THE TOTAL SYNTHESIS OF HIPPADINE AND PRATOSINE VIA AN INTRAMOLECULAR DE MAYO PHOTOCYCLIZATION

by

CHARLES ISRAEL OCHOA

Bachelor of Science, 2012
Texas Christian University
Fort Worth, Texas

Submitted to the Graduate Faculty of the
College of Science and Engineering
Texas Christian University
in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy

August 2018

ACKNOWLEDGMENTS

The path toward acquiring a Ph.D. is neither easy nor short, and this path is typically not travelled alone. Our interactions with others indubitably shape us in ways we may have never imagined. I would like to thank everyone who has been a part of my journey – family, friends, and colleagues alike. There are, however, some individuals who deserve special mention due to their enormous contribution and support throughout my career. First, I would like to thank my wife, Samantha Brewer Ochoa, for all her love and support – I've always believed that, without her, I would not have completed this degree. Samantha always encouraged me and pushed me to be better by challenging my ideas and asking the "why" of everything. I am extremely fortunate to have someone like her by my side.

I am infinitely indebted to my closest family members who are also my best friends: Luis Rasgado, Mary Rasgado, and Shawn Gonzales. They were there during my highest highs and my lowest lows – there are no words that can express how much they have influenced my life and how grateful I am to have them be part of my journey. One other individual who deserves to be highlighted is Adam Montoya. Since he joined the Minter group in August 2015, my knowledge of chemistry has grown exponentially through our talks and discussions. Not only did I grow as a scientist, but I also grew as a person. My friendship with him and the others mentioned above is one I cherish very dearly, and I am thankful that they became part of my life.

I would like to thank my advisor David E. Minter for his guidance and patience through my graduate career. I am extremely grateful for the opportunity to work under his supervision and direction and for always believing in my ability to overcome any obstacle I have faced. Finally, I would like to thank my committee members for their encouragement and friendship during all these years.

Charles I. Ochoa, August 2018

TABLE OF CONTENTS

ACKNOWLEDGMENTS ii

LIST OF SCHEMES iv

LIST OF FIGURES vi

1. BACKGROUND AND SIGNIFICANCE 1

    1.1. The Galanthan Skeleton 1

    1.2. Hippadine and Pratosine 8

    1.3. Past Syntheses of Hippadine and Pratosine 11

    1.4. The de Mayo Reaction 18

2. RESULTS AND DISCUSSION 22

    2.1. Our Synthesis of the Galanthan Skeleton 22

    2.2. Synthesis of Hippadine and Pratosine 28

3. EXPERIMENTAL SECTION 43

    3.1. Instrumentation, Solvents, and Reagents 43

    3.2. General Procedures 45

APPENDIX 81

REFERENCES 104

VITA

ABSTRACT

LIST OF SCHEMES

Scheme 1.1 4

Scheme 1.2 5

Scheme 1.3 6

Scheme 1.4 7

Scheme 1.5 8

Scheme 1.6 12

Scheme 1.7 13

Scheme 1.8 14

Scheme 1.9 15

Scheme 1.10 16

Scheme 1.11 17

Scheme 1.12 19

Scheme 1.13 20

Scheme 1.14 21

Scheme 2.1 22

Scheme 2.2 23

Scheme 2.3 23

Scheme 2.4 24

Scheme 2.5 24

Scheme 2.6 25

Scheme 2.7 26

Scheme 2.8 27

Scheme 2.9 27

Scheme 2.10 28
Scheme 2.11 29
Scheme 2.12 29
Scheme 2.13 30
Scheme 2.14 31
Scheme 2.15 31
Scheme 2.16 32
Scheme 2.17 32
Scheme 2.18 33
Scheme 2.19 34
Scheme 2.20 34
Scheme 2.21 35
Scheme 2.22 36
Scheme 2.23 36
Scheme 2.24 38
Scheme 2.25 39
Scheme 2.26 40
Scheme 2.27 41
Scheme 2.28 42

LIST OF FIGURES

Figure 1.1: Skeleton of three *Amaryllidaceae* alkaloid subclasses.....1

Figure 1.2: Structures of (+)-kirkine, (-)-siculinine, and (+/-)-fortucine.....2

Figure 1.3: Galanthan ring system.....3

Figure 1.4: Structures of hippadine and pratosine.....9

Figure 1.5: Structures of atenolol and prazosin.....10

Figure 1.6: Substrates for late-stage B-ring closures.....18

Figure 2.1: X-ray crystal structure of 105.....28

Figure 2.2: X-ray crystal structure of 131b.....37

Figure 2.3: Structures of oxoassoanine and anhydrolycorinone.....39

Figure 2.4: Structures of lycosprenine and 2-methoxyanhydrolycorinone.....40

Chapter 1

Background and Significance

1.1 The Galanthan Skeleton

For centuries, humans have used plant natural products for medicinal purposes relying on knowledge handed down through generations. This is the basis for traditional medicine, but the study of natural products has also developed as a source for modern pharmaceuticals. It has been estimated that over 70% of the most important drugs in use today originated from natural products as lead compounds.[1] Alkaloids constitute a salient group of natural products; many of these are found in plants of the family *Amaryllidaceae* which consists of about 85 genera and around 1100 species. *Amaryllidaceae* alkaloids have a variety of therapeutic properties such as anticancer, antibacterial, antiviral and acetylcholinesterase inhibitory activities among others.[2] There are several subclasses of alkaloids within the *Amaryllidaceae* family of plants; the three most important subclasses are the lycorine-type (**1**), the crinine-type (**2**) and the galanthamine-type (**3**). The lycorine-type alkaloids have received special attention due to the wide range of pharmacological properties displayed by these compounds.[3-5] As a result, a larger number of compounds from this group have been isolated and fully characterized to date.

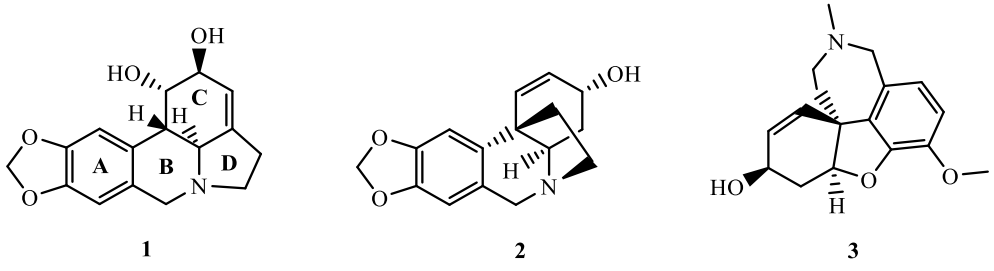


Figure 1.1. Skeletons of three *Amaryllidaceae* alkaloid subclasses

Lycorine (**1**) is one of the most studied natural products from this class of alkaloids due not only to its biological activity but also to the synthetic challenges presented by this intriguing

molecule.[6-7] Most of the lycorine-type alkaloids display a *trans*-B,C ring junction. However, the narcissus genus of the *Amaryllidaceae* family produces natural products with the rare *cis*-B,C ring fusion as seen in (+)-kirkine (**4**),[8] (-)-siculinine (**5**),[9] and fortucine (**6a** and **6b**).[10] Although the pharmacological activities of these natural products have not been studied, their unique structural properties (especially the absolute configuration of each structure) have been of interest for a number of years. Recently, an asymmetric synthesis of the compound previously identified as (+)-fortucine (**6a**) was carried out by Canesi and coworkers. They found that the optical rotation of naturally-occurring fortucine was exactly the opposite of the synthetic enantiomerically-pure (+)-fortucine.[11] Thus, the compound isolated from the narcissus plant had been misidentified and is actually the enantiomer (-)-fortucine (**6b**).

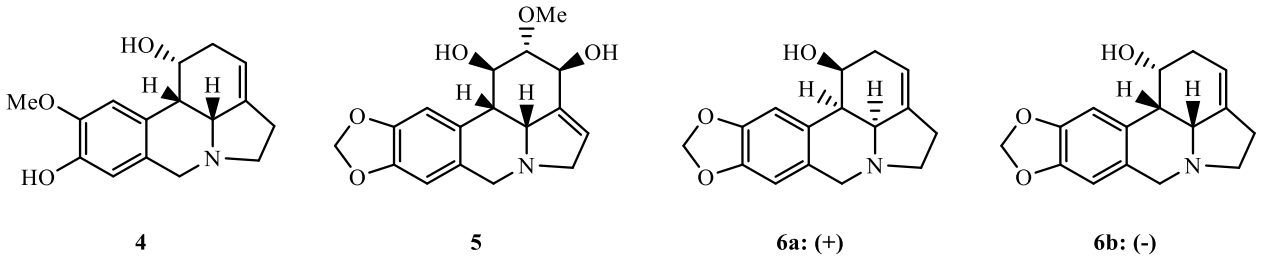
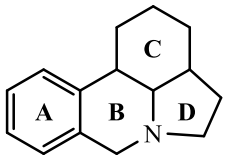


Figure 1.2. Structures of (+)-kirkine (4), (-)-siculinine (5), (+)-fortucine (6a), and (-)-fortucine (6b)

All lycorine-type alkaloids exhibit the tetracyclic skeleton known as the galanthan ring system (**7**). The most common published synthetic pathways for the construction of **7** are of the general types A→C→D→B and A→C→B→D, where the letters represent the sequence used to generate each ring. Other strategies that have also been used include late-stage formation of the B-ring,[12] D-ring formation using phenanthridone derivatives, and multiple ring formations that employ both simultaneous and tandem approaches.[13-15] A brief overview of some of the methods used to prepare the galanthan ring system is presented below. The specific examples have been

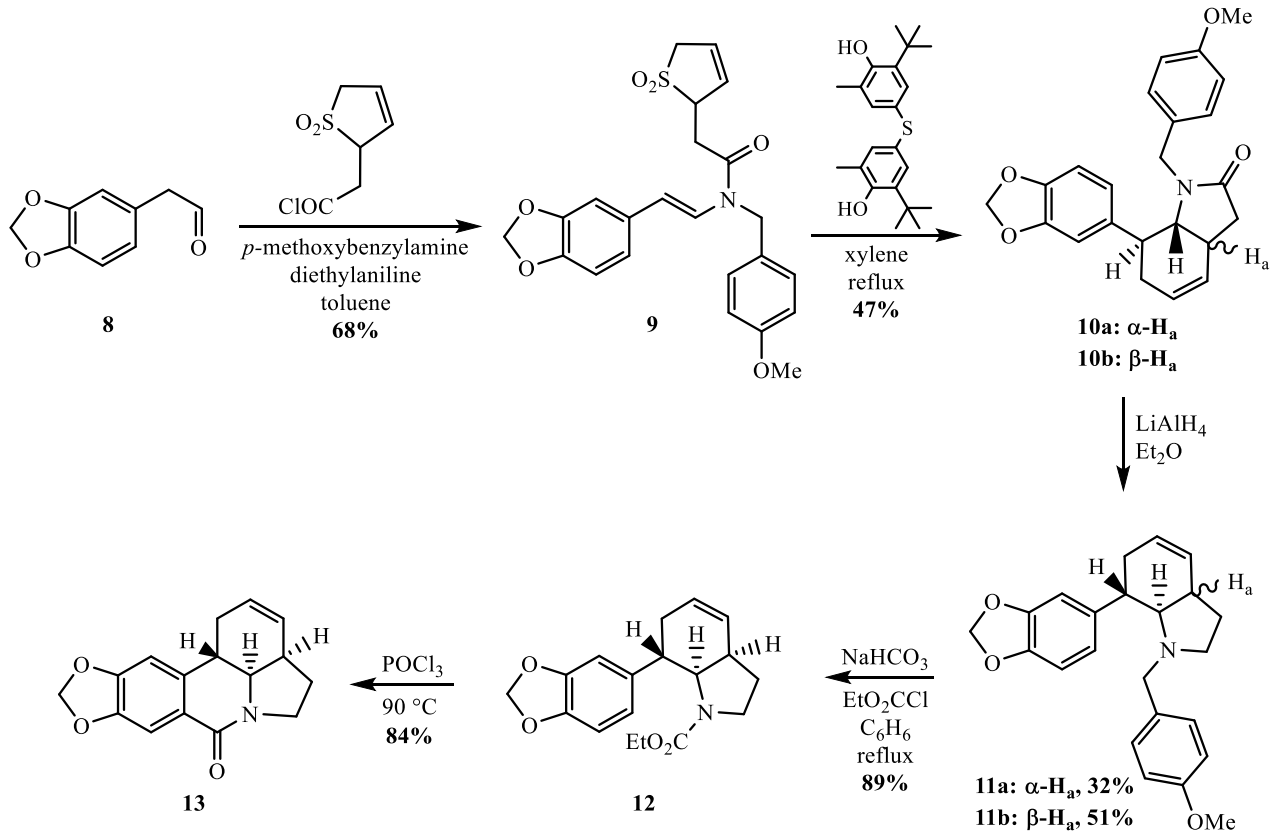
chosen to illustrate the diversity of synthetic strategies that have been devised in previous research rather than a complete history of the preparation of **7**.



7

Figure 1.3. Galanthan ring system

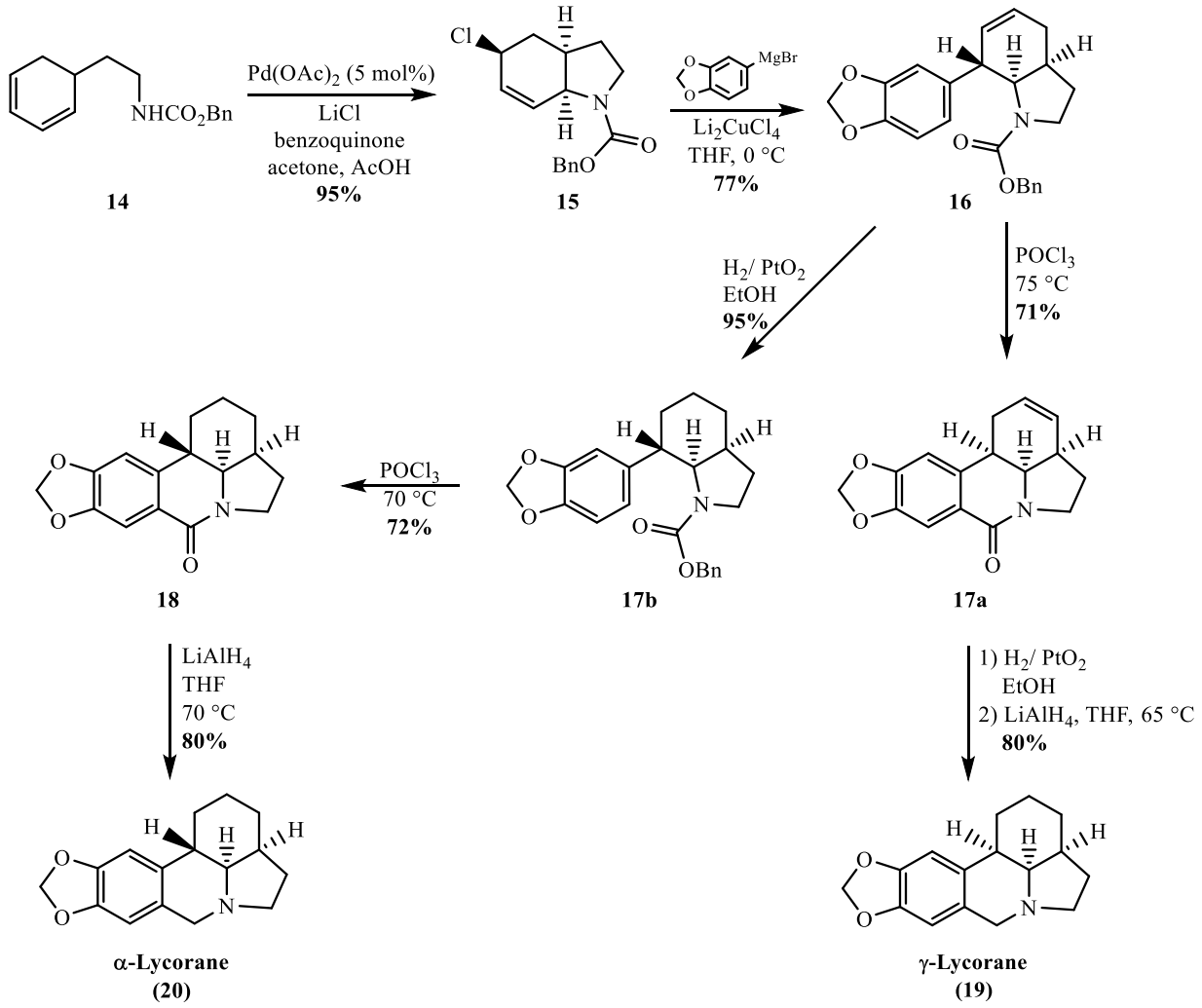
In 1979, Stork and coworkers designed an intramolecular Diels-Alder approach in the synthesis of **7** for the first time.[16] Soon after, Martin's group employed this approach for the formal synthesis of lycorine (**1)** as depicted in Scheme 1.1.[17] The reaction of **8** with *p*-methoxybenzylamine followed by acylation of the imine intermediate with a sulfolene acid chloride produced **9**. Concomitant extrusion of sulfur dioxide and intramolecular Diels-Alder cycloaddition gave a mixture of *cis*- and *trans*- γ-lactams **10a** and **10b**, respectively. Since the hydrolactams were inseparable at this stage, lithium aluminum hydride was used to reduce the amide functional group. The products of the reaction were easily separated by HPLC to give the corresponding tertiary amines **11a** and **11b** in 35% and 50% yield, respectively. Regretfully, the major product of the reaction (**11b**) possessed the incorrect stereochemistry for lycorine. Nevertheless, reaction of **11a** with ethyl chloroformate gave **12** which was subsequently cyclized by treatment with $POCl_3$ to yield tetracycle **13**, an intermediate that had already been converted to **1** in previous studies.[18]



Scheme 1.1

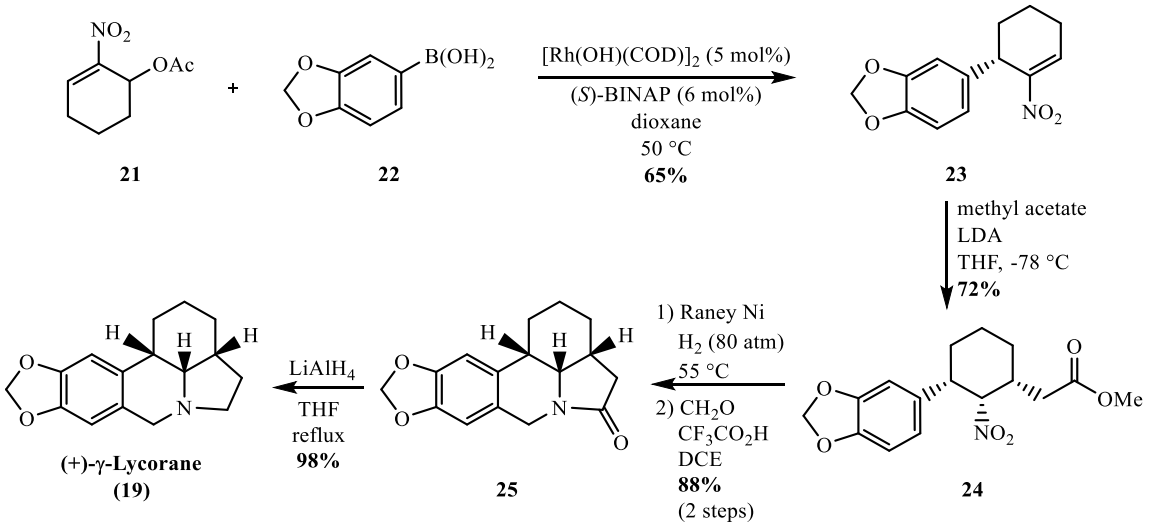
Gogoll and coworkers made use of an elegant palladium-catalyzed intramolecular 1,4-chloroamidation reaction to produce **15** from carbamate **14**. This highly regio- and stereoselective approach (>98% selectivity) is shown in Scheme 1.2.[19] The reaction of **15** with 3,4-methylenedioxyphenylmagnesium bromide in the presence of Li_2CuCl_4 produced **16** in a 1:4 α:γ ratio. Unfortunately, the cyclization of **16** using $POCl_3$ produced **17a**, an isomeric product that contained a *cis*-B,C ring junction and thus could not be used to prepare lycorine (**1**). Therefore, the double bond in **16** was reduced to yield **17b**, a carbamate containing the desired *trans* configuration along with an unfunctionalized C-ring. Both **17a** and **18** (formed by cyclization of **17b** using $POCl_3$) were transformed to γ-lycorane (**19**) and α-lycorane (**20**), respectively. Although this research proved unsuccessful in the preparation of lycorine (**1**), it

established a synthetic route for the formation of molecules containing the γ-lycorane skeleton over the α-lycorane skeleton.



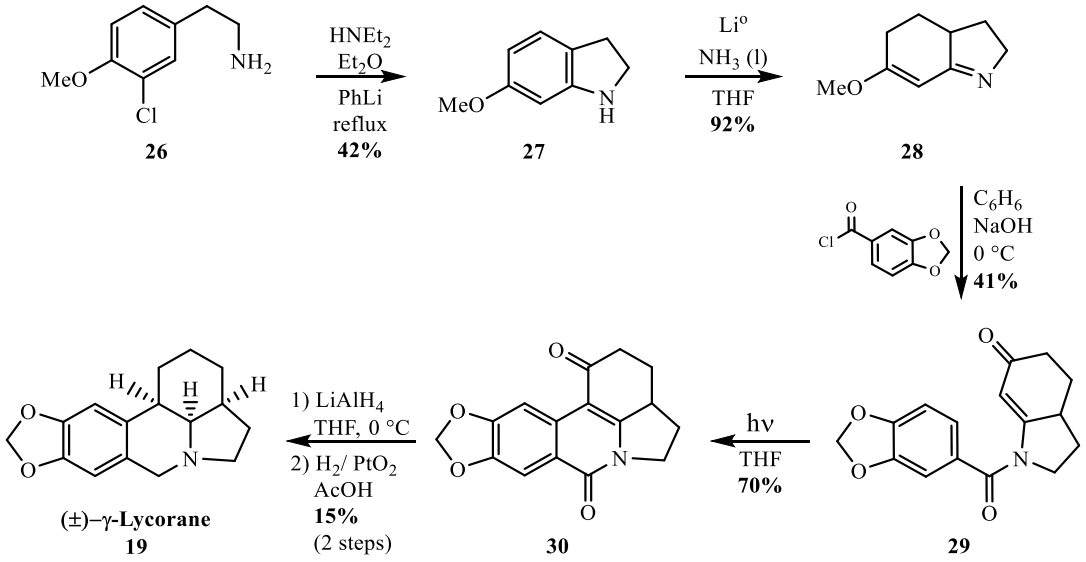
Scheme 1.2

More recently, a highly enantioselective synthesis of (+)-γ-lycorane (**19)** has been reported using **21** and *(S)*-BINAP as a chiral ligand for a rhodium catalyst as shown in Scheme 1.3.[20] Asymmetric allylation of **22** to produce **23** followed by a Michael addition of methyl acetate anion to **23** provided all-*cis* 1,2,3-trisubstituted **24**. Reduction of the nitro group, cyclization, and a modified Pictet-Spengler ring closure reaction afforded **25**. Finally, reduction of the lactam functionality gave (+)-γ-lycorane (**19)**.



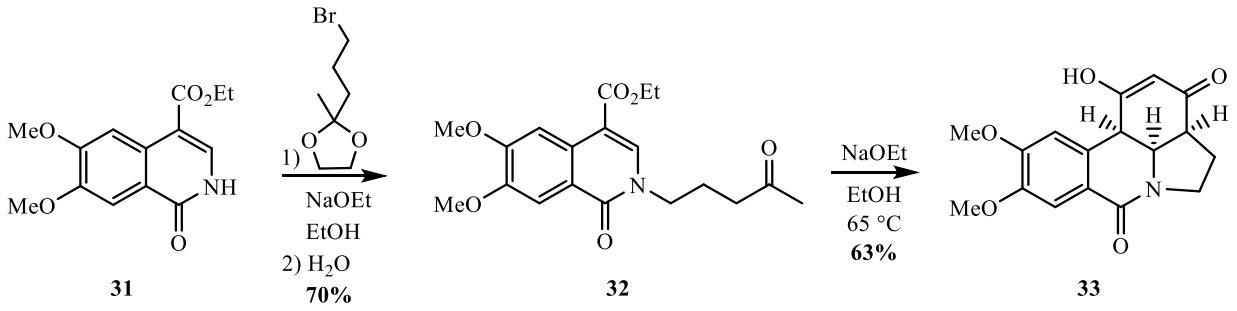
Scheme 1.3

The first synthetic route utilizing a photochemical approach for the construction of the galanthan tetracyclic skeleton is shown in Scheme 1.4.[21-22] A benzyne-mediated cyclization of **26** using phenyllithium afforded 6-methoxyindole (**27**) which was subjected to Birch reduction conditions using lithium metal to give **28**. Furthermore, acylation of **28** with an acid chloride followed by hydrolysis of the enol ether yielded **29**. Irradiation of **29** for one hour with a 100W high-pressure mercury arc lamp induced a photochemical cyclization to give tetracycle **30** in good yield. Reduction using lithium aluminum hydride followed by catalytic hydrogenation gave (±)-γ-lycorane (**19**).



Scheme 1.4

To the best of our knowledge, there has only been one instance[14] in which the preparation of tetracyclic skeleton **7** began with the A and B rings intact (Scheme 1.5), while most of the other synthetic routes focus on a late-stage formation of the B-ring. The synthesis began with an alkylation of **31** with 5-bromo-2-pentanone ethylene ketal followed by hydrolysis to give isocarbostyril **32**. The isocarbostyril was transformed to **33** through an alkoxide-catalyzed cyclization. This strategy is particularly interesting since it employs a tether on the nitrogen of an isocarbostyril where the tether contains a functional group that eventually becomes part of the tetracyclic ring system.

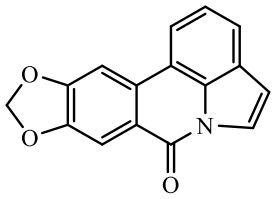


Scheme 1.5

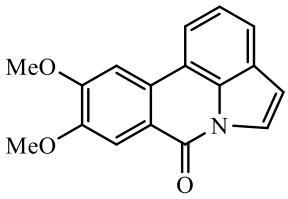
Our proposed synthetic scheme, which will be described in detail later, uses a similar strategy with a much more highly functionalized tether that contains all of the missing carbon atoms to construct the C and D rings. Thus, our approach focuses on using an isoquinoline as a primary starting material with substituents on the A-ring that will vary depending on the specific galanthan target.

1.2 Hippadine and Pratosine

Like all lycorine-type alkaloids, both hippadine (**34**) and pratosine (**35**) contain the tetracyclic pyrrolophenanthridone galanthan skeleton. They are isolated from the *Crinum* genus of tropical plants from the family *Amaryllidaceae*. Hippadine was first isolated in 1975 from the *H. vittatum L.* herb.[23-24] A few years later, Ghosal and coworkers isolated and characterized pratosine for the first time from the bulbs of *Crinum latifolium* collected at flowering.[25] Structurally, hippadine is different from pratosine only by the substituents present on the A-ring of the galanthan skeleton; specifically, hippadine contains a 9,10-methylenedioxy group (effectively adding an extra ring to the structure) whereas pratosine contains two methoxy substituents on ring A.



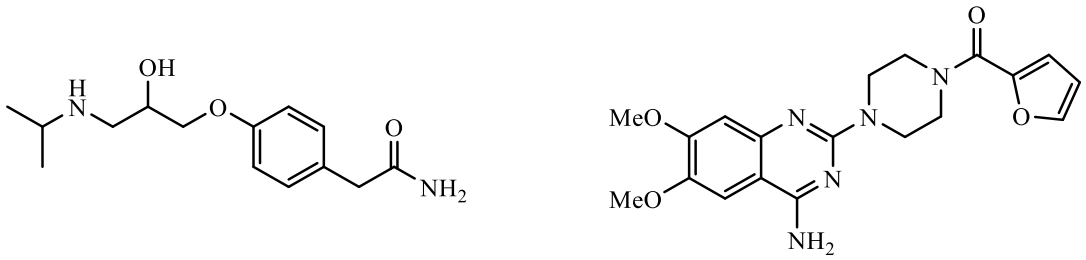
34



35

Figure 1.4. Structures of hippadine (34) and pratosine (35)

When tested in rats, hippadine has shown spermicidal activity; however, spermatogenesis can be re-established by simply suspending treatment.[26] Hippadine works by reducing the number of germ cells in addition to decreasing testicular weight and DNA content. Aside from its ability to inhibit spermatogenesis, hippadine has also been shown to decrease cardiac output while decreasing systolic and diastolic pressures.[27] *In vivo,* the negative inotropic (decreased myocardial contractility) and negative chronotropic (decreased heart rate) effects that hippadine displays were similar to those exhibited by atenolol **36** (a selective β_1 adrenoreceptor antagonist) and prazosin **37** (a selective α_1 adrenoreceptor antagonist).[28-29] These cardiovascular effects were significantly reversed when adrenaline (a non-selective alpha- and beta- adrenoreceptor agonist) was administered to the rats that had been dosed with hippadine. Therefore, it is hypothesized that these cardiac effects may be the result of inhibition of α_1 and β_1 adrenoreceptors. Ruan and coworkers isolated hippadine from the bulbs of *Lycoris sprengeri* and they found that the alkaloid displays significant neuroprotective activity (cell viability %) against H_2O_2- (57.3%), $CoCl_2$- (62.3%) and $A\beta_{25\text{-}35}$- (64.3%) induced SH-SY5Y cell death (100 μM test concentrations).[30] Hippadine has been shown to have a moderate effect on the mortality (33±6 %) of adult *Ae. aegypti,* a mosquito known to be a Zika virus vector.[31]



36 **37**

Figure 1.5. Structures of atenolol (36) and prazosin (37)

With all the potentially useful properties that hippadine displays, it comes as no surprise that numerous efforts to synthesize a quantifiable supply have been made in order to facilitate testing its properties more extensively and to evaluate the material as a lead compound for drug development. It becomes even more surprising that the biological activity of pratosine, which differs from hippadine only by the A-ring substituents, has not been studied. Other galanthan alkaloids have shown a variety of properties including antitumor activity.[32] Additionally, lycorine-type (**1**) and galanthamine-type (**3**) alkaloids have exhibited significant activity in reversing Alzheimer's disease.[33] Thus, the ability to synthesize pratosine in appreciable amounts will facilitate a study of the effects of this natural product on biological systems.

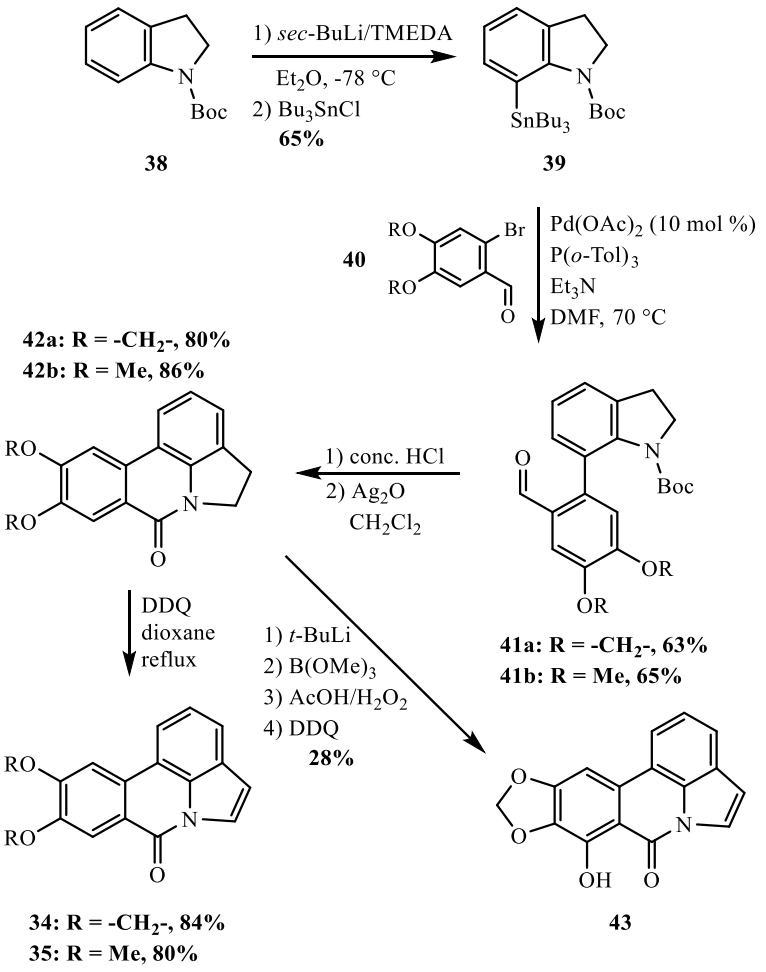
Since the first synthesis of hippadine in the late 1980's, there have been 25 syntheses of hippadine and 15 syntheses of pratosine reported in the literature. As mentioned earlier, late-stage formation of the B-ring is the most popular approach, accounting for more than 80% of the synthetic strategies employed. Closure of the D-ring at the end of the synthesis has been used in only around 15% of the synthetic routes to hippadine and pratosine. As far as we have seen, there is but one report in the literature describing a late-stage C-ring formation. The majority of the syntheses utilize Suzuki-, Suzuki-Miyaura-, or Heck- type palladium-catalyzed biaryl coupling reactions to establish the B-ring. The remaining approaches include free radical-mediated reactions or cycloaddition reactions such as the Diels-Alder [4+2] cyclization.

Interestingly, there are very few published strategies which do not employ any of the reaction types described above. Not only does our approach consist of a late-stage C-ring formation while avoiding the use of any heavy metal catalysts but also the primary starting material contains the A and B rings of the final product intact in the form of a readily available substituted isoquinoline. There are no precedents in the literature for this strategy.

The following section describes six total syntheses from the literature that will serve as an overview to illustrate the synthetic strategies already described above in general terms for the preparations of hippadine (**34**) and pratosine (**35**).

1.3 Past Syntheses of Hippadine and Pratosine

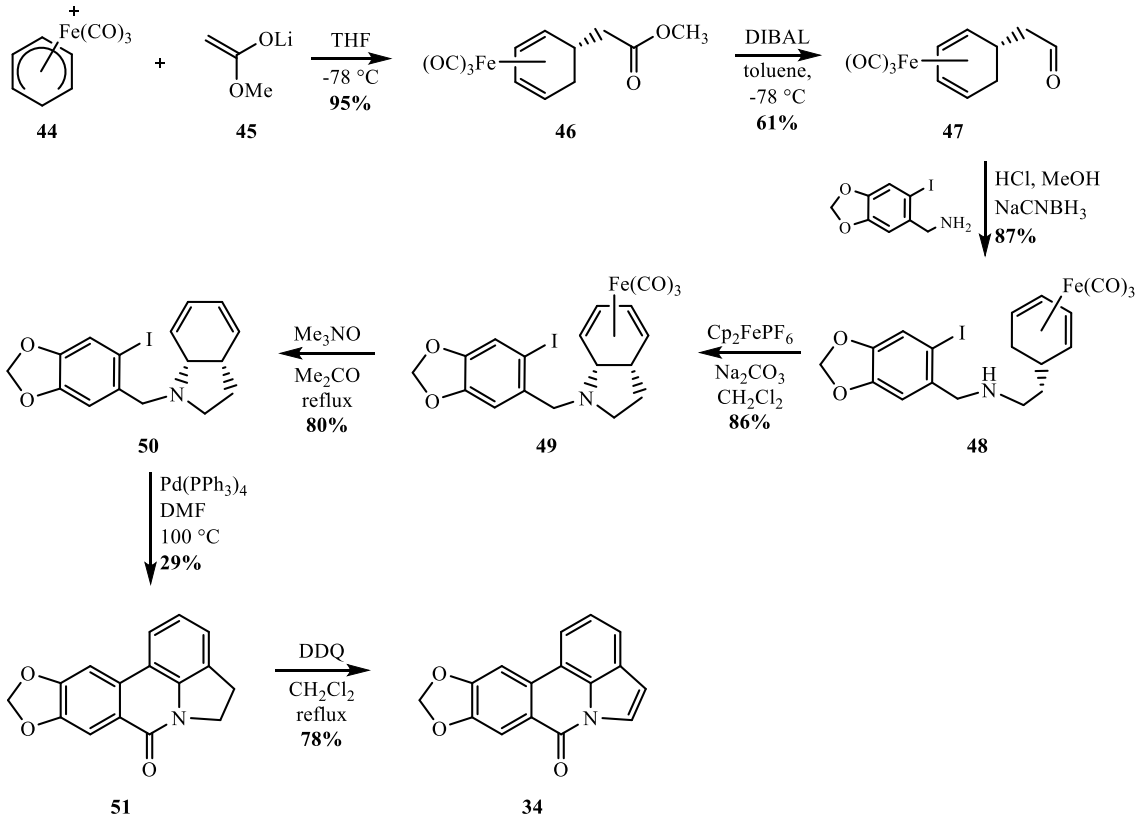
Watanabe and co-workers designed a convergent synthesis of hippadine and pratosine which used directed lithiation and a palladium-catalyzed Stille cross-coupling reaction as the key steps of the synthesis (Scheme 1.6).[34] Directed lithiation of 1-*tert*-butoxycarbonylindole (**38**) followed by reaction with $SnBu_3Cl$ gave 7-stannylated indoline **39**. Stille cross coupling of **39** with **40** resulted in the formation of **41**. Simultaneous deprotection and cyclization of **41** with concentrated HCl followed by Ag_2O-mediated oxidation of the hemiaminal intermediate (not isolated) resulted in the formation of **42**. Finally, a DDQ-mediated aromatization reaction of **42** gave hippadine and pratosine in good yields using this 6-step synthetic scheme. Kalbetorine (**43**), a natural product that exhibits antitumor activity, was also synthesized by the route described above by taking anhydrolycorin-7-one (**42a**) and hydroxylating the A ring by using another directed lithiation promoted by the amide carbonyl. Synthetic pathway: **CD→A→B**



Scheme 1.6

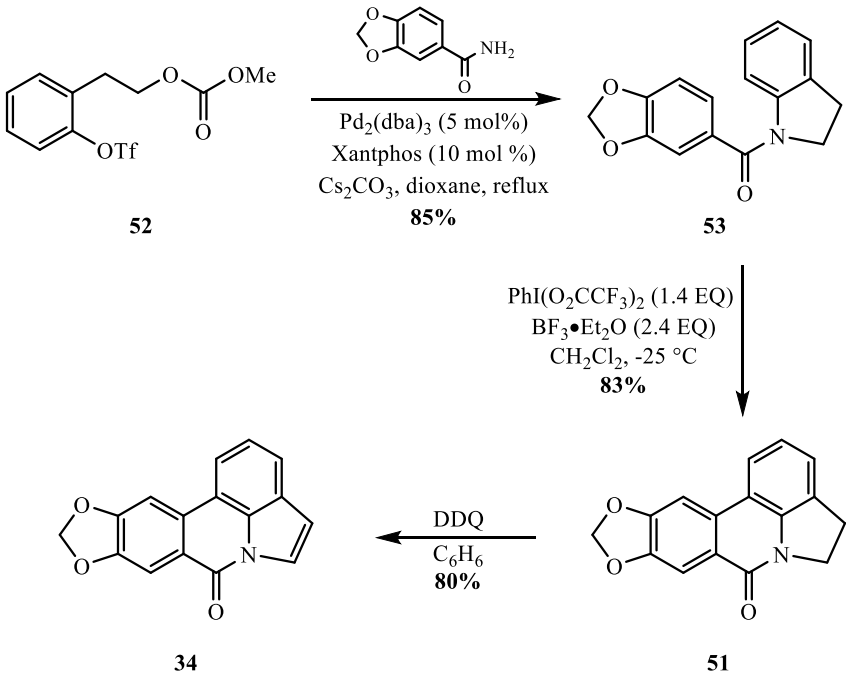
In 2003, Filali and Knölker synthesized hippadine by using an iron-mediated alkylamine cyclization followed by a Heck-type palladium-catalyzed intramolecular biaryl coupling in order to achieve formation of the C-ring (Scheme 1.7).[35] 1,3-Cyclohexadiene was transformed to the tetrafluoroborate salt **44** by azadiene-catalyzed complexation with pentacarbonyliron followed by hydride abstraction using trityl tetrafluoroborate. The reaction of salt **44** with lithium ester enolate **45** gave complex **46** in 95% yield. DIBAL reduction of the ester gave **47** in 61% yield. Reductive amination of **47** using iodopiperonylamine gave complex **48**; oxidative cyclization of **48** using an iron catalyst followed by demetallation of **49** afforded **50** which was transformed to anhydrolycorinone **51** employing a Heck-type intramolecular biaryl coupling

reaction using tetrakis[triphenylphosphine]palladium in DMF in the presence of air. The last step involved aromatization using DDQ in dichloromethane to afford hippadine (**34**). Synthetic pathway: **A→C→D→B**



Scheme 1.7

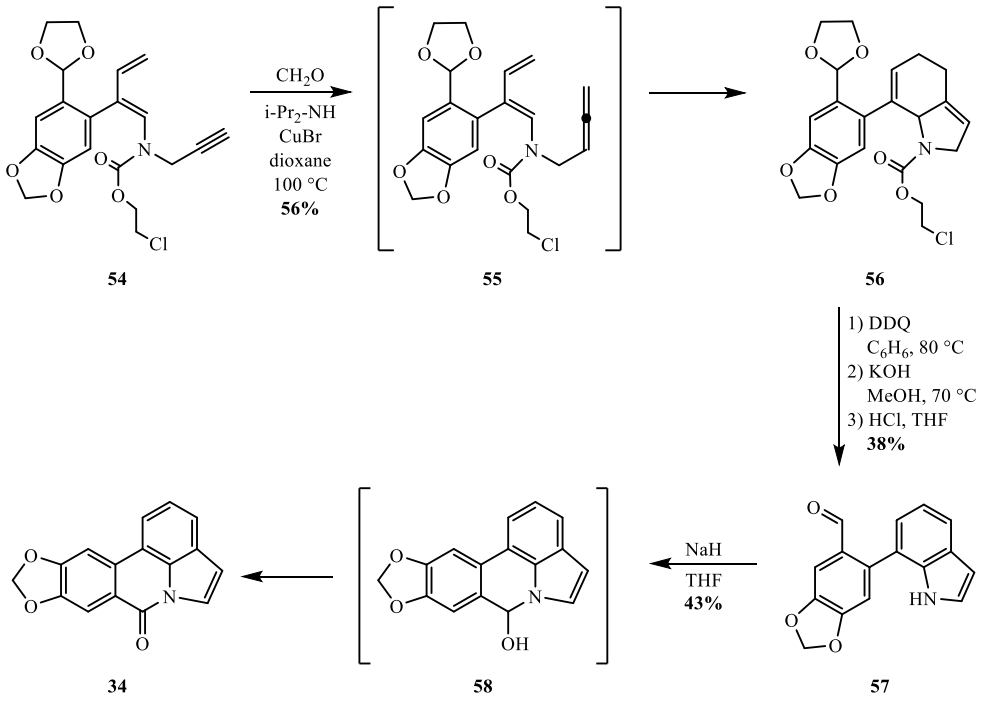
A palladium coupling reaction was also used in 2005 by Ganton and Kerr, who prepared hippadine and pratosine in three steps (Scheme 1.8).[36] Treatment of **52** with piperonylamide in the presence of tris(dibenzylideneacetone)dipalladium(0) and Xantphos gave **53** which is a precursor to hippadine. A biaryl radical coupling reaction followed by oxidation with DDQ afforded **34**. Pratosine was synthesized by the same route using veratramide instead of piperonylamide. While this approach produced the alkaloids in relatively few steps with acceptable yields, the use of expensive reagents makes the synthetic idea less attractive for large-scale production. Utilizing heavy metal catalysts near the end of the synthesis can also be problematic if the alkaloids are to be tested *in vivo*. Synthetic pathway: **A→C→D→B**



52 **53** **34** **51**

Scheme 1.8

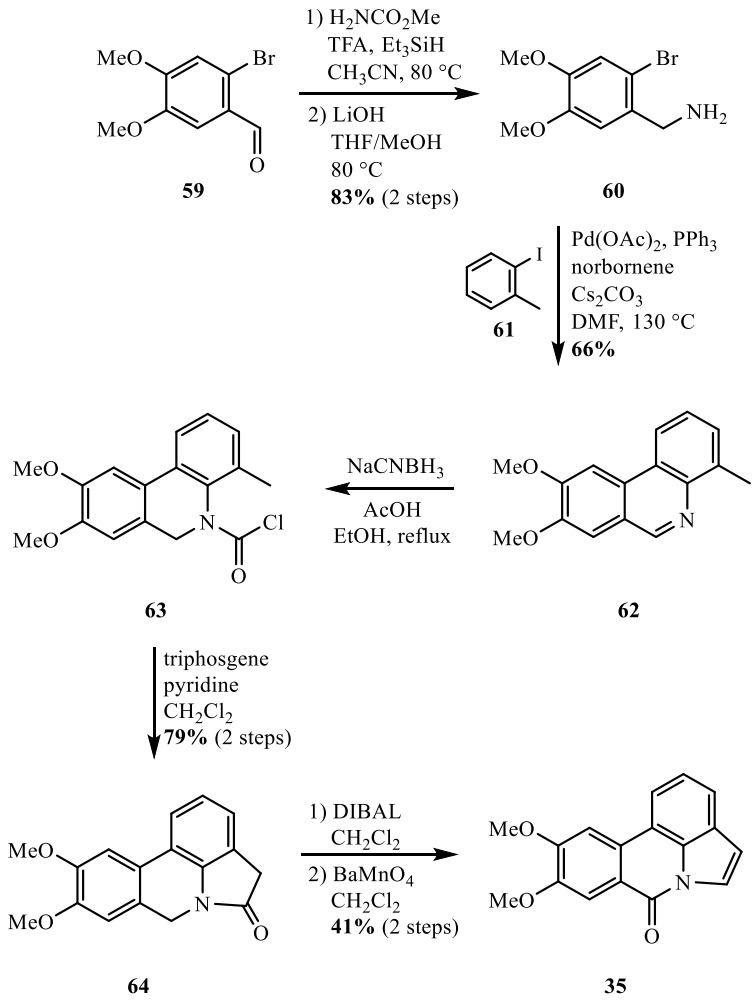
Kanematsu and co-workers at Kyushu University achieved the earliest synthesis of hippadine in 1987.[37] In essence, they achieved the simultaneous construction of the C and D rings via an intramolecular Diels-Alder reaction of allenic dienamide **55** which resulted in the formation of **56**. The alkaline hydrolysis of **56** followed by deprotection of the acetal group provided **57**. Finally, formation of the B-ring was achieved by treatment of **57** with NaH in THF gave **58**; oxidation in the presence of air during the workup afforded hippadine (**34**) (Scheme 1.9). This route is certainly an elegant one that makes use of classical chemistry. However, the overall yield of the synthesis is only 2%. While most of the reagents are relatively inexpensive, the inefficiency of the process prevents the molecule from being synthesized in large quantities without substantial material loss. Thus, the cost of the process is greatly increased. Synthetic pathway: **A→C-D→B**



Scheme 1.9

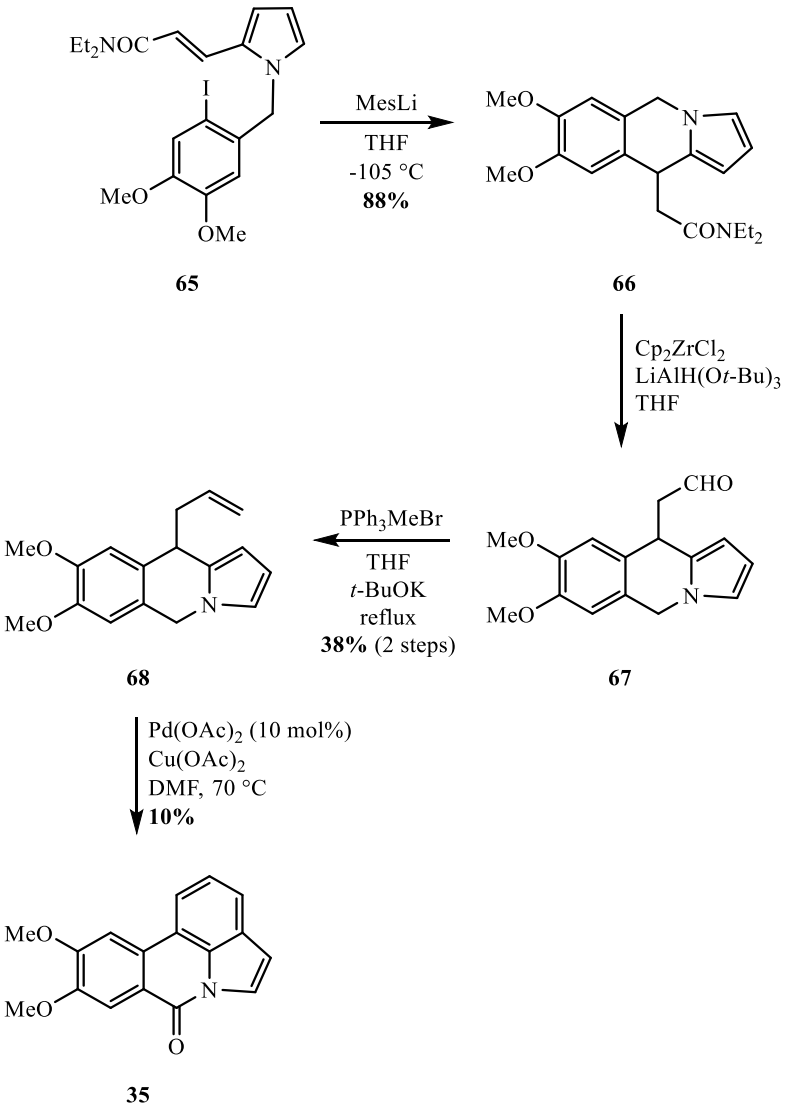
All of the strategies presented thus far have ended with the formation of the B-ring. However, there are a few atypical approaches including Takemoto's syntheses of hippadine and pratosine in 2014 (Scheme 1.10).[38] The key steps involved a C(sp^3)-H functionalization followed by a C(sp^2)-H functionalization known as the Catellani reaction. Reductive amination of **59** followed by hydrolysis of the carbamate with LiOH gave **60** in 83% yield. Amine **60** was coupled with 2-iodotoluene (**61**) using a Catellani reaction with $Pd(OAc)_2$, PPh_3, Cs_2CO_3, and 2-norbornene in DMF, resulting in the formation of molecule **62** which contains rings A, B, and C. Reduction of **62** with $NaCNBH_3$ followed by treatment with triphosgene yielded **63** in 79% yield over 2 steps. Using a C(sp^3)-H functionalization reaction, **63** was treated with $Pd(OAc)_2$, Ad_2P*n*-Bu, Cs_2CO_3, and PivNHOH in mesitylene to give the desired tetracyclic compound **64**. Finally, reduction of **64** with DIBAL followed by a $BaMnO_4$-mediated benzylic oxidation afforded pratosine in 13% overall yield. A similar route starting with 6-bromopiperonal yielded hippadine in 6% overall yield. Not only is this a concise route but also it showcases the

syntheses of hippadine and pratosine by a rare late-stage D-ring formation. Synthetic pathway: **A→B-C→D**



Scheme 1.10

To date, there has only been one synthesis that relies on a late-stage C ring formation (Scheme 1.11).[39] Pyrrolo[1,2-*b*]isoquinoline **66** was formed by reaction of pyrrole **65** with MesLi in THF. Generation of the Schwartz reagent *in situ* reduced the amide functional group giving **67** which was immediately transformed to 10b-allylpyrroloisoquinoline (**68**) using a Wittig reaction. The last step is an intramolecular alkenylation reaction known as the Fujiwara-Moritani reaction. Treatment of **68** with $Pd(OAc)_2$ and $Cu(OAc)_2$ in DMSO formed the C-ring present in pratosine. Synthetic pathway: **A-D→B→C**



Scheme 1.11

Most of the remaining syntheses of these *Amaryllidaceae* alkaloids solicit the concept of late-stage formation of the B-ring through an intramolecular biaryl cross-coupling catalyzed by a heavy metal. A summary of all the reported syntheses that use this strategy is presented below (Figure 1.6). Each structure is a biaryl material that leads to the natural product (R = -CH_2-, hippadine; R = -CH_3, pratosine) itself or an immediate precursor thereof. The type of coupling that was employed and the specific catalyst system is also included.

