THE METHODS DEVELOPMENT APPROACH TO THE SYNTHESIS OF PHENANTHRIDINONE ANALOGS

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INTRODUCTION

1.1 Phenanthridinone Alkaloids

Plants of the family *Amaryllidaceae* have been used throughout history to treat a variety of human ailments due to the presence of biologically active alkaloids.[1] As far back as 460 B.C., Hippocrates of Kos was recommending the use of narcissus oil for the treatment of tumors.[2] Though the nature of the therapeutic effects of these compounds was completely unknown at this time, recent research has confirmed their anticancer activity and revealed the mode of action for many of these natural products.[3] For example, the molecular basis for cytotoxicity in several compounds can be traced to their ability to disrupt the peptide bond-forming step during protein synthesis.[4,5] Still today, there is an interest in isolating and fully characterizing *Amaryllidaceae* alkaloids in the search for potential drug candidates.[6] However, since natural abundance is often limited, many of the less plentiful compounds require a laboratory synthesis in order to obtain sufficient quantities for testing. In addition, some alkaloids of this class such as *y*-lycorane have become popular synthetic targets despite having no useful pharmaceutical properties in order to develop new strategies for preparing the more important natural products.[7,8,9]

Of the many sub-classes of alkaloids in this family, the phenanthridinone-type compounds are among the most interesting. The phenanthridinone skeleton contains three fused rings denoted A, B and C as shown in Figure 1, but the alkaloids themselves are tetracyclic and possess the characteristic methylenedioxy group annelated at the A-ring. Included in this sub-class are the

alkaloids pancratistatin, narciclasine, and lycoricidine all of which, along with their naturally occurring derivatives, are popular synthetic targets due to their biological activity.

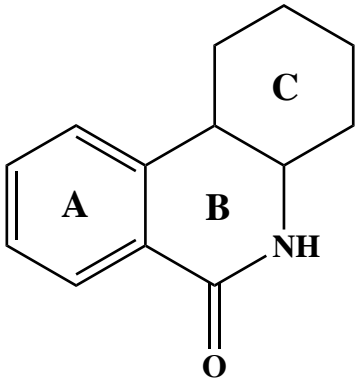


Figure 1: Phenanthridinone skeleton

Of these three examples, narciclasine was the first to be isolated in 1967 from *Narcissus* bulbs. The crude plant material was processed using an ethanol extraction technique followed by a more refined chromatographic purification and finally a recrystallization to yield the natural product in a pure form. A complete characterization of the molecule was done using nuclear magnetic resonance techniques as well as mass spectral, infrared and optical rotation studies.[10,11] A natural derivative of this alkaloid, *trans*-dihydronarciclasine, has also been isolated in small quantities from the bulbs of *Zephyranthes candida.*[12]

The following year, lycoricidine was obtained in trace amounts using a similar process from the bulbs of *L. radiate*.[13] This newly discovered alkaloid was found to be a plant growth inhibitor and a potent insecticide similar to narciclasine.[14] A better source for this compound was found to be the bulbs of *Hymenocallis littoralis*, which is native to Hawaii. The plant can also be cultivated in Arizona though the yield of lycoricidine obtained from these plants is much lower due to the harsher climate in which they are grown.[15] A natural derivative of this alkaloid, *trans*-dihydrolycoricidine, has also been isolated and fully characterized from both *H. littoralis* and *H.*

caribaea in moderate yields.[16,17] This natural product lacks the double bond found in lycoricidine and instead is fully saturated with a *trans* B/C ring fusion (see Figure 2).

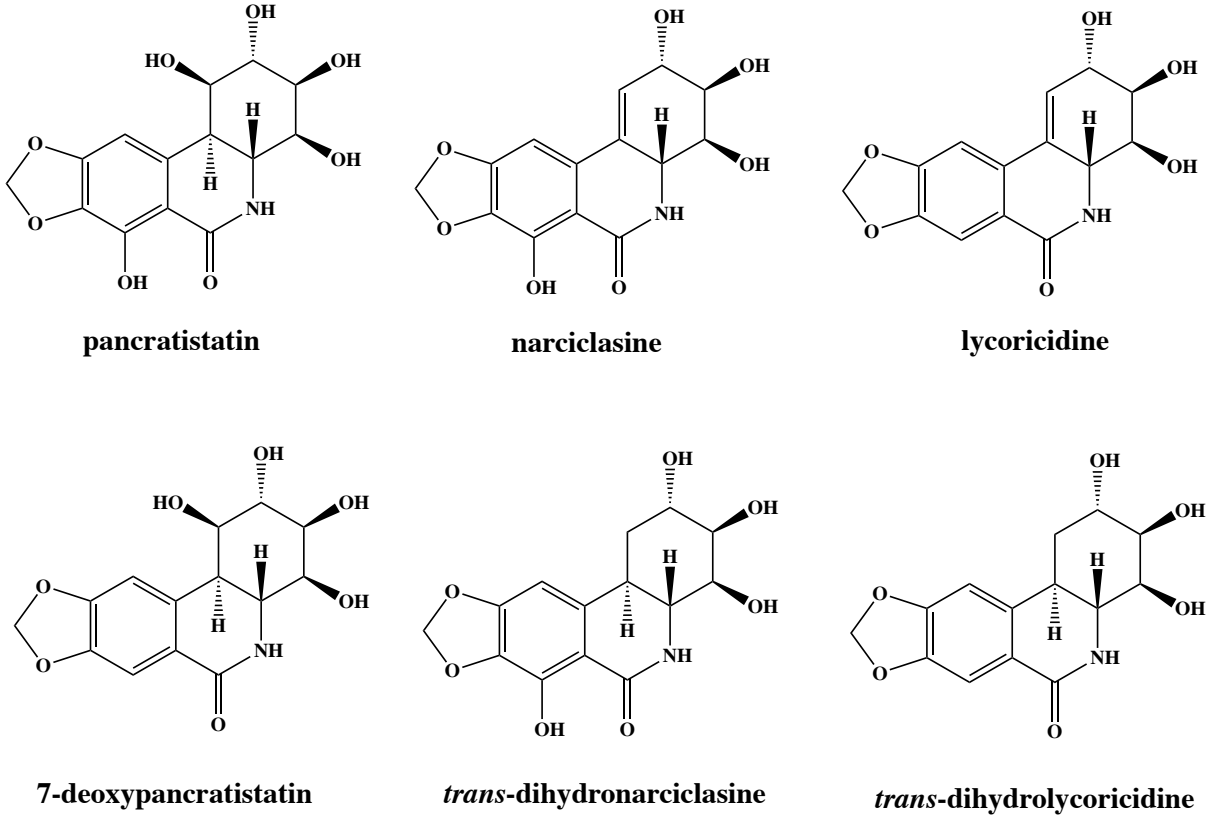


Figure 2: Examples of phenanthridinone alkaloids

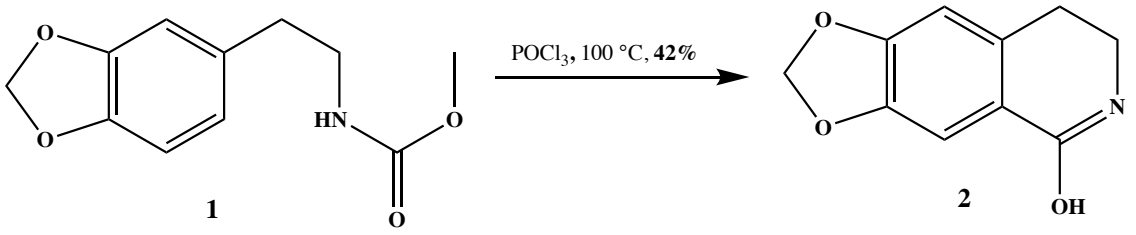
In 1984, pancratistatin was isolated from the aqueous extract of *H. littoralis* bulbs grown in Hawaii.[18] The extraction process was effective for obtaining sufficient quantities needed for laboratory studies, but the high cost made large scale production impractical. Like the natural products discussed previously, this alkaloid was found to possess strong biological activity. For example, pancratistatin was highly active against cancers such as murine P-388 lymphocytic leukemia and murine M-5076 and substantially reduced the growth of subcutaneous colon HT-29 tumors.[19,20] It was also found that pancratistatin was capable of inducing apoptosis in these cell lines while having little effect on non-cancerous cells.[21] In addition, *in vivo* studies using rats

infected with Japanese encephalitis showed a 100% survival rate. Finally, pancratistatin proved to be a potent antiviral agent against flaviviruses and bunyaviruses.[22] One naturally-occurring derivative, 7-deoxypancratistatin, has also been extracted and identified from *H. kalbreyeri* in small quantities.[23]

All of the aforementioned alkaloids have been synthesized in the laboratory. Because of the complexity of these structures and the necessity to control multiple stereo centers and ring fusions, these total syntheses have required the development of new reactions and procedures some of which are now standard methods with applications that go well beyond alkaloid research. A brief overview of work relevant to the preparation of the phenanthridinone ring system is presented below. These examples have been chosen to illustrate the diversity of the chemistry that has been described in previous research.

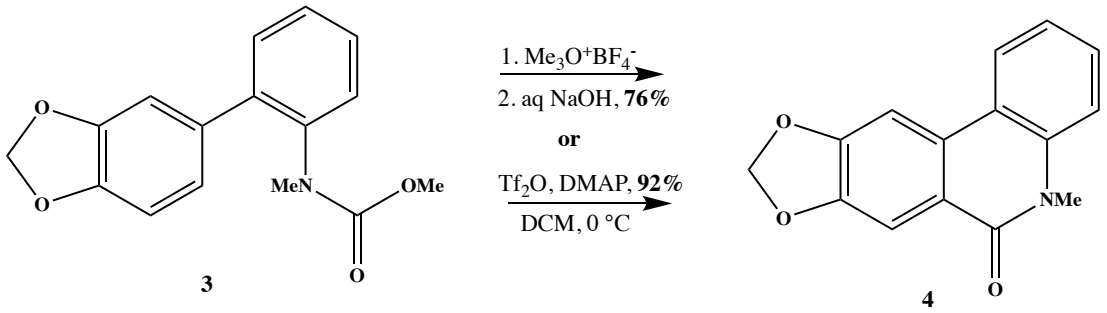
1.2 Past Syntheses of Phenanthridinone Alkaloids

The most common approach to constructing the phenanthridinone ring system uses the Bischler-Napieralski reaction to close the B-ring after the A and C-rings have been established. Phosphoryl chloride ($POCl_3$), phosphorus pentoxide and phosphorus pentachloride are the traditional reagents used to induce an electrophilic aromatic acylation leading to isoquinolone derivatives.[24] For example, in 1945 Dey and Parikshit[25] reported the synthesis of **2** from the urethane **1** in 42% yield using $POCl_3$ at 100 °C (Scheme 1). This product lacked the C-ring of phenanthridinone, but the reaction served as a promising model. As for regioselectivity in the ring closure, a mixture of isomers that can be difficult or impossible to separate has been observed; but the major product was typically the isoquinolone **2**. By delaying the purification until later in the synthetic scheme, the undesired isomer could be removed more conveniently.[26,27]



Scheme 1: The Bischler-Napieralski reaction

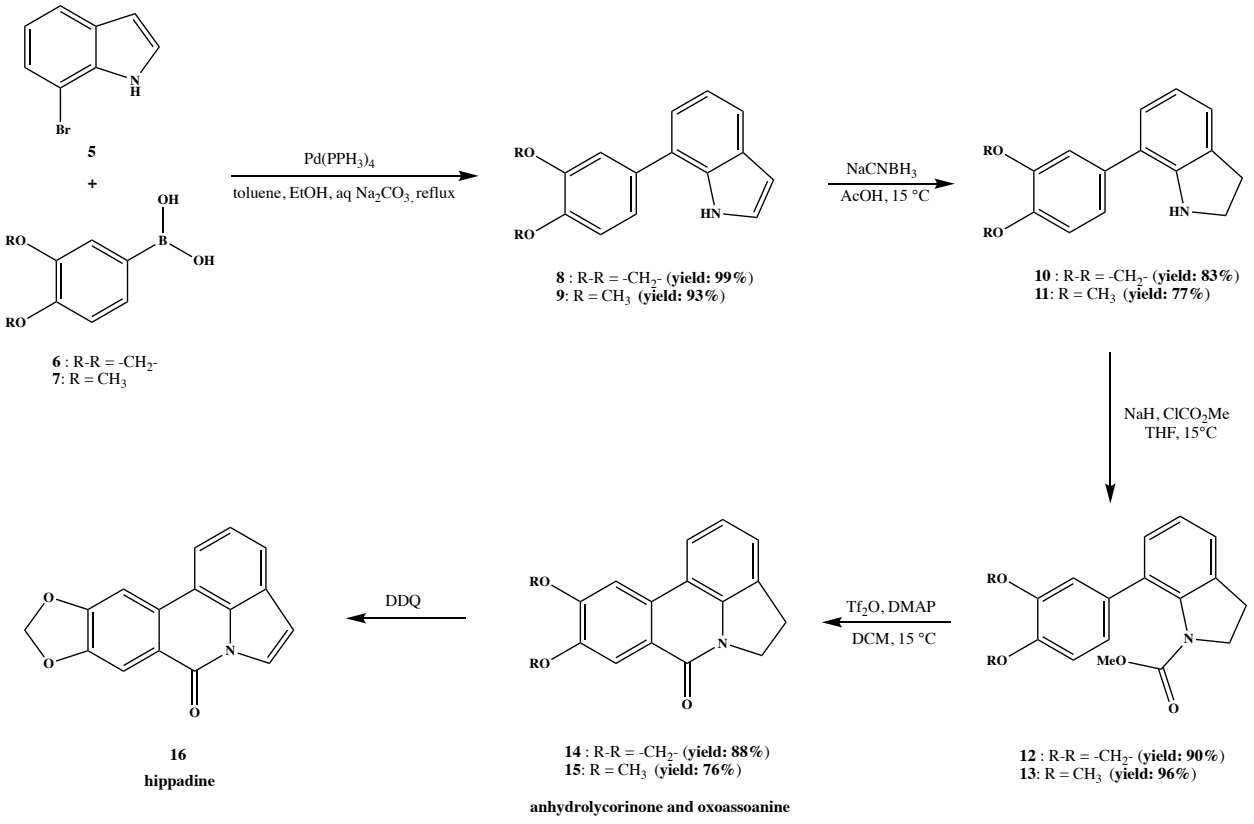
Unfortunately, the use of phosphorus reagents to effect the cyclization reaction was not suitable for substrates containing sensitive functionalities, and this prompted the search for other reagents and conditions.[28] For example, when Banwell et al. treated the urethane **3** with $POCl_3$ at temperatures upwards of 200 °C, the cyclization failed; but trimethyloxonium tetrafluoroborate ($Me_3O^+BF_4^-$) followed by aqueous alkali gave **4** (Scheme 2) in 76% yield.[29] Likewise, in 1995 Banwell and coworkers found that the reaction of **3** with an excess of trifluoromethanesulfonic anhydride (Tf_2O) and 4-(N,N-dimethylamino)pyridine (DMAP) at 0 °C produced **4** in 92% yield.[30]



Scheme 2: Alternative reagents for Bischler-Napieralski-type reactions

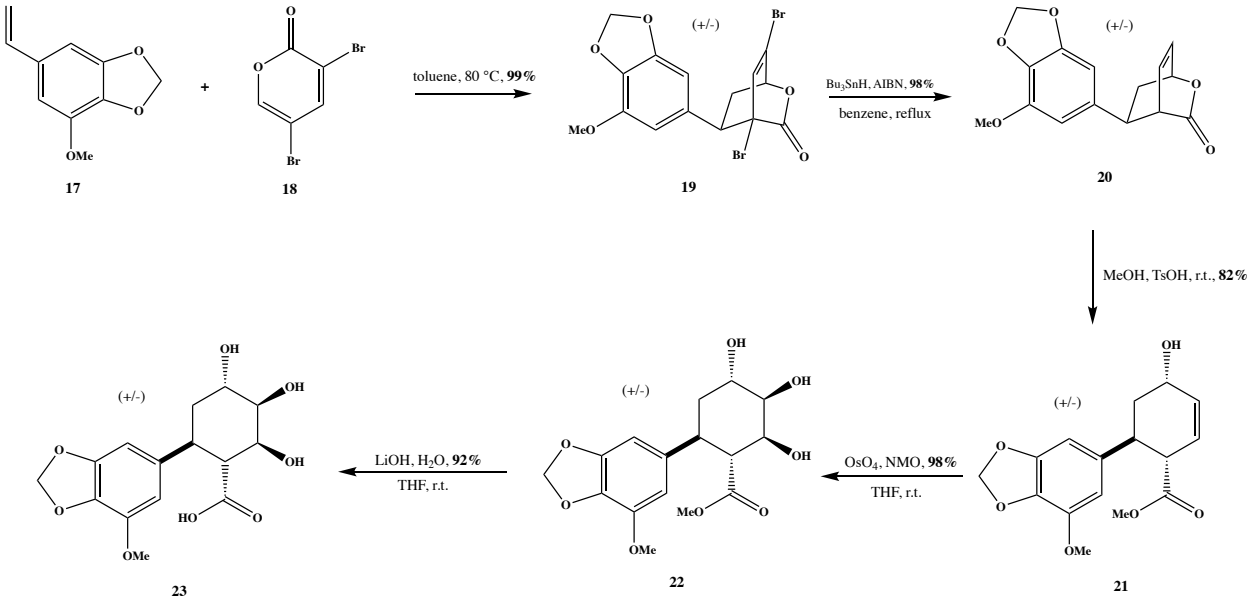
In the same publication, Banwell et al were able to use the optimized reaction shown in Scheme 2 to complete the total syntheses of numerous phenanthridinone alkaloids and their analogs. The natural products anhydrolycorinone (**14**) and oxoassoanine (**15**), which differ only by the ether functionalities on the A-ring, were effectively synthesized through a 4-step sequence

starting with **5** in combination with either **6** or **7** (Scheme 3). Using a Suzuki cross-coupling reaction, the aryl boronic acids **6** and **7** were converted to **8** and **9**, respectively, by their reactions with 7-bromoindole catalyzed by $Pd(PPh_3)_4$. Reduction of the enamine in the resulting products with sodium cyanoborohydride ($NaBH_3CN$) in acetic acid produced the corresponding 2° amines **10** and **11**. After conversion of **10** and **11** to the carbamate derivatives **12** and **13**, the Bischler-Napieralski-type reactions were performed to give the alkaloids **14** and **15** in 88% and 76% yields, respectively. The overall yields from the boronic acids were 65% for **14** and 52% for **15**. Anhydrolycorinone (**14**) was easily converted to another alkaloid, hippadine (**16**), by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 71% yield (37% overall from the boronic acid **6**).



Scheme 3: Banwell syntheses of anhydrolycorinone (**14**), oxoassoanine (**15**) and hippadine (**16**)

Another group that used Tf_2O and DMAP to induce a B-ring closure near the end of the synthetic scheme was Shin and coworkers in their total synthesis of *trans*-dihydronarciclasine (**29**), which utilized an *endo*-selective Diels-Alder cycloaddition (see Scheme 4).[31] Unlike the example discussed previously, this synthesis required the stereospecific functionalization of the C-ring with three hydroxyl groups as well as the incorporation of an additional hydroxyl group on the A-ring. Notice that the Diels-Alder reaction established the required stereochemical relationships between the three substituents on the cyclohexene ring in **21**.

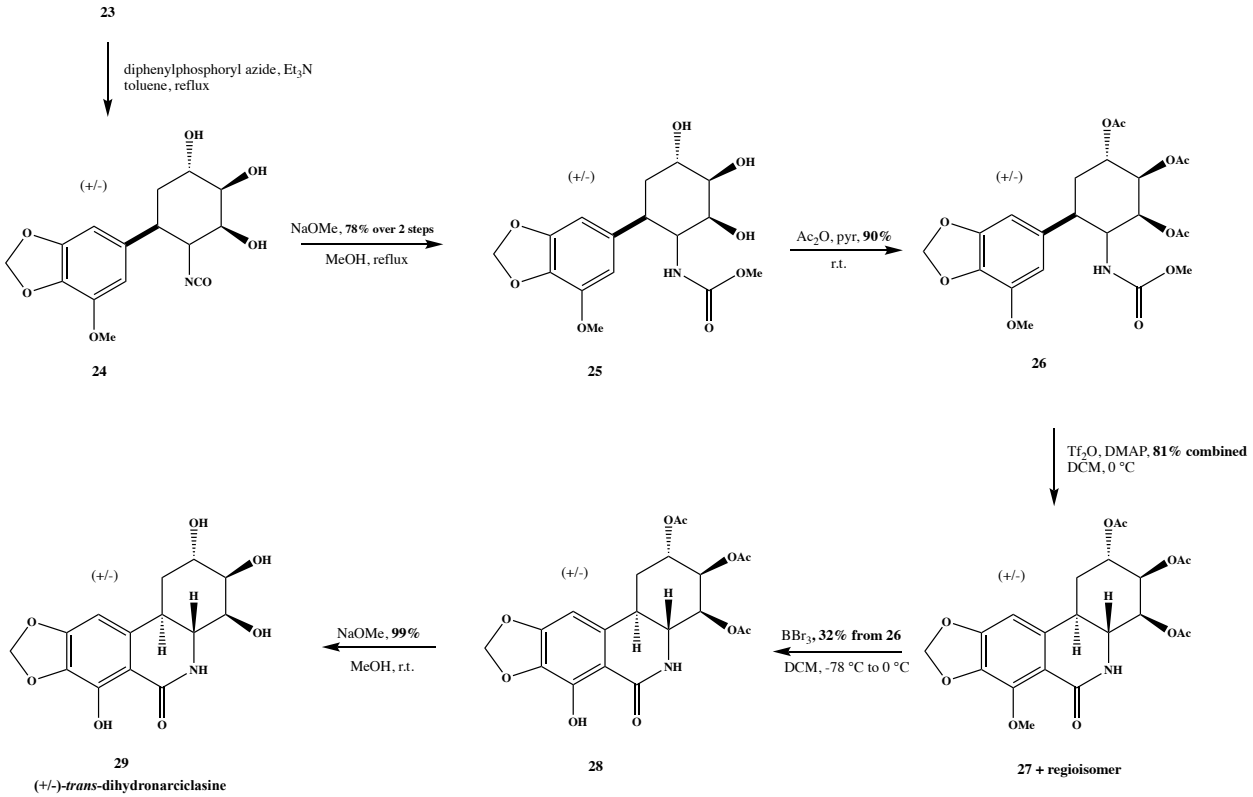


Scheme 4: Shin synthesis of the carboxylic acid intermediate **23**

The synthesis began with the formation of the required dienophile **17** through processes developed previously in the literature.[32,33,34] A thermally-induced Diels-Alder reaction of **17** with the diene **18** gave the *endo* adduct **19** after purification from a 98:2 mixture of *endo*:*exo* isomers. The debromination of **19** was achieved using an excess of tributyltin hydride (Bu_3SnH) with azobisisobutyronitrile (AIBN) as initiator. Acid-catalyzed methanolysis of the lactone gave the ester **21** in good yield. Without protecting the allylic alcohol in **21**, the alkene was oxidized to the

diol from the less hindered face of the ring using N-methylmorpholine-N-oxide (NMO) and catalytic osmium tetroxide (OsO_4) to give the triol **22**. Hydrolysis of the methyl ester with aqueous lithium hydroxide completed the synthesis of the carboxylic acid **23**.

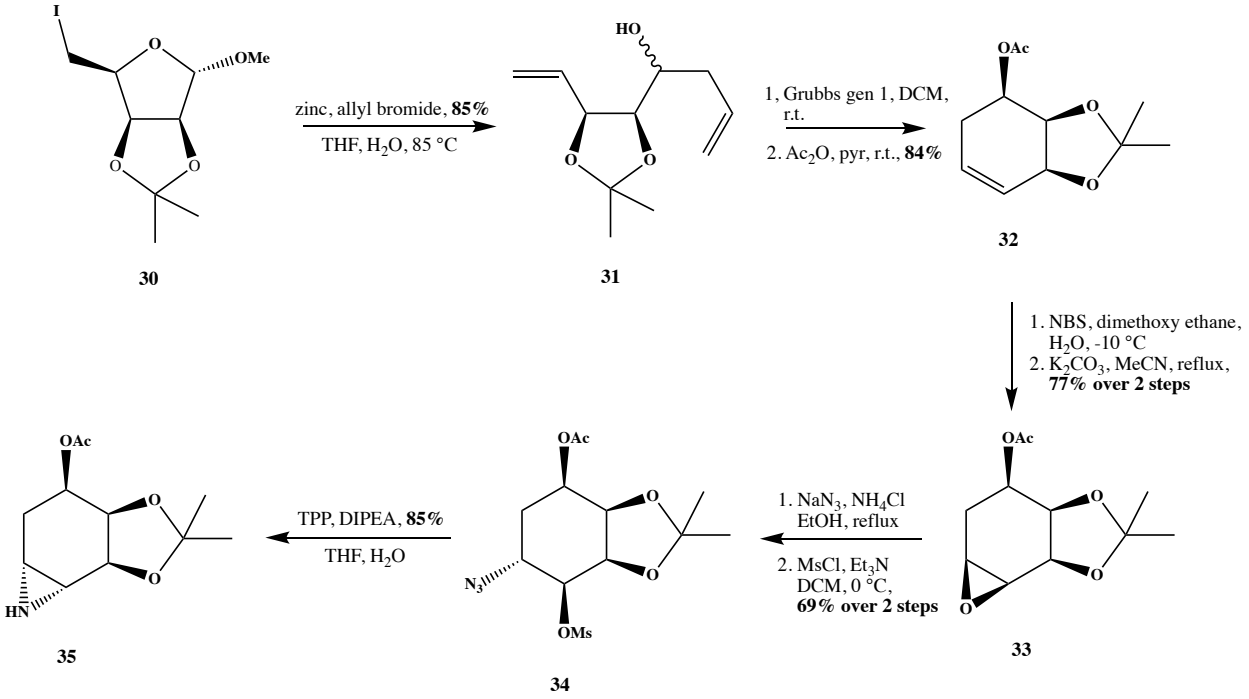
The last six steps of the synthesis are shown in Scheme 5. The acid **23** was converted to the methyl carbamate **25** using a Curtius rearrangement to give the isocyanate **24** followed by a reaction with sodium methoxide. The hydroxyl groups were protected as acetates and the B-ring was closed using a Bischler-Napieralski reaction to convert **26** to an inseparable 3:1 mixture of **27** and the regioisomer. However, the unwanted isomer could be separated after cleavage of the methyl ether using BBr_3 to give pure **28**. In the last reaction, deprotection of the three C-ring hydroxyls gave (+/-)-*trans*-dihydronarciclasine (**29**) with an overall yield of 15.8% over 11 steps from **17**.



Scheme 5: Shin completed total synthesis of (+/-)-*trans*-dihydronarciclasine (**29**)

Yadav and coworkers revealed a different approach to closing the B-ring in their total synthesis of (+)-lycoricidine (**41**), which features a late-stage intramolecular Heck cyclization. Unlike the alkaloids discussed previously, lycoricidine contains one degree of unsaturation in the C-ring the source of which is an α, β-unsaturated cyclohexenone. As seen later in Scheme 7, this synthesis also incorporates a silica gel mediated oxidative ring opening of an aziridine.

The acetonide **30** (Scheme 6) was available from D-(+)-mannose using a 5-step method reported previously in the literature.[35,36,37] Upon reaction with excess zinc and allyl bromide, **30** was converted to the diene **31** as a mixture of diastereomers.[38] A ring-closing metathesis using the Grubbs generation 1 ruthenium catalyst produced cyclohexenes at which point the undesired

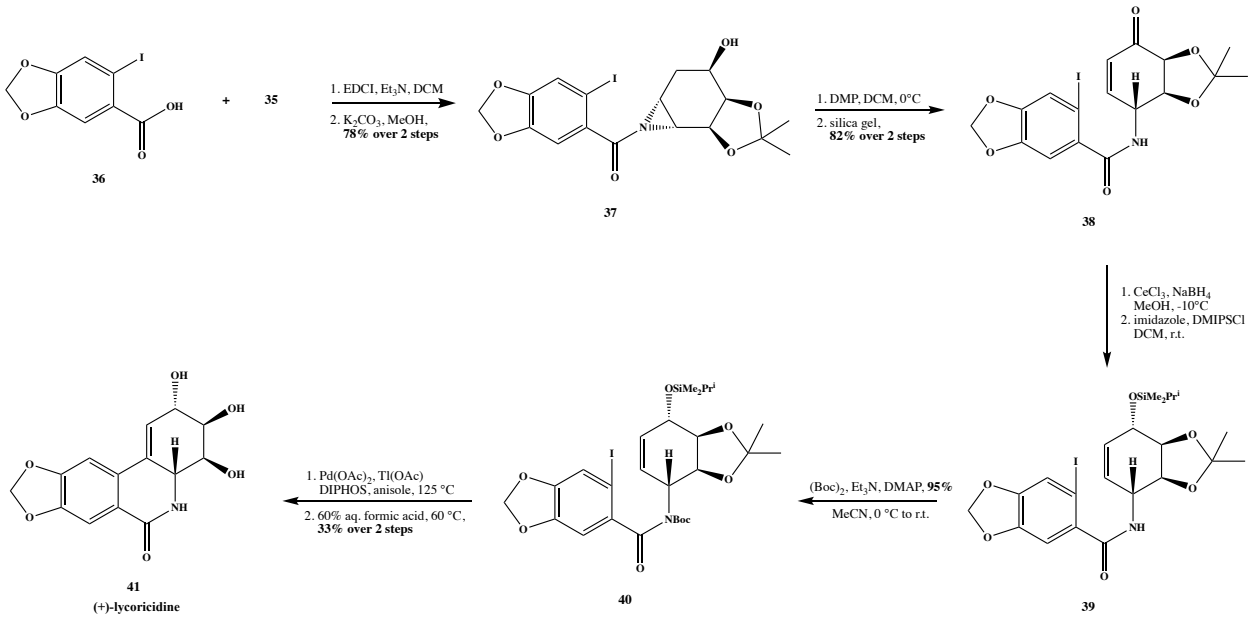


Scheme 6: Yadav synthesis of the aziridine intermediate **35**

isomer could be separated and discarded prior to acetylation to give pure ester **32**. The epoxide **33** was produced as a single isomer by converting the alkene to a mixture of bromohydrins using water and N-bromosuccinimide (NBS) followed by treatment with potassium carbonate (K_2CO_3)

under anhydrous conditions to close the ring with a yield of 77% over 2 steps. The epoxide was then opened regiospecifically with sodium azide (NaN_3) in the presence of ammonium chloride (NH_4Cl) to the azido alcohol. After converting the alcohol to the mesylate **34**, the aziridine **35** was generated in 85% yield using triphenylphosphine (TPP) and diisopropylethylamine (DIPEA).

The last five steps of the synthesis are shown in Scheme 7. The carboxylic acid **36** was coupled with the aziridine **35** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) to yield the amide **37** in 78% yield after removal of the ester protecting group. Upon oxidation of the resulting alcohol using Dess-Martin periodinane (DMP), it was discovered that purification of the crude product using chromatography on silica gel had serendipitously opened the aziridine to



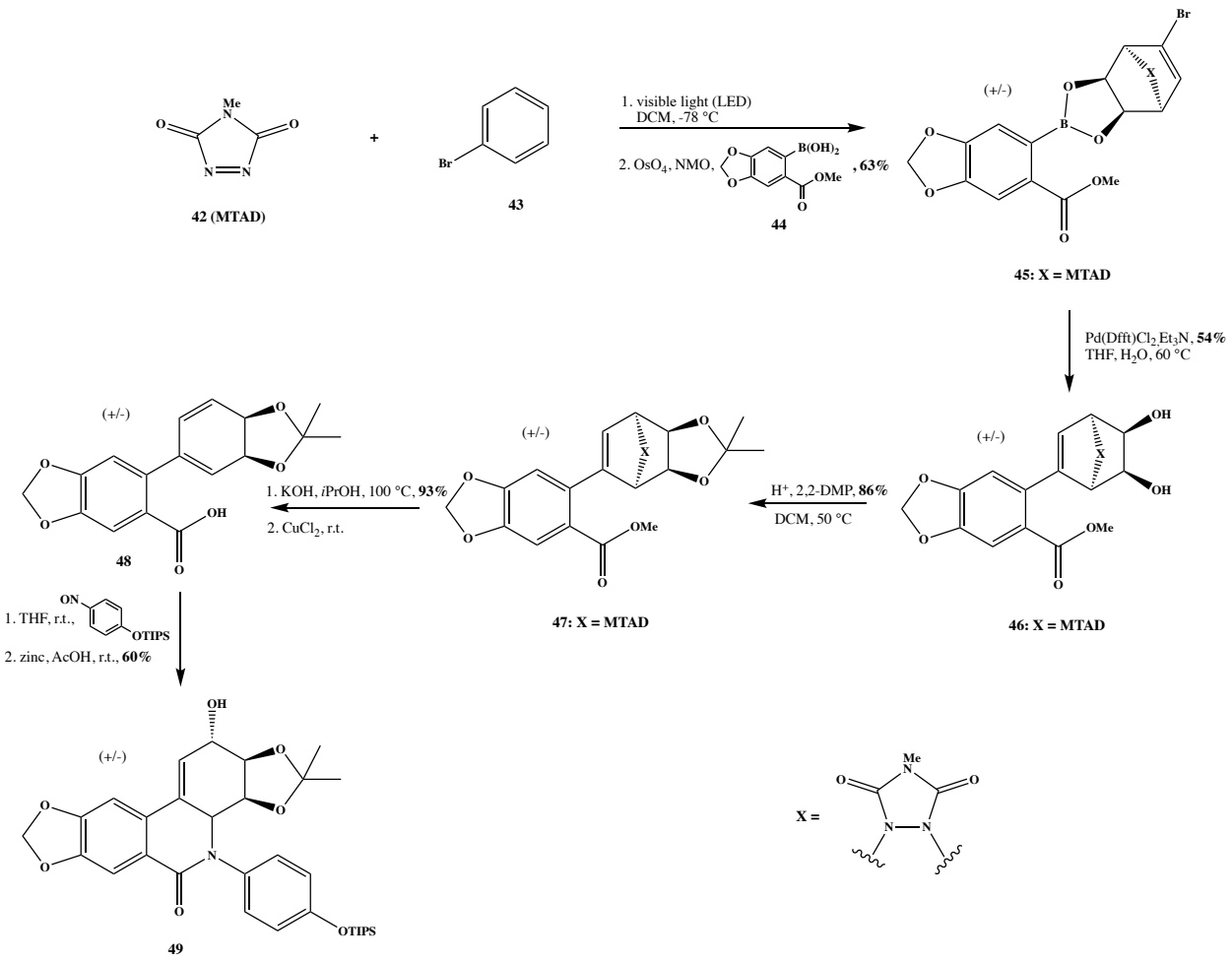
Scheme 7: Yadav's completed total synthesis of (+)-lycoricidine (**41**)

give the α,β-unsaturated ketone **38** in high yield. A Luche reduction of this enone using cerium (III) chloride ($CeCl_3$) and sodium borohydride gave a mixture of two diastereomers that could be separated only after converting the alcohols to their silyl ethers with dimethylisopropylsilyl chloride. The amide nitrogen of **39** was protected with a *tert*-butyloxycarbonyl (BOC) group prior

to performing an intramolecular Heck cyclization using 1,2-bis-diphenylphosphinoethane (DIPHOS), palladium acetate [$Pd(OAc)_2$] and thallium acetate [Tl(OAc)] to close the B-ring of the phenanthridinone skeleton. The protecting groups were cleaved by 60% aqueous formic acid to yield (+)-lycoricidine (**41)** in 33% yield from **40** and 20% overall from **36**.

In 2017, Southgate and coworkers developed synthetic routes to both lycoricidine (**50**) and narciclasine (**52**) from the same starting material.[39] They also closed the B-ring last but not by using the classic Bischler-Napieralski reaction to do so. Instead, they carried out a nitroso Diels-Alder reaction on the C-ring followed by the addition of metallic zinc and acetic acid to cleave the resulting N-O bond. Subsequently, the amide bond was created to close the B-ring using the carboxylic acid function on the A-ring (see Scheme 8). This group also developed a unique approach to synthesizing one of the key intermediates by the reaction of bromobenzene with 4-methyl-1,2,4-triazoline-3-5-dione (MTAD) under Narasaka-Sharpless dihydroxylation conditions.

The synthesis began by irradiating a mixture of MTAD (**42**) and bromobenzene (**43**) with visible light from a white light-emitting diode (LED).[40] The boronic acid **44** was added along with N-methylmorpholine-N-oxide (NMO) and catalytic osmium tetroxide (OsO_4), to form **45** in a large scale process. The transpositive Suzuki coupling developed by Southgate was carried out using $Pd(dppf)Cl_2$ [dppf = 1,1'-bis(diphenylphosphino)ferrocene] and triethylamine to give **46** in 54% yield.[41] Protection of the *cis*-diol using 2,2-dimethoxypropane (2,2-DMP) with catalytic pyridinium *p*-toluenesulfonate (PPTS) provided the acetonide **47**. After hydrolysis of the methyl ester and subsequent cycloreversion using KOH and copper (II) chloride ($CuCl_2$), the resulting acid **48** was cyclized to the key intermediate **49** using *p*-nitrosophenol protected as the TIPS ether followed by the addition of zinc metal and acetic acid as shown in Scheme 8.

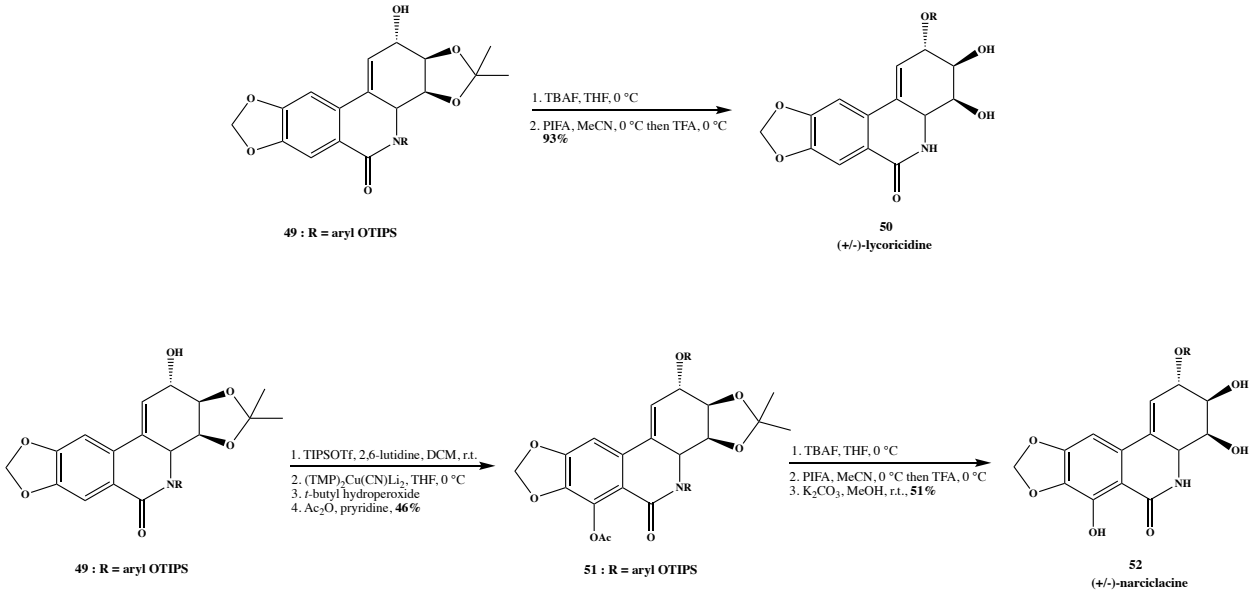


Scheme 8: Southgate synthesis of the key intermediate **49**

From this intermediate, removal of the silyl protecting group on the phenol using tetrabutylammonium fluoride (TBAF) followed by a one-pot oxidative cleavage of the phenol group using bis(trifluoracetoxy)iodobenzene (PIFA) and subsequent removal of the acetonide by the addition trifluoroacetic acid (TFA) yielded lycoricidine (**50**) as a single diastereomer in 93% yield (see Scheme 9).

The intermediate **49** could also be converted to narciclasine through a late-stage hydroxylation of the A-ring, which had not previously been accomplished from a lycoricidine derivative (see Scheme 9). First, the allylic alcohol was protected as a silyl ether. This was

followed by a deprotonative cupration, and the resulting aryl cuprate was then oxidized with *tert*-butyl hydroperoxide according to the recently developed procedure by Uchiyama and coworkers.[42] It was theorized and verified that the benzamide functionality on the B-ring would effectively direct the hydroxylation to the correct position. The conditions that were reported by Uchiyama effectively hydroxylated the A-ring in a 46% yield over 4 steps from **49** after acetylation of the resulting phenol to form compound **51**. A 3-step process to remove all protecting groups then yielded narciclasine (**52**) in 51% yield. The two alkaloids were synthesized with overall yields of 15% and 4%, respectively.

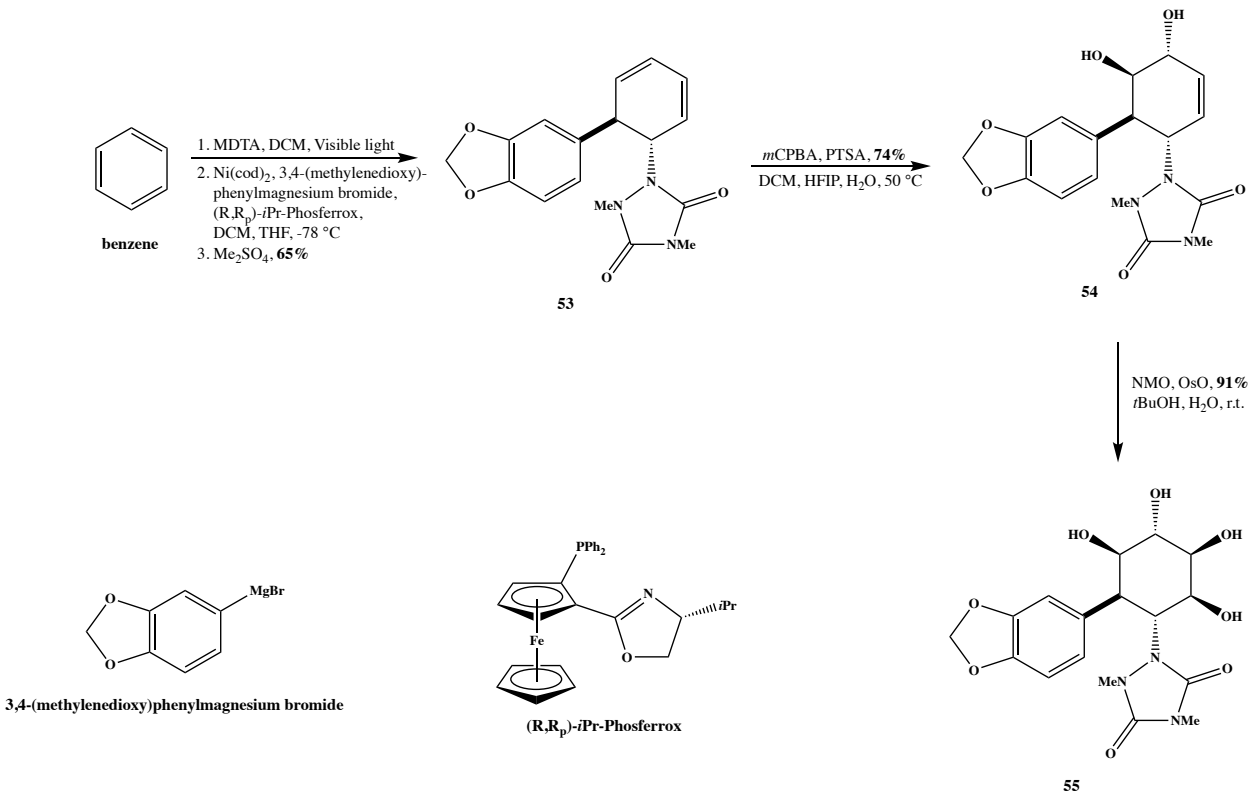


Scheme 9: Southgate completed synthesis of lycoricidine and narciclacine

Also in 2017, Hernandez and co-workers established a streamlined synthetic route to both (+)-7-deoxypancratistatin (**58**) and pancratistatin (**59**) starting from benzene (Scheme 10 and 11).[43] This group also incorporated a dearomatization process using MTAD and visible light somewhat similar to that of the Southgate approach mentioned previously. However, instead of a Suzuki cross-coupling reaction to incorporate the aryl group used to form the A-ring, they used a nickel

catalyst along with an aryl Grignard. The reaction established by Uchiyama to incorporate the hydroxyl group on the A-ring was also used in this synthesis to convert a derivative of (+)-7-deoxypancratistatin to pancratistin (Scheme 11).

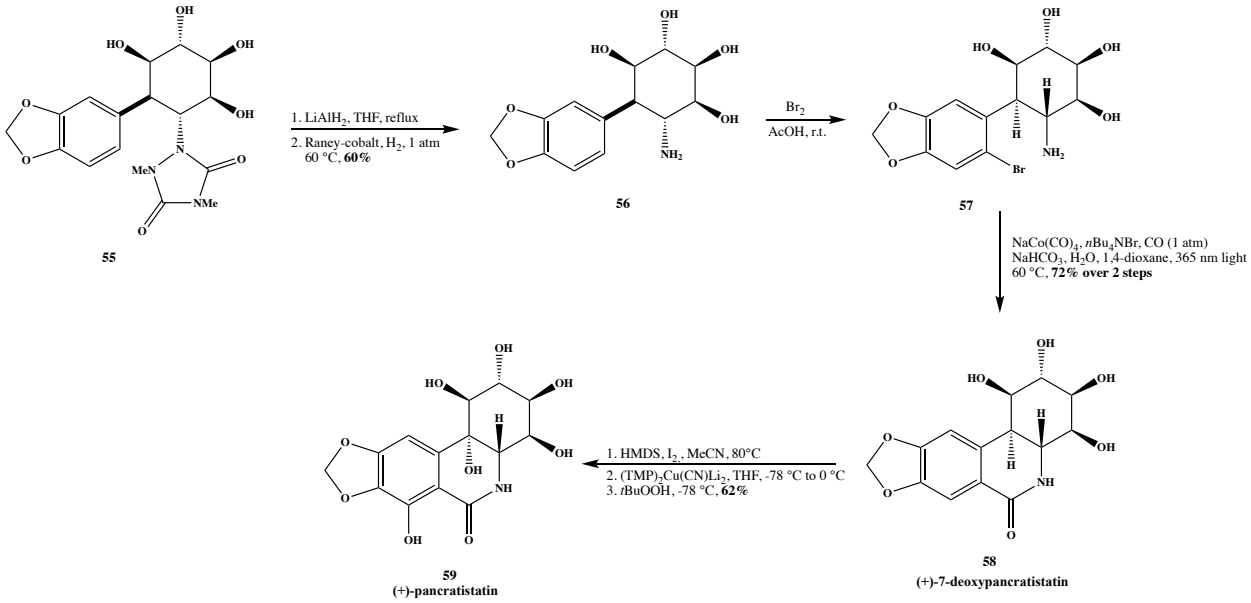
Similar to the Southgate synthesis, Hernandez used a one-pot procedure starting with the reaction of benzene with MTAD in the presence of visible light to form a cycloadduct followed by direct addition of the nickel catalyst ($Ni(Cod)_2$) plus (R,R_p)-*i*Pr-Phosferrox and then 3,4-(methylenedioxy)phenylmagnesium bromide. After the allotted reaction time, the solution was quenched with a solution of dimethyl sulfate (Me_2SO_4) and compound **53** was isolated as a single diastereomer in 65% yield (Scheme 10). The electron-withdrawing effect of the urazole nitrogen allowed for the regioselective epoxidation of **53** using *m*CPBA, followed by subsequent acidic hydrolysis of the epoxide to give the vicinal *trans* diol **54**. The use of hexafluoroisopropanol (HFIP) was found to be critical in this step in order to produce **54** in good yield.[44,45] Oxidation of the remaining alkene using osmium tetroxide (OsO_4) and N-methylmorpholine-N-oxide (NMO) then gave the tetraol **55** intermediate in good yield.



Scheme 10: Hernandez synthesis of tetraol intermediate

At this point in the synthesis, all 6 stereocenters had been installed in preparation for lactam formation to give the B-ring of the phenanthridinone core. Reduction of the urazole in **55** to form the free amine was then accomplished through a one-pot process using lithium aluminum hydride ($LiAlH_4$) followed by the addition of Raney-cobalt and hydrogen gas at 60 °C resulting in the amine **56** (see Scheme 11).[46] The B-ring was closed and the amide carbonyl was introduced by brominating **56** using molecular bromine in acetic acid to give **57** followed by treatment with $NaCo(CO)_4$ under an atmosphere of carbon monoxide (CO) to yield (+)-7-deoxypancratistatin (**58**) in 72% yield over two steps.[47] This one-pot transformation was accomplished without protecting the four hydroxyls on the C-ring. However, in order to perform the hydroxylation of the A-ring using the reaction conditions provided by Uchiyama, the tetraol **58** was first fully

silylated using hexamethyldisilazane (HDMS). Pancratistatin (**59**) was thus obtained in a 62% yield over the two steps. The two alkaloids were thus synthesized in overall yields from benzene of 19% and 12%, respectively.

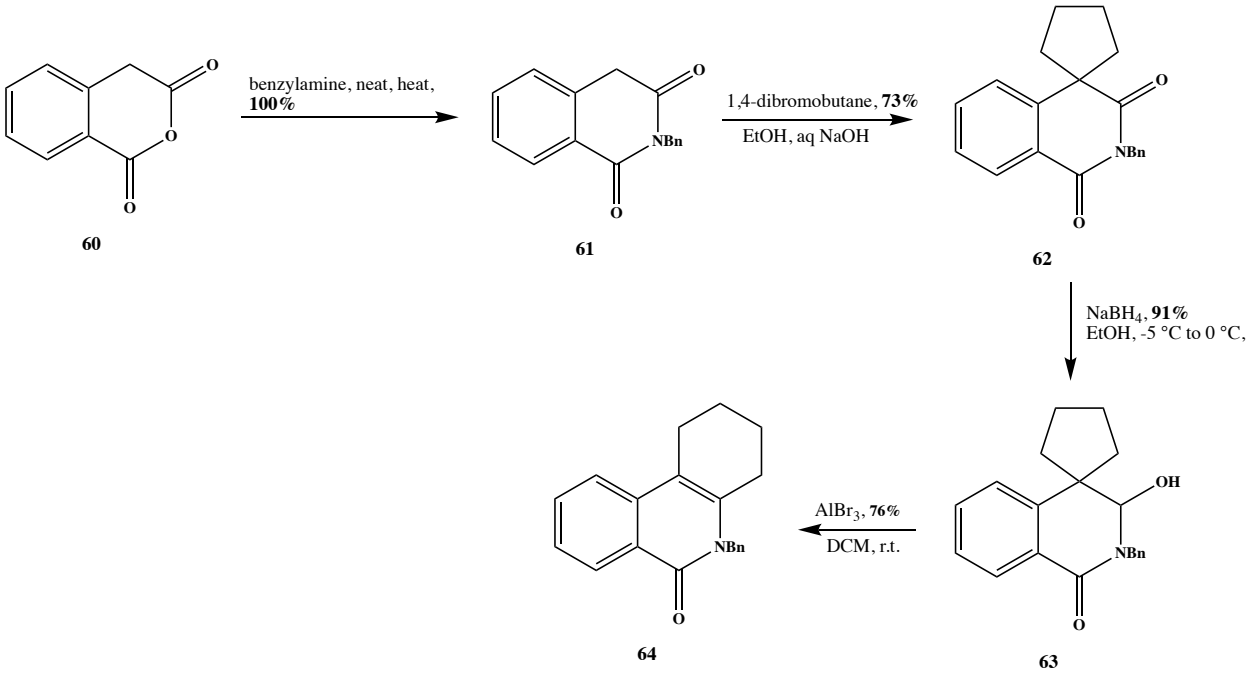


Scheme 11: Hernandez completed synthesis of (+)-7-deoxypancratistatin and pancratistatin

Although the aforementioned syntheses of phenanthridinone alkaloids have proceeded by closing the B-ring of the skeleton last, there are a small number of examples in which the C-ring is installed last. In 1996, Heaney and co-workers developed a route to the phenanthridinone 3-ring system starting from the commercially available homophthalic anhydride in this fashion.[48] This new 4-step method was initially used to form compound **64** (Scheme 12) in 51% overall yield, which was significantly more efficient than previously reported procedures.[49,50,51,52] It also served as our premise for creating this ring system in the work presented in this dissertation project.

The synthesis begins with the quantitative formation of *N*-benzylhomophthalimide[53] by simply heating a mixture of homophthalic anhydride and benzylamine. This imide was found to undergo a multitude of base-induced geminal dialkylations[54] such as the reaction with 1,4-

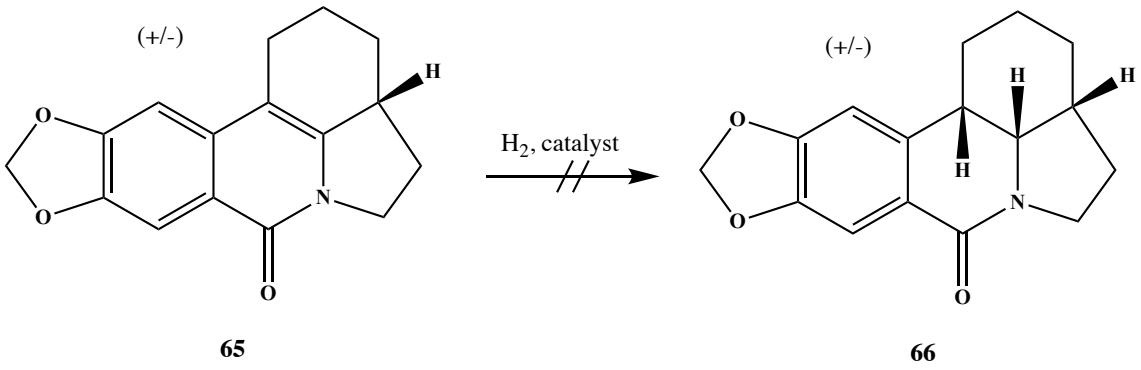
dibromobutane to form the spirocyclic derivative **62**. Interestingly, there are many dialkylated homophthalimides of this type that possess hypnotic action as found by Harriman, et al. in the 1920's.[55,56] The imide was then reduced regioselectively at the non-conjugated carbonyl with sodium borohydride ($NaBH_4$) to give a *a*-hydroxyamide **63**. A 1,2-alkyl shift was then induced with aluminum bromide ($AlBr_3$) to form *N*-benzyl-1,2,3,4-tetrahydrophenanthridinone (**64**) in 76% yield.



Scheme 12: Heaney synthesis of phenathridone ring system using 1,2-alkyl ring expansion

During their synthesis of the *Amaryllidaceae* alkaloids *y*-lycorane and 1-deoxylycorine, Padwa and co-workers discovered that is was difficult to form the desired saturated B,C-ring juncture through hydrogenation of the tetrasubstituted double bond at that position while an amide functionality was present on the B-ring (see Scheme13).[57] For this reason, they were forced to alter their reaction scheme by reducing the amide to the corresponding amine prior to reducing the olefin. A similar problem occurred during the research carried out in this project, and a similar

adjustment was made to allow the synthesis to continue. The following is a brief description of the synthetic scheme that led to Padwa's synthesis of *y*-lycorane using this process.

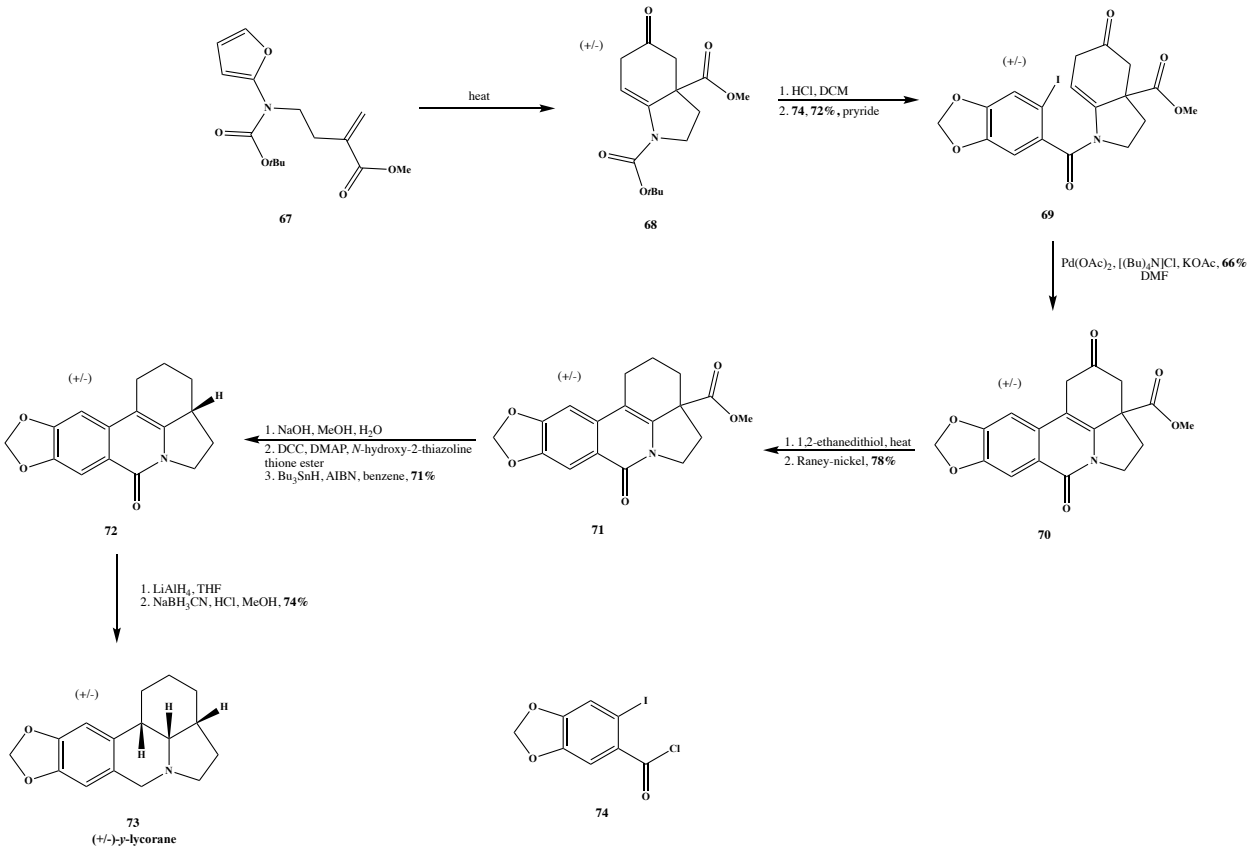


65 **66**

Scheme 13: Padwa failed reduction of tetra-substituted double bond

The synthesis begins with the thermolysis of the furanyl carbamate **67** to yield the [4+2]-cycloaddition product **68** (see Scheme 14). Acidic hydrolysis to form the free enamine followed by an acylation reaction with 6-iodobenzo[1,3]dioxole-5-carbonyl chloride (**74**) gave the amide **69**. A protocol developed by Rigby and coworkers[58] was then employed to form **70** exclusively through the use of a Jeffrey palladium catalyst in 68% yield.[59] The ketone functionality was then converted to the thioketal derivative followed by a reduction to the alkane using Raney-nickel in 78% yield over two steps. After hydrolysis of the methyl ether, the resulting carboxylic acid was then decarboxylated to give **72** in 71% yield using a modified Barton-McCombie deoxygenation procedure.[60,61,62] The reduction of the tetrasubstituted double bond at this stage gave only trace amounts of product through the use of traditional hydrogenation catalysts in an atmosphere of hydrogen gas. Therefore, the amide was first reduced using lithium aluminum hydride ($LiAlH_4$), and the resulting enamine was subsequently reduced with sodium cyanoborohydride ($NaBH_3CN$) in methanolic HCl to yield (+/-)-*y*-lycorane (**73**) in 74% yield as a single diastereomer. It was

assumed that both the protonation of the enamine and the subsequent hydride attack occurred from the less sterically hindered face of the molecule to give this stereochemical result.



Scheme 14: Padwa completed synthesis of (+/-)-*y*-lycorane

Though there have been a number of total syntheses of *Amaryllidaceae* alkaloids of the phenanthridinone type, very few have used the strategy of incorporating the C-ring at the end of the route. In fact, the Lewis acid-induced alkyl shift to form the C-ring as reported by Heaney has not been used in a published total synthesis of a natural product. This project is designed to illustrate that the use of this reaction is an important methodology to produce alkaloids and their analogs in a streamlined process. As described in the following chapter, this reaction proved to be very reliable on a plethora of substrates. Through the investigation of this process, many other

surprising and useful transformations were discovered that could, in theory, be useful in future strategies towards the total synthesis of natural products in general.

Chapter 2

RESULTS AND DISCUSSION

2.1 Model for the Phenanthridinone Skeleton

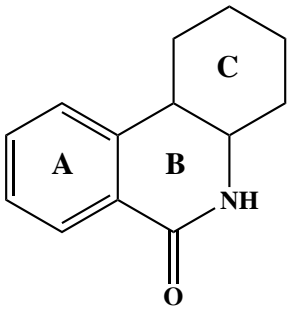
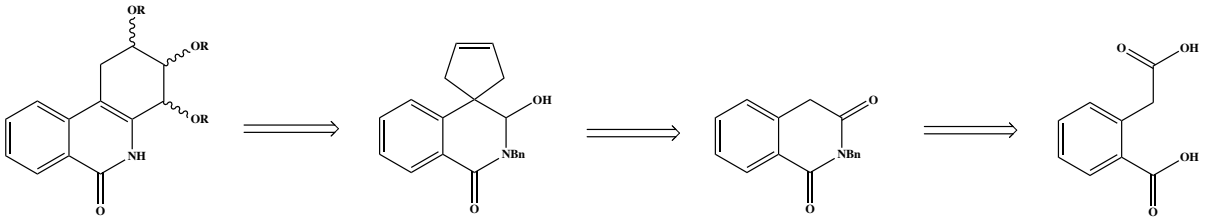


Figure 3: Phenanthridinone skeleton

As described previously, there are a number of well-established methods to synthesize the phenanthridinone skeleton the most common of which involve a late-stage formation of the B-ring using cross-coupling procedures. Our goal was to develop a novel route where the A and B-rings are installed early in the synthetic scheme followed by a ring expansion process to create the C-ring with appropriate functionalization to incorporate numerous hydroxyl groups (see scheme 15).



Scheme 15: Retrosynthetic analysis of the phenanthridinone skeleton

The viability of this approach was tested using a series of model studies designed to assess three important factors. First, the specific C-ring functionalities that could be transformed easily to the requisite hydroxyl groups must be identified. Second, the conditions for reducing the unavoidable tetrasubstituted double bond at the B/C ring fusion must be found. Third, the choice of protecting groups for hydroxyls and other functions must be established with the idealized goal of being able to remove all of them in one step at the end of the synthesis.

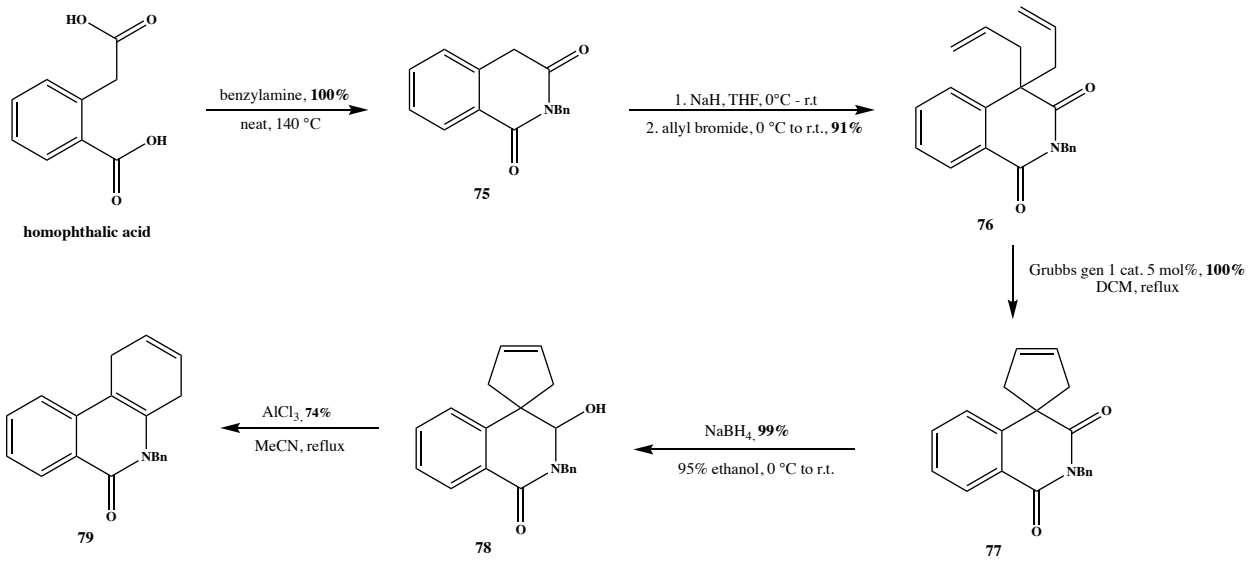
To reduce the cost and shorten the schemes, model studies were carried out on substrates that lacked the methylenedioxy and dimethoxy substitutions on the A-ring since these functions are relatively inert. The A and B-rings were established (see Scheme 16) initially by converting commercially available homophthalic acid to the anhydride using thionyl chloride followed by heating the anhydride with benzylamine. However, it was discovered later that the imide could be formed directly and quantitatively by simply stirring a mixture of the diacid and benzylamine at 140 °C in the absence of solvent.

The alpha position of the resulting imide was then dialkylated smoothly using sodium hydride (NaH) and allyl bromide. Ring-closing metathesis (RCM) using a 5 mol% loading of generation 1 Grubbs catalyst gave the spirocyclopentene whose structure was confirmed by X-ray diffraction studies (see Figure 4). Regioselective reduction of the non-conjugated carbonyl of the imide to its hemiaminal derivative using excess sodium borohydride in methanol set up the key step to our synthetic route—a Lewis acid catalyzed ring-expansion to produce the C-ring of the phenanthridinone skeleton.

As discussed in the previous section, this type of ring expansion has been reported in the literature[48] using aluminum bromide, and a modified procedure using sulfuric acid[63] was also developed in our laboratory. However, these methods were incompatible with several of the

functionalities encountered in other systems to be discussed later. The use of aluminum chloride in refluxing anhydrous acetonitrile proved to be an efficient and relatively mild procedure.

This six-step sequence of transformations led to the complete phenanthridinone skeleton in 68% yield overall and provided a substrate to test the oxidation reactions to be used for incorporation of hydroxyl substituents on the C-ring. The tetrasubstituted double bond at the B/C ring junction could also be used as a model for developing reduction reactions.



Scheme 16: Synthesis of the phenanthridinone skeleton

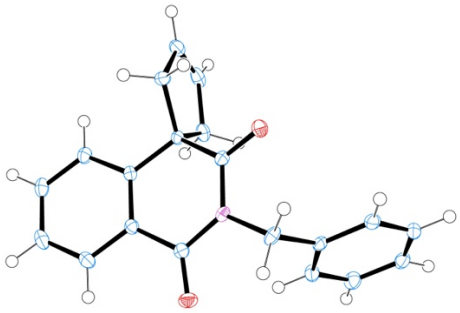
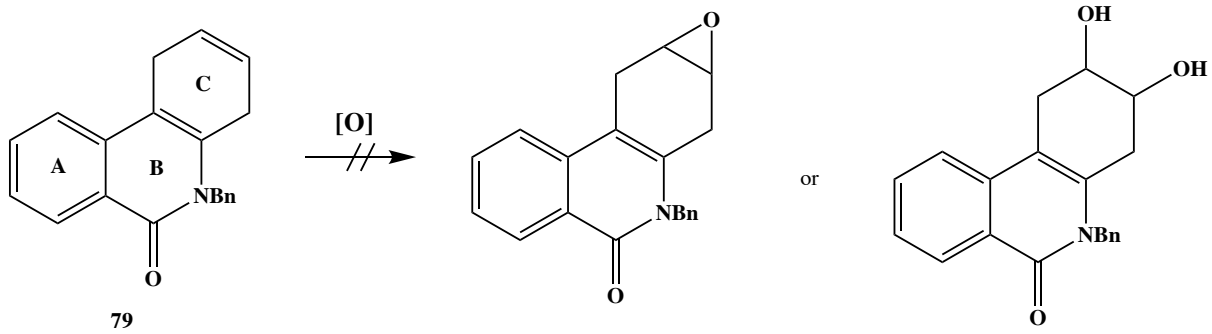


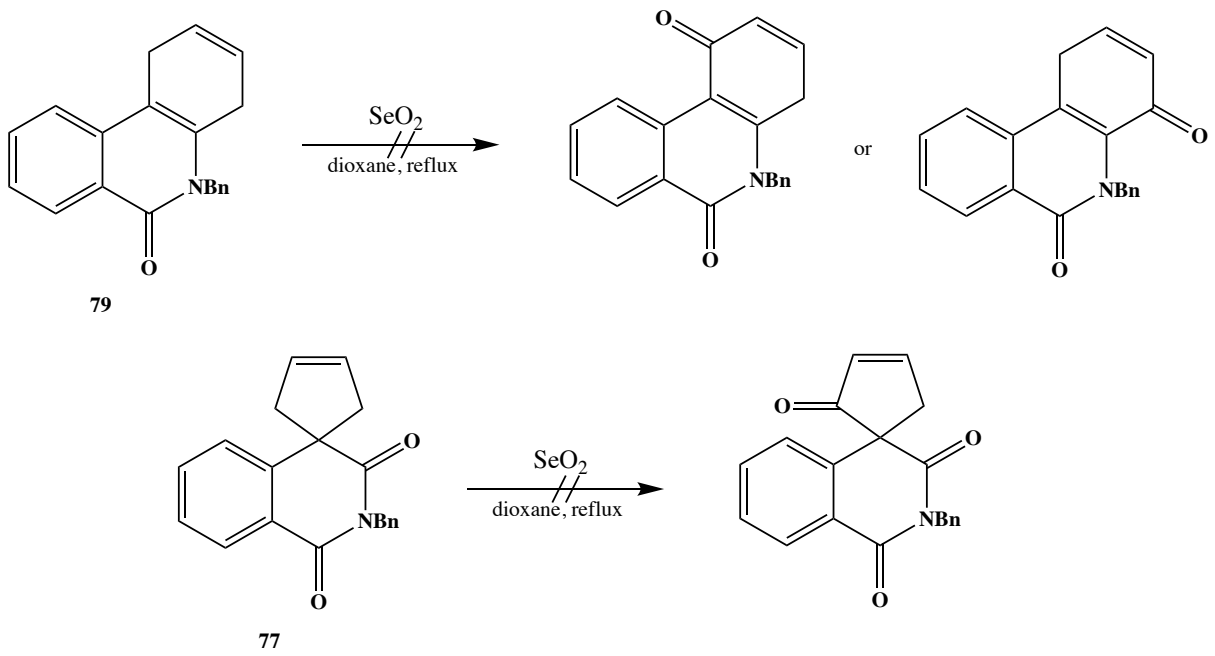
Figure 4: X-ray structure of **77**

We initially hypothesized that resonance stabilization of the tetrasubstituted double bond of the B-ring would decrease its reactivity and allow the selective oxidation of the disubstituted alkene to either a vicinal *trans* or *cis* diol directly or through an epoxide intermediate. However, attempts to oxidize this olefin with *m*-CPBA or Oxone resulted exclusively in reactions with the tetrasubstituted double bond to give unidentified products. In other words, the normal reactivity order for alkene oxidations based on substitution pattern appears to be operating. Surprisingly, an attempt to carry out the Woodward dihydroxylation procedure gave no reaction at all.



Scheme 17: Failed oxidations of the disubstituted double bond

In addition, we attempted to oxidize **79** to an unsaturated ketone using half an equivalent of selenium dioxide (SeO_2) in refluxing dioxane (see Scheme 18). This could have provided another pathway to install additional hydroxyl groups in the C-ring. However, the reaction resulted only in decomposition. Another attempt to utilize this reaction on **77** gave a similar result.



Scheme 18: Failed allylic oxidations using selenium dioxide

The issue of selectivity in functionalizing the disubstituted alkene was finally resolved by oxidizing the double bond in **77** prior to performing the ring expansion step. Oxidation of the cycloalkene using potassium permanganate ($KMnO_4$) in a biphasic ethyl acetate/water medium with tetrabutylammonium iodide (TBAI) as a phase-transfer catalyst resulted in the formation of the *cis* diol **83** (scheme 19) in 36% yield after separation of the unreacted starting material. However, the method was deemed unsatisfactory because the reaction never went to completion; and separation of the starting material from the product was tedious.

Later, it was found that the *cis* vicinal diol **80** (Scheme 19) could be prepared efficiently using the Woodward dihydroxylation procedure with silver acetate (AgOAc), molecular iodine (I_2) and water in acetic acid in 97% overall yield. Both the *cis* diol (one diastereomer) as well as a monoacetate-protected *cis* diol (mixture of diastereomers) were present in 11% and 86% yields, respectively. These two products could be separated using column chromatography or converted

quantitatively to the diol by hydrolysis of the acetate ester with potassium carbonate (K_2CO_3) in methanol (see Scheme 19). Furthermore, the *cis* stereochemistry of **80** was confirmed by an X-ray structure of the fully acetylated derivative of **84** (see Figure 5).

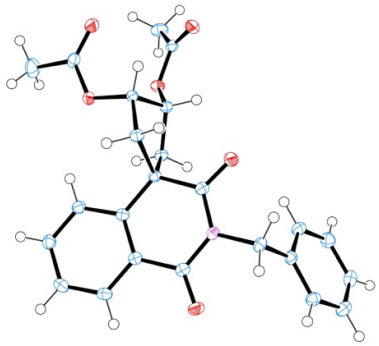


Figure 5: X-Ray crystal structure of **84**

An attempt to install a *trans* diol directly on the spirocyclopentene using the Prévost *trans*-hydroxylation procedure with silver acetate and molecular iodine in anhydrous benzene gave no reaction. However, oxidation using *m*-CPBA gave a mixture of the two epoxides in 35% yield. Interestingly, the dioxirane-mediated epoxidation with Oxone and acetone[64] gave a single diastereoisomer **81** in 87% yield with the epoxide ring directed over the aromatic ring as confirmed through proton NMR analysis as well as X-ray crystallography (see Figure 6). Hydrolysis of this epoxide gave a mixture of two isomeric *trans* diols **82** in quantitative yield. This reaction became the preferred method to oxidize the olefin.

