistry to form barrelenes (**25**). The partially aromatic nature of pyrones (calculated to be ca. 30% as aromatic as benzene)[7] means that they are less reactive than discrete 1,3-dienes. Together, therefore, these upper and lower reactivity limits manifest themselves in a "thermal window" for accessing bicyclic lactone products (**21**) from pyrone Diels–Alder reactions, although several strategies have been introduced to partially offset this limitation (*vide infra*).

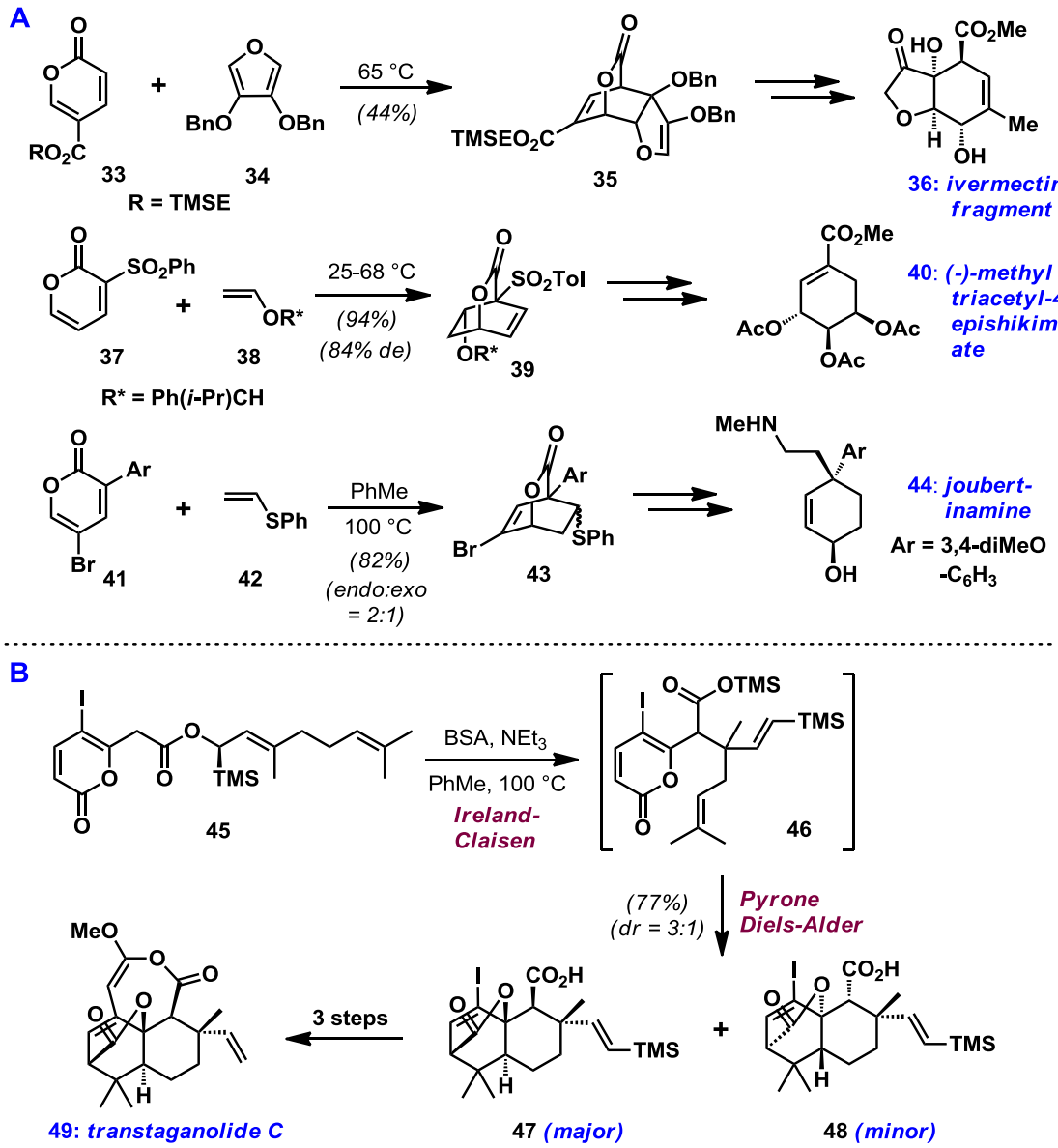
Electronically, the parent 2-pyrone (**17**) is a weakly activated diene that prefers to undergo normal electron-demand Diels–Alder reactions with alkenes; unfortunately, however, they often suffer from poor regiocontrol and efficiency, though exceptions do exist (see **17**→**26**, Scheme 4).[5a] Importantly, though, the introduction of substituents onto the pyrone typically overrides the ring's innate reactivity, allowing efficient normal and

inverse electron-demand Diels–Alder reactions, often with good regio- and stereocontrol (Scheme 4). Substituents, too, can lower the activation barrier for the Diels–Alder process, increasing both the ease of formation and stability of the bicyclic lactone products (**21**). In the same vein, other strategies to target and maintain bicyclic lactones **21** aim to lower reaction temperatures through the use of Lewis acids or high pressures, as is typical for Diels–Alder chemistry.



Scheme 4. Pyrone Diels-Alder reactions to form bicylic lactone products.

Although these stereochemically rich bicyclic adducts have been exploited as useful synthons in total synthesis (see examples in Scheme 5A below), the use of the bicyclic lactones in their original form is rather rare, despite these motifs being present in many natural products.[5] A notable exception can be found in the elegant work of Stoltz and co-workers towards the transtaganolides (e.g **49**), where a tandem Ireland–Claisen rearrangement/intramolecular pyrone Diels–Adler reaction was used to expediently prepare their characteristic [2.2.2]-bicyclic lactone motif (**45**→**47**/**48**, Scheme 5B).[8]



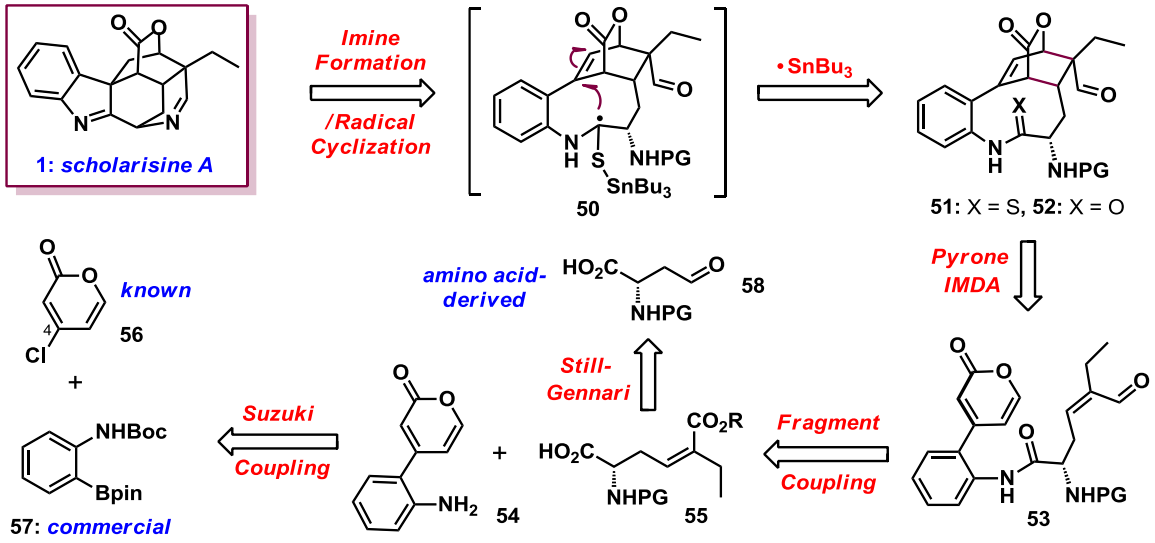
Scheme 5. The use of bicyclic lactone pyrone Diels-Alder products in total synthesis: (**A**) as stereochemically rich cyclohexanes; (**B**) for expedient access to the transtaganolide framework.

Given the context of this literature precedent, we set about applying pyrone Diels–Alder logic to the complex problem of scholarisine A (**1**), aiming to utilize the lessons learned from the many years of work in this field, as well as to substantively contribute to the expansion of the scope and power of pyrone Diels–Alder chemistry through some unique explorations.

2.4. Early, Unsuccessful Intramolecular Pyrone Diels–Alder Approaches

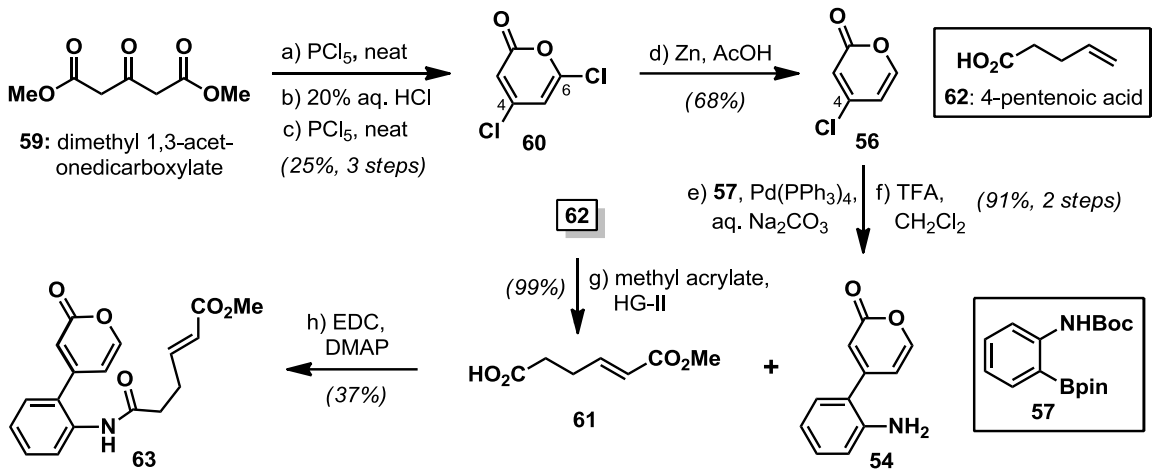
2.4.1. Initial Macrocylic Pyrone IMDA Strategy

Our first approach using a pyrone-based Diels–Alder disconnection is outlined retrosynthetically in Scheme 6. Specifically, we sought to trace scholarisine A (**1**) back to thiolactam **51**, a material we hoped, in the forward sense, would be able to engage in a transannular *5-exo-trig* radical cyclization using tin-radical conditions similar to those used in the venerable Fukuyama indole synthesis (i.e. via **50**).[9] Functional group interconversion led back to lactam **52**, which was seen to be the product of an intramolecular Diels–Alder (IMDA) reaction of an aryl pyrone (**53**) bearing a tethered alkene dienophile. The choice of an intramolecular process (versus an intermolecular one) was based on the expectation that both the type (aryl) and position (4-) of the pyrone substituent (unlike the substituents mentioned earlier) would not control regio- and stereoselectivity effectively.[5a] It was hoped, therefore, that a tethered approach would allow for expedient access to the near-complete stereoarray of **1**. Importantly, compound **53** lends itself to a convergent assembly through amide bond formation between pyrone aniline **54** and acid **55**, the former a likely Suzuki coupling product and the latter potentially available from an amino acid.



Scheme 6. Initial intramolecular pyrone Diels-Alder approach to scholarisine A (**1**).

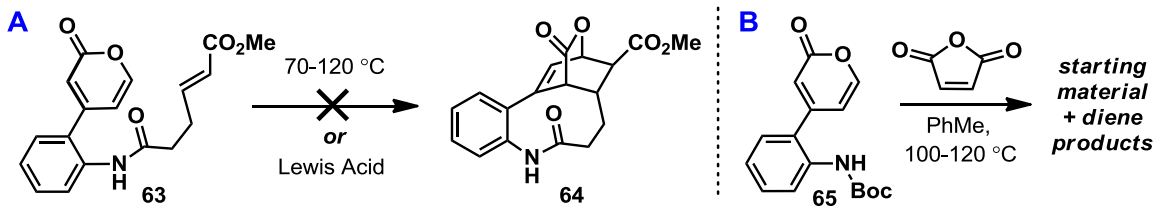
As an initial model substrate for the key Diels–Alder process, we targeted the simplified unsaturated ester **63** (Scheme 7). Our studies along these lines began with the preparation of pyrone aniline **54**, which was seen to be available through a Suzuki coupling between 2-(*N*-Boc-amino)phenylboronic acid pinacol ester **57** and the known 4-chloropyrone **56**.[10] Thus, from inexpensive dimethyl acetonedicarboxylate, we were able to arrive at gram quantities of 4,6-dichloropyrone (**60**) through the procedure of Afarankia[10] (25% yield, 3 steps). The more activated 6-chloro substituent could then be selectively removed using zinc in AcOH (68% yield) to arrive at the desired electrophile for the Suzuki coupling.[10] Pleasingly, application of fairly standard Suzuki conditions (cat. $Pd(PPh_3)_4$, aq. Na_2CO_3, DME, 70 °C) with boronate **57** delivered the desired biaryl product in excellent yield (92%), whereafter the *N*-Boc group could be cleanly removed with TFA in CH_2Cl_2 from 0 to 23 °C to deliver aniline **54** in essentially quantitative yield.



Scheme 7. *Reagents and conditions:* (a) PCl_5 (1.05 equiv), neat, 23 to 50 °C, 0.5 h; (b) 20% aq. HCl, Δ, 2.5 h; (c) PCl_5 (2.0 equiv), neat, 0 to 100 °C, 1.25 h 25% (3 steps); (d) Zn (1.2 equiv), AcOH, 23 °C, 26 h, 68%; (e) **57** (1.0 equiv), **56** (1.4 equiv), $Pd(PPh_3)_4$ (0.05 equiv), 3 M aq. Na_2CO_3, DME (2:5 v/v), 70 °C, 3.75 h, 92%; (f) TFA, CH_2Cl_2 (1:4 v/v), 0 to 23 °C, 50 min, 99%; (g) methyl acrylate (5.0 equiv), HG-**II** (0.001 equiv), CH_2Cl_2, Δ, 17h, 99%, *E:Z* = 11:1; (h) **61** (1.2 equiv), EDC (1.5 equiv), 4-DMAP (1.5 equiv), CH_2Cl_2, 23 °C, 20 h, 37%.

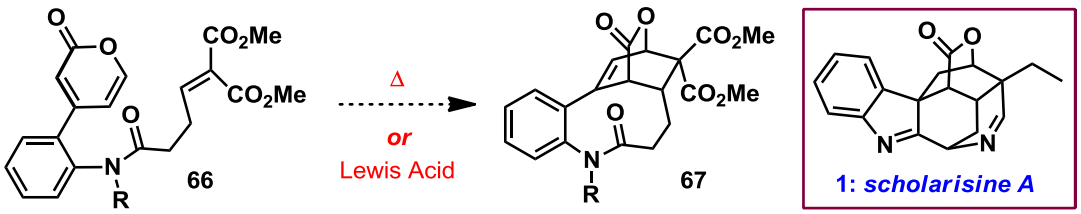
To complete our model IMDA substrate **63**, we only needed to attach a simple (*E*)-enoate ester dienophile. This transformation was accomplished in moderate yield (37%) by EDC-mediated coupling with acid **61**, itself prepared in quantitative yield by cross-metathesis of 4-pentenoic acid (**62**) with methyl acrylate using the Hoveyda–Grubbs second-generation intiator (HG-II). With access to the desired IMDA precursor (**63**), we immediately set about probing its reactivity. As noted above, to avoid decomposition of the targeted lactone through loss of CO_2, reactions were typically heated between 70–120 °C and closely monitored by TLC. Unfortunately, despite much experimentation under thermal and Lewis acid [e.g. $ZnCl_2$, BF_3•OEt_2, $Yb(OTf)_3$] promoted conditions, no Diels–Alder products (intra- or intermolecular) were observed (Scheme 8A). Indeed, we found that when tested in *inter*molecular Diels–Alder reactions, *N*-Boc-pyrone **65** only reacted effectively with highly activated dienophiles such as dimethyl maleate and maleic anhydride, and then affording only partial conversion (temperature: 100–120 °C), with either diene products (maleic anhydride) or a mixture of bicyclic and diene products

(dimethyl maleate) obtained (Scheme 8B). The formation of significant quantities of products resulting from the loss of CO_2 validated our earlier concerns about using higher temperatures.



Scheme 8. (**A**) Failure of ester **63** to undergo IMDA reaction; (**B**) Intermolecular D-A Reaction of **65**.

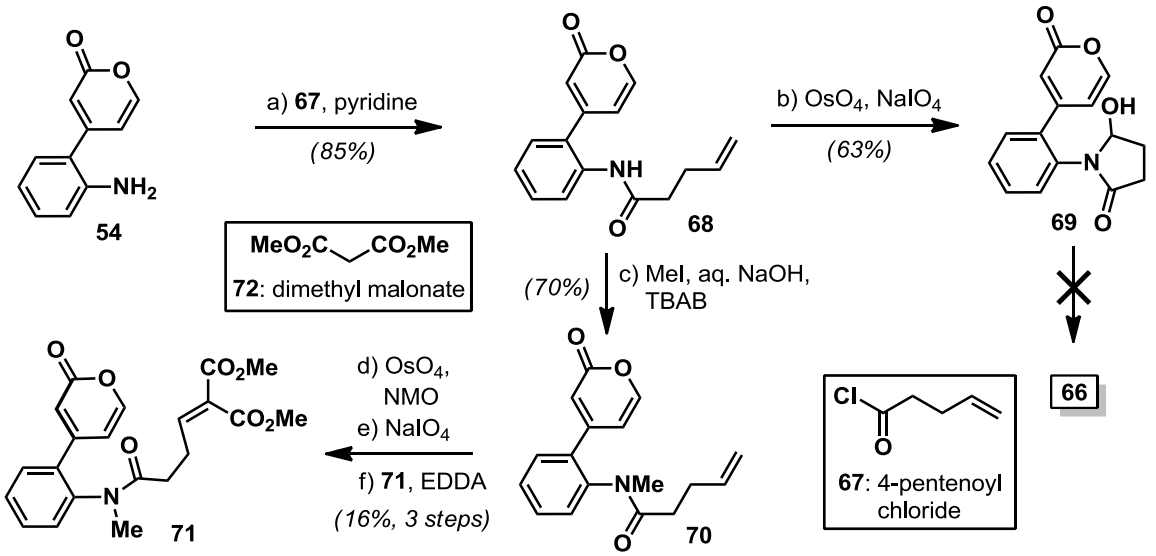
In light of this outcome, we sought to improve the reactivity of our dienophile and hence targeted malonylidene **66** as an alternate IMDA substrate (Scheme 9). It was hoped that this more activated dienophile, with an additional ester group that could be positioned *endo* in the desired IMDA transition state, might sufficiently lower the activation barrier and facilitate the desired cyclization. Additionally, more facile Lewis acid activation of the 1,3-dicarbonyl motif of the dienophile could be exploited to further enhance reactivity. Equally appealing was the fact that the final IMDA product (i.e. **67**) could be potentially useful in its own right en route to scholarisine A (**1**), particularly since its *exo*-CO_2Me substituent might serve as a precursor to the ethyl group of **1**.



Scheme 9. Proposed use of malonylidene **66** as a more activated IMDA substrate.

As shown in Scheme 10, compound **71** was synthesized from previously prepared aniline **54**. At this stage, we discovered that acylation of **54** with 4-pentenoyl chloride (**67**)

proceeded far more effectively than the previously employed carbodiimide-based methods to provide amide **68** (85% yield). We then sought to apply an oxidative cleavage/Knoevenagel sequence (noting that cross metatheses with unreactive alkylidene malonates unsurprisingly failed) but quickly found that the generated amidoaldehyde (63% yield) existed preferentially in its cyclized form (**69**), which resisted further functionalization towards **66**.

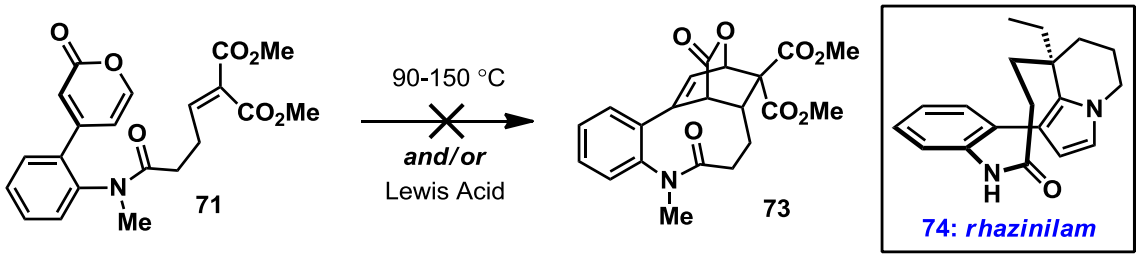


Scheme 10. *Reagents and conditions:* (a) **67** (1.1 equiv), pyridine (2.0 equiv), PhMe, CH_2Cl_2, 23 °C, 0.5 h, 85%; (b) OsO_4 (0.05 equiv), $NaIO_4$ (5.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane, H_2O, 23 °C, 4.5 h, 63%; (c) MeI (2.0 equiv), *n*-Bu_4NBr (1.1 equiv), 10% aq. NaOH (excess), PhH, CH_2Cl_2, 23 °C, 10 min, 70%; (d) OsO_4 (0.05 equiv), NMO (1.5 equiv), THF, *t*-BuOH, H_2O, 23 °C, 4.75 h; (e) $NaIO_4$ (1.5 equiv), CH_2Cl_2, H_2O, 0 to 23 °C, 15.75 h, 72% (2 steps); (f) **72** (1.2 equiv), EDDA (1.2 equiv), MeOH, 23 °C, 4.5 h, 22% (38% brsm).

We therefore resorted to *N*-protection, selecting a simple methyl group as an initial model for its stability and particular ease of NMR studies, since even this small group resulted in slow rotation about the C(Ar)-axis (and/or rotamers about the amide bond), making its ^1H NMR signals broaden and harder to interpret; larger groups were expected to exacerbate this effect. Methylation was accomplished by treatment with aqueous NaOH and MeI under phase-transfer conditions (70% yield) to give **70**, whereafter two step

oxidative cleavage and Knoevenagel condensation with dimethyl malonate (**72**) using ethylenediamine diacetate (EDDA) gave the targeted malonylidene IMDA substrate **71** in moderate yield (16% yield over three steps, 27% brsm, unoptimized).

Disappointingly, however, **71** also proved to be an ineffective substrate for the desired IMDA process; in fact, it was somewhat more sensitive than **63**, often undergoing retro-Knoevenagel reaction back to its aldehyde precursor (particularly when activated with a Lewis acid). Even attempting forcing conditions (up to 150 °C), with or without Lewis acid additives such as $Sc(OTf)_3$, $Al(OTf)_3$, $Zn(OTf)_2$, $BF_3{\bullet}OEt_2$, $TiCl_4$, $Mg(ClO_4)_2$, $Cu(TFA)_2$ or $EtAlCl_2$ in a range of solvents did not yield the products of a Diels–Alder reaction, with starting material often partially recovered (Scheme 11).



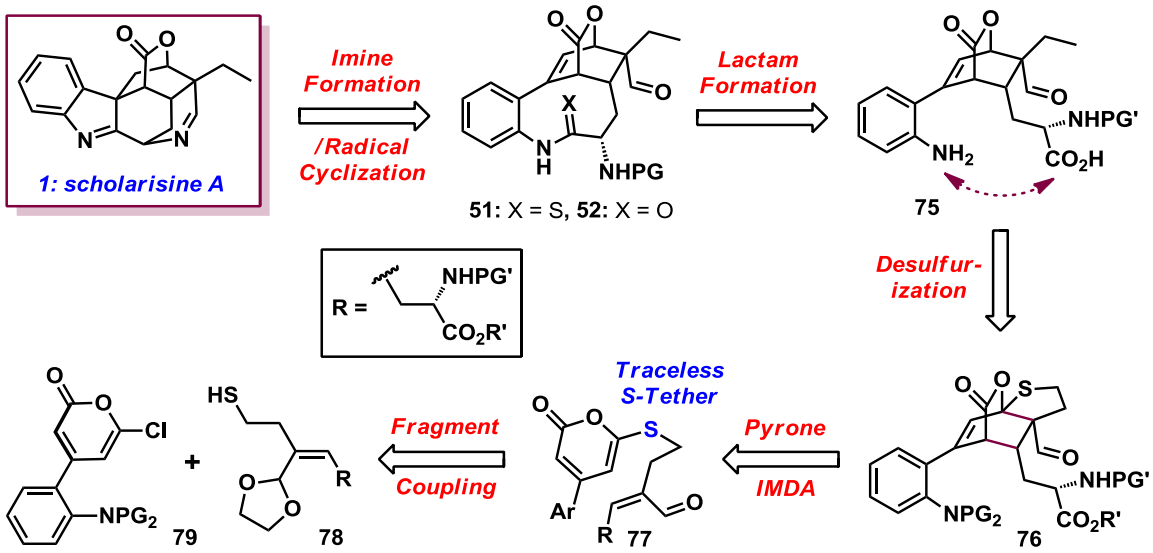
Scheme 11. Failure of malonylidene **71** to undergo desired IMDA reaction and nine-membered lactam alkaloid rhazinilam (**74**).

With no trace of IMDA product obtained with either **63** or **71,** we felt it necessary to take stock of the situation; our only conclusion was that perhaps the resulting nine-membered macrocyclic lactam in the desired product (**64** or **73**) was too strained to be formed effectively. It is worth noting that at the planning stage, this problem had been considered, but we drew some confidence in the fact that similar biaryl-containing nine-membered lactams are found in several natural products such as rhazinilam (**74**, Scheme 11).[11] In hindsight, however, these systems are often formed synthetically through *irreversible* macrolactamization,[12] in stark contrast to the potentially reversible Diels–

Alder reaction, with the partially aromatic nature of the pyrone no doubt enhancing this reversibility relative to more standard diene substrates. Additionally, we speculate that the high number of sp^2 atoms in the tether could reduce its flexibility, potentially precluding access to a suitably reactive conformer.

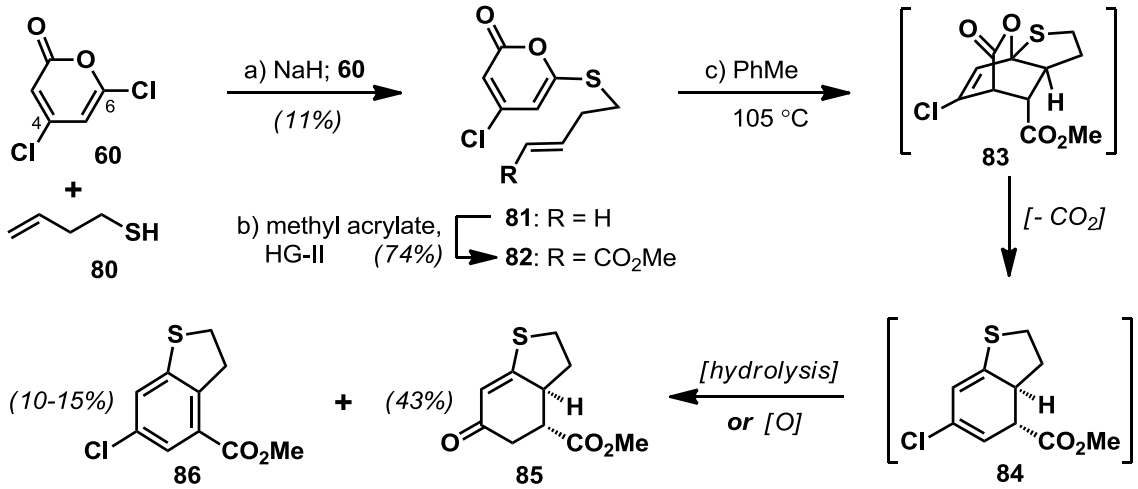
2.4.2. Pyrone IMDA Strategy Employing a Traceless Sulfide Tether

With these insights in mind, we sought to design a new IMDA process that addressed both of the potential problems listed above by 1) utilizing a more flexible tether containing only sp^3 hybridized atoms and 2) having this tether lead to the formation of an unstrained five-membered ring instead of the nine-membered macrolactam. This new plan is laid out retrosynthetically in Scheme 12, wherein a sulfide tether would serve to link the dienophile to the pyrone diene through an ethylene chain (in the form of **77**) that would ultimately be unveiled as the ethyl group of scholarisine A by reductive desulfurization with Raney nickel. Eventual macrolactamization of aniline acid **75**, a process more in line with literature precedent,[12] would then provide previously targeted lactam **52**.



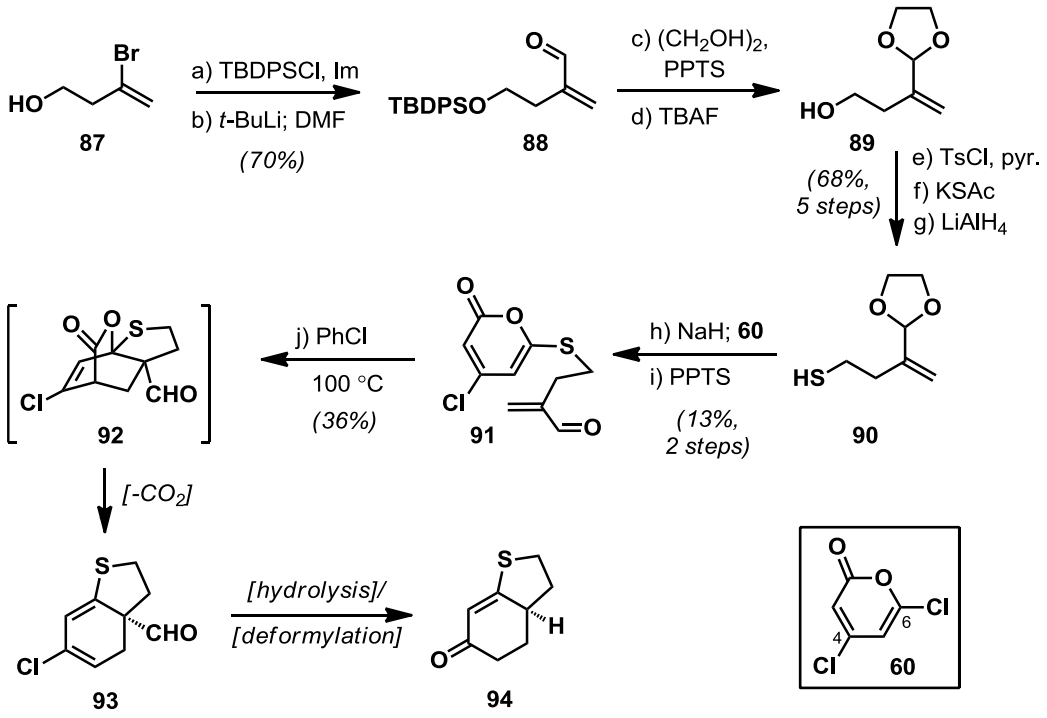
Scheme 12. Revised pyrone IMDA approach to scholarisine A (**1**) employing a traceless sulfur tether.

To probe this strategy we initially targeted the simple alkene-containing substrate **81** (Scheme 13). This compound was readily prepared from 4,6-dichloropyrone (**60**) using the sodium salt of known[13] 3-butenylthiol (**80**) to give selective displacement of the 6-chloro substituent. The low isolated yield (11%) is hard to reconcile with the fairly clean reaction profile, though admittedly, this was based on the rather volatile, crude 3-butenylthiol which may not have been present in the expected amounts. While **81** did not yield any of the desired bicyclic lactone when subjected to thermal IMDA conditions, we were pleased to find that its enoate ester congener **82**, obtained in good yield (74%) through cross metathesis with methyl acrylate, did undergo reaction upon prolonged heating at 105 °C in toluene. Unfortunately, the obtained product was not the desired tricyclic lactone **83**, but rather vinylogous thioester **85**, which was isolated in 43% yield along with 10–15% of aromatized product **86**. Thus, although the Diels–Alder reaction was clearly occurring, the loss of CO_2 followed rapidly to give diene **84** (not observed), which, in turn, underwent rapid hydrolysis by adventitious moisture to give **85** or aerobic oxidation to afford **86**.



Scheme 13. *Reagents and conditions:* (a) NaH (1.0 equiv), THF, 23 °C, 5 min; **60** (1.0 equiv), -78 to 0 °C, 3 h, 11%; (b) methyl acrylate (5.0 equiv), HG-II (0.05 equiv), CH_2Cl_2, Δ, 16 h, 74%, *E*:*Z* >10:1; (c) PhMe, 105 °C, 66 h, **85**: 43%, **86**: 10-15%.

Despite this failure, we noted the differences in the structure of **82** and our desired IMDA substrate for scholarisine A (cf. **77** in Scheme 12). Thus, we set about preparing pyrone **91** bearing an α-substituted enal of the type contained in **77**. Beginning with 3-bromo-3-buten-1-ol (**87**), we were able to prepare thiol **90**, containing a protected enal, through a fairly standard seven step sequence; the only notable experimental operation being vinyllithium formylation (silyl-protected **87**→**88**), a process which had to be conducted at –130 °C (liquid N_2, pentane) to prevent migration of the TBDPS group onto carbon. Regioselective coupling of **90** to pyrone **60** proceeded as before, whereafter treatment with PPTS in acetone (99% yield) unveiled its enal dienophile to give the targeted IMDA substrate **91**.



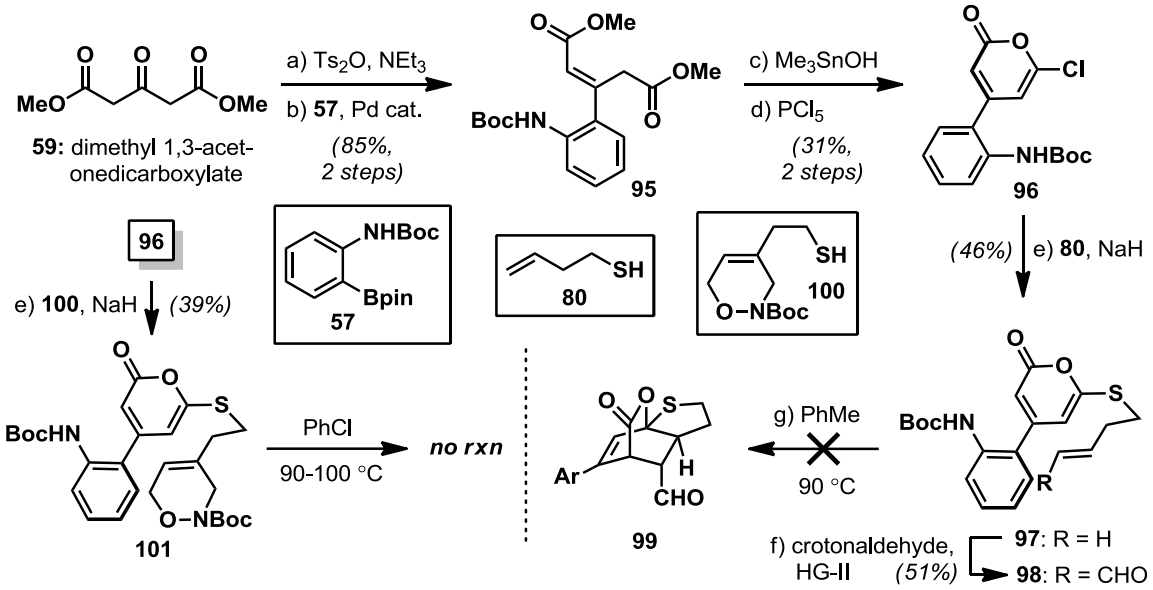
Scheme 14. *Reagents and conditions:* (a) TBDPSCl, Im, CH_2Cl_2, 23 °C, 16 h, >99%; (b) *t*-BuLi (2.5 equiv), THF, Et_2O, hex, -130 °C, 10 min; DMF (3.0 equiv), -130 to 23 °C, 2.5 h, 70%; (c) $(CH_2OH)_2$ (3.0 equiv), PPTS (0.05 equiv), PhH, 80 °C, 24 h; (d) TBAF (1.2 equiv), THF, 0 to 23 °C, 3 h; (e) TsCl (1.1 equiv), NEt_3 (1.1 equiv), 4-DMAP (0.1 equiv), 23 °C, 17 h, 74% (3 steps); (f) KSAc (1.2 equiv), acetone, 23 to 56 °C, 24 h, 92%; (g) $LiAlH_4$ (1.0 equiv), THF, Et_2O, 0 to 23 °C, 1 h; h) NaH (1.0 equiv), THF, 23 °C, 5 min; **60** (1.0 equiv), -78 to 0 °C, 3.5 h, 13%; (i) PPTS, acetone, 56 °C, 12 h, 99%; (j) PhCl, 100 °C, μW, 38 h, 36%.

Upon heating, we were excited to find that **91** provided a new product; however, NMR analysis quickly established its structure as **93**, the product of a retro-[4+2] loss of CO_2. Moreover, upon standing, **93** converted to vinylogous thioester **94** via hydrolysis and deformylation. Again, no trace of the desired tricyclic lactone was observed. We ascribe the rapid loss of CO_2 from initial Diels–Alder products **83** and **92** to the mesomeric effect of the sulfur atom assisting in expulsion of the adjacent lactone bridge. In the case of intermediate **92**, the process may also be driven by the release of strain accrued due to the vicinal quaternary centers present in this species.

The influence of a pyrone aryl group on the IMDA process was also briefly probed in the form of substrates **98** and **101** (Scheme 15). To summarize those explorations, an optimized route to 4-aryl-6-chloropyrone **96** was devised based on the cross coupling of an intermediate vinyl tosylate (generated from dimethylacetone dicarboxylate **59**) with the previously used boronate **57** to give substituted cinnamate **95**.[i] With the aryl group in place, Me_3SnOH-mediated hydrolysis[14] of the two esters followed by chlorinative cyclization as effected by PCl_5 in CH_2Cl_2 yielded chloropyrone substrate **96**. Displacement of the chloro substituent with 3-butenylthiol (**80**) proceeded smoothly and in better yield than with dichloropyrone **60** (46% vs 11–13%). Hereafter, cross metathesis with crotonaldehyde delivered enal IMDA substrate **98**, noting that this dienophile was chosen to maximize IMDA reactivity. In a similar fashion, IMDA precursor **101** was prepared from chloropyrone **96** and thiol **100** (itself formed through nitroso Diels–Alder chemistry). Although heating of enal **98** at 90 °C did rather cleanly yield a new aldehyde-containing species with no enal olefinic signals, it was clear from ^{1}H NMR that some reaction

[i] The corresponding vinyl triflate proved capricious.

involving the aryl group had occurred given that it possessed one less aromatic signal. By contrast, **101**, which lacked an electron-withdrawing group, simply did not react upon prolonged heating at 90–100 °C in chlorobenzene under microwave irradiation.



Scheme 15. *Reagents and conditions:* (a) Ts_2O (1.05 equiv), NEt_3 (1.05 equiv), 0 to 23 °C, 1.75 h; (b) **57** (1.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), 2 M aq Na_2CO_3, THF, 40 °C, 4.5 h, 85% (2 steps); (c) Me_3SnOH (5.0 equiv), DCE, 80 °C, 20 h; (d) PCl_5 (2.0 equiv), CH_2Cl_2, 0 to 23 °C, 5.5 h, 31% (2 steps); (e) **80** or **100** (2.3 or 1.0 equiv), NaH (2.3 or 1.0 equiv), THF, 23 °C, 5 min; **96** (1.0 equiv), -78 to -50 °C, 1.5 h, **97**: 46%, **101**: 39%; (f) crotonaldehyde (5.0 equiv), HG-II (0.02 equiv), CH_2Cl_2, Δ, 1.25 h, 51%, *E:Z* >10:1; (g) PhMe, 90 °C, 20.5 h.

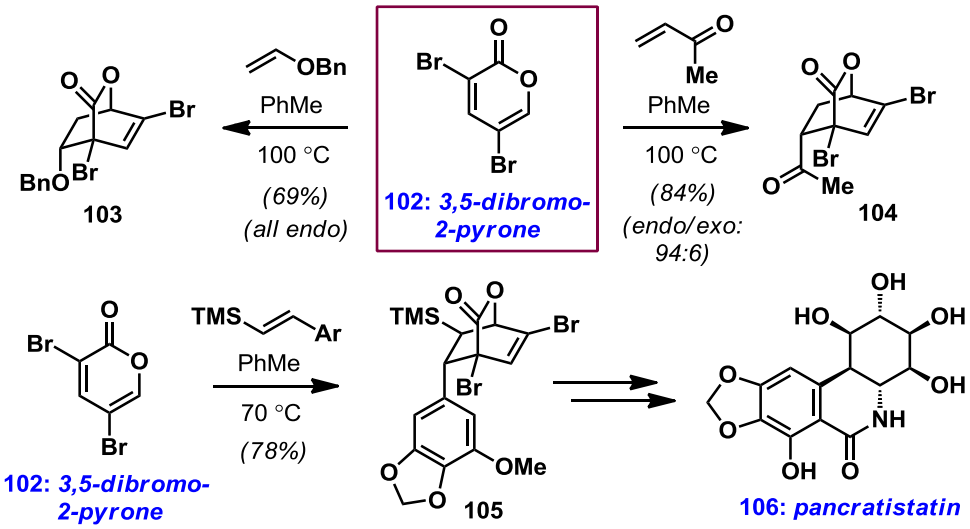
At this juncture, we had the option of optimizing both the pyrone and dienophile structures to address the issues plaguing the assembly of IMDA substrates as well as their reactivity and stability in the ensuing Diels–Alder reactions. Overall, however, we felt that the instability of the type of adducts that we sought to form (specifically illustrated by lability of initially formed bicycles **83** and **92**) meant this approach would be difficult, if not impossible, to reduce to practice.

Collectively, therefore, these two intramolecular pyrone Diels–Alder approaches informed our transition to an intermolecular process – a choice that was ultimately vindicated. Noteworthy, too, is the fact that the sulfur-tethered strategy laid out in the above

section spawned a novel method for the preparation of aromatic and non-aromatic fused heterocycles, one which will be discussed briefly in Section 2.6.

2.5. Intermolecular Pyrone Diels–Alder Approach

Central to our decision to move to an intermolecular Diels–Alder reaction was the extensive work undertaken by Cho and co-workers, which has shown that 3,5-dibromopyrone (**102**, Scheme 16) is an excellent diene for Diels–Alder reactions, reacting with both electron-deficient and electron-rich dienophiles to yield bicyclic lactone products.[5b] Selected examples are shown in Scheme 16. Importantly, these reactions typically proceed with a high degree of regio- and stereoselectivity, indicating that there may not be a need for an intramolecular approach to control these aspects.

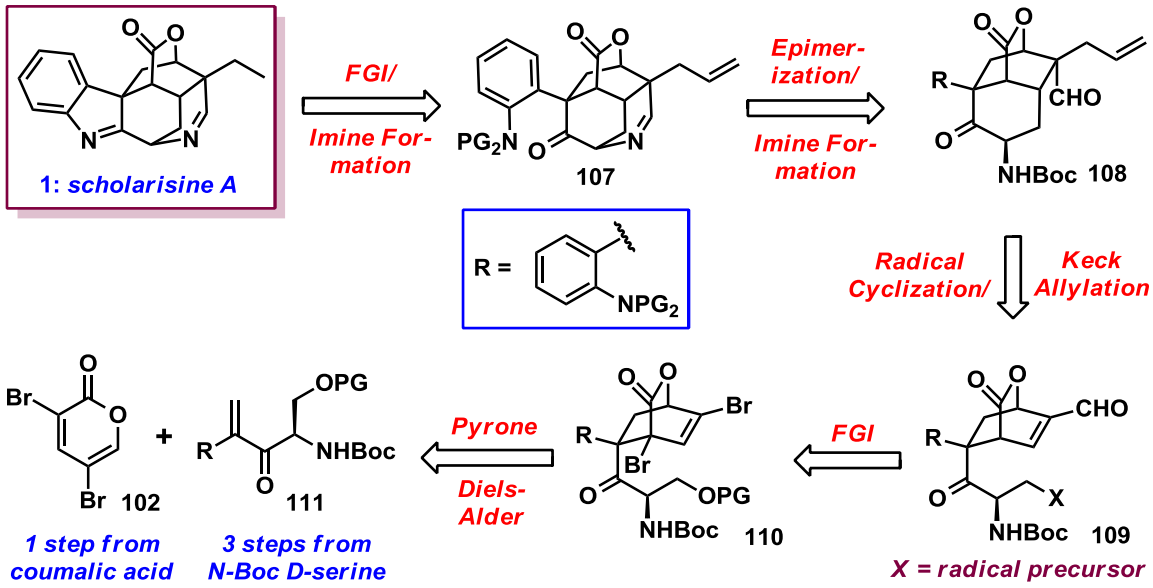


Scheme 16. Cho's 3,5-dibromo-2-pyrone as a versatile diene for intermolecular D-A reactions.

2.5.1. Initial 3,5-dibromopyrone-based Strategy

A strategy incorporating the use of dibromopyrone diene **102** was thus formulated and is outlined in Scheme 17. Here, disconnection of the indolenine system of scholarisine A (**1**) leads back to aniline precursor **107**, one bearing the full cage structure of scholarisine

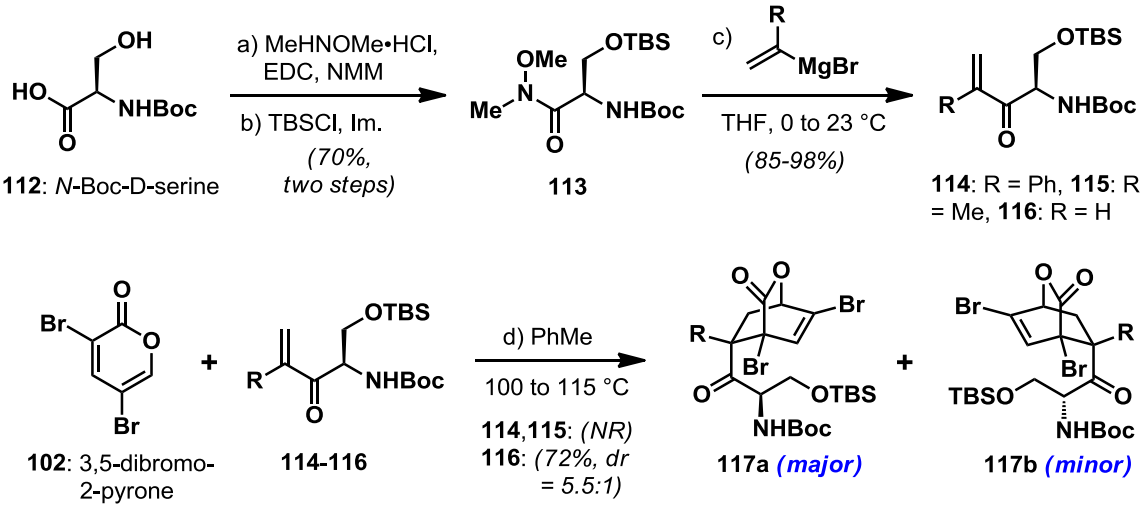
A. Imine **107**, in turn, is seen to arise from aldehyde **108**, itself available in the forward direction from a tandem 6-*exo*-*trig* radical cyclization/Keck allylation of enal **109**. Through functional group manipulations, this new compound led back to **110**, the product of an *endo*-Diels–Alder reaction of 3,5-dibromopyrone **102** and serine-derived dienophile **110**, noting that similar structures are known compounds.[15] Worth mentioning is the fact that, in contrast to the approaches delineated above, the dienophile was now set to form part of the opposite side of the cage structure of scholarisine A (cf. Schemes 6 and 12), demonstrating the versatility of the pyrone Diels–Alder retron in this particular context.



Scheme 17. Revised approach to scholarisine A (**1**) using 3,5-dibromopyrone Diels-Alder retron.

With this general plan in mind, we set about testing the initial Diels–Alder reaction between 3,5-dibromopyrone (**102**) and a serine-derived dienophile (Scheme 18). Since pyrone **102** has only been used in Diels–Alder reactions with relatively simple electron-deficient dienophiles, with only one example bearing α-substitution having been reported,[16] we thought it would be prudent to first probe the tolerance of the desired α-aryl group or some reasonable precursor to it. We thus prepared a series of dienophiles bearing

α-substitution (**114**, R = Ph, **115**, R = Me), as well as an unsubstituted congener **116** (R = H), from *N*-Boc-serine via the corresponding Weinreb amide **113**.[ii]



Scheme 18. *Reagents and conditions:* (a) MeHNMeOMe•HCl (1.1 equiv), EDC (1.1 equiv), NMM (1.1 equiv), CH_2Cl_2, -5 °C, 1 h; (b) TBSCl (1.1 equiv), Im (2.0 equiv), DMF, 0 to 23 °C, 3 h, 70% (2 steps); (c) H_2C=CRMgBr (3.5 equiv), THF, 0 to 23 °C, 3.5 h, **114**: 98%, **115**: 93%, **116**: 85%; (d) **102** (1.1 equiv), PhMe, 100 °C, 16 h, 72%, **117a**:**117b** = 5.5:1.

Mixing enones **114** or **115** with a slight excess of dibromopyrone **102** and heating in toluene at 100–115 °C, we found that only trace amounts of product formed after several days of heating; higher temperatures were expected to lead to erosion of yield through loss of CO_2. In contrast, unsubstituted **116** reacted smoothly at 100 °C, delivering *endo*-[2.2.2]-bicyclic lactone products **117a** and **117b** in 72% yield and 5.5:1 dr (each formed by approaching a different enantiotopic pyrone face). We rationalize the failure of α-substituted dienophiles **114** and **115** to react effectively in the Diels–Alder reaction due to steric clashing (shown for **114**) between the α-substituent and the approaching pyrone in the transition state (**118**, Figure 2); importantly, the installation of an *ortho*-amino group or some precursor to it onto the aryl group of **114** is only expected to further disfavor this

[ii] Although our initial studies were conducted in the less expensive L-series, we later transitioned to D-serine-derived materials – for the sake of consistency, the D-series is depicted throughout this chapter.

process, since the C–C rotamer with the aryl group oriented orthogonal to the dienophile plane is likely to be favored, blocking approach of the diene.[iii]

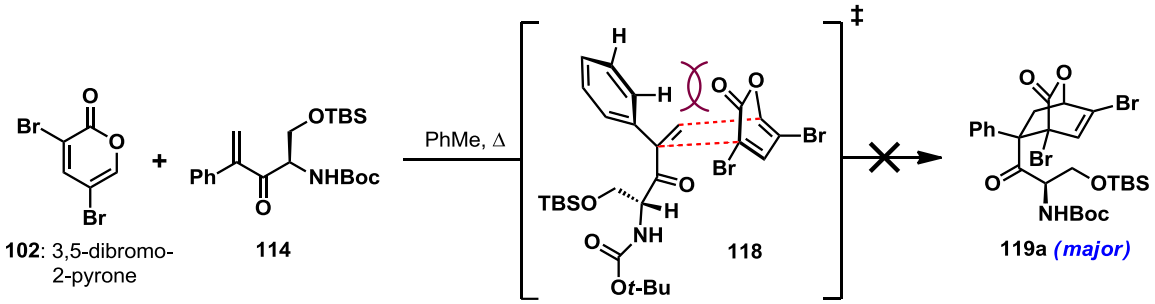


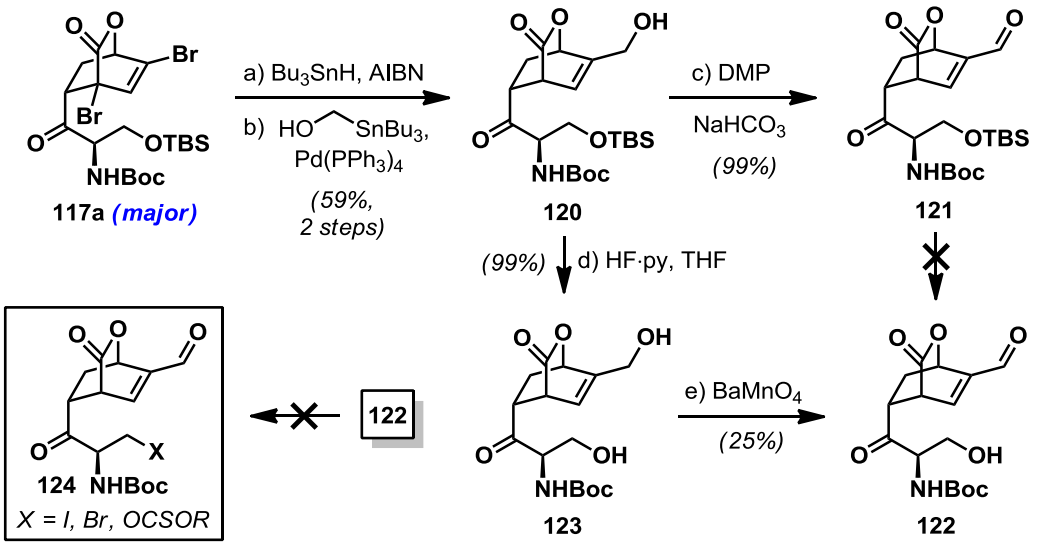
Figure 2. Rationale for the failure of α-substituted enone **114** to react due to steric clashing in transition state.

Given the failure of α-substituted dienophiles to engage in the Diels–Alder reaction, we were faced with a critical decision: should we turn our attention to other, likely more circuitous routes to arylated bicycle **110** (c.f. Scheme 17), or would it be possible to forge ahead as intended, deferring aryl group installation to a later stage of the synthesis? Upon reflection, we resolved to continue with the general plan laid out in Scheme 17, a choice that brought with it the non-trivial questions of when and how this C-H arylation would be achieved, but also a potential opportunity to develop new tools to effect this process within the functionally-dense, strained context of **1**.

Of more immediate concern, however, was advancing bicyclic lactones **117a** and **117b** toward a radical cyclization precursor (**124**, Scheme 19). As reported by Cho,[16] selective removal of the superfluous bridgehead bromide could be achieved using radical reduction with 1.1 equivalents of Bu_3SnH, whereafter a hydroxymethyl substituent could be appended through a Stille coupling of the remaining vinyl bromide with Bu_3SnCH_2OH to afford allylic alcohol **120**. These two operations proceeded in 59% overall yield, noting

[iii] Supported by molecular mechanics calculations (Chem3D) on **114** and its ortho $–NO_2$ congener.

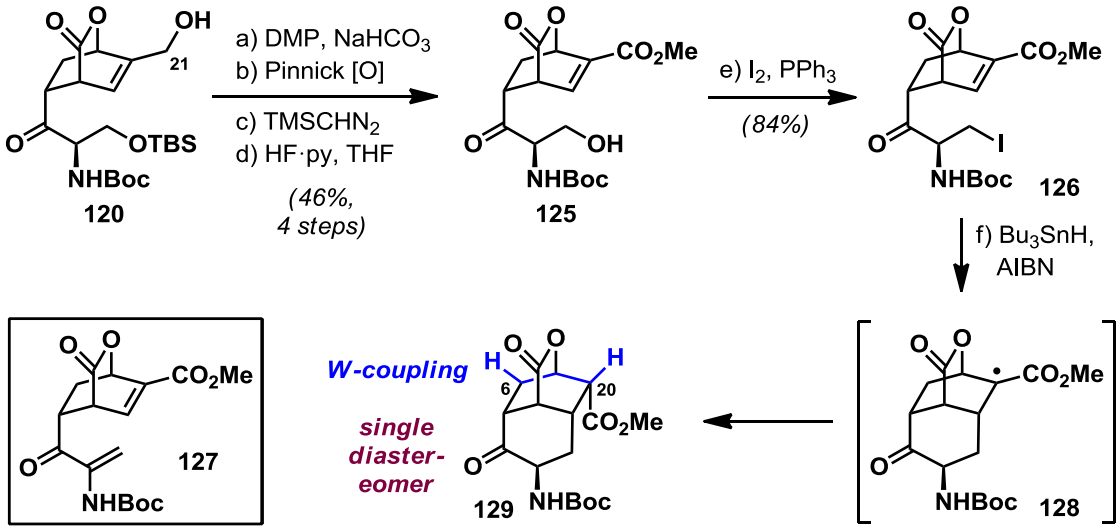
that reversing the order of these steps was not beneficial to material throughput. It is worth mentioning, too, that attempts at palladium-catalyzed methoxycarbonylation or cyanation of **117a**, resulted in apparent ring-opening[iv] and/or β-elimination of TBSOH, attesting to the sensitivity of the bicyclic lactone and the mildness of the Stille procedure. Next, oxidation of **120** with Dess–Martin periodinane[17] provided the protected enal **121** (99%). At this point, all that remained en route to **124** was alcohol deprotection and conversion to an appropriate radical precursor. However, we quickly found that enal **121** was rather sensitive and TBS deprotection could not be effected under a range of standard conditions. As a work-around, TBS deprotection of **120** with HF•py (99%), followed by selective allylic alcohol oxidation of **123** with MnO_2 or $BaMnO_4$ provided enal **122** in low yield (<30%). Again, however, the sensitivity of this group precluded transformation of **122** into appropriate halide or thionocarbonate/carbamate radical precursors.



Scheme 19. *Reagents and conditions:* (a) Bu_3SnH (1.1 equiv), AIBN (0.1 equiv), PhH, 80 °C, 15 h, 74%; (b) $HOCH_2SnBu_3$ (2.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), 1,4-dioxane, 95 °C, 1 h, 79%; (c) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 1 h, 99%; (d) HF·py (xs), THF, 0 to 23 °C, 2.5 h, 99%; (e) $BaMnO_4$ (excess), CH_2Cl_2, 23 °C, 18 h, 25%.

[iv] Aromatic species, presumably formed through lactone opening/elimination, were isolated.

With the difficulties all seemingly stemming from the enal group, we reasoned that a more stable enoate ester would alleviate many of these encountered problems; this change, however, would necessitate a reduction at a later stage to correct the oxidation state at C-21. Thus, from allylic alcohol **120**, DMP oxidation as before, followed by a simple two step Pinnick oxidation/methylation procedure, gave enoate ester **125** (Scheme 20). Pleasingly, ester **125** could be quantitatively deprotected with HF•py (46% over four steps), whereafter iodination under Appel-type conditions provided the sensitive β-iodo ketone **126**. In particular, **126**'s propensity to eliminate HI meant that it was necessary to avoid aqueous work-up, with the reaction best quenched and purified by directly loading the cold reaction mixture onto a short silica gel column and quickly (<5 min) eluting with 2:3 EtOAc/hexanes. This procedure gave **126** along with a small amount of HI-elimination product **127** (typically 4–8:1) in 84% yield.

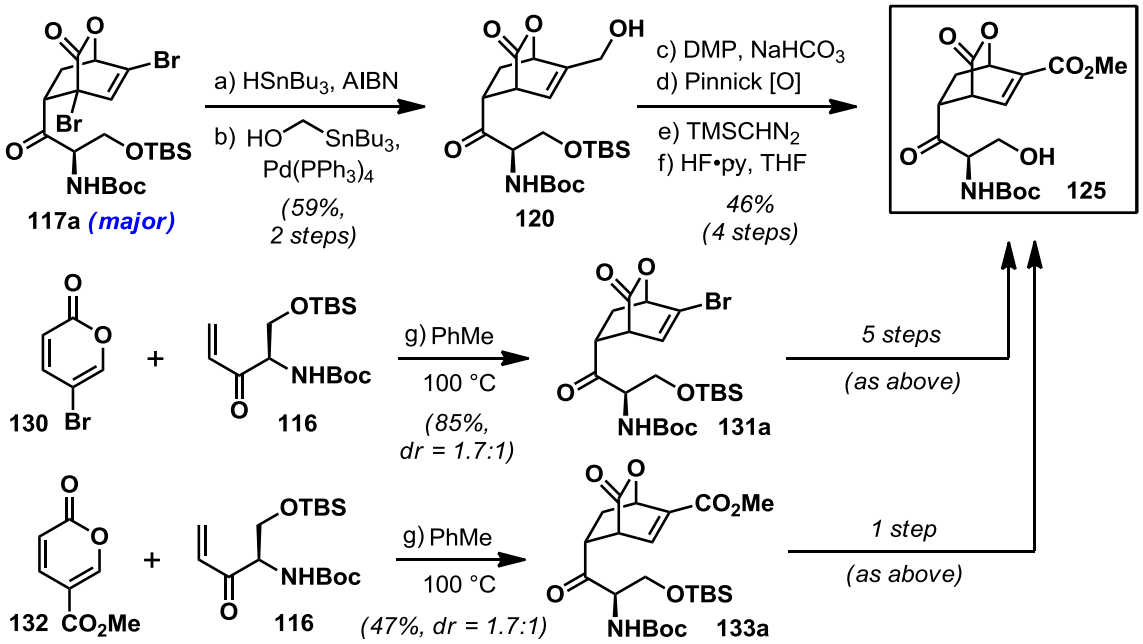


Scheme 20. *Reagents and conditions:* (a) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 1 h, 99%; (b) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (8.0 equiv), 2-methyl-2-butene (10 equiv), THF, *t*-BuOH, H_2O, 23 °C, 1 h; (c) $TMSCHN_2$ (1.1 equiv), MeOH, Et_2O, 0 °C, 15 min; (d) HF·py (excess), THF, 0 to 23 °C, 4 h, 46% (4 steps); (e) I_2 (1.5 equiv), PPh_3 (1.5 equiv), Im (1.5 equiv), CH_2Cl_2, 0 °C, 40 min, 84%; (f) Bu_3SnH (1.5 equiv), AIBN (0.1 equiv), PhH, Δ, 40 min.

With this material in hand, subjecting it to standard radical cyclization conditions involving syringe pump addition of a Bu_3SnH/AIBN solution to a solution of **126** at 80 °C in degassed benzene excitingly afforded desired [3.3.1]-bicycle **129** seemingly as a single diastereomer. The connectivity of **129** was confirmed by NMR via a COSY experiment, and the stereochemistry at the newly formed C-20 stereocenter was confirmed through the observation of four-bond "W-coupling" (shown in blue) between H-6β and H-20, only possible in this configuration. Importantly, this stereochemical outcome, where the incipient α-carbonyl radical **128** was trapped exclusively from the *exo*-face of the bicyclic structure, boded well for the planned trapping with a carbon-based group.

*2.5.2. Optimization of the Synthesis of Alcohol **125***

Before moving on to such investigations, there were a few issues in the assembly of **125** to address. First, although the route described above reliably delivered enoate alcohol **125**, it required six steps to manipulate the functionality brought in by the starting pyrone into that required for **125** (Scheme 21). Thus, as an initial simplification, we attempted the Diels–Alder reaction with the known[18] 5-bromopyrone **130**, a diene which pleasingly gave the Diels–Alder adducts **131a**/**131b** in an improved 85% yield, though with reduced diastereoselection (dr = 1.7:1.0), thus obviating the initial debromination step en route to **125**. More significantly, we were delighted to find that commercially available methyl coumalate (**132**) was a competent diene for the process, delivering enoate ester-containing materials **133a**/**133b** directly in 47% yield and a dr of 1.7:1.0:0.1; the major diastereomers correspond to those obtained previously, while the minor species is an uncharacterized *exo*-diastereomer or regioisomer.

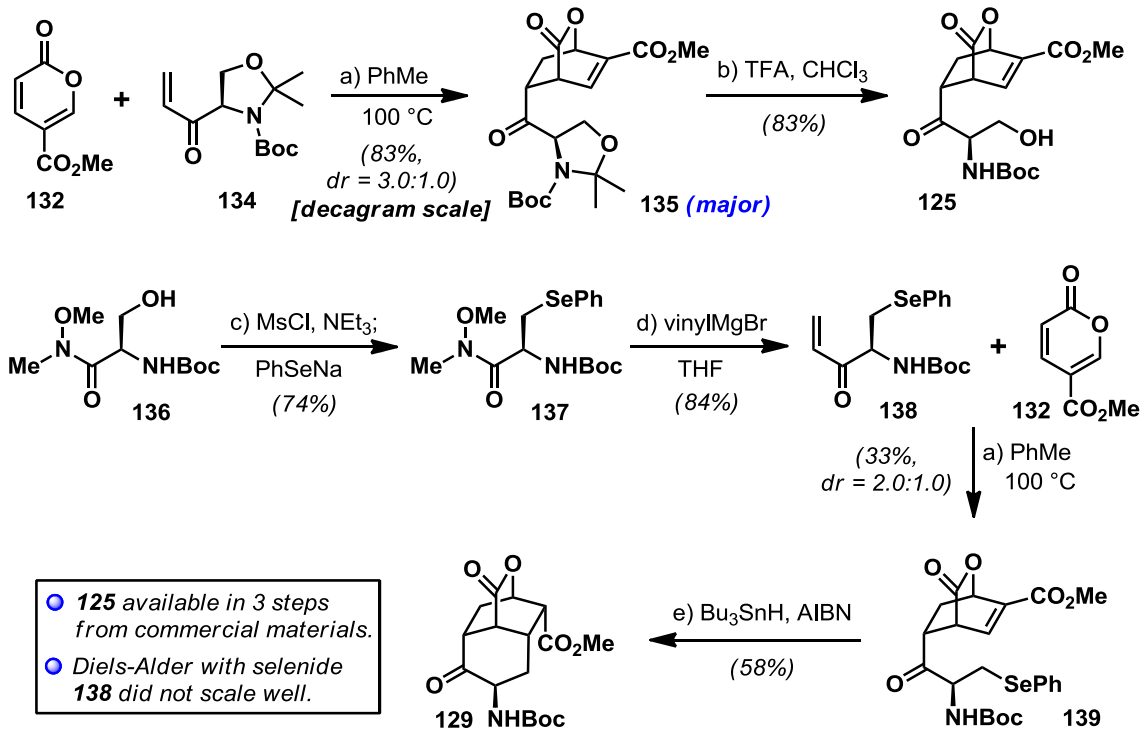


Scheme 21. *Reagents and conditions:* (a) Bu_3SnH (1.1 equiv), AIBN (0.1 equiv), PhH, 80 °C, 15 h, 74%; (b) $HOCH_2SnBu_3$ (2.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), 1,4-dioxane, 95 °C, 1 h, 79%; (c) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 1 h; (d) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (8.0 equiv), 2-methyl-2-butene (10 equiv), THF, *t*-BuOH, H_2O, 23 °C, 1 h; (e) $TMSCHN_2$ (1.1 equiv), MeOH, Et_2O, 0 °C, 15 min; (f) HF·py (excess), THF, 0 to 23 °C, 4 h, 46% (4 steps); (g) **130** (1.2 equiv) or **132** (1.2 equiv), PhMe, 100 °C, 15-35 h, **131**: 85%, dr = 1.7:1.0, **133**: 47%: dr = 1.7:1.0:0.1.

This result was surprising to us since the electron-deficient nature of both the diene and dienophile seemed to predict that the reaction would be inefficient; indeed, literature reports of Diels–Alder reactions of methyl coumalate have typically either employed electron-rich (e.g. methoxyfuran, vinylsulfide) or highly electron-deficient dienophiles (e.g. maleimides, *p*-benzoquinones).[19] Despite these initial concerns, this route was now able to provide alcohol **125** in only 2 steps from dienophile **116**.

As a final improvement to the Diels–Alder reaction, a switch of protecting group from the TBS ether **116** to the more rigid *N*,*O*-acetonide **134** gave an improvement in both yield (83% vs 47%) and dr (3.0:1.0:0.1 vs 1.7:1.0:0.1), ultimately yielding decagram quantities of our desired [2.2.2]-bicyclic lactone **135** (top half of Scheme 22). That material

could then be transformed into alcohol **125** in 83% yield through chemoselective acetonide deprotection with TFA in $CHCl_3$ at 0 °C.[20]



Scheme 22. *Reagents and conditions:* (a) **132** (1.2-1.8 equiv), PhMe, 100 °C, 33 h, **135**: 83%, dr = 3.0:1.0:0.1, **139**: 33%: dr = 2.0:1.0; (b) TFA, $CHCl_3$ (6% v/v), 0 °C, 12 h, 83%; (c) MsCl (1.2 equiv), NEt_3 (1.3 equiv), THF, 0 °C, 20 min; $(PhSe)_2$ (0.7 equiv), $NaBH_4$ (1.7 equiv), EtOH, THF, 0 to 23 °C, 17 h, 74%; (d) vinylMgBr (5.0 equiv), THF, 0 to 23 °C, 3.5 h, 84%; (e) Bu_3SnH (1.5 equiv), AIBN (0.1 equiv), PhH, 80 °C, 1.5 h, 58%.

Attempts to further streamline the synthesis through the use of a selenide-containing dienophile **138**, prepared as outlined in Scheme 22, were only moderately successful. While the desired Diels–Alder reaction with methyl coumalate (**132**) did occur in this variant (33%, dr = 2:1), the yield dropped precipitously upon scale-up, presumably due to the leaving group ability of the β-keto selenide, making this route impractical.[v]

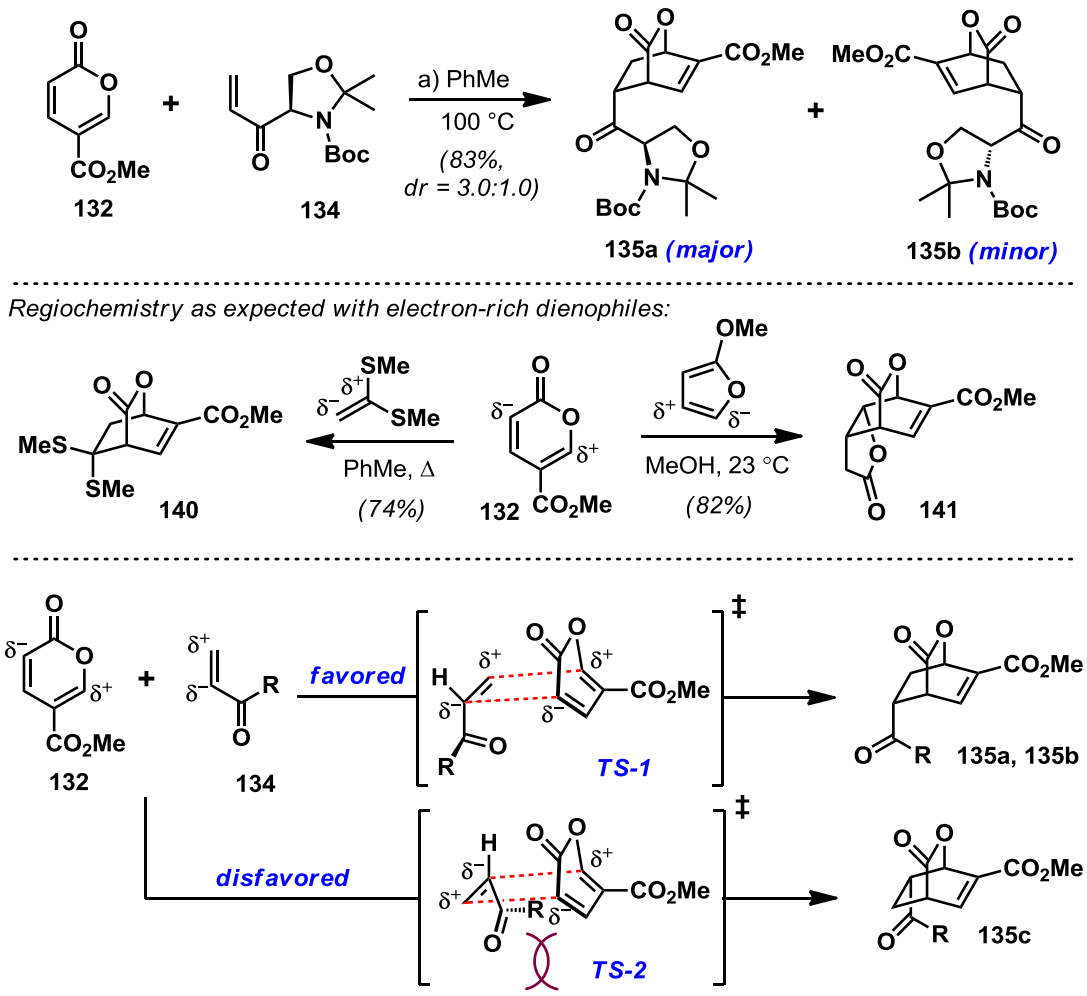
[v] A slightly more stable phenylsulfide was also investigated but was not a competent radical precursor.

Nevertheless, we did show that the selenide **139** performed analogously to the corresponding iodide in the radical cyclization, delivering **129** in 58% yield.

2.5.3. Regiochemistry of the Diels–Alder Reaction

Before leaving the Diels–Alder portion of the synthesis behind, a discussion of the observed regiochemical outcome is in order. Indeed, the regiochemistry for both major adducts **135a** and **135b** is somewhat unexpected based on consideration of diene and dienophile polarity through simple resonance arguments. As illustrated for **135** in Scheme 23, the observed products arise from joining positions bearing partial charges (indicated by δ^+ and δ^-) of methyl coumalate (**132**) with similarly polarized ones on the enone (Scheme 23). It is noteworthy that methoxyfuran and 1,1-bis(methylthio)ethane, electron-rich dienophiles, react with **132** to give the expected regiochemistry (**132**→**140** or **141**).[19c,d] Similar observations of "fixed regiochemistry" regardless of dienophile character have been observed with 3,5-dibromopyrone (**102**), which reacts with both electron-deficient and electron-rich dienophiles with the same regiochemical outcome (Scheme 16).[5b] In the present case, we tentatively propose that the *endo*-transition states (**TS-1**) leading to the observed adducts **135a**/**135b** minimize steric clashing between the dienophile substituent (-COR) and the pyrone -CO_2Me group (vs regioisomeric *endo*-**TS-2** leading to **135c**).[vi] Thus, in all of our Diels–Alder reactions, the 5-substituent on the pyrone (Br or CO_2Me) may steer the regiochemical outcome.

[vi] Strictly speaking, *ent*-**TS-1** would be required for accessing **135b**.



Scheme 23. Preliminary rationale for the Diels-Alder regiochemistry based on steric control.

The issue is likely more complicated, however, and we have therefore undertaken computational investigations to probe the relative energies of the transition states involved.[vii] Using methyl vinyl ketone as a model for enone dienophile **134**, DFT calculations performed at the B3LYP/6-31G* level by former group member Dr. Adel ElSohly have yielded the relative energies for the transition states leading to each of the four possible Diels–Alder products with methyl coumalate (**132**) (two regioisomeric pairs

[vii] Noting that similar computational studies have rationalized the experimentally observed product ratios for 4-halopyrone Diels-Alder reactions.[10,21]

of *endo* and *exo* products). The calculated energies predict that the two *endo*-transition states (*endo*-**TS-1** and *endo*-**TS-2**) are substantially lower in energy relative to their *exo* counterparts, with *endo*-**TS-1** – the transition state that would lead to major products **135a**/**135b** – favored by 1.3 kcal/mol over the regioisomeric *endo*-**TS-2** (Figure 3). This energy difference predicts a 6.2:1 ratio of the resulting *endo* products **143a** and **143b** at 100 °C, although in the real system the ratio of **135a**/**135b**:**135c** is larger at ~40:1 potentially due to the influence of the side-chain.

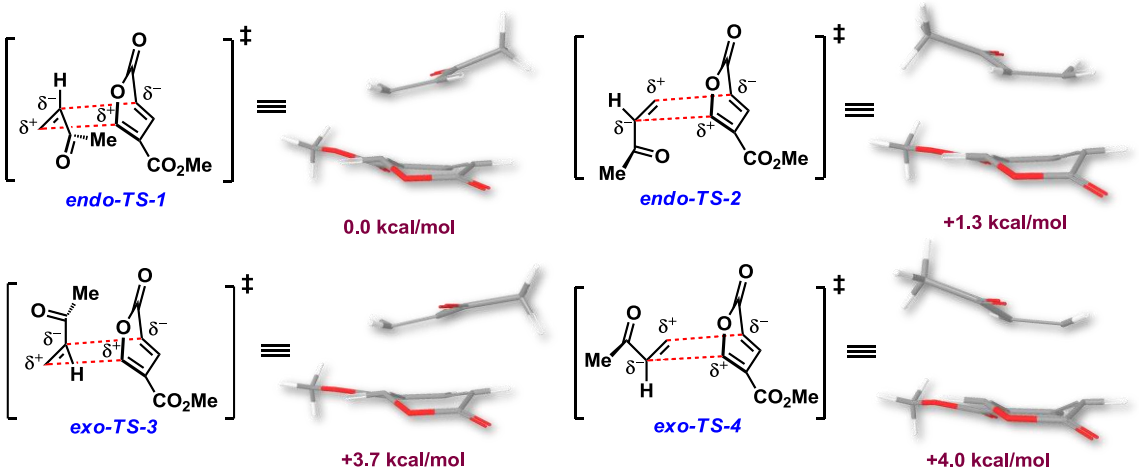
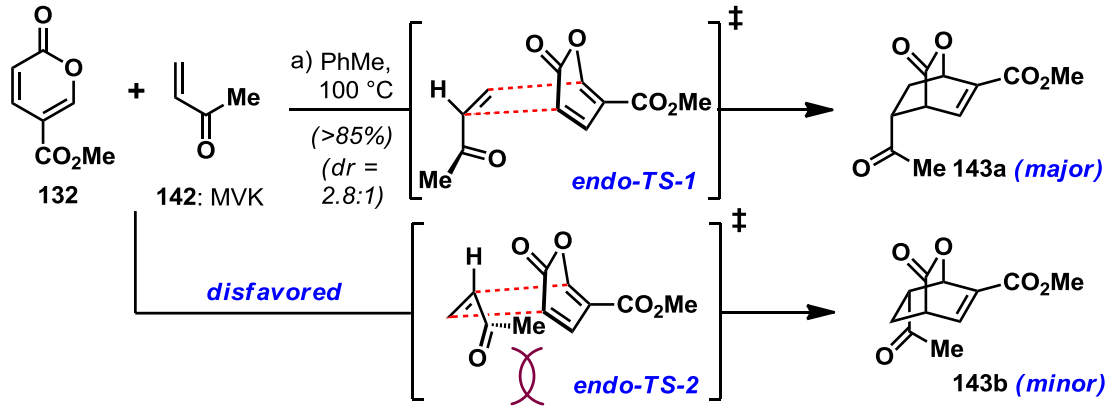


Figure 3. Calculated relative energies ($\Delta\Delta G^{\ddagger}$) for the transition states leading to the four possible Diels-Alder products between methyl vinyl ketone and methyl coumalate (B3LYP/3-31G*).

We have also attempted to experimentally corroborate these theoretical results. As shown in Scheme 24, reacting methyl vinyl ketone (**142**) and methyl coumalate (**132**) at 100 °C in toluene for 26 h showed a ~2.8:1 ratio of the two *endo*-products **143a** and **143b** by crude ^{1}H NMR (isolated in >85% yield). Wondering if the discrepancy in the magnitude of this preference was due to partial reversibility in the Diels–Alder reaction, we computed the thermodynamic stabilities of the regioisomeric products **143b** and **143b**. Indeed, their relative stabilities (ΔG = 0.6 kcal/mol at 100 °C) predict a narrowed 1.7:1 ratio. However,

running the reaction to partial conversion (~25%) for only 1 h at 100 °C, gave a ratio (2.7:1) close to that previously observed, suggesting that equilibration towards the thermodynamic ratio is not likely.



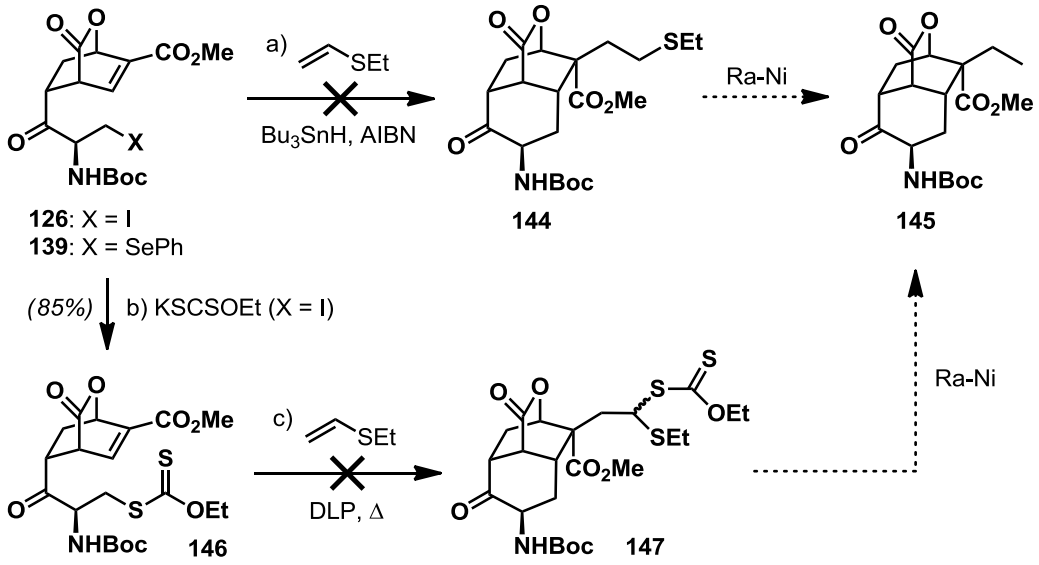
Scheme 24. Experimental confirmation of predicted product preference for Diels-Alder reaction between MVK (**142**) and methyl coumalate (**132**).

Collectively, these preliminary computational investigations do support the observed regio- and stereochemical sense of the Diels–Alder reaction of **134** with methyl coumalate (**132**), though further refinement will clearly be required to arrive at a more quantitative prediction of product ratios for specific systems. Studies along these lines, as well as investigations into the relevant frontier molecular orbitals and electronic character of the Diels–Alder process, are underway.

2.5.4. Studies with a Carbon-based Radical trap – Forging the C-20 Quaternary Center

At this stage, we were poised to investigate the key radical cyclization with a carbon-based trap for the formed α-carbonyl radical, hoping to stereoselectively introduce the C-20 quaternary center of **1** in the process. In initial studies, we employed ethyl vinyl sulfide (3 equiv) as a nucleophilic olefin trap for the electrophilic α-carbonyl radical based on precedent by Zard and co-workers[22] (Scheme 25); we hoped to ultimately reveal the

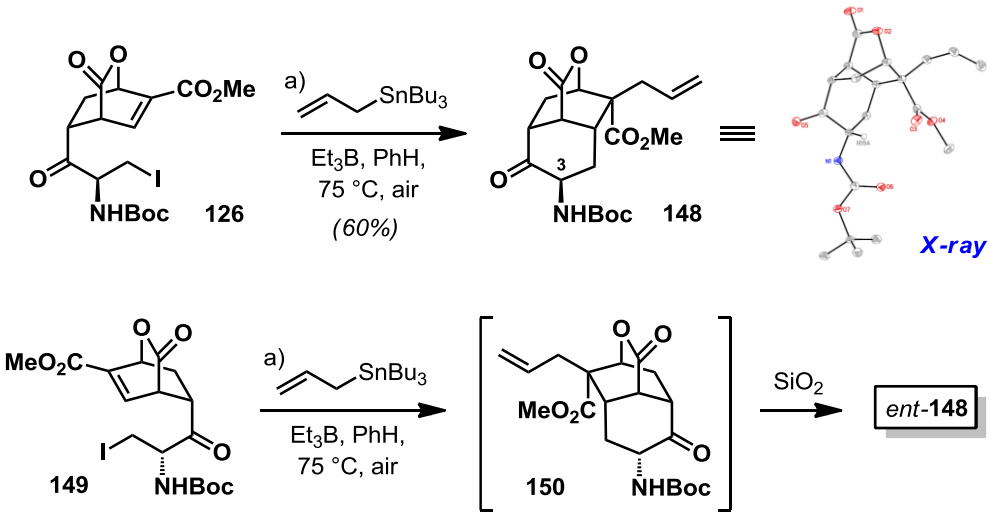
desired ethyl group of **145** through desulfurization with Raney nickel. Unfortunately, experiments using iodide **126** or selenide **139** both yielded only previously obtained reduction product **129**, indicating that the rate of radical reduction was greater than that of radical trapping by ethyl vinyl sulfide. Thus, we attempted a non-reductive process using the atom-transfer radical cyclization conditions (dilauroyl peroxide, EtOAc, Δ) of Zard with iodide-derived xanthate **146**; unfortunately, no reaction was observed in our case.