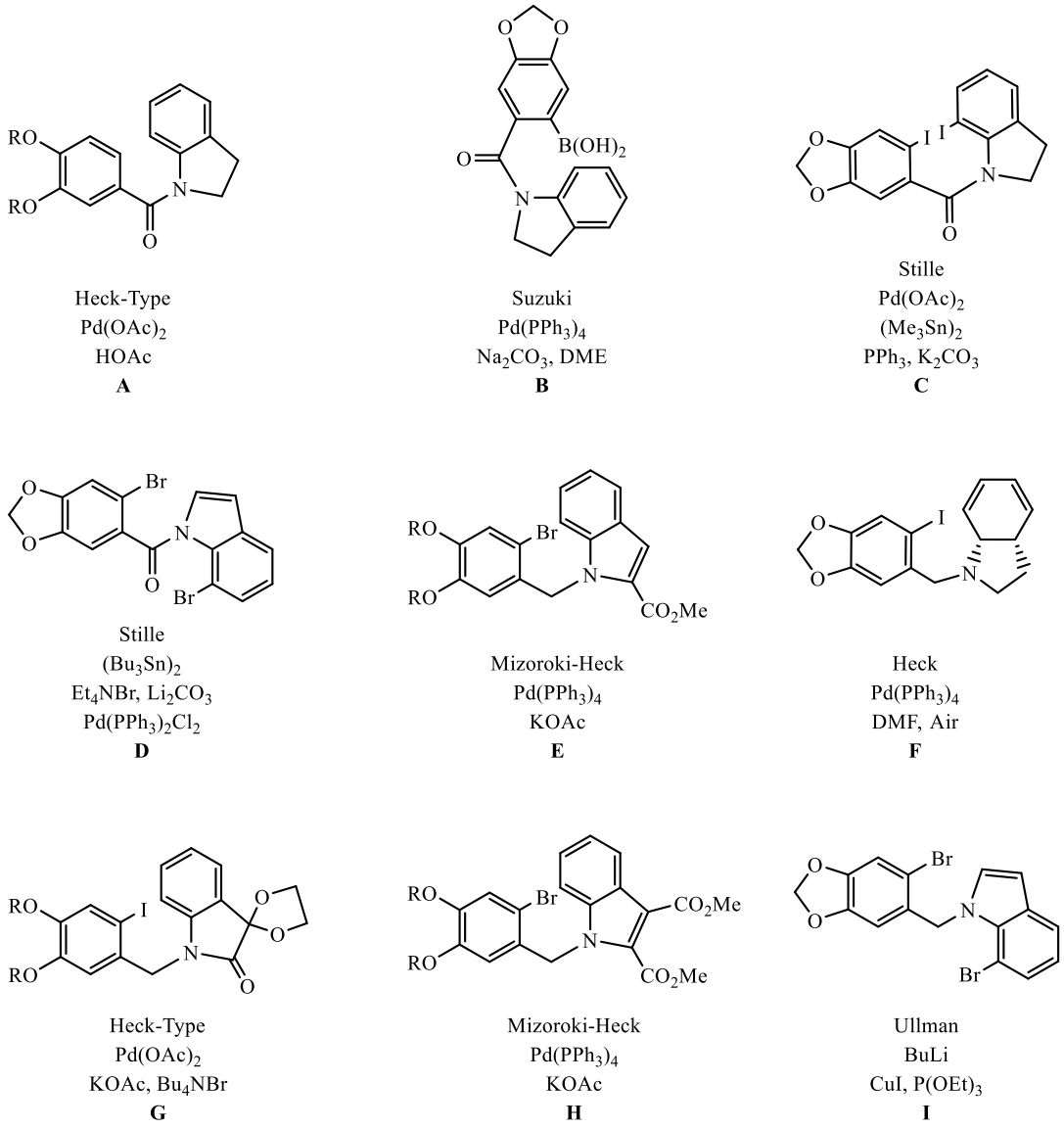


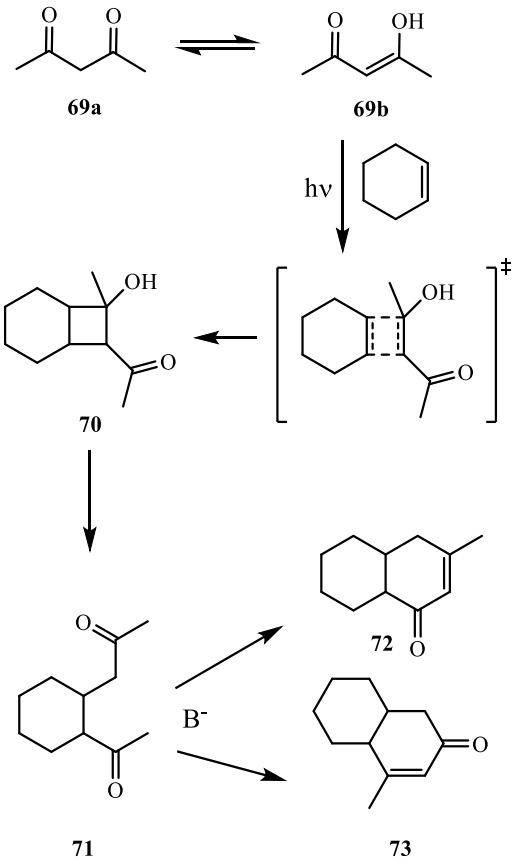
Figure 1.6. Substrates for late-stage B-ring closure strategies

A[40], B[41], C[42], D[43], E[44], F[35], G[45], H[46], I[47]

1.4 The de Mayo Reaction

The de Mayo photocyclization reaction is a key step in our approach to the syntheses of hippadine and pratosine. The photochemical addition of a β-dicarbonyl compound to a simple alkene was first published by Paul de Mayo's group at the University of Western Ontario in 1972.[48-49] This reaction proceeds through the hydrogen-bonded enol tautomer of the dicarbonyl substrate making it analogous to an α,β-unsaturated ketone. Thus, the reaction of the enol

double bond in **69b** with cyclohexene yields the [2+2] photoproduct **70** (Scheme 1.12). The cyclobutanol ring opens spontaneously *via* a retro-aldol reaction producing the 1,5-diketone **71**. Moreover, this diketone can be cyclized under normal aldol addition reaction conditions to generate cyclohexenones such as **72** and **73**.

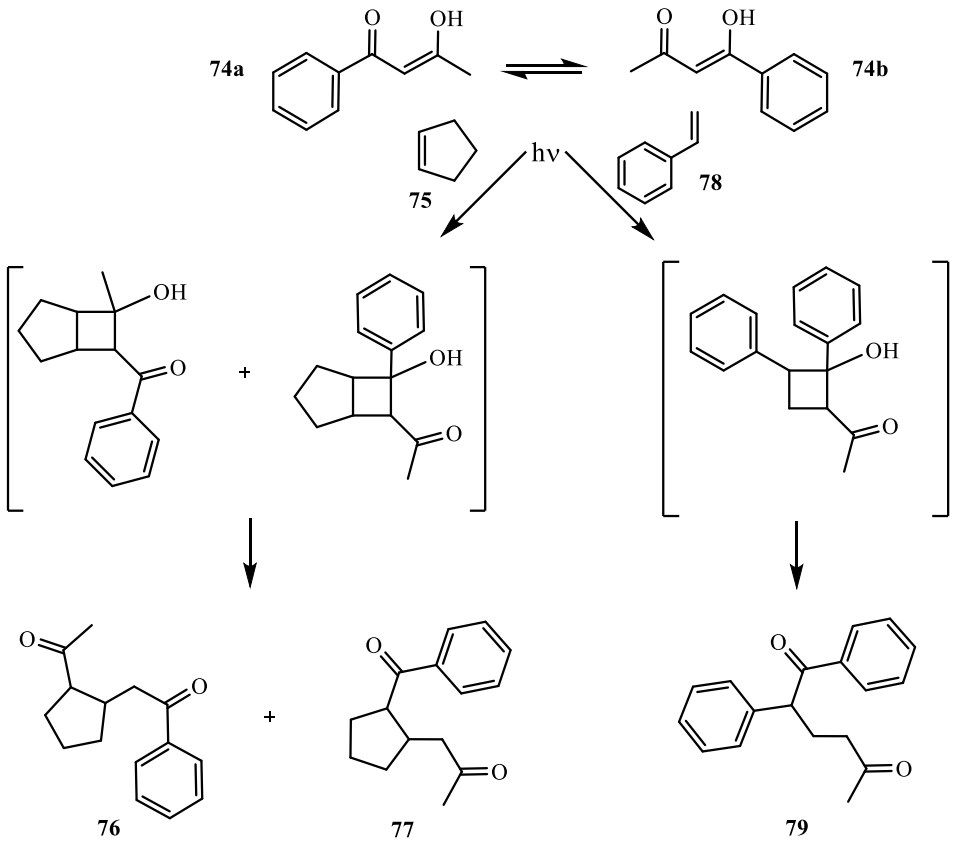


Scheme 1.12

Although this is a very intriguing way of forming a functionalized 6-membered ring from a β-diketone and a simple alkene, there are two obvious problems that must be addressed. First, although a number of simple β-diketones are commercially available, the preparations of specific 1,3-dicarbonyl compounds with additional functional groups can be challenging. A much larger problem is the regiochemical aspect of the cyclization step. As seen in Scheme 1.12, even when a symmetrical alkene reacts with a symmetrical dicarbonyl compound, two

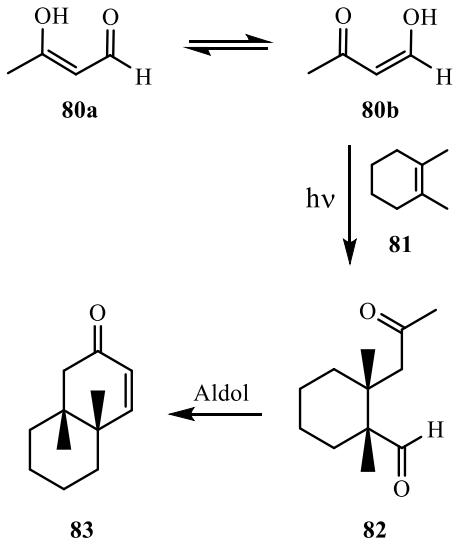
regioisomers can result in the second stage of the reaction depending on the direction of the aldol addition reaction. Furthermore, if an unsymmetrical alkene reacts with an unsymmetrical β-diketone, as many as eight regioisomers can be obtained. Perhaps this lack of regioselectivity has kept the de Mayo reaction from being a popular synthetic method.

The regioselectivity of the photocycloaddition step itself is also a complicated problem since there is limited data regarding cyclobutane ring formation.[50] Additionally, the direction of the enolization is usually not controllable when unsymmetrical β-diketones are used. For example, the reaction of benzoylacetone (**74**) with cyclopentene (**75**) gives photoproducts **76** (from **74a**) and **77** (from **74b**) in a 4:1 ratio in favor of the reaction with tautomer **74b**. However, when **74** is irradiated with styrene (**78**), a single product **79** from tautomer **74b** is observed (Scheme 1.13).[51]



Scheme 1.13

On the other hand, acetopyruvates [52] and β-ketoaldehydes[53] show a remarkable enol specificity in [2+2] photochemical reactions. Each of these substrates gives a single product in reactions with symmetrical alkenes (Scheme 1.14). These substrates do not incur the problem that is very evident in Scheme 1.12; namely, the direction of the aldol addition reaction.



Scheme 1.14

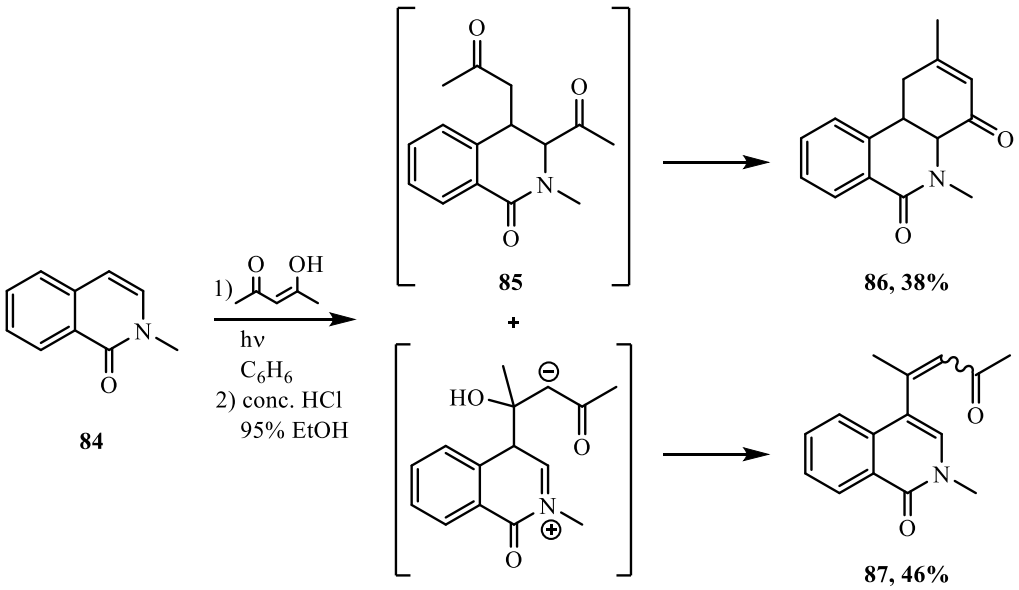
Although the syntheses of hippadine and pratosine using an intramolecular version of the de Mayo reaction as a key step would seem to be a risky strategy, this project benefitted from the model work of Chris Winslow, a former member of the Minter group.[54] As described in the following chapter, this approach proved to be viable after several problems that were not encountered in the model system were solved.

Chapter 2

Results and Discussion

2.1 Our Synthesis of the Galanthan Skeleton

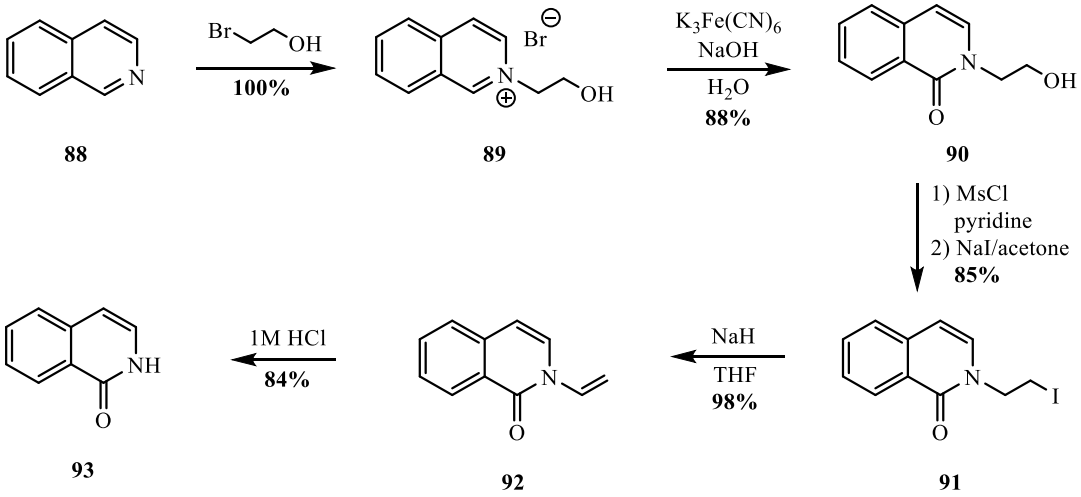
In his model study, Winslow used an intramolecular de Mayo photocyclization reaction to produce the key tricyclic precursor to the tetracyclic core of the galanthan ring system.[55] Since this required the use of an isocarbostyril double bond as the alkene component in the cyclization and no examples were found in the literature, a model reaction shown in Scheme 2.1 was carried out. The photolysis of *N*-methylisocarbostyril (**84**) with 2,4-pentanedione in benzene followed immediately by an acid-catalyzed aldol condensation gave a mixture of **86** (38%) and **87** (46%). The presence of **86** provided indirect proof of the existence of the 1,5-diketone **85** as a photoproduct.



Scheme 2.1

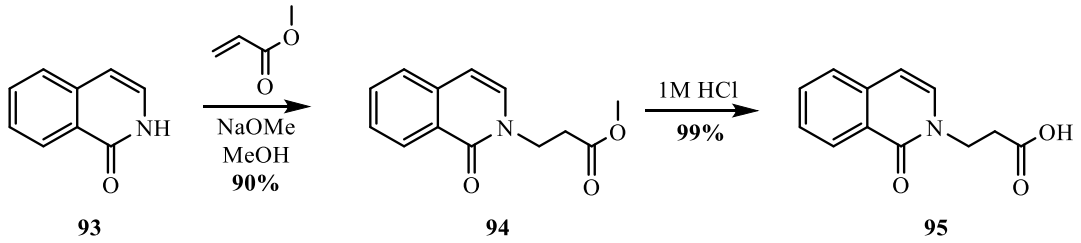
To carry out an intramolecular version of this process required an isocarbostyril with a six-carbon tether on nitrogen containing the requisite 1,3-dione unit. The synthesis began with isocarbostyril (**93**), which was prepared in our laboratory by Winslow using the five-step route

shown in Scheme 2.2 since purchasing the material would have been prohibitively expensive. Oxidation of the isoquinolinium salt **89** with potassium ferricyanide in alkaline solution gave **90**. Conversion of the hydroxyl group to the chloride followed by a Finkelstein reaction afforded the iodo derivative **91**. Finally, an elimination to produce *N*-vinylisocarbostyril (**92**) and removal of the vinyl group with HCl gave isocarbostyril (**93**) in 62% overall yield



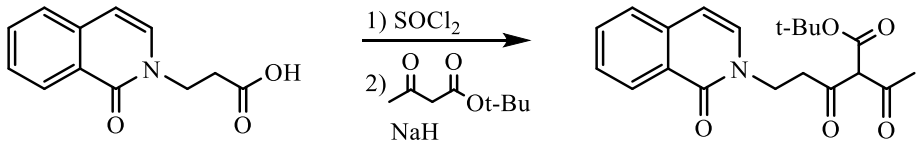
Scheme 2.2

In Winslow's work, three of the carbon atoms in the tether were attached using a Michael addition of isocarbostyril anion to methyl acrylate. The resulting ester **94** was hydrolyzed to **95** (Scheme 2.3). More recently, we found that the carboxylic acid **95** can be synthesized in only two steps from isoquinoline by preparing an isoquinolinium salt with 3-bromopropionic acid in triethylamine followed by oxidation of the salt with basic $K_3Fe(CN)_6$ and subsequent acidification of the reaction mixture (see Scheme 2.11).



Scheme 2.3

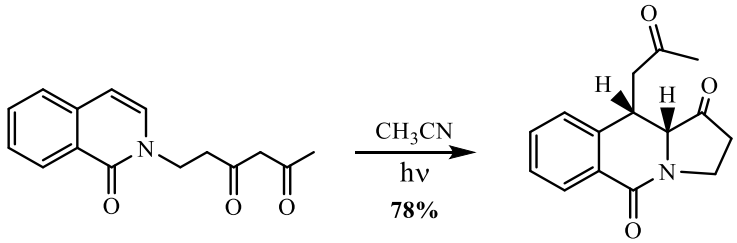
With the carboxylic acid **95** in hand, the synthesis of the 1,3-diketone necessary for the de Mayo photocyclization was undertaken. The acid chloride from a reaction of **95** with thionyl chloride in benzene was used to acylate the anion of *t*-butylacetoacetate in diethyl ether to give tricarbonyl **96** as the main product (Scheme 2.4). The product of O-acylation was minimized to less than 10% using ether as the solvent whereas the O-acylation product constituted a third of the mixture when THF was used.



95 **96**

Scheme 2.4

The β-diketone **97** was generated in 88% yield from **96** via a decarboxylation procedure with *p*-TsOH in refluxing benzene. Photolysis of this dione in acetonitrile with UV light from a 500-watt mercury arc lamp resulted in the isolation of **98** (Scheme 2.5) as a white crystalline solid in 78% yield after chromatographic purification. The relative stereochemistry of the vicinal tertiary hydrogens was established through 1-D and 2-D NMR studies.

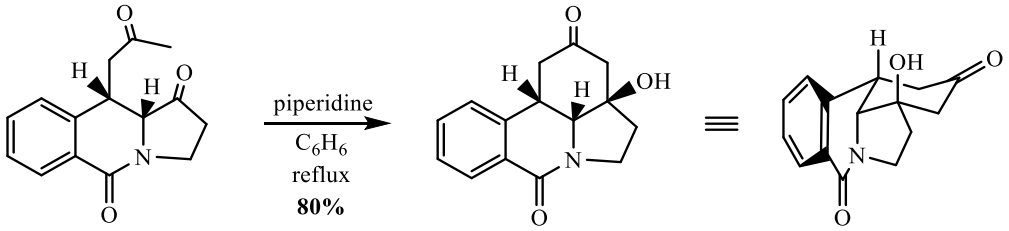


97 **98**

Scheme 2.5

Once the 1,5-diketone **98** was obtained, an aldol addition reaction under basic conditions was carried out. Various bases were surveyed; however, piperidine proved to be superior to LDA, methoxide and pyridine, which gave either no product at all or else mixtures of

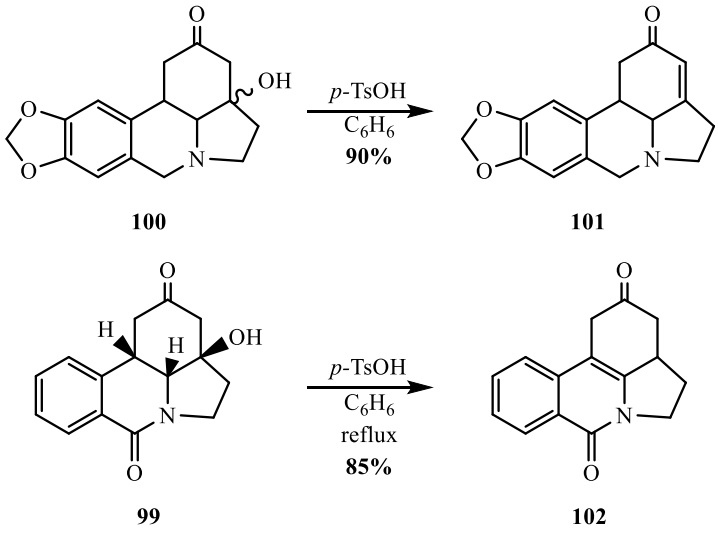
decomposition products. The relative stereochemistry of the three chiral centers in **99** was established by X-ray crystallography as shown in Scheme 2.6. This is not an unexpected result, however. If a molecular model is used to predict the intramolecular attack of the anion onto the carbonyl carbon, the approach of the anion can only occur from the *endo* face of the carbonyl due to the rigidity of the ring system.



98 **99**

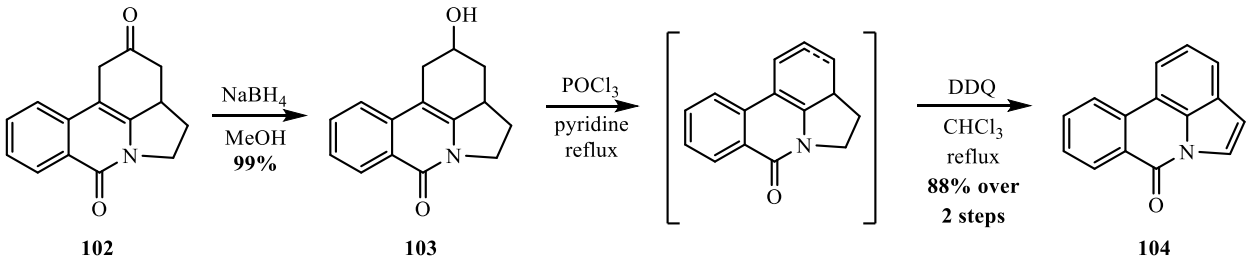
Scheme 2.6

The next step in the model study was the dehydration of **99**, which was expected to give the normal aldol condensation product—the α,β-enone. This was supported by Ganem's work on a similar system **100**, which was dehydrated under acidic conditions to give **101** (Scheme 2.7).[56] However, the dehydration of **99** produced the β,γ-enone **102** instead.[57] It is likely that the initially formed carbocation undergoes a spontaneous hydride shift before losing the proton to give a conjugated tetrasubstituted alkene thus making the two rings aromatic and providing greater stability to the system.



Scheme 2.7

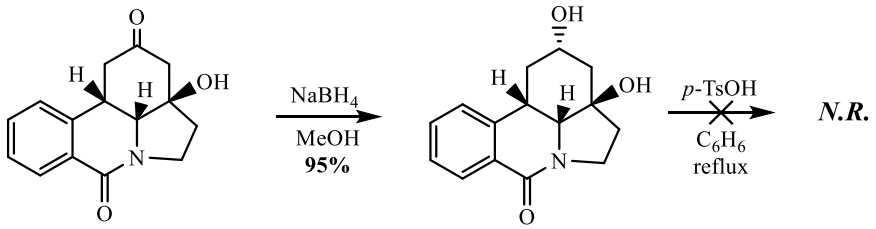
In order to complete the model study that Winslow had begun, a method for removing the oxygen atom from the C-ring and aromatizing both the C and D rings was required for producing pyrrolo[3,2,1-*de*]phenanthridone-7-one (**104**) (Scheme 2.8). Reduction of the ketone **102** with sodium borohydride gave **103** in quantitative yield. A dehydration reaction using *p*-TsOH under conditions identical to those described earlier was attempted, but only the starting material was recovered. Another common method for dehydrating alcohols using $POCl_3$ under basic conditions was selected as the best alternative.[58] As expected, this E2 pathway gave a mixture of two dienes that were not separated since both would give the same product in the subsequent aromatization reaction. Thus, oxidation of the crude diene mixture with either 2,3-dichloro-5,6-dicyanoquinone (DDQ) or 2,3,5,6-tetrachloroquinone (chloranil) in refluxing toluene afforded the pyrrolophenanthridone **104** in good yields after chromatographic purification (Scheme 2.8). Other less expensive oxidizing agents such as elemental sulfur or SeO_2 might be worth exploring in the future.



102 **103** **104**

Scheme 2.8

Since the aromatization reaction gives the same product regardless of the specific diene isomer precursor, we considered the possibility of preparing a diene mixture directly from the aldol addition product **99**. Reduction of the carbonyl in **99** with $NaBH_4$ produced **105** in quantitative yield (Scheme 2.9). However, attempts to dehydrate **105** using *p*-TsOH in refluxing benzene gave only the recovered starting diol.



99 **105**

Scheme 2.9

Interestingly, the reaction appeared to be completely stereoselective based on the ^{13}C spectrum consisting of only one set of lines. Based on the 3D structure of **99** (see Scheme 2.6), it was expected that the product would have both hydroxyl groups in a *trans*- configuration relative to one another. The *trans*- relationship of the hydroxyl groups was confirmed by X-ray analysis (Figure 2.1).

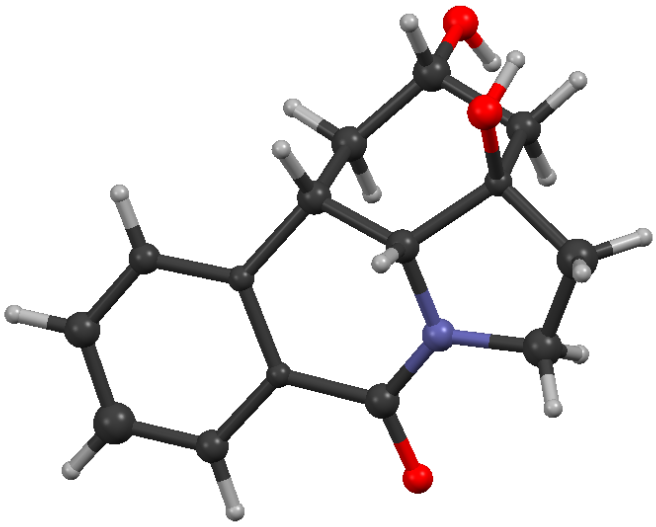
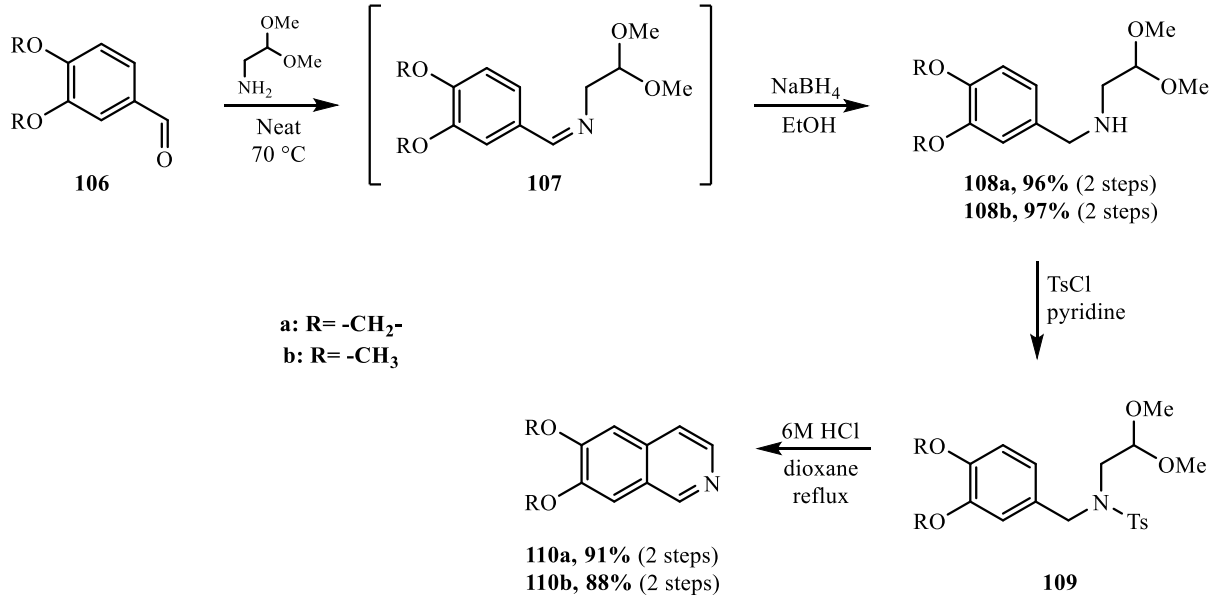


Figure 2.1 X-ray crystal structure of 105

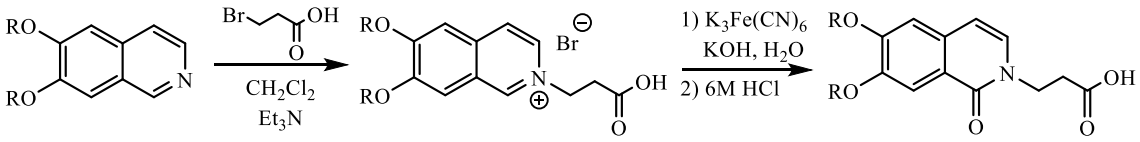
2.2 Synthesis of Hippadine and Pratosine

Extending the model study to the total syntheses of hippadine and pratosine required the availability of isoquinolines **110a** and **110b**, which were prepared from piperonal (**106a)** and vanillin methyl ether (**106b)**, respectively, using a modification of the Pomeranz-Fritsch isoquinoline synthesis[59-60] as shown in Scheme 2.10.



Scheme 2.10

The carboxylic acids **112a** and **112b** were obtained in two steps by the reaction of the 6,7-disubstituted isoquinoline with 3-bromopropionic acid and triethylamine followed by oxidation of the resulting isoquinolinium salts with alkaline potassium ferricyanide (Scheme 2.11). This process, reported by McElvain and Prill, was developed for the facile synthesis of *N*-substituted pyridones from pyridinium salts.[61] The alkaline ferricyanide oxidation reaction proceeds through a free-radical SET mechanism that produces 2 molecules of $K_2Fe(CN)_6$, where the iron has been reduced from Fe^{3+} to Fe^{2+}.



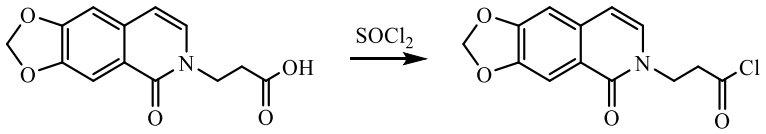
110a, R = -CH_2-
110b, R = -CH_3

111a, 100%
110b, 100%

112a, 90%
112b, 88%

Scheme 2.11

Subsequently, we attempted to follow the procedure established by Winslow to prepare dione **97**. Reaction of **112a** with thionyl chloride gave what was clearly the acid chloride **113** based on an IR spectral analysis. However, when attempting to react the acid chloride with the anion of *t*-butyl acetoacetate, we found that **113** was completely insoluble in both THF and ether, which are the solvents of choice for such acylation reactions (Scheme 2.12). To circumvent this issue, we turned to several alternatives to synthesize the 1,3-dicarbonyl compound.

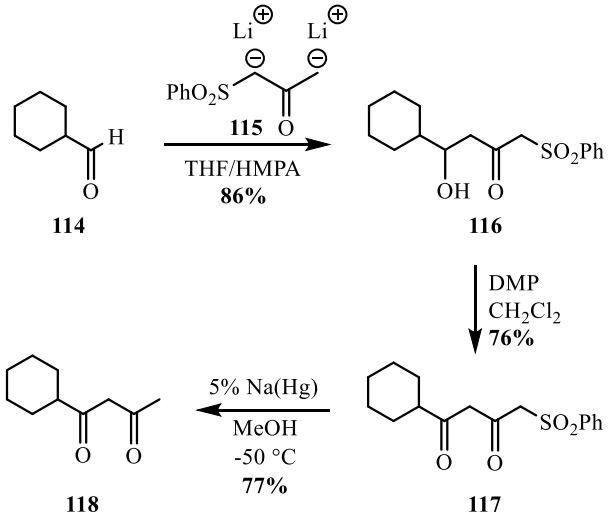


112a **113**

Scheme 2.12

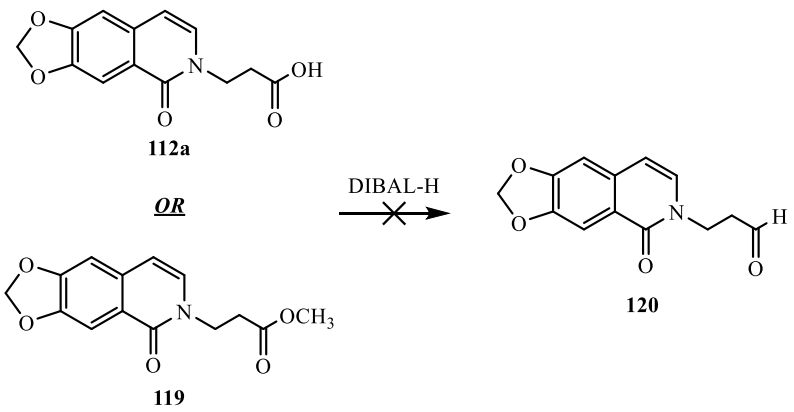
The reactions of aldehydes with acetone dianion equivalents such as the one shown in Scheme 2.13 had already been reported in the literature.[62] Oxidation of the resulting alcohol

(**116**) gave the sulfone **117**, which was desulfonated in good yield using sodium amalgam and methanol to provide **118**.



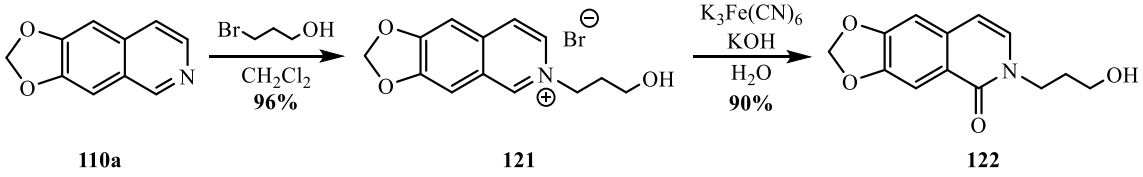
Scheme 2.13

To incorporate this strategy, aldehyde **120** (Scheme 2.14) was required. The first attempt to synthesize **120** followed a literature procedure involving a partial reduction of **112a** using Red-Al with a *t*-BuOH additive. When this method was applied to **112a**, the carboxylic acid was reduced all the way to the primary alcohol and the amide was reduced to the tertiary amine. DIBAL-H has also been used to reduce both carboxylic acids and esters to aldehydes.[63] Both **112a** and its methyl ester **119** were treated with DIBAL-H. Unfortunately, low yields of the aldehyde were obtained from the ester while the carboxylic acid did not react at all (Scheme 2.14).



Scheme 2.14

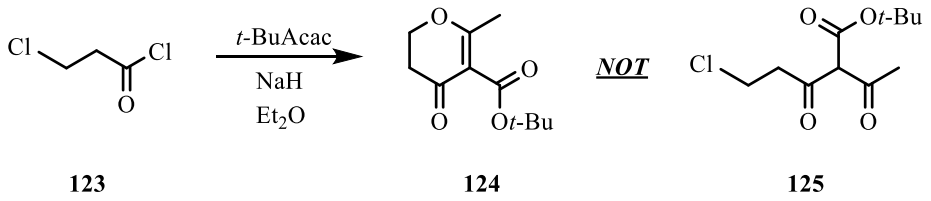
In other efforts to synthesize **120**, a selective oxidation of alcohol **122** (formed as shown in Scheme 2.15) to the aldehyde was attempted using PCC, the most common oxidant for this type of transformation.[64-65] Surprisingly, neither PCC nor PDC oxidized **122** to the desired aldehyde. The Swern oxidation has also been effective in converting alcohols to aldehydes; but when both the Swern and the Swern-Moffatt oxidation reactions failed, the aldehyde approach was abandoned.[66-67]



Scheme 2.15

A few attempts were made to synthesize the six-carbon tether as a unit before attaching it to the isocarbostyril. Since the literature contained no useful leads, classical acylation chemistry provided the possibility of using the reaction of 3-chloropropionyl chloride (**123**) with the anion of *t*-butyl acetoacetate to synthesize tricarbonyl compound **125**. However, the actual product was the result of an unexpected cyclization to the dihydropyranone **124** (Scheme 2.16). Furthermore, an attempt to acquire the diketone tether directly by the reaction of the dianion of

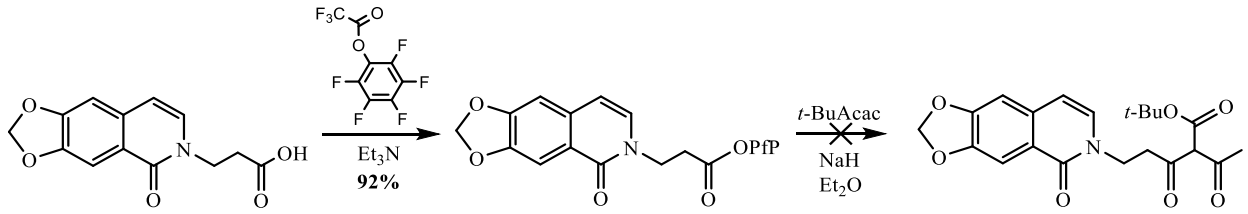
acetylacetone with either dibromo or diiodomethane led only to a complex mixture of unidentified products.