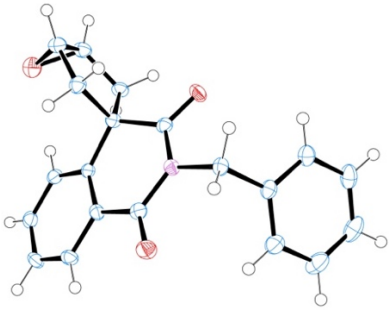
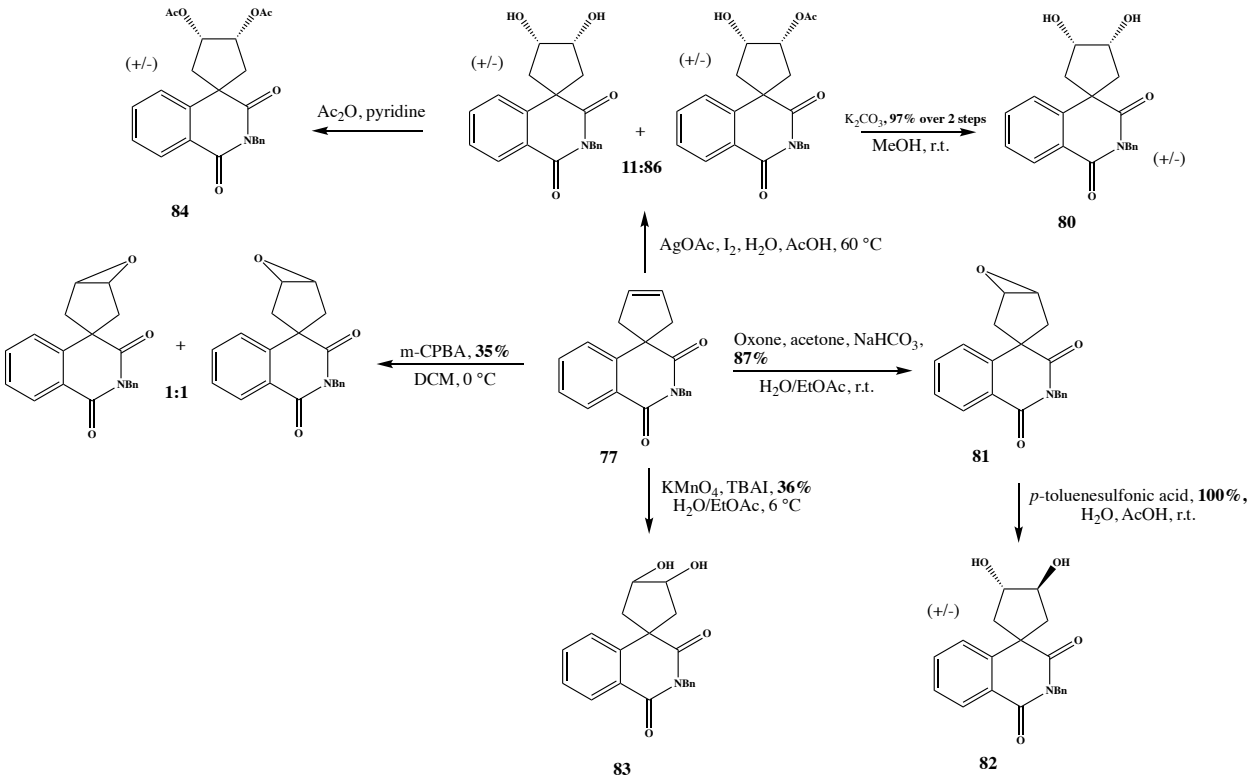
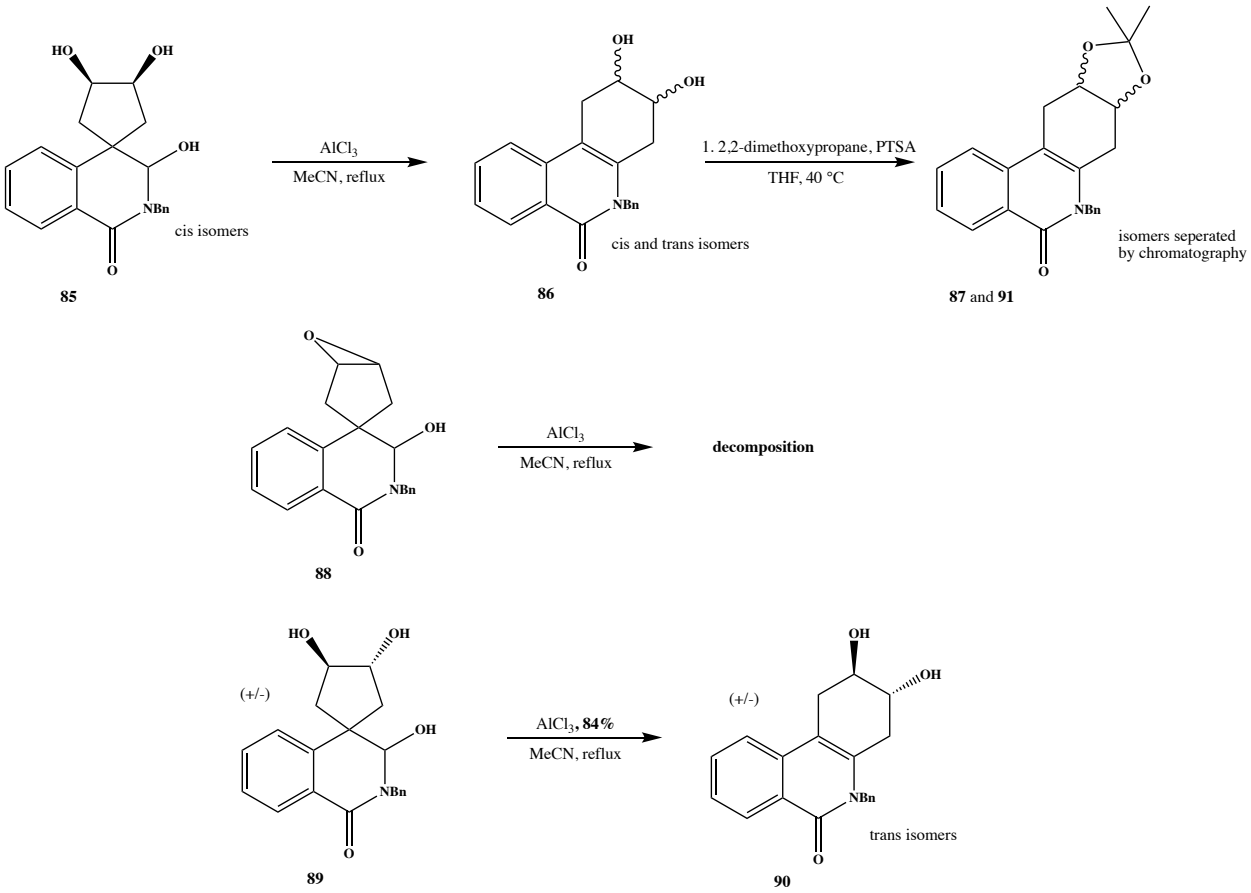


Figure 6: X-ray crystal structure of **81**



Scheme19: Successful disubstituted double bond oxidations

Reduction of the non-conjugated imide carbonyl in the *cis* diol **80** gave a mixture of hemiaminals **85** (see Scheme 20) that were subjected to the optimized conditions for ring expansion. Unfortunately, a partial isomerization of *cis* diol to *trans* diol occurred during ring expansion, and this made the route unfavorable. However, the mixture of *cis* and *trans* isomers of **86** could be separated by first protecting the vicinal diols with an acetonide group followed by column chromatography. The purified *cis* isomer **87** became a useful substrate to test tetrasubstituted double bond reductions, which will be discussed later. The epoxide isomers **88** decomposed under these same conditions with $AlCl_3$. Thankfully, the *trans* diol **89** afforded the ring-expanded product in good yield. The stereochemistry for the acetonide protected *cis* diol **87** as well as the *trans* diol products **90** were confirmed by X-ray diffraction studies (see Figure 7).



Scheme 20: Ring-expansion attempts with hydroxyl derivatives using $AlCl_3$

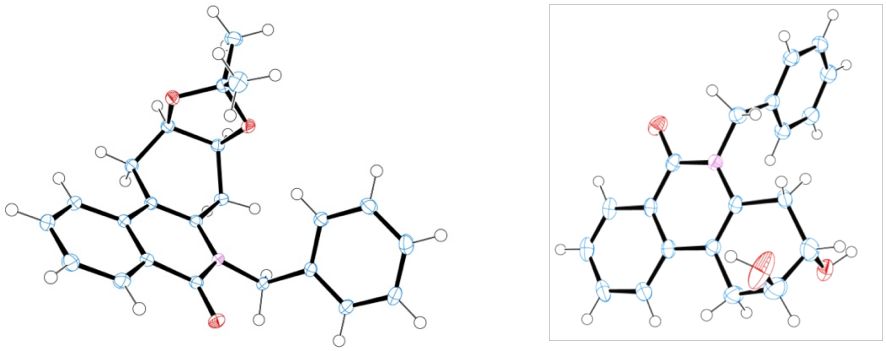
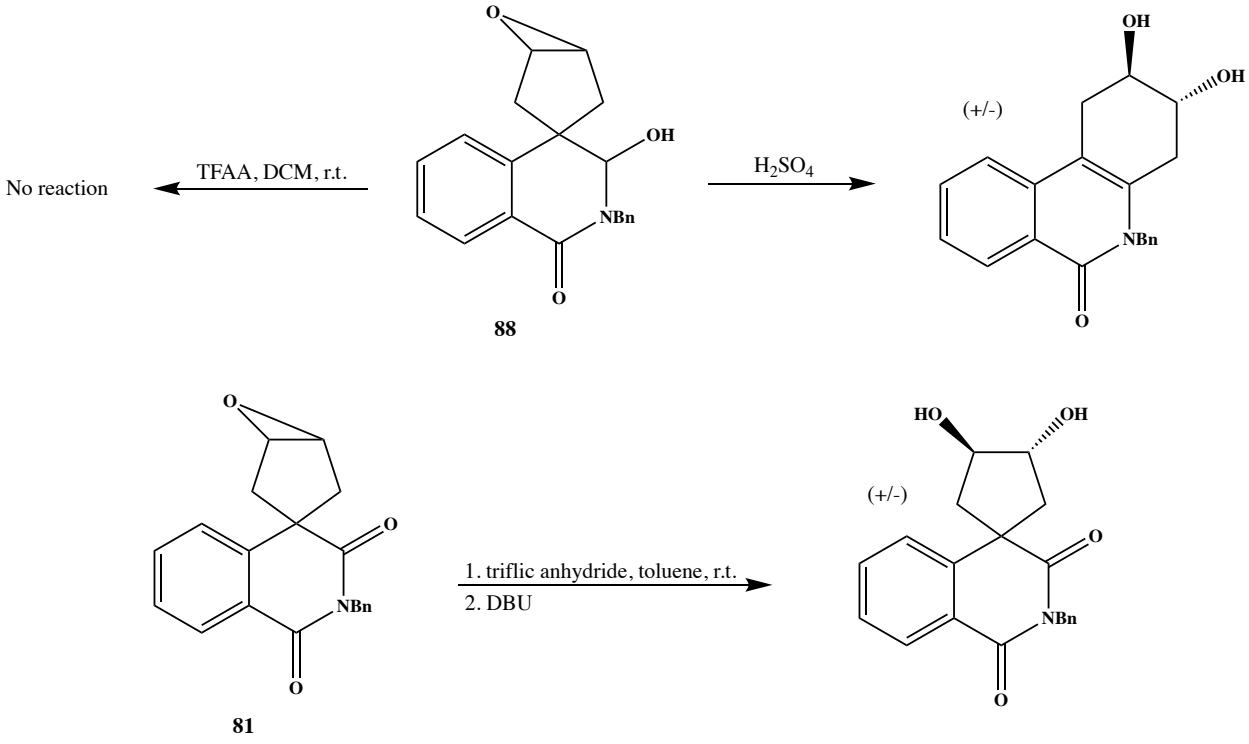


Figure 7: X-ray structures of **87** and **90**

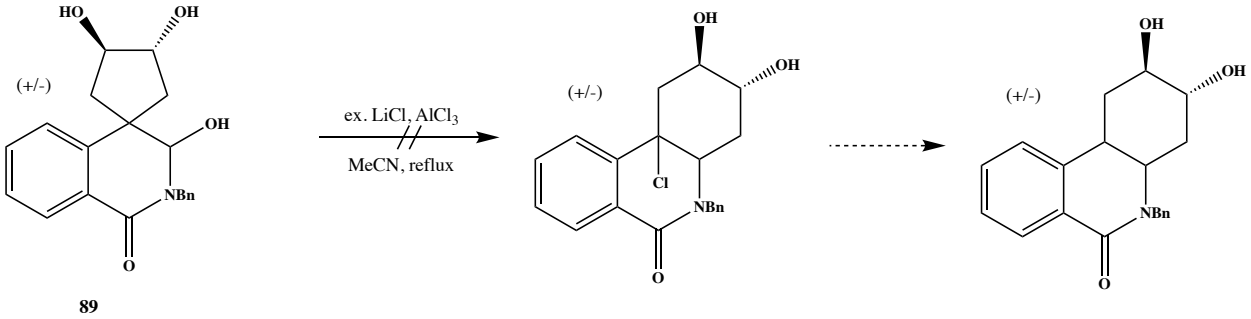
The advantage of obtaining a ring expanded product containing the epoxide function lies in the possibility of its transformation to an allylic alcohol that could undergo further oxidation to

obtain triol substitution. For this reason, attempts were made to find alternative reagents to induce ring expansion in **88** without disturbing the epoxide functional group (see Scheme 21). Trifluoroacetic anhydride (TFAA) in dichloromethane gave no reaction at all and sulfuric acid followed by a basic workup gave the ring-expanded *trans* diol. An attempt to form an allylic alcohol using spiro **81** prior to reduction of the imide and subsequent ring expansion with trimethylsilyl triflate (TMSOTf) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in the formation of a *trans* diol. In this case, we suspect that the epoxide was unable to undergo an axial attack by the triflate anion due to the 5-membered ring. The diol probably resulted from hydrolysis of the epoxide during workup. Therefore, we moved forward in the route using the diol intermediates instead.



Scheme 21: Additional epoxide trials

As mentioned previously, the reduction of the tetrasubstituted double bond formed during the ring expansion step is a major obstacle that must be faced in order to have a viable project. In an attempt to prevent the double bond from forming in the first place, the reaction solvent for **89** was first saturated with lithium chloride prior to the addition of $AlCl_3$ in the ring-expansion step. The goal was to "trap" the benzylic carbocation intermediate with chloride anion before it lost a proton to become the alkene. The resulting alkyl halide could then be reduced using any of several reagents. However, the reaction was unaffected by this change in the conditions.

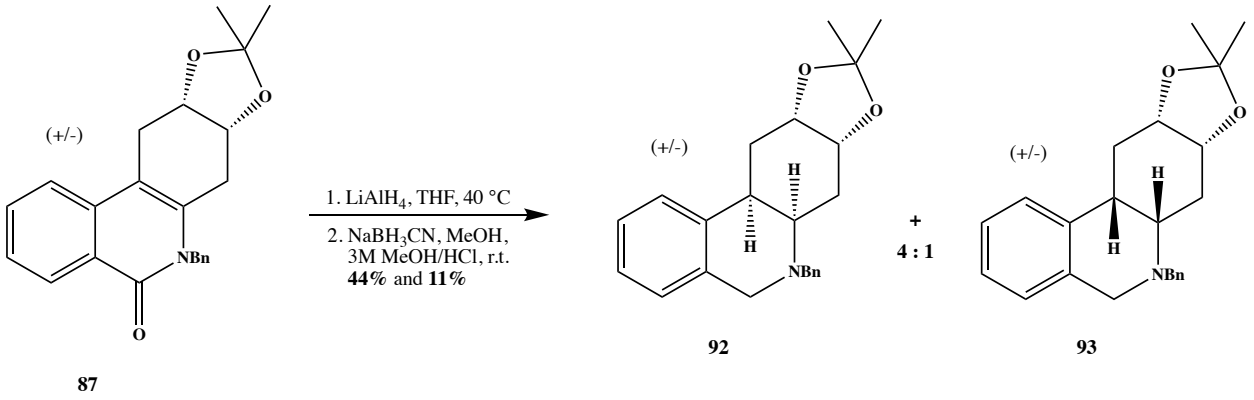


Scheme 22: Attempt to bypass the tetrasubstituted double bond

Our initial investigation for reducing the tetrasubstituted alkene included many classical techniques all of which proved ineffective in our system. Hydrogenation using platinum oxide (PtO_2) and hydrogen at 50 psi gave no reaction. Other attempts using various hydride sources under acidic conditions also failed including triethylsilane (Et_3SiH) in trifluoroacetic acid and sodium cyanoborohydride ($NaBH_3CN$) in acetic acid. As already mentioned in the introduction, we are not the only group to face the same issue (see Scheme 13). The lack of reactivity of the double bond is related to the presence of the amide function. Removing the amide carbonyl makes the double bond more electron rich so that it behaves like an enamine, which can be easily reduced. One solution that allows the original amide targets to be maintained is to reduce both the amide

and the alkene followed by a selective oxidation of the benzylic methylene to reestablish the amide function.

Initial studies on **87** showed that reduction of the amide carbonyl with either Red-Al® or lithium aluminum hydride ($LiAlH_4$) occurred smoothly according to high resolution mass spectrometry (HRMS) although attempts to isolate and purify the resulting enamine failed. A logical work-around for the instability of the product was to reduce the crude material after the initial workup. Treatment of a suspension of the crude enamine and sodium cyanoborohydride in methanol with 3M methanolic hydrochloric acid followed by base gave a mixture containing two diastereomers **92** and **93** in 44% and 11% yield, respectively (see Scheme 23) among other products. Fractional recrystallization of this mixture from ethyl ether using a slow evaporation technique gave a clean sample of each isomer. Surprisingly, X-ray crystallographic data collected from both samples confirmed that both ring fusions are *cis*. These results were promising although the yields were low and side products were being generated. We continued to screen other variables to determine their effects on the reduction stereochemistry as well as the ratio of isomers.



87 **92** **93**

Scheme 23: Reduction of both amide and enamine

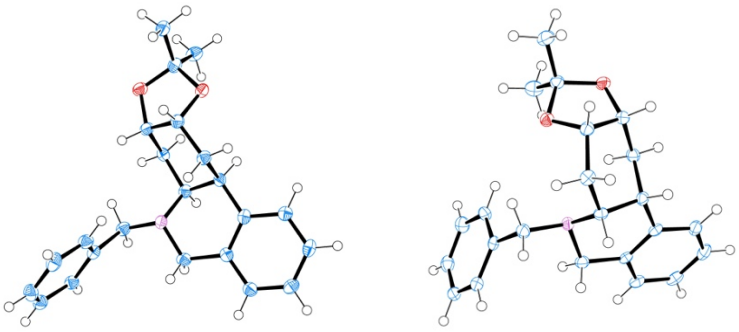
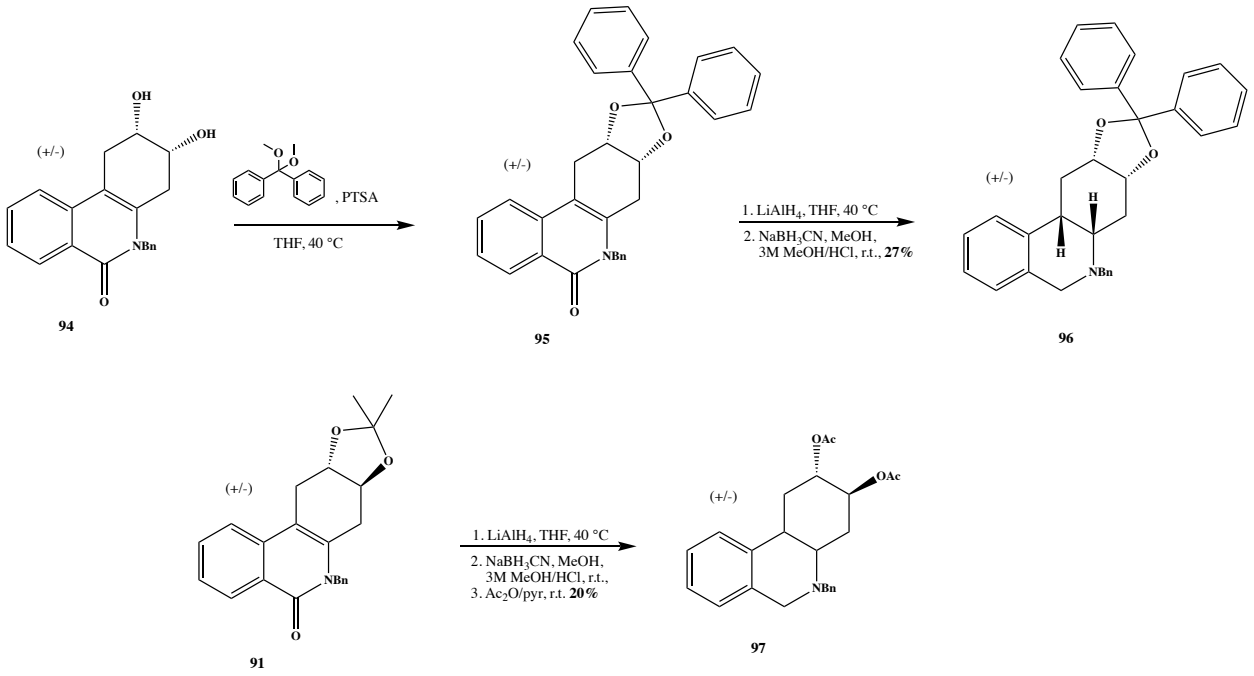


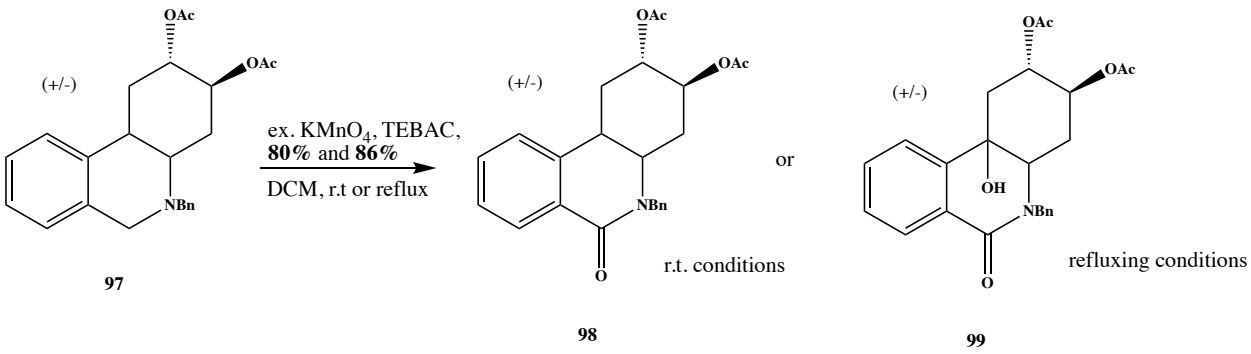
Figure 8: X-ray structures of **92** and **93** respectively

We hypothesized that the stereochemistry of the alkene reduction might be directed by the ether oxygen atoms in the acetonide protecting group on the C-ring. To provide additional insight, the *cis* diol **94** was first protected as a diphenyl acetal to give **95**, which is a much bulkier group than the acetonide used in the previous study. The same reductive reaction conditions were then used to determine possible steric effects on the reaction (see Scheme 24). Upon workup, only one isomer of the reduction product **96** was isolated in 19% yield. Thus, the reaction was much more selective but the yield suffered drastically. Through HRMS monitoring, we were able to detect other aspects of this reaction. For example, these acetals were observed to cleave slowly under the reaction conditions although the double bond appeared to be reduced prior to cleavage of the protecting group. This undoubtedly led to by-products and called for more stable protecting groups. In fact, the use of non-cyclic acetals will be discussed in great detail later in systems containing the methylenedioxy group on the A-ring. In order to determine the effects of a *trans* diol substituted C-ring, **91** was subjected to the same reaction conditions, which resulted in the production of only one isomer **97** of unknown stereochemistry upon acetylation of the now unprotected diol.



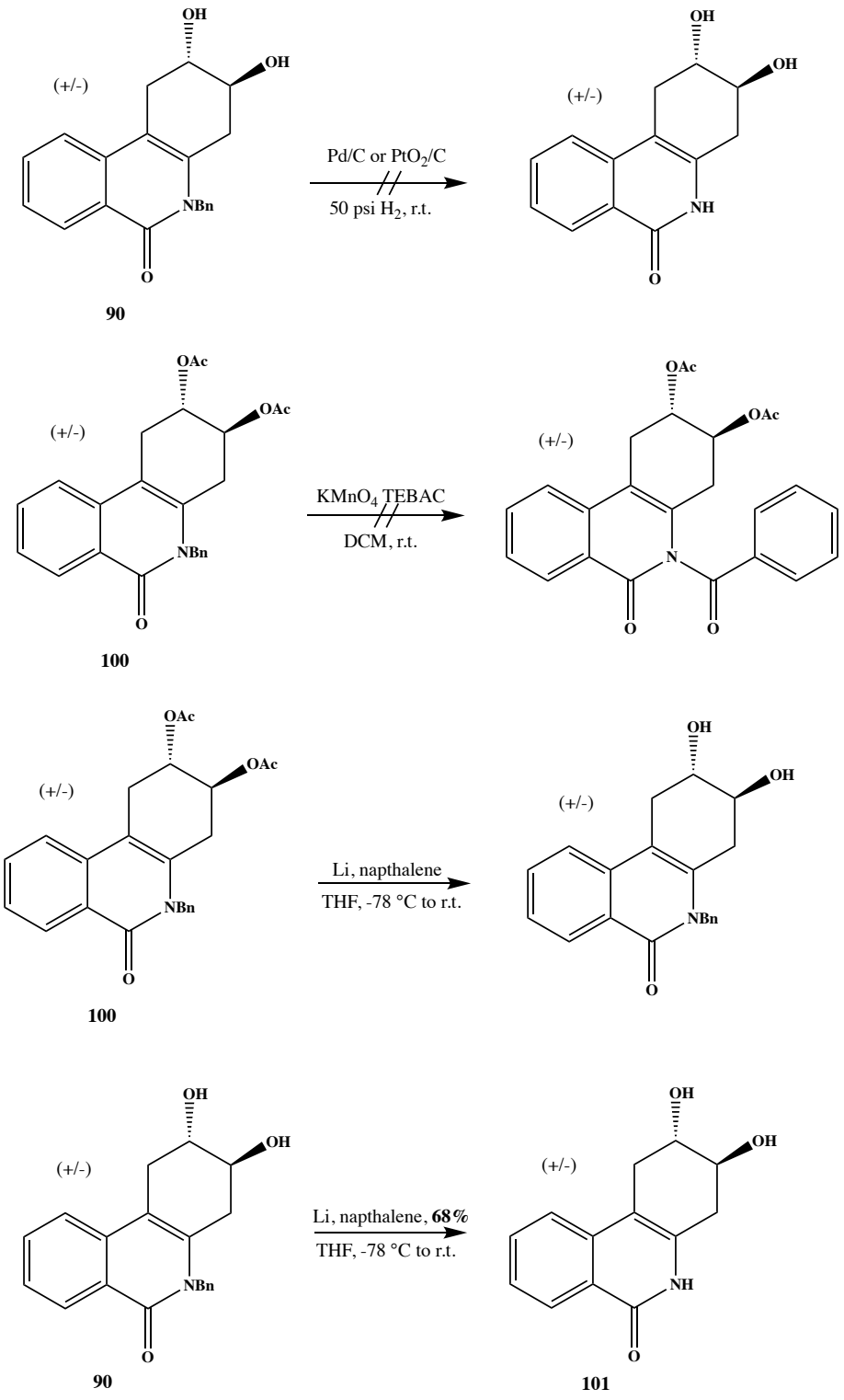
Scheme 24: Reduction of both the amide and the enamine

Converting the amide to the amine certainly appeared to facilitate the reduction of the tetrasubstituted double bond, but the ability to reintroduce the amide function by oxidation was also required. To test the use of manganese dioxide (MnO_2) for this purpose the diacetate **97** was treated with freshly prepared MnO_2 in dichloromethane, a common reagent for benzylic oxidations of this type. However, the reaction failed even under forcing conditions; and a similar approach using barium manganate ($BaMnO_4$) was also unsuccessful. We then turned to a homogeneous system using excess potassium permanganate ($KMnO_4$) with benzyltriethylammonium chloride (TEBAC) in dichloromethane. The reaction gave two products depending on the reaction conditions. In initial trials at reflux, conditions found in the literature[65], the reaction was observed to give **99** in which the remaining benzylic position was oxidized to an alcohol at extended reaction times. However, the desired product predominated at short reaction times run at room temperature. Under optimum conditions, **98** was produced in 80% yield.



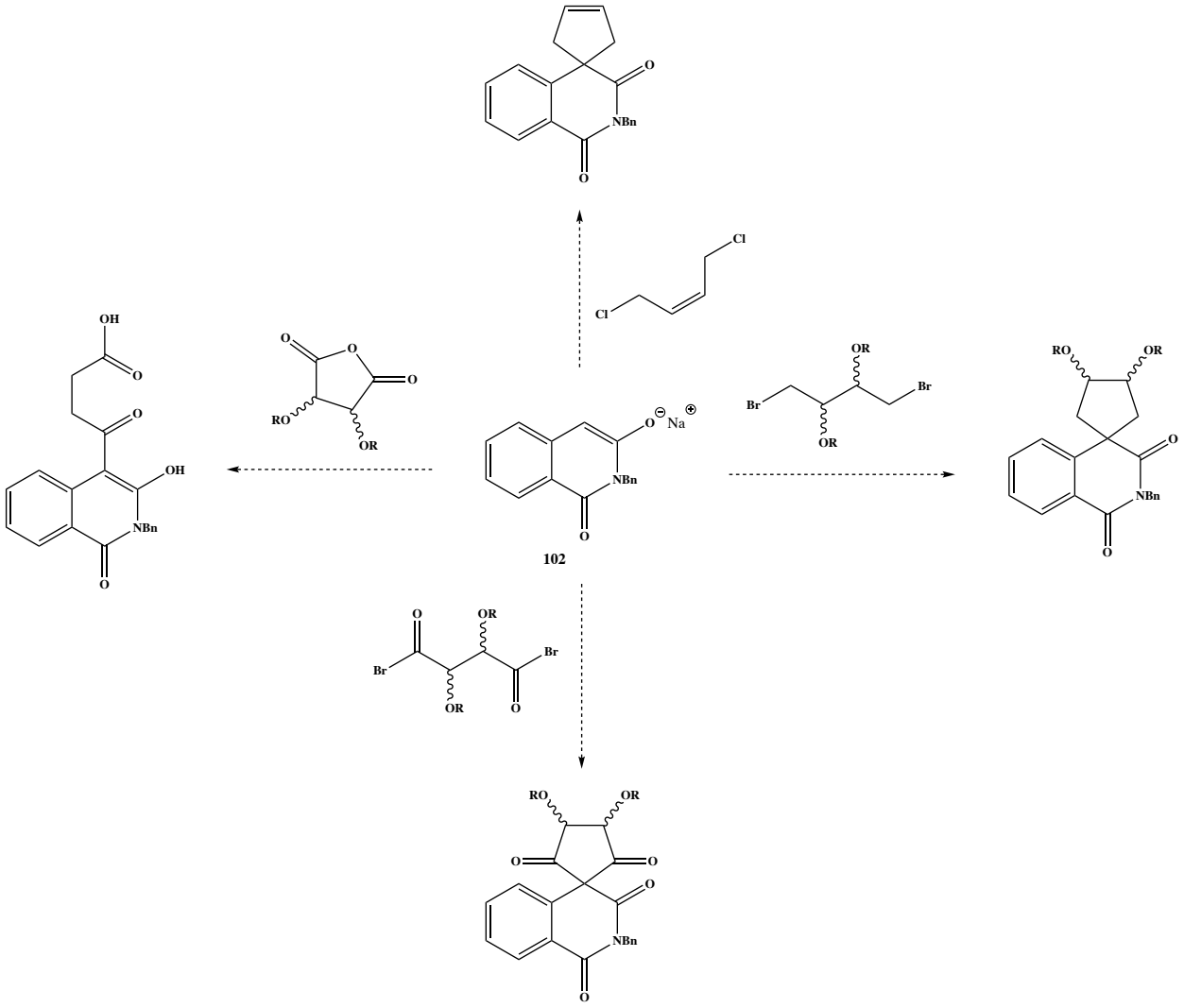
Scheme 25: Re-oxidation of endocyclic amine

The benzyl group of **90**, used to protect the amide functionality, was found to be stable to typical methods used for removing such groups. Hydrogenation at 50 psi using both palladium and platinum catalysts was ineffective. We attempted to make the protecting group labile to hydrolysis by oxidizing it to the benzimide, but this reaction using $KMnO_4$ failed. Finally, the benzyl group was cleaved successfully with lithium naphthalenide radical anion in 68% yield, but this procedure also removed the acetate protecting groups on the C-ring. In fact, the acetates were removed faster than the benzyl group. The unprotected amide **101** was efficiently produced from **90** under these conditions.



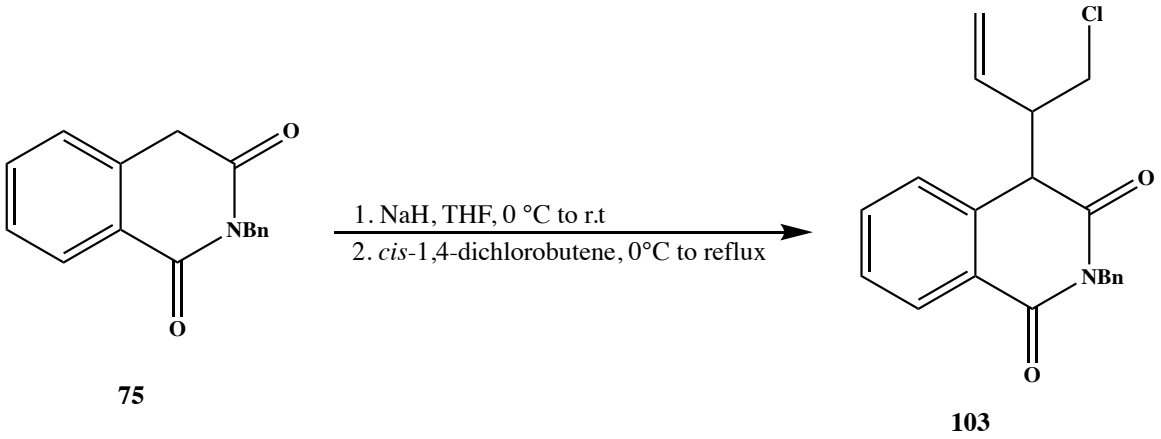
Scheme 26: Deprotection of the N-benzyl amide

The use of Grubbs catalyst to generate the spirocyclopentene ring as shown in Scheme 16 is a convenient, high yielding process but involves an expensive catalyst and is limited in producing analogs. Finding a more versatile procedure that could make installing additional functionality and chirality on the C-ring is one of the goals of this project. As mentioned earlier, alkylation of the benzylic methylene group on **75** using 1,4-dibromobutane has been studied before. To expand on this work by testing other alkylating and acylating agents, the reactions depicted in Scheme 27 below were investigated.



Scheme 27: Strategies to install the spiro group without ring-closing metathesis

We began with an attempt to alkylate the sodium enolate **102** with *cis*-1,4-dichloro-2-butene. The reaction took place only at reflux in THF and was monitored using thin-layer chromatography. The sole product of the reaction was **103**, which is the result of an S_N2' reaction rather than sequential S_N2 reactions to produce **77**. However, this reagent was found to be useful in preparing a spirane on a different non-imide substrate that will be discussed later.

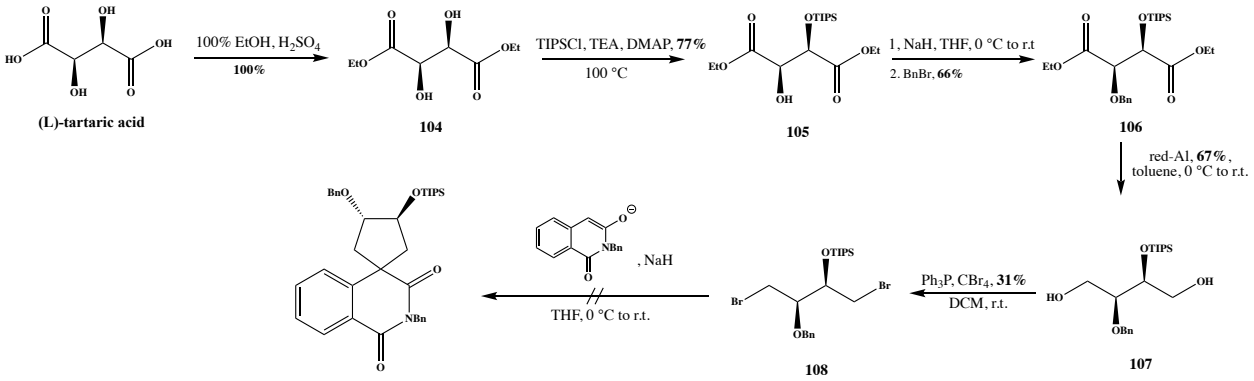


75 **103**

Scheme 28: Model imide reaction with 1,4-dichlorobutene

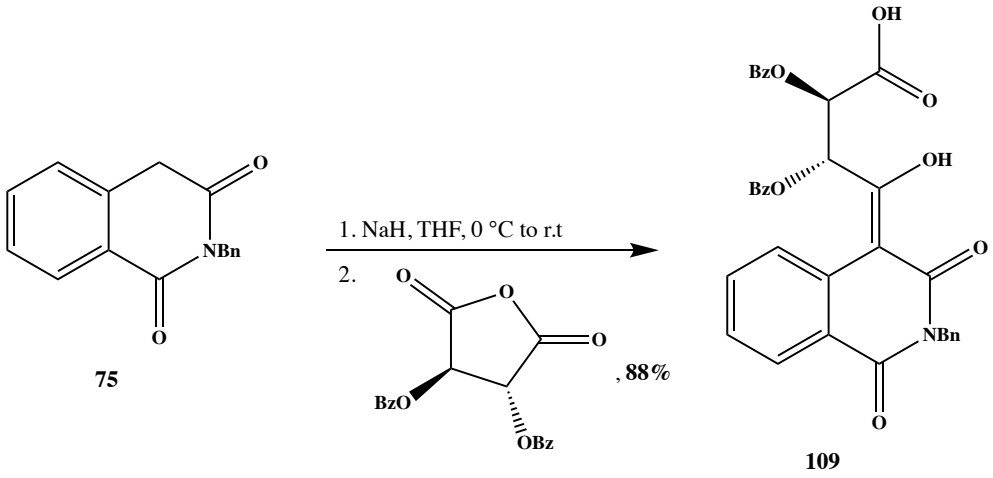
Since 1,4-dibromobutane had been used previously to generate spirocyclopentanes, we extended this reaction to include a 2,3-disubstituted derivative containing preinstalled protected hydroxyl groups of known stereochemistry to produce a functionalized cyclopentane ring. To that end, commercially available (L)-tartaric acid was first esterified using a classic Fischer esterification with absolute ethanol and catalytic H_2SO_4 (see Scheme 29) to give **104**. An attempt to protect the alcohols as triisopropylsilyl (TIPS) ethers using triisopropylsilyl chloride, triethylamine (TEA) and 4-N,N-dimethylaminopyridine (DMAP) at 100 °C gave only a mono-protected product **105**, which was probably too sterically hindered for the second hydroxyl to react.[66] The remaining alcohol was then protected as a benzyl ether using NaH in THF followed by benzyl bromide to produce **106**. Both esters were reduced with excess Red-Al® in toluene, and

the resulting diol was converted to the dibromide **108** using an Appel reaction with triphenylphosphine and carbon tetrabromide in dichloromethane at room temperature. Unfortunately, this dibromide failed to react with the enolate **98** in THF even under refluxing conditions.



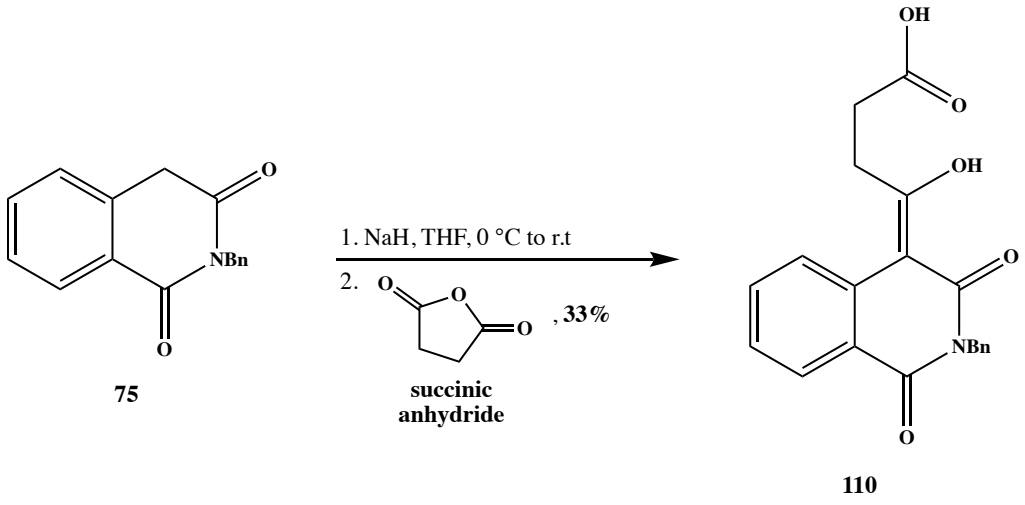
Scheme 29: Synthesis and failed alkylation using 2,3-hydroxylated dibromoalkane

Since both alkylation attempts failed to produce spirane products, our attention turned to acylation reactions using tartaric acid derivatives. Using diethyl tartrate alone with the **104** gave no product, likely complicated by an acid/base reaction between the enolate and the hydroxyl group of diethyl tartrate. Likewise, the enolate also failed to react with a protected form of tartaric acid chloride. Surprisingly, the use of anhydrides as acylating agents gave the most promising results. The cyclic anhydride of (L)-tartaric acid with the hydroxyls protected as benzoate esters[67] reacted with the enolate of **75** to give **109** (Scheme 30) isolated as the enol tautomer in 88% yield.



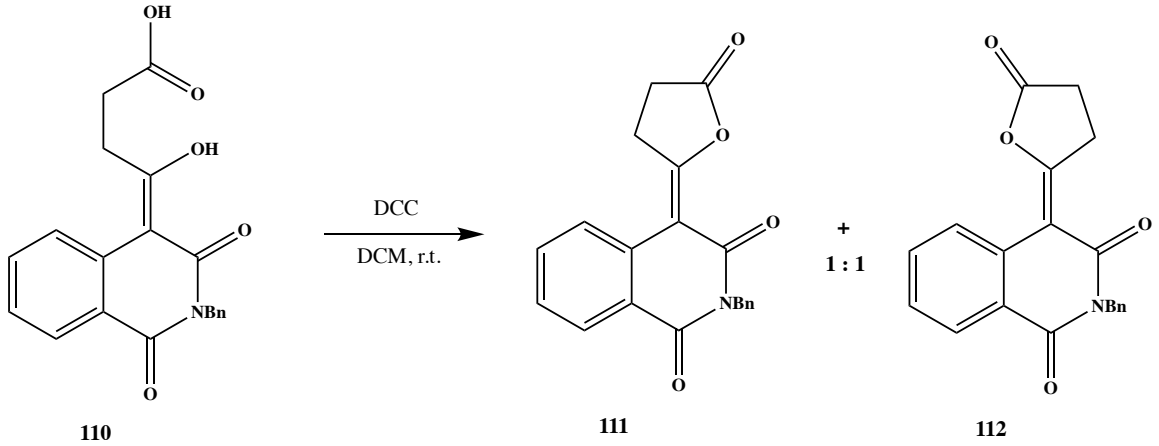
Scheme 30: Successful acylation using a substituted tartaric acid anhydride

To study this reaction further, succinic anhydride was used as a simple model and the acylation was carried out with **75** as described above. The reaction proceeded only to 33% completion but gave the expected product **110**, and the starting imide could be easily recovered during the workup. An NMR analysis of the product showed only one isomer of the exocylic double bond in support of the structure shown in Scheme 31 where the enol tautomer is hydrogen bonded to the imide carbonyl oxygen.



Scheme 31: Acylation using succinic anhydride

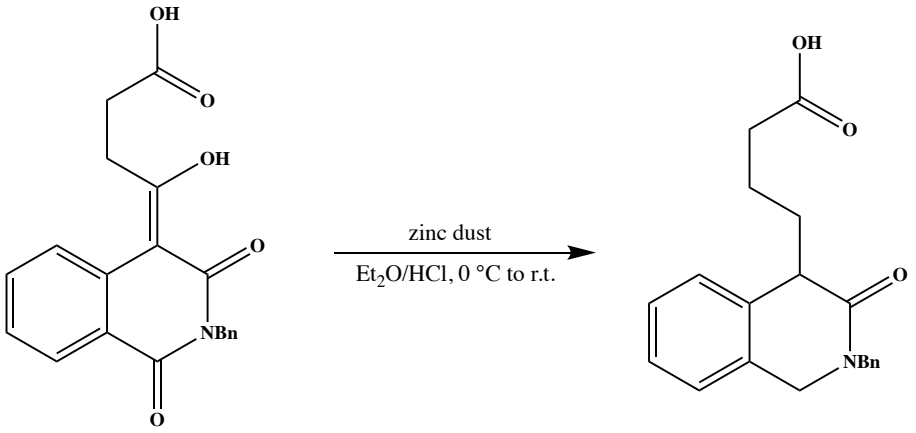
Although converting **109** to a spirocyclopentanone would have been a way to salvage this reaction, the stability of the hydrogen bonded enol tautomer prevented the use of the benzylic carbon atom as a nucleophile to close the ring. To illustrate this problem, **110** was subjected to Steglich esterification conditions using dicyclohexylcarbodiimide (DCC) in DCM at room temperature. The products were found to be a 1:1 mixture of the two geometric isomers of the lactone shown in Scheme 32.



110 **111** **112**

Scheme 32: Steglich esterification of **110** using DCC

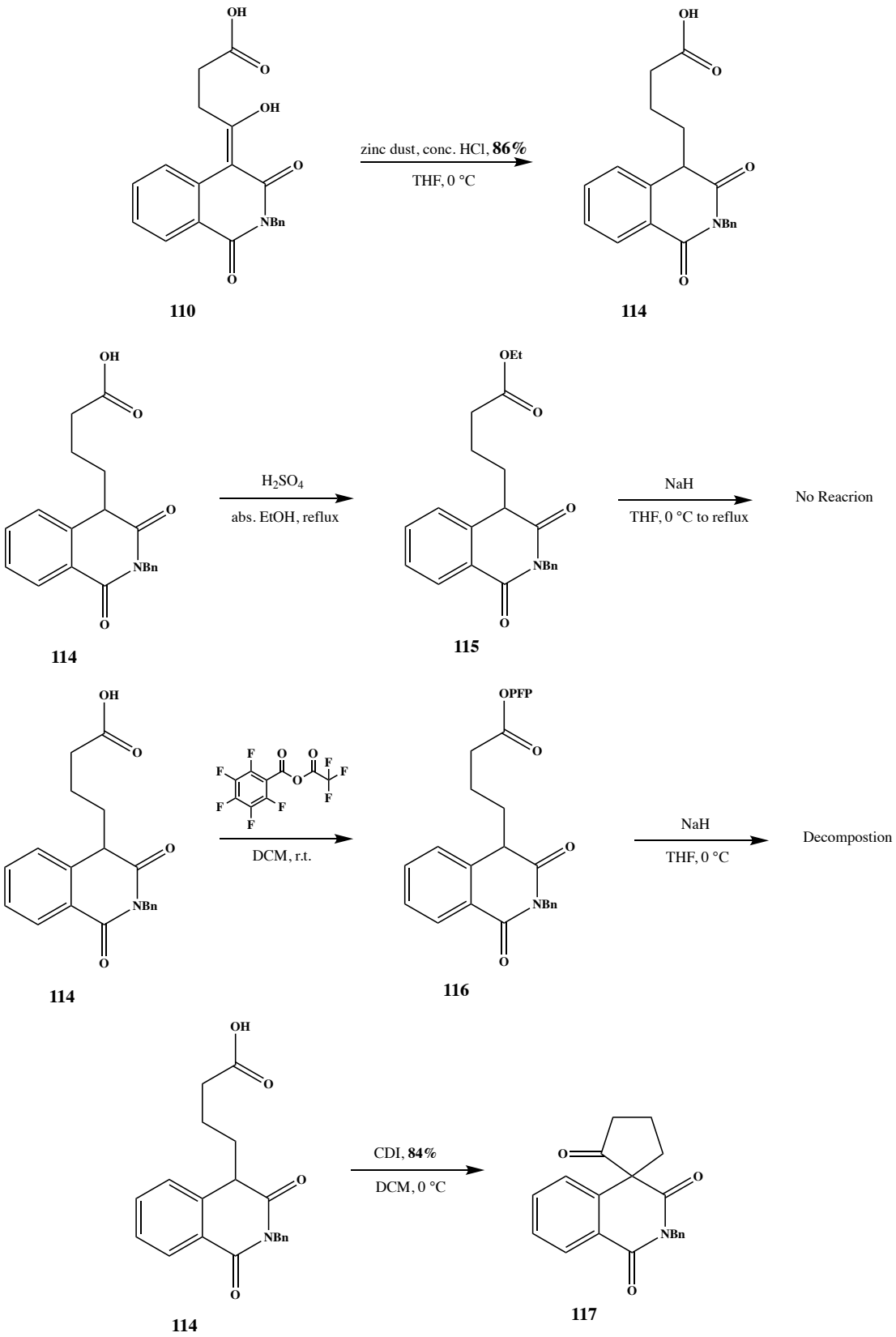
In order to force acylation to occur on carbon rather than oxygen, the first step required the removal of the enol function of **110** using a Clemmensen reduction with activated zinc dust in ethereal hydrochloric acid. This reaction gave varying results leading to the conclusion that both the enol and the conjugated carbonyl of the imide functionality were reduced under these conditions to give **113** as indicated in Scheme 33. The exothermic nature of this reaction was likely the cause of over reduction. However, this discovery has led to a new project in our laboratory to assess the use of the Clemmensen reaction to reduce imide carbonyls.



110 **113**

Scheme 33: Over-reduction using traditional Clemmensen conditions

As a way to reduce only the enol selectively, a reaction was developed using activated zinc dust and concentrated hydrochloric acid in tetrahydrofuran (THF) at 0 °C to provide **114** in 86% yield (Scheme 34). Unfortunately, many attempts to close the spirocyclopentanone by using an acid derivative and a base to generate an enolate at the benzylic carbon atom were unsuccessful. Converting the acid to its ethyl ester using a Fischer esterification followed by treatment with sodium hydride gave no cyclization product, and conversion of the acid to the pentafluorophenyl ester with pentafluorophenyl trifluoroacetate in dichloromethane followed by base led only to decomposition. Interestingly, treatment of the acid with carbonyldiimidazole (CDI) to generate the imidazole derivative of **114** initiated an intramolecular acylation to form **117** in one step in 84% yield. X-ray structures for **114** and **117** are shown in Figure 8.



Scheme 34: Reduction of enol and formation of spiro with carbonyldiimidazole

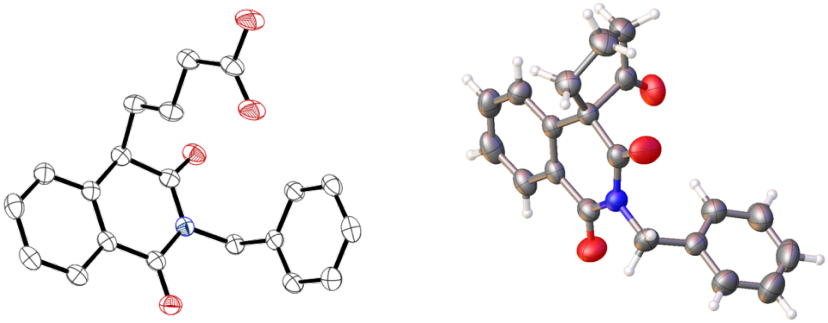
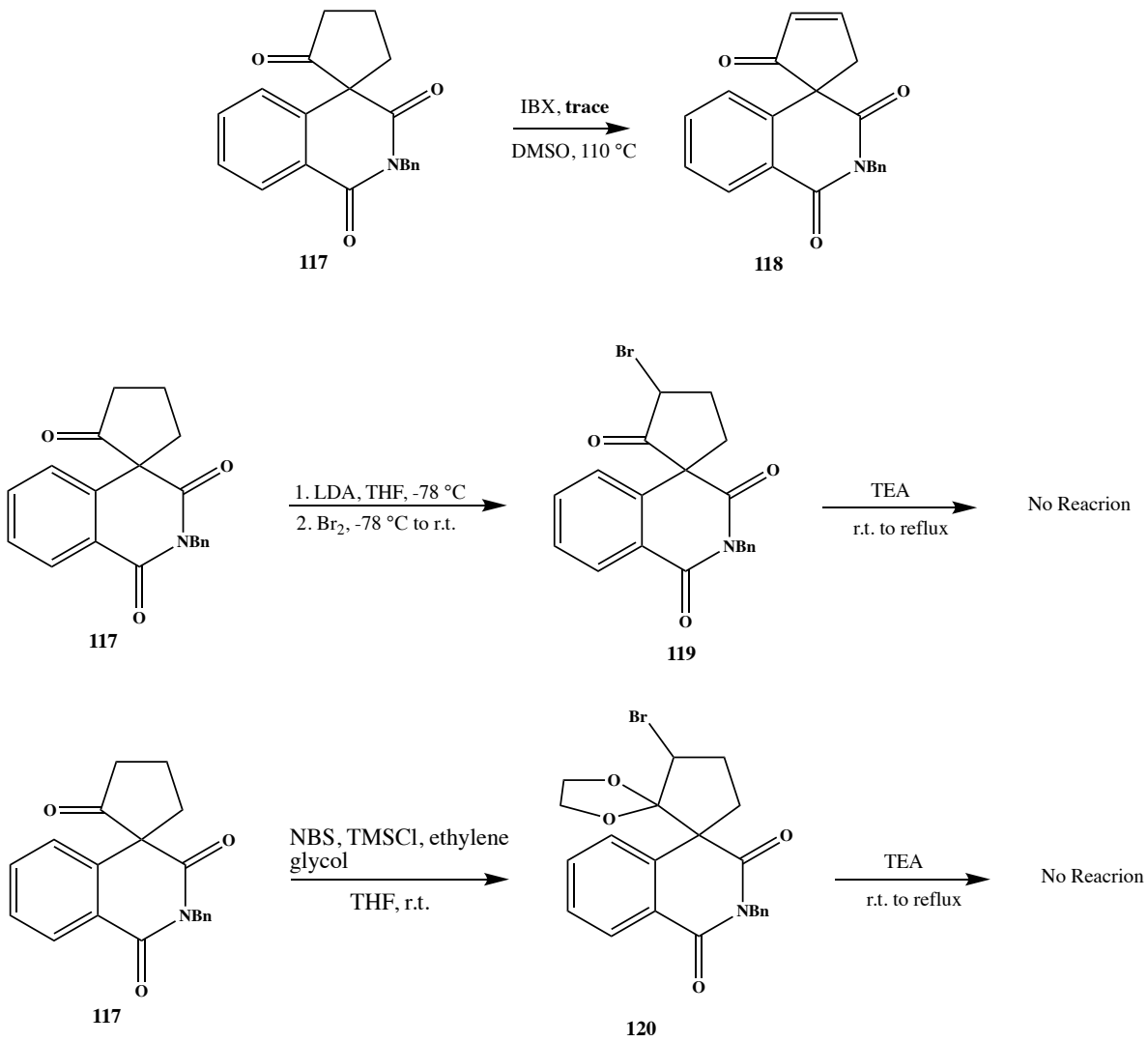


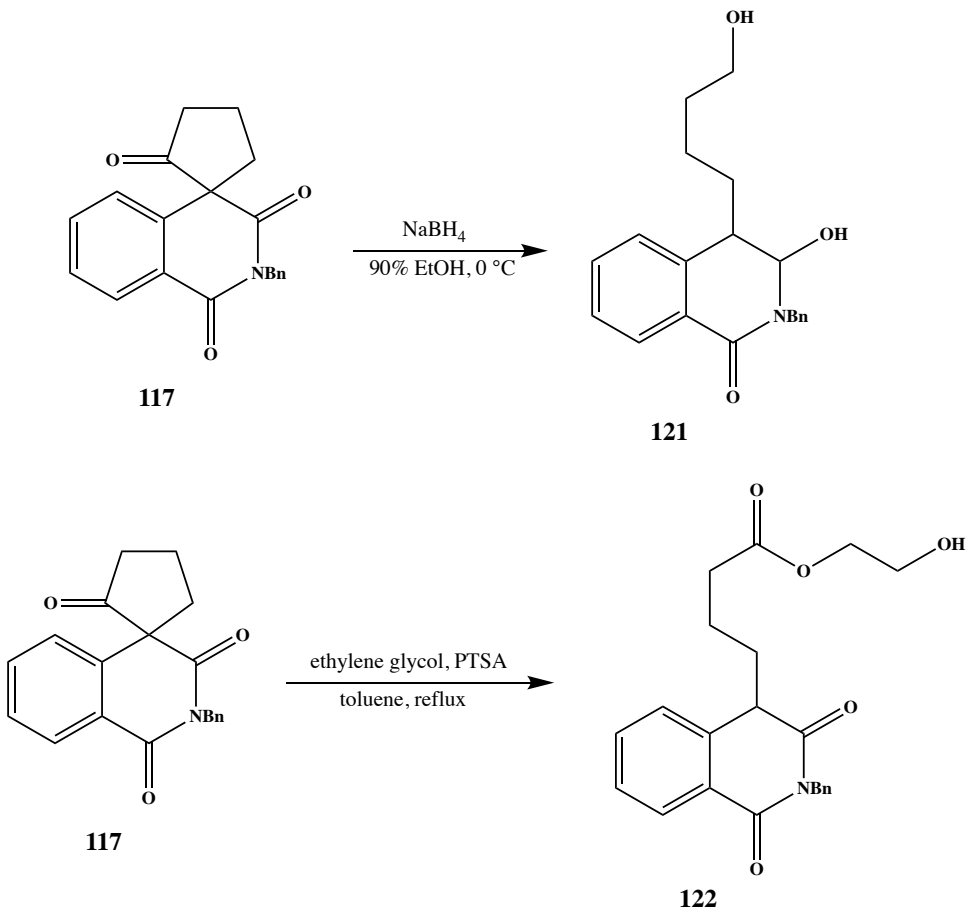
Figure 9: X-ray structures of **114** and **117** respectively

An attempt to expand the utility of our new method for forming spirocyclopentanones involved an oxidation reaction to furnish the α,β-unsaturated ketone. A direct introduction of the double bond using 2-iodoxybenzoic acid (IBX) was explored first using **117** as the substrate, but only a trace of the product **18** was produced.[68] A two-step process using an E2 reaction to generate the alkene began with a reaction of **117** with lithium diisopropylamide (LDA) followed by quenching the enolate with Br_2 to give the α-bromoketone in 65% yield. However, the elimination reaction using triethylamine (TEA) at reflux was unsuccessful. In a final attempt to synthesize an unsaturated carbonyl, the ketone was converted in one step to the brominated acetal **120** using ethylene glycol, *N*-bromosuccinimide, and trimethylsilyl chloride.[69] Once again, the elimination of HBr to produce **118** was not successful (see Scheme 35).



Scheme 35: Attempts to form the α,β-unsaturated ketone

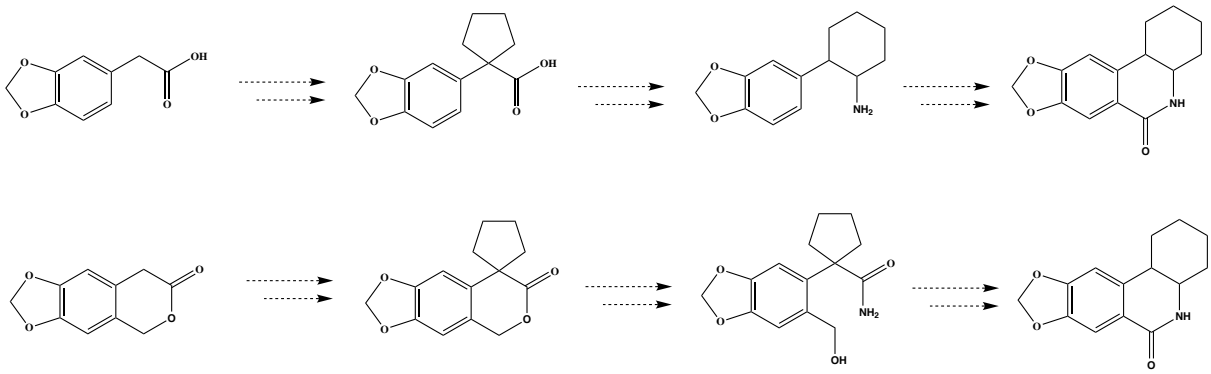
We also investigated the possibility of expanding the five-membered ring prior to introducing other functionalities. Surprisingly, a reaction using excess sodium borohydride in ethanol at 0 °C designed to reduce both the ketone and one of the imide carbonyls cleaved the cyclopentanone ring to form **121**. To avoid the problem, we attempted to protect the ketone first using ethylene glycol under standard conditions. Again, the ring proved to be labile and was cleaved under acidic conditions to the ester **122**.



Scheme 36: Attempts to prepare substrates for ring expansion

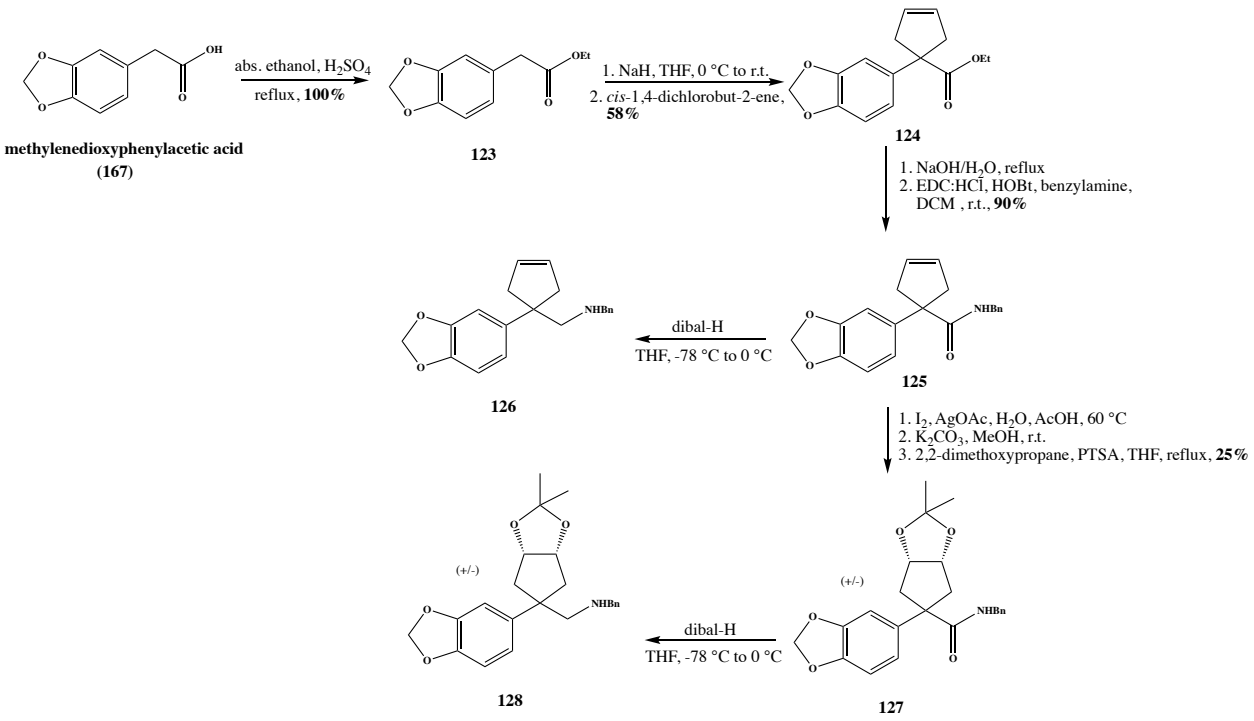
2.2 Attempts to Close the B-ring Last

As discussed previously, most approaches to the syntheses of phenanthridinone alkaloids use a late-stage closure of the B-ring. Although our primary objective was to develop new routes by which the C-ring is closed last, we did not want to ignore the possibility that some of our new reactions could be incorporated into the more traditional pathways. For this reason, we decided to investigate the use of a commercially available building block methylenedioxyphenylacetic acid to create precursors that would lead to the alkaloid skeleton with a B-ring closure reaction (see Scheme 37).



Scheme 37: Proposed schemes for closing the B-ring last

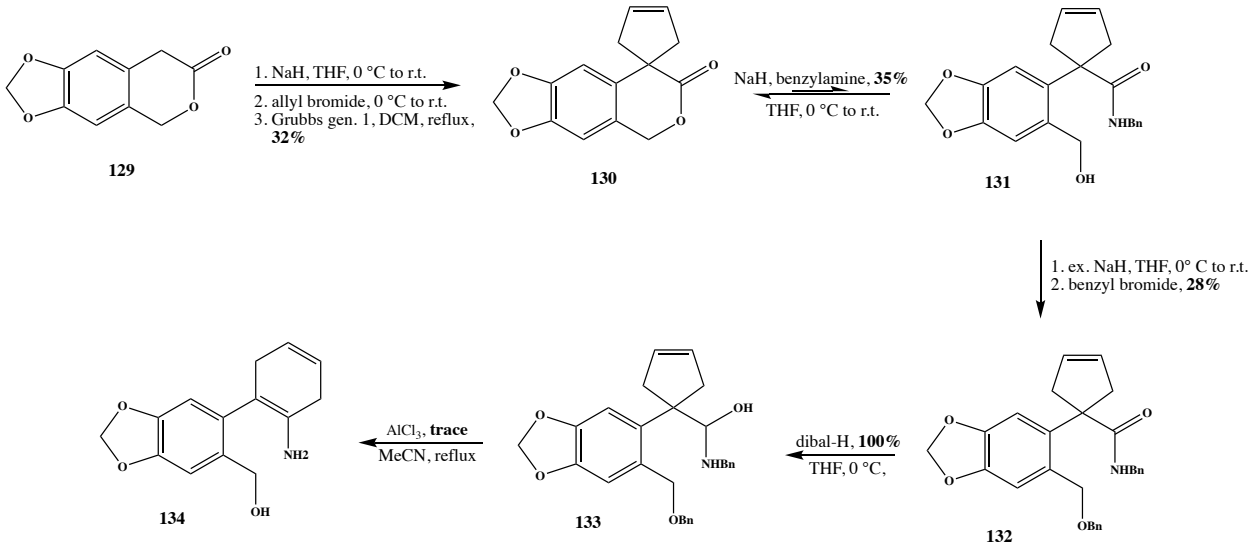
Methylenedioxyphenylacetic acid was converted easily to the ethyl ester, but attempts to alkylate the benzylic methylene carbon twice using NaH and allyl bromide—a reaction that had worked nicely on cyclic imides—gave mostly the monoalkylated product. However, the use of *cis*-1,4-dichloro-2-butene as the alkylating agent gave the desired spirocyclopentene **124** in good yield. The ester was hydrolyzed and the resulting acid was converted successfully to the N-benzylamide **125**. Oxidation of the double bond also proceeded smoothly using methods used in previous schemes, but attempts to reduce the amide functionality in **125** and **127** to a hemiaminal using dibal-H were unsuccessful. The major product was the result of a complete reduction of the carbonyl group to give secondary amines such as **126** and **128** (see Scheme 38).



Scheme 38: Attempts to form non-cyclic hemiaminals from methylenedioxyphenylacetic acid

In a last attempt to form non-cyclic hemiaminals, we developed a route starting from the lactone **129** the synthesis of which will be discussed in a later section. A dialkylation with allyl bromide followed by a ring-closing metathesis reaction using Grubbs generation 1 catalyst gave the spirocyclopentene **130** (Scheme 39). Opening the lactone with sodium N-benzylamide is not the type of reaction we would expect to be reversible, but nevertheless the process could not be forced to completion. However, a small amount of the product was isolated, and the primary alcohol in **131** was protected as the benzyl ether. Reduction of the amide functionality with dibal-H resulted in the formation of a stable hemiaminal **133**. Expansion of the cyclopentene ring using aluminum chloride was accompanied by the removal of the benzyl protecting groups to give the aminoalcohol **34**. With higher yields, this discovery could have provided a path to the tricyclic

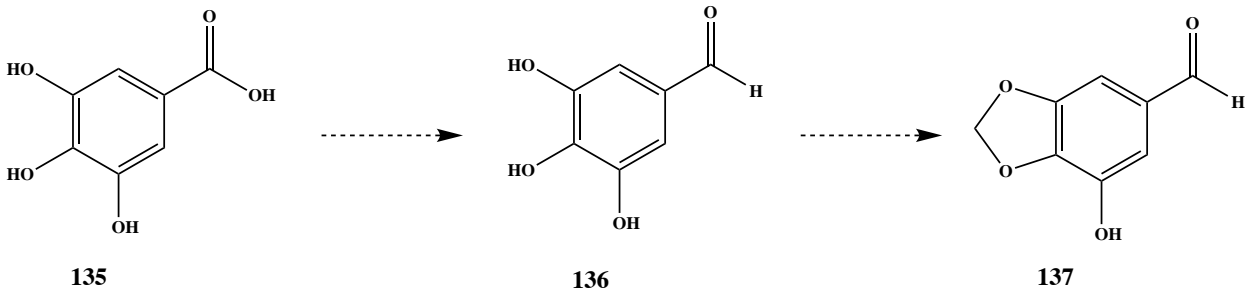
system using a late-stage B-ring closure. Unfortunately, we were forced to abandon this approach and return to the original strategy of forming the C-ring last.



Scheme 39: Successful ring expansion from non-cyclic hemiaminal

2.3 Incorporation of the Phenol Function Starting from Various Aromatic Aldehydes

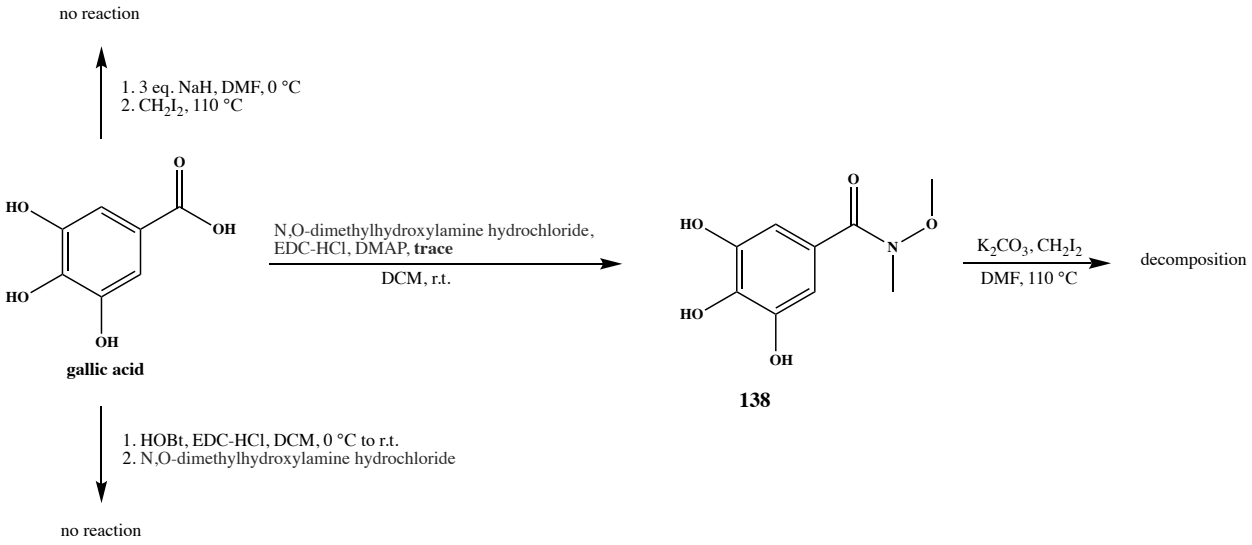
A number of *Amaryllidaceae* alkaloids contain a phenol functionality on the A-ring in addition to the ether groups that appear routinely. As an addendum to the present study, we also investigated the possibility of incorporating a protected phenol or a phenol precursor at a very early stage in the synthetic route. To this end, we targeted gallic acid, vanillin and isovanillin as possible building blocks that could be substituted effectively into the schemes already developed and optimized in our previous work. The first goal was to synthesize the aldehyde **137** shown in Scheme 40 from gallic acid. This would require converting the carboxyl function to an aldehyde and a regioselective reaction using two of the phenol groups to create a cyclic ether in as few steps as possible.



135 **136** **137**

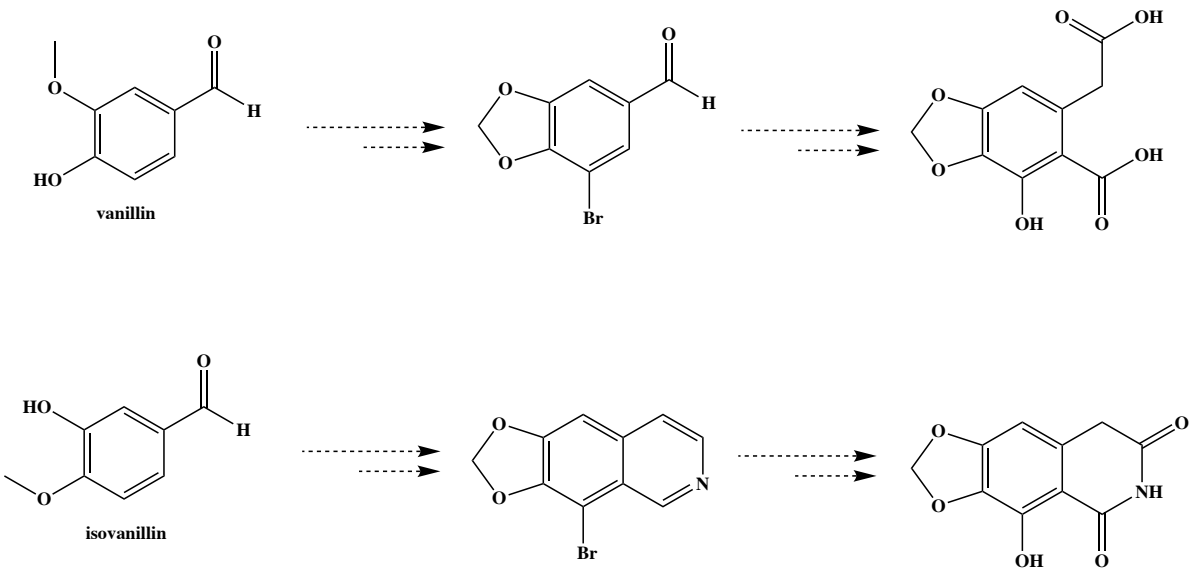
Scheme 40: Proposed scheme for phenol containing aldehyde from gallic acid

Our first study was an attempt to convert gallic acid to its Weinreb amide **138** to be used later in reactions with magnesium borohydride derivatives to give the aldehyde. Numerous problems were encountered including solubility issues and difficulties in choosing the proper base. It is likely that the enhanced acidity of the phenol *para* to the carboxyl group was a complicating factor. The only reaction that provided any product at all used N,O-dimethylhydroxylamine hydrochloride and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDC-HCl) under basic conditions and the yield was poor. Neither the Weinreb amide derivative **138** nor gallic acid itself could be converted to the methylenedioxy function (see Scheme 41). Although a literature report indicated that the methylenedioxy group could be installed on ethyl gallate,[70] this would have added two steps to the synthesis and was not investigated.



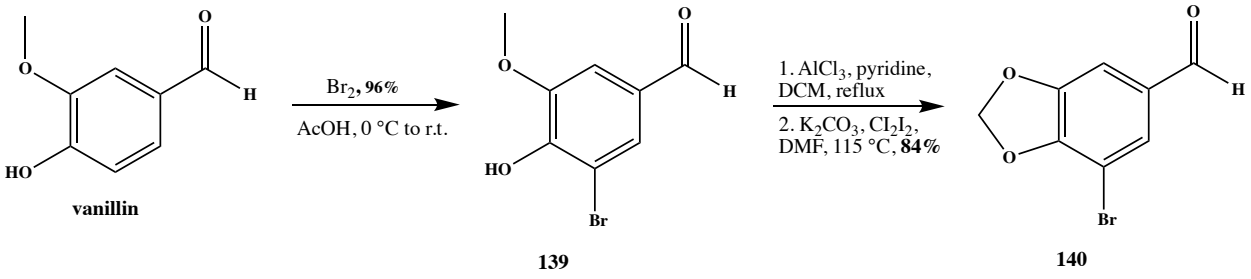
Scheme 41: Failed use of gallic acid

With preliminary tests using gallic acid as a building block showing little promise, other starting materials were investigated. There is literature precedent for adding an additional hydroxyl group to vanillin by first selectively brominating the position adjacent to the existing hydroxyl.[71] Isovanillin is also a relatively inexpensive starting material that might be useful for preparing cyclic imides with chemistry developed in our laboratory.[72] These possibilities are summarized in Scheme 42.



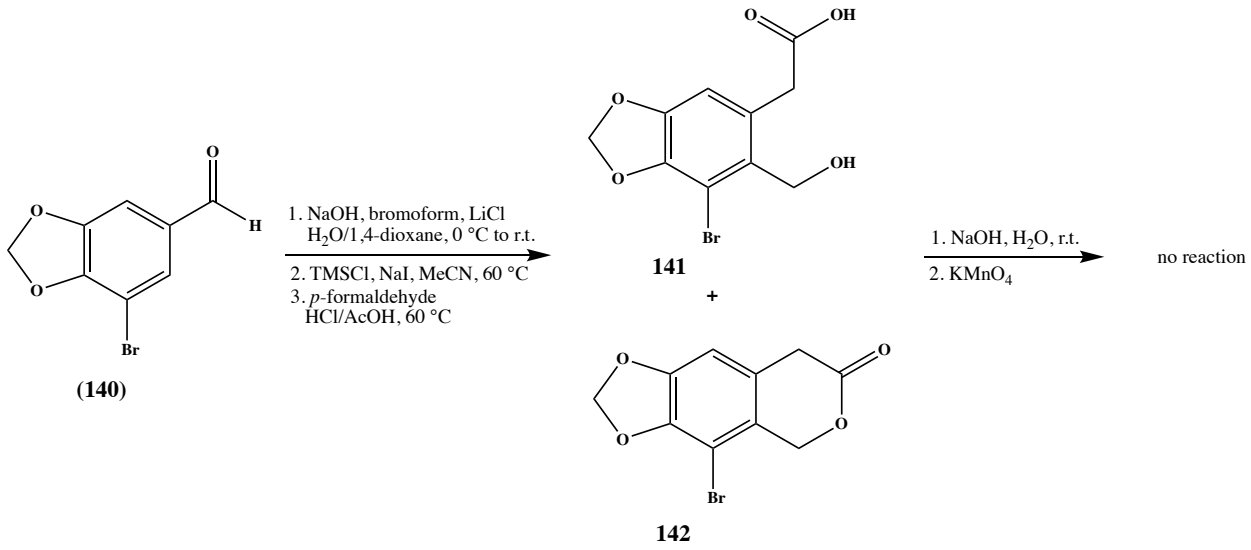
Scheme 42: Possible phenol intermediates derived from vanillin and isovanillin

Vanillin was brominated selectively using Br_2 in acetic acid to form **139** in high yield, and cleavage of the methyl ether with aluminum chloride and pyridine in dichloromethane produced the corresponding catechol. The methylenedioxy group was incorporated under basic conditions using either potassium fluoride (KF) or potassium carbonate (K_2CO_3) as the base and diiodomethane (CH_2I_2) as an alkylating agent in DMF to give 5-bromopiperonal (**140**) in an overall yield of 81% from vanillin.