Scheme 25. *Reagents and conditions:* (a) H_2C=CHSEt (3.0 equiv), Bu_3SnH (1.5 equiv), AIBN (0.1 equiv), PhH, 80 °C, 2 h; (b) KSCSOEt (1.2 equiv), THF, -78 to 10 °C, 3.5 h, 85%; (c) H_2C=CHSEt (2.0 equiv), DLP (3 x 0.05 equiv), EtOAc, Δ, 8 h.

Gratifyingly, though, we found that by employing allyltributylstannane with Et_3B as a radical initiator under air at 75–80 °C, the desired allylated compound **148** could be isolated in 60% yield as a single diastereomer (Scheme 26). Its structure was confirmed by single crystal X-ray analysis; this determination, in turn, allowed the stereochemistry of the Diels–Alder adducts **135a** and **135b** to be firmly assigned. It is worth noting that the stereochemistry of the α-NHBoc C-3 center of **148**, derived from the major Diels–Alder diastereomer **135a**, is opposite to that required for scholarisine A. However, while use of

the minor iodide **149** (prepared analogously from **135b**) resulted initially in a different product diastereomer (**150**) based on crude ^{1}H NMR, this compound epimerized to *ent*-**148** during silica gel purification. While this outcome was not unwelcome in that it allowed both major Diels–Alder diastereomers to be converted to **148** in a racemic sense for initial studies, it did mean that an epimerization (either *in situ* or as a discrete step) would be needed to form the final C-N bond of the cage structure.

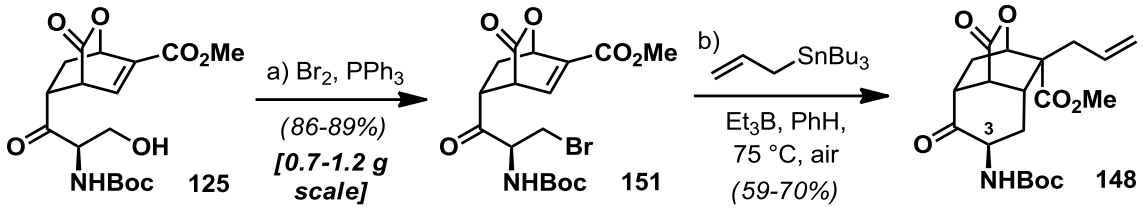


Scheme 26. *Reagents and conditions:* (a) allyltributylstannane (3.0 equiv), Et_3B (5 × 0.2 equiv), PhH, 75 °C, 4 h, 60%

Curiously, use of AIBN in place of Et_3B, or Et_3B at lower temperatures in the radical cascade either led to no reaction (AIBN) or reduced the conversion. On larger scales it was important to add Et_3B portionwise (5 × 0.2 equiv) to reach full conversion, probably indicative of the need to re-initiate the radical chain, which might be shut down in the presence of too much O_2.[viii] Conducting the reaction under argon (without solvent degassing) or under an oxygen atmosphere (balloon) did not remedy the situation. Finally, although the iodide **126** proved workable on small scales (<100 mg), its sensitivity was

[viii] For example, through formation of stannylperoxyl radicals, $Bu_3SnOO\cdot$, which are not chain carriers.

unsuitable for preparative scale work. Thus, we investigated the analogous bromide **151**, which could be prepared reproducibly on 0.7 to 1.2 g scale with minimal elimination to **127** and performed well in the subsequent radical cascade to **148** (59–70% yield, Scheme 27).



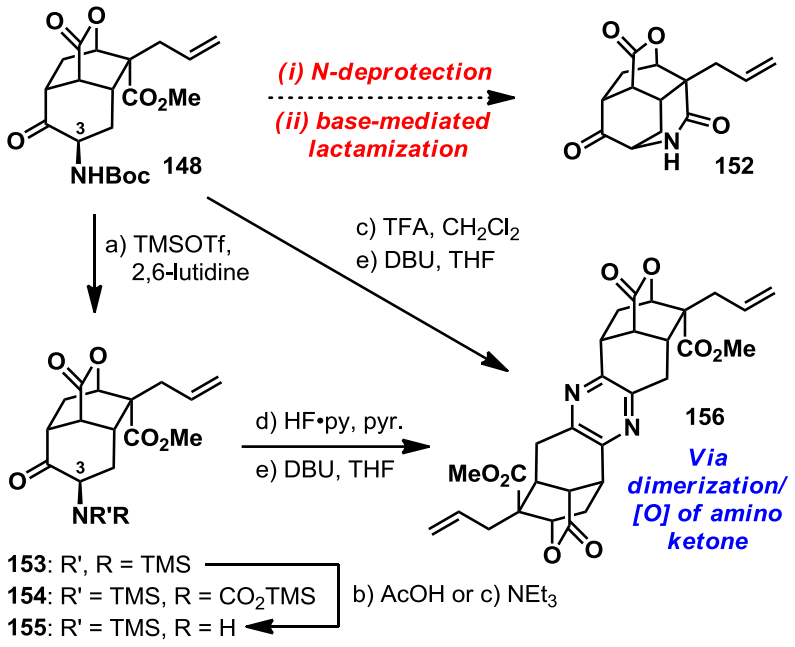
Scheme 27. *Reagents and conditions:* (a) PPh_3 (1.5 equiv), Im (1.5 equiv), Br_2 (1.5 equiv), CH_2Cl_2, 0 °C, 40 min, 86-89%; (b) allyltributylstannane (3.0 equiv), Et_3B (5 × 0.2 equiv), PhH, 75 °C, 5 h, 59-70%

It is worth mentioning, too, that although the allyl group of **148** would seem less than ideal, requiring a few steps to be transformed into the desired ethyl group of scholarisine A (**1**), its presence ultimately turned out to be critical for effecting chemoselective late-stage functionalization en route to **1** (*vide infra*).

2.5.5. Completion of the Full Cage Framework of Scholarisine A.

With reproducible access to [3.3.1]-bicycle **148**, we sought to validate the final part of our designed bond connections by forming the lactam bond necessary to complete the cage structure of **1**. This transformation was envisaged as occurring through a deprotection/epimerization/lactamization sequence (Scheme 28). Thus, our efforts began by treatment of Boc-protected amine **148** with TMSOTf/2,6-lutidine in the hopes of delivering the free amine upon aqueous work-up; however, we were surprised to obtain what we have assigned as the diTMS-amine **153** as a surprisingly stable and cleanly formed product. We favor the diTMS-amine form **153** over the possible diTMS-carbamate **154** on the basis of the H-3 chemical shift, one which moves upfield from δ 4.38 to δ 3.08 in ^{1}H

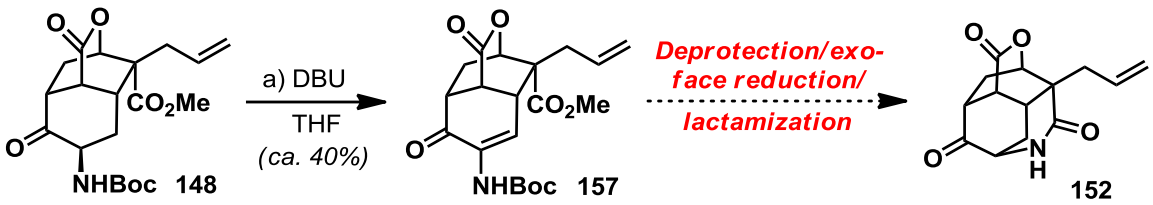
NMR spectrum of **153** relative to the starting carbamate (**148**). Subsequent stirring of this species in AcOH/H_2O/THF or treatment with NEt_3 in *t*-BuOH/CH_2Cl_2 led to removal of one of the TMS groups, revealing an N-H peak (δ 5.53, singlet) to give **155**. On the other hand, HF•py/pyr treatment of **153** or TFA deprotection of **148** appeared to remove all protecting groups, providing a fairly messy crude ^{1}H NMR which, upon silica gel purification or treatment of the crude material with base, underwent conversion to one major product (which was also present in the crude ^{1}H NMR in variable amounts). This product was identified as pyrazine dimer **156**, presumably formed through dimerization and oxidation of the nascent α-amino ketone.



Scheme 28. *Reagents and conditions:* (a) TMSOTf (4.0 equiv), 2,6-lutidine (5.0 equiv), CH_2Cl_2, 0 °C, 20 min; (b) AcOH, H_2O, THF, 0 to 23 °C, 2.5 h; (c) NEt_3 (1.5 equiv), *t*-BuOH, CH_2Cl_2, -50 to 23 °C, 24 h; (d) HF•py (excess), pyr., THF, 0 °C, 1.75 h; (e) DBU (1.5 equiv), THF, 0 to 23 °C, 21 h.

In light of these results, an α-amino ketone intermediate appeared to be a dead-end; hence, we briefly explored epimerization of carbamate **148**. In one of these trials, treatment

of **148** with DBU in THF and stirring overnight at 50 °C led cleanly to a new species which was identified as enone **157** (Scheme 29). Thus, rather serendipitously, ketone **148** had undergone aerobic oxidation presumably due to adventitious oxygen present either in the solvent or headspace of the flask, noting that, although the reaction was conducted under an Ar atmosphere, no attempt was made to purge air from the flask prior to sealing with a rubber septum. This result was of interest because a deprotection/*exo*-face reduction/lactamization sequence could be seen to deliver the desired cage compound **152** from this alternate material.

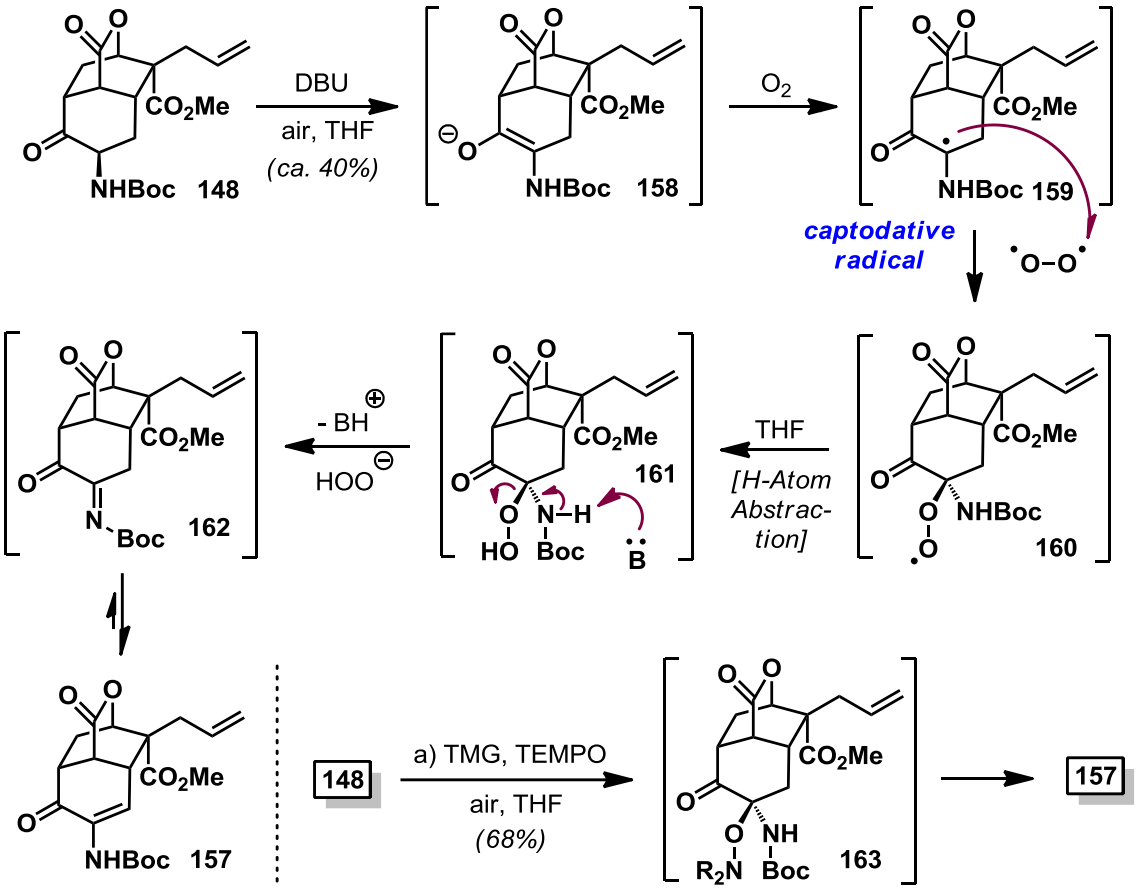


Scheme 29. *Reagents and conditions:* (a) DBU (1.1 equiv), THF, 50 °C, 24 h, 40%.

Mechanistically, we believe the oxidation of **148** to **157** occurs through oxidation of the initially formed enolate **158** by O_2 to radical **159**, a process favored by its captodative nature (Scheme 30).[ix] This radical **159** then reacts further with O_2 to yield α-peroxyl radical **160**, which can abstract a hydrogen atom, likely from the THF solvent, to yield hydroperoxide **161**. Since **161** is a protected hydroperoxyhemiaminal, base-mediated expulsion of the labile hydroperoxide, followed by tautomerization of the resulting imine (**162**), then yields enone product **157**. Indeed, an improved procedure employing TEMPO as a more suitable radical trap and TMG as base under air gave enone **157** in 68% yield on gram-scale (vs ca. 40% using only air). We ascribe this boost in yield to the cleaner

[ix] Reaction mixtures usually turn pink-orange upon addition of base, potentially indicative of intermediates **158** or **159**.

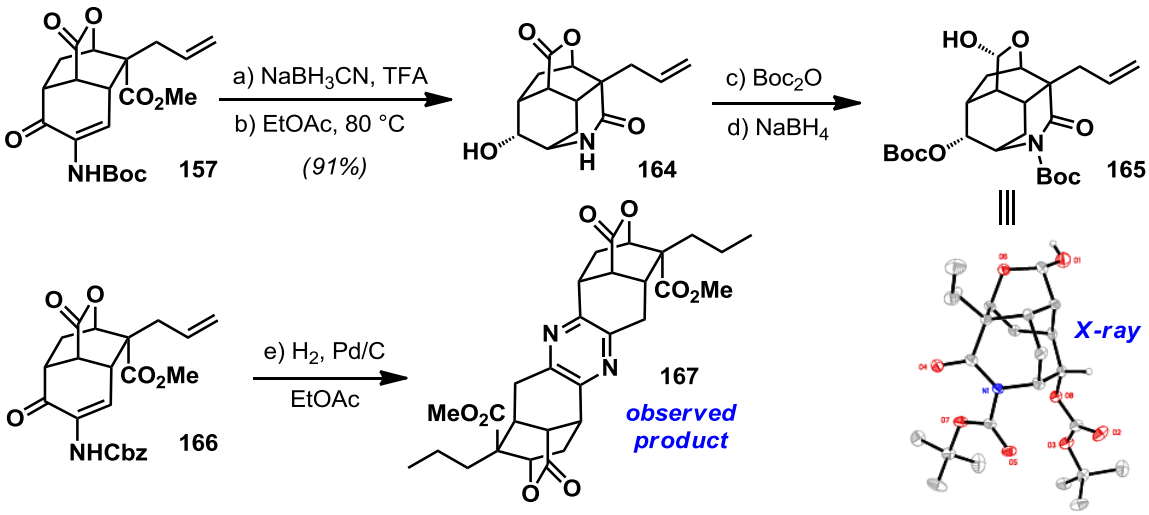
conversion of TEMPO adduct **163** to the desired product versus its peroxyl radical alternative (**160**), which may lead to other deleterious processes such as C-C cleavage, which impacts the overall yield.



Scheme 30. Mechanism of the oxidation of **148** to **157** and an improved TEMPO-based procedure. *Reagents and conditions:* (a) TEMPO (1.1 equiv), TMG (1.1 equiv), THF, 50 °C, air, 12 h, 68%.

With ready access to enone **157**, we next set about testing the proposed deprotection/*exo*-face reduction/lactamization sequence (Scheme 31). In the event, addition of TFA to a suspension of $NaBH_3CN$ and **157** in CH_2Cl_2 at 0 °C, followed by stirring for 40 min and aqueous work-up under mildly basic conditions gave a mixture of lactam **164** and presumed uncyclized amino ester. Upon dissolution in EtOAc and heating at 80 °C for 4 h, this mixture converged to **164**. After purification by preparative TLC, lactam **164** could be isolated in 91% yield over the two steps. The cage structure of **164**

was established by 2D NMR experiments, in particular an HMBC correlation between H-3 and the C-20 lactam carbonyl confirmed the desired N-C bond had formed. A subsequent X-ray crystallographic analysis of a derivative **165** secured this assignment and determined the stereochemistry of the carbinol.

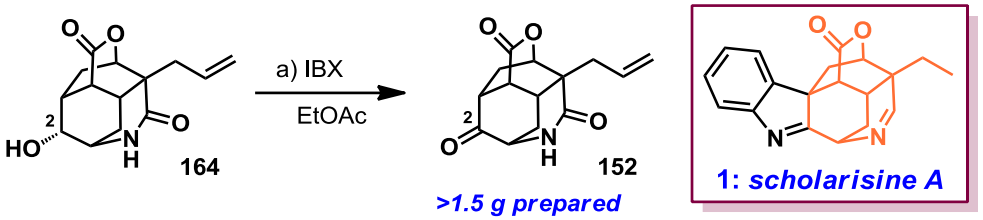


Scheme 31. *Reagents and conditions:* (a) $NaBH_3CN$ (5.0 equiv), TFA (18 equiv), CH_2Cl_2, 0 °C, 40 min; (b) EtOAc, 80 °C, 4 h, 91%; (c) Boc_2O (4.5 equiv), 4-DMAP (0.2 equiv), THF, 23 °C, 20 h, 41%; (d) $NaBH_4$ (4.5 equiv), MeOH, 0 °C, 4.5 h; (e) H_2, Pd/C, EtOAc, (AcOH), 23 °C, 4 h.

Although at first glance the concomitant reduction of the ketone to the *endo*-alcohol would seem unfortunate given the required C-2 ketone oxidation state of scholarisine A, control experiments employing Cbz-protected analogue **166** to effect the same process without ketone reduction (H_2, Pd/C, with or without added AcOH), only yielded tetrahydropyrazine dimer **167**. Thus, serendipitous ketone reduction allowed the desired bond formation to take place by eliminating the facile dimerization pathway.

Final re-oxidation of C-2 using IBX in EtOAc at 80 °C gave ketone **152** in >85% yield (Scheme 32).[23] Importantly, this set of conditions required only cooling, filtration of the insoluble IBX-derived solids and direct concentration to yield almost pure ketone **152** contaminated with small amounts of an IBX-derived aromatic impurity (ca. 5:1). Attempts

with other oxidants and reaction conditions, requiring aqueous work-up and/or chromatographic purification with either silica gel or basic alumina, gave only miniscule amounts of ketone **152**, a material which for unknown reasons appeared to be sensitive to these routine manipulations. Notably, >1.5 g of **152** has been prepared through this route, providing a concise and efficient material supply to fuel the next round of studies.



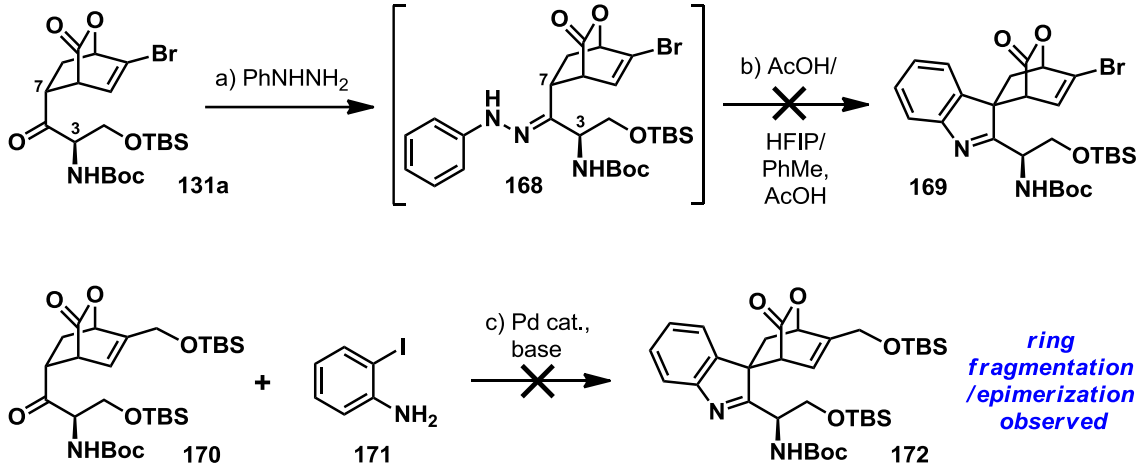
Scheme 32. *Reagents and conditions:* (a) IBX (3.5 equiv), EtOAc, 80 °C, 12 h, >85%.

2.5.6. Arylation Studies

While we were happy to have attained proof of principle for the key steps in our cage-forming sequence, we were still left with the quandary of when and how the aryl group of scholarisine A was to be installed. Early efforts along these lines involved attempting Fischer indole synthesis and palladium-catalyzed α-arylation on bicyclic lactones **131a** and **170**. The key challenges for such a transformation involved controlling the regiochemistry (i.e. C-3 vs C-7 selectivity) as well as the stereochemistry of the arylation (Scheme 33). While the latter issue might be controlled by the facial bias of the bicycle, the regiochemical outcome was much less predictable.

Beginning our trials with Fischer indole syntheses using compound **131a**, we hoped to form the desired indolenine (i.e. by reaction at C-7) through the use of a weakly acidic medium such as AcOH in accordance with literature reports.[24] While formation of hydrazone **168** was facile, occurring at room temperature (this could be followed in C_6D_6),

heating this species in benzene, AcOH, toluene with a catalytic amount of AcOH or hexafluoroisopropanol (HFIP) all yielded no discernible Fischer indole synthesis products, with non-specific decomposition chiefly observed.[x] We then briefly explored (aza)-enolate arylation protocols on compound **170**, using 2-iodoaniline (**171**) with $Pd(dppf)_2Cl_2$, Cs_2CO_3 or $Pd(OAc)_2$, DABCO. However, these efforts also proved fruitless with either bicycle degradation (cf. section 2.5.1) or epimerization of starting material being the only discernible results.

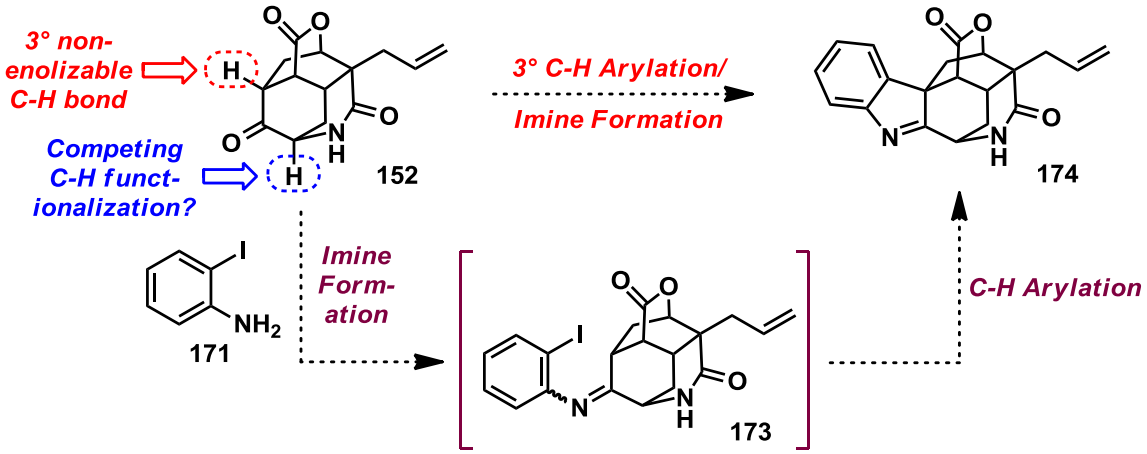


Scheme 33. *Reagents and conditions:* (a) $PhNHNH_2$ (1.05 equiv), PhH, 23 °C, 0.5 h; (b) AcOH, 90 °C; HFIP, 60 to 90 °C; AcOH (0.5 equiv), PhMe, 90 °C; (c) **171** (1.2 equiv), Cs_2CO_3 (2.5 equiv), $Pd(dppf)Cl_2$ (0.05 equiv), PhMe, 100 °C, 1 h; **171** (1.2 equiv), DABCO (3.0 equiv), $Pd(OAc)_2$ (0.05 equiv), DMF, 100 °C, 21.5 h.

In light of these failures, we began to formulate a new plan based on executing a late-stage C-H arylation process, one which we could ideally apply to the advanced cage ketone **152** already formed. This plan is outlined in general terms in Scheme 34. First, condensation of a 2-haloaniline [shown here as 2-iodoaniline (**171**)] with cage ketone **152** should provide imine(s) **173** from which we hoped that an intramolecular C-H arylation process would occur to deliver the desired indolenine **174**. While the hallmarks of this route

[x] Indolenine synthesis at C-3 is unlikely to be productive since a competitive fragmentation of α-amino ketones is preferred.[25]

are similar to the Pd-catalyzed α-arylations attempted above, the key difference resides in the fact that the α-positions of cage ketone **152** and imine **173** are non-enolizable (i.e. an anti-Bredt aza-enolate would be required to form), requiring a formal C-H activation to react. Apparent, too, is that both α-positions contain a similar tertiary C-H bond (circled in red and blue in **152**, respectively), which may result in the formation of regioisomers of product **174**.



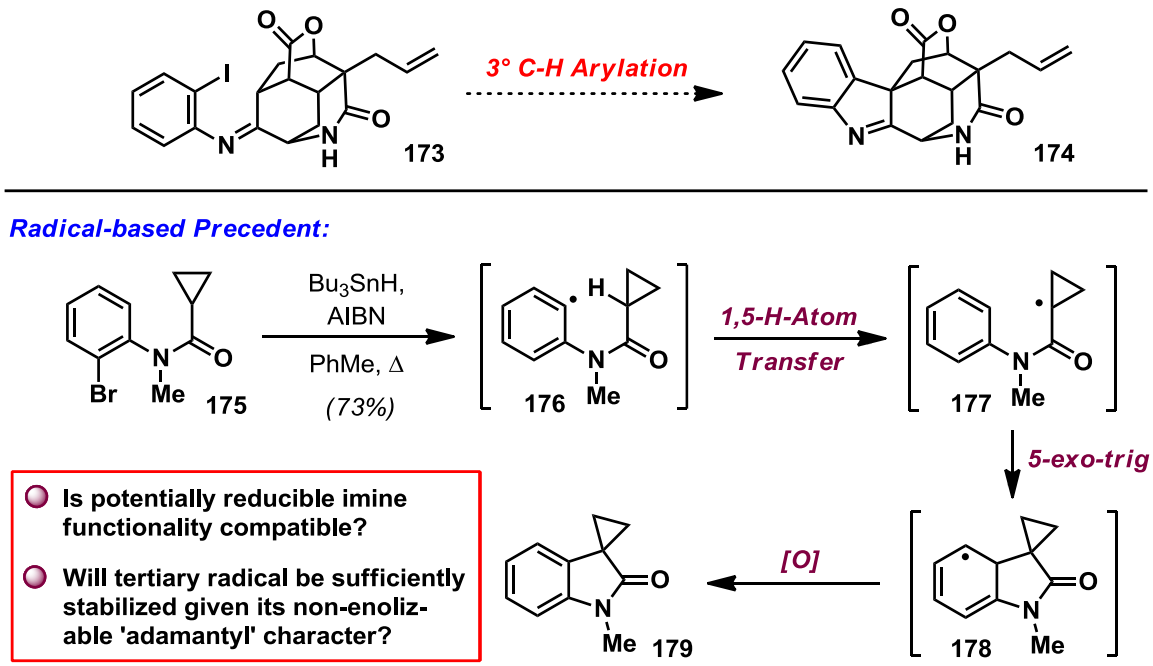
Scheme 34. Plan for potential late-stage C-H arylation of cage ketone **152**.

While this plan appeared promising, two key questions arose: 1) what mode of C-H functionalization would be appropriate for a tertiary, non-enolizable C-H bond, and 2) what role, if any, would the presence of imine isomers play in the process? Specifically, would it be possible to effect *in situ* isomerization to funnel all material through to the desired regioisomer of product, and, if not, would the initial imine ratio dictate that of the products?

In answering the first of these questions we were mindful of the fact that the palladium(II) catalysis often employed is extremely rare for tertiary C-H bonds,[26] likely due to the concerted metallation-deprotonation process being disfavored both sterically and

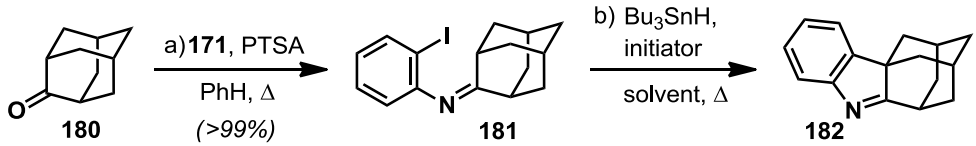
electronically. This fact, coupled with the Lewis basic nature of the intermediate imine and product, led us to disfavor this approach. Thus, we focused on strategies that favor reaction at tertiary C-H bonds, namely carbenoid and radical-based processes.

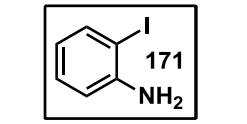
Looking to the literature we found promising precedent for the latter in the work of Beckwith[27] who had shown that under tin-mediated radical conditions, *ortho*-haloanilides such as **175** could be converted to oxindoles (**179**, Scheme 35). This process is proposed to involve initial aryl radical generation (**176**) followed by a 1,5-H-atom transfer (1,5-HAT) to form tertiary radical **177**. This new species (**177**), in turn, cyclizes onto the pendant aryl group in a 5-*exo*-*trig* fashion to give cyclohexadienyl radical **178**, which is finally oxidized to give the rearomatized product **179** likely by the azo initiator.[27b] While this precedent was certainly encouraging, there are several key differences between the Beckwith process and our proposed transformation. First, their example uses a robust amide-linked substrate while ours contains a far more labile *N*-arylimine, a motif which may be subject to ionic reduction by Bu_3SnH at high temperatures. Second, their generated tertiary radical (**177**) is able to be stabilized by the neighboring carbonyl group and planarize (though admittedly strained for the cyclopropyl case shown), while the adamantyl-type radical formed in our case would be far less stabilized, meaning that it might hinder the 1,5-HAT process.

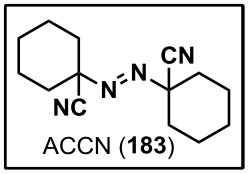


Scheme 35. Precedent and concerns for radical C-H arylation of tertiary C-H bonds based on Beckwith's conversion of anilide **175** to oxindole **179**.

Given our concerns, the most prudent course of action seemed to be to model the desired transformation. The closest and most readily accessible model compound seemed to be 2-adamantanone-derived imine **181** (Scheme 36). This species was prepared in near quantitative yield through condensation of 2-adamantanone (**180**) with the 2-iodoaniline under Dean–Stark conditions. Subjection of **181** to the Beckwith conditions involving syringe pump addition of a solution of Bu_3SnH (1.1 equiv) and AIBN (1.2 equiv) to a solution of **181** in refluxing toluene, pleasingly afforded the desired indolenine (**182**) in ca. 60% yield (product co-eluted with minor impurities, ca. 5-10%). A small screen of conditions using this model substrate (Table, Scheme 36) confirmed that the original Beckwith conditions seemed optimal for this compound.







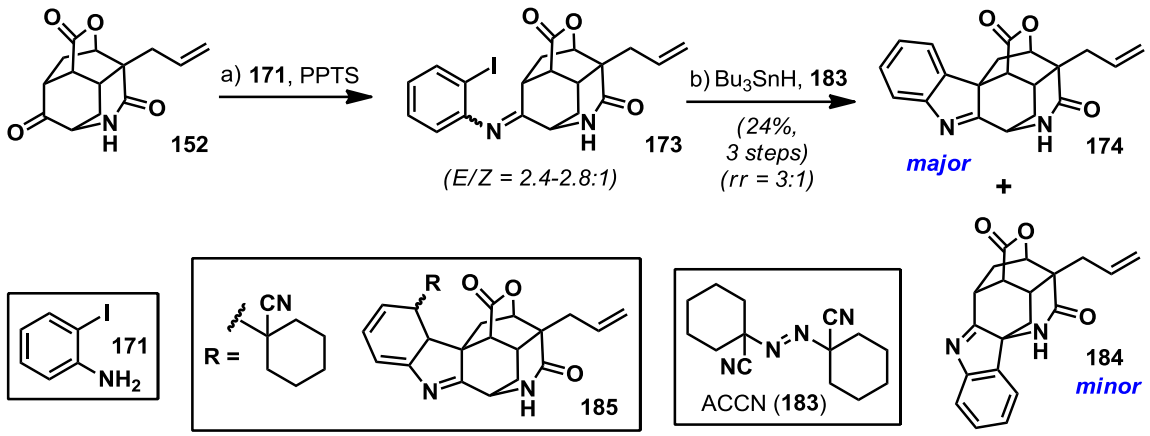
INITIATOR	SOLVENT	YIELD
AIBN	PhMe	*60%*
ACCN	PhMe	*49%*
$(t\text{-BuO})_2$	PhMe	*22%*
AIBN	*m*-xylene	*56%*
AIBN	PhMe	*20%**

* with $(TMS)_3SiH$ instead of Bu_3SnH

Scheme 36. Optimization of HAT/cyclization with adamantanone imine model **181**. *Reagents and conditions:* (a) **171** (1.05 equiv), PTSA·H_2O (0.02 equiv), PhH, Δ, Dean-Stark, 18 h, >99%; (b) Bu_3SnH (1.1 equiv), initiator/oxidant (1.2 equiv), solvent, Δ, 4 h.

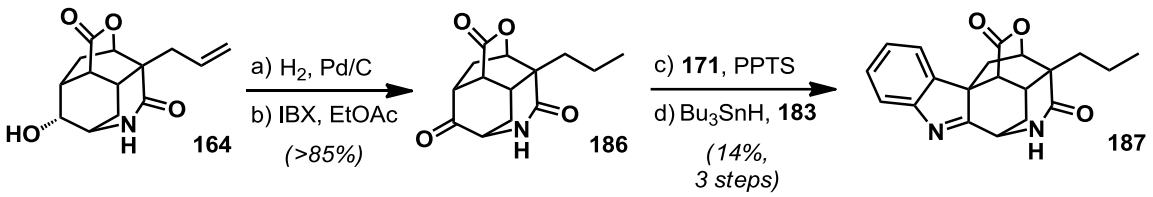
Encouraged by this crucial result, we set about applying these HAT/cyclization conditions to fully functionalized materials for scholarisine A. Cage ketone **152** was therefore condensed with 2-iodoaniline (**171**) by heating a toluene/THF solution (**152** did not dissolve well in toluene alone) at 90 °C in the presence of crushed 4Å molecular sieves and a catalytic amount of PPTS for 17 h. After cooling, filtration and concentration gave the somewhat unstable imine **173** as a mixture of geometric isomers in a batch dependent 2.4-2.8:1 ratio. Dissolution in degassed toluene and running the reaction as before excitingly gave a small amount of the desired product (**174**), though it was hard to separate from an impurity that seemed, at least by LRMS, to be a result of trapping of the intermediate cyclohexadienyl radical with $NC(Me)_2C•$ derived from AIBN. Optimization of the reaction conditions, in particular using the less thermally labile 1,1'-azobis(cyclohexanecarbonitrile) (ACCN, **183**) instead of AIBN, improved the yield and allowed the isolation of pure **174** by preparative TLC (18% yield over the three steps from alcohol **164**), along with its less polar regioisomer **184** (6% yield). A small amount of what

appeared to be ACCN-trapped species tentatively assigned as **185** was also formed in <5% yield.



Scheme 37. *Reagents and conditions:* (a) **171** (1.1 equiv), PPTS (0.09 equiv), THF, PhMe, 4Å MS, 90 °C, 18 h, *E*/*Z* = 2.4-2.8:1; (b) Bu_3SnH (1.2 equiv), ACCN (1.2 equiv), PhMe, Δ, 4.5 h, 24%, 3 steps, **174**:**184** = 3:1.

Further modification to the conditions, for example employing the higher boiling chlorobenzene (known to be compatible with tin-radical conditions) or use of $(TMS)_3SiH$/AIBN in refluxing *m*-xylene – conditions later discovered to be optimal for model substrate **181** by postdoctoral fellow Dr. Denise Rageot – both gave poor yields and impure samples of **174**. Similarly, attempts at dissolving imine **173** in a small amount of THF prior to dilution with toluene (like ketone **152**, the residue from the imine formation was not completely soluble in toluene, even at reflux), led to a messier reaction, and addition of 4Å MS to prevent possible imine hydrolysis also proved deleterious. Use of the corresponding propyl congener, formed analogously from **186** (Scheme 38), in an attempt to gauge whether the alkene of the allyl group was interfering in the process, proved this group to have little effect, delivering product **187** in a comparable 14% yield (three steps).

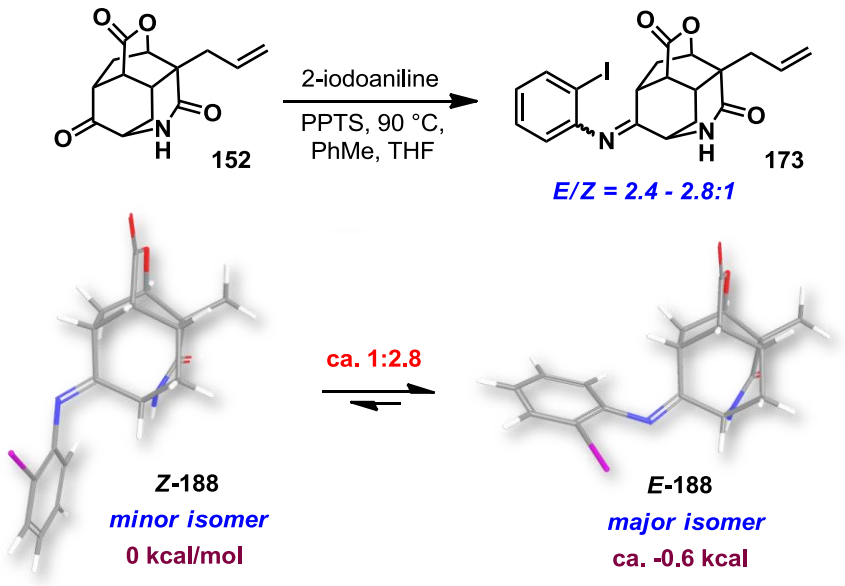


Scheme 38. *Reagents and conditions:* (a) H_2 (1 atm), Pd/C (0.1 equiv), EtOAc, 23 °C, 16 h, >99%; (b) IBX (3.5 equiv), EtOAc, 80 °C, 12 h, >85%; (c) **171** (1.1 equiv), PPTS (0.09 equiv), THF, PhMe, 4Å MS, 90 °C, 18 h; (d) Bu_3SnH (1.2 equiv), ACCN (1.2 equiv), PhMe, Δ, 4.5 h, 14%, 3 steps.

Thus, although the overall yield of 24% for this process is modest, it is worth noting that this value amounts for three steps – IBX oxidation, imine formation and HAT/cyclization – representing an average yield of 62% per step. Perhaps more importantly, however, it is hard to envisage another process to effect this annulation on such a functionally-dense and unique framework without incurring several additional steps.

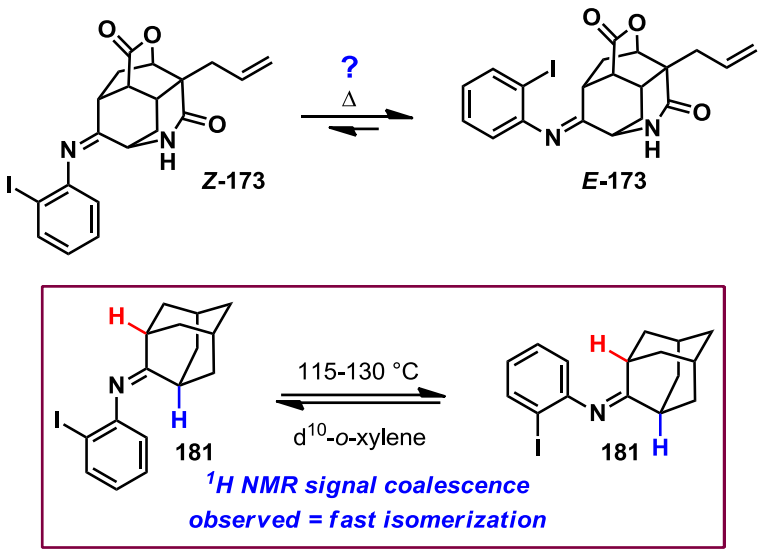
Before moving on to discuss our efforts to elaborate **174** to the final target, an analysis of the regiochemical outcome of the HAT/cyclization reaction is warranted. In particular, it was not lost on us that the ratio of starting imine geometric isomers (2.4-2.8:1) was fairly close to the ratio of product regioisomers obtained (3.0:1), implying that this initial ratio may be determining the product regioisomer ratio. DFT calculations, again performed by Dr. Adel ElSohly, on the relative energies of the imine isomers at the B3LYP/3-21G* level of theory seem to support this notion.[xi] The calculated energy difference between the *E*- and *Z*-isomers of **188** is predicted to be 0.6 kcal/mol, translating to a ratio of approximately 2.8:1 at 25 °C, favoring *E*-**188**, the isomer which leads to the major indolenine product **174** (Scheme 39). The observed imine ratio may therefore reflect the thermodynamic stabilities of the *E/Z*-forms of **173**.

[xi] To reduce computational time, these calculations employed imines **188**, where the remote allyl group of **173** has been replaced with a methyl group.



Scheme 39. Calculated relative energies of the *E*- and *Z*-forms of imine **188** (B3LYP/3-21G*).

If this is the case, when this mixture is dissolved and heated to reflux in toluene, while the Bu_3SnH/ACCN solution is slowly added over 4 h, this ratio is expected to be maintained (although adjusting to ~2.2:1 at this higher temperature), even if isomerization is occurring. To probe whether imine isomerization is occurring at reflux in toluene, something which literature reports would seem to suggest, we conducted variable temperature NMR (VT-NMR) studies of model adamantanone imine **181** in d^{10}-*o*-xylene, an experiment which showed coalescence of the α-imino proton signals between 115 and 130 °C – indicating fast imine isomerization on the NMR time scale (Scheme 40). This outcome suggests that isomerization is likely to occur to some degree under the HAT/cyclization conditions.

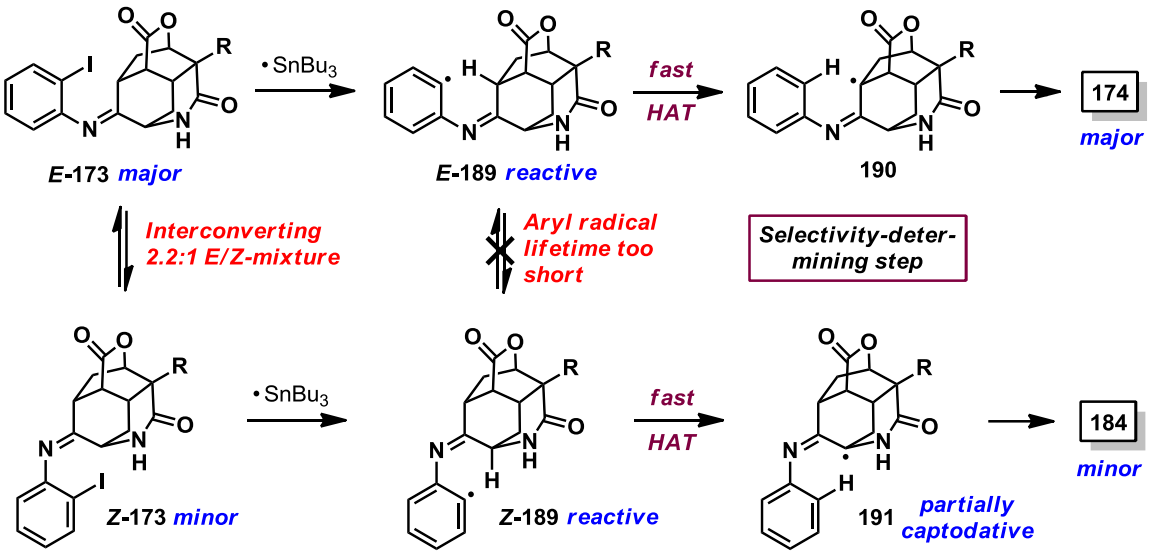


Scheme 40. VT-NMR studies with **181** show likely isomerization of *E*- and *Z*-**173** at elevated temperatures.

Thus, with a likely interconverting ~2.2:1 mixture of imines (**173**) present, the key factor in determining the selectivity becomes the relative rates of the subsequent steps. Assuming that the aryl iodides of both imine isomers react at a comparable rate with $Bu_3Sn•$,[xii] this 2.2:1 ratio of imine isomers will be transformed to a 2.2:1 ratio of reactive aryl radicals *E/Z*-**189**. Even if the *E/Z*-forms of aryl radicals **189** were able to interconvert, the rate of this process would likely not compete with the rapid 1,5-H atom transfer process to generate more stable tertiary radicals **190** and **191**. Thus, in this fast, irreversible step, the initial imine ratio is translated to that of radicals **190** and **191**, ultimately being selectivity-determining, since these species can only lead to **174** and **184** respectively, in a productive sense. We posit that the small difference (likely within experimental error) between the computationally-determined ratio of *E*- and *Z*-**173** (~2.2:1) and products **174** and **184** (3:1) may lie in the tertiary radical **191** not undergoing the cyclization to **184** quite

[xii] We consider this to be a reasonable assumption, given that the rate of reaction of tin radicals with aryl iodides is fast and that radical species are not particularly sensitive to steric effects.

so efficiently given its mildly captodative, and hence less reactive, nature.[xiii] Nevertheless, this analysis is only our preliminary theory and will require further examples, as well as firm proof of imine stereochemistry through nOe-studies, to prove that this is a general phenomenon.



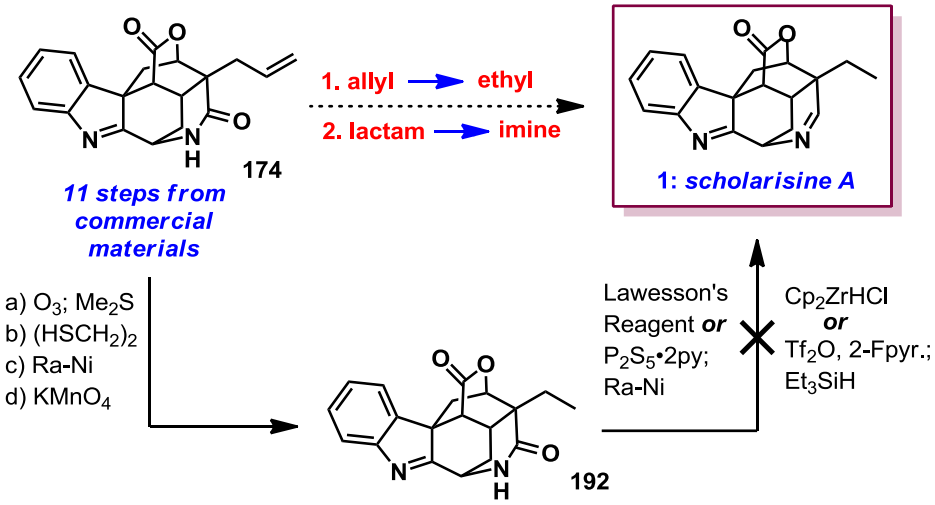
Scheme 41. Rationale for initial *E*/*Z*-mixture of imines **173** leading to observed ratio of indolenine products **174** and **184**.

*2.5.7. Elaboration of **174** to Scholarisine A*

With the synthesis of indolenine **174**, the full carbon framework of scholarisine had been secured in only 13 steps from *N*-Boc-D-serine (i.e. 11 steps from a commercially available Weinreb amide). All that remained to complete the target were the seemingly straightforward conversions of its allyl and lactam groups into the ethyl and imine groups of the natural product (Scheme 42). The first of these tasks could be readily achieved through a standard sequence of ozonolysis, dithiolane formation and Raney Nickel treatment, although concomitant reduction to the indoline occurred in this final step;

[xiii] **191** is not truly captodative as the adjacent EDG and EWG are not fully able to stabilize the radical center because of its admantyl character.

straightforward oxidation using $KMnO_4$ and a phase transfer catalyst at low temperature restored the C-2 imine to give **192**.

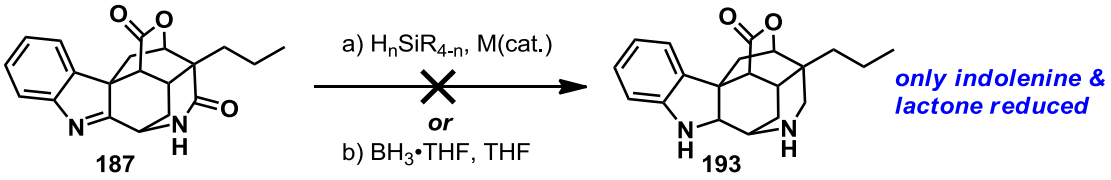


Scheme 42. *Reagents and conditions:* (a) O_3, MeOH, CH_2Cl_2, -78 °C, 1 min; Me_2S (50 equiv), -78 °C, 10 h, 34%; (b) $(HSCH_2)_2$ (10 equiv), BF_3•OEt_2 (8 equiv), CH_2Cl_2, -78 to -15 °C, 1.5 h, 64%; (c) Ra-Ni (excess), EtOH, THF, 0.5 h, 35%; (d) $KMnO_4$ (1.0 equiv), $BnNEt_3Cl$ (1.1 equiv), CH_2Cl_2, -50 to 5 °C, 2 h.

Our initial attempts at reducing the lactam of **192** focused on chemoselective reduction methods, ideally aiming to form the imine directly without engaging the lactone. A procedure developed by Ganem[28] for partial reduction of secondary amides to the corresponding imines using Schwartz's reagent (Cp_2ZrHCl, THF, –40 °C) seemed particular appealing. Unfortunately, despite being shown to be effective on secondary lactams,[29] these conditions led to no reaction in our case and under more vigorous conditions (–20 to 23 °C) afforded only reduction of the indolenine of **192**. Similarly, attempts to form the corresponding thiolactam – a species that could lead directly to the imine of **1** through the use of acetone-deactivated Raney Nickel[30] – using Lawesson's reagent or freshly prepared P_2S_5•2py even under forcing conditions of up to 180 °C, led to partial recovery of starting material and no lactam thionation. Ineffective, too, was the application of Charette's procedure[31] for secondary amide to imine reduction (Tf_2O, 2-

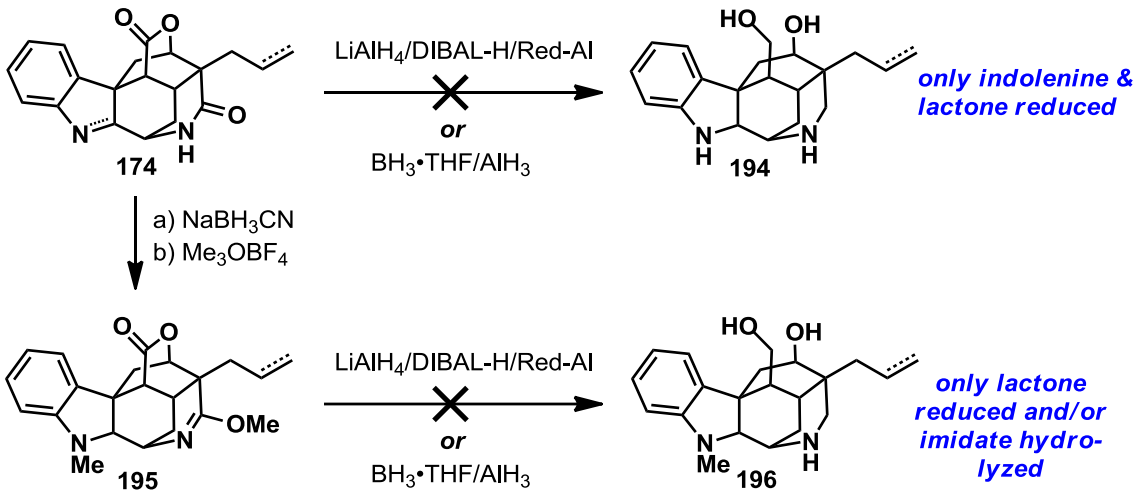
fluoropyridine; Et_3SiH), which gave only the *N*-Tf lactam and some indolenine reduction, although admittedly there was no precedent for its use in cyclic systems of the type probed.

Since the late-stage oxidation of a C-21 secondary amine to the corresponding imine using PhIO was known from the earlier Smith synthesis of scholarisine A,[3] we next focused on methods to access bis-amine **193** through hydrosilylation of the more easily accessed propyl homologue **187** (prepared as detailed in section 2.5.5). Procedures using Karstedt's catalyst/1,1,3,3-tetramethyldisiloxane (TMDS),[32] $Zn(OTf)_2$/TMDS[33] or $[Ir(COE)_2Cl]_2$/ Et_2SiH_2[34] (the latter reported to stop at the imine stage) typically effected only indolenine reduction, with further lactone reduction observed upon prolonged heating.



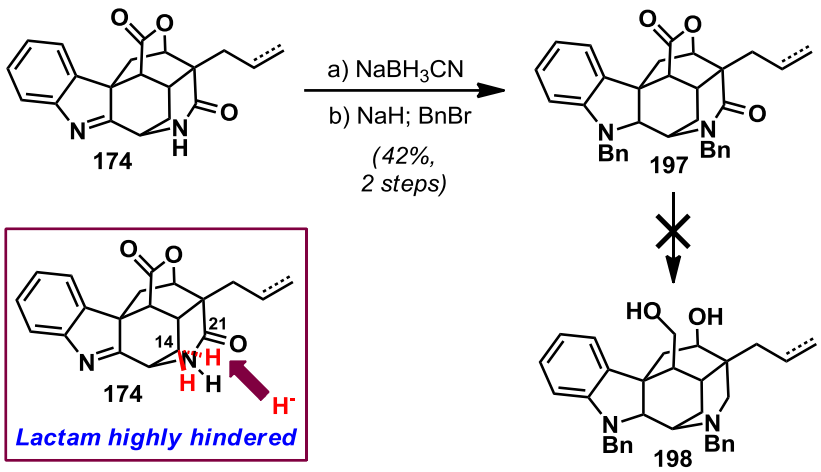
Scheme 43. Failed hydrosilylation and borane reductions of **187**. *Reagents and conditions:* (a) Karstedt's catalyst, TMDS, PhMe or THF, 70 to 110 °C; $Zn(OTf)_2$, TMDS, PhMe, 110 °C; $[Ir(COE)_2Cl]_2$, Et_2SiH_2, CH_2Cl_2, 23 °C or PhH, 80 °C; (b) BH_3•THF, THF, 0 °C to Δ.

BH_3•THF, known to be able to effect chemoselective reductions of amides in the presence of esters,[35] produced similar results when allowed to react with **187** in THF from 0 to 23 °C, while at higher temperatures additional reduction of the lactone to the corresponding ether was observed. In fact, attempts at global reduction to amino diol **194** with $LiAlH_4$, Red-Al, DIBAL-H, AlH_3, BH_3•THF or AlH_3•NMe_2Et in several solvents (up to 100 °C), surprisingly, and worryingly, never touched the C-21 lactam, thereby attesting to its extremely unreactive nature (Scheme 44).



Scheme 44. Failed global reductions of lactam **174** and imidate **195**. *Reagents and conditions:* (a) $NaBH_3CN$ (2.5 equiv), MeOH, 0 to 23 °C, 3.5 h; (b) Me_3OBF_4 (4.0 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, 23 °C, 18 h.

In an attempt to activate the C-21 position, we prepared methyl imidate **195** in two steps ($NaBH_3CN$; Me_3OBF_4) from **174**. Unfortunately, this functionality proved similarly unreactive when subjected to the same battery of reductants, with regeneration of the lactam occasionally observed, presumably through attack on the imidate methyl group. Efforts to access imidoyl halides or sulfonates were either unsuccessful or met a similar fate when treated with hydride reducing agents or nucleophiles such as NaSH. Finally, to determine whether the secondary nature of the amide was contributing to the deactivation of the lactam (e.g. by deprotonation), a tertiary amide derivative **197** was prepared (Scheme 45). It likewise proved recalcitrant to reduction.

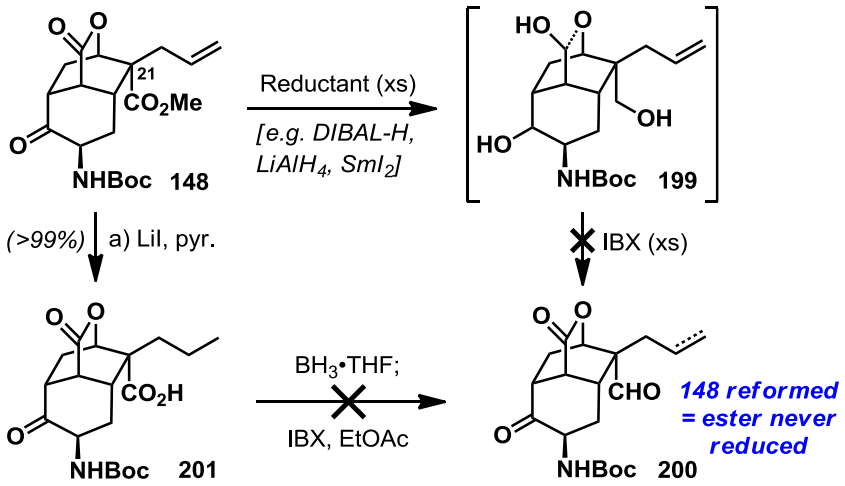


Scheme 45. Failed reductions of tertiary lactam **197**. *Reagents and conditions:* (a) $NaBH_3CN$ (2.5 equiv), MeOH, 0 to 23 °C, 4.5 h; (b) NaH (7.0 equiv), DMF, 0 to 23 °C, 0.5 h; BnBr (3.0 equiv), TBAI (0.2 equiv), 0 to 23 °C, 2.5 h, 42% (2 steps).

Clearly, the highly hindered nature of the C-21 lactam group, being both neopentyl and *endo*- with respect to the [2.2.2]- and [3.3.1]-bicycles, renders it exceptionally unreactive, likely due to the formation of a tetrahedral intermediate upon hydride addition at this position being energetically prohibitive. The possibility also exists that the preferred attack trajectory (Bürgi-Dunitz angle) may be sterically obstructed by, *inter alia*, one of the C-14 methylene protons (Scheme 45, inset).

In light of these consistent failures, we took a step back and contemplated adjusting the C-21 oxidation state earlier in the route, specifically through global reduction of ester **148**, the product of the tandem radical cyclization/Keck allylation, followed by reoxidation to aldehyde **200** (Scheme 46). Typically, executing this idea involved subjecting **148** to a range of standard ester reductions using excess reductant (8-10 equiv) [$LiAlH_4$, Red-Al, DIBAL-H, BH_3•THF (on the dihydro congener), $SmI_2/NEt_3/H_2O$], followed by work-up and oxidation of the resulting over-reduced compound (**199**) by IBX in EtOAc at 80 °C (8

equiv) overnight.[xiv] Surprisingly, crude ^{1}H NMR after filtration and concentration routinely showed regeneration of **148**, indicating that C-21 ester had survived the reduction step. Attempts at BH_3•THF reduction of the corresponding acid **201** (prepared in quantitative yield by treating dihydro-**148** with LiI in pyridine at 115 °C) in an attempt at intramolecular hydride delivery also failed to reduce this position. Evidently, a C-21 ester or acid retained the reactivity issues that plagued the late-stage lactam.



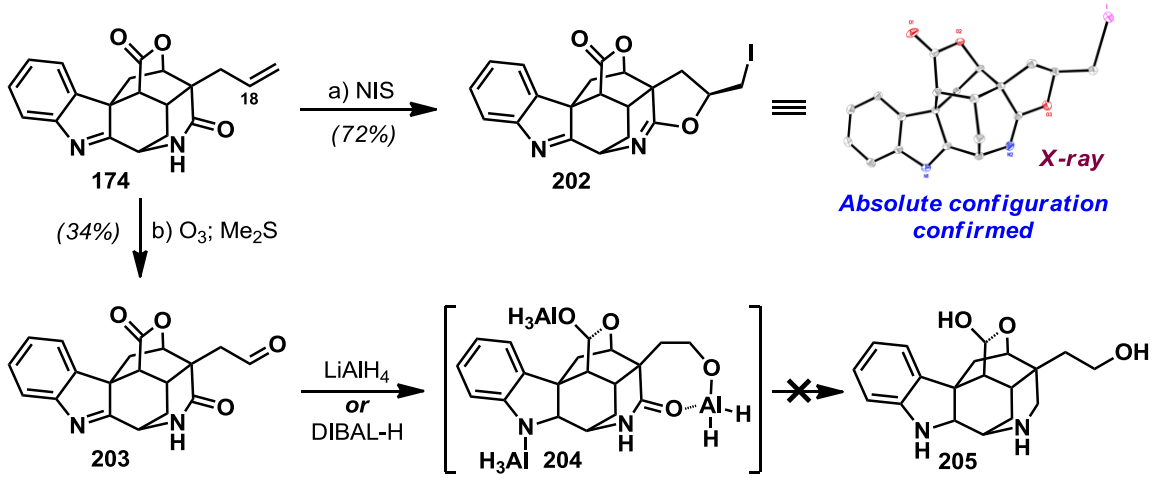
Scheme 46. Unsuccessful earlier adjustment of C-21 oxidation state. *Reagents and conditions:* (a) LiI (5.0 equiv), pyr., 115 °C, 13 h, >99%;

Eventually, our first clue in the right direction came in subjecting HAT/cyclization product **174** to iodoetherification conditions (NIS, CH_2Cl_2, 23 °C). This process delivered the crystalline iodoimidate **202** (Scheme 47) in 72% yield as a single diastereomer. Its structure was confirmed by single crystal X-ray analysis, confirming both the gross constitution of the indolenine compounds prepared thus far, as well as the absolute stereochemistry (through anomalous dispersion of the heavy iodine atom) as that required for natural scholarisine A (**1**). While **202** did not prove to be useful in its own right

[xiv] Crude ^{1}H NMR at this intermediate stage was typically very messy and judging the presence/absence of the methyl ester was not trivial in the presence of many α-oxy proton signals.

(reductions of the sort detailed above did not affect C-21), it did steer our thinking towards using the proximal alkene of the allyl group, or some functionality derived from it, as a means to facilitate the reduction of the obstinate C-21 lactam.

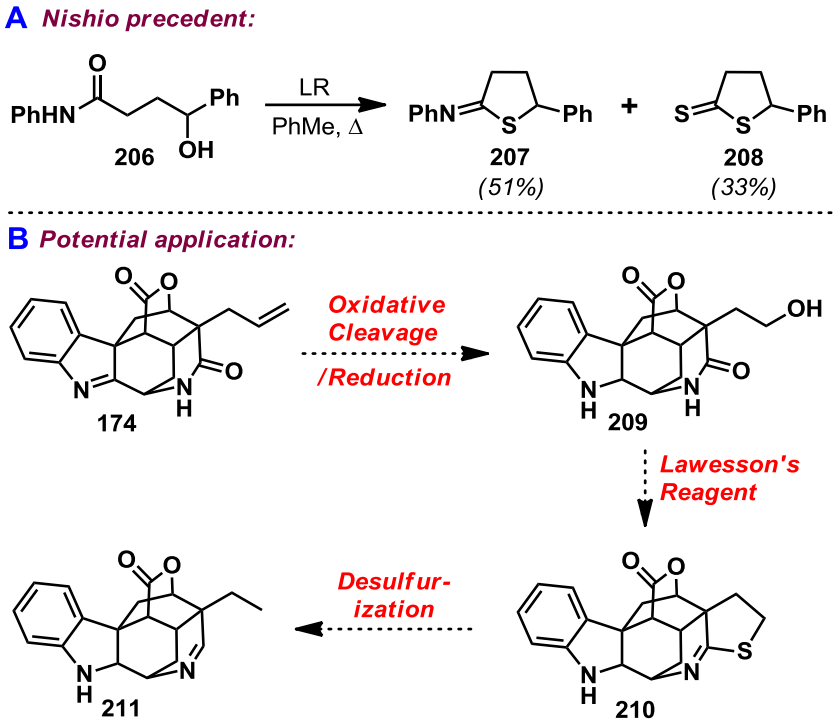
Our first venture in this direction aimed to use a C-18 alcohol or alkoxide as a handle to direct (or activate) the reduction of the C-21 lactam. Thus, ozonolysis of **174** gave aldehyde **203**, which was subjected to reduction with excess $LiAlH_4$ or DIBAL-H from –78 °C to reflux in THF. The goal of this protocol was to initially reduce the aldehyde and then have the resulting aluminate either deliver a hydride intramolecularly to the lactam upon warming or to activate the carbonyl by coordination (see **204**). Unfortunately, in contrast to the cases above, only nonspecific decomposition was observed.



Scheme 47. *Reagents and conditions:* (a) NIS (2.0 equiv), CH_2Cl_2, 23 °C, 20 h, 72%; (b) O_3, MeOH, CH_2Cl_2, -78 °C, 1 min; Me_2S (50 equiv), -78 to 23 °C, 10 h, 34%.

In one of our final avenues of exploration, we then attempted to effect a dehydrative thiation to access the thioimidate **210** in the hopes that a compound of this sort would be able to be desulfurized with Raney nickel to either the desired imine (**211**) or secondary amine (Scheme 48B). Precedent in this regard for the initial step was found in the work of

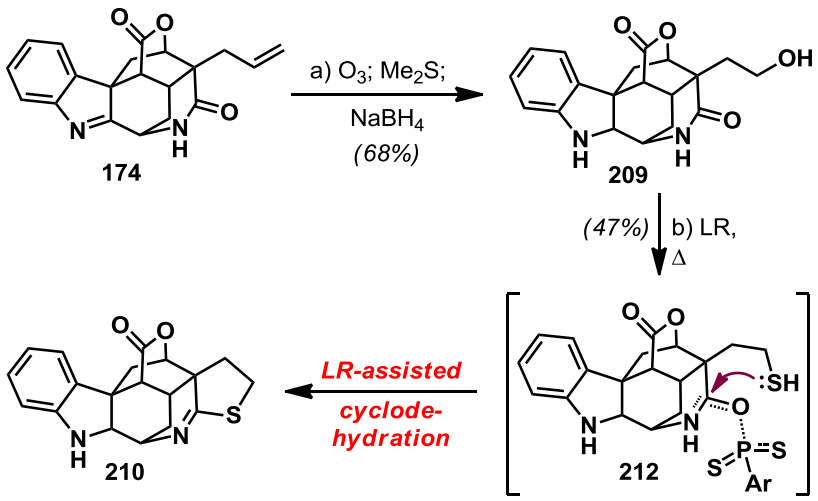
Nishio *et al.*, who had shown this process to be feasible on simple γ-hydroxy lactams such as **206** using Lawesson's reagent (LR) in refluxing toluene (Scheme 48A).[36] Worryingly though, they proposed this transformation to proceed through initial alcohol thiation, followed by lactam thionation and subsequent attack of the nucleophilic thiolactam onto the thiol, expelling H_2S. In our case, it had already been shown that thionation the lactam of **174** was unlikely to occur, as discussed earlier.



Scheme 48. (**A**) Nishio precedent for thioimidate formation from γ-hydroxy lactams; (**B**) Potential use of this process to effect lactam reduction.

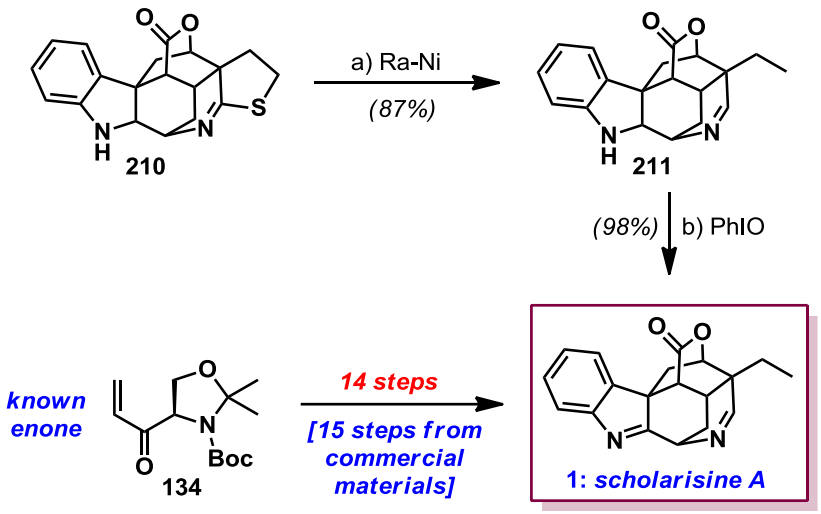
Nevertheless, we resolved to test this process. Initial ozonolysis as performed above, followed by quenching of the ozonide with excess Me_2S and subsequent one-pot reduction under conditions specific for aldehyde reduction (lactone reduction had been observed earlier under typical $NaBH_4$ conditions, see Scheme 31) delivered amino alcohol **209** in 67% yield (Scheme 49). Heating this compound with Lawesson's reagent in a mixture of toluene and THF in a sealed tube for 19 h excitingly delivered the desired

thioimidate **210** in 47% yield. Given the mechanistic issues discussed above, we believe that in our case this transformation occurs through an alcohol thiation/cyclodehydration process, potentially assisted by Lawesson's reagent in the fashion shown (via **212**).



Scheme 49. *Reagents and conditions:* (a) O_3, MeOH, CH_2Cl_2, -78 °C, 2 min; Me_2S (22 equiv), -78 to 23 °C, 16 h; $NaBH_4$ (2.6 equiv), EtOH, CH_2Cl_2, -40 to -10 °C, 1.5 h, 68%; (b) LR (2.1 equiv), THF, PhMe, 110 °C, 16 h, 47%.

With thioimidate **210** in hand, we could now test its desulfurization. In the event, treatment of **210** with an excess of Raney Nickel at 23 °C in THF, smoothly excised the sulfur atom (87% yield), simultaneously forming the imine and the ethyl group of scholarisine A (**1**) in the form of **211** (Scheme 50). Thus, after attempting over 25 different conditions on a range of derivatives, we had finally succeeded in reducing C-21 to the desired imine oxidation state! From dihydro-scholarisine A (**211**), only a final oxidation of the indoline remained. Delightfully, this occurred in almost quantitative yield (98%) using PhIO in CH_2Cl_2 at 23 °C,[3] thus completing our synthesis of scholarisine A (**1**).



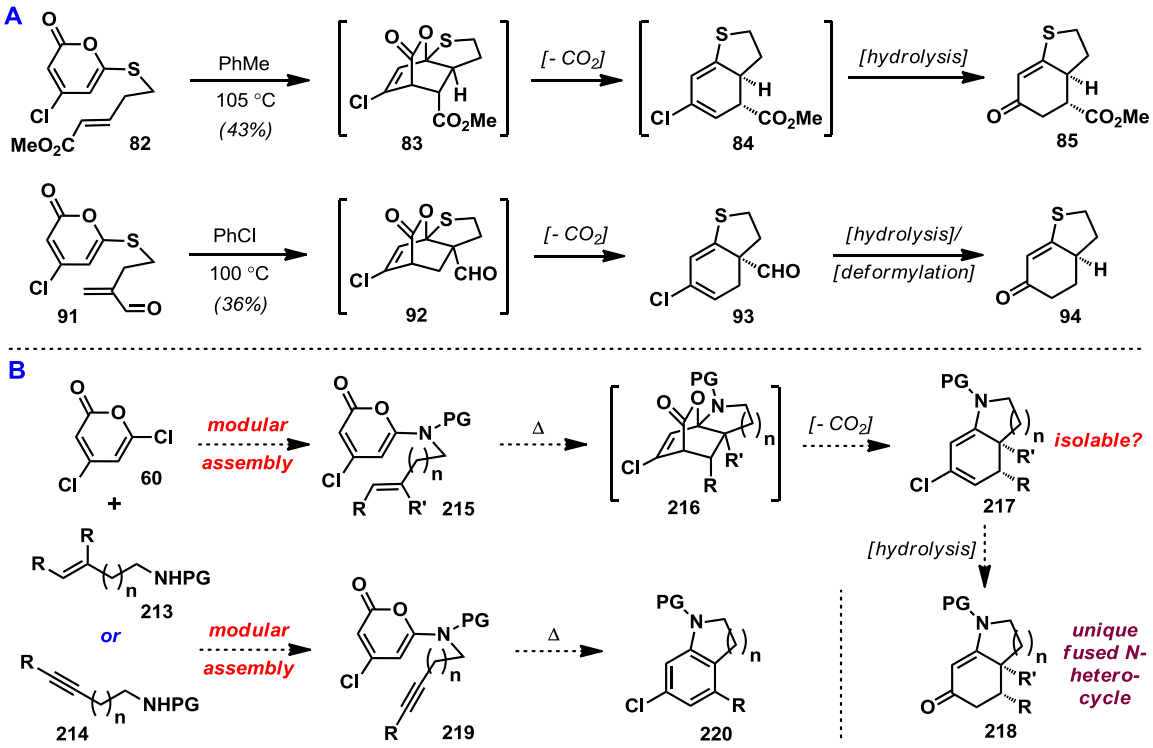
Scheme 50. *Reagents and conditions:* (a) Ra-Ni, THF, 23 °C, 1.5 h, 87%; (b) PhIO, CH_2Cl_2, 23 °C, 16 h, 98%.

The spectral properties of our synthetic **1** agreed with those reported by Luo[2] for the naturally isolated material as well as that synthesized by the Smith group[3] (see Tables 1 and 2, Section 2.9). The optical rotation confirmed that we had prepared the natural antipode $\{[\alpha]_D^{22} = +554.6°$ (c = 0.135, $CHCl_3$)$\}$, though, as found by Smith $\{[\alpha]_D^{24} = +663°$ (c = 0.25, $CHCl_3$)$\}$, the magnitude was far greater than that of the natural material $\{[\alpha]_D^{20} = +188°$ (c = 0.55, $CHCl_3$)$\}$. We ascribe the lower value for the natural material to possible impurities and our slightly lower value versus that of Smith to the imprecision of the instrument and the large absolute value of the optical rotation in this case.

Globally, we had succeeded in preparing (+)-scholarisine A (**1**) in an enantiospecific fashion in 14 steps from known[15] enone **134** and 15 steps from its commercially available Weinreb amide precursor. This length compares favorably to the previous Smith synthesis[3] (20 steps from a known compound, 25 steps from commercial materials) in terms of overall step-economy.

2.6. Extension of Early Unsuccessful IMDA Method to the Preparation of Aromatic and Non-aromatic Heterocycles

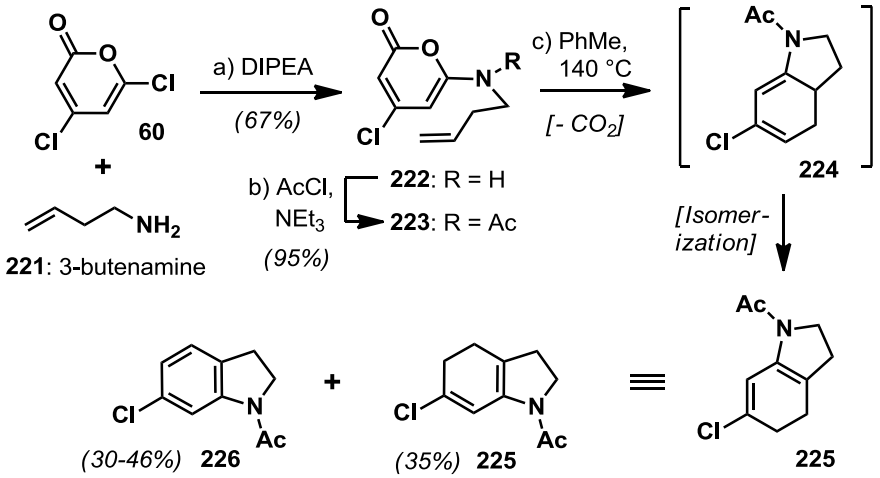
To conclude this chapter, an interesting offshoot from the early IMDA work detailed in section 2.3 will be discussed. Specifically, although the *S*-tethered pyrone Diels–Alder approach bore little fruit en route to **1**, the facile formation of fused heterocyclic compounds **85** and **93**/**94** (summarized below in Scheme 51A) spurred us to investigate the utility of this process for the formation of both aromatic and non-aromatic heterocycles. In particular, we realized that if the modular assembly of IMDA precursors from 4,6-dichloropyrone (**60**) could be extended to nitrogen-linked compounds, then this process would allow access to a range of fused nitrogen-containing ring systems (Scheme 51B). Our initial efforts focused on 5/6-fused systems targeting indoline (**220**, n = 1) and dihydroindoline scaffolds (**217**, and potentially their derived vinylogous amides **218**), structural motifs found in numerous pharmaceutical agents and natural bioactive alkaloids.



Scheme 51. (**A**) Early sulfide-tethered pyrone IMDA approach leads to 5/6-ring systems; (**B**) Possible extension to the synthesis of aromatic and non-aromatic nitrogen-containing heterocycles.

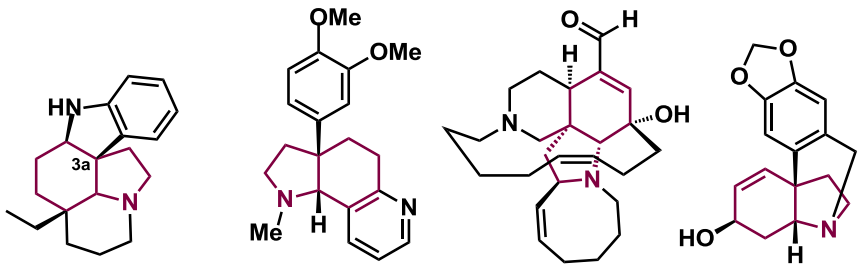
Thus, in collaboration with Mr. Nathaniel Braffman, an undergraduate student who undertook the majority of the early experimental work, we set about testing this idea through the simple amino-alkene IMDA substrate **222** (Scheme 52). Pleasingly, **222** could be straightforwardly assembled from dichloropyrone **60** employing conditions modelled on those used for sulfide formation earlier. Namely, treatment of **60** with 3-butenamine (**221**) and *i*-Pr_2NEt as base at –78 °C in CH_2Cl_2 followed by slow warming to 0 °C (to amplify selectivity for the 6-position) afforded aminopyrone **222** in 67% yield. Heating the free amine **222** in toluene unfortunately led to decomposition, while its *N*-methyl congener gave no reaction; however, protection with an electron-withdrawing group such as acetate gave a species (**223**, 95% yield) that upon heating at 140 °C delivered the dihydroindoline compound **225** (35% yield) along with a sizeable amount of aromatized **226** (typically 30-

46% yield). In this process, the expected Diels–Alder/retro-[4+2] process has occurred to give diene **224** (not observed), followed by alkene isomerization to the presumably more stable **225**. Attempts to limit the formation of aromatic compound **226** through rigorous degassing of the reaction solvent and/or addition of BHT led to no meaningful improvement.



Scheme 52. *Reagents and conditions:* (a) **60** (1.0 equiv), *i*-Pr_2NEt (1.1 equiv), CH_2Cl_2, -78 to 0 °C, 4 h, 67%; (b) AcCl (1.3 equiv), NEt_3 (1.3 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 to 23 °C, 3 h, 95%; (c) PhMe, 140 °C, μW, 4 h, **225**: 35%, **226**: 30-46%.

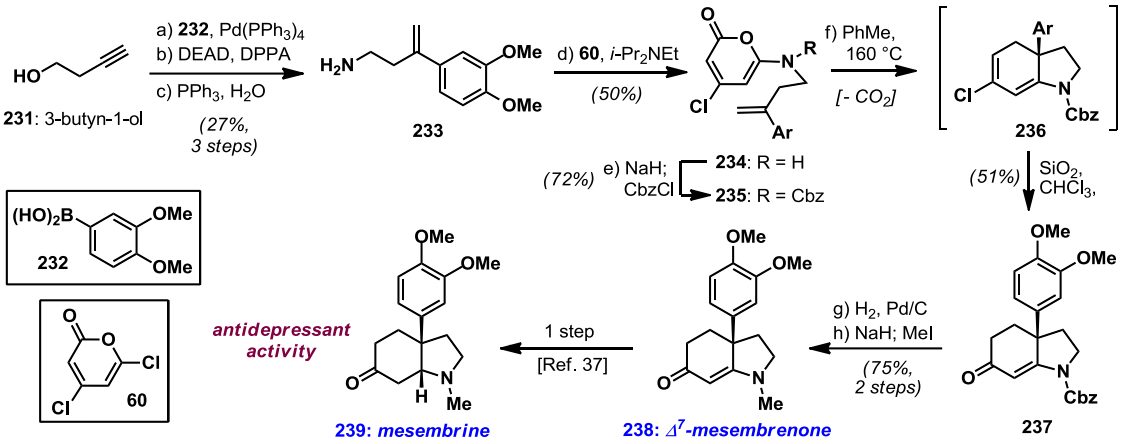
Realizing that dihydroindoline aromatization may be problematic, we resolved to target compounds bearing a quaternary center at C-3a of this scaffold (Scheme 53). Indeed, examination of the literature showed this scaffold (highlighted in purple) to be present in many bioactive alkaloids of the sceletium, amaryllidaceae, aspidosperma and manzamine families, to name a few (see **227-230**, Scheme 53). Moreover, aside from being an intriguing functionality in its own right, the chlorodienamine initially formed might serve as a ready precursor to a vinylogous amide through hydrolysis (analogous to the conversion of **84** to **85**), installing an oxygen atom in a position required for many of the aforementioned natural products.