123 **124** **125**

Scheme 2.16

At this point, the original strategy that had worked so well in Winslow's model system was revisited with the idea of replacing the chlorine of the acid chloride with a different leaving group that might not present the same solubility problems. Accordingly, the first of three such groups—pentafluorophenoxy—was investigated by converting the carboxylic acid **112a** into the pentafluorophenyl ester **126** using pentafluorophenyl trifluoroacetate (Scheme 2.17). However, when **126** was used to acylate the anion of *t*-butyl acetoacetate in Et_2O, only the starting material was recovered. The second attempt used the simple methyl ester **119** prepared by the Fisher esterification of **112a**. Again, no reaction could be forced to occur between **119** and the anion of *t*-butyl acetoacetate.

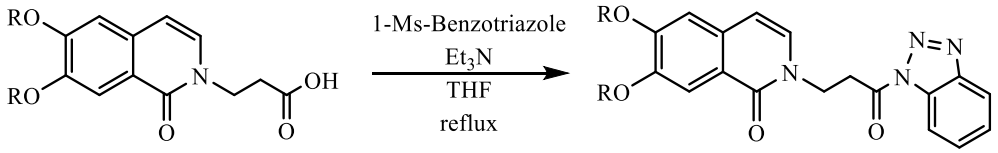


112a **126** **128a**

Scheme 2.17

Finally, the work of Katritzky and coworkers on the use of *N*-acylbenzotriazoles as the equivalents of acid chlorides provided a viable alternative.[68] Katritzky's procedure to prepare *N*-acylbenzotriazoles was not applicable since it used the acid chloride as an intermediate.

However, the recent work of Wilkerson showed that carboxylic acids whose acid chlorides were either too unstable or otherwise too difficult to synthesize could be easily transformed to their *N*-acylbenzotriazoles by treatment of the carboxylic acid with 1-(methanesulfonyl)benzotriazole in refluxing THF with triethylamine as a base.[69] Moreover, 1-(methanesulfonyl)benzotriazole can be formed by the reaction of 1*H*-benzotriazole with methanesulfonyl chloride in the presence of triethylamine as a base. To our delight, the *N*-acylbenzotriazole derivatives **127a** and **127b** were synthesized in good yields after a simple workup (Scheme 2.18). Both benzotriazolyl derivatives were sufficiently soluble in THF and provided reasonable substitutes for the acid chlorides.

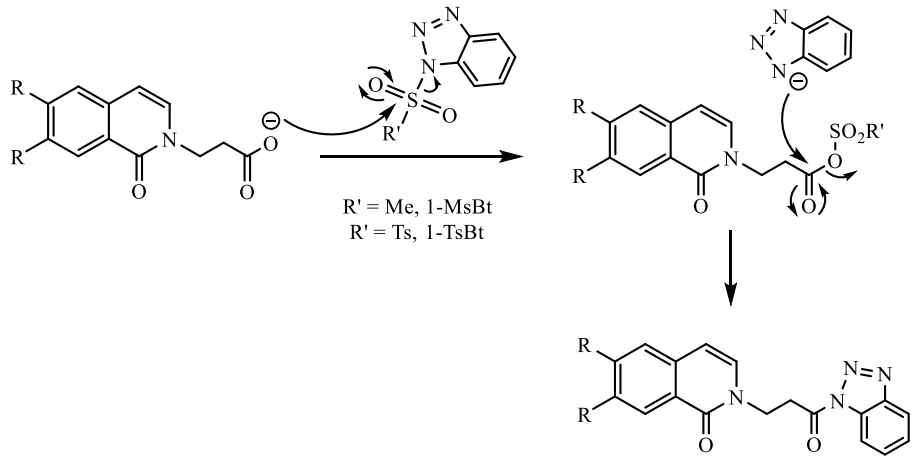


112a, R = -CH_2-
112b, R = -CH_3

127a, 94%
127b, 96%

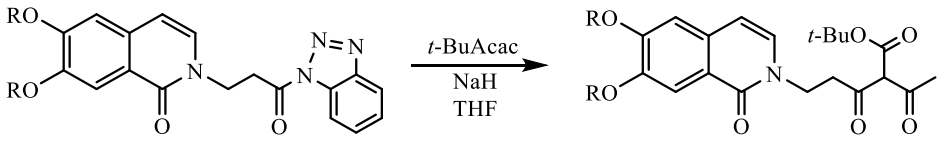
Scheme 2.18

We also attempted the syntheses of these acylbenzotriazole derivatives by using 1-(*p*-toluenesulfonyl)benzotriazole, which can be synthesized by using *p*-toluenesulfonyl chloride as the electrophile.[70] However, these reactions did not give any product. Mechanistic considerations suggest that the reaction proceeds through a mixed carboxylic sulfonic anhydride intermediate that undergoes attack by the benzotriazole anion at the carbonyl carbon (Scheme 2.19). The sterically demanding tosyl group may interfere with nucleophilic attack of the carboxylate during formation of the mixed anhydride. Previous reports in the literature have shown that carboxylic acids can be converted into their carboxylic sulfonic anhydrides by treatment with triethylamine and *p*-TsCl.[71] When we attempted this transformation with molecule **112a** and triethylamine using *p*-toluenesulfonyl chloride as the electrophile, no anhydride was produced.



Scheme 2.19

Once the *N*-acylbenzotriazole derivatives were obtained, the syntheses of compounds **128a** and **128b** were resumed. Winslow's model study showed that the reaction of **95** was significantly more selective for C-acylation when carried out in diethyl ether compared to THF. Fortunately, even though acylbenzotriazoles **127a** and **127b** were only partially soluble in THF and completely insoluble in ether, the C-acylation products were obtained as the major isomers in decent yields (Scheme 2.20). Simple decarboxylation reactions of **128a** and **128b** with *p*-TsOH in refluxing benzene gave the desired β-diketones in excellent yields present almost exclusively in their enol form..



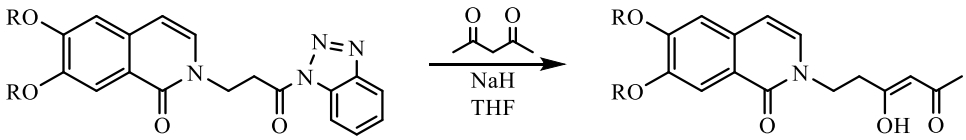
127a, R = -CH_2-
127b, R = -CH_3

128a, 54%
128b, 45%

Scheme 2.20

Additionally, we recently discovered that the 1,3-dicarbonyl compounds **129a** and **129b** can be obtained directly from the reaction of the *N*-acylbenzotriazole with the anion of 2,4-pentanedione in THF in high yields. This reaction was developed by Katritzky and coworkers,

who used a very complicated workup procedure with ammonium chloride, ammonium hydroxide and water.[72] We were able to obtain the product more easily by diluting the reaction mixture with CH_2Cl_2 and water followed by a simple extraction procedure. *N*-acetylbenzotriazole and the desired diketone were obtained as a solid mixture that could be dissolved in 4:1 hexanes/EtOAc and purified by filtration through a plug of silica. The *N*-acetylbenzotriazole moved through the silica while the diketone compound stayed at the origin. After the *N*-acetylbenzotriazole stopped coming through, washing the silica with ethyl acetate gave the desired 1,3-diketone upon removal of the solvent by rotary evaporation (Scheme 2.21).

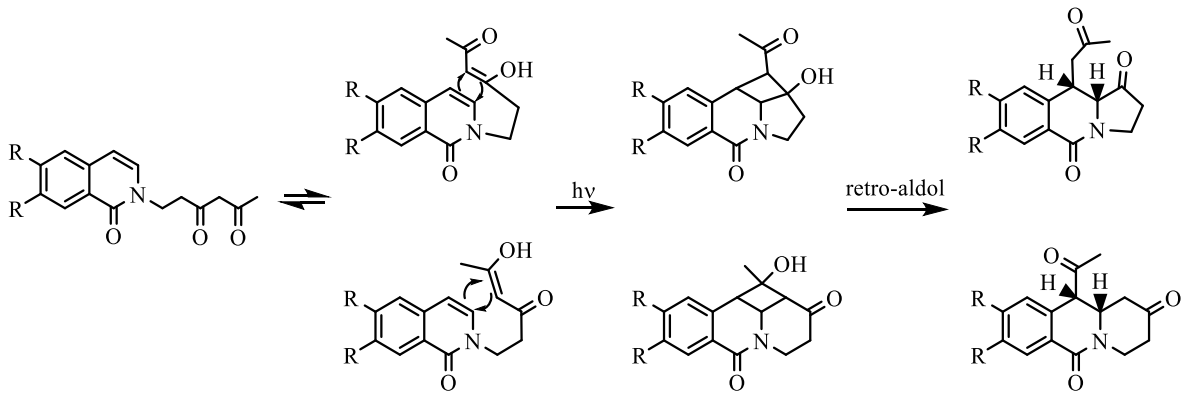


127a, R = -CH_2-
127b, R = -CH_3

129a, 89%
129b, 92%

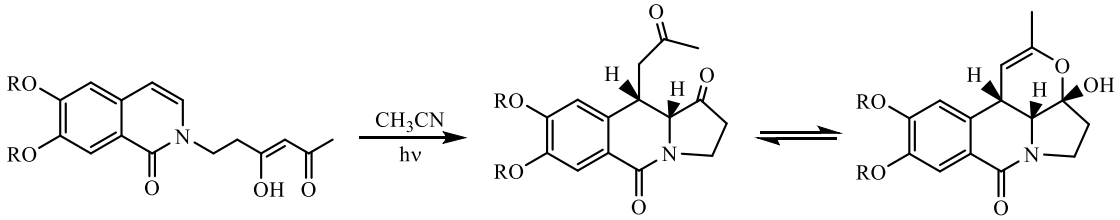
Scheme 2.21

Once the β-diketones were obtained, the intramolecular de Mayo photocyclization was carried out using the conditions already developed for the model system. The mechanism shown in Scheme 2.22 depicts the two possible parallel addition modes for the [2 + 2] cycloaddition step leading to the cyclobutanol intermediates. Each of these may undergo a retro-aldol process giving two possible 1,5-diketone final products. However, only one of these modes of reaction occurs due to a much higher rate of formation for the five-membered ring (between 2 and 3 orders of magnitude faster than six-membered ring formation). Thus, the de Mayo photocyclization reaction is completely regioselective.



Scheme 2.22

Dissolving the 1,3-diones **129a** and **129b** in dry acetonitrile followed by irradiation with UV light from a 500W medium pressure mercury arc lamp for 24 hours resulted in both cases in a precipitate that was expected to be the tricyclic diketone **130** (Scheme 2.23). Interestingly, the NMR analyses of these solids in DMSO-d_6 revealed proton spectra which lacked all of the signals that characterized the analogous photoproduct in the model system (see compound **98**, Scheme 2.5). Additionally, there were three proton signals in the aromatic region; however, the expected tricyclic products have only two aromatic protons. Furthermore, the ^{13}C NMR analyses indicated that the ketone carbonyl signals in the region of 195 ppm δ were absent. Instead, the amide carbonyl signal at approximately 160 ppm δ was the only carbonyl resonance.



129a, R = -CH_2-
129b, R = -CH_3

130a, 99%
130b, 99%

131a, R = -CH_2-
131b, R = -CH_3

Scheme 2.23

When the one-bond ^1H - ^{13}C correlation spectra were acquired (HSQC, heteronuclear single-quantum correlation), it was observed that one of the proton signals in the aromatic region

showed no correlation with a carbon atom. This is consistent with a hydrogen atom bonded to a heteroatom such as in OH and NH groups, but the expected photoproducts **130a** and **130b** do not possess such functions.

After extensive NMR studies including 1-D carbon and proton spectra as well as a gamut of 2-D spectra including COSY, HSQC and HMBC experiments (see Appendix), these molecules were identified as the tetracyclic hemiketals **131a** and **131b**. Additionally, the structure of **131b** has been confirmed by X-ray crystal analysis (Figure 2.2). These compounds represent masked forms of the 1,5-diones **130a** and **130b**. When the NMR sample of hemiketal **131b** was heated for a few hours at 45 °C, the molecule transformed to the open-chain diketone **130b** whose NMR characteristics in the alkyl region matched those of the model system. We speculate that the hemiketals and their corresponding diketones are in equilibrium during the reaction; since these hemiketals are insoluble in acetonitrile and are effectively removed from the equilibrium mixture by precipitation, the equilibrium shifts according toward the hemiketals according to Le Chatelier's principle.

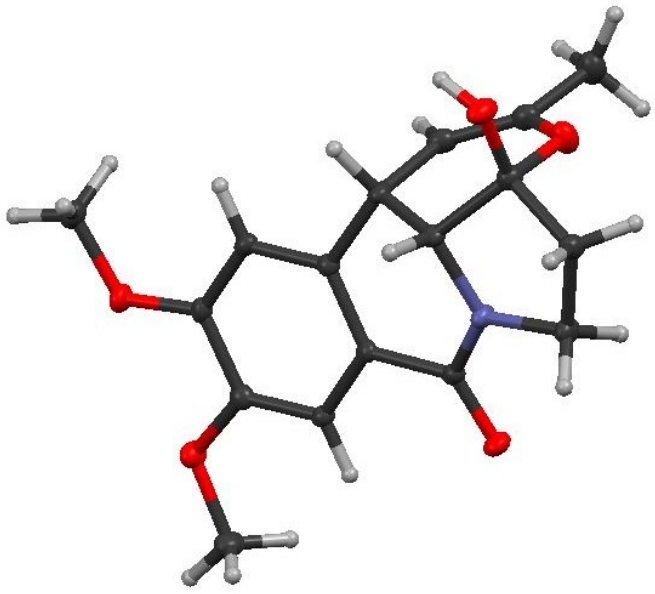
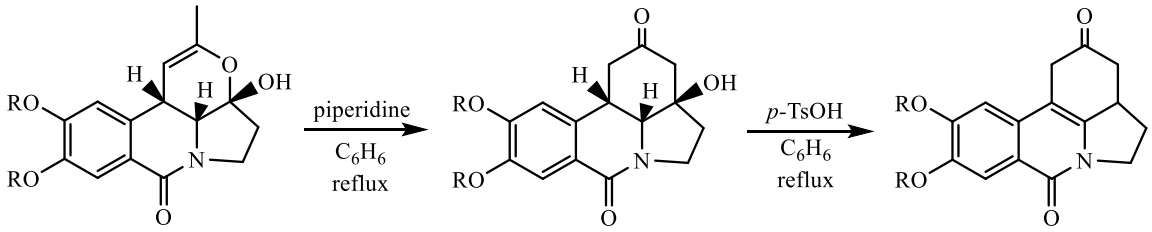


Figure 2.2 X-ray crystal structure of 131b

It might be interesting to reinvestigate this reaction in the model system. No precipitation was observed during the photolysis of **97**, but this does not rule out the possibility of a similar equilibrium mixture if both compounds are soluble in acetonitrile. Moreover, the purification of the 1,5-diketone **98** was done using silica gel which is slightly acidic and could have reversed the cyclization to give **98** as the only observed product.

Although the photoproducts were the cyclic hemiketals rather than 1,5-diones, the basic conditions of the subsequent aldol addition reaction were expected to open the ring and produce the diones *in situ*. To our delight, the reactions of **131a** and **131b** with piperidine in refluxing benzene afforded the aldol addition products **132a** and **132b**, respectively, in excellent yields after a simple chromatographic purification. The acid-catalyzed dehydrations of **132a** and **132b** with *p*-TsOH in refluxing benzene gave the expected dehydration products **133a** and **133b**, respectively, in high purity just as in the model system (Scheme 2.24).



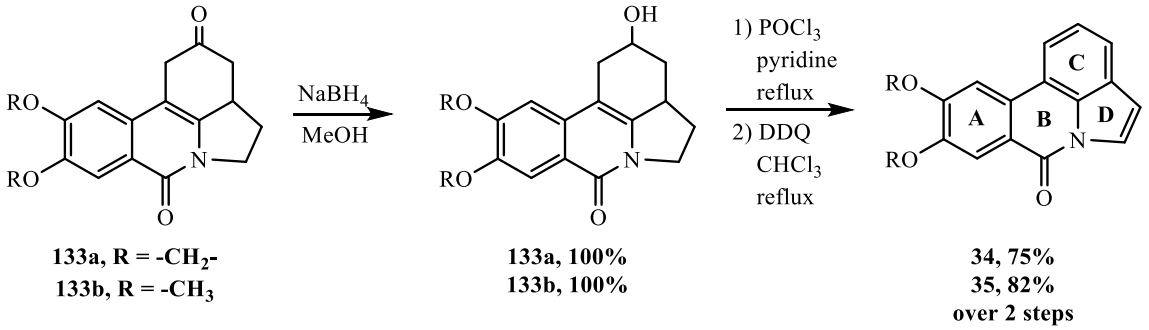
131a, R = -CH_2-
131b, R = -CH_3

132a, 90%
132b, 87%

133a, 93%
133b, 94%

Scheme 2.24

The aromatization process began with the reductions of **133a** and **133b** with $NaBH_4$ in MeOH to give the corresponding alcohols **134a** and **134b** in quantitative yields. Dehydration reactions with $POCl_3$ and pyridine followed by oxidations with DDQ in refluxing chloroform gave pure samples of the desired alkaloids hippadine (**34**) and pratosine (**35**) after chromatographic purification (Scheme 2.25).



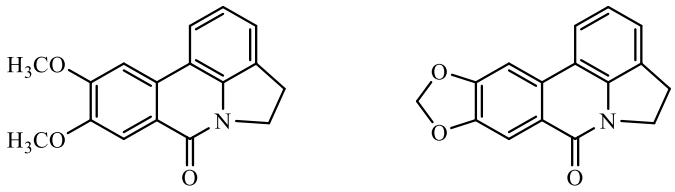
133a, R = -CH_2-
133b, R = -CH_3

133a, 100%
133b, 100%

34, 75%
35, 82%
over 2 steps

Scheme 2.25

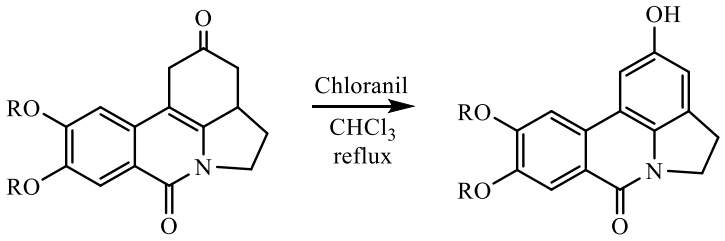
The aromatization reaction in the model system (Scheme 2.8) could be accomplished using either DDQ or chloranil, which is a milder and less expensive reagent. However, attempts to use chloranil to synthesize **34** and **35** led to products in which the D-ring was not oxidized. These two materials were identified as oxoassoanine (**135**) and anhydrolycorinone (**51**) from their NMR analyses,[36] which revealed a triplet-triplet pattern characteristic of an ethylene bridge (Figure 2.3). Since these two compounds are also natural products, the unexpected selectivity of the chloranil oxidation has a practical application.



135 **51**

Figure 2.3. Structures of oxoassoanine (135) and anhydrolycorinone (51)

Considering that the ketones **133a** and **133b** exist in their enol forms to a negligible but finite extent, we investigated the possibility of aromatizing the C-ring to give a phenolic product. In fact, the reactions of **133a** and **133b** with chloranil in refluxing chloroform gave **136a** and **136b** in high yields (Scheme 2.26).

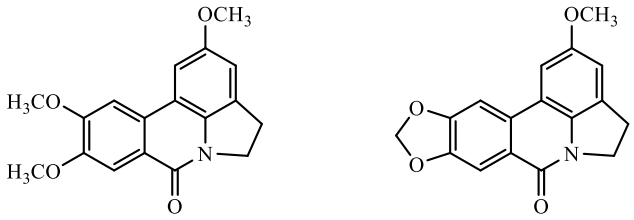


133a, R = -CH_2-
133b, R = -CH_3

136a, 91%
136b, 99%

Scheme 2.26

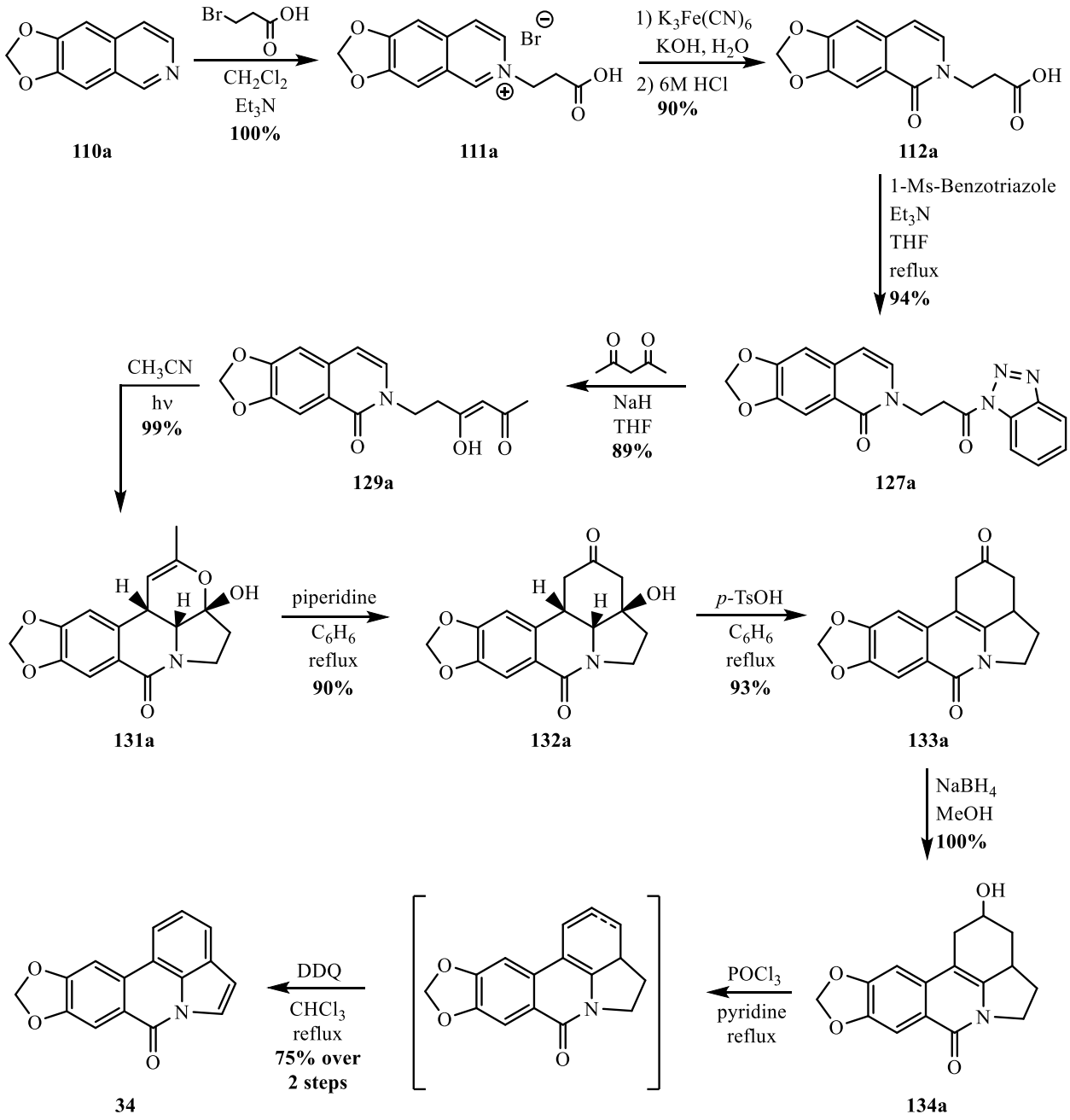
To obtain the fully aromatized products, the more aggressive oxidant DDQ was also tested. However, these reactions gave only decomposition products. We are not aware of any other examples of the oxidation of a β,γ-cyclohexenone to a phenol. This allows for an easy route to lycosprenine (**137**), an alkaloid isolated recently from the bulbs of *Lycoris sprengeri*,[30] and 2-methoxyanhydrolycorinone (**138**),[73] which is an interesting compound but not a natural product (Figure 2.4).



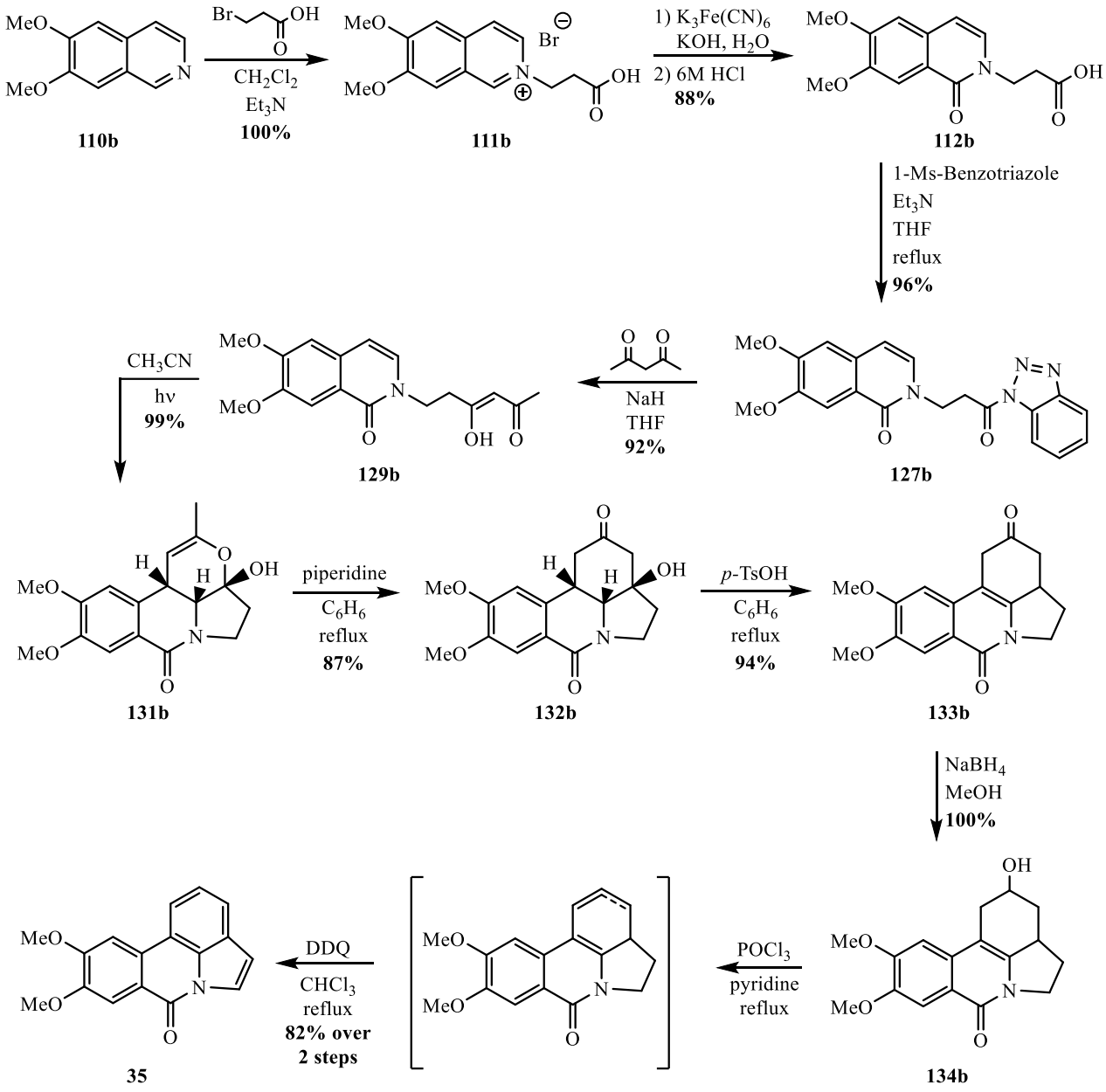
137 **138**

Figure 2.4. Structures of lycosprenine (137) and 2-methoxyanhydrolycorinone (138)

In summary, the alkaloids hippadine (**34**) and pratosine (**35**) have been prepared in overall yields of 46% and 52%, respectively, from the corresponding isoquinolines using the 10-step total synthetic routes shown in Schemes 2.27 and 2.28.


Br
OH
O
CH_2Cl_2
Et_3N
100%
1) $K_3Fe(CN)_6$
KOH, H_2O
2) 6M HCl
90%
110a
111a
112a
1-Ms-Benzotriazole
Et_3N
THF
reflux
94%
CH_3CN
hν
99%
NaH
THF
89%
129a
127a
piperidine
C_6H_6
reflux
90%
p-TsOH
C_6H_6
reflux
93%
131a
132a
133a
$NaBH_4$
MeOH
100%
DDQ
$CHCl_3$
reflux
75% over
2 steps
$POCl_3$
pyridine
reflux
34
134a

Scheme 2.27


110b
111b
112b
1-Ms-Benzotriazole
Et3N
THF
reflux
96%
127b
NaH
THF
92%
129b
CH3CN
hν
99%
131b
piperidine
C6H6
reflux
87%
132b
p-TsOH
C6H6
reflux
94%
133b
NaBH4
MeOH
100%
134b
POCl3
pyridine
reflux
DDQ
CHCl3
reflux
82% over
2 steps
35

Scheme 2.28

Chapter 3

Experimental Section

3.1 Instrumentation, Solvents, and Reagents

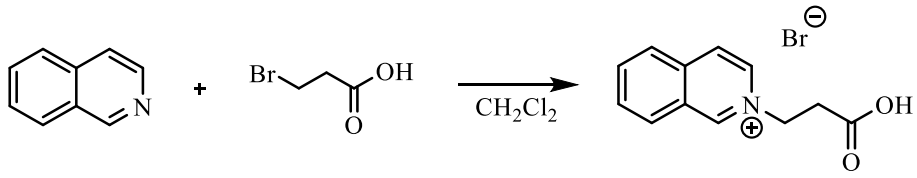
NMR spectra were acquired with a Bruker Avance-400 NMR spectrometer (operating at 400.03 MHz for ^{1}H and 100.24 MHz for ^{13}C) or a Varian Inova 400 NMR spectrometer (operating at 399.97 MHz for ^{1}H and 100.58 MHz for ^{13}C) using TMS as an internal standard and $CDCl_3$ as the solvent unless otherwise indicated. Chemical shifts are reported in ppm (δ) and multiplicity is reported as: singlet (s), broad singlet (bs), doublet (d), broad doublet (bd), triplet (t), quartet (q), and multiplet (m). Coupling constants (J) are reported in Hertz (Hz). Column chromatography was performed using Sigma-Aldrich silica gel (32-63 μm) and thin-layer chromatography was done using Dynamic Adsorbents silica gel (200 μm) on polyester-backed TLC plates coated with fluorescent indicator.

Most reagents were obtained from Sigma-Aldrich Chemical Company, Alfa-Aesar Chemical Company, or Acros Chemical Company and were used as acquired without further purification. Tetrahydrofuran and acetonitrile were acquired from a Solvent Purification System and used immediately. All reactions were run under a nitrogen atmosphere unless otherwise specified.

X-ray diffraction data was collected on a Bruker D8 Quest diffractometer equipped with a Photon 100 CMOS detector and Kα radiation (λ = 0.71073 Å) at 100(1) K under the flow of liquid nitrogen using Oxford Cryosystem. The Bragg intensities of data sets consisting of ω and f scans were indexed using APEX3 package whereas the data reduction and absorption corrections were carried out with the SAINT and SADABS packages respectively. The space group was determined using XPREP through analysis of the Laue symmetry and systematic

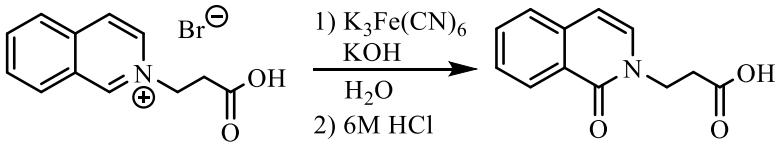
absences. Structures were solved by the intrinsic phasing method using the SHELXT software. The solution of each compound with the best figure of merit revealed the coordinates of all non-hydrogen atoms which were refined using SHELXL program embedded in the OLEX2 package. The hydrogen atoms were located by the difference Fourier analysis and during the structure refinement. The atomic displacement parameters of hydrogen atoms were treated isotropically and non-hydrogen atoms were anisotropically refined using the full-matrix least squares procedure on F2 (using all data). The hydrogen atoms attached to the carbon atoms were allowed to ride on their carrying atoms, whereas those attached to heteroatoms were refined freely.

3.2 General Procedures



88 **139**

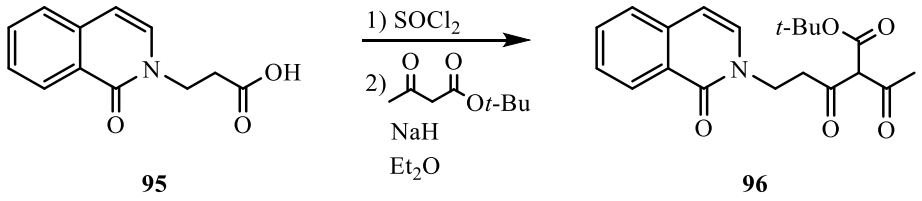
2-(2-Carboxyethyl)isoquinolin-2-ium bromide (139). A solution of isoquinoline (**88)** (8.0 g, 62 mmol) and 3-bromopropionic acid (10.4 g, 68 mmol) in 100 mL of CH_2Cl_2 was stirred for 2 days at room temperature after which time a copious solid had formed. The precipitate was isolated by filtration through a Buchner funnel and rinsed with CH_2Cl_2 to afford 18 g of crude **139** as a white solid that was sufficiently pure by NMR analysis to be used in the next step without further purification. ^{1}H NMR (DMSO-d_6) δ 3.19 (t, J = 6.7 Hz, 2H), 4.92 (t, J = 6.7 Hz, 2H), 8.09 (ddd, appears as td, J = 7.6, 1.2 Hz, 1H), 8.28 (ddd, appears as td, J = 7.6, 1.2 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H), 8.50 (d, J = 8.3 Hz, 1H), 8.60 (d, J = 6.8 Hz, 1H), 8.83 (dd, J = 6.8, 1.2 Hz, 1H), 10.13 (s, 1H), 12.74 (s, 1H).



139 **95**

3-(1-Oxoisoquinolin-2(1*H*)-yl)propanoic acid (95). The isoquinolinium salt **139** (15.0 g, 53.2 mmol) was dissolved in 70 mL of water and the resulting solution was cooled to 0 °C. Two solutions, one containing potassium ferricyanide (70 g, 212 mmol) in 200 mL of water and another containing KOH (24 g, 324 mmol) in 70 mL of water, were added simultaneously over one hour at such rate that all the KOH solution was added when only half of the ferricyanide solution had been added. Once the addition was complete, the reaction mixture was stirred overnight at room temperature open to the atmosphere after which 6M HCl was added dropwise

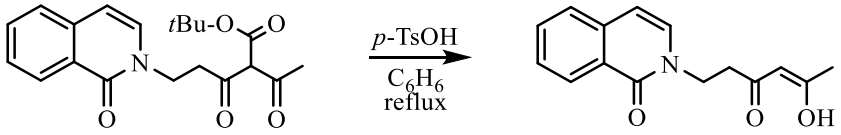
until the pH of the solution was about 4. The product was extracted with CH_2Cl_2 (3 x 125 mL) and the organic extracts were combined and dried over Na_2SO_4. Removal of the solvents by rotary evaporation followed by pumping under high vacuum afforded a crude solid that was recrystallized from benzene to give 10.0 g (86.9%) of pure **95**: mp 128-130 °C (lit.[55] 127-129 °C). ^{1}H NMR (DMSO-d_6) δ 2.71 (t, J = 6.8 Hz, 2H), 4.15 (t, J = 6.8 Hz, 2H), 6.61 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.51 (dd, J = 7.4, 1.3 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.72 (dd, J = 7.4, 1.3 Hz, 1H), 8.22 (ddd, J = 7.4, 1.3, 0.6 Hz, 1H), 12.41 (s, 1H).



95 **96**

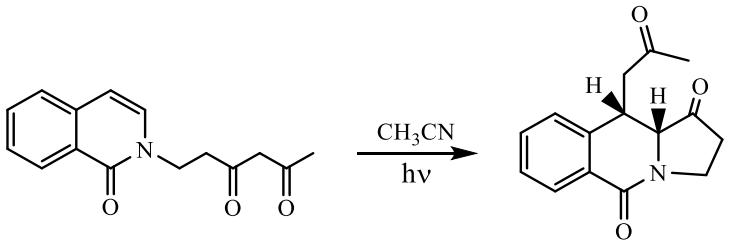
***tert*-Butyl-2-acetyl-3-oxo-5-(1-oxoisoquinolin-2(1*H*)-yl)pentanoate (96).** A solution of the carboxylic acid **95** (2.84 g, 13.1 mmol) and thionyl chloride (5.5 g, 46.2 mmol) in 60 mL of dry benzene was stirred at room temperature for 48 hours. The removal of volatiles by rotary evaporated followed by pumping at high vacuum gave a residual oil that was re-dissolved in 100 mL of dry Et_2O and cooled to 0 °C. In a separate flask, NaH (1.3 g of 60% dispersion in mineral oil, 32.5 mmol) was washed 3 times with hexanes to remove the mineral oil followed by the addition of 80 mL of dry Et_2O. *tert*-Butyl acetoacetate (6.21 g, 39.3 mmol) was added dropwise to the cooled slurry of NaH and allowed to stir at that temperature for 10 minutes. The acid chloride was added via cannula, using positive nitrogen pressure, into the clear solution of the sodium salt of *tert*-butyl acetoacetate over a 10-minute period. After the addition was complete, the solution was warmed to room temperature and stirred for 1 hour. The entire lot was poured into 100 mL of 1M HCl previously cooled in an ice bath. The mixture was stirred for 15 minutes followed by the removal of the organic solvents by rotary evaporation. The resulting aqueous slurry was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were washed

with 50 mL of saturated $NaHCO_3$ followed by 50 mL of brine. The organic layer was separated, dried over Na_2SO_4, and rotary evaporated to remove volatiles followed by pumping at high vacuum. Flash column chromatographic purification of the residual material (silica gel, 3:1 hexanes/EtOAc) gave 4.3 g (92%) of the dione **96** as a white solid: mp 88-90 °C (lit.[55] 89-91 °C). ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H), 2.32 (s, 3H), 3.27 (t, J = 6.5 Hz, 2H), 4.33 (t, J = 6.5 Hz, 2H), 6.47 (d, J = 7.4 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.49 (m, 2H), 7.64 (dd, J = 7.6, 1.3 Hz, 1H), 8.42 (ddd, J = 7.6, 1.3, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 28.2, 37.1, 45.6, 82.0, 105.9, 110.8, 125.9, 126.2, 126.7, 127.7, 132.1, 132.5, 137.1, 162.1, 166.0, 193.6, 196.4.



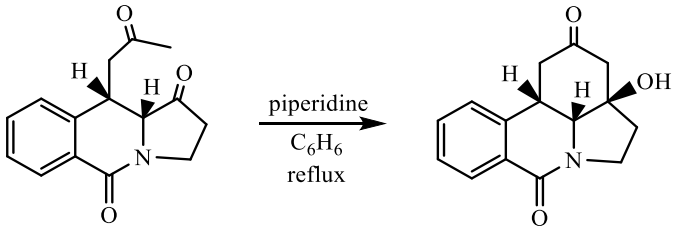
96 **97**

6-(1-Oxoisoquinolin-2(1*H*)-yl)hexane-2,4-dione (97). The dione **96** (1.89 g, 5.3 mmol) was dissolved in 100 mL of benzene and *p*-toluenesulfonic acid monohydrate (1.1 g) was added. The mixture was heated at reflux for 2 hours. After the heating period was over, the reaction mixture was washed with 50 mL of dilute $NaHCO_3$ followed by 50 mL of brine and dried over Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove all the volatiles gave 2.1 g of semi-solid product. Flash column chromatography (silica gel, 2:1 hexanes/EtOAc) afforded 1.20 g (88.2%) of 1,3-diketone **97** as a white solid: mp 63-65 °C (lit.[55] 62-63 °C). ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.87 (t, J = 6.5 Hz, 2H), 4.30 (t, J = 6.5 Hz, 2H), 5.49 (s, 1H), 6.48 (d, J = 7.3 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.51 (m, 2H), 7.65 (dd, J = 7.4, 1.4 Hz, 1H), 8.43 (ddd, J = 7.4, 1.4, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.4, 37.4, 45.9, 100.9, 105.9, 125.9, 126.1, 126.8, 127.6, 132.2, 132.5, 137.2, 162.2, 190.1, 191.8.



97 **98**

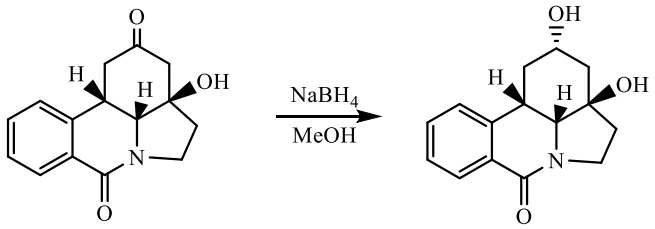
(10*S*,10a*R*)-10-(2-Oxopropyl)-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinoline-1,5-dione (98). The diketone **97** (100 mg, 0.39 mmol) was dissolved in 10 mL of dry acetonitrile and the mixture was sealed in a test tube under a nitrogen atmosphere. The solution was irradiated with a medium pressure mercury lamp through a Pyrex filter at room temperature for 2 hours. The solvent was removed by rotary evaporation followed by pumping at high vacuum. Flash column chromatography (silica gel, 2:1 EtOAc/hexanes) gave 78 mg (78%) of product **98** as a white solid: mp 183-184 °C (lit.[55] 184-185 °C). ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H), 2.47 (dd, J = 16.2, 3.6 Hz, 1H), 2.63-2.73 (m, 1H), 2.69 (dd, J = 16.2, 9.7 Hz, 1H), 2.79 (dddd, J = 19.4, 8.8, 4.1, 0.7 Hz, 1H), 3.76 (dddd, appears as tdd, J = 12.5, 8.8, 0.7 Hz, 1H), 3.92 (ddd, J = 9.7, 4.1, 3.6 Hz, 1H), 4.24 (d, J = 4.3 Hz, 1H), 4.41 (dddd, J = 12.5, 9.7, 3.6, 0.7 Hz, 1H), 7.39 – 7.48 (complex, 3H), 8.09 (dd, J = 8.5, 2.0 Hz, 1H).



98 **99**

(3a*R*,3a^1*R*,11b*S*)-3a-Hydroxy-3,3a,3a^1,4,5,11b-hexahydro-1*H*-pyrrolo[3,2,1-*de*] phenanthridine-2,7-dione (99). A solution containing the photoproduct **98** (100 mg, 0.39 mmol) and piperidine (170 mg) in 15 mL of benzene was heated at reflux for 21 hours. The volatiles were removed by rotary evaporation followed by pumping at high vacuum. Flash

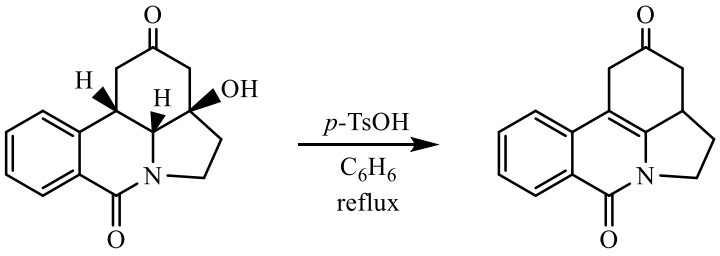
column chromatography (silica gel, 10:1 EtOAc/hexanes) gave 77 mg (77%) of the tetracyclic product **99** as an off-white solid: mp 230 °C (decomp.) (lit.[55] 235 °C (decomp.)). ^{1}H NMR (DMSO-d_6) δ 1.82 – 1.97 (complex, 2H), 2.15 (ddd, J = 14.4, 5.3, 1.8 Hz, 1H), 2.32 (bd, J = 14.4 Hz, 1H), 2.42 (dd, J = 14.4, 13.2 Hz, 1H), 2.77 (d, J = 14.4, 1H), 3.54 (ddd, J = 13.2, 5.3, 4.8 Hz, 1H), 3.62 (ddd, J = 12.1, 9.2, 8.0 Hz, 1H), 3.73 (ddd, J = 12.1, 9.2, 2.8 Hz, 1H), 3.83 (d, J = 4.7 Hz, 1H), 5.67 (s, 1H), 7.39 – 7.43 (complex, 2H), 7.52 (ddd, J = 8.1, 6.8, 1.5 Hz, 1H), 7.91 (dd, J = 8.1, 1.5 Hz, 1H).



99 **105**

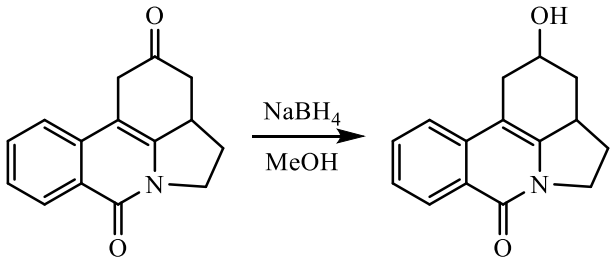
(2*S*,3a*R*,3a^1*R*,11b*S*)-2,3a-Dihydroxy-1,2,3,3a,3a^1,4,5,11b-octahydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (105). A solution of the aldol addition product **99** (100 mg, 0.39 mmol) in 10 mL of MeOH was stirred as solid $NaBH_4$ (40 mg, 1 mmol) was added. The progress of the reaction was monitored by TLC (silica, 10:1 EtOAc/hexanes). Once the starting material disappeared and the TLC showed the appearance of only one product, the entire lot was rotary evaporated to remove all volatiles. Water (2 mL) was added to quench the reaction, and the insoluble solid was isolated by filtration through a Buchner funnel. The solid was dried by pumping at high vacuum affording 83 mg (83%) of diol **105** as an off-white solid: mp 188-190 °C . ^{1}H NMR ($CDCl_3$) δ 1.37 (dd, appears as q, J = 12.8, 2H), 1.54 (dd, J = 13.5, 11.7 Hz, 1H), 1.97 – 2.19 (complex, 5H), 3.22 (dt, J = 12.8, 4.7 Hz, 1H), 3.58 (ddd, J = 18.8, 11.1, 7.6 Hz, 1H), 3.71 (bd, J = 4.7 Hz, 1H), 3.91 (dd, J = 12.5, 9.6 Hz, 1H), 4.10 (tt, J = 11.5, 3.7 Hz, 1H), 7.24 (ddd, J = 7.5, 2.3, 0.6 Hz, 1H), 7.38 (td, J = 7.6, 2.3 Hz, 1H), 7.48 (td, J = 7.5,

1.4 Hz, 1H), 8.08 (dd, J = 7.6, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.3, 35.8, 36.1, 36.4, 42.1, 61.8, 66.6, 76.3, 127.3 (two signals), 127.9, 128.7, 132.1, 141.9, 163.3.