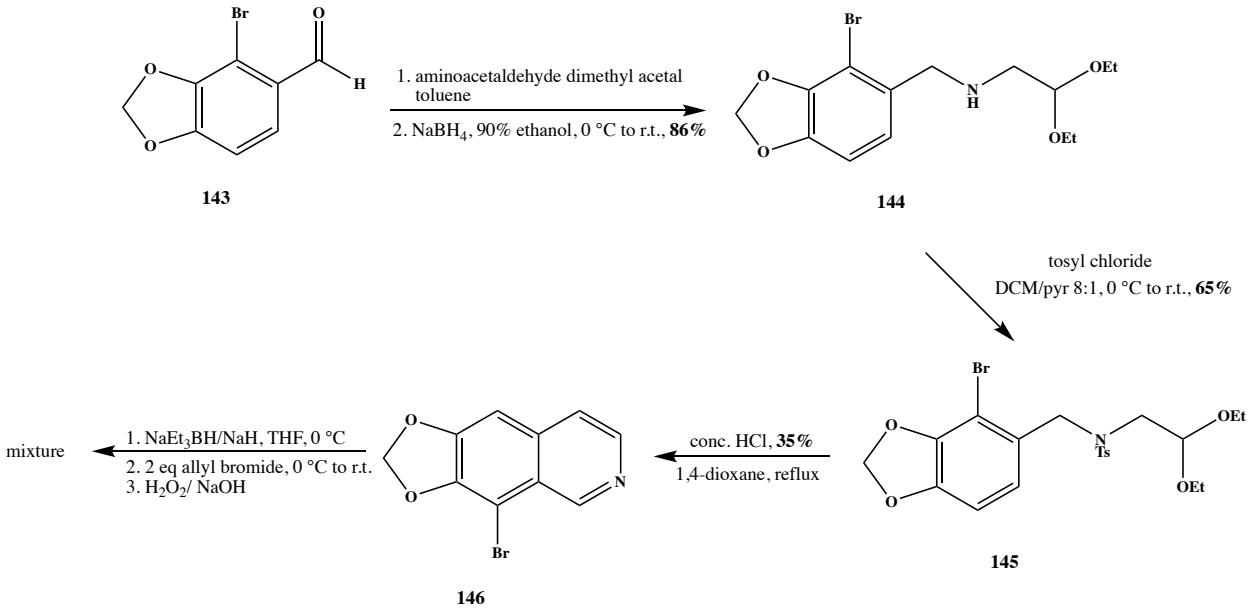
Scheme 43: Synthesis of 5-bromopiperonal (**140**)

Using a strategy that will be discussed in greater detail (see Schemes 53-55) for the transformation of piperonal to the bicyclic imide, **140** was converted to a mixture containing the hydroxyacid **141** and the corresponding lactone **142** (see Scheme 44). However, this mixture failed to react with basic potassium permanganate to give the expected dicarboxylic acid.



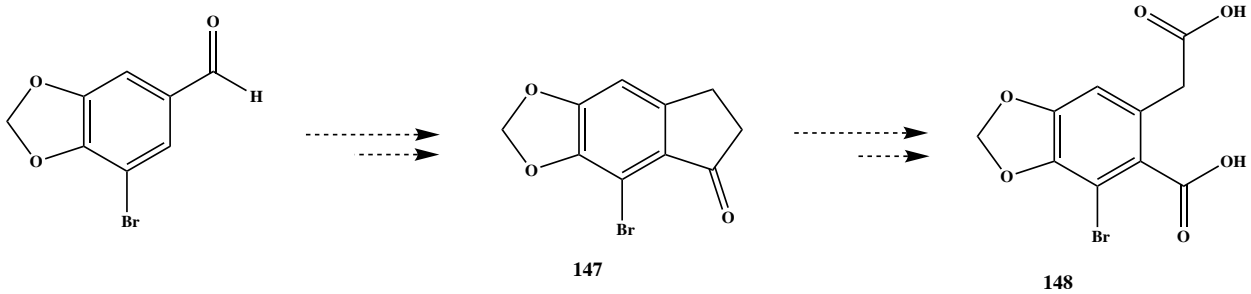
Scheme 44: Failed conversion of 5-bromopiperonal to the dicarboxylic acid

Having failed to synthesize the required dicarboxylic acid, we turned our attention to the use of isovanillin to create a useful cyclic imide. First, isovanillin was converted to 2-bromopiperonal **143** using exactly the same series of reactions shown in Scheme 43 for preparing the 5-bromo isomer. This aldehyde was condensed with aminoacetaldehyde dimethyl acetal in toluene under Dean-Stark conditions followed by reduction to the imine with excess sodium borohydride in 90% ethanol. The resulting amine **144** was converted to the tosylamide. Treatment of the tosylamide with conc. HCl in dioxane at reflux gave the substituted isoquinoline **146**. However, a reductive alkylation sequence designed to produce the 4,4-diallyl-1,4-dihydroisoquinoline gave inconclusive results as determined by NMR analysis.



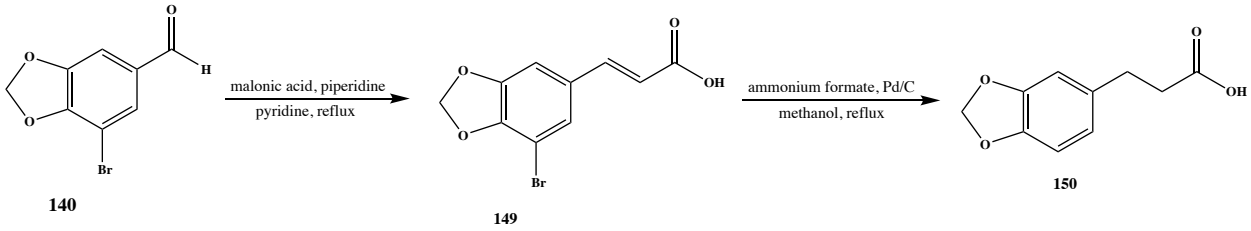
Scheme 45: Synthesis of brominated isoquinoline

Rather than pursue this avenue, the use of vanillin as a starting point was revisited using a published scheme that allowed piperonal to be transformed to a tricyclic system containing a fused cyclopentanone ring.[73] Specifically, we investigated the possibility of using 5-bromopiperonal to synthesize the brominated tricyclic system **147** shown in Scheme 46. Subsequently, an oxidative cleavage of the cyclopentanone ring could provide the elusive dicarboxylic acid **148**.



Scheme 46: Proposed synthesis of the diacid **148** from 5-bromopiperonal

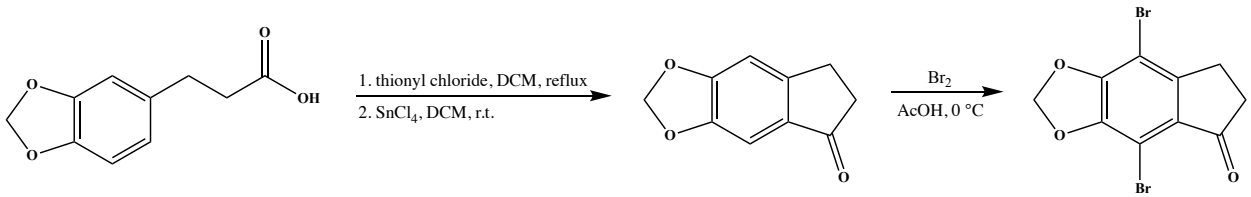
The first step was a Knoevenagel reaction to convert 5-bromopiperonal to the chain-extended α,β-unsaturated carboxylic acid **149** using malonic acid and piperidine. To reduce the resulting alkene, both hydrogen with Pd/C under pressure as well as the use of ammonium formate in refluxing methanol as a source of hydrogen were investigated. In each case, the double bond and the aryl bromide were reduced without selectivity to give **150** (see Scheme 47).



140 **149** **150**

Scheme 47: Over-reduction of the aryl halide

A possible solution to the over reduction problem was to brominate the aromatic ring after the cyclopentanone unit had been constructed. To test this, the carboxylic acid **150** was converted to the acid chloride; and the intramolecular Friedel-Crafts acylation reaction was carried out using tin(IV) chloride ($SnCl_4$) in dichloromethane. Unfortunately, the bromination reaction using Br_2 in acetic acid could not be controlled and led to the dibromide **152** regardless of conditions.

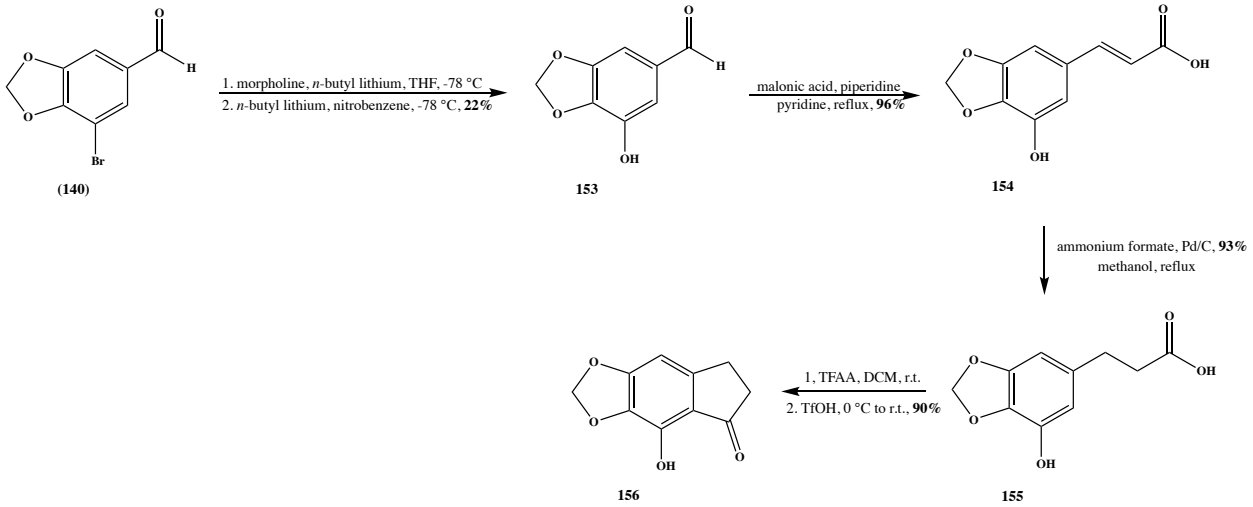


150 **151** **152**

Scheme 48: Overbromination of the aromatic ring

In a final attempt to use vanillin as a starting point, we prepared 5-bromopiperonal as described earlier and converted the bromine to hydroxyl before carrying out the Knoevenagel

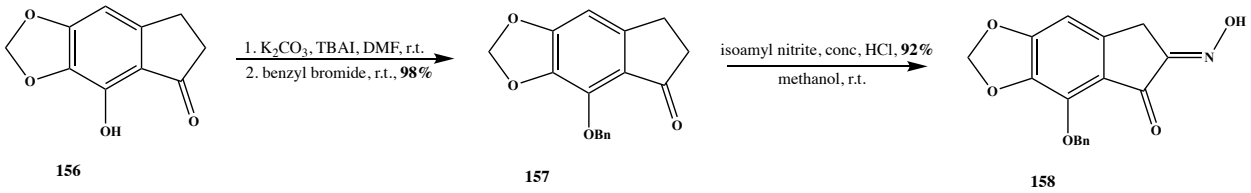
reaction. First, the aldehyde **140** was protected as the lithium morpholinoalkoxide, followed by the addition of *n*-butyl lithium to induce lithium bromide exchange. Upon quenching the reaction mixture with nitrobenzene and using an aqueous acidic workup to hydrolyze the protecting group, the phenol **153** was produced in 22% yield. The major by-product of this reaction was piperonal, which resulted from a reaction of the aryl lithium intermediate with an unknown proton source. The Knoevenagel reaction gave the unsaturated carboxylic acid **154**. The double bond was reduced using a hydrogen transfer-type reduction with ammonium formate and Pd/C in refluxing methanol to give the saturated acid **155**.[74] Initially the ammonium carboxylate was isolated, but acidification of the concentrated reaction mixture caused the product to precipitate. In situ formation of the mixed anhydride using trifluoroacetic anhydride (TFAA) in dichloromethane followed by the addition of triflic acid (TfOH) to induce an intramolecular Friedel-Crafts acylation yielded the ketone **156**.[75] (see Scheme 49)



Scheme 49: Synthesis of cyclopentanone derivative

With **156** in hand, we attempted to install an oxime at the position alpha to the carbonyl using isoamyl nitrite under acidic conditions. However, the work-up was complicated by the high

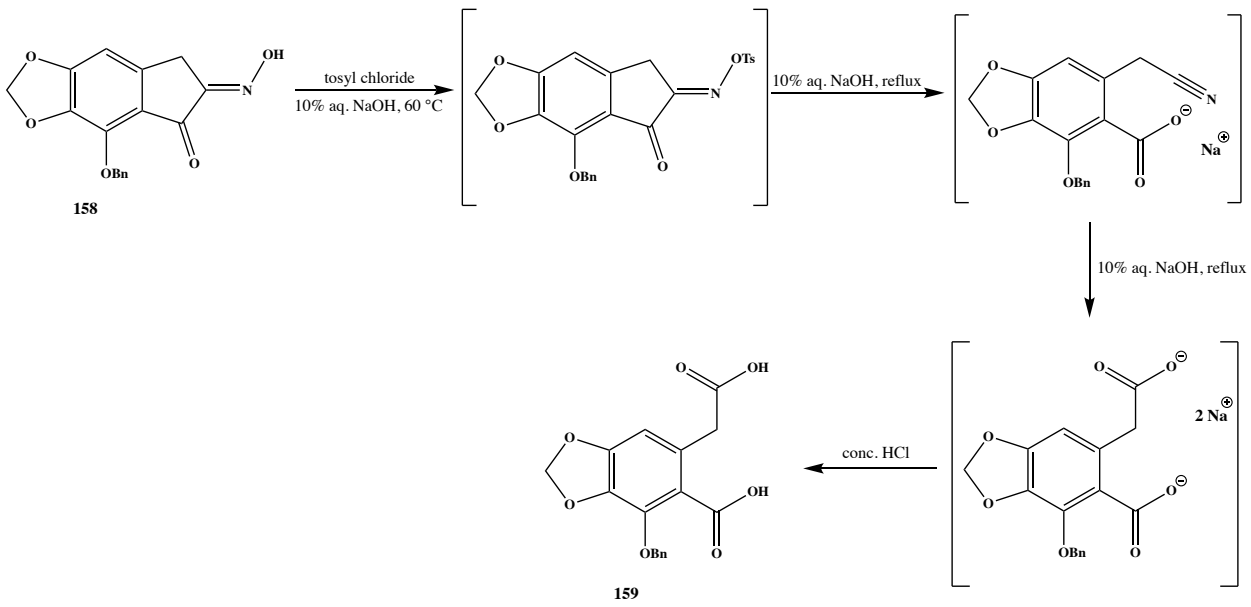
water solubility of this product. The problem was solved by converting the phenol to its benzyl ether to decrease water solubility. The reaction of **157** with acidic isoamyl nitrite gave the intended oxime **158**, which precipitated from the reaction mixture and could be isolated as a single isomer by simple filtration (see Scheme 50).



156 **157** **158**

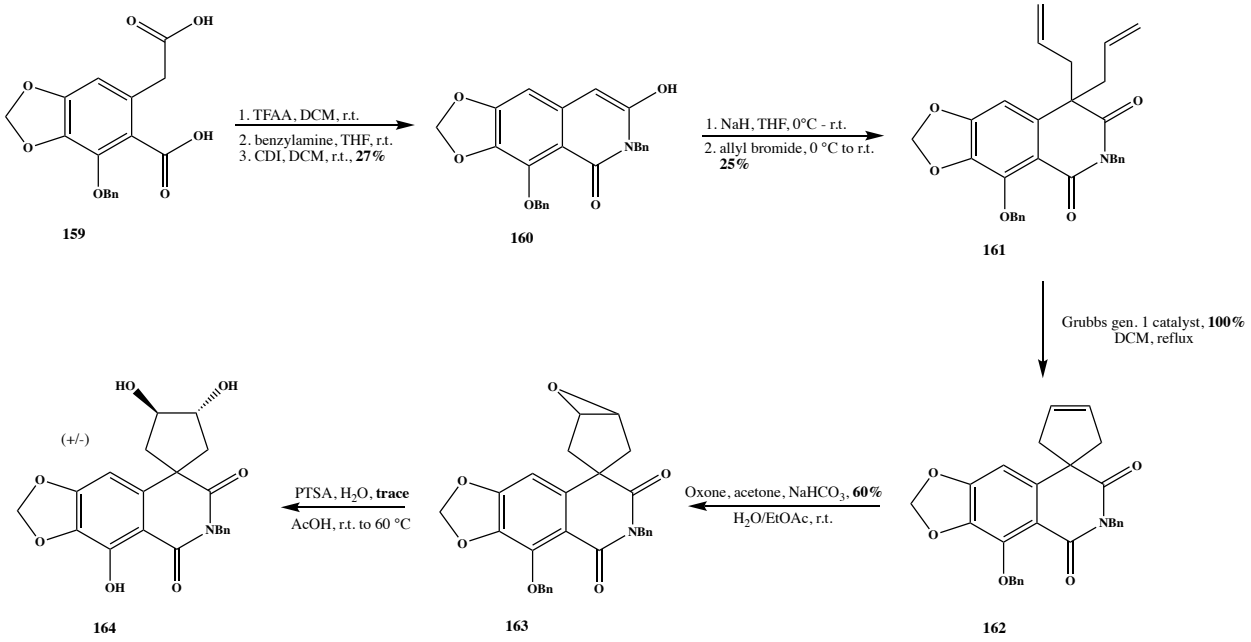
Scheme 50: Synthesis of the oxime derivative

The dicarboxylic acid **159** was prepared in 85% yield from the oxime using a one-pot tandem sequence via the oxime tosylate as shown in Scheme 51. The reaction of the oxime with tosyl chloride in 10% aqueous NaOH was carried out for 40 minutes at 60 °C after which the reaction mixture was heated at reflux for 18 hours. The diacid was isolated after acidification by gravity filtration. The process involves tosylation of the oxime followed by a basic hydrolysis that leads to loss of the tosyl group and cleavage of the ring. The published work by Wu and coworkers[73] describes the reaction as a Beckmann rearrangement, but a more proper term is Beckmann fragmentation which proceeds through a nitrile intermediate as depicted in Scheme 51.



Scheme 51: Tandem tosylation and hydrolysis of the oxime

Attempts to carry the acquired diacid through the steps previously optimized in the model system (see Scheme 16, page 23; see Scheme 19, page 27) were met with varying degrees of success. Several of the reactions behaved as well or better than in the model study although the diallylation of the cyclic imide in particular was disappointing. It is also interesting to note that the imide **160** was the only substrate of this type to exist solely in the enol form as determined through NMR analysis. The reaction sequence was completed successfully all the way to the diol **164** as shown in Scheme 52. Removal of the benzyl protecting group on the phenol did not require an additional step since it hydrolyzed during the epoxide ring opening. Considering the low overall yield of this procedure, it was apparent that a more efficient method of incorporating the phenol group would be required in order to pursue alkaloid targets that possess this particular function.



Scheme 52: Scope of reactions with phenol substrate

2.4 Incorporation of the methylenedioxy moiety into the phenanthridinone skeleton

With the model studies complete, the next goal was to incorporate this chemistry into a synthetic plan to generate precursors to the phenanthridinone skeleton with methylenedioxy substitution on the A-ring. This required the availability of methylenedioxyhomophthalic acid (**170**) (see Figure 9), which is prohibitively expensive from commercial sources. Accordingly, a synthesis of this compound that could be scaled to produce large quantities was developed starting with piperonal.

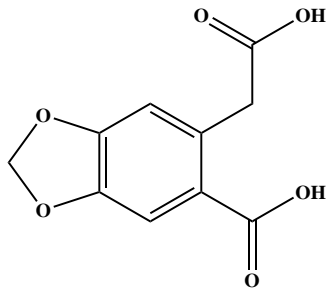
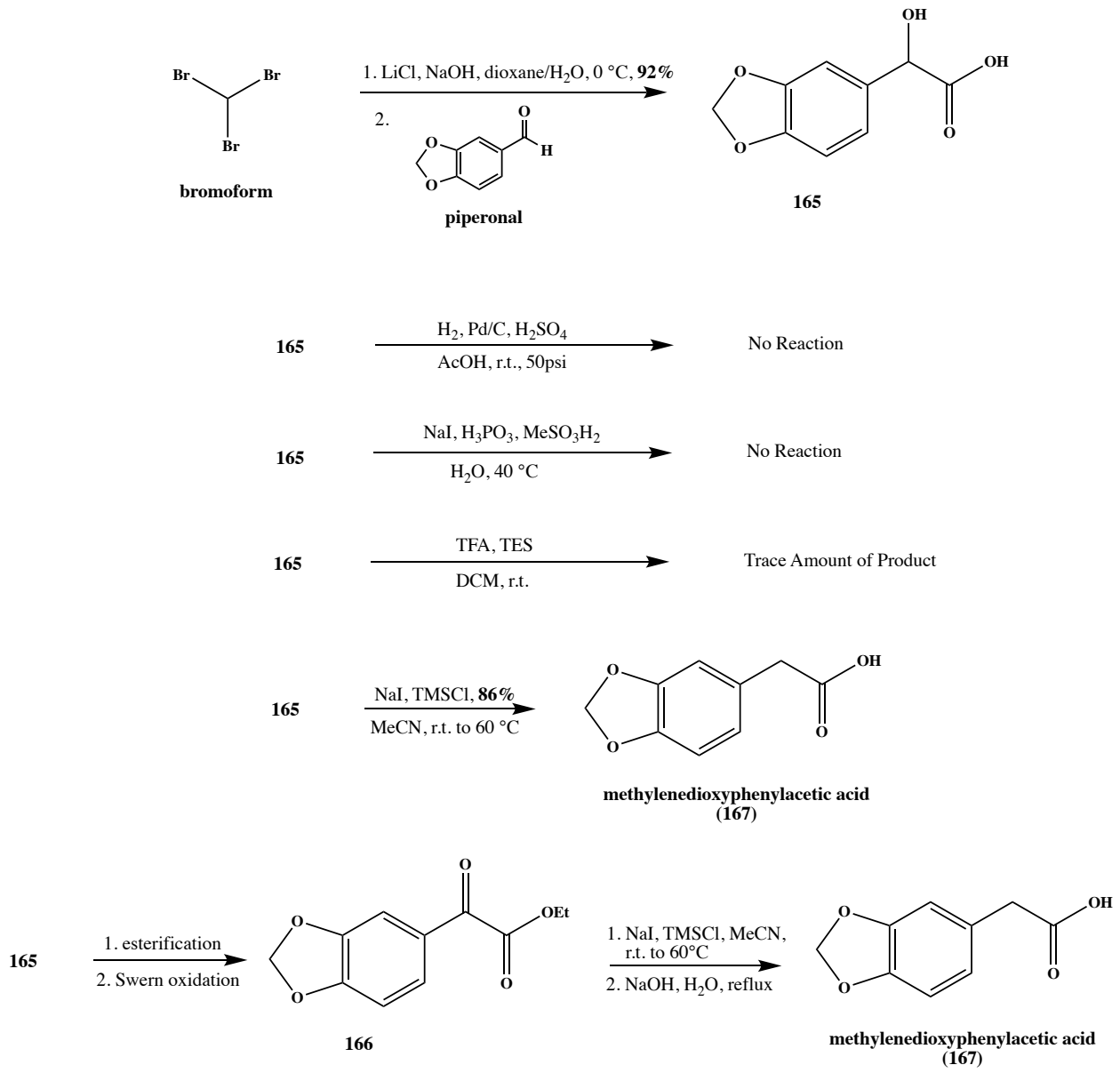


Figure 10: Methylenedioxyhomophthalic acid (**170)**

An obvious starting point for the synthesis of **170** is 3,4-methylenedioxyphenylacetic acid (**167**), but this starting material is also costly at $2.50 per gram from the commercial source. However, piperonal costs only $0.20 per gram and was used successfully to prepare large quantities of (**167**) and finally **170** as shown below.

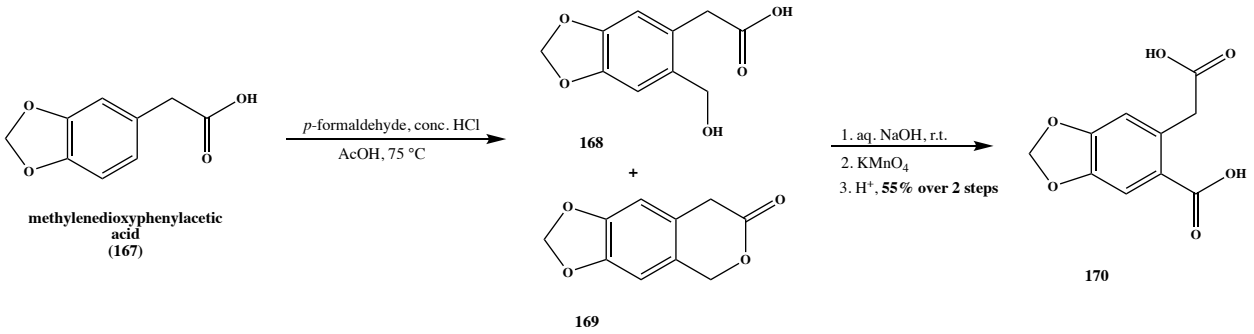
The synthesis began with a homologation reaction between piperonal and bromoform under basic conditions to produce the α-hydroxy acid **165** in 74% yield (see Scheme 53). Several standard methods to reduce the secondary benzylic alcohol to the methylene group were attempted, but **165** proved to be inert to catalytic hydrogenation with Pd/C and hydrogen at 50 psi under acidic conditions as well as phosphorous acid (H_3PO_3) and sodium iodide under acidic aqueous conditions.[76] A small amount of methyenedioxyphenylacetic acid was isolated from the reaction with triethylsilane (TES) and trifluoroacetic acid (TFA) in dichloromethane at room temperature using a very large excess of TES.[77] More promising results came from oxidizing the alcohol to a ketone using a Swern oxidation at -78 °C to form **166**. The ketone was reduced successfully to the methylene using trimethylsilyl chloride (TMSCl) and sodium iodide in anhydrous acetonitrile.[78] Upon further investigation, it was discovered that this reduction also worked on the benzylic alcohol itself to produce methylenedioxyacetic acid (**167**) in 86% yield using 2 equivalents of TMSCl.



Scheme 53: Novel synthesis of methylenedioxyphenylacetic acid (**167**)

The synthesis of **170** from methylenedioxyphenylacetic acid was a two-step process beginning with an electrophilic aromatic substitution using formaldehyde from *p*-formaldehyde under acidic conditions. The reaction was completely regioselective, but the product was a mixture of the hydroxymethylene adduct **168** and the lactone **169**. The ratio of these products could not be controlled using reaction time as a parameter. For this reason, we proceeded to the next step

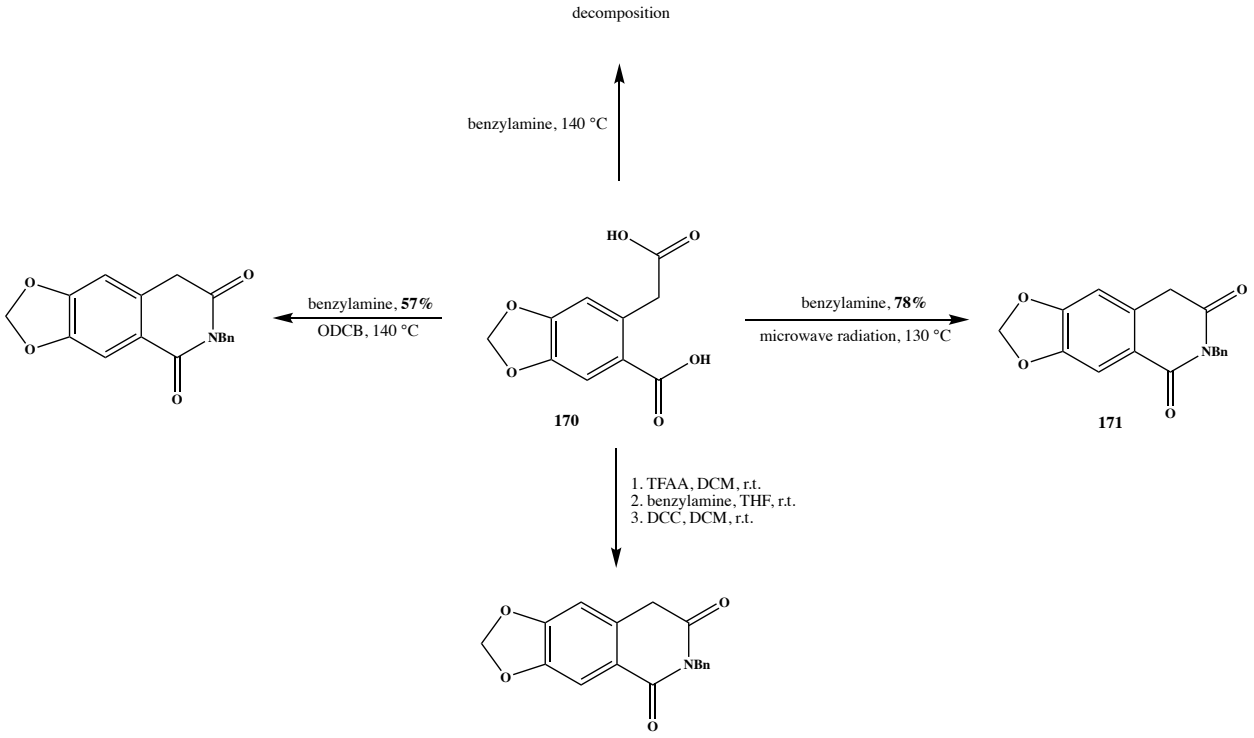
using the mixture assuming that the basic conditions of the reaction would convert **169** to **168** in situ. Basic potassium permanganate was used to convert the primary alcohol to the acid function. The reaction was conveniently monitored by TLC analysis using 100% methanol to elute and 2,4-dinitrophenylhydrazine stain to develop the plate to ensure that no aldehyde was present prior to work-up. After removing the manganese dioxide by simple filtration and acidifying the filtrate, the diacid **170** precipitated from the solution and could be isolated in sufficient purity for use in subsequent reactions.



Scheme 54: Synthesis of methylenedioxyhomophthalic acid (**170)**

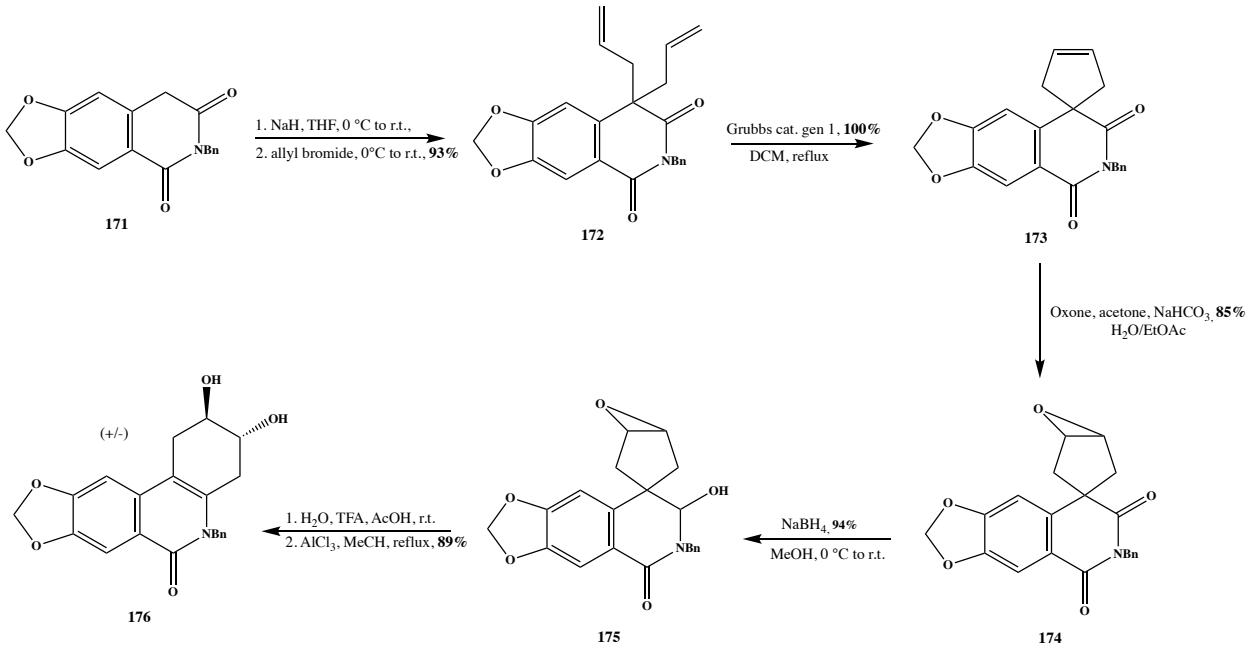
With the diacid **170** in hand, we proceeded to reproduce the reactions shown in the model study (see Scheme 16, page 23; see Scheme 19, page 27) beginning with a synthesis of the cyclic N-benzylimide **171**. Unlike the model system, the reaction of **170** with benzylamine at 140 °C in the absence of solvent resulted in significant decomposition. Using *o*-dichlorobenzene as a solvent prevented decomposition but led to a maximum yield of only 57% even at extended reaction times, and much of the product was the noncyclic amide intermediate. Resorting to a multistep process, we generated the cyclic anhydride using trifluoroacetic anhydride (TFAA). The ring was opened with benzylamine and then reclosed using various dehydrating agents such as carbonyldiimidazole (CDI) with various levels of success. However, none of these procedures were efficient and added steps to the synthesis. Finally, the imide was produced with an acceptable yield of 78% from the

diacid with one equivalent of benzylamine using microwave irradiation at 130 °C for 2.5 hours (see Scheme 55). The reaction was not as efficient as the model system, but it did avoid the use of a multistep reaction sequence.



Scheme 55: Synthesis of the cyclic imide **171**

Once the conditions for synthesizing the cyclic imide were optimized, the next three steps duplicated the model study almost perfectly to give the epoxide **174** in 79% yield overall from **171** (see Scheme 16, page 23; also Scheme 19, page 27). To avoid problems associated with isolating a highly water soluble triol, the imide was reduced to the cyclic hemiaminal **175** with sodium borohydride prior to opening the epoxide. Finally, the epoxide was hydrolyzed under acidic conditions, and the resulting triol as a crude product was used for the ring expansion reaction to give the diol **176** in 89% yield as shown in Scheme 56.

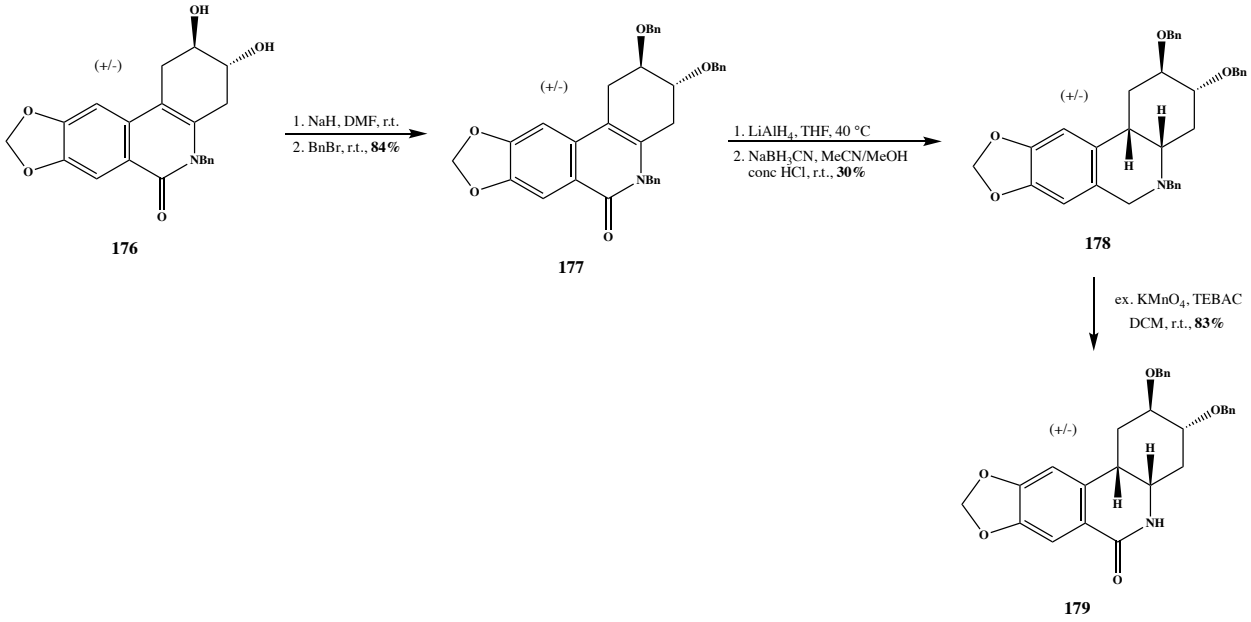


Scheme 56: Initial sequence with incorporated methylenedioxy substituent

Upon protecting the *trans* diol **176** with benzyl groups, other reactions depicted the model system began to be tested. (see Scheme 23, page 31; also Scheme 25, page 34). Note, it was at this time that the COVID-19 pandemic caused all laboratory related chemistry to be halted. For this reason, the reactions discussed from this point forward are preliminary trials, and most of the yields are not optimized. Some crude yields and NMR spectra are also reported.

The dibenzyl ether **176** was first subjected to the reaction conditions used in the model study (Scheme 23, page 31) to reduce both the amide and tetrasubstituted double bond functionalities to yield the tertiary amine **178** in 30% yield. The enamine intermediate in this reaction was found to be only sparingly soluble in 100% methanol during the second step of this process and this undoubtedly led to the low yield. One solution that marginally improved the yield, was to use acetonitrile as a cosolvent to improve solubility. The product that was obtained was found to be a single isomer through NMR analysis. The amine **178** was then successfully oxidized

to the corresponding cyclic amide through the process found in Scheme 25 (page 34) using $KMnO_4$ and a phase transfer catalyst in DCM at room temperature to form **179**. A crystal structure obtained from this compound showed that the reduction of the double bond resulted in a *cis* ring fusion between the B and C rings shown in Figure 10.



Scheme 57: Continued sequence with incorporated methylenedioxy substituent

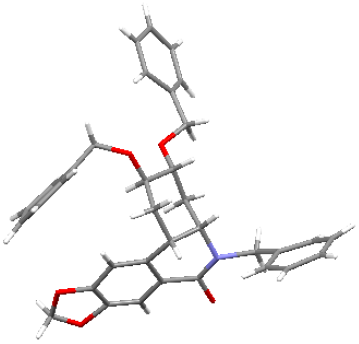
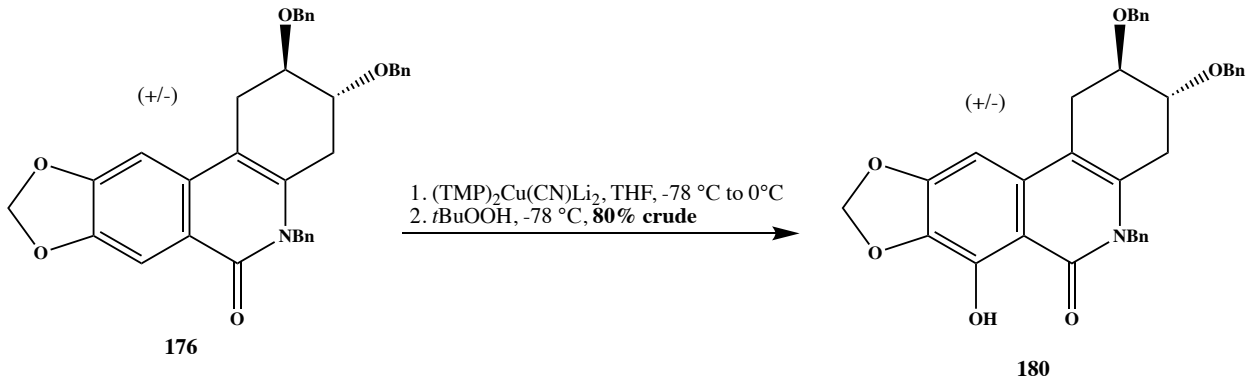


Figure 11: X-ray structure of **179**

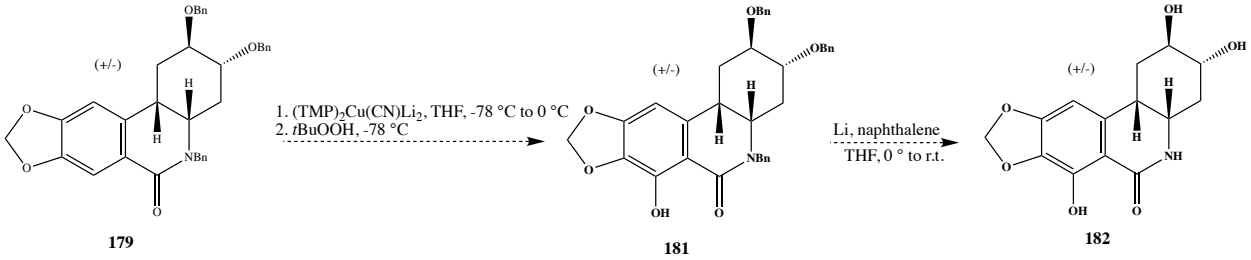
In addition, **176** was subjected to the aromatic hydroxylation process provided by Uchiyama and coworkers. (see Scheme 9, page 13) The copper catalyzed hydroxylation produced

180 with a crude yield of 80%, similar to the published syntheses discussed previously. This newly acquired reaction provides access to hydroxyl functionalized analogs of natural products without the need for lengthy transformations that were performed in our previous research.



Scheme 58: Copper catalyzed hydroxylation of the A-ring

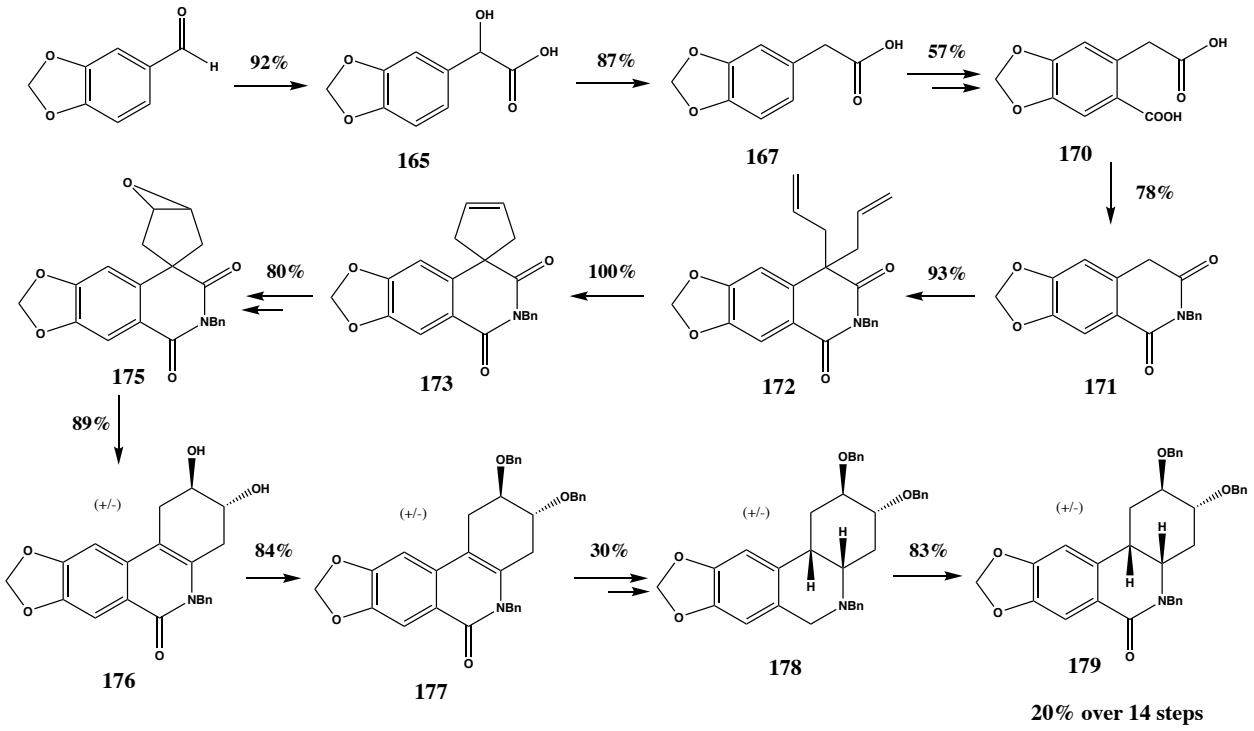
With the success of these last reactions we are confident that an analog of the alkaloid *trans*-dihydrolycoricidine, that differs by just one oxygen atom as well as the stereochemistry at the A and B ring fusion, can be synthesized through our novel route. The hydroxylation of the A-ring on **179** would ideally yield a protected derivative of this analog **181**. Deprotection with an excess of lithium naphthalenide radical anion could then yield **182**.



Scheme 59: Proposed completion of synthesis

In conclusion, a large library of phenanthridinone analogs was synthesized using methods optimized through the use of a model system. A lewis acid induced ring expansion reaction was

used as the key step in completing the phenanthridinone ring system. This transformation was reliable across many substrates, and also formed the C-ring of the system near the end of the synthesis unlike many previous methods found in the literature. Although the unintended stereochemistry obtained at the B-C ring fusion as well as the inability to further functionalize the C-ring in order to fully synthesize an alkaloid were significant issues in this project, the chemistry developed is still significant. A completed synthetic scheme which contains the methylenedioxy substituent is shown in the following scheme (Scheme 60).



Scheme 60: Completed synthetic scheme to **179**

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) 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.

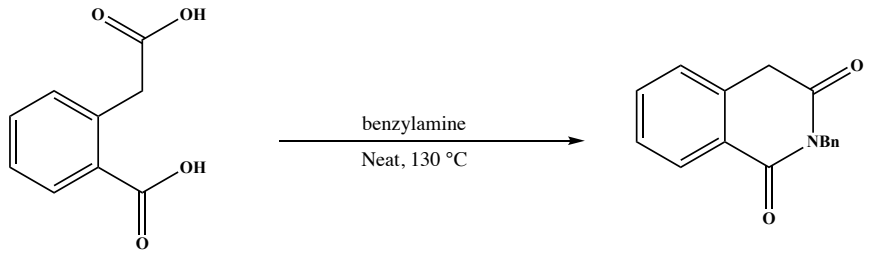
Most reagents were obtained from Sigma-Aldrich Chemical Company, Alfa-Aesar Chemical Company, or Acros Chemical Company and were used as acquired without further purification unless otherwise specified. Tetrahydrofuran and acetonitrile were acquired from a Solvent Purification System and used immediately.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

X-ray diffraction data was collected by Arshad Mehmood 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

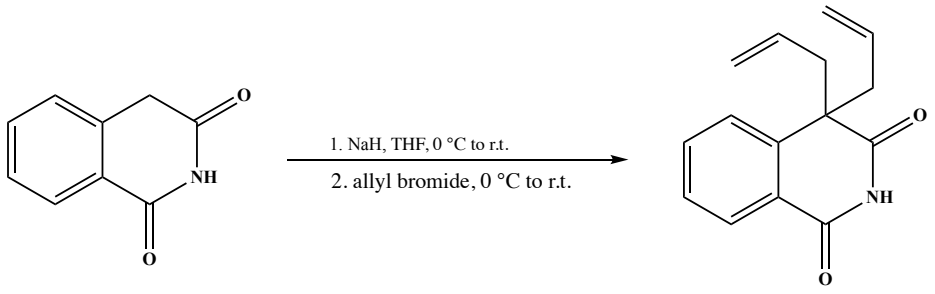
Experimental Section



homophthalic acid **75**

To **homophthalic acid** (15.13 g, 84.0 mmol, 1.0 eq) at room temperature, was added benzylamine (9.00 g, 84.0 mmol, 1.0 eq) and the reaction mixture was stirred at 130 °C for 6 h. The reaction mixture was allowed to cool slightly before 95% ethanol was added prior to the product solidifying completely. The ethanol was then removed under reduced pressure before placing the flask under vacuum to remove residual water. **75** was obtained without further purification (21.11 g, 84.0 mmol, 100%) as a tan solid: mp 121-123 °C. ^{1}H NMR ($CDCl_3$) δ 4.03 (s, 2H), 5.19 (s, 2H), 7.29 (m, 4H), 7.50 (m, 3H), 7.57 (td, J = 7.6, 1.2 Hz, 1H), 8.22 (dd, J = 7.6,

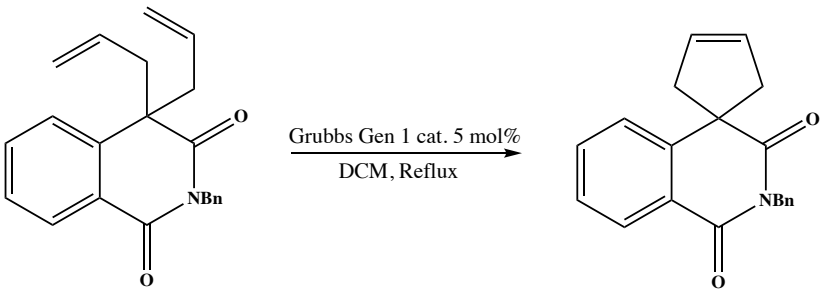
0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 36.5, 43.3, 125.4, 127.1, 127.6, 127.8, 128.5, 129.0, 129.3, 133.7, 134.1, 137.1, 164.9, 169.9.



75 **76**

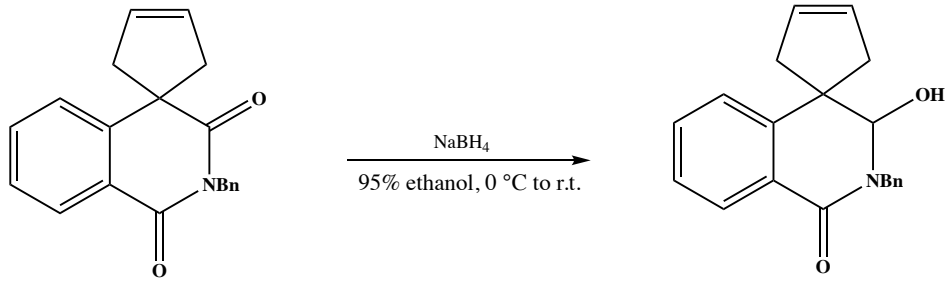
To a stirring suspension of sodium hydride (1.99 g, 60% dispersed in mineral oil, 49.8 mmol, 2.5 eq) in anhydrous THF (10 mL) at 0 °C, was added a solution of **75** (5.00 g, 19.9.0 mmol, 1 eq) in anhydrous THF (47 mL) via canula over 15 min. The suspension was then warmed to r.t. and stirred an additional 20 min. Upon cooling to 0 °C, allyl bromide (3.78 mL, 43.8 mmol, 2.2 eq) was then added dropwise over 5 min before allowing the reaction mixture to warm to r.t.. After 2 hrs, the reaction mixture was cooled to 0 °C and carefully quenched dropwise with ice water until H_2 gas evolution subsided. The volatiles were concentrated under reduced pressure, and the resulting green oil was taken up in a 1:1 biphasic solution of EtOAc and water (50 mL). The organic layer was isolated and the aqueous layer was extracted with additional EtOAc (2 x 10 mL). The combined organic layers were then washed with brine (1 x 25 mL)dried over sodium sulfate and concentrated under reduced pressure. The resulting oil was dissolved in DCM and filtered through a short pad of silica gel. Upon further elution with DCM the solvent was removed. The resulting colorless oil was partitioned between a 1:1 ratio of hexanes and MeCN (30 mL). The MeCN layer was isolated and the hexanes layer diluted with additional hexanes (10 mL) before being extracted with additional MeCN (2 x 10 mL). The combined MeCN layers were concentrated to provide **76** (6.00 g, 18.1 mmol, 91%) as a slightly yellow solid: mp 48-49 °C. ^{1}H NMR ($CDCl_3$)

δ 2.66 (dd, J = 13.6, 6.8 Hz, 2H), 3.03 (dd, J = 13.2, 8.0 Hz, 2H), 4.75 – 4.86 (m, 4H), 5.12 – 5.18 (m, 4H), 7.24 – 7.3 (m, 3H), 7.42 – 7.48 (m, 4H), 7.68 (td, J = 1.6, 0.8 Hz, 1H), 8.26 (ddd, J = 8.0, 1.6, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.6, 46.4, 52.7, 119.5, 125.6, 126.2, 127.3, 127.4, 128.2, 128.9 (two signals), 131.5, 134.0, 137.1, 141.0, 164.1.



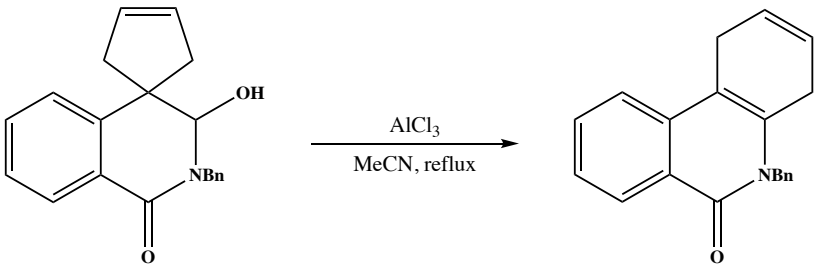
76 **77**

To a stirring solution of **76** (4.44 g, 18.1 mmol, 1 eq) in DCM (175 mL) at r.t., was added Grubbs Gen 1 catalyst (0.44 g, 0.54 mmol, 0.04 eq) and the reaction mixture was refluxed for 4 hrs. Most of the DCM was removed under reduced pressure before being filtered through a short pad of silica gel to remove catalyst and colored impurities. Upon elution with additional DCM, concentrating the filtrate provided **77** (4.06 g, 18.1 mmol, 100%) as a white crystalline solid: mp 104-105 °C. ^{1}H NMR ($CDCl_3$) δ 2.76 (dd, J = 16.0, 2.4 Hz, 2H), 3.33 (dd, J = 16.0, 2.4 Hz, 2H), 5.24 (s, 2H), 5.83 (s, 2H), 7.30 (m, 3H), 7.44 (m, 4H), 7.61 (dd, J = 8.0, 1.6 Hz, 1H), 8.22 (J = 8.0, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.7, 50.8, 51.1, 123.1, 124.6, 127.4, 127.5, 128.5 (three signals), 128.9, 134.6, 137.2, 146.6, 164.4, 177.5. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65. Found: C, 79.05; H, 5.39.



77 **78**

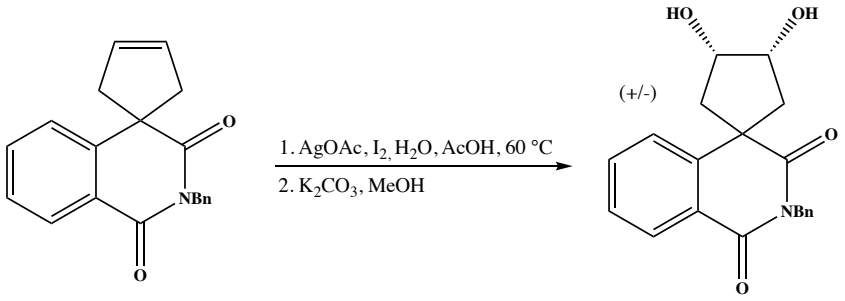
To a stirring suspension of **77** (7.62 g, 25.1 mmol, 1 eq) in 90% ethanol (150 mL) at 0 °C, was added $NaBH_4$ (1.42 g, 37.7 mmol, 1.5 eq) in pellet form. After 5 min the ice bath was removed and the reaction was stirred an additional 2 hrs before being diluted with water (300 mL). The aqueous solution was then extracted with DCM (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to yield **78** (7.60 g, 24.9 mmol, 99%) as a white foam: mp 63-64 °C. ^{1}H NMR ($CDCl_3$) δ 2.07 (d, J = 18.0, 1H), 2.32 (dt, J = 18.0, 1.6 Hz, 1H), 2.72 (dt, J = 18.0, 2.4 Hz, 1H), 2.88 (d, 18 Hz, 1H), 4.38 (d, 14.4 Hz, 1H), 4.75 (s, 1H), 5.39 (d, 14.4 Hz, 1H), 5.46 (m, 1H), 5.85 (m, 1H), 7.35 (m, 7H), 7.48 (dt, 7.6, 1.6 Hz), 8.18 (dd, 7.6, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 40.3, 46.1, 48.7, 50.0, 86.9, 125.2, 126.8, 127.2, 127.8, 128.1, 128.8 (two signals), 128.9, 129.6, 132.6, 137.2, 143.7, 163.8.



78 **79**

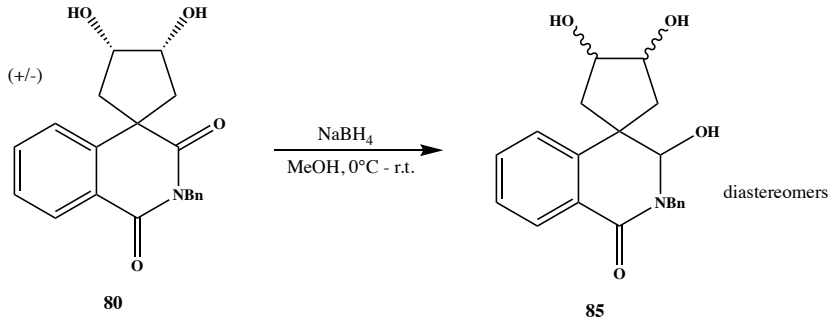
To a stirring solution of **78** (1.00 g, 3.30 mmol, 1 eq) in MeCN (10 mL) at r.t., was added $AlCl_3$ (0.44 g, 3.30 mmol, 1 eq). The reaction mixture was then refluxed for 1 hr. The reaction mixture was quenched with 3M HCl (20 mL). The MeCN was then removed under reduced pressure and the resulting aqueous solution was extracted with EtOAc (3 x 20 mL). The combined

organic layers were dried over sodium sulfate, concentrated under reduced pressure and dried under vacuum to yield **79** (0.70 g, 2.43 mmol, 74%) as a white crystalline solid. Product fluoresces bright blue upon either short or long wave UV exposure. mp 156-157 °C



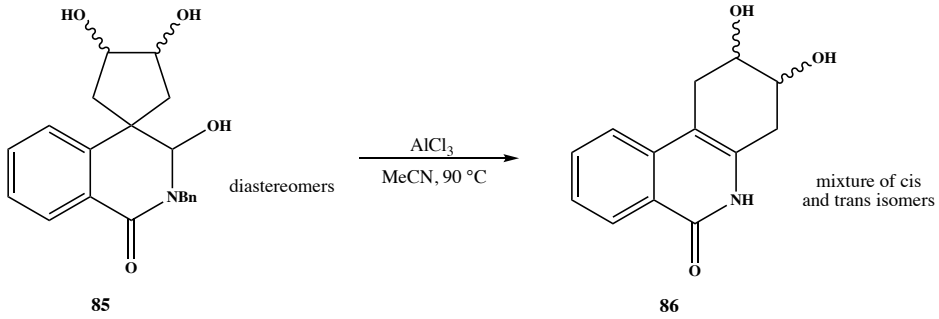
77 **80**

To a stirring solution of **77** (5.05 g, 16.6 mmol, 1 eq) in glacial AcOH (75 mL) at r.t., was added AgOAc (6.27 g, 37.3 mmol, 2.25 eq) followed by portion-wise addition of I_2 (4.65 g, 18.26 mmol, 1.10 eq). The reaction mixture was then stirred at r.t. until the iodine color disappeared (30 min). Water (0.60 mL, 33.2 mmol, 2 eq) was then added and the reaction mixture was brought to 90 °C. After 1 hr at this temperature, the reaction mixture was hot-filtered to remove precipitated solids and the filter cake was washed with additional AcOH (100 mL). The AcOH was concentrated under reduced pressure. The resulting residue was dissolved in EtOAc (150 ml) and washed with sat $NaHCO_3$ solution (1 x 200 mL). The aqueous layer was then extracted with additional EtOAc (2 x 50 mL), and the combined organic layers were then dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was dissolved in MeOH (50 mL) and K_2CO_3 (5.00 g) was added with strong stirring. After 1 hr, the solvent was removed under reduced pressure and the resulting residue was suspended in boiling MeCN. Upon hot filtration and washing of the filter cake with additional hot MeCN, the filtrate was cooled to r.t. and concentrated under reduced pressure to yield compound **80** (5.45 g, 16.1 mmol, 97%) as a white foam. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68. Found: C, 69.87; H, 5.09.



80 **85**

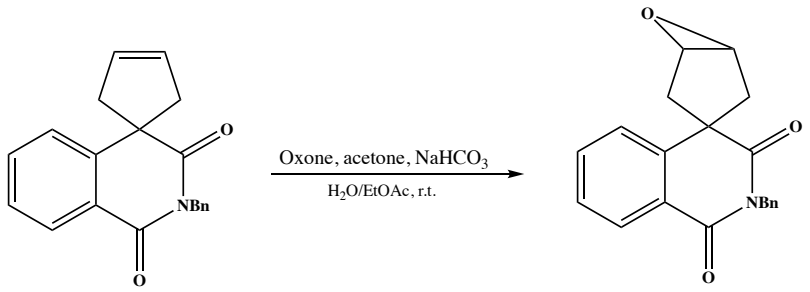
To a stirring solution of **80** (5.40 g, 16.0 mmol, 1 eq) in MeOH (180 mL) at 0 °C, was added $NaBH_4$ (0.91 g, 24.0 mmol, 1.5 eq) in pellet form. The reaction mixture was then allowed to warm to r.t.. After 18 hrs, the reaction mixture was quenched with water (500 mL) along with a large excess of NaCl (12 g) before being extracted with EtOAc (6 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and dried under vacuum to yield **85** (4.51 g, 13.3 mmol, 83%) as a white foam.



85 **86**

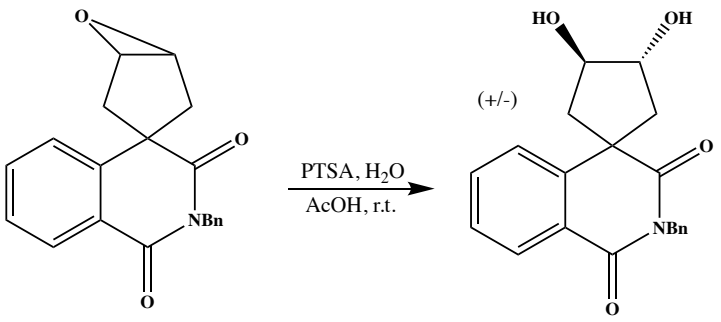
To a stirring solution of **85** (1.43 g, 4.2 mmol, 1 eq) in MeCN (30 mL) at r.t., was added $AlCl_3$ (0.56 g, 4.2 mmol, 1 eq). The reaction mixture was then refluxed for 1 hr. Upon cooling to r.t., the reaction mixture was quenched with 3M HCl (30 mL) and the MeCN was removed under reduced pressure. The aqueous solution was then saturated with NaCl (15 g) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and dried under vacuum to yield **86** as a mixture of stereoisomers (1.10 g, 3.4 mmol, 82%) as a white waxy solid. Product fluoresces bright blue upon either short or long

wave UV exposure. Isomers do not separate on TLC. Anal. Calcd for $C_{20}H_{19}NO_3 \cdot H_2O$: C, 70.99; H, 5.96. Found: C, 70.43; H, 5.71.



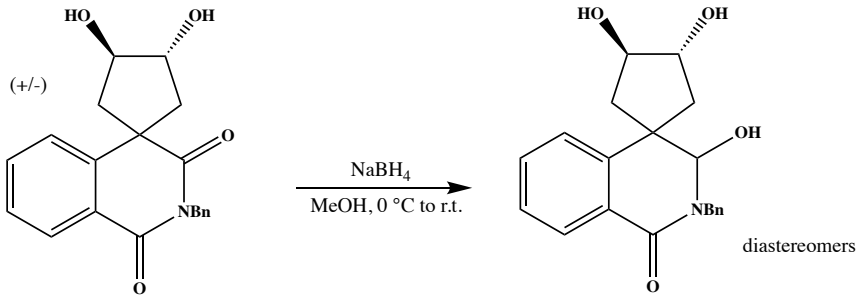
77 **81**

To a stirring solution of **77** (3.68 g, 12.1 mmol, 1 eq) in EtOAc (40 mL) at r.t., was added water (5 mL), powdered $NaHCO_3$ (5.09 g, 60.7 mmol, 5 eq), and an excess of acetone (5 mL). The biphasic solution was stirred vigorously as a solution of Oxone® (14.88 g, 24.3 mmol, 2 eq) in water (60 mL) was added dropwise over 2 hr. After 18 hrs, the reaction mixture was filtered through a pad of celite and the organic layer was isolated. The aqueous layer was then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over sodium sulfate, concentrated and dried under vacuum to yield **81** (3.12 g, 9.8 mmol, 81%) as a white crystalline solid. mp 108-109 °C. ^{1}H NMR ($CDCl_3$) δ 2.34 (d, J = 15.0, 2H), 2.75 (dd, J = 15.0, 1.6 Hz, 2H), 3.78 (d, J = 1.6 Hz), 5.20 (s, 2H), 7.2 – 7.46 (m, 6H), 7.65 (dt, J = 7.2, 1.6 Hz), 7.75 (dd, J = 8.0, 1.0 Hz, 1H), 8.18 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.8, 43.9, 53.6, 60.3, 124.1, 127.3, 127.6, 128.5, 128.6, 128.8, 134.4, 136.9, 144.8, 164.2. Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37. Found: C, 75.01; H, 5.32.



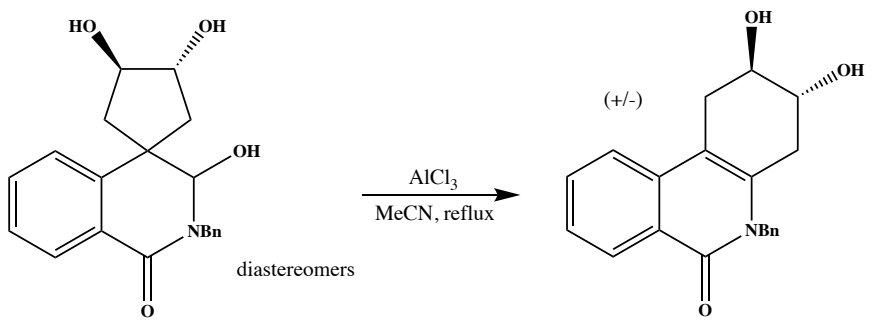
81 **82**

To a stirring solution of **81** (4.80 g, 15.0 mmol) in glacial AcOH (70 mL) at r.t., was added an excess of water (5 mL) and *p*-toluenesulfonic acid (2.00 g). After 3 hrs, the reaction mixture was concentrated at r.t. under reduced pressure. The resulting residue was dissolved in EtOAc (100 mL) and washed with sat. $NaHCO_3$ solution (30 mL). The aqueous layer was then extracted with addition EtOAc (3 x 25 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure, and dried under vacuum to yield **82** (4.99 g, 14.8 mmol, 98%) as a white crystalline solid. mp 150-151 °C



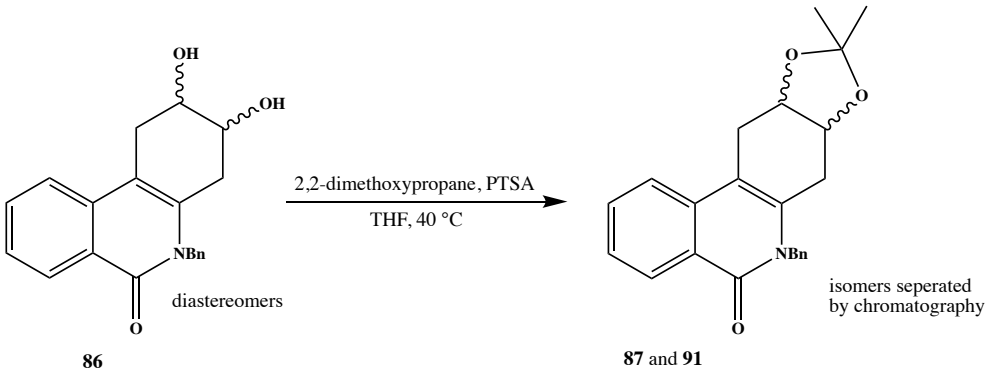
82 **89**

To a stirring solution of **82** (3.84 g, 11.3 mmol, 1 eq) in MeOH (70 mL) at 0 °C, was added $NaBH_4$ () in small portions. The reaction mixture was then allowed to warm to r.t.. After 18 hrs, the reaction mixture was quenched with water (70 mL) along with a large excess of NaCl (12 g) before being extracted with EtOAc (6 x 30 mL). The combined organic layers were dried over sodium sulfat, concentrated and dried under vacuum to yield **89** (3.22 g, 9.5 mmol, 84%) as a white foam and mixture of diastereomers.



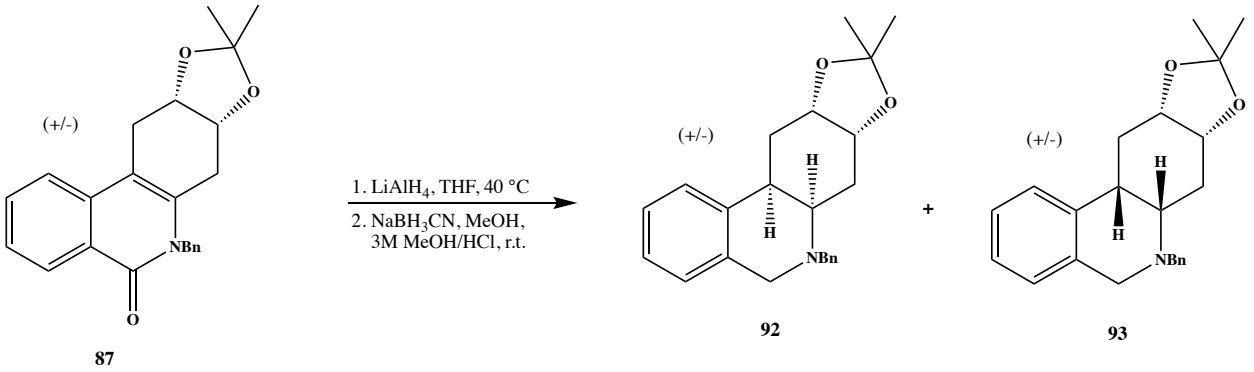
89 **90**

To a stirring solution of **89** (3.04 g, 8.96 mmol, 1 eq) in MeCN (60 mL) at r.t., was added $AlCl_3$ (1.19 g, 8.96 mmol, 1 eq). The reaction mixture was then refluxed. After 1 hr, the reaction was cooled to r.t. prior to being quenched with 3M HCl (60 mL) and removal of the MeCN under reduced pressure. The aqueous solution was then saturated with NaCl (15g) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and dried under vacuum to yield **90** (2.42 g, 7.53 mmol, 84%) as a white powder. Product fluoresces bright blue upon either short or long wave UV exposure. mp 187-188 °C. ^{1}H NMR (DMSO-d_6) δ 2.60 (m, 2H), 2.99 (m, 2H), 3.74 (2H), 5.02 (dt, J = 24.0, 2.8 Hz, 2H), 5.40 (AB quartet, J = 9.6 Hz, 2H), 7.13 (d, J = 7.6 Hz), 7.2 – 7.35 (m, 3H), 7.52 (t, 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz), 7.78 (t, 7.6 Hz, 1H), 8.31 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96. Found: C, 74.56; H, 6.00.



86 **87** and **91**

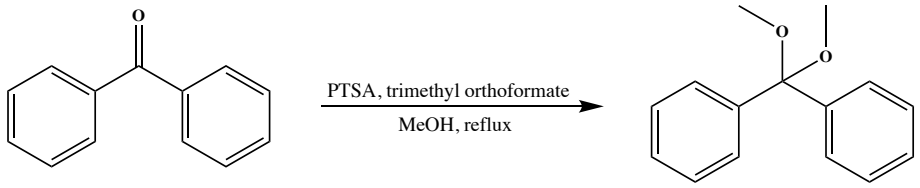
To a stirring solution **86** (2.17 g, 6.8 mmol, 1 eq) in anhydrous THF (70 mL) at r.t., was added 2,2-dimethoxypropane (5 mL, 40.8 mmol, 6 eq), PTSA monohydrate (0.25 g, 1.3 mmol, 0.19 eq) and activated powdered molecular sieves (0.5 g, 2Å). Heat was needed to get the starting material into solution prior to addition of reagents. The reaction mixture was then stirred at 40 °C. After 18, the reaction mixture was quenched with sat. $NaHCO_3$ solution (40 mL) and the organic layer was separated. The aqueous layer was then extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure. The resulting mixture was subjected to column chromatography (silica gel, hexanes:EtOAc, 1:1) to yield **87** (*cis* isomer, 1.08 g, 3.00 mmol, 44%) and **91** (*trans* isomer, 1.13 g, 3.2 mmol, 47%) as a white crystalline solids. Products fluoresce bright blue upon either short or long wave UV exposure. mp 178-180 °C (*cis*). Anal. Calc for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41. Found: C, 76.25; H, 6.39.



87 **92** **93**

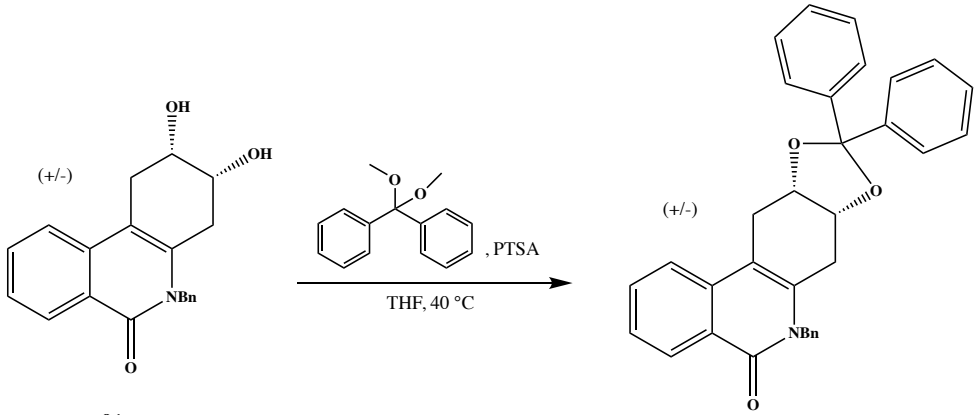
To a stirring solution of **87** (0.75g, 2.1 mmol, 1 eq) in anhydrous THF (120 mL) at 0 °C, was added a solution of 2M $LiAlH_4$ (2.1 mL, 4.2 mmol, 2 eq) in THF (10 mL), dropwise over 5 min. The reaction was then heated at 40 °C. After 1 hr, the reaction mixture was cooled to 0 °C followed by dropwise quenching with ice-water, waiting for the evolution of H_2 gas to subside completely before addition of next drop. Once the evolution of gas subsided completely, $MgSO_4$ (1 g) was added and the suspended solids were filtered and the filter cake was washed with additional THF. The THF was removed under reduced pressure and the resulting residue was briefly dried under vacuum (10 min) before being dissolved in methanol (10 mL). To the stirring solution at r.t., was added $NaCNBH_3$ (0.39 g, 6.3 mmol, 3 eq) followed by the dropwise addition of 3 M methanoic HCl until testing acidic to blue pH paper. The reaction mixture was then stirred for 4 min before being quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with EtOAc (4 x 10 mL). The Combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Chromatography (silica gel, hexanes:EtOAc 1:1), yielded an amorphous semi-solid containing two isomers. The amorphous semi-solid was dissolved in Et_2O (5 mL) and allowed to crystallize slowly. The minor product, **92**, (0.08 g, 0.2 mmol, 11%) crystallized first after 15 hr as a white crystalline solid, which was then removed from the mother liqueur before allowing more solvent to evaporate. The major product, **93**, (0.32 g, 0.90 mmol, 44%) then crystallized after an additional 10 min as a white crystalline solid. Both isomers come as one

streak on TLC when stained in an iodine chamber. mp (minor) decomp 149-153 °C mp (major) 99-104 °C. Anal. Calcd for $C_{23}H_{27}NO_2$ (minor): C, 79.05; H, 7.79. Found: C, 78.8; H, 7.26.



benzophenone

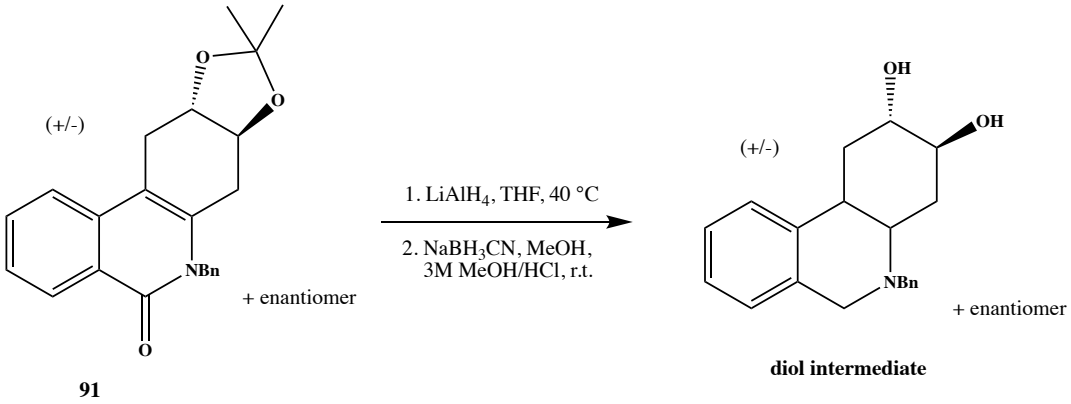
To a stirring solution of benzophenone (2.00 g, 11.0 mmol) in methanol (15 mL) at r.t., was added PTSA monohydrate (0.20 g, 1.1 mmol, 0.1 eq) and trimethyl orthoformate (2 mL). The reaction mixture was then refluxed under nitrogen. After 24 h, the reaction mixture was cooled to r.t. and was undisturbed for 1 h. The precipitated solid was filtered, washed with cold MeOH, and dried under vacuum to yield the dimethyl ketal of benzophenone (1.71 g, 7.5 mmol, 68%) as a white crystalline solid.