227: *aspidospermine* **228: *sceletium A-4*** **229: *ircinal A*** **230: *crinine***

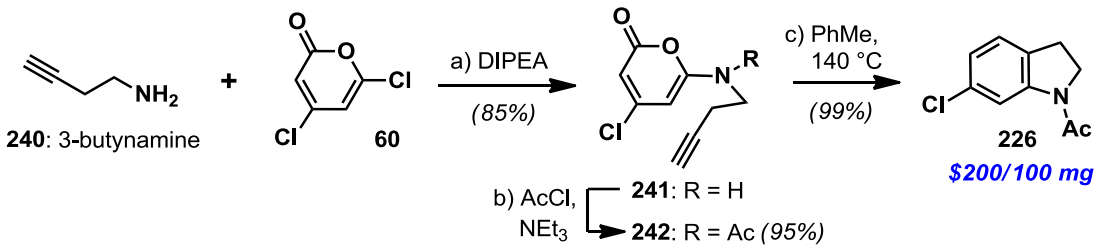
Scheme 53. Alkaloid natural products containing a (per)hydroindoline with a C-3a quaternary center.

As an initial target, we selected the sceletium alkaloid, Δ^7-mesembrenone (**238**, Scheme 54), a minor constituent of *Sceletium namaquense*[37] and a known synthetic precursor[38] to the popular target, mesembrine (**239**), which displays antidepressant activity.[39] The required aryl dienophile was prepared from 3-butyn-1-ol (**231**), through regioselective hydroarylation with boronic acid **232**, followed by Mitsunobu azidation and Staudinger reduction to the primary amine (**233**). Coupling to 4,6-dichloropyrone (**60**) occurred smoothly as above to give pyrone **234** (50% yield), whereafter a Cbz-group was installed on the nitrogen atom (72% yield). Heating **235** in toluene at 160 °C for 10 h, followed by evaporation, gave a mixture of chlorodienamine **236** and vinylogous amide **237**, which, in the same pot, could be stirred in wet $CHCl_3$ with silica gel at 25 °C to convert all material to **237** in 51% overall yield. From **237**, straightforward hydrogenolytic removal of the Cbz-group followed by *N*-methylation of the crude material gave Δ^7-mesembrenone (**238**, 75% yield over the two steps) in only eight steps from commercial materials, a step count that compares well with the reported preparations of **238**.[39] Ms. Pei Gan, a graduate student who recently joined the project, has further extended the process to a range of aromatic (electron-rich, -neutral and -deficient) as well as cyclic alkene-containing dienophiles, auguring well for the substrate scope of the process and its extension towards other alkaloid targets.



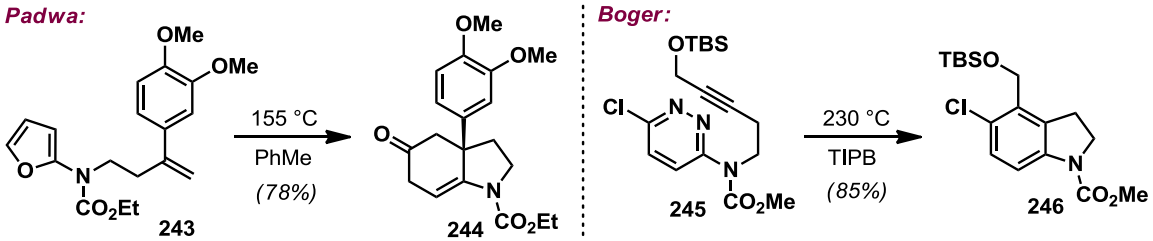
Scheme 54. The total synthesis of Δ^7-mesembrenone. *Reagents and conditions:* (a) **232** (1.2 equiv), AcOH (0.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), 1,4-dioxane, 80 °C, 14 h, 44%; (b) DEAD (1.5 equiv), DPPA (1.5 equiv), PPh_3 (1.5 equiv), THF, 0 to 23 °C, 5 h, 62%; (c) PPh_3 (1.5 equiv), H_2O (1.5 equiv), MeOH, 70 °C, 14 h, 99%; (d) **60** (1.2 equiv), *i*-Pr_2NEt (1.2 equiv), CH_2Cl_2, -78 to 0 °C, 4 h, 50%; (e) NaH (1.5 equiv), DMF, THF, 23 °C, 15 min; CbzCl (3.0 equiv), 0 to 23 °C, 2.5 h, 72%; (f) PhMe, 160 °C, μW, 10 h; SiO_2, $CHCl_3$, 23 °C, 16 h, 51%; (g) H_2 (1 atm), Pd/C (0.2 equiv), EtOAc, 23 °C, 3 h; (h) NaH (2.2 equiv), THF, 23 °C, 10 min; MeI (1.5 equiv), 0 to 23 °C, 45 min, 75% (2 steps).

Additionally, we have shown that the use of alkyne dienophiles in this chemistry readily leads to indolines bearing hard-to-access 4,6-substitution patterns (formally *meta*- to the electron-donating nitrogen atom). Initial proof of concept was achieved with unsubstituted alkyne **242**, which delivered 6-chloroindoline **226** in quantitative yield when subjected to the standard IMDA conditions (140 °C, Scheme 55). Indeed, while **226** is commercially available, it is prohibitively expensive ($200/100 mg), likely reflective of the challenge associated with accessing such substitution. Ms. Gan has likewise gone on to significantly extend the scope of the alkyne IMDA process, which routinely proceeds in quantitative yield to deliver a range of 4,6-disubstituted indolines as useful medicinal building blocks.



Scheme 55. *Reagents and conditions:* (a) **60** (1.0 equiv), *i*-Pr_2NEt (1.1 equiv), CH_2Cl_2, -78 to 0 °C, 4 h, 85%; (b) AcCl (1.3 equiv), NEt_3 (1.3 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 to 23 °C, 3 h, 95%; (c) PhMe, 140 °C, μW, 4 h, 99%.

It should also be mentioned that although the use of a pyrone Diels–Alder reaction to form fused heterocyclic structures is rare[5] (possibly due to a dearth of methods for assembling the required precursors), the concept of using a Diels–Alder disconnection to form similar scaffolds has been elegantly demonstrated in the intramolecular furan Diels–Alder work of Padwa[41] (to access non-aromatic as well as aromatic 5/6-heterocycles), as well as the impressive pyridazine-Diels–Alder method of Boger[42] (for indolines and indoles, Scheme 56). Our method is complementary to both of these protocols in terms of the resulting substitution or oxidation pattern, in the latter case, being better suited for accessing several alkaloid natural products (e.g. **238**).

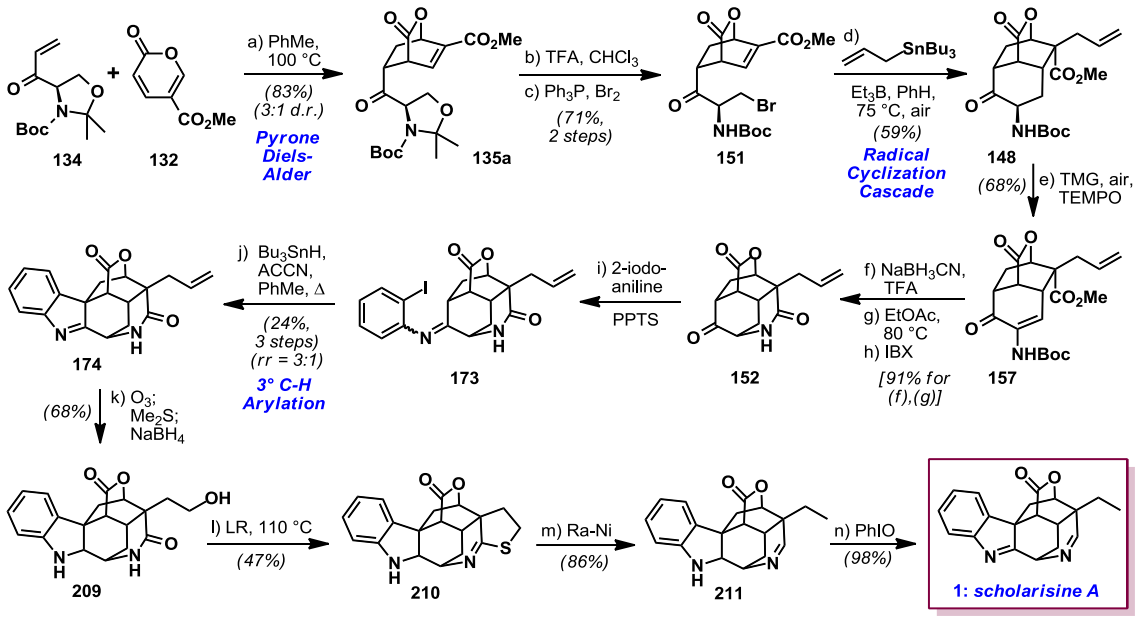


Scheme 56. Related intramolecular Diels-Alder approaches of Padwa and Boger, allowing complementary access to alternate oxidation and substitution patterns.

2.7 Conclusions and Outlook

As detailed in the above sections, we have completed an enantiospecific synthesis of the cage indole alkaloid (+)-scholarisine A (**1**) which proceeded in 14 steps from the known enone **134** and 15 steps from its commercial Weinreb amide precursor as summarized in Scheme 57 below. Our strategy was guided by the notion that a pyrone Diels–Alder reaction, proceeding either intra- or intermolecularly, could rapidly forge the stereochemically rich bicyclic lactone core of this target. Ultimately, key to enabling this concise synthesis was the development of four empowering synthetic solutions:

1. A unique application of underutilized pyrone Diels-Alder chemistry to forge the [2.2.2]-bicyclic lactone of **1** in a scalable and expedient fashion (**132** + **134**→**135a**).
2. A tandem radical cyclization/Keck allylation to simultaneously form the [3.3.1]-bicycle of **1** and its challenging C-20 all-carbon quaternary center (**151**→**148**).
3. A unique indolenine annulation based on a late-stage radical arylation of a tertiary, non-enolizable C-H bond (**152**→**174**).
4. The use of a pendant hydroxyl group to facilitate the chemoselective reduction of an extremely unreactive lactam in the presence of a readily reduced lactone (**209**→**211**).

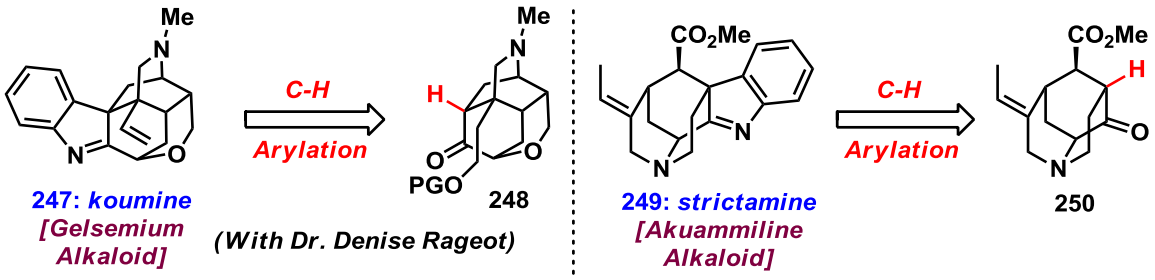


Scheme 57. Summary of our 14-step enantiospecific synthesis of (+)-scholarisine A (**1**) featuring a pyrone Diels-Alder reaction, tandem radical cyclization/Keck allylation and C-H arylation sequence.

As outlined in the preceding section, we have already begun to leverage the expertise gained in pyrone Diels–Alder chemistry towards a broadly useful method for the preparation fused indoline and perhydroindoline heterocycles. Thus far, these studies have culminated in an eight-step preparation of Δ^7-mesembrenone (**238**), with additional synthetic conquests remaining to be achieved.

Similarly, further applications of our powerful indolenine annulation chemistry can also be envisaged, noting that the indolenine motif is common across several indole alkaloid families. Current work (not mentioned above), conducted in collaboration with former post-doctoral fellow Dr. Denise Rageot, has involved its application to the *Gelsemium* alkaloid koumine (**247**),[43] a compound with useful antitumor activity (Scheme 58).[44] Further applications of this arylation can be readily envisaged, particularly where retrosynthetic removal of the indolenine reveals a tertiary, and critically non-enolizable, α-keto-C-H bond, for which established methods (e.g. Fischer indole synthesis) are

ineffective. Indeed, a large subsection of the akuammiline alkaloids (e.g. strictamine, **249**) conform to this pattern and retrosynthetic simplification back to a cage ketone precursor (i.e. **250**) may significantly shorten their synthesis.



Scheme 58. Potential application of the developed C-H arylation method to other alkaloid targets.

Aside from future synthetic studies, we have begun in-depth computational studies (with Dr. Adel ElSohly) to probe two of the key reactions of the sequence through DFT calculations. The first is the pyrone Diels–Alder reaction, where, in particular, we hope to understand the regiochemical outcome and its underlying mechanism and potentially distill out generalizable trends for 4- and 5-substituted pyrones (as shown for methyl coumalate in Section 2.5.3). Secondly, we aim to study the HAT/cyclization reaction, both to confirm the proposed mechanism and to bolster our theory for the observed regioselectivity, hoping ultimately, with additional experimental examples, to arrive at a simple predictive model for which C-H bond is likely to react in this process.

Finally, with sufficient quantities of scholarisine A (**1**) prepared, biological testing of **1** and several related compounds has begun with collaborators in a variety of biomedical fields. We hope to communicate any interesting discoveries in these medicinal arenas in the near future.

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2.9 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. Dry methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), benzene (PhH) and toluene (PhMe) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; triethylamine (Et_3N) was distilled from KOH; acetone, methanol (MeOH), and dimethylformamide (DMF) were purchased in anhydrous form from Sigma-Aldrich and used as received. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and an aqueous solution of cerium ammonium sulfate and ammonium molybdate and heat as visualizing agents. Preparative TLC was carried out on 0.50 mm E. Merck silica gel plates (60F-254). SiliCycle silica gel (60 Å, academic grade, particle size 40-63 μm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-300, DRX-400, DRX-500, and 500 ASCEND instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations are used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer Spectrum Two FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded in the Columbia University Mass

Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (Fast Atom Bombardment). Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter.

Weinreb Amide 136. *N*,*O*-dimethylhydroxylamine hydrochloride (13.1 g, 0.134 mol, 1.1 equiv) and *N*-methylmorpholine (14.7 mL, 0.134 mol, 1.1 equiv) were added to a stirred solution of *N*-Boc-D-serine (25.0 g, 0.122 mol, 1.0 equiv) in CH_2Cl_2 (480 mL) at –5 °C. EDCI (25.7 g, 0.134 mol, 1.1 equiv) was added portionwise over the course of 30 min at –5 °C. Following an additional 1 h of stirring at this temperature after that addition was complete, the reaction contents were quenched by the addition of 1% aqueous HCl (200 mL) and transferred to a separatory funnel, diluting with water (100 mL) and CH_2Cl_2 (150 mL). The layers were then separated and the organic layer was washed sequentially with 1% aqueous HCl (2 × 200 mL), saturated aqueous $NaHCO_3$ (250 mL), and brine (250 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated. The resulting material was essentially pure Weinreb amide **136**, obtained as a white solid (20.5 g, 68% yield), with ^{1}H NMR data that matched that obtained previously by Mochizuki and co-workers.[1]

Enone 134. Following the procedure of Mochizuki,[1] BF_3•OEt_2 (0.15 mL, 1.23 mmol, 0.02 equiv) was slowly added to a stirred solution of Weinreb amide **136** (15.2 g, 61.3 mmol, 1.0 equiv) and 2,2-dimethoxypropane (45.0 mL, 368 mmol, 6.0 equiv) in acetone (25 mL) at 23 °C. After stirring the resultant solution for 2 h at 23 °C, the reaction contents were quenched with Et_3N (0.25 mL) and concentrated directly by rotary evaporation. The resultant residue was dissolved in EtOAc (400 mL) and transferred to a

separatory funnel. The organic layer was then washed sequentially with 10% citric acid (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to afford acetonide-protected Weinreb amide as a clear, colorless oil (17.8 g, 100% yield) that solidified slowly upon standing. The ^1H NMR data for this material matched that obtained previously by Mochizuki and co-workers.[1]

To a stirred solution of the so-obtained acetonide (8.81 g, 30.6 mmol, 1.0 equiv) in THF (200 mL) at 0 °C was added vinylmagnesium bromide (1.0 M in THF, 46.0 mL, 46.0 mmol, 1.5 equiv) was slowly added. The resulting tan solution was then allowed to warm to 23 °C and stirred for 16 h. Upon completion, 1 M aqueous HCl (150 mL) was added rapidly and the reaction contents were transferred to a separatory funnel, diluting with water (80 mL) and EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (250 mL). The combined organic layers were then washed sequentially with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:19→1:4) to give enone **134** (7.45 g, 96% yield) as a clear, colorless oil. The ^1H NMR data for this material matched that obtained previously by Guanti and co-workers.[2]

Diels–Alder Products 135a and 135b. A solution of enone **11** (3.14 g, 12.3 mmol, 1.0 equiv) and methyl coumalate (**12**, 3.47 g, 22.5 mmol, 1.8 equiv) in toluene (25 mL) was heated at 100 °C under an Ar atmosphere in a sealed tube. After stirring at 100 °C for 33 h, the reaction contents were cooled to 23 °C and then were concentrated

directly. Purification of the resultant crude material by flash column chromatography (silica gel, Et_2O/hexanes, 1:9→1:1) gave the major diastereomer **135a** (1.25 g, 25% yield) as a white foam, along with a mixture of major and minor diastereomers **135a** and **135b**, contaminated with a small amount of a structurally undetermined diastereomer/regioisomer **135c** (2.90 g, **135a**:**135b**:**135c** = 1.7:1.0:0.3, 58% yield combined) as a white foam (total yield = 83%, **135a**:**135b**:**135c** = 3.0:1.0:0.3). This mixture could be rechromatographed to obtain additional **135a**. **135a**: R_f = 0.26 (silica gel, Et_2O/hexanes, 7:3); $[\alpha]_D^{23}$ = +49.2° (*c* = 1.01, $CHCl_3$); IR (film) ν_{max} 2980, 1764, 1714, 1684, 1393, 1368, 1265, 1167, 1099, 1011, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (2 rotamers, ~ 2.5:1.0; for integration purposes, 1 minor rotamer proton = 1 H) δ 7.28 (d, *J* = 5.8 Hz, 2.5 H), 7.24 (m, 1 H), 5.81–5.72 (m, 3.5 H), 4.59 (dd, *J* = 7.5, 3.2 Hz, 2.5 H), 4.40 (br d, *J* = 7.7 Hz, 1 H), 4.24–4.05 (m, 6 H), 3.95 (br s, 1 H), 3.86–3.76 (m, 13 H), 3.48–3.37 (m, 3.5 H), 2.57–2.47 (m, 1 H), 2.42 (ddd, *J* = 13.8, 9.7, 4.1 Hz, 2.5 H), 1.97 (dd, *J* = 13.3, 4.2 Hz, 2.5 H), 1.88 (d, *J* = 12.3 Hz, 1 H), 1.72 (s, 3 H), 1.64 (s, 7.5 H), 1.55–1.44 (m, 33 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 205.4, 204.9, 171.2, 170.6, 162.5, 162.3, 152.4, 151.2, 139.4, 138.3, 136.6, 136.0, 95.8, 95.0, 81.6, 81.4, 73.9, 73.8, 65.8, 65.3, 64.8, 64.0, 52.4, 52.3, 43.9, 43.3, 41.6, 39.8, 29.4, 28.8, 28.4, 28.4, 26.1, 25.5, 24.9, 23.4; HRMS (FAB) calcd for $C_{20}H_{28}NO_8^+$ [M + H^+] 410.1815, found 410.1825. **135b**: R_f = 0.22 (silica gel, Et_2O/hexanes, 7:3); $[\alpha]_D^{23}$ = +51.6° (c = 0.315); IR (film) ν_{max} 2979, 1763, 1710, 1379, 1265, 1167, 1093, 1060, 1011, 845, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (2 rotamers, ~ 1.4:1.0; for integration purposes, 1 minor rotamer proton = 1 H) δ 7.43 (d, *J* = 6.3 Hz, 1H), 7.35 (d, *J* = 6.2 Hz, 1.4 H), 5.77 (s, 2.4 H), 4.48 (dd, *J* = 7.6, 3.2 Hz, 1.4 H), 4.42 (d, *J* = 7.9 Hz, 1 H), 4.25–

4.08 (m, 2.4 H), 3.86 (br d, *J* = 6.2 Hz, 3.4 H), 3.79 (s, 7.2 H), 3.39 (ddd, *J* = 10.1, 4.7, 2.1 Hz, 2.4 H), 2.74–2.52 (m, 2.4 H), 2.10 (dd, *J* = 13.5, 4.7 Hz, 1.4 H), 1.86 (d, *J* = 13.5 Hz, 1 H), 1.68 (s, 3 H), 1.64 (s, 4.2 H), 1.54–1.41 (m, 19.8 H), 1.36 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) (2 rotamers, some signal overlap) δ 205.1, 204.0, 171.3, 171.0, 162.5, 152.6, 151.2, 140.2, 139.7, 135.7, 135.4, 95.9, 95.0, 81.8, 81.4, 73.9, 73.5, 65.7, 65.3, 64.5, 64.2, 52.3, 43.6, 43.5, 41.8, 41.4, 29.8, 29.7, 28.4, 26.1, 25.3, 24.9, 23.7; HRMS (FAB) calcd for $C_{20}H_{27}NNaO_8^+$ [M + H^+] 432.1634, found 432.1643.

Alcohol 125. TFA (1.0 mL, 4% v/v) was slowly added to a solution of Diels–Alder product **135a** (1.04 g, 2.53 mmol) in wet $CHCl_3$ (25 mL) at 0 °C. After stirring for 4.25 h at 0 °C, an additional portion of trifluoroacetic acid (0.5 mL) was added and the reaction contents were sitrred for an additional 7.5 h at 0 °C. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and transferred to a separatory funnel, diluting with water (10 mL) and CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:3→7:3) to give alcohol **125** (0.78 g, 83% yield) as a white foam. **125**: R_f = 0.53 (silica gel, EtOAc/hexanes, 7:3); $[\alpha]_D^{23}$ = –5.9° (*c* = 1.16, $CHCl_3$); IR (film) ν_{max} 3393, 2978, 1761, 1710, 1503, 1368, 1287, 1264, 1164, 1007, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 6.4, 2.2 Hz, 1 H), 5.75 (br s, 1 H), 5.55 (d, *J* = 8.1 Hz, 1 H), 4.35 (br s, 1 H), 4.06 – 3.94 (m, 2 H), 3.79 (s, 3 H), 3.78 (m, 1 H), 3.52 (ddd, *J* = 10.0, 4.5, 2.3 Hz, 1 H), 2.61–2.45 (m, 2 H), 1.95 (dd, *J* = 13.6, 4.1 Hz, 1 H), 1.45 (s, 9 H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 206.9, 171.7, 162.5, 155.8, 139.6, 136.0, 81.0, 74.0, 62.7, 59.9, 52.4, 43.7, 42.3, 29.1, 28.4; HRMS (FAB) calcd for $C_{17}H_{24}NO_8^+$ [M + H^+] 370.1502, found 370.1508.

Bromide 151. A solution of Ph_3P (0.755 g, 2.88 mmol, 1.5 equiv) and imidazole (0.197 g, 2.89 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL) was cooled to 0 °C and liquid Br_2 (~ 0.15 mL, 2.85 mmol, 1.5 equiv) was added dropwise until the solution displayed a persistent yellow color. At this point, the cooling bath was removed and the solution allowed to stir at 23 °C for 10 min. The contents were then recooled to 0 °C and a solution of alcohol **125** (0.701 g, 1.90 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 ml + 2 × 0.75 mL washings) was added dropwise. After stirring the mixture for 40 min at 0 °C, the reaction contents were directly loaded onto a short silica gel column (rinsing the flask with CH_2Cl_2) and rapidly flushed with EtOAc/hexanes (2:3) into a large round bottom flask (<3 min for elution) [Note: longer elution times resulted in partial elimination of HBr; for this reason, this reaction process was typically conducted on batches of 0.7 to 1.2 g of starting material **125**, with the final product pooled for the subsequent reaction]. Concentration of the eluent gave bromide **151** (0.702 g, 86%) as a white foam. **151**: R_f = 0.28 (silica gel, EtOAc/hexanes, 3:7); $[\alpha]_D^{23}$ = –14.1° (*c* = 0.475, $CHCl_3$); IR (film) ν_{max} 3363, 2979, 1765, 1713, 1504, 1369, 1286, 1264, 1161, 1092, 1013, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 6.4, 2.1 Hz, 1 H), 5.72 (s, 1 H), 5.47 (d, *J* = 8.6 Hz, 1 H), 4.63 (dt, *J* = 9.1, 4.5 Hz, 1 H), 3.91 (br d, *J* = 4.4 Hz, 1 H), 3.76 (s, 3 H), 3.73 (m, 1 H), 3.57 (dd, *J* = 10.6, 4.5 Hz, 1 H), 3.48 (br d, *J* = 7.6 Hz, 1 H), 2.53 (ddd, *J* = 14.0, 10.1, 4.0 Hz, 1 H), 1.86 (dd, *J* = 13.9, 4.3 Hz, 1 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 204.5, 171.1, 162.3, 155.1, 139.7, 135.8, 81.3, 73.7, 58.1, 52.3, 43.4, 42.1, 32.2, 29.2, 28.3; HRMS (FAB) calcd for $C_{17}H_{23}BrNO_7^+$ [M + H^+] 432.0658, found 432.0664.

Radical Cyclization Product 148. To a solution of bromide **151** (2.12 g, 4.91 mmol, 1.0 equiv) in benzene (55 mL) under air (headspace of capped reaction vessel) was added allyltributylstannane (4.5 mL, 14.66 mmol, 3.0 equiv) followed by Et_3B (1.0 M in hexanes, 1.0 mL, 1.0 mmol, 0.2 equiv) at 23 °C. The reaction mixture was then heated to 75 °C and additional portions of Et_3B (1.0 M in hexanes, 4 × 1.0 mL, 0.2 equiv each portion) were added every hour. After the final addition, the heating bath was switched off and the reaction mixture allowed to cool slowly to 23 °C overnight (13 h). The solution was then concentrated directly and the resultant crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:9→2:3) to give ketone **148** (1.14 g, 59% yield) as a white crystalline solid [Note: on smaller scales, yields typically ranged between 64 and 70%]. **148**: R_f = 0.36 (silica gel, EtOAc/hexanes, 2:3); $[\alpha]_D^{23}$ = –77.0° (*c* = 0.80, $CHCl_3$); IR (film) ν_{max} 2978, 1766, 1711, 1493, 1365, 1321, 1221, 1166, 1012, 924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (m, 1 H), 5.32 (br d, *J* = 4.0 Hz, 1 H), 5.28–5.16 (m, 2 H), 4.90 (dd, *J* = 3.7, 1.7 Hz, 1 H), 4.38 (dt, *J* = 12.9, 6.3 Hz, 1 H), 3.98 (s, 3 H), 3.07 (ddd, *J* = 14.0, 6.6, 3.0 Hz, 1 H), 2.97 (m, 1 H), 2.88 (t, *J* = 3.5 Hz, 1 H), 2.63–2.38 (m, 4 H), 2.20 (br s, 1 H), 1.49 (td, *J* = 13.6, 4.2 Hz, 1 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 172.4, 171.7, 154.9, 131.0, 121.0, 80.0, 75.1, 53.3, 52.2, 51.8, 45.6, 43.3, 42.3, 38.0, 35.9, 28.4, 26.1; HRMS (FAB) calcd for $C_{20}H_{28}NO_7^+$ [M + H^+] 394.1866, found 394.1882.

Pyrazine Dimer 156. **156**: R_f = 0.31 (silica gel, hexanes:EtOAc, 1:4); IR (film) ν_{max} 2925, 1763, 1725, 1443, 1403, 1357, 1297, 1221, 1199, 1160, 1016, 934 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (m, 2 H), 5.27–5.11 (m, 4 H), 4.68 (t, *J* = 2.5 Hz, 2 H), 3.59 (dd, *J* = 17.7, 2.2 Hz, 2 H), 3.50 (s, 6 H), 3.44 (ddt, *J* = 11.7, 4.0, 1.9 Hz, 2 H), 2.98 (dd, *J* = 17.5, 4.9 Hz, 2 H), 2.94 (dd, *J* = 4.6, 2.4 Hz, 2 H), 2.71–2.50 (m, 6 H), 2.49–2.37 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 171.3, 151.9, 147.3, 131.3, 121.0, 75.1, 52.2, 51.5, 43.5, 41.4, 38.0, 33.2, 33.1, 32.7; HRMS (FAB) calcd for $C_{30}H_{33}N_2O_8^+$ [M + H^+] 549.2237, found 549.2256.

Enone 157. To a solution of ketone **148** (1.00 g, 2.55 mmol, 1.0 equiv) in THF (34 mL) under an air atmosphere at 23 °C was sequentially added TMG (0.35 mL, 2.80 mmol, 1.1 equiv) and TEMPO (0.438 g, 2.80 mmol, 1.1 equiv). The reaction flask was then capped and the solution heated at 50 °C for 12.5 h. Upon completion, the reaction contents were cooled to 23 °C and then quenched by the addition of saturated aqueous NH_4Cl (15 mL). The reaction contents were then poured into a separatory funnel, further diluting with water (40 mL). The aqueous layer was extracted with EtOAc (3 × 60 mL), and the organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:19→1:3) to give enone **157** (0.68 g, 68% yield) as a faint orange foam. **157**: R_f = 0.52 (silica gel, EtOAc/hexanes, 3:7); $[\alpha]_D^{23}$ = +22.7° (*c* = 1.35, $CHCl_3$); IR (film) ν_{max} 3404, 2976, 2928, 1767, 1728, 1684, 1358, 1341, 1232, 1156, 1002, 931, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 1 H), 6.99 (s, 1 H), 5.61 (ddt, *J* = 17.3, 10.2, 7.4 Hz, 1 H), 5.26–5.15 (m, 2 H), 4.88 (d, *J* = 4.3 Hz, 1 H), 3.74 (s, 3 H), 3.34 (t, *J* = 3.6 Hz,

1 H), 2.88 (m, 1 H), 2.73 (m, 1 H), 2.63 (dd, *J* = 13.6, 7.1 Hz, 1 H), 2.52–2.38 (m, 3 H), 1.47 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 171.8, 170.9, 152.2, 130.5, 128.7, 122.6, 120.6, 80.8, 76.5, 52.2, 51.9, 41.3, 41.1, 37.0, 36.8, 27.9, 24.6; HRMS (FAB) calcd for $C_{20}H_{26}NO_7^+$ [M + H^+] 392.1709, found 392.1706.

Cage Alcohol 164. A solution of enone **157** (58 mg, 0.148 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was cooled to 0 °C and $NaCNBH_3$ (46 mg, 0.738 mmol, 5.0 equiv) was added in a single portion. Next, TFA (0.2 mL, 2.61 mmol, 17.6 equiv) was added dropwise (with effervescence), and the resulting suspension was stirred vigorously at 0 °C for 40 min. Upon completion, the reaction contents were quenched by the slow addition of saturated aqueous $NaHCO_3$ (5 mL) and the reaction contents were transferred to a separatory funnel, further diluting with EtOAc (10 mL) and water (5 mL). The layers were separated and the aqueous layer was reextracted with EtOAc (2 × 10 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was then dissolved in EtOAc (2.5 mL) and heated at 80 °C for 2 h in a capped, round-bottom flask under an air atmosphere. Upon completion, the reaction contents were cooled to 23 °C, concentrated and purified directly by preparative TLC (silica gel, EtOAc) to give alcohol **164** (36 mg, 91% yield) as a clear, colorless gum [Note: compound **164** was not UV-active nor was it able to be visualized using a range of stains. Thus, PTLC presented the best option for purification, where a faint outline at the top of the product band was visible. The yield dropped slightly on larger scale (180 mg scale, 84%)]. **164**: R_f = 0.15 (silica gel, EtOAc); $[\alpha]_D^{23}$ = +28.8° (*c* = 0.78, CH_3OH); IR (film) ν_{max} 3330, 1752, 1642, 1451, 1361, 1201, 1138, 1054, 957, 719 cm^{-1}; ^{1}H NMR

(400 MHz, CD_3OD) δ 5.71 (dddd, *J* = 17.0, 10.1, 9.2, 5.4 Hz, 1 H), 5.21–5.05 (m, 2 H), 4.45 (t, *J* = 2.5 Hz, 1 H), 3.87 (dd, *J* = 5.3, 3.6 Hz, 1 H), 3.55 (d, *J* = 3.4 Hz, 1 H), 2.95 (dd, *J* = 13.2, 5.5 Hz, 1 H), 2.65 (dd, *J* = 4.3, 2.3 Hz, 1 H), 2.51–2.41 (m, 2 H), 2.16–2.06 (m, 2 H), 1.90 (dt, *J* = 13.5, 3.8 Hz, 1 H), 1.83 (dt, *J* = 13.5, 2.7 Hz, 1 H), 1.72 (ddd, *J* = 15.7, 11.6, 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.4, 174.7, 133.9, 119.6, 83.7, 71.7, 53.0, 50.7, 44.0, 41.6, 34.3, 34.0, 31.0, 26.2; HRMS (FAB) calcd for $C_{14}H_{18}NO_4^+$ [M + H^+] 264.1236, found 264.1234.

HAT/Cyclization Products 174 and 184. Alcohol **164** (0.174 g, 0.66 mmol, 1.0 equiv) was dissolved in EtOAc (8 mL) and IBX (0.652 g, 2.33 mmol, 3.5 equiv) was added at 23 °C. The reaction flask was then capped and the resultant suspension was heated at 80 °C for 14.5 h under an air atmosphere. Upon completion, the reaction contents were cooled to 23 °C and filtered through Celite (rinsing with EtOAc). Direct concentration afforded crude ketone **152** (0.177 g) containing a small amount of IBX-derived side-products as a white foam. [Note: extremely poor mass recovery was observed upon attempted purification of **152**]. Pressing forward without any additional purification, the so-obtained crude **152** was then treated sequentially with 2-iodoaniline (0.162 g, 0.740 mmol, 1.1 equiv) and PPTS (0.015 g, 0.060 mmol, 0.09 equiv). The flask was evacuated and backfilled with Ar (× 3), crushed and activated 4Å molecular sieves (~0.69 g) were added, and then the contents were taken up in a minimal amount of THF (1.8 mL). Toluene (7.2 mL) was added and the resulting suspension then heated at 90 °C for 18 h. Upon completion, the reaction contents were cooled to 23 °C, filtered, and concentrated to give crude imines **173** (0.322 g) as an amber foam. Next, the so obtained

crude imines **173** (typically a 2.4-2.8:1.0 mixture of geometric isomers) was dissolved in degassed toluene (10 mL) and heated at 110 °C under Ar. A solution of (*n*-Bu)$_3$SnH (0.21 mL, 0.794 mmol, 1.2 equiv) and ACCN (194 mg, 0.794 mmol, 1.2 equiv) in degassed toluene (8 mL) was slowly added to the heated solution via syringe pump over the course of 3.75 h. After the addition was complete, the contents were stirred at 110 °C for an additional 45 min before being cooled to 23 °C and concentrated directly. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4→1:0 then MeOH/EtOAc, 1:19→1:9), followed by further purification by PTLC (silica gel, MeOH/Et$_2$O, 3:97) to give indolenine **174** (38.9 mg, 18% yield over three steps) as a slightly opaque gum and its isomer **184** (13.4 mg, 6% yield over three steps) as a clear gum. **174**: R_f = 0.40 (silica gel, EtOAc); $[\alpha]_D^{23}$ = +110.6° (*c* = 0.335, $CHCl_3$); IR (film) ν_{max} 3334, 2928, 1765, 1672, 1443, 1206, 1139, 753, 724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1 H), 7.41 (td, *J* = 7.3, 2.1 Hz, 1 H), 7.34–7.27 (m, 2 H), 6.95 (br d, *J* = 5.7 Hz, 1 H), 5.77 (dtd, *J* = 17.0, 9.8, 5.2 Hz, 1 H), 5.28–5.15 (m, 2 H), 4.79–4.69 (m, 2 H), 3.20 (dd, *J* = 13.2, 5.2 Hz, 1 H), 2.44 (s, 1 H), 2.41–2.24 (m, 5 H), 1.94 (d, *J* = 13.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0, 171.5, 171.0, 153.1, 141.8, 132.0, 129.4, 127.5, 122.5, 121.7, 120.3, 80.4, 52.5, 52.3, 49.9, 49.6, 41.0, 34.8, 34.4, 33.4; HRMS (FAB) calcd for $C_{20}H_{19}N_2O_3^+$ [M + H$^+$] 335.1396, found 335.1399. **184**: R_f = 0.66 (silica gel, EtOAc); $[\alpha]_D^{23}$ = +28.9° (*c* = 0.260, $CHCl_3$); IR (film) ν_{max} 3227, 3076, 2925, 1763, 1666, 1591, 1441, 1383, 1360, 1206, 1048, 1024, 923, 770, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.7 Hz, 1 H), 7.48 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.33 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.11 (d, *J* = 8.0 Hz, 1 H), 5.81 (dtd, *J* = 17.2, 9.8, 5.2 Hz, 1 H), 5.29–5.20 (m, 2 H),

4.69 (t, *J* = 2.4 Hz, 1 H), 3.64 (ddt, *J* = 10.9, 3.7, 1.8 Hz, 1 H), 3.17 (dd, *J* = 13.2, 5.1 Hz, 1 H), 2.74 (dd, *J* = 4.5, 2.2 Hz, 1 H), 2.54–2.48 (m, 2 H), 2.42–2.26 (m, 3 H), 1.65 (dd, *J* = 14.5, 2.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.0, 172.1, 171.7, 153.8, 136.9, 131.8, 131.0, 127.3, 122.5, 121.9, 120.5, 81.3, 66.5, 49.6, 45.7, 40.9, 38.5, 34.3, 34.1, 29.5; HRMS (FAB) calcd for $C_{20}H_{19}N_2O_3^+$ [M + H^+] 335.1396, found 335.1409.

Iodoimidate 202. NIS (4.5 mg, 0.020 mmol, 2.0 equiv) was added to a solution of alkene **174** (3.4 mg, 0.010 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at 23 °C. The resulting reddish solution was stirred at 23 °C for 20 h before being quenched with 10% aqueous $Na_2S_2O_3$ (3 mL). The reaction contents were then transferred to a separatory funnel, further diluting with EtOAc (10 mL) and water (5 mL). The layers were separated and the aqueous layer was reextracted with EtOAc (10 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by PTLC (silica gel, EtOAc) to give iodoimidate **202** (3.4 mg, 72% yield) as a white crystalline solid. Alternatively, **202** could also be prepared by adding a solution of IDSI (10.6 mg, 0.013 mmol, 1.2 equiv) in $MeNO_2$ (0.15 mL) dropwise to a solution of alkene **202** (3.7 mg, 0.011 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at 0 °C. TLC analysis after 30 min of stirring at 0 °C indicated that a small portion of starting material remained, so an additional aliquot of IDSI (4.6 mg, 0.006 mmol, 0.5 equiv) in $MeNO_2$ (0.05 mL) was added. After stirring for a further 5 min at 0 °C, the reaction contents were quenched with a mixture of saturated aqueous $NaHCO_3$ and 10% aqueous Na_2SO_3 (1:1, 6 mL) and transferred to a separatory funnel, further diluting with CH_2Cl_2 (10 mL) and water (5 mL). The layers were separated and the aqueous layer was reextracted with

CH_2Cl_2 (10 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by PTLC (silica gel, EtOAc) to give iodoimidate **202** (1.4 mg, 27% yield) as a white crystalline solid. **202**: R_f = 0.37 (silica gel, EtOAc); $[\alpha]_D^{23}$ = +267.4° (*c* = 0.175, $CHCl_3$); IR (film) ν_{max} 2929, 1763, 1686, 1454, 1340, 1202, 1061, 999, 899, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 1 H), 7.41 (td, *J* = 7.4, 1.8 Hz, 1 H), 7.32 – 7.25 (m, 2 H), 5.19 (br s, 1 H), 4.78 (d, *J* = 4.9 Hz, 1 H), 4.69 (dddd, *J* = 9.7, 7.4, 5.6, 4.1 Hz, 1 H), 3.52 (dd, *J* = 10.3, 4.2 Hz, 1 H), 3.37 (dd, *J* = 10.3, 7.4 Hz, 1 H), 2.93 (dd, *J* = 13.0, 5.6 Hz, 1 H), 2.56 (brd, *J* = 2.1 Hz, 1 H), 2.41 (d, *J* = 2.3 Hz, 1 H), 2.22 (d, *J* = 2.5 Hz, 2H), 2.16 (ddd, *J* = 13.7, 4.1, 2.9 Hz, 1 H), 1.92 (dd, *J* = 13.0, 9.7 Hz, 1 H), 1.84 (d, *J* = 13.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 171.0, 170.9, 153.5, 141.7, 129.4, 127.2, 122.2, 121.6, 77.6, 76.7, 57.4, 52.3, 49.8, 47.6, 40.1, 34.1, 33.9, 33.6, 7.0; HRMS (FAB) calcd for $C_{20}H_{18}IN_2O_3^+$ [M + H^+] 461.0362, found 461.0352.

Amino Alcohol 209. Ozonized oxygen was passed through a solution of alkene **174** (31.2 mg, 0.0933 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (4:1, 4.0 mL) at –78 °C. After 2 min, at which point the solution had become a faint but persistent blue, the ozonizer was switched off and the solution was flushed with oxygen gas for 5 min. Me_2S (0.15 mL, 2.04 mmol, 21.9 equiv) was added at –78 °C and the solution was allowed to warm to 23 °C. After stirring for an additional 16 h at 23 °C, the reaction mixture was concentrated directly. The resultant residue was then dissolved in CH_2Cl_2/EtOH (2:1, 3.0 mL), cooled to –40 °C, and $NaBH_4$ (9.1 mg, 0.241 mmol, 2.6 equiv) was added. The reaction mixture was then allowed to warm slowly to –10 °C over the course of 1.5 h, at

which point 1 M aqueous Rochelle's salt solution (2 mL) was added. After transferring to a separatory funnel and diluting with water (5 mL), the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by PTLC (silica gel, MeOH/EtOAc, 1:19) to give alcohol **209** (21.5 mg, 68% yield) as a fine white solid. **209**: R_f = 0.22 (silica gel, MeOH/EtOAc, 1:9); $[\alpha]_D^{23}$ = +64.3° (*c* = 0.165, CH_3OH); IR (film) ν_{max} 3319, 2933, 1751, 1649, 1466, 1199, 1137, 1054, 1018, 752 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.08 (td, *J* = 7.6, 1.3 Hz, 1 H), 6.92 (d, *J* = 7.3 Hz, 1 H), 6.77–6.72 (m, 2 H), 4.60 (t, *J* = 2.5 Hz, 1 H), 3.81 (d, *J* = 3.0 Hz, 1 H), 3.63 (d, *J* = 7.0 Hz, 2 H), 3.58 (br s, 1 H), 2.52–2.42 (m, 2 H), 2.34–2.22 (m, 3 H), 2.13–2.03 (m, 2 H), 1.77 (dt, *J* = 13.4, 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.8, 174.6, 150.7, 134.6, 129.6, 122.8, 120.4, 111.7, 83.9, 73.5, 59.1, 49.2 (HSQC), 48.9, 48.5 (HSQC), 43.8, 40.4, 36.5, 33.9, 27.0; HRMS (FAB) calcd for $C_{19}H_{21}N_2O_4^+$ [M + H^+] 341.1501, found 341.1482.

Thioimidate 210. To a vial containing alcohol **209** (15.2 mg, 0.0449 mmol, 1.0 equiv) was added Lawesson's reagent (39.0 mg, 0.0965 mmol, 2.1 equiv) at 23 °C. The vial was evacuated and backfilled with Ar (× 3) and the contents taken up in a small amount of THF (1.0 mL). Toluene (3.0 mL) was then added and the vial was capped and heated to 110 °C for 16.5 h. Upon completion, the reaction contents were cooled to 23 °C, the vial was opened, and the contents were transferred directly to a separatory funnel, diluting with EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the organic phase washed again with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layers were then back-extracted with EtOAc (10 mL) and the combined

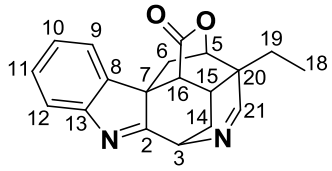
organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by PTLC (silica gel, EtOAc) to give thioimidate **210** (7.1 mg, 47% yield) as an off-white solid. **210**: R_f = 0.25 (silica gel, EtOAc); $[\alpha]_D^{23}$ = +162.9° (*c* = 0.145, $CHCl_3$); IR (film) ν_{max} 3350, 2927, 1761, 1620, 1482, 1466, 1354, 1245, 1188, 1066, 970, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (td, *J* = 7.7, 1.3 Hz, 1 H), 6.97 (d, *J* = 7.0 Hz, 1 H), 6.83 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.74 (d, *J* = 7.8 Hz, 1 H), 4.70 (t, *J* = 2.6 Hz, 1 H), 4.39 (s, 1 H), 3.95 (br s, 1 H), 3.67 (s, 1 H), 3.37 (td, *J* = 11.6, 6.0 Hz, 1 H), 3.20 (dd, *J* = 11.6, 7.9 Hz, 1 H), 2.51 (dd, *J* = 12.9, 6.0 Hz, 1 H), 2.48–2.41 (m, 2 H), 2.19 (br s, 1 H), 2.13–1.92 (m, 4 H), 1.69 (dt, *J* = 13.8, 3.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 173.1, 148.8, 133.2, 128.9, 122.4, 120.4, 110.9, 76.7, 68.2, 56.2, 51.6, 48.1, 43.2, 35.9, 35.4, 32.3, 28.3, 24.4; HRMS (FAB) calcd for $C_{19}H_{19}N_2O_2S^+$ [M + H^+] 339.1167, found 339.1154.

Imine 211. A suspension of Raney® Nickel (2800, 5 drops of aqueous slurry from a Pasteur pipette, excess) was added to a round bottom flask under Ar and rinsed with THF (2 × 2 mL), syringing off the solvent each time. A solution of thioimidate **211** (5.0 mg, 0.0148 mmol, 1.0 equiv) in THF (1.0 mL + 2 × 0.5 mL washings to complete the transfer) was then added dropwise at 23 °C and the resultant suspension was stirred vigorously at 23 °C for 1 h. Upon completion, the reaction mixture was filtered through a Celite (rinsing with EtOAc then MeOH) and concentrated directly. The resultant crude product was purified by PTLC (silica gel, EtOAc) to give **211** (3.9 mg, 86% yield) as a white crystalline solid. **211**: R_f = 0.10 (silica gel, EtOAc); $[\alpha]_D^{23}$ = +128.2° (*c* = 0.050, $CHCl_3$); IR (film) ν_{max} 3352, 2917, 1754, 1612, 1466, 1240, 1191, 1067, 754 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 7.71 (br s, 1 H), 7.11 (td, *J* = 7.6, 1.3 Hz, 1 H), 6.95 (d, *J* = 7.3 Hz, 1 H), 6.82 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.75 (d, *J* = 7.9 Hz, 1 H), 4.55 (t, *J* = 2.5 Hz, 1 H), 4.38 (br s, 1 H), 3.92 (br s, 1 H), 3.65 (br s, 1 H), 2.42 (d, *J* = 1.6 Hz, 1 H), 2.34 (dd, *J* = 15.2, 2.4 Hz, 1 H), 2.12 (d, *J* = 13.3 Hz, 1 H), 1.99 (br s, 1 H), 1.91 (dd, *J* = 15.1, 2.1 Hz, 1 H), 1.83 (q, *J* = 7.5 Hz, 2 H), 1.64–1.57 (m, 1 H), 0.96 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 169.1, 148.6, 133.4, 128.8, 122.3, 120,3, 110.8, 80.5, 67.2, 53.9, 48.3, 46.9, 43.2, 36.9, 31.0, 30.4, 24.9, 8.8; HRMS (FAB) calcd for $C_{19}H_{21}N_2O_2^+$ [M + H^+] 309.1603, found 309.1617.

Scholarisine A (**1**). To a solution of imine **211** (3.9 mg, 0.013 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at 23 °C was added PhIO[3] (15.0 mg, 0.068 mmol, 5.4 equiv). After stirring for 1 h at 23 °C the reaction mixture was filtered through Celite (rinsing with additional CH_2Cl_2) and concentrated directly. The crude product was purified by PTLC (silica gel, EtOAc) to give scholarisine A (**1**, 3.8 mg, 98% yield) as a white crystalline solid. **1**: R_f = 0.48 (silica gel, MeOH/EtOAc, 1:9); $[\alpha]_D^{23}$ = +554.6° (*c* = 0.135, $CHCl_3$); IR (film) ν_{max} 2931, 1762, 1642, 1576, 1457, 1359, 1307, 1207, 1066, 1056, 988, 774, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.40 (td, *J* = 7.3, 1.9 Hz, 1 H), 7.30–7.23 (m, 2 H), 5.45 (s, 1 H), 4.66 (t, *J* = 2.5 Hz, 1 H), 2.30 (br s, 2 H), 2.14 (dd, *J* = 15.2, 2.4 Hz, 1 H), 2.07 (dd, *J* = 15.2, 2.7 Hz, 1 H), 2.04–1.93 (m, 3 H), 1.87 (br d, *J* = 13.3 Hz, 1 H), 1.05 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 171.5, 170.0, 153.5, 142.2, 129.2, 127.1, 122.3, 121.5, 78.7, 58.5, 53.3, 50.3, 47.8, 35.0, 33.4, 32.5, 30.4, 8.9; HRMS (FAB) calcd for $C_{19}H_{19}N_2O_2^+$ [M + H^+] 307.1447, found 307.1462. All spectral data matched that reported by Luo[4] and Smith[5]

for their natural and synthetic samples of **1**, respectively. The optical rotation, $[\alpha]_D^{23}$ = +554.6° (*c* = 0.135, $CHCl_3$), is of the same sign as those reported by Luo [$[\alpha]_D^{20}$ = +188° (*c* = 0.55, $CHCl_3$)][4] and Smith [$[\alpha]_D^{24}$ = +663° (*c* = 0.25, $CHCl_3$)][5], although the magnitude more closely matches that of Smith and co-workers. For a comparison of NMR shifts, see Tables S1 and S2.



1: scholarisine A

Table 1: Comparison of ^{1}H NMR shifts (δ) of natural[4] **1**, Smith[5] and co-workers' synthetic **1** and our own synthetic **1**.

Carbon	*Natural **1****	*Synthetic **1** (Smith)*	*Synthetic **1** (Snyder)*
2			
3	5.45 (br s, 1 H)	5.45 (br s, 1 H)	5.45 (br s, 1 H)
5	4.66 (br s, 1 H)	4.65 (t, *J* = 2.4 Hz, 1 H)	4.66 (t, *J* = 2.5 Hz, 1 H)
6	2.11 (br d, *J* = 17 Hz, 1 H) 2.09 (br d, *J* = 17 Hz, 1 H)	2.13 (dd, *J* = 15.2, 2.3 Hz, 1H), 2.07 (dd, J = 15.2, 2.6 Hz, 1H)	2.14 (dd, *J* = 15.2, 2.4 Hz, 1 H), 2.07 (dd, *J* = 15.2, 2.7 Hz, 1 H)
7			
8			
9	7.26 (d, *J* = 7.5 Hz, 1 H)	7.29 – 7.23 (m, 1 H)	7.30 – 7.23 (m, 2 H)
10	7.26 (t, *J* = 7.5 Hz, 1 H)	7.29 – 7.23 (m, 1 H)	7.30 – 7.23 (m, 2 H)
11	7.40 (t, *J* = 7.5 Hz, 1 H)	7.39 (td, *J* = 7.4, 1.6 Hz, 1 H)	7.40 (td, *J* = 7.3, 1.9 Hz, 1 H)
12	7.65 (d, *J* = 7.5 Hz, 1 H)	7.65 (d, *J* = 7.7 Hz, 1 H)	7.65 (d, *J* = 7.8 Hz, 1 H)
13			
14	1.77 (br d, *J* = 12.0 Hz, 1 H), 2.02 (br d, *J* = 12.0 Hz, 1 H)	1.87 (br d, *J* = 13.5 Hz, 1 H), 2.04 – 1.93 (m, 1 H)	1.87 (br d, *J* = 13.3 Hz, 1 H), 2.04 – 1.93 (m, 1 H)
15	2.30 (br s, 1 H)	2.30 (br s, 1 H)	2.30 (br s, 1 H)
16	2.30 (br s, 1 H)	2.30 (br s, 1 H)	2.30 (br s, 1 H)
18	1.04 (t, *J* = 8.0 Hz, 3 H)	1.04 (t, *J* = 7.5 Hz, 3	1.05 (t, *J* = 7.5 Hz, 3

		H)	H)
19	1.99 (q, *J* = 8.0 Hz, 2 H)	2.04 – 1.93 (m, 2 H)	2.04 – 1.93 (m, 2 H)
20			
21	7.85 (s, 1 H)	7.85 (s, 1 H)	7.85 (s, 1 H)
C=O			

*Referenced to residual $CHCl_3$ at 7.23 ppm; both we and Smith reference $CHCl_3$ at 7.26 ppm.

Table 2: Comparison of ^{13}C NMR shifts (δ) of natural[4] **1**, Smith[5] co-workers' synthetic **1** and our own synthetic **1**.

Carbon	*Natural **1****	*Synthetic **1** (Smith)*	*Synthetic **1** (Snyder)*
2	180.1	180.3	180.3
3	58.2	58.5	58.5
5	78.5	78.7	78.7
6	34.7	35.0	35.0
7	53.1	53.3	53.3
8	142.0	142.2	142.2
9	122.1	122.3	122.3
10	126.9	127.1	127.1
11	129.0	129.2	129.2
12	121.3	121.5	121.5
13	153.2	153.5	153.5
14	33.2	33.4	33.4
15	32.2	32.5	32.5
16	50.0	50.3	50.3
18	8.7	8.9	8.9
19	30.1	30.4	30.4
20	47.5	47.8	47.8
21	169.8	169.9	170.0
C=O	171.4	171.5	171.5

*Referenced to $CDCl_3$ at 77.00 ppm; both we and Smith reference $CDCl_3$ at 77.16 ppm.

Dihydroindoline 225. A microwave vial containing amido pyrone **223** (10 mg, 0.041 mmol, 1.0 equiv) was backfilled with argon gas three times before toluene (1 mL) was added. The tube was sealed, heated to 140 °C under microwave irradiation for 18

hours. After returning to 23 °C, the solution was concentrated and the resulting crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1) to give dihydroindoline **225** (3 mg, 37% yield) as white crystalline solid. Additionally, aromatized product **226** (3 mg, 37% yield) was also recovered. **225**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 4.1, 2.2 Hz, 1 H), 3.89 – 3.79 (m, 2 H), 3.71 (q, *J* = 7.5, 5.9 Hz, 2H), 2.79 (td, *J* = 8.7, 8.2, 3.2 Hz, 2 H), 2.53 (t, *J* = 8.9 Hz, 2H), 2.05 (s, 3 H).

Amine 233. 3,4-dimethoxyphenyl boronic acid (**232**, 1.67 g, 9.172 mmol, 1.3 equiv) dissolved in EtOH (10 mL) was added dropwise to a stirred solution of 3-bromo-3-buten-1-ol (700 µL, 7.056 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (244 mg, 0.212 mmol, 3 mol%) in 2 M aqueous Na_2CO_3 (7 mL) and benzene (14 mL) at 23 °C. Following an additional minute of stirring at this temperature, the reaction was heated up to 75 °C and allowed to reflux for 14 hours. After returning to 23 °C, the reaction contents were quenched by the dropwise addition of 30% H_2O_2 (1 mL), allowed to stir for 30 additional minutes and then transferred to a separatory funnel, diluting with Et_2O (20 mL). The layers were separated and the aqueous layer was extracted a second time with Et_2O (20 mL). The combined organic layers were washed with brine (20 mL) before being dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 0:1→9:11) to give the styrenyl alcohol (903 mg, 61% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 – 6.89 (m, 2 H), 6.81 (d, *J* = 8.9 Hz, 1 H), 5.32 (d, *J* = 1.4 Hz, 1 H), 5.07 (q, *J* = 1.3 Hz, 1 H), 3.86 (d, *J* = 4.4 Hz, 6 H), 3.71 (t, *J* = 6.5 Hz, 2 H), 2.74 (td, *J* = 6.5, 1.1 Hz, 2 H). [Note: this alcohol

could also be prepared from 3-butyn-1-ol (**231**) in 44% yield through a Pd-catalyzed hydroarylation using **232**].

This alcohol (196 mg, 0.941 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (6 mL), cooled to 0 °C and NEt_3 (150 µL, 1.129 mmol, 1.2 equiv) was added, followed by dropwise addition of MsCl (80 µL, 1.035 mmol, 1.1 equiv). The reaction was allowed to slowly warm to 23 °C over 24 hours. At this point, the reaction contents were quenched by the addition of water (10 mL) and transferred to a separatory funnel, diluting with CH_2Cl_2 (5 mL). The organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The resulting crude product (260 mg) was subsequently dissolved in DMF (5 mL) and NaN_3 (118 mg, 1.816 mmol, 1.9 equiv) was added in a single portion at 23 °C. The reaction was heated to 55 °C and allowed to stir at this temperature for 15 hours. After returning to 23 °C, the reaction contents were quenched with water (20 mL) and then transferred to a separatory funnel, diluting with Et_2O (20 mL). The layers were separated and the aqueous layer was further extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with water (20 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 0:1→1:4) to give the azide (187 mg, 85% yield, two steps) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 – 6.89 (m, 2 H), 6.84 (d, *J* = 8.9 Hz, 1 H), 5.33 (d, *J* = 1.1 Hz, 1 H), 5.12 (q, *J* = 1.2 Hz, 1 H), 3.90 (d, *J* = 3.5 Hz, 6 H), 3.37 (t, *J* = 7.1 Hz, 2 H), 2.78 (td, *J* = 7.1, 1.1 Hz, 2 H). [Note: this azide could also be prepared from the corresponding alcohol in one step in 62% yield through a Mitsunobu azidation].

To a stirred solution of this azide (107 mg, 0.479, 1.0 equiv) in MeOH (5 mL) at 23 °C was added PPh_3 (188 mg, 0.719 mmol, 1.5 equiv) and H_2O (12 μL, 0.719 mmol, 1.5 equiv). The reaction was heated to 70 °C and allowed to stir for 14 hours. After returning to 23 °C, the solution was concentrated and the resulting crude product was purified by flash chromatography (silica gel, NH_4OH/MeOH/CH_2Cl_2, 1:5:54) to give amine **233** (99 mg, quantitative yield) as a clear, colorless oil. **233**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 2 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 5.30 (d, *J* = 1.4 Hz, 1 H), 5.05 (q, *J* = 1.3 Hz, 1 H), 3.89 (d, *J* = 4.4 Hz, 6 H), 2.82 (t, *J* = 6.7 Hz, 2 H), 2.64 (dd, *J* = 7.3, 6.1 Hz, 2 H).

Amino Pyrone 234. Amine **233** (200 mg, 0.965 mmol, 1.0 equiv), followed by *i*-Pr_2NEt (200 μL, 1.158 mmol, 1.2 equiv) were added dropwise to a stirred solution of 4,6-dichloro-2-pyrone (**60**, 191 mg, 1.158 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) at -78 °C. Following an additional minute of stirring at this temperature, the reaction was allowed to slowly warm to 23 °C over three hours. After an additional hour of stirring at this temperature, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (5 mL) and transferred to a separatory funnel, diluting with water (10 mL) and CH_2Cl_2 (5 mL). The organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 0:1→2:3) to give amino pyrone **234** (160 mg, 49% yield) as a yellow oil. **234**: R_f = 0.45 (silica gel, EtOAc/hexanes, 3:2); IR (film) ν_{max} 3300, 2950, 1700, 1588, 1510, 1450, 1244, 1060, 200 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 6.97 – 6.88 (m, 2 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 5.54 (d, *J* = 1.7 Hz, 1 H), 5.37 – 5.30 (m, 2 H), 5.09 (dd, *J* = 5.3, 1.4 Hz, 2 H), 3.90 (d, *J* = 5.2 Hz, 6 H), 3.24 (q, *J* = 6.4 Hz, 2 H), 2.86 – 2.77 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 160.3, 155.9, 149.4, 149.2, 144.1, 132.2, 118.6, 114.4, 111.2, 109.6, 96.9, 82.4, 56.1, 40.3, 34.7; HRMS (FAB) calcd for $C_{17}H_{18}ClNO_4$ 335.0924, found 335.0928.

***N*-Cbz Pyrone 235**. NaH (60% in mineral oil, 21 mg, 0.536 mmol, 1.5 equiv) was added to a stirred solution of amino pyrone **234** (120 mg, 0.357 mmol, 1.0 equiv) in 2:1 THF/DMF (4.5 mL) at 0 °C and the solution was then warmed to 23 °C. After 15 minutes of additional stirring at this temperature, benzyl chloroformate (153 µL, 1.072 mmol, 3.0 equiv) was added dropwise to the reaction contents. After 2.5 hours of stirring, the reaction was quenched with saturated aqueous NH_4Cl, transferred to a separatory funnel, diluting with H_2O (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous layer was further extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 0:1→3:7) to give protected amino pyrone **235** (120 mg, 72% yield) as a yellow oil. **235**: R_f = 0.27 (silica gel, EtOAc/hexanes, 3:7); IR (film) ν_{max} 3420, 2932, 1739, 1597, 1516, 1461, 1400, 1259, 1187, 1144, 1024, 806, 763, 734, 698, 581 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 5 H), 6.97 – 6.88 (m, 2 H), 6.73 (d, *J* = 8.2 Hz, 1 H), 6.57 (d, *J* = 1.7 Hz, 1 H), 6.04 (d, *J* = 1.6 Hz, 1 H), 5.30 (d, *J* = 1.2 Hz, 1 H), 5.23 (s, 2 H), 5.02 (d, *J* = 1.2 Hz, 1 H), 3.98 – 3.90 (m, 2 H), 3.87 (d, *J* = 0.8 Hz, 6 H), 2.90 – 2.81 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 154.6, 154.3, 152.8, 149.1, 149.1, 144.0, 135.0, 132.5, 128.9,

128.5, 118.5, 113.7, 111.1, 109.3, 106.8, 98.3, 69.1, 56.1, 56.0, 46.4, 35.0; HRMS (FAB) calcd for $C_{25}H_{24}ClNO_6$ 469.1292, found 469.1310.

Hydrolyzed Diels–Alder Product 237. A microwave vial containing *N*-Cbz pyrone **235** (52 mg, 0.111 mmol, 1.0 equiv) was backfilled with argon gas three times toluene (4 mL) was added. The solution was then degassed by argon sparge for 15 minutes. The tube was then sealed and heated to 160 °C under microwave irradiation for ten hours. After returning to 23 °C, the solution was concentrated and the resulting crude product was dissolved in $CHCl_3$ (1.5 mL) and silica gel (120 mg) was added to the reaction mixture. The resulting slurry was allowed to stir for 15 hours at 23 °C. Finally, the reaction contents were filtered, concentrated, purified by preparative TLC (silica gel, EtOAc/hexanes, 3:2) to give hydrolyzed Diels–Alder adduct **237** (23 mg, 51% yield) as a yellow oil. **237**: R_f = 0.16 (silica gel, EtOAc/hexanes, 3:2); IR (film) ν_{max} 2925, 1725, 1648, 1612, 1514,1456, 1392, 1392, 1307, 1207, 1141, 1025, 861, 766, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5 H), 6.85 – 6.75 (m, 3 H), 6.69 (s, 1 H), 5.27 (q, *J* = 12.2 Hz, 2 H), 3.90 – 3.83 (m, 4 H), 3.80 (s, 3 H), 3.31 (ddd, *J* = 11.9, 10.9, 5.6 Hz, 1 H), 2.47 – 2.30 (m, 2 H), 2.28 – 1.90 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 162.9, 152.6, 149.3, 148.6, 135.5, 132.7, 128.8, 128.7, 128.5, 119.5, 111.2, 109.9, 109.9, 68.4, 56.1, 56.1, 51.8, 47.9, 37.8, 36.4, 33.3, 29.8; HRMS (FAB) calcd for $C_{24}H_{26}NO_5^+$ 408.1805, found 408.1795.

Alternate Preparation of Hydrolyzed Diels-Alder Product 237. A microwave vial containing *N*-Cbz pyrone **235** (120 mg, 0.256 mmol, 1.0 equiv) was backfilled with

argon gas three times toluene (10 mL) was added. The solution was then degassed by argon sparge for 15 minutes. Water (18 μL, 0.999 mmol, 3.9 equiv) was then added and the tube was sealed and heated to 160 °C under microwave irradiation for ten hours. After returning to 23 °C, the solution was concentrated and the resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 3:7→3:2) to give hydrolyzed Diels–Alder product **237** (34 mg, 33% yield) as a yellow oil. Additionally, unhydrolyzed Diels–Alder product **236** (72 mg, 66% yield) was also recovered and subsequently hydrolyzed to **237** by dissolution in MeOH (5 mL) and stirring for 5 minutes. After this time, the solution was concentrated to give hydrolyzed Diels–Alder adduct **237** (43 mg, 62% yield, 88% yield overall).

Δ^7-Mesembrenone (238). 10% Pd/C (10 mg, 0.009 mmol, 0.2 equiv) was added to a stirred solution of hydrolyzed Diels–Alder product **237** (20 mg, 0.047 mmol, 1.0 equiv) in EtOAc (2 mL) at 23 °C. The reaction was then placed under a hydrogen atmosphere (balloon) and was stirred for 3 hours at 23 °C. At this point, the solution was filtered through Celite and concentrated to give the *N*-H vinylogous amide (13 mg, quantitative yield) as a green, viscous oil. R_f = 0.40 (silica gel, MeOH/CH_2Cl_2, 1:10); IR (film) ν_{max} 2937, 2359, 1577, 1512, 1457, 1263, 1194, 1143, 1026, 814, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 – 6.84 (m, 2 H), 6.78 (d, *J* = 8.9 Hz, 1 H), 6.18 (s, 1 H), 5.37 (s, 1 H), 3.85 (d, *J* = 2.1 Hz, 6 H), 3.42 (ddd, *J* = 10.3, 7.9, 2.3 Hz, 1 H), 3.17 (td, *J* = 10.6, 5.1 Hz, 1 H), 2.47 – 2.36 (m, 1 H), 2.31 (dd, *J* = 11.8, 5.0 Hz, 1 H), 2.19 – 2.01 (m, 3 H), 2.01 – 1.86 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 172.7, 149.0,

148.2, 133.3, 119.6, 111.1, 110.3, 95.2, 56.2, 56.0, 51.3, 45.0, 40.2, 36.2, 33.6; HRMS (FAB) calcd for $C_{16}H_{20}NO_3^+$ 274.1443, found 274.1430.

To a stirred solution of this vinylogous amide (9.4 mg, 0.034 mmol, 1.0 equiv) in THF (3.4 mL) at 0 °C was added 60% NaH in mineral oil (3 mg, 0.075 mmol, 2.2 equiv) was added. The solution was allowed to warm to 23 °C and stirred for 10 minutes at that temperature. MeI (3.2 µL, 0.052 mmol, 1.5 equiv) was then added slowly. After 45 min the reaction contents were quenched with saturated aqueous NH_4Cl (5 mL) and transferred to a separatory funnel, diluting with EtOAc (5 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 x 5 mL). The combined organic layers were then washed with brine (15 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0:1→3:97) to give **238** (7.4 mg, 75% yield) as a clear, colorless oil. **238**: R_f = 0.60 (silica gel, MeOH/CH_2Cl_2, 1:10); IR (film) ν_{max} 2924, 2853, 1586, 1513, 1253, 1024, 800; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 – 6.70 (m, 2 H), 5.34 (s, 1 H), 3.86 (d, *J* = 1.1 Hz, 6 H), 3.39 – 3.26 (m, 2 H), 3.01 (s, 3 H), 2.45 – 2.36 (m, 1 H), 2.28 (dd, *J* = 11.8, 4.8 Hz, 1 H), 2.24 – 2.04 (m, 4 H), 1.94 (ddd, *J* = 16.6, 12.6, 4.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 119.5, 111.0, 110.1, 93.6, 60.5, 56.1, 56.0, 53.0, 39.2, 36.1, 33.2, 32.8, 29.8, 21.2, 14.3, 1.2; HRMS (FAB) calcd for $C_{17}H_{22}NO_3^+$ 288.1600, found 288.1605.

Amino Pyrone 241. 3-Butynamine (**240**, 33 µL, 0.40 mmol, 1.0 equiv), followed by *i*-Pr_2NEt (76 µL, 0.44 mmol, 1.1 equiv) were added dropwise to a stirred solution of 4,6-dichloro-2-pyrone (**60**, 66 mg, 0.40 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at –78 °C.

The reaction was allowed to slowly warm to 23 °C over 3 hours. After an additional hour of stirring at this temperature, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (5 mL) and transferred to a separatory funnel, diluting with water (10 mL) and CH_2Cl_2 (5 mL). The organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 0:1→1:4) to give amino pyrone **241** (67 mg, 85% yield) as a pale yellow solid. **241**: R_f = 0.40 (silica gel, EtOAc/hexanes, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1 H), 5.60 (s, 1 H), 5.23 (d, *J* = 1.2 Hz, 1 H), 3.35 – 3.38 (dd, J = 12.4, 6.3 Hz, 2 H), 2.51-2.55 (td, J = 6.3, 2.6 Hz, 2 H), 2.08 – 2.09 (t, *J* = 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 160.2, 155.9, 97.3, 82.7, 80.1, 71.4, 40.6, 19.1.

***N*-Acetyl Pyrone 242**. To a solution of amino pyrone **241** (52 mg, 0.264 mmol, 1.0 equiv) and 4-DMAP (one crystal) in DCM (4 mL) at 0 °C was slowly added acetyl chloride (24 µL, 0.343 mmol, 1.3 equiv), followed by Et_3N (50 µL, 0.343 mmol, 1.3 equiv). The reaction allowed to warm to 23 °C and stirred for 3 hours. At this point, saturated aqueous $NaHCO_3$ (10 mL) was added and the reaction contents were transferred to a separatory funnel, diluting with CH_2Cl_2 (5 mL). The organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL).The organic layers were combined, dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 0:1→1:4) to give protected amino pyrone (60 mg, 95% yield) as a pink solid. **242**: R_f = 0.4 (silica gel,

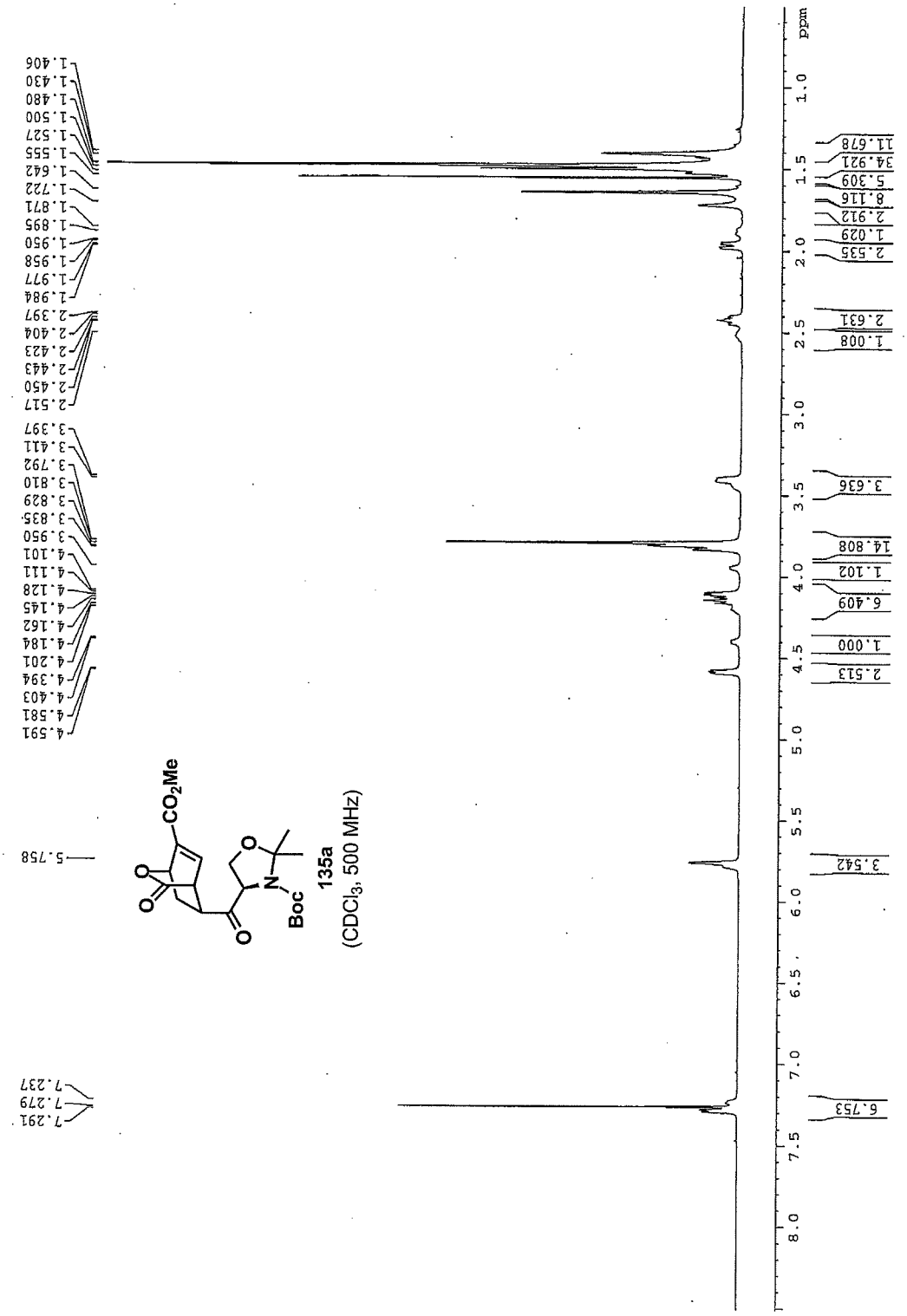
EtOAc/hexanes, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, J = 1.5 Hz, 1 H), 6.28 (d, J = 1.6 Hz, 1 H), 3.85 (t, J = 6.8 Hz, 2 H), 2.55 (dd, J = 6.7, 2.7 Hz, 2 H), 2.22 (s, 3H), 2.01 (t, J = 2.7 Hz, 1 H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 158.9, 155.1, 152.7, 111.1, 103.0, 97.3, 80.5, 71.0, 46.4, 23.2, 18.6.

6-Chloro Indoline 226. A microwave vial containing amido pyrone **242** (20 mg, 0.083 mmol, 1.0 equiv) was evacuated and backfilled with argon gas three times before toluene (2 mL) was added. The solution was then degassed by argon sparge for 15 minutes. After the tube was sealed, it reaction was heated at 140 °C for 8 hours under microwave irradiation. After returning to 23 °C, the solution was concentrated and the resulting crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:4) to give indoline **226** (16 mg, 99% yield) as a white solid. **226**: R_f = 0.28 (silica gel, EtOAc/hexanes, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.26 (s, 1 H), 7.04 (s, 1 H), 6.97 (s, 1 H), 4.06 (t, J = 8.5 Hz, 2 H), 3.14 (t, J = 8.5 Hz, 2 H), 2.21 (s, 1 H), 1.25 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 144.0, 133.1, 129.6, 125.2, 123.7, 117.4, 49.4, 29.8, 27.6, 24.2.

Experimental References:

1. Mochizuki, A.; Naito, H.; Nakamoto, Y.; Uoto, K.; Ohta, T. *Heterocycles* **2008**, *75*, 1659.
2. Ageno, G.; Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Riva, R.; Rocca, V. *Tetrahedron* **1995**, *51*, 8121.
3. Saltzman, H.; Sharefkin, J. G. *Org. Synth.* **1963**, *43*, 60.
4. Cai, X. H.; Tan, Q. G.; Liu, Y. P.; Feng, T.; Du, Z. Z.; Li, W. Q.; Luo, X. D. *Org. Lett.* **2008**, *10*, 577.