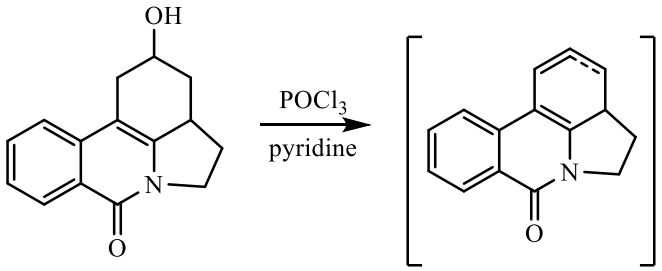
99 **102**

3,3a,4,5-Tetrahydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine-2,7-dione (102). A solution containing 100 mg (0.39 mmol) of alcohol **99** and 20 mg (0.12 mmol) of *p*-toluenesulfonic acid monohydrate in 25 mL of benzene was heated at reflux for ~3 hours while being monitored by TLC (silica, 2:1 EtOAc/hexanes). After TLC showed the disappearance of the starting material and formation of a single product, the reaction mixture was cooled to room temperature and washed with saturated $NaHCO_3$ (2 x 10 mL). The organic layer was separated, dried over Na_2SO_4 and rotary evaporated. Remaining volatiles were removed by pumping at high vacuum to give 135 mg of a light brown oil. Flash column chromatography (silica gel, 2:1 EtOAc/hexanes) gave 80 mg (86%) of **102** as a white semi-solid. ^{1}H NMR ($CDCl_3$) δ 1.97 (complex, 1H), 2.52 (dd, J = 14.5, 12.5 Hz, 1H), 2.63 (m, 1H), 3.05 (dd, J = 14.5, 5.3 Hz, 1H), 3.44 (dd, J = 21.2, 2.1 Hz, 1H), 3.54 (m, 1H), 3.63 (dd, J = 21.2, 1.4 Hz, 1H), 3.99 (ddd, J = 12.4, 11.6, 6.2 Hz, 1H), 4.56 (dd, J = 12.4, 8.4 Hz, 1H), 7.45 (bd, J = 8.0 Hz, 1H), 7.52 (ddd, J = 8.0, 7.2, 1.3 Hz, 1H), 7.72 (ddd, J = 8.0, 7.2, 1.4 Hz, 1H), 8.50 (dd, J = 8.0, 0.9 Hz, 1H)



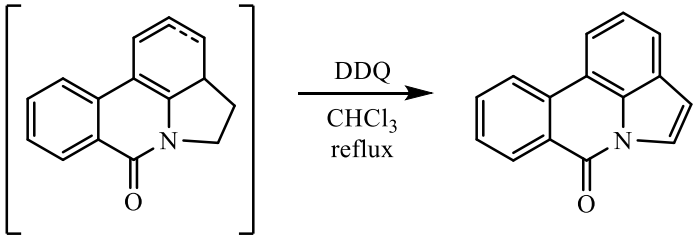
102 **103**

2-Hydroxy-1,2,3,3a,4,5-hexahydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (103). The ketone **102** (100 mg, 0.42 mmol) was dissolved in 5 mL of methanol and solid $NaBH_4$ (50 mg, 1.3 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred at room temperature and monitored by TLC (silica, 4:1 EtOAc/hexanes) until the starting material disappeared and a single product was observed. The methanol was removed by rotary evaporation affording a semi-solid. A small amount of water was added and the insoluble solid was isolated by filtration through a Buchner funnel. Residual volatiles were removed by pumping at high vacuum to give 90 mg (89%) of alcohol **103** as a white solid deemed pure by NMR analysis and suitable for the next step without further treatment. ^{1}H NMR ($CDCl_3$) δ 1.60 (dd, J = 23.2, 11.5 Hz, 1H), 1.82 (ddd, J = 23.2, 11.5, 8.4 Hz, 1H), 2.41 – 2.56 (complex, 3H), 3.21 (m, 1H), 3.28 (dd, J = 15.8, 6.2 Hz, 1H), 3.90 (ddd, J = 11.7, 11.5, 6.2 Hz, 1H), 4.31 (m, 1H), 4.45 (dd, J = 11.5, 8.3 Hz, 1H), 7.48 (td, J = 8.0, 1.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.68 (ddd, J = 8.0, 1.4, 1.2 Hz, 1H), 8.46 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.5, 31.9, 37.6, 39.7, 47.4, 68.6, 104.7, 121.5, 125.7 (two signals), 128.1, 132.1, 137.1, 141.1, 160.8.



103

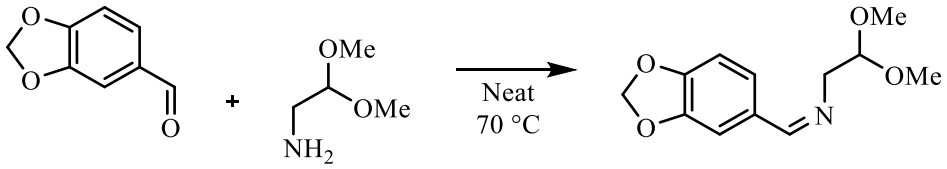
3,3a,4,5-Tetrahydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one. The alcohol **103** (30 mg, 0.12 mmol) was dissolved in 3 mL of dry pyridine and the solution was cooled to 0 °C. Excess $POCl_3$ (2 mL) was added dropwise to the flask after which the reaction mixture was stirred at room temperature for 36 hours. Progress of the reaction was monitored by mass spectrometry. When the mass of the dehydration product was the only observed signal, the mixture was diluted with CH_2Cl_2 and quenched by slow addition of 4 mL of cold dilute HCl. The organic layer was separated, dried over Na_2SO_4, and the volatiles were removed by rotary evaporation followed by pumping at high vacuum. The resulting oil (20 mg) proved to be a mixture of several products by NMR analysis. However, since the only peak present in the mass spectrum corresponded to the mass of a dehydration product, it was concluded that the oil was a mixture of alkenes that could be used in the aromatization step without further purification.



104

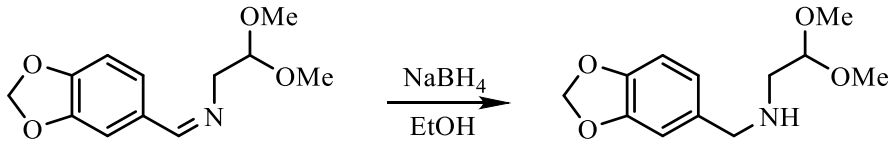
7*H*-Pyrrolo[3,2,1-*de*]phenanthridin-7-one (104). A solution containing 10 mg (0.04 mmol) of the oil from the previous step and 30 mg (0.13 mmol) of 2,3-dichloro-5,6-dicyanoquinone (DDQ) in 5 mL of $CHCl_3$ was heated at reflux for 30 hours after which the reaction mixture was filtered through a plug of Celite. The Celite was rinsed with fresh CH_2Cl_2

and both organic filtrates were combined and dried over Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove all volatiles gave 10 mg of an orange oil. Flash column chromatography (silica gel, 4:1 hexanes/EtOAc) gave 6 mg (68.5%) of **104** as a white solid: mp 144-145 °C (lit.[74] 145-147 °C). The spectral and physical properties of the synthesized product matched those found in the literature.[74] ^{1}H NMR ($CDCl_3$) δ 6.97 (d, J = 3.5 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.67 (td, J = 7.7, 1.4 Hz, 1H), 7.82 (dd, J = 7.6, 0.4 Hz, 1H), 7.86 (td, J = 7.6, 1.4 Hz, 1H), 8.11 (d, J = 3.5 Hz, 1H), 8.13 (bd, J = 8.2 Hz, 1H), 8.36 (d, J = 8.2 Hz, 1H), 8.66 (dd, J = 8.2, 0.4 Hz, 1H).



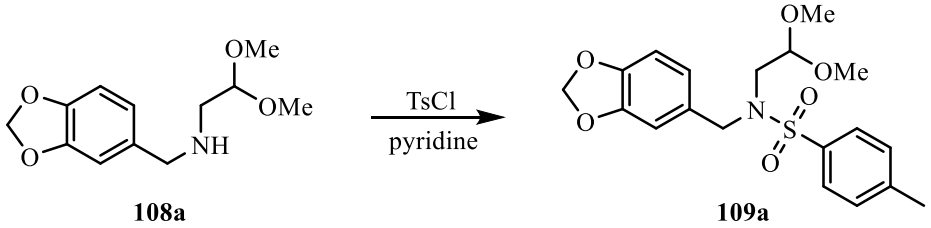
106a **107a**

(3,4-Methylenedioxybenzylidene)-(2,2-dimethoxyethyl)imine (107a). A 500-mL three-necked flask equipped with a condenser and a thermometer was charged with piperonal **106a** (45.0 g, 0.30 mol) and aminoacetaldehyde dimethyl acetal (38.0 g, 0.36 mol). The mixture was stirred overnight at 70 °C. Following the heating period, the reaction mixture was cooled to room temperature to give 71 g of crude imine **107a** as a pale-yellow oil that was deemed sufficiently pure by NMR analysis to be used directly in the next step without purification. ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 6H), 3.72 (dd, J = 5.2, 1.2 Hz, 2H), 4.65 (t, J = 5.2 Hz, 1H), 5.99 (s, 2H), 6.81 (d, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.0, 1.6 Hz, 1H) 7.35 (d, J = 1.6 Hz, 1H), 8.16 (s, 1H).



107a **108a**

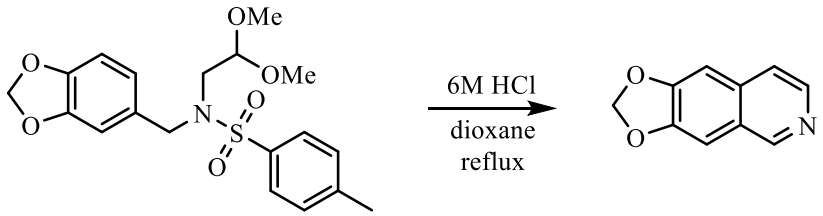
***N*-(2,2-Dimethoxyethyl)-3,4-methylenedioxybenzylamine (108a).** The imine **107a** (71.0 g, 0.30 mol) was dissolved in 350 mL of 90% ethanol and cooled to 0 °C. Solid sodium borohydride (10.0 g, 0.27 mol) was added over a 45-minute period as hydrogen gas evolution was observed. After the addition of $NaBH_4$ was complete, the reaction was warmed to room temperature and stirred overnight. After the stirring period, 350 mL of water was added to the white suspension to quench the reaction. When the evolution of hydrogen gas stopped, the entire mixture was transferred to a 2-L separatory funnel containing 750 mL of water. The amine was extracted with CH_2Cl_2 (3 x 250 mL) and the organic extracts were combined and dried over Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove all volatiles gave 69.0 g (96.2% over 2 steps) of amine **108a** as a yellow oil that was used in the next step without purification. ^{1}H NMR ($CDCl_3$) δ 2.70 (d, J = 5.6 Hz, 2H), 3.35 (s, 6H), 3.69 (s, 2H), 4.46 (t, J = 5.6 Hz, 1H), 5.90 (s, 2H), 6.73 (s, 2H), 6.81 (s, 1H).



108a **109a**

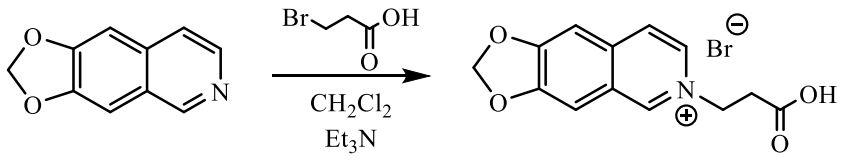
***N*-(3,4-Methylenedioxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-toluenesulfonamide (109a).** A solution containing 69.0 g (0.29 mol) of the amine **108a** in 300 mL of dry pyridine in a 1-L round-bottom flask was cooled to 0 °C. *p*-Toluenesulfonyl chloride (63.0 g, 0.33 mol) was added all at once and the reaction mixture was allowed to stir for 48 hours at room temperature. After the stirring period, the mixture was cooled to 0 °C and 500 mL of saturated $NaHCO_3$ was

added. The product was extracted with CH_2Cl_2 (4 x 200 mL). The combined organic layers were washed with 250 mL of 5% KOH, 250 mL of brine, and dried over Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove all volatiles gave tosylamide **109a** as a dark brown oil (130 g) which crystallized upon standing. NMR analysis showed the solid to contain the desired product along with residual pyridine. ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.22 (d, J = 5.6 Hz, 2H), 3.25 (s, 6H), 4.34 (t, J = 5.6 Hz, 1H), 4.36 (s, 2H), 5.92 (s, 2H), 6.67 – 6.72 (complex, 3H), 7.30 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H).



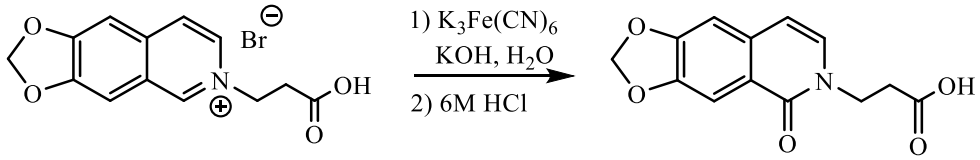
109a **110a**

6,7-Methylenedioxyisoquinoline (110a). The crude tosylamide **109a** (16.0 g, 40.7 mmol) was placed in a 500-mL round-bottom flask and dissolved in 265 mL of dioxane. To the resulting solution, 65 mL of 6M HCl was added slowly. The mixture was heated at reflux for 5 hours. After the heating period, approximately 160 mL of dioxane was removed by simple distillation. A solution of saturated $NaHCO_3$ was added until the mixture became basic to red litmus paper and brown in appearance. The entire lot was extracted with CH_2Cl_2 (3 x 85 mL); the organic extracts were combined and dried over $MgSO_4$. Rotary evaporation followed by pumping at high vacuum to remove all volatiles gave 8.06 g of crude **110a** as a light brown solid. Recrystallization from cyclohexane gave 6.4 g (91%) of 6,7-methylenedioxyisoquinoline (**110a)** as an off-white powder: mp 119-121 °C (lit.[75] 121-122 °C). ^{1}H NMR (DMSO-d_6) δ 6.19 (s, 2H), 7.32 (s, 1H), 7.45 (s, 1H), 7.63 (d, J = 5.6 Hz, 1H), 8.29 (d, J = 5.6 Hz, 1H), 9.00 (s, 1H).



110a **111a**

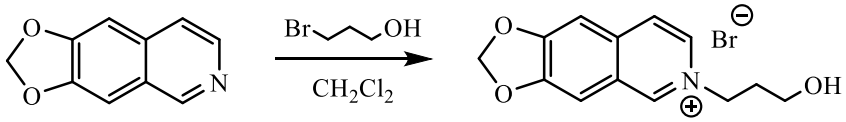
6-(2-Carboxyethyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium bromide (111a). To a solution containing 1.73 g (10.0 mmol) of **110a** and 1.53 g (10.0 mmol) of 3-bromopropionic acid in 10 mL of CH_2Cl_2 was added 0.69 g (6.8 mmol) of Et_3N all at once and the mixture was stirred overnight at room temperature. The resulting suspension was filtered through a Buchner funnel and the filtered solid was washed with fresh CH_2Cl_2. The isoquinolinium salt **111a** was obtained as a white solid (3.4 g, 100%) that was used without purification in the next step. ^{1}H NMR (DMSO-d_6) δ 3.13 (t, J = 6.7 Hz, 2H), 4.79 (t, J = 6.7 Hz, 2H), 6.44 (s, 2H), 7.72 (s, 1H), 7.77 (s, 1H), 8.28 (d, J = 6.8 Hz, 1H), 8.63 (dd, J = 6.8, 1.2 Hz, 1H), 9.63 (s, 1H), 12.72 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 34.8, 56.3, 103.5, 104.6 (two signals), 124.2, 125.6, 134.7, 138.0, 146.5, 151.7, 156.7, 172.0.



111a **112a**

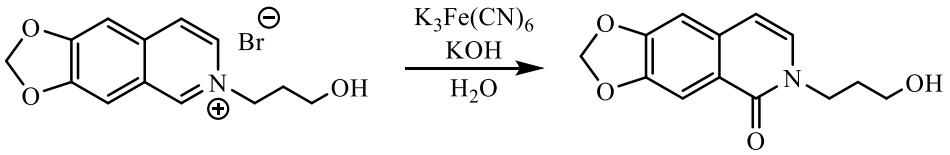
3-(5-Oxo-[1,3]dioxolo[4,5-*g*]isoquinolin-6(5*H*)-yl)propanoic acid (112a). A solution containing 4.15 g (12.7 mmol) of the salt **111a** in 27 mL of DI water was prepared in a 100-mL round-bottom flask and cooled to 0 °C. A solution of potassium ferricyanide (5.87 g, 17.8 mmol) in 25 mL of water was added all at once. A solution of potassium hydroxide (2.15 g, 38.3 mmol) in 18 mL of water was added at a rate such that the internal temperature never exceeded 15 °C. The mixture was stirred overnight at room temperature open to the atmosphere resulting in a bright yellow solution that was washed with 100 mL of CH_2Cl_2. The aqueous layer was

carefully acidified by the addition of 6M HCl during which a copious amount of solid formed. The solid was isolated by filtration through a Buchner funnel followed by rinsing with fresh DI water to give 3.01 g (90.1%) of isocarbostyril **112a** as a white powder: mp 224 °C (decomp.) ^{1}H NMR (DMSO-*d*$_6$) δ 2.68 (t, J = 6.8 Hz, 2H), 4.11 (t, J = 6.8 Hz, 2H), 6.16 (s, 2H), 6.49 (d, J = 7.2 Hz, 1H), 7.13 (s, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.52 (s, 1H), 12.41 (bs, 1H); ^{13}C NMR (DMSO-*d*$_6$) δ 33.6, 45.5, 102.4, 104.2, 104.6, 105.3, 121.1, 132.5, 134.7, 147.8, 151.9, 160.6, 172.9.



110a **121**

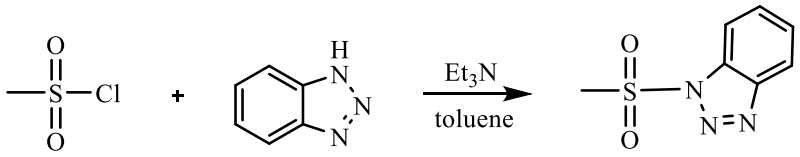
6-(3-Hydroxypropyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium bromide (121). A solution containing 3.0 g (17.3 mmol) of 6,7-methylenedioxyisoquinoline **110a** and 2.60 g (18.7 mmol) of 3-bromopropan-1-ol in 25 mL of CH_2Cl_2 was stirred overnight at room temperature. The reaction mixture was concentrated by rotary evaporation followed by pumping at high vacuum to give 5.41 g (100%) of the salt **121** as a white solid that was used without purification in the next step. ^{1}H NMR (DMSO-*d*$_6$) δ 2.13 (m, 2H), 3.47 (t, J = 5.9 Hz, 2H), 4.69 (t, J = 5.9 Hz, 2H), 6.44 (s, 2H), 7.73 (s, 1H), 7.76 (s, 1H), 8.29 (d, J = 6.8 Hz, 1H), 8.61 (dd, J = 6.8, 1.2 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$) δ 33.6, 57.6, 58.4, 103.5, 104.5, 104.7, 124.3, 125.8, 134.7, 137.9, 146.2, 151.7, 156.5.



121 **122**

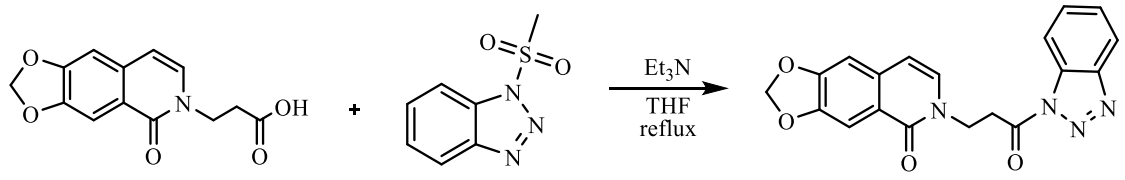
6-(3-Hydroxypropyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (122). A solution of 5.41 g (17.3 mmol) of the salt **121** in 30 mL of DI water was prepared and cooled to 0 °C. A

solution of potassium ferricyanide (6.2 g, 18.3 mmol) in 30 mL of water was added all at once followed by slow addition of a solution of potassium hydroxide (2.15 g, 38.3 mmol) in 20 mL of water at a rate such that the internal temperature never exceeded 15 °C. The reaction mixture was stirred overnight at room temperature open to the atmosphere resulting in the formation of a large amount of precipitate. The suspension was filtered through a Buchner funnel and the solid was washed with DI water. Drying the solid under high vacuum gave 4.0 g (93%) of alcohol **122** as a white powder: mp 129-130 °C ^{1}H NMR ($CDCl_3$) δ 1.96 (m, 2H), 3.53 (dd, J = 5.8, 5.3 Hz, 2H), 3.97 (t, J = 6.6 Hz, 1H), 4.20 (t, J = 6.1 Hz, 2H), 6.10 (s, 2H), 6.48 (d, J = 7.3 Hz, 1H), 6.89 (s, 1H), 7.00 (d, J = 7.3 Hz, 1H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.4, 45.2, 57.7, 101.8, 103.7, 105.7, 107.1, 121.3, 130.1, 134.4, 148.1, 152.0, 162.4.



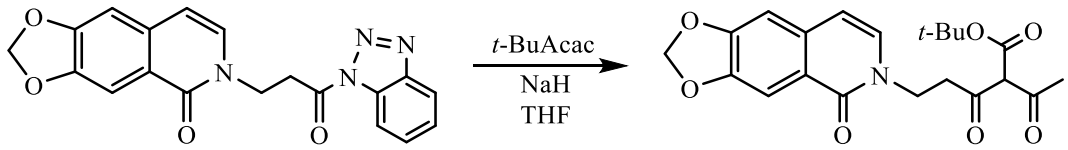
140

***N*-(1-Methanesulfonyl)benzotriazole (140).** Triethylamine (20 mL) was added all at once to a solution of benzotriazole (11.9 g, 100 mmol) in 120 mL of toluene and the mixture was cooled to 0 °C. A solution of methanesulfonyl chloride (10.0 mL, 14.8 g, 129 mmol) in 50 mL of toluene was added dropwise resulting in the formation of a precipitate. The reaction mixture was warmed to room temperature and stirred for 24 hours after which 150 mL of EtOAc and 100 mL of water were added. The organic layer was separated and washed with an additional 100 mL of water, 100 mL of brine, and finally dried over $MgSO_4$. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave 18.9 g of an off-white solid. Recrystallization from toluene gave 18.1 g (91.8%) of benzotriazole **140** as a white solid: mp 107-109 °C (lit.[76] 104-106 °C). ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 7.54 (ddd, J = 7.1, 1.2, 1.0 Hz, 1H), 7.68 (ddd, J = 7.1, 1.2, 1.0 Hz, 1H), 8.01 (dt, J = 8.4, 0.9 Hz, 1H), 8.16 (dt, J = 8.4, 0.9 Hz, 1H).



112a **140** **127a**

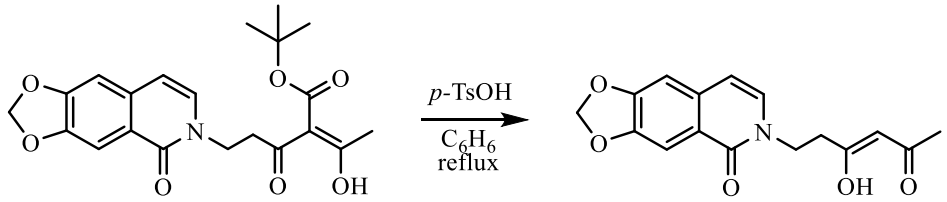
6-(3-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-oxopropyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (127a). A solution containing 8.09 g (31.0 mmol) of acid **112a**, 6.5 g (33 mmol) of the benzotriazole **140** and 6 mL of Et_3N in 150 mL of THF was heated at reflux for 24 hours. The solution was cooled to room temperature and the precipitate that formed was isolated by filtration through a Buchner funnel. After washing with fresh THF, the off-white solid was placed under high vacuum to remove volatiles giving 9.5 g of crude **127a.** The filtrate from the reaction was rotary evaporated to give a pale yellow solid that was dissolved in 125 mL of $CHCl_3$ and washed once with 125 mL of water and once with 100 mL of a dilute $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and rotary evaporated. The resulting solid was dissolved in 25 mL of THF and stirred for 3 days after which time a precipitate formed. Filtration through a Buchner funnel followed by pumping at high vacuum afforded an additional 1.0 g of crude **127a**. NMR analysis of the combined solids (10.5 g, 93.8%) showed the compound to be sufficiently pure for use in the next step. ^{1}H NMR (DMSO-d_6) δ 3.86 (t, J = 6.5 Hz, 2H), 4.44 (t, J = 6.5 Hz, 2H), 6.15 (s, 2H), 6.54 (d, J = 7.2, 1H), 7.13 (s, 1H), 7.46 (s, 1H), 7.48 (d, J = 7.2, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.77 (t, J = 8.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 35.3, 45.0, 102.4, 104.3, 104.6, 105.6, 114.4, 120.5, 121.0, 126.9, 130.9, 131,3, 132.5, 134.8, 141.9, 147.8, 151.9, 160.8, 170.9.



127a **128a**

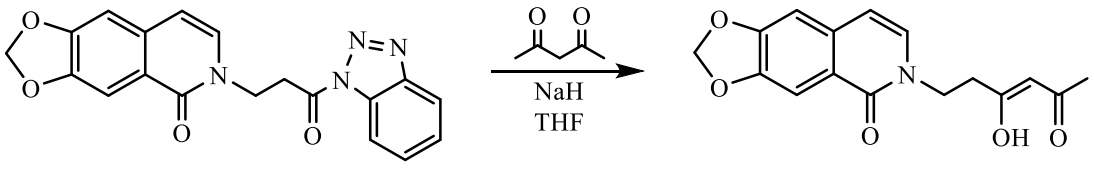
***tert*-Butyl-2-acetyl-3-oxo-5-(5-oxo-[1,3]dioxolo[4,5-*g*]isoquinolin-6(5*H*)-yl)pentanoate (128a).** The acylbenzotriazole **127a** (250 mg, 0.69 mmol) was dissolved in 20 mL of THF and heated gently to effect complete solution. In a separate flask, NaH (110 mg, 60% dispersion in mineral oil, 2.75 mmol) was rinsed 3 times with hexanes to remove the mineral oil and 10 mL of Et_2O was added. The slurry was cooled to 0 °C and *tert*-butyl acetoacetate (320 mg, 2.03 mmol) was added. The mixture was stirred at that temperature for 10 minutes giving a cloudy solution of the *tert*-butyl acetoacetate anion. The acylbenzotriazole-THF solution was added dropwise through an addition funnel over a 15-minute period. After addition was complete, the reaction mixture was warmed to room temperature and stirred for 1.5 hours. At the end of the stirring period, the mixture was poured into 10 mL of cold 1M HCl. After 20 minutes of stirring, the THF and Et_2O were removed by rotary evaporation. The resulting aqueous slurry was extracted with CH_2Cl_2 (3 x 20 mL) and the extracts were combined and dried over Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave 300 mg of viscous oil. NMR analysis showed the oil to contain the expected product plus benzotriazole and *t*-butyl acetoacetate. This crude mixture was suitable for use in the next reaction without further purification. However, the purification of a 300-mg sample of crude **128a** using flash column chromatography (silica gel, 2:1 EtOAc/hexanes) gave 150 mg (54.2% yield) of pure **128a** as a white solid: mp 97-98 °C. ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H), 2.30 (s, 3H), 3.24 (t, J = 6.5 Hz, 2H), 4.29 (t, J = 6.5 Hz, 2H), 6.06 (s, 2H), 6.34 (d, J = 7.3 Hz, 1H), 6.83 (s, 1H), 7.08 (d, J = 7.3

Hz, 1H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9, 30.1, 32.4, 45.8, 51.5, 82.0, 101.8, 103.9, 105.4, 106.4, 121.5, 130.9, 134.6, 148.1, 152.1, 161.5, 166.4, 167.9, 201.3.



128a **129a**

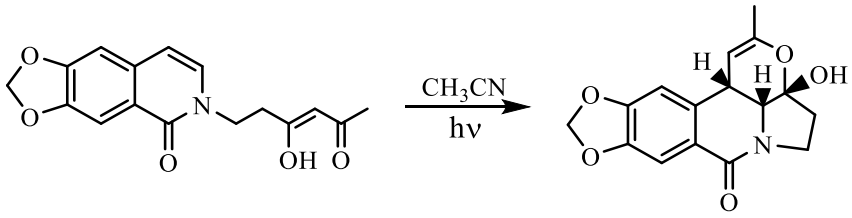
(*Z*)-6-(3-Hydroxy-5-oxo-hex-3-en-1-yl)-[1,3]-dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (129a). A solution containing 300 mg of crude **128a** from the previous step and 130 mg (0.75 mmol) of *p*-toluenesulfonic acid monohydrate in 15 mL of benzene was heated at reflux as the progress of the reaction was monitored by TLC (silica, 10:1 EtOAc/hexanes). Once the starting material was consumed, the reaction mixture was cooled and washed with dilute $NaHCO_3$ (2 x 25 mL) followed by 25 mL of brine. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave 250 mg of green oil. Flash column chromatography (silica gel, 10:1 EtOAc/hexanes) gave 100 mg (48.1% over two steps) of **129a** as a white solid: mp 144-145 °C. NMR analysis revealed that **129a** exists exclusively in an enol form. ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.86 (t, J = 6.6 Hz, 2H), 4.28 (t, J = 6.6 Hz, 2H), 5.49 (s, 1H), 6.09 (s, 2H), 6.36 (d, J = 7.4 Hz, 1H), 6.86 (s, 1H), 7.07 (d, J = 7.4 Hz, 1H), 7.78 (s, 1H), 15.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.4, 37.4, 45.9, 77.2 (under $CDCl_3$ signal), 100.9, 106.0, 125.9, 126.1, 126.8, 127.6, 132.2, 132.5, 137.2, 162.2, 190.1, 191.8.



127a **129a**

(*Z*)-6-(5-Hydroxy-3-oxo-hex-4-en-1-yl)-[1,3]-dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (129a). Sodium hydride (0.35 g of 60% dispersion in mineral oil, 8.75 mmol) was added to a

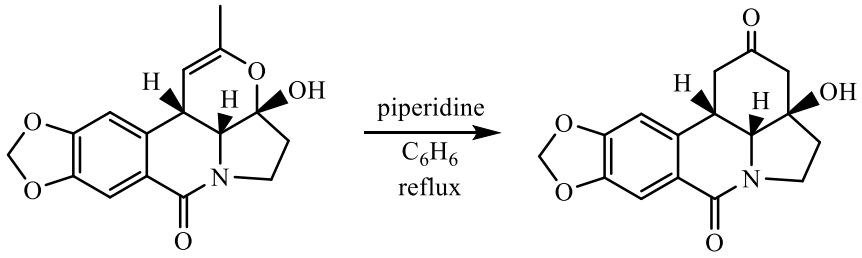
solution of acetylacetone (0.83 g, 8.30 mmol) in 60 mL of dry THF, and the mixture was stirred for 1 hour at room temperature. The *N*-acylbenzotriazole **127a** (2.0 g, 5.5 mmol) was added all at once and the suspension was stirred at room temperature for 3 hours. The reaction mixture was diluted with 40 mL of CH_2Cl_2 and 30 mL of water and stirred for 15 minutes after which all the solids had dissolved. The organic layer was separated and washed with 30 mL of dilute $NaHCO_3$, dried over Na_2SO_4, and concentrated by rotary evaporation. The resulting semi-solid was dissolved in 10 mL of CH_2Cl_2 and filtered through a plug of silica gel. The silica gel was rinsed with 4:1 hexanes/EtOAc until the *N*-acetylbenzotriazole stopped coming through as determined by spotting on a TLC plate. The silica was then rinsed with fresh EtOAc until no more product came through determined by spotting on a TLC plate. Removal of solvents by rotary evaporation followed by pumping at high vacuum gave 1.48 g (89%) of diketone **129a** as a white solid: mp 143-145 °C. The ^1H and ^{13}C NMR spectra were identical to those obtained for **129a** prepared using the 2-step route described above.



129a **131a**

(3a*R*,3a^1*R*,12b*S*)-3a-Hydroxy-2-methyl-3a^1,4,5,12b-tetrahydro-[1,3]dioxolo[4',5':4,5] benzo[1,2-*f*]pyrano[4,3,2-*hi*]indolizin-7(3a*H*)-one (131a). The diketone **129a** (125 mg, 0.41 mmol) was dissolved in 10 mL of dry CH_3CN and the reaction flask was sealed under nitrogen. The solution was irradiated with a 500-W medium pressure mercury arc lamp overnight. After the irradiation period, a large amount of solid had precipitated out of solution. The suspension was filtered through a Buchner funnel and the solid was rinsed with fresh CH_3CN affording 100 mg (80.0%) of a white solid identified as hemiketal **131a**: mp 146-148 °C. The mother liquor

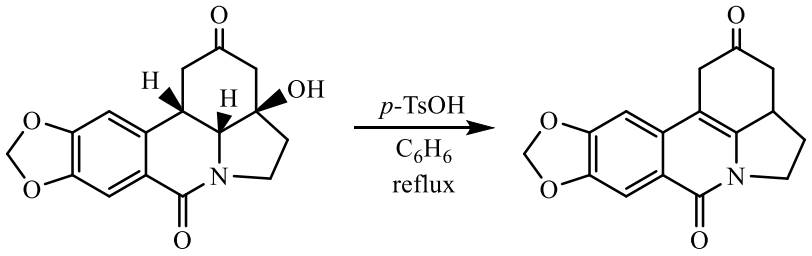
was rotary evaporated followed by pumping at high vacuum to remove volatiles. This resulted in the isolation of 25 mg of a brown semisolid that was shown by NMR analysis to contain mostly starting material with a few impurities. Based on recovered starting material, the yield of this reaction is 99%. ^{1}H NMR (DMSO-d_6) δ 1.65 (AB qd, J = 1.2, 0.8 Hz, 3H), 2.05 (ddd, J = 24.1, 12.4, 9.9 Hz, 1H), 2.20 (dd, J = 12.4, 6.7 Hz, 1H), 3.34 (complex, 1H), 3.56 – 3.63 (complex, 2H), 3.94 (bd, J = 5.8 Hz, 1H), 4.27 (t, J = 1.2 Hz, 1H), 6.08 (AB qd, J = 6.7, 0.9 Hz, 2H), 6.99 (s, 1H), 7.25 (s, 1H), 7.38 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.3, 31.5, 35.7, 42.9, 56.8, 96.2, 101.0, 102,1, 106.6, 108.2, 122.9, 136.1, 146.8, 147.0, 150.8, 161.1.



131a **132a**

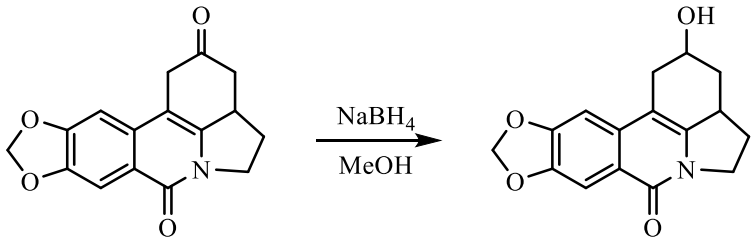
3a-Hydroxy-3,3a,4,5,12b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*] phenanthridine-2,7-dione (132a). A solution containing 100 mg (0.33 mmol) of the hemiketal **131a** and 1 mL of piperidine in 15 mL of benzene was heated at reflux for 48 hours as the progress of the reaction was monitored by TLC (silica, 10:1 EtOAc/hexanes). Once the starting material was consumed, rotary evaporation of the reaction mixture followed by pumping at high vacuum gave 150 mg of a dark semisolid. Flash column chromatography (silica gel, 10:1 EtOAc/hexanes) gave 90 mg (90%) of the aldol addition product **132a** as a white solid: mp 210-212 °C ^{1}H NMR (DMSO-d_6) δ 1.89 (complex, 2H), 2.17 (ddd, J = 12.2, 5.2, 1.5 Hz, 1H), 2.28 (bd, J = 14.5 Hz, 1H), 2.31 (dd, J = 14.5, 13.5 Hz, 1H), 2.75 (bd, J = 14.5 Hz, 1H), 3.43 (dt, J = 12.2, 5.2 Hz, 1H), 3.57 – 3.61 (complex, 1H), 3.70 (td, J = 8.8, 2.3 Hz, 1H), 3.77 (d, J = 4.8 Hz, 1H), 5.65 (s, 1H), 6.08 (AB quartet, J = 7.6 Hz, 2H), 7.02 (s, 1H), 7.32 (s, 1H); ^{13}C NMR

(DMSO-d_6) δ 36.3, 37.4, 42.5, 43.1, 48.2, 61.6, 81.1, 102.2, 107.0, 108.1, 123.0, 136.8, 147.3, 150.6, 161.7, 208.1.



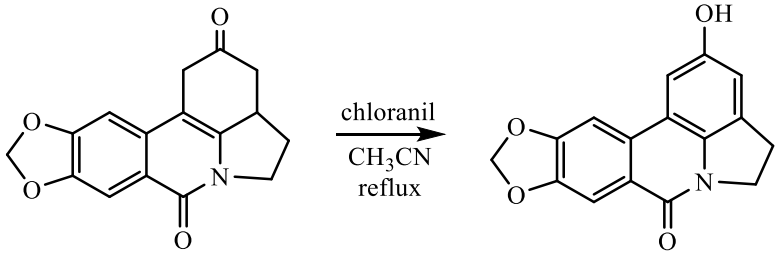
132a **133a**

3,3a,4,5-Tetrahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-2,7-dione (133a). A solution containing 85 mg (0.28 mmol) of the aldol addition product **132a** and 100 mg (0.53 mmol) of *p*-toluenesulfonic acid monohydrate in 15 mL of benzene was heated at reflux under a nitrogen atmosphere as the progress of the reaction was monitored by TLC (silica gel, 10:1 EtOAc/hexanes). Once the starting material was consumed, the reaction mixture was cooled to room temperature, washed with 10 mL of saturated $NaHCO_3$, and dried with Na_2SO_4. Rotary evaporation of the solution followed by pumping at high vacuum to remove volatiles gave 110 mg of an orange oil. Flash column chromatography (silica gel, 10:1 EtOAc/hexanes) afforded 74 mg (93%) of the dehydration product **133a** as an off-white solid: 219-220 °C. ^{1}H NMR ($CDCl_3$) δ 1.96 (ddd, J = 23.7, 11.6, 8.7 Hz, 1H), 2.50 (dd, J = 14.6, 12.6 Hz, 1H), 2.61 (m, 1H), 3.02 (dd, J = 14.6, 5.3 Hz, 1H), 3.37 (dd, J = 21.6, 2.2 Hz, 1H), 3.51 (m, 1H), 3.52 (dd, J = 21.6, 1.5 Hz, 1H), 3.97 (ddd, J = 12.6, 11.6, 6.1 Hz, 1H), 4.53 (dd, J = 12.6, 8.7 Hz, 1H), 6.12 (AB qd, J = 1.8, 1.3 Hz, 2H), 6.79 (s, 1H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.2, 36.8, 38.6, 45.1, 47.5, 99.8, 101.9, 103.1, 106.4, 121.3, 133.7, 139.6, 147.4, 152.2, 159.8, 207.3.



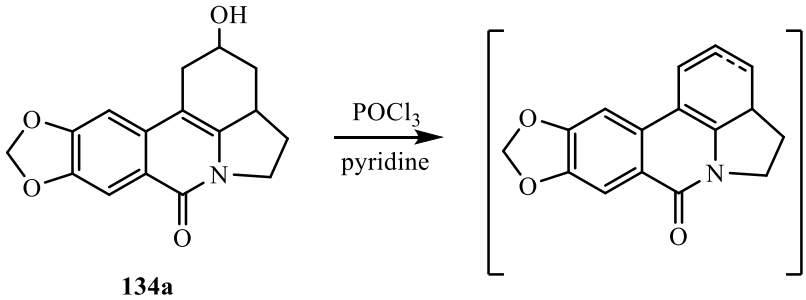
133a **134a**

2-Hydroxy-1,2,3,3a,4,5-hexahydro-7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*] phenanthridine-7-one (134a). A solution containing 200 mg (0.71 mmol) of **133a** in 20 mL of methanol was cooled to 0 °C and 100 mg (2.65 mmol) of $NaBH_4$ was added all at once. The ice bath was removed and the progress of the reaction was monitored by TLC (silica, 10:1 EtOAc/hexanes). Once the starting material was consumed, the methanol was removed by rotary evaporation. Water (4 mL) was added to the resulting semisolid to quench the reaction. The product was isolated by filtration through a Buchner funnel to give 201 mg (100%) of **134a** as a white solid: mp 234-236 °C. ^{1}H NMR (DMSO-d_6) δ 1.36 (dd, 23.1, 11.5 Hz, 1H), 1.71 (ddd, 23.1, 11.7, 8.4 Hz, 1H), 2.21 – 2.33 (complex, 3H), 3.01 (dd, J = 15.6, 6.0 Hz, 1H), 3.17 (m, 1H), 3.76 (ddd, J = 11.7, 11.6, 6.0 Hz, 1H), 4.02 (m, 1H), 4.17 (dd, J = 11.6, 8.4 Hz, 1H), 5.10 (d, J = 4.8 Hz, 1H), 6.16 (s, 2H), 7.02 (s, 1H), 7.54 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.5, 32.3, 37.9, 47.6, 67.3, 100.7, 102.3, 104.4, 105.2, 120.6, 134.9, 141.5, 146.8, 151.9, 159.0.



133a **136a**

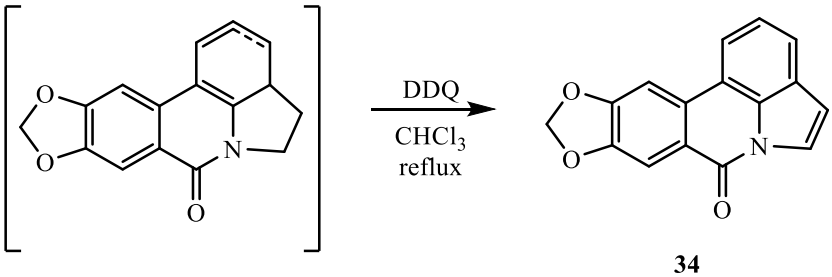
2-Hydroxy-4,5-dihydro-7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one (136a, 2-hydroxyanhydrolycorinone). A solution containing 10 mg (0.04 mmol) of **133a** and 25 mg (0.1 mmol) of tetrachloro-*p*-benzoquinone (chloranil) in 3 mL of CH_3CN was heated at 40 °C for 2 days while being monitored by mass spectrometry. The CH_3CN was removed by rotary evaporation and the resulting semisolid was dissolved in 10 mL of CH_2Cl_2. The solution was extracted with 10 mL of 1M NaOH and the aqueous layer was acidified with dilute HCl. The resulting precipitate was isolated by filtration through a Buchner funnel to give 9 mg (91%) of phenol **136a** as a white solid: mp 245-247 °C (lit.[77] 244-245 °C). The spectral and physical properties of the synthesized product matched those found in the literature.[77] ^{1}H NMR (DMSO-d_6) δ 3.24 (t, J = 8.0 Hz, 2H), 4.31 (t, J = 8.0 Hz, 2H), 6.23 (s, 2H), 6.89 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.80 (s, 1H), 9.38 (s, 1H).



134a

3,3a,4,5-Tetrahydro-7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one. A solution of the alcohol **134a** (25 mg, 0.09 mmol) was dissolved in 4 mL of pyridine and the solution was cooled to 0 °C. Excess $POCl_3$ (1.2 mL) was added slowly and the reaction mixture

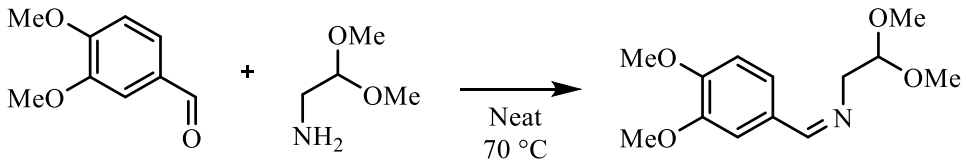
was stirred at room temperature until the mass spectrum showed the dehydration product to be the only component present. The reaction mixture was cooled to 0 °C and a gram of cracked ice was added to quench the reaction. The product was removed by extraction with CH_2Cl_2 (3 x 30 mL); the combined organic extracts were washed with 35 mL of 2M HCl and the organic layer was dried with Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave 20 mg of brown oil. NMR analysis showed the sample to be a mixture of several products. However, since the only peak present in the mass spectrum corresponded to the dehydration product, it was concluded that several dehydration isomers were present. The crude mixture was carried on to the aromatization step without further purification.