94 **95**

To a stirring solution of **94** (0.47 g, 1.5 mmol, 1.0 eq) in THF (70 mL) at r.t., was added PTSA monohydrate (0.10 g, 0.5 mmol, 0.3 eq) and the solution was heated at 40 °C. Heat was needed to get the starting material into solution prior to addition of PTSA. After 5 min, an excess of the dimethyl ketal of benzophenone (2.00 g) was added followed by additional heating at 40 °C. After 48 hrs, the reaction mixture was quenched with sat. $NaHCO_3$ solution (50 mL) and the

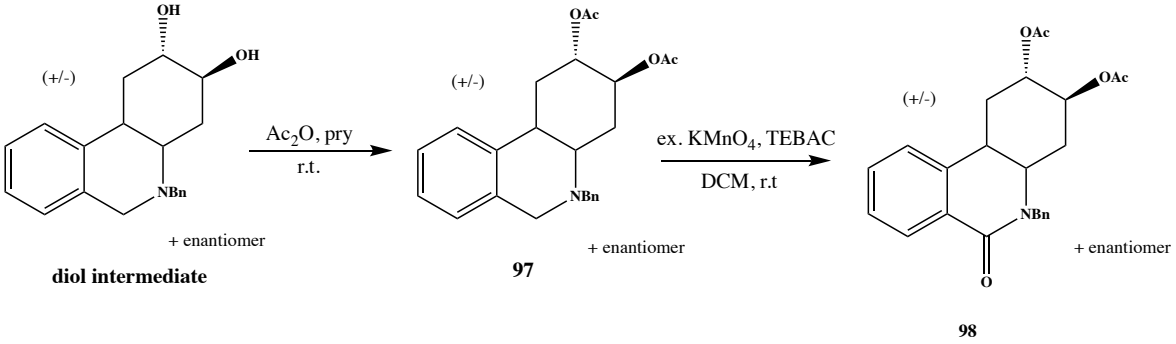
organic layer was isolated. The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Chromatography (silica gel, hexanes/EtOAc 1:1) to remove the excess dimethyl ketal yielded **95** (0.54 g, 1.1 mmol, 76%) as a white crystalline solid. Product is closer to the baseline than the dimethyl ketal on TLC. mp 180-182 °C



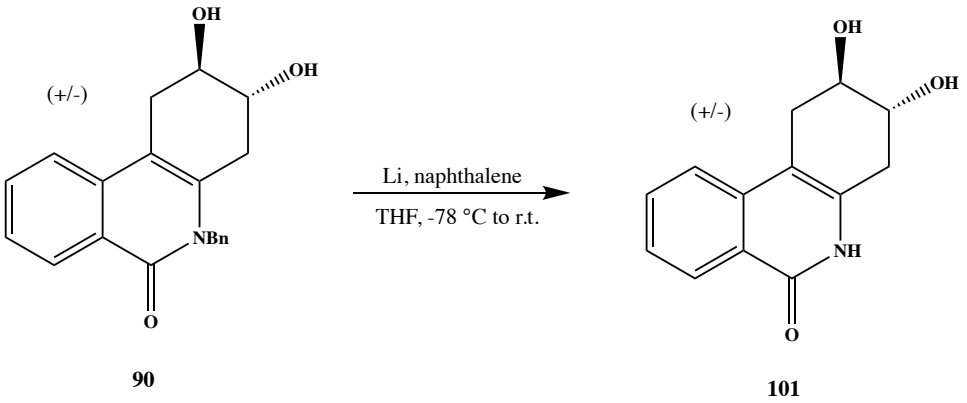
91 **diol intermediate**

To a stirring solution of **91** (0.75g, 2.1 mmol, 1 eq) in anhydrous THF (120 mL) at 0 °C, was added a solution of 2M $LiAlH_4$ (2.1 mL, 4.2 mmol, 2 eq) in THF (10 mL), dropwise over 5 min. The reaction was then heated at 40 °C. After 1 hr, the reaction mixture was cooled to 0 °C followed by dropwise quenching with ice-water, waiting for the evolution of H_2 gas to subside completely before addition of next drop. Once the evolution of gas subsided completely, $MgSO_4$ (1 g) was added and the suspended solids were filtered and the filter cake was washed with additional THF. The THF was removed under reduced pressure and the resulting residue was briefly dried under vacuum (10 min) before being dissolved in methanol (10 mL). To the stirring solution at r.t., was added $NaCNBH_3$ (0.39 g, 6.3 mmol, 3 eq) followed by the dropwise addition of 3 M methanoic HCl until testing acidic to blue pH paper. The reaction mixture was then stirred for 4 min before being quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with EtOAc (4 x 10 mL). The Combined organic layers were dried over sodium sulfate and concentrated under

reduced pressure. Chromatography (silica gel, hexanes:EtOAc 1:1), yielded the diol intermediate (0.18 g, 0.57 mmol, 27%) as a white crystalline solid.

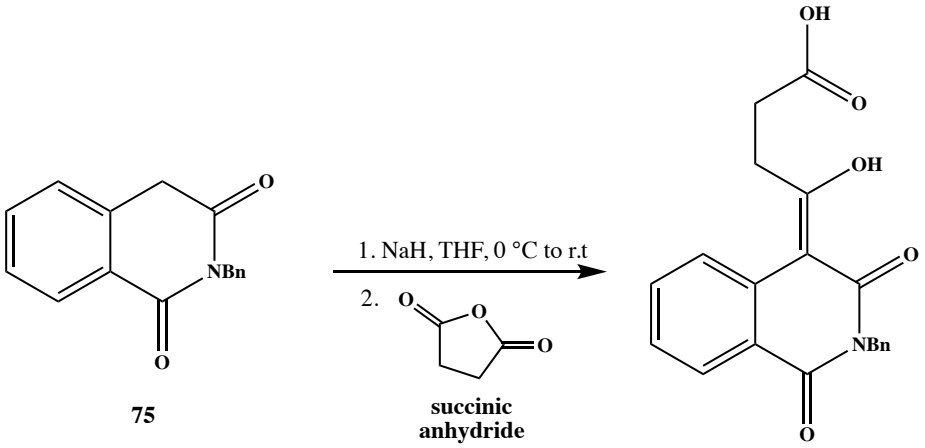


A solution of diol (0.04 g, 0.13 mmol, 1 eq) in a 1:1 mixture of Ac_2O/pyridine (1 mL) was stirred at r.t. for 4 hrs. **97** (0.05 g, 0.13 mmol, 100% yield) was then directly isolated from the reaction mixture by column chromatography (silica gel, hexanes/EtOAc, 1:1). To a stirring solution of **97** in DCM (2 mL) at r.t., was added triethylbenzylammonium chloride (0.09 g, 3 eq) and $KMnO_4$ (0.06 g, 3 eq). After 1 hr, the reaction was quenched with sat. aq. Sodium bisulfite solution (6.5 mL). The now colorless biphasic solution was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated. The resulting residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 1:1 – EtOAc) to yield **98** (0.04 g, 0.10 mmol, 80% from **92**) as a white amorphous solid.



90 **101**

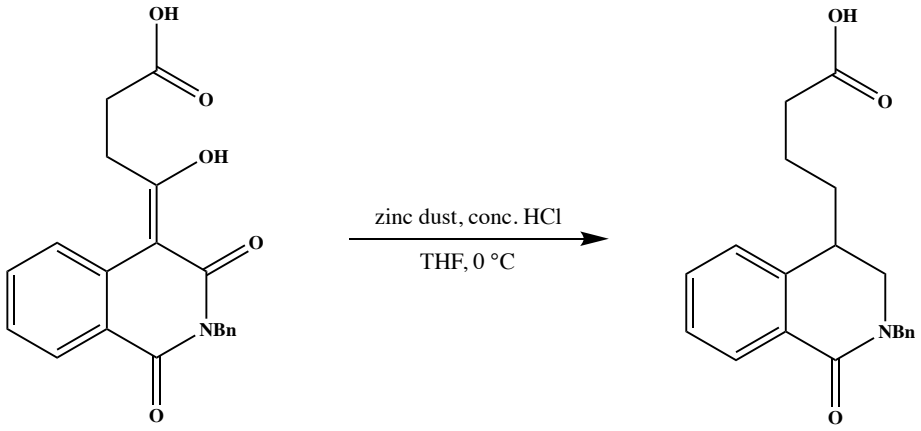
To a stirring solution of naphthalene (0.12 g, 0.9 mmol, 1 eq) at r.t., was added an excess of lithium metal (0.5 g). The solution was sonicated until a deep green color was observed (1 hr). To this stirring solution at -78 °C, was added a solution of **90** (0.30 g, 0.9 mmol, 1 eq) in THF (10 mL) over 1 hr. The reaction mixture was then allowed to warm to warm to r.t.. After 8 hrs, the reaction mixture was cooled to 0 °C and slowly quenched slowly with ice-water (50 mL) before being extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over sodium sulfate, concentrated and dried under vacuum to yield **101** (0.15 g, 0.6 mmol, 68%) as a tan solid.



75 **succinic anhydride** **110**

To a suspension of sodium hydride (2.30 g, 60% dispersed in mineral oil, 57.7 mmol, 1 eq) in anhydrous THF (20 mL) at 0 °C, was added a solution of **75** (14.49 g, 57.7 mmol, 1 eq) in anhydrous THF (200 mL) via cannula over 15 min. The suspension was then brought to r.t. for 1

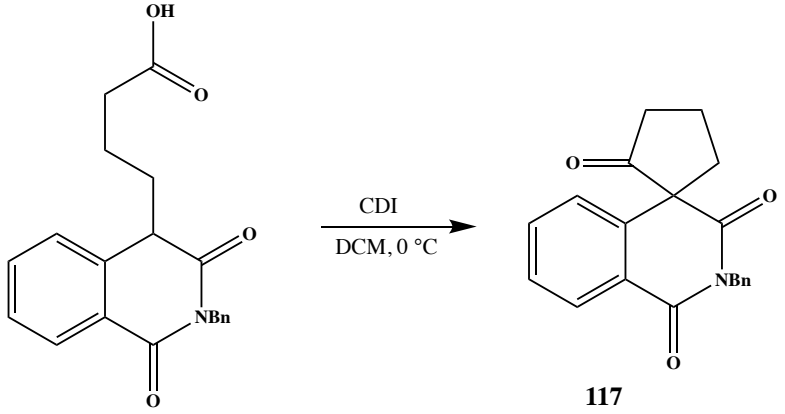
hr. The reaction mixture was again cooled to 0 °C before a solution of succinic anhydride (5.77 g, 57.7 mmol, 1 eq) in anhydrous THF was added all at once. The reaction was again warmed to r.t.. After 15 hrs, the reaction was acidified to a pH of 2 by slow addition of 6 M aq HCl. The resulting precipitate was collected by vacuum filtration, which upon drying was triturated with hot THF to yield **110** (6.54 g, 18.5 mmol, 32%) as a white powder. The unreacted starting material could be recovered by concentrating the filtrate, partitioning the remaining residue between a 1:1 ratio of EtOAc/water (100 mL), isolating the organic phase, which was then dried over sodium sulfate and concentrated under reduced pressure. The crude material could then be recrystallized from 95% ethanol. mp 230-232 °C



110 **114**

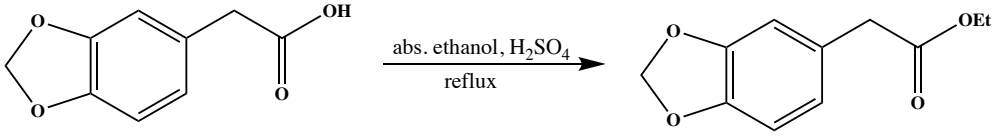
To a suspension of **110** (8.31 g, 23.7 mmol) and an excess of activated zinc dust (10.42 g) in reagent grade THF (490 mL) at 0 °C, was added conc. HCl (53 mL) dropwise over 5min. The reaction was then stirred vigorously at this temperature for 1hr before being poured into ice water (490 mL). After stirring for 15 min, the solution was diluted with diethyl ether (300 mL) and the organic layer was isolated. The aqueous layer was then extracted further with additional ether (2 x 150 mL). The combined organic layers were then washed with brine (1x 100 mL), dried over sodium sulfate, and concentrated to yield a slightly yellow oil that crystallized upon standing. The

crude material was then recrystallized from hexanes/EtOAc to yield **114** (7.38 g, 21.8 mmol, 92%) as colorless needles. mp 132-134 °C



114 **117**

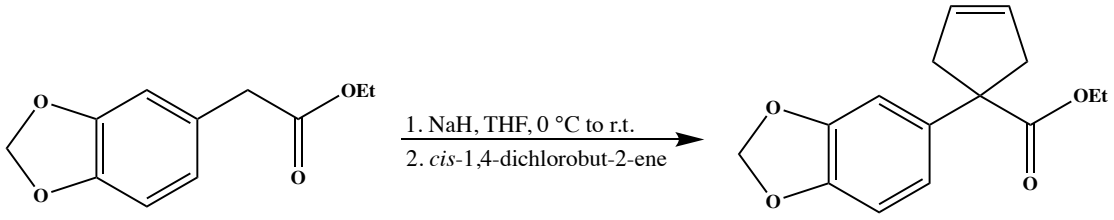
To a suspension of **114** (0.47 g, 1.39 mmol, 1 eq) in anhydrous DCM (2 mL) at 0 °C, was added carbonyldiimidazole (0.27 g, 1.67 mmol, 1.2 eq) all at once. The reaction was stirred at this temperature for 10 min prior to being filtered directly through a plug of silica gel. Upon further elution with hexanes/EtOAc (3:1), the solvent was removed. The resulting residue was the crystallized from diethyl ether to yield **117** (0.38 g, 1.17 mmol, 84%) as colorless prisms. mp 100-102 °C



methylenedioxyphenylacetic acid **(167)** **123**

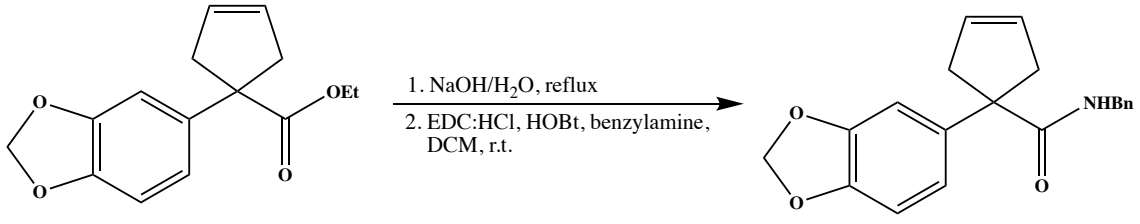
To a solution of methylenedioxyphenylacetic acid **(167)** (5.00 g, 27.8 mmol) in absolute ethanol (50 mL) at r.t., was added 3 drops of sulfuric acid. The reaction was then refluxed overnight prior to concentrating to a volume of 10 mL by simple distillation. The remaining solution was cooled to r.t., then quenched with sat. $NaHCO_3$ solution (50 mL). The aqueous suspension was then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (1

x 50 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resulting colorless oil was dried under vacuum to yield **123** (5.77 g, 2.77 mmol, 100%).



123 **124**

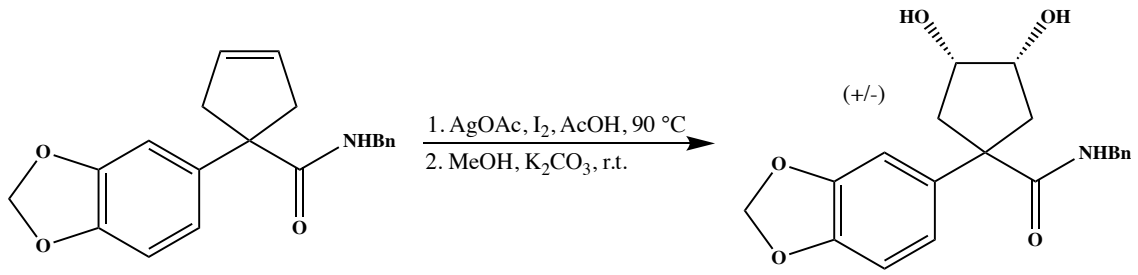
To a suspension of sodium hydride (0.88 g, 60% dispersed in mineral oil, 22.08 mmol, 4 eq) in anhydrous THF (1 mL) at 0 °C, was added a solution of **123** (1.15 g, 5.52 mmol, 1 eq) in anhydrous THF (10 mL) over 20 min. The reaction was then brought to r,t. and stirred an additional 20 min. Upon cooling again to 0 °C, *cis*-1,4-dichlorobut-2-ene (1.16 mL, 11.0 mmol, 2 eq) was added all at once. The reaction was then refluxed for 2 hrs. Upon cooling to r.t., the reaction was quenched by slow addition of sat. NH_4Cl aq. solution (30 mL) before being extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine (1 x 30 mL), dried over sodium sulfate and concentrated. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to yield **124** (0.83 g, 3.20 mmol, 58%) as an off white oil. Further acidification of the initial aqueous layer with 6 M aq HCl precipitated unreacted starting material.



124 **125**

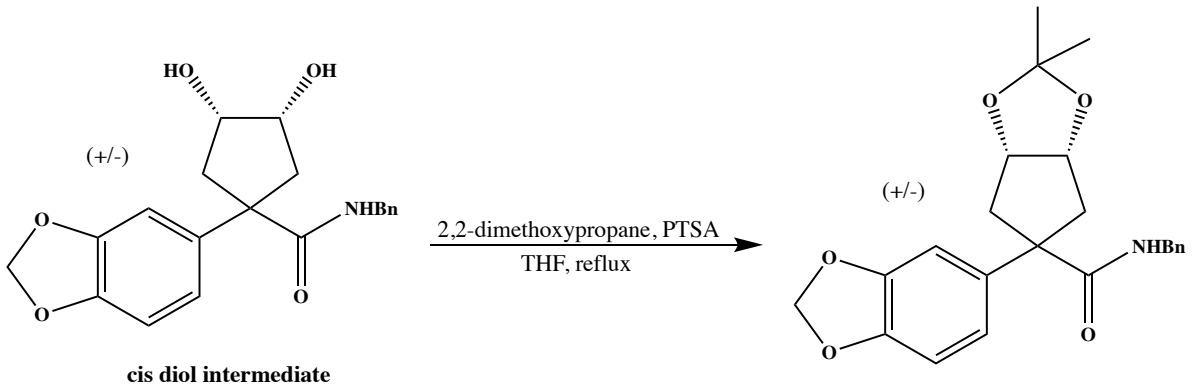
A suspension of **124** (3.50 g, 13.4 mmol) in 10% aq NaOH (35 mL) was refluxed for overnight. The now now homogeneous solution was diluted with water (100 mL), cooled to r.t. and washed with diethyl ether (1 x 50 mL). The aqueous phase was then acidified to a pH of 2

with conc. HCl before being extracted with EtOAc (3 x 50 mL). The combined organic layers were then washed with brine (1 x 25 mL), dried over sodium sulfate, and concentrated to yield the crude carboxylic acid (2.57 g) as a white crystalline solid. To a solution of this intermediate in DCM (25 mL) at r.t., was added EDC hydrochloride (2.49 g, 1.30 mmol, 1.2 eq) and HOBt (1.99 g, 1.30 mmol, 1.2 eq). After 10 minutes of stirring, benzylamine (1.42 mL, 1.30 mmol, 1.2 eq) was added all at once. The reaction was stirred for an additional 8 hrs before being diluted with an additional DCM (50 mL). The organic solution was then washed with 10% aq. HCl solution (1 x 30 mL), sat. $NaHCO_3$ solution (1 x 50 mL), dried over sodium sulfate and concentrated to yield **125** (3.11 g, 9.68 mmol, 90%) as a colorless amorphous solid.



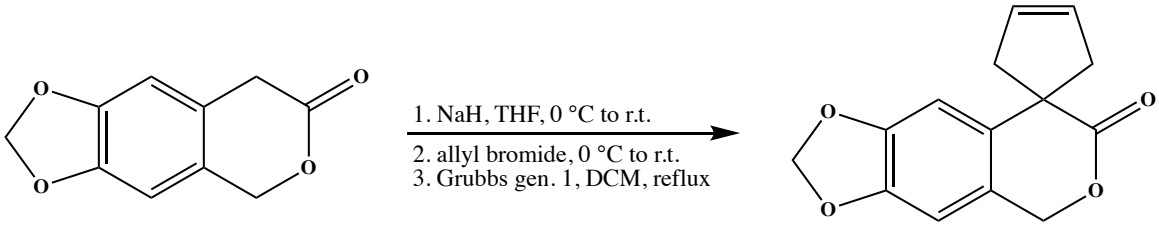
125 **cis diol intermediate**

To a solution of **125** (0.90 g, 2.80 mmol, 1 eq) in glacial acetic acid (10 mL) at r.t., was added AgOAc (1.05 g, 6.3 mmol, 2.25 eq) and molecular iodine (0.39 g, 3.08 mmol, 1.1 eq). The resulting suspension was stirred at this temperature for 30 min before water (0.1 mL) was added. The reaction mixture was then heated to 90 °C for 1 hr. The silver salts were filtered off and the filter cake was rinsed with EtOAc. The filtrate was then concentrated and the resulting residue was dissolved in MeOH (10 mL) and an excess of K_2CO_3 (1 g) was added. The resulting suspension was then stirred at r.t. for 3 hrs. The solids were filtered off using a fine frit and evaporated of the filtrate yielded the intermediate diol (0.37 g, 1.04 mmol, 37%) as a white foam.



cis diol intermediate **127**

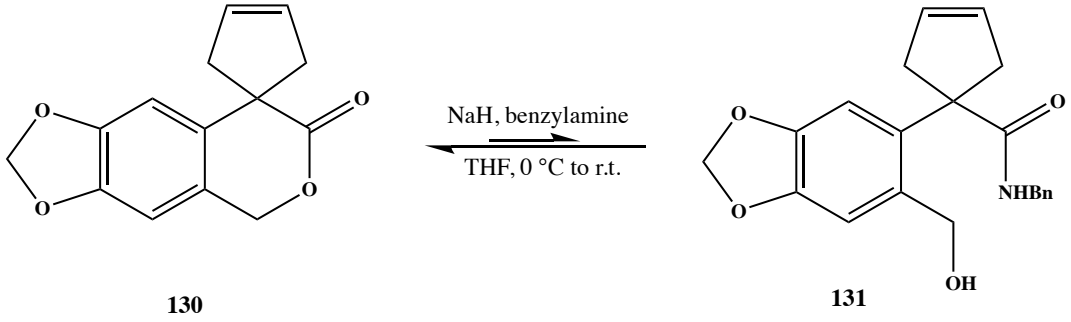
To a solution of the cis diol intermediate (0.37 g, 1.04 mmol, 1 eq) in anhydrous THF (5 mL) at r.t., was added a catalytic amount of PTSA and 2,2-dimethoxypropane (0.26 mL, 2.08 mmol, 2 eq). The reaction was then refluxed for 24 hrs. Upon cooling to r.t., the reaction was quenched with sat. $NaHCO_3$ solution (10mL) before being extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over sodium sulfate and concentrated to yield **127** (0.28 g, 0.71 mmol, 68%) as an amorphous white solid.



129 **130**

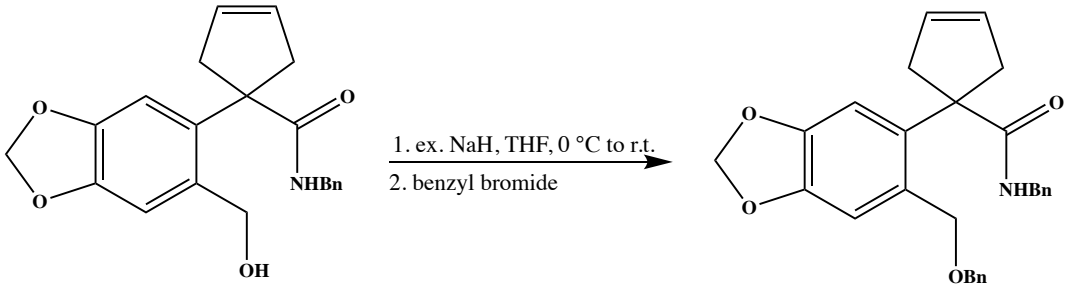
To a solution of **129** (1.00 g, 5.20 mmol, 1eq) in anhydrous THF (30 mL) at 0 °C, was added sodium hydride (0.83 g, 60%, 20.8 mmol, 4 eq) in portions over 5 min. The resulting suspension was then stirred for 10 min at this temperature before allyl bromide (1.12 mL, 13.0 mmol, 2.5 eq) was added all at once. The reaction mixture was then allowed to warm to r.t. and stirred an additional 2 hrs before being quenched by dropwise addition of water, being careful to allow hydrogen gas evolution to subside in the process. The aqueous suspension was then extracted

with EtOAc (3 x 20 mL). The combined organic layers were then washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography to yield the di-allyl intermediate (0.45 g, 1.65 mmol). This product was then dissolved in DCM (45 mL) and Grubbs gen 1 catalyst (0.07 g, 0.08 mmol, 5 mol%) was added. The resulting purple solution was then refluxed overnight. The reaction was cooled to r.t. and concentrated to a small volume prior to being filtered through a short plug of silica get. Upon further elution with DCM, the filtrate was concentrated to yield **130** (0.40 g, 1.65 mmol, 32% over 2 steps) as a white solid.



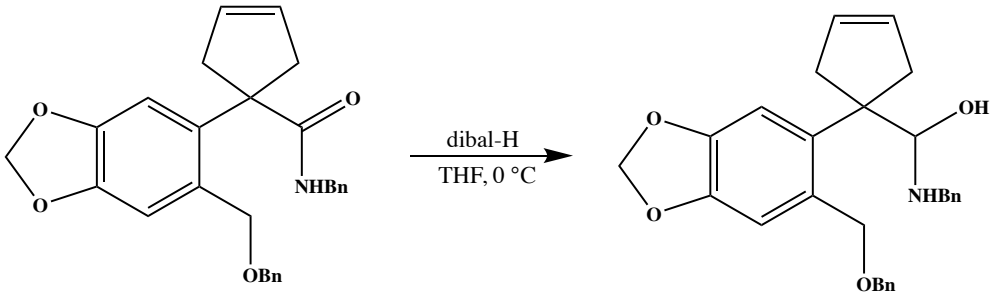
130 **131**

To a suspension of sodium hydride (0.15 g, 60%, 3.68 mmol, 3 eq) in anhydrous THF (1 mL) at 0 °C, was added a solution of benzylamine (0.40 mL, 1.23 mmol, 1 eq) dropwise over 5 min. After 10 min at this temperature, a solution of **130** (0.30 g, 1.23 mmol, 1 eq) in anhydrous THF (5 mL) was added dropwise over 5 min. The reaction mixture was then warmed to r.t. and stirred an additional 12 hrs. The reaction was then quenched by slow addition of sat. NH_4Cl aq solution (10 mL). The aqueous solution was then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated. The resulting residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to yield **131** (0.15 g, 0.43 mmol, 35%) as a colorless oil.



131 **132**

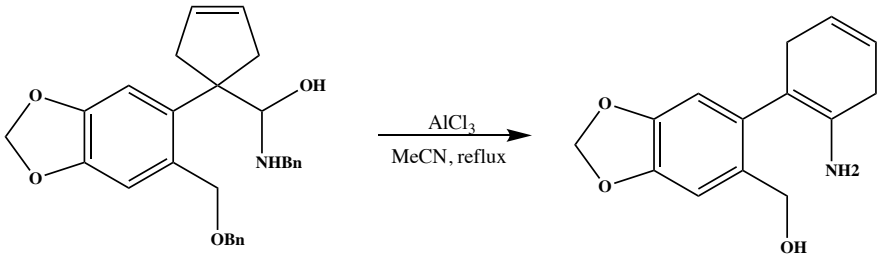
To a solution of **131** (0.15 g, 0.43 mmol, 1 eq) in anhydrous THF (3 mL) at 0 °C, was added benzyl bromide (0.06 mL, 0.51 mmol, 1.2 eq) followed by sodium hydride (0.05 g, 1.28 mmol, 3 eq). The reaction was then refluxed for 1 hr. Upon cooling to r.t., the reaction was quenched by slow addition of sat. NH_4Cl aq solution (10 mL). The aqueous solution was then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 4:1) to yield **132** (0.05 g, 0.12 mmol, 28%) as a white amorphous solid.



132 **133**

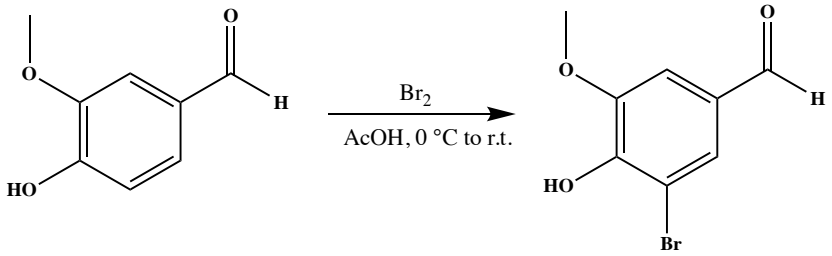
To a solution of **132** (0.01 g, 0.02 mmol), 1 eq in anhydrous hexanes (0.50 mL) at 0 °C, was added dibal-H solution (28.5 µL, 0.02 mmol, 0.9 eq) all at once. The reaction was then warmed to r.t. and stirred for 2 hrs. TLC analysis showed incomplete reaction so an additional portion of dibal-H solution (28.5 µL, 0.02 mmol, 0.9 eq) was added all at once again at this temperature. After an additional 15 min, the reaction was cooled to 0 °C and carefully quenched with water (3

mL) and diluted with EtOAc (3 mL). Rochelles salt was then added and the cloudy mixture was stirred until a clear biphasic solution was obtained. The organic layer was isolated and the aqueous layer further extracted with EtOAc (2 x 5 mL). The combined organic layers were then washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc, 4:1) to yield **133** (0.01, 0.02 mmol, 100%) as a colorless oil.



133 **134**

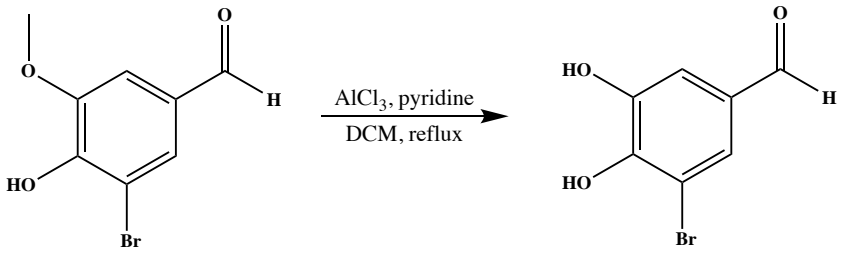
To a solution of **133** (0.01 g, 0.02 mmol, 1 eq) in anhydrous acetonitrile (1 mL) at r.t., was added aluminum chloride(0.01 g, excess). The reaction was then stirred at this temperature for 30 min before being quenched by slow addition of water (3 mL). The resulting aqueous suspension was then extracted with EtOAc (3 x 5 mL). The combined organic layers were then washed with brine (5 mL), dried over sodium sulfate and concentrated to yield a mixture of **134** (trace) and benzyl chloride.



vanillin **139**

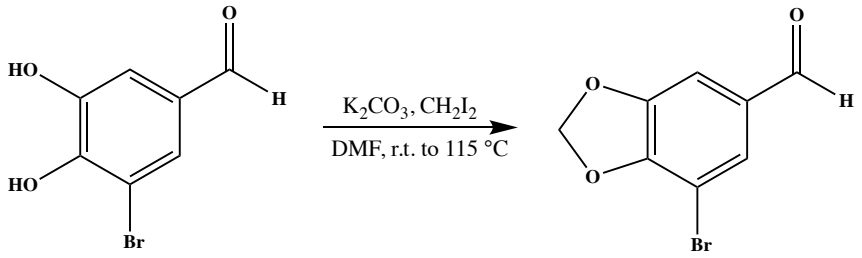
To a suspension of vanillin (10.0 g, 65.7 mmol, 1 eq) in glacial acetic acid (80 mL) at 0 °C, was added molecular bromine (3.40 mL, excess) dropwise over 5 min. After an additional 5

min of stirring at this temperature, the reaction was warmed to r.t. and stirred for another 2 hrs. The reaction was then cooled to 0 °C and was quenched by slow addition of ice water (150 mL) with strong stirring. The resulting precipitate was then collected by suction filtration before being dried in a desiccator to yield **139** (14.5 g, 62.8 mmol, 96%) as a white powder. mp decomp 159-162 °C



139 phenol intermediate

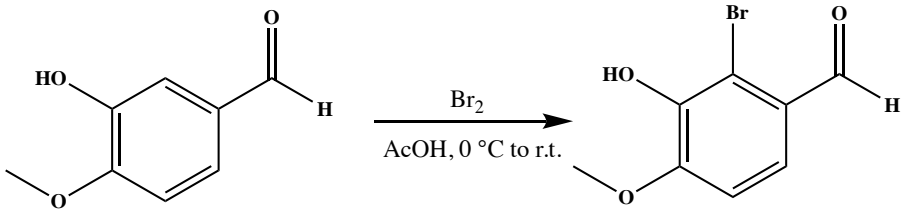
To a suspension of **139** (14.5g, 62.8 mmol, 1 eq) in anhydrous DCM (250 mL) at r.t., was added aluminum chloride (10.1 g, 75.4 mmol, 1.2 eq) in portions over 5 min. After an additional 5 min of stirring, pyridine (22.5 mL) was added dropwise to the now bright pink suspension over 10 min. The reaction was then refluxed for 24 hrs. The resulting homogeneous solution was then cooled to 0 °C and quenched by slow addition of 3M aqueous HCl (150 mL) with strong stirring. The resulting precipitate was collected by suction filtration and dried in a desiccator to yield the phenol intermediate (12.2 g, 56.3 mmol, 90%) as a light grey powder. mp decomp 210-220 °C



phenol intermediate **140**

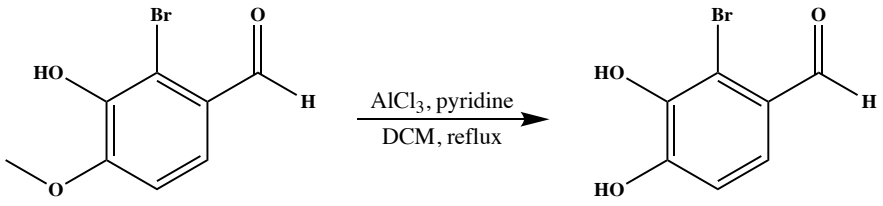
To a solution of the diphenol intermediate (8.02 g, 37.0 mmol, 1 eq) in anhydrous DMF (35 mL) at r.t., was added K_2CO_3 (25.5 g, 185 mmol, 5 eq) all at once. After 15 min of stirring at

this temperature, diiodomethane (3.57 mL, 44.3 mmol, 1.2 eq) was added all at once and the reaction was heated at 115 °C for 2 hrs. Upon cooling to r.t., the solvent was removed under reduced pressure and the resulting residue was suspended in boiling EtOAc (60 mL) with strong stirring. The suspension was then hot filtered and the filter cake rinsed with additional hot EtOAc. The filtrate was then concentrated to yield **140** (7.84 g, 34.2 mmol, 93%) as a tan solid. Trace DMF may be removed under vacuum. mp 118-120 °C



isovanillin bromide intermediate

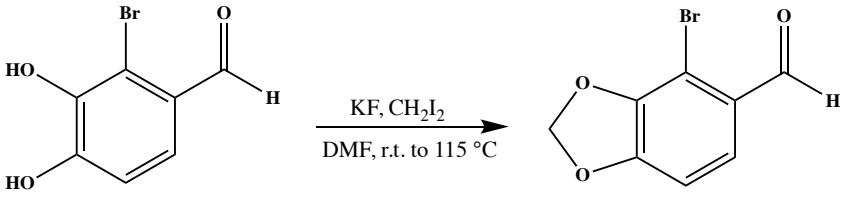
To a suspension of isovanillin (3.00 g, 19.7 mmol, 1 eq) in glacial acetic acid (24 mL) at r.t., was added a solution of molecular bromine (1.00 mL, excess) in glacial acetic acid (3.2 mL) dropwise over 30 min. The reaction was then stirred for an additional 2 hrs at this temperature. The reaction was then cooled to 0 °C before being quenched by slow addition of ice water (40 mL) with strong stirring. The resulting precipitate was collected by suction filtration and dried in a desiccator to yield the bromide intermediate (3.67 g, 15.9 mmol, 80%) as a white powder. mp 203-204 °C



bromide intermediate diphenol intermediate

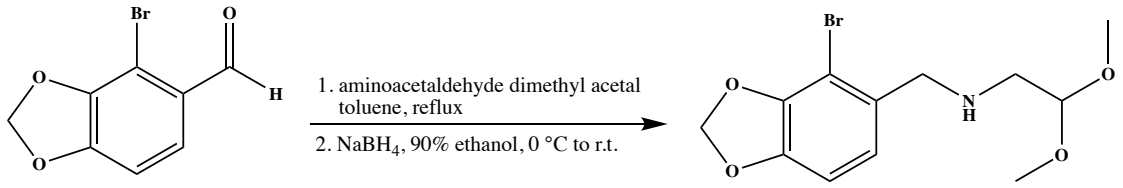
To a suspension of the bromide intermediate (1.86 g, 8.05 mmol, 1 eq) in anhydrous DCM (32 mL) at r.t., was added aluminum chloride (1.29 g, 9.66 mmol, 1.2 eq) in portions over 5 min.

After an additional 5 min of stirring, pyridine (2.85 mL) was added dropwise to the now bright pink suspension over 10 min. The reaction was then refluxed for 24 hrs. The resulting homogeneous solution was then cooled to 0 °C and quenched by slow addition of 3M aqueous HCl (20 mL) with strong stirring. The resulting precipitate was collected by vacuum filtration and dried in a desiccator to yield the diphenol intermediate (1.72 g, 7.93 mmol, 99%) as a light grey powder. mp decomp 176 °C



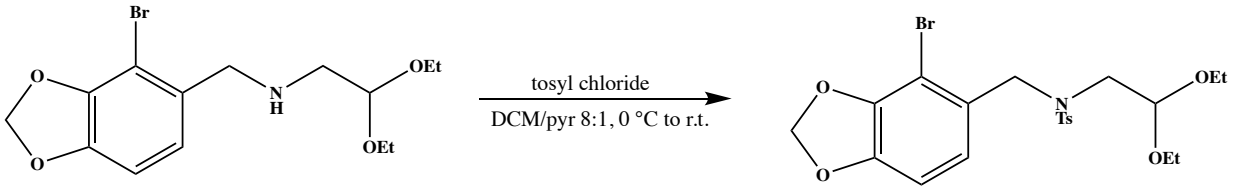
diphenol intermediate **143**

To a solution of the diphenol intermediate (1.45 g, 6.68 mmol, a eq) in anhydrous DMF (20 mL) at r.t., was added KF (1.94 g, 33.4 mmol, 5 eq) all at once. After 15 min of stirring at this temperature, diiodomethane (0.59 mL, 7.35 mmol,1.1 eq) was added all at once and the reaction was heated at 115 °C for 2 hrs. Upon cooling to r.t., the solvent was removed under reduced pressure and the resulting residue was suspended in boiling EtOAc (20 mL) with strong stirring. The suspension was then hot filtered and the filter cake rinsed with additional hot EtOAc. The filtrate was then concentrated to yield **143** (1.04 g, 4.54 mmol, 68%) as a tan solid. Trace DMF may be removed under vacuum.



143 **144**

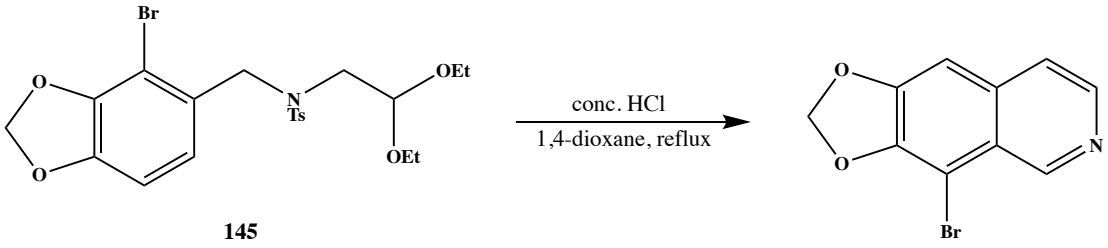
To a solution of **143** in toluene (1.04 g, 4.54 mmol, 1 eq) at r.t., was added diethylaminoacetaldehyde (0.69 mL, 6.36 mmol, 1.4 eq) all at once. The reaction was then refluxed under dean-stark conditions for 2 hrs. The solvent was removed and the resulting residue was dissolved in 90% ethanol (10 mL) and the resulting solution was cooled to 0 °C. Sodium borohydride (0.22 g, 5.90 mmol, 1.3 eq) in pellet form was then added and the reaction was allowed to warm to r.t. and stir overnight before being quenched with water (20 mL). The aqueous suspension was then extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over sodium sulfate and concentrated to yield **144** (1.24 g, 3.99 mmol, 86%) as a brown oil that was used in the next step without further purification.



144 **145**

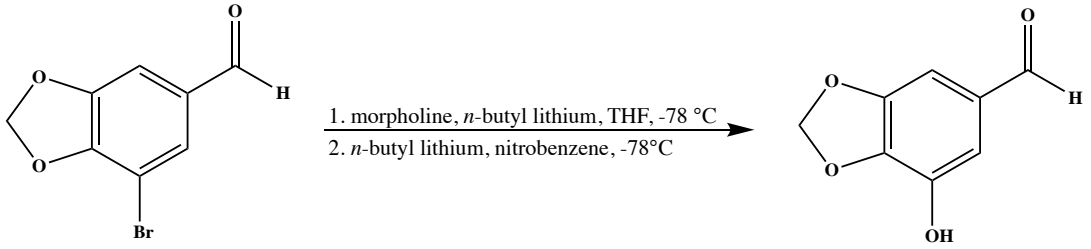
To a solution of **144** (1.24 g, 3.90 mmol, 1 eq) in an 8:1 mixture of DCM/pyridine (5.5 mL) at 0 °C, was added tosyl chloride (1.56 g, excess) all at once. The reaction was then warmed to r.t. and stirred for an additional 3 hrs. The reaction was then diluted with DCM (5 mL) and quenched with sat aqueous $NaHCO_3$ (10 mL). The biphasic solution was then stirred for 1 hr to hydrolyze any additional tosyl chloride present. The organic layer was then isolated and the aqueous layer extracted with additional DCM (5 mL). The combined organic layers were then washed sequentially with 2M HCl (2 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL) prior to

drying over sodium sulfate and concentrating to yield a brown oil. The crude product was re-dissolved in DCM and filtered through a short pad of silica gel to remove colored impurities. Upon further elution with DCM the filtrate was concentrated to yield **145** (1.24 g, 2.54 mmol, 65%) as a colorless oil that crystallized upon standing.



145 **146**

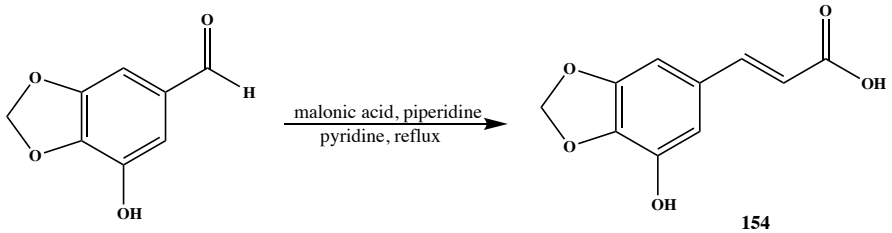
To a solution of **145** (5.00 g, 10.6 mmol, 1 eq) in 1,4-dioxane (30 mL) at r.t., was added conc HCl (30 mL). The biphasic solution was then refluxed for 18 hrs. The reaction was then cooled to r.t. and concentrated to half of its volume under reduced pressure before being diluted with 10% aq NaOH (30 mL). The aqueous solution was then extracted with EtOAc (3 x 20 mL). The combined organic layers were then dried over sodium sulfate and concentrated. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to yield **146** (0.90, 3.57 mmol, 35%) as a tan crystalline solid.



140 **153**

To a solution of morpholine (2.09 mL, 24.2 mmol, 1.2 eq) in anhydrous THF (38 mL) at -78 °C, was added n-butyl lithium solution in hexanes (9.68 mL, 24.2 mmol, 1.2 eq) all at once. After an additional 20 min at this temperature, a solution of **140** (4.62 g, 20.2 mmol, 1 eq) in

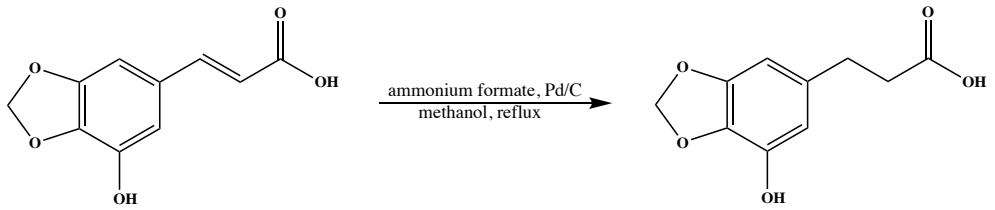
anhydrous THF (30 mL) was added dropwise over 2 min. After another 35 min, n-butyl lithium solution in hexanes (12.91 mL, 32.3 mmol, 1.6 eq) was added dropwise making sure to keep the temperature at -78 °C. After addition was complete and additional 15 min was allowed to pass before a solution of nitrobenzene (5.79 mL, 56.6 mmol, 2.8 eq) in anhydrous THF (10 mL) was added dropwise, again making sure to keep the temperature at -78 °C. After 4 hrs at this temperature, the reaction was warmed to r.t. prior to acidifying to a pH of 1 with 6M HCl. After dilution with brine (50 mL), the organic layer was isolated and the aqueous layer was further extracted with diethyl ether (2 x 30 mL). The combined organic layers were then extracted with 2M NaOH solution (3 x 20 mL). The alkaline solution was then washed with ether (2 x 20 mL) before being acidified to a pH of 1 with conc HCl. The aqueous suspension was then extracted with EtOAc (3 x 20 mL). The combined organic layers were then dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to yield **153** (0.75 g, 4.51 mmol, 22%) as a white powder.



153 **154**

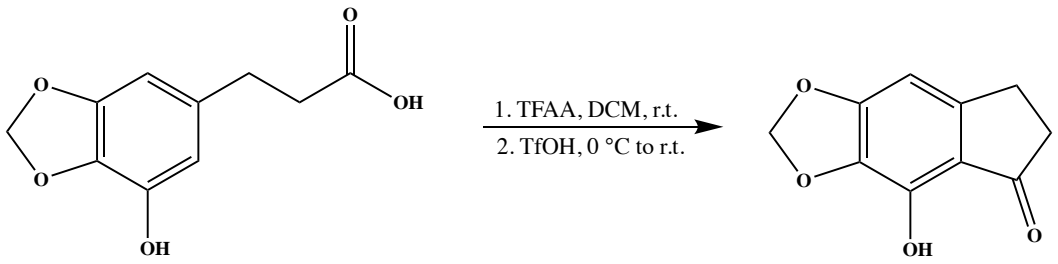
To a solution of **153** (0.75 g, 4.51 mmol, 1 eq) in pyridine (4.34 mL) at r.t., was added piperidine (0.37 g, excess) malonic acid (0.94 g, 9.03 mmol, 2 eq). The reaction was then refluxed for 3 hrs. The reaction was then cooled to r.t and acidified to a pH of 1 with 6M HCl with strong stirring. The resulting precipitate was then collected by suction filtration and dried in a desiccator. A second crop was obtained by extracting the aqueous phase with EtOAc (3 x 3 mL). The

combined organic layers were washed with brine (1 x 3 mL), dried over sodium sulfate and concentrated. The resulting product possessed the same purity and the product obtained through precipitation so the two crops were combined to yield **154** (0.90 g, 4.32 mmol, 96%) as a white powder



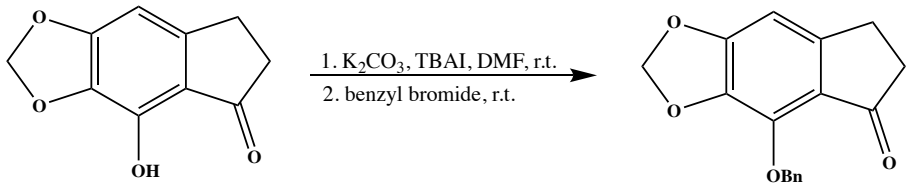
154 **155**

To a solution of **154** (0.89 g, 4.28 mmol, 1 eq) in methanol (22 mL) at r.t., was added ammonium formate (2.84 g, excess) and Pd/C (0.09 g, 10% by mass). The resulting suspension was refluxed for 2 hrs, ensuring that the reflux condenser was cleared periodically of sublimed ammonium formate. The Pd/C was removed by filtration and the filtrate was concentrated under reduced pressure. The remaining residue was then suspended in water (10 mL) before acidification with 6M HCl to a pH of 1 with strong stirring. The resulting precipitate was collected by suction filtration and dried in a desiccator. A second crop was obtained by extracting the aqueous phase with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (1 x 5 mL), dried over sodium sulfate and concentrated. The resulting material possessed the same purity as the product obtained through precipitation so the two crops were combined to yield **155** (0.84 g, 4.00 mmol, 93%) as a white powder.



155 **156**

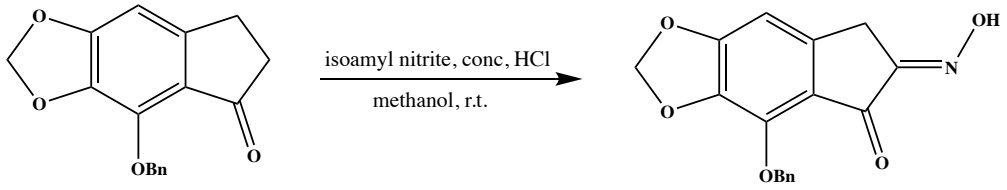
To a solution of **155** (1.74 g, 8.28 mmol, 1 eq) in anhydrous DCM (17 mL) at r.t., was added trifluoroacetic anhydride (3.45 mL, 24.8 mmol, 3 eq). The reaction was stirred at this temperature for 15 min before triflic acid (1.10 mL, 12.4 mmol, 1.5 eq) was added all at once. The now dark red reaction was stirred for an additional 2 hrs before being diluted with additional DCM (17 mL) and quenched with water (17 mL). The organic layer was isolated and the aqueous phase extracted with additional DCM (2 x 5 mL). The combined organic layers were dried over sodium sulfate and directly filtered through a short plug of silica gel to remove colored impurities. Upon further elution with DCM, the filtrate was concentrated to yield **156** (1.43 g, 7.44 mmol, 90%) as a white crystalline solid.



156 **157**

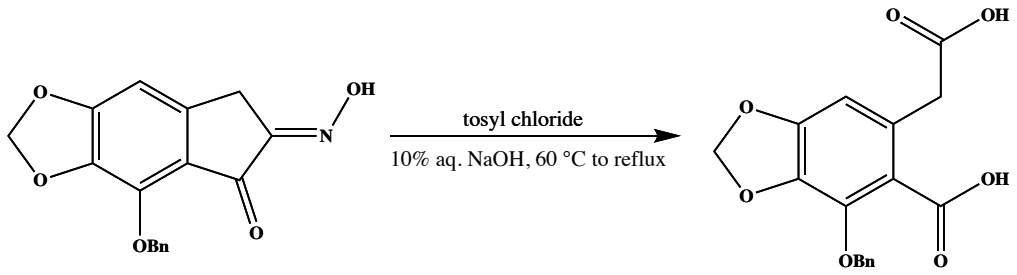
To a solution of **156** (0.58 g, 3.02 mmol, 1 eq) in DMF (7.5 mL) at r.t., was added K_2CO_3 (4.17 g, 30.2 mmol, 10 eq) and tetrabutylammonium iodide (0.11 g, 0.30 mmol, 0.1 eq). After 10 min, benzyl bromide (0.54 mL, 4.53 mmol, 1.5 eq) was added all at once and the reaction was stirred for an additional 18 hrs. The reaction was then quenched with a 1:1 ratio of water/brine (15 mL). The aqueous suspension was then extracted with EtOAc (3 x 7 mL). The combined organic layers were then washed with brine (1 x 7 mL), dried over sodium sulfate and concentrated. The

resulting residue was then purified my column chromatography (silica gel, hexanes/EtOAc, 4:1) to yield **157** (0.83 g, 2.94 mmol, 98%) as a colorless oil.



157 **158**

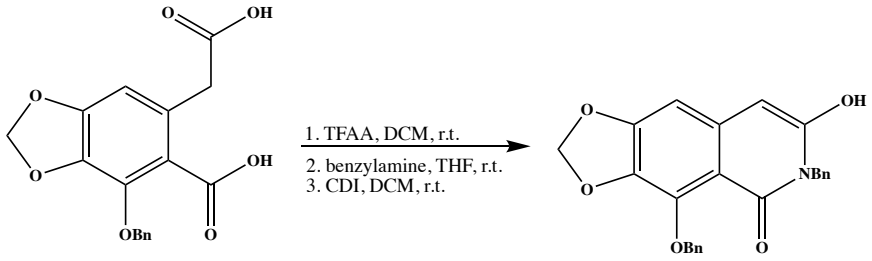
To a solution of **157** (1.81 g, 6,41 mmol, 1 eq) in methanol (55 mL) at r.t., was added isoamyl nitrite (1.12 mL, 8.34 mmol, 1.3 eq) and conc HCl (1.81 mL). The reaction was then stirred for 2 hrs, at which point the resulting precipitate was collected by suction filtration, rinsed with a minimal amount of cold methanol and dried under vacuum to yield **158** (1.83 g, 5.88 mmol, 92%) as a colorless powder.



158 **159**

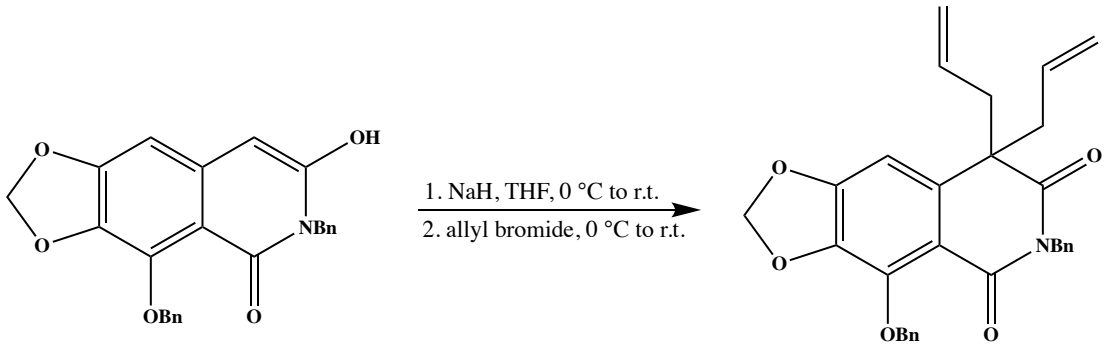
To a suspension of **158** (0.70 g, 2.25 mmol, 1 eq) in 10% aqueous NaOH (9.1 mL) at r.t., was added an excess of tosyl chloride (0.84 g). The was then heated at 60 °C for 40 min before being refluxed for 18 hrs. The now dark solution was then cooled to r.t. and acidified to a pH of 1 with 6M HCl. The resulting precipitate was then collected by suction filtration and dried in a desiccator. A second crop was obtained by extracting the aqueous phase with EtOAc (2 x 4 mL). The combined organic layers were washed with brine (1 x 4 mL), dried over sodium sulfate and concentrated. The resulting product possessed the same purity and the product obtained through

precipitation so the two crops were combined to yield **159** (0.63 g, 1.91 mmol, 85%) as a tan powder. mp 119-122 °C



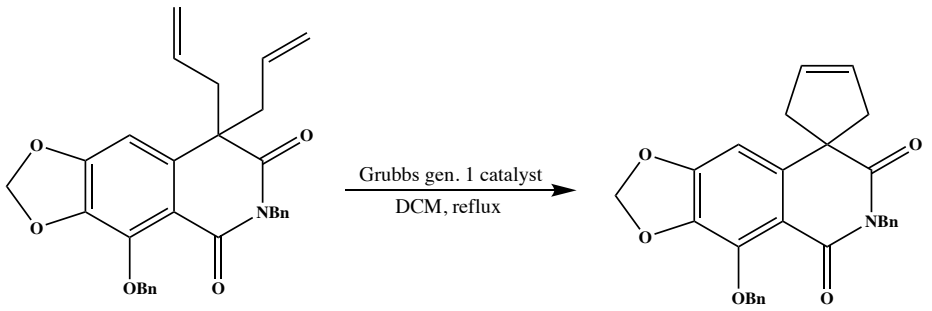
159 **160**

To a suspension of **159** (1.19 g, 3.60 mmol, 1 eq) in anhydrous DCM (12 mL) at r.t., was added trifluoroacetic anhydride (0.65 mL, 4.68 mmol, 1.3 eq) all at once. After 1 hr, the solvent was removed and the resulting residue was taken up in THF (12 mL) before benzylamine (0.39 mL, 4.68 mmol, 1.3 eq) was added all at once. After 2 hrs, the solvent was again removed and the resulting residue was dissolved in EtOAc (25 mL). The organic solution was then washed with 2M aqueous HCl (1 x 25 mL) before being dried with sodium sulfate and concentrated. The resulting residue was dissolved in anhydrous DMF (10 mL) and carbonyl diimidazole (0.58 g, 3.60 mmol, 1 eq) was added all at once at r.t.. The reaction was then stirred overnight before the solvent was removed under reduced pressure. The resulting residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 2:1) to yield **160** (0.39 g, 0.97 mmol, 27%) as a light yellow solid.



160 **161**

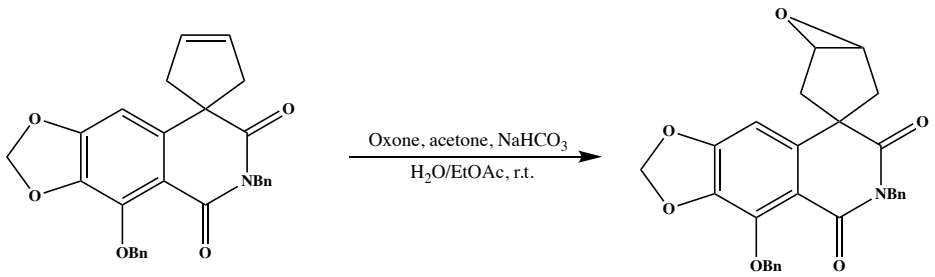
To a solution of **160** (0.23 g, 0.57 mmol, 1 eq) in anhydrous THF (2.5 mL) at r.t., was added sodium hydride (0.06 g, 60%, 1.43 mmol, 2.5 eq) all at once. The suspension was then stirred for 30 min prior to cooling to 0 °C and the addition of allyl bromide (0.10 mL, 1.15 mmol, 2 eq) all at once. The reaction was then brought to r.t. and allowed to stir for an additional 2 hrs before being quenched by slow addition of water (10 mL). The THF was then removed under reduced pressure and the remaining aqueous solution extracted with EtOAc (3 x 5 mL). The combined organic layers were then washed with brine (1 x 1 mL), dried over sodium sulfate and concentrated. The resulting residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 4:1) to yield **161** (0.07 g, 0.15 mmol, 25%) as a white solid.



161 **162**

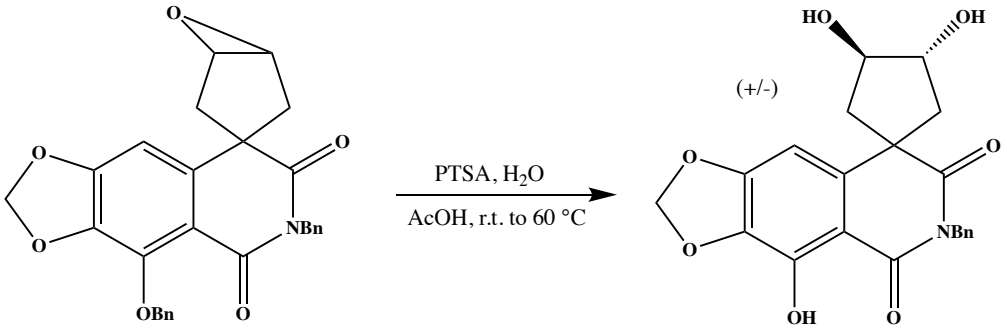
To a stirring solution of **161** compound (0.07 g, 1.45 mmol, 1 eq) in DCM (5 mL) at r.t., was added Grubbs Gen 1 catalyst (0.01 g, 5 mol%) and the reaction mixture was refluxed for 3 hrs. Most of the DCM was removed under reduced pressure before being filtered through a short

pad of silica gel to remove catalyst and colored impurities. Upon elution with additional DCM, concentrating the filtrate provided **162** (0.07g, 1.45 mmol, 100%) as a white crystalline solid.



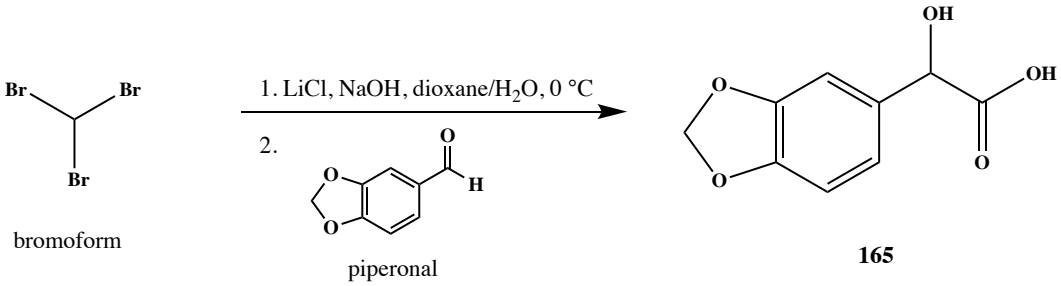
162 **163**

To a stirring solution of **162** (0.07 g, 0.15 mmol, 1 eq) in EtOAc (1 mL) at r.t., was added water (1 mL), an excess of powdered $NaHCO_3$ (0.19 g), and an excess of acetone (0.5 mL). The biphasic solution was stirred vigorously as a solution of Oxone® (0.28 g, 0.46 mmol, 3 eq) in water (1 mL) was added dropwise over 10 min. After 18 hrs, the reaction mixture was filtered through a pad of celite and the organic layer was isolated. The aqueous layer was then extracted with EtOAc (2 x 1 mL). The combined organic layers were dried over sodium sulfate and concentrated. The resulting residue was the purified by column chromatography (silica gel, hexanes/EtOAc, 4:1) to remove trace starting materiel to provide **163** (0.04 g, 0.09 mmol, 60%) as a white crystalline solid.



163 **164**

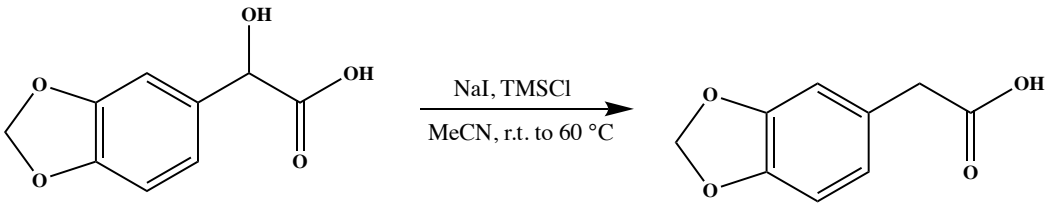
To a solution of **163** (0.04 g, 0.09 mmol, 1 eq) in glacial acetic acid (1 mL) at r.t., was added a catalytic amount of PTSA and water (3 drops). After 4 hrs, a precipitate had formed but TLC analysis still showed starting material to the reaction was heated at 60 °C for 1 hr. The solvent was then removed under reduced pressure. The resulting residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to yield trace amounts of **164** as an amorphous white solid.



bromoform piperonal **165**

To a degassed biphasic 1:1 solution of water/1,4-dioxane (264 mL) at 0 °C, was added bromoform (16.7 mL, 183 mmol, 1.1 eq) and lithium chloride (15.5 g, 366 mmol, 2.2 eq) all at once. To this stirring solution was added KOH (48.36 g, 733 mmol, 4.4 eq) in pellet form over 15 min. Piperonal (25.0 g, 167 mmol, 1 eq) was then added all at once. After 12 hrs at this temperature the reaction was allowed to warm to r.t. and stir an additional 50 hrs, which resulted in the formation of a copious amount of precipitate. After carefully acidifying to a pH of 2 with conc HCl, the reaction was extracted with diethyl ether (3 x 50 mL), The combined organic layers were

then extracted with 2M aqueous NaOH solution (3 x 33 mL). The combined alkaline layers were then washed with ether (1 x 25 mL) before again carefully acidifying to a pH of 2 with conc HCl. The aqueous suspension was then extracted with ether (3 x 50 mL). The combined organic layers were then washed with brine, dried over sodium sulfate and concentrated. The resulting residue was then triturated with petroleum ether and vacuum filtered to yield **165** (30.2 g, 153 mmol, 92%) as a tan powder: mp 151-153 °C. ^{1}H NMR (DMSO-d_6) δ 4.93 (s, 1H), 6.00 (s, 1H), 6.88 – 6.93 (m, 3H), 12.58 (bs, 1H).

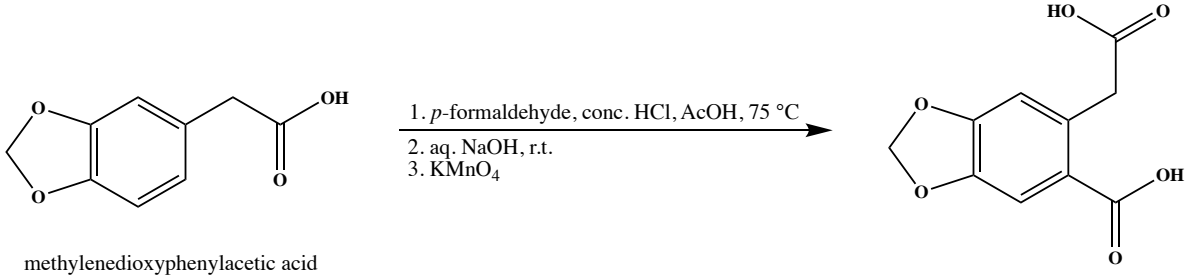


165 **methylenedioxyphenylacetic acid**

167

To a suspension of **165** (13.2 g, 67.4 mmol, 1 eq) in anhydrous acetonitrile (100 mL) at r.t., was added sodium iodide (22.2 g, 148 mmol, 2.2 eq) and freshly distilled trimethylsilyl chloride (18.7 mL, 148 mmol, 2.2 eq) all at once. The reaction was then stirred at 60 °C for 24 hrs before being cooled to r.t.. The solvent was then removed under reduced pressure and the resulting residue taken up in a 1:1 ratio of EtOAc/water (300 mL). The organic layer was isolated and the aqueous phase was extracted with additional ether (1 x 50 mL). The combined organic layers were then extracted with 2M aqueous NaOH (1 x 150 mL). The alkali solution was then washed with ether (1 x 25 mL) prior to being acidified to a pH of 1 with conc HCl. The resulting suspension was then extracted with ether (1 x 150, 1 x 50). The combined organic layers were then washed sequentially with sat. sodium thiosulfate aqueous solution (1 x 150 mL) and brine (1 x 150 mL) before drying over sodium sulfate and concentrating. The resulting residue was triturated with petroleum ether

to yield **167** (11.3 g, 62.6 mmol, 93%) as a tan powder. ^{1}H NMR (DMSO-d_6) δ 3.48 (s, 2H), 5.98 (s, 2H), 6.71 (dd, J = 8, 1.6 Hz, 1 Hz), 6.83 (m, 2H), 12.29 (bs, 1H).



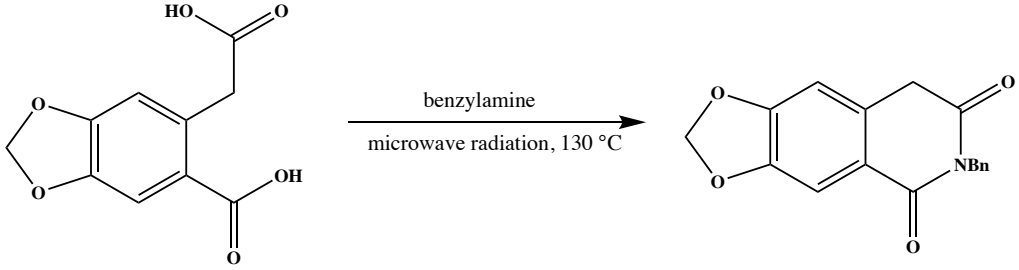
methylenedioxyphenylacetic acid

(162)

170

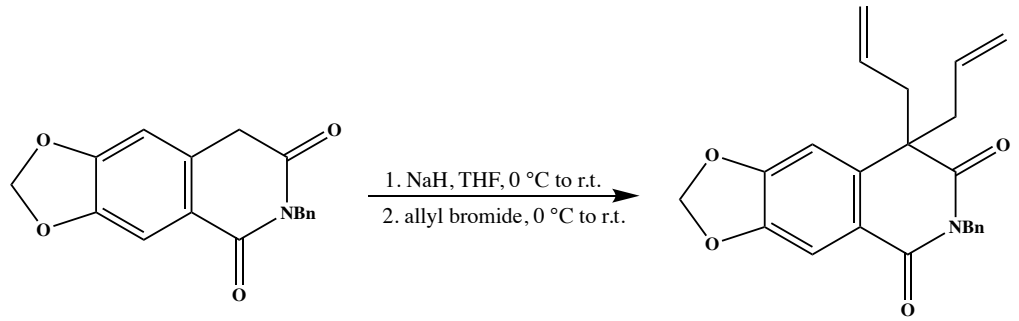
To a suspension of methylenedioxyphenylacetic acid (**162**)(14.72 g, 81.7 mmol, 1 eq) in glacial acetic acid (250 mL) at r.t., was added an excess of *p*-formaldehyde (5.28 g) and conc aq HCl (25 mL). The reaction was then heated at 75 °C for 2 hrs. After cooling to r.t., the solvent was removed under reduced pressure to yield a dark brown oil that was taken up in DCM and filtered through a short pad of silica gel to remove colored impurities. After elution with additional DCM, the filtrate was concentrated to yield the lactone/acid derivatives as a tan solid. This crude material was suspended along with KOH (11.46 g, 204 mmol, 2.5 eq) in pellet form in water (63 mL). The reaction was then stirred at r.t. overnight to yield a dark homogeneous solution, which was cooled to 0 °C as $KMnO_4$ (38.7 g, 245 mmol, 3 eq) was added over 45 min while open to air. The reaction was then allowed to warm to r.t. and stir an additional 2 hrs. The MnO_2 byproduct was then removed by suction filtration and the filter cake washed with water. The filtrate was then concentrated to a volume of approximately 90 mL, ensuring that no potassium chloride has precipitated in the final volume. The solution was then cooled to 0 °C and slowly and carefully acidified with conc HCl to a pH of 2 with strong stirring. The resulting precipitate was collected by suction filtration and dried in a desiccator to yield **170** (9.98 g, 44.5 mmol, 55%) as a tan powder: mp decomp 221 °C. ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 2H), 6.10 (s, 2H), 6.93 (s, 1H), 7.37

(s, 1H), 12.38 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 102.4, 110.3, 112.7, 124.0, 133.5, 146.5, 150.5, 167.8, 172.9.



170 **171**

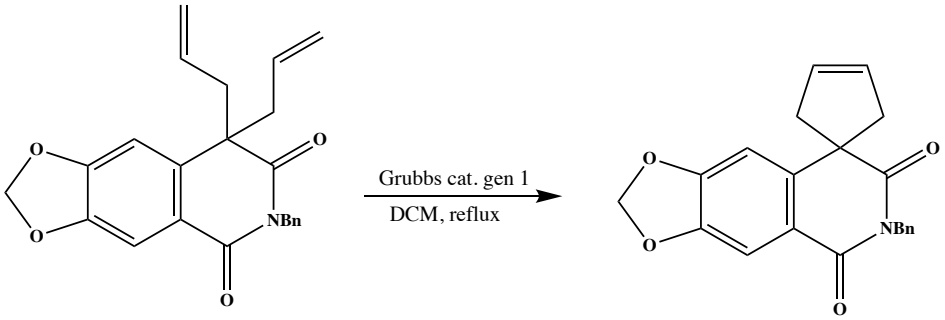
A mixture of **170** (3.91 g, 17.4 mmol, 1 eq) and benzylamine (1.87 g, 17.4 mmol, 1 eq) was irradiated in a microwave reactor at 130 °C for 2.5 hrs. The resulting dark brown oil residue was dissolved in DCM and filtered through a plug of silica gel to remove colored impurities. After further elution with DCM, the filtrate was concentrated to yield **171** (4.01 g, 13.6 mmol, 78%) as a tan solid: mp 124-126 °C. ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 2H), 5.18 (s, 2H), 6.07 (s, 2H), 6.67 (s, 1H), 2.25 – 7.32 (m, 3H), 7.46 (d, 6.8 Hz, 2H), 7.61 (s, 1H)); ^{13}C NMR ($CDCl_3$) δ 36.7, 43.3, 102.1, 106.4, 108.1, 119.5, 127.5, 128.4, 129.0, 130.4, 137.1, 147.8, 152.6, 164.2, 169.9. Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44. Found: C, 69.15; H, 4.45.



171 **172**

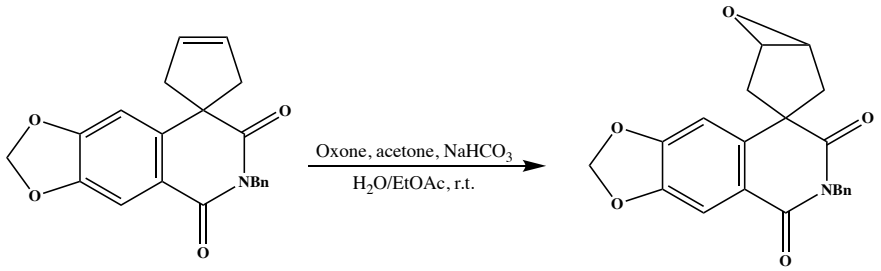
To a suspension of sodium hydride (0.92 g, 60%, 23.0 mmol, 2.5 eq) in anhydrous THF (5 mL) at 0 °C, was added a solution of **171** (2.72 g, 9.21 mmol, 1 eq) in anhydrous THF (22 mL) over 15 min via cannula. The resulting bright orange suspension was then warmed to r.t. and stirred

until hydrogen evolution ceased (30 min). The reaction was again cooled to 0 °C and allyl bromide (1.75 mL, 20.3 mmol, 2.2 eq) was added dropwise over 5 minutes before allowing the reaction to warm again to r.t. After 12 hrs, the reaction was quenched by slow addition of water until homogenous. The solvent was then removed under reduced pressure and the resulting oil was taken up in a 1:1 ratio of EtOAc/water (25 mL). The organic layer was isolated and the aqueous phase further extracted with EtOAc (2 x 5 mL). The combined organic layers were then washed with brine (1 x 13 mL), dried over sodium sulfate and concentrated to yield a blue oil. The oil was then dissolved in DCM and filtered through a plug of silica gel to remove colored impurities. Upon elution with additional DCM, the filtrate was concentrated to yield a colorless oil. The oil was then partitioned between a 3:1 ratio of acetonitrile/hexanes (20). The acetonitrile was isolated and the hexanes layer was diluted with additional hexanes (15) prior to additional extractions with acetonitrile (2 x 5). The combined acetonitrile layers were concentrated under reduced pressure to yield **172** (3.22 g, 8.58 mmol, 93%) as a light yellow oil that crystallized on standing: mp 79-81 °C. ^{1}H NMR ($CDCl_3$) δ 2.56 (dd, J = 13.4, 6.8 Hz, 2H), 3.00 (dd, 13.4, 7.6 Hz, 2H), 4.78 – 4.89 (m, 4H), 5.13 – 5.21 (m, 4H), 6.10 (s, 1H), 7.26 (m, 3H), 7.41 (d, 6.8 Hz, 2H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 43.6, 46.5, 52.8, 102.1, 104.8, 107.5, 119.5, 120.7, 127.3, 128.2, 128.8, 131.4, 137.1, 137.4, 147.4, 153.1, 163.4, 174.7. Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64. Found: C, 73.33; H, 5.41.



172 **173**

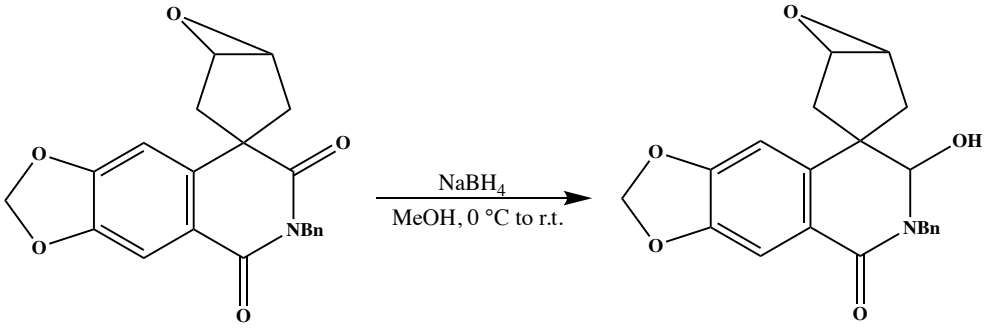
To a solution of **172** (3.22 g, 8.58 mmol, 1 eq) in DCM (113 mL) at r.t., was added Grubbs generation 1 catalyst (0.28 g, 4 mol%, 0.03 mmol). The reaction was then refluxed for 1.5 hrs. Upon cooling to r.t., the reaction was concentrated to a small volume before being filtered directly through a plug of silica gel to remove catalyst and colored impurities. Upon further elution with DCM, the filtrate was concentrated to yield **173** (2.97 g, 8.55 mmol, 100%) as a white crystalline solid: mp 123-125 °C. ^{1}H NMR ($CDCl_3$) δ 2.72 (d, J = 15.2 Hz, 2H), 3.29 (d, J = 15.2 Hz, 2H), 5.20 (s, 2H), 5.82 (s, 2H), 6.06 (s, 2H), 6.81 (s, 1H), 7.22 – 7.35 (m, 3H), 7.46 (d, 8 Hz), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 43.7, 51.0, 51.1, 102.0, 104.1, 107.0, 117.3, 127.4, 128.4, 128.6, 128.8, 137.2, 143.2, 147.4, 153.4, 163.7, 177.6. Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93. Found: C, 72.71; H, 4.86.