5. Adams, G. L.; Carroll, P. J.; Smith, A. B. III *J. Am. Chem. Soc.* **2012**, *134*, 4037.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4.0
3.5
3.0
2.5
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3.397
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2.450
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2.423
2.404
2.397
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1.895
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1.722
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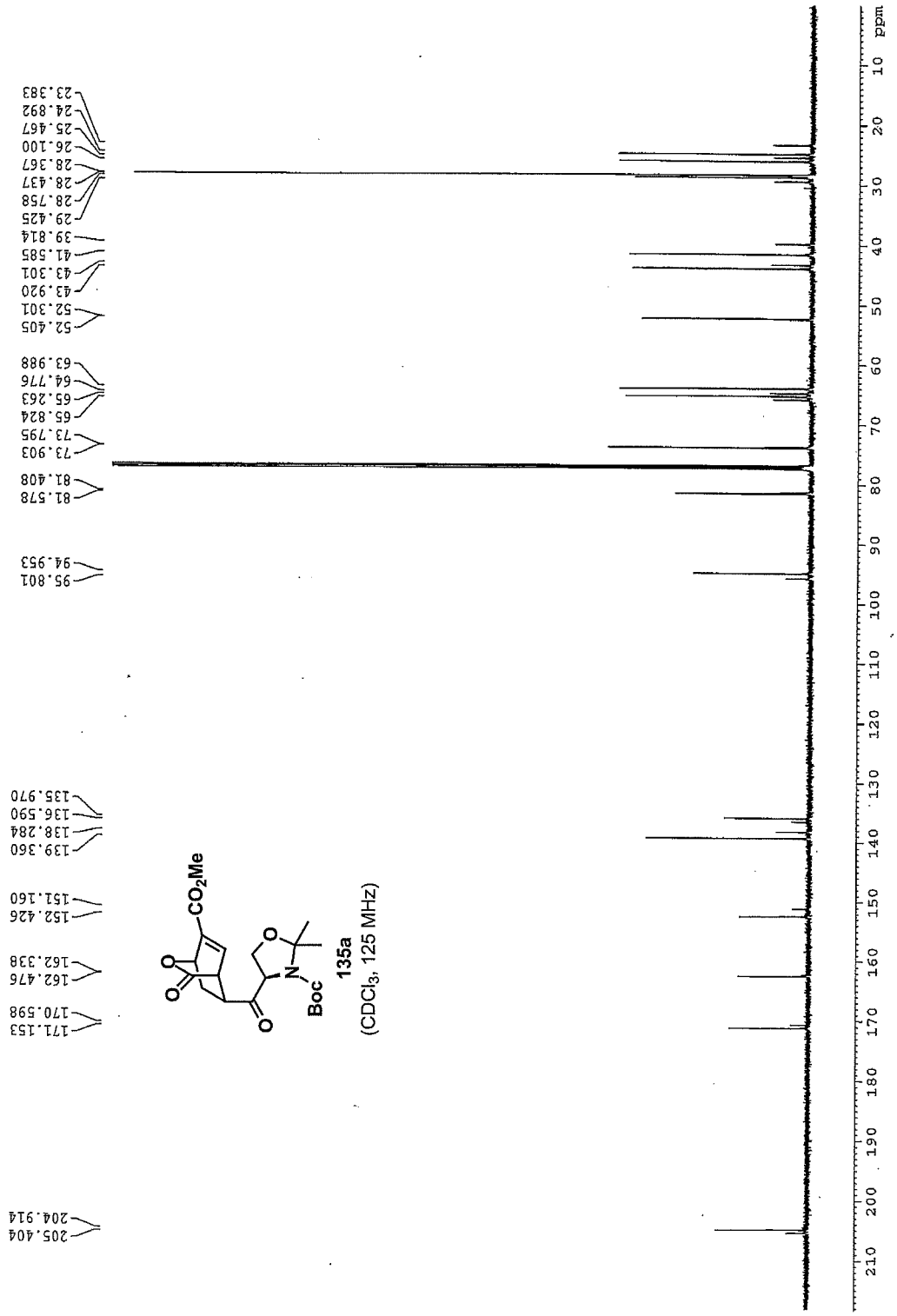
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43.301
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28.367
26.100
25.467
24.892
23.383
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Boc
135a
(CDCl3, 125 MHz)
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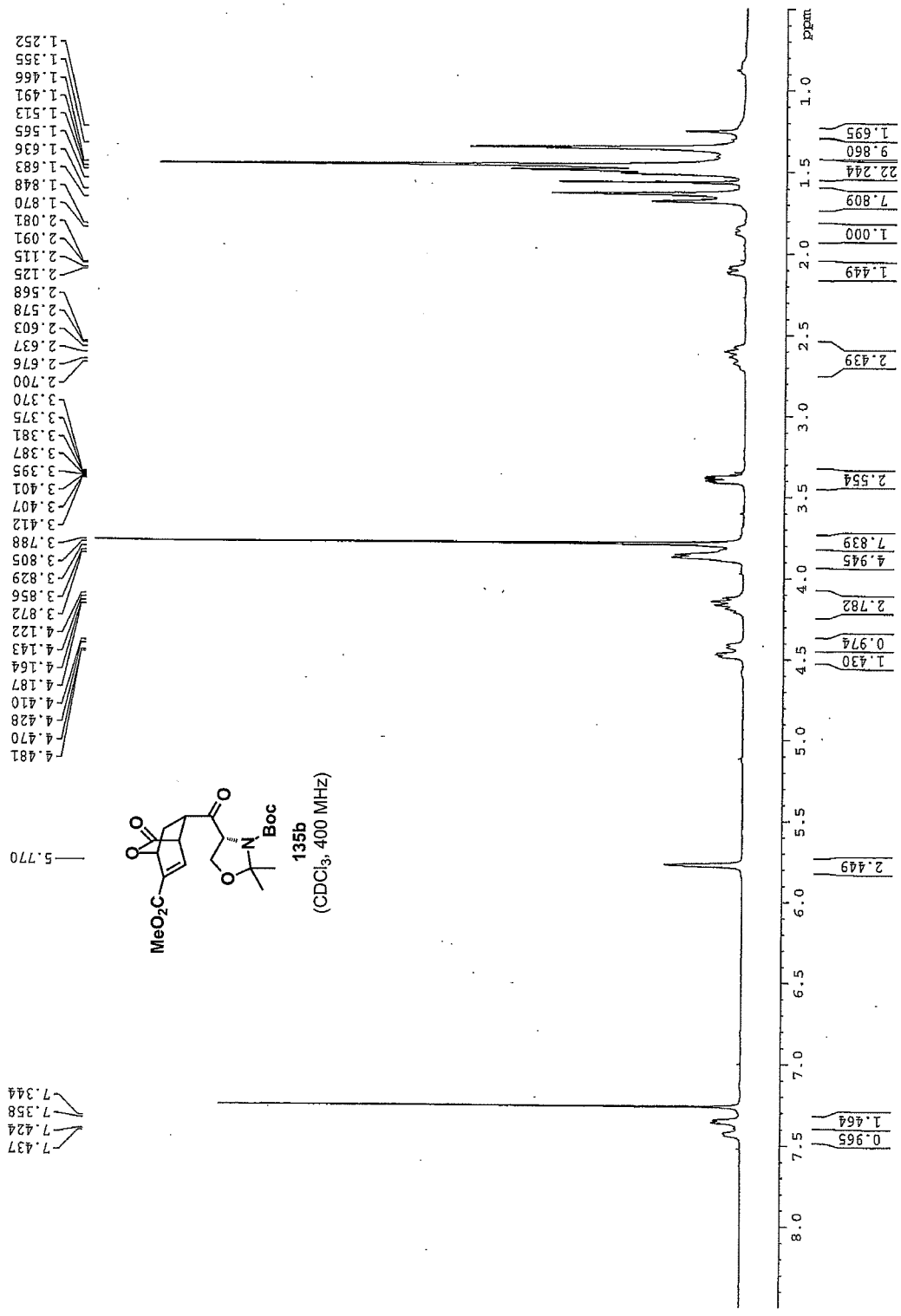
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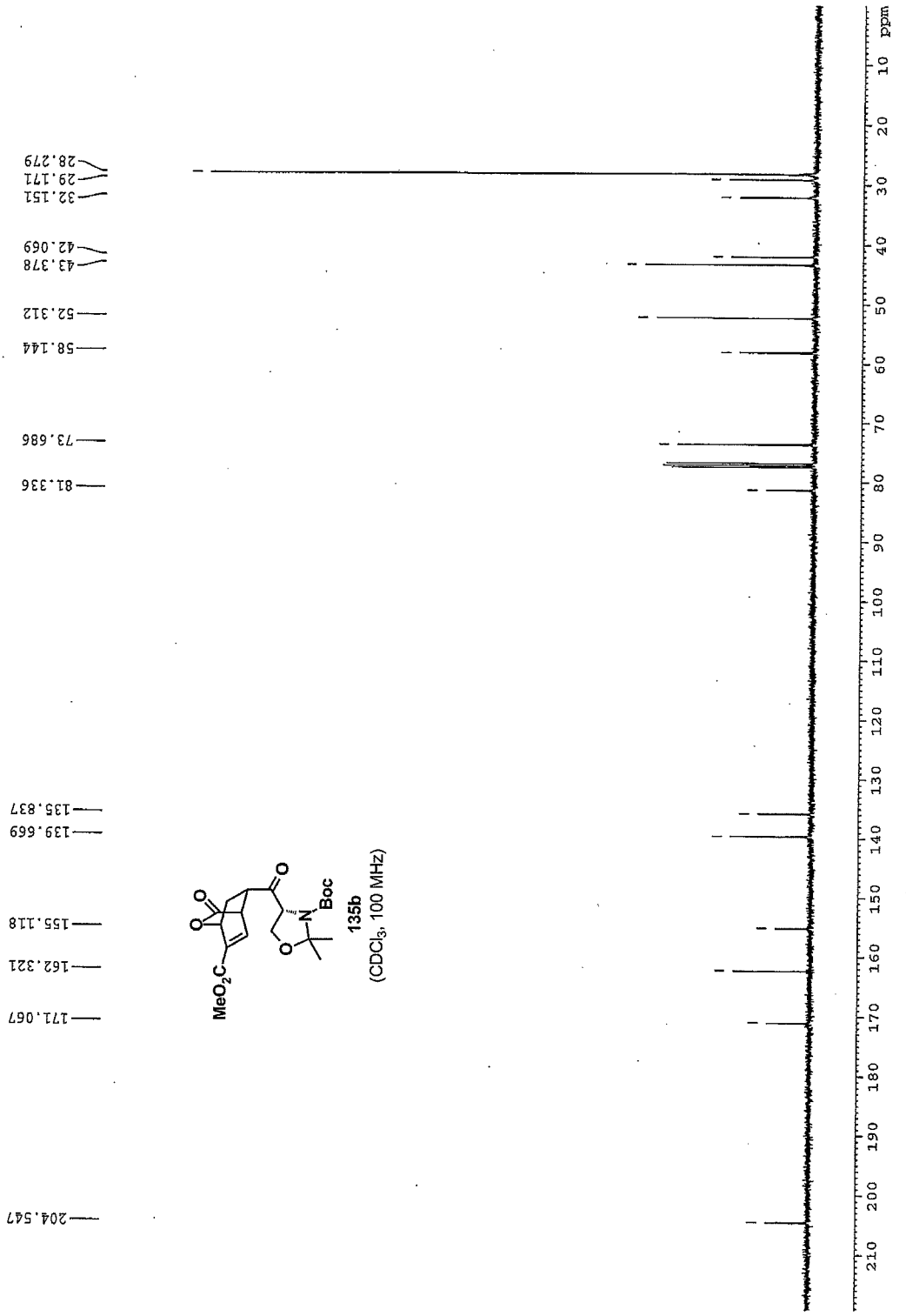
ppm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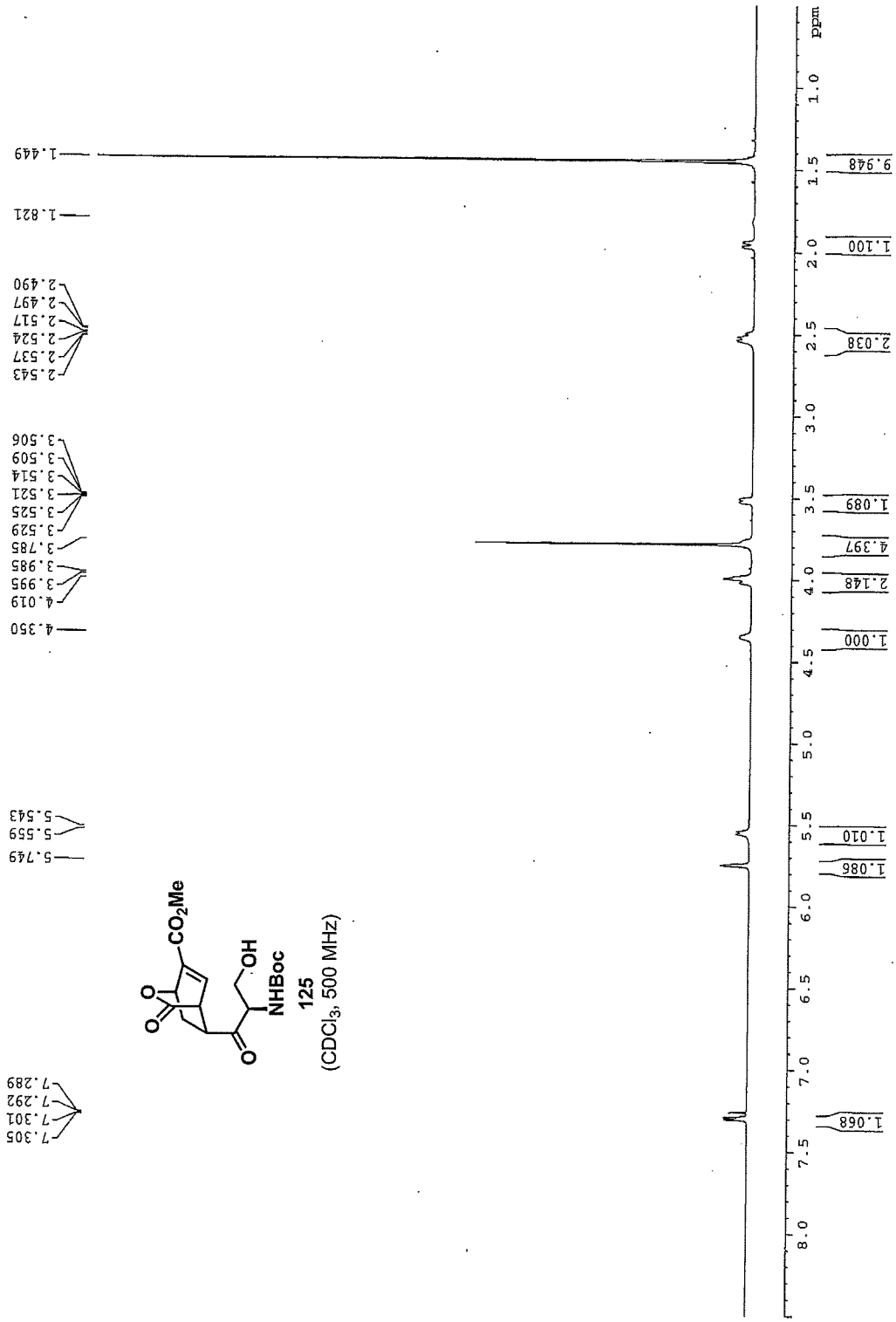
171.067
204.547
Boc
MeO2C
135b
(CDCl3, 100 MHz)
ppm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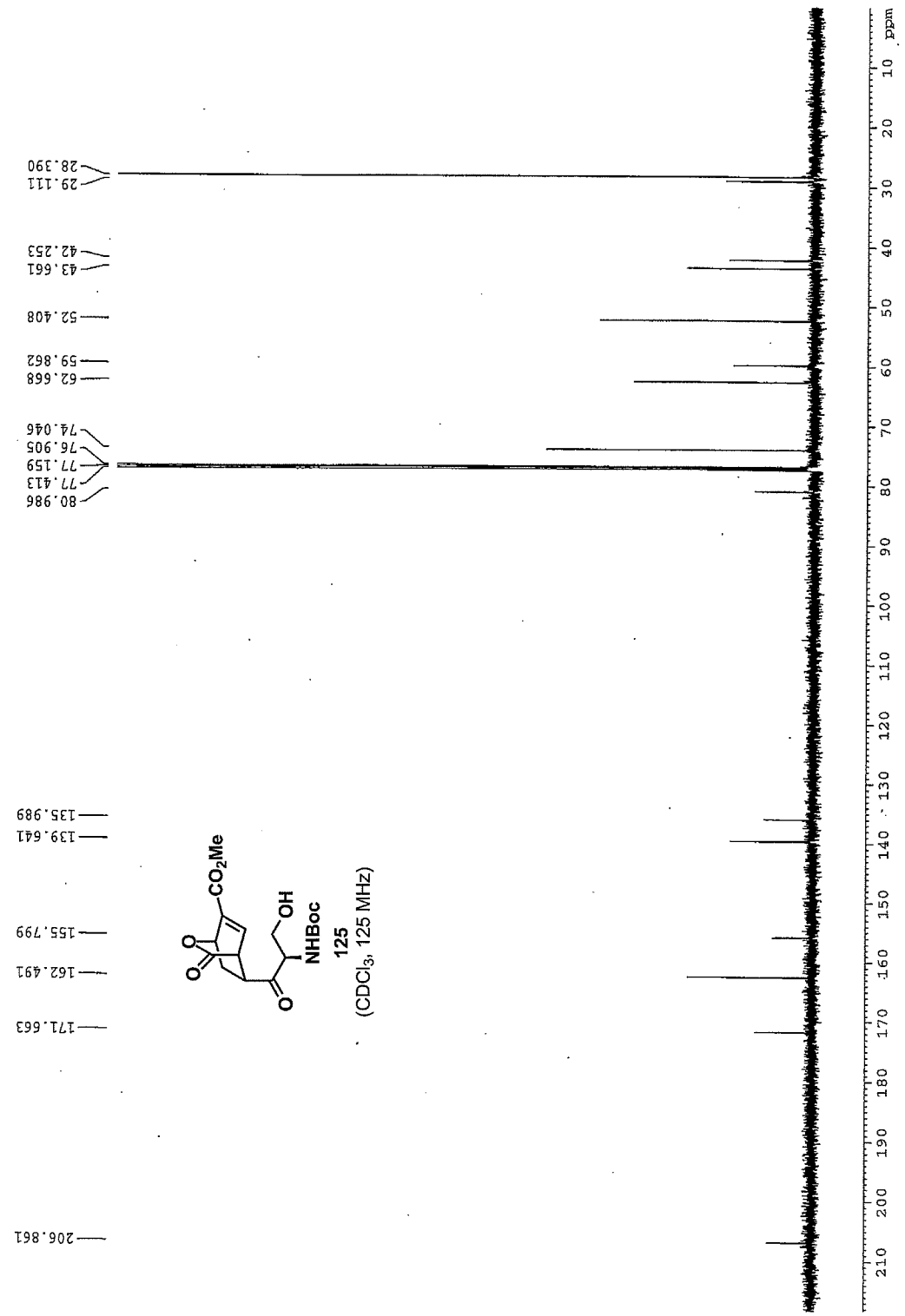
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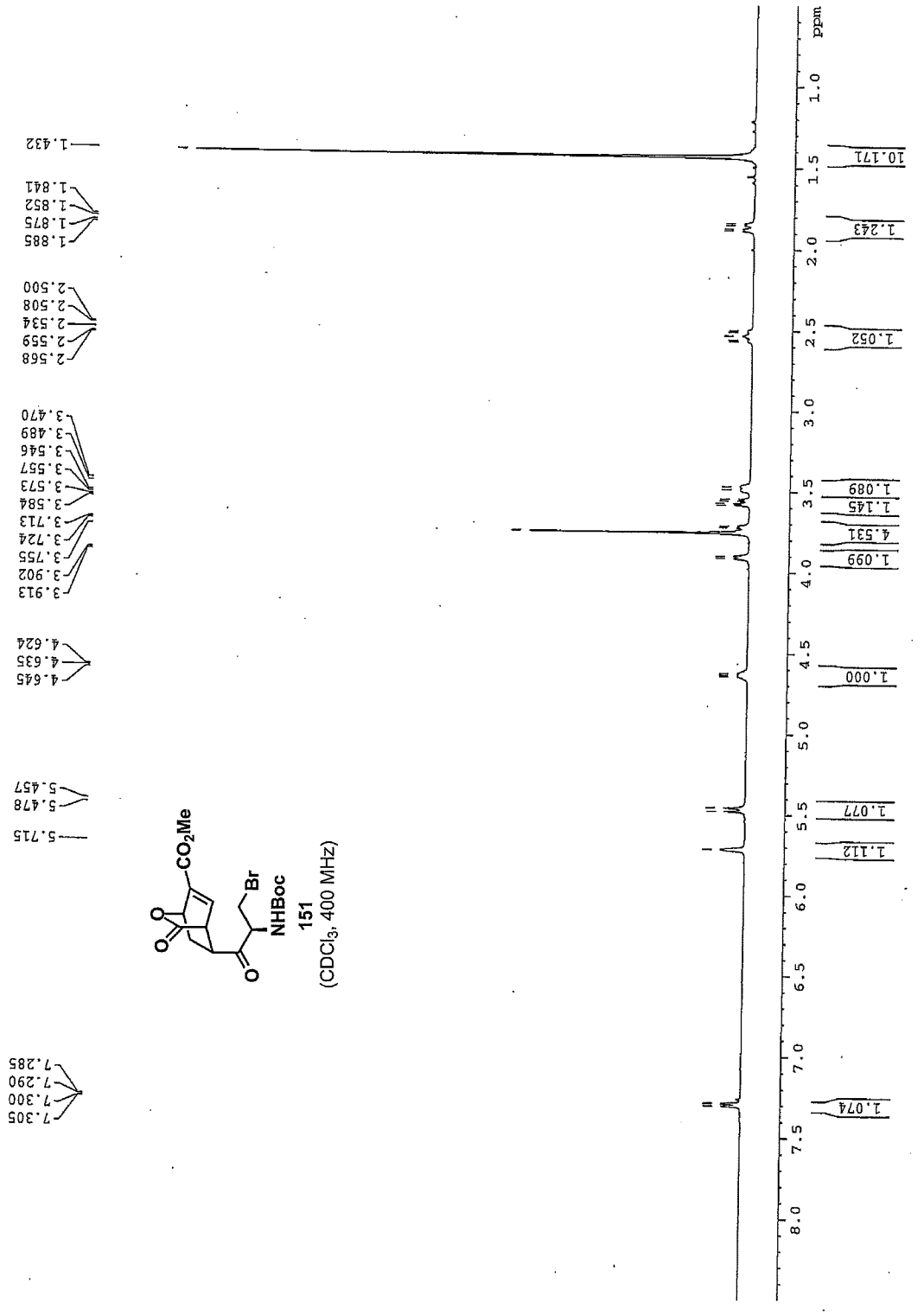
ppm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3.546
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3.713
3.724
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3.902
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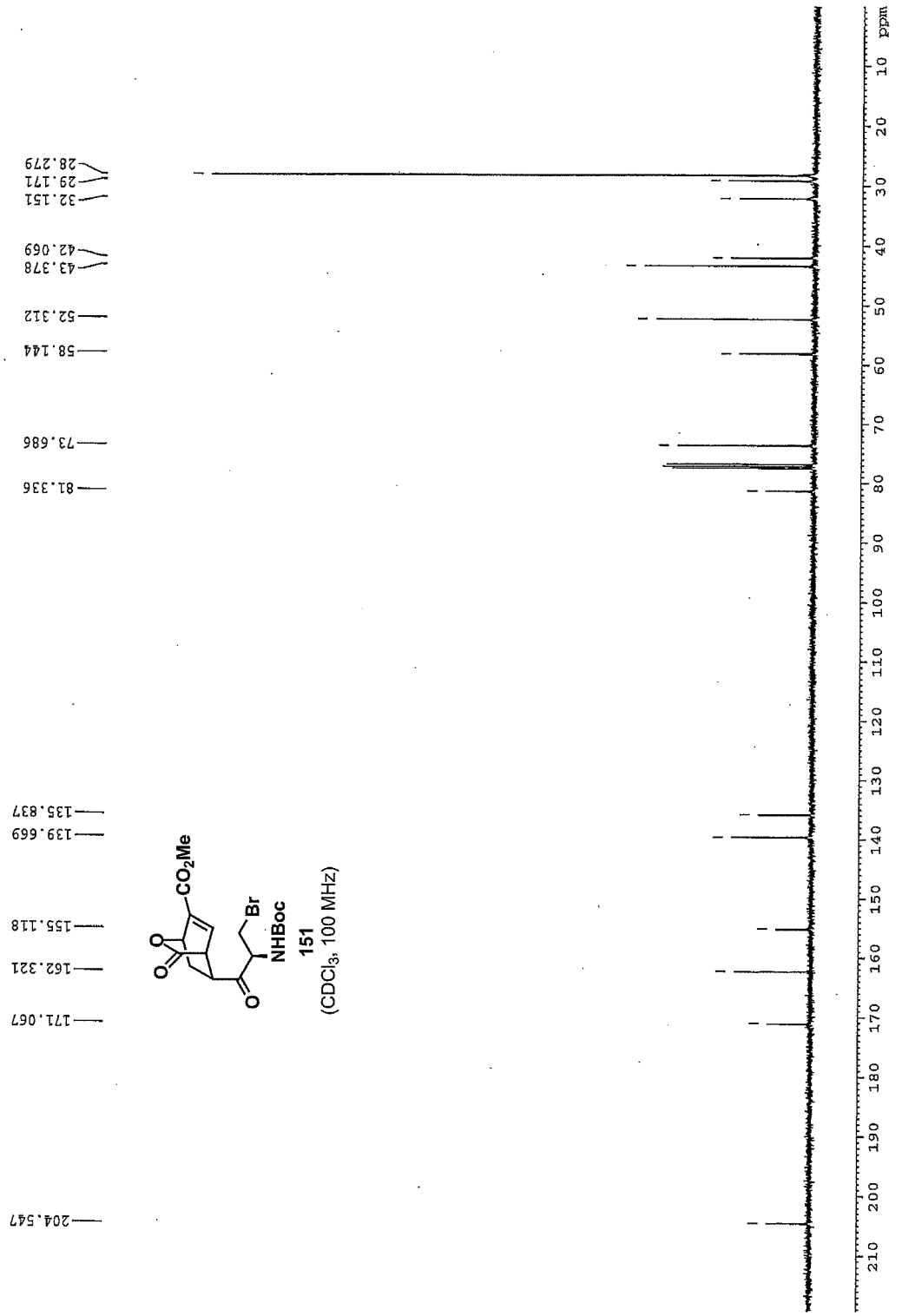
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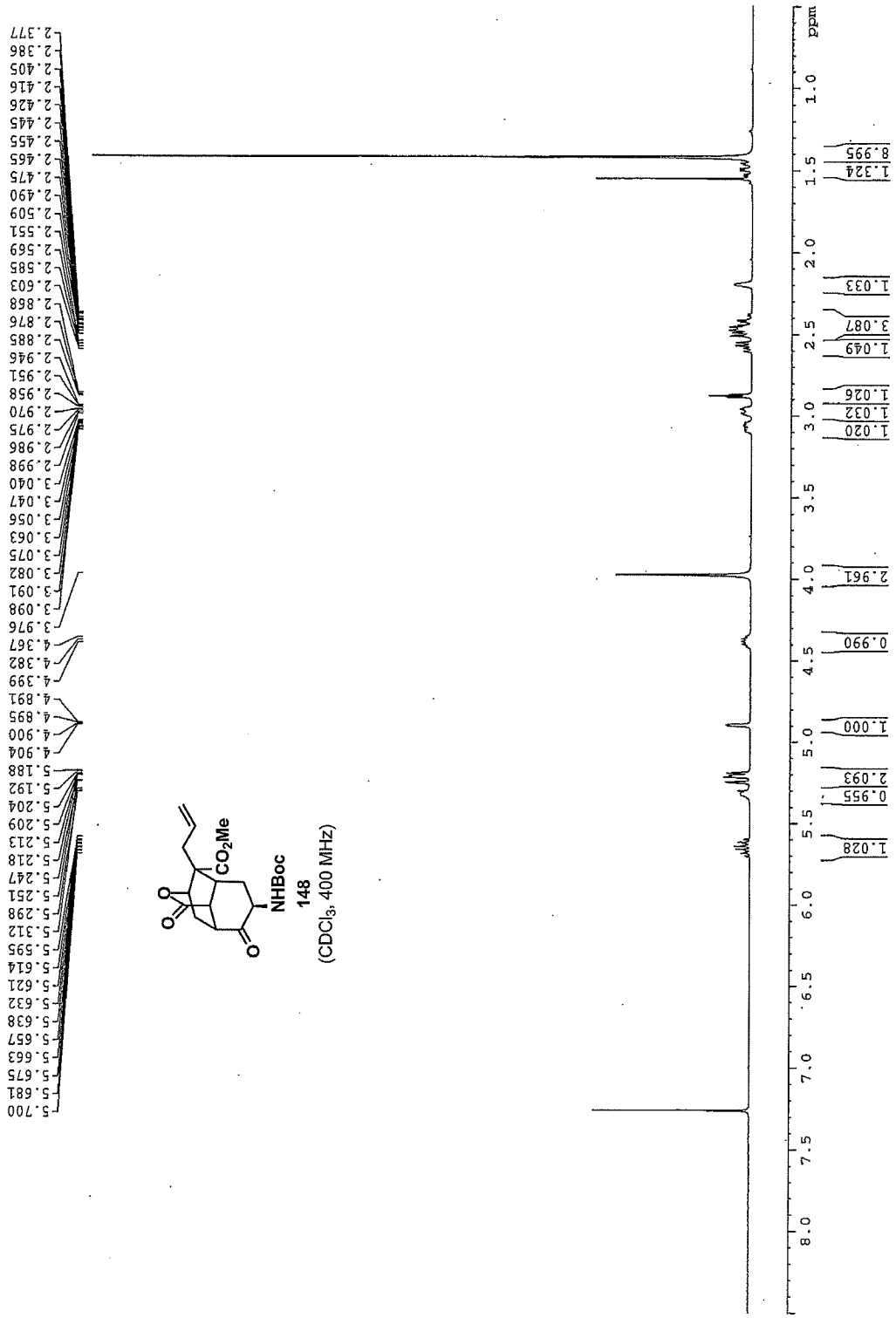
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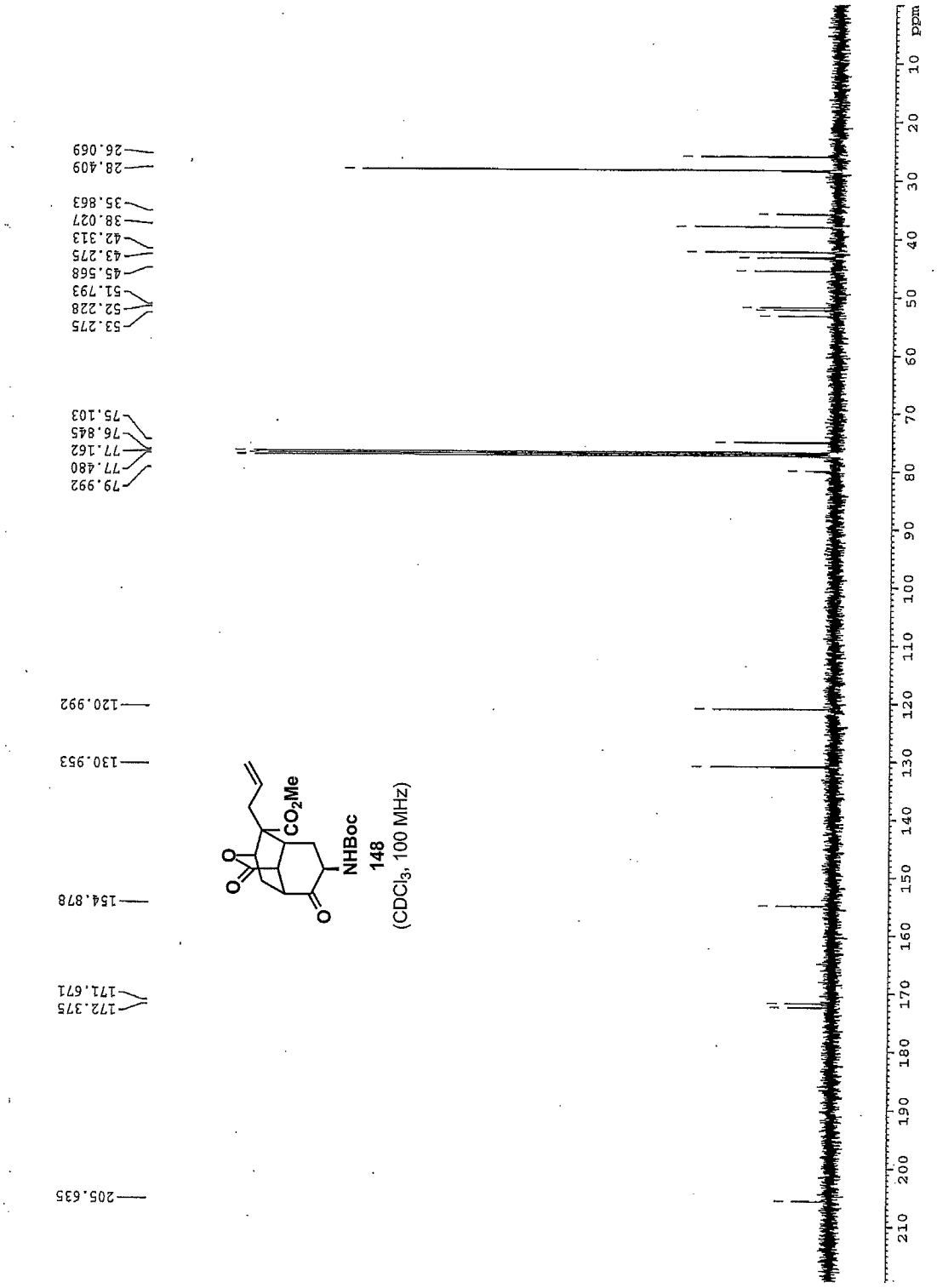
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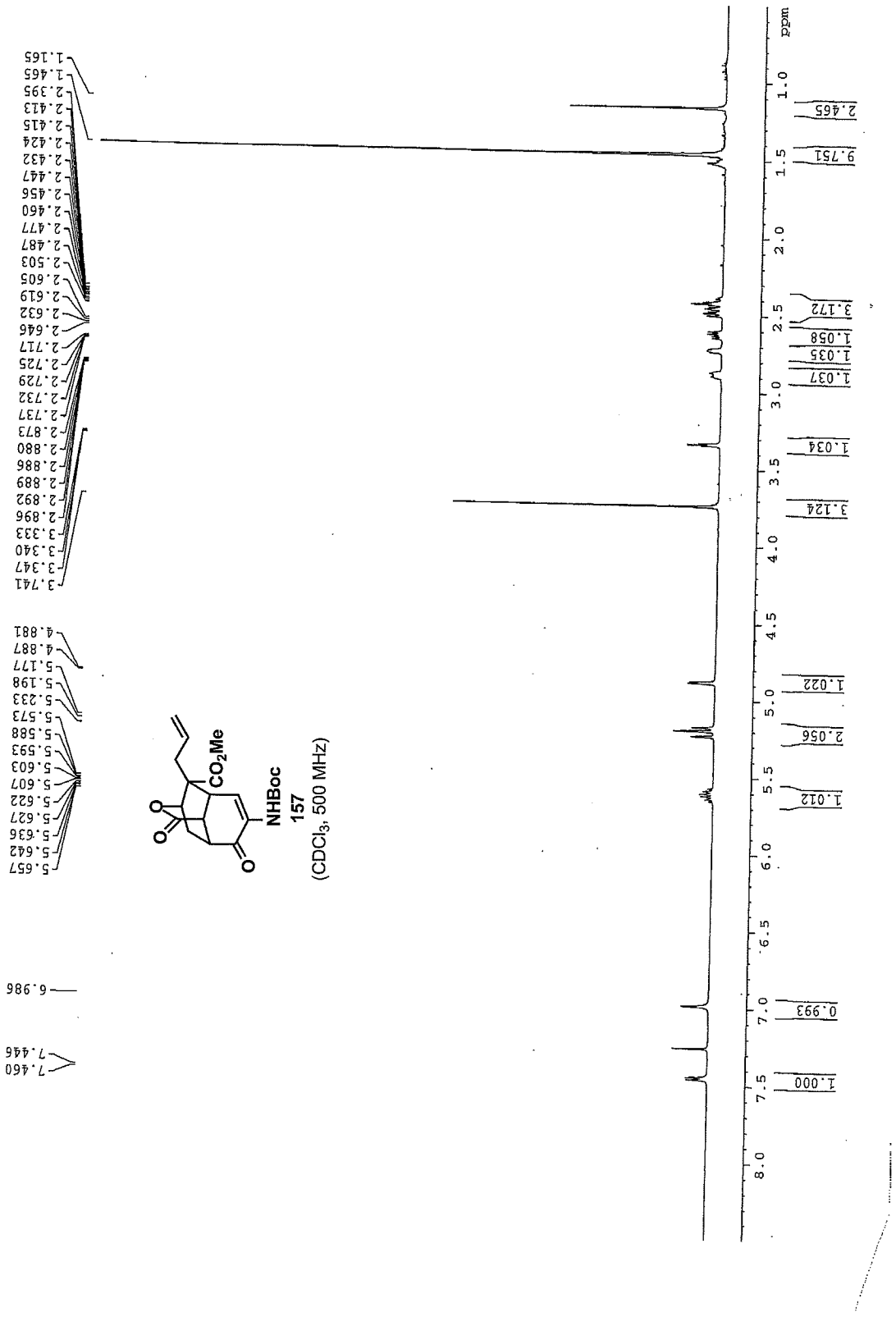
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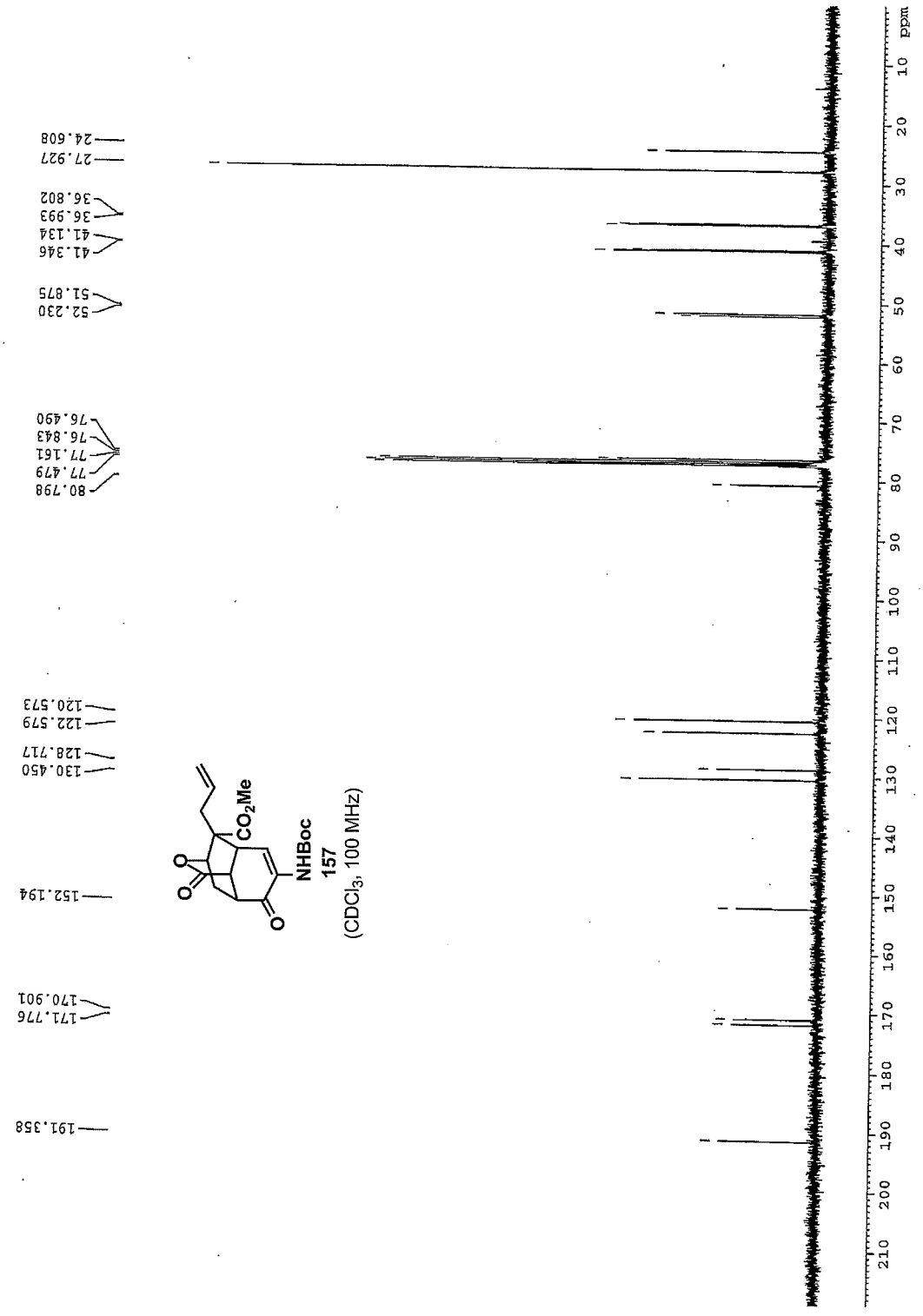
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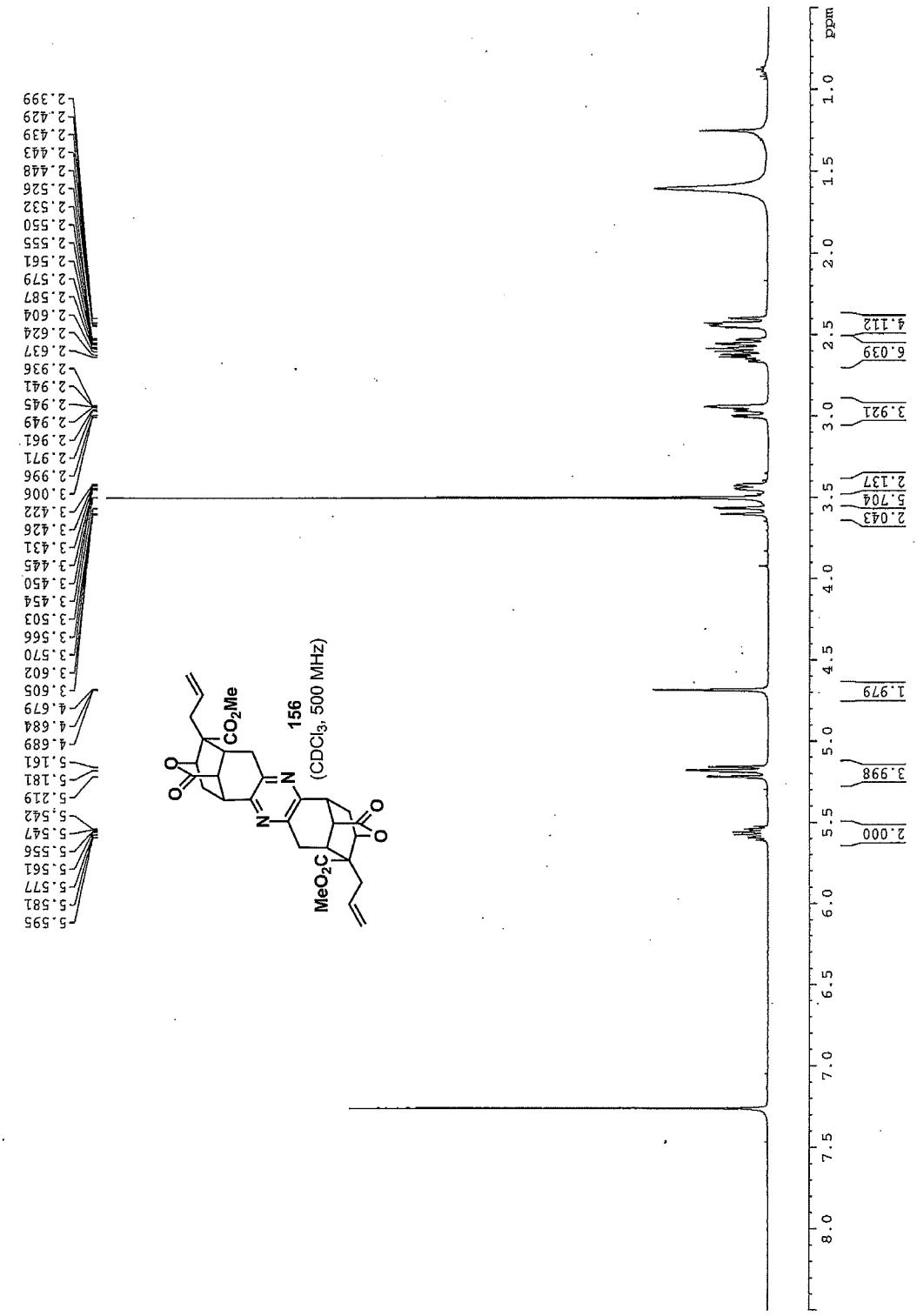
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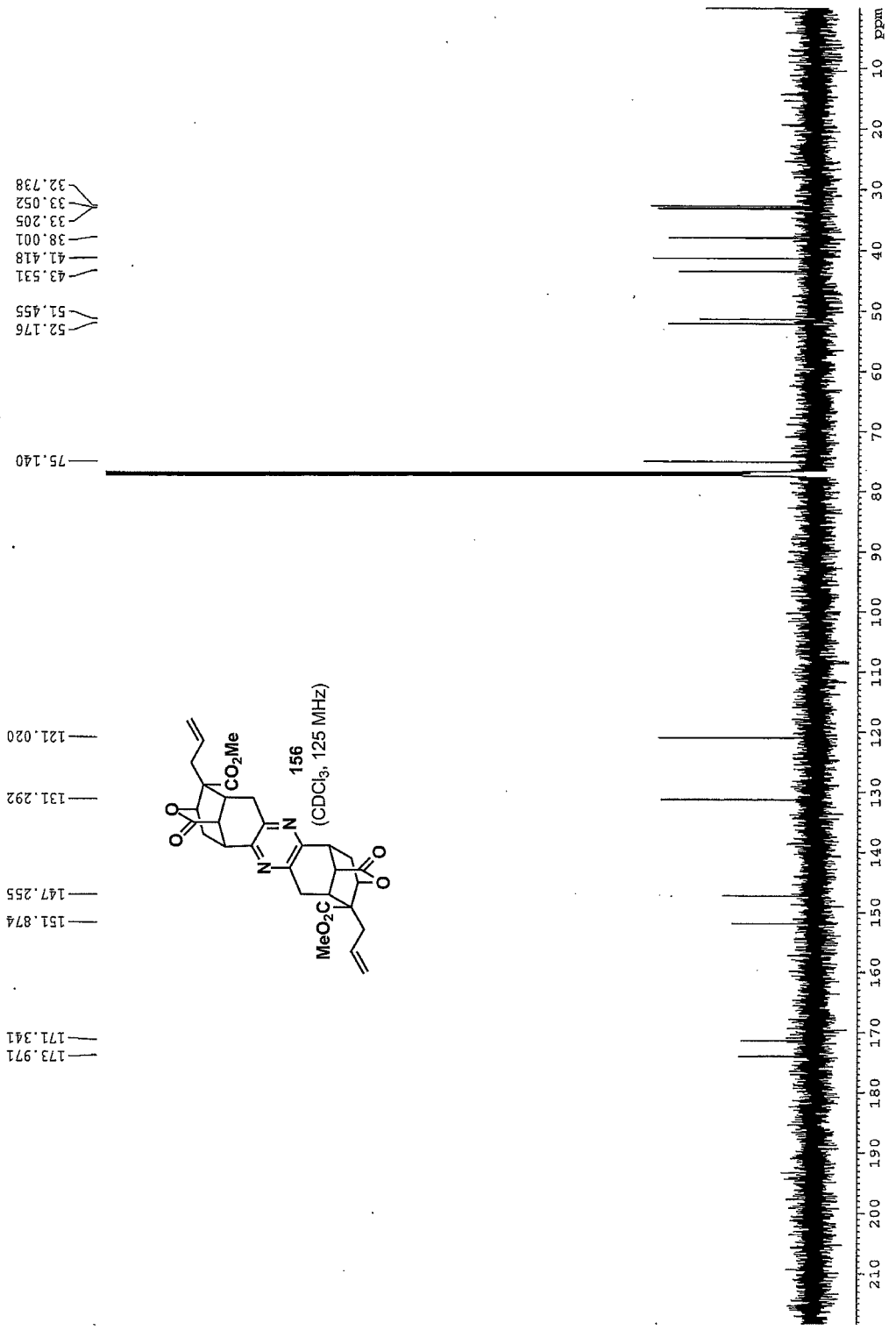
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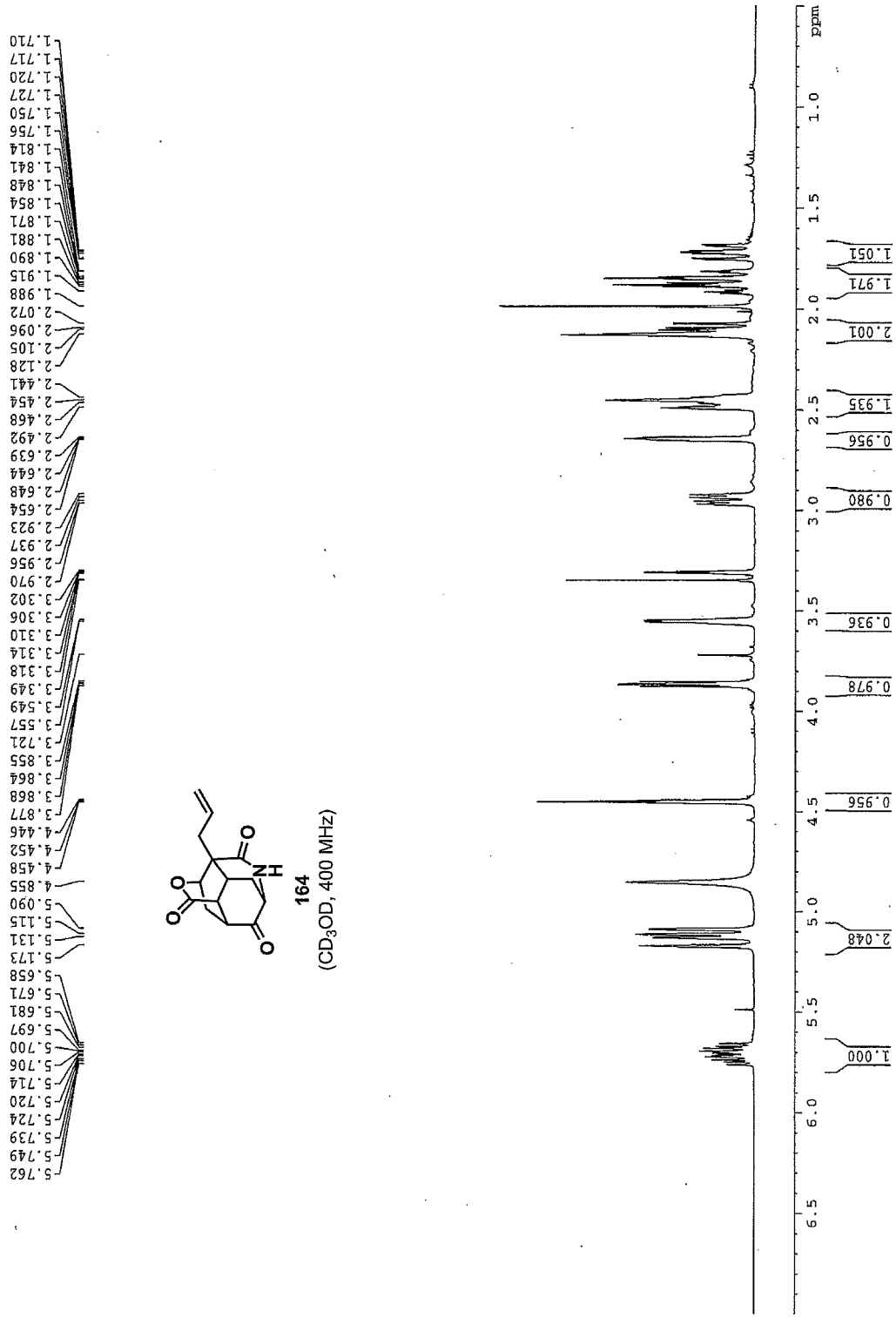
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3.306
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3.877
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4.452
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5.724
5.739
5.749
5.762
O
O
O
N
H
164
(CD3OD, 400 MHz)
ppm
6.5
6.0
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4.0
3.5
3.0
2.5
2.0
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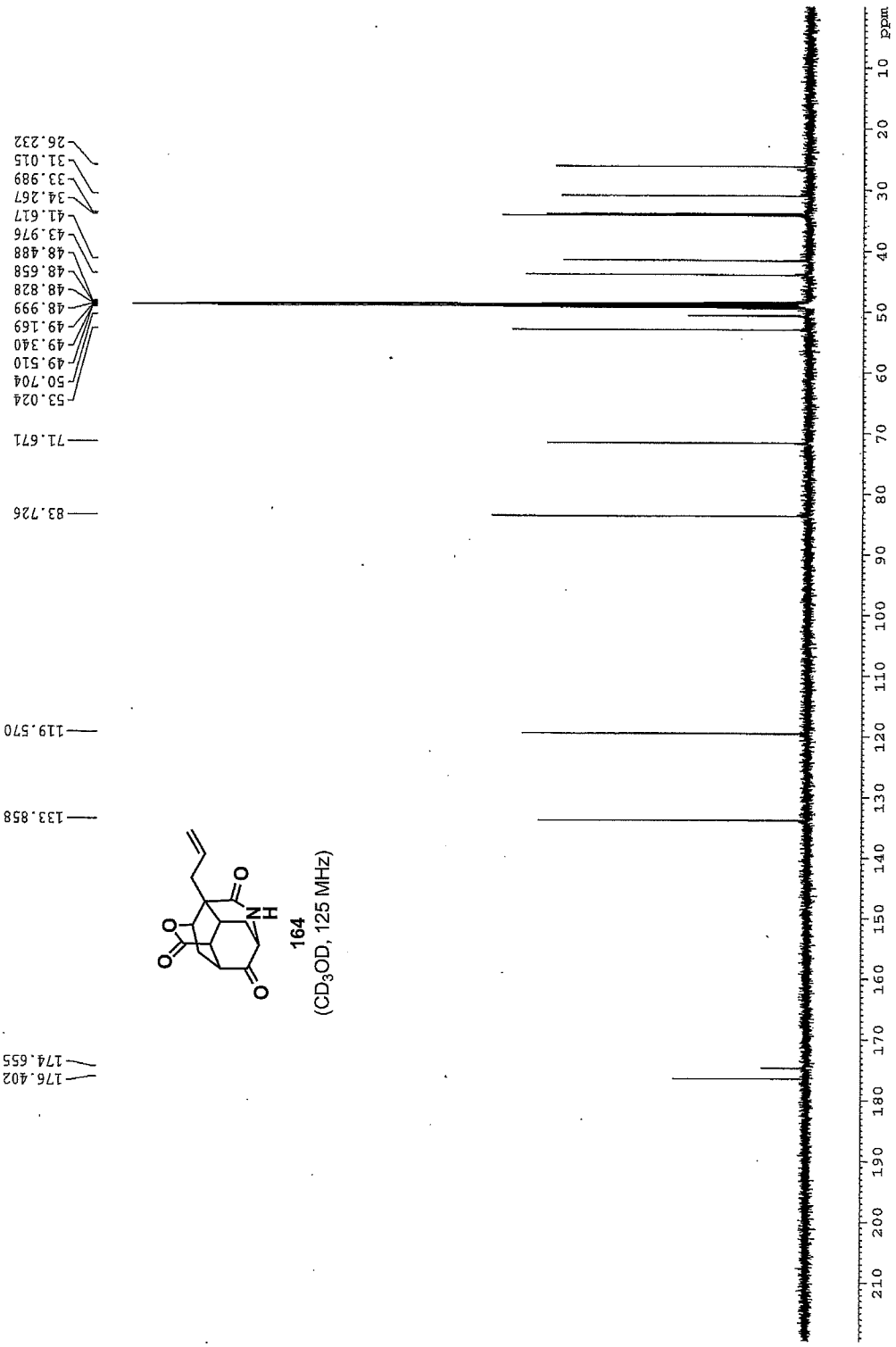
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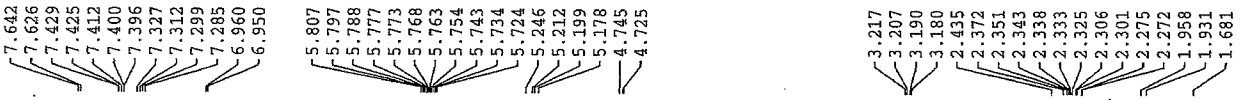

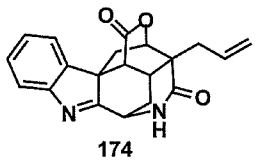

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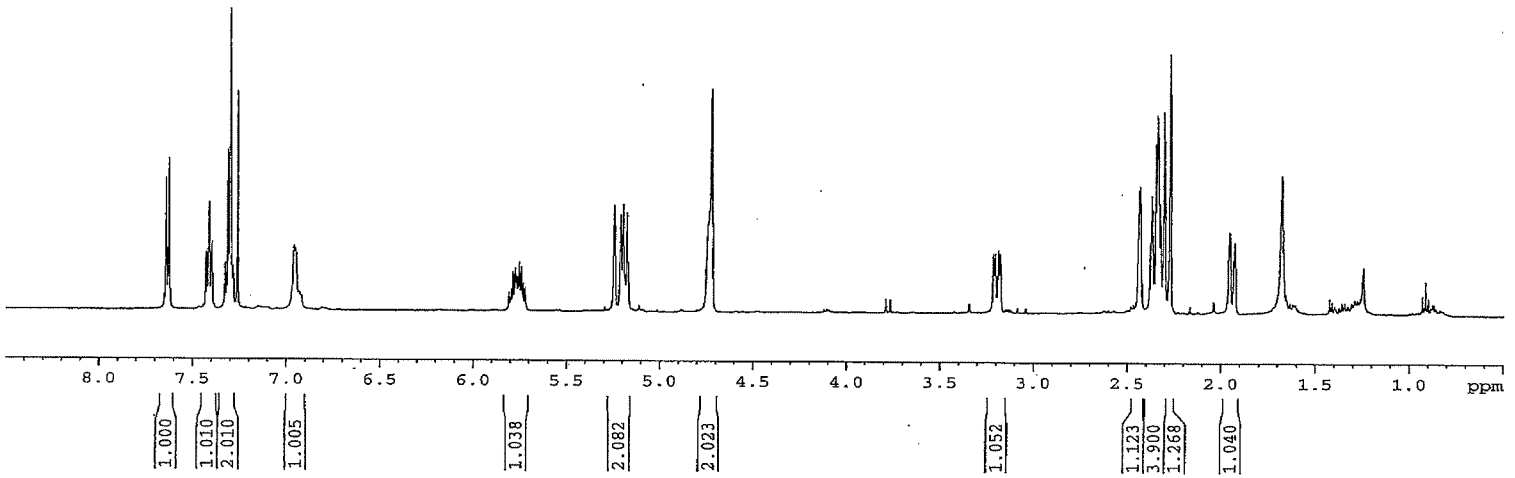
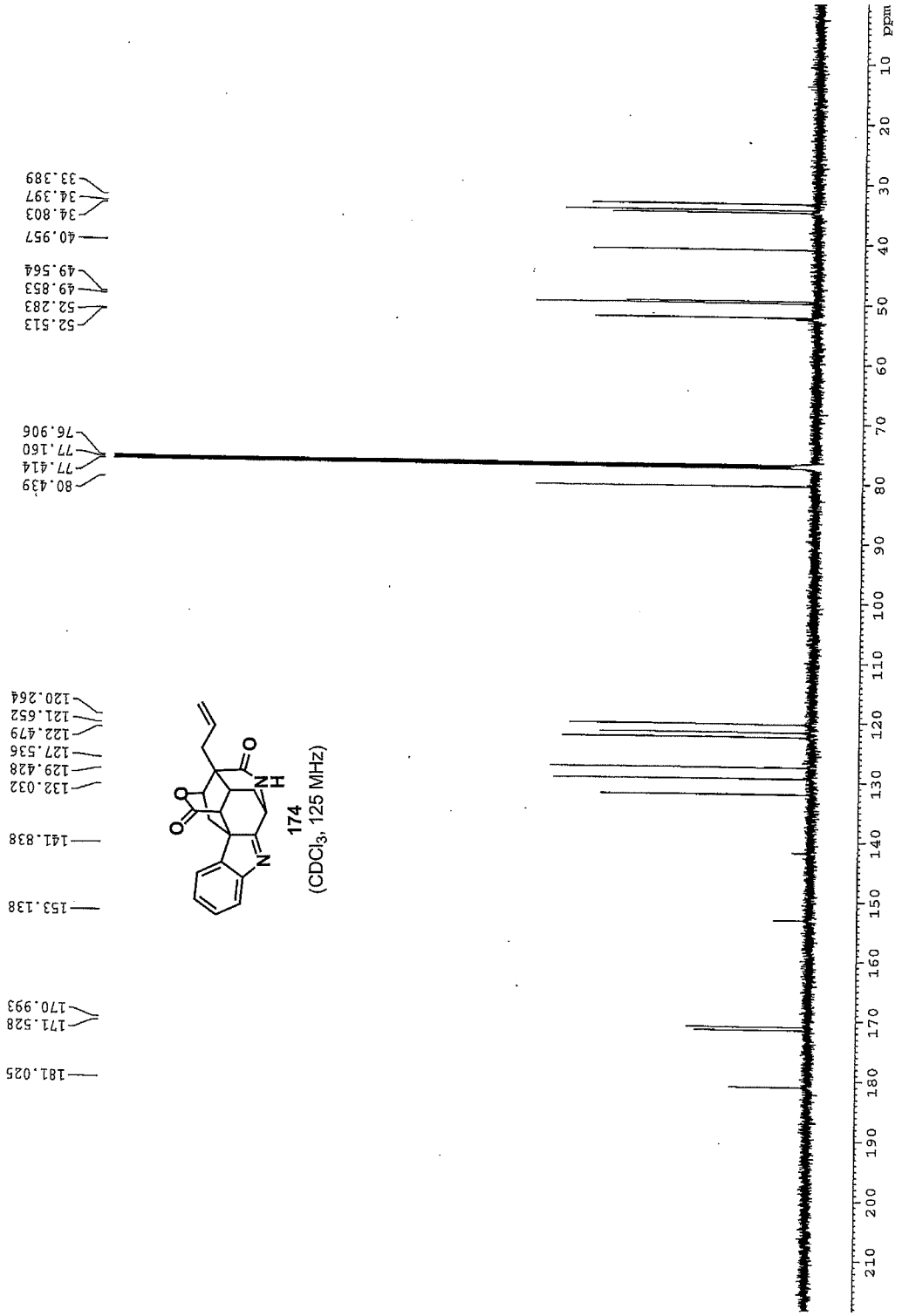
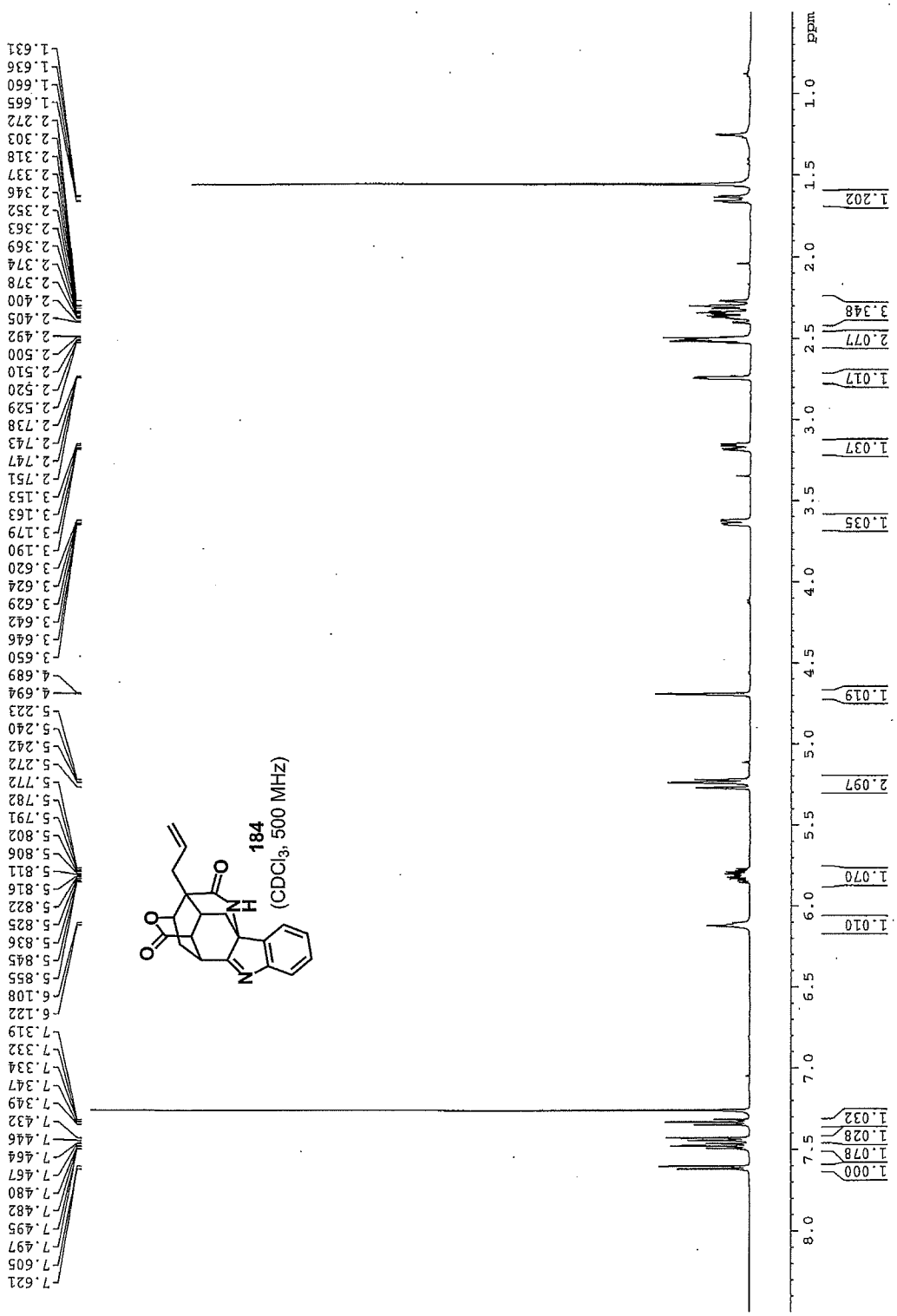
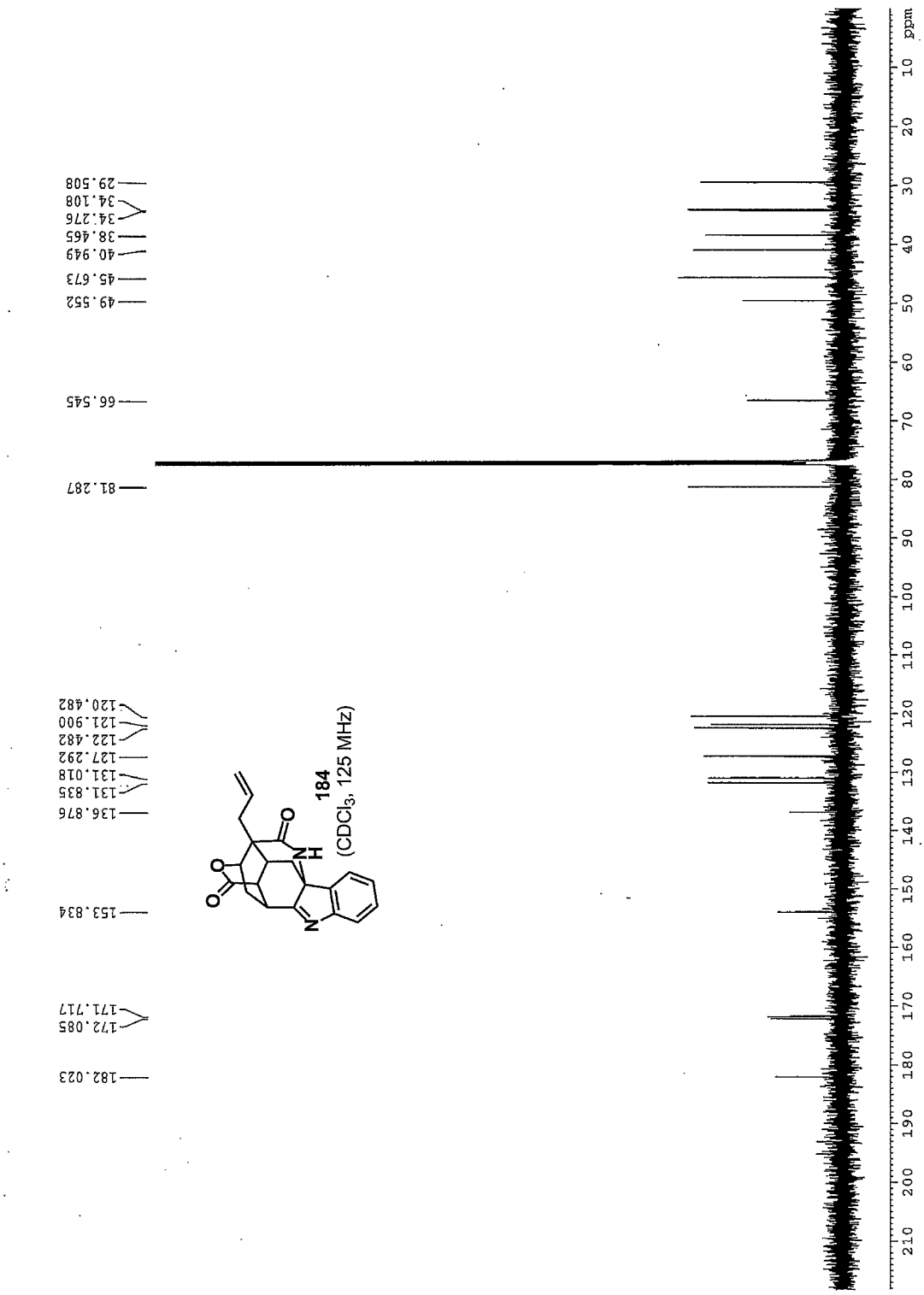
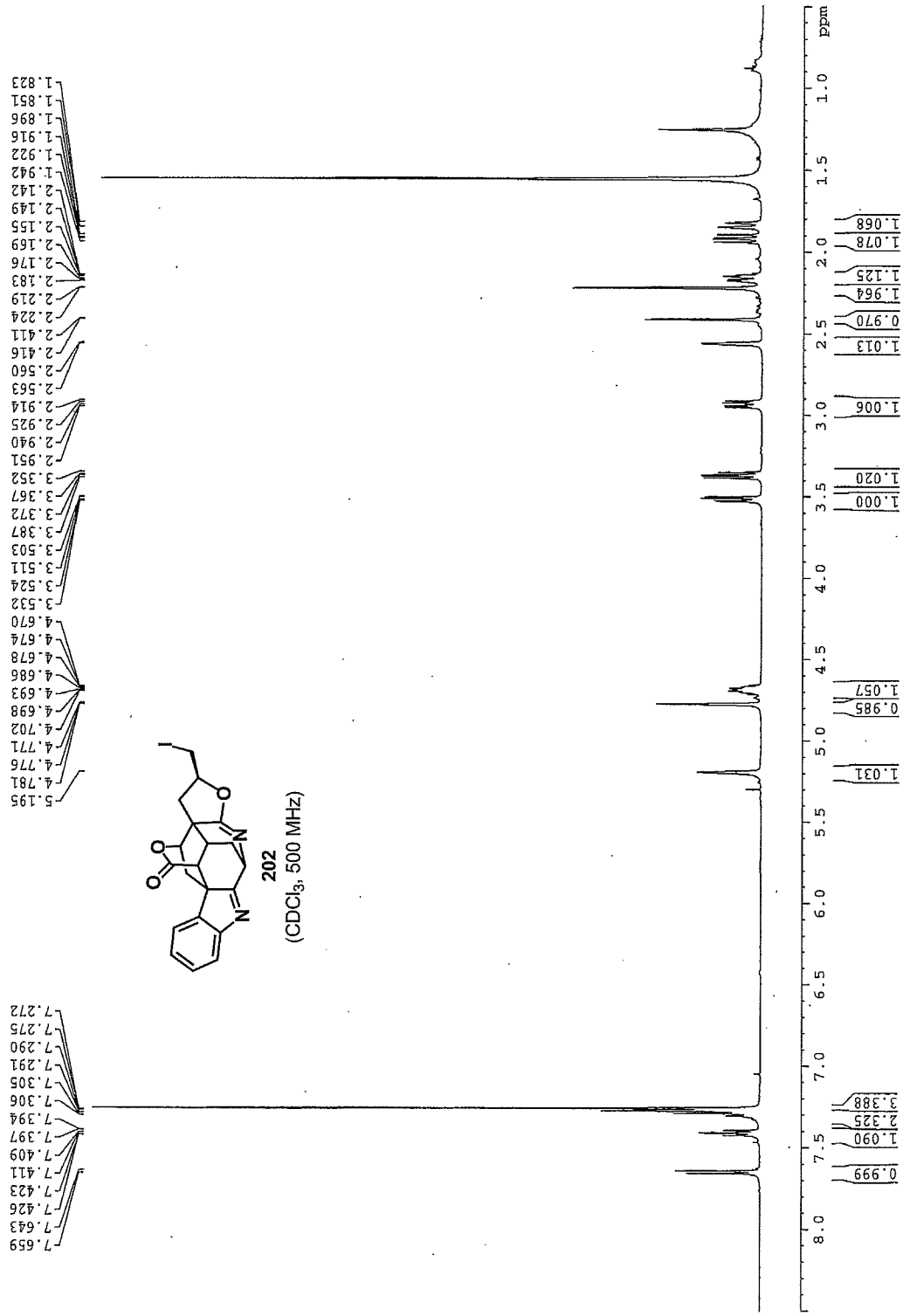
($CDCl_3$, 500 MHz)

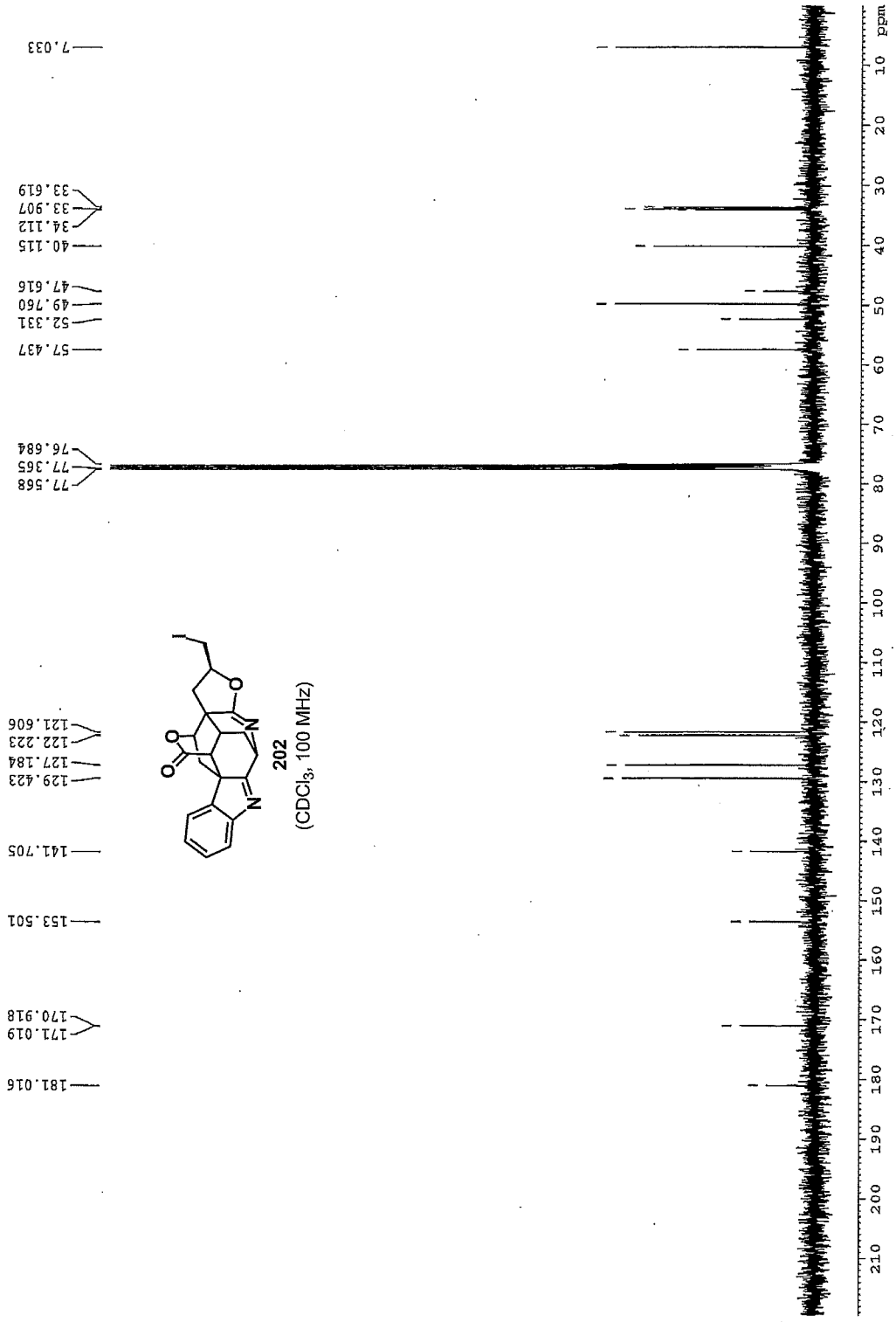


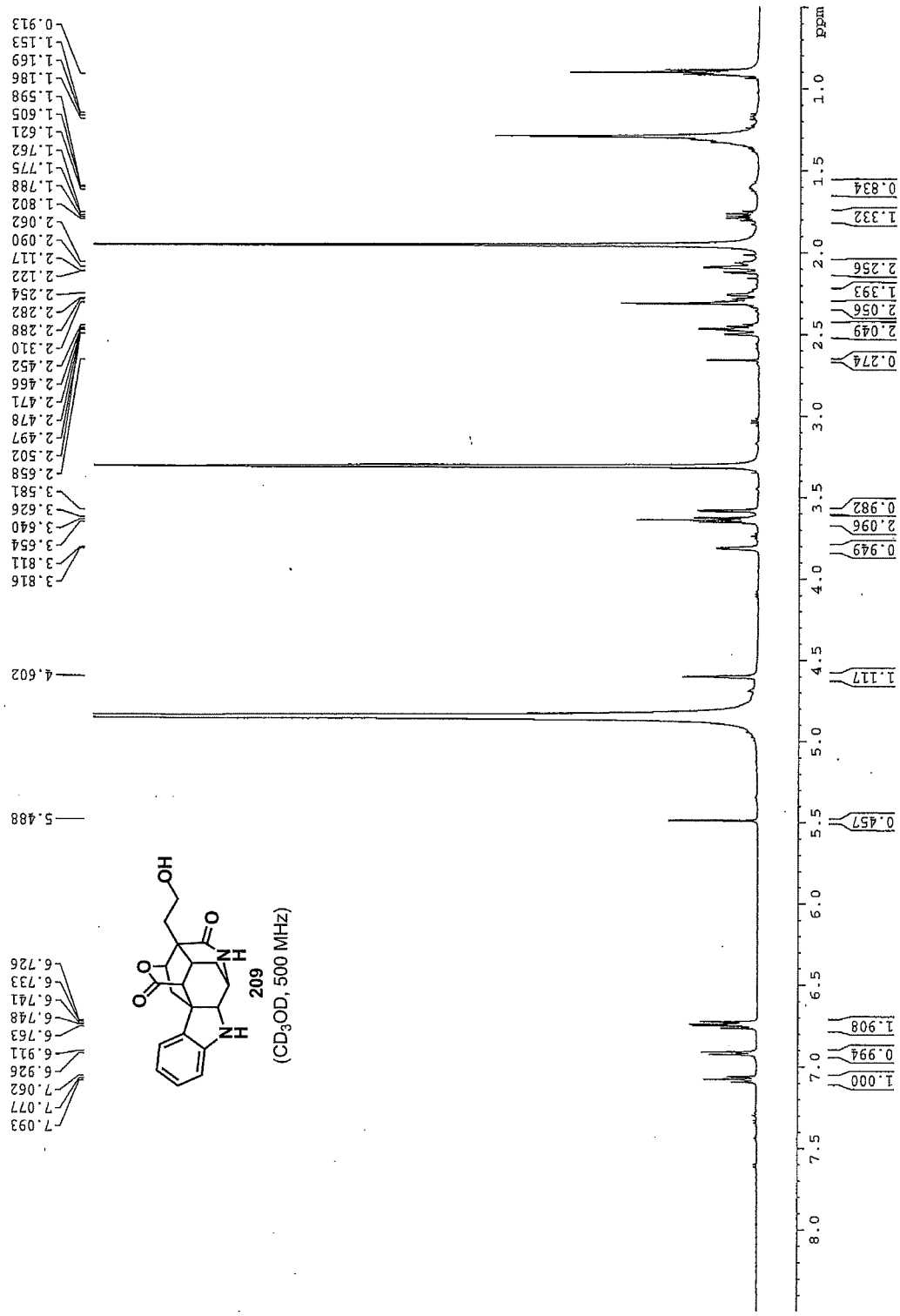

33.389
34.397
34.803
40.957
49.564
49.853
52.283
52.513
76.906
77.160
77.414
80.439
120.264
121.652
122.479
127.536
129.428
132.032
141.838
153.138
170.993
171.528
181.025
O
O
N
H
N
174
(CDCl3, 125 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

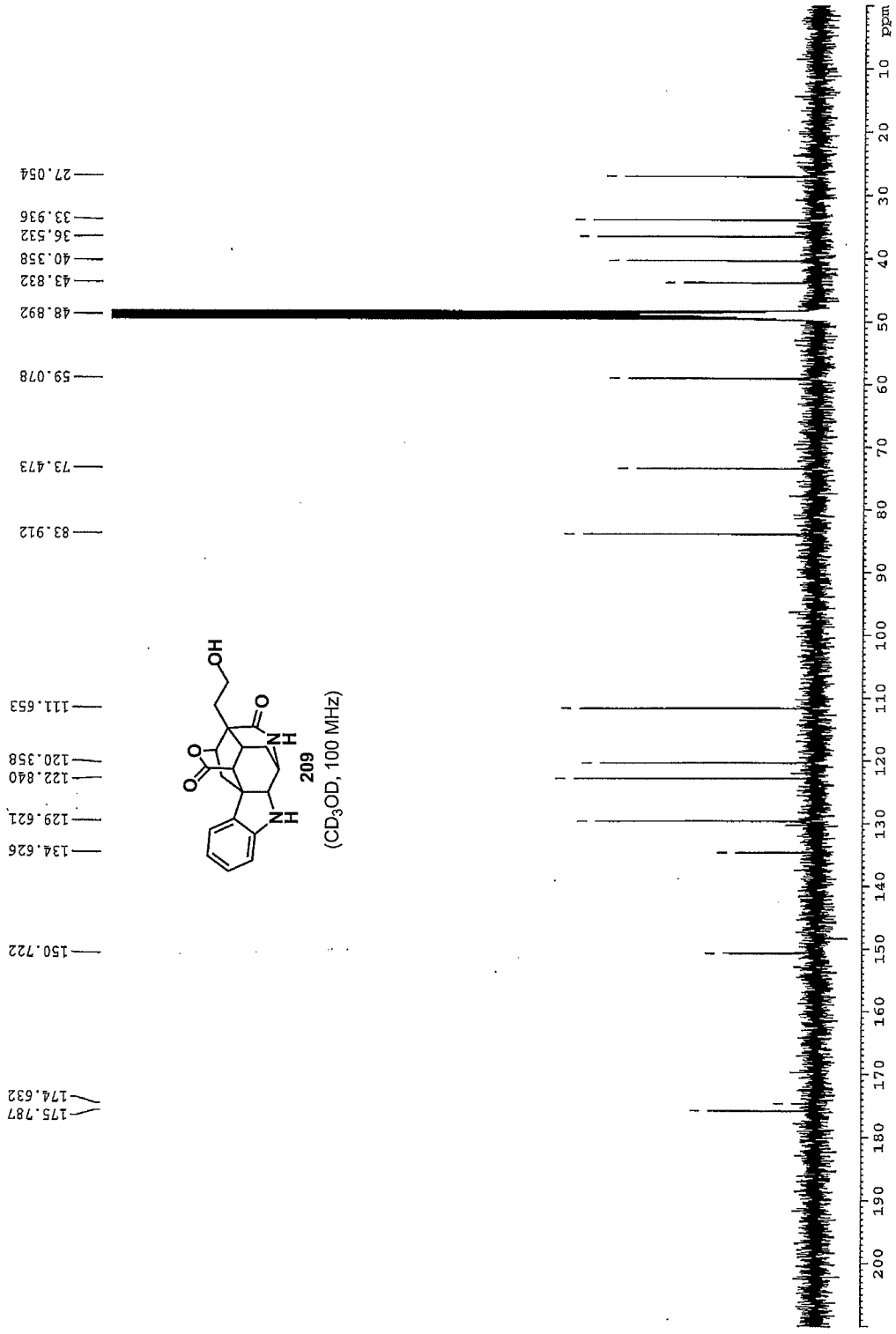

184
(CDCl3, 500 MHz)
ppm
1.202
3.348
2.077
1.017
1.037
1.035
1.019
2.097
1.070
1.010
1.032
1.028
1.078
1.000

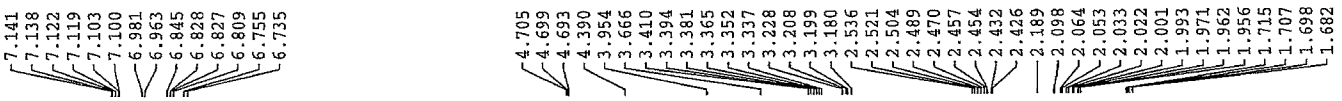

29.508
34.108
34.276
38.465
40.949
45.673
49.552
66.545
81.287
120.482
121.900
122.482
127.292
131.018
131.835
136.876
153.834
171.717
172.085
182.023
ppm
184
(CDCl3, 125 MHz)

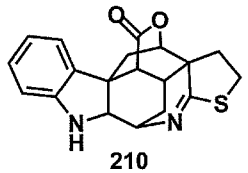

202
(CDCl3, 500 MHz)
ppm


7.033
33.619
33.907
34.112
40.115
47.616
49.760
52.331
57.437
76.684
77.365
77.568
121.606
122.223
127.184
129.423
141.705
153.501
170.918
171.019
181.016
202
(CDCl3, 100 MHz)
ppm


209
(CD3OD, 500 MHz)
ppm

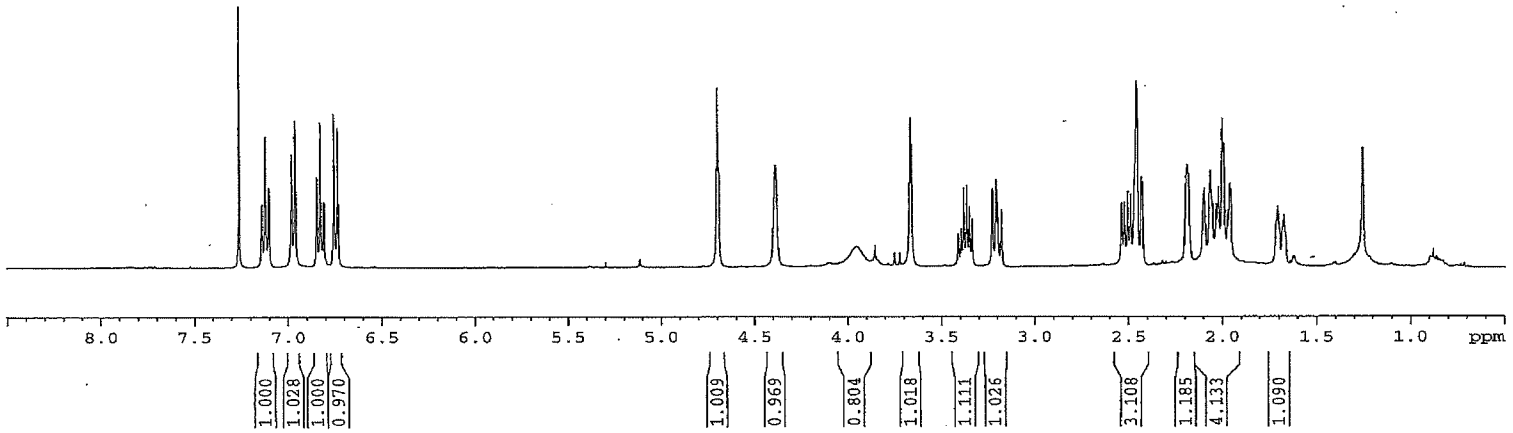

27.054
33.936
36.532
40.358
43.832
48.892
59.078
73.473
83.912
111.653
120.358
122.840
129.621
134.626
150.722
174.632
175.787
209
(CD3OD, 100 MHz)
ppm