34

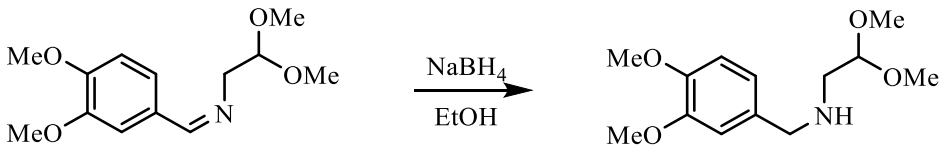
7*H*-[1,3]Dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one (34) (Hippadine). The mixture of dehydration products from the previous step (20 mg) was dissolved in 3 mL of $CHCl_3$ and an excess of DDQ (50 mg) was added. The reaction mixture was heated at reflux for 30 hours. After the heating period, the suspension was filtered through a plug of Celite to remove the insoluble hydroquinone (reduced DDQ). The Celite was rinsed with CH_2Cl_2 and both organic filtrates were combined and dried over Na_2SO_4. The volatiles were removed by rotary evaporation followed by pumping at high vacuum to give a pale orange semi-solid. Flash column chromatography (silica gel, 4:1 hexanes/EtOAc) gave 16 mg (70% over 2 steps) of hippadine **34** as a white solid: mp 214-216 °C (lit.[74] 217 °C). The physical and spectral properties of the synthesized product matched those found in the literature.[74] ^{1}H NMR ($CDCl_3$)

δ 6.19 (s, 2H), 6.93 (d, J = 3.6 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.69 (s, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H), 8.02 (s, 1H), 8.07 (d, J = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 101.8, 102.3, 108.1, 110.8, 116.7, 118.4, 122.5 (two signals), 123.6, 124.0, 128.4, 130.9, 131.7, 148.6, 152.6, 158.2.



106b **107b**

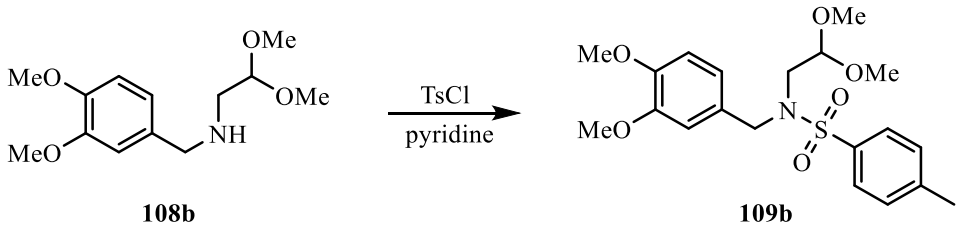
***N*-(2,2-Dimethoxyethyl)-1-(3,4-dimethoxyphenyl)methanimine (107b).** A 500-mL three-necked flask equipped with a condenser and a thermometer was charged with veratraldehyde **106b** (30.0 g, 0.18 mol) and aminoacetaldehyde dimethyl acetal (23.0 g, 0.22 mol). The mixture was stirred overnight at 70 °C. Following the heating period, the reaction mixture was cooled to room temperature which gave the imine **107b** as a pale-yellow oil (51 g) containing a small amount of the unreacted acetal by NMR analysis but suitable for use in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 6H), 3.76 (dd, J = 5.3, 1.2 Hz, 2H), 3.92 (s, 3H), 3.95 (s, 3H), 4.68 (t, J = 5.3 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 7.17 (dd, J = 8.2, 1.9 Hz, 1H), 7.44 (d, J = 1.9 Hz, 1H), 8.21 (s, 1H).



107b **108b**

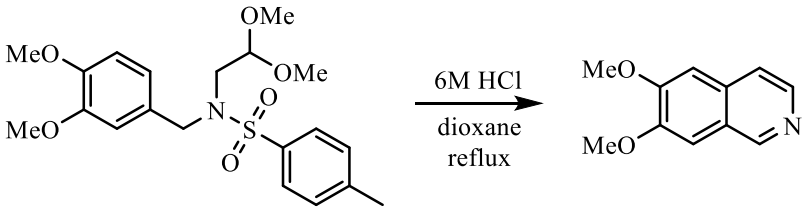
***N*-(3,4-Dimethoxybenzyl)-2,2-dimethoxyethan-1-amine (108b).** The imine **107b** (51 g) was dissolved in 300 mL of 90% ethanol and cooled to 0 °C. Solid $NaBH_4$ (10 g, 0.26 mol) was added over a 45-minute period as hydrogen gas evolution was observed. After the addition of $NaBH_4$ was complete, the reaction was warmed to room temperature and stirred overnight.

After the stirring period, 150 mL of water was added to the white suspension to quench the reaction. When the evolution of hydrogen gas stopped, the entire mixture was transferred to a 2-L separatory funnel containing 500 mL of water. The amine was extracted with CH_2Cl_2 (3 x 200 mL) and dried with Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave amine **108b** as a yellow oil (45 g, 97% over 2 steps) which was pure by NMR analysis. ^{1}H NMR ($CDCl_3$) δ 2.75 (d, J = 5.5 Hz, 2H), 3.38 (s, 6H), 3.76 (s, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 4.49 (t, J = 5.5 Hz, 1H), 6.82 – 6.89 (complex, 3H).



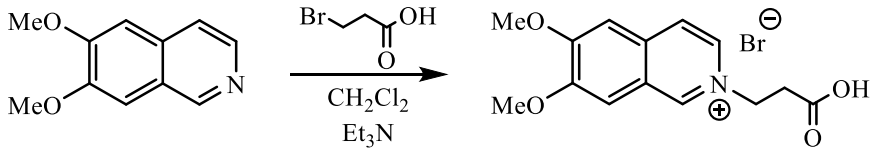
108b **109b**

***N*-(3,4-Dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (109b).** A solution of the amine **108b** (45.0 g, 0.176 mol) in 200 mL of dry pyridine in a 1-L round-bottom flask was cooled to 0 °C. *p*-Toluenesulfonyl chloride (38.0 g, 0.20 mol) was added all at once causing the solution to become cloudy and yellow in color. The mixture was capped and stirred for 48 hours at room temperature. After the stirring period, the mixture was cooled to 0 °C and 200 mL of saturated $NaHCO_3$ was added. The product was extracted with CH_2Cl_2 (4 x 125 mL). The combined organic layers were washed with 250 mL of 5% KOH, 250 mL of brine, and dried over Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave the tosylamide **109b** as a dark brown oil (75 g) which crystallized upon standing. NMR analysis showed the solid to contain the desired product along with residual pyridine. ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.22 (d, J = 5.3 Hz, 2H), 3.27 (s, 6H), 3.76 (s, 3H), 3.86 (s, 3H), 4.37 (t, J = 5.3 Hz, 1H), 4.42 (s, 2H), 6.69-6.77 (complex, 3H), 7.31 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H).



109b **110b**

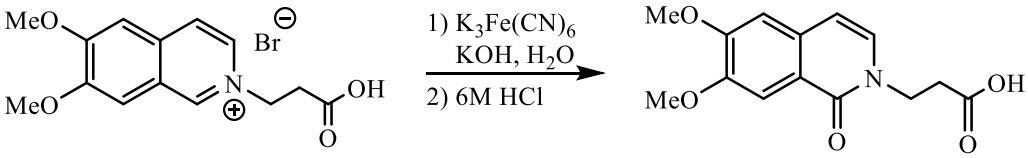
6,7-Dimethoxyisoquinoline (110b). The crude tosylamide **109b** (16.0 g, 39.1 mmol) was placed in a 500-mL round-bottomed flask and dissolved in 275 mL of dioxane. To the resulting solution, 65 mL of 6M HCl was added slowly and the mixture was heated at reflux for 5 hours. After the heating period, approximately 160 mL of dioxane was removed by simple distillation. A solution of saturated $NaHCO_3$ was added until the mixture became basic to red litmus paper and brown in appearance. The entire lot was extracted with CH_2Cl_2 (3 x 100 mL); the organic extracts were combined and dried over $MgSO_4$. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave 9.0 g of crude 6,7-dimethoxyisoquinoline as an orange oil. The crude material was purified by vacuum distillation giving 6.5 g (88%) of 6,7-dimethoxyisoquinoline **110b** as a pale green liquid: bp 124-126 °C (0.025 mm Hg). The spectral properties of the synthesized product matched those found in the literature.[78] ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 6H), 7.08 (s, 1H), 7.21 (s, 1H), 7.52 (d, J = 5.5 Hz, 1H), 8.40 (d, J = 5.5 Hz, 1H), 9.06 (s, 1H).



110b **111b**

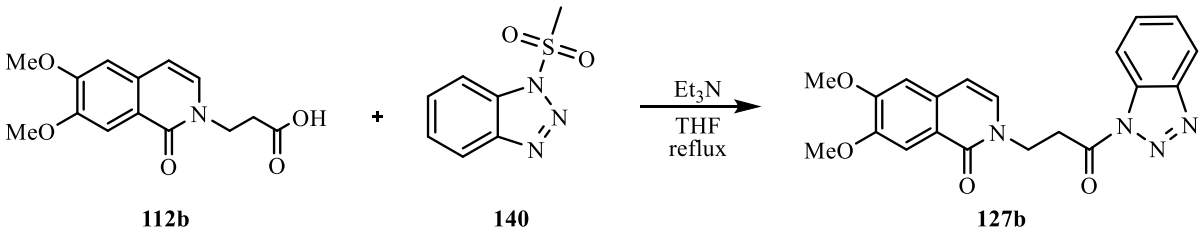
2-(2-Carboxyethyl)-6,7-dimethoxyisoquinolin-2-ium bromide (111b). A solution containing 8.0 g (42.3 mmol) of 6,7-dimethoxyisoquinoline **110b** and 6.8 g (44.5 mmol) of 3-bromopropionic acid in 50 mL of CH_2Cl_2 was prepared. Triethylamine (3 mL) was added all at once and the mixture was stirred overnight at room temperature. The resulting suspension was

filtered through a Buchner funnel and the solid was washed with fresh CH_2Cl_2 to give 14.5 g (100%) of the isoquinolinium salt **111b**, which was pure by NMR analysis. ^{1}H NMR (DMSO-d_6) δ 3.08 (t, J = 6.5 Hz, 2H), 4.01 (s, 3H), 4.07 (s, 3H), 4.81 (t, J = 6.5 Hz, 2H), 7.75 (s, 1H), 7.78 (s, 1H), 8.28 (d, J = 6.8 Hz, 1H), 8.60 (d, J = 6.8 Hz, 1H), 9.64 (s, 1H).



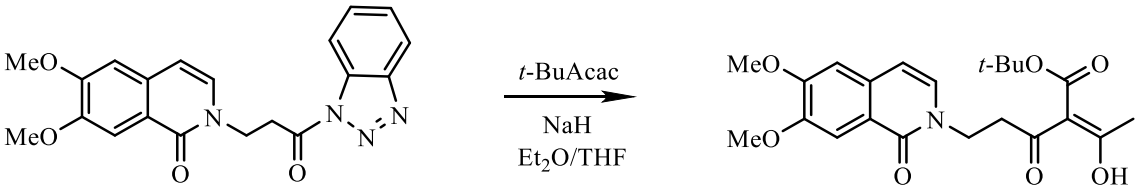
111b **112b**

3-(6,7-Dimethoxy-1-oxoisoquinolin-2(1*H*)-yl)propanoic acid (112b). A solution of the salt **111b** (21.0 g, 61.4 mmol) in 120 mL of DI water was prepared in a 1-L round-bottom flask and cooled to 0 °C. Two solutions, one containing potassium ferricyanide (81.0 g, 246 mmol) in 250 mL of water, and another containing KOH (28.0 g, 499 mmol) in 100 mL of water, were added simultaneously at a rate such that the internal temperature never exceeded 15 °C. Once both solutions were added, the reaction was stirred overnight at room temperature open to the atmosphere. The mixture was washed with 300 mL of CH_2Cl_2 and the aqueous layer was carefully acidified by the addition of 6M HCl during which a copious amount of solid formed. Filtration through a Buchner funnel followed by rinsing the solid with DI water gave 15.0 g (88.2%) of isocarbostyril **112b** as an off-white powder: mp 197 °C (decomp.) ^{1}H NMR (DMSO-d_6) δ 2.69 (t, J = 6.9 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 4.13 (t, J = 6.9 Hz, 2H), 6.52 (d, J = 7.3 Hz, 1H), 7.14 (s, 1H), 7.34 (d, J = 7.3 Hz, 1H), 7.58 (s, 1H), 12.37 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 33.7, 45.4, 49.1, 55.9, 56.2, 105.0, 107.2 (two signals), 119.5, 132.2, 132.9, 149.2, 153.5, 160.7, 172.9.



112b **140** **127b**

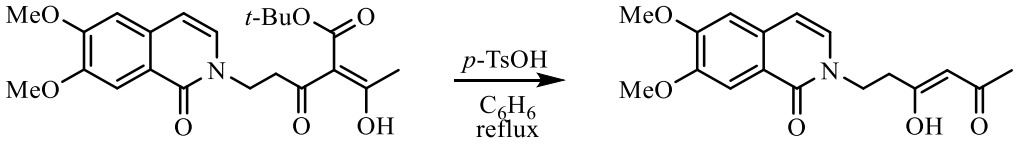
2-(3-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-oxopropyl)-6,7-dimethoxyisoquinolin-1(2*H*)-one (140). A solution containing 8.1 g (29.2 mmol) of **112b**, 6.0 g (30.4 mmol) of **140** and 6 mL of Et_3N in 150 mL of THF was heated at reflux for 24 hours. The solution was cooled to room temperature and the precipitate that formed was isolated by filtration through a Buchner funnel. After washing with fresh THF, the off-white solid was placed under high vacuum to remove volatiles giving 9.2 g of **127b** that was pure by NMR analysis. The filtrate was rotary evaporated to remove volatiles giving a pale yellow solid that was dissolved in 125 mL of $CHCl_3$ and washed with 125 mL of water followed by 100 mL of dilute $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and rotary evaporated. The resulting solid was dissolved in 25 mL of THF and stirred for 3 days, after which time a precipitate formed. Filtration through a Buchner funnel followed by pumping at high vacuum afforded an additional 1.3 g of **127b** as a white solid resulting in a combined yield of 10.5 g (95.1%). The compound was sufficiently pure by NMR analysis for use in the next step. ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H), 4.01 (s, 3H), 4.06 (t, J = 6.7 Hz, 2H), 4.57 (t, J = 6.7 Hz, 2H), 6.46 (d, J = 7.3 Hz, 1H), 6.88 (s, 1H), 7.26 (d, J = 7.3 Hz, 1H), 7.53 (td, J = 8.2, 0.9 Hz, 1H), 7.68 (td, J = 8.2, 0.9 Hz, 1H), 7.79 (s, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.29 (d, J = 8.2 Hz, 1H).



127b **128b**

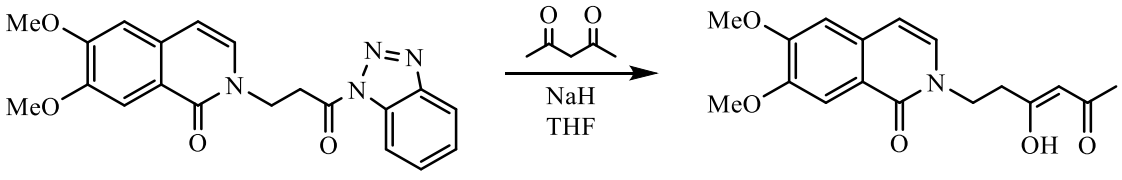
***tert*-Butyl-2-acetyl-5-(6,7-dimethoxy-1-oxoisoquinolin-2(1*H*)-yl)-3-oxopentanoate (128b).** A solution containing 250 mg (0.66 mmol) of **127b** was prepared by warming the sample in 30 mL of THF to dissolve the sample completely. In a separate flask, NaH (110 mg, 60% dispersion in mineral oil, 2.75 mmol) was rinsed 3 times with hexanes to remove the mineral oil and 10 mL of Et_2O was added. The suspension was cooled to 0 °C and *tert*-butyl acetoacetate (320 mg, 2.02 mmol) was added. The mixture was stirred at that temperature for 10 minutes giving a cloudy solution of the *tert*-butyl acetoacetate anion. The acylbenzotriazole-THF solution was added dropwise through an addition funnel over a 15-minute period. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 1.5 hours. At the end of the stirring period, the mixture was added to 10 mL of cold 1M HCl. After 20 minutes of stirring, the THF and Et_2O were removed by rotary evaporation. The resulting aqueous slurry was extracted with CH_2Cl_2 (3 x 20 mL); the organic extracts were combined and dried over Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave 350 mg of viscous oil. NMR analysis showed the oil to contain **128b** plus benzotriazole and *t*-butyl acetoacetate. This crude mixture was suitable for use in the next reaction without further purification. However, the purification of a 350-mg sample of the oil using flash column chromatography (silica gel, 2:1 EtOAc/hexanes) gave 125 mg (45%) of pure **128b** as a white solid: mp 102-103 °C. ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.32 (s, 3H), 3.26 (t, J = 6.5 Hz, 2H), 4.00 (s, 3H), 4.02 (s, 3H), 4.33 (t, J = 6.5 Hz, 2H), 6.40 (d, J = 7.3 Hz, 1H), 6.87 (s, 1H), 7.12 (d, J = 7.3 Hz, 1H), 7.80 (s, 1H), 17.44 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0, 28.2,

37.3, 45.7, 56.0, 56.2, 81.9, 105.4, 105.9, 107.6, 110.8, 120.2, 131.2, 132.6, 149.1, 153.3, 161.4, 166.1, 193.7, 196.5.



128b **129b**

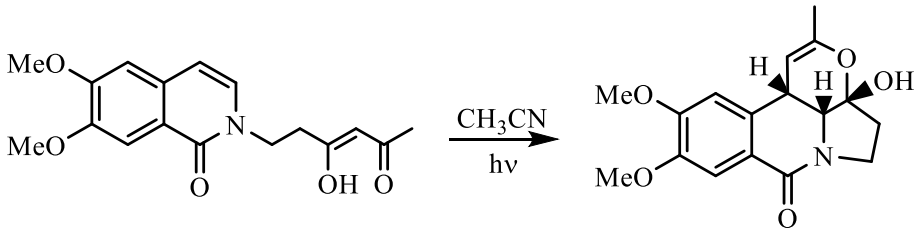
(*Z*)-2-(3-Hydroxy-5-oxohex-3-en-1-yl)-6,7-dimethoxyisoquinolin-1(2*H*)-one (129b). A solution containing 125 mg (0.30 mmol) of **128b** and 100 mg (0.6 mmol) of *p*-toluenesulfonic acid monohydrate in 15 mL of benzene was heated at reflux as the progress of the reaction was monitored by TLC (silica, 10:1 EtOAc/hexanes). Once the starting material was consumed, the reaction was cooled and washed with dilute $NaHCO_3$ (2 x 20 mL) followed by 25 mL of brine. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave 110 mg of a brown oil. Flash column chromatography (silica gel, 10:1 EtOAc/hexanes) gave 70 mg (77%) of **129b** as a white solid: mp 121-123 °C. NMR analysis revealed that **129b** exists almost exclusively in an enol form. ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.87 (t, J = 6.5 Hz, 2H), 4.01 (s, 3H), 4.03 (s, 3H), 4.30 (t, J = 6.5 Hz, 2H), 5.49 (s, 1H), 6.41 (d, J = 7.3 Hz, 1H), 6.88 (s, 1H), 7.09 (d, J = 7.3 Hz, 1H), 7.81 (s, 1H), 15.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.5, 37.5, 46.1, 56.2 (two signals), 77.2 (between $CDCl_3$ signal), 100.9, 105.5, 106.0, 107.4, 131.2, 132.7, 149.2, 153.4, 161.5, 190.3, 191.7.



127b **129b**

(*Z*)-2-(3-Hydroxy-5-oxohex-3-en-1-yl)-6,7-dimethoxyisoquinolin-1(2*H*)-one (129b). Sodium hydride (0.18 g, 60% dispersion in mineral oil, 4.5 mmol) was added to a solution of

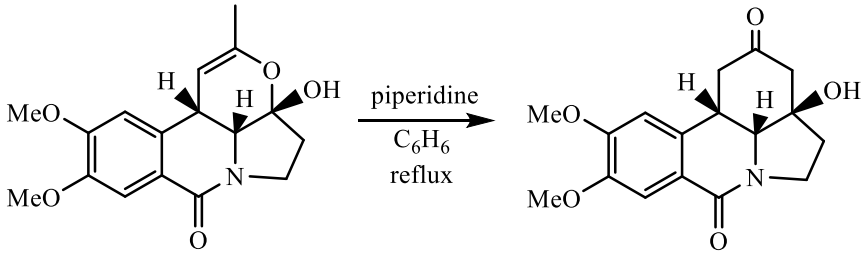
0.41 g (4.0 mmol) of acetylacetone in 30 mL of dry THF and the mixture was stirred for 1 hour at room temperature. Solid **127b** (1.0 g, 2.6 mmol) was added all at once, and the reaction mixture was stirred at room temperature for 3 hours after which 35 mL of CH_2Cl_2 and 20 mL of water were added. The mixture was stirred for 15 minutes causing all the solids to dissolve. The organic layer was separated and washed with 25 mL of dilute $NaHCO_3$, dried over Na_2SO_4, and concentrated by rotary evaporation. The resulting semi-solid was dissolved in 10 mL of CH_2Cl_2 and filtered through a plug of silica gel. The silica gel was rinsed with 4:1 hexanes/EtOAc until the *N*-acetylbenzotriazole stopped coming through as determined by spotting on a TLC plate. The silica was then rinsed with fresh EtOAc until no more product came through determined by spotting on a TLC plate. Removal of the solvents by rotary evaporation followed by pumping at high vacuum gave 0.77 g (92%) of diketone **129b** as a white solid: mp 121-122 °C. The ^1H and ^{13}C NMR spectra were identical to those obtained for **129b** prepared using the 2-step route described above.



129b **131b**

(3a*R*,3a^1*R*,11b*S*)-3a-Hydroxy-9,10-dimethoxy-2-methyl-3a^1,4,5,11b-tetrahydrobenzo[*f*]pyrano[4,3,2-*hi*]indolizin-7(3a*H*)-one (131b). A solution of 1.0 g (3.15 mmol) of the dione **129b** in 80 mL of dry CH_3CN was prepared in a 100-mL round-bottom flask and irradiated with a 500-W medium pressure mercury arc lamp for 30 hours. The copious precipitate that formed was isolated by filtration through a Buchner funnel and rinsed with fresh CH_3CN affording 750 mg (75.0%) of a white solid identified as hemiketal **131b**: mp 183 °C (decomp.) The mother

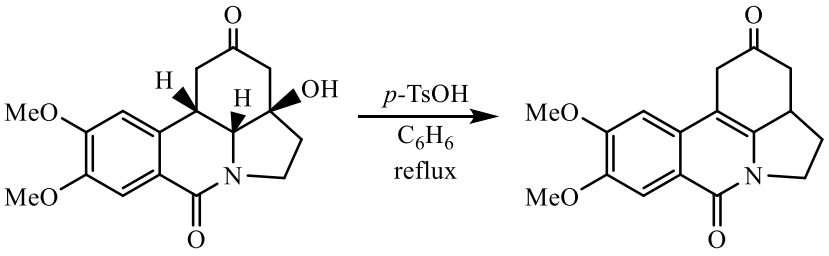
liquor was rotary evaporated followed by pumping at high vacuum to remove volatiles. This resulted in the isolation of 248 mg of a brown semisolid that was shown by NMR analysis to contain mostly starting material along with a small amount of decomposition products. Based on recovered starting material, the yield of this reaction is 99%. ^{1}H NMR (DMSO-d_6) δ 1.65 (d, J = 1.2 Hz, 3H), 2.03 (complex, 1H), 2.20 (dd, J = 12.5, 6.8 Hz, 1H), 3.32 (m, 1H), 3.59 – 3.63 (complex, 2H), 3.77 (s, 3H), 3.84 (s, 3H), 3.95 (d, J = 6.1 Hz, 1H), 4.31 (t, J = 1.0 Hz, 1H), 6.99 (s, 1H), 7.32 (s, 1H), 7.36 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.3, 31.2, 35.7, 42.8, 56.0, 56.2, 57.0, 96.5, 101.1, 109.8, 111.1, 121.2, 134.1, 146.7, 148.1, 152.4, 161.5.



131b **132b**

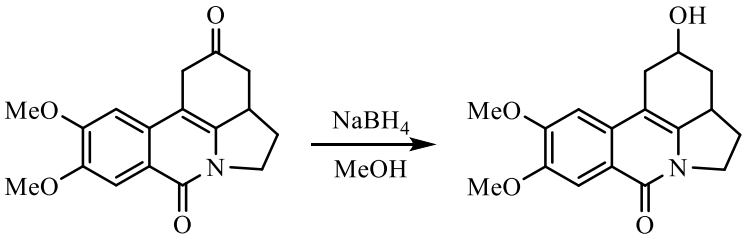
(3a*R*,3a^{1}*R*,11b*S*)-3a-Hydroxy-9,10-dimethoxy-3,3a,3a^{1},4,5,11b-hexahydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine-2,7-dione (132b). Piperidine (1 mL) was added dropwise to a solution containing 700 mg (2.21 mmol) of **131b** in 50 mL of benzene. The mixture was heated at reflux as the progress of the reaction was monitored by TLC (silica gel, 20:1 EtOAc/hexanes). After 48 hours, the solvent was removed by rotary evaporation followed by pumping at high vacuum to remove volatiles to give 1.2 g of dark green semi-solid. Purification using column chromatography (silica gel, 19:1 CH_2Cl_2/MeOH) afforded 610 mg (87.1%) of **132b** as a pale yellow powder: mp 210 °C (decomp.) ^{1}H NMR ($CDCl_3$) δ 2.07 – 2.16 (complex, 2H), 2.40 (ddd, J = 14.0, 5.4, 1.8 Hz, 1H), 2.51 (dd, J = 14.0, 13.1 Hz, 1H), 2.79 (bd, J = 14.4 Hz, 1H), 3.49 (dt, J = 12.8, 5.2 Hz, 1H), 3.61 – 3.68 (complex, 1H), 3.94 (s, 3H), 3.96 (s, 3H), 3.98 (d, J =

4.4 Hz, 1H), 6.67 (s, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.0, 37.6, 42.4, 43.4, 48.3, 56.2 (two signals), 62.0, 81.9, 109.2, 110.4, 120.9, 133.3, 148.6, 152.4, 163.3, 207.4.



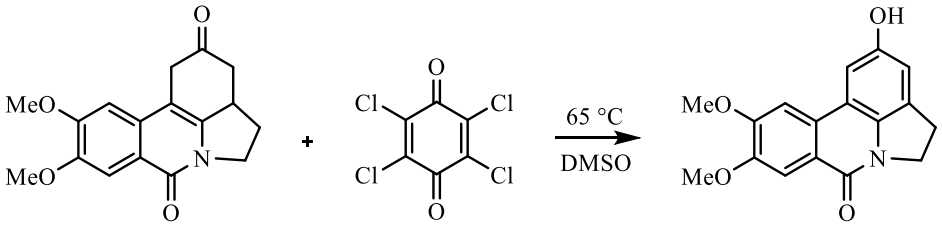
132b **133b**

9,10-Dimethoxy-3,3a,4,5-tetrahydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine-2,7-dione (133b). A solution containing 300 mg (0.95 mmol) of **132b** and 150 mg (0.87 mmol) of *p*-toluenesulfonic acid monohydrate in 50 mL of benzene was heated at reflux for 5 hours and monitored by TLC (silica, 20:1 EtOAc/hexanes). After being cooled to room temperature, the solution was extracted with saturated $NaHCO_3$ (2 x 30 mL) and dried over Na_2SO_4. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave a residue that was purified by flash column chromatography (silica gel, 20:1 EtOAc/hexanes) to afford 265 mg (93.3%) of **133b** as a white solid: mp 235 °C (decomp.) ^{1}H NMR ($CDCl_3$) δ 1.97 (ddd, J = 23.6, 11.6, 8.7 Hz, 1H), 2.50 (dd, J = 14.5, 12.5 Hz, 1H), 2.62 (m, 1H), 3.04 (dd, J = 14.5, 5.2 Hz, 1H), 3.44 (dd, J = 20.9, 2.0 Hz, 1H), 3.54 (m, 1H), 3.58 (dd, J = 20.9, 1.5 Hz, 1H), 3.98 (ddd, J = 12.5, 11.6, 6.2 Hz, 1H), 4.03 (s, 3H), 4.05 (s, 3H), 4.55 (dd, J = 12.5, 8.7 Hz, 1H), 6.76 (s, 1H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.2, 36.7, 38.6, 45.2, 47.5, 56.1 (two signals), 101.8, 102.8, 108.4, 119.6, 131.7, 139.4, 148.7, 153.5, 159.9, 207.5.



133b **134b**

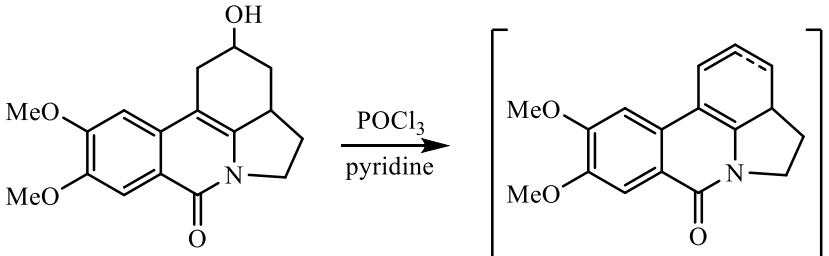
2-Hydroxy-9,10-dimethoxy-1,2,3,3a,4,5-hexahydro-7*H*-pyrrolo[3,2,1-*de*] phenanthridin-7-one (134b). Solid sodium borohydride (50 mg, 1.3 mmol) was added all at once to a solution containing 70 mg (0.23 mmol) of **133b** in 10 mL of MeOH. The reaction mixture turned a pale yellow color almost instantaneously. After stirring for 15 minutes at room temperature, a TLC analysis (silica, 9:1 CH_2Cl_2/MeOH) of the suspension indicated the complete disappearance of starting material and the presence of a single product. The product was removed by filtration through a fritted funnel and rinsed with fresh cold MeOH to afford 66 mg (95%) of alcohol **134b**: mp 248-249 °C. ^{1}H NMR ($CDCl_3$) δ 1.62 (AB quartet, J = 11.6 Hz, 1H), 1.83 (ddd, J = 12.2, 11.8, 8.4 Hz, 1H), 1.99 (d, J = 4.9 Hz, 1H), 4.26 – 2.54 (complex, 3H), 3.23 (dd, J = 14.4, 6.1 Hz, 1H), 3.91 (td, J = 11.8, 5.8 Hz, 1H), 4.02 (s, 3H), 4.03 (s, 3H), 4.33 (m, 1H), 4.44 (dd, J = 12.2, 8.4 Hz, 1H), 6.86 (s, 1H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.7, 32.2, 37.7, 39.6, 47.5, 56.0, 56.2, 68.8, 102.0, 104.2, 108.2, 119.4, 132.5, 139.9, 148.3, 153.2, 160.1.



133b **136b**

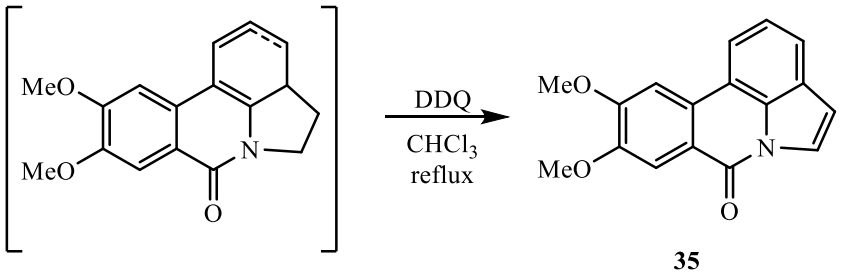
2-Hydroxy-9,10-dimethoxy-4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (136b). The β,γ-enone **133b** (6 mg) was dissolved in DMSO-d_6 in an NMR tube and an excess

of chloranil was added. The tube was capped under a nitrogen atmosphere and heated at 65 °C. The proton NMR analysis showed that the reaction was complete after 30 hours and gave a quantitative transformation to the phenolic compound **136b**. ^{1}H NMR (DMSO-d_6) δ 3.33 (t, J = 8.5 Hz, 2H), 3.89 (s, 3H), 3.99 (s, 3H), 4.31 (t, J = 8.5 Hz, 2H), 6.88 (d, J = 1.7 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.66 (s, 1H), 7.71 (s, 1H).



134b

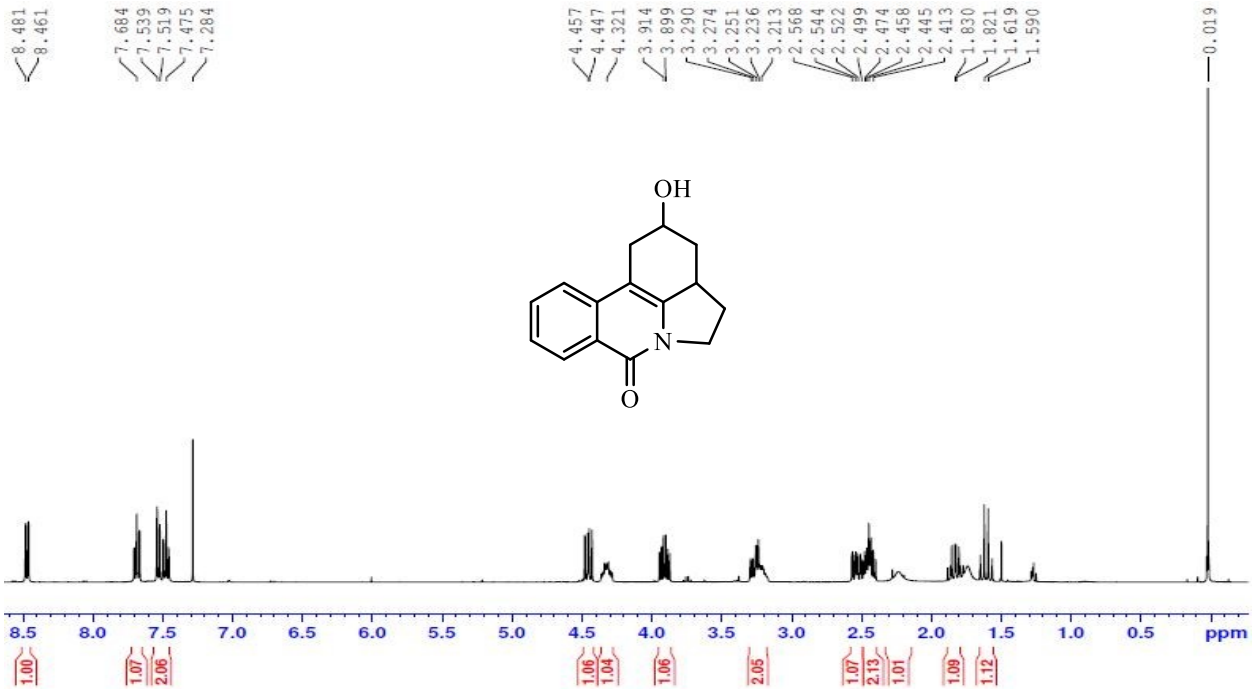
9,10-Dimethoxy-3,3a,4,5-tetrahydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one. A solution containing 15 mg (0.05 mmol) of the alcohol **134b** in 4 mL of pyridine was cooled to 0 °C and an excess (2.5 mL) of $POCl_3$ was added dropwise to the reaction mixture. After complete addition, the reaction mixture was stirred for 2 days at room temperature followed by heating at reflux for 24 hours. The reaction mixture was cooled to 0 °C and quenched by adding a gram of crushed ice. The product was removed by extraction with CH_2Cl_2 (2 x 10 mL), and the organic extracts were combined and washed with dilute HCl (2 x 10 mL) before drying over $MgSO_4$. Rotary evaporation followed by pumping at high vacuum to remove volatiles gave 5 mg of a semi-solid. NMR analysis showed the sample to be a mixture of dehydration products that were carried on to the next step without further purification.



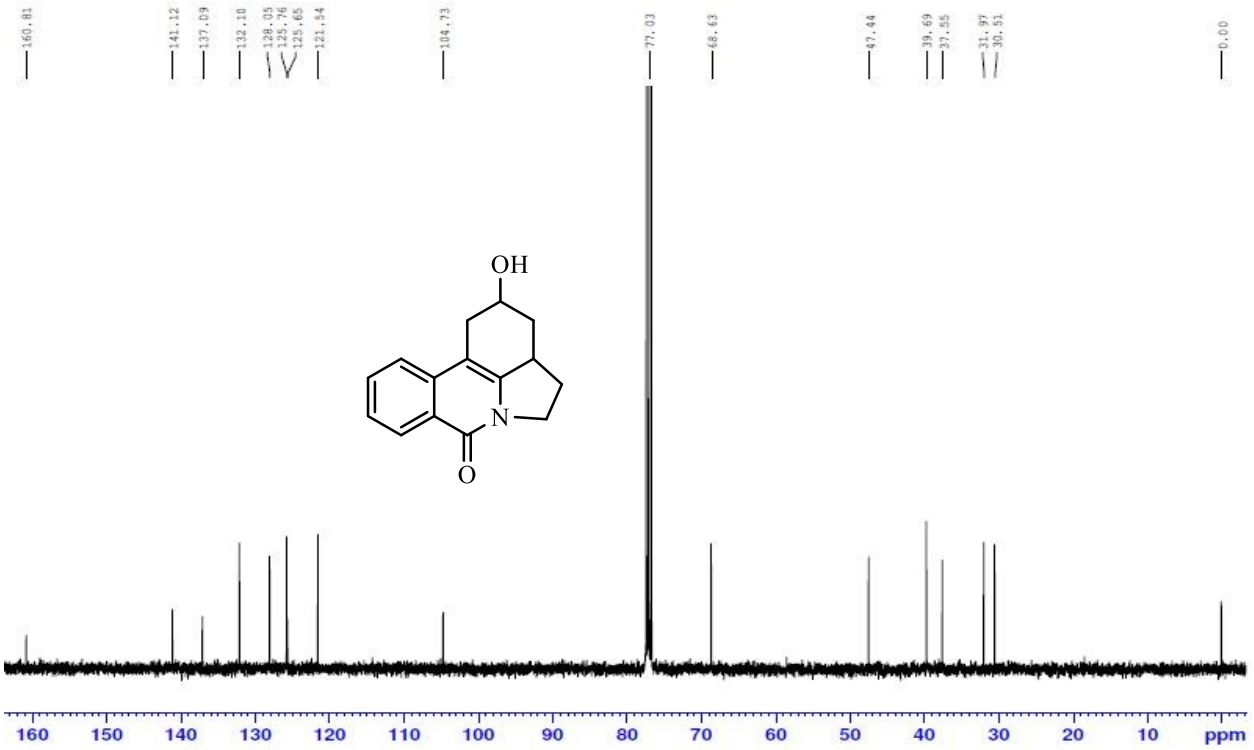
35

9,10-Dimethoxy-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (35) (pratosine). The mixture of the dehydration products from the previous reaction (5 mg, 0.018 mmol) was dissolved in 3 mL of $CHCl_3$ and an excess (20 mg) of DDQ was added. The reaction mixture was heated at reflux for 48 hours and monitored by TLC (silica, 4:1 hexanes/EtOAc) after which the solvent was removed by rotary evaporation followed by pumping at high vacuum to give an orange semi-solid. Purification by preparatory thin layer chromatography (silica gel, 4:1 hexanes/EtOAc) gave 3.7 mg (74%) of pratosine (**35)** as an off-white solid: mp 231-234 °C (lit.[36] 234-235). The physical and spectral properties were consistent with those found in the literature.[36] ^{1}H NMR ($CDCl_3$) δ 4.10 (s, 3H), 4.16 (s, 3H), 6.94 (d, J = 3.6 Hz, 1H), 7.52 (t, J = 7.6, 1H), 7.71 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 8.05 (s, 1H), 8.10 (d, J = 3.6 Hz, 1H).