173 **174**

To a biphasic suspension of **173** (2.97 g, 8.55 mmol, 1 eq), an excess of powdered $NaHCO_3$ (8.98 g) and acetone (15 mL) in a 2:1 ratio of EtOAc/water (30 mL) at r.t., was added a solution of Oxone (15.79 g, 25.6 mmol, 3 eq) in water (95 mL) dropwise over 1 hr with rapid stirring. After

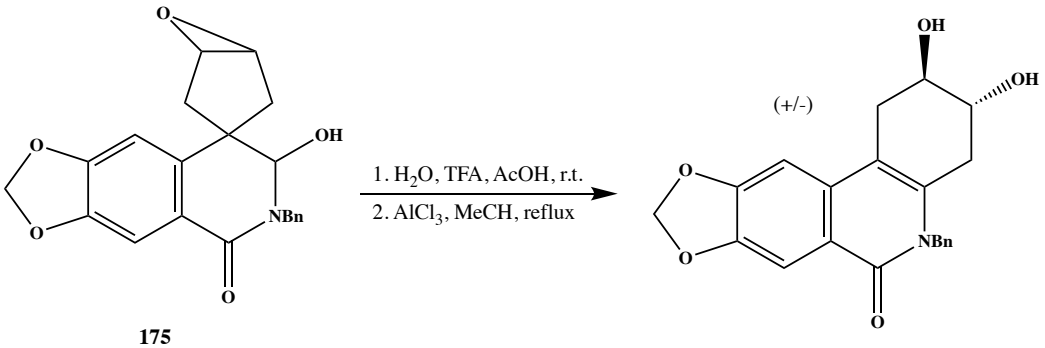
12 hrs, the reaction was diluted with additional EtOAc (15 mL) before being filtered through a pad of celite to remove solids. The organic layer was then isolated and the aqueous phase further extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (1 x 25 mL), dried over sodium sulfate and concentrated. The resulting solid was triturated with a small volume of hot methanol. The suspension was then cooled to 0 °C and filtered to yield **174** (2.65 g, 7.28 mmol, 85%) as a white powder: mp 150-152 °C. ^{1}H NMR ($CDCl_3$) δ 2.34 (d, J = 15.0 Hz, 2H), 2.75 (dd, J = 15.0, 1.6 Hz, 2H), 3.78 (d, 1.6 Hz, 2H), 5.20 (s, 2H), 7.27 – 7.46 (m, 5H), 7.66 (dt, J = 5.6, 1.6 Hz, 1H), 7.75 (dd, J = 5.6, 1.6 Hz), 8.19 (dd, J = 5.6, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 43.9, 44.3, 53.8, 60.5, 102.1, 107.0, 108.4, 118.3, 127.6, 128.5, 128.7, 137.0, 141.6, 147.2, 153.1, 163.5, 177.4. Anal. Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72. Found: C, 68.94; H, 4.71.



174 **175**

To a stirring suspension of **174** (2.46 g, 6.77 mmol, 1 eq) in methanol (43 mL) at 0 °C, was added sodium borohydride (0.38 g, 10.2 mmol, 1.5 eq) in pellet form. After 5 min the reaction was brought to r.t. and stirred for an additional 12 hrs. The resulting suspension was then cooled to 0 °C and quenched by slow addition of ice water (50 mL) with strong stirring. The resulting precipitate was collected by suction filtration and dried in a desiccator to yield **175** (2.31 g, 6.32 mmol, 94%) as a white powder: mp 164-166 °C. ^{1}H NMR ($CDCl_3$) δ 1.60 (dd, J = 15.2, 1.4 Hz, 1H), 1.86 (d, J = 15.2 Hz, 1H), 2.13 (dd, J = 15.8, 1.4 Hz, 1H), 2.23 (d, J = 9.6 Hz, 1H), 2.64 (d, J = 15.8 Hz, 1H), 3.38 (s, 1H), 3.62 (s, 1H), 4.27 (d, J = 15.6 Hz, 1H), 4.44 (d, J = 9.6 Hz, 1 H), 5.36

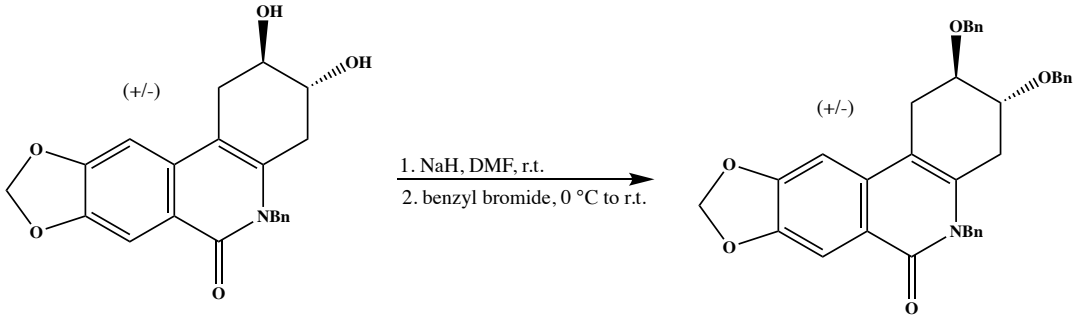
(d, 15.6 Hz, 1H), 6.02 (s, 1H), 6.99 (s, 1H), 7.28 – 7.40 (m, 5H), 7.57(s, 1H); ^{13}C NMR ($CDCl_3$) δ 36.6, 41.3, 48.3, 48.4, 57.3, 58.1, 88.0, 101.7, 108.2, 109.0,121.4, 127.9, 128.9 (two signals), 137.1, 139.4, 146.8, 151.1, 163.0. Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24. Found: C, 67.71; H, 5.20.



175 **176**

To a solution of **175** (3.63 g, 9.93 mmol, 1 eq) in glacial acetic (47 mL) at r.t., was added trifluoroacetic acid (0.08 mL) and water (4.26 mL). The reaction was then stirred at r.t. for 12 hrs, prior to the solvent being removed under reduced pressure. The resulting residue was then dissolved in methanol (87 mL) and an excess of powdered K_2CO_3 (8.43 g) was added. The suspension was then stirred at r.t. for 4 hrs before the solvent was removed. The resulting residue was then suspended in boiling EtOAc (50 mL) for 2 hrs before the solids were removed by hot filtration. Upon rinsing the filter cake with additional EtOAc (25 mL), the filtrate was removed to produce the triol intermediate as a white foam. The intermediate was then dissolved in anhydrous acetonitrile (33 mL) and aluminum chloride (1.46 g, 10.9 mmol, 1.1 eq) was added all at once. The reaction was then refluxed for 1 hr, at which point a white precipitate had formed. Upon cooling to r.t, the reaction was quenched by slow addition of 3M aqueous HCl (75 mL) before the acetonitrile was removed under reduced pressure. The aqueous suspension was then extracted with EtOAc (3 x 33 mL). The combined organic layers were then dried over sodium sulfate and concentrated. The resulting residue was then suspended in methanol (87 mL) along with an excess

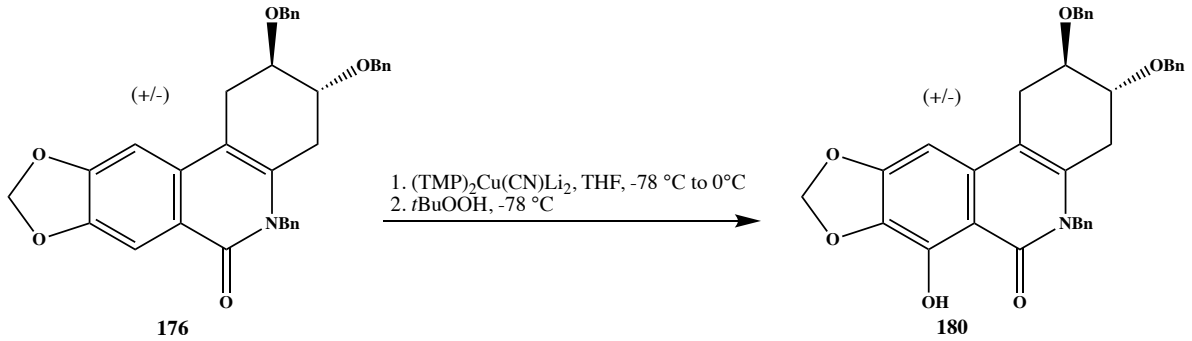
of powdered K_2CO_3 (8.43 g). The reaction was then refluxed for 1 hr before being cooled to r.t. and the solvent removed under reduced pressure. The flask was then cooled to 0 °C and 3M aqueous solution (75 mL) was added very slowly with strong stirring to neutralize and dissolve the salt bi-products. The remaining solids were collected by suction filtration and dried in a desiccator to yield **176** (3.23 g, 8.84 mmol, 89%) as a white powder: mp decomp 165 °C. ^{1}H NMR (DMSO-*d*$_6$) δ 2.51 (m, 2H), 2.91 (m, 2H), 3.70 (m, 2H), 4.94 (d, J = 3.6 Hz, 1H), 5.00 (d, 4 Hz, 1H), 5.36 (AB quartet, J = 9.2 Hz, 2H), 6.18 (s, 1H), 7.11 (d, J = 7.2 Hz, 1H), 7.15 (s, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.61 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$) δ 30.6, 33.0, 46.2, 68.2, 68.6, 101.0, 102.4, 105.4, 107.6,119.5, 126.5, 127.3, 129.1, 134.3, 134.4, 138.2, 147.1, 152.4, 161.3. Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24. Found: C, 68.53; H, 5.16.



176 **177**

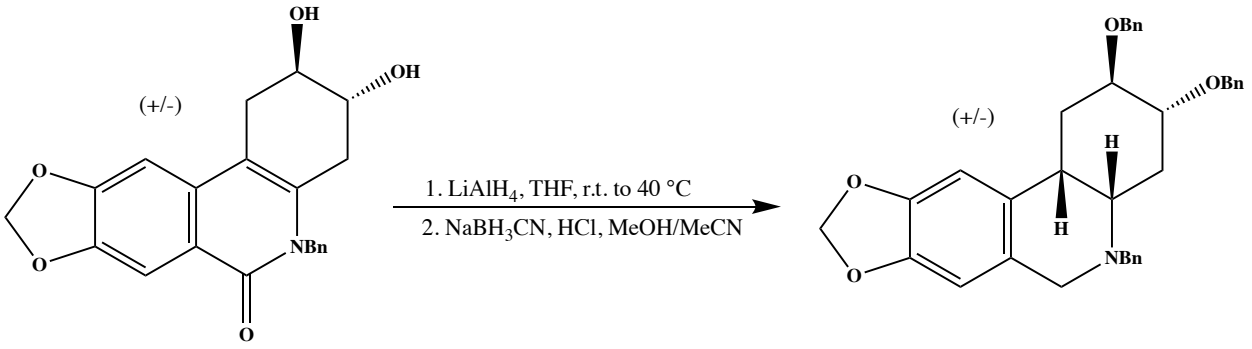
To a suspension of **176** (3.67 g, 10.0 mmol, 1 eq) in anhydrous DMF (34 mL) at r.t., was added sodium hydride (0.96 g, 60%, 24.0 mmol, 2.4 eq) all at once. The suspension was then stirred until hydrogen evolution ceased (30 min). The resulting solution was then cooled to 0 °C and benzyl bromide (2.86 mL, 24.0 mmol, 2.4 eq) was added all at once. The reaction was then brought to r.t. and stirred an additional 5 hrs before being quenched by slow addition of saturated aqueous ammonium chloride solution (40 mL). The solvent was then concentrated under reduced pressure at 35 °C. The resulting residue was then triturated with water and the remaining solids collected by suction filtration and dried in a desiccator. The crude material was then recrystallized

from methanol to yield **177** (4.60 g, 8.43 mmol, 84%) as white prisms: mp 148-149 °C. ^{1}H NMR ($CDCl_3$) δ 2.81 (m, 2H), 3.04 (m, 2H), 3.85 (m, 1H), 3.94 (m, 1H), 4.47 (AB quartet, J = 12 Hz, 2H), 4.70 (s, 2H), 5.30 (d, J = 15.2 Hz, 1H), 5.57, (d, J = 15.2 Hz, 1H), 6.10 (s, 2H), 6.99 (s, 1H), 7.15 – 7.35 (m, 15H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 29.9, 46.6, 71.6, 71.9, 74.4, 74.5, 100.1, 101.7, 106.5, 107.5, 120.2, 126.2, 127.1, 127.5, 127.6, 12772 (two signals), 128.4, 128.5, 128.8, 132.8, 134.1, 137.3, 138.1, 138.4, 147.1, 152.2, 162.1. Anal. Calcd for $C_{35}H_{31}NO_5$: C, 77.05; H, 5.73. Found: C, 76.78; H, 5.60.



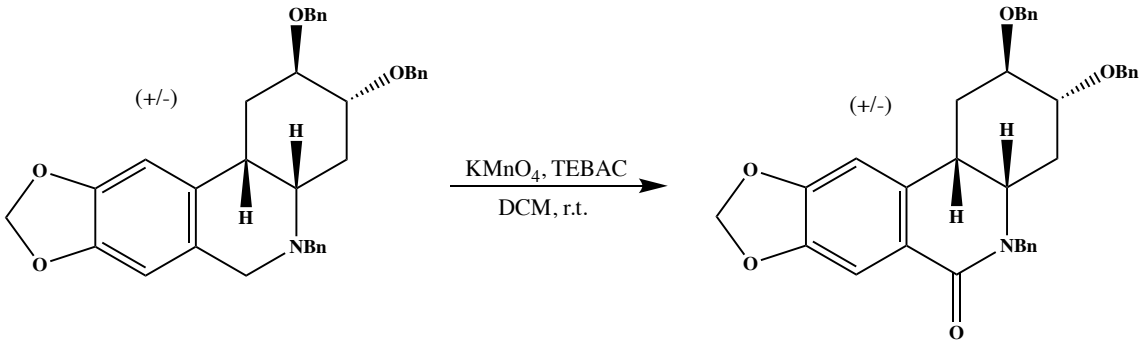
To a solution of 2,2,6,6-tetramethylpiperidine (0.34 mL, 2.00 mmol, 4 eq) in anhydrous THF (2 mL) at -78 °C, was added 2.5M *n*-butyl lithium solution (0.80 mL, in hexanes, 2.00 mmol, 4 eq) all at once. This solution was then stirred at 0 °C for an additional 30 min prior to being added to a suspension of copper cyanide (0.09 g, 1.00 mmol, 2 eq) in anhydrous THF dropwise over 5 min at -78 °C. This suspension was then stirred another 30 min at 0 °C before being added dropwise to a solution of **176** (0.27 g, 0.50 mmol, 1 eq) in anhydrous THF (1.5 mL) at -78 °C. The reaction turned purple at this stage and it was stirred an additional 2 hrs at 0 °C at which time the color deepened to a darker shade. Upon cooling again to -78 °C, a solution of *t*-butylhydroperoxide (0.23 mL, 1.25 mmol, 2.5 eq) was then added dropwise over 5 min. After stirring at this temperature for another 30 min, the reaction was carefully quenched with a 1:1 mixture of sat. aq sodium thiosulfate and sat. aq ammonium chloride solutions (15 mL). The biphasic mixture was

then diluted with EtOAc (5 mL) and the organic layer was isolated. The aqueous layer was then extracted with additional EtOAc (2 x 5 mL). The combined organic layer were washed with brine (1 x 15 mL), dried over sodium sulfate, and concentrated to yield **180** (0.22 g, 0.39 mmol, 80%) in its crude form as a colorless amorphous solid.



177 **178**

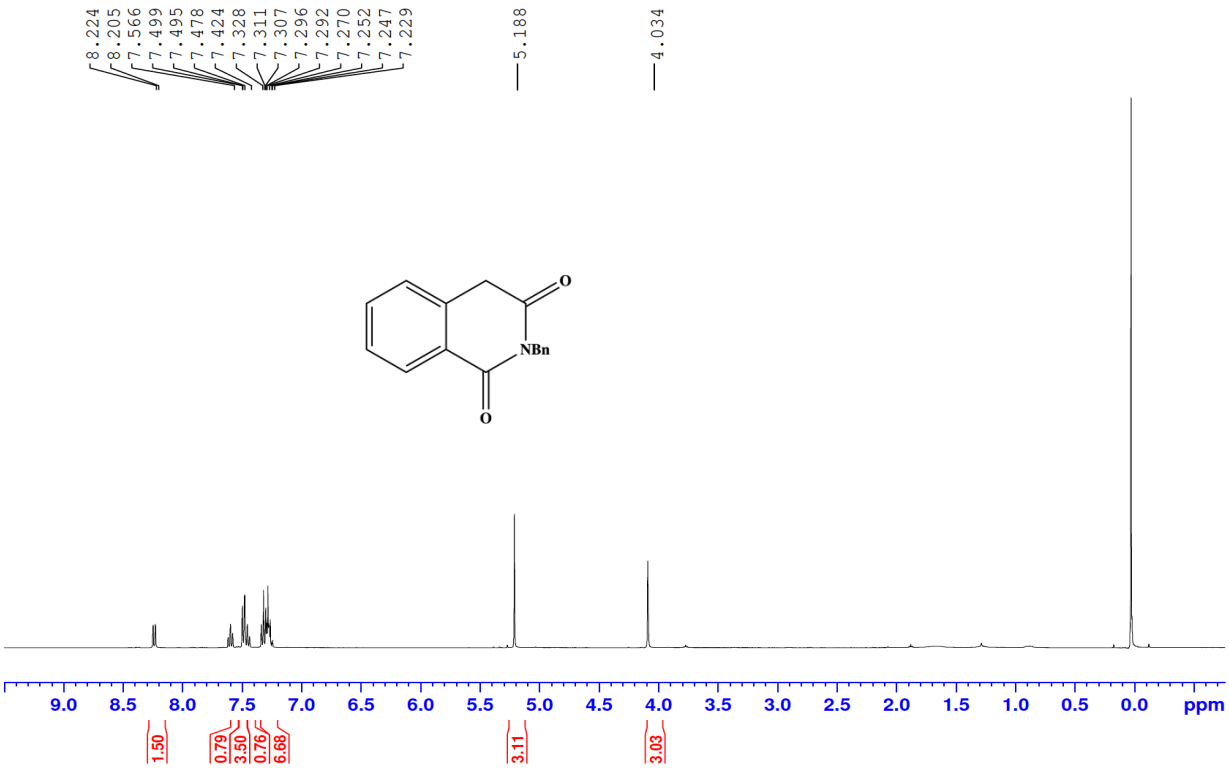
To a solution of **177** (2.37g, 4.34 mmol, 1 eq) in anhydrous THF (13 mL) at r.t., was added powdered $LiAlH_4$ (0.17 g, 4.34 mmol, 1 eq). The resulting suspension was then stirred at 40 °C for 2 hrs. Upon cooling to r.t., the reaction was quenched by the dropwise addition of ice water until no further bubbles were observed. Sodium sulfate was the added and the resulting suspension was gravity filtered and the filter cake rinsed with additional THF. The filtrate was then concentrated and the resulting crude intermediate was suspended in a 1:1 mixture of MeOH/MeCN (26 mL). To this suspension was added an excess of $NaBH_3CN$ (1.64 g) and the mixture was slowly acidified to a pH of 3 with 3M aq HCl while stirring at r.t.. After 20 min, the reaction was quenched with 2M aq NaOH (50 mL). The resulting mixture was then extracted with EtOAc (4 x 13 mL). The combined organic layers were then washed with brine (1 x 13 mL), dried over sodium sulfate and concentrated to yield a dark red oil. Purification by column chromatography (silica gel, hexanes/EtOAc, 4:1) yielded **178** (0.69 g, 1.29 mmol, 30%) as a yellow amorphous semisolid.



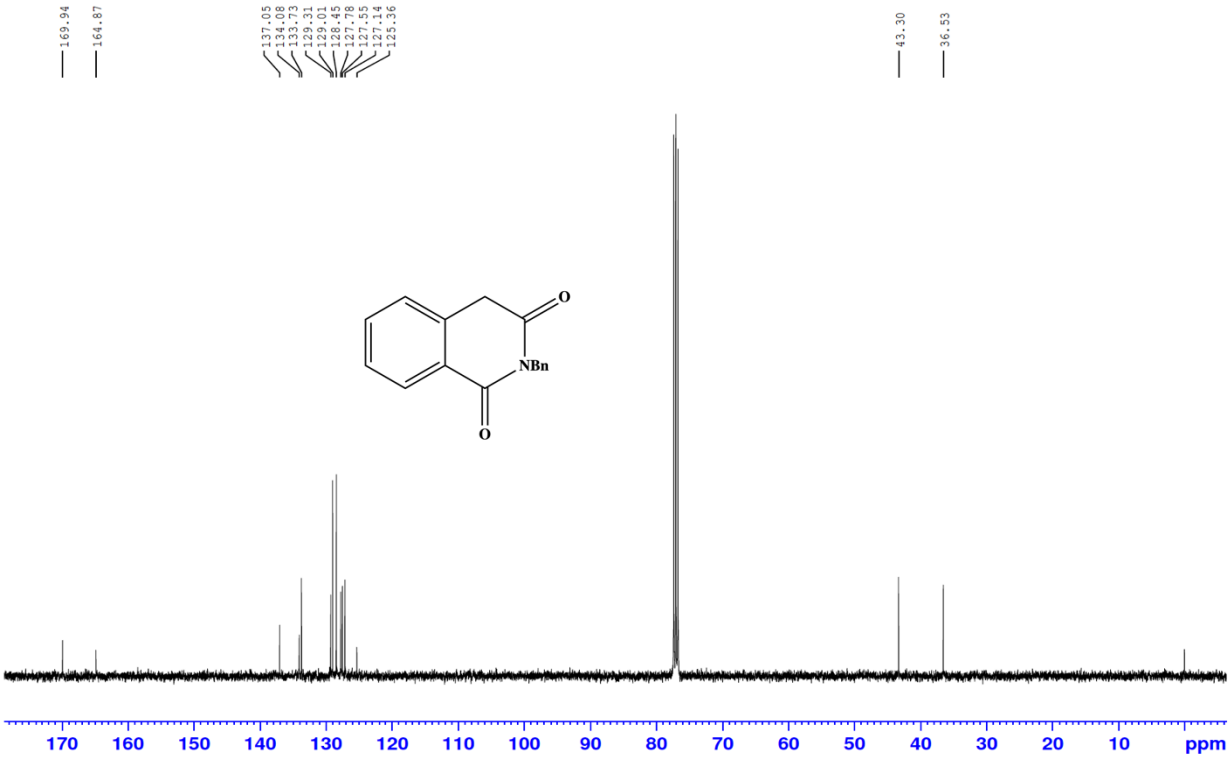
178 **179**

To a stirring solution of **178** (0.65 g, 1.22 mmol, 1 eq) in DCM (11 mL) at r.t., was added benzyltriethylammonium chloride (0.28 g, 1.22 mmol, 1 eq) and $KMnO_4$ (0.58 g, 3.65 mmol, 3 eq) all at once. After 25 min, the reaction was quenched with sat. aq sodium bisulfite sol (33 mL) as well as diluted with additional DCM (66 mL). Upon the color dissipating, the organic layer was isolated, dried over sodium sulfate, and concentrated. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to yield **179** (0.55 g, 1.00 mmol, 82%) as a white crystalline solid: mp 138-139 °C. ^{13}C NMR ($CDCl_3$) δ 30.3, 30.8, 36.3, 48.4, 53.5, 55.4, 72.3, 73.1, 80.0, 101.6, 104.8, 109.0, 123.2, 127.5, 127.6, 127.9, 128.2, 128.4, 128.5, 128.7 (two signals), 133.0, 137.9, 138.5, 138.7, 146.7, 151.3, 163.1.

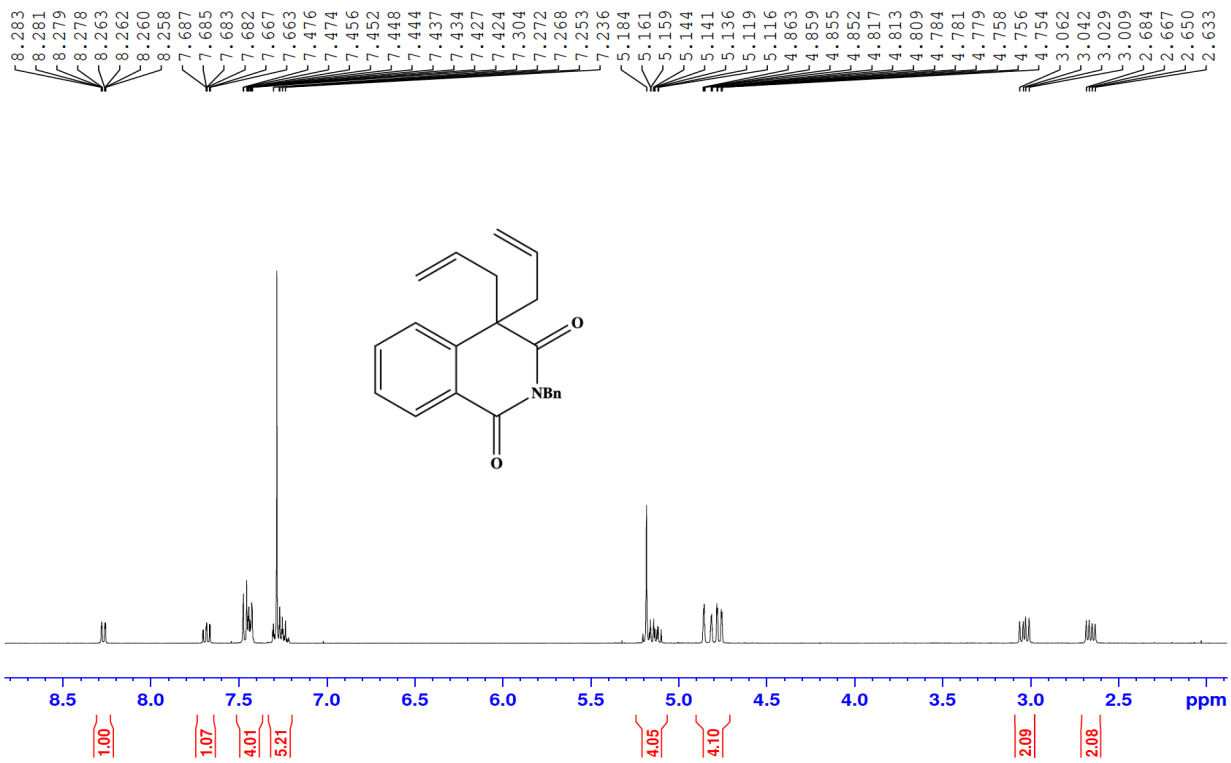
Appendix 1



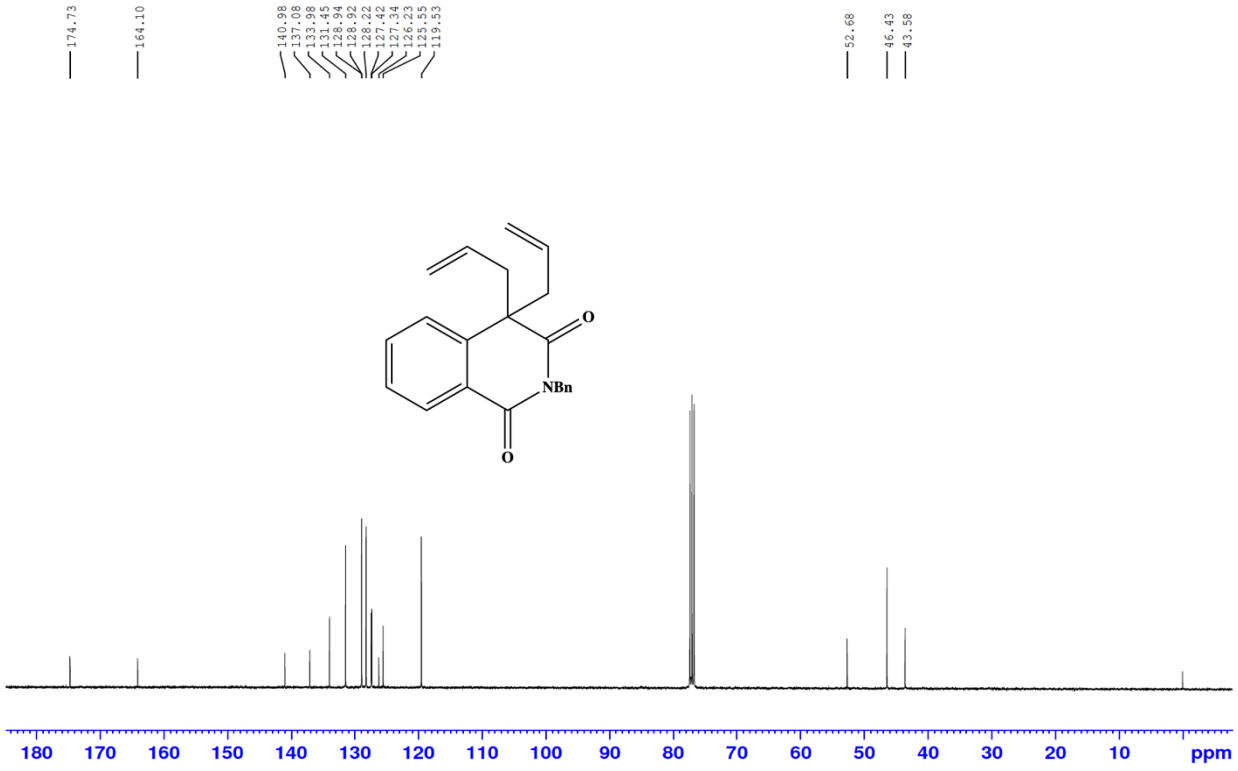
^{1}H NMR of 75



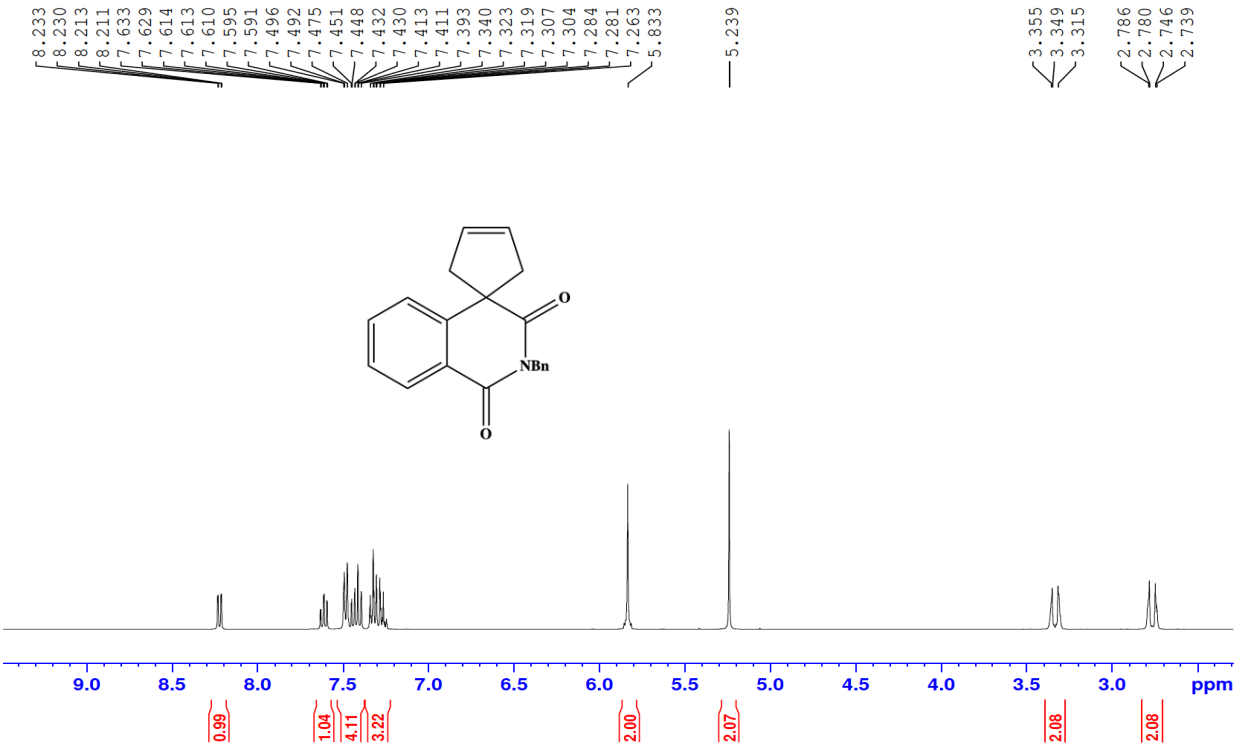
^{13}C NMR of 75



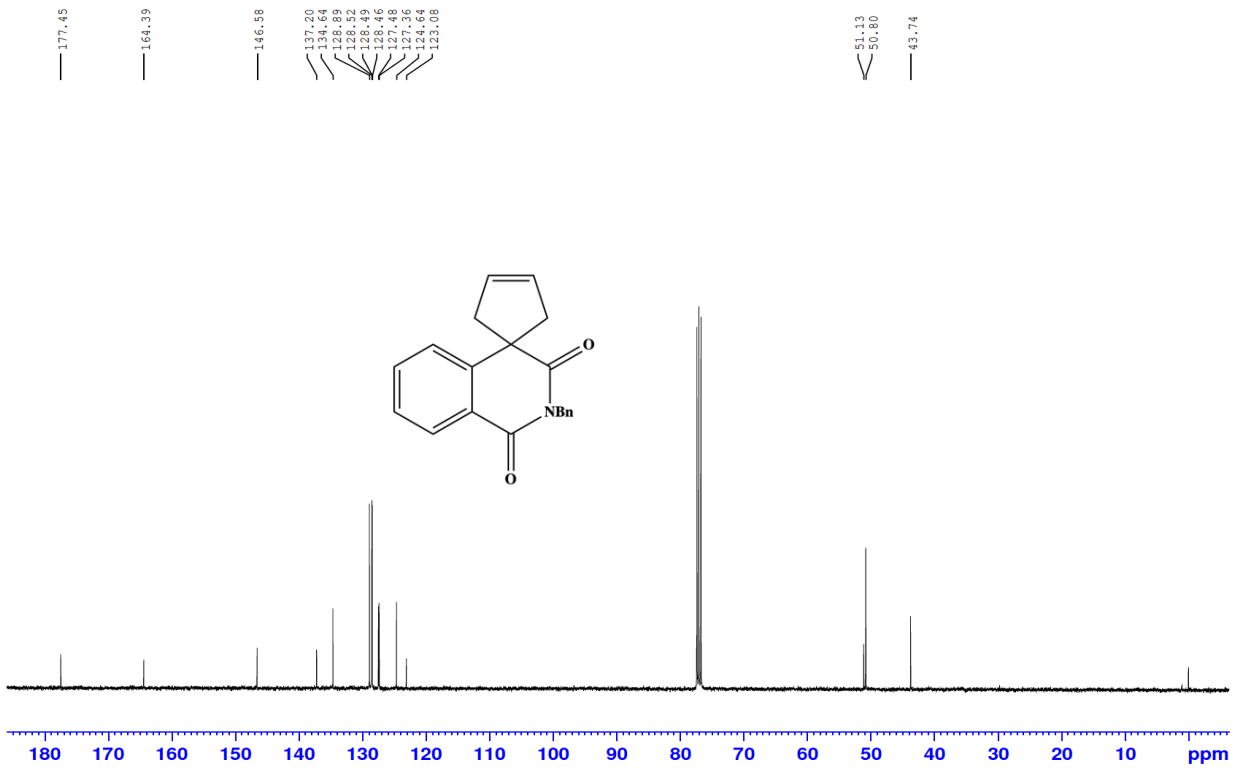
^{1}H NMR of 76



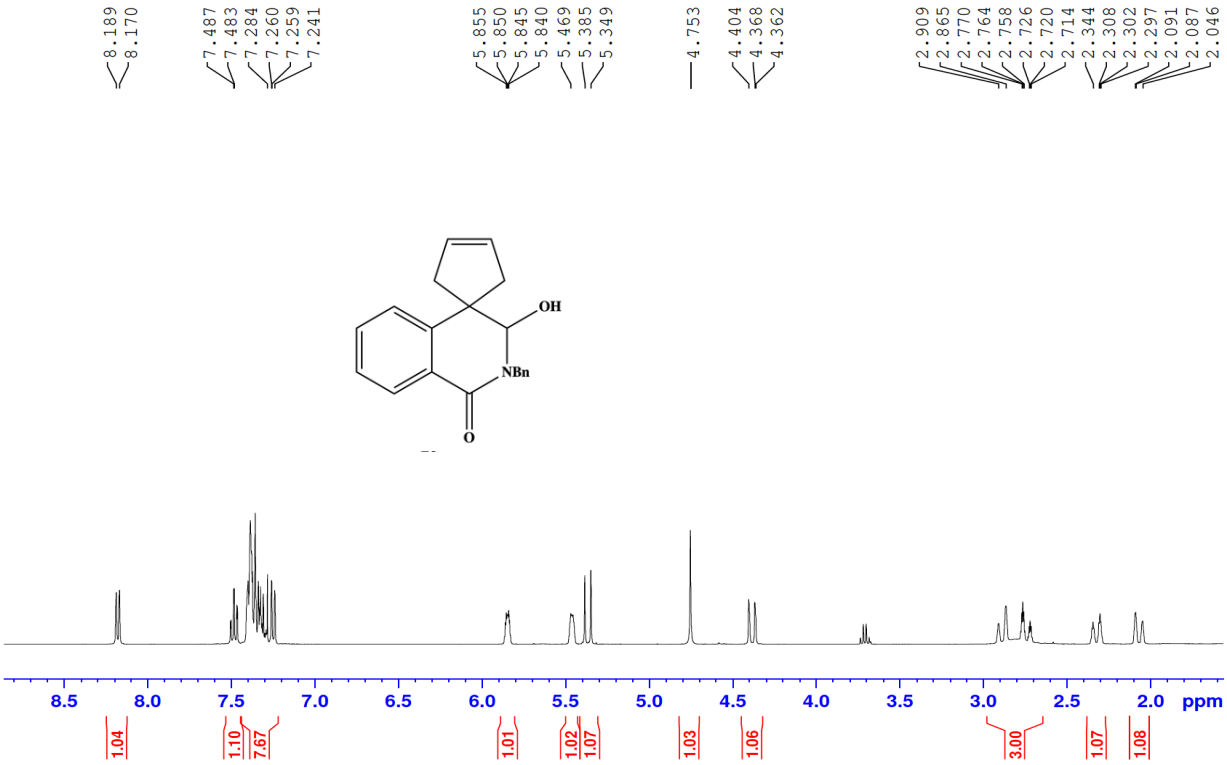
^{13}C NMR of 76



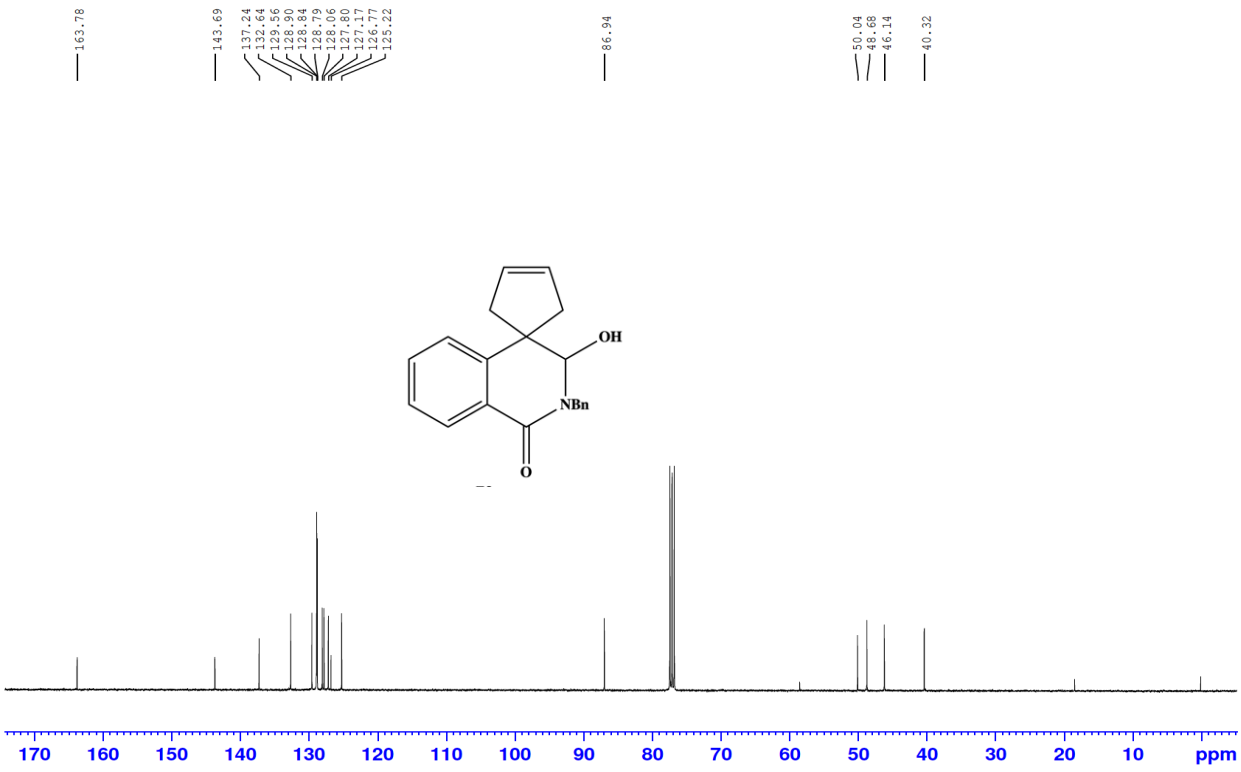
^{1}H NMR of 77



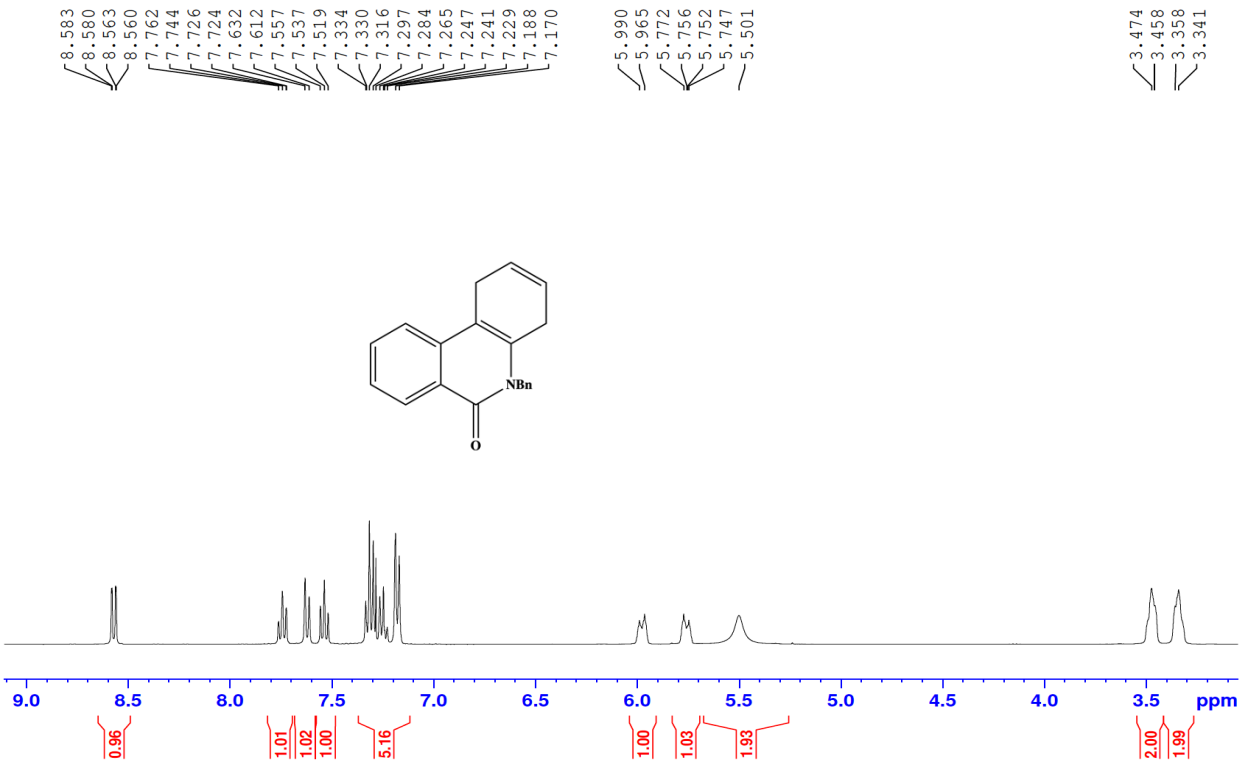
^{13}C NMR of 77



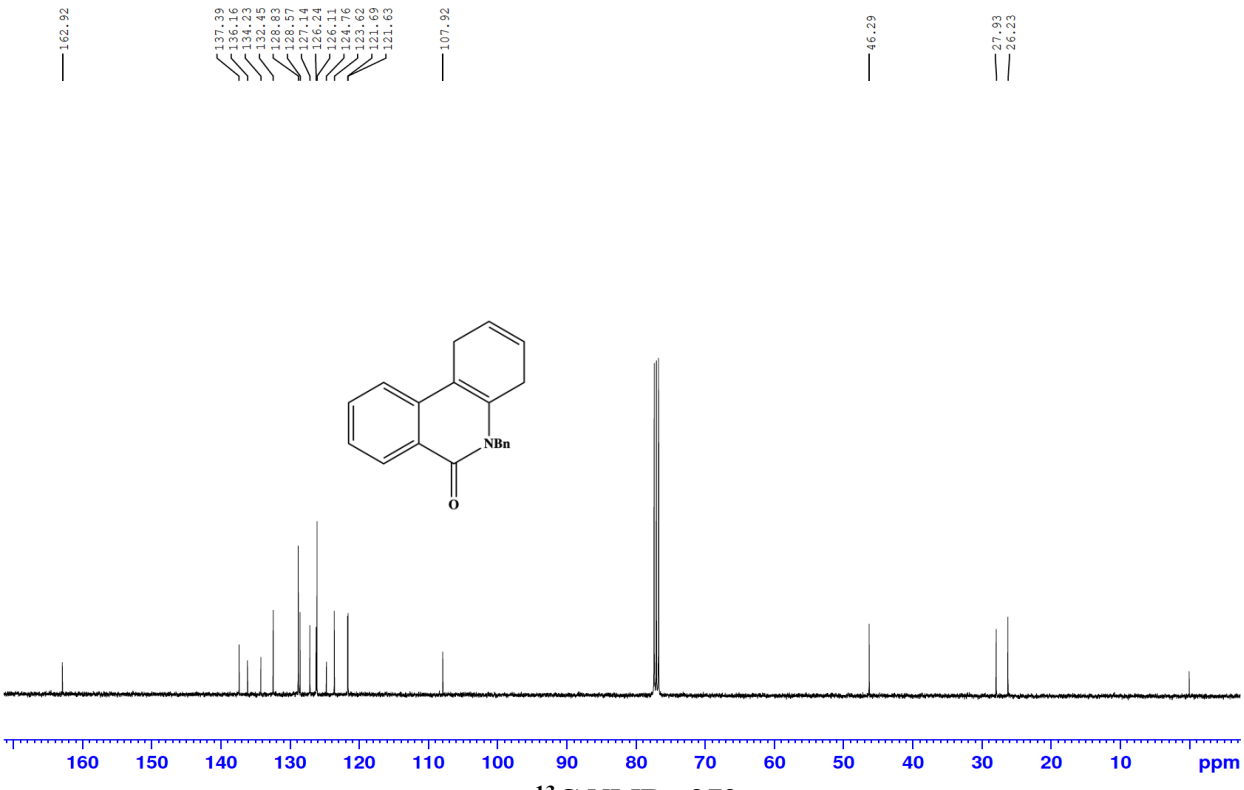
^{1}H NMR of 78



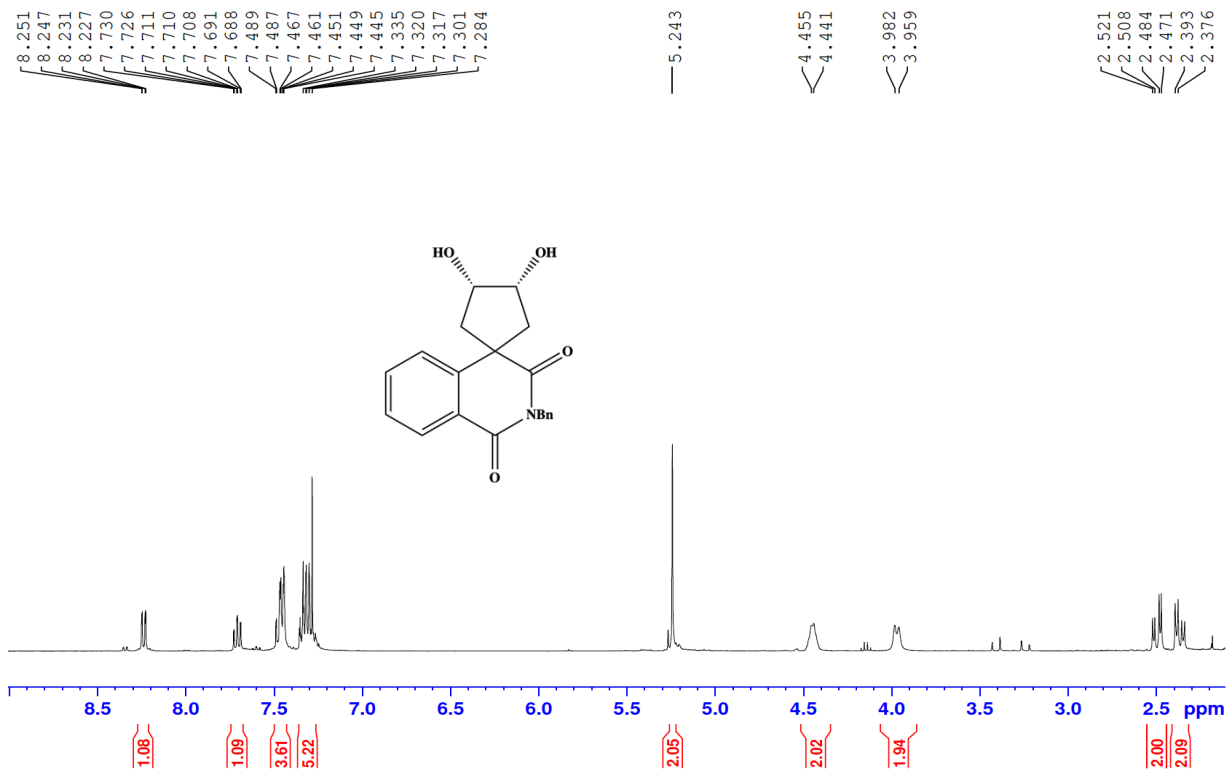
^{13}C NMR of 78



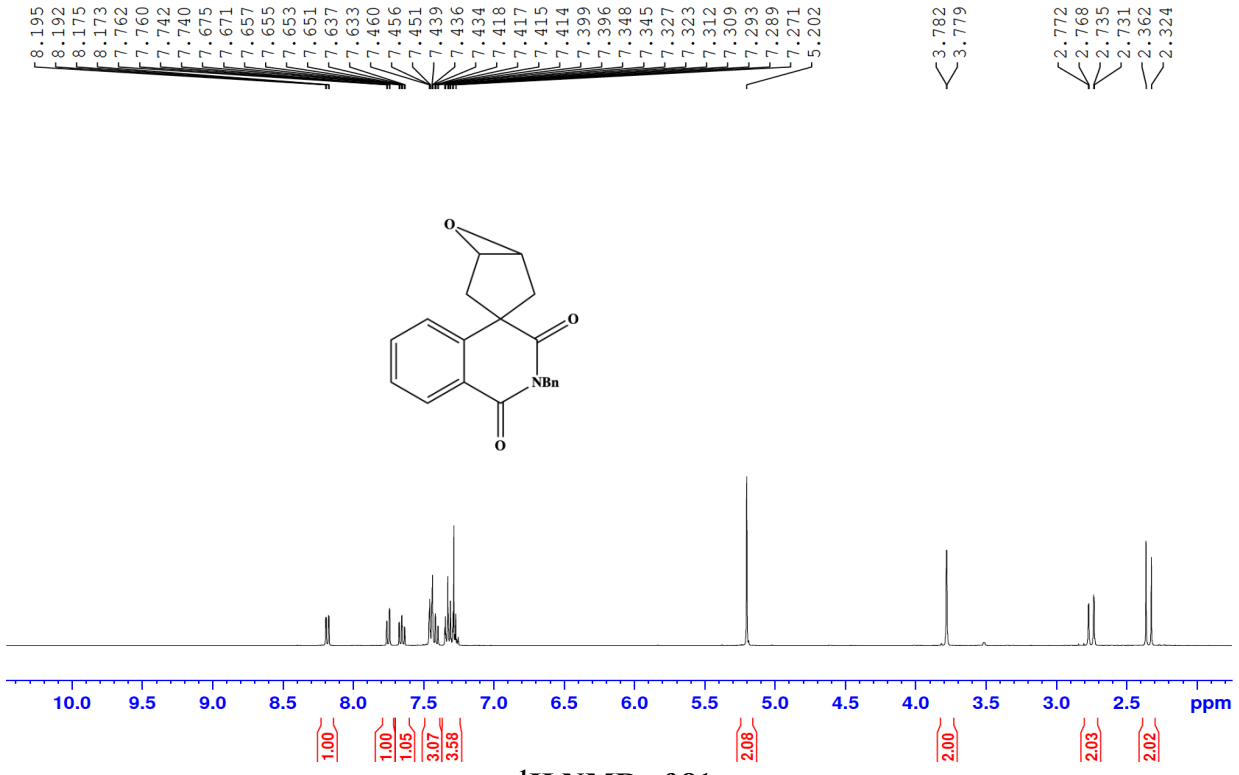
^{1}H NMR of 79



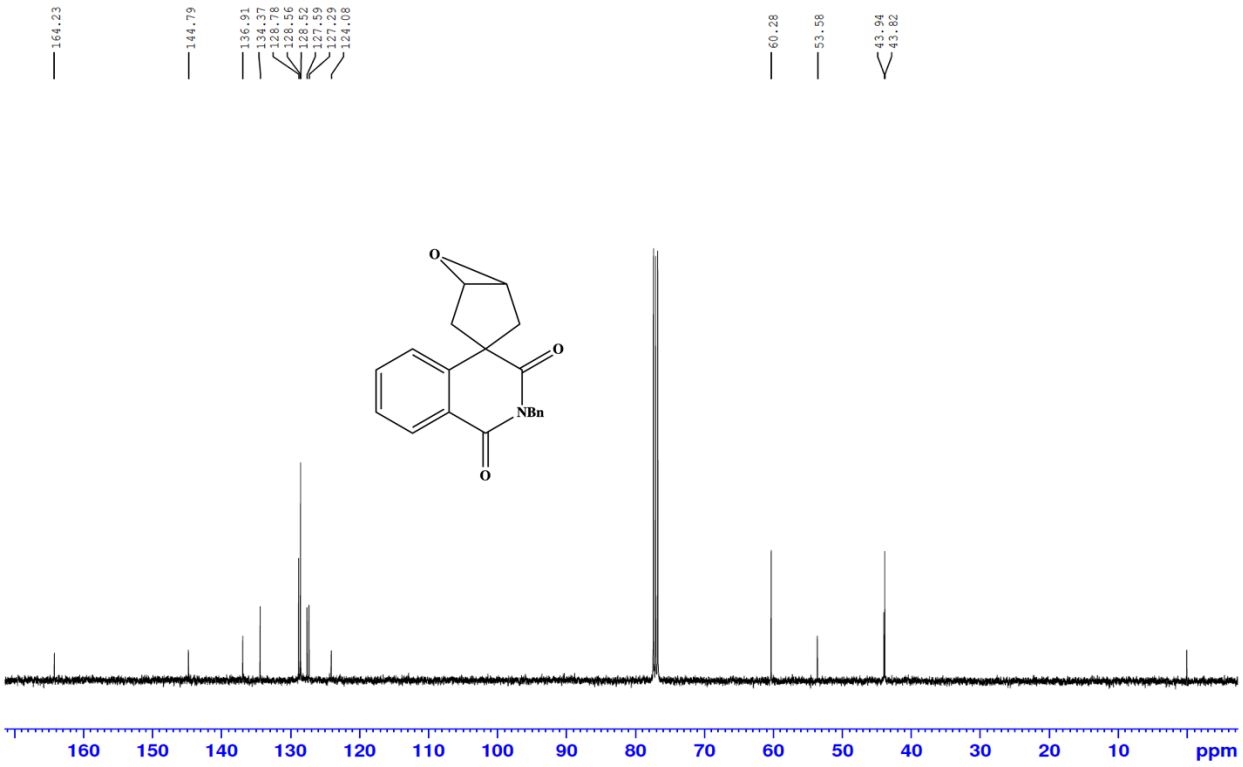
^{13}C NMR of 79



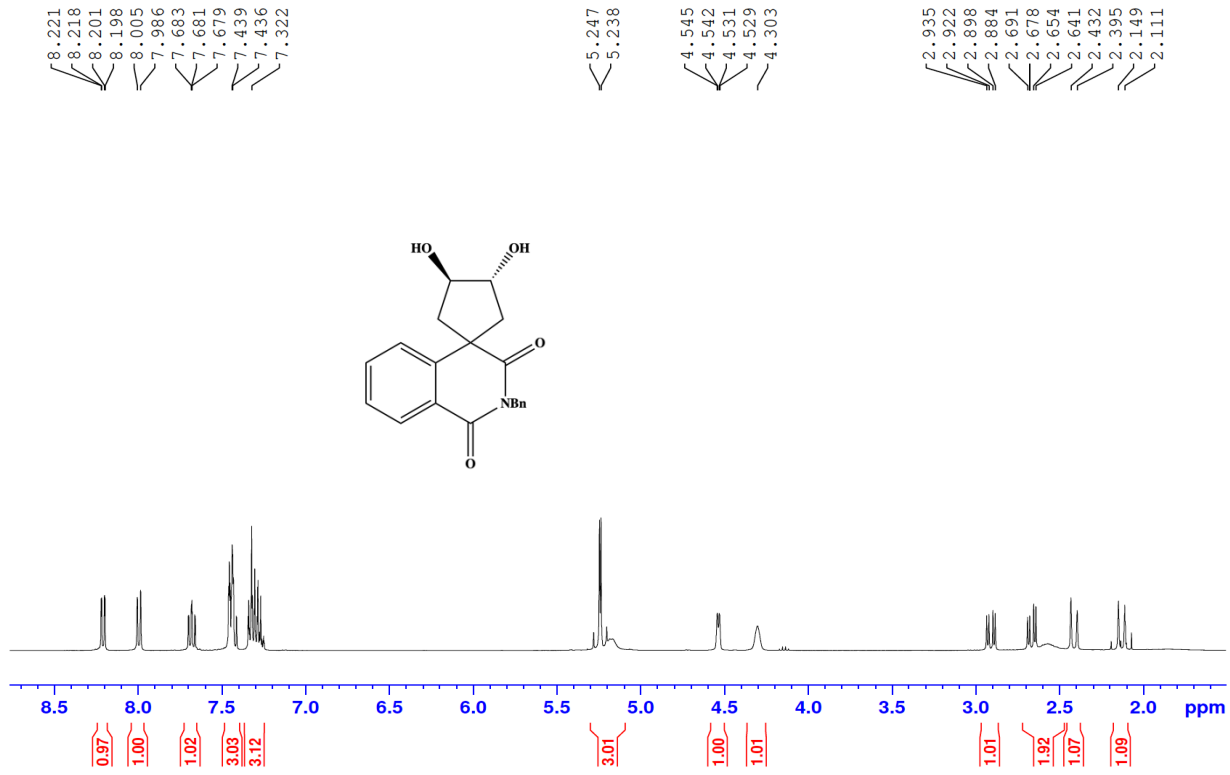
^{1}H NMR of 83



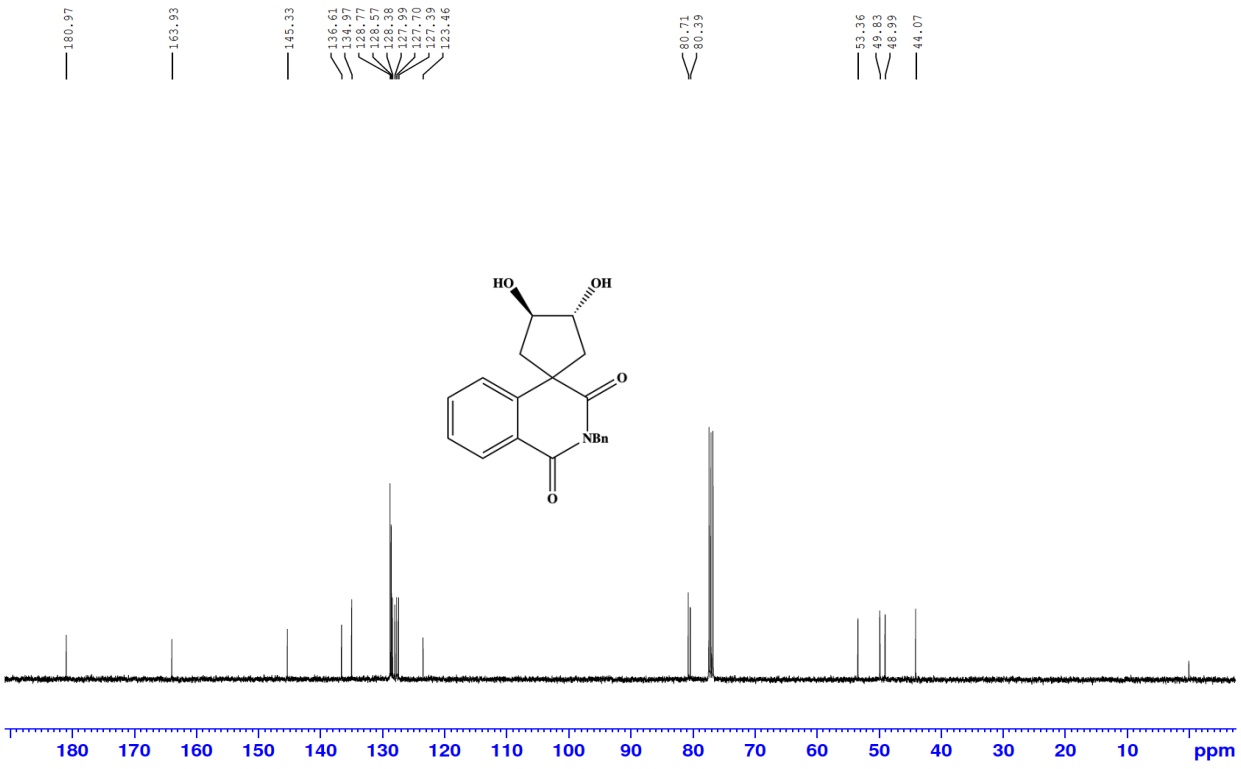
^{1}H NMR of 81



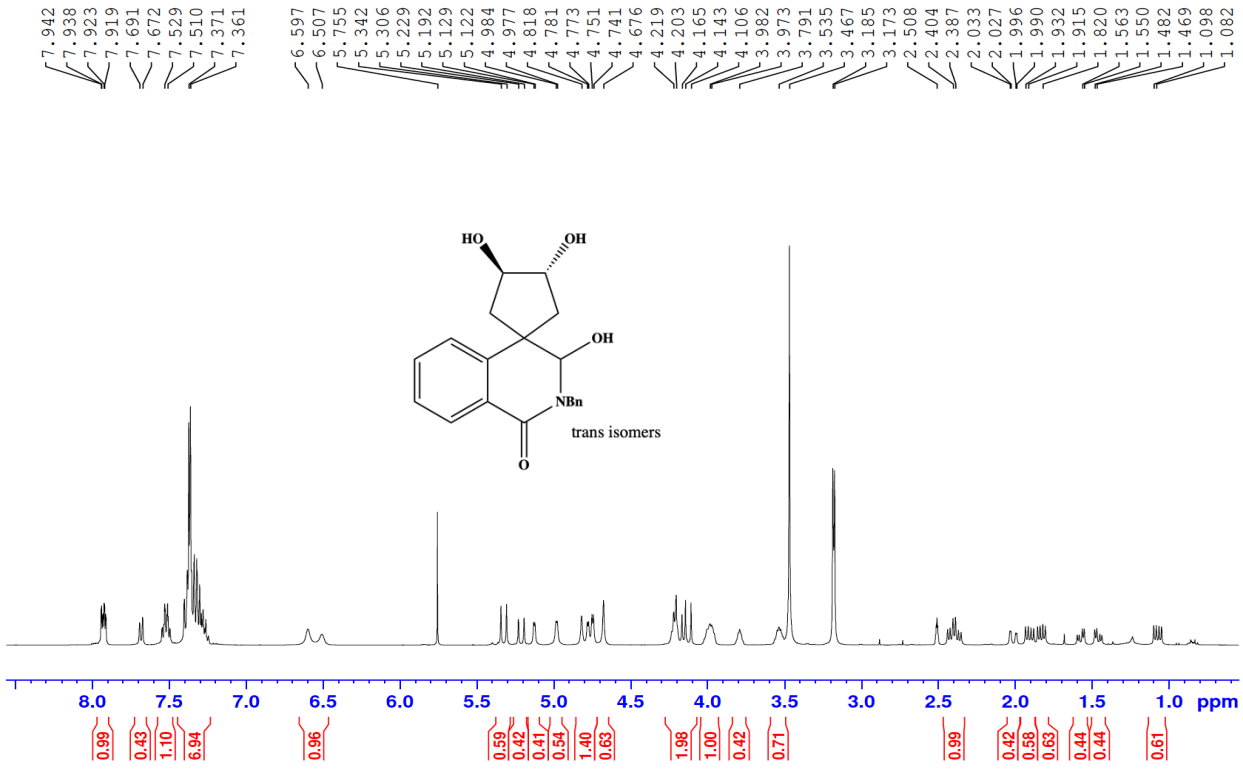
^{13}C NMR of 81



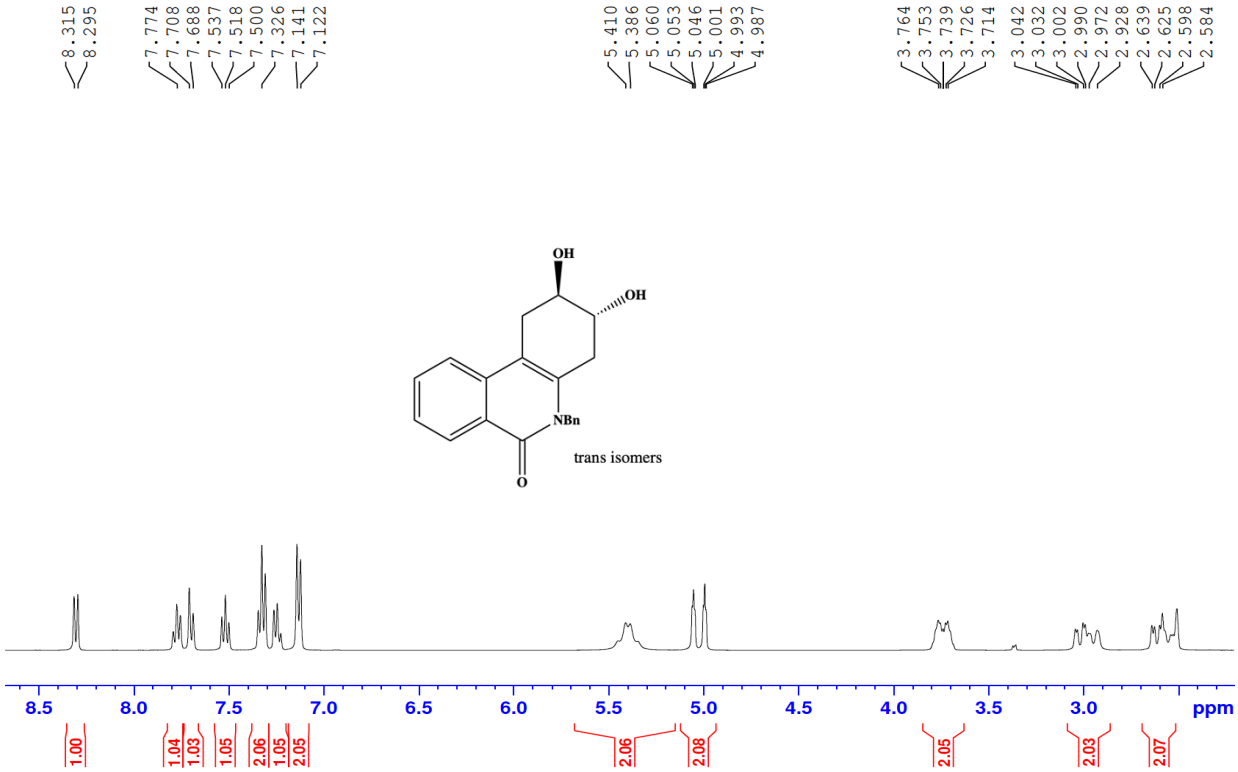
^{1}H NMR of 82



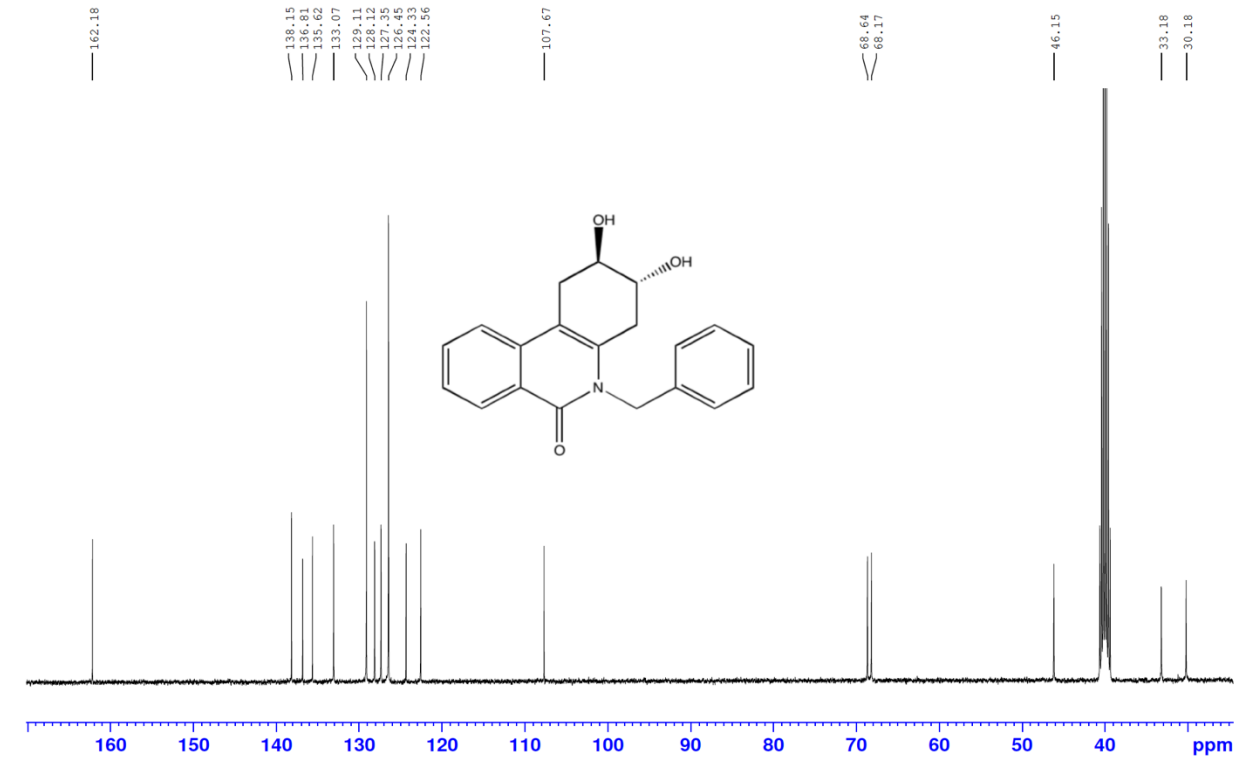
^{13}C NMR of 82



^{1}H NMR of 89



^{1}H NMR of 90



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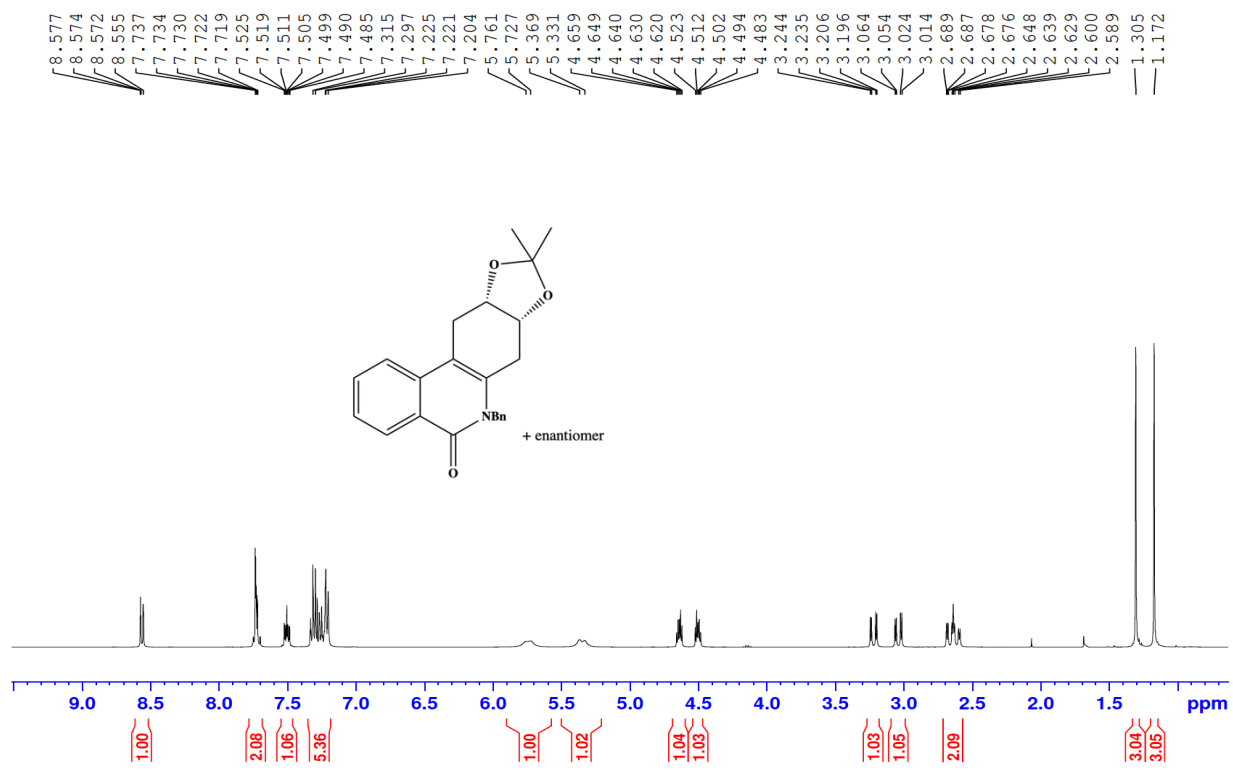
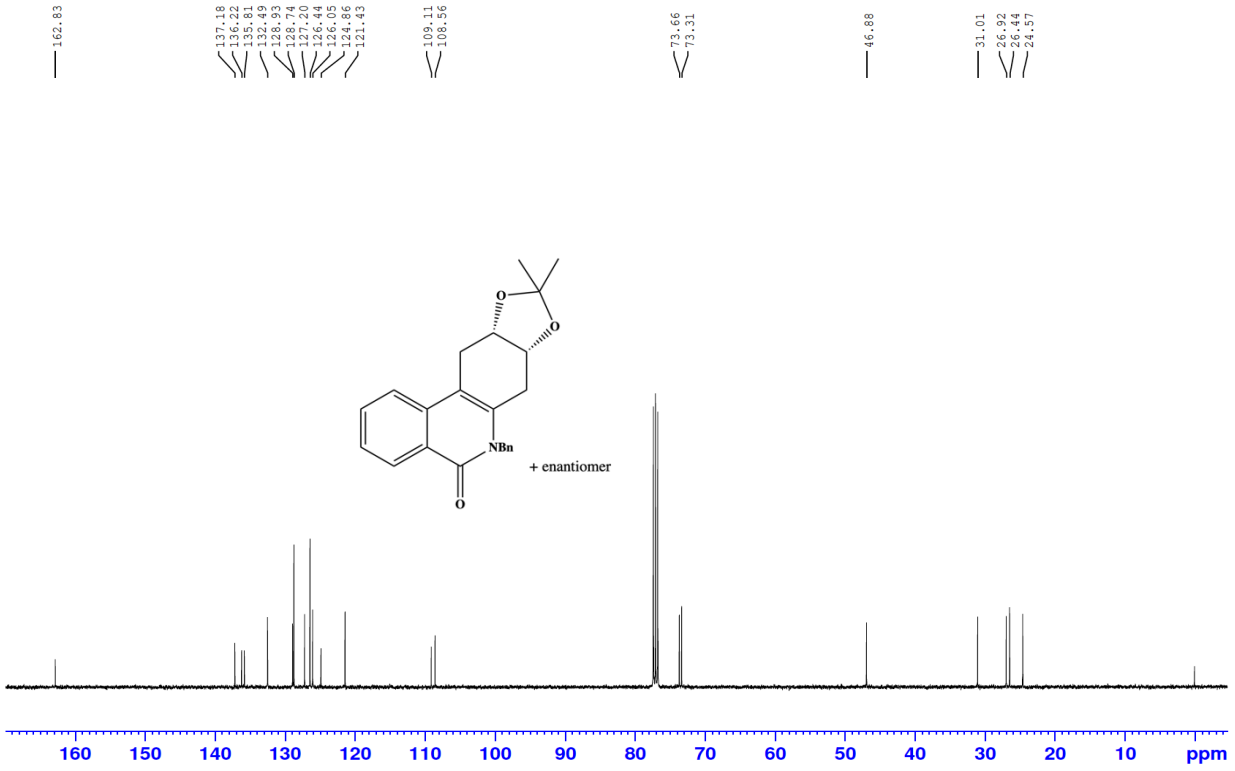
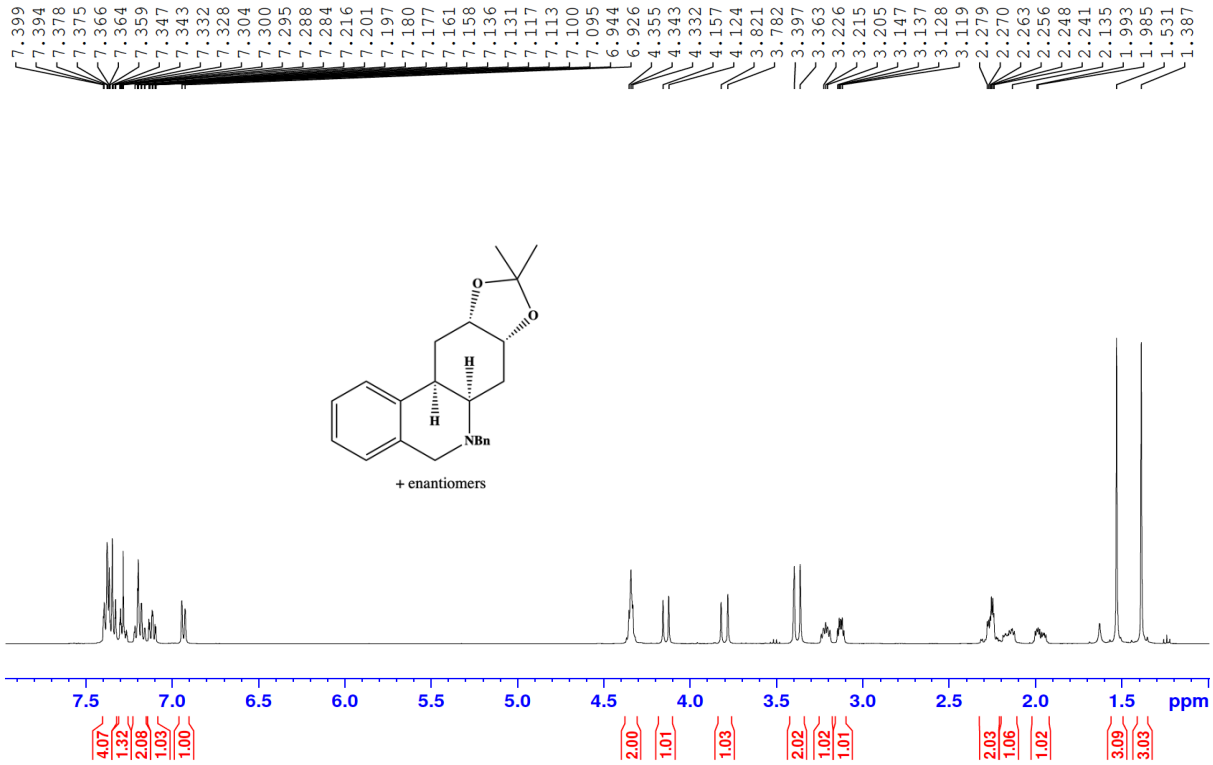