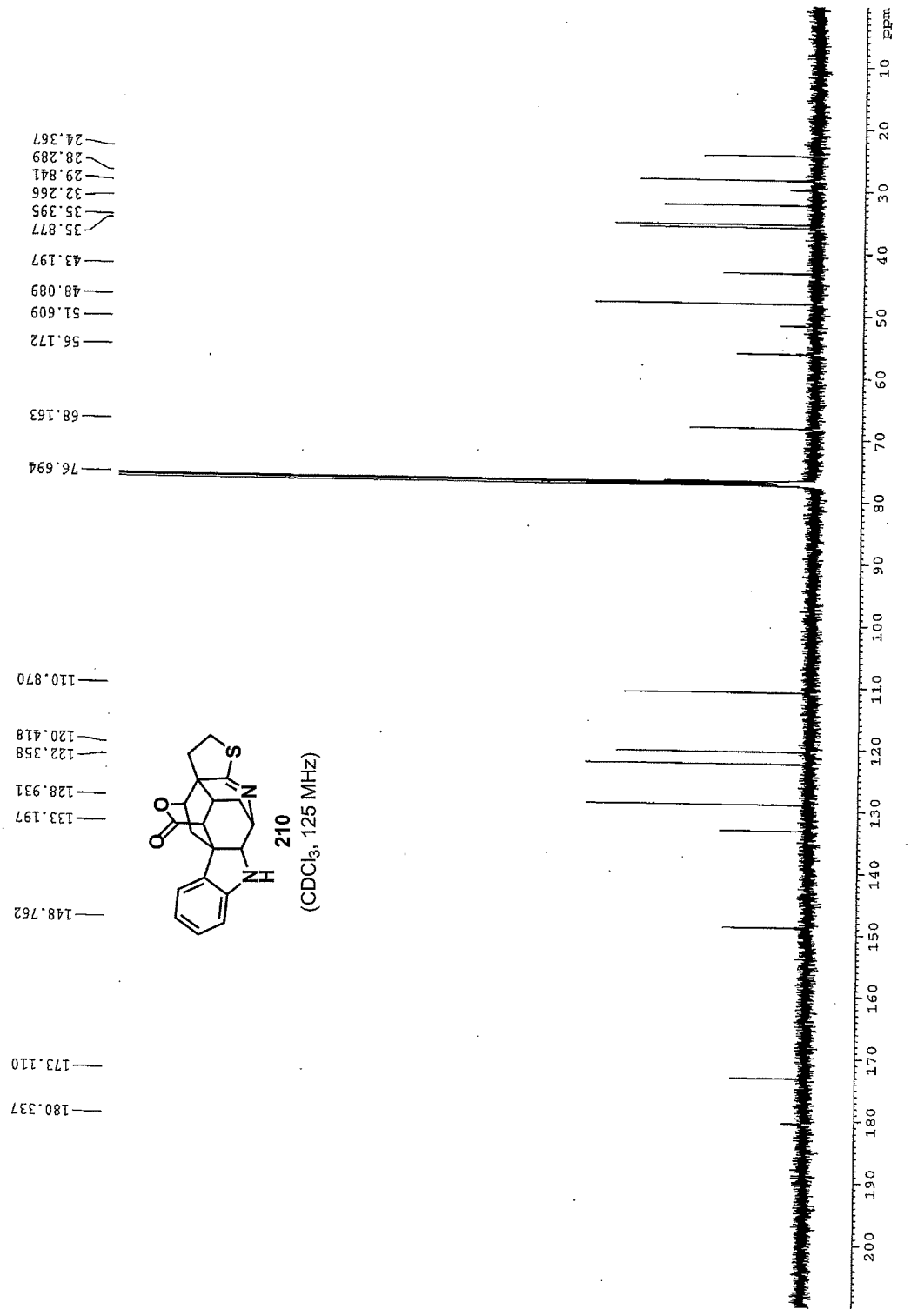


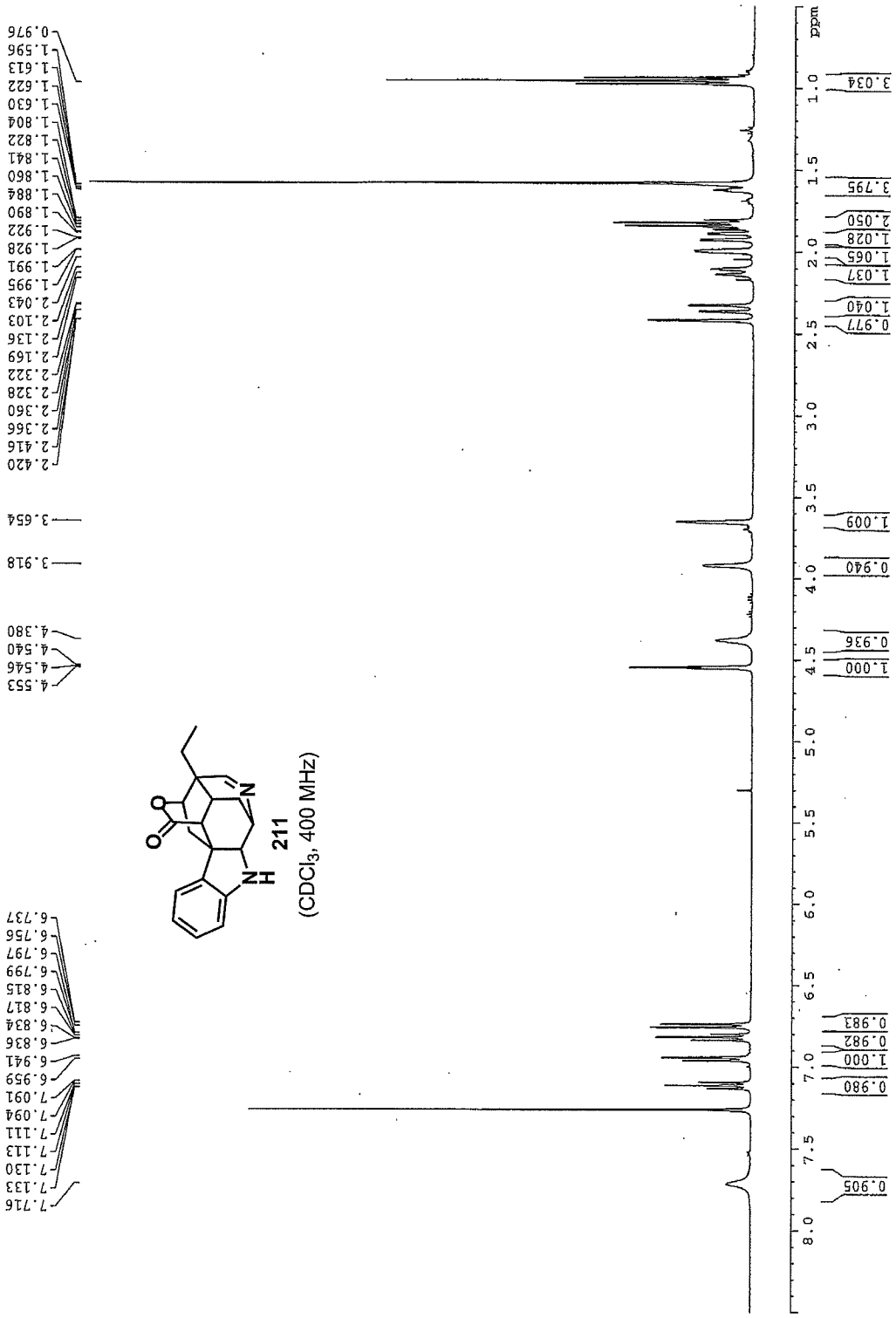


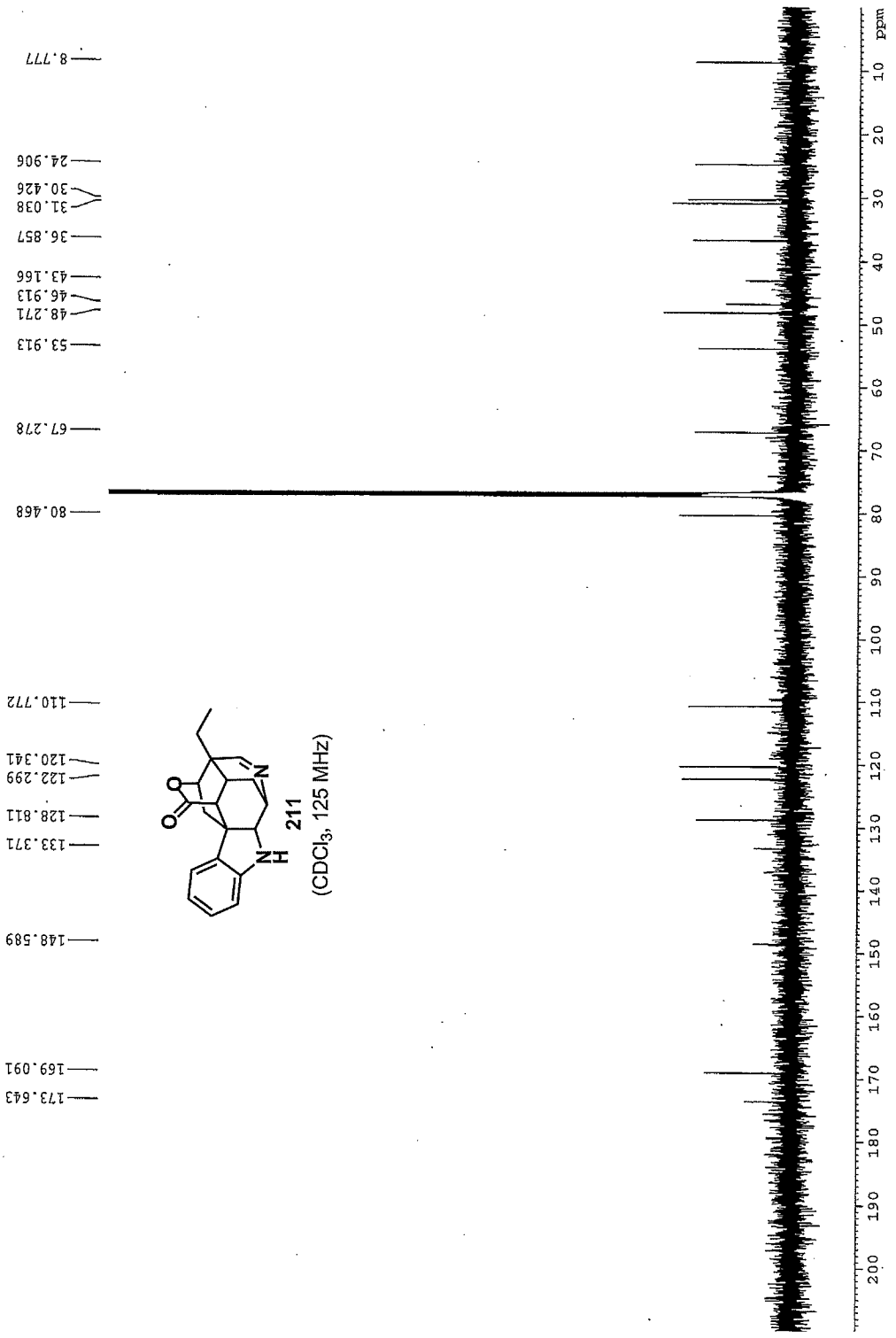
210

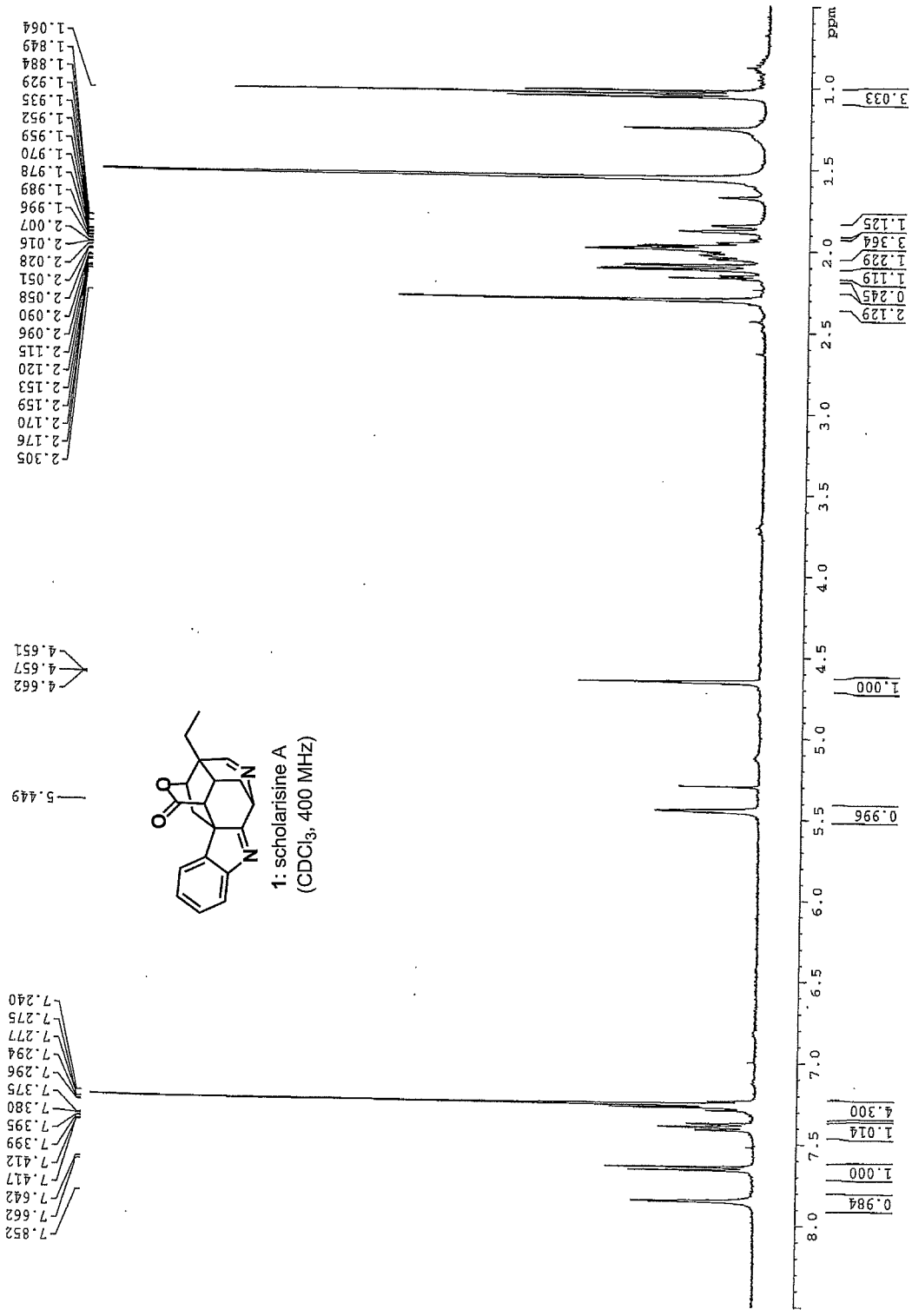
($CDCl_3$, 400 MHz)

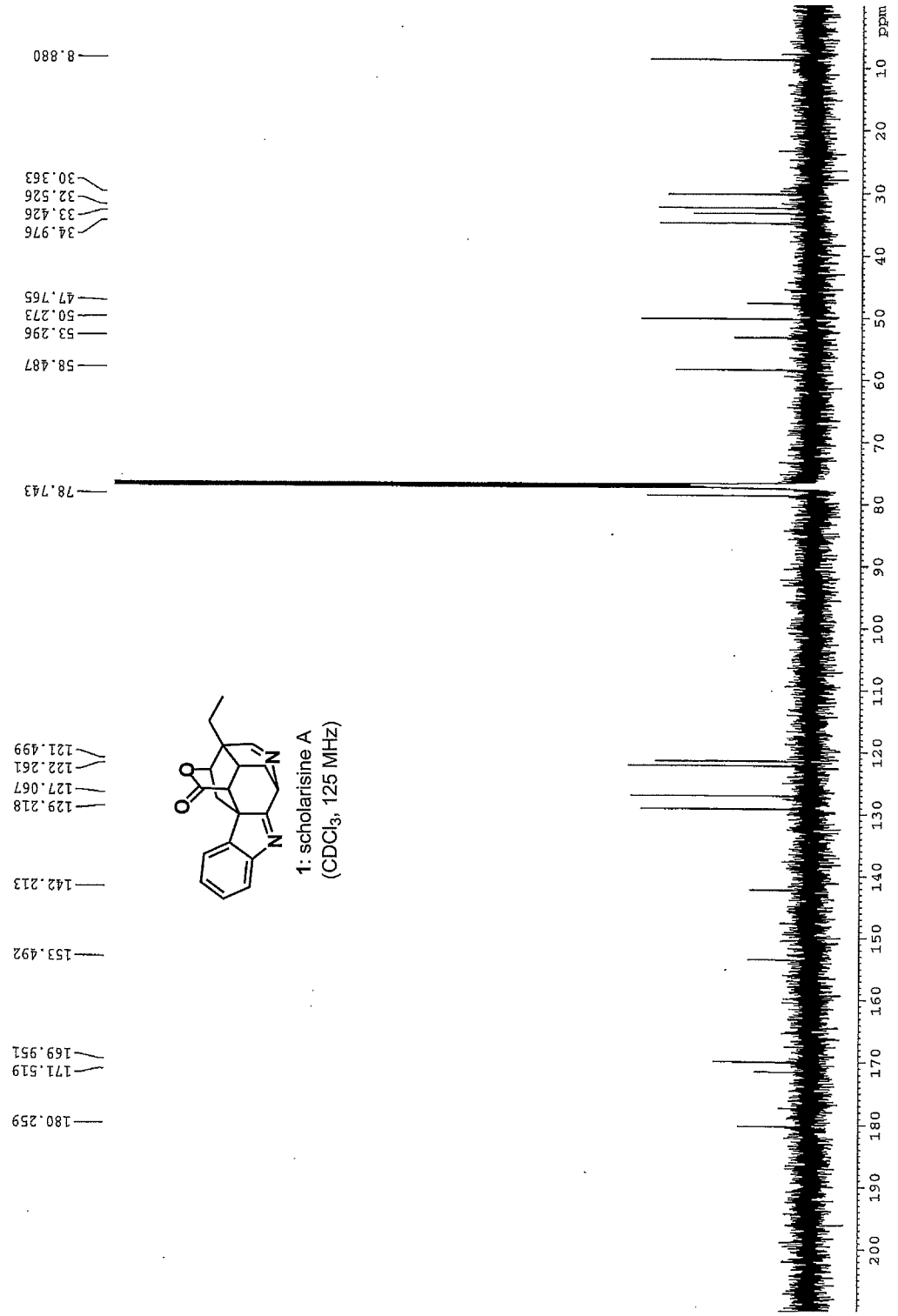



24.367
28.289
29.841
32.266
35.395
35.877
43.197
48.089
51.609
56.172
68.163
76.694
110.870
120.418
122.358
128.931
133.197
148.762
173.110
180.337
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
O
O
S
N
H
210
(CDCl3, 125 MHz)

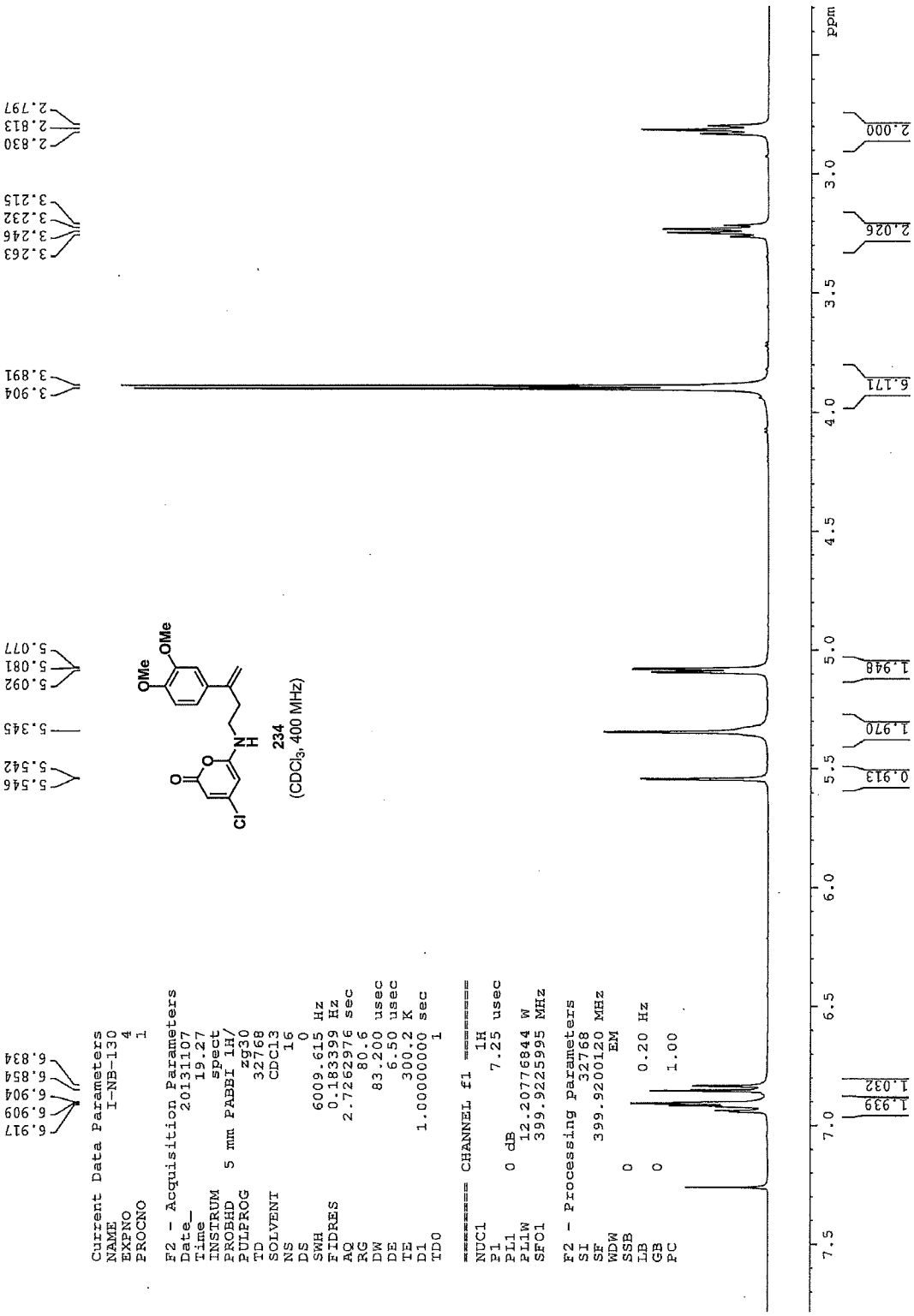

211
(CDCl3, 400 MHz)
ppm

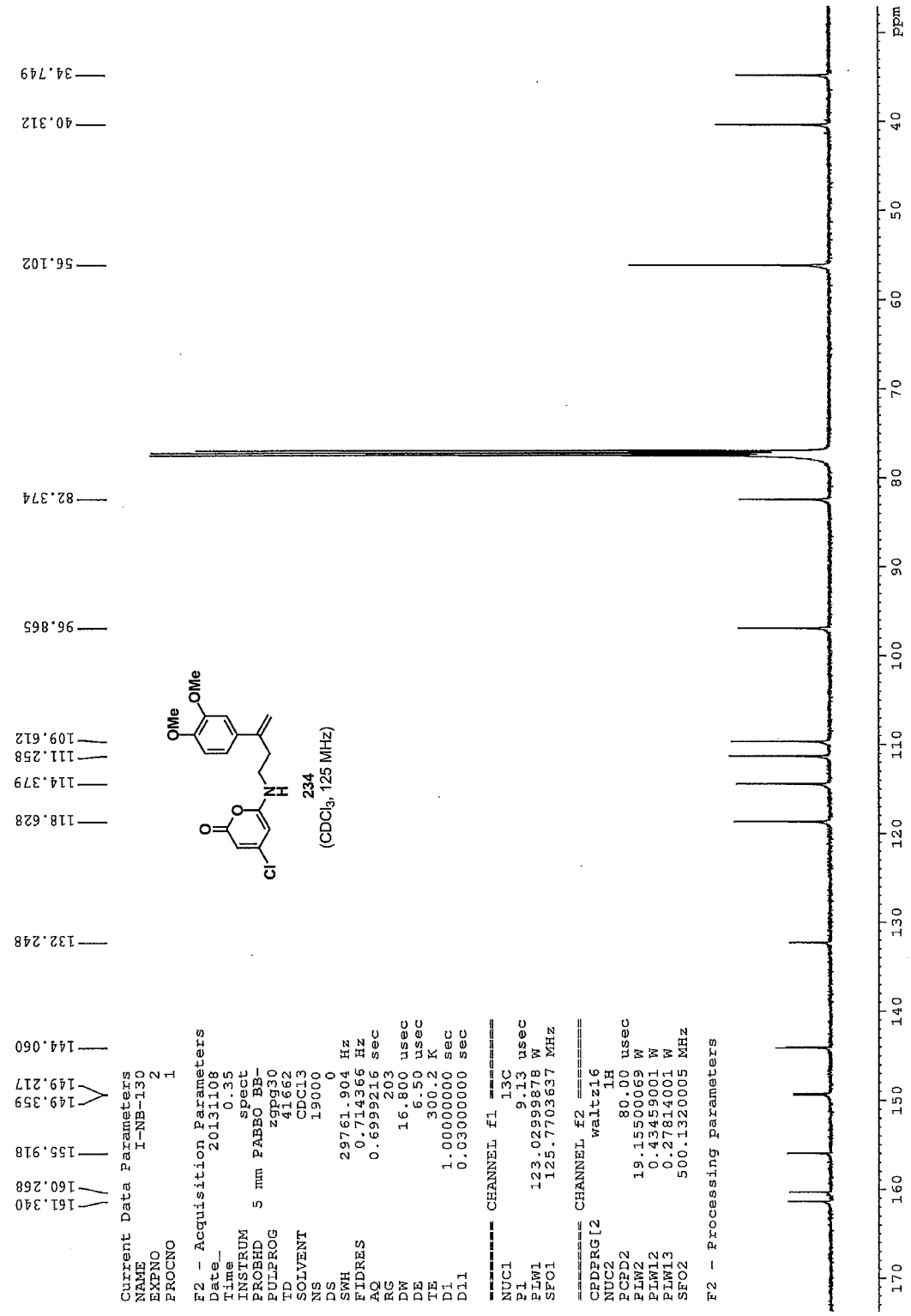

8.777
24.906
30.426
31.038
36.857
43.166
46.913
48.271
53.913
67.278
80.468
110.772
120.341
122.299
128.811
133.371
148.589
169.091
173.643
211
(CDCl3, 125 MHz)
ppm

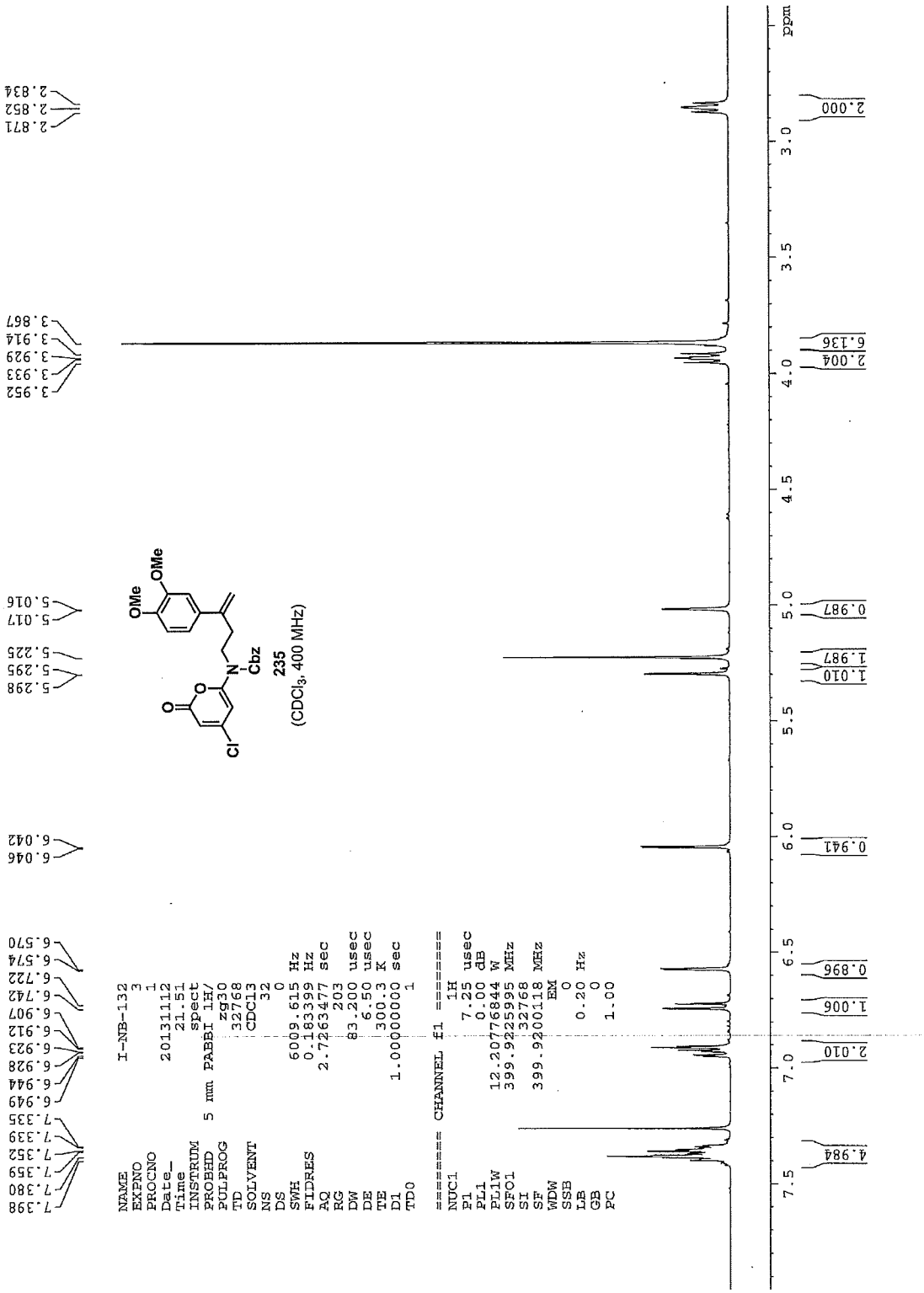

7.852
7.662
7.642
7.417
7.412
7.399
7.395
7.380
7.375
7.296
7.294
7.277
7.275
7.240
5.449
4.662
4.657
4.651
2.305
2.176
2.170
2.159
2.153
2.120
2.115
2.096
2.090
2.058
2.051
2.028
2.016
2.007
1.996
1.989
1.978
1.970
1.959
1.952
1.935
1.929
1.884
1.849
1.064
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
3.033
1.125
3.364
1.229
1.119
0.245
2.129
1.000
0.996
4.300
1.014
1.000
0.984
1: scholarisine A
(CDCl3, 400 MHz)

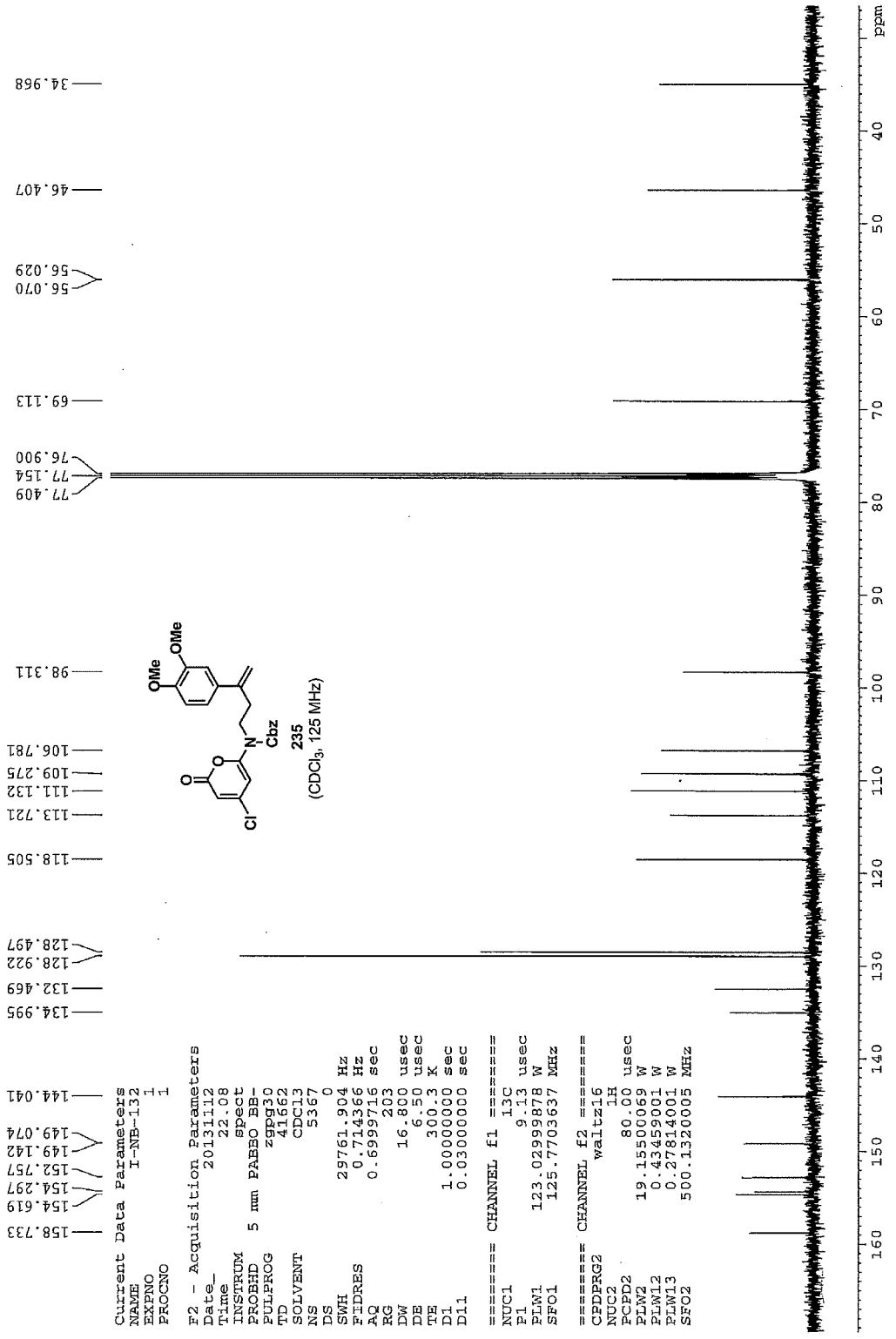


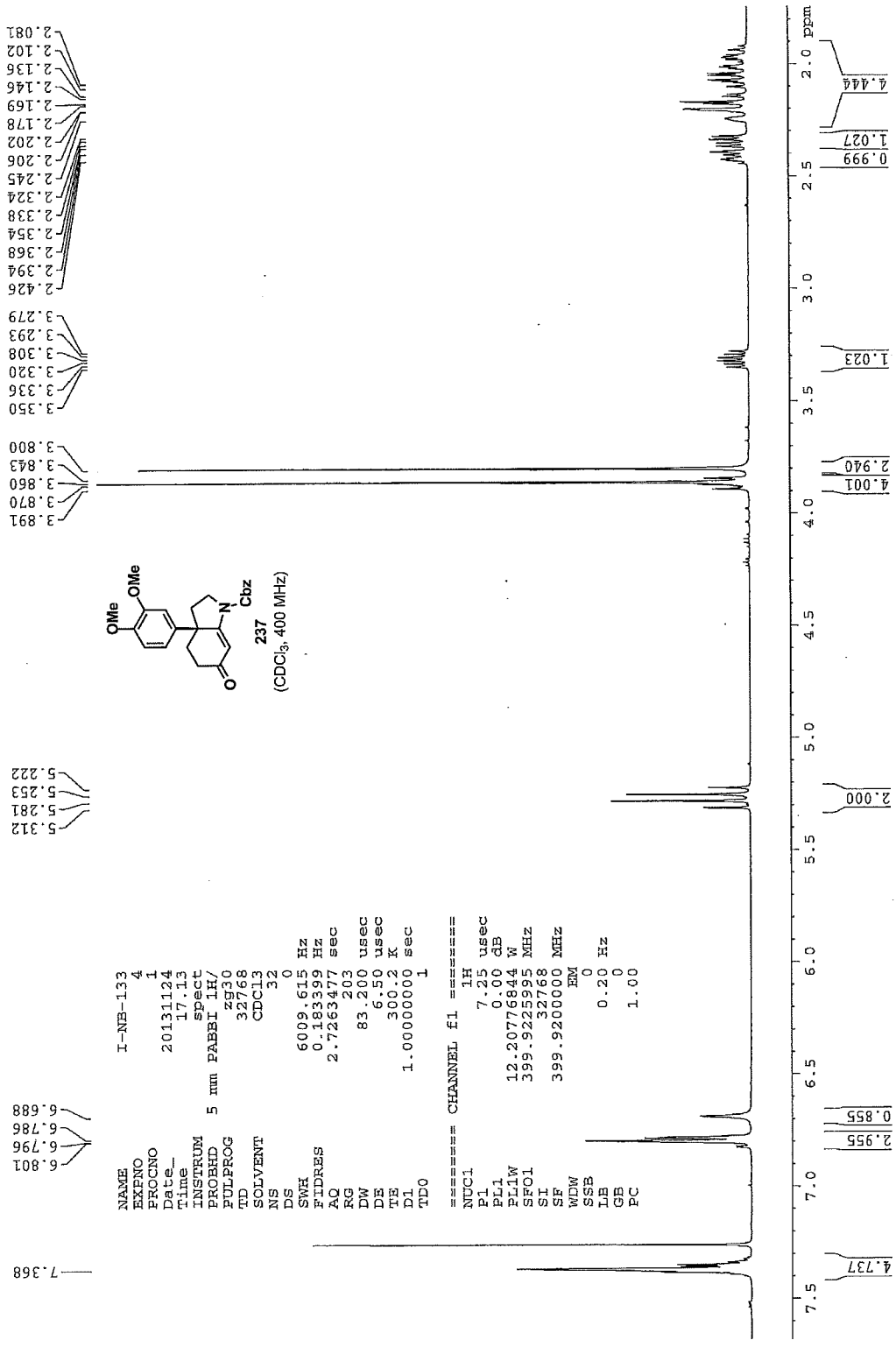
1: scholarisine A
($CDCl_3$, 125 MHz)

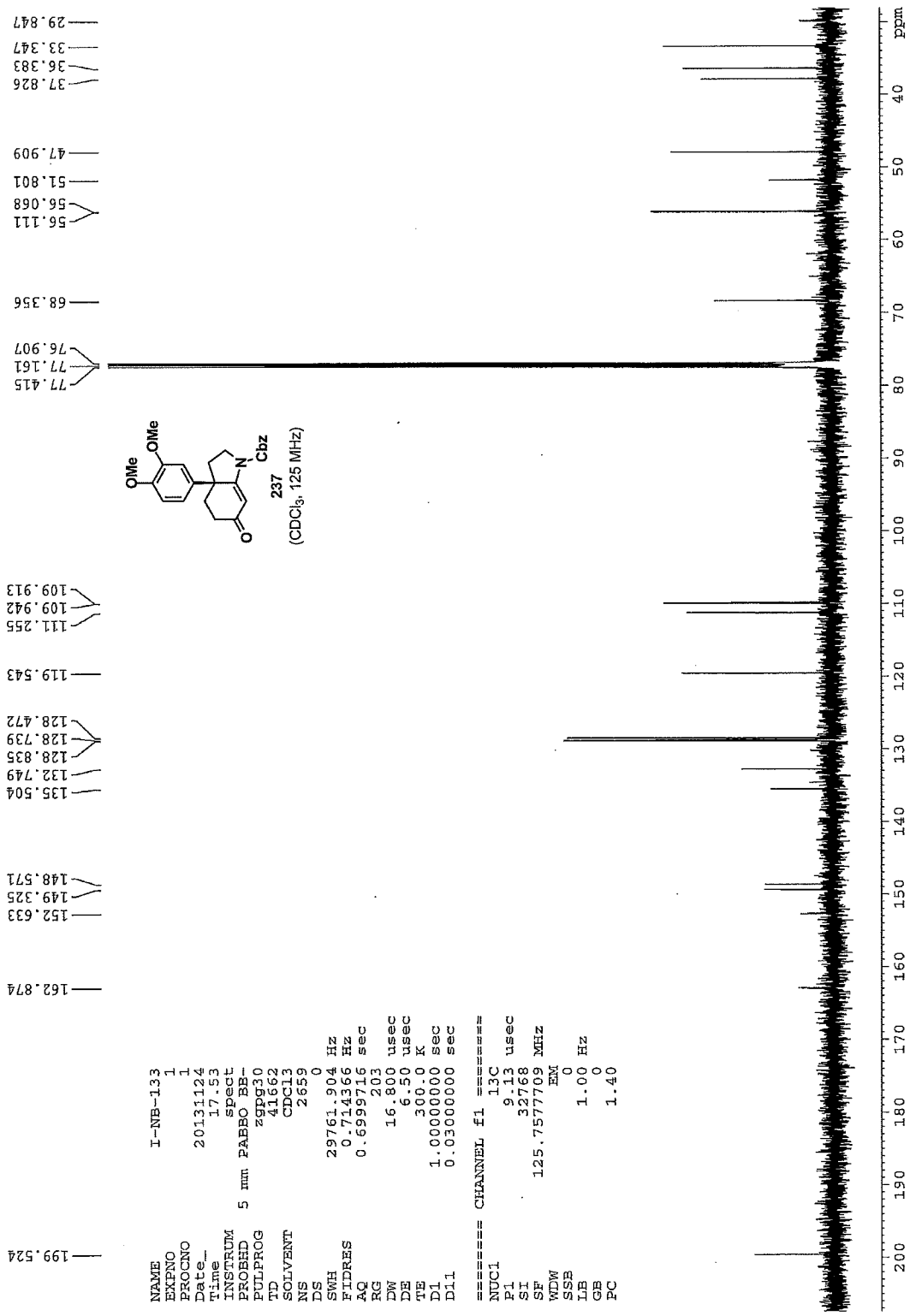

234
(CDCl3, 400 MHz)
OMe
OMe
Cl
Current Data Parameters
NAME I-NB-130
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20131107
Time 19.27
INSTRUM spect
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 6009.615 Hz
FIDRES 0.183399 Hz
AQ 2.7262976 sec
RG 80.6
DW 83.200 usec
DE 6.50 usec
TE 300.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 7.25 usec
PL1 0 dB
PL1W 12.20776844 W
SFO1 399.9225995 MHz
F2 - Processing parameters
SI 32768
SF 399.9200120 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
6.917
6.909
6.904
6.854
6.834
5.546
5.542
5.345
5.092
5.081
5.077
3.904
3.891
3.263
3.246
3.232
3.215
2.830
2.813
2.797
1.939
1.032
0.913
1.970
1.948
6.171
2.026
2.000
ppm

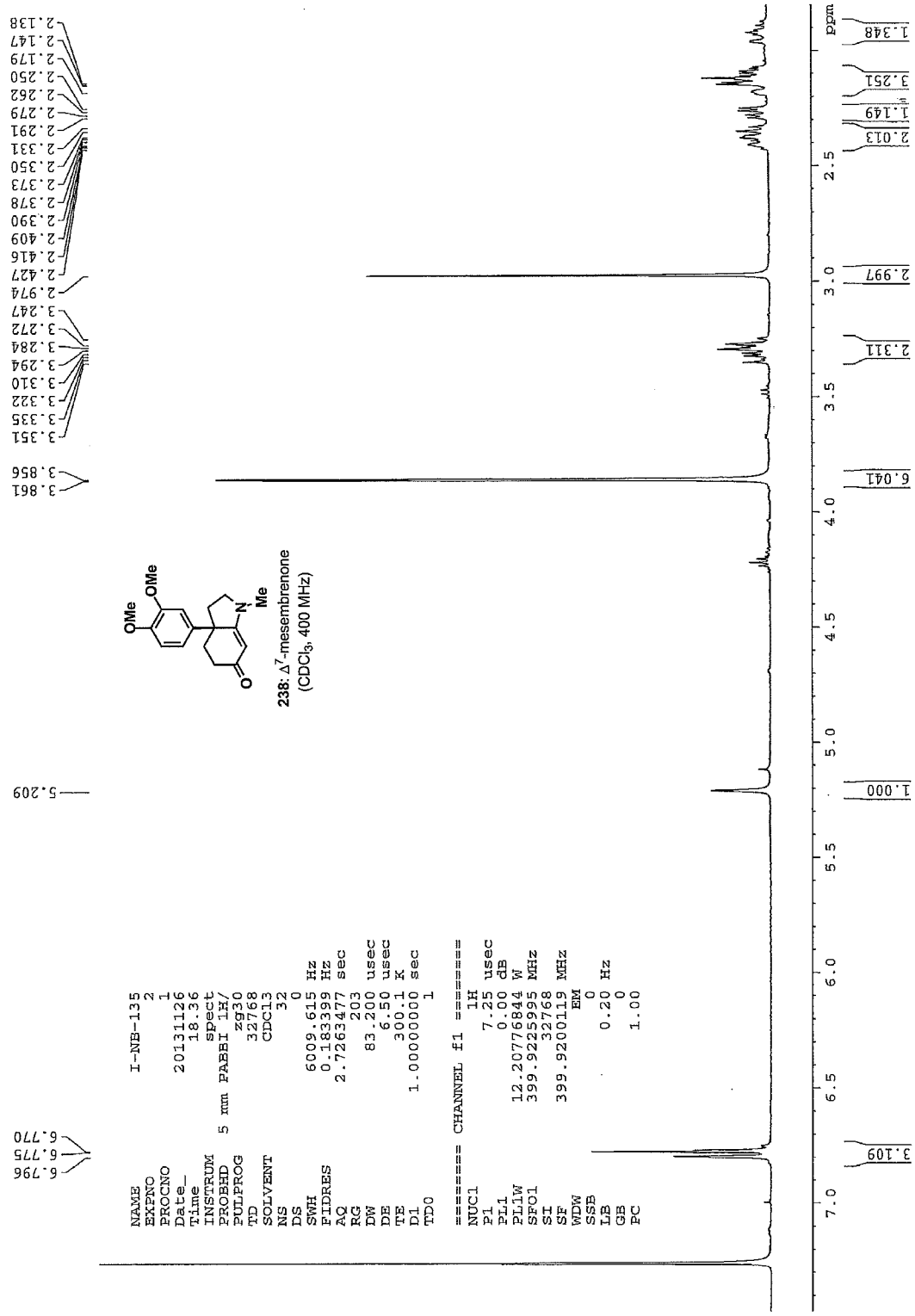

Current Data Parameters
NAME 1-NB-130
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20131108
Time 0.35
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 41662
SOLVENT CDCl3
NS 19000
DS 0
SWH 29761.904 Hz
FIDRES 0.714366 Hz
AQ 0.69999216 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 300.2 K
D1 1.00000000 sec
D11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 9.13 usec
PLW1 123.02999878 W
SFO1 125.7703637 MHz
CHANNEL f2
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PLW2 19.15500069 W
PLW12 0.43459001 W
PLW13 0.27814001 W
SFO2 500.1320005 MHz
F2 - Processing parameters
OMe
OMe
N
H
O
O
Cl
234
(CDCl3, 125 MHz)
161.340
160.268
155.918
149.359
149.217
144.060
132.248
118.628
114.379
111.258
109.612
96.865
82.374
56.102
40.312
34.749
ppm

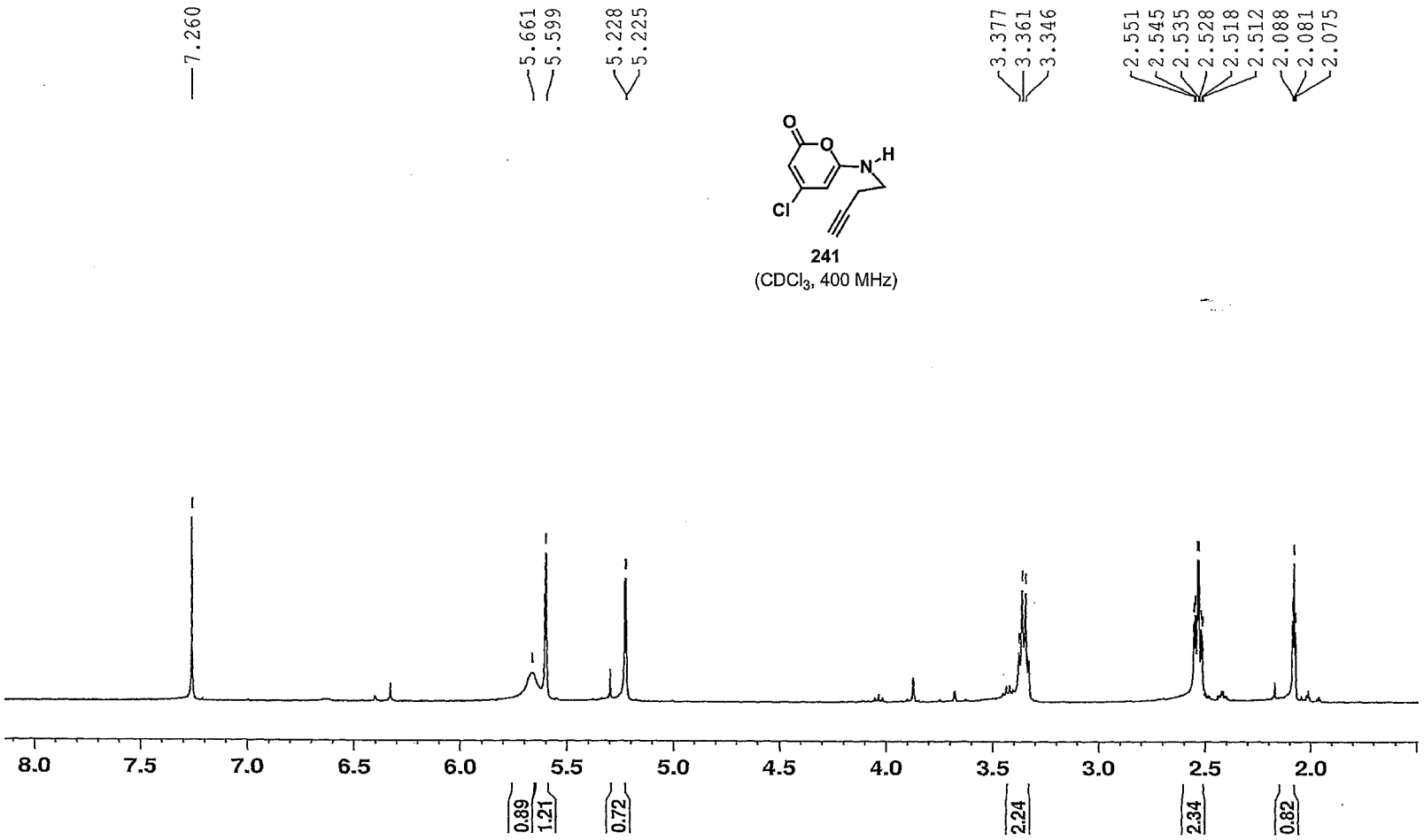

OMe
OMe
N
Cbz
O
O
Cl
235
(CDCl3, 400 MHz)
ppm


158.733
154.619
154.297
152.757
149.142
149.074
144.041
134.995
132.469
128.922
128.497
118.505
113.721
111.132
109.275
106.781
98.311
77.409
77.154
76.900
69.113
56.070
56.029
46.407
34.968
OMe
OMe
Cbz
N
O
O
Cl
235
(CDCl3, 125 MHz)
ppm
Current Data Parameters
NAME I-NB-132
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20131112
Time 22.08
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 41662
SOLVENT CDCl3
NS 5367
DS 0
SWH 29761.904 Hz
FIDRES 0.714366 Hz
AQ 0.6999716 sec
RG 203
DW 16.800 usec
DB 6.50 usec
TE 300.3 K
D1 1.00000000 sec
D11 0.03000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 9.13 usec
PLW1 123.02999878 W
SFO1 125.7703637 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PLW2 19.15500069 W
PLW12 0.43459001 W
PLW13 0.27814001 W
SFO2 500.1320005 MHz

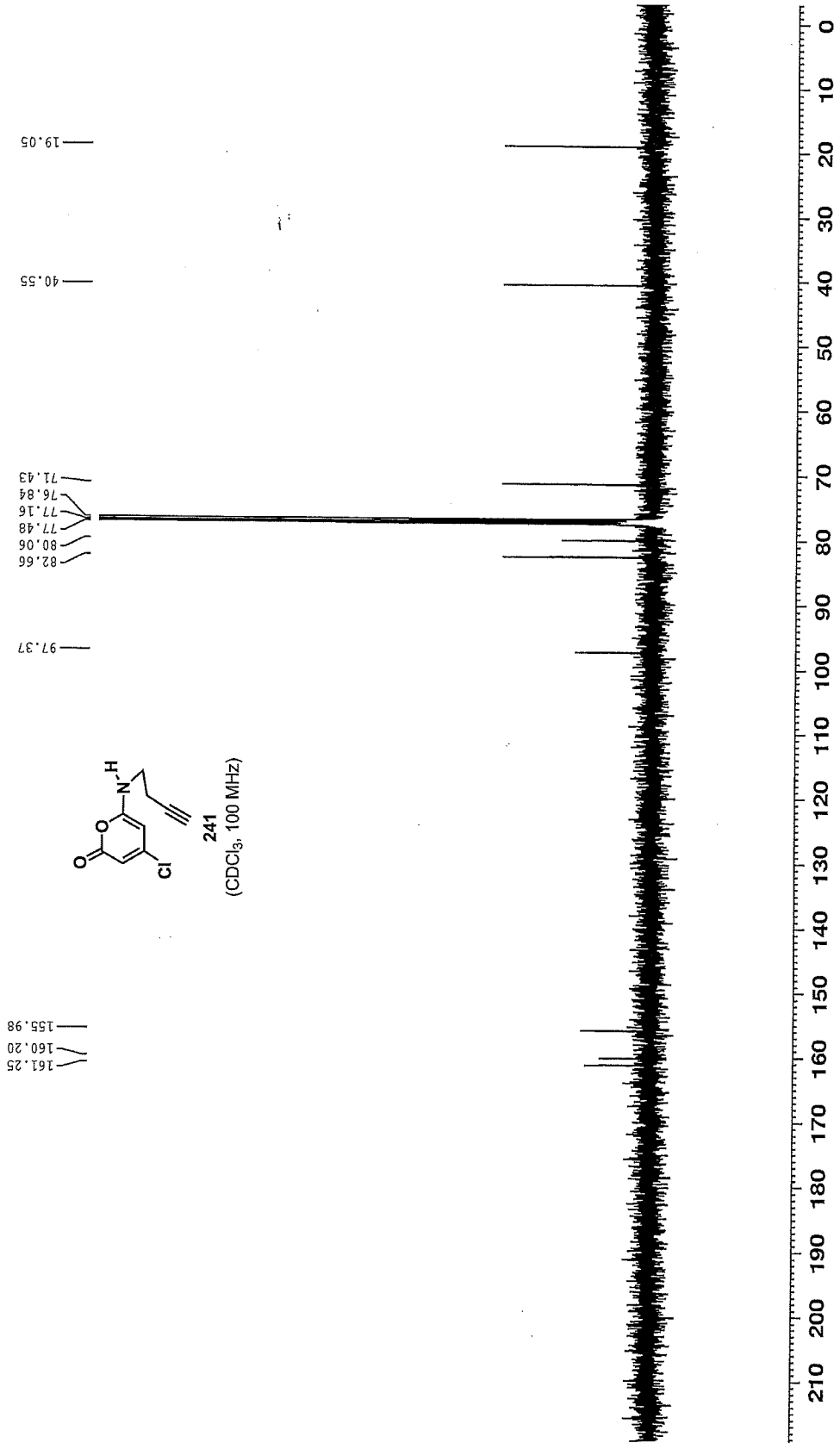

OMe
OMe
N
Cbz
O
237
(CDCl3, 400 MHz)
NAME I-NB-133
EXPNO 4
PROCNO 1
Date_ 20131124
Time 17.13
INSTRUM spect
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 0
SWH 6009.615 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 203
DW 83.200 usec
DE 6.50 usec
TE 300.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 7.25 usec
PL1 0.00 dB
PL1W 12.20776844 W
SFO1 399.9225995 MHz
SI 32768
SF 399.9200000 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
7.368
6.801
6.796
6.786
6.688
5.312
5.281
5.253
5.222
3.891
3.870
3.860
3.843
3.800
3.350
3.336
3.320
3.308
3.293
3.279
2.426
2.394
2.368
2.354
2.338
2.324
2.245
2.206
2.202
2.178
2.169
2.146
2.136
2.102
2.081
4.737
2.955
0.855
2.000
4.001
2.940
1.023
0.999
1.027
4.444
ppm

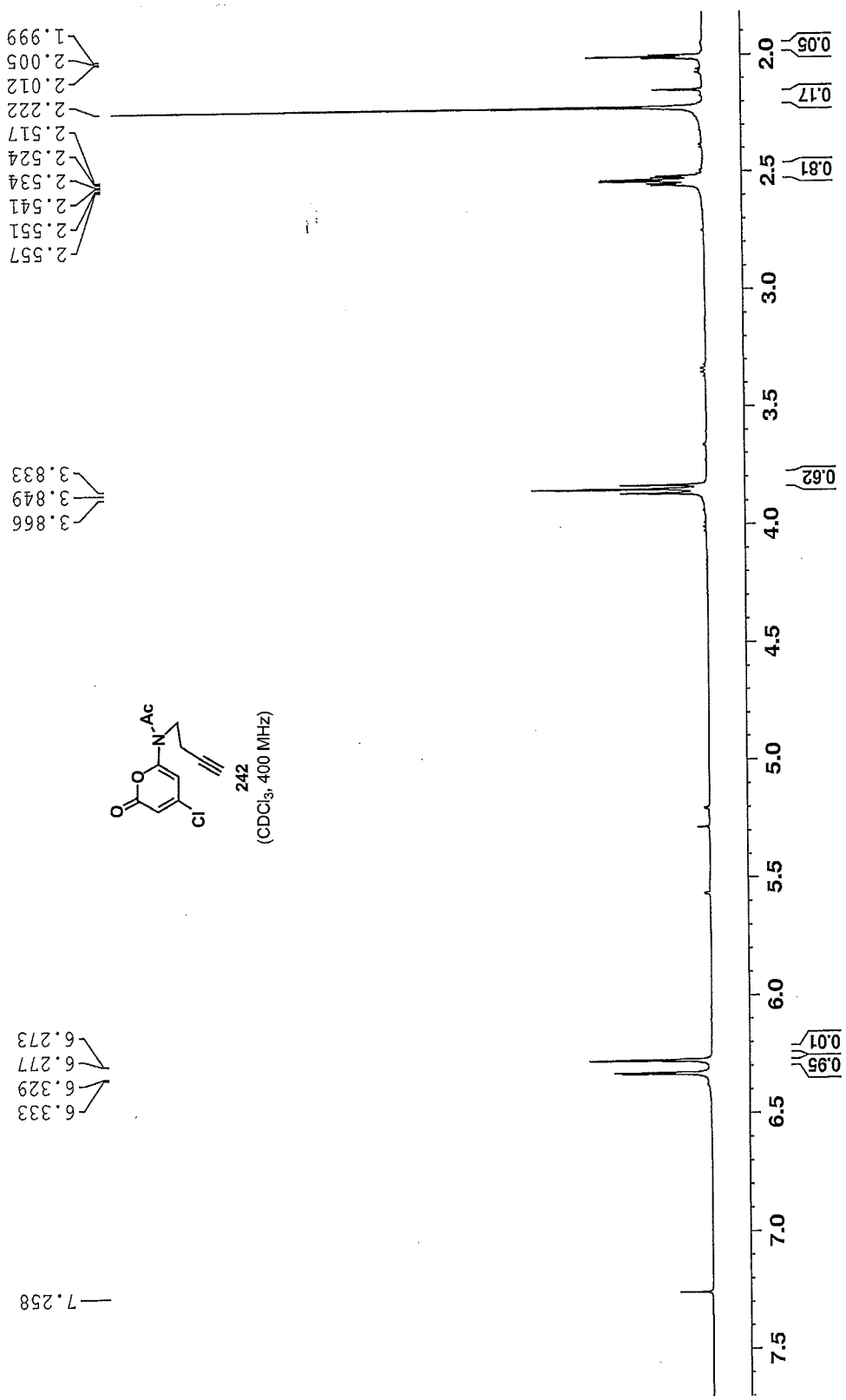

OMe
OMe
Cbz
O
N
237
(CDCl3, 125 MHz)
199.524
162.874
152.633
149.325
148.571
135.504
132.749
128.835
128.739
128.472
119.543
111.255
109.942
109.913
77.415
77.161
76.907
68.356
56.111
56.068
51.801
47.909
37.826
36.383
33.347
29.847
ppm
NAME I-NB-133
EXPNO 1
PROCNO 1
Date_ 20131124
Time 17.53
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 41662
SOLVENT CDCl3
NS 2659
DS 0
SWH 29761.904 Hz
FIDRES 0.714366 Hz
AQ 0.6999716 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
D11 0.03000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 9.13 usec
SI 32768
SF 125.7577709 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

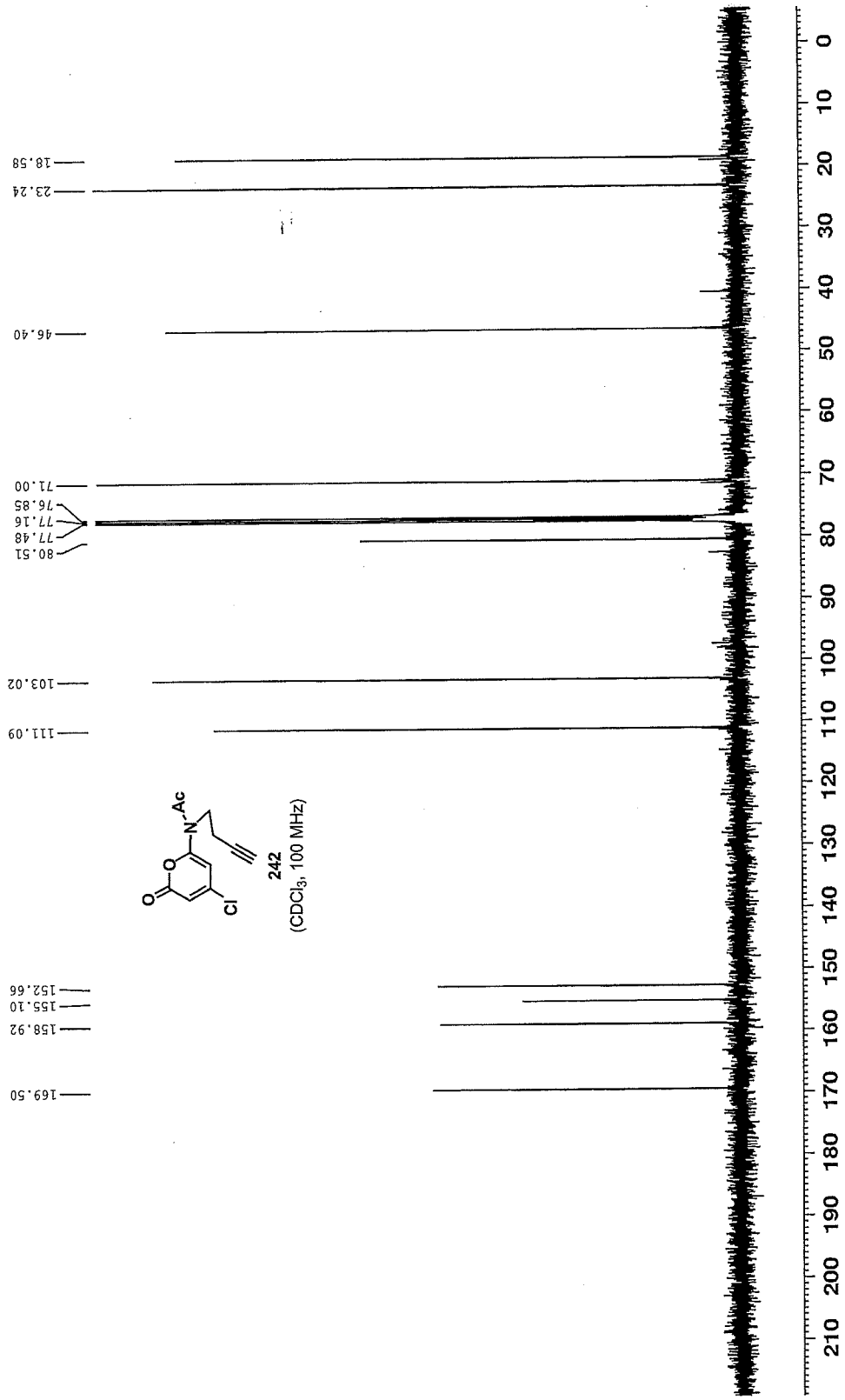

238: Δ7-mesembrenone
(CDCl3, 400 MHz)
OMe
OMe
N
Me
O
NAME I-NB-135
EXPNO 2
PROCNO 1
Date_ 20131126
Time_ 18.36
INSTRUM spect
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 0
SWH 6009.615 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 203
DW 83.200 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 7.25 usec
PL1 0.00 dB
PL1W 12.20776844 W
SFO1 399.9225995 MHz
SI 32768
SF 399.9200119 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
6.796
6.775
6.770
5.209
3.861
3.856
3.351
3.335
3.322
3.310
3.294
3.284
3.272
3.247
2.974
2.427
2.416
2.409
2.390
2.378
2.373
2.350
2.331
2.291
2.279
2.262
2.250
2.179
2.147
2.138
1.000
6.041
2.311
2.997
2.013
1.149
3.251
1.348
3.109
ppm



241
($CDCl_3$, 400 MHz)


19.05
40.55
71.43
76.84
77.16
77.48
80.06
82.66
97.37
155.98
160.20
161.25
241
(CDCl3, 100 MHz)
Cl
O
N
H
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


1.999
2.005
2.012
2.222
2.517
2.524
2.534
2.541
2.551
2.557
3.833
3.849
3.866
6.273
6.277
6.329
6.333
7.258
0.05
0.17
0.81
0.62
0.95
0.01
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
Ac
N
O
O
Cl
242
(CDCl3, 400 MHz)


18.58
23.24
46.40
71.00
76.85
77.16
77.48
80.51
103.02
111.09
152.66
155.10
158.92
169.50
N
Ac
O
O
Cl
242
(CDCl3, 100 MHz)
0
10
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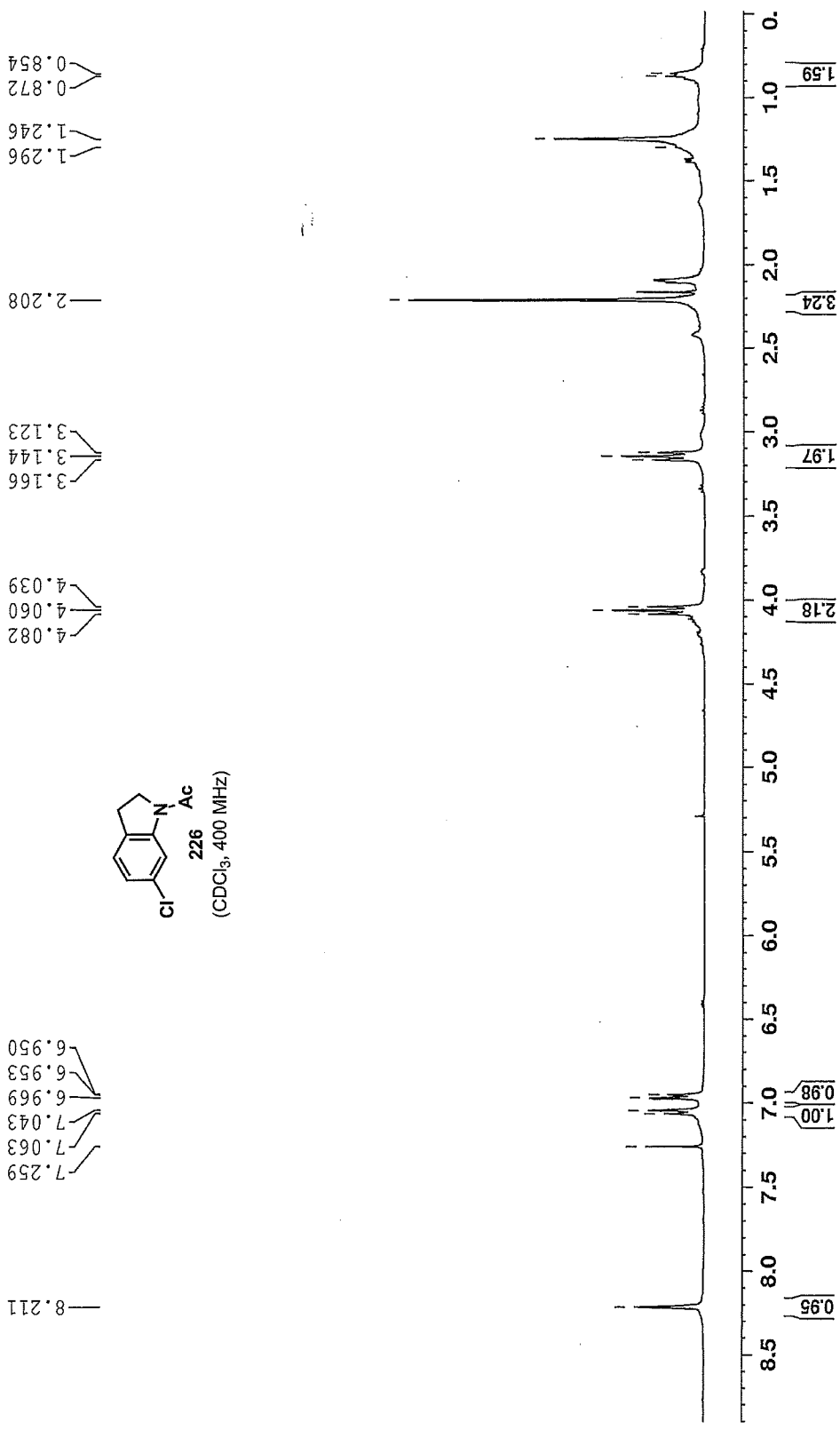
8.211
7.259
7.063
7.043
6.969
6.953
6.950
4.082
4.060
4.039
3.166
3.144
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1.296
1.246
0.872
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0.95
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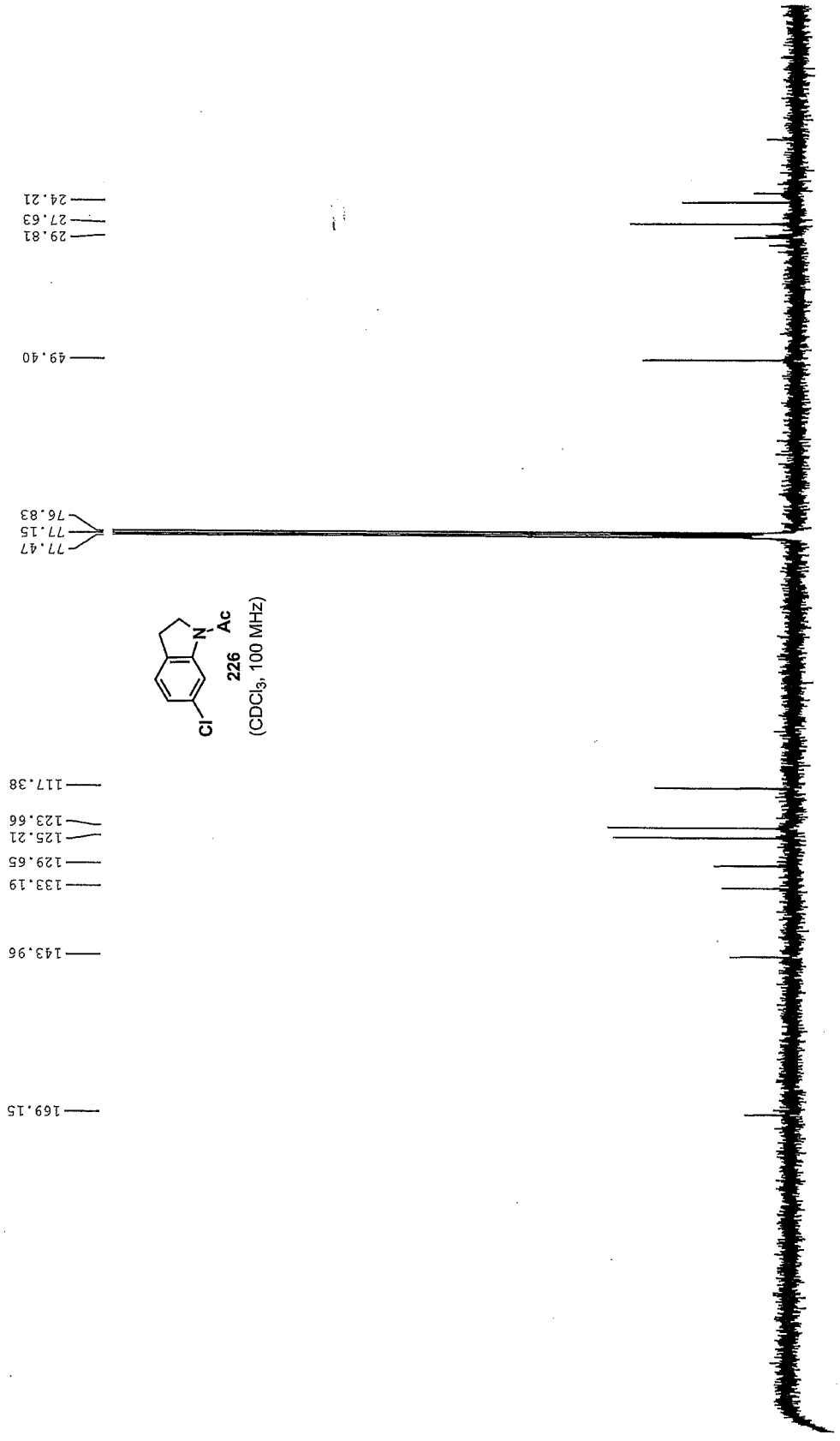
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27.63
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77.15
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169.15
N
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(CDCl3, 100 MHz)

CHAPTER 3

STUDIES TOWARD STRICTAMINE AND RELATED AKUAMMILINE ALKALOIDS

3.1. Introduction

Having successfully completed a concise synthesis[1] of the rather unique akuammiline alkaloid (+)-scholarisine A (**1**, Figure 1) as described in the previous chapter, we next set our sights on a more general synthetic solution to this alkaloid class,[2] wherein the efficient preparation of the core scaffold **2** would be paramount – a structure which, until Garg's elegant synthesis of picrinine (**3**) in 2014, had never been formed synthetically, despite considerable effort.[3] As a less-oxygenated member of akuammiline class that embodies this framework, and one that could potentially lead to other related scaffolds (e.g. **4**, **6**–**8**, *vide infra*), we selected strictamine (**5**) as a logical first target.[4] Indeed, this structure bears a rich history as a challenging molecule for synthesis, having not succumbed to total synthesis at the time we began our studies, despite efforts dating back to the early 1970s. Additionally, we were drawn to the fact that **5** possesses several known biological activities (e.g. MAO inhibition, antiviral activity), which augurs well for its use in possible biomedical applications.[5]

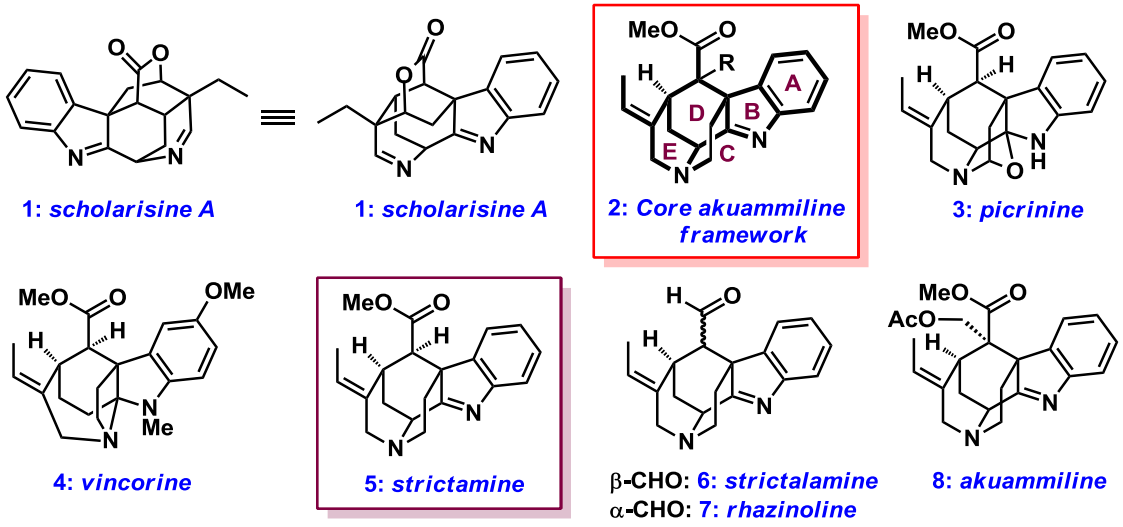


Figure 1. Completed target scholarisine A (**1**) and a a cross section of akuammiline alkaloids of interest to the present synthetic study.

In this chapter, the isolation, biosynthesis and activity of strictamine (**5**) will be briefly detailed, followed by a summary of the previous synthetic efforts toward this target, with an emphasis on how these studies informed our own approach to this complex alkaloid. We then report in detail our own efforts to synthesize **5**, which, through a number of empowering methodological advances, have culminated in a concise and readily scalable route to a number of advanced tetracyclic intermediates. These intermediates, many embodying all the carbon atoms of strictamine (**5**), are poised for final E-ring formation to complete the total syntheses of **5** and related targets such as strictalamine (**6**). Finally, we disclose additional discoveries that should allow for general access to akuammiline class, having identified facile means to transition from the strictamine series to other subfamilies.

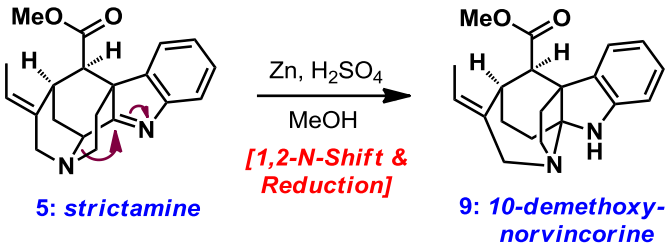
3.2 Isolation, Biological Activity and Biosynthesis of Strictamine

3.2.1 Isolation and Structure Determination

Strictamine was isolated in 1966 by the teams of Biemann and Chatterjee, who proposed its structure on the basis of UV (which indicated the indolenine), IR (which indicated the ester C=O, C=N and C=C), ^{1}H NMR and HRMS data, supported by an array of additional chemical transformations.[4a] Amongst these reactions, particularly intriguing is the reductive rearrangement of strictamine to 10-demethoxynorvincorine (**9**, Scheme 1), an alkaloid isolated half a century later from *Ervatamia officinalis*,[6] through the use of Zn and H_2SO_4 in MeOH (although in unspecified yield and scale).[i] Later, in 1977, the teams of Ahmad, Clardy and Le Quesne confirmed the previous structural assignment through

[i] It was our hope to utilize such conversions to access the full breadth of structures of the akuammiline class, in this case to translate strictamine-type stuctures into those of the vincorine-type alkaloids.

single crystal X-ray analysis, securing both the relative and absolute configuration of **5** (the latter through anomalous dispersion with Cu Kα radiation).[4b]



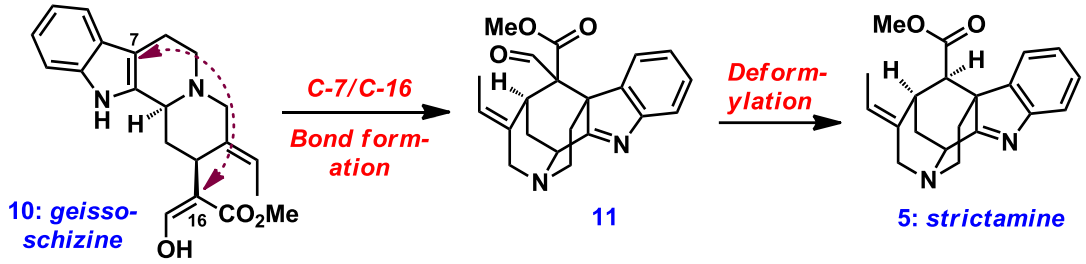
Scheme 1. Reductive conversion of strictamine (**5**) into 10-demethoxy-norvincorine (**9**).

3.2.2 Biological Activity

As one of the more abundant akuammiline members, strictamine (**5**) is available in fair amounts from natural sources (0.00175 wt% from the dried leaves of *Rhazya stricta*)[4b] and, as such, has been subjected to several biological assays. As mentioned in Section 1.2.1, **5** was found to possess monoamine oxidase antagonist activity,[5a] while recent *in vitro* studies have uncovered encouraging antiviral activity against herpes simplex virus (HSV) and adenovirus (Adv) with EC_{50} values of 0.36 μM and 0.28 μM, respectively.[5b] The latter activities were greater than those of the positive control acyclovir (ACV) [HSV: EC_{50} = 0.38 μM, Adv: EC_{50} = 1.97 μM], though **5** proved far less selective in its effect on uninfected cells. Additionally, strictamine has been shown to act as an inhibitor of nuclear factor-κB (NF-κB), a protein complex that plays an important role in regulating gene expression involved in the immune and inflammatory responses.[5c] Indeed, this cellular target is the subject of active investigation in the pharmaceutical industry for potential cancer therapies.[7]

3.2.3 Biosynthesis

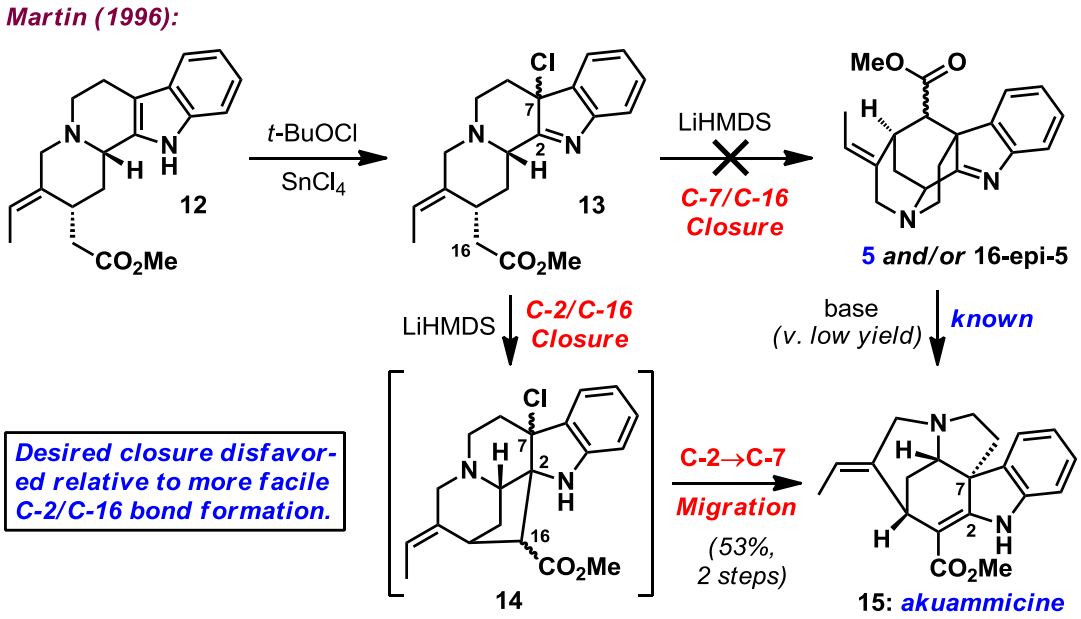
As noted in Section 1.2.2, being an archetypal akuammiline alkaloid, **5** is thought to derive biosynthetically from geissoschizine (**10**) through an unspecified bond formation between C-7 and C-16 to initially deliver **11** (both epimers of which are natural products: β-CHO: rhazinaline; α-CHO: rhazimal). From this compound (**11**), strictamine (**5**) could be readily formed through deformylation as shown in Scheme 2.[2]



Scheme 2. Proposed biosynthesis for strictamine (**5**) from key biosynthetic precursor geissoschizine (**10**).