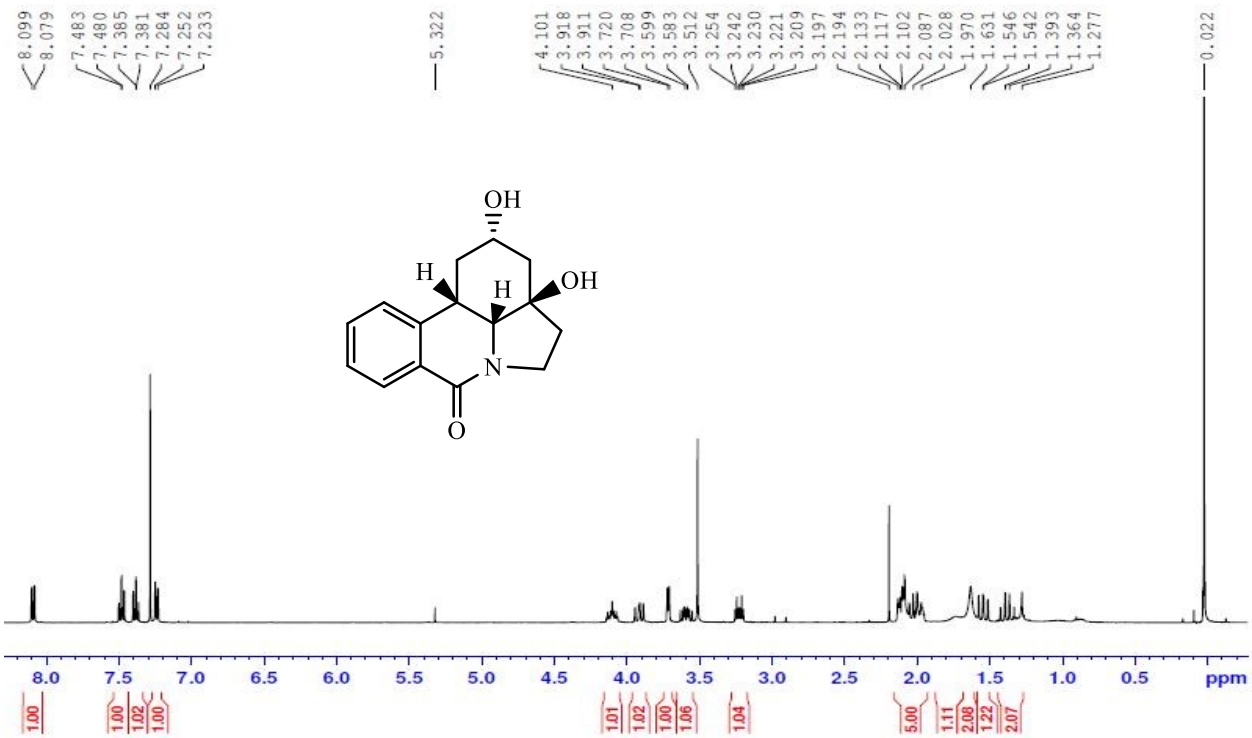
Appendix



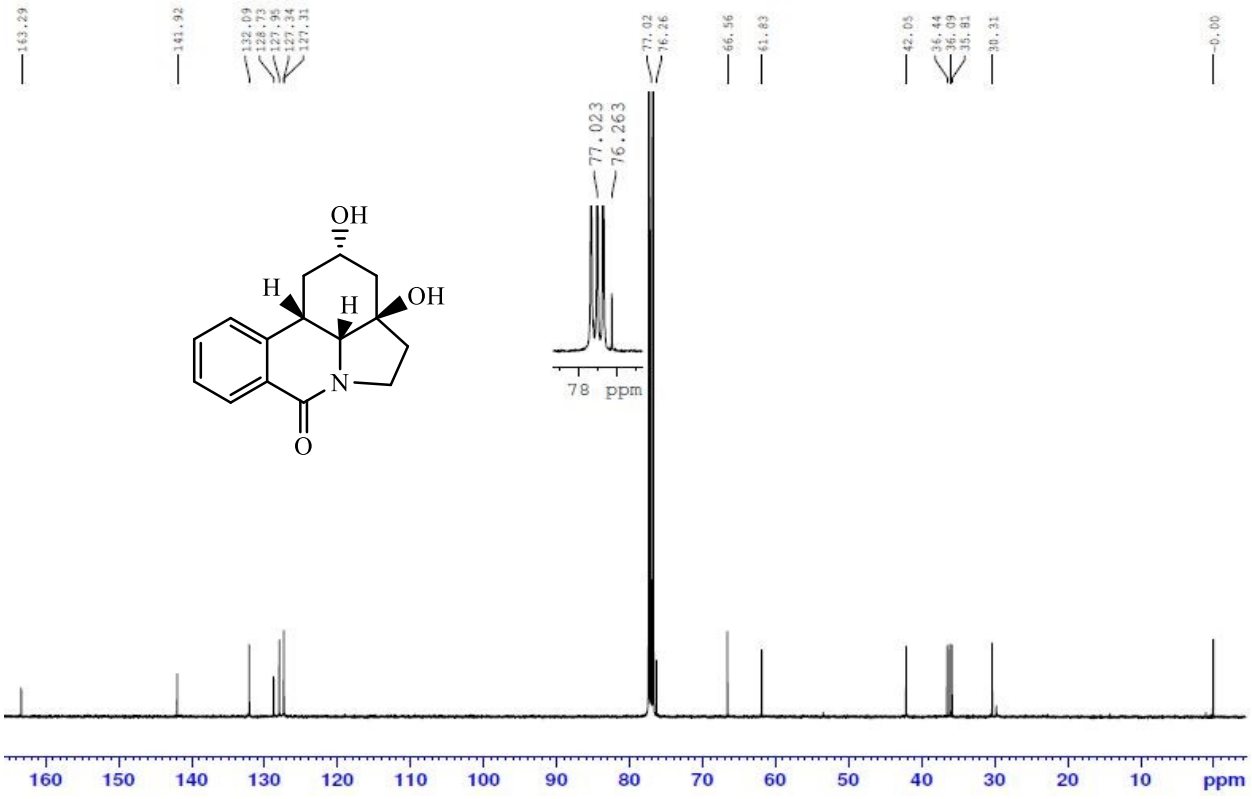
^{1}H NMR of 103



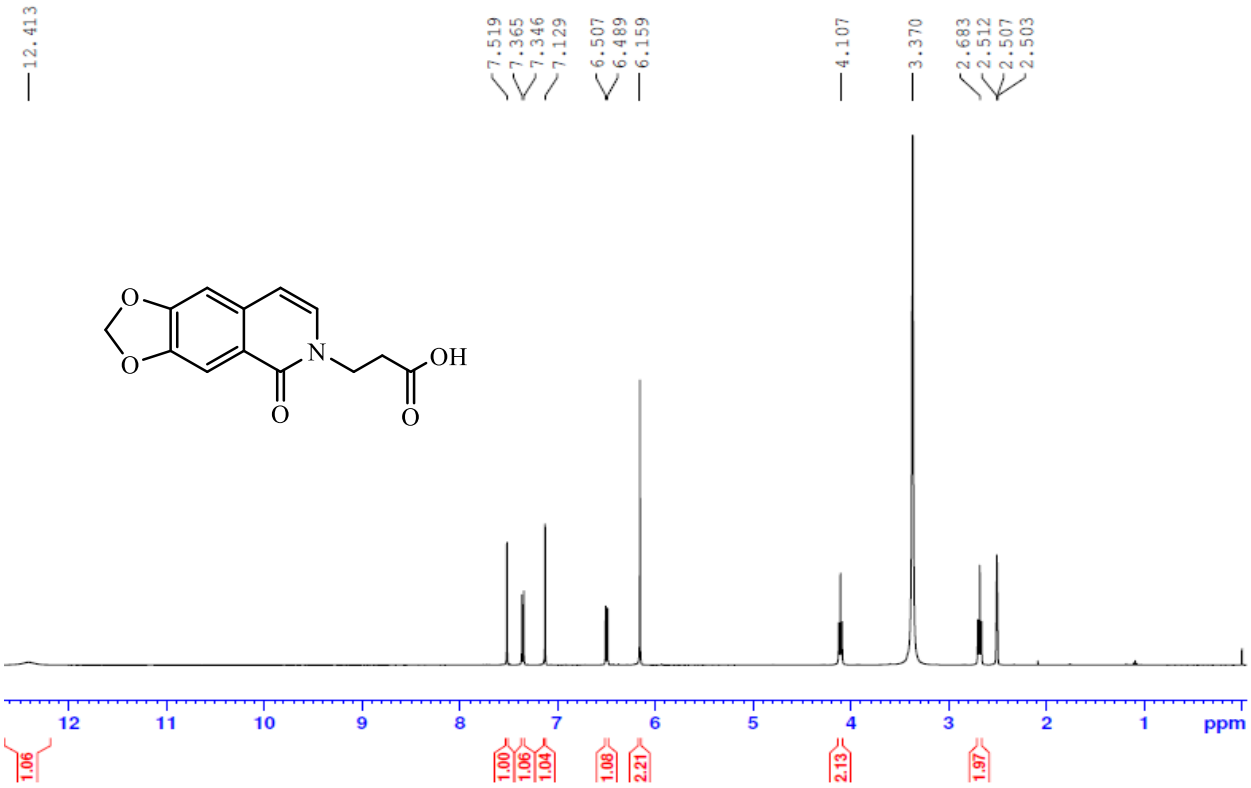
^{13}C NMR of 103



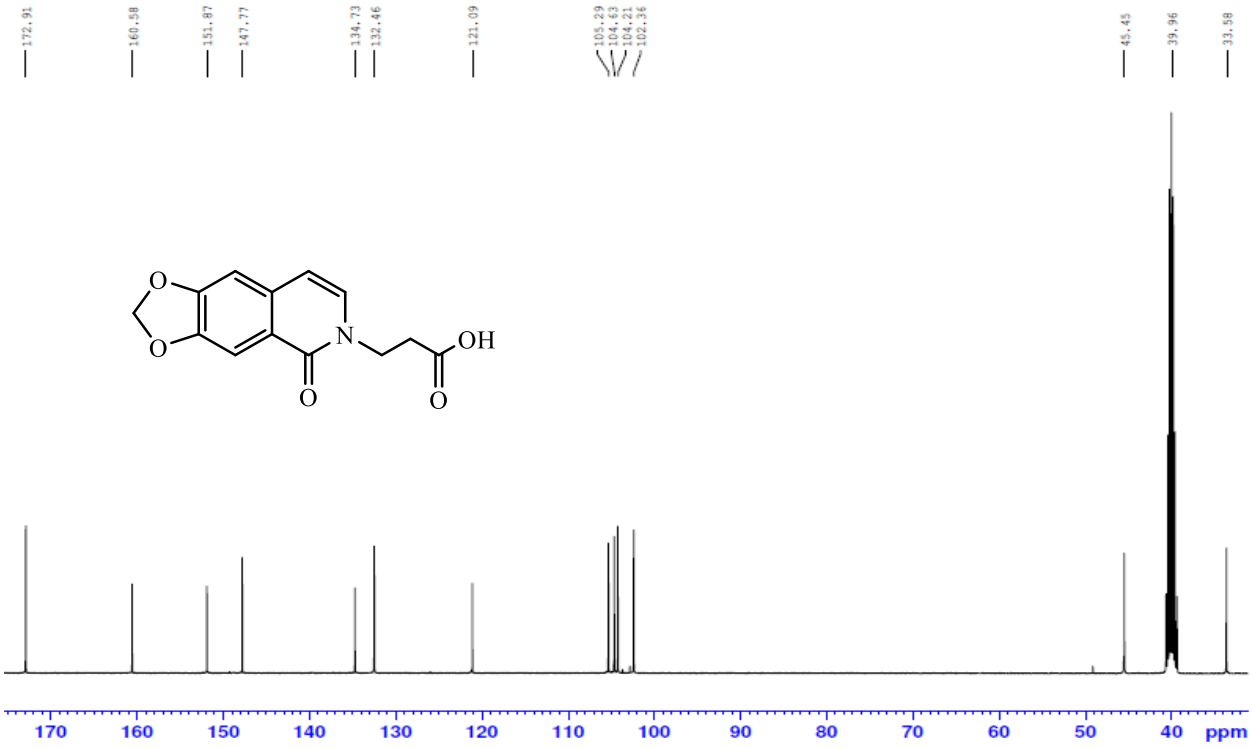
^{1}H NMR of 105



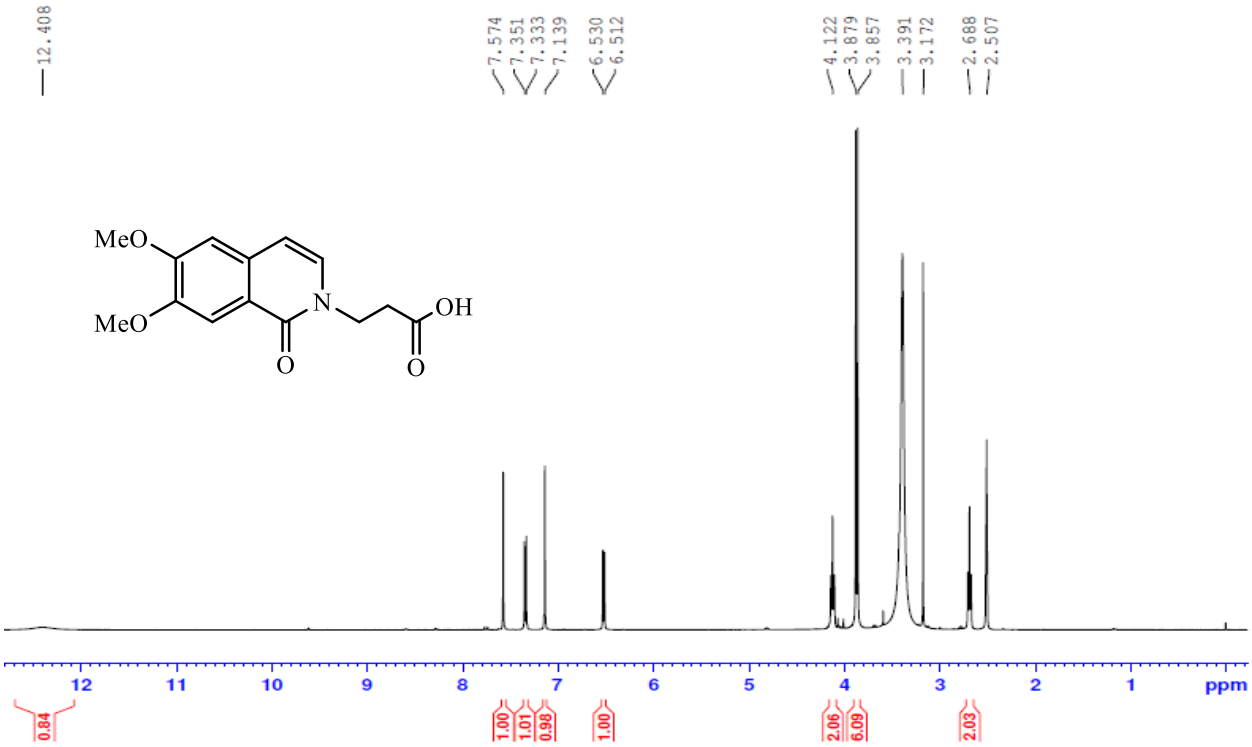
^{13}C NMR of 105



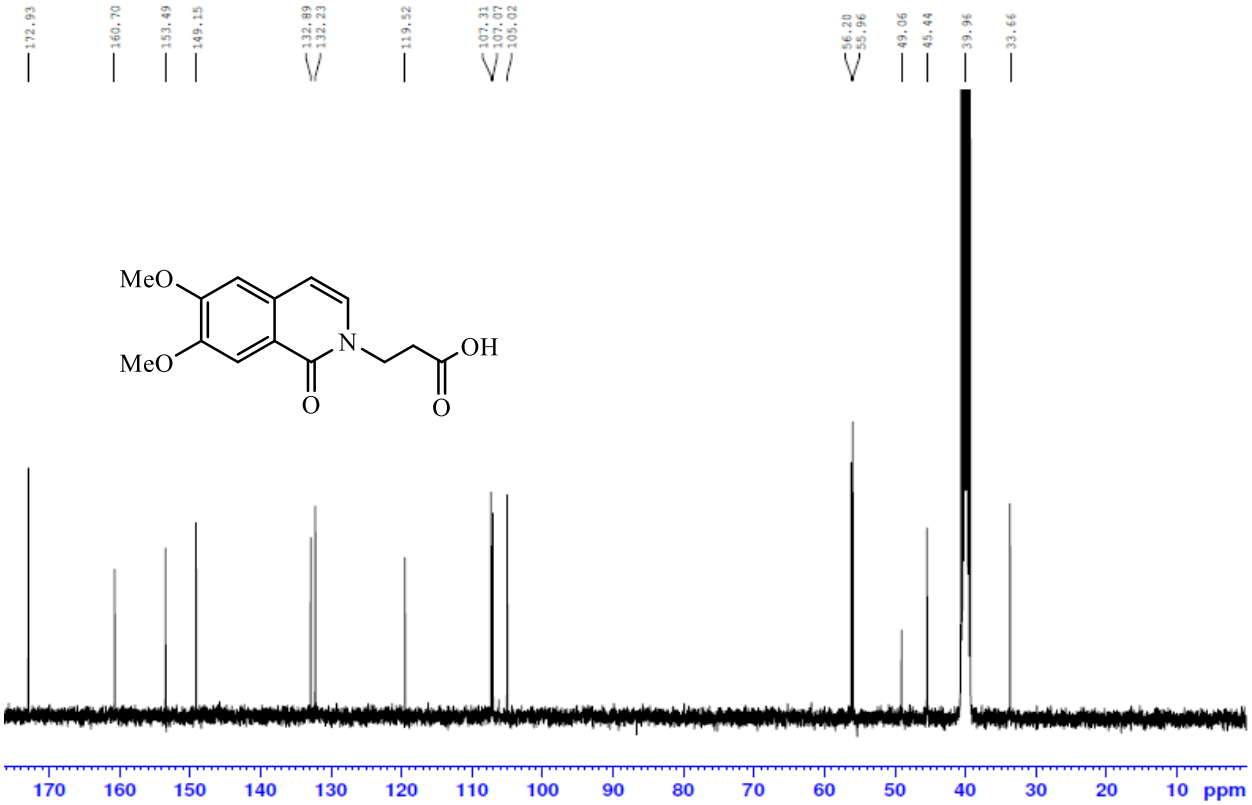
^{1}H NMR of 112a



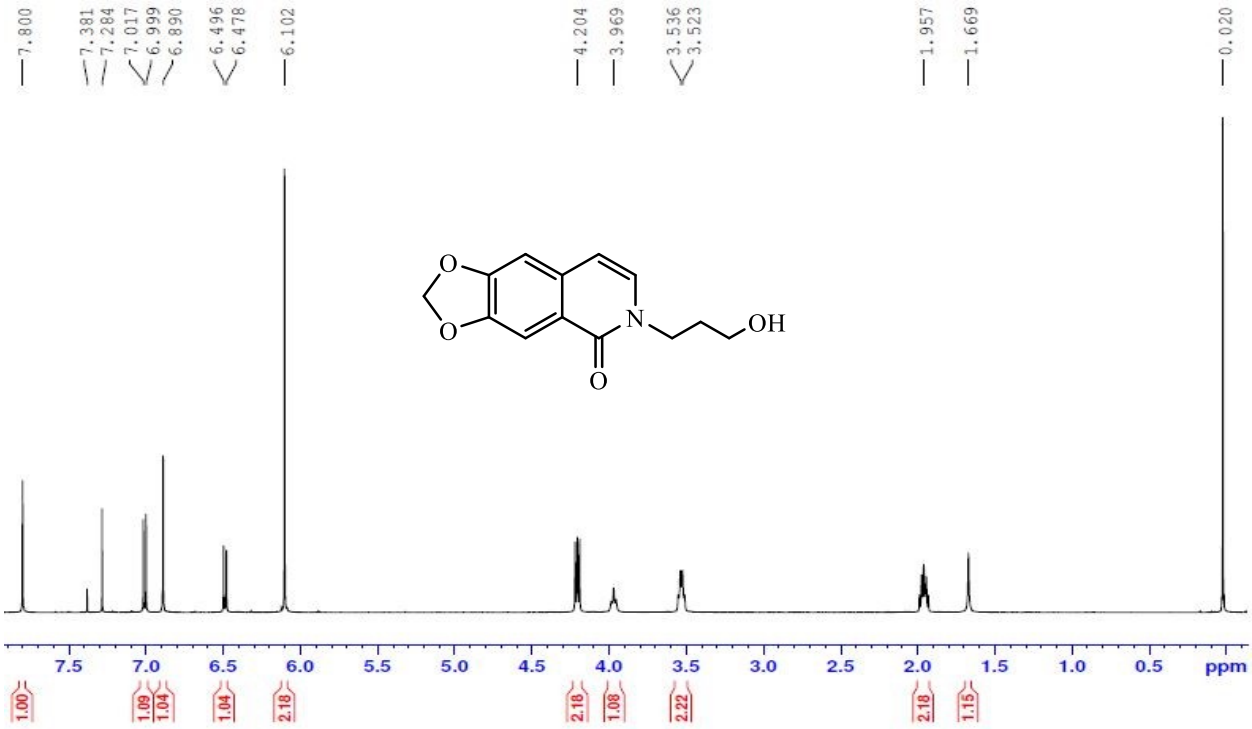
^{13}C NMR of 112a



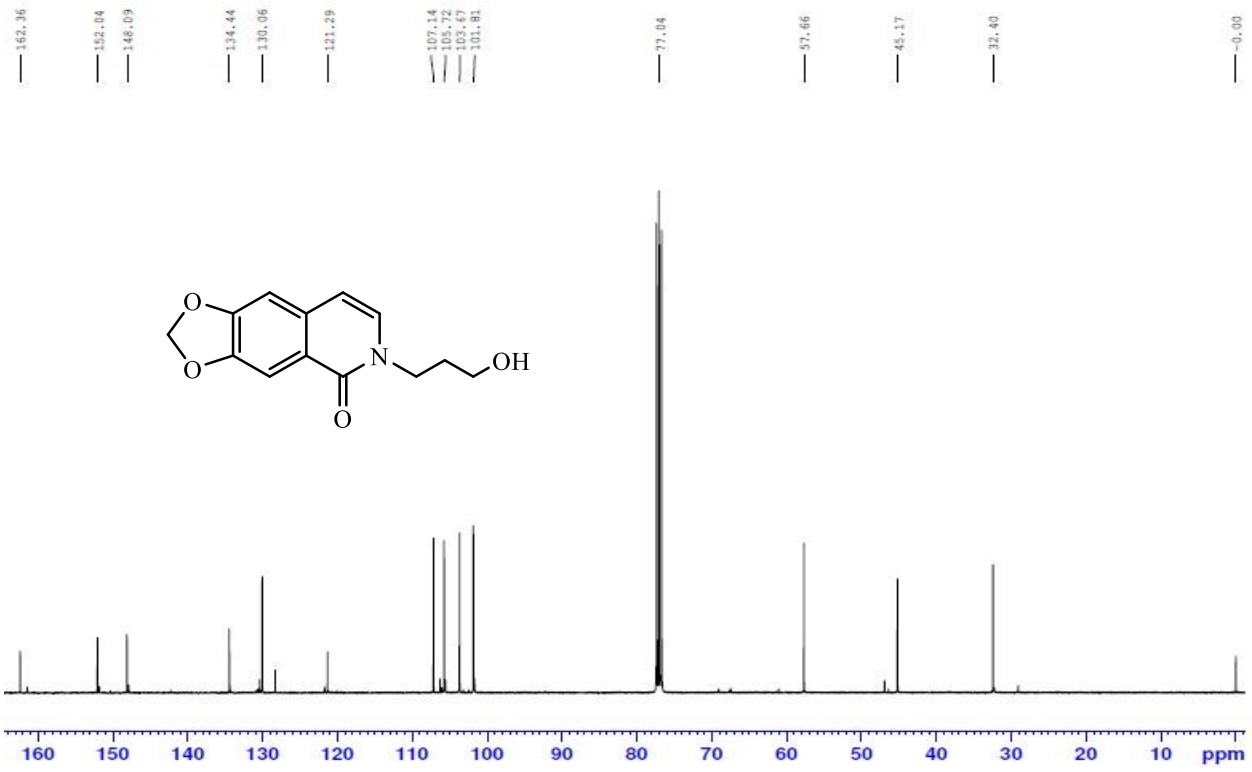
^{1}H NMR of 112b



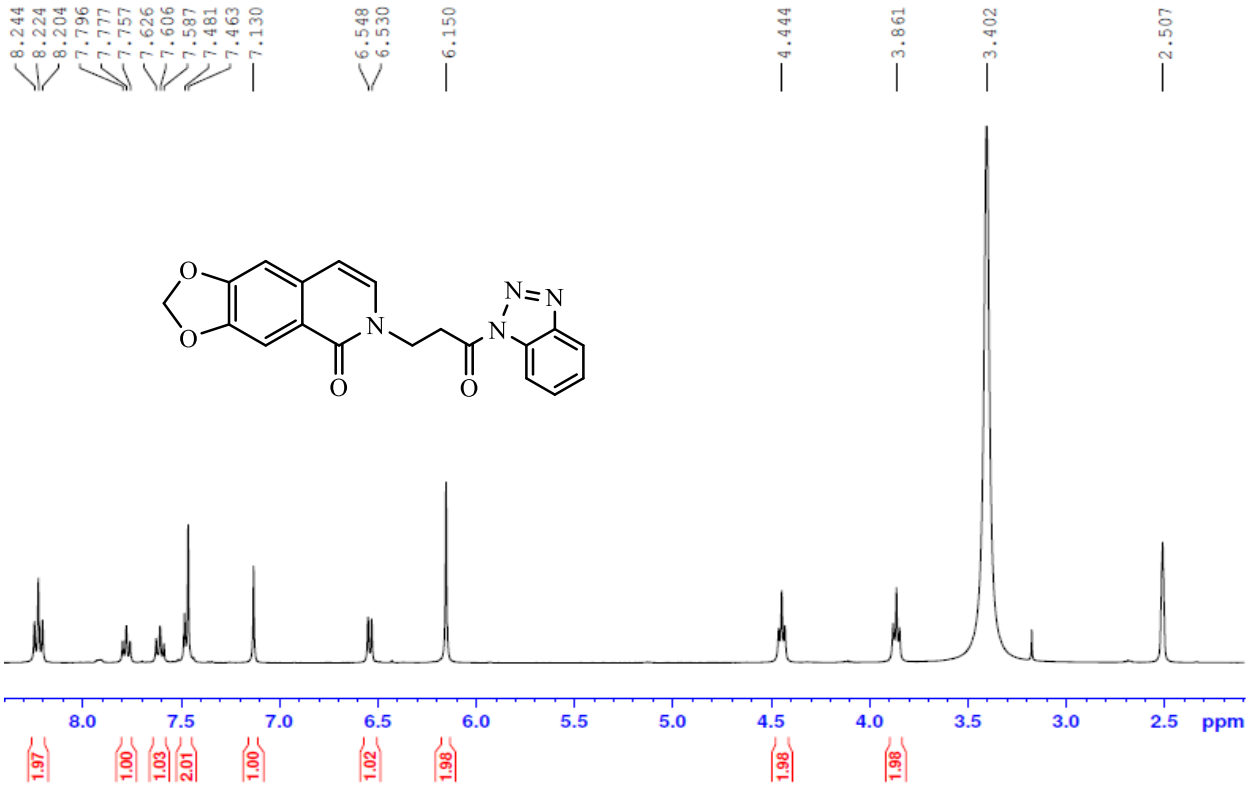
^{13}C NMR of 112b



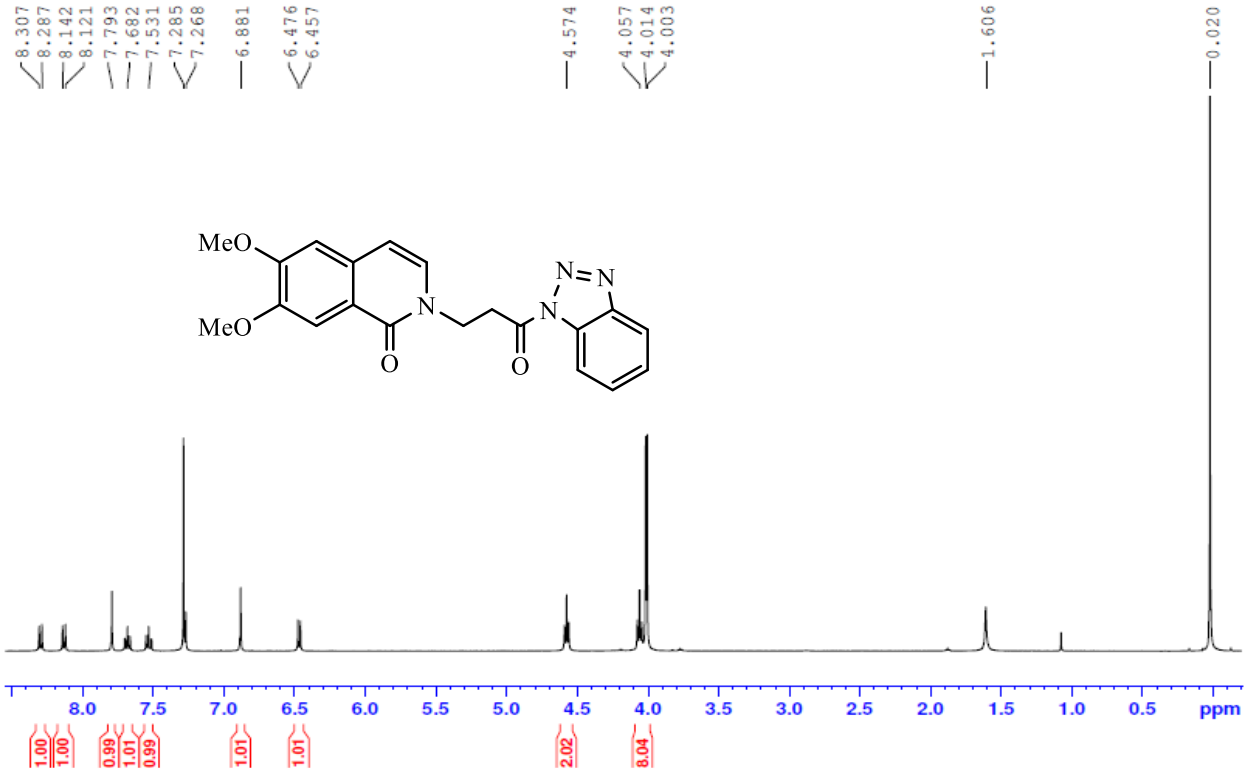
^{1}H NMR of 122



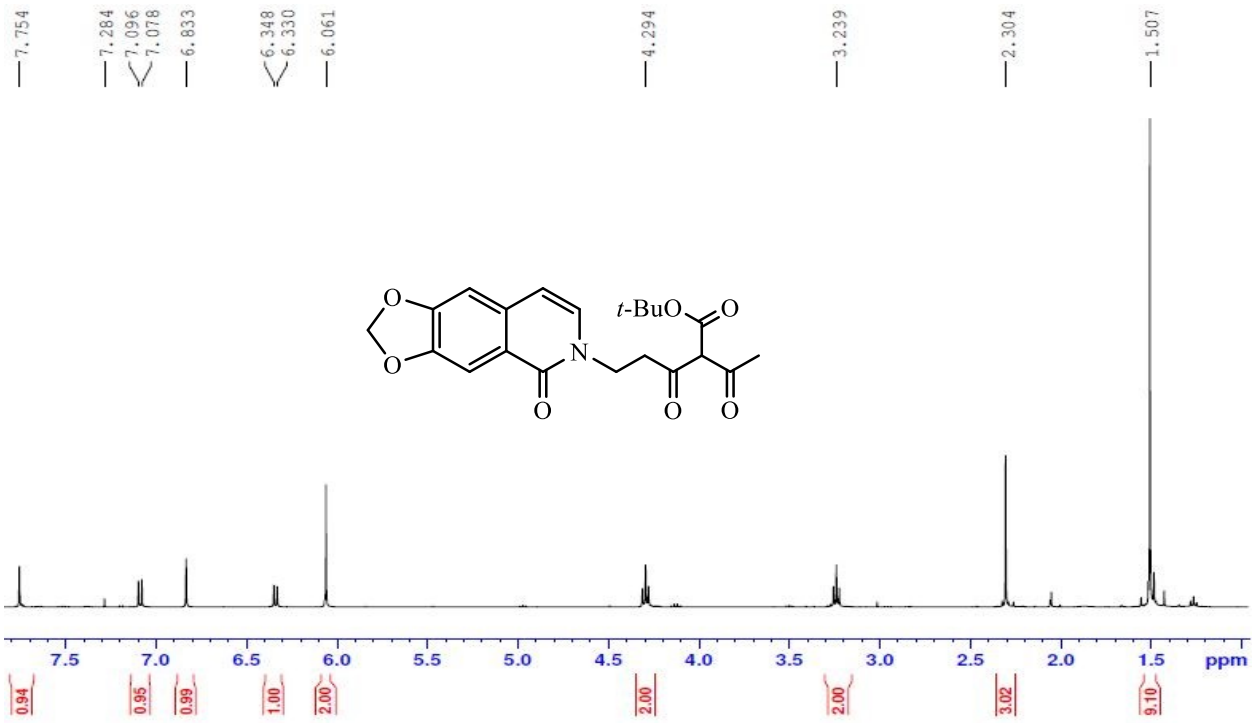
^{13}C NMR of 122



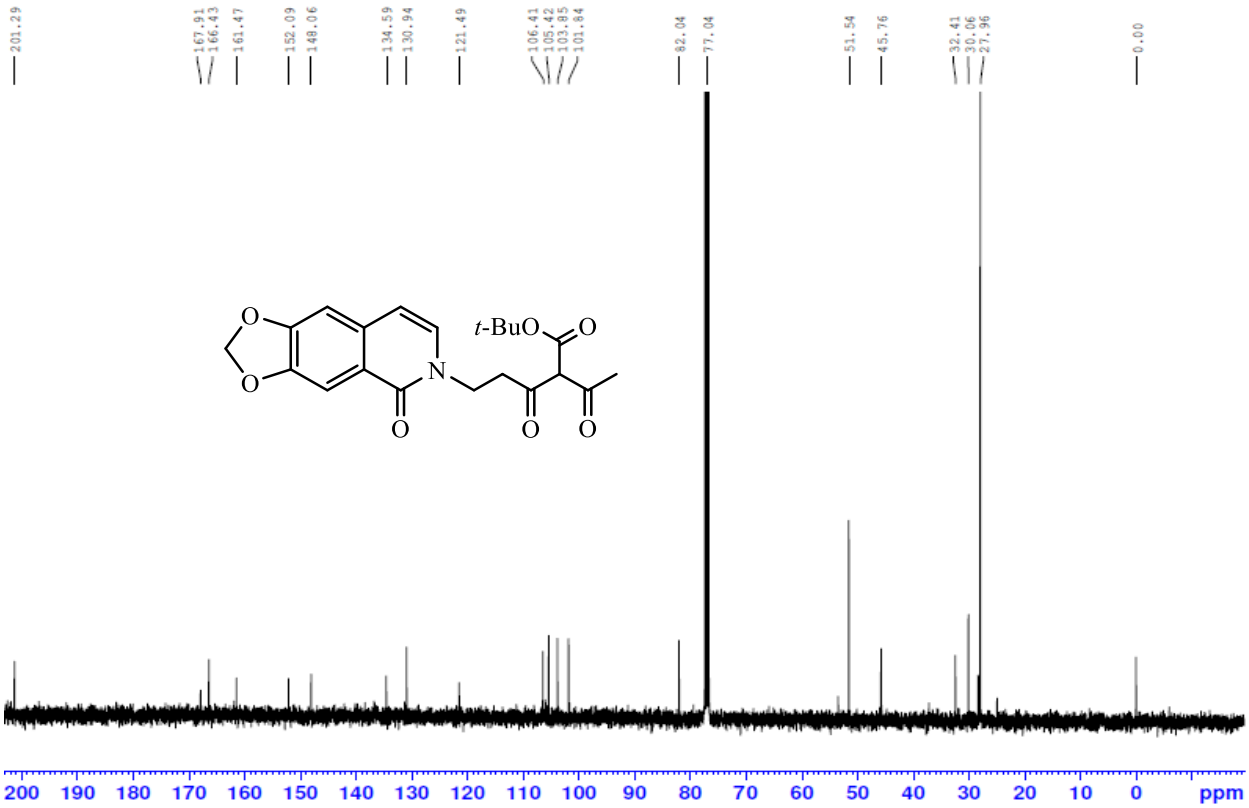
^{1}H NMR of 127a



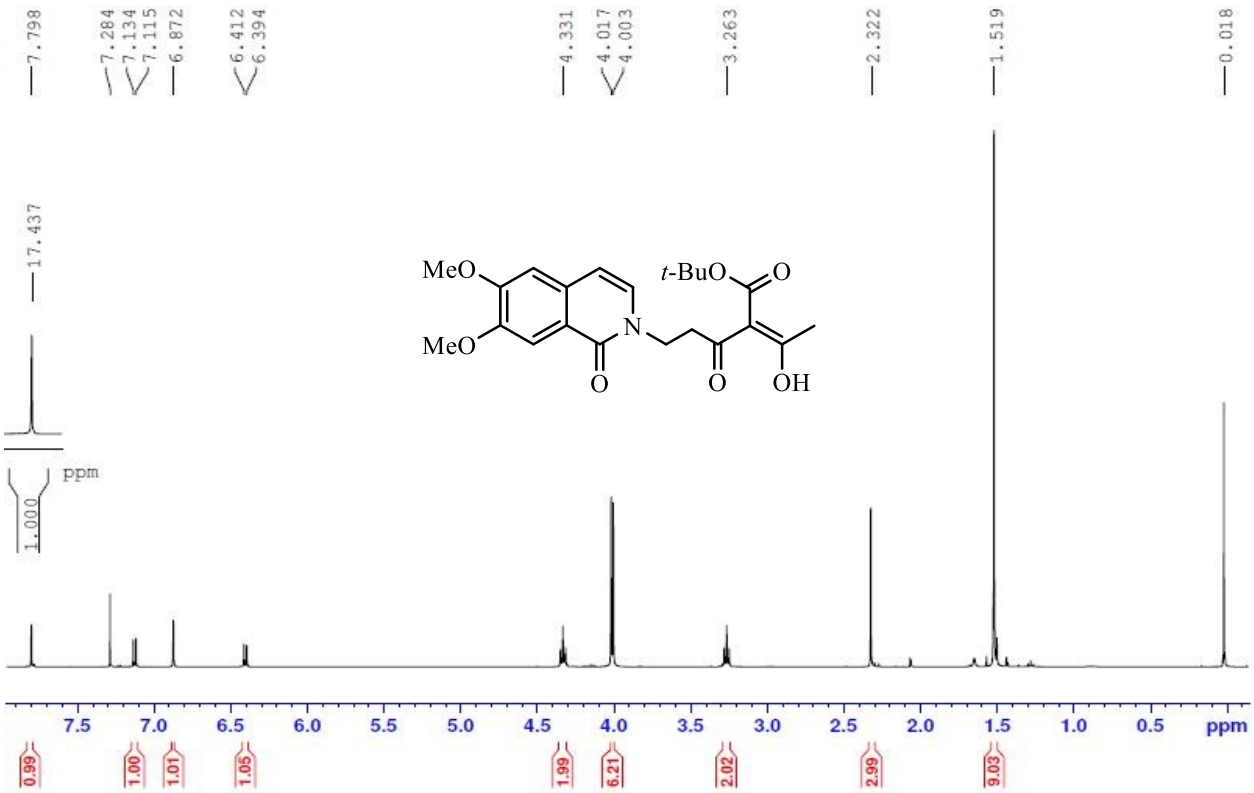
^{1}H NMR of 127b



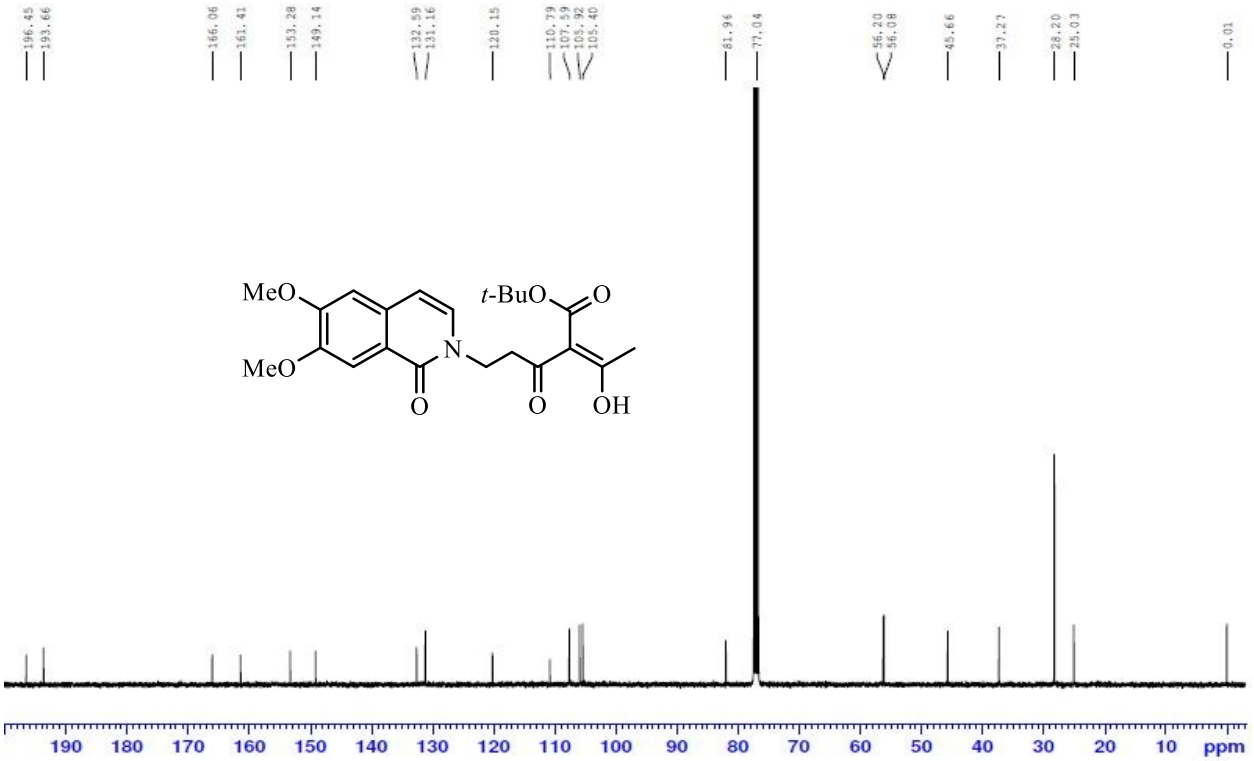
^{1}H NMR of 128a



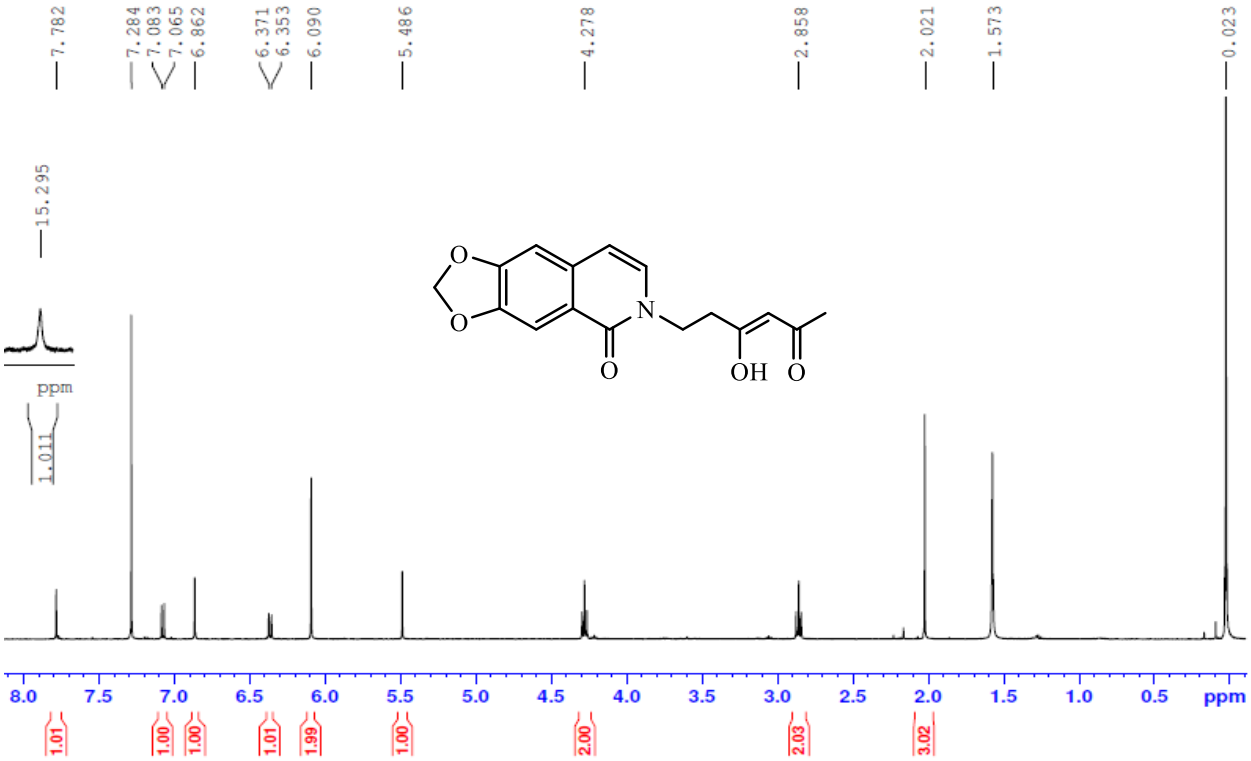
^{13}C NMR of 128a



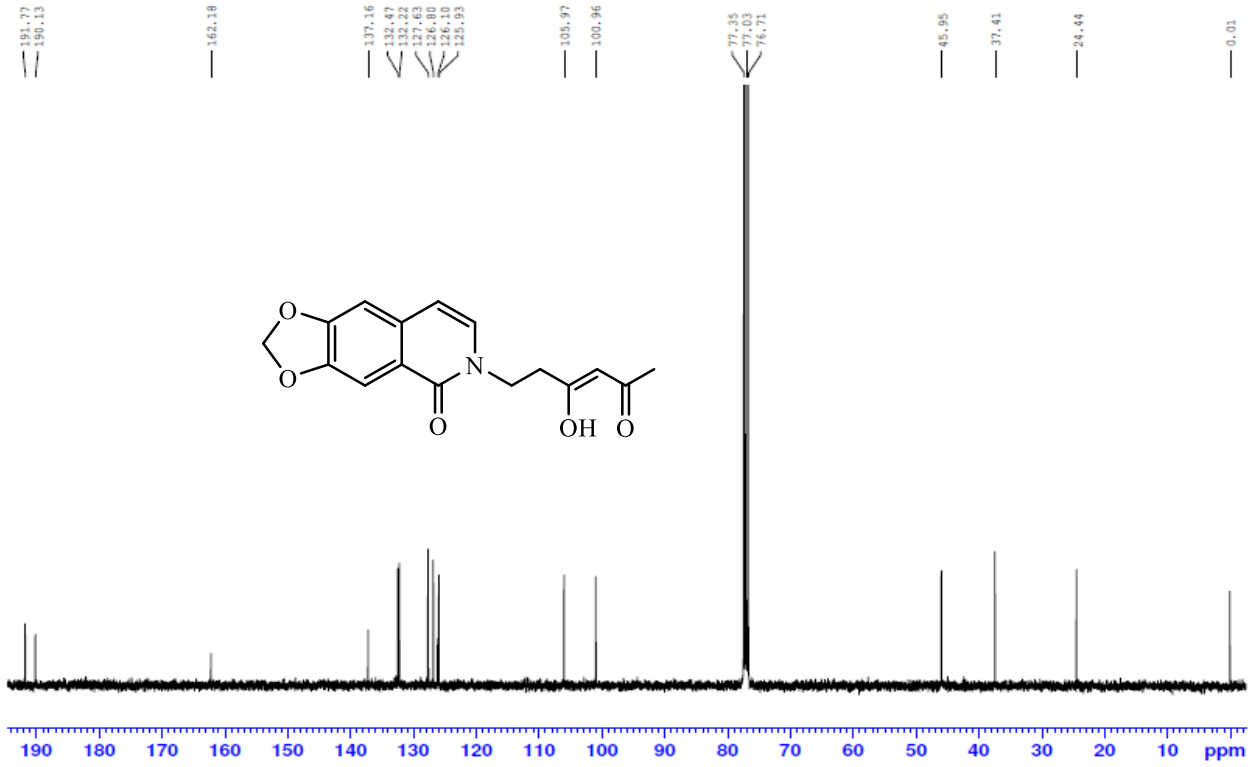
^{1}H NMR of 128b



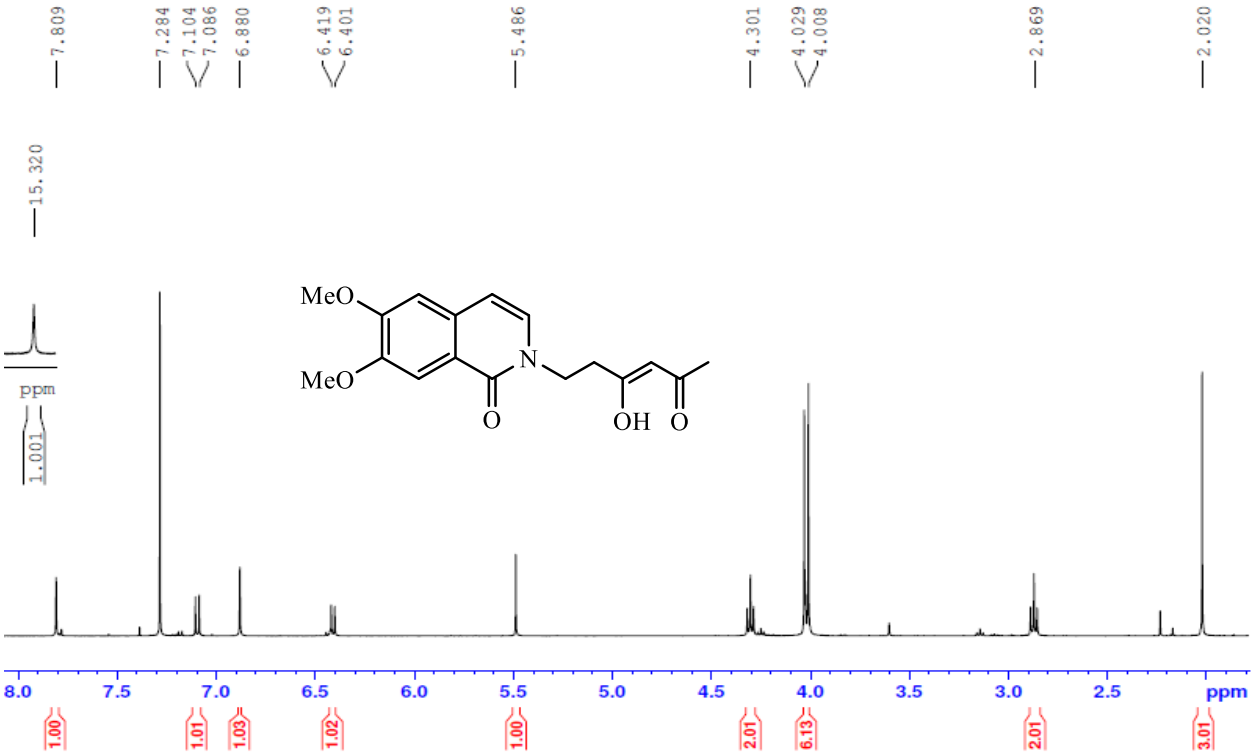
^{13}C NMR of 128b



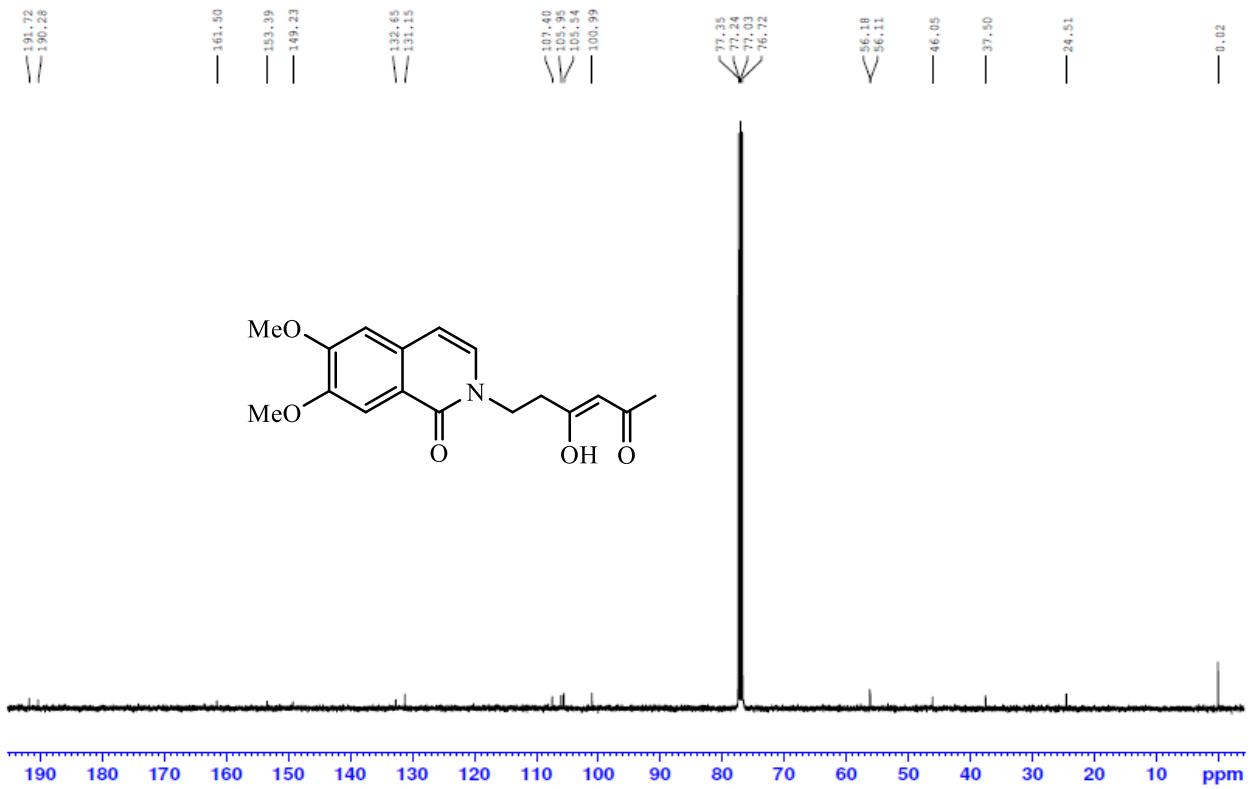
^{1}H NMR of 129a



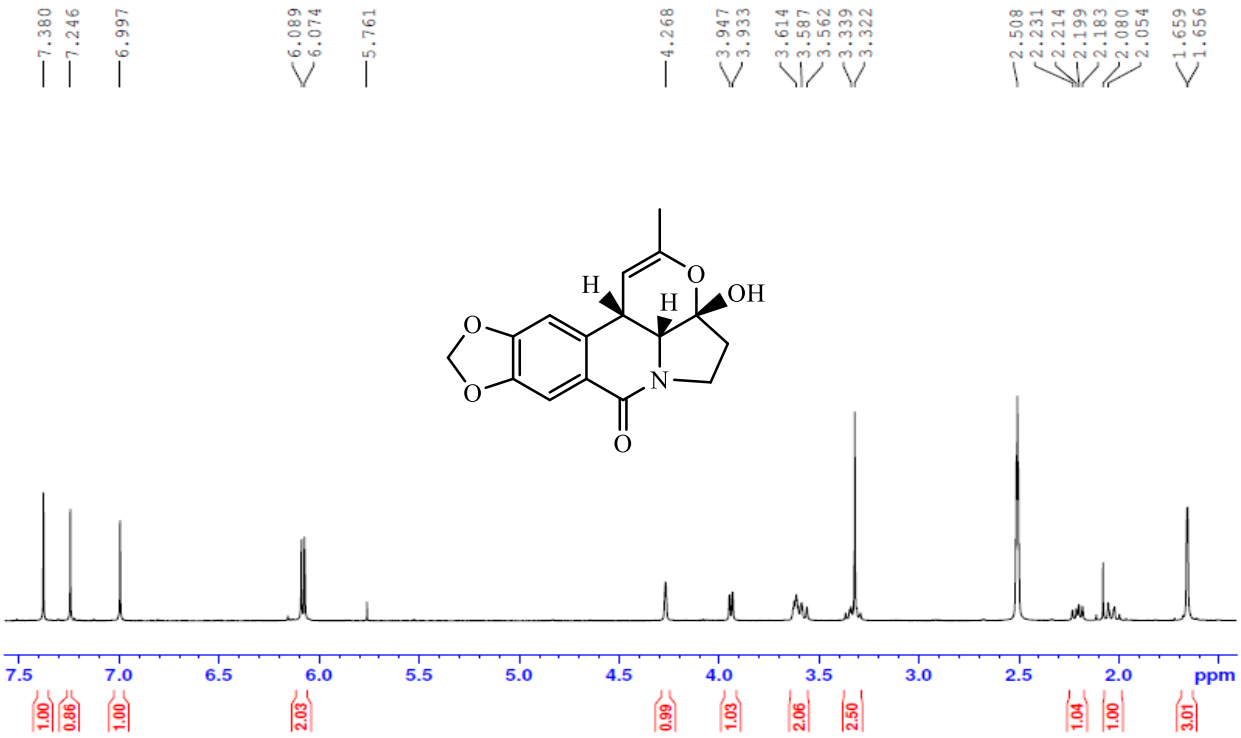
^{13}C NMR of 129a



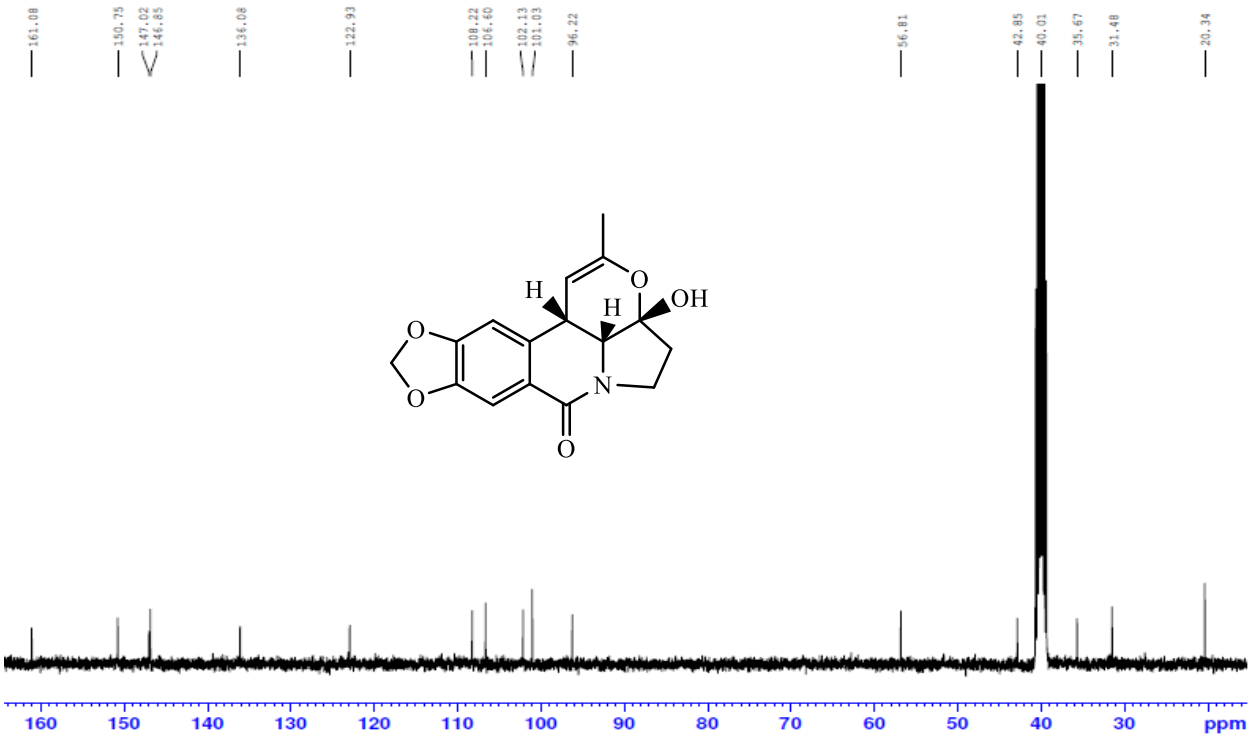
^{1}H NMR of 129b



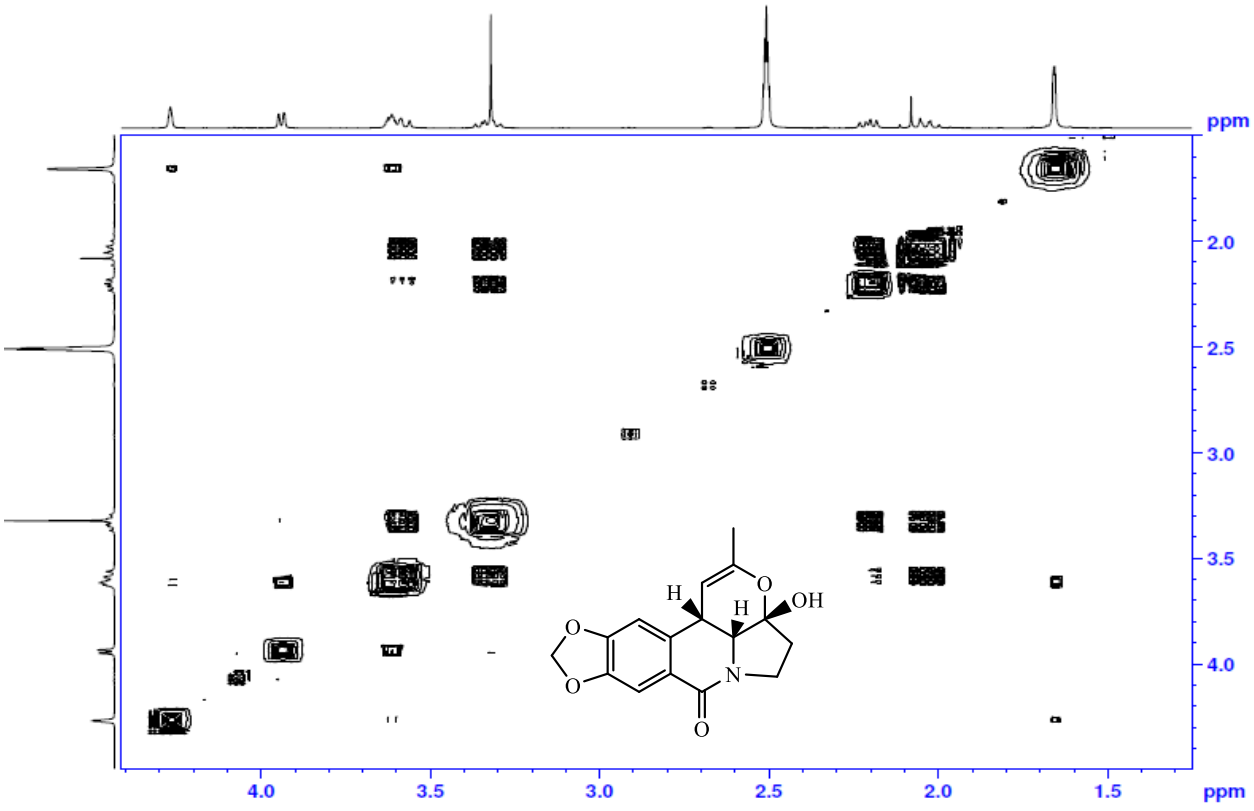
^{13}C NMR of 129b



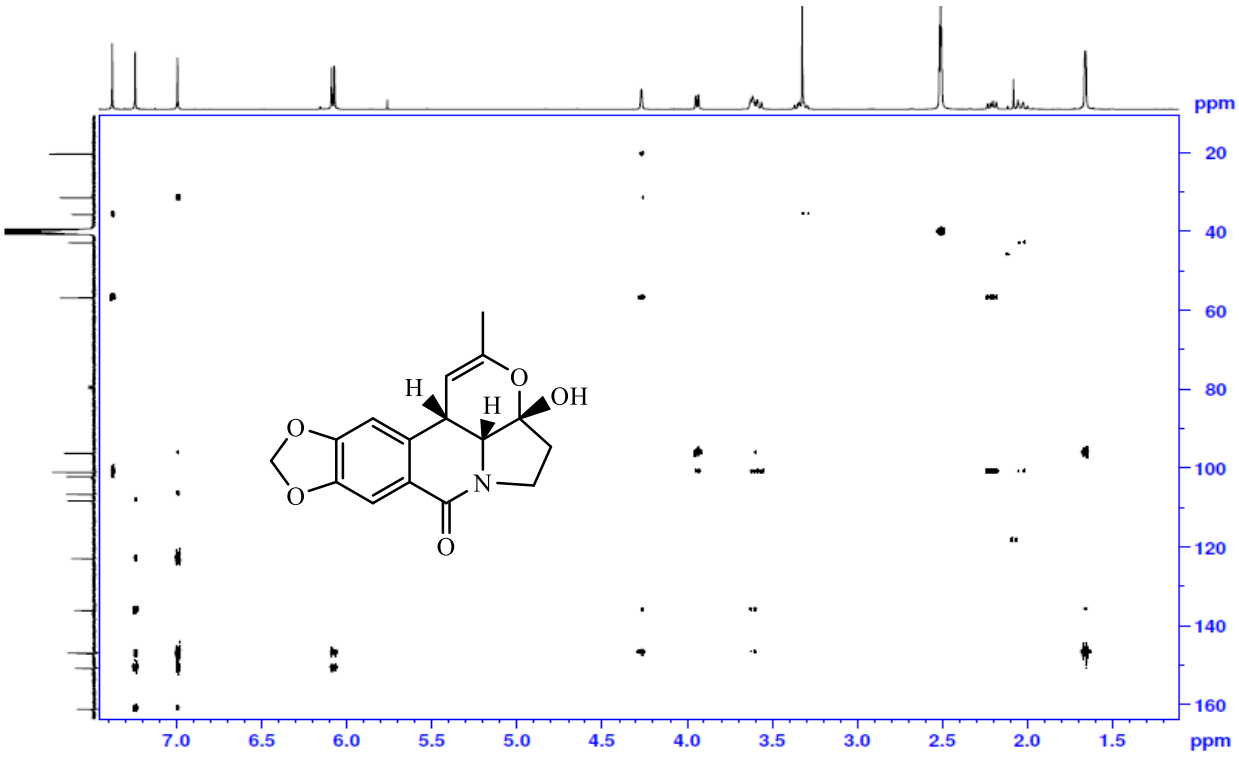
^{1}H NMR of 131a



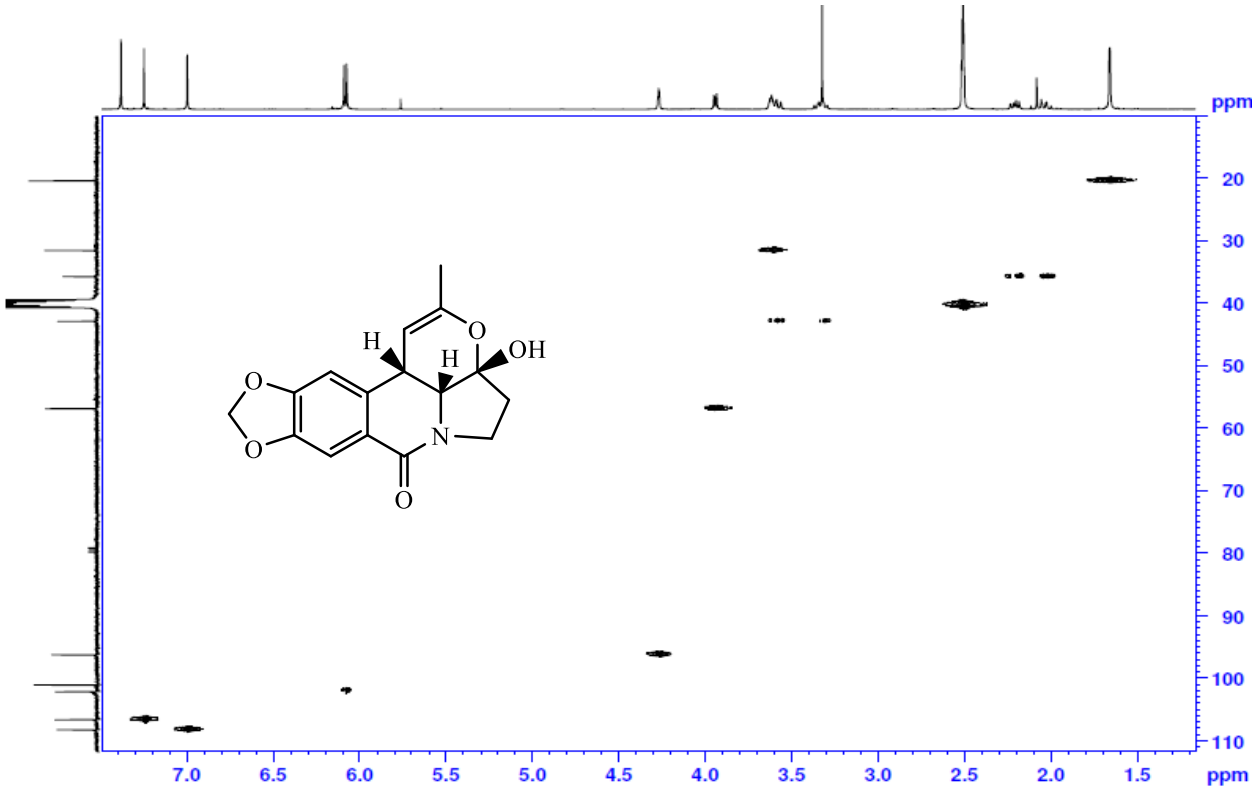
^{13}C NMR of 131a



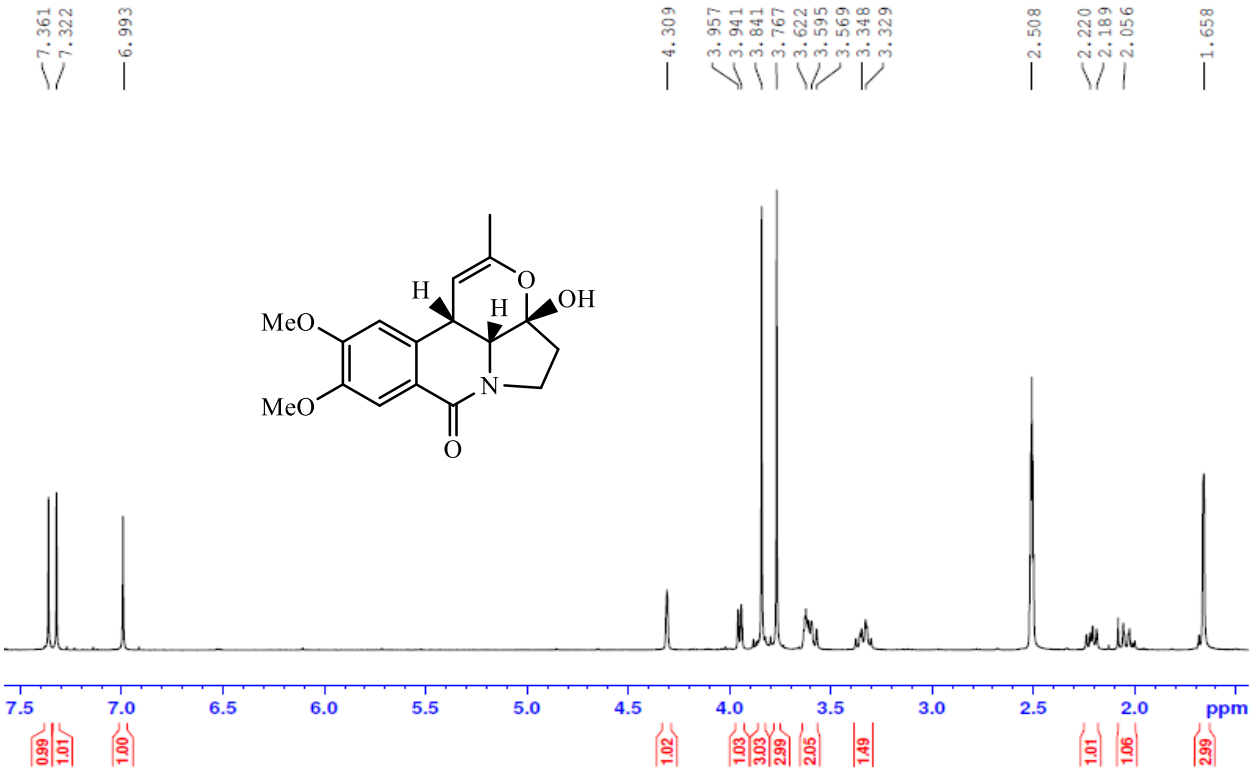
COSY of 131a



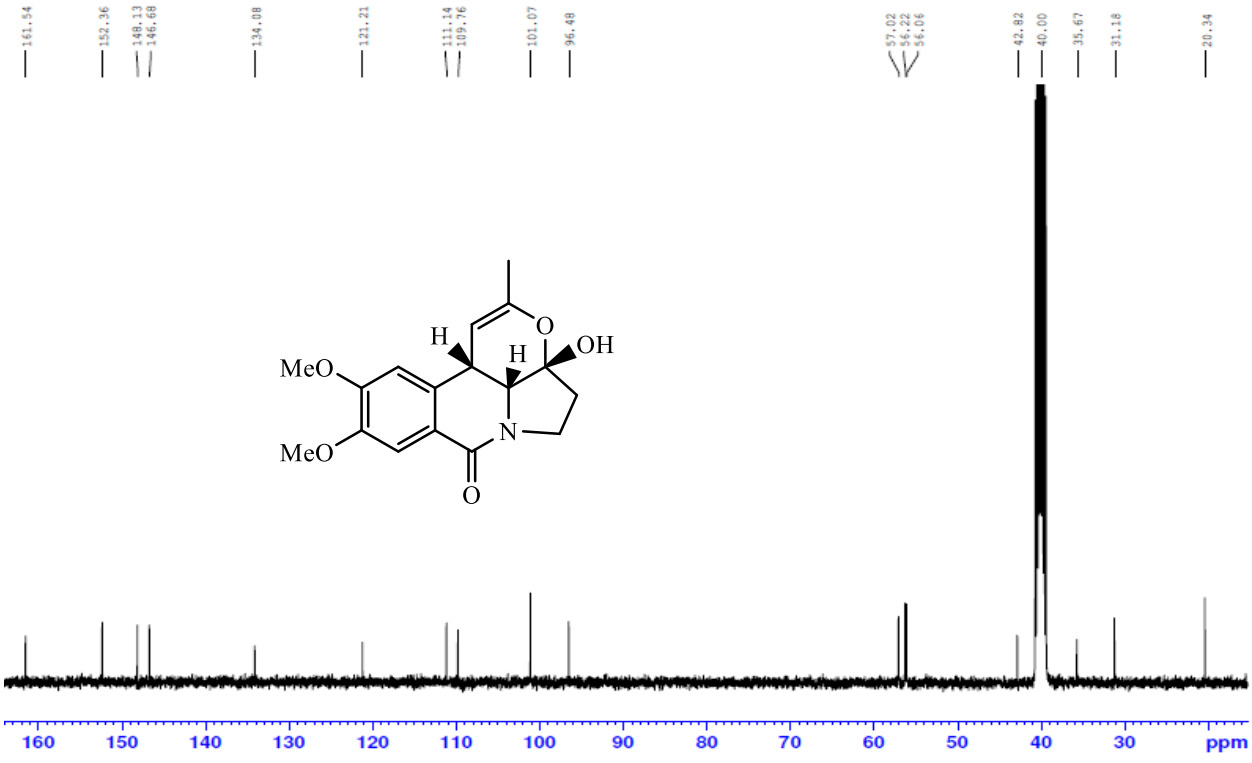
HMBC of 131a



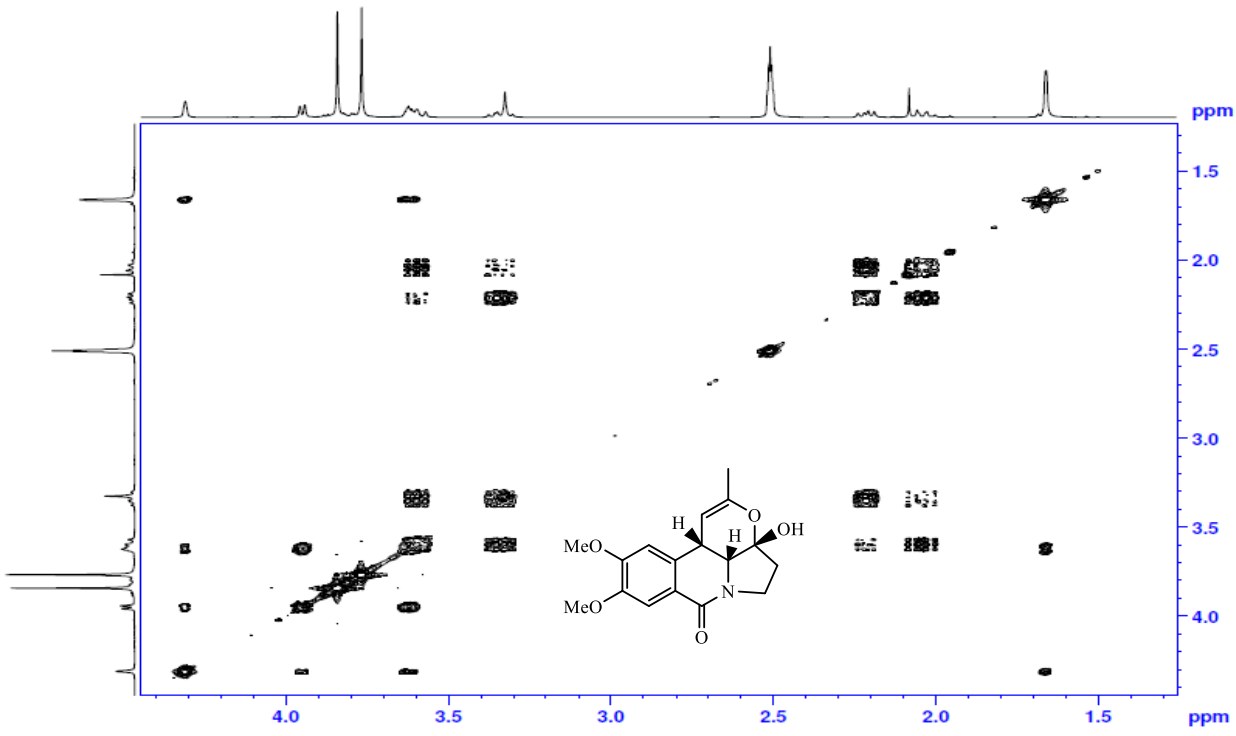
HSQC of 131a



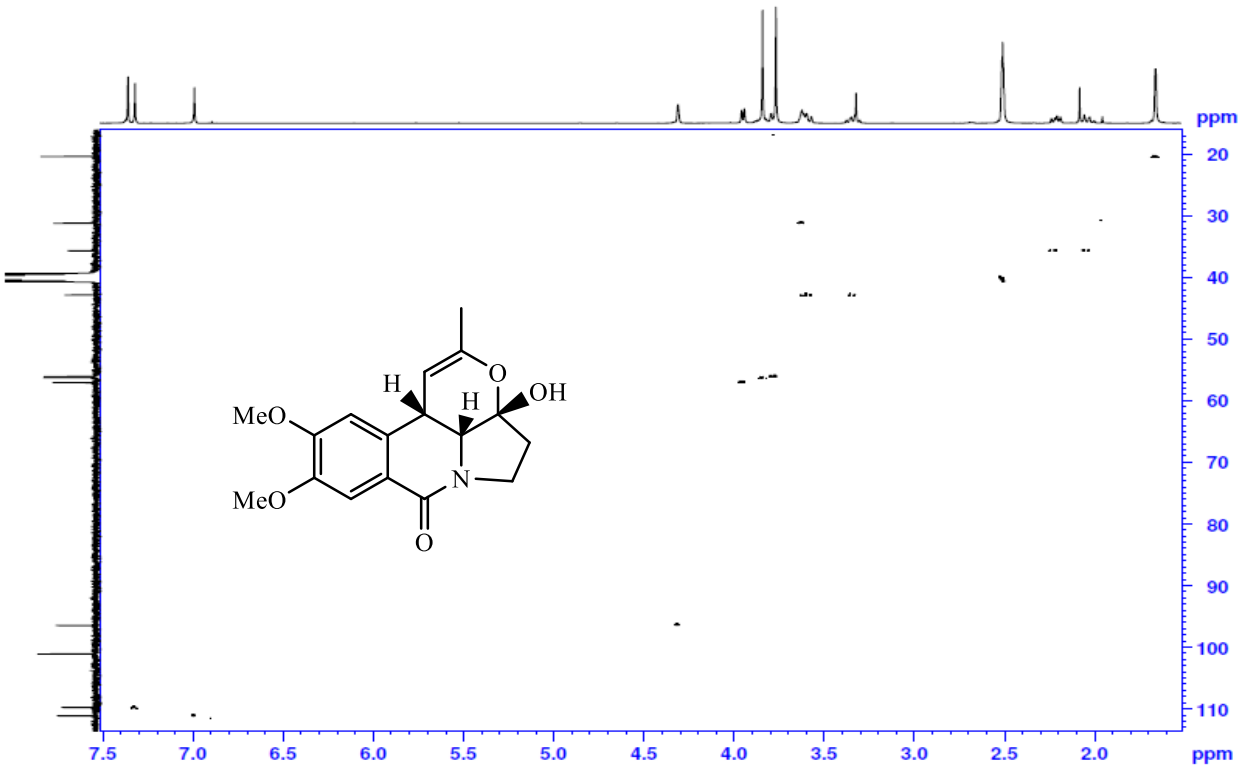
^{1}H NMR of 131b



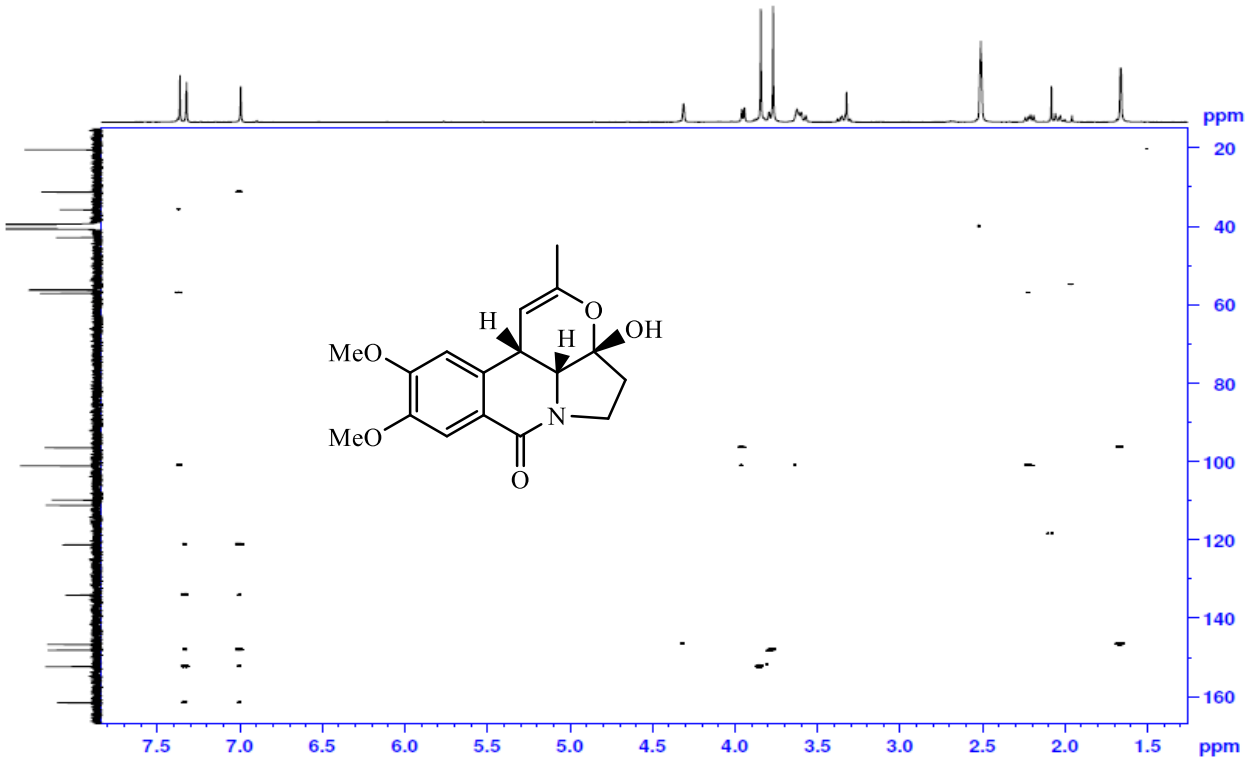
^{13}C NMR of 131b



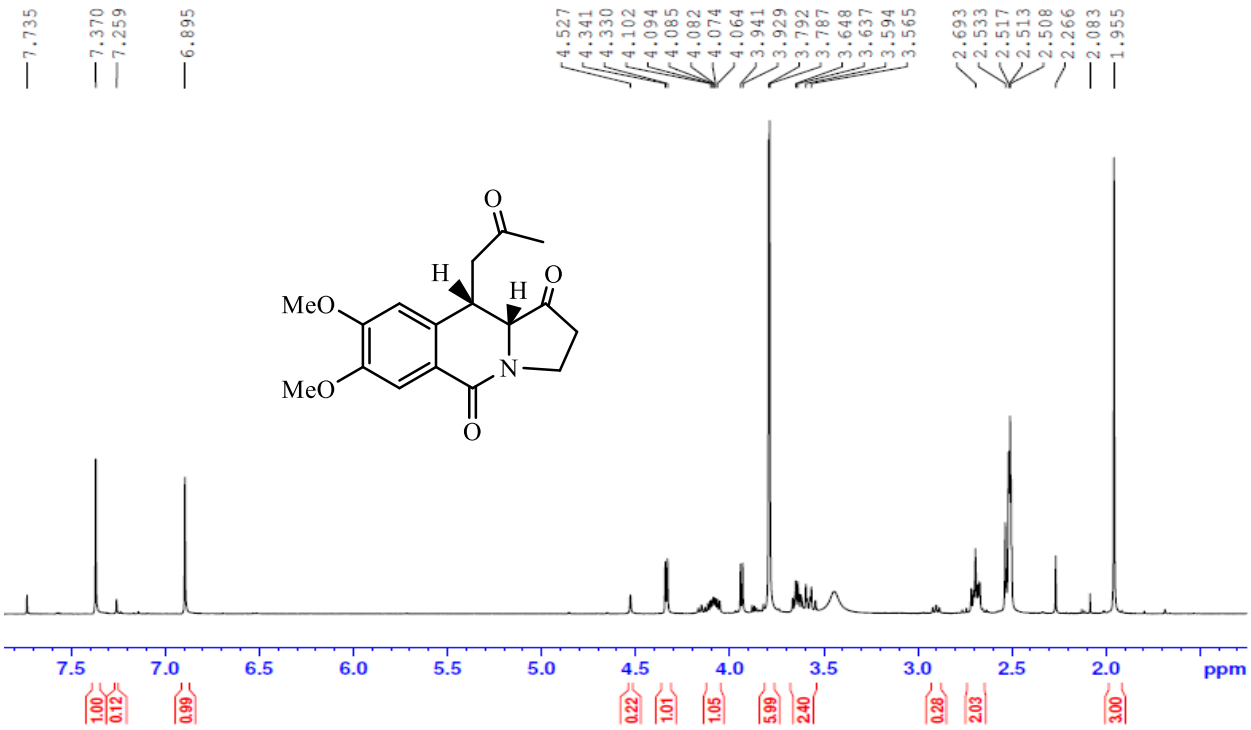
COSY90 of 131b



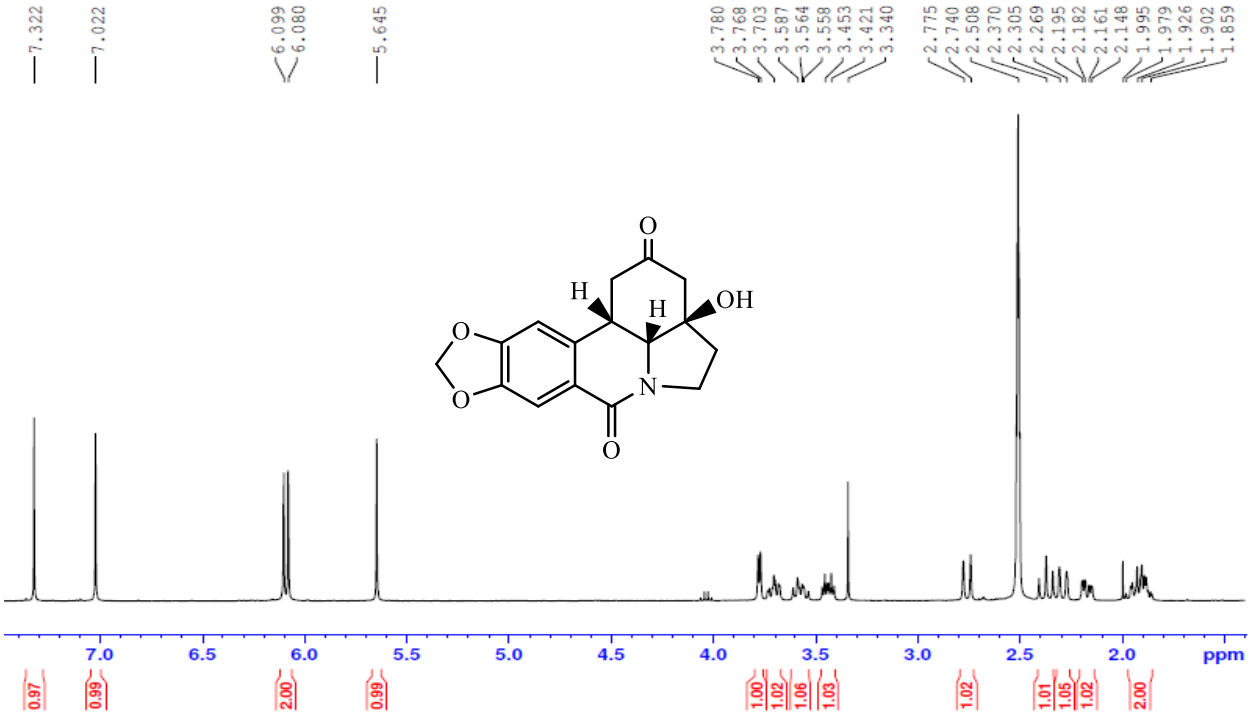
HSQC of 131b



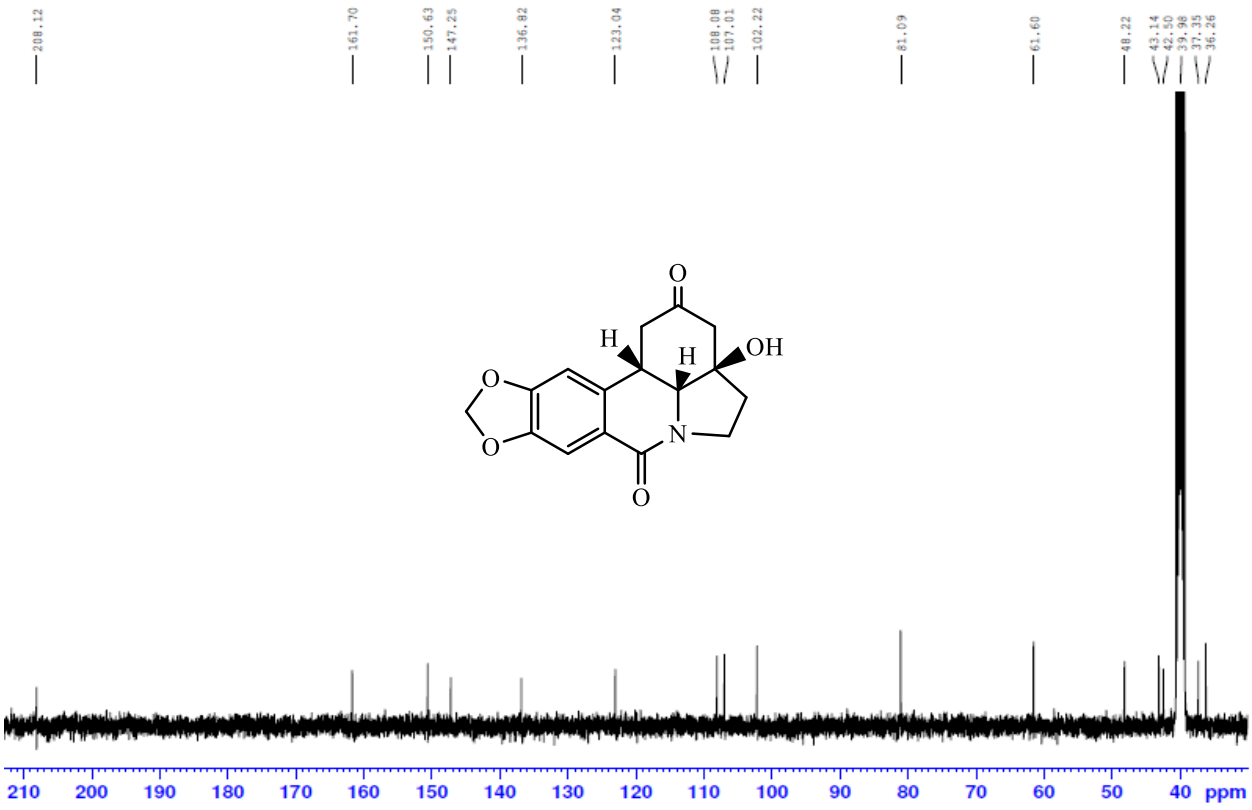
HMBC of 131b



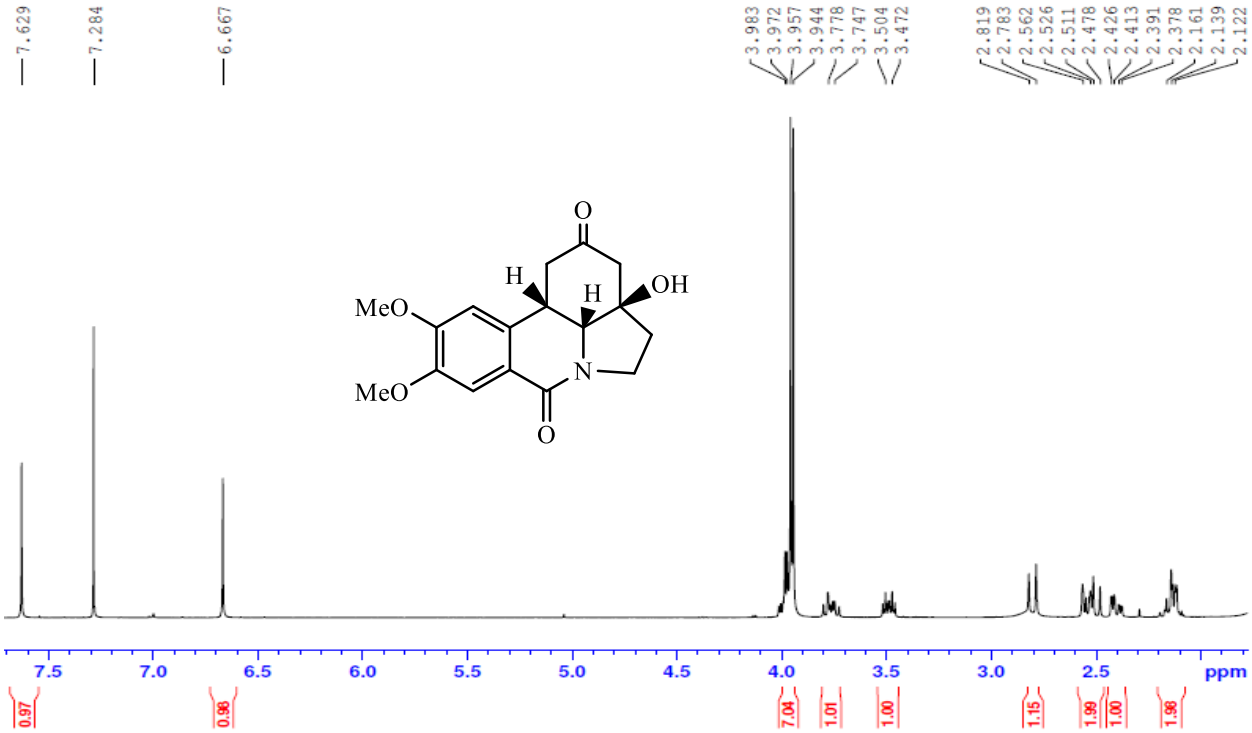
^{1}H NMR of 130b



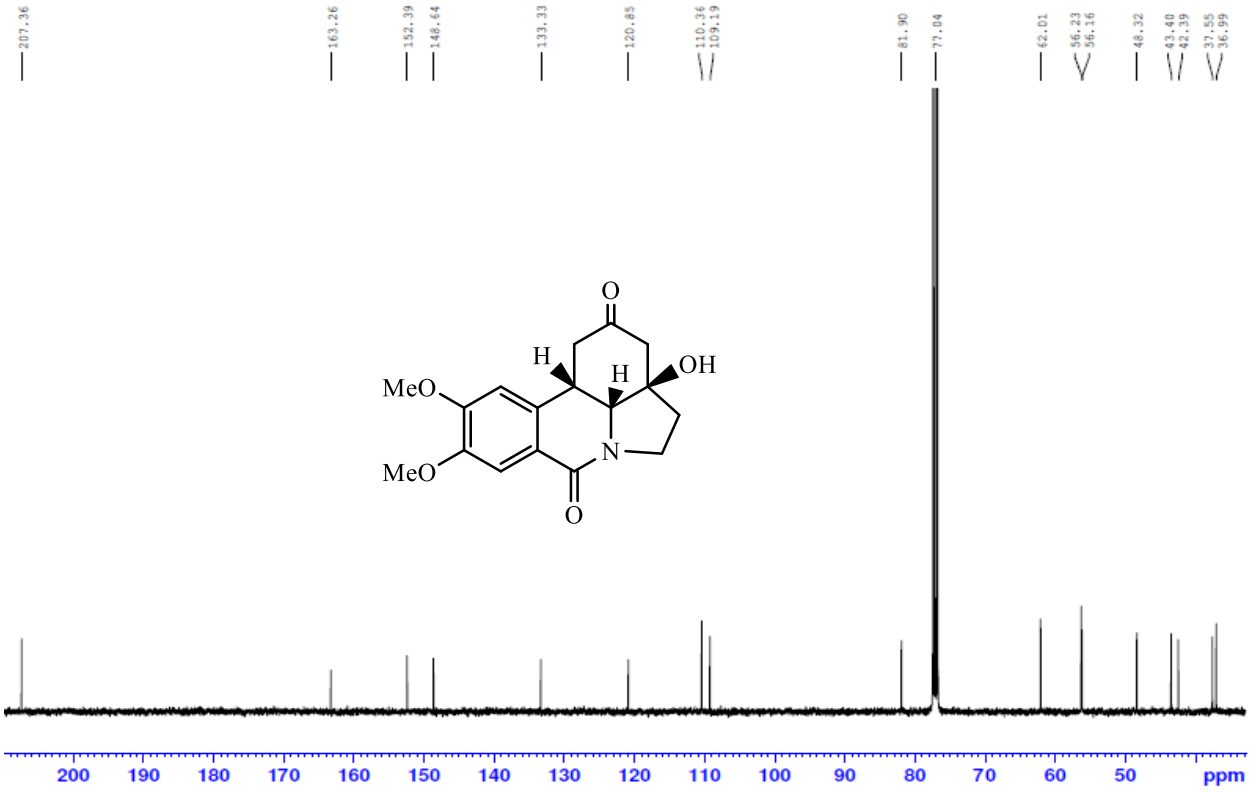
^{1}H NMR of 132a



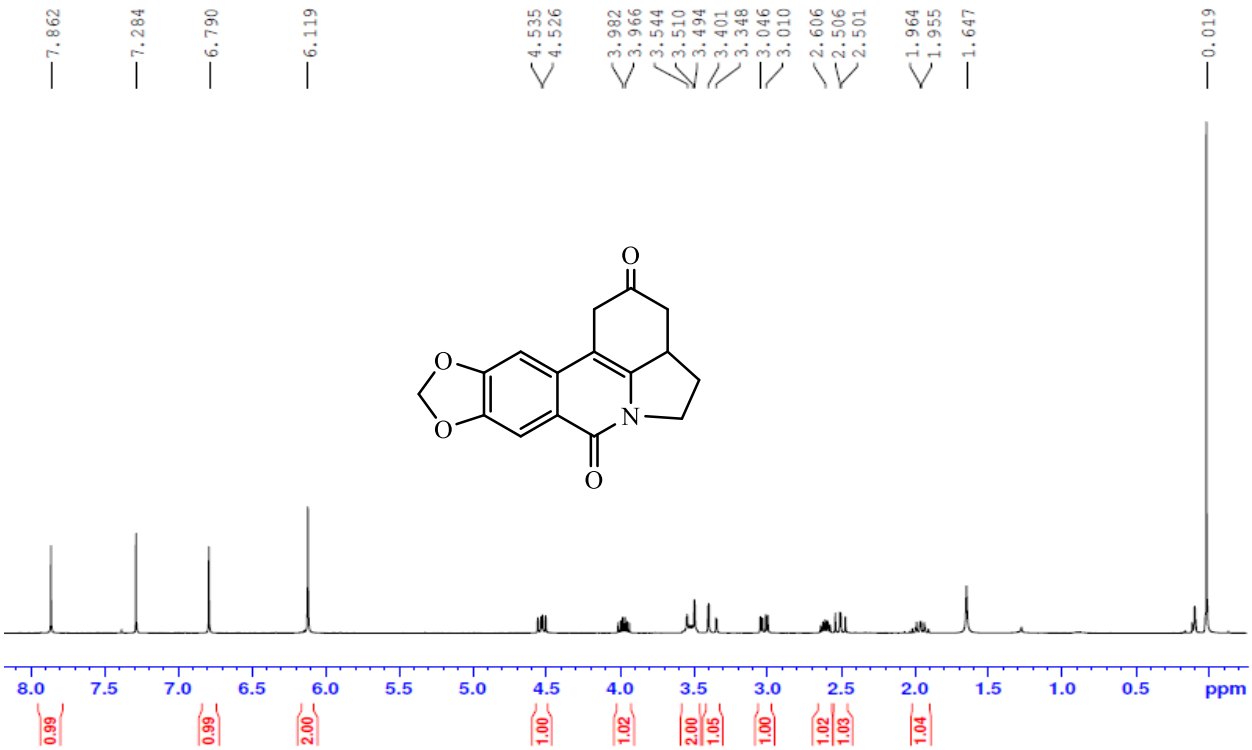
^{13}C NMR of 132a



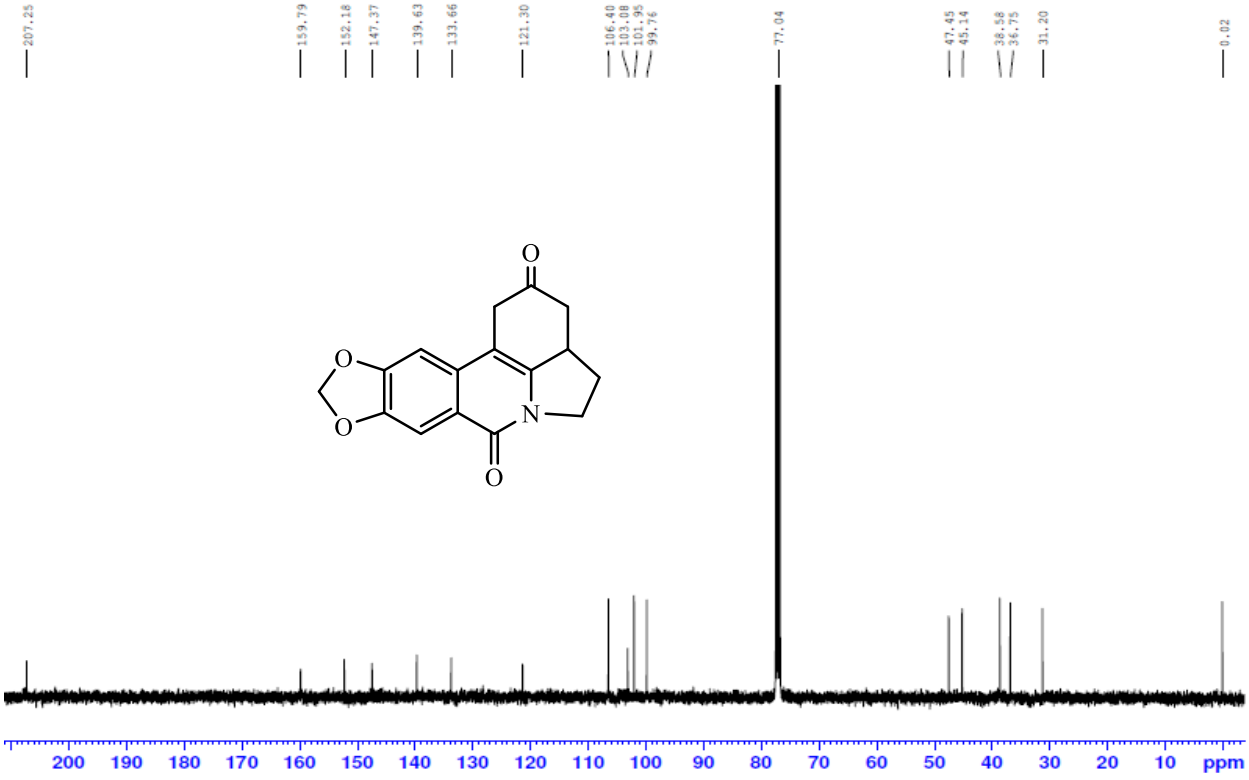
^{1}H NMR of 132b



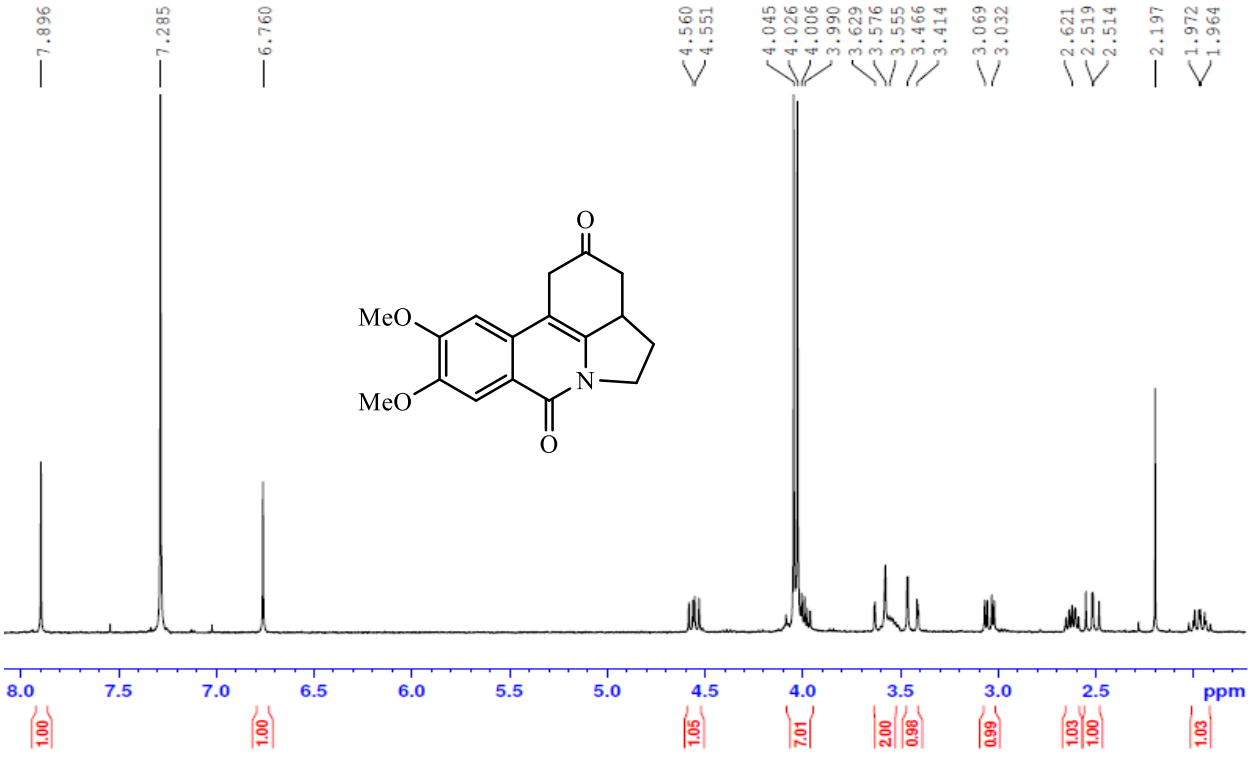
^{13}C NMR of 132b



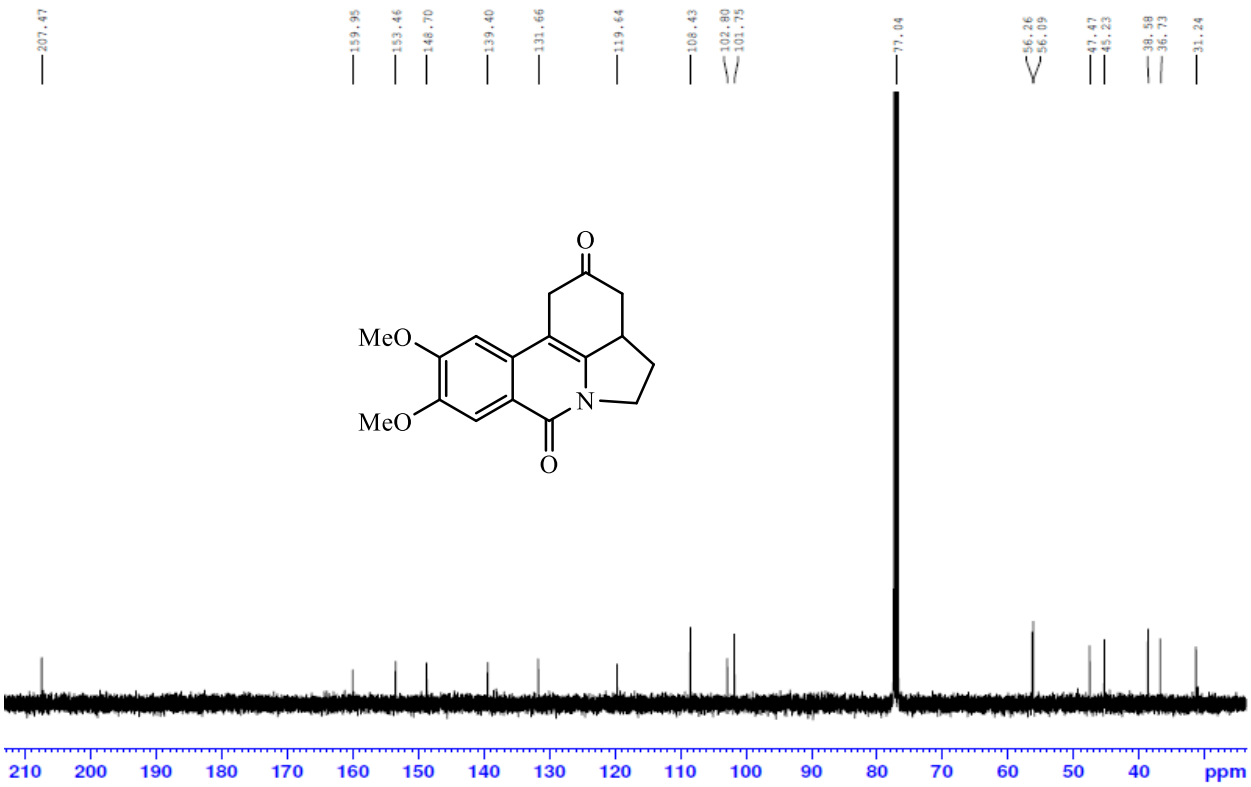
^{1}H NMR of 133a



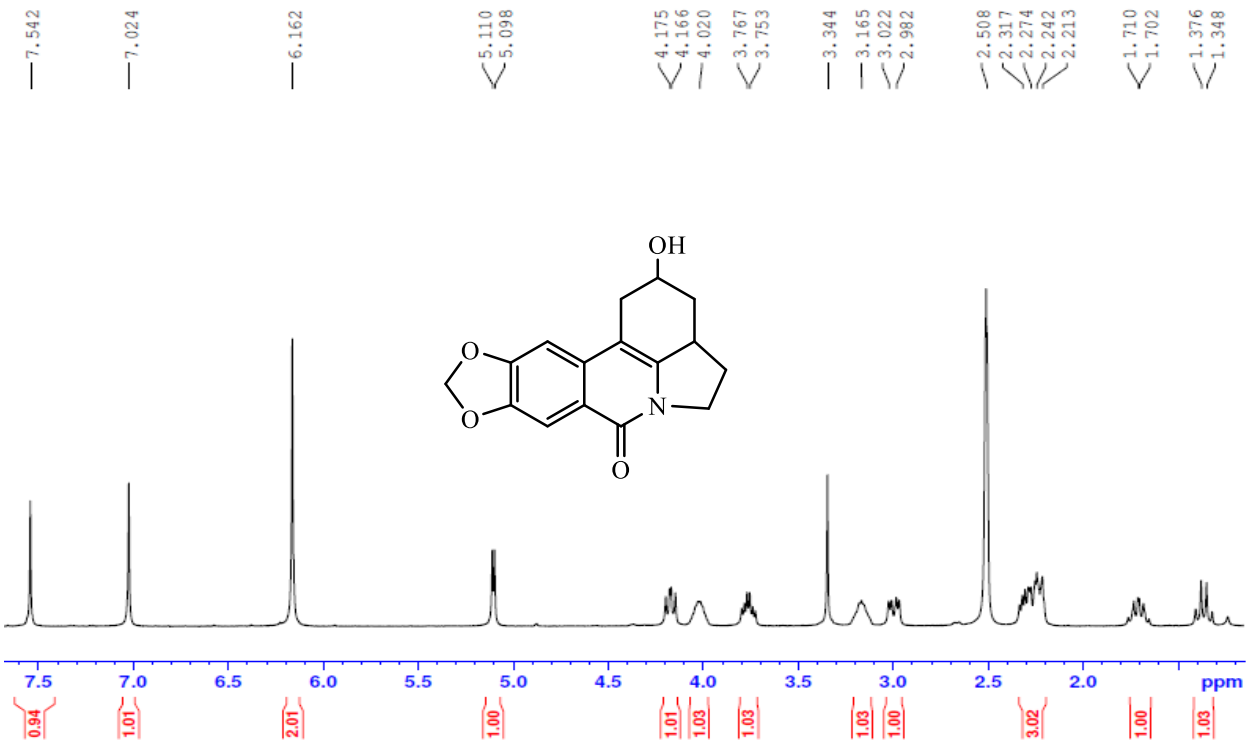
^{13}C NMR of 133a



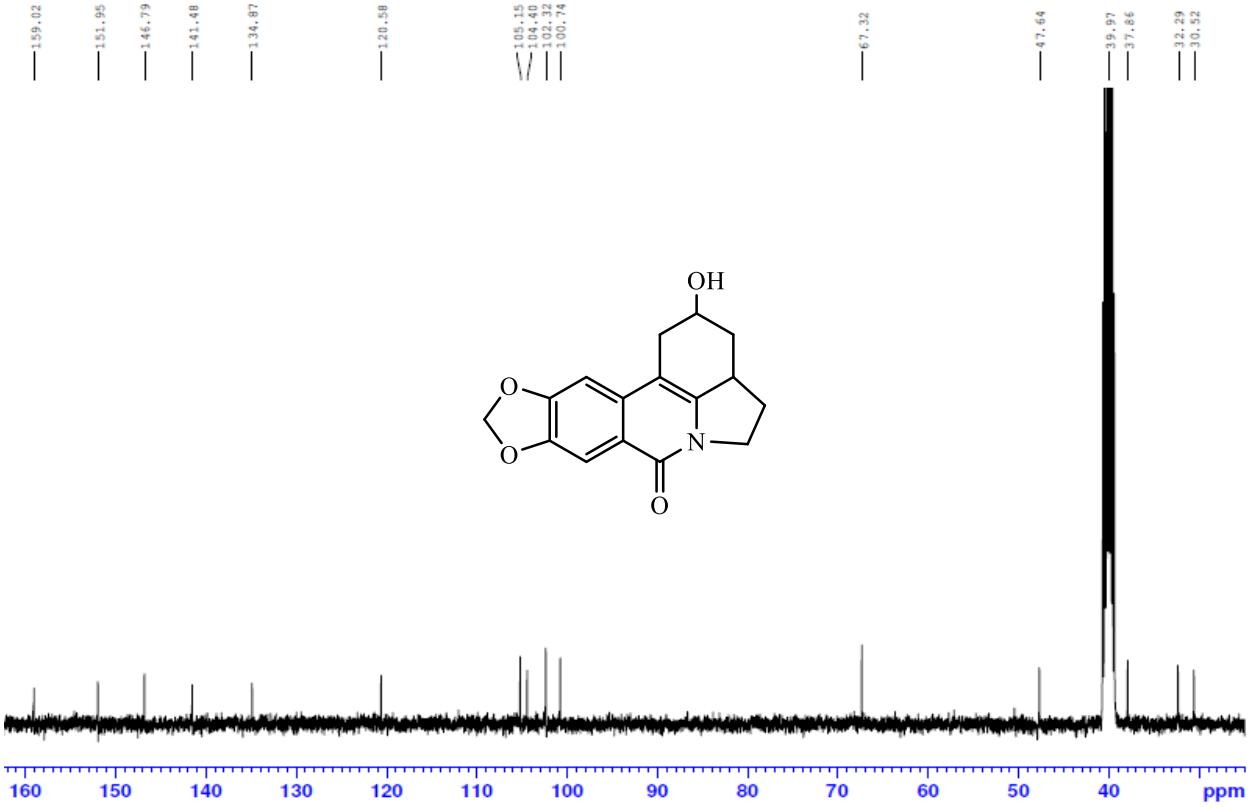
^{1}H NMR of 133b



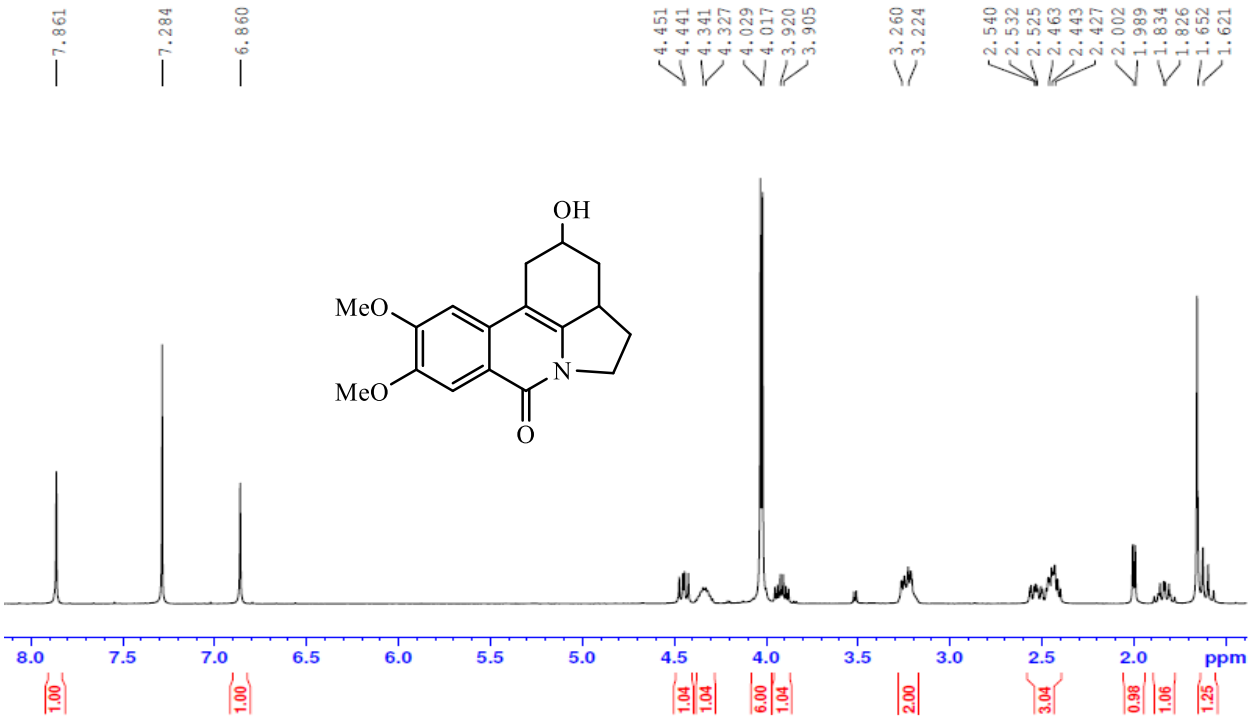
^{13}C NMR of 133b



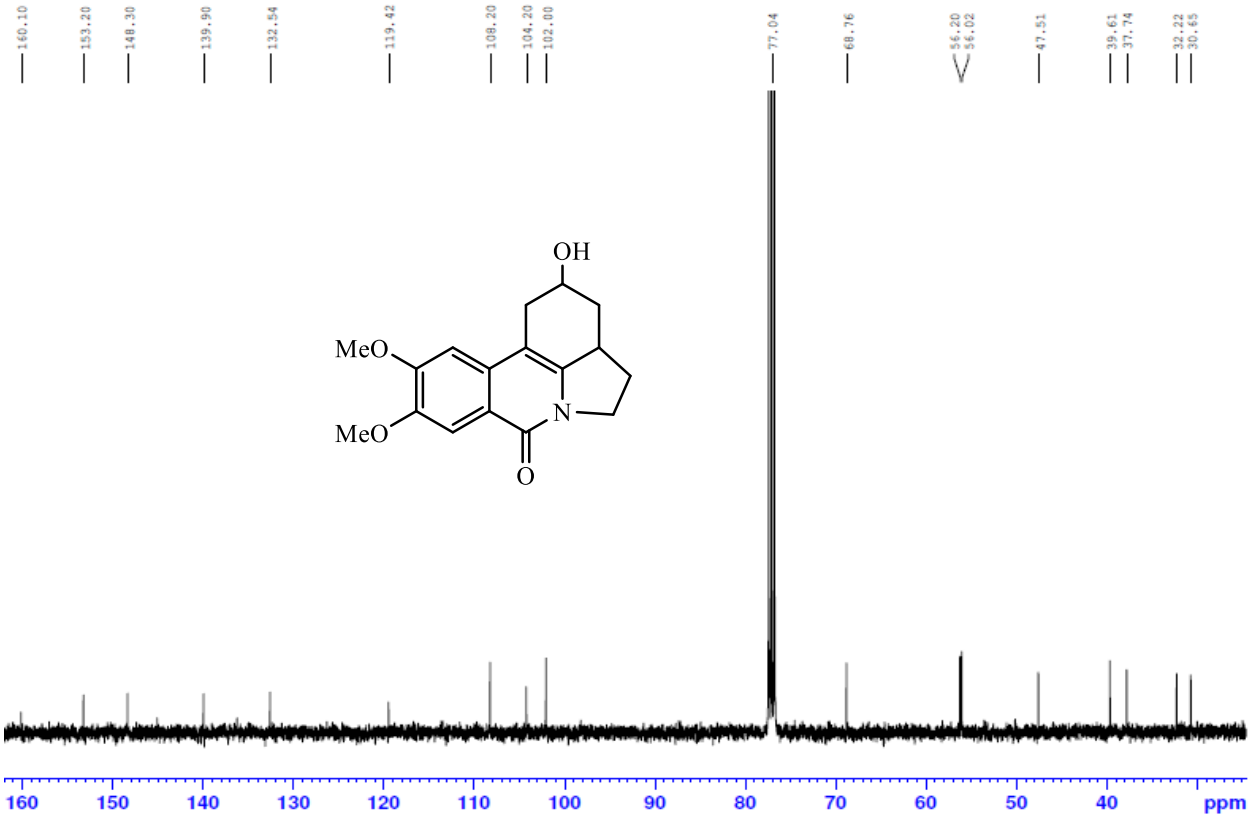
^{1}H NMR of 134a



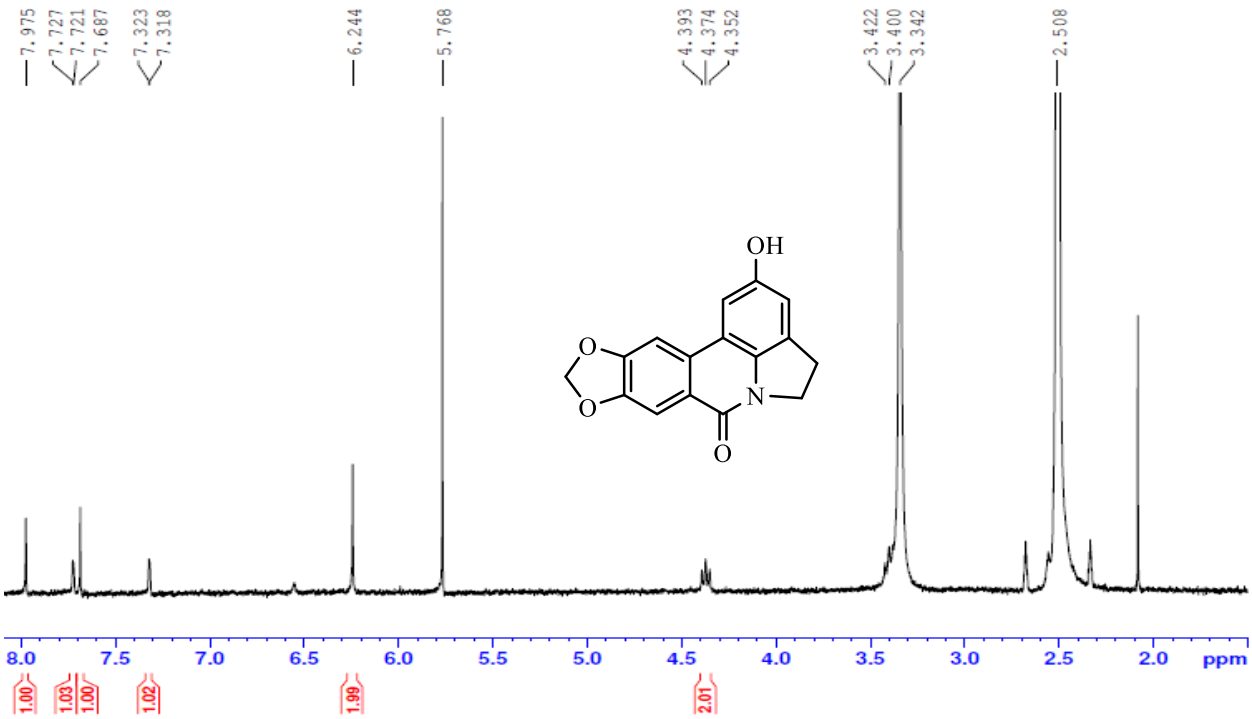
^{13}C NMR of 134a



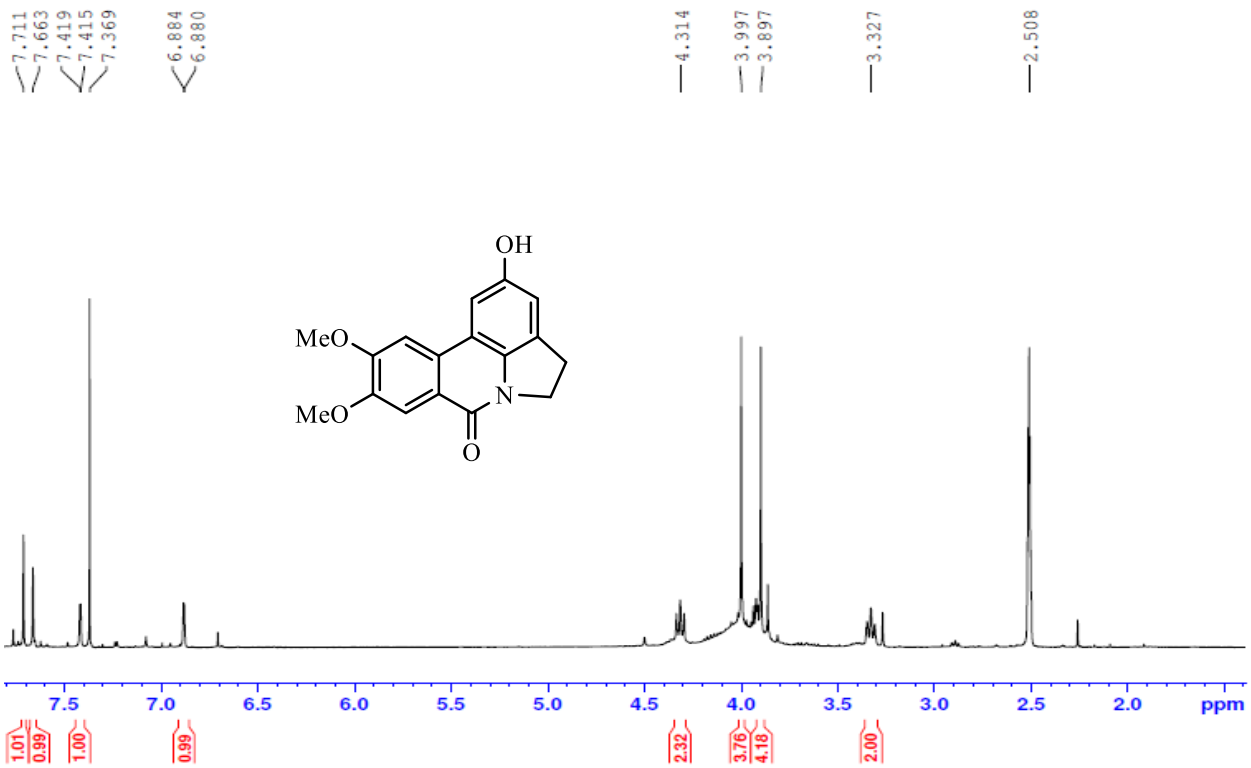
^{1}H NMR of 134b



^{13}C NMR of 134b



^{1}H NMR of 136a



^{1}H NMR of 136b

References

1. Newman, J. D.; Cragg, G. M. *J. Nat. Prod.* **2007,** *70*, 461-477.
2. Jin, Z. *Nat. Prod. Rep.* **2016,** *33*, 1318-1343.
3. Jahn, S.; Seiwert, B.; Kretzing, S.; Abraham, G.; Regenthal, R.; Karst, U. *Anal. Chim. Acta* **2012,** *756*, 60-72.
4. Li, L.; Dai, H.; Ye, M.; Wang, S.; Xiao, X.; Zheng, J.; Chen, H.; Luo, Y.; Liu, J. *Cancer Cell Int.* **2012,** *12*, 49-54.
5. Matsui, S. *Yakur. Zass.* **1962,** *58*, 309-321.
6. J. Bastida; R. Lavilla; Viladomat, F. In *The Alkaloids*; Elsevier Scientific Publishing: Amsterdam, 2006; Vol. 63.
7. Yamada, I.; Yamashita, M.; Sumiyoshi, K.; Nishimura, K. *Org. Lett.* **2009,** *11*, 1631-1633.
8. Richomme, P.; Gozler, T.; Freyer, A.; Shamma, M. *J. Nat. Prod.* **1989,** *52*, 1150-1152.
9. Bastida, J.; Codina, P.; Peeters, P.; Rubiralta, M.; Orozco, M.; Luque, F.; Charbra, S. *Phytochemistry* **1995,** *40*, 1291-1293.
10. Gorbunova, G. M.; Sheichenko, V. I.; Tolkachev, O. N. *Khim. Prir. Soedin.* **1984**, 800.
11. Canesi, S.; Beaulieu, M.; Ottenwaelder, X. *Chem. Eur. J.* **2014**, *20*, 7581-7584.
12. Banwell, M. G.; Harvey, J. E.; Hockless, D. C. *J. Org. Chem.* **2000,** *65*, 4241-4250.
13. Irie, H.; Nishitani, Y.; Sugita, M.; Tamoto, K.; Uyeo, S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 588-590.
14. Wenkert, E.; Chawla, H. P.; Schell, F. M. *Synth. Comm.* **1973,** *3*, 381-386.
15. Wokenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002,** *67*, 7361-7364.
16. Stork, G.; Morgans, D. J. *J. Am. Chem. Soc.* **1979,** *101*, 7110-7111.