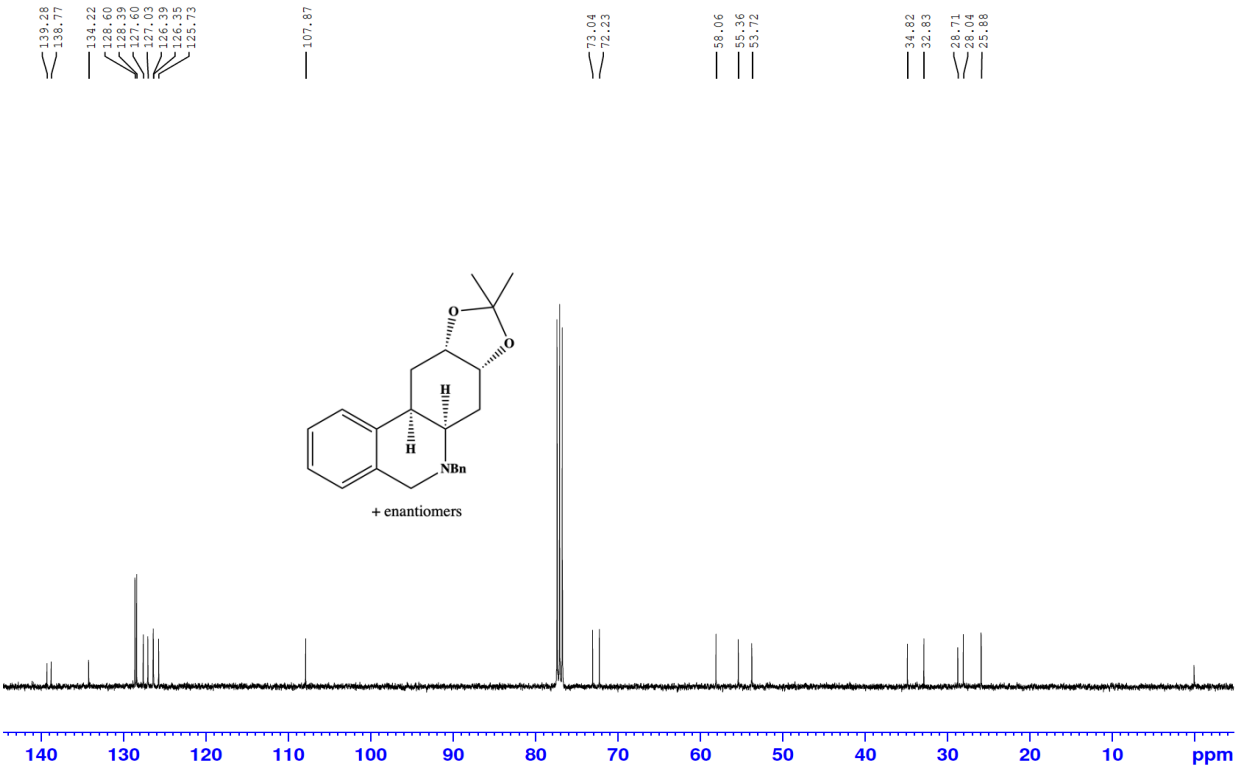
^{1}H NMR of 87



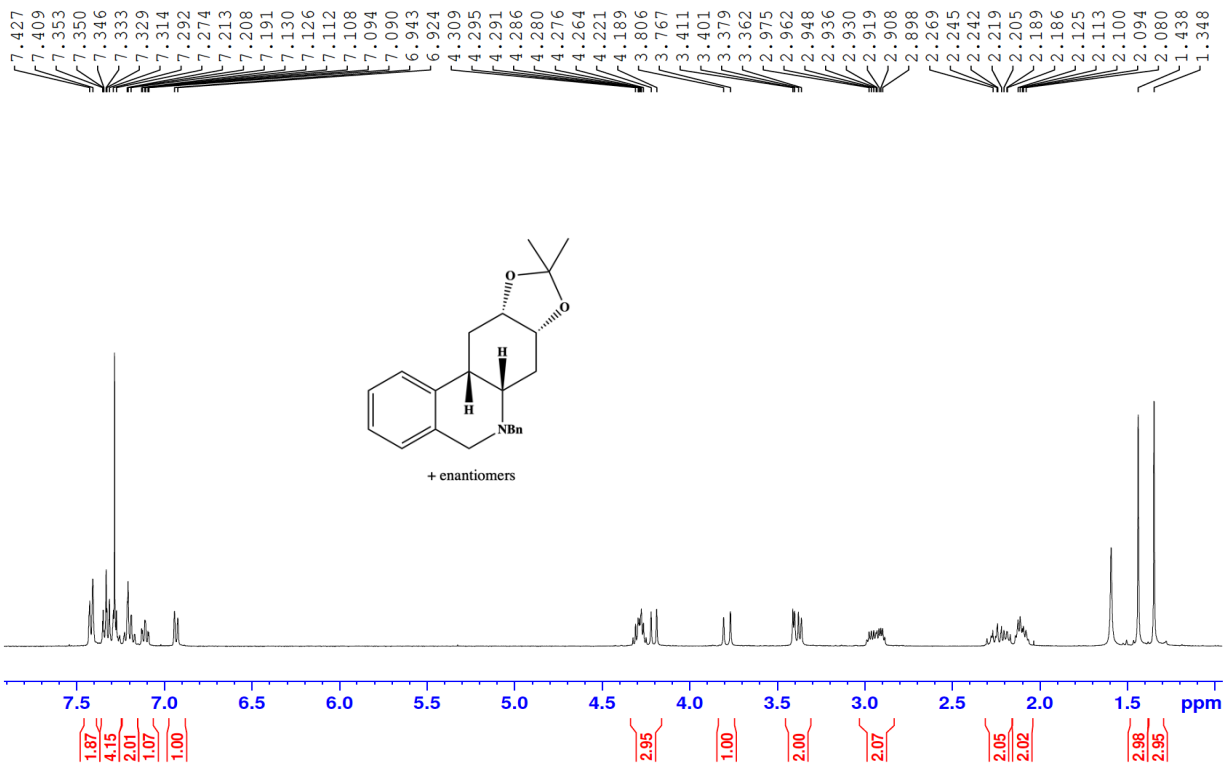
^{13}C NMR of 87



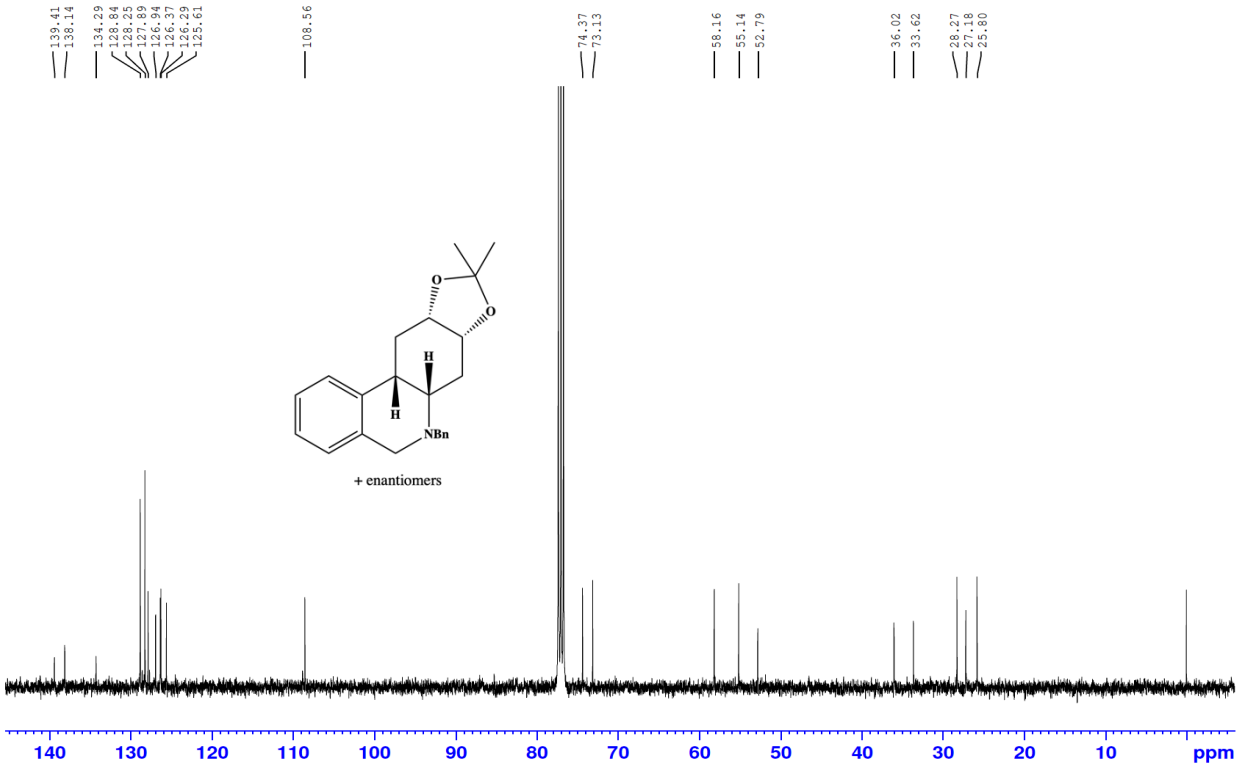
^{1}H NMR of 92



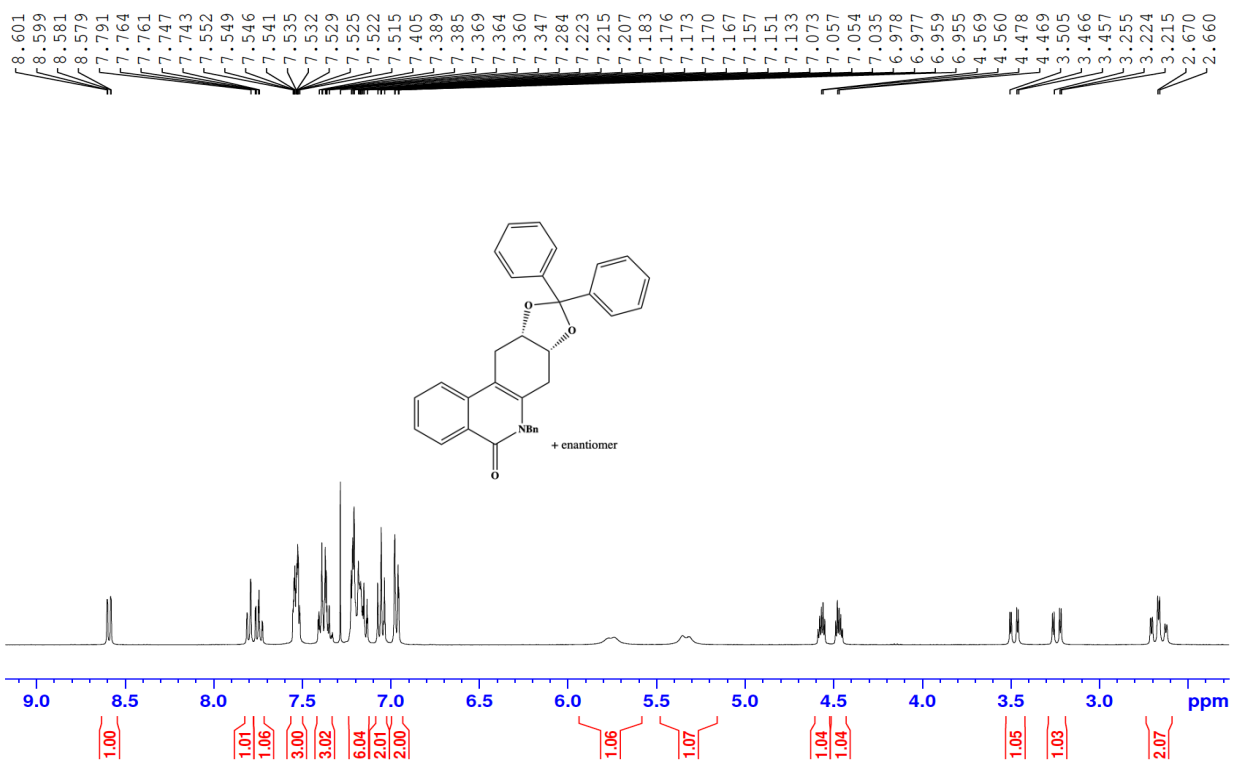
^{13}C NMR of 92



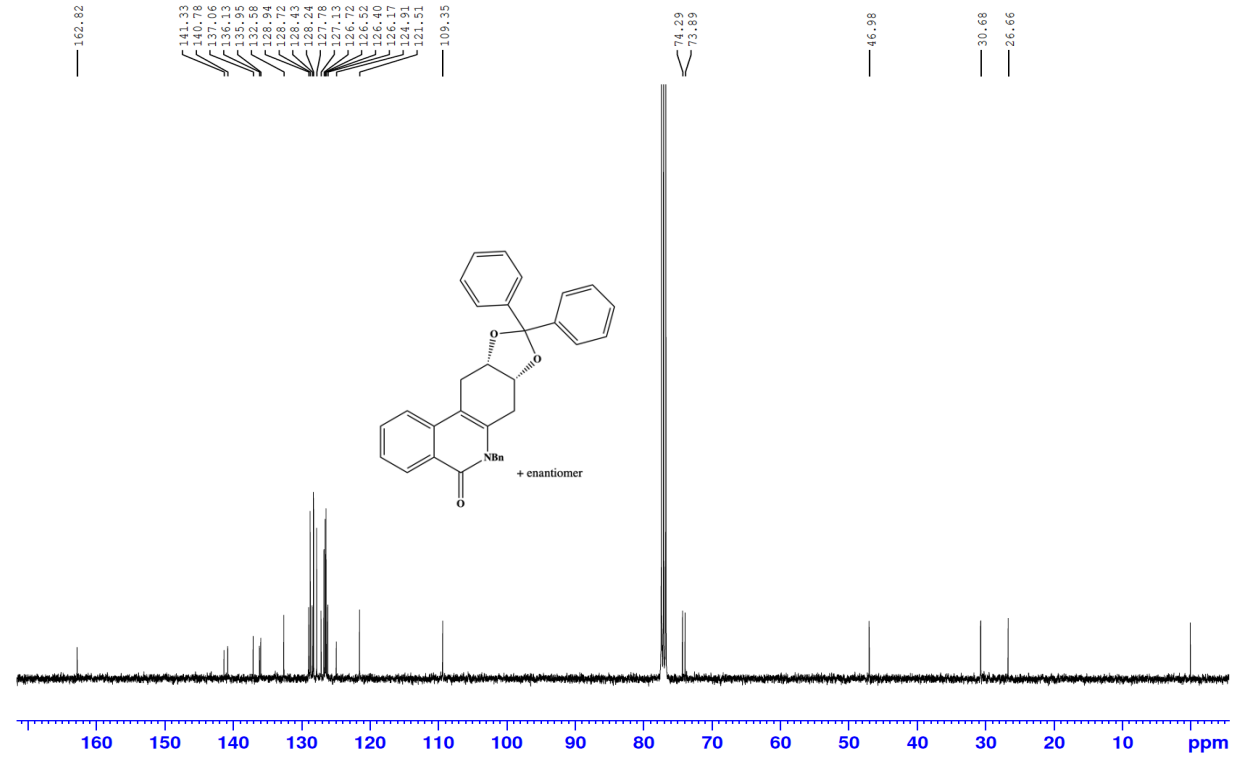
^{1}H NMR of 93



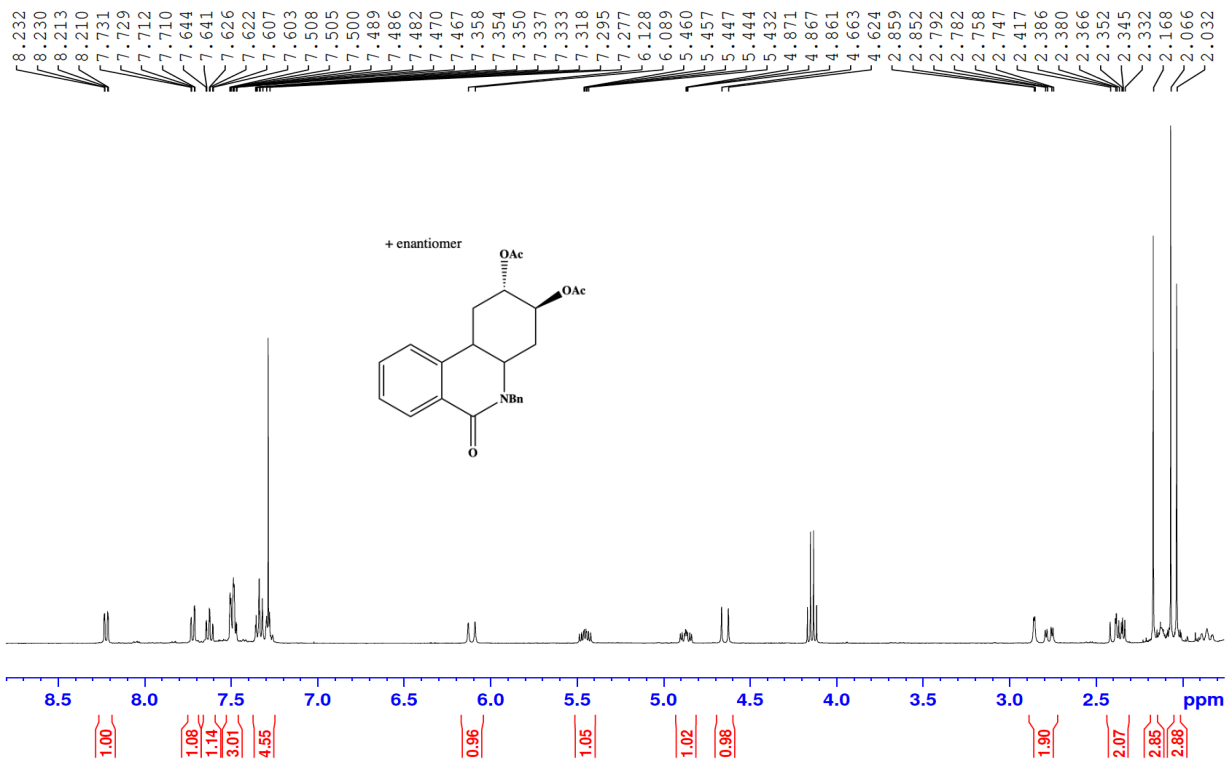
^{13}C NMR of 93



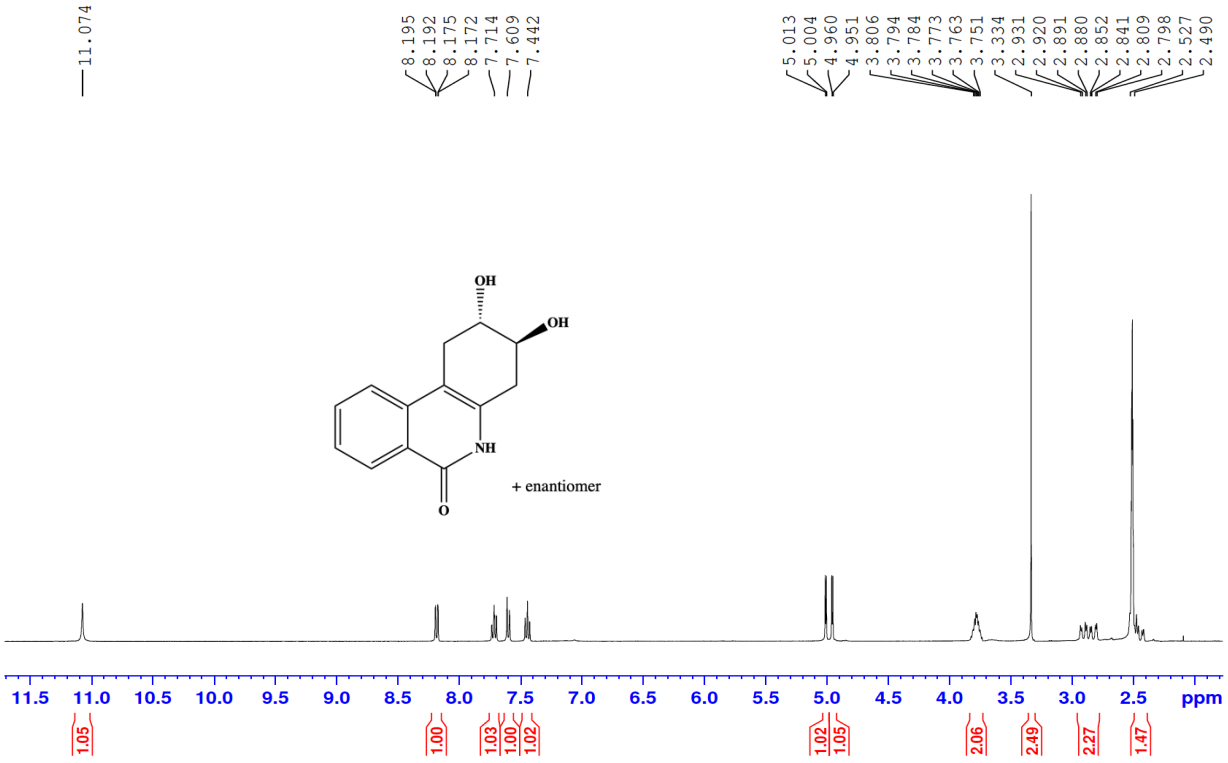
^{1}H NMR of 95



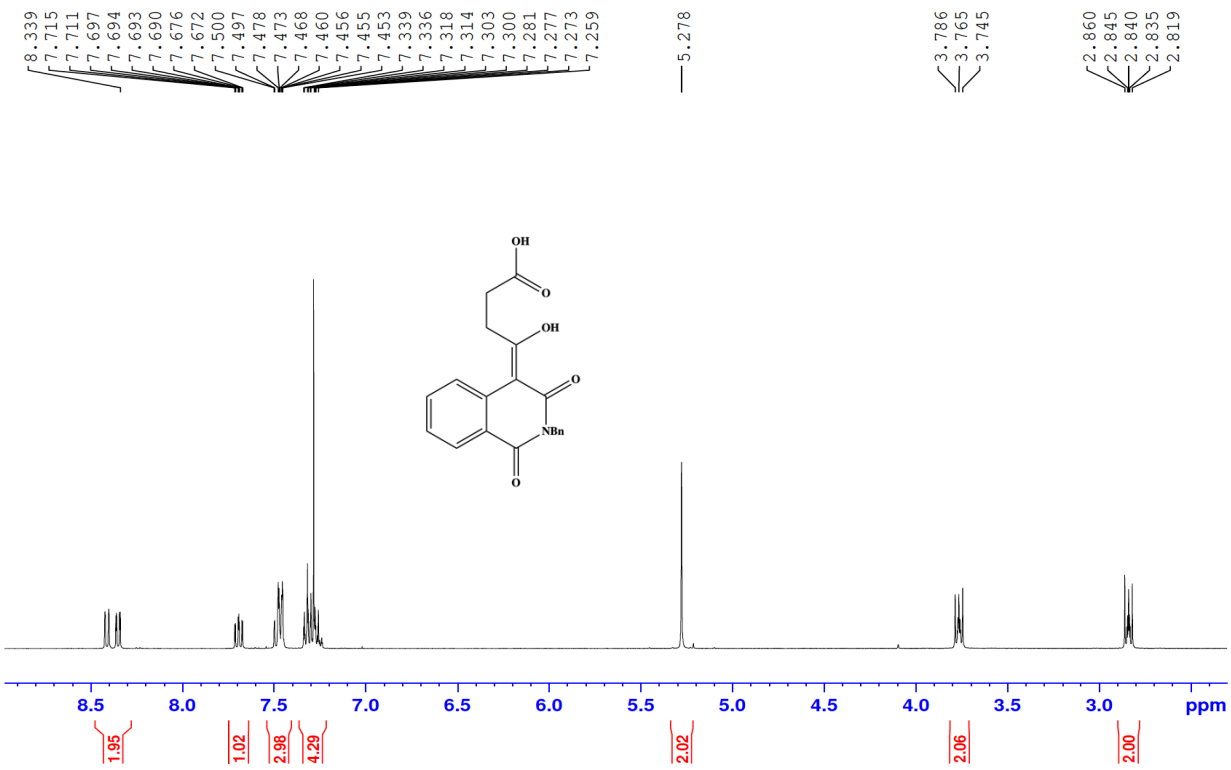
^{13}C NMR of 95



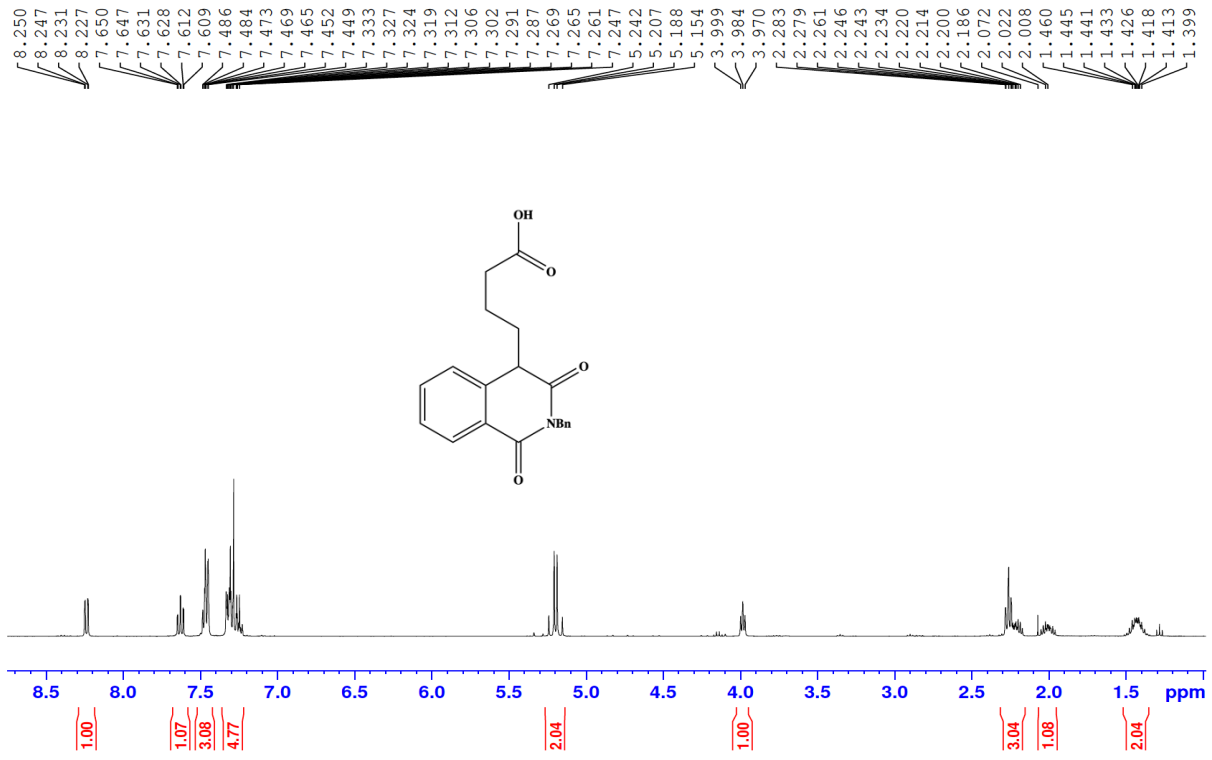
^{1}H NMR of 98



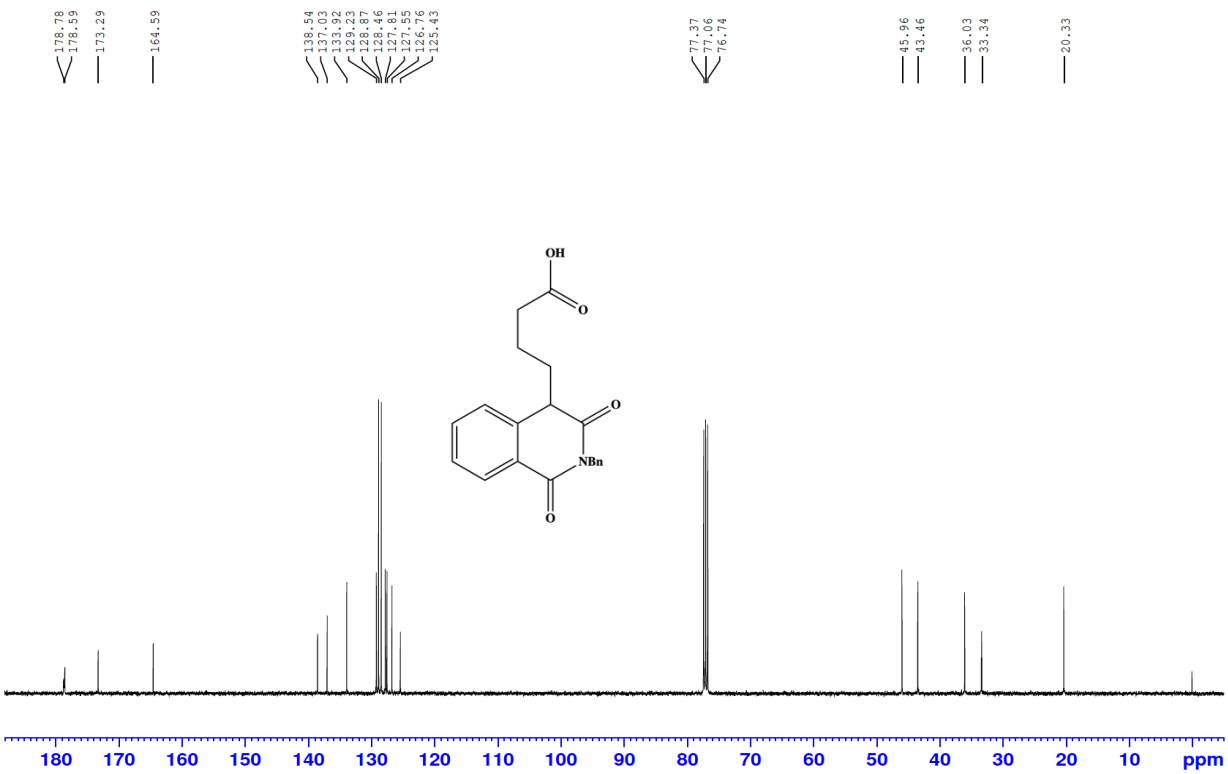
^{1}H NMR of 101



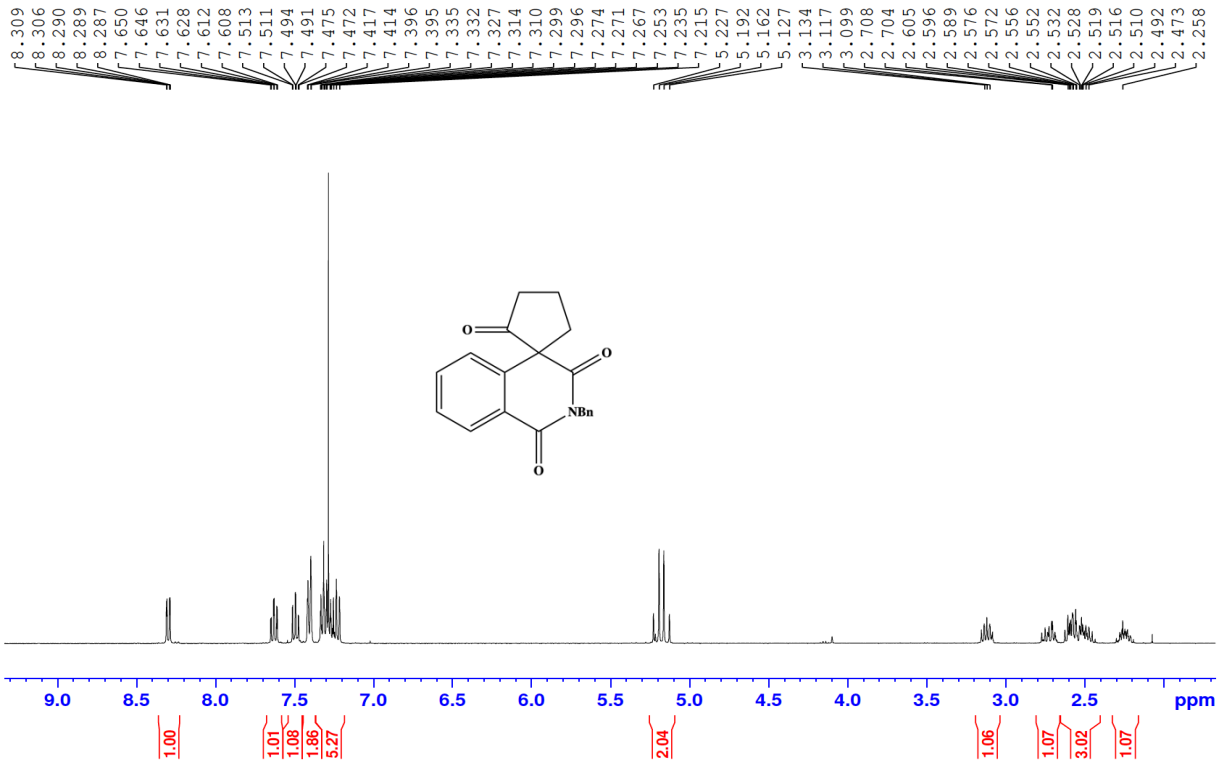
^{1}H NMR of 110



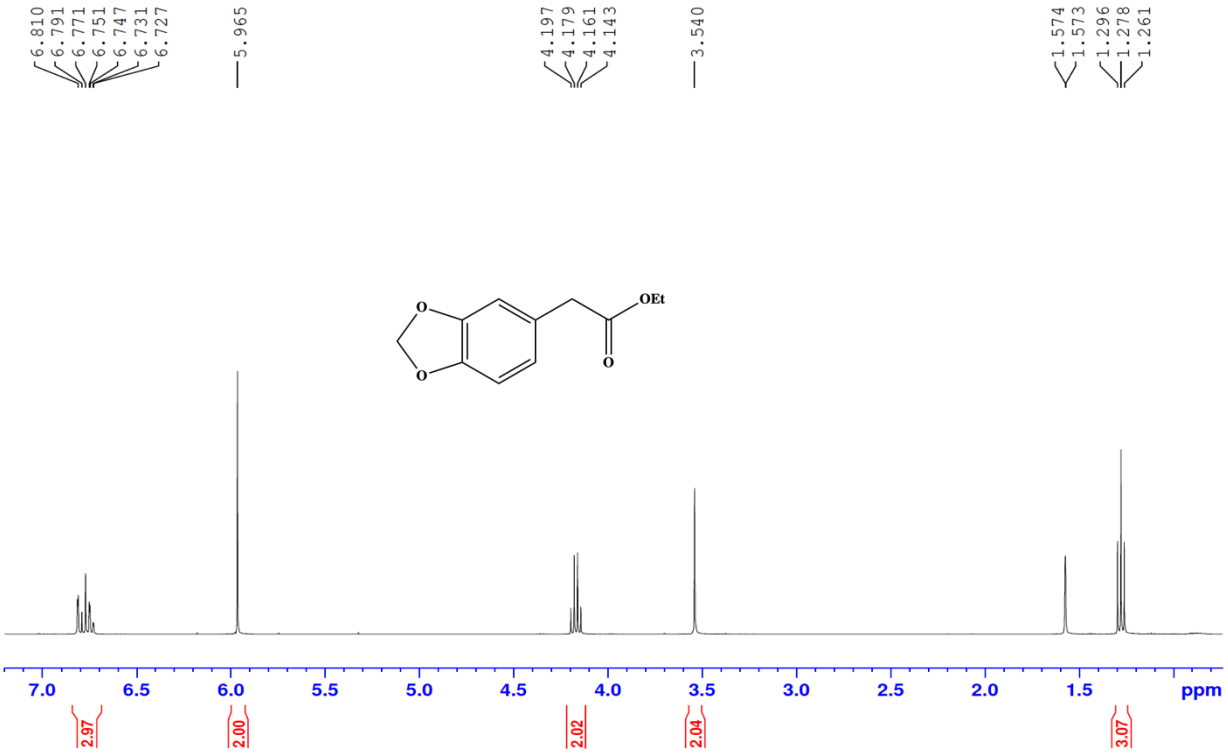
^{1}H NMR of 114



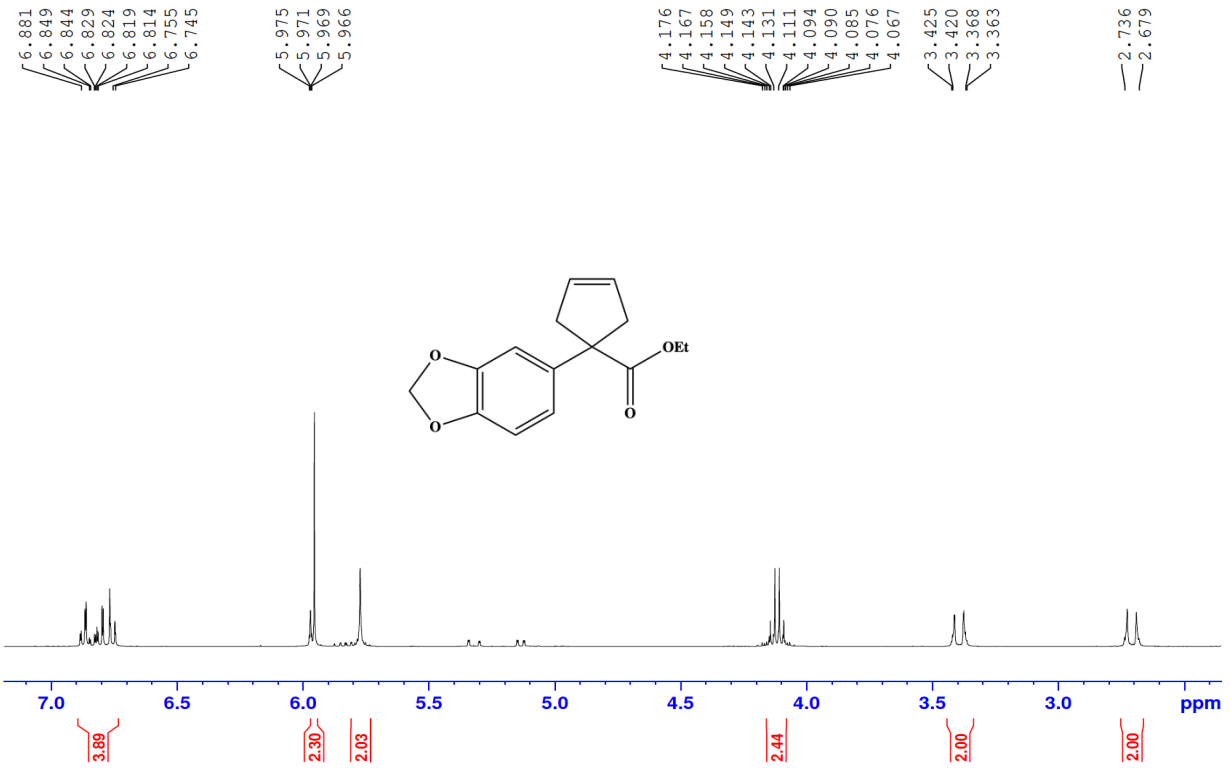
^{13}C NMR of 114



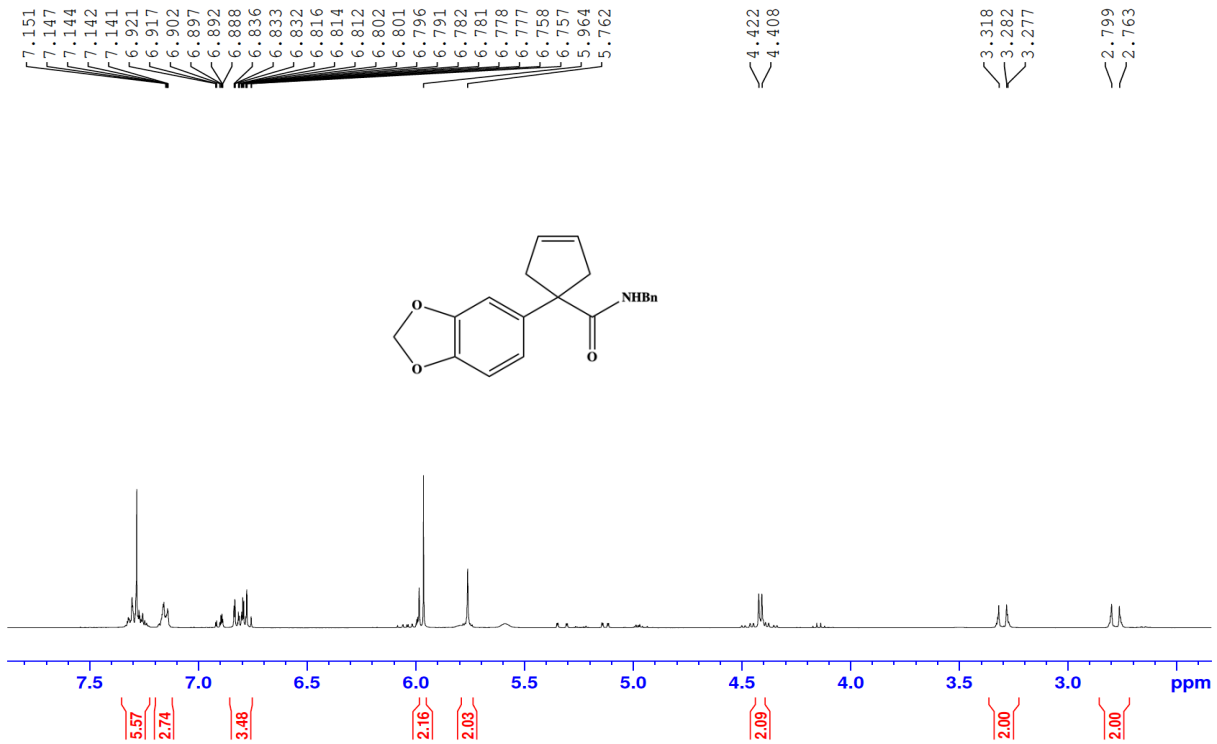
^{1}H NMR of 117



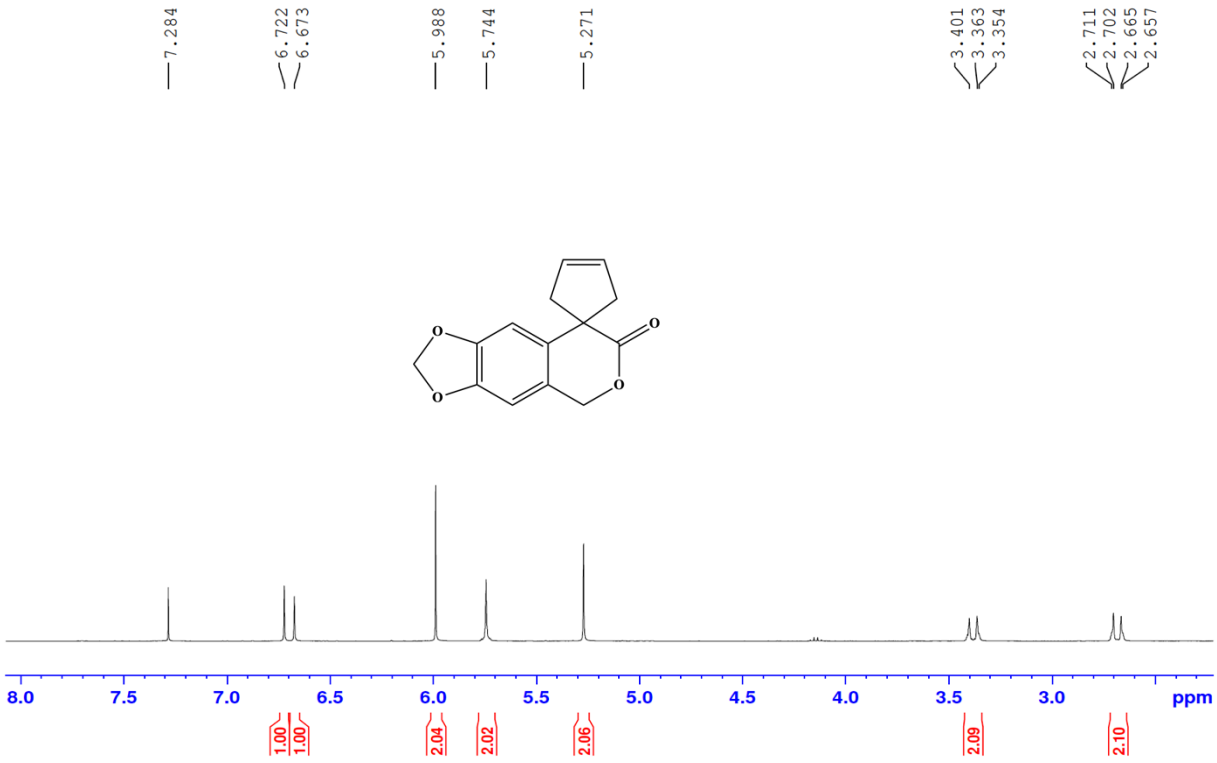
^{1}H NMR of 123



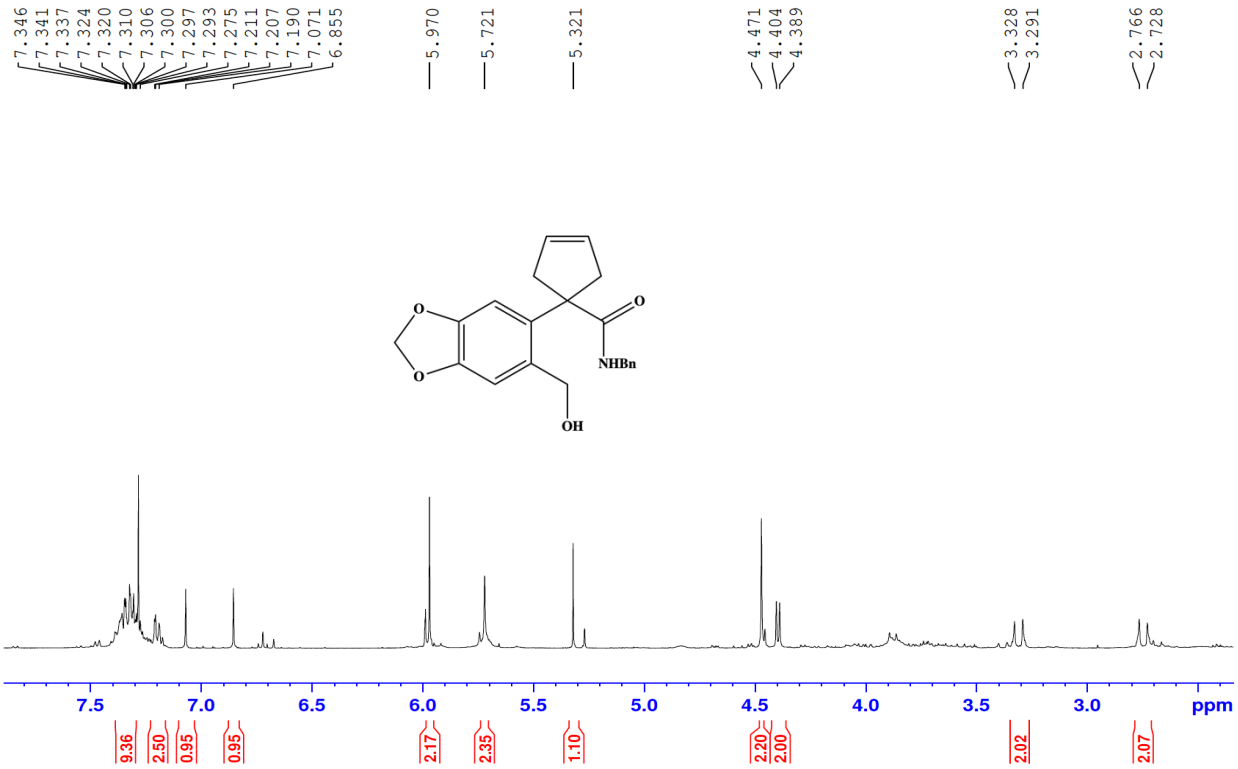
^{1}H NMR of 124



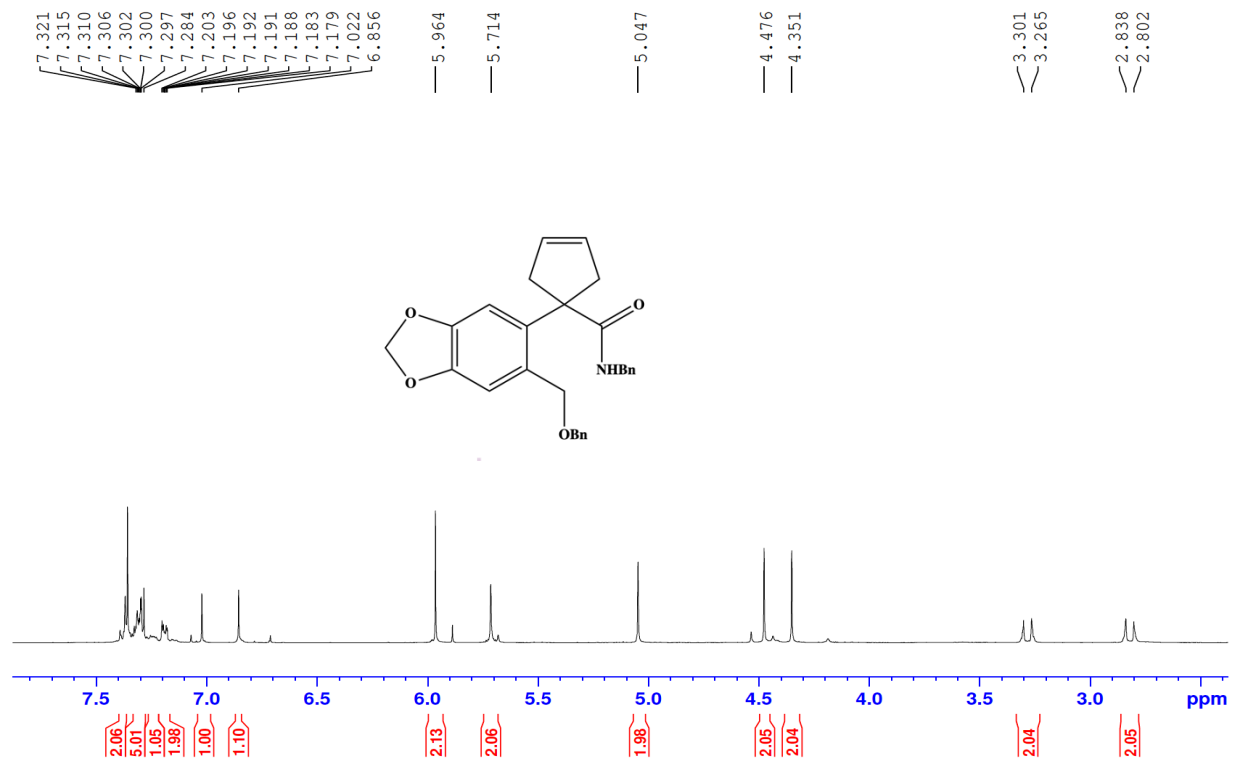
^{1}H NMR of 125



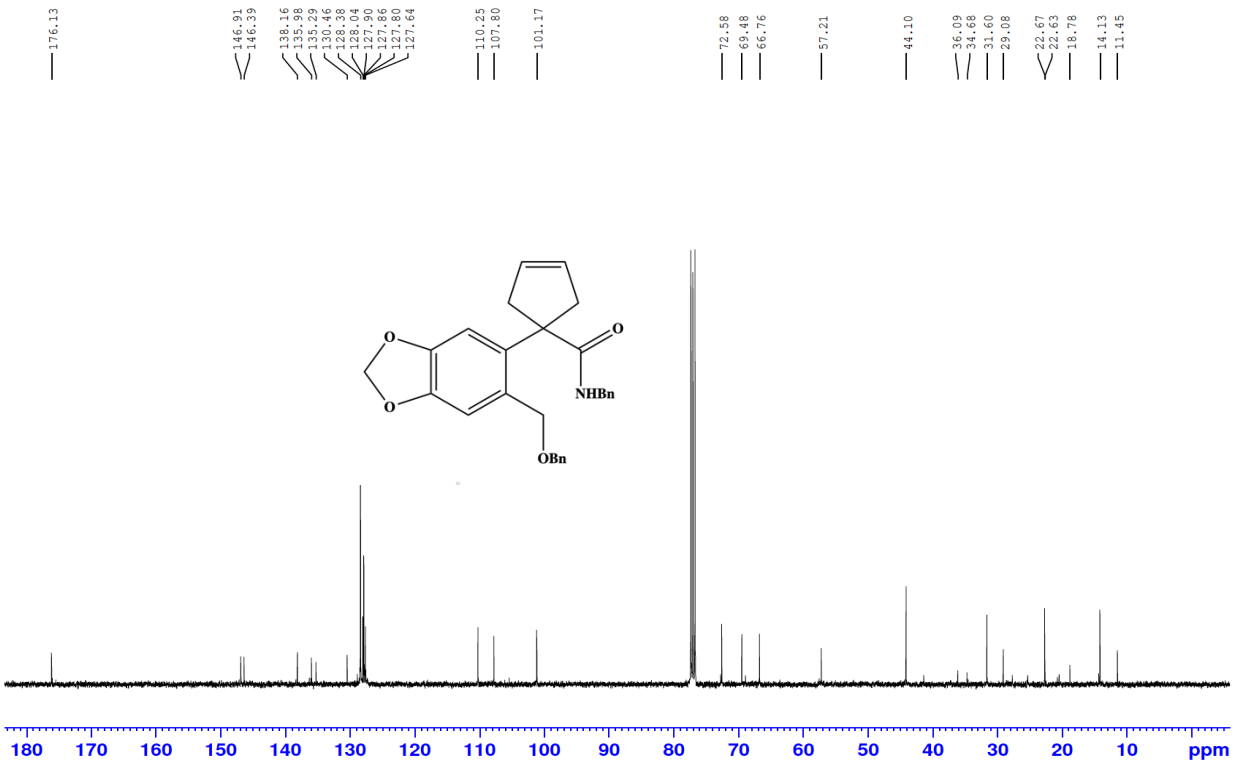
^{1}H NMR of 130



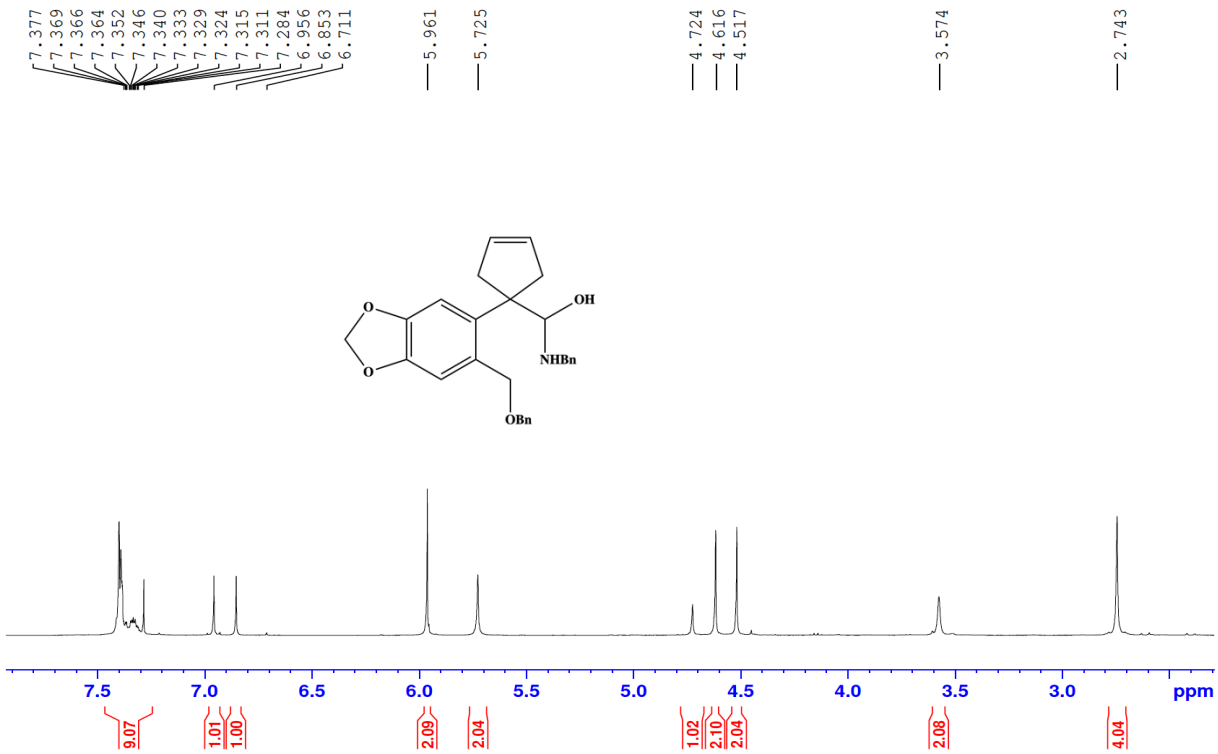
^{1}H NMR of 131



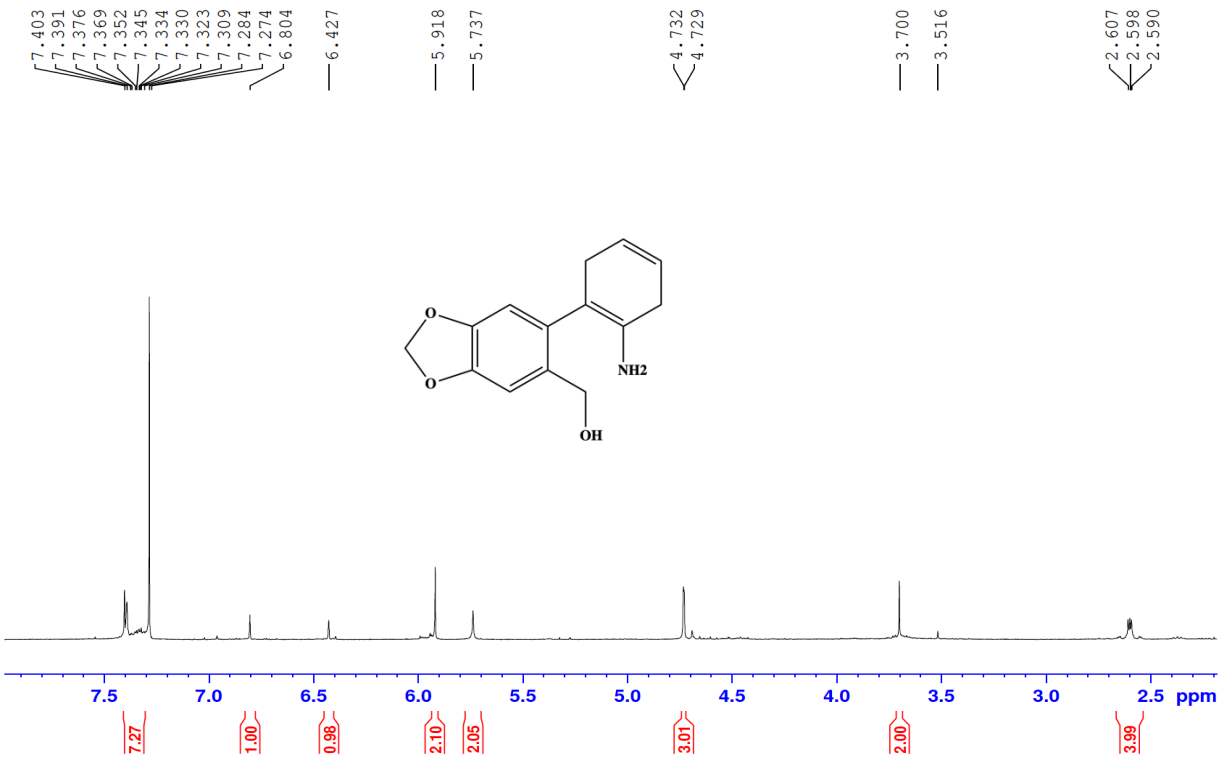
^{1}H NMR of 132



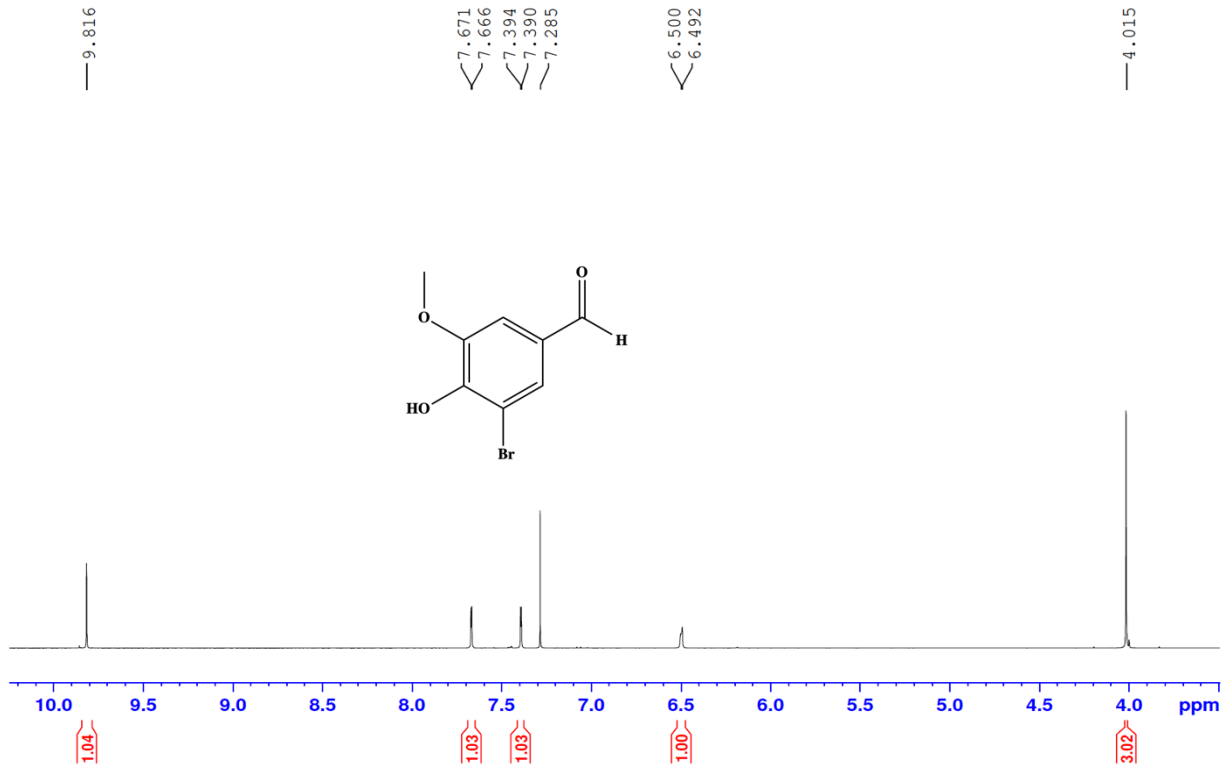
^{13}C NMR of 132



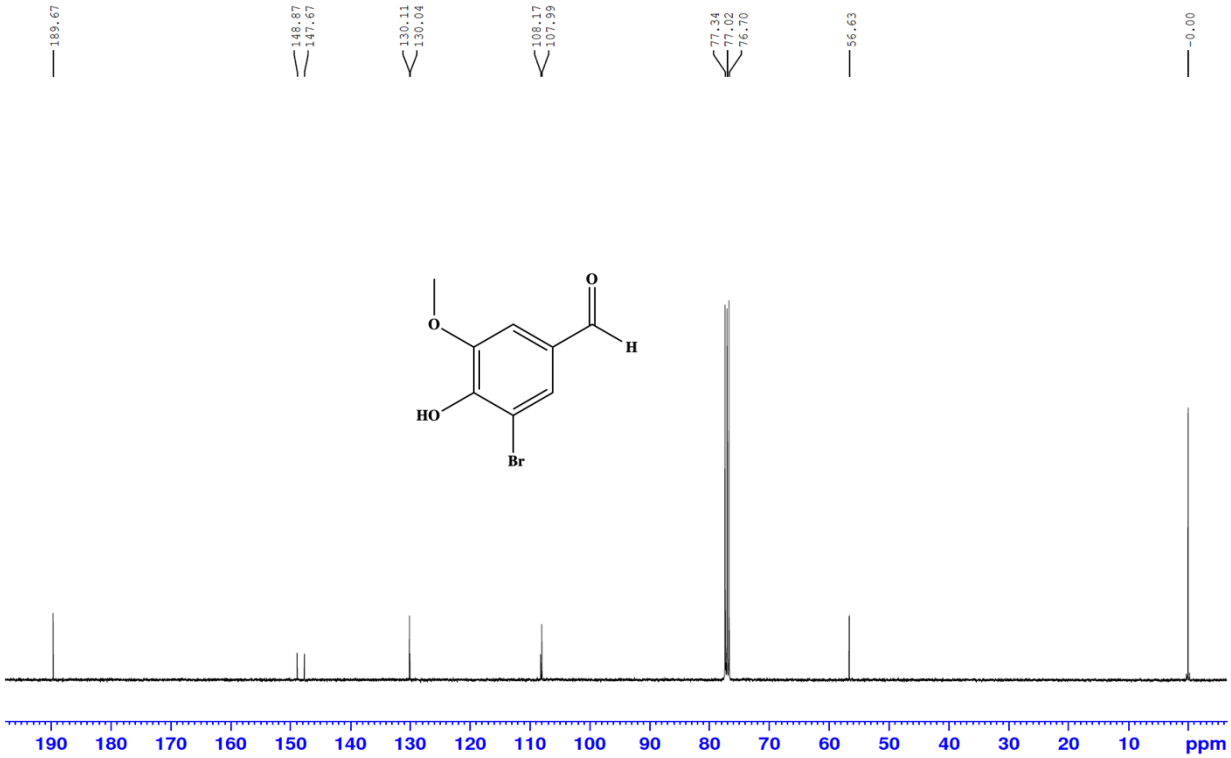
^{1}H NMR of 133



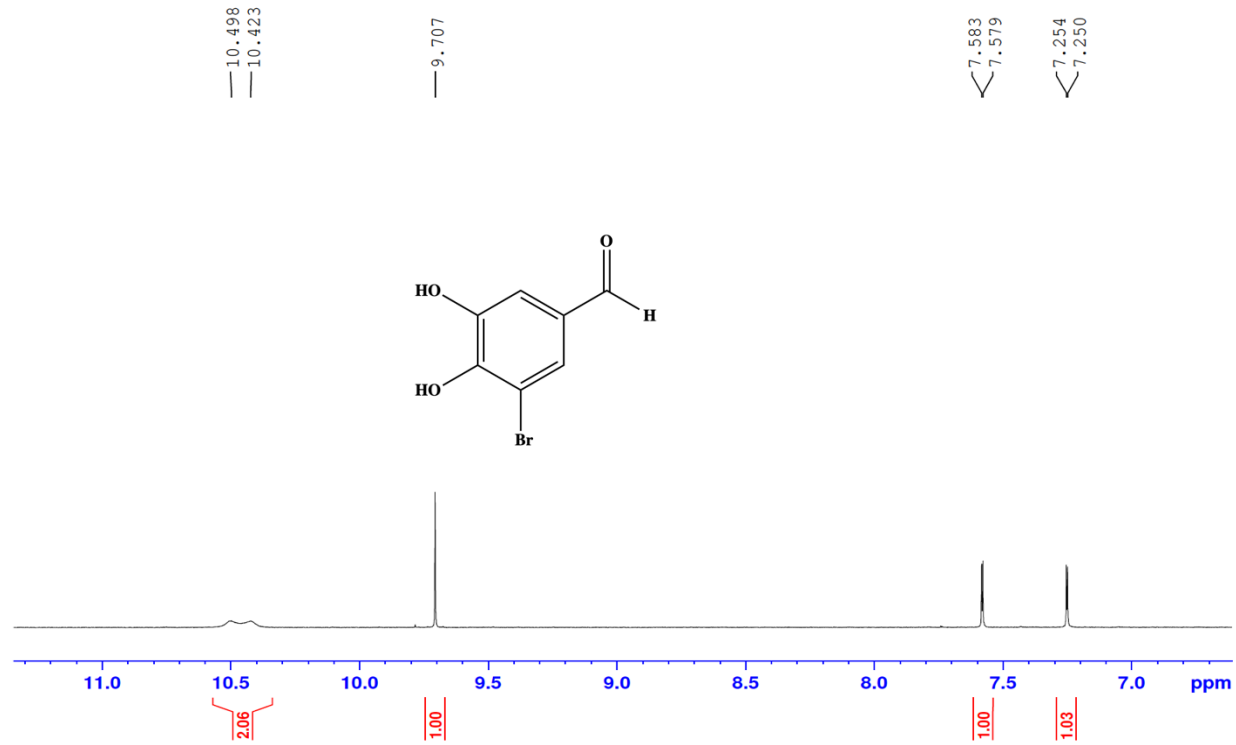