3.3 Previous Synthetic Efforts toward Strictamine

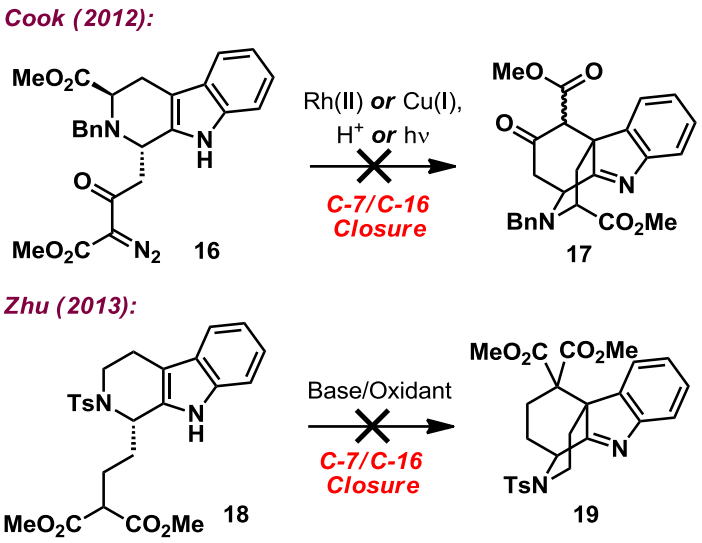
In light of the many impressive syntheses of geissoschizine and related compounds (proceeding in as few as eight steps from tryptamine),[3] it is not surprising that the strategy of fashioning the akuammiline framework through a biomimetic C-7/C-16 union has been explored synthetically.



Scheme 3. Martin's attempts to effect a biomimetic C-7/C-16 bond formation from chloroindolenine **13**.

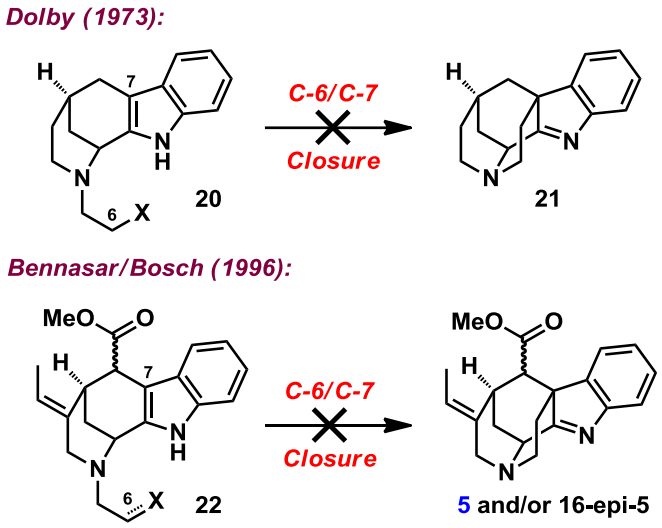
Indeed, studies by Martin found that chloroindolenine **13**, generated from deformylgeissoschizine (**12**) by treatment with *t*-BuOCl, reacted exclusively at the C-2 imine when treated with strong base, rather than C-7 (Scheme 3).[9] This bond formation ultimately delivers the *Strychnos* alkaloid akuammicine (**15**) and not akuammiline-type frameworks such as **5**.[ii] Later, Cook[10] attempted to effect transformation using diazo compounds such as **16** (a strategy originally pioneered by Qin and co-workers, see Section 1.3.2), while Zhu[11] and Vanderwal[12] have employed an oxidative coupling approach (Scheme 4). All, however, were unable to effect the desired closure, clearly pointing to the difficulty of reducing such an approach to practice.

[ii] It should be noted that although the conversion of strictamine (**5**) into akuammicine (**15**) under basic conditions is known, it occurs in extremely low yield and thus is unlikely to be a principal pathway in the transformation depicted.[4b]



Scheme 4. Alternate studies towards C-7/C-16 bond formation by Cook and Zhu.

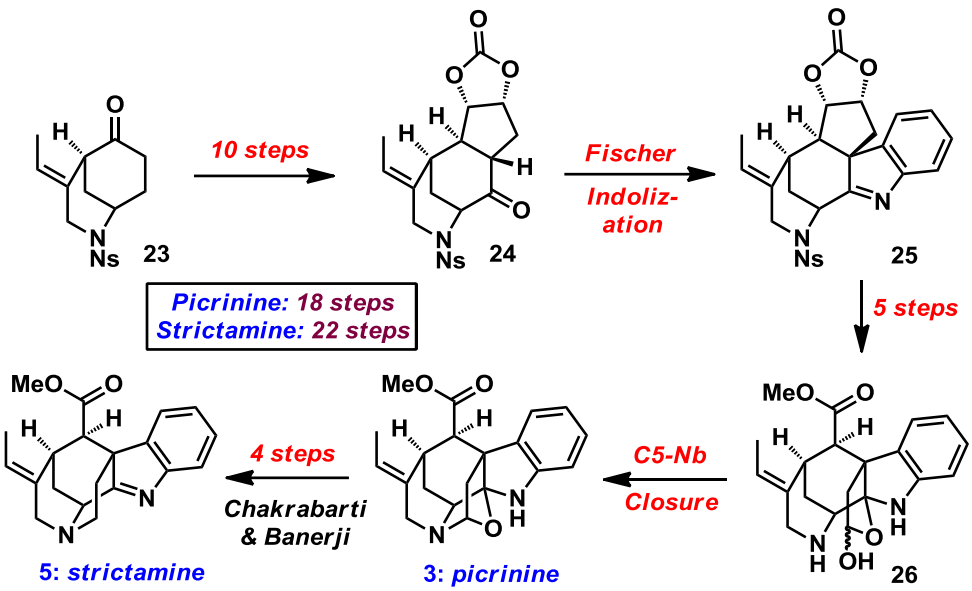
Also informative for our synthetic plan was some of the earliest work towards scaffolds represented by **2**, particularly those undertaken by Dolby and co-workers (Section 1.3.1, summarized in Scheme 5) wherein attempts to fashion the core framework **21** through an intramolecular alkylation at the β-position of indole **20** (C-7 akuammiline numbering) were unsuccessful.[13] Similarly, more extensive efforts reported by the Bennasar/Bosch group using an array of electrophilic traps on more advanced substrates like **22** also found this mode of construction to be ineffective.[14] Collectively, these studies suggested that the electrophilic C-6 and nucleophilic C-7 carbons are not close enough in three-dimensional space in the lowest energy conformers of such structures, thereby favoring alternate reaction pathways.



Scheme 5. Early studies toward the the akuammiline framework have shown a C-6/C-7 bond formation to be unproductive.

While other inventive approaches to strictamine (**5**) have been disclosed,[15] prior to 2014 none had secured access to the hallmark framework represented by **2**. This breakthrough was finally achieved in 2014 by Garg with the synthesis of picrinine (**3**),[3] an oxidized congener of **5**. While discussed in detail earlier in Section 1.3.5 (summarized in Scheme 6), the key lesson to be taken from this synthesis is that the core framework can be fashioned through C-5/N bond formation (**26**→**3**). Indeed, with this impressive preparation of picrinine (**3**), a formal synthesis of strictamine (**5**) was achieved based on the demonstrated conversion of picrinine into strictamine in four steps by Banerji and Chakrabarti.[16] Notwithstanding the impressive preparation of picrinine (**3**, 18 steps from commercial materials, 20 steps from standard chemical suppliers)[iii], we felt that the 22 steps (24 from standard chemical suppliers) required to access the arguably simpler strictamine left some room for improvement.

[iii] The known starting material employed by Garg is available from only one supplier, Aurora Fine Chemicals, at high cost (at the time of writing, minimum order = $1,290, regardless of quantity).

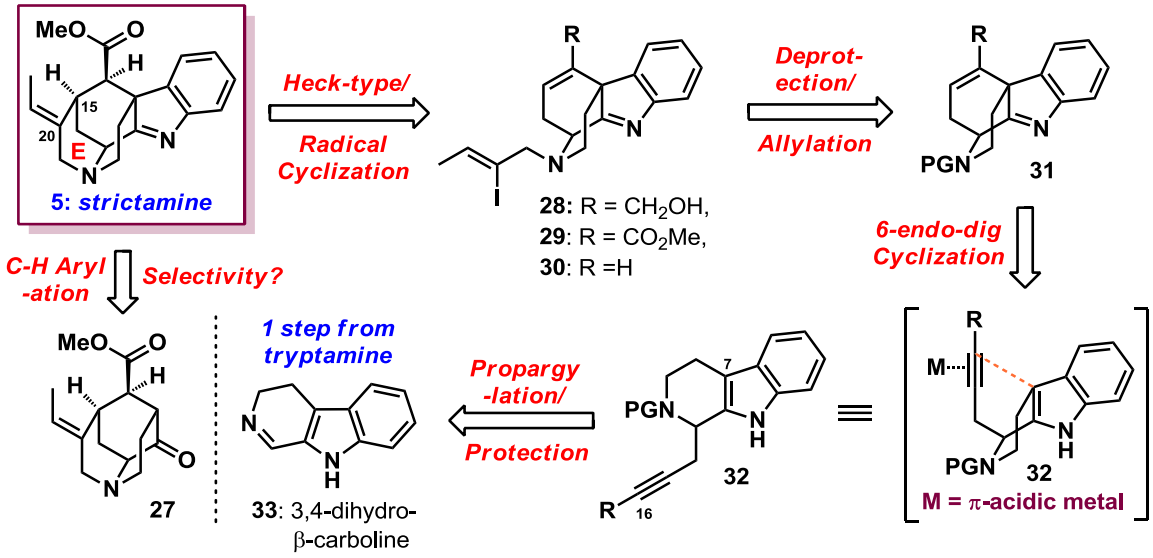


Scheme 6. Summary of Garg's total synthesis of picrinine (**3**) and consequent formal synthesis of strictamine (**5**).

3.4 Our Approach to Strictamine

Guided by the path-pointing studies outlined above, in the spring of 2013 we set about formulating our own strategy towards strictamine (**5**). In particular, it was clear from the work of Dolby and Bennasar/Bosch that attempting to build the cage structure of the akuammilines through attack of the indole C-7 position onto C-6 was unlikely to be productive. Likewise, late-stage formation of the C-7/C-16 bond appeared unlikely given the work of Martin and others. Finally, although as mentioned in section 2.7 we could retrosynthetically simplify strictamine to cage ketone **27** through application of our developed indolenine annulation retron, concerns over the regioselectivity of the C-H arylation step led us to consider other approaches (Scheme 7).[iv]

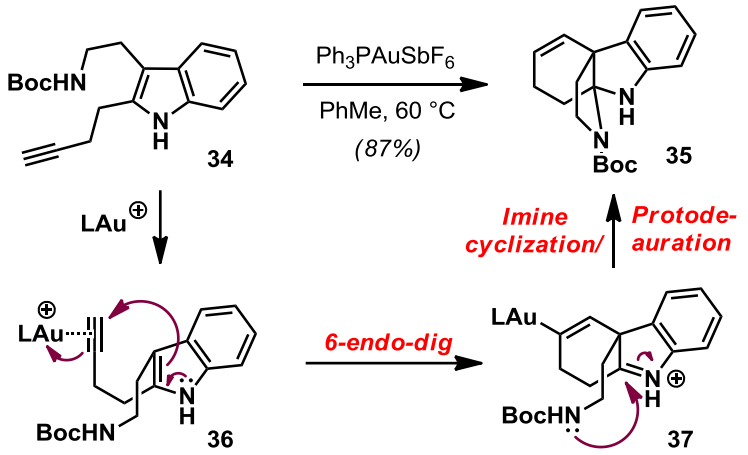
[iv] DFT calculations of the type used to rationalize the regiochemical outcome of the HAT/cyclization en route to scholarisine A (**1**, Section 2.5.6) predicted a mild preference (ca. 1.5:1) for the desired indolenine isomer.



Scheme 7. Retrosynthetic analysis of strictamine (**5**) based on a final C-15/C-20 Heck or radical closure.

After much thought, an approach predicated on the use of a versatile Heck-type disconnection (proposed before for strictamine)[11,17] which could lead back to a scaffold of type **28**–**30** seemed particularly appealing; in this case, a final C-15/C-20 E-ring closure was envisaged to complete the carbon framework of **5** in the forward direction. Tricyclic indolenine **31**, in turn, would appear to be available via a gold-catalyzed 6-*endo-dig* cyclization of propargyl carboline **32**, a reaction process previously reported by Wang for related indole systems (**34**→**35**, Scheme 8).[18] Despite this encouraging precedent, however, Wang had not reported any examples using fused indolic compounds, and we did harbor some concerns for this idea based on the reported failure of C-6/C-7 bond formations from β-carboline frameworks in the work of Cook and Zhu (Scheme 4). Overall, however, we reasoned that the approach would be relatively simple to test since compounds of type **32** should be readily accessible through propargylation of the widely-

used 3,4-dihydro-β-carboline (**33**).[v] Imine **33** is itself available from tryptamine through a two-stage, one-pot procedure on multi-gram scale.[20] Equally attractive was the fact that this concise strategy appeared to be readily adaptable to an asymmetric synthesis through the preparation of enantioenriched propargyl carboline **32**; from this species, all remaining stereocenters could be set diastereoselectively. Although **32** has not been prepared in enantioenriched form to date, many approaches for its synthesis can be envisaged, most conveniently through an asymmetric propargylation of imine **33**.



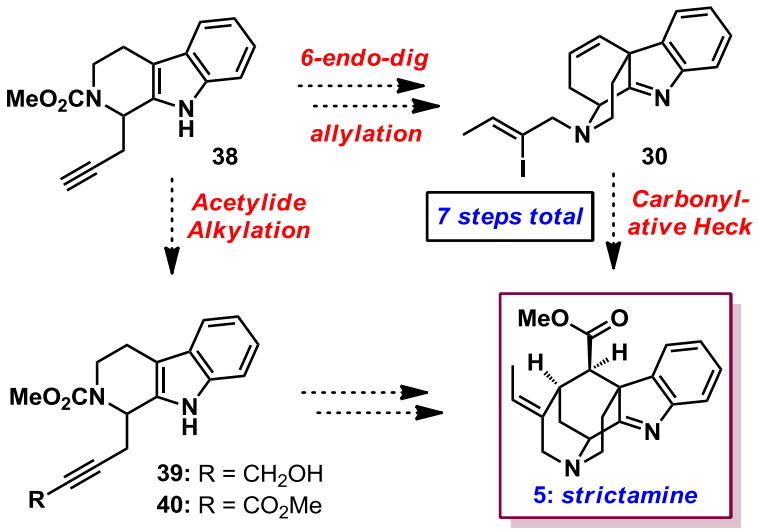
Scheme 8. Gold-catalyzed indole-alkyne cyclization reported by Wang.

3.5 Development of Expedient Access to the Akuammiline Core

In terms of overall step count, and moreover initial ease of assembly, a strategy centered upon the use of a simple, unsubstituted version of the endocyclic alkene (**30**) appeared to be the most appealing initial path (Scheme 9). Indeed, this approach could be seen to directly deliver strictamine (**5**) in only 7 steps from tryptamine, through a potentially challenging, but extremely expedient, carbonylative Heck closure of **30**. This

[v] The TMS-alkyne corresponding to **32** (PG = H) has been prepared through addition of TMS-allenylmagnesium bromide to **33**.[19]

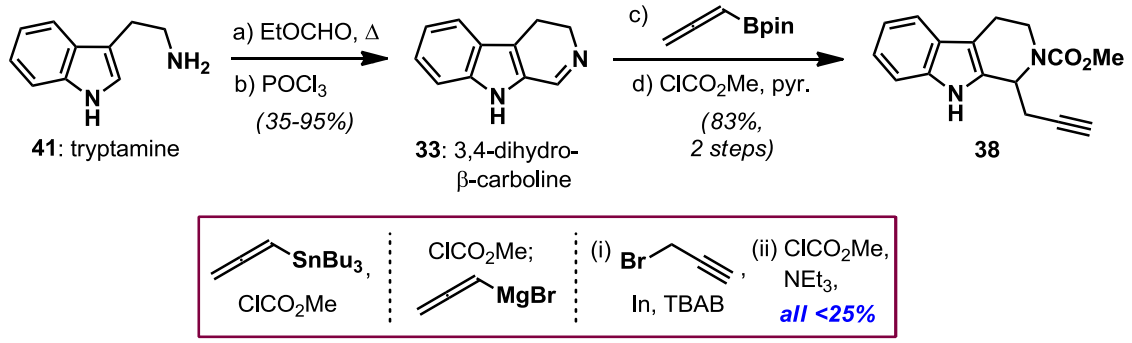
plan would aim to access targeted alkene **30** through 6-*endo-dig* cyclization of readily accessible propargyl carboline **38**. In addition, we expected to be able to functionalize the terminal position of the alkyne within **38** to access other targeted Heck and reductive Heck cyclization precursors (e.g. **39**, **40**) to test these alternate modes of C-15/C-20 bond formation.



Scheme 9. Initial plan to directly access strictamine (**5**) through a carbonylative Heck closure using **30**.

To begin our studies, 3,4-dihydro-β-carboline (**33**) was prepared from tryptamine (**41**) (routinely on 10 g scale), through formylation and Bischler–Napieralski reactions to give material of purity sufficient to be used in the subsequent propargylation chemistry directly following a simple acid-base extraction (Scheme 10).[17,20] Initial attempts at accessing propargyl carboline **38** using an *in situ* formed allenylindium species[21] led to mixtures of propargylated and allenylated material, from which low yields (<25%) of the desired protected propargyl compound could be isolated following carbamate protection of the crude material ($ClCO_2Me$, pyridine, CH_2Cl_2, 0 to 23 °C). Attempts at propargylating an *in situ*-formed acyliminium ($ClCO_2Me$ or CbzCl) with either allenylmagnesium

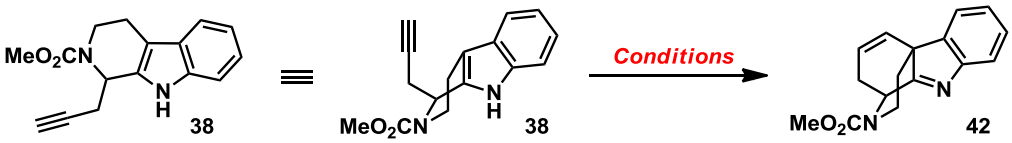
bromide or allenyltributylstannane similarly led to low yields of the desired product (**38**), despite the latter condition's similarity to an analogous and effective allylation of **33** with allyltributylstannane.[22] Pleasingly, however, we found that simply stirring imine **33** with allenylboronic acid pinacol ester (1.3 equiv) in THF at 23 °C cleanly produced the corresponding propargylamine **38** (with no traces of allenyl-containing material). This crude material could be protected as before to give methyl carbamate **38** in 83% over the two steps of the sequence, with the operations performed on up to 2.5 g scale.



Scheme 10. *Reagents and conditions:* (a) EtOCHO, neat, Δ, 17 h; (b) $POCl_3$, CH_3CN, 0 °C, 4.5 h, 35-95% (2 steps); (c) allenylBpin (1.3 equiv), THF, 23 °C, 16 h; (d) $ClCO_2Me$ (1.3 equiv), pyr. (1.5 equiv), CH_2Cl_2, 0 to 23 °C, 4 h, 83% (2 steps).

With ready access to propargylated material (**38**), we next set about testing the planned 6-*endo*-*dig* closure. We began our investigations using the conditions[18] reported by Wang (10 mol % $Ph_3PAuCl/AgSbF_6$, toluene, 60 °C), which have been shown to be effective for forming pyrroloindolines such as **35**. Unfortunately, in our fused ring case, this protocol achieved very low conversions with no desired product **42** isolated; attempts to change the counterion (BF_4^-) or solvent (CH_2Cl_2) had little impact (Table 1, entries 1–3). Clearly, the less flexible nature of substrate **38** relative to **34** for example, or the greater strain of the product, prevented the effective formation of indolenine **42**. Similarly, efforts

to use a more electrophilic gold(I) catalyst such as $Ar_3PAuSbF_6$ (Ar = 4-$CF_3C_6H_4$) or other π-acidic metal salts such as $PtCl_2$,[23] $InBr_3$[24] or $In(OTf)_3$, resulted in very little reaction (entries 3–6).[vi]



Entry	Catalyst	Conditions	Result
1	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2, 23 °C; PhMe, 60 °C	<10% conv., no **42**
2	$Ph_3PAuCl/AgBF_4$	PhMe, 70 to 100 °C	<10% conv., no **42**
3	$Ar_3PAuCl/AgBF_4$	PhMe, 70 to 100 °C	<10% conv., no **42**
4	$PtCl_2$	PhMe, 100 °C; DCE, 80 °C	<10% conv., trace **42**
5	$InBr_3$	CH_2Cl_2, 23 °C; DCE, 80 °C	<10% conv., trace **42**
6	$In(OTf)_3$	CH_2Cl_2, 23 °C; DCE, 80 °C	<10% conv., no **42**
7	**$AuCl_3$**	**DCE, 23 to 50 °C; PhMe; THF**	**40-100% conv., some 42 & allene**
8	**JohnPhosAu(MeCN)SbF_6**	**CH_2Cl_2, 23 to 50 °C; DCE; PhMe**	**ca. 25% conv., some 42**
9	**$AuCl_3$, $AgSbF_6$**	**DCE, 23 °C**	**ca. 50% conv., some 42**
10	**$AuCl_3$, $AgBF_4$**	**DCE, 23 °C**	**100% conv., some 42**
11	***$AgBF_4$***	***DCE, 23 °C; CH_2Cl_2, 23 °C***	***56-69%* 42**

Table 1. Optimization of 6-endo-dig cyclization of **38**. *Reagents and conditions:* catalyst added in portions of 0.1-0.2 equiv; conversions estimated based on TLC and/or crude ^{1}H NMR.

Finally, it was discovered that the use of $AuCl_3$ in DCE resulted in meaningful, albeit often incomplete, conversion of substrate **38**, usually requiring multiple additions of catalyst (entry 7). These experiments delivered our first isolable amounts of indolenine **42** alongside the allene isomer of the starting material. That the cyclization had occurred at the C-3 of the indole rather the indole nitrogen was evident from a signal for the imine carbon at 183.0 ppm in the ^{13}C NMR spectrum. Further exploration showed that using $AuCl_3/AgBF_4$ led to lower amounts of the allene while maintaining decent conversion (ca.

[vi] Later inspection of the crude ^{1}H NMRs of reactions using $InBr_3$ and $PtCl_2$ revealed trace amounts of product **42** once the correct signals had been discerned.

50%, entry 9). By contrast, the more easily handled JohnPhosAu(MeCN)SbF_6 also produced **42** but in lower conversions (entry 8).

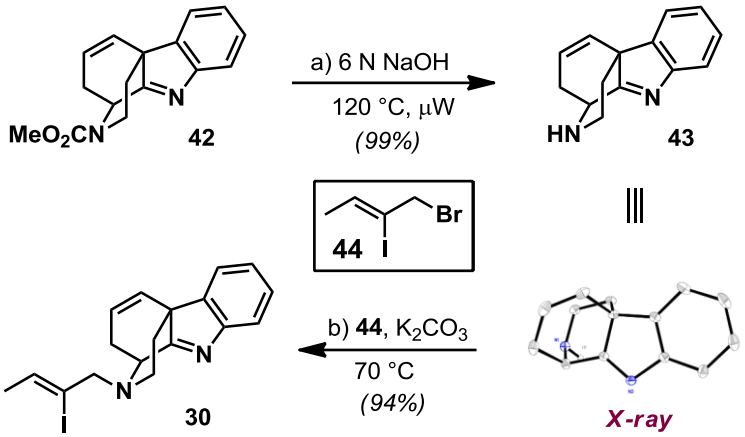
Our best lead, therefore, seemed to be the $AuCl_3$/AgX system, so we chose to focus on further optimizing these reaction conditions. Executing this procedure typically involved premixing $AuCl_3$ and 3 equivalents (relative to $AuCl_3$) of a silver salt followed by addition of the resulting opaque solution (via syringe) to a stirred solution of **38** in DCE. In one of these trials, an excess amount of $AgBF_4$ (ca. 8.5 equiv relative to $AuCl_3$) was (accidentally) added and the reaction continued as before; following TLC analysis, we were excited to observe far greater conversion than usual. In fact, we later found that leaving out the $AuCl_3$ altogether and simply employing either $AgSbF_6$ or $AgBF_4$ in DCE or CH_2Cl_2 at 23 °C could achieve full conversion of starting material (entry 11). Typically, depending on the scale, a few additions of silver salt were required with ca. 1 equiv being required for full conversion. This result indicated that catalyst turnover was ineffective, either due to stability of the intermediate vinylsilver species, or, more likely, product inhibition through catalyst binding. Attempts at increasing reaction temperature (50 °C) or adding a Brønsted acid (TFA, 5 equiv) did not allow for the use of substoichiometric amounts of silver. It is worth noting, however, that silver salts such as $AgBF_4$ ($2.05/mmol) are far cheaper than their gold counterparts (e.g. $AuCl_3$ = $34.58/mmol; JohnPhosAu(MeCN)SbF_6 = $300.00/mmol) and their use as stoichiometric additives/oxidants in C-H activation chemistry is quite common, even on large scale.[vii]

[vii] Prices obtained from Sigma-Aldrich at the time of writing (June 2014).

We chose to focus on the use of the relatively inexpensive $AgBF_4$ ($2.05/mmol) rather than the more costly $AgSbF_6$ ($4.25/mmol) for final improvements given that the least expensive silver salts, $AgNO_3$ ($0.76/mmol) and AgOAc ($0.96/mmol) proved ineffective. Ultimately, we found that conducting the reaction at 23 °C in CH_2Cl_2 with $AgBF_4$ (1-1.5 equiv added in 2-3 portions) gave clean conversion to product **42** which, after work-up with aqueous $NaHCO_3$ and silica gel chromatography, could be isolated in 55–69% yield on up to 950 mg scale.

3.6 Carbonylative Heck Approach

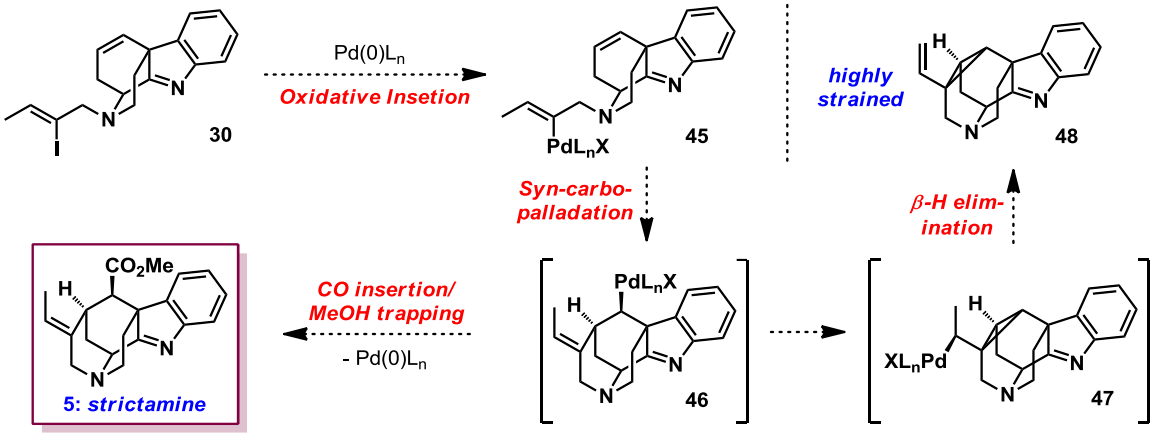
From indolenine **42**, we aimed to advance to a vinyl iodide-containing substrate (**30**) to test the carbonylative Heck formation of the E-ring to complete our synthesis of strictamine (**5**). Initial attempts at deprotecting **42** under nucleophilic acidic conditions (TMSI, LiI, BBr_3) did not deliver any amine **43** but, pleasingly, the use of aqueous 6 N NaOH in MeOH at 120 °C for 2 h under microwave irradiation quantitatively formed **43** (Scheme 11). Indeed, its structure was confirmed by single crystal X-ray diffraction analysis, verifying the structural assignment for indolenine **42**, which had thus far relied primarily on 1D and 2D NMR experiments. A final allylation of **43** with known bromide **44** (K_2CO_3, CH_3CN, 70 °C) gave the targeted vinyl iodide **30** (94% yield) in just 6 steps from commercial materials.



Scheme 11. *Reagents and conditions:* (a) aq. 6 N NaOH (excess), MeOH, 120 °C, μW, 2 h, 99%; (b) **44** (1.4 equiv), K_2CO_3 (2.3 equiv), CH_3CN, 70 °C, 4.5 h, 94%.

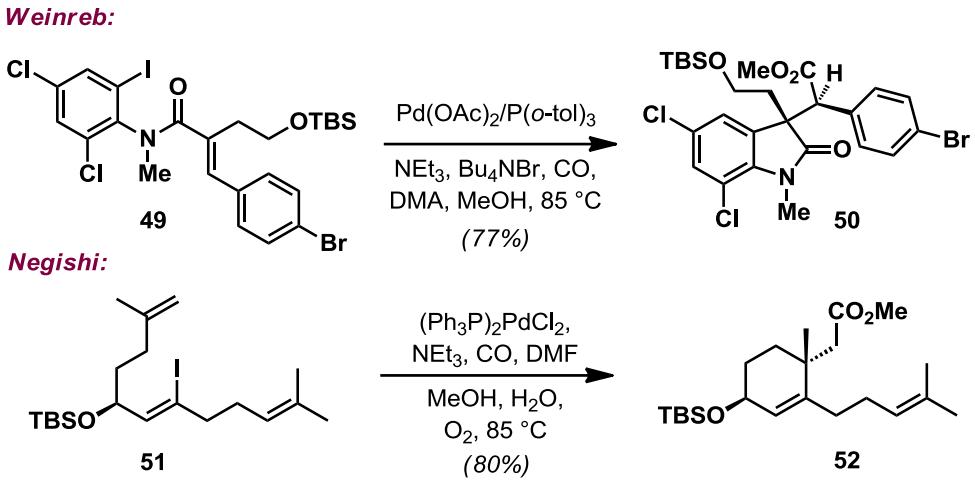
With our vinyl iodide (**30**) in hand, we were now poised to test the planned carbonylative Heck process, the details of which are outlined in Scheme 12. This proposed reaction would proceed through initial formation of vinylpalladium(II) species **45** via oxidative insertion of the palladium(0) catalyst into the vinyl iodide **30**, whereafter *syn*-carbopalladation of the proximal olefin should deliver alkyl palladium(II) intermediate **46**. This species could then undergo CO insertion to give an acylpalladium(II) intermediate, which, in turn, should react with MeOH to deliver the methyl ester of **5** and regenerate the palladium(0) catalyst. Crucially, alkylpalladium **46** cannot undergo competitive β-hydride elimination given the absence of *syn*-hydrogen atoms.[viii] Once formed, **46** can either undergo the desired carbonylative process or potentially cyclize onto the proximal alkene to deliver vinyl cyclopropane **48** via alkylpalladium(II) species **47**. The latter process, however, is expected to be energetically unfavorable given the amount of strain it would engender.

[viii] Even if epimerization could occur to give an α-alkylpalladium version of **46**, β-H elimination would be disfavored due to the formation of an anti-Bredt olefin.



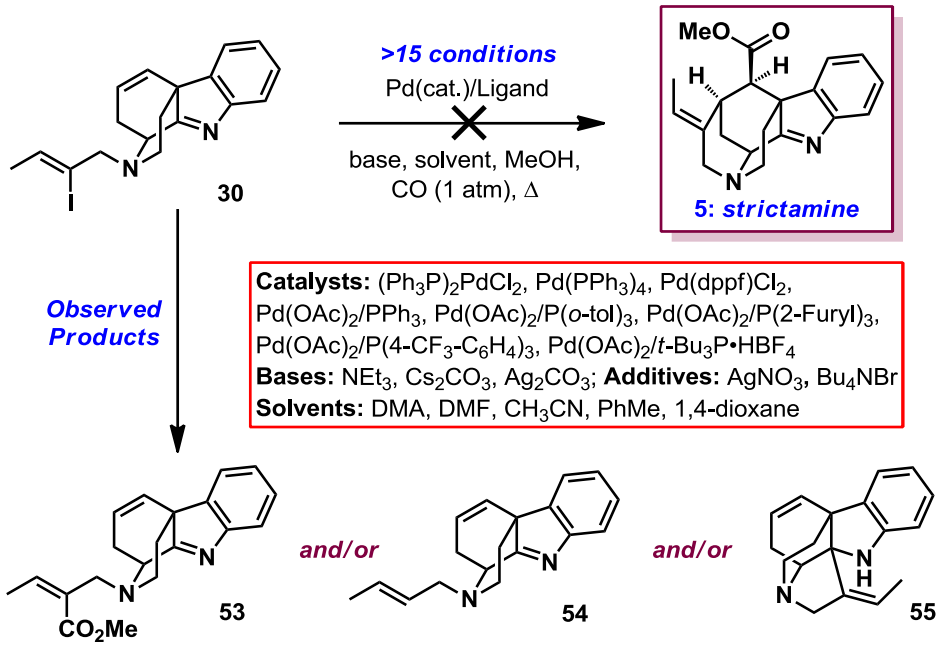
Scheme 12. Mechanism and possible alternate pathway for the proposed carbonylative Heck process.

While clearly well-suited to the case at hand concurrently forging not only the C-15/C-20 bond but also the E-ring of **5** and the desired methyl ester epimer, the relative scarcity of literature examples of this clearly powerful process made us cautious. In particular, most examples of this process involve five-membered ring formation (e.g. **49**→**50**, Scheme 13);[25] to the best of our knowledge, only a handful of reports describe the formation of six-membered rings through this process (e.g. **51**→**52**).[26] Delving more deeply into reports and theses detailing the efforts towards the related alkaloids minfiensine[27] and vincorine,[28] we noted the failure of this process in these settings (6- and 7-membered ring formation, respectively). Nevertheless, given the structural differences presented by our system and the impact that these subtle changes might have on the proposed transformation, as well as the highly direct formation of strictamine (**5**) it would afford if successful, we decided to thoroughly investigate the conversion of vinyl iodide **30** into **5**.



Scheme 13. Literature examples of similar carbonylative Heck processes.

Initial studies employed literature conditions, which typically prescribed using a $Pd(OAc)_2/PPh_3$ catalyst combination, with Et_3N as base and a mixture of DMA or DMF and MeOH as solvent under a CO atmosphere at elevated temperatures (Scheme 14). Use of these routine conditions (1 atm of CO) did, in fact, produce a new major product, but this compound was found to be the enoate ester **53**, formed through premature carbonylation of the vinylpalladium species **45** prior to olefin insertion. Although the formation of **53** was unwelcome, it did confirm that oxidative addition to the vinyl iodide was occurring and that the methoxycarbonylation process was viable under these conditions. Apparent, too, was the fact that increasing the CO pressure beyond the convenient 1 atm employed would be unnecessary, since already at this low pressure carbonylation was competing with olefin insertion.

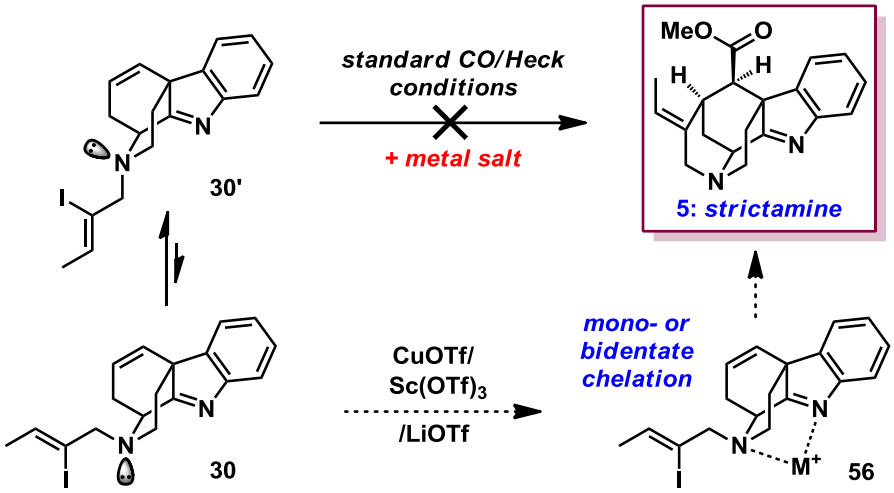


Scheme 14. Unsuccessful carbonylative Heck attempts with vinyl iodide **30**.

We therefore elected to screen many different catalysts, bases, solvents and temperatures. Unfortunately, all were uniformly ineffective, delivering only **53** or protodeiodination product **54**. At higher temperatures another product was isolated that was determined to be the product of cyclization onto the imine (**55**), readily apparent from inspection of its ^{1}H NMR spectrum since this exhibited an upfield shift of its aromatic protons, indicative of an indoline, rather than indolenine, structure. This unanticipated cyclization led us to question whether the vinyl iodide-bearing group of the tertiary amine was in fact closer in space to the imine rather than the olefin in the lowest energy conformer of **30**; that is to say the preferred nitrogen invertomer has this group placed in the conformation shown in **30'** rather than **30** (Scheme 15).[ix] In an attempt to bias the nitrogen configuration in favor of invertomer **30'**, we included a Lewis acid additive in hopes that

[ix] Additionally, the conformation of the piperidine ring (i.e. boat vs chair) would also impact the orientation of the vinyl iodide side-chain.

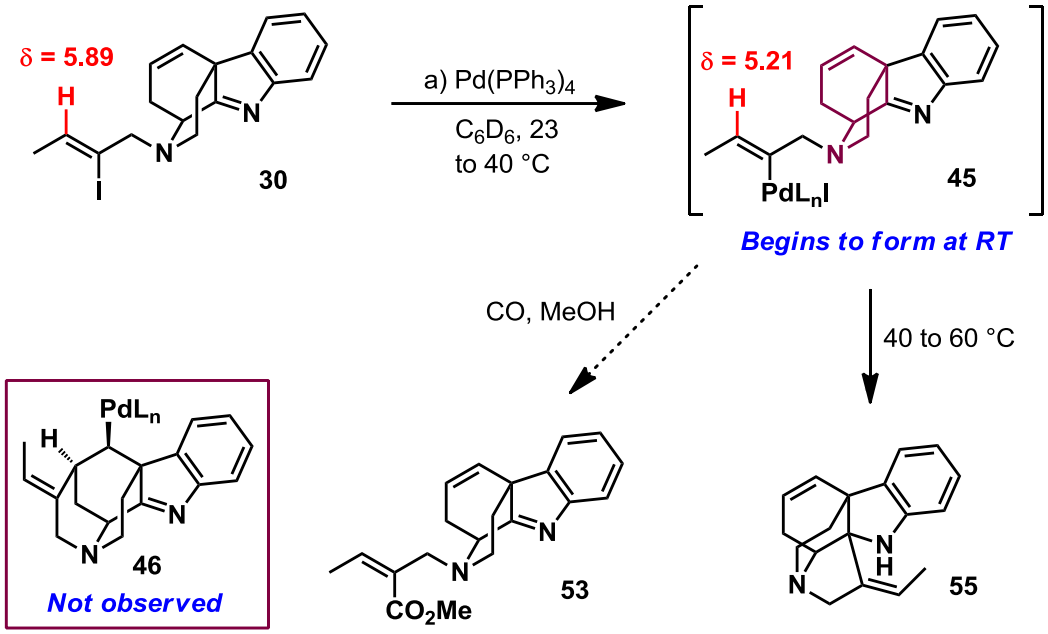
it would coordinate to the tertiary amine and/or imine, ideally in a bidentate fashion (i.e. **56**). Unfortunately, inclusion of $Sc(OTf)_3$, LiOTf or CuOTf did not facilitate the desired process, with $Sc(OTf)_3$ interestingly leading to clean cyclization onto the imine to give **55**, while CuOTf predominantly gave protodeiodination to **54**.



Scheme 15. Attempted use of a chelating metal salt to favor reactive nitrogen epimer **30**.

It was clear from these experiments that the carbopalladation step of the process was problematic, which through inspection of molecular models appeared to be due to the congested nature of the bond formation on the concave face of the [3.3.1]-bicycle of **45** (highlighted in purple, Scheme 16). In an attempt to reduce the size of the vinylpalladium intermediate (**45**), we sought to apply the well-known Jeffery[29] conditions [$Pd(OAc)_2$, Bu_4NCl, K_2CO_3, DMF], a procedure known to be effective for sterically challenging Heck couplings.[30] Conducting this protocol with added CO and MeOH, however, also proved to be ineffective. To investigate the facility of alkylpalladium **46** formation without the complication of premature CO insertion, we undertook ^1H NMR studies of **30** with a stoichiometric amount of $Pd(PPh_3)_4$ in C_6D_6. Even at 23 °C the formation of putative vinylpalladium **45** (vinyl H: δ = 5.21 vs 5.89 for **30**) could be observed, with ~50%

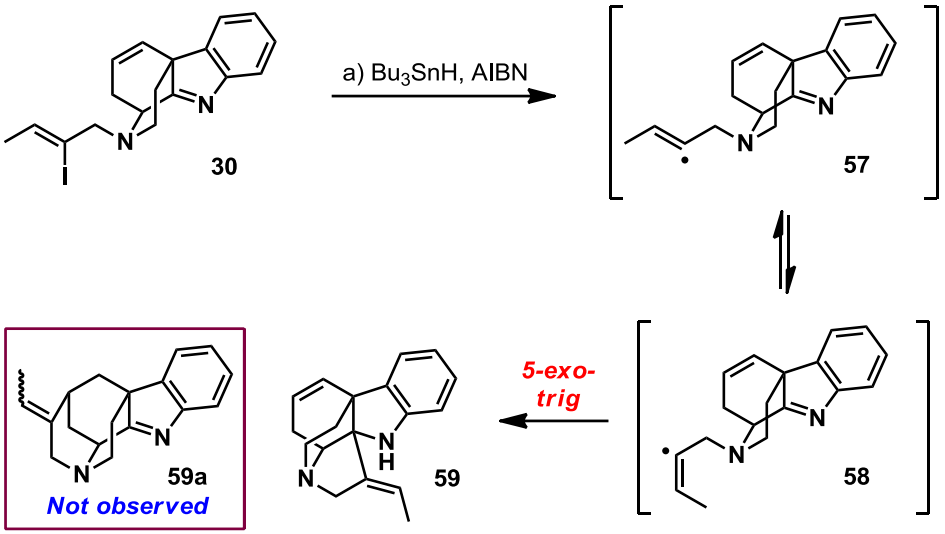
conversion to this species achieved after 45 min of heating at 40 °C. Further incremental heating resulted in formation of imine cyclization product **55** at temperatures above 50 °C, with no evidence for carbopalladation to **46** observed. Collectively, therefore, the intervention of the premature carbonylation (**45**→**53**) and/or imine cyclization (**45**→**55**) pathways clearly presented far more facile pathways for vinylpalladium species **45**.



Scheme 16. Stoichiometric studies to probe the formation of vinylpalladium **45** and alkylpalladium **46**. *Reagents and conditions:* (a) $Pd(PPh_3)_4$ (1.0 equiv), C_6D_6, 40 to 60 °C, 14 h.

To probe whether ring closure through a radical manifold might be feasible, we next attempted radical cyclization of **30** under standard Bu_3SnH/AIBN conditions (as a prelude to employing carbon-based radical traps such as *t*-BuNC, Scheme 17).[31] Radical cyclization had not been our primary choice for such a bond closure since the stereochemistry of the initial vinyl radical is liable to be compromised through radical inversion to lead to a mixture of *E*/*Z*-cyclized products. However, the small size of radical

species in general, intermediates which do not carry a solvation shell due to their uncharged nature, may allow for the formation of the sterically congested C-15/C-20 bond. In the event, slow addition of a solution of Bu_3SnH and AIBN in degassed toluene via syringe pump to a solution of **30** at 110 °C in toluene gave a major product by crude ^1H NMR; unfortunately, it retained the endocyclic alkene and looked strikingly similar to previously obtained **55**. The only major differences appeared to be in the region occupied by the ethylidene chain. Thus, given the ability of intermediate vinyl radical **57** to isomerize to **58**, we postulate that the observed product is the geometric isomer of **55** (**59**).[x] Again, cyclization onto the imine (5-*exo*-*trig*) appeared to be more facile than formation of the C-15/C-20 bond.



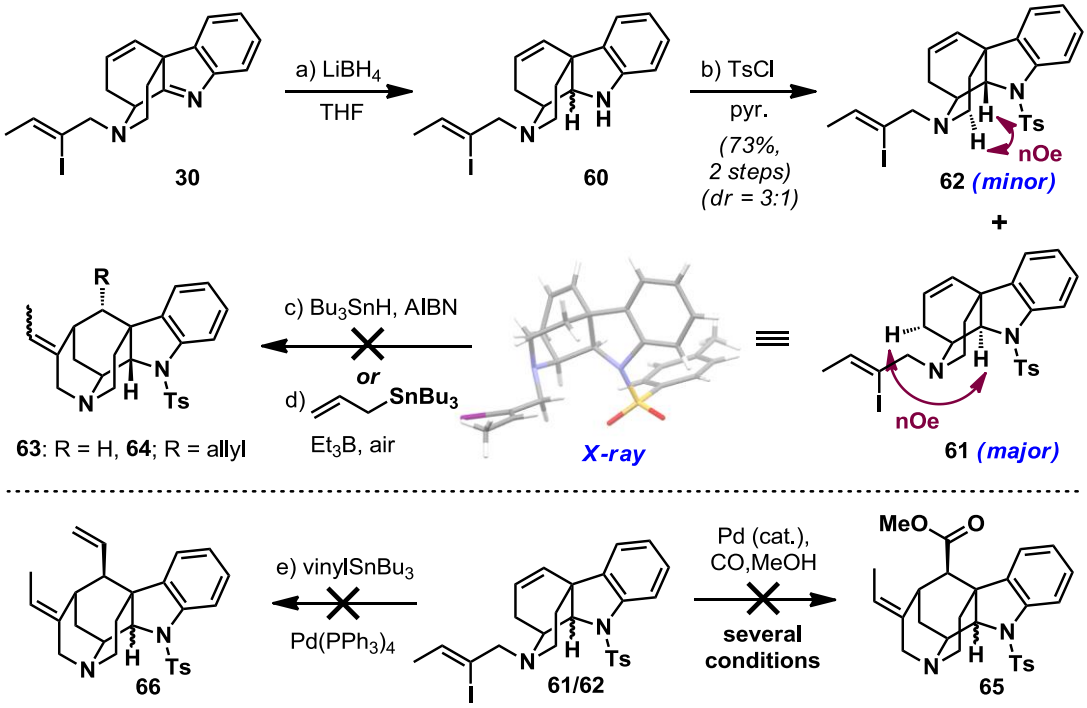
Scheme 17. *Reagents and conditions:* a) Bu_3SnH (1.2 equiv), AIBN (0.2 equiv), PhMe, 110 °C, 2.75 h.

In an attempt to remove this competing imine cyclization pathway, we targeted reduced indoline **60**. We hoped, too, that **60** would give us the opportunity to potentially bias the nitrogen epimers in favor of the desired one through the installation of a bulky *N*-

[x] Some **55** also appeared to be present as a minor product.

protecting group. After screening a few reductants, the best appeared to be $LiBH_4$ (THF, 0 °C), which cleanly effected the desired reduction of **30** to a 3:1 mixture of indolines **60** (Scheme 18). These compounds were unstable to silica gel purification so direct protection with a tosyl group gave a 3:1 ratio of sulfonamides **61** and **62** in 73% combined yield over the two steps. These compounds could be separated by careful preparative TLC and their stereochemistry deduced through the diagnostic NOESY correlations as shown. This assignment was later confirmed by X-ray analysis of the major isomer **61**, which also showed that the vinyl iodide bearing side-chain occupied a position distal to the endocyclic alkene as we had suspected.[xi] Moreover, the observed orientation of the *N*-Ts group was such that this motif did not really sterically impact the positioning of this group as we might have hoped.

[xi] This results from both the chair conformation of the piperidine ring and the undesired configuration at nitrogen being favored (in this case in the solid state).

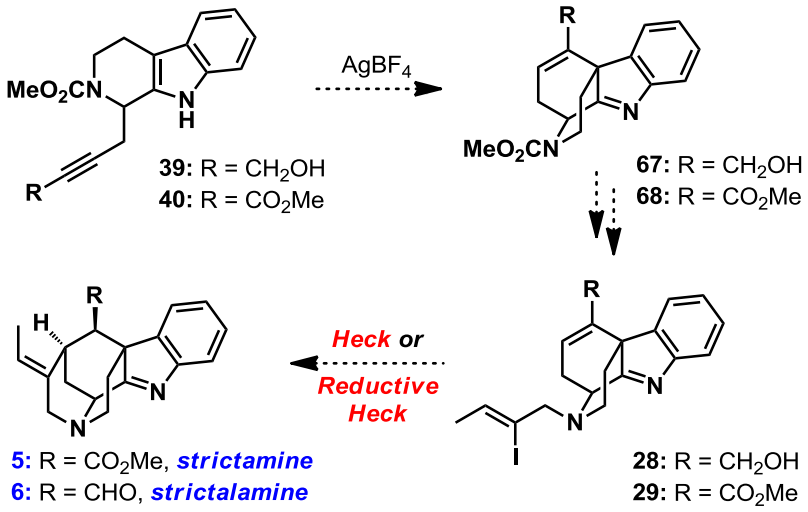


Scheme 18. *Reagents and conditions: (*a) $LiBH_4$ (4.2 equiv), THF, 0 to 23 °C, 5.5 h; (b) TsCl (3.0 equiv), pyr. 23 °C, 11.5 h, 73% (2 steps); (c) Bu_3SnH (1.2 equiv), AIBN (0.2 equiv), PhMe, Δ, 2 h; (d) allylSnBu$_3$ (5.0 equiv), Et_3B (0.5 equiv), PhMe, 80 °C, air, 9 h; (e) vinylSnBu$_3$ (7-9 equiv), $Pd(PPh_3)_4$ (0.1 equiv), PhMe, 150 °C, 5 h.

Disappointingly, though perhaps unsurprisingly given the ground state conformation, attempting carbonylative Heck processes with either **61** or **62** under several conditions resulted in no formation of the desired products (**65**). In an effort to limit the amount of the trapping reagent, we also investigated the use of vinyltributylstannane to achieve a carbopalladation/Stille coupling as had been reported in Njardarson's studies toward vinigrol.[32] Unfortunately, no desired product **66** arose under their conditions, with the major species being the diene from simple Stille coupling of the vinyl iodide (structure not shown). Additionally, radical cyclization of major diastereomer **62** under the conditions employed earlier or using non-reductive Keck allylation conditions, as used previously in our synthesis of scholarisine A (**1**),[1] gave no pentacyclic products (**63** or **64**).

3.7 Traditional Heck Approach

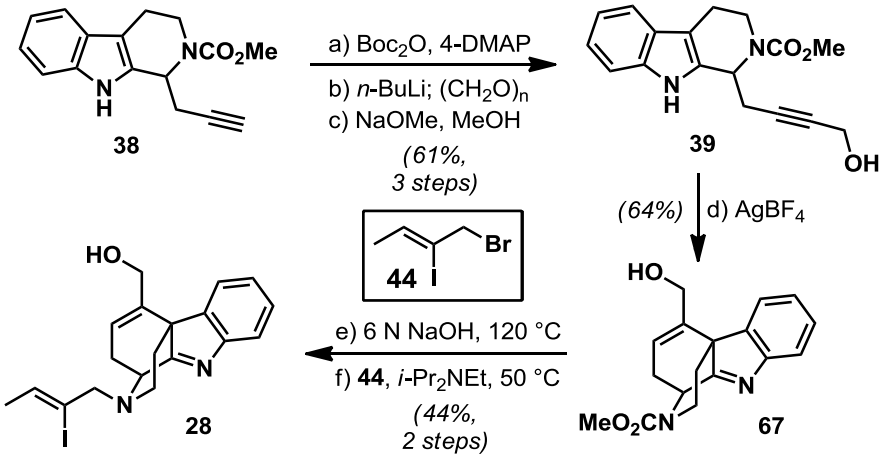
With unsubstituted alkene substrates failing to yield any productive C-15/C-20 bond formation, we adjusted our focus to targeting substituted alkene precursors **28** and **29**, which we planned to use in Heck or reductive-Heck type chemistries, respectively, as well as radical cyclizations (Scheme 19). The obvious advantage to such processes would be the removal of the complicating CO-insertion step of the carbonylative transformation, since this carbon atom would be pre-installed in substrates **28** and **29**. The most expedient way to access such materials would be to use the previously developed silver(I)-mediated cyclization to deliver substituted indolenines **67** and **68** directly. This would, in turn, necessitate the preparation of the corresponding hydroxymethylated (**39**) and methoxycarbonylated (**40**) variants of alkyne **38**.



Scheme 19. Heck and Reductive Heck strategies using subsituted alkenes **28** and **29**.

As shown in Scheme 20, we began by synthesizing hydroxymethyl alkyne **39**. Although typical lithium acetylide chemistries did not proceed with free indole **38** (employing 2 equiv of base), prior *N*-Boc-protection (Boc_2O, DMAP, THF) allowed the

desired propargyl alcohol to be generated in 67% yield (94% brsm) using paraformaldehyde as the CH_2O source. It is likely that conversion could be boosted by exploring alternate CH_2O sources like dried gaseous CH_2O, but at this stage 67% yield represented adequate material throughput to fuel our studies.[xii] Removal of the more labile indole carbamate with NaOMe cleanly gave the desired cyclization precursor **39** (91% yield). To our delight, **39** reacted under the previously optimized $AgBF_4$-conditions to give allylic alcohol **67** (64% yield, 300 mg scale) along with a somewhat unstable by-product (ca. 30%) that may be dimeric based on preliminary LRMS data. With **67** in hand, CO_2Me deprotection and allylation as before gave the targeted Heck precursor (**28**) in 44% yield over these final two steps.

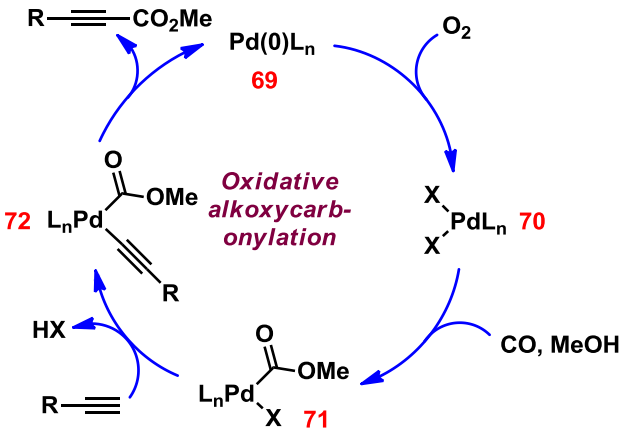


Scheme 20. *Reagents and conditions:* (a) Boc_2O (1.3 equiv), 4-DMAP (0.1 equiv), THF, 23 °C, 1 h, >99%; (b) *n*-BuLi (1.3 equiv), THF, -78 °C, 1 h; $(CH_2O)_n$, -78 to 23 °C, 4 h, 67% (94% brsm); (c) NaOMe, MeOH, THF, 0 to 23 °C, 45 min, 91% (d) $AgBF_4$ (ca. 2.5 equiv), CH_2Cl_2, 23 °C, 18 h, 64%; (e) aq. 6 N NaOH (excess), MeOH, 120 °C, μW, 2.5 h, 88%; (f) **44** (1.4 equiv), *i*-Pr_2NEt (2.5 equiv), CH_3CN, 50 °C, 1.75 h, 50%.

For ynoate ester substrate **40**, we hoped to obviate the need for the protection/deprotection sequence required for the acetylide chemistry by employing the

[xii] Alternative approaches, such as reduction of the corresponding ynoate ester (*vide infra*) with $LiAlH_4$ or DIBAL-H proved inefficient.

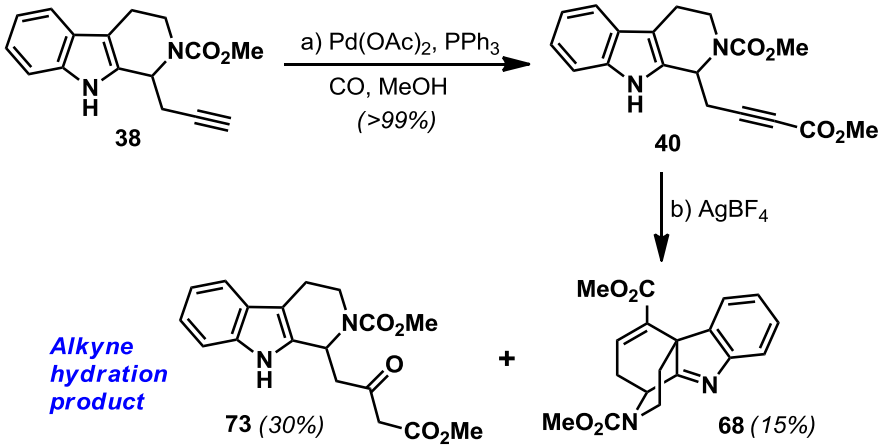
conditions developed by Yamamoto and co-workers for oxidative methoxycarbonylation of terminal alkynes (Scheme 21).[33] Extensive mechanistic investigations have shown that this transformation proceeds through aerobic oxidation of an initially formed Pd(0) species (**69**) to give a Pd(II) intermediate (**70**) that can subsequently react with MeOH and CO to form methoxycarbonylpalladium(II) complex **71**. This species then reacts with the alkyne substrate to give alkynylpalladium(II) **72**, which undergoes reductive elimination to furnish the ynoate ester and reform the Pd(0) catalyst (**69**).



Scheme 21. Proposed mechanism for the oxidative alkoxycarbonylation reaction of Yamamoto *et al*.

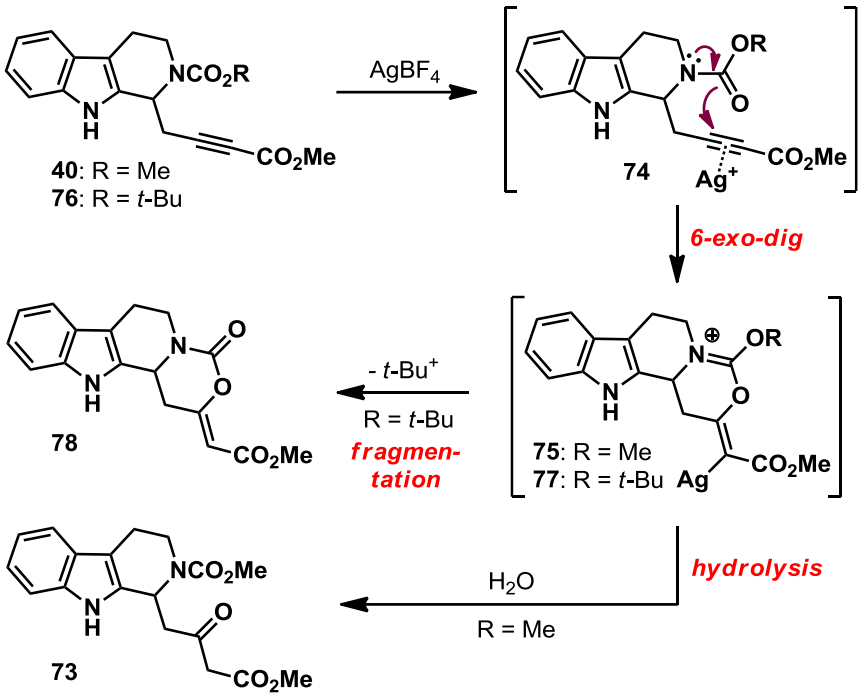
Pleasingly, using slightly modified conditions [$Pd(OAc)_2$, PPh_3, DMF, MeOH, CO, O_2, 23 °C] reported by Kim,[34] clean conversion to the targeted ynoate ester **40** could be achieved in near quantitative yield (Scheme 22). In considering the silver-mediated cyclization of **40**, we realized at the outset that this step would prove substantially more challenging with a sensitive ynoate ester, the alkyne of which was both less electron-rich [and therefore a worse π-base for the Ag(I) species] and polarized to react with the opposite regiochemistry to that desired. Despite these reservations, we were pleased to discover that the use of the standard cyclization conditions with ynoate **40** did, indeed, result in the

formation of product **68**, albeit in low yield (15%). The major species isolated (30%) was β-keto ester **73**, the product of alkyne hydration.



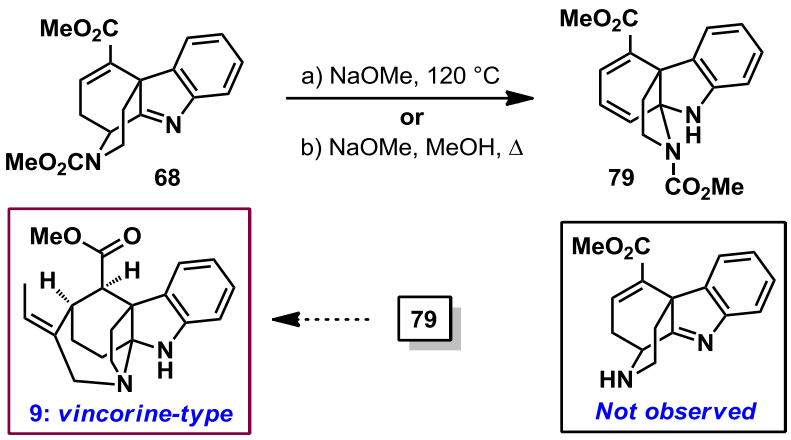
Scheme 22. *Reagents and conditions:* (a) $Pd(OAc)_2$ (0.3 equiv), PPh_3 (0.6 equiv), DMF, MeOH, CO, O_2, 23 °C, 45 h, >99%; (b) $AgBF_4$ (2.1 equiv), CH_2Cl_2, 23 °C, 9 h, **68**: 15%, **73**: 30%.

This side-product persisted even with rigorous exclusion of water (freshly dried solvent, flame-dried flask, substrate dried azeotropically with benzene), which led us to conclude that the nucleophilic carbamate oxygen was likely attacking the activated alkyne (**74**) in a 6-*exo*-*dig* sense to generate a stabilized cation **75** that yielded **73** via hydrolysis during aqueous work-up (Scheme 23). Support for this theory was confirmed when the corresponding *N*-Boc congener of **40** (**76**, prepared analogously) was used in the $AgBF_4$-cyclization reaction, where enol carbamate **78** (double bond geometry tentatively assigned) was quantitatively generated. In this case, the intermediate cation **77** would be able to lose the stable *t*-butyl cation to generate enol carbamate **78**, instead of undergoing hydrolysis to the β-keto ester.



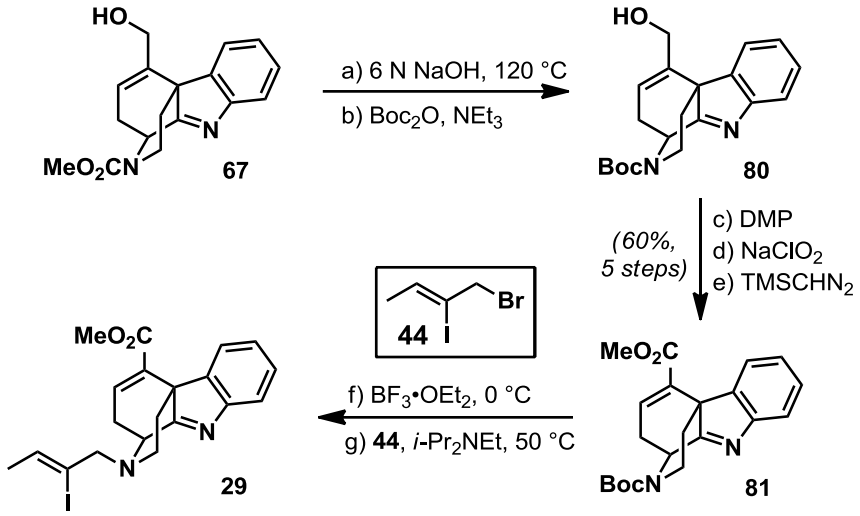
Scheme 23. Rationale and evidence for the formation of hydration product **73**.

Nevertheless, having secured access to enoate **68** in some yield, we attempted carbamate deprotection (Scheme 24) under similar conditions to those used before (NaOMe, MeOH, 120 °C, μW); crude ^{1}H NMR showed what appeared to be a skeletal rearrangement without methyl carbamate removal. Conducting the reaction under slightly milder conditions (NaOMe, MeOH, Δ, 1 h) resulted in a similar outcome and showed this rearrangement to be facile, producing what appeared to be pyrroloindoline **79**. This species likely forms through an E1cB-type elimination of the carbamate that then attacks the proximal imine to generate **79**. While clearly not suited to a preparation of strictamine (**5**), we note that facile access to pyrroloindoline **79** (and derivatives, *vide infra*) may suggest a straightforward preparation of vincorine-type akuammiline alakoids (e.g. **9**) through such a process.



Scheme 24. *Reagents and conditions:* (a) NaOMe (excess), MeOH, 120 °C, μW, 1 h; (b) NaOMe (excess), MeOH, Δ, 1 h.

Knowing that we could already access a secondary amine from *N*-CO_2Me allylic alcohol **67**, we reasoned that as a first pass, we could access **29** by switching protecting groups at this stage to a group removable in the presence of the enoate ester (Scheme 25). Thus, deprotection of **67** as before followed by treatment of crude amine with Boc_2O with NEt_3 smoothly gave *N*-Boc allylic alcohol **80**. A routine three-step oxidation/methylation procedure (DMP; Pinnick [O]; $TMSCHN_2$) subsequently afforded the *N*-Boc enoate ester **81** in excellent yield (60%) over the five step sequence from **67**. While standard TFA deprotection of **81** resulted in decomposition and TMSOTf/2,6-lutidine surprisingly gave no reaction, TMSOTf alone did furnish the corresponding amine, albeit with poor mass recovery. Finally, we found that treatment with BF_3•OEt_2 (5 equiv) at 0 °C in CH_2Cl_2 cleanly afforded the desired amine. This species could then be allylated as before to yield reductive Heck precursor **29**.

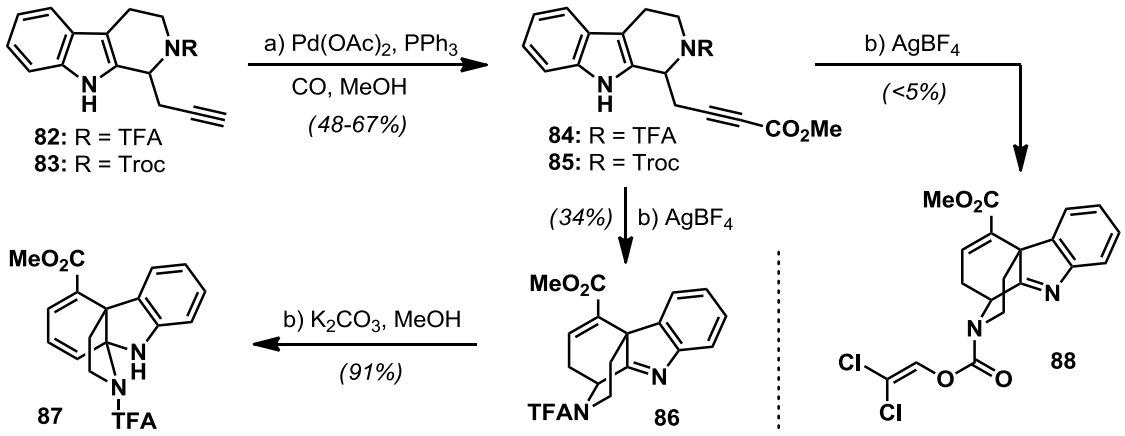


Scheme 25. *Reagents and conditions:* (a) aq. 6 N NaOH (excess), MeOH, 120 °C, μW, 2.5 h; (b) Boc_2O (1.1 equiv), NEt_3 (1.2 equiv), THF, 23 °C, 12.5 h; (c) DMP (1.1 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, 23 °C, 0.5 h, 77% (3 steps); (d) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (8.0 equiv), 2-methyl-2-butene (10 equiv), THF, *t*-BuOH, H_2O, 23 °C, 45 min; (e) $TMSCHN_2$ (1.2 equiv), MeOH, Et_2O, 0 °C, 20 min, 78% (2 steps); (f) BF_3•OEt_2 (5.0 equiv), CH_2Cl_2, 0 °C, 45 min; (g) **44** (1.4 equiv), *i*-Pr_2NEt (2.5 equiv), CH_3CN, 50 °C, 1.75 h.

Before detailing the use of **28** and **29** in Heck-type transformations, our concurrent efforts to improve the synthesis of enoate **29** will be described. Specifically, we aimed to identify a protecting group that could survive the silver-mediated cyclization and subsequent chemistry and then be effectively removed to give the required amine. We already knew that a Boc carbamate was unsuitable for the $AgBF_4$ step (see **76**→**78**, Scheme 23) and that a methyl carbamate, although being moderately competent in the silver-mediated cyclization (15%), was unable to be removed without causing rearrangement. We therefore targeted several other electron-withdrawing protecting groups,[xiii] beginning with less electron-rich options which we hoped would be less inclined to cyclize onto the Ag-

[xiii] Literature reports[35] of related systems have shown that alternate fragmentation pathways are possible when the carboline nitrogen does not bear an electron-withdrawing group. In addition to the protecting groups mentioned, a nosylate was also attempted but caused issues in substrate preparation.

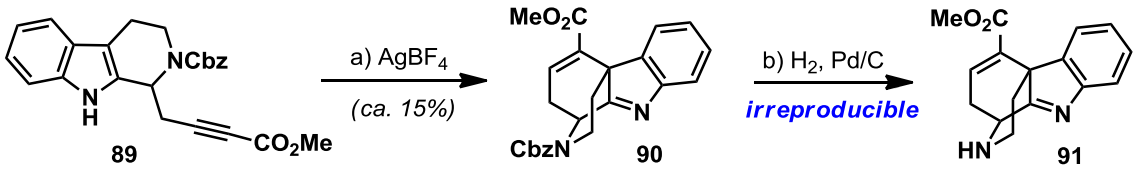
activated ynoate. As such, *N*-trifluoroacetyl (**84**) and *N*-Troc (**85**) ynoates were prepared from protected propargylamines **82** and **83** through the same chemistry as described for methyl carbamate **40** (Scheme 26). While the *N*-trifluoroacetyl compound (**84**) underwent the silver-mediated cyclization (34% yield) to form **86**, this material also proved unable to be deprotected, undergoing facile rearrangement to **87** even under mild reaction conditions (K_2CO_3, MeOH, 0 to 23 °C). Indeed, **87** appears to be a more viable precursor to targets like 10-demethoxynorvincorine (**9**) than the corresponding methylcarbamate **79**. Troc carbamate **85**, despite being shown to be compatible with the use of silver(I) salts in glycosylation reactions (although admittedly with sulfur-based glycosyl donor tying up this species),[36] performed poorly giving only a small amount of cyclized product in which the Troc group had been converted to dichloroenol carbamate **88**.



Scheme 26. *Reagents and conditions:* (a) $Pd(OAc)_2$ (0.25 equiv), PPh_3 (0.5 equiv), DMF, MeOH, CO, O_2, 23 °C, 18-20 h, **84**: 67%, **85**: 48%; (b) $AgBF_4$ (2.5 to 3.5 equiv), CH_2Cl_2, 23 °C, **86**: 34%, **88**: <5%; (c) K_2CO_3 (5.0 equiv), MeOH, 0 to 23 °C, 1.5 h, 91%.

In light of these difficulties, we explored other carbamates in the form of Cbz and Alloc. The Cbz carbamate **89** could be prepared as above and, although it did undergo the silver-mediated cyclization in moderate yield (~15-20%), the desired cyclization product

(**90**) was hard to separate from several impurities, even by preparative TLC (Scheme 27). Although **90** could be deprotected under standard hydrogenolytic conditons (Pd/C, H_2) to furnish the targeted amine (**91**), this reaction proved to be irreproducible, a fact we ascribe to the variable amounts of residual impurities from the preceding silver-mediated cyclization step.

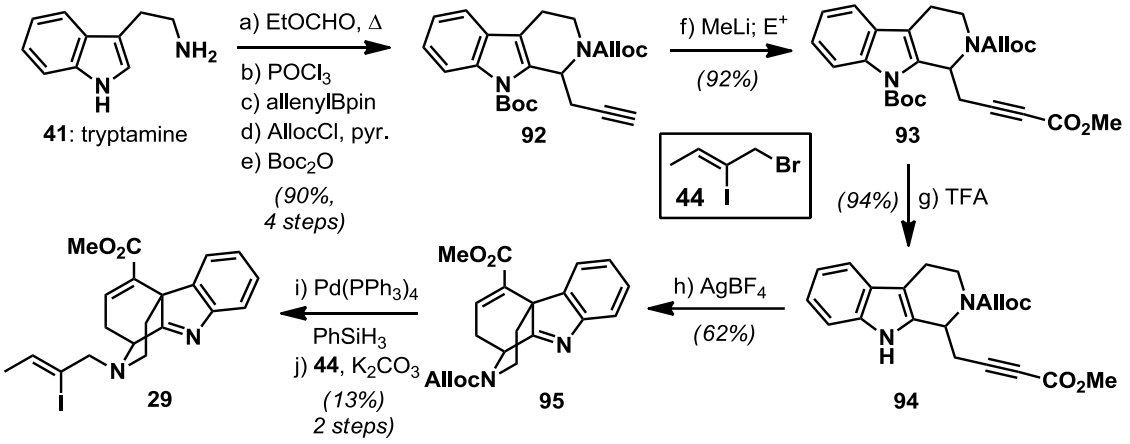


Scheme 27. *Reagents and conditions:* (a) $AgBF_4$ (3.5 equiv), CH_2Cl_2, 23 °C, 18 h, ca. 15%; (b) H_2 (1 atm), Pd/C (0.2 equiv), EtOAc, 23 °C, 45 min.

For the preparation of Alloc congener **95**, we suspected the Pd-catalyzed alkyne methoxycarbonylation would not be compatible with this group[xiv] so we adapted the approach used for propargyl alcohol **39**, where temporary *N*-Boc protection would allow the use of lithium acetylide chemistry (Scheme 28). In the event, Alloc protection of crude propargylation product of **33** followed by indole *N*-Boc protection gave bis-carbamate **92** in 90% yield over four steps from tryptamine on multigram-scale (with only one final chromatographic purification). From this material, formation of the lithium acetylide followed by treatment with MeOCOCl afforded ynoate **93** in 92% yield with a small amount of starting material recovered. Subsequent *N*-Boc deprotection with TFA (94% yield) then gave Alloc cyclization precursor **94**. Excitingly, subjecting **94** to the standard cyclization conditions gave the desired enoate ester **95** with a marked improvement in yield

[xiv] Although these are oxidative conditions, a suspension of an initial light yellow catalyst species appears to form when $Pd(OAc)_2$ and PPh_3 are mixed which could conceivably effect Alloc deprotection; this species slowly dissolves under a CO/O_2 atmosphere to give a dark red solution.

(62% vs 15% previously). At present, we cannot account for the dramatic difference in efficiencies between *N*-Alloc ynoate ester **94** and, for example, its *N*-Cbz congener **89** in this process, but perhaps interaction of Ag^+ with the olefin of the allyl group plays some role in the process.

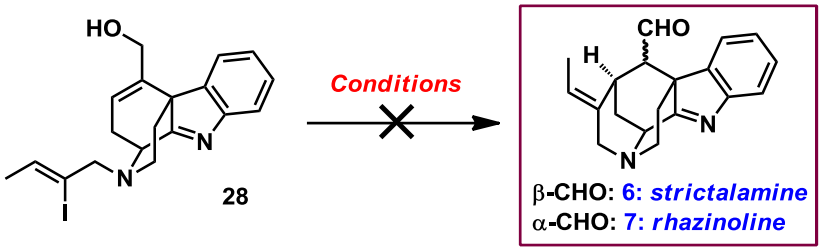


Scheme 28. *Reagents and conditions:* (a) EtOCHO, neat, Δ, 15.5 h; (b) $POCl_3$ (1.6 equiv), CH_3CN, 0 °C, 4 h; (c) allenylBpin (1.2 equiv), THF, 23 °C, 14 h; (d) AllocCl (1.3 equiv), pyr. (1.5 equiv), CH_2Cl_2, 0 to 23 °C, XX h; (e) Boc_2O (1.4 equiv), 4-DMAP (0.05 equiv), THF, 23 °C, 6.5 h, 90% (4 steps); (f) MeLi (1.1 equiv), THF, -78 °C, 55 min; MeOCOCl (1.3 equiv), -78 to 0 °C, 3 h, 92%; (g) TFA, CH_2Cl_2 (1:4 v/v), 0 to 23 °C, 5.5 h, 94%;; (h) $AgBF_4$ (5.0 equiv), CH_2Cl_2, 23 °C, 24 h, 62%; (i) $PhSiH_3$ (5.0 equiv), $Pd(PPh_3)_4$ (0.05 equiv), THF, 23 °C, 20 min; (j) **44** (2.0 equiv), K_2CO_3 (2.5 equiv), Bu_4NCl (1.0 equiv), DMF, 0 °C, 3.5 h, 13% (2 steps).

From here, Alloc deprotection [$(PPh_3)_4Pd$, $PhSiH_3$] of enoate ester **95** gave crude amine **91**, which could be allylated in low yield with bromide **44** in a one-pot process (13% yield). While these conditions are actively under optimization, we believe that the residual Pd catalyst from the previous step is interfering with the vinyl iodide of **44** (and/or its allylic bromide) to complicate the process.

Nevertheless, having access to both allylic alcohol **28** and enoate ester **29**, we began our investigations of Heck cyclizations starting with **28**, hoping to form one or both of the aldehyde natural products strictalamine (**6**) or rhazinoline (**7**). Disappointingly, cyclization using a range of standard Heck protocols (selected examples shown in Table 2), as well as

under the 'ligandless' Jeffery conditions[29] afforded no aldehyde-containing products, with mostly non-specific decomposition observed.

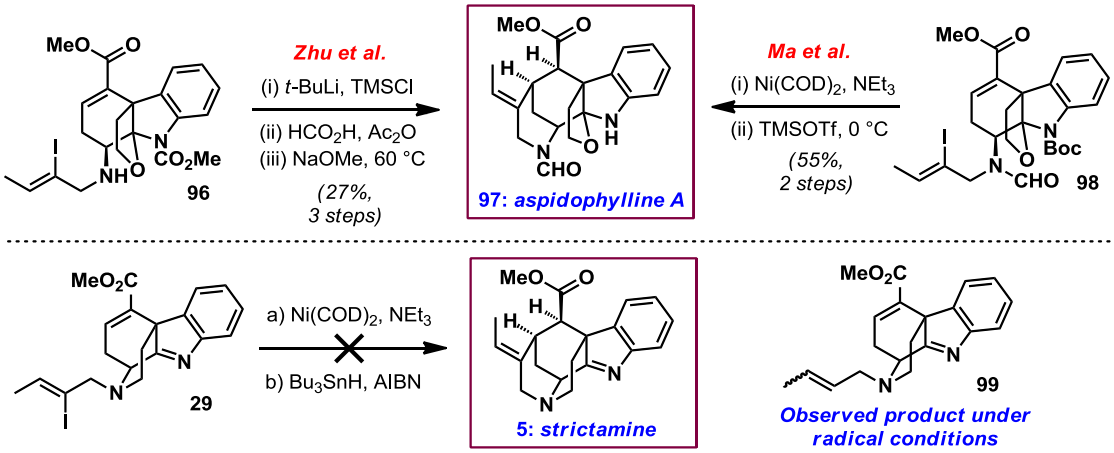


Reaction Conditions	Result
$Pd(OAc)_2$, PPh_3, K_2CO_3, NEt_3, DMF, 80 °C	*decomp.*
$Pd(OAc)_2$, K_2CO_3, Bu_4NCl, DMF, H_2O, 80 °C	*decomp.*
$Pd(OAc)_2$, PPh_3, NEt_3, CH_3CN, 80 °C	*some rec. SM*
$Pd(PPh_3)_4$, NEt_3, PhMe, Δ	*some rec. SM*

Table 2. Selected Heck reactions attempted with allylic alcohol **28**.

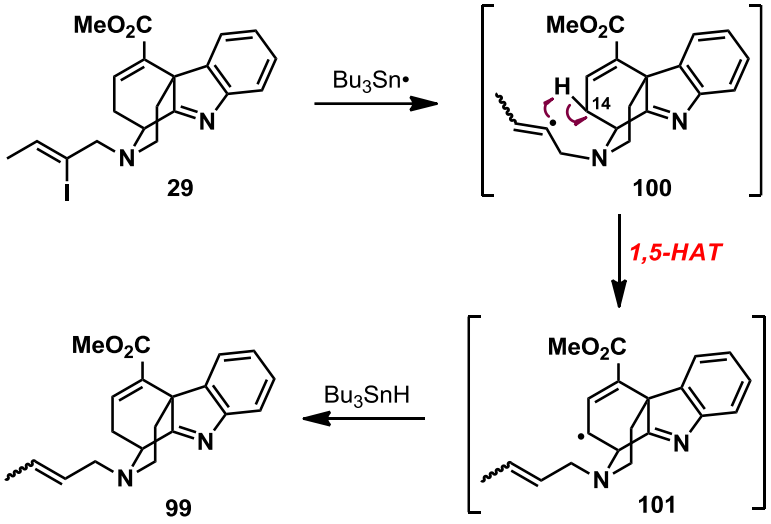
Our preliminary efforts using enoate ester **29** have been informed by the syntheses of aspidophylline A (**97**, Scheme 29) of Ma[37] and Zhu,[38] where a similar C-15/C-20 bond was formed, either via Ni(0)-mediated cyclization, radical means (although with concomitant alkene isomerization) or intramolecular conjugate addition of a vinyllithium (Section 1.3.3). Importantly, in both of their studies reductive Heck processes using Pd catalysis proved ineffective so we initially chose to avoid this method. Similarly, we felt that the presence of an imine in **29** (versus the Zhu substrate **96**), meant that an *in situ*-generated vinyllithium (or cuprate) would be incompatible with this functionality or cyclize as observed previously. Thus, we began by subjecting **29** to the $Ni(COD)_2$-based conditions used by Ma (**98**→**97**); unfortunately, these gave poor mass recovery and no traces of strictamine (**5**) by crude ^1H NMR. We were initially happy to find that standard tin-mediated radical cyclization conditions (Bu_3SnH, AIBN, toluene, 100 °C) quite cleanly

delivered a more polar spot by TLC, but by crude ^{1}H NMR this was shown to be reduction product **99**.