17. Martin, S. F.; Tu, C.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982,** *47*, 3634-3643.

18. Moller, O.; Steinberg, E. M.; Torssell, K. *Acta. Chem. Scand., Ser. B* **1978,** *32*, 98-104.

19. Baeckvall, J. E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991,** *56*, 2988-2993.

20. Dong, L.; Xu, Y.; Yuan, W.; Cui, X.; Cun, L.; Gong, L. *Eur. J. Org. Chem.* **2006**, 4093-4105.

21. Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2502-2506.

22. Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979,** *44*, 1236-1241.

23. Ali, A.; Mesbah, M.; Frahm, A. *Planta Med.* **1981,** *43*, 407-409.

24. El Moghazi, A. M.; Ali, A.; Mesbah, M. *Planta Med.* **1975,** *28*, 336-342.

25. Ghosal, S.; Saini, K.; Frahm, A. *Phytochemistry* **1983,** *22*, 2305-2309.

26. Chattopadhyay, S.; Chattopadhyay, U.; Mathur, P.; Saini, K.; Ghosal, S. *Planta Med.* **1983,** *49*, 252-254.

27. Mugabo, P.; Philander, A.; Raji, I.; Dietrich, D.; Green, I. *J. Ethnopharmacol.* **2014,** *158*, 123-131.

28. Khwanchuea, R.; Mulvany, M. J.; Jansakul, C. *Eur. J. Pharmacol.* **2008,** *579*, 308-317.

29. Poirier, L.; Lacourciere, Y. *Can. J. Cardiol.* **2012,** *28*, 334-340.

30. Wu, W. M.; Zhu, Y. Y.; Li, H. R.; Yu, H. Y.; Zhang, P.; Pi, H. F.; Ruan, H. L. *J. Asian Nat. Prod. Res.* **2014,** *16*, 192-199.

31. Masi, M.; Cala, A.; Tabanca, N.; Cimmino, A.; Green, I. R.; Bloomquist, J. R.; van Otterlo, W. A.; Macias, F. A.; Evidente, A. *Molecules* **2016,** *21*, 1431-1442.

32. Luo, Z.; Wang, F.; Zhang, J.; Li, X.; Zhang, M.; Hao, X.; Xue, Y.; Li, Y.; Horgen, D.; Yao, G.; Zhang, Y. *J. Nat. Prod.* **2012,** *75*, 2113-2120.

33. Lopez, S.; Bastida, J.; Viladomat, F.; Codina, C. *Life Sci.* **2002,** *71*, 2521-2529.

34. Watanabe, M.; Masatomo, I.; Hirokazu, T.; Obata, S. *Heterocycles* **1994,** *38*, 1717-1720.

35. Knölker, H.-J.; Filali, S. *Synlett* **2003,** *11*, 1752-1754.

36. Ganton, M.; Kerr, M. *Org. Lett.* **2005,** *7*, 4777-4779.

37. Kanematsu, K.; Hayakawa, K.; Yasukouchi, T., *Tetrahedron Lett.* **1987,** *28*, 5895-5898.

38. Tsukano, C.; Muto, N.; Enkhtaivan, I.; Takemoto, Y. *Chem. Asian J.* **2014,** *9*, 2628-2634.

39. Sotomayor, N.; Lete, E.; Coya, E. *Heterocycles* **2016,** *93*, 114-126.

40. Black, D.; Keller, P.; Kumar, N. *Tetrahedron Lett.* **1989,** *30*, 5807-5808.

41. Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1990,** *31*, 1523-1526.

42. Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1991,** *32*, 3859-3862.

43. Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1993,** *36*, 2597-2600.

44. Miki, Y.; Shirokoshi, H.; Matsushita, K. *Tetrahedron Lett.* **1999,** *40*, 4347-4348.

45. Torres, J. C.; Pinto, A. C.; Garden, S. J. *Tetrahedron* **2004,** *60*, 9889-9900.

46. Miki, Y.; Umemoto, H.; Dohshita, M.; Hamamoto, H. *Heterocycles* **2011,** *83*, 1111-1119.

47. Harrowven, D.; Lai, D.; Lucas, M. *Synthesis* **1999,** *8*, 1300-1302.

48. de Mayo, P.; Takeshita, H. *Can. J. Chem.* **1963,** *41*, 440-449.

49. de Mayo, P.; Takeshita, H.; Sattar, A. B. *Proc. Chem. Soc.* **1962**, 119.

50. Crimmins, M. T.; Reinhold, T. In *Organic Reactions*; John Wiley & Sons: New York, 1993; Vol. 44.

51. Casals, P.; Ferard, J.; Ropert, R. *Tetrahedron Lett.* **1976**, 3077-3080.

52. Takeshita, H.; Iwabuchi, H.; Kouno, I.; Iino, M.; Monura, D. *Chem. Lett.* **1979**, 649-652.

53. Baldwin, S.; Gawley, R. E. *Tetrahedron Lett.* **1975**, 3969-3972.

54. Winslow, C. D. A Methods Development Approach towards the Galanthan Skeleton Starting with Isoquinoline. Ph.D. Thesis, Texas Christian University, December 2000.

55. Minter, D. E.; Winslow, C. D. *J. Org. Chem.* **2004,** *69*, 1603-1606.

56. Ganem, B. *Tetrahedron Lett.* **1971,** *44*, 4105-4108.

57. Minter, D. E.; Winslow, C. D.; Watson, W. H.; Bodige, S. *Magn. Reson. Chem.* **2006,** *44*, 969-971.

58. Rinehart, K. L.; Perkins, E. G. *Org. Synth.* **1957,** *37*, 37-40.

59. Fritsch, P. *Berich. Gesselsch.* **1893,** *26*, 419-422.

60. Pomeranz, C. *Monat. fur Chem.* **1893,** *14*, 116-119.

61. McElvain, S. M.; Prill, E. A. *Org. Synth.* **1935,** *15*, 41-43.

62. Fargeas, V.; Baalouch, M.; Metay, E.; Baffreau, J.; Ménard, D.; Gosselin, P.; Bergé, J.-P.; Barthomeuf, C.; Lebreton, J. *Tetrahedron* **2004,** *60*, 10359-10364.

63. Dickson, H. D.; Smith, S. C.; Hinkle, K. W. *Tetrahedron Lett.* **2004,** *45*, 5597-5599.

64. Hamdany, A.; Jihad, T. *Tikr. J. Pur. Sci.* **2012,** *17*, 72-76.

65. Luzzio, F.; Fitch, R.; Moore, W.; Mudd, K. *J. Chem. Ed.* **1999,** *76*, 974-975.

66. Dondoni, A.; Perrone, D. *Org. Synth.* **2000,** *77*, 64-70.

67. Moffatt, J. G.; Pfitzner, K. E. *J. Am. Chem. Soc.* **1963,** *85*, 3027-3028.

68. Katritzky, A. R.; Pastor, A.; Voronkov, M. V. *J. Heterocyclic Chem.* **1999,** *36*, 777-781.

69. Wilkerson, C. R. Benzotriazole Mediated Synthesis of *N*-acylbenzotriazoles and 2*H*-azirines. M.S. Thesis, University of Florida, 2003.

70. Katritzky, A. R.; Abdel-Fattah, A.; Vakulenko, A.; Tao, H. *J. Org. Chem.* **2005,** *70*, 9191-9197.

71. Urbanski, J.; Manek, M. B. *Polish J. Chem.* **1984,** *48*, 1227-1229.

72. Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, D.; Akhmedov, N. *J. Org. Chem.* **2004,** *69*, 6617-6622.

73. Toda, J.; Sano, T.; Tsuda, Y.; Itatani, Y. *Chem. Pharm. Bull.* **1982,** *30*, 1322-1332.

74. Hartung, C.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003,** *5*, 1899-1902.

75. Hendrickson, J.; Rodriguez, C. *J. Org. Chem.* **1983,** *48*, 3344-3346.

76. Katritzky, A. R.; Shobana, N.; Pernak, J.; Afridi, A. S.; Fan, W. *Tetrahedron* **1992,** *48*, 7817-7822.

77. Fischer, W.; Durst, D.; Lauk, U. *Tetrahedron Lett.* **1991,** *32*, 65-68.

78. Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008,** *10*, 1107-1110.

VITA

Charles Israel Ochoa was born August 10th, 1990, in San Salvador, El Salvador. He arrived in the United States of America at age 13 on September 13th, 2003. He graduated Skyline High School in 2008, after which he went on to earn a Bachelor of Science degree with a major in Chemistry from Texas Christian University, Fort Worth, in 2012.

In August 2012, he started his graduate studies at Texas Christian University, where he earned his Doctor of Philosophy degree in 2018. During his graduate career, he served as a Teaching Assistant from 2012 through 2014. In August 2018, he started as a Postdoctoral Fellow at the University of Texas Southwestern Medical Center, Dallas, in Professor Uttam Tambar's lab.

He is married to Samantha Brewer Ochoa, from Fort Worth, who also earned her Doctor of Philosophy degree from Texas Christian University, Fort Worth, in 2018.

ABSTRACT

THE TOTAL SYNTHESIS OF HIPPADINE AND PRATOSINE VIA AN INTRAMOLECULAR DE MAYO PHOTOCYCLIZATION

by Charles Israel Ochoa, Ph.D., 2018
Department of Chemistry and Biochemistry
Texas Christian University

Dissertation Advisor: David E. Minter, Professor of Chemistry

Hippadine and pratosine are lycorine-type pharmacologically active Amaryllidaceae alkaloids. Various total syntheses of these natural products have been developed. However, most of these synthetic routes require prohibitively expensive materials and/or achieve yields that are subpar, making these schemes unlikely to be used in an industrial setting. Herein, a better synthetic method for these two alkaloids starting with a 6,7-disubstituted isoquinoline is presented. The key step in the synthetic scheme centers around an intramolecular de Mayo photocyclization which involves a reaction between an alkene moiety in the isocarbostyril system and a 1,3-diketone (a functionalized tether on nitrogen), which forms a third ring in the structure of the molecule.

When the photochemical reaction was attempted, an unexpected cyclic photoproduct was obtained; fortunately, this product is a cyclic hemiketal of the expected 1,5-dicarbonyl compound. A base-catalyzed aldol addition affords the final ring in the system; dehydration of this product affords a β-enone that can be transformed to a diene. Oxidation of the diene with DDQ affords the target natural products after simple chromatographic purification. This new synthetic pathway circumvents the need for catalysts that are either expensive or contain metals such as palladium or iridium; moreover, our method allows for the synthesis of various natural and unnatural alkaloids in high yields by modification of the N-tether.