^{1}H NMR of 134



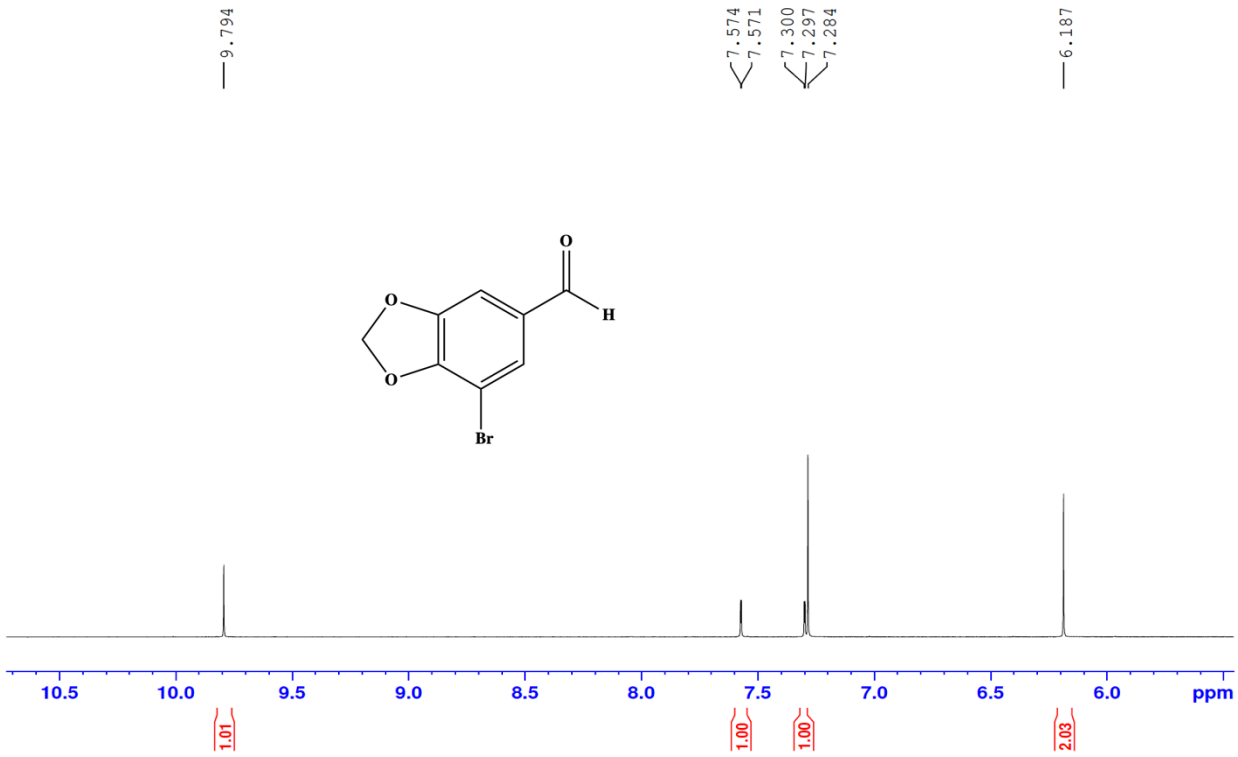
^{1}H NMR of 139



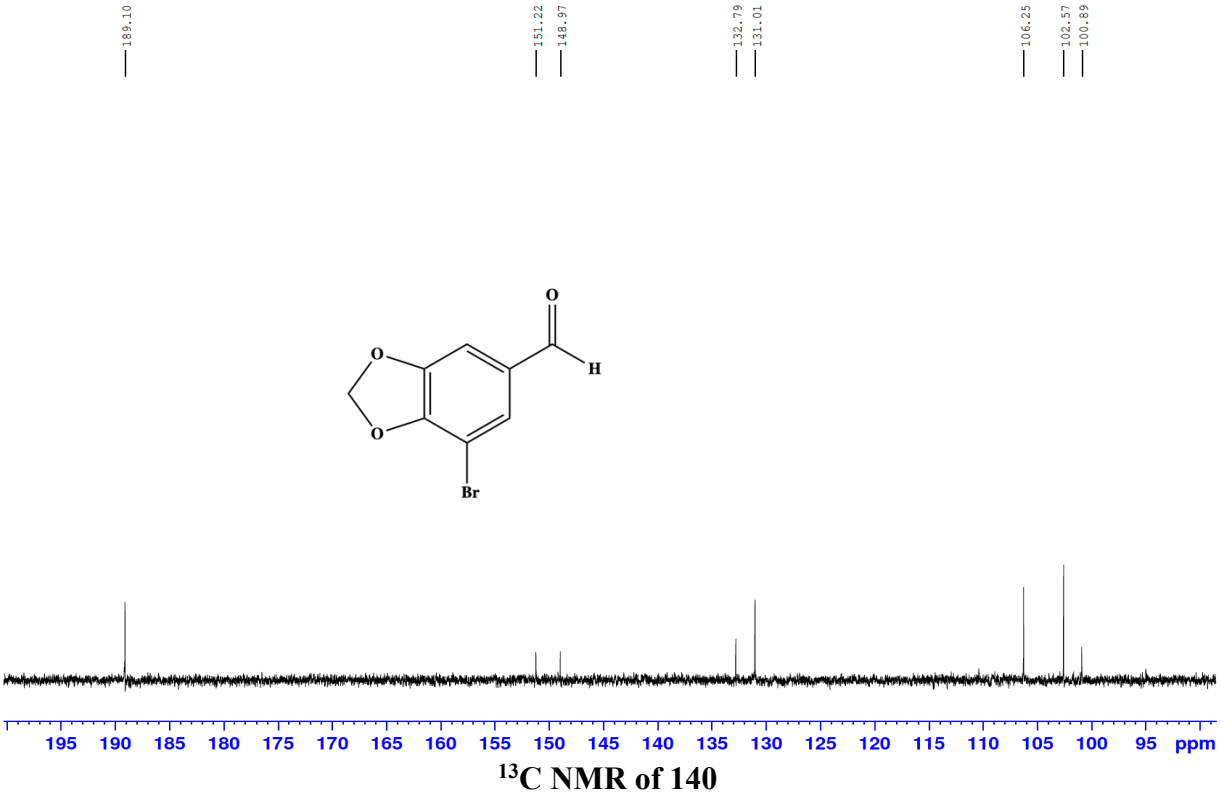
^{13}C NMR of 139



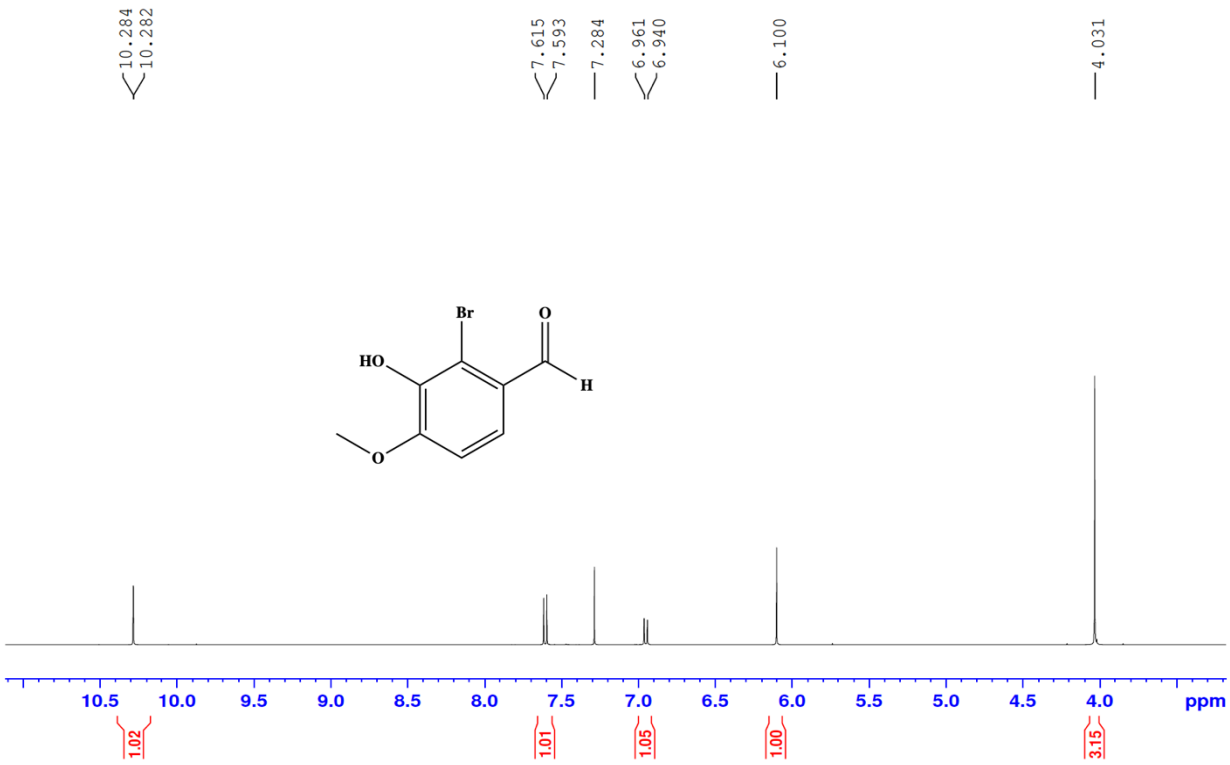
^{1}H NMR of catechol intermediate



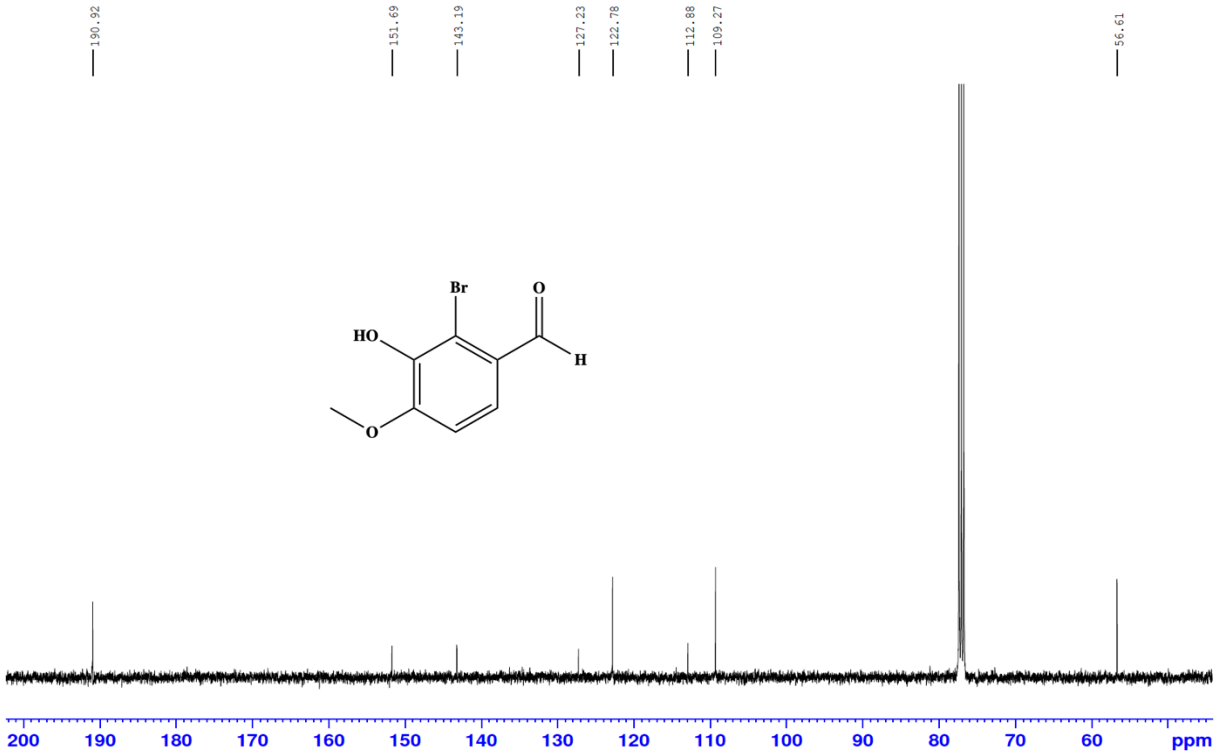
^{1}H NMR of 140



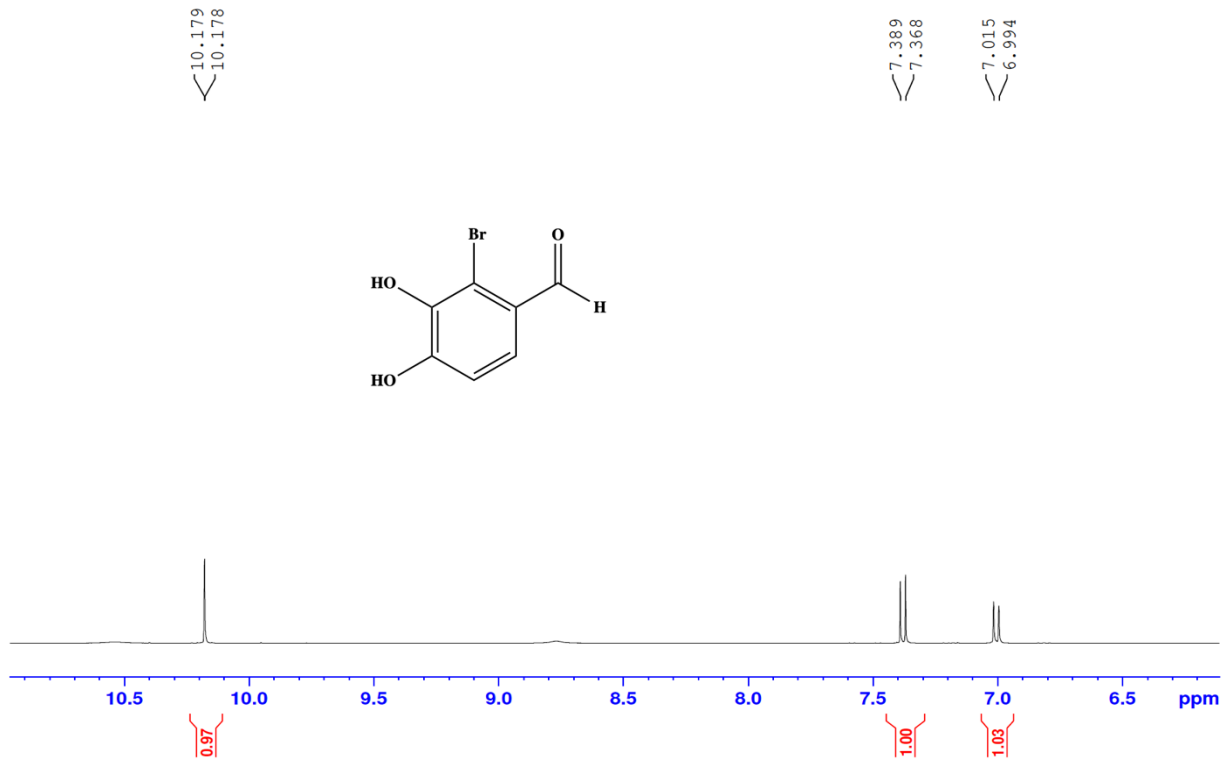
^{13}C NMR of 140



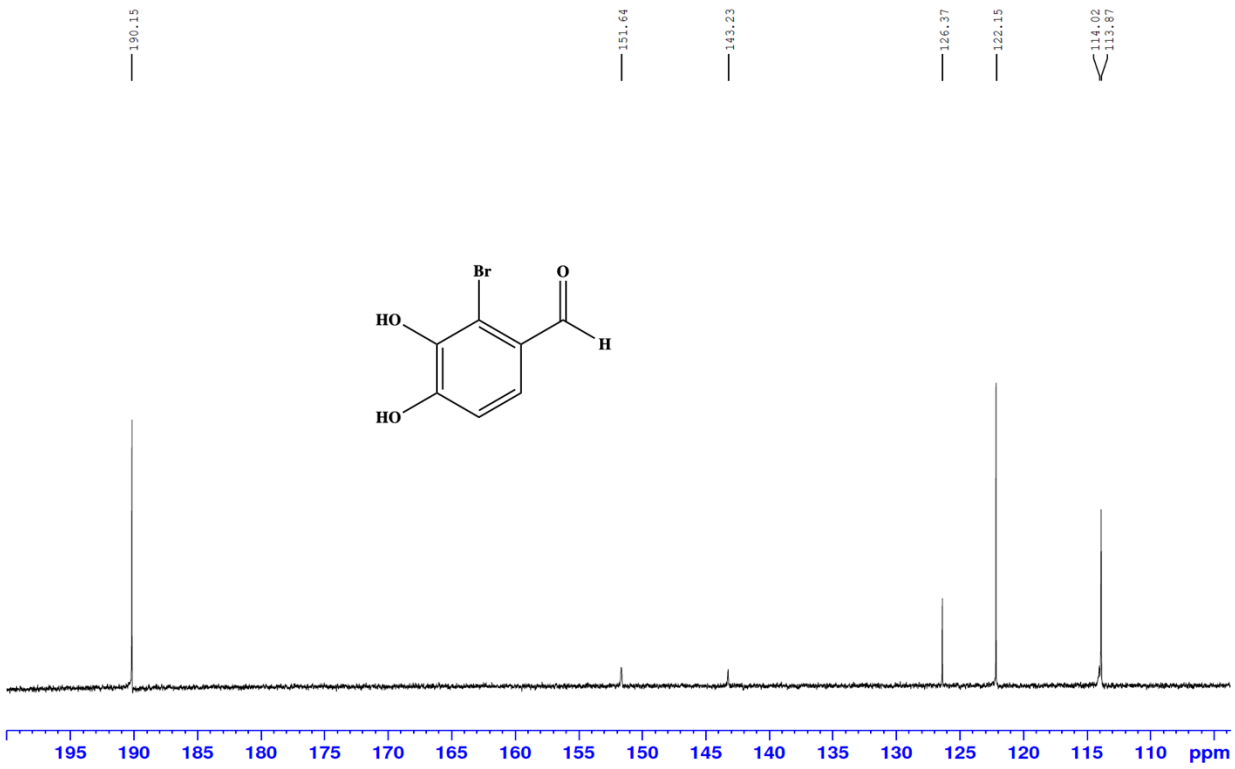
^{1}H NMR of



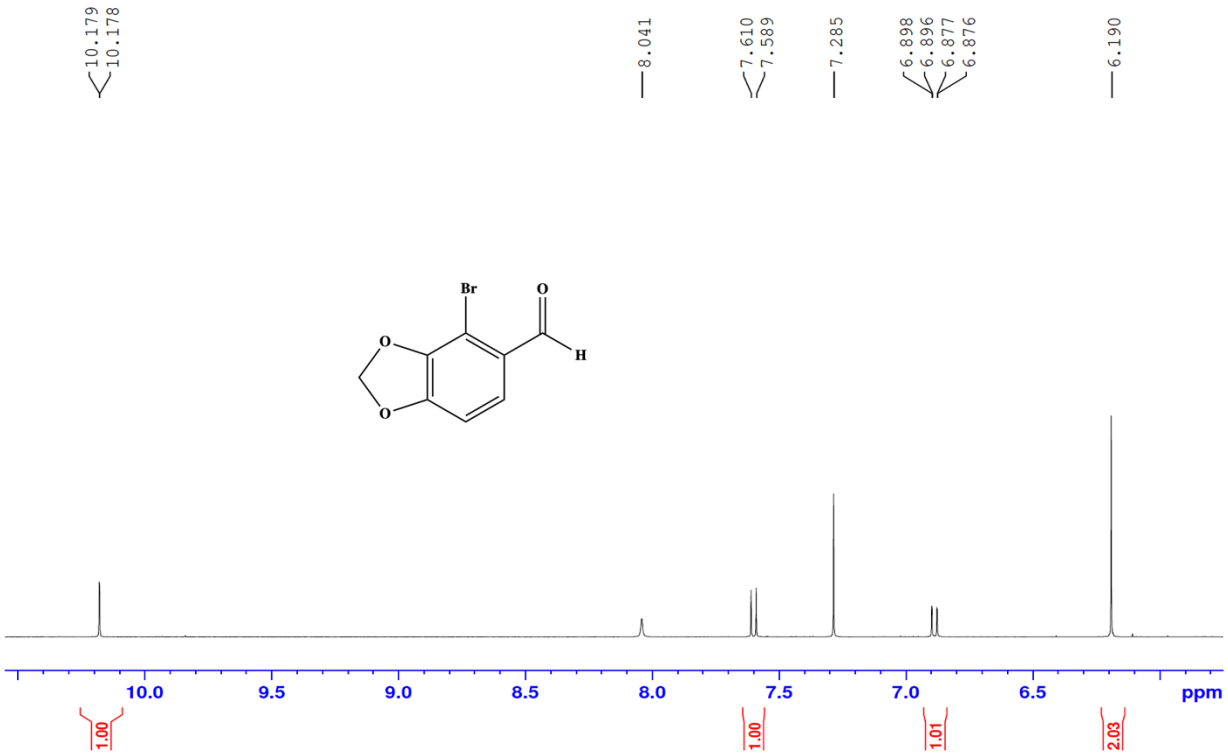
^{13}C NMR of 2-bromoisovanillin



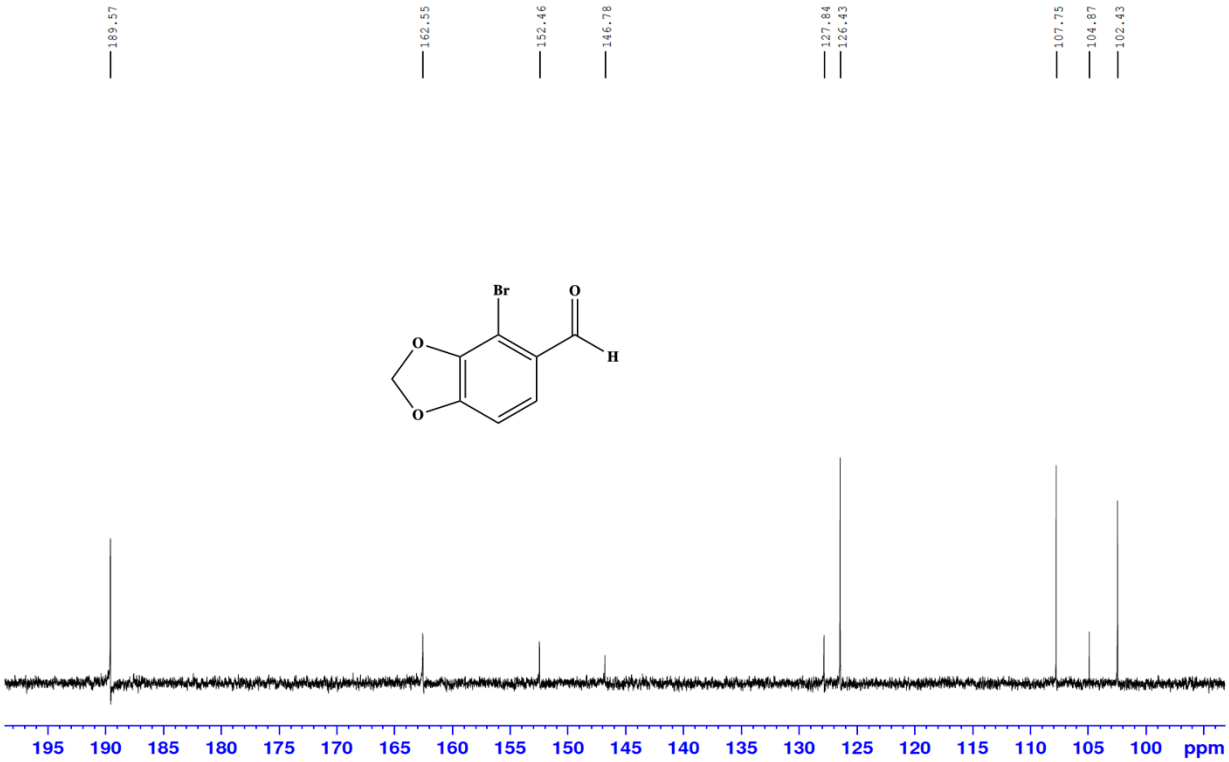
^{1}H NMR of catechol intermediate



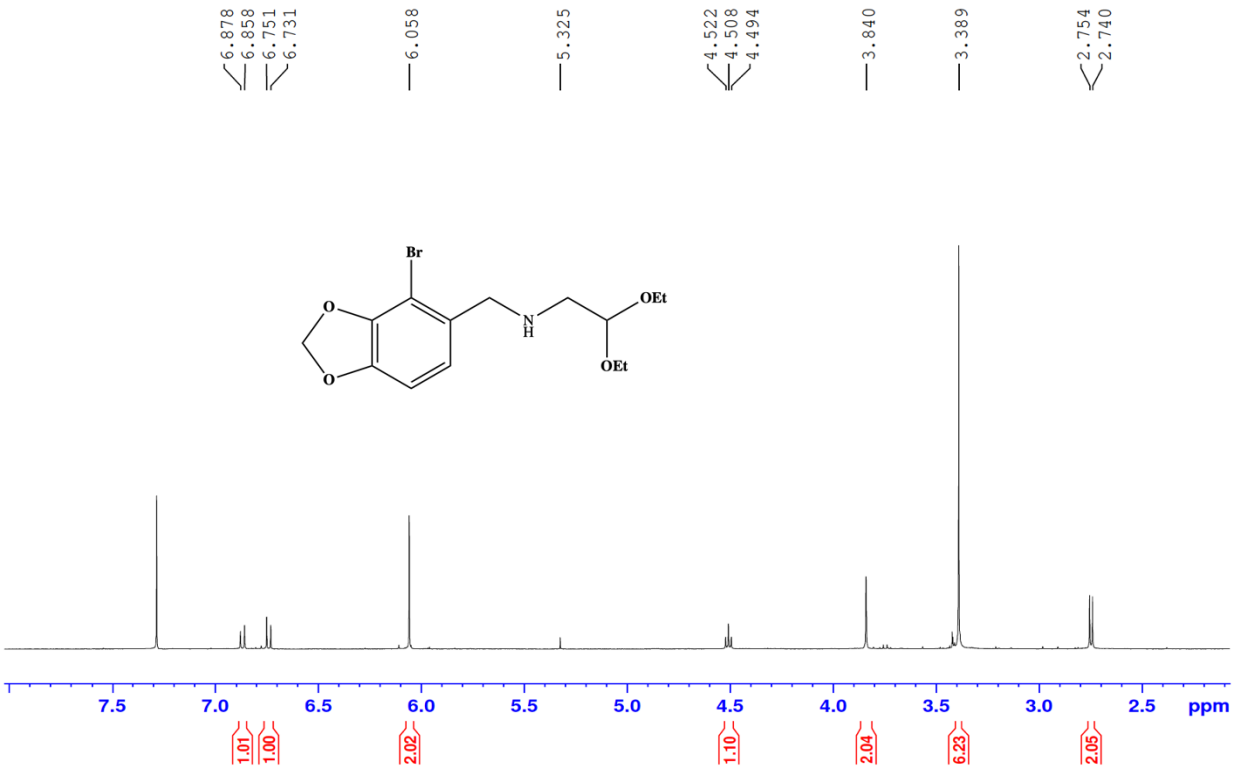
^{13}C NMR of catechol intermediate



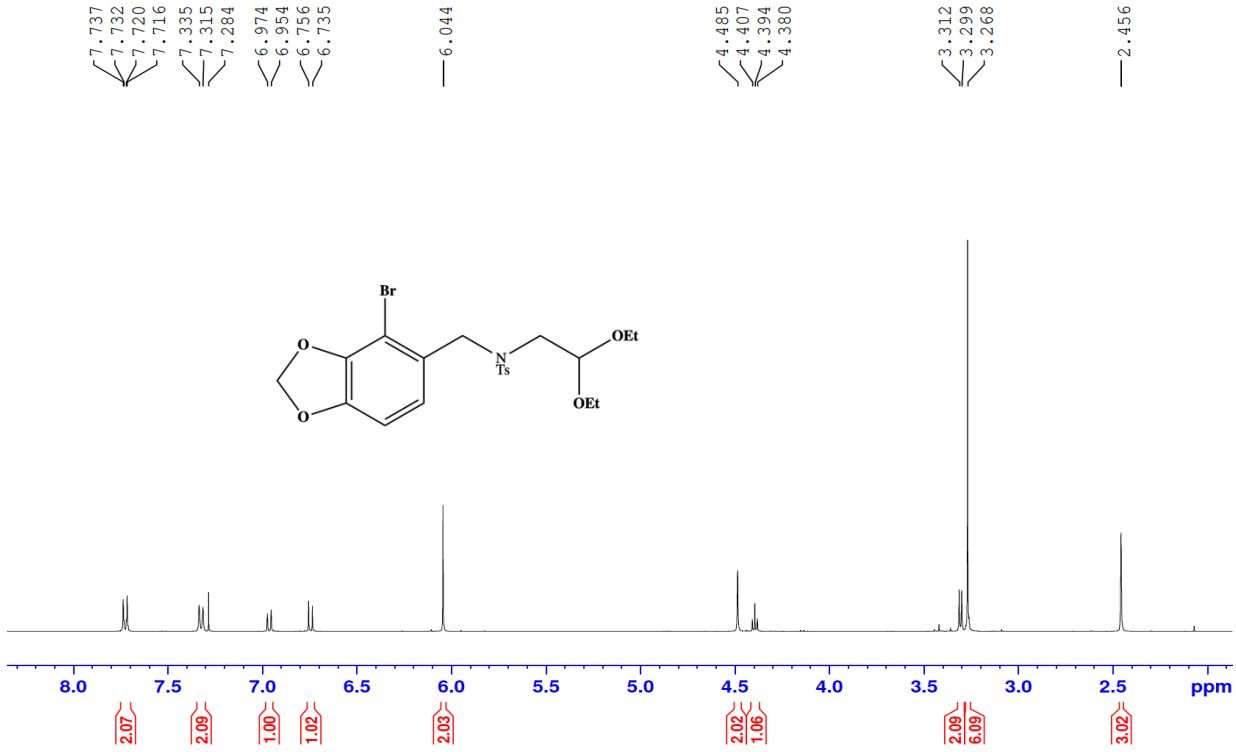
^{1}H NMR of 143



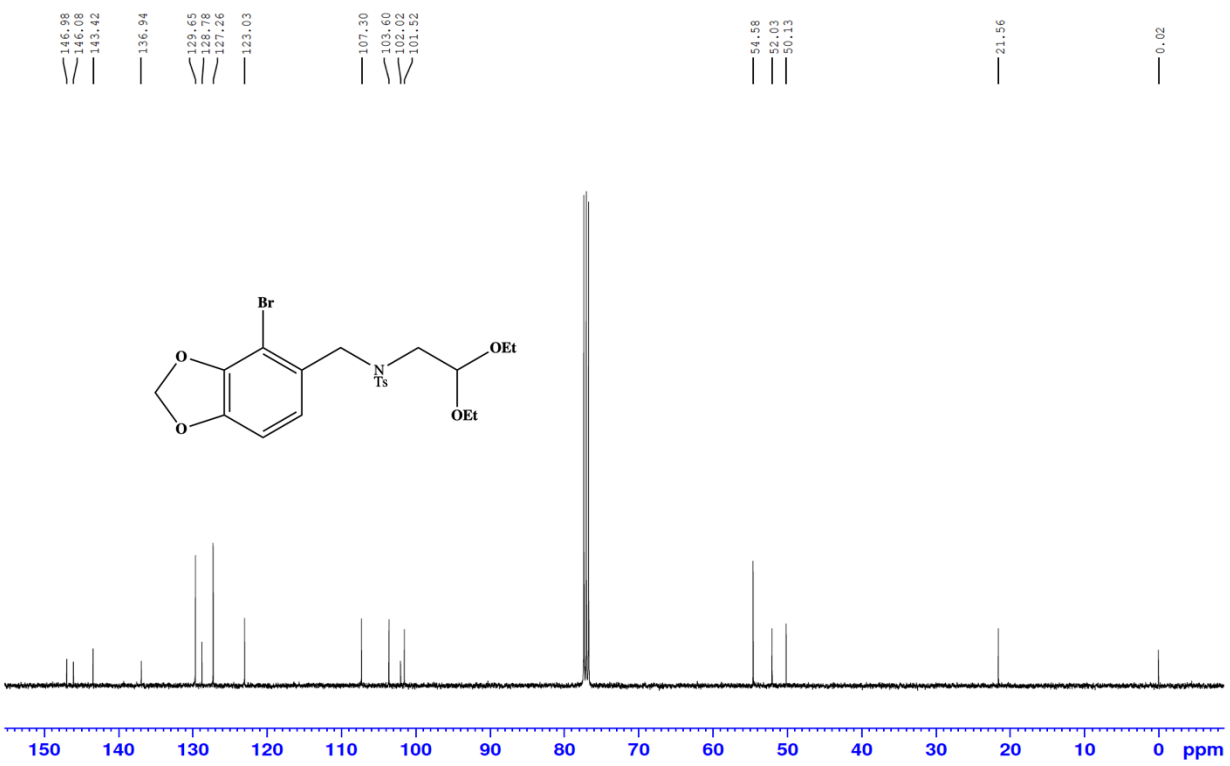
^{13}C NMR of 143



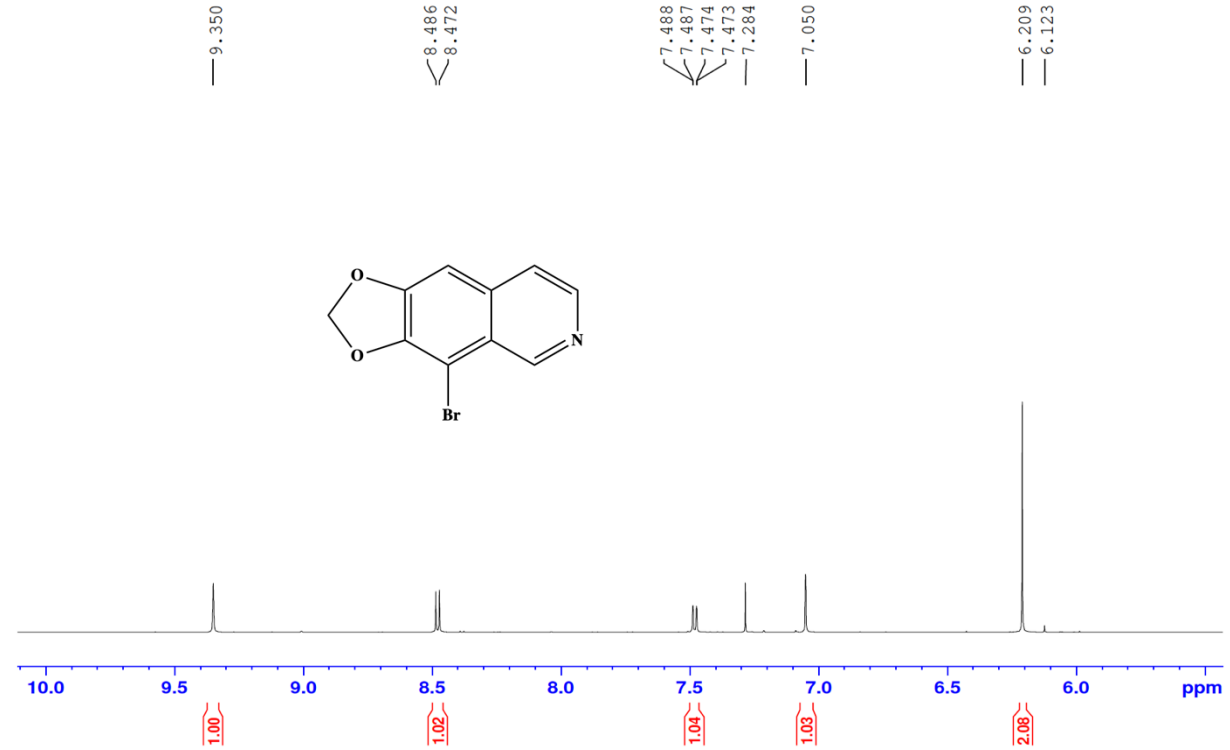
^{1}H NMR of 144



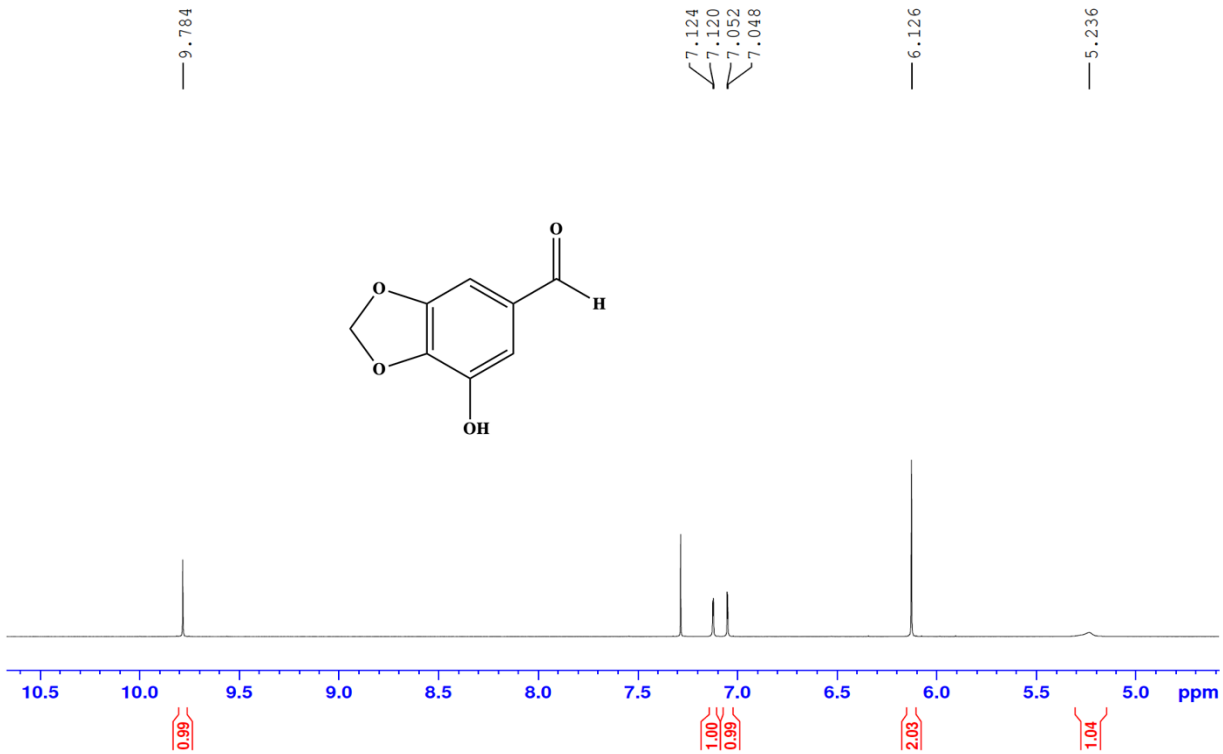
^{1}H NMR of 145



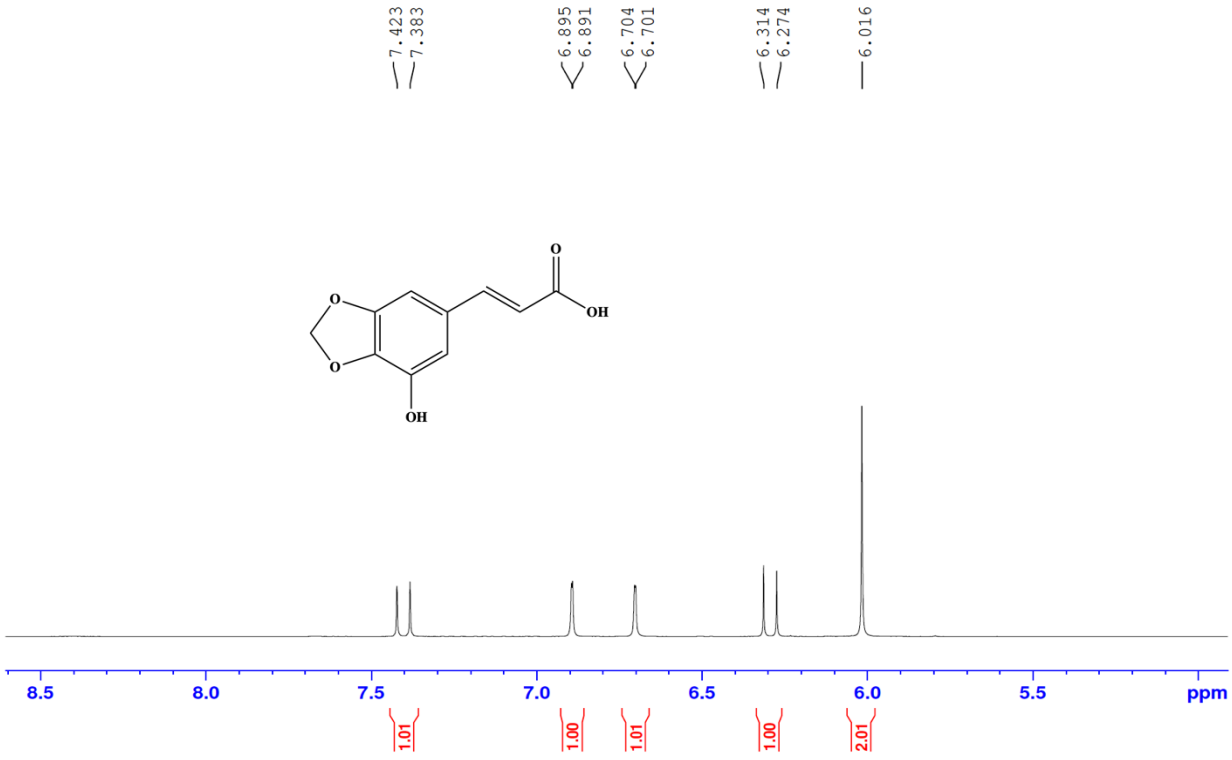
^{13}C NMR of 145



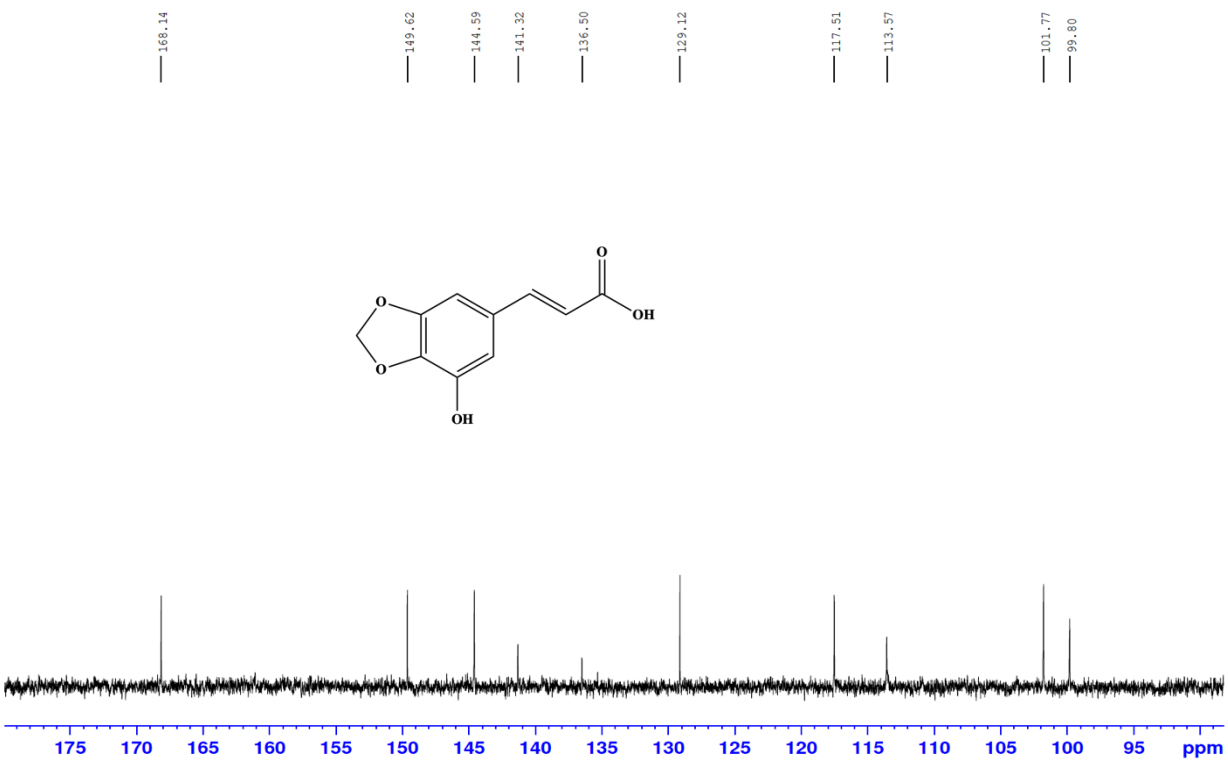
^{1}H NMR of 146



^{1}H NMR of 153



^{1}H NMR of 154



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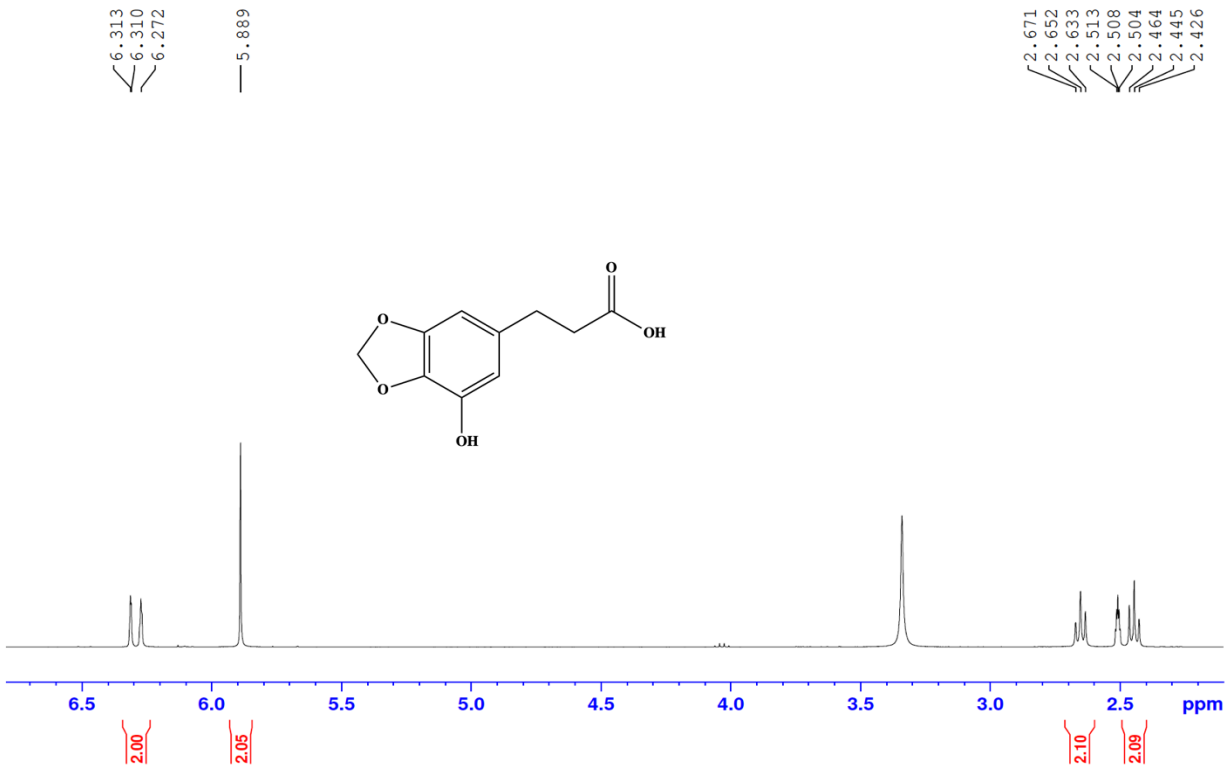
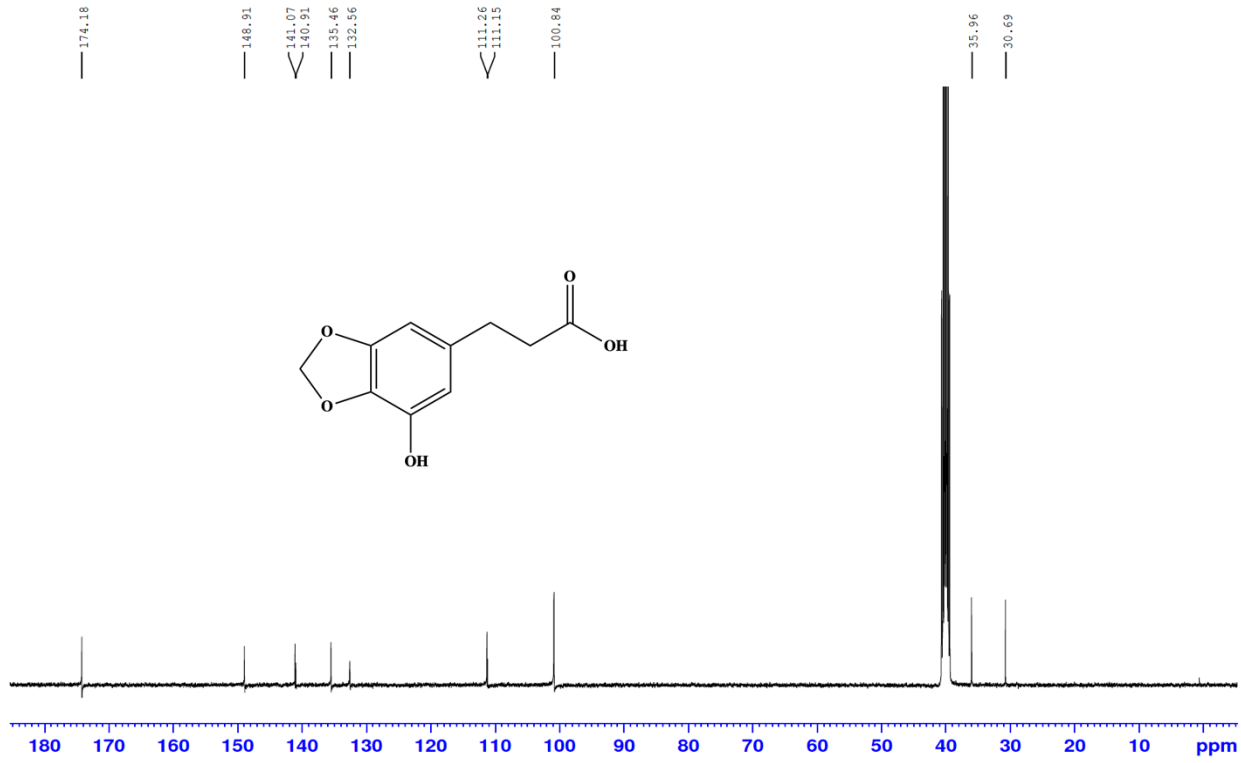


^{1}H NMR of 155



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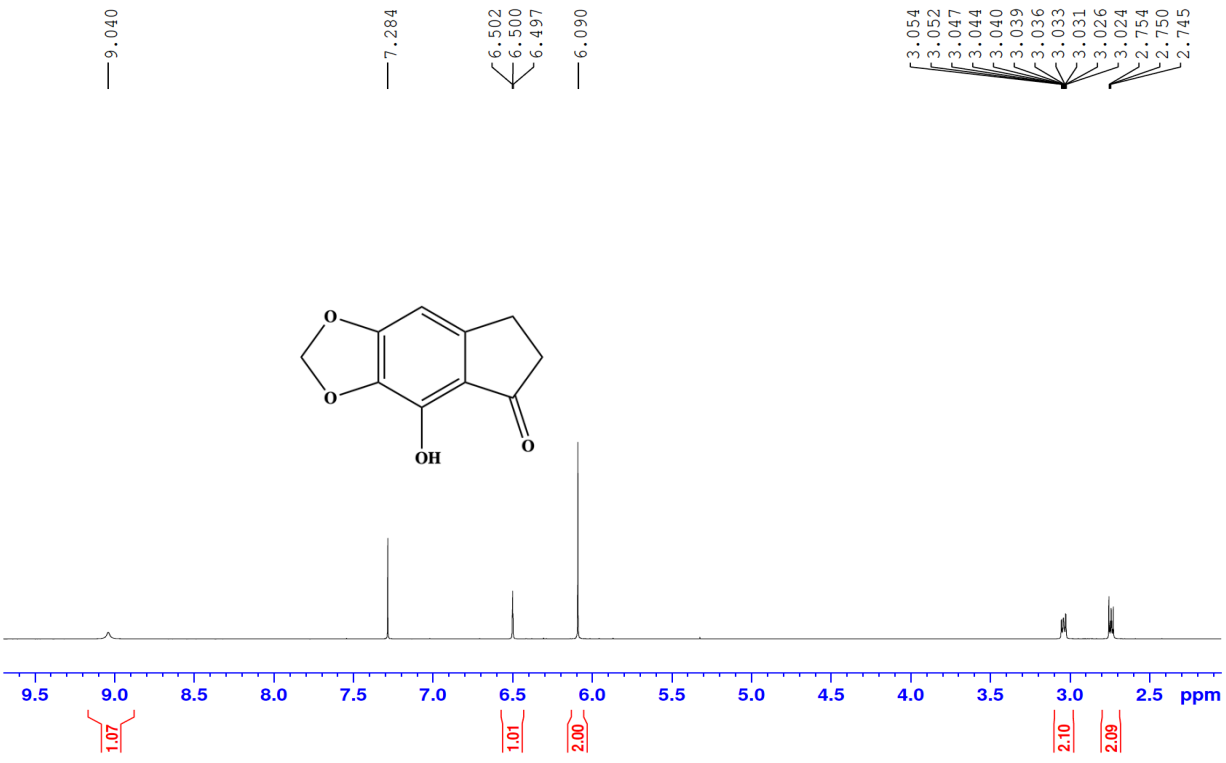
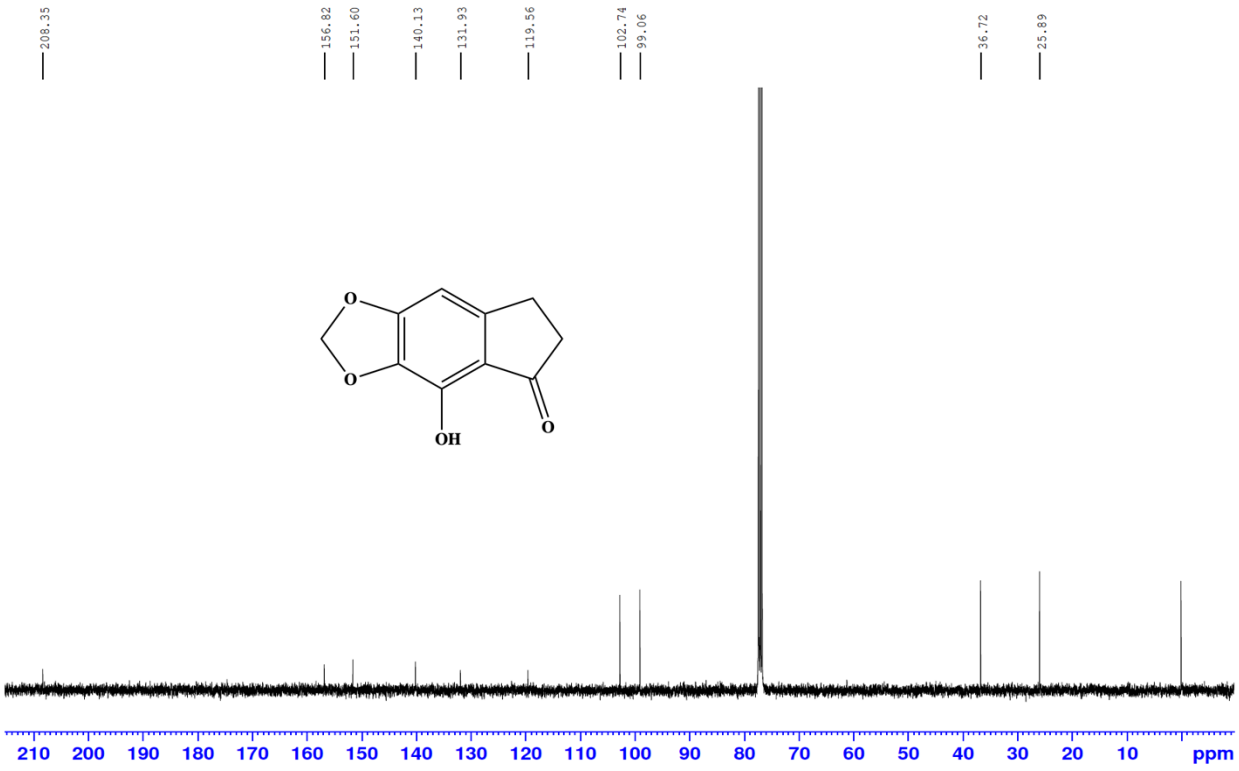
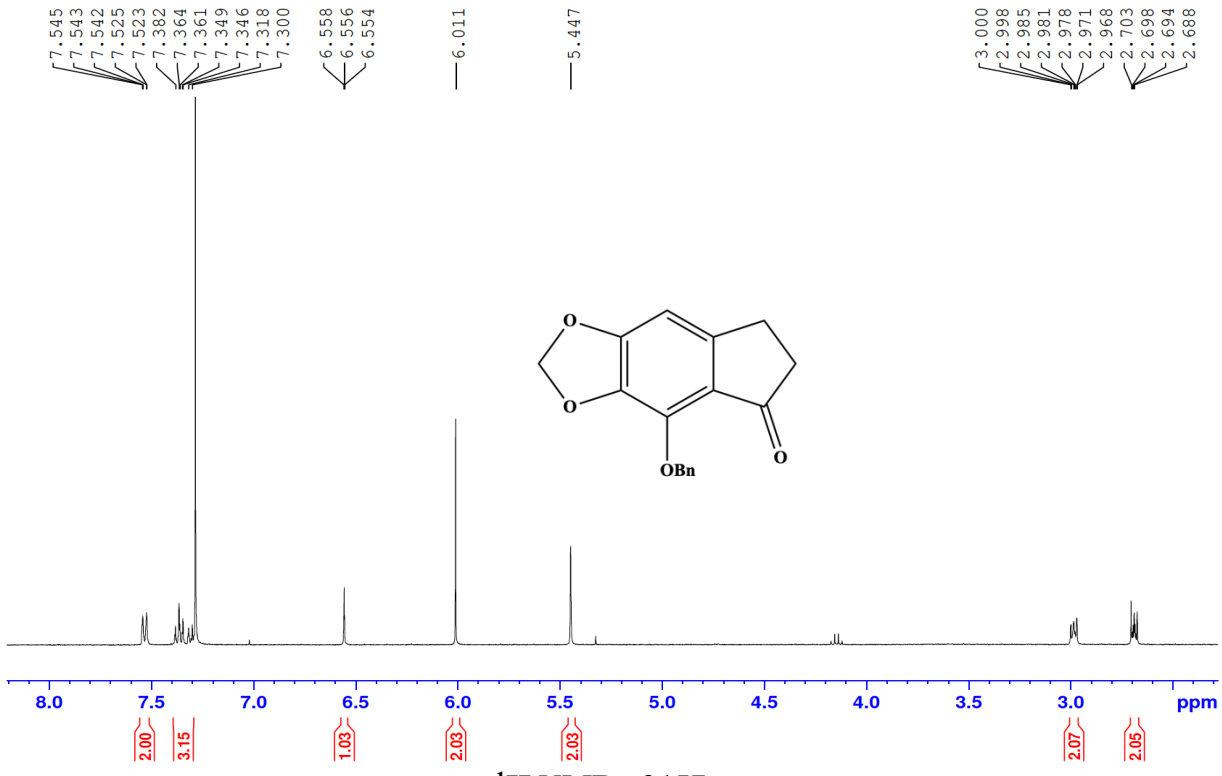


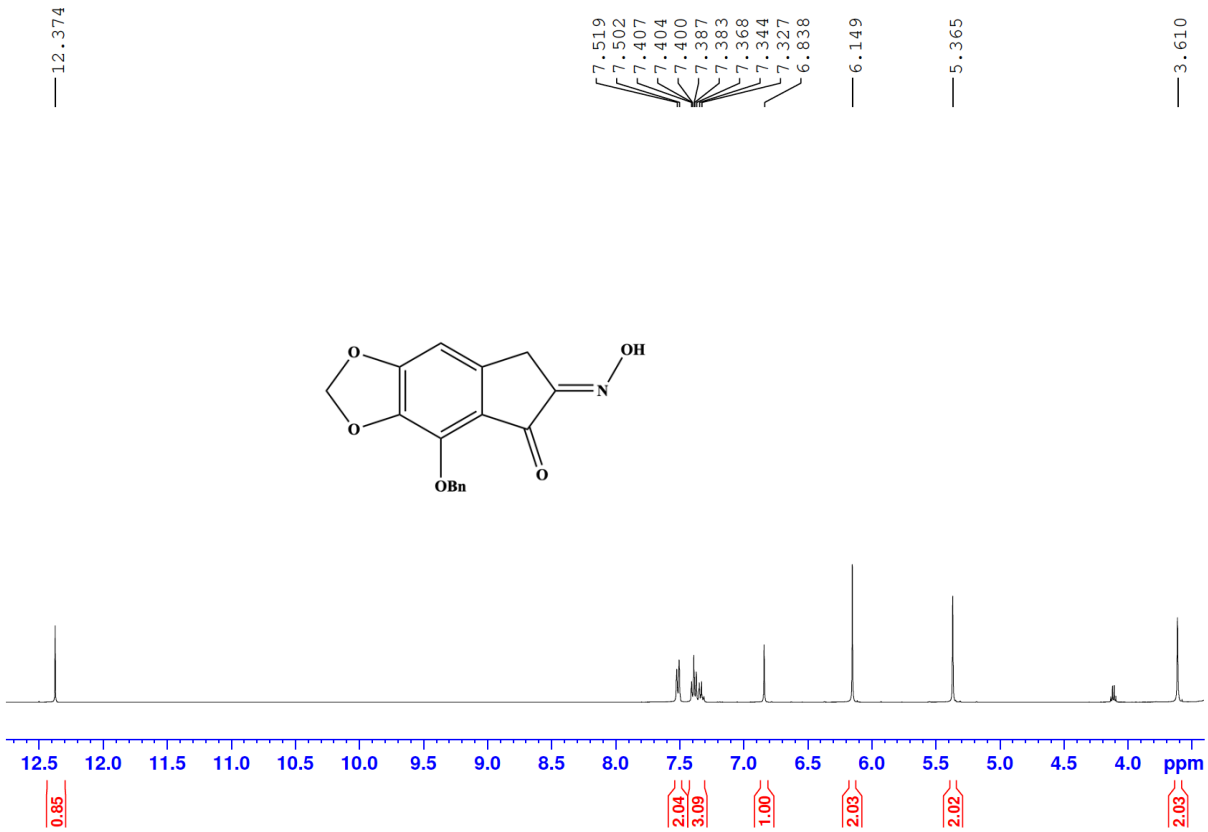
^{1}H NMR of 156



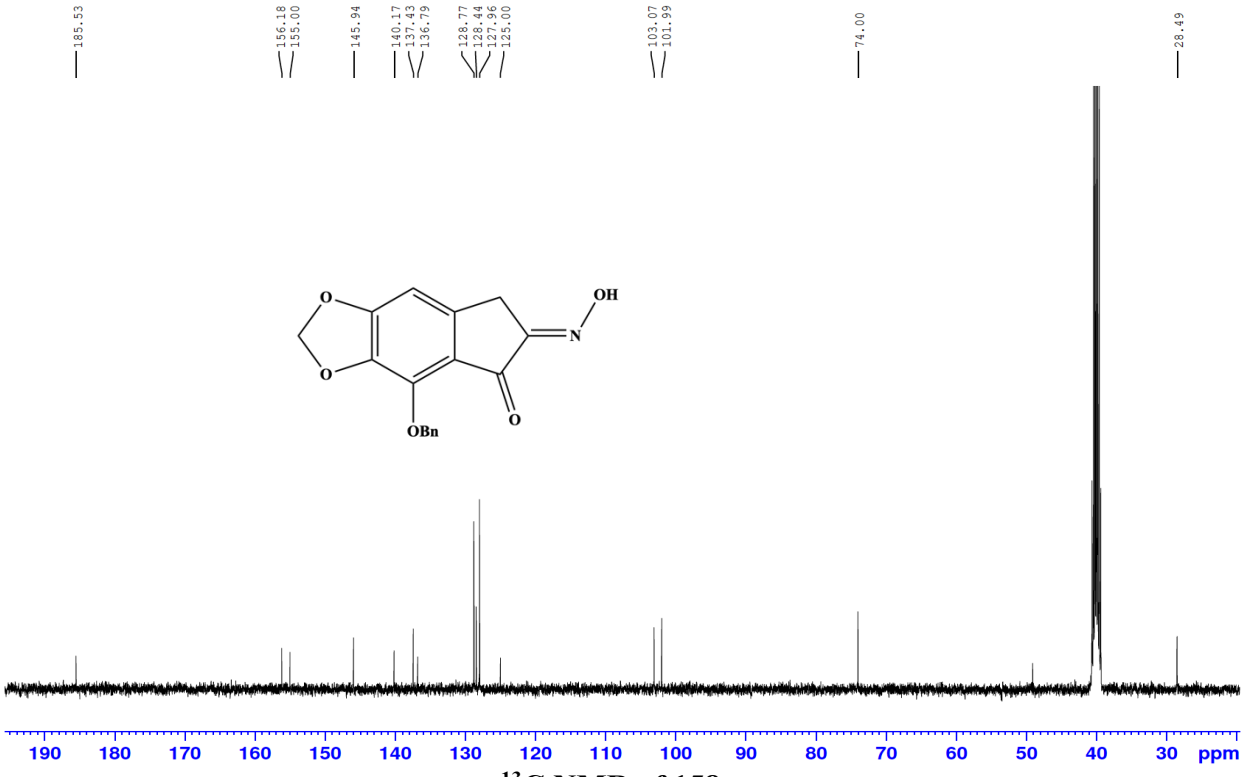
^{13}C NMR of 156



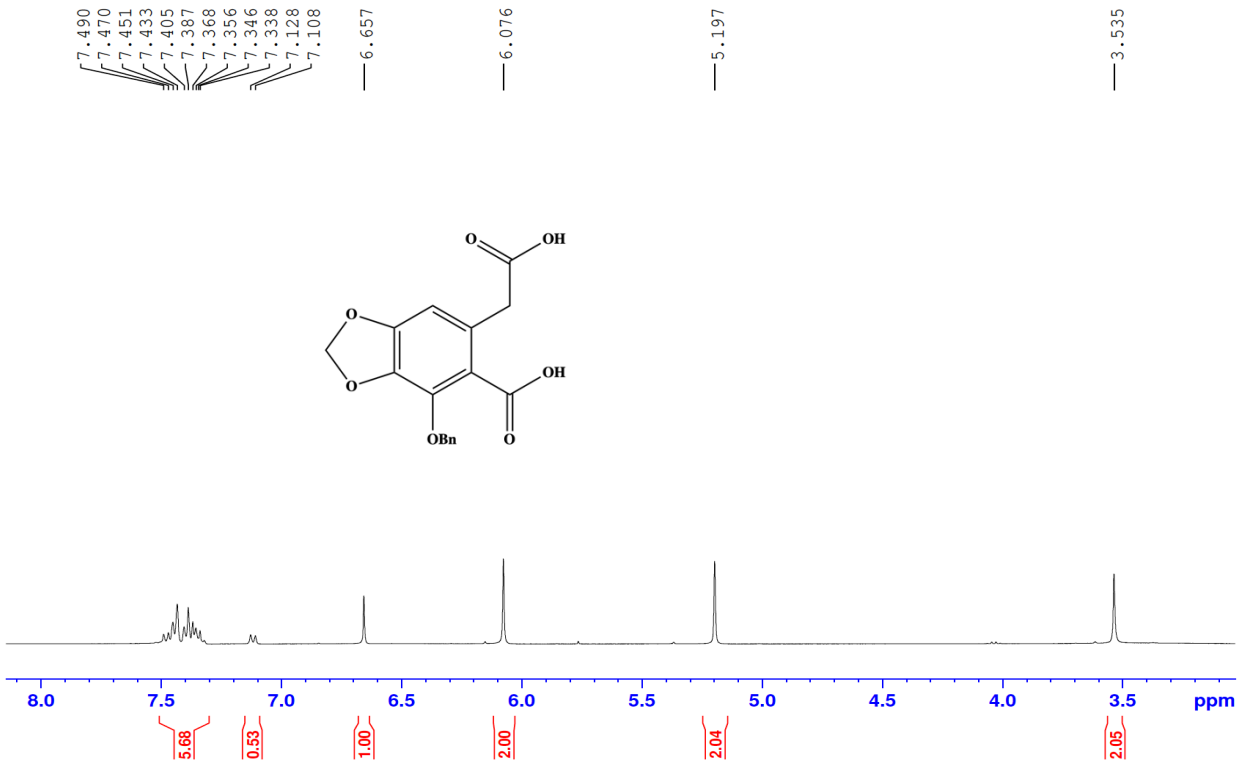
^{1}H NMR of 157



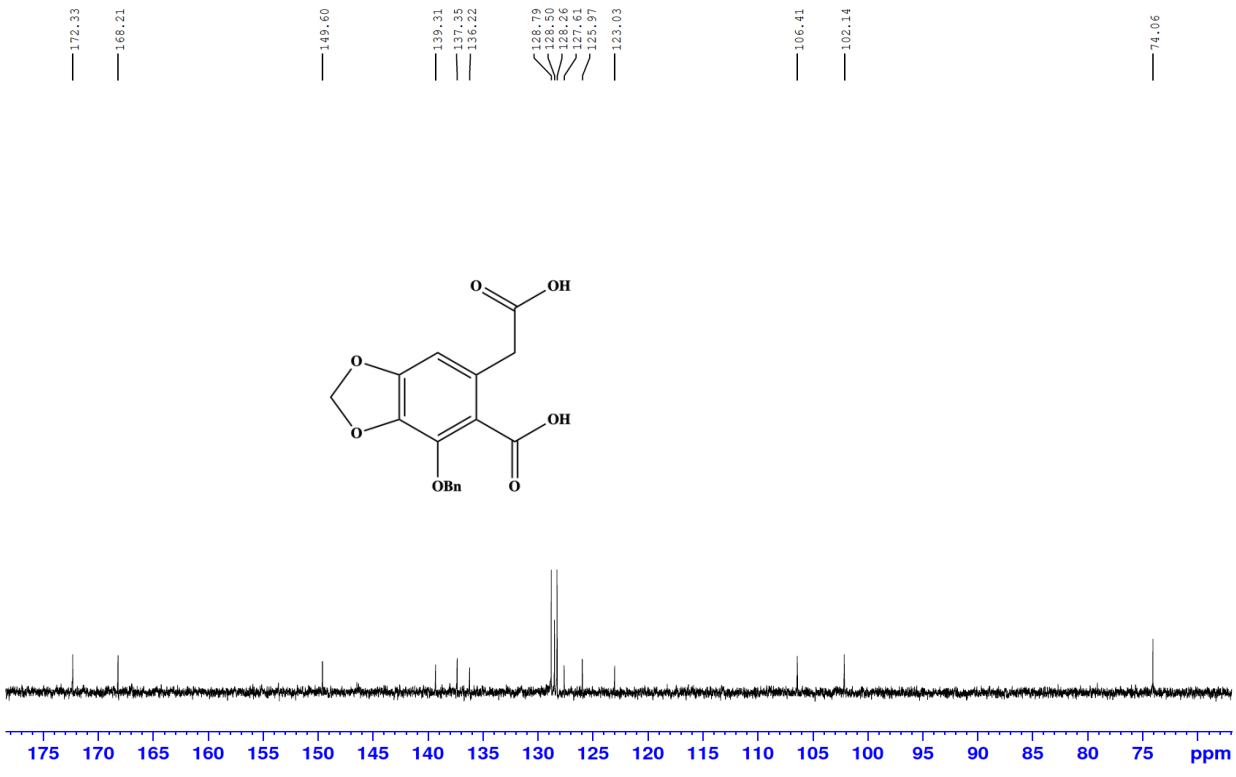
^{1}H NMR of 158



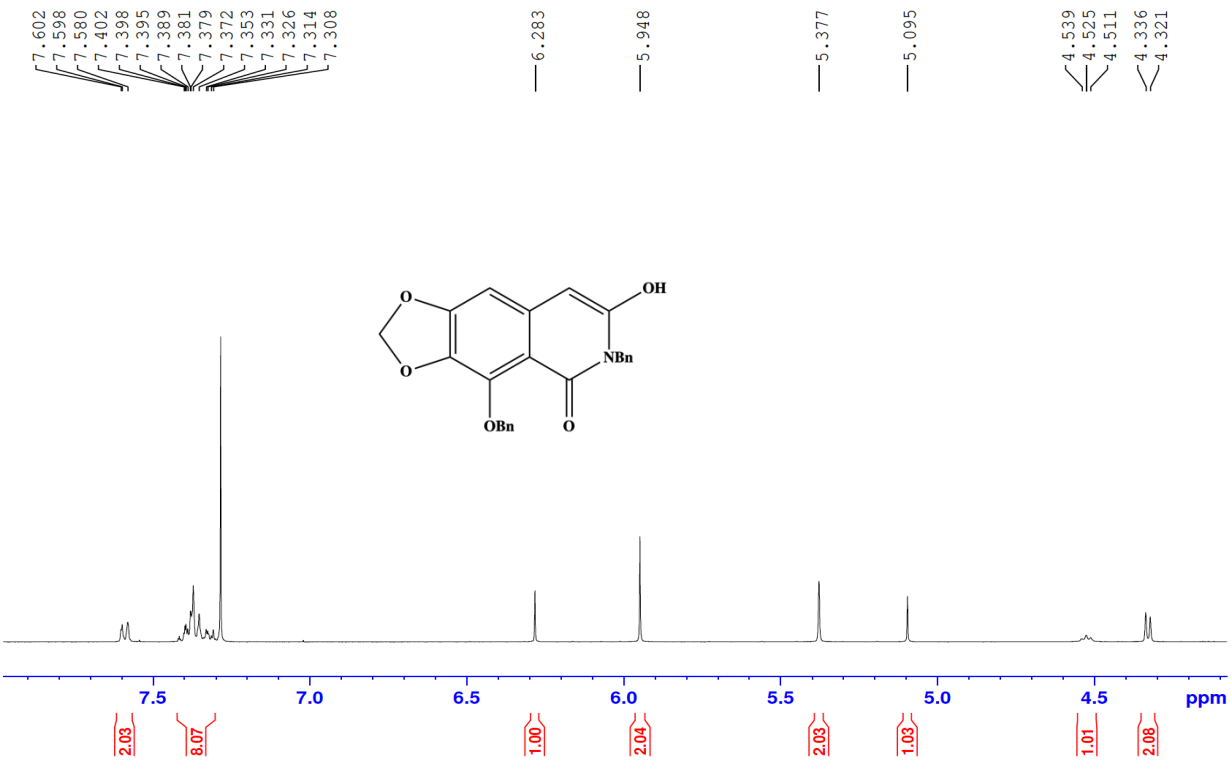
^{13}C NMR of 158



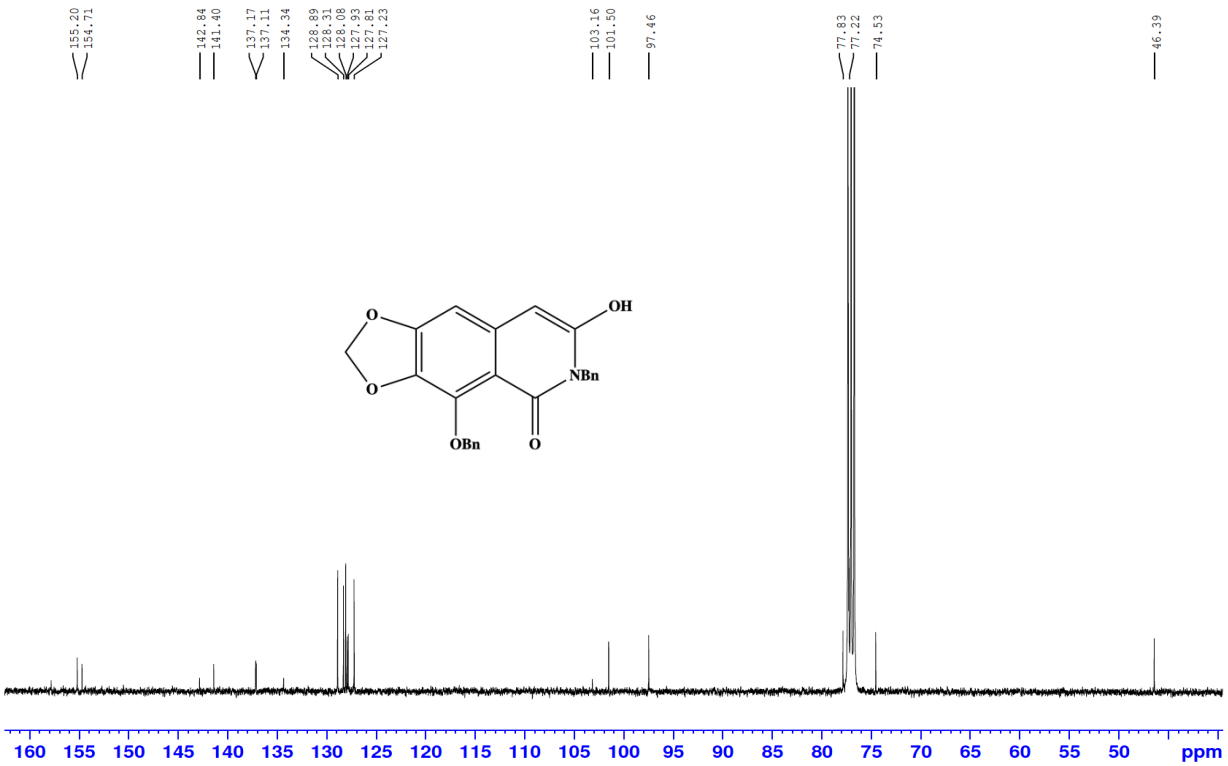
^{1}H NMR of 159



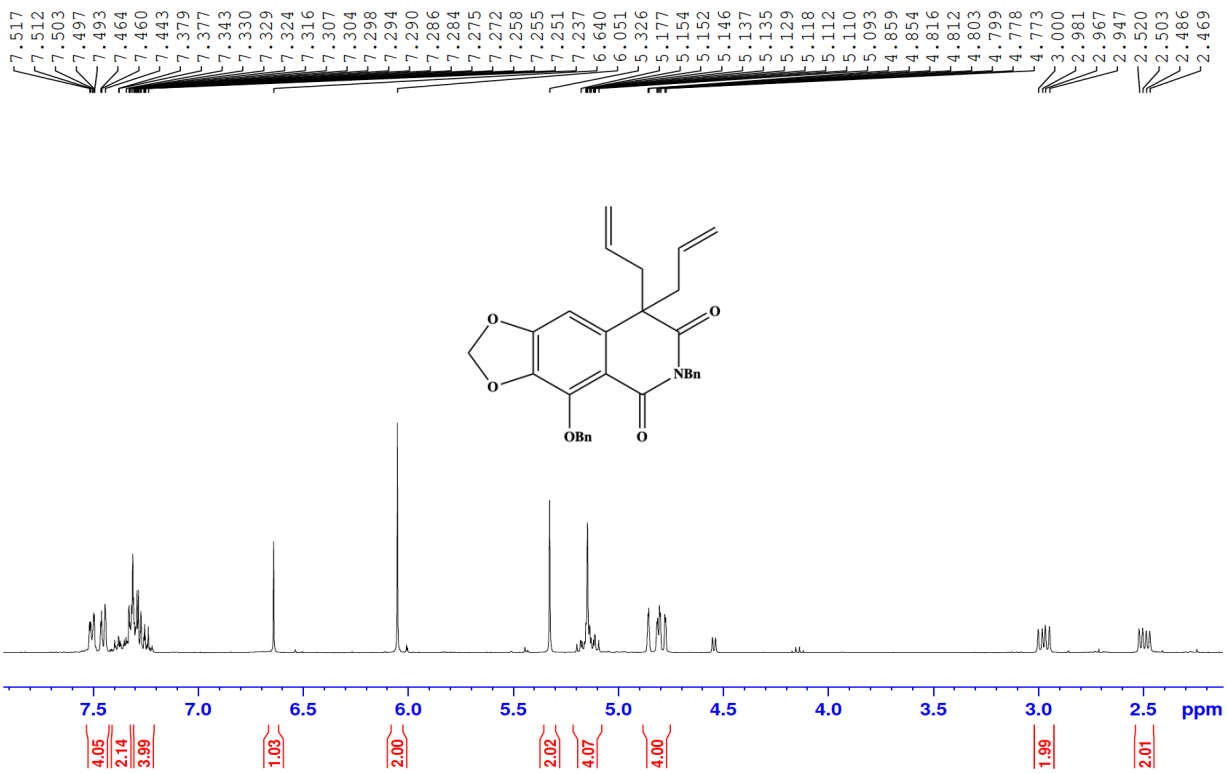
^{13}C NMR of 159



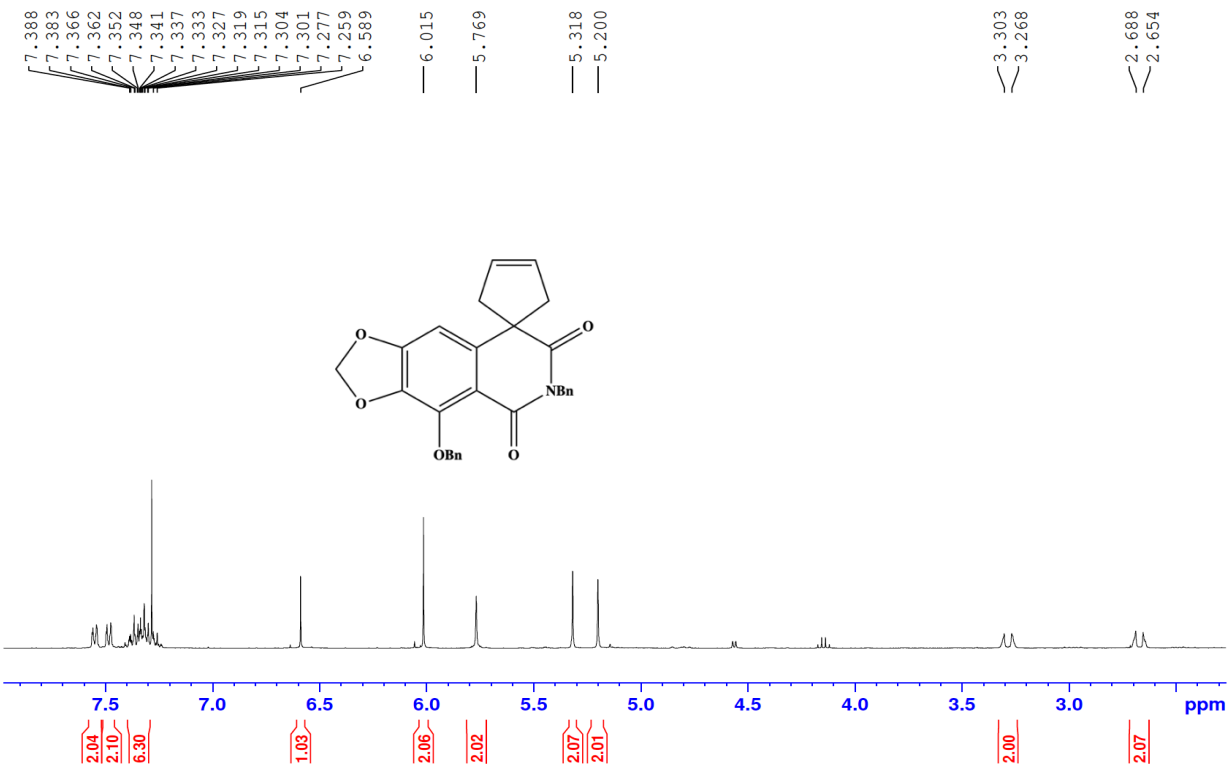
^{1}H NMR of 160



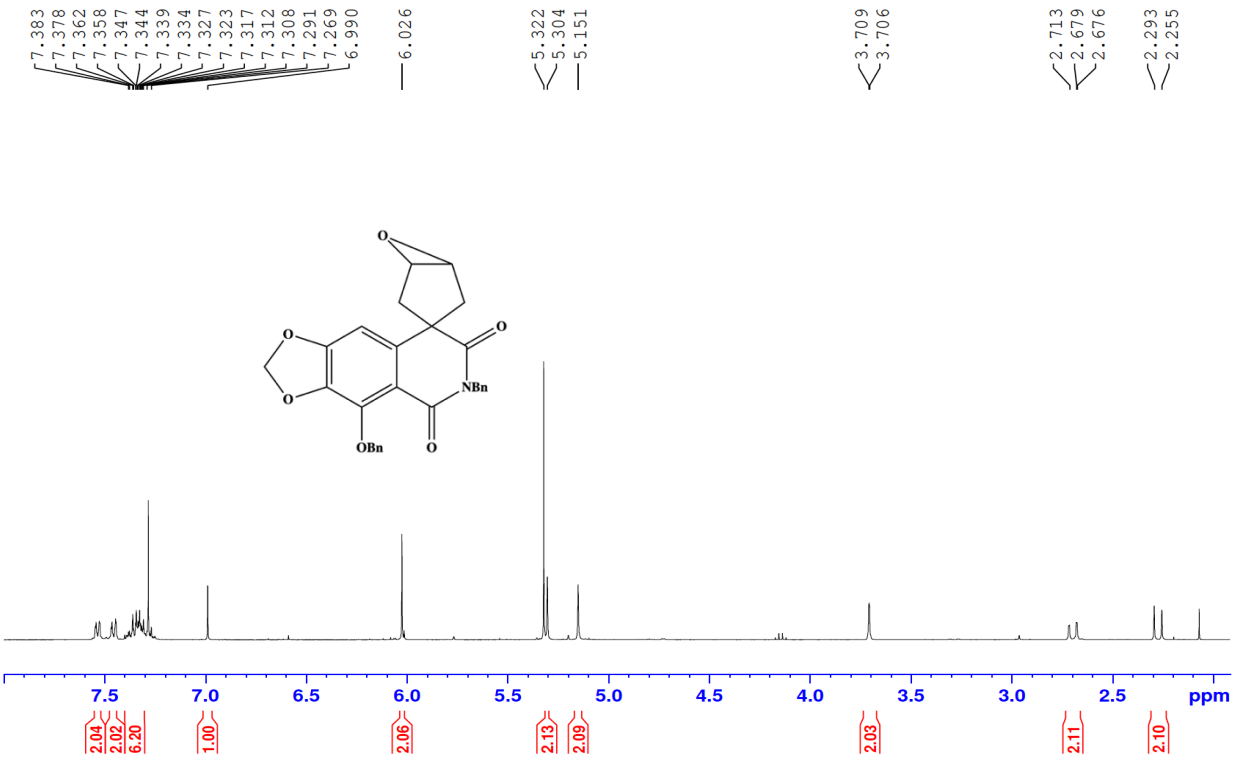
^{13}C NMR of 160



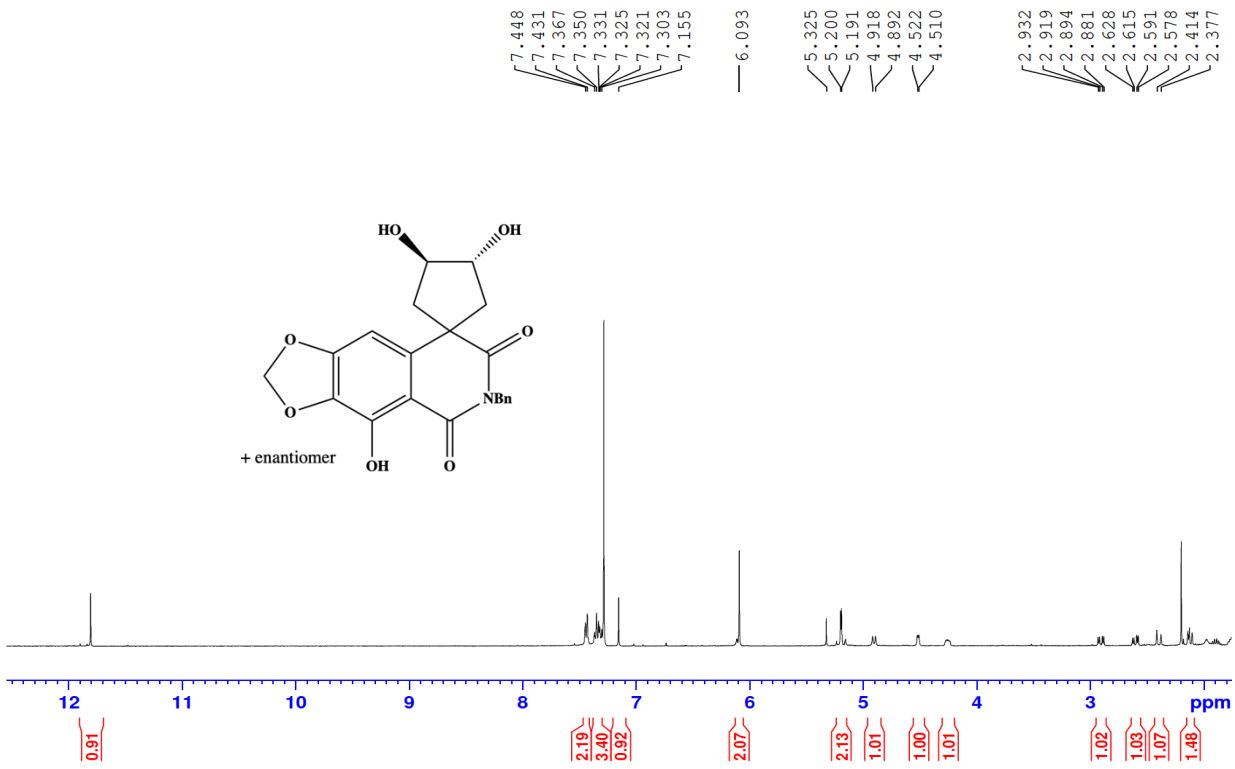
^{1}H NMR of 161



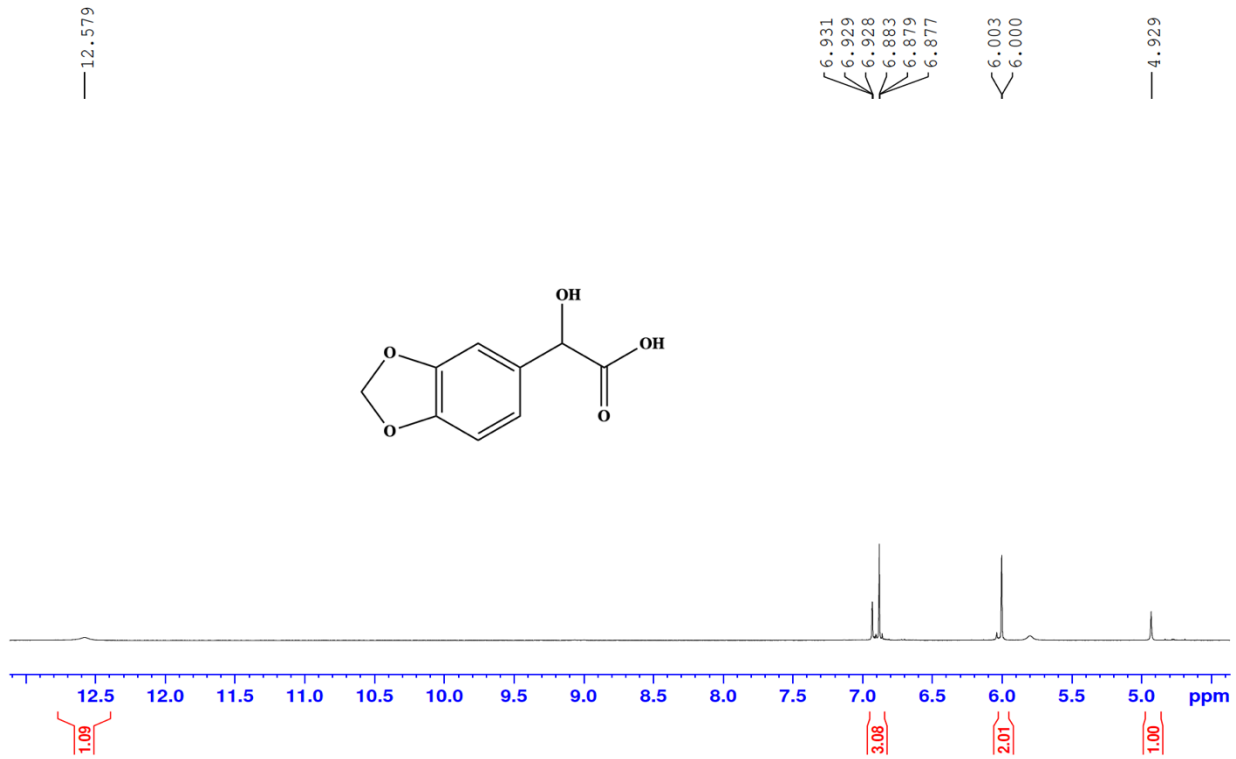
^{1}H NMR of 162



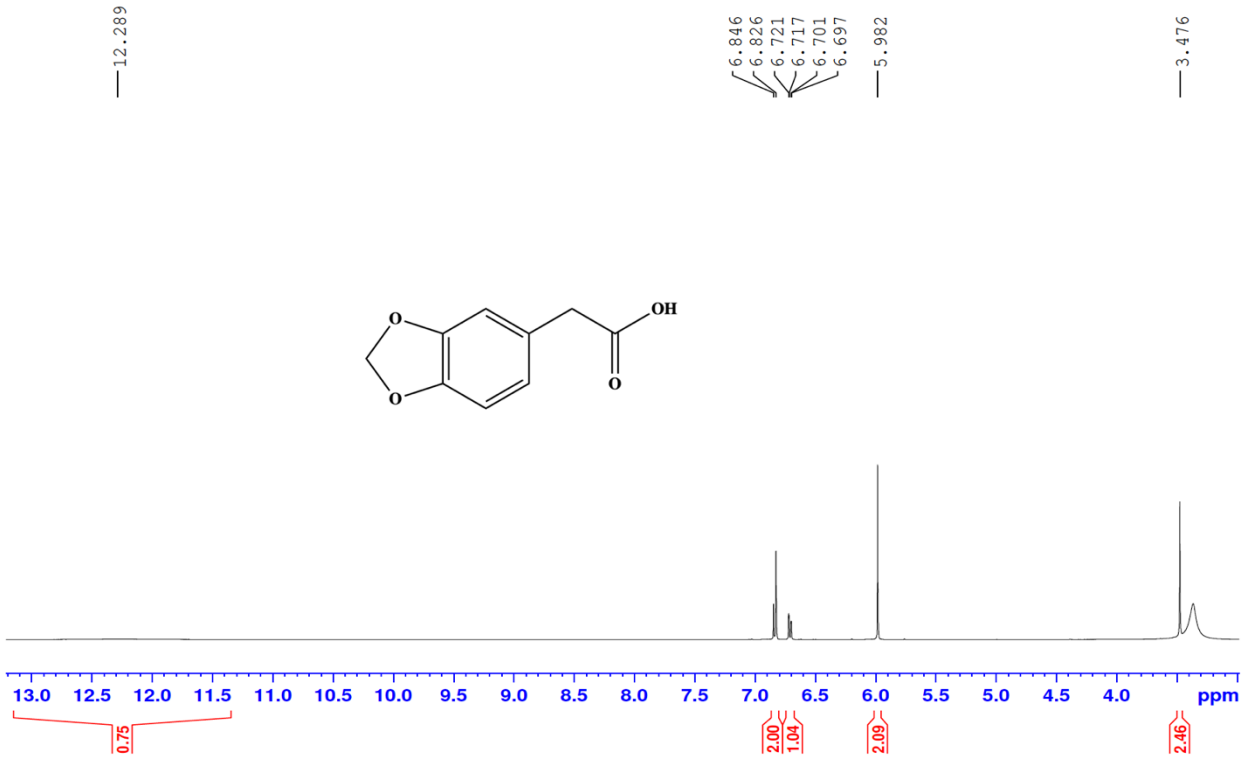
^{1}H NMR of 163



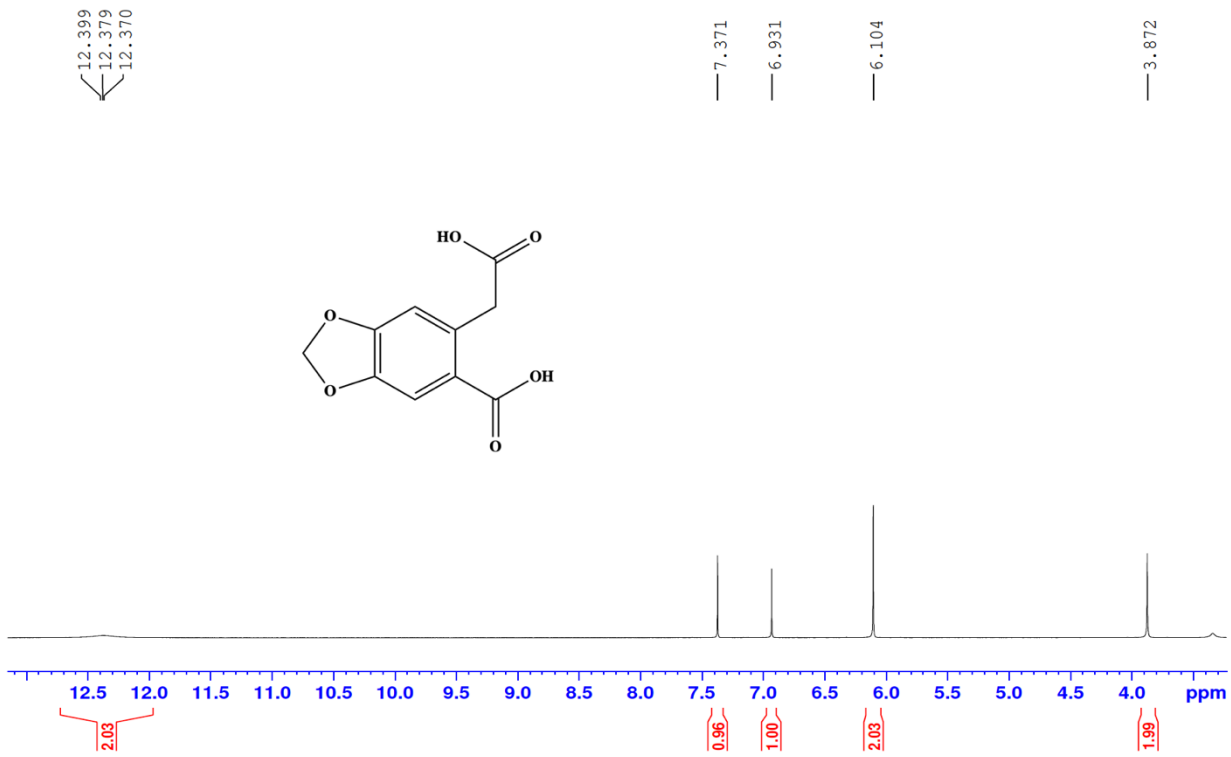
^{1}H NMR of 164



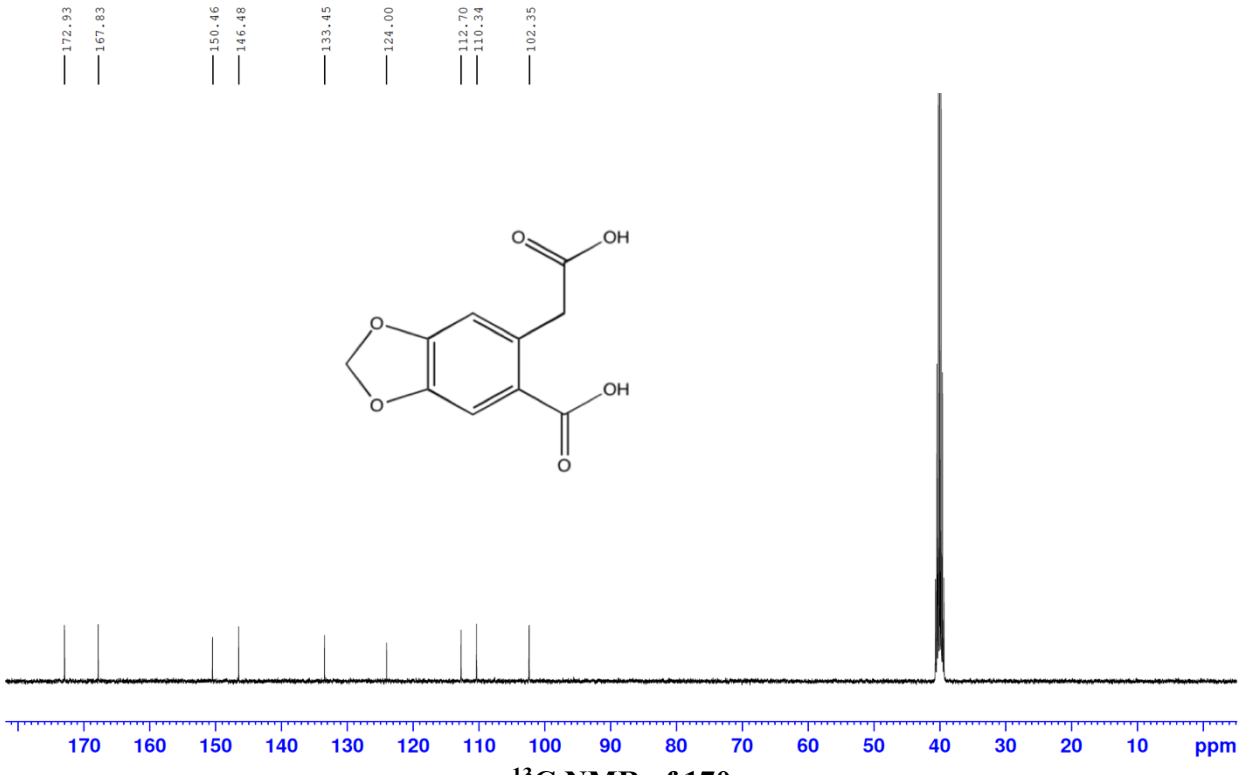
^{1}H NMR of 165



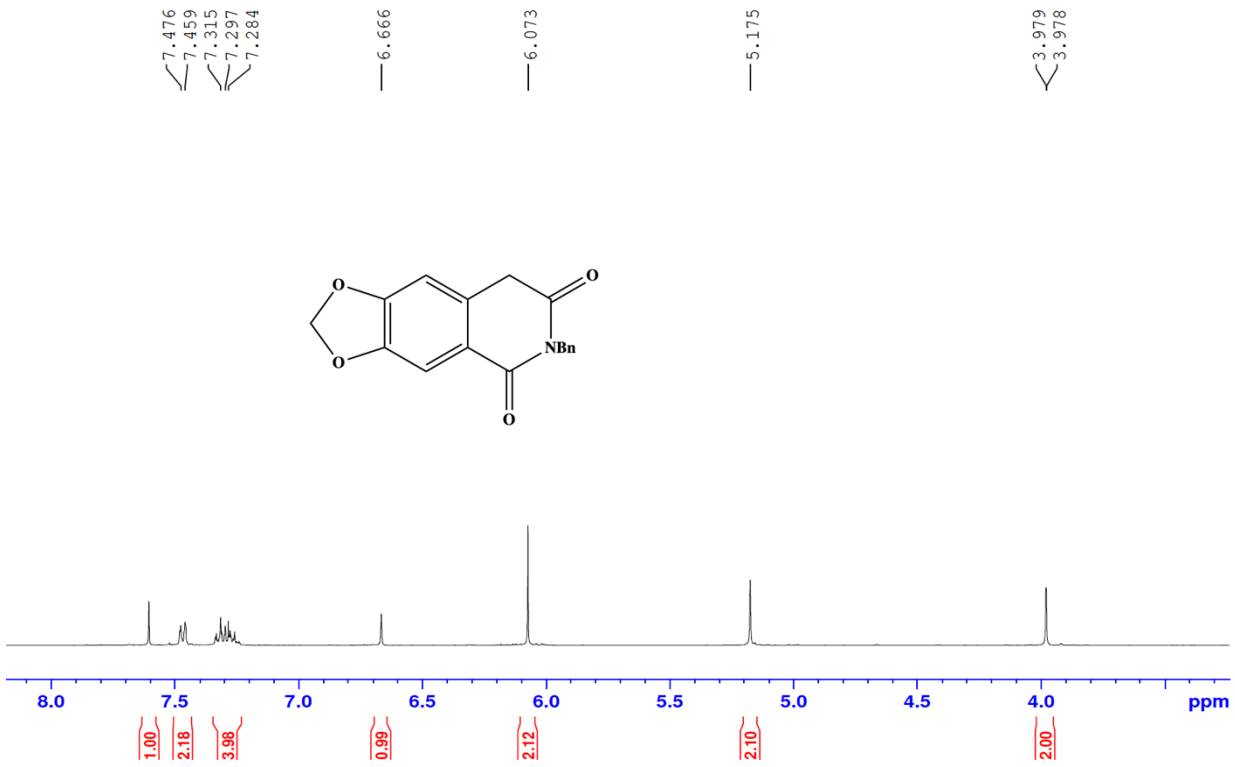
^{1}H NMR of 167



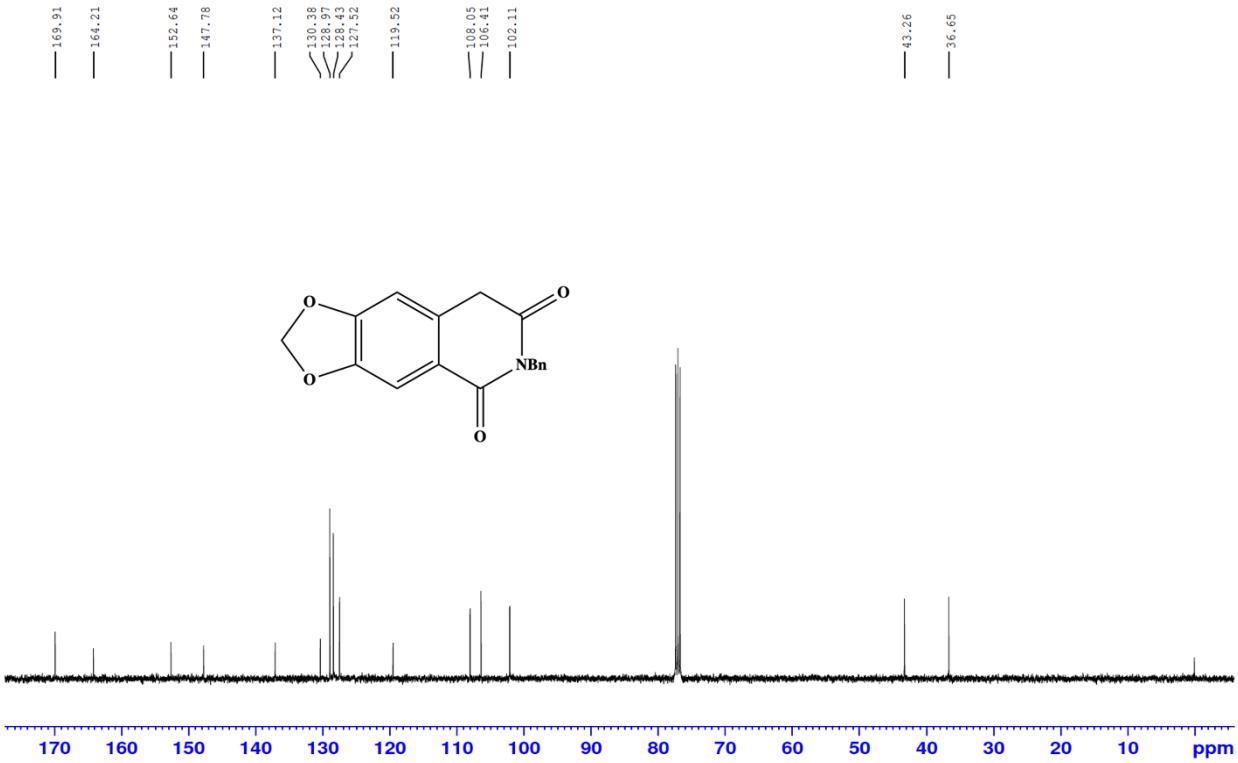
^{1}H NMR of 170



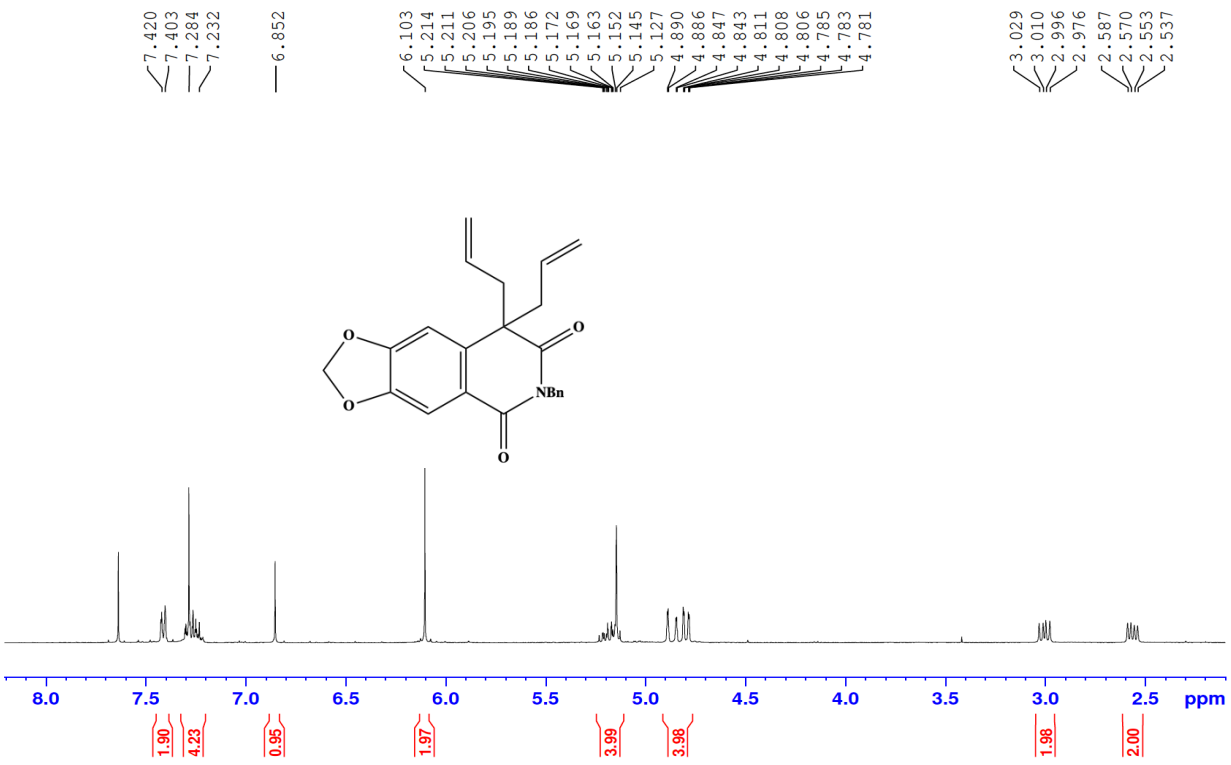
^{13}C NMR of 170



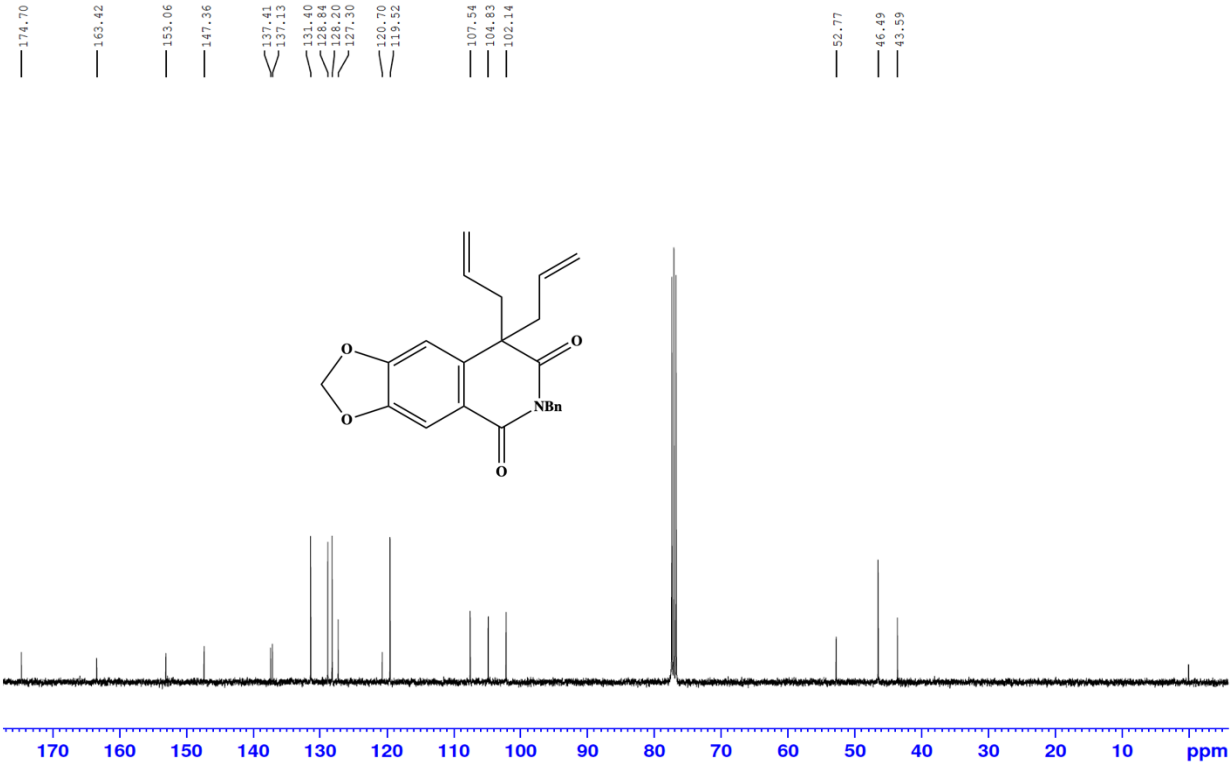
^{1}H NMR of 171



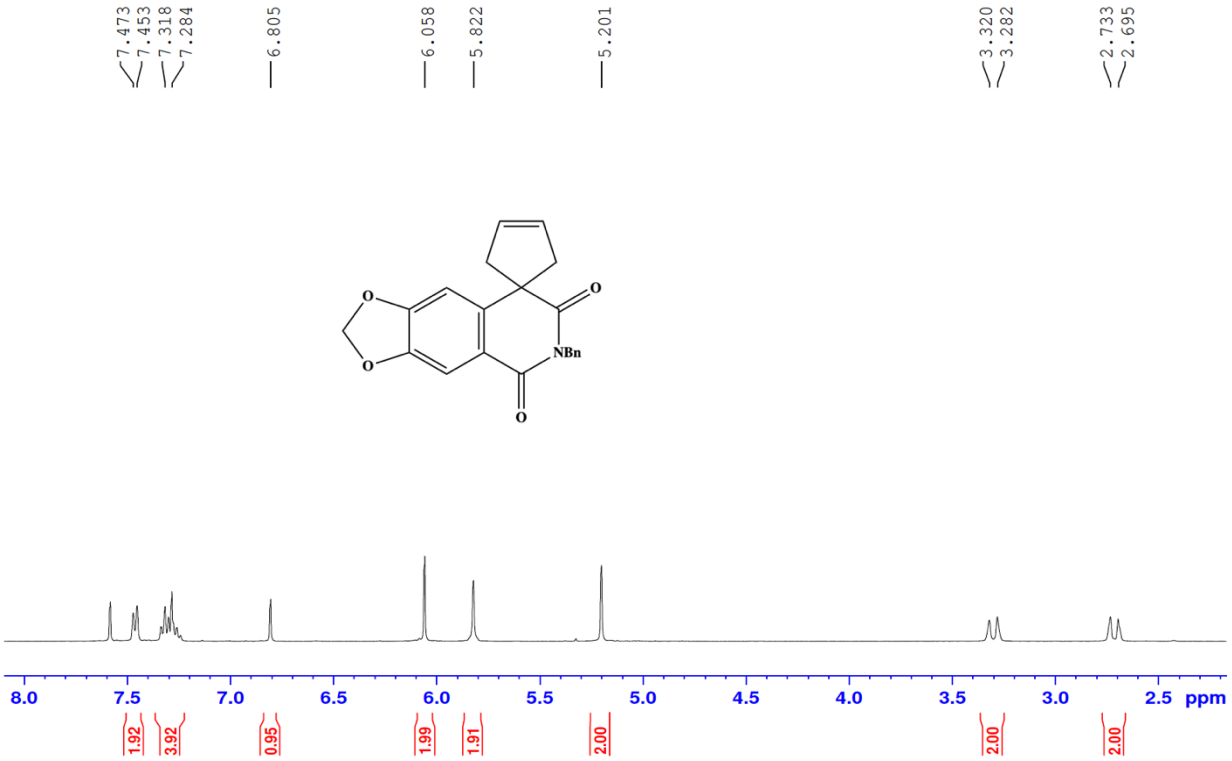
^{13}C NMR of 171



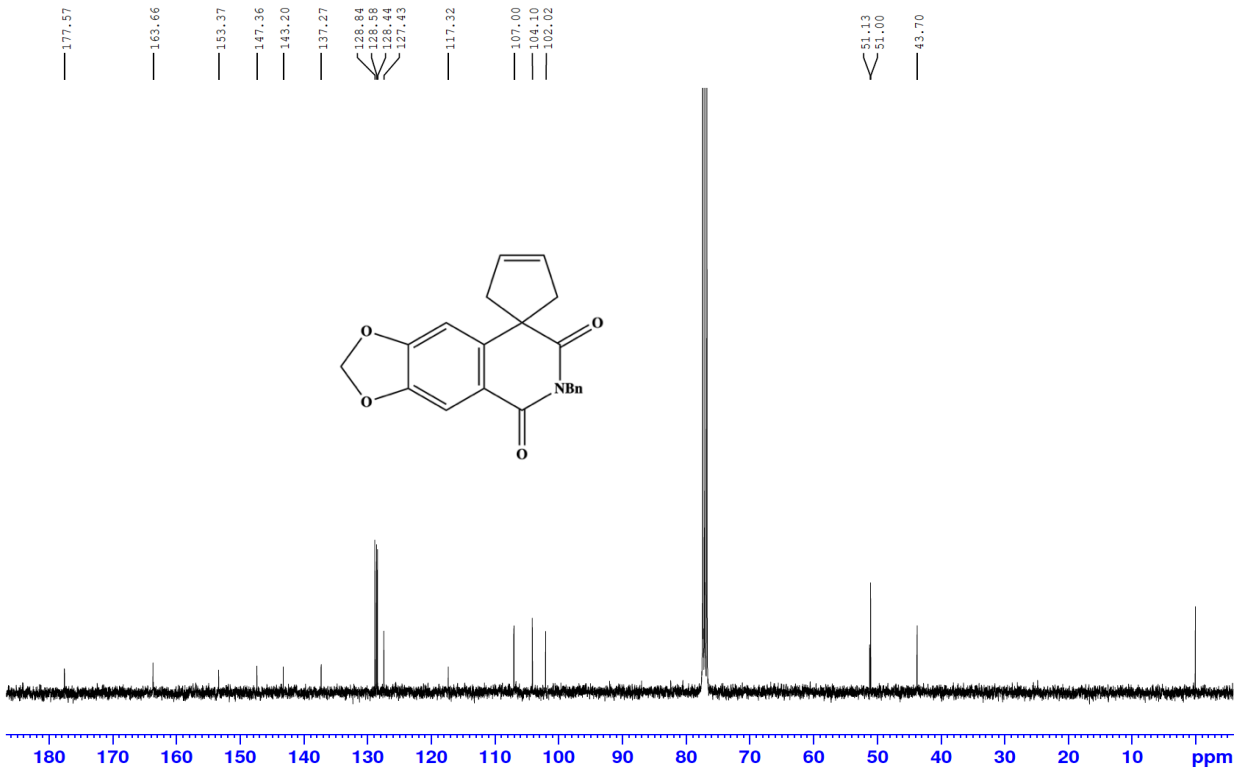
^{1}H NMR of 172



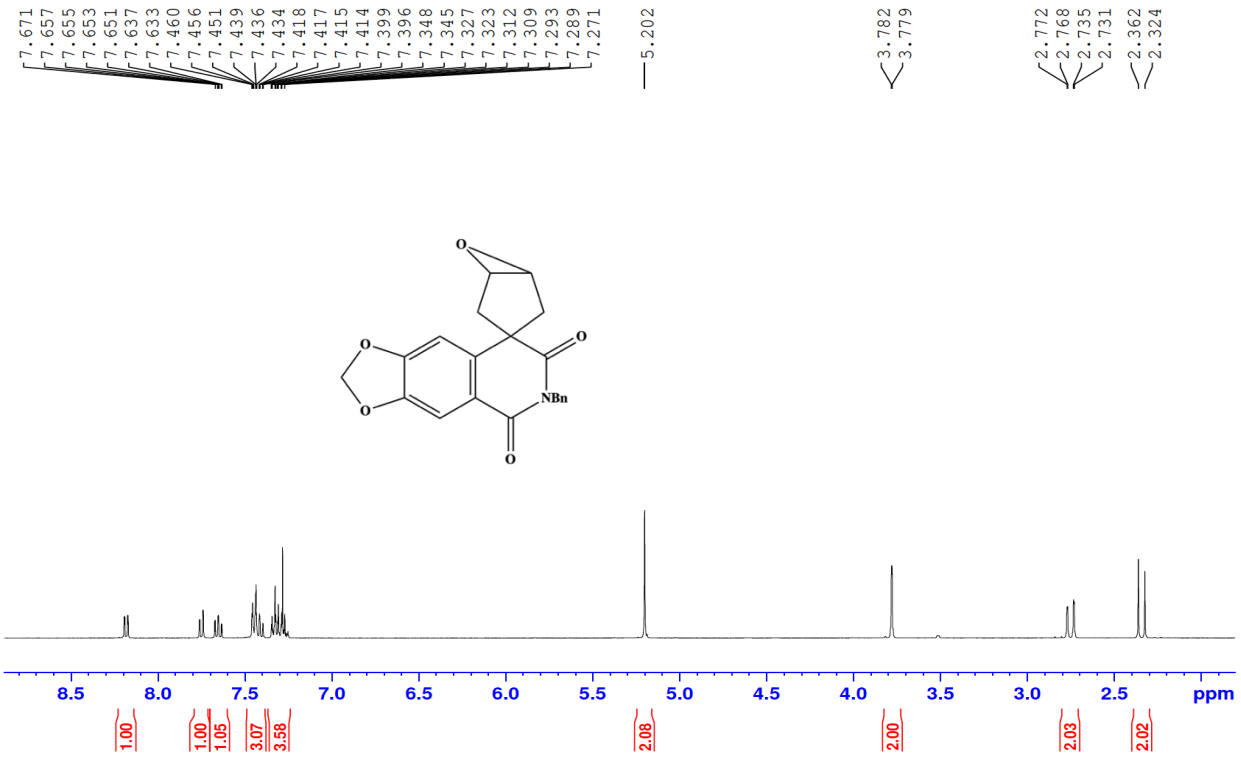
^{13}C NMR of 172



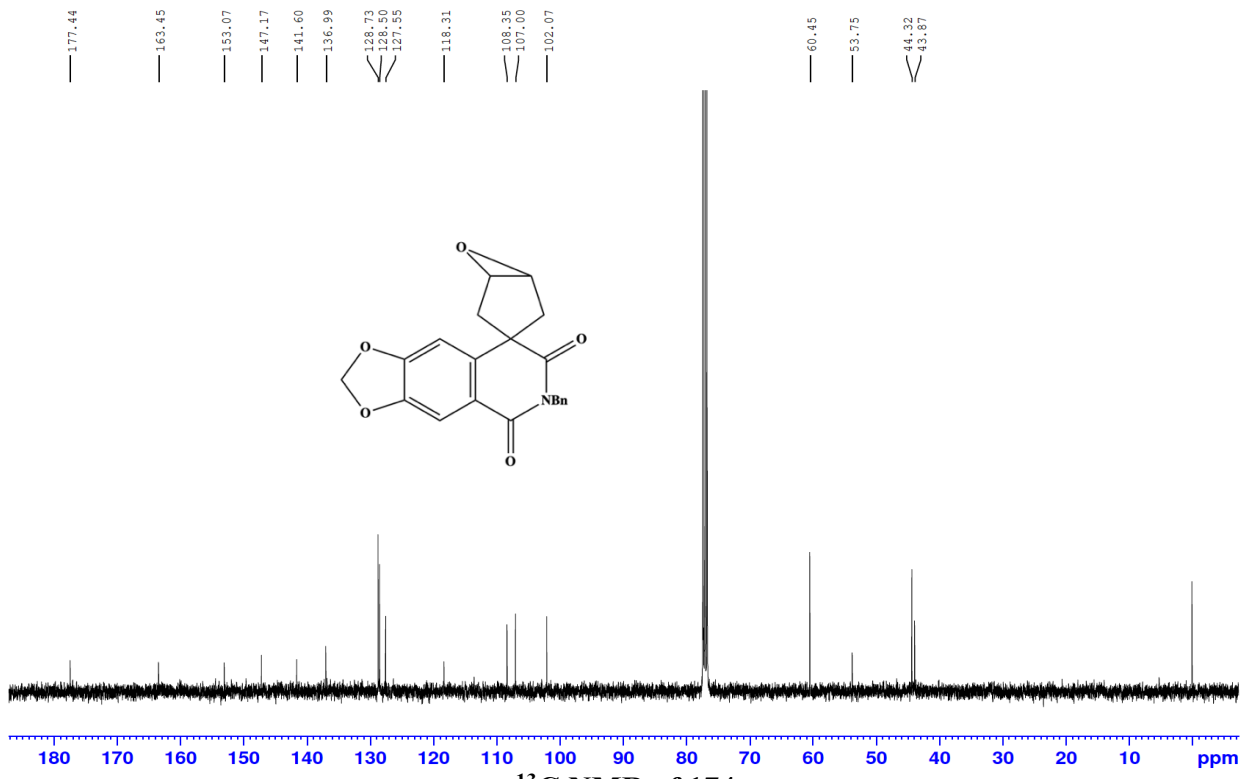
^{1}H NMR of 173



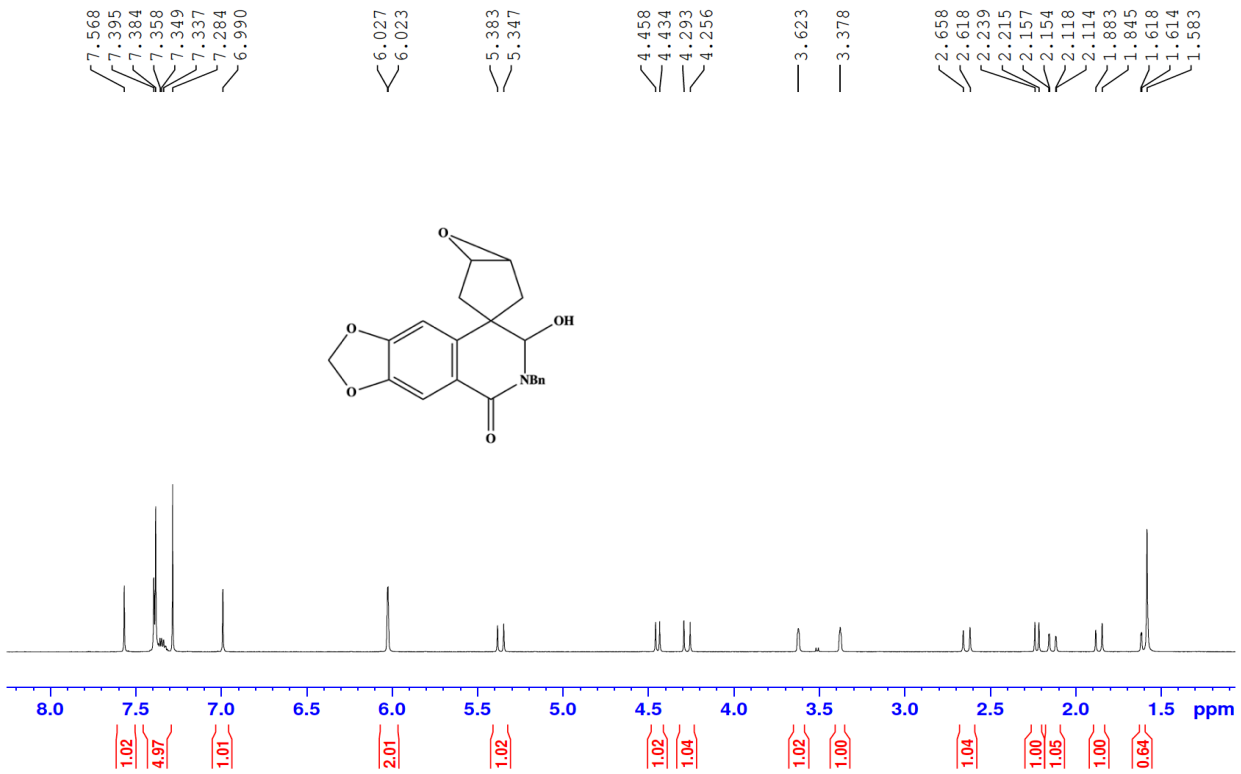
^{13}C NMR of 173



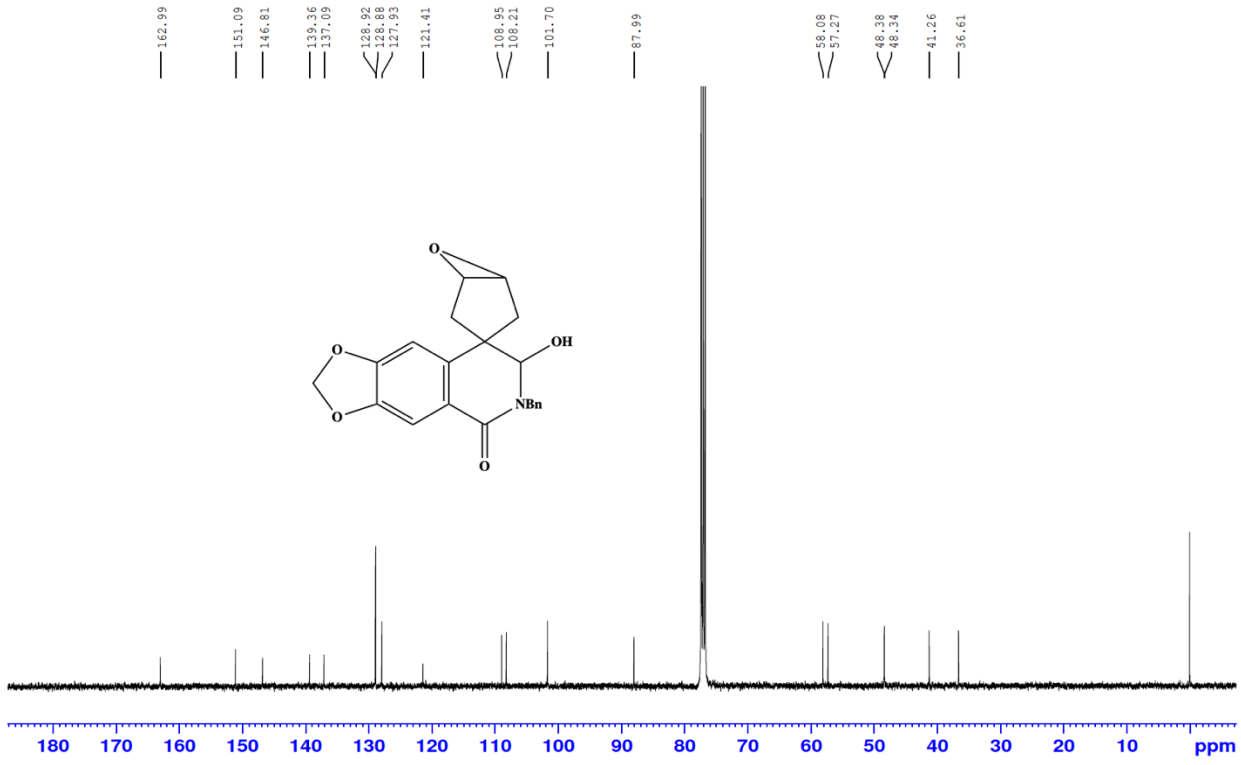
^{1}H NMR of 174



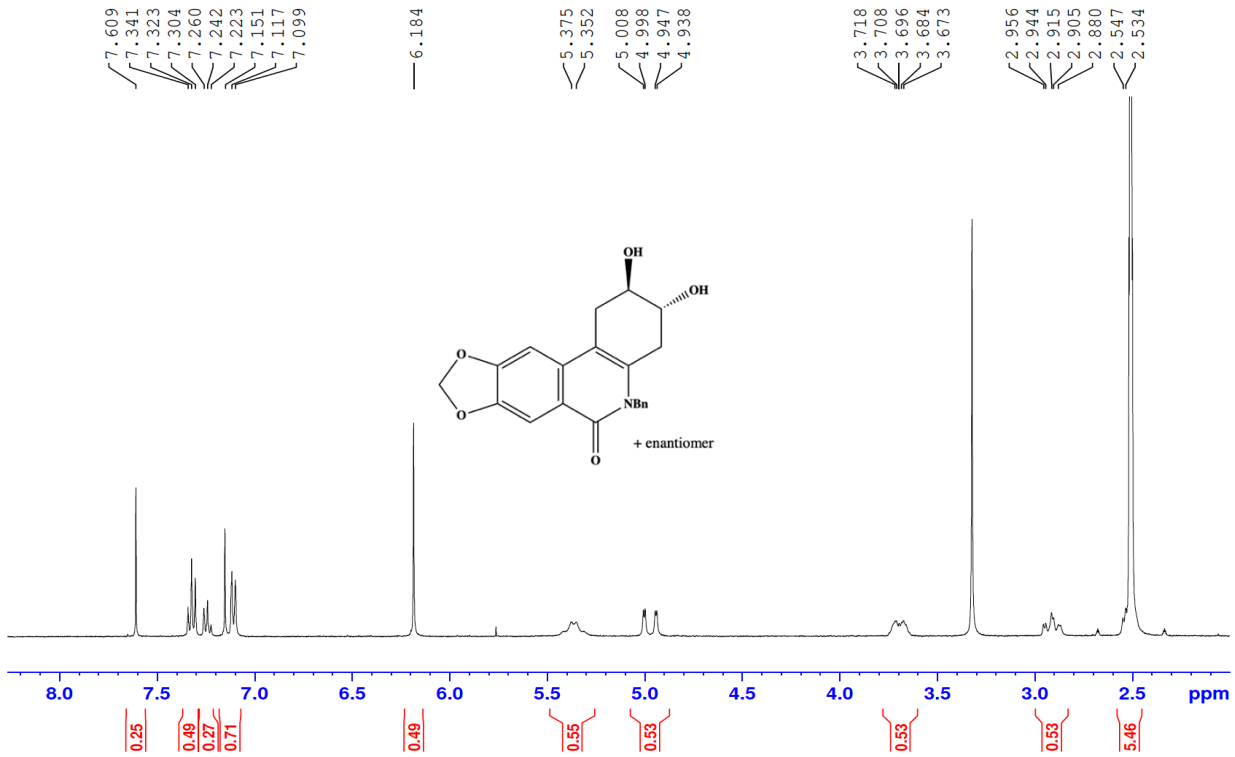
^{13}C NMR of 174



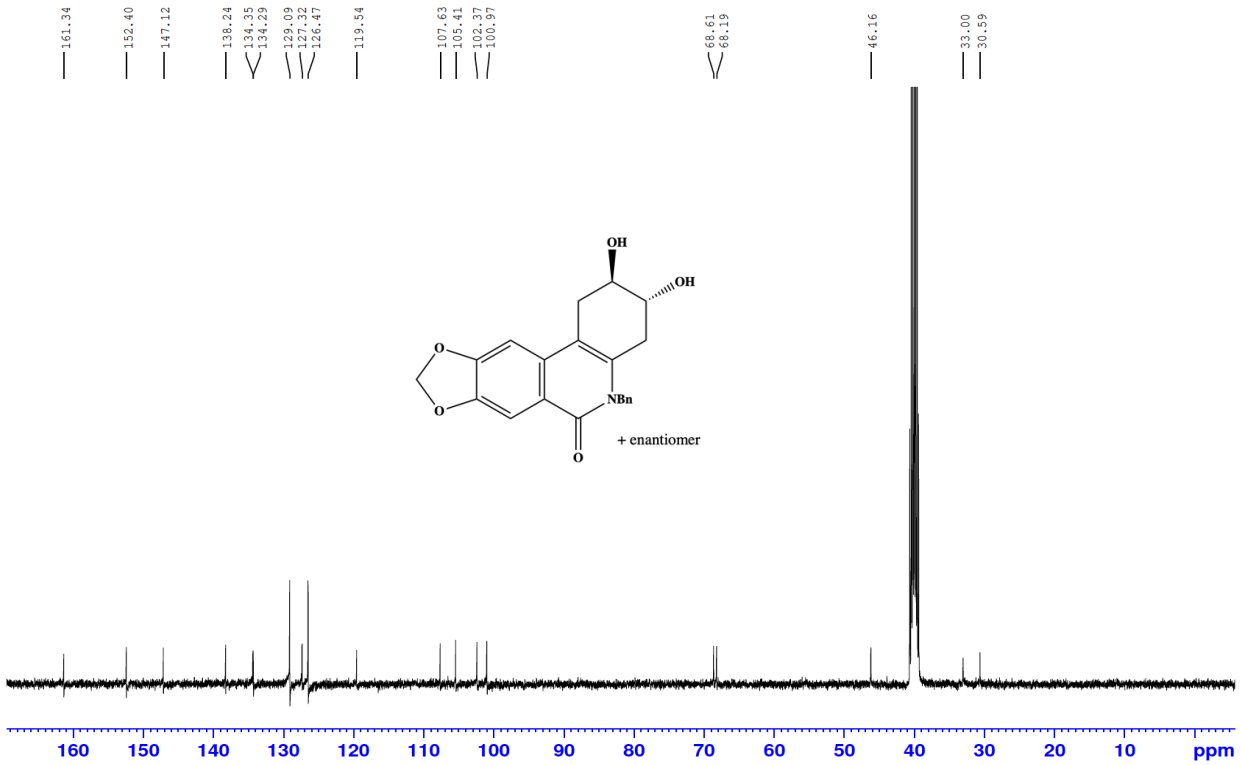
^{1}H NMR of 175



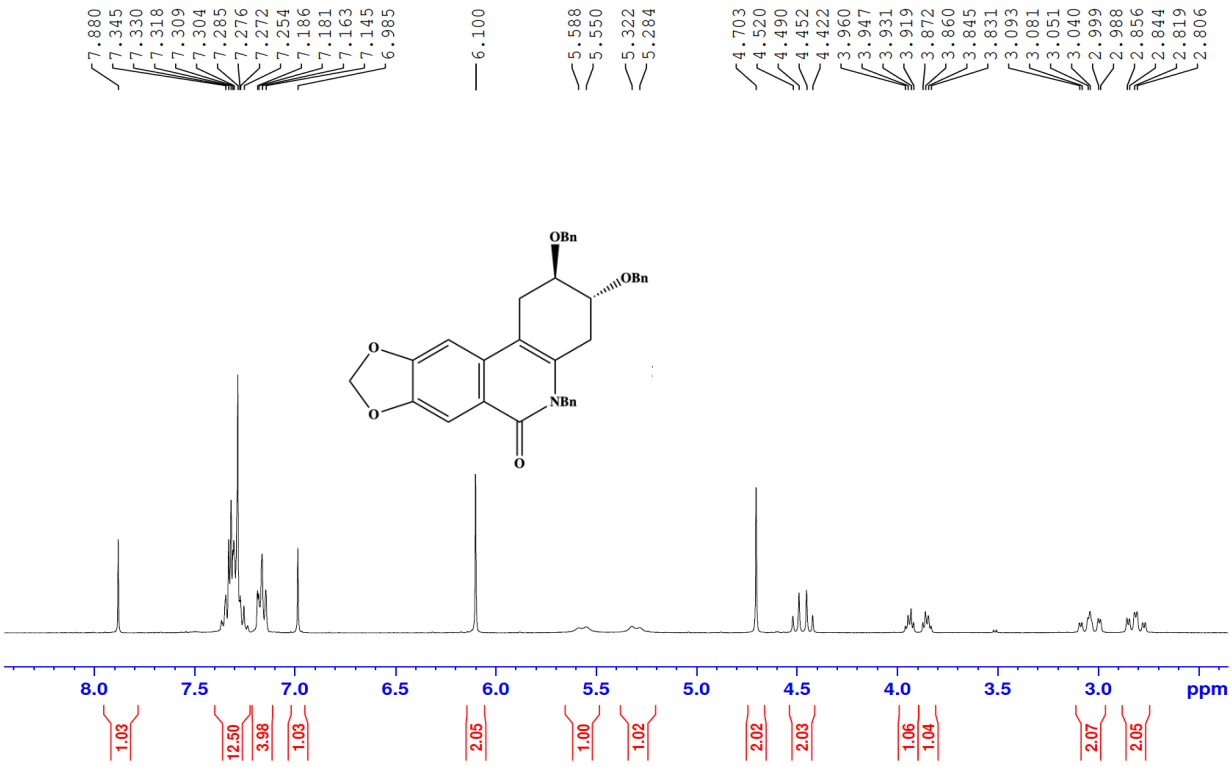
^{13}C NMR of 175



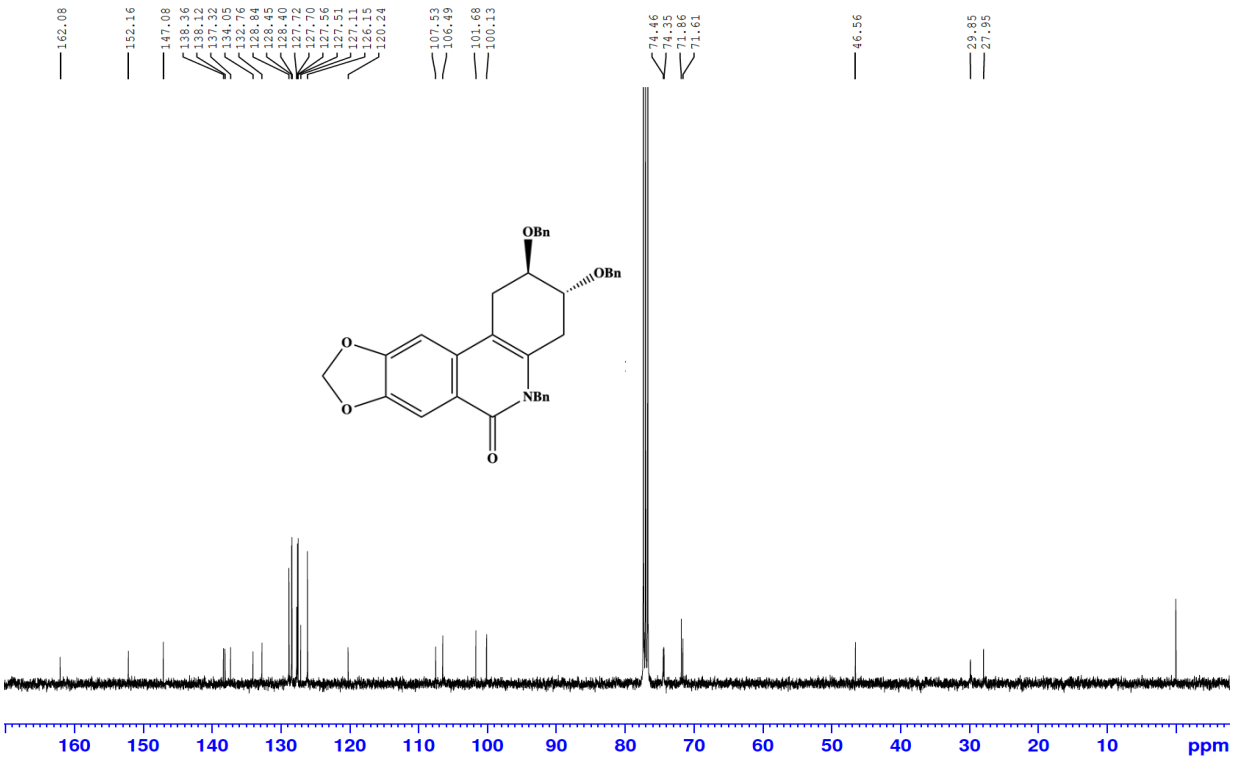
^{1}H NMR of 176



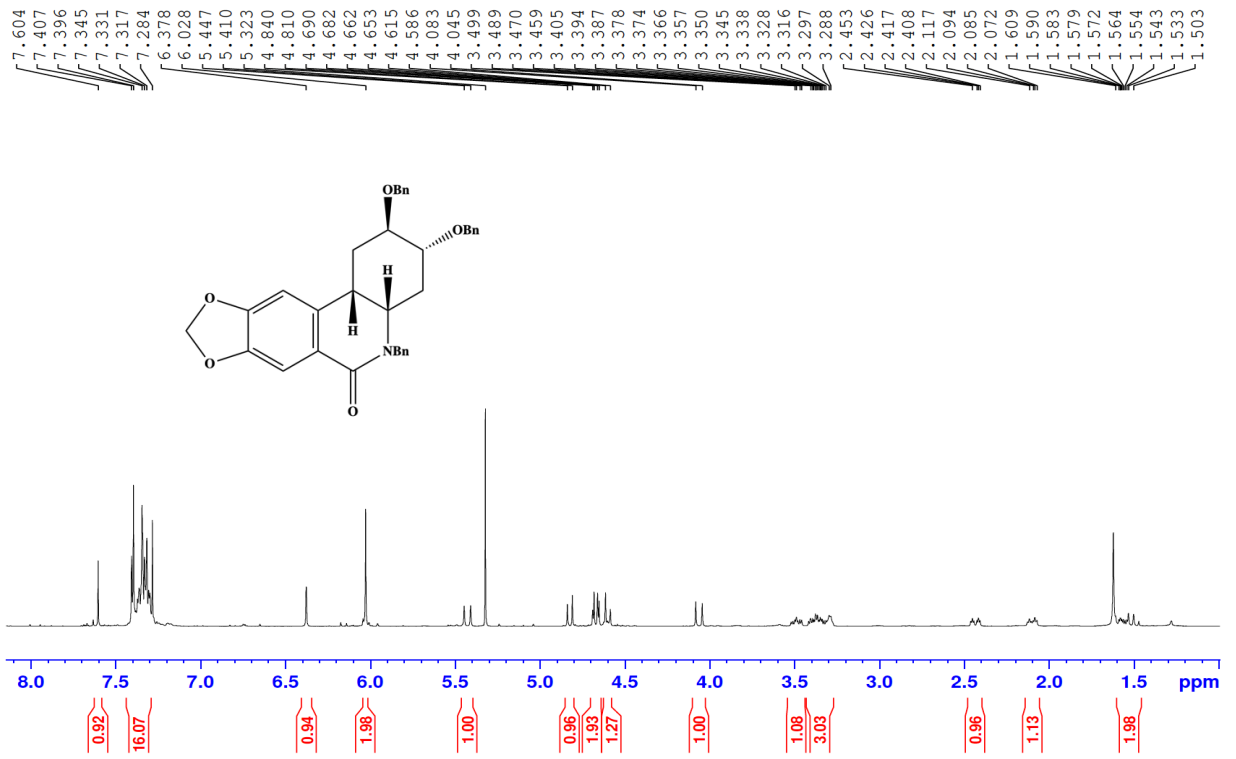
^{13}C NMR of 176



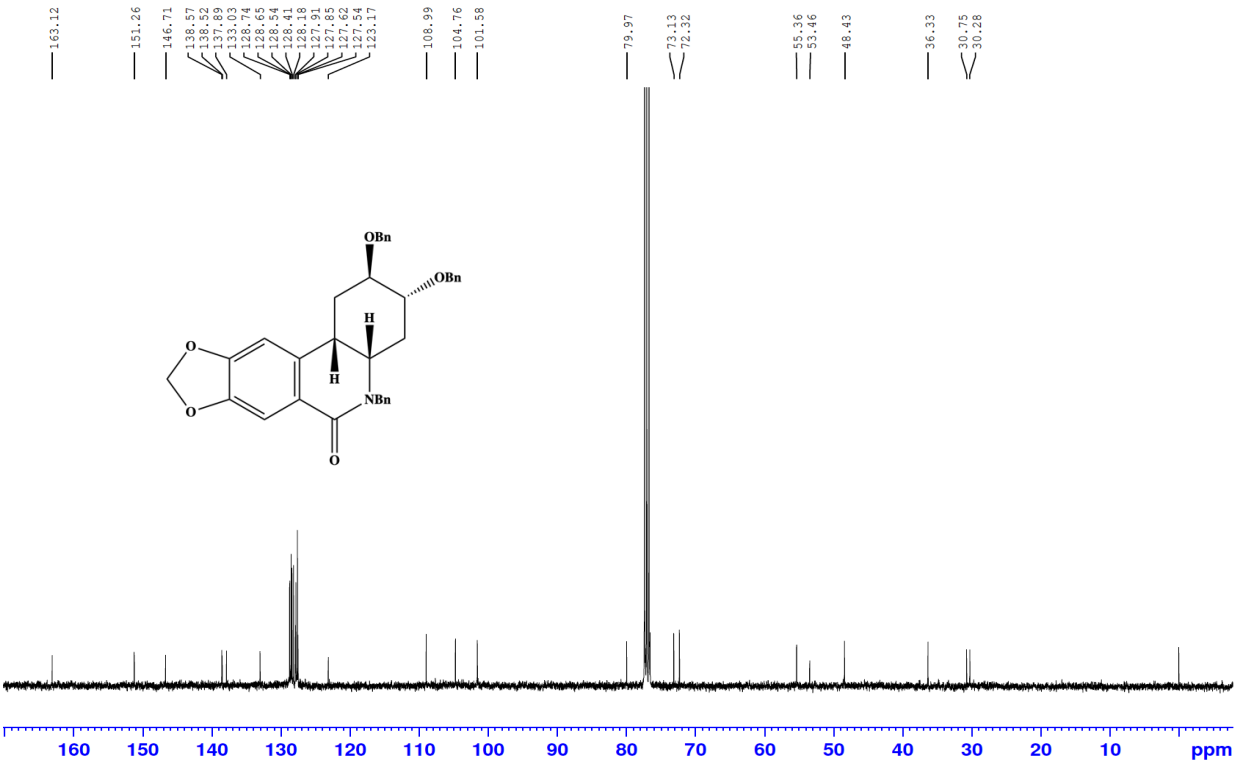
^{1}H NMR of 177



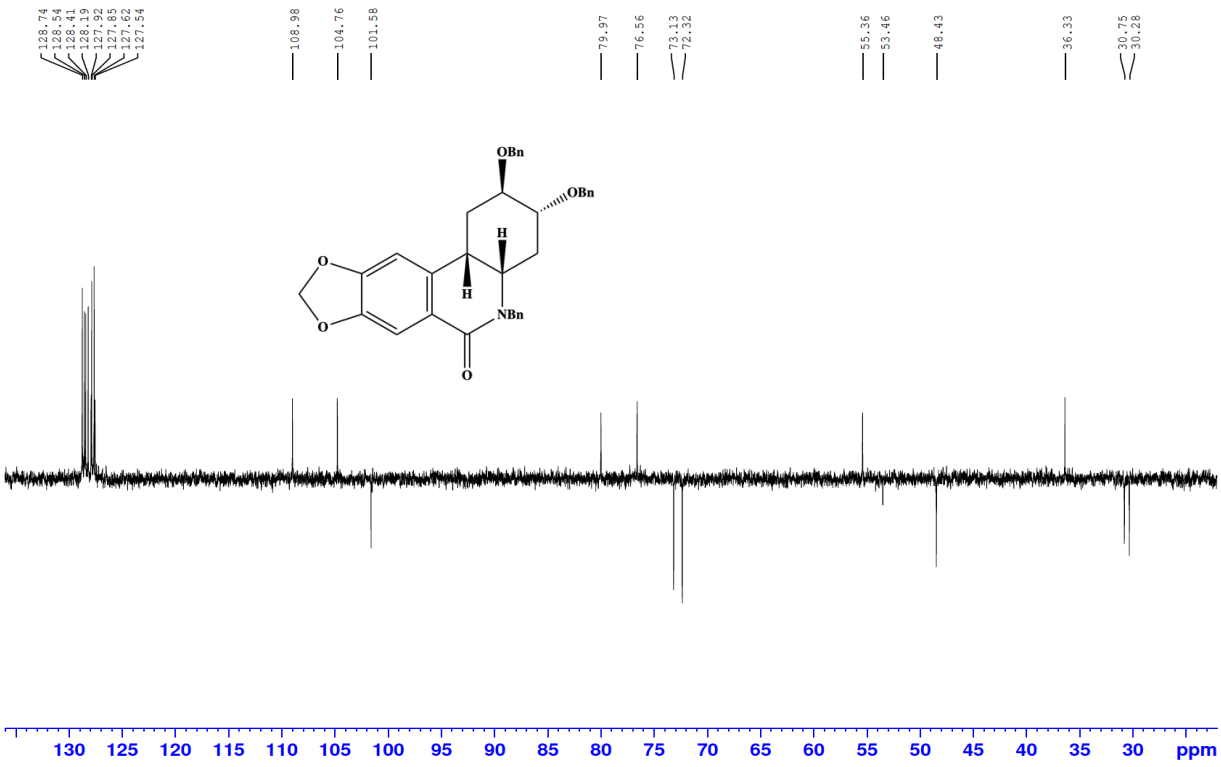
^{13}C NMR of 177



^{1}H NMR of 179



^{13}C NMR of 179



DEPT 135 NMR of 179

Appendix 2

Single Crystal X-ray (SC-XRD) diffraction data collection and refinement statistics

Molecule	**77**	**81**	**84**	**87**	**90**	**92**	**93**	**117**	**179**
Empirical formula	$C_{20}H_{17}NO_2$	$2(C_{20}H_{17}NO_3)$	$C_{24}H_{23}NO_6$	$C_{23}H_{23}NO_3$	$C_{21}H_{23}NO_4$	$C_{23}H_{27}NO_2$	$C_{23}H_{27}NO_2$	$C_{20}H_{17}NO_3$	$0.5(C_{35}H_{33}NO_5)$
Formula weight	303.35	638.69	421.43	361.42	353.40	349.45	349.45	319.35	273.81
Temperature (K)	100	100	100	100	100	298	100	100	298
Crystal system	Monoclinic	Monoclinic	Triclinic	Triclinic	Triclinic	Monoclinic	Orthorhombic	Triclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	P-1	P-1	P-1	$P2_1/n$	$P2_12_12_1$	P-1	Cc
a (Å)	8.9444 (4)	11.6352 (10)	10.0670 (4)	9.7700 (5)	8.6457 (4)	7.1187 (6)	6.2230 (3)	9.578 (3)	37.845 (12)
b (Å)	22.3989 (9)	8.7398 (7)	10.3851 (4)	10.7223 (6)	10.1609 (5)	10.6194 (9)	16.0485 (8)	10.064 (3)	6.295 (2)
c (Å)	7.5246 (3)	30.251 (3)	11.0499 (5)	10.7754 (6)	11.1389 (5)	24.770 (2)	18.6793 (8)	17.595 (5)	26.817 (8)
α (°)	90.000	90.000	87.580 (1)	65.271 (2)	103.711 (1)	90.000	90.000	95.544 (7)	90.000
β (°)	94.630	97.522	82.292 (1)	64.794 (2)	94.993 (1)	92.892 (3)	90.000	91.428 (10)	119.746 (8)
γ (°)	90.000	90.000	63.541 (1)	88.550 (2)	110.737 (1)	90.000	90.000	103.672 (11)	90.000
Volume (Å^3)	1502.59 (11)	3049.7 (4)	1024.68 (7)	911.47 (9)	873.18 (7)	1870.1 (3)	1865.50 (15)	1638.3 (9)	5546 (3)
Z	4	4	2	2	2	4	4	4	8
Radiation, λ (Å)	Mo Kα, 0.71073	Mo Kα, 0.71073	Mo Kα, 0.71073	Mo Kα, 0.71073	Mo Kα, 0.71073	Mo Kα, 0.71073	Mo Kα, 0.71073	Mo Kα, 0.71073	Mo Kα, 0.71073
μ (mm^{-1})	0.09	0.09	0.10	0.09	0.09	0.08	0.08	0.09	0.04
ρ (gcm^{-3})	1.341	1.391	1.366	1.317	1.344	1.241	1.244	1.295	0.656
F(000)	640	1344	444	384	376	752	752	672	1160
Crystal size (mm^3)	0.29 × 0.29 × 0.21	0.24 × 0.22 × 0.21	0.39×0.23 × 0.22	0.35 × 0.32 × 0.29	0.27 × 0.21 × 0.24	0.32 × 0.24 × 0.23	0.39 × 0.26 × 0.22	0.37 × 0.36 × 0.29	0.46 × 0.20 × 0.12
GOF	1.11	1.03	1.04	1.02	1.02	1.19	1.09	1.08	1.04
Reflections collected	75524	104502	61174	43013	55580	33192	23760	25853	3457
Independent reflections	4601	6250	5132	4549	4362	4155	4103	3899	4442
θ range (°)	3.3–30.5	2.9-27.8	2.8-28.4	3.5-28.3	3.2-28.3	2.9-27.1	3.4–27.1	3.2-22.7	2.6-19.0
R_{int} (%)	0.032	0.184	0.028	0.023	0.026	0.113	0.044	0.026	0.156
parameters	208	433	282	246	248	237	237	437	162
Final R_1 (%)	0.041	0.082	0.038	0.041	0.058	0.098	0.039	0.074	0.099
Final wR_2 (%)	0.117	0.208	0.106	0.110	0.160	0.198	0.077	0.207	0.261
max, min. peaks (e Å^{-3})	0.40/-0.27	0.37/-0.35	0.36/-0.25	0.39/-0.31	1.42/-0.50	0.28/-0.39	0.18/-0.24	0.60/-0.26	0.44/-0.48

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VITA

Adam Patrick Montoya was born July 24th, 1992, in Española, New Mexico. He is the son of Dennis and Deirdra Montoya. He graduated from Española Valley High School in 2010, after which he went on to earn a Bachelor of Arts degree with a major in chemistry from the University of New Mexico, Alburquerque, in 2015. At his time at the University of New Mexico, he worked as an undergraduate chemistry researcher.

In August 2015, he started his graduate studies at Texas Christian University, where he earned his Doctor of Philosophy degree in 2020. During his graduate career, he served as a Teaching Assistant from 2015 through 2016.

ABSTRACT

THE METHODS DEVELOPMENT APPROACH TO THE SYNTHESIS OF PHENANTHRIDINONE ANALOGS

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The phenanthridinone alkaloids pancratistatin, *tran*-dihydrolycoricidine and lycoricidine; isolated from certain plants of the *amaryllidaceae* family, have all been found to be biologically active species. Analogs of these natural products, such as *cis*-dihydrolycoricidine, have not yet been discovered in nature but have also been found to be anti-tumor agents. For this reason, these compounds have been the target of many synthetic chemists. Herein, is presented a synthetic scheme that provides analogs of these natural products while forming the ring system through a non-traditional manor using a lewis acid to induce an alkyl shift from a hemiaminal.

The double bond that is formed with the alkyl shift can be reduced in a *cis* manor to give analogs of these alkaloids that are not commonly targeted. Manipulations of the reaction scheme also show that unique functionalities and specific stereochemistry can be incorporated into the substrates if needed to provide a large library of derivatives. This new synthetic pathway circumvents the need for expensive catalysts typically used for late-stage reactions to close the ring system found in these compounds.