Scheme 29. Efforts to utilize Ma and Zhu precedent to effect E-ring closure with **29**. *Reagents and conditions:* (a) $Ni(COD)_2$ (8.0 equiv), NEt_3 (15 equiv), DMF, CH_3CN, 23 °C, 10 h; BHT (2.5 equiv), 2 h; (b) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), PhMe, 100 °C, 3 h.

Since previous radical cyclizations with imine substrates had contained no reduction product (see **30**→**59**, Scheme 17), we speculate that this process occurs via a 1,5-H atom abstraction from the now more activated allylic C-14 position, a fact consistent with similar observations made by Zhu in his aspidophylline A studies[38] as well as by Qin[39] and MacMillan[28b] en route to vincorine (Scheme 30). Going forward, we do take heart from the fact that this proposed H-atom abstraction would mean that the vinyl radical-bearing side-chain is able to access the space near to the desired site of reaction (i.e. some *N*-inversion/conformational flip is able to occur at 100 °C). Indeed, methods to advance enoate **29** to strictamine (**5**) are still under active investigation.

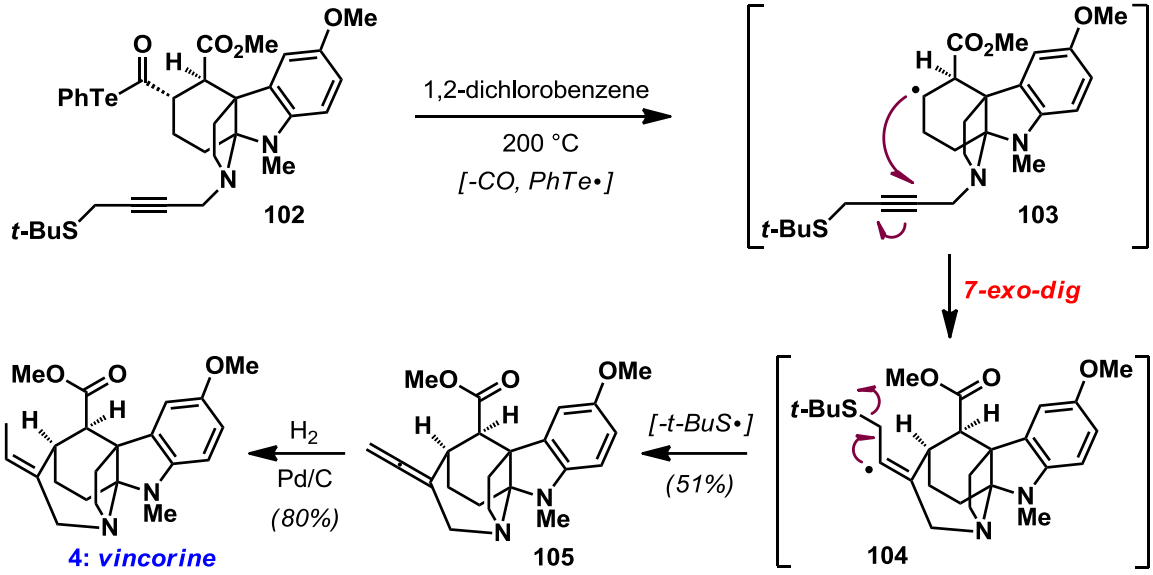


Scheme 30. Rationale for the facile radical reduction observed with **29**.

3.8 Alternate Radical Cyclization Approach

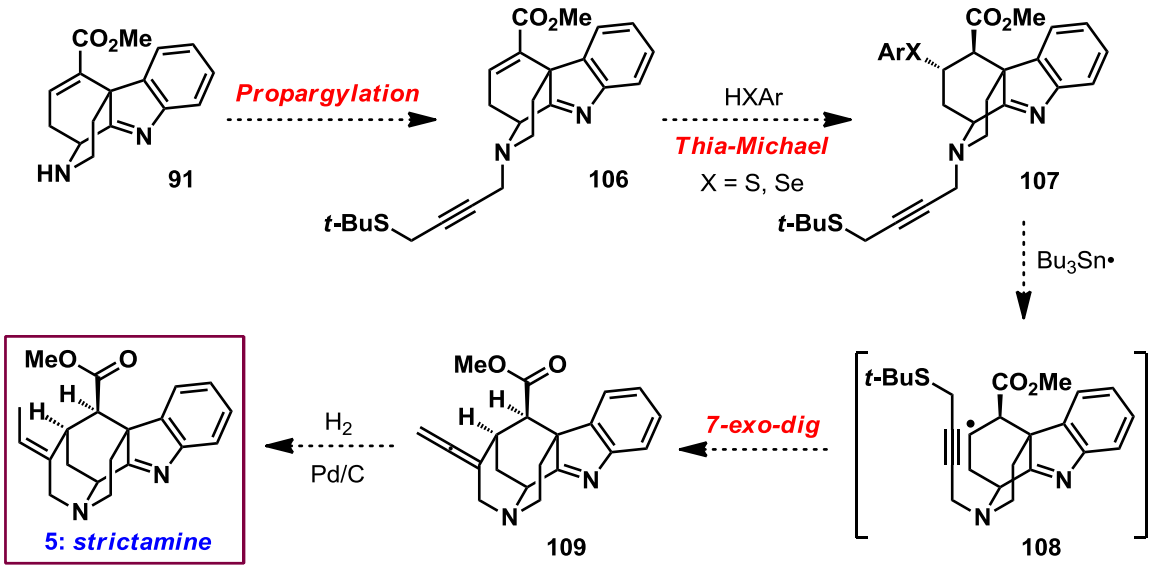
Concurrent with the aforementioned studies using substituted alkenes **28** and **29**, we considered other possibilities for E-ring formation that would not involve this "bottom-up" bond formation. In particular, we were mindful of a radical cyclization strategy utilized by MacMillan and Horning[40] to form the E-ring of vincorine (Section 1.3.2).[xv] As shown in Scheme 31 below, in this process a β-radical intermediate (**103**) was formed through thermolysis of acyltelluride **102**, which then undergoes a 7-*exo-dig* cyclization onto a propargyl sulfide radical trap to initially give vinyl radical **104**; this intermediate finally undergoes β-fragmentation to expel a *t*-butylthiyl radical and deliver allene **105**. Stereoselective semi-reduction of **105** at low temperature ultimately revealed the *E*-ethylidene chain of vincorine (**4**).

[xv] The MacMillan group had earlier utilized this strategy for the formation of the five-membered ethylidene-containing ring of the Strychnos alkaloid minfiensine under tin-radical conditions.[41]



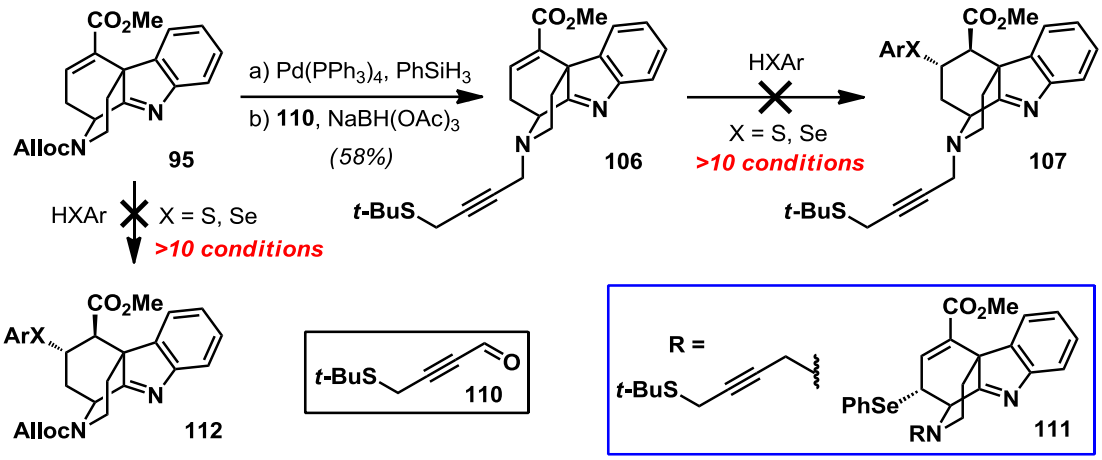
Scheme 31. Radical-based E-ring formation developed by MacMillan en route to vincorine (**4**).

We thus formulated a plan wherein attachment of MacMillan's propargyl sulfide trap to previously accessed amine **91** would yield an enoate ester (**106**) which could then be subject to a 1,4-addition of an aryl thiol or selenol to deliver **107**, a β-radical precursor for a projected tin-mediated radical cyclization to **109** (Scheme 32). Moreover, we anticipated that the slender nature of the alkyne in **107** would allow for a more favorable equilibrium for reactive conformer **108** in the key β-radical intermediate compared with previously explored approaches.



Scheme 32. Planned use of the MacMillan radical cyclization to effect E-ring formation.

Thus, using Alloc protected **95**, a one-pot deprotection/reductive amination with aldehyde **110** under MacMillan's conditions gave propargyl sulfide **106** in 58% yield over these operations with no observable reduction of the existing imine (Scheme 33). We quickly found, however, that conjugate addition of an arylthiol or selenol to **106** posed a significant challenge, with no reaction typically observed even under forcing conditions (up to 80 °C with >10 equivalents of thiol/selenol). Use of freshly prepared PhSeLi in THF at temperatures of 23 to 50 °C for prolonged periods of time gave small amounts of material containing a phenylselenide moiety, but this was later confirmed to be allylic selenide **111** where the activated allylic position (*vide supra*) has been selenylated. While we are hesitant to put forth a mechanism for the formation of **111** at present, we suspect that $(PhSe)_2$ that formed *in situ* by oxidation over time (noting that the solution gradually turns yellow) may be responsible.

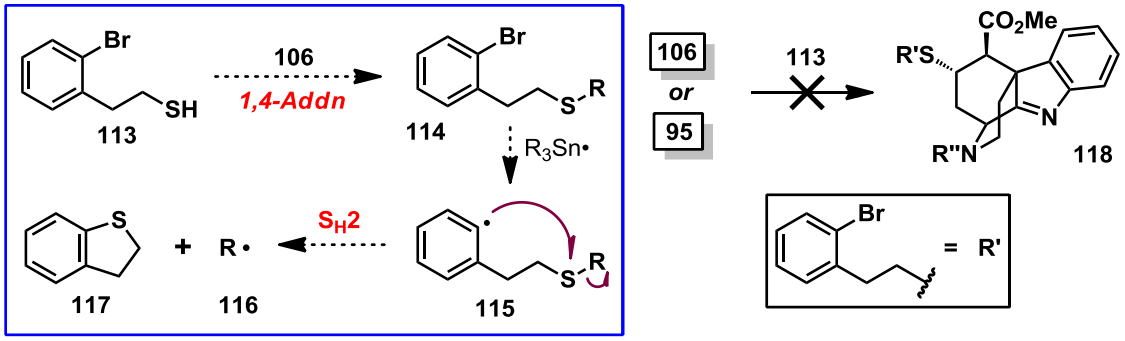


Scheme 33. Efforts to prepare a sulfide or selenide radical precursor **107** or **XX**. *Reagents and conditions:* (a) $Pd(PPh_3)_4$, $PhSiH_3$ (5.0 equiv), THF, 23 °C, 30 min; (b) **10** (2.0 equiv), $NaBH(OAc)_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 10 min, 58%.

Considering the possibility that the tertiary amine in **106** may be hampering the process, we attempted similar reactions using Alloc carbamate **95**. Like our experiments with **106**, these investigations led to no reaction and additionally underwent similar rearrangement to those observed for **68** and **86** under even mildy basic (NaSPh, LiSePh) conditions at elevated temperatures (>45 °C), especially when protic (co)solvents were employed. Although there is a great body of work on thia-Michael reactions in general, examples with α,β-disubstituted enoates are far less common. Application of conditions similar to these literature reports with aryl thiols have thus far proven ineffective with **95** or **106**.

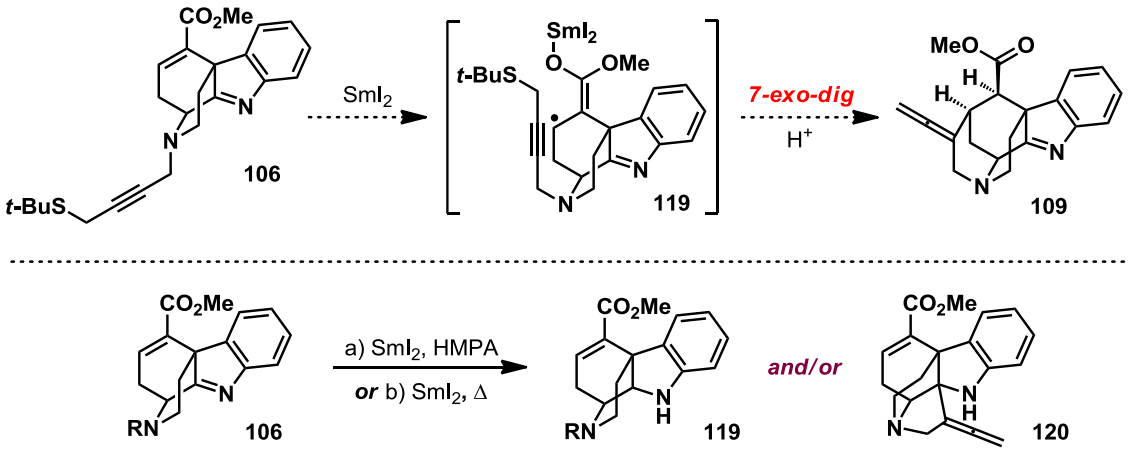
Although alkyl sulfides are typically poor radical precursors,[42] their more nucleophilic alkyl thiol precursors would likely add to the enoate ester of **106** more effectively. As a solution to this quandary, we took note of the work of Crich and co-workers[43] who have used 2-bromophenethylsulfides (generalized as **114**) which, despite being alkyl sulfide (and thus unlikely to react with tin radicals at sulfur in a productive manner), bears a reactive aryl bromide (Scheme 34). This group allows for the generation

of an aryl radical (**115**), which then attacks the sulfur atom in an S_H2 reaction to give the desired alkyl radical **116** and 1,2-dihydrobenzothiophene (**117**). We therefore prepared thiol **113** using a sequence modeled on that of Malacria and co-workers.[44] Disappointingly, though, even this alkyl thiol did not undergo productive addition to enoate esters **106** or **95**.



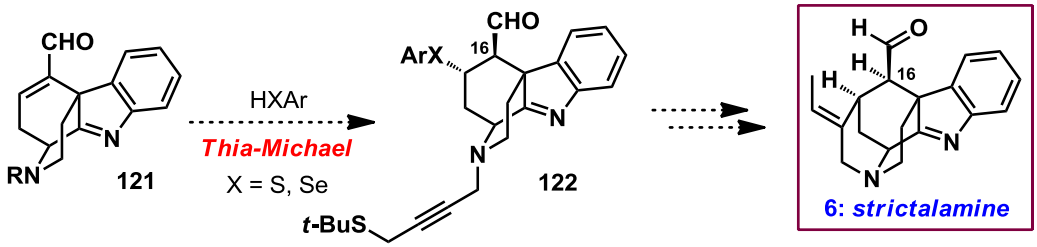
Scheme 34. Attempted use of alkyl thiol **113** as a more nucleophilic thiol to generate radical precursor **118**.

We additionally attempted to generate the targeted β-radical directly from enoate **106** through a single electron reduction using SmI_2/HMPA. These conditions were modeled on those used previously to induce β-dimerization of enoate esters[45] and enones[46] (Scheme 35). In the event, applying these conditions to **106** did provide some allene-containing material alongside a large amount of recovered starting material; however, this was shown to be indoline **120**, where a presumed ketyl-type radical derived from the imine has cyclized onto the proximal propargyl sulfide trap. Attempting the same reaction using SmI_2 alone at higher temperature in refluxing THF gave reduction product **119** as the major species along with some **120**. These experiments suggest that, not unexpectedly, the indolenine of **106** is a better electron acceptor than the enoate ester. Any further efforts in this regard would therefore likely require prior reduction to the indoline.



Scheme 35. Attempts at direct β-cyclization using samarium diiodide. *Reagents and conditions*: SmI_2 (2.5 equiv), HMPA, THF, 23 °C, 15 min; (b) SmI_2 (2 x 2.5 equiv), THF, Δ, 2 h.

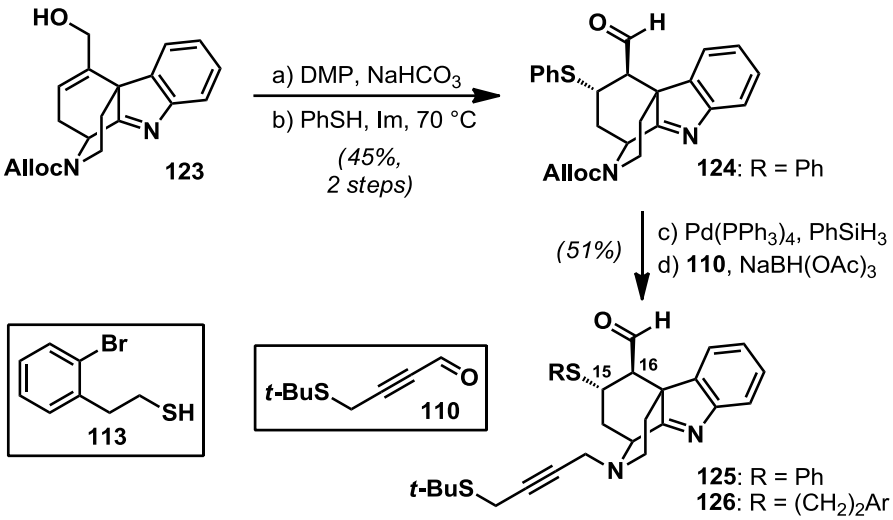
Given the failure of enoate esters **95** or **106** to undergo effective thia- or selena-Michael additions, we turned our attention to the more electrophilic enal **121** (Scheme 37). The execution of the planned radical cyclization with this substrate would afford either strictalamine[4b] (**6**) or its epimer rhazinoline[47] (**7**) depending on the C-16 stereochemistry of precursor **122**, the former being able to deliver strictamine through an oxidation/esterification sequence as previously reported by Banerji and Chakrabarti.[16]



Scheme 36. Potential use of enal **121** as a more electrophilic Michael acceptor en route to strictalamine (**6**).

An enal could be prepared from *N*-Alloc allylic alcohol **123** in high yield (93%) by Dess–Martin oxidation (Scheme 37).[47] Pleasingly, this compound proved capable of undergoing reaction with PhSH to give sulfide **124** as a single diastereomer, though full

conversion could not be attained, possibly due to the high temperatures required which may entropically favor starting materials.[xvi] Excitingly, **124** was able to be effectively deprotected and propargylated as before to give **125** in 51% yield without interference of the aldehyde or β-elimination of the sulfide. The *trans*-orientation of the sulfide and aldehyde groups in **125** was apparent from the large coupling constant between H-15 and H-16 (J = 12.4 Hz) and NOESY studies have confirmed that the C-16 stereochemistry of **125** is that required for strictalamine (**6**) and strictamine (**5**). In a similar fashion, we were able to prepare sulfide **126** using alkyl thiol **113**.

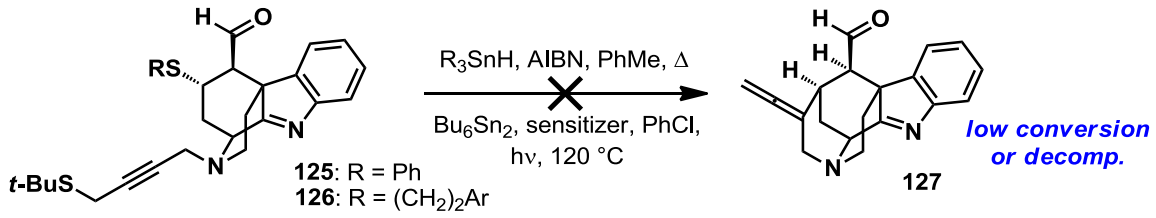


Scheme 37. *Reagents and conditions:* (a) DMP (1.2 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, 23 °C, 1 h, 93%; (b) PhSH (4.5 equiv), Im (1.9 equiv), CH_2Cl_2, 70 °C, 10 h, 48% (71% brsm); (c) $PhSiH_3$ (5.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), THF, 30 min; (b) **110** (2.0 equiv), $NaBH(OAc)_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 10 min, 51%.

Efforts to date have shown sulfides **125** and **126** to be surprisingly unreactive under typical tin-mediated radical cyclization conditions (Bu_3SnH or Ph_3SnH, AIBN, PhMe, 100–110 °C), which is unexpected given the many literature reports of effective reduction of secondary phenylsulfides (Scheme 38).[42] The difference between these protocols and

[xvi] At present we have been unable to prepare the corresponding phenylselenide.

that executed on **125**, however, is that in these reductions the tin hydride source is typically present in the reaction mixture in high concentration as opposed to the necessarily slow addition of this species in our case. Indeed, we found that adding another portion of Bu_3SnH and AIBN directly to the heated reaction mixture did consume that starting material but, not surprisingly, no desired product was obtained; alkyne hydrostannylation seemed to be the predominant pathway. Similar results were obtained with **126**. Thus, we have recently switched focus to non-reductive cyclizations using $Bu_3SnSnBu_3$ as the source of tin radicals, which was also explored by MacMillan and Horning in their vincorine studies.[40] Heating **125** with $Bu_3SnSnBu_3$ (1.5 equiv) at 120 °C in chlorobenzene in a sealed tube, with irradiation by a high pressure mercury lamp and acetone as a triplet photosensitizer, resulted in very little conversion; addition of benzophenone as a less volatile sensitizer, on the other hand, did consume starting material.[49] No desired product could be obtained from the reaction mixture, and a similar outcome was obtained using 4,4'-dimethoxybenzophenone added at the start of the reaction. It may be that aldehyde **125** (and/or product **127**) is unstable to the combination of heating and irradiation with a triplet photosensitizer. Investigations with **125**, **126** and related compounds are ongoing.

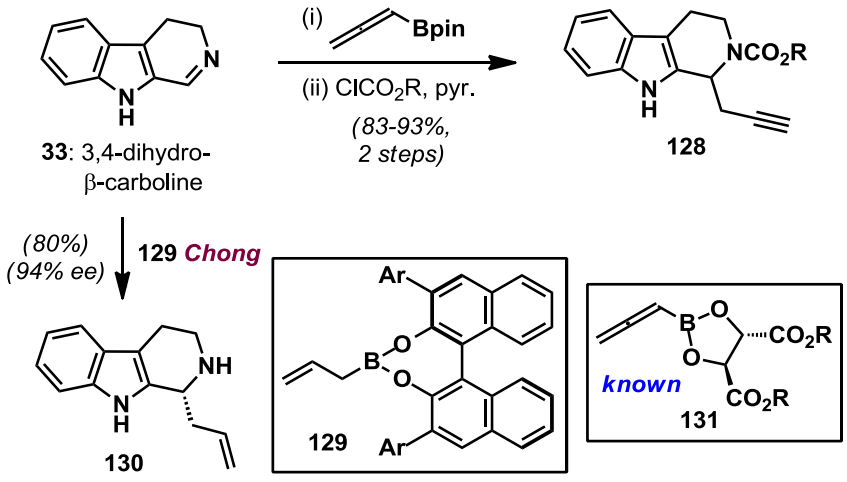


Scheme 38. Preliminary radical cyclization attempts undertaken with sulfides **125** and **126**.

3.9 Conclusions and Outlook

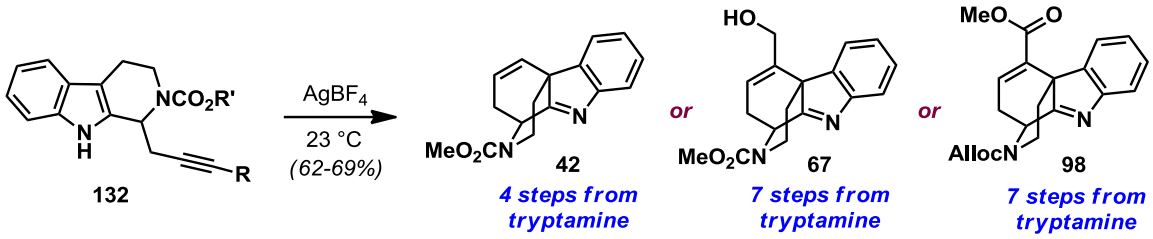
This chapter has detailed our synthetic efforts towards the complex akuammiline alkaloid strictamine (**5**) through the development of a potentially generalizable strategy for the akuammiline family at large. Specifically, an approach centered upon a final C-15/C-20 bond formation to complete the characteristic pentacyclic akuammiline framework has been devised, which relied entirely on the efficient preparation of a number of endocyclic alkene-containing tetracyclic intermediates, structures which to date have not been synthetically accessible in a concise fashion.

To deliver the target intermediates, we have developed several novel synthetic transformations. The first is a unprecedented use of an allenylboronate to effect a mild propargylation of a cyclic aldimine, 3,4-dihydro-β-carboline (**33**), a process we hope to translate into an asymmetric variant based on strong precedent from the allylation work of Chong and co-workers (**33**→**130**, Scheme 39),[50] as well as the known[51] and easily envisaged chiral allenylboronates (e.g. **131**).



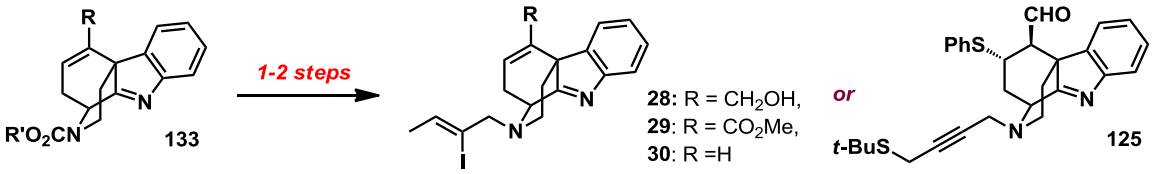
Scheme 39. The developed propargylation procedure and possible extension to an asymmetric variant based on the work of Chong.

Secondly, a novel silver(I)-mediated cyclization of fused indoles onto alkynes has been discovered to arrive at appropriately functionalized tetracyclic structures (**42**, **67**, **98**, Scheme 40) in only 4-7 steps from tryptamine (**41**) in a scalable and efficient fashion (0.2-1.5 g of each have been prepared to date). Indeed, this method has proven to be fairly versatile, proceeding effectively with a range of alkyne substrates bearing both varied substitution and unprotected termini.



Scheme 40. ABCD tetracyclic intermediates rapidly obtained from tryptamine through a novel silver-mediated indole/alkyne cyclization.

From the readily available tetracyclic intermediates, we have been able to advance to a variety of E-ring precursors in only 1–2 steps (Scheme 41). Although extensive investigations (>15 conditions) into a carbonylative Heck process to fashion strictamine (**5**) from unsubstituted alkene **30** proved unsuccessful, we drew significant intelligence about the conformational preferences of the tetracycle and competitive pathways that its imine might engender.

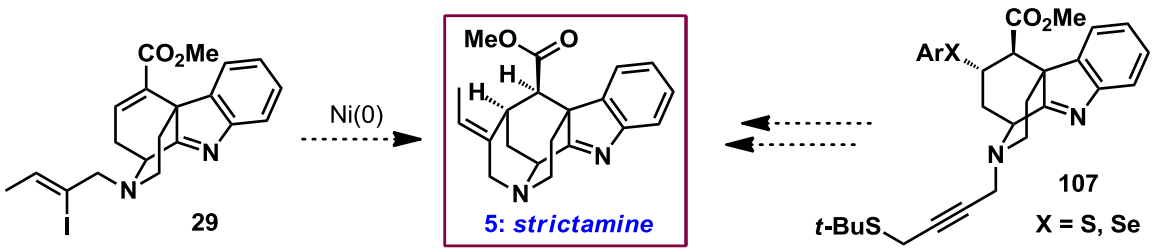


Scheme 41. Elaboration of ABCD tetracyclic intermediates to a variety of E-ring precursors

From allylic alcohol **28**, we were likewise unable to effect the desired Heck closure to strictalamine (**6**) or rhazinoline (**7**), but its precursor compound **67** served as a means of

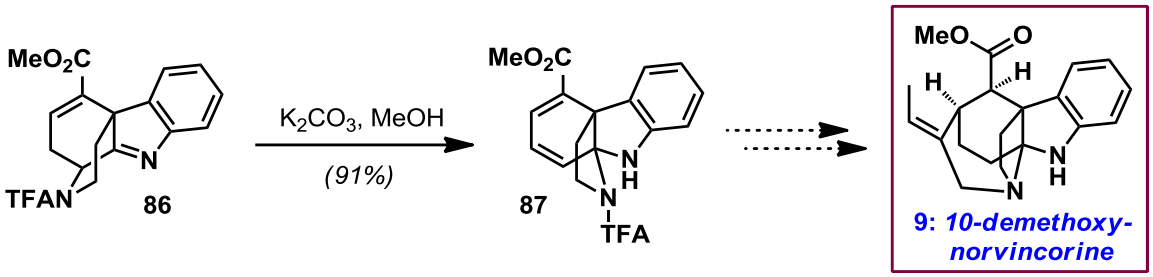
accessing a crucial enal intermediate for a later radical cyclization approach. Indeed, we are hopeful that sulfide **125** with serve as a viable intermediate towards **6** once the appropriate radical cyclization conditions can be found. Moreover, future studies will aim to access its selenide congener as a means to facilitate initial radical generation.

In terms of an expedient preparation of strictamine (**5**), our primary focus in future efforts will center upon the enoate ester **29**, wherein we hope to uncover reductive cyclization conditions based on several reported Ni(0)-mediated procedures (Scheme 42).[52] It may turn out that reduction (and/or protection) of the imine will be necessary for these and related (e.g. intramolecular conjugate addition) cyclizations to proceed. Similarly, if an ester analogue of **125** (i.e. **107**) can be prepared through a thia-Michael addition to **106**, then another potential avenue to explore in regards to accessing **5** would be opened.



Scheme 42. Most appealing avenues of further exploration toward strictamine (**5**).

Finally, through the facile rearrangement of **86** to pyrroloindoline **87** under basic conditions, we have established the basis for a synthesis of vincorine-type alkaloids, which we aim to target through radical cyclization processes that build on the work of MacMillan and Horning (Scheme 43).[40]



Scheme 43. Proposed access to vincorine-type alkaloids through a highly efficient rearrangement.

Globally, through the work delineated in this chapter, we are confident that an effective synthetic solution for the akuammiline alkaloids strictamine (**5**), its reduced congener strictalamine (**6**), and 10-demethoxynorvincorine (**9**) will be available in the near future. From these initial advances, an effective course for accessing the full diversity represented by this intriguing alkaloid family can be confidently plotted.

3.10 References

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3.11 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. Dry methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), benzene (PhH) and toluene (PhMe) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; triethylamine (Et_3N) was distilled from KOH; acetone, methanol (MeOH), and dimethylformamide (DMF) were purchased in anhydrous form from Sigma-Aldrich and used as received. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and an aqueous solution of cerium ammonium sulfate and ammonium molybdate and heat as visualizing agents. Preparative TLC was carried out on 0.50 mm E. Merck silica gel plates (60F-254). SiliCycle silica gel (60 Å, academic grade, particle size 40-63 μm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-300, DRX-400, and DRX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations are used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer Spectrum Two FT-IR spectrometer. High resolution mass spectra (HRMS) were

recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (Fast Atom Bombardment).

Methyl Carbamate 38. To a solution of crude 3,4-dihydro-β-carboline (**33**, 2.47 g, 14.49 mmol, 1.0 equiv) in THF (60 mL) at 23 °C was slowly added allenylboronic acid pinacol ester (3.4 mL, 18.13 mmol, 1.25 equiv). After a further 15 hours of stirring at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL) and the reaction contents were transferred to a separatory funnel, diluting with CH_2Cl_2 (120 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (120 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give a red oil (6.04 g) that was used in the next step without further purification.

The so-obtained crude propargyl amine was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C, whereafter pyridine (2.3 mL, 28.55 mmol, 2.0 equiv) was added followed by dropwise addition of methyl chloroformate (1.7 mL, 21.66 mmol, 1.5 equiv) at which point the red-orange solution darkens. The resulting solution was allowed to warm to 23 °C slowly over 11 hours, at which point 0.5 M aqueous HCl (50 mL) was added and the reaction contents were transferred to a separatory funnel diluting with water (50 mL) and CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (150 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:9→2:3) to give methyl carbamate **38** (3.21 g, 83% yield, two steps) as a beige foam. **38**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.19 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1 H), 7.11 (t, *J* = 7.0 Hz, 1 H),

5.37 (br d, *J* = 46.5 Hz, 1 H), 4.46 (br dd, *J* = 67.7, 7.6 Hz, 1H), 3.78 (s, 3H), 3.18 (m, 1H), 2.90 – 2.62 (m, 4H), 2.26 (d, *J* = 11.7 Hz, 1 H).

Indolenine 42. To a solution of alkyne **38** (951 mg, 3.45 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at 23 °C was added $AgBF_4$ (705 mg, 3.62 mmol, 1.0 equiv) and the reaction stirred at this temperature for 14 h. At his point, saturated aqueous $NaHCO_3$ (50 mL) was added and the reaction mixture was stirred vigorously for 30 min. The reaction contents were then transferred to a separatory funnel diluting with water (30 mL) and CH_2Cl_2 (80 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (120 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:9→1:1) to give indolenine **42** (525 mg, 55% yield) as a slightly yellow gum [Note: on smaller scales the yield was slightly higher, e.g. 67% (40 mg scale)]. **42**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1 H), 7.44 (d, *J* = 7.3 Hz, 1 H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.25 (td, *J* = 7.5, 1.1 Hz, 1 H), 5.94 (m, 1H), 5.74 (d, *J* = 9.5 Hz, 1 H), 5.50 (br d, *J* = 50.3 Hz, 1 H), 4.11 (br dd, *J* = 68.1, 12.1 Hz, 1 H), 3.71 (s, 3 H), 3.45 (br t, *J* = 13.1 Hz, 1 H), 2.85 – 2.56 (m, 2 H), 2.20 (d, *J* = 13.4 Hz, 1 H), 1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 155.4, 155.2, 141.1, 129.8, 128.2, 126.3, 125.6, 122.1, 121.2, 54.0, 53.4, 52.8, 50.9, 37.1, 36.8, 35.0, 24.7 (Note: some peaks are doubled due to rotamers).

Amine 43. To a solution of methyl carbamate **42** (63 mg, 0.233 mmol, 1.0 equiv) in MeOH (4 mL) in a microwave vial under air was added 6 M aqueous NaOH (0.5 mL, 3

mmol, 12.9 equiv) and the vial capped. The reaction mixture was heated at 120 °C for 2 h under microwave irradiation before being allowed to cool to room temperature. The reaction contents were then transferred to a separatory funnel diluting with water (10 mL) and CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to give pure **43** (49 mg, 99% yield) as a white crystalline solid. **43**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.7 Hz, 1 H), 7.37 (d, *J* = 7.3 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 5.93 (dt, *J* = 9.5, 3.4 Hz, 1 H), 5.64 (d, *J* = 9.5 Hz, 1 H), 4.14 (d, *J* = 6.1 Hz, 1 H), 3.20 (ddd, *J* = 15.1, 12.5, 3.3 Hz, 1 H), 2.80 (dd, *J* = 14.2, 4.7 Hz, 1 H), 2.77 – 2.57 (m, 2 H), 2.26 (dd, *J* = 12.9, 3.1 Hz, 1 H), 1.95 (br s, 1 H), 1.33 (td, *J* = 12.6, 4.7 Hz, 1 H).

Vinyl Iodide 30. Bromide **44** (204 mg, 0.782 mmol, 1.4 equiv) was weighed directly into a flask containing amine **43** (116 mg, 0.554 mmol, 1.0 equiv), whereafter CH_3CN (6 mL) was added at 23 °C. K_2CO_3 (173 mg, 1.252 mmol, 2.3 equiv) was then added and the stirred reaction mixture heated to 70 °C. After 4.5 h, the reaction was allowed to cool then quenched with water (5 mL) and the reaction contents were transferred to a separatory funnel diluting with water (10 mL) and CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (25 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:19→1:4) to give vinyl iodide **30** (204 mg, 94% yield) as a clear colorless gum. **30**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 1 H), 7.37 (td, *J*

= 7.6, 1.3 Hz, 1 H), 7.23 (td, *J* = 7.4, 1.1 Hz, 1 H), 5.96 (dt, *J* = 9.4, 3.3 Hz, 1 H), 5.88 (qt, *J* = 6.4, 1.3 Hz, 1 H), 5.68 (ddd, *J* = 9.4, 2.5, 1.6 Hz, 1 H), 3.94 (d, *J* = 6.3 Hz, 1 H), 3.38 (d, *J* = 14.1 Hz, 1 H), 3.29 – 3.18 (m, 2H), 2.80 (dd, *J* = 19.6, 2.8 Hz, 1 H), 2.69 – 2.57 (m, 2 H), 2.08 (dd, *J* = 13.2, 1.9 Hz, 1 H), 1.78 (d, *J* = 6.4 Hz, 3 H), 1.58 (td, *J* = 12.8, 4.4 Hz, 1 H).

Tosyl Indolines 61 and 62. To a solution of vinyl iodide **30** (127 mg, 0.325 mmol, 1.0 equiv) in THF (6 mL) at 0 °C was added $LiBH_4$ (30 mg, 1.377 mmol, 4.2 equiv) in a single portion. The reaction mixture was slowly allowed to warm to room temperature and after 5.5 h was quenched with saturated aqueous $NaHCO_3$ (5 mL). The reaction contents were transferred to a separatory funnel, diluting with water (10 mL) and CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give a crude mixture of diastereomeric indolines **60** (112 mg).

A portion of the so-obtained crude material (67 mg) was then dissolved in pyridine (1.5 mL) and TsCl (103 mg, 0.540 mmol, 2.8 equiv) was added at 23 °C. After 11.5 h at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The reaction contents were transferred to a separatory funnel, diluting with water (10 mL) and CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (15 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated; a small amount of residual pyridine was then removed through azeotroping with toluene once. Purification of the crude material by preparative TLC (EtOAc/hexanes, 1:4, run up twice) gave less polar sulfonamide **61** (19 mg, 18%, two

steps) as a colorless gum and its diastereomer **62** (58 mg, 55%, two steps) as a white crystalline solid. **61**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.75 (m, 2 H), 7.26 (d, *J* = 7.7 Hz, 2 H), 7.20 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1 H), 7.07 (dd, *J* = 7.4, 1.5 Hz, 1 H), 7.00 (td, *J* = 7.4, 1.0 Hz, 1 H), 5.93 (dt, *J* = 9.8, 3.3 Hz, 1 H), 5.87 (q, *J* = 6.4 Hz, 1 H), 5.02 (d, *J* = 9.9 Hz, 1 H), 3.96 (t, *J* = 4.2 Hz, 1 H), 3.45 (dt, *J* = 14.0, 1.3 Hz, 1 H), 3.35 (d, *J* = 2.5 Hz, 1 H), 3.29 (d, *J* = 14.1 Hz, 1 H), 2.73 (td, *J* = 11.5, 3.9 Hz, 1 H), 2.64 (ddd, *J* = 11.5, 5.1, 1.8 Hz, 1 H), 2.56 (ddt, *J* = 19.2, 5.1, 2.6 Hz, 1 H), 2.37 (s, 3 H), 2.24 – 2.15 (m, 1 H), 1.85 (d, *J* = 6.4 Hz, 3 H), 1.76 (td, *J* = 11.9, 5.1 Hz, 1 H). **62**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.72 (m, 3 H), 7.24 – 7.16 (m, 3 H), 7.10 (dd, *J* = 7.4, 1.3 Hz, 1 H), 7.00 (td, *J* = 7.4, 1.0 Hz, 1 H), 6.10 – 6.05 (m, 1 H), 6.02 (dt, *J* = 9.6, 2.0 Hz, 1 H), 5.91 (dt, *J* = 9.7, 3.3 Hz, 1 H), 4.23 (dd, *J* = 5.7, 2.3 Hz, 1 H), 3.58 (d, *J* = 1.3 Hz, 1 H), 3.24 (d, *J* = 2.3 Hz, 1 H), 2.62 – 2.50 (m, 2 H), 2.49 – 2.41 (m, 1 H), 2.34 (s, 3 H), 2.25 (ddt, *J* = 19.1, 5.7, 2.7 Hz, 1 H), 1.80 (dt, *J* = 6.4, 1.4 Hz, 3 H), 1.68 (ddd, *J* = 13.3, 11.3, 5.8 Hz, 1 H), 1.20 (dt, *J* = 13.3, 2.5 Hz, 1 H).

Propargyl Alcohol 39. To a solution of indole **38** (871 mg, 3.25 mmol, 1.0 equiv) in THF (17 mL) at 23 °C was added Boc_2O (1.002 g, 4.59 mmol, 1.4 equiv) followed by 4-DMAP (25 mg, 0.20 mmol, 0.06 equiv). After 40 min the reaction mixture was concentrated directly and the crude material purified by flash chromatography (silica gel, EtOAc/hexanes, 1:19→3:7) to afford the corresponding *N*-Boc-protected indole (1.196 g, >99%).

This material was dissolved in THF (30 mL) and cooled to –78 °C and *n*-BuLi (1.6 M solution in hexanes, 2.74 mL, 4.38 mmol, 1.35 equiv) was added dropwise. After stirring

for a further 1 h at –78 °C, paraformaldehyde (341 mg, 11.36 mmol, 3.5 equiv) was added in one portion and the reaction mixture allowed to warm slowly to room temperature over 4 h. At this point saturated aqueous NH_4Cl (25 mL) was added and the reaction contents were transferred to a separatory funnel, diluting with water (50 mL) and CH_2Cl_2 (80 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (60 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting purified by flash chromatography (silica gel, EtOAc/hexanes, 1:19→3:2) to afford the corresponding *N*-Boc-propargyl alcohol (871 mg, 67%, 94% brsm) as a slightly yellow foam, along with recovered starting material (342 mg).

A portion of this product (92 mg, 0.231 mmol, 1.0 equiv) was dissolved in THF/MeOH (6.3 mL, 20:1) and cooled to 0 °C. NaOMe (78 mg, 1.444 mmol, 6.3 equiv) was added in one portion and after 10 min the ice-water bath was removed and the solution allowed to warm to 23 °C. After 45 min, the reaction was quenched with saturated aqueous NH_4Cl (8 mL) and and the reaction contents were transferred to a separatory funnel, diluting with water (10 mL) and CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting purified by flash chromatography (silica gel, EtOAc/hexanes, 1:4→3:2) to afford *N*-H propargyl alcohol **39** (63 mg, 91%) as a slightly beige foam. **39**: ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ~ 2:1; signals that are resolved for each are indicated with * for the major and $^{\#}$ for minor rotamers, respectively) δ 9.22* (s, 1 H), 8.60$^{\#}$ (s, 1 H), 7.48 (d, *J* = 7.7 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.17 (t, *J* = 7.5 Hz, 1 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 5.55* (t, *J* = 7.1 Hz, 1

H), 5.30[#] (br s, 1 H), 4.55[#] (d, *J* = 13.0 Hz, 1 H), 4.44 – 4.20 (m, 3 H), 3.83* (s, 3 H), 3.78[#] (s, 3 H), 3.56* (br s, 1 H), 3.30 – 3.08 (m, 1 H), 2.90 – 2.67 (m, 4 H), 2.30[#] (br s, 1H).

Allylic Alcohol 67. To a solution of alkyne **39** (307 mg, 1.027 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) at 23 °C was added $AgBF_4$ (266 mg, 1.366 mmol, 1.3 equiv). After 2.5 an additional portion of $AgBF_4$ (266 mg, 1.366 mmol, 1.3 equiv) was added. After 18 h (total), saturated aqueous $NaHCO_3$ (15 mL) was added and the reaction mixture was stirred vigorously for 30 min. The reaction contents were then transferred to a separatory funnel diluting with water (20 mL) and CH_2Cl_2 (60 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (60 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:4→1:0) to give indolenine **67** (195 mg, 64% yield) as a colorless oil. **67**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 2 H), 7.41 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 6.03 (s, 1 H), 5.49 (br d, *J* = 46.7 Hz, 1 H), 4.35 (d, *J* = 13.3 Hz, 1 H), 4.20 (d, *J* = 12.9 Hz, 1 H), 3.98 – 4.26 (m, 1 H), 3.73 (s, 3 H), 3.45 (app d, *J* = 12.7 Hz, 1 H), 2.87 – 2.76 (m, 1 H), 2.71 (d, *J* = 19.0 Hz, 1 H), 2.58 (d, *J* = 13.1 Hz, 1 H), 1.47 – 1.33 (m, 1 H).

Vinyl Iodide 28. To a solution of methyl carbamate **67** (27 mg, 0.088 mmol, 1.0 equiv) in MeOH (1.8 mL) in a microwave vial under air was added 6 M aqueous NaOH (0.2 mL, 1.2 mmol, 13.6 equiv) and the vial capped. The reaction mixture was heated at 120 °C for 2.5 h under microwave irradiation before being allowed to cool to room temperature. The reaction contents were then transferred to a separatory funnel diluting

with water (8 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to give essentially pure secondary amine (18 mg, 86% yield) as an off-white crystalline solid.

Without further purification, this material was dissolved in CH_3CN (1.2 mL) and a solution of bromide **44** (50 mg, 0.192 mmol, 2.2 equiv) in CH_3CN (1.0 mL) was added at 23 °C. K_2CO_3 (36 mg, 0.260 mmol, 3.0 equiv) was then added and the stirred reaction mixture heated to 50 °C. After 2 h, TLC indicated very little conversion so the reaction was allowed to cool then *i*-Pr_2NEt (0.02 mL, ca. 1.5 equiv) was added and the reaction reheated to 50 °C. After 1.75 h more, the reaction mixture was allowed to cool and quenched with water (5 mL) and the reaction contents were transferred to a separatory funnel diluting with water (5 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 3:2) to give vinyl iodide **28** (16 mg, 43% yield, two steps) as a clear colorless gum. **28**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 1 H), 7.65 (d, *J* = 7.2 Hz, 1 H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.25 (d, *J* = 7.9 Hz, 1 H), 6.01 (s, 1 H), 5.88 (q, *J* = 6.4 Hz, 1 H), 4.30 (d, *J* = 13.1 Hz, 1 H), 4.15 (d, *J* = 13.2 Hz, 1 H), 3.89 (d, *J* = 6.4 Hz, 1 H), 3.38 (d, *J* = 14.1 Hz, 1 H), 3.26 – 3.17 (m, 2 H), 2.82 (d, *J* = 19.2 Hz, 1 H), 2.69 – 2.59 (m, 2 H), 2.40 (d, *J* = 11.7 Hz, 1 H), 1.78 (d, *J* = 6.6 Hz, 3 H), 1.56 (td, *J* = 12.9, 4.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2, 155.5, 140.6, 135.2, 133.2, 128.3, 126.8, 125.3, 124.3, 121.1, 108.2, 65.1, 65.0, 56.4, 55.3, 42.8, 36.5, 33.6, 21.9.

Ynoate Ester 40. A solution of alkyne **38** (103 mg, 0.382 mmol, 1.0 equiv) in DMF/MeOH (1:1, 1 mL + 2 × 0.75 mL DMF washes) was added to a stirred suspension of $Pd(OAc)_2$ (26 mg, 0.115 mmol, 0.3 equiv) and PPh_3 (62 mg, 0.229 mmol, 0.6 equiv) in DMF (4 mL) at 23 °C. The mixture was then placed under an atmosphere of CO and O_2 (~1:1) and stirred overnight. After 16 h at 23 °C, TLC analysis of the dark red solution showed some staring material remained (~40%), so the CO/O_2 balloon was refilled and stirring continued. After 44.5 h, TLC analysis indicated that the reaction was complete. Water (10 mL) was added to the reaction mixture and the reaction contents were then transferred to a separatory funnel diluting with Et_2O (25 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted a second time with Et_2O (25 mL). The combined organic layers were washed with water (15 mL) then brine (15 mL) and dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:9→1:1) to give ynoate ester **40** (136 mg, >80% yield) containing an aromatic impurity as a slightly yellow gum. **40**: ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ~ 1.15:1; signals that are resolved for each are indicated with * for the major and $^{\#}$ for minor rotamers, respectively) δ 8.63* (s, 1H), 8.52$^{\#}$ (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.44 – 7.29 (m, 1 H), 7.19 (td, *J* = 7.1, 1.1 Hz, 1 H), 7.11 (t, *J* = 6.9 Hz, 1 H), 5.52* (br s, 1 H), 5.40$^{\#}$ (br s, 1 H), 4.58$^{\#}$ (d, *J* = 12.6 Hz, 1 H), 4.39* (d, *J* = 13.4 Hz, 1 H), 3.87 – 3.73 (m, 6 H), 3.35 – 3.22* (m, 1 H), 3.17$^{\#}$ (br t, *J* = 11.3 Hz, 1 H), 3.01 – 2.71 (m, 4 H).

Enoate Ester 68. To a solution of alkyne **40** (50 mg, 0.153 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) at 23 °C was added $AgBF_4$ (62 mg, 0.318 mmol, 2.1 equiv). After 9 h (total) the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) was added and the reaction mixture was stirred vigorously for 30 min. The reaction contents were then transferred to a separatory funnel diluting with water (5 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1) to give indolenine **68** (8.7 mg, 15% yield) along with the less polar hydration product **73** (16.0 mg, 30% yield), both as colorless oils. 7.91 (dd, *J* = 7.6, 0.6 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H), 7.26 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.06 (t, *J* = 3.3 Hz, 1 H), 5.50 (br d, *J* = 47.9 Hz, 1 H), 4.12 (br dd, *J* = 73.5, 14.6 Hz, 1 H), 3.78 (s, 3H), 3.74 (s, 3 H), 3.35 – 3.21 (m, 1H), 2.96 – 2.76 (m, 3H), 1.40 (br t, *J* = 12.7 Hz, 1 H).

***N*-TFA Enoate Ester 86.** To a solution of alkyne **84** (59 mg, 0.162 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at 23 °C was added $AgBF_4$ (50 mg, 0.255 mmol, 1.6 equiv) and the reaction stirred at this temperature for 2.5 h. At this point, TLC analysis indicated partial conversion so an additional portion of $AgBF_4$ (50 mg, 0.255 mmol, 1.6 equiv) was added. Further portions of $AgBF_4$ (50 mg, 0.255 mmol, 1.6 equiv) were added after 4.5 h and 7.5 h. After 20 h (total), saturated aqueous $NaHCO_3$ (8 mL) was added and the reaction mixture was stirred vigorously for 30 min. The reaction contents were then transferred to a separatory funnel diluting with water (10 mL) and CH_2Cl_2 (15 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (15 mL). The combined

organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 3:7, run up twice) to give indolenine **86** (20 mg, 34% yield) as a colorless gum. **87**: ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ~ 1.7:1; signals that are resolved for each are indicated with * for the major and # for minor rotamers, respectively) δ 7.92 (d, *J* = 7.6 Hz, 1 H), 7.69 (app dd, *J* = 7.7, 4.3 Hz, 1 H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.31 – 7.25 (m, 1 H), 7.11 – 7.05 (m, 1 H), 5.91* (d, *J* = 5.7 Hz, 1 H), 5.34# (d, *J* = 5.7 Hz, 1 H), 4.59# (dd, *J* = 15.0, 4.1 Hz, 1 H), 3.99* (dd, *J* = 13.7, 4.1 Hz, 1 H), 3.80# (s, 3 H), 3.79* (s, 3 H), 3.68 – 3.58* (m, 1 H), 3.36 – 3.24# (m, 1 H), 3.13 – 2.98 (m, 1 H), 2.97 – 2.80 (m, 2 H), 1.47 (qd, *J* = 13.6, 4.9 Hz, 1 H).

Pyrroloindoline 87. To a solution of indolenine **86** (5.5 mg, 0.0151 mmol, 1.0 equiv) in MeOH (1.5 mL) at 0 °C was added K_2CO_3 (10.5 mg, 0.0750 mmol, 5.0 equiv) and the reaction stirred at this temperature for 1.5 h at which point it had just reached 23 °C. At this point, TLC analysis indicated clean conversion to a more polar product so water (4 mL) was added. The reaction contents were then transferred to a separatory funnel diluting with water (4 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (15 mL). The combined organic layers were washed with brine (8 mL), dried with $MgSO_4$, filtered and concentrated to give almost pure pyrroloindoline **87** (5.0 mg, 91% yield) as a yellow oil. **87**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.6 Hz, 1 H), 7.68 (d, *J* = 7.7 Hz, 1 H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.12 (d, *J* = 6.0 Hz, 1 H), 7.02 (d, *J* = 9.5 Hz, 1 H), 6.73 (dd, *J* = 9.5, 5.9

Hz, 1 H), 5.79 (br s, 1 H), 3.84 (s, 3 H), 2.96 – 2.86 (m, 1 H), 2.86 – 2.77 (m, 1 H), 2.75 – 2.65 (m, 1H), 2.18 – 2.09 (m, 1H).

Alloc Boc Amine 92. To a solution of crude 3,4-dihydro-β-carboline [**33**, 14.12 mmol based on tryptamine (**41**)] in THF (65 mL) at 23 °C was slowly added allenylboronic acid pinacol ester (2.9 mL, 16.14 mmol, 1.14 equiv). After a further 14 hours of stirring at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL), diluting with CH_2Cl_2 (110 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (110 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give a red oil (4.17 g) that was used in the next step without further purification.

The so-obtained crude propargyl amine was dissolved in CH_2Cl_2 (85 mL) and cooled to 0 °C, whereafter pyridine (1.6 mL, 20.37 mmol, 1.44 equiv) was added followed by dropwise addition of allyl chloroformate (1.9 mL, 17.66 mmol, 1.25 equiv) at which point the red-orange solution darkens. The resulting solution was allowed to warm to 23 °C slowly over 24 hours, at which point 0.5 M aqueous HCl (50 mL) was added and the reaction contents were transferred to a separatory funnel diluting with water (50 mL) and CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (120 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to give crude *N*-Alloc propargylamine (4.2 g) as an amber gum.

Without purification this material was dissolved in THF (75 mL) and Boc_2O (3.59 g, 16.44 mmol, 1.17 equiv) was added at 23 °C, followed by a catalytic amount of 4-DMAP (104 mg, 0.85 mmol, 0.06 equiv). The reaction was stirred at this temperature for 5.5 h, at

which point TLC analysis indicated a small amount of starting material remained. Addition of a further portion of Boc_2O (0.38 g, 1.74 mmol, 0.12 equiv), followed by an additional 1 h stirring led to full conversion, after which the reaction mixture was directly concentrated. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:9→1:3) to give Alloc Boc amine **92** (5.0 g, 90% yield from tryptamine) as a thick slightly yellow-green oil. **92**: ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ~ 1.3:1; signals that are resolved for each are indicated with * for the major and # for minor rotamers, respectively) δ 8.19# (d, *J* = 8.4 Hz, 1 H), 8.16* (d, *J* = 8.3 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.31 (t, *J* = 7.1 Hz, 1 H), 7.27 – 7.21 (m, 1 H), 6.13# (br dd, *J* = 9.0, 2.6 Hz, 1 H), 6.06* (br dd, *J* = 9.4, 2.6 Hz, 1 H), 6.03 – 5.91 (m, 1 H), 5.41 – 5.30 (m, 1 H), 5.27 – 5.18 (m, 1 H), 4.75 – 4.52 (m, 3 H), 4.44# (dd, *J* = 14.0, 6.1 Hz, 1 H), 3.48# (ddd, *J* = 13.9, 11.8, 4.8 Hz, 1H), 3.35* (ddd, *J* = 13.6, 11.7, 4.8 Hz, 1H), 2.99 – 2.64 (m, 4 H), 2.00 (t, *J* = 2.6 Hz, 1 H), 1.73# (s, 9 H), 1.72* (s, 9 H).

Ynoate Ester 94. To a solution of alkyne **92** (218 mg, 0.553 mmol, 1.0 equiv) in THF (6 mL) at –78 °C was slowly added MeLi (1.6 M solution in Et_2O, 0.38 mL, 0.608 mmol, 1.1 equiv). After stirring for a further 55 min at –78 °C, methyl chloroformate (0.06 mL, 0.777 mmol, 1.4 equiv) was added dropwise and the reaction mixture allowed to warm slowly to room temperature over 3 h. At this point saturated aqueous NH_4Cl (10 mL) was added and the reaction contents were transferred to a separatory funnel, diluting with water (5 mL) and CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash

chromatography (silica gel, EtOAc/hexanes, 1:19→1:3) to afford the *N*-Boc ynoate ester **93** (229 mg, 92%) as a slightly yellow foam.

Next, TFA (0.94 mL) was added dropwise to a solution of *N*-Boc ynoate ester **93** (229 mg, 0.507 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C and the allowed to warm slowly to 23 °C over 3.5 h. At this point, TLC analysis indicated a small amount of starting material remained so an additional aliquot of TFA (0.25 mL) was added after recooling to 0 °C. After 2 h more, saturated aqueous $NaHCO_3$ (10 mL) was carefully added and the reaction mixture was stirred vigorously for 10 min. The reaction contents were then transferred to a separatory funnel diluting with additional saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:9→3:7) to give ynoate ester **94** (167 mg, 94% yield) as a colorless gum. **94**: ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ~ 1.X:1; signals that are resolved for each are indicated with * for the major and $^{\#}$ for minor rotamers, respectively) δ 8.52* (s, 1 H), 8.40$^{\#}$ (s, 1 H), 7.50 (d, *J* = 6.5 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 6.05 – 5.91 (m, 1 H), 5.54* (t, *J* = 6.9 Hz, 1 H), 5.46$^{\#}$ (t, *J* = 6.8 Hz, 1 H), 5.34 (dd, *J* = 17.2, 9.2 Hz, 1 H), 5.25 (app t, *J* = 8.5 Hz, 1 H), 4.69 (d, *J* = 5.5 Hz, 2 H), 4.58$^{\#}$ (dd, *J* = 13.3, 5.1 Hz, 1 H), 4.46* (dd, *J* = 13.5, 4.9 Hz, 1 H), 3.84$^{\#}$ (s, 3 H), 3.79* (s, 3 H), 3.34 – 3.23* (m, 1 H), 3.23 – 3.12$^{\#}$ (m, 1 H), 3.02 – 2.73 (m, 4 H).

Alloc Enoate Ester 95. To a solution of alkyne **94** (167 mg, 0.474 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) at 23 °C was added $AgBF_4$ (120 mg, 0.616 mmol, 1.3 equiv) and the reaction stirred at this temperature for 4.25 h. At this point, TLC analysis indicated poor conversion so an additional portion of $AgBF_4$ (250 mg, 1.284 mmol, 2.7 equiv) was added. Additional portions of $AgBF_4$ (100 mg, 0.514 mmol, 1.1 equiv) were added after 7.25 h, 16 h, 18.5 h and 21 h, and after a further 2 h TLC analysis indicated full conversion of starting material. At this point, saturated aqueous $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred vigorously for 30 min. The reaction contents were then transferred to a separatory funnel diluting with water (15 mL) and CH_2Cl_2 (40 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:9→2:3) to give indolenine **95** (104 mg, 62% yield) as a colorless gum. **95**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.5 Hz, 1 H), 7.68 (d, *J* = 7.7 Hz, 1 H), 7.41 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.27 (t, *J* = 7.6 Hz, 1 H), 7.07 (t, *J* = 3.6 Hz, 1 H), 5.94 (br s, 1 H), 5.62 – 5.50 (m, 1 H), 5.39 – 5.18 (m, 2 H), 4.68 – 4.58 (m, 2 H), 4.27 – 4.04 (m, 1 H), 3.79 (s, 3 H), 3.38 – 3.22 (m, 1 H), 2.99 – 2.70 (t, *J* = 13.5 Hz, 3 H), 1.42 (br td, *J* = 12.8, 4.2 Hz, 1 H).

Vinyl iodide 29. To a solution of Alloc carbamate **95** (16 mg, 0.0448 mmol, 1.0 equiv) in THF (2 mL) at 23 °C was added $PhSiH_3$ (0.03 mL, 0.243 mmol, 5.4 equiv) followed by $Pd(PPh_3)_4$ (2.5 mg, 0.0022 mmol, 0.05 equiv). The reaction was stirred for 15 min at this temperature then concentrated and filtered through a Pasteur pipette containing

silica gel, eluting with MeOH/EtOAc (1:9, 10 mL). Concentration afforded crude amine **91** which was carried into the next step without further purification.

The so-obtained **91** was dissolved in DMF (1.5 mL) and cooled to 0 °C. K_2CO_3 (27 mg, 0.195 mmol, 4.4 equiv) was then added, followed by a solution of bromide **44** (33 mg, 0.126 mmol, 2.8 equiv) in DMF (0.2 mL) and Bu_4NCl (12.5 mg, 0.0448 mmol, 1.0 equiv). After 2.5 h at 0 °C, the reaction was allowed to warm to 23 °C. Since only a small amount of product was visible by TLC after 3.75 h, an additional portion of bromide (12 mg, 0.0413, 0.9 equiv) was added along with Cs_2CO_3 (40 mg, 0.123 mmol, 2.7 equiv). After 4.75 h, the reaction was quenched with water (5 mL) and the reaction contents were then transferred to a separatory funnel diluting with water (5 mL) and Et_2O (10 mL). The layers were separated and the aqueous layer was further extracted with Et_2O (10 mL). The combined organic layers were washed with water (2 × 8 mL), dried with $MgSO_4$, filtered and concentrated. The resulting crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1) to give vinyl iodide **29** (2.7 mg, 13% yield) as a colorless oil. **29**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.3 Hz, 1 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.21 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.03 (t, *J* = 3.6 Hz, 1 H), 5.87 (q, *J* = 6.4 Hz, 1 H), 3.93 (d, *J* = 6.2 Hz, 1 H), 3.74 (s, 3 H), 3.37 (d, *J* = 14.0 Hz, 1 H), 3.21 (d, *J* = 14.0 Hz, 1 H), 3.03 (ddd, *J* = 14.2, 12.6, 3.1 Hz, 1 H), 2.91 (dd, *J* = 20.5, 4.2 Hz, 1 H), 2.75 (ddd, *J* = 20.5, 6.4, 3.1 Hz, 1 H), 2.70 – 2.59 (m, 2 H), 1.77 (d, *J* = 6.4 Hz, 3 H), 1.55 (td, *J* = 12.9, 4.4 Hz, 1 H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 165.8, 157.0, 141.2, 140.1, 133.0, 129.7, 128.4, 126.3, 125.5, 120.8, 108.6, 65.1, 55.2, 54.7, 51.7, 43.2, 35.9, 33.9, 21.8.

Propargyl sulfide 106. To a solution of Alloc carbamate **95** (18 mg, 0.0505 mmol, 1.0 equiv) in THF (2 mL) at 23 °C was added $PhSiH_3$ (0.03 mL, 0.243 mmol, 4.8 equiv) followed by $Pd(PPh_3)_4$ (4.2 mg, 0.0036 mmol, 0.07 equiv). The reaction was stirred for 15 min at this temperature then concentrated.

The so-obtained crude amine **91** was dissolved in CH_2Cl_2 (2 mL) and $NaBH(OAc)_3$ (54 mg, 0.253 mmol, 5.0 equiv) was then added, followed by a solution of aldehyde **210** (16 mg, 0.101 mmol, 2.0 equiv) in CH_2Cl_2 (0.2 mL). After 10 min stirring at 23 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (4 mL) and the reaction contents were transferred to a separatory funnel diluting with CH_2Cl_2 (10 mL) and water (4 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1) to give propargyl sulfide **106** (11.9 mg, 58% yield) as a colorless gum. **106**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.6, 0.6 Hz, 1 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.23 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.05 (t, *J* = 3.6 Hz, 1 H), 4.21 (d, *J* = 6.1 Hz, 1 H), 3.76 (s, 3 H), 3.42 (qt, *J* = 16.4, 2.3 Hz, 2 H), 3.29 (t, *J* = 2.2 Hz, 2 H), 3.11 – 2.96 (m, 2 H), 2.89 (dd, *J* = 14.0, 4.0 Hz, 1 H), 2.75 – 2.63 (m, 2 H), 1.65 – 1.52 (m, 1 H), 1.35 (s, 9 H).

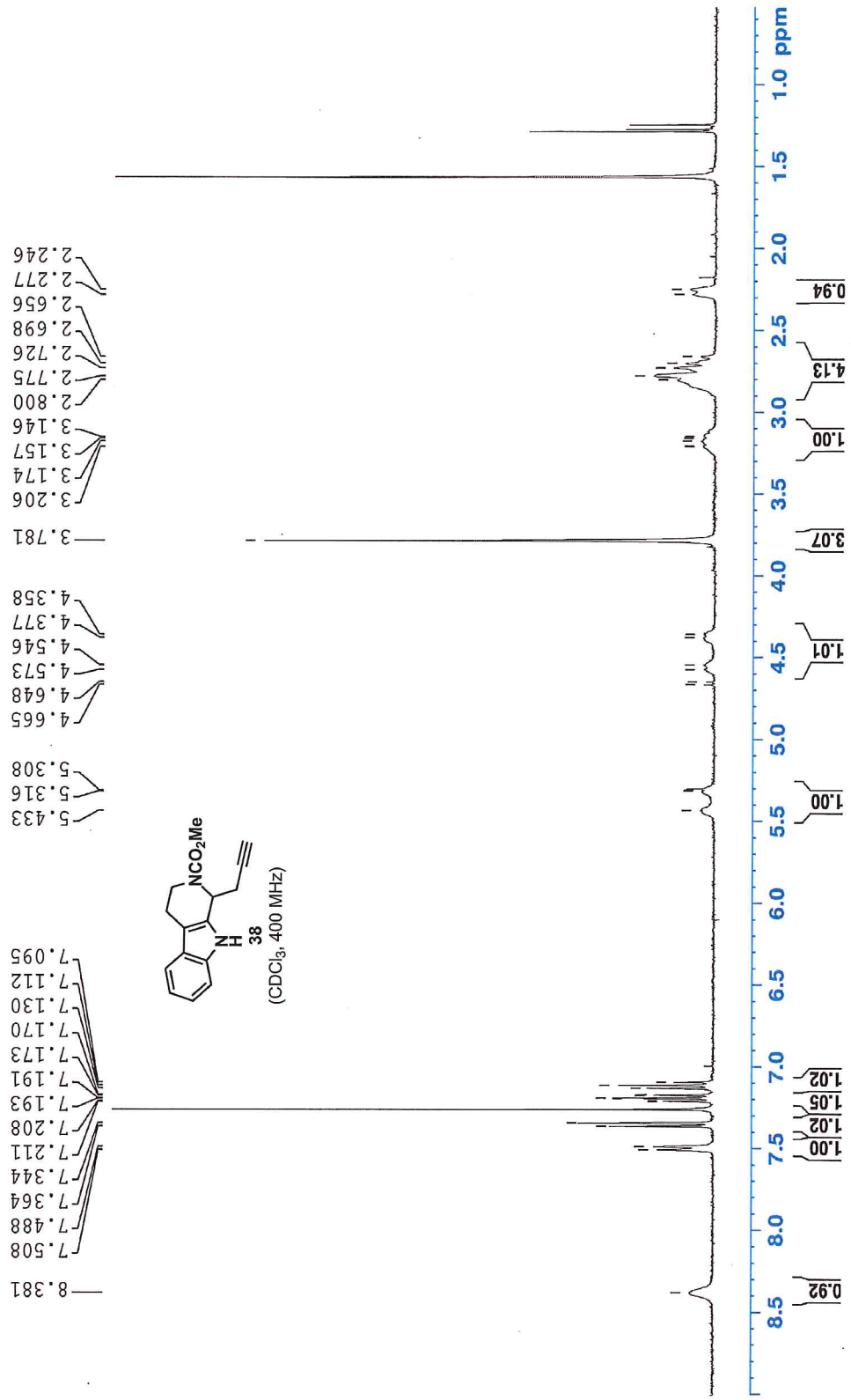
Phenyl sulfide 124. To a solution of enal (derived from **123**, 21 mg, 0.0651 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) at 23 °C in a microwave vial was added PhSH (0.02 mL, 0.195 mmol, 3.0 equiv) and imidazole (8.4 mg, 0.123 mmol, 1.9 equiv). The vial was then capped and the reaction mixture heated at 70 °C for 6 h under microwave irradiation. At this point,

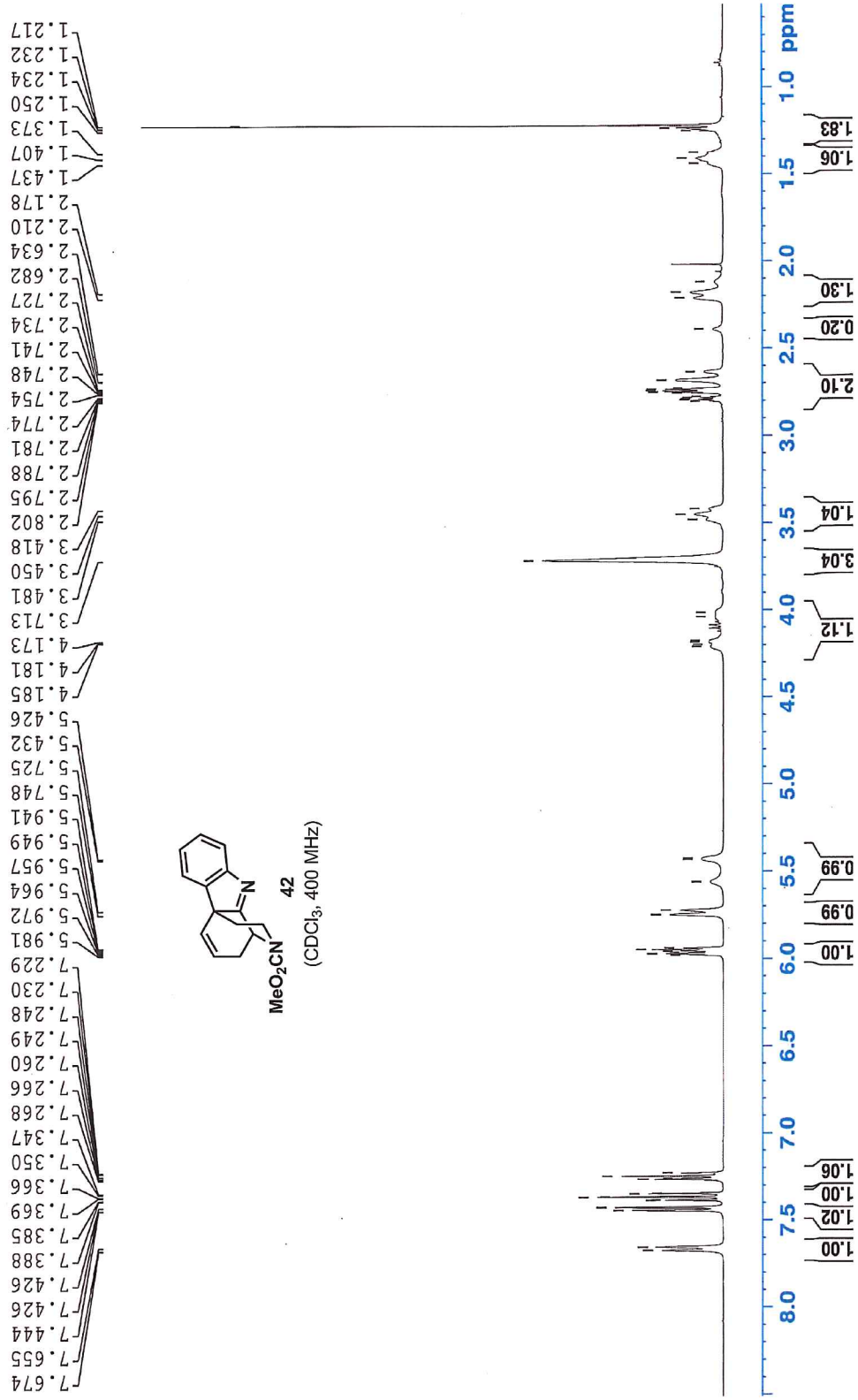
TLC analysis showed partial conversion so additional PhSH (0.01 mL, 0.0975 mmol, 1.5 equiv) was added and the reaction heated for a further 3 h at 70 °C. After this time, the reaction was concentrated and the crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1) to give phenyl sulfide **124** (12.8 mg, 46% yield, 71% brsm) as a colorless gum, along with recovered starting material (7.6 mg). **124**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 7.45 – 7.36 (m, 4 H), 7.35 – 7.24 (m, 4 H), 6.00 – 5.81 (m, 1H), 5.29 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.22 (dd, *J* = 10.4, 1.4 Hz, 1 H), 5.16 (d, *J* = 16.4 Hz, 1 H), 4.63 (d, *J* = 5.6 Hz, 2 H), 4.06 – 3.77 (m, 2 H), 3.23 – 2.90 (m, 2 H), 2.79 – 2.66 (m, 1 H), 2.29 (d, *J* = 11.8 Hz, 1 H), 2.01 – 1.66 (m, 2 H).

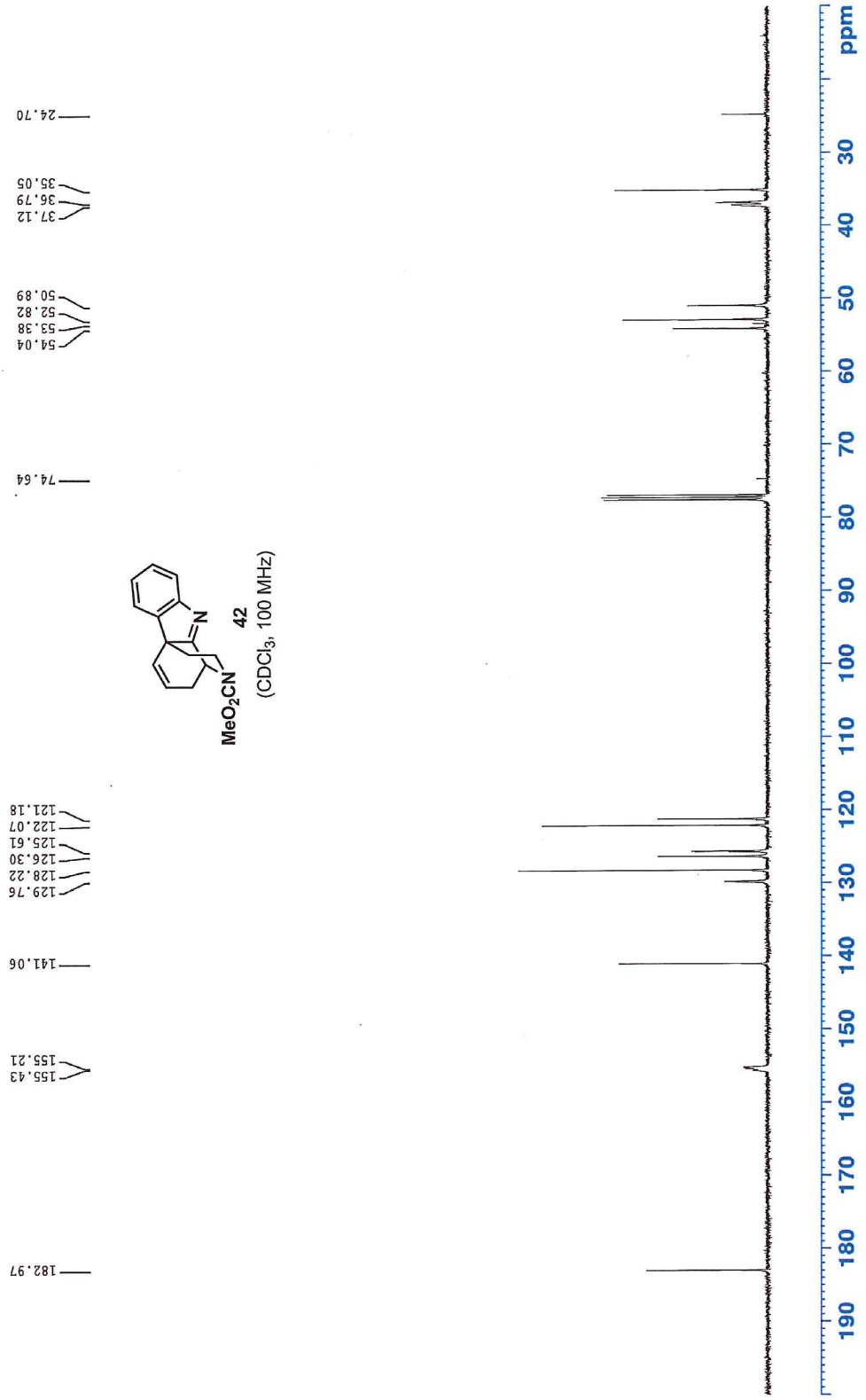
Propargyl sulfide 125. To a solution of Alloc carbamate **124** (11 mg, 0.0247 mmol, 1.0 equiv) in THF (2 mL) at 23 °C was added $PhSiH_3$ (0.01 mL, 0.0823 mmol, 3.3 equiv) followed by $Pd(PPh_3)_4$ (3.4 mg, 0.0029 mmol, 0.12 equiv). The reaction was stirred for 15 min at this temperature then concentrated.

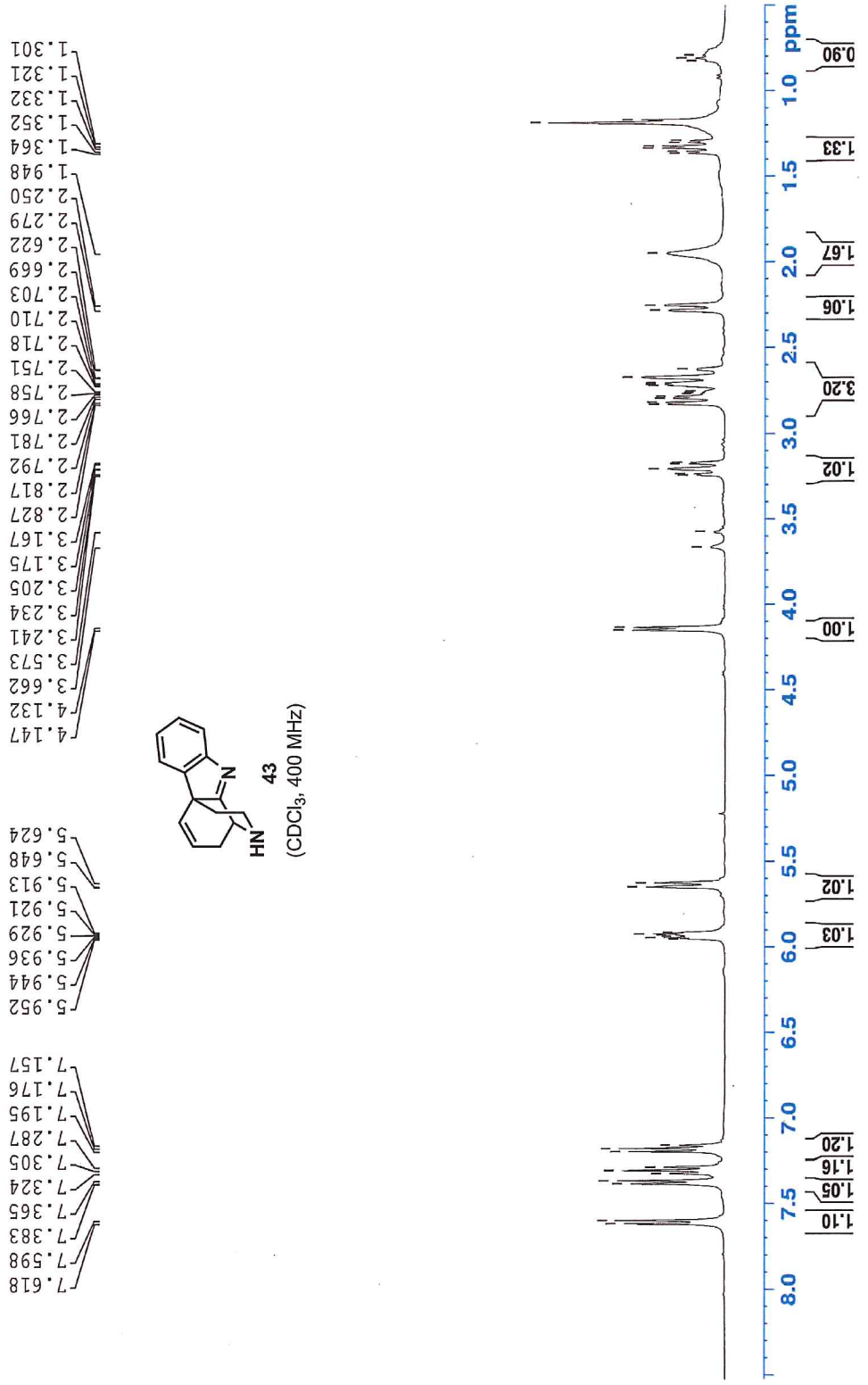
The so-obtained crude amine was dissolved in CH_2Cl_2 (1.8 mL) and $NaBH(OAc)_3$ (25 mg, 0.118 mmol, 4.8 equiv) was then added, followed by a solution of aldehyde **210** (15 mg, 0.096 mmol, 3.9 equiv) in CH_2Cl_2 (0.4 mL). After 10 min stirring at 23 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (4 mL) and the reaction contents were transferred to a separatory funnel diluting with CH_2Cl_2 (10 mL) and water (4 mL). The layers were separated and the aqueous layer was extracted a second time with CH_2Cl_2 (10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1, run up twice) to give propargyl sulfide **125** (6.2 mg, 51% yield) as a colorless gum. **125**:

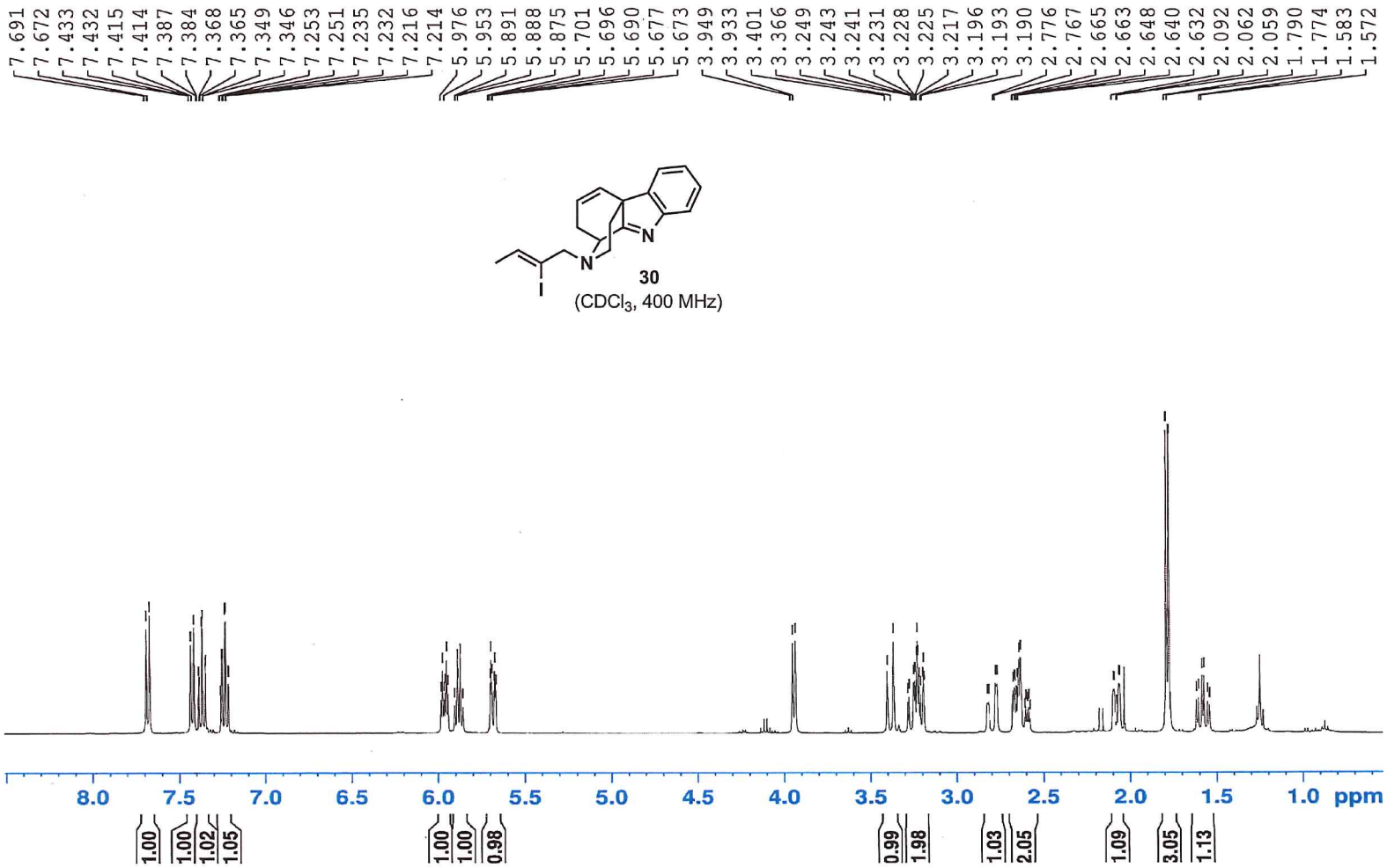
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (d, *J* = 2.3 Hz, 1 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.44 – 7.39 (m, 2 H), 7.39 – 7.34 (m, 2 H), 7.34 – 7.25 (m, 3 H), 7.22 (td, *J* = 7.5, 1.1 Hz, 1 H), 4.28 (td, *J* = 12.3, 5.6 Hz, 1 H), 4.06 (s, 1 H), 3.48 (s, 2 H), 3.20 (q, *J* = 2.0 Hz, 2 H), 3.10 (ddd, *J* = 13.0, 8.6, 4.4 Hz, 1 H), 2.97 (d, *J* = 13.6 Hz, 1 H), 2.73 – 2.60 (m, 1 H), 2.56 (dt, *J* = 12.0, 5.6 Hz, 1 H), 2.29 (dd, *J* = 12.4, 2.3 Hz, 1 H), 1.90 (ddd, *J* = 13.7, 12.1, 3.4 Hz, 1 H), 1.69 (m, 1 H), 1.34 (s, 9 H).

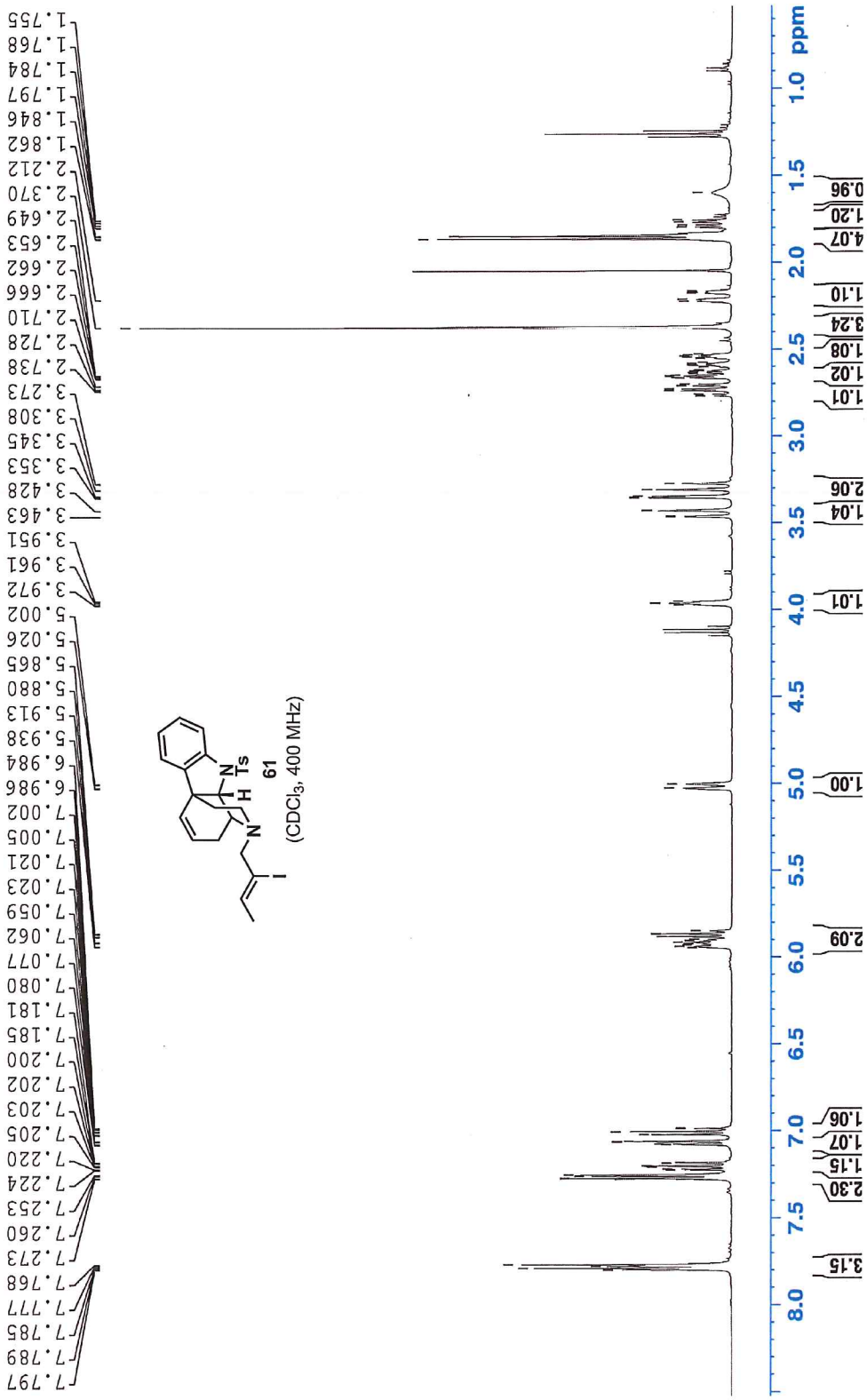

NCO2Me
H
N
38
(CDCl3, 400 MHz)
8.381
7.508
7.488
7.364
7.344
7.211
7.208
7.193
7.191
7.173
7.170
7.130
7.112
7.095
5.433
5.316
5.308
4.665
4.648
4.573
4.546
4.377
4.358
3.781
3.206
3.174
3.157
3.146
2.800
2.775
2.726
2.698
2.656
2.277
2.246
0.92
1.00
1.02
1.05
1.02
7.00
6.5
6.0
5.5
1.00
5.0
4.5
1.01
4.0
3.07
3.5
3.0
1.00
2.5
4.13
2.0
0.94
1.5
1.0 ppm

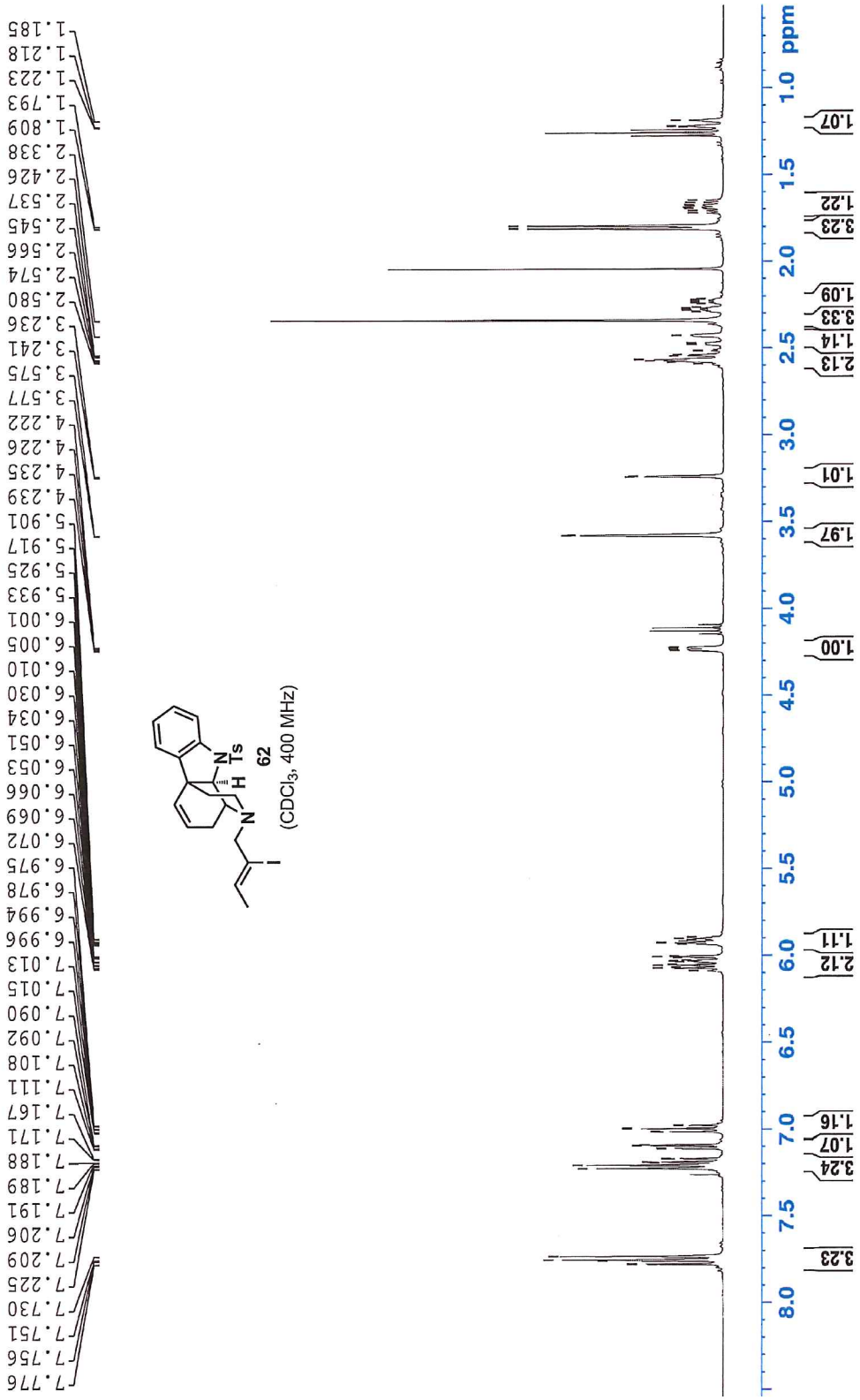

MeO2CN
42
(CDCl3, 400 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.00
1.02
1.00
1.06
1.00
0.99
0.99
1.12
3.04
1.04
2.10
0.20
1.30
1.06
1.83
7.674
7.655
7.444
7.426
7.426
7.388
7.385
7.369
7.366
7.350
7.347
7.268
7.266
7.260
7.249
7.248
7.230
7.229
5.981
5.972
5.964
5.957
5.949
5.941
5.748
5.725
5.432
5.426
4.185
4.181
4.173
3.713
3.481
3.450
3.418
2.802
2.795
2.788
2.781
2.774
2.754
2.748
2.741
2.734
2.727
2.682
2.634
2.210
2.178
1.437
1.407
1.373
1.250
1.234
1.232
1.217

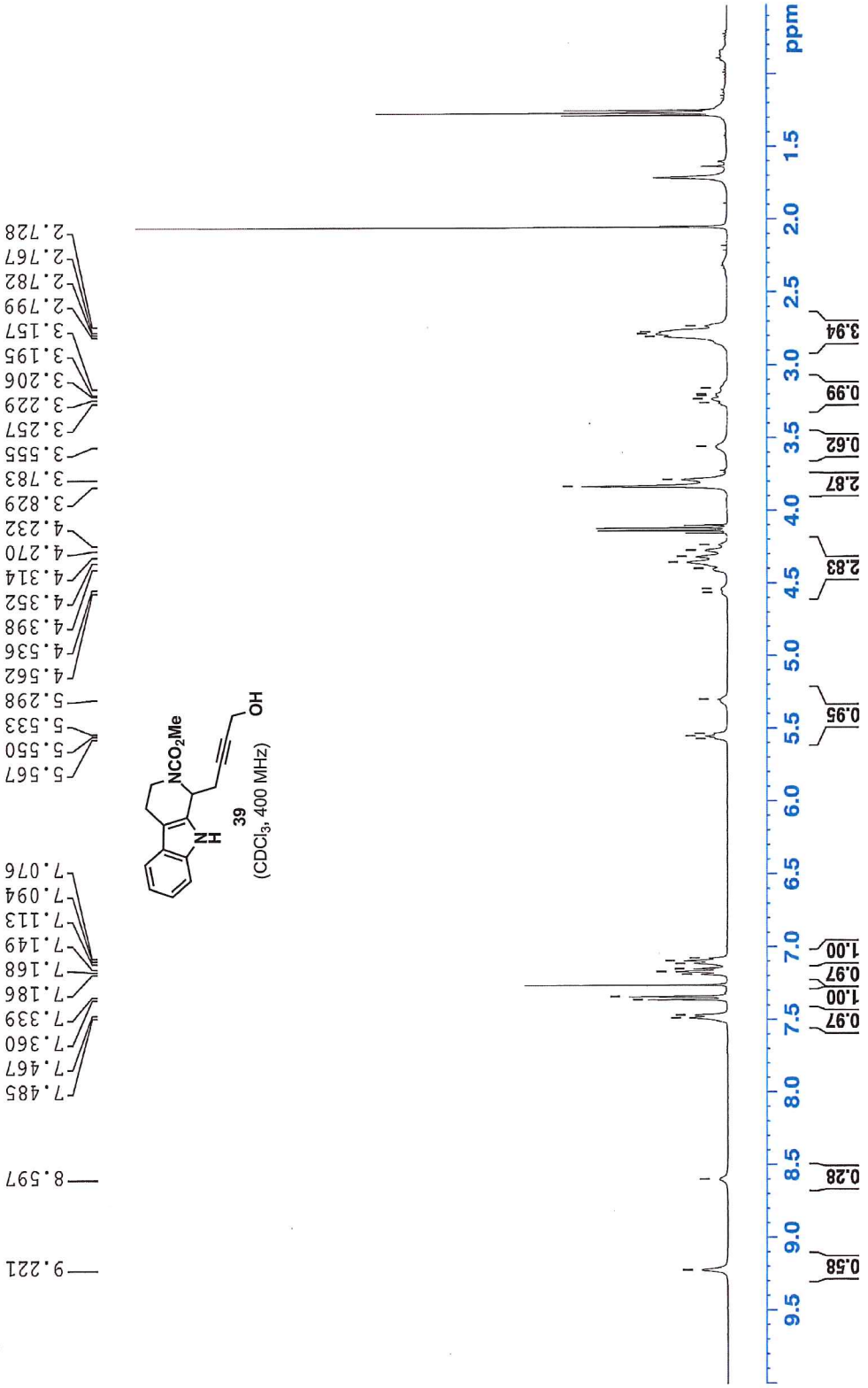

182.97
155.43
155.21
141.06
129.76
128.22
126.30
125.61
122.07
121.18
74.64
54.04
53.38
52.82
50.89
37.12
36.79
35.05
24.70
MeO2CN
42
(CDCl3, 100 MHz)
ppm

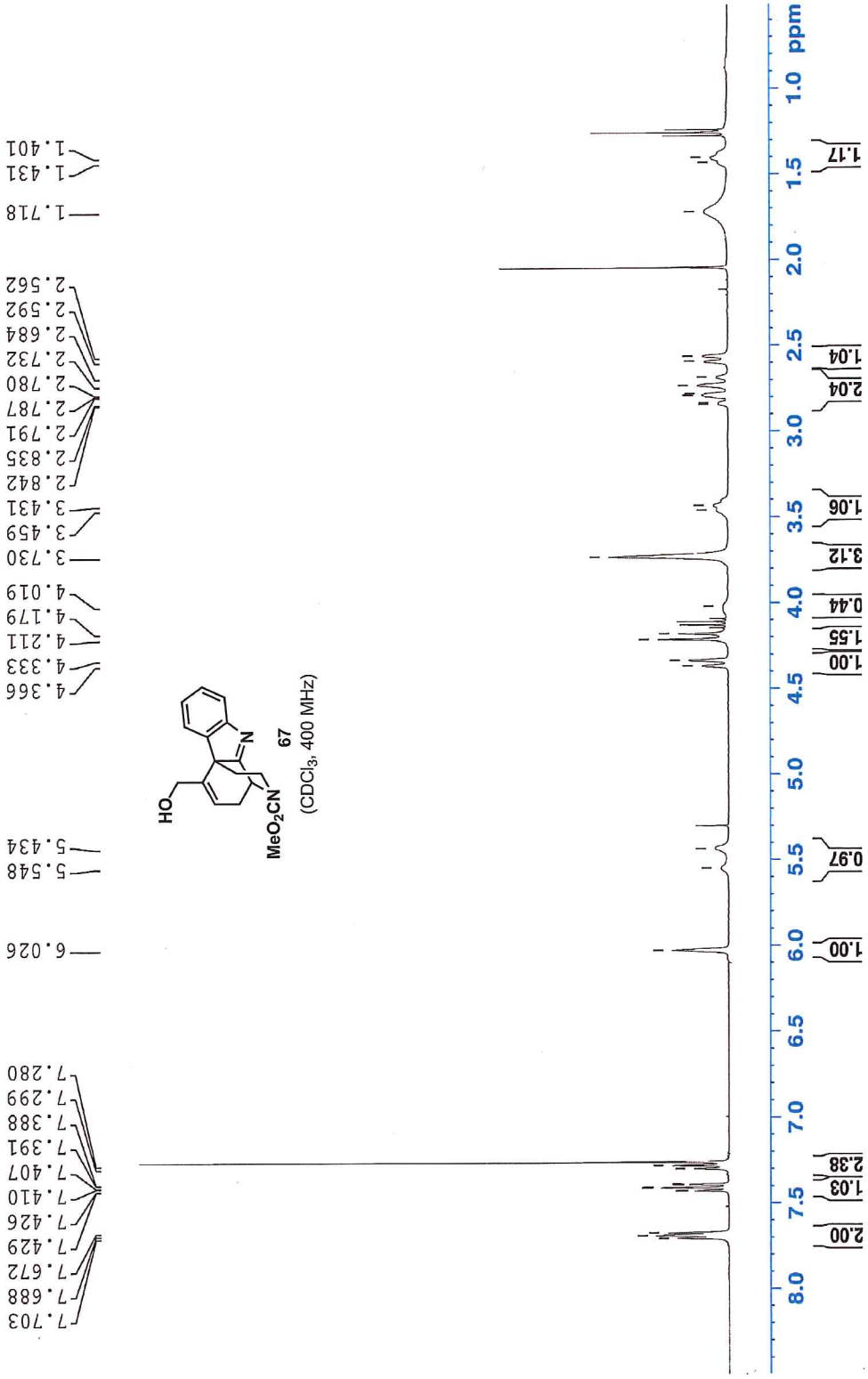

7.618
7.598
7.383
7.365
7.324
7.305
7.287
7.195
7.176
7.157
5.952
5.944
5.936
5.929
5.921
5.913
5.648
5.624
4.147
4.132
3.662
3.573
3.241
3.234
3.205
3.175
3.167
2.827
2.817
2.792
2.781
2.766
2.758
2.751
2.718
2.710
2.703
2.669
2.622
2.279
2.250
1.948
1.364
1.352
1.332
1.321
1.301
HN
N
43
(CDCl3, 400 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.90
1.33
1.67
1.06
3.20
1.02
1.00
1.02
1.03
1.10
1.05
1.16
1.20

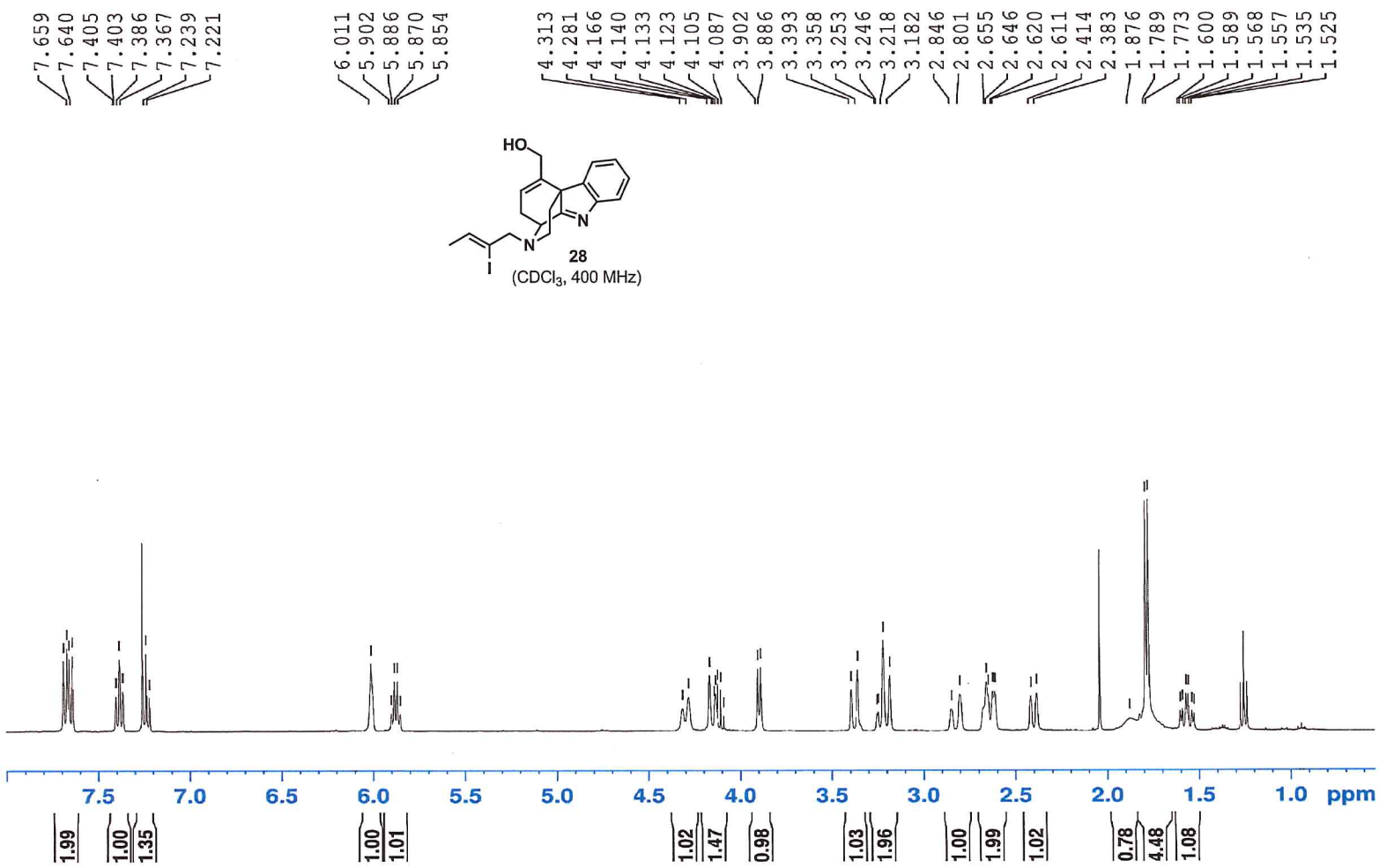

7.691
7.672
7.433
7.432
7.415
7.414
7.387
7.384
7.368
7.365
7.349
7.346
7.253
7.251
7.235
7.232
7.216
7.214
5.976
5.953
5.891
5.888
5.875
5.701
5.696
5.690
5.677
5.673
3.949
3.933
3.401
3.366
3.249
3.243
3.241
3.231
3.228
3.225
3.217
3.196
3.193
3.190
2.776
2.767
2.665
2.663
2.648
2.640
2.632
2.092
2.062
2.059
1.790
1.774
1.583
1.572
N
N
30
(CDCl3, 400 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.00
1.02
1.05
1.00
1.00
0.98
0.99
1.98
1.03
2.05
1.09
3.05
1.13

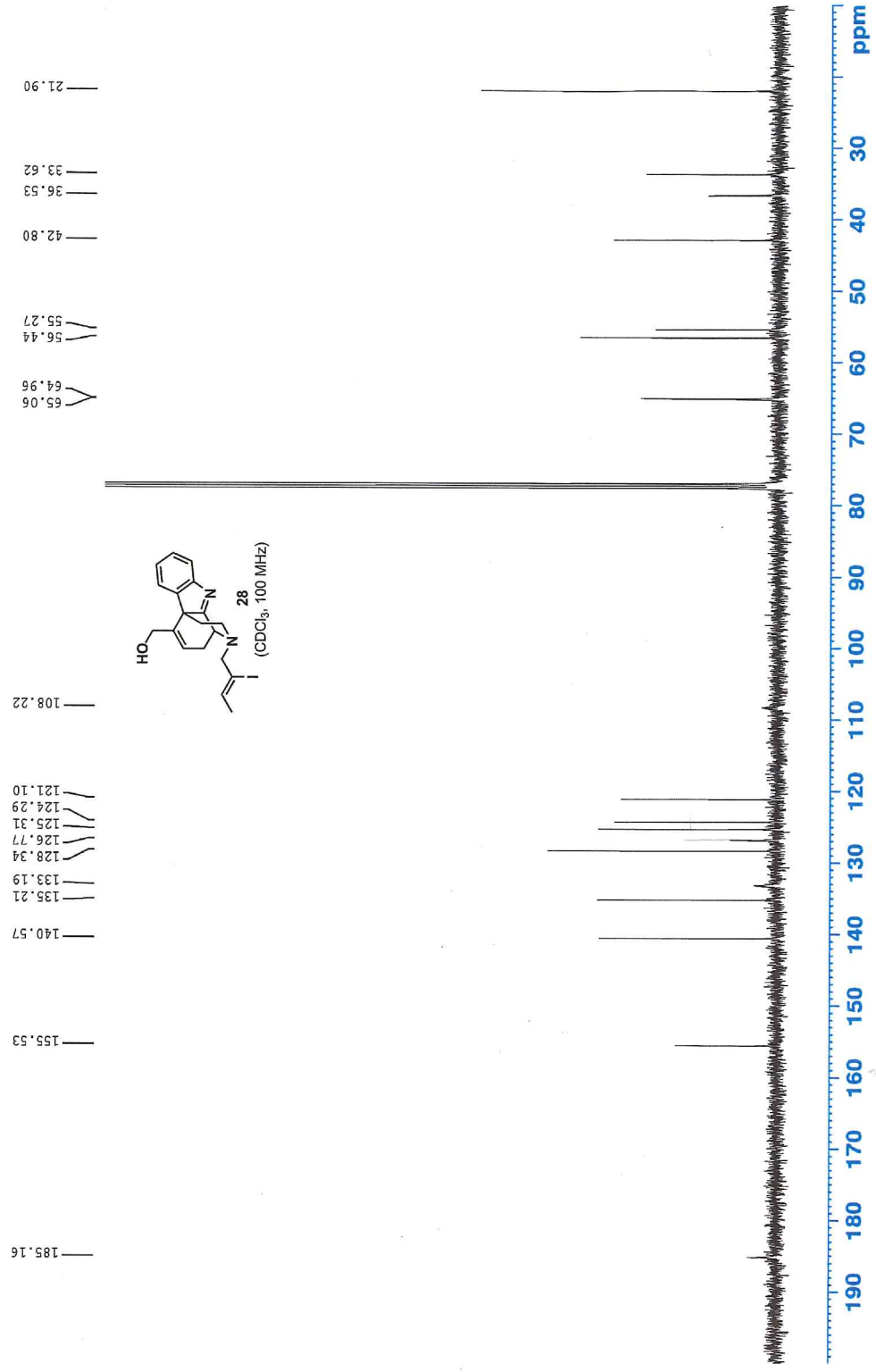

61
(CDCl3, 400 MHz)
Ts
N
H
I
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
3.15
2.30
1.15
1.07
1.06
2.09
1.00
1.01
1.04
2.06
1.01
1.02
1.08
3.24
1.10
4.07
1.20
0.96
7.797
7.789
7.785
7.777
7.768
7.273
7.260
7.253
7.224
7.220
7.205
7.203
7.202
7.200
7.185
7.181
7.080
7.077
7.062
7.059
7.023
7.021
7.005
7.002
6.986
6.984
5.938
5.913
5.880
5.865
5.026
5.002
3.972
3.961
3.951
3.463
3.428
3.353
3.345
3.308
3.273
2.738
2.728
2.710
2.666
2.662
2.653
2.649
2.370
2.212
1.862
1.846
1.797
1.784
1.768
1.755

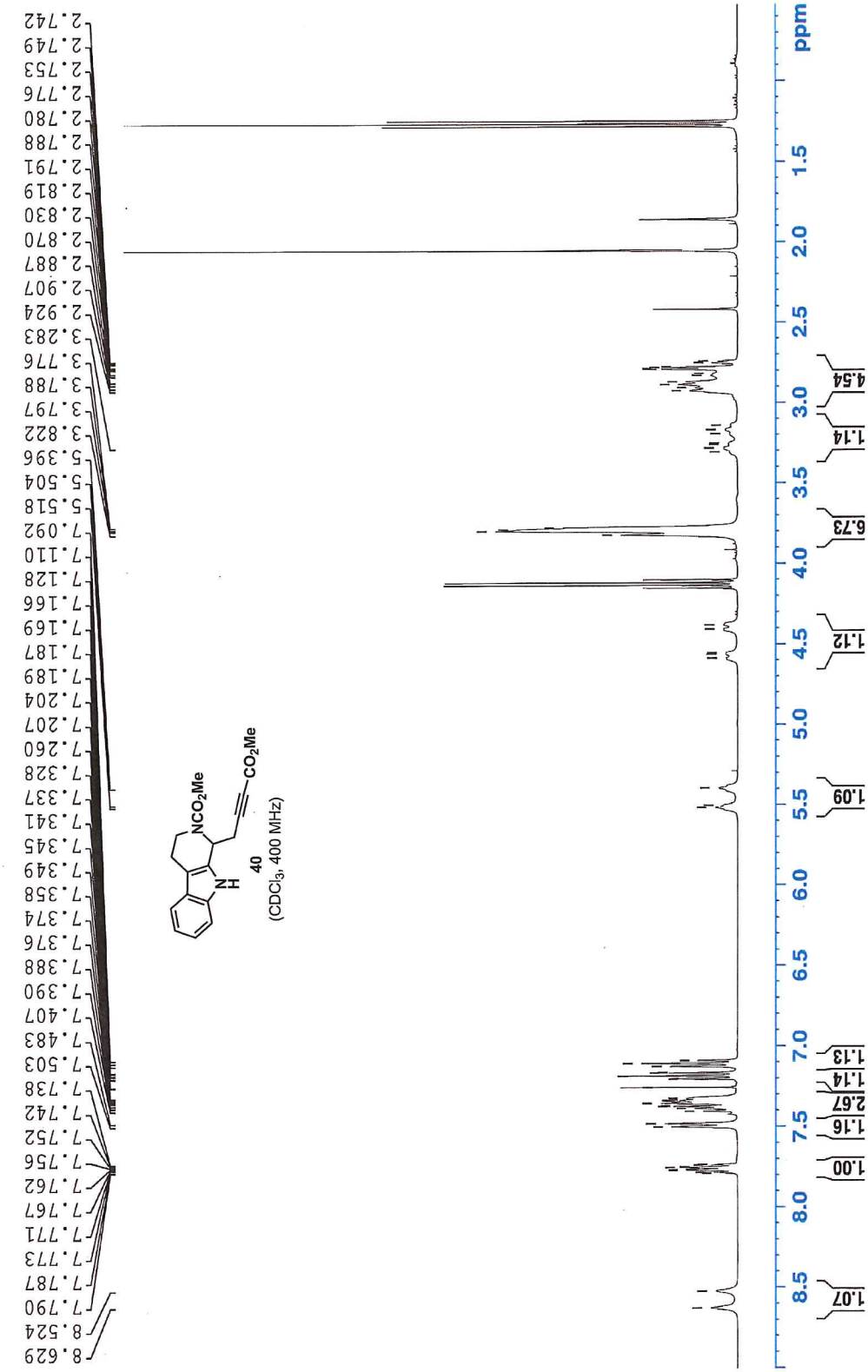

62
(CDCl3, 400 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
3.23
3.24
1.07
1.16
2.12
1.11
1.00
1.97
1.01
2.13
1.14
3.33
1.09
3.23
1.22
1.07
7.776
7.756
7.751
7.730
7.225
7.209
7.206
7.191
7.189
7.188
7.171
7.167
7.111
7.108
7.092
7.090
7.015
7.013
6.996
6.994
6.978
6.975
6.072
6.069
6.066
6.053
6.051
6.034
6.030
6.010
6.005
6.001
5.933
5.925
5.917
5.901
4.239
4.235
4.226
4.222
3.577
3.575
3.241
3.236
2.580
2.574
2.566
2.545
2.537
2.426
2.338
1.809
1.793
1.223
1.218
1.185

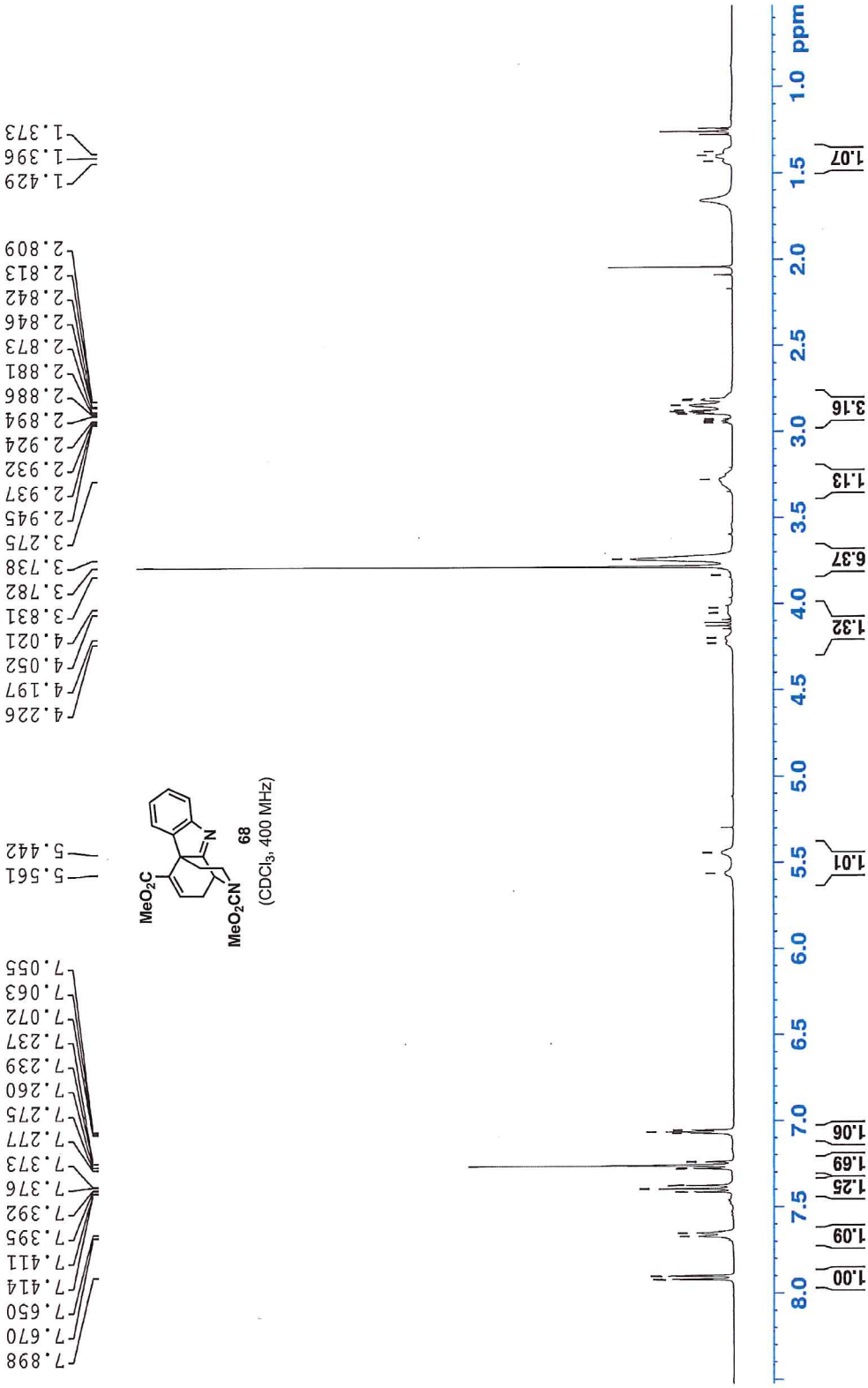

NCO2Me
OH
N
H
39
(CDCl3, 400 MHz)
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0.58
0.28
0.97
1.00
0.97
1.00
0.95
2.83
2.87
0.62
0.99
3.94
9.221
8.597
7.485
7.467
7.360
7.339
7.186
7.168
7.149
7.113
7.094
7.076
5.567
5.550
5.533
5.298
4.562
4.536
4.398
4.352
4.314
4.270
4.232
3.829
3.783
3.555
3.257
3.229
3.206
3.195
3.157
2.799
2.782
2.767
2.728

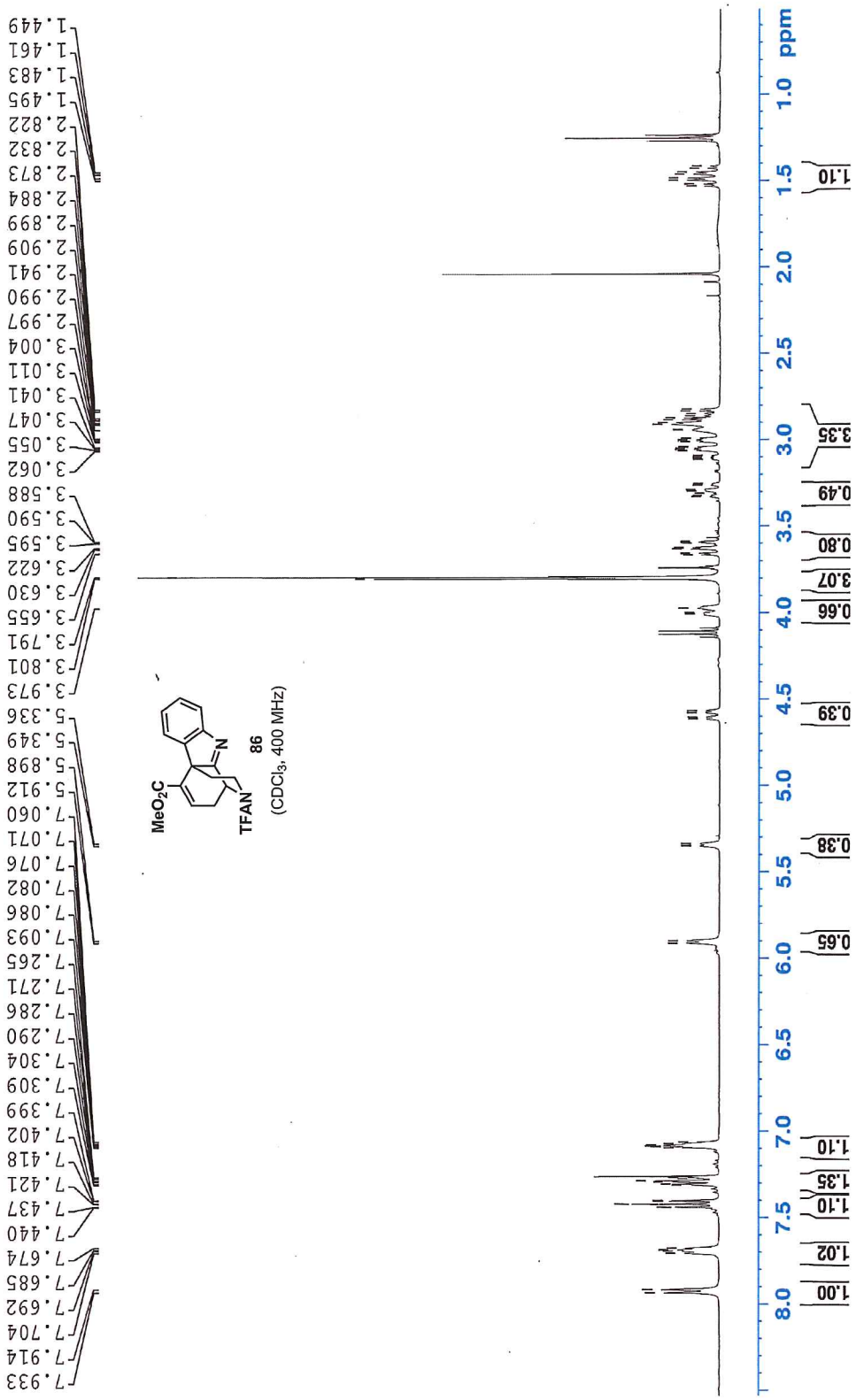

7.703
7.688
7.672
7.429
7.426
7.410
7.407
7.391
7.388
7.299
7.280
6.026
5.548
5.434
4.366
4.333
4.211
4.179
4.019
3.730
3.459
3.431
2.842
2.835
2.791
2.787
2.780
2.732
2.684
2.592
2.562
1.718
1.431
1.401
HO
N
MeO2CN
67
(CDCl3, 400 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
1.03
2.38
1.00
0.97
1.00
1.55
1.00
0.44
3.12
1.06
2.04
1.04
1.17

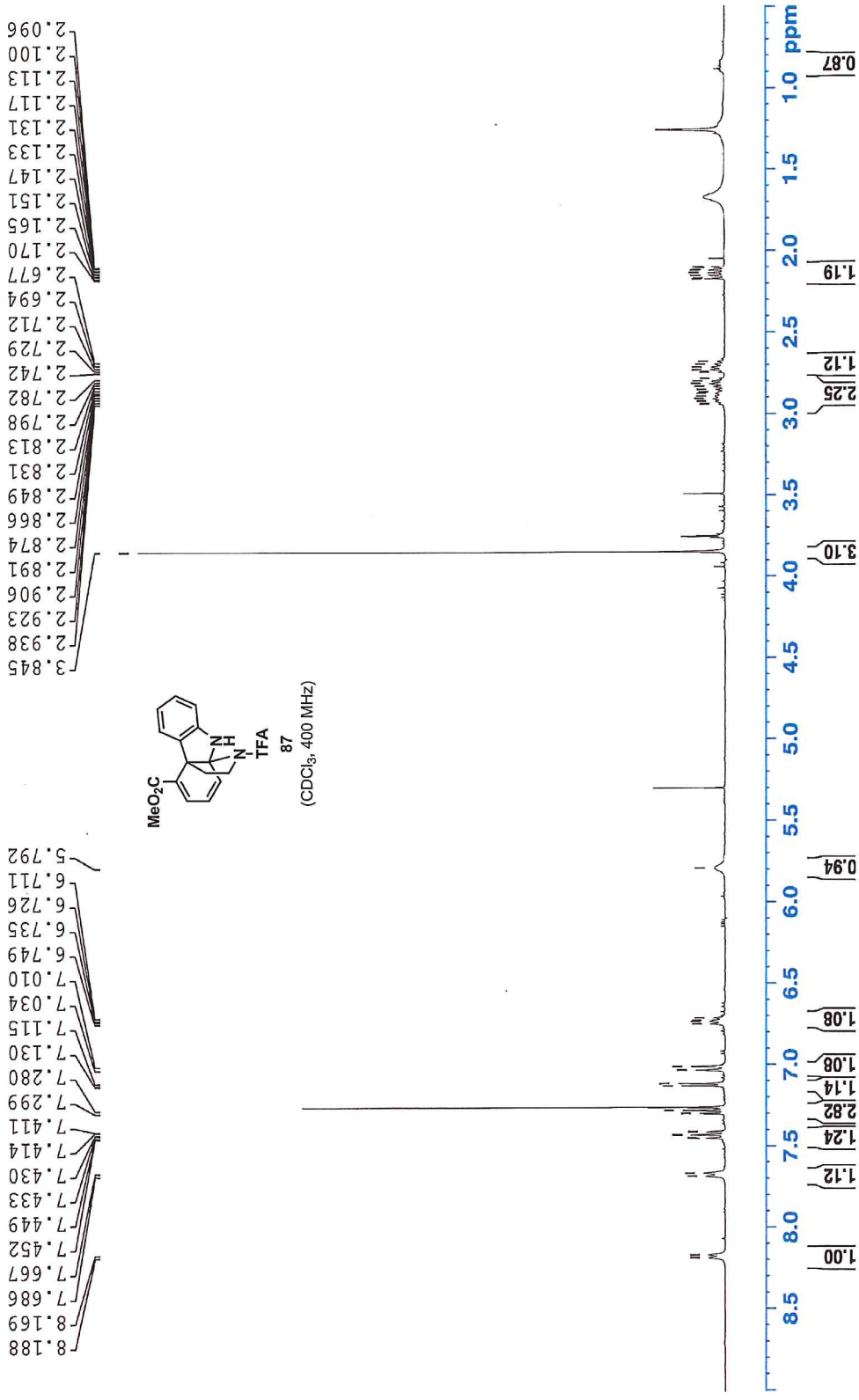

7.659
7.640
7.405
7.403
7.386
7.367
7.239
7.221
6.011
5.902
5.886
5.870
5.854
4.313
4.281
4.166
4.140
4.133
4.123
4.105
4.087
3.902
3.886
3.393
3.358
3.253
3.246
3.218
3.182
2.846
2.801
2.655
2.646
2.620
2.611
2.414
2.383
1.876
1.789
1.773
1.600
1.589
1.568
1.557
1.535
1.525
HO
N
N
28
(CDCl3, 400 MHz)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.99
1.00
1.35
1.00
1.01
1.02
1.47
0.98
1.03
1.96
1.00
1.99
1.02
0.78
4.48
1.08

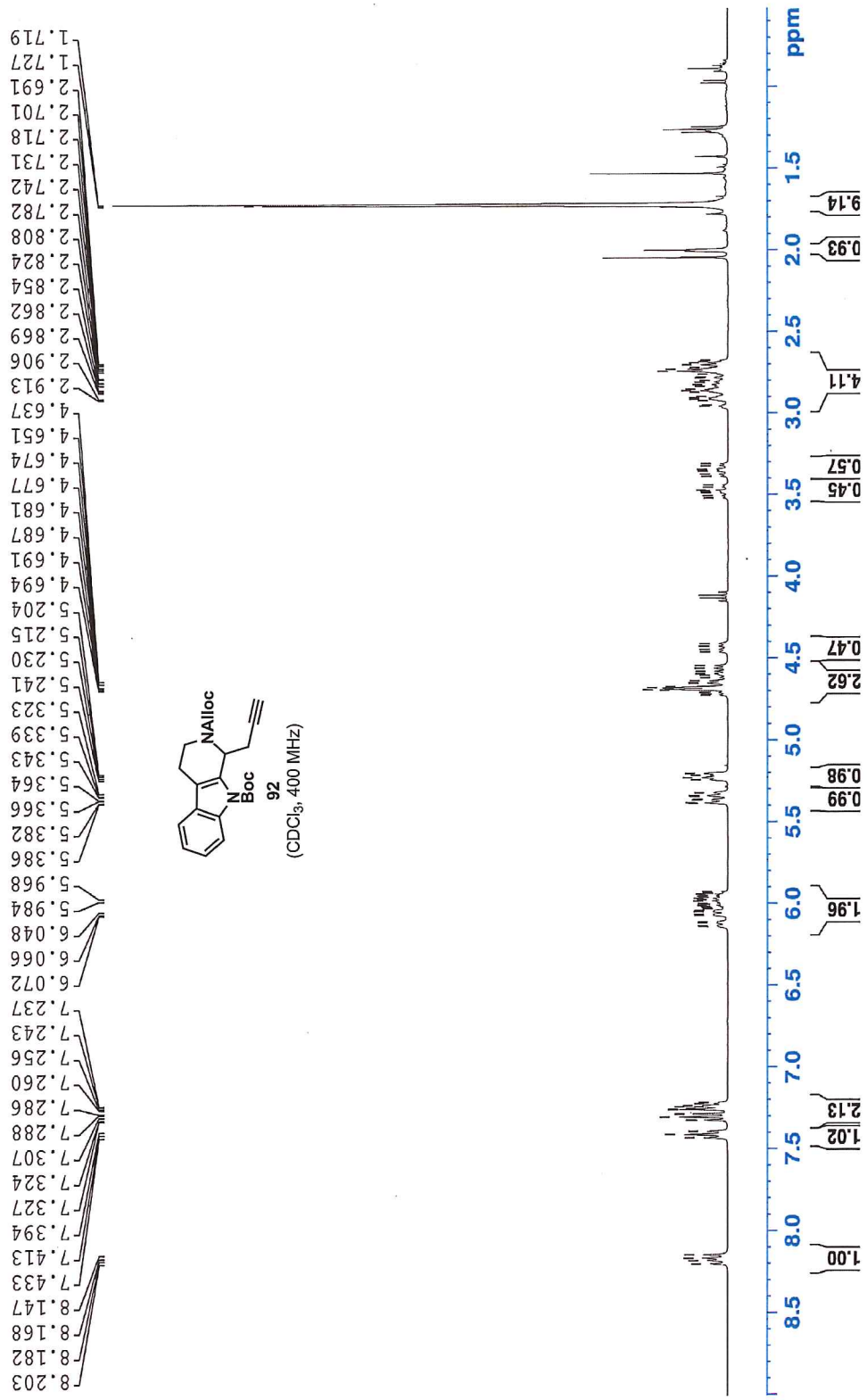

28
(CDCl3, 100 MHz)
HO
N
N
I
21.90
33.62
36.53
42.80
55.27
56.44
64.96
65.06
108.22
121.10
124.29
125.31
126.77
128.34
133.19
135.21
140.57
155.53
185.16
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30

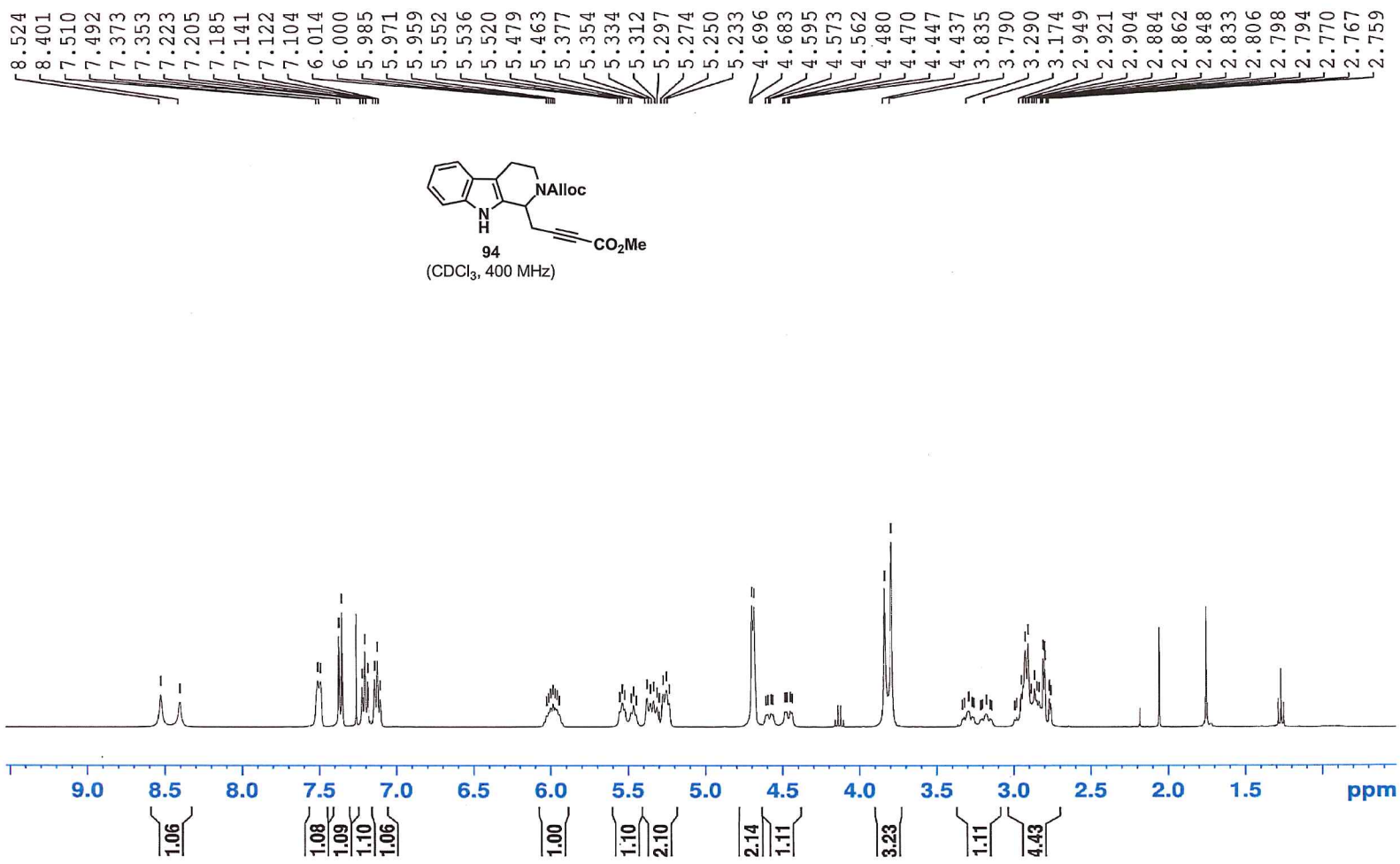

NCO2Me
CO2Me
NH
40
(CDCl3, 400 MHz)
ppm
1.07
1.00
1.16
2.67
1.14
1.13
1.09
1.12
6.73
1.14
4.54


MeO2C
MeO2CN
68
(CDCl3, 400 MHz)
ppm
1.00
1.09
1.25
1.69
1.06
1.01
1.32
6.37
1.13
3.16
1.07

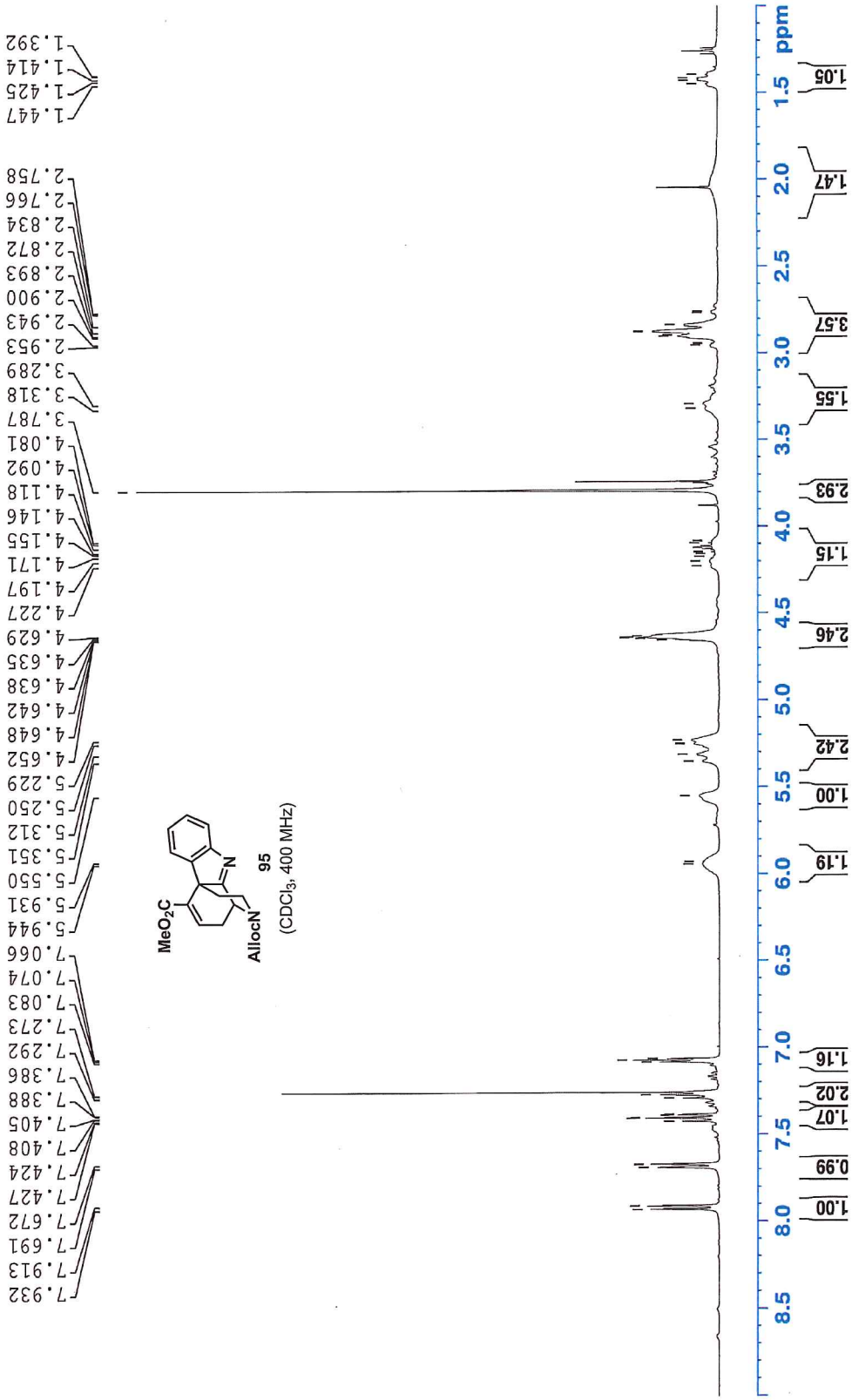

MeO2C
TFAN
86
(CDCl3, 400 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.00
1.02
1.10
1.35
1.10
0.65
0.38
0.39
0.66
3.07
0.80
0.49
3.35
1.10
7.933
7.914
7.704
7.692
7.685
7.674
7.440
7.437
7.421
7.418
7.402
7.399
7.309
7.304
7.290
7.286
7.271
7.265
7.093
7.086
7.082
7.076
7.071
7.060
5.912
5.898
5.349
5.336
3.973
3.801
3.791
3.655
3.630
3.622
3.595
3.590
3.588
3.062
3.055
3.047
3.041
3.011
3.004
2.997
2.990
2.941
2.909
2.899
2.884
2.873
2.832
2.822
1.495
1.483
1.461
1.449

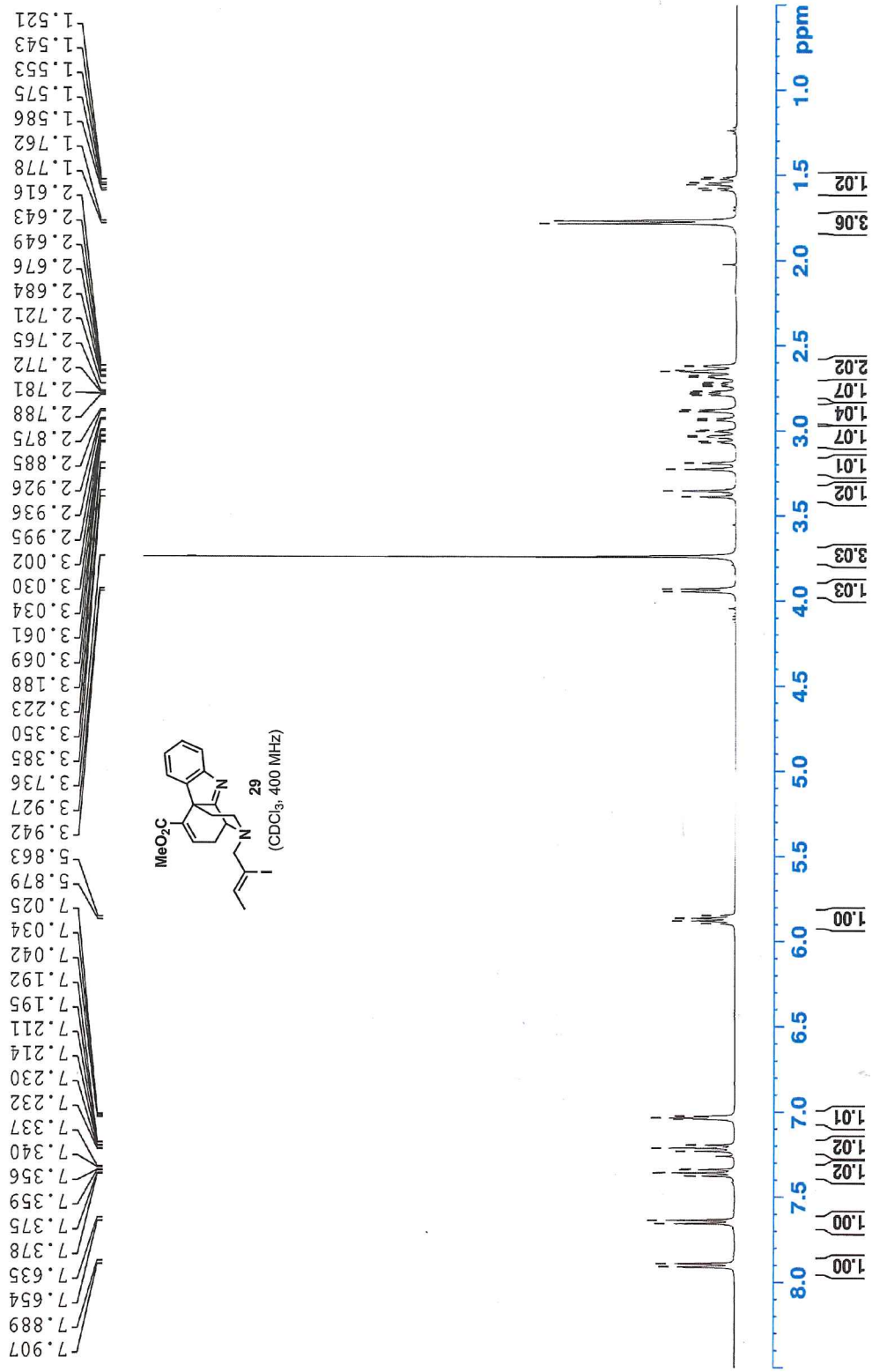

MeO2C
N
H
N
TFA
87
(CDCl3, 400 MHz)
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.00
1.12
1.24
2.82
1.14
1.08
1.08
0.94
3.10
2.25
1.12
1.19
0.87

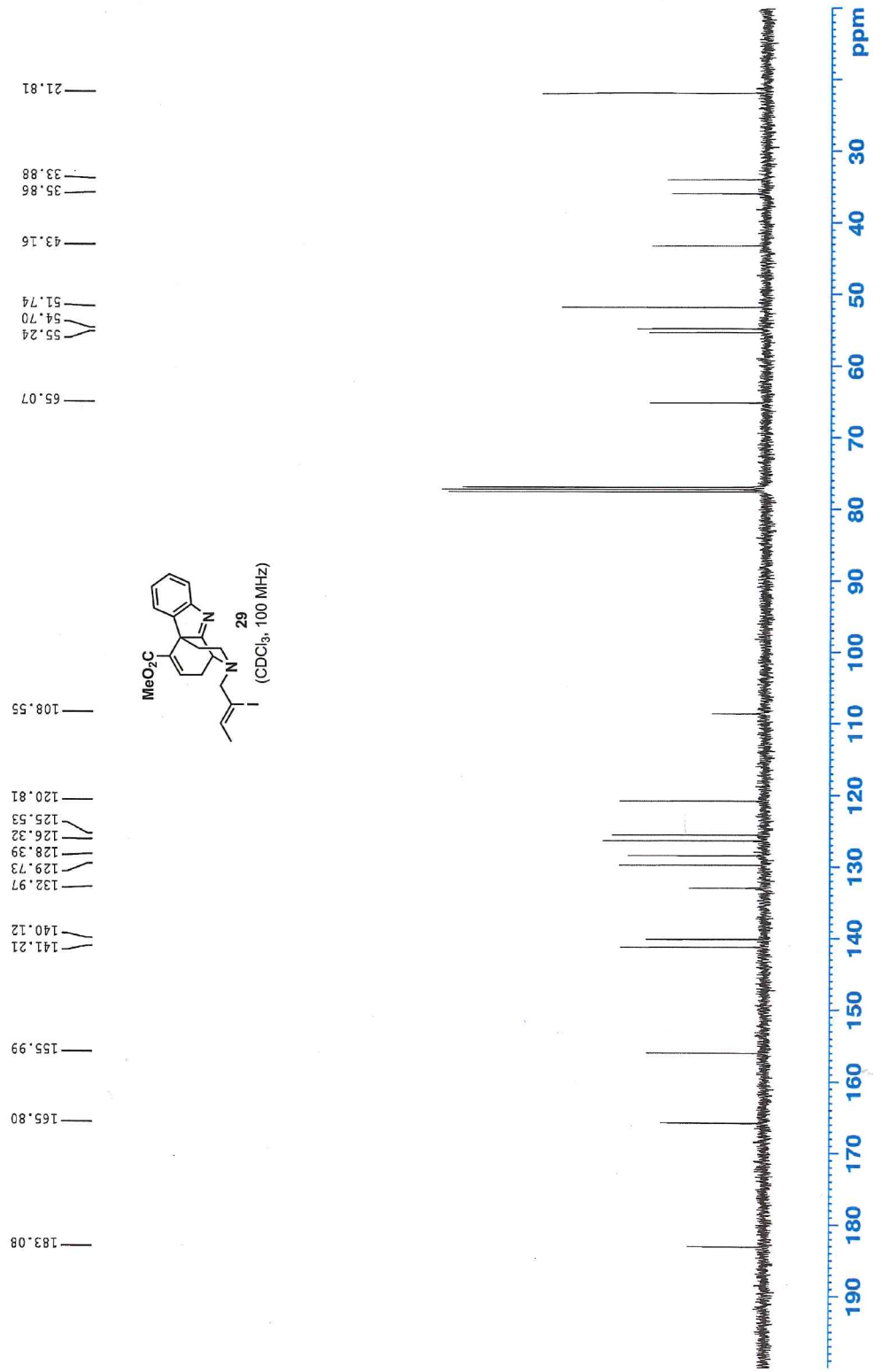

8.203
8.182
8.168
8.147
7.433
7.413
7.394
7.327
7.324
7.307
7.288
7.286
7.260
7.256
7.243
7.237
6.072
6.066
6.048
5.984
5.968
5.386
5.382
5.366
5.364
5.343
5.339
5.323
5.241
5.230
5.215
5.204
4.694
4.691
4.687
4.681
4.677
4.674
4.651
4.637
2.913
2.906
2.869
2.862
2.854
2.824
2.808
2.782
2.742
2.731
2.718
2.701
2.691
1.727
1.719
NAlloc
N
Boc
92
(CDCl3, 400 MHz)
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.00
1.02
2.13
1.96
0.99
0.98
2.62
0.47
0.45
0.57
4.11
0.93
9.14

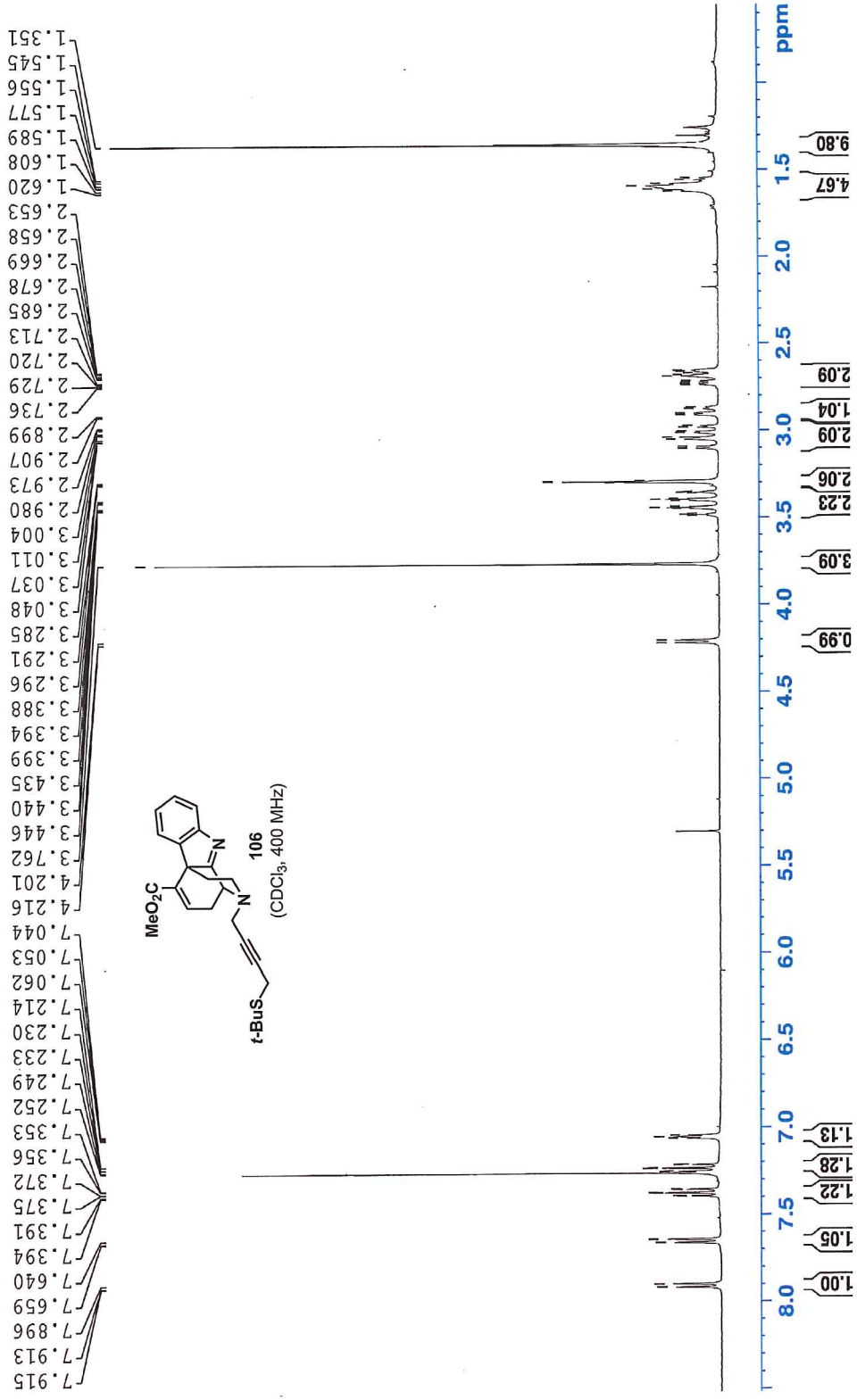


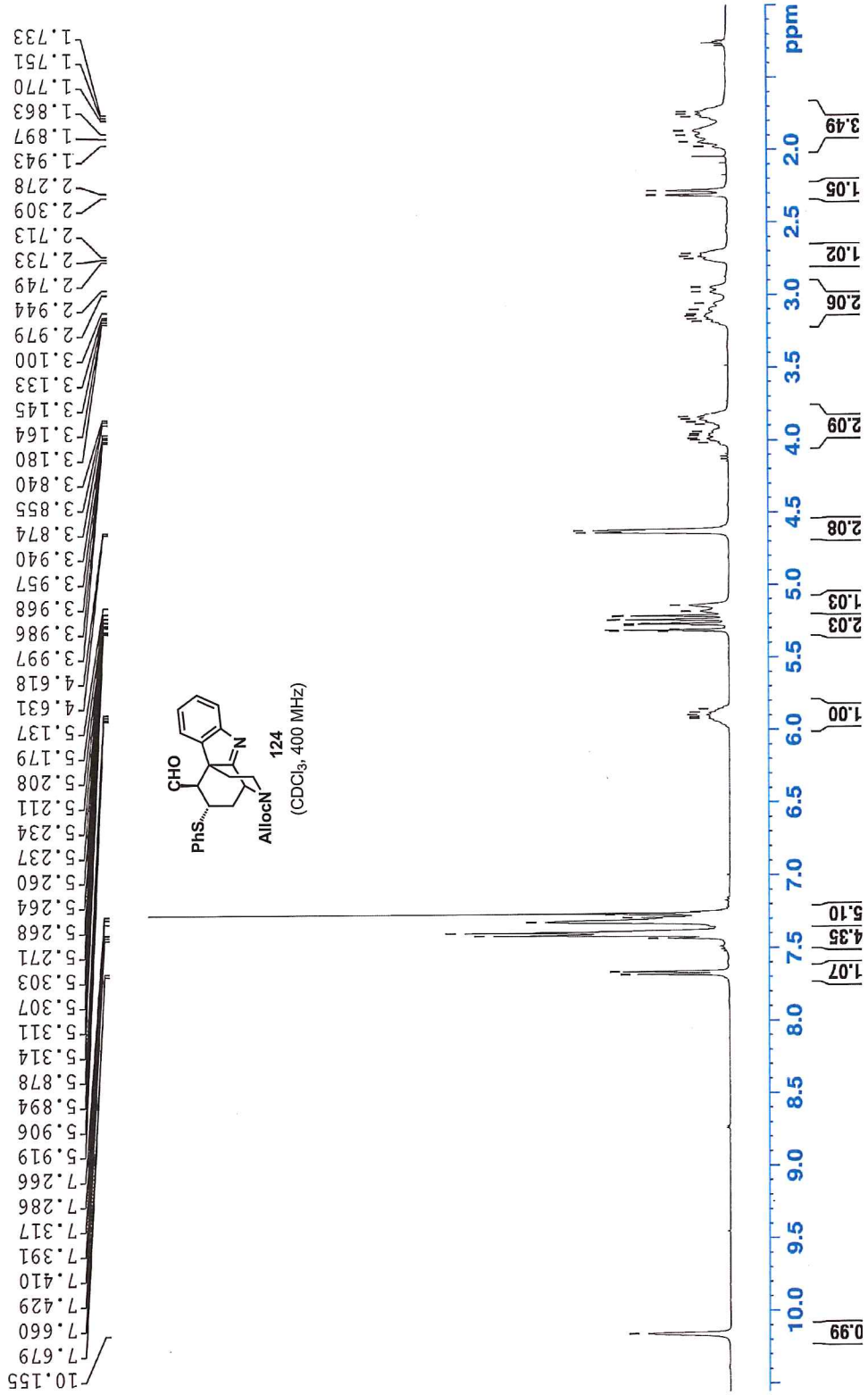
94
($CDCl_3$, 400 MHz)

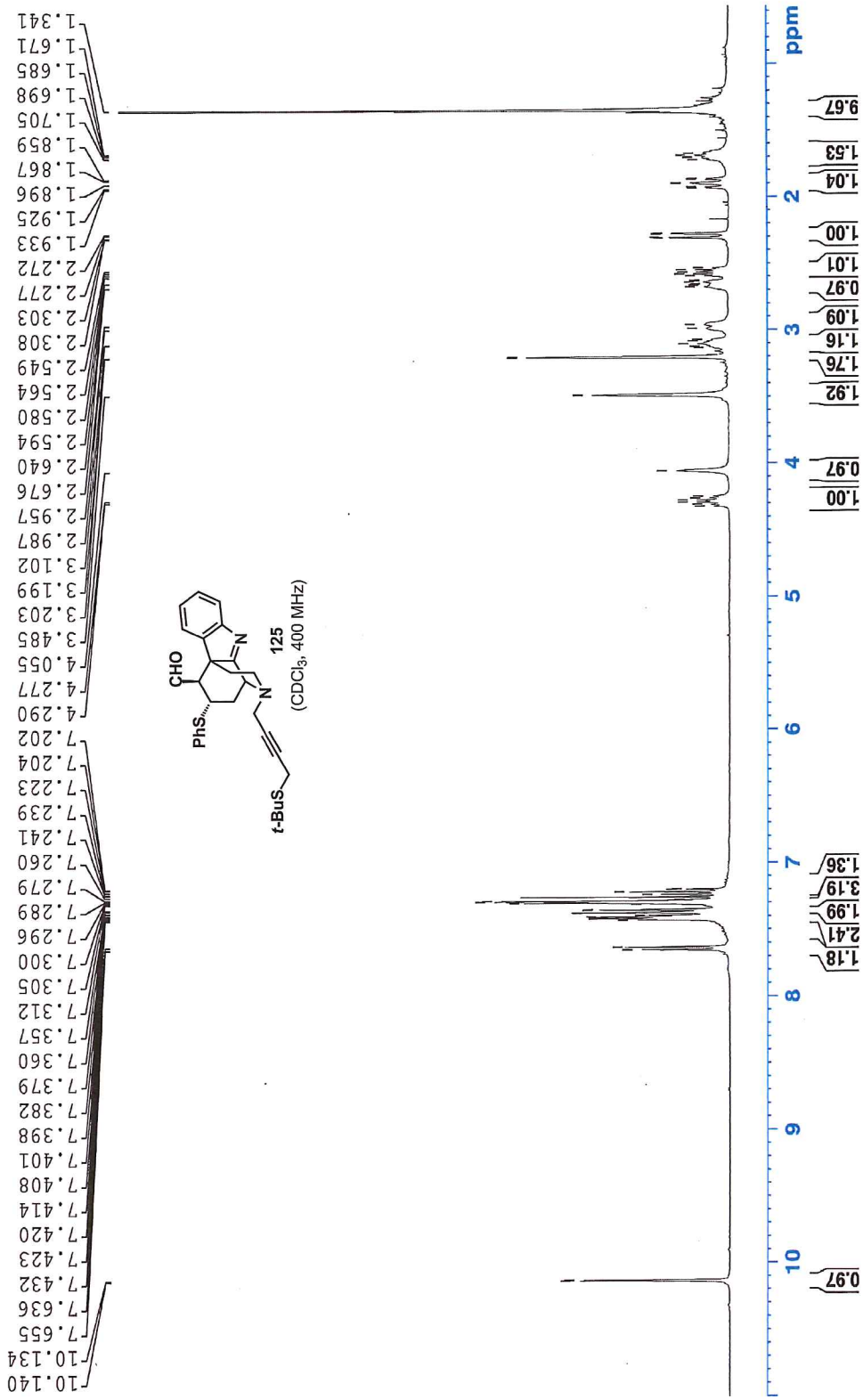

MeO2C
AllocN
95
(CDCl3, 400 MHz)
ppm


MeO2C
N
N
I
29
(CDCl3, 400 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.00
1.00
1.02
1.02
1.01
1.00
3.03
1.03
1.02
1.01
1.07
1.04
1.07
2.02
3.06
1.02
7.907
7.889
7.654
7.635
7.378
7.375
7.359
7.356
7.340
7.337
7.232
7.230
7.214
7.211
7.195
7.192
7.042
7.034
7.025
5.879
5.863
3.942
3.927
3.736
3.385
3.350
3.223
3.188
3.069
3.061
3.034
3.030
3.002
2.995
2.936
2.926
2.885
2.875
2.788
2.781
2.772
2.765
2.721
2.684
2.676
2.649
2.643
2.616
1.778
1.762
1.586
1.575
1.553
1.543
1.521


MeO2C
N
N
I
29
(CDCl3, 100 MHz)
21.81
33.88
35.86
43.16
51.74
54.70
55.24
65.07
108.55
120.81
125.53
126.32
128.39
129.73
132.97
140.12
141.21
155.99
165.80
183.08
ppm
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


MeO2C
N
N
t-BuS
106
(CDCl3, 400 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.00
1.05
1.22
1.28
1.13
0.99
3.09
2.23
2.06
2.09
1.04
2.09
4.67
9.80
7.915
7.913
7.896
7.659
7.640
7.394
7.391
7.375
7.372
7.356
7.353
7.252
7.249
7.233
7.230
7.214
7.062
7.053
7.044
4.216
4.201
3.762
3.446
3.440
3.435
3.399
3.394
3.388
3.296
3.291
3.285
3.048
3.037
3.011
3.004
2.980
2.973
2.907
2.899
2.736
2.729
2.720
2.713
2.685
2.678
2.669
2.658
2.653
1.620
1.608
1.589
1.577
1.556
1.545
1.351


CHO
PhS
AllocN
124
(CDCl3, 400 MHz)
ppm
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
0.99
1.07
4.35
5.10
1.00
2.03
1.03
2.08
2.09
2.06
1.02
1.05
3.49
10.155
7.679
7.660
7.429
7.410
7.391
7.317
7.286
7.266
5.919
5.906
5.894
5.878
5.314
5.311
5.307
5.303
5.271
5.268
5.264
5.260
5.237
5.234
5.211
5.208
5.179
5.137
4.631
4.618
3.997
3.986
3.968
3.957
3.940
3.874
3.855
3.840
3.180
3.164
3.145
3.133
3.100
2.979
2.944
2.749
2.733
2.713
2.309
2.278
1.943
1.897
1.863
1.770
1.751
1.733


125
(CDCl3, 400 MHz)
CHO
PhS
N
N
t-BuS
ppm
9.67
1.53
1.04
1.00
1.01
0.97
1.09
1.16
1.76
1.92
0.97
1.00
1.36
3.19
1.99
2.41
1.18
0.97
10.140
10.134
7.655
7.636
7.432
7.423
7.420
7.414
7.408
7.401
7.398
7.382
7.379
7.360
7.357
7.312
7.305
7.300
7.296
7.289
7.279
7.260
7.241
7.239
7.223
7.204
7.202
4.290
4.277
4.055
3.485
3.203
3.199
3.102
2.987
2.957
2.676
2.640
2.594
2.580
2.564
2.549
2.308
2.303
2.277
2.272
1.933
1.925
1.896
1.867
1.859
1.705
1.698
1.685
1.671
1